DEVELOPMENT OF A SYNTHETIC STRATEGY TOWARD FALCATIN A; DEVELOPMENT OF AN ASYMMETRIC DIELS–ALDER REACTION OF α-ACYLOXY ENONES

Thesis by

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To my family and friends

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Ruben and Shawni Mendoza: To my Mom and Dad, I love you guys. I would like to give a brief intro to how these two awesome folks have impacted me as a person. Their story starts before I was born. Many years ago, in eastern Washington, my parents met, fell in love, moved in together, and had my brother Cody Mendoza. It came as no surprise that a white woman and a Mexican man would struggle to convince their families that they should be together. Somewhere along the way, they started to fall away from each other and before they knew it, they were no longer living together. One day, my dad and his best friend took a trip to Hawaii. It was there, away from all of the family drama that my dad made the realization that he truly loved my mom and didn't care what other people thought. He wanted to be with her. So he convinced her to give it another shot. They got back together and had me but the family drama continued. But then one day, my parents packed their bags and flew away together to Maui to raise me and my brother away from the chaos. My parents always made sure they put their children first. They raised me and my brother on Maui and taught to be good respectful people. I am forever grateful to them for everything they have done for me. They have always supported me throughout my journey and for that I will always be thankful. Mom and Dad, I love you.

Lynne Hokama: During high school, I had the pleasure of being mentored by some of the greatest teachers ever. One such teacher, Lynne Hokama (aka. Hokama mama), was a huge supporter of me when I absolutely did not deserve it. In my second year of high school, I took Algebra I with Mrs. Hokama and I was a nightmare student. I could understand material but hated doing homework and so I never got great grades because I basically just

didn't care enough to put in the work. I always knew I was smart, but I was always too lazy to put in the effort. It wasn't until I met Mrs. Hokama that I learned how important it was for me to do my best. She constantly encouraged me to work harder and be better and eventually, when I tried to move forward in math, she was the only one to encourage me to shoot higher. Later in high school, I was told not to take Calculus because "I wasn't the type to do well in that kind of class". Mrs. Hokama was the one to tell me that I should do it anyway and show everyone why they're wrong. So, I did. I took calc and did well and showed the doubters they were wrong. But it all started with Mrs. Hokama believing in my potential. I will always be grateful to her and can never express just how grateful I am to her for all that she has done for me.

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Julie Nguyen: To my best friend in college. I love you so much. I want to thank you so much for being my friend. Julie, you have such an incredible energy about you. You make me so happy just by being yourself. I love the way you tell stories. I love the way you talk about your friends. I love the way you are willing to just spontaneously go on a trip to Portland. I love how even if we don't talk for a long time, when we chat again it's as if no time has passed. You are amazing and I am so incredibly proud of you for all that you have accomplished. Thank you for being one of the greatest people I have ever known.

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Nick Fastuca: Dude. Thank you so much for being my friend. I love how we can send each other memes on Instagram every day and not get tired of each other. You have been there for me all throughout this grad school experience and I'm so happy to have had you and Caitlin for this. You are way cooler and more amazing than you give yourself credit for. I love watching how excited you get about baseball and bread. It's awesome to see you having fun and I am so glad to know that our friendship is not one that ends after grad school. I know that you and I are lifelong friends and that's amazing. Thanks for everything.

Wendy Zhang: We met about 5 years ago at visitation weekend. I could never have imagined how different my life would be with you in it. I remember the first time I considered you my friend. We were at a department social and there was a photo booth. We wore funny props and took a couple pictures together. And then we hang out and studied together. We graded MO diagram in chem 1a together. And stayed up way too late every night and went to chandler to get chicken tenders and tofu nuggets. And then we went through tough times together. We experienced depression and anxiety and struggled to get through the day for a long time. But things slowly got better. We moved in together

and got the cats. We found you a boyfriend and figured out how to make things work even when life got hard. Even in the middle of a pandemic, we made things work because our friendship was so strong. I am so grateful to have had you in my life during the PhD. I am ecstatic that I got to marry you and Zak and be a part of your life. I love you and I want to say thank you for everything. Also, just a couple of quotes to remind you of the laughs we've had: "Are you thinking what I'm thinking?" "I'd give them all C's" "You Christ!" "If you wake me up, I'll break your nose" and lastly "squatty potty make you duck"

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Alice Wong: Alice wong big bong.com Dude. You're so awesome. Thank you for always being so nice to me. I really appreciate your patience with me when I would ask dumb

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about me and even when you are also going through a hard time, you make it a point to prioritize me anyways. I am so proud of you and I'm so happy for you as you make your way through this new chapter of your life outside the Reisman group. Thank you for everything. You're amazing.

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Emily Chen: Where to even begin. I am so glad I met you. You're like the peanut butter to my jelly. I don't know how it's possible for me to just feel so comfortable around you. When I'm talking to you, I don't ever feel tired. It's just so natural to be your friend. Emily you are such an awesome person. I love your confidence and ability to just be yourself. Hearing you talk about how you want to be the old woman from sweeny todd or be an old Asian grandma in the park is so funny. Thanks for being such a kind and caring friend. You have been there for me in good and bad times and I can tell how much you truly care about me. Thank you for being so amazing. Caitlin is lucky to have mentored you.

Jordan Thompson: Jordie!!! It's June! Automatic! Jordan, you are a ball of energy that can't be contained. I am in awe of your ability to stay so upbeat and positive even when things are really hard. Having you in the bay has been such a joy and I really appreciate

you for being such a kind and caring person. Thanks for keeping my mental attitude afloat when I felt like being down and depressed. Just having you around is a comforting and wonderful experience. Thanks for everything.

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Jaika Doeffler: Jaika. My first real gay friend. Thank you for showing me what it looks life to be an out and proud person in science. I have learned so much about myself by just knowing you. I am so appreciative that you took me to my first pride parade and were there for me through the good times and the bad. Thanks for everything.

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Anyone else that I missed: first of all, I am so sorry. I am writing this literally the night before it is due. If I have missed you, I apologize dearly. I appreciate everyone in my life that helped shape me to be the person that I am today. Because I you, I have taken one step closer to being me and getting this PhD. Thank you.

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ABSTRACT

Accessing natural products via *de novo* synthetic methods is important for the discovery of new medicines, antibiotics, agrochemicals and more. Design and investigation of efficient strategies is of interest to many pharmaceutical industries.

Herein, we discuss several strategies geared towards the synthesis of the natural product falcatin A. First, a general discussion of the class of natural products is discussed. Secondly, we discuss our first generation photoredox cascade cyclization approach toward the synthesis of falcatin A. This strategy allows for the efficient and convergent synthesis of two halves of falcatin. Next, a transition metal-catalyzed cascade cyclization approach is discussed in which we were able to successfully synthesize the core of the natural product on a model system. Efforts are ongoing to elaborate to more advanced fragments for the synthesis of falcatin A. Lasty, we discuss our work on the yttrium-catalyzed asymmetric Diels–Alder reaction of α-acyloxy enone dienophiles, performed in collaboration with BASF. We demonstrate that this methodology can be utilized to access enantioenriched natural product T-4-ol.

LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
alk	alkyl
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere(s)
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
BiOX	bi(oxazoline)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bis(oxazoline)
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	supported on activated carbon charcoal
°C	degrees Celsius
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
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIPEA	*N*,*N*-diisopropylethylamine
DIBAL	diisobutylaluminum hydride
DKR	dynamic kinetic resolution
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	*N*,*N*'-dimethylpropylene urea
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppbz	1,2-bis(diphenylphosphino)benzene
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
DYKAT	dynamic kinetic asymmetric transformation
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile

E	trans (entgegen) olefin geometry
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
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
HC	homocoupling
hex	hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
$h\nu$	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)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves or mass spectrometry
m/*z*	mass-to-charge ratio
n	normal
naph	naphthyl
nbd	norbornadiene
NBS	*N*-bromosuccinimide
ND	not determined
NHC	*N*-heterocyclic carbene
NHP	*N*-hydroxyphthalimide
nm	nanometer(s)
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
[O]	oxidation
p	para

Pc	phthalocyanine
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
phen	1,10-phenanthroline
PHOX	phosphinooxazoline
pin	pinacol
Piv	pivaloyl
pK_a	acid dissociation constant
Pr	propyl
^{i}Pr	isopropyl
^{n}Pr	propyl or *norm*-propyl
py	pyridine
PyBOX	pyridine-bis(oxazoline)
PyBim	pyridine-bis(imidazoline)
PyOx	pyridine-oxazoline
pyphos	(2-diphenylphosphino)ethylpyridine
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
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBS	*tert*-butyldimethylsilyl
TDAE	tetrakis(dimethylamino)ethylene
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
temp	temperature
terpy	2,2′:6′,2″-terpyridine
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	anionic ligand or halide
xs	excess
Y	anionic ligand or halide
Z	cis (zusammen) olefin geometry

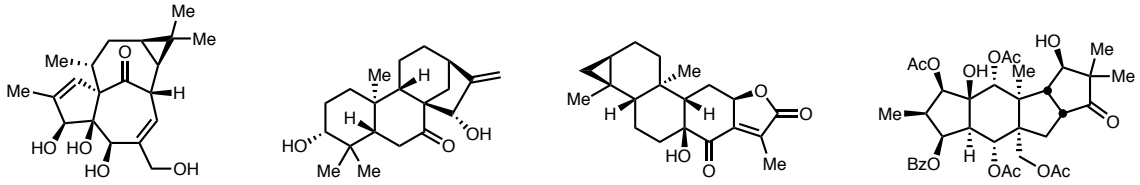
Chapter 1

An Introduction to the Myrsinane Family of Natural Products

1.1 INTRODUCTION

Extracts from the roots, leaves, and flowering parts of the *Euphorbia* genus of plants have long been used in traditional Chinese medicine.[1,2] In efforts to identify the chemical components which make the Euphorbiaceae medicinally relevant, isolation chemists have elucidated the structure of a number of natural products from these plants (**Figure 1.1**).

Figure 1.1 *Terpenes isolated from the Euphorbia genus*



ingenol **(1)**
Euphorbia ingens

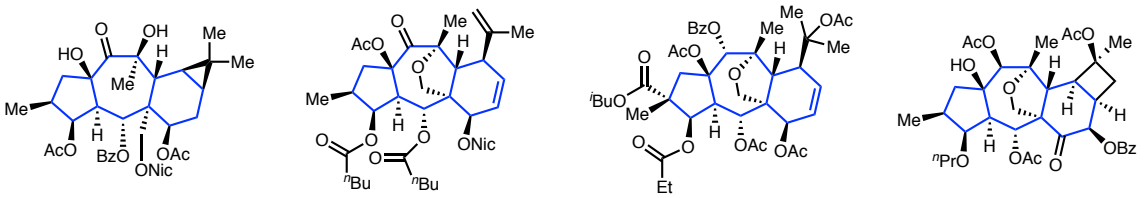
euphorangionol B **(2)**
Euphorbia wangii

retusolide A **(3)**
Euphorbia retusa

paralianone **(4)**
Euphorbia paralias

One subclass of these natural products is known as the myrsinane diterpenoids. Myrsinane natural products possess a highly conserved 5-7-6 carbocyclic framework and are of particular interest to both biologists and chemists alike. Several myrsinane diterpenoids have been shown to demonstrate a variety of excellent medicinal properties such as anti-inflammatory (euphorbialoid B), anti-HIV (15-*O*-acetyl-3,5-*O*-dibutanoyl-7-nicotinoylmyrsinol), anti-cancer (proliferin), and K-channel blocking (euphorproliferin D) activities (**Figure 1.2**).[3–8]

Figure 1.2 *Bioactive myrsinane-related terpenes*



euphorbialoid B **(5)**
anti-inflammatory
BV-2 IC_{50} = 15.6 μM

15-*O*-acetyl-3,5-*O*-dibutanoyl -7-*O*-nicotinoylmyrsinol **(6)**
anti-HIV
HIV-RTase IC_{50} = 0.119 μM

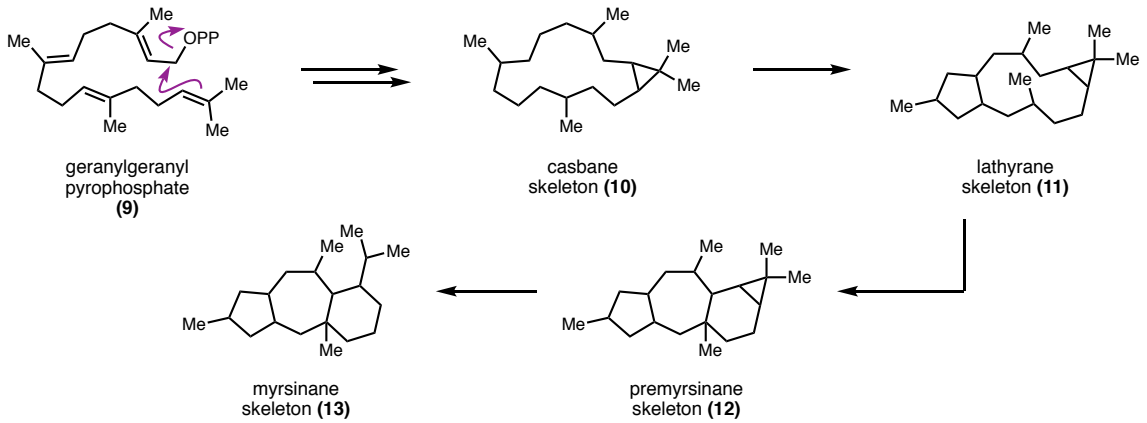
proliferin A **(7)**
anti-cancer
A2780 IC_{50} = 7.7 μM

euphorprolitherin D **(8)**
K-channel blocking
HEK-hERG IC_{50} = <30 μM

1.2 PROPOSED BIOSYNTHESIS OF THE MYRSINANE FAMILY

It has been proposed that the myrsinane family of natural products originates biosynthetically from geranylgeranyl pyrophosphate (GGPP) (**Figure 1.3**).[3,4,9,10] A cationic cyclization is proposed to effect the first cyclization of GGPP to access the casbane skeleton **10**. Subsequent cyclization affords the five-membered ring-containing lathyrane skeleton **11**. Next, a transannular cyclization then furnishes both the six- and seven-membered rings, giving rise to the premyrsinane skeleton **12**. Lastly, a cyclopropane opening of **12** affords the myrsinane skeleton **13**. Due to the interesting biological activities of natural products from the myrsinane family, efforts have been made to elucidate the biosynthetic pathway by which these natural products arise (**Figure 1.4**).

Figure 1.3 *Proposed skeletal rearrangement pathway to access myrsinane family*



geranylgeranyl pyrophosphate **(9)**

casbane skeleton **(10)**

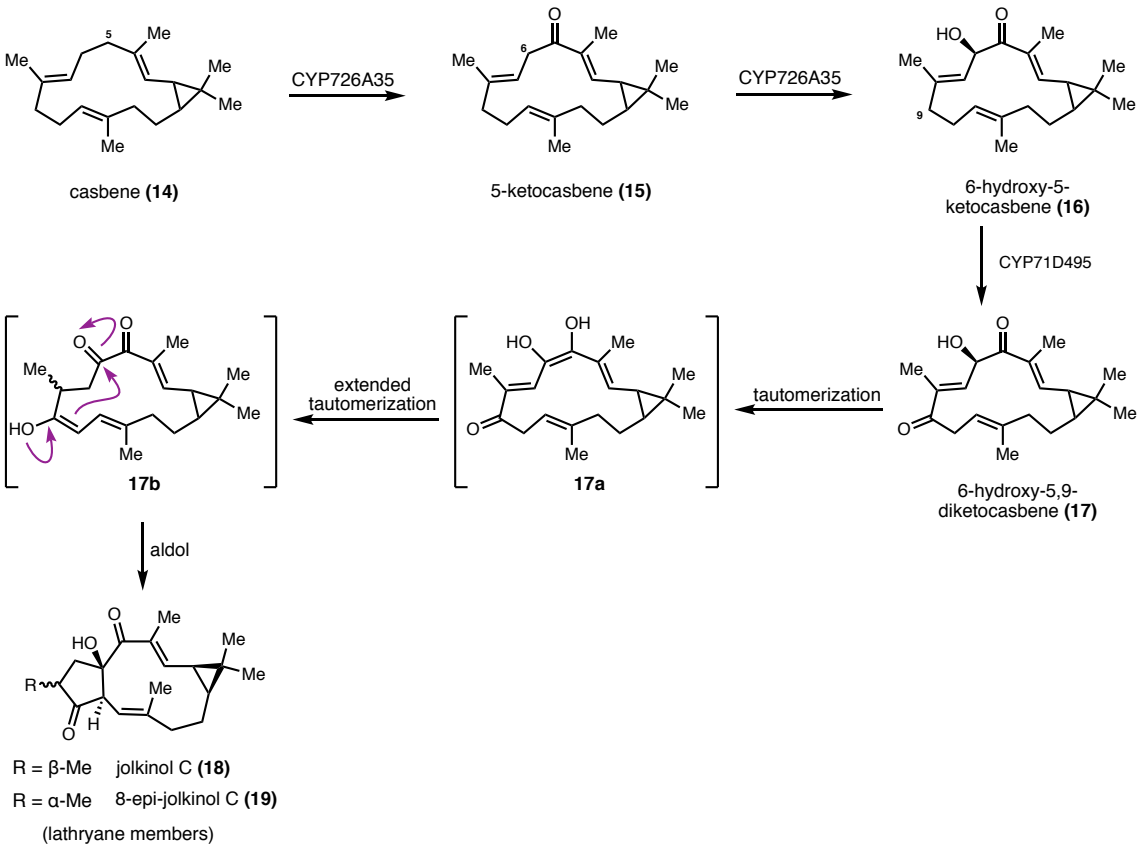
lathyrane skeleton **(11)**

premyrsinane skeleton **(12)**

myrsinane skeleton **(13)**

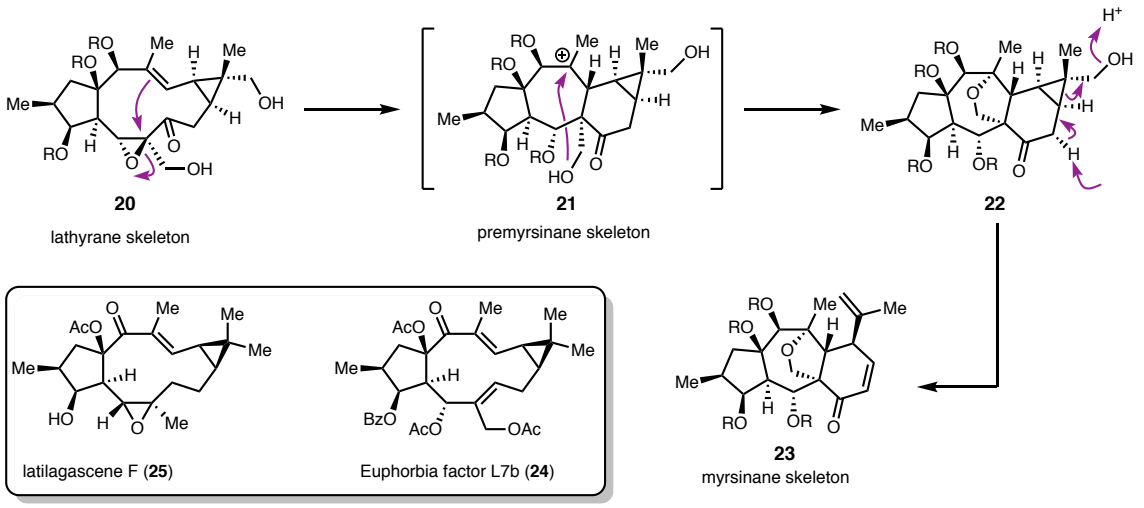
In 2016, the Graham group detailed their work on the elucidation of the biosynthetic pathways for the production of jolkinol C (**18**) and 8-*epi*-jolkinol C (**19**).[9] It is proposed that casbene (**14**) is oxidized by the enzyme CYP726A35 at C5 to form 5-ketocasbene (**15**) followed by a second enzymatic oxidation alpha to the carbonyl to furnish α-hydroxy ketone **16**. Next, enzyme CYP71D495 can effect oxidation at C9 to afford diketone **17**. Tautomerization of **17** to dienol **17a** followed by extended tautomerization affords intermediate **17b**. Intramolecular cyclization of **17b** then furnishes the five-membered ring of the lathyrane natural products jokinol C and 8-*epi*-jolkinol C. Currently, the biosynthetic pathways from lathyrane to premyrsinane and myrsinane natural products are not well studied. However, a single report from 1995 provides some evidence towards this goal.

Figure 1.4 *Bioenzymatic pathway from casbene to lathyrane member*



In 1995, the Berendsohn group isolated several new natural products from *Euphorbia seguieriana* (**Figure 1.5**).[11] In this report, the Berendsohn group hypothesized that lathryane **20** may undergo a cationic epoxide-opening reaction to afford tertiary carbocation **21**. Next, a pendant alcohol could trap the cation followed by an acid-mediated cyclopropane opening to afford the myrsinane core **23**. However, it is noteworthy that the only evidence for this hypothesis is the isolation of several myrsinane natural products of the form **23** and prior isolation of similar but non-identical lathyrane natural products such as **24** and **25**.

Figure 1.5 *Proposed biosynthesis of myrsinane natural products*

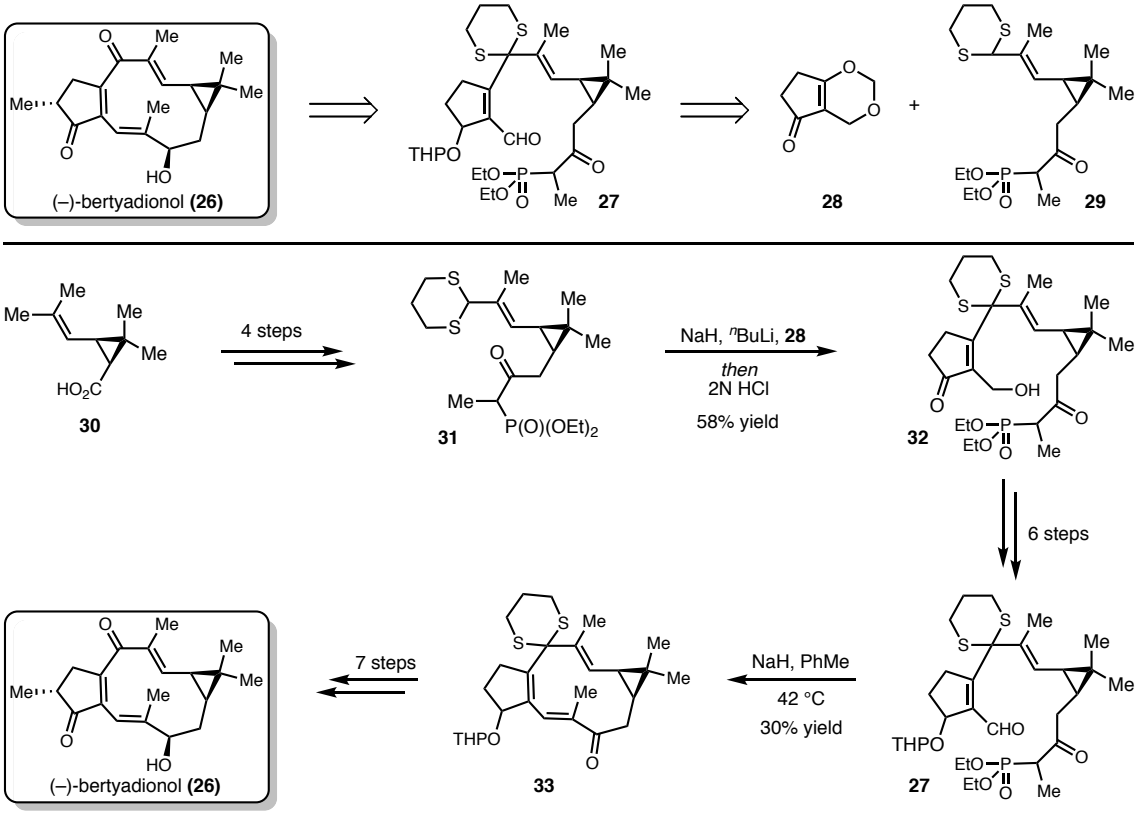


1.3 SYNTHESIS OF RELATED NATURAL PRODUCTS

To date, few reports have been published investigating the *de novo* synthesis of myrsinane natural products and their derivatives. Herein, we would like to present a summary of that work including the total synthesis of a single lathyrane natural product, several synthetic efforts towards lathyrane natural products, as well as a study in the degradation of natural product extracts for semi-synthesis.

1.3.1 Total Synthesis Efforts Toward Euphorbia Natural Products

Figure 1.6 *Synthesis of (–)-bertyadionol*



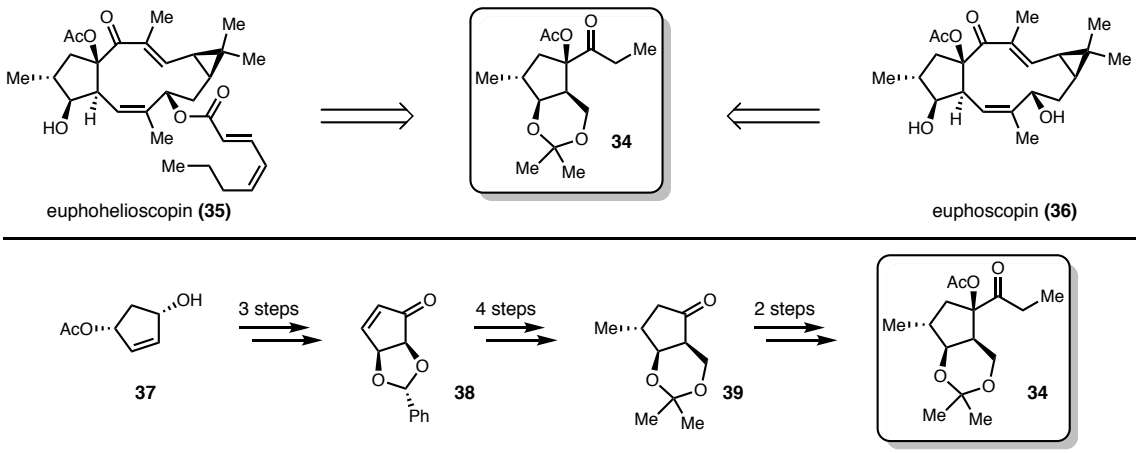
In the literature, there has only been a single total synthesis of a lathyrane natural product. In 1986, the Smith group detailed the synthesis of (–)-bertyadionol accomplished in 19 steps (**Figure 1.6**).[12,13] Retrosynthetically, the Smith group aimed to construct the macrocycle through the use of a Horner-Wadsworth-Emmons (HWE) reaction of intermediate **27**. Disconnection of this intermediate resulted in the identification of **28** and **29** as valuable targets.

In the forward sense, Arndt-Eistert homologation of (–)-*cis*-chrysanthemic acid (**30**) followed by regioselective oxidation, dithioacetal formation, and condensation with lithioethyl diethylphosphonate provided **31** in 1:1 dr. Next, deprotonation of the

phosphonate followed by lithiation of the dithiane allowed the coupling of **31** and **28** to furnish **32** in 58% yield. In 6 additional steps, the Smith group was able to obtain cyclization precursor **27**. Subsequent HWE reaction of **27** afforded the desired macrocycle, albeit in only 30% yield. In an additional 7 steps, the Smith group was able to elaborate macrocycle **33** to the natural product. In addition to the single reported total synthesis of lathyrane diterpenoid bertyadional, there has been some work towards the synthesis of other related natural products.

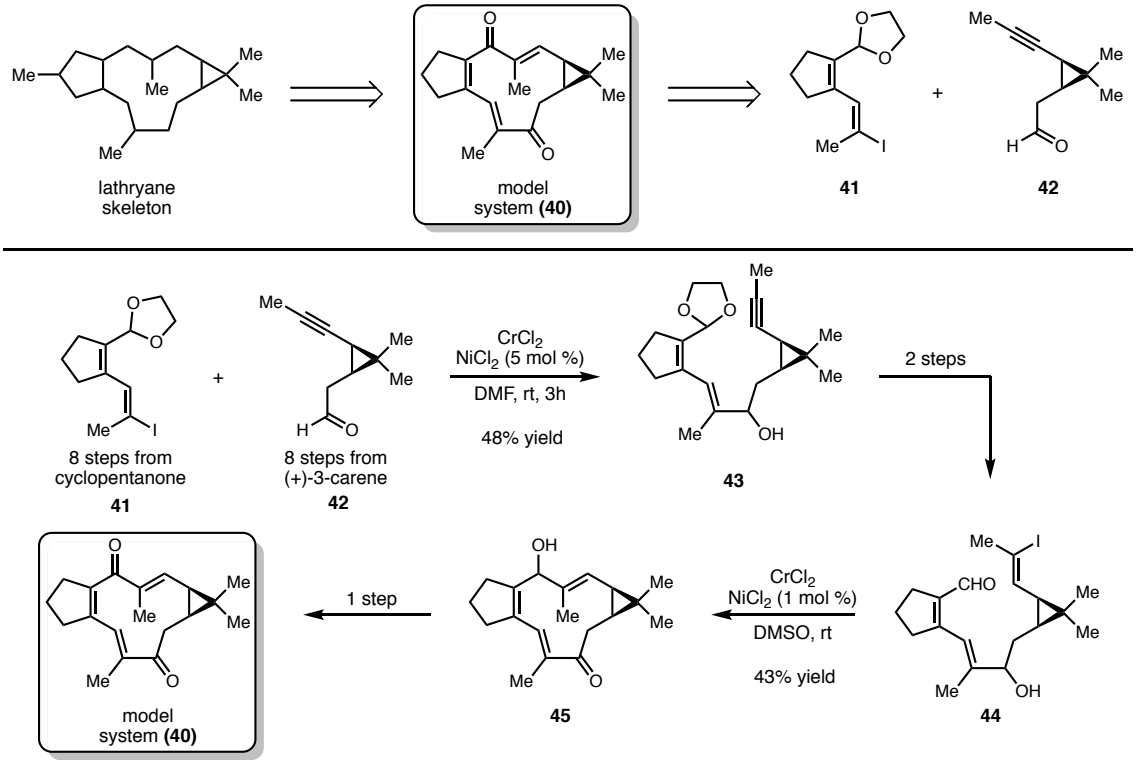
In 1993, the Yamamura group detailed the synthesis of an optically active cyclopentane derivative as a versatile intermediate toward the *Euphorbia* diterpenes (**Figure 1.7**).[14] This group identified euphohelioscopin and euphoscopin as suitable natural product targets for which intermediate **34** may be a valuable synthon. **34** was synthesized in 9 steps starting from resolved cyclopentene **37**. In three steps, they achieved the cyclopentenone **38** containing a benzylidene acetal. From there, four steps were required to install the methyl group diastereoselectively and homologate the acetal. A final two-step sequence allowed them to achieve their desired intermediate **34**. To date, there have been no further studies reported towards the use of intermediate **34** in the synthesis of any euphorbia natural products; however, this synthon possesses significant homology to this class of natural products quite nicely and thus could prove valuable for future synthetic endeavors.

Figure 1.7 *Synthetic work towards euphohelioscopin and euphoscopin*



In 2000, the Terada group detailed the facile construction of the lathyrane-type framework via sequential NHK reactions as their key step (**Figure 1.8**).[15] With much interest in the lathyrane scaffold, this group sought to synthesize **40** as a model system for studying the lathyrane skeletal framework. Retrosynthetically, intermediate **40** could be disconnected via two sequential NHK reactions, leading back to **41** and **42** as two useful coupling partners. First, an NHK reaction between **41** and **42** afforded **43**, which could be deprotected and converted to the alkenyl iodide precursor for a subsequent cyclization. A second NHK reaction then provided macrocycle **45** in 43% yield. A final oxidation of the bis-allylic alcohol furnished the desired model system **40** in an overall 13 steps from commercially available starting materials.

Figure 1.8 *Synthetic work towards a lathyrane model system*

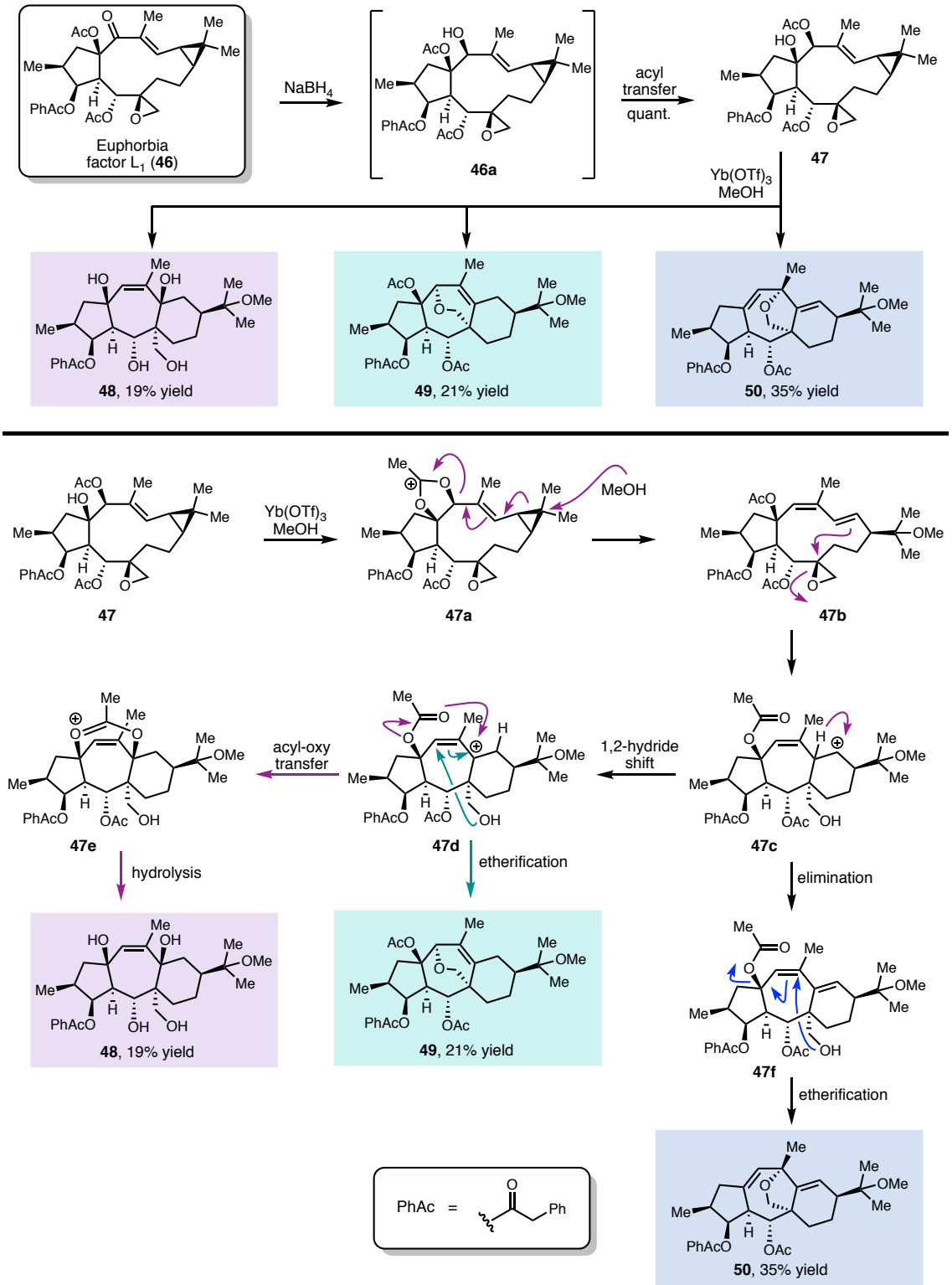


1.3.2 Natural Product Derivatization

In 2001, the Sterner group detailed the synthesis of unnatural products isolated from the transannular cyclization of *Euphorbia* factor L_1, an agricultural commodity (**Figure 1.9**).[16] First, reduction of **46** by $NaBH_4$ with concomitant acyl transfer provided **47** in quantitative yield. Next, $Yb(OTf)_3$-meditated transannular cyclization provided the three products **48**, **49**, and **50**. The proposed mechanism for transannular cyclization first involves Lewis acid coordination to the acyl group and dehydration followed by cyclopropane opening with methanol trapping of the resulting tertiary carbocation to furnish intermediate **47b**. Next, epoxide opening provides secondary carbocation **47c**. This intermediate carbocation can then undergo one of two different processes: 1) elimination to diene **47f** followed by etherification to afford **50** or 2) 1,2-hydride shift to afford intermediate **47d**. Intermediate

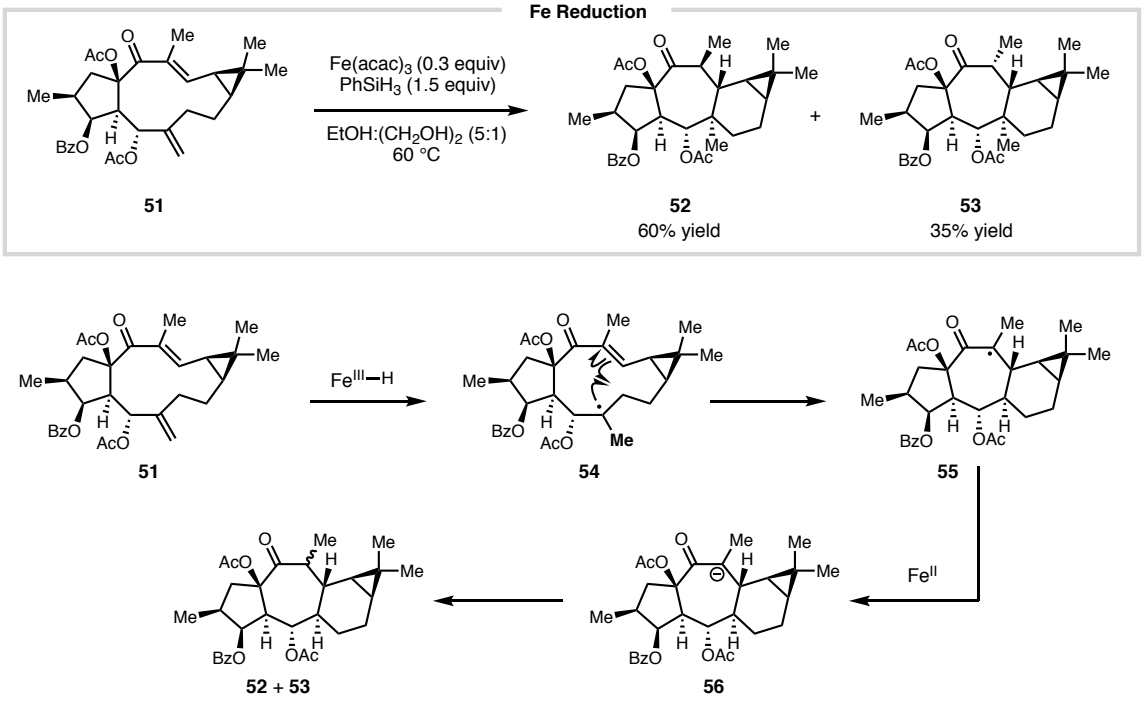
47d can then undergo either etherification to afford **49** or acyloxy transfer followed by hydrolysis to give **48**.

Figure 1.9 *Natural product degradation studies for semi-synthesis*



In 2021, the Gao group reported the iron-catalyzed skeletal conversion of lathyrane to premyrsinane diterpenes (**Figure 1.10**).[17] In this report, it was found that subjection of **51** to reductive iron conditions led to the conversion of lathyrane **51** to premyrsinanes **52** and **53**. It is hypothesized that an iron-hydride complex first delivers a hydrogen atom to **51** to generate tertiary radical **54**. This is then followed by reduction to enolate **56**, which can be quenched with a proton to give **52** and **53**.

Figure 1.10 *Iron-catalyzed conversion of lathyrane to premyrsinane skeleton*



1.4 CONCLUDING REMARKS

A number of groups, including our own, have been interested in the synthesis of the myrsinane natural products. Their complex skeletal structures, dense oxidation, and promising biological activities have attracted the attention of many synthetic chemists. We feel that the complexity of these natural products demonstrates the difficulties and shortcomings inherent in natural product total synthesis, and as such, continued synthetic

campaigns will be instructive and informative.

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Chapter 2

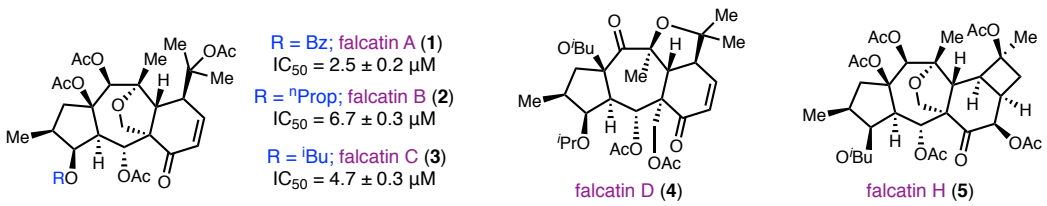
A Photoredox Cascade Cyclization Approach to the Synthesis of Falcatin A

2.1 INTRODUCTION

G protein-activated inwardly rectifying potassium ion (GIRK) channels have been shown to regulate the electrical activity of several cell types including: neurons, cardiac atrial myocytes, and β-pancreatic cells.[1] The dysfunction of GIRK channels has also been implicated in disorders such as neuropathic pain, drug addiction, and cardiac arrhythmias.[2] It has been shown in animal models that selective inhibition of myocardial GIRK channels can reduce the number and duration of provoked atrial fibrillation episodes.[3] Therefore, selective blocking of the GIRK channel may provide a useful tool in the treatment of atrial fibrillation.[2–6]

In 2016, the Hohmann group reported the isolation of several new myrsinane-related diterpenoid natural products from the plant *Euphorbia falcate*, which exhibit selective inhibition of GIRK channels (**Figure 2.1**).[4] The falcatins are structurally unified in that they contain a highly oxygenated 5-7-6 ring system as well as a geminal-dimethyl substitution.[7] While each of these molecules have been demonstrated to exhibit K-channel inhibition, we were particularly drawn to falcatin A (**1**), as it exhibits the most potent K-channel inhibition of the group (IC_{50} HEK-293 GIRK1/4 = 2.5 μM) making it a promising candidate for drug development.

Figure 2.1 *Falcatin Natural Products Possessing GIRK Channel Inhibitory Properties*

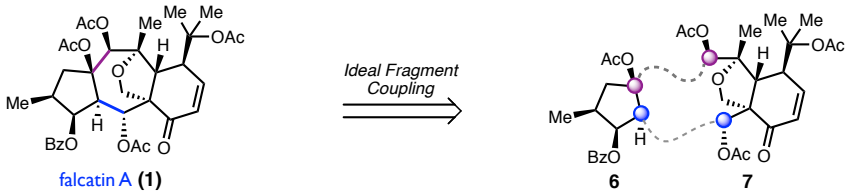


2.2 RETROSYNTHETIC STRATEGY

The structural complexity of falcatin A (**1**) provides an interesting challenge for the modern synthetic chemist. The most difficult features of this molecule include the polycyclic framework, oxidation pattern, and all-carbon quaternary center. A convergent approach to **1** would represent a significant contribution to myrsinane natural product total synthesis. In general, the Reisman lab is dedicated to furthering our understanding and the application of convergent fragment coupling strategies in the context of natural product total synthesis.[8] Thus, we have elected to pursue this strategy towards the synthesis of falcatin A (**1**). The most convergent application of this strategy would bring as much complexity as possible as shown in the ideal fragment coupling between **6** and **7** (**Figure**

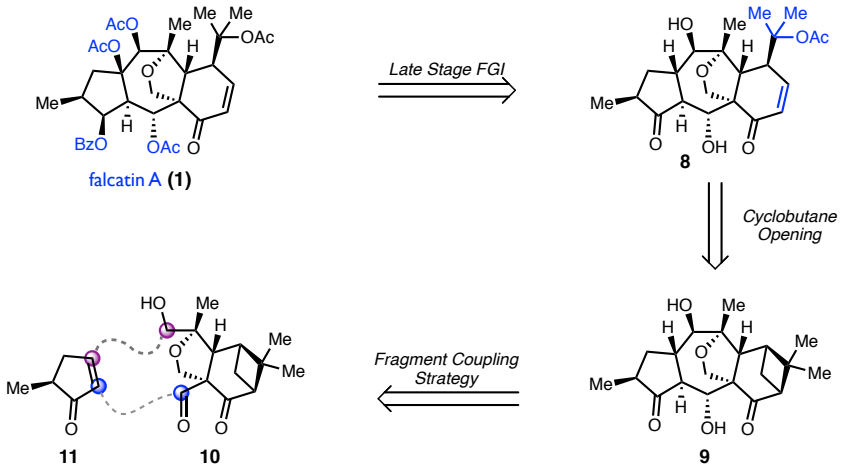
2.2). Therefore, we were tasked with the objective of designing a retrosynthesis with complex fragments in mind.

Figure 2.2 *Ideal Convergent Fragment Coupling Strategy*



In a retrosynthetic sense, it was believed that falcatin A (**1**) could be obtained through late-stage functional group manipulations to install the acetoxy and benzoyloxy groups highlighted in blue (**Scheme 2.1**). Next, the isopropoxyl motif could be obtained via a cyclobutane ring opening of **9**. Lastly, it was envisioned that intermediate **9** could arise from the convergent coupling of complex fragments **10** and **11** via a photochemical cascade cyclization reaction.

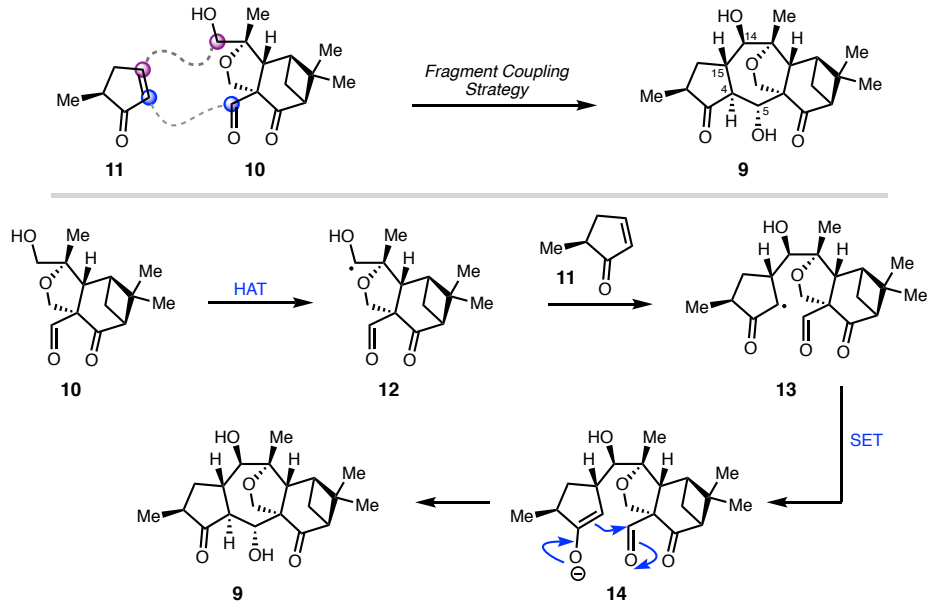
Scheme 2.1 *Retrosynthetic Analysis of Falcatin A*



We sought to use a photoredox cascade cyclization to forge the central seven-membered ring of the natural product. Specifically, we envisioned utilizing alcohol **10** and performing a hydrogen atom transfer (HAT) reaction to selectively generate neutral ketyl

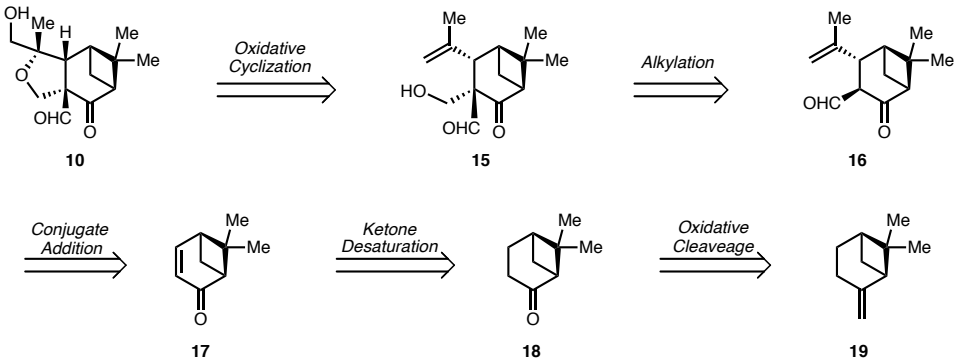
radical **12** (**Figure 2.3**). Next, neutral ketyl radical **12** could engage in a Giese reaction with cyclopentenone **11** to forge the C15–C14 bond. A photoredox-mediated reduction of radical **13** would then generate enolate **14** which would be poised to undergo an intramolecular aldol reaction to forge the central seven-membered ring **9**.

Figure 2.3 *Fragment Coupling Strategy Proposal*



This strategy would inherently require asymmetric synthesis of each fragment to avoid making mixtures of diastereomers since two chiral fragments will be brought together. It was clear at the outset that the synthesis of **10** would be challenging given its structural complexity. To this end, it was envisioned that both the primary alcohol and THF ring could be synthesized in a single oxidative cyclization reaction of **15** (**Scheme 2.2**). The requisite all-carbon quaternary center could then be installed via an alkylation of **16** into formaldehyde. α,β-difunctionalized intermediate **16** could arise from enone **17** which is known in 2 steps from commercially available **19**.[9–11]

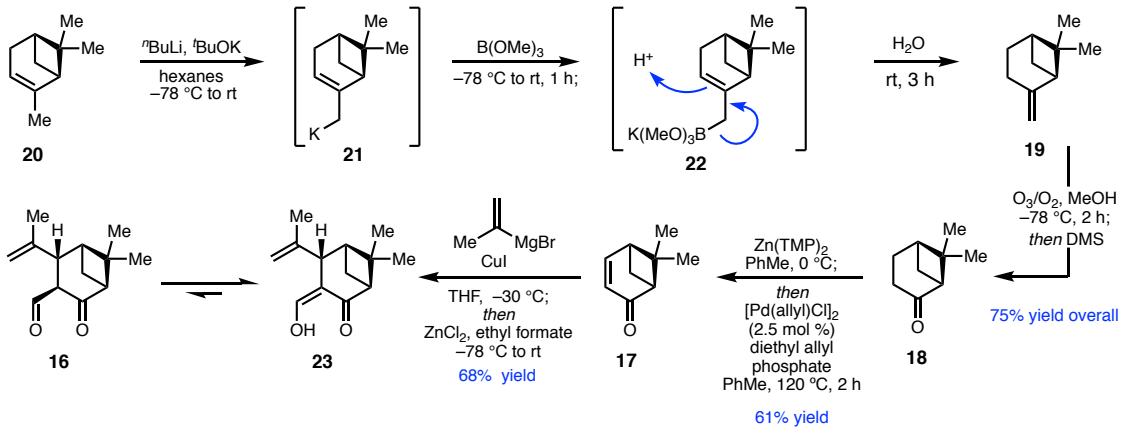
Scheme 2.2 *Retrosynthetic Analysis of Tricycle* ***10***



2.3 SYNTHETIC PROGRESS

2.3.1 Investigation of Quaternary Center Formation

Scheme 2.3 *Synthesis of Enol* ***23***

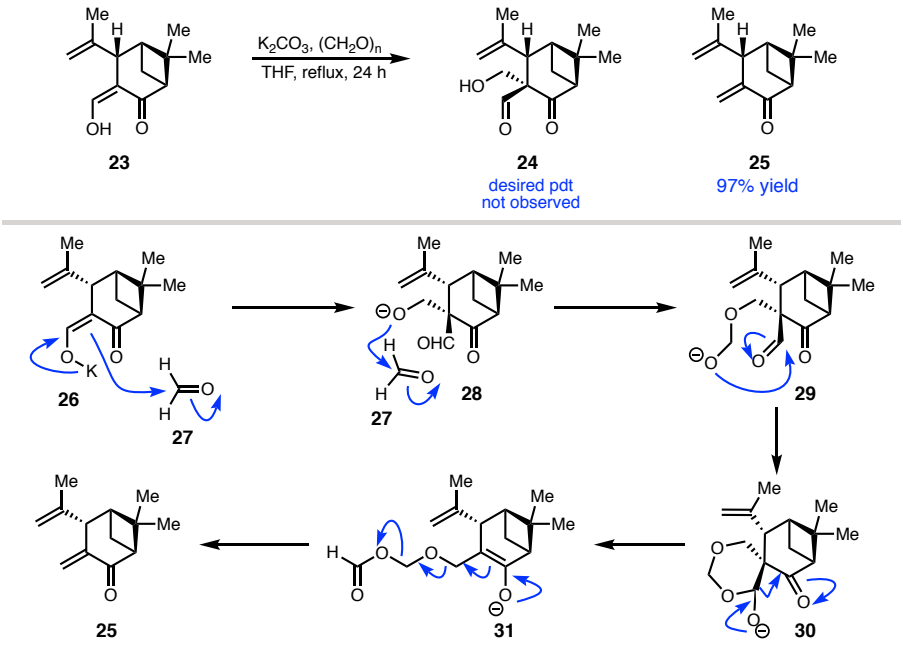


Though **19** is known and commercially available, we elected to begin the synthesis starting with **20** as this material is less expensive (**Scheme 2.3**). Deprotonation of **20** with a combination of ^{n}BuLi and ^{t}BuOK, also known as Schlosser's base, gives alkyl potassium species **21**.[12] Next, a transmetallation with trimethyl borate affords intermediate **22**, which upon exposure to water results in transposition of the olefin to yield exo-methylene **19**. Ozonolysis of **19** followed by desaturation yields enone **17**.[9–11] Next, conjugate addition of

isopropenyl cuprate into **17** followed by enolate trapping with ethyl formate furnished β-keto aldeyhyde **23** in 68% yield. In deuterated chloroform, this compound exists solely in its tautomeric enol form **23**. With **23** in hand, we were then poised to begin testing our alkylation reaction to install the challenging all-carbon quaternary center.

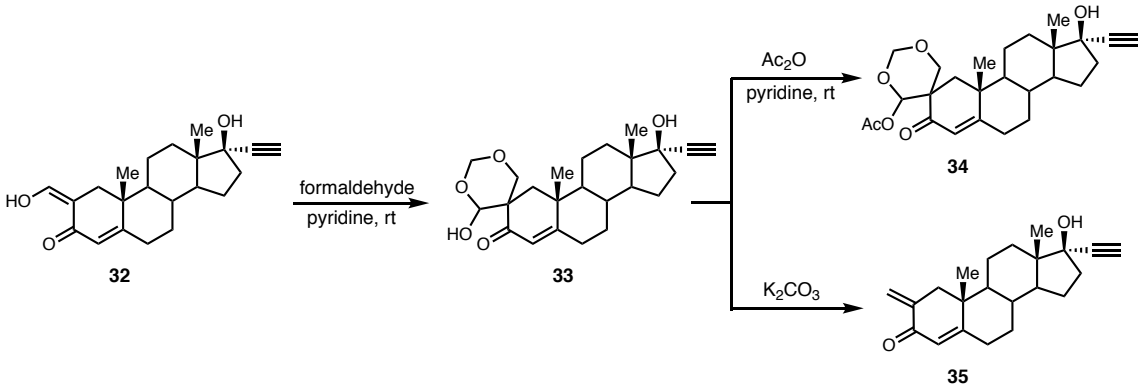
Initial attempts to alkylate β-keto aldeyhyde **23** with paraformaldehyde were unsuccessful, giving only exocyclic enone **25** as the major product (**Figure 2.4**). Our mechanistic proposal for the observed reactivity is summarized below. First, it is presumed that enol **23** is first deprotonated by K_2CO_3 to generate enolate **26**. Next, an aldol reaction with monomeric formaldehyde generated *in situ* affords alkoxide **28**. Alkoxide **28** can then undergo addition into a second equivalent of formaldehyde to furnish **29**. This intermediate is then believed to undergo intramolecular addition into the aldehyde to generate spirocycle **30**. From here, **30** can undergo a Grob-like fragmentation to give **31**. **31** can then undergo an E1cB elimination to deliver the observed product **25**.

Figure 2.4 *Attempts to Alkylate β-Keto Aldehyde* ***23***



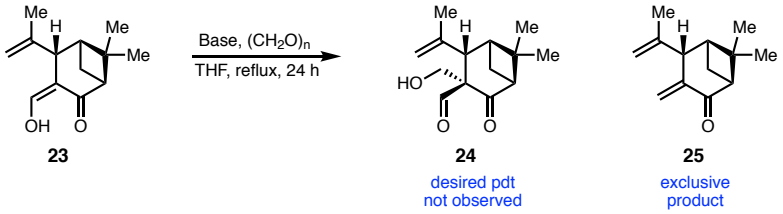
Indeed, similar reactivity has been observed in the literature (**Scheme 2.4**).[13] In 1967, Manson and Wood reported the isolation of related compounds. It was found that subjection of ketoaldehyde **32** to formaldehyde in pyridine resulted in the formation of **33** which could either be: 1.) acylated to form stable spirodioxolane **34** or 2.) reacted with base to deliver exocyclic enone **35**.

Scheme 2.4 *Literature Precedence for Spirodioxolane*



Our hypothesis at this stage was that a screen of different metal bases may affect the coordination and in turn, affect the nucleophilicity of alkoxide **28**. It was hypothesized that moving to more tightly coordinated metals such as lithium would reduce the nucleophilicity of alkoxide **28** such that **24** could be isolated instead of decomposing to **25**. To test this hypothesis, we screened several bases and found in all cases only product **25** was observed (**Table 2.1**).

Table 2.1 *Optimization Efforts*



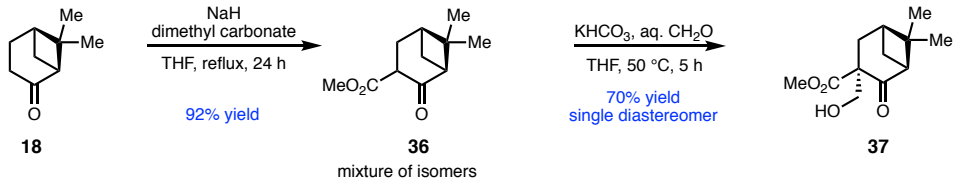
23 | **24** desired pdt not observed | **25** exclusive product

Entry	Base	Temp	Yield **25** (%)
1	LiOH	reflux	60
2	LiHMDS	0 °C to rt	50
3	NaOH	reflux	45
4	NaH	reflux	61
5	K_2CO_3	reflux	97

Given the lack of progress from screening bases, we next hypothesized that the aldehyde carbonyl may be too electrophilic and thereby resulting in high levels of alkoxide addition into the aldehyde of intermediate **29**. We reasoned that by using a less electrophilic aldehyde surrogate functional group, we could lower the rate of this decomposition pathway. To this end, we first elected to test a methyl ester as a less electrophilic functional handle which could later be converted to an aldehyde (**Scheme 2.5**).

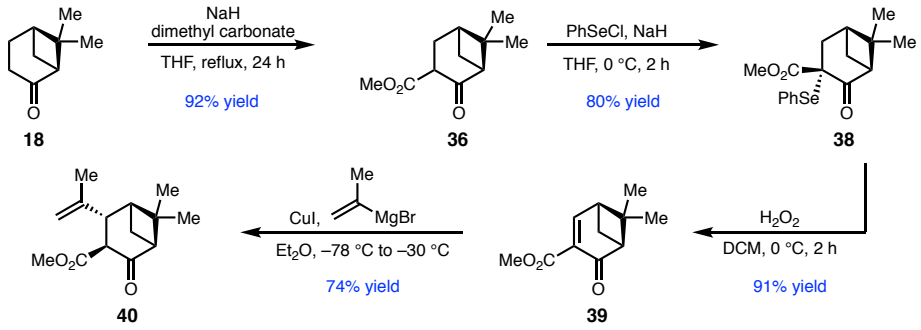
Subjecting **18** to base and dimethyl carbonate affords **36** in good yield as a complex mixture of enol tautomers and diastereomers. We then found that under conditions combining $KHCO_3$ and aqueous formaldehyde, we could affect our desired aldol reaction in good yield and as a single diastereomer. We were particularly encouraged by this result as it provided evidence in support of our hypothesis that a less electrophilic carbonyl could prevent the decomposition pathway observed with aldehyde **23**. We next pursued installation of an isopropenyl group to **36** to allow for further progression of the synthesis.

Scheme 2.5 *Synthesis of Ester and Alkylation*



To this end, subjection of **18** to base and dimethyl carbonate afforded **36** in good yield as a complex mixture of enol tautomers and diastereomers (**Scheme 2.6**). Next, selenation followed by oxidative elimination yields enone **39** in good yield. Finally, conjugate addition of isopropenyl cuprate in to enone **39** delivers **40**.

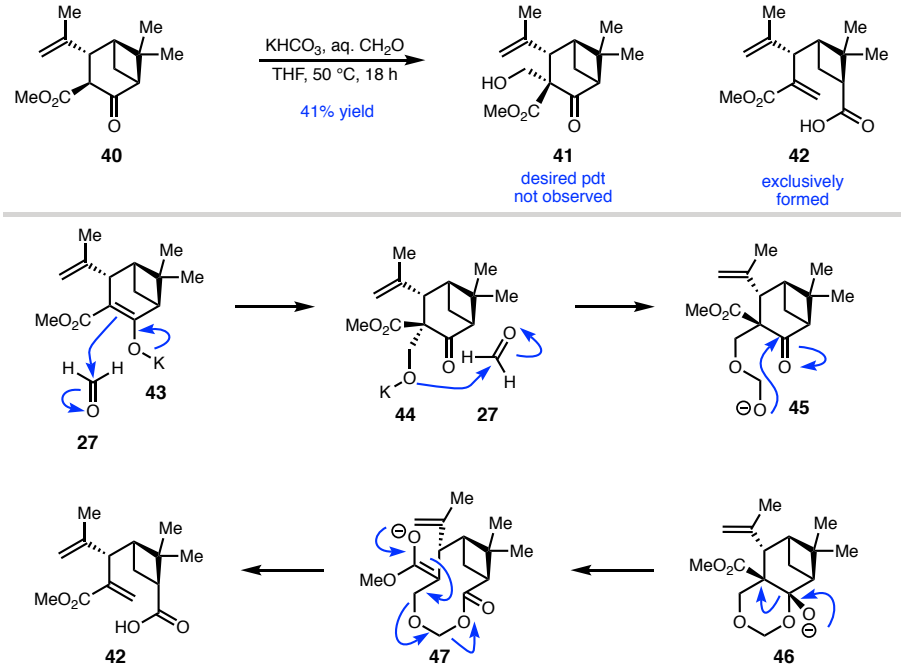
Scheme 2.6 *Synthesis of Ester **40***



At this stage, we were able to test our alkylation conditions but unfortunately found that subjection of **40** to $KHCO_3$ in the presence of aqueous formaldehyde led exclusively to the formation of undesired product **42** (**Figure 2.5**). Our mechanistic hypothesis for the formation of **42** is similar to the formation of **25**. First, deprotonation of **40** with $KHCO_3$ would yield enolate **43**, which could perform an aldol reaction with one equivalent of monomeric formaldehyde **27** to generate alkoxide **44**. Next, a second addition into formaldehyde would yield intermediate **45**. **45** is proposed to then undergo an intramolecular addition of the alkoxide into the ketone carbonyl to access spirodioxolane

46. Next, a Grob-like fragmentation would reveal macrocycle **47** which could then eliminate out formaldehyde to furnish the observed product **42**.

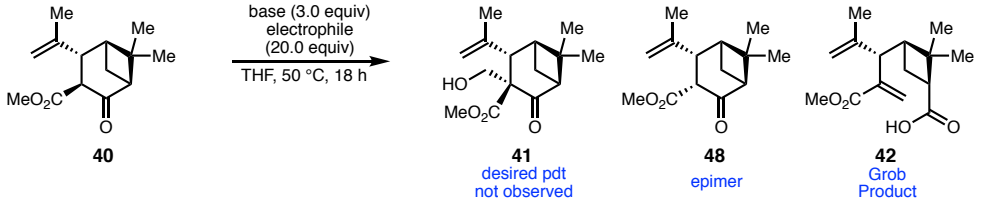
Figure 2.5 *Attempts to Alkylate β-Keto Ester* ***40***



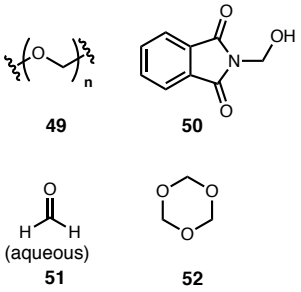
We hypothesize that the isopropenyl group may provide some conformational gearing, adding strain which can be relieved by ring opening to form **42**. Again, we hoped at this stage that by utilizing a stronger coordinating cation from our base, we may be able to reduce the reactivity of alkoxide **44** and trap out the desired aldol product **41**. Unfortunately, screening of bases led only to the observation of the epimer of starting material **48** as well as undesired acid **42** (**Table 2.2**). Our second hypothesis at this stage was that if we could slow the rate of formaldehyde generation, we could potentially lower the concentration of formaldehyde in solution thereby making the addition into a second equivalent of formaldehyde a slower process. Thus, we elected to screen reagents which

would generate monomeric formaldehyde over the course of the reaction. However, only the formation of epimer **48** and acid **42** was observed.

Table 2.2 *Optimization Efforts*



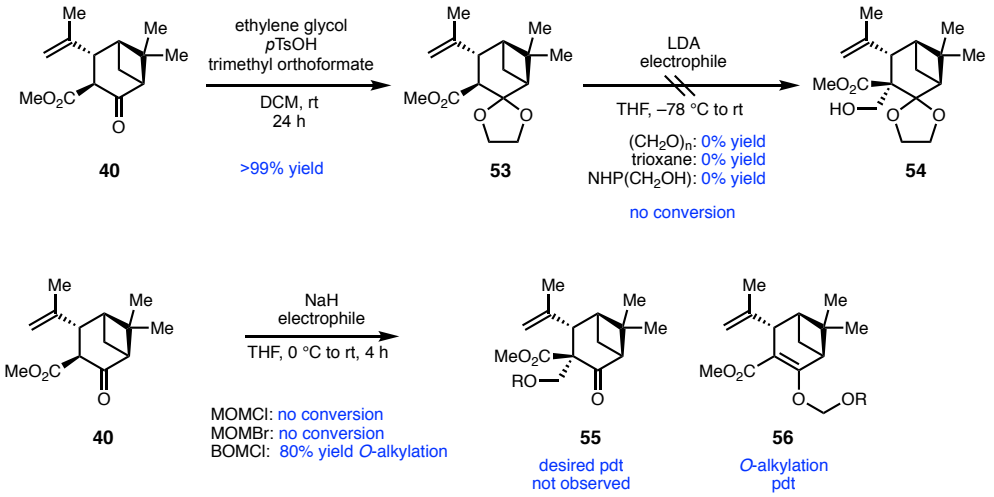
Entry	Electrophile	Base	Yield epimer(%)	Yield Grob(%)
1	**49**	$LiNH_2$	7	28
2	**49**	LiH	0	23
3	**50**	$LiNH_2$	27	0
4	**50**	LiH	0	0
5	**51**	$LiNH_2$	0	30
6	**51**	LiH	0	36
7	**52**	$LiNH_2$	37	0
8	**52**	LiH	0	0
9	**49**	NaH	0	89
10	**49**	NaOH	0	91
11	**50**	NaH	0	61
12	**50**	NaOH	0	0
13	**51**	NaH	0	95
14	**51**	NaOH	0	52
15	**52**	NaH	60	0
16	**52**	NaOH	0	29



Given our work with both the aldehyde **23** and ester **40**, we hypothesized that potentially both a ketone and aldehyde carbonyl were both too electrophilic to avoid the Grob-like fragmentation decomposition pathways. To combat this problem, we sought to first protect the ketone carbonyl prior to alkylation (**Scheme 2.7**). To this end, protection with ethylene glycol yields ketal **53** in excellent yield. However, attempts to alkylate this material proved unsuccessful. Our next hypothesis was that we could potentially avoid the intramolecular addition into our carbonyl by using a protected alcohol as our alkylating

agent. Unfortunately, alkylations with MOMCl, MOMBr, and BOMCl were unsuccessful, leading only to either no conversion or exclusively *O*-alkylation product **56**.

Scheme 2.7 *Alternative Attempts to Alkylate*



We next sought to synthesize weinreb amide **58** as a potentially useful substrate for our alkylation chemistry (**Figure 2.6**). Our first attempt to synthesize this material was unsuccessful and led only to the formation of dimer **59**. Our current mechanistic proposal for the formation of **59** is summarized below. First, deprotonation of ketone **18** with LDA yields enolate **60**. Next, an aldol reaction with formaldehyde generates alkoxide **62**. This alkoxide could then add into one equivalent of cyanoformate **57** , giving carbamate **63**. A second deprotonation of **63** would then yield enolate **64** which could undergo an E1cB elimination to give enone **65**. Lastly, Michael addition of a second equivalent of enolate **60** into enone **65** followed by protonation would yield the observed product **59**. It should be noted that nowhere in the reaction setup is there formaldehyde added to the reaction. The presence of this reagent can however be explained (**Figure 2.7**). It is known that Weinreb amides in the presence of a strong base have the ability to undergo rearrangement to generate formaldehyde although the exact mechanism of this transformation is debated.[14]

Figure 2.6 *Attempt to Synthesize Weinreb Amide*

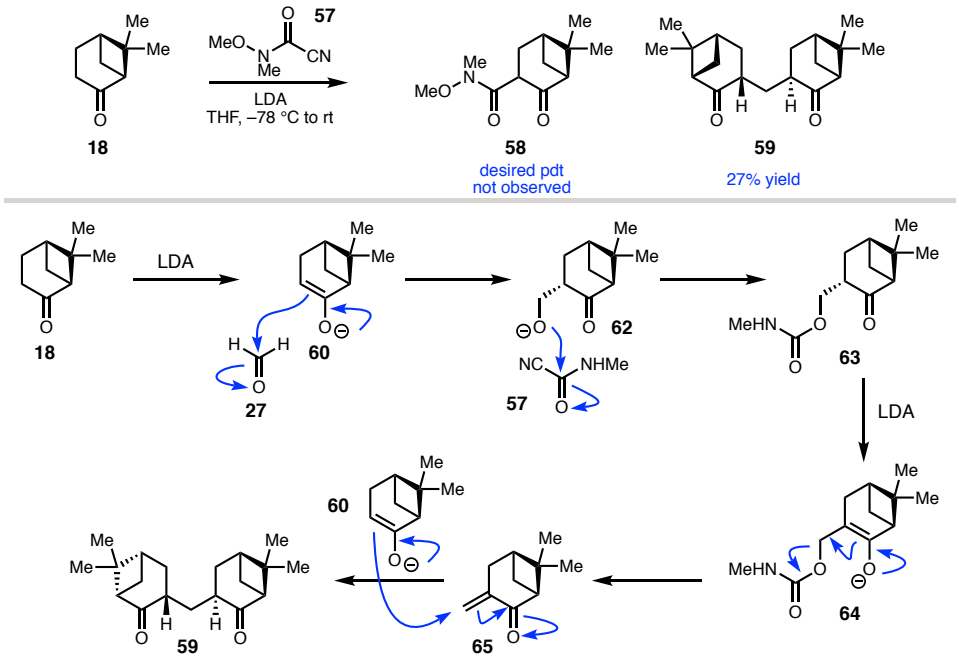
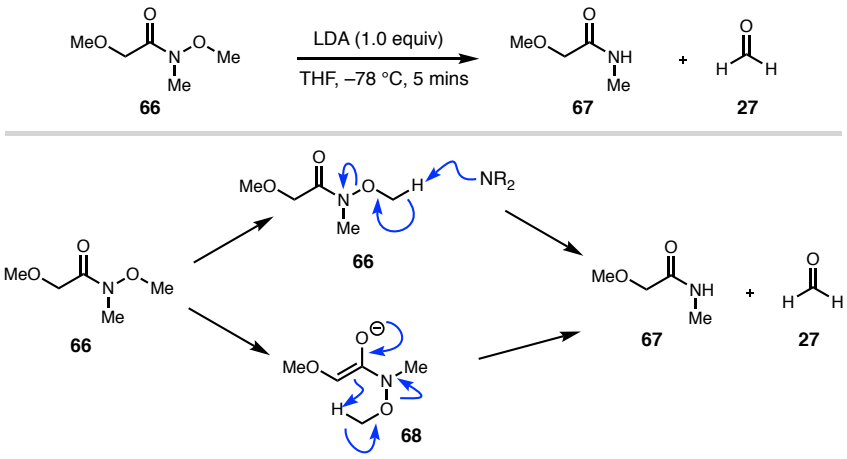


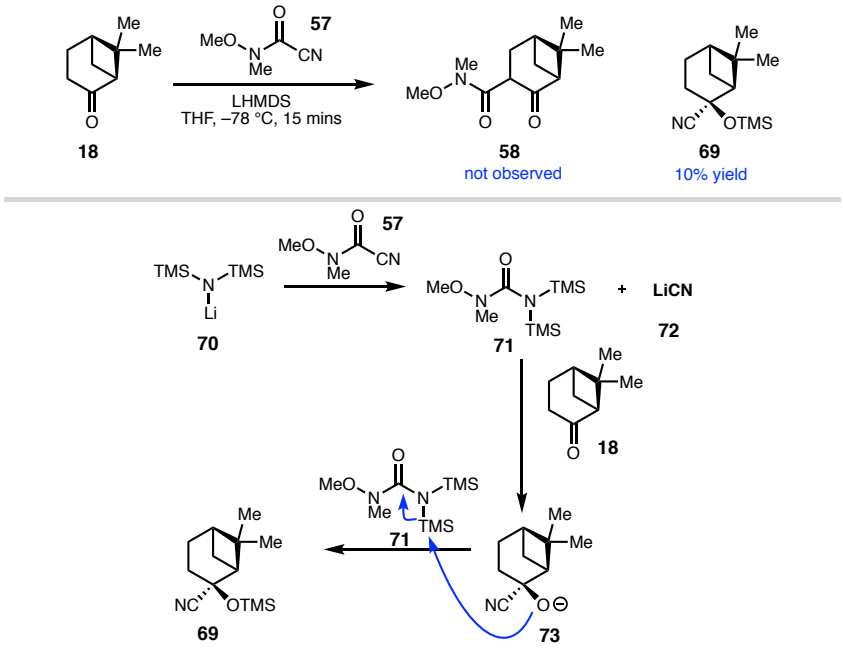
Figure 2.7 *Literature Precedence for Generation of Formaldehyde*



With the knowledge that LDA is too strong a base for the desired reactivity, we elected to test LHMDS instead. Interestingly, no desired product was formed but instead, TMS protected cyanohydrin **69** was isolated from the reaction (**Figure 2.8**). The mechanistic proposal for the formation of **69** is as follows. First, LHMDS reacts with the

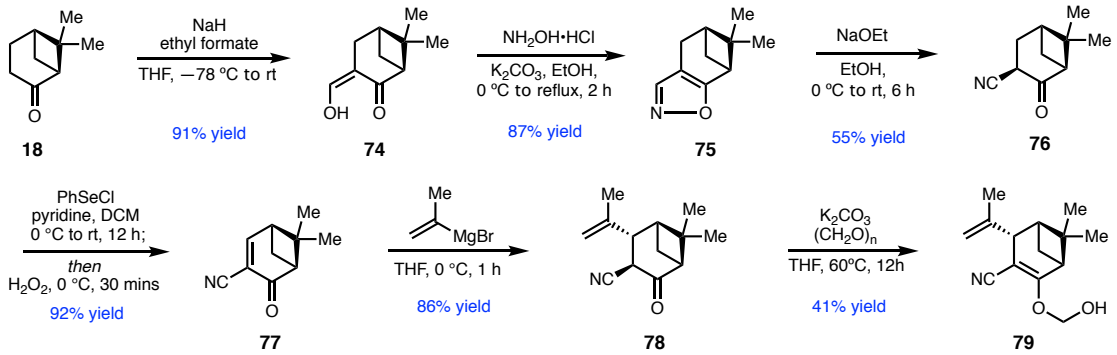
cyanoformate **57** to generate carbamate **58** and lithium cyanide. Next, cyanide addition into ketone **18** would generate **73** which could then undergo TMS protection by desilylation of carbamate **73** to generate the observed product **69**.

Figure 2.8 *Further Attempts to Synthesize Weinreb Amide*



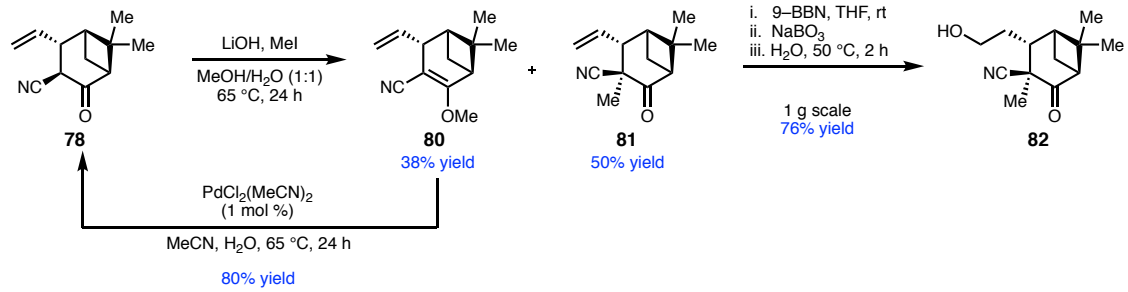
We turned next to the synthesis of cyanoketone **78** as a final attempt to synthesize the desired quaternary center (**Scheme 2.8**). First, formylation of ketone **18** with ethyl formate proceeds in good yield followed by condensation of hydroxylamine to generate isoxazole **75**. Base-mediated rearrangement of isoxazole **75** then delivers cyanoketone **76**. Selenation and oxidative elimination reveals enone **77** which then undergoes a conjugate addition with isopropenyl Grignard to afford cyanoketone **78**. Attempts to alkylate with formaldehyde led only to the formation of undesired *O*-alkylation product **79**.

Scheme 2.8 *Synthesis of Nitrile* ***78*** *and Alkylation Attempts*



Given the lack of success in our studies in trying to set the quaternary center with formaldehyde, we then elected to instead use MeI to form the quaternary center so that progress could be made moving forward (**Scheme 2.9**). Thus, methylation of cyanoketone **78** proceeds to deliver a a 1.3:1 mixture of *C*-alkylation (**81**) to *O*-alkylation (**80**) products. Olefin **81** could then undergo a hydroboration oxidation to reveal primary alcohol **82**. At this point, we were now prepared to begin investigating an intermolecular coupling of **82** to forge the central seven-membered ring of the natural product.

Scheme 2.9 *Alkylation of Nitrile* ***78*** *and Elaborate to Radical Cyclization Precursor*



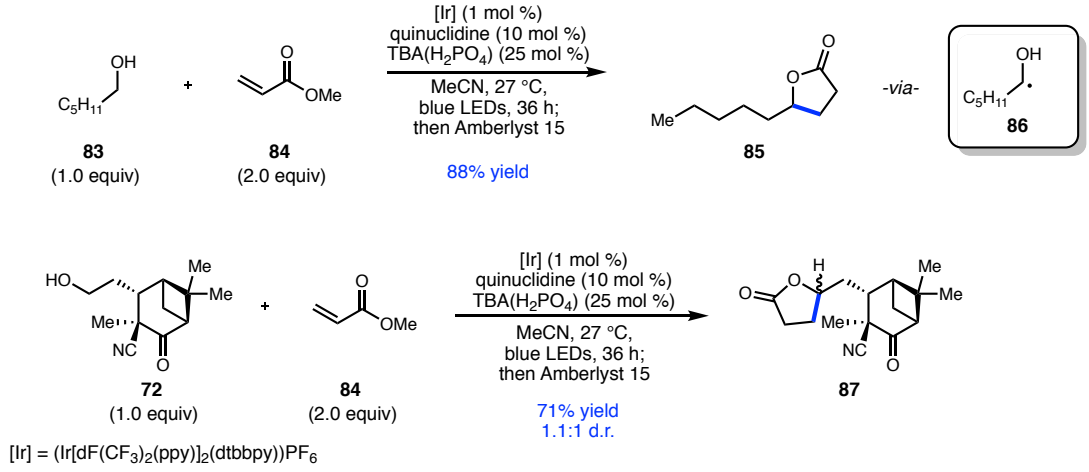
2.3.2 Investigation of an Intermolecular Coupling

We next elected to begin investigating our proposed photoredox cascade cyclization. In the literature, there has been some work done towards our ultimate goal. One particularly interesting result was reported in 2015 by MacMillan and cowerkers

(**Scheme 2.10**).[15] In this report, they found that the use of an iridium photocatalyst along with quinuclidine and a phosphate base could catalyze the reaction between alcohol **83** and methyl acrylate **84** to generate lactone product **85**. This reaction is presumed to proceed via generation of intermediate neutral ketyl radical **86**.

Given the challenges associated with synthesizing **10**, we elected to test these photoredox conditions on model system **72**. We were pleased to find that the reaction between alcohol **72** and methyl acrylate proceeded smoothly to deliver a 1.1:1 mixture of diastereomers of lactone **87**. This result demonstrated that the alcohol of **72** could be selectively utilized to generate a neutral ketyl radical and that the intermolecular Giese reaction with this *in situ* generated radical is chemically competent. Encouraged by this result, we next turned to investigate the desired reaction between **72** and cyclopentenone **88**.

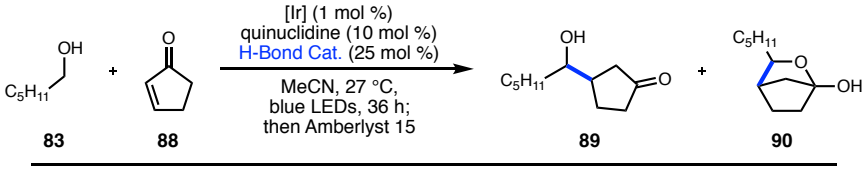
Scheme 2.10 *Successful C–H bond Functionalization in Model System*



To this end, we screened hydrogen bonding catalysts in an attempt to optimize the reaction between model alcohol **83** and cyclopentenone **88** (**Table 2.3**). It was found that reactions with cyclopentenone performed best in the presence of TBA(TFA) as the

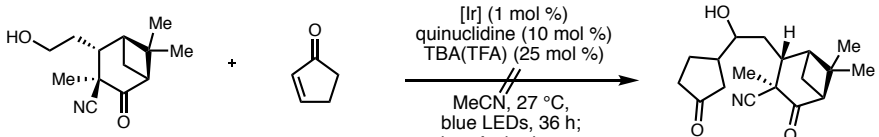
hydrogen bond acceptor. Unfortunatley, translating these conditions to the reaction with **72** proved unsuccessful leading to a complex mixture of products from which the desired product **91** was not observed.

Table 2.3 *Optimization Efforts*



83 **88** **89** **90**

Entry	alcohol:enone	H-Bonding Catalyst	Yield of mixture (%)	RSM (%)
1	1:1	TBA(H_2PO_4)	38	4
2	2:1	TBA(H_2PO_4)	66	30
3	1:2	TBA(H_2PO_4)	56	24
4	1:2	TBA(TFA)	99	0
5	1:2	TBA(BF_4)	37	26



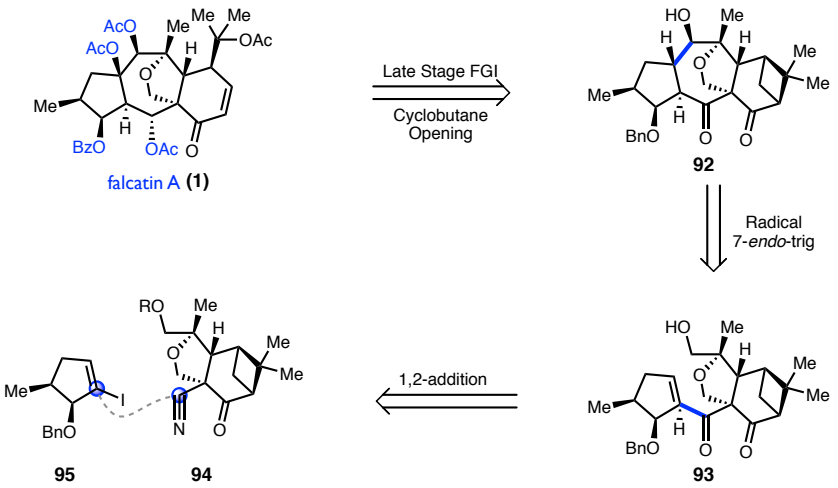
72 (1.0 equiv) **88** (2.0 equiv) 0.04 mmol scale 28% RSM **91** not observed

[Ir] = $(Ir[dF(CF_3)_2(ppy)]_2(dtbbpy))PF_6$

2.3.3 Investigation of an Intramolecular Coupling

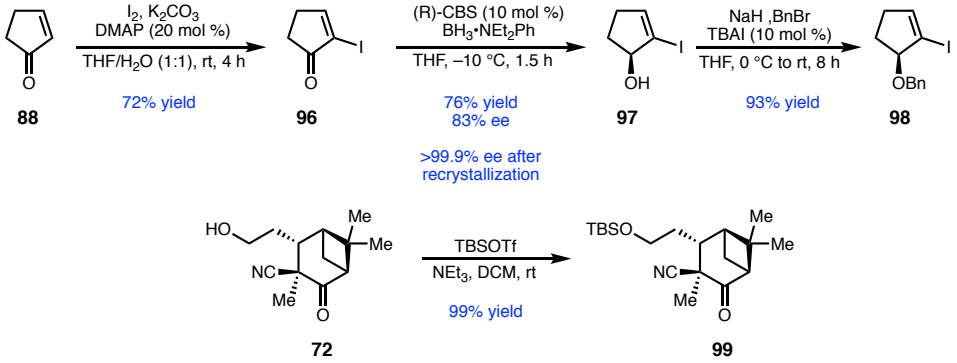
Given the challenges associated with the intermolecular Giese reaction, we revised our strategy to incorporate the five-membered A ring fragment prior to the Giese reaction (**Scheme 2.11**). We envisioned that intermediate **92** could arise from an intermolecular 7-*endo*-trig radical cyclization of substrate **93**. Substrate **93** could arise from a 1,2-addition reaction between nitrile **94** and alkenyl iodide **95**. This strategy could potentially overcome the inherent lack of desired reactivity between **72** and **88** by positioning the radical acceptor nearby in an intramolecular reaction. Additionally, this strategy would take advantage of compounds which had already been synthesized, which would allow us to test our hypothesis quickly and efficiently.

Scheme 2.11 *Revised Retrosynthetic Analysis*



To begin, fragment **98** was synthesized in short order starting from cyclopentenone **88** (**Scheme 2.12**). The iodination of **88** delivered **96** which could then undergo an enantioselective CBS-catalyzed reduction to deliver **97** in good yield and ee. Notably, **97** could be recrystallized to >99% ee after only one recrystallization. Lastly, benzyl protection of the secondary alcohol delivered fragment **98**. Next, alcohol **72** could be protected as the silyl ether in good yield.

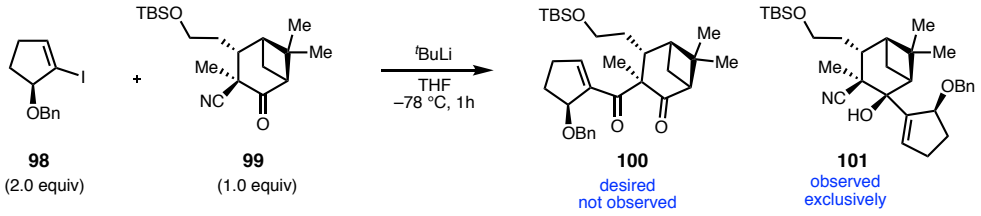
Scheme 2.12 *Synthesis of Coupling Fragments*



Initial attempts to perform the 1,2-addition between **98** and **99** were unsuccessful (**Figure 2.9**). Instead, we observed good levels of 1,2-addition into the ketone to afford

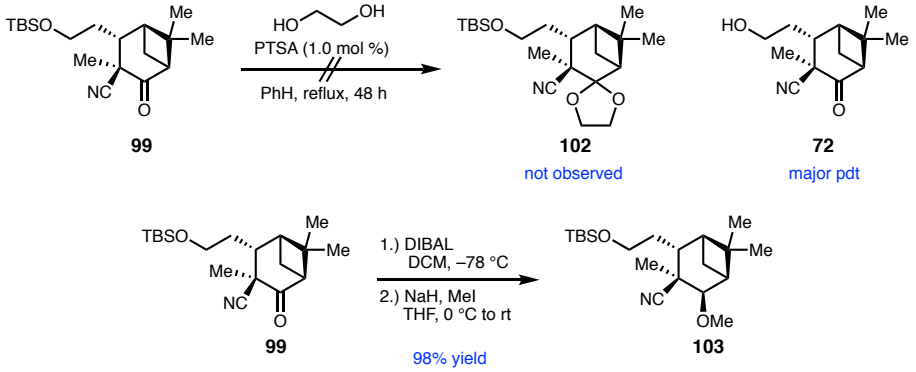
tertiary alcohol **101**. This experiment however did demonstrate that lithiation of alkenyl iodide **98** was chemically feasible. We hypothesize that the nitrile is both less electrophilic and more sterically hindered leading to selective addition at the ketone carbonyl.

Figure 2.9 *Synthesis of Coupling Fragments*



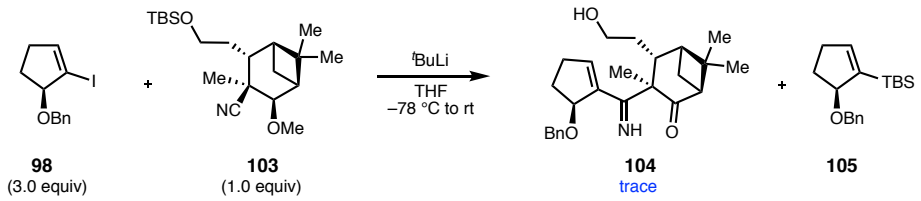
To address this issue of 1,2-addition selectivity, we decided to protect ketone **99** (**Scheme 2.13**). Attempts to ketalize the carbonyl were unsuccessful. However, reduction with DIBAL followed by methylation were successful in protecting the carbonyl group.

Scheme 2.13 *Synthesis of Coupling Fragments*



Our attempts to perform the 1,2-addition between alkenyl iodide **98** and nitrile **103** were still largely unsuccessful (**Figure 2.10**). In a single case, we were able to observe formation of the intermediate imine **104**. However, the reaction was low yielding and irreproducible. Additionally, it was found that desilylation occurred as it was observed that the isolated imine **104** lacked the TBS ether from starting material **103**. Additionally, we isolated α-silylated cyclopentene **105** as a byproduct of this reaction.

Figure 2.10 *Efforts Toward Fragment Coupling*



2.4 CONCLUDNG REMARKS

In conclusion, we have reported our attempts to utilize a photoredox cyclization strategy towards the synthesis of falcatin A. In our efforts, we learned about the challenges and ultimate solutions to install an all-carbon quaternary center. Additionally, we found that a photoredox mediated generation of neutral ketyl radicals on complex substrates is chemically feasible. However, this strategy was ultimately unable to afford our desired intermediates. Thus, we have elected to pursue alternative strategies which will be discussed in Chapter 3.

2.5 EXPERIMENTAL SECTION

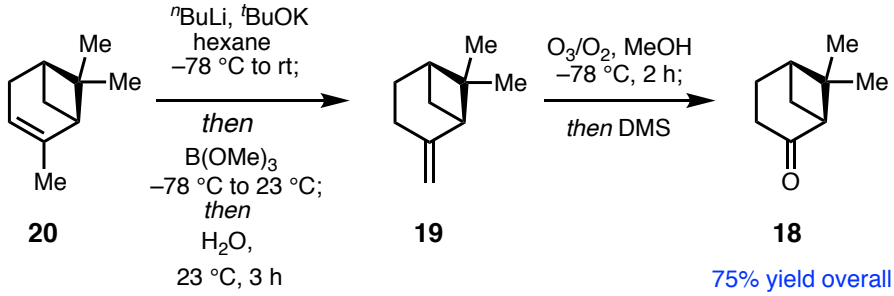
2.5.1 Materials and Methods

Unless otherwise stated, reactions were performed with freshly dried solvents utilizing standard Schlenk techniques. Glassware was oven-dried at 120 °C for a minimum of four hours or flame-dried utilizing a Bunsen burner under high vacuum. THF, DCM, MeCN, PhH, and PhMe were dried by passing through activated alumina columns. DCE, Et_3N, *i*-Pr_2NH, DIPEA, Pyr, and 2,6- lutidine were distilled from calcium hydride prior to use and stored under N_2 or Ar. Commercial reagents were used directly as supplied from

commercial sources and without further purification unless otherwise specified. 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 (254 nm) and $KMnO_4$, p-anisaldehyde, iodine, or CAM staining. Flash column chromatography was performed as described by Still et al.[16] using silica gel (SiliaFlash® P60, particle size 40-63 microns [230 to 400 mesh]) purchased from Silicycle. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance III HD with Prodigy Cryoprobe (at 400 MHz and 101 MHz, respectively) or Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to internal $CDCl_3$ (^1H, δ = 7.26), $CDCl_3$ (^{13}C, δ = 77.16). 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, p = pentet, hept = heptet, m = multiplet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system (CO_2 = 1450 psi, column temperature = 40 °C) with a Chiralcel AD-H column (4.6 mm x 25 cm). Molecular formulas of the compounds [M] are given, with the observed ion fragment in brackets, e.g. [M+H]+. Deuteriochloroform was purchased from Cambridge Isotope Laboratories.

2.5.2 Substrate Preparation

Preparation of ketone 18:



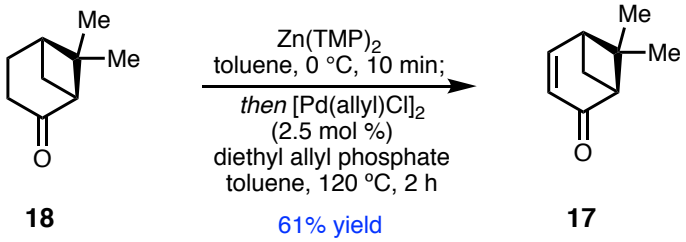
Procedure: To an oven dried 500 mL round bottom flask, equipped with a large stir bar, in a N_2-filled glovebox, was added ^{t}BuOK (28.0g, 250 mmol, 1.25 equiv). Reaction sealed with a red rubber septum and electrical tape and then removed from the glovebox. Next, ^{n}BuLi (100 mL of 2.5 M in hexanes, 250 mmol, 1.25 equiv) cannulated into ^{t}BuOK and stirred at room temperature, then cooled to –78 °C. Then **20** (27.2 g/31.7 mL, 200 mmol, 1.0 equiv) added via syringe pump over 30 mins. Reaction then warmed to room temperature over 1 hour and stirred at room temperature for 48 hours. Next, reaction was cooled to –78 °C and $B(OMe)_3$ (67.0 g, 650 mmol, 3.25 equiv) mixed with Et_2O (50 mL) added slowly over 1 hour via syringe pump. Then reaction was warmed to room temperature over 1 hour and then stirred at room temperature for 1 hour. Then water (100 mL) added slowly over 1 hour via syringe pump and stirred at room temperature for 3 hours. Reaction then extracted with hexanes (3 x 200 mL), dried over $MgSO_4$, filtered, and concentrated. Then MeOH (200 mL) added in a 500 mL round bottom flask, equipped with a stir bar, and fitted with a gas dispersion tube. Reaction was cooled to –78 °C and then ozone bubbled through for 2 hours at which point the reaction turned pale blue. Reaction

was then sparged first with oxygen followed by nitrogen and then DMS (20 mL) added. Reaction was then allowed to warm to room temperature and stirred overnight. Reaction was then extracted with Et_2O (3 x 150 mL) and then washed with water (250 mL). Combined organic fractions were then concentrated in vacuo and subjected to column chromatography (10 to 15% Et2O/Hexanes) to afford **18** (20.69 g, 150 mmol, 75%) as a clear colorless oil. Spectral data matched the literature.[17]

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.62 – 2.54 (m, 2H), 2.52 (dtt, *J* = 11.9, 5.6, 1.4 Hz, 1H), 2.34 (ddd, *J* = 19.1, 9.3, 2.0 Hz, 1H), 2.23 (dtd, *J* = 6.4, 4.3, 2.0 Hz, 1H), 2.04 (dddd, *J* = 13.3, 11.2, 4.0, 2.0 Hz, 1H), 1.94 (dddt, *J* = 13.3, 9.2, 6.3, 1.9 Hz, 1H), 1.58 (d, *J* = 10.4 Hz, 1H), 1.33 (s, 3H), 0.85 (s, 3H).

R_f = 0.40 in 20% EtOAc/hexanes ($KMnO_4$)

Preparation of enone 17:



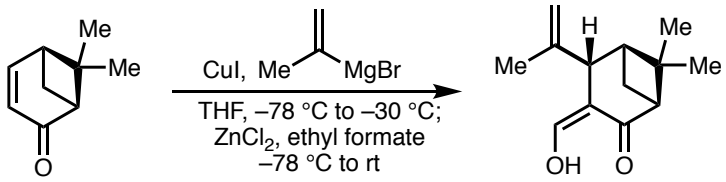
Procedure: To an oven-dried 2-dram vial, equipped with a stir bar, was added ketone **18** (138.2 mg, 1.0 mmol, 1.0 equiv) and PhMe (2.5 mL). Reaction cooled to 0 °C and then $Zn(TMP)_2$ (0.5M in PhMe, 2.0 mL, 1.0 mmol, 1.0 equiv) added and stirred for 10 mins. Next, a solution of $[Pd(allyl)Cl]_2$ (9.2 mg, 0.025 mmol, 2.5 mol %) and diethyl allyl phosphate (0.18 mL, 1.0 mmol, 1.0 equiv) in PhMe (0.82 mL) added. Reaction then sealed and heated to 120 °C for 2 hours. Reaction then quenched with aqueous ammonium

chloride, extracted with Et_2O (3 x 1 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Reaction then purified via column chromatography (10% EtOAc/Hexanes) to afford **17** (83.1 mg, 0.061 mmol, 61%) as a clear colorless oil. Spectral data matched the literature.[18,19]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 5.95 (ddd, *J* = 8.9, 1.9, 1.0 Hz, 1H), 2.84 (dtd, *J* = 9.2, 5.5, 1.0 Hz, 1H), 2.72 (td, *J* = 5.9, 1.9 Hz, 1H), 2.59 (tdd, *J* = 6.4, 5.3, 1.1 Hz, 1H), 2.14 (d, *J* = 9.2 Hz, 1H), 1.51 (s, 3H), 1.03 (s, 3H).

R_f = 0.40 in 20% EtOAc/hexanes ($KMnO_4$, UV-Active)

Preparation of enol 23:



17 68% yield **23**

Procedure: To an oven-dried 100-mL flask, equipped with a stir bar, in a nitrogen-filled glovebox, was charged CuI (1.397 g, 7.34 mmol, 2.0 equiv), sealed with a red rubber septum, and removed from the glovebox. To this was added THF (freeze-pump-thawed 3X, 18.4 mL), and the mixture was cooled to –50 °C. To the resulting suspension was slowly added isopropenyl grignard (0.5 M in THF, 29.4 mL, 14.69 mmol, 4.0 equiv) over 5 mins. After stirring for 2 hours at –50 °C, the reaction mixture was cooled to –78 °C. To this cuprate mixture was slowly added enone **17** (500 mg, 3.67 mmol, 1.0 equiv) as a stock solution in THF (7.5 mL). After 2 hours of stirring, ZnCl2 (1.9 M in 2-MeTHF, 3.86 mL, 7.34 mmol, 2.0 equiv) was added, followed by ethyl formate (5.932 mL, 73.43 mmol, 20.0

equiv). Then the reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of water, diluted with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3X) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation. Residue was then purified by column chromatography (10% EtOAc/Hexanes) to afford **23** (515 mg, 2.49 mmol, 68%) as a slight pink oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.90 (s, 1H), 7.30 (s, 1H), 4.92 (p, *J* = 1.5 Hz, 1H), 4.83 (dt, *J* = 1.9, 0.9 Hz, 1H), 3.27 – 3.22 (m, 1H), 2.47 (t, *J* = 5.4 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.17 (td, *J* = 5.7, 2.4 Hz, 1H), 1.79 – 1.75 (m, 3H), 1.54 (d, *J* = 10.6 Hz, 1H), 1.37 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.55, 168.59, 146.90, 113.65, 54.48, 43.81, 43.08, 41.53, 26.46, 24.28, 22.16, 21.25.

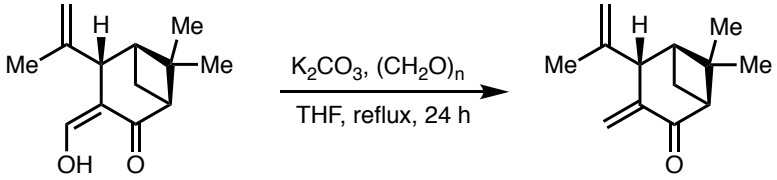
FTIR (NaCl, thin film, cm^{-1}): 3083, 2933, 2871, 1649, 1592, 1450, 1393, 1216, 1186, 1107, 1059, 1000, 897, 937.

HRMS (ESI+, m/z): calc'd for $C_{13}H_{18}O_2$ 207.1385 $[M+H]^+$; found: 207.1393

$\boldsymbol{\alpha_D^{21}}$ = +110° (c = 0.375, $CHCl_3$).

R_f = 0.53 in 10% EtOAc/hexanes (stains brown in p-anisaldehyde)

Preparation of enone 25:



23 **25**

Procedure: To an oven-dried ½-dram vial, equipped with a stir bar, was added enol **23** (5 mg, 0.024 mmol, 1.0 equiv), p-formaldehyde (14.6 mg, 0.485 mmol, 20.0 equiv), K_2CO_3 (5mg, 0.036 mmol, 1.5 equiv), and THF (240 uL). Reaction was capped and then heated to 70 °C for 16 hours. Reaction then quenched with water (200 uL) and extracted with EtOAc (3 x 300 uL). Combined organic layers were then dried over Mg2SO4, filtered, and concentrated in vacuo. Reaction purified via prep plate (20% EtOAc/Hexanes) to afford enone **25** (4.5 mg, 0.0232 mmol, 97%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 – 6.51 (m, 1H), 5.48 – 5.42 (m, 1H), 4.92 (p, *J* = 1.5 Hz, 1H), 4.81 (dt, *J* = 1.9, 0.9 Hz, 1H), 3.51 – 3.40 (m, 1H), 2.65 – 2.57 (m, 1H), 2.49 (dtd, *J* = 11.0, 6.0, 1.6 Hz, 1H), 2.27 (d, *J* = 0.7 Hz, 0H), 2.23 – 2.14 (m, 1H), 1.76 (t, *J* = 1.1 Hz, 3H), 1.62 (d, *J* = 11.0 Hz, 1H), 1.38 (s, 3H), 0.92 (s, 3H).

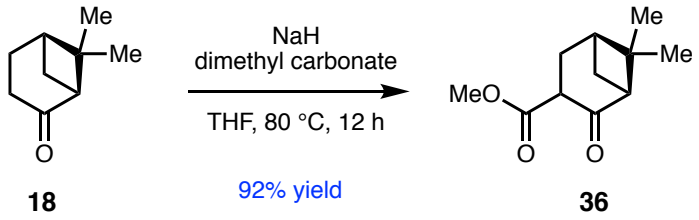
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.37, 146.34, 143.01, 125.57, 114.07, 55.86, 47.29, 43.98, 41.33, 30.46, 29.85, 26.61, 24.54, 21.76, 21.55.

FTIR (NaCl, thin film, cm^{-1}): 2921, 2851, 1707, 1613, 1466, 1372, 1265, 1164, 949, 897.

HRMS (ESI+, m/z): calc'd for $C_{13}H_{18}O$ 209.1541 $[M+H_2O]^+$; found: 209.1594

$\boldsymbol{\alpha_D^{21}}$ = +62° (c = 0.255, $CHCl_3$).

Preparation of ester 36:

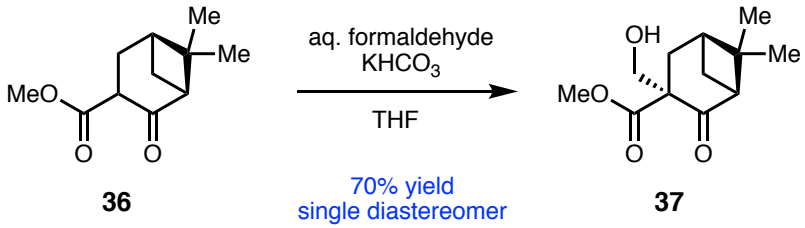


18 **36**

Procedure: To an oven-dried 250 mL round bottom flask, equipped with a stir bar, was added ketone **18** (21.00 g, 151.9 mmol, 1.0 equiv), dimethyl carbonate (15.4 g, 182.3 mmol, 1.2 equiv), and THF (760 mL). The reaction mixture was cooled to 0 °C and then NaH (60% dispersion in mineral oil, 13.4 g, 334.3 mmol, 2.2 equiv) was added. Reaction stirred for 1 hour at 0 °C and then fitted with a reflux condenser and heated to 70 °C for 12 hours. Reaction was quenched with aqueous sodium bicarbonate solution (500 mL), then extracted with Et_2O (3 x 200 mL). Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Residue was purified via column chromatography (15% EtOAc/Hexanes) to afford a 2:1:1 mixture of enol and epimeric β-ketoesters **36** (26.9 g, 167.7 mmol, 92%) as a pale-yellow oil. Spectral data matched the literature.[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.92 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.65 (t, J = 5.1 Hz, 1H), 2.62 – 2.44 (m, 1H), 2.44 – 2.16 (m, 2H), 1.90 – 1.82 (m, 1H), 1.79 (d, J = 10.8 Hz, 3H), 1.66 (d, J = 10.7 Hz, 3H), 1.35 (d, J = 1.8 Hz, 3H), 1.33 (s, 3H), 0.95 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H).

Preparation of alcohol 37:



36 **37**

Procedure: To an oven-dried 1-dram vial, equipped with a stir bar, wa charged ketoester **36** (30.0 g, 153 μmol, 1.0 equiv), $KHCO_3$ (45.9 mg, 459 μmol, 3.0 equiv), THF (750 uL), and aqueous formaldehyde (35% in water, 120 μL, 1.53 mmol, 10.0 equiv). Reaction was stirred at room temperature for 16 hours. Reaction then diluted with water and extracted with Et_2O (3X). Combined organic layers were then dried over MgSO4, filtered, and concentrated. Crude material was then purified by preparative TLC (40% EtOAc/hexanes) to afford alcohol **37** (24.2 mg, 107 μmol, 70%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (d, *J* = 11.1 Hz, 1H), 3.70 (s, 3H), 3.62 (d, *J* = 11.1 Hz, 1H), 2.69 – 2.57 (m, 2H), 2.44 (dddd, *J* = 11.4, 6.8, 5.1, 1.8 Hz, 1H), 2.16 (dtd, *J* = 6.3, 4.8, 1.4 Hz, 1H), 1.60 (dt, *J* = 14.2, 1.6 Hz, 1H), 1.41 (d, *J* = 11.4 Hz, 1H), 1.30 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.26, 173.53, 67.47, 58.76, 57.12, 53.20, 46.04, 40.31, 30.37, 26.78, 25.44, 22.05.

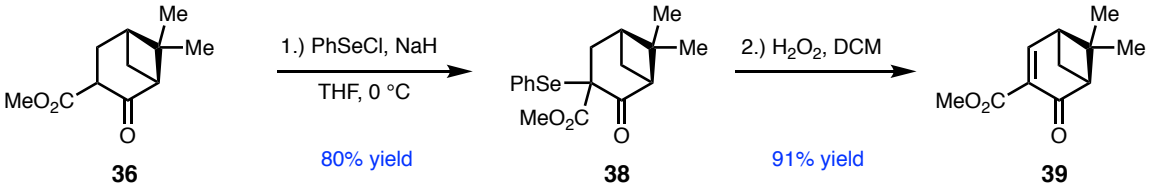
FTIR (NaCl, thin film, cm^{-1}): 3516, 2952, 2874, 1736, 1709, 1456, 1434, 1246, 1217, 1182, 1148, 1059, 1034, 931.

HRMS (ESI+, m/z): calc'd for $C_{12}H_{18}O_4$ 249.1103 $[M+Na]^+$; found: 249.1178

$\boldsymbol{\alpha_D^{22}}$ = –120° (c = 0.59, $CHCl_3$).

R_f = 0.37 in 50% EtOAc/hexanes (stains dark purple in p-anisaldehyde)

Preparation of enone 39:



Procedure: To an oven-dried 1L flask, equipped with a stir bar, was charged NaH (60% dispersion in mineral oil, 4.176 g, 104.4 mmol, 1.2 equiv) followed by THF (300 mL). The reaction was then cooled to 0 °C and stirred for 10 mins. Next, a solution of ester **36** (17.0 g, 87.0 mmol, 1.0 equiv) in THF (50 mL total) was slowly cannulated from a 100mL pointed flask into the reaction flask. 10 mL of THF was then added to the pointed flask to ensure quantitative transfer. Reaction then stirred at 0 °C for 10 mins. Next, a solution of PhSeCl (20.0 g, 104.4 mmol, 1.2 equiv) in THF (50 mL total) was cannulated into the reaction mixture over 10 mins and stirred at 0 °C for 20 mins. Reaction was then warmed to room temperature and stirred for 30 mins. Reaction was then quenched with saturated aquoues sodium bicarbonate solution (200 mL), diluted with water (100 mL), extracted with Et_2O (3 x 150 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated. Residue was purified via column chromatography (10 to 20% EtOAc.Hexanes) to afford selenide **38** (20.0 g, 83.5 mmol, 80%).

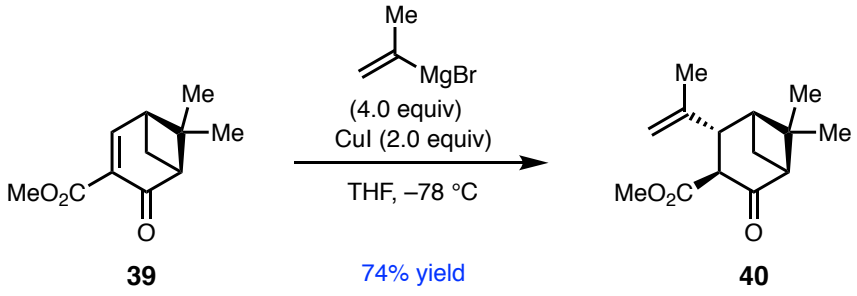
Procedure: Next, to an oven-dried 500 mL round bottom flask, equipped with a stir bar, was added selenide **38** (19 g, 54.1 mmol, 1.0 equiv) followed by DCM (216 mL). The reaction was then cooled to 0 °C for 20 mins. Meanwhile, a fresh solution of 15% aqueous H_2O_2 was prepared by combining 50% aqueous H_2O_2 (16.2 mL) with water (37.8 mL), in a 100mL pointed flask. This mixture was then cannulated into the reaction over 30 mins. Reaction then stirred at 0 °C for 3 hours and then warmed to room temperature and stirred

for 24 hours. Reaction was then quenched with saturated aqueous NaHCO3, extracted with DCM (3x), washed with brine, dired over MgSO4, filtered and concentrated. Residue was then purified by column chromatography (20 to 30 to 40% EtOAc/Hexanes) to afford **39** (9.51 g, 49.0 mmol, 91%) as a pale-yellow oil. Spectral data matched the literature.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 6.8, 1.0 Hz, 1H), 3.83 (s, 3H), 2.91 – 2.73 (m, 4H), 2.13 (d, *J* = 9.0 Hz, 1H), 1.53 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.04, 165.86, 164.36, 128.12, 58.95, 54.99, 52.18, 44.39, 40.43, 26.66, 22.51.

Preparation of ketoester 40:



39 74% yield **40**

Procedure: To an oven-dried 1 L flask, equipped with a stir bar, in a nitrogen-filled glovebox, was charged CuI (7.55 g, 39.6 mmol, 1.1 equiv), sealed with a red rubber septum, and removed from the glovebox. To this was added THF (freeze-pump-thawed 3X, 150 mL), and the mixture was cooled to –50 °C. To the resulting suspension was slowly added isopropenyl grignard (0.5 M in THF, 158.6 mL, 79.3 mmol, 2.2 equiv) over 5 mins. After stirring for 2 hours at –50 °C, the reaction mixture was cooled to –78 °C. To this cuprate mixture was slowly added enone **39** (7.0 g, 36.0 mmol, 1.0 equiv) as a stock solution in THF (40 mL). The reaction was quenched by the addition of water, diluted with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3X)

and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation. Residue was then purified by column chromatography (10% EtOAc/Hexanes) to afford **40** (6.33 g, 26.64 mmol, 74%) as a dark green oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.67 – 3.58 (m, 1H), 3.14 (d, *J* = 8.8 Hz, 1H), 2.73 – 2.60 (m, 1H), 2.55 – 2.45 (m, 1H), 2.29 (ddd, *J* = 6.3, 4.8, 1.3 Hz, 1H), 1.83 – 1.68 (m, 4H), 1.38 (d, *J* = 1.5 Hz, 3H), 0.99 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.98, 170.83, 145.29, 111.23, 57.25, 55.37, 52.52, 44.24, 43.74, 42.78, 26.89, 23.80, 21.84, 21.35.

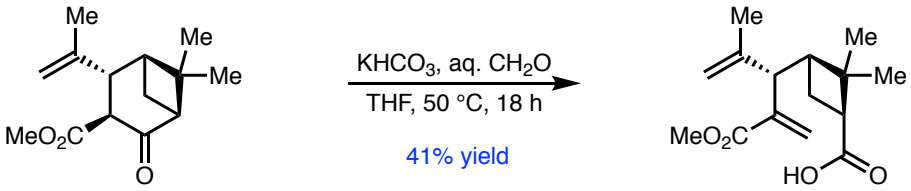
FTIR (NaCl, thin film, cm^{-1}): 2950, 1744, 1714, 1645, 1436, 1374, 1310, 1254, 1211, 1148, 1030, 900.

HRMS (ESI+, m/z): calc'd for $C_{14}H_{20}O_3$ 259.1310 $[M+Na]^+$; found: 259.1315

$\boldsymbol{\alpha_D^{22}}$ = –42° (c = 0.855, $CHCl_3$).

R_f = 0.58 in 20% EtOAc/hexanes (stains brown in p-anisaldehyde)

Preparation of acid 42:



40 **42**

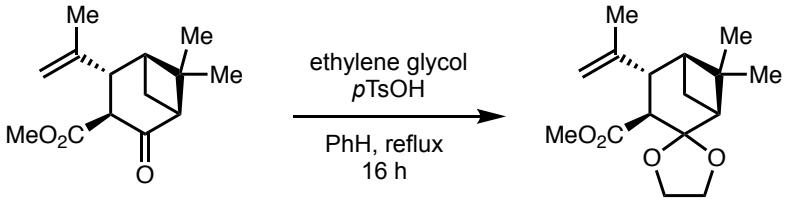
Procedure: To an oven-dried ½-dram vial, equipped with a stir bar, was added ketoester **40** (5 mg, 0.024 mmol, 1.0 equiv), p-formaldehyde (14.6 mg, 0.485 mmol, 20.0 equiv), K_2CO_3 (5mg, 0.036 mmol, 1.5 equiv), and THF (240 uL). Reaction was capped and then

heated to 70 °C for 16 hours. Reaction then quenched with water (200 uL) and extracted with EtOAc (3 x 300 uL). Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Reaction purified via prep plate (20% EtOAc/Hexanes) to afford acid **42** (2.3 mg, 0.00984 mmol, 41%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 1.1 Hz, 1H), 5.52 (t, *J* = 1.0 Hz, 1H), 4.94 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.93 – 4.84 (m, 1H), 3.74 (s, 3H), 3.46 – 3.37 (m, 1H), 2.74 – 2.56 (m, 1H), 2.39 (ddd, *J* = 11.8, 10.8, 7.8 Hz, 1H), 1.95 – 1.76 (m, 2H), 1.61 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.25 (d, *J* = 1.6 Hz, 4H), 1.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.01, 167.82, 144.39, 140.57, 125.17, 113.93, 60.57, 52.06, 48.85, 45.72, 43.59, 42.81, 30.69, 23.69, 19.93.

Preparation of ketal 53:



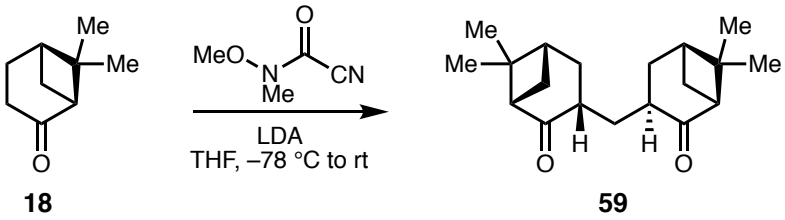
40 >99% yield **53**

Procedure: To a 200 mL round bottom flask was added ketone **40** (2.215 g, 9.375 mmol, 1.0 equiv), ethylene glycol (1.31 g, 23.44 mmol, 2.5 equiv), p-toluenesufonic acid (0.8 mg, 4.68 umol, 0.5 mol %) and benzene (75 mL). Reaction was fitted with a reflux condenser and heated to reflux overnight (16 hours). Reaction was then quenched with water (50 mL) and then extracted into EtOAc (3X). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Material was then purified via column chromatography

(10 to 20% EtOAc/hexanes) to afford **53** (2.62 g, 9.275 mmol, 99%) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (dp, *J* = 1.6, 0.8 Hz, 1H), 4.72 (t, *J* = 1.5 Hz, 1H), 4.03 (ddd, *J* = 7.4, 6.2, 4.8 Hz, 1H), 3.93 (ddd, *J* = 7.3, 6.5, 4.8 Hz, 1H), 3.86 (td, *J* = 7.2, 6.2 Hz, 1H), 3.83 – 3.78 (m, 1H), 3.73 (s, 3H), 3.27 (d, *J* = 9.3 Hz, 1H), 3.22 – 3.12 (m, 1H), 2.34 – 2.20 (m, 1H), 1.98 (d, *J* = 5.9 Hz, 2H), 1.69 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.47 (d, *J* = 10.9 Hz, 1H), 1.25 (s, 3H), 1.05 (s, 3H).

Preparation of dimer 59:



18 **59**

27% yield

Procedure: To a flame-dried 100mL flask was charged diisopropyl amine (1.23 mL, 8.68 mmol, 1.2 equiv) followed by THF (20 mL). Solution was then cooled to –78 °C and then ^{n}BuLi (2.5 M in hexanes, 3.47 mL, 8.68 mmol, 1.2 equiv) was added and stirred at –78 °C for 5 minutes. Ketone **18** (1.00 g, 7.24 mmol, 1.0 equiv) then added slowly as a solution in THF (8 mL) over 5 minutes. Reaction then slowly warmed to –50 °C and then cooled back down to –78 °C. Next, cyanoformate (1.01 g, 8.68 mmol, 1.2 equiv) added as a solution in THF (8 mL) and reaction allowed to warm slowly to rt over 4 hours. Reaction then quenched by addition of saturated aqueous NH_4Cl solution (25 mL). Reaction extracted with EtOAc (3X). Combined organic layers then dried over $MgSO_4$, filtered, and

concentrated. Material was then purified via column chromatography (10% EtOAc/hexanes) to afford **59** (564 mg, 1.95 mmol, 27%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (dq, *J* = 10.2, 7.4 Hz, 2H), 2.60 (t, *J* = 5.3 Hz, 2H), 2.55 (s, 2H), 2.27 (ddd, *J* = 11.5, 6.9, 5.5 Hz, 2H), 1.99 (t, *J* = 7.1 Hz, 2H), 1.71 (d, *J* = 10.5 Hz, 2H), 1.52 (ddt, *J* = 13.1, 7.7, 1.5 Hz, 2H), 1.32 (s, 6H), 0.75 (s, 6H).

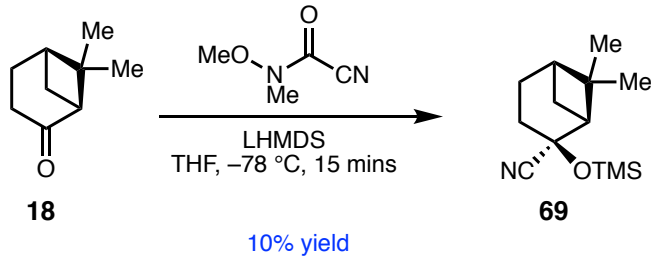
^{13}C NMR (101 MHz, $CDCl_3$) δ 216.59, 57.97, 43.11, 40.92, 39.66, 29.80, 28.83, 26.42, 25.56, 22.23.

FTIR (NaCl, thin film, cm^{-1}): 2937, 2871, 1701, 1243, 1193.

HRMS (ESI+, m/z): calc'd for $C_{19}H_{28}O_2$ 289.2167 $[M+H]^+$; found: 289.2221

$\boldsymbol{\alpha_D^{22}}$ = 0° (c = 0.51, $CHCl_3$).

Preparation of cyanohydrin 69:



18 **69**

10% yield

Procedure: To a flame-dried 100 mL flask, equipped with a stir bar, was charged ketone **18** (1.00 g, 7.23 mmol, 1.0 equiv), followed by THF (36 mL). Reaction was cooled to –78 °C and then LHMDS (1.0 M in THF, 8.68 mL, 8.68 mmol, 1.2 equiv) added and stirred at –78 °C for 1 hour. Next, cyanoformate (990.6 mg, 8.68 mmol, 1.2 equiv) added and stirred for 15 minutes at –78 °C then allowed to warm to room temperature slowly over 16 hours. Reaction then quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3X). Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Material

was then purified by column chromatography (10% EtOAc/hexanes) to afford **69** (155 mg, 0.653 mmol, 10%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 – 2.51 (m, 1H), 2.44 – 2.32 (m, 1H), 2.29 (dd, *J* = 6.6, 4.7 Hz, 1H), 2.15 – 2.03 (m, 1H), 2.03 (s, 2H), 1.93 – 1.81 (m, 1H), 1.24 (s, 3H), 1.01 (s, 3H), 0.23 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 123.78, 74.55, 51.78, 40.38, 38.02, 33.11, 27.97, 27.51, 24.31, 22.71, 1.50.

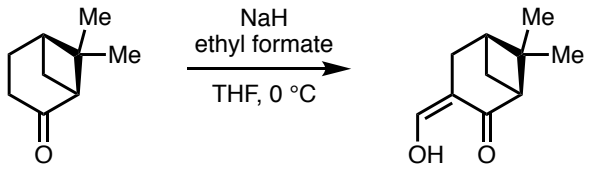
FTIR (NaCl, thin film, cm^{-1}): 2954, 1459, 1252, 1128, 1102, 1052, 865, 843, 757.

HRMS (ESI+, m/z): calc'd for $C_{13}H_{23}ONSi$ 165.1153 $[M+H–TMS]^+$; found: 165.1120

$\boldsymbol{\alpha_D^{21}}$ = –12° (c = 0.480, $CHCl_3$).

R_f = 0.80 in 30% EtOAc/hexanes (stains purple/brown in p-anisaldehyde)

Preparation of ketoaldehyde 74:



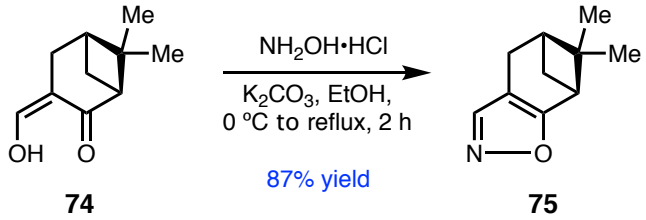
18 61% yield **74**

Procedure: To a flame-dried 2 L round bottom flask, equipped with a stir bar, was added NaH (60% dispersion in mineral oil, 8.94 g, 223.5 mmol, 2.0 equiv) and THF (300 mL). Reaction cooled to 0 °C and then ethyl formate (250 mL, 3.35 mol, 30 equiv) was added. A solution of ketone **18** (15.45 g, 111.8 mmol, 1.0 equiv) in THF (250 mL) with ethanol (2.2 mL) was added dropwise at over 40 mins and then warmed to room temperature and stirred for 4 hours. Reaction quenched with saturated aqueous NH_4Cl (250 mL) and then

extracted with Et_2O (3 x 100 mL). Washed with water (50 mL), brine (50 mL), then dried over $MgSO_4$, filtered and concentrated in vacuo. Residue was then purified by column chromatography (5 to 10% EtOAc/Hexanes) to afford **74** (11.278g, 67.8 mmol, 61%) as a white solid. Spectral data matched the literature.[22]

^{1}H NMR (500 MHz, $CDCl_3$) δ 13.35 (d, *J* = 11.1 Hz, 1H), 7.20 (d, *J* = 6.6 Hz, 1H), 2.61 – 2.45 (m, 4H), 2.26 (tt, *J* = 5.8, 3.0 Hz, 1H), 1.46 – 1.38 (m, 1H), 1.34 (s, 4H), 0.93 (s, 4H).

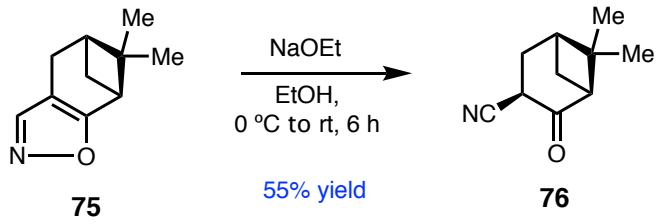
Preparation of isoxazole 75:



74 **75**

Procedure: To a 200 mL flask, equipped with a stir bar, was charged enol **74** (2.58 g, 15.52 mmol, 1.0 equiv). Next EtOH (64.2 mL) added and reaction cooled to 0 °C. Next, K_2CO_3 (3.24 g, 23.46 mmol, 1.5 equiv) added followed by hydroxylamine hydrochloride (2.19 g, 42.81 mmol, 2.0 equiv). The reaction was then fitted with a reflux condenser and refluxed for 2 hours. Reaction then quenched with water and acidified to pH 7 using 1.0 M HCl. Reaction mixture extracted with DCM (3 X 60 mL), washed with brine. Combined organic layer were then dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **75** (2.65 g, 13.50 mmol, 87%) as a white solid. Material was used crude in the next reaction.

Preparation of ketonitrile 76:



75 **76**

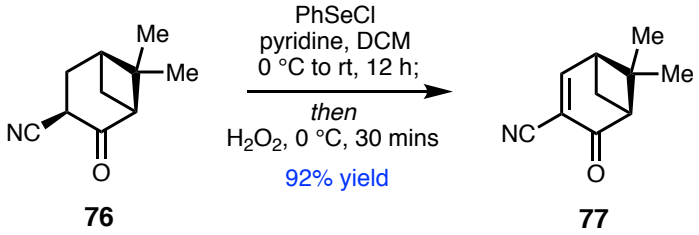
Procedure: To a 50 mL round bottom flask, equipped with a stir bar, was charged solid sodium metal (577 mg, 25.10 mmol, 2.0 equiv) followed by EtOH (14.4 mL) and stirred at room temperature until all sodium had disappeared (2 hours). Next, isoxaxole **75** (2.048 g, 12.55 mmol, 1.0 equiv) was added as a solution in EtOH (7.2 mL). Reaction then warmed to room temperature and stirred for 6 hours. Reaction then acidified to pH 7 with 2N HCl, diluted with H_2O, and extracted with DCM (3X), washed with brine, dried over MgSO4, filtered, and concentrated. Material then purified by column chromatography (10 to 15 to 20% EtOAc/hexanes) to afford **76** (1.716 g, 10.54 mmol, 84%) as a white solid. Spectral data matched the literature.[22]

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (dd, *J* = 8.9, 2.0 Hz, 1H), 2.82 (t, *J* = 5.4 Hz, 1H), 2.79 – 2.63 (m, 2H), 2.55 (ddd, *J* = 15.6, 3.9, 2.0 Hz, 1H), 2.25 (d, *J* = 11.0 Hz, 1H), 1.38 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.16, 58.51, 41.93, 41.31, 40.93, 34.25, 25.85, 25.72, 22.74.

FTIR (NaCl, thin film, cm^{-1}): 2987, 2958, 2931, 1713, 1690, 1444, 1195, 1089, 1034, 905, 553.

Preparation of enone 77:



76 **77**

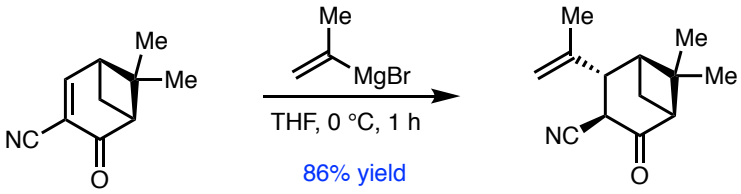
Procedure: To a 200 mL flask, equipped with a stir bar, was charged PhSeCl (2.416 g, 12.62 mmol, 1.2 equiv) followed by DCM (60 mL). Solution was cooled to 0 °C and then pyridine (1.275 mL, 15.77 mmol, 1.5 equiv) added. After stirred for 20 mins at 0 °C, a solution of nitrile ketone **76** (1.716 g, 10.51 mmol, 1.0 equiv) in DCM (12 mL) added slowly, dropwise, over a period of 20 mins. The reaction was then allowed to warm to room temperature and stirred overnight (16 h). Excess pyridine was removed by sequential washing with 1N HCl. The remaining organic layer was cooled to 0 °C and treated with H_2O_2 (30% in water, 2.714 mL, 31.53 mmol, 3.0 equiv) and stirred for 30 mins. Rection then quenched with water, and the aqueous layer was extracted with DCM (3X). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Material was then purified by column chromatography (10 to 20 to 30% EtOAc/hexanes) to afford **77** (1.56 g, 9.67 mmol, 92%) as a white solid. Spectral data matched the literature.[22]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 6.9, 1.0 Hz, 1H), 2.95 (dtd, *J* = 9.7, 5.5, 1.1 Hz, 1H), 2.89 (t, *J* = 5.9 Hz, 1H), 2.82 (dt, *J* = 6.9, 5.6 Hz, 1H), 2.21 (d, *J* = 9.7 Hz, 1H), 1.57 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.65, 169.07, 113.93, 113.59, 57.70, 55.43, 44.77, 40.64, 26.72, 22.49.

FTIR (NaCl, thin film, cm^{-1}): 2978, 1702, 1333, 1236, 1020, 916, 821, 514.

Preparation of alkene 78:



77 **78**

Procedure: To a flame-dried 100 mL flask, equipped with a stir bar, was charged enone **77** (1.0 g, 6.20 mmol, 1.0 equiv), followed by THF (36 mL). Reaction was then cooled to 0 °C and then Grignard (0.5 M in THF, 24.8 mL, 12.4 mmol, 2.0 equiv) added slowly, dropwise, over 20 mins. Reaction then stirred for 2 hours at 0 °C. Reaction then quenched with saturated aqueous NH_4Cl, extracted with Et_2O (3X), dried over $MgSO_4$, filtered, and concentrated. Material was then purified via column chromatography (10 to 20 to 30% EtOAc/hexanes) to afford **78** (1.0825 g, 5.33 mmol, 86%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 – 4.96 (m, 1H), 4.90 (d, J = 1.4 Hz, 1H), 3.59 (d, J = 8.6 Hz, 1H), 2.96 (d, J = 8.6 Hz, 1H), 2.74 (t, J = 5.1 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.39 – 2.31 (m, 1H), 1.90 – 1.86 (m, 3H), 1.69 (d, J = 11.5 Hz, 1H), 1.42 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.94, 143.30, 117.43, 112.79, 56.47, 44.83, 44.13, 42.93, 40.91, 26.24, 22.81, 22.03, 21.79.

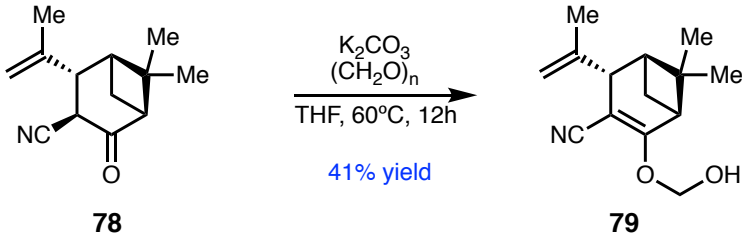
FTIR (NaCl, thin film, cm^{-1}): 2966, 1727, 1450, 1376, 1194, 894, 807.

HRMS (GC-EI+, m/z): calc'd for $C_{13}H_{17}ON$ 222.1494 $[M+H_3O]^+$; found: 222.1468

$\boldsymbol{\alpha_D^{21}}$ = +89° (c = 0.285, $CHCl_3$).

R_f = 0.47 in 25% EtOAc/hexanes (stains orange with p-anisaldehyde)

Preparation of enol ether 79:



78 **79**

Procedure: To an oven-dried ½-dram vial, equipped with a stir bar, was added ketone **78** (25.2 mg, 0.124 mmol, 1.0 equiv), p-formaldehyde (11.2 mg, 0.372 mmol, 3.0 equiv), K_2CO_3 (25.7 mg, 0.186 mmol, 1.5 equiv), and THF (2.5 mL). Reaction was capped and then heated to 60 °C for 16 hours. Reaction then quenched with water and extracted with EtOAc (3X). Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Reaction purified via prep plate (20% EtOAc/Hexanes) to afford enol ether **79** (11.8 mg, 0.051 mmol, 41%) as a clear colorless oil.

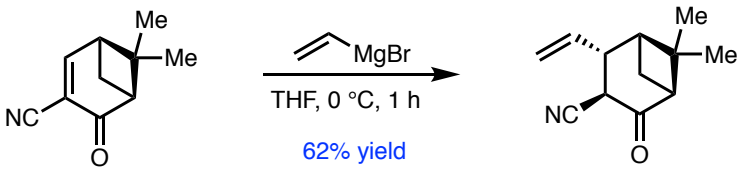
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.75 (s, 1H), 5.00 (q, *J* = 1.3 Hz, 2H), 2.82 – 2.72 (m, 2H), 2.49 (ddd, *J* = 11.7, 10.5, 7.9 Hz, 1H), 2.06 (dt, *J* = 11.5, 7.9 Hz, 1H), 1.82 (dt, *J* = 11.6, 10.5 Hz, 1H), 1.72 (t, *J* = 1.1 Hz, 3H), 1.28 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.26, 142.14, 131.04, 124.14, 117.67, 114.52, 54.13, 45.35, 43.42, 41.36, 30.79, 23.63, 21.11, 17.24.

FTIR (NaCl, thin film, cm^{-1}): 2956, 1700, 1432, 1368, 1251, 1214, 1158, 942, 906, 626.

$\boldsymbol{\alpha_D^{22}}$ = +59° (c = 0.580, $CHCl_3$).

Preparation of alkene 78:



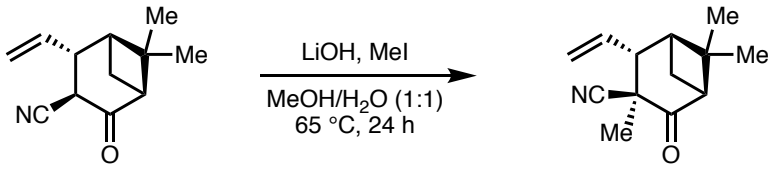
77 **78**

Procedure: To a flame-dried 100 mL flask, equipped with a stir bar, was charged enone **77** (1.0 g, 6.20 mmol, 1.0 equiv), followed by THF (36 mL). Reaction was then cooled to 0 °C and then Grignard (1.0 M in THF, 12.4 mL, 12.4 mmol, 2.0 equiv) added slowly, dropwise, over 20 mins. Reaction then stirred for 2 hours at 0 °C. Reaction then quenched with saturated aqueous NH_4Cl, extracted with Et_2O (3X), dried over $MgSO_4$, filtered, and concentrated. Material was then purified via column chromatography (10 to 20 to 30% EtOAc/hexanes) to afford **78** (727 mg, 3.84 mmol, 62%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.30 (dt, *J* = 16.9, 1.0 Hz, 1H), 5.24 (dt, *J* = 10.2, 0.9 Hz, 1H), 3.45 (d, *J* = 8.0 Hz, 1H), 3.03 (tq, *J* = 7.1, 1.3 Hz, 1H), 2.75 (t, *J* = 5.1 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.26 (ddd, *J* = 6.5, 4.7, 1.6 Hz, 1H), 1.67 (d, *J* = 11.5 Hz, 1H), 1.41 (s, 3H), 0.96 (s, 3H).

R_f = 0.44 in 25% EtOAc/hexanes (stains orange with p-anisaldehyde)

Preparation of 81:



78 **81**

50% yield

Procedure: To a flame-dried 50 mL pressure flask, equipped with a stir bar, was charged nitrile ketone **78** (2.00 g, 10.6 mmol, 1.0 equiv), LiOH (304 mg, 12.7 mmol, 1.2 equiv), MeI (691 uL, 11.1 mmol, 1.05 equiv), H_2O (13.25 mL), and MeOH (13.25 mL). Reaction was then sealed and reated to 65 °C behind a blast shield for 24 hours. Reaction then quenched with saturated aqueous NH_4Cl, extracted with EtOAc (3X), washed with brine. Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Material was then purified by column chromatography (10% EtOAc/hexanes) to afford **81** (1.0718 g, 5.3 mmol, 50%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H), 5.34 – 5.23 (m, 2H), 3.26 – 3.19 (m, 1H), 2.78 (t, *J* = 5.3 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.23 (ddd, *J* = 6.8, 5.0, 1.8 Hz, 1H), 1.77 (d, *J* = 11.5 Hz, 1H), 1.63 (s, 3H), 1.41 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.87, 134.17, 122.15, 118.78, 56.93, 46.13, 46.05, 45.67, 42.35, 26.02, 24.84, 23.17, 22.20.

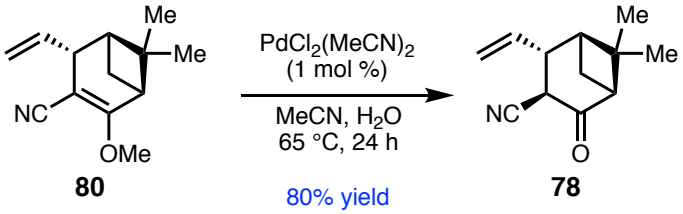
FTIR (NaCl, thin film, cm^{-1}): 3080, 2991, 2965, 1716, 1482, 1463, 1373, 1255, 1008, 926, 757.

HRMS (GC-EI+, m/z): calc'd for $C_{13}H_{17}ON$ 222.1494 $[M+H_3O]^+$; found: 222.1469

$\boldsymbol{\alpha_D^{22}}$ = +103° (c = 0.735, $CHCl_3$).

$\mathbf{R_f}$ = 0.40 in 20% EtOAc/hexanes ($KMnO_4$)

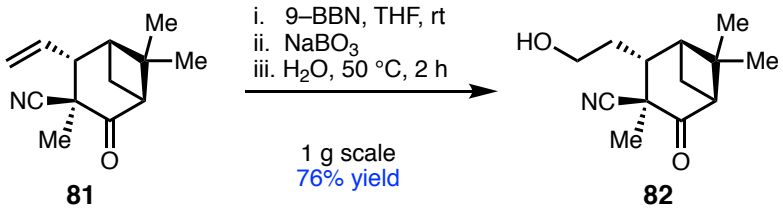
Preparation of 78:



Procedure: To a 1-dram vial, equipped with a stir bar, was charged methyl ether **80** (100 mg, 0.492 mmol, 1.0 equiv) followed by MeCN (0.5 mL). To this mixture was added H_2O (44.3 uL), and $PdCl_2$•(MeCN) (1.3 mg, 0.0049 mmol, 1 mol %). Reaction then sealed with a Teflon cap and heated to 65 °C for 24 hours. Reaction was then filtered over silica eluting with 50% EtOAc/hexanes to afford **78** (74.6 mg, 0.394 mmol, 80%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.30 (dt, *J* = 16.9, 1.0 Hz, 1H), 5.24 (dt, *J* = 10.2, 0.9 Hz, 1H), 3.45 (d, *J* = 8.0 Hz, 1H), 3.03 (tq, *J* = 7.1, 1.3 Hz, 1H), 2.75 (t, *J* = 5.1 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.26 (ddd, *J* = 6.5, 4.7, 1.6 Hz, 1H), 1.67 (d, *J* = 11.5 Hz, 1H), 1.41 (s, 3H), 0.96 (s, 3H).

Preparation of alcohol 82:



Procedure: To a flame-dried 25 mL round bottom flask, equipped with a stir bar, was charged vinyl ketone **81** (1.07 g, 5.26 mmol, 1.0 equiv) under argon. Then 9-BBN (0.5 M in THF, 10.52 mL, 5.26 mmol, 1.0 equiv) was added and stirred at room temperature for 20 mins. During these 20 minutes, the reaction became very thick and therefore THF (2

mL) was added to dilute the reaction mixture. Then stir rate was increased to 1200 RPM and stirred for 4 hours. Next, $NaBO_3 \bullet H_2O$ (1.576 g, 15.79 mmol, 3.0 equiv) were added in a single portion. After 2 hours of stirring, the reaction was cooled to 0 °C and water (5.26 mL, 292.1 mmol, 55.5 equiv) was added slowly dropwise over 5 minutes. Reaction was then heated to 50 °C for 2 hours and then cooled to room temperature and stirred overnight (16 hours). Reaction was then transferred to a separatory funnel, extracted with Et_2O (3X), and washed with brine. Combined organic layers were then dried over MgSO4, filtered, and concentrated in vacuo. Material was then purified by column chromatography (5% MeOH/DCM) to afford alcohol **82** (884 mg, 3.99 mmol, 76%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 – 3.71 (m, 2H), 2.51 (dddd, *J* = 12.0, 6.8, 5.5, 1.4 Hz, 1H), 2.24 (ddd, *J* = 6.7, 5.0, 1.7 Hz, 1H), 2.01 (dtd, *J* = 13.7, 6.8, 5.9 Hz, 1H), 1.70 (d, *J* = 2.0 Hz, 4H), 1.68 – 1.58 (m, 3H), 1.40 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.19, 122.36, 60.82, 57.23, 45.68, 45.47, 42.32, 38.00, 32.18, 26.11, 23.83, 22.99, 22.17.

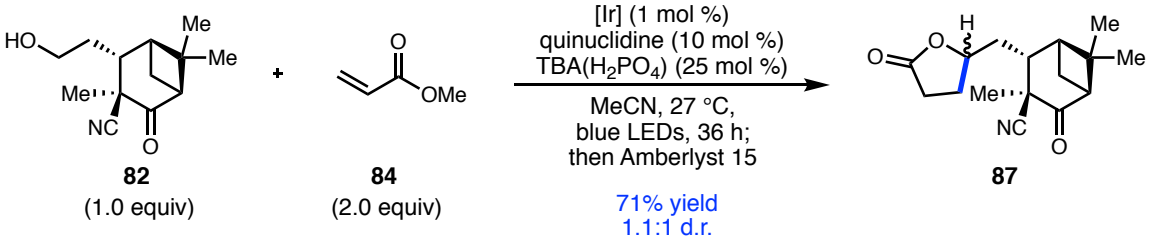
FTIR (NaCl, thin film, cm^{-1}): 3418, 2935, 1721, 1390, 1202, 1049, 682, 597.

HRMS (GC-EI+, m/z): calc'd for $C_{13}H_{19}O_2N$ 222.1494 $[M+H]^+$; found: 222.1467

$\boldsymbol{\alpha_D^{22}}$ = –72° (c = 0.455, $CHCl_3$).

R_f = 0.26 in 5% MeOH/DCM (stains purple with p-anisaldehyde)

Preparation of lactone 87:



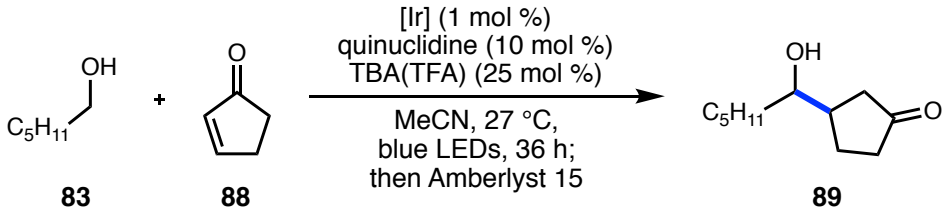
Procedure: To an oven-dried ½-dram vial, equipped with a stir bar, in a N_2-filled glovebox, was charged (Ir[dF(CF_3)ppy]$_2$(dtbbpy))PF_6 (0.68 mg, 0.6 umol, 1.0 mol %), quinuclidine (0.66 mg, 6.0 umol, 10 mol %), ^{n}Bu$_4$NH_2PO_4 (5.10 mg, 15.0 umol, 25 mol %), and MeCN (200 uL). The solids were shaken by hand until dissolved. Next, the catalyst solution was added to a ½-dram vial containing ketone **82** (13.3 mg, 60 umol, 1.0 equiv) followed by methyl acrylate (10.8 uL, 120 umol, 2.0 equiv). Reaction was then sealed and removed from the glovebox. Reaction was stirred and irradiated by blue LEDs (kessil lamp) in a hepatochem setup for 48 hours. Then Amberlyst 15 (20 mg) added and reaction heated to 40 °C for 2 hours. Reaction then filtered through a silica plug eluting with 50% EtOAc/hexanes. Mixture was concentrated in vacuo and then transferred to an NMR tube for obtaining an NMR yield. 71% yield by ^{1}H-NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 – 4.51 (m, 2H), 3.72 – 3.64 (m, 2H), 2.89 – 2.82 (m, 1H), 2.82 – 2.71 (m, 3H), 2.66 – 2.39 (m, 10H), 2.39 – 2.21 (m, 2H), 2.12 (ddd, J = 14.2, 8.8, 5.5 Hz, 1H), 2.03 – 1.81 (m, 4H), 1.70 (s, 3H), 1.68 (s, 2H), 1.41 (s, 3H), 1.41 (s, 2H), 1.02 (s, 3H), 1.01 (d, J = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.07, 176.97, 79.89, 57.53, 45.82, 45.39, 44.15, 43.71, 39.92, 38.73, 35.52, 28.90, 28.69, 26.54, 23.04, 21.83, 13.12.

HRMS (ESI+, m/z): calc'd for $C_{16}H_{21}O_3N$ 276.1599 $[M+H]^+$; found: 276.1591

Preparation of alcohol 89:



83 **88** **89**

99% yield

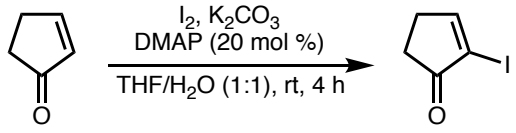
Procedure: To an oven-dried ½-dram vial, equipped with a stir bar, in a N_2-filled glovebox, was charged $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (1.68 mg, 1.5 umol, 1.0 mol %), quinuclidine (1.67 mg, 15.0 umol, 10 mol %), $^nBu_4NH_2PO_4$ (12.7 mg, 37.5. umol, 25 mol %), and MeCN (500 uL). The solids were shaken by hand until dissolved. Next, the catalyst solution was added to a ½-dram vial containing alcohol **83** (18.8 uL, 150 umol, 1.0 equiv) followed by cyclopentene **88** (25.1 uL, 300 umol, 2.0 equiv). Reaction was then sealed and removed from the glovebox. Reaction was stirred and irradiated by blue LEDs (kessil lamp) in a hepatochem setup for 48 hours. Then Amberlyst 15 (20 mg) added and reaction heated to 40 °C for 2 hours. Reaction then filtered through a silica plug eluting with 50% EtOAc/hexanes. Mixture was concentrated in vacuo and then transferred to an NMR tube for obtaining an NMR yield. 99% yield by ^{1}H-NMR.

^{1}H NMR (500 MHz, cdcl$_3$) δ 3.61 (ddd, *J* = 9.2, 5.9, 3.2 Hz, 1H), 2.56 – 2.14 (m, 4H), 2.14 – 2.00 (m, 1H), 1.85 – 1.74 (m, 1H), 1.60 (s, 4H), 1.58 – 1.44 (m, 2H), 1.40 – 1.27 (m, 6H), 0.98 – 0.89 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 205.58, 74.40, 42.75, 41.88, 38.50, 35.88, 31.81, 25.36, 24.69, 22.63, 14.04.

HRMS (ESI+, m/z): calc'd for $C_{11}H_{20}O_2$ 167.1435 $[M - H_2O + H]^+$; found: 167.1470

Preparation of enone 96:



88 **96**

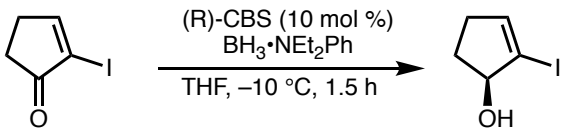
Procedure: To a 500 mL round bottom flask, equipped with a stir bar, was charged enone **88** (5.0 g, 61.0 mmol, 1.0 equiv) followed by THF (125 mL). Next, water (125 mL) was added followed by K_2CO_3 (10.1 g, 73.2 mmol, 1.2 equiv), I_2 (23.2 g, 91.5 mmol, 1.5 equiv), and lastly DMAP (1.4 g, 12.2 mmol, 20 mol %). Reaction sealed under nitrogen and stirred for 4 hours at room temperature. Reaction was then quenched at 0 °C with saturated aqueous $Na_2S_2O_3$ (3X), extracted with EtOAc (3X), and washed with brine. Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Material was then purified via column chromatography (35% EtOAc/Hexanes) to afford **96** (9.15 g, 43.9 mmol, 72%) as a white solid. Spectral data matched the literature.[23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 2.9 Hz, 1H), 2.81 – 2.74 (m, 2H), 2.54 – 2.47 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.18, 169.69, 103.05, 31.39, 31.07.

FTIR (NaCl, thin film, cm^{-1}): 2923, 2853, 1710, 1574, 1283, 1153, 926, 896, 781, 742.

Preparation of alcohol 97:



96 **97**

Procedure: To a flame-dried 250 mL round bottom flask, equipped with a stir bar, was charged (*R*)-(+)-2-Me-CBS-oxazaborolidine (266.5 mg, 0.962 mmol, 10 mol %) and anhydrous THF (45 mL). The resulting solution was cooled to –10 °C via ice/acetone bath. After 15 minutes of stirring, BH_3•NEt_2Ph (2.56 mL, 14.42 mmol, 1.5 equiv) was added slowly dropwise via syringe over 10 minutes. After 15 minutes of stirring at –10 °C, cyclopentenone **96** (2.0 g, 9.62 mmol, 1.0 equiv) as a solution in THF (40 mL) was added slowly, dropwise, over 1 hour via cannula transfer. Vial was rinsed with THF (10 mL) to ensure quantitative transfer of cyclopentenone. Upon complete addition, reaction stirred for 15 minutes and then was diluted with Et_2O. Reaction then carefully quenched with MeOH (10 mL) followed by 1N NaOH (90 mL) at –10 °C and then allowed t warm to room temperature. Mixture was extracted with Et_2O (3X), and then washed with brine. Combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Material was then purified via column chromatography (20% EtOAc/hexanes) to afford **97**. **97** was then recrystallized by heating in hexanes and then cooling to 0 °C in an ice bath to afford recrystallized **97** (1.53 g, 7.31 mmol, 76% yield, 99% ee) as a white cotton candy like solid. Spectral data matched the literature.[23]

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (td, *J* = 2.5, 1.0 Hz, 1H), 4.69 (dqt, *J* = 6.5, 2.5, 1.1 Hz, 1H), 2.56 – 2.40 (m, 1H), 2.40 – 2.24 (m, 2H), 1.92 – 1.79 (m, 2H).

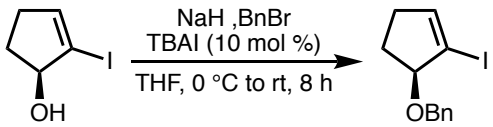
^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.79, 100.39, 82.42, 32.91, 31.60.

FTIR (NaCl, thin film, cm^{-1}): 3337, 2917, 2847, 1435, 1303, 1044, 805.

$\boldsymbol{\alpha_D^{22}}$ = –23° (c = 0.500, $CHCl_3$).

R_f = 0.43 in 30% EtOAc/hexanes (stains green in p-anisaldehyde)

Preparation of benzyl ether 98:



97 **98**

Procedure: To a flame-dried 15 mL round bottom flask, equipped with a stir bar, was charged alcohol **97** (150 mg, 0.714 mmol, 1.0 equiv), TBAI (26.4 mg, 0.0714 mmol, 10 mol %), THF (7.1 mL), and BnBr (203.6 uL, 1.714 mmol, 2.4 equiv). Reaction mixture was then cooled to 0 °C and then NaH (60% dispersion in mineral oil, 68.6 mg, 1.714 mmol, 2.4 equiv) was added. Reaction was sealed with a red rubber septum under nitrogen. Reaction stirred overnight for 16 hours. Reaction was then quenched with saturated aqueous NH_4Cl, extracted with Et_2O (3X). Combined organic layers were then dried over MgSO4, filtered, and concentrated in vacuo. Material was then purified via column chromatography (10% EtOAc/hexanes) to afford **98** (199 mg, 0.664 mmol, 93%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.26 (m, 5H), 6.37 (td, *J* = 2.5, 1.1 Hz, 1H), 4.67 – 4.59 (m, 2H), 4.55 (dddq, *J* = 7.6, 3.9, 2.6, 1.3 Hz, 1H), 2.49 (dddt, *J* = 16.6, 8.7, 4.3, 2.6 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.18 (dddd, *J* = 13.4, 8.8, 7.5, 4.3 Hz, 1H), 2.03 – 1.91 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.76, 138.37, 128.37, 127.90, 127.63, 96.37, 88.33, 70.67, 33.02, 28.92.

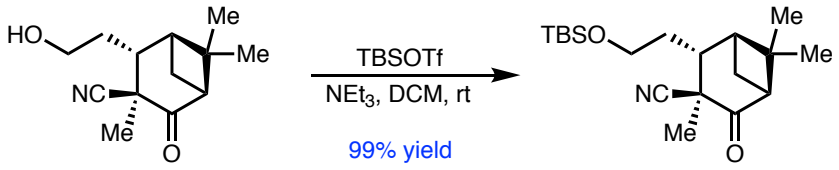
FTIR (NaCl, thin film, cm^{-1}): 2850, 1454, 1340, 1157, 1072, 806, 735, 696, 668.

HRMS (GC-EI+, m/z): calc'd for $C_{12}H_{13}OI$ 300.0061 $[M\bullet]^+$; found: 300.0089

$\boldsymbol{\alpha_D^{22}}$ = +4° (c = 0.685, $CHCl_3$).

R_f = 0.75 in 30% EtOAc/hexanes (stains green with p-anisaldehyde)

Preparation of silyl ether 99:



72 **99**

Procedure: To a flame-dried 100 mL round bottom flask, equipped with a stir bar, was charged alcohol **72** (1.00 g, 4.52 mmol, 1.0 equiv) under nitrogen followed by DCM (45 mL). Reaction mixture was cooled to 0 °C and then NEt_3 (1.26 mL, 9.04 mmol, 2.0 equiv) added followed by TBSOTf (1.56 mL, 6.78 mmol, 1.5 equiv) slowly over 1 minute. Reaction was stirred at 0 °C for 45 minutes. Reaction then quenched by addition of saturated aqueous NH_4Cl (30 mL) and extracted with DCM (3X). Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Material was then purified via column chromatography (10 to 20 % EtOAc/hexanes) to afford **99** (1.50 g, 4.47 mmol, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 – 3.63 (m, 2H), 2.81 – 2.72 (m, 2H), 2.54 – 2.44 (m, 1H), 2.28 (ddd, *J* = 6.7, 5.0, 1.7 Hz, 1H), 1.97 (dddd, *J* = 14.1, 7.7, 6.5, 4.8 Hz, 1H), 1.71 – 1.64 (m, 4H), 1.62 – 1.52 (m, 2H), 1.40 (s, 3H), 1.00 (s, 3H), 0.90 (s, 8H), 0.07 (d, *J* = 4.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.51, 122.22, 60.88, 57.28, 45.79, 44.87, 42.16, 37.95, 31.98, 26.13, 26.01, 23.93, 22.94, 22.15, 18.34, -5.16, -5.25.

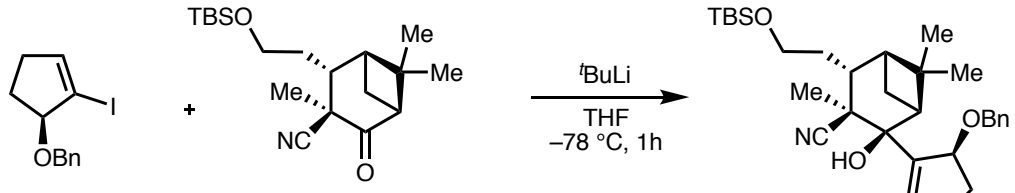
FTIR (NaCl, thin film, cm^{-1}): 2928, 1724, 1254, 1097, 835, 777.

HRMS (GC-EI+, m/z): calc'd for $C_{18}H_{29}O_2NSi$ 337.2311 $[M+NH_4]^+$; found: 337.2315

$\boldsymbol{\alpha_D^{22}}$ = –57° (c = 0.300, $CHCl_3$).

R_f = 0.80 in 5% MeOH/DCM (stains purple with p-anisaldehyde)

Preparation of alcohol 101:



98 (2.0 equiv) **99** (1.0 equiv) **101**

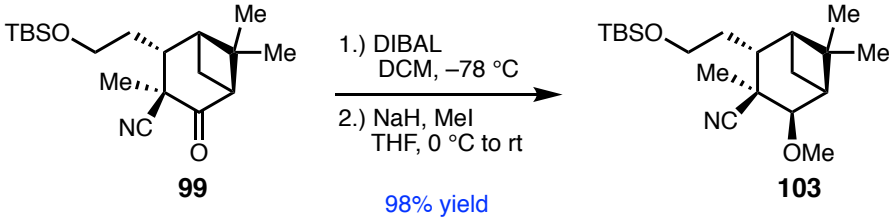
Procedure: To an oven-dried 1-dram vial, equipped with a stir bar, was charged vinyl iodide **98** (30.0 mg, 0.1 mmol, 1.0 equiv) and THF (1 mL). Reaction placed under an atmosphere of N2 and then cooled to –78 °C. ^{t}BuLi (1.7 M in pentanes, 118 uL, 0.2 mmol, 2.0 equiv) then added slowly dropwise. Next, a solution of ketone **99** (33.6 mg, 0.1 mmol, 1.0 equiv) in THF (1.0 mL) added slowly dropwise. Reaction then stirred at –78 °C for 1 hour. Reaction then quenched at –78 °C with MeOH (0.5 mL) and warmed to room temperature. Then 1 N HCl (0.1 mL) added and stirred for 1 hour. The reaction was then diluted with Et_2O, and saturated aqueous $NaHCO_3$. Reaction extracted with Et_2O (3X). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Material purified via preparatory TLC (20% EtOAc/hexanes) to afford **101** as the major product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 5H), 5.80 (td, *J* = 2.5, 0.9 Hz, 1H), 5.69 (s, 1H), 5.07 – 4.89 (m, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 3.71 (ddd, *J* = 10.3, 5.1, 4.0 Hz, 1H), 3.60 – 3.49 (m, 1H), 2.54 – 2.40 (m, 2H), 2.37 – 2.11 (m, 3H), 2.03 – 1.92 (m, 3H), 1.89 (d, *J* = 11.3 Hz, 1H), 1.84 (t, *J* = 5.5 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.45 (s, 3H), 1.30 (s, 3H), 0.86 (s, 9H), 0.73 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.49, 136.90, 135.52, 128.79, 128.59, 128.29, 123.22, 86.86, 78.17, 71.43, 60.13, 54.10, 47.60, 42.84, 42.27, 37.39, 35.56, 30.87, 29.26, 27.69, 25.99, 25.66, 25.22, 22.81, 18.24, -5.22, -5.26.

R_f = 0.48 in 20% EtOAc/hexanes (stains blue in p-anisaldehyde)

Preparation of methyl ether 103:



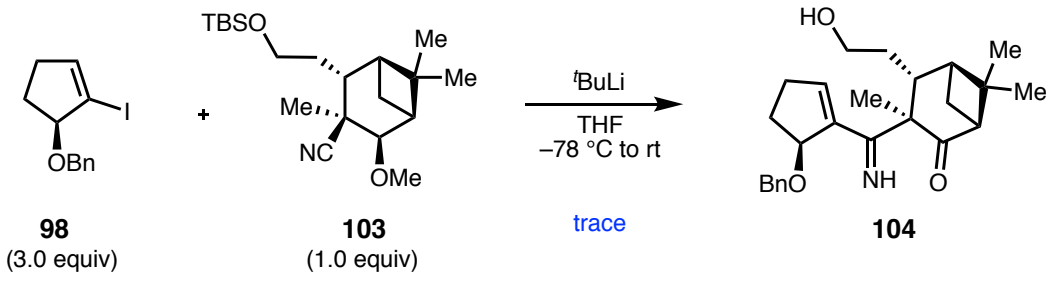
Procedure: To an oven-dried 2-dram vial, equipped with a stir bar, was charged ketone **99** (100 mg, 0.300 mmol, 1.0 equiv). To this vial was added DCM (3 mL) and then cooled to –78 °C. Next, DIBAL (1.0 M in DCM, 330 uL, 0.330 mmol, 1.1 equiv) added slowly, carefully. Reaction stirred for 5 minutes and then quenched by addition of MeOH (0.5 mL) and then saturated aqueous rochelle's salt. Reaction extracted with DCM (3X). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Material then used crude in the next step.

To a 0 °C solution of NaH (60% dispersion in mineral oil, 2.5 mg, 0.0623 mmol, 1.5 equiv) in THF (0.5 mL), was added crude material (14.5 mg, 0.0415 mmol, 1.0 equiv) from previous reaction and stirred at 0 °C for 15 minutes. Next, MeI (3.9 uL, 0.0623 mmol, 1.5 equiv) added and allowed to warm to room temperature. After stirred for 4 hours, additional NaH (2.5 mg, 0.0623 mmol, 1.5 equiv) added and stirred for another 2 hours. Reaction then quenched with H_2O, and extracted with Et_2O (3X), and washed with brine. Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Material purified via pipette column (10% EtOAc/hexanes) to afford **103** (14.5 mg, 0.0407 mmol, 98%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, cdcl$_3$) δ 2.77 (ddt, *J* = 10.3, 4.3, 1.5 Hz, 1H), 2.33 (ddd, *J* = 6.6, 4.6, 3.6 Hz, 1H), 2.15 (dtd, *J* = 11.0, 6.4, 1.5 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.62 (s, 3H), 1.51 – 1.41 (m, 1H), 1.24 (s, 5H), 1.13 (s, 3H), 0.97 (d, *J* = 11.0 Hz, 1H), 0.90 (s, 9H), 0.06 (d, *J* = 3.8 Hz, 6H).

R_f = 0.74 in 30% EtOAc/hexanes (stains green with p-anisaldehyde)

Preparation of imine 104:



Procedure: To an oven-dried 1-dram vial, equipped with a stir bar, was charged vinyl iodide **98** (30.7 mg, 0.102 mmol, 3.0 equiv) and THF (0.5 mL). Reaction placed under an atmosphere of N_2 and then cooled to –78 °C. ^{t}BuLi (1.7 M in pentanes, 120 uL, 0.205

mmol, 6.0 equiv) then added slowly dropwise. Next, a solution of nitrile **103** (12.0 mg, 0.0341 mmol, 1.0 equiv) in THF (0.5 mL) added slowly dropwise. Reaction then stirred at –78 °C for 1 hour. Reaction then quenched at –78 °C with MeOH (0.5 mL) and warmed to room temperature. Then 1 N HCl (0.1 mL) added and stirred for 1 hour. The reaction was then diluted with Et_2O, and saturated aqueous $NaHCO_3$. Reaction extracted with Et_2O (3X). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Material purified via preparatory TLC (20% EtOAc/hexanes) to afford **104** as the major product.

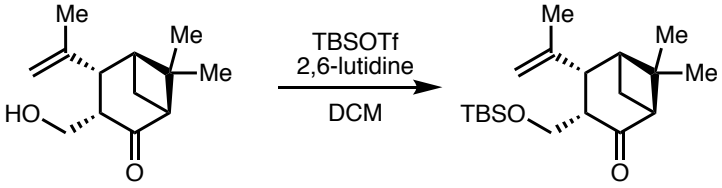
^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 6H), 6.04 (t, *J* = 2.7 Hz, 1H), 4.77 (dt, *J* = 6.6, 2.7 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 3.67 (d, *J* = 4.7 Hz, 1H), 3.60 – 3.42 (m, 3H), 3.03 (s, 3H), 2.65 (dddt, *J* = 17.7, 8.3, 6.0, 2.3 Hz, 1H), 2.42 (ddt, *J* = 11.9, 5.9, 4.0 Hz, 2H), 1.56 (d, *J* = 9.5 Hz, 4H), 1.21 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.12, 128.63, 128.20, 127.87, 92.13, 86.20, 71.17, 60.63, 55.74, 49.38, 48.82, 42.53, 40.61, 36.22, 33.10, 31.50, 31.10, 29.62, 28.80, 27.49, 22.92, 22.64.

HRMS (GC-EI+, m/z): calc'd for $C_{26}H_{38}O_3N$ 412.2846 $[M+H]^+$; found: 412.2830

R_f = 0.17 in 20% EtOAc/hexanes (stains yellow in p-anisaldehyde)

Preparation of silyl ether:



87% yield

Procedure: To an oven-dried 1-dram vial, equipped with a stir bar was added alcohol starting material (14.1 mg, 0.067 mmol, 1.0 equiv), DCM (212 uL), and 2,6-lutidine (15.8 uL, 0.135 mmol, 2.0 equiv). Reaction cooled to 0 °C and then TBSOTf (23.4 uL, 1.5 equiv) was added. Reaction warmed to room temperature and then stirred for 2 hours. Reaction then quenched with H_2O (200 uL), then extracted with DCM (3x). Dried over $MgSO_4$, filtered, concentrated and then purified via column chromatography (15% EtOAc/Hex) to afford silyl ether product (19 mg, 0.059 mmol, 87% yield) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (p, *J* = 1.5 Hz, 1H), 4.73 (dq, *J* = 1.9, 0.8 Hz, 1H), 4.04 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.73 (dd, *J* = 10.0, 2.7 Hz, 1H), 3.02 – 2.88 (m, 1H), 2.64 (ddt, *J* = 9.8, 5.1, 2.5 Hz, 1H), 2.51 – 2.43 (m, 2H), 2.29 – 2.14 (m, 2H), 1.81 (ddd, *J* = 19.8, 1.5, 0.8 Hz, 4H), 1.33 (d, *J* = 11.4 Hz, 4H), 0.88 – 0.85 (m, 7H), 0.83 (s, 8H), 0.00 (s, 3H), -0.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.90, 146.11, 112.81, 62.82, 57.44, 50.35, 44.96, 42.32, 41.13, 26.18, 25.98, 25.84, 23.77, 22.89, 21.75, -5.59, -5.64.

FTIR (NaCl, thin film, cm^{-1}): 2928, 1712, 1463, 1250, 1129, 1081, 891, 834, 776.

$\boldsymbol{\alpha_D^{22}}$ = +29° (c = 0.385, $CHCl_3$).

