SYNTHETIC STRATEGIES FOR THE TOTAL SYNTHESIS OF THE RYANOID AND ISORYANOID DITERPENES

Thesis by

Arthur Han

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2019

(Defended Sep 24th, 2018)

Arthur Han

ORCID: 0000-0001-8691-699X

To Professor Samuel J. Danishefsky

a mentor, a teacher, an inspiration

ABSTRACT

Highly oxygenated, polycyclic terpenoids provide a rich source of biologically active natural products, yet the translation of their activity to lead candidate analogs and useful biological probes requires *concise* solutions to address, at once, accessibility and diversification. This dissertation will disclose our efforts to bridge that gap through the development of synthetic strategies for the total synthesis of the ryanoid and isoryanoid diterpenes. The studies herein will address the strategy and logic that rendered the success of a challenging C3 acylation to directly incorporate a pyrrole-2-carboxylate ester, ultimately resulting in an 18-step total synthesis of (+)-ryanodine. The versatility of the route was demonstrated by the preparation of the related ryanoid diterpene (+)-20-deoxyspiganthine. Enabling the success of both syntheses was the development of robust conditions to induce late-stage reductive ring closure and forge the C1–C15 bond.

The lessons learned from these synthetic efforts drew us thereafter to the complex, polycyclic structure of the isoryanoid diterpene (+)-perseanol. The evaluation of several different approaches culminated in the discovery of a successful fragment coupling approach, hinging on a 2-step sequence involving (1) 1,2-addition to induce convergent union of two fragments of equal complexity and (2) Heck-Stille cyclization/cross-coupling cascade to complete the preparation of the ABC tricyclic core. Emphasis will be placed on the strategic use of our fragment coupling approach to overcome the inherent stereochemical bias presented by late-stage intermediates, thereby enabling an 18-step total synthesis. The oxidation tactics developed herein should find broad utility in the preparation of other ryanoid, isoryanoid, and highly oxidized diterpenoids.

PUBLISHED CONTENT AND CONTRIBUTIONS

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

Xu, C.; Han, A.; Virgil, S. C.; Reisman, S. E. *ACS Cent. Sci.* **2017**, *3*, 278-282.

DOI: 10.1021/acscentsci.6b00361

This article is available online at: http://pubs.acs.org/doi/abs/10.1021/acscentsci.6b00361

Xu, C.; Han, A.; Reisman, S. E. *Org. Lett.* **2018**, *20*, 3793-3796.

DOI: 10.1021/acs.orglett.8b01387

This article is available online at: http://pubs.acs.org/doi/abs/10.1021/acs.orglett.8b01387

A.H. contributed to the development of the synthetic strategy, conducted the experiments described herein, prepared the supporting data, and participated in writing the manuscript.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
ABNO	9-azabicyclo[3.3.1]nonane *N*-oxyl
Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
Anth	anthracene
APCI	atmospheric-pressure chemical ionization
aq	aqueous
atm	atmosphere(s)
bipy	2,2'-bipyridine
BMEA	bis(2-methoxyethyl)amine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
c	concentration of sample for measurement of optical rotation

^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
cf.	consult or compare to (Latin: *confer*)
cis	on the same side
cm^{-1}	wavenumber(s)
CO	carbon monoxide
conv.	conversion
COSY	homonuclear correlation spectroscopy
CSA	camphor sulfonic acid
Δ	heat or difference
δ	chemical shift in ppm
d	doublet
d	deutero or dextrorotatory
D	deuterium
DBB	4,4'-di-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBNap	2,6-di-*tert*-butylnaphthalene
DCB	dichlorobenzene

DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de novo	starting from the beginning; anew
DIBAL	diisobutylaluminum hydride
DMA	*N,N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
E^+	electrophile
E	*trans* (entgegen) olefin geometry
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
ent	enantiomer of
epi	epimeric
equiv	equivalent(s)

ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
FTIR	fourier transform infrared spectroscopy
Fur	furyl
g	gram(s)
h	hour(s)
^{1}H	proton
[H]	reduction
HFIP	hexafluoroisopropanol
HG-II	Hoveyda–Grubbs' catalyst™ 2nd generation
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
$h\upsilon$	irradiation with light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	hertz
i.e.	that is (Latin: *id est*)
iso	isomeric
in situ	in the reaction mixture

J	coupling constant in Hz
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter
l	levorotatory
LCMS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
m	multiplet or meter(s)
M	molar or molecular ion
m	*meta*
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
MeCN	acetonitrile
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl

Ms	methanesulfonyl (mesyl)
MS	molecular sieves
m/z	mass-to-charge ratio
Nap	naphthalene
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
ND	not determined
Nf	nonafluorobutanesulfonyl
nm	nanometer(s)
nM	nanomolar
NMI	1-methylimidazole
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	*ortho*
[O]	oxidation
n-Oct	octyl or *norm*-octyl
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution

PhH	benzene
PhMe	toluene
PIDA	[bis(acetoxy)iodo]benzene
PIFA	[bis(trifluoroacetoxy)iodo]benzene
Pin	pinacol
pK_a	acid dissociation constant
pm	picometer(s)
PMB	*para*-methoxybenzyl
PNap	2-phenylnaphthalene
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
Pyr	pyridine
q	quartet
quant.	quantitative
R	generic (alkyl) group
R_L	large group
R	rectus
RCM	ring-closing metathesis
recry.	recrystallization

ref	reference
R_f	retention factor
rgt.	Reagent
rr	regioisomeric ratio
rt	room temperature
RyR	ryanodine receptor
s	singlet or seconds
S	sinister
SAR	structure-activity relationship
sat.	saturated
SFC	supercritical fluid chromatography
t	triplet
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBABr	tetra-*n*-butylammonium bromide
TBACl	tetra-*n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBP	4,4'-thiobis(6-*tert*-butyl-3-methylphenol)
TBS	*tert*-butyldimethylsilyl
temp	temperature
TEACl	tetraethylammonium chloride

TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidine
TOF	time-of-flight
Tol	tolyl
trans	on the opposite side
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
vide infra	see below
w/v	weight per volume
X	anionic ligand or halide
xs	excess
Z	*cis* (zusammen) olefin geometry

Chapter 1

An Introduction to Ryanoid and Isoryanoid Diterpenes

1.1 INTRODUCTION

Naturally occurring terpenes and their derivatives remain a rich source of biologically active small molecules, with a diverse array of properties as imparted by their unique and nonmodular structures. Since its discovery nearly 70 years ago, the ryanoid diterpene (+)-ryanodine (**1**) has provoked significant interest and research efforts dedicated toward understanding its structure, biological activity, and chemical synthesis. Almost three decades were required to elucidate its complex and highly caged structure, which has since captivated the attention of synthetic chemists for over half a century. The challenge presented by the ryanoid diterpenes is only matched by their cousin family, hitherto referred to as the *iso*ryanoid diterpenes (**4**-**6**). While less attention has been given to the isoryanoids, their isomeric framework and oxidation state present a distinct synthetic challenge and rich ground for new candidate ligands to the RyR. The following

introductory chapter will summarize the isolation, structure, and biological activity of these two diterpene families, and highlight the different approaches directed toward the total synthesis of these highly oxygenated, polycyclic natural products.

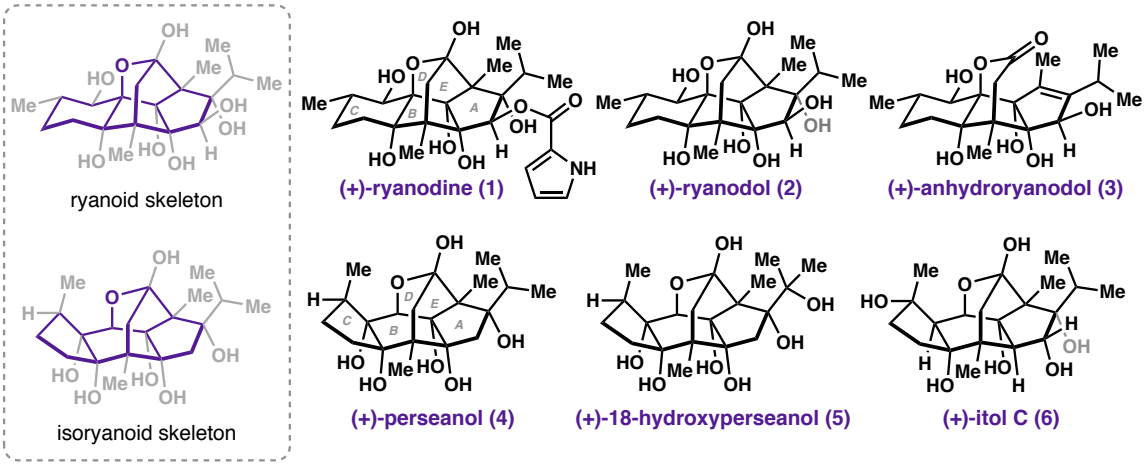


Figure 1. *The ryanoid and isoryanoid diterpenes.*

1.2 OVERVIEW OF RYANOID DITERPENES

Extracts from the genus *Ryania* have long been of interest due to their biological activity in both insects and humans.[1] Historically, these extracts had been utilized as arrowhead poisons in Central and South America. While first used as a toxicant for mammals, *Ryania* later became recognized as a potent insecticide, particularly effective against corn borer, codling moth, other lepidopterous insects, and pests of stored food.[2] Questions surrounding its detailed metabolism and environmental fate drove an underlying interest in determining the constituent responsible for the extracts' activity. Consequently, Folkers and coworkers isolated a unique diterpenoid from the stem and root material of the South American tropical shrub *Ryania speciosa* Vahl in 1948. Continuous extraction with wet chloroform, followed by repeated recrystallizations from

diethyl ether afforded pure (+)-ryanodine (**1**), a compound that exhibited insecticidal potency 700 times greater than the crude extracts alone.[3] Although a molecular formula was provided in the original report, the limited physical data obtained at the time did not permit a full structural assignment.