2.6 NOTES AND REFERENCES

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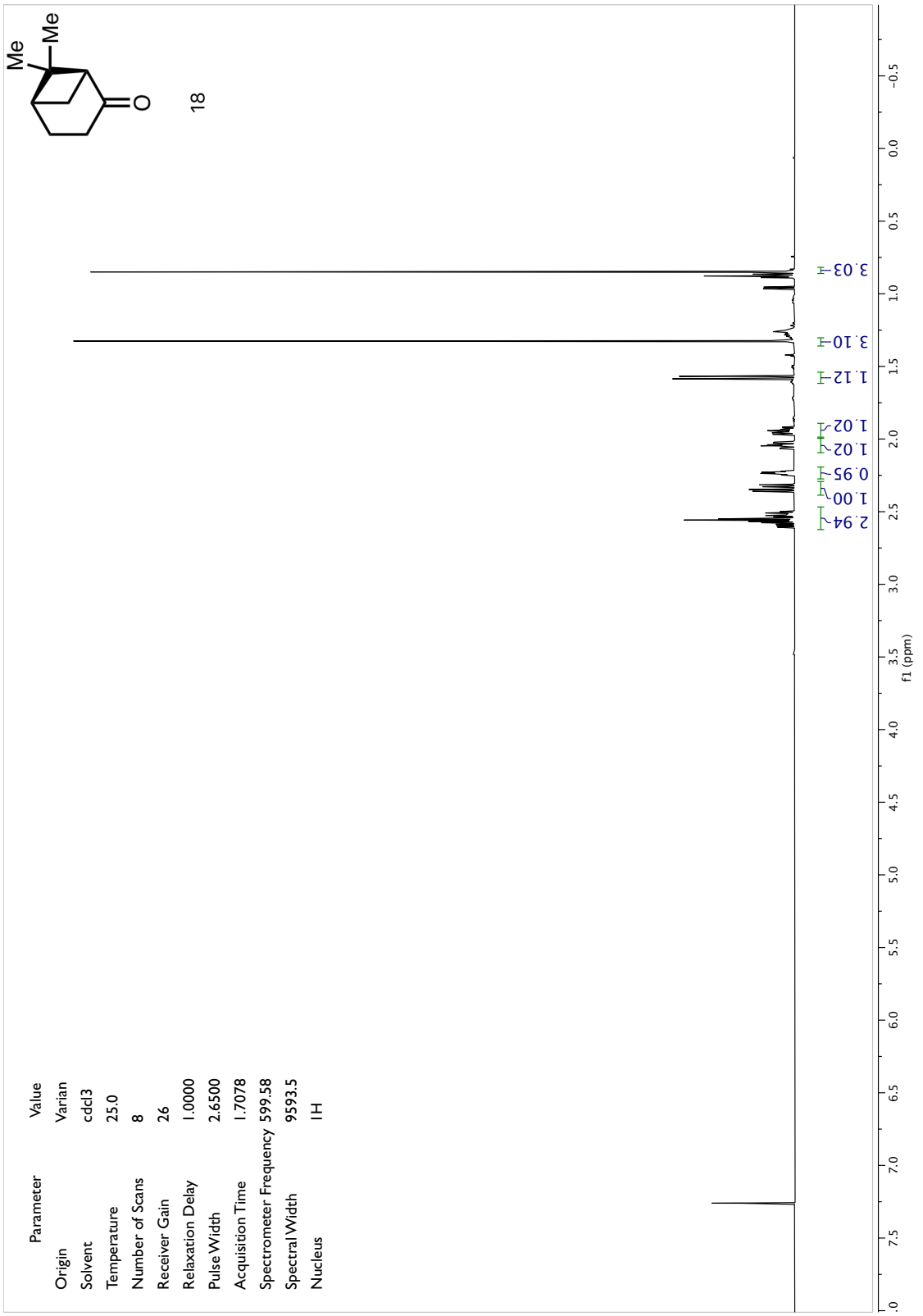
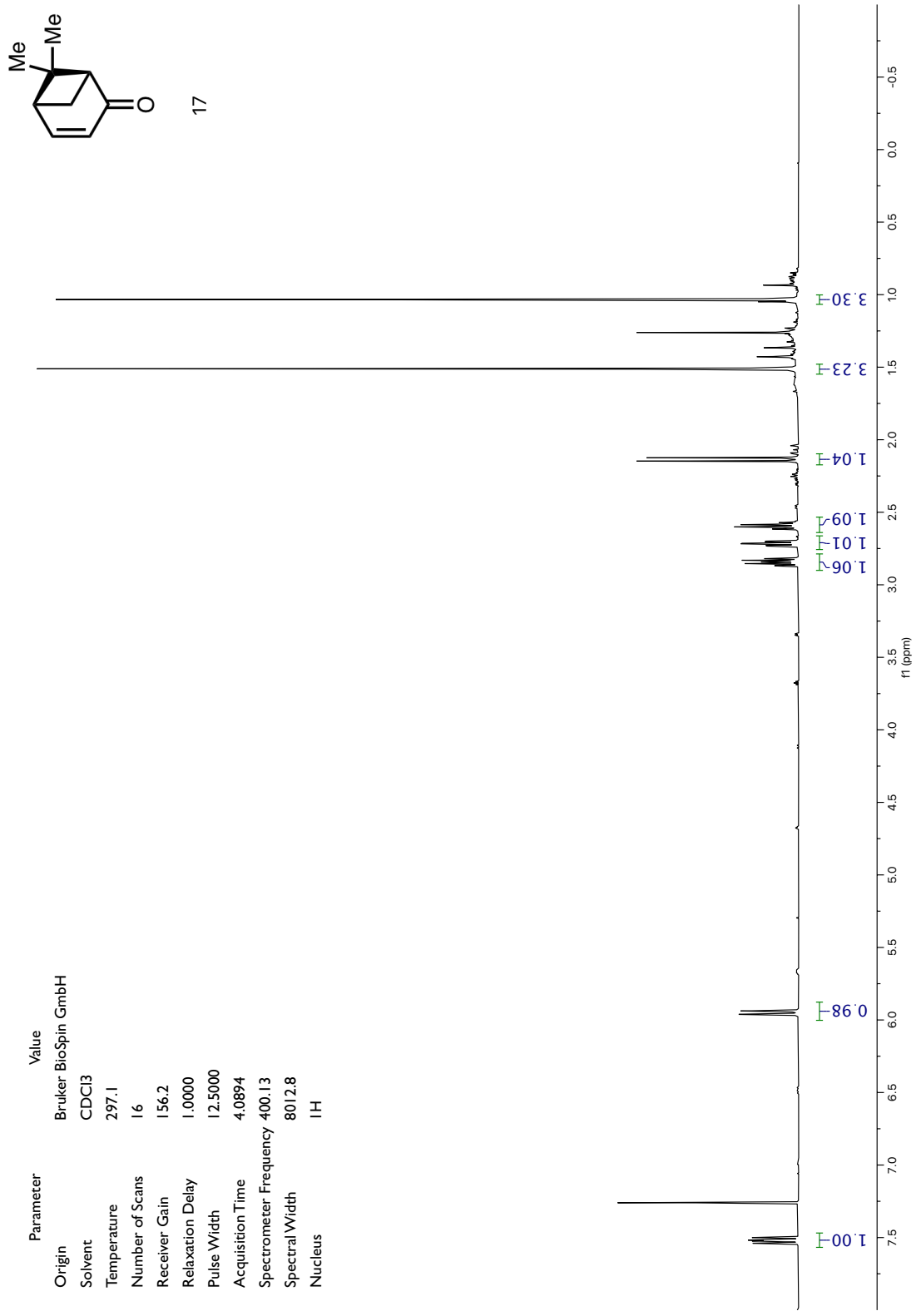
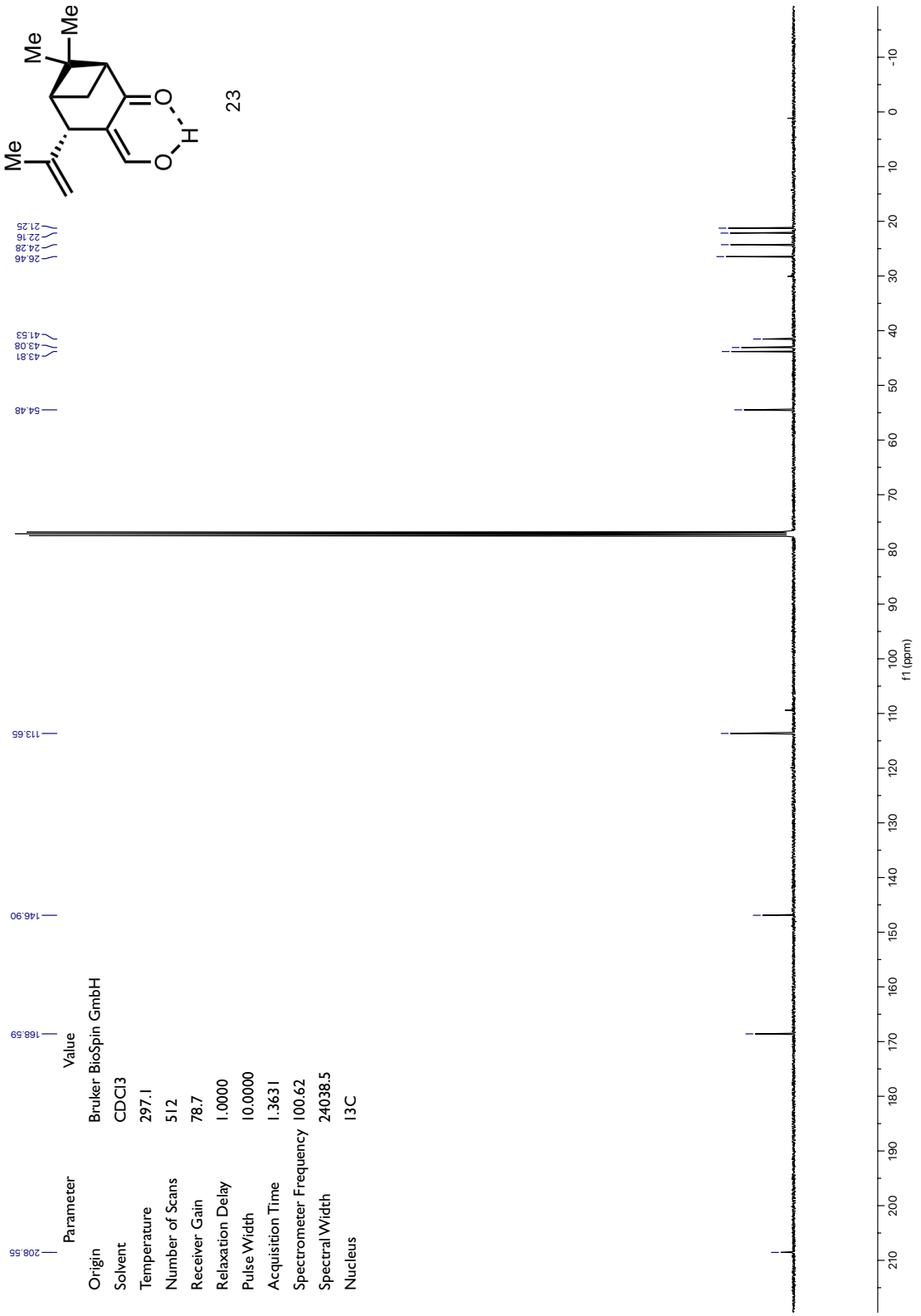
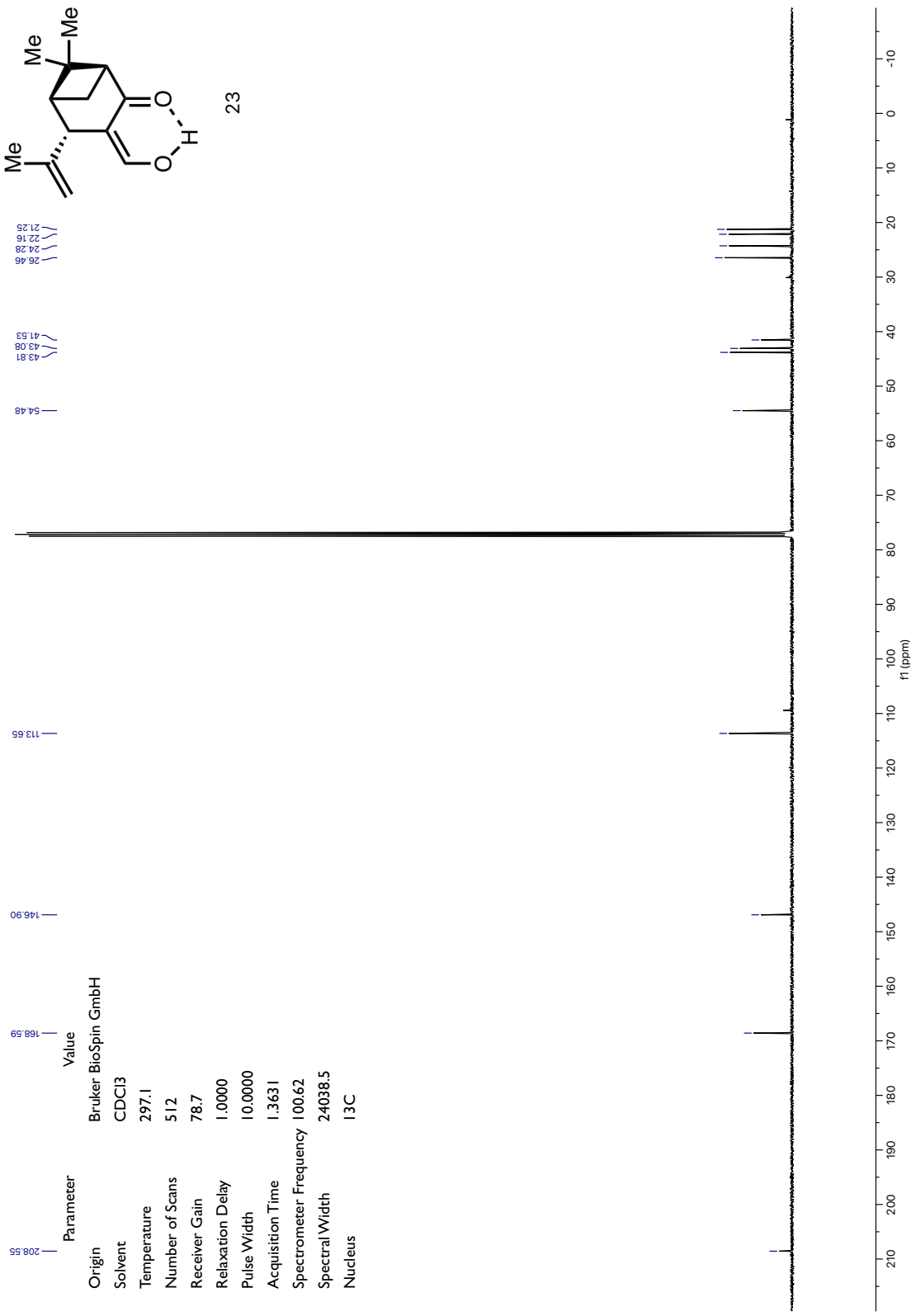
Appendix 1

Spectra Relevant to Chapter 2: A Photoredox Cascade Cyclization Approach to the Synthesis of Falcatin A

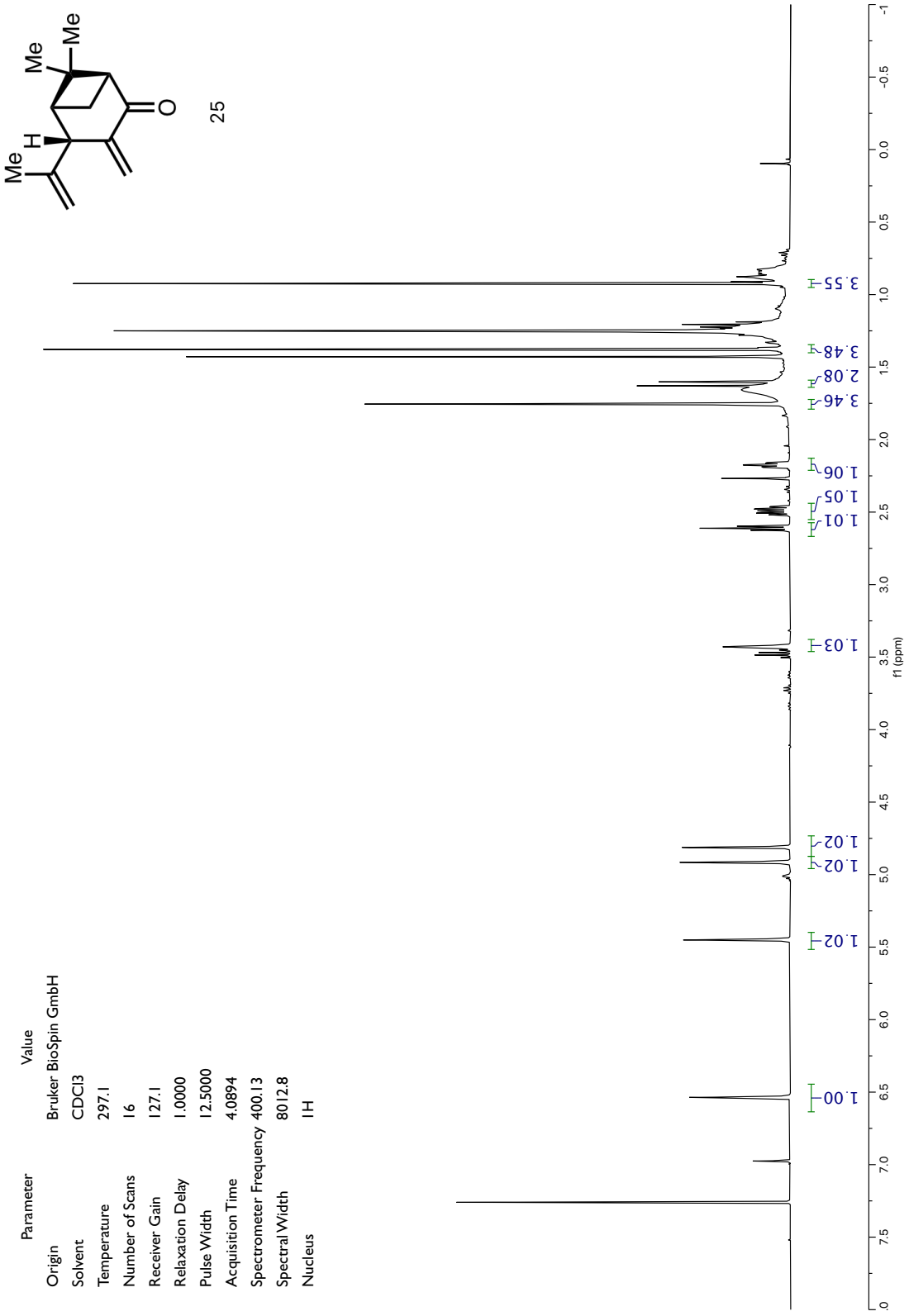

Me
Me
O
18
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 8
Receiver Gain 26
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7078
Spectrometer Frequency 599.58
Spectral Width 9593.5
Nucleus 1H
3.03
3.10
1.12
1.02
1.02
0.95
1.00
2.94
f1 (ppm)

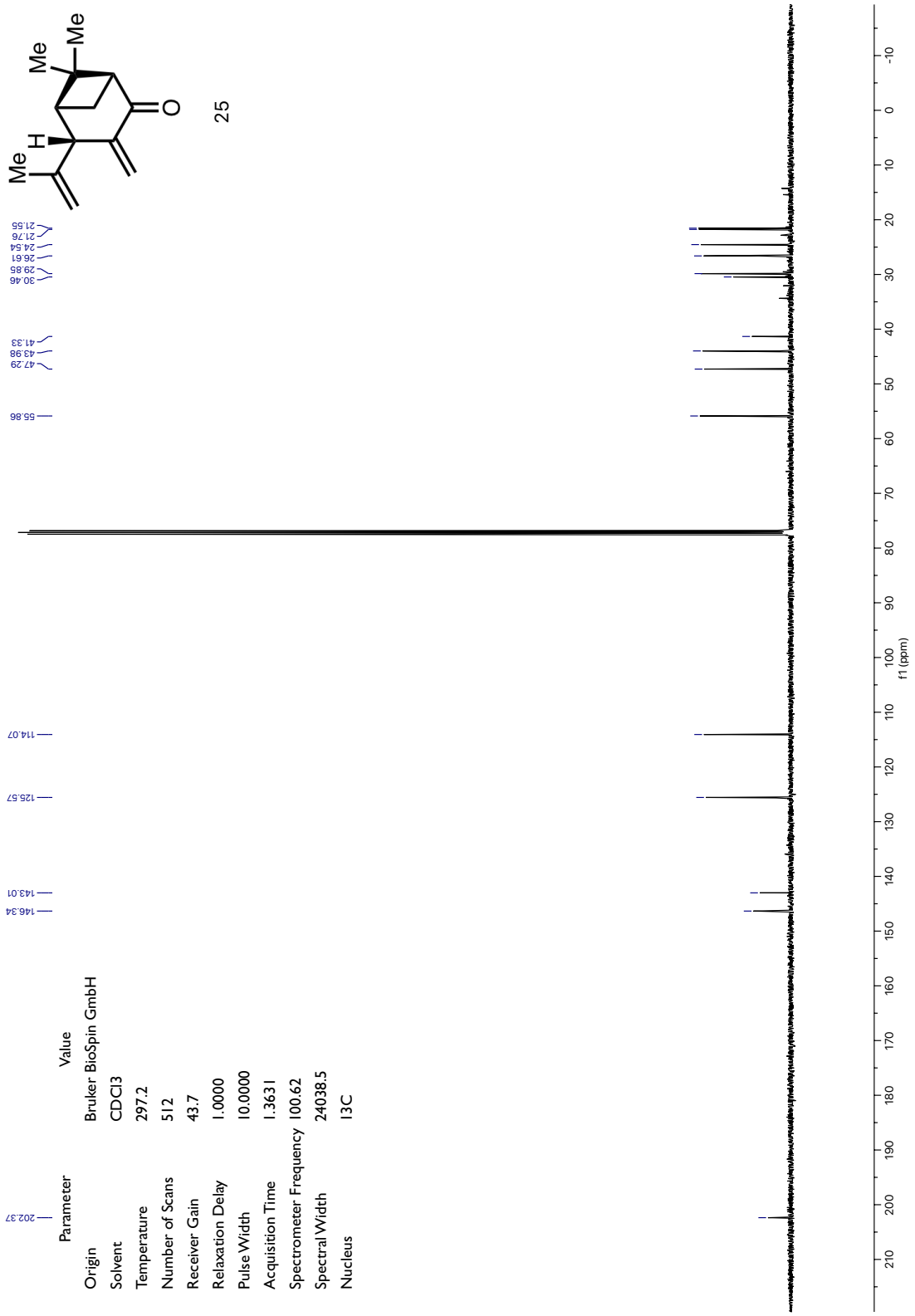

Me
Me
O
17
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.30
3.23
1.04
1.09
1.01
1.06
0.98
1.00
f1 (ppm)


Me
Me
Me
O
O
H
23
208.55
168.59
146.90
113.65
54.48
43.81
43.08
41.53
26.46
24.28
22.16
21.25
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C

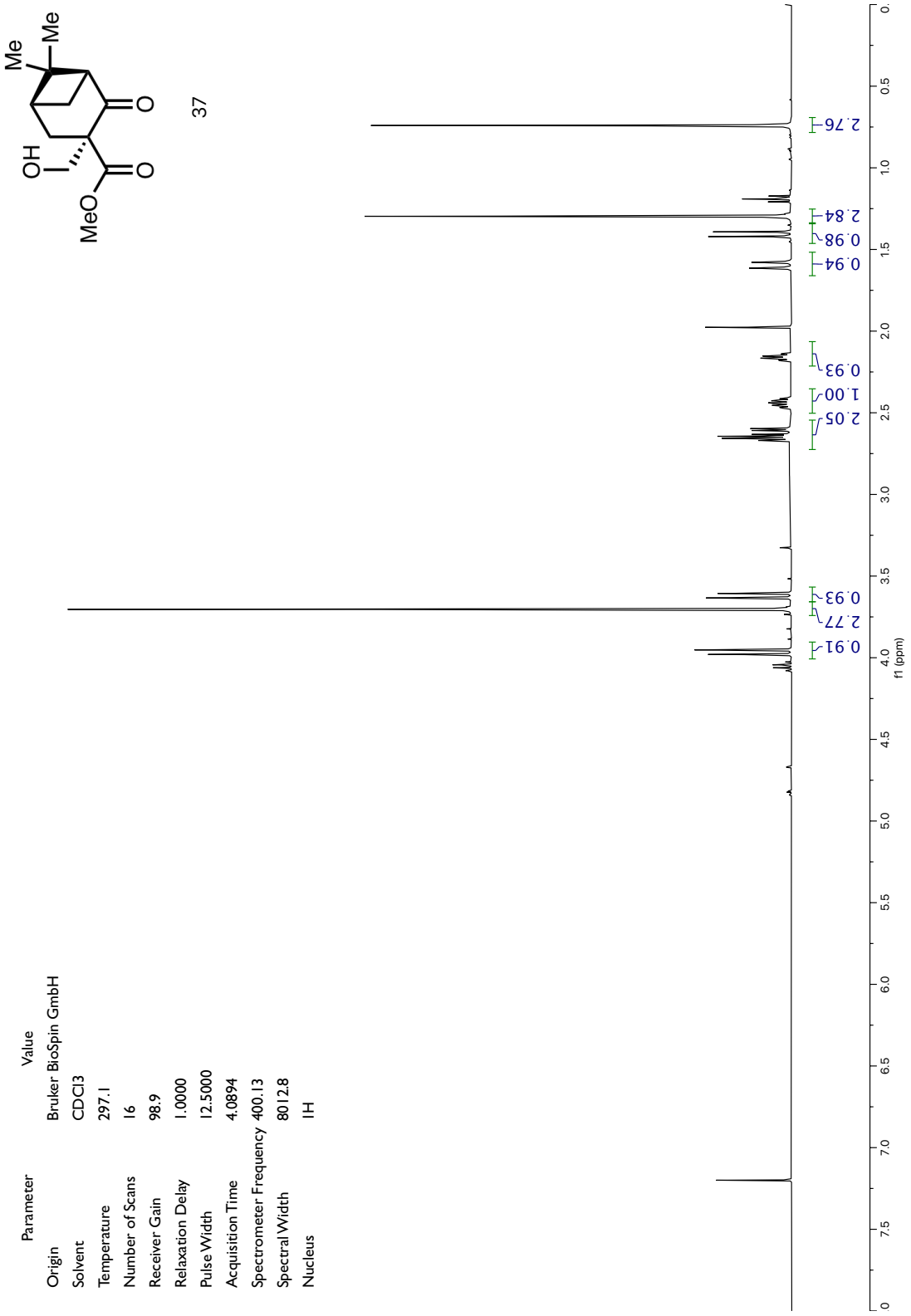


Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	512
Receiver Gain	78.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

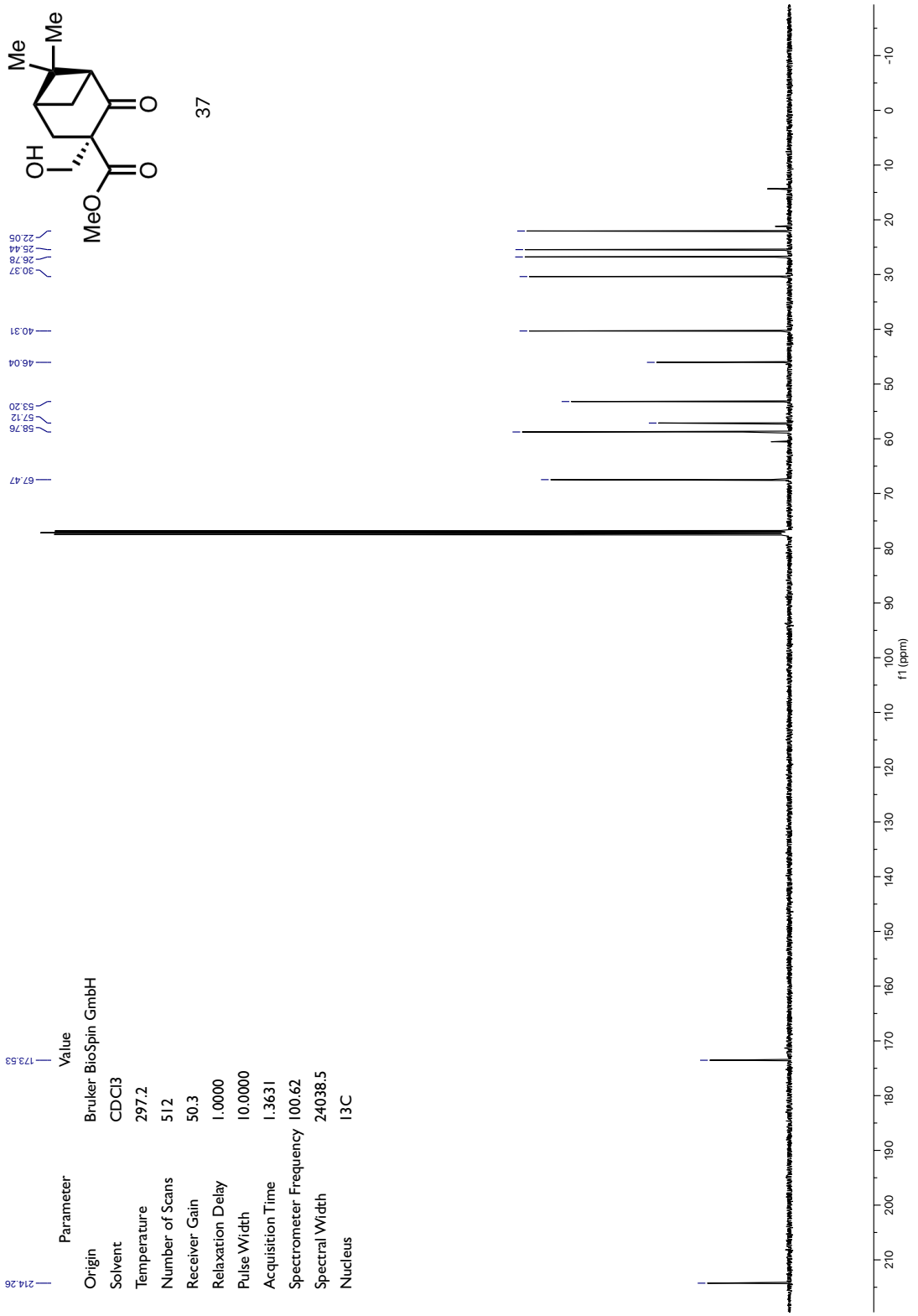

Me
Me
H
Me
O
25
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
1.00
1.02
1.02
1.02
1.03
1.01
1.05
1.06
3.46
2.08
3.48
3.55
f1 (ppm)

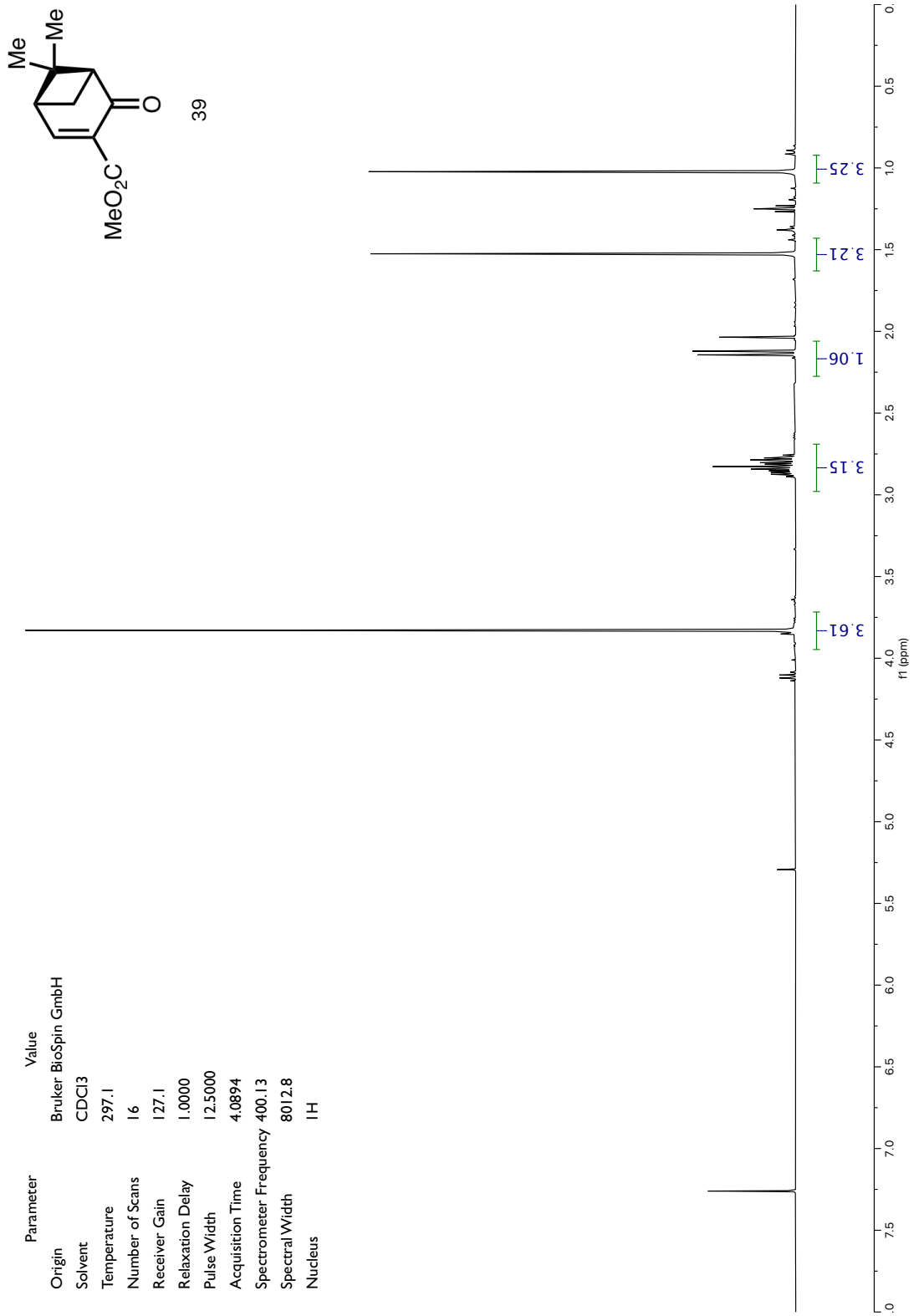


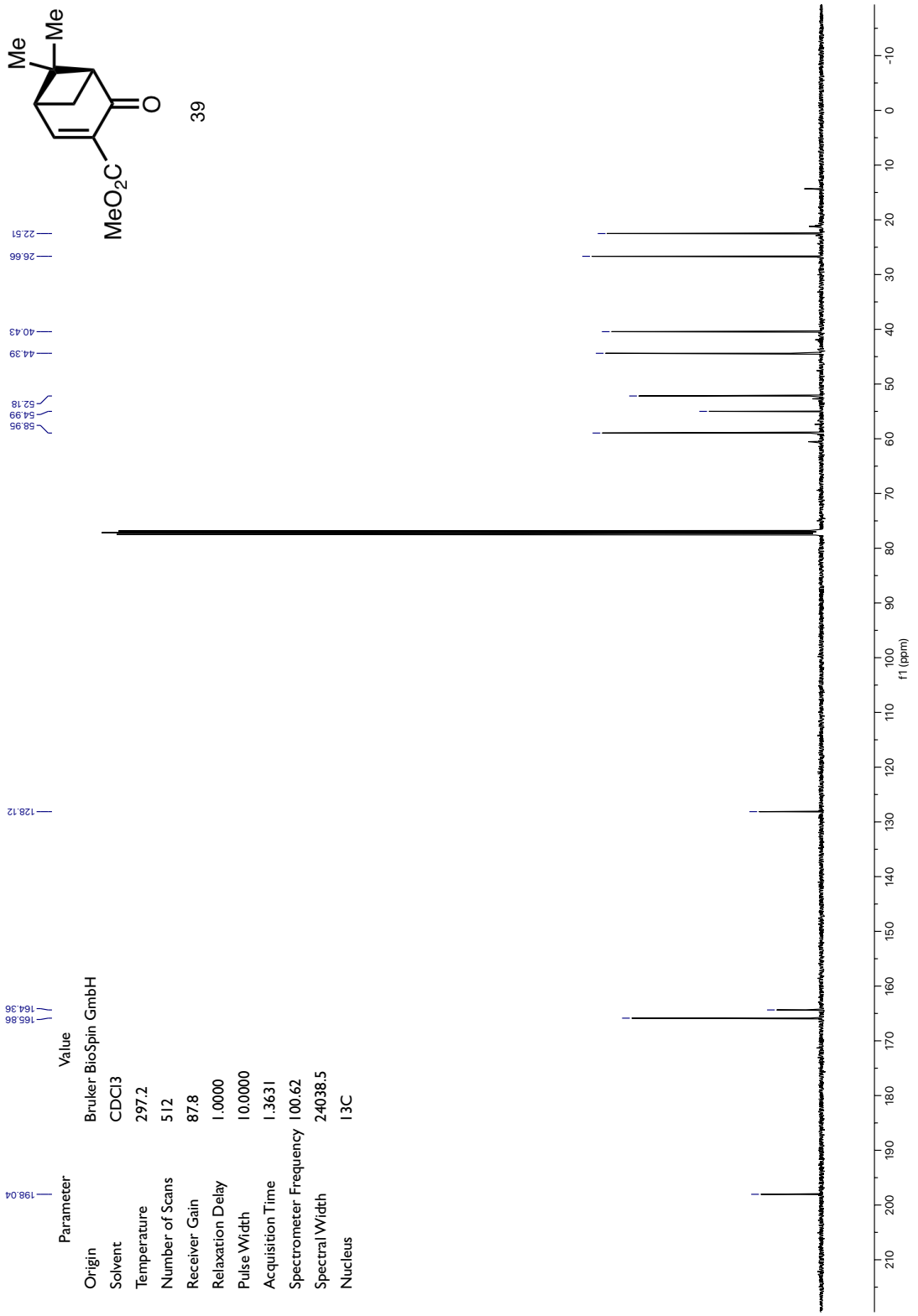
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	43.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

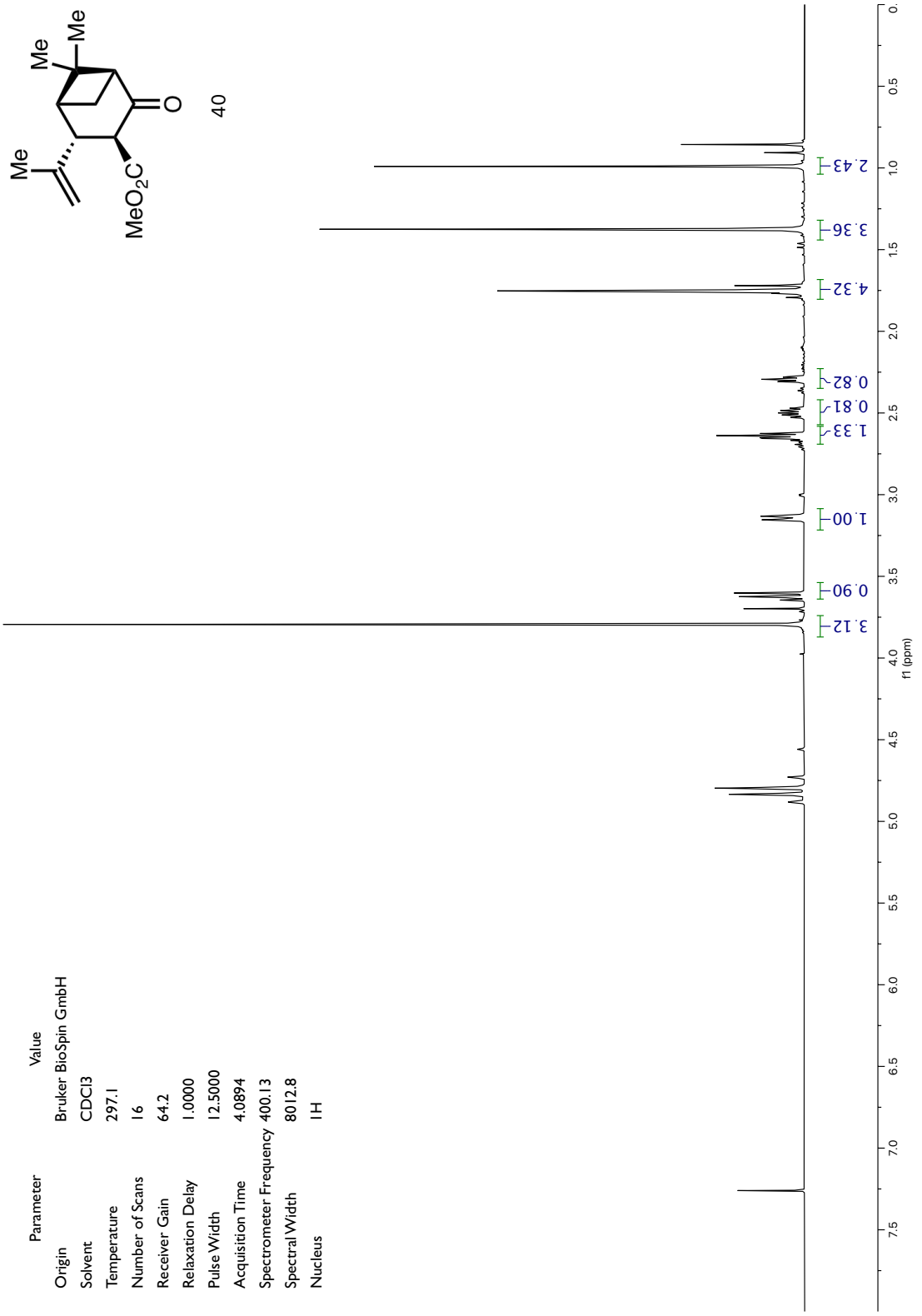


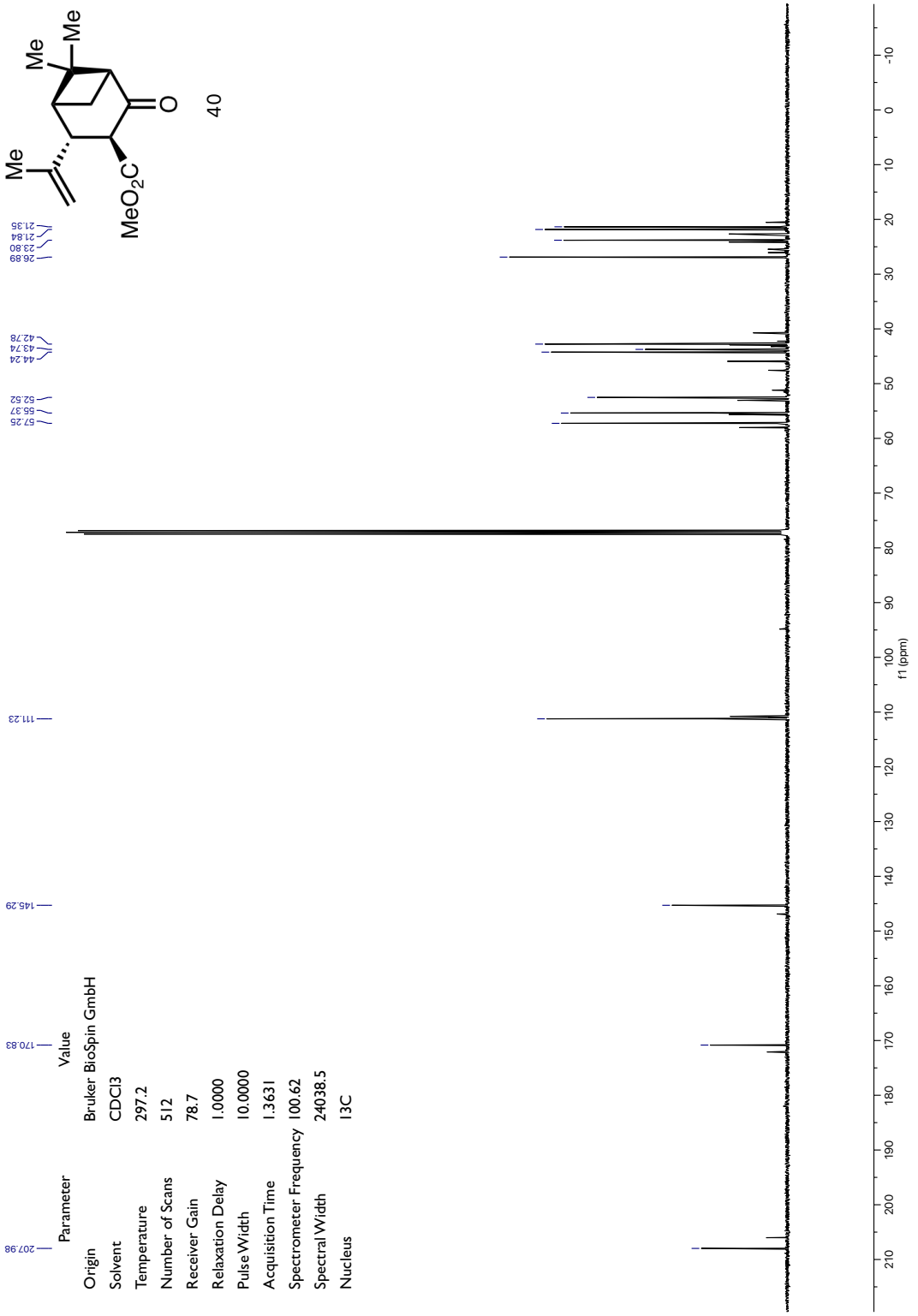
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	16
Receiver Gain	98.9
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H

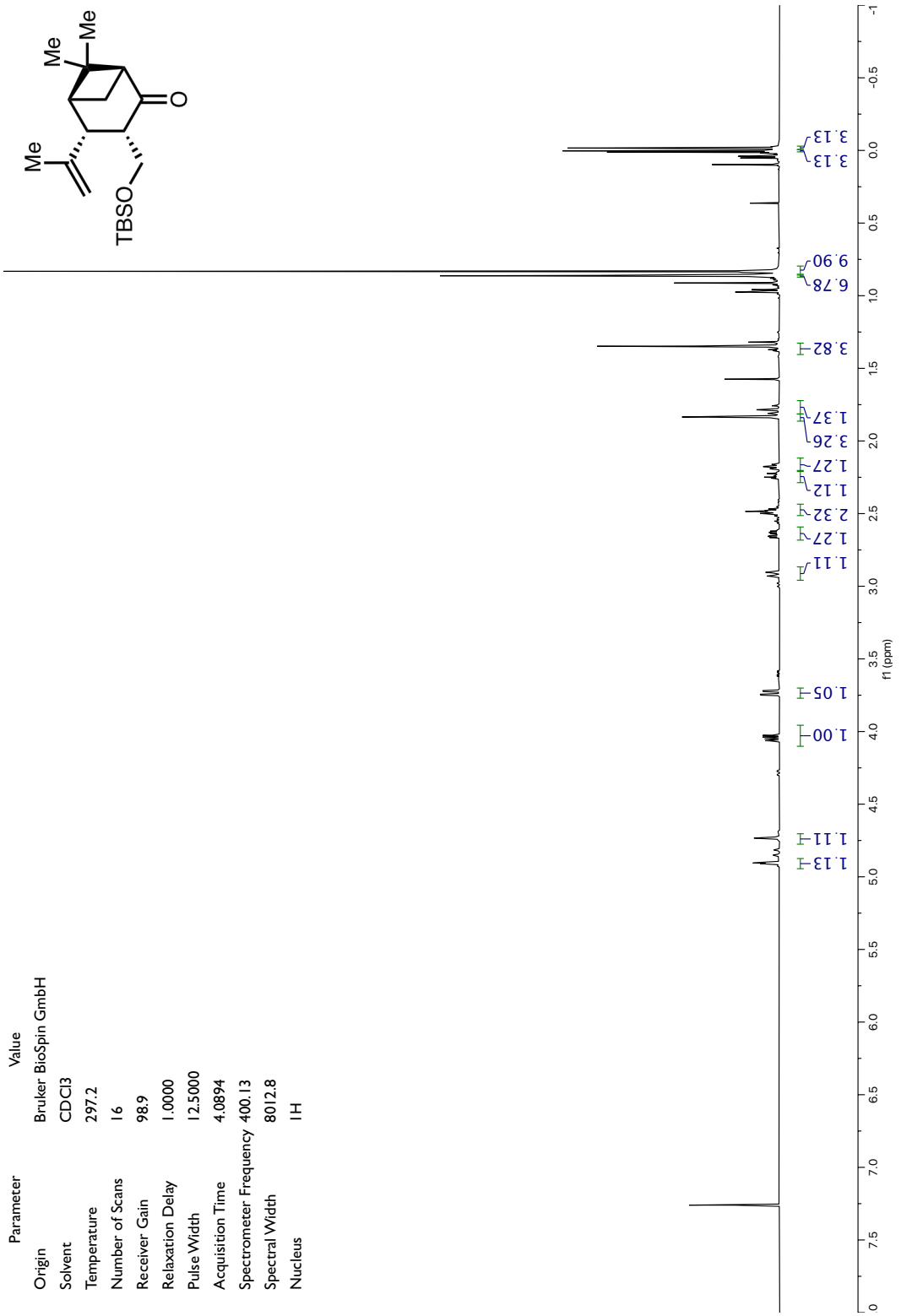

Me
Me
O
OH
O
MeO
37
214.26
173.53
67.47
58.76
57.12
53.20
46.04
40.31
30.37
26.78
25.44
22.05
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
512
Receiver Gain
50.3
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)


Me
Me
O
MeO2C
39
3.25
3.21
1.06
3.15
3.61
f1 (ppm)
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
127.1
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H

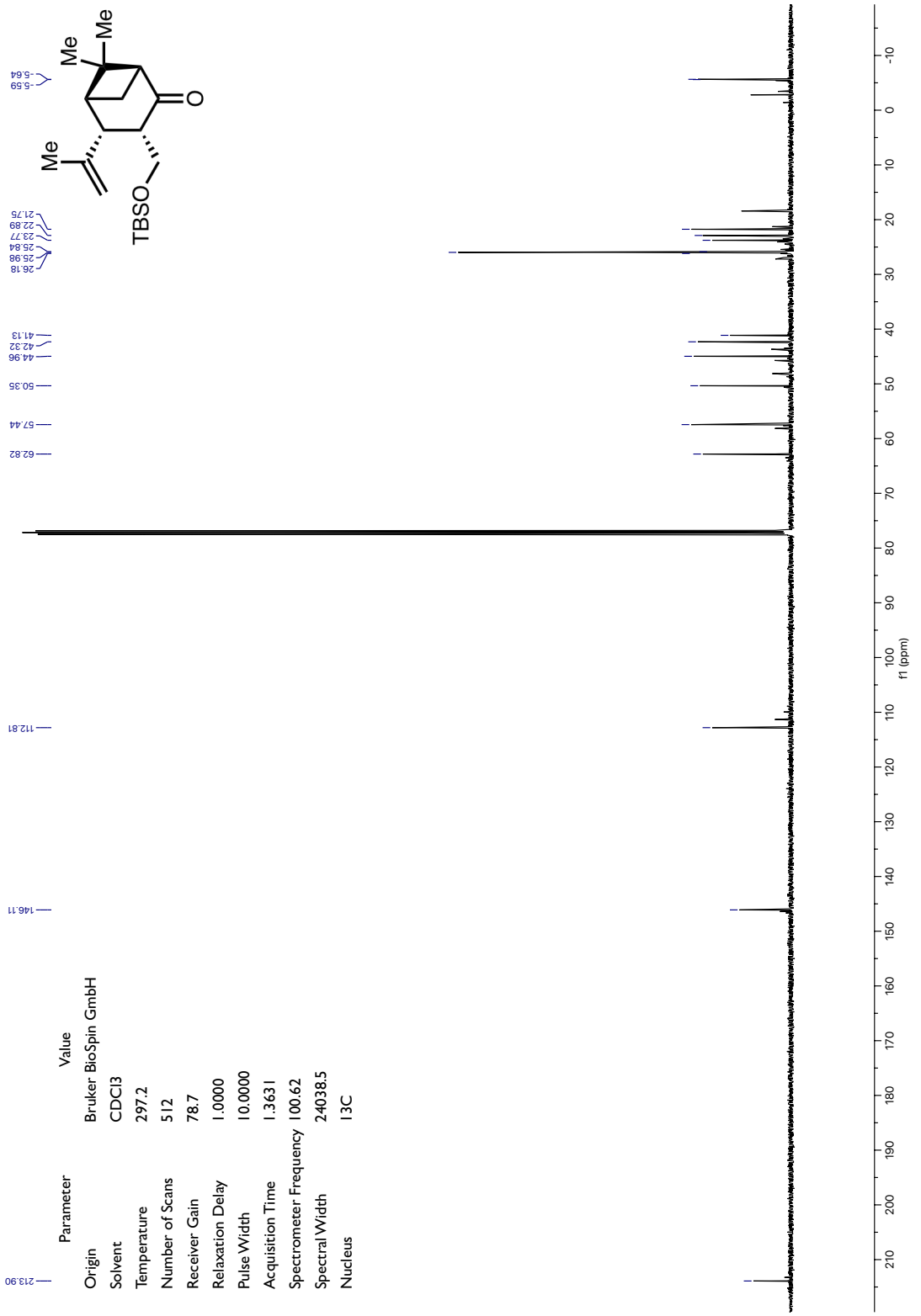

Me
Me
O
MeO2C
39
22.51
26.66
40.43
44.39
52.18
54.99
58.95
128.12
165.86
164.36
198.04
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

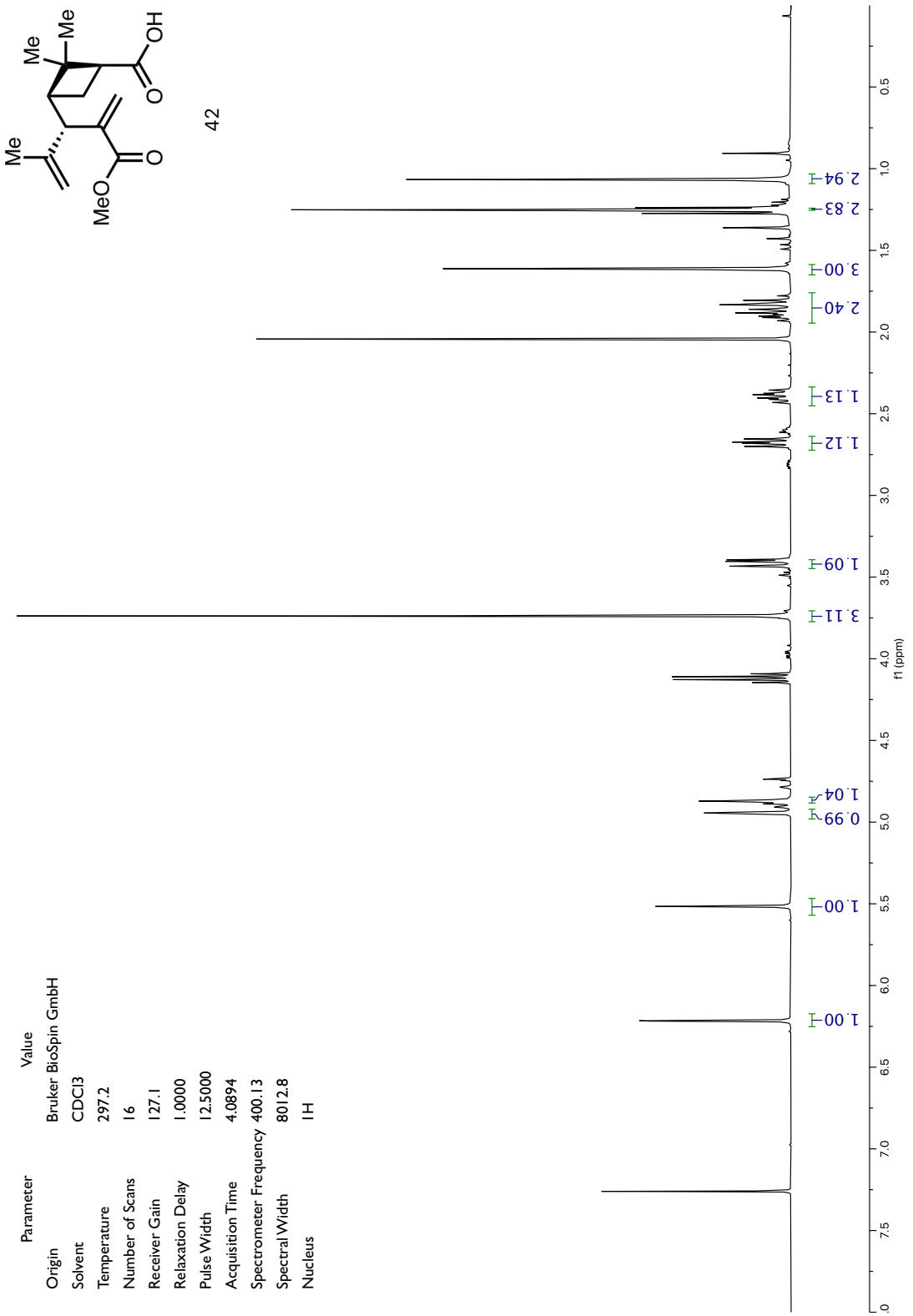

Me
Me
Me
O
MeO_2C
40
2.43
3.36
4.32
0.82
0.81
1.33
1.00
0.90
3.12
f1 (ppm)
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
64.2
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H

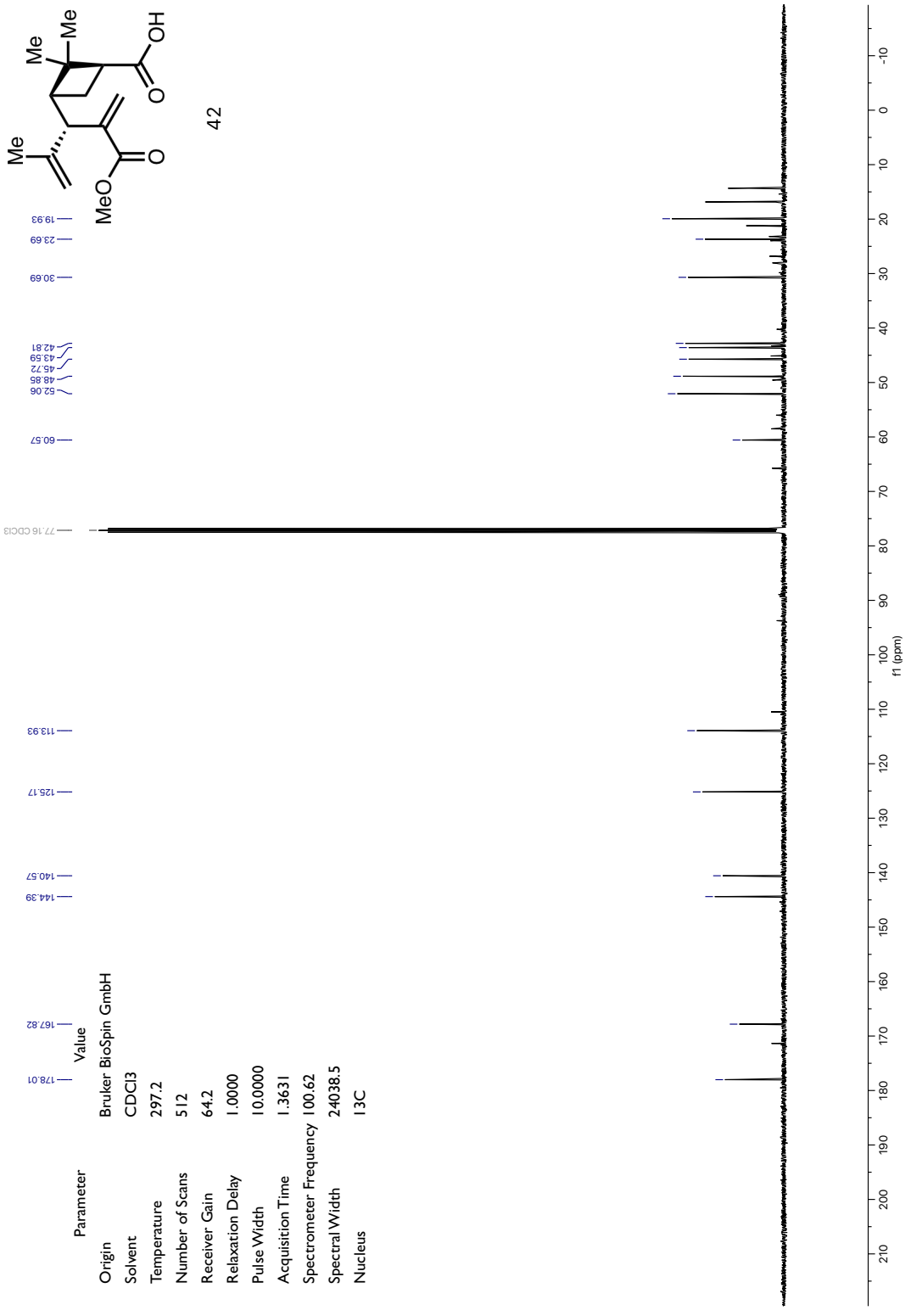

Me
Me
Me
O
MeO_2C
40
207.98
170.83
145.29
111.23
57.25
55.37
52.52
44.24
43.74
42.78
26.89
23.80
21.84
21.35
f1 (ppm)
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
512
Receiver Gain
78.7
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C

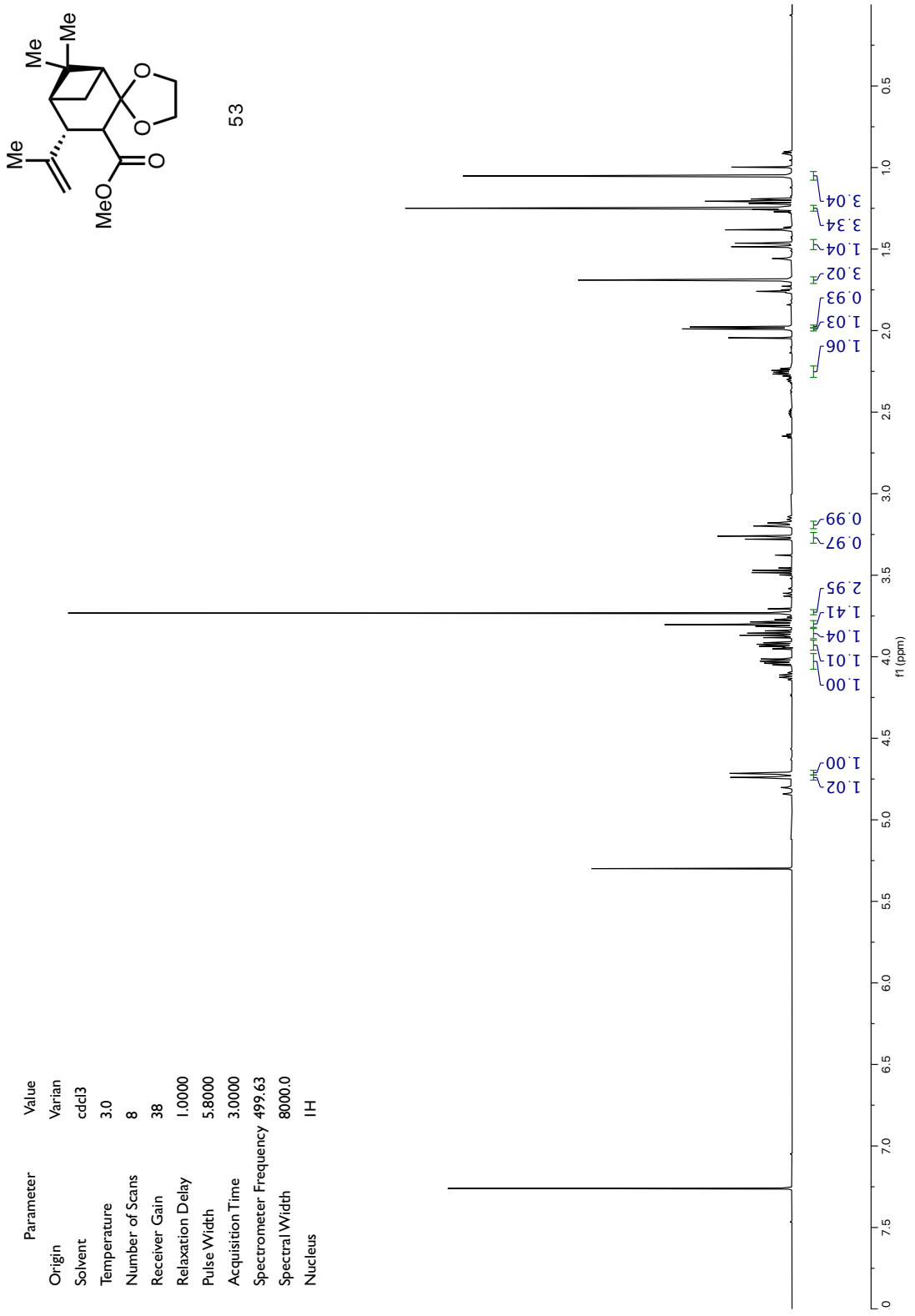


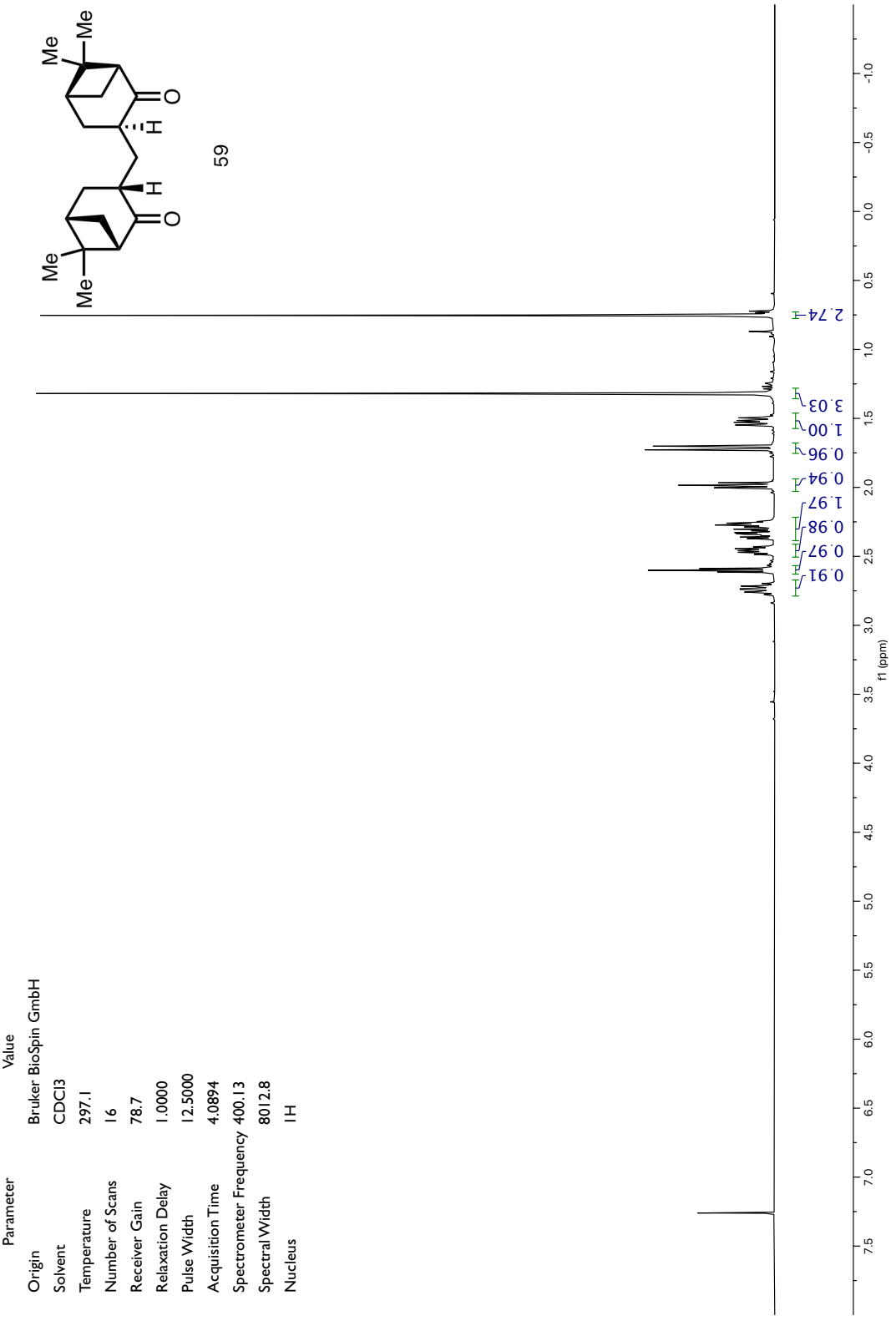
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	16
Receiver Gain	98.9
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H


Me
Me
Me
O
TBSO
-5.64
-5.59
21.75
22.89
23.77
25.84
25.98
26.18
41.13
42.32
44.96
50.35
57.44
62.82
112.81
146.11
213.90
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C

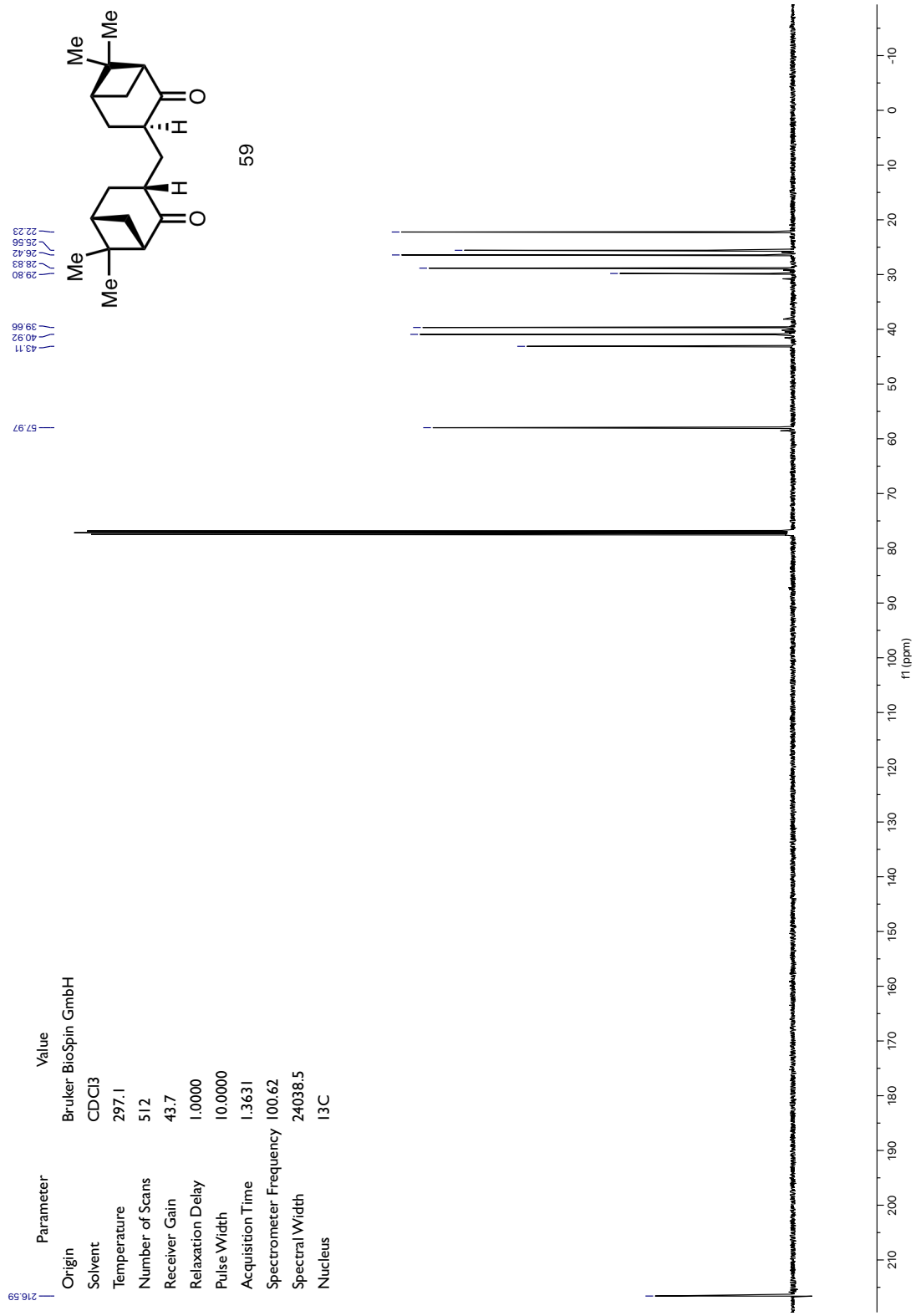

Me
Me
OH
O
Me
O
MeO
42
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
1.00
1.00
0.99
1.04
1.00
3.11
1.09
1.12
1.13
2.40
3.00
2.83
2.94
f1 (ppm)


Me
Me
OH
O
Me
O
MeO
42
19.93
23.69
30.69
42.81
43.59
45.72
48.85
52.06
60.57
77.16 CDCl3
113.93
125.17
140.57
144.39
167.82
178.01
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
512
Receiver Gain
64.2
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)

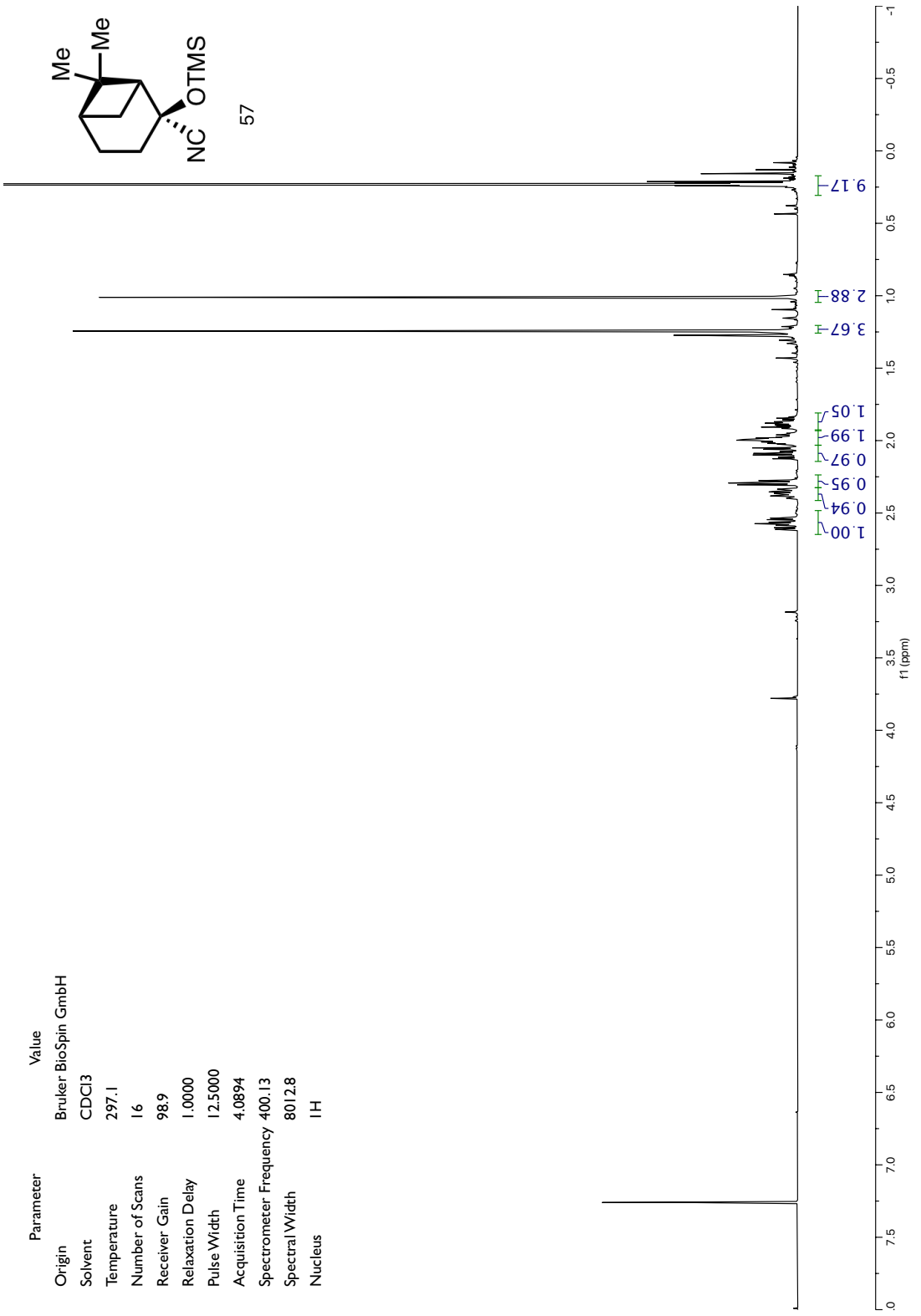

Me
Me
Me
O
O
O
MeO
53
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 3.0
Number of Scans 8
Receiver Gain 38
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Spectrometer Frequency 499.63
Spectral Width 8000.0
Nucleus 1H
1.02
1.00
0.97
0.99
1.00
1.01
1.04
1.41
2.95
1.06
1.03
0.93
3.02
1.04
3.34
3.04
f1 (ppm)

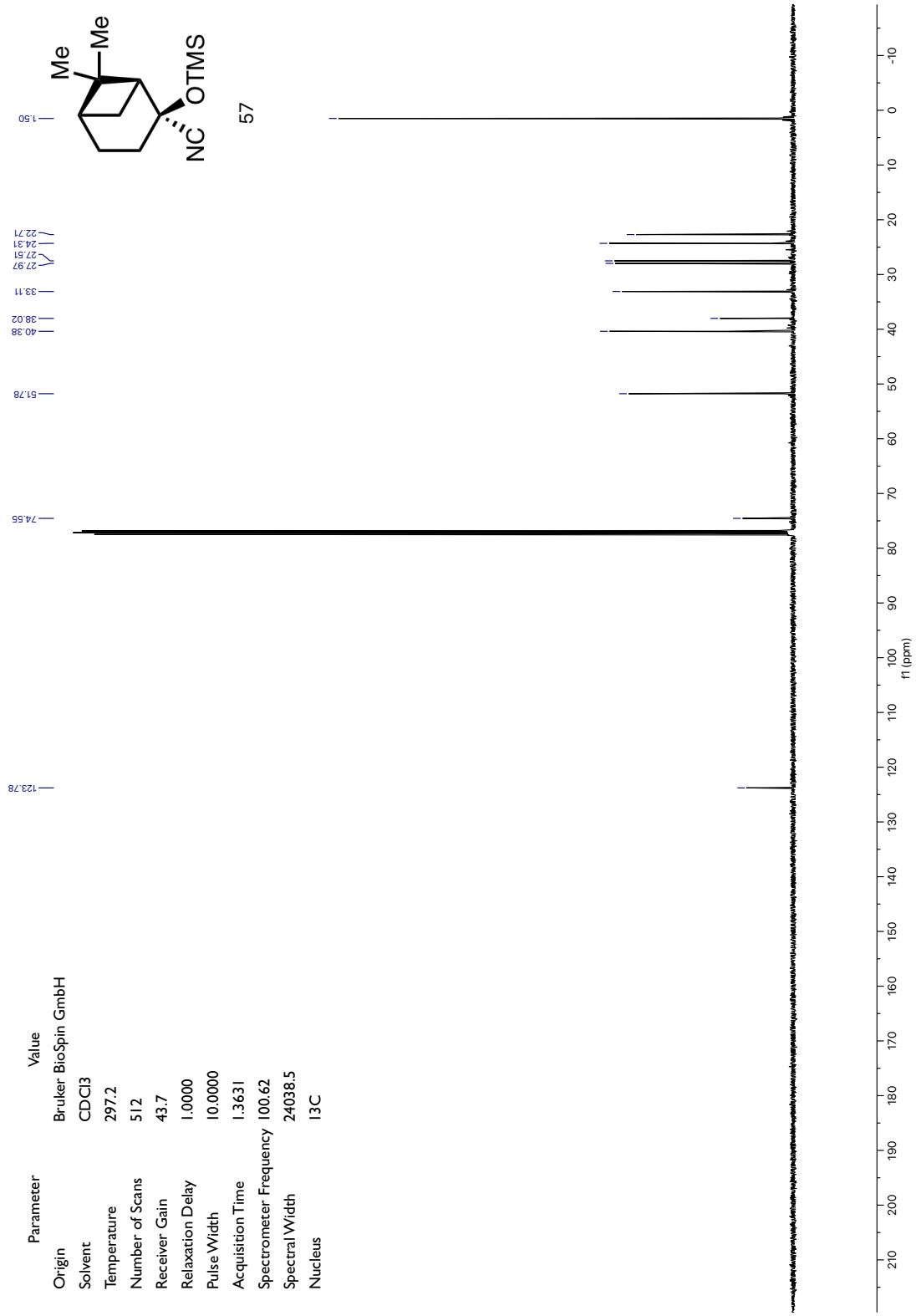


Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	16
Receiver Gain	78.7
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H

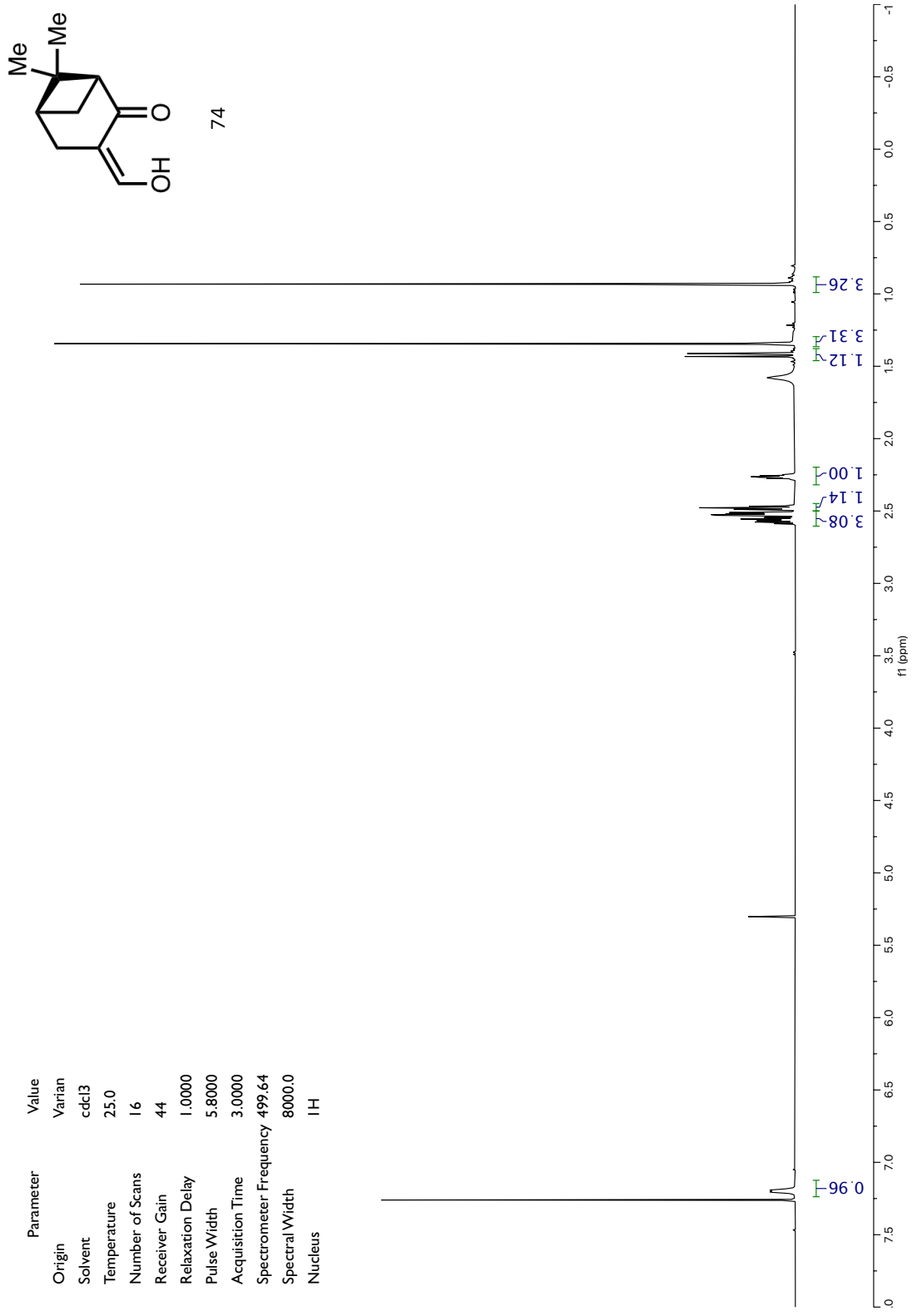


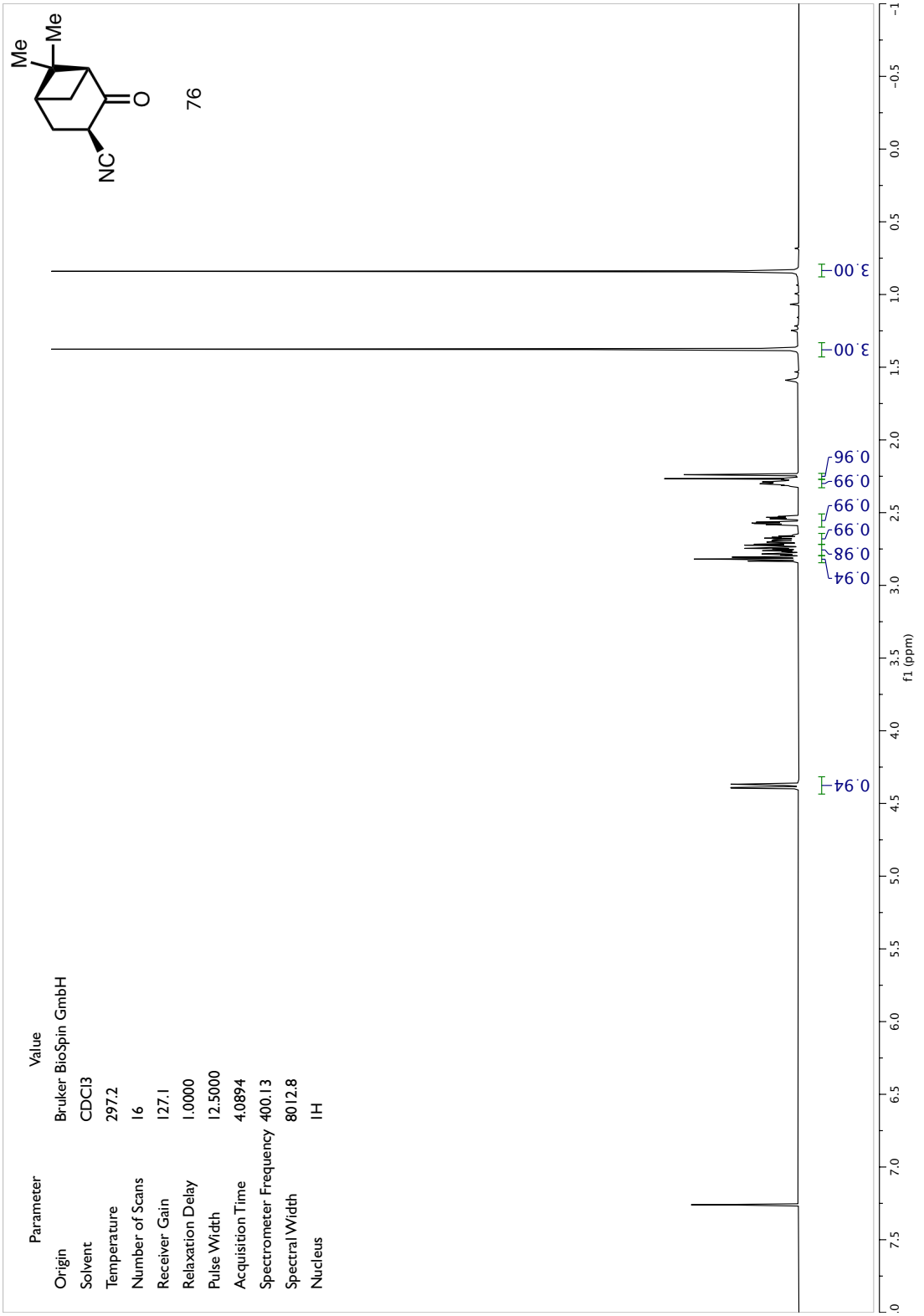
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	512
Receiver Gain	43.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

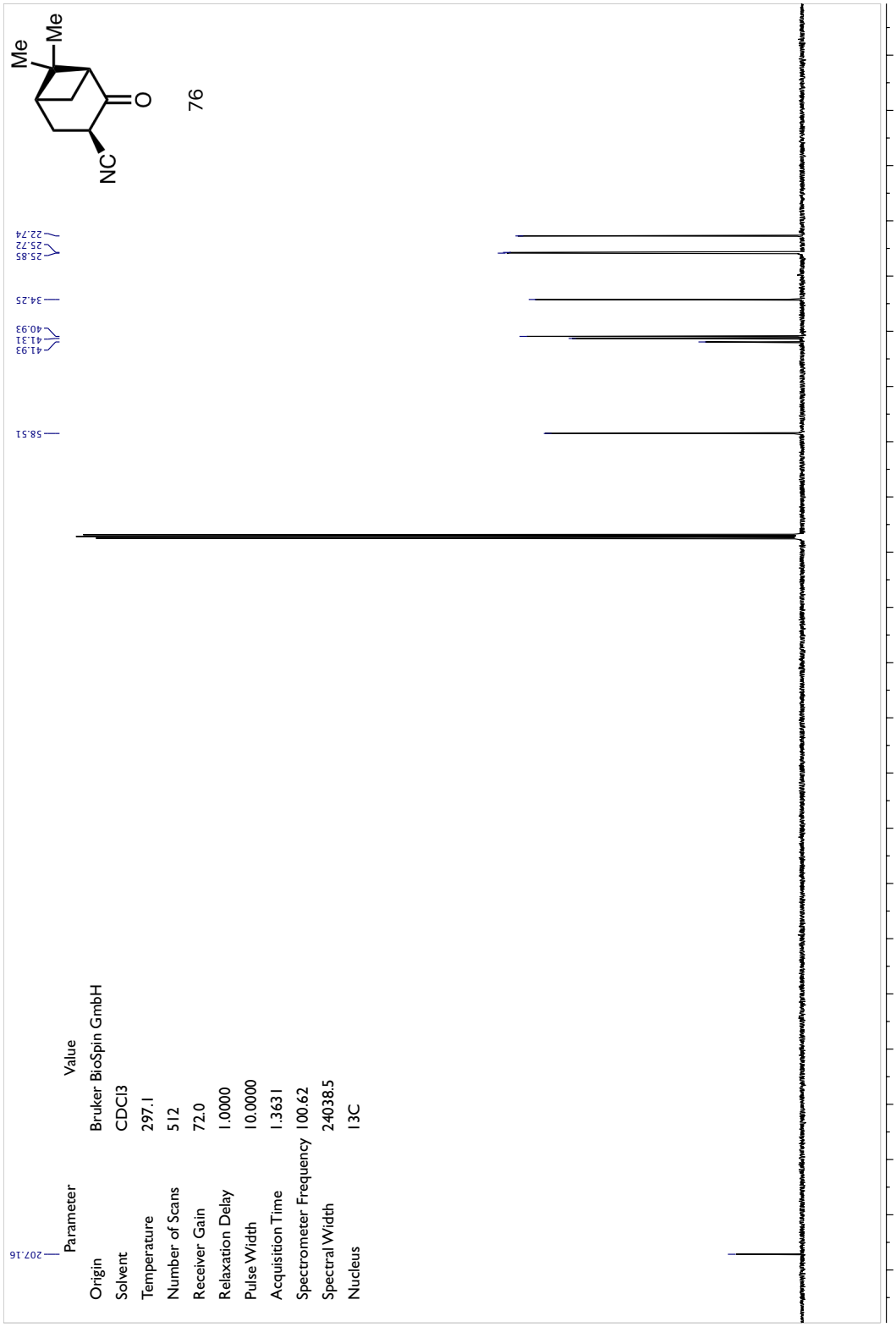

Me
Me
NC
OTMS
57
9.17
2.88
3.67
1.05
1.99
0.97
0.95
0.94
1.00
f1 (ppm)
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
98.9
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H



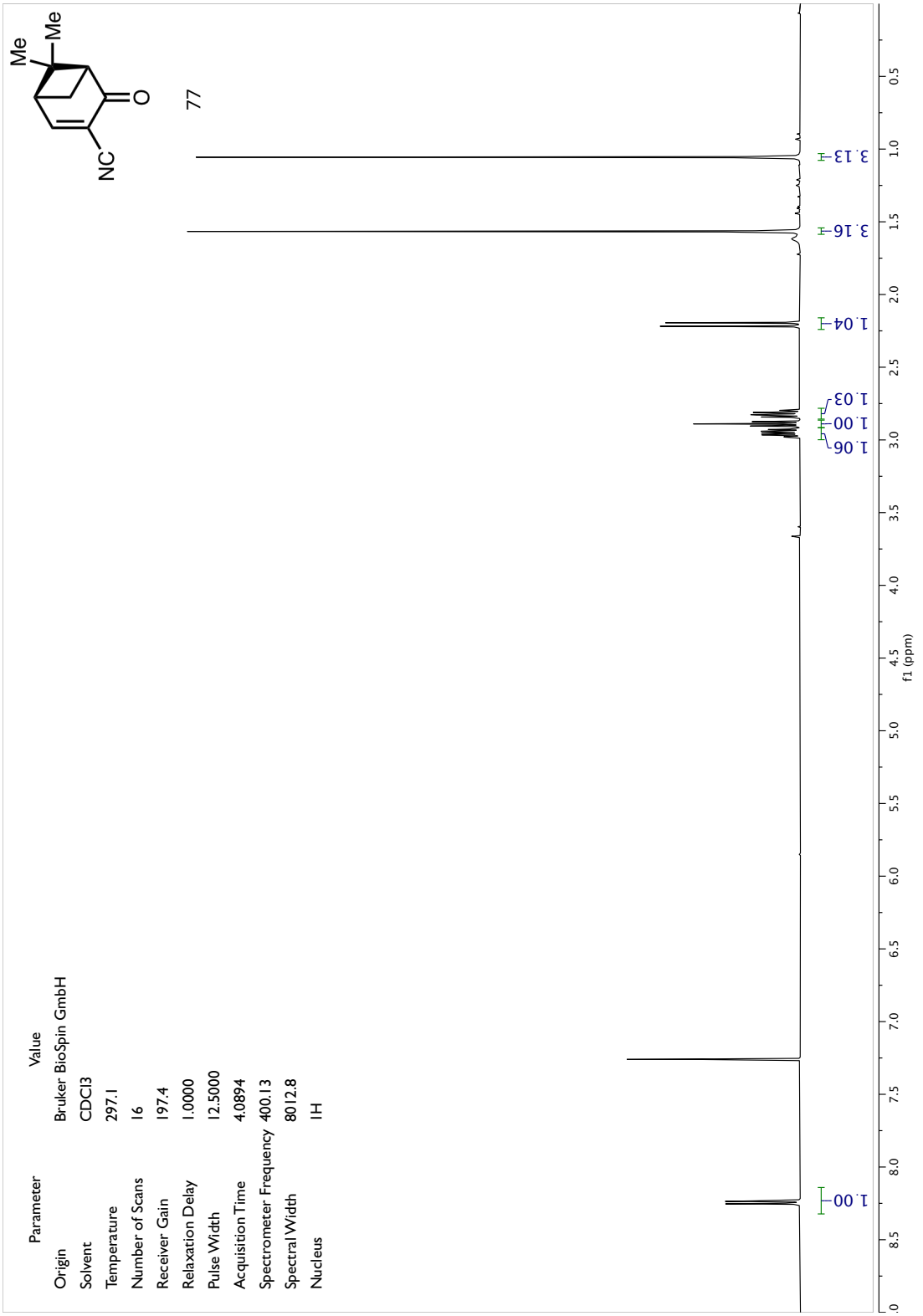
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	43.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

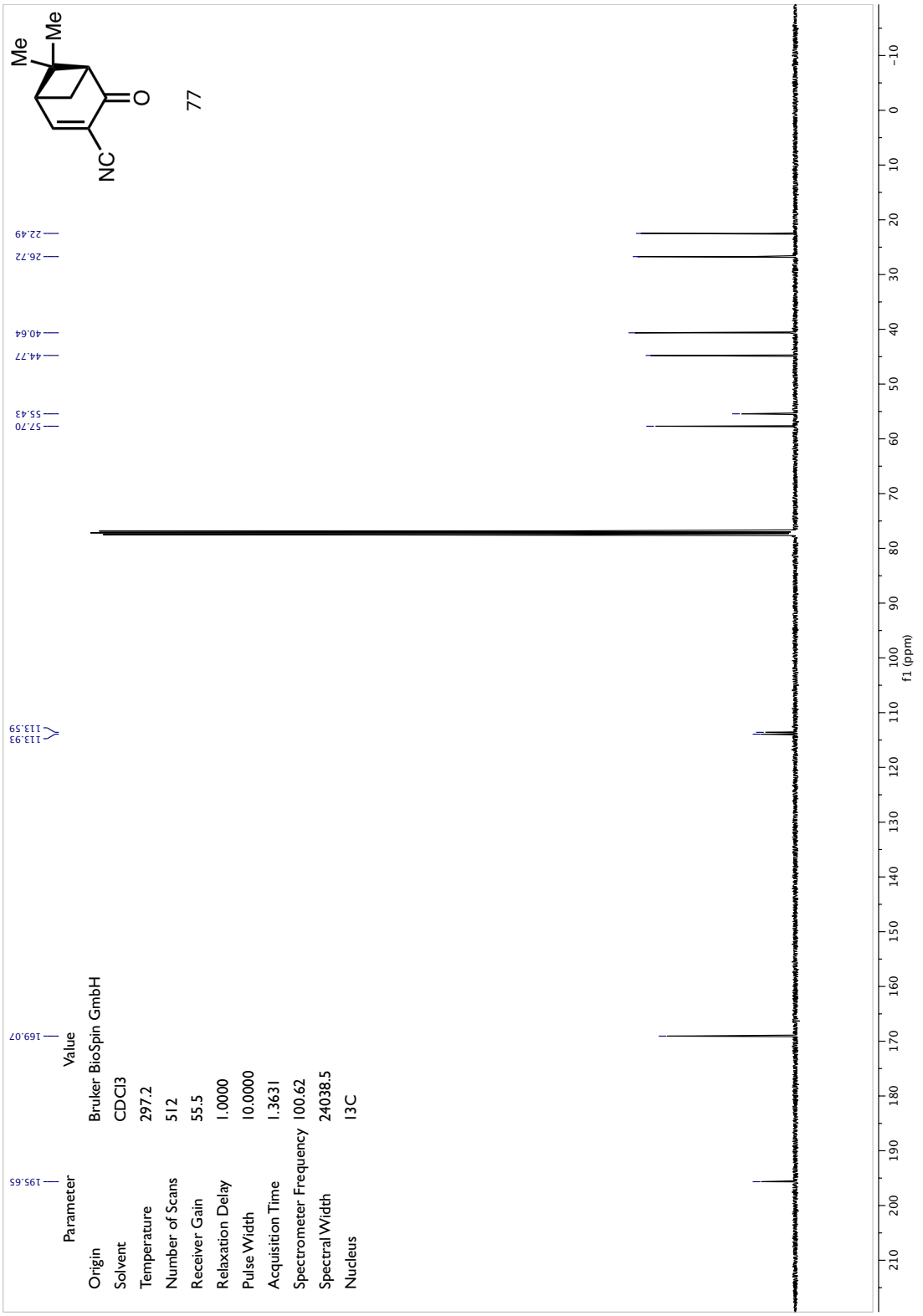

Me
Me
O
OH
74
3.26
3.31
1.12
1.00
1.14
3.08
0.96
f1 (ppm)
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 16
Receiver Gain 44
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Spectrometer Frequency 499.64
Spectral Width 8000.0
Nucleus 1H

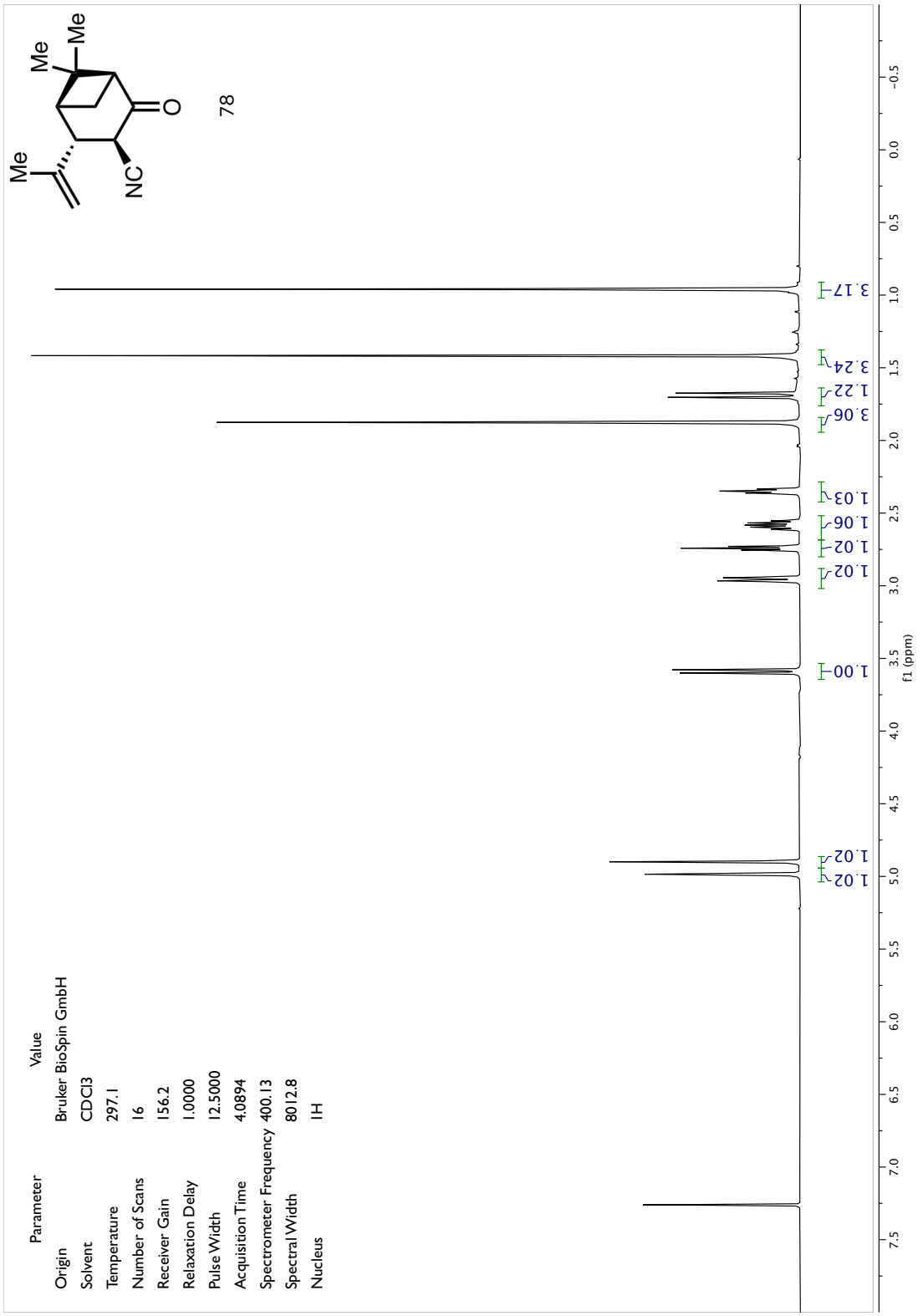

Me
Me
O
NC
76
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.00
3.00
0.96
0.99
0.99
0.99
0.98
0.94
0.94
f1 (ppm)

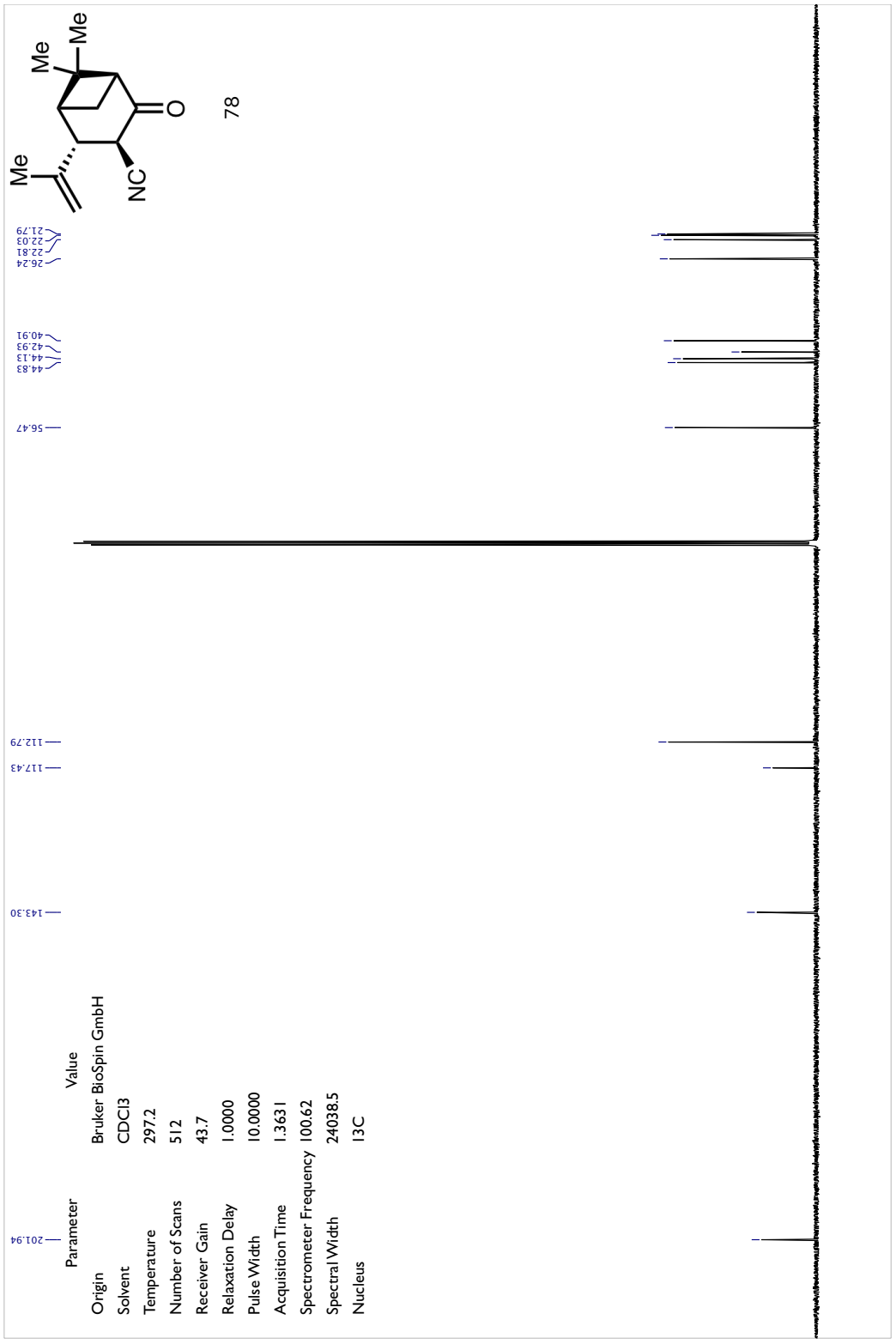


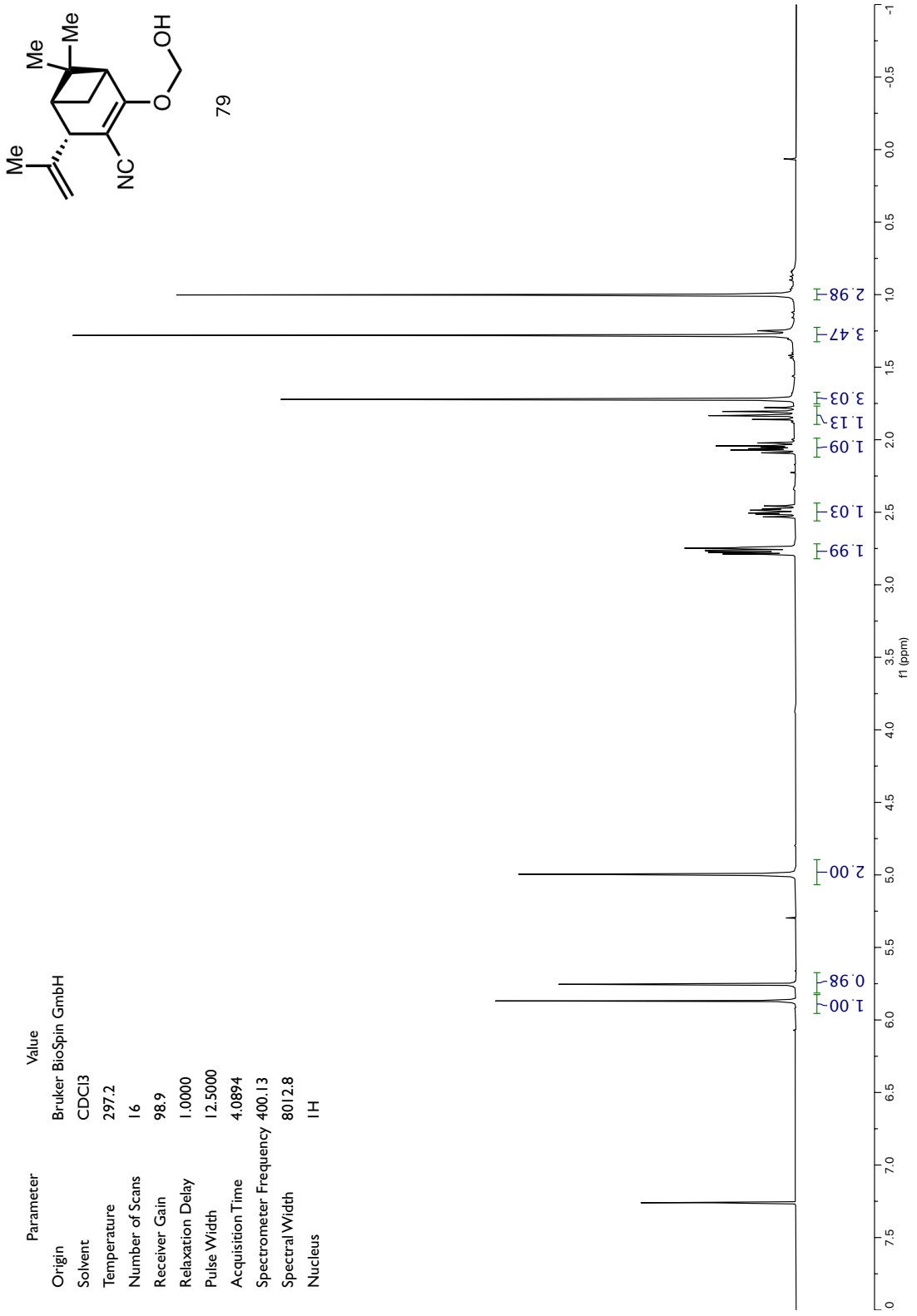
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

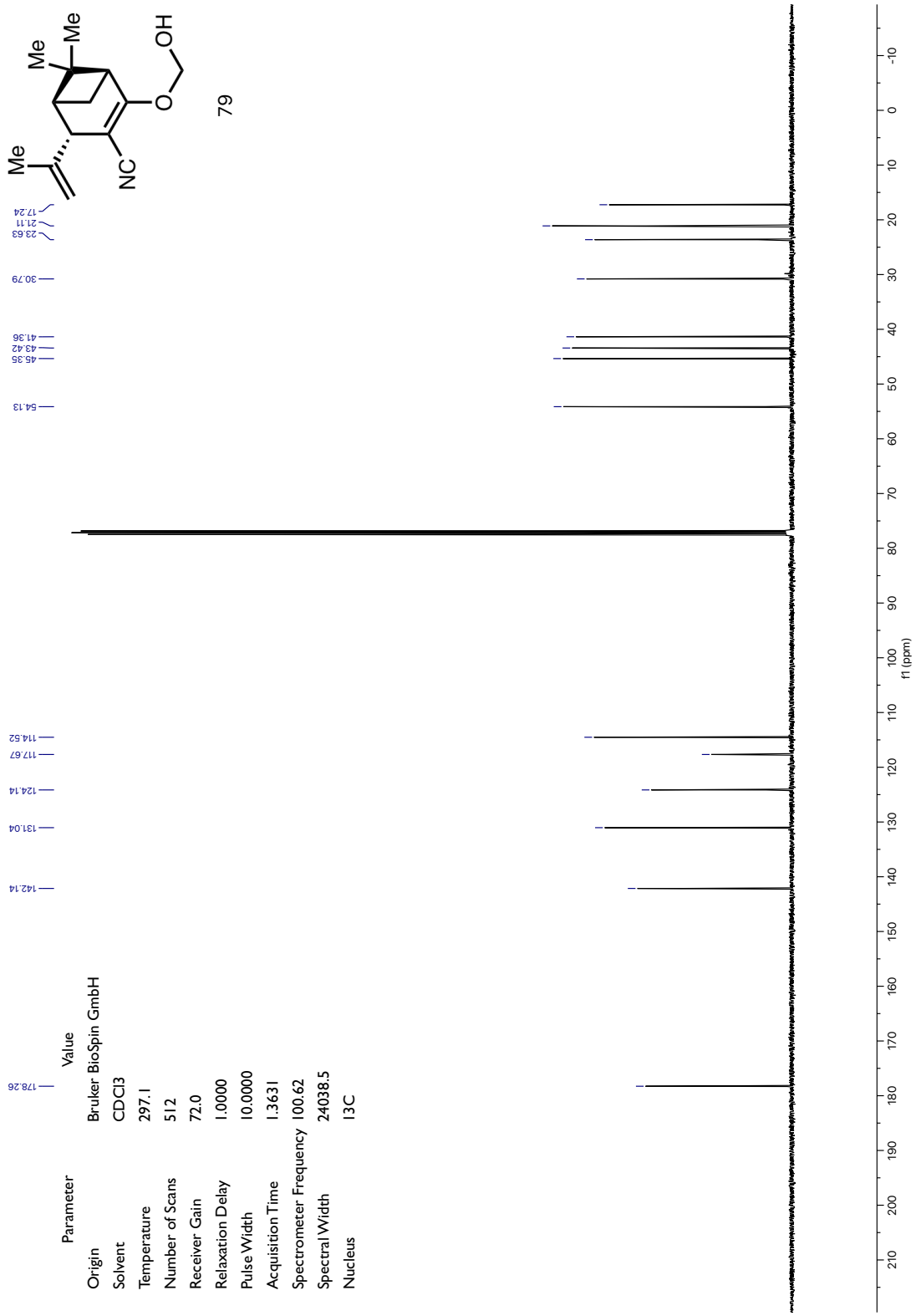

Me
Me
O
NC
77
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
1.00
3.13
3.16
1.04
1.03
1.00
1.06
f1 (ppm)


Me
Me
O
NC
77
195.65
169.07
113.93
113.59
57.70
55.43
44.77
40.64
26.72
22.49
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

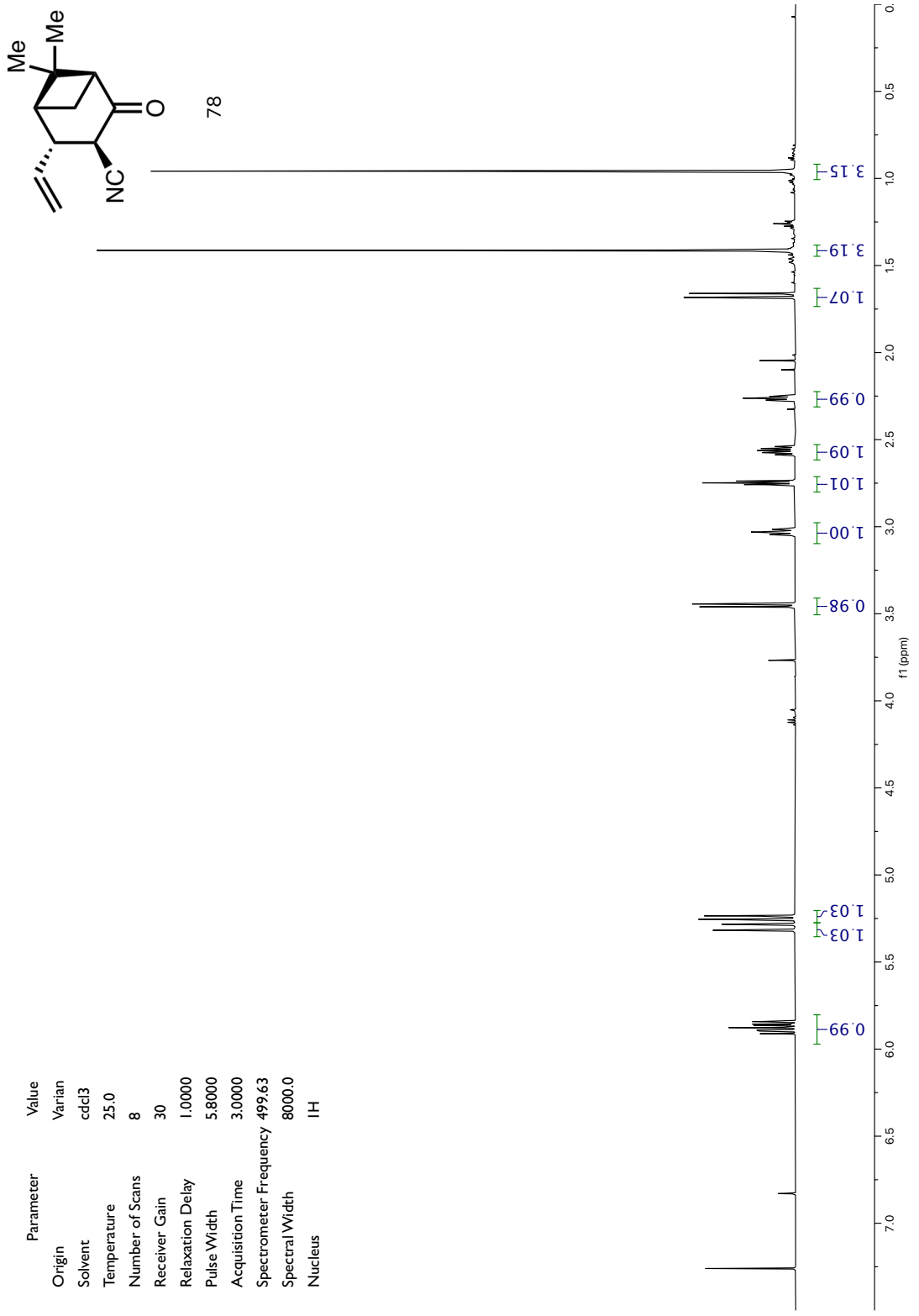

Me
Me
Me
NC
O
78
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.17
3.24
1.22
3.06
1.03
1.06
1.02
1.02
1.00
1.02
1.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

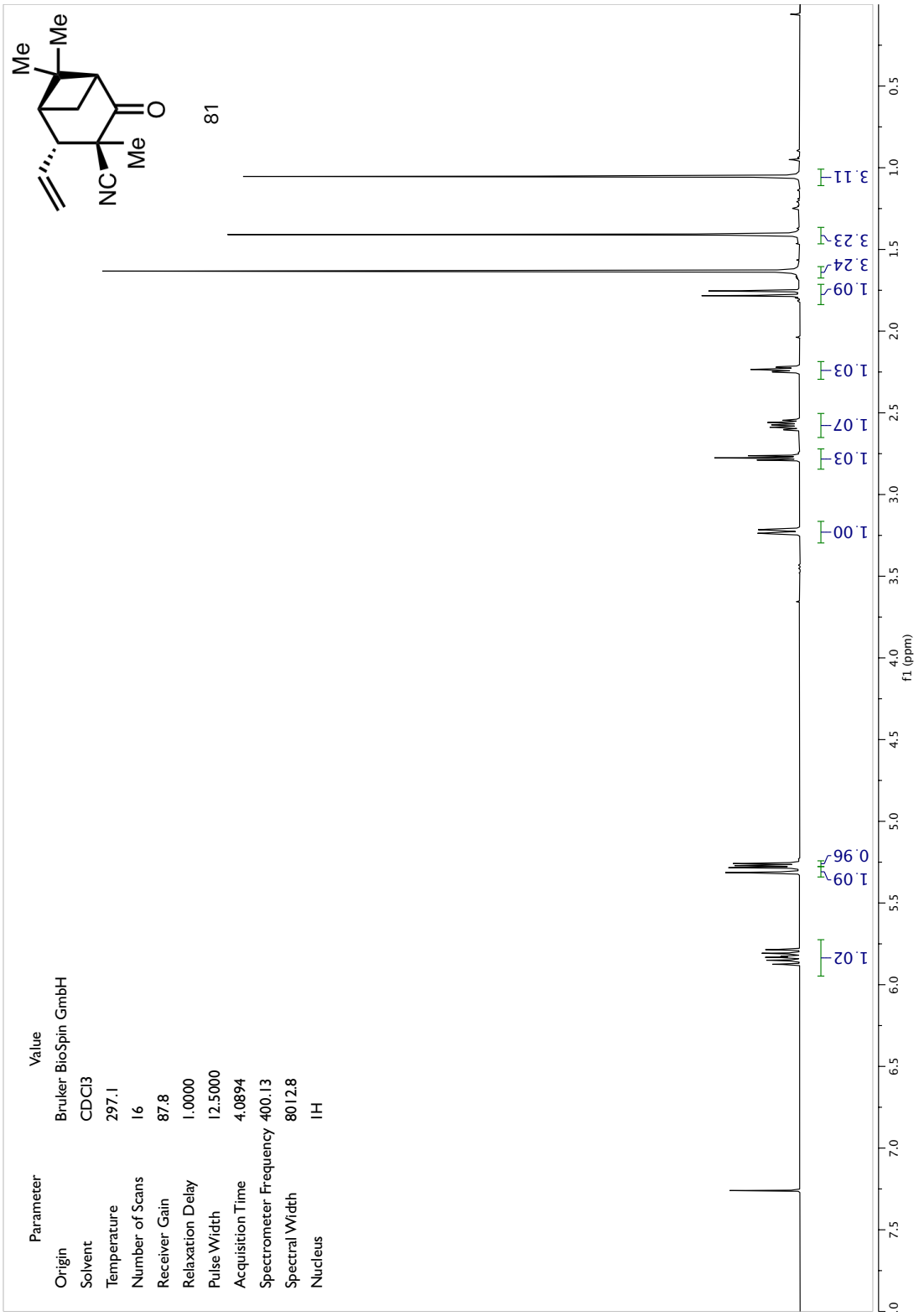

Me
Me
Me
NC
O
78
201.94
143.30
117.43
112.79
56.47
44.83
44.13
42.93
40.91
26.24
22.81
22.03
21.79
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

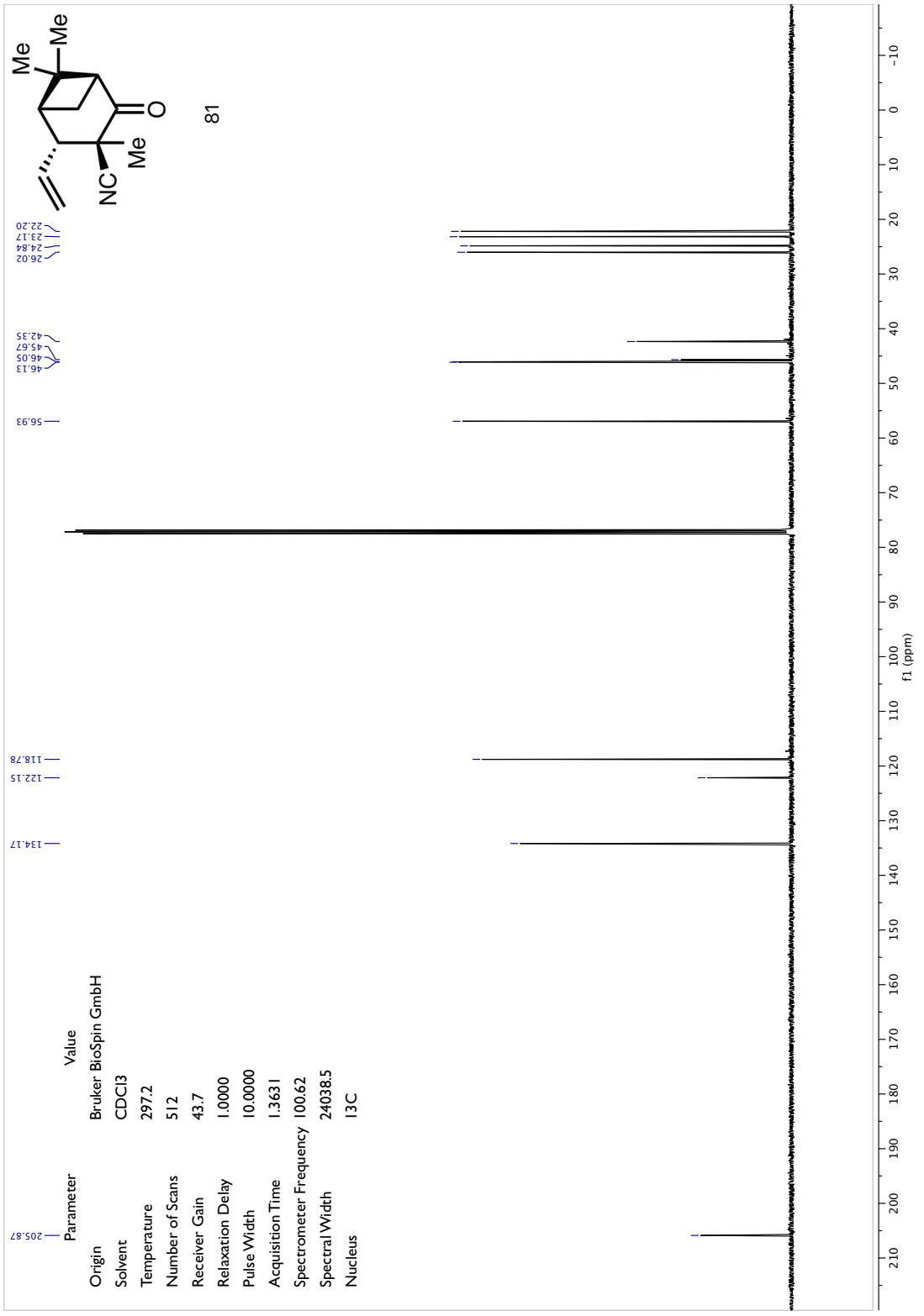

Me
Me
Me
NC
O
OH
79
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
16
Receiver Gain
98.9
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
2.98
3.47
3.03
1.13
1.09
1.03
1.99
2.00
0.98
1.00
f1 (ppm)

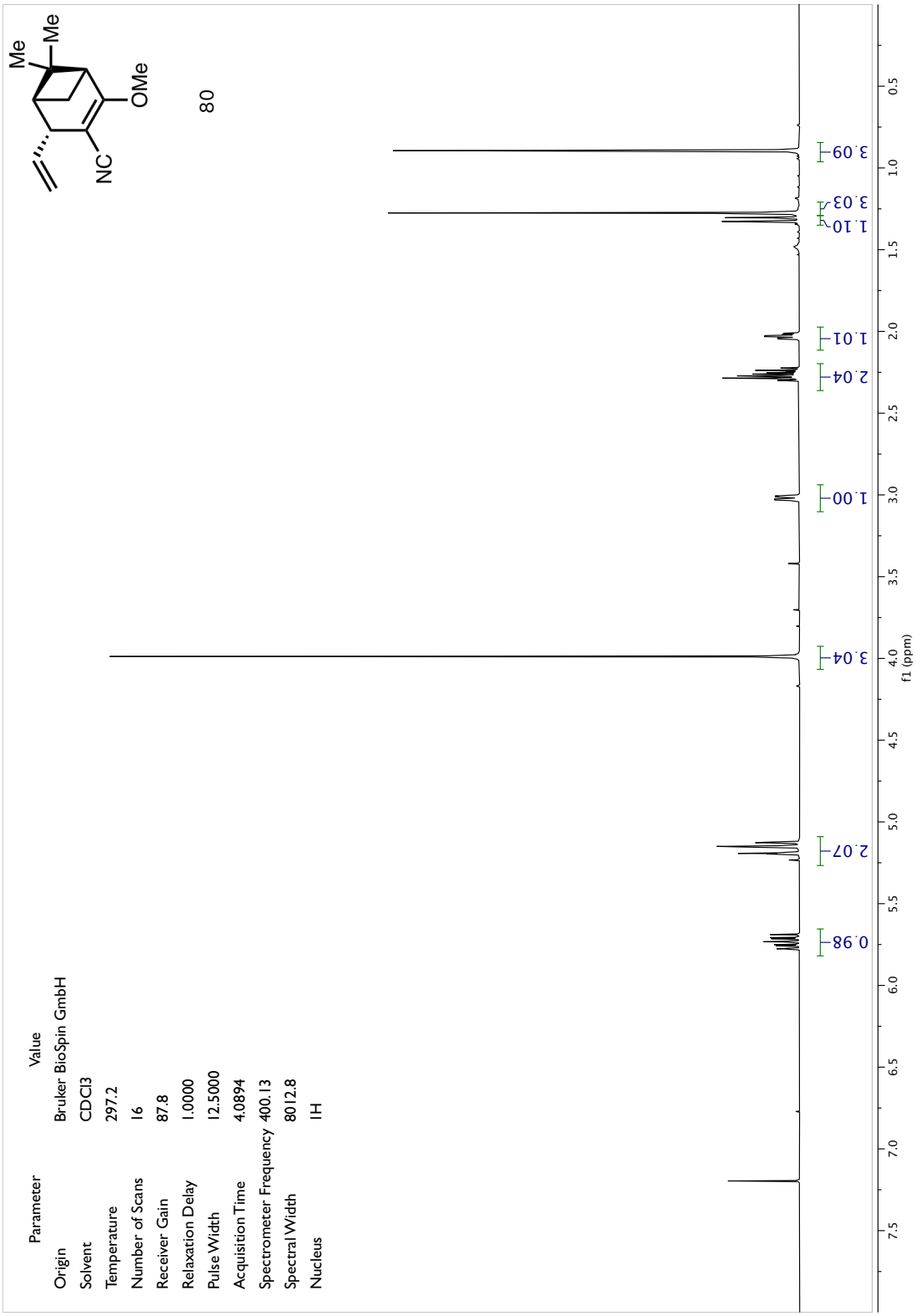


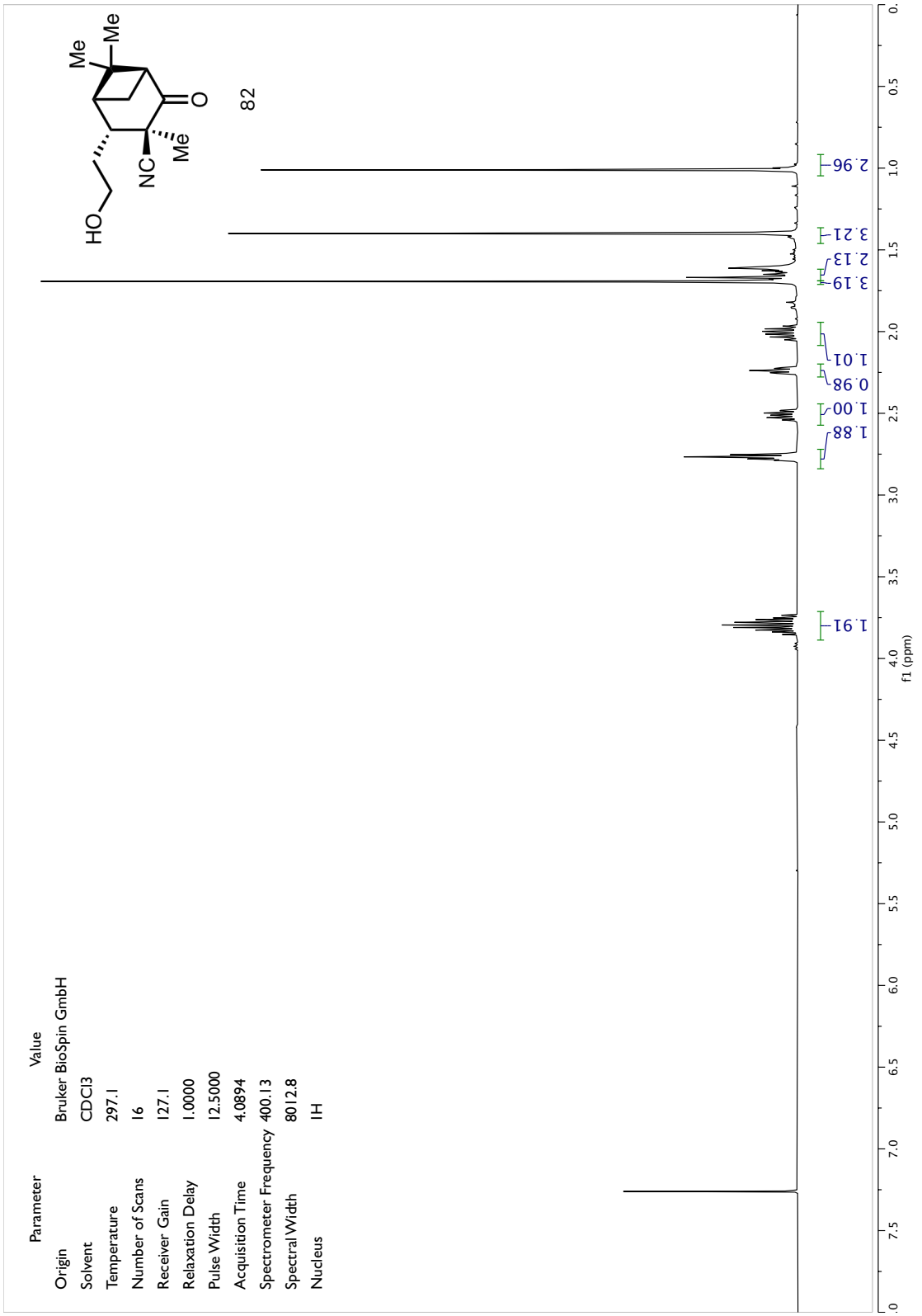
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

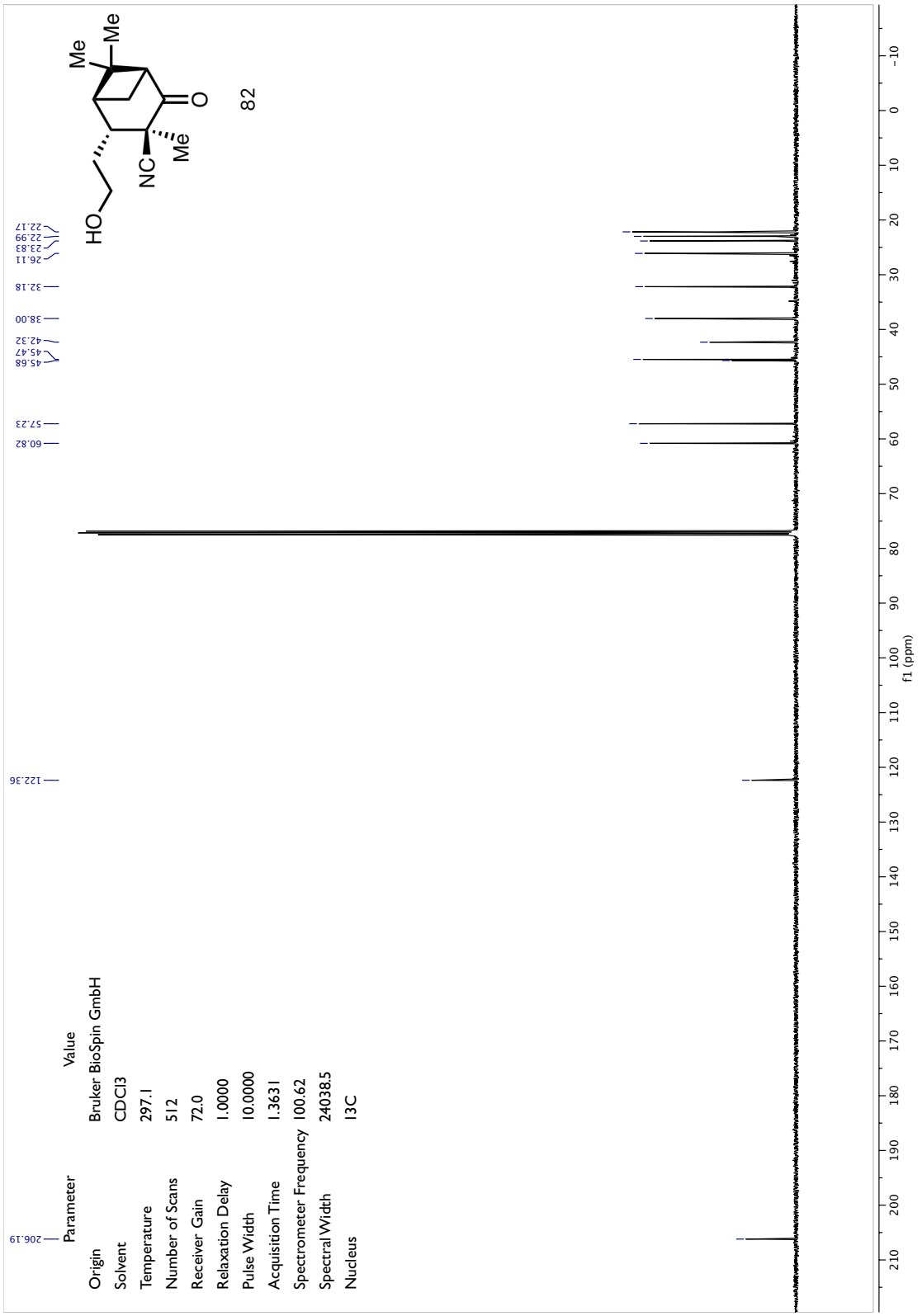

Me
Me
O
NC
78
3.15
3.19
1.07
0.99
1.09
1.01
1.00
0.98
1.03
1.03
0.99
f1 (ppm)
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 8
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Spectrometer Frequency 499.63
Spectral Width 8000.0
Nucleus 1H

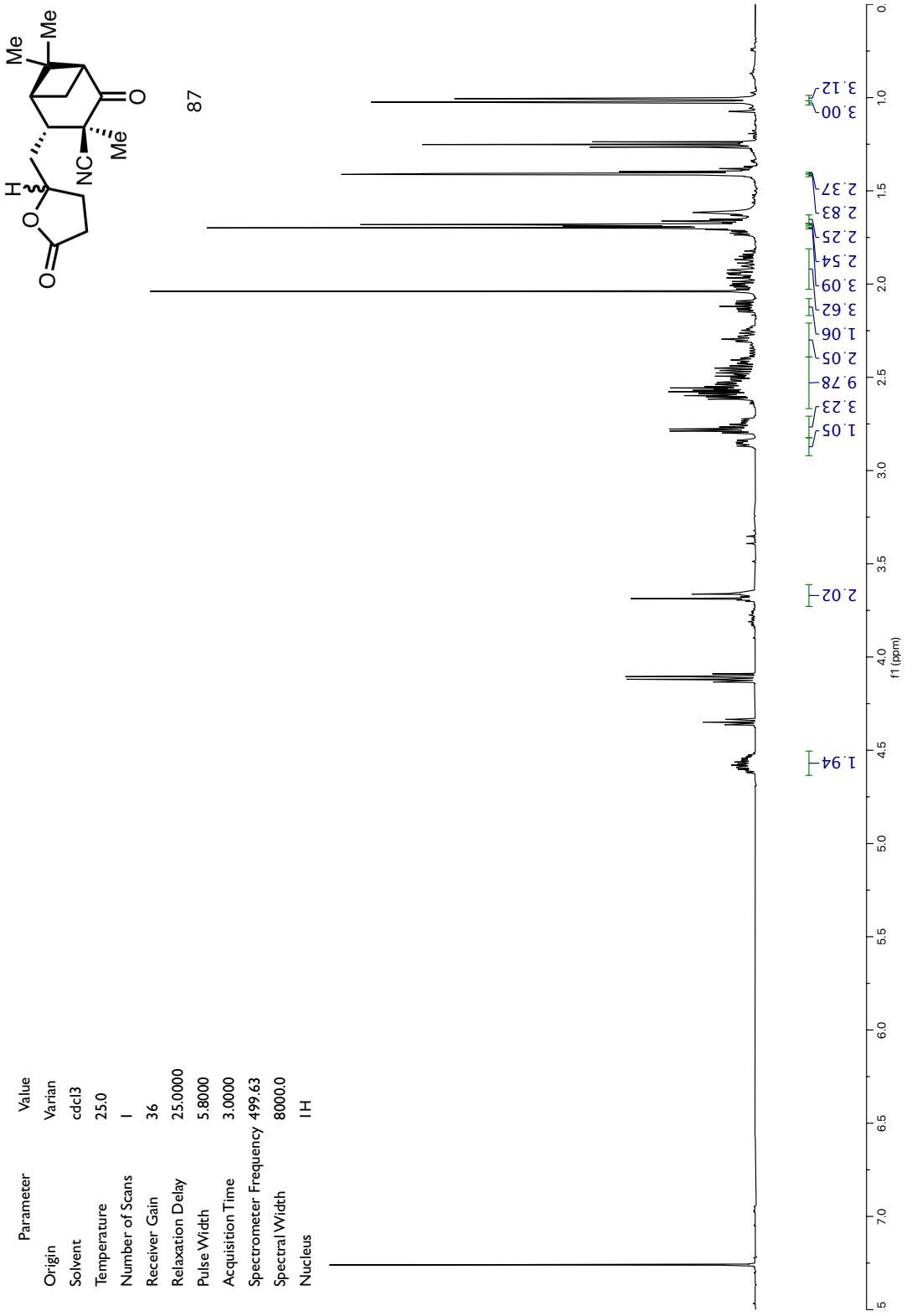

Me
Me
O
Me
NC
81
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.11
3.23
3.24
1.09
1.03
1.07
1.03
1.00
1.09
0.96
1.02
f1 (ppm)

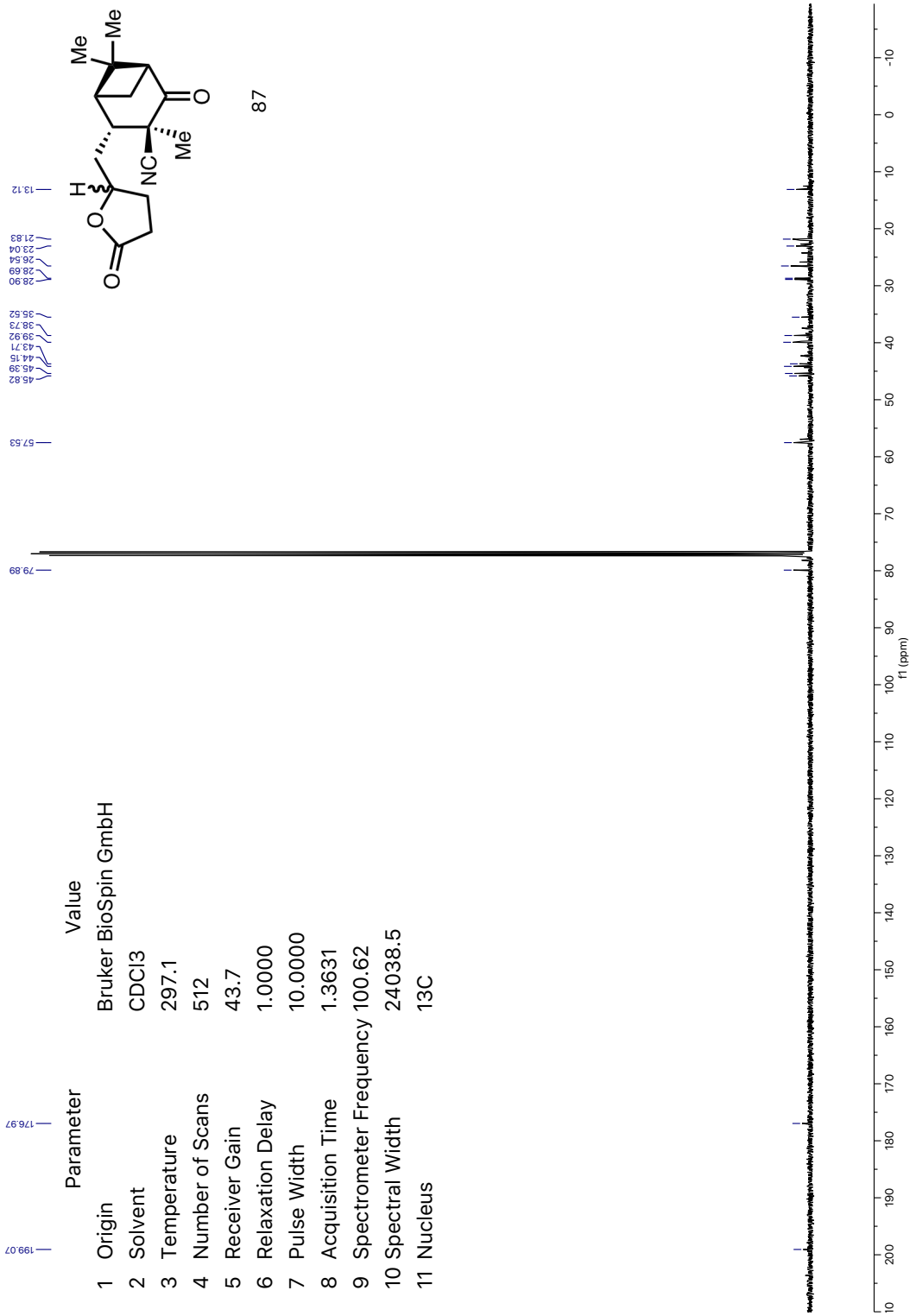

Me
Me
O
Me
NC
81
205.87
134.17
122.15
118.78
56.93
46.13
46.05
45.67
42.35
26.02
24.84
23.17
22.20
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)


Me
Me
OMe
NC
80
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.09
3.03
1.10
1.01
2.04
1.00
3.04
2.07
0.98
f1 (ppm)

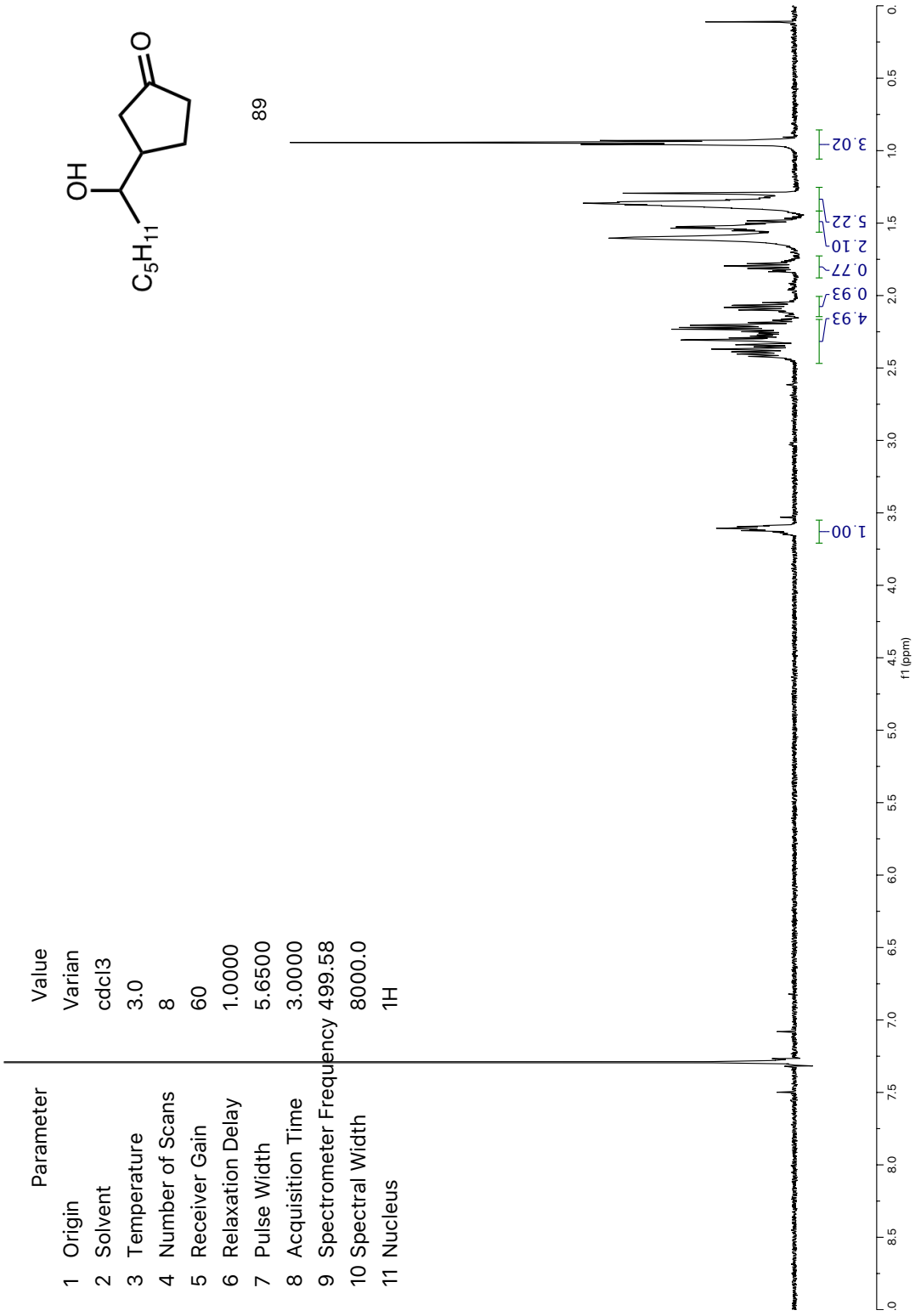

Me
Me
O
Me
NC
HO
82
2.96
3.21
2.13
3.19
1.01
0.98
1.00
1.88
1.91
f1 (ppm)
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
127.1
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H


Me
Me
O
NC
Me
HO
82
206.19
122.36
60.82
57.23
45.68
45.47
42.32
38.00
32.18
26.11
23.83
22.99
22.17
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
512
Receiver Gain
72.0
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)

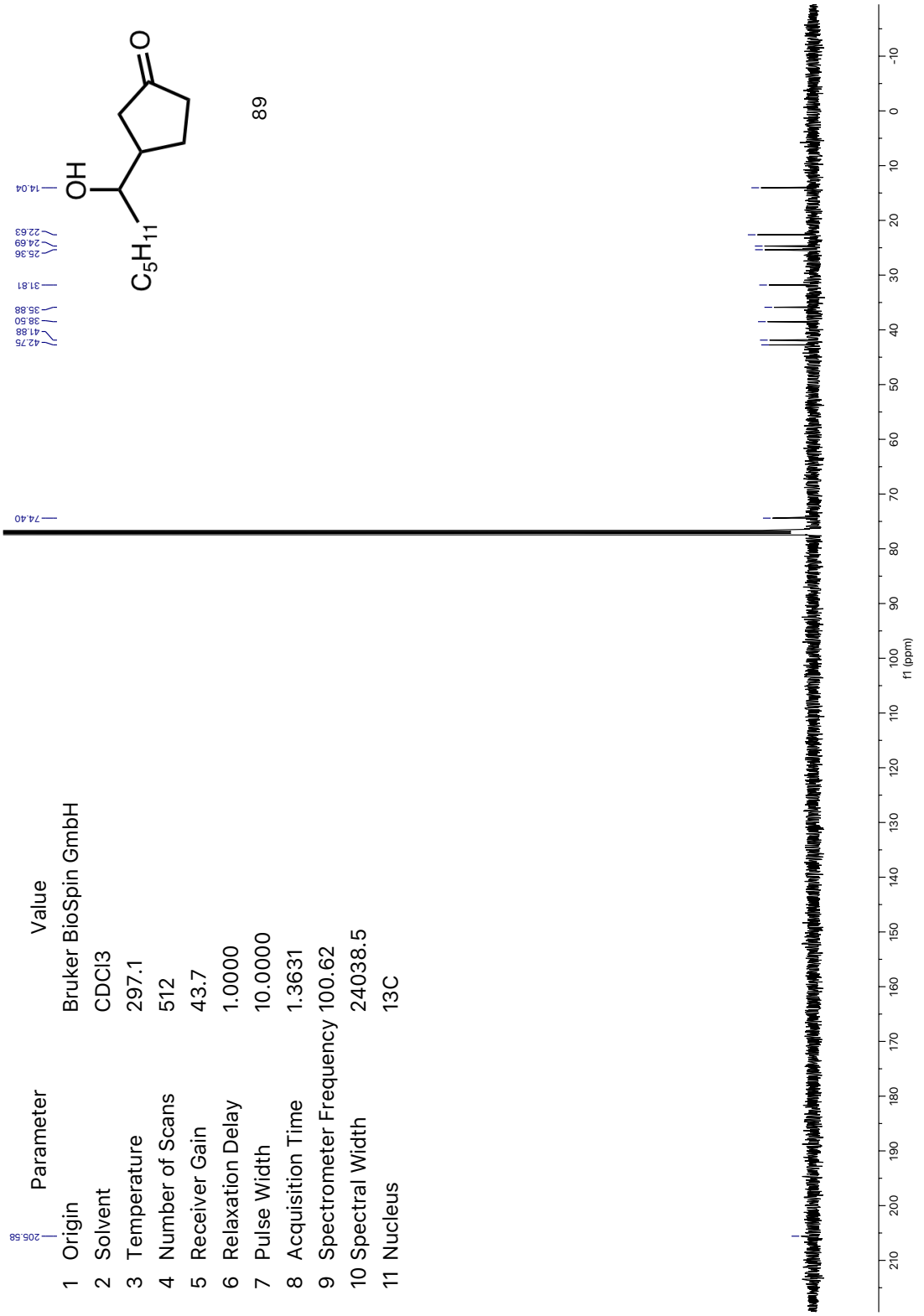

Me
Me
O
Me
NC
H
O
O
87
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 1
Receiver Gain 36
Relaxation Delay 25.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Spectrometer Frequency 499.63
Spectral Width 8000.0
Nucleus 1H
3.12
3.00
2.37
2.83
2.25
2.54
3.09
3.62
1.06
2.05
9.78
3.23
1.05
2.02
1.94
f1 (ppm)



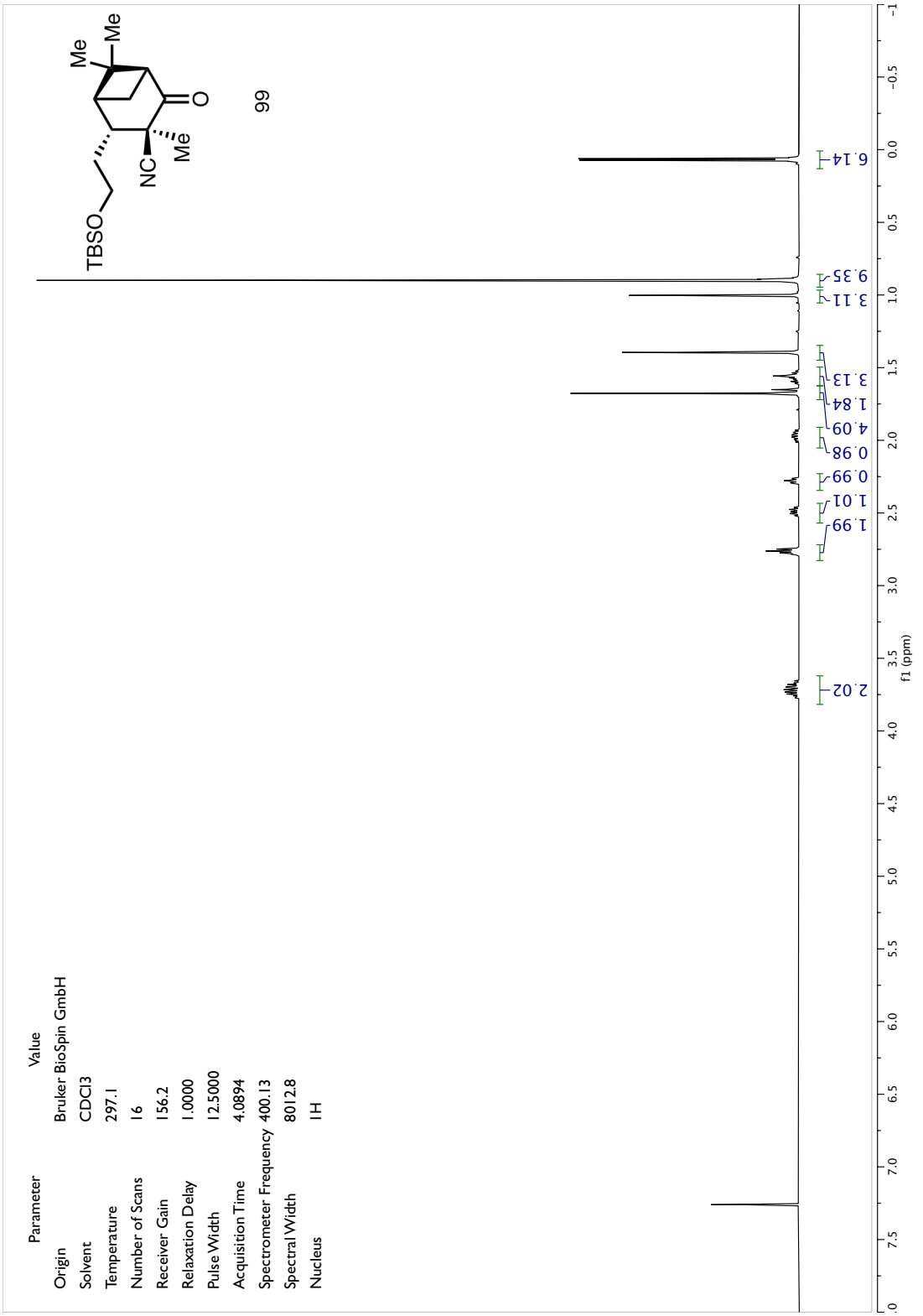
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl3
3 Temperature	297.1
4 Number of Scans	512
5 Receiver Gain	43.7
6 Relaxation Delay	1.0000
7 Pulse Width	10.0000
8 Acquisition Time	1.3631
9 Spectrometer Frequency	100.62
10 Spectral Width	24038.5
11 Nucleus	13C

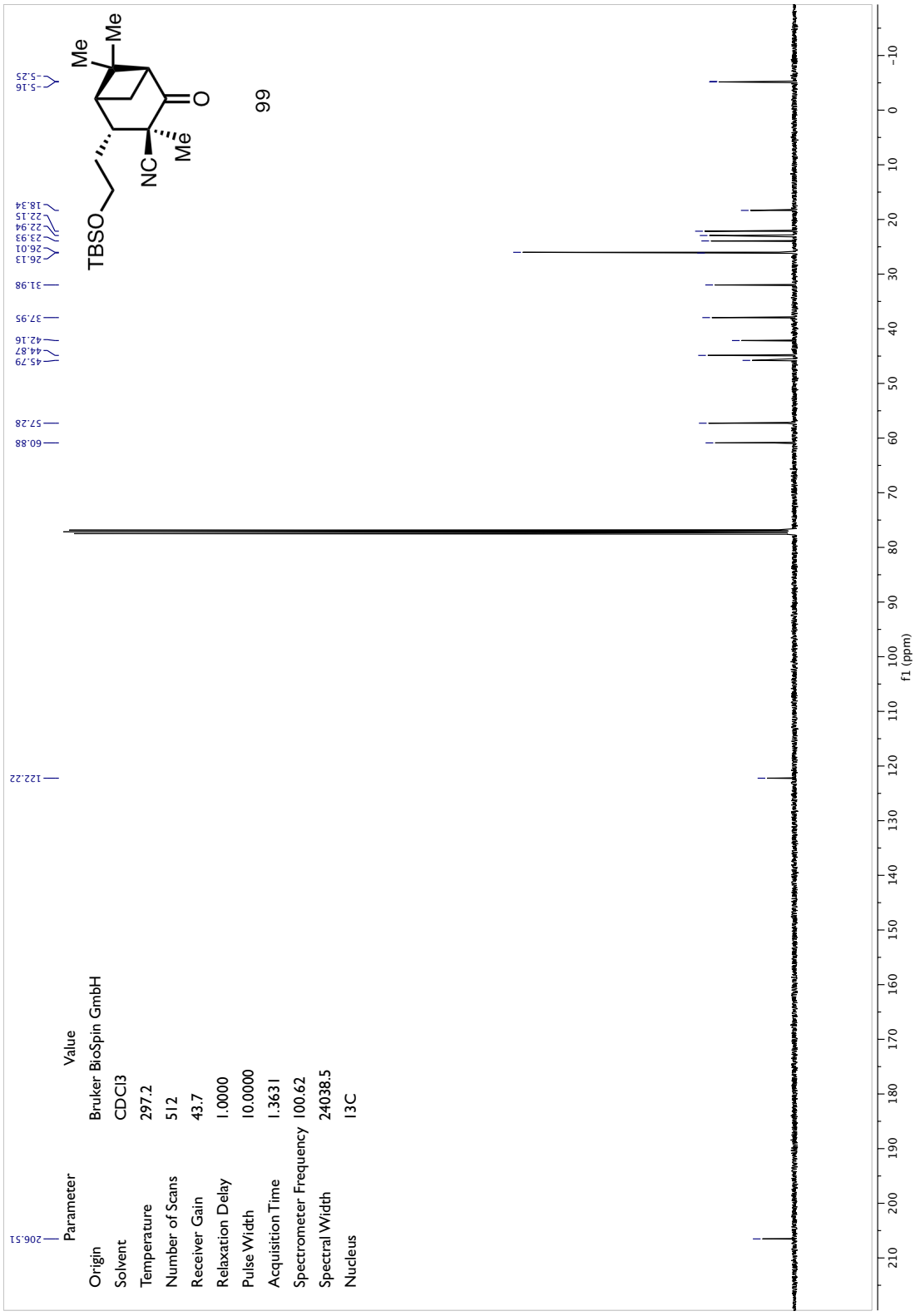


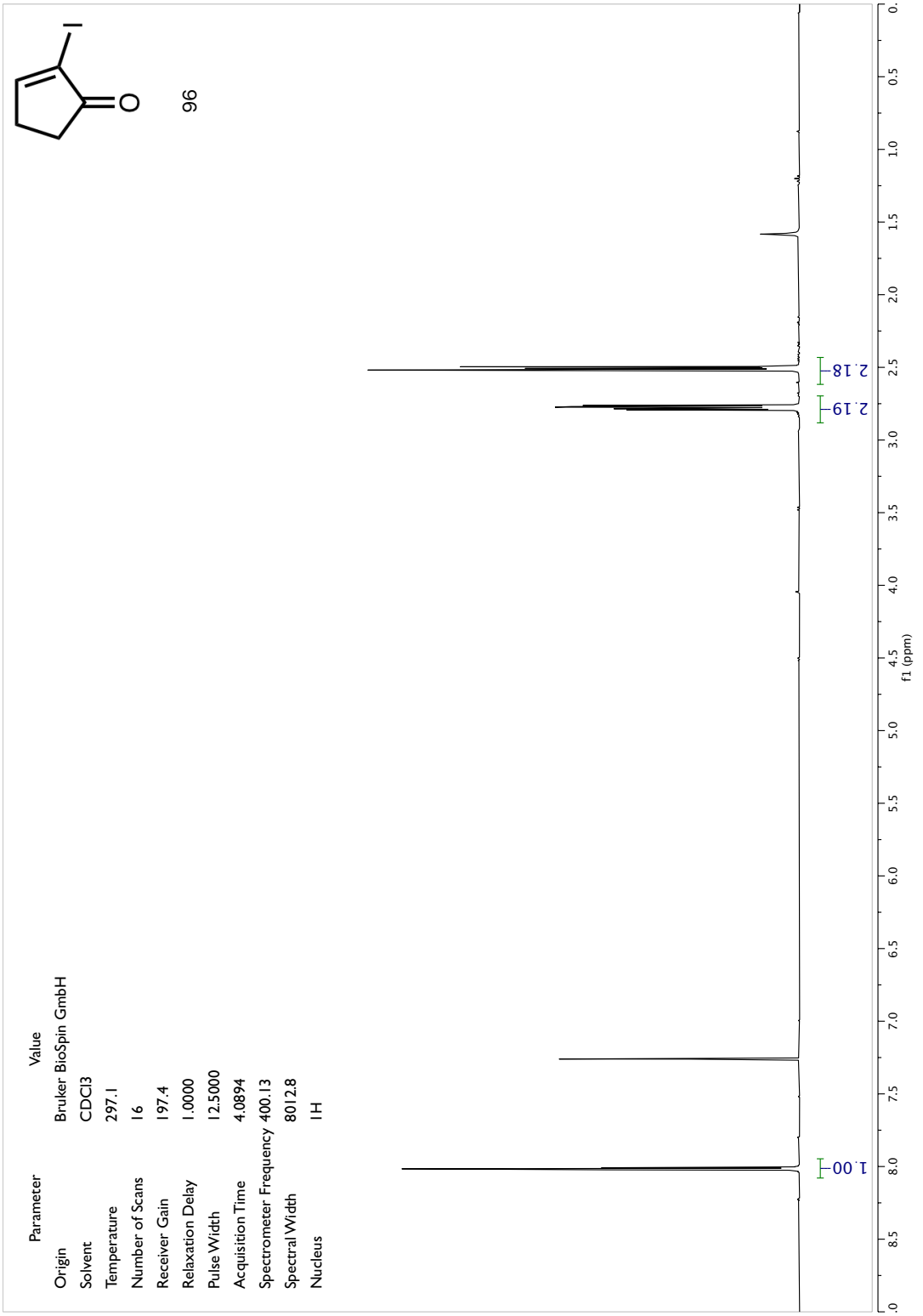
Parameter	Value
1 Origin	Varian
2 Solvent	cdcl3
3 Temperature	3.0
4 Number of Scans	8
5 Receiver Gain	60
6 Relaxation Delay	1.0000
7 Pulse Width	5.6500
8 Acquisition Time	3.0000
9 Spectrometer Frequency	499.58
10 Spectral Width	8000.0
11 Nucleus	1H

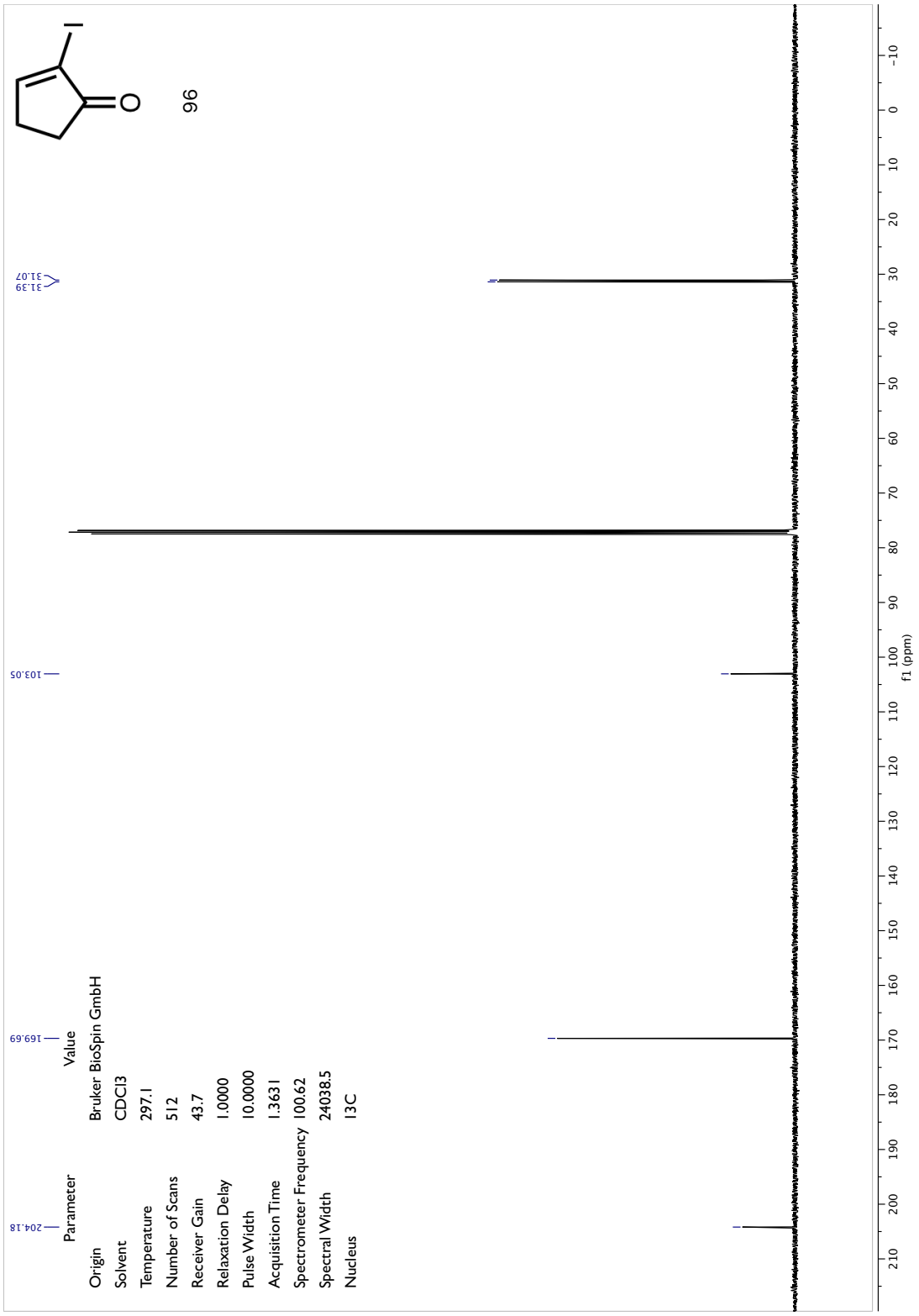


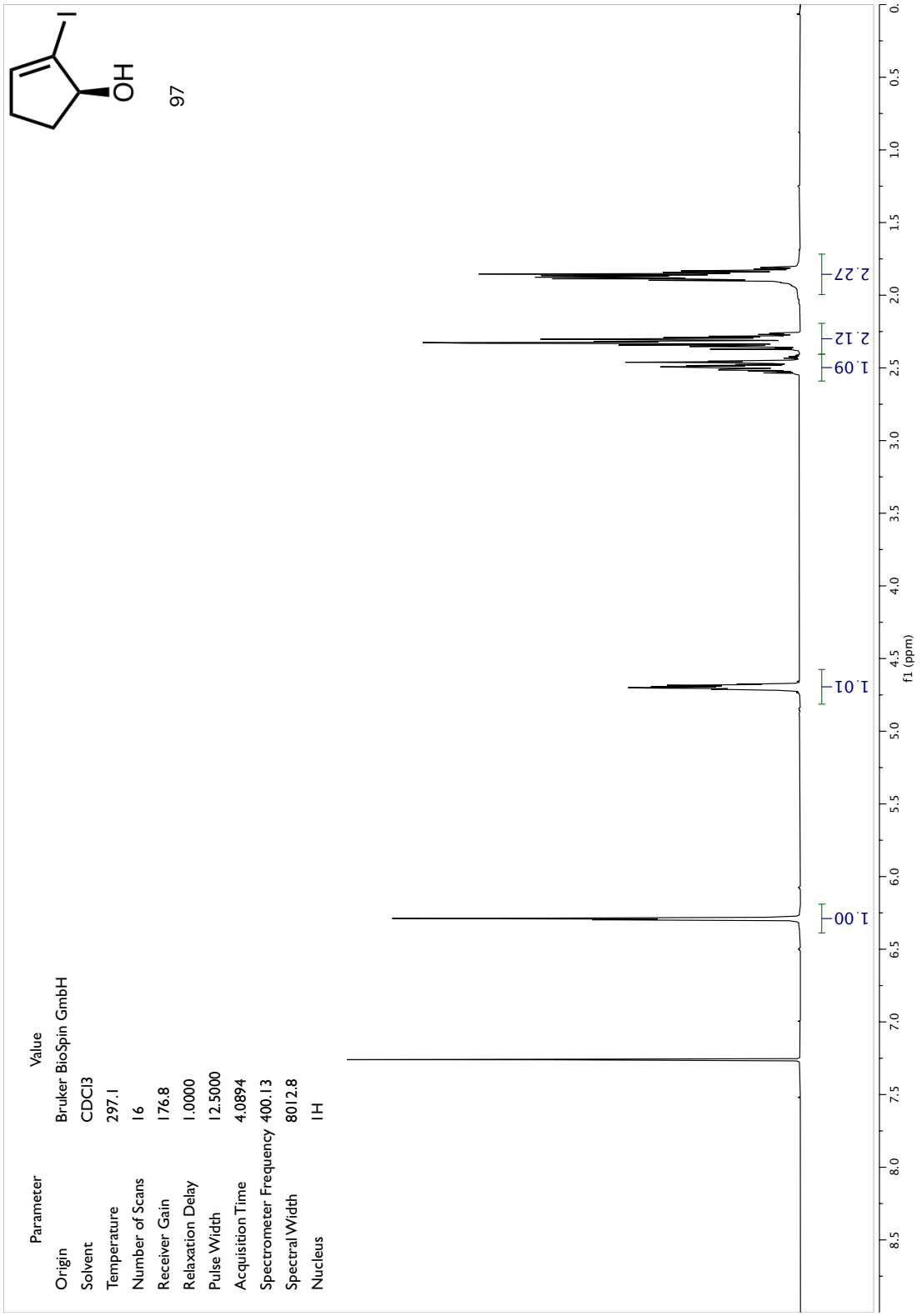
	Parameter	Value
1	Origin	Bruker BioSpin GmbH
2	Solvent	CDCl3
3	Temperature	297.1
4	Number of Scans	512
5	Receiver Gain	43.7
6	Relaxation Delay	1.0000
7	Pulse Width	10.0000
8	Acquisition Time	1.3631
9	Spectrometer Frequency	100.62
10	Spectral Width	24038.5
11	Nucleus	13C

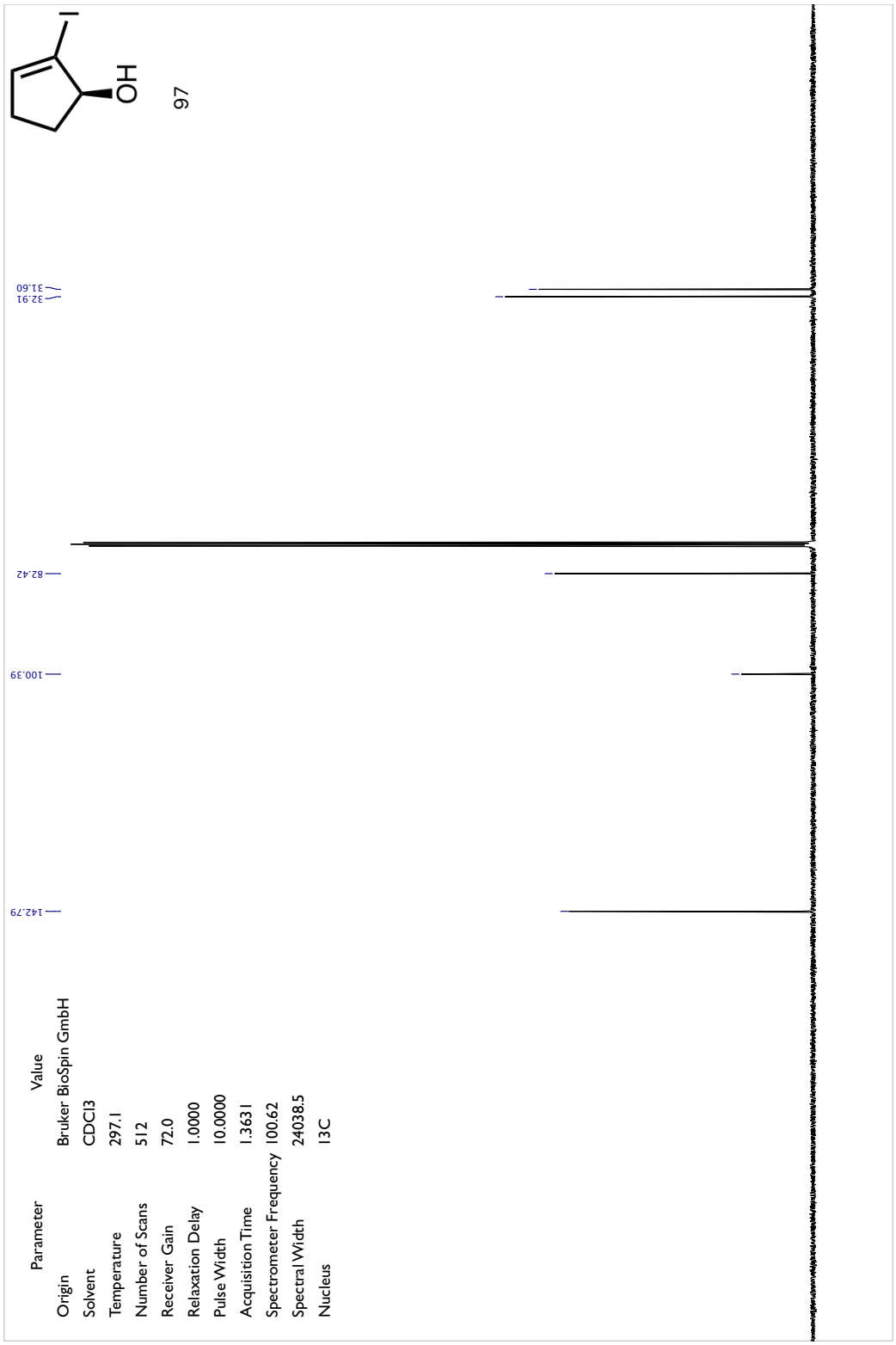

Me
Me
O
Me
NC
TBSO
99
6.14
9.35
3.11
3.13
1.84
4.09
0.98
0.99
1.01
1.99
2.02
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H

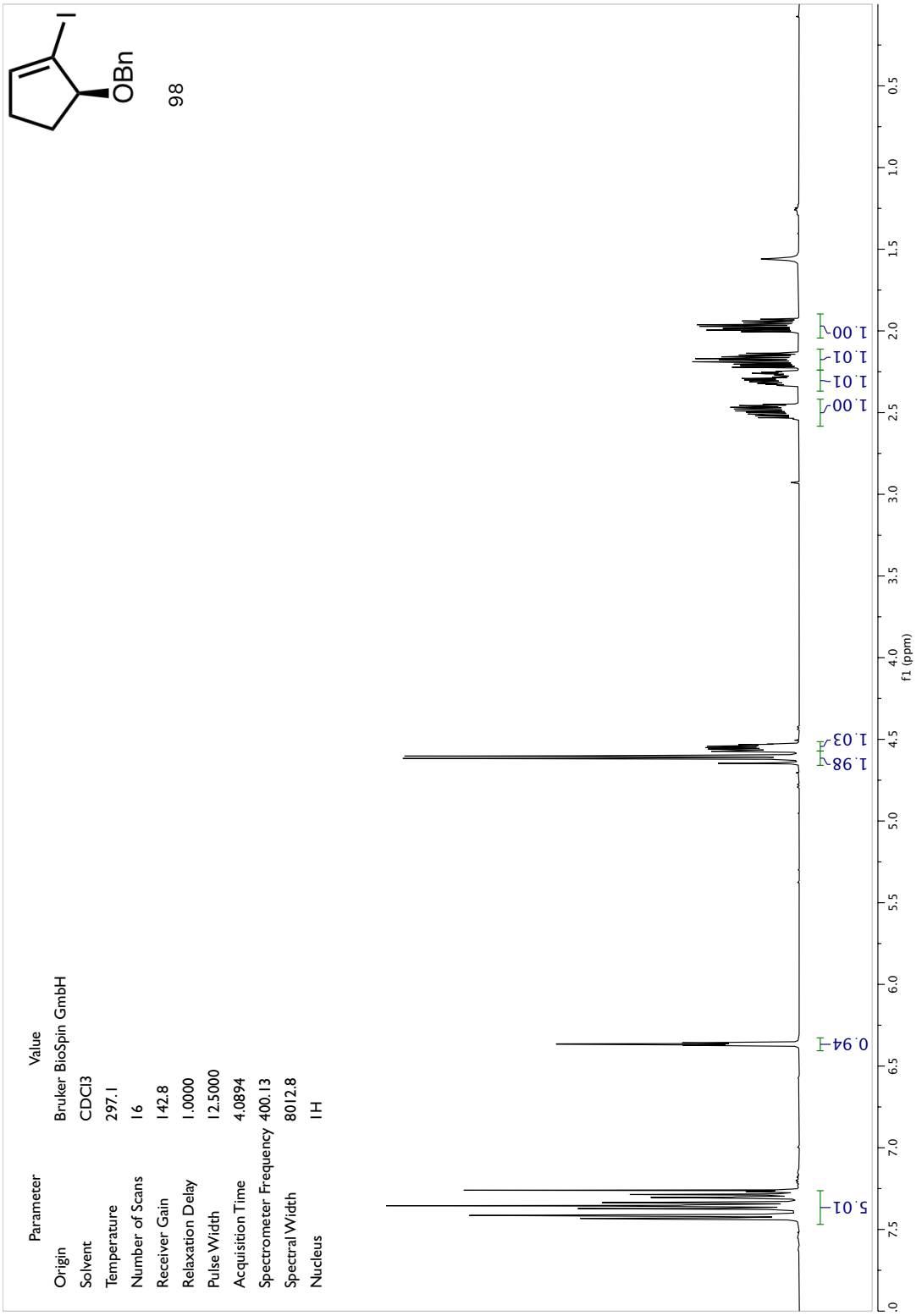

Me
Me
O
Me
NC
TBSO
99
-5.16
-5.25
18.34
22.15
22.94
23.93
26.01
26.13
31.98
37.95
42.16
44.87
45.79
57.28
60.88
122.22
206.51
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

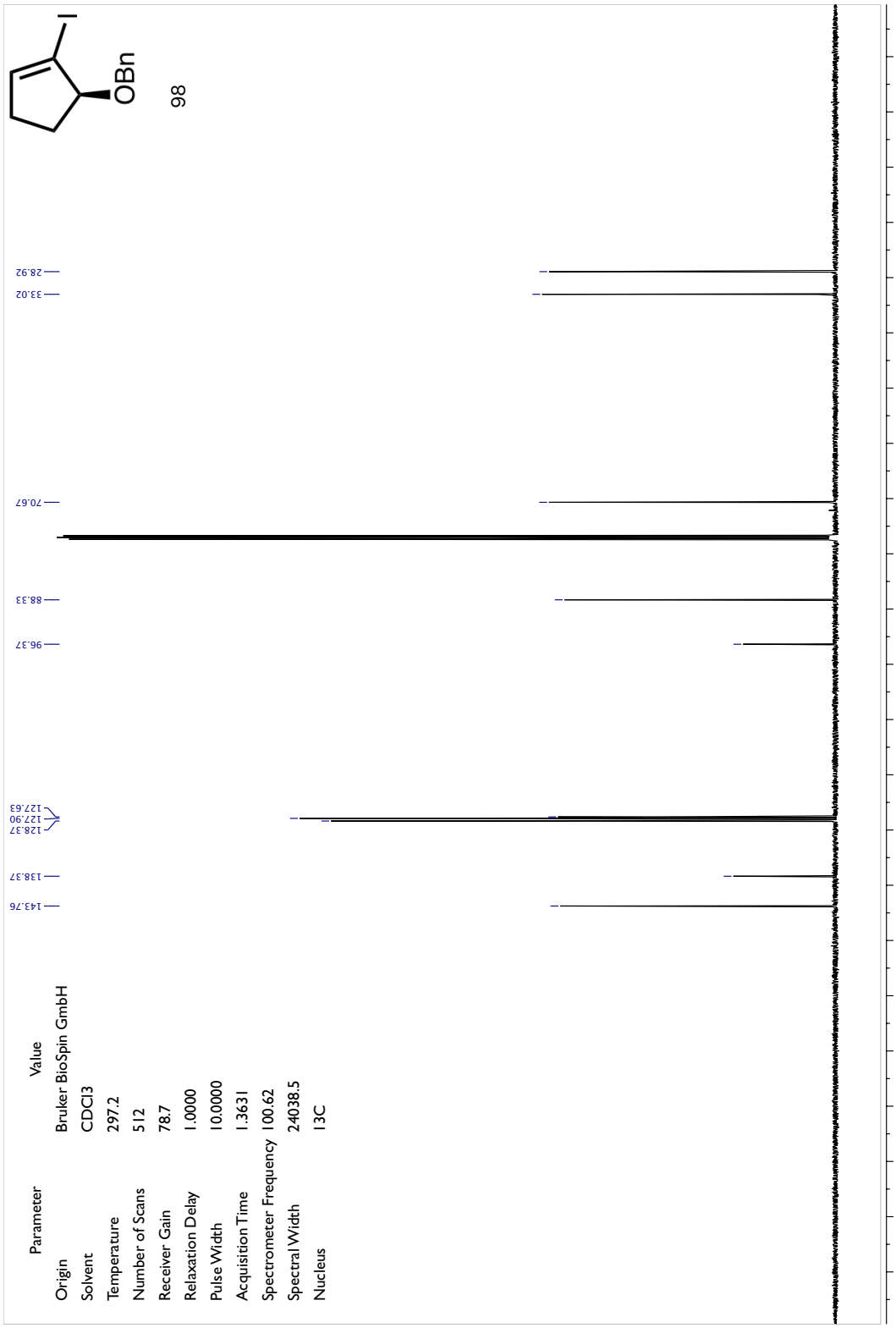

96
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
1.00
2.19
2.18
f1 (ppm)


96
204.18
169.69
103.05
31.39
31.07
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)


I
OH
97
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 176.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
1.00
1.01
1.09
2.12
2.27
f1 (ppm)


I
OH
97
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
142.79
100.39
82.42
32.91
31.60
f1 (ppm)


I
OBn
98
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
5.01
0.94
1.03
1.98
1.00
1.01
1.01
1.00
f1 (ppm)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OBn
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138.37
128.37
127.90
127.63
96.37
88.33
70.67
33.02
28.92
f1 (ppm)
Parameter Value
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Solvent CDCl3
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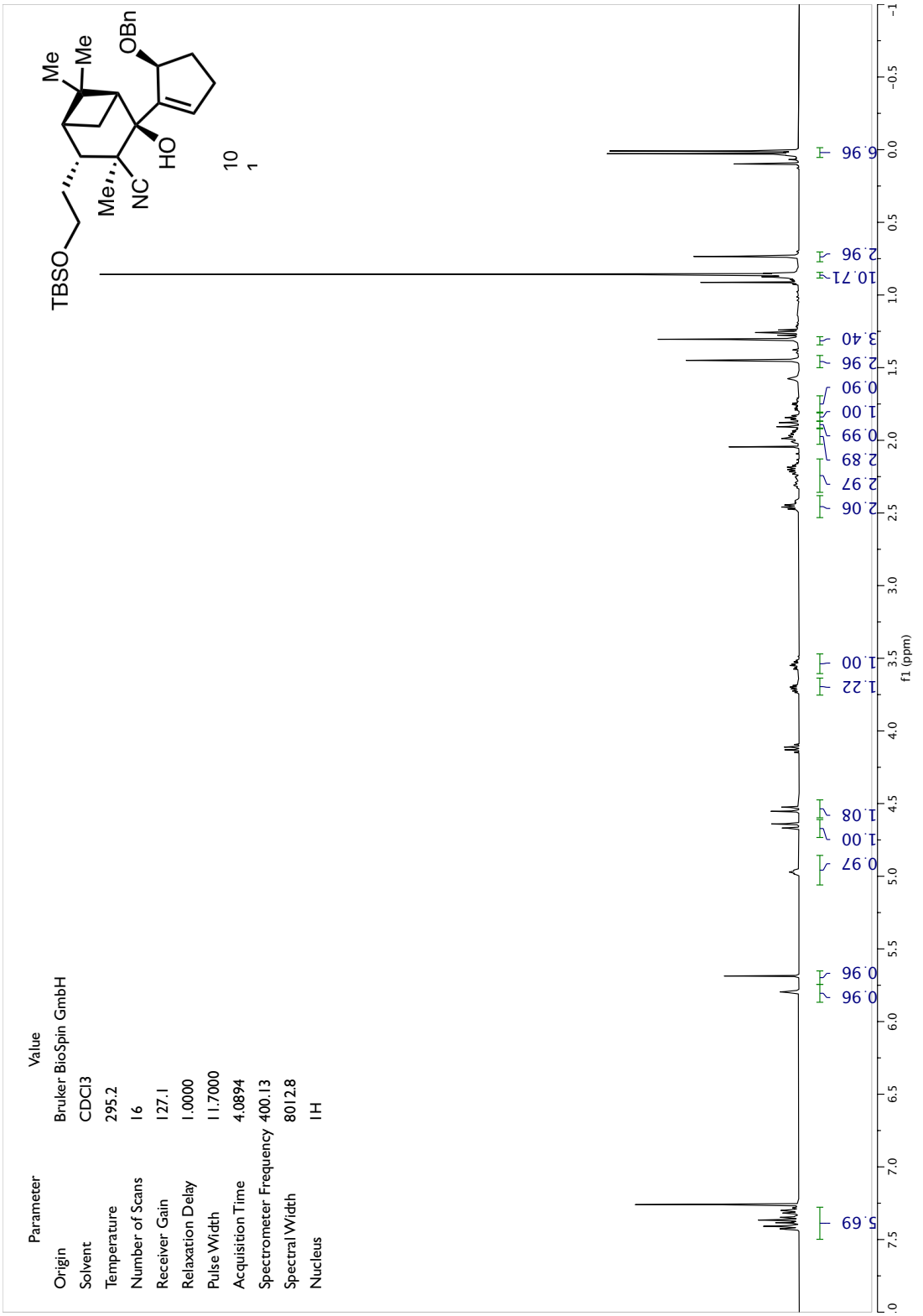
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C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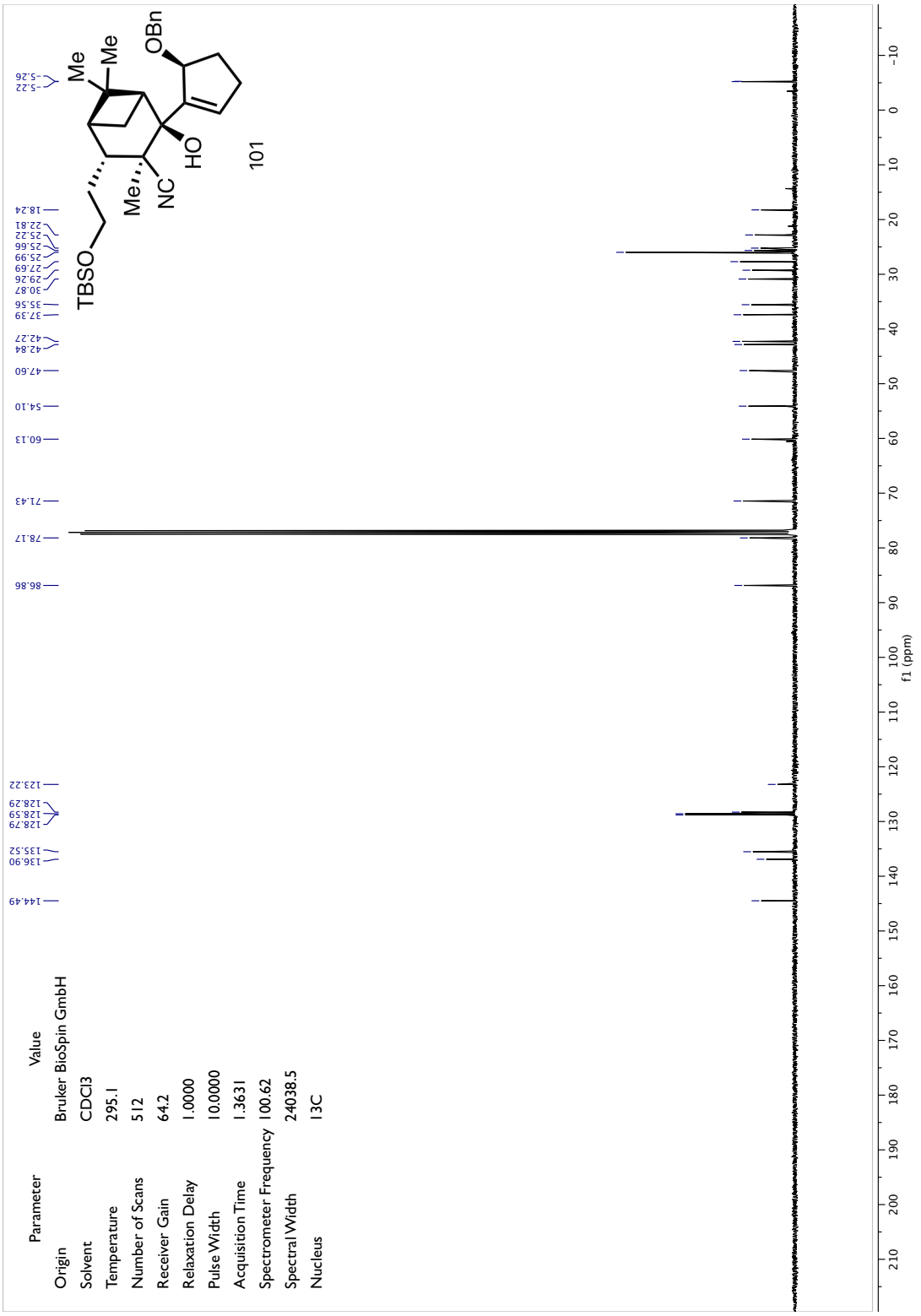
Me
OBn
TBSO
Me
NC
HO
10
1
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Number of Scans 16
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
6.96
2.96
10.71
3.40
2.96
0.90
1.00
0.99
2.89
2.97
2.06
1.00
1.22
1.08
1.00
0.97
0.96
0.96
5.69
f1 (ppm)


Me
Me
OBn
TBSO
Me
NC
HO
101
-5.26
-5.22
18.24
22.81
25.22
25.66
25.99
27.69
29.26
30.87
35.56
37.39
42.27
42.84
47.60
54.10
60.13
71.43
78.17
86.86
123.22
128.29
128.59
128.79
135.52
136.90
144.49
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
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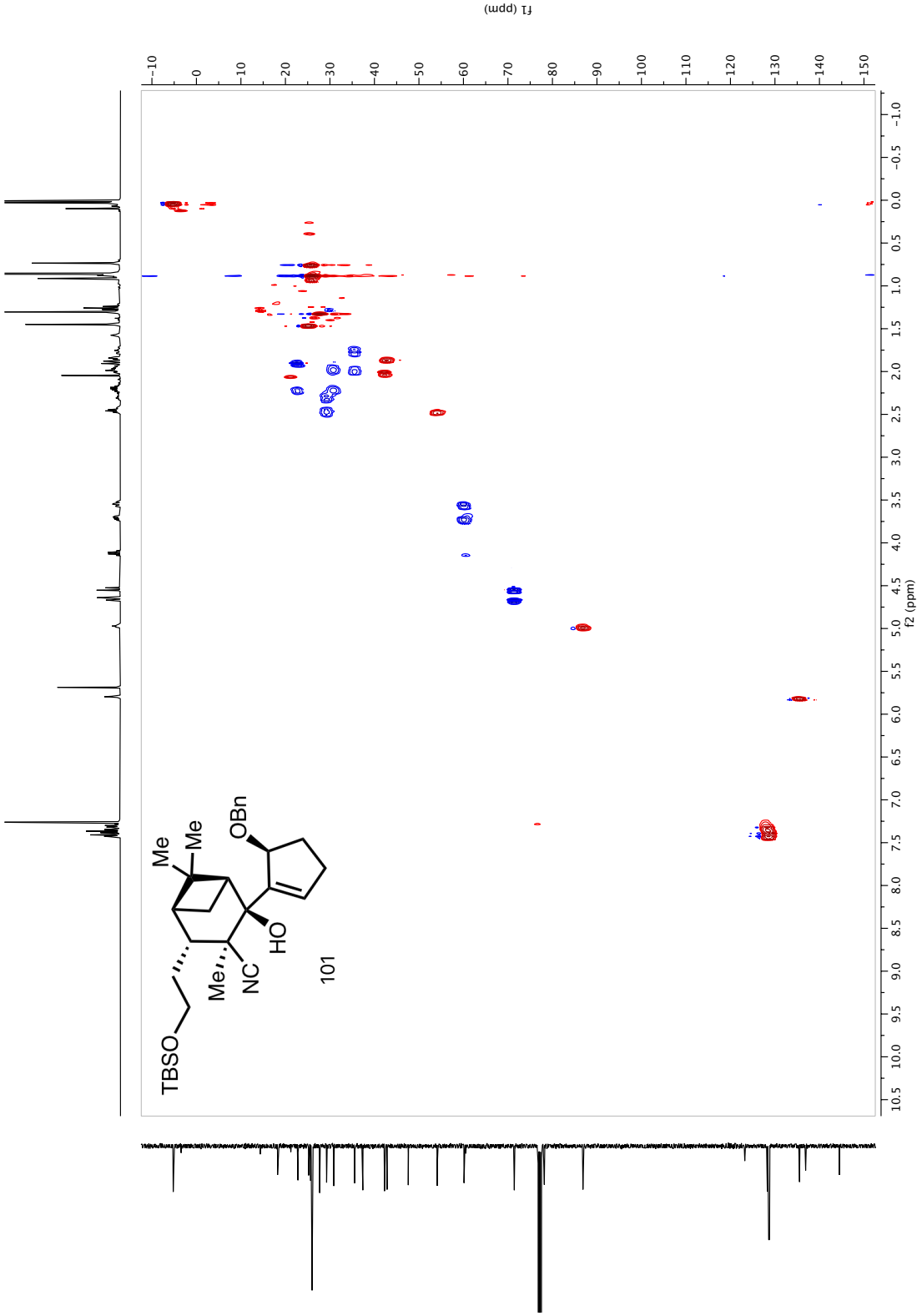
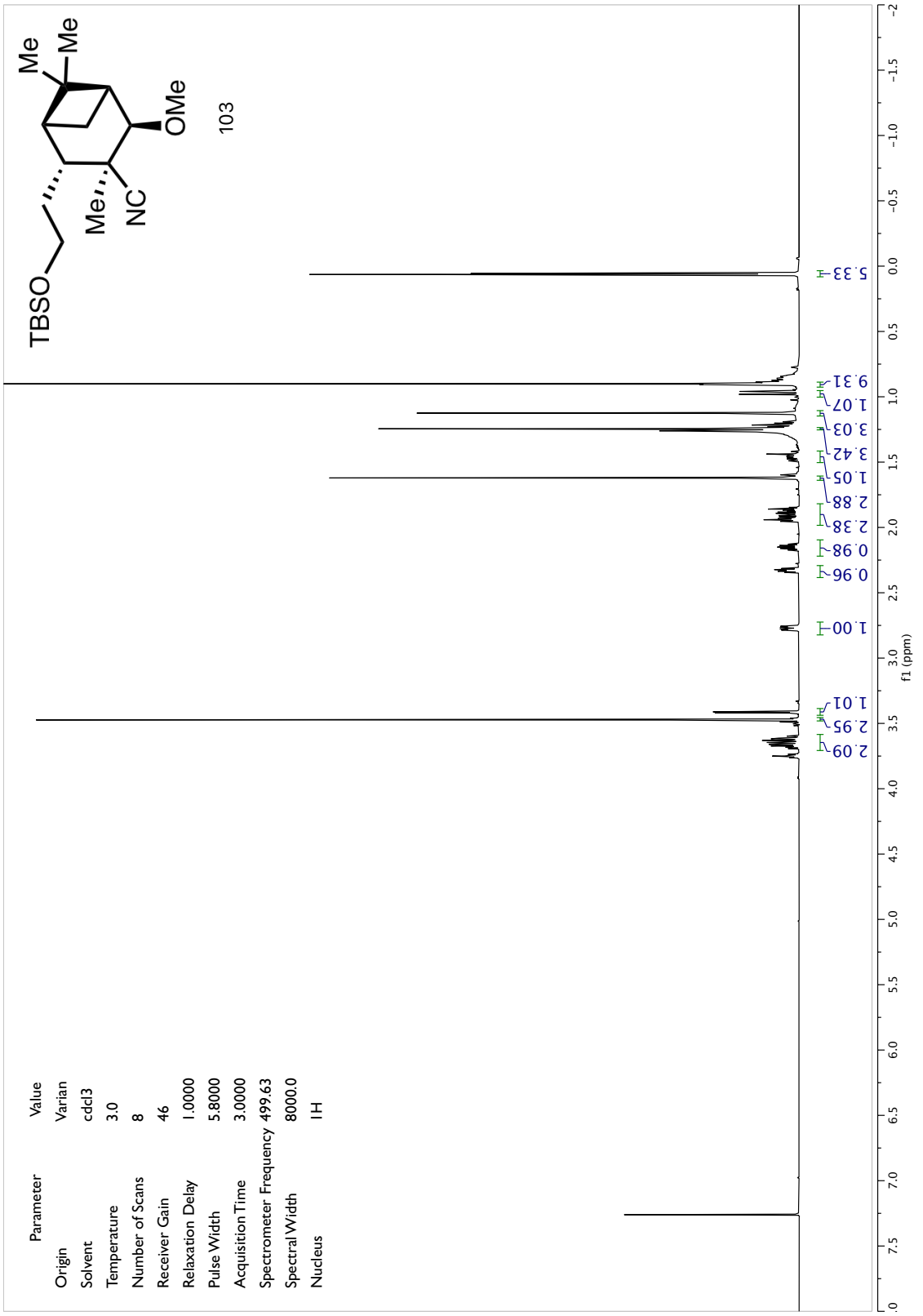
Nucleus 13C
f1 (ppm)


f1 (ppm)
f2 (ppm)
TBSO
Me
Me
OBn
HO
Me
NC
101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OMe
Me
NC
TBSO
103
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Solvent cdcl3
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Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Spectrometer Frequency 499.63
Spectral Width 8000.0
Nucleus 1H
5.33
9.31
1.07
3.03
3.42
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2.88
2.38
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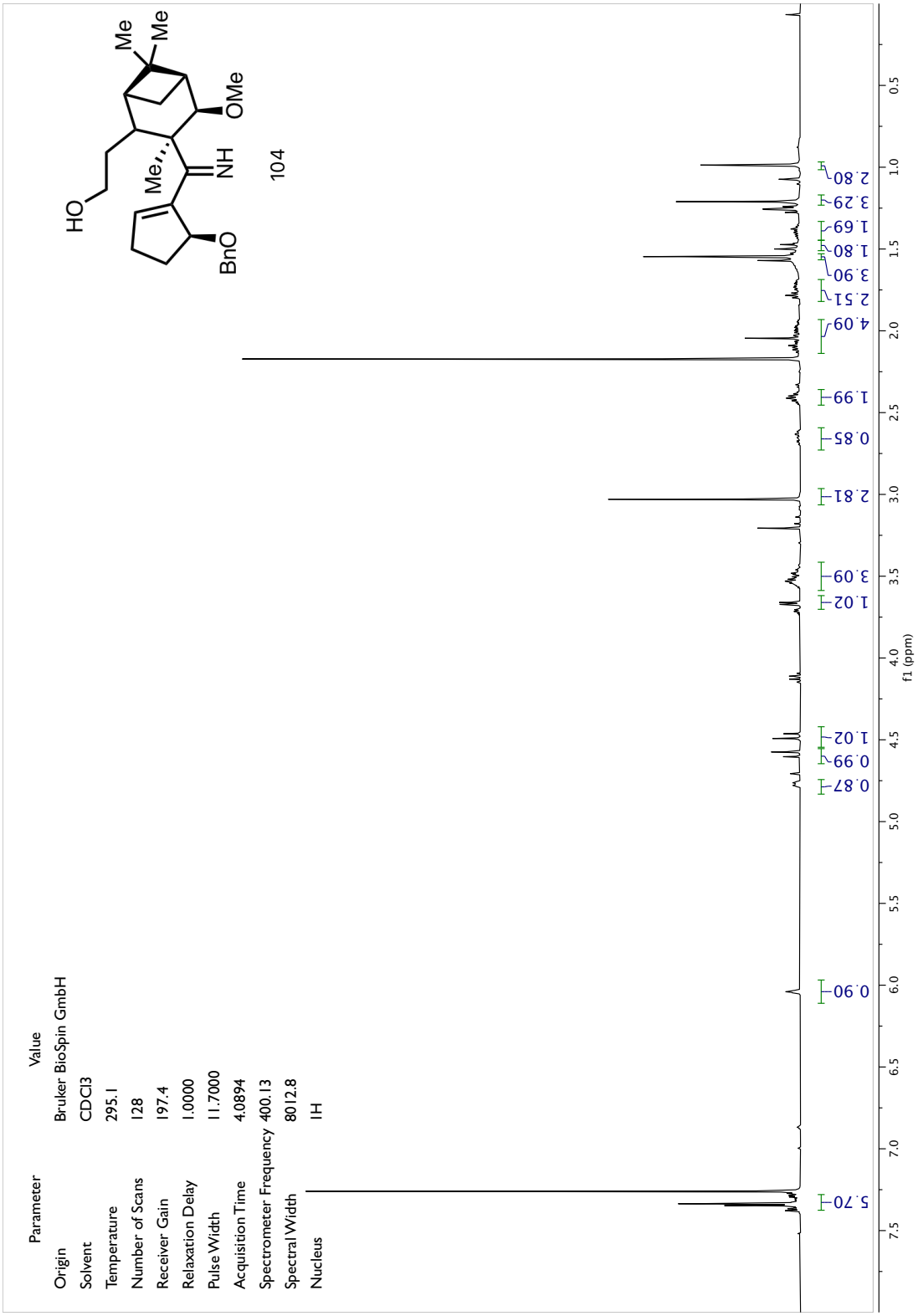
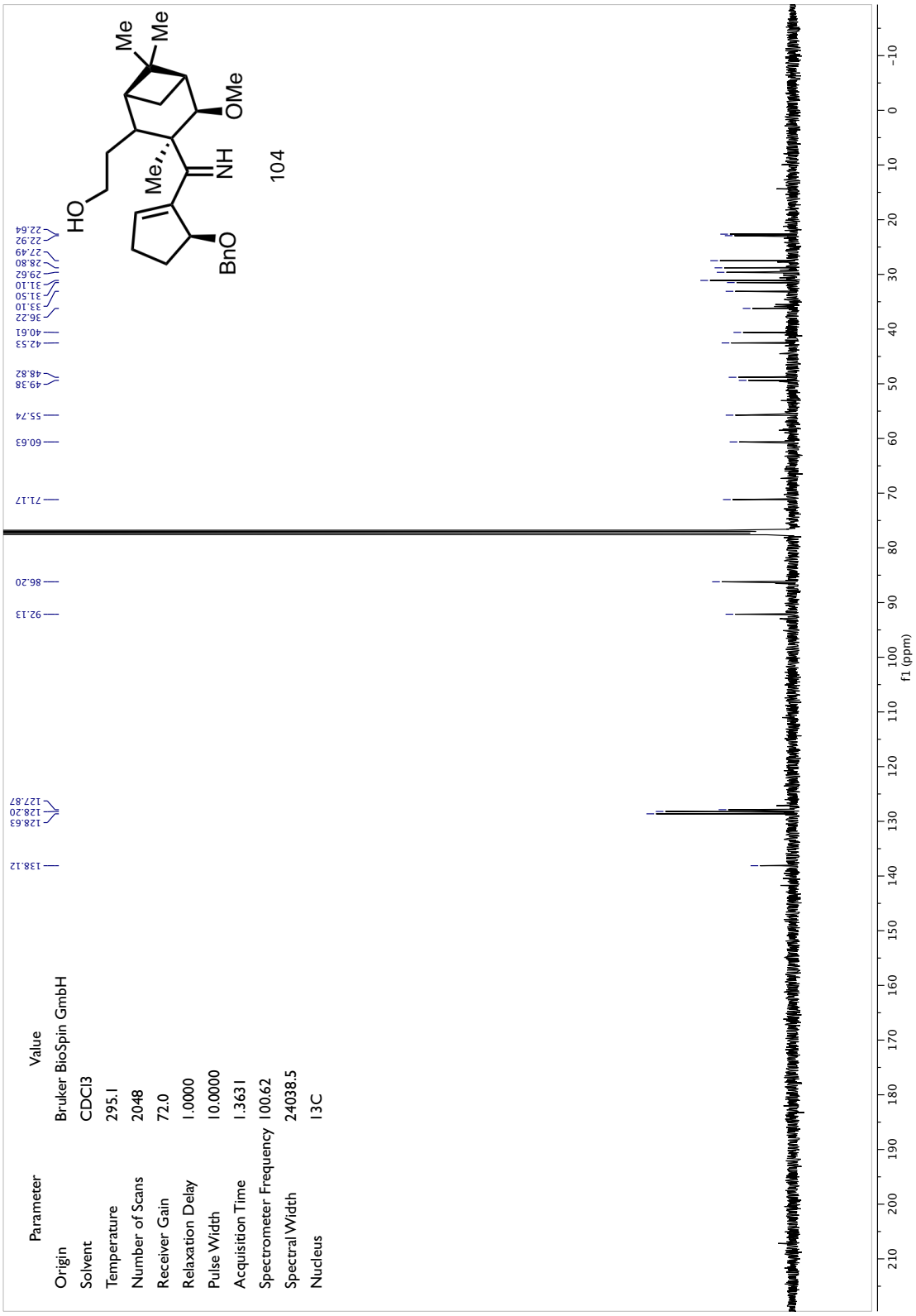
0.96
1.00
1.01
2.95
2.09
f1 (ppm)


Me
Me
OMe
NH
Me
HO
BnO
104
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Number of Scans 128
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
5.70
0.90
1.02
0.87
0.99
1.02
3.09
1.02
2.81
0.85
1.99
4.09
2.51
3.90
1.80
1.69
3.29
2.80
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Me
Me
OMe
NH
Me
HO
BnO
104
22.64
22.92
27.49
28.80
29.62
31.10
31.50
33.10
36.22
40.61
42.53
48.82
49.38
55.74
60.63
71.17
86.20
92.13
127.87
128.20
128.63
138.12
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.1
Number of Scans
2048
Receiver Gain
72.0
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)

Chapter 3

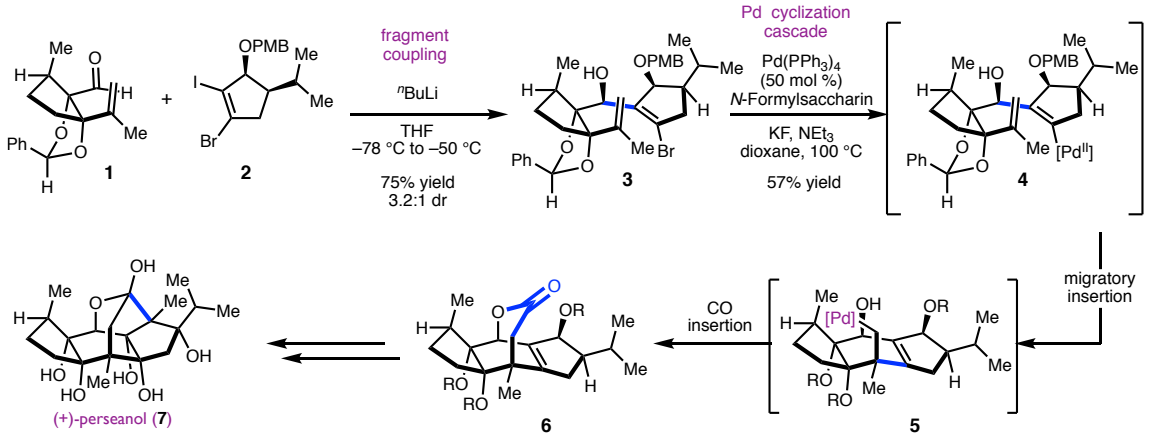
A Transition-Metal Catalyzed Cascade Cyclization Approach to the Synthesis of Falcatin A

3.1 INTRODUCTION

3.1.1 Transition Metal Catalyzed Cyclization Approach to Natural Product Total Synthesis

As discussed in Chapter 2, efforts to apply a photoredox catalyzed strategy to the synthesis of falcatin were unsuccessful. Therefore, we elected to revise our retrosynthetic approach to the natural product and elected to pursue a transition-metal catalyzed cascade cyclization approach. Transition-metal catalyzed cascade cyclizations are of particular interest to the Reisman group.[1] In particular, the synthesis of (+)-perseanol (**7**) in 2019 featured a Pd-catalyzed cascade cyclization (**Scheme 3.1**).[2] Our approach began with a 1,2-addition between fragments **1** and **2**. Next, subjection of **3** to $Pd(PPh_3)_4$ affected an oxidative addition into the alkenyl bromide to give intermediate **4**. Then, a migratory insertion forged the central six-membered ring giving alkyl palladium species **5 w**hich could then undergo CO insertion and lactonization to afford the desired lactone **6**. This could then be taken forward in a series of step to the natural product (**7**).

Scheme 3.1 *Palladium Cascade Cyclization Approach to (+)-Perseanol*

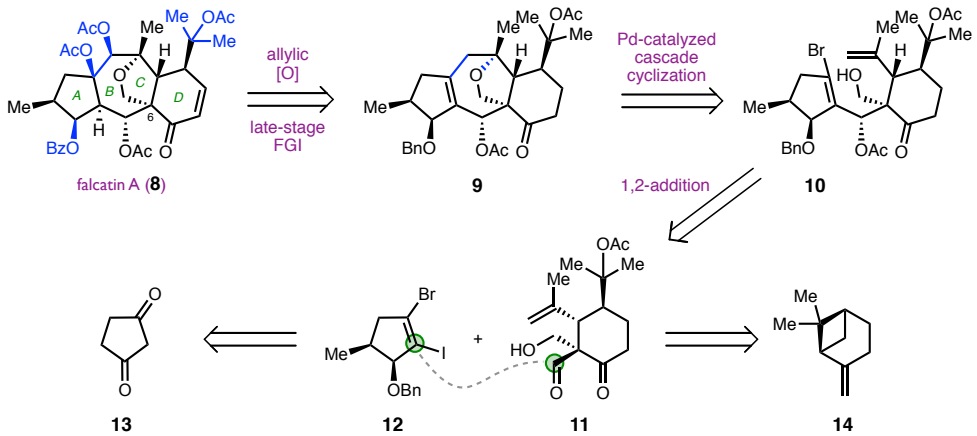


3.2 RETROSYNTHETIC PLANNING

3.2.1 Retrosynthesis

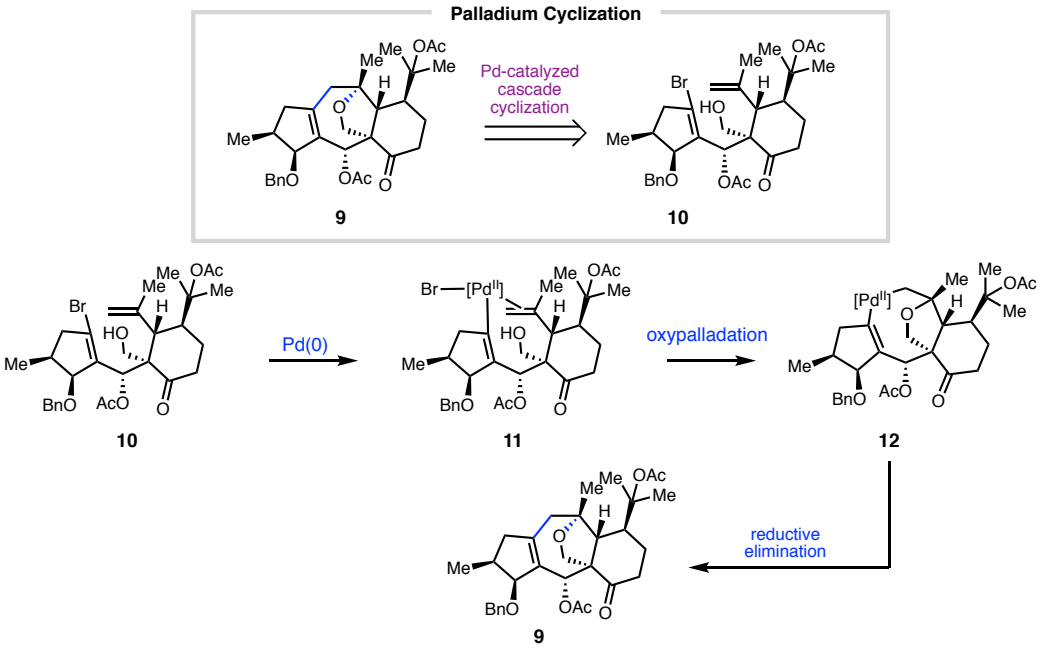
Retrosynthetically, we believed we could disconnect falcatin A (**8**) back, via a series of late-stage function group interconversions and an allylic oxidation, to **9** (**Scheme 3.2**). We envisioned accessing **9** via a Pd-catalyzed cascade cyclization of **10** which could then arise from the 1,2-addition between alkenyl iodide **12** and aldehyde **11**. It is believed that iodide **12** could arise from **13** and aldehyde **11** could come from β-pinene (**14**).

Scheme 3.2 *Retrosynthetic Analysis*



The palladium-catalyzed cascade cyclization is proposed to form both the tetrahydrofuran (C ring) and the central seven-membered ring (B ring) in a single reaction (**Figure 3.1**). Specifically, we envision that subjection of **10** to a palladium(0) source could first facilitate an oxidative addition to access alkenyl palladium complex **11**. Next, an oxypalladation across the isopropenyl olefin would result in formation of the tetrahydrofuran ring and deliver the 8-membered palladacycle **12**. Finally, a reductive elimination would forge the central seven-membered B ring to give product **9**. We believe this strategy could be used to concisely and efficiently build two out of the four rings of the natural product and add a significant contribution to the field of total synthesis.

Figure 3.1 *Proposed Palladium Cascade Cyclization*

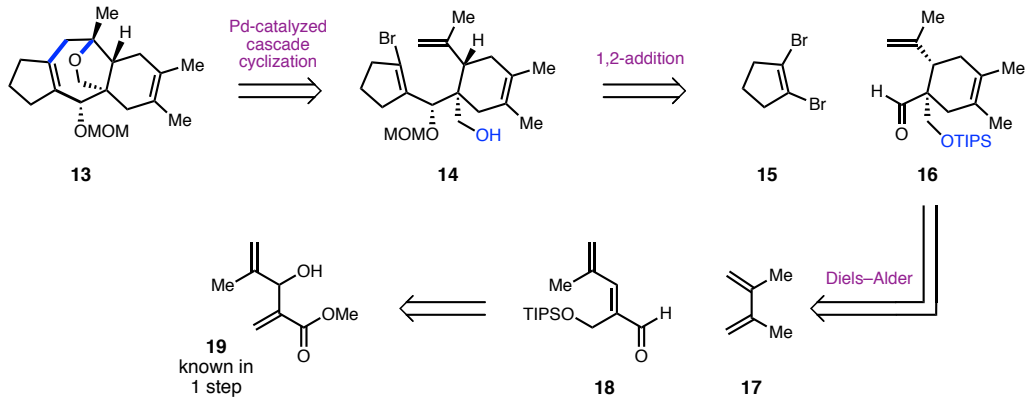


3.3 MODEL SYSTEM STUDIES

3.3.1 Substrate Synthesis

To begin, we elected to study a model system which would allow us to test the key Pd-catalyzed cascade cyclization (**Scheme 3.3**). Given the challenges of installing the quaternary center with a hydroxymethyl group via an alkylation strategy (see chapter 2), we elected to pursue instead a Diels–Alder approach to forge both the quaternary center as well as the six-membered D ring fragment. Specifically, we aimed to synthesize **14** via a 1,2-addition reaction between known dibromocyclopentene (**15**)[3] and aldehyde **16**. Aldehyde **16** could then arise from a Diels-Alder reaction between 2,3-dimethylbutadiene (**17**) as the diene and enal **18** as the dienophile. Enal **18** could then arise from known alcohol **19**.[4]

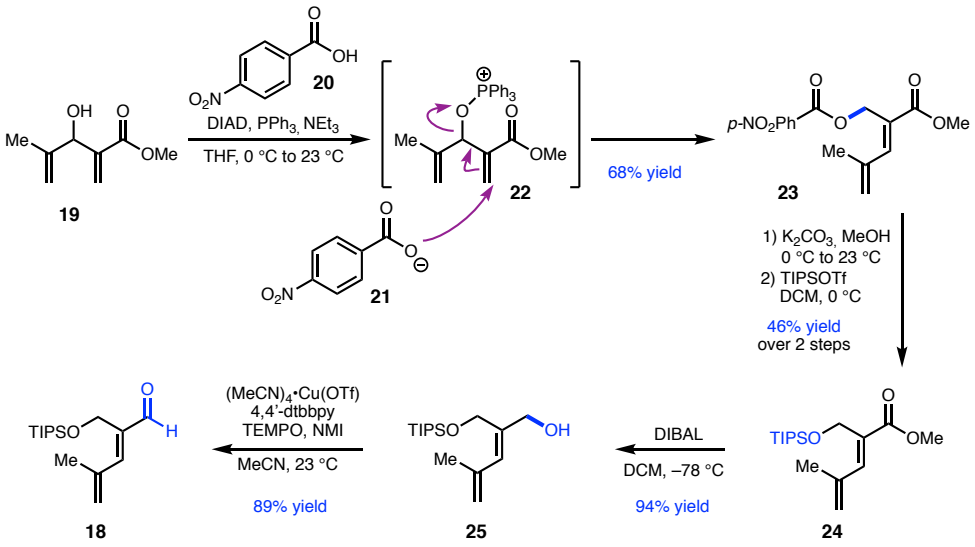
Scheme 3.3 *Model System Retrosynthetic Analysis*



The synthesis of aldehyde **18** began with known alcohol which can be prepared in 1 step from methyl acrylate and acrolein.[4] A S_N2'-mitsunobu between alcohol **19** and 4-nitro-benzoic acid (**20**) afforded diene **23** in good yield (**Scheme 3.4**).[5] Methanolysis of the *p*-nitro-benzoate and subsequent protection as the silyl ether proceeded smoothly to yield

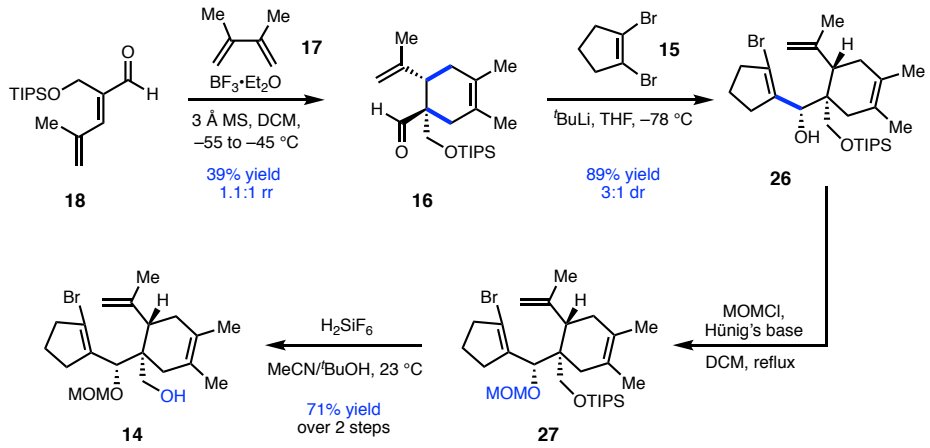
24. Reduction of methyl ester **24** followed by Stahl oxidation[6] of allylic alcohol **25** afforded enal **18** in good yield.

Scheme 3.4 *Synthesis of Dienophile* ***18***



Next, a Lewis acid-catalyzed Diels–Alder reaction between enal **18** and 2,3-dimethylbutadiene (**17**) afforded cyclohexene **16**. Monolithiation of 2,3-dibromocyclopentene (**15**) followed by addition into aldehyde **16** afforded allylic alcohol **26** with 3:1 dr favoring the desired diastereomer. Lastly, a protection of the secondary alcohol and subsequent desilylation delivered primary alcohol **14**.

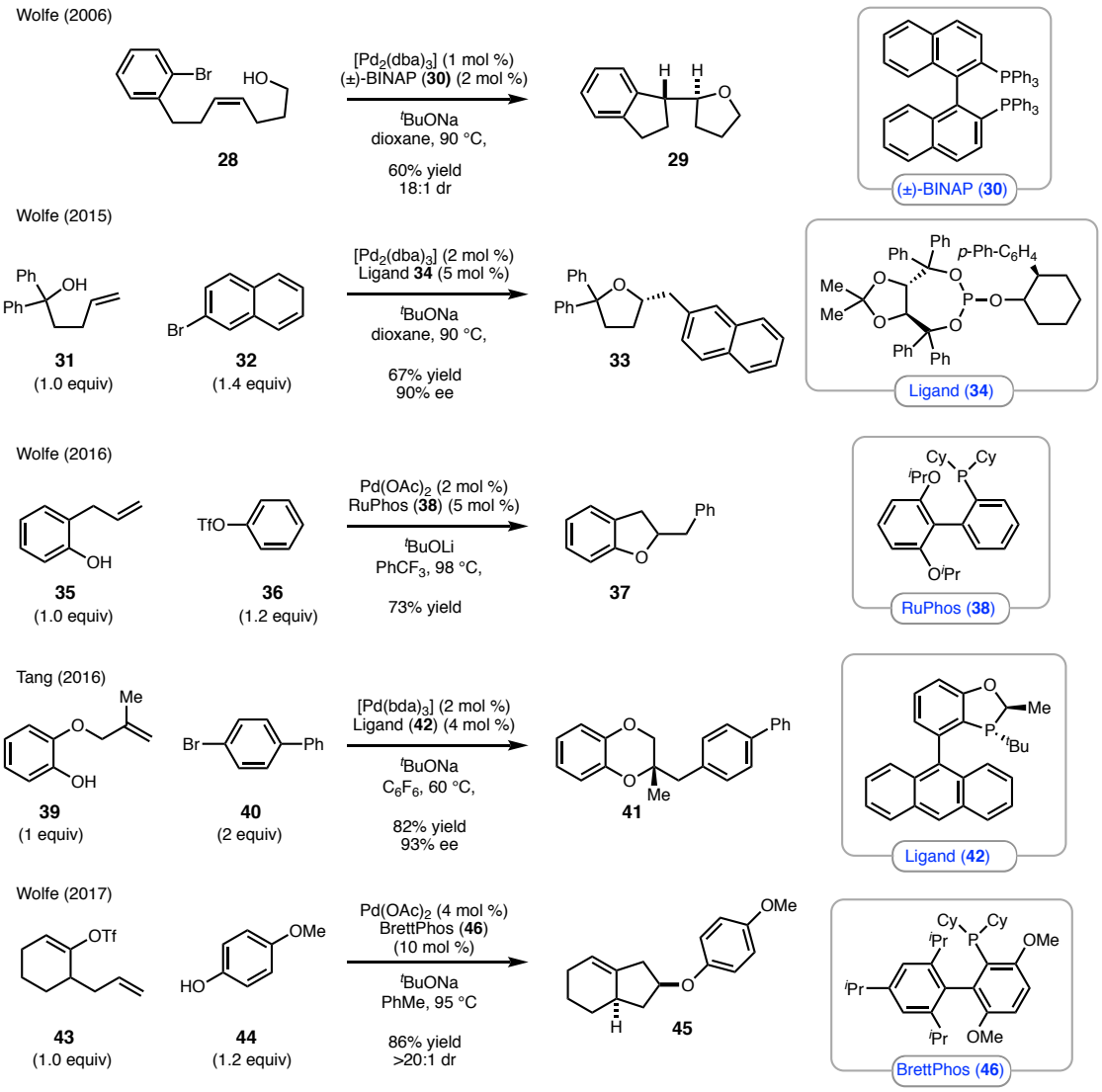
Scheme 3.5 *Synthesis of Model System* ***27***



3.3.2 Palladium Cyclization Studies

The Pd-catalyzed cascade cyclization involving an oxypalladation step is precedented in the literature (**Figure 3.2**).[7–13] In 2006, the Wolfe group demonstrated that an appropriate combination of a palladium(0) source and bisphosphine ligand could promote the bis-cyclization of **28** involving an oxypalladation step to afford **29** in moderate yield.[8] In 2015, it was shown that oxypalladation could be achieved both enantioselectivity and intermolecularly through the use of a chiral phosphite ligand.[7] Then in 2016, the Wolfe group showed that this methodology could be extended from aryl halides into aryl triflates and could couple with phenol nucleophiles.[12] The Tang group in 2016 arrived at a similar conclusion with their report on the synthesis of 1,4-benzodioxanes.[13] Then in 2017, the Wolfe group demonstrated that alkenyl halides were suitable electrophiles for this chemistry as well.[9]

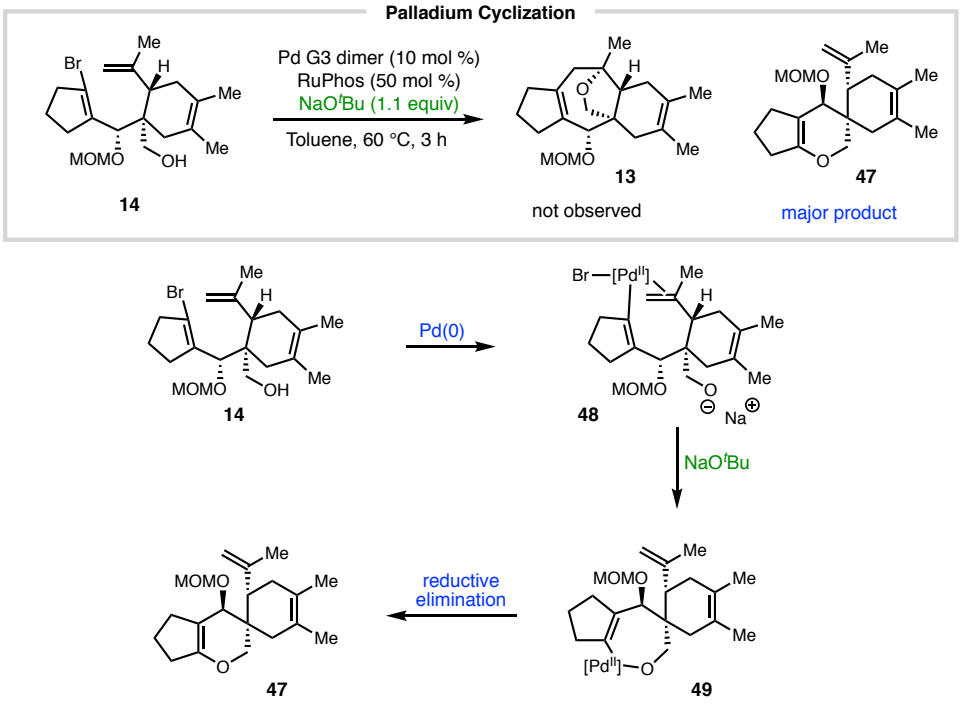
Figure 3.2 *Oxypalladation Precedent*



We began our studies using conditions similar to what had been described in the literature. It was found that subjection of **14** to Pd G3 dimer[14] as the Pd(0) source in the presence of RuPhos as a ligand, NaO^{t}Bu as a base, in PhMe at 60 °C did not afford the desired product but instead the product of direct C–O cross-coupling between the alkenyl bromide and primary alcohol (**47**) (**Figure 3.3**). We hypothesize that this process occurs first via an oxidative addition of Pd into the alkenyl bromide to give alkenyl palladium(II)

species **48**. Next, coordination of the sodium alkoxide and subsequent reductive elimination yields the observed product **47**. While this is not the desired process, this does indicate that oxidative addition of the Pd catalyst is a chemically feasible step.

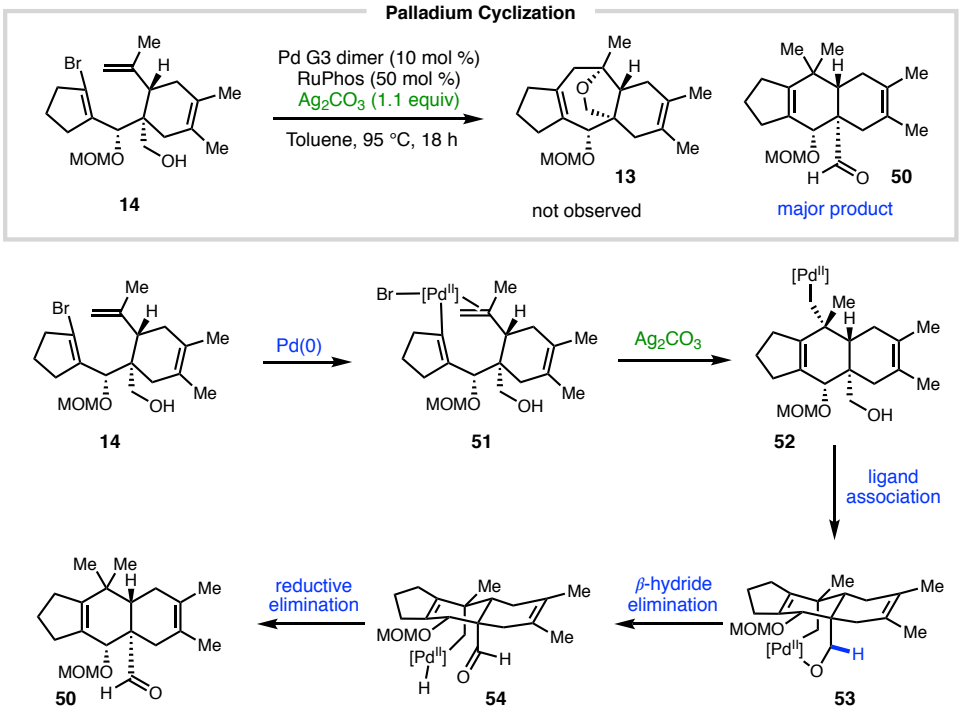
Figure 3.3 *Direct C–O Coupling*



We reasoned that by using a weaker base in the reaction, we may be able to lower the concentration of deprotonated substrate during the reaction to avoid direct C–O cross-coupling. Additionally, we believed that the use of a silver(I) additive could facilitate the removal of bromide anions in solution to form a more cationic palladium species thereby encouraging the oxypalladation step. To this end, we performed the reaction in the presence of Pd G3 dimer, RuPhos, and Ag_2CO_3, which is both a weaker base compared to NaO^{t}Bu and a Ag(I) source. We found no formation of the desired product but rather central six-membered ring-containing product **50** with concomitant oxidation of the primary alcohol to the aldehyde **50** as the major product (**Figure 3.4**).

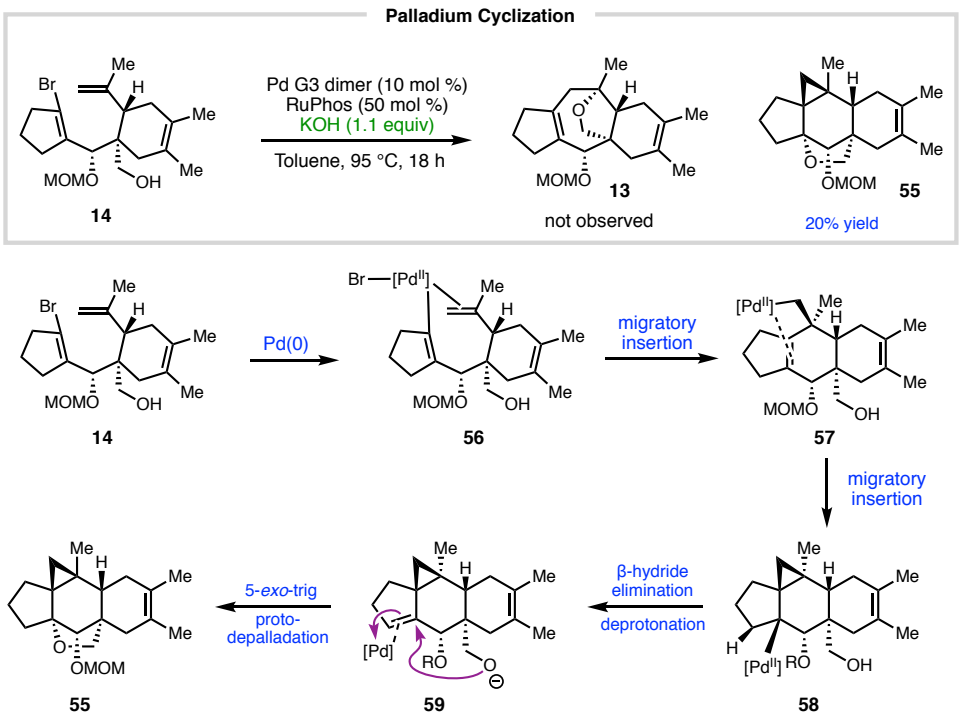
Mechanistically, we hypothesized that product **50** arises via first an oxidative addition of palladium(0) into the alkenyl bromide to form alkenyl palladium(II) complex **51**. Next, a migratory insertion across the isopropenyl olefin would afford neopentyl alkyl palladium(II) species **52**. Neopentyl palladium species **52** has no β-hydrides for elimination. We hypothesized that a coordination to the primary alcohol could occur to give oxapalladacycle **53** which can then undergo β-hydride elimination and subsequent reductive elimination to give the observed product accounting for the concomitant alcohol oxidation. While the desired reactivity was not observed, this reaction does provide evidence that the oxidative addition complex is geometrically capable of engaging with the isopropenyl olefin.

Figure 3.4 *Migratory Insertion Product*



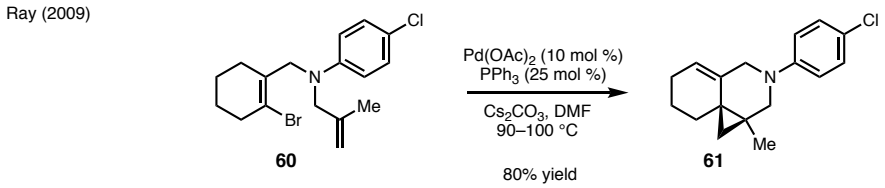
We next hypothesized that Ag_2CO_3 may be too insoluble/weak of a base to get an appropriate rate of deprotonation of the primary alcohol to facilitate oxypalladation. Thus, we next attempted to use a base with an intermediate basicity (pK_b of KOH = –0.7). In this case, we found the formation of cyclopropane **55** (**Figure 3.5**). Mechanistically, we hypothesize that this product **55** arises via first an oxidative addition of palladium(0) into the alkenyl bromide to form alkenyl palladium(II) complex **56**. Next, a migratory insertion across the isopropenyl olefin would afford neopentyl alkyl palladium(II) species **57**. Palladium complex **57** could then undergo coordination to the cyclopentenyl olefin and subsequent migratory insertion to forge the cyclopropane a give alkyl palladium species **58**. Then β-hydride elimination and deprotonation of the primary alcohol would afford intermediate **59**. Lastly, a 5-*exo*-trig and protodepalladation would afford the observed product.

Figure 3.5 *Cyclopropanation*



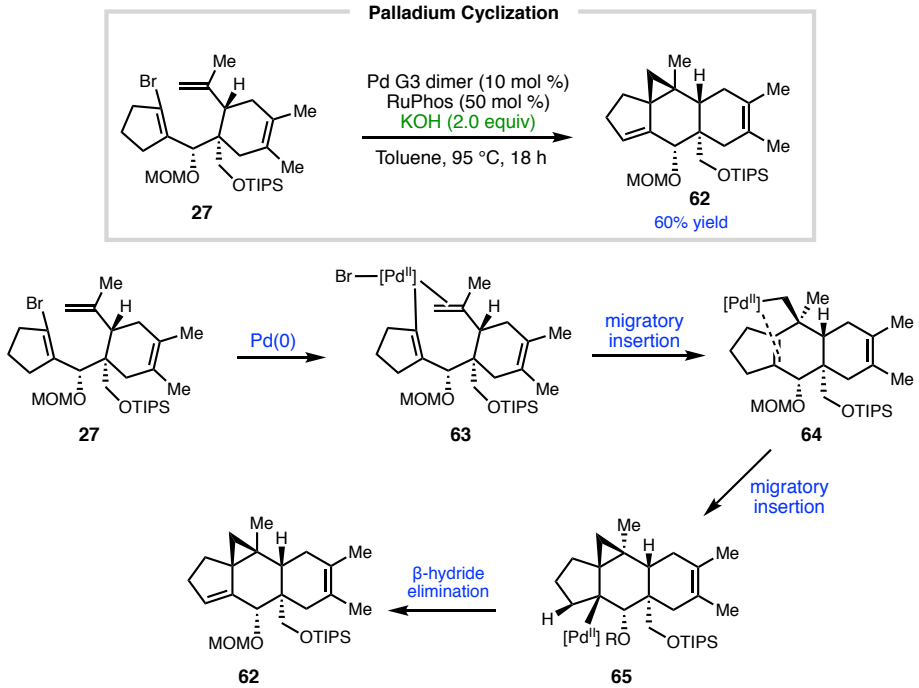
We were interested to understand this cyclopropanation reaction in further detail. In 2009, Ray and coworkers published the report of a palladium-catalyzed cyclization/cyclopropanation reaction of alkenyl halide substrate **60** in which a similar mechanism was proposed (**Figure 3.6**).[15]

Figure 3.6 *Cyclopropanation Precedent*



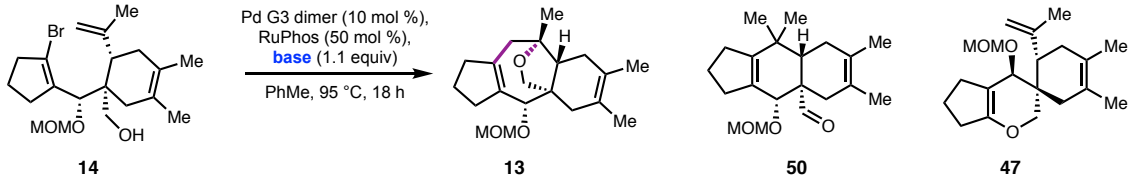
To investigate our mechanistic proposal further, we subjected protected alcohol **27** to the same reaction conditions and found that **62** was formed in good yield (**Figure 3.7**). This is consistent with our mechanistic hypothesis as the intermediate following β-hydride elimination is incapable of undergoing further 5-*exo*-trig cyclization.

Figure 3.7 *Further Cyclopropanation Studies*



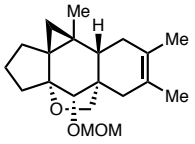
Having identified the base as being a critical variable in this reaction, we next turned to investigate a variety of bases (**Table 3.1**). Despite looking at a variety of bases across different pK_b values, we found low levels of reactivity. While KOH gave a mixture of **47, 50** and **55** as products, all other reactions failed to afford any of the previously observed products.

Table 3.1 *Attempted Optimization via Base Screen*



14 **13** **50** **47**

entry	base	13 (%)	50 (%)	47 (%)	55 (%)	% RSM
1	LiOMe	0	0	0	0	54
2	KOH	0	4	52	20	0
3	LiOH	0	0	0	0	48
4	K_3PO_4	0	0	0	0	64
5	Cs_2CO_3	0	0	0	0	70
6	Li_2CO_3	0	0	0	0	64
7	$NaHCO_3$	0	0	0	0	71
8	KOAc	0	0	0	0	37



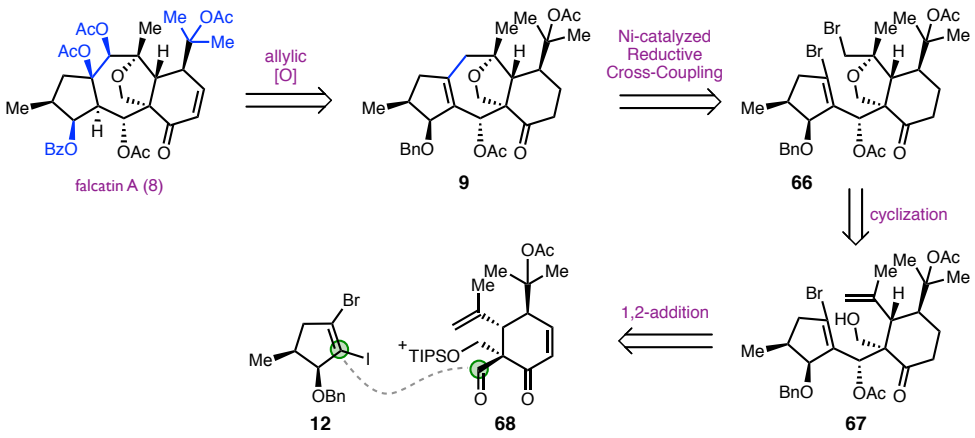
55

While we were excited about the general reactivity we had observed in our palladium studies, we were unable to find any conditions in which oxypalladation had occurred. Thus, we elected to continue forward in the synthesis by pursuing a stepwise approach to the synthesis of both the B and C rings.

3.3.3 Nickel Studies

Retrosynthetically, we believed we could disconnect falcatin A (**8**) back via a series of late-stage functional group interconversions and an allylic oxidation of **9** (**Scheme 3.6**). We then envisioned accessing **9** via an intramolecular Ni-catalyzed reductive coupling of **66**. It was envisioned that the tetrahydrofuran ring of **66** could be constructed via a bromoetherification reaction of alcohol **67**.

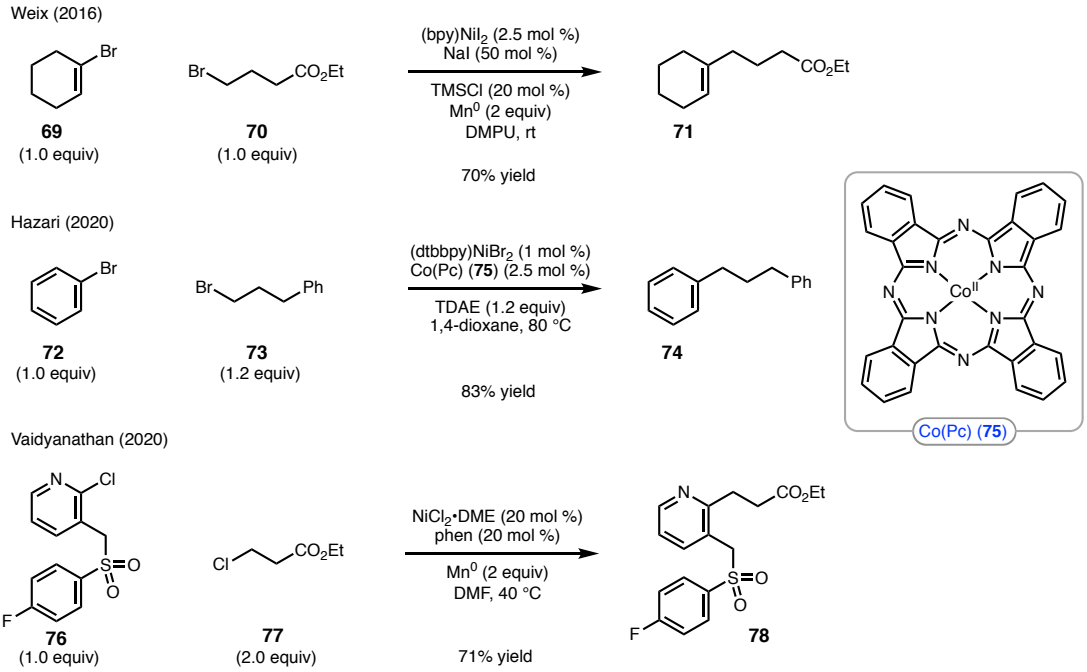
Scheme 3.6 *Retrosynthetic Analysis*



Nickel-catalyzed reductive cross-coupling is of particular interest to the Reisman group.[16] The Reisman group has reported a variety of reductive cross-couplings in recent years.[17–24]. In 2016, the Weix group published a report in which they demonstrated that alkenyl bromide electrophiles could be coupled with alkyl bromide electrophiles using a Ni(II) catalyst with Mn^0 as the stoichiometric reductant (**Figure 3.8**).[25] In 2020, the Hazari group reported the nickel-catalyzed reductive cross-coupling of aryl bromides with alkyl bromide electrophiles.[26] Additionally, reductive cross-coupling has been shown to be of significant interest in industry. In 2020, the scientist at Bristol-Meyer-Squibb demonstrated that reductive cross-couplings could afford value added products.[27] Based on these

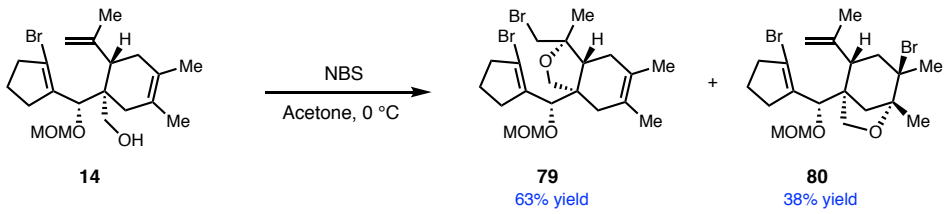
precedents, we envisioned utilizing a reductive coupling between a alkenyl halide and an alkyl halide.

Figure 3.8 *Nickel-Catalyzed Reductive Cross-Coupling Precedent*



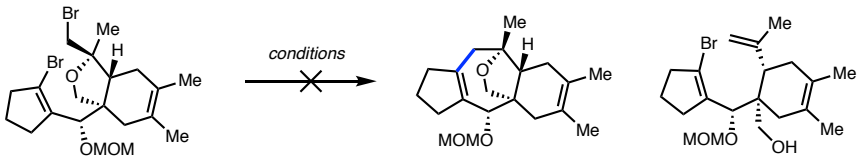
We began by investigating the bromoetherification reaction of **14** (**Figure 3.9**). We were pleased to find that **14** undergoes the desired cyclization to afford **79** as a single diastereomer along with regioisomer **80**.

Figure 3.9 *Synthesis of Substrate **79***



With **79** in hand, we began investigating the nickel-catalyzed reductive cross-coupling reaction (**Table 3.2**). Utilizing similar conditions to the reported literature, we found in all cases a lack of the desired cross-coupled product (**13**). It was found that in most cases, substrate **79** was either unreactive or decomposed under the reaction conditions. In one case (entry 4), we observed reductive opening of the tetrahydrofuran to form **81**.

Table 3.2 *Attempts to Perform Reductive Cross-Coupling*



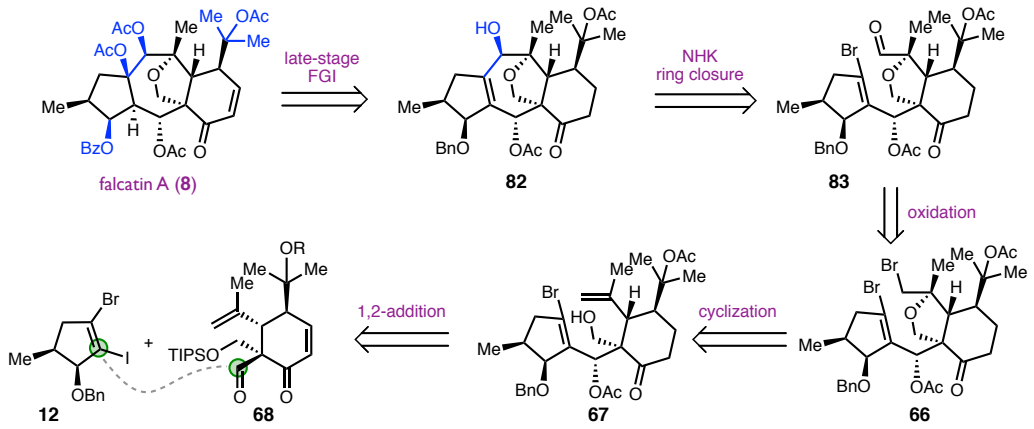
79 **13** **81**

entry	conditions	result
1	$NiBr_2$(dme), MeObpy, Zn^0 or Mn^0, NaI, DMPU or DMA, 20 °C	no reaction
2	$NiBr_2$(dme), MeObpy, Zn^0 or Mn^0, NaI, DMPU or DMA, 60 °C	partial conversion, complex mixture
3	$NiBr_2$(dtbbpy), CoPc, TDAE, NaI, DMPU or dioxane, 80 °C	no reaction
4	NiX_2(dme), MeObpy or phen, Mn^0, DMF, 40 °C	reductive ether opening
5	phen, Mn^0, DMF, 40 °C	no reaction

3.3.4 NHK Studies

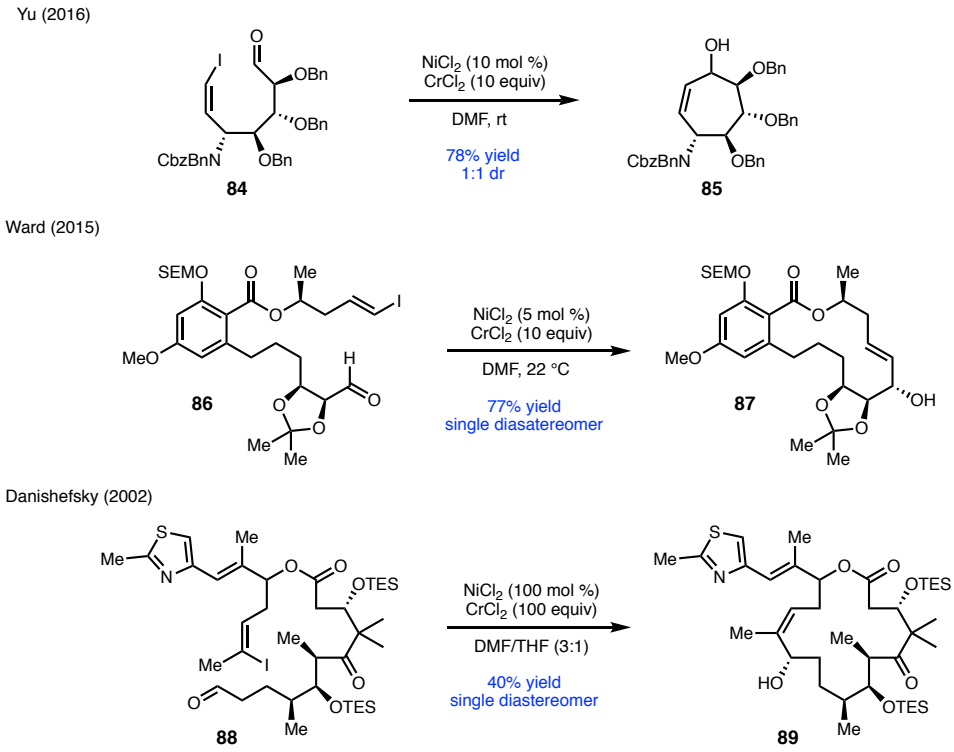
After facing limited success with our attempts at a nickel-catalyzed reductive cross-coupling, we elected to explore other ring closing reactions for the formation of our central seven-membered B ring. We were particularly attracted to the Nozaki-Hiyama-Kishi (NHK) reaction as it would allow us to install an alcohol oxidation without the use of an allylic oxidation reaction. Specifically, we envisioned accessing falcatin A (**8**) via a series of late-stage functional group interconversions of **82** (**Scheme 3.7**). We then envisioned accessing **82** via an intramolecular NHK reaction of **83** which could then arise from the oxidation of alkyl bromide **66**.

Scheme 3.7 *Retrosynthetic Analysis*



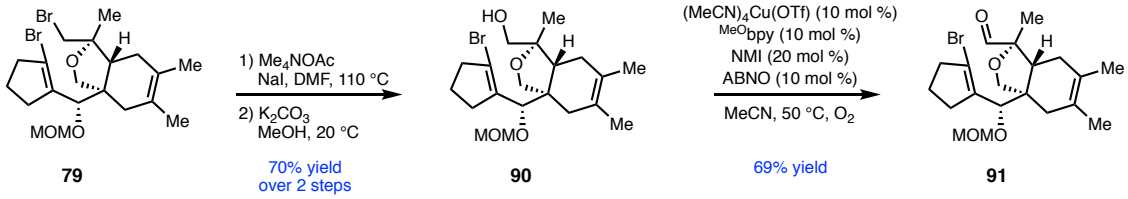
Intramolecular NHK reactions have been previously reported in the literature (**Figure 3.10**). To the best of our knowledge, only a single example has been reported of an intramolecular NHK to form specifically a seven-membered ring.[28] This report by Yu in 2016 demonstrated that **84** could be cyclized in the presence of an appropriate nickel catalyst using an excess of chromium(II) chloride to afford a 1:1 mixture of the diastereomers of **85**. In addition to seven-membered rings, intramolecular NHK reactions have proven useful in the synthesis of many different medium and large-sized rings.[29] In 2015, the Ward group published a report on the use of an NHK reaction to forge macrocycle **87**.[31] Additionally, in 2002, the Danishefsky group reported the use of an NHK reaction for the formation of macrocycle **89**.[30]

Figure 3.10 *NHK Precedent*



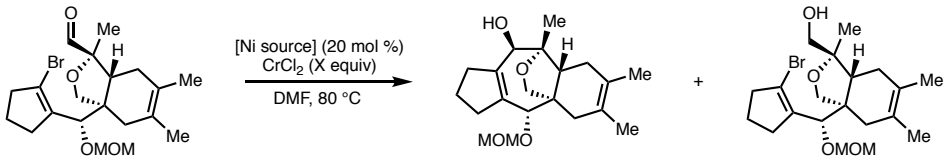
To test our NHK strategy, we synthesized **91** (**Scheme 3.8**). First, an S_N2 displacement of alkyl bromide **79** with an acetate group followed by subsequent methanolysis afforded alcohol **90**. Alcohol **90** could then be oxidized via a Stahl oxidation in good yield to deliver aldehyde **91**.

Scheme 3.8 *Synthesis of Substrate* ***91***



We began our investigations by first screening nickel catalyst sources (**Table 3.3**). It was found that $Ni(cod)_2$ performed best giving the desired product in 12% yield (entry 5). Doubling the scale of the reaction improved the yield to 29% (entry 6). Finally, doubling the amount of $CrCl_2$ to 4 equivalents improved the yield slightly to 34% (entry 7).

Table 3.3 *NHK Studies*



91 **92** **93**

entry	Ni source	equiv $CrCl_2$	scale (mmol **91**)	yield **92** (%)	% RSM	% **93**
1	$NiCl_2$	2	0.01	4	20	3
2	$NiBr_2$(dtbbpy)	2	0.01	6	11	3
3	Ni(cod)(DQ)	2	0.01	4	2	6
4	$NiCl_2$	2	0.01	9	11	8
5	$Ni(cod)_2$	2	0.01	12	6	1
6	$Ni(cod)_2$	2	0.02	29	20	0
7	$Ni(cod)_2$	4	0.02	34	0	0

Having finally identified a successful strategy for the synthesis of the core of the natural product (**8**), we next investigated the synthesis of fragments **12** and **68** for the completion of the synthesis.

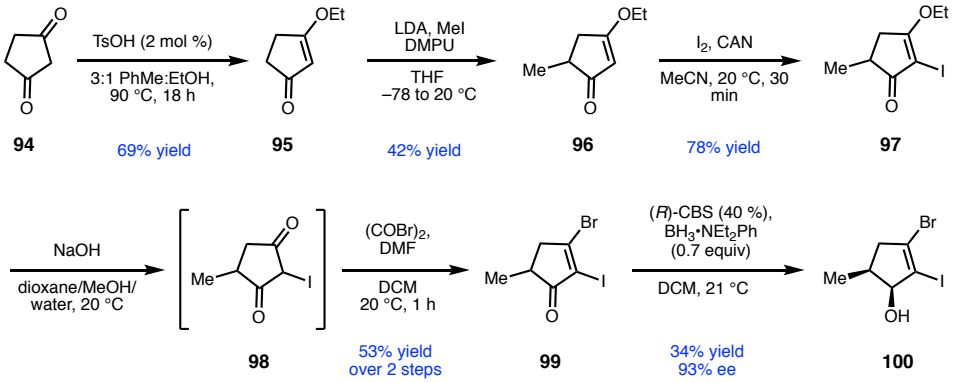
3.4 SUBSTRATE SYNTHESIS EFFORTS

3.4.1 A Ring Fragment Synthesis

Towards the synthesis of **12**, we began with diketone **94**. Taking inspiration from the fragment synthesis in our recently reported synthesis of (+)-perseanol (**7**)[2], we began first with a protection of the diketone as the vinylogous ester **95** (**Scheme 3.9**). Next, **95** could be methylated followed by an α-iodination to afford **97**. A base-mediated deprotection of the vinylogous ester could be followed by conversion to the alkenyl

bromide to afford **99** in a modest yield over 2 steps. Lastly, a kinetic resolution via a Corey-Bakshi-Shibata (CBS) reduction afforded allylic alcohol **100** in 34% yield and 93% ee.

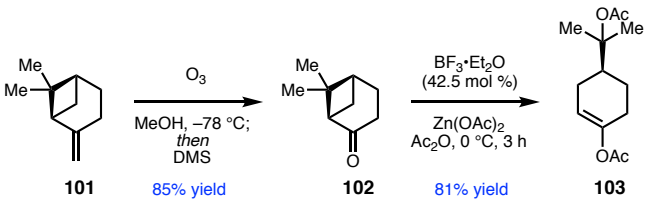
Scheme 3.9 *A Ring Fragment Synthesis*



3.4.2 D Ring Fragment Efforts

Towards the synthesis of the D ring fragment, we first began with commercially available β-pinene (**101**) (**Scheme 3.10**). **101** can be converted to enol acetate **103** via a two-step sequence previously reported by Yoshikoshi in 1989.[32] **101** is first ozonolyzed to produce ketone **102**, which is followed by a Lewis acid-mediated cyclobutene ring opening to afford **103**.

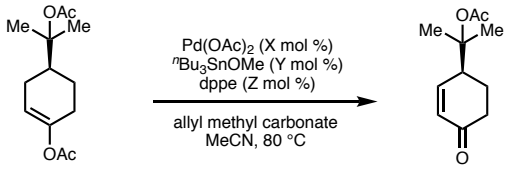
Scheme 3.10 *Synthesis of Enol Acetate* ***103***



We next investigated the previously reported desaturation of enol acetate **103** (**Table 3.4**).[33] Following the conditions reported by Kobayashi in 2002, using 5 mol % $Pd(OAc)_2$, and 5 mol % dppe as a ligand, we found only a 12% yield compared to the

reported 85% yield (entry 1). We hypothesized that perhaps a lack of catalyst turnover could be an issue and thus attempted to remedy this by using a balloon of oxygen to help facilitate the oxidation of the catalyst (entry 2). Although we did see an improvement in the yield to 25%, this was unsatisfactory for our desired material throughput. Thus, we investigated the reaction in the absence of ligand with higher catalyst loading and found a marked increase in the yield up to 65% (entry 3). After screening various loadings of $^{n}Bu_3SnOMe$ (entries 4–7), it was found that 50 mol % was optimal giving the desired product in 75% yield (entry 5). We lastly found that running the reaction with a reflux condenser instead of in a heavy walled pressure tube was also satisfactory giving the product in 82% yield (entry 8).

Table 3.4 *Optimization of Desaturation Reaction*



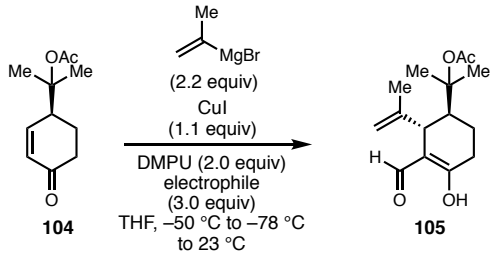
103 **104**

entry	ligand loading (mol %)	$^{n}Bu_3SnOMe$ loading (mol %)	$Pd(OAc)_2$ loading (mol %)	notes	yield (XX)
1	5	20	5	under N_2	12
2	5	20	5	O_2 balloon added	25
3	0	20	10	sealed	65
4	0	0	10	sealed	25
5	0	50	10	sealed	75
6	0	75	10	sealed	57
7	0	100	10	sealec	58
8	0	50	10	under N_2	82

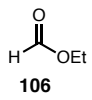
We next investigated the conjugate addition reaction of **104**. It was found that the dialkenyl cuprate generated *in situ* from isopropenyl magnesium bromide and Cu(I) iodide could react with enone **104** followed by trapping with a formate electrophile (**Table 3.5**). A short screen of electrophiles identified formyloxy(acetonitrile) **(108)** as being optimal

giving the product in 20% yield (entry 3). Scaling up this reaction to 500 mg improved the yield slightly up to 29% yield.

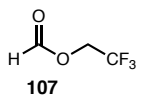
Table 3.5 *Optimization of Conjugate Addition*



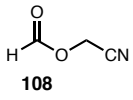
entry	electrophile	scale (mg)	yield **XX** (%)	RSM (%)
1	**106**	20	0	51
2	**107**	20	3	44
3	**108**	20	20	47
4	**108**	500	29	0



106



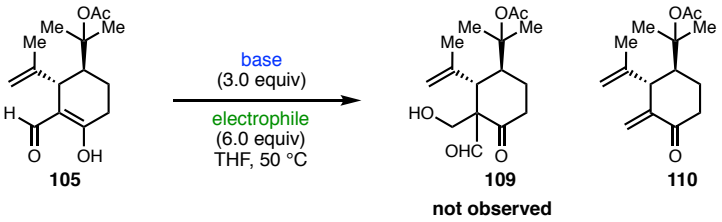
107



108

With **105** in hand, we could next test the alkylation of **105** with formaldehyde to form the quaternary center of the natural product. Subjection of **105** to a variety of bases in the presence of either aqueous formaldehyde (**111**) or paraformaldehyde (**112**) gave none of the desired product (**Table 3.6**). Instead, **110** was observed as the only isolable product from these reactions. Our mechanistic proposal for the observed reactivity is similar to that demonstrated previously in chapter 2 (**Figure 3.11**).

Table 3.6 *Attempts to Alkylate Aldehyde* ***105***



105 **109** **110**

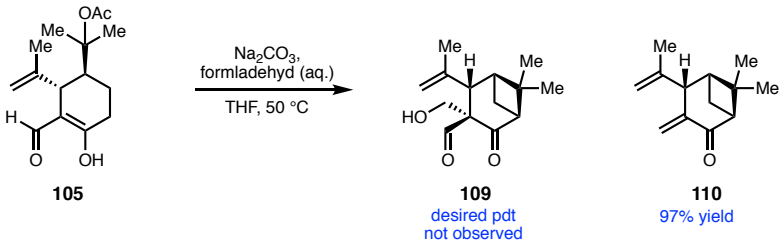
not observed

entry	electrophile	base	result
1	**111**	K_2CO_3	decomp
2	**111**	$KHCO_3$	36% **110**, 22% RSM
3	**111**	NaH	decomp
4	**111**	Na_2CO_3	55% **110**
5	**111**	$NaHCO_3$	12% **110**, 50% RSM
6	**112**	K_2CO_3	decomp
7	**112**	$KHCO_3$	6% **110**, 45% RSM
8	**112**	NaH	55% **110**
9	**112**	Na_2CO_3	22% **110**, 12% RSM
10	**112**	$NaHCO_3$	59% RSM

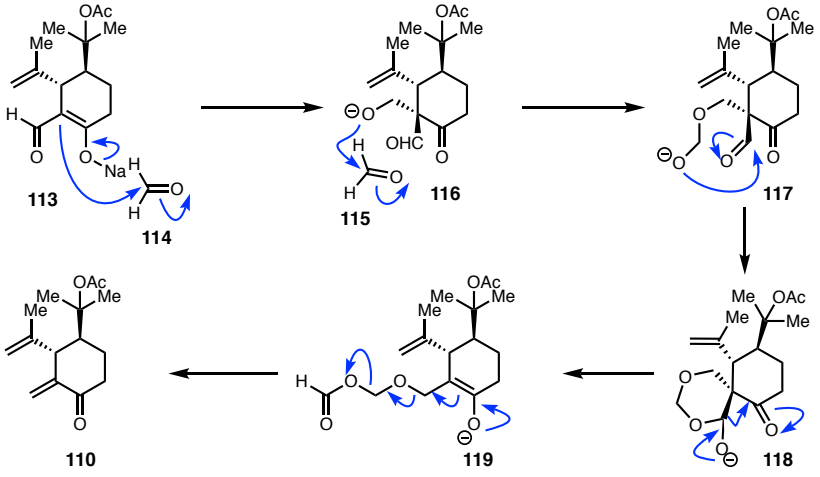
(aqueous)

111 **112**

Figure 3.11 *Mechanistic Hypothesis for the Formation of* ***110***



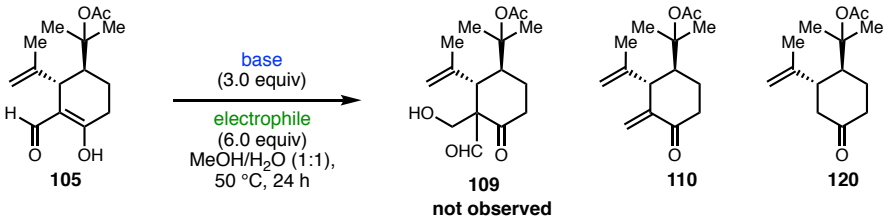
105 **109** desired pdt not observed **110** 97% yield



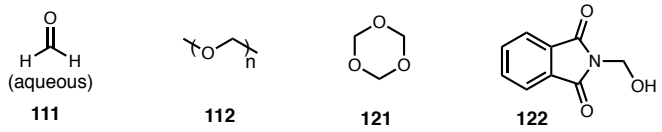
113 **114** **115** **116** **117** **118** **119** **110**

We hypothesized that if we could slow the rate of formaldehyde generation, we could potentially lower the concentration of formaldehyde in solution thereby making the addition into a second equivalent of formaldehyde a slower process. Thus, we elected to screen reagents which would generate monomeric formaldehyde over the course of the reaction (**Table 3.7**). However, only the formation of epimer retro aldol product **120** and recovered starting material were observed.

Table 3.7 *Additional Attempts to Alkylate* ***105***



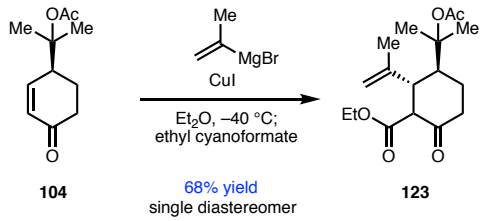
entry	electrophile	base	result
1	**111**	Na_2CO_3	decomp
2	**112**	Na_2CO_3	decomp
3	**121**	Na_2CO_3	66% **120**
4	**122**	Na_2CO_3	59% **120**, 41% RSM
5	**111**	LiOH	decomp
6	**112**	LiOH	decomp
7	**121**	LiOH	74% **120**
8	**122**	LiOH	35% **120**, 52% RSM



Given the lack of progress with aldehyde substrate **105**, we next hypothesized that the aldehyde carbonyl may be too electrophilic and thereby resulted in high levels of alkoxide addition into the aldehyde of intermediate **117**. We therefore reasoned that by using a less electrophilic aldehyde surrogate functional group, we could lower the rate of this decomposition pathway. To this end, we first elected to test a methyl ester as a less electrophilic functional handle which could later be converted to an aldehyde (**Figure**

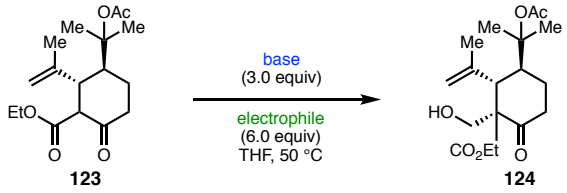
3.12). Ketoester **123** could be prepared in a single step from enone **104** by reacting in a conjugate addition, and trapping the enolate with ethyl cyanoformate to afford **123** as a single diastereomer.

Figure 3.12 *Synthesis of Substrate* ***123***

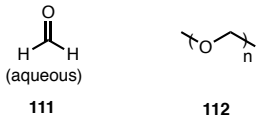


To our delight, we found that subjection of **123** to alkylation conditions with formaldehyde resulted in the formation of the desired quaternary center (**Table 3.8**). It was found that with various bases, alcohol **124** could be formed in low yield.

Table 3.8 *Optimization of Alkylation of* ***123***



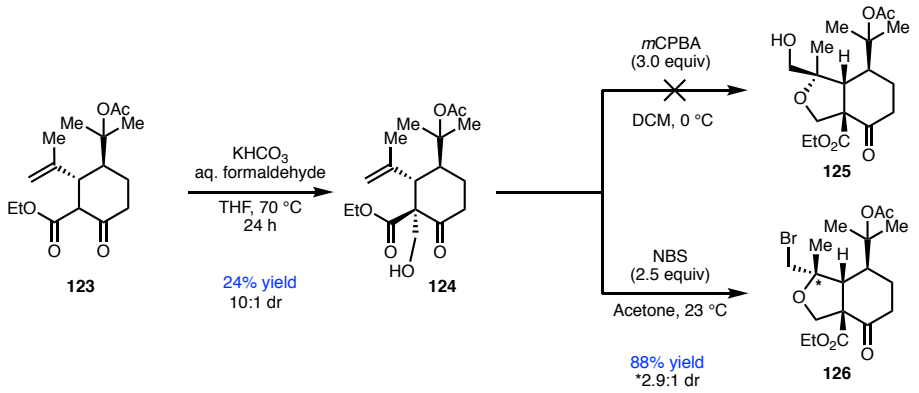
entry	electrophile	base	yield (%)	RSM (%)
1	**111**	K_2CO_3	0	56
2	**111**	$KHCO_3$	24	72
3	**111**	Na_2CO_3	23	60
4	**111**	$NaHCO_3$	24	68
5	**111**	Li_2CO_3	23	78
6	**111**	LiOH	0	80
7	**112**	$KHCO_3$	15	44



With **124** in hand, we could next test the intramolecular cyclization of alcohol **124** across the isopropenyl olefin (**Scheme 3.11**). It was found that under oxidative conditions

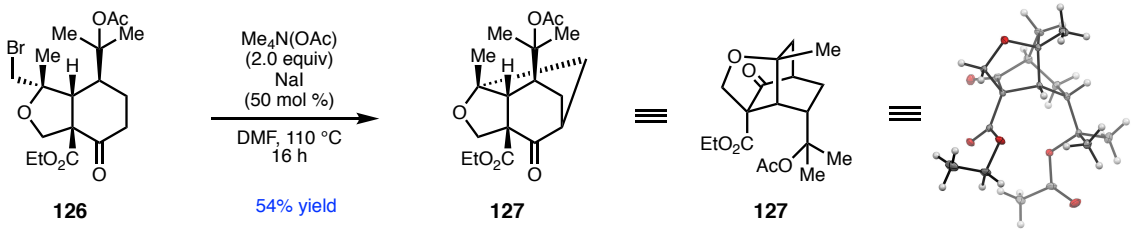
with *m*CPBA, substrate **124** decomposed. Alternatively, subjection to NBS in acetone afforded the desired cyclized product in good yield albeit favoring the undesired diastereomer (**126**).

Scheme 3.11 *Cyclization to Form C Ring*



Initial attempts to displace alkyl bromide with an acetate nucleophile were met instead with intramolecular displacement to afford the caged intermediate **127** which could be recrystallized to give x-ray quality crystals.

Figure 3.13 *Synthesis of Caged System **127***



3.5 CONCLUDING REMARKS

In summary, we were able to demonstrate a transition metal-mediated synthesis of the core of the natural product falcatin A (**8**). We discovered several possible pathways for synthesis of complex polycyclic intermediates using palladium catalysis. Nickel-catalyzed reductive cross-coupling to forge the central seven-membered ring was ultimately

unsuccessful. However, an NHK-strategy was found to be successful in the synthesis of the core structure in a model system. The synthesis of more complex fragments is ongoing in the laboratory. In our studies of complex fragment synthesis, we were able to successfully install the challenging quaternary center at C6 and forge the bridging tetrahydrofuran C ring. This chapter represents a significant contribution to the synthesis of small complex organic molecules.

3.6 EXPERIMENTAL SECTION

General Information

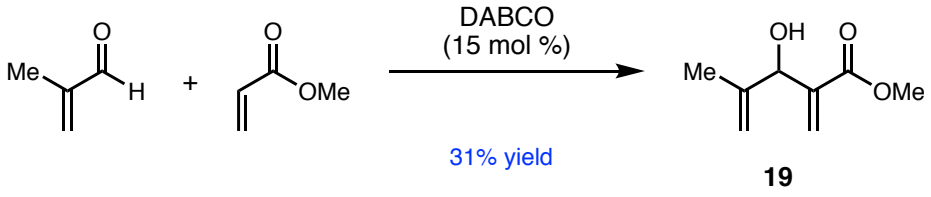
3.6.1 Materials and Methods

Unless otherwise stated, reactions were performed with freshly dried solvents utilizing standard Schlenk techniques. Glassware was oven-dried at 120 °C for a minimum of four hours or flame-dried utilizing a Bunsen burner under high vacuum. THF, Et_2O, DCM, MeCN, PhH, and PhMe were dried by passing through activated alumina columns. Et_3N, *i*-Pr_2NH, DIPEA, Pyr, and 2,6- lutidine were distilled from calcium hydride prior to use and stored under N_2 or Ar. Commercial reagents were used directly as supplied from commercial sources and without further purification unless otherwise specified. 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 (254 nm) and $KMnO_4$, p-anisaldehyde, iodine, or CAM staining. Flash column chromatography was performed as described by Still et al.[34] using silica gel (SiliaFlash® P60, particle size 40-63 microns [230 to 400 mesh]) purchased from Silicycle. ^1H and ^{13}C NMR spectra were recorded on a

Bruker Advance III HD with Prodigy Cryoprobe (at 400 MHz and 101 MHz, respectively) or Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to internal $CDCl_3$ (^1H, δ = 7.26), $CDCl_3$ (^{13}C, δ = 77.16). 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, p = pentet, hept = heptet, m = multiplet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system (CO_2 = 1450 psi, column temperature = 40 °C) with a Chiralcel OB-H column (4.6 mm x 25 cm). Molecular formulas of the compounds [M] are given, with the observed ion fragment in brackets, e.g. [M+H]+. Deuteriochloroform was purchased from Cambridge Isotope Laboratories.

3.6.2 Model System Synthesis

Preparation of 19:



19

Procedure: To a flame-dried 1L flask, equipped with a stir bar, was charged methyl acrylate (172 mL, 1.91 mol, 1.0 equiv), DABCO (32.2 g, 287 mmol, 15 mol %), and methacrolein (158, 1.91 mol, 1.0 equiv). Reaction sparged with N_2 for 60 mins, then allowed to stir for 10 days, wrapped in foil at room temperature. Remaining starting materials were then distilled away via rotary evaporation. Then DCM (300 mL) added

followed by 0.1 M HCL (300 mL). Reaction extracted 3X with DCM and washed with brine. Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Material was then purified via column chromatography (15% to 50% EtOAc/hexanes) to afford **19** (92.2g, 590 mmol, 31% yield) as a pale-yellow oil. Spectral data matched the literature.[35]

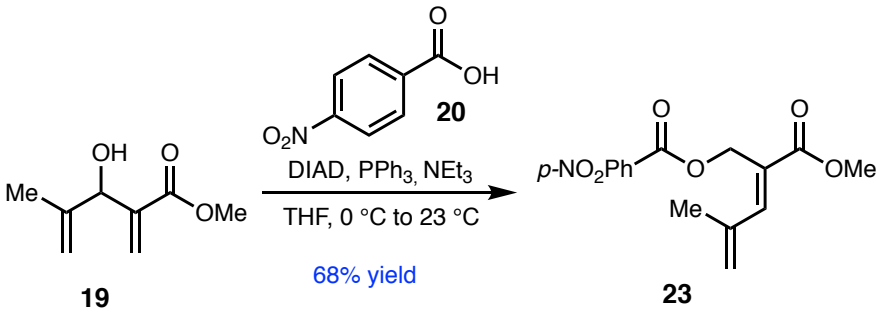
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (d, *J* = 1.1 Hz, 1H), 5.85 (t, *J* = 1.2 Hz, 1H), 5.08 (q, *J* = 1.2 Hz, 1H), 4.98 (dt, *J* = 2.9, 1.5 Hz, 1H), 4.90 (d, *J* = 1.4 Hz, 1H), 3.77 (s, 3H), 1.71 (dd, *J* = 1.4, 0.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.07, 144.64, 140.44, 126.40, 112.72, 74.72, 52.10, 18.90.

FTIR (NaCl, thin film): 2924, 2864, 1723, 1492, 1455, 1374, 1336, 1213, 1152, 1125, 1100, 1040, 918, 803, 734 cm^{-1}.

R_f = 0.25 in 20%EtOAc/hexanes (stains blue with p-anisaldehyde)

Preparation of 23:



Procedure: To a dry 2L flask, equipped with a stir bar, was charged PPh_3 (75.6 g, 288 mmol, 1.5 equiv), 4-nitrobenzoic acid (48.2 g, 288 mmol, 1.5 equiv), and placed under nitrogen. To this was added THF (1.60 L), followed by triethylamine (40.2 mL, 288 mmol,

1.5 equiv). Reaction then cooled to –10 °C for 1 h. Then DIAD (56.7 mL, 288 mmol, 1.5 equiv) added slowly over 1 h. Once DIAD finished adding, reaction stirred for 15 mins, and then alcohol **19** (30.0 g, 192 mmol, 1.0 equiv) was cannulated over 1 h, rinsed with THF (20 mL) to ensure quantitative transfer. Reaction then stirred overnight (16 hours) at room temperature. Reaction then quenched by addition of Et_2O and water. Mixture was then transferred to a separatory funnel and washed with H_2O, washed with 1N NaOH solution, and then extracted with Et_2O (3X). Combined organic layers were then washed with saturated aqueous $NaHCO_3$, and then washed with brine. Combined organic layers were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Material was then purified via column chromatography (10% EtOAc/hexanes) to afford **23** (58.6 g, 130.6 mmol, 68% yield) as an off white amorphous solid. Spectral data matched the literature.[36]

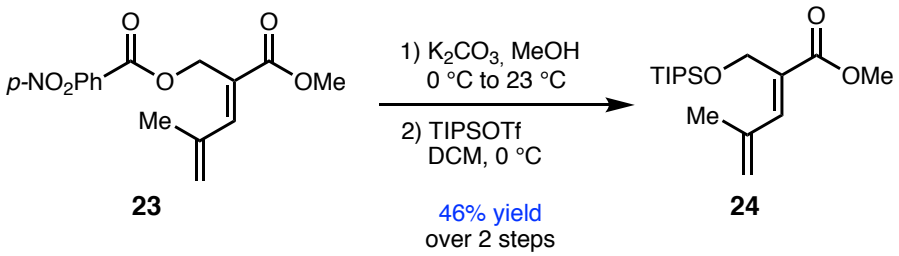
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.23 (m, 2H), 8.23 – 8.13 (m, 2H), 7.49 (s, 1H), 5.31 (t, *J* = 1.8 Hz, 1H), 5.23 (s, 2H), 5.21 (s, 1H), 3.81 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.32, 164.44, 150.71, 148.10, 139.91, 135.57, 130.92, 125.38, 123.68, 122.30, 60.32, 52.47, 22.14.

FTIR (NaCl, thin film): 2953, 1723, 1608, 1528, 1436, 1410, 1346, 1272, 1237, 1100, 957, 719.

R_f = 0.4 in 20%EtOAc/hexanes (stains blue with p-anisaldehyde)

Preparation of 24:



Procedure: To a 2L round bottomed flask, equipped with a stir bar, was charged **23** (33.0 g, 108 mmol, 1.0 equiv) followed by MeOH (1.00 L) and cooled to 0 °C under N_2. To this solution was added K_2CO_3 (29.9 g, 216 mmol, 2.0 equiv) as a solid. Reaction then warmed to room temperature and stirred for 4 hours. Whole flask then concentrated via rotary evaporation to remove MeOH. Then water (300 mL) added followed by DCM (500 mL). Mixture was then extract into DCM (4X), and then washed with brine. Combined organic layers were then dried over Na_2SO_4, filtered, and concentrated in vacuo. Mixture was then azeotroped with hexanes (2X) to remove any last traces of MeOH. Crude alcohol used in next step without further purification.

Procedure: To a 2L flask, equipped with a stir bar, was charged crude material from above followed by DCM (1.09 L). Reaction cooled to 0 °C, and then 2,6-lutidine (18.9 mL, 162 mmol, 1.5 equiv) added followed by TIPS(OTf) (37.8 mL, 141 mmol, 1.3 equiv). Reaction warmed to room temperature and stirred overnight. Reaction then quenched with saturated aqueous $NaHCO_3$ (400 mL) and then extracted with DCM (3X). Combined organic layers were then dried over Na_2SO_4, filtered, and concentrated in vacuo. Material was then purified via column chromatography (2.5% to 5% EtOAc/hexanes) to afford **24** (15.5 g, 49.7 mmol, 46% over 2 steps) as a pale-yellow oil.

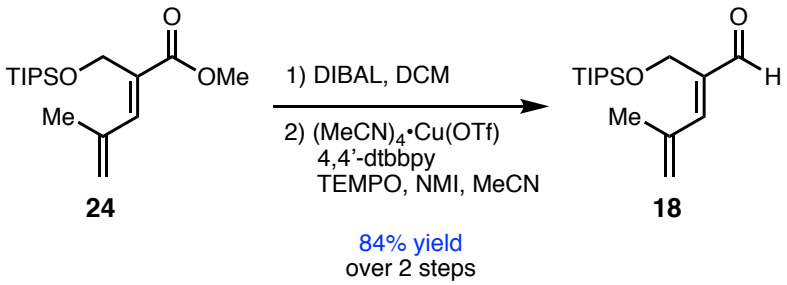
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 1.2 Hz, 1H), 5.33 (dp, *J* = 2.0, 0.9 Hz, 1H), 5.26 – 5.20 (m, 1H), 4.54 (s, 2H), 3.77 (s, 3H), 1.99 – 1.94 (m, 3H), 1.16 – 1.02 (m, 27H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.60, 144.22, 140.23, 131.11, 120.83, 57.78, 51.95, 22.32, 18.09, 17.84, 12.19.

FTIR (NaCl, thin film): 2943, 2866, 1721, 1611, 1462, 1433, 1296, 1234, 1117, 1081, 1063, 882, 752, 682, 658.

HRMS: (ESI) calc'd for $C_{17}H_{32}O_3Si$ $[M + H]^+$ 313.2198, found 313.2917.

Preparation of 18:



Procedure: To a 1L round bottom flask, equipped with a stir bar, was charged **24** (19.0 g, 60.8 mmol, 1.0 equiv), followed by DCM (553 mL). Solution was cooled to –78 °C and then DIBAL (1.0 M in DCM, 152 mL, 152 mmol, 2.5 equiv) added via cannula over 20 mins. Reaction stirred until complete consumption of ester **24** (1.5 hours). Reaction then quenched with saturated aqueous Rochelle's salt solution and stirred overnight (16 hours). To the reaction was then added H_2O and DCM. Reaction was extracted with DCM (6X), dried over Na_2SO_4, filtered, and concentrated in vacuo. Material was then purified via column chromatography (10% to 20% EtOAc/hexanes) to afford a crude oil (16.2 g). Material used directly in next step without further purification.

Procedure: To a 1L round bottom flask, equipped with a stir bar, was added crude material from above, $(MeCN)_4$•Cu(OTf) (795 mg, 2.11 mmol, 4 mol %), 4,4-dimethoxy-2,2'-bipyridine (456 mg, 2.11 mmol, 4 mol %), NMI (346 mg, 4.22 mmol, 8 mol %), TEMPO (330 mg, 2.11 mmol, 4 mol %), and MeCN (527 mL). Stirred at room temperature open to air for 3 hours. Reaction then filtered thru silica plug (250 g) eluting with 10% EtOAc/hexanes. Material was further purified via column chromatography (% EtOAc/hexanes) to afford **18** (14.43g, 51.1 mmol, 84%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 6.87 (d, *J* = 0.9 Hz, 1H), 5.56 (dq, *J* = 1.8, 0.9 Hz, 1H), 5.41 (p, *J* = 1.6 Hz, 1H), 4.51 (s, 2H), 2.15 (t, *J* = 1.2 Hz, 3H), 1.10 – 0.99 (m, 22H).

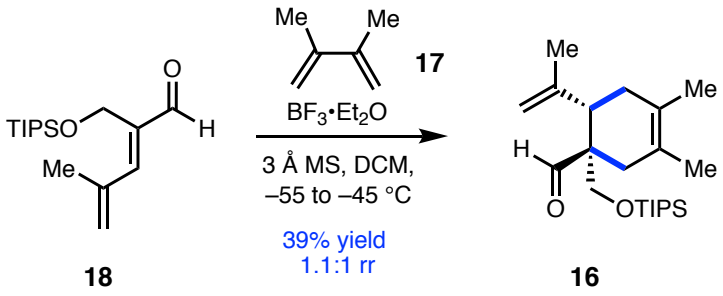
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.72, 154.86, 140.79, 139.74, 124.99, 54.29, 21.39, 17.85, 12.11.

FTIR (NaCl, thin film): 2942, 2865, 1687, 1620, 1461, 1382, 1174, 1085, 1065, 1015, 918, 881, 794, 680.

HRMS: (ESI) calc'd for $C_{16}H_{30}O_2Si$ $[M + H]^+$ 283.2093, found 283.2111.

R_f = 0.4 in 10% EtOAc/hexanes (stains gray in p-anisaldehyde)

Preparation of 16:



Procedure: To a 250 mL round-bottomed flask, equipped with a stir bar, was charged with 3 Å MS (powdered, 5.65 g), and a stir bar, then flame-dried under high vacuum for 5 minutes. The flask was cooled under N_2 then charged with dienophile **18** (5.65 g, 20.0 mmol, 1.0 equiv), 2,3-dimethylbutadiene (9.05 mL, 80.0 mmol, 4.0 equiv), and anhydrous DCM (100 mL). Reaction was then sparged with argon for 20 mins. Then the septum was sealed around the edges with parafilm and the reaction was transferred to the cryocool. The mixture was stirred at –55 °C under Ar for 15 mins, then BF_3•Et_2O (2.47, 20.0 mmol, 1.0 equiv) was added last, slowly, dropwise via syringe over 7 minutes. The balloon was removed, and 2 pieces of electric tape was placed on top of the septum. The reaction was warmed to –45 °C and stirred at –45 °C for 16 hours. The reaction was brought to the fume hood and quenched with sat. aq. $NaHCO_3$, with rapid stirring and agitation. The mixture was then filtered through a celite plug (NOTE!: make sure to stir the celite up and wash it with a good amount of DCM to ensure no product sticks to the celite). H_2O was added, and then the product was extracted 3x with DCM, dried over Na_2SO_4, filtered, and concentrated in vacuo. Material was further purified via column chromatography (2% Et2O/hexanes) to afford **16** (3.23 g, 7.80 mmol, 39%) as a murky white oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 4.85 (p, *J* = 1.6 Hz, 1H), 4.76 (d, *J* = 2.0 Hz, 1H), 3.95 (d, *J* = 9.5 Hz, 1H), 3.64 (d, *J* = 9.5 Hz, 1H), 2.73 (dd, *J* = 6.7, 4.5 Hz, 1H), 2.40 (d, *J* = 17.6 Hz, 1H), 2.16 – 2.05 (m, 1H), 2.00 (d, *J* = 16.3 Hz, 2H), 1.94 – 1.82 (m, 1H), 1.73 – 1.68 (m, 3H), 1.68 (s, 3H), 1.58 (s, 3H), 1.15 – 0.91 (m, 21H).

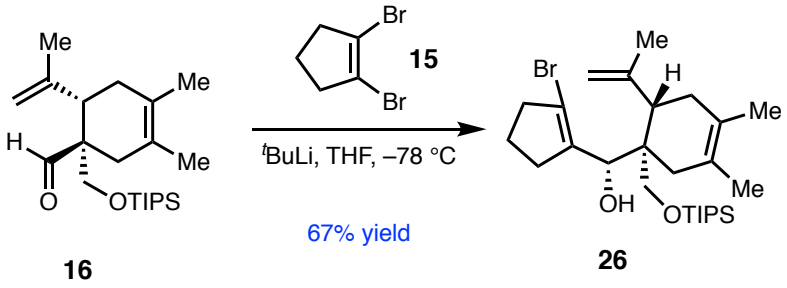
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.33, 146.19, 125.33, 123.51, 113.72, 66.45, 53.55, 41.90, 34.83, 32.77, 23.62, 19.24, 18.92, 18.10, 12.01.

FTIR (NaCl, thin film): 2940, 2865, 1728, 1457, 1377, 1105, 1067, 882, 801, 682, 523.

HRMS: (ESI) calc'd for $C_{22}H_{40}O_2Si$ $[M + H]^+$ 365.2876, found 365.2882.

R_f = 0.4 in 10% EtOAc/hexanes (stains gray in p-anisaldehyde)

Preparation of 26:



Procedure: To a flame-dried 250 mL round bottomed flask, equipped with a stir bar, was charged 1,2-dibromocyclopentene (1.91 mL, 16.0 mmol, 2.0 equiv) followed by THF (40 mL). The solution was cooled to –78 °C and then ^{t}BuLi (1.55 M in hexanes, 20.7 mL, 32.0 mmol, 4.0 equiv) added slowly via syringe. Solution stirred for 30 mins. Then aldehyde **16** (2.92 g, 8.00 mmol, 1.0 equiv) cannulated at –78 °C as a solution in THF (30 mL). Flask of aldehyde rinsed with THF (10 mL) to ensure quantitative transfer. Reaction stirred at –78 ° C for 30 mins. Reaction quenched with methanol (10 mL). Water (~50 mL) and Et_2O (100 mL) then added and layers separated. Extracted with Et_2O (3X) and the combined

organic layers dried over $MgSO_4$, filtered, and concentrated in vacuo. Material was then further purified via column chromatography (4% Et_2O/hexanes) to afford **26** (2.52 g, 5.36 mmol, 67%) as a thick pale-yellow oil.

26:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (t, *J* = 1.9 Hz, 1H), 4.69 (d, *J* = 2.3 Hz, 1H), 4.65 (d, *J* = 7.4 Hz, 1H), 4.34 (d, *J* = 7.5 Hz, 1H), 4.03 (d, *J* = 10.2 Hz, 1H), 3.62 (d, *J* = 10.3 Hz, 1H), 2.79 – 2.47 (m, 5H), 2.44 – 2.30 (m, 2H), 2.14 (dd, *J* = 7.1, 3.8 Hz, 1H), 2.06 – 1.96 (m, 3H), 1.82 – 1.77 (m, 1H), 1.68 (s, 6H), 1.62 (s, 4H), 1.17 – 1.00 (m, 32H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.47, 141.26, 123.84, 123.55, 121.33, 112.97, 74.02, 70.60, 44.17, 43.09, 40.20, 35.44, 35.06, 31.74, 31.35, 22.81, 22.55, 19.46, 18.76, 18.08, 14.27, 11.98.

FTIR (NaCl, thin film): 2928, 2863, 1733, 1457, 1381, 1264, 1096, 1015, 880, 808, 677, 598.

HRMS: (ESI) calc'd for $C_{27}H_{47}O_2BrSi$ $[M + H - H_2O]^+$ 493.2501, found 493.2490.

R_f = 0.40 in 7.5% Et_2O/hexanes (stains green in p-anisaldehyde)

26' (minor diastereomer):

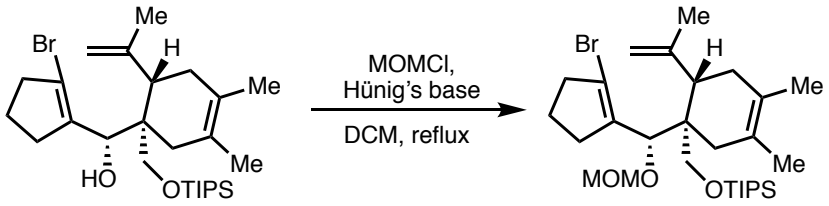
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 – 4.67 (m, 3H), 3.91 (d, *J* = 9.7 Hz, 1H), 3.72 (d, *J* = 9.7 Hz, 1H), 2.68 (t, *J* = 6.2 Hz, 1H), 2.53 (ttd, *J* = 8.0, 6.7, 5.4, 2.3 Hz, 4H), 2.38 (dtt, *J* = 15.8, 5.9, 2.8 Hz, 1H), 2.23 – 2.12 (m, 1H), 1.92 – 1.73 (m, 6H), 1.65 (s, 3H), 1.52 (dd, *J* = 5.8, 3.2 Hz, 10H), 1.02 (q, *J* = 5.8, 4.6 Hz, 27H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.81, 140.88, 124.58, 123.91, 121.46, 113.85, 75.64, 69.34, 44.35, 44.25, 40.17, 35.78, 33.84, 31.52, 22.65, 22.44, 19.38, 18.79, 18.17, 12.30.

HRMS: (ESI) calc'd for $C_{27}H_{47}O_2BrSi$ $[M + H - H_2O]^+$ 493.2501, found 493.2493.

$\mathbf{R_f}$ = 0.45 in 7.5% Et_2O/hexanes (stains purple in p-anisaldehyde)

Preparation of 27:



26 **27**

Procedure: A oven-dried, 25ml vial, equipped with a stir bar, was charged with **26** (2.00 g, 3.91 mmol, 1.0 equiv), anhydrous DCM (39.1 mL), freshly distilled Hunig's base (15.0 mL, 86.0 mmol, 22.0 equiv). To the homogeneous solution was added MOMCl (5.94 mL, 78.2 mmol, 20.0 equiv) dropwise over 10 min, taking care to vent HCl fumes formed via the use of a needle. The reaction was stirred at room temperature for 36 hours. The resulting mixture was quenched via addition of sat. aq. $NaHCO_3$ and stirred at room temperature for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated. Material was further purified via column chromatography (20% EtOAc/hexanes) to afford **27** as a white amorphous solid which was used directly in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 – 4.77 (m, 2H), 4.56 – 4.38 (m, 4H), 3.74 (d, *J* = 10.0 Hz, 1H), 3.64 (d, *J* = 10.0 Hz, 1H), 3.37 (s, 3H), 2.87 (dd, *J* = 11.3, 5.9 Hz, 1H), 2.58 (tdd, *J* = 14.2, 11.9, 5.6 Hz, 3H), 2.44 (ddd, *J* = 15.0, 9.2, 3.5 Hz, 1H), 2.36 – 2.12

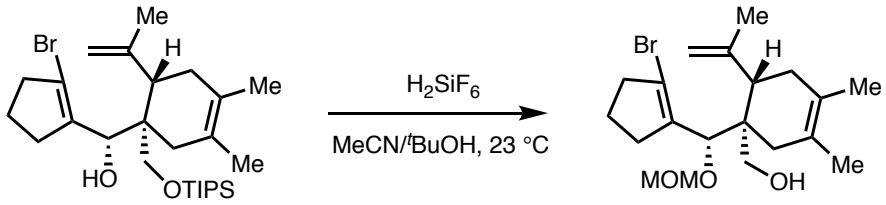
(m, 4H), 1.90 (ttd, J = 17.4, 8.8, 4.1 Hz, 3H), 1.77 (s, 3H), 1.70 – 1.47 (m, 9H), 1.10 – 0.92 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.67, 140.49, 125.07, 123.44, 121.47, 114.37, 96.01, 78.10, 62.70, 56.63, 46.73, 40.08, 36.07, 32.67, 32.43, 22.74, 22.06, 19.41, 18.59, 18.18, 18.04, 12.23.

FTIR (NaCl, thin film): 2941, 2865, 1633, 1462, 1379, 1149, 1080, 1030, 883, 812, 682.

HRMS: (ESI) calc'd for $C_{29}H_{51}O_3BrSi$ $[M + H - OMOM]^+$ 493.2501, found 493.2508.

Preparation of 14:



26 **14**

Procedure: To a 100 mL round bottomed flask, equipped with a stir bar, was charged alcohol **26** (640 mg, 1.25 mmol, 1.0 equiv) followed by 9:1 MeCN/^{t}BuOH (37.9 mL) [34.11 mL of MeCN, 3.79 mL of ^{t}BuOH]. Solution cooled to 0 °C and then H_2SiF_6 (1.30 mL, 3.75 mmol, 3.0 equiv) added via microsyringe. Reaction stirred at 0 °C and monitored by TLC until complete consumption of starting material (12 h). Reaction was then quenched with brine, diluted with DCM, extract with DCM (3X), filtered over celite, and concentrated in vacuo. Material was then further purified via column chromatography (40% EtOAc/hexanes) to afford **14** (329 mg, 0.925 mmol, 74% yield over 2 steps) as a clear colorless thick oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 – 4.71 (m, 1H), 4.68 (dd, *J* = 2.5, 0.8 Hz, 2H), 4.50 (d, *J* = 6.6 Hz, 1H), 4.44 (d, *J* = 6.6 Hz, 1H), 3.95 (d, *J* = 11.6 Hz, 1H), 3.46 – 3.40 (m, 1H), 3.40 (s, 0H), 3.19 (d, *J* = 9.7 Hz, 1H), 2.86 – 2.68 (m, 1H), 2.67 – 2.46 (m, 3H), 2.44 – 2.31 (m, 1H), 2.18 – 2.08 (m, 2H), 2.07 – 1.88 (m, 2H), 1.81 – 1.72 (m, 1H), 1.68 (qd, *J* = 1.5, 1.0 Hz, 6H), 1.66 – 1.61 (m, 3H).

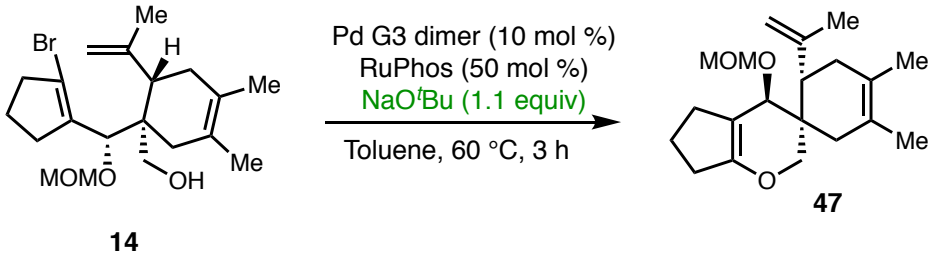
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.63, 138.12, 125.10, 124.35, 123.19, 113.13, 94.72, 79.38, 68.47, 56.63, 43.80, 43.50, 40.27, 35.42, 34.48, 31.87, 22.87, 22.72, 19.39, 18.80.

FTIR (NaCl, thin film): 3515, 2914, 1631, 1441, 1208, 1150, 1025, 894, 524.

HRMS: (ESI) calc'd for $C_{20}H_{31}O_3Br$ $[M + Na]^+$ 421.1354, found 421.1357.

3.6.3 Palladium Cyclization Studies

Preparation of 47:



14 **47**

Procedure: To a 1-dram vial, equipped with a stir bar, in a nitrogen filled glovebox, was added Pd G3 dimer (5.6 mg, 0.00751 mmol, 10 mol), RuPhos (17.5 mg, 0.0376 mmol, 50 mol %), NaO^{t}Bu (7.9 mg, 0.0826 mmol, 1.1 equiv), alcohol **14** (30 mg, 0.075 mmol, 1.0 equiv) followed by PhMe (2.0 mL). Reaction capped and removed from glovebox. Then brought to hood and stirred at 60 °C for 3 hours. Reaction then quenched with sat. aq. $NaHCO_3$, extracted with Et_2O (3X), washed with water, dried over $MgSO_4$, filtered,

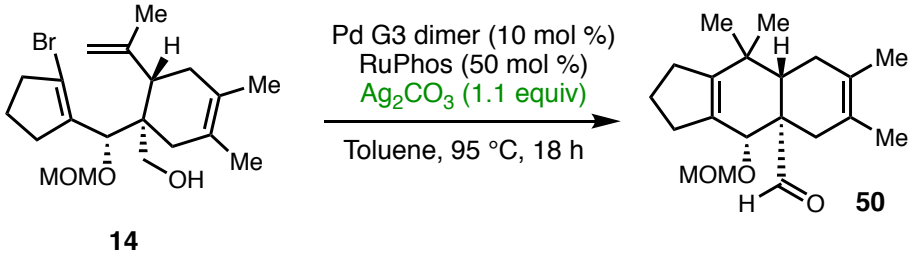
concentrated in vacuo. Material was then purified by preparatory TLC (40% EtOAc/hexanes) to afford **47**.

^{1}H NMR (500 MHz, cdcl$_3$) δ 7.26 (s, 2H), 4.84 (t, *J* = 1.9 Hz, 1H), 4.76 (d, *J* = 2.4 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 3.73 (s, 1H), 3.70 – 3.63 (m, 2H), 3.38 (s, 3H), 2.55 (dt, *J* = 14.3, 7.3 Hz, 1H), 2.42 – 2.19 (m, 5H), 2.00 – 1.83 (m, 4H), 1.76 (s, 3H), 1.71 (d, *J* = 17.9 Hz, 1H), 1.62 (s, 6H).

^{13}C NMR (101 MHz) δ 154.33, 148.51, 124.92, 123.36, 112.88, 106.27, 96.81, 77.48, 77.16, 76.84, 72.65, 69.21, 55.72, 41.08, 39.53, 35.14, 31.35, 31.32, 30.91, 24.05, 20.04, 19.31, 18.77.

HRMS: (ESI) calc'd for $C_{20}H_{30}O_3$ $[M + NH_4]^+$ 336.2538, found 336.2496.

Preparation of 50:



14 **50**

Procedure: To a 1-dram vial, equipped with a stir bar, in a nitrogen filled glovebox, was added Pd G3 dimer (5.6 mg, 0.00751 mmol, 10 mol), RuPhos (17.5 mg, 0.0376 mmol, 50 mol %), Ag_2CO_3 (20.7 mg, 0.0751 mmol, 1.0 equiv), alcohol **14** (30 mg, 0.075 mmol, 1.0 equiv) followed by PhMe (2.0 mL). Reaction capped and removed from glovebox. Then brought to hood and stirred at 95 °C for 18 hours. Reaction then quenched with sat. aq. $NaHCO_3$, extracted with Et_2O (3X), washed with water, dried over MgSO4, filtered,

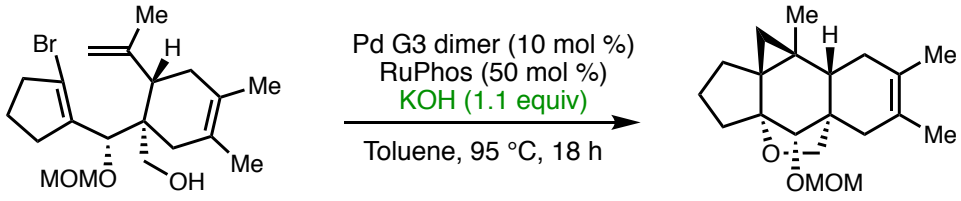
concentrated in vacuo. Material was then purified by preparatory TLC (40% EtOAc/hexanes) to afford **50**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.02 (s, 1H), 3.39 (s, 3H), 2.78 – 2.70 (m, 1H), 2.64 – 2.54 (m, 1H), 2.43 – 2.31 (m, 2H), 2.21 – 2.11 (m, 2H), 1.86 – 1.78 (m, 3H), 1.71 – 1.67 (m, 3H), 1.64 (ddt, *J* = 2.3, 1.6, 0.8 Hz, 3H), 1.09 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.72, 147.74, 132.30, 124.48, 122.28, 97.66, 72.73, 56.20, 53.42, 41.13, 36.31, 35.22, 31.81, 30.47, 30.02, 28.53, 22.64, 22.29, 19.12, 18.99.

HRMS: (ESI) calc'd for $C_{20}H_{30}O_3$ $[M + NH_4]^+$ 336.2538, found 336.2500.

Preparation of 55:



14 20% yield **55**

Procedure: To a 1-dram vial, equipped with a stir bar, in a nitrogen filled glovebox, was added Pd G3 dimer (5.6 mg, 0.00751 mmol, 10 mol), RuPhos (17.5 mg, 0.0376 mmol, 50 mol %), Ag_2CO_3 (20.7 mg, 0.0751 mmol, 1.0 equiv), alcohol **14** (30 mg, 0.075 mmol, 1.0 equiv) followed by PhMe (2.0 mL). Reaction capped and removed from glovebox. Then brought to hood and stirred at 95 °C for 18 hours. Reaction then quenched with sat. aq. $NaHCO_3$, extracted with Et_2O (3X), washed with water, dried over $MgSO_4$, filtered, concentrated in vacuo. Material was then purified by preparatory TLC (40% EtOAc/hexanes) to afford **55**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 1.1 Hz, 2H), 4.69 – 4.61 (m, 2H), 3.83 (dd, *J* = 8.5, 1.6 Hz, 1H), 3.64 (d, *J* = 1.4 Hz, 1H), 3.63 – 3.59 (m, 1H), 3.41 (d, *J* = 1.2 Hz, 3H), 2.16 – 1.65 (m, 8H), 1.61 (d, *J* = 8.6 Hz, 6H), 1.54 (d, *J* = 18.8 Hz, 2H), 1.43 (ddt, *J* = 9.7, 7.4, 3.0 Hz, 1H), 1.30 – 1.24 (m, 2H), 0.99 (d, *J* = 10.1 Hz, 1H), 0.94 (s, 3H).

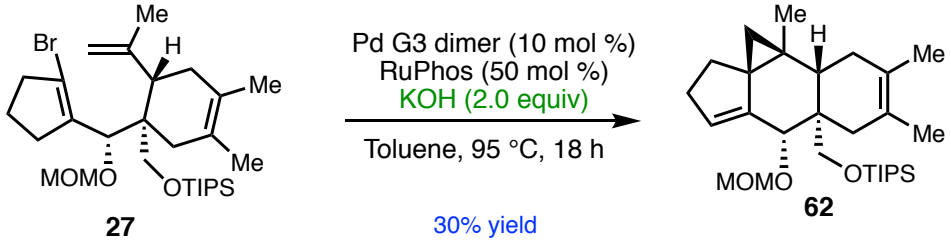
^{13}C NMR (101 MHz, $CDCl_3$) δ 125.34, 123.69, 96.75, 84.49, 82.86, 62.51, 56.68, 56.04, 45.00, 44.23, 41.03, 38.70, 31.94, 31.21, 28.22, 26.01, 19.18, 16.58.

FTIR (NaCl, thin film): 2924, 2864, 1723, 1492, 1455, 1374, 1336, 1213, 1152, 1125, 1100, 1040, 918, 803, 734 cm^{-1}.

HRMS: (ESI) calc'd for $C_{20}H_{30}O_3$ $[M + H]^+$ 319.2273, found 319.2263.

TLC (8% Et_2O/hexanes): R_f 0.15 (anisaldehyde, stains blue).

Preparation of 62:



Procedure: To an oven-dried 2-dram vial, equipped with a stir bar, in an N_2-filled glovebox, was charged Pd G3 dimer (3.70 mg, 0.005 mmol, 10 mol %), RuPhos (11.7 mg, 0.0250 mmol, 50 mol %), KOH (5.61 mg, 0.100 mmol, 2.0 equiv), and alcohol **14** (27.8 mg, 0.005 mmol, 1.0 equiv). The reaction was sealed with a Teflon-lined cap and electrical tape, removed from the glovebox, and stirred at 95 °C for 23 hours. The reaction was cooled to ambient temperature, then run through a silica plug (30% EtOAc/hexanes) and

concentrated in vacuo. Material then further purified via column chromatography (1% Et_2O/hexanes) to afford **62** (7.2 mg, 0.0015 mmol, 30%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 – 5.33 (m, 1H), 4.64 (dd, *J* = 37.6, 6.8 Hz, 3H), 3.87 (s, 1H), 3.71 – 3.53 (m, 4H), 3.42 (s, 4H), 2.82 – 2.43 (m, 2H), 2.44 – 2.18 (m, 4H), 2.18 – 1.96 (m, 7H), 1.90 – 1.66 (m, 4H), 1.66 – 1.51 (m, 12H), 1.10 – 0.93 (m, 36H), 0.62 – 0.50 (m, 3H).

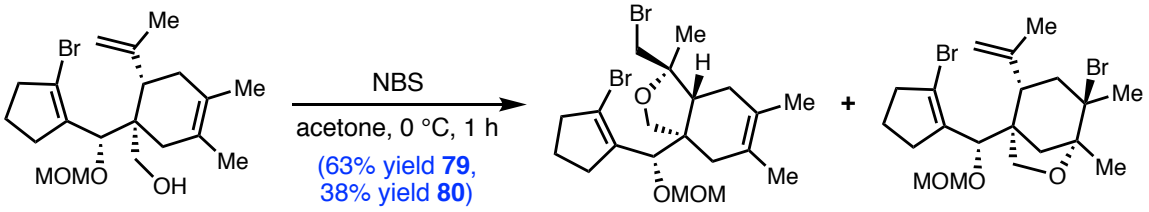
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.84, 125.77, 124.46, 124.33, 120.41, 120.02, 118.93, 108.52, 96.44, 83.09, 77.45, 77.34, 77.14, 76.82, 62.79, 60.52, 55.92, 47.45, 44.10, 39.18, 39.08, 33.74, 31.68, 31.64, 30.47, 21.18, 21.07, 19.08, 18.93, 18.80, 18.15, 18.09, 14.33, 12.07.

FTIR (NaCl, thin film): 3045, 2924, 2864, 1590, 1462, 1380, 1245, 1215, 1153, 1124, 1103, 1038, 918, 842, 836, 807, 683, 657.

TLC (8% Et_2O/hexanes): R_f 0.15 (anisaldehyde, stains blue).

3.6.4 Nickel Reductive Coupling Studies

Preparation of 79 and 80:



14 **79** **80**

Procedure: In a 50-mL round-bottomed flask, alcohol **14** (304 mg, 0.761 mmol, 1.0 equiv) was dissolved in anhydrous acetone (7.61 mL). The solution was cooled to 0 °C under an atmosphere of N_2, and then *N*-bromosuccinimide (142 mg, 0.799 mmol, 1.05 equiv) was

added as a solid. The reaction was stirred at 0 °C for 1 h under N_2 then quenched with 10% aqueous $NaHSO_3$ (5 mL). The mixture was diluted with H_2O (25 mL) then extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (5 to 10% EtOAc/hexanes) to afford ether **79** (231 mg, 0.483 mmol, 63% yield) as a white solid and ether **80** (140 mg, 0.293 mmol, 38% yield) as a colorless oil.

79:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47 (s, 1H), 4.44 (s, 2H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.54 (d, *J* = 8.9 Hz, 1H), 3.41 (s, 3H), 3.40 – 3.31 (m, 2H), 2.79 – 2.57 (m, 2H), 2.56 – 2.42 (m, 1H), 2.42 – 2.32 (m, 1H), 2.32 – 2.21 (m, 2H), 2.17 (dt, *J* = 8.0, 1.4 Hz, 1H), 2.09 – 1.86 (m, 3H), 1.81 (d, *J* = 17.7 Hz, 1H), 1.67 (s, 6H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 124.7, 124.3, 124.3, 94.7, 84.4, 77.7, 74.1, 56.5, 50.3, 44.9, 43.6, 40.3, 36.5, 32.0, 31.1, 22.7, 21.3, 19.7, 18.8.

FTIR (NaCl, thin film): 2927, 2854, 1443, 1208, 1143, 1094, 1027, 921 cm^{-1}.

HRMS: (FAB) calc'd for $C_{18}H_{25}Br_2O$ $[M - OMOM]^+$ 417.0252, found 417.0238.

TLC (10% EtOAc/hexanes): R_f 0.32 (anisaldehyde, stains orange).

80:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (dt, *J* = 2.2, 0.7 Hz, 1H), 4.90 (t, *J* = 1.7 Hz, 1H), 4.52 (d, *J* = 6.3 Hz, 1H), 4.50 – 4.43 (m, 2H), 4.16 – 4.06 (m, 1H), 3.54 (dd, *J* = 8.8, 1.4 Hz, 1H), 3.39 (s, 3H), 3.14 – 3.04 (m, 1H), 2.74 (d, *J* = 12.4 Hz, 1H), 2.71 – 2.58 (m, 2H), 2.58 – 2.36 (m, 2H), 2.19 – 2.05 (m, 2H), 2.03 – 1.88 (m, 2H), 1.85 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.80 (d, *J* = 12.4 Hz, 1H), 1.73 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.8, 139.1, 122.7, 115.0, 96.8, 85.6, 76.8, 71.8, 71.4, 56.9, 52.6, 47.3, 45.3, 45.0, 40.1, 33.0, 28.8, 23.0, 21.7, 21.4.

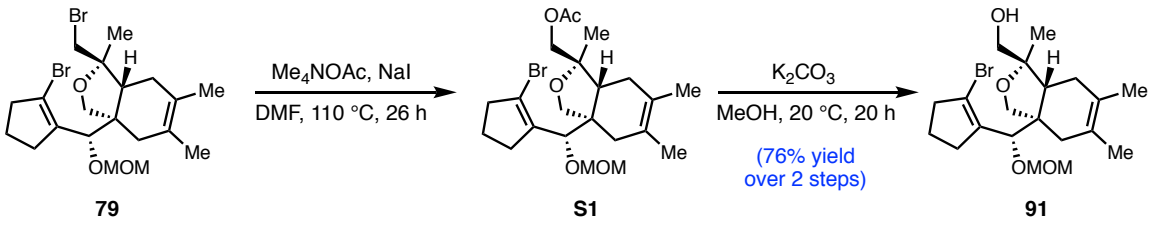
FTIR (NaCl, thin film): 2934, 1449, 1378, 1154, 1093, 1034, 1014, 903 cm^{-1}.

HRMS: (ESI) calc'd for $C_{20}H_{34}NO_3Br_2$ $[M + NH_4]^+$ 494.0905, found 494.0903.

TLC (10% EtOAc/hexanes): R_f 0.40 (anisaldehyde, stains green).

3.6.5 NHK Studies

Preparation of 91:



Procedure: A 2-dram vial was charged with alkyl bromide **79** (291 mg, 0.608 mmol, 1 equiv) and a stir bar then brought into an N_2-filled glovebox. Me_4NOAc (162 mg, 1.22 mmol, 2 equiv), NaI (18.2 mg, 0.122 mmol, 20 mol %), and DMF (3.04 mL) were added in that order. The vial was sealed with a Teflon-lined screw cap, removed from the glovebox, and stirred at 110 °C for 26 h. The reaction was cooled to ambient temperature, diluted with H_2O (20 mL), then extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with 1 M aqueous LiCl (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude acetate **S1** was carried forward without further purification.

A 50 mL round-bottomed flask was charged with crude **S1** and a stir bar. K_2CO_3 (252 mg, 1.82 mmol, 3 equiv) was added, followed by MeOH (12.2 mL). The reaction was

stirred at 20 °C under N_2 for 20 h, then quenched with saturated aqueous NH_4Cl (10 mL). The mixture was diluted with H_2O (10 mL), then extracted with DCM (4 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (30% EtOAc/hexanes) to afford alcohol **90** (191 mg, 0.462 mmol, 76% yield) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.46 (s, 1H), 4.45 – 4.36 (m, 2H), 3.87 (d, *J* = 8.7 Hz, 1H), 3.51 (d, *J* = 8.7 Hz, 1H), 3.38 (s, 3H), 3.37 – 3.24 (m, 2H), 2.76 – 2.56 (m, 2H), 2.50 – 2.24 (m, 3H), 2.22 – 2.14 (m, 2H), 2.04 – 1.81 (m, 3H), 1.71 (d, *J* = 10.4 Hz, 1H), 1.69 – 1.64 (m, 6H), 0.97 (s, 3H).

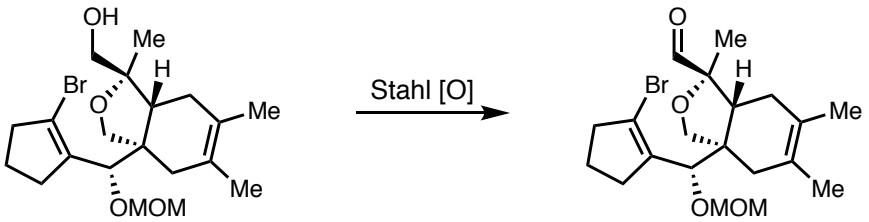
^{13}C NMR (101 MHz, CD_2Cl_2): δ 138.6, 125.4, 124.4, 124.3, 94. 9, 86.5, 78.5, 74.7, 69.7, 56.4, 49.9, 41.7, 40.5, 36.9, 32.0, 30.6, 22.9, 19.7, 19.5, 18.8.

FTIR (NaCl, thin film): 3426, 2924, 2855, 1443, 1155, 1142, 1094, 1027 cm^{-1}.

HRMS: (ESI) calc'd for $C_{20}H_{31}O_4BrNa$ $[M + Na]^+$ 437.1303, found 437.1307.

TLC (30% EtOAc/hexanes): R_f 0.25 (anisaldehyde, stains dark purple).

Preparation of 91:



90 (54% yield) **91**

Procedure: A 50 mL round-bottomed flask was charged with $(MeCN)_4CuOTf$ (15.1 mg, 0.04 mmol, 0.10 equiv), 4,4'-dimethoxy-2,2'-bipyridine (8.65 mg, 0.04 mmol, 0.10 equiv), MeCN (8 mL), and a stir bar then stirred at ambient temperature until a bright blue complex

formed. *N*-methylimidazole (6.38 μL, 0.08 mmol, 0.20 equiv) and ABNO (5.61 mg, 0.04 mmol, 0.10 equiv) were added, followed by alcohol **90** (166 mg, 0.40 mmol, 1 equiv). The flask was equipped with a rubber septum, and then the reaction was stirred at 50 °C under a balloon of O_2 for 19 h.

The reaction was cooled to ambient temperature and then extracted with pentane (3 x 30 mL). Water (5 mL) was added to the MeCN layer, which was then extracted again with pentane (3 x 30 mL). The combined pentane extracts were then concentrated *in vacuo* onto Celite. The crude mixture was purified by silica gel chromatography (12% EtOAc/hexanes) to afford aldehyde **91** (89.2 mg, 0.216 mmol, 54% yield) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 4.46 (s, 1H), 4.42 (d, *J* = 1.6 Hz, 2H), 3.99 (d, *J* = 9.0 Hz, 1H), 3.69 (d, *J* = 8.9 Hz, 1H), 3.39 (s, 3H), 2.74 – 2.57 (m, 2H), 2.42 – 2.22 (m, 4H), 2.17 (dd, *J* = 17.1, 7.2 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.99 – 1.87 (m, 2H), 1.87 – 1.78 (m, 1H), 1.70 – 1.65 (m, 6H), 1.14 (s, 3H).

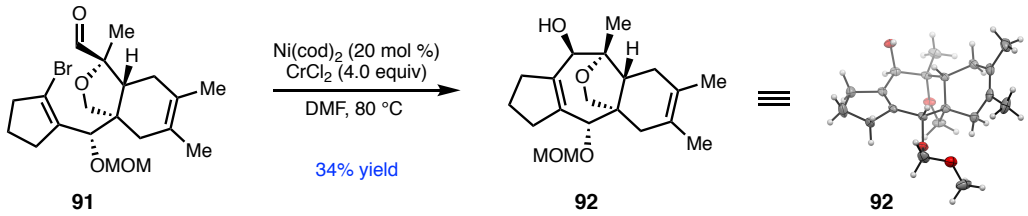
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.2, 137.7, 125.3, 125.0, 124.8, 94.5, 89.2, 77.8, 76.0, 56.5, 50.6, 41.6, 40.2, 37.1, 31.9, 29.9, 22.5, 19.5, 18.8, 17.2.

FTIR (NaCl, thin film): 2929, 1733, 1440, 1142, 1094, 1028, 921 cm^{-1}.

HRMS: (ESI) calc'd for $C_{20}H_{29}O_4BrNa$ $[M + Na]^+$ 435.1147, found 435.1130.

TLC (20% EtOAc/hexanes): R_f 0.35 (anisaldehyde, stains gray).

Preparation of 92:



Procedure: A 1-dram vial was charged with aldehyde **91** (8.27 mg, 0.0200 mmol, 1.0 equiv) and a stir bar then brought into the glovebox. $Ni(cod)_2$ (0.0730 uL, 0.004 mmol, 20 mol %) and $CrCl_2$ (1.70 uL, 0.08 mmol, 4.0 equiv) were added as solids, followed by DMF (200 uL). The vial was sealed with a Teflon-lined screw cap, removed from the glovebox, and then stirred at 80 °C for 18 h. The reaction was cooled to ambient temperature then filtered over a silica plug eluting with 50% EtOAc/hexane. Sample then concentrated in vacuo and transferred to an NMR tube with an internal standard of tetrachloroethane. 34% yield by NMR. **92** could be recrystallized to afford X-ray quality crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80 – 4.70 (m, 2H), 4.04 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 1H), 3.79 (s, 1H), 3.45 (s, 3H), 3.41 (dd, *J* = 8.3, 1.2 Hz, 1H), 2.77 – 2.66 (m, 2H), 2.52 – 2.32 (m, 2H), 2.28 – 2.18 (m, 1H), 2.06 – 2.01 (m, 1H), 2.00 (d, *J* = 1.9 Hz, 3H), 1.96 (s, 1H), 1.88 – 1.78 (m, 1H), 1.77 (s, 3H), 1.74 (s, 4H), 1.73 – 1.65 (m, 1H), 1.27 – 1.24 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.39, 135.33, 129.00, 127.33, 99.54, 86.18, 85.52, 74.68, 56.65, 54.43, 44.39, 38.48, 37.99, 37.90, 32.01, 29.86, 22.17, 21.43, 19.63, 18.83.

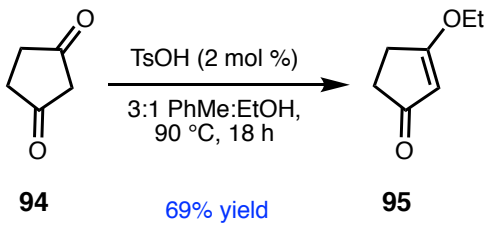
FTIR (NaCl, thin film): 2853, 1458, 1376, 1027, 723, 671 cm^{-1}.

HRMS: (ESI) calc'd for $C_{20}H_{29}O_4BrNa$ $[M + Na]^+$ 435.1147, found 435.1130.

TLC (20% EtOAc/hexanes): R_f 0.35 (anisaldehyde, stains gray).

3.6.6 A Ring Progress

Preparation of 95:



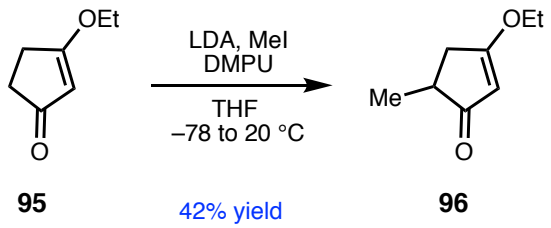
Procedure: A 250 mL round-bottomed flask equipped with a reflux condenser was charged with 1,3-cyclopentanedione **94** (4.18 g, 42.6 mmol, 1.0 equiv TsOH (162 mg, 0.852 mmol, 0.5 mol %), EtOH (21.3 mL), and PhMe (63.9 mL). The reaction was stirred at 90 °C under N_2 for 18 hours. The reaction mixture then was cooled to ambient temperature, concentrated, and then diluted with Et_2O and water. The organic layer was washed twice with sat. aq. $NaHCO_3$ then once with brine. Basified with $NaHCO_3$ then extracted once with ether, still not good enough. Added NaCl and extracted 3x with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to afford **95** (3.71 g, 29.40 mmol, 69%) as an orange oil. Spectral data matched the literature.[37]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (t, *J* = 1.2 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.64 – 2.56 (m, 2H), 2.48 – 2.40 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.29, 190.39, 104.79, 67.85, 34.07, 28.69, 14.27.

FTIR (NaCl, thin film): 2983, 2929, 1703, 1678, 1592, 1440, 1374, 1342, 1289, 1274, 1184, 1028, 876, 842, 657 cm^{-1}.

Preparation of 96:



95 42% yield **96**

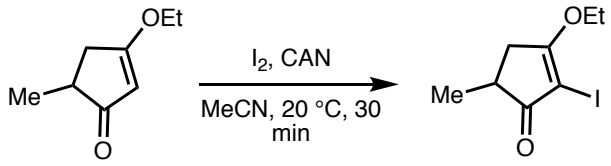
Procedure: A flame-dried round-bottomed flask was charged with diisopropylamine (20.4 mL, 145 mmol, 1.4 equiv) and THF (60 mL) then cooled to –78 °C under N_2. ^{n}BuLi (2.5 M in hexanes, 56.9 mL, 142 mmol, 1.37 equiv) was added via cannula, and the reaction was stirred for 30 minutes. Enone **95** (1.31 g, 104 mmol, 1.0 equiv) was added over 30 minutes as a solution in THF (60 mL), and then the solution was stirred for an additional 45 minutes. MeI (9.70 mL, 156 mmol, 1.5 equiv) and DMPU (25.1 mL, 208 mmol, 2.0 equiv) were added slowly as a solution in THF (60 mL), and then the reaction was slowly allowed to warm to ambient temperature, stirring for an additional 1 hour. The reaction was quenched with water, and then the aqueous layer was extracted 3x with EtOAc. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Material was further purified via column chromatography (30% EtOAc/hexanes) to afford **96** (7.73 g, 43.68 mmol, 42%) as a dark yellow oil. Spectral data matched the literature.[38]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (t, *J* = 1.2 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.82 (ddd, *J* = 17.5, 7.3, 1.2 Hz, 1H), 2.49 (pd, *J* = 7.4, 2.8 Hz, 1H), 2.20 (ddd, *J* = 17.7, 2.8, 1.1 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.20, 188.76, 103.38, 67.68, 39.78, 37.24, 16.86, 14.28.

FTIR (NaCl, thin film, cm^{-1}): 2929, 1696, 1593, 1373, 1341, 1278, 1247, 1221, 1193, 1175, 1027, 920, 862, 813, 635.

Preparation of 97:



96 78% yield **97**

Procedure: An oven-dried round-bottomed flask was charged with vinylogous ester **96** (7.73 g, 44.1 mmol, 1.0 equiv) and MeCN (294 mL). The solution was cooled to 0 ºC via an ice/water bath and stirring was continued for 15 min prior to the addition of iodine (11.8 g, 46.3 mmol, 1.05 equiv), then CAN (25.4 g, 46.3 mmol, 1.05 equiv) in quick succession. The reaction mixture was immediately removed from the ice/water bath and the reaction was continued for 30 min at ambient temperature, during which time CAN slowly solubilized to give a deep red-black solution. The reaction mixture was recooled to 0 º C via an ice/water bath and carefully quenched with the addition of sat. aq. $Na_2S_2O_3$. The resulting biphasic mixture was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Material further purified via column chromatography (35% to 45% EtOAc/hexanes) to afford **97** (9.54 g, 34.40 mmol, 78%) as an off-white solid.

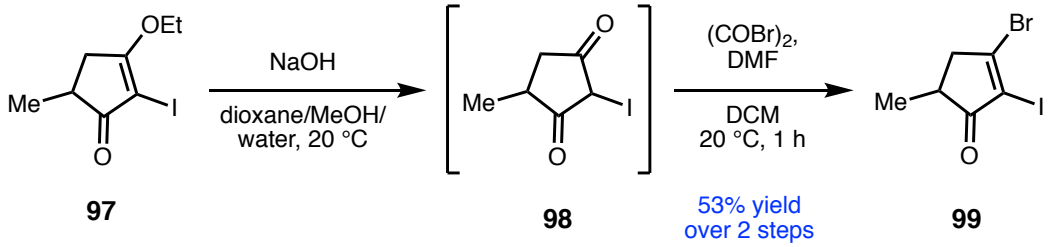
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (q, *J* = 7.1 Hz, 2H), 3.09 (dd, *J* = 17.4, 7.0 Hz, 1H), 2.72 (pd, *J* = 7.3, 2.4 Hz, 1H), 2.43 (dd, *J* = 17.4, 2.4 Hz, 1H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.78, 187.49, 72.89, 66.72, 38.92, 36.25, 17.38, 15.28.

FTIR (NaCl, thin film, cm^{-1}): 2977, 2927, 1690, 1585, 1371, 1337, 1268, 1108, 1043, 1019, 922, 859, 832, 597.

HRMS: (ESI) calc'd for $C_8H_{11}O_2I$ $[M + H]^+$ 266.9882, found 266.9876.

Preparation of 99:



Procedure: A round-bottomed flask was charged with iodoester **97** (1.33 g, 5.00 mmol, 1.0 equiv), dioxane (20.0 mL), MeOH (20.0 mL), and then NaOH (1M in H_2O, 50.0 mL, 50.0 mmol, 10 equiv). The resulting reaction mixture was stirred at ambient temperature for 20 hours. The reaction was quenched with 1 M HCl (final pH = 1) and diluted with 10% ^{i}PrOH/$CHCl_3$.The layers were separated, and the aqueous layer was extracted 7x with 10% ^{i}PrOH/$CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.The crude residue was then semi-purified via a SiO_2 plug (12/1/87 MeOH/Et_3N/$CHCl_3$) to afford a yellow oil. This material was then dried thoroughly on high vac, azeotroping 3x with hexanes then stirring on high vac, and carried directly forward into the next step.

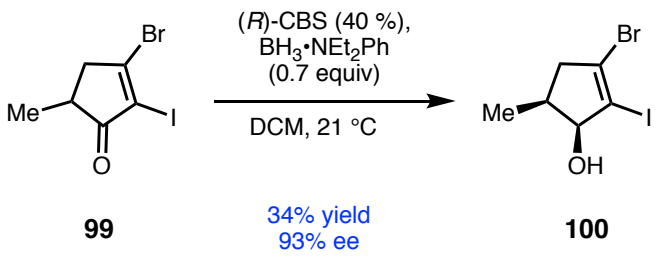
Procedure: An oven-dried round-bottomed flask was charged with 1,3-diketone **98** (1.19 g, 5 mmol, 1.0 equiv) and anhydrous DCM (50.0 mL), then stirred at 0 °C under N_2. Anhydrous DMF (1.16 mL, 15.0 mmol, 3.0 equiv) was next added, and stirring continued for 15 min at 0 º C before the dropwise addition of oxalyl bromide (1.07 mL, 7.50 mmol, 1.5 equiv) via syringe [Caution! Rapid generation of CO and CO_2. A vent needle was routinely used during this addition to prevent over-pressurization.]. Upon complete addition, the ice/water bath was removed and stirring was continued for 1 hour before pouring the reaction mixture over DCM and ice-cold H_2O. The layers were separated, and the aqueous layer was extracted 3x with DCM. The combined organic layers were washed with sat. aq. $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated. The material was further purified via column chromatography (9% Et_2O/hexanes) to afford **99** (793 mg, 2.65 mmol, 53% over 2 steps) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (dd, *J* = 18.3, 7.0 Hz, 1H), 2.83 – 2.72 (m, 1H), 2.68 (dd, *J* = 18.3, 2.5 Hz, 1H), 1.27 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.88, 165.18, 107.39, 46.61, 41.19, 16.53.

FTIR (NaCl, thin film, cm^{-1}): 2975, 1706, 1687, 1561, 1199, 1171, 848, 804, 733.

Preparation of 100:



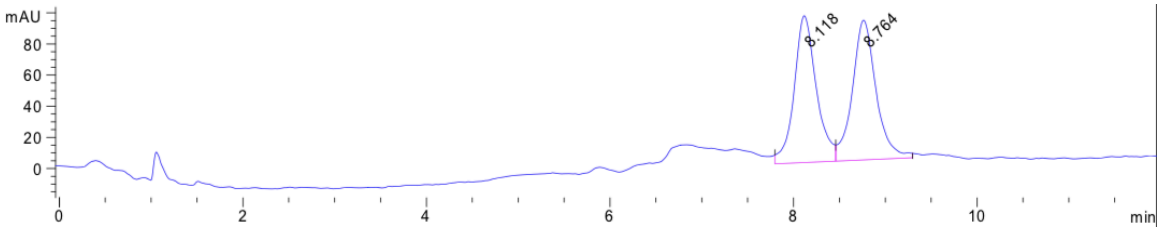
Procedure: An oven-dried, 2-dram vial was charged with (R)-CBS catalyst (11.1 mg, 0.0400 mmol, 40 mol %) and anhydrous DCM (1.0 mL) then stirred for 15 minutes. BH_3•NEt_2Ph (12.4 uL, 0.700 mmol, 70 mol %) was added dropwise via microsyringe, then the reaction was stirred for an additional 10 minutes. Then enone **99** (30.1 mg, 0.1 mmol, 1.0 equiv) was added as a solution in the remaining DCM (1.0 mL) over 1 h via syringe pump, and then the reaction was stirred at ambient temperature under N_2 for an additional 2.5 hours. The reaction was diluted with Et_2O and quenched with the careful addition of MeOH followed by H_2O. The layers were separated, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. TCNB (0.75 equiv, 19.6 mg) was added to obtain an ^{1}H-NMR yield of 34%. Material further purified via preparatory TLC (20% EtOAc/hexanes) to obtain a pure sample for SFC analysis which determined the ee to be 93%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (dd, *J* = 6.8, 2.2 Hz, 1H), 2.74 (ddd, *J* = 16.0, 7.9, 0.7 Hz, 1H), 2.43 (ddd, *J* = 15.9, 6.2, 2.2 Hz, 1H), 1.65 (s, 2H), 1.15 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.46, 103.57, 82.92, 46.38, 37.20, 14.26.

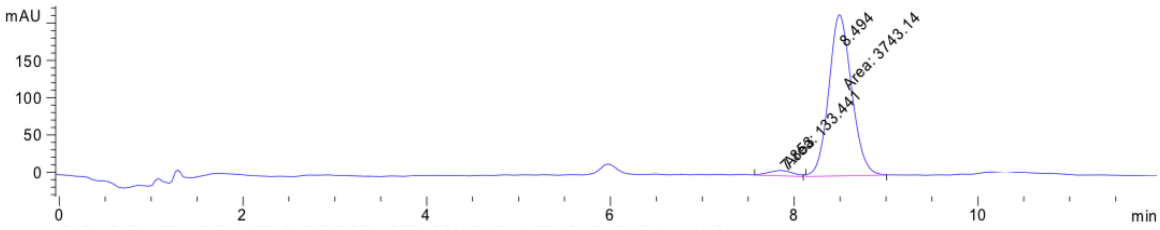
Chiral SFC: (OB-H column, 2.5 mL/min, 3% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 8.7 min, $t_{minor\ enantiomer}$ = 8.1 min;

100: racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.118	BV	0.2484	1584.84717	94.15912	49.5294
2	8.764	VB	0.2702	1614.96204	89.62744	50.4706

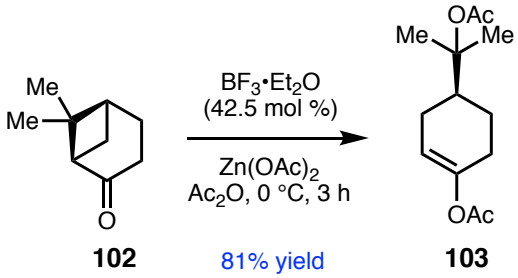
100: enantioenriched (93% ee)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.853	MM	0.3042	133.44066	7.31096	3.4422
2	8.494	MM	0.2885	3743.13940	216.21317	96.5578

3.6.7 D Ring Progress

Preparation of 103:



102 81% yield **103**

Procedure: To an flame-dried 250 mL round bottomed flask, equipped with a stir bar, was charged ketone **102** (6.00 g, 43.4 mmol, 1.0 equiv), $Zn(OAc)_2$ (7.96 g, 43.4 mmol, 1.0 equiv), and acetic anhydride (72.4 mL). This solution was cooled to 0 °C and then BF_3•OEt_2 (2.28 mL, 18.5 mmol, 42.5 mol %) was added dropwise. The resulting mixture was allowed to stir at 0 °C for 3 h. The reaction mixture was then quenched with ice water

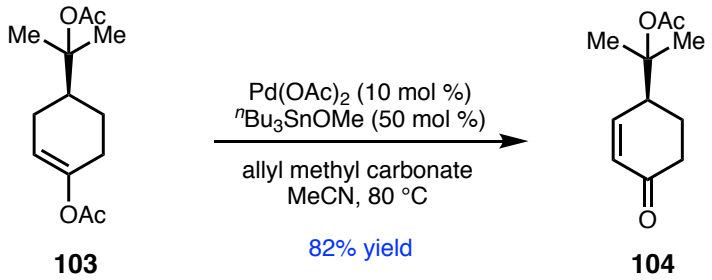
(100 mL), and poured into a 1L Erlenmeyer flask. To this was added K_2CO_3 in small portions until vigorous bubbling ceased. The resulting mixture was then transferred into a large separatory funnel. The product was extracted with Et_2O (3x) and combined extracts were washed successively with saturated $NaHCO_3$, water, and brine and dried, filtered, and concentrated. Material was further purified via column chromatography (10 to 20 % EtOAc/hexanes) to afford **103** (8.40 g, 35.15 mmol, 81%) as a clear colorless oil. Spectral data matched the literature.[39]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 – 5.31 (m, 1H), 2.34 – 2.20 (m, 1H), 2.17 – 2.06 (m, 6H), 1.99 (s, 0H), 1.97 (s, 3H), 1.87 (ddq, *J* = 12.3, 6.0, 2.1 Hz, 1H), 1.55 – 1.49 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.59, 169.64, 148.34, 113.33, 84.31, 60.54, 42.33, 27.42, 24.69, 23.51, 23.30, 22.59, 21.20, 14.33.

FTIR (NaCl, thin film, cm^{-1}): 2936, 1754, 1727, 1368, 1258, 1221, 1117, 1016, 909, 829, 681.

Preparation of 104:



103 **104**

Procedure: To a flame-dried 250 mL round bottom flask, equipped with a stir bar, in a nitrogen-filled glovebox, was charged $Pd(OAc)_2$ (344 mg, 1.53 mmol, 10 mol %). Reaction

removed from glovebox, then opened to atmosphere and enol acetate **103** (3.68 g, 15.3 mmol, 1.0 equiv), allyl methyl carbonate (3.56 g, 30.6 mmol, 2.0 mmol), MeCN (76.6 mL) and lastly, $^{n}Bu_3SnOMe$ (2.21 mL, 7.66 mmol, 50 mol %) was added at room temperature. Reaction fitted with a reflux condenser under N_2 and then submerged into a preheated oil bath at 80 °C. Reaction stirred for 4 hours behind a blast shield and then stir plate unplugged and reaction allowed to cool to room temperature overnight. The reaction was filtered over celite eluting with EtOAc. Reaction then concentrated in vacuo. Material was further purified via column chromatography (20% EtOAc/hexanes) to afford **104** (2.46 g, 12.55 mmol, 82% yield) as an orange oil. Spectral data matched the literature.[39]

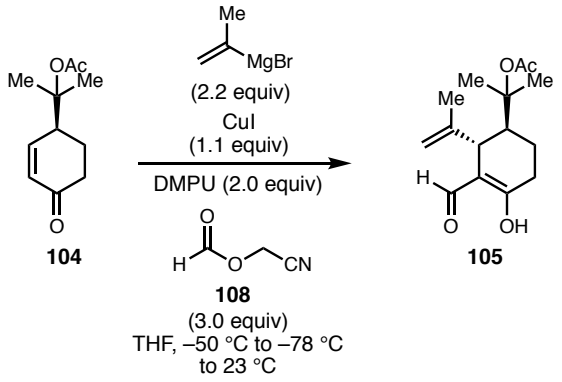
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dt, *J* = 10.4, 2.0 Hz, 1H), 6.08 (ddd, *J* = 10.4, 2.9, 1.1 Hz, 1H), 3.19 (ddt, *J* = 11.4, 4.8, 2.5 Hz, 1H), 2.54 (dddd, *J* = 16.7, 4.3, 3.2, 1.1 Hz, 1H), 2.38 (ddd, *J* = 16.6, 14.3, 5.0 Hz, 1H), 2.08 (tq, *J* = 6.8, 5.0 Hz, 1H), 2.02 (s, 3H), 1.78 (dddd, *J* = 14.3, 13.0, 11.4, 4.3 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.51, 170.53, 150.43, 130.55, 83.46, 45.04, 37.45, 24.45, 23.92, 23.47, 22.53.

FTIR (NaCl, thin film, cm^{-1}): 2983, 1726, 1680, 1369, 1253, 1209, 1187, 1127, 1016, 845.

R_f = 0.27 in 20% EtOAc/hexanes (stains purple in p-anisaldehyde)

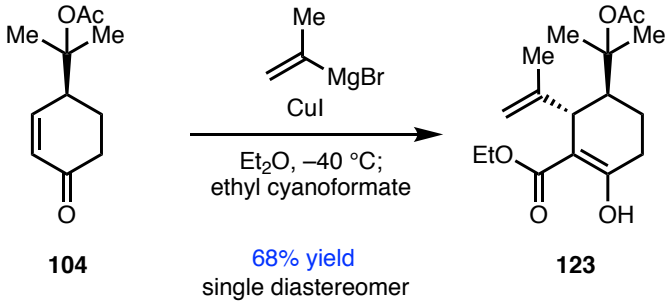
Preparation of 105:



Procedure: To an oven-dried 25-mL flask, equipped with a stir bar, in a nitrogen-filled glovebox, was charged CuI (534 mg, 2.80 mmol, 1.1 equiv), sealed with a red septum, and removed from the glovebox. To this was added THF (freeze-pump-thawed 3X) (5 mL), and the mixture was cooled to –50 °C. To the resulting suspension was slowly added isopropenyl Grignard (1.0 M in THF, 5.61 mL, 5.61 mmol, 2.20 equiv) over 5 mins. After stirring for 2 hours at –50 °C, the reaction mixture was cooled to –78 °C. To this cuprate mixture was slowly added enone **104** (500 mg, 2.55 mmol, 1.0 equiv) as a stock solution in THF (7.5 mL). After 2 hours of stirring, DMPU (1.08 mL, 8.92 mmol, 3.50 equiv) was added, followed by formyloxyacetonitrile **108** (548 uL, 7.64 mmol, 3.0 equiv). Then the reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched by the addition of water, diluted with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3X) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation. Material was then further purified via column chromatography (10 to 20% EtOAc/hexanes) to afford **105** (200 mg, 0.739 mmol, 29%) as a yellow oil.

^{1}H NMR (600 MHz, cdcl$_3$) δ 8.67 (d, *J* = 2.5 Hz, 1H), 4.91 (p, *J* = 1.4 Hz, 1H), 4.73 (dt, *J* = 1.7, 0.9 Hz, 1H), 3.28 (d, *J* = 4.6 Hz, 1H), 2.38 – 2.33 (m, 2H), 2.29 – 2.21 (m, 1H), 1.91 (s, 3H), 1.84 (dddd, *J* = 13.9, 7.6, 6.2, 4.4 Hz, 1H), 1.74 (dd, *J* = 1.4, 0.7 Hz, 3H), 1.68 – 1.59 (m, 1H), 1.57 (s, 6H), 1.50 (s, 3H).

Preparation of 123:



104 68% yield single diastereomer **123**

Procedure: To an oven-dried 500-mL flask, equipped with a stir bar, in a nitrogen-filled glovebox, was charged CuI (4.80 mg, 25.2 mmol, 1.1 equiv), sealed with a red septum, and removed from the glovebox. To this was added THF (freeze-pump-thawed 3X) (45 mL), and the mixture was cooled to –50 °C. To the resulting suspension was slowly added isopropenyl Grignard (1.0 M in THF, 50.4 mL, 50.4 mmol, 2.20 equiv) over 20 mins. After stirring for 2 hours at –50 °C, the reaction mixture was cooled to –78 °C. To this cuprate mixture was slowly added enone **104** (4.5 g, 22.9 mmol, 1.0 equiv) as a stock solution in THF (75 mL). After 2 hours of stirring, DMPU (9.70 mL, 80.3 mmol, 3.50 equiv) was added, followed by ethyl cyanoformate (6.80 mL, 68.8 mmol, 3.0 equiv). Then the reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched by the addition of water, diluted with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3X) and the combined organic

layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation. Material was then further purified via column chromatography (10 to 20 to 30% EtOAc/hexanes) to afford **123** (4.84 g, 15.57 mmol, 68%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.40 (s, 1H), 4.80 (dp, *J* = 17.1, 1.5 Hz, 1H), 4.59 (dt, *J* = 1.8, 0.9 Hz, 1H), 4.28 – 4.06 (m, 3H), 3.21 (s, 1H), 2.36 – 2.16 (m, 2H), 2.01 (ddd, *J* = 5.5, 4.0, 1.7 Hz, 1H), 1.93 (s, 4H), 1.91 – 1.82 (m, 1H), 1.81 – 1.69 (m, 4H), 1.60 (s, 3H), 1.56 (s, 3H), 1.47 (s, 3H), 1.35 – 1.20 (m, 4H).

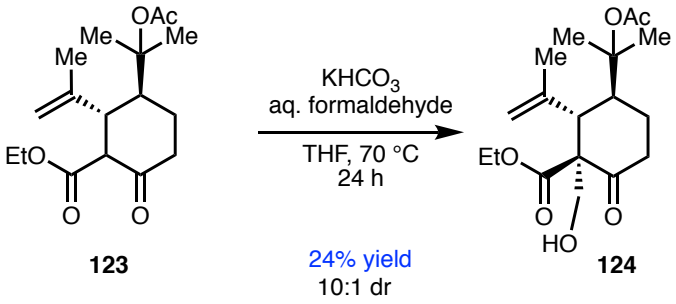
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.77, 172.49, 170.46, 149.06, 111.28, 100.07, 85.16, 60.35, 43.05, 40.31, 26.62, 25.23, 24.95, 22.73, 22.19, 18.68, 14.21.

FTIR (NaCl, thin film, cm^{-1}): 2929, 1732, 1654, 1368, 1282, 1252 1223, 837, 681.

HRMS: (ESI) calc'd for $C_{16}H_{24}O_5$ $[M + H - OAc]^+$ 238.1568, found 238.1572.

$\boldsymbol{\alpha_D^{22}}$ = +36° (c = 1.0, $CHCl_3$).

Preparation of 124:



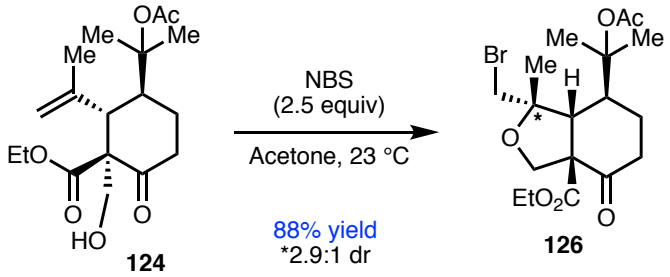
Procedure: To a 1-dram vial, equipped with a stir bar, was charged ketoester **123** (25 mg, 0.0805 mmol, 1.0 equiv), $KHCO_3$ (24.2 mg, 0.242 mmol, 3.0 equiv), and then THF (1.61

mL). To this was added formaldehyde solution (35% in water, 38.0 uL, 0.483 mmol, 6.0 equiv). Reaction was heated to 70 °C and stirred for 12 hours. Reaction then filtered over $MgSO_4$ plug and concentrated. Material was further purified via preparatory TLC (40% EtOAc/hexanes) to afford **124** (6.6 mg, 0.0193 mmol, 24%) as a 10:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 – 4.79 (m, 2H), 4.34 – 4.08 (m, 2H), 3.76 (dd, *J* = 16.2, 11.6 Hz, 1H), 3.51 – 3.45 (m, 1H), 3.45 – 3.37 (m, 1H), 2.75 (ddd, *J* = 19.8, 4.6, 2.2 Hz, 1H), 2.61 (ddd, *J* = 13.7, 6.4, 4.7 Hz, 1H), 2.36 – 2.21 (m, 1H), 1.89 – 1.74 (m, 1H), 1.68 – 1.56 (m, 1H), 1.52 (s, 3H), 1.39 (s, 3H), 1.29 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.18, 170.60, 116.77, 84.47, 66.30, 62.13, 48.24, 38.27, 25.09, 23.79, 22.50, 21.15, 13.98.

Preparation of 126:



Procedure: To an oven-dried 1/2-dram vial, equipped with a stir bar, was added alcohol **124** (10.0 mg, 0.00147 mmol, 1.0 equiv) and anhydrous acetone (147 uL) and cooled to 0 °C. To this mixture was added NBS (6.5 mg, 0.0367 mmol, 2.50 equiv) and stirred at 0 °C for 21 hours. The reaction mixture was then quenched with 10% $NaHSO_3$ and extracted 3x with Et_2O. The organic extracts were dried over Na_2SO_4 and concentrated. Crude NMR

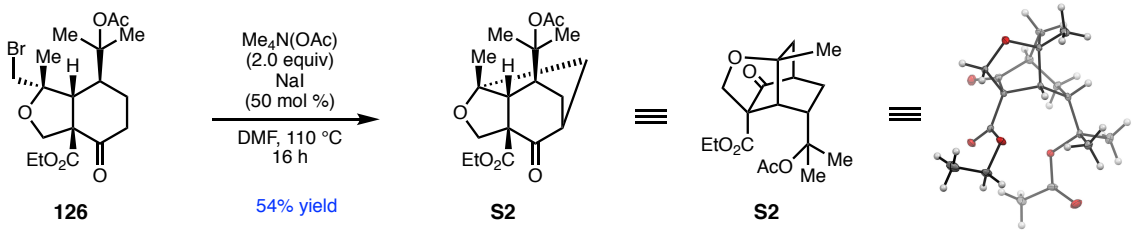
taken with internal standard first to give 88% yield by NMR. Then prep plate with 50% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 – 4.03 (m, 1H), 4.00 (d, *J* = 7.6 Hz, 1H), 3.93 (d, *J* = 7.6 Hz, 1H), 2.81 (s, 1H), 2.50 (tt, *J* = 4.0, 2.1 Hz, 1H), 1.95 (s, 6H), 1.90 – 1.80 (m, 1H), 1.81 – 1.71 (m, 1H), 1.65 (d, *J* = 1.5 Hz, 1H), 1.47 (d, *J* = 8.1 Hz, 8H), 1.26 (t, *J* = 7.2 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.73, 170.83, 167.58, 83.86, 82.40, 74.68, 62.26, 61.17, 49.46, 42.29, 40.79, 38.39, 25.82, 24.57, 24.26, 23.79, 22.64, 14.19.

R_f = 0.6 in 40% EtOAc/hexanes (stains yellow with p-anisaldehyde)

Preparation of S2:



Procedure: To an oven-dried 1-dram vial, equipped with a stir bar, was charged alkyl bromide **126** (140 mg, 0.334 mmol, 1.0 equiv), $Me_4N(OAc)$ (88.9 mg, 0.668 mmol, 2.0 equiv), NaI (10.0 mg, 0.00668 mmol, 20 mol %), and DMF (1.67 mL). Vial capped with a white teflon cap and then heated to 110 °C for 18 hours. Reaction then diluted with water, extracted into EtOAc (3X). combined organics were dried over $MgSO_4$, filtered, and concentrated. Material further purified via column chromatography (10 to 20 to 30% EtOAc/hexanes) to afford **S2** (60.5 mg, 0.180 mmol, 54%) as a white solid. **S2** could be recrystallized via slow evaporation from Et_2O to obtain X-ray quality crystals.

Crystal Structure Data for compound **92**:

V20219_a

Table 1 Crystal data and structure refinement for V20219_a.

Identification code	V20219_a
Empirical formula	$C_{20}H_{30}O_4$
Formula weight	334.459
Temperature/K	106.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.9957(11)
b/Å	20.179(2)
c/Å	10.0496(12)
α/°	90
β/°	117.989(4)
γ/°	90
Volume/Å^3	1789.9(4)
Z	4
ρ_{calc}g/cm^3	1.241
μ/mm^{-1}	0.678
F(000)	730.3
Crystal size/mm^3	0.25 × 0.15 × 0.10
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	8.76 to 159
Index ranges	-12 ≤ h ≤ 12, -25 ≤ k ≤ 25, -12 ≤ l ≤ 12
Reflections collected	39690
Independent reflections	3846 [R_{int} = 0.0550, R_{sigma} = 0.0265]

Data/restraints/parameters	3846/0/254
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0402, wR_2 = 0.1063
Final R indexes [all data]	R_1 = 0.0438, wR_2 = 0.1094
Largest diff. peak/hole / e $Å^{-3}$	0.33/-0.23

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$×10^3) for V20219_a. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O2	5006.2(9)	2943.2(4)	6719.6(9)	25.6(2)
O1	3881.1(9)	1691.0(4)	3730.2(9)	25.8(2)
O3	8805.3(9)	3381.7(4)	6440.0(9)	26.1(2)
O4	9806.0(10)	4239.8(5)	5616.0(10)	34.0(2)
C4	7459.5(12)	2379.7(5)	5504.6(12)	20.5(2)
C11	4542.8(12)	3193.5(5)	4218.4(11)	19.2(2)
C5	7395.0(12)	3121.1(5)	5262.3(12)	19.7(2)
C6	6093.2(12)	3496.6(5)	5335.7(12)	20.3(2)
C12	4200.3(12)	2700.4(6)	5187.6(11)	21.0(2)
C14	6452.0(13)	1946.5(5)	5512.0(12)	21.1(2)
C10	3339.9(13)	3730.6(6)	3418.9(13)	25.2(2)
C13	4809.8(13)	2005.9(6)	5151.3(12)	21.7(2)
C8	5276.3(15)	4451.6(6)	3398.4(15)	28.6(3)
C9	3870.8(15)	4216.2(6)	2620.8(14)	28.6(3)
C7	6184.8(14)	4241.1(6)	5027.1(14)	27.3(3)
C3	8932.8(13)	2036.6(6)	5823.0(16)	29.5(3)
C15	6189.5(14)	3382.8(7)	6894.6(13)	28.9(3)

C16	2547.2(13)	2641.9(7)	4837.2(14)	29.2(3)
C1	7105.4(15)	1252.7(6)	5870.4(15)	30.8(3)
C19	9905.7(15)	3568.9(7)	6006.3(17)	35.0(3)
C18	6021(2)	4960.4(7)	2872.3(19)	41.3(4)
C17	2746.8(19)	4404.9(7)	1038.5(16)	42.6(4)
C2	8650.6(18)	1302.5(7)	5944(2)	43.7(4)
C20	10248(2)	4666.4(8)	6884.2(17)	46.3(4)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for V20219_a. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{12}**	**U_{13}**	**U_{23}**
O2	27.2(4)	37.1(5)	14.0(4)	-3.5(3)	11.0(3)	-3.7(3)
O1	26.8(4)	33.0(4)	19.6(4)	-8.9(3)	12.5(3)	-5.3(3)
O3	19.6(4)	29.3(4)	25.3(4)	-3.2(3)	7.1(3)	3.1(3)
O4	32.6(5)	36.2(5)	29.4(5)	-8.2(4)	11.5(4)	5.9(4)
C4	19.4(5)	24.8(5)	14.1(5)	3.8(4)	5.3(4)	0.4(4)
C11	19.0(5)	24.4(5)	14.1(5)	3.0(4)	7.6(4)	-0.4(4)
C5	17.8(5)	24.2(5)	16.1(5)	1.3(4)	7.2(4)	1.2(4)
C6	20.6(5)	24.4(5)	16.3(5)	0.9(4)	8.9(4)	-2.4(4)
C12	19.6(5)	31.3(6)	12.2(5)	0.7(4)	7.7(4)	-1.0(4)
C14	24.8(5)	23.4(5)	13.3(5)	2.7(4)	7.4(4)	2.0(4)
C10	23.4(5)	30.2(6)	19.8(5)	7.2(4)	8.3(4)	1.0(4)
C13	24.8(5)	26.8(5)	14.7(5)	-2.4(4)	10.3(4)	0.8(4)
C8	41.4(7)	19.6(5)	33.5(6)	7.7(5)	24.9(6)	0.2(4)
C9	39.6(7)	24.2(6)	23.5(6)	11.2(5)	16.0(5)	3.2(4)
C7	26.8(6)	22.2(5)	32.6(6)	2.1(4)	13.7(5)	-4.7(4)

C3	18.9(5)	27.4(6)	33.6(7)	4.2(4)	5.1(5)	-2.6(5)
C15	26.4(6)	43.1(7)	18.9(6)	-7.1(5)	12.0(5)	-8.3(5)
C16	21.7(6)	43.7(7)	24.4(6)	-0.1(5)	12.5(5)	1.5(5)
C1	32.8(6)	23.5(6)	30.6(6)	2.9(5)	10.4(5)	2.4(5)
C19	22.7(6)	37.8(7)	44.0(8)	-0.6(5)	15.4(6)	10.2(6)
C18	65.0(10)	23.8(6)	53.5(9)	1.8(6)	43.1(8)	-1.2(6)
C17	57.2(9)	35.5(7)	27.4(7)	11.7(6)	13.5(6)	9.0(5)
C2	36.4(8)	31.3(7)	61.4(10)	13.9(6)	21.3(7)	15.9(7)
C20	52.8(9)	45.5(8)	30.8(7)	-23.9(7)	11.3(6)	-0.2(6)

Table 4 Bond Lengths for V20219_a.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O2	C12	1.4475(12)	C6	C7	1.5453(16)
O2	C15	1.4219(15)	C6	C15	1.5410(15)
O1	C13	1.4355(13)	C12	C13	1.5355(16)
O3	C5	1.4486(13)	C12	C16	1.5238(16)
O3	C19	1.4116(16)	C14	C13	1.5105(16)
O4	C19	1.3998(17)	C14	C1	1.5150(16)
O4	C20	1.4255(18)	C10	C9	1.5115(17)
C4	C5	1.5122(15)	C8	C9	1.334(2)
C4	C14	1.3363(16)	C8	C7	1.5129(18)
C4	C3	1.5193(16)	C8	C18	1.5027(18)
C11	C6	1.5503(15)	C9	C17	1.5030(18)
C11	C12	1.5390(15)	C3	C2	1.5234(19)
C11	C10	1.5360(15)	C1	C2	1.515(2)
C5	C6	1.5372(15)			

Table 5 Bond Angles for V20219_a.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C15	O2	C12	110.98(8)	C16	C12	C11	116.30(9)
C19	O3	C5	116.45(10)	C16	C12	C13	108.85(10)
C20	O4	C19	112.46(11)	C13	C14	C4	133.13(10)
C14	C4	C5	132.29(10)	C1	C14	C4	111.34(10)
C3	C4	C5	116.66(10)	C1	C14	C13	115.41(10)
C3	C4	C14	111.05(10)	C9	C10	C11	110.58(10)
C12	C11	C6	103.91(8)	C12	C13	O1	110.44(9)
C10	C11	C6	111.81(9)	C14	C13	O1	109.03(9)
C10	C11	C12	115.79(9)	C14	C13	C12	117.73(9)
C4	C5	O3	106.01(8)	C7	C8	C9	117.79(11)
C6	C5	O3	107.64(9)	C18	C8	C9	126.64(13)
C6	C5	C4	116.94(9)	C18	C8	C7	115.31(12)
C5	C6	C11	110.59(9)	C8	C9	C10	117.09(11)
C7	C6	C11	111.81(9)	C17	C9	C10	116.83(12)
C7	C6	C5	109.77(9)	C17	C9	C8	126.05(13)
C15	C6	C11	104.00(9)	C8	C7	C6	115.34(10)
C15	C6	C5	108.96(9)	C2	C3	C4	105.22(11)
C15	C6	C7	111.57(9)	C6	C15	O2	108.41(9)
C11	C12	O2	106.04(9)	C2	C1	C14	105.44(10)
C13	C12	O2	107.77(9)	O4	C19	O3	112.46(11)
C13	C12	C11	111.49(9)	C1	C2	C3	106.46(11)
C16	C12	O2	105.89(9)				

Table 6 Torsion Angles for V20219_a.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O2	C12	C11	C6	25.99(9)	C4	C5	C6	C11	-54.85(10)
O2	C12	C11	C10	-97.01(9)	C4	C5	C6	C7	-178.68(10)
O2	C12	C13	O1	169.95(8)	C4	C5	C6	C15	58.87(10)
O2	C12	C13	C14	-63.96(9)	C4	C14	C13	C12	-20.07(14)
O2	C15	C6	C11	11.27(11)	C4	C14	C1	C2	-5.29(12)
O2	C15	C6	C5	-106.69(10)	C4	C3	C2	C1	-6.25(11)
O2	C15	C6	C7	131.94(10)	C11	C6	C7	C8	-30.86(10)
O1	C13	C12	C11	-74.07(9)	C11	C12	C13	C14	52.02(10)
O1	C13	C12	C16	55.54(9)	C11	C10	C9	C8	-47.23(11)
O1	C13	C14	C4	106.70(10)	C11	C10	C9	C17	134.60(10)
O1	C13	C14	C1	-68.92(10)	C5	C6	C7	C8	92.26(10)
O3	C5	C4	C14	134.03(9)	C6	C7	C8	C9	44.17(12)
O3	C5	C4	C3	-45.14(10)	C6	C7	C8	C18	-141.31(10)
O3	C5	C6	C11	-173.95(8)	C12	C13	C14	C1	164.31(10)
O3	C5	C6	C7	62.22(9)	C14	C1	C2	C3	6.95(11)
O3	C5	C6	C15	-60.23(9)	C10	C9	C8	C7	-3.04(12)
O3	C19	O4	C20	69.37(14)	C10	C9	C8	C18	-176.87(10)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for V20219_a.

Atom	*x*	*y*	*z*	U(eq)
H1	4167(13)	1808(7)	3102(5)	38.7(3)
H11	4678.0(12)	2937.6(5)	3437.7(11)	23.0(3)
H5	7352.8(12)	3211.3(5)	4264.8(12)	23.6(3)

H10a	2383.0(13)	3520.7(6)	2678.2(13)	30.2(3)
H10b	3138.9(13)	3969.5(6)	4167.2(13)	30.2(3)
H13	4694.1(13)	1738.7(6)	5929.1(12)	26.0(3)
H7a	5831.9(14)	4500.0(6)	5639.6(14)	32.8(3)
H7b	7260.2(14)	4357.3(6)	5374.7(14)	32.8(3)
H15a	6080.3(14)	3809.6(7)	7319.9(13)	34.7(3)
H15b	7185.0(14)	3189.0(7)	7593.2(13)	34.7(3)
H16a	2470.5(19)	2348(4)	5574(7)	43.8(4)
H16b	2157(4)	3081.3(10)	4889(12)	43.8(4)
H16c	1951(3)	2459(5)	3823(5)	43.8(4)
H18a	5408(8)	5028(5)	1784(3)	62.0(5)
H18b	6109(13)	5379.8(19)	3399(11)	62.0(5)
H18c	7033(6)	4806(3)	3091(13)	62.0(5)
H17a	2379(11)	4004.2(9)	420(4)	63.9(5)
H17b	1892(7)	4638(6)	1049(2)	63.9(5)
H17c	3237(4)	4695(5)	615(5)	63.9(5)
H20a	10186(15)	5128.6(9)	6561(3)	69.5(6)
H20b	9570(10)	4599(5)	7328(9)	69.5(6)
H20c	11291(6)	4565(5)	7635(7)	69.5(6)
H19a	9745(19)	3318(8)	5050(20)	38(4)
H19b	10910(20)	3488(9)	6890(20)	42(5)
H3a	9170(20)	2123(9)	4990(20)	39(4)
H1a	7190(20)	1108(10)	6860(20)	51(5)
H3b	9740(20)	2215(9)	6760(20)	47(5)
H1b	6440(20)	917(10)	5100(20)	56(5)
H2a	8620(30)	1048(13)	5000(30)	89(8)

H2b	9370(30)	1108(13)	6720(30)	76(7)

Experimental

Single crystals of $C_{20}H_{30}O_4$ [V20219_a] were []. A suitable crystal was selected and [] on a Bruker APEX-II CCD diffractometer. The crystal was kept at 106.0 K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the olex2.refine [3] refinement package using Levenberg-Marquardt minimisation.

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Crystal structure determination of [V20219_a]

Crystal Data for $C_{20}H_{30}O_4$ (*M* =334.459 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 9.9957(11) Å, *b* = 20.179(2) Å, *c* = 10.0496(12) Å, *β* = 117.989(4)°, *V* = 1789.9(4) $Å^3$, *Z* = 4, *T* = 106.0 K, μ(Cu Kα) = 0.678 mm^{-1}, *Dcalc* = 1.241 g/cm^3, 39690 reflections measured (8.76° ≤ 2Θ ≤ 159°), 3846 unique (R_{int} = 0.0550, R_{sigma} = 0.0265) which were used in all calculations. The final R_1 was 0.0402 (I>=2u(I)) and wR_2 was 0.1094 (all data).