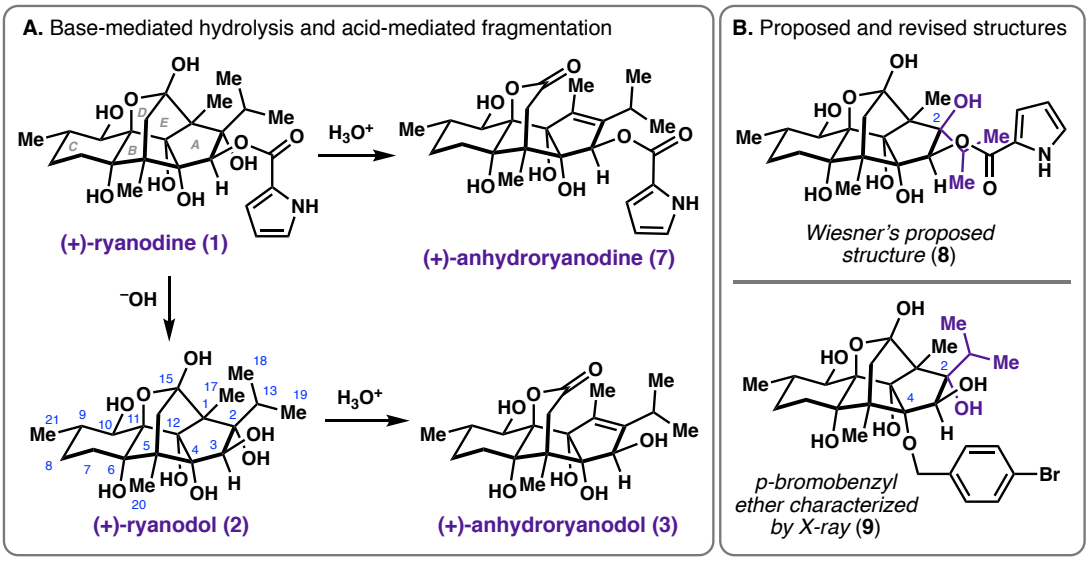


Figure 2. *Degradation studies leading to the structural elucidation of ryanodine.*

Subsequent work spanning nearly three decades by Wiesner and coworkers finally established the complex molecular structure of ryanodine in an impressive example of structure elucidation by chemical degradation.[4-10] Driving their structural analysis were two key observations on its reactivity (Figure 2): (1) ryanodine undergoes basic hydrolysis to liberate one equivalent of pyrrole-2-carboxylic acid and ryanodol (**2**), its deacylated congener; and (2) both ryanodine and ryanodol succumb to a Grob-like fragmentation under acidic conditions, resulting in the respective tetracyclic products, termed anhydroryanodine (**7**) and anhydroryanodol (**3**). These exhaustive studies combined enabled Wiesner and coworkers to propose that ryanodine possesses the structure shown in Figure 2 (**8**), harboring an isopropyl group on the convex face of the

molecule. A subsequent X-ray crystal structure of the C4 *para*-bromobenzyl ether derivative of ryanodol (**9**) was obtained in 1968 by Srivastava and Przybylska that corroborated all major structural features of Wiesner's assignment with a minor revision of the C2-stereocenter, instead placing the isopropyl group in the concave AE-ring pocket of the molecule.[11-12]

Both the ryanoid carbon numbering system and the ring-lettering conventions are illustrated in Figure 2. Of the five rings within its polycyclic system, the D-ring is the only heterocyclic one with an oxygen atom, while the remaining ABCE-rings are all carbocyclic in nature. Viewed from a structural standpoint, ryanodol exhibits a highly caged and functionalized pentacyclic core, containing 11 contiguous stereocenters (two are all-carbon quaternary centers) and seven free hydroxyl groups, one of which is part of an acidic hemiketal. Of these, the C3 alcohol bearing the pyrrole-2-carboxylate ester in ryanodine (**1**) is sterically encumbered within the concave AE ring system. The oxygenation of the molecule is largely distributed on one face of the ring system, thus discriminating the two faces of the molecule as hydrophilic and hydrophobic. Amphoteric in nature, ryanodol (**2**) is soluble in both organic solvents and highly soluble in water, and attempts to extract **2** from an aqueous solution require continuous extraction with refluxing chloroform over several days.[3, 8, 13]

Since the initial discovery of ryanodine, a diverse array of ryanoid-type natural products have been isolated and characterized, not only from the genus *Ryania*,[14-19] but also from the genera *Cinnamomum*,[20-25] *Spigelia*,[26-27] and *Persea*[28-30] (Figure 3). The new molecular entities isolated vary substantially in both substitution and oxidation level along the molecular periphery, providing a large family of ryanoids with a wide range of

biological activities. Of note, isolation from certain genera tend to lack the pyrrole-2-carboxylate ester that is necessary for bioactivity in mammals, such as the C3-deoxy natural products cinnzeylanol (**10**) and cinnzeylanine (**11**) from *Cinnamomum*,[31-32] and the C3-epimeric natural product 3-*epi*-ryanodol (**13**) from *Persea*.[33]

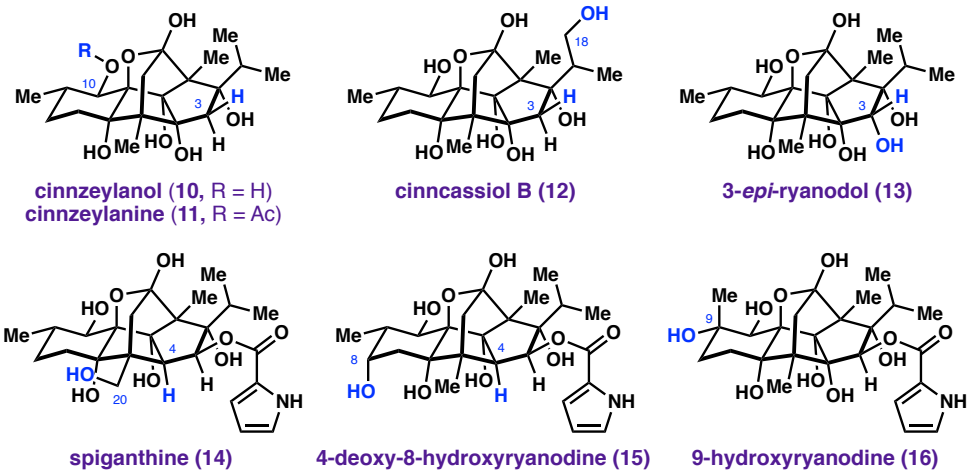


Figure 3. *Structural diversity in the ryanoid diterpene family.*

1.3 BIOLOGICAL ACTIVITY AND RYANODINE RECEPTORS

Although first noted for its potent insecticidal activity, (+)-ryanodine (**1**) bears historical significance as the namesake to the ryanodine receptors (RyR), a group of intracellular calcium ion channels present in skeletal muscle, cardiac muscle, as well as the brain.[34-35] Ryanodine potently binds to RyRs with exceptionally high affinity; interestingly, at nanomolar concentrations, **1** locks RyRs in a half-open sub-conductance state,[36] whereas at higher concentrations, ryanodine causes closure of the ion channels leading to muscular contractions in both mammals and insects.[37] Capitalizing on this potent affinity, radiolabeled [^{3}H]-ryanodine was first used as a tag for the purification and

characterization of the RyR, and has subsequently proven to be an indispensable tool in investigating the functional aspects of these proteins.[34, 38-40]

In mammalian cells, these proteins exist in three different isoforms (termed RyR1, RyR2, and RyR3) with varying distribution dependent on the tissue type, and play a critical role in signal transduction, thus mediating both our movement and cognitive function.[41-42] Mutations of RyRs are associated with numerous genetic diseases including central core disease,[43] malignant hyperthermia,[44] and catecholaminergic polymorphic ventricular tachycardia (CPVT).[45] Furthermore, leaky hippocampal RyR2 channels have been demonstrated to contribute to stress-induced cognitive dysfunction,[46] and altered expression of RyR2 and RyR3 have been implicated in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease.[47-48] Given the potential of these proteins to serve as therapeutic targets for a wide range of different diseases, including heart disease and neurodegenerative disorder, further investigation into their structure, function, and mechanism is warranted.[49-52]

To establish important structural features for biological activity and to prepare experimentally useful analogues, significant *semi*synthetic research has been dedicated to understanding the key structure-activity relationships (SAR) in the ryanoids.[35] Collectively, the data suggest that the pyrrole-2-carboxylate ester moiety is critical for high binding affinity in mammals, and is the major orienting factor in binding to the RyRs.[53-54] Thus the deacylated compound ryanodol (**2**) binds to mammalian RyRs with significantly lower affinity; however, recent data has revealed that **2** still induces a subconductance state and has been reported to be an effective reversible probe of RyR-mediated Ca^{2+} release in cells.[55-56] More recently, chemical modifications of the

molecular periphery have impressively demonstrated the ability to achieve binding selectivity amongst RyR isoforms.[57-58] Notwithstanding these data, the number and location of binding sites, the precise nature of the protein-ligand complex, and the molecular mechanism of channel modulation have not yet been fully determined.[55] However, point mutation studies suggest that ryanodine modulates Ca^{2+} ion gating not through blocking of the pore, but likely through an allosteric binding site.[59] Despite these extensive studies, the structure of ryanoid analogues prepared and studied have been limited by the available chemistry for ryanodine/ryanodol modification and degradation. Further insight into these important ion channels will require the development of a concise, efficient, and modular *de novo* approach to these diterpenes. Such a feat would enable SAR studies that have been limited in scope by existing synthetic routes.