Refinement model description

Number of restraints - 0, number of constraints - 33.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups, All O(H) groups
2.a Ternary CH refined with riding coordinates:
 C11(H11), C5(H5), C13(H13)
2.b Secondary CH2 refined with riding coordinates:
 C10(H10a,H10b), C7(H7a,H7b), C15(H15a,H15b)
2.c Idealised Me refined as rotating group:
 C16(H16a,H16b,H16c), C18(H18a,H18b,H18c), C17(H17a,H17b,H17c),
C20(H20a,H20b,
 H20c)
2.d Idealised tetrahedral OH refined as rotating group:
 O1(H1)
```

3.7 NOTES AND REFERENCES

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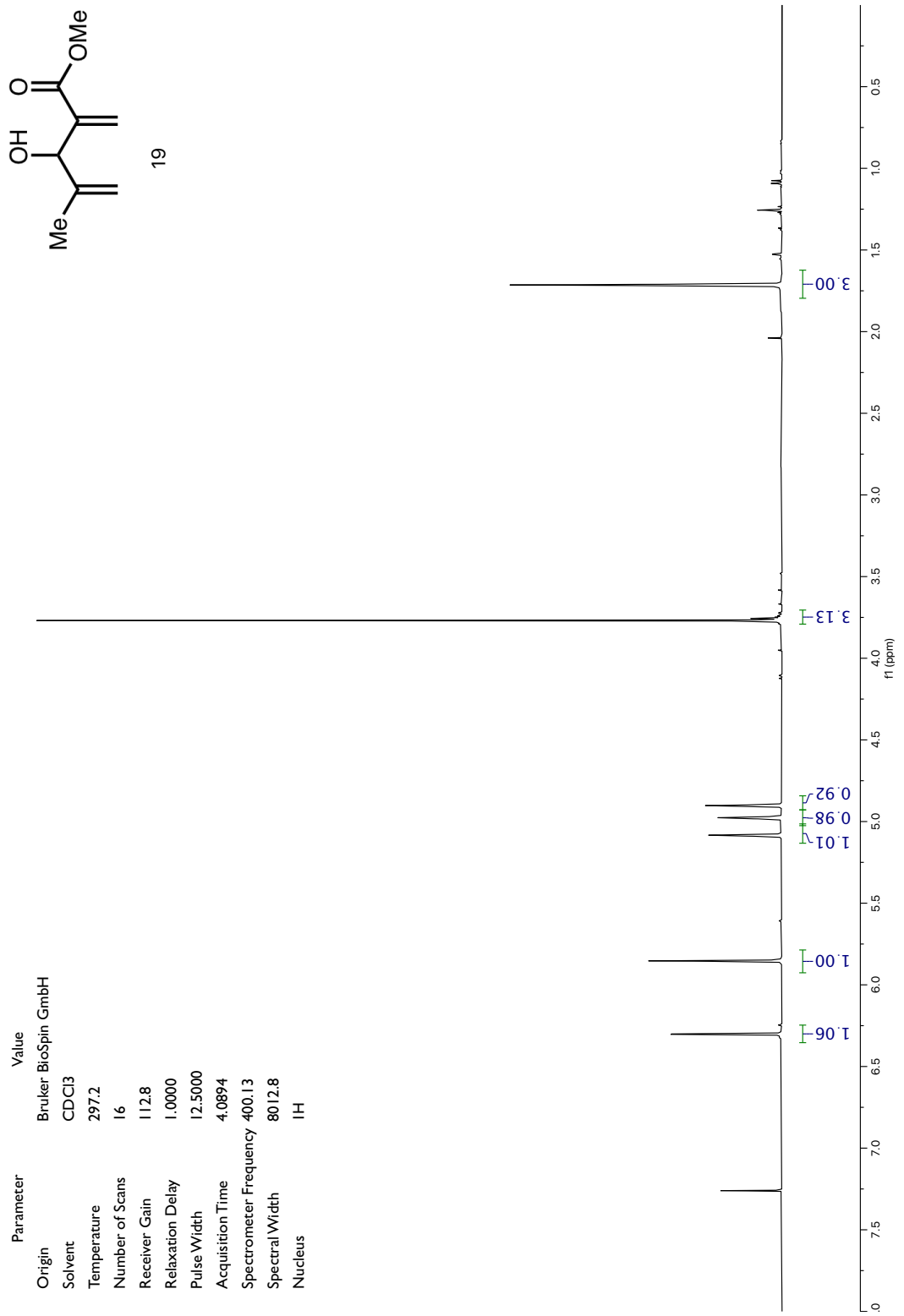
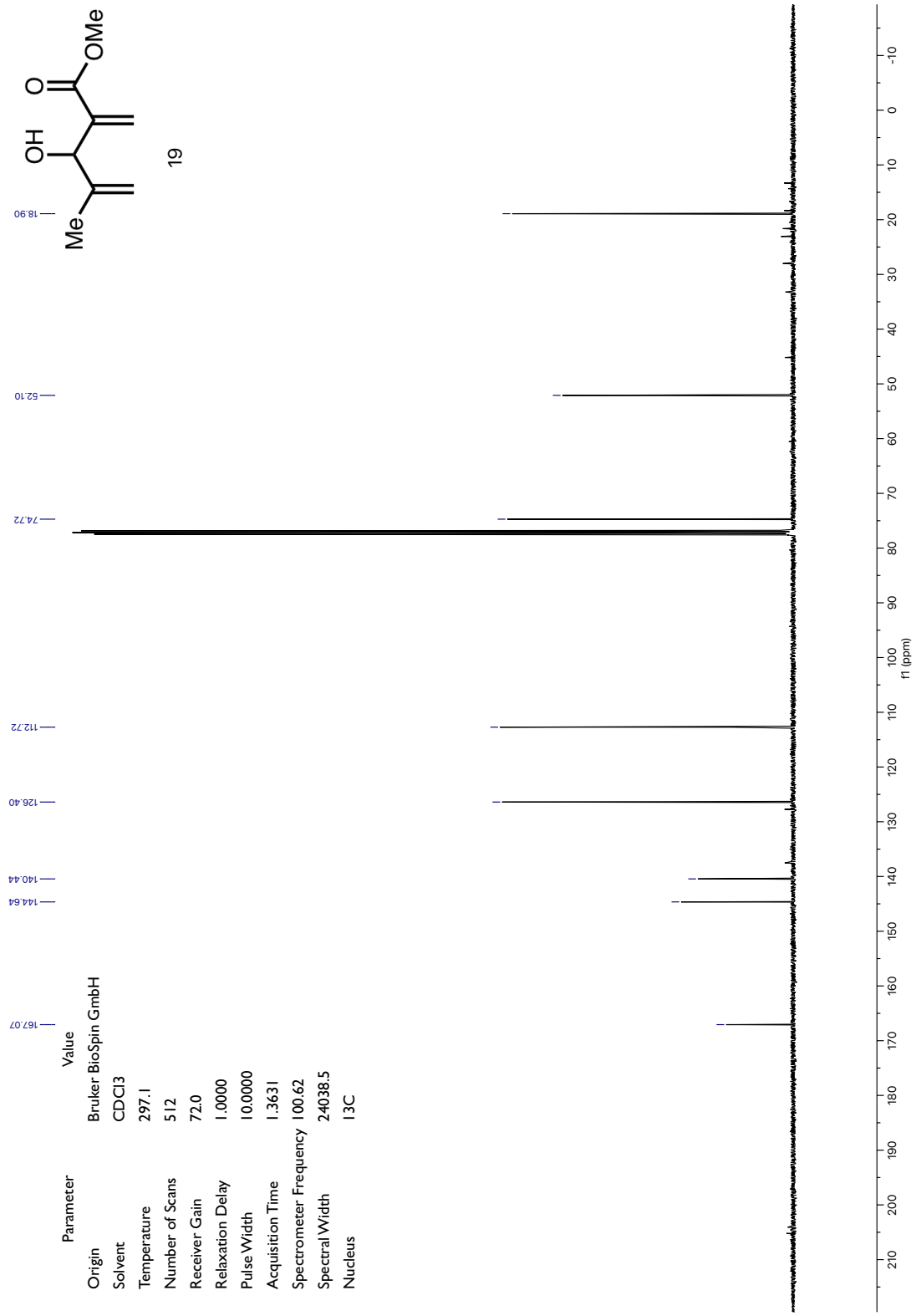
Appendix 2

Spectra Relevant to Chapter 3: A Transition Metal-Catalyzed Cascade Cyclization Approach Towards the Total Synthesis of Falcatin A


OMe
O
OH
Me
19
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.00
3.13
0.92
0.98
1.01
1.00
1.06
f1 (ppm)



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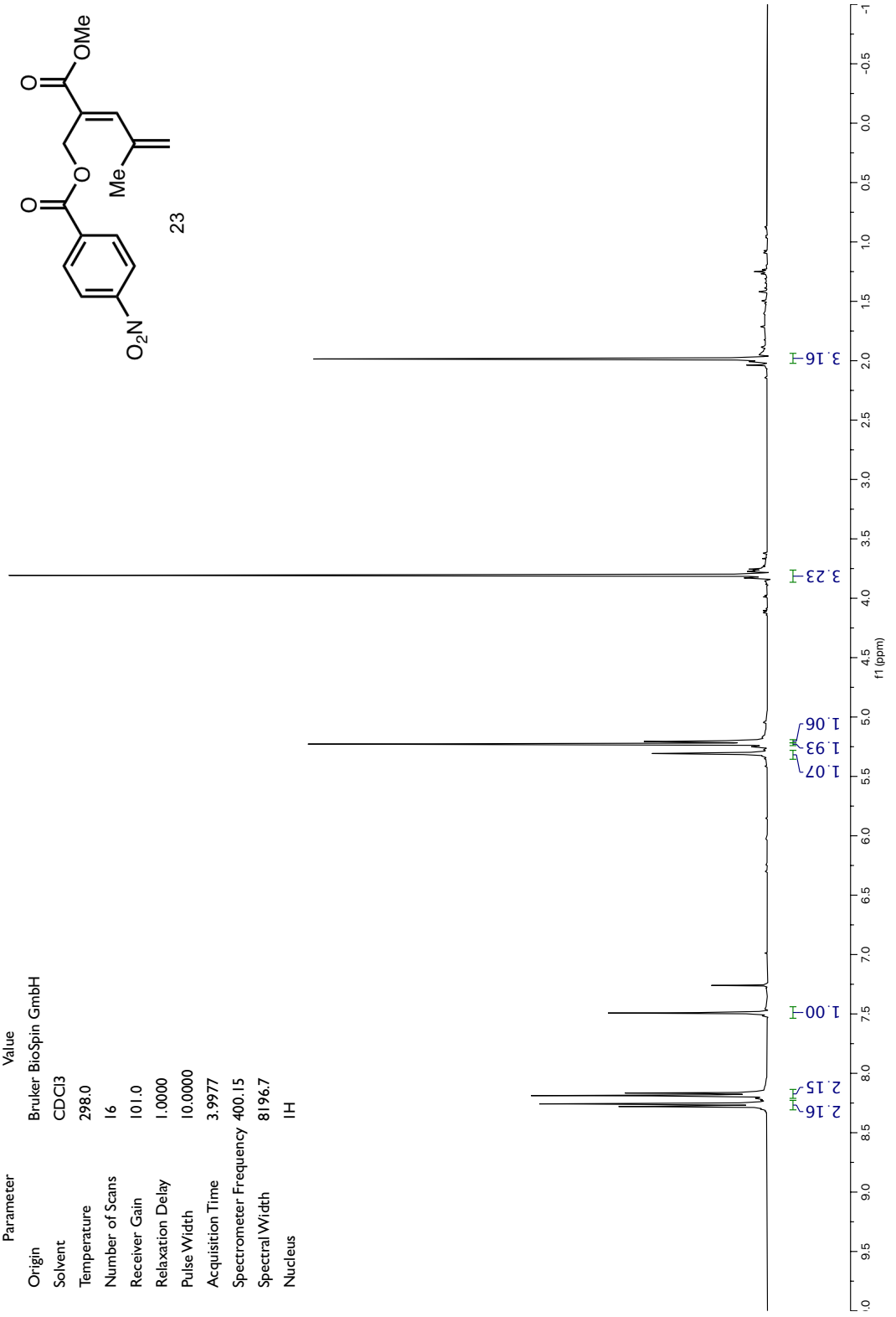
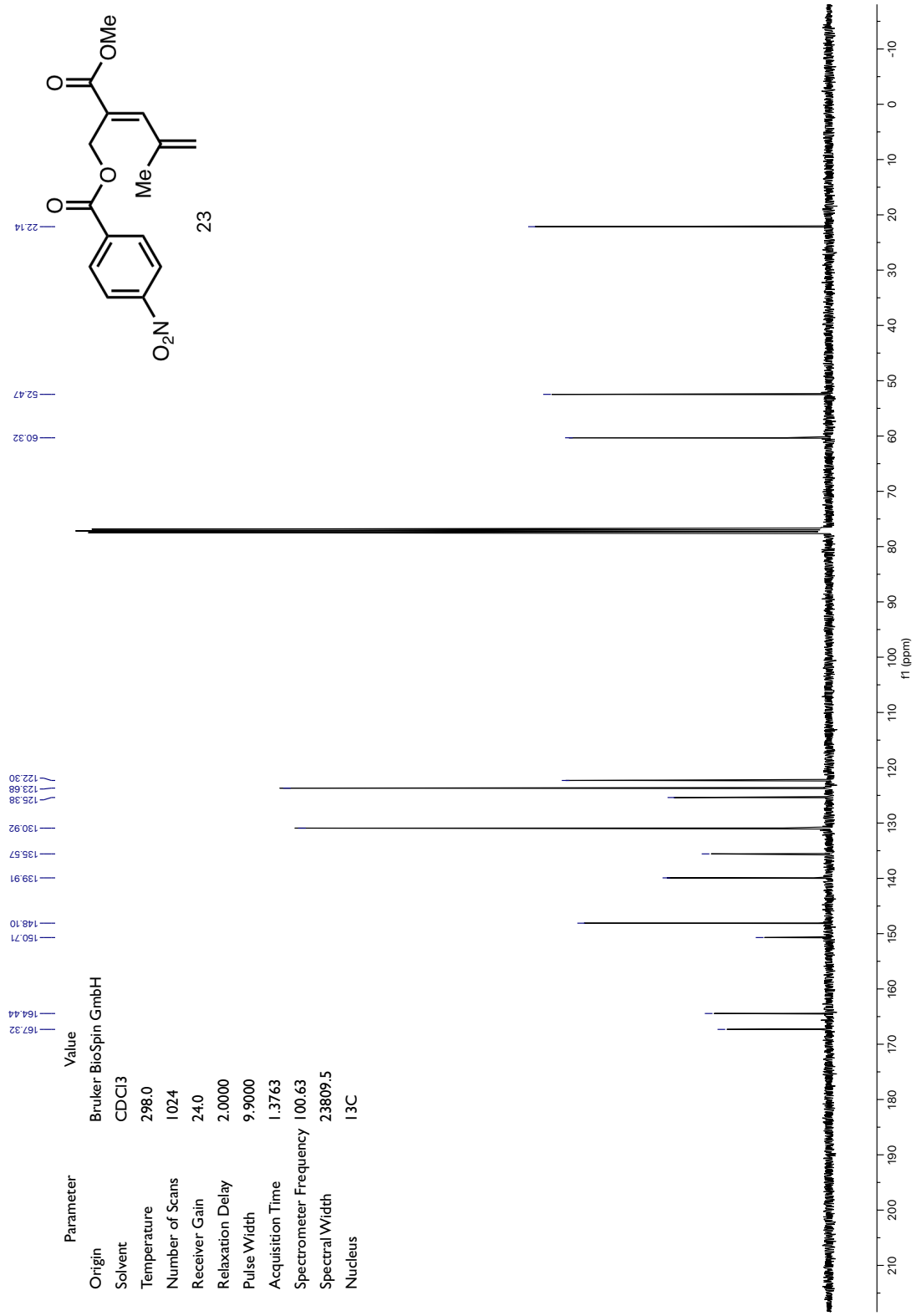
Solvent	CDCl3
Temperature	297.1
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C


OMe
O
O
O
Me
O_2N
23
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
298.0
Number of Scans
16
Receiver Gain
101.0
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
3.9977
Spectrometer Frequency
400.15
Spectral Width
8196.7
Nucleus
1H
3.16
3.23
1.06
1.93
1.07
1.00
2.15
2.16
f1 (ppm)



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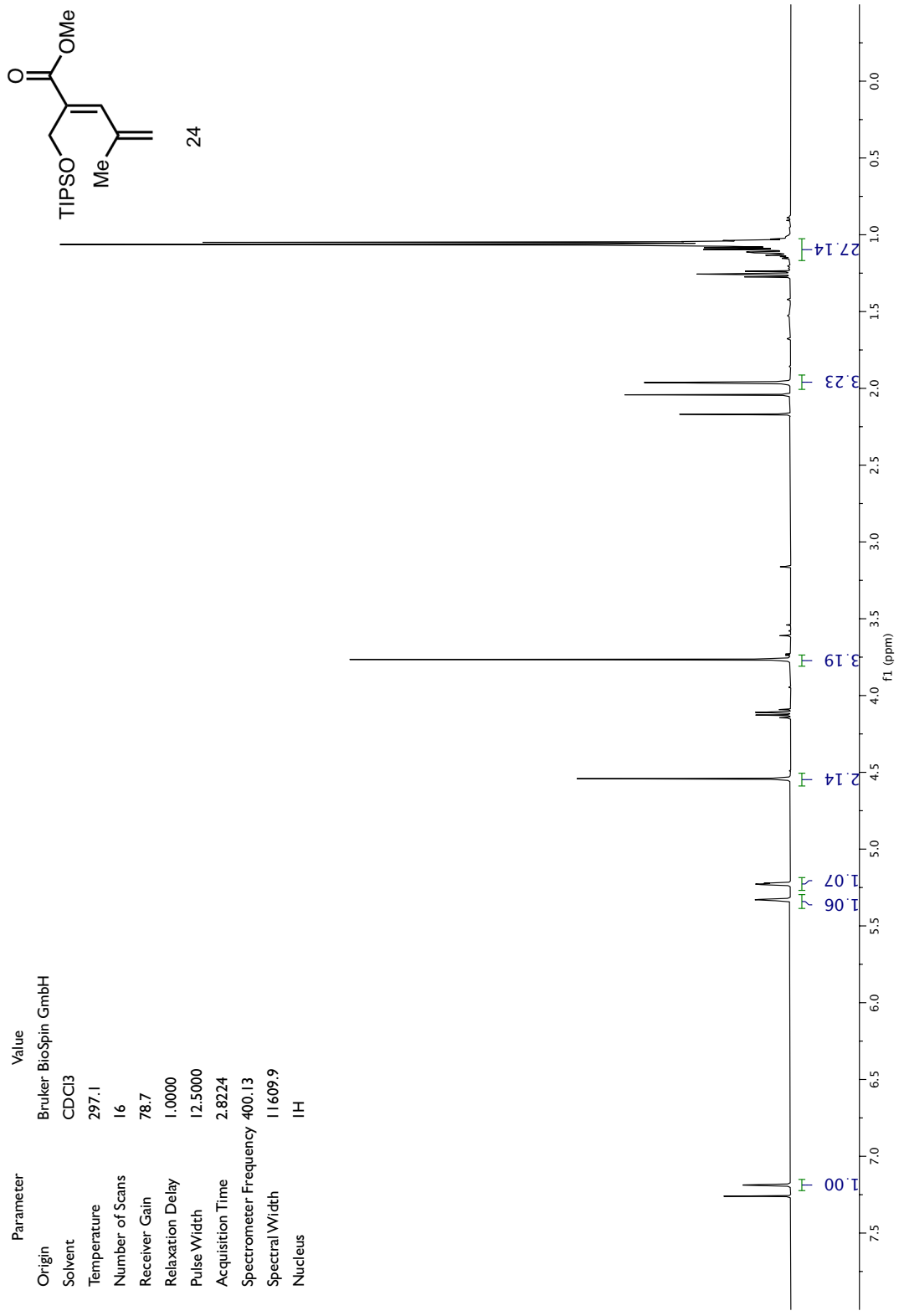
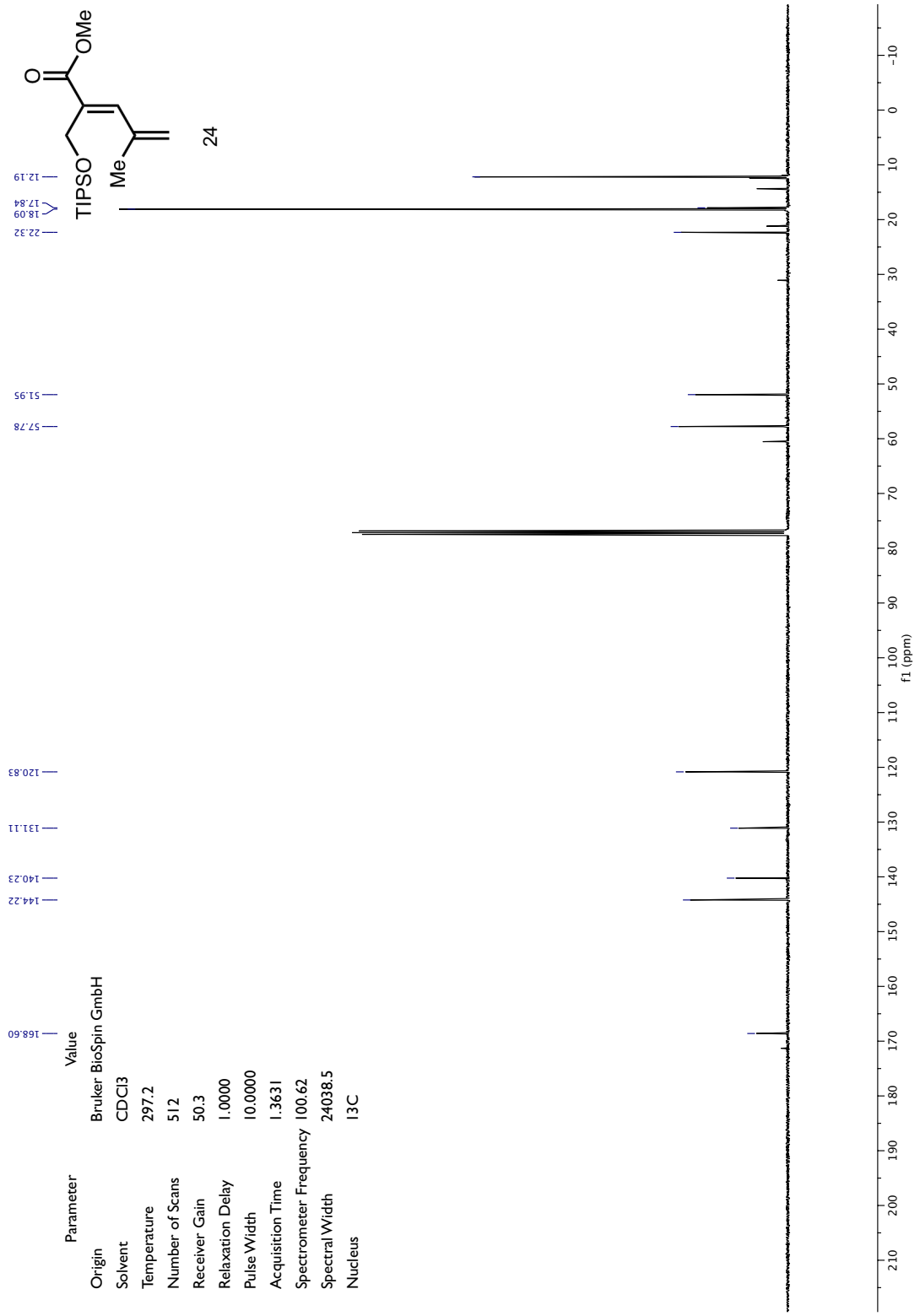
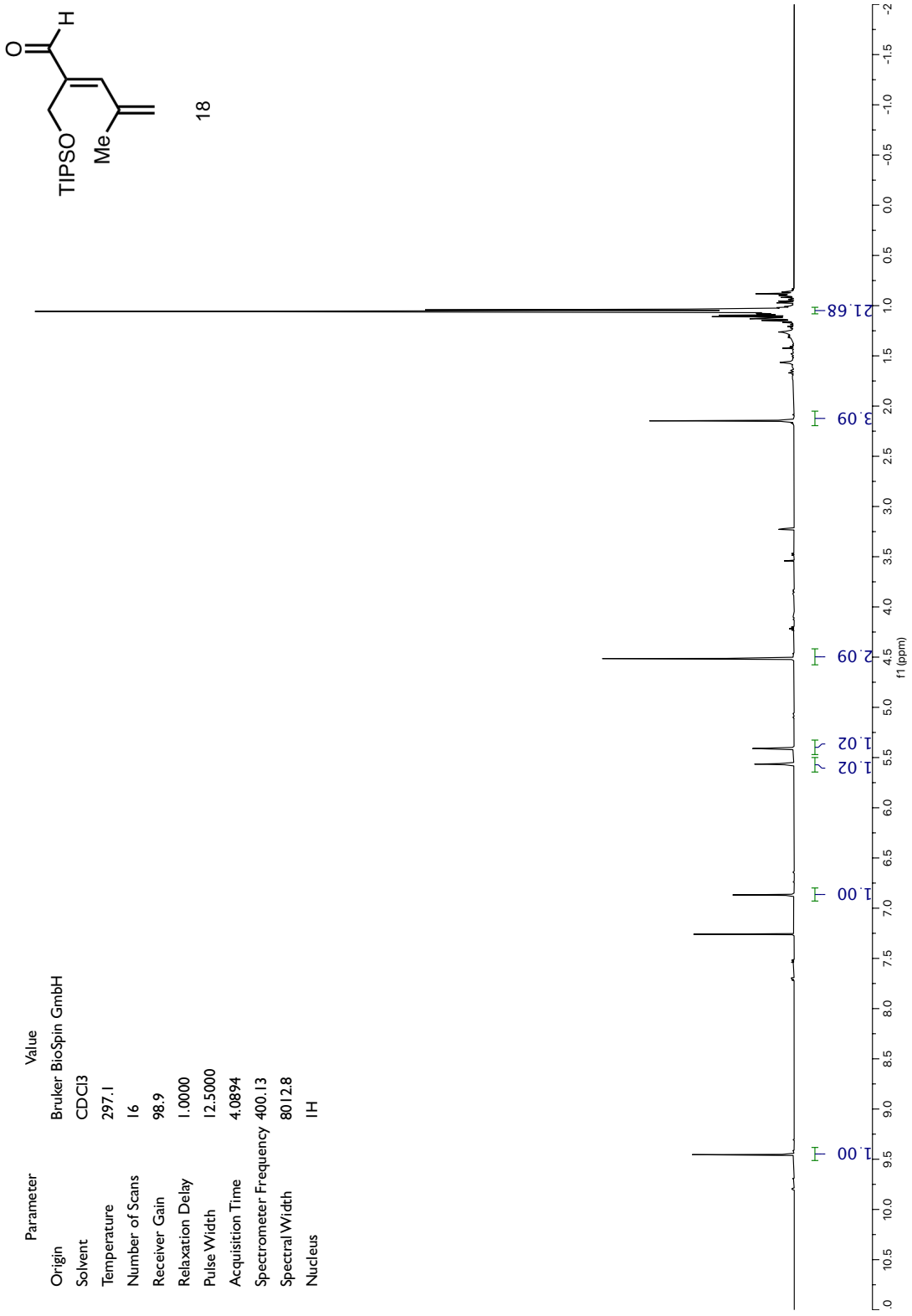
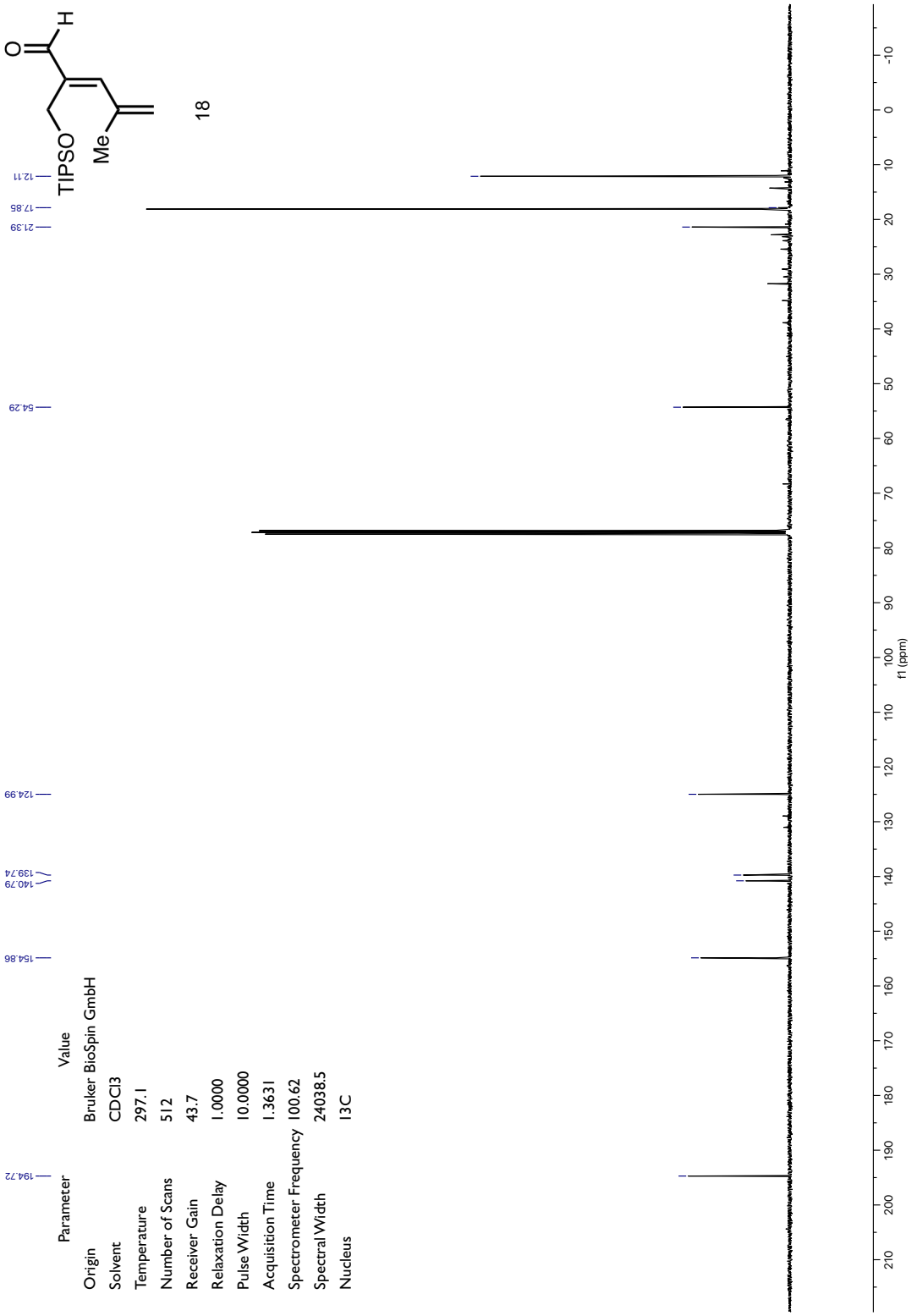
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	298.0
Number of Scans	1024
Receiver Gain	24.0
Relaxation Delay	2.0000
Pulse Width	9.9000
Acquisition Time	1.3763
Spectrometer Frequency	100.63
Spectral Width	23809.5
Nucleus	13C


OMe
O
TIPSO
Me
24
27.14
3.23
3.19
2.14
1.07
1.06
1.00
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H


OMe
O
TIPSO
Me
24
12.19
17.84
18.09
22.32
51.95
57.78
120.83
131.11
140.23
144.22
168.60
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)


O
H
TIPSO
Me
18
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
98.9
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
21.68
3.09
2.09
1.02
1.02
1.00
1.00
f1 (ppm)


O
H
TIPSO
Me
18
12.11
17.85
21.39
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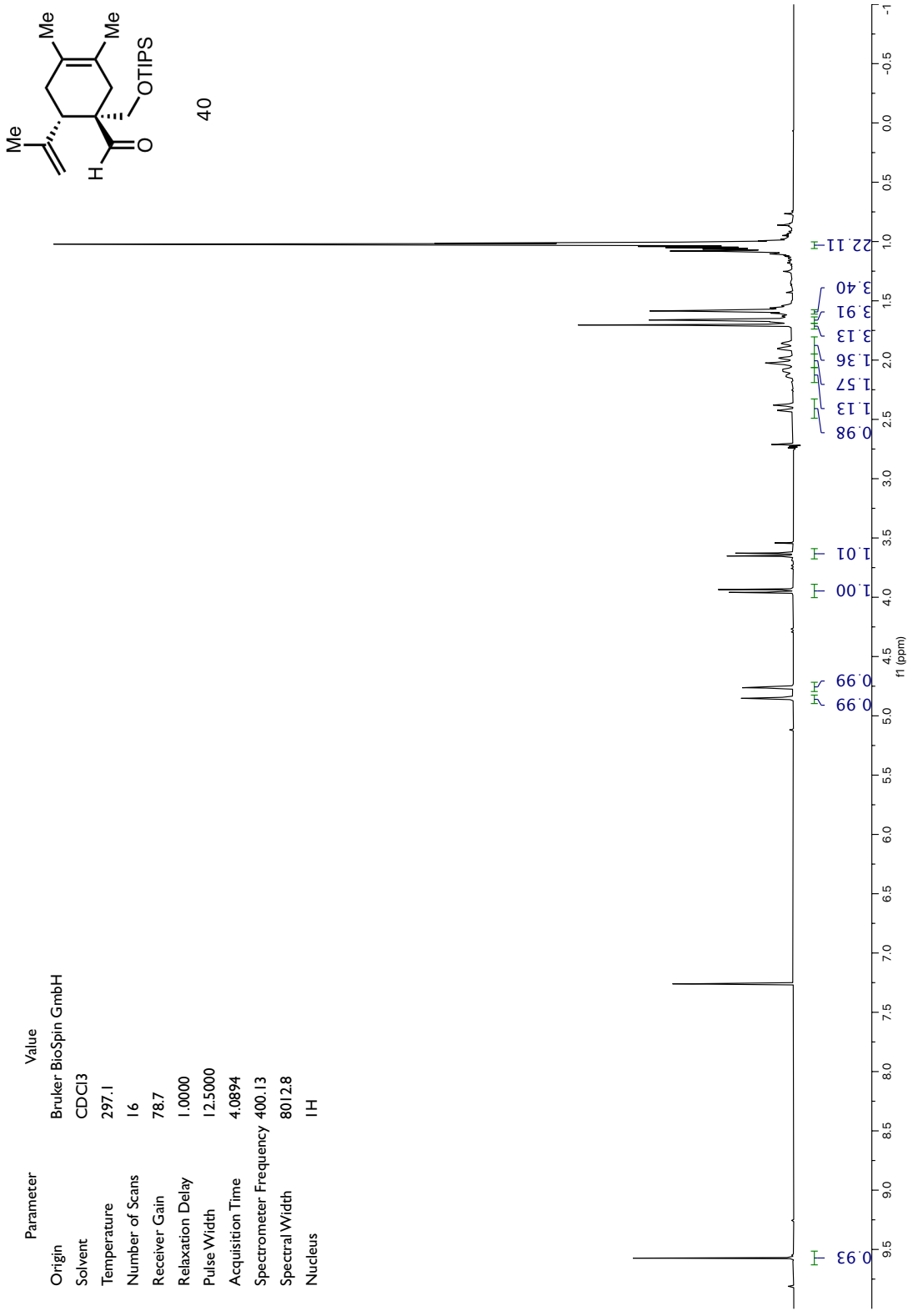
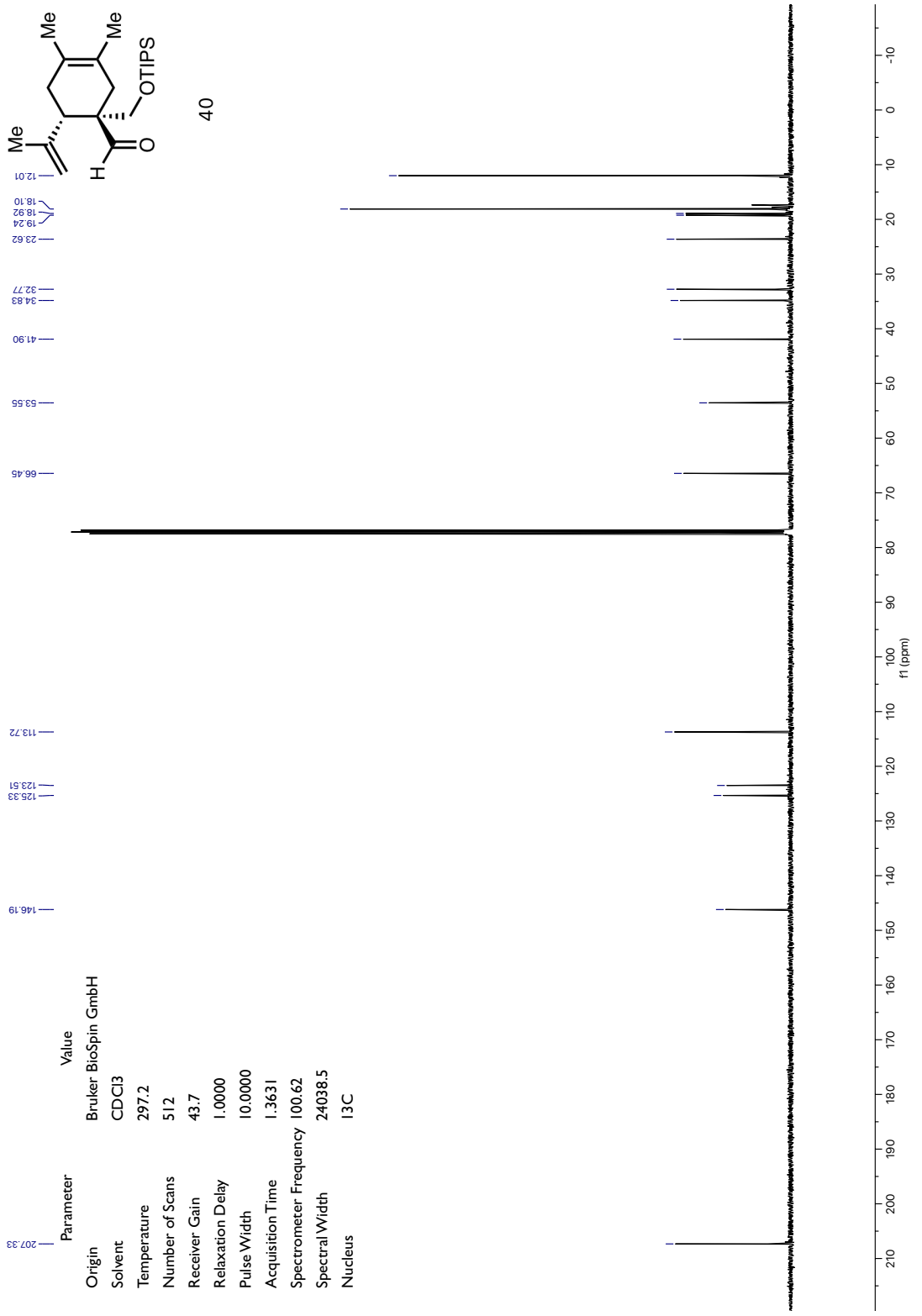
124.99
139.74
140.79
154.86
194.72
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)



Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	16
Receiver Gain	78.7
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H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Me
OTIPS
O
H
Me
40
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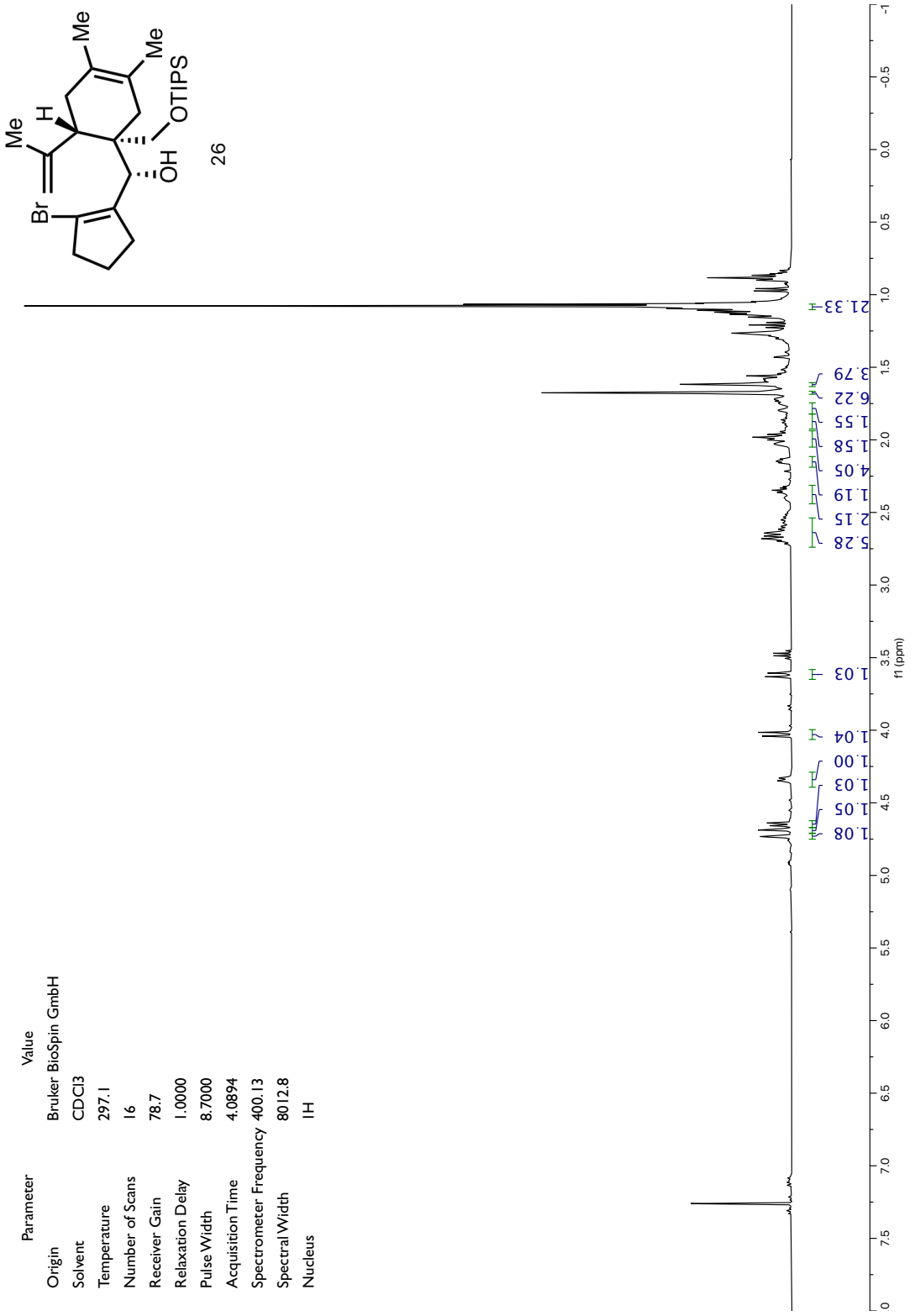
18.10
18.92
19.24
23.62
32.77
34.83
41.90
53.55
66.45
113.72
123.51
126.33
146.19
207.33
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)


Me
H
Me
Me
OTIPS
OH
Br
26
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 8.7000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
21.33
3.79
6.22
1.55
1.58
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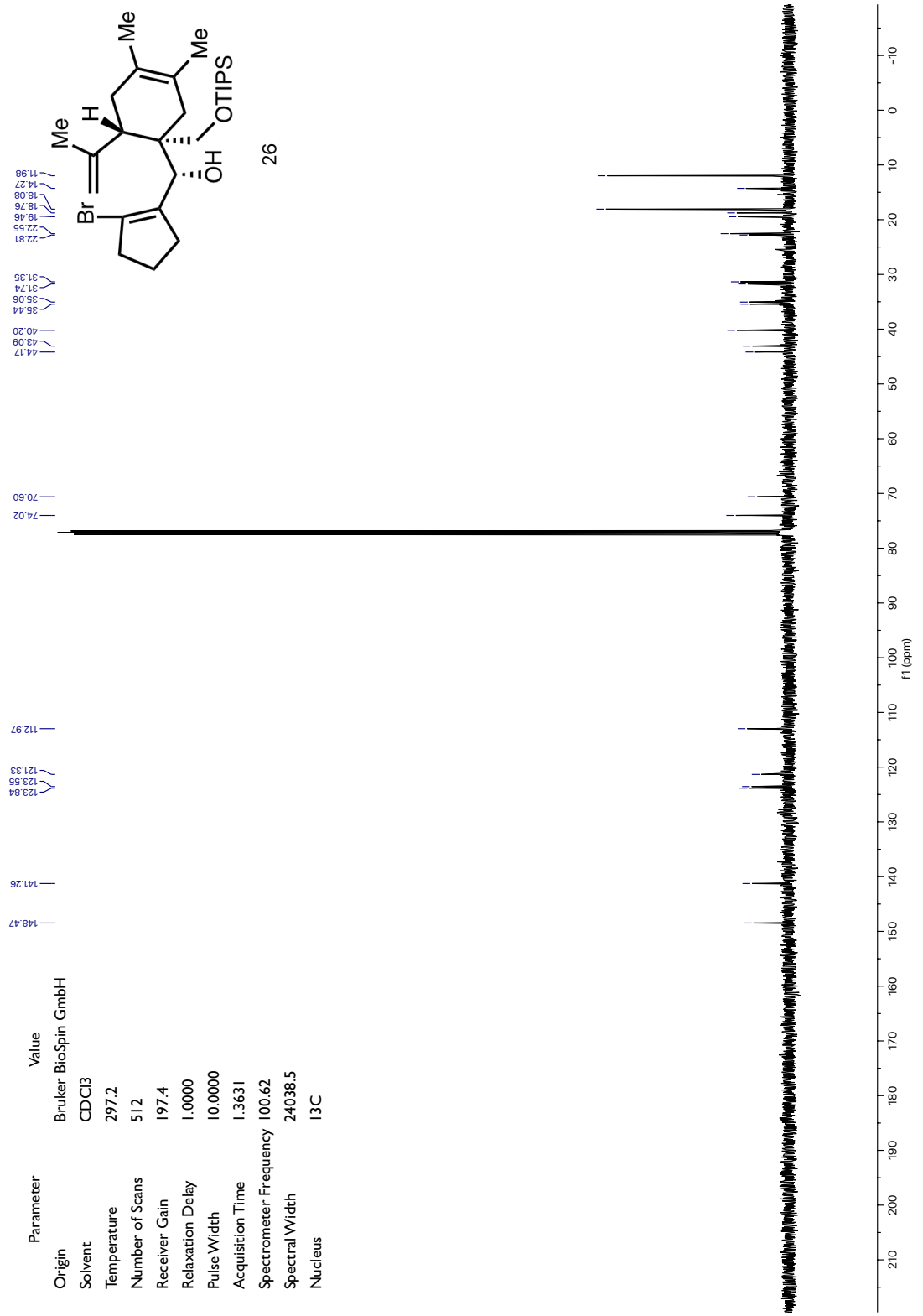
2.15
5.28
1.03
1.04
1.00
1.03
1.05
1.08
f1 (ppm)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H
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31.35
31.74
35.06
35.44
40.20
43.09
44.17
70.60
74.02
112.97
121.33
123.55
123.84
141.26
148.47
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
512
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
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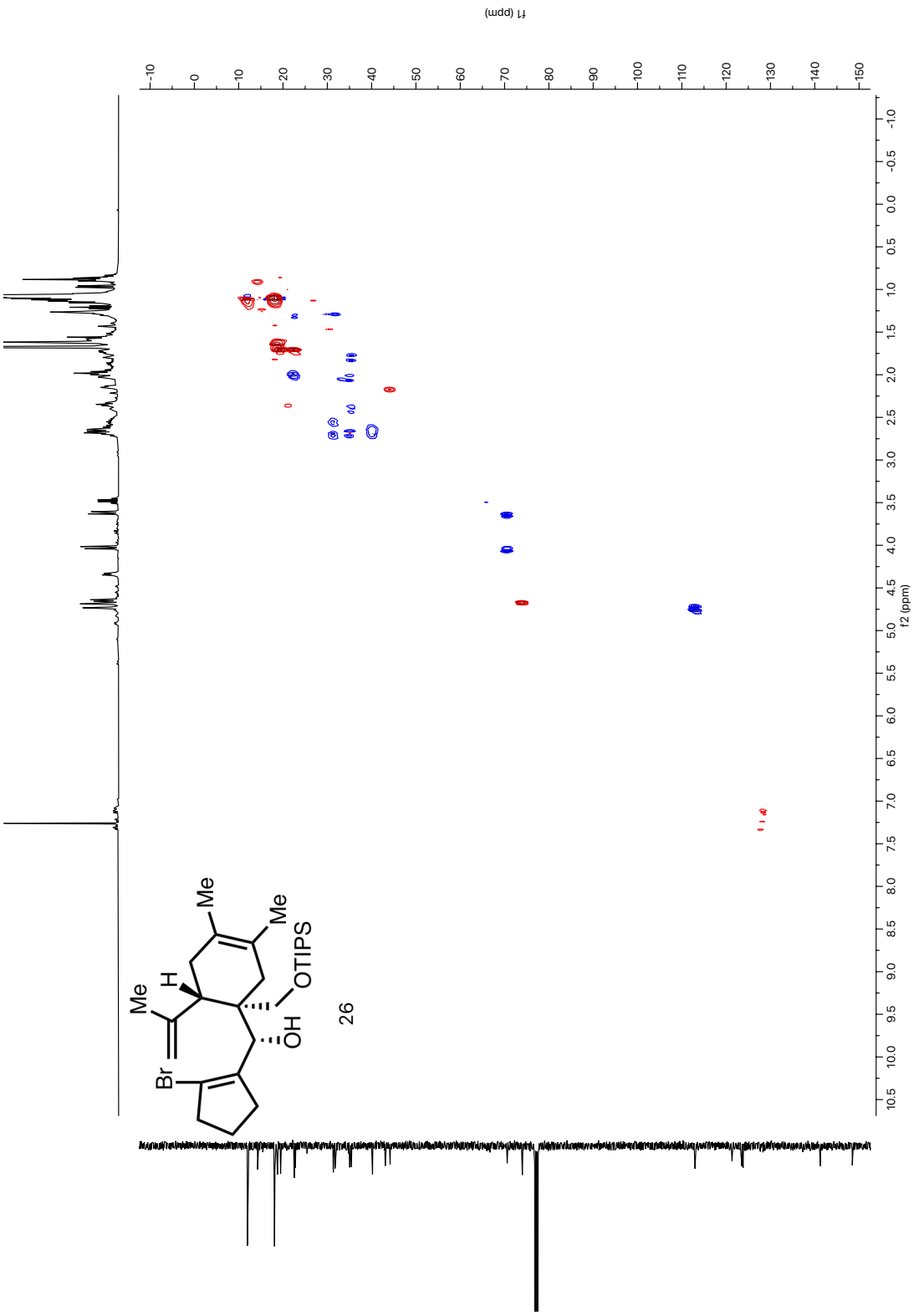
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)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f2 (ppm)
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OTIPS
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OH
Br
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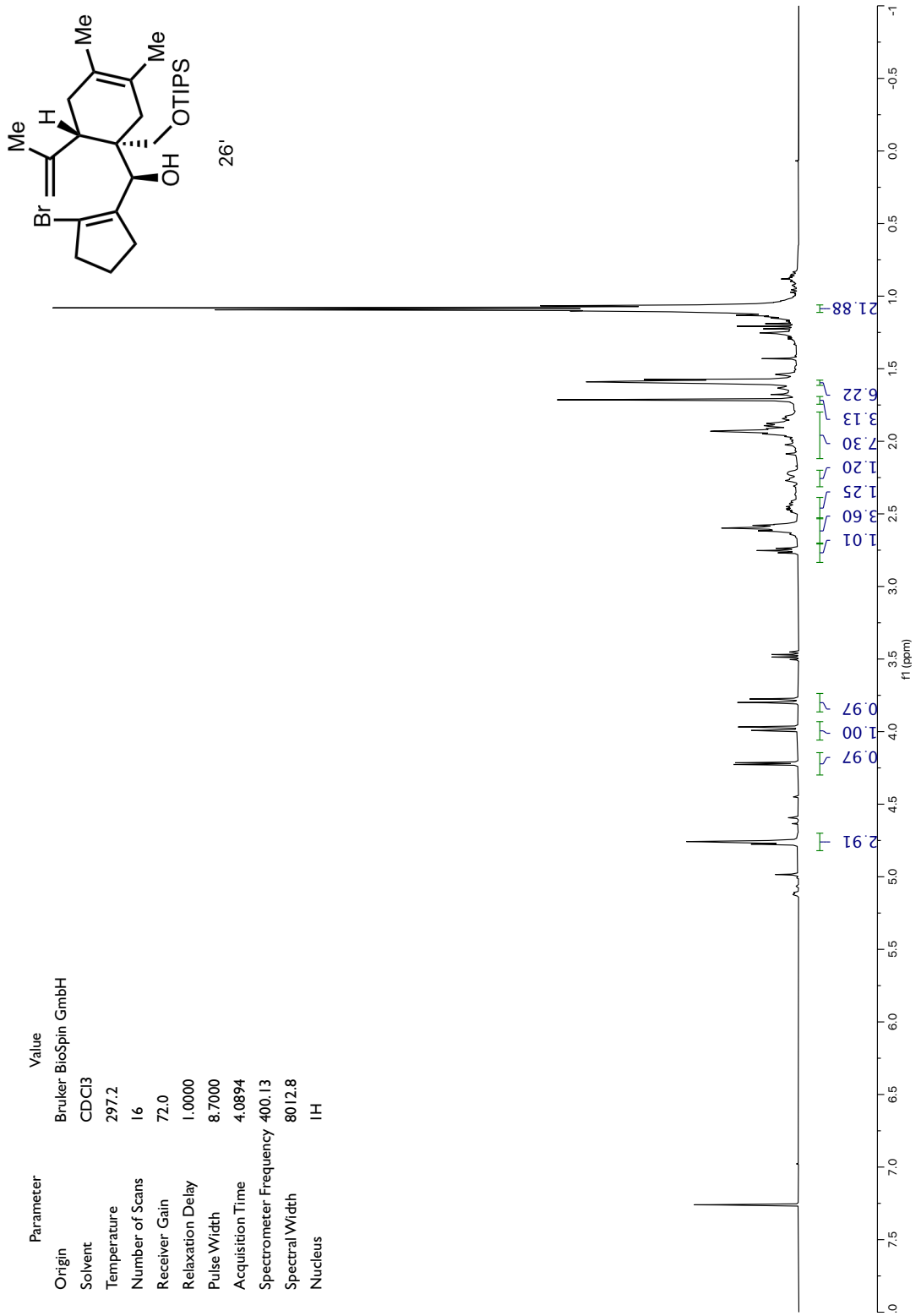
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H
OTIPS
Br
OH
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Number of Scans 16
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 8.7000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
21.88
6.22
3.13
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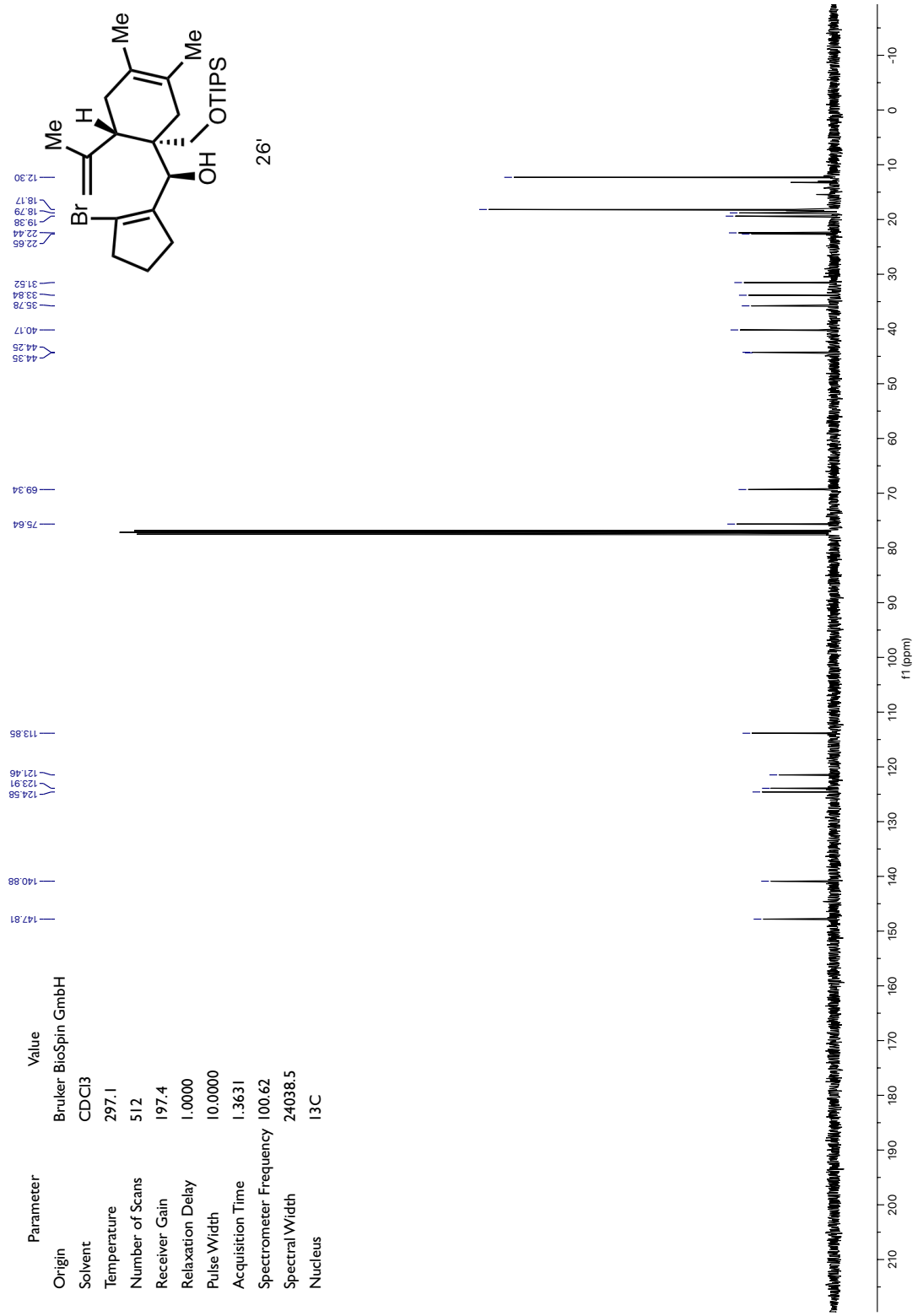
1.20
1.25
3.60
1.01
0.97
1.00
0.97
2.91
f1 (ppm)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Me
Me
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Br
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19.38
22.44
22.65
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35.78
40.17
44.25
44.35
69.34
75.64
113.85
121.46
123.91
124.58
140.88
147.81
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 197.4
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Pulse Width 10.0000
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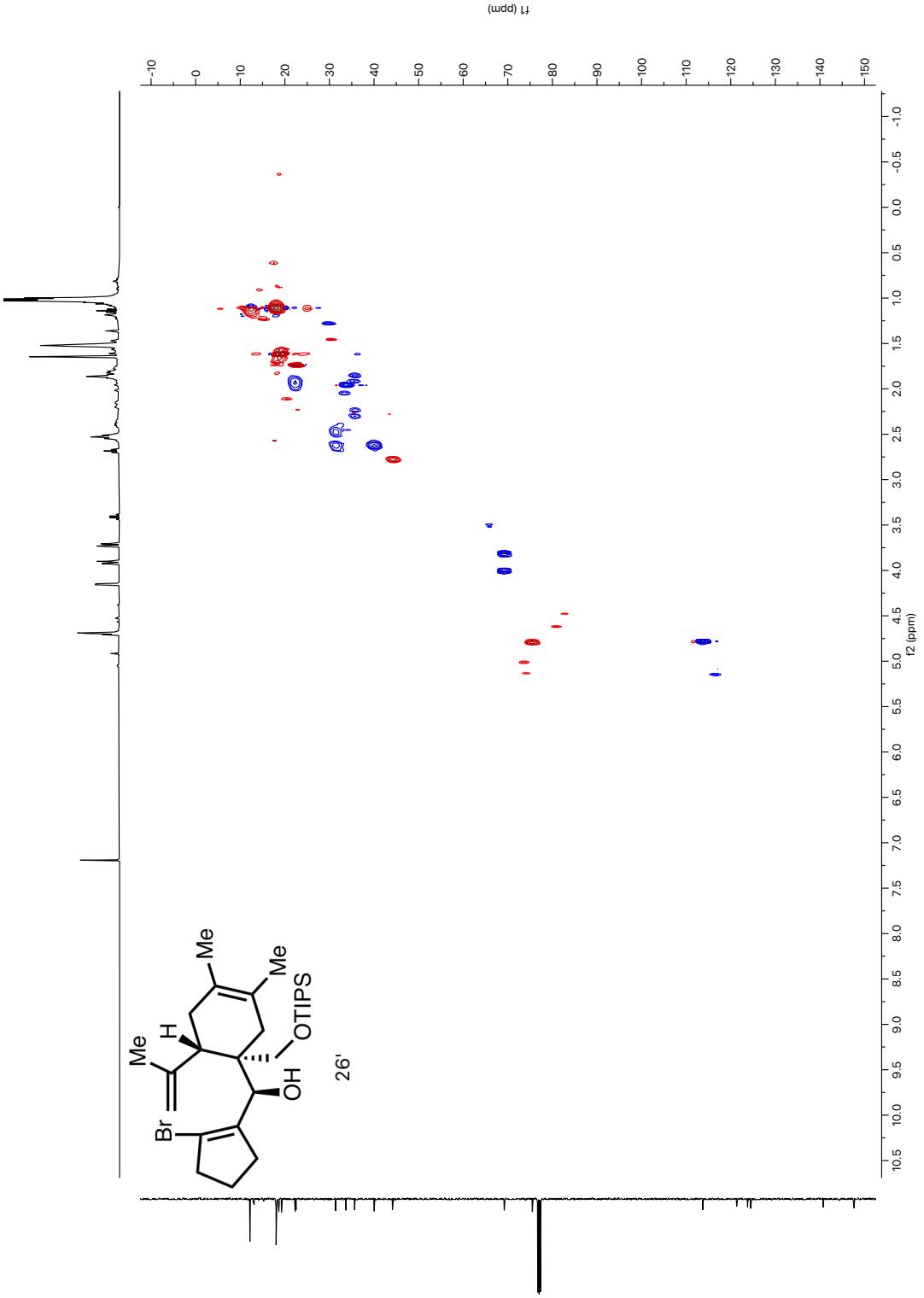
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)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f2 (ppm)
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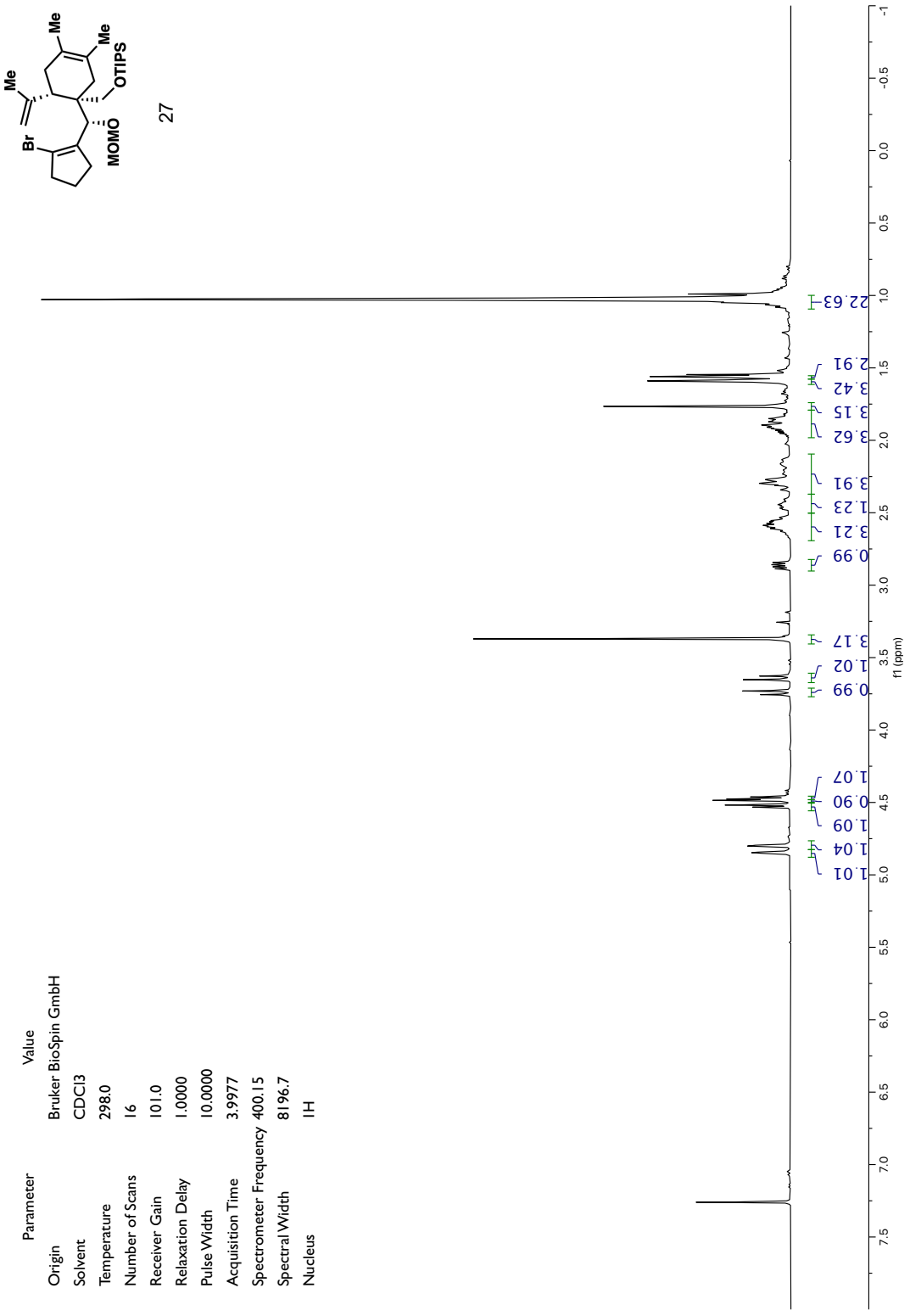
Me
H
OTIPS
Me
OH
Br
26'


Me
Me
Me
OTIPS
Br
MOMO
27
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Number of Scans 16
Receiver Gain 101.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 3.9977
Spectrometer Frequency 400.15
Spectral Width 8196.7
Nucleus 1H
22.63
2.91
3.42
3.15
3.62
3.91
1.23
3.21
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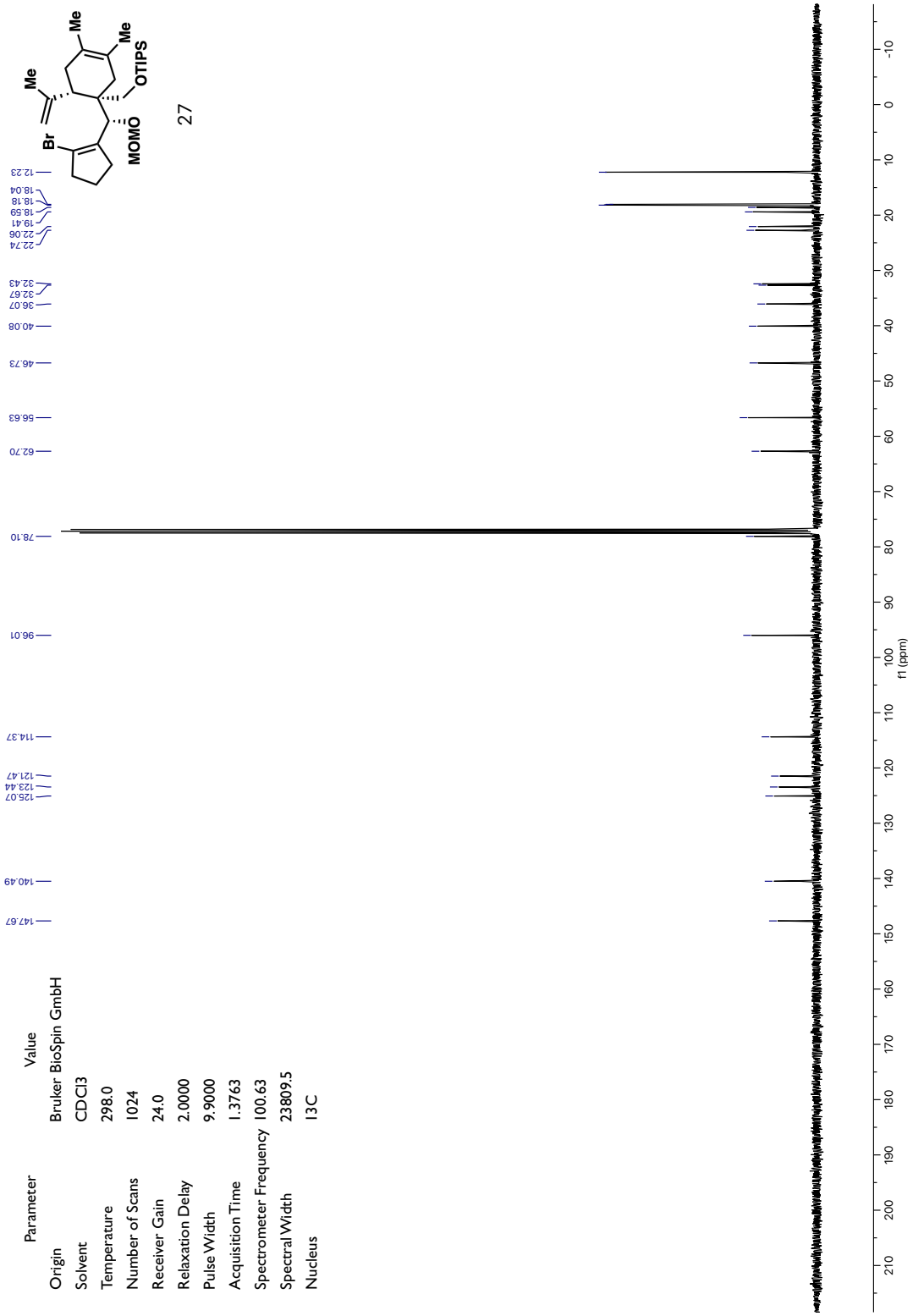
3.17
1.02
0.99
1.07
0.90
1.09
1.04
1.01
f1 (ppm)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Me
OTIPS
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18.18
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19.41
22.06
22.74
32.43
32.67
36.07
40.08
46.73
56.63
62.70
78.10
96.01
114.37
121.47
123.44
125.07
140.49
147.67
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
298.0
Number of Scans
1024
Receiver Gain
24.0
Relaxation Delay
2.0000
Pulse Width
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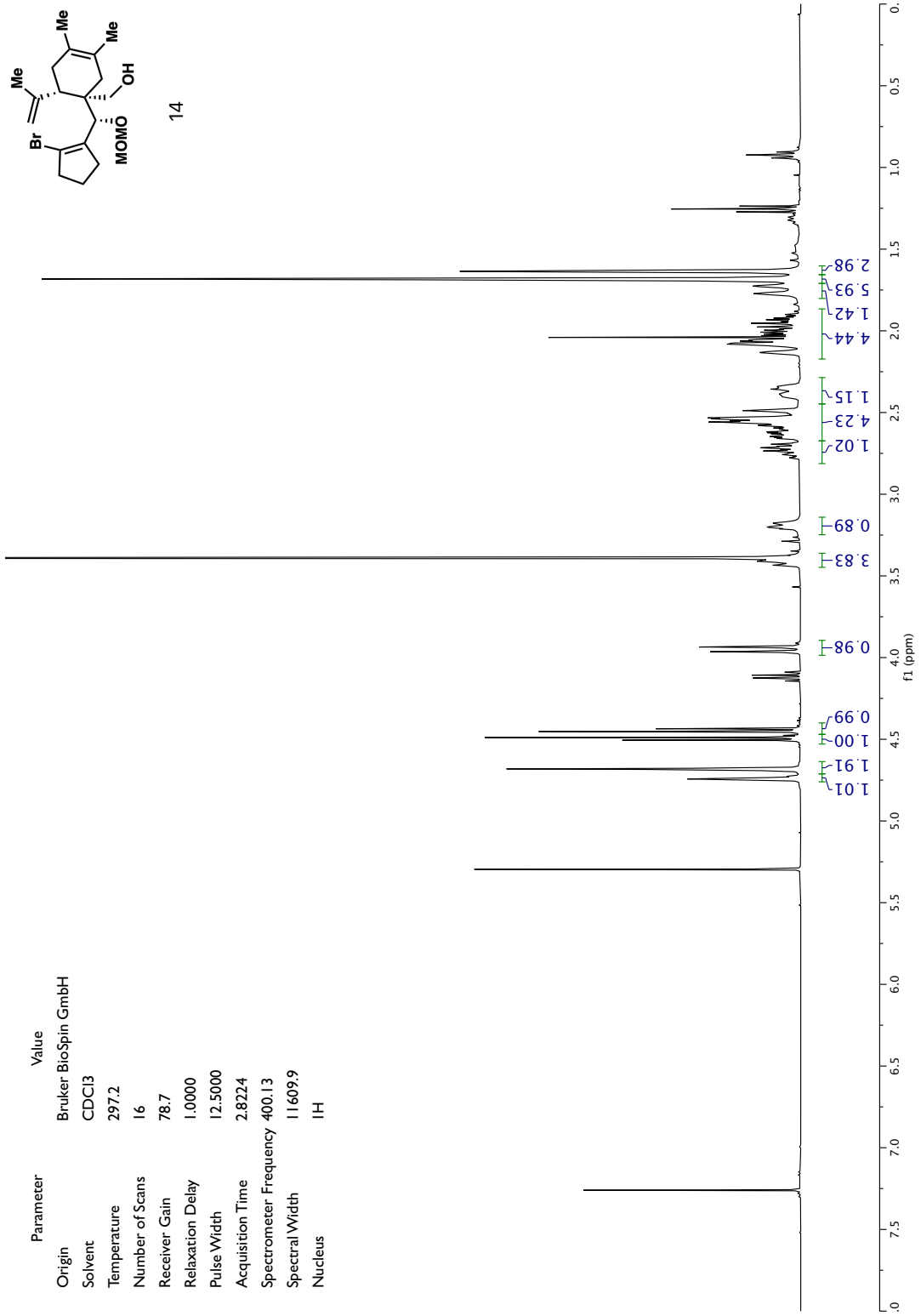
Acquisition Time
1.3763
Spectrometer Frequency
100.63
Spectral Width
23809.5
Nucleus
13C
f1 (ppm)


Me
Me
Me
OH
MOMO
Br
14
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
1.01
1.91
1.00
0.99
0.98
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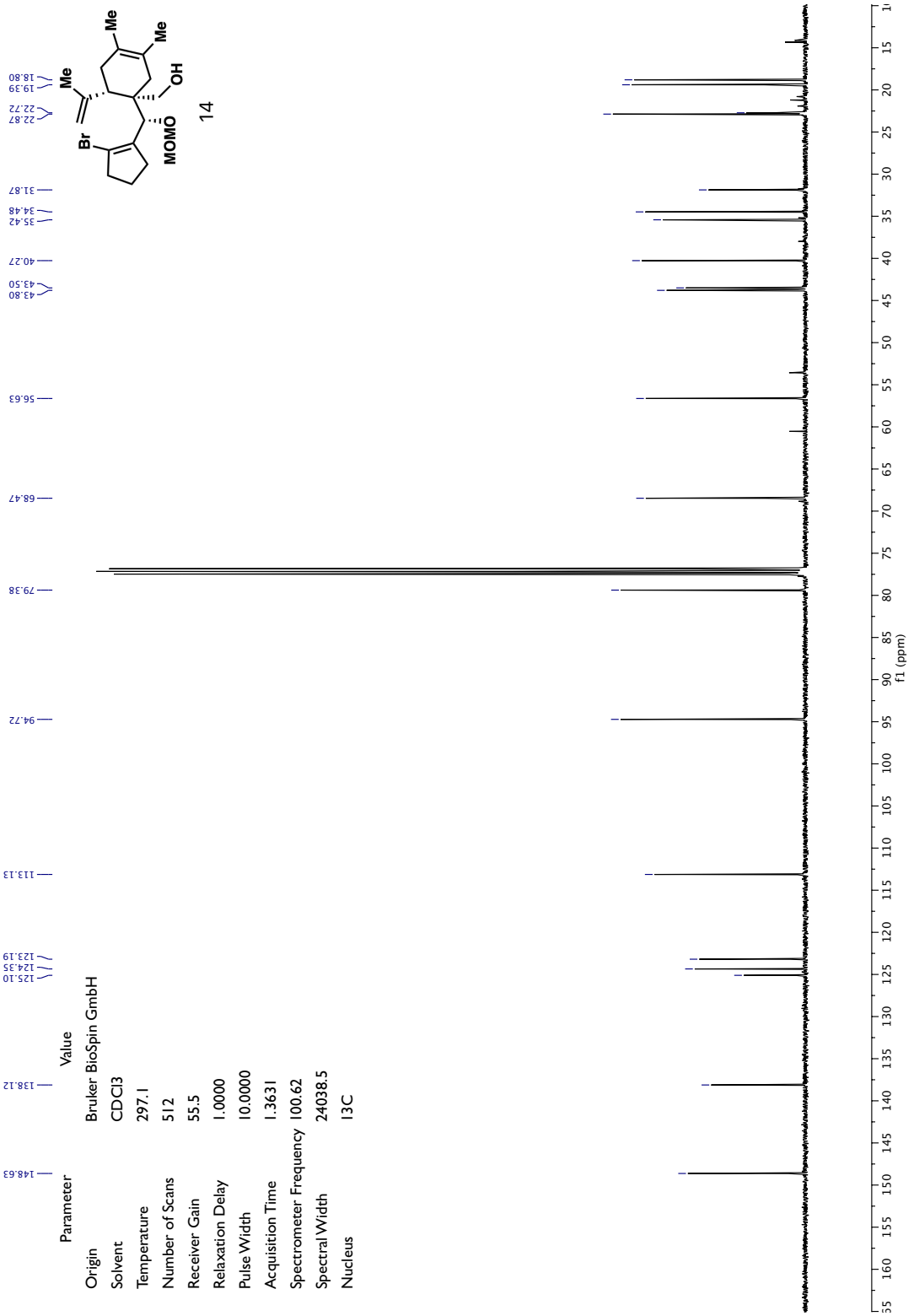
0.89
1.02
4.23
1.15
4.44
1.42
5.93
2.98
f1 (ppm)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Br
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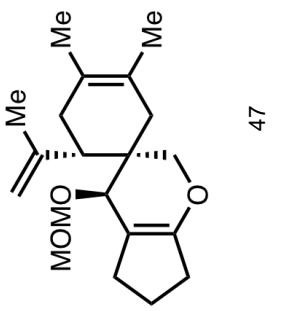
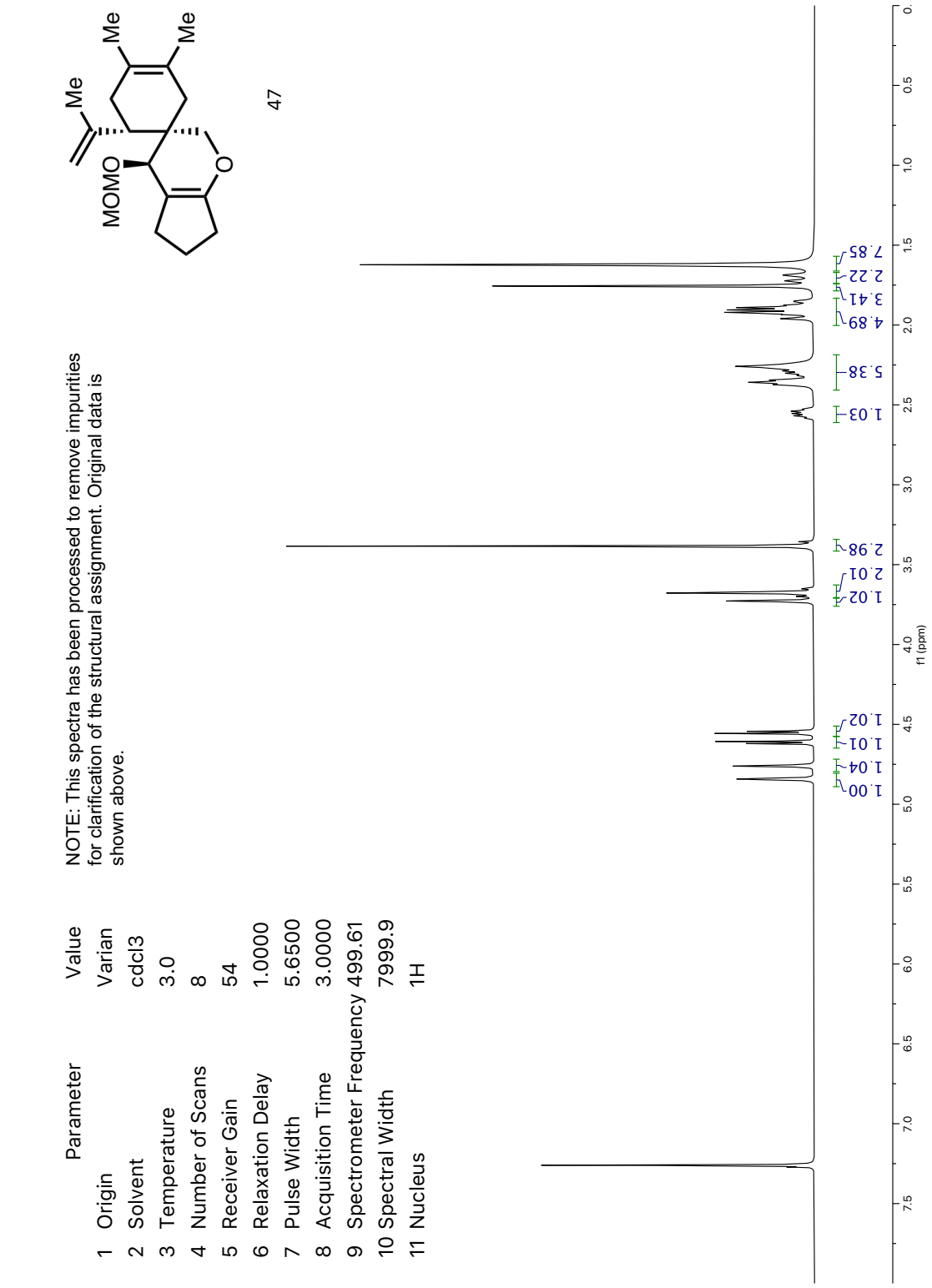
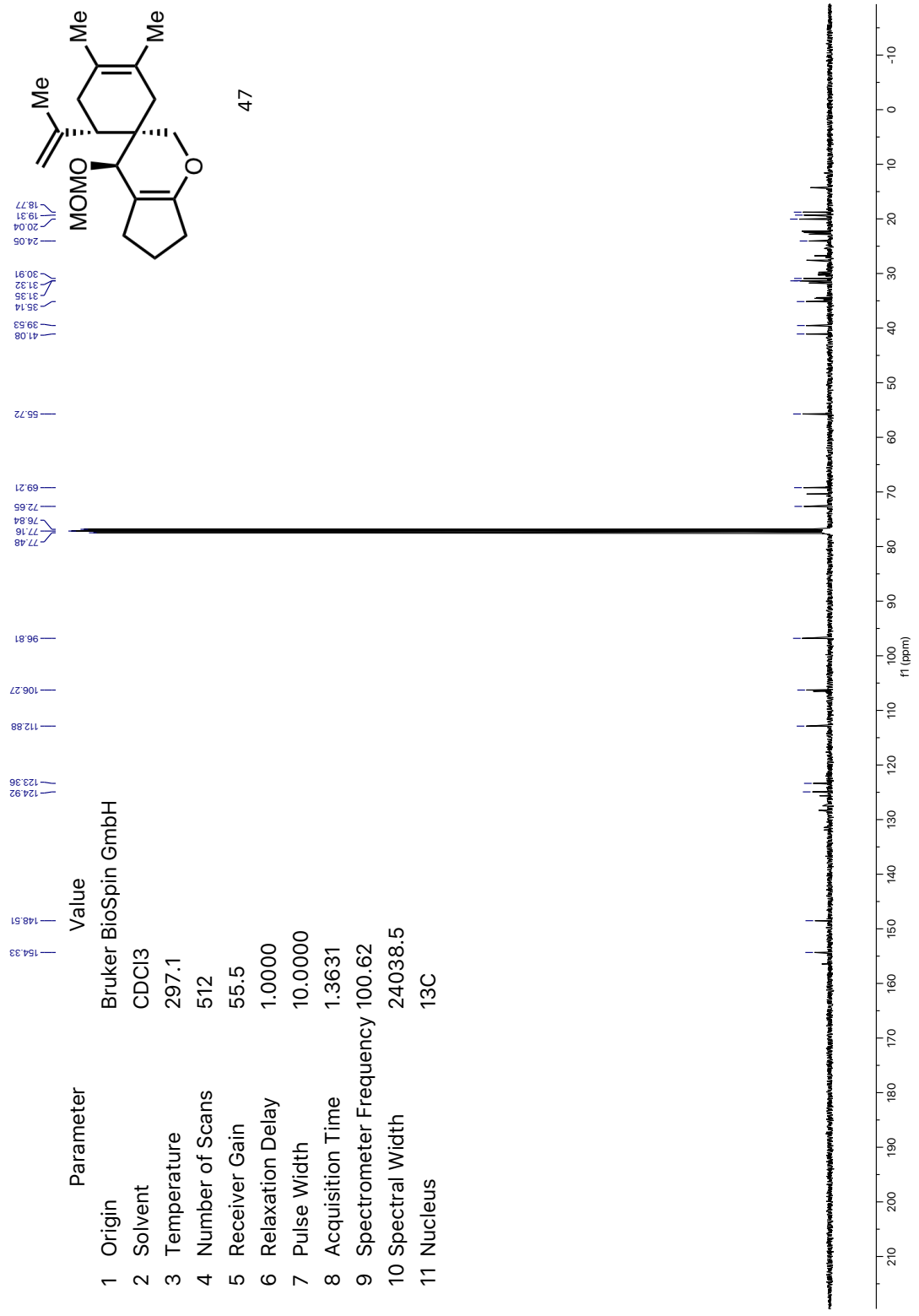
31.87
34.48
35.42
40.27
43.50
43.80
56.63
68.47
79.38
94.72
113.13
123.19
124.35
125.10
138.12
148.63
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C



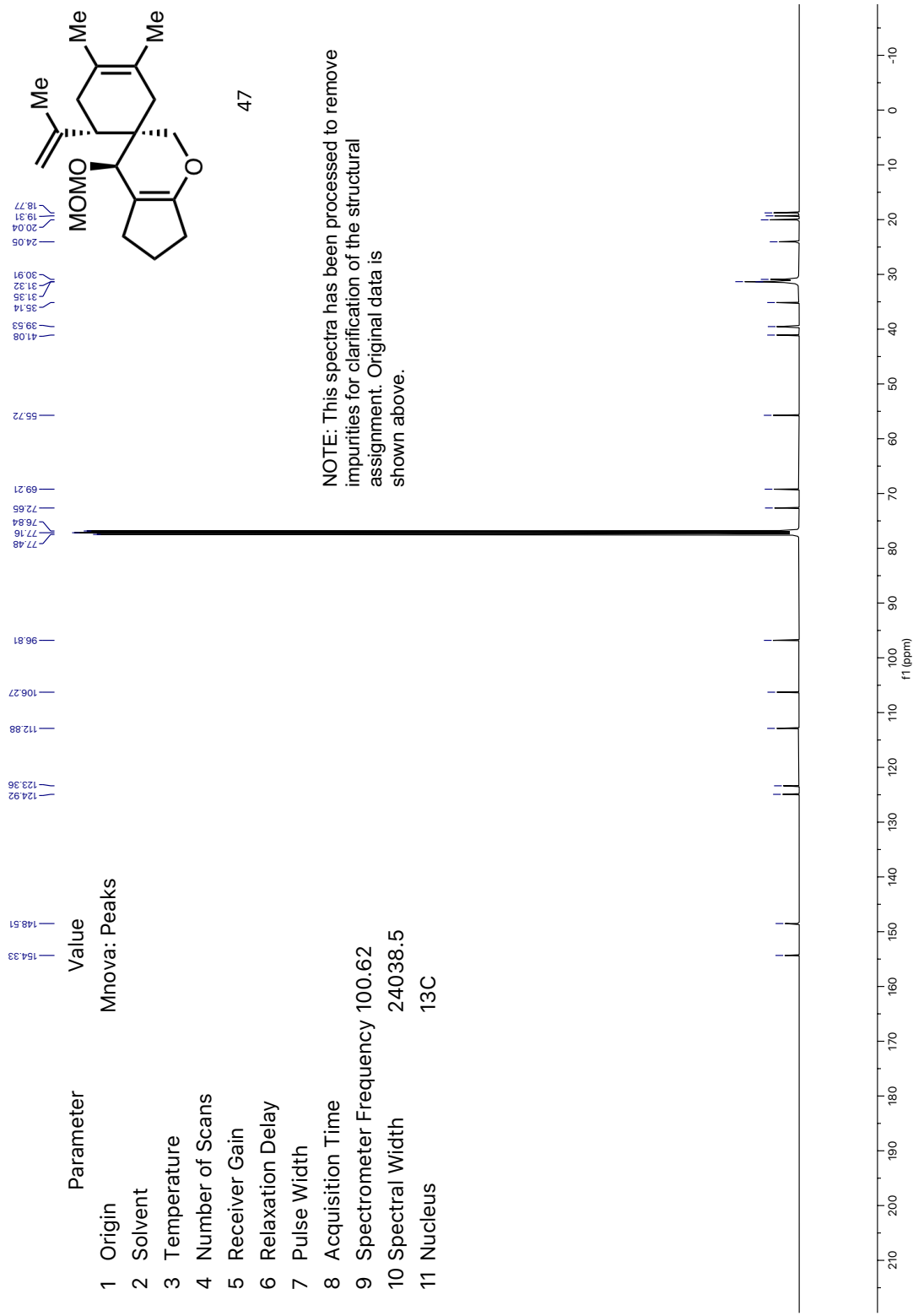
47

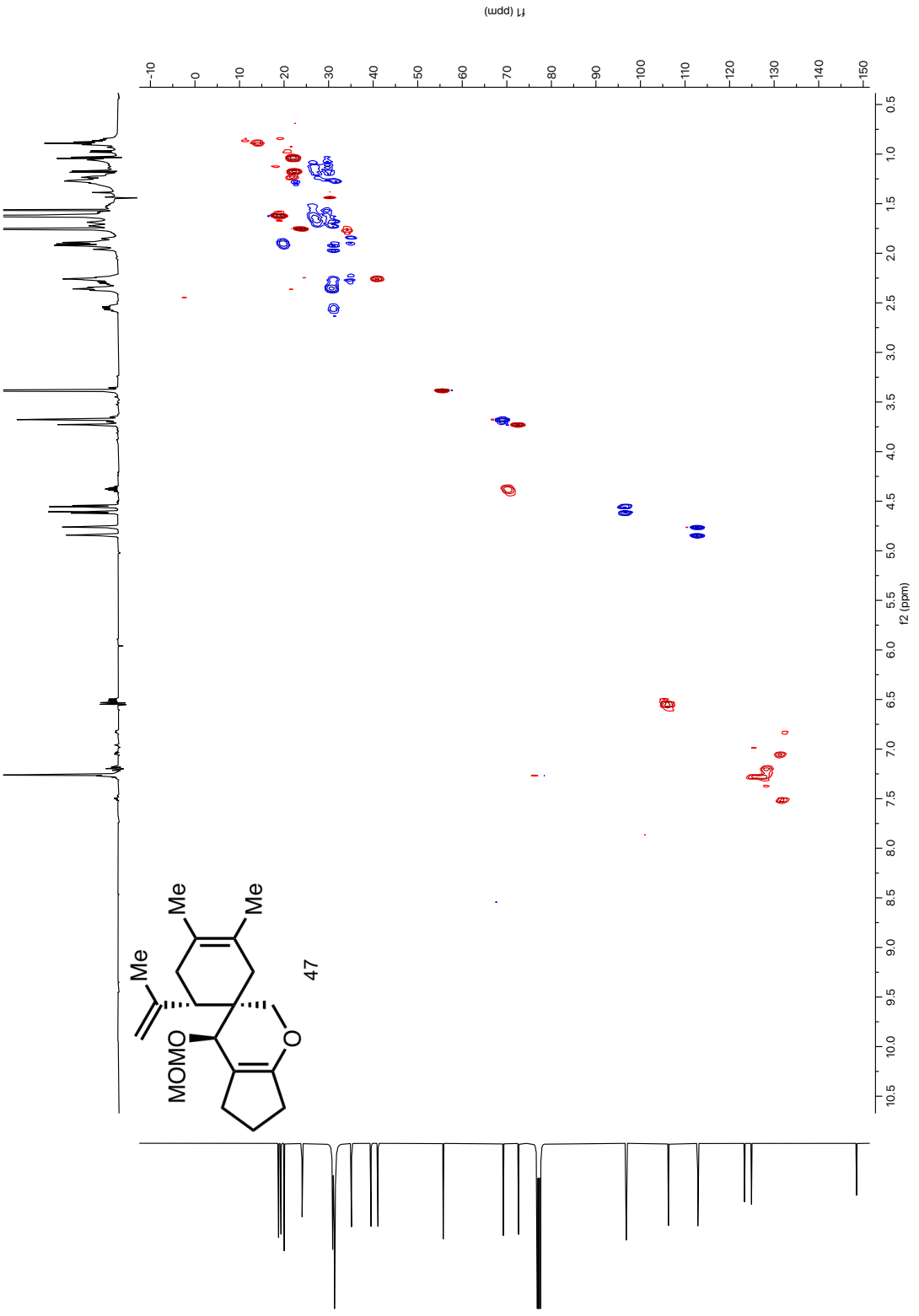
	Parameter	Value
1	Origin	Bruker BioSpin GmbH
2	Solvent	CDCl3
3	Temperature	297.2
4	Number of Scans	16
5	Receiver Gain	197.4
6	Relaxation Delay	1.0000
7	Pulse Width	12.5000
8	Acquisition Time	4.0894
9	Spectrometer Frequency	400.13
10	Spectral Width	8012.8
11	Nucleus	1H

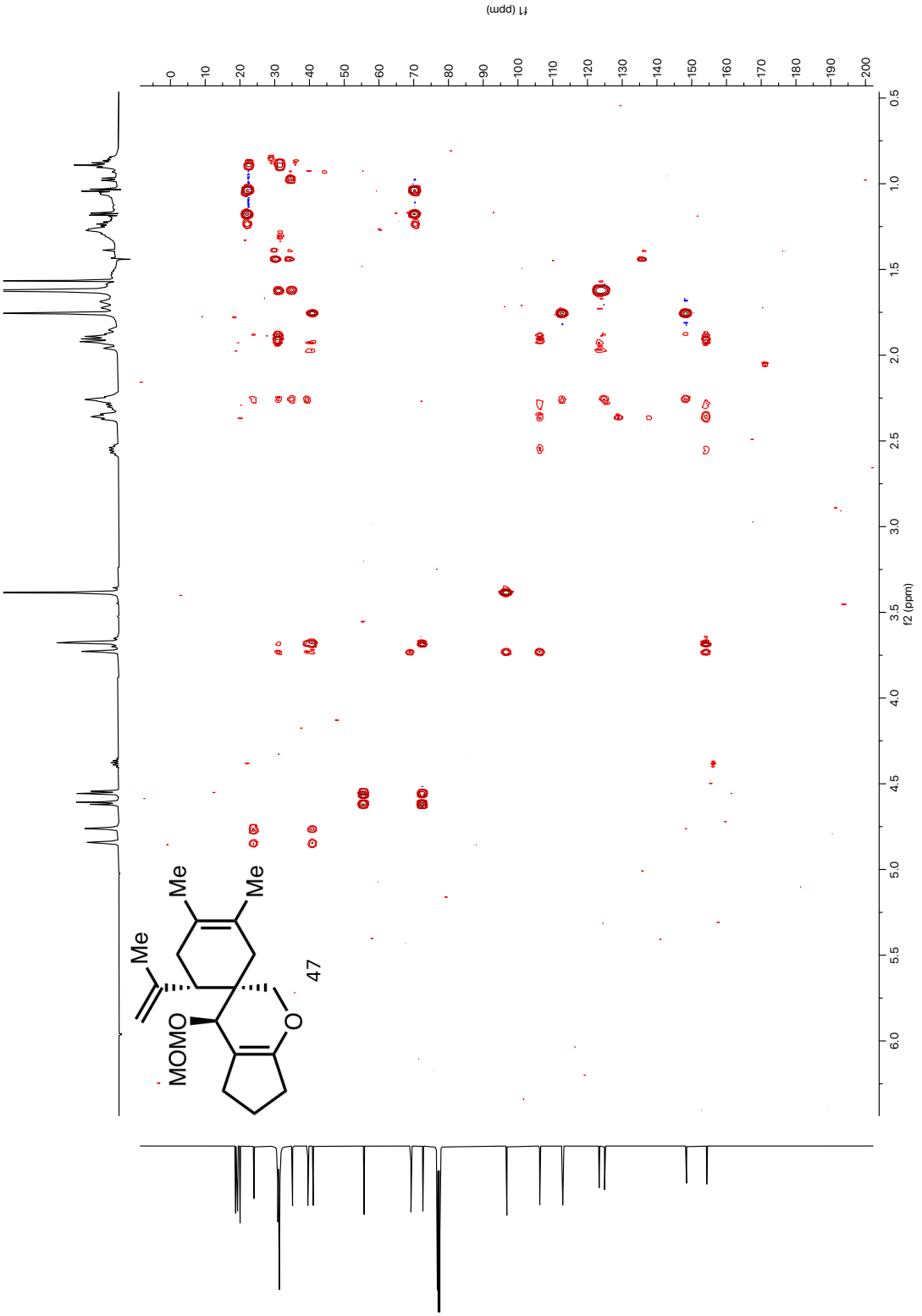

Me
Me
Me
MOMO
O
47
NOTE: This spectra has been processed to remove impurities for clarification of the structural assignment. Original data is shown above.
Parameter Value
1 Origin Varian
2 Solvent cdcl3
3 Temperature 3.0
4 Number of Scans 8
5 Receiver Gain 54
6 Relaxation Delay 1.0000
7 Pulse Width 5.6500
8 Acquisition Time 3.0000
9 Spectrometer Frequency 499.61
10 Spectral Width 7999.9
11 Nucleus 1H
1.00
1.04
1.01
1.02
2.98
1.02
2.01
1.03
5.38
4.89
3.41
2.22
7.85
f1 (ppm)

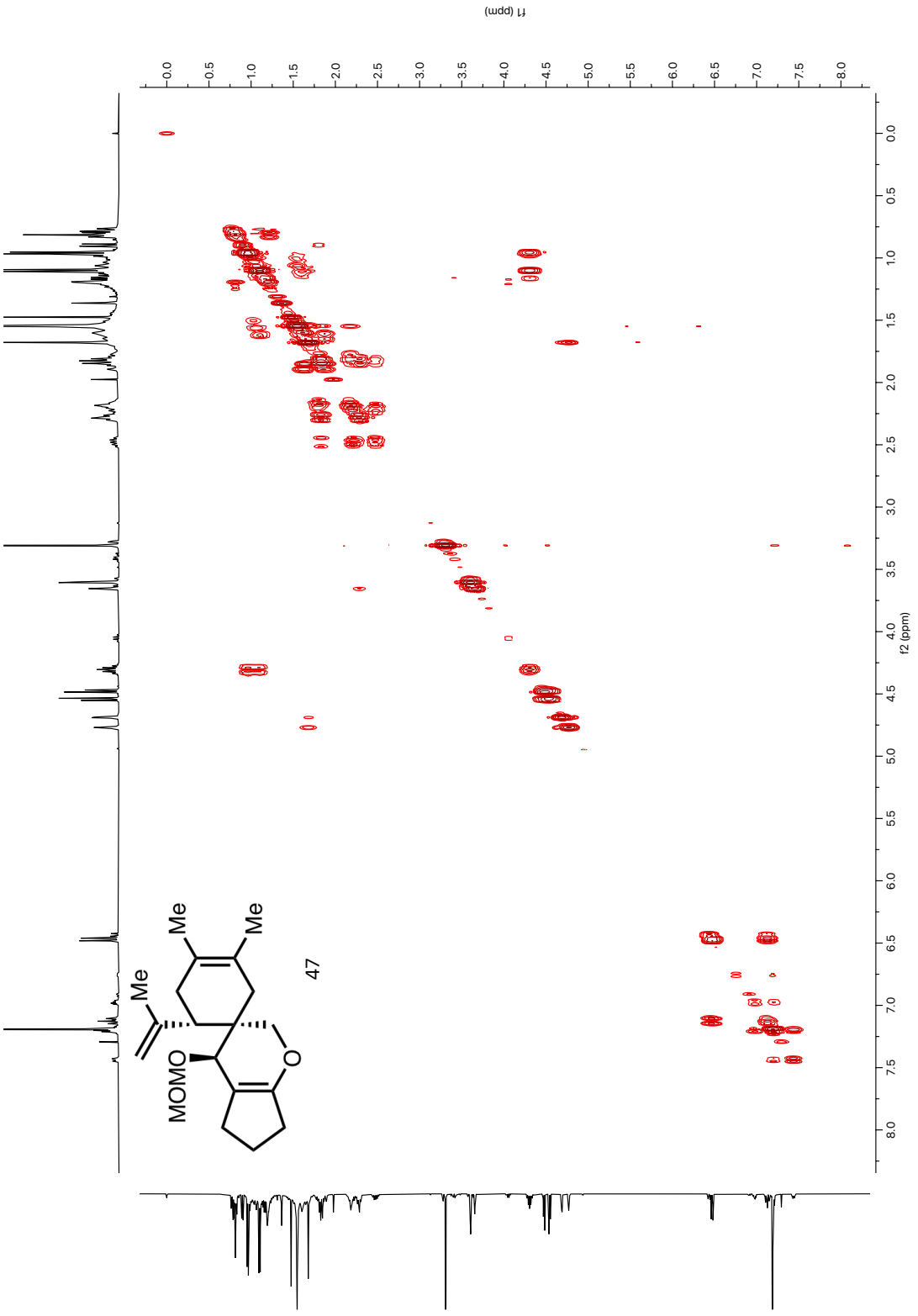


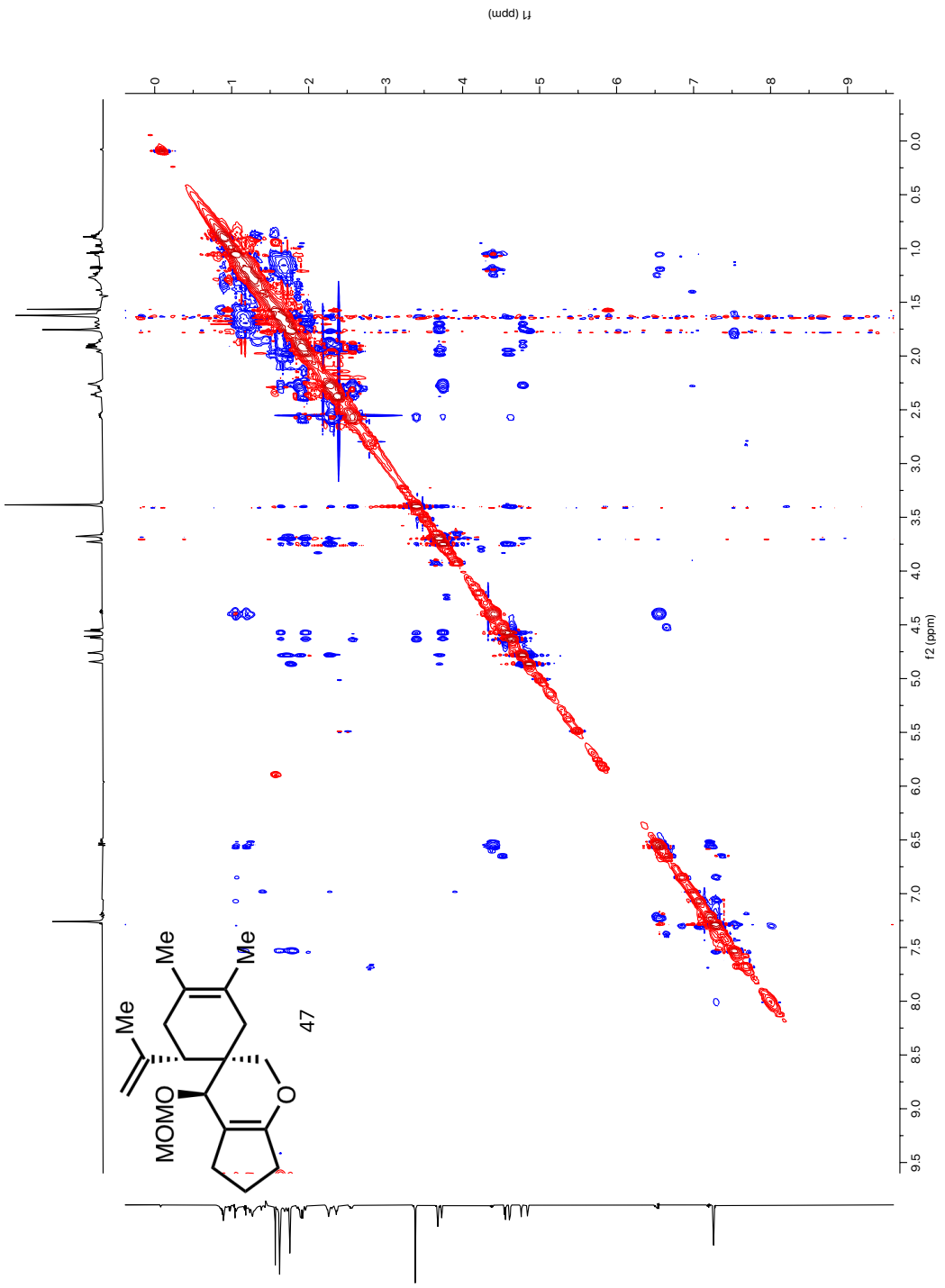
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl3
3 Temperature	297.1
4 Number of Scans	512
5 Receiver Gain	55.5
6 Relaxation Delay	1.0000
7 Pulse Width	10.0000
8 Acquisition Time	1.3631
9 Spectrometer Frequency	100.62
10 Spectral Width	24038.5
11 Nucleus	13C

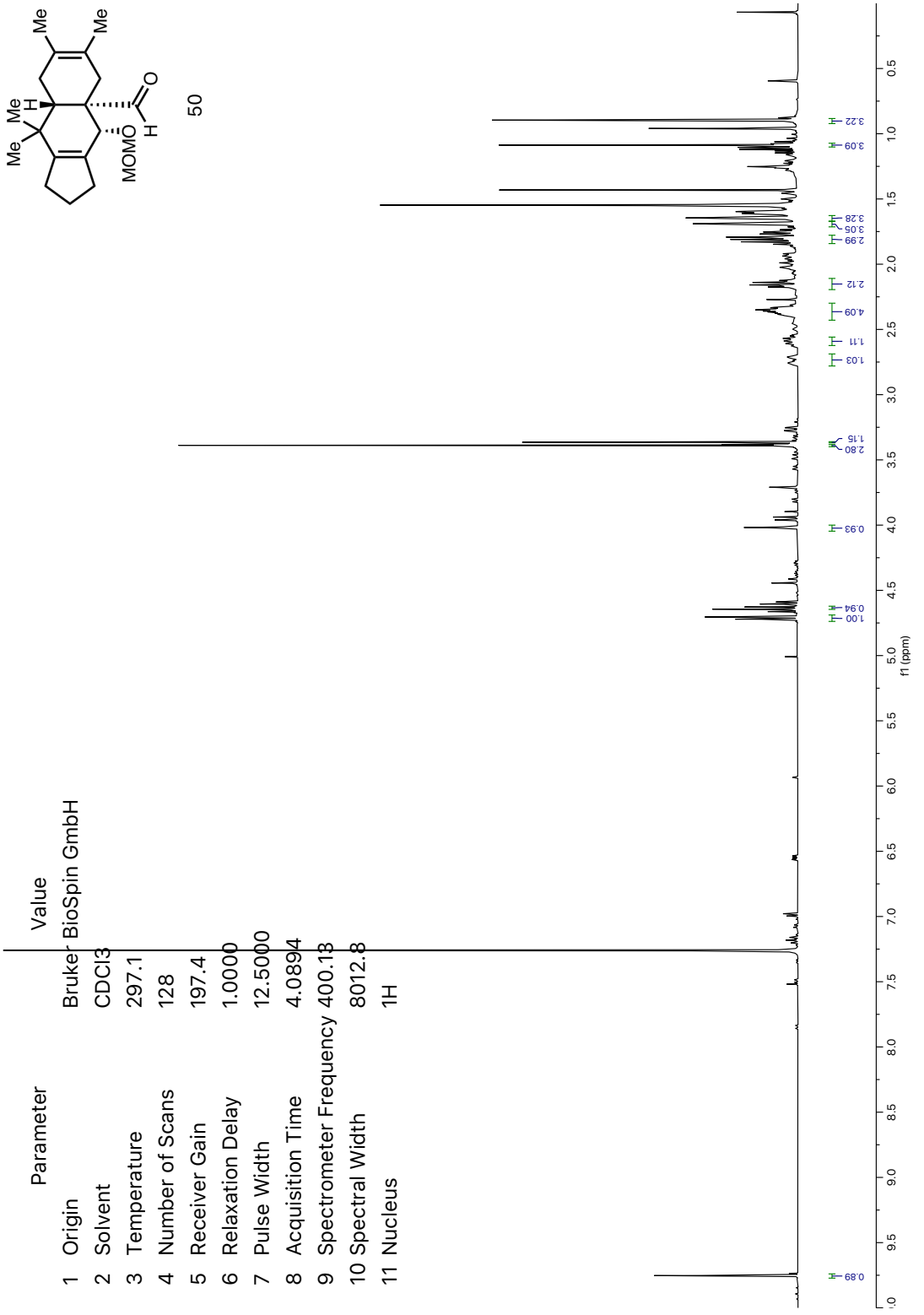

Me
Me
Me
MOMO
O
47
NOTE: This spectra has been processed to remove impurities for clarification of the structural assignment. Original data is shown above.
Parameter Value
1 Origin Mnova: Peaks
2 Solvent
3 Temperature
4 Number of Scans
5 Receiver Gain
6 Relaxation Delay
7 Pulse Width
8 Acquisition Time
9 Spectrometer Frequency 100.62
10 Spectral Width 24038.5
11 Nucleus 13C
154.33
148.51
124.92
123.36
112.88
106.27
96.81
77.48
77.16
76.84
72.65
69.21
55.72
41.08
39.53
35.14
31.35
31.32
30.91
24.05
20.04
19.31
18.77
f1 (ppm)

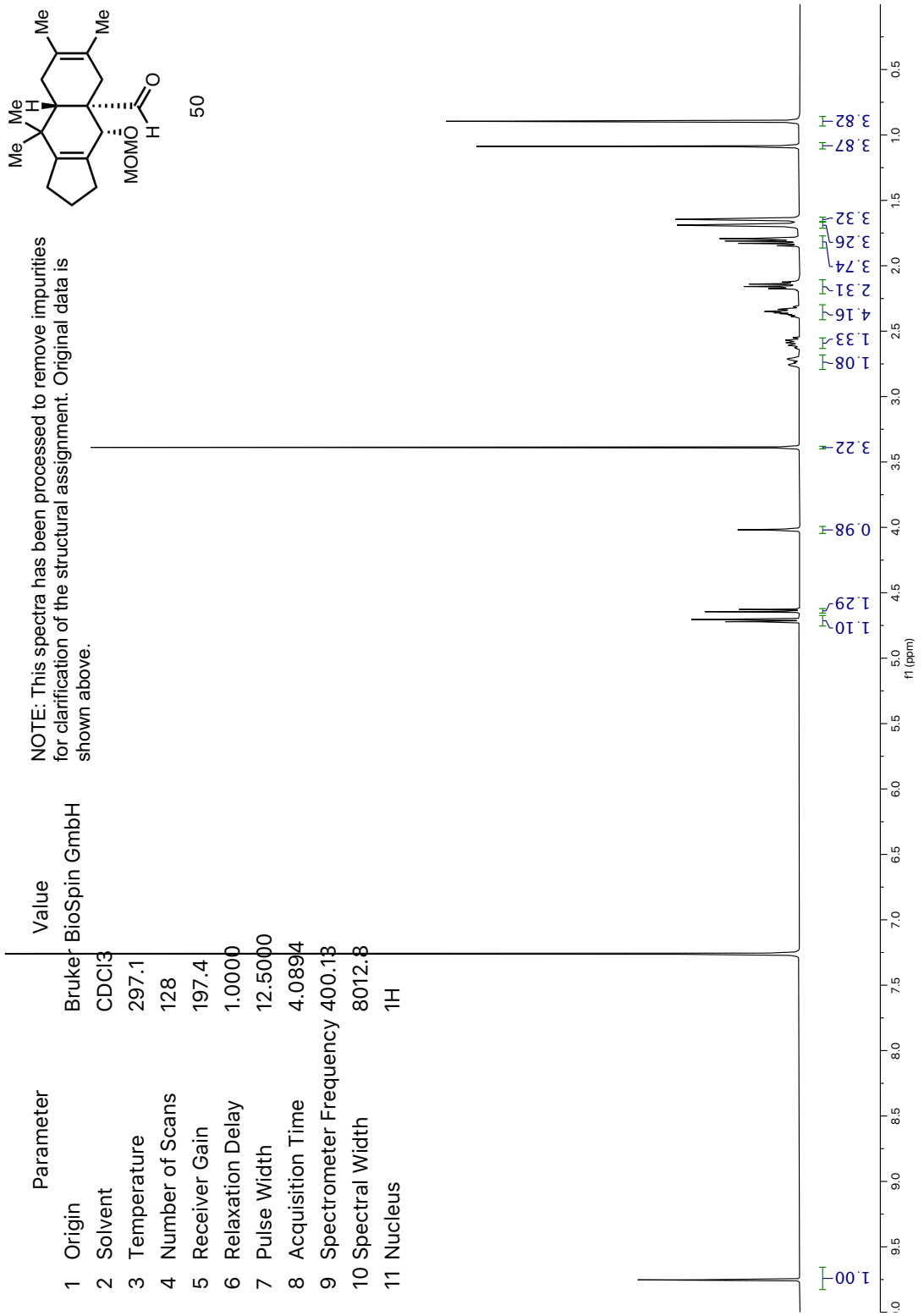

f1 (ppm)
f2 (ppm)
Me
Me
Me
MOMO
O
47

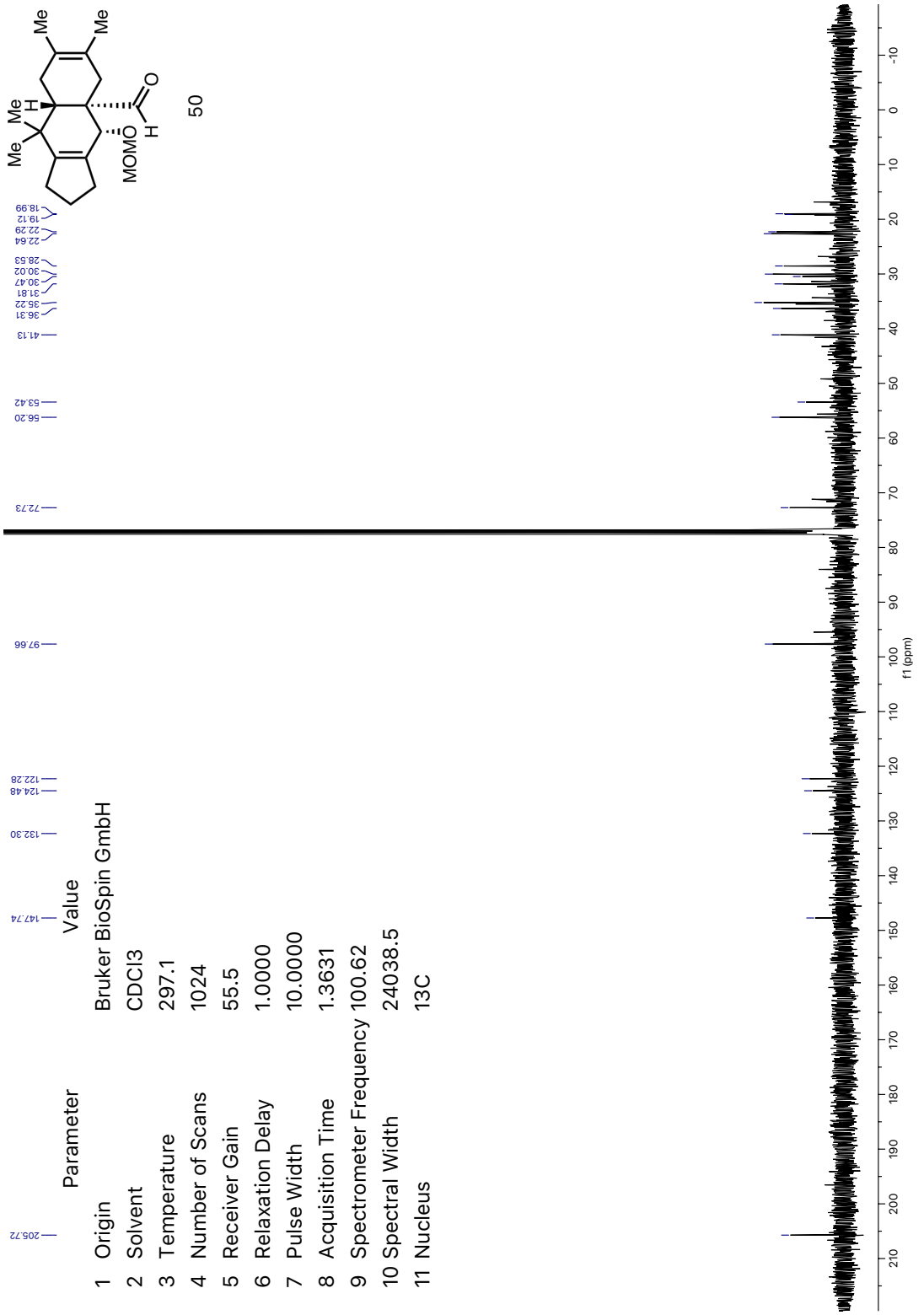

f1 (ppm)
f2 (ppm)
Me
Me
Me
MOMO
O
47

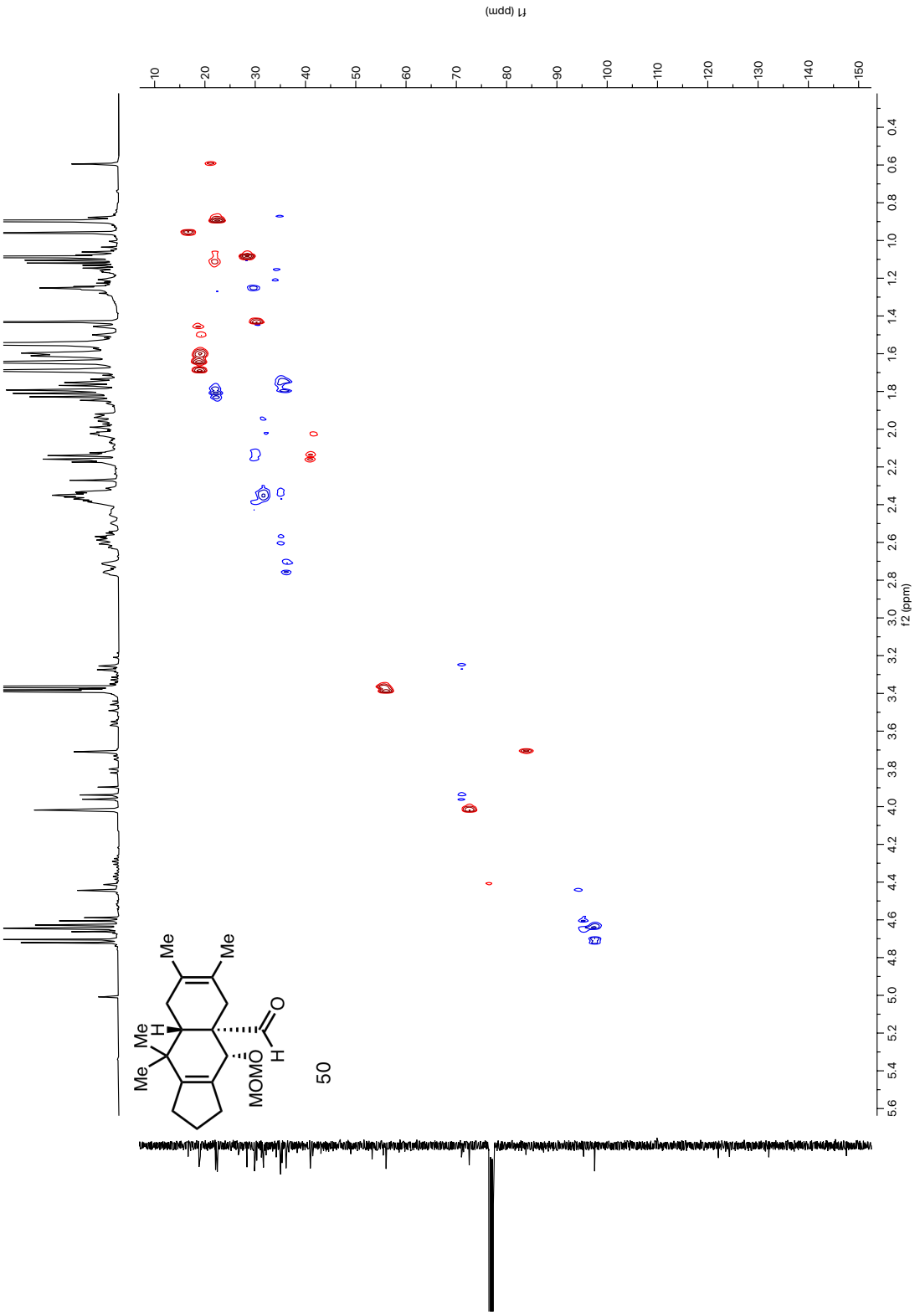

f1 (ppm)
f2 (ppm)
Me
Me
Me
MOMO
O
47

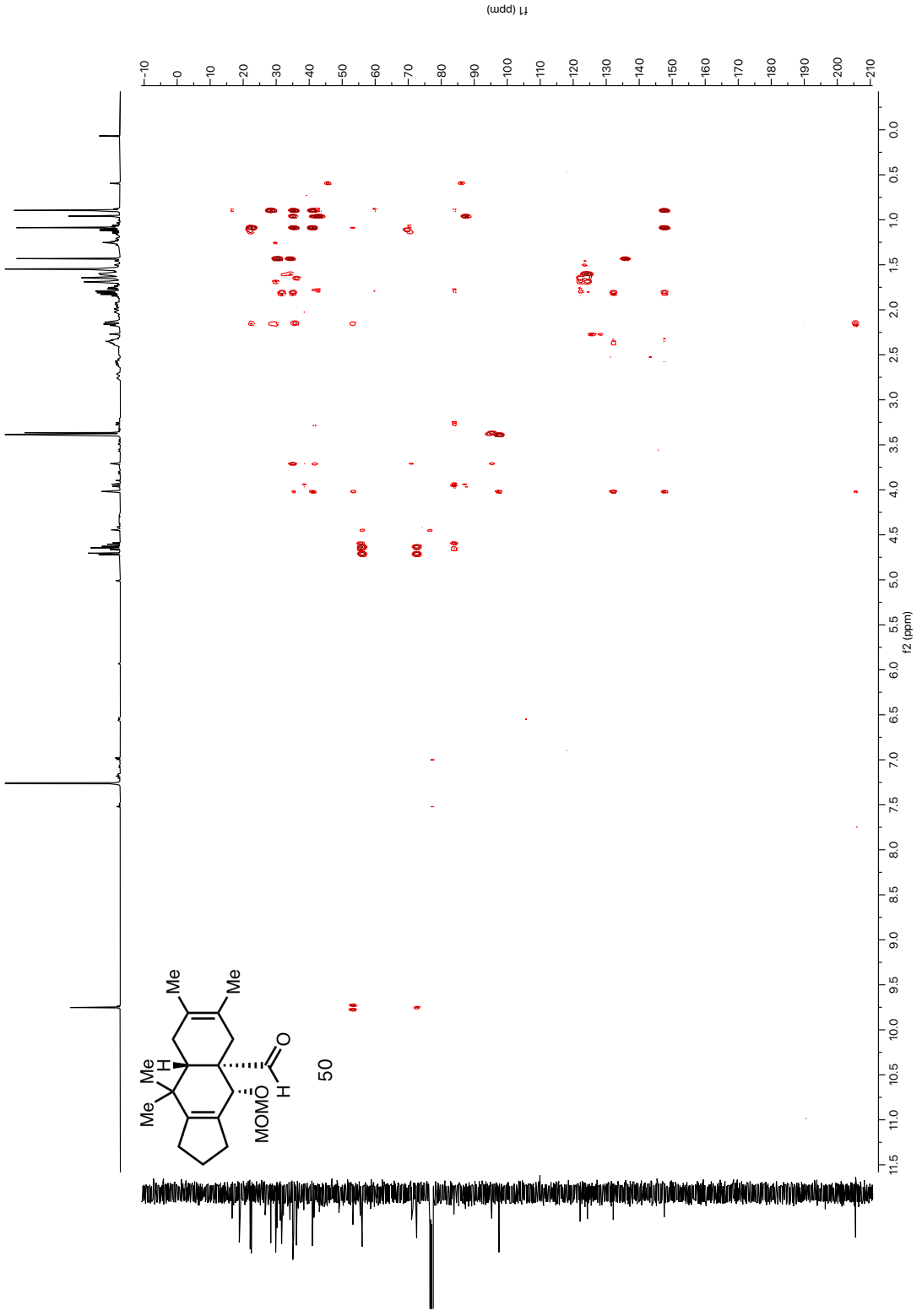

f1 (ppm)
f2 (ppm)
Me
Me
Me
MOMO
O
47

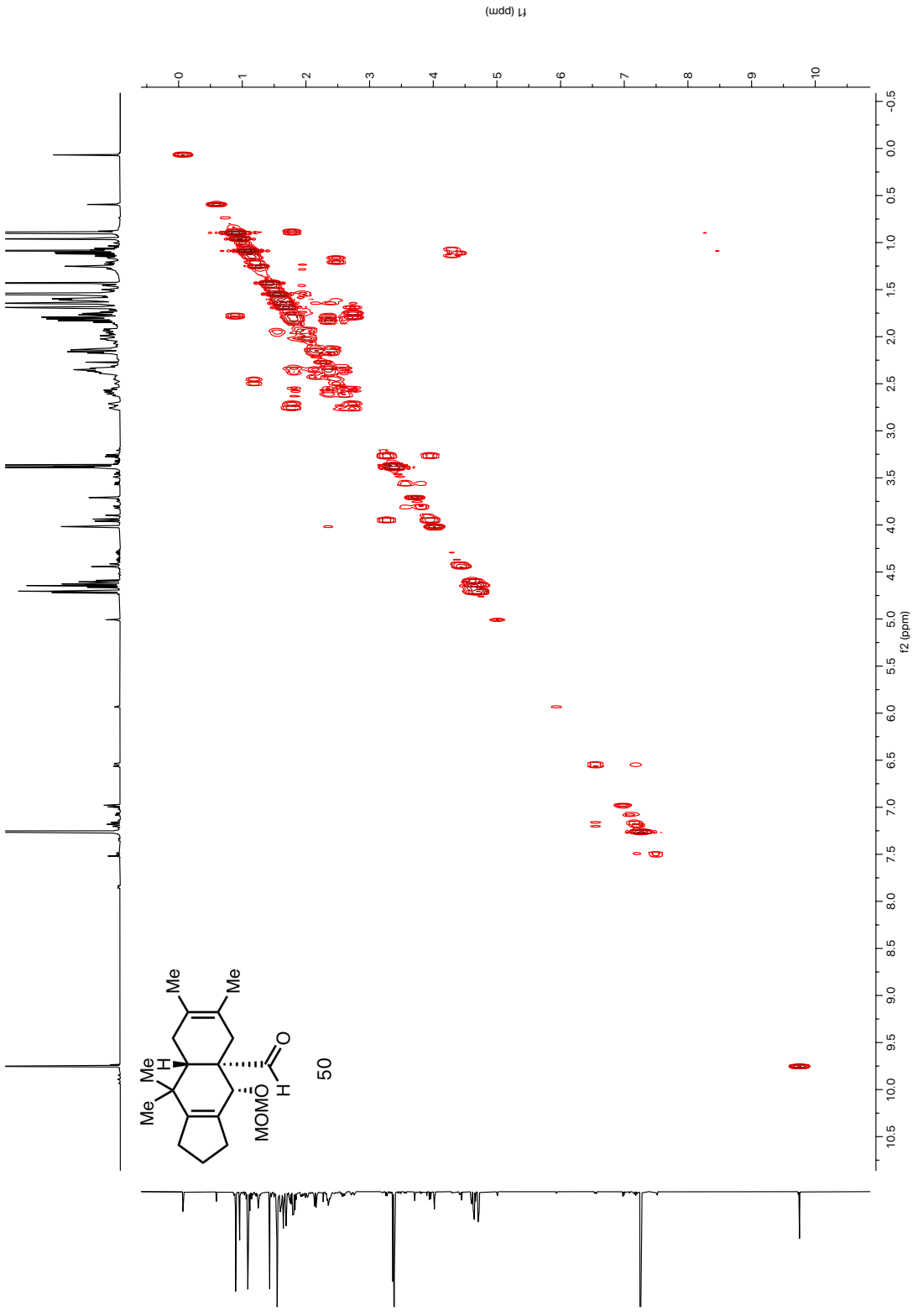

Me
Me
Me
H
MOMO
O
H
50
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Solvent CDCl3
3 Temperature 297.1
4 Number of Scans 128
5 Receiver Gain 197.4
6 Relaxation Delay 1.0000
7 Pulse Width 12.5000
8 Acquisition Time 4.0894
9 Spectrometer Frequency 400.13
10 Spectral Width 8012.8
11 Nucleus 1H
0.89
3.22
3.09
2.99
3.05
3.28
2.12
4.09
1.11
1.03
2.80
1.15
0.93
1.00
0.94
f1 (ppm)

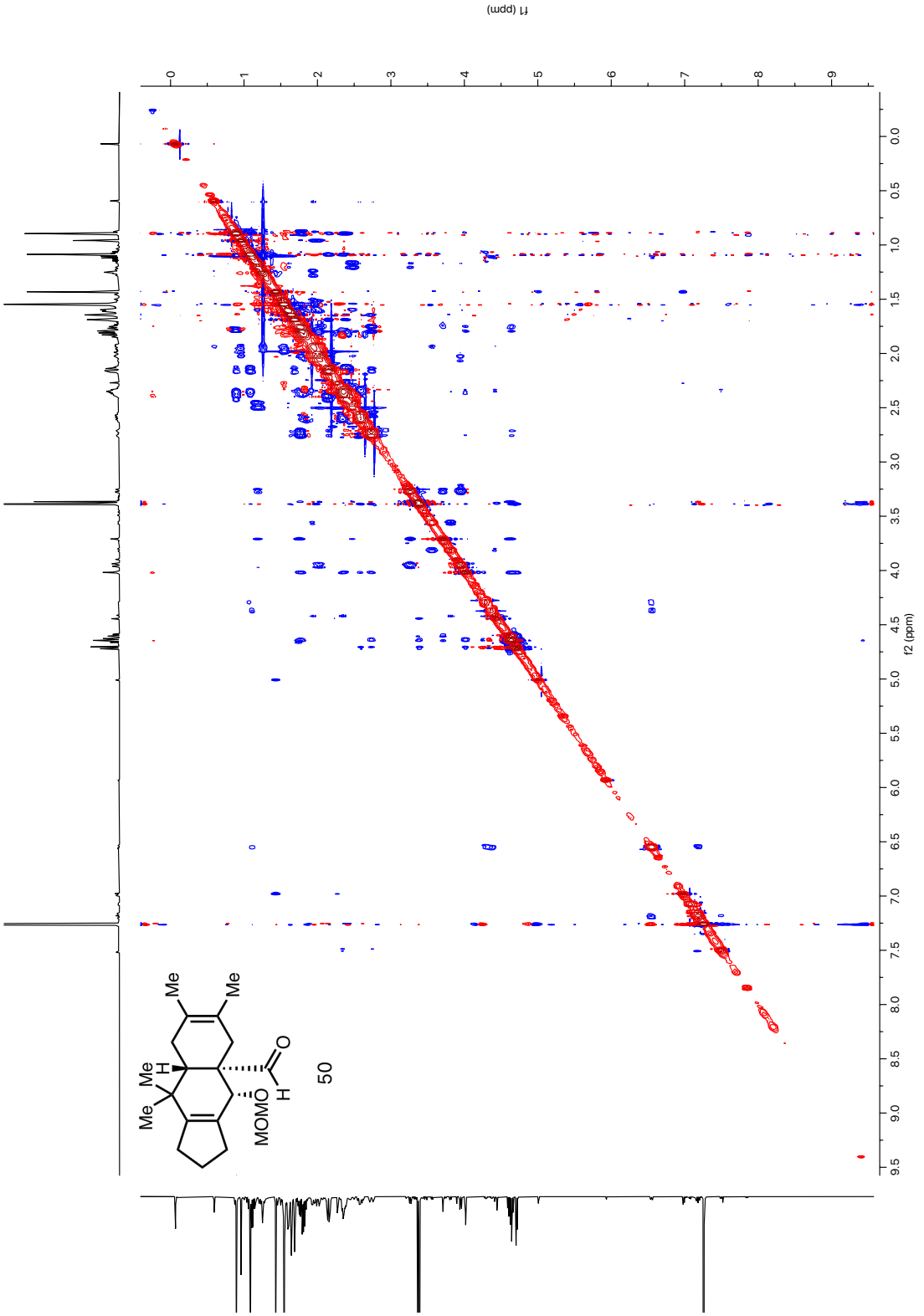

Me
Me
Me
H
MOMO
O
H
50
NOTE: This spectra has been processed to remove impurities for clarification of the structural assignment. Original data is shown above.
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Solvent CDCl3
3 Temperature 297.1
4 Number of Scans 128
5 Receiver Gain 197.4
6 Relaxation Delay 1.0000
7 Pulse Width 12.5000
8 Acquisition Time 4.0894
9 Spectrometer Frequency 400.13
10 Spectral Width 8012.8
11 Nucleus 1H
1.00
1.10
1.29
0.98
3.22
1.08
1.33
4.16
2.31
3.74
3.26
3.32
3.87
3.82
f1 (ppm)

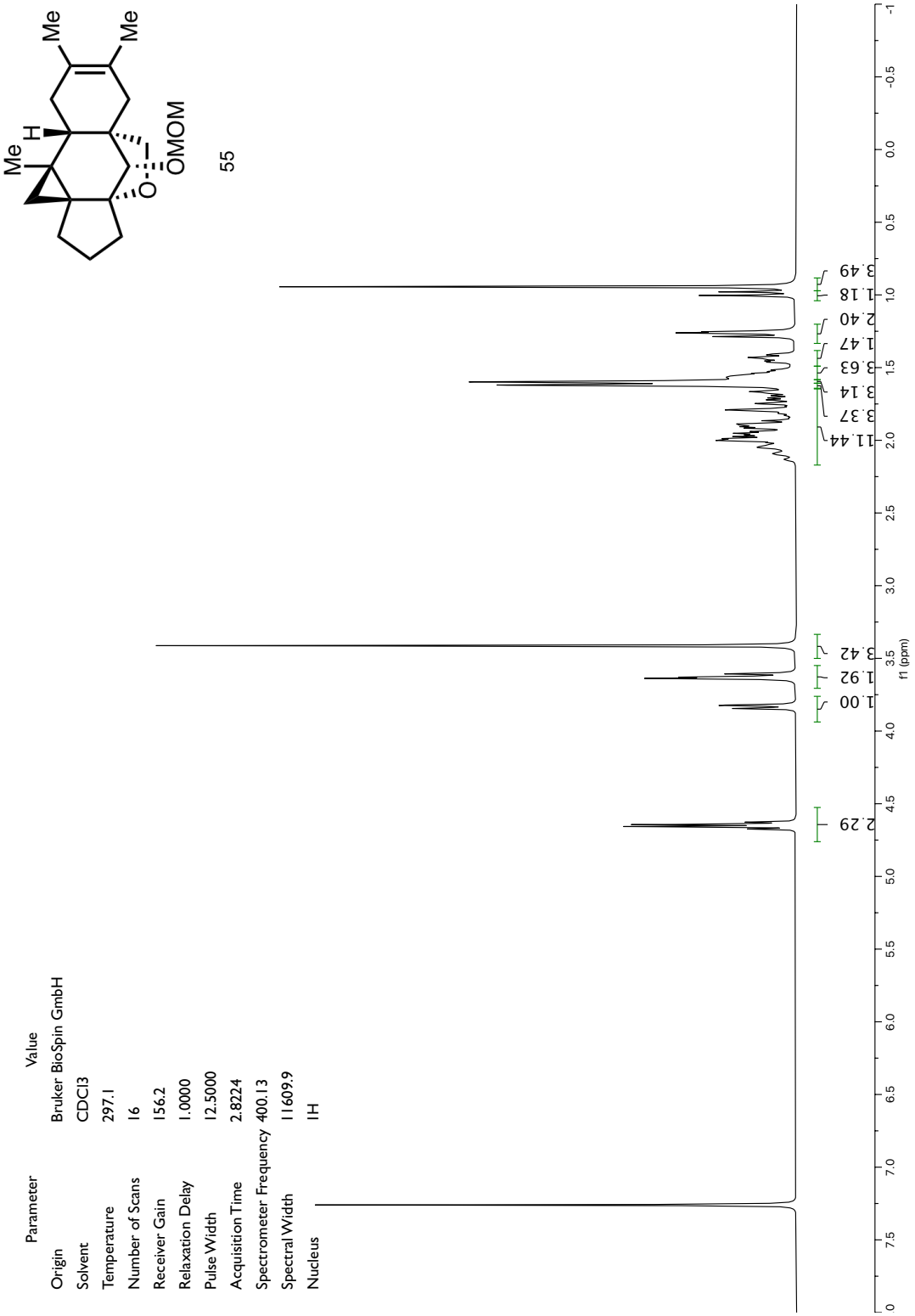

Me
Me
Me
H
Me
MOMO
O
H
50
18.99
19.12
22.29
22.64
28.53
30.02
30.47
31.81
35.22
36.31
41.13
53.42
56.20
72.73
97.66
122.28
124.48
132.30
147.74
205.72
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Solvent CDCl3
3 Temperature 297.1
4 Number of Scans 1024
5 Receiver Gain 55.5
6 Relaxation Delay 1.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.3631
9 Spectrometer Frequency 100.62
10 Spectral Width 24038.5
11 Nucleus 13C
f1 (ppm)

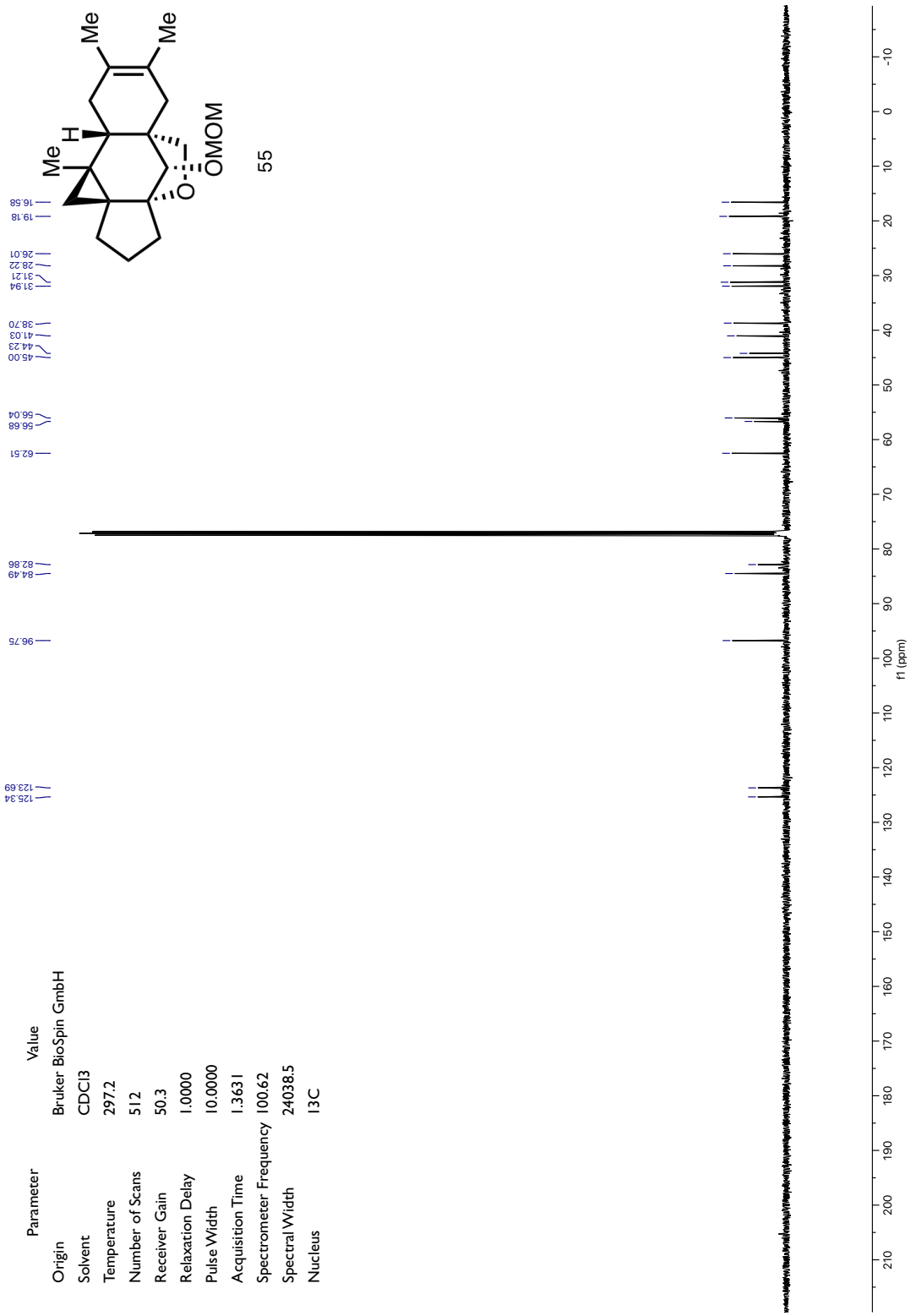

f1 (ppm)
f2 (ppm)
Me
Me
Me
H
Me
MOMO
O
H
50


f1 (ppm)
f2 (ppm)
Me
Me
Me
Me
H
MOMO
O
H
50

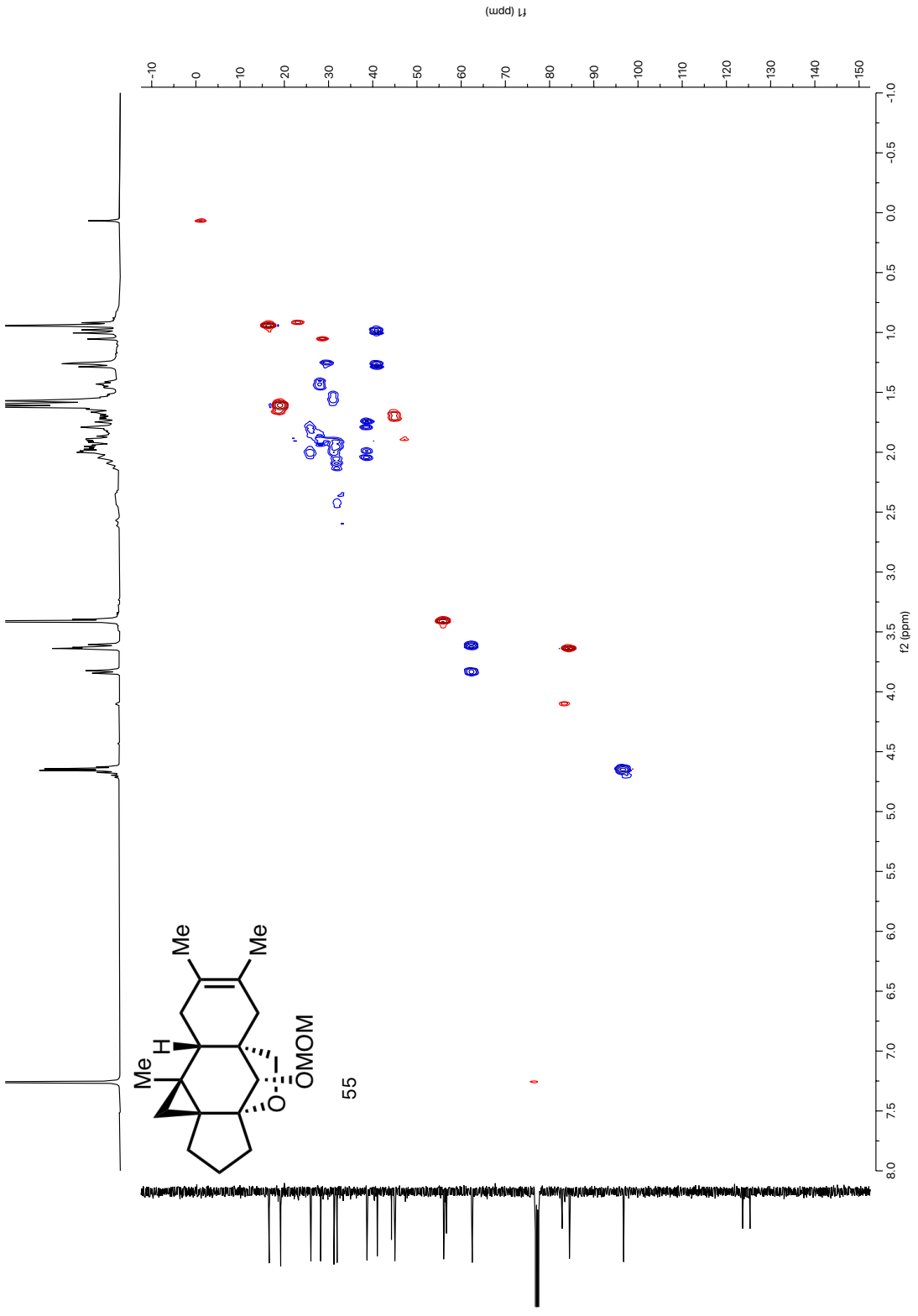

f1 (ppm)
f2 (ppm)
Me
Me
Me
H
MOMO
O
H
50

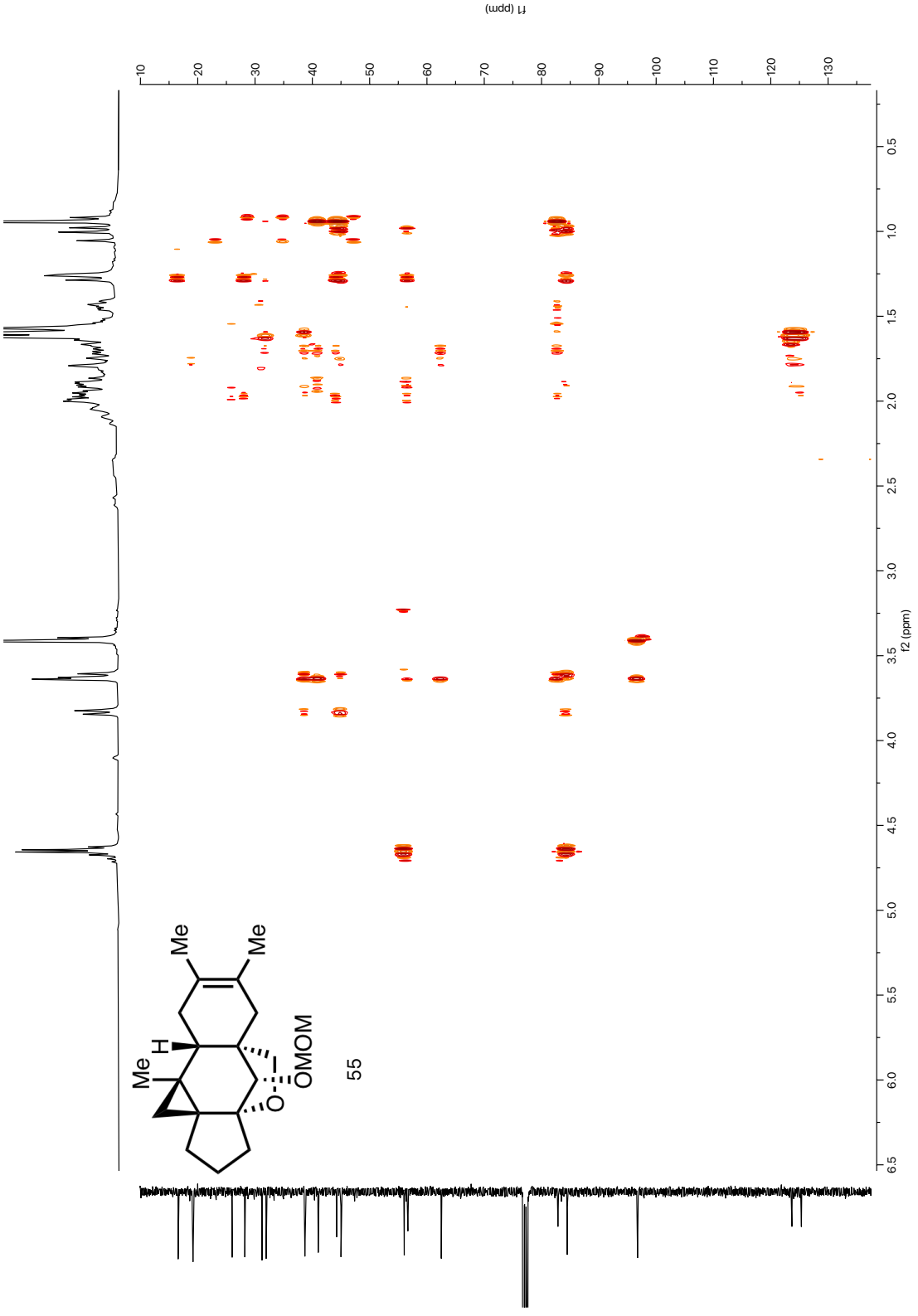

f1 (ppm)
f2 (ppm)
Me
Me
Me
H
MOMO
O
H
50

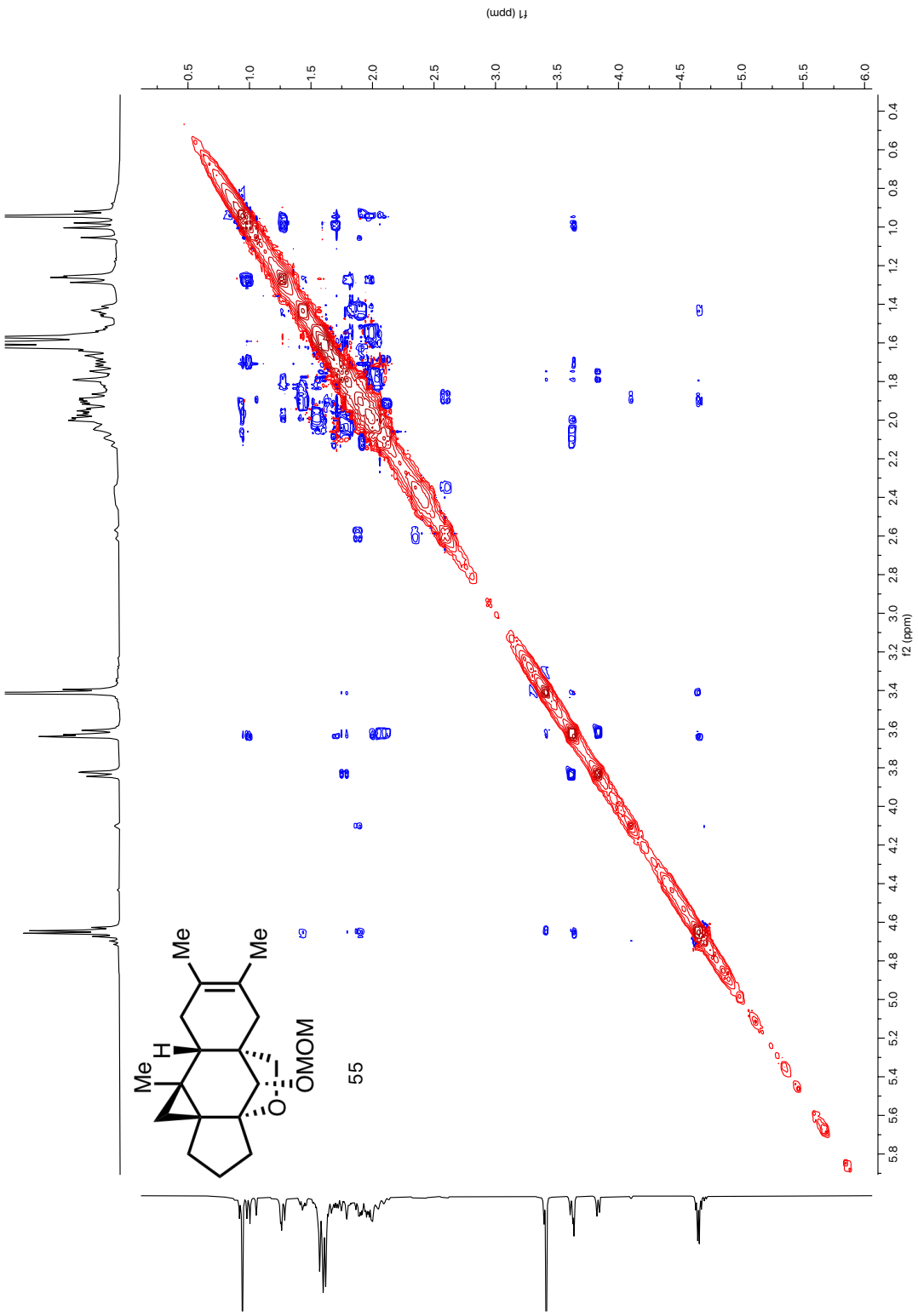

Me
Me
H
Me
O
OMOM
55
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
156.2
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
2.8224
Spectrometer Frequency
400.13
Spectral Width
11609.9
Nucleus
1H
2.29
1.00
1.92
3.42
11.44
3.37
3.14
3.63
1.47
2.40
1.18
3.49
f1 (ppm)

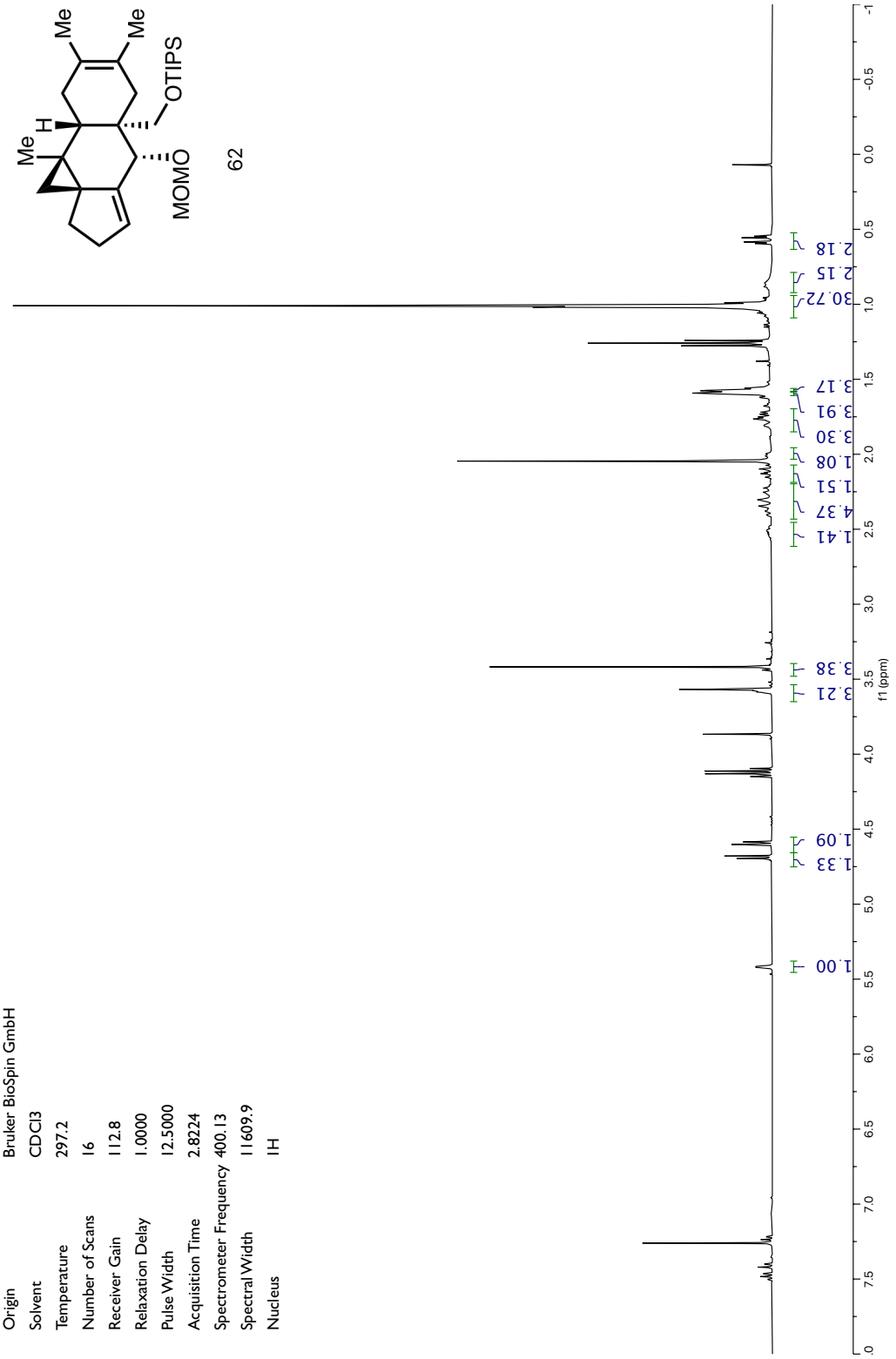


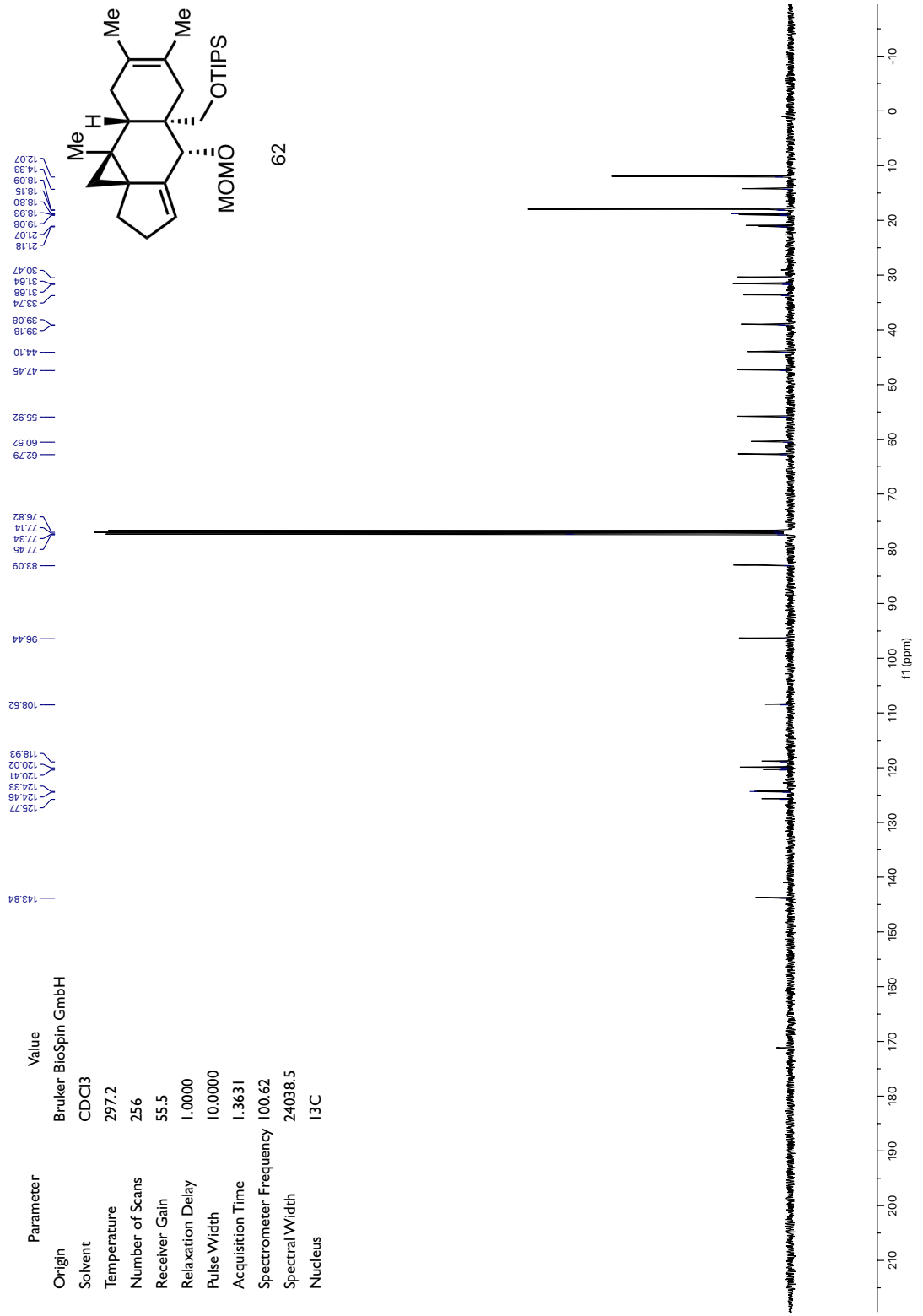
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	50.3
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

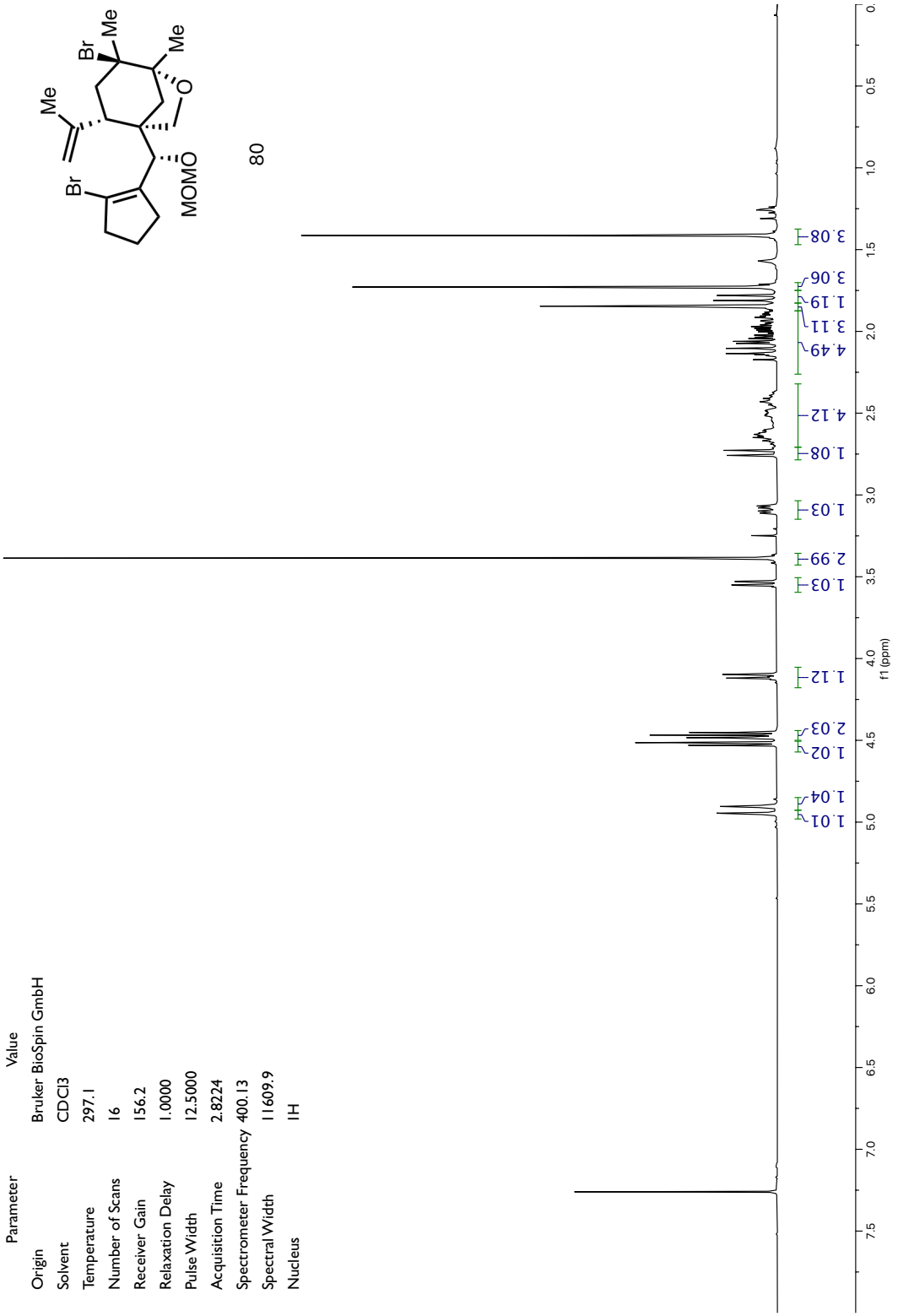

f1 (ppm)
f2 (ppm)
Me
Me
H
Me
OMOM
55

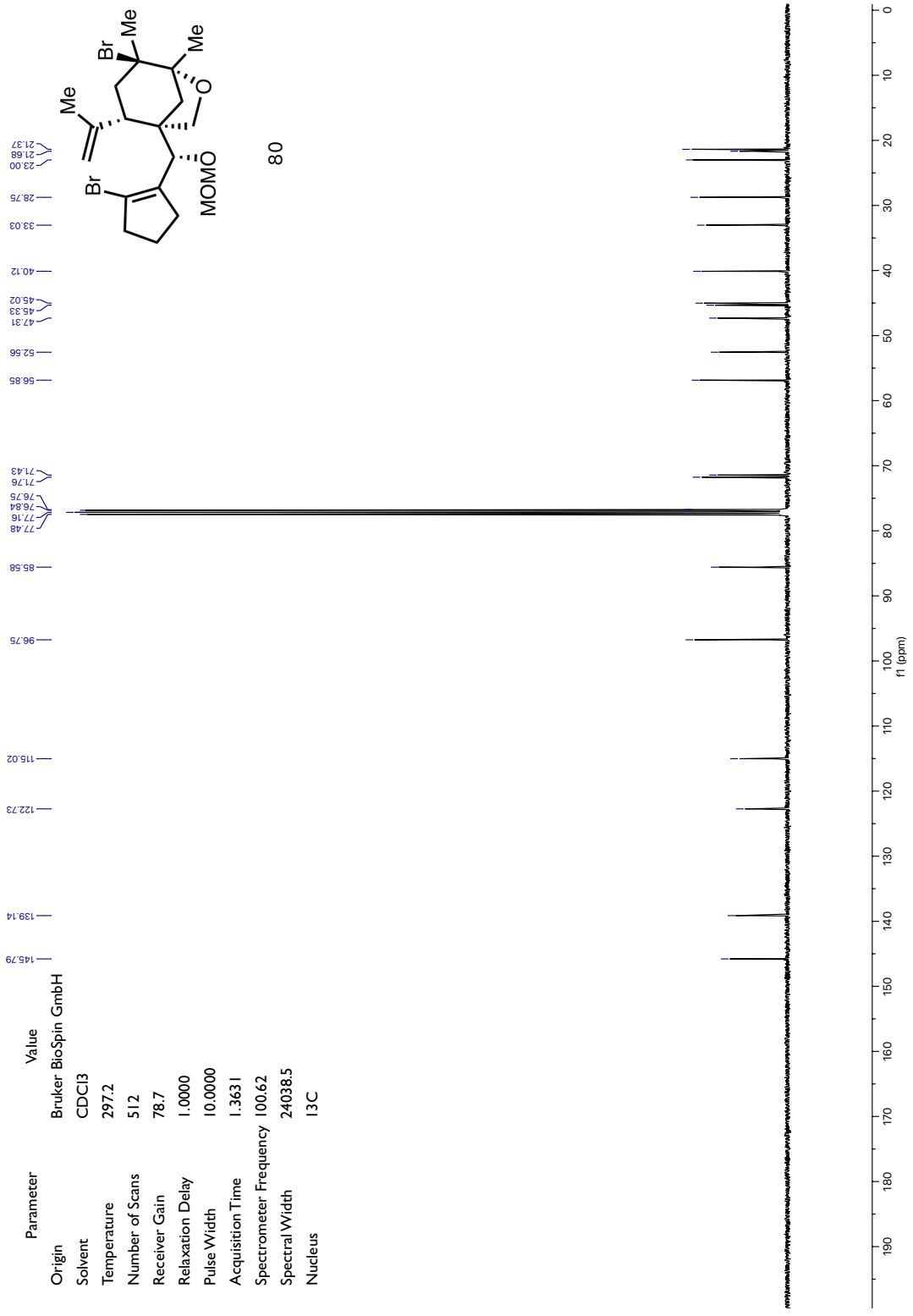

f1 (ppm)
f2 (ppm)
Me
Me
H
Me
OMOM
O
55


f1 (ppm)
f2 (ppm)
Me
Me
H
Me
OMOM
O
55

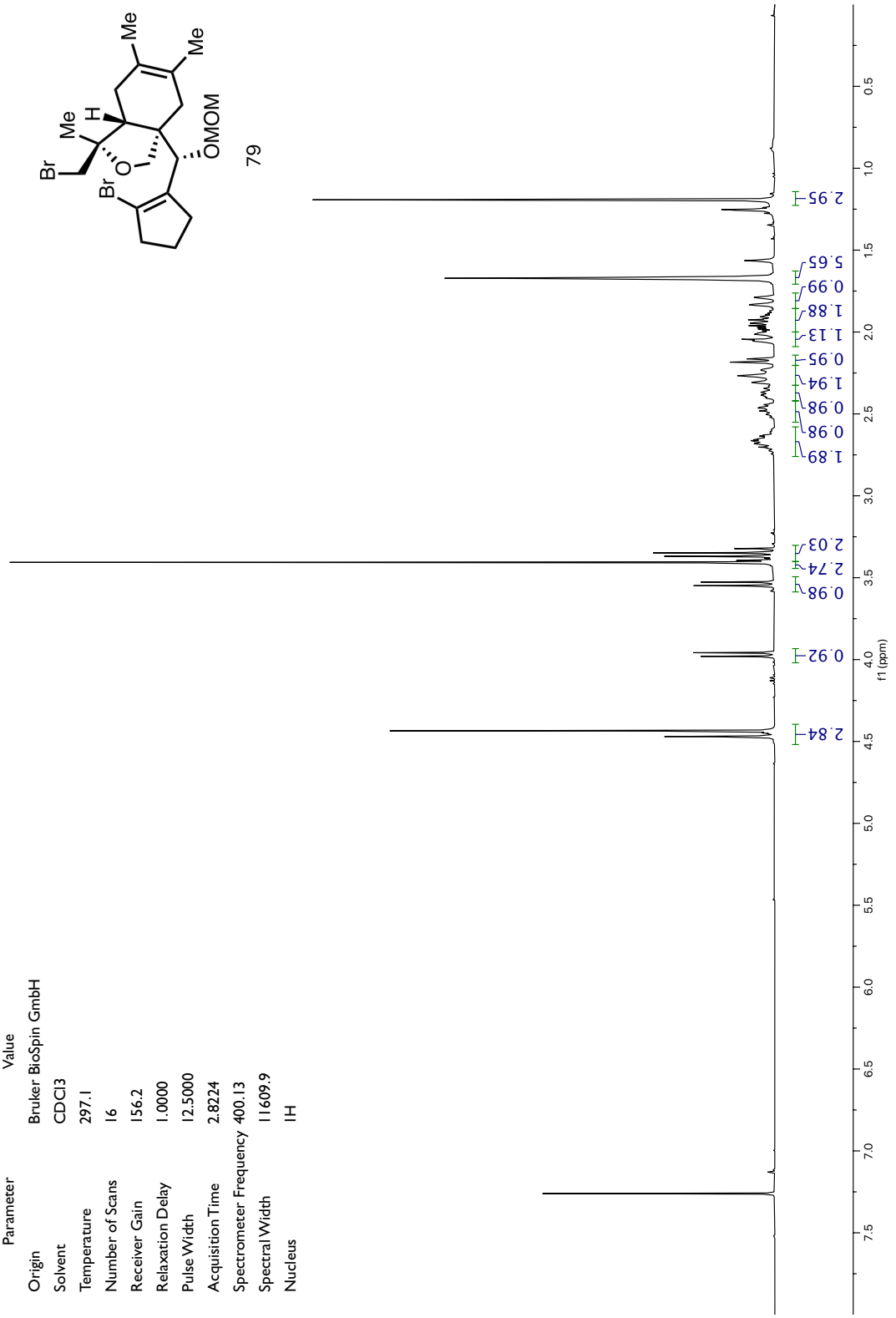

Me
Me
H
Me
OTIPS
MOMO
62
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
1.00
1.33
1.09
3.21
3.38
1.41
4.37
1.51
1.08
3.30
3.91
3.17
30.72
2.15
2.18
f1 (ppm)

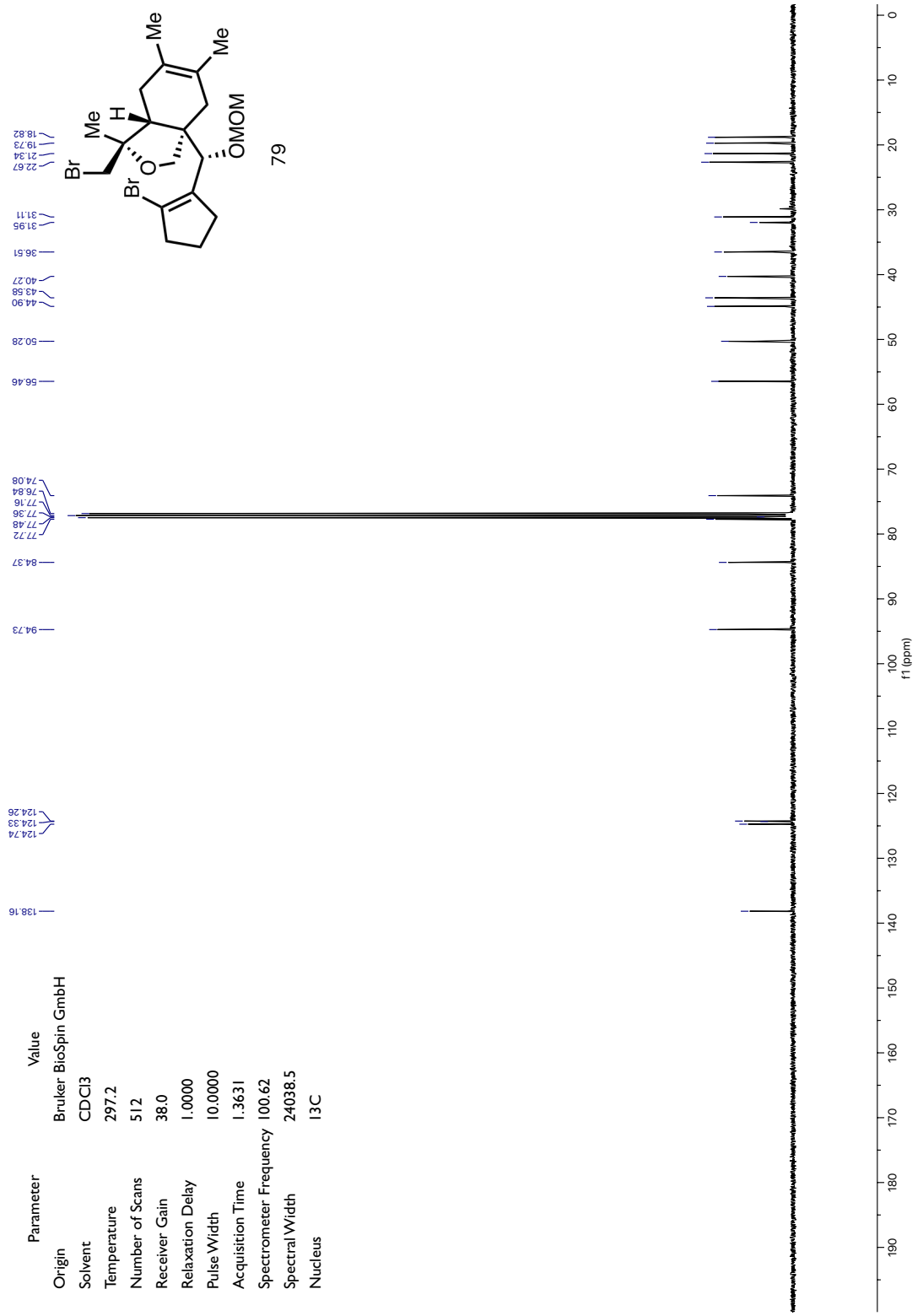

Me
Me
H
Me
OTIPS
MOMO
62
12.07
14.33
18.09
18.15
18.80
18.93
19.08
21.07
21.18
30.47
31.64
31.68
33.74
39.08
39.18
44.10
47.45
55.92
60.52
62.79
76.82
77.14
77.34
77.45
83.09
96.44
108.52
118.93
120.02
120.41
124.33
124.46
125.77
143.84
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
256
Receiver Gain
55.5
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)

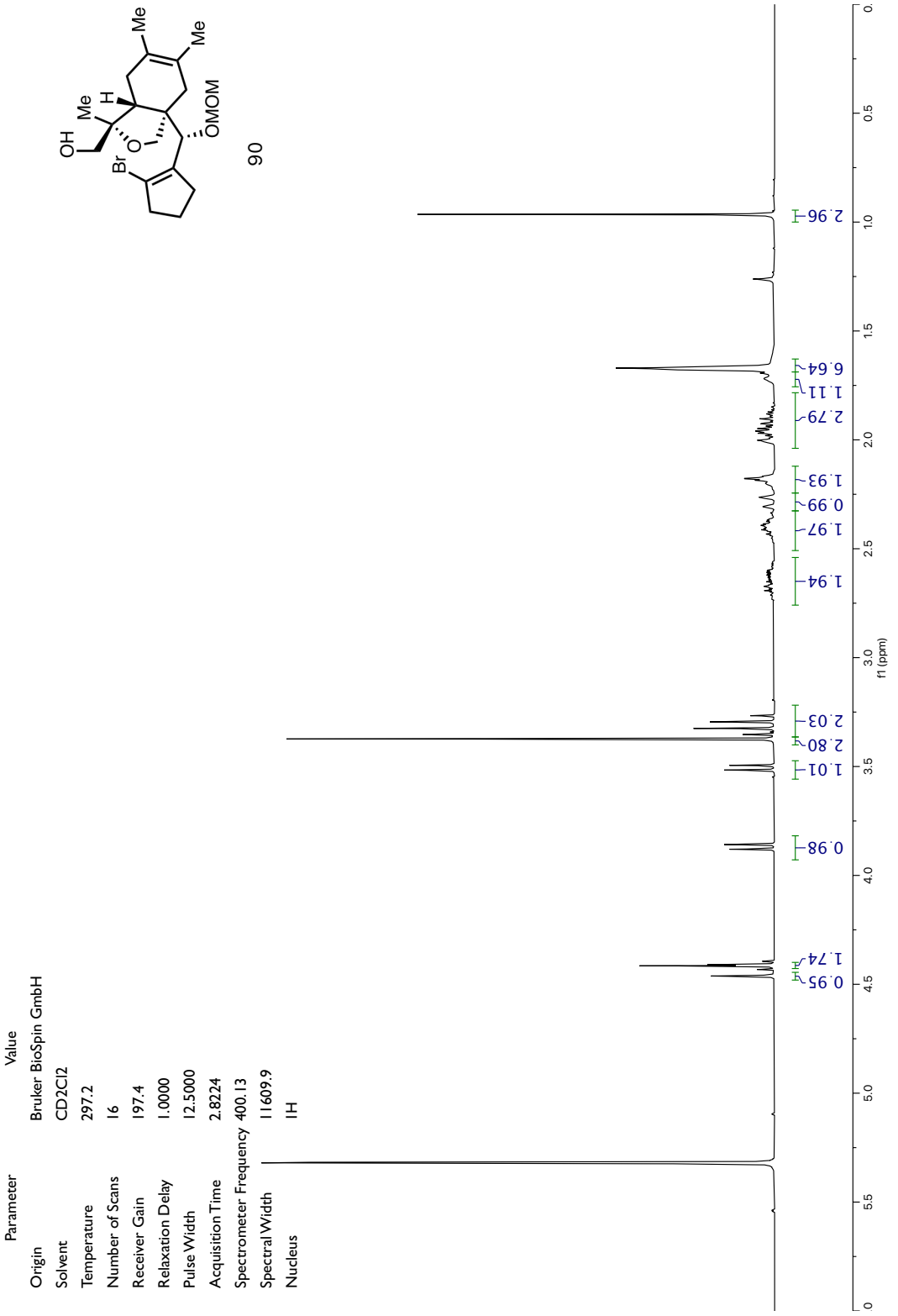

Br
Me
Me
O
Me
Br
MOMO
80
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
3.08
3.06
1.19
3.11
4.49
4.12
1.08
1.03
2.99
1.03
1.12
2.03
1.02
1.04
1.01
f1 (ppm)

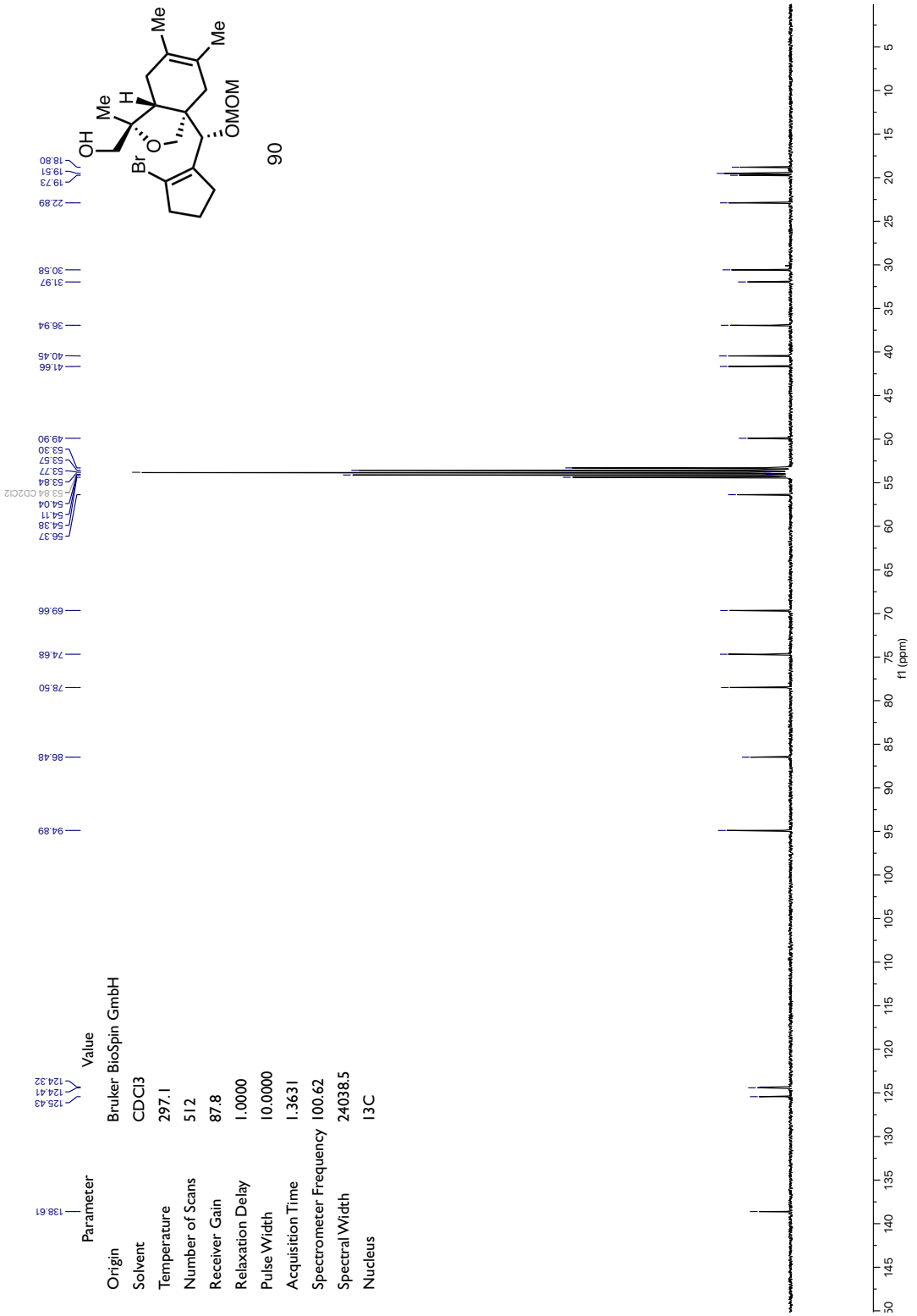


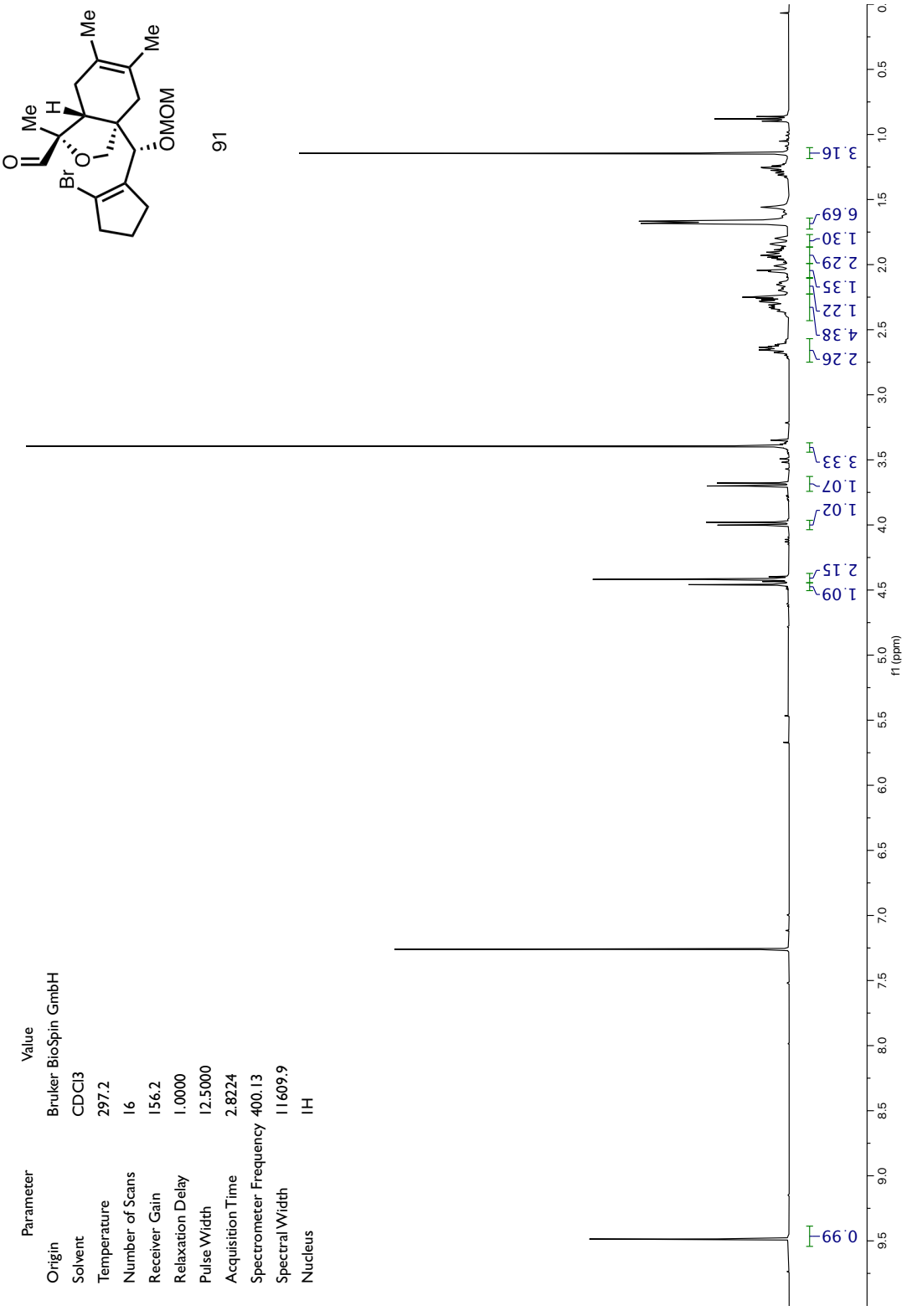
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	78.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

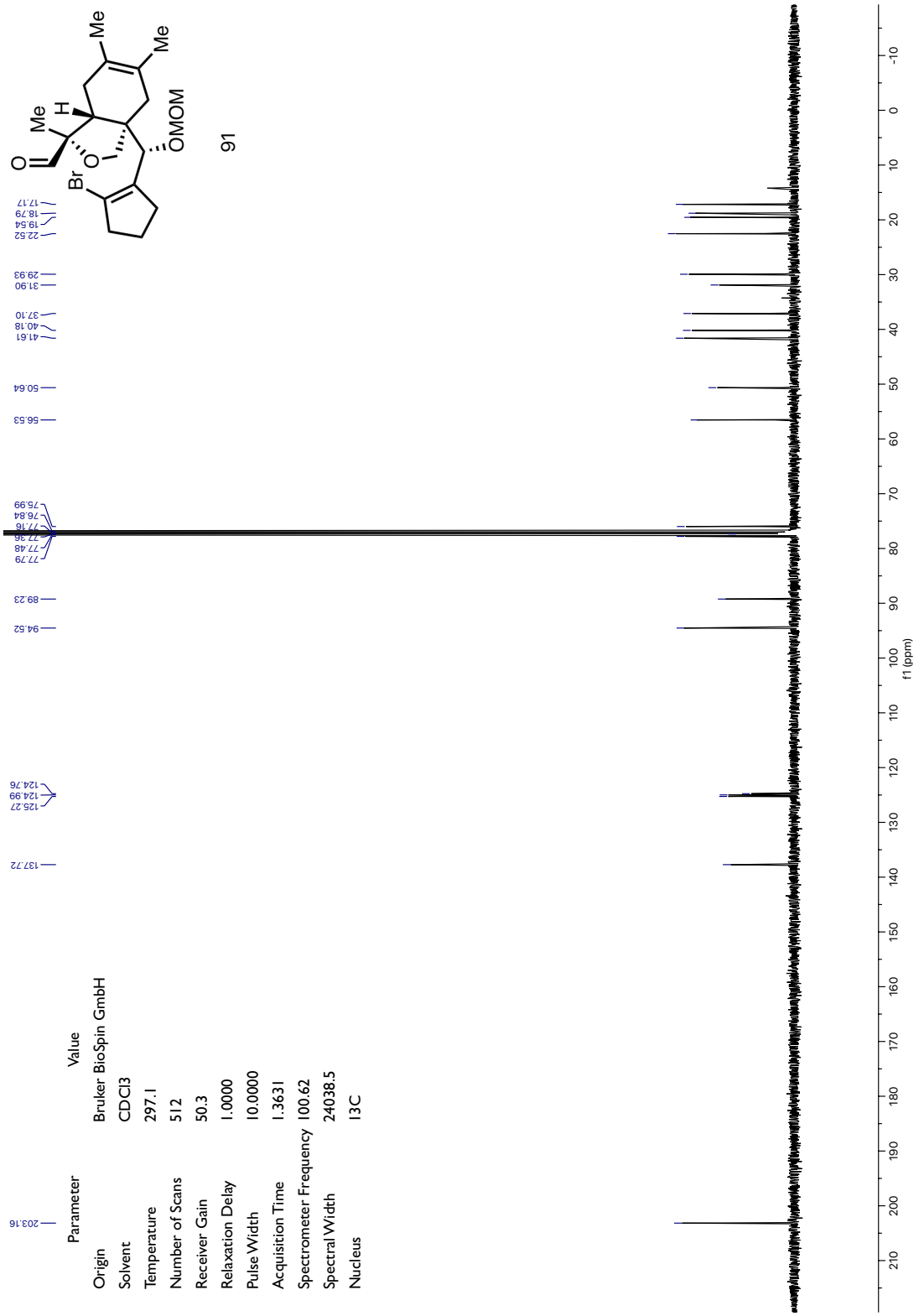

Me
Me
H
Me
Br
Br
O
OMOM
79
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
156.2
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
2.8224
Spectrometer Frequency
400.13
Spectral Width
11609.9
Nucleus
1H
2.95
5.65
0.99
1.88
1.13
0.95
1.94
0.98
0.98
1.89
2.03
2.74
0.98
0.92
2.84
f1 (ppm)

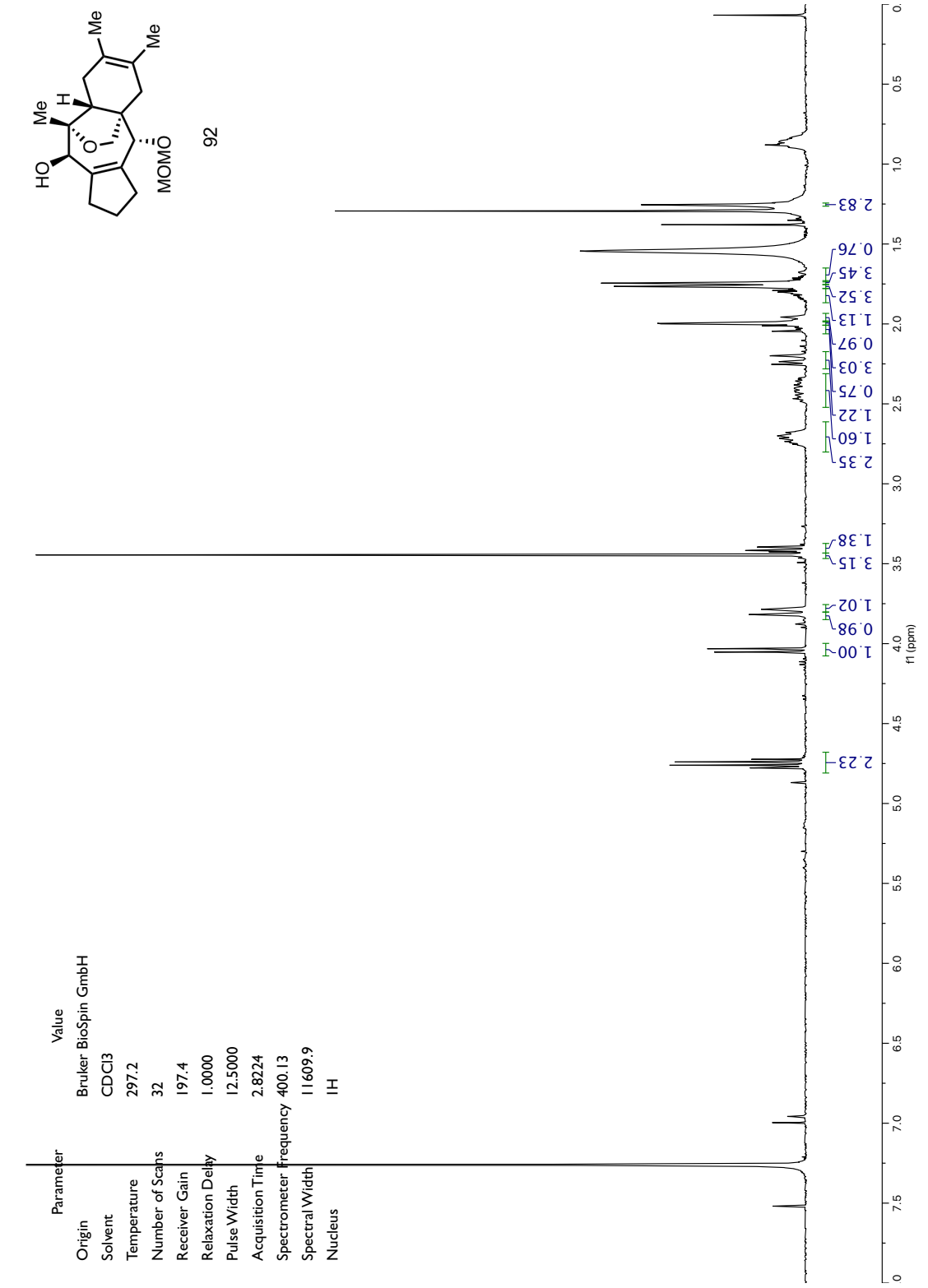

Me
Me
H
Me
Br
O
Br
OMOM
79
18.82
19.73
21.34
22.67
31.11
31.95
36.51
40.27
43.58
44.90
50.28
56.46
74.08
76.84
77.16
77.36
77.48
77.72
84.37
94.73
124.26
124.33
124.74
138.16
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 38.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

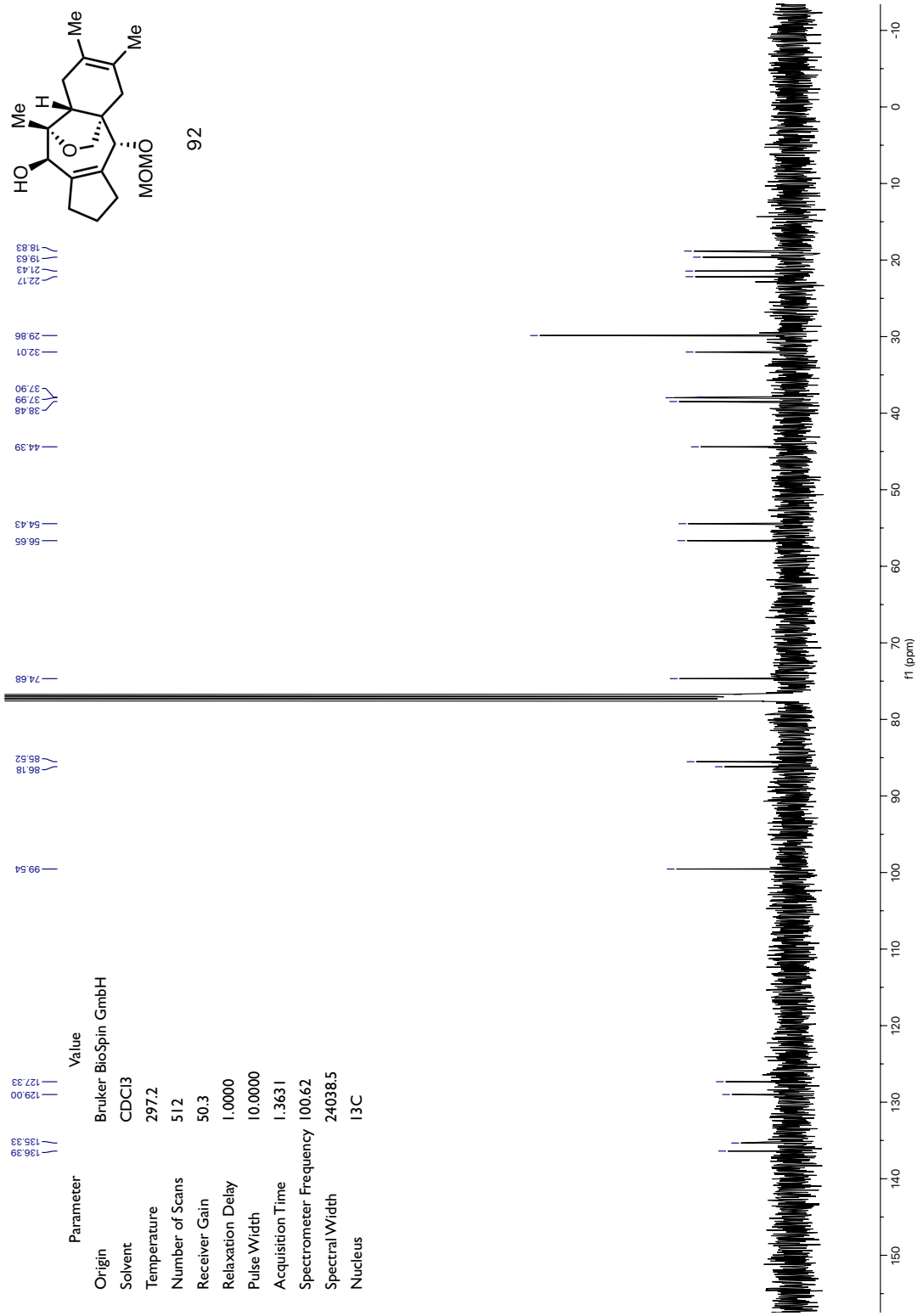

Me
Me
H
Me
OH
Br
O
OMOM
90
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CD2Cl2
Temperature 297.2
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
2.96
6.64
1.11
2.79
1.93
0.99
1.97
1.94
2.03
2.80
1.01
0.98
1.74
0.95
f1 (ppm)

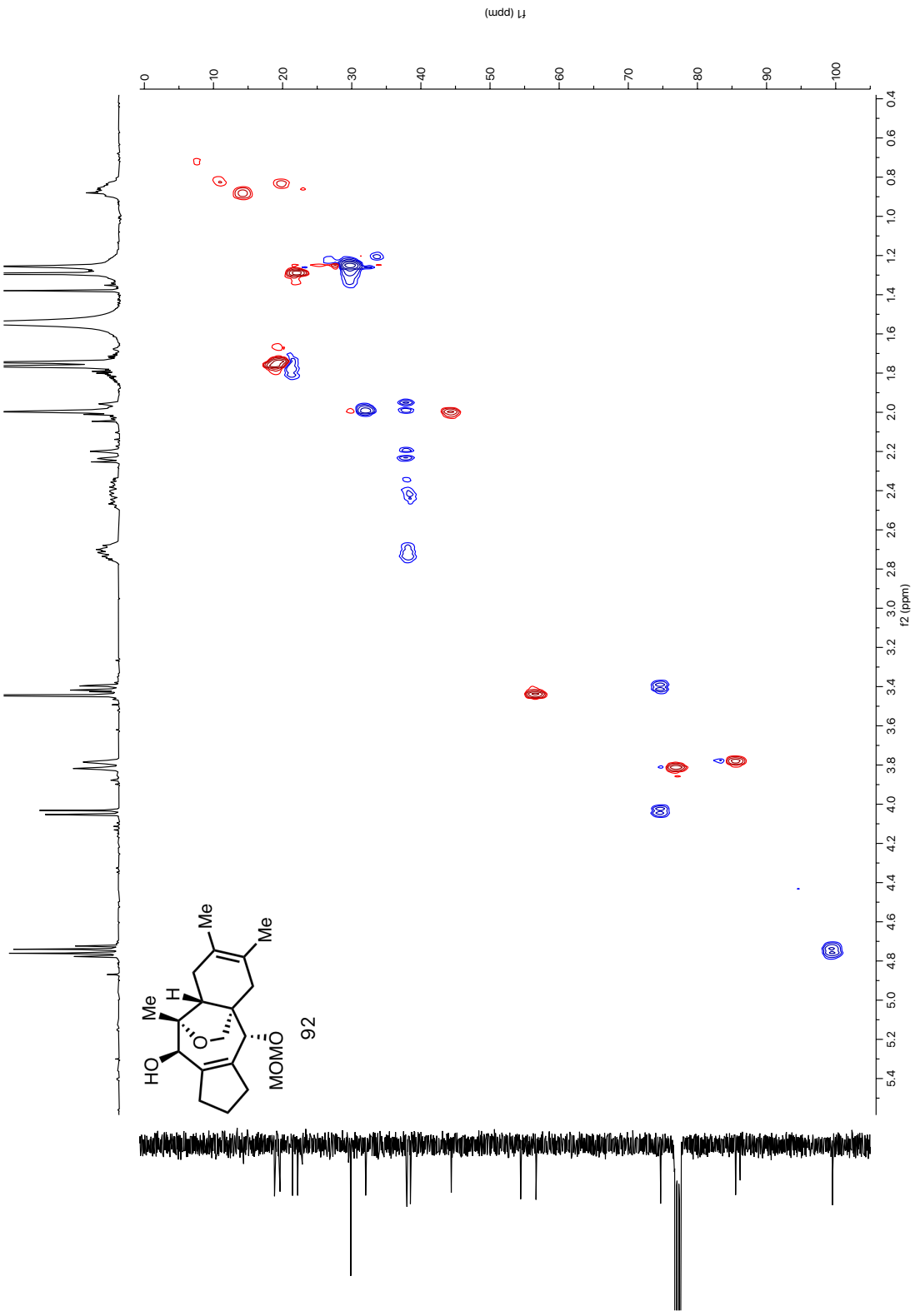

Me
Me
H
Me
OH
Br
O
OMOM
90
18.80
19.51
19.73
22.89
30.58
31.97
36.94
40.45
41.66
49.90
53.30
53.57
53.77
53.84
53.84 CD2Cl2
54.04
54.11
54.38
56.37
69.66
74.68
78.50
86.48
94.89
124.32
124.41
125.43
138.61
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

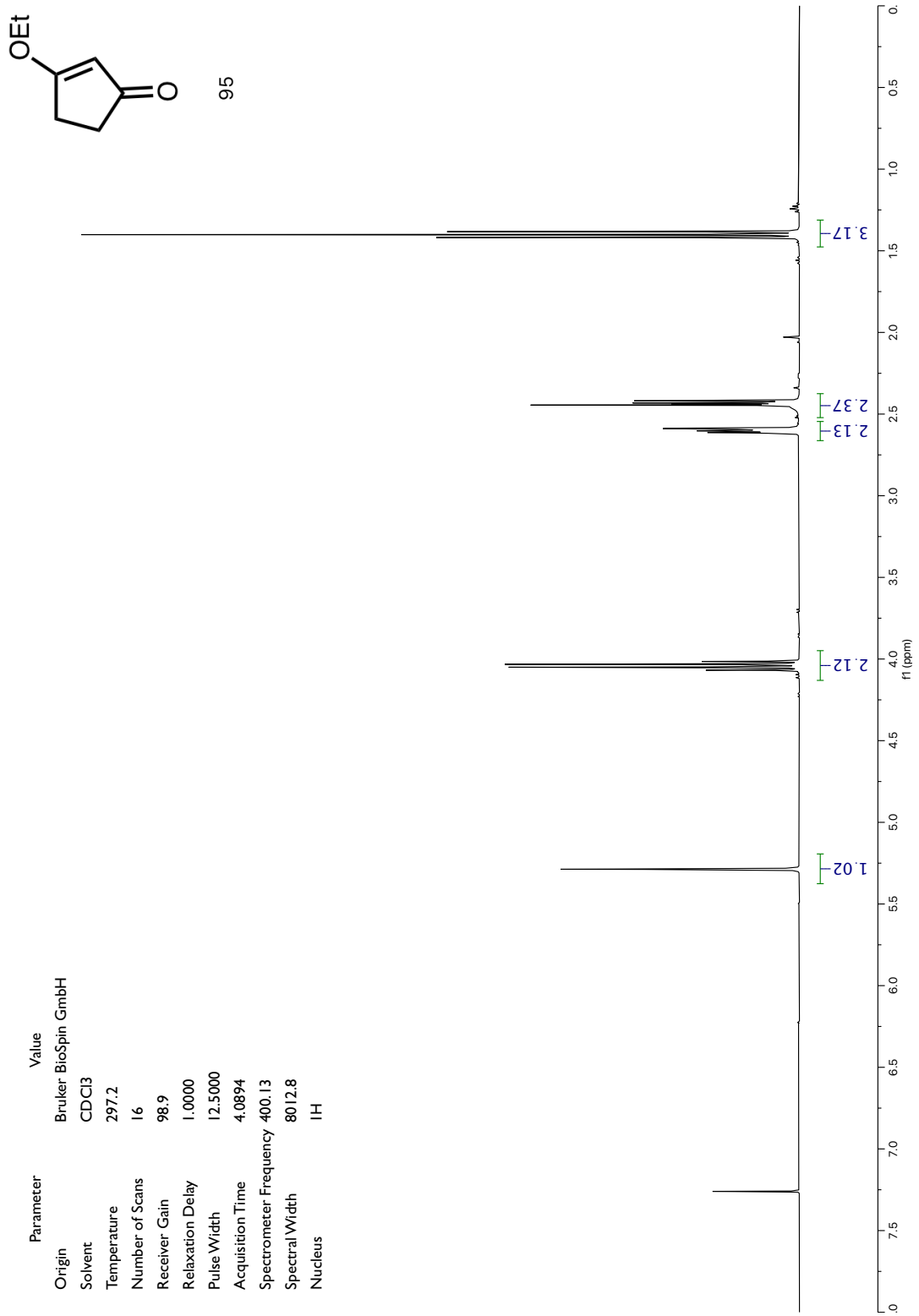

Me
Me
H
O
Me
O
Br
O
OMOM
91
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
0.99
1.09
2.15
1.02
1.07
3.33
2.26
4.38
1.22
1.35
2.29
1.30
6.69
3.16
f1 (ppm)

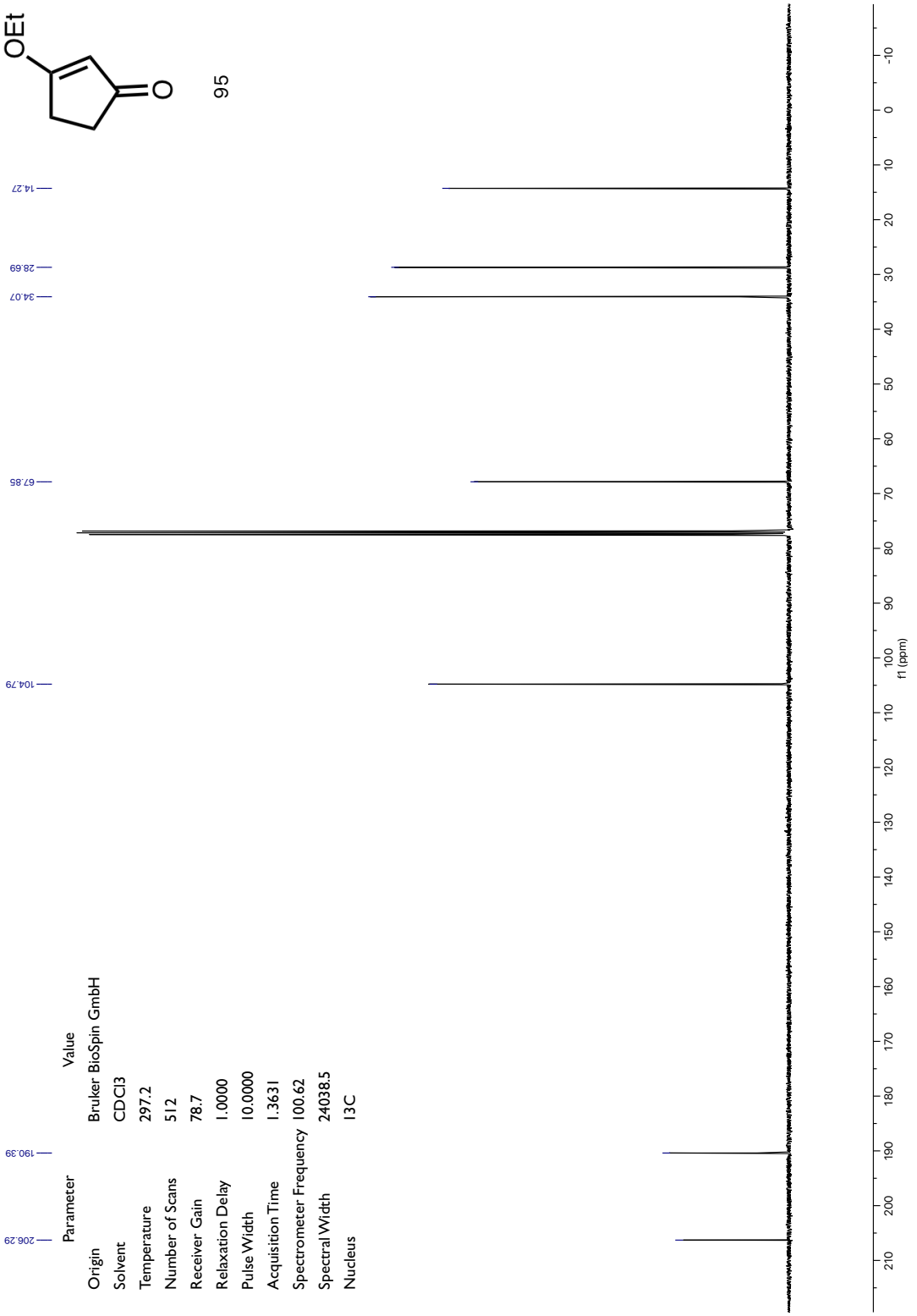

Me
Me
H
O
Me
OMOM
Br
O
91
17.17
18.79
19.54
22.52
29.93
31.90
37.10
40.18
41.61
50.64
56.53
75.99
76.84
77.16
77.36
77.48
77.79
89.23
94.52
124.76
124.99
125.27
137.72
203.16
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)


Me
Me
H
Me
HO
O
MOMO
92
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 32
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer frequency 400.13
Spectral Width 11609.9
Nucleus 1H
2.83
0.76
3.45
3.52
1.13
0.97
3.03
0.75
1.22
1.60
2.35
1.38
3.15
1.02
0.98
1.00
2.23
f1 (ppm)

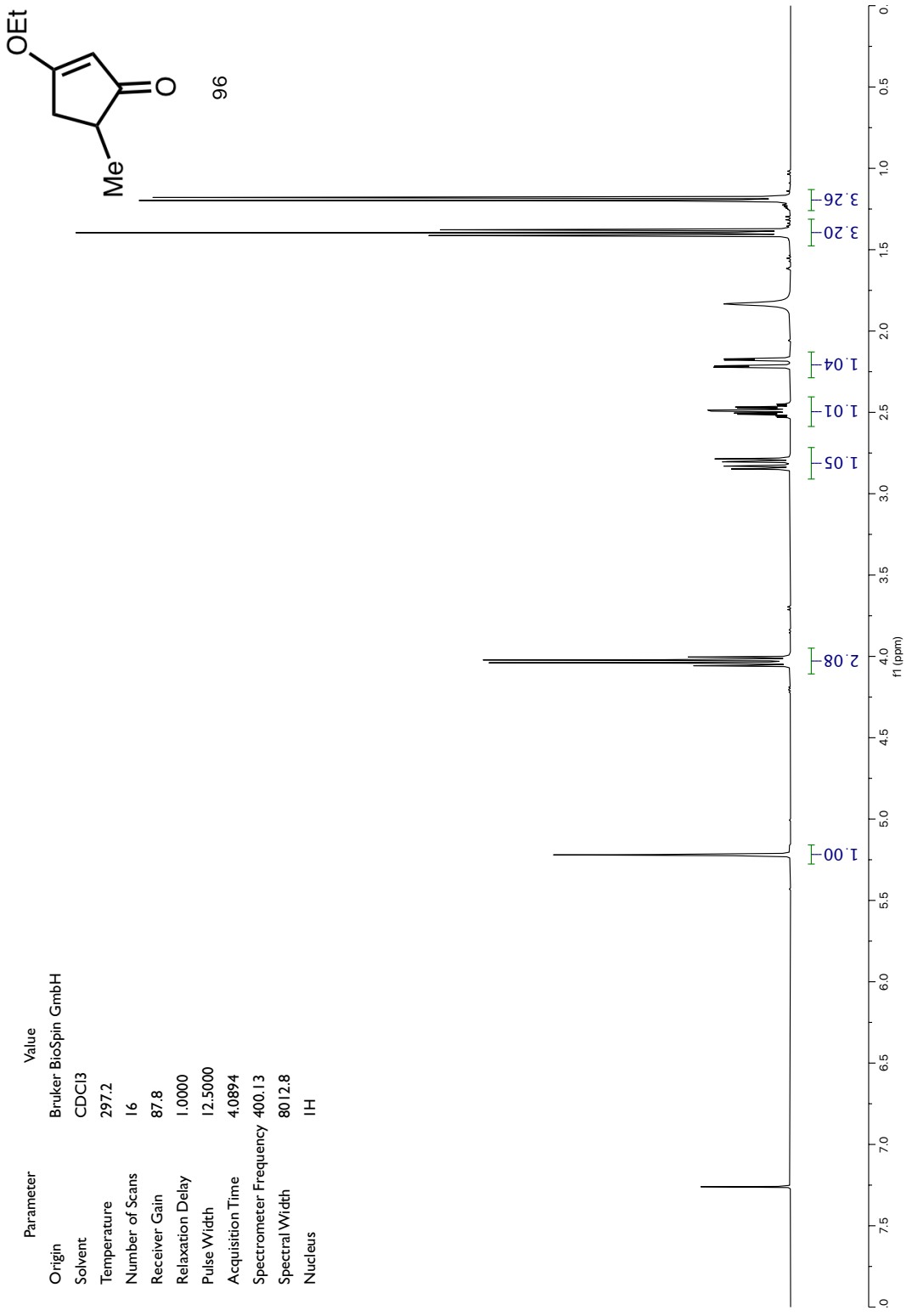

Me
Me
H
Me
HO
O
MOMO
92
18.83
19.63
21.43
22.17
29.86
32.01
37.90
37.99
38.48
44.39
54.43
56.65
74.68
85.18
85.52
99.54
127.33
129.00
135.33
136.39
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

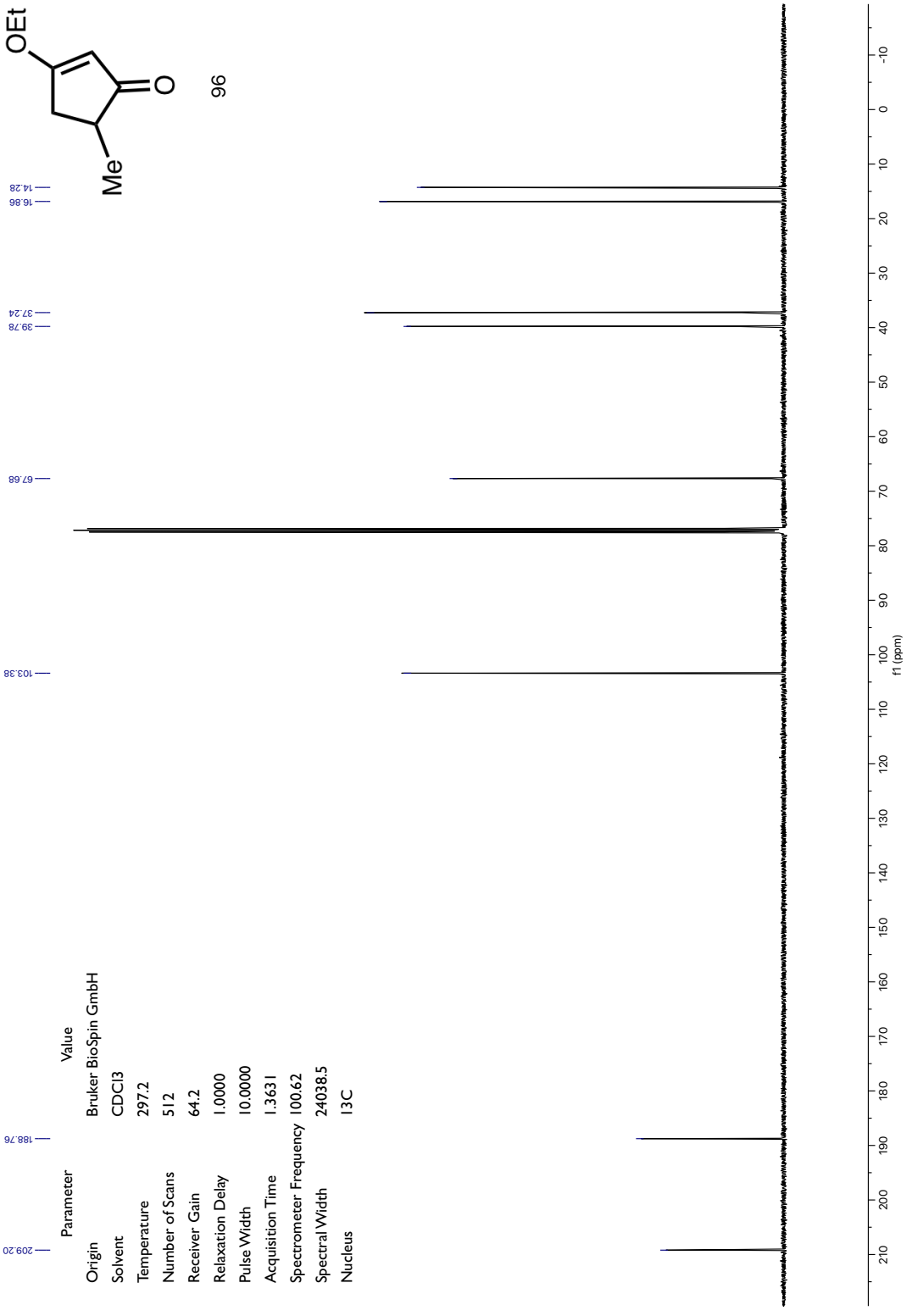

f1 (ppm)
f2 (ppm)
Me
Me
H
Me
HO
O
MOMO
92

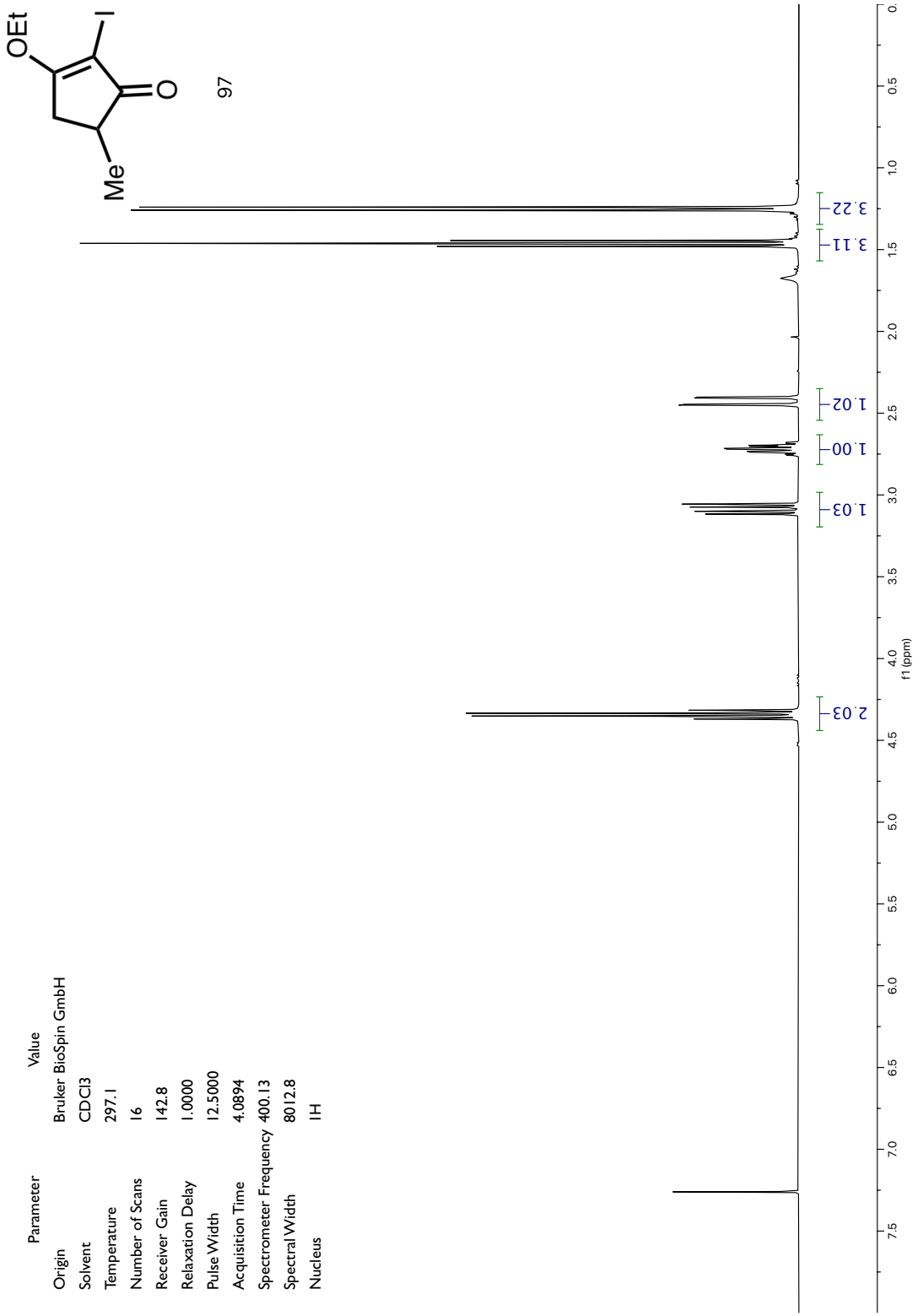

OEt
O
95
3.17
2.37
2.13
2.12
1.02
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H

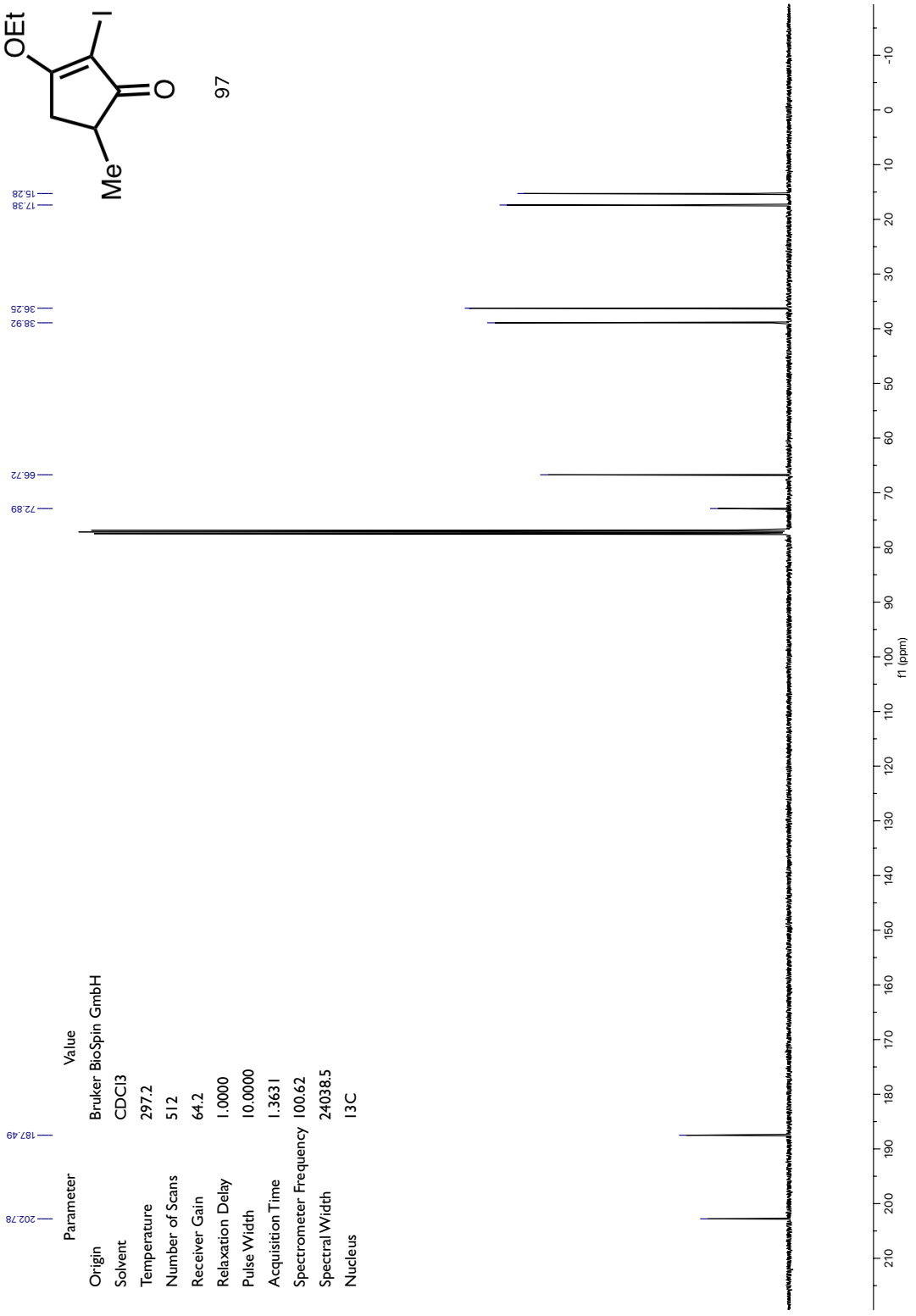


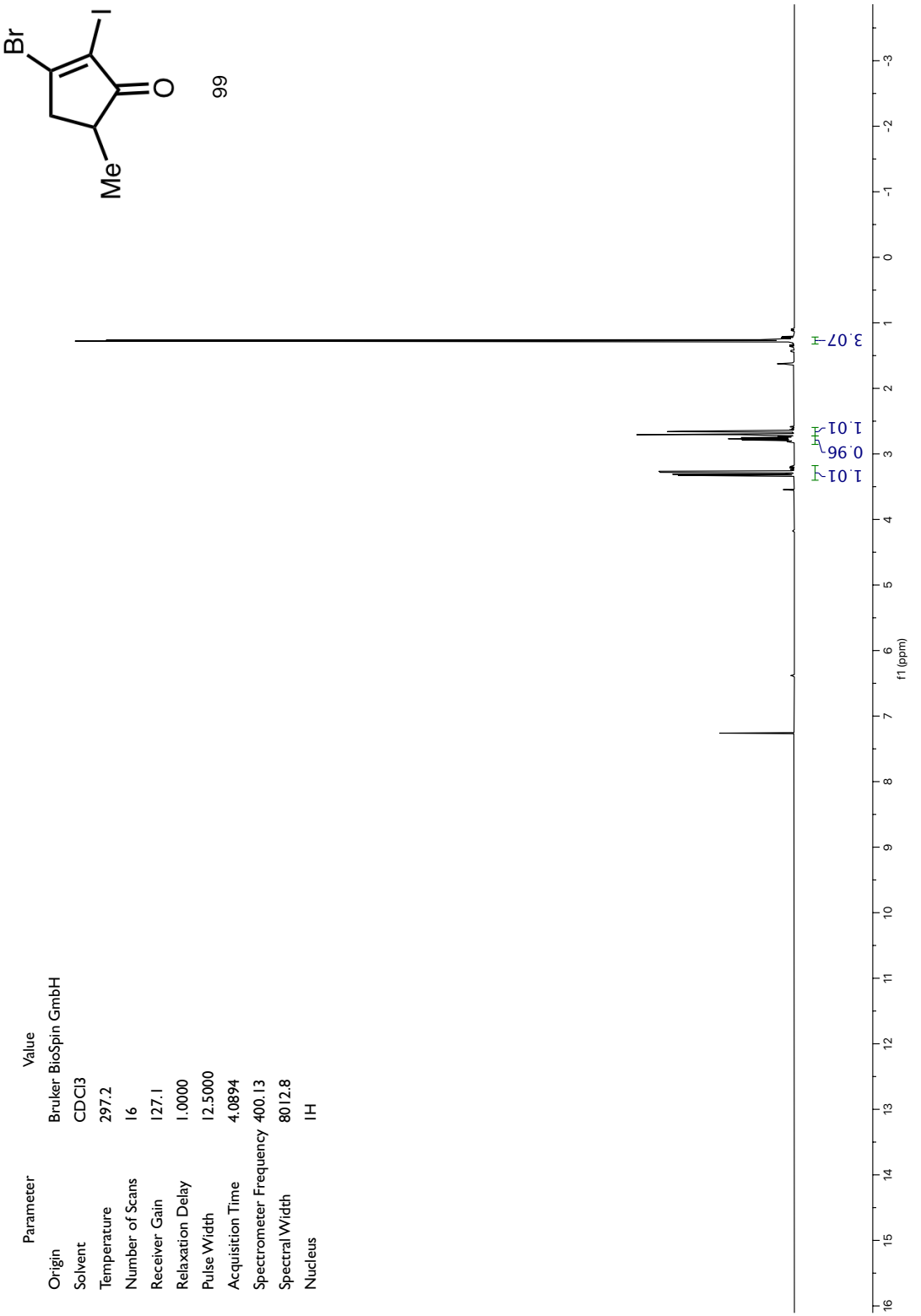
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	78.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C


OEt
O
Me
96
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.26
3.20
1.04
1.01
1.05
2.08
1.00
f1 (ppm)

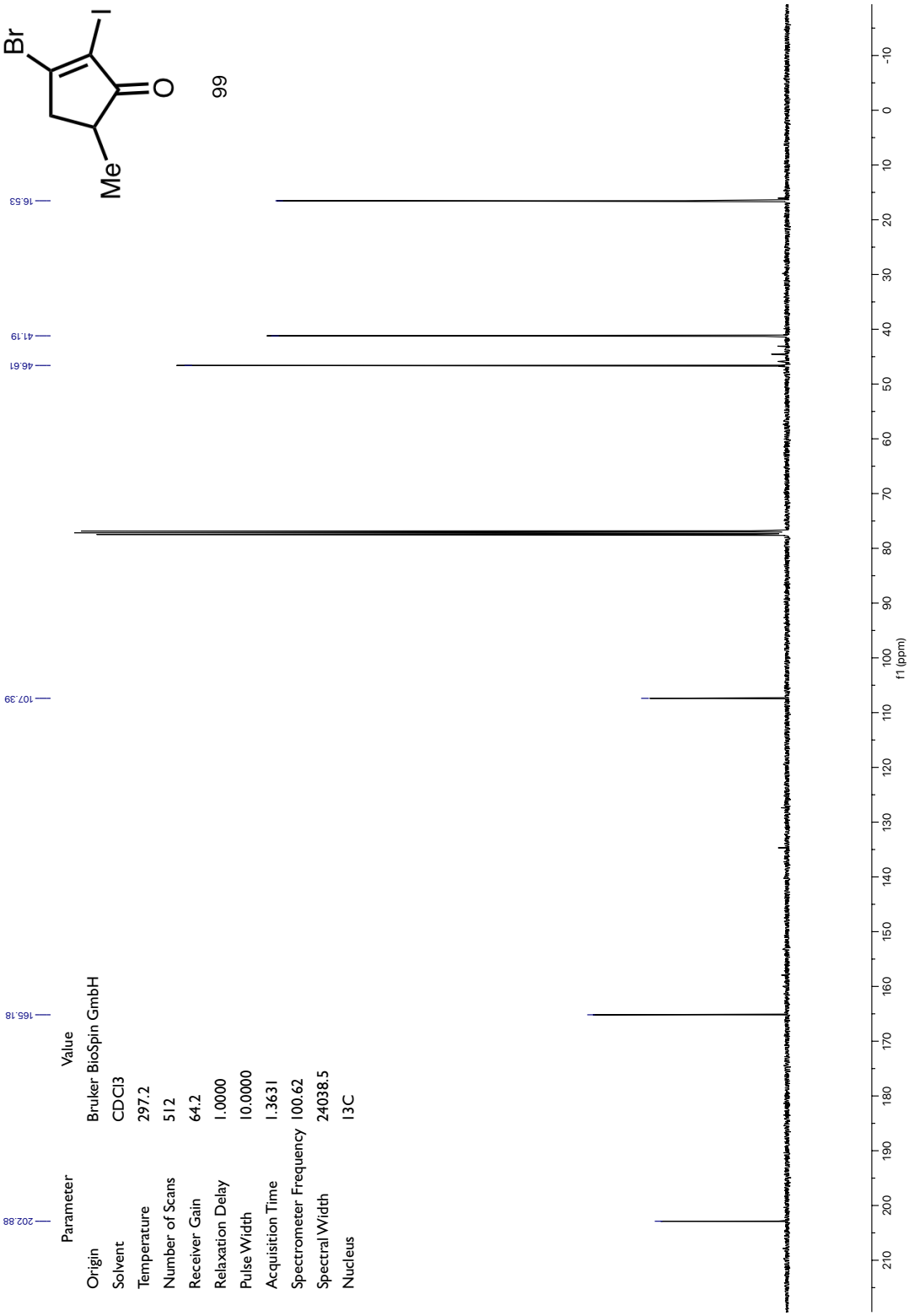

OEt
O
Me
96
14.28
16.86
37.24
39.78
67.68
103.38
188.76
209.20
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

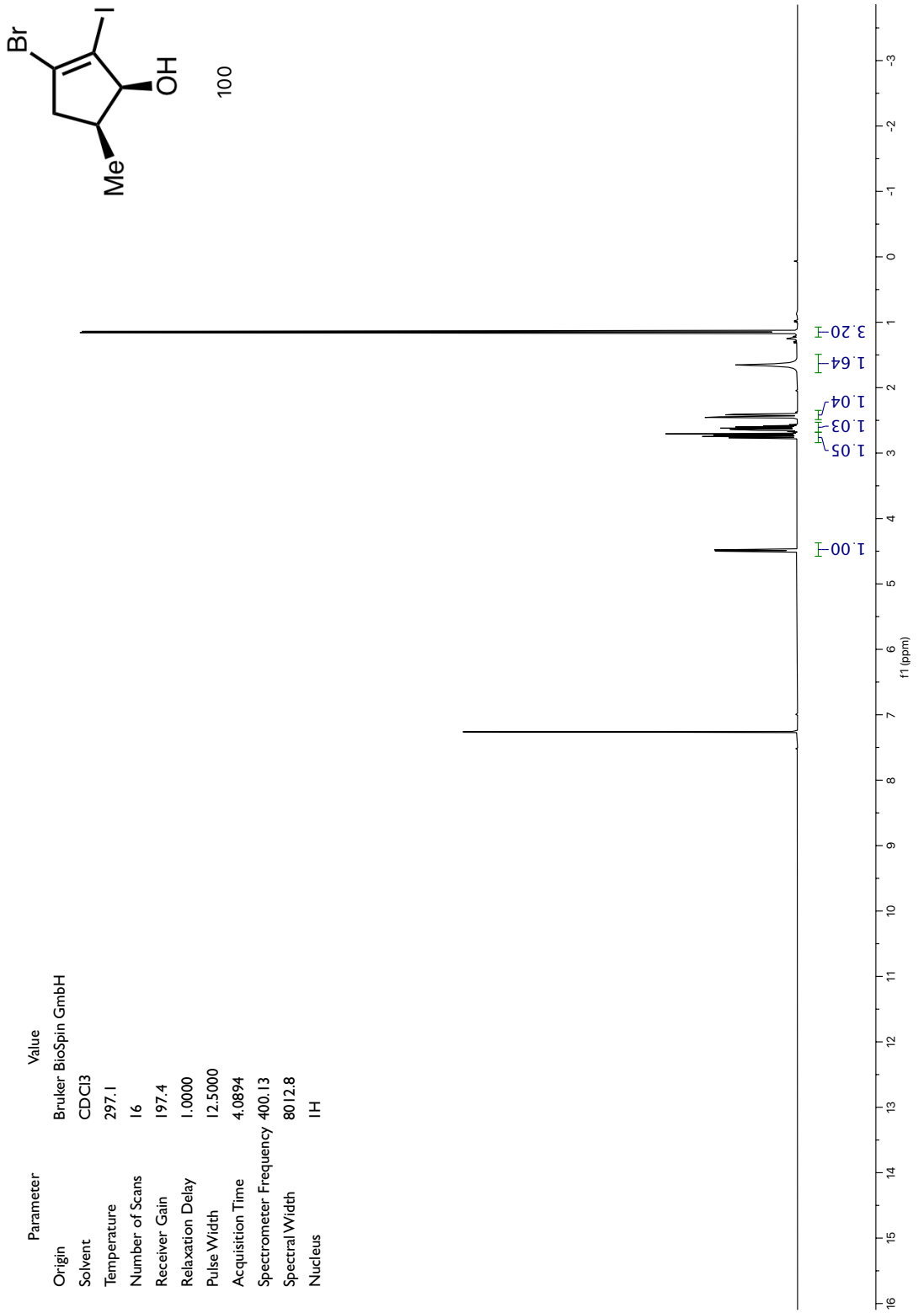

OEt
I
O
Me
97
3.22
3.11
1.02
1.00
1.03
2.03
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H


OEt
I
O
Me
97
15.28
17.38
36.25
38.92
66.72
72.89
187.49
202.78
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

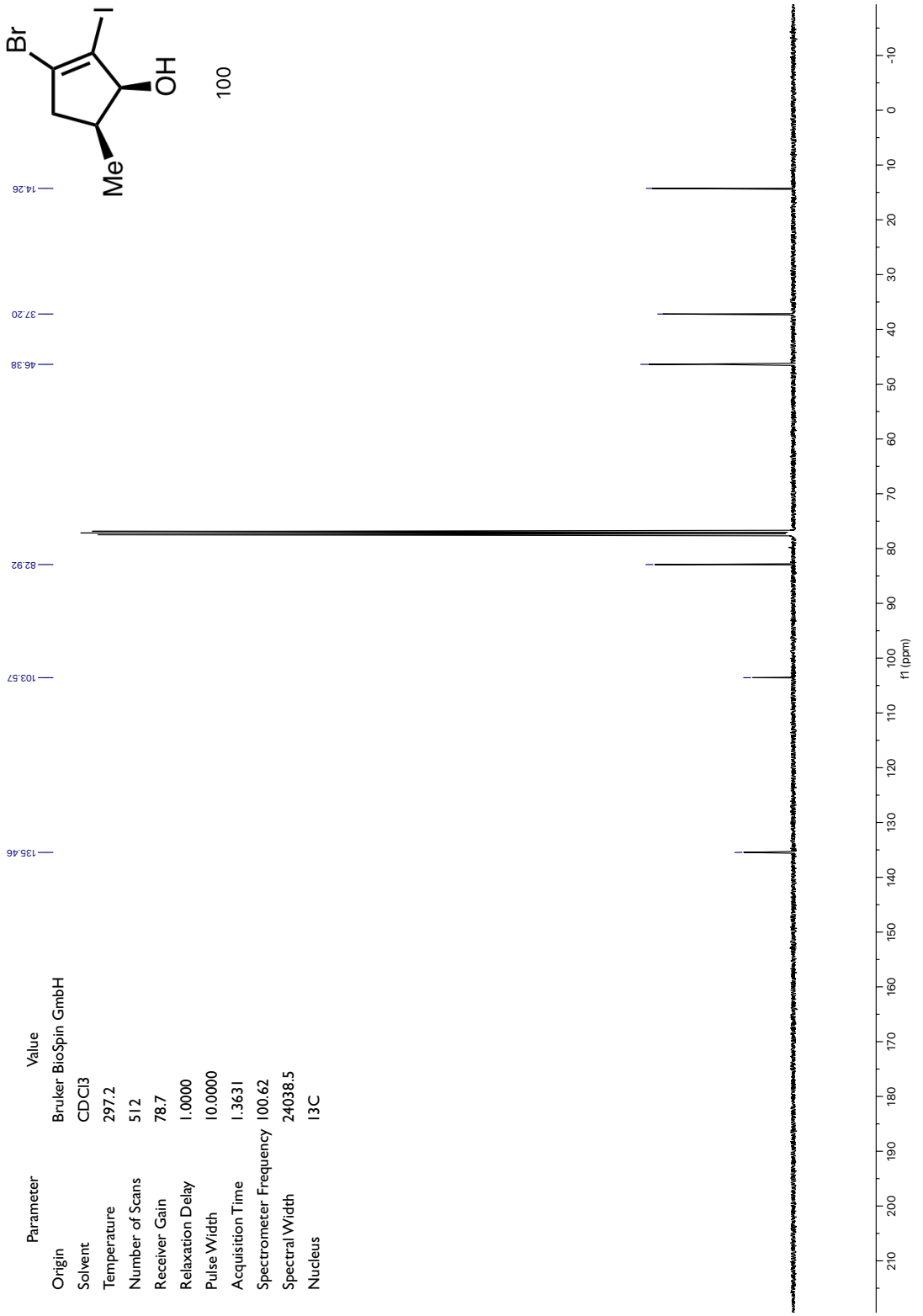


Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H

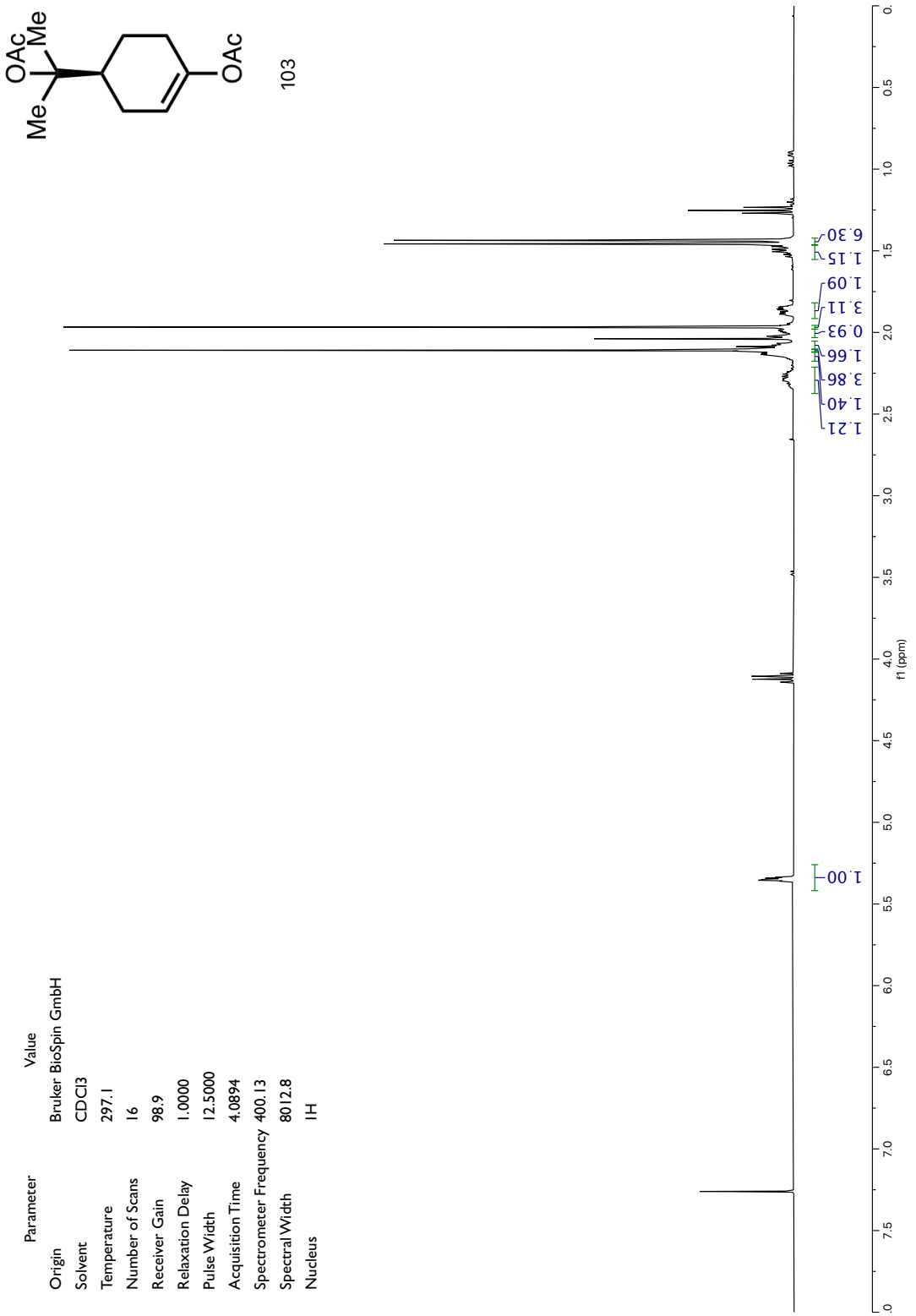

Br
I
O
Me
99
16.53
41.19
46.61
107.39
165.18
202.88
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

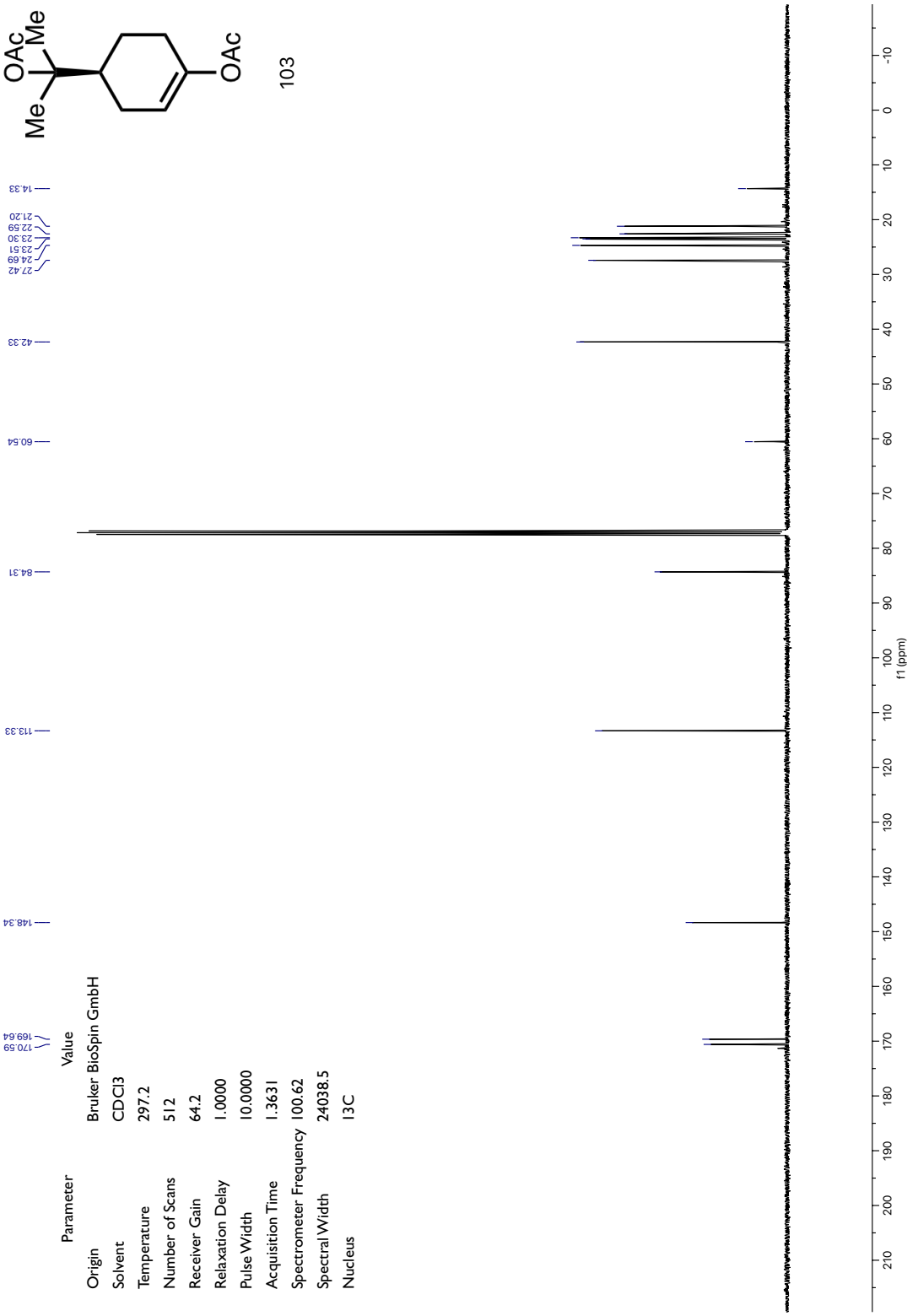


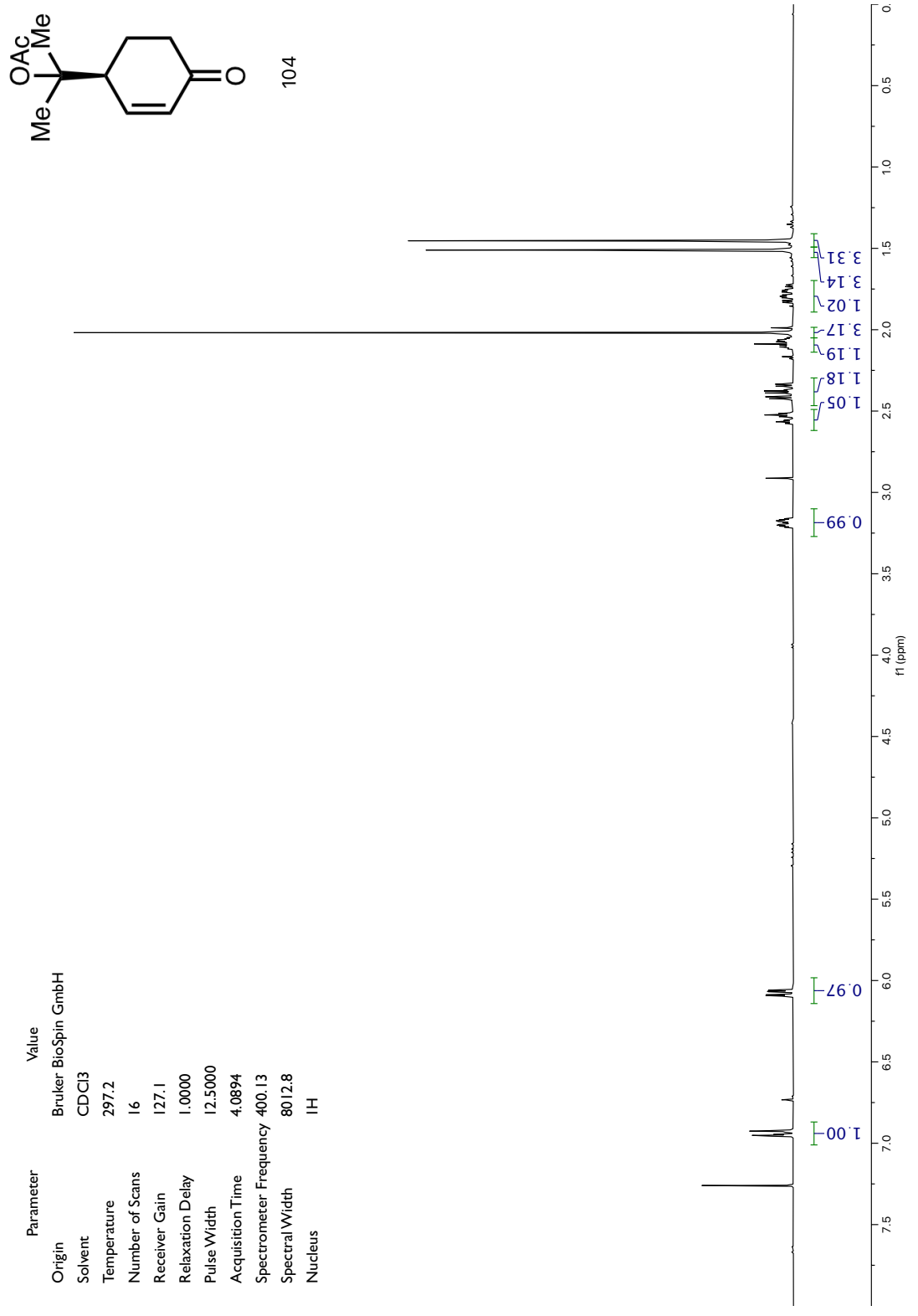
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	16
Receiver Gain	197.4
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H

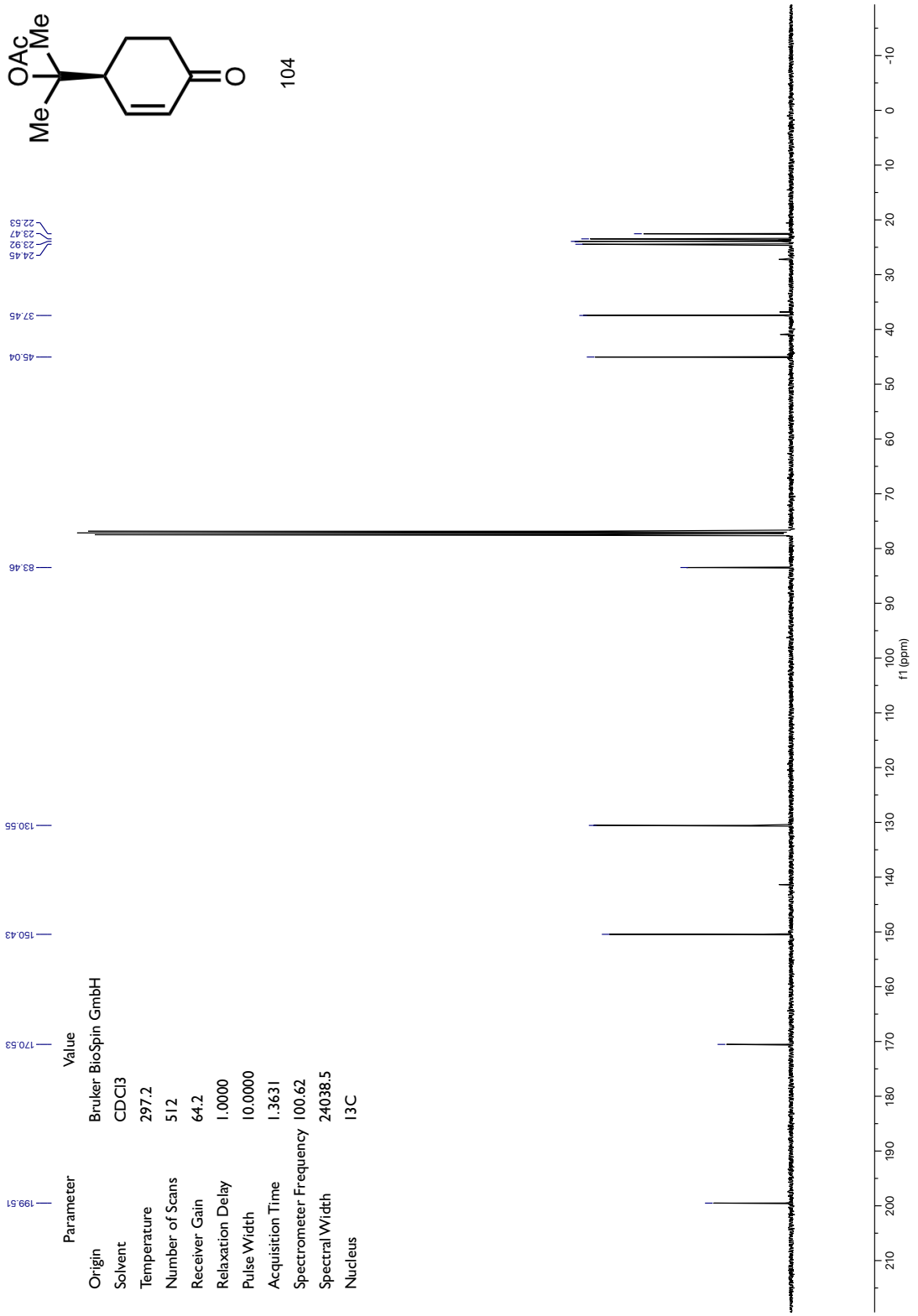


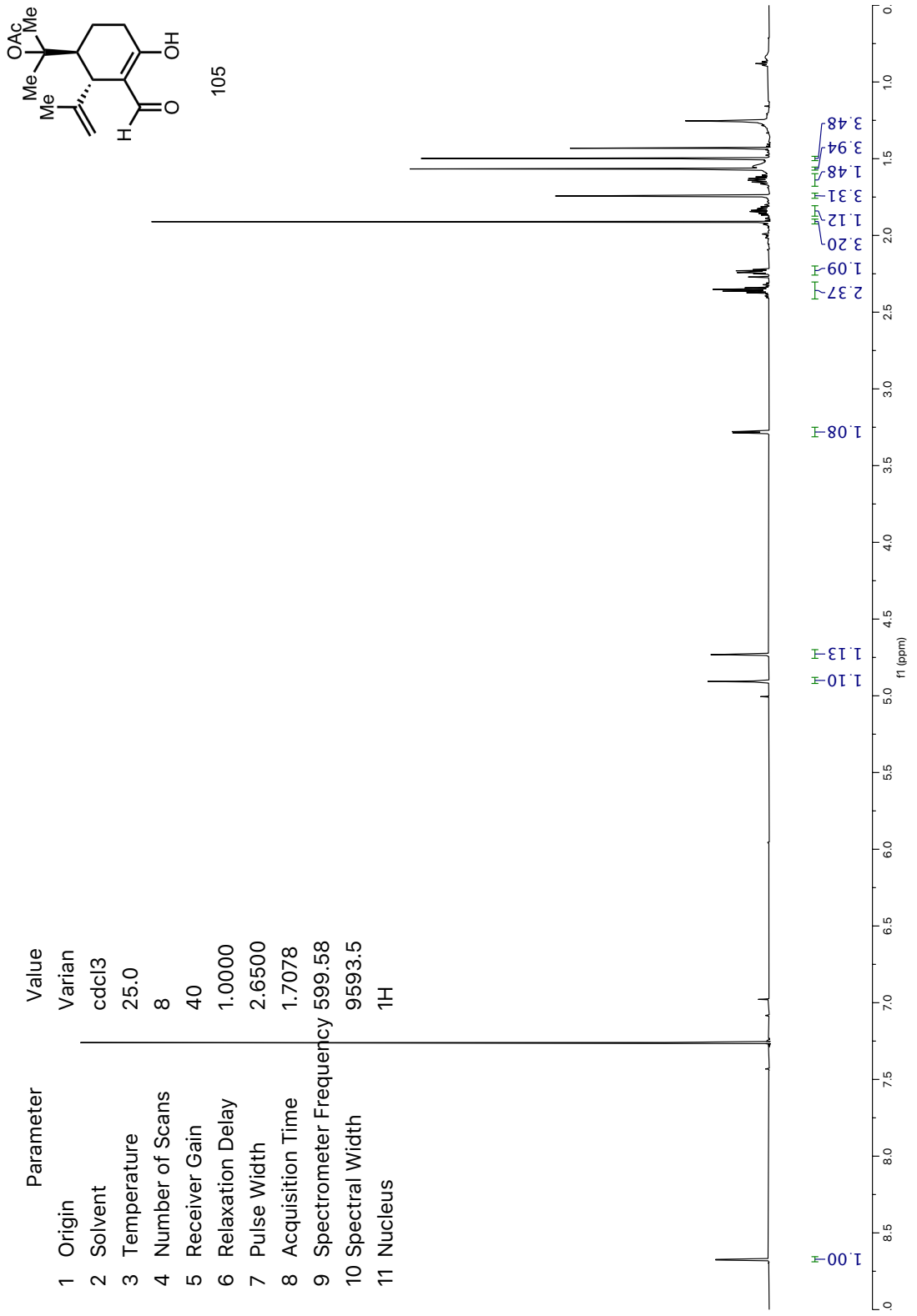
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	78.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

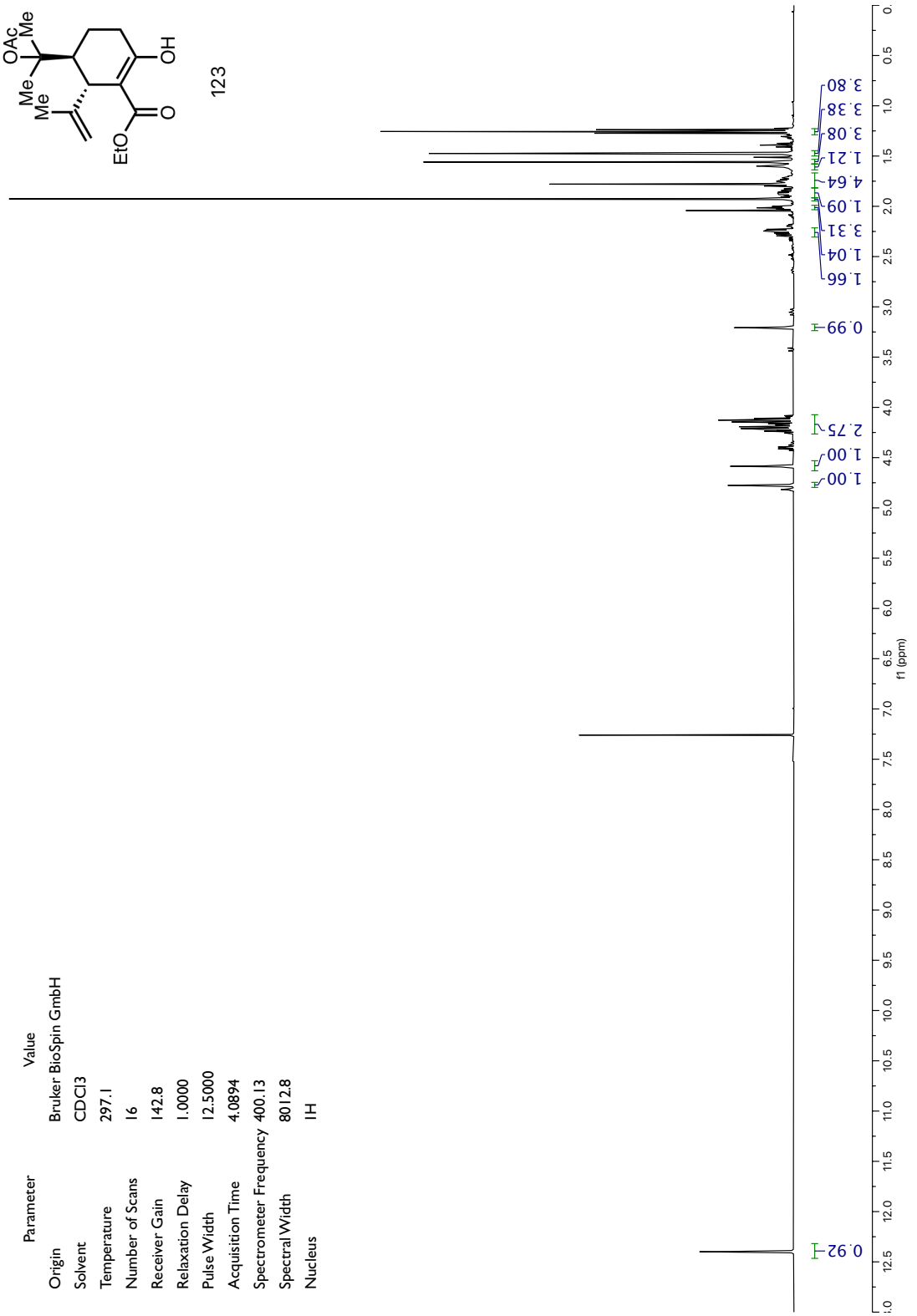

OAc
Me
Me
OAc
103
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
98.9
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
1.00
6.30
1.15
1.09
3.11
0.93
1.66
3.86
1.40
1.21
f1 (ppm)


OAc
Me
Me
OAc
103
14.33
21.20
22.59
23.30
23.51
24.69
27.42
42.33
60.54
84.31
113.33
148.34
169.64
170.59
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

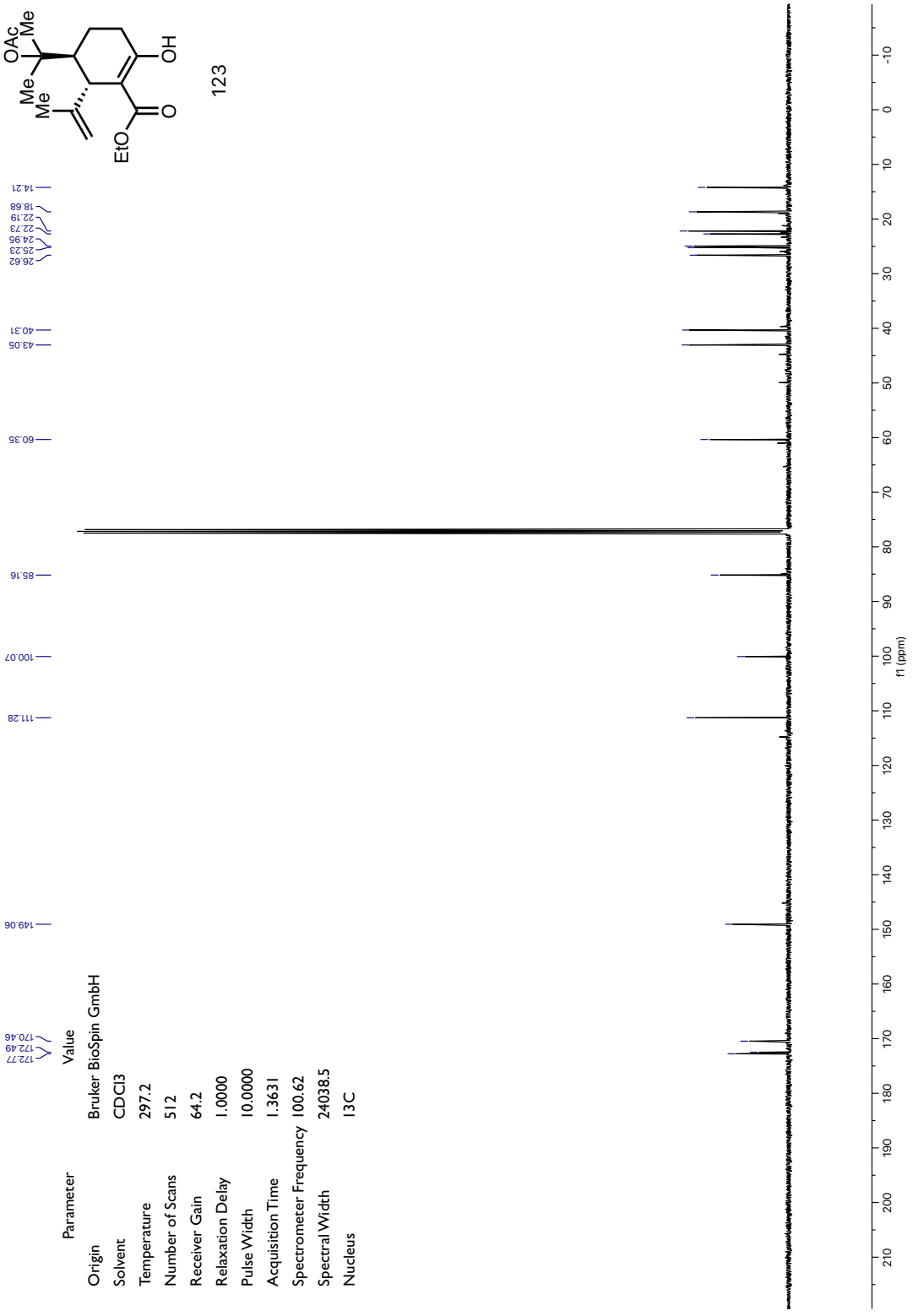

OAc
Me
Me
O
10-4
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
1.00
0.97
0.99
1.05
1.18
1.19
3.17
1.02
3.14
3.31
f1 (ppm)

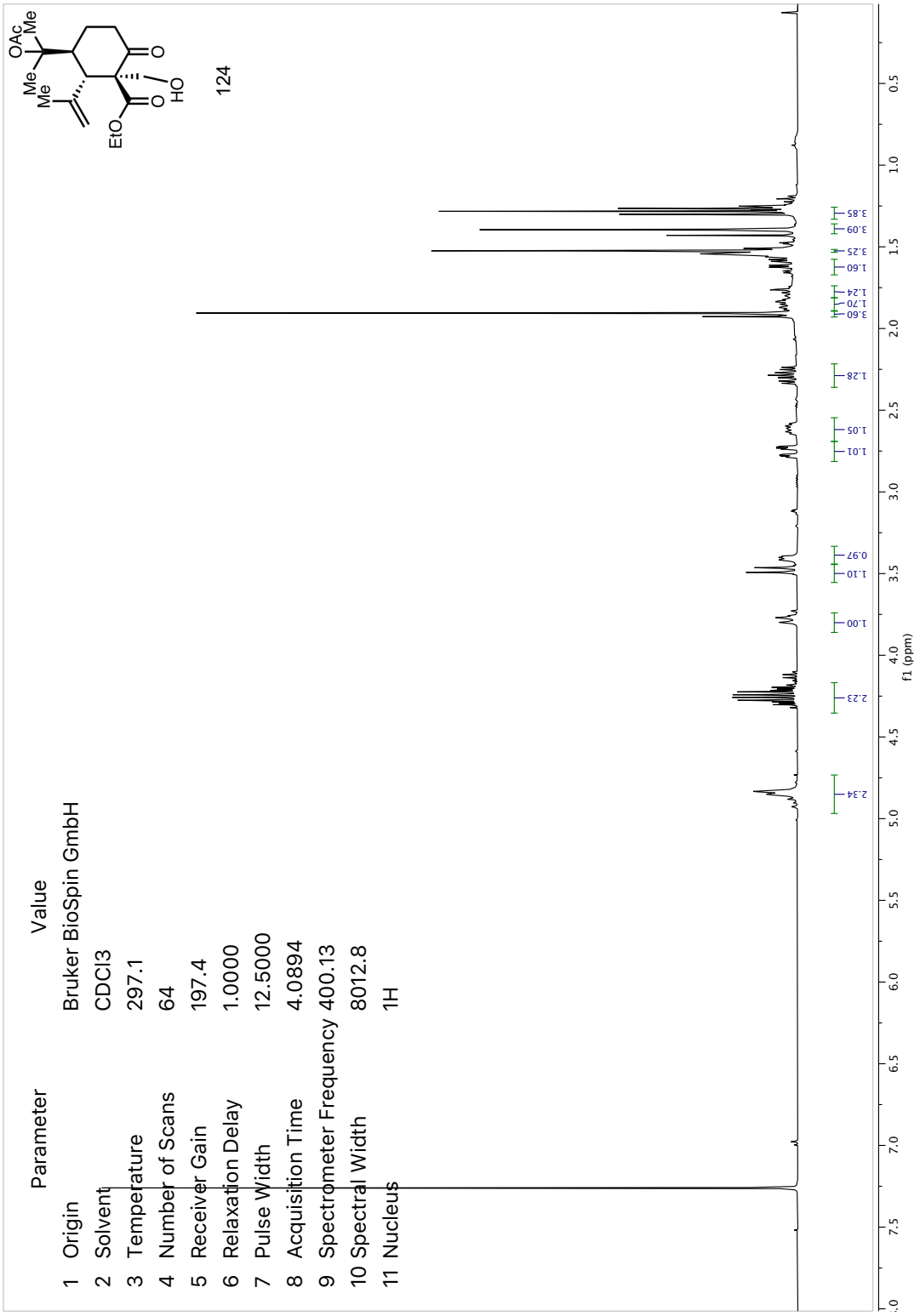

OAc
Me
Me
O
104
22.53
23.47
23.92
24.45
37.45
45.04
83.46
130.55
150.43
170.53
199.51
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

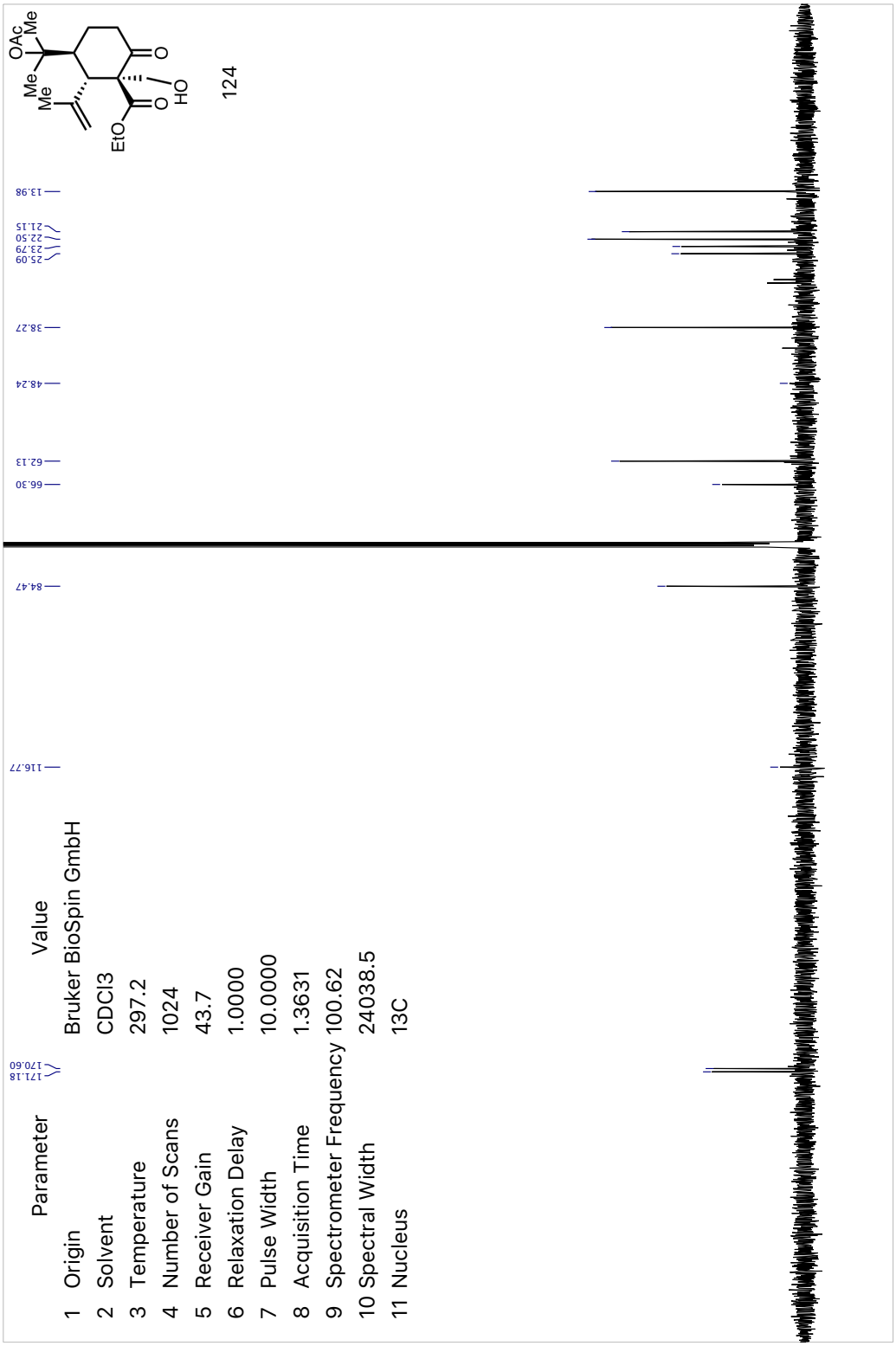

OAc
Me
Me
Me
OH
O
H
105
Parameter Value
1 Origin Varian
2 Solvent cdcl3
3 Temperature 25.0
4 Number of Scans 8
5 Receiver Gain 40
6 Relaxation Delay 1.0000
7 Pulse Width 2.6500
8 Acquisition Time 1.7078
9 Spectrometer Frequency 599.58
10 Spectral Width 9593.5
11 Nucleus 1H
1.00
1.13
1.10
1.08
2.37
1.09
3.20
1.12
3.31
1.48
3.94
3.48
f1 (ppm)

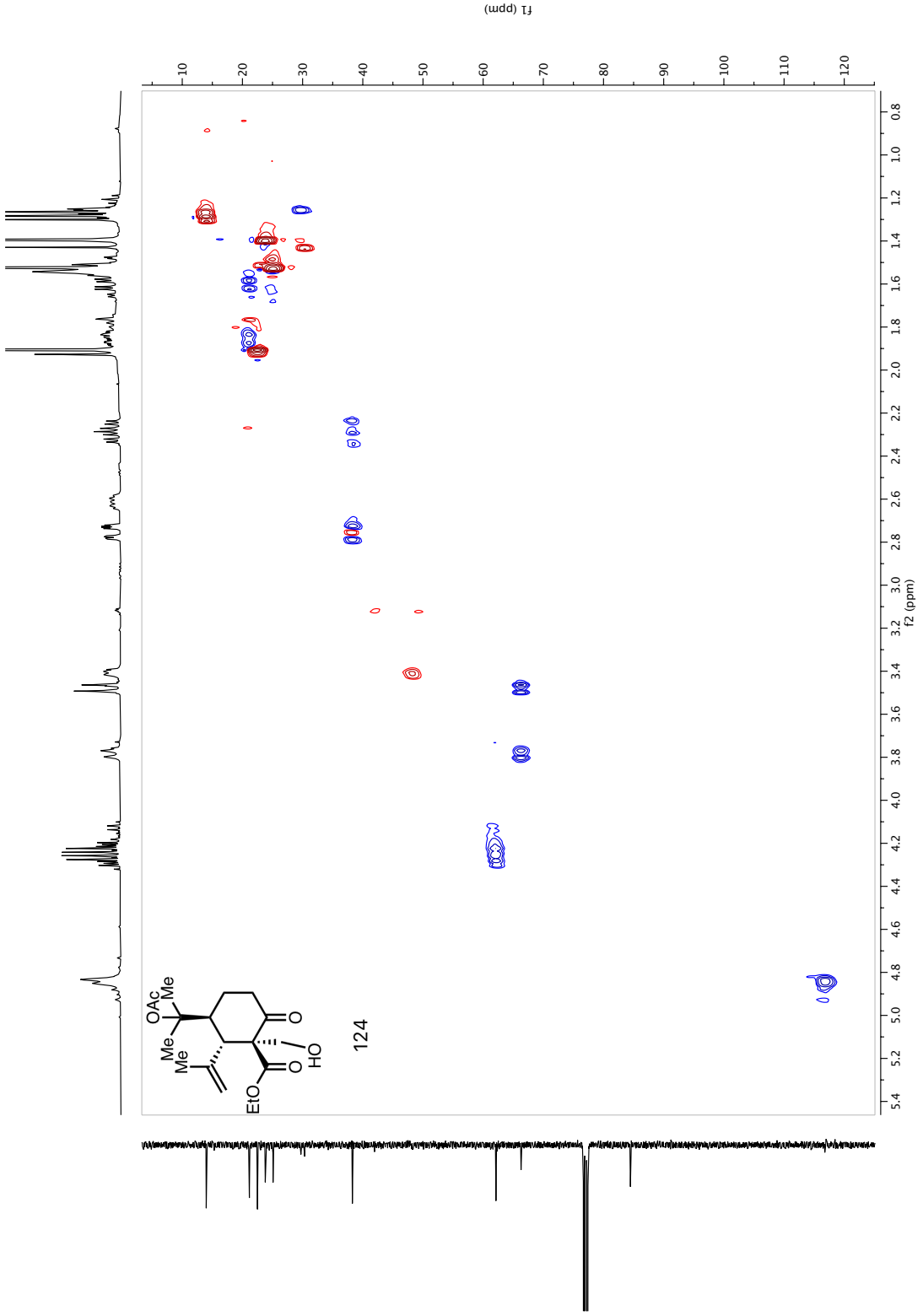


Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	16
Receiver Gain	142.8
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H


OAc
Me
Me
Me
OH
O
EtO
123
14.21
18.68
22.19
22.73
24.95
25.23
26.62
40.31
43.05
60.35
85.16
100.07
111.28
149.06
170.46
172.49
172.77
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)


OAc
Me
Me
Me
O
O
HO
EtO
124
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Solvent CDCl3
3 Temperature 297.1
4 Number of Scans 64
5 Receiver Gain 197.4
6 Relaxation Delay 1.0000
7 Pulse Width 12.5000
8 Acquisition Time 4.0894
9 Spectrometer Frequency 400.13
10 Spectral Width 8012.8
11 Nucleus 1H
2.34
2.23
1.00
1.10
0.97
1.28
1.05
1.01
3.60
1.70
1.24
1.60
3.25
3.09
3.85
f1 (ppm)


OAc
Me
Me
Me
O
O
HO
EtO
124
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Solvent CDCl3
3 Temperature 297.2
4 Number of Scans 1024
5 Receiver Gain 43.7
6 Relaxation Delay 1.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.3631
9 Spectrometer Frequency 100.62
10 Spectral Width 24038.5
11 Nucleus 13C
171.18
170.60
116.77
84.47
66.30
62.13
48.24
38.27
25.09
23.79
22.50
21.15
13.98
f1 (ppm)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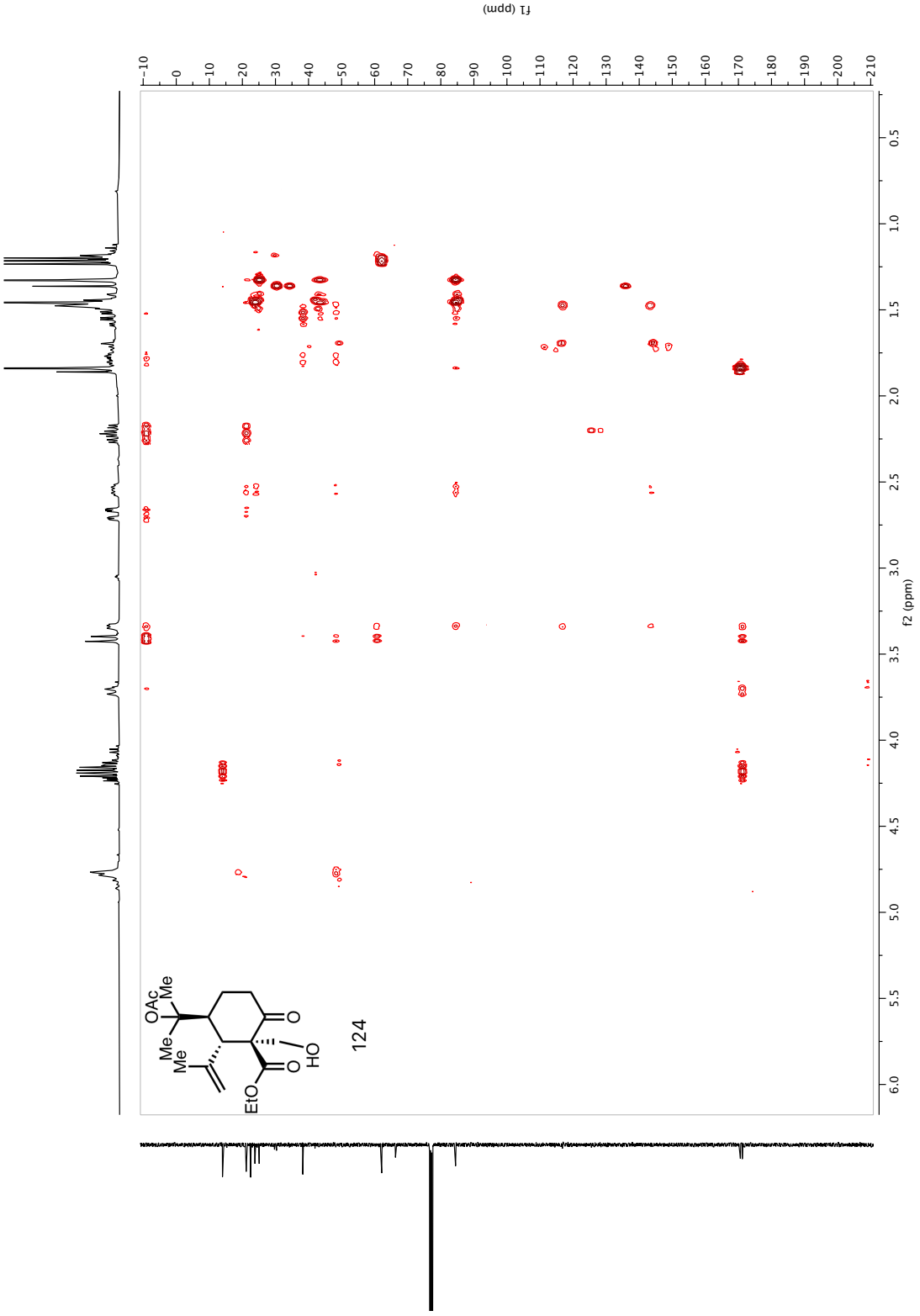
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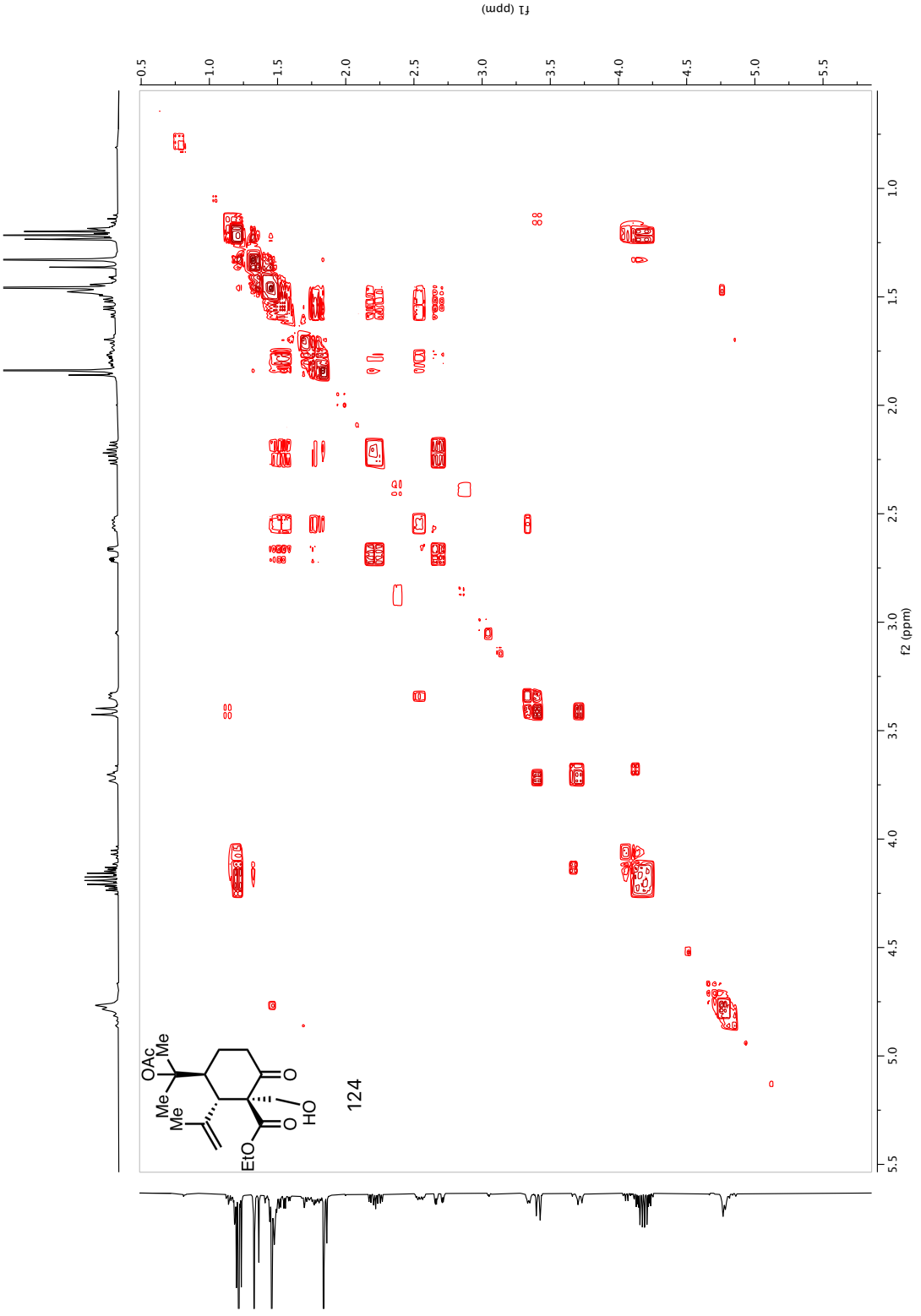
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EtO
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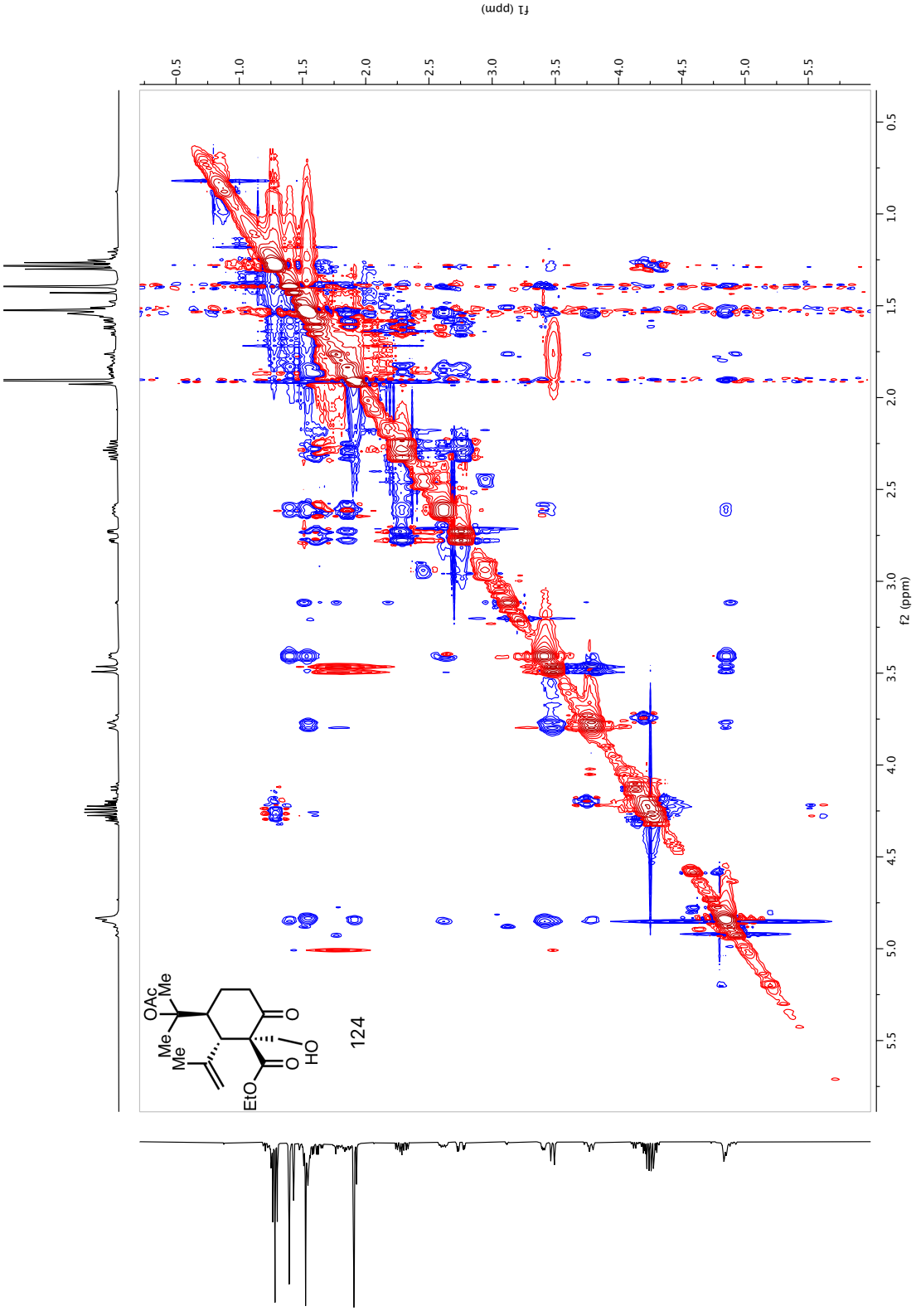
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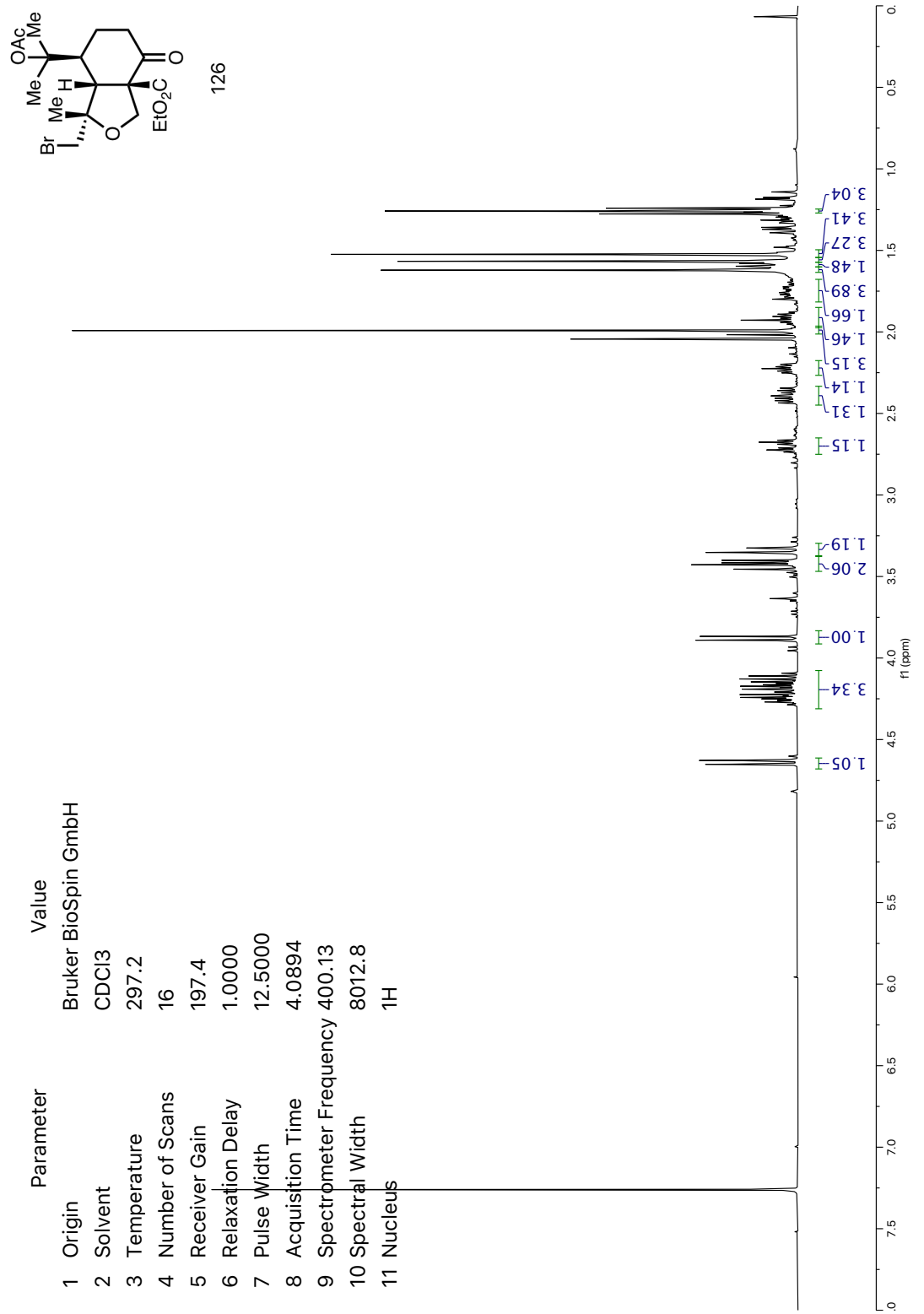
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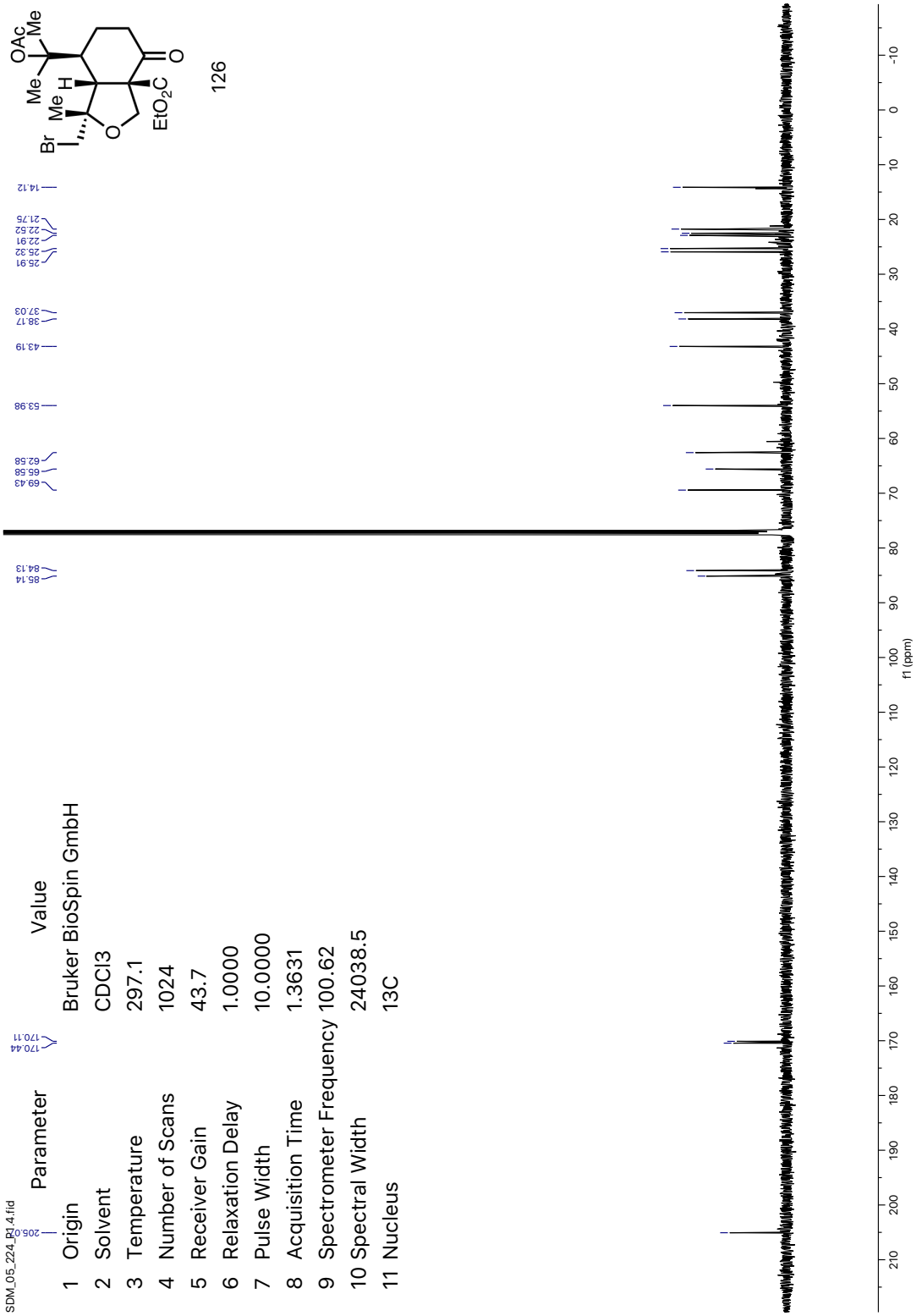
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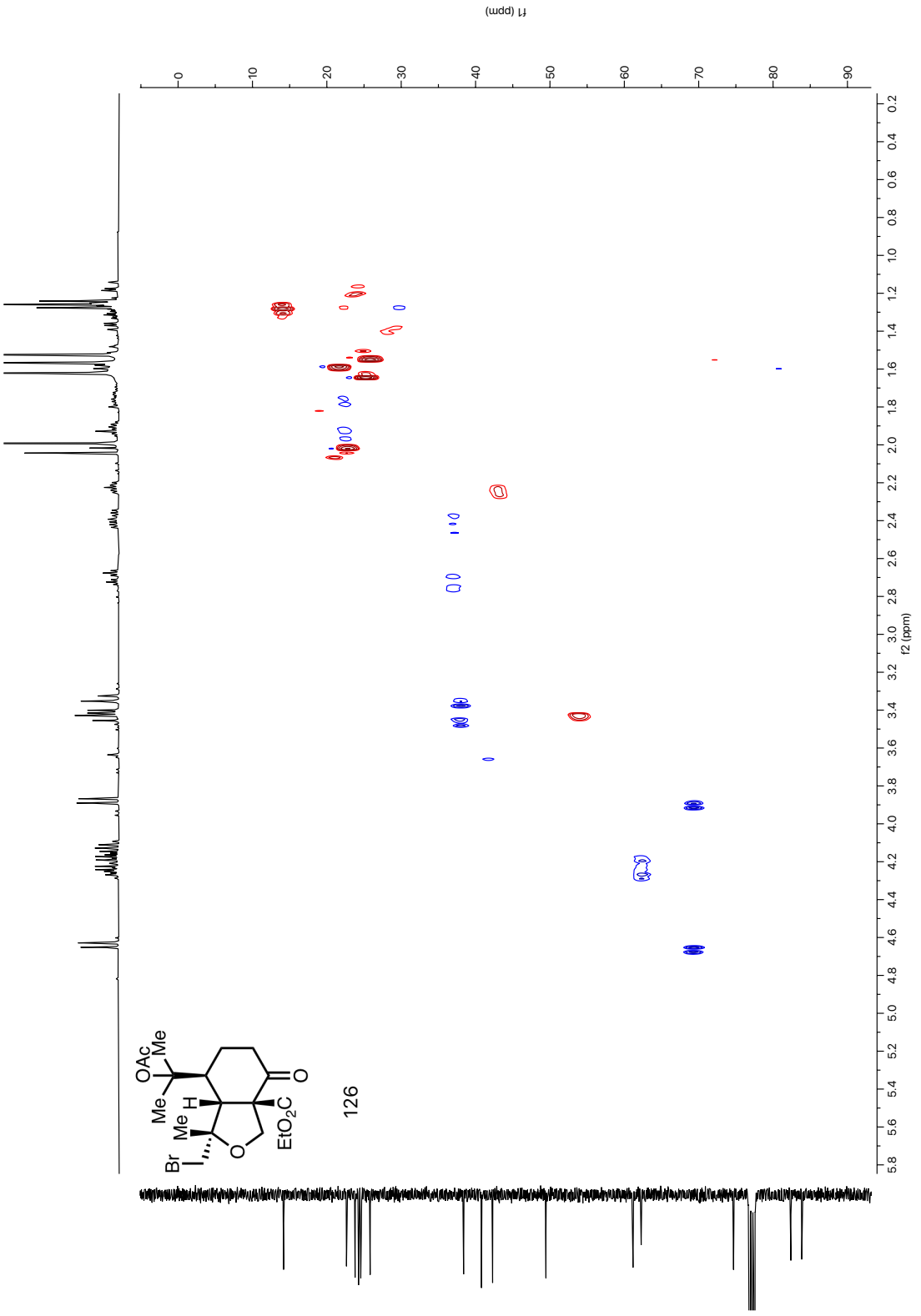
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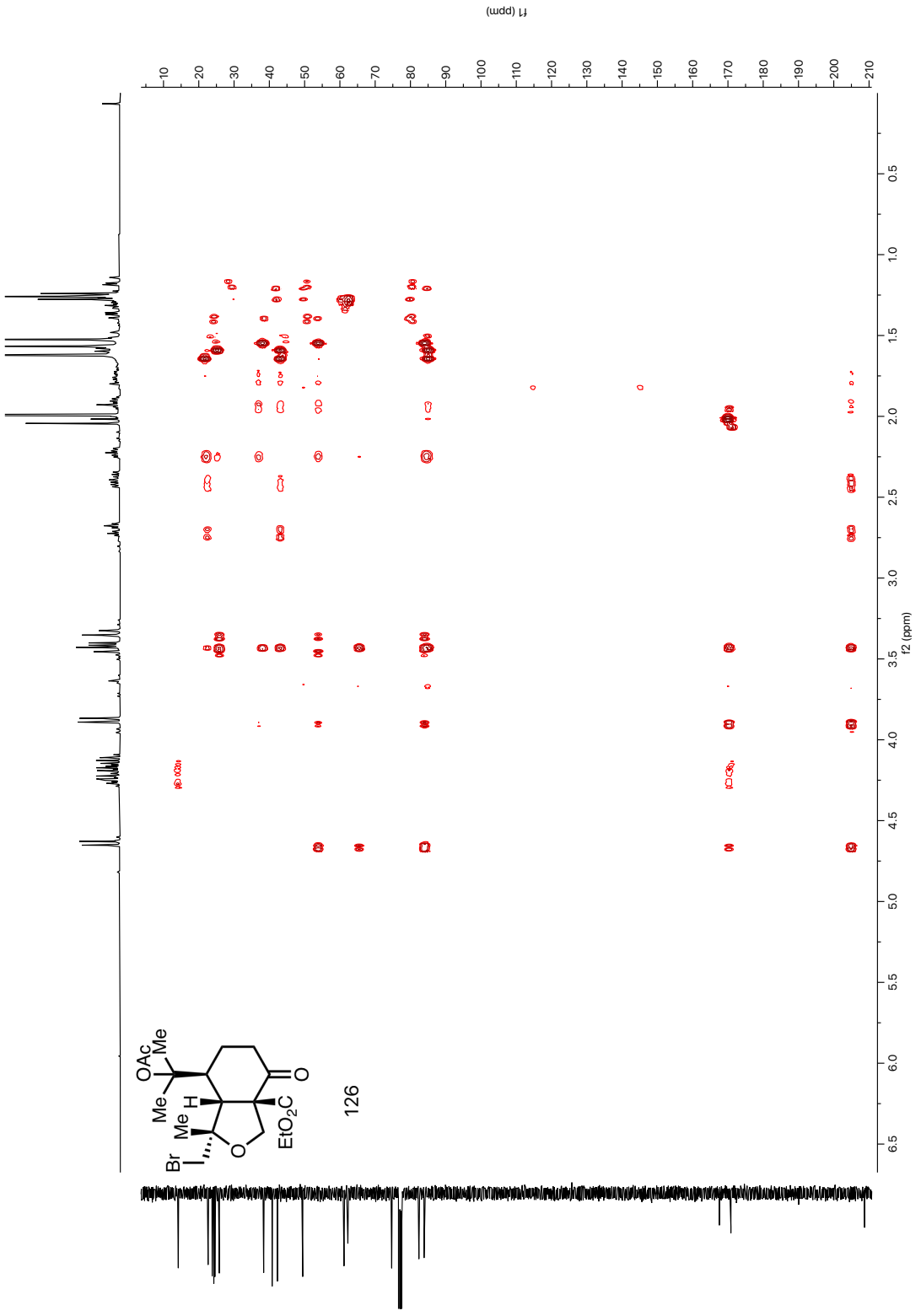
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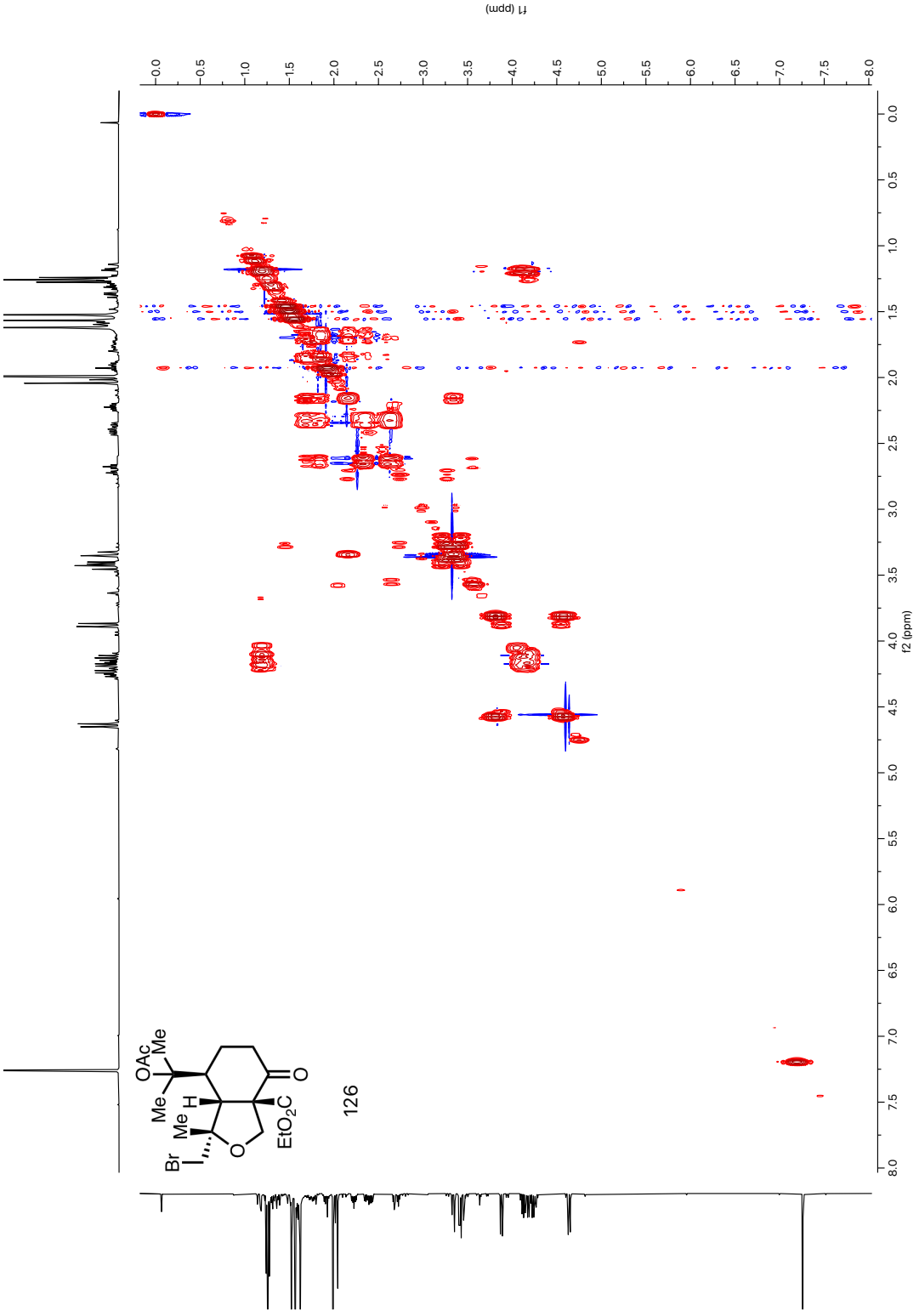
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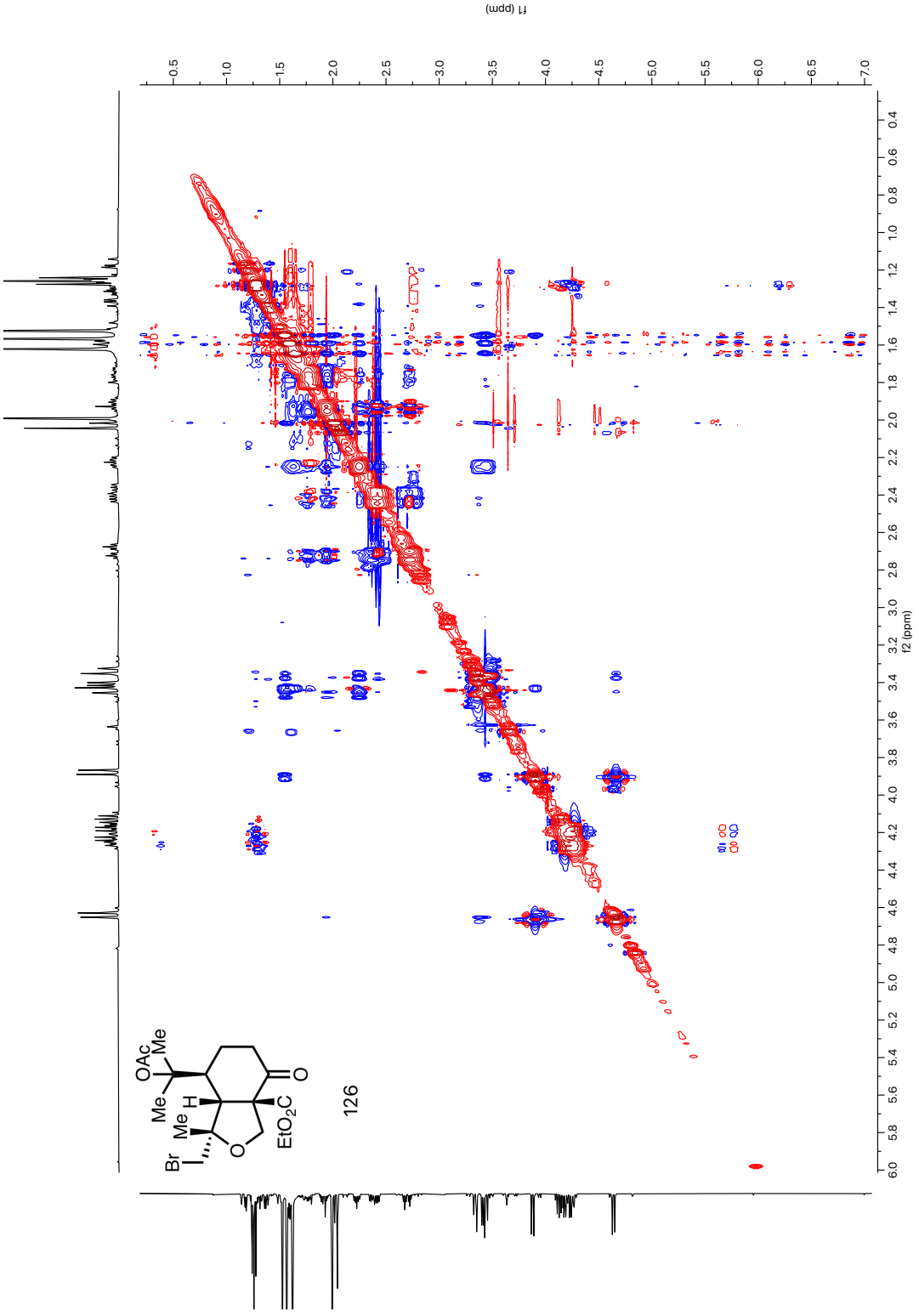
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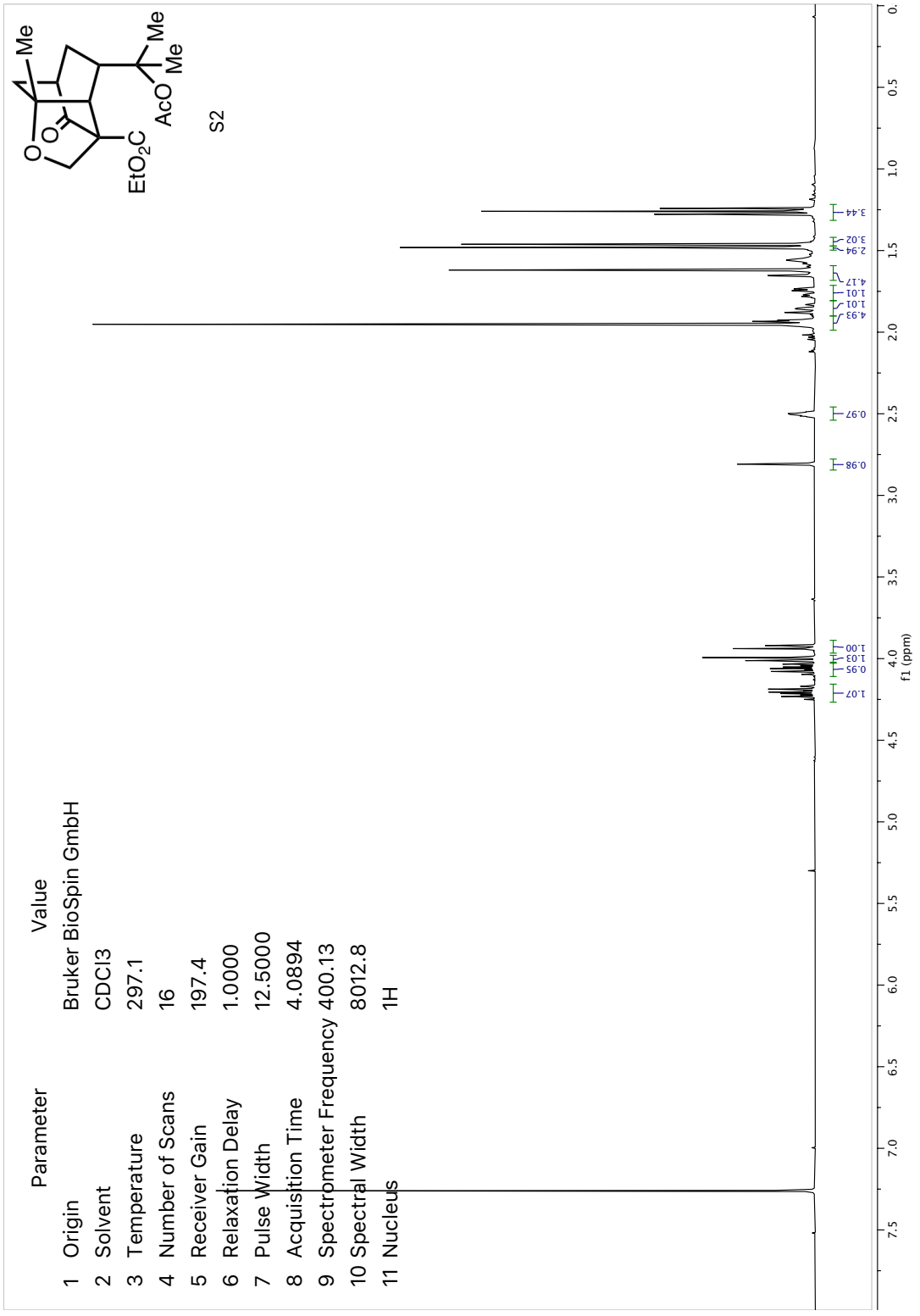
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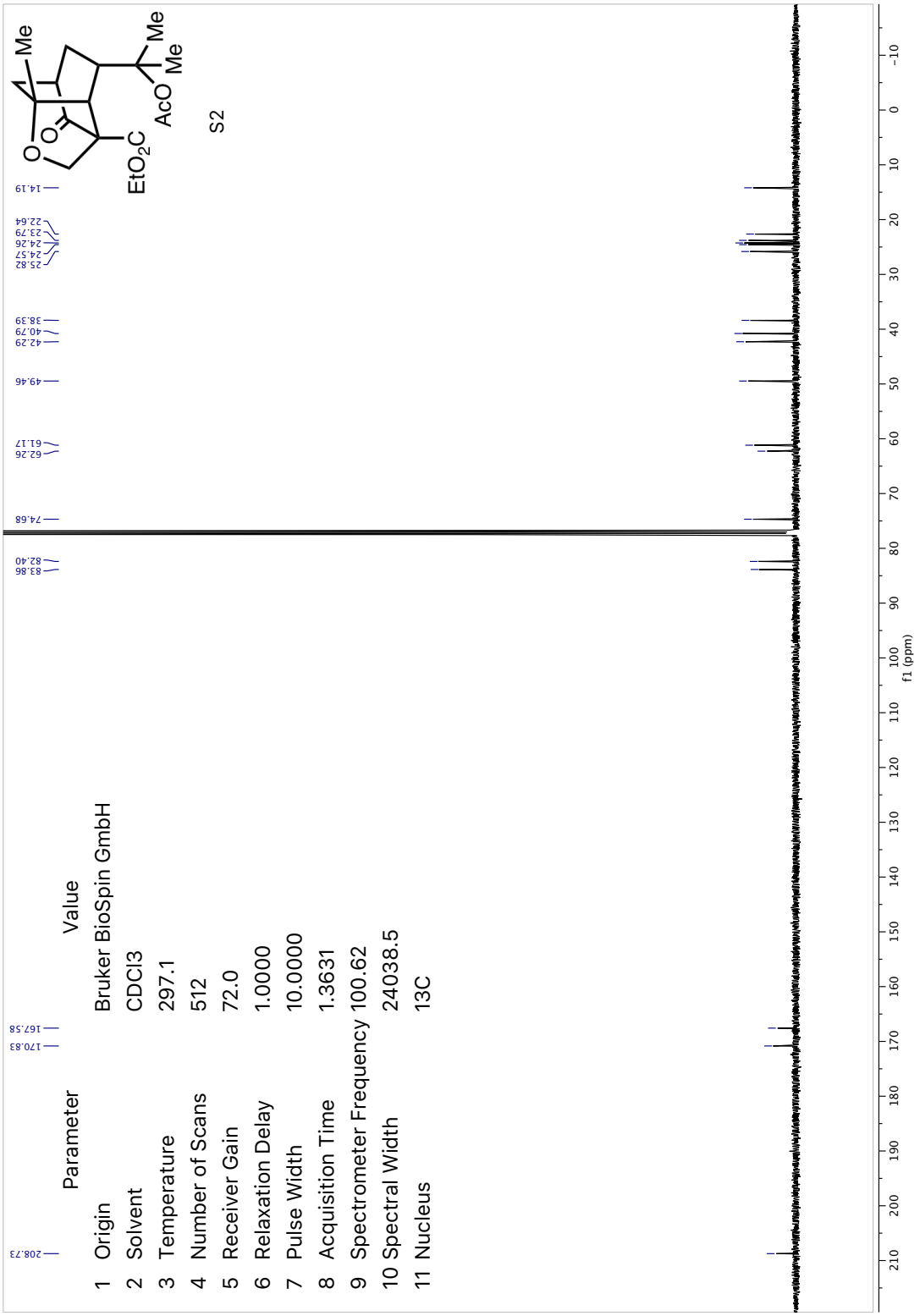
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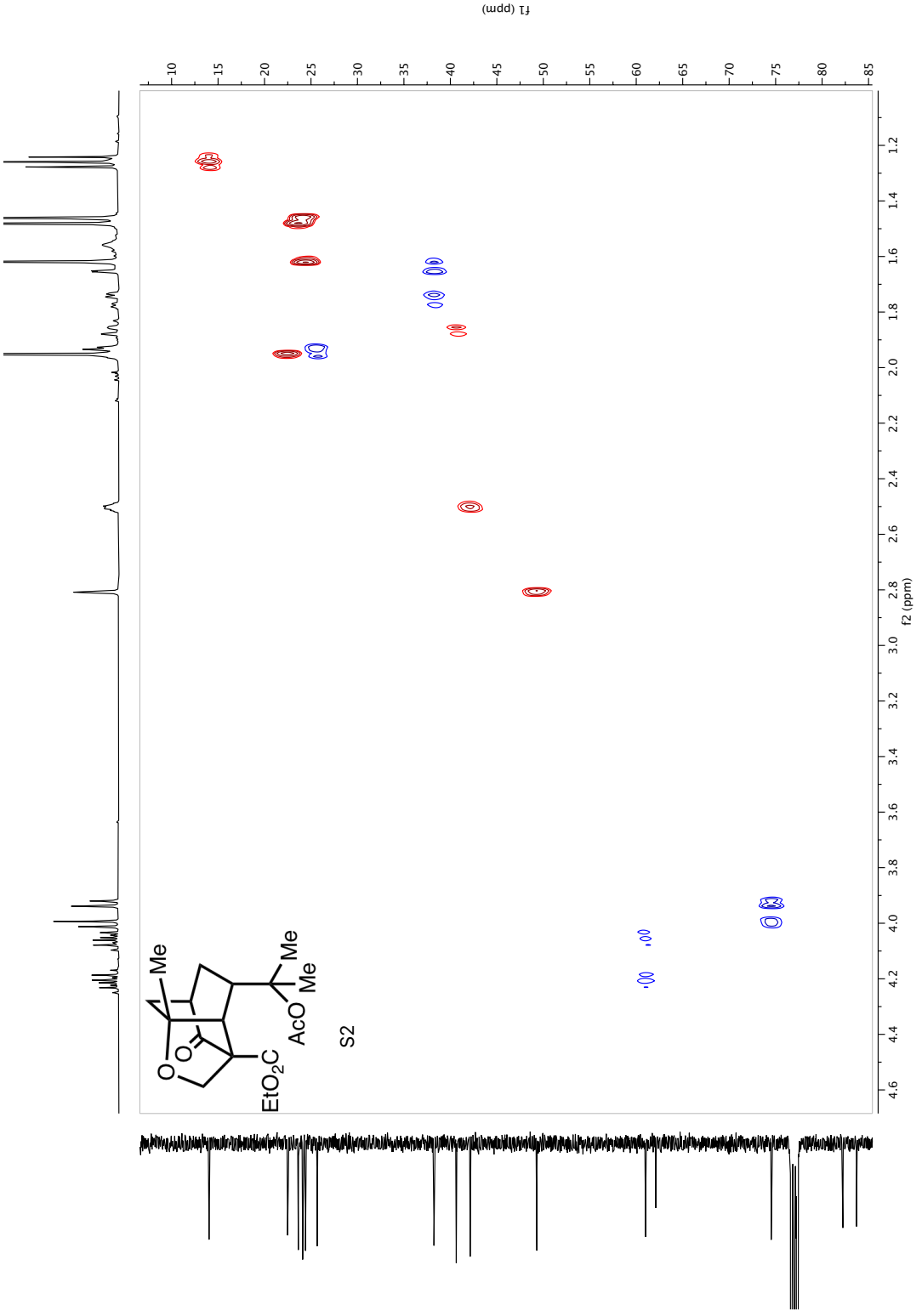
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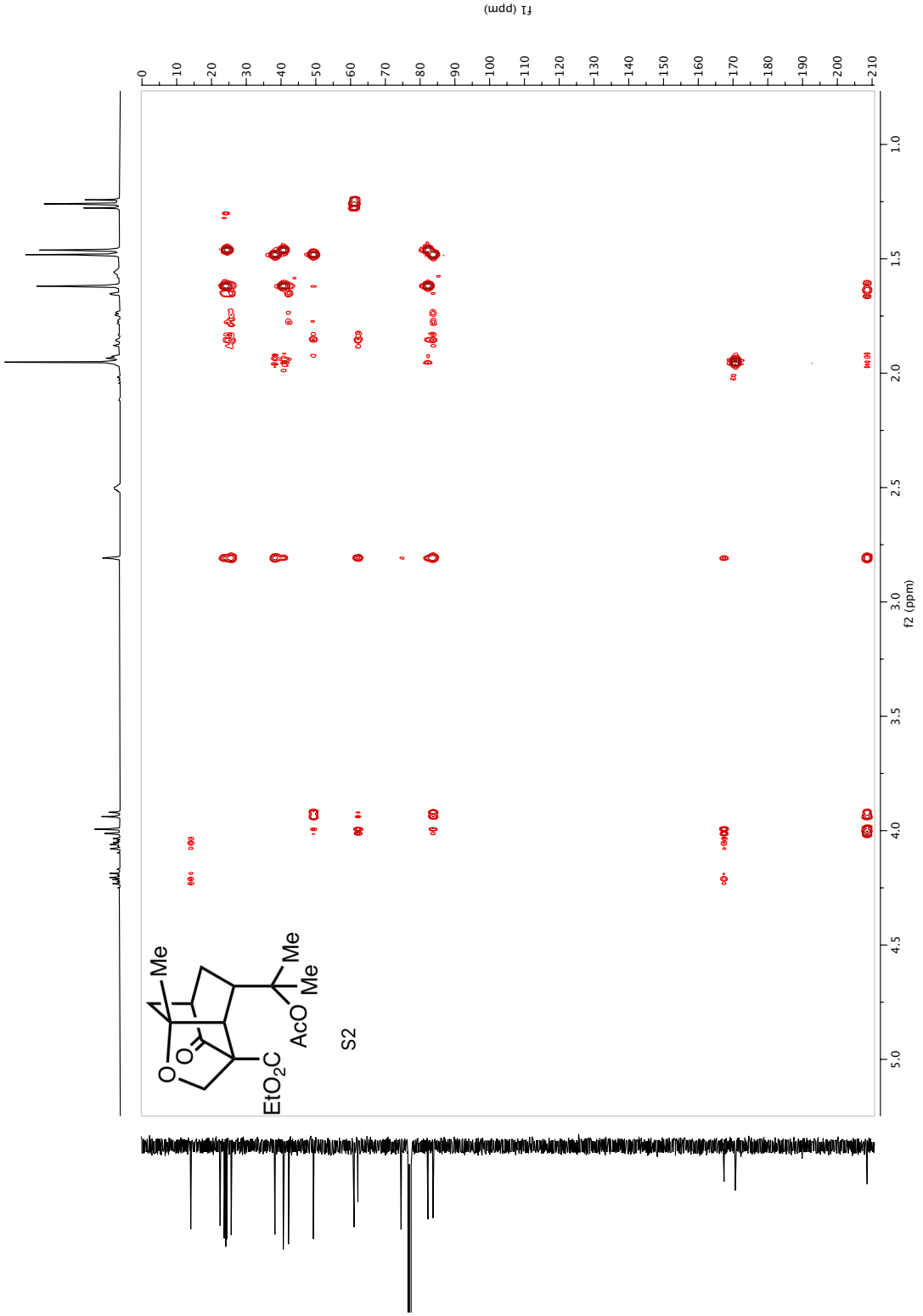
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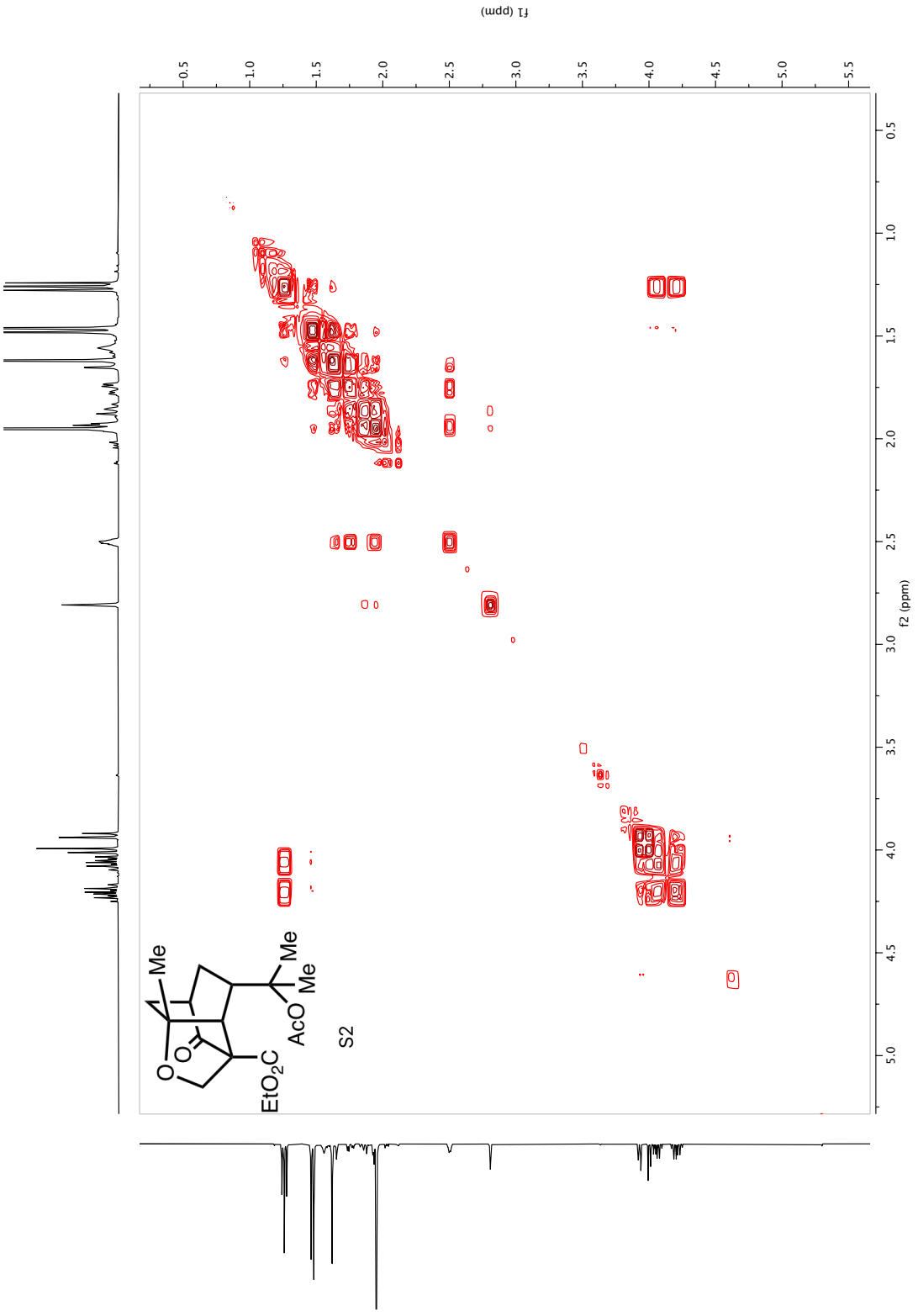
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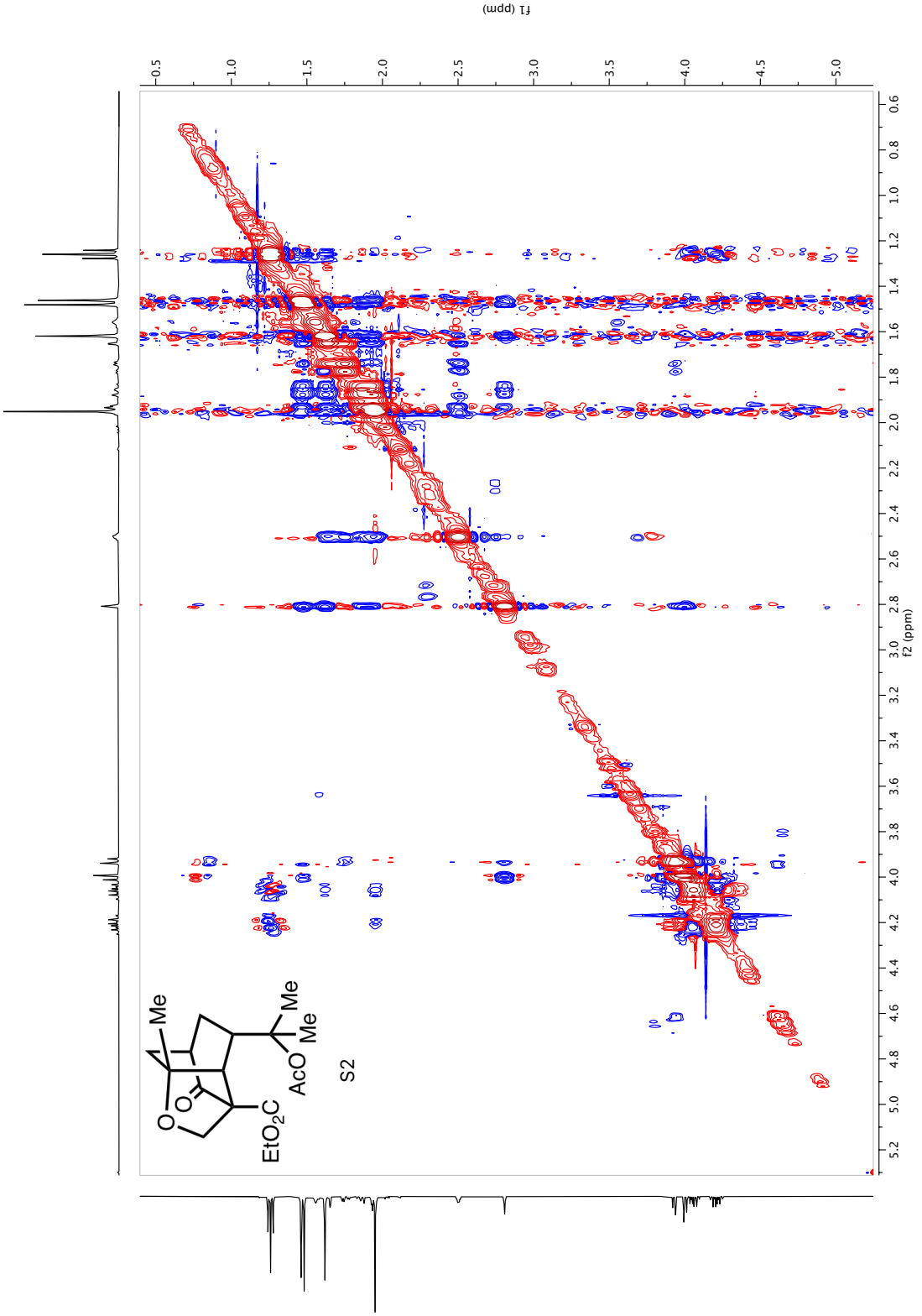
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Chapter 4

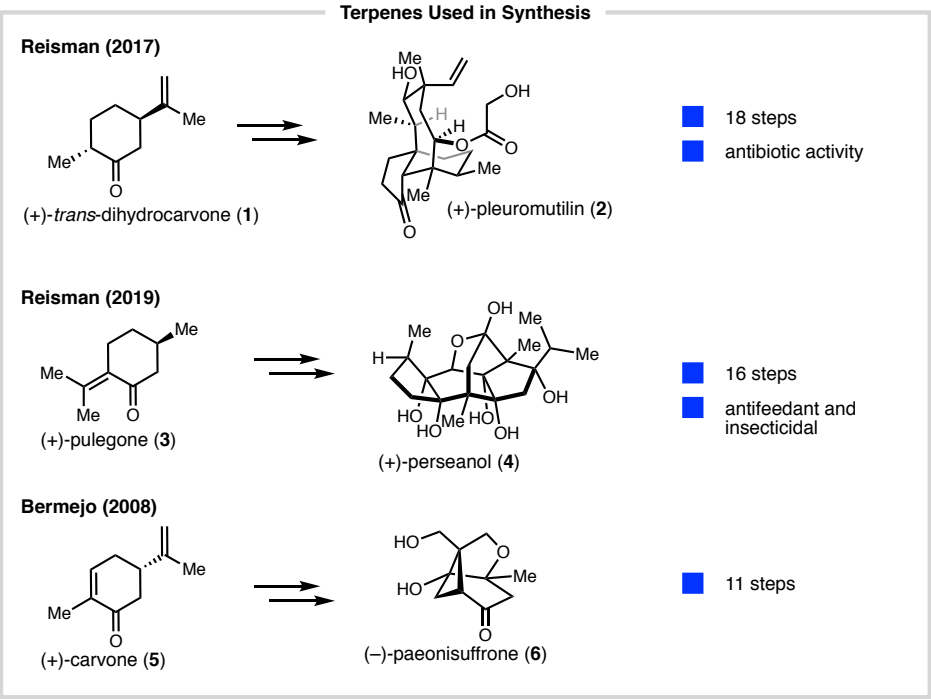
Enantioselective Diels-Alder Reactions of α-Acyloxy Enones

4.1 INTRODUCTION

Naturally occurring monoterpenes serve as important chiral building blocks for the synthesis of natural products, medicines, and agrochemicals.[1] For example, the monocyclic cyclohexene-containing terpenes (+)-*trans*-dihydrocarvone (**1**), (+)-pulegone (**3**) and (+)-carvone (**5**) are frequently used members of the 'chiral pool' (**Figure 4.1**).[1–4] Given the importance of oxidized monoterpenes as entry points to higher order terpenes and other complex molecules, we sought to develop an enantioselective synthesis of related oxidized cyclohexenes that could expand the pool of chiral building blocks.

Portions of this chapter were adapted from the following patent: Reisman, S.; Rombola, M.; Ladd, C.; McLaughlin, M. J.; Zuend, S.; Göetz, R. *Process for the synthesis of non-racemic cyclohexenes*. US Patent WO 2021/007141 A1, January 2021. The research discussed in this chapter was completed in collaboration with Karli Holman, a graduate student, and Dr. Michael Rombola, a former in the Reisman Lab.

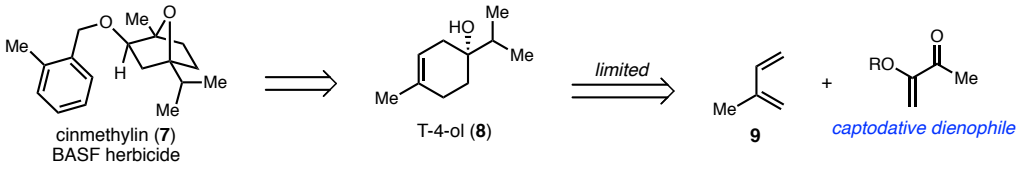
Figure 4.1 *Terpene use in Total Synthesis*



The starting material for the BASF herbicide cinmethylin (**7**) is terpinene-4-ol (T-4-ol, **8**, **Figure 4.2**), a naturally occurring monoterpene that is only available either as a racemate or as a 2:1 scalemic mixture of enantiomers. Cinmethylin (**7**), marketed under the name Luximo™, is a terpene herbicide that was first discovered in 1981 by Shell.[5] By 1989, cinmethylin had been brought to market and was used to treat otherwise difficult to control grassweeds for rice cultivation.[6] However, the industrial synthesis of cinmethylin was deemed economically challenging; Coupled with the identification of other highly potent herbicides such as acetohydroxyacid synthase (AHAS), acetyl-coenzyme A carboxylase (ACCase) and very long chain fatty acid (VLCFA) around the same time, cinmethylin production proved to be short lived.[7] However, resistance to these herbicides developed over time, resulting in a need for new herbicides with a new mode of action.[8] In 2018, a new interest in cinmethylin arose from the discovery of a new site of action in which it was

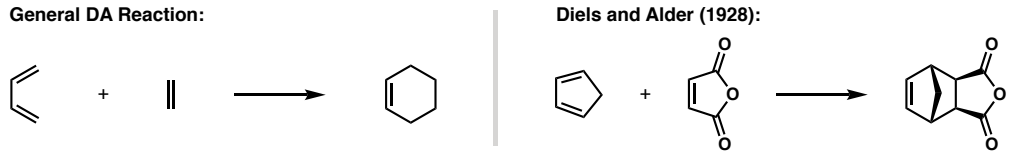
found that cinmethylin binds to acyl-ACP thioesterase and inhibits plant fatty acid biosynthesis.[7] Due to a lack of enantiopure terpinene-4-ol, currently, cinmethylin is produced on an industrial scale through BASF as a racemate despite one enantiomer being significantly more active.[9] Partnering with BASF, we sought to intercept a chiral intermediate en route to cinmethylin and render the synthesis asymmetric. We believed this could be accomplished via a Diels-Alder reaction between isoprene (**9**) and an α–oxygenated captodative dienophile.

Figure 4.2 *Industrial Motivation*



Since its discovery in 1928[10], the [4+2] cycloaddition between diene and dienophile (Diels-Alder reaction) has been established as one of the most powerful synthetic methodologies for the construction of six-membered rings (**Figure 4.3**).[11–15] Immense research effort has been expended studying the reaction and continues to be spent.

Figure 4.3 *Diels-Alder Reaction*

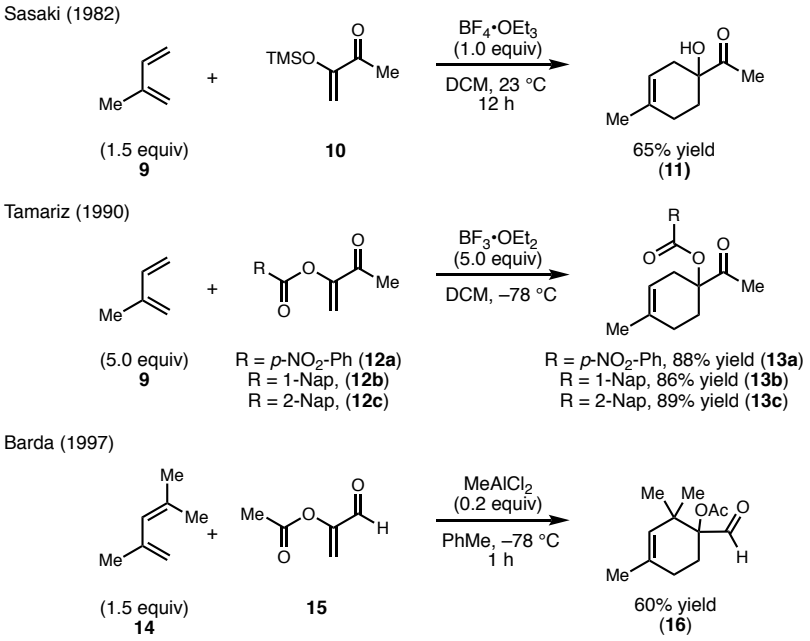


4.2 PRIOR ART

4.2.1 Racemic Examples

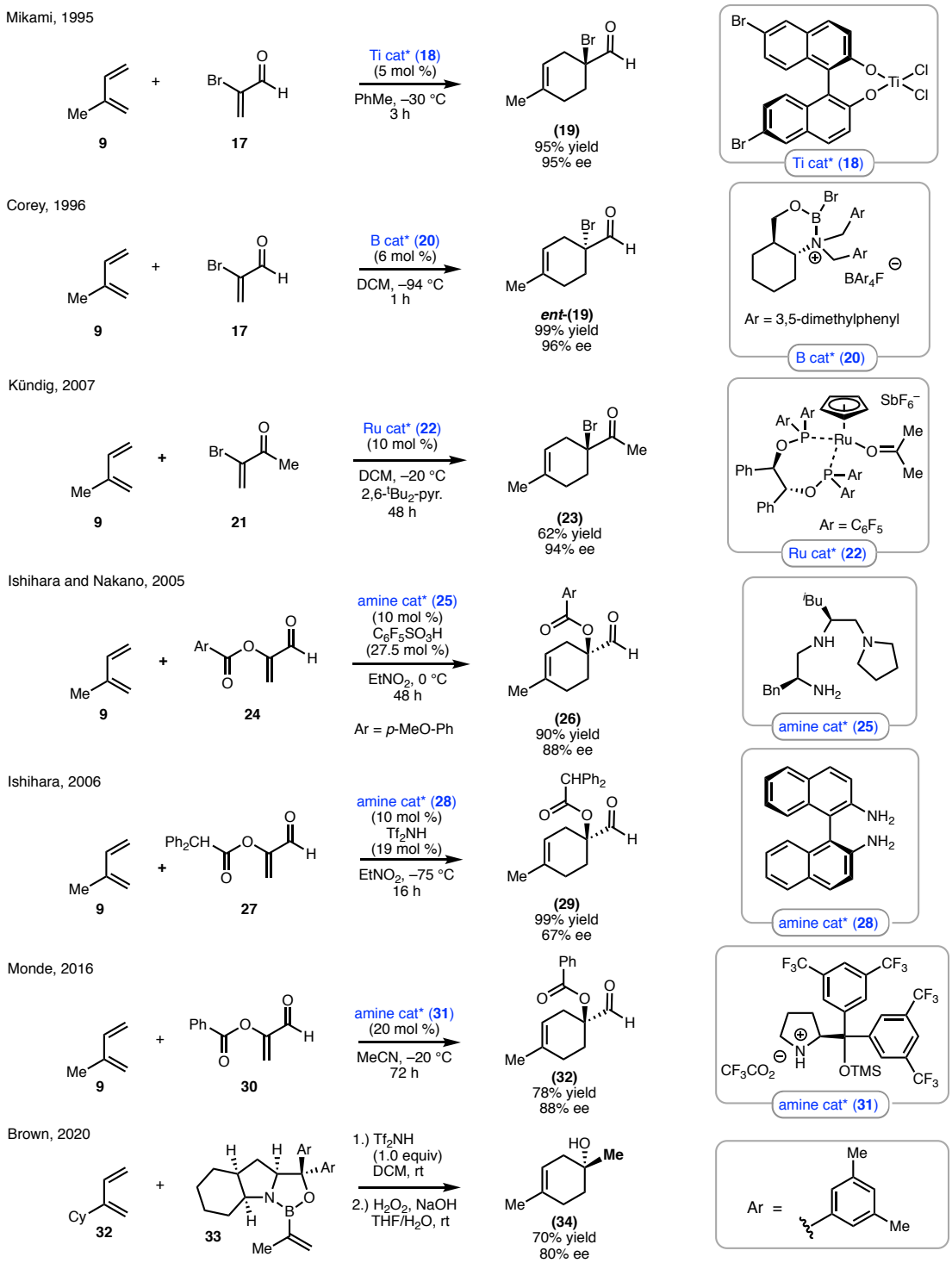
The previously been accomplished in a racemic manner. In 1982, the Sasaki group reported the Diels-Alder reaction of α-silyloxy enone **10** and isoprene **(9)** to deliver α-hydroxyketone product **11** in moderate yield (**Figure 4.4**).[16] In 1990, the Tamariz group was able to expand into α–acyloxy dienophiles.[17] The reaction between isoprene (**9**) and α–oxygenated ester derivatives **12a-c** was shown to deliver cyclohexene products **13a-c** in good yields. Lastly, in 1997, the Barda group demonstrated that $MeAlCl_2$ could also be used to affect a Diels-Alder reaction to deliver **16** in moderate yield.[18]

Figure 4.4 *Racemic Diels-Alder Examples*



4.2.2 Asymmetric Examples

Figure 4.5 *Related Asymmetric Diels-Alder Examples*



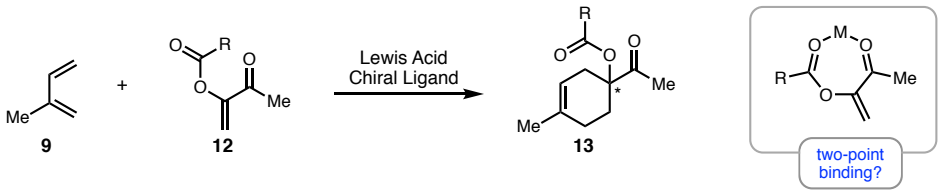
While there have been no reported examples of the desired asymmetric Diels-Alder reaction, there have been several examples of enantioselective [4+2] reactions of captodative dienophiles (**Figure 4.5**). Several examples using α-bromo dienophiles have been reported.[19–21] While these examples provide Diels–Alder products in good yields and ee's, there are currently no methods to stereospecifically convert these to the corresponding tertiary alcohol products. Alternatively, there have been several reports of using α-oxygenated enal dienophiles in the presence of chiral amine catalysts.[22–24] However, these reactions could not be extended into the methyl ketone dienophiles required for the desired transformation. Lastly, in 2020, the Brown group reported the stereoselective cycloaddition of chiral alkenylboranes to afford enantioenriched cyclohexenyl boranes which can be oxidized to the corresponding tertiary alcohols, but stoichiometric chiral borane precursor is a requirement for this methodology.[25]

4.3 METHOD DEVELOPMENT

4.3.1 Proposed Reaction

In our efforts to target the synthesis of **8**, we envisioned using an α-acyloxy dienophile. We reasoned that an α-acyloxy dienophile may form a 7-membered chelate to a Lewis acid catalyst through its two carbonyl oxygens, which should both cloak the intrinsic electron donating property of the ester and provide a sterically-defined environment for asymmetric induction (**Figure 4.6**).[26,27]

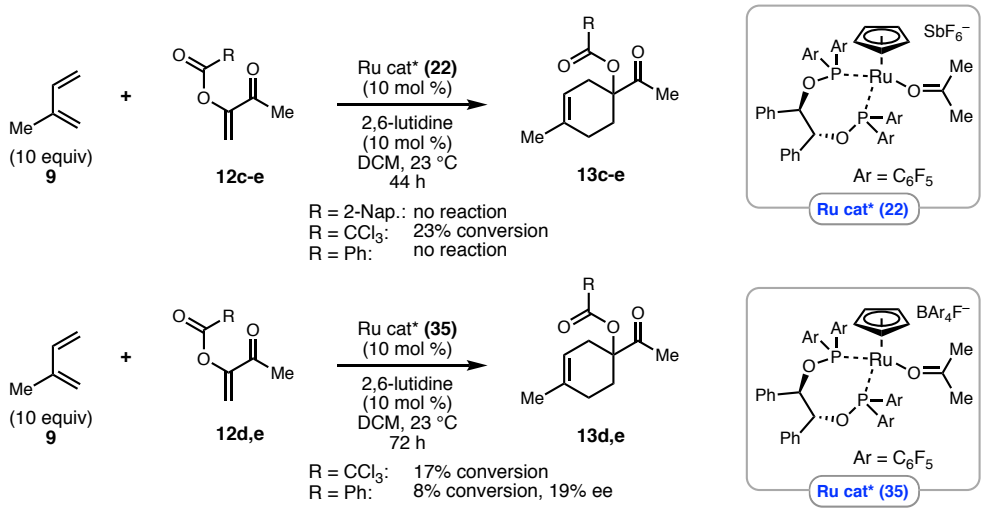
Figure 4.6 *Proposed Reaction*



4.3.2 Early Ruthenium Work

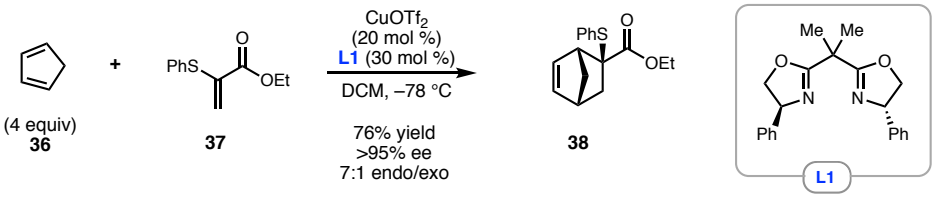
Having recognized a large limitation for most methods to contain only aldehyde dienophiles, we started our search with the only catalyst system known to work with methyl ketone dienophiles (**Figure 4.7**). Applying the catalyst system from Kündig's[21] work to α-acyloxy dienophiles **12c-e** resulted in little to no conversion. Additionally, modifying the salt counterion to tetraarylboronate provided little change in conversion and was demonstrated to be poorly enantioselective.

Figure 4.7 *Attempts to Expand Ru Catalysis Scope*



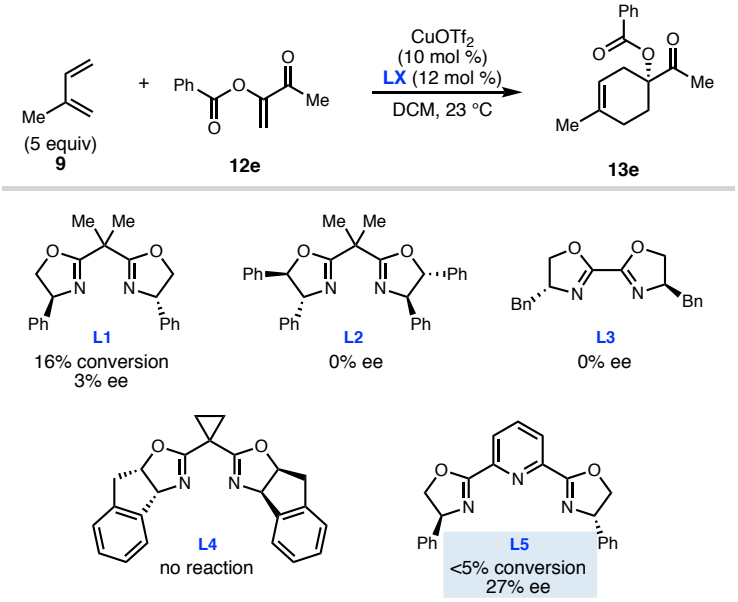
4.3.3 Chiral Lewis Acid Catalysis

Figure 4.8 *Prior Art*



With the idea of two-point binding in mind, we next turned to conditions reported in the literature for the catalytic asymmetric Diels-Alder of α-thioacrylates with cyclopentadiene (**Figure 4.8**).[28] With these conditions in mind, we started off with a brief ligand screen (**Figure 4.9**). While BOX-ligand **L1** gave some conversion, the product was found to be essentially racemic. Further screening identified PyBox ligand **L5** to afford low levels of conversion but in a promising 27% ee.

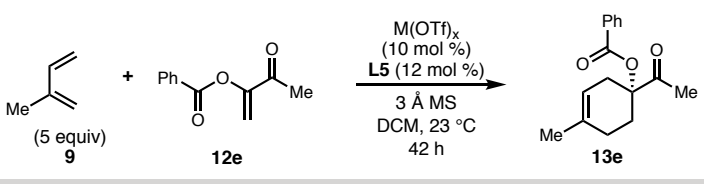
Figure 4.9 *Ligand Screening*

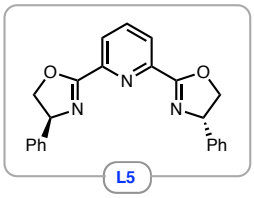


Having identified the PyBOX ligand scaffold as being particularly promising, we elected to investigate the identity of the metal Lewis acid. Looking to other divalent triflate

salts, we found Mg, Zn, and Sc (entries 1-3) all performed poorly, giving little to no enantioselectivity (**Figure 4.10**). Moving to trivalent Sc (entry 4) showed a promising increase in reactivity but again with no enantioselectivity. However, we were pleased to find that moving to lanthanum metals (entries 5-18), we observed both an increase in conversion and enantioselectivity with Yb serving as the optimal catalyst tested giving 65% conversion and 63% ee. It is important to note that 3 Å molecular sieves were used to ensure an anhydrous reaction environment.

Figure 4.10 *Metal Screening*





Entry	$M(OTf)_x$	Conv.	ee	Entry	$M(OTf)_x$	Conv.	ee
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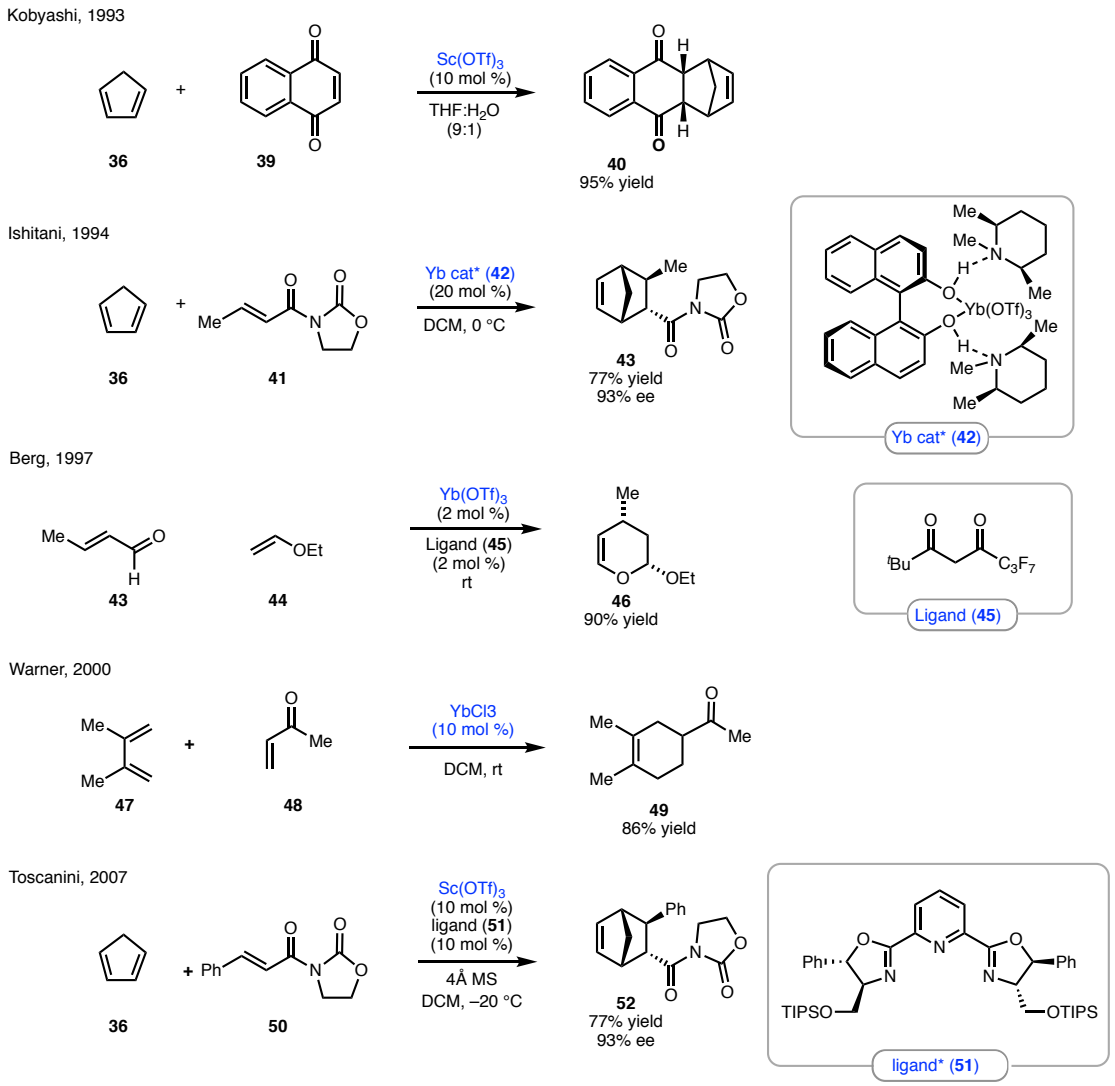
2	$Zn(OTf)_2$	5%	4%	11	$Gd(OTf)_3$	40%	58%
3	$Sn(OTf)_2$	4%	<2%	12	$Tb(OTf)_3$	49%	62%
4	$Sc(OTf)_3$	17%	<2%	13	$Dy(OTf)_3$	35%	41%
5	$La(OTf)_3$	9%	11%	14	$Ho(OTf)_3$	39%	56%
6	$Ce(OTf)_3$	18%	19%	15	$Er(OTf)_3$	21%	28%
7	$Pr(OTf)_3$	29%	43%	16	$Tm(OTf)_3$	44%	49%
8	$Nd(OTf)_3$	22%	39%	17	$Yb(OTf)_3$	65%	63%
9	$Sm(OTf)_3$	35%	46%	18	$Lu(OTf)_3$	47%	47%

The use of lathanide salts as catalysts for DA reactions is well precedented (**Figure 4.11**). In 1993, Kobayashi showed that $Sc(OTf)_3$ could be used to catalyze the reaction between cyclopentadiene **(36)** and dienophile **39** to give **40** in good yield.[29] In 1994, Ishitani and coworkers demonstrated that a chiral BINOL ligated ytterbium(III) complex could catalyst the asymmetric DA reaction between **36** and **41** to afford cycloadduct **43** in good yield and ee.[30] Racemically, Yb has been shown to be a useful catalyst for both the DA reaction and hetero-Diels–Alder reaction.[31,32] Lastly, Toscianini showed in 2007 that

chiral PyBox frameworks were useful in developing an asymmetric scandium(III)-catalyzed DA reaction between **36** and **50**.[33]

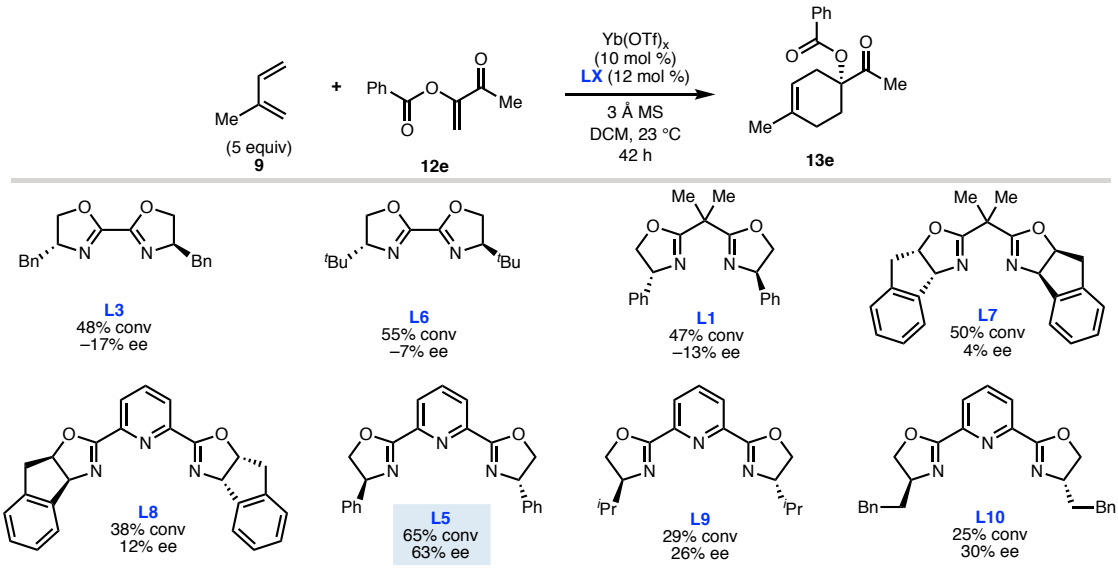
Figure 4.11 *Prior Art in Lathanides Catalysis for Diels–Alder Reactions*



Having identified an optimal metal salt, the ligand identity was then revisited (**Figure 4.12**). BiOX ligands gave good levels of conversion but with poor enantioselectivity. BOX ligands similarly saw good levels of reactivity but with low

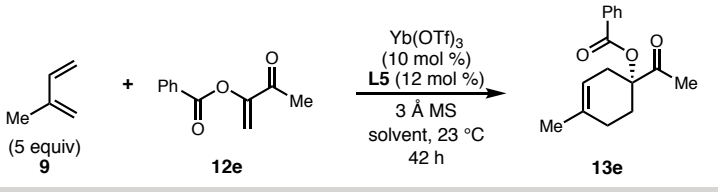
enantioselectivity. Returning to PyBox systems, we observe the best results with Ph-PyBox ligand **L5**.

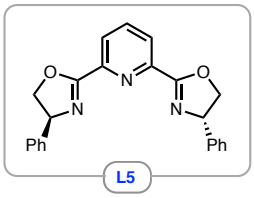
Figure 4.12 *Ligand Screening*



Additional attempts to increase reactivity and enantioselectivity by adjusting solvent were unsuccessful. Amongst various halogenated solvents (entries 1-5), DCM remained superior (**Figure 4.13**). Exploring ethereal solvents (entries 8-14) again led to inferior levels of conversion and enantioselectivity.

Figure 4.13 *Solvent Screening*

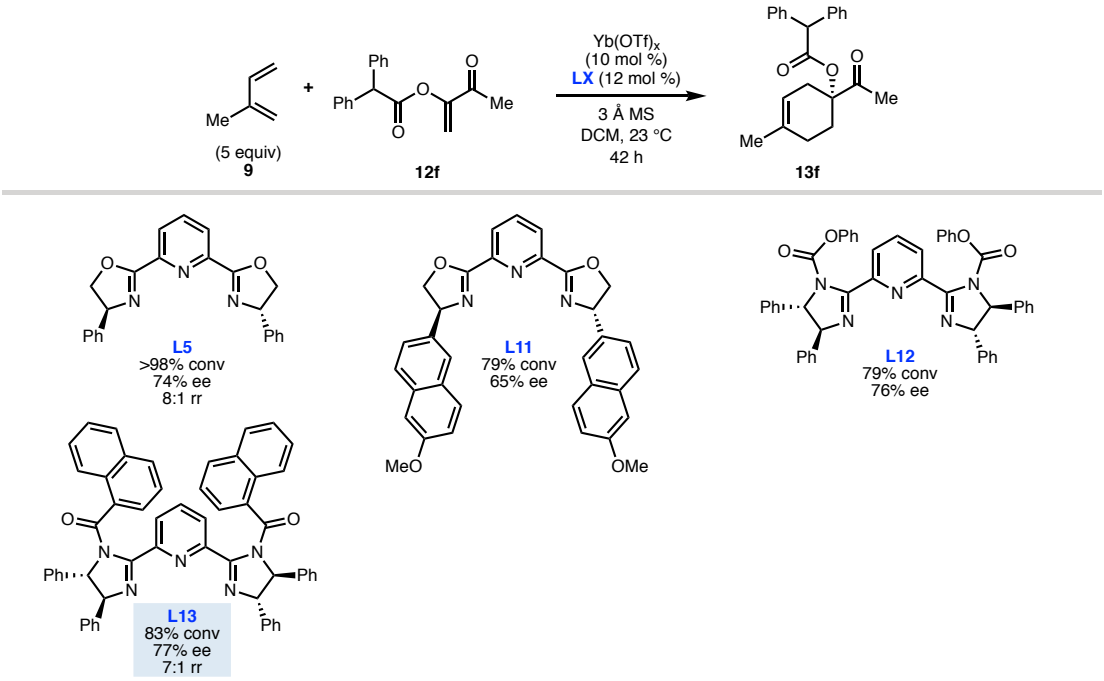




Entry	Solvent	Conv.	ee	Entry	Solvent	Conv.	ee
1	DCM	65%	63%	8	THF	–	29%
2	1,2-DCE	50%	50%	9	MTBE	54%	58%
3	$CDCl_3$	46%	66%	10	Et_2O	46%	53%
4	CCl_4	22%	27%	11	1,4-dioxane	34%	58%
5	trichloroethylene	33%	40%	12	2,5-dimethyl-THF	29%	49%
6	MeCN	–	–5%	13	CPME	48%	50%
7	PhMe	–	25%	14	$^{i}Pr_2O$	10%	35%

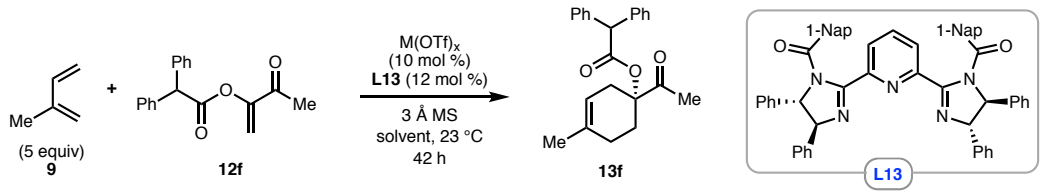
With dichloromethane proving to be the most promising solvent, we next investigated additional ligands in hopes of increasing reactivity and enantioselectivity. Further exploration into alternative PyBox ligands such as **L11** proved unsuccessful (**Figure 4.14**). However, we were pleased to find that moving into a structurally similar tridentate pyridinebisimidazoline (PyBim)[34] framework afforded improved levels of enantioselectivity with ligand **L13** as the optimal ligand.

Figure 4.14 *Ligand Screening*



With **L13** as the optimal ligand, we once again investigated the effect of metal identity and solvent on the reaction (**Figure 4.15**). It was found that moving to yttrium in DCM afforded full conversion with up to 85% ee (entry 3). It was also found that PhCl as a solvent afforded the desired product in excellent enantioselectivity (entry 4).

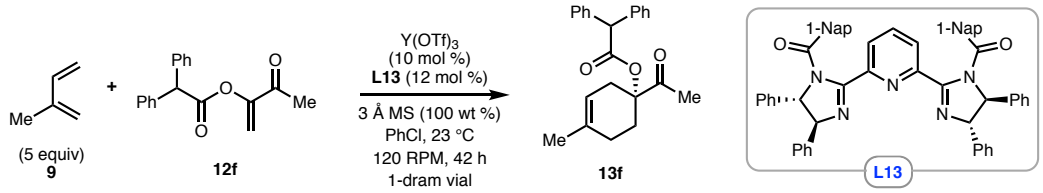
Figure 4.15 *Additional Optimization*



Entry	$M(OTf)_x$	Solvent	Conv.	ee
1	$Yb(OTf)_3$	DCM	83%	77%
2	$Sc(OTf)_3$	DCM	93%	57%
3	$Y(OTf)_3$	DCM	>98%	85%
4	$Y(OTf)_3$	PhCl	93%	87%

Additionally, we were interested to understand the role of molecular sieves in the reaction. We had hypothesized that trace water could potentially cause quenching of the yttrium catalyst and therefore we believed adding molecular sieves could prevent this issue. However, we noticed that there was irreproducibility in the reaction and thought that perhaps the heterogeneity of the molecular sieves could be causing issues. To this end, we studied how changing the amount of molecular sieves and how the stirring rate could affect the reaction. Interestingly, it was found that removal of molecular sieves was beneficial to the reaction (**Figure 4.16**).

Figure 4.16 *Additional Optimization*



Entry	Deviation	Conv.	ee
1	none	79%	84%
2	fast stirring	77%	84%
3	1/2-dram vial	52%	78%
4	No MS	>98%	90%
5	excess MS	52%	78%

4.4 SCOPE EXPLORATION

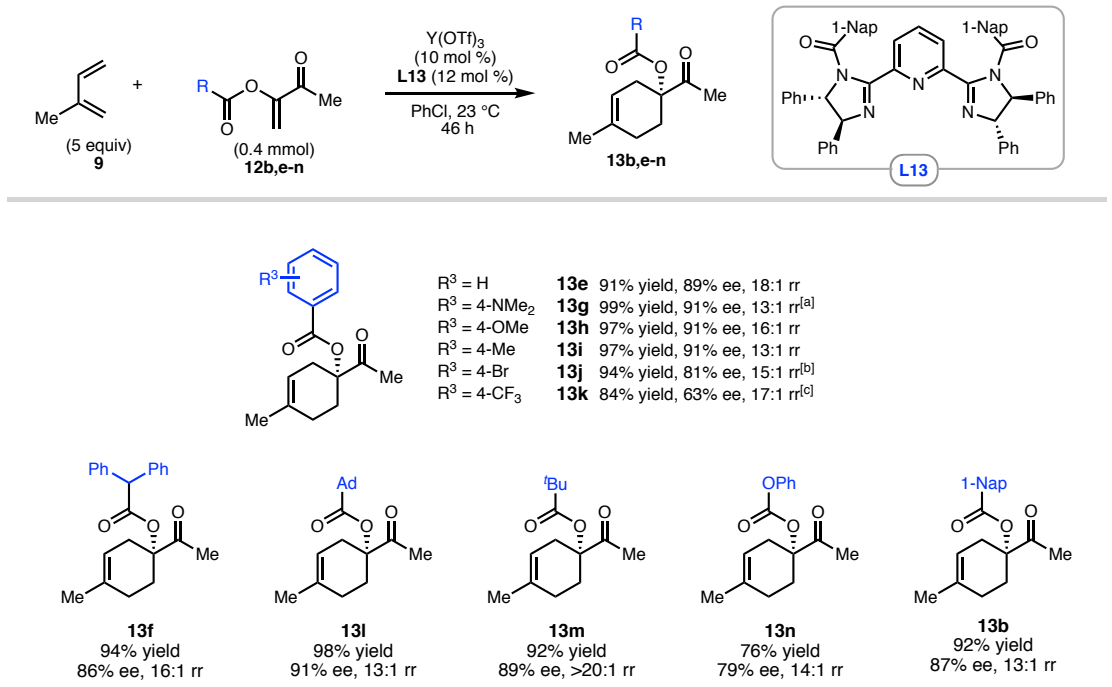
4.4.1 Ester Scope

With optimized conditions in hand, we next interrogated the influence of the ester substituent on the yield and ee of the reaction (Figure **4.17**). A series of benzoate esters revealed that esters with electron donating substituents in the para position perform best in terms of enantio- and regioselectivity (**13e,g-i**). Electron deficient benzoate esters required

long reaction times to achieve high conversion and the products were formed in lower ee (**13j,k**). We hypothesized that the lower enantioselectivity may result from dienophile hydrolysis by adventitious water during the extended reaction times, which produces the corresponding benzoic acid. Thus, we tested this hypothesis by doping in exogenous benzoic acid into the standard reaction and found a decrease in both yield and ee (51% yield, 37% ee). Given this finding, we tested whether catalyst deactivation was operative with slow-reacting dienophiles. Indeed, the results of a same excess experiment for the reaction between **9** and **12j** were consistent with catalyst deactivation over time (**Figure 4.18**).[35]

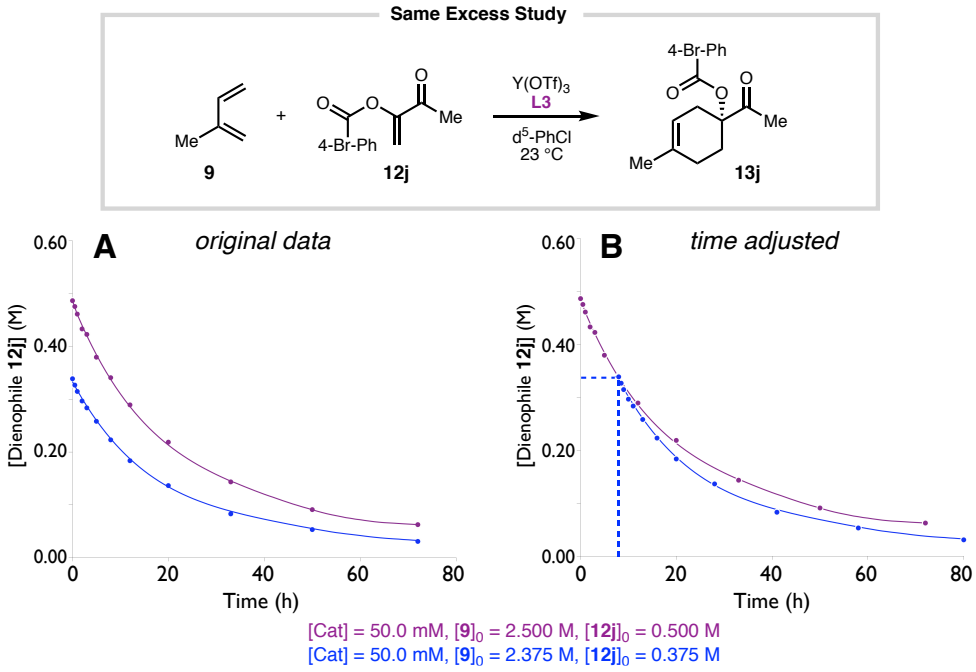
Sterically encumbered aliphatic esters also performed well, giving the corresponding products in good yield and high ee (**13f,l-m**). The phenyl carbonate dienophile could also be used; however, the product was formed in lower yield and ee (**13n**). The reaction to give cycloadduct **13f** was scaled to 1.0 mmol with no decrease in yield or selectivity (92% yield, 86% ee, 16:1 rr).

Figure 4.17 *Ester Scope*



[a] Reaction time of 3 days. [b] Reaction time of 5 days. [c] Reaction time of 14 days.

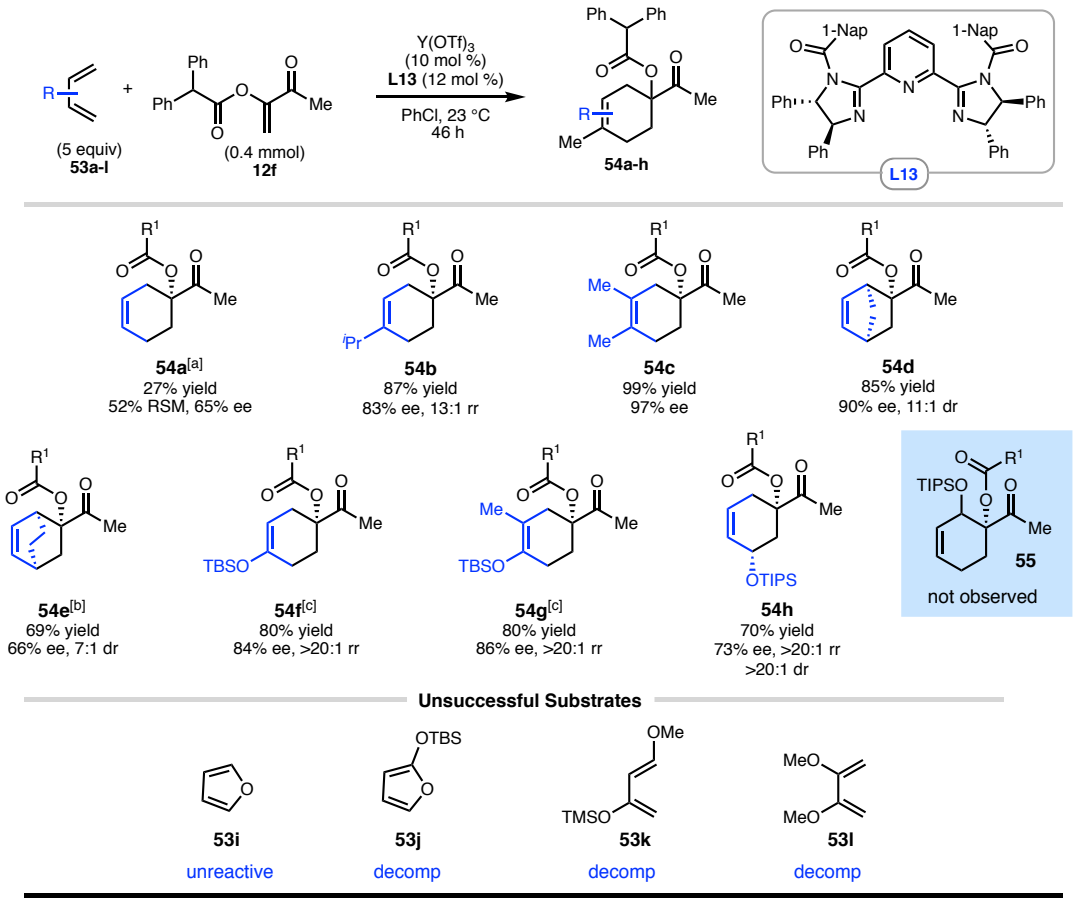
Figure 4.18 *Same Excess Study Between* ***9*** *and* ***12j***



4.4.2 Diene Scope

Next, we investigated the diene scope (Figure **4.19**). For these studies, dienophile **12f** was used due to its ease of handling. Although the simple 1,3-butadiene undergoes cycloaddition, the reaction was very slow and the product (**54a**) was formed in low yield with poor ee. Substitution at the 2-position of the diene with isopropyl is tolerated with only a minor decrease in ee (**54b**) compared to **13f**. 2,3-dimethylbutadiene was found to be an excellent substrate, providing product **54c** in 99% yield and 97% ee. Whereas cyclopentadiene undergoes cycloaddition to form **54d** in high yield, ee, and dr favoring the endo-cycloadduct, the corresponding cyclohexa-1,3-diene is less reactive and the product is formed in lower ee (**54e**). Electron-rich 2-silyloxy dienes also perform well (**54f,g**), giving products with high regioselectivity and comparable ee to **13f**. In contrast, slightly lower ee is observed when the 1-silyloxydiene is employed (**13h**). However, it is noteworthy that the reaction with 1-silyloxydiene **53** gives the cycloadduct with regioselectivity opposite to its electronic bias. We hypothesize that this occurs due to a steric repulsion effect between the large TIPS group of the diene and the ligand of our catalyst. Indeed, it was found that reaction of **53f** with **12f** in the presence of $Sc(OTf)_3$ in the absence of ligand delivers the electronically matched product **55**. Unsuccessful diene substrates include furan **53i**, which was unreactive, and dienes **53j-l**, which suffered from decomposition under the reaction conditions despite the use of varied temperatures and catalyst loading.

Figure 4.19 *Diene Scope*



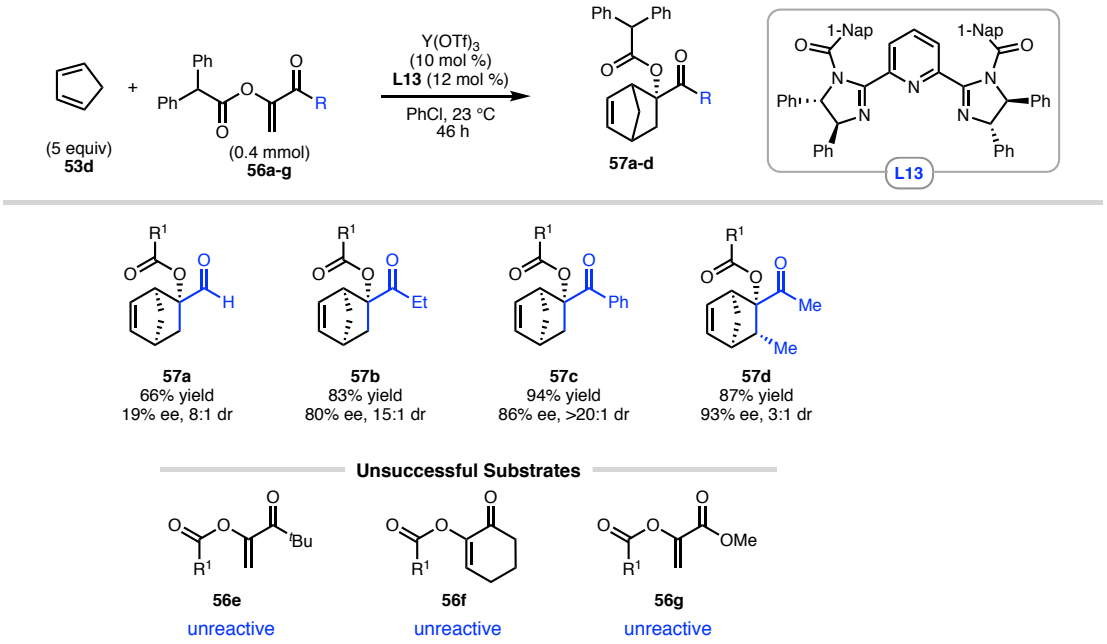
[a] Reaction time of 18 days. [b] Reaction time of 13 days. [c] Reaction performed at 0 °C.

4.4.3 Dienophile Scope

We lastly turned to investigate different dienophiles (**Figure 4.20**). In general, increasing the steric bulk of the ketone decreased the reaction rates; however, when the more reactive cyclopentadiene was used, good reactivity could be achieved. Aldehyde **56a** was found to react but gave the product **57a** in with low selectivity presumably due to a lack of steric bias. Dienophiles **56b** and **56c** gave the respective cycloadducts in good yield, albeit with slightly lower ee than when **12f** is employed. Dienophile **56d**, with a β- methyl group, underwent the cycloaddition in good yield and ee, but only modest selectivity for the endo-diastereomer was observed (**57d**). Further increasing of the steric bulk to tert-

butyl (**56e**) gave no conversion. Additionally, cyclic dienophile **56f** as well as ester **56g** were not tolerated.

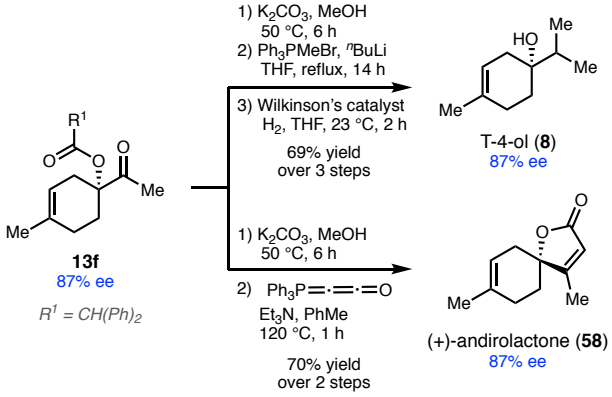
Figure 4.20 *Ketone Scope*



4.4.4 Product Utility

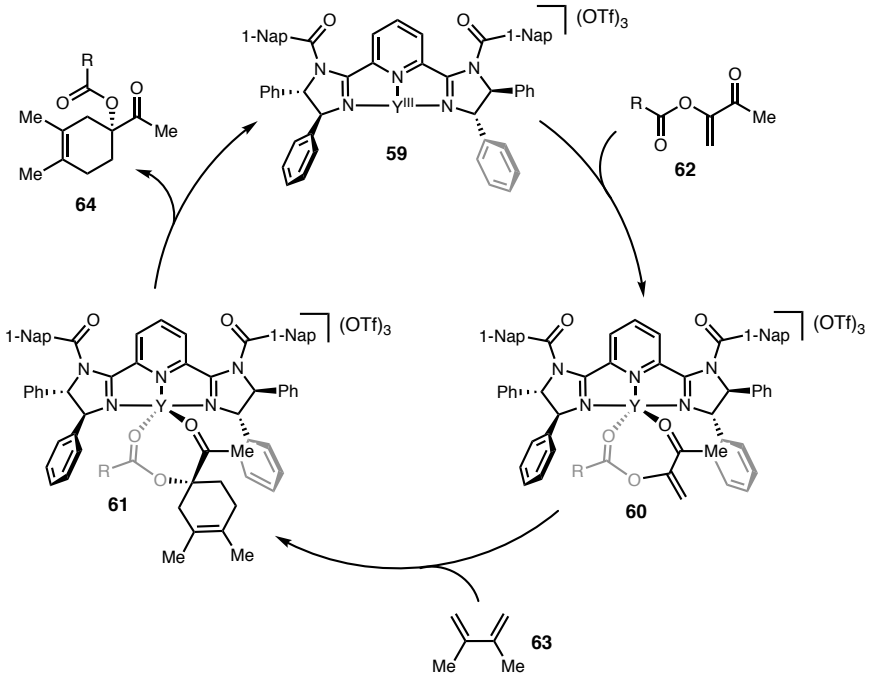
To demonstrate the synthetic utility of these products, we elaborated **13f** to **8**, the key intermediate in the BASF synthesis of cinmethylin (**Scheme 1**). Although cinmethylin is chiral, it is currently manufactured as a racemate;[36] however, with the changing regulatory landscape, an enantioselective synthesis is of high value. To this end, methanolysis of **13f** followed by Wittig olefination and subsequent hydrogenation afforded **8** in good yield with preservation of ee. Alternatively, the natural product (+)-andirolactone (**58**)[37] could be prepared by methanolysis of **13f** followed by reaction with Bestmann ylide[38], also with complete retention of ee.

Scheme 1. *Product Derivatization*



4.5 MECHANISTIC STUDIES

Figure 4.21 *Proposed Catalytic Cycle*

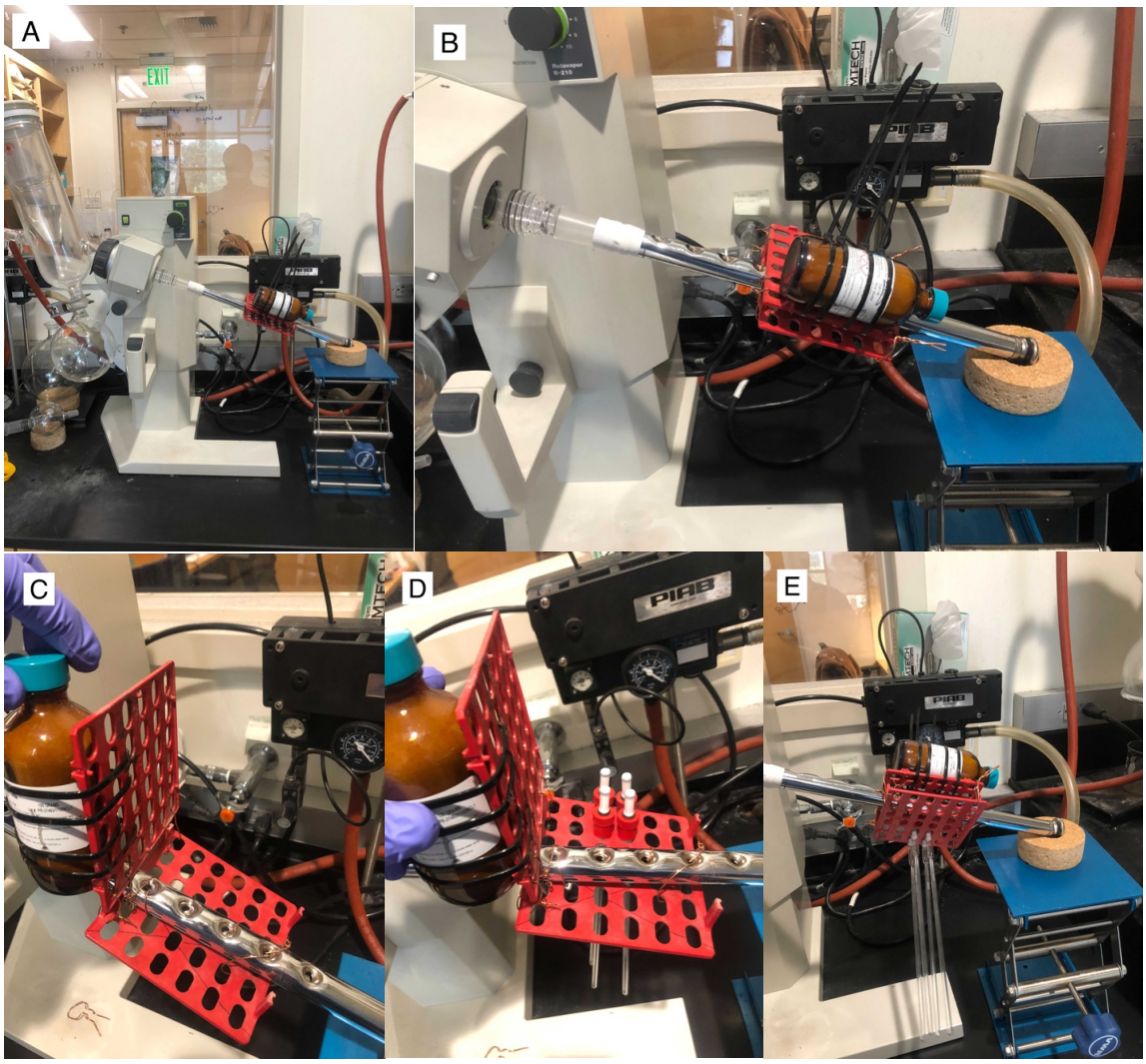


We next turned to investigate the mechanism of this transformation (**Figure 4.21**). We hypothesized that ligated yttrium(III) complex **59** could first undergo coordination to dienophile **62** via a seven-membered chelation to give **60** which could activate the enone carbonyl and establish a sterically well-defined geometry of the dienophile. Next, a

cycloaddition with diene **63** would afford cycloadduct **64** bound to the yttrium catalyst. Lastly, product dissociation would then turn over the catalytic cycle.

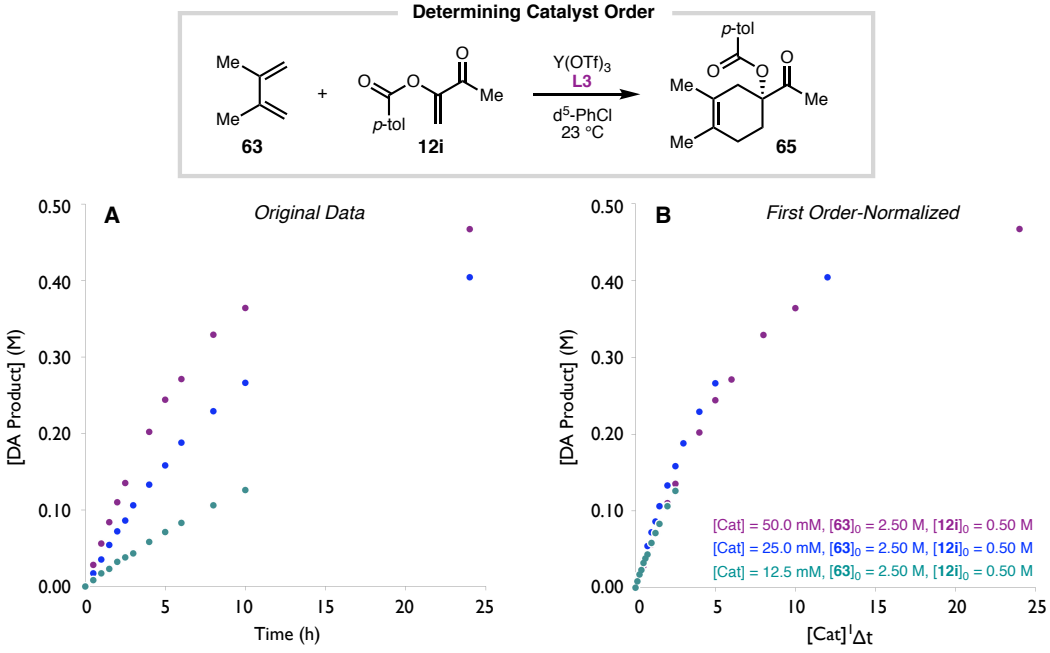
To interrogate this mechanistic hypothesis, we first performed kinetic studies using variable time normalization analysis (VTNA), a technique developed by Jordie Bures.[39] To run these kinetics experiments, we first needed to develop an experimental set up to acquire our data. We elected to utilize NMR as a method of obtaining concentration of each species over time given the ability to use a sealed tube which would prevent the loss of any volatile diene over the course of the reaction. However, given the heterogeneous nature of the reaction, we required a setup which would allow good stirring of the reaction. To achieve this, we used a combination of J-Young tubes and a rotoray evaporator. Specifically, J-Young tubes were rotated using the setup shown below (**Figure 4.22**). First, a small test tube rack was cut horizontally to allow a top and bottom half. Along one edge, copper wire was used to make small hinges such that the tube rack would be allowed to open and close (similar to a book). The bottom half of this rack was then affixed to a stool leg using copper wire such that the stool leg would exist between the two rack layers (**Figure 4.22C**). J-Young tubes could then be inserted into the holes to rest (**Figure 4.22D**). The top rack layer could then close over the tops of the J-Young tubes and was held together by copper wire. It was found that the installation of a counterweight (small glass bottle filled with sand) was necessary to achieve slow enough sample rotation for solid suspension. The stool leg was then attached to the rotovap with electrical tape while the other end rested on a cork ring (allowing for smooth rotation).

Figure 4.22 *Experimental Setup for Kinetics Studies*



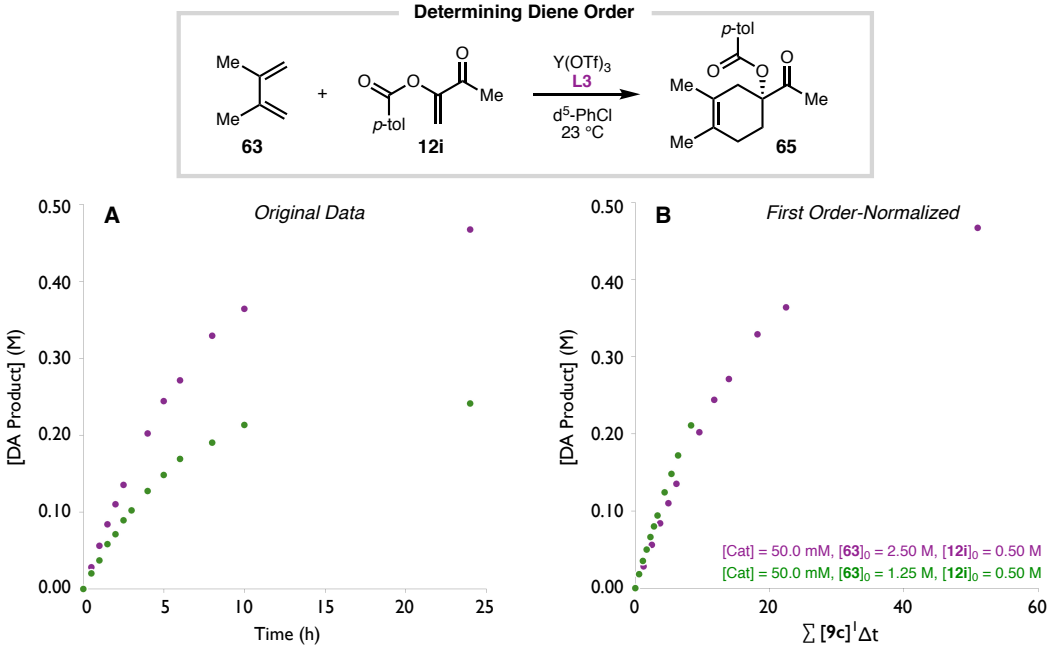
With a proper experimental setup finally developed, we began studying the kinetics of our reaction. We elected to study the reaction between dienophile **12i** and diene **63** as this combination gave good levels of both yield and ee. We began by studying the effect of catalyst loading on the rate of the reaction. The standard reaction was run with 10 mol % catalyst (**Figure 4.23**, plum). From there, we lowered the catalyst down to 5 (blue) and 2.5 mol % (teal). Normalizing this data with first order approximation in catalyst revealed graphical overlay of the data allowing us to conclude that the data is consistent with first order kinetics in catalyst.

Figure 4.23 *Determining Order in Catalyst*



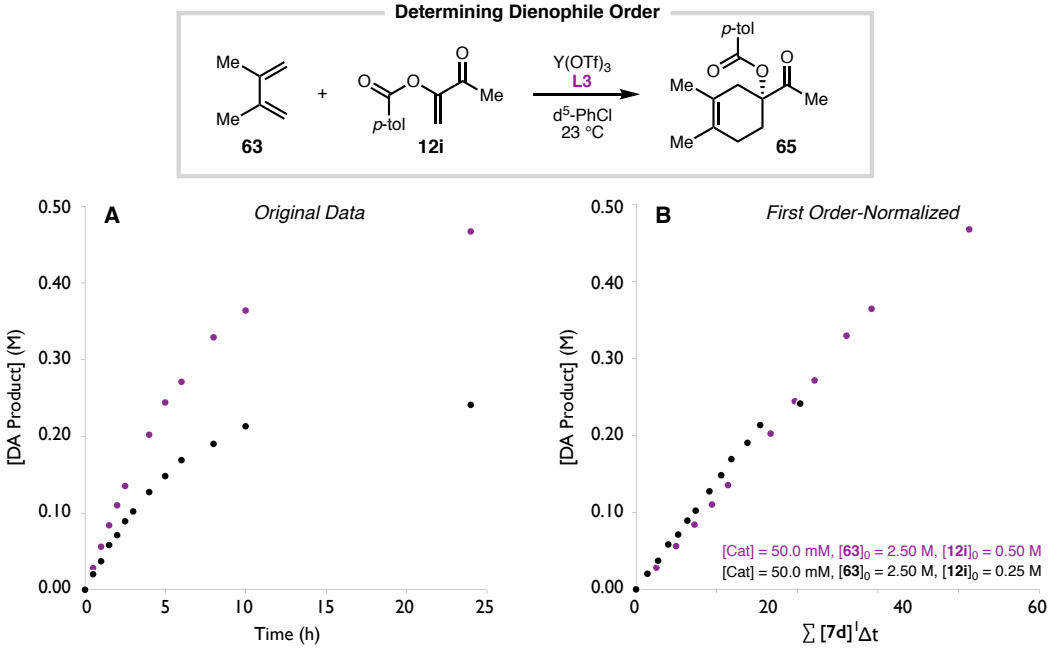
We next studied the effect of diene concentration on the rate of the reaction. The standard reaction was run with diene **63** at 2.50 M (**Figure 4.24**, plum). From there, we lowered the diene concentration down to 1.25 M (green). Normalizing this data with first order approximation in catalyst revealed graphical overlay of the data allowing us to conclude that the data is consistent with first order kinetics in diene.

Figure 4.24 *Determining Order in Diene*



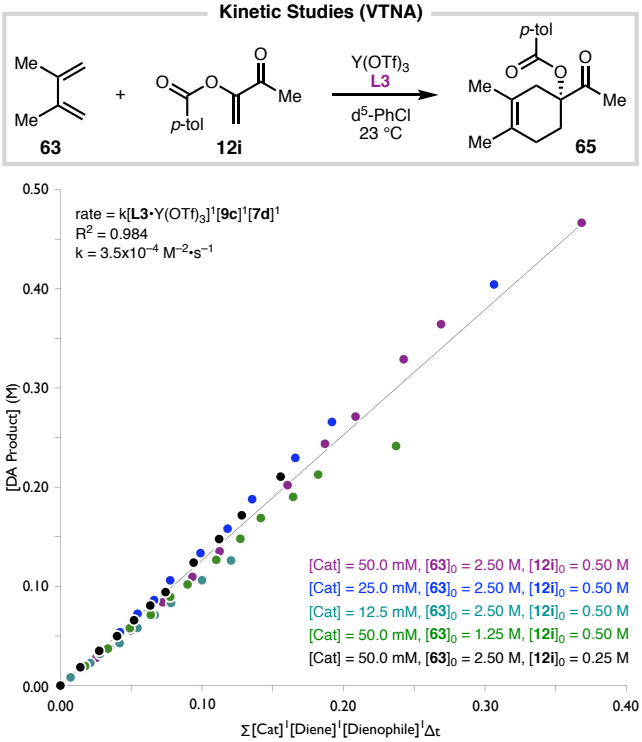
Lastly, we next studied the effect of dienophile concentration on the rate of the reaction. The standard reaction was run with dienophile **12i** at 0.50 M (**Figure 4.25,** plum). From there, we lowered the dienophile concentration down to 0.25 M (green). Normalizing this data with first order approximation in catalyst revealed graphical overlay of the data allowing us to conclude that the data is consistent with first order kinetics in dienophile.

Figure 4.25 *Determining Order in Dienophile*



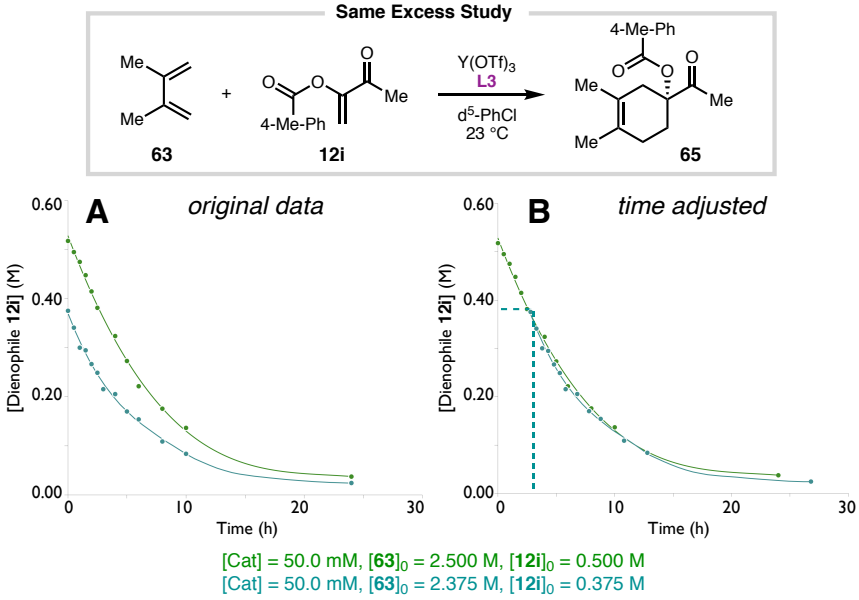
In summary, it was found that the reaction displays an observed first order dependence on catalyst, first order dependence on dienophile **12i**, and first order dependence on diene **63**. This observation is consistent with the proposed mechanism and provides evidence in support of **59** being the resting state of the catalyst and cycloaddition between **60** and diene **63** as being the rate-determining step. When the data was fully normalized with respect to all components (catalyst, diene, and dienophile) a linear trend was observed which is self-consistent with our earlier assignments of the order in each component (**Figure 4.26**). Additionally, from a linear model fit to this data, we were able to extract a calculated rate constant of 3.5 X 10^{-4} M^{-2}•s^{-1}.

Figure 4.26 *Fully Normalized Kinetics Data*



Additionally, we wanted to determine if catalyst inhibition was operative under the reaction conditions. To this end, we performed a same excess study between **65** and **12i** and found no evidence for significant catalyst deactivation over the course of the reaction (**Figure 4.27**).

Figure 4.27 *Same Excess Study Between* ***63*** *and* ***12i***



4.6 CONCLUDING REMARKS

In summary, we have developed an enantioselective Diels–Alder reaction of α–acyloxy enone dienophiles. This method has been shown to be tolerant of a variety of dienophiles and dienes. Additionally, the products of this transformation can be used to generate enantioenriched terpenes which as relevant to the agrochemical industry. Mechanistically, the reaction is believed to have a free catalyst as a resting state with cycloaddition as the rate-determining step.

4.7 EXPERIMENTAL SECTION

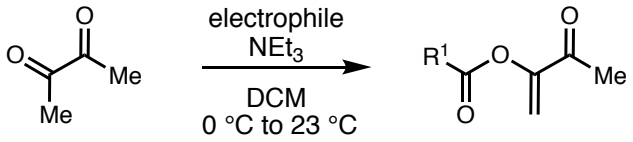
General Information

4.7.1 Materials and Methods

Unless otherwise stated, reactions were performed with freshly dried solvents utilizing standard Schlenk techniques. Glassware was oven-dried at 120 °C for a minimum of four hours or flame-dried utilizing a Bunsen burner under high vacuum. THF, DCM, MeCN, PhH, and PhMe were dried by passing through activated alumina columns. PyBim ligands were synthesized using the procedure reported by Beller and coworkers.[40] MeOH (HPLC grade) was purchased from Fisher Scientific. Chlorobenzene, anhydrous 99.8%, was purchased from Millipore Sigma. DCE, Et_3N, *i*-Pr_2NH, DIPEA, Pyr, and 2,6- lutidine were distilled from calcium hydride prior to use and stored under N_2 or Ar. Commercial reagents were used directly as supplied from commercial sources and without further purification unless otherwise specified. 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 (254 nm) and $KMnO_4$, p-anisaldehyde, iodine, or CAM staining. Flash column chromatography was performed as described by Still et al.[41] using silica gel (SiliaFlash® P60, particle size 40-63 microns [230 to 400 mesh]) purchased from Silicycle. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance III HD with Prodigy Cryoprobe (at 400 MHz and 101 MHz, respectively) or Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to internal $CDCl_3$ (^1H, $\delta = 7.26$), $CDCl_3$ (^{13}C, $\delta = 77.16$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations

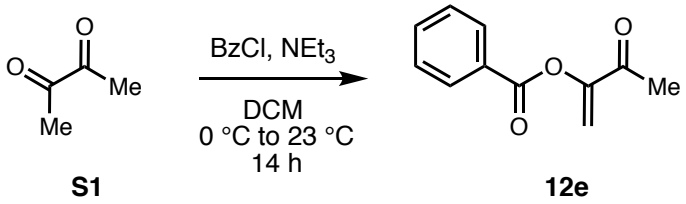
are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system (CO_2 = 1450 psi, column temperature = 40 °C) with either a Chiralcel IC column (4.6 mm x 25 cm), a Chiralcel AD-H column (4.6 mm x 25 cm), or a Chiralcel OJ-H column (4.6 mm x 25 cm). Molecular formulas of the compounds [M] are given, with the observed ion fragment in brackets, e.g. [M+H]+. Benzoyl chloride, diphenylacetyl chloride, Ytterbium(III) triflate, 2,6-bis[(4*S*)-4-phenyl-2-oxazolinyl]pyridine and 2,6-Bis((*S*)-4,5-dihydro-4-phenethyloxazol-2-yl)pyridine were purchased from Millipore Sigma and used as received. Isoprene was purchased from Millipore Sigma and distilled prior to use. Diacetyl was purchased from TCI America and used as received. Yttrium(III) triflate, lanthanum(III) triflate, cerium(III) triflate, praseodymium(III) triflate, neodymium(III) triflate, europium(III) triflate, gadolinium(III) triflate, terbium(III) triflate, dysprosium(III) triflate, holmium(III) triflate, erbium(III) triflate, and lutetium(III) triflate were purchased from Strem Chemicals, Inc. and used as received. Scandium(III) triflate, samarium(III) triflate, and ytterbium(III) triflate were purchased from Millipore Sigma and used as received. Deuteriochloroform was purchased from Cambridge Isotope Laboratories. Deuteriochlorobenzene was purchased from Sigma-Aldrich. The 3Å molecular sieve was purchased from Millipore Sigma and activated by heating under a flame at reduced pressure (100 mTorr) for 20 minutes prior to use.

4.7.2 Dienophile Preparation



General Procedure A: To a dry round-bottomed flask, equipped with a magnetic stir bar, was added diketone (1.0 equiv), triethylamine (1.2 equiv) and dry DCM. To this solution was added electrophile (1.0 equiv) at 0 °C under N_2. The reaction was allowed to slowly warm to 23 °C and monitored by TLC. Upon completion, hexanes (volume = reaction volume) was added, and the reaction mixture was filtered through a plug of celite. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography.

3-oxobut-1-en-2-yl benzoate (12e)



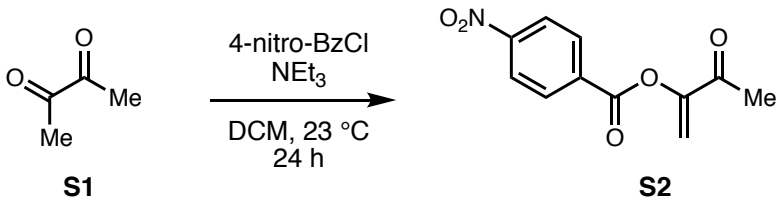
S1 **12e**

Prepared from diacetyl **S1** (2.62 mL, 30.0 mmol, 1.0 equiv.), triethylamine (5.02 mL, 36.0 mmol, 1.2 equiv.), benzoyl chloride (3.48 mL, 30.0 mmol, 1.0 equiv), and dry DCM (35 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 EtOAc/hexanes → 1:10 EtOAc/hexanes) to afford **12e** (2.38 g, 12.5 mmol, 42%) as a

yellow oil which solidifies upon storage at –20 °C. Spectroscopic data matched previously reported values.[42]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 7.0, 1.4 Hz, 2H), 7.74 – 7.56 (m, 1H), 7.56 – 7.40 (m, 2H), 6.04 (d, *J* = 2.4 Hz, 1H), 5.74 (d, *J* = 2.4 Hz, 1H), 2.42 (s, 3H).

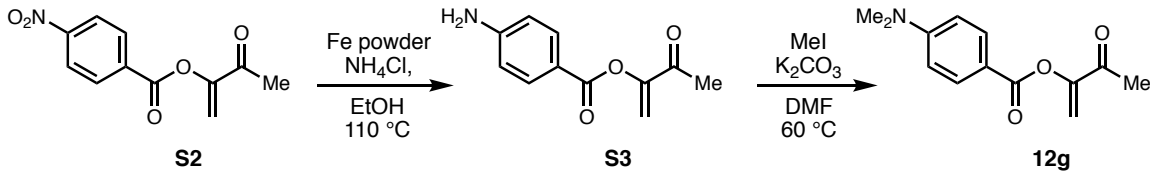
3-oxobut-1-en-2-yl 4-nitrobenzoate (S2):



Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), 4-nitro-benzoyl chloride (2.78 g, 15.0 mmol, 1.0 equiv), and dry DCM (35 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 to 1:10 EtOAc/hexanes) to afford **S2** (2.99 mg, 12.75 mmol, 85%) as a white solid. Spectroscopic data matched previously reported values.[42]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 – 8.26 (m, 4H), 6.10 (d, *J* = 2.7 Hz, 1H), 5.85 (d, *J* = 2.8 Hz, 1H), 2.45 (s, 3H).

3-oxobut-1-en-2-yl 4-(dimethylamino)- benzoate (12g):



S2 **S3** **12g**

Procedure: To an oven-dried 150 mL pressure flask, equipped with a stir bar, was added **S2** (4.00 g, 17.0 mmol, 1.0 equiv) followed by ethanol (90 mL). The mixture was heated in a preheated oil bath (110 °C) until **S2** dissolved (~5 min). Next, iron powder (9.5 g, 170 mmol, 10 equiv) added followed by a solution of NH_4Cl (9.1 g, 170 mmol, 10 equiv) in water (27 mL). The resulting suspension was heated at reflux for 10 mins (110 °C). The hot mixture was then filtered through a Celite pad. The residue was dissolved in EtOAc and washed with H_2O (30 mL), and the aqueous phase was further extracted with EtOAc (2 × 20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated under vacuum. Residue was subjected to silica gel column chromatography (50% EtOAc/hexanes) to afford **S3** (440 mg, 2.21 mmol, 13% yield).

Procedure: To an oven-dried 2-dram vial, equipped with a stir bar, was added **S3** (420 mg, 2.05 mmol, 1.0 equiv), and K_2CO_3 (622 mg, 4.5 mmol, 2.2 equiv) in DMF (4.1 mL). To this was added MeI (280 uL, 4.5 mmol, 2.2 equiv). Reaction then capped and heated to 60 °C overnight. Reaction was quenched with water and extracted with EtOAc (3 x 10 mL). Washed with brine, dried over $MgSO_4$, filtered, and concentrated. Residue subjected to silica gel column chromatography (40% EtOAc/hexanes) to afford **12g** (276 mg, 1.19 mmol, 58%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 6.74 – 6.65 (m, 2H), 5.97 (d, *J* = 2.0 Hz, 1H), 5.62 (d, *J* = 2.0 Hz, 1H), 3.07 (s, 6H), 2.37 (s, 3H).

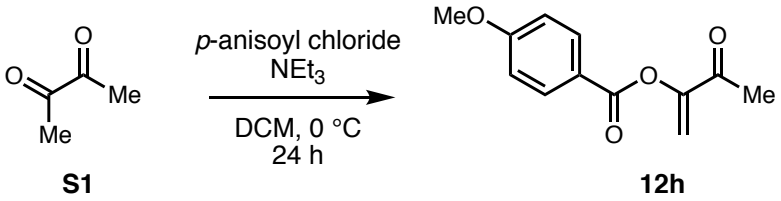
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.84, 165.08, 153.86, 152.19, 132.27, 115.38, 113.07, 111.12, 40.33, 25.86.

FTIR (NaCl, thin film, cm^{-1}): 2911, 1713, 1688, 1652, 1614, 1379, 1274, 1184, 1125, 1080, 939

HRMS (GC-EI+, m/z): calc'd for $C_{13}H_{15}NO_3$ 233.1052 $[M\bullet]^+$; found: 233.1058

R_f = 0.54 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

3-oxobut-1-en-2-yl 4-methoxybenzoate (12h):



S1 **12h**

Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), *p*-anisoyl chloride (2.56 g, 15.0 mmol, 1.0 equiv), and dry DCM (35 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:1 DCM/hexanes) to afford **7c** (495 mg, 2.25 mmol, 15%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 7.99 (m, 2H), 7.02 – 6.89 (m, 2H), 6.01 (d, *J* = 2.3 Hz, 1H), 5.69 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 3H), 2.39 (s, 3H).

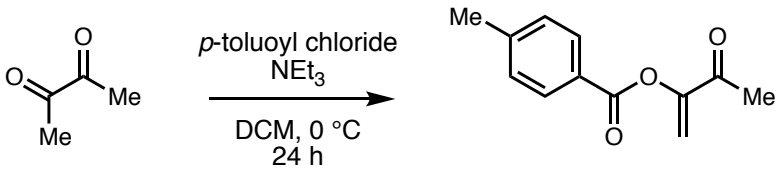
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.18, 164.21, 152.01, 132.25, 121.05, 113.82, 55.65, 25.76.

FTIR (NaCl, thin film, cm^{-1}): 3627, 3382, 3127, 3006, 2940, 2842, 1714, 1600, 1504, 1371, 1122, 1019, 971, 852, 762, 692

HRMS (GC-EI+, m/z): calc'd for $C_{12}H_{12}O_4$ 220.0736 $[M\bullet]^+$; found: 220.0748

R_f = 0.58 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

3-oxobut-1-en-2-yl 4-methylbenzoate (12i):



S1 **12i**

Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), *p*-toluoyl chloride (1.98 mL, 15.0 mmol, 1.0 equiv), and dry DCM (35 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 → 1:10 EtOAc/hexanes) to afford **12i** (915 mg, 4.48 mmol, 30%) as a yellow solid. **12i** can be recrystallized after column chromatography by leaving the compound in a minimal amount of EtOAc/hexanes after rotovaping in a flask overnight open to atmosphere to give pale yellow blocky crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.98 (m, 2H), 7.31 – 7.27 (m, 2H), 6.02 (d, *J* = 2.3 Hz, 1H), 5.71 (d, *J* = 2.3 Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.05, 164.84, 151.99, 144.84, 130.44, 129.44, 126.01, 113.90, 25.75, 21.90.

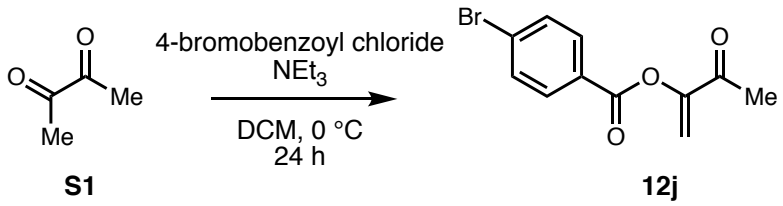
FTIR (NaCl, thin film, cm^{-1}): 3854, 3842, 2980, 1343, 2321, 1718, 1676, 1610, 1419, 1284, 1167, 1117, 942

HRMS (GC-EI+, m/z): calc'd for $C_{12}H_{12}O_3$ 204.0784 $[M\bullet]^+$; found: 204.0787

R_f = 0.69 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

Melting point = 69–70 °C

3-oxobut-1-en-2-yl 4-bromobenzoate (12j):



S1 **12j**

Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), 4-bromobenzoyl chloride (3.29 g, 15.0 mmol, 1.0 equiv), and dry DCM (35 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 → 1:10 EtOAc/hexanes) to afford **12j** (3.43 g, 12.7 mmol, 85%) as a yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 – 7.91 (m, 2H), 7.68 – 7.57 (m, 2H), 6.04 (d, *J* = 2.5 Hz, 1H), 5.76 (d, *J* = 2.5 Hz, 1H), 2.41 (s, 3H).

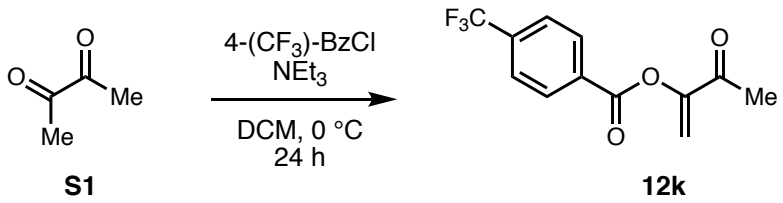
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.53, 164.06, 151.84, 132.11, 131.86, 129.23, 127.71, 114.48, 25.67.

FTIR (NaCl, thin film, cm^{-1}): 3904, 3888, 3663, 3216, 3020, 2807, 2504, 2262, 1723, 1678, 1523, 1477, 1410, 1273

HRMS (GC-EI+, m/z): calc'd for $C_{11}H_9O_3Br$ 267.9735 $[M\bullet]^+$; found: 267.9743

R_f = 0.69 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

3-oxobut-1-en-2-yl 4-(trifluoromethyl) benzoate (12k):



S1 **12k**

Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), 4-(trifluoromethyl)-benzoyl chloride (3.12 g, 15.0 mmol, 1.0 equiv), and dry DCM (35 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 → 1:10 EtOAc/hexanes) to afford **7f** (3.29 g, 12.7 mmol, 85%) as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dp, *J* = 7.7, 0.9 Hz, 2H), 7.84 – 7.67 (m, 2H), 6.07 (d, *J* = 2.6 Hz, 1H), 5.81 (d, *J* = 2.6 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.28, 163.56, 151.81, 135.49, 135.17, 134.84, 127.72, 125.82, 125.78, 125.75, 125.71, 125.01, 122.30, 119.59, 114.77, 25.63.

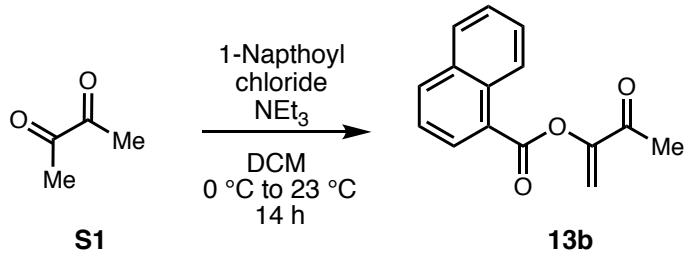
^{19}F NMR (282 MHz, $CDCl_3$) δ 66.41

FTIR (NaCl, thin film, cm^{-1}): 3462, 3384, 3076, 3020, 2934, 2356, 1975, 1919, 1868, 1738, 1703, 1641, 1621, 1587, 1514, 1410, 1361, 1328, 1291, 1265, 1179, 1113, 1065, 1014, 976, 928, 869, 841, 827, 768, 733, 698, 612.

HRMS (GC-EI+, m/z): calc'd for $C_{12}H_9O_3F_3$ 258.0504 $[M\bullet]^+$; found: 258.0521

R_f = 0.69 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

3-oxobut-1-en-2-yl 1-naphthoate (13b):

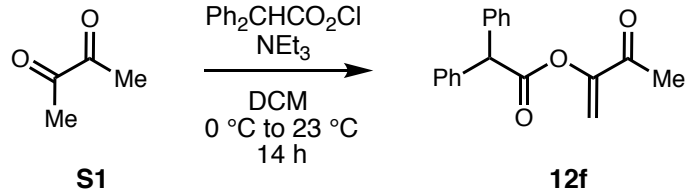


Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), 1-napthoyl chloride (2.26 mL, 15.0 mmol, 1.0 equiv), and dry DCM (18 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 EtOAc/hexanes → 1:10 EtOAc/hexanes) to afford **13b** (1.54 g, 6.4 mmol, 43%). Spectroscopic data matched previously reported values.[42]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (dq, *J* = 8.7, 0.8 Hz, 1H), 8.39 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.09 (ddt, *J* = 8.2, 1.3, 0.6 Hz, 1H), 7.91 (ddt, *J* = 8.2, 1.3, 0.6 Hz, 1H), 7.64 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1H), 7.60 – 7.51 (m, 2H), 6.09 (d, *J* = 2.4 Hz, 1H), 5.81 (d, *J* = 2.4 Hz, 1H), 2.47 (s, 3H).

HRMS (GC-FAB+, m/z): calc'd for $C_{15}H_{13}O_3$ 241.0865 $[M+H]^+$; found: 241.0859

3-oxobut-1-en-2-yl 2,2-diphenylacetate (12f)



Prepared from diacetyl (2.19 mL, 25.0 mmol, 1.0 equiv), triethylamine (4.18 mL, 30.0 mmol, 1.2 equiv), benzoyl chloride (2.90 mL, 25.0 mmol, 1.0 equiv), and dry DCM (35 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 EtOAc/hexanes → 1:10 EtOAc/hexanes) to afford **12f** (3.1 g, 12.7 mmol, 74%) as a white solid. **7g** can be recrystallized after column chromatography by leaving the compound in a minimal amount of EtOAc/Hex. after rotovaping in a flask overnight open to atmosphere to give clear colorless blocky crystals. Spectroscopic data matched previously reported values.[43]

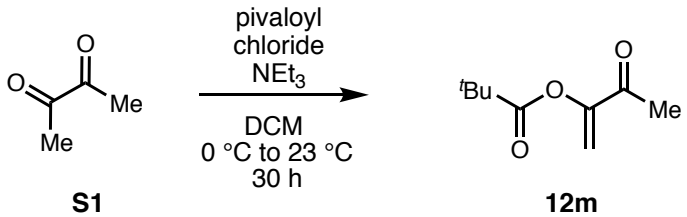
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.50 (m, 10H), 5.93 (d, *J* = 2.5 Hz, 1H), 5.57 (d, *J* = 2.5 Hz, 1H), 5.22 (s, 2H), 2.28 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.54, 170.58, 151.67, 137.88, 128.78, 128.70, 127.53, 113.93, 56.60, 25.48.

HRMS (GC-FAB+, m/z): calc'd for $C_{18}H_{17}O_3$ 281.1178 $[M+H]^+$; found: 281.1165

Melting point = 61–62 °C.

3-oxobut-1-en-2-yl pivalate (12m):



Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), pivaloyl chloride (1.85 mL, 15.0 mmol, 1.0 equiv), and dry DCM (15

mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 EtOAc/hexanes → 1:10 EtOAc/hexanes) to afford **12m** (443 mg, 2.6 mmol, 17%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (dd, *J* = 2.3, 1.2 Hz, 1H), 5.56 (dd, *J* = 2.3, 1.3 Hz, 1H), 2.34 (d, *J* = 1.6 Hz, 3H), 1.31 (d, *J* = 1.5 Hz, 8H).

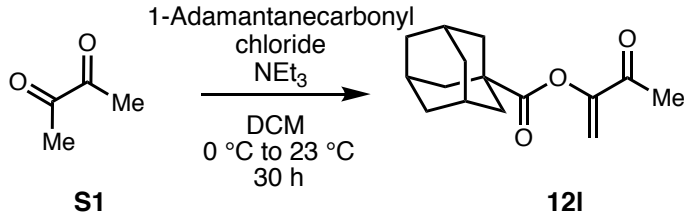
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.88, 176.81, 152.08, 113.45, 39.03, 27.20, 25.66.

FTIR (NaCl, thin film, cm^{-1}): 2976, 1752, 1700, 1640, 1480. 1367, 1275, 1170, 1119, 1032, 918

HRMS (GC-FAB+, m/z): calc'd for $C_9H_{14}O_3$ 171.1021 $[M+H]^+$; found: 171.1013

R_f = 0.74 in 40% EtOAc/hexanes ($KMnO_4$)

3-oxobut-1-en-2-yl (3*r*,5*r*,7*r*)-adamantane-1-carboxylate (12l)



Prepared from diacetyl (1.32 mL, 15.0 mmol, 1.0 equiv), triethylamine (2.51 mL, 18.0 mmol, 1.2 equiv), 1-adamantanecarbonyl chloride (2.98 g, 15 mmol, 1.0 equiv), and dry DCM (20 mL) following General Procedure A with 30h at 23 °C. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 EtOAc/hexanes → 1:10 EtOAc/hexanes) to afford **12l** (816 mg, 3.29 mmol, 22%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (d, *J* = 2.2 Hz, 1H), 5.54 (d, *J* = 2.2 Hz, 1H), 2.34 (s, 3H), 2.06 (q, *J* = 3.0 Hz, 3H), 2.01 (d, *J* = 2.9 Hz, 6H), 1.75 (dt, *J* = 4.5, 2.9 Hz, 6H).

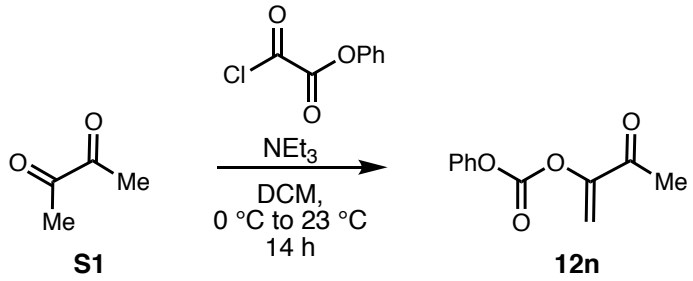
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.00, 175.91, 152.09, 113.37, 41.01, 38.81, 36.54, 27.98, 25.70.

FTIR (NaCl, thin film, cm^{-1}): 3584, 2905, 1748, 1694, 1453, 1361, 1212, 1122, 1057

HRMS (GC-FAB+, m/z): calc'd for $C_{15}H_{20}O_3$ 249.1491 $[M+H]^+$; found: 249.1513

R_f = 0.63 in 40% EtOAc/hexanes ($KMnO_4$)

phenyl (3-oxobut-1-en-2-yl) carbonate (12n):



S1 **12n**

Prepared from diacetyl (2 g, 23.23 mmol, 1.0 equiv), triethylamine (3.84 mL, 27.87 mmol, 1.2 equiv), phenyl chlorooxoacetate (2.9 mL, 23,23 mmol, 1.0 equiv), and dry DCM (53 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 EtOAc/hexanes → 1:10 EtOAc/hexanes) to afford **12n** (1 g, 4.83 mmol, 21%) as pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 2H), 7.33 – 7.22 (m, 3H), 6.01 (d, *J* = 2.8 Hz, 1H), 5.87 (d, *J* = 2.8 Hz, 1H), 2.44 (s, 3H).

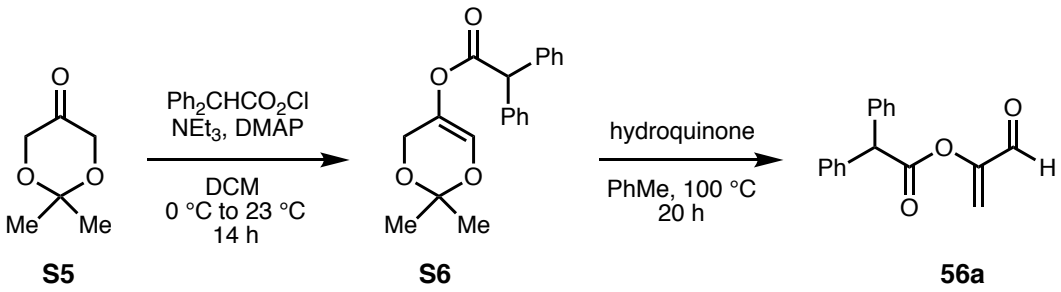
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.20, 151.44, 151.06, 129.71, 126.55, 120.98, 114.14, 25.56.