1.4 OVERVIEW OF ISORYANOID DITERPENES

In their continued studies on the fractions exhibiting anti-complement activity of the water extracts from *Cinnamomi cortex*, Nohara and coworkers isolated and elucidated the structures of the first isoryanoid diterpenes, (+)-cinncassiol D_1 (**17**) and its glucoside, in 1980.[60] X-ray analysis of the monoacetyl monobrosylate **18** (generated in 2 steps from **17**) provided the isolation team unambiguous confirmation of their structural assignment first deduced from a series of spectral data. At the time, the framework was recognized as a "new skeleton" comprising "novel type diterpenes," yet the discovery of the larger diterpene family would not occur until further analysis of the extracts from the genus *Persea* revealed the presence of three additional related diterpenes perseanol (**4**), vignaticol (**19**), and indicol (**20**) in 1997 (Figure 4).[61]

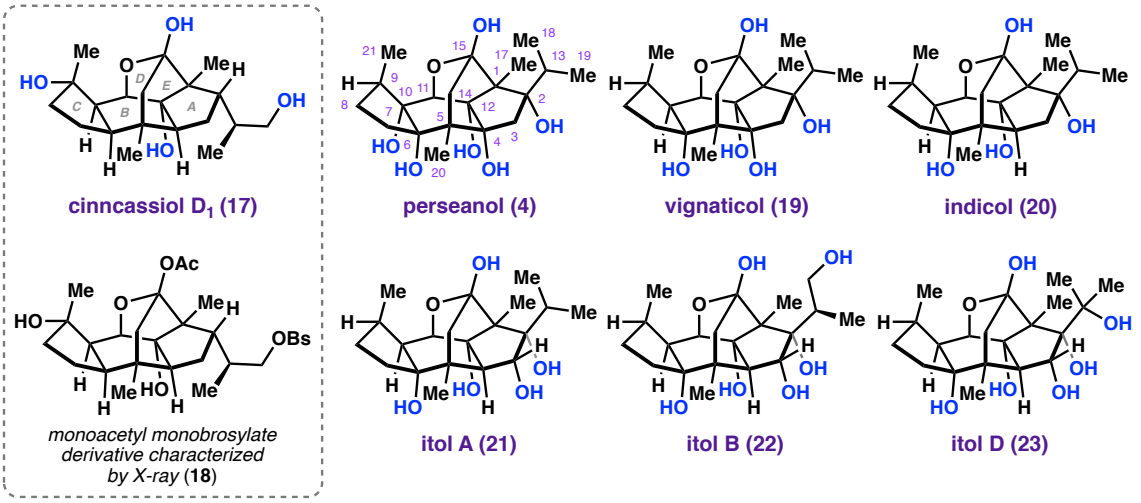


Figure 4. *The isoryanoid diterpenes.*

All three diterpenes possess the same skeleton as **17** but varying levels of peripheral oxidation and thus a family was established, termed the *isoryanodane* diterpenes by Fraga and coworkers. Since the isolation of these hallmark members of the isoryanoid family, several different research groups[62-65] have isolated new molecular entities possessing unique oxidation patterns (e.g. **21**-**23**); interestingly, structurally rearranged isolates have also been characterized, primarily resulting from C1–C2,[66-67] C1–C15,[66] and C6–C7[68] bond cleavage. Biosynthetically, Zhang and coworkers hypothesize that perseanol (**4**) serves as a precursor to these isoryanoid members via the mechanism illustrated in Figure 5.[67] C1–C2 bond cleavage is presumed to occur through a retro-aldol reaction (**30**→**31**) and a subsequent series of ketalization events would then funnel toward cinncassiol F (**25**). This diversity in skeletal frameworks has imbued the family with a range of different biological activities including anti-complement,[60] antifeedant,[61] anti-allergic,[63] anti-COX2,[64] immunosuppressive,[66] and immunostimulative[67] activity.

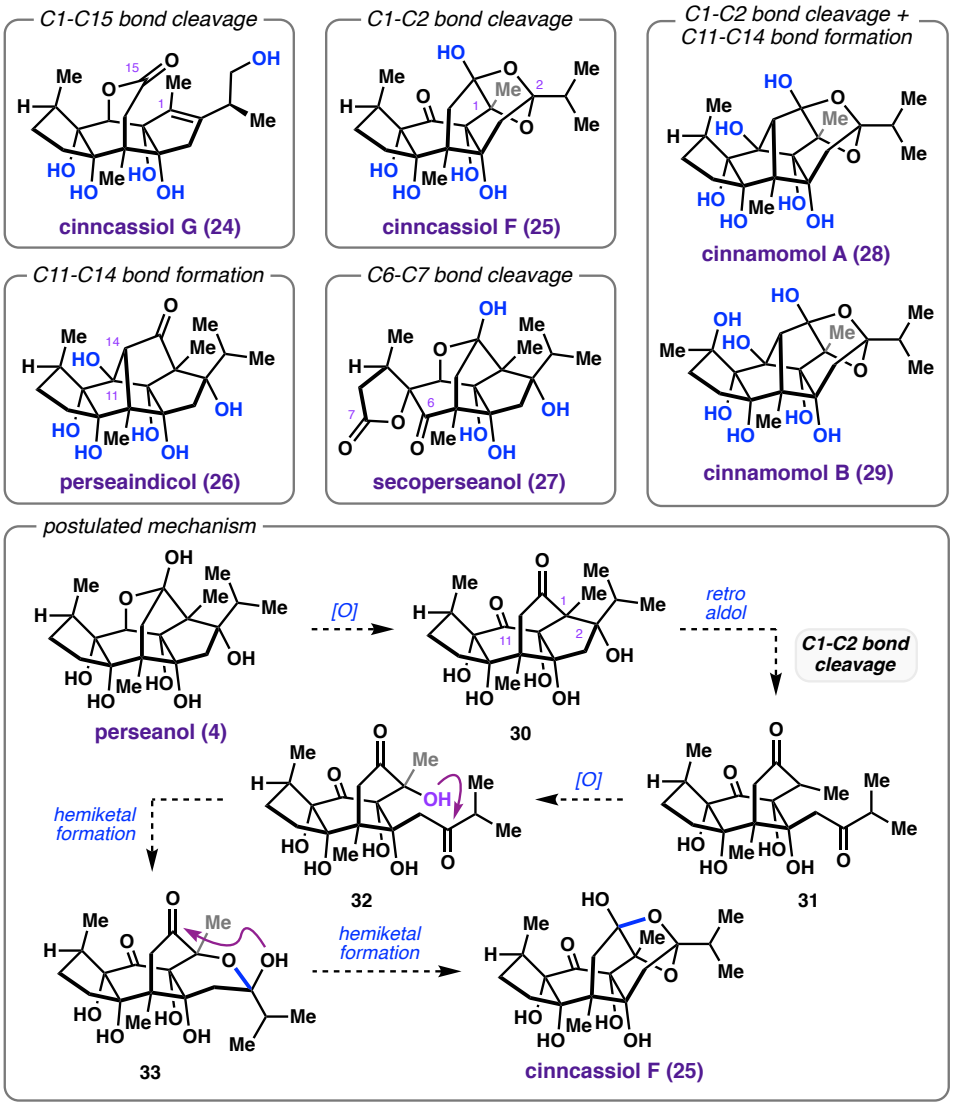


Figure 5. *Structural diversity in the isoryanoid diterpene family.*

While the family continues to grow, several key features have distinguished the isoryanoids from the ryanoid diterpene family (Figure 6). Most notably, the isoryanoids harbor an isomeric 5-6-5 ABC tricyclic core whereas that present in the ryanoids is a distinct 5-5-6 system. The effect of this isomeric system on RyR binding affinity has not been carefully studied as the isoryanoids have not been isolated as their pyrrole-2-carboxylate ester as in (+)-ryanodine (**1**). The absence of this motif is less surprising

given that most of the isoryanoids isolated to date do not harbor oxidation at C3; however, those that do exhibit an epimeric secondary alcohol, as demonstrated by itols A (**21**) and B (**22**).