FTIR (NaCl, thin film, cm^{-1}): 3887, 3022, 2258, 1774, 1696, 1492, 1361, 1300, 1235, 1209, 1161, 1123, 1072, 1022, 941

HRMS (TOF-ESI, m/z): calc'd for $C_{11}H_{11}O_4$ 207.0657 $[M+H]^+$; found: 207.0644

R_f = 0.63 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

3-oxoprop-1-en-2-yl 2,2-diphenylacetate (56a):



Procedure: To a flame-dried 50 mL round bottom flask, equipped with a stir bar, was added ketone **S5** (1 g, 7.68 mmol, 1.0 equiv), triethylamine (2.14 mL, 15.0 mmol, 2 equiv), and DMAP (188 mg, 1.5 mmol, 20 mol %) followed by DCM (15 mL). To this solution was added diphenylacetyl chloride (2.3 g, 9.98 mmol, 1.3 equiv). The reaction was allowed to stir for 12 h at 23 °C. The reaction was then quenched with hexanes, filtered through celite, and concentrated. The residue was then subjected to silica column chromatography (10% EtOAc/Hexanes) to afford **S6**. **S6** was used crude in the following reaction.

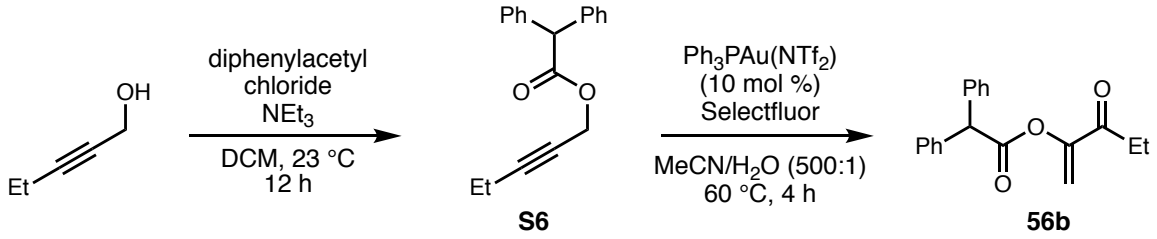
To an oven-dried 50 mL round bottom flask, equipped with a stir bar, was added crude **S6**, hydroquinone (333 mg, 3.02 mmol, 0.4 equiv), and PhMe (17 mL). Reaction was fitted with a reflux condenser and heated to 100 °C for 20 h. The reaction was then concentrated *in vacuo* and purified via flash column chromatography (10% EtOAc/Hexanes) to give **56a**

(1.33 g, 4.98 mmol, 65%) as a white amorphous solid. Spectroscopic data matched previously reported values.[44]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.49 – 7.27 (m, 10H), 6.03 (d, *J* = 2.4 Hz, 1H), 5.93 (d, *J* = 2.4 Hz, 1H), 5.24 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.02, 170.07, 152.83, 137.91, 128.88, 128.87, 127.70, 121.57, 56.69.

3-oxopent-1-en-2-yl 2,2-diphenylacetate (56b):



Procedure: To a flame-dried 100 mL round bottom flask, equipped with a stir bar, was added pent-2-yn-1-ol (1 g, 11.9 mmol, 1.0 equiv), triethylamine (5 mL, 35.7 mmol, 3 equiv), and DMAP (290 mg, 2.38 mmol, 20 mol %) followed by DCM (40 mL). To this solution was added diphenylacetyl chloride (3.02 g, 13.1 mmol, 1.1 equiv). The reaction was allowed to stir for 12 h at 23 °C. The reaction was then quenched with hexanes, filtered through celite, and concentrated. The residue was then subjected to silica column chromatography (10% EtOAc/Hexanes) to afford **S6** (3.15 g, 11.3 mmol, 95%).

PPh_3AuNTf_2 (74 mg, 0.1 mmol, 5 mol %) was added to a solution of a propargylic benzoate **S6** (555 mg, 2.0 mmol, 1.0 equiv) and Selectfluor® (1.06 g, 3.0 mmol, 1.5 equiv) in CH_3CN (40mL) and water (80 uL) (MeCN: water = 500:1, 0.05 M). The reaction was heated in an oil bath pre-heated to 80 ºC and monitored by TLC. Upon completion (approx.

4 h), the reaction was allowed to cool to room temperature and treated with Me_2S (excess) for 5 min before the removal of most of the solvent. The resulting residue was dissolved in diethyl ether and then washed with water and brine. The ethereal layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified through silica gel flash column chromatography (1:20 EtOAc/hexanes → 1:10 EtOAc/hexanes) to afford **56b** as a pale yellow solid (170 mg, 0.57 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.22 (m, 10H), 5.91 (d, *J* = 2.4 Hz, 1H), 5.54 (d, *J* = 2.4 Hz, 1H), 5.22 (s, 1H), 2.61 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H).

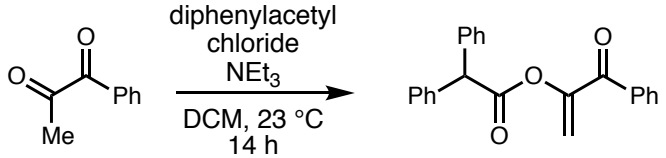
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.72, 170.75, 151.54, 138.05, 128.92, 127.64, 113.08, 56.80, 31.09, 7.94.

FTIR (NaCl, thin film, cm^{-1}): 3488, 3064, 3029, 2980, 2940, 1955, 1737, 1731, 1759, 1642, 1600, 1494, 1454, 1379, 1359, 1309

HRMS (GC-EI+, m/z): calc'd for $C_{19}H_{18}O_3$ 294.1256 $[M\bullet]^+$; found: 294.1278

R_f = 0.70 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

3-oxo-3-phenylprop-1-en-2-yl 2,2-diphenylacetate (56c):



S7 **56c**

Prepared from 1-phenyl-1,2-propanedione (1.08 mL, 8.00 mmol, 1.0 equiv), triethylamine (1.34 mL, 9.6 mmol, 1.2 equiv), diphenylacetyl chloride (1.85 g, 8.0 mmol, 1.0 equiv), and dry DCM (27 mL) following General Procedure A. The resulting solution was concentrated

under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford **56c** (1.57 g, 4.59 mmol, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 2H), 7.61 – 7.51 (m, 1H), 7.47 – 7.38 (m, 2H), 7.37 – 7.27 (m, 10H), 5.68 (dd, *J* = 2.2, 0.5 Hz, 1H), 5.58 (dd, *J* = 2.1, 0.6 Hz, 1H), 5.23 (s, 1H).

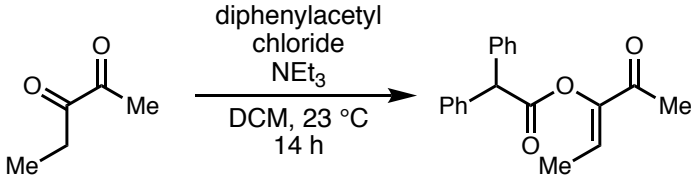
^{13}C NMR (126 MHz, $CDCl_3$) δ 189.60, 170.78, 151.30, 137.85, 136.18, 132.99, 129.59, 128.81, 128.75, 128.40, 127.55, 114.55, 77.42, 77.16, 76.90, 56.42.

FTIR (NaCl, thin film, cm^{-1}): 3030, 1755, 1666, 1498, 1121, 962, 773, 756, 741

HRMS (GC-EI+, m/z): calc'd for $C_{23}H_{18}O_3$ 342.1256 $[M\bullet]^+$; found: 342.1241

R_f = 0.70 in 40% EtOAc/hexanes ($KMnO_4$, UV-Active)

(*Z*)-4-oxopent-2-en-3-yl 2,2-diphenylacetate (56d)



S8 **56d**

Procedure: Prepared from diketone **S8** (4 g, 39.9 mmol, 1.0 equiv), triethylamine (6.7 mL, 48.0 mmol, 1.2 equiv), diphenylcetyl chloride (9.2 mL, 39.9 mmol, 1.0 equiv), and dry DCM (93 mL) following General Procedure A. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (10% EtOAc/hexanes) to afford **56d** (8.08 g, 29.92 mmol, 75%) as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.24 (m, 11H), 6.53 (q, *J* = 7.1 Hz, 1H), 5.28 (s, 1H), 2.25 (s, 3H), 1.59 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.13, 170.40, 147.30, 138.15, 128.98, 128.79, 128.47, 127.62, 56.81, 25.29, 11.78.

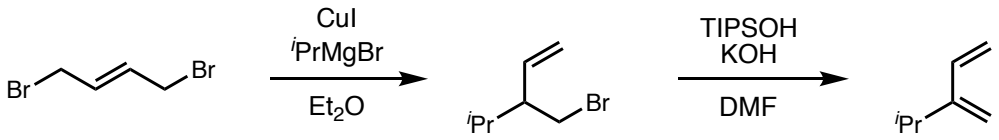
FTIR (NaCl, thin film, cm^{-1}): 3503, 3361, 3062, 3029, 2006, 2921, 1956, 1889, 1755, 1683, 1659, 1600, 1495, 1452, 1380, 1361

HRMS (GC-EI+, m/z): calc'd for $C_{19}H_{18}0_3$ 294.1256 $[M\bullet]^+$; found: 294.1249

R_f = 0.67 in 40% EtOAc/Hex. ($KMnO_4$, UV-Active)

4.7.3 Diene Preparation

4-methyl-3-methylenepent-1-ene (53b):



S9 **S10** **53b**

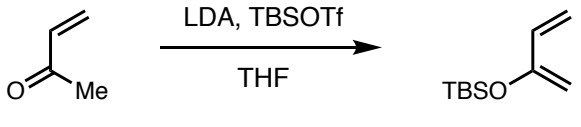
Procedure: To a mixture of CuI (3.31 g, 17.5 mmol) and 1,4-dibromo-2-butene (4.8 g, 23 mmol) in ether (35 mL) under N_2, at –10 °C, was added dropwise a freshly prepared solution of isopropylmagnesium bromide in ether (2.5 M, 14 mL, 35 mmol). The reaction was followed by TLC (hexanes), and after consumption of 1 the mixture was diluted with saturated NH4Cl solution. The aqueous phase was extracted with ether (2 × 20 mL), and the combined organics were washed with brine (20 mL), dried over MgSO4, and concentrated to give crude **S10**.

To a solution of KOH (3.14 g, 48 mmol) in DMF (70 mL) was added triisopropylsilanol (39 mg, 0.2 mmol). After the mixture was stirred at rt for 1 h, crude **S10** (5 g, 28 mmol) was added dropwise. After being stirred for an additional 12 h, the reaction was judged

complete by TLC (hexanes) and the product was distilled directly from the reaction mixture (200 mtorr, 70 °C) to give **53b** as a colorless oil (2.08 g, 77%). Spectroscopic data matched previously reported values.[45]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.28 (ddt, *J* = 17.7, 1.2, 0.6 Hz, 1H), 5.05 (dtd, *J* = 10.9, 1.2, 0.7 Hz, 1H), 5.00 (s, 2H), 2.71 – 2.52 (m, 1H), 1.13 – 1.06 (m, 6H).

(buta-1,3-dien-2-yloxy)(*tert*-butyl)dimethylsilane (53f):



S11 **53f**

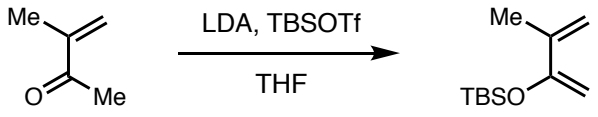
Procedure: Di-isopropylamine (3.9 mL, 27.9 mmol, 1.16 equiv) was dissolved in anhydrous THF (60 mL) and the resultant solution cooled to –78 °C, followed by the dropwise addition of *n*-BuLi (18.3 mL, 1.5 M in hexanes, 27.9 mmol, 1.16 equiv). The reaction mixture was allowed to warm to 0 °C and stirred 30 min after which time the solution was re-cooled to –78 °C. In a separate vessel, methyl vinyl ketone (2.1 mL, 24.0 mmol, 1.0 equiv) was dissolved in THF (7.5 mL) and the resultant mixture added to the solution of LDA dropwise. After 1 hr, TBSOTf (6.41 mL, 27.9 mmol, 1.16 equiv) was slowly added and the reaction mixture allowed to warm to room temperature overnight (16 h). The reaction was quenched with ice cold water (20 mL) and the aqueous layer extracted with 1:1 hexanes/Et_2O (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield the crude product as a yellow oil. Purification by silica plug

with hexanes gives **53f** (2.69 g, 14.60 mmol, 61%) as a clear colorless oil. Spectroscopic data matched previously reported values.[46]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 16.9, 10.5 Hz, 1H), 5.51 (ddt, *J* = 16.9, 1.9, 0.6 Hz, 1H), 5.08 (dddd, *J* = 10.5, 2.1, 1.5, 0.7 Hz, 1H), 4.36 – 4.29 (m, 2H), 0.97 (s, 10H), 0.18 (s, 6H).

R_f = 0.7 (Hexanes, UV-active, $KMnO_4$)

***tert*-butyldimethyl((3-methylbuta-1,3-dien-2-yl)oxy)silane (53g):**



S12 **53g**

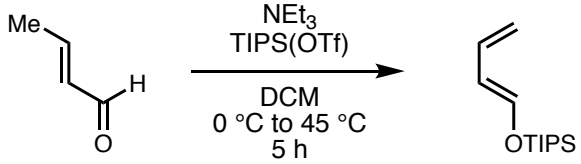
Procedure: Di-isopropylamine (3.9 mL, 27.9 mmol, 1.16 equiv) was dissolved in THF (60 mL) and the resultant solution cooled to –78 °C, followed by the dropwise addition of *n*-BuLi (18.3 mL, 1.5 M in hexanes, 27.9 mmol, 1.16 equiv). The reaction mixture was allowed to warm to 0 °C and stirred 30 min after which time the solution was re-cooled to –78 °C. In a separate vessel, 3-methyl-3-butene-2-one (**S12**) (2.01 g, 24.0 mmol, 1.0 equiv) was dissolved in THF (7.5 mL) and the resultant mixture added to the solution of LDA dropwise. After 1 hr, TBSOTf (6.41 mL, 27.9 mmol, 1.16 equiv) was slowly added and the reaction mixture allowed to warm to room temperature overnight (16 h). The reaction was quenched with ice cold water (20 mL) and the aqueous layer extracted with 1:1 hexanes/Et_2O (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield the crude product as a yellow oil. Purification by silica plug

with hexanes gives **53g** (2.62 g, 13.20 mmol, 55%) as a clear colorless oil. Spectroscopic data matched previously reported values.[47]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (dh, *J* = 2.1, 0.7 Hz, 1H), 4.96 (dpd, *J* = 2.3, 1.4, 0.8 Hz, 1H), 4.48 (dt, *J* = 1.5, 0.8 Hz, 1H), 4.35 – 4.29 (m, 1H), 1.88 (dd, *J* = 1.4, 0.7 Hz, 3H), 0.97 (s, 9H), 0.17 (s, 6H).

R_f = 0.7 (Hexanes, UV-active, $KMnO_4$)

(*E*)-(buta-1,3-dien-1-yloxy)triisopropylsilane (54h):

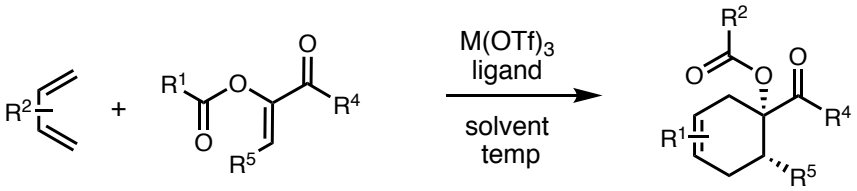


S13 **54h**

Procedure: To an oven-dried 25mL round bottom flask was added (E)-2-butenal (**S13**) (1.40 g, 20.0 mmol, 1.35 equiv) in dry DCM (8.0 mL) at 0 ˚C. To this solution was added triethylamine (3.82 mL, 27.4 mmol, 1.85 equiv) and triisopropylsilyl trifluoromethanesulfonate (3.98 mL, 14.8 mmol, 1.0 equiv). The reaction solution was heated at 45 ˚C for 5 h then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with $NaHCO_3$ (2 x 10.0 mL) and brine (10 mL), dried over MgSO4, filtered, and concentrated in vacuo. The resulting residue was flushed through a silica plug (30 mL) with hexanes to afford a clear, colorless oil **54h** (1.70 g, 7.5 mmol, 51%). Spectroscopic data matched previously reported values.[45]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 11.8, 0.8 Hz, 1H), 6.26 (dddd, *J* = 16.9, 11.0, 10.2, 0.6 Hz, 1H), 5.78 (ddt, *J* = 11.7, 10.9, 0.8 Hz, 1H), 5.01 (ddt, *J* = 16.9, 1.7, 0.7 Hz, 1H), 4.87 – 4.77 (m, 1H), 1.25 – 1.15 (m, 3H), 1.13 – 1.05 (m, 18H).

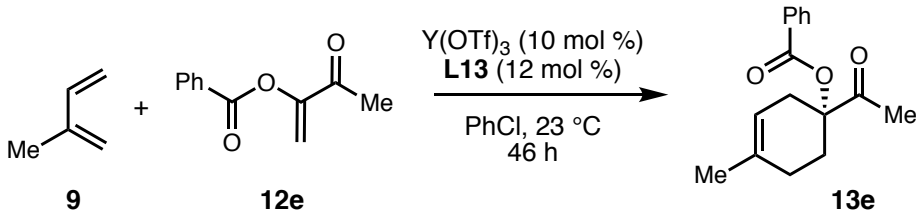
4.7.4 Diels–Alder Reaction



General Procedure B: In a nitrogen-filled glovebox, to a dry 1-dram vial, equipped with a magnetic stir bar, was charged with $M(OTf)_x$ and capped with a Teflon cap. The reaction vial was then removed from the glovebox. The cap was removed and to the reaction vial was then quickly added ligand, and solvent and then recapped. The reaction was allowed to stir at 100 RPM for 3 hours at 23 °C. The cap was then removed and to the reaction vial was quickly added diene and dienophile, and the reaction vial was recapped and sealed with electrical tape. The reaction was stirred at 23 °C and monitored by TLC. Upon completion, the reaction mixture was filtered through a plug of silica gel, eluting with DCM. The resulting solution was concentrated under reduced pressure. The entire residue was taken up in $CDCl_3$ and conversion/yield were determined by ^{1}H NMR spectroscopy.

Ester Scope

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl benzoate (13e):



9 **12e** **13e**

Prepared from **12e** (76.1 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 18:1 mixture of regioisomers favoring **13e** (94.1 mg, 0.364 mmol, 91%) in 89% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 – 7.98 (m, 2H), 7.66 – 7.56 (m, 1H), 7.51 – 7.42 (m, 2H), 5.40 – 5.29 (m, 1H), 2.72 – 2.58 (m, 1H), 2.54 – 2.42 (m, 1H), 2.42 – 2.32 (m, 1H), 2.19 (s, 3H), 2.13 (ddddd, *J* = 12.1, 6.7, 3.2, 2.2, 1.1 Hz, 1H), 1.99 (ddt, *J* = 13.1, 10.6, 4.8 Hz, 2H), 1.76 – 1.66 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.93, 166.01, 133.53, 133.35, 129.94, 129.90, 128.64, 116.77, 84.22, 31.83, 27.83, 26.72, 24.09, 23.31.

FTIR (NaCl, thin film, cm^{-1}): 3773, 3662 3343, 3904, 2415, 2204, 1718, 1709, 1690, 1286

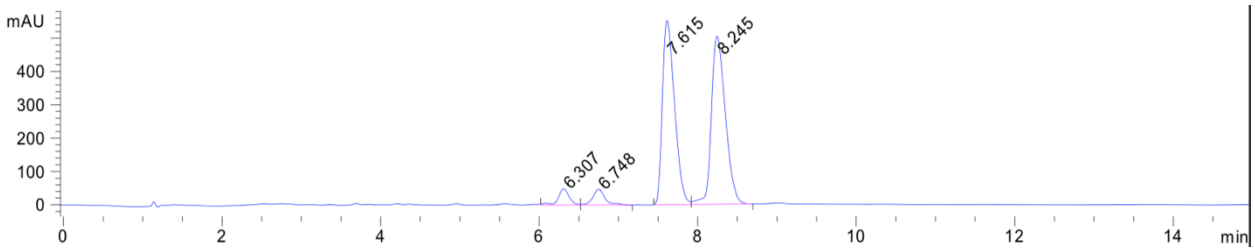
HRMS (TOF-ESI, m/z): calc'd for $C_{16}H_{18}O_3$ 259.1334 $[M+H]^+$; found: 259.1338

R_f = 0.60 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +26° (c = 1.0, $CHCl_3$).

Chiral SFC: (IC column, 2.5 mL/min, 10% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 7.6 min, $t_{minor\ enantiomer}$ = 8.2 min; Minor regioisomer: $t_{major\ enantiomer}$ = 6.3 min, $t_{minor\ enantiomer}$ = 6.7 min

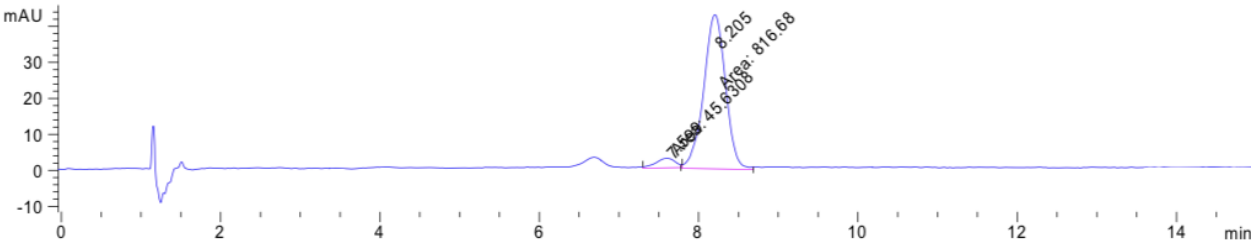
13e: racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.307	BV	0.1487	471.67725	48.81064	3.6156
2	6.748	VB	0.1587	495.27405	47.08922	3.7965

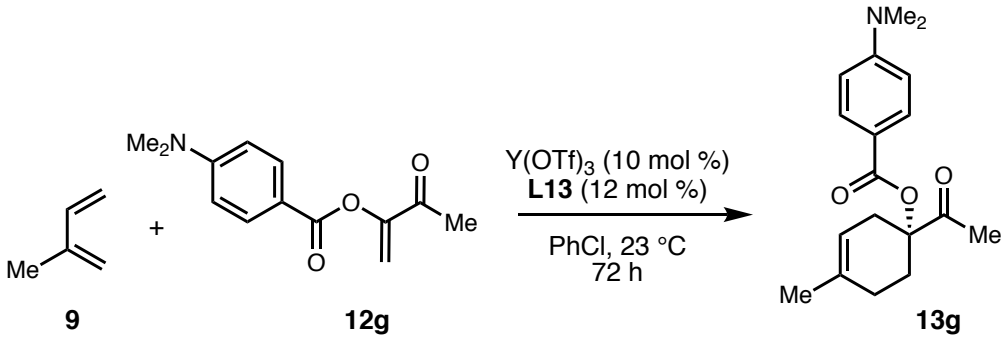
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
3	7.615	BV	0.1647	5901.84375	551.98633	45.2403
4	8.245	VB	0.1910	6176.74121	503.81226	47.3475

(+)-**13e**: enantioenriched, 89% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.599	MM	0.2851	45.63080	2.66765	5.2917
2	8.205	MM	0.3175	816.67999	42.87407	94.7083

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl 4-(dimethylamino)benzoate (13g):



Prepared from **12g** (93.3 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B allowing the reaction to run for 72 hours. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (20% EtOAc/hexanes) to afford a 13:1 mixture of regioisomers favoring **13g** (119.4 mg, 0.396 mmol, 99%) in 91% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.78 (m, 2H), 6.64 – 6.56 (m, 2H), 5.26 (qt, *J* = 2.8, 1.3 Hz, 1H), 2.98 (s, 6H), 2.54 (dp, *J* = 17.9, 2.4 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.31 – 2.20 (m, 1H), 2.10 (s, 3H), 2.06 – 1.74 (m, 2H), 1.65 – 1.60 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.68, 166.31, 153.65, 133.26, 131.70, 116.98, 116.69, 111.00, 83.21, 40.30, 31.95, 27.87, 26.80, 23.96, 23.32.

FTIR (NaCl, thin film, cm^{-1}): 2922, 1717, 1697, 1605, 1528, 1483, 1445, 1370, 1318, 1293, 1250, 1181, 1103

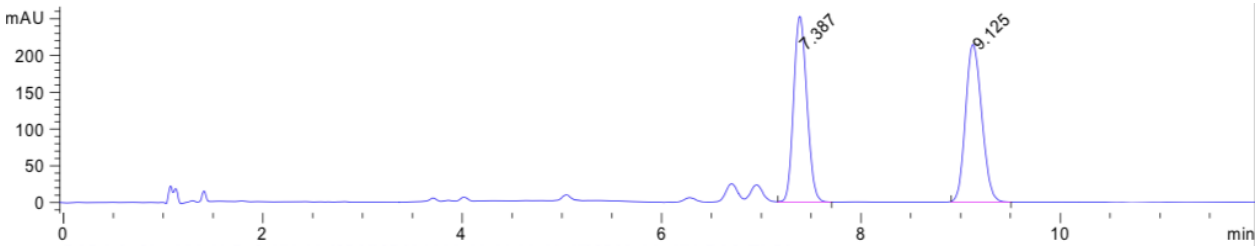
HRMS (GC-EI+, m/z): calc'd for $C_{18}H_{23}NO_3$ 301.1678 $[M\bullet]^+$; found: 301.1658

R_f = 0.38 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +51° (c = 1.0, $CHCl_3$).

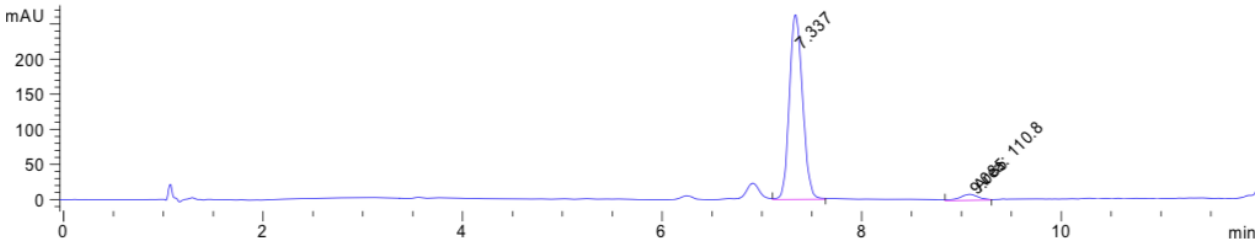
Chiral SFC: (AD-H column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 7.4 min, $t_{minor\ enantiomer}$ = 9.1 min;

13g: racemic



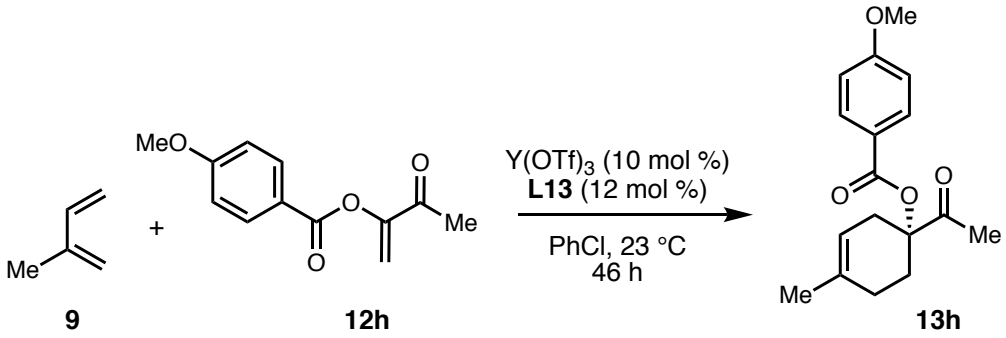
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.387	VB	0.1480	2336.65820	252.51112	48.9523
2	9.125	BB	0.1807	2436.68311	214.18430	51.0477

(+)-**13g**: enantioenriched, 91% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.337	VB	0.1475	2421.88574	262.72153	95.6252
2	9.085	MM	0.2153	110.80032	8.57795	4.3748

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl 4-methoxybenzoate (13h):



9 **12h** **13h**

Prepared from **12h** (88.1 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 16:1 mixture of regioisomers favoring **13h** (111.9 mg, 0.388 mmol, 97%) in 91% ee as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.86 (m, 2H), 6.92 – 6.82 (m, 2H), 5.26 (tq, *J* = 2.8, 1.4 Hz, 1H), 3.80 (s, 3H), 2.56 (dp, *J* = 17.9, 2.5 Hz, 1H), 2.44 – 2.22 (m, 2H), 2.11 (s, 3H), 2.00 – 1.83 (m, 2H), 1.66 – 1.60 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.19, 165.74, 163.88, 133.31, 131.99, 122.29, 116.84, 113.88, 83.81, 55.63, 31.89, 27.83, 26.74, 24.04, 23.30.

FTIR (NaCl, thin film, cm^{-1}): 3416, 2932, 2839, 2039, 1712, 1606, 1580, 1554, 1512, 1442, 1350, 1318, 1262, 1199, 1170

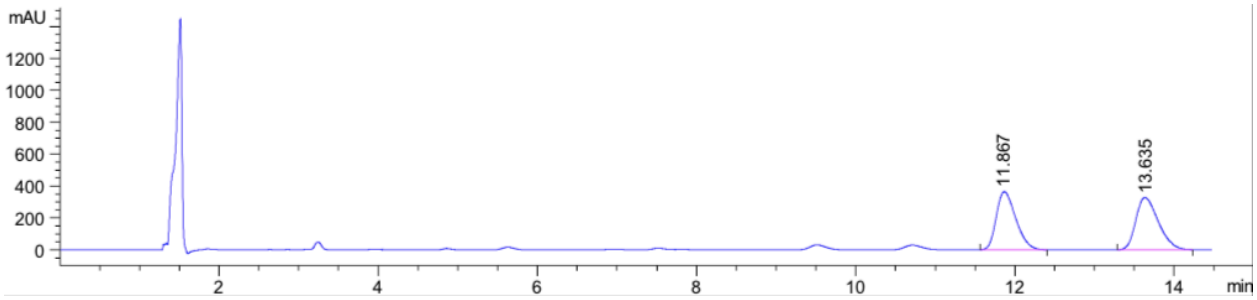
HRMS (TOF-ESI, m/z): calc'd for $C_{17}H_{21}O_4$ 289.1440 $[M+H]^+$; found: 289.1432

R_f = 0.49 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +33° (c = 1.0, $CHCl_3$).

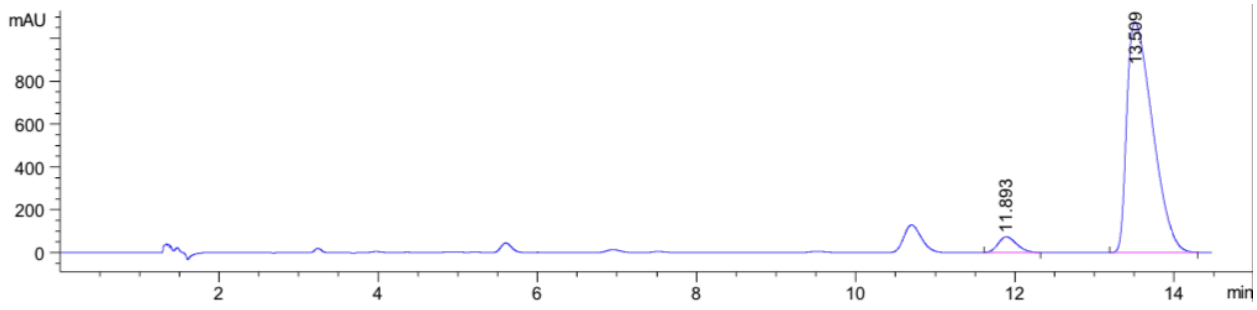
Chiral SFC: (IC column, 2.5 mL/min, 10% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 13.6 min, $t_{minor\ enantiomer}$ = 11.9 min;

13h: racemic



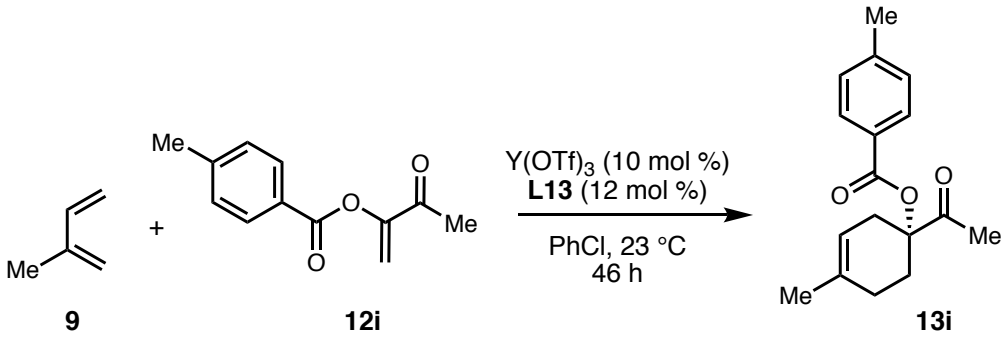
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.867	BB	0.2628	6201.40918	363.87622	49.0663
2	13.635	BB	0.2991	6437.41406	327.75925	50.9337

(+)-**13h**: enantioenriched, 91% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.893	BB	0.2490	1199.89209	73.67332	4.7463
2	13.509	BB	0.3513	2.40809e4	1075.01965	95.2537

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl 4-methylbenzoate (13i):



Prepared from **12i** (81.7 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 13:1 mixture of regioisomers favoring **13i** (105.7 mg, 0.388 mmol, 97%) in 91% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.87 (m, 2H), 7.29 – 7.20 (m, 3H), 5.33 (dtq, *J* = 4.2, 2.8, 1.4 Hz, 1H), 2.63 (dp, *J* = 18.0, 2.5 Hz, 1H), 2.42 (s, 4H), 2.40 – 2.30 (m, 1H), 2.18 (s, 3H), 2.13 – 1.86 (m, 3H), 1.70 (tt, *J* = 2.2, 1.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.11, 166.08, 144.34, 133.34, 129.96, 129.35, 127.20, 116.81, 84.00, 31.86, 27.81, 26.73, 24.05, 23.30, 21.86.

FTIR (NaCl, thin film, cm^{-1}): 2916, 1714, 1611, 1508, 1448, 1354, 1312, 1288, 1248, 1198, 1177, 1106, 1067, 1018

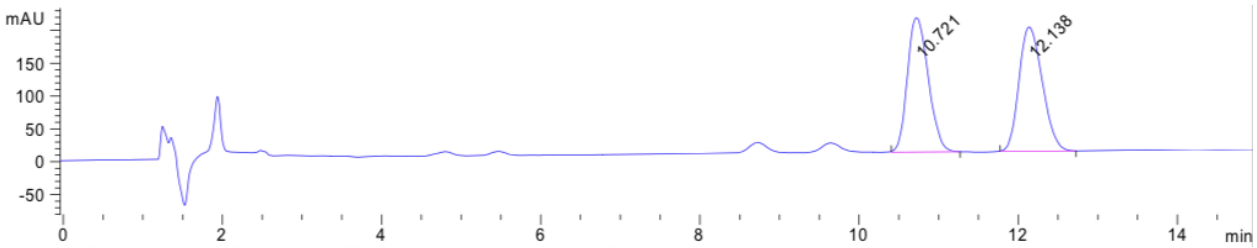
HRMS (GC-EI+, m/z): calc'd for $C_{17}H_{20}O_3$ 272.1413 $[M\bullet]^+$; found: 272.1434

R_f = 0.60 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +29° (c = 1.0, $CHCl_3$).

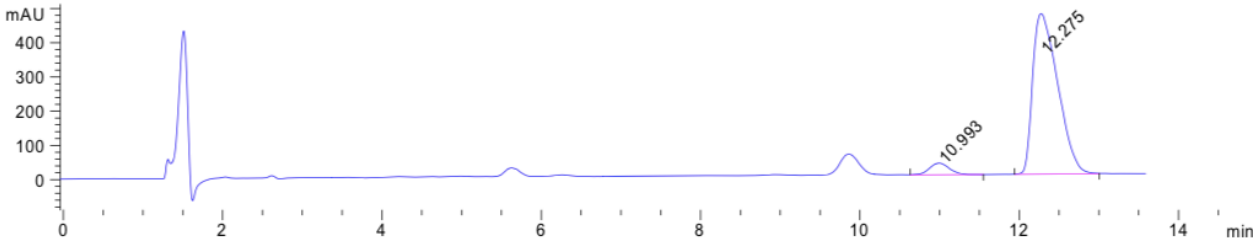
Chiral SFC: (IC column, 2.5 mL/min, 10% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 12.1 min, $t_{minor\ enantiomer}$ = 10.7 min;

13i: racemic



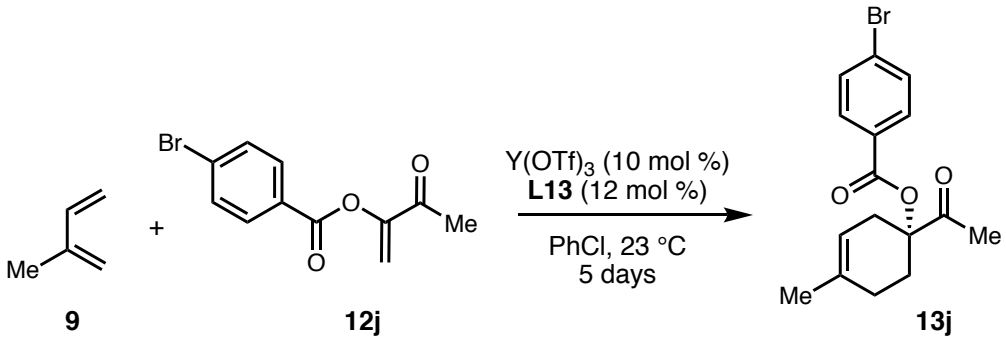
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.721	BB	0.2889	3736.39014	204.73465	49.1538
2	12.138	BB	0.3222	3865.04248	189.27350	50.8462

(+)-**13i**: enantioenriched, 91% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.993	BB	0.2703	588.84955	33.95292	5.4310
2	12.275	BB	0.3589	1.02536e4	469.28918	94.5690

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl 4-bromobenzoate (13j):



Prepared from **12j** (108 mg, 0.40 mmol, 1.0 equiv), isoprene (200 µL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B allowing the reaction to run for 5 days. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 15:1 mixture of regioisomers favoring **13j** (126.8 mg, 0.376 mmol, 94%) in 81% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.82 (m, 2H), 7.65 – 7.55 (m, 2H), 5.34 (tp, *J* = 4.0, 1.4 Hz, 1H), 2.72 – 2.57 (m, 1H), 2.45 (dtd, *J* = 18.2, 3.3, 1.7 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.19 (s, 3H), 2.15 – 1.93 (m, 3H), 1.70 (qd, *J* = 1.5, 0.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.63, 165.28, 133.40, 132.01, 131.39, 128.82, 128.75, 116.67, 84.53, 31.86, 27.77, 26.69, 24.18, 23.29.

FTIR (NaCl, thin film, cm^{-1}): 3433, 2910, 2143, 1715, 1589, 1433, 1397, 1359, 1291, 1246, 1173, 1113, 1103

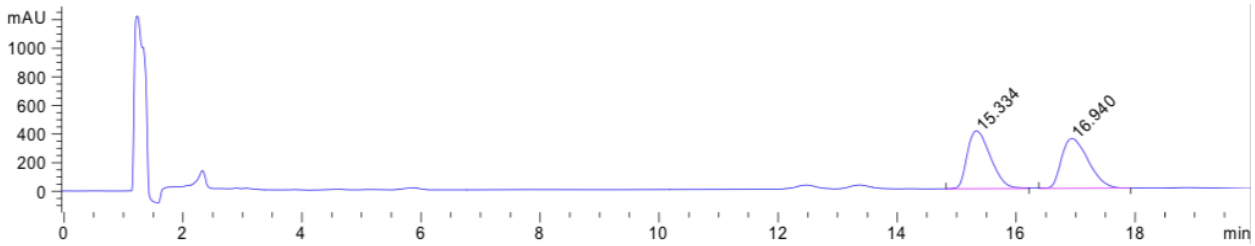
HRMS (TOF-ESI, m/z): calc'd for $C_{16}H_{17}Br_1O_3$ 337.0493 $[M+H]^+$; found: 337.0416

R_f = 0.64 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +19° (c = 1.0, $CHCl_3$).

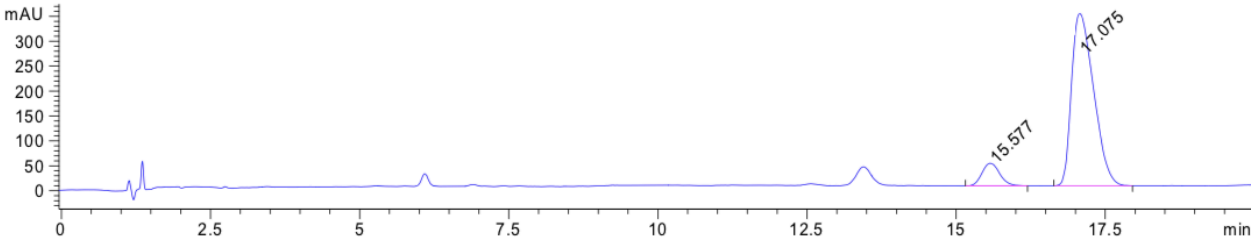
Chiral SFC: (IC column, 2.5 mL/min, 7% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 16.9 min, $t_{minor\ enantiomer}$ = 15.3 min;

13j: racemic



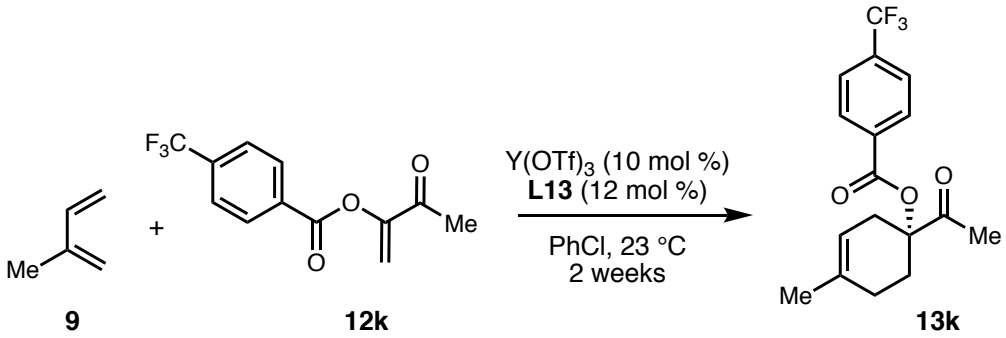
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.334	BB	0.4320	1.09629e4	404.74283	50.1629
2	16.940	BB	0.4962	1.08917e4	348.91562	49.8371

(+)-**13j**: enantioenriched, 81% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.577	BB	0.3328	940.32367	45.56255	9.5389
2	17.075	BB	0.4088	8917.47949	345.83725	90.4611

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl 4-(trifluoromethyl)benzoate (13k):



9 **12k** **13k**

Prepared from **12k** (103.3 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B allowing the reaction to run for 2 weeks. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 17:1 mixture of regioisomers favoring **13k** (109.6 mg, 0.336 mmol, 84%) in 63% ee as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dp, *J* = 7.7, 0.8 Hz, 2H), 7.72 (ddt, *J* = 8.3, 2.1, 1.1 Hz, 2H), 5.35 (tq, *J* = 2.8, 1.3 Hz, 1H), 2.66 (dp, *J* = 18.1, 2.6 Hz, 1H), 2.54 – 2.34 (m, 2H), 2.20 (s, 3H), 2.14 – 1.92 (m, 3H), 1.71 (tt, *J* = 3.1, 2.3, 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.16, 164.78, 134.99 (q, *J* = 32.6 Hz), 133.45, 133.16, 130.30, 125.70 (q, *J* = 3.7 Hz), (d, *J* = 272.9 Hz), 116.62, 84.90, 31.84, 27.78, 26.67, 24.23, 23.27.

^{19}F NMR (282 MHz, $CDCl_3$) δ 66.39

FTIR (NaCl, thin film, cm^{-1}): 2917, 1722, 1585, 1514, 1440, 1412, 1358, 1327, 1291, 1248, 1167, 1131, 1101, 1065

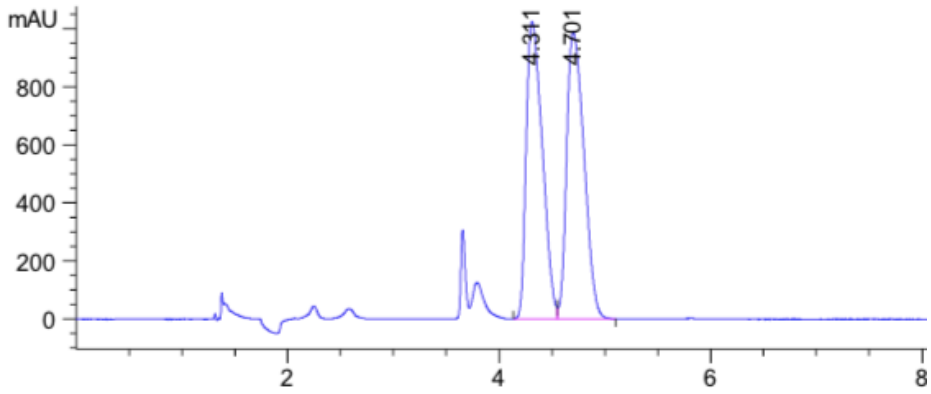
HRMS (TOF-ESI, m/z): calc'd for $C_{17}H_{18}F_3O_3$ 327.1208 $[M+H]^+$; found: 327.1228

R_f = 0.64 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +14° (c = 1.0, $CHCl_3$).

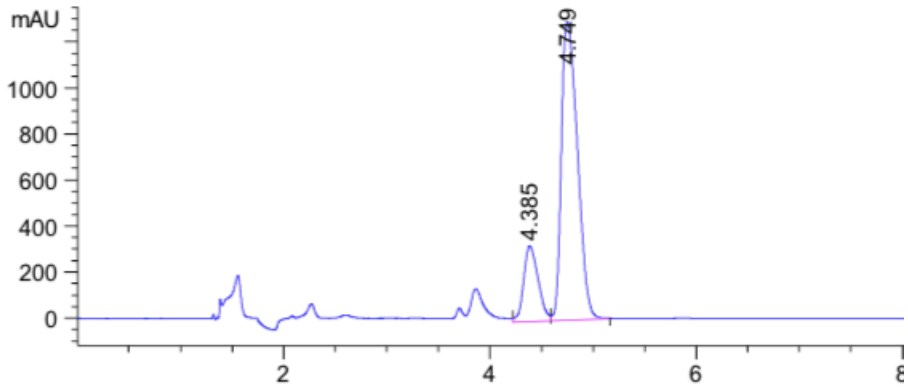
Chiral SFC: (IC column, 2.5 mL/min, 5% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 4.7 min, $t_{minor\ enantiomer}$ = 4.3 min;

13k: racemic



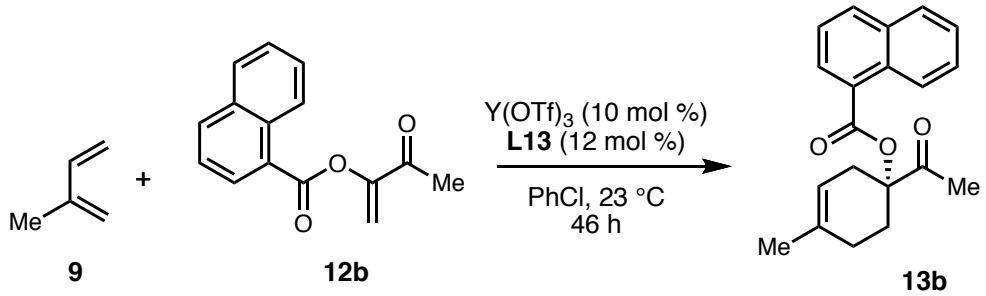
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.311	BV	0.1779	1.08909e4	1025.27612	49.1257
2	4.701	VB	0.1860	1.12785e4	989.35620	50.8743

(+)-**13k**: enantioenriched, 63% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.385	BV	0.1553	3207.35132	327.33887	18.5877
2	4.749	VB	0.1765	1.40479e4	1295.83130	81.4123

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl 1-naphthoate (13b):



9 **12b** **13b**

Prepared from **12b** (96.1 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 13:1 mixture of regioisomers favoring **13b** (113.5 mg, 0.368 mmol, 92%) in 87% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (ddt, *J* = 8.6, 1.3, 0.8 Hz, 1H), 8.25 – 8.13 (m, 1H), 8.05 (ddt, *J* = 8.2, 1.3, 0.6 Hz, 1H), 7.95 – 7.87 (m, 1H), 7.65 – 7.46 (m, 3H), 5.48 – 5.39 (m, 1H), 2.80 – 2.66 (m, 1H), 2.56 (dd, *J* = 18.6, 4.2 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.28 (s, 3H), 2.26 – 2.16 (m, 1H), 2.15 – 1.97 (m, 2H), 1.80 – 1.72 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.00, 167.18, 134.05, 133.98, 133.49, 131.54, 130.82, 128.77, 128.12, 126.80, 126.49, 125.79, 124.69, 117.10, 84.56, 31.80, 27.86, 26.90, 24.14, 23.33.

FTIR (NaCl, thin film, cm^{-1}): 3773,3663, 3344, 2904, 2415, 2204, 1752, 1718, 1710, 1690, 1286, 1241, 1108

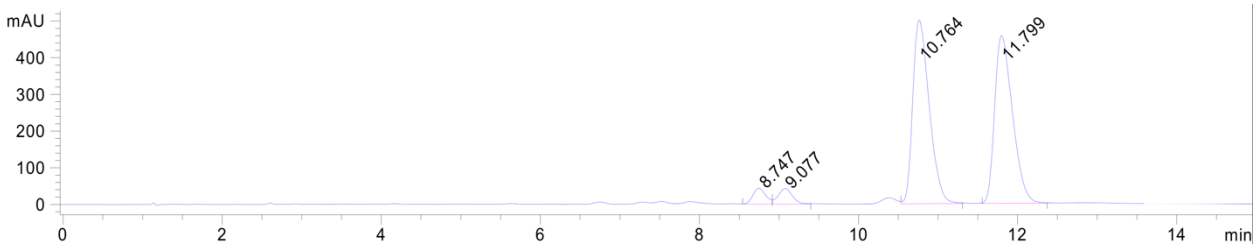
HRMS (TOF-ESI, m/z): calc'd for $C_{20}H_{20}O_3$ 309.1491 $[M+H]^+$; found: 309.1482

R_f = 0.58 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +55° (c = 1.0, $CHCl_3$).

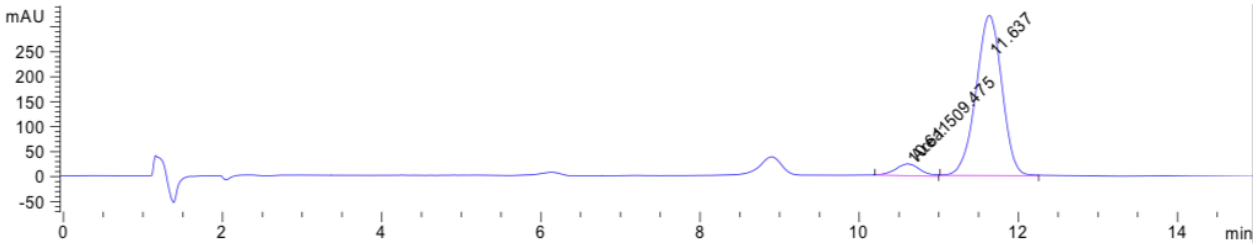
Chiral SFC: (IC column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 11.8 min, $t_{minor\ enantiomer}$ = 10.8 min; Minor regioisomer: $t_{major\ enantiomer}$ = 9.1 min, $t_{minor\ enantiomer}$ = 8.7 min

13b: racemic



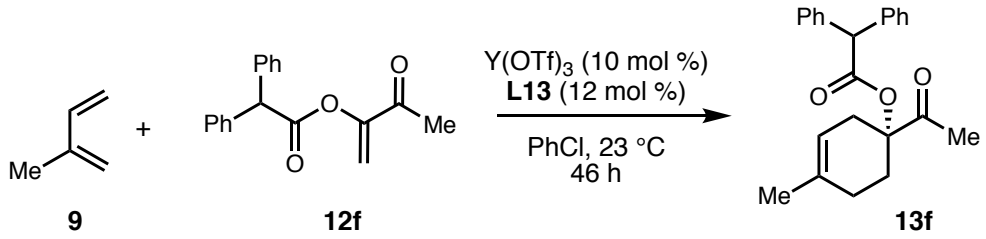
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.747	BV	0.1750	489.84641	43.63551	3.1926
2	9.077	VB	0.1883	525.65002	42.50008	3.4259
3	10.764	VB	0.2240	7208.45752	500.47107	46.9809
4	11.799	BB	0.2419	7119.42334	456.73462	46.4006

(+)-**13b**: enantioenriched, 87% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.611	MM	0.3593	509.47491	23.63209	6.5651
2	11.637	VB	0.3558	7250.85791	320.69696	93.4349

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl 2,2-diphenylacetate (13f):



9 **12f** **13f**

Prepared from **12f** (112 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 16:1 mixture of regioisomers favoring **13f** (131.0 mg, 0.376 mmol, 94%) in 86% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.24 (m, 10H), 5.24 (ddq, *J* = 4.8, 3.3, 1.5 Hz, 1H), 5.04 (s, 1H), 2.57 – 2.44 (m, 1H), 2.32 (dtd, *J* = 18.1, 3.2, 1.6 Hz, 1H), 2.16 (ddt, *J* = 11.4, 5.8, 2.1 Hz, 1H), 2.00 (s, 3H), 1.90 – 1.66 (m, 3H), 1.62 – 1.57 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.60, 171.84, 138.20, 138.17, 133.48, 128.83, 128.77, 128.74, 128.71, 127.53, 127.50, 116.50, 84.48, 57.28, 31.49, 27.63, 26.40, 24.00, 23.16.

FTIR (NaCl, thin film, cm^{-1}): 3752, 3058, 3027, 2921, 2355, 1733, 1718, 1685, 1507, 1492, 1449

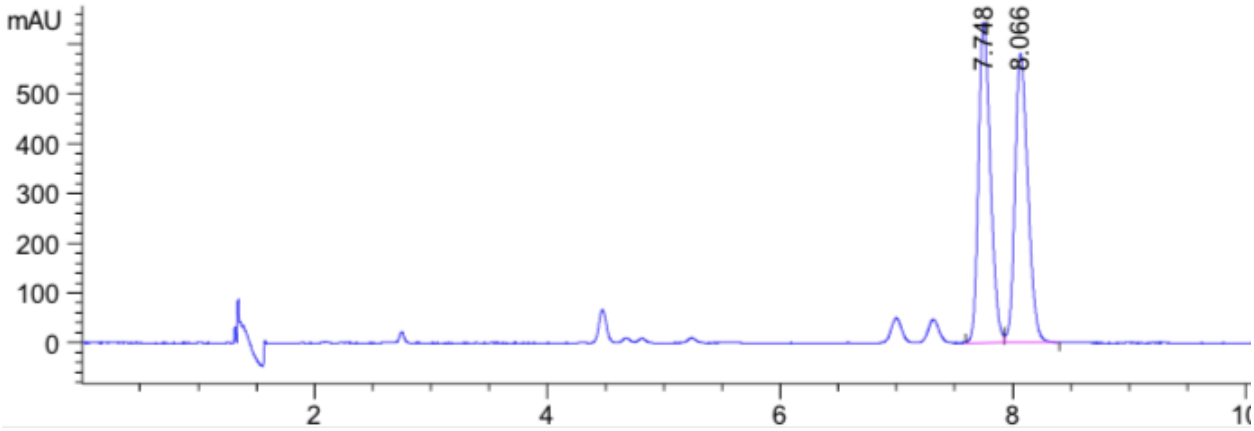
HRMS (TOF-ESI, m/z): calc'd for $C_{23}H_{24}O_3$ 349.1804 $[M+H]^+$; found: 349.1806

R_f = 0.58 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +15° (c = 1.0, $CHCl_3$).

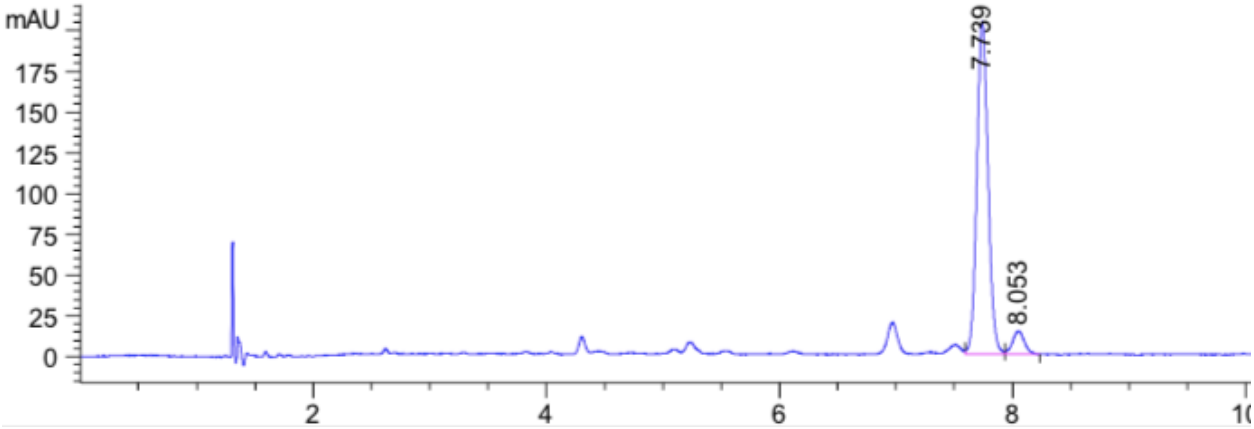
Chiral SFC: (IF-3 column, 2.5 mL/min, 7% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 11.8 min, $t_{minor\ enantiomer}$ = 10.8 min; Minor regioisomer: $t_{major\ enantiomer}$ = 9.1 min, $t_{minor\ enantiomer}$ = 8.7 min

13f: racemic



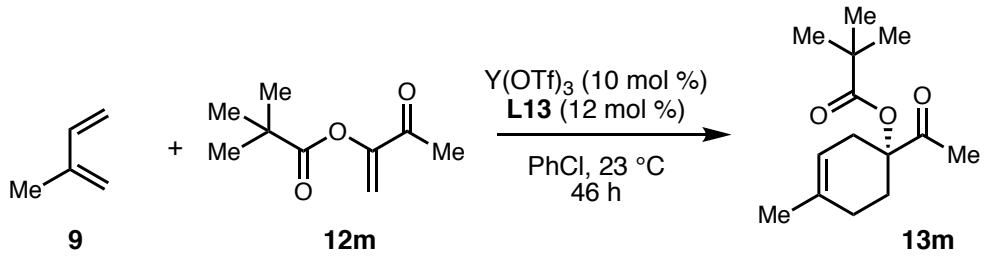
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.748	BV	0.1102	4588.94629	643.10370	50.6114
2	8.066	VB	0.1190	4478.07568	580.59039	49.3886

(+)-**13f**: enantioenriched, 86% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.739	VV	0.1037	1358.74060	203.95042	93.0916
2	8.053	VB	0.1076	100.83260	14.07512	6.9084

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl pivalate (13m):



9 **12m** **13m**

Prepared from **12m** (68.1 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a >20:1 mixture of regioisomers favoring **13m** (87.7 mg, 0.368 mmol, 92%) in 89% ee as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.34 – 5.23 (m, 1H), 2.53 (ddq, *J* = 18.0, 5.3, 2.5 Hz, 1H), 2.28 (dtd, *J* = 18.1, 3.2, 1.6 Hz, 1H), 2.20 (dddd, *J* = 13.3, 5.5, 3.2, 2.2 Hz, 1H), 2.10 (s, 3H), 2.08 – 1.91 (m, 2H), 1.85 (ddd, *J* = 13.3, 10.9, 6.0 Hz, 1H), 1.68 (dtt, *J* = 2.4, 1.6, 0.8 Hz, 3H), 1.21 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.06, 177.97, 133.20, 116.74, 83.23, 39.01, 31.44, 27.73, 27.09, 26.72, 23.78, 23.19.

FTIR (NaCl, thin film, cm^{-1}): 3613, 2971, 2933, 1729, 1479, 1455, 1395, 1357, 1292, 1255, 1208, 1165, 1068

HRMS (TOF-ESI, m/z): calc'd for $C_{14}H_{22}O_3$ 239.1647 $[M+H]^+$; found: 239.1633

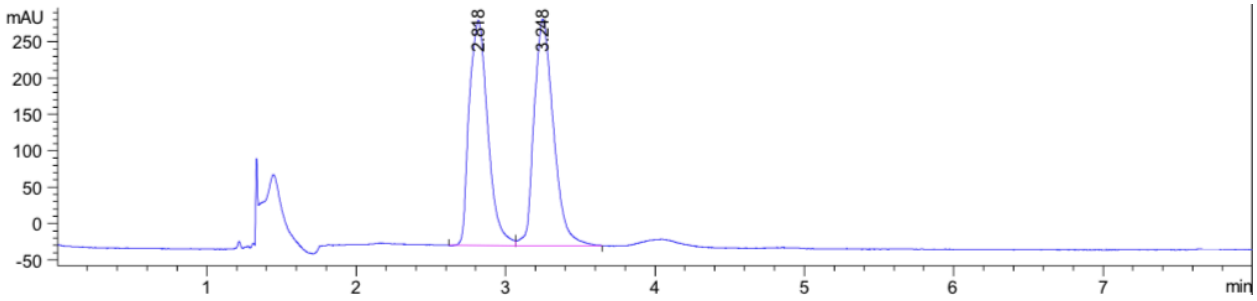
R_f = 0.62 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = –1° (c = 1.0, $CHCl_3$).

Chiral SFC: (AD-H column, 2.5 mL/min, 3% IPA/CO_2, λ = 210 nm): Major regioisomer:

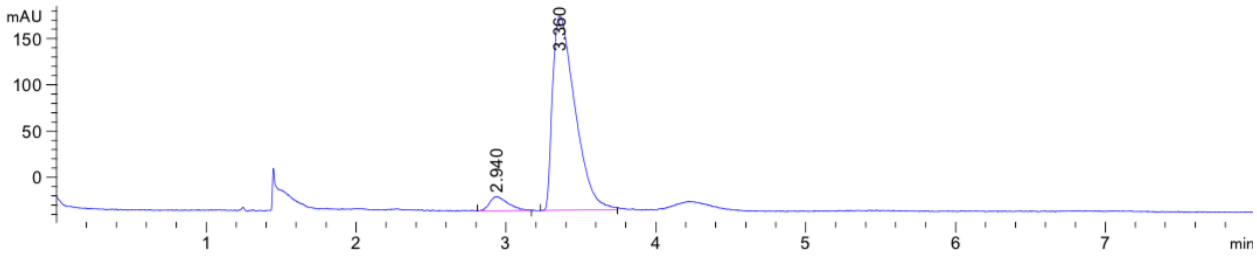
$t_{major\ enantiomer}$ = 3.2 min, $t_{minor\ enantiomer}$ = 2.8 min;

13m: racemic



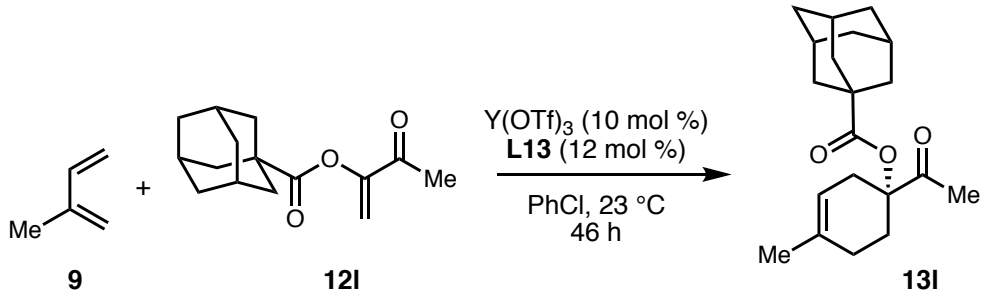
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.818	BV	0.1398	2670.98022	309.19012	48.6754
2	3.248	VB	0.1466	2816.35327	311.27582	51.3246

(–)-**13m**: enantioenriched, 89% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.940	BB	0.1025	131.24997	15.38453	5.6570
2	3.360	BB	0.1557	2188.86890	209.89313	94.3430

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl (3*R*,5*R*,7*R*)-adamantane-1-carboxylate (13l):



9 **12l** **13l**

Prepared from **12l** (99.3 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 13:1 mixture of regioisomers favoring **13l** (124.0 mg, 0.392 mmol, 98%) in 91% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 – 5.25 (m, 1H), 2.57 – 2.45 (m, 1H), 2.31 – 2.15 (m, 2H), 2.08 (s, 3H), 2.06 – 1.95 (m, 5H), 1.95 – 1.80 (m, 7H), 1.80 – 1.65 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.02, 176.92, 133.11, 116.59, 82.88, 40.77, 38.64, 36.43, 31.50, 27.86, 27.45, 26.54, 23.63, 23.12.

FTIR (NaCl, thin film, cm^{-1}): 2904, 2853, 1718, 1452, 1326, 1272, 1236, 1197, 1100, 1072

HRMS (TOF-ESI, m/z): calc'd for $C_{20}H_{28}O_3$ 317.2117 $[M+H]^+$; found: 317.2134

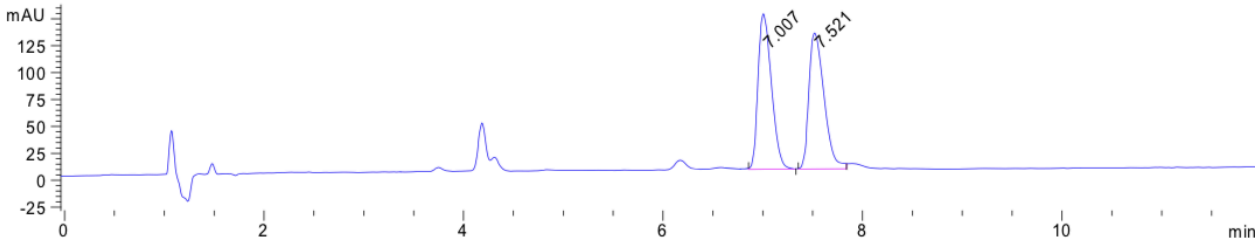
R_f = 0.62 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = –2° (c = 1.0, $CHCl_3$).

Chiral SFC: (AD-H column, 2.5 mL/min, 7% IPA/CO_2, λ = 210 nm): Major regioisomer:

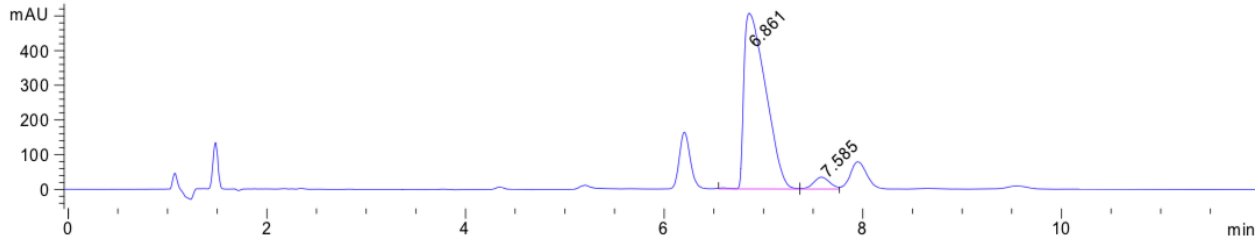
$t_{major\ enantiomer}$ = 5.1 min, $t_{minor\ enantiomer}$ = 5.5 min;

13l: racemic



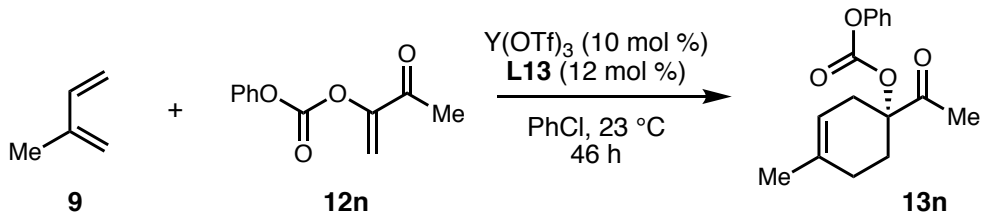
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.007	BB	0.1453	1348.42590	143.88983	50.2828
2	7.521	BB	0.1673	1333.25940	126.16438	49.7172

(–)-**13l**: enantioenriched, 91% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.861	BV	0.2493	7704.52588	506.91257	95.2684
2	7.585	VV	0.1753	382.65335	34.00994	4.7316

(*R*)-1-acetyl-4-methylcyclohex-3-en-1-yl phenyl carbonate (13n):



9 **12n** **13n**

Prepared from **12n** (82.5 mg, 0.40 mmol, 1.0 equiv), isoprene (200 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 14:1 mixture of regioisomers favoring **13n** (83.4 mg, 0.304 mmol, 76%) in 79% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.26 (m, 2H), 7.13 – 7.06 (m, 2H), 5.27 (dtt, *J* = 4.4, 2.8, 1.4 Hz, 1H), 2.62 – 2.49 (m, 1H), 2.45 – 2.33 (m, 1H), 2.31 – 2.14 (m, 4H), 2.11 – 2.01 (m, 1H), 2.00 – 1.81 (m, 2H), 1.66 (dq, *J* = 2.7, 1.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.06, 152.72, 151.05, 133.62, 129.65, 126.32, 121.05, 116.35, 86.47, 31.55, 27.79, 26.44, 24.27, 23.31.

FTIR (NaCl, thin film, cm^{-1}): 3416, 3021, 2918, 1754, 1731, 1592, 1555, 1493, 1455, 1357, 1274, 1190, 1161, 1071, 1024

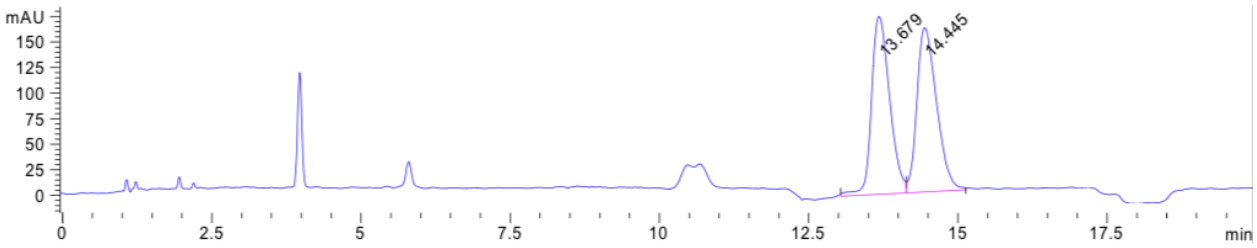
HRMS (TOF-ESI, m/z): calc'd $[M+H]^+$; found:

R_f = 0.58 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = –13° (c=1.0, $CHCl_3$)

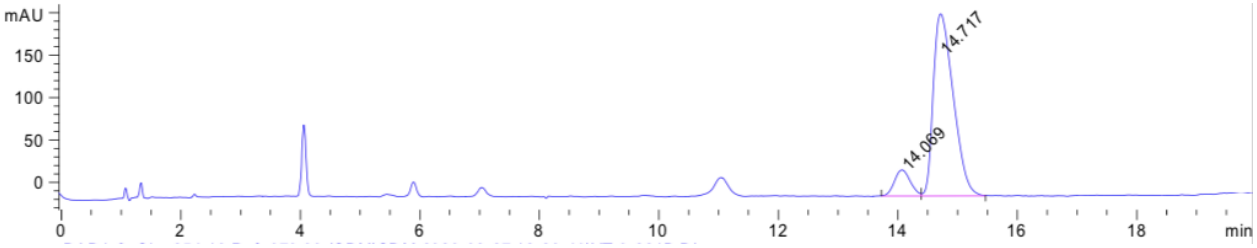
Chiral SFC: (IC column, 2.5 mL/min, 2% MeOH/CO_2, λ = 210 nm): $t_{major\ enantiomer}$ = 14.4 min, $t_{minor\ enantiomer}$ = 13.7 min

13n: racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.679	BV	0.3269	3680.62793	173.95299	49.9402
2	14.445	VB	0.3560	3689.43726	160.62555	50.0598

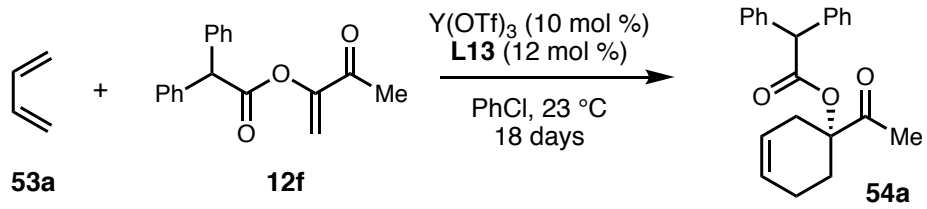
(–)-**13n**: enantioenriched, 79% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.069	BV	0.2923	570.79614	30.79262	10.2720
2	14.717	VB	0.3631	4985.99414	214.57884	89.7280

Diene Scope

(*R*)-1-acetylcyclohex-3-en-1-yl 2,2-diphenylacetate (54a):



53a **12f** **54a**

Prepared from **12f** (112 mg, 1.00 mmol, 1.0 equiv), 1,3-butadiene (20 wt% in PhMe) (671 μL, 5.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.7 mg, 0.10 mmol, 10 mol %), **L13** (39.7 mg, 0.12 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B stirring for 18 days. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford **54a** (36.1 mg, 0.108 mmol, 27%) in 65% ee as a thick pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.19 (m, 11H), 5.68 – 5.53 (m, 1H), 5.53 – 5.44 (m, 1H), 4.98 (s, 1H), 2.58 – 2.47 (m, 1H), 2.33 – 2.18 (m, 1H), 2.15 – 2.00 (m, 1H), 1.93 (s, 3H), 1.92 – 1.80 (m, 1H), 1.77 – 1.67 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.31, 171.88, 138.17, 128.80, 128.78, 128.75, 127.55, 126.20, 122.65, 84.51, 57.13, 31.17, 27.34, 23.84, 21.67.

FTIR (NaCl, thin film, cm^{-1}): 3028, 2926, 2847, 1813, 1731, 1600, 1557, 1494, 1453, 1359, 1234, 1183, 1148

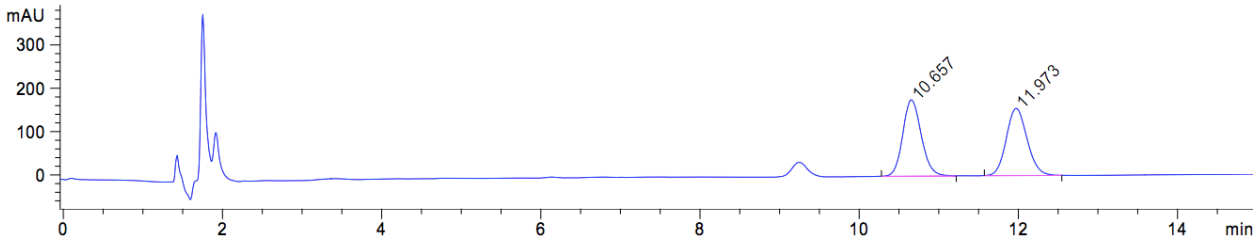
HRMS (GC-EI+, m/z): calc'd for $C_{22}H_{22}O_3$ 334.1569 $[M\bullet]^+$; found: 334.1588

R_f = 0.52 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +4 ° (c=1.0, $CHCl_3$)

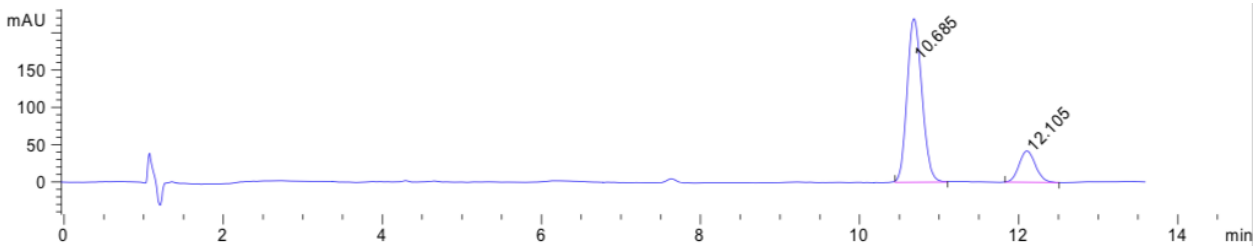
Chiral SFC: (AD-H column, 2.5 mL/min, 7% IPA/CO_2, λ = 210 nm): $t_{major\ enantiomer}$ = 10.6 min, $t_{minor\ enantiomer}$ = 12.0 min

54a: racemic



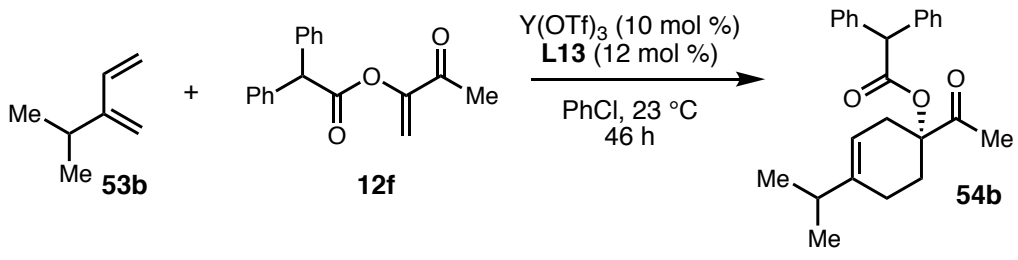
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.657	BB	0.2508	2854.31250	176.41522	50.2077
2	11.973	BB	0.2824	2830.69409	155.48384	49.7923

(+)-**54a**: enantioenriched, 65% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.685	BB	0.2038	2851.74634	219.10468	82.6104
2	12.105	BB	0.2225	600.29523	42.06343	17.3896

(*R*)-1-acetyl-4-isopropylcyclohex-3-en-1-yl 2,2-diphenylacetate (54b):



Prepared from **12f** (112 mg, 0.4 mmol, 1.0 equiv), diene **53b** (192 mg, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.04 mmol, 10 mol %), **L13** (39.7 mg, 0.05 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 13:1 mixture of regioisomers favoring **54b** (131.0 mg, 0.348 mmol, 87%) in 83% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.21 (m, 13H), 5.26 (td, *J* = 3.2, 1.7 Hz, 1H), 5.04 (s, 1H), 2.60 – 2.51 (m, 1H), 2.34 (dd, *J* = 18.9, 4.7 Hz, 1H), 2.24 – 2.05 (m, 2H), 2.02 (s, 3H), 1.94 – 1.73 (m, 2H), 0.91 (dd, *J* = 6.8, 3.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.59, 171.94, 142.89, 138.25, 138.18, 128.80, 128.79, 128.74, 127.58, 127.50, 113.87, 84.76, 57.20, 34.72, 31.43, 27.81, 24.06, 22.32, 21.51, 21.17.

FTIR (NaCl, thin film, cm^{-1}): 3027, 2961, 1731, 1694, 1600, 1494, 1454, 1350, 1235, 1189, 1146, 1065, 985

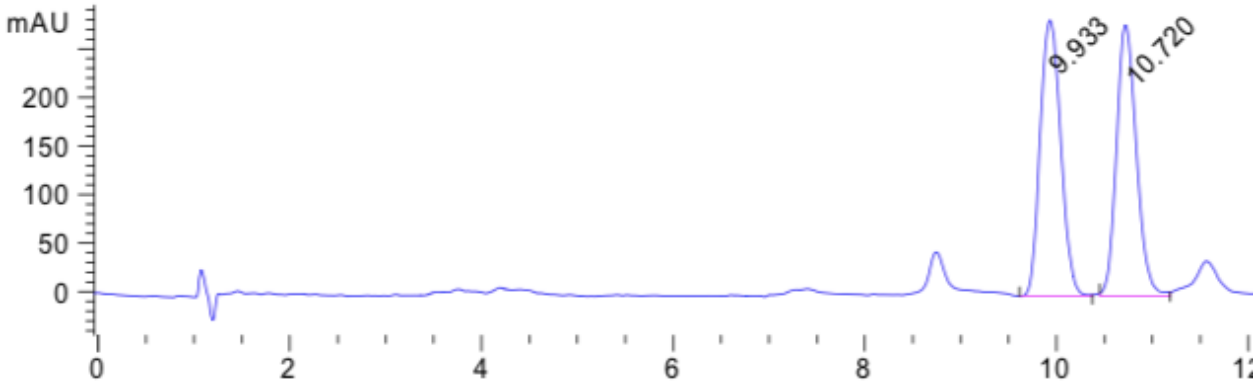
HRMS (TOF-ESI, m/z): calc'd for $C_{25}H_{29}O_3$ 377.2117 $[M+H]^+$; found: 377.2135

R_f = 0.59 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +15° (c = 1.0, $CHCl_3$).

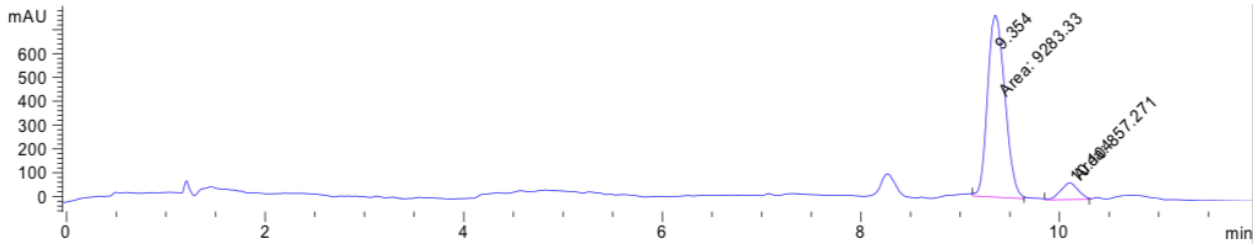
Chiral SFC: (IC column, 2.5 mL/min, 20% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 9.2 min, $t_{minor\ enantiomer}$ = 11.9 min

54b: racemic



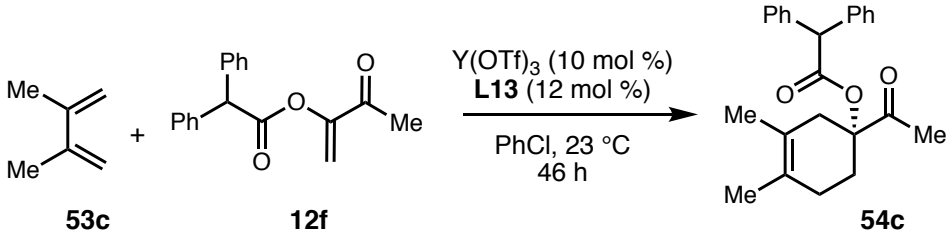
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.933	BB	0.2385	4245.60010	283.90033	51.1328
2	10.720	BB	0.2257	4057.47949	279.00244	48.8672

(+)-**54b**: enantioenriched, 83% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.354	MM	0.2025	9283.33203	763.99982	91.5462
2	10.104	MM	0.2016	857.27051	70.86095	8.4538

(*R*)-1-acetyl-3,4-dimethylcyclohex-3-en-1-yl 2,2-diphenylacetate (54c):



53c **12f** **54c**

Prepared from **12f** (112 mg, 0.40 mmol, 1.0 equiv), 2,3-dimethylbutadiene (226 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford **54c** (144 mg, 0.397 mmol, 99%) in 97% ee as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 10H), 5.05 (s, 1H), 2.55 (d, *J* = 17.9 Hz, 1H), 2.21 (d, *J* = 17.9 Hz, 1H), 2.10 (dtd, *J* = 13.1, 4.2, 2.2 Hz, 1H), 2.02 (s, 3H), 1.89 – 1.82 (m, 2H), 1.81 – 1.71 (m, 1H), 1.57 (d, *J* = 11.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.58, 171.84, 138.20, 129.85, 128.79, 128.75, 128.70, 127.49, 127.48, 126.57, 124.87, 121.37, 85.48, 57.22, 36.66, 28.12, 27.91, 23.97, 18.92, 18.63.

FTIR (NaCl, thin film, cm^{-1}): 2915, 1732, 1496, 1452, 1352, 1184, 1149, 1077, 747, 700

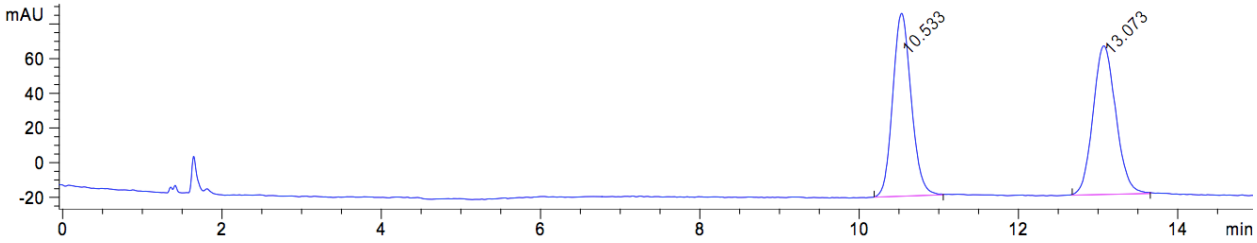
HRMS (TOF-ESI, m/z): calc'd for $C_{24}H_{26}O_3$ 363.1960 $[M+H]^+$; found: 363.1988

R_f = 0.56 in 25% EtOAc/Hex. ($KMnO_4$, UV-Active)

$\boldsymbol{\alpha_D^{22}}$ = +1° (c = 1.0, $CHCl_3$).

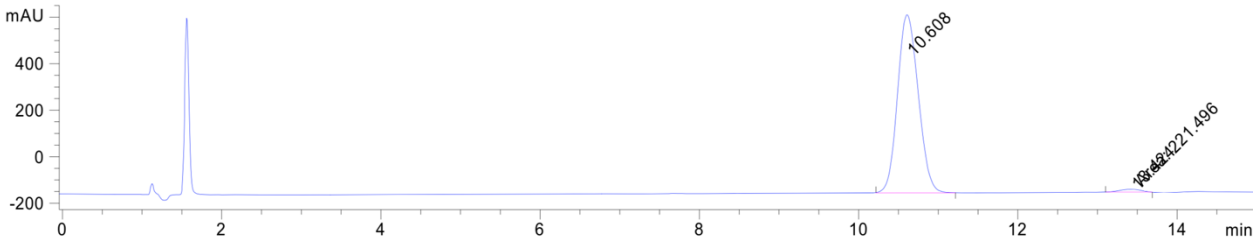
Chiral SFC: (AD-H column, 2.5 mL/min, 7% IPA/CO_2, λ = 210 nm): $t_{major\ enantiomer}$ = 10.5 min, $t_{minor\ enantiomer}$ = 13.1 min

54c: racemic



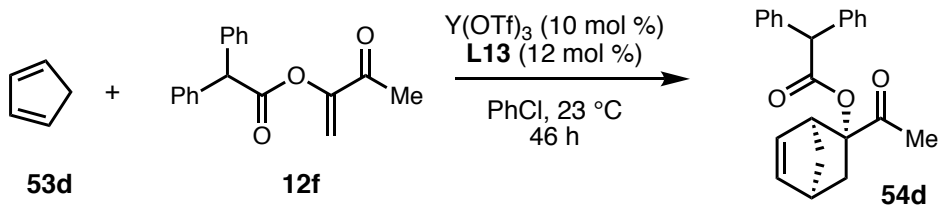
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.533	BB	0.2460	1699.43506	105.47459	49.9032
2	13.073	BB	0.3080	1706.02844	85.78955	50.0968

(+)-**54c**: enantioenriched, 97% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.608	BB	0.2877	1.39016e4	766.23273	98.4317
2	13.424	MM	0.3005	221.49564	12.28451	1.5683

(1*S*,2*R*,4*S*)-2-acetylbicyclo[2.2.1]hept-5-en-2-yl 2,2-diphenylacetate (54d):



53d **12f** **54d**

Prepared from **12f** (112 mg, 0.40 mmol, 1.0 equiv), cyclopentadiene (168 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:20 EtOAc/Hexanes) to afford a 11:1 mixture of diastereomers favoring **54d** (120 mg, 0.346 mmol, 87%) in 90% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.15 (m, 10H), 6.22 (dd, *J* = 5.6, 3.0 Hz, 1H), 5.85 (dd, *J* = 5.7, 3.0 Hz, 1H), 4.89 (s, 1H), 3.02 (dq, *J* = 3.2, 1.7 Hz, 1H), 2.79 (dq, *J* = 3.3, 1.7 Hz, 1H), 2.55 (dd, *J* = 12.9, 3.6 Hz, 1H), 1.88 (s, 3H), 1.51 (dd, *J* = 9.3, 1.7 Hz, 1H), 1.32 (ddt, *J* = 9.1, 3.6, 1.8 Hz, 1H), 1.05 (dd, *J* = 13.0, 3.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.46, 172.22, 140.38, 137.91, 137.75, 132.83, 128.83, 128.76, 128.75, 128.71, 127.64, 127.57, 93.82, 56.91, 49.45, 46.76, 42.13, 38.15, 24.60.

FTIR (NaCl, thin film, cm^{-1}): 3063, 2980, 1732, 1600, 1496, 1455, 1354, 1335, 1242, 1186, 1146, 1082, 1050, 982, 727, 700

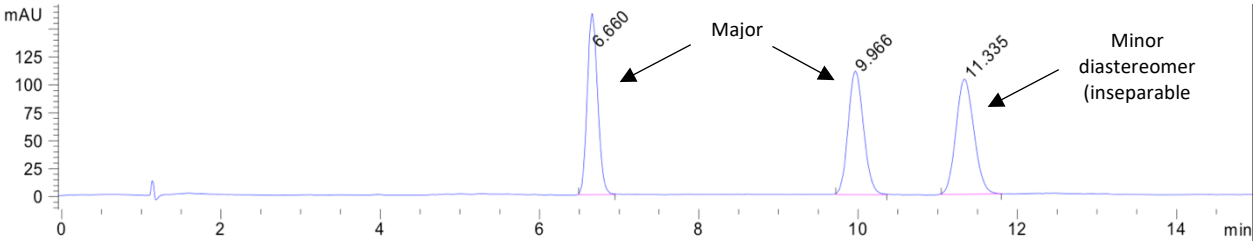
HRMS (GC-FAB+, m/z): calc'd for $C_{23}H_{22}O_3$ 347.1647 $[M+H]^+$; found: 347.1642

R_f = 0.52 (20% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +60° (c = 1.0, $CHCl_3$).

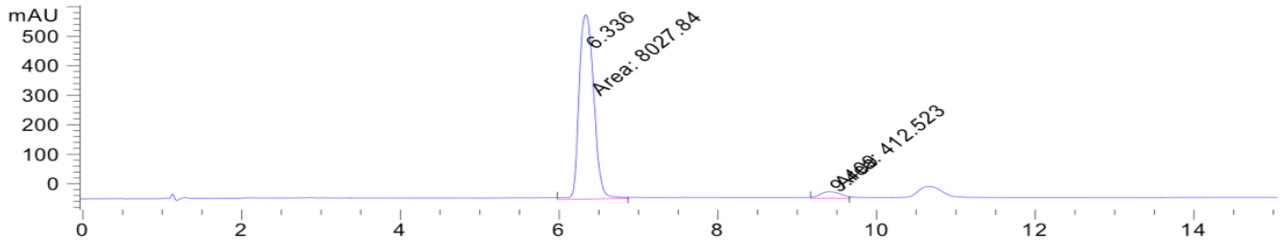
Chiral SFC: (IC column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): $t_{major\ enantiomer}$ = 6.6 min, $t_{minor\ enantiomer}$ = 10.0 min

54d: racemic



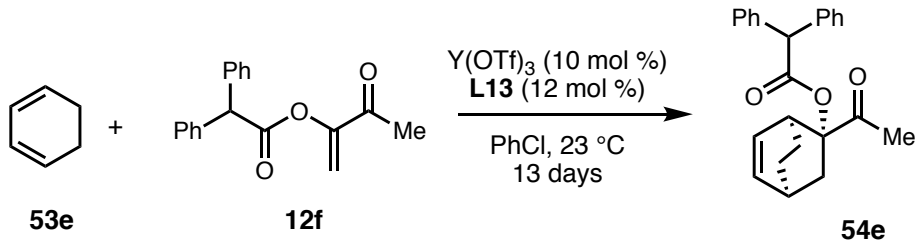
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.660	BB	0.1422	1471.86182	161.76608	32.1574
2	9.966	BB	0.2090	1487.06177	110.51853	32.4894
3	11.335	BB	0.2472	1618.13733	103.03159	35.3532

(+)-**54d**: enantioenriched, 90% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.336	MM	0.2139	8027.84229	625.65503	95.1125
2	9.409	MM	0.3097	412.52322	22.20121	4.8875

(1*S*,2*R*,4*S*)-2-acetylbicyclo[2.2.2]oct-5-en-2-yl 2,2-diphenylacetate (54e):



53e **12f** **54e**

Prepared from **12f** (112 mg, 0.40 mmol, 1.0 equiv), 1,3-cyclohexadiene (190 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B allowing the reaction to run for 13 days. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford 7:1 mixture of diastereomers favoring **54e** (99.5 mg, 0.276 mmol, 69%) in 66% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (m, 10H), 6.29 (ddd, *J* = 7.9, 6.5, 1.1 Hz, 1H), 6.00 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 5.08 (s, 1H), 2.85 (dtd, *J* = 6.7, 2.7, 1.1 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.37 (dt, *J* = 14.2, 3.1 Hz, 1H), 1.95 (s, 3H), 1.88 – 1.80 (m, 1H), 1.29 (ddd, *J* = 14.2, 5.2, 2.2 Hz, 2H), 1.20 (tq, *J* = 12.0, 3.3 Hz, 1H), 1.11 – 0.99 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.37, 171.94, 146.08, 137.99, 135.99, 129.50, 128.86, 128.78, 128.76, 128.75, 127.63, 127.58, 88.41, 57.07, 36.37, 35.91, 30.11, 24.50, 23.73, 19.87.

FTIR (NaCl, thin film, cm^{-1}): 3028, 3060, 2947, 2864, 1731, 1600, 1495, 1453, 1432, 1354, 1275, 1227, 1168, 1149

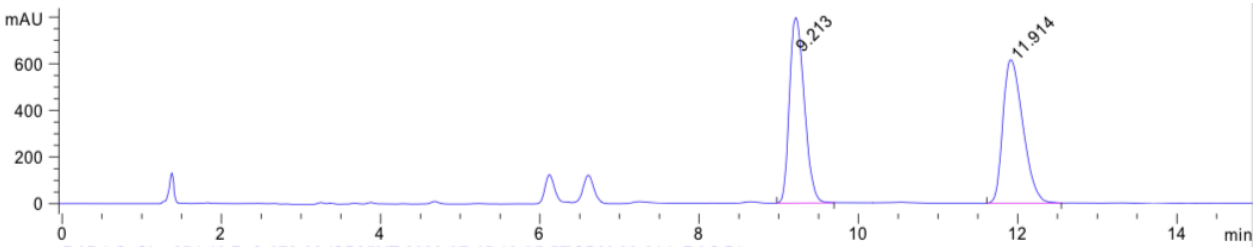
HRMS (GC-Ei+, m/z): calc'd for $C_{24}H_{24}O_3$ 360.1726 $[M\bullet]^+$; found: 360.1746

R_f = 0.52 (25% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = –7.3° (c = 1.0, $CHCl_3$).

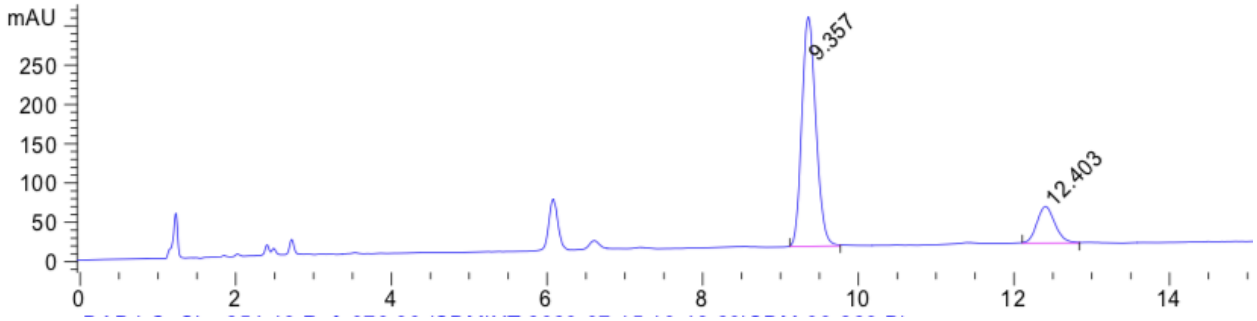
Chiral SFC: (IC column, 2.5 mL/min, 20% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 9.2 min, $t_{minor\ enantiomer}$ = 11.9 min

54e: racemic



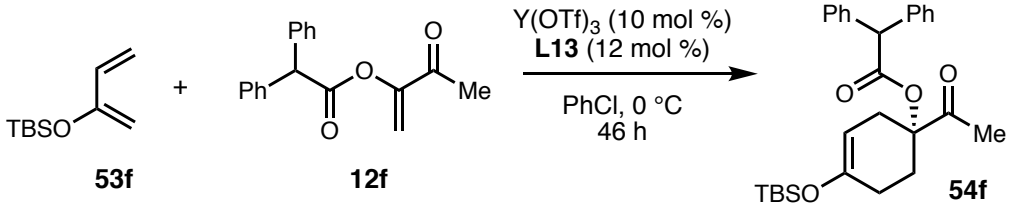
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.213	BB	0.2073	1.02989e4	794.21033	48.9473
2	11.914	BB	0.2758	1.07419e4	614.86285	51.0527

(–)-**54e**: enantioenriched, 66% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.357	BB	0.1985	3664.80786	291.90411	83.0375
2	12.403	BB	0.2437	748.62927	46.53930	16.9625

(*R*)-1-acetyl-4-((*tert*-butyldimethylsilyl)oxy)cyclohex-3-en-1-yl 2,2-diphenylacetate (54f):



53f **12f** **54f**

Prepared from **12f** (112 mg, 0.40 mmol, 1.0 equiv), diene **53f** (369 mg, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B at 0 °C. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a >20:1 mixture of regioisomers favoring **54f** (148.7 mg, 0.32 mmol, 80%) in 84% ee as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.18 (m, 10H), 4.97 (s, 1H), 4.60 (ddt, *J* = 5.0, 2.6, 1.2 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.28 (ddq, *J* = 17.4, 4.9, 1.6 Hz, 1H), 2.21 – 2.02 (m, 1H), 1.92 (s, 3H), 1.91 – 1.78 (m, 3H), 0.83 (d, *J* = 6.7 Hz, 9H), 0.00 (s, 3H), -0.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.20, 172.05, 149.80, 138.19, 138.10, 128.87, 128.79, 128.72, 128.70, 127.64, 127.56, 99.04, 84.09, 56.99, 30.69, 27.60, 26.03, 25.77, 24.06, 18.12, -4.26, -4.41.

FTIR (NaCl, thin film, cm^{-1}): 3416, 3334, 3087, 3005, 3062, 3029, 2857, 1951, 1805, 1731, 1681, 1632, 1510, 1495, 1360

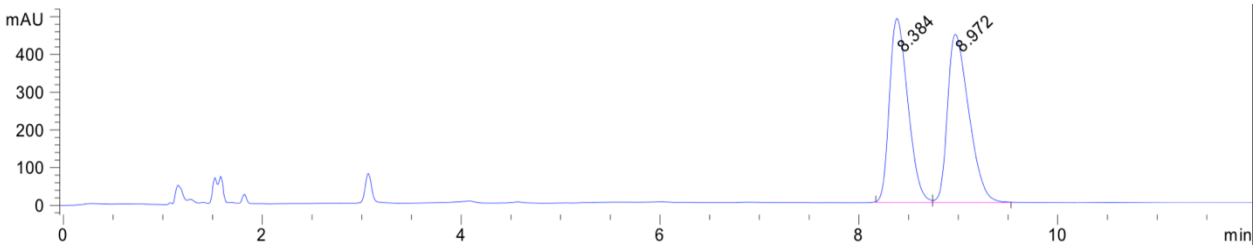
HRMS (GC-FAB+, m/z): calc'd for: $C_{28}H_{37}SiO_4$ 465.2461 $[M+H]^+$; found: 465.2463

R_f = 0.60 (25% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +7.6° (c = 1.0, $CHCl_3$).

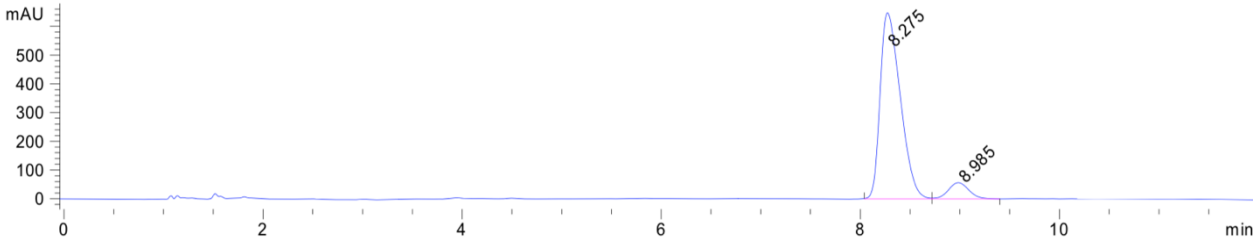
Chiral SFC: (OJ-H column, 2.5 mL/min, 5% IPA/CO_2, λ = 210 nm): $t_{major\ enantiomer}$ = 8.4 min, $t_{minor\ enantiomer}$ = 9.0 min

54f: racemic



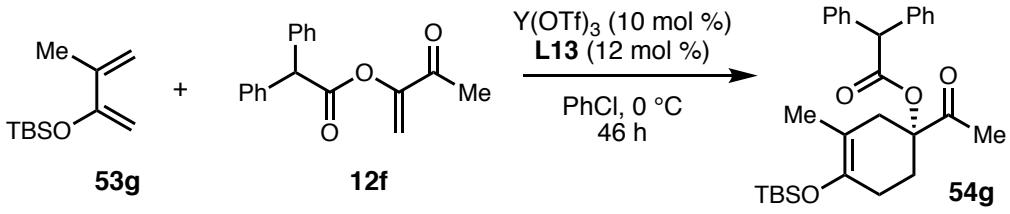
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.384	BV	0.1987	6302.90332	487.85507	48.6900
2	8.972	VB	0.2298	6642.07227	445.80899	51.3100

(+)-**54f**: enantioenriched, 84% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.275	BV	0.2201	9092.65234	646.55402	91.8949
2	8.985	VB	0.2217	801.97186	56.47663	8.1051

(*R*)-1-acetyl-4-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-3-en-1-yl 2,2-diphenylacetate (54g):



Prepared from **12f** (112 mg, 0.40 mmol, 1.0 equiv), diene **53g** (397 mg, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %)

and chlorobenzene (0.4 mL) following General Procedure B at 0 °C. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a >20:1 mixture of regioisomers favoring **54g** (153.2 mg, 0.320 mmol, 80%) in 86% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.17 (m, 11H), 5.04 (s, 1H), 2.52 (ddt, *J* = 17.7, 2.8, 1.5 Hz, 1H), 2.27 – 2.14 (m, 2H), 2.00 (s, 3H), 1.97 – 1.84 (m, 3H), 1.56 – 1.51 (m, 3H), 0.90 (s, 9H), -0.01 (d, *J* = 4.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.03, 172.08, 142.10, 138.25, 138.08, 128.88, 128.79, 128.70, 128.63, 127.66, 127.56, 107.00, 84.78, 56.88, 36.30, 28.15, 26.35, 24.04, 18.26, 16.09, -3.70, -3.87.

FTIR (NaCl, thin film, cm^{-1}): 3451, 3061, 3029, 2942, 2865, 2725, 1952, 1806, 1733, 1692, 1623, 1600, 1495, 1464, 1453, 1380, 1352

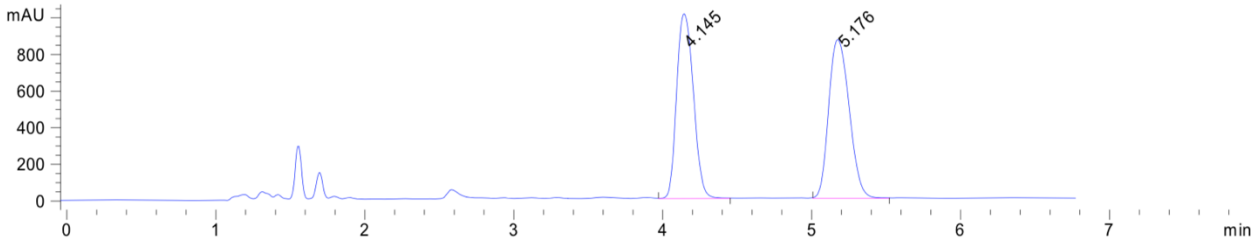
HRMS (GC-FAB+, m/z): calc'd for: $C_{29}H_{39}SiO_4$ 479.2618 $[M+H]^+$; found: 479.2622

R_f = 0.64 (25% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +0.48° (c = 1.0, $CHCl_3$).

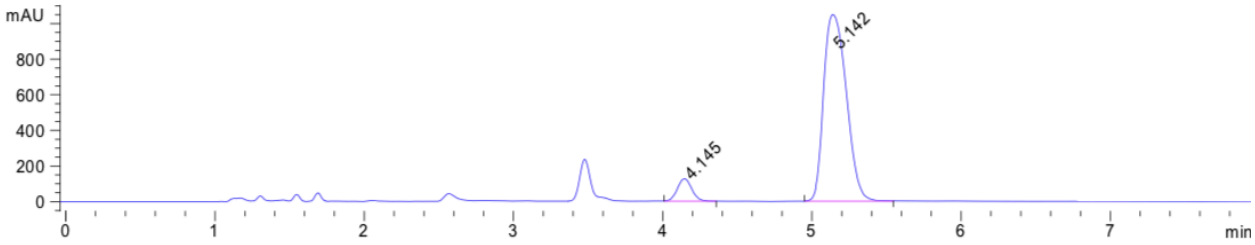
Chiral SFC: (OJ-H column, 2.5 mL/min, 5% IPA/CO_2, λ = 210 nm): $t_{major\ enantiomer}$ = 5.1 min, $t_{minor\ enantiomer}$ = 4.1 min

54g: Racemic



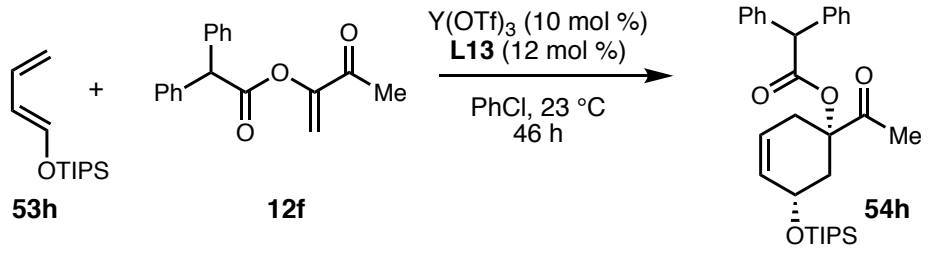
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.145	VB	0.1275	7899.81055	1006.79230	48.7013
2	5.176	BB	0.1520	8321.12695	866.71655	51.2987

(+)-**54g**: enantioenriched, 86% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.145	BB	0.1065	849.96973	126.33739	7.1055
2	5.142	BB	0.1718	1.11122e4	1047.52942	92.8945

(1*S*,5*S*)-1-acetyl-5-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl 2,2-diphenylacetate (54h):



Prepared from **12f** (112 mg, 0.40 mmol, 1.0 equiv), diene **53h** (453 mg, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a >20:1 mixture of regioisomers and >20:1 mixture of diastereomers favoring **54f** (191 mg, 0.376 mmol, 94%) in 73% ee as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.19 (m, 11H), 6.25 (dd, *J* = 11.8, 0.7 Hz, 1H), 5.10 – 4.98 (m, 2H), 3.06 – 2.96 (m, 1H), 2.64 – 2.52 (m, 1H), 1.99 – 1.79 (m, 2H), 1.73 (s, 3H), 1.69 – 1.59 (m, 1H), 1.13 – 0.98 (m, 27H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.42, 171.64, 143.42, 137.98, 137.88, 128.84, 128.82, 128.74, 127.64, 127.56, 108.59, 88.38, 57.02, 41.89, 26.70, 24.12, 22.59, 17.87, 17.84, 12.09.

FTIR (NaCl, thin film, cm^{-1}): 3417, 3062, 3030, 2942, 2869, 2728, 2307, 1953, 1714, 1567, 1600, 1496, 1463, 1453, 1354

HRMS (GC-FAB+, m/z): calc'd for $C_{31}H_{43}SiO_4$ 507.2931 $[M+H]^+$; found: 507.2923

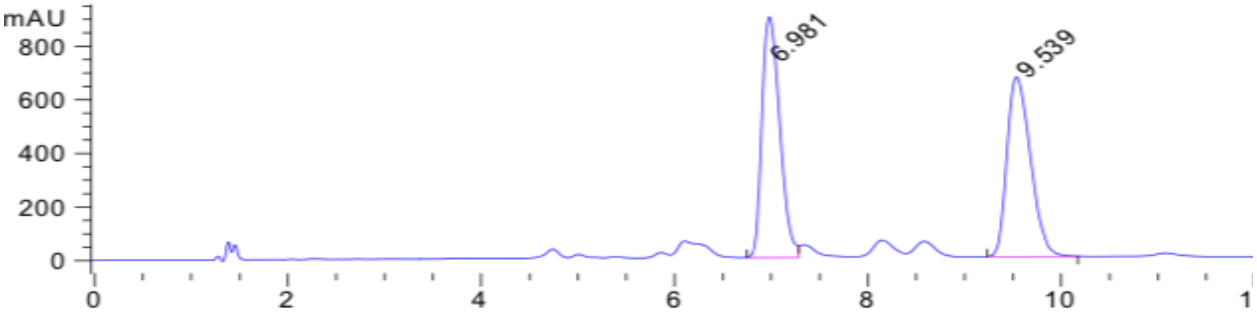
R_f = 0.68 (25% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = –17° (c = 1.0, $CHCl_3$).

Chiral SFC: (IC column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): Major regioisomer:

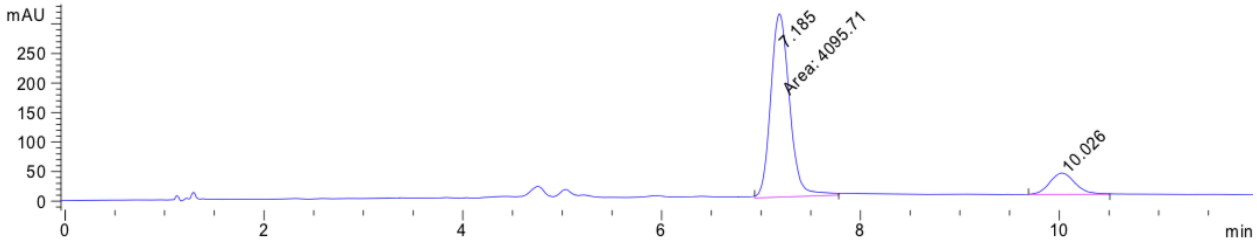
$t_{major\ enantiomer}$ = 7.0 min, $t_{minor\ enantiomer}$ = 9.5 min

54f: racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.981	BV	0.2058	1.15219e4	897.21442	50.3593
2	9.539	BB	0.2698	1.13575e4	669.96619	49.6407

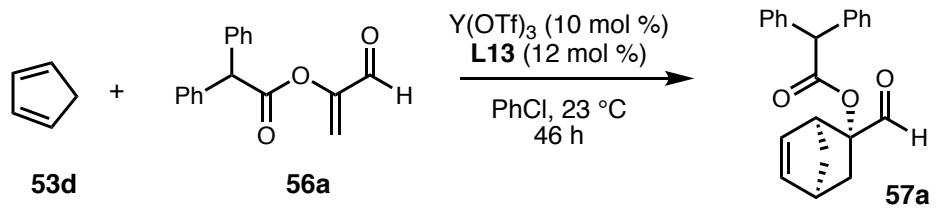
(–)-**54f**: enantioenriched, 73% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.185	MM	0.2195	4095.71118	310.97922	86.4563
2	10.026	BB	0.2754	641.61078	36.10050	13.5437

Dienophile Scope

(1*S*,2*R*,4*S*)-2-propionylbicyclo[2.2.1]hept-5-en-2-yl 2,2-diphenylacetate (57a):



53d **56a** **57a**

Prepared from **56a** (107 mg, 0.40 mmol, 1.0 equiv), cyclopentadiene (168 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 8:1 mixture of diastereomers favoring **57a** (119.7 mg, 0.332 mmol, 66%) in 19% ee as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.37 – 7.24 (m, 15H), 6.31 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.89 (dd, *J* = 5.6, 3.0 Hz, 1H), 5.00 (s, 1H), 3.16 (s, 1H), 2.93 (s, 1H), 2.49 (dd, *J* = 13.1, 3.6 Hz, 1H), 1.68 (d, *J* = 9.3 Hz, 1H), 1.46 – 1.39 (m, 1H), 1.18 (dd, *J* = 13.1, 3.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.60, 172.65, 140.67, 138.04, 132.53, 128.75, 128.66, 127.62, 127.55, 92.20, 56.67, 48.74, 45.87, 42.25, 38.04.

FTIR (NaCl, thin film, cm^{-1}): 3027, 2978, 1731, 1598, 1494, 1453, 1333, 1235, 1151, 1045, 724, 702, 677, 587.

HRMS (GC-EI+, m/z): calc'd for $C_{22}H_{20}O_3$ 332.14070 $[M+H]^+$; found: 332.14106

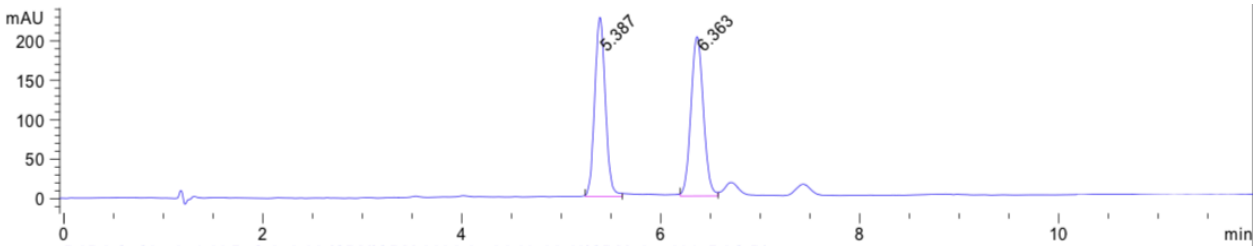
R_f = 0.63 (15% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +14° (c = 1.0, $CHCl_3$).

Chiral SFC: (IC column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): Major regioisomer:

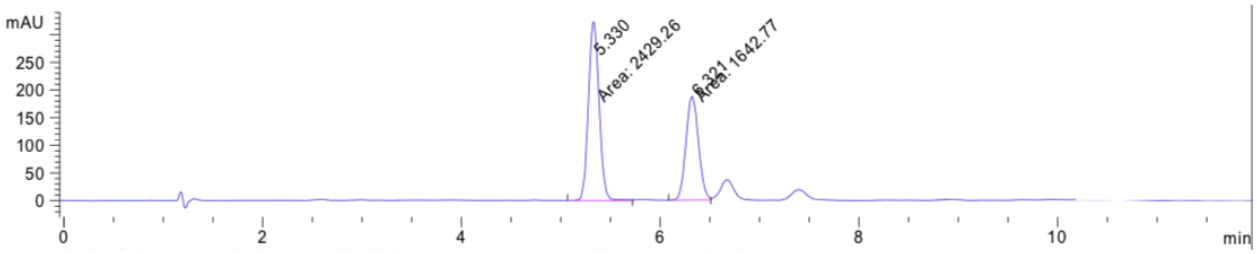
$t_{major\ enantiomer}$ = 5.3 min, $t_{minor\ enantiomer}$ = 6.3 min

57a: racemic



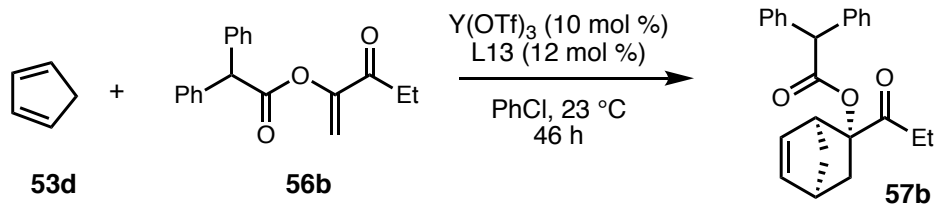
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.387	BB	0.1149	1686.46667	226.53426	49.0412
2	6.363	BV	0.1375	1752.40991	201.48439	50.9588

(+)-**57a**: enantioenriched, 19% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.330	MM	0.1247	2429.25513	324.58899	59.6571
2	6.321	MM	0.1457	1642.77222	187.97464	40.3429

(1*S*,2*R*,4*S*)-2-propionylbicyclo[2.2.1]hept-5-en-2-yl 2,2-diphenylacetate (57b):



53d **56b** **57b**

Prepared from **56b** (118 mg, 0.40 mmol, 1.0 equiv), cyclopentadiene (168 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 15:1 mixture of diastereomers favoring **57b** (119.7 mg, 0.332 mmol, 83%) in 80% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.22 (m, 12H), 6.34 – 6.24 (m, 1H), 5.90 (dd, *J* = 5.6, 3.0 Hz, 1H), 4.95 (s, 1H), 3.12 – 3.06 (m, 1H), 2.92 – 2.83 (m, 1H), 2.73 – 2.57 (m, 1H), 2.31 (dq, *J* = 17.7, 7.3 Hz, 1H), 1.67 – 1.48 (m, 3H), 1.39 (ddt, *J* = 9.2, 3.7, 1.8 Hz, 1H), 1.13 (dd, *J* = 13.0, 3.7 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.42, 172.18, 140.29, 137.81, 132.94, 128.73, 127.55, 93.73, 56.96, 49.71, 46.86, 42.11, 38.42, 29.65, 8.26.

FTIR (NaCl, thin film, cm^{-1}): 3417, 3063, 3030, 2953, 2979, 2876, 1956, 1731, 1714, 1680, 1600, 1512, 1479, 1454, 1335, 1311, 1274, 1231

HRMS (GC-EI+, m/z): calc'd for $C_{24}H_{24}O_3$ 360.1726 $[M\bullet]^+$; found: 360.1737

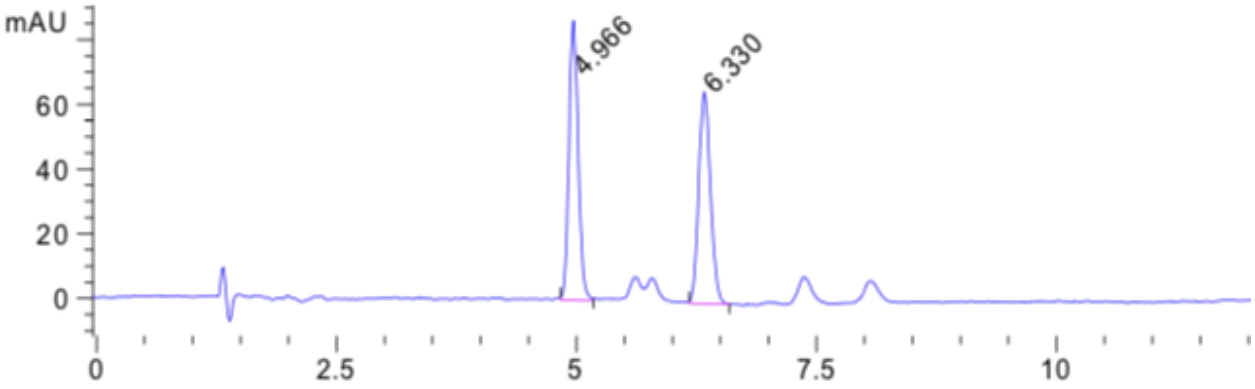
R_f = 0.63 (25% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +61° (c = 1.0, $CHCl_3$).

Chiral SFC: (IC column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): Major regioisomer:

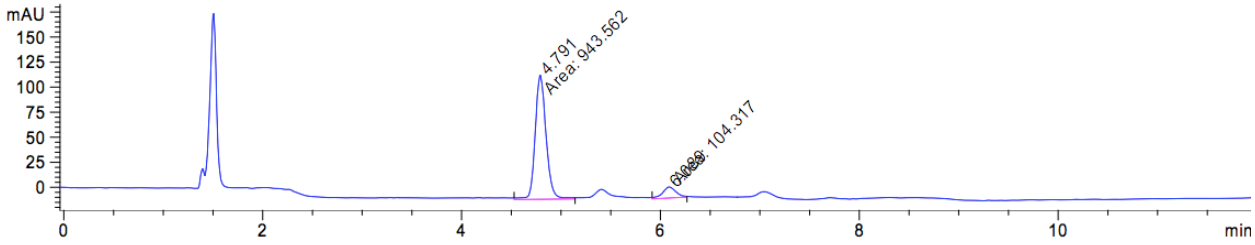
$t_{major\ enantiomer}$ = 5.0 min, $t_{minor\ enantiomer}$ = 6.3 min

57b: racemic



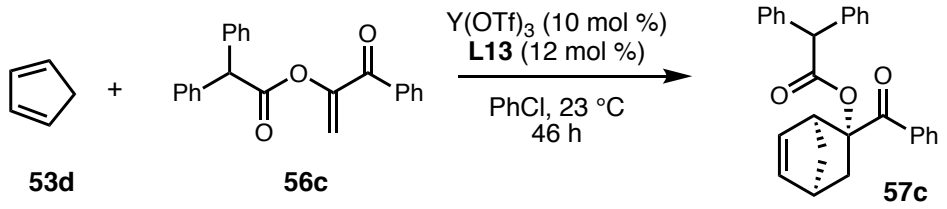
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.966	BB	0.1064	579.53247	86.19553	51.0291
2	6.330	BB	0.1314	556.15833	65.26940	48.9709

(+)-**57b**: enantioenriched, 80% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.791	MM	0.1262	943.56219	124.56985	90.0450
2	6.089	MM	0.1576	104.31657	11.02837	9.9550

(1*S*,2*R*,4*S*)-2-benzoylbicyclo[2.2.1]hept-5-en-2-yl 2,2-diphenylacetate (57c):



53d **56c** **57c**

Prepared from **56c** (137 mg, 0.40 mmol, 1.0 equiv), cyclopentadiene (168 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford **57c** (153.6 mg, 0.376 mmol, 94%) in 86% ee as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.75 (m, 2H), 7.42 (ddt, *J* = 7.7, 7.0, 1.3 Hz, 1H), 7.28 – 7.07 (m, 9H), 7.04 – 6.97 (m, 2H), 6.90 – 6.82 (m, 2H), 6.39 (dd, *J* = 5.7, 3.0 Hz, 1H), 5.92 (dd, *J* = 5.7, 3.0 Hz, 1H), 4.75 (s, 1H), 3.65 (dtd, *J* = 2.9, 1.9, 1.1 Hz, 1H), 2.95 (ddp, *J* = 4.0, 3.2, 1.2 Hz, 1H), 2.70 (dd, *J* = 12.5, 3.7 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.59 – 1.47 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.55, 171.49, 140.23, 137.51, 134.75, 132.87, 132.18, 129.01, 128.54, 128.42, 128.32, 127.99, 127.16, 126.99, 92.23, 56.68, 50.30, 47.93, 41.95, 40.24.

FTIR (NaCl, thin film, cm^{-1}): 3027, 3061, 2982, 1731, 1688, 1651, 1598, 1495, 1448, 1333, 1309, 1269, 1246, 1146, 1138, 1117, 1029

HRMS (TOF-ESI, m/z): calc'd for $C_{28}H_{25}O_3$ 409.1804 $[M+H]^+$; found: 409.1816

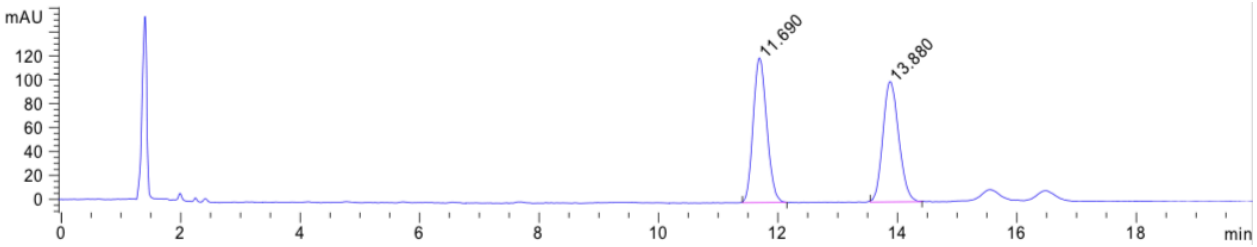
R_f = 0.59 (25% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +2.4° (c = 1.0, $CHCl_3$).

Chiral SFC: (IC column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): Major regioisomer:

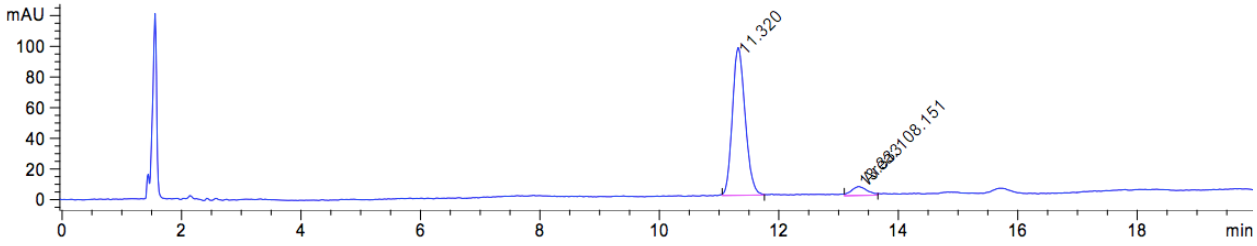
$t_{major\ enantiomer}$ = 11.7 min, $t_{minor\ enantiomer}$ = 13.9 min

57c: racemic



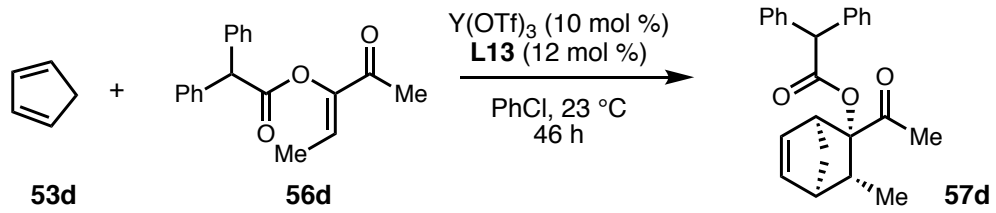
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.690	BB	0.2439	1907.50488	120.98746	50.6005
2	13.880	BB	0.2838	1862.23389	100.66818	49.3995

(+)-**57c**: enantioenriched, 86% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.320	BB	0.2294	1431.49072	96.28727	92.9756
2	13.333	MM	0.3084	108.15099	5.84496	7.0244

(1*S*,2*R*,3*R*,4*R*)-2-acetyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl 2,2-diphenylacetate (57d):



53d **56d** **57d**

Prepared from **56d** (118 mg, 0.40 mmol, 1.0 equiv), cyclopentadiene (168 μL, 2.0 mmol, 5.0 equiv), $Y(OTf)_3$ (21.4 mg, 0.040 mmol, 10 mol %), **L13** (39.7 mg, 0.048 mmol, 12 mol %) and chlorobenzene (0.4 mL) following General Procedure B. The resulting solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (1:10 EtOAc/hexanes) to afford a 3:1 mixture of diastereomers favoring **56d** (125.2 mg, 0.347 mmol, 87%) in 93% ee as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.11 (m, 13H), 6.20 (ddd, *J* = 13.0, 5.7, 3.0 Hz, 1H), 5.69 (ddt, *J* = 5.7, 3.1, 0.8 Hz, 1H), 4.90 (s, 1H), 3.38 (dq, *J* = 4.5, 1.6 Hz, 1H), 2.61 (dp, *J* = 4.6, 1.5 Hz, 1H), 2.31 (qt, *J* = 7.1, 3.6 Hz, 1H), 1.83 (d, *J* = 0.9 Hz, 4H), 1.57 (dtt, *J* = 9.2, 1.5, 0.7 Hz, 1H), 1.41 (tt, *J* = 9.2, 1.9 Hz, 1H), 0.75 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.41, 171.98, 138.13, 137.90, 134.52, 128.85, 128.83, 128.74, 128.71, 127.63, 127.59, 92.93, 57.03, 49.85, 47.90, 47.67, 43.11, 25.39, 14.84.

FTIR (NaCl, thin film, cm^{-1}): 3065, 3022, 2929, 2967, 1730, 1600, 1493, 1452, 1352, 1308, 1228, 1185, 1149, 1102, 1080

HRMS (GC-EI+, m/z): calc'd for $C_{24}H_{24}O_3$ 360.1726 $[M\bullet]^+$; found: 360.1707

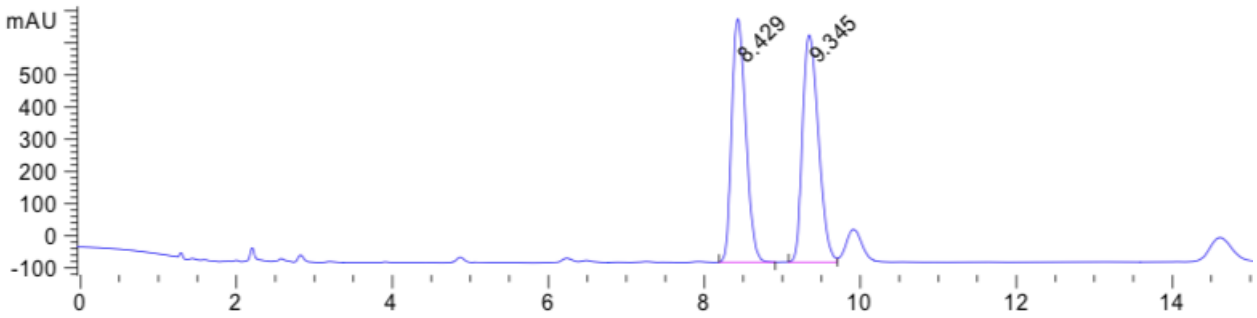
R_f = 0.59 (25% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +42° (c = 1.0, $CHCl_3$).

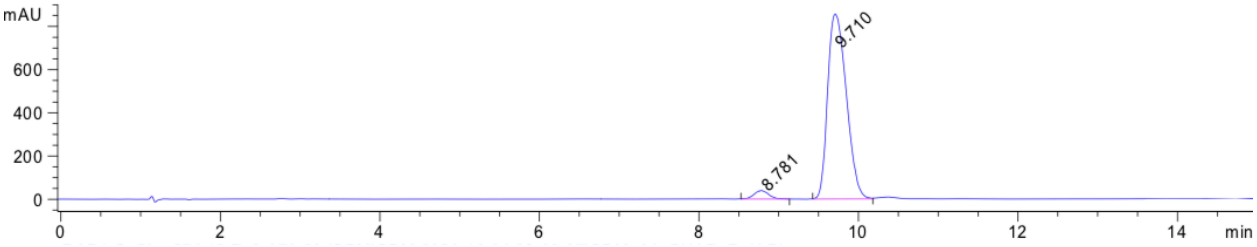
Chiral SFC: (IC column, 2.5 mL/min, 15% IPA/CO_2, λ = 210 nm): Major regioisomer:

$t_{major\ enantiomer}$ = 9.3 min, $t_{minor\ enantiomer}$ = 8.4 min

57d: racemic



(+)-**57d**: enantioenriched, 93% ee

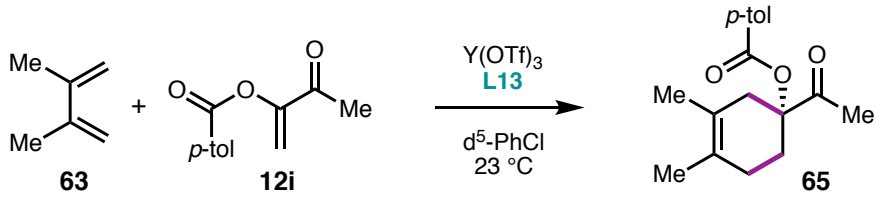


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.781	BB	0.1986	494.85995	39.38503	3.4315
2	9.710	BV	0.2618	1.39263e4	855.80060	96.5685

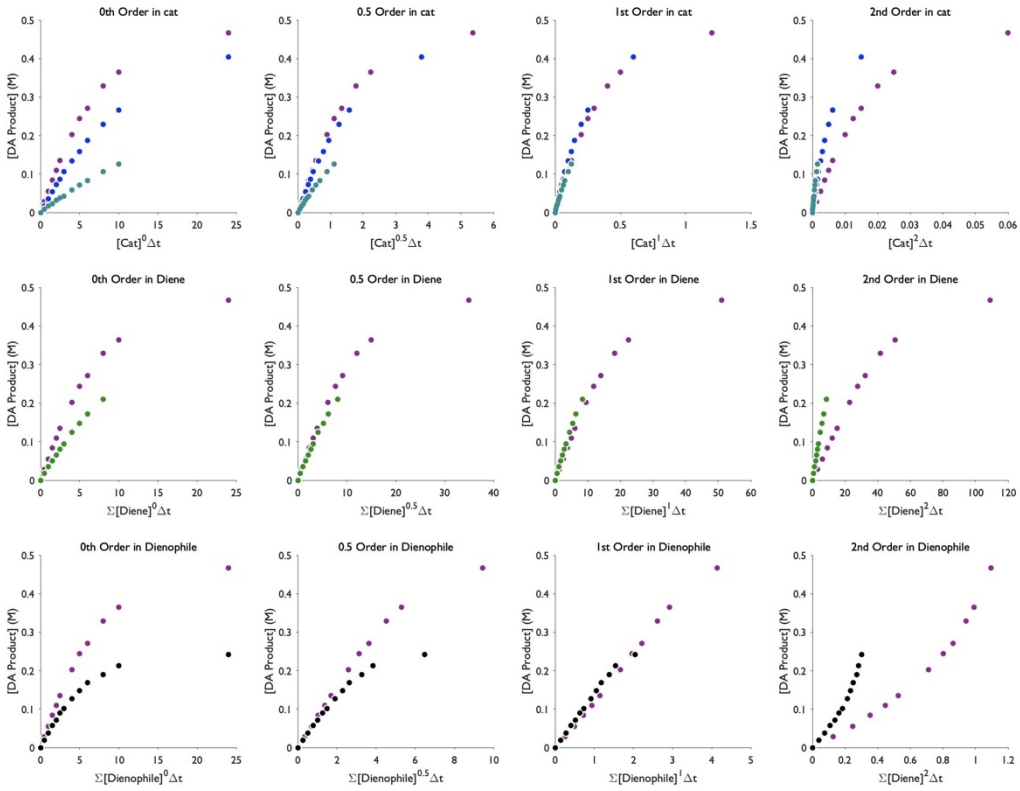
4.7.4 Mechanistic Studies

VTNA Kinetic Studies

Kinetic analysis performed using the Variable Time Normalization Analysis (VTNA) developed by Burés and coworkers.[49]



- [Cat] = 0.0500 M, [**63**] = 2.50 M, [**12i**] = 0.50 M
- [Cat] = 0.0250 M, [**63**] = 2.50 M, [**12i**] = 0.50 M
- [Cat] = 0.0125 M, [**63**] = 2.50 M, [**12i**] = 0.50 M
- [Cat] = 0.0500 M, [**63**] = 1.25 M, [**12i**] = 0.50 M
- [Cat] = 0.0500 M, [**63**] = 2.50 M, [**12i**] = 0.25 M



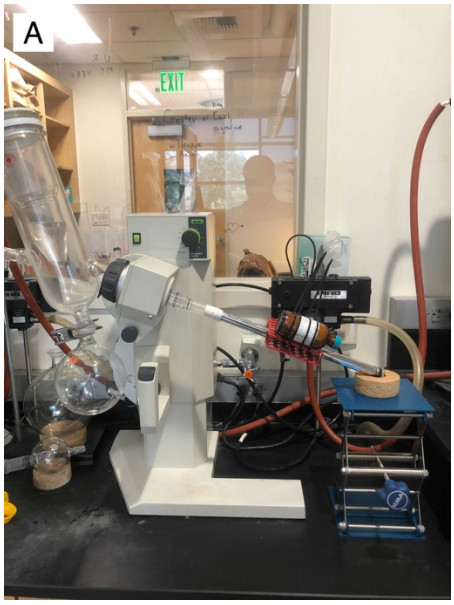
Supplemental Figure 6. Variable Time Normalization Analysis

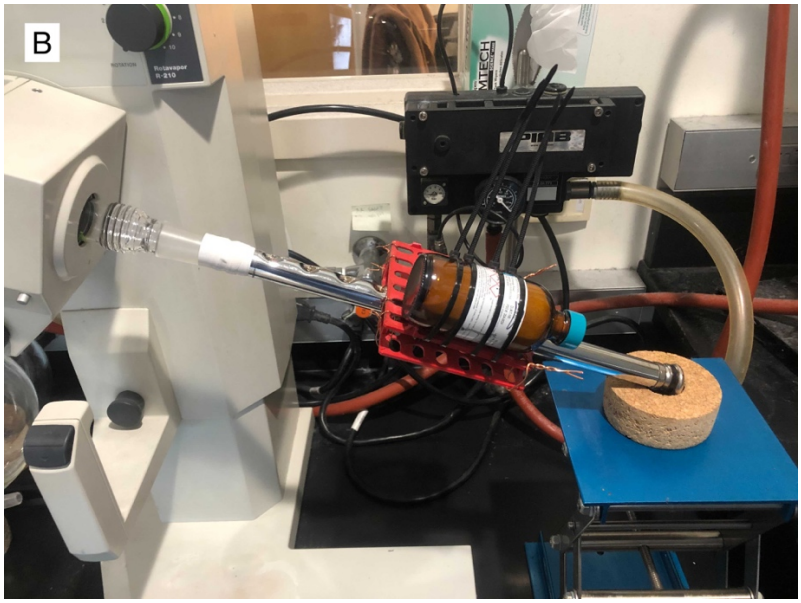
General Procedure: To a clean, dried 1 mL volumetric flask, in a N_2-filled glovebox, was added $Y(OTf)_3$, ligand (1.2x the mmol of metal), 1,3,5-trimethoxybenzene, and dienophile. Next, d^5-PhCl (~0.35 mL) was added. The vial was then capped with a glass stopper, and removed from glovebox. Then vial was agitated by hand for 3h at 23 °C. Then the glass stopper was removed and diene was added. Flask filled to 1 mL mark with d^5-PhCl. Reaction mixture then mixed by pipetting up and down several times and then transferred to a J-Young tube. Reaction analyzed by ^{1}H-NMR. NMR parameters: number of scans = 1, pulse angle = 90 °, ss=0, auto-gain: off, spin frequency = 0Hz. At the very end of the time course, reaction mixture filtered through a silica plug, eluting with EtOAc/hexanes

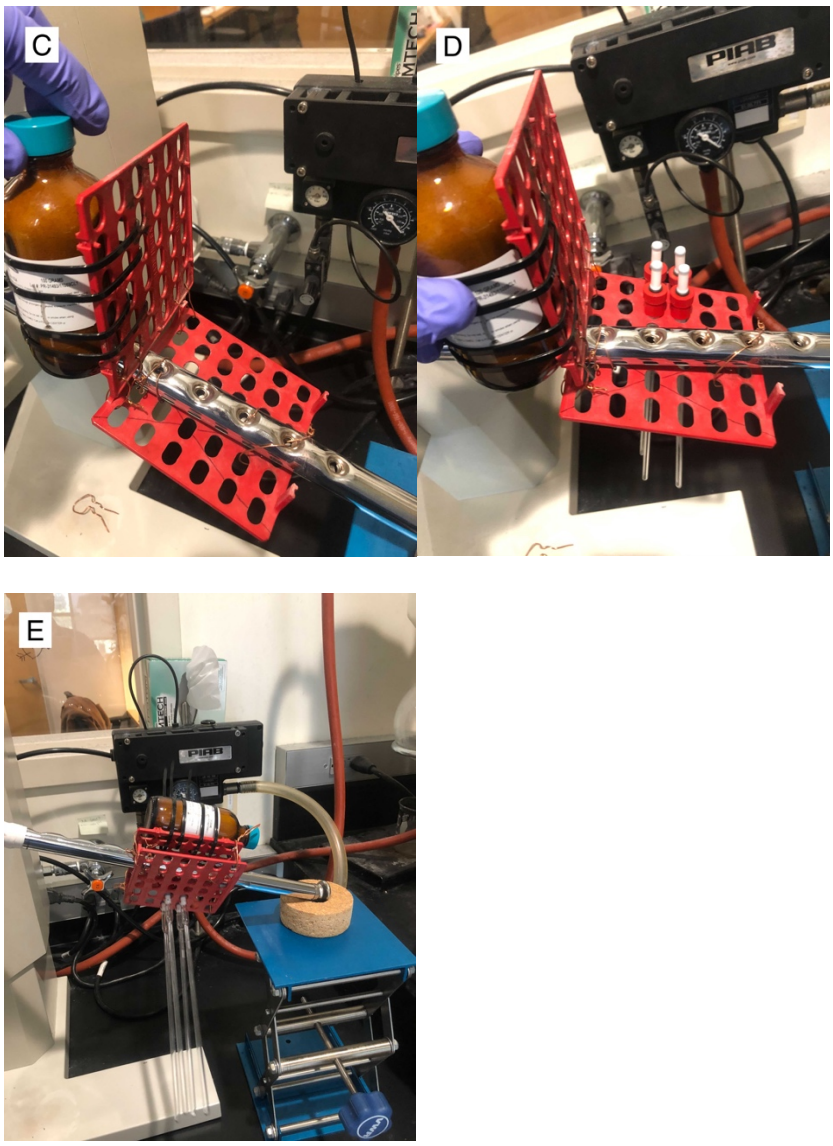
(1:1). Sample then concentrated, and loaded a small sample onto a prep plate (30% EtOAc/Hex.) to isolate band for ee determination.

Sample Spinning Setup

J-Young tubes were rotated using the setup shown below (Supplemental figure 7). Specifically, a small test tube rack was cut to allow a top and bottom half. Along one edge, copper wire was used to make small hinges such that the tube rack would be allowed to open and close (similar to a book). The bottom half of this rack was then affixed to a stool leg using copper wire such that the stool leg would exist between the two rack layers (Supplemental figure 7C). J-Young tubes could then be inserted into the holes to rest (Supplemental figure 7D). The top rack layer can then close over the tops of the J-Young tubes and is held together by copper wire. It was found that the installation of a counterweight (small bottle filled with sand) was necessary to achieve slow enough sample rotation for solid suspension. The stool leg was then attached to the rotovap with electrical tape while the other end rested on a cork ring (allowing for smooth rotation).


A
EXIT


B



Supplemental Figure 7. J-Young Tube Spinning Setup

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.85 (m, 2H), 7.29 – 7.18 (m, 2H), 2.72 – 2.57 (m, 1H), 2.42 (s, 3H), 2.39 – 2.22 (m, 2H), 2.18 (s, 4H), 2.05 – 1.85 (m, 2H), 1.71 – 1.59 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.97, 166.11, 144.30, 129.97, 129.32, 127.23, 124.81, 121.66, 93.04, 85.06, 55.48, 37.43, 28.20, 28.18, 24.05, 21.86, 19.01, 18.81.

FTIR (NaCl, thin film, cm^{-1}): 2908, 1719, 1610, 1456, 1438, 1310, 1287, 1254, 1250, 1204, 1166, 1105, 1076, 842, 758.

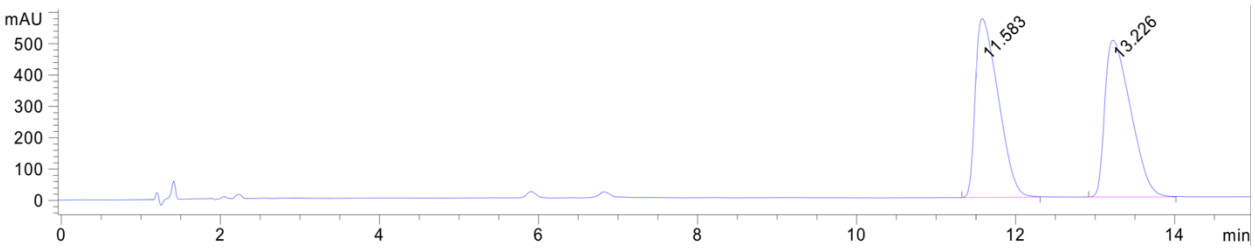
HRMS (TOF-ESI, m/z): calc'd for $C_{18}H_{23}O_3$ 287.1647 $[M+H]^+$; found: 287.1667

R_f = 0.61 (20% EtOAc/hexanes, UV, $KMnO_4$)

$\boldsymbol{\alpha_D^{22}}$ = +3.2° (c = 1.0, $CHCl_3$).

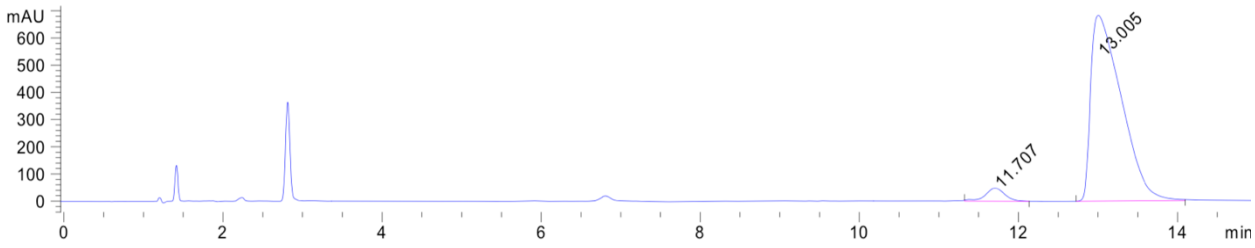
Chiral SFC: (AD-H column, 2.5 mL/min, 3% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 13.2 min, $t_{minor\ enantiomer}$ = 11.6 min

65: racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.583	BB	0.3224	1.14795e4	571.44482	50.4970
2	13.226	BB	0.3585	1.12536e4	500.08527	49.5030

(+)-65: enantioenriched, 92% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.707	BB	0.2570	806.38019	47.75460	4.2395
2	13.005	BB	0.4232	1.82143e4	682.86053	95.7605

Tables of concentration data:

- [Cat] = 0.0500 M, [**63**] = 2.50 M, [**65**] = 0.50 M

Time (h)	[**63**]	[**12i**]	[**65**]
0	2.52	0.518	0.000
0.5	2.50	0.495	0.028
1	2.47	0.475	0.056
1.5	2.45	0.448	0.084
2	2.43	0.415	0.110
2.5	2.39	0.382	0.135
4	2.14	0.323	0.202
5	2.29	0.273	0.244
6	2.07	0.221	0.271
8	2.21	0.175	0.329
10	2.02	0.136	0.364
24	2.06	0.037	0.467

- [Cat] = 0.0250 M, [**63**] = 2.50 M, [**65**] = 0.50 M

Time (h)	[**63**]	[**12i**]	[**65**]
0	2.44	0.525	0.000
0.5	2.25	0.512	0.017
1	2.23	0.475	0.035
1.5	2.22	0.462	0.054
2	2.20	0.440	0.072
2.5	2.19	0.413	0.086
3	2.18	0.418	0.106
4	2.15	0.375	0.133
5	2.10	0.345	0.158
6	2.06	0.321	0.188
8	2.03	0.275	0.229
10	2.00	0.238	0.266
24	1.87	0.099	0.404

- [Cat] = 0.0125 M, [**63**] = 2.50 M, [**65**] = 0.50 M

Time (h)	[**63**]	[**12i**]	[**65**]
0	2.25	0.512	0.000
0.5	2.25	0.509	0.008
1	2.22	0.499	0.017
1.5	2.23	0.489	0.023
2	2.25	0.491	0.032
2.5	2.42	0.477	0.038

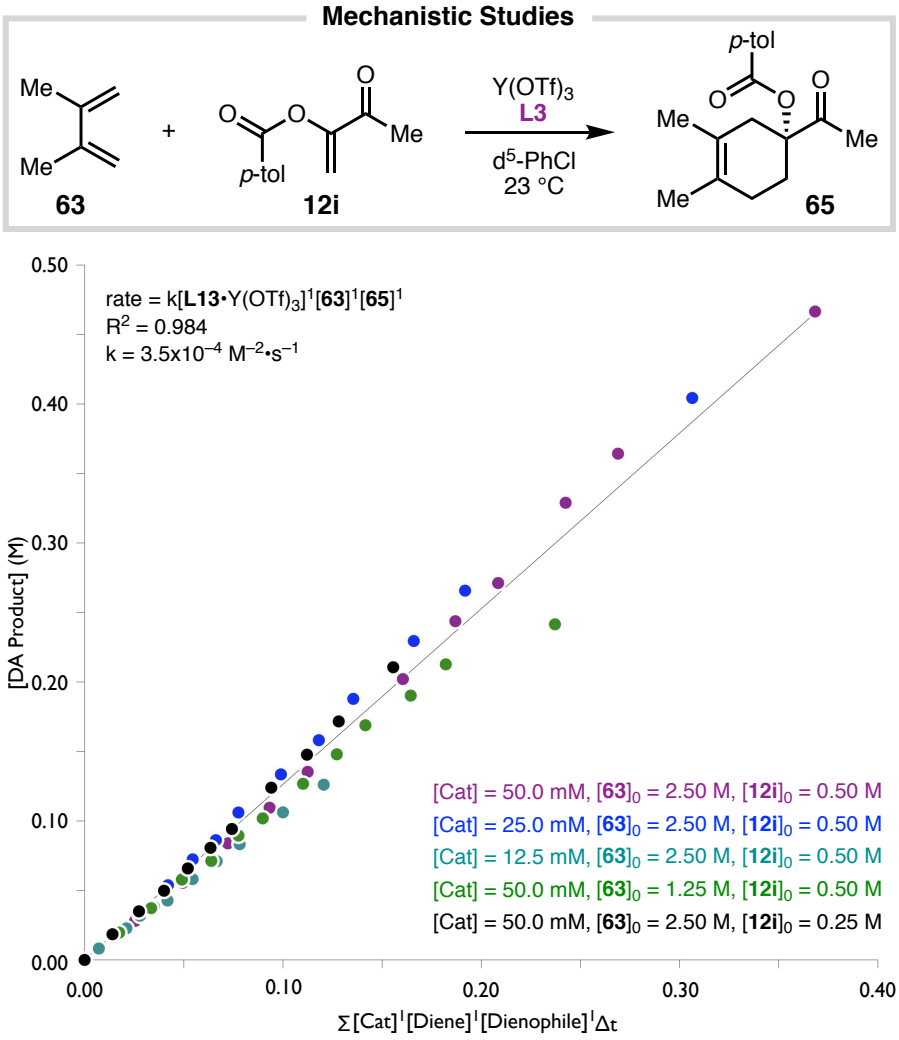
3	2.21	0.461	0.043
4	2.20	0.454	0.058
5	2.16	0.438	0.071
6	2.11	0.426	0.083
8	2.10	0.402	0.106
10	2.08	0.383	0.126

- [Cat] = 0.0500 M, [**63**] = 1.25 M, [**65**] = 0.50 M

Time (h)	[**63**]	[**12i**]	[**65**]
0	1.16	0.499	0.000
0.5	1.14	0.480	0.018
1	1.13	0.463	0.035
1.5	1.11	0.441	0.050
2	1.09	0.431	0.066
2.5	1.08	0.412	0.080
3	1.06	0.392	0.094
4	1.04	0.361	0.124
5	1.01	0.339	0.148
6	0.97	0.304	0.172
8	0.95	0.265	0.211

- [Cat] = 0.0500 M, [**63**] = 2.50 M, [**65**] = 0.25 M

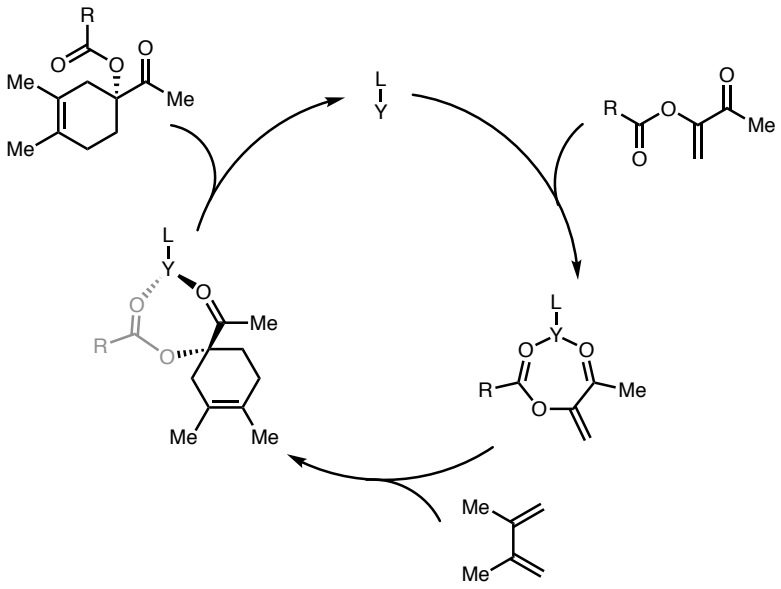
Time (h)	[**63**]	[**12i**]	[**65**]
0	2.46	0.293	0.000
0.5	2.45	0.274	0.020
1	2.45	0.252	0.037
1.5	2.42	0.257	0.058
2	2.41	0.234	0.071
2.5	2.41	0.222	0.089
3	2.38	0.187	0.102
4	2.34	0.157	0.127
5	2.32	0.135	0.148
6	2.29	0.115	0.169
8	2.26	0.086	0.190
10	2.23	0.071	0.213
24	2.18	0.000	0.241



Supplemental Figure 7. Fully Normalized Kinetics Data

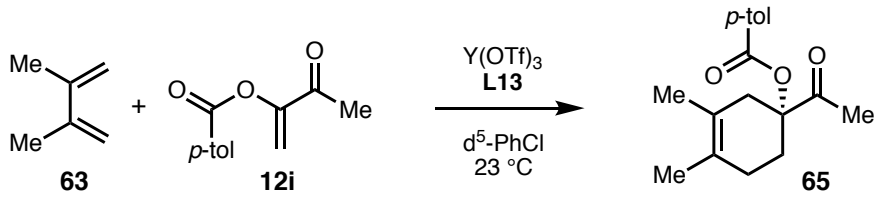
Rate constant = 3.51×10^{-4} $M^{-2} \cdot s^{-1}$

Discussion: Based on the available data, we can conclude the following rate law: rate = $[cat]^1[\mathbf{7d}]^1[\mathbf{9c}]^1$. This rate law is consistent with the following proposed catalytic cycle. (**Supplemental Figure 8**).



Supplemental Figure 8. Proposed Catalytic Cycle

Same Excess Experiments:

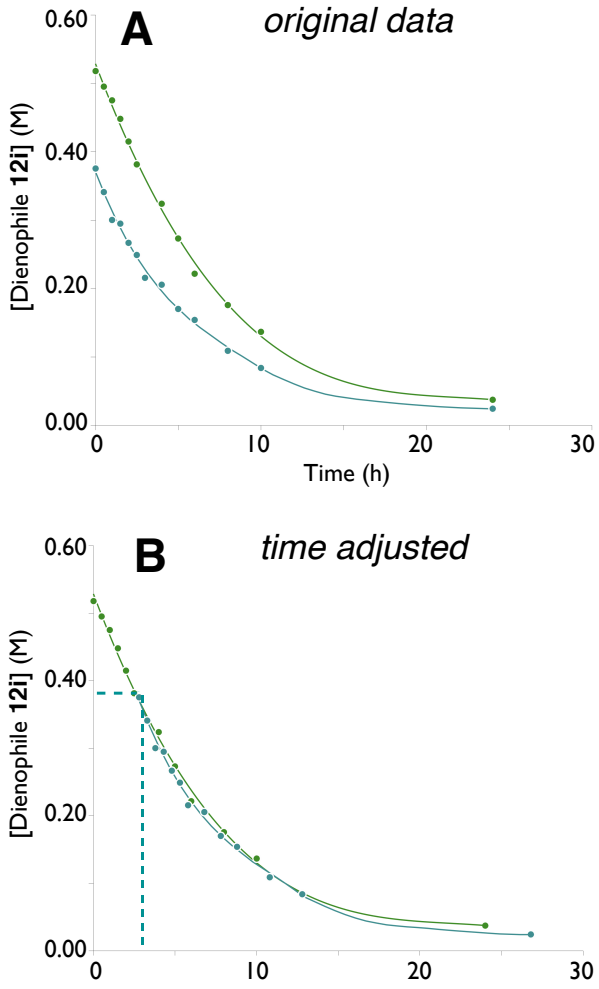


● [Cat] = 0.0500 M, [**63**] = 2.50 M, [**65**] = 0.50 M
● [Cat] = 0.0500 M, [**63**] = 2.35 M, [**65**] = 0.35 M

General Procedure: To a clean, dried 1 mL volumetric flask, in a N_2-filled glovebox, was added $Y(OTf)_3$, ligand (1.2x the mmol of metal), 1,3,5-trimethoxybenzene, and dienophile. Next, d^5-PhCl (~0.35 mL) was added. The vial was then capped with a glass stopper, and removed from glovebox. Then vial was agitated by hand for 3h at 23 °C. Then the glass stopper was removed and diene was added. Flask filled to 1 mL mark with d^5-PhCl.

Reaction mixture then mixed by pipetting up and down several times and then transferred to a J-Young tube. Reaction analyzed by ^{1}H-NMR. NMR parameters: number of scans = 1, pulse angle = 90 °, ss=0, auto-gain: off, spin frequency = 0Hz. At the very end of the time course, reaction mixture filtered through a silica plug, eluting with EtOAc/hexanes (1:1). Sample then concentrated and loaded a small sample onto a prep plate (30% EtOAc/Hex.) to isolate band for ee determination.

Note: Same excess time adjusted by 2.8h to observe overlay.