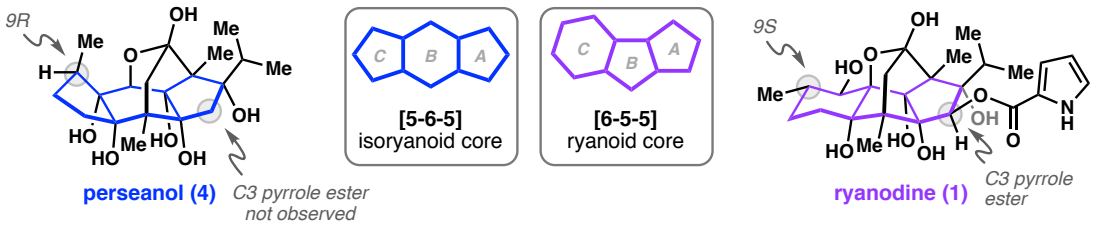


Figure 6. *Critical differences between the ryanoid and isoryanoid diterpenes.*

Notwithstanding this complication, preliminary antifeedant assays by Fraga and coworkers have already deduced that the C10 oxidation state and the polarity of the A-ring are important structural features for bioactivity.[61] Thus in targeting new potential candidate ligands for the RyR based on the isoryanoid scaffold, it appears members of the highest oxidation state would serve as ideal starting points for *de novo* entry into C3 pyrrole-2-carboxylate ester derivatives. Aside from the tantalizing structural complexity of the isoryanoid diterpenes, this goal would be a driving factor for our synthetic studies.

1.5 BIOSYNTHESIS AND BIOSYNTHETIC RELATIONSHIP

Despite the discovery of the ryanoid and isoryanoid diterpenes several decades ago, no studies have been performed to elucidate the biosynthesis of and biosynthetic relationship between the two families. Two prominent hypotheses have been developed and the challenges to validate these hypotheses have been recognized (Figure 7). The first hypothesis was presented by Wiesner and coworkers soon after elucidating the structure of (+)-ryanodine. Breaking critical C–C bonds revealed geranyl geraniol (**34**), drawn suggestively for both the ryanoid and isoryanoid case in Figure 7.[69]

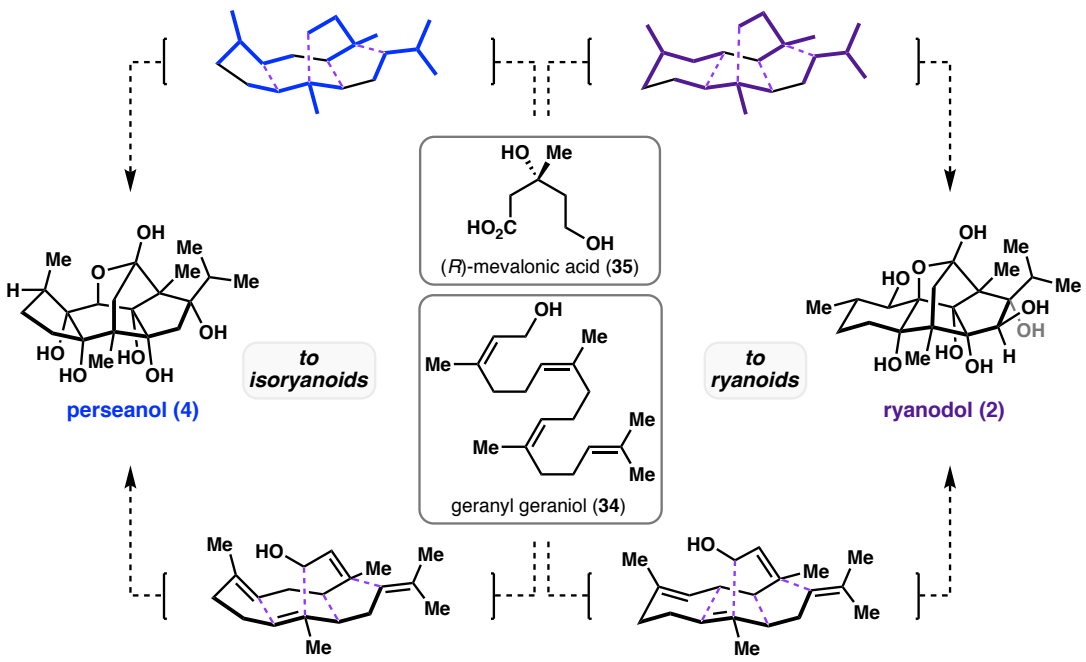
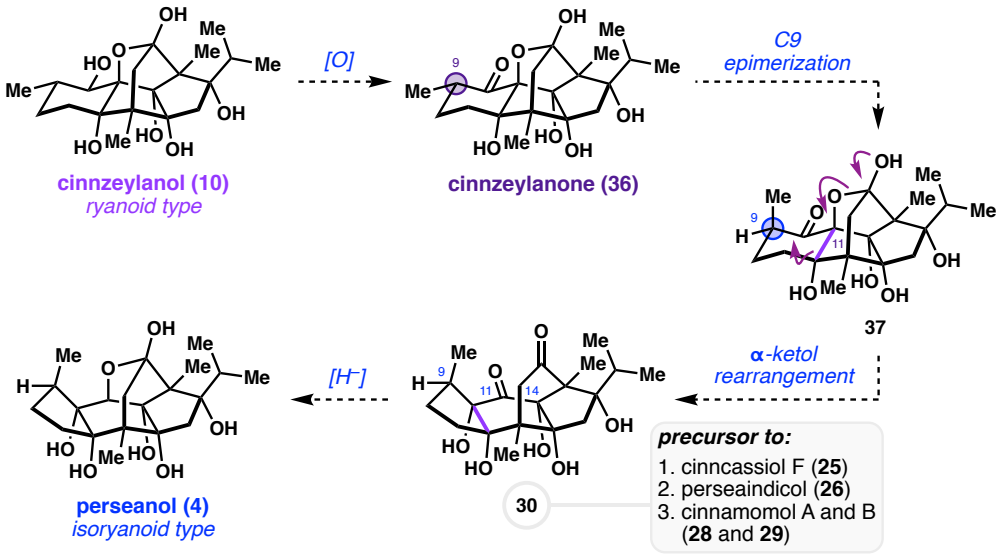


Figure 7. *Biosynthetic hypotheses for the ryanoid and isoryanoid diterpenes.*

The discussion, however, was limited to the identification of a potential terpene precursor, and no postulation was provided on the sequence of bond formation or the mechanism/order of C–H oxidation. Later, upon isolation of the isoryanoid diterpene cinncassiol D_1 (**17**), Nohara and coworkers disclosed a second hypothesis that proceeded through stitching of several units of (*R*)-mevalonic acid (**35**).[62] Yet again, the discussion was limited to the identification of building blocks for the carbon core, with no hypotheses on the oxidase phase of biosynthesis.

The discovery of the isoryanoid diterpenes raises the question of the biosynthetic relationship between the two families. No hypothesis has been made or reported in the literature to the best of our knowledge; however, a plausible relationship can be drawn (Scheme 1). We postulate that the ryanoid diterpenes serve as the precursor to the isoryanoid diterpenes, and thus begin with the ryanoid diterpene cinnzeylanol (**10**).



Scheme 1. *A hypothetical biosynthetic relationship.*

Enzymatic oxidation leads to cinnzeylanone (**36**), a natural ryanoid-type metabolite isolated by Fraga and coworkers in 1996.[29] The C10 ketone enables an epimerization event to generate the correct 9*S* stereochemistry present in the isoryanoid diterpenes. Interestingly, no C9*S* ryanoid diterpenes have been isolated to date (unless oxidized as in 9-hydroxyryanodine, or **16**). Thus the *syn*-pentane interaction between the C9 methyl group and the C11 alcohol may potentially render the proposed subsequent α-ketol rearrangement (**37**→**30**) a thermodynamically downhill process. Critically, this formal 1,2-shift invokes a conformational change that places the C9 methyl group in an equatorial position (confirmed by X-ray structures) in the isoryanoid framework. As a testament to the possibility of the intermediacy of **30** en route to the isoryanoid diterpene perseanol (**4**), Fraga and coworkers recently isolated perseaindicol (**26**), a product of aldol ring closure, to forge the C11–C14 bond from **30**.[68] Intermediate **30** has additionally been proposed to serve as an intermediate en route to cinncassiol F and the cinnamomols (as described in Figure 4).[66-67] A simple chemoselective reduction of the C11 ketone,

occurring from the convex face of the ABCE ring system, would then generate the hemiketal present in the isoryanoid diterpenes and produce perseanol (**4**). While no studies have been performed to confirm this hypothesis, the intermediates proposed herein have seemingly given rise to several different isolated isoryanoid diterpenes.

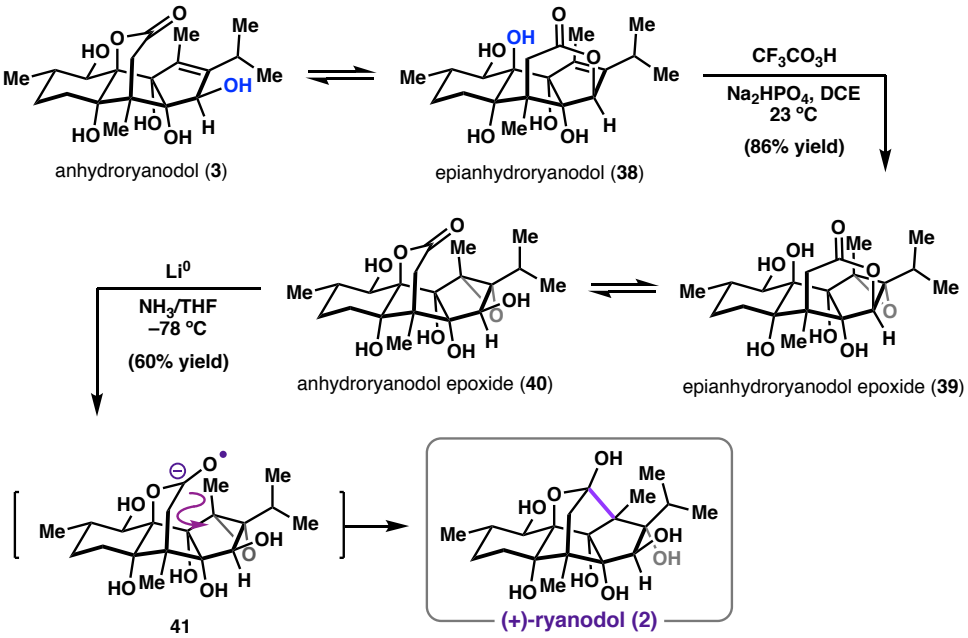
1.6 PRIOR TOTAL SYNTHESES OF (+)-RYANODOL

1.6.1 *Deslongchamps' Total Synthesis of (+)-Ryanodol*

Despite the fact that ryanodine was first isolated over 60 years ago, there were only two completed total syntheses of ryanodol (**2**) prior to our engagement with the complex diterpene. In 1979, Deslongchamps and coworkers reported the first total synthesis of (+)-ryanodol.[13, 70-73] Ready access to natural (+)-ryanodol enabled the team to rapidly assess their synthetic endgame strategy: specifically, it was conceived that the primary degradation product, anhydroryanodol (**3**), could be reconverted to ryanodol (**2**) via the appropriate oxidation/reduction sequence. These relay studies on anhydroryanodol (**3**) obtained from natural sources permitted the establishment of several key, late-stage processes that proved essential for the identification of suitable reaction conditions (Scheme 2).

Although attempts to functionalize the C1–C2 olefin of anhydroryanodol proved unfruitful, epianhydroryanodol (**38**), an isomer resulting from translactonization, was noted to succumb to epoxidation. Leveraging this difference in reactivity between the two lactone isomers, it was established that by employing trifluoroperacetic acid under phosphate buffered conditions, equilibration to **38** could *precede* oxidation, providing direct access to epianhydroryanodol epoxide (**39**). As with anhydroryanodol, epoxide **39**

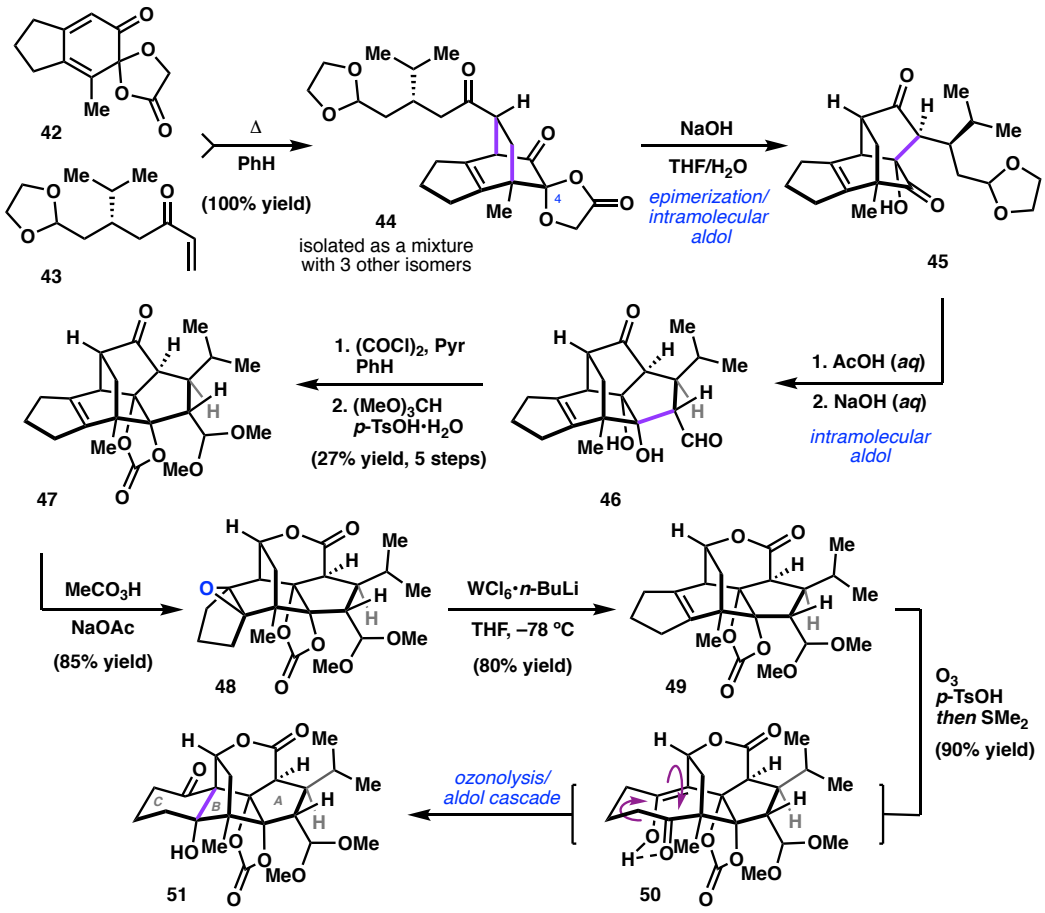
readily equilibrates to anhydroryanodol epoxide (**40**) under basic conditions. As a result, subjection of either epoxide to Li(0) in NH_3 at –78 ºC effected an intramolecular, reductive cyclization to provide ryanodol with a 60% isolated yield. Productive cyclization chemistry is believed to occur from the ketyl anion (**41**) derived from anhydroryanodol epoxide (**40**), whereas premature reduction of epianhydroryanodol epoxide (**39**) results in the generation of carbonyl-reduction side products.[13]



Scheme 2. *Relay studies by Deslongchamps: anhydroryanodol to ryanodol.*

In tandem with these relay studies assessing the viability of the late-stage conversion of **3** to **2** were synthetic efforts aimed at the chemical synthesis of anhydroryanodol (Scheme 3). The synthesis commenced with a Diels-Alder cycloaddition between *rac*-spirolactone **42** and enone **43**, derived from (*S*)-carvone, which proceeds in quantitative yield to provide a mixture of diastereomeric Diels-Alder adducts (**44**). Recognizing that cleavage of the spirolactone under basic conditions results in ablation of the C4-stereocenter, the isomeric mixture obtained from the Diels-Alder

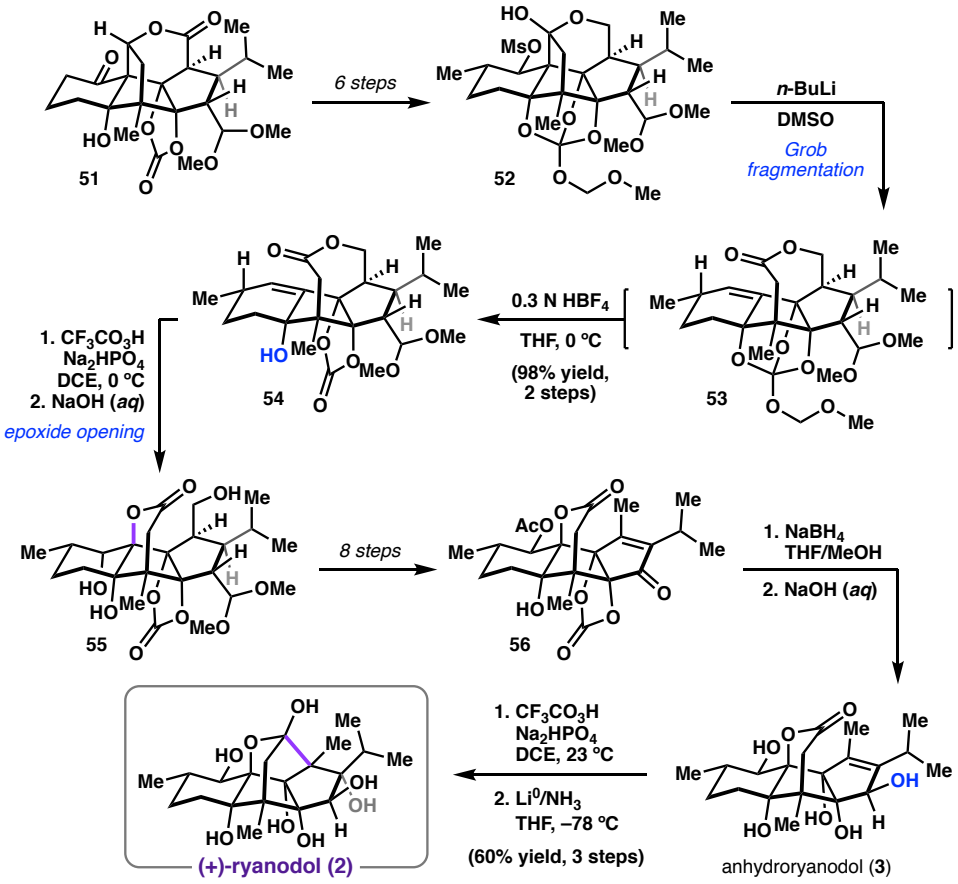
reaction (**44**) was treated with aqueous sodium hydroxide to induce a diastereoconvergent, epimerization/aldol cascade, affording ketone **45**.



Scheme 3. *Sequential aldol cyclization to forge ABC tricyclic core of ryanodol.*

Hydrolysis of the dioxolane moiety was followed by basification to affect an additional intramolecular aldol reaction, affording pentacyclic aldehyde **46**. Protection of the 1,2-diol and aldehyde moieties generated carbonate **47**, which was further elaborated via (1) Baeyer-Villiger oxidation and (2) tungsten-mediated epoxide reduction to olefin **49**. Subjection of **49** to ozonolytic conditions with an acidic workup effected an intramolecular aldol to forge the necessary 5-5-6 ABC tricyclic ring system of ryanodol.

With the ABC tricyclic framework in place, functional group manipulations were performed to generate mesylate **52**, which cleanly underwent Grob fragmentation by use of dimsyllithium in DMSO. Hydrolysis of the orthocarbonate protecting group with aqueous tetrafluoroboric acid was followed by treatment with trifluoroperacetic acid under buffered conditions to induce epoxidation of the lone C10–C11 alkene.

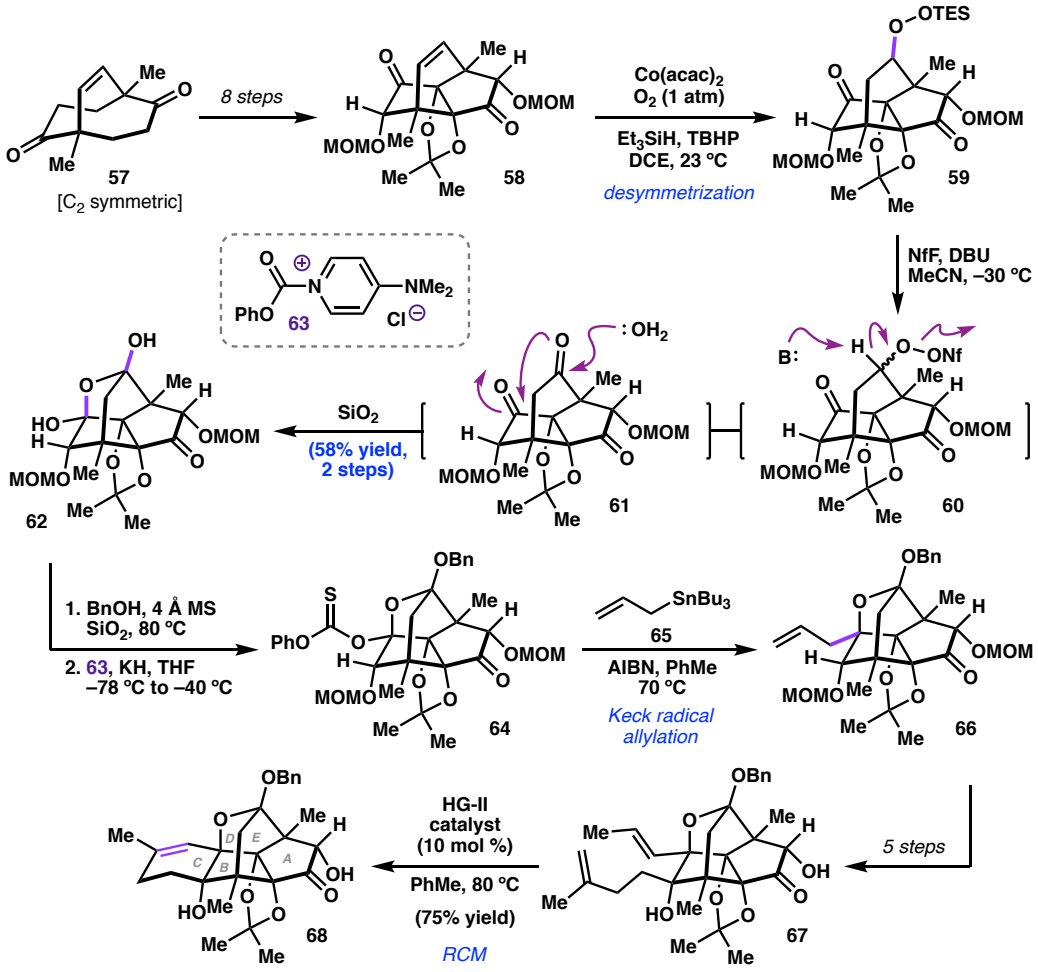


Scheme 4. *The first total synthesis of ryanodol by Deslongchamps (1979).*

Saponification of the seven-membered lactone resulted in epoxide opening, thereby forming the tetracyclic framework of anhydroryanodol (**55**). Subsequent functional group adjustments and removal of the protecting groups provided (+)-anhydroryanodol (**3**) in a total of 35 steps (LLS), and the conversion to (+)-ryanodol (**2**) was achieved by epoxidation and reductive cyclization as established in their relay protocol.

1.6.2 *Inoue's Total Synthesis of (+)-Ryanodol and (+)-Ryanodine*

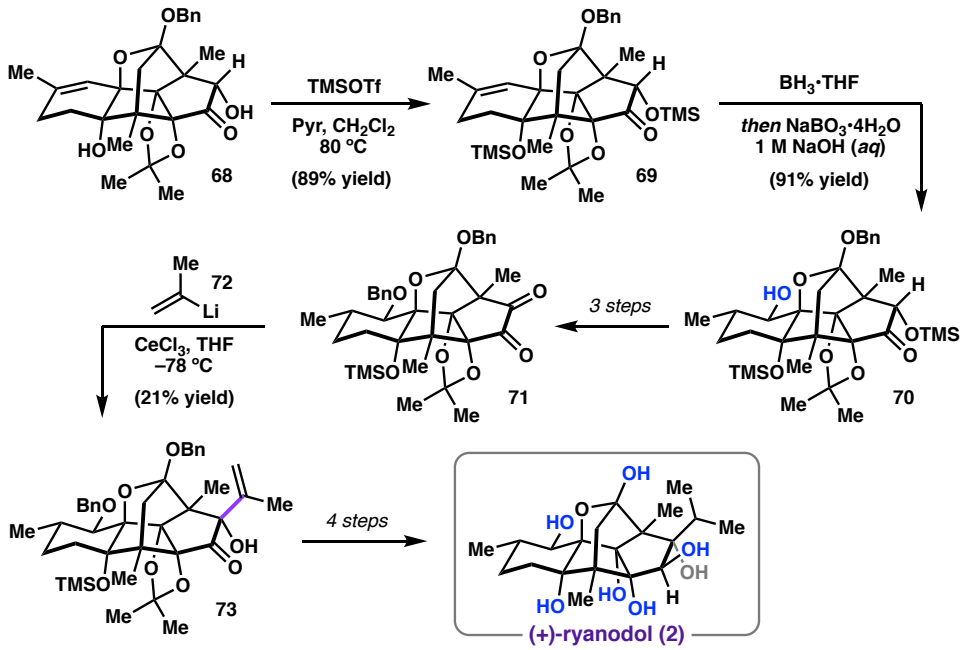
In 2014, Inoue and coworkers completed the second total synthesis of (+)-ryanodol, capitalizing on latent C_2-symmetry embedded within ryanodol's pentacyclic core, a feature that was first detailed by Sieburth and coworkers in 1994 (*vide infra*).[33, 74] The C_2-symmetric building block **58**, harboring the functionalized ABE-ryanodol ring system, was prepared in 14 steps from commercially available starting materials.[75-77]



Scheme 5. *Inoue's construction of the ryanodol pentacyclic ring system.*

Treatment of **58** with $Co(acac)_2$, Et_3SiH, and catalytic TBHP under an atmosphere of O_2 resulted in desymmetrization by a Mukaiyama peroxysilylation.[78] A Kornblum-

DeLaMare rearrangement was then effected with TES-protected peroxide **59** by treatment with NfF and DBU to provide triketone **61**, that spontaneously hydrates upon contact with silica gel to generate hemiketal **62**. Protection of the C15-hemiketal as its benzyl ketal was followed by generation of a thiocarbonate at the C11-hemiketal (**64**) to provide a handle for the generation of an oxygen-stabilized, bridgehead carbon-based radical. Leveraging this radical, a Keck radical allyation was thereafter performed with allyltributylstannane (**65**) to effect C-allylation.

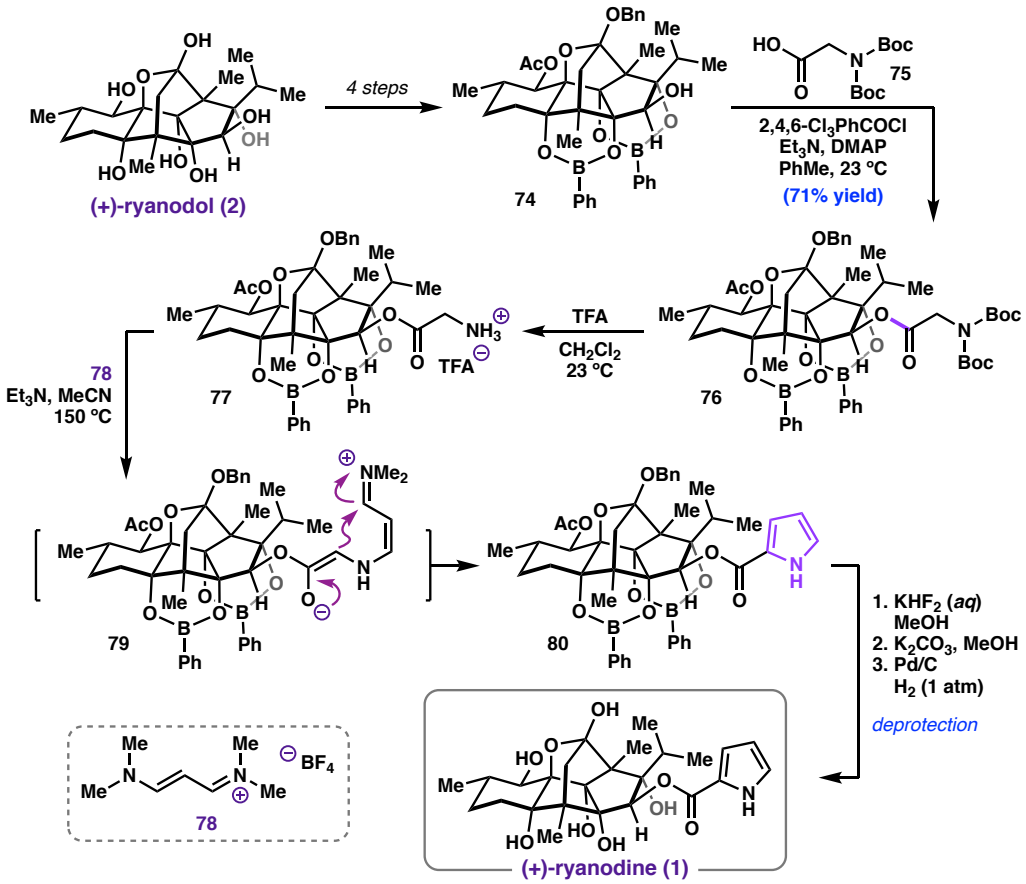


Scheme 6. *Total synthesis of ryanodol by Inoue.*

Construction of the ryanodol C-ring was subsequently realized in a 6-step sequence via installation of two tethered alkenes and a ring-closing metathesis reaction utilizing the 2nd generation Hoveyda-Grubbs catalyst, thereby completing the preparation of the full pentacyclic ryanoid ring system (**68**). A series of functional group manipulations then provided 1,2-diketone **71**, which underwent a chemoselective 1,2-addition reaction with 2-propenyllithium (**72**) to install the final three-carbon unit in 21%

yield. An additional four synthetic steps enabled the removal of the necessary protecting groups to finally provide (+)-ryanodol in a total of 35 steps (LLS).

Completion of the hydrolysis product **2** prompted Inoue and coworkers to next focus on its conversion to (+)-ryanodine (**1**).[79] Early attempts by Deslongchamps and coworkers had previously demonstrated that the steric hindrance of the C3 alcohol prohibited selective acylation of the free polyol, instead favoring reactivity at the more accessible C10 secondary alcohol.[13, 70]



Scheme 7. *Inoue's 10-step conversion of ryanodol to ryanodine.*

In 2016, Inoue successfully demonstrated the conversion of (+)-ryanodol to (+)-ryanodine by employing a carefully orchestrated protecting group strategy. In the event, having effectively protected the polyol system to only expose the sterically encumbered

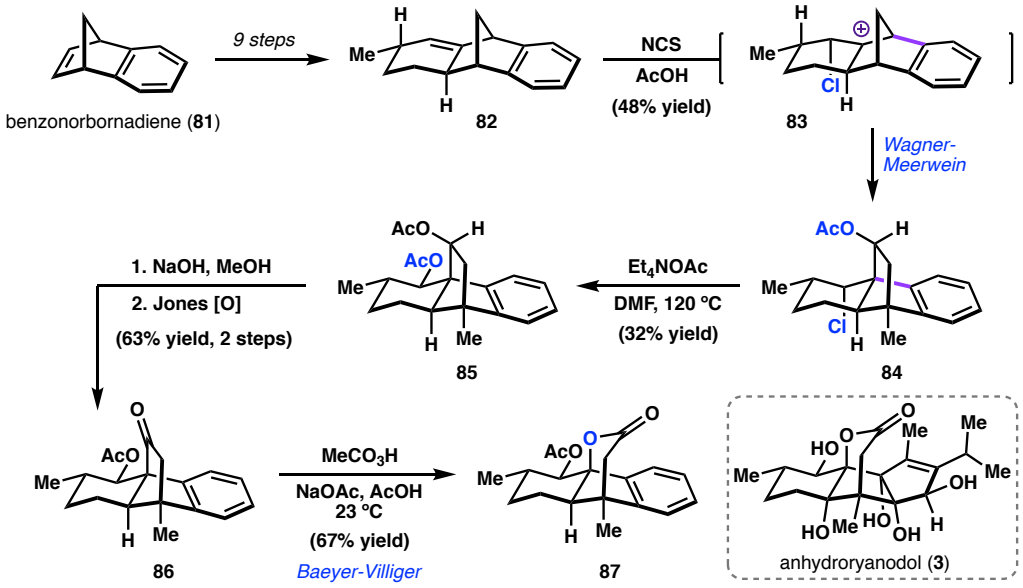
C3 alcohol, the team was able to realize conditions to acylate the free alcohol with a glycine derivative (**75**) under Yamaguchi esterification conditions. Success in this regard was followed by Boc deprotection to generate aminium salt **77**, which was then engaged with vinamidinium salt **78** at elevated temperatures under microwave irradiation to induce cyclocondensation and reveal the C3 pyrrole-2-carboxylate ester. Completion of the synthesis was achieved following a 3-step series of deprotection manipulations. The implementation of this study subsequently informed the choice of protecting groups necessary to intercept previously described synthetic intermediates in their prior total synthesis of (+)-ryanodol, thus enabling the first chemical synthesis of (+)-ryanodine. The synthetic route to (+)-ryanodine proceeds in 42 steps from commercially available starting materials.[80-81]

1.7 PRIOR EFFORTS TOWARD RYANOID DITERPENES

Although the Deslongchamps and Inoue approaches outlined in the previous section constituted the only two completed total syntheses reported prior to our own work in this arena, the pursuit of ryanodol and the related natural products has been the emphasis of a number of publications and dissertations[82-84] since the disclosure of its complex polycyclic structure. Together, these reports have established the viability of new and creative synthetic strategies for the preparation of simplified model fragments that map on to the pentacyclic framework of ryanodol. While the studies below have not led to successful syntheses of the title compound, they prove instructive in the design of synthetic work in this arena.

1.7.1 *Wiesner's Approach toward Anhydroryanodol*

Wiesner and coworkers published an early report of a model system toward the anhydroryanodol framework in 1972 (Scheme 8), utilizing a chloronium-triggered rearrangement to build the BCD-ring system.[85] While the team did not originally have intentions of pursuing a total synthesis, the versatility of the synthetic methods developed in their diterpenoid alkaloid program prompted them to pursue model studies.

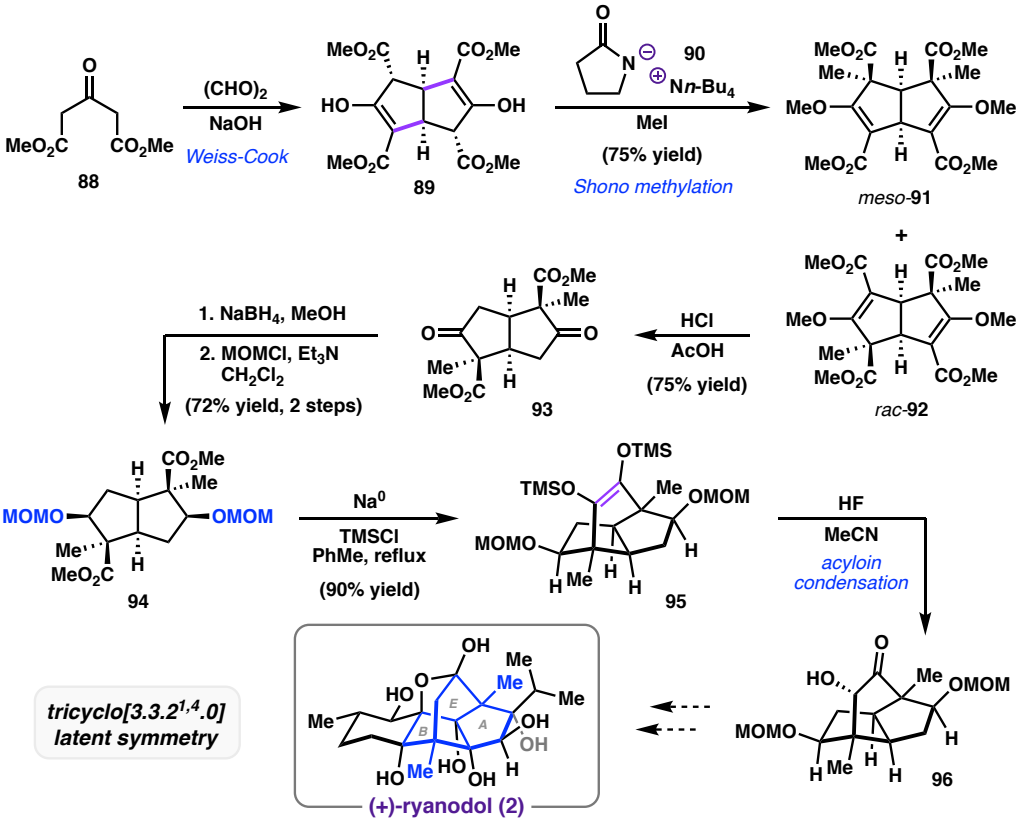


Scheme 8. *Wiesner's Wagner-Meerwein approach to anhydroryanodol.*

Commencing from benzonorbornadiene (**81**), tetracyclic olefin **82** was treated with *N*-chlorosuccinimide (NCS) in acetic acid, resulting in a Wagner-Meerwein shift to generate chloroacetate **84**. Selective displacement of the chloride moiety with Et_4NOAc in DMF afforded bisacetate **85**, which was then selectively saponified and subsequently oxidized using Jones reagent to furnish tetracyclic ketone **86**. Baeyer-Villiger oxidation generated the ring-expanded lactone **87**, providing a tetracyclic structure that maps onto the anhydroryanodol BCD-ring system.

1.7.2 *Sieburth's Approach toward Ryanodol*

Inspired by the tricyclo[3.3.2^{1,4}.0]decane ring system present in ryanodol and other complex targets, Sieburth and Santos reported a concise method to access the target structure in 1994 (Scheme 9).[86] These studies were driven by the recognition of latent C_2-symmetry present within the diterpenoid framework, a feature that was capitalized by Inoue and coworkers in their successful synthetic campaign (Scheme 5).



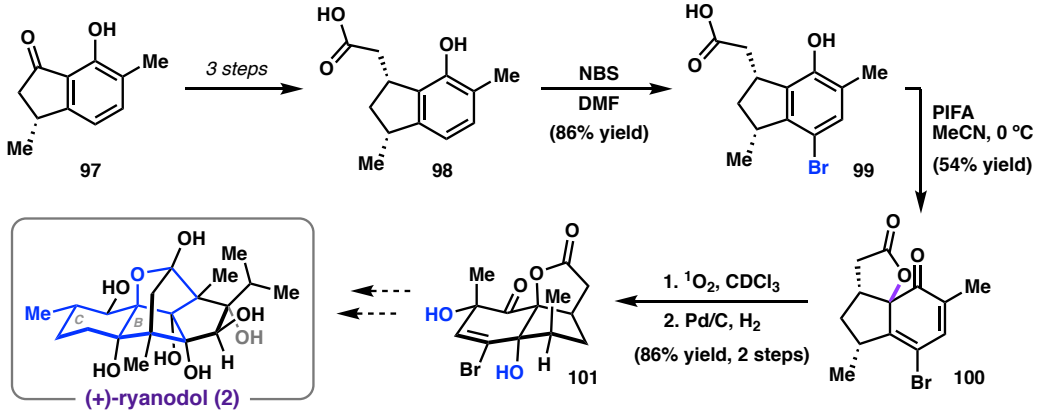
Scheme 9. *Sieburth's symmetry-driven synthesis of ryanodol ABE tricycle.*

Condensation of dimethylacetonedicarboxylate (**88**) with glyoxal resulted in the C_2-symmetric tetraester **89**, which could be methylated under Shono's mild conditions to afford a 1:1 mixture of *meso*- to *rac*-bicycles **91** and **92**. Krapcho decarboxylation under acidic conditions, followed by diastereoselective 1,2-carbonyl reduction and bis-

protection of the product secondary alcohols as their MOM ethers, provided diester **94**. An acyloin condensation employing Na(0) in the presence of TMSCl resulted in bis(trimethylsiloxy)alkene **95**, in the process establishing the ABE-ring system of ryanodol.

1.7.3 *Wood's Approach toward Ryanodol*

Wood and coworkers reported an oxidative dearomatization strategy to access the BC ring system of the ryanodol core in 2003, wherein the tetrahydrofuran ring was envisioned to arise from intramolecular cyclization of a pendant nucleophile onto the *ortho* position of a suitably functionalized phenolic C-ring precursor (Scheme 10).[87]



Scheme 10. *Wood's phenolic oxidation approach to the ryanoid BC ring system.*

To this end, phenol **99**, bearing a *para* bromide as a blocking group, was readily prepared from hydroxyindanone **97**. Oxidative dearomatization using PIFA in acetonitrile afforded the *ortho* dearomatization product, lactone **100**, in 80% yield. While this transformation could be effected without the *para* bromide blocking group (i.e. **98**), significantly lower yields were observed due to the formation of decomposition products arising from nucleophilic trapping with the solvent. Nevertheless, the desired dearomatization product

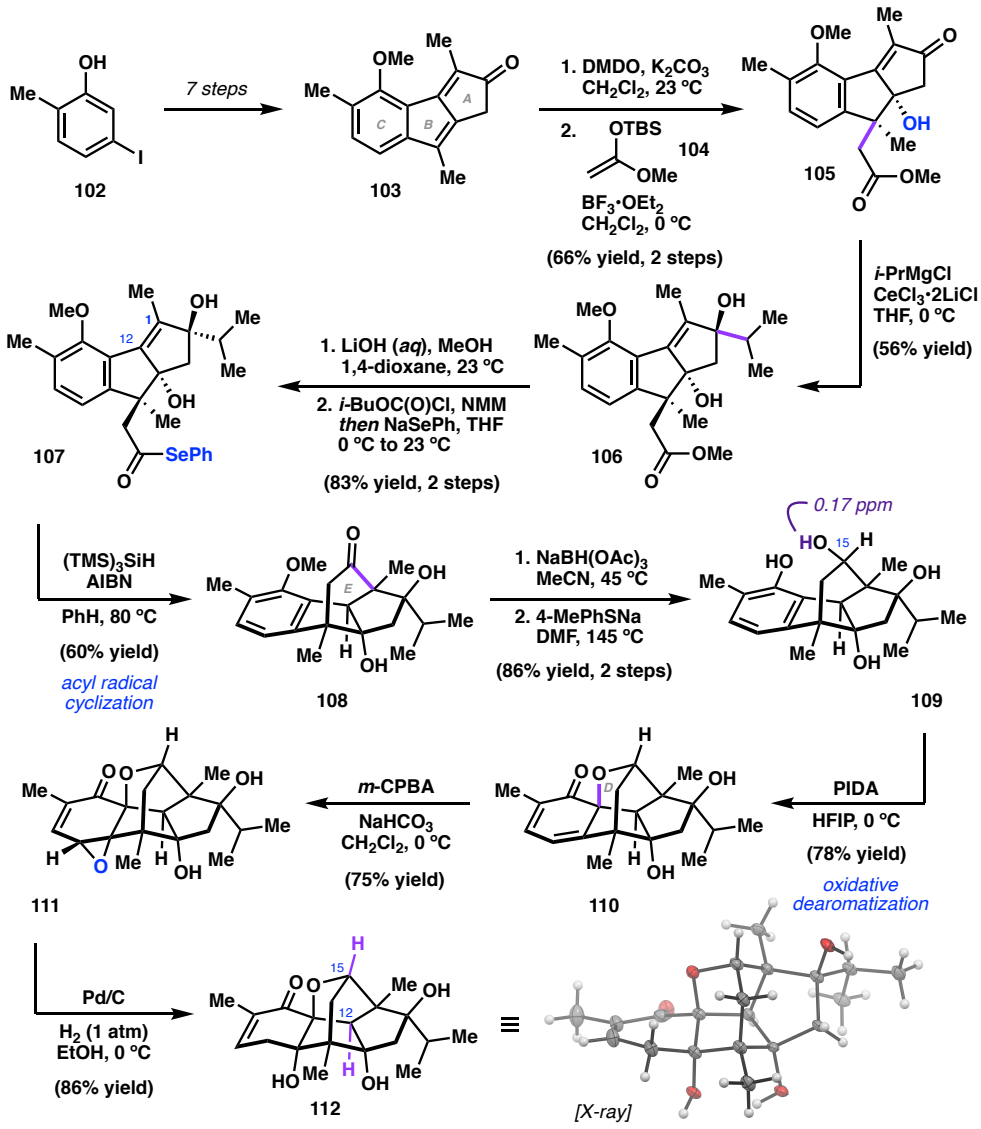
100 was further elaborated via a [4+2] cycloaddition with singlet oxygen to provide an intermediate endoperoxide that was thereafter reduced via Pd-catalyzed hydrogenation to afford the hydroxylated BC ring system (**101**) in