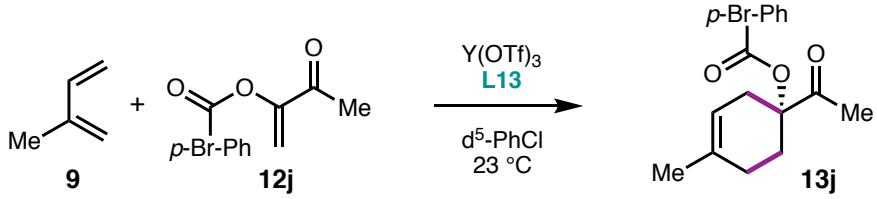
[Cat] = 50.0 mM, [**63**]$_0$ = 2.500 M, [**12i**]$_0$ = 0.500 M

Time (h)	[**63**]	[**12i**]	[**65**]

0	2.52	0.518	0.000
0.5	2.50	0.495	0.028
1	2.47	0.475	0.056
1.5	2.45	0.448	0.084
2	2.43	0.415	0.110
2.5	2.39	0.382	0.135
4	2.14	0.323	0.202
5	2.29	0.273	0.244
6	2.07	0.221	0.271
8	2.21	0.175	0.329
10	2.02	0.136	0.364
24	2.06	0.037	0.467

[Cat] = 50.0 mM, [**63**]$_0$ = 2.375 M, [**12i**]$_0$ = 0.375 M

Time (h)	[**63**]	[**12i**]	[**65**]
0	2.12	0.375	0.000
0.5	2.11	0.341	0.028
1	2.23	0.300	0.052
1.5	2.21	0.295	0.073
2	2.19	0.267	0.092
2.5	2.00	0.249	0.109
3	2.14	0.216	0.131
4	1.97	0.206	0.162
5	1.92	0.170	0.187
6	1.89	0.154	0.210
8	1.87	0.109	0.242
10	1.86	0.084	0.268
24	1.78	0.024	0.325

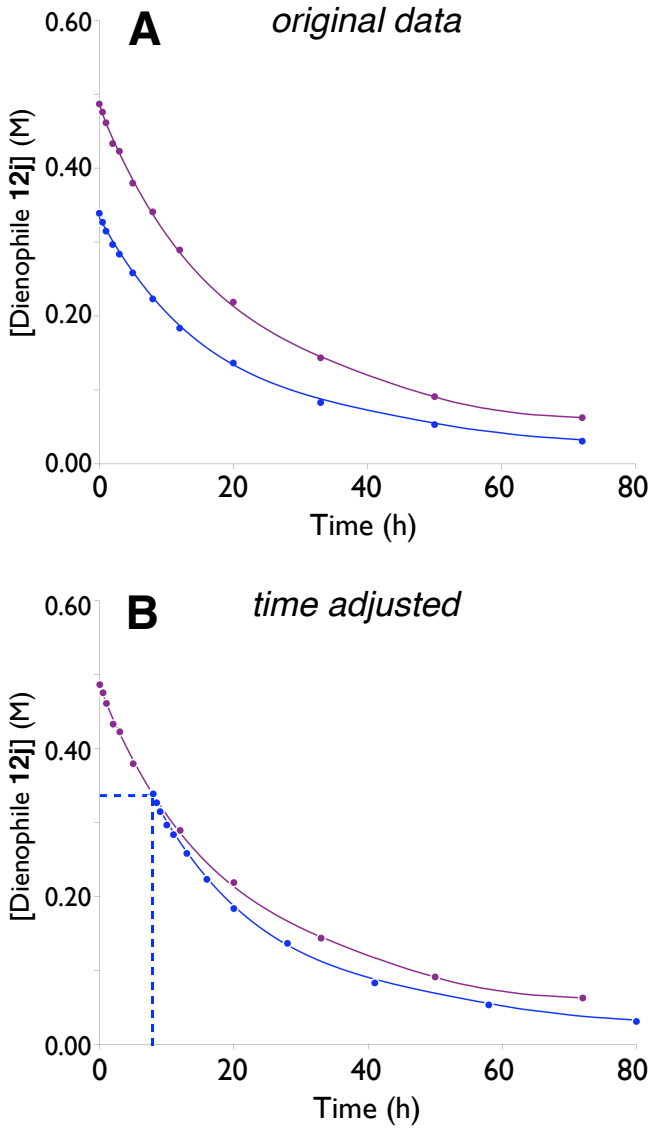


[Cat] = 50.0 mM, [**9**]$_0$ = 2.500 M, [**12j**]$_0$ = 0.500 M
[Cat] = 50.0 mM, [**9**]$_0$ = 2.375 M, [**12j**]$_0$ = 0.375 M

General Procedure: To a clean, dried 1 mL volumetric flask, in a N_2-filled glovebox, was added $Y(OTf)_3$, ligand (1.2x the mmol of metal), 1,3,5-trimethoxybenzene, and dienophile.

Next, d^5-PhCl (~0.35 mL) was added. The vial was then capped with a glass stopper, and removed from glovebox. Then vial was agitated by hand for 3h at 23 °C. Then the glass stopper was removed and diene was added. Flask filled to 1 mL mark with d^5-PhCl. Reaction mixture then mixed by pipetting up and down several times and then transferred to a J-Young tube. Reaction analyzed by ^{1}H-NMR. NMR parameters: number of scans = 1, pulse angle = 90 °, ss=0, auto-gain: off, spin frequency = 0Hz. At the very end of the time course, reaction mixture filtered through a silica plug, eluting with EtOAc/hexanes (1:1). Sample then concentrated, and loaded a small sample onto a prep plate (30% EtOAc/Hex.) to isolate band for ee determination.

Note: Same excess time adjusted by 8.0 h. Curves were fitted to a 4th-order polynomial. Curves are only intended to show the difference in traces.



[Cat] = 50.0 mM, $[\mathbf{9}]_0$ = 2.500 M, $[\mathbf{12j}]_0$ = 0.500 M

Time (h)	[**3a**]	[**7e**]	[**8e**]
0	1.8507	0.4868	0.0000
0.5	1.8634	0.4758	0.0113
1	1.8660	0.4611	0.0163
2	1.9599	0.4333	0.0359
3	2.0910	0.4228	0.0548
5	2.0657	0.3797	0.0894
8	1.8692	0.3410	0.1295
12	1.9833	0.2894	0.1685
20	1.9218	0.2187	0.2410
33	1.5524	0.1432	0.3150
50	1.6223	0.0910	0.3584

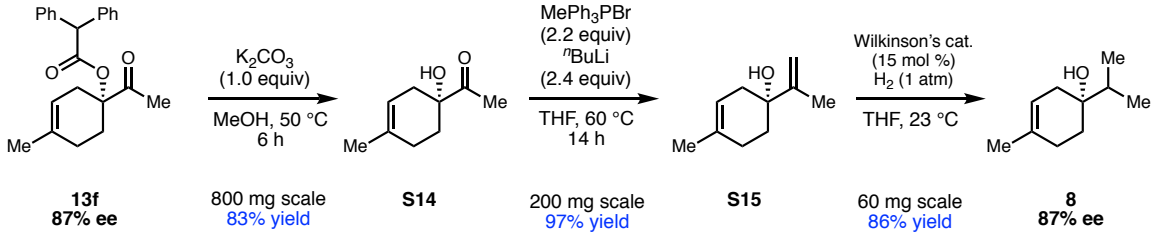
72	1.4474	0.0625	0.3968

[Cat] = 50.0 mM, [**9**]$_0$ = 2.375 M, [**12j**]$_0$ = 0.375 M

Time (h)	[**3a**]	[**7e**]	[**8e**]
0	1.8993	0.3389	0.0000
0.5	1.7798	0.3267	0.0054
1	1.7643	0.3147	0.0139
2	1.7107	0.2968	0.0269
3	1.6736	0.2834	0.0431
5	1.6654	0.2582	0.0682
8	1.6278	0.2231	0.0976
12	1.6217	0.1835	0.1293
20	1.5646	0.1364	0.1795
33	1.5770	0.0828	0.2362
50	1.4595	0.0531	0.2564
72	1.5484	0.0307	0.2756

4.7.6 Product Derivitization

(*R*)-1-isopropyl-4-methylcyclohex-3-en-1-ol (8):



Procedure: To an oven-dried 25 mL round bottom flask, equipped with a stir bar, was charged ester **13f** (800 mg, 2.30 mmol, 1.0 equiv) and K_2CO_3 (317 mg, 2.3 mmol, 1.0 equiv). MeOH (11.5 mL, 0.2 M) then added and reaction heated to 50 °C for 6 h with stirring. Reaction was then concentrated in vacuo, water added, and product extracted into ether (3X), washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was subjected to silica gel chromatography (20% EtOAc:hexanes) to afford a **S14**

(295 mg, 1.913 mmol, 83%) as a clear colorless oil. Spectroscopic data matched previously reported values.[45]

Procedure: To an oven-dried 2-dram vial, equipped with a stir bar, under nitrogen, was charged methyltriphenylphosphonium bromide (1.02 g, 2.85 mmol, 2.20 equiv) in anhydrous THF (1.5 ml) was stirred and *n*-butyllithium (2.5M in hexanes, 1.23 mL, 3.07 mmol, 2.37 equiv) was added at room temperature. The mixture was stirred for 30 min and a solution of **S14** (200 mg, 1.30 mmol, 1.0 equiv) in THF (0.5 ml) was added dropwise and the mixture was heated to 60°C for 14 h. Then, it was diluted with aqueous saturated solution of NH_4Cl (2 ml) and extracted with EtOAc (3 x 3 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by column chromatography (15% EtOAc/hexanes) to afford **S15** (192 mg, 1.261 mmol, 97%) as a clear colorless oil. Spectroscopic data matched previously reported values.[45]

Procedure: To an oven-dried 2-dram vial, in a nitrogen-filled glovebox, was charged Wilkinson's catalyst (54.7 mg, 0.059 mmol, 15 mol %) and alkene **S15** (60 mg, 0.39 mmol, 1.0 equiv). A stir bar was added, the reaction was capped with a septa cap and then removed from glovebox. THF (3.94 mL) added and stirred at room temperature. Hydrogen gas then added via balloon with a vent needle and sparged through the reaction until complete consumption of SM observed as indicated by TLC. The reaction mixture was then filtered over celite and eluted with ether. The resulting mixture was concentrated and the residue was subjected to column chromatography (10% Et_2O/pentanes) to afford **8** (52.3 mg, 0.339 mmol, 86%) in 87% ee as a clear colorless oil. Spectroscopic data matched previously reported values.[41]

^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (dtq, *J* = 4.9, 2.4, 1.4 Hz, 1H), 2.23 – 2.09 (m, 2H), 2.00 – 1.84 (m, 2H), 1.75 – 1.60 (m, 5H), 1.61 – 1.50 (m, 1H), 1.50 – 1.40 (m, 1H), 0.93 (dd, *J* = 9.6, 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.03, 118.58, 71.90, 36.92, 34.75, 30.92, 27.19, 23.44, 16.97.

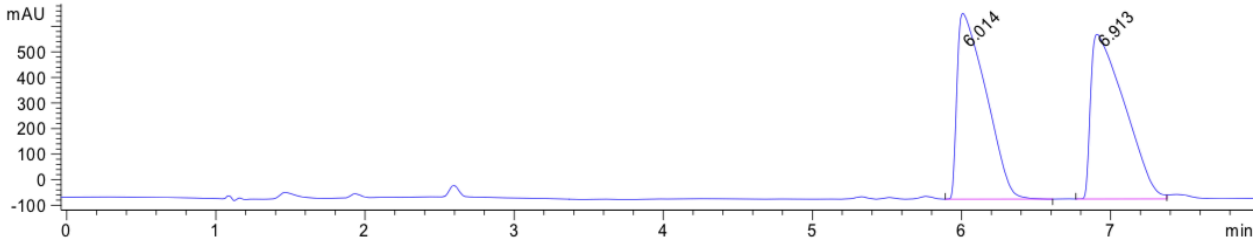
FTIR (NaCl, thin film, cm^{-1}): 3456, 3012, 2961, 2914, 2724, 1468, 1438, 1377, 1362, 1304, 1250, 1224, 1190, 1122, 1091, 1049, 1012, 948, 925, 886, 866, 797, 780, 724, 699.

R_f = 0.5 (DCM, p-anisaldehyde)

$\boldsymbol{\alpha_D^{22}}$ = –28° (c = 0.1, $CHCl_3$).

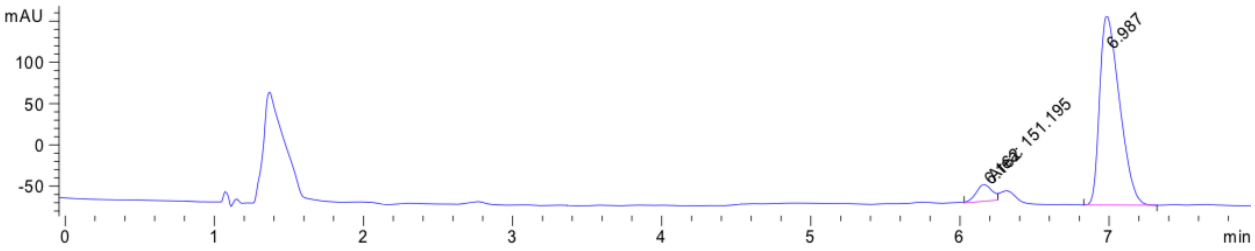
Chiral SFC: (AD-H column, 2.5 mL/min, 3% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 6.9 min, $t_{minor\ enantiomer}$ = 6.0 min

8: racemic



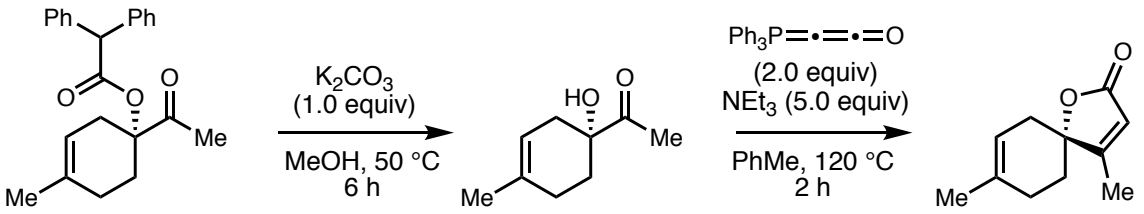
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.014	VB	0.2325	9746.58887	726.78754	49.0451
2	6.913	BV	0.2720	1.01261e4	642.07300	50.9549

(–)-**8**: enantioenriched, 87% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.162	MM	0.1245	151.19460	20.23345	6.6419
2	6.987	BB	0.1444	2125.17114	228.79486	93.3581

(*R*)-4,8-dimethyl-1-oxaspiro[4.5]deca-3,7-dien-2-one (58):



13f
87% ee

800 mg scale
83% yield

S16

40 mg scale
84% yield

58
87% ee

Procedure: To an oven-dried 25 mL round bottom flask, equipped with a stir bar, was charged ester **13f** (800 mg, 2.3 mmol, 1.0 equiv) and K_2CO_3 (317 mg, 2.3 mmol, 1.0 equiv). MeOH (11.5 mL) then added and reaction heated to 50 °C for 6 h with stirring. Reaction then concentrated in vacuo, water added, and product extracted into ether (3X), washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was subjected to silica gel chromatography (20% EtOAc:hexanes) to afford a **S16** (295 mg, 1.91 mmol, 83%) as a clear colorless oil.

Procedure: To an oven-dried 25mL round bottomed flask, was charged **S16** (40 mg, 0.259 mmol, 1.0 equiv) followed by Bestmann ylide (156.8 mg, 0.519 mmol, 2.0 equiv). PhMe (13 mL) added and then NEt_3 (180 µL, 1.295 mmol, 5.0 equiv) and reaction capped under nitrogen. Reaction heated to 120 °C for 2 hours and was monitored by TLC. Reaction quenched by addition of 13 mL of saturated NH_4Cl solution. The aqueous layer was then extracted with Et_2O (3x10 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated. The resuting residue was subjected to column chromatography (20% EtOAc/hexanes) to afford **58** (39 mg, 0.218 mmol, 84% yield) in 87% ee as a clear colorless oil.

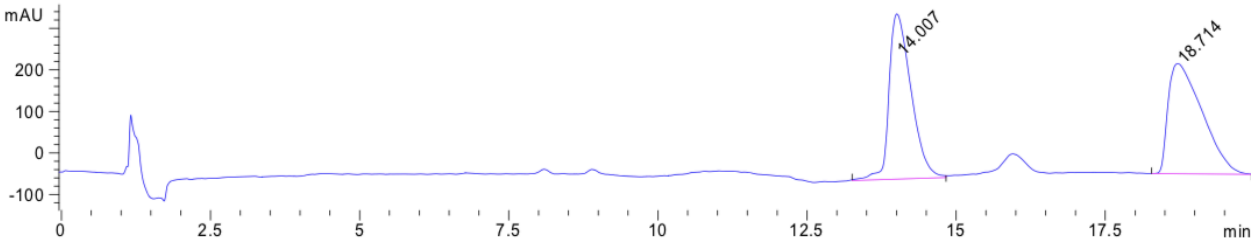
^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (q, *J* = 1.5 Hz, 1H), 5.37 (dtt, *J* = 5.0, 2.5, 1.3 Hz, 1H), 2.55 – 2.31 (m, 1H), 2.11 – 1.82 (m, 6H), 1.77 – 1.69 (m, 3H), 1.69 – 1.58 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.74, 172.45, 134.07, 116.62, 116.50, 87.31, 33.23, 29.95, 27.03, 23.49, 13.42.

$\boldsymbol{\alpha_D^{22}}$ = +52° (c = 1.0, $CHCl_3$).

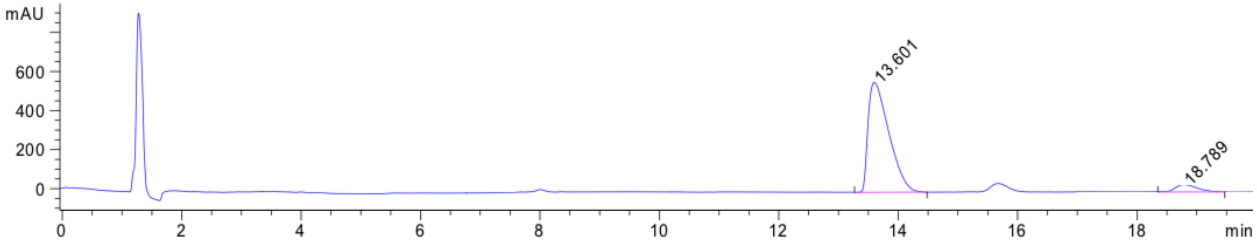
Chiral SFC: (AD-H column, 2.5 mL/min, 3% IPA/CO_2, λ = 210 nm): Major regioisomer: $t_{major\ enantiomer}$ = 14.0 min, $t_{minor\ enantiomer}$ = 18.7 min

58: racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.007	BB	0.4004	1.02402e4	397.63651	49.3162
2	18.714	BB	0.5740	1.05242e4	265.76379	50.6838

(+)-58: enantioenriched, 87% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.601	BB	0.3741	1.35997e4	562.40338	93.3916
2	18.789	BB	0.3993	962.30969	37.51068	6.6084

4.7.7 Stereochemical Analysis

The optical rotation of (+)-andirolactone (**58**) is known in the literature to be +100°. Comparing the sign of this to our synthesized **58** shows a match indicating that the enantiomer generated in the Diels-Alder reaction leads to (+)-andirolactone. The enantiomeric assignments of all other Diels-Alder products were assigned by analogy.

4.7 NOTES AND REFERENCES

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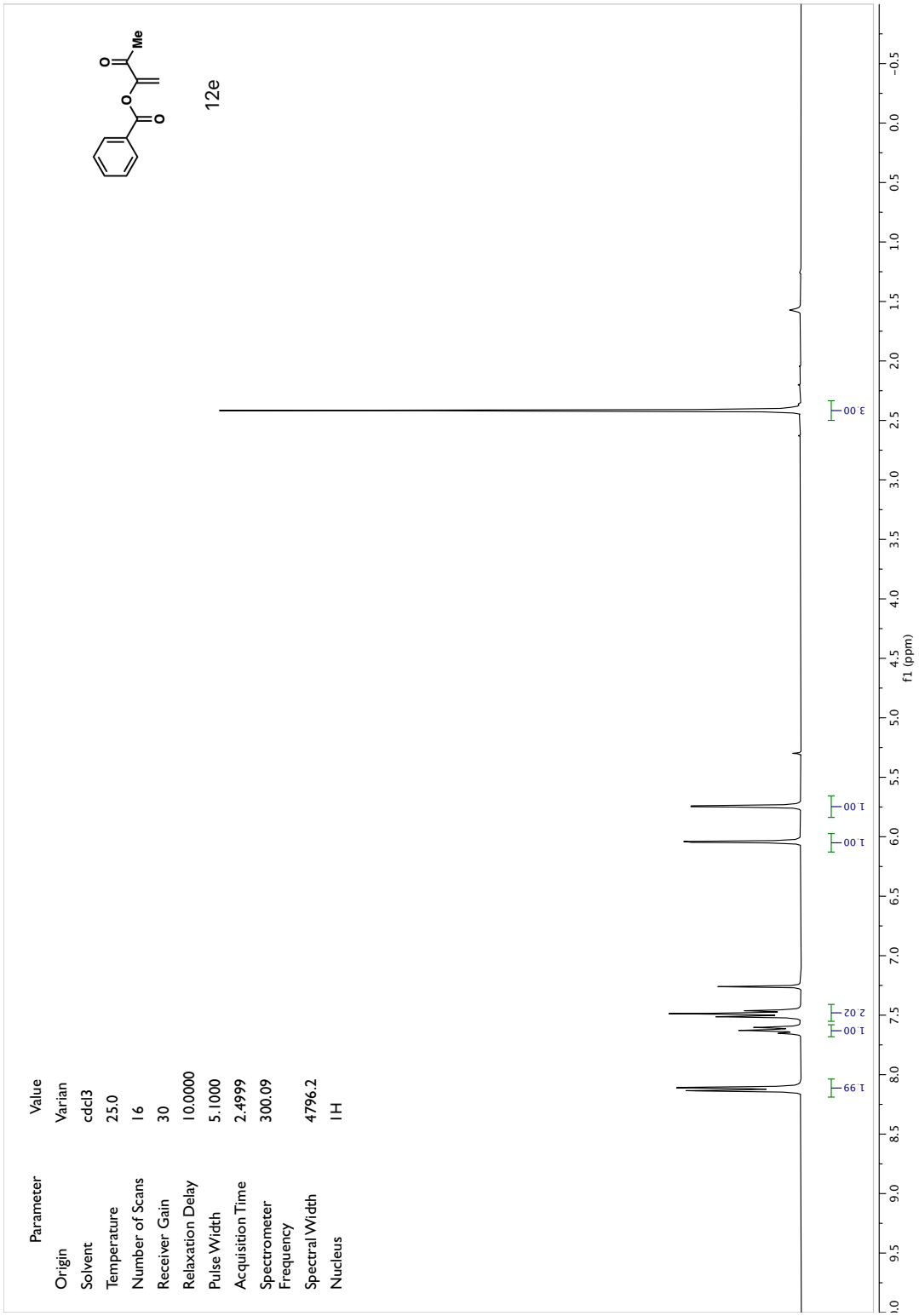
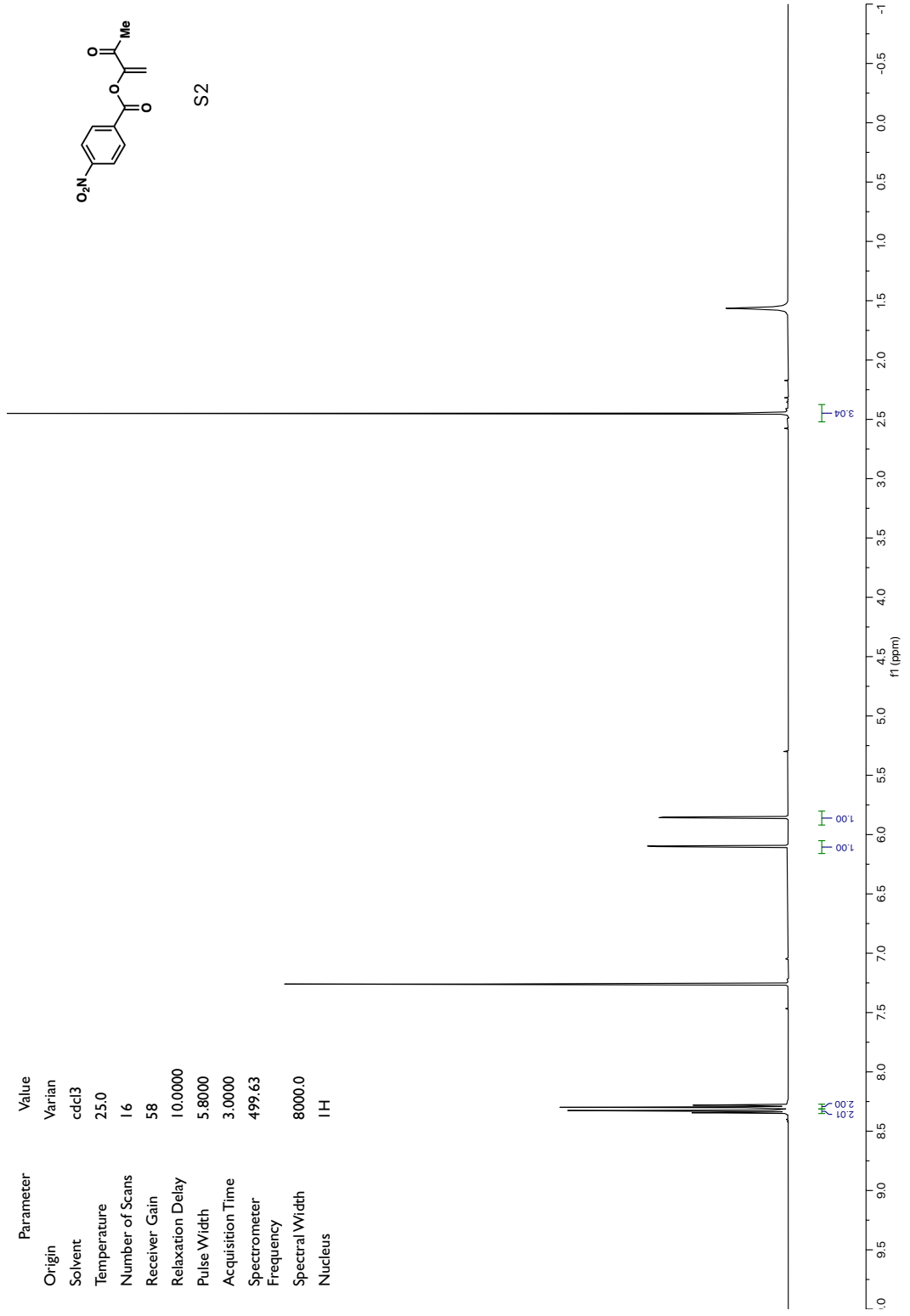
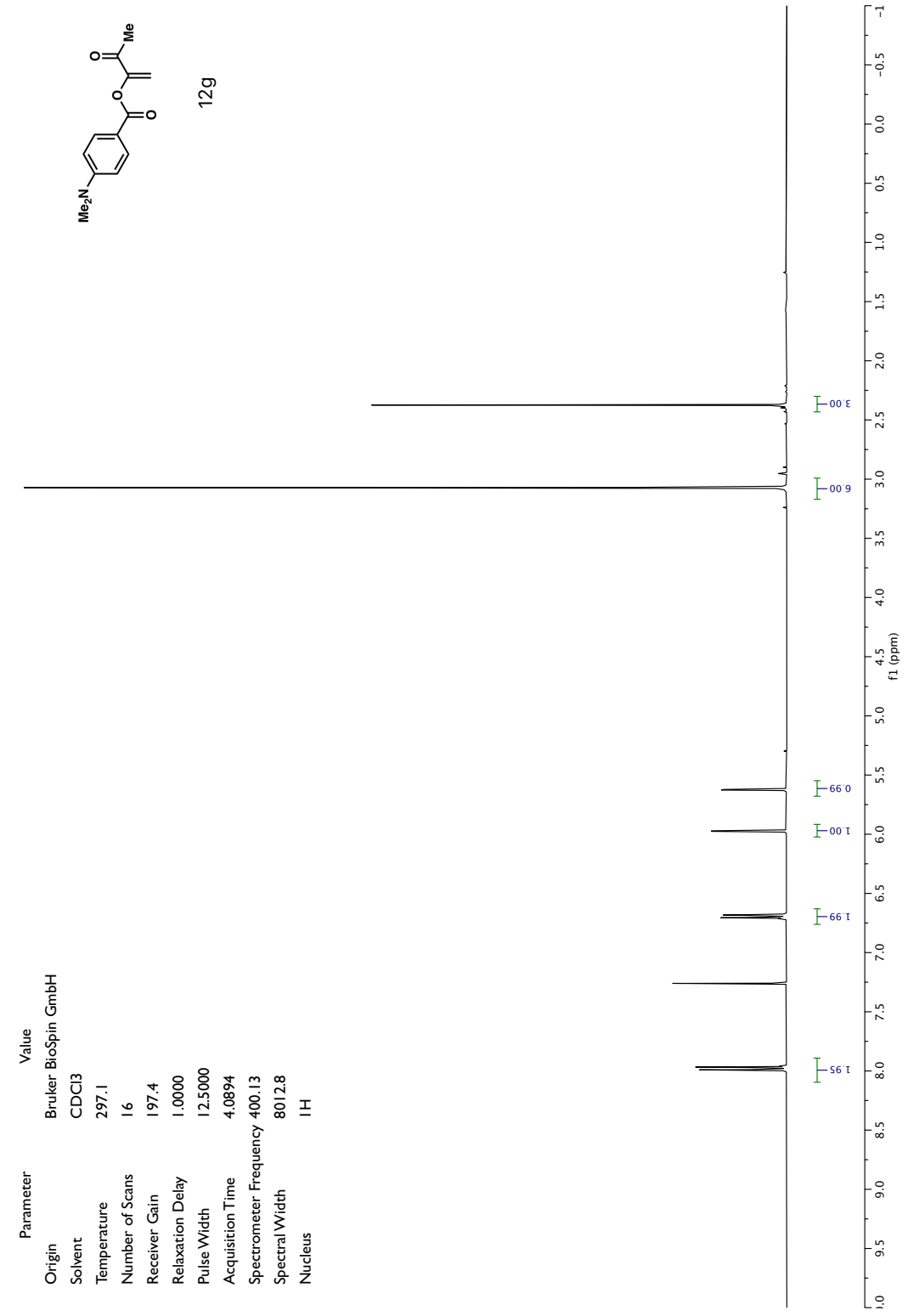
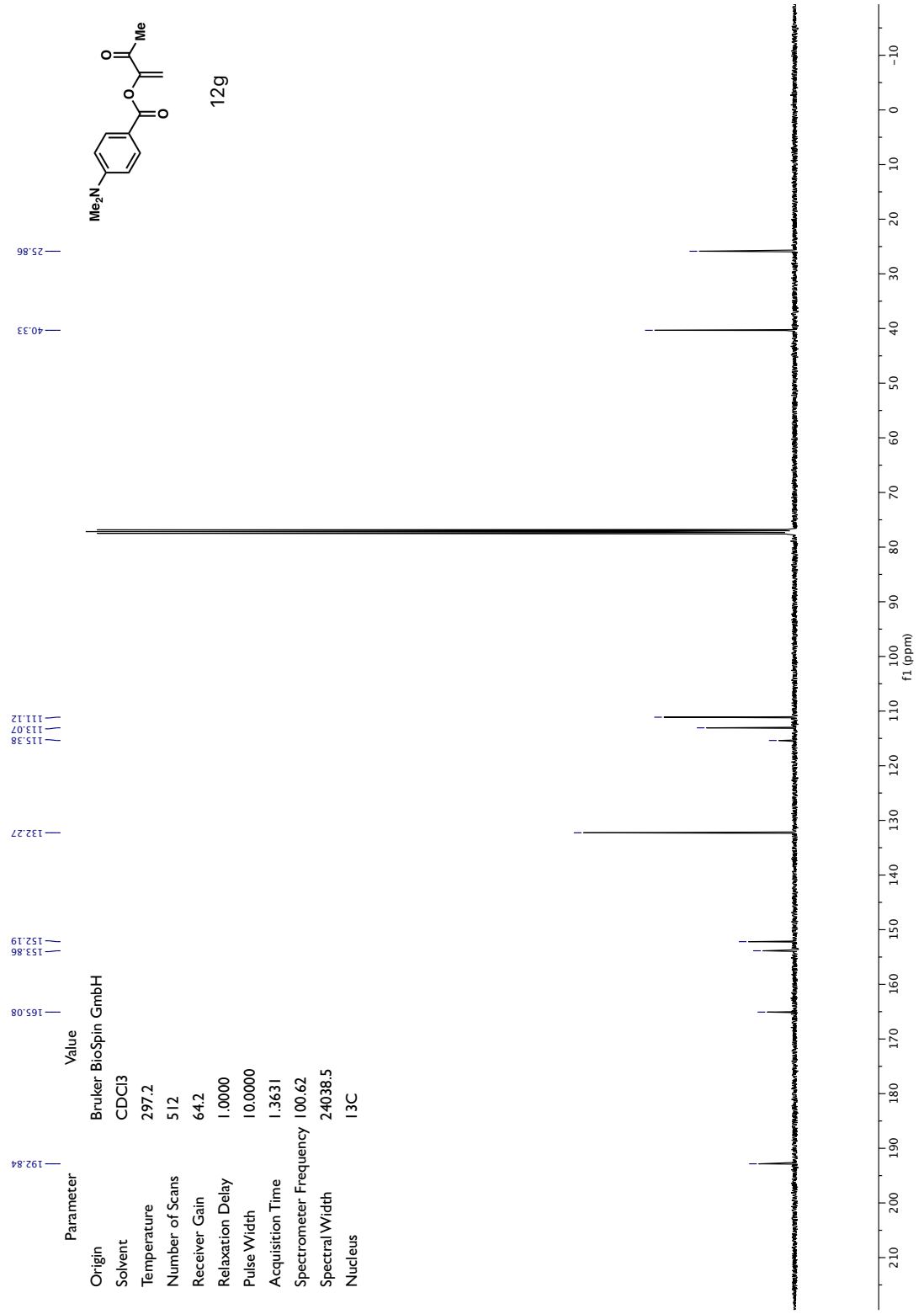
Appendix 3

Spectra Relevant to Chapter 4: Enantioselective Diels–Alder Reaction of α-Acyloxy Enones

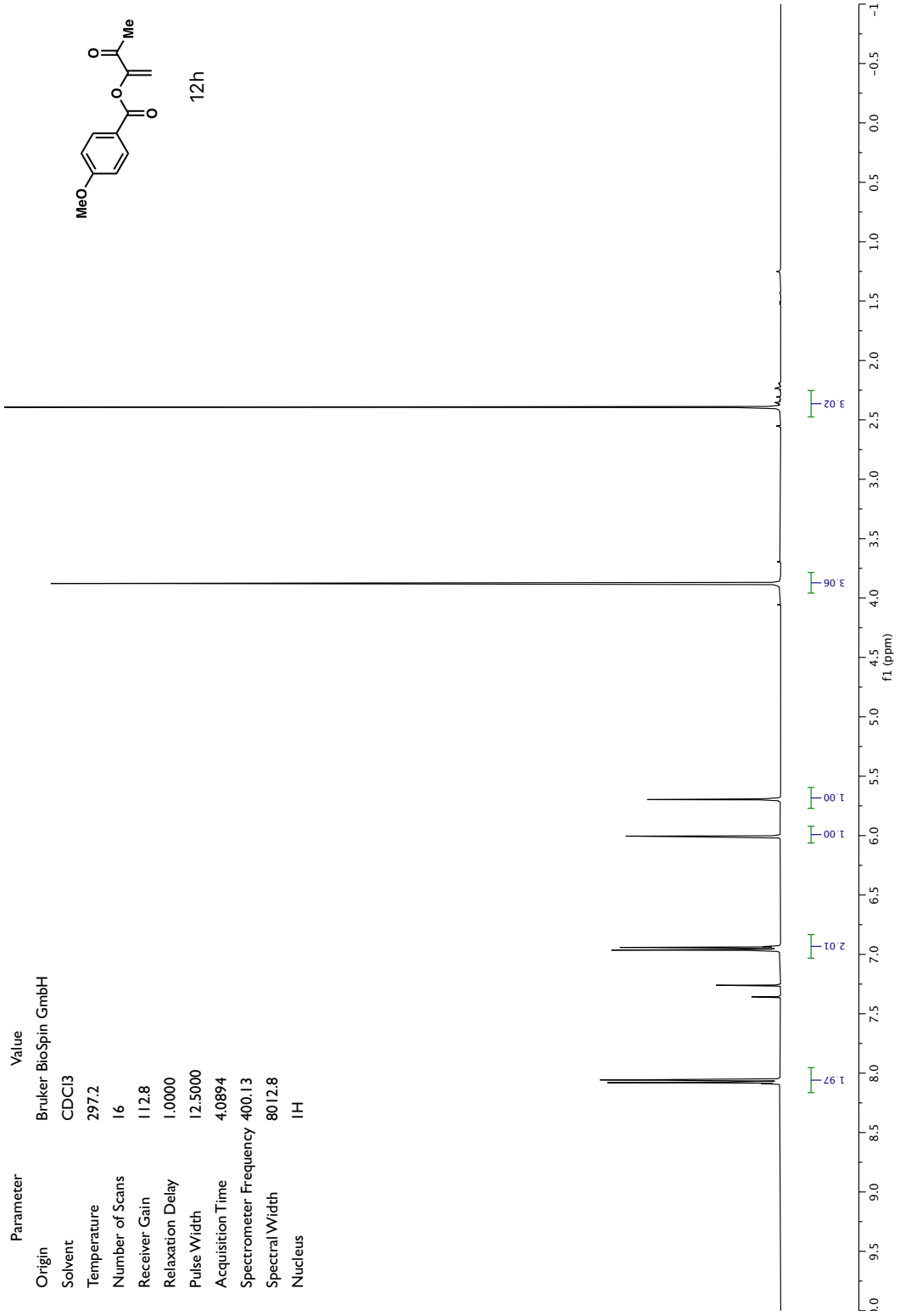

Me
O
O
O
12e
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 16
Receiver Gain 30
Relaxation Delay 10.0000
Pulse Width 5.1000
Acquisition Time 2.4999
Spectrometer Frequency 300.09
Spectral Width 4796.2
Nucleus 1H
3.00
1.00
1.00
2.02
1.00
1.99
f1 (ppm)

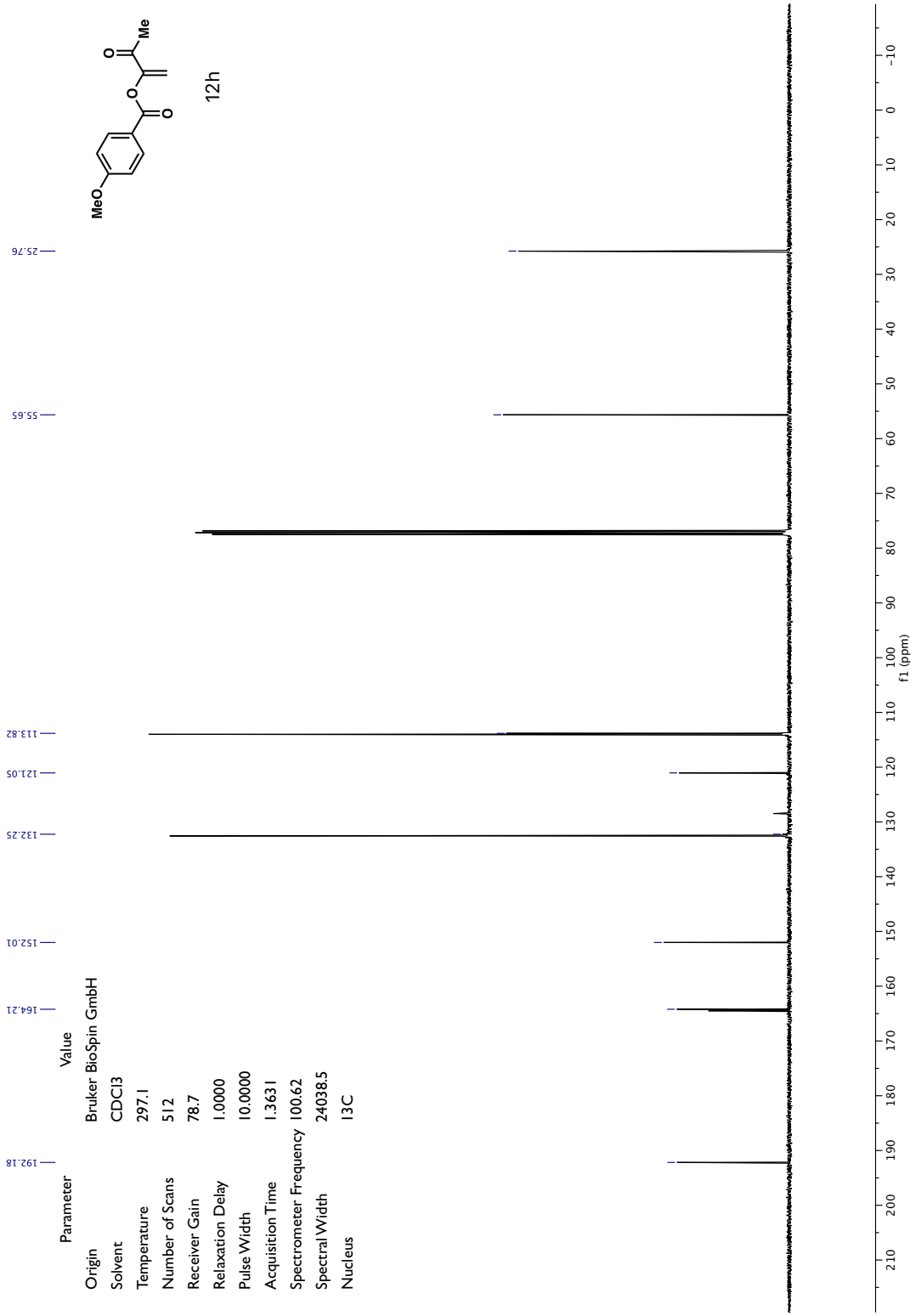

S2
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 16
Receiver Gain 58
Relaxation Delay 10.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Spectrometer Frequency 499.63
Spectral Width 8000.0
Nucleus 1H
3.04
1.00
1.00
2.01
2.00
f1 (ppm)

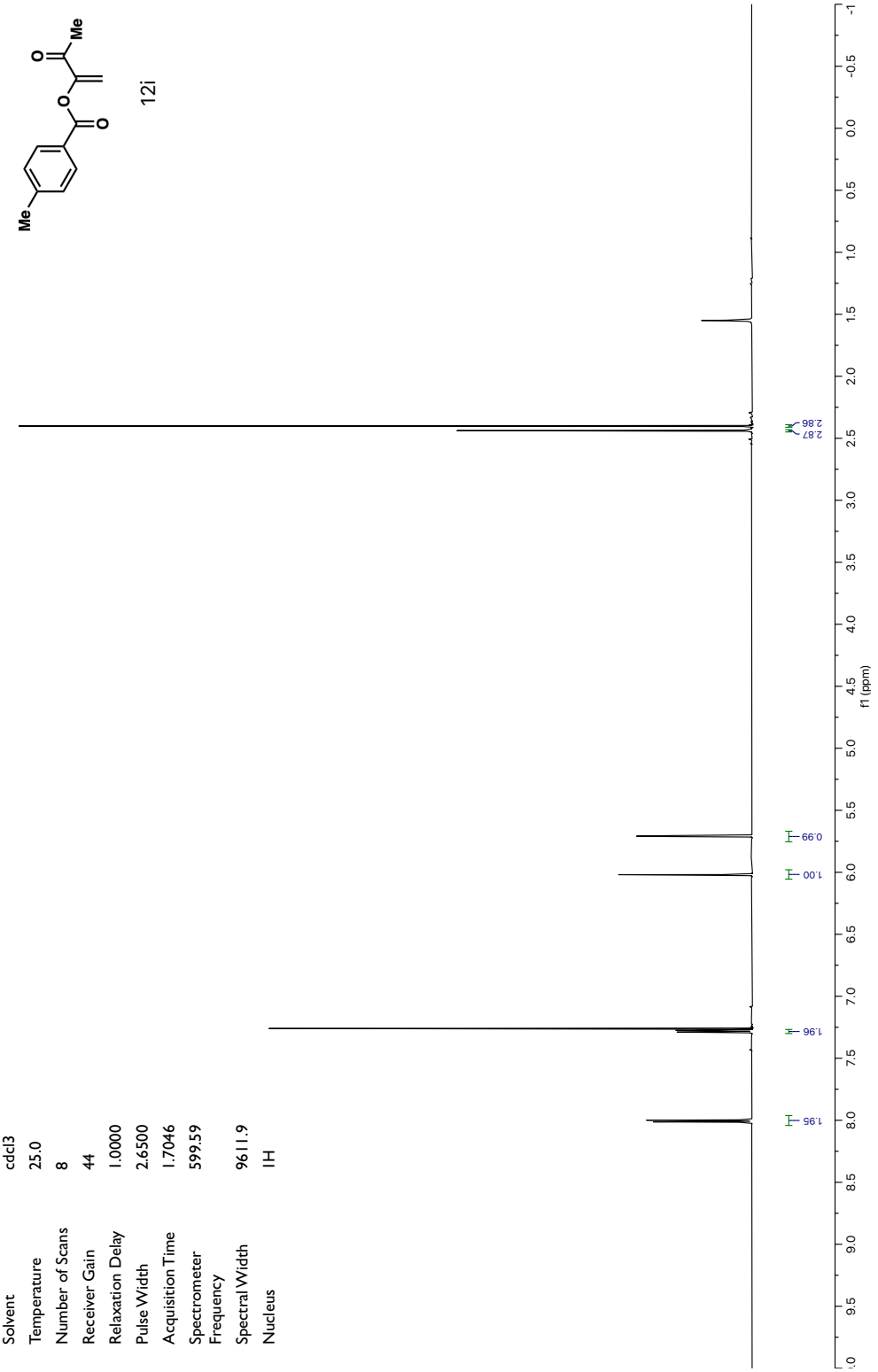

12g
Me2N
O
O
O
Me
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.00
6.00
0.99
1.00
1.99
1.95
f1 (ppm)



Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C


12h
MeO
O
O
O
Me
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
3.02
3.06
1.00
1.00
2.01
1.97
f1 (ppm)


12h
MeO
O
O
O
Me
25.76
55.65
113.82
121.05
132.25
152.01
164.21
192.18
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C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Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 8
Receiver Gain 44
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Spectrometer Frequency 599.59
Spectral Width 9611.9
Nucleus 1H
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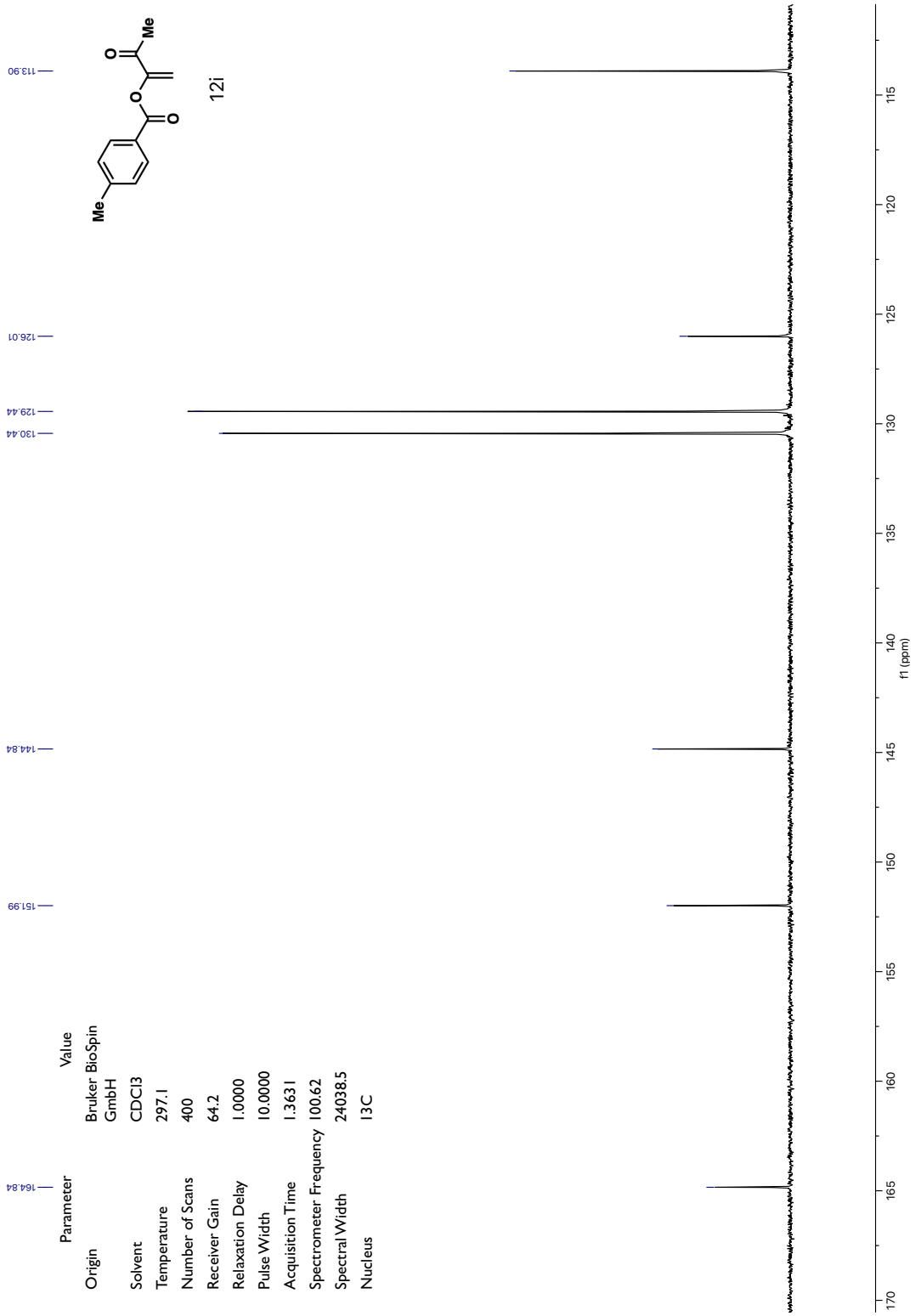
2.86
0.99
1.00
1.96
1.95
f1 (ppm)


12i
Me
Me
O
O
O
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 400
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
164.84
151.99
144.84
130.44
129.44
126.01
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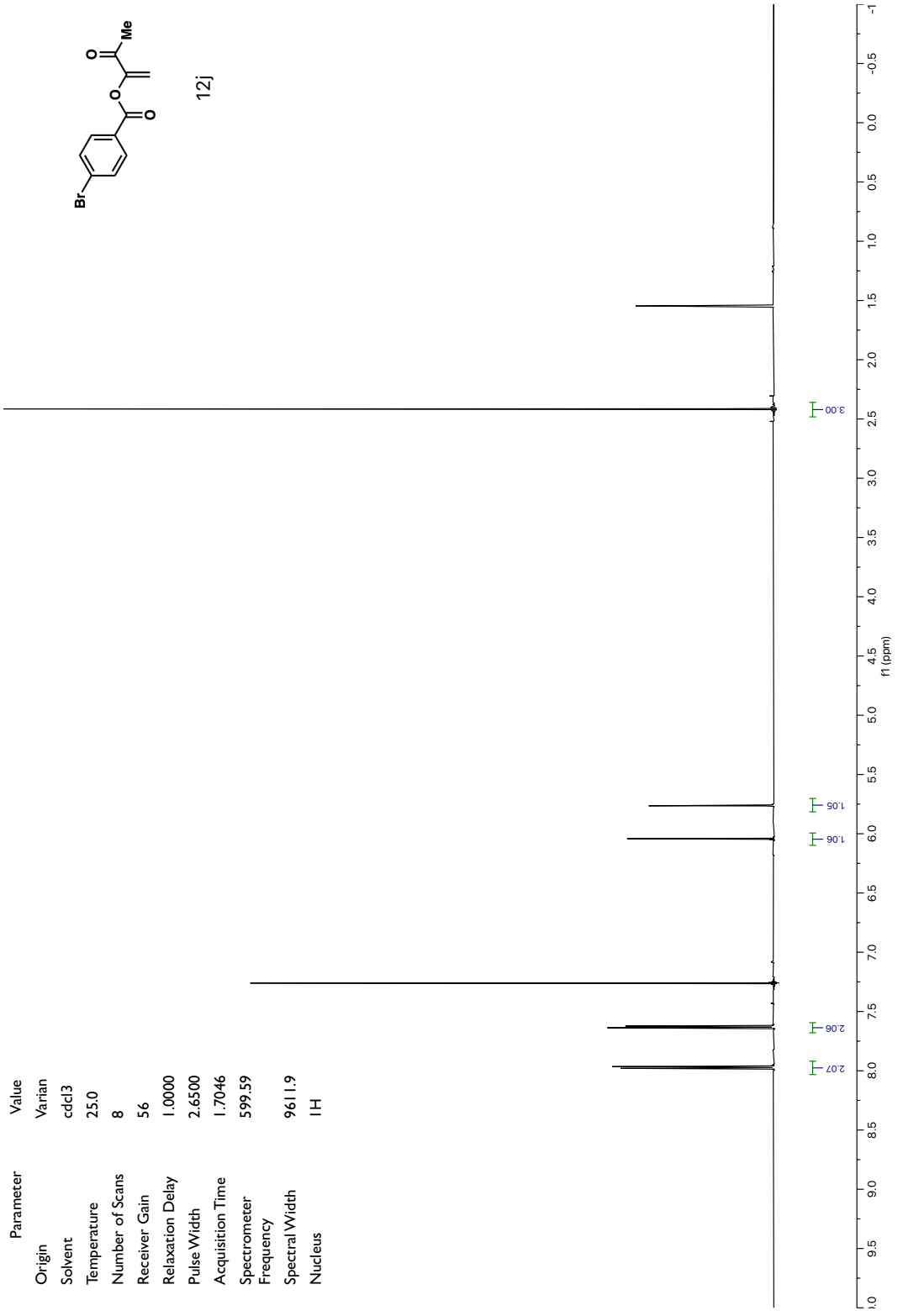
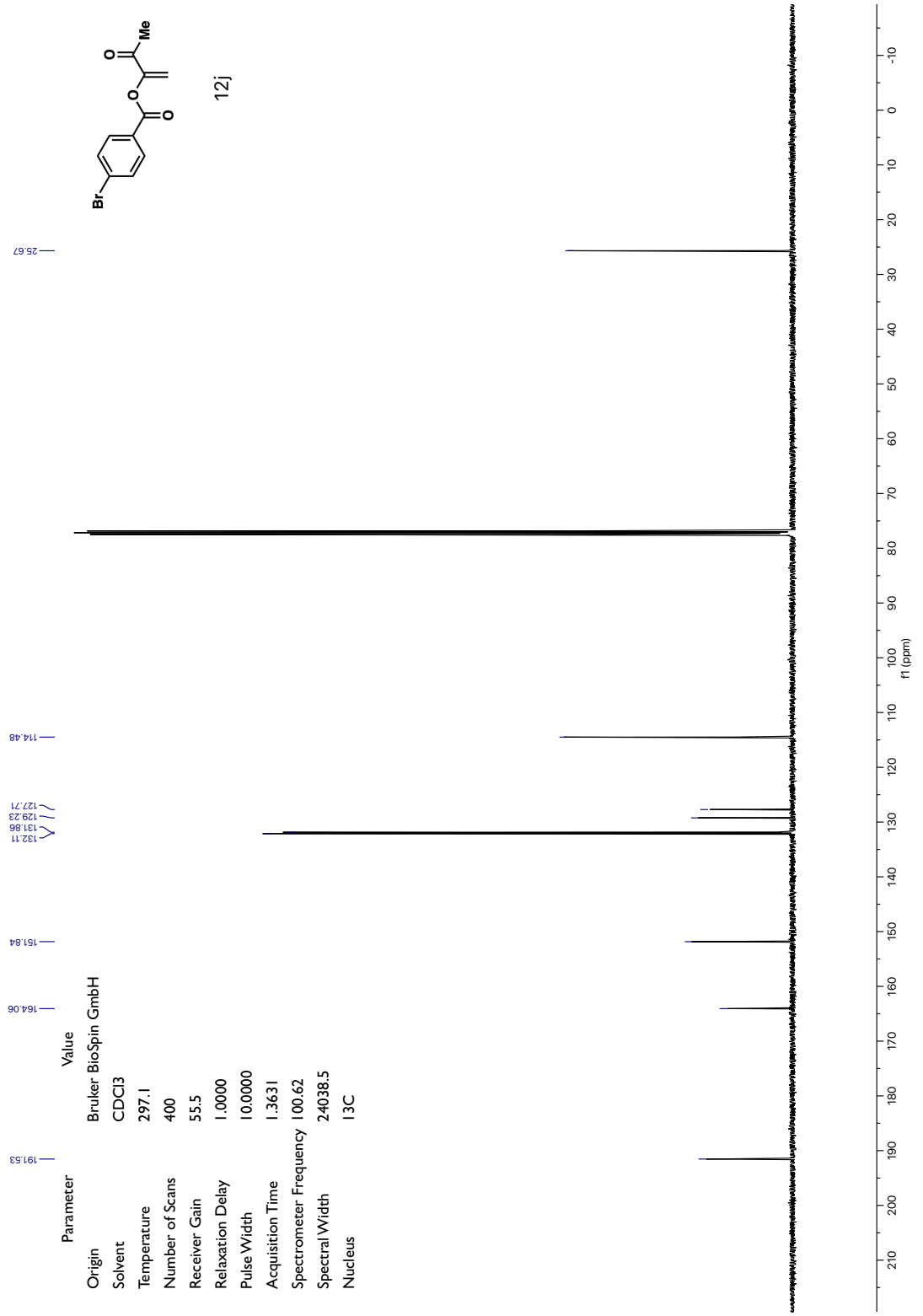
150
145
140
135
130
125
120
115
f1 (ppm)


Me
O
O
O
Br
12j
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 8
Receiver Gain 56
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Spectrometer Frequency 599.59
Spectral Width 9611.9
Nucleus 1H
3.00
1.05
1.06
2.06
2.07
f1 (ppm)


Me
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Br
12j
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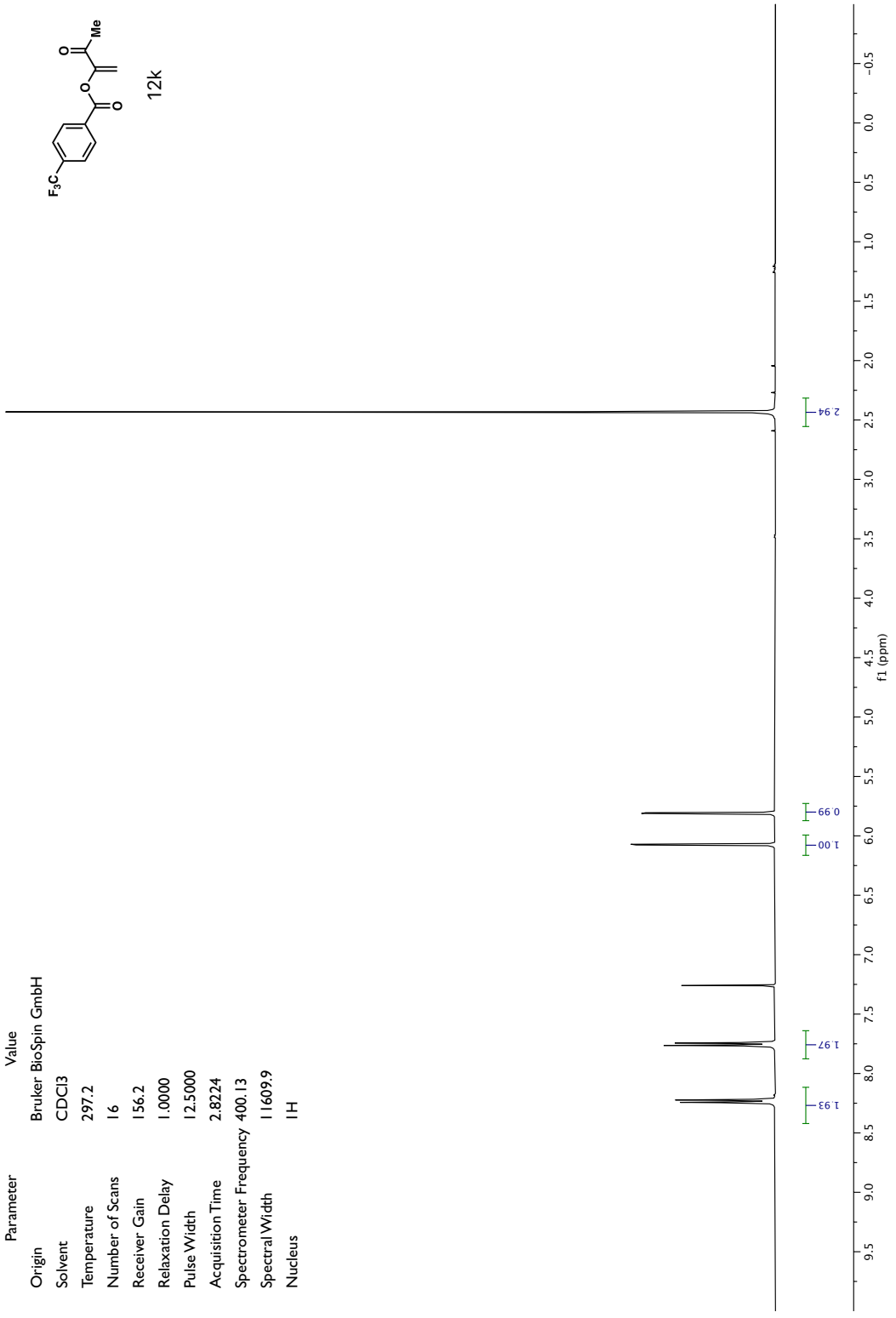
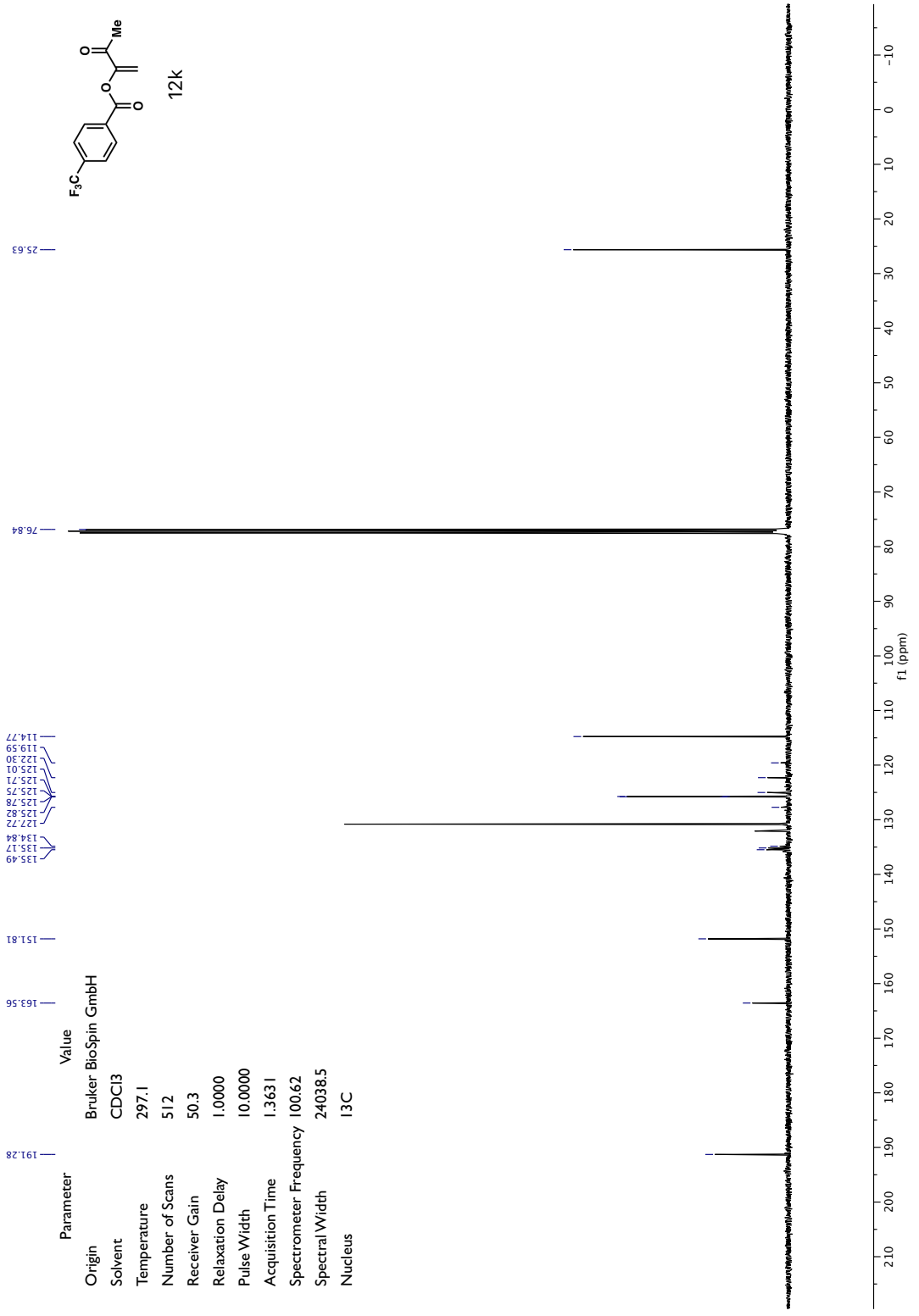
129.23
131.86
132.11
151.84
164.06
191.53
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 400
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C


12k
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
1.93
1.97
1.00
0.99
2.94
f1 (ppm)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O
O
O
F3C
12k
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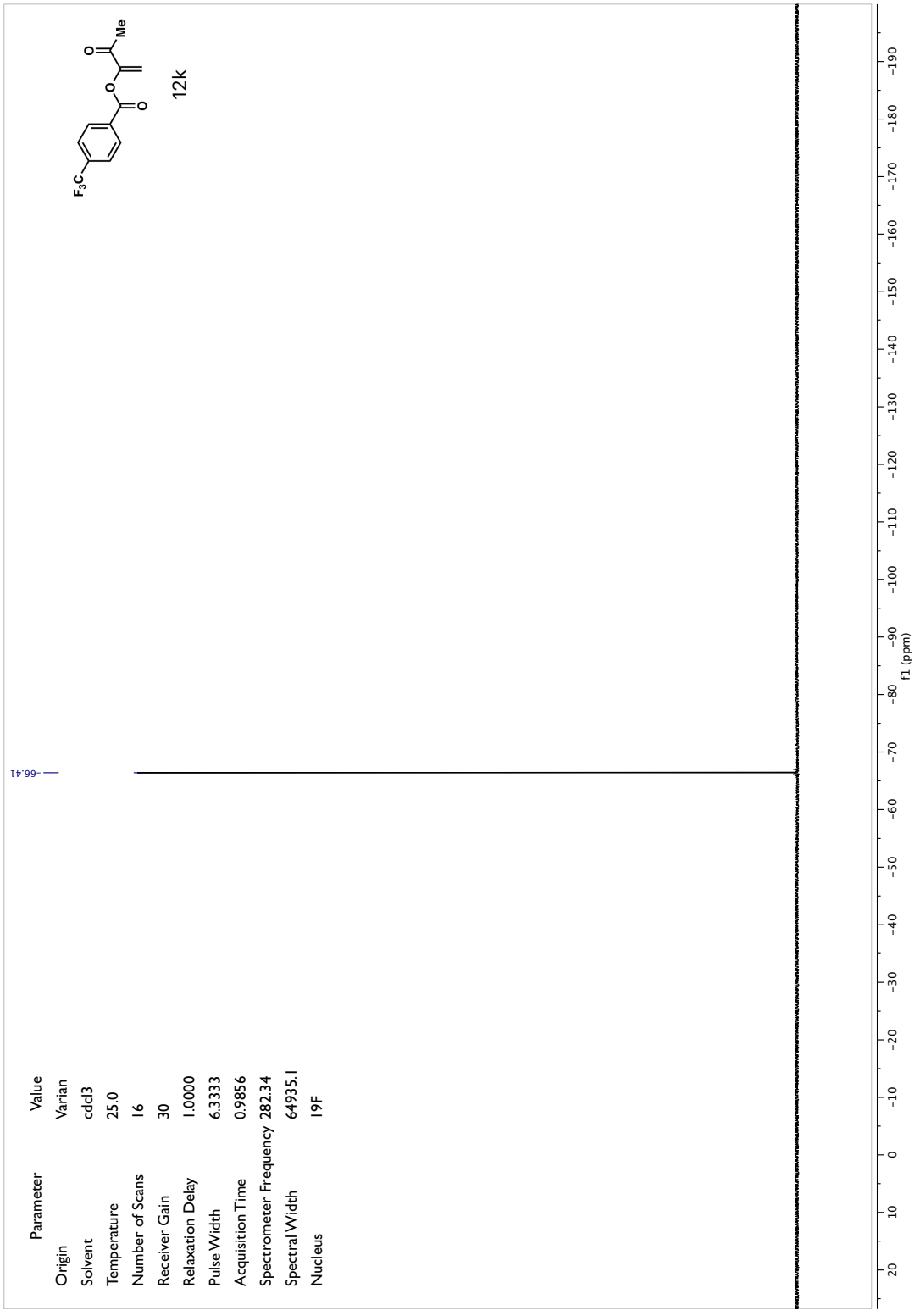
122.30
125.01
125.71
125.75
125.78
125.82
127.72
134.84
135.17
135.49
151.81
163.56
191.28
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)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Solvent cdcl3
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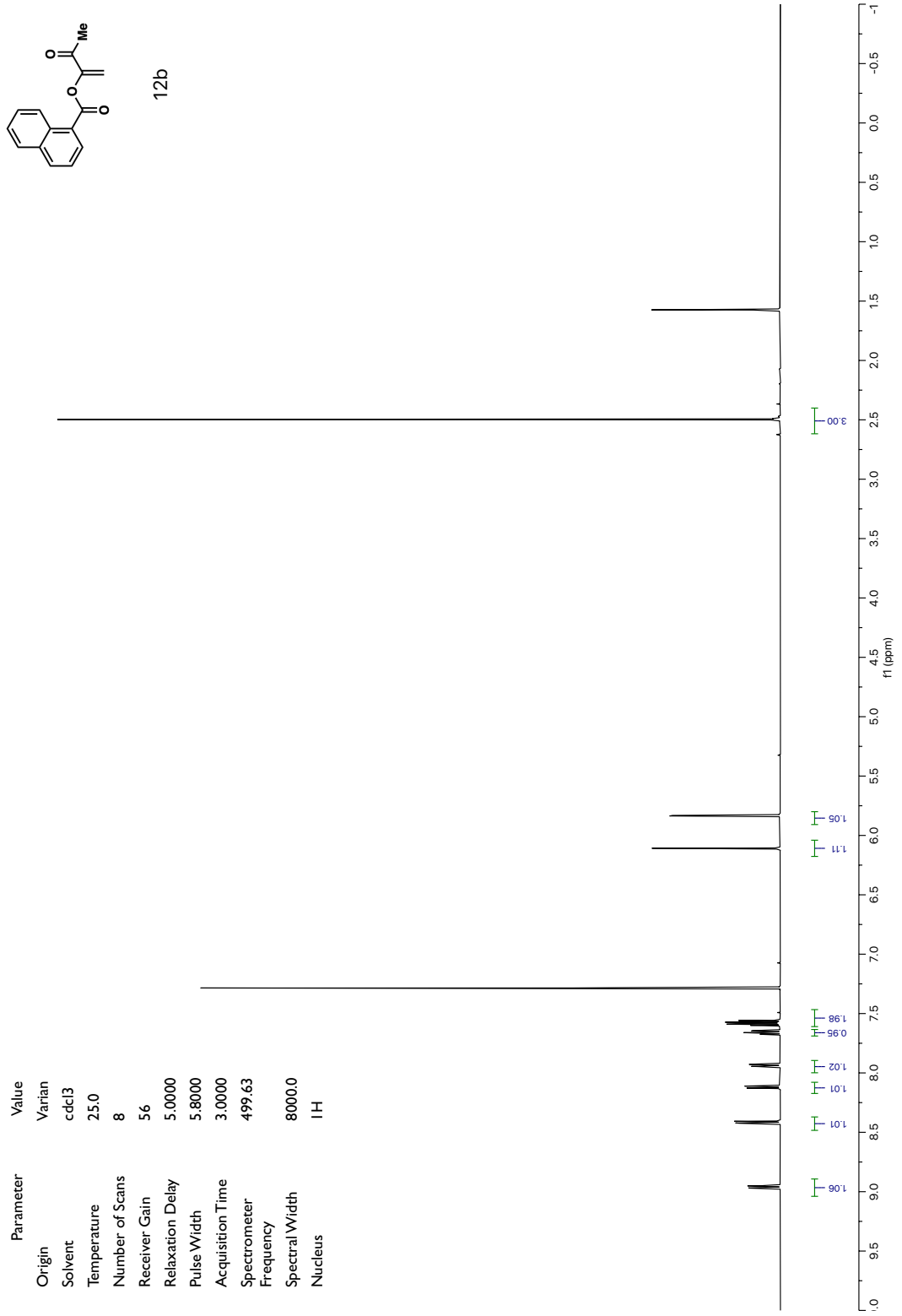
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 6.3333
Acquisition Time 0.9856
Spectrometer Frequency 282.34
Spectral Width 64935.1
Nucleus 19F
-66.41
12k
Me
O
O
O
F3C
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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O
O
O
12b
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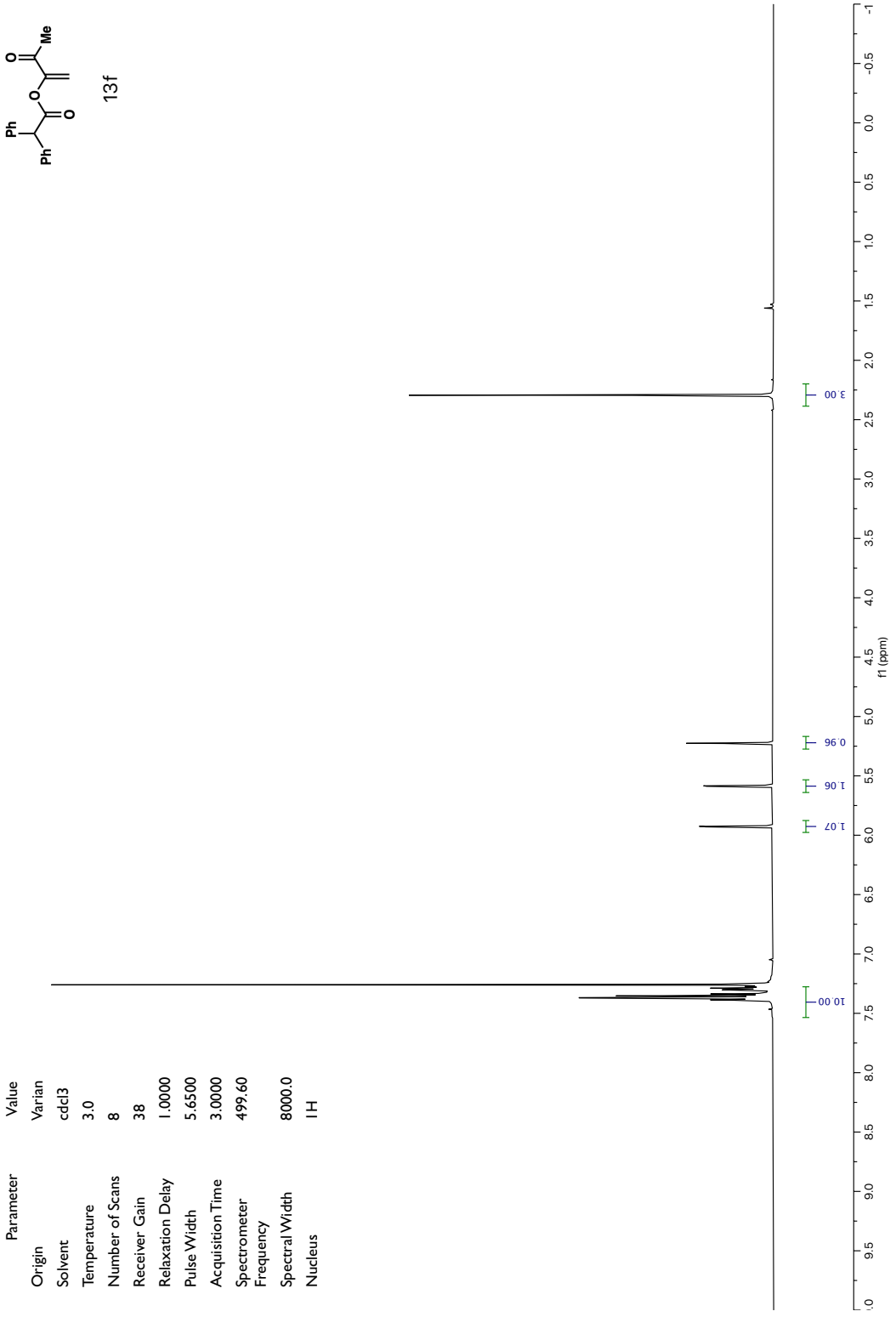
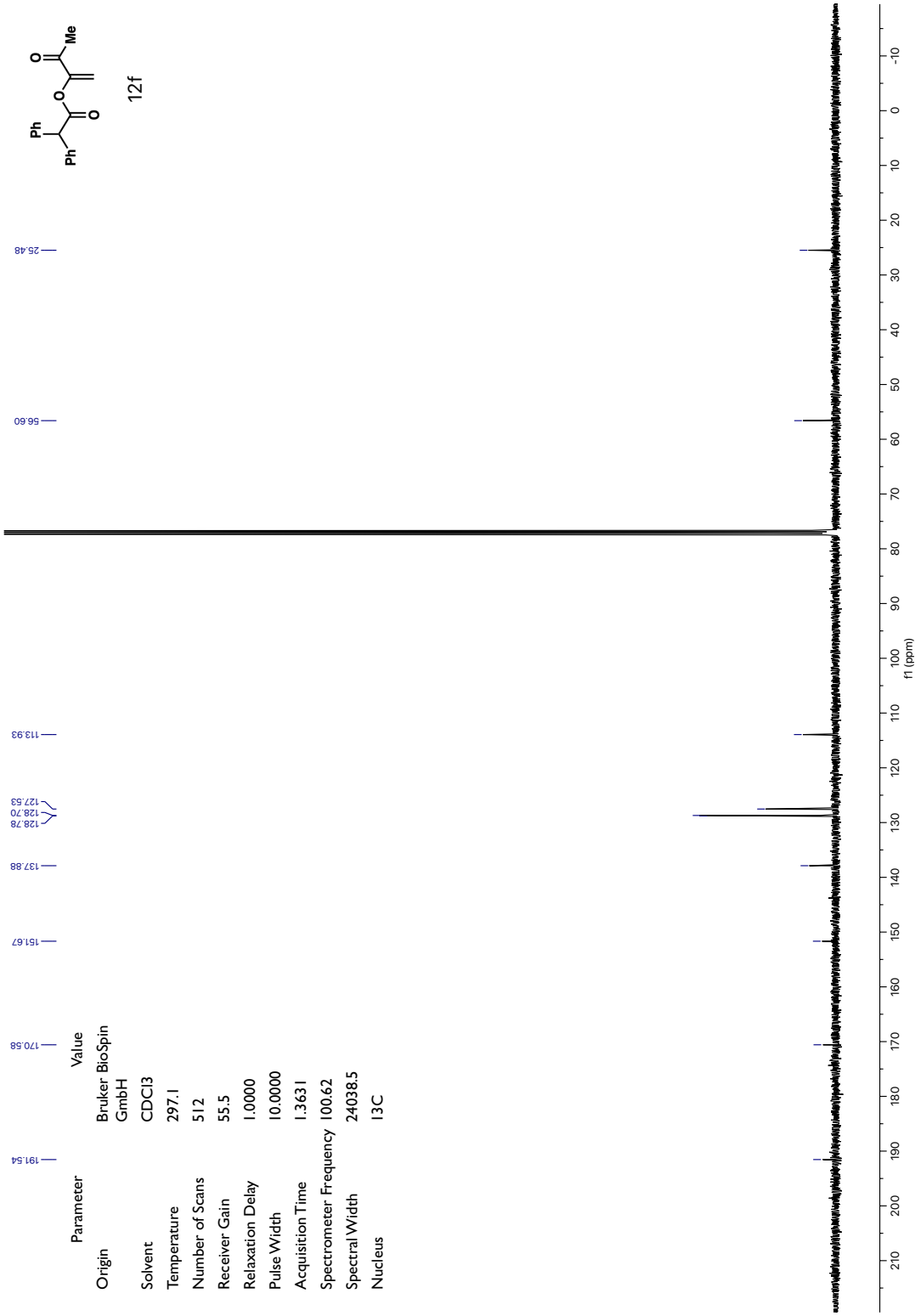
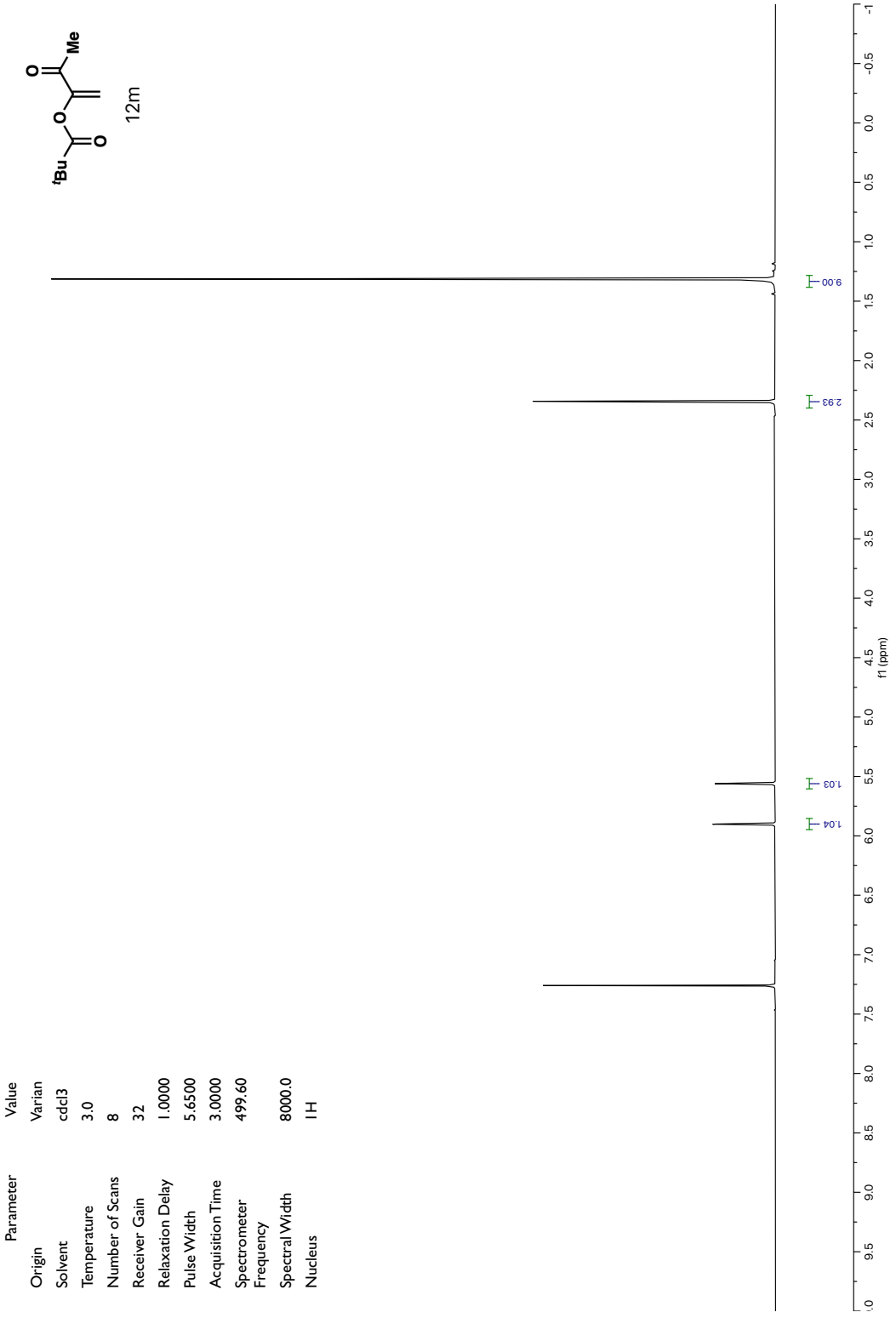
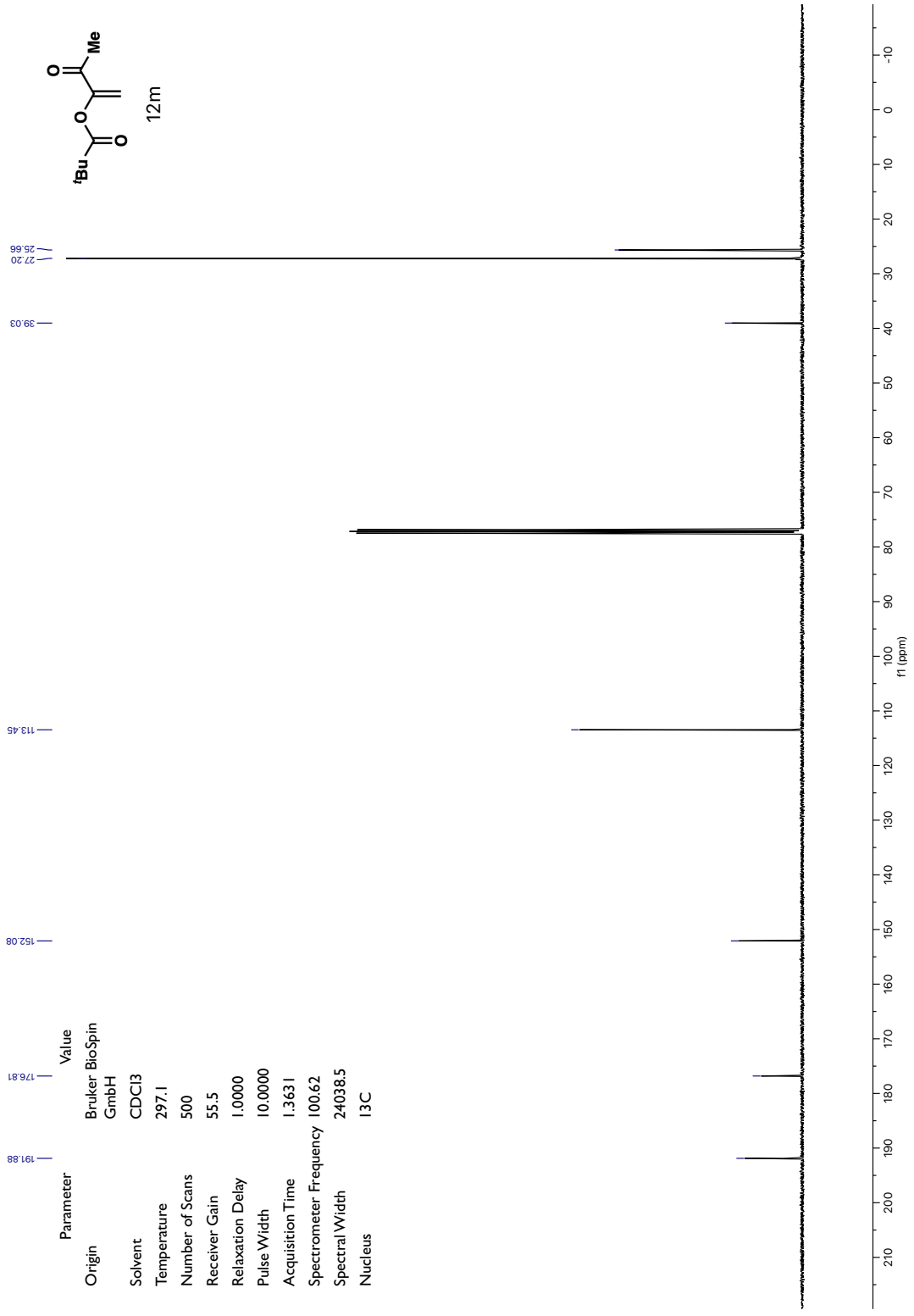
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 8
Receiver Gain 56
Relaxation Delay 5.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Spectrometer Frequency 499.63
Spectral Width 8000.0
Nucleus 1H
3.00
1.05
1.11
1.98
0.95
1.02
1.01
1.01
1.06
f1 (ppm)

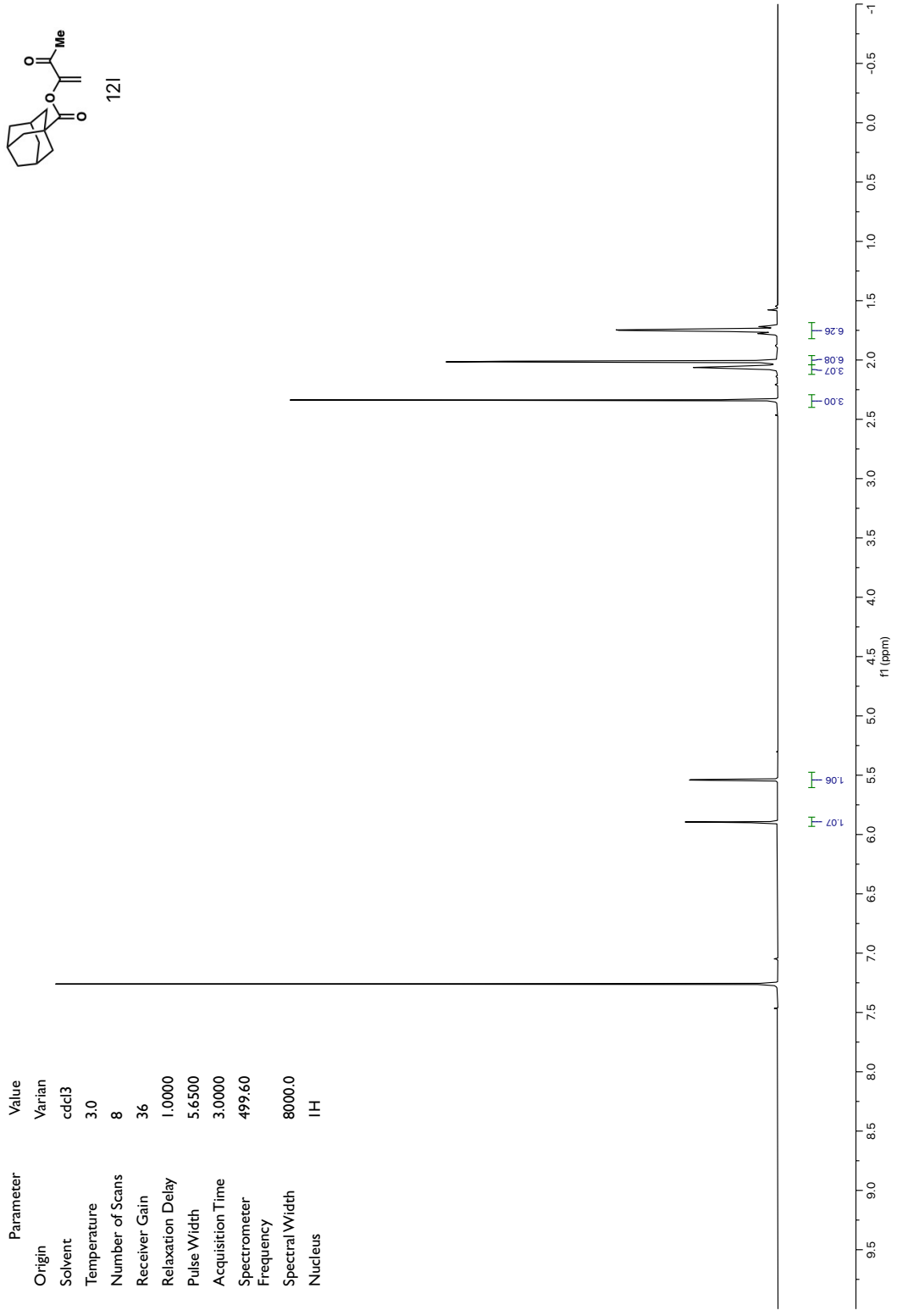

13f
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 3.0
Number of Scans 8
Receiver Gain 38
Relaxation Delay 1.0000
Pulse Width 5.6500
Acquisition Time 3.0000
Spectrometer Frequency 499.60
Spectral Width 8000.0
Nucleus 1H
10.00
1.07
1.06
0.96
3.00
f1 (ppm)

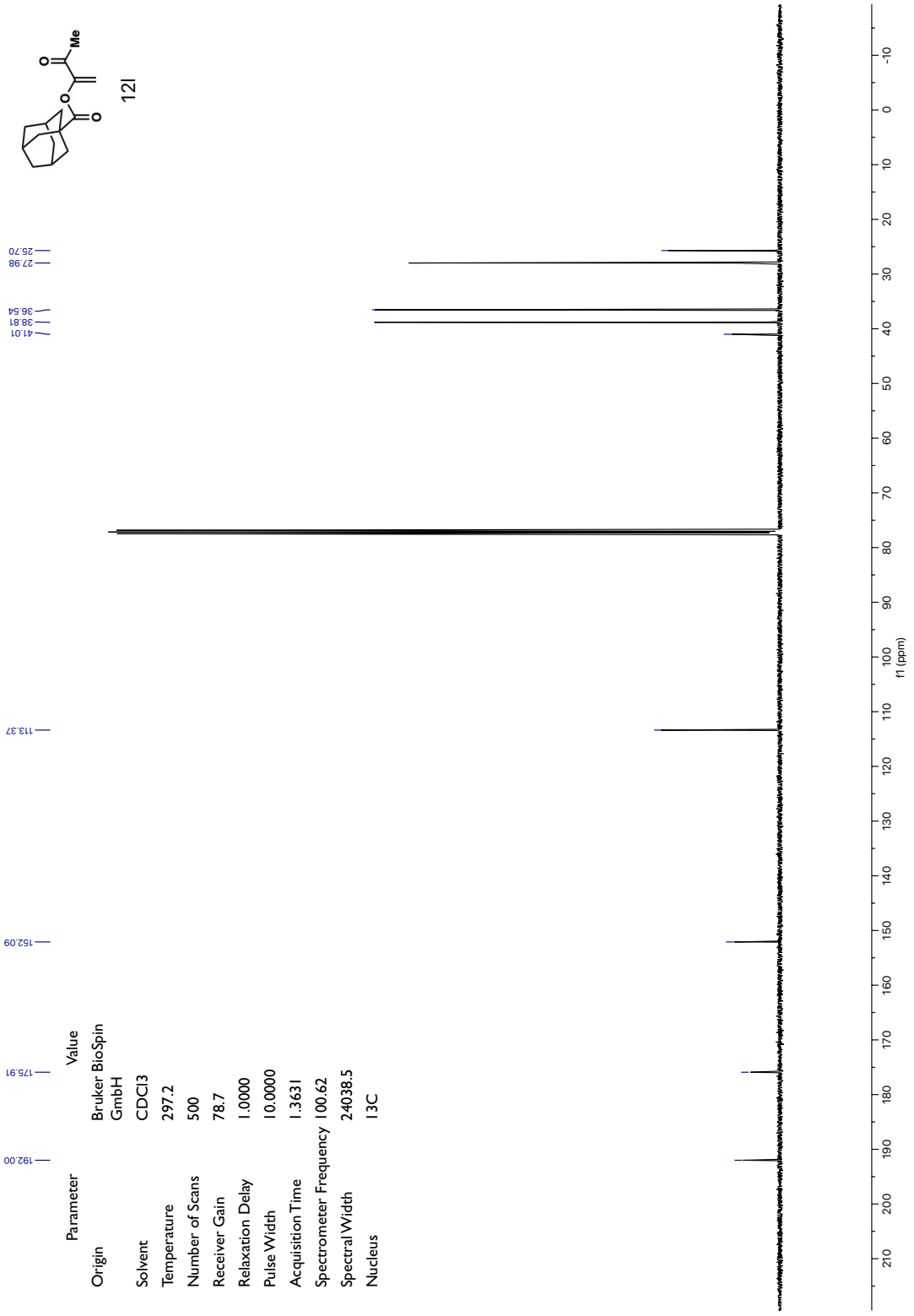

12f
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
191.54
170.58
151.67
137.88
128.78
128.70
127.53
113.93
56.60
25.48
f1 (ppm)

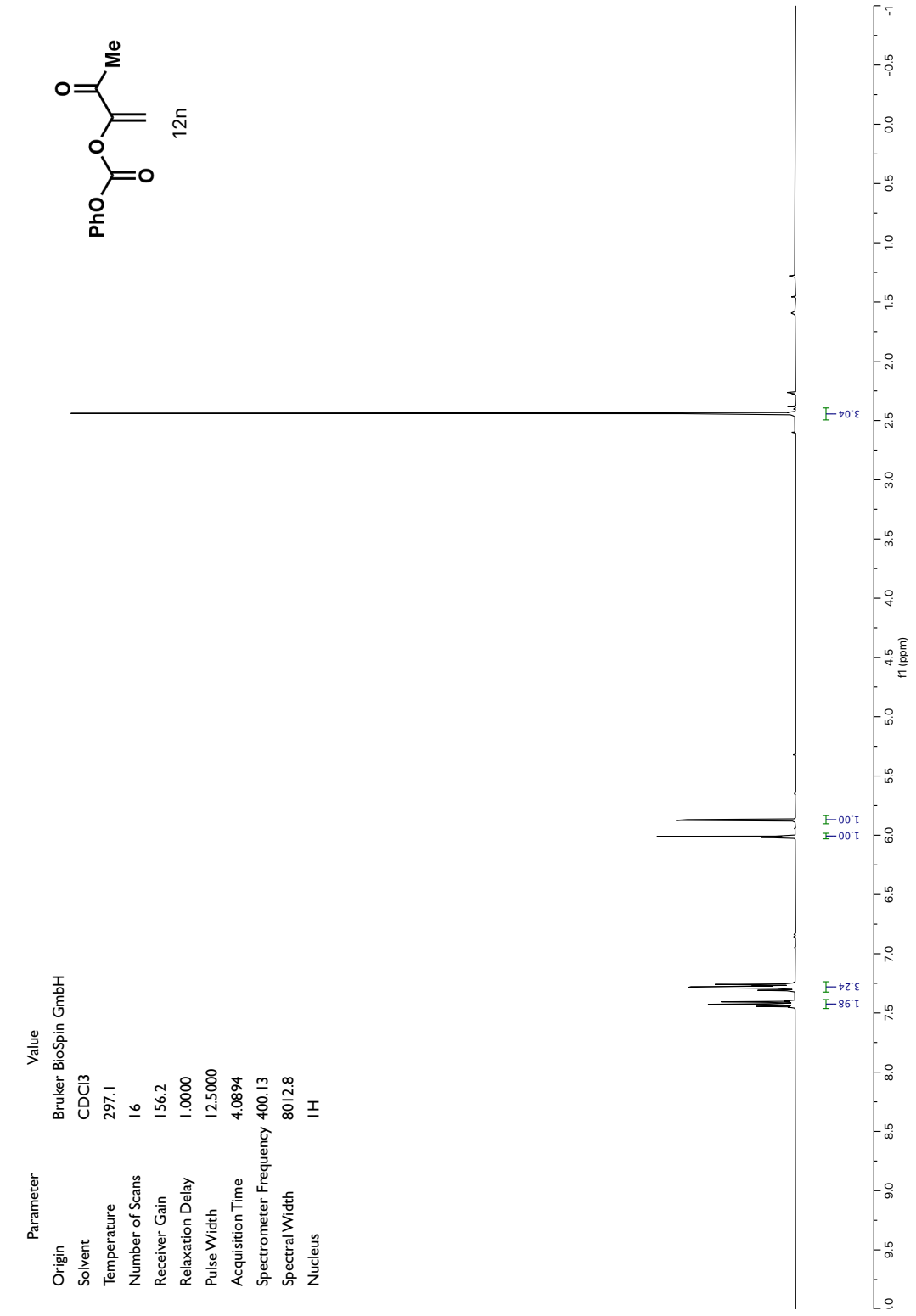


Parameter	Value
Origin	Varian
Solvent	cdcl3
Temperature	3.0
Number of Scans	8
Receiver Gain	32
Relaxation Delay	1.0000
Pulse Width	5.6500
Acquisition Time	3.0000
Spectrometer Frequency	499.60
Spectral Width	8000.0
Nucleus	1H

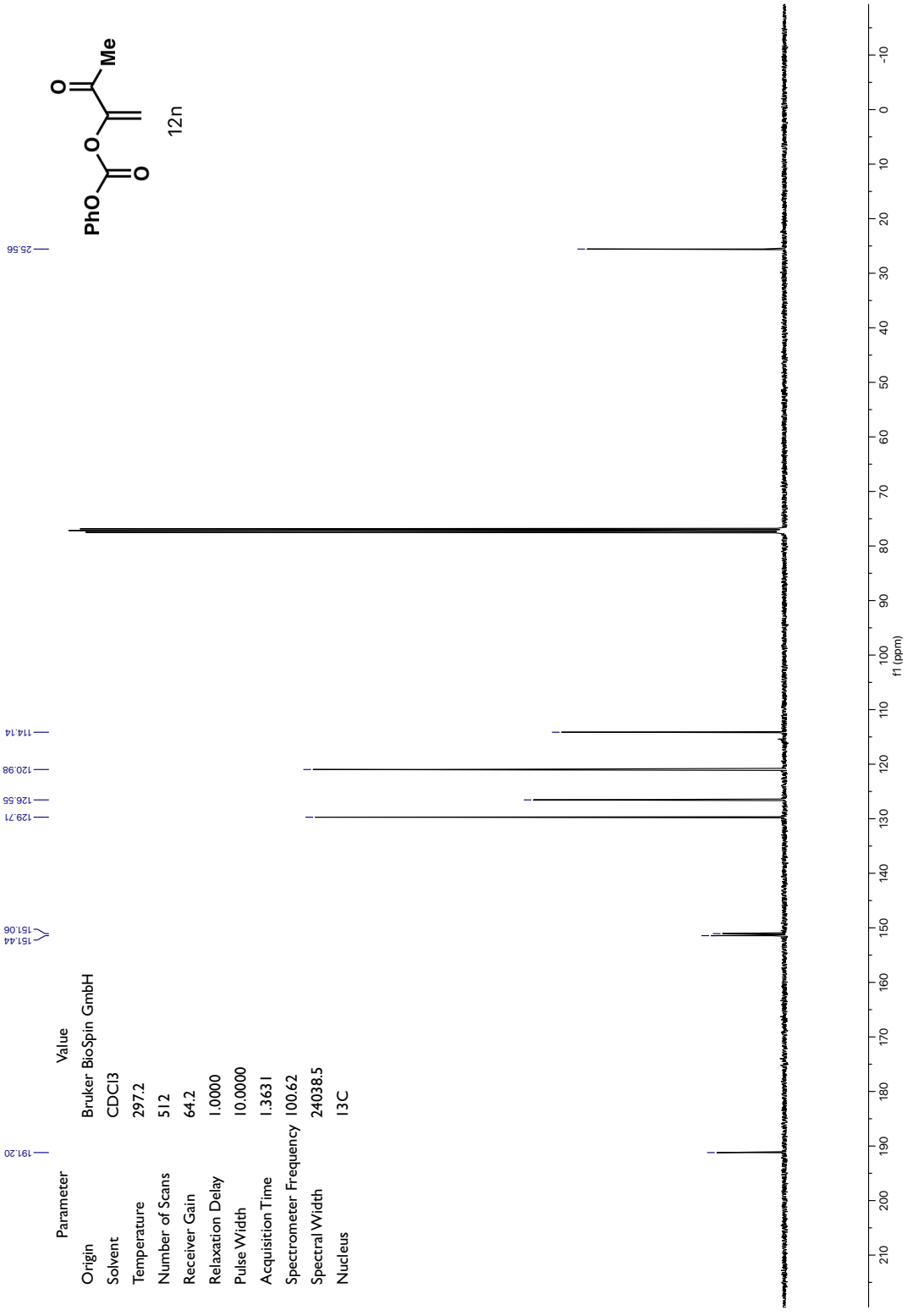

12m
Me
O
O
O
tBu
O
25.66
27.20
39.03
113.45
152.08
176.81
191.88
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 500
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C

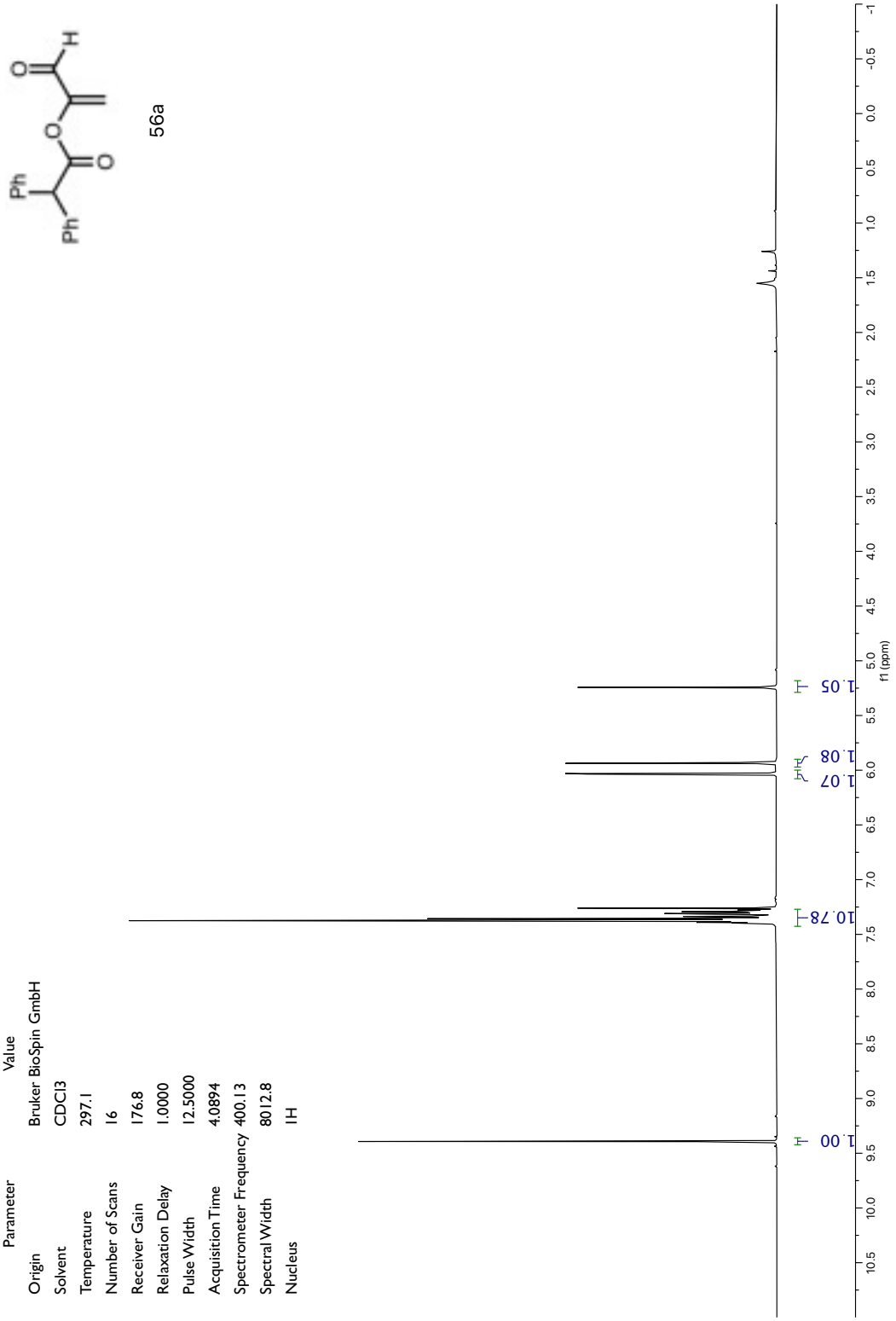

Me
O
O
O
O
12l
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 3.0
Number of Scans 8
Receiver Gain 36
Relaxation Delay 1.0000
Pulse Width 5.6500
Acquisition Time 3.0000
Spectrometer Frequency 499.60
Spectral Width 8000.0
Nucleus 1H
6.26
6.08
3.07
3.00
1.06
1.07
f1 (ppm)

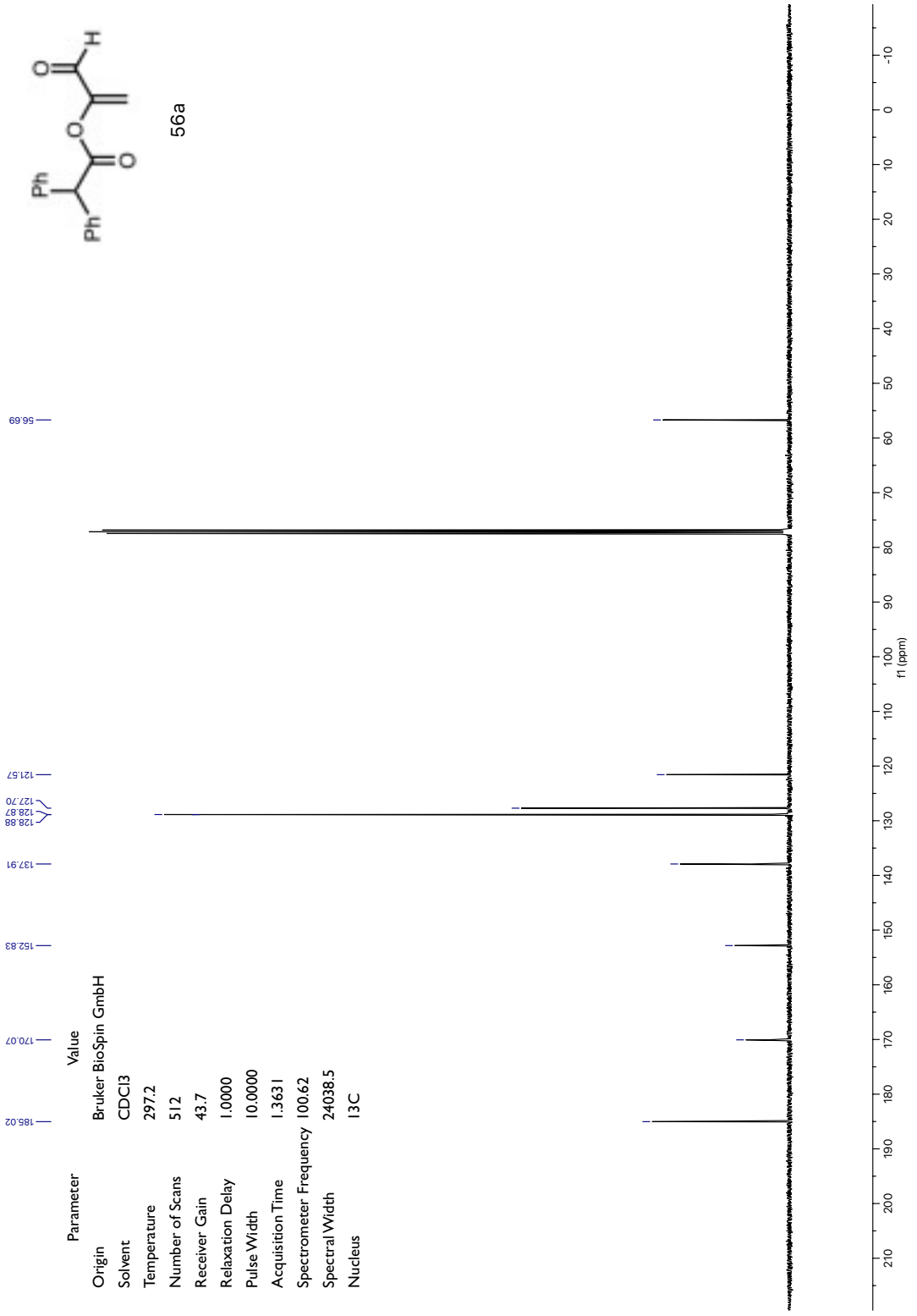

Me
O
O
O
O
12l
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 500
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
25.70
27.98
36.54
38.81
41.01
113.37
152.09
175.91
192.00
f1 (ppm)

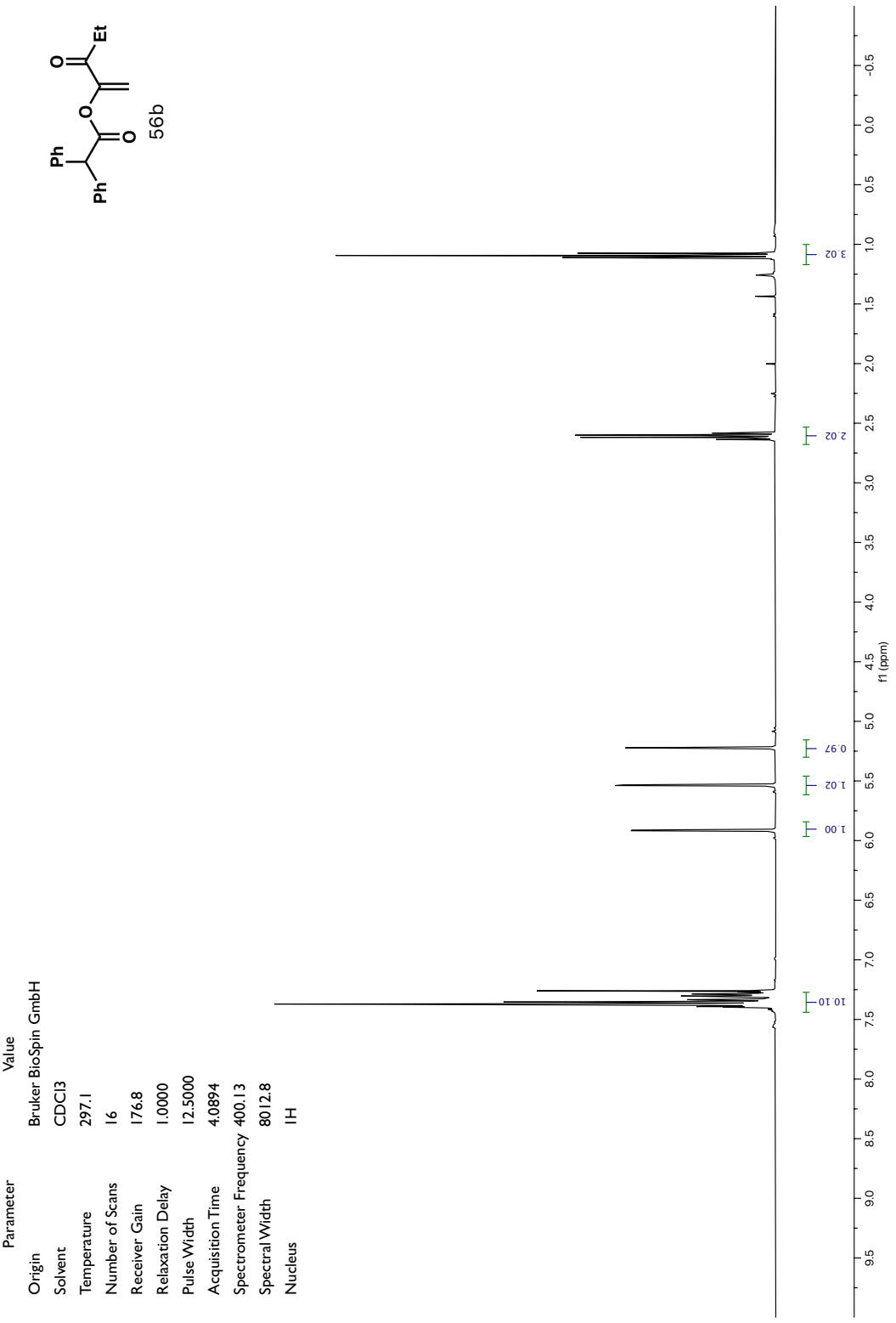


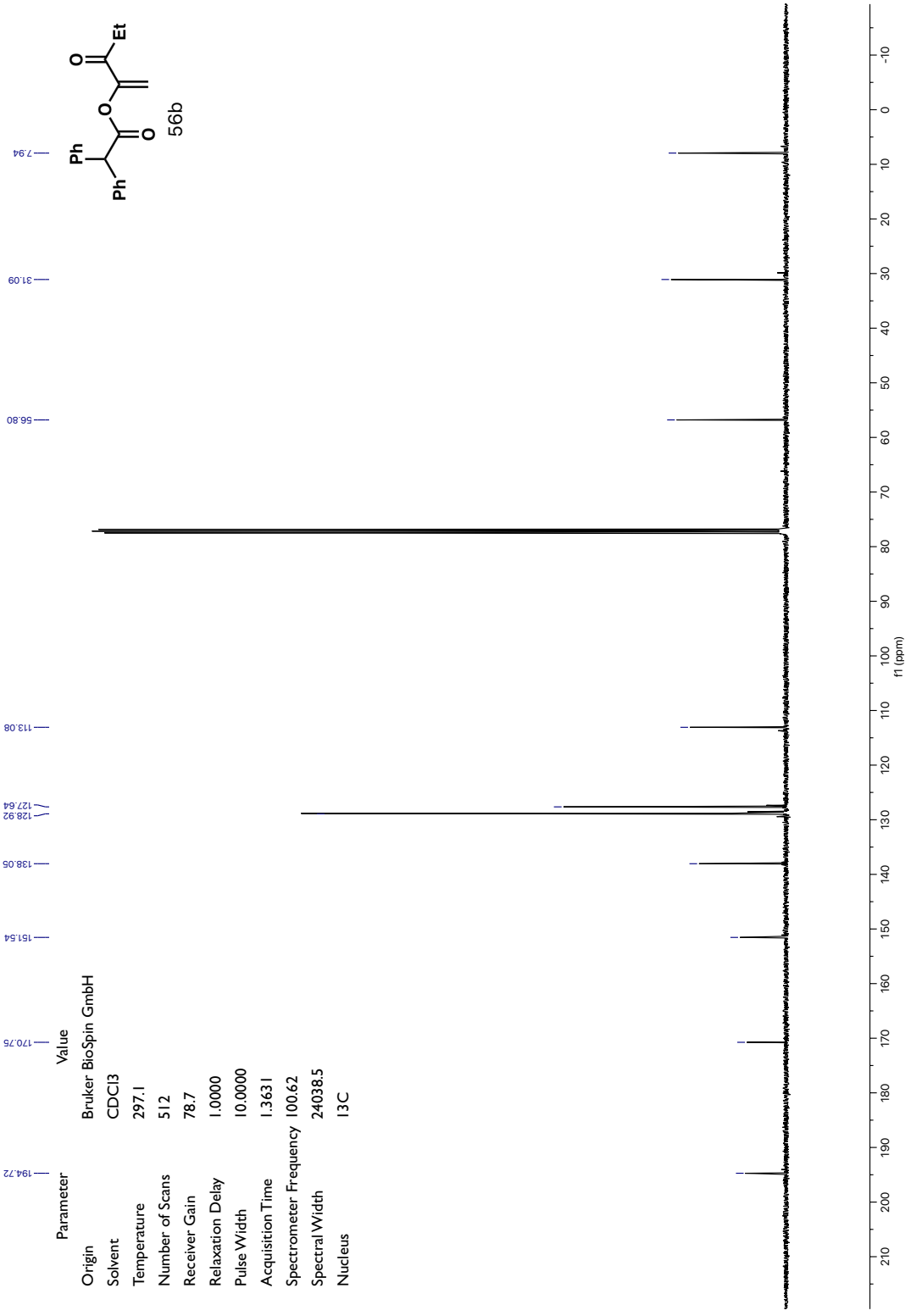
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	16
Receiver Gain	156.2
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H

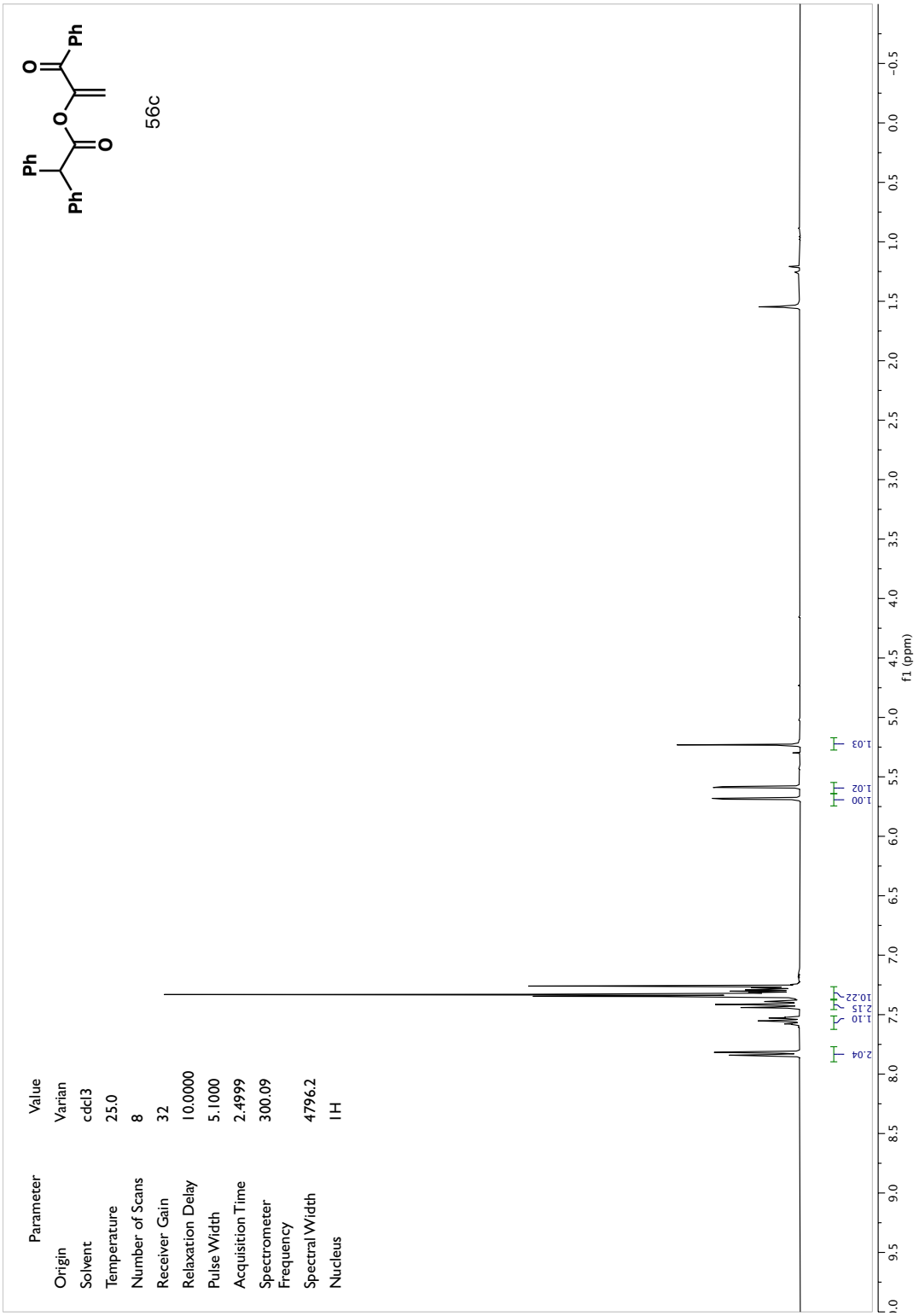

Me
O
O
O
PhO
O
12n
25.56
114.14
120.98
126.55
129.71
151.44
151.06
191.20
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

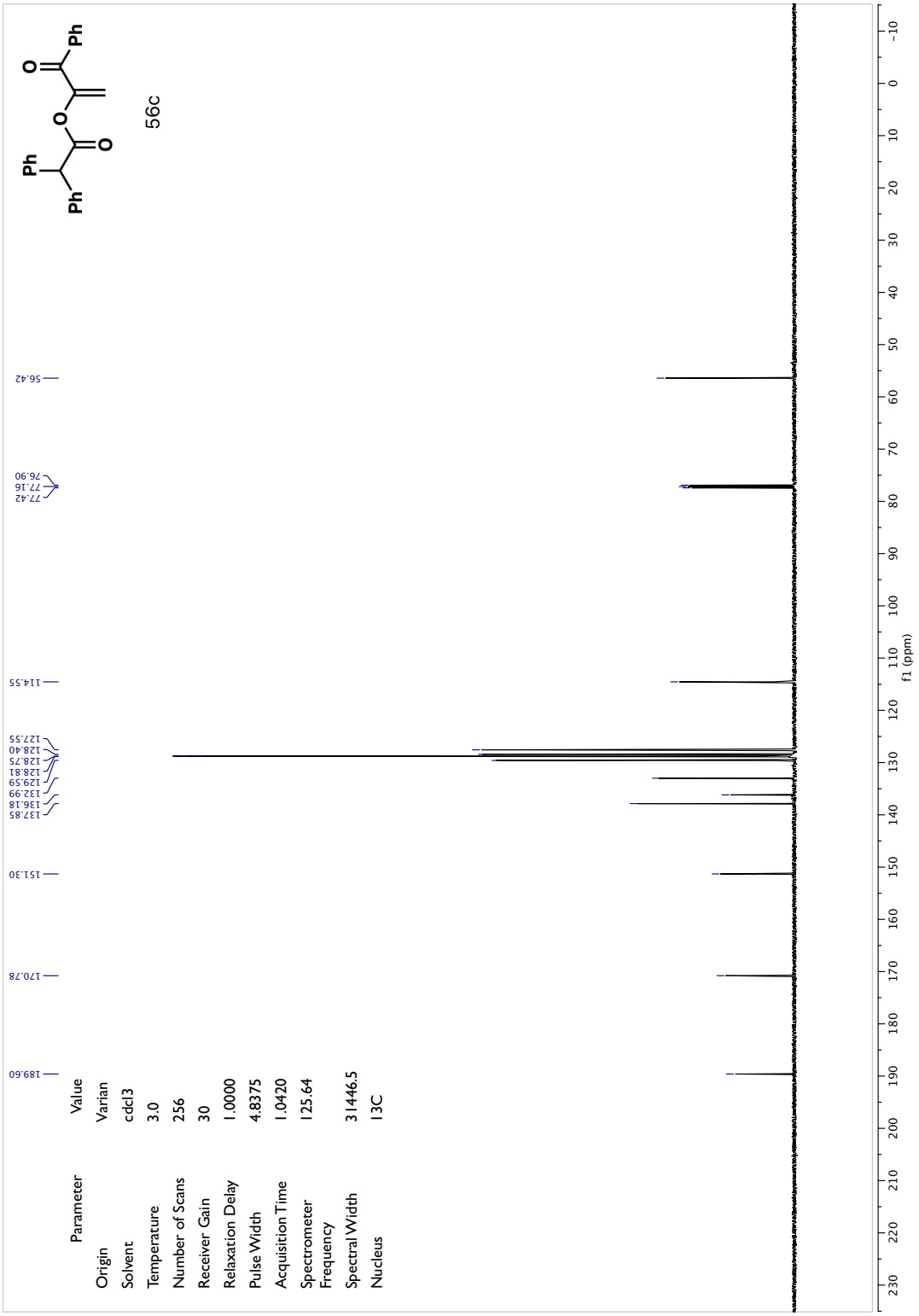

56a
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 176.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
1.00
10.78
1.07
1.08
1.05
f1 (ppm)

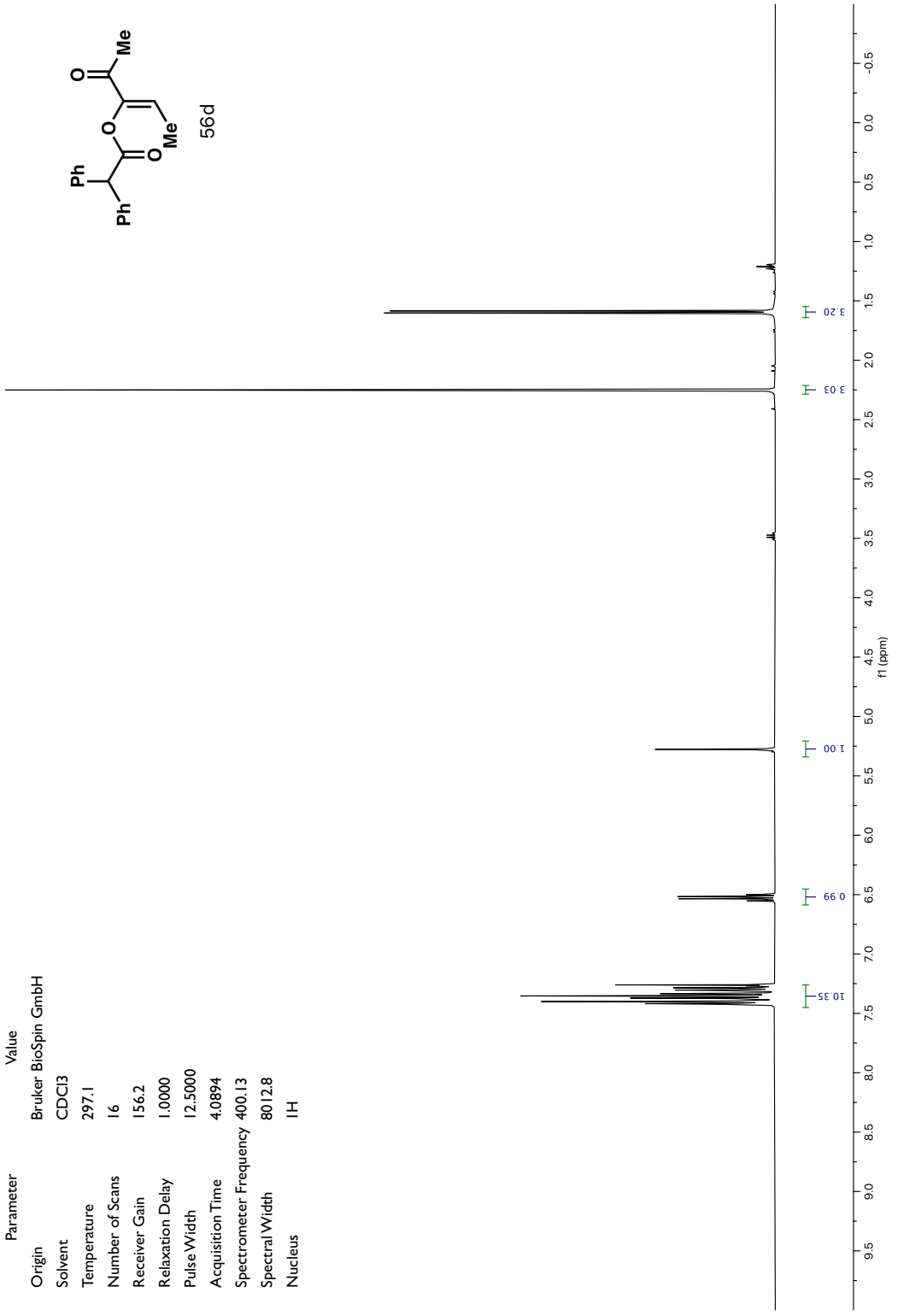

56a
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
185.02
170.07
152.83
137.91
128.88
128.87
127.70
121.57
56.69
f1 (ppm)

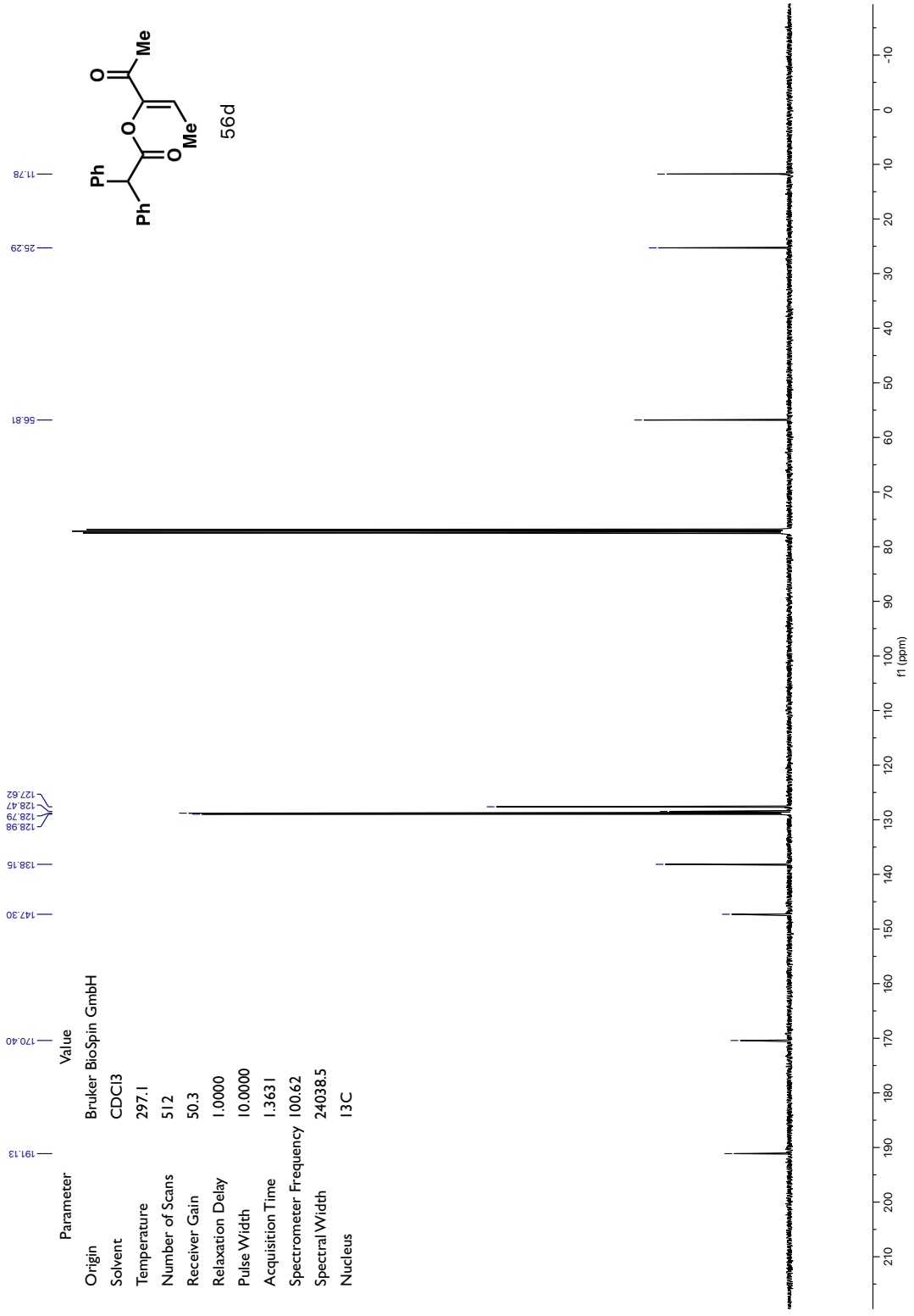

Et
O
O
O
Ph
Ph
56b
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 176.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
10.10
1.00
1.02
0.97
2.02
3.02
f1 (ppm)

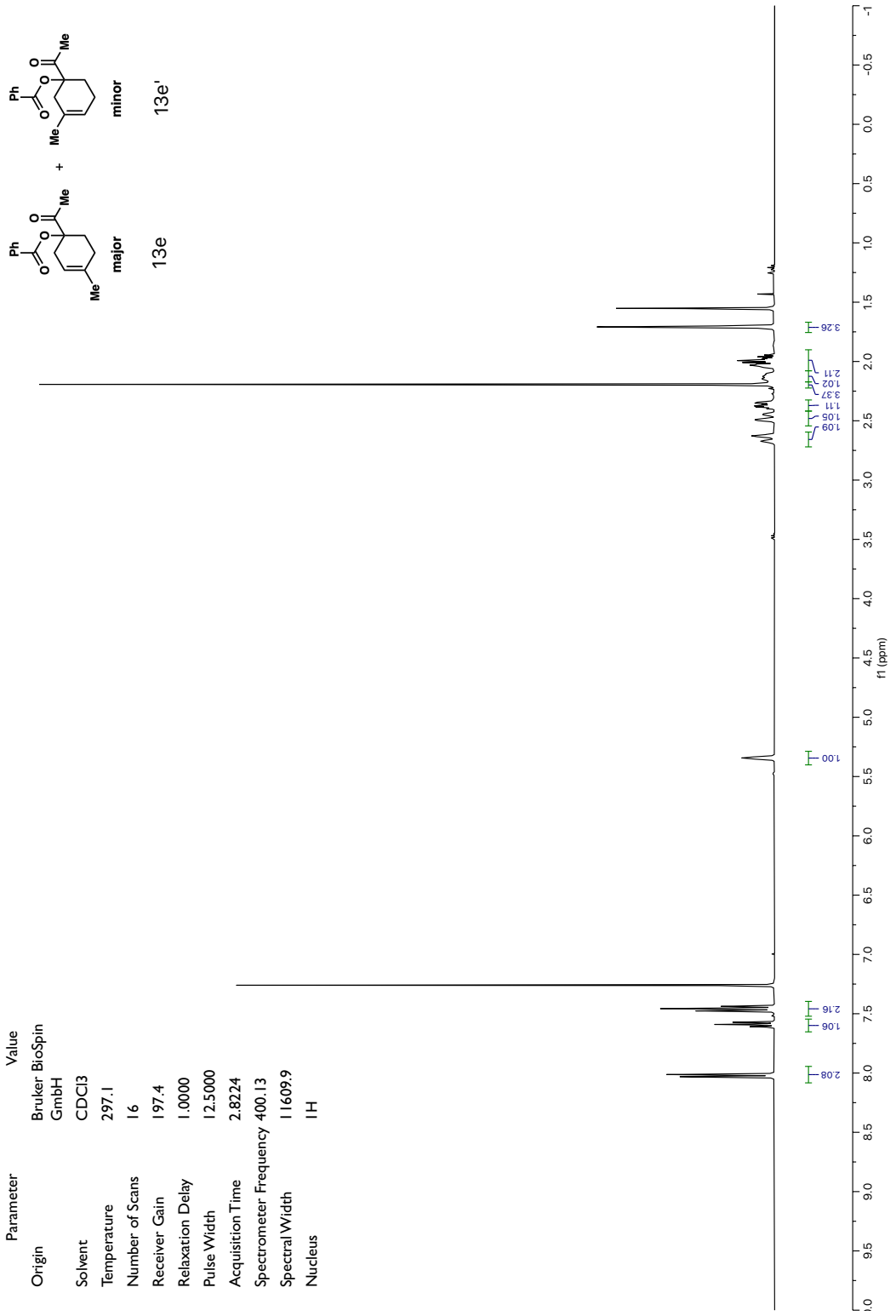

56b
Ph
Ph
O
O
O
Et
194.72
170.75
151.54
138.05
128.92
127.64
113.08
56.80
31.09
7.94
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

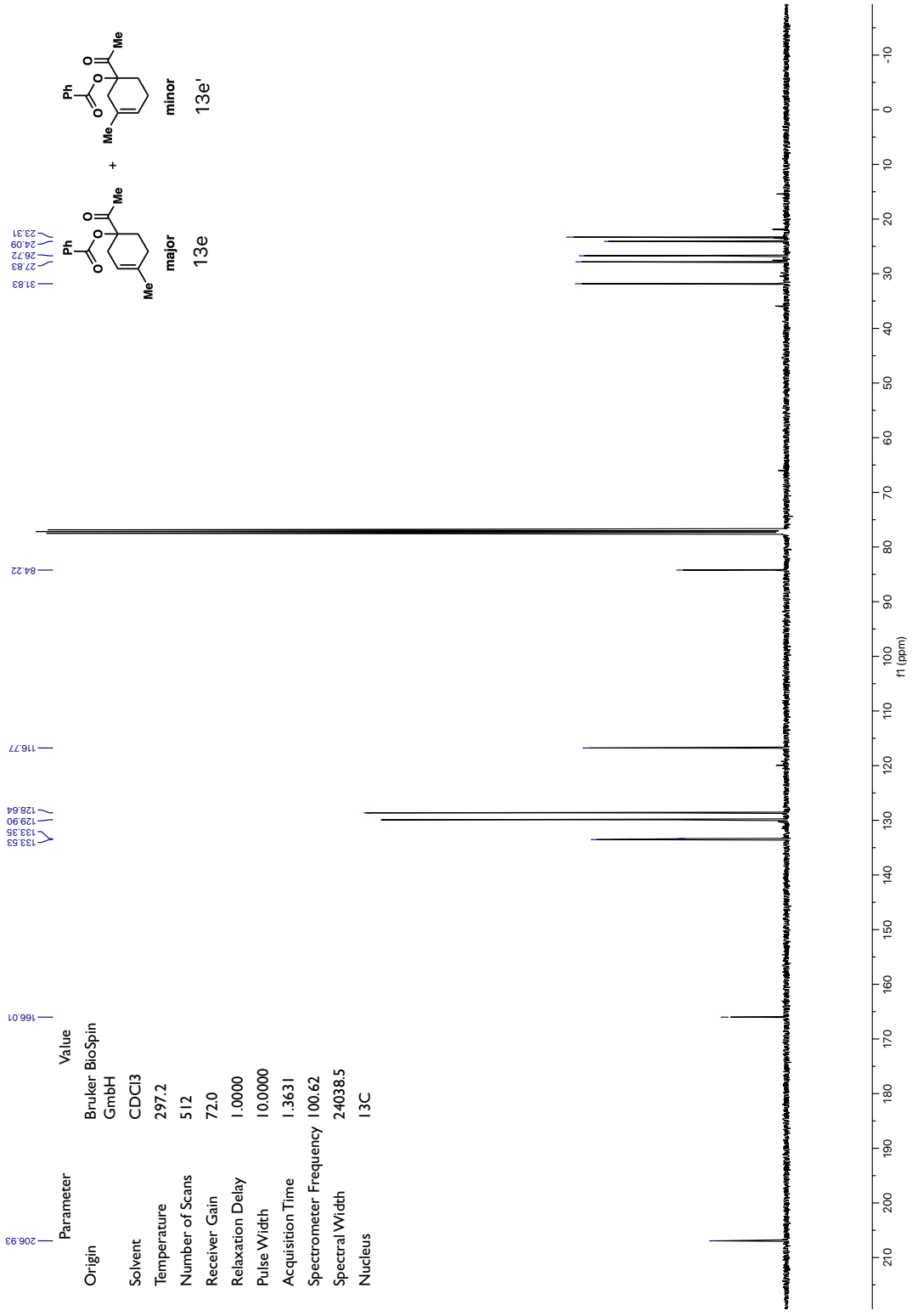

Ph
O
O
O
Ph
Ph
56c
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 25.0
Number of Scans 8
Receiver Gain 32
Relaxation Delay 10.0000
Pulse Width 5.1000
Acquisition Time 2.4999
Spectrometer Frequency 300.09
Spectral Width 4796.2
Nucleus 1H
2.04
1.10
2.19
10.22
1.00
1.02
1.03
f1 (ppm)

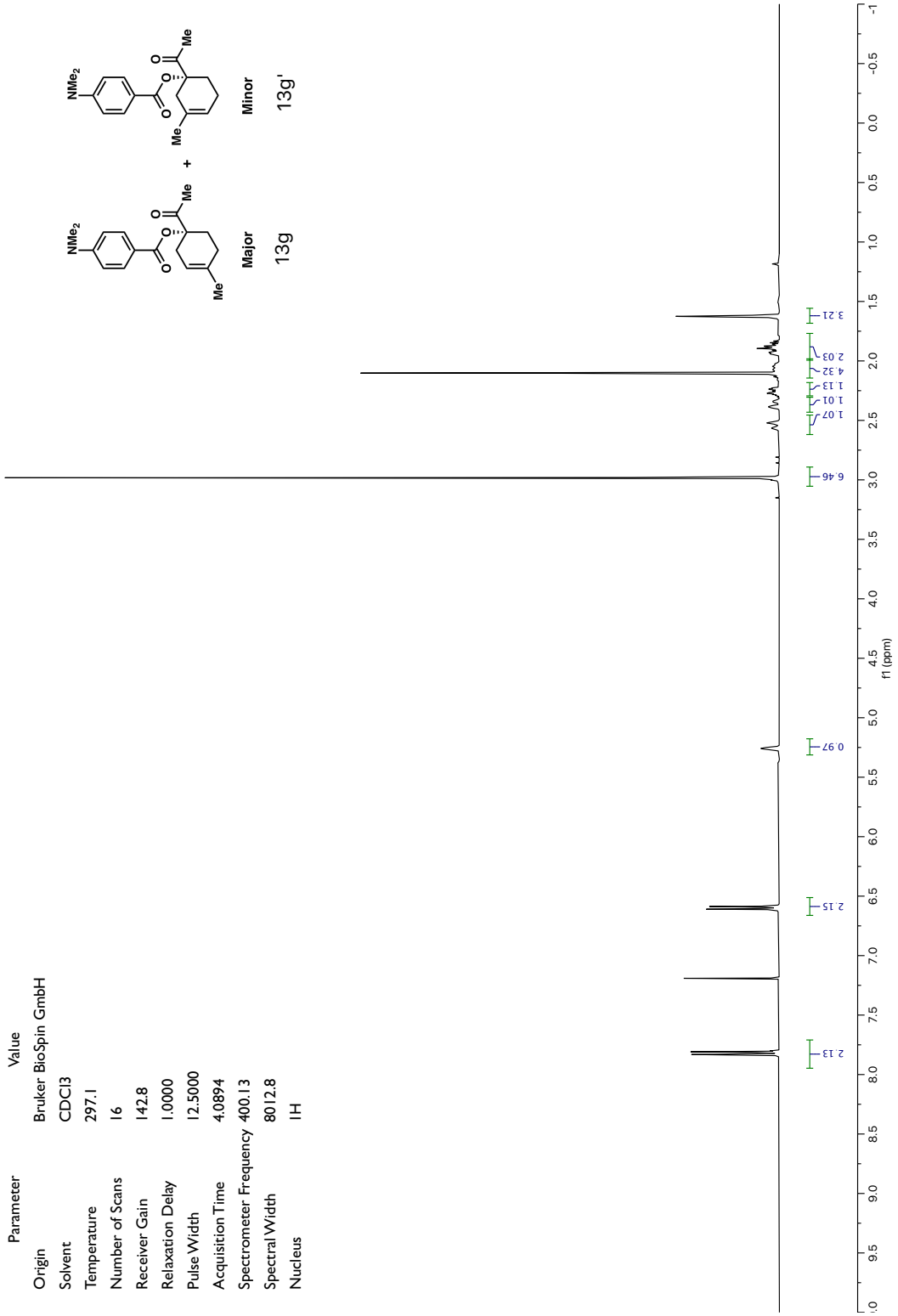

56c
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 3.0
Number of Scans 256
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 4.8375
Acquisition Time 1.0420
Spectrometer Frequency 125.64
Spectral Width 31446.5
Nucleus 13C
189.60
170.78
151.30
137.85
136.18
132.99
129.59
128.81
128.75
128.40
127.55
114.55
77.42
77.16
76.90
56.42
f1 (ppm)

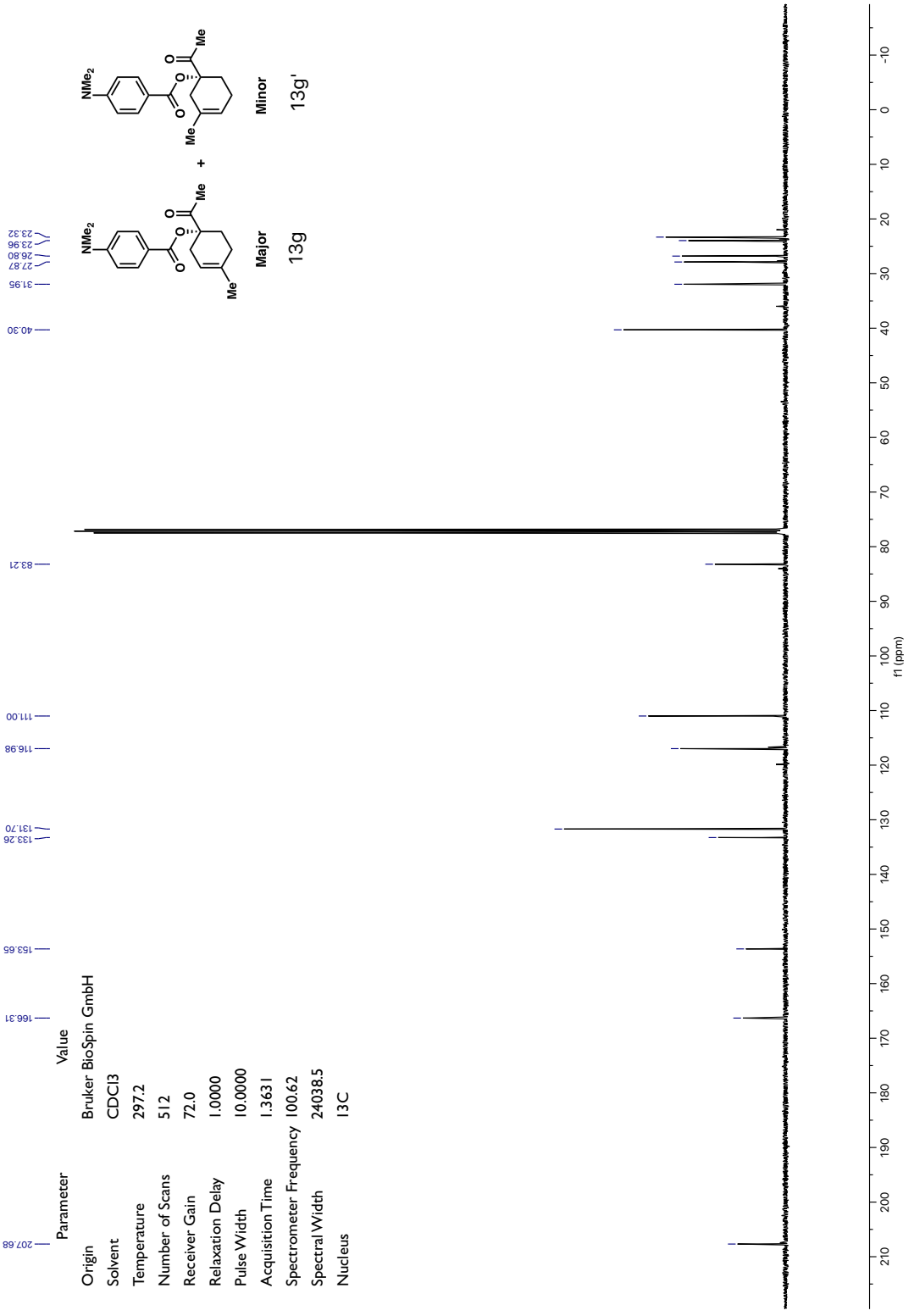

Me
O
O
O
Me
Ph
Ph
56d
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
156.2
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
10.35
0.99
1.00
3.03
3.20
f1 (ppm)


Me
O
O
Me
Ph
Ph
56d
11.78
25.29
56.81
127.62
128.47
128.79
128.98
138.15
147.30
170.40
191.13
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

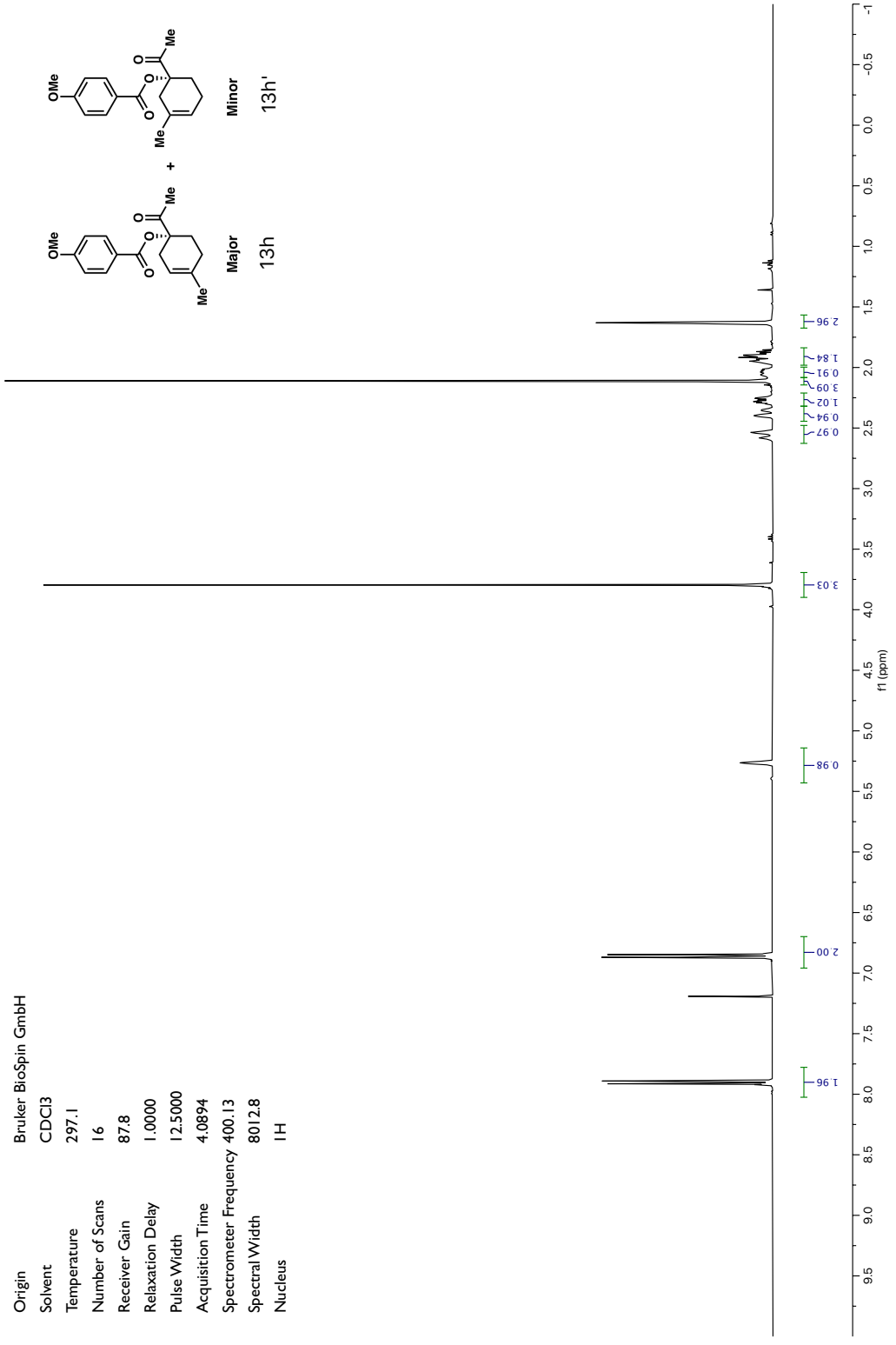

major
minor
13e
13e'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
f1 (ppm)

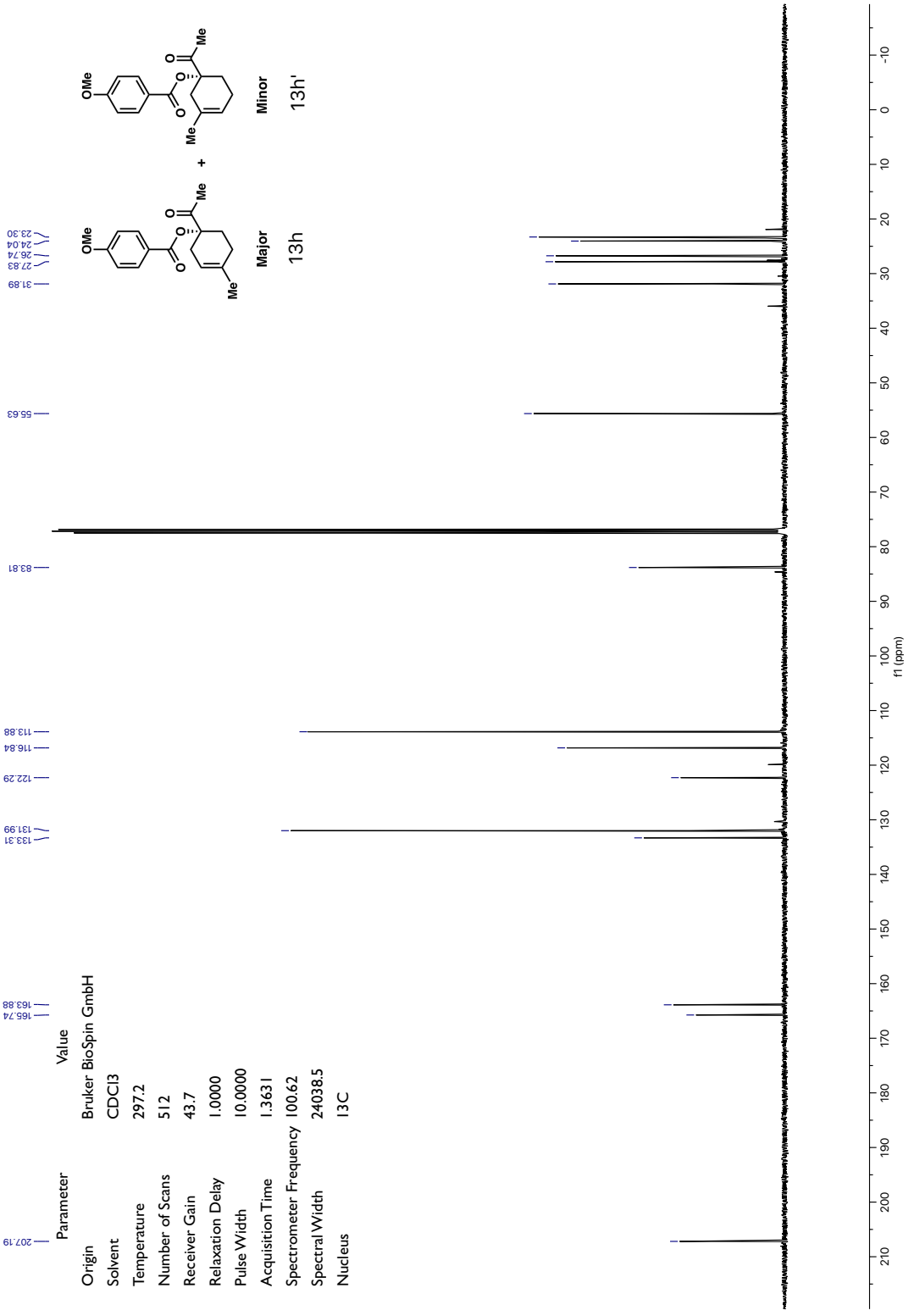

major
13e
minor
13e'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
206.93
166.01
133.53
133.35
129.90
128.64
116.77
84.22
31.83
27.83
26.72
24.09
23.31
f1 (ppm)

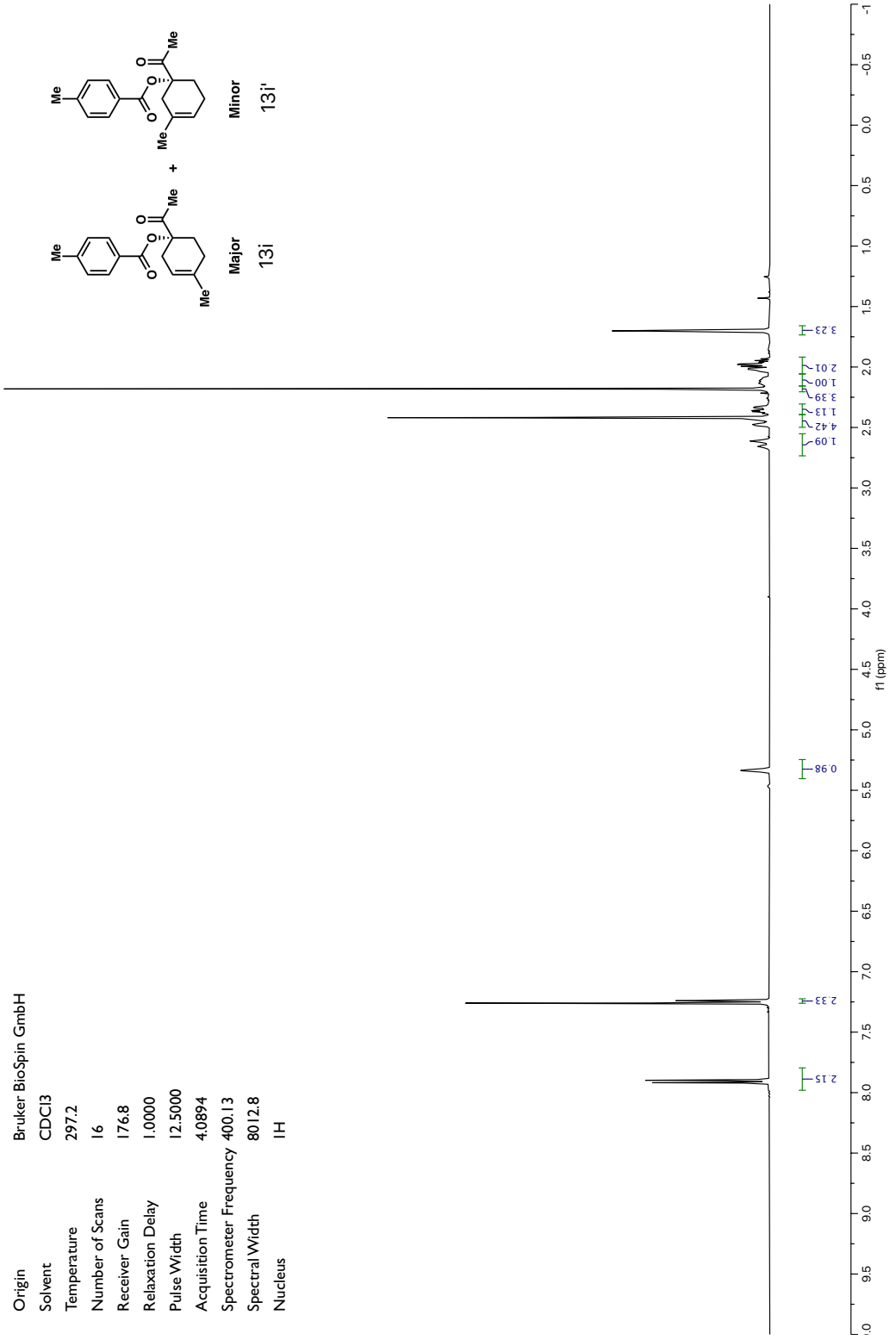

Major
13g
+
Minor
13g'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
2.13
2.15
0.97
6.46
1.07
1.01
1.13
4.32
2.03
3.21
f1 (ppm)

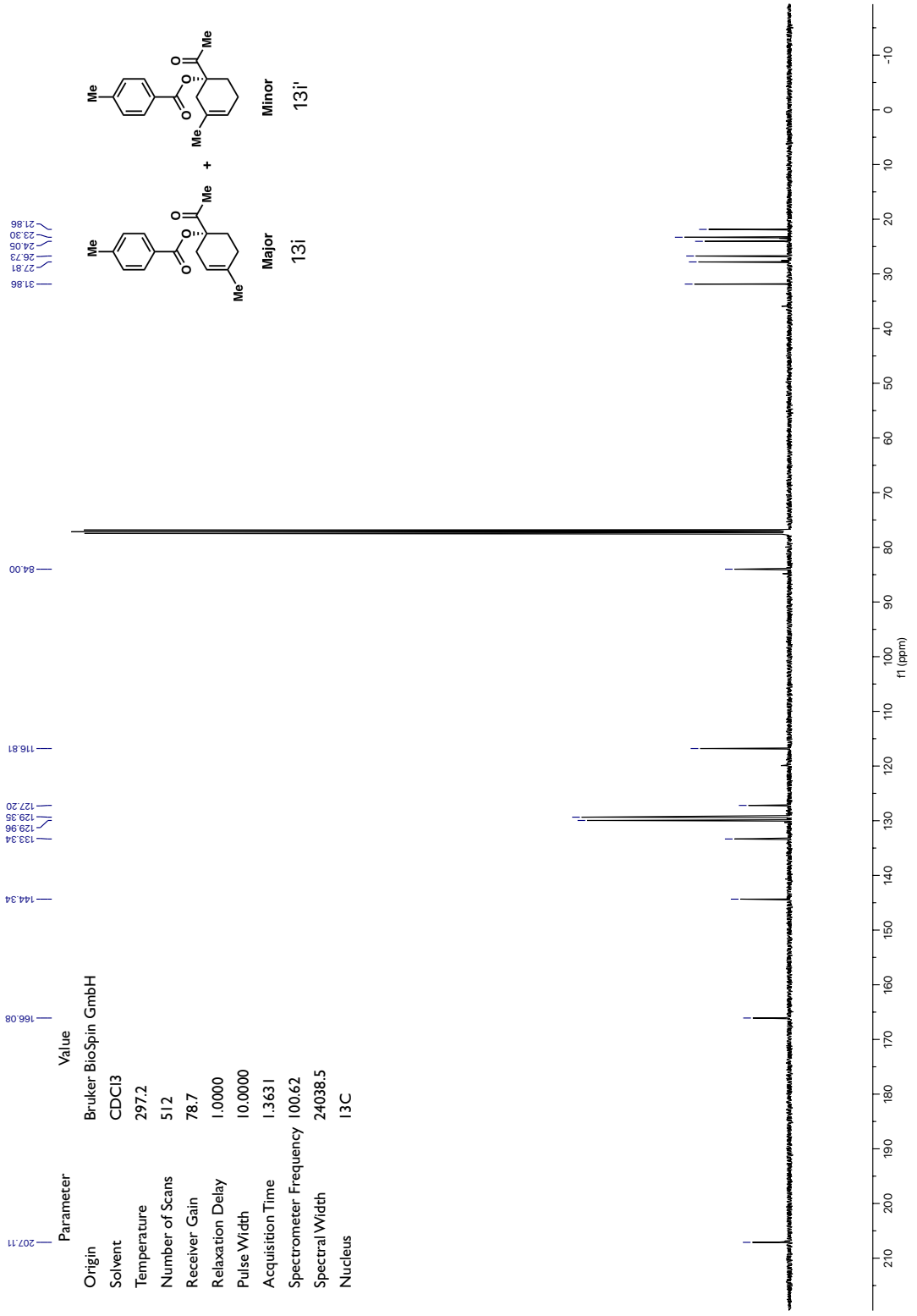


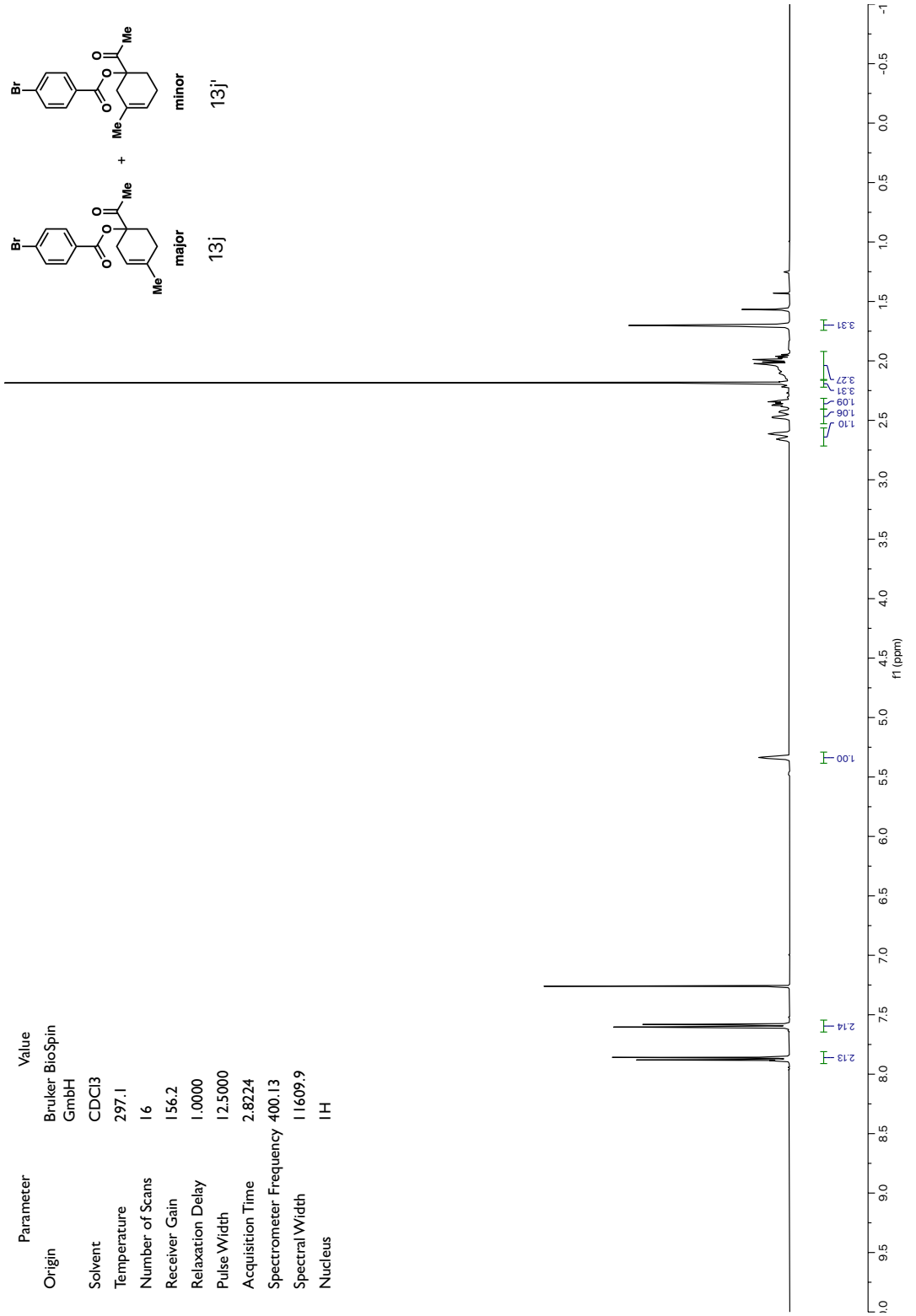
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

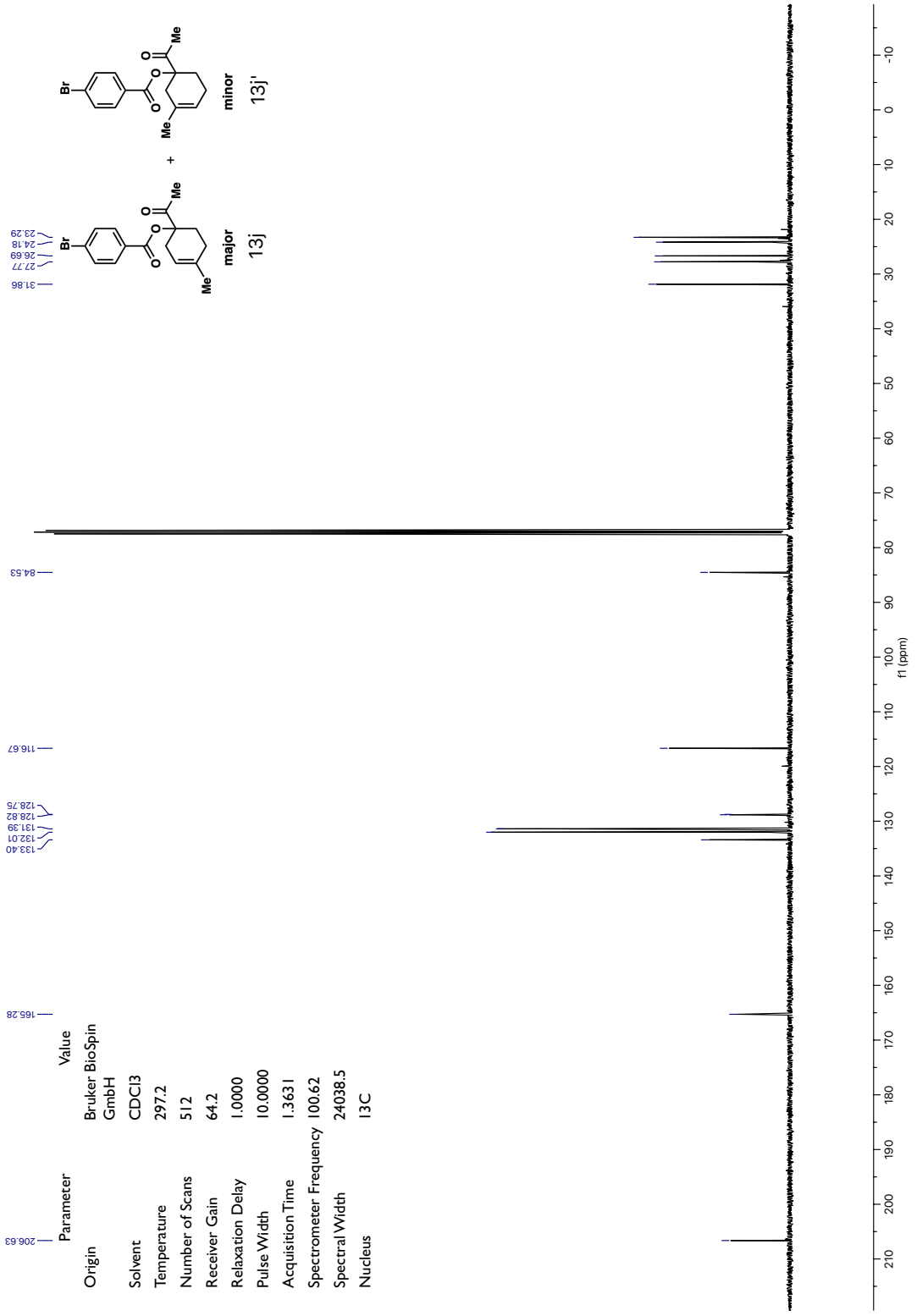

Major
13h
Minor
13h'
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
87.8
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
1.96
2.00
0.98
3.03
0.97
0.94
1.02
3.09
0.91
1.84
2.96
f1 (ppm)

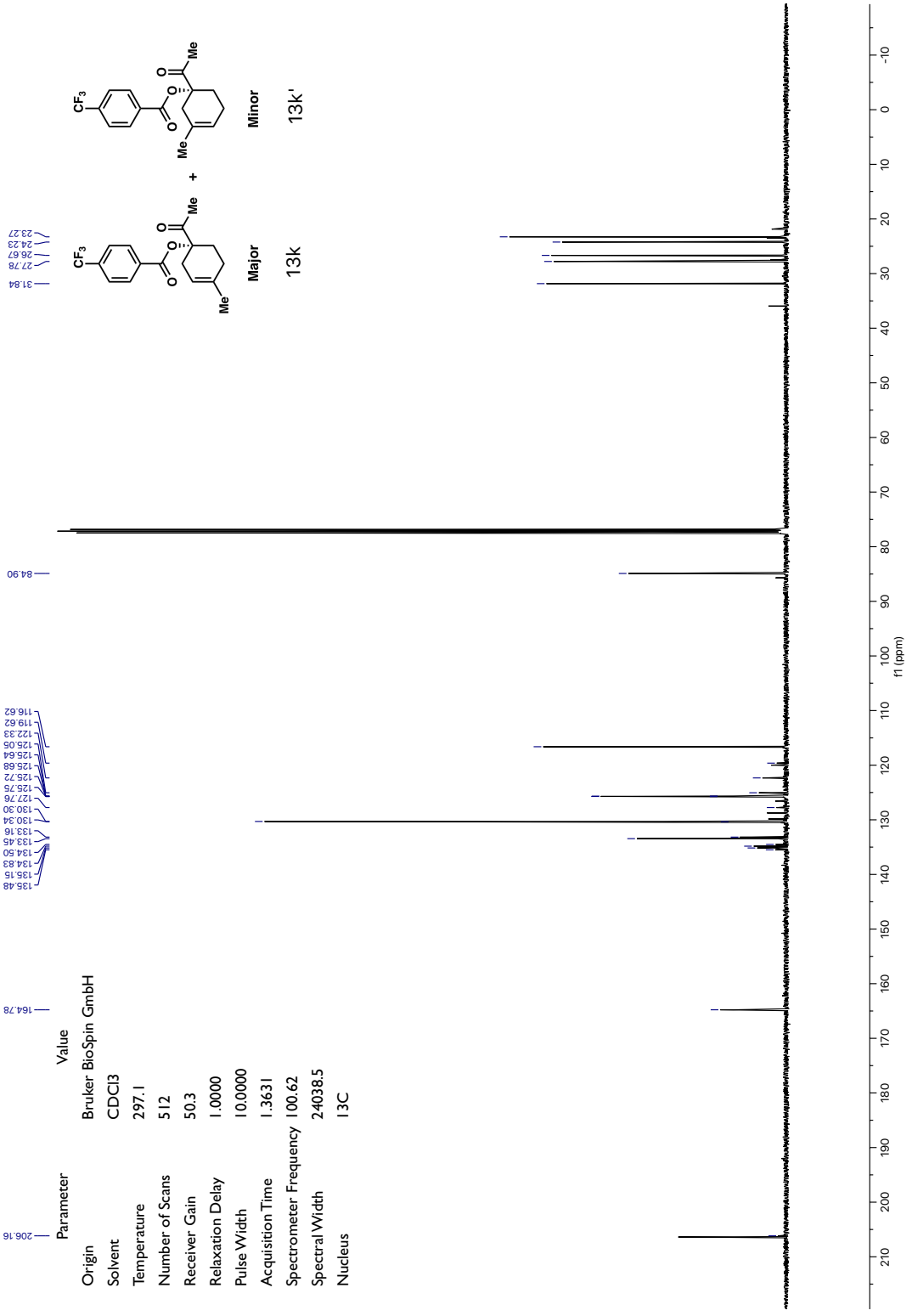

OMe
Me
Me
Major
13h
+
OMe
Me
Me
Minor
13h'
207.19
165.74
163.88
133.31
131.99
122.29
116.84
113.88
83.81
55.63
31.89
27.83
26.74
24.04
23.30
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

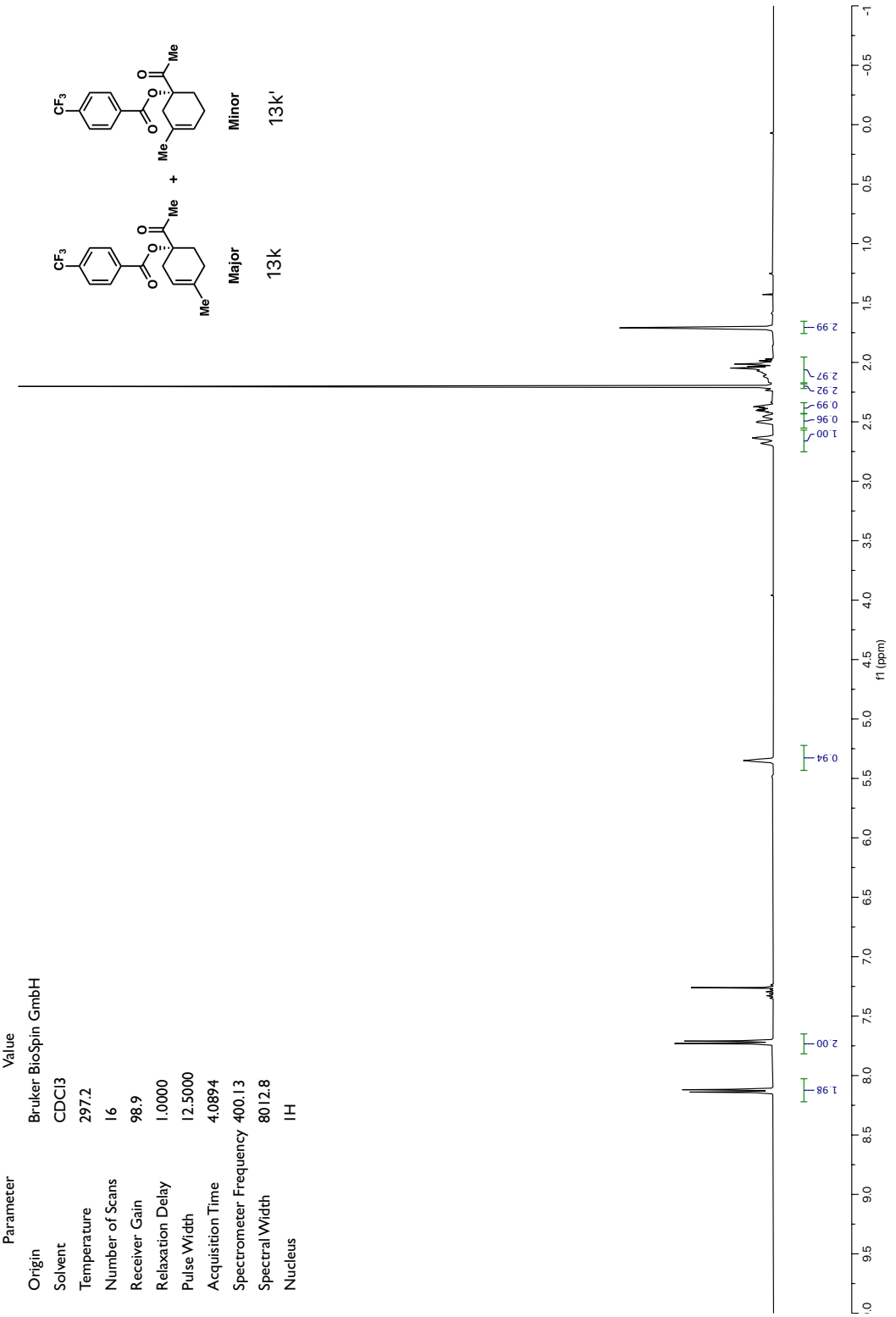

Me
Me
Me
Me
+
Major
13i
Minor
13i'
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
16
Receiver Gain
176.8
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
2.15
2.33
0.98
1.09
4.42
1.13
3.39
1.00
2.01
3.23
f1 (ppm)

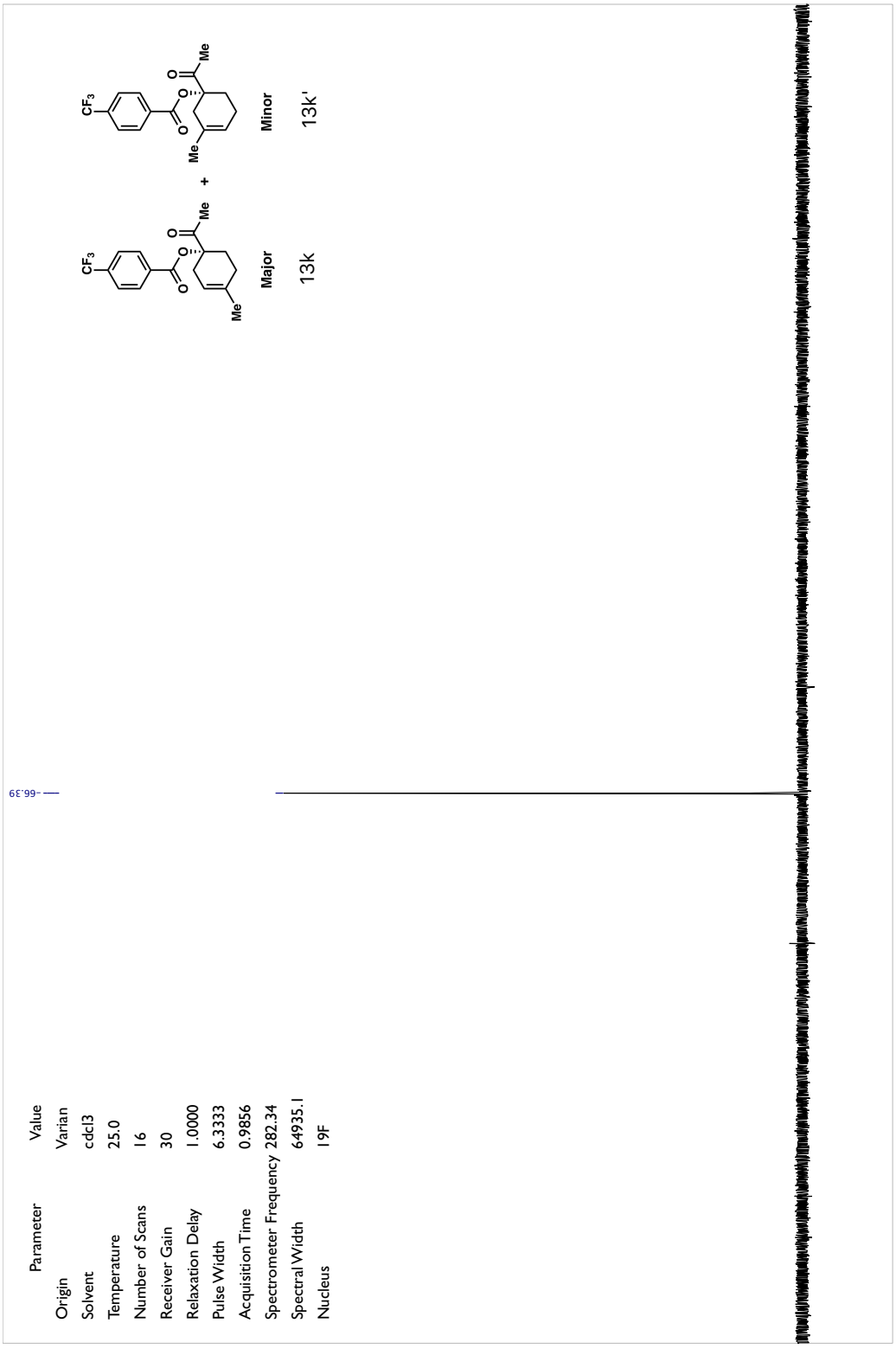

Me
Me
Me
Me
Major
13i
+
Me
Me
Me
Me
Minor
13i'
207.11
166.08
144.34
133.34
129.96
129.35
127.20
116.81
84.00
31.86
27.81
26.73
24.05
23.30
21.86
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
512
Receiver Gain
78.7
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)


major
13j
+
minor
13j'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
2.13
2.14
1.00
1.10
1.06
1.09
3.27
3.31
3.31
f1 (ppm)

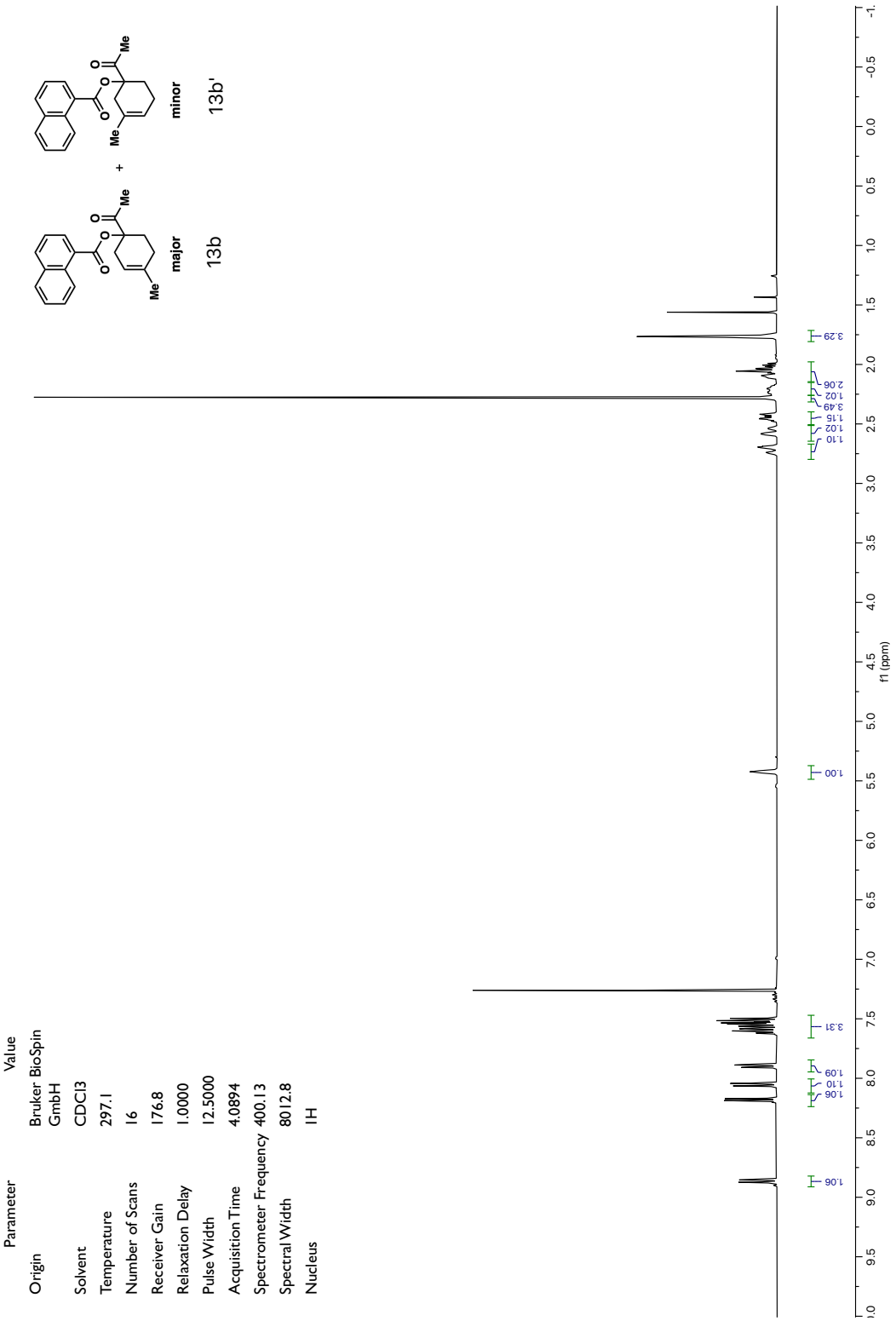

Br
Me
O
O
O
Me
major
13j
+
Br
Me
O
O
O
Me
minor
13j'
206.63
165.28
133.40
132.01
131.39
128.82
128.75
116.67
84.53
31.86
27.77
26.69
24.18
23.29
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
512
Receiver Gain
64.2
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)

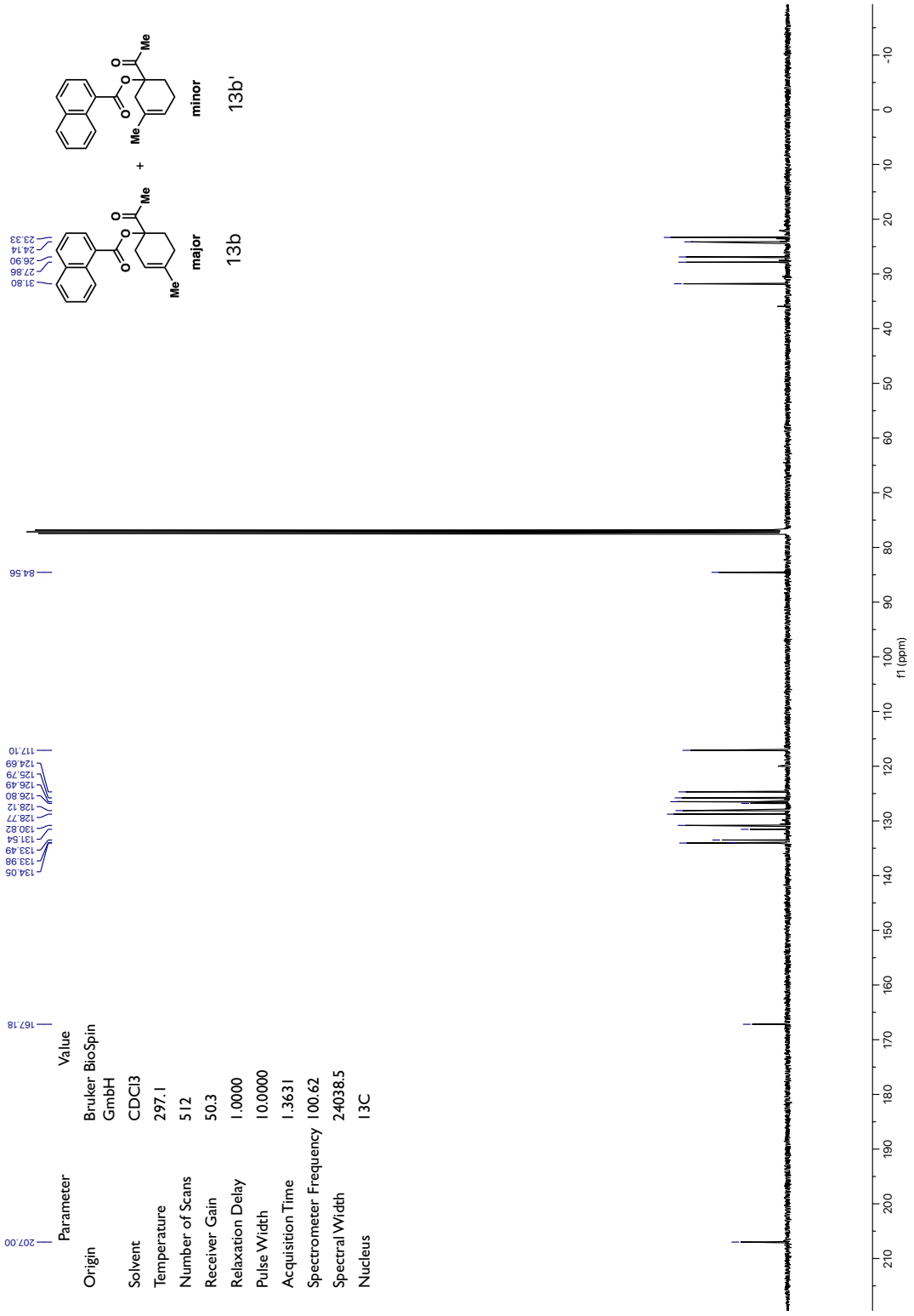

Major
13k
Minor
13k'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

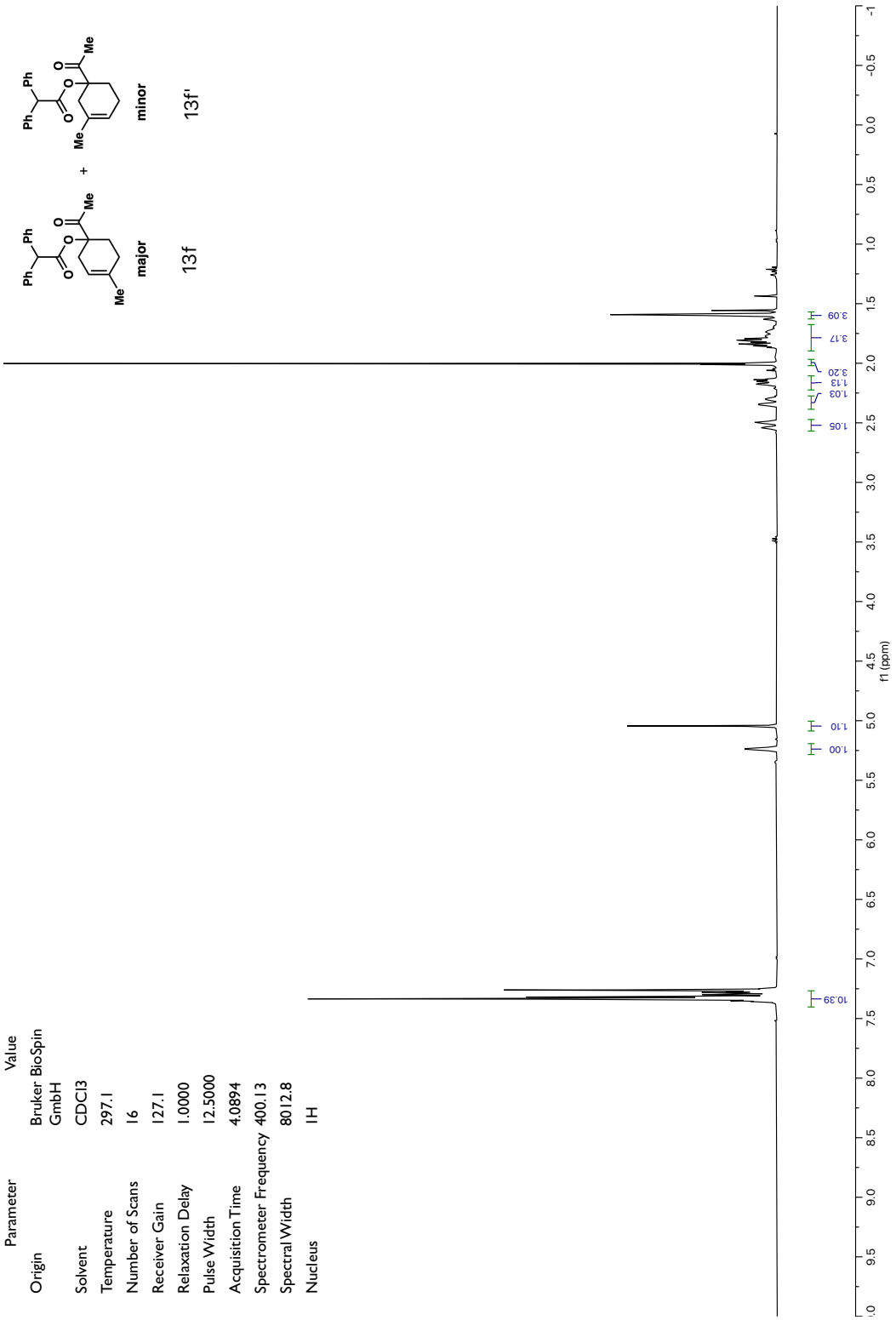

Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
Major
13k
Minor
13k'
f1 (ppm)

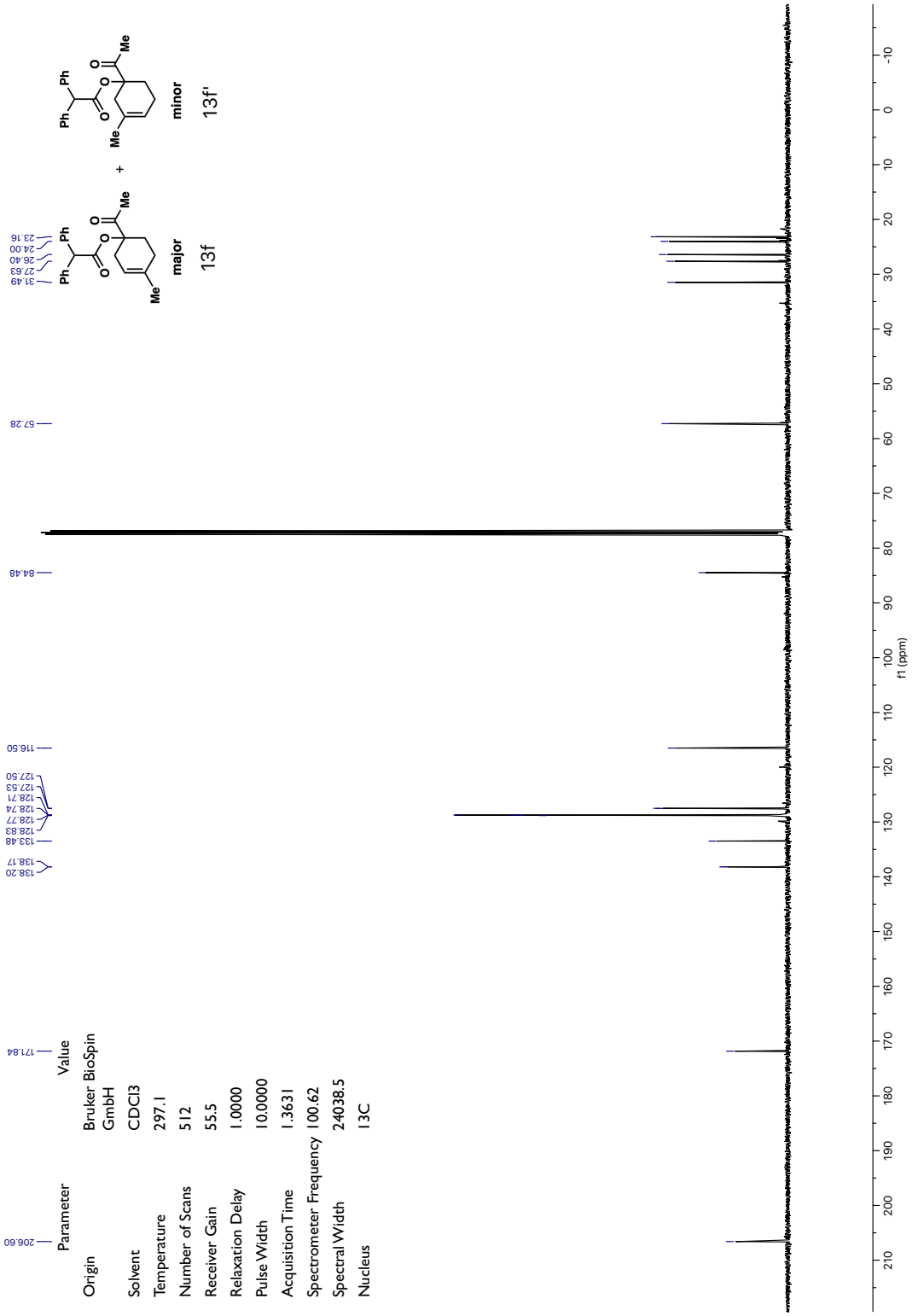


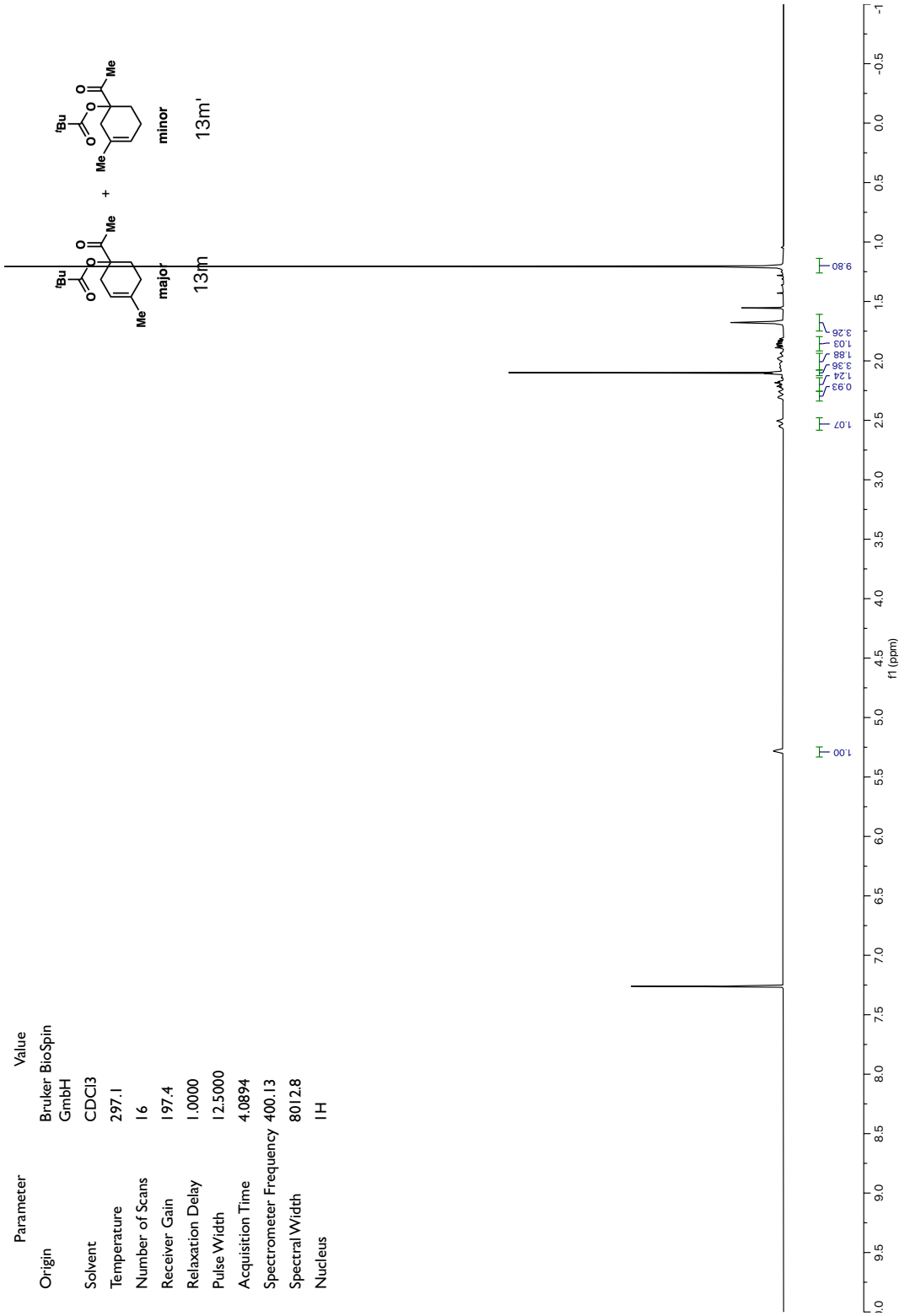
Parameter	Value
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	6.3333
Acquisition Time	0.9856
Spectrometer Frequency	282.34
Spectral Width	64935.1
Nucleus	19F

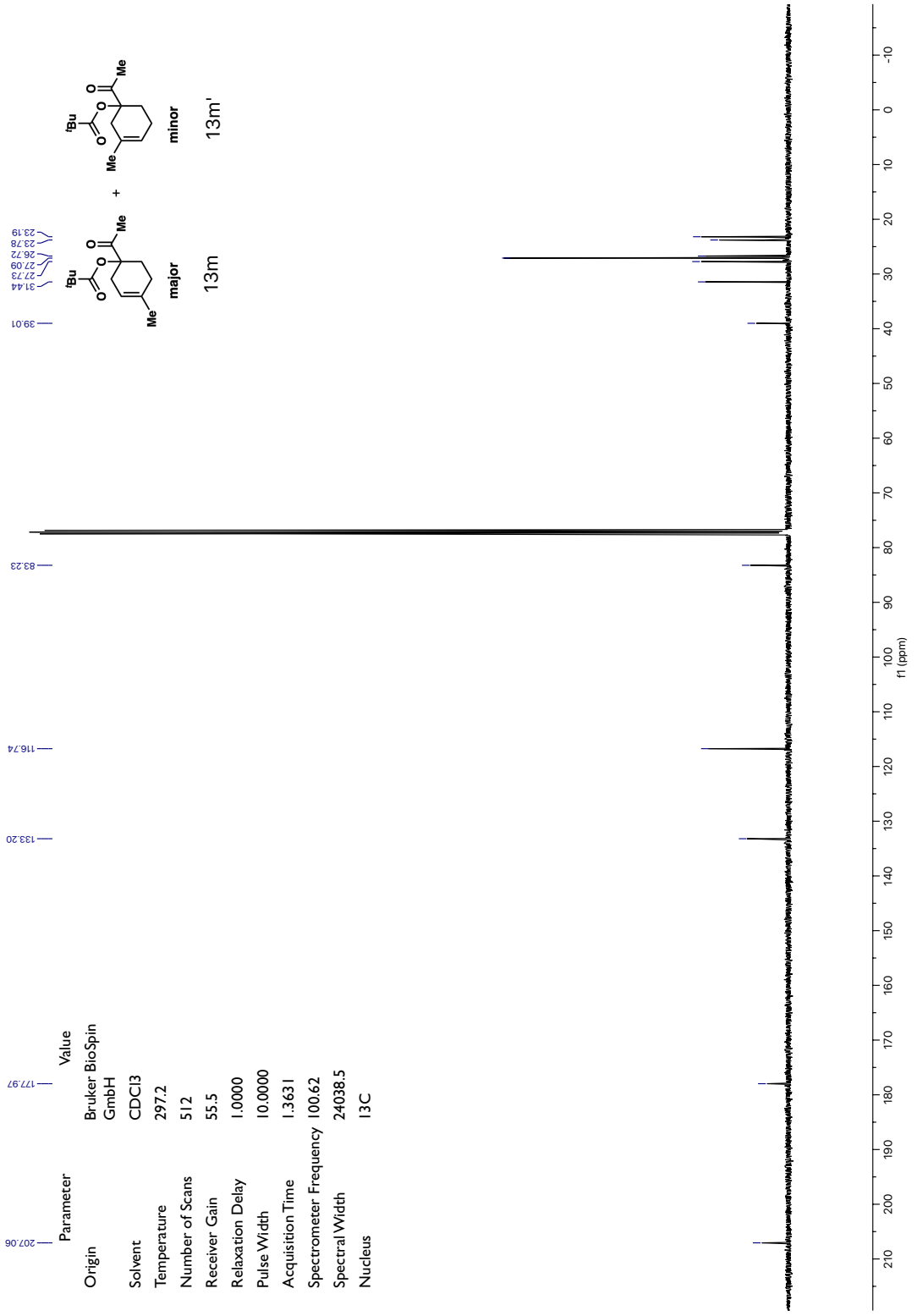

major
minor
13b
13b'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 176.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
f1 (ppm)

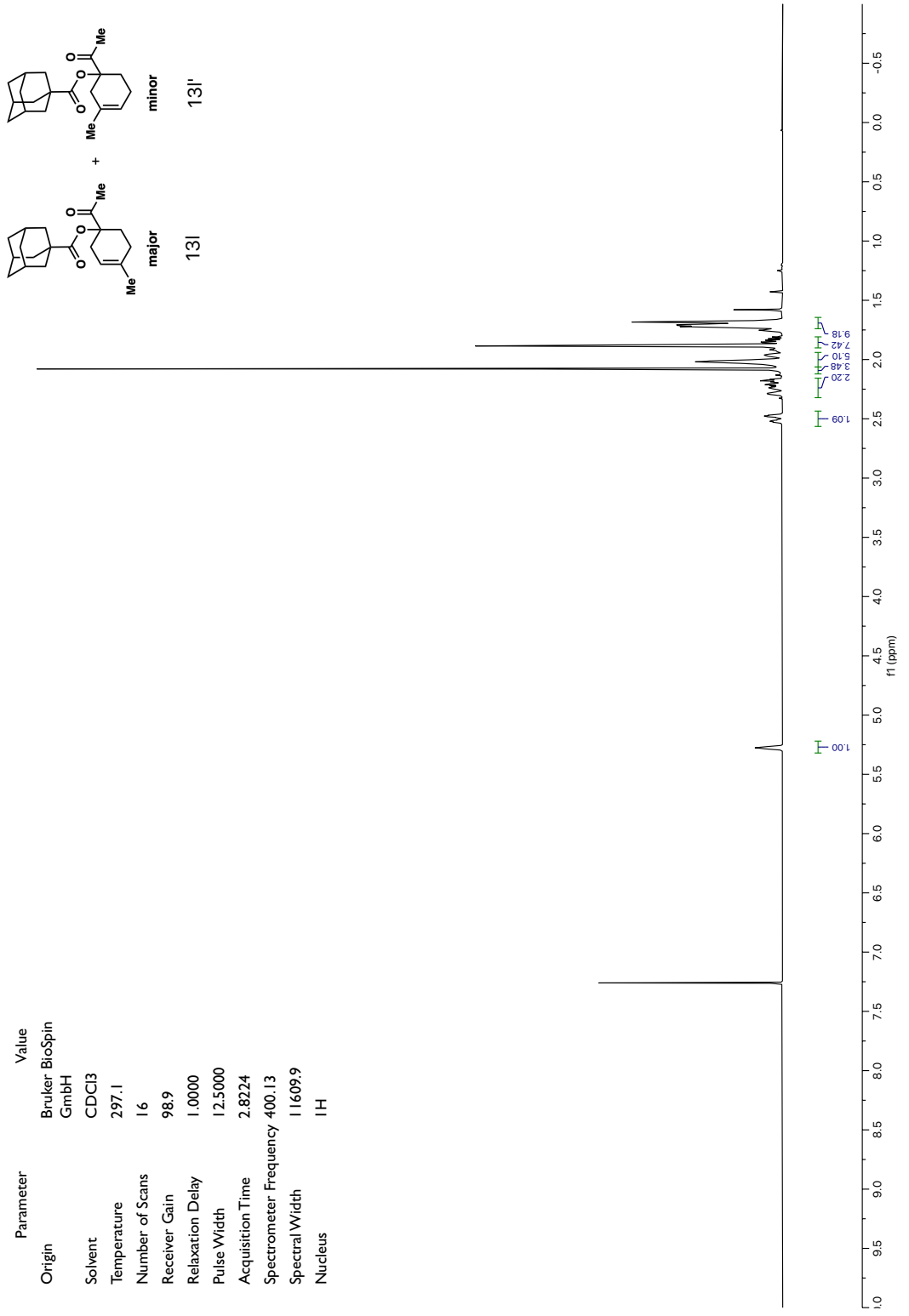

major
13b
minor
13b'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

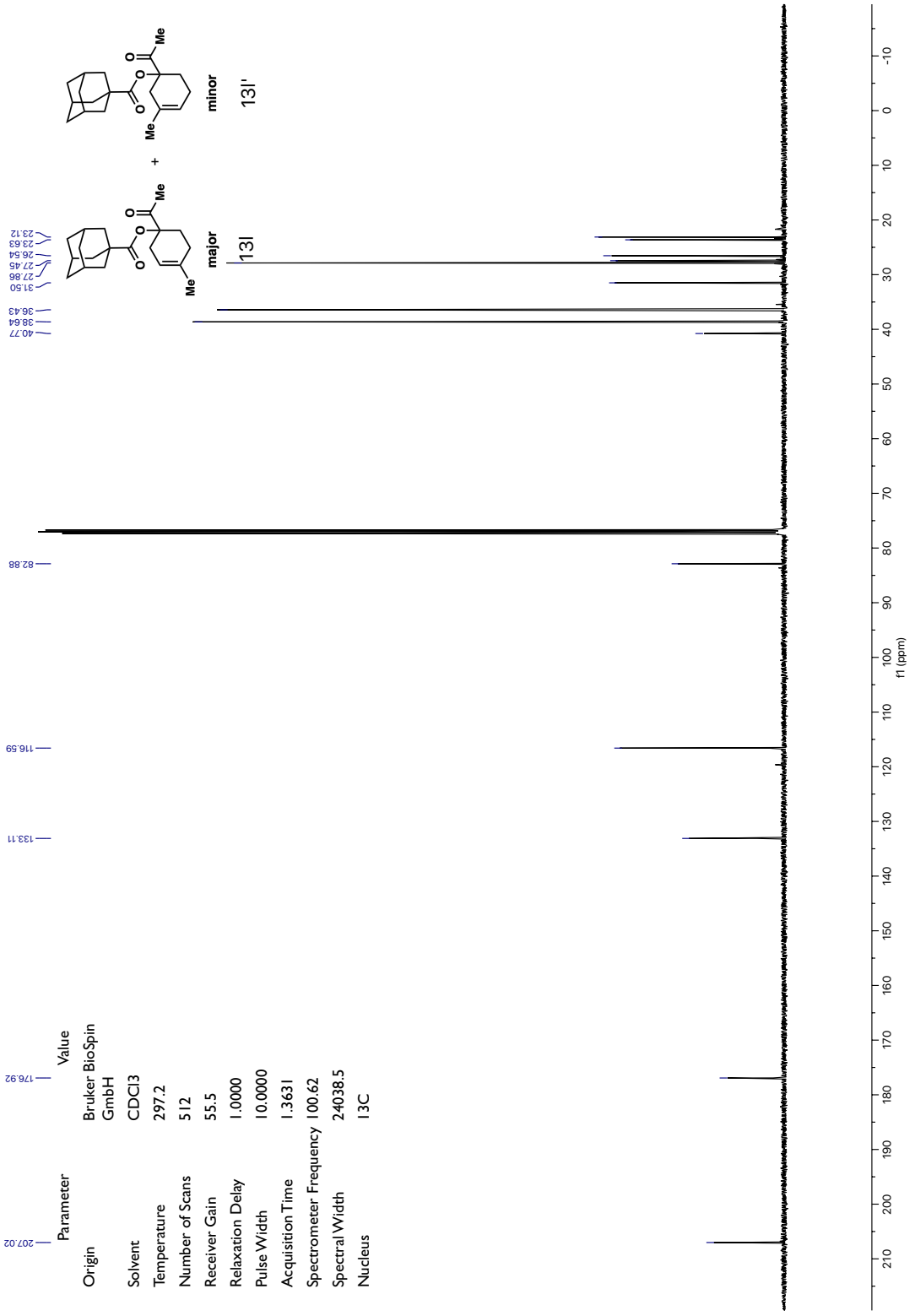

major
+
minor
13f
13f'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
10.39
1.00
1.10
1.05
3.20
1.13
1.03
3.17
3.09
f1 (ppm)

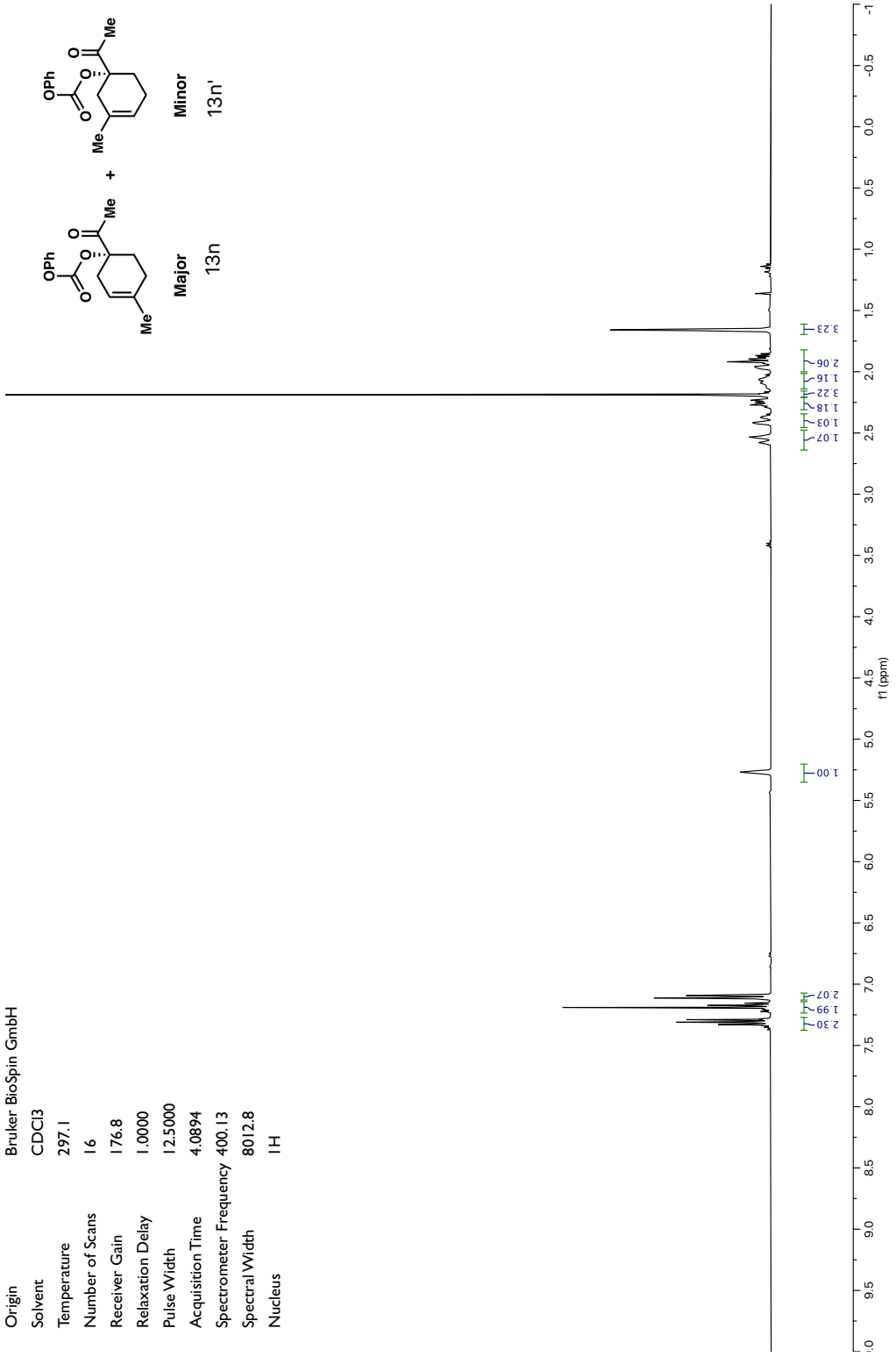

major
13f
minor
13f'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

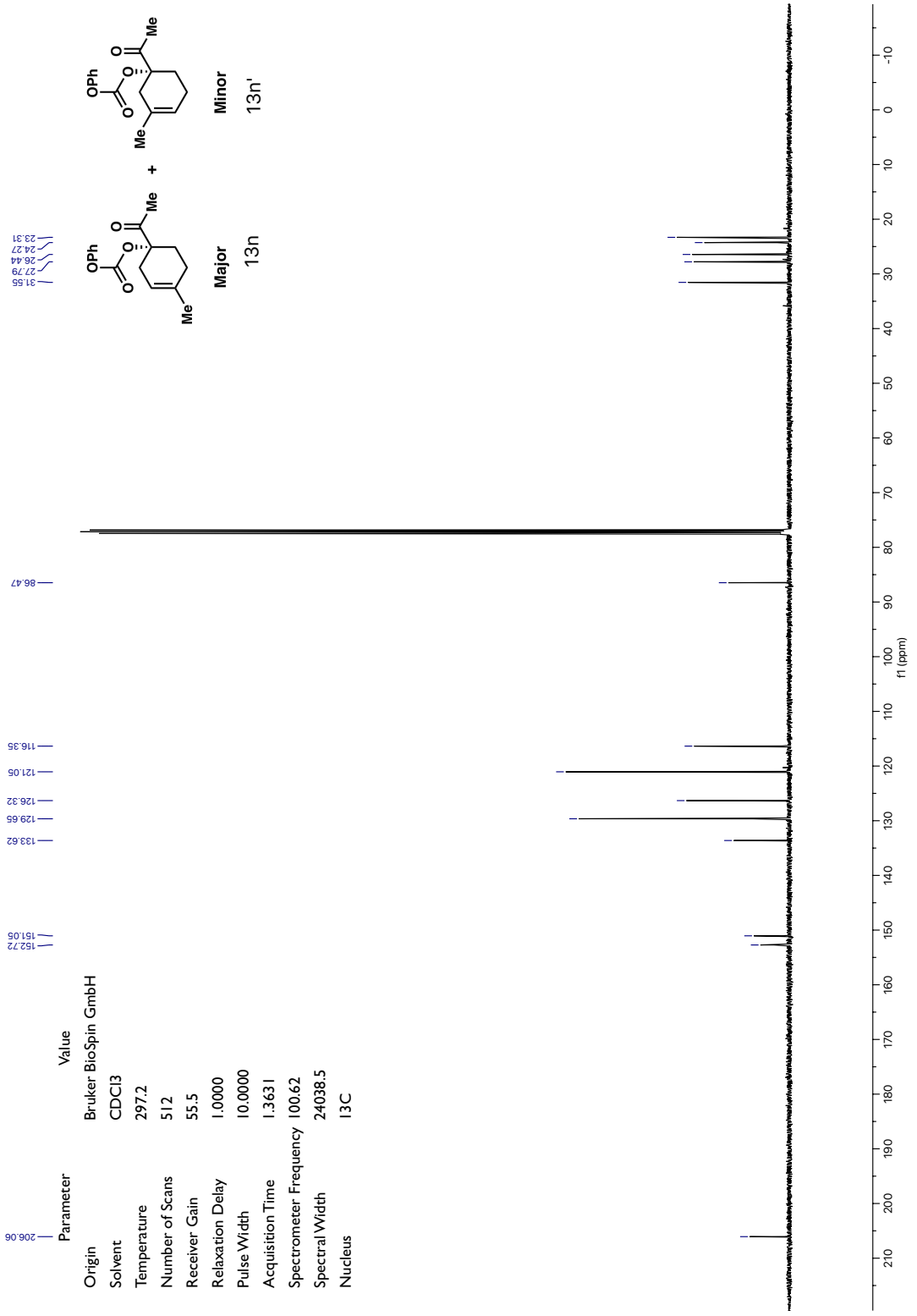

major
13m
+
minor
13m'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
9.80
3.26
1.03
1.88
3.36
1.24
0.93
1.07
1.00
f1 (ppm)

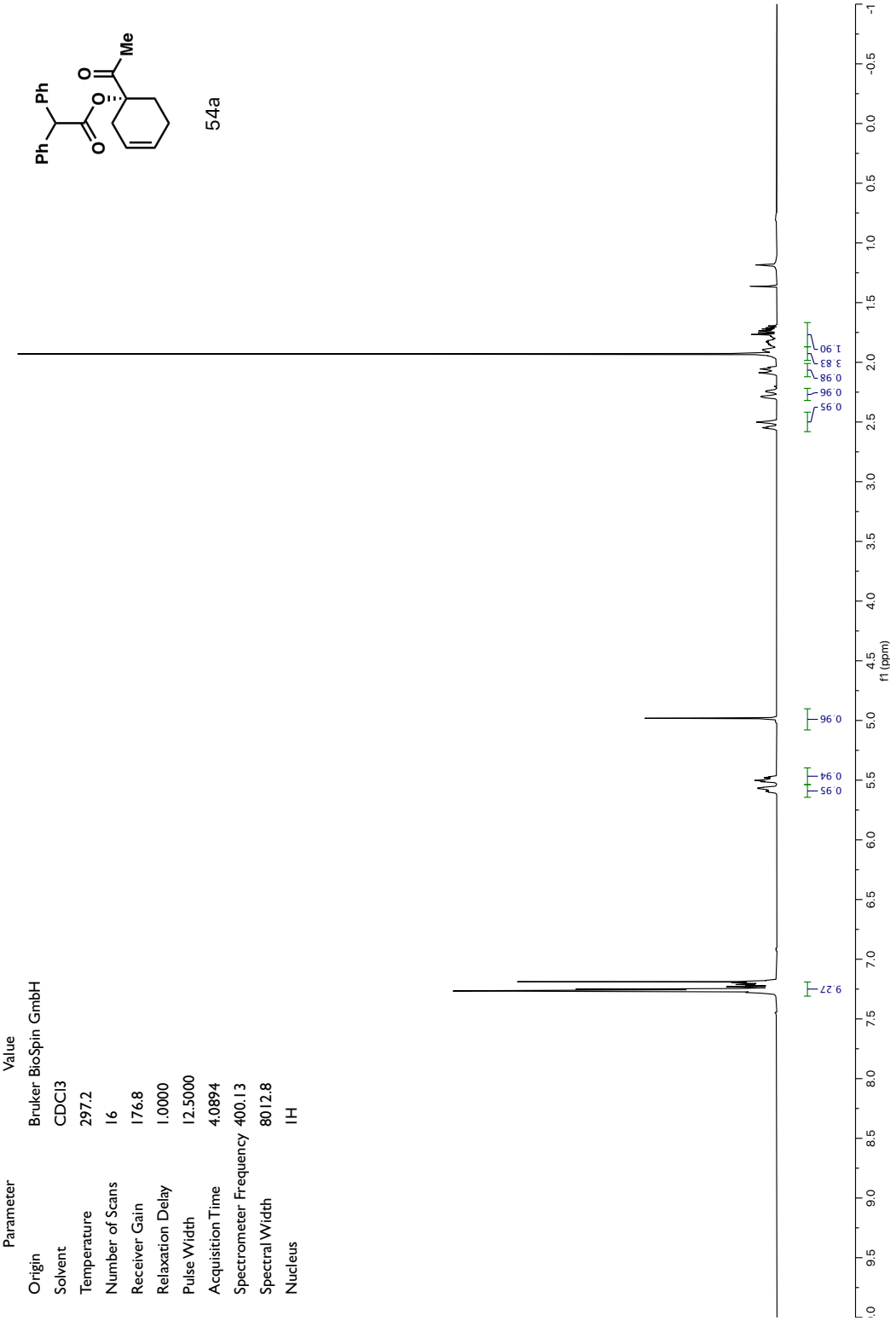

major
13m
minor
13m'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

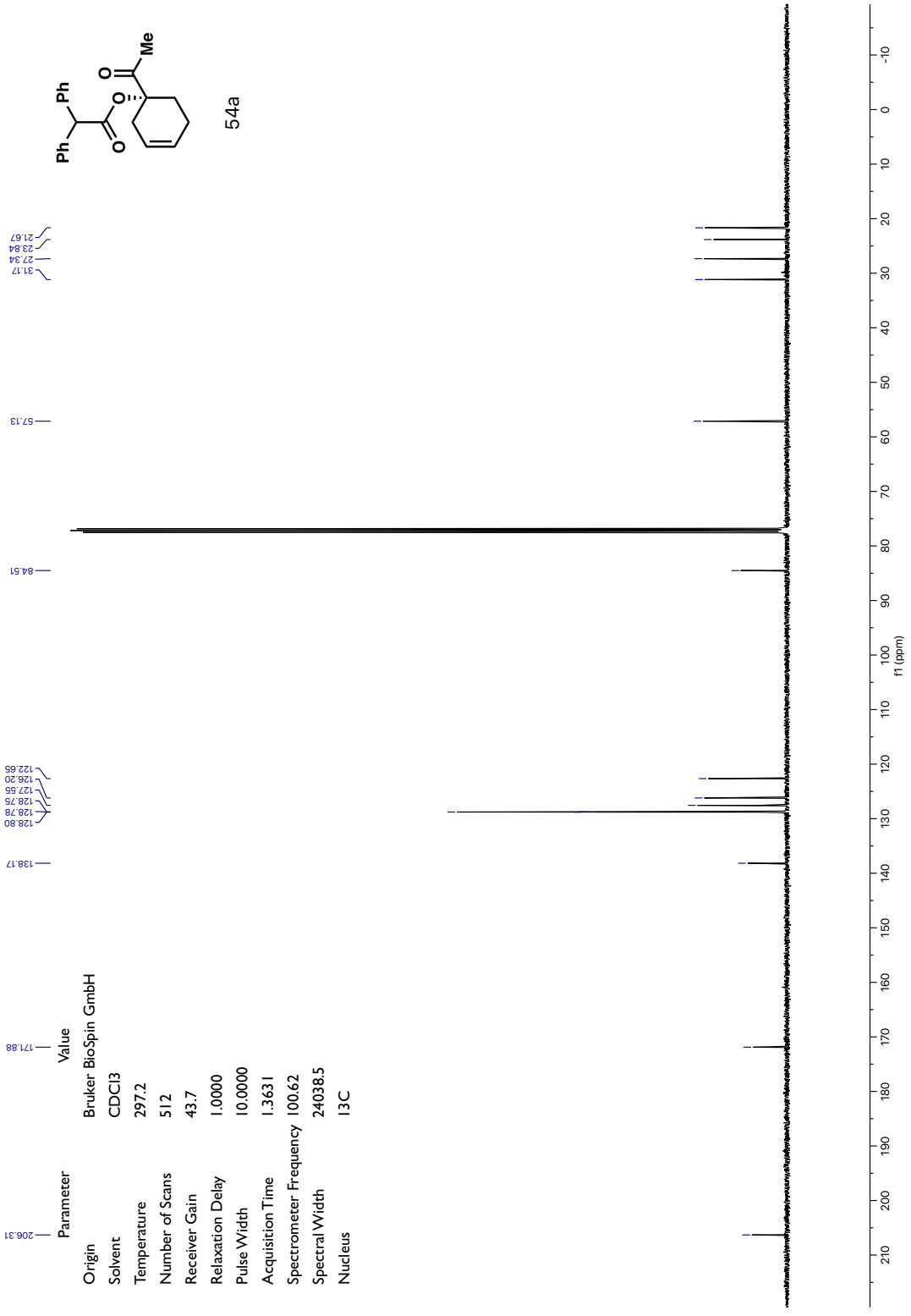

major
minor
13l
13l'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
1.00
1.09
2.20
3.48
5.10
7.42
9.18
f1 (ppm)

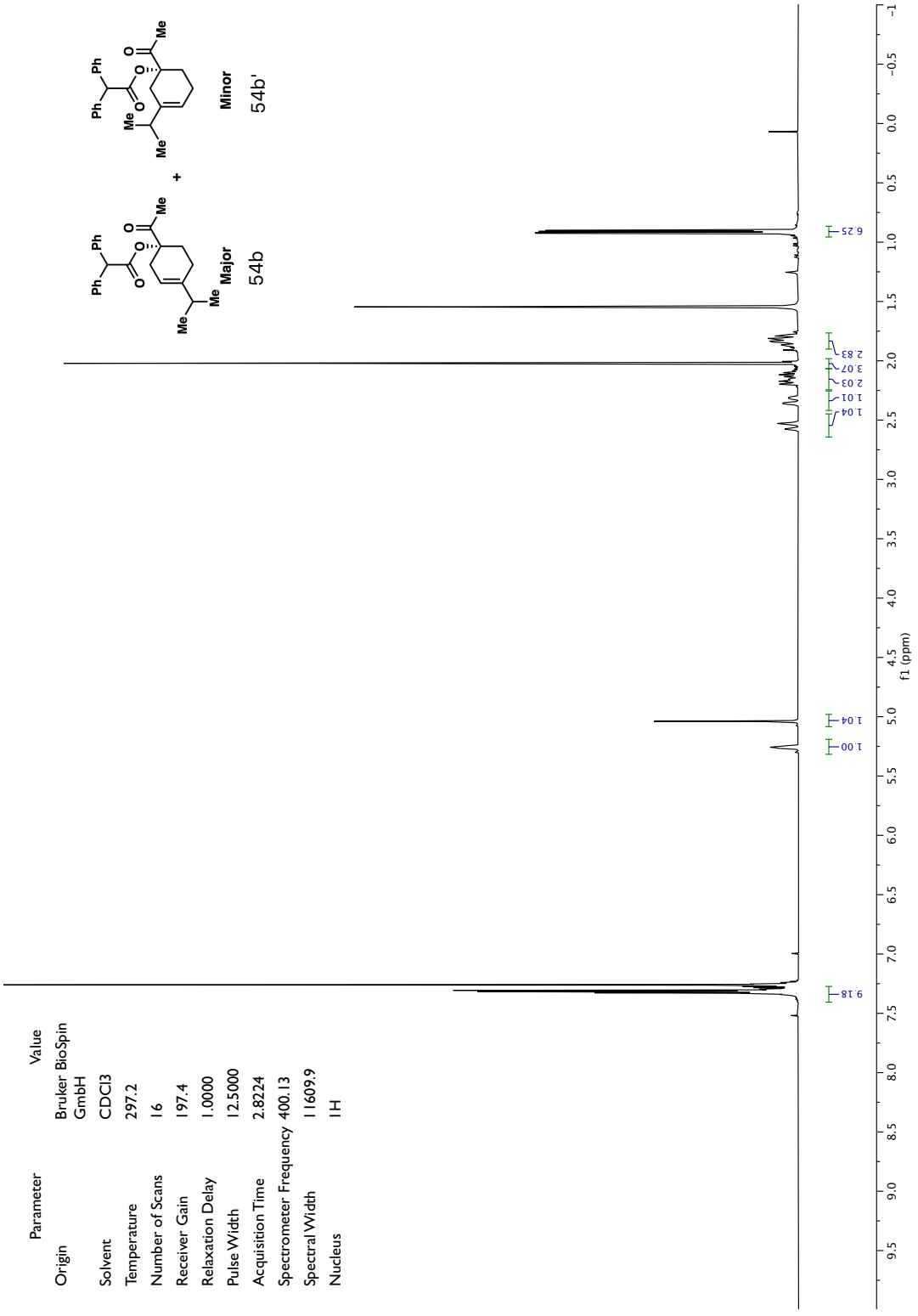

major
minor
13l
13l'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
207.02
176.92
133.11
116.59
82.88
40.77
38.64
36.43
31.50
27.86
27.45
26.54
23.63
23.12
f1 (ppm)

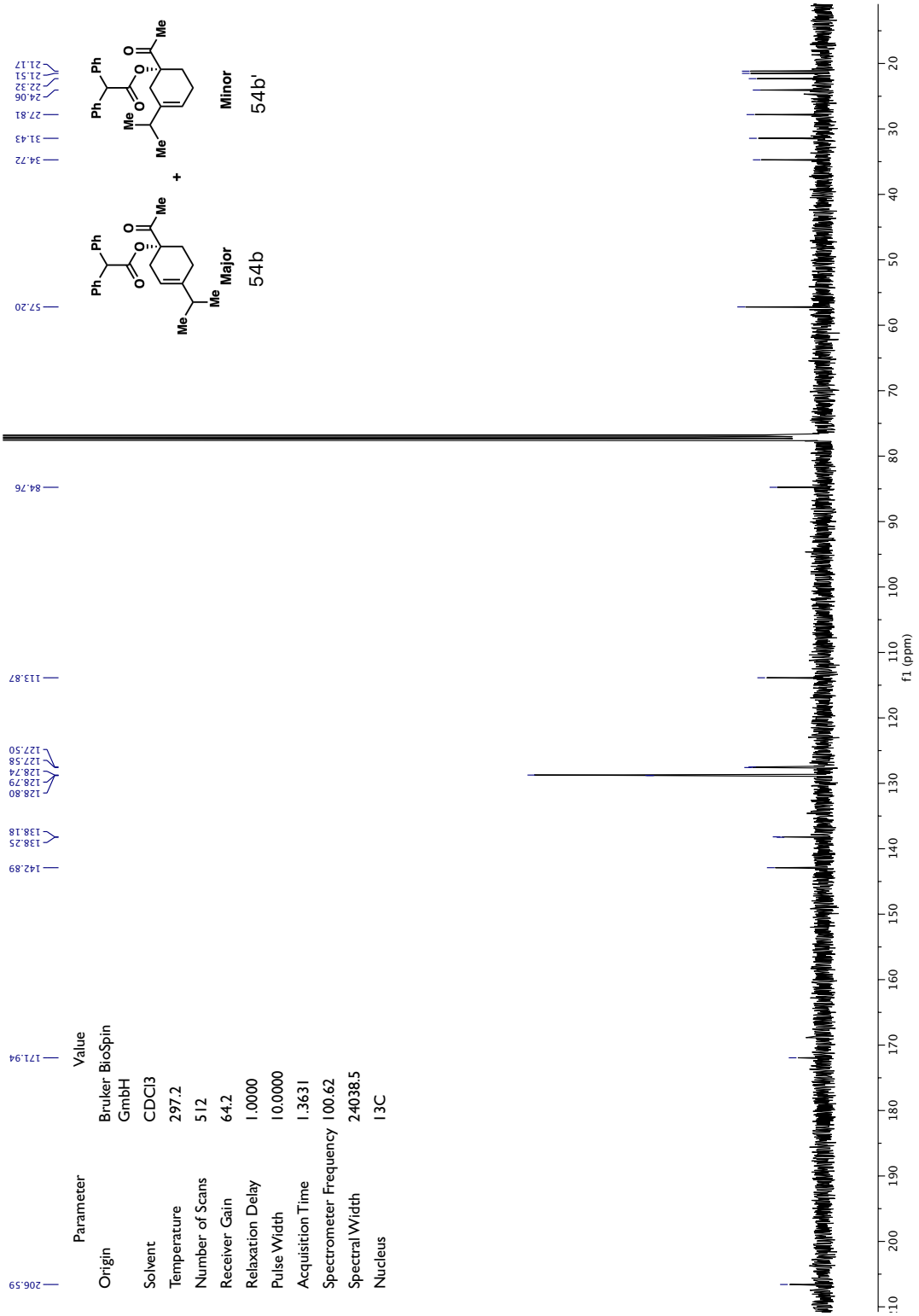

OPh
O
O
O
Me
Me
Major
13n
+
OPh
O
O
O
Me
Me
Minor
13n'
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
176.8
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
2.30
1.99
2.07
1.00
1.07
1.03
1.18
3.22
1.16
2.06
3.23
f1 (ppm)

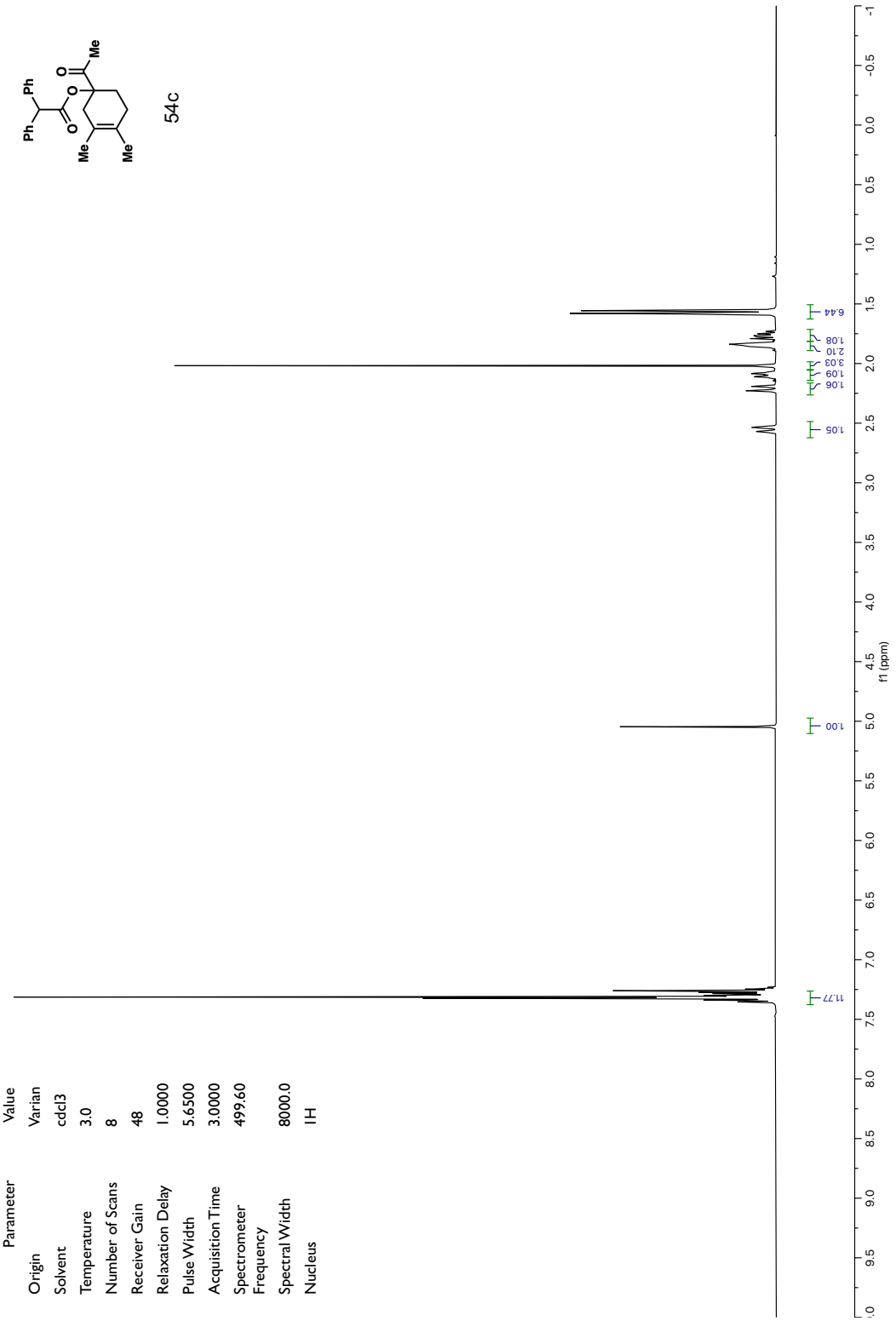

OPh
O
O
O
Me
Me
Major
13n
+
OPh
O
O
O
Me
Me
Minor
13n'
206.06
152.72
151.05
133.62
129.65
126.32
121.05
116.35
86.47
31.55
27.79
26.44
24.27
23.31
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
512
Receiver Gain
55.5
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Spectrometer Frequency
100.62
Spectral Width
24038.5
Nucleus
13C
f1 (ppm)

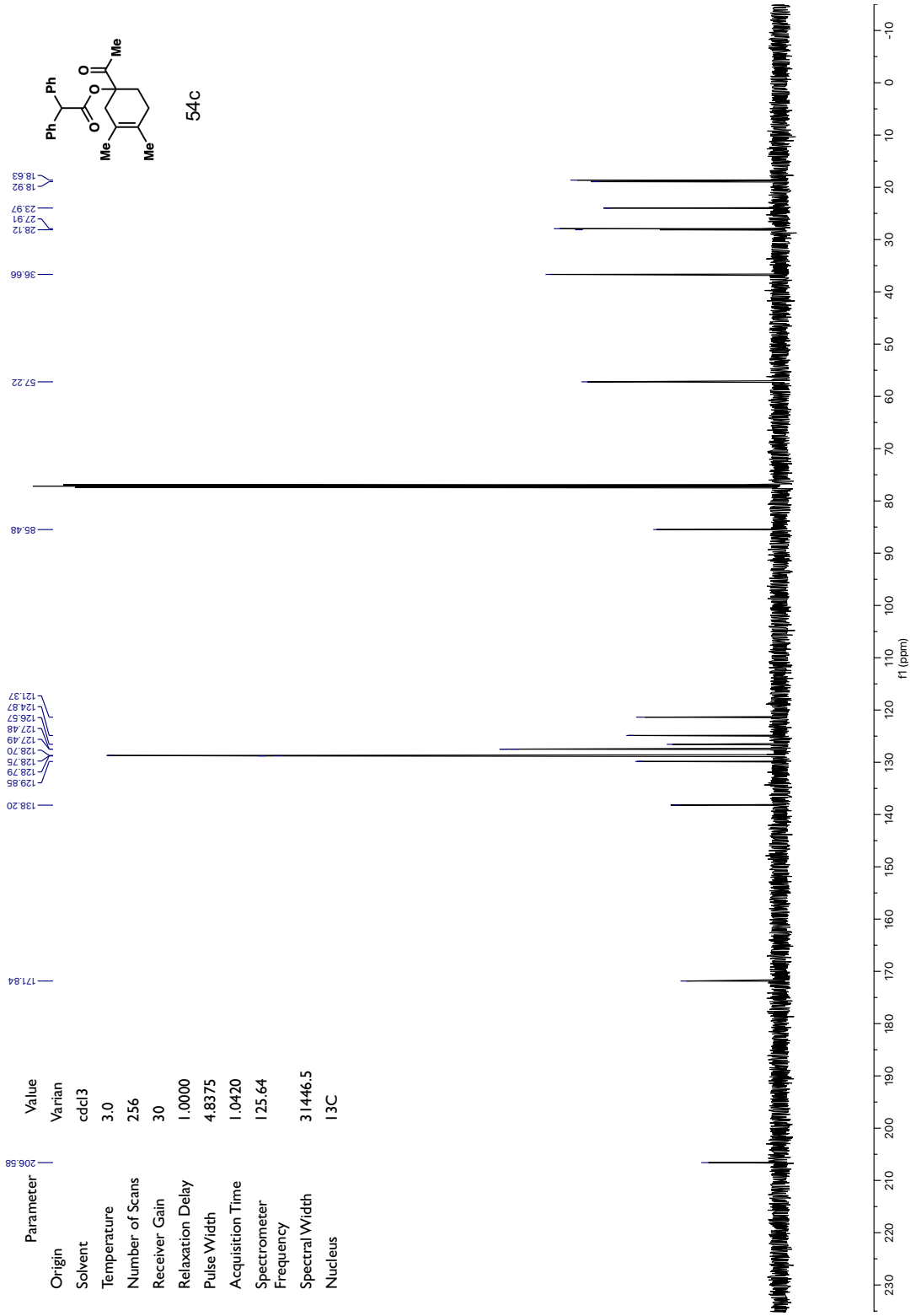

Ph
Ph
O
O
O
Me
54a
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
16
Receiver Gain
176.8
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
4.0894
Spectrometer Frequency
400.13
Spectral Width
8012.8
Nucleus
1H
9.27
0.96
0.95
0.94
0.95
0.96
0.98
3.83
1.90
f1 (ppm)

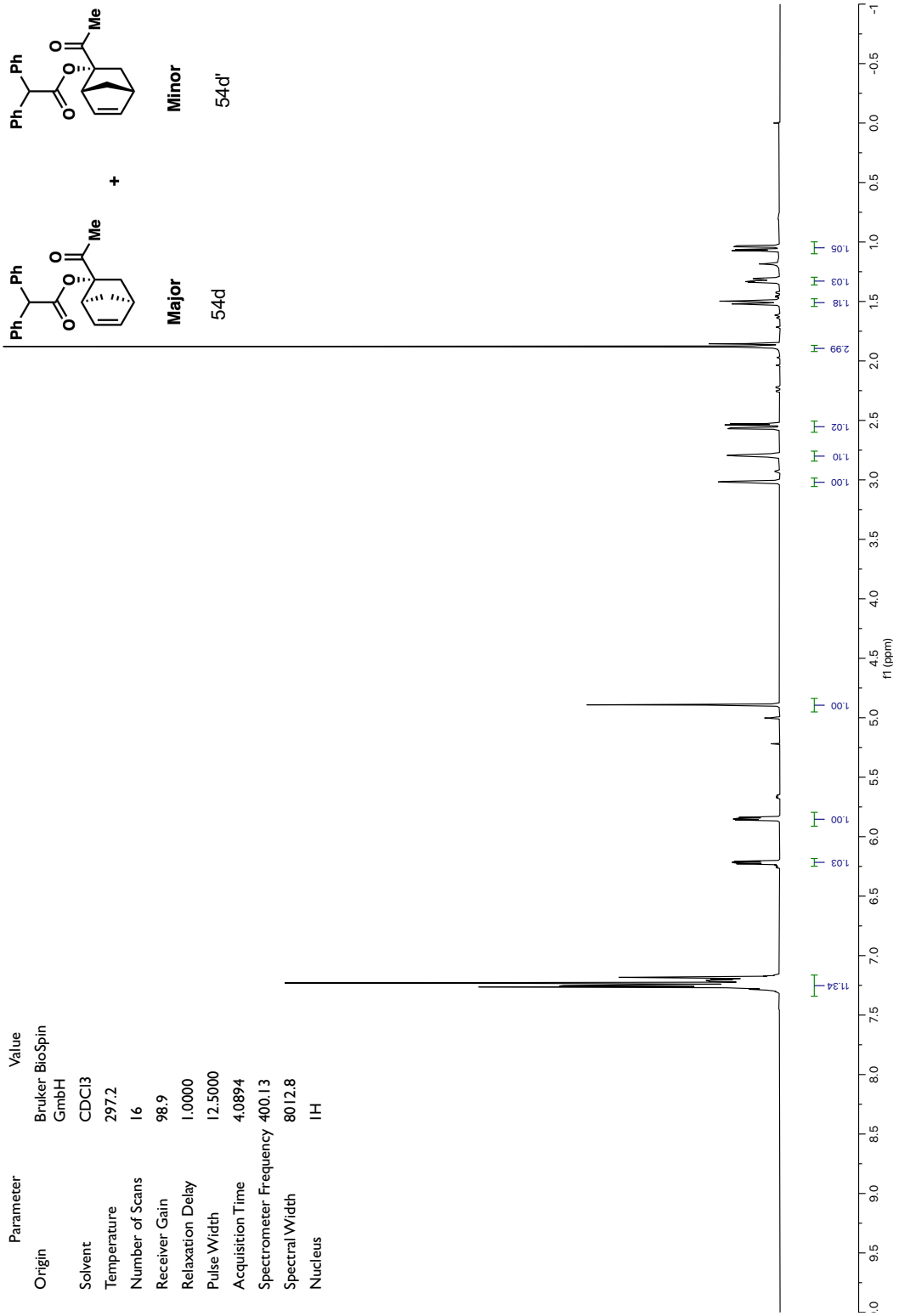

Ph
Ph
O
O
O
Me
54a
206.31
171.88
138.17
128.80
128.78
128.75
127.55
126.20
122.65
84.51
57.13
31.17
27.34
23.84
21.67
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

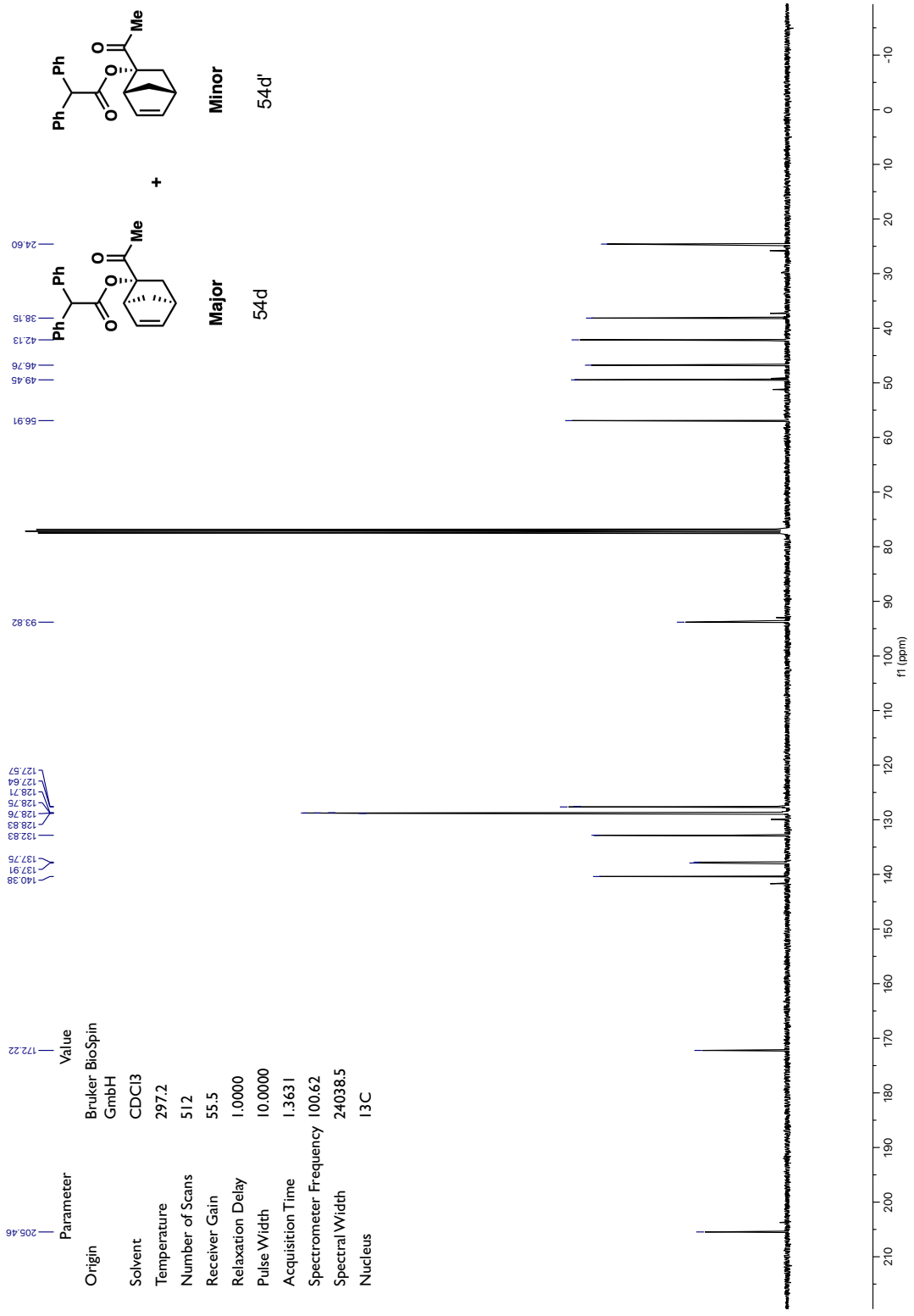

Major
54b
Minor
54b'
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.2
Number of Scans
16
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
2.8224
Spectrometer Frequency
400.13
Spectral Width
11609.9
Nucleus
1H
9.18
1.00
1.04
6.25
2.83
3.07
2.03
1.01
1.04
f1 (ppm)

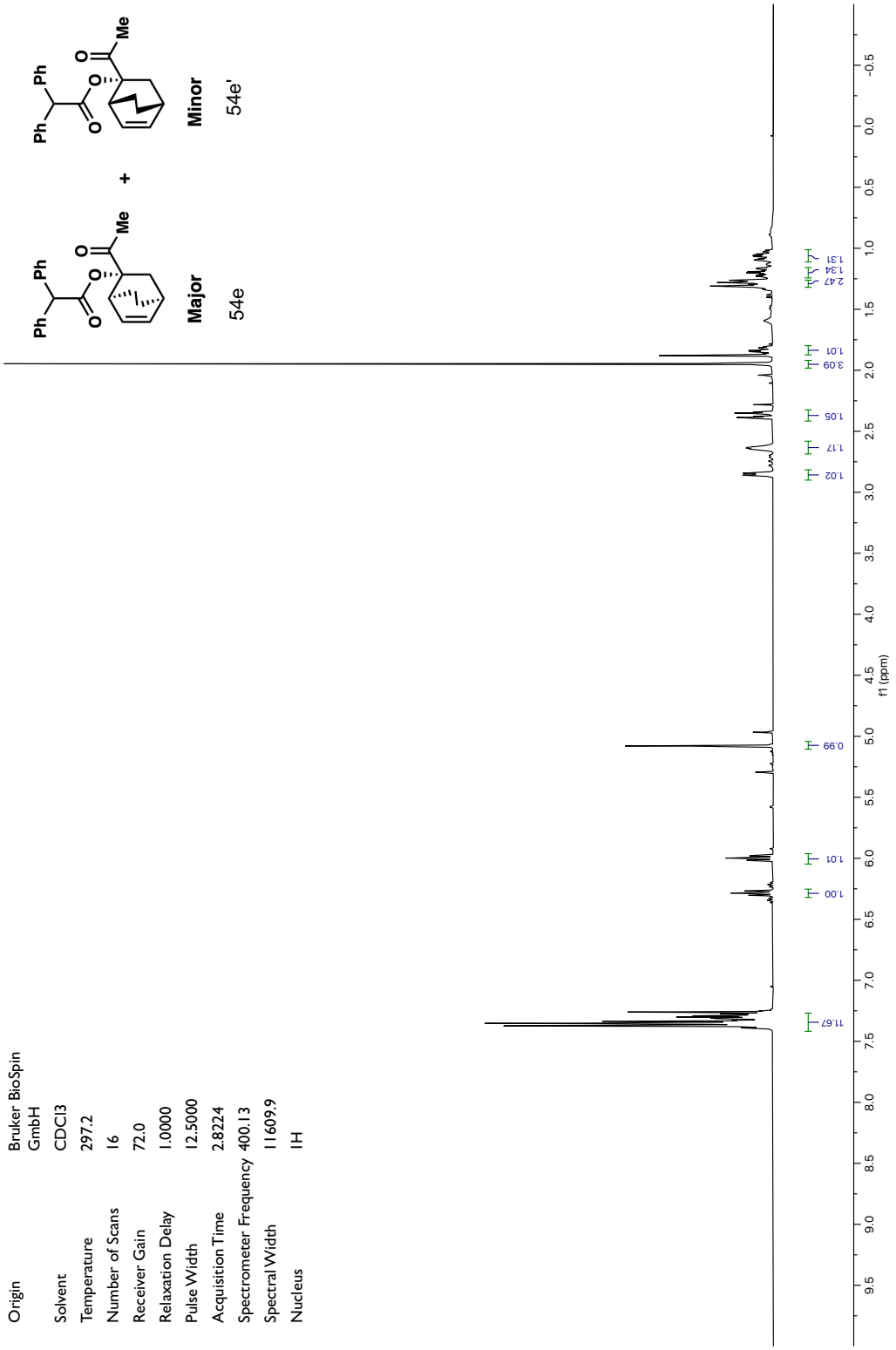

Minor
54b'
+
Major
54b
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

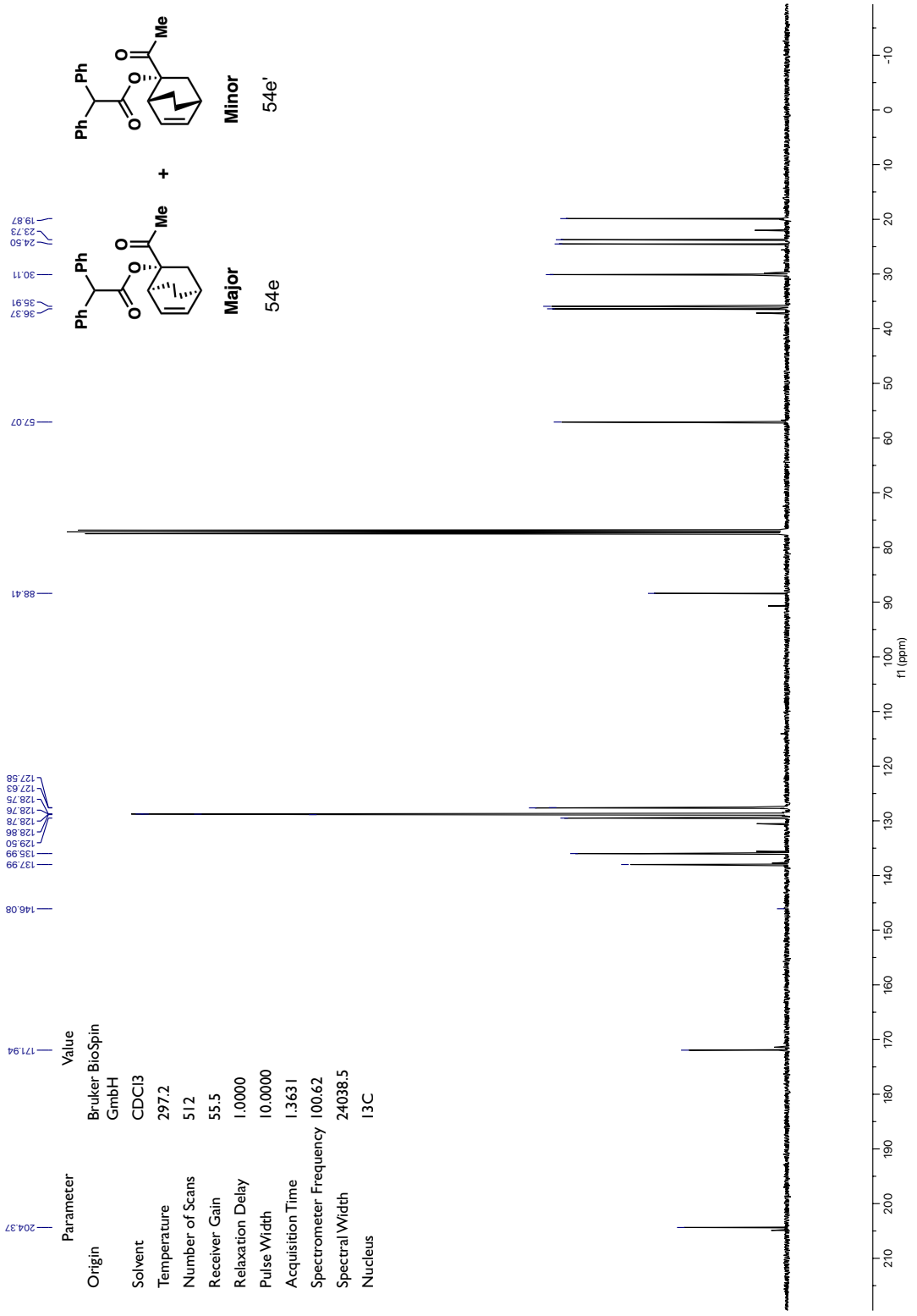

Ph
Ph
O
O
O
Me
Me
Me
54c
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 3.0
Number of Scans 8
Receiver Gain 48
Relaxation Delay 1.0000
Pulse Width 5.6500
Acquisition Time 3.0000
Spectrometer Frequency 499.60
Spectral Width 8000.0
Nucleus 1H
11.77
1.00
1.05
1.06
1.09
3.03
2.10
1.08
6.44
f1 (ppm)

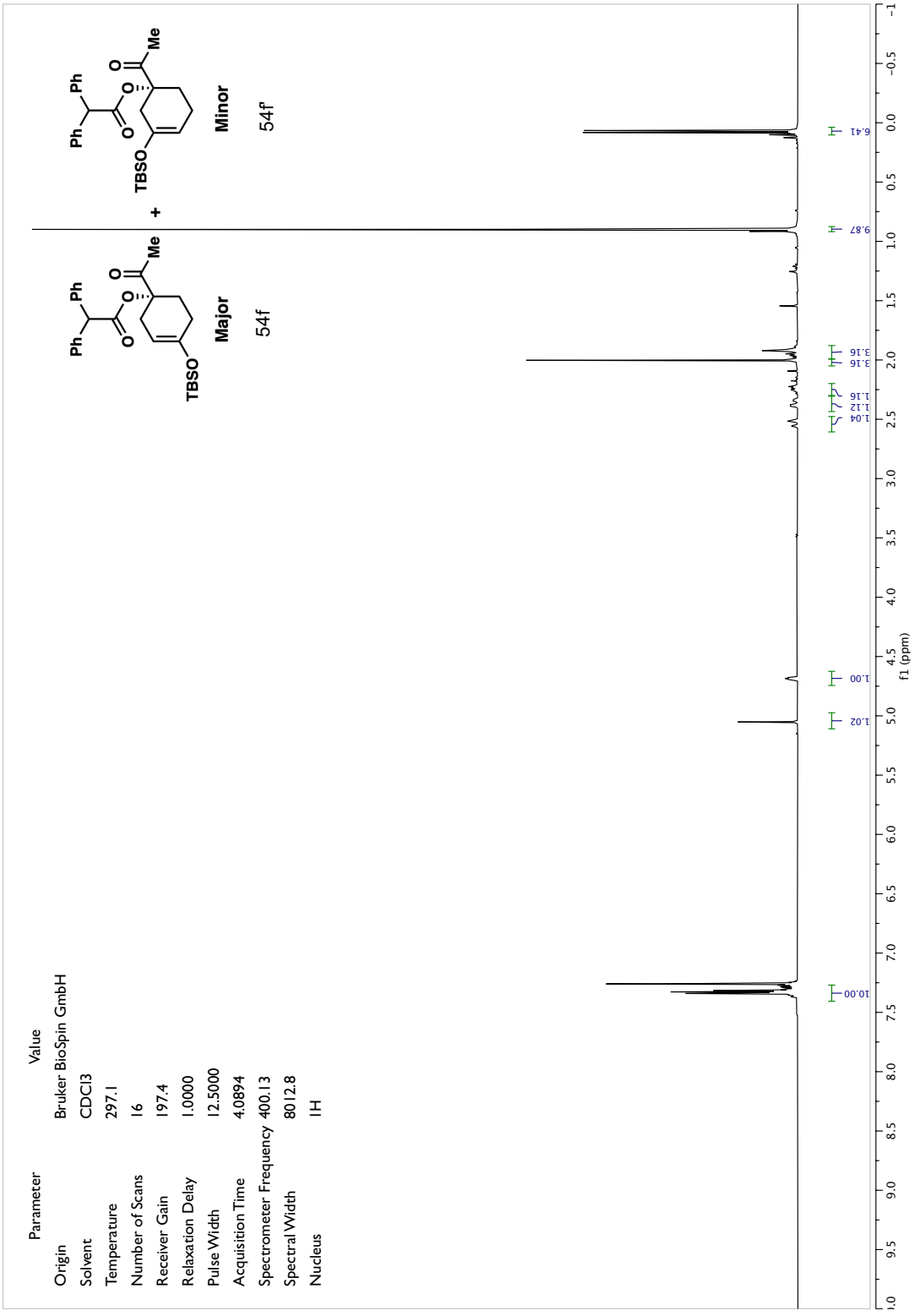

54c
Parameter Value
Origin Varian
Solvent cdcl3
Temperature 3.0
Number of Scans 256
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 4.8375
Acquisition Time 1.0420
Spectrometer Frequency 125.64
Spectral Width 31446.5
Nucleus 13C
206.58
171.84
138.20
129.85
128.79
128.75
128.70
127.49
127.48
126.57
124.87
121.37
85.48
57.22
36.66
28.12
27.91
23.97
18.92
18.63
f1 (ppm)

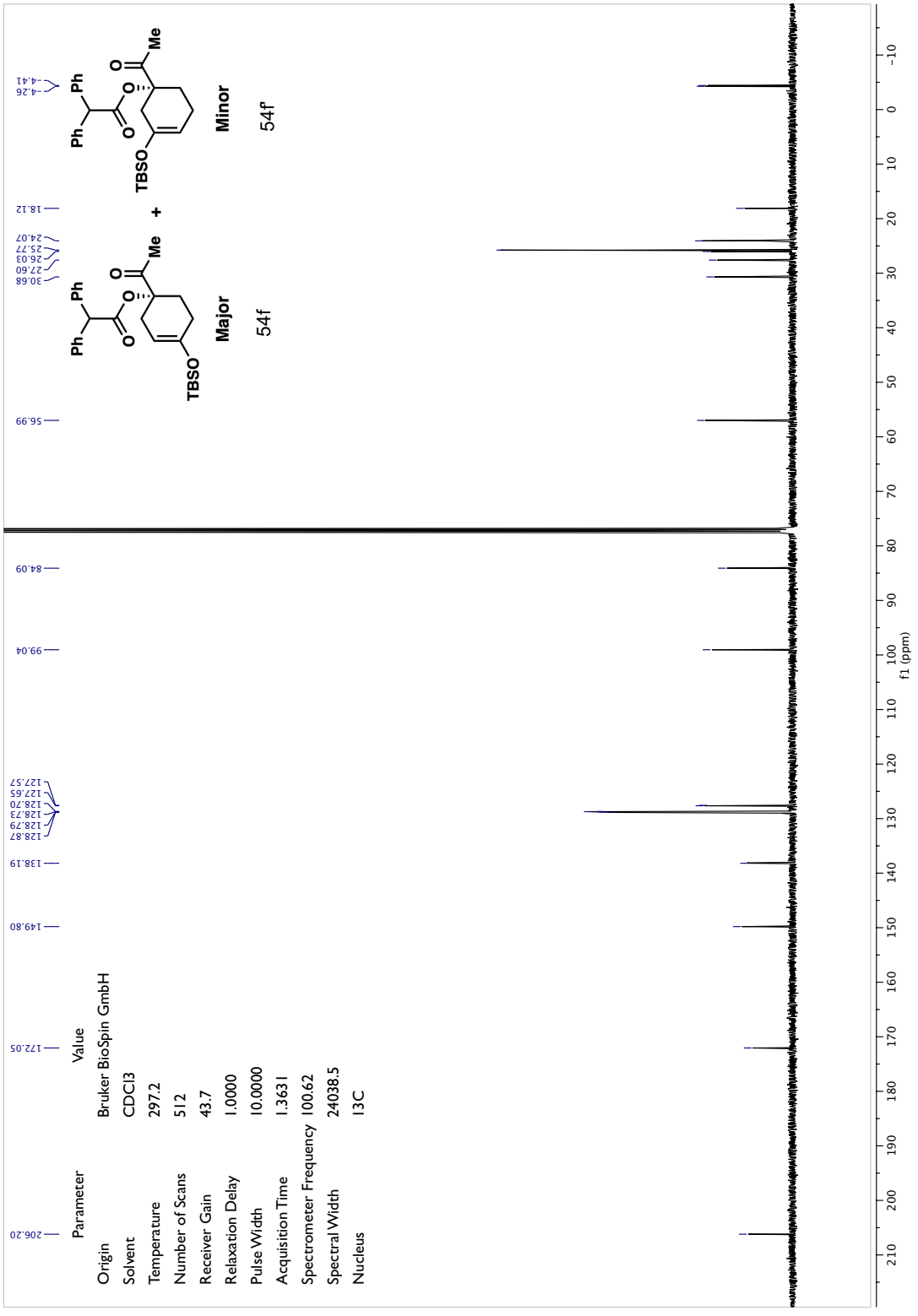

Major
54d
+
Minor
54d'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
11.34
1.03
1.00
1.00
2.99
1.18
1.03
1.05
f1 (ppm)

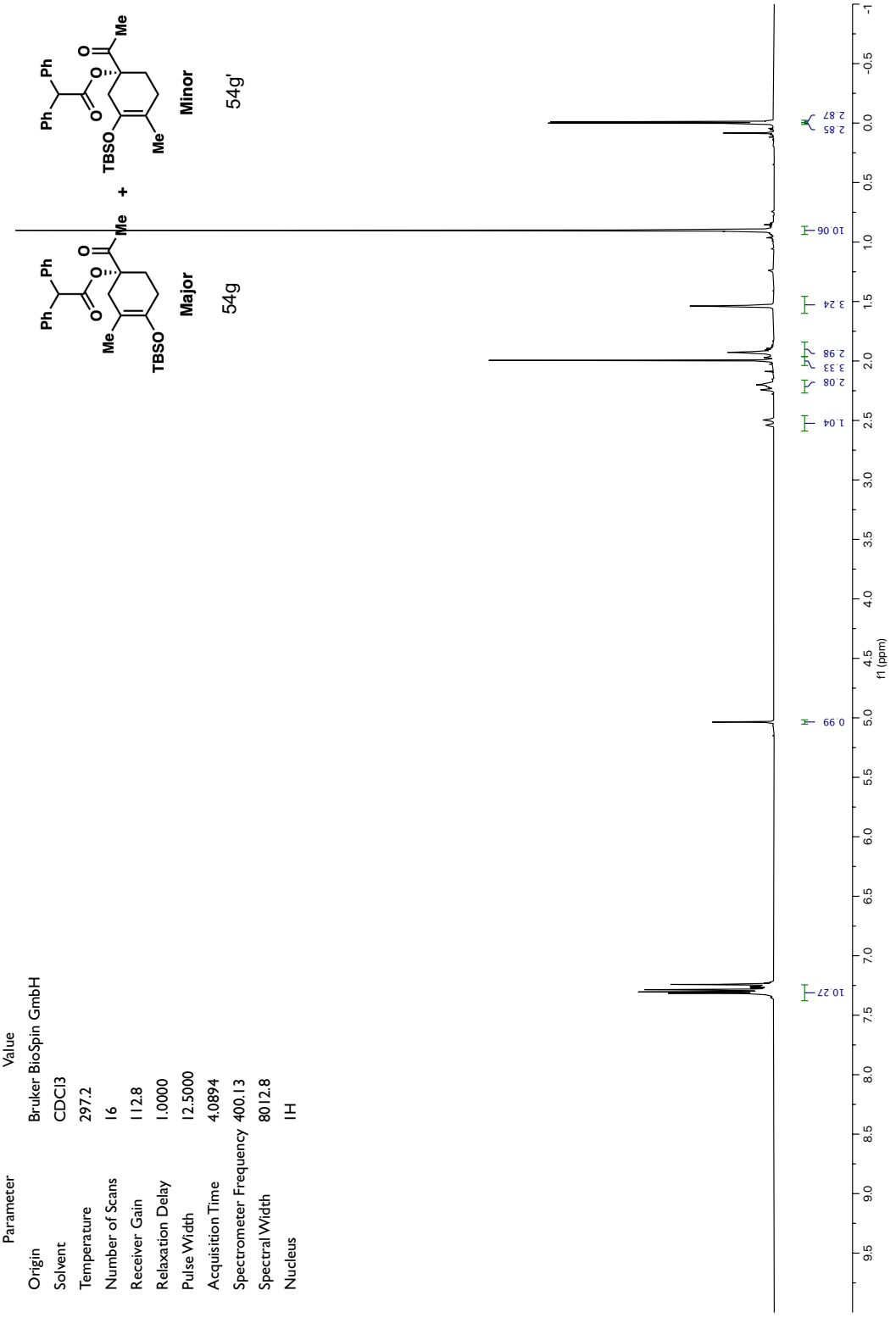

Major
54d
Minor
54d'
+
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
205.46
172.22
140.38
137.91
137.75
132.83
128.83
128.76
128.75
128.71
127.64
127.57
93.82
56.91
49.45
46.76
42.13
38.15
24.60
f1 (ppm)

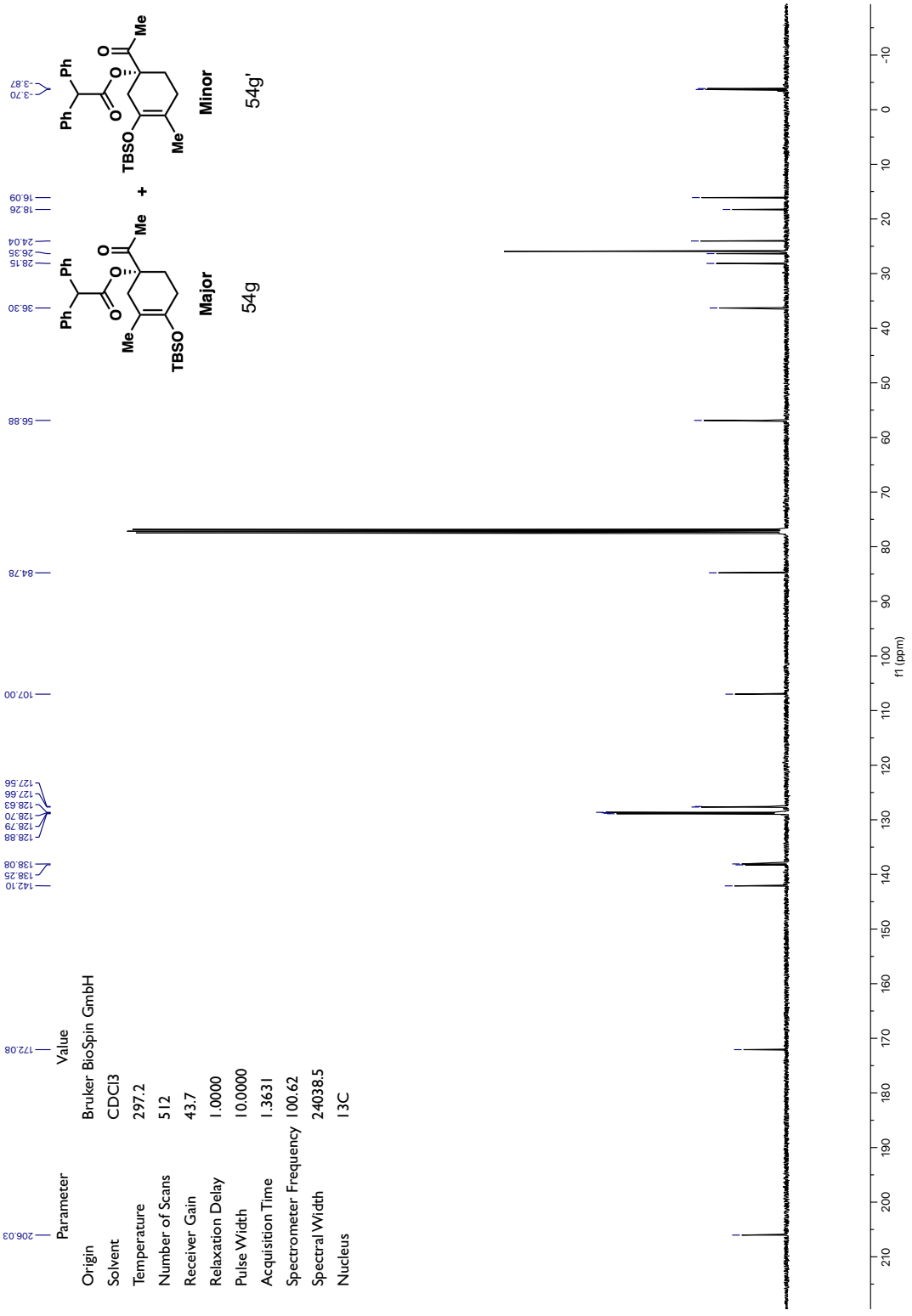

Ph
Ph
O
O
O
Me
Major
54e
+
Minor
54e'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
11.67
1.00
1.01
0.99
1.01
1.02
1.17
1.05
3.09
1.01
2.47
1.34
1.31
f1 (ppm)

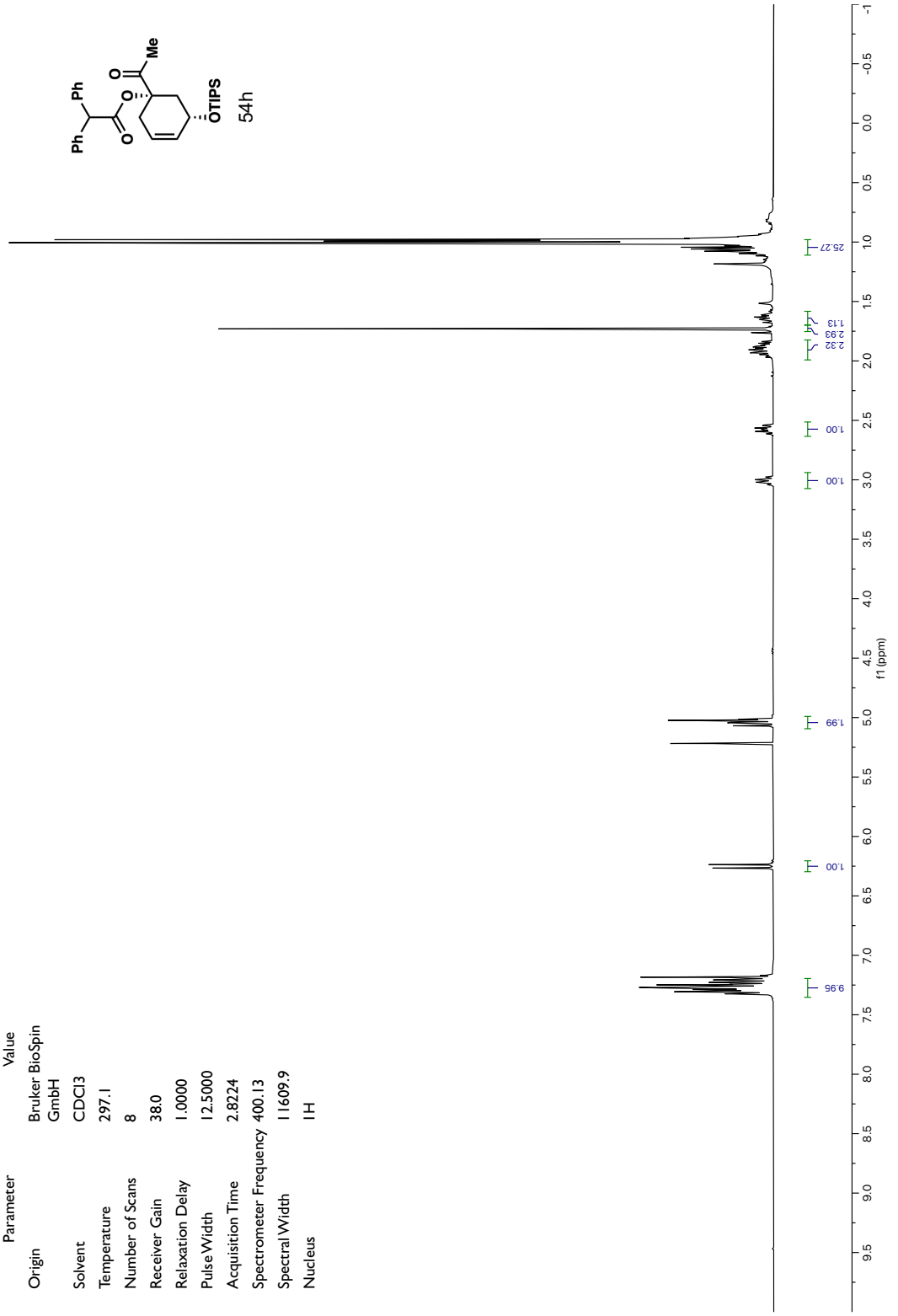

Major
54e
+
Minor
54e'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
204.37
171.94
146.08
137.99
135.99
129.50
128.86
128.78
128.76
128.75
127.63
127.58
88.41
57.07
36.37
35.91
30.11
24.50
23.73
19.87
f1 (ppm)

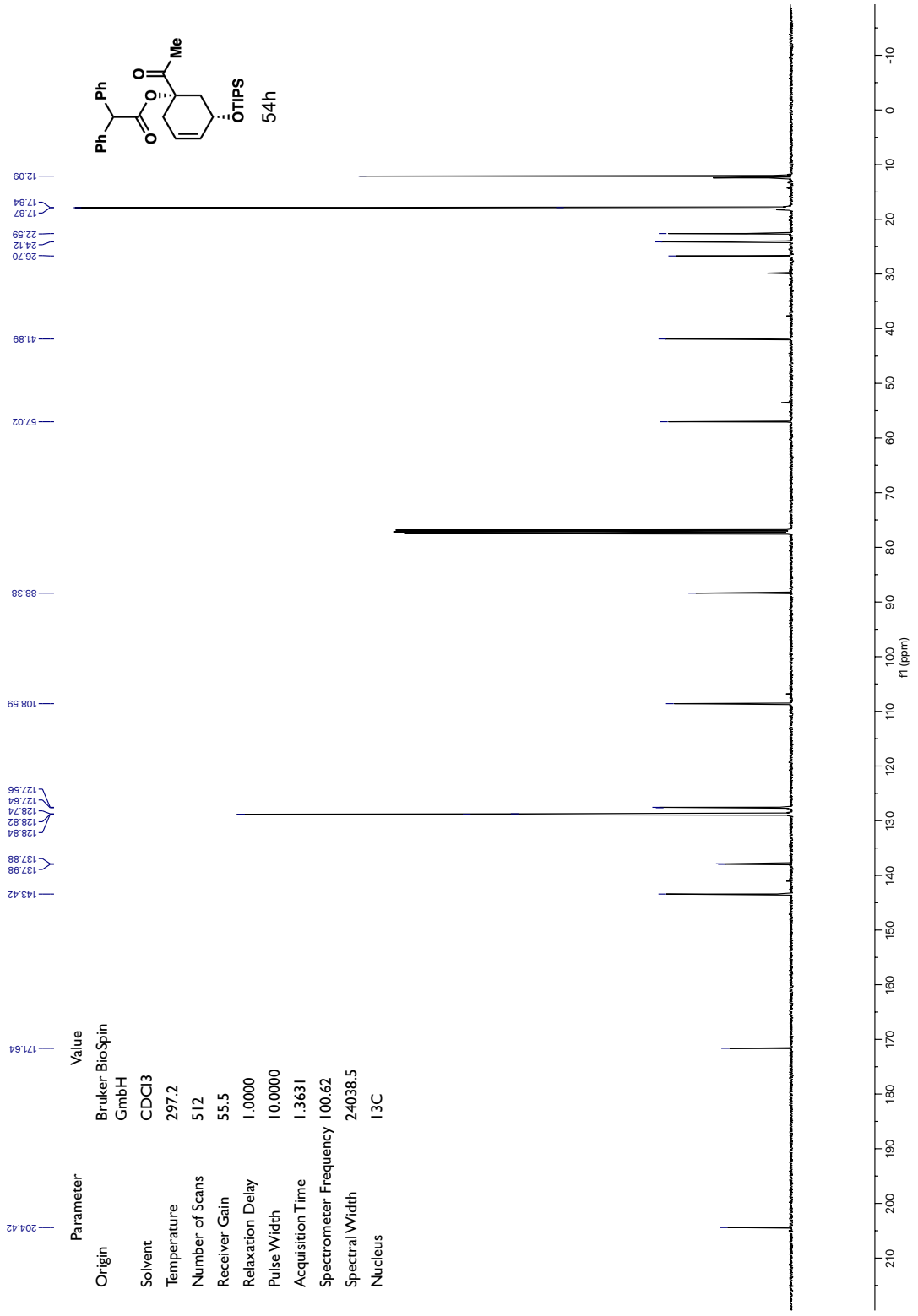

Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
Major
54f
+
Minor
54f
f1 (ppm)
10.00
1.02
1.00
3.16
3.16
1.16
1.12
1.04
9.87
6.41

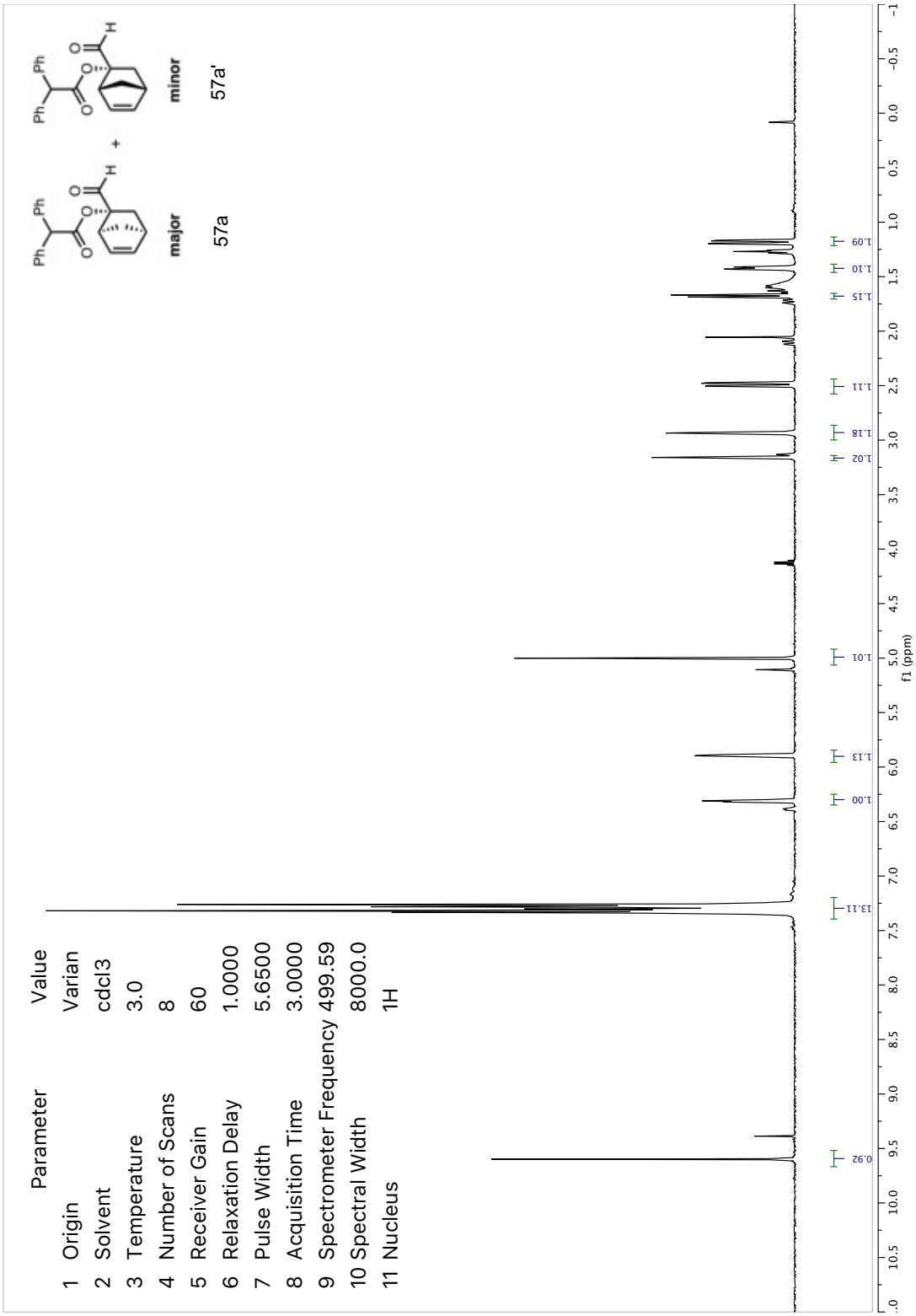

Ph
Ph
O
O
O
Me
TBSO
Minor
54f
+
Major
54f
206.20
172.05
149.80
138.19
128.87
128.79
128.73
128.70
127.65
127.57
99.04
84.09
56.99
30.68
27.60
26.03
25.77
24.07
18.12
-4.26
-4.41
f1 (ppm)

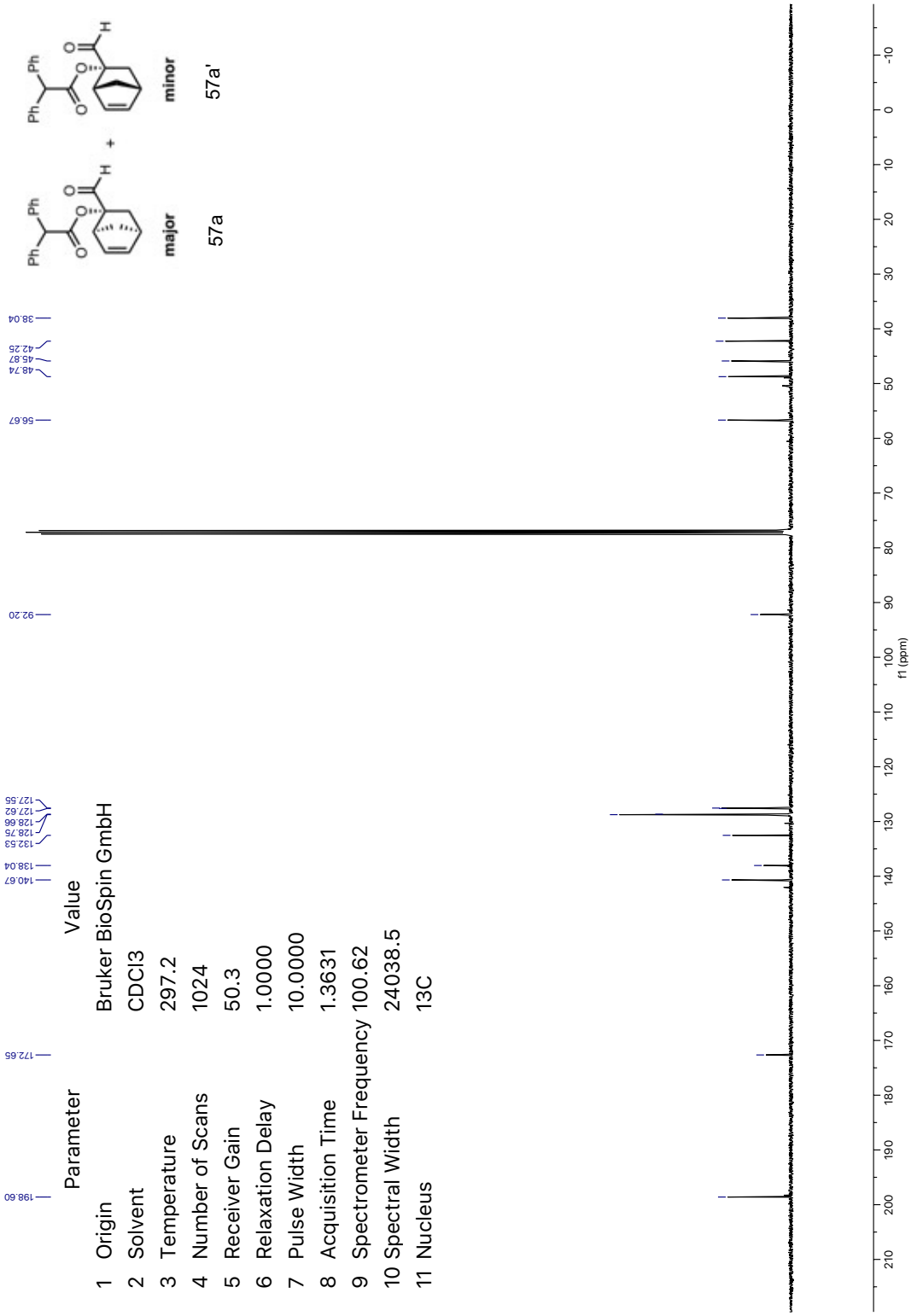

Major
54g
+
Minor
54g'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
10.27
0.99
1.04
2.08
3.33
2.98
3.24
10.06
2.85
2.87
f1 (ppm)


Major
Minor
54g
54g'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

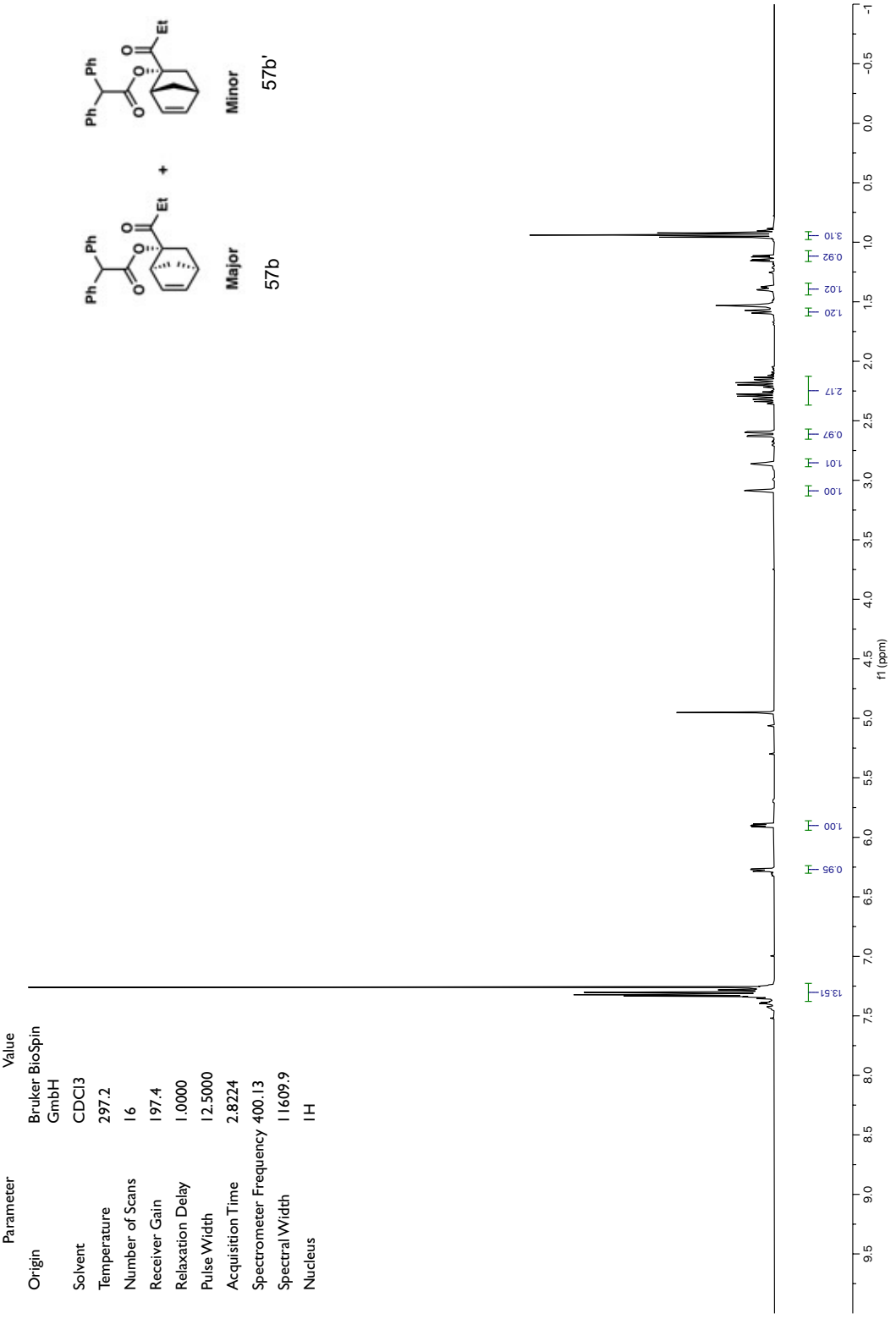

Ph
Ph
O
O
O
Me
OTIPS
54h
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 8
Receiver Gain 38.0
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
25.27
1.13
2.93
2.32
1.00
1.00
1.99
1.00
9.95
f1 (ppm)

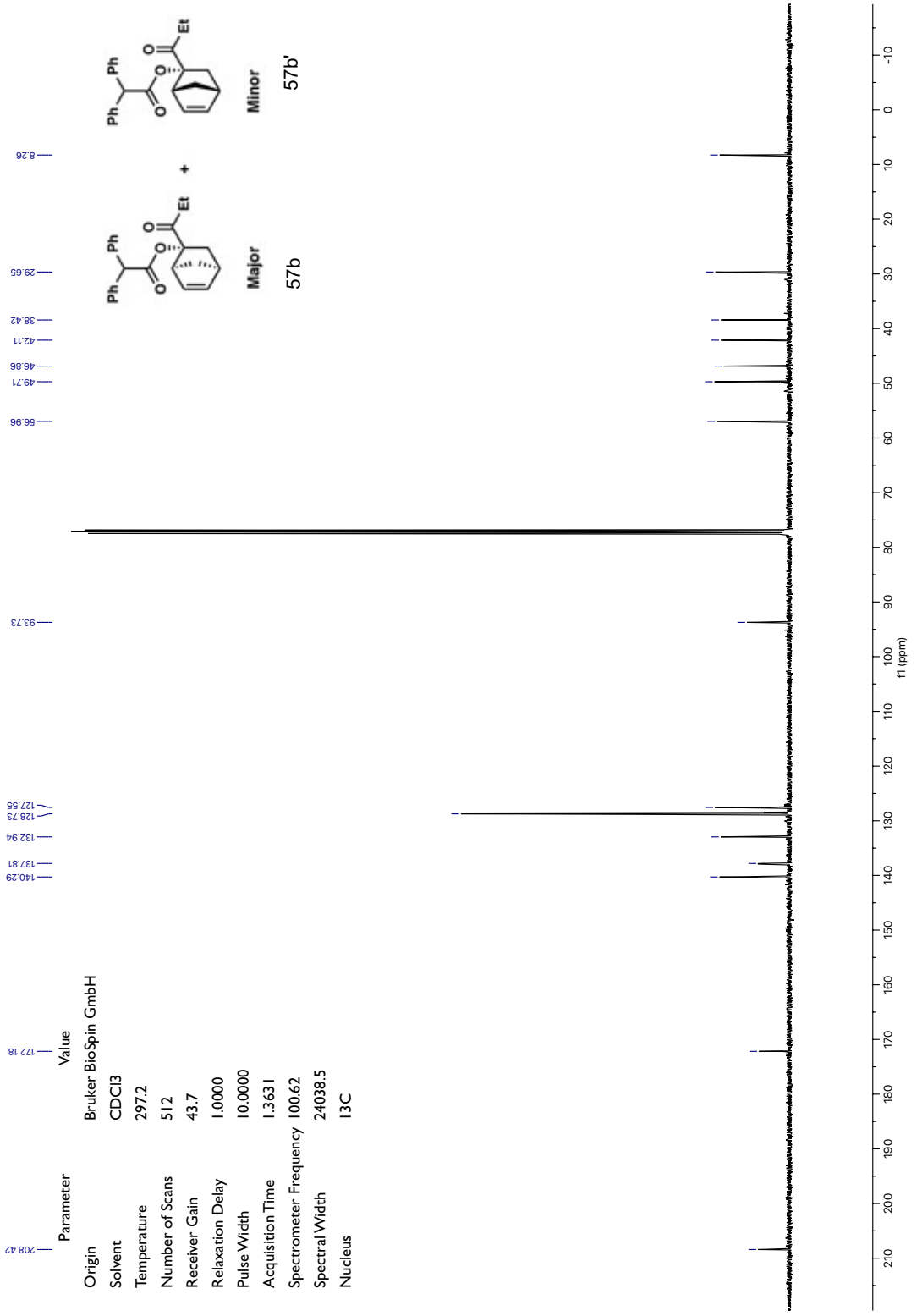

Ph
Ph
O
O
O
Me
OTIPS
54h
12.09
17.84
17.87
22.59
24.12
26.70
41.89
57.02
88.38
108.59
127.56
127.64
128.74
128.82
128.84
137.88
137.98
143.42
171.64
204.42
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
f1 (ppm)

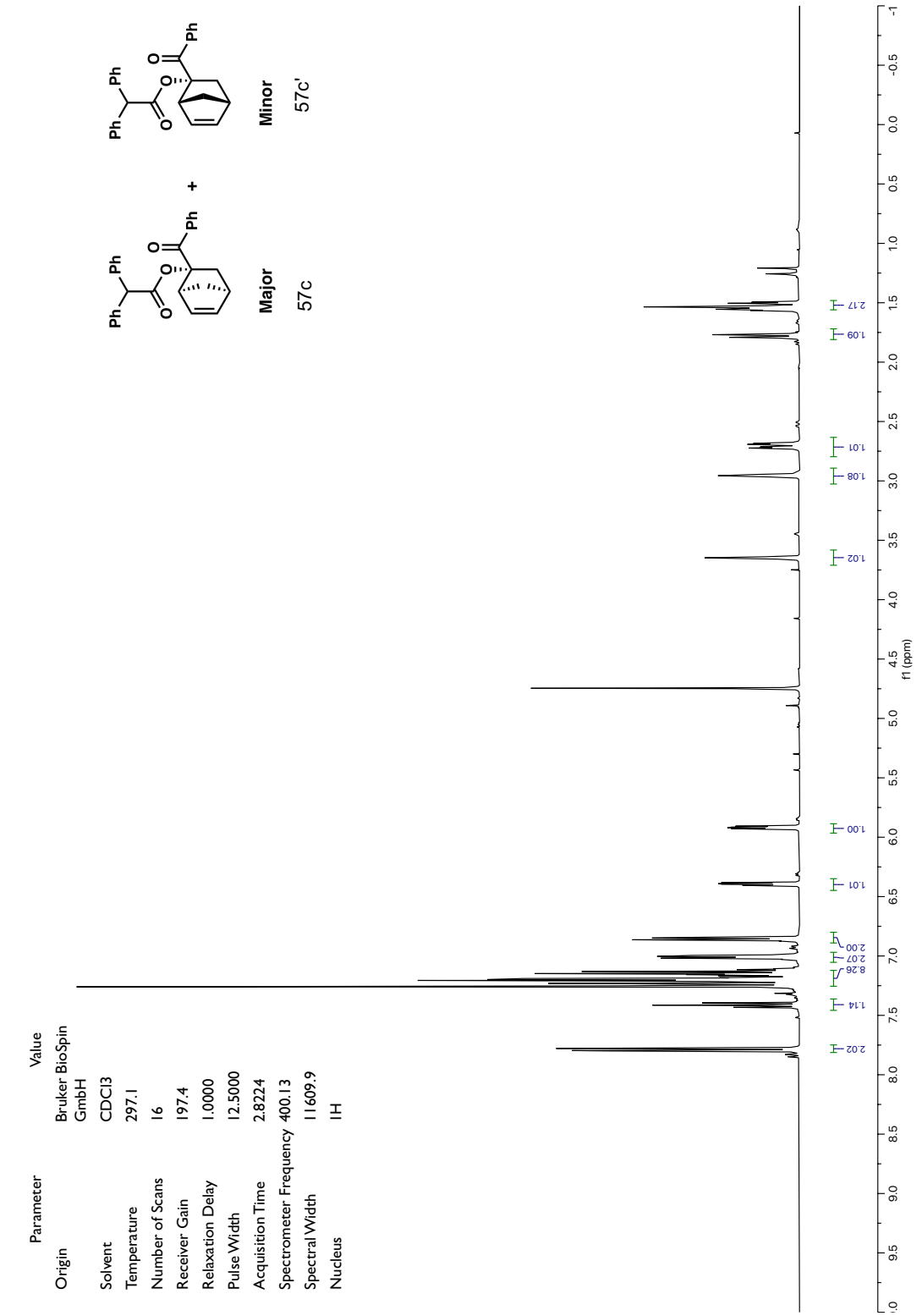

major
minor
57a
57a'
Parameter Value
1 Origin Varian
2 Solvent cdcl3
3 Temperature 3.0
4 Number of Scans 8
5 Receiver Gain 60
6 Relaxation Delay 1.0000
7 Pulse Width 5.6500
8 Acquisition Time 3.0000
9 Spectrometer Frequency 499.59
10 Spectral Width 8000.0
11 Nucleus 1H
13.11
1.00
1.13
1.01
1.02
1.18
1.11
1.15
1.10
1.09
0.92
f1 (ppm)

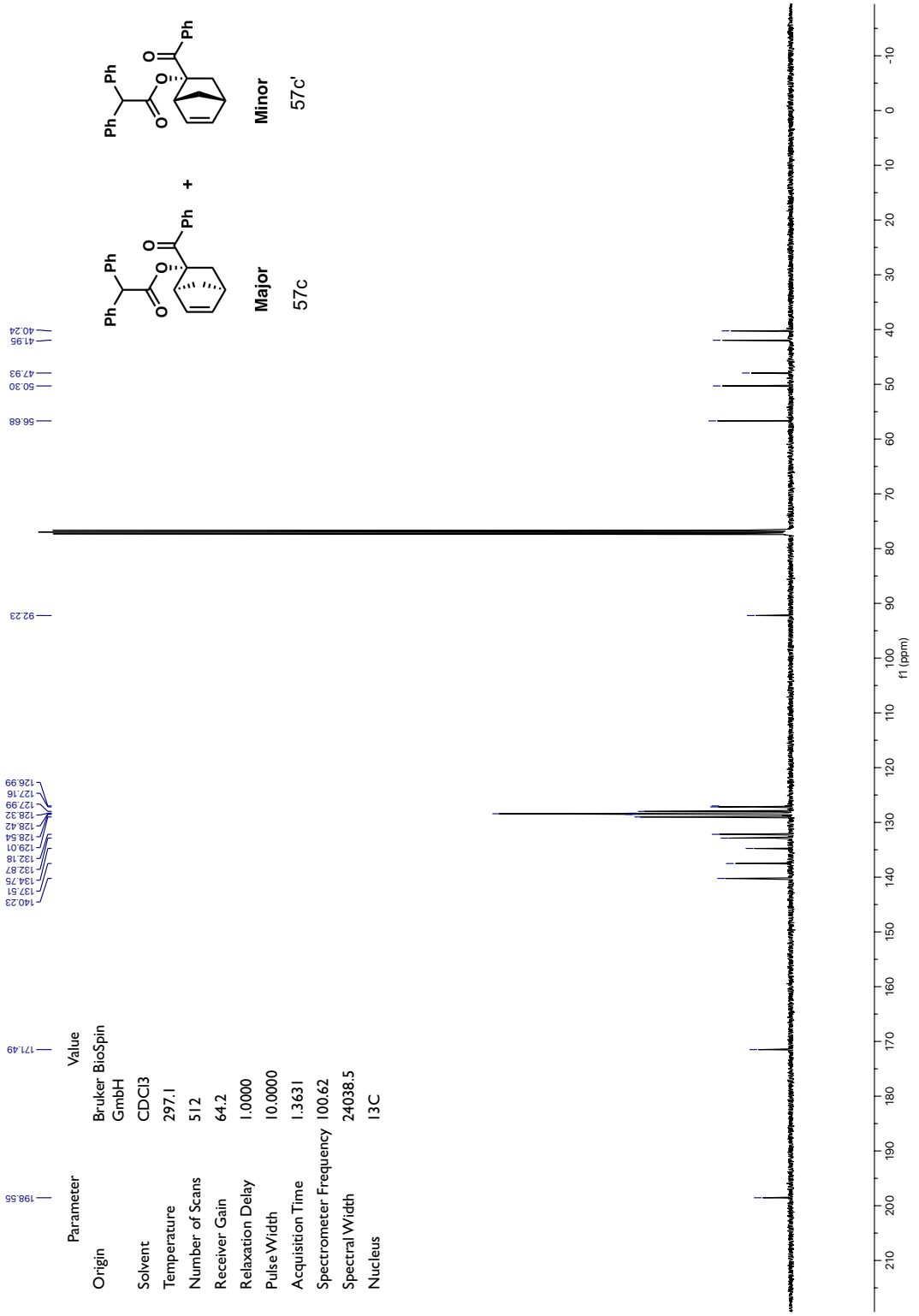


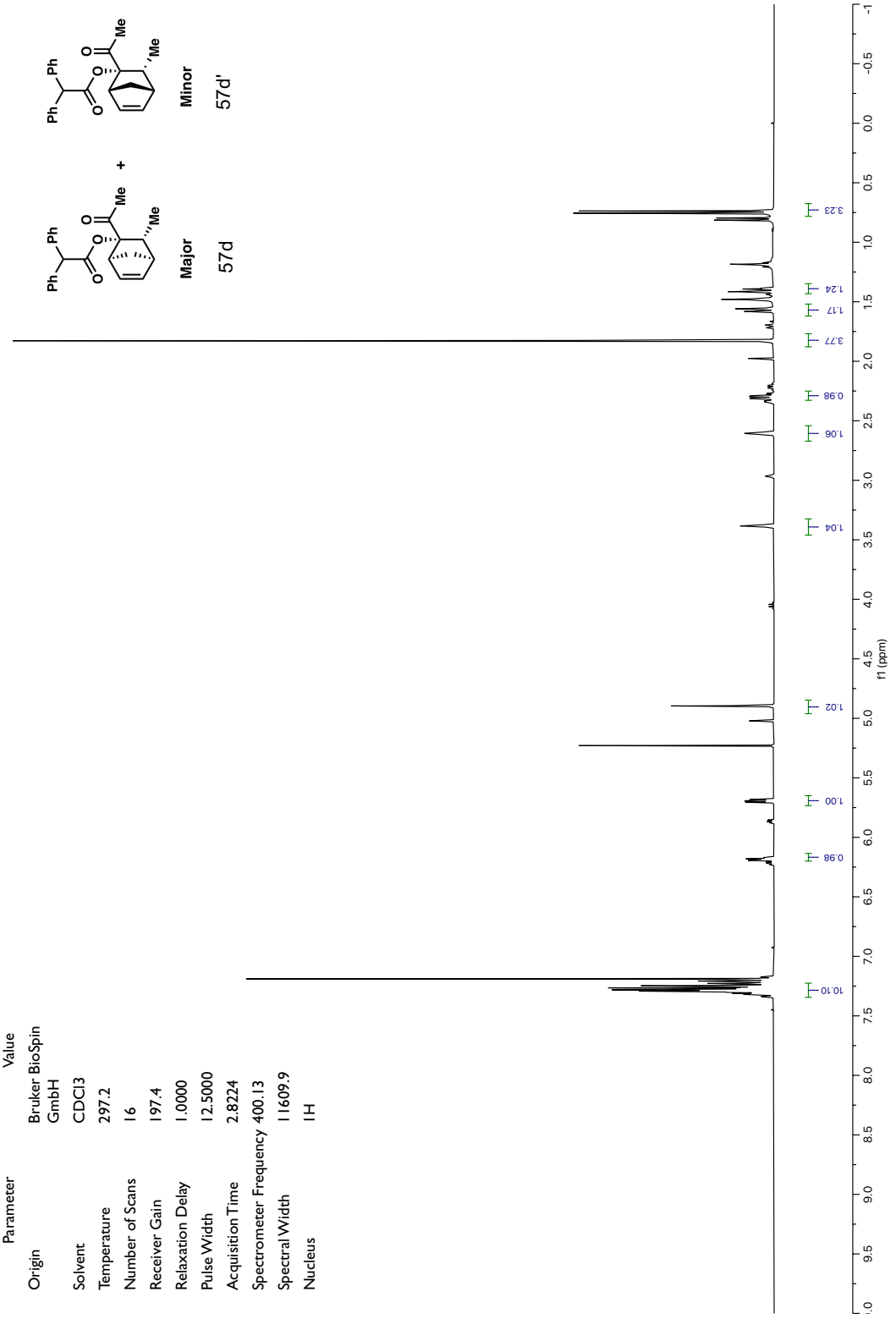
	Parameter	Value
1	Origin	Bruker BioSpin GmbH
2	Solvent	CDCl3
3	Temperature	297.2
4	Number of Scans	1024
5	Receiver Gain	50.3
6	Relaxation Delay	1.0000
7	Pulse Width	10.0000
8	Acquisition Time	1.3631
9	Spectrometer Frequency	100.62
10	Spectral Width	24038.5
11	Nucleus	13C


Major
57b
+
Minor
57b'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
13.51
1.00
0.95
1.00
1.01
0.97
2.17
1.20
1.02
0.92
3.10
f1 (ppm)

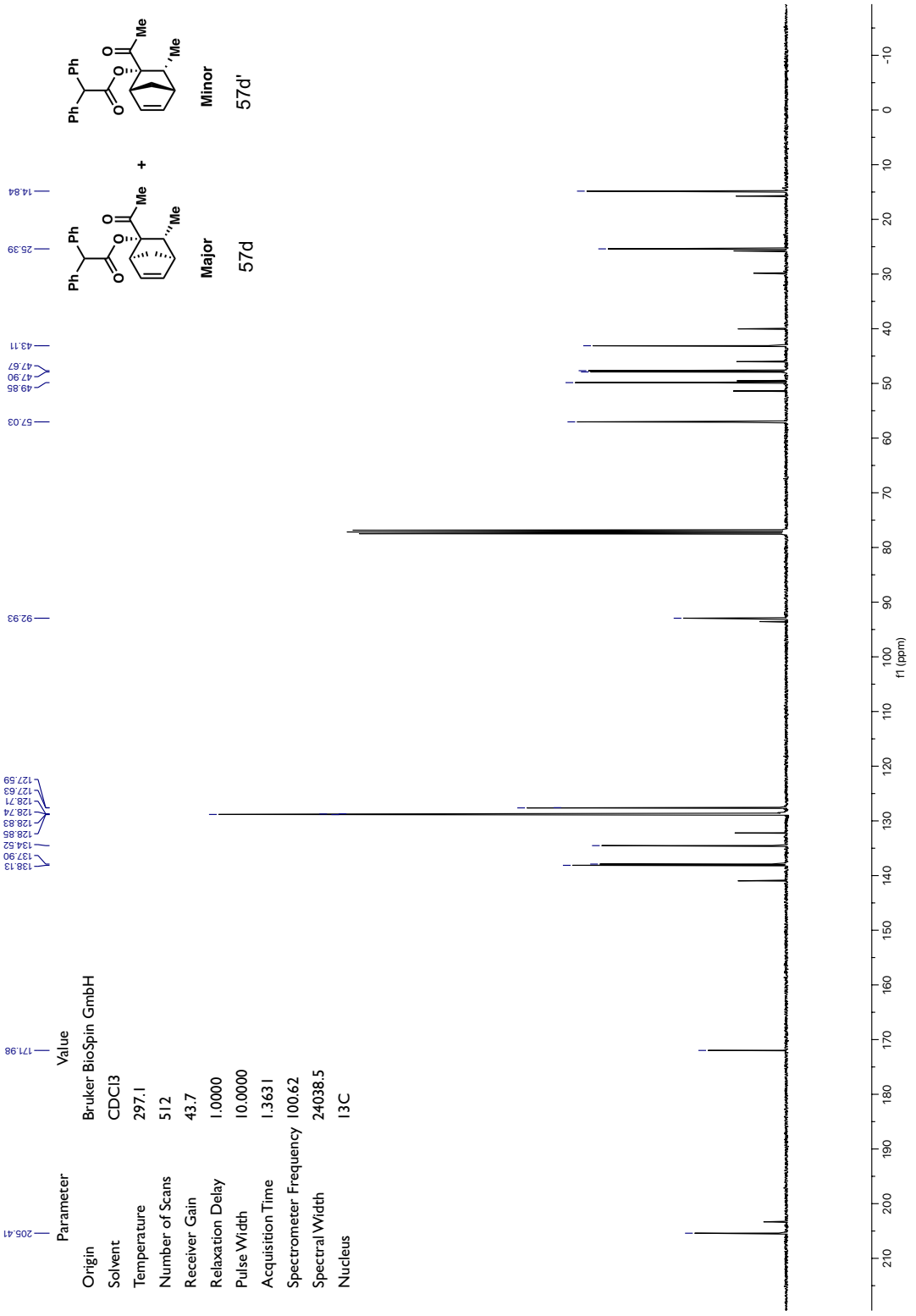

Major
57b
+
Minor
57b'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
208.42
172.18
140.29
137.81
132.94
128.73
127.55
93.73
56.96
49.71
46.86
42.11
38.42
29.65
8.26
f1 (ppm)

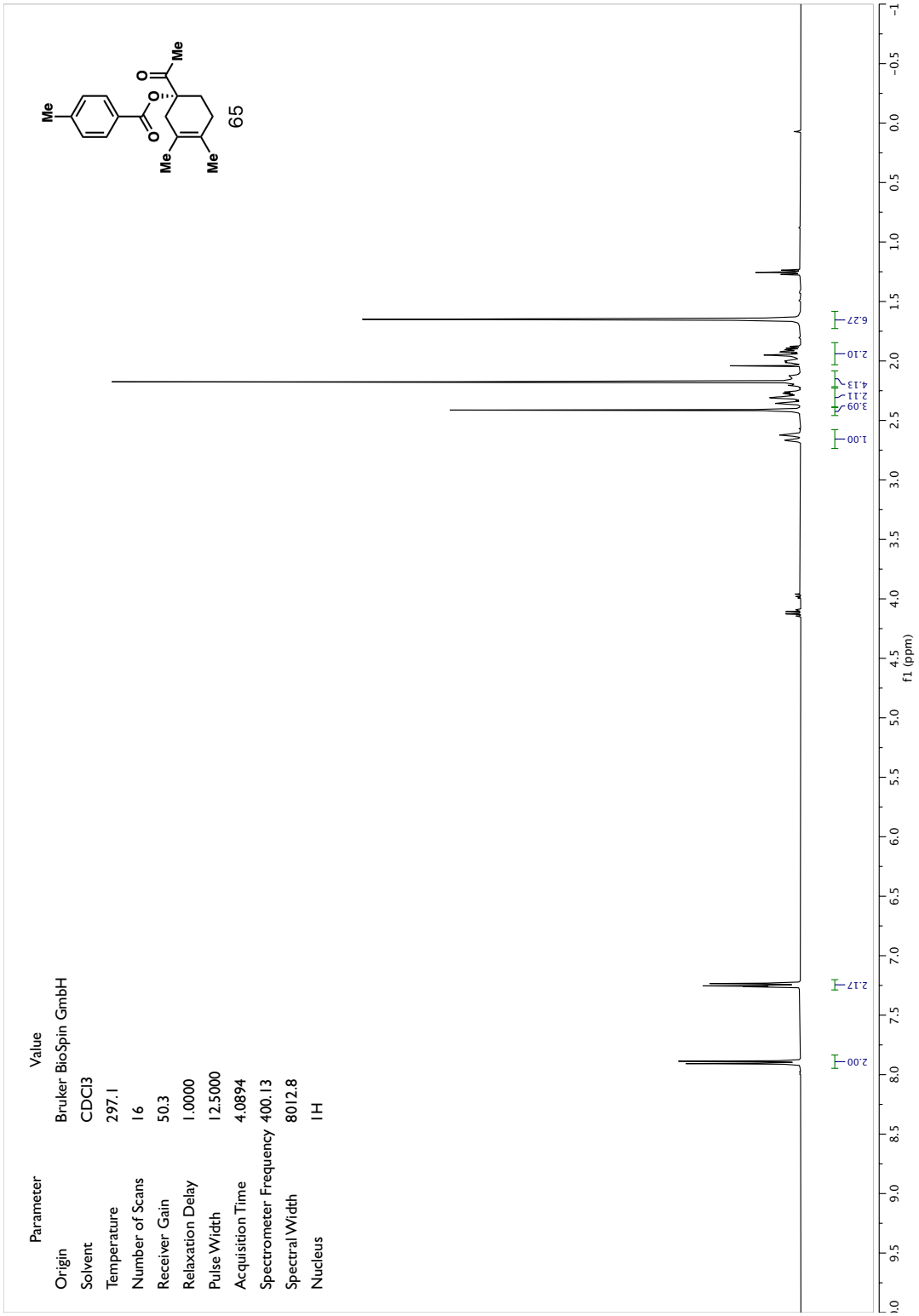

Ph
Ph
O
O
O
Ph
+
Major
57c
Minor
57c'
Parameter
Value
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Number of Scans
16
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
12.5000
Acquisition Time
2.8224
Spectrometer Frequency
400.13
Spectral Width
11609.9
Nucleus
1H
2.17
1.09
1.01
1.08
1.02
1.00
1.01
2.00
2.07
8.26
1.14
2.02
f1 (ppm)

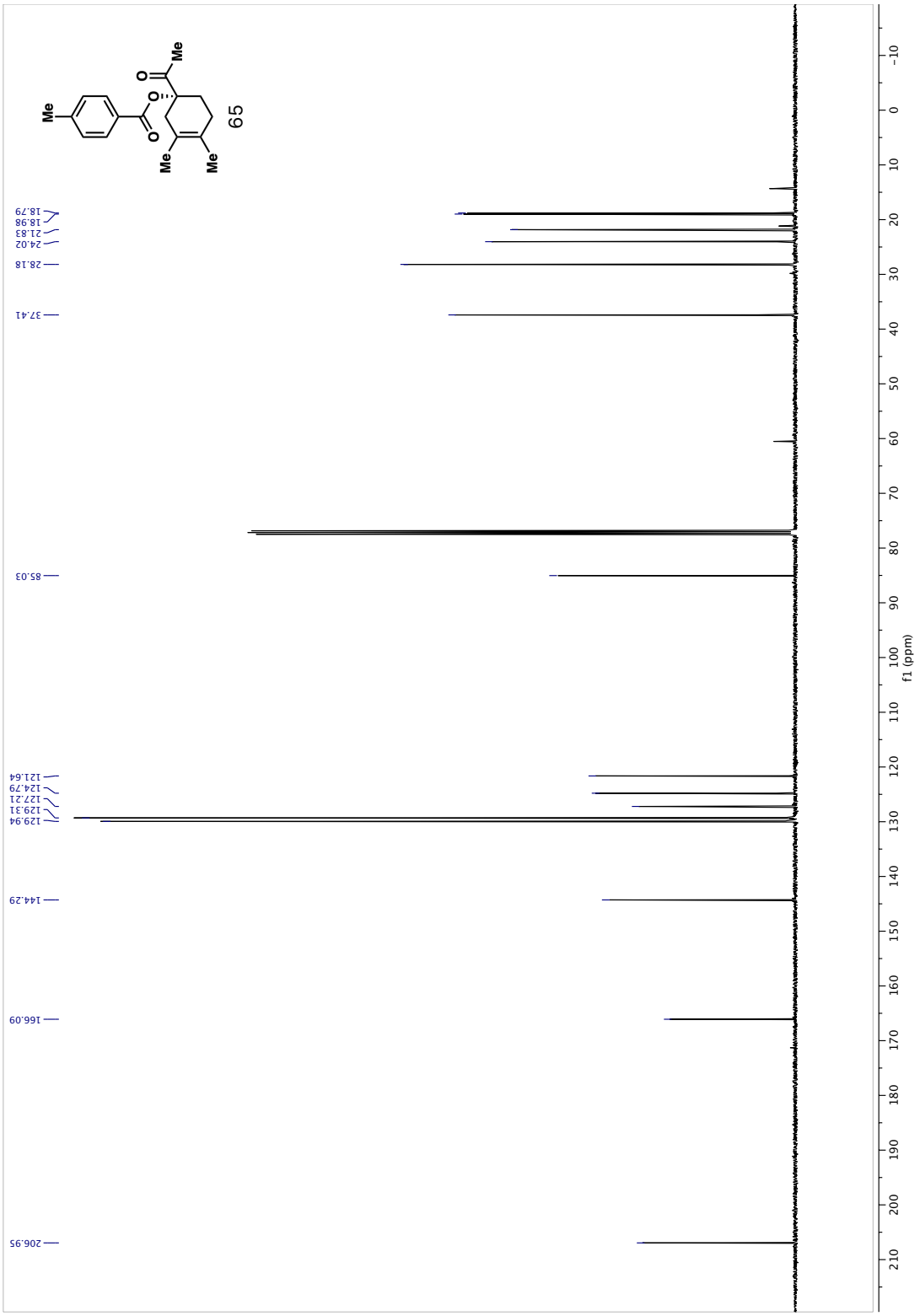

Major
57c
+
Minor
57c'
198.55
171.49
140.23
137.51
134.75
132.87
132.18
129.01
128.54
128.42
128.32
127.99
127.16
126.99
92.23
56.68
50.30
47.93
41.95
40.24
f1 (ppm)
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C

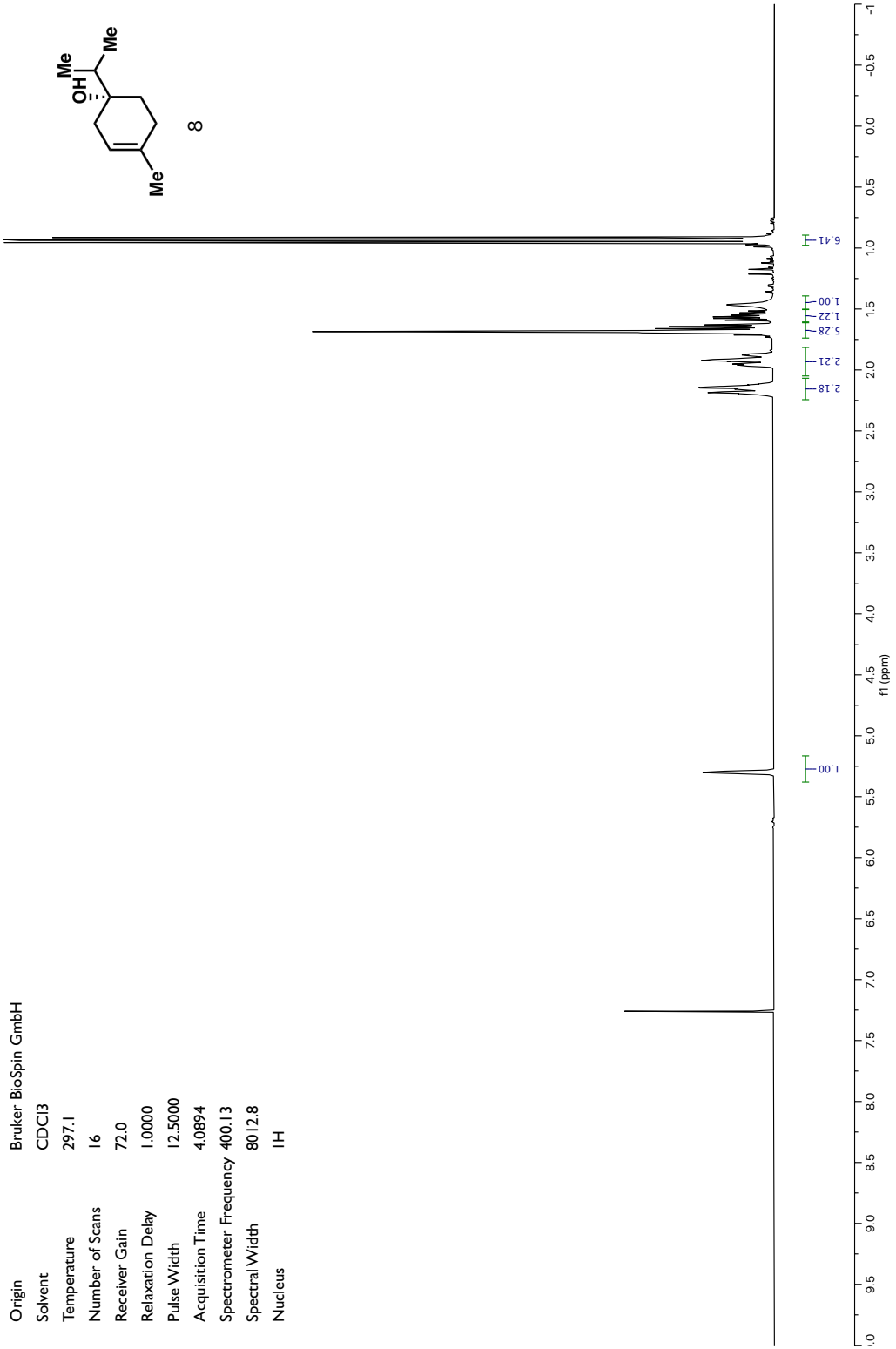


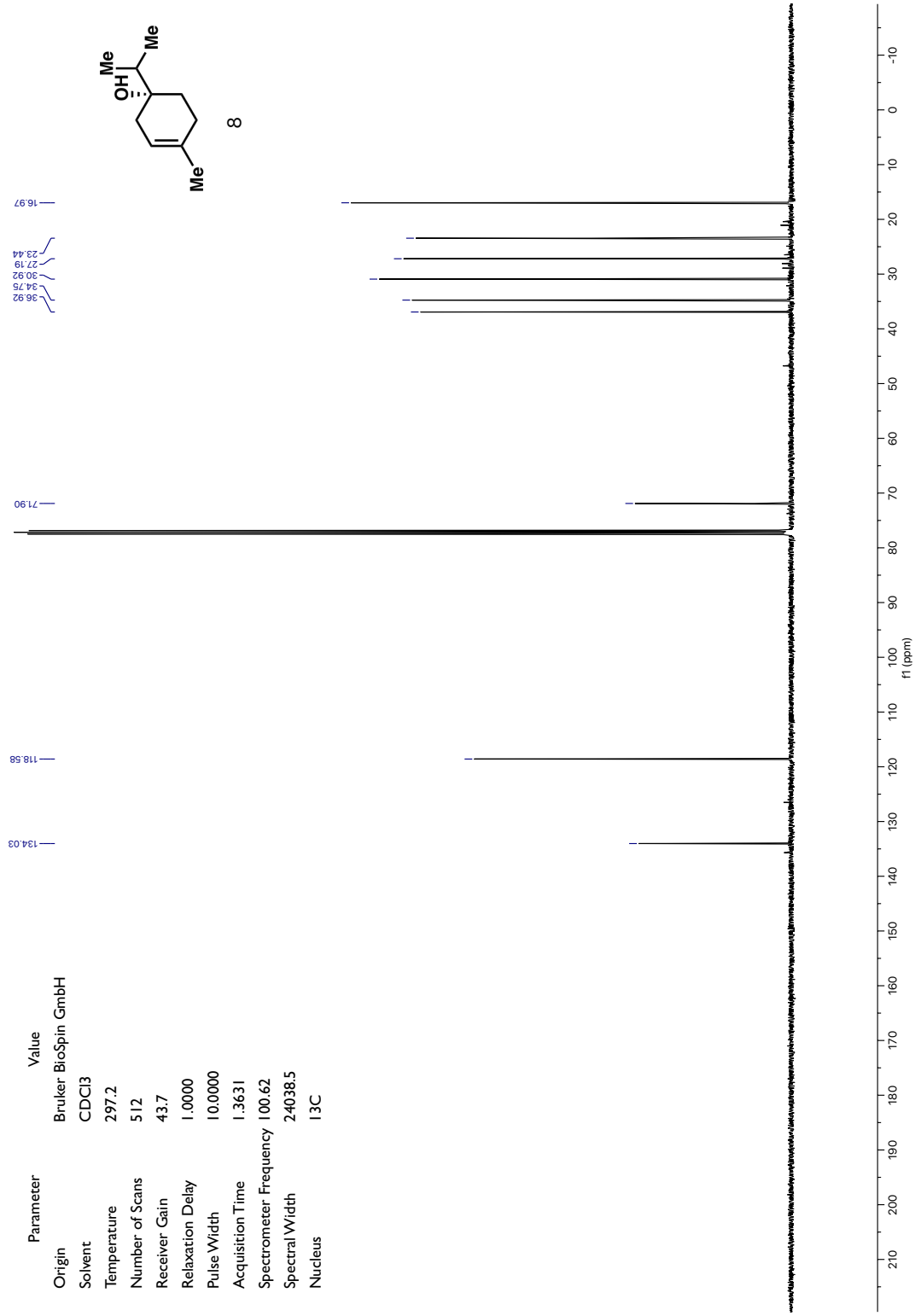
Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	16
Receiver Gain	197.4
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	2.8224
Spectrometer Frequency	400.13
Spectral Width	11609.9
Nucleus	1H


Major
57d
Minor
57d'
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Spectrometer Frequency 100.62
Spectral Width 24038.5
Nucleus 13C
205.41
171.98
138.13
137.90
134.52
128.85
128.83
128.74
128.71
127.63
127.59
92.93
57.03
49.85
47.90
47.67
43.11
25.39
14.84
f1 (ppm)

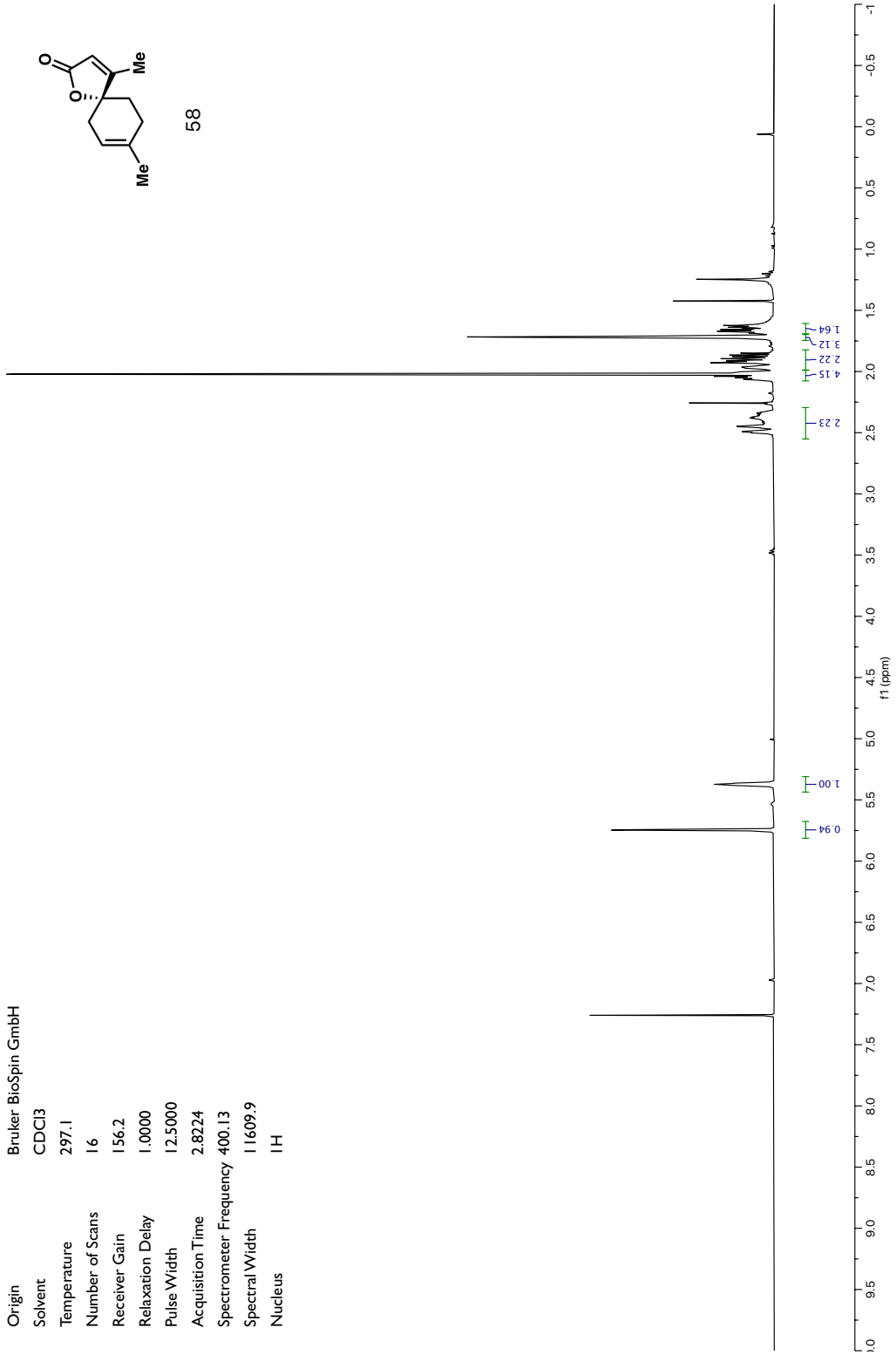

Me
O
O
Me
Me
Me
65
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
6.27
2.10
4.13
2.11
3.09
1.00
2.17
2.00
f1 (ppm)

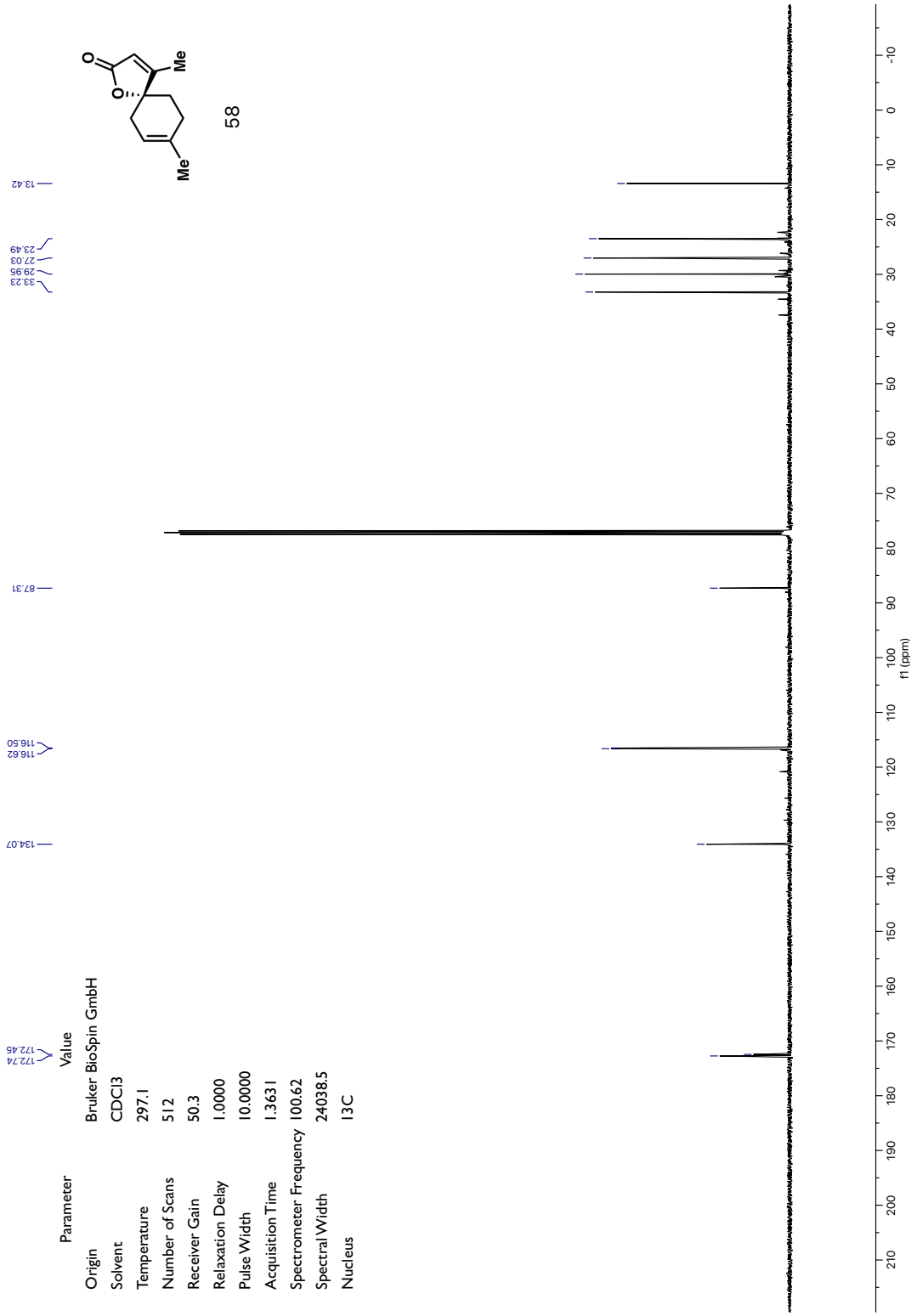

Me
O
O
O
Me
Me
Me
65
18.79
18.98
21.83
24.02
28.18
37.41
85.03
121.64
124.79
127.21
129.31
129.94
144.29
166.09
206.95
f1 (ppm)


Me
OH
Me
Me
8
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 4.0894
Spectrometer Frequency 400.13
Spectral Width 8012.8
Nucleus 1H
6.41
1.00
5.28
1.22
2.21
2.18
1.00
f1 (ppm)



Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Number of Scans	512
Receiver Gain	43.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C


Me
Me
58
Parameter Value
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Acquisition Time 2.8224
Spectrometer Frequency 400.13
Spectral Width 11609.9
Nucleus 1H
1.64
3.12
2.22
4.15
2.23
1.00
0.94
f1 (ppm)



Parameter	Value
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Number of Scans	512
Receiver Gain	50.3
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C

ABOUT THE AUTHOR

Skyler Dakota Mendoza was born on February 14, 1994 to Ruben Mendoza and Shawni R. Mendoza in Kennewick, Washington. He then moved at an early age to and grew up in Maui, Hawaii.

In 2012, Skyler began his undergraduate education at the University of Washington, initially wanting to pursue a career in medicine. However, he very quickly became fascinated with organic chemistry after studying it for the first time during his sophomore year. He immediately became interested in summer research and had the privilege of working in the laboratory of Professor Gregory Horwitz. It was with his support and encouragement that he applied for graduate school to pursue his doctorate.

Following his graduation from UW, Skyler moved south to pursue his graduate studies under the direction of Professor Sarah E. Reisman at the California Institute of Technology. His graduate work allowed him to study a variety of topics, with a focus on synthetically challenging approaches towards the synthesis of falcatin A. Following the completion of his Ph.D, Skyler will move to San Diego to conduct postdoctoral studies under the direction of Professor Keary M. Engle at the Scripps Institute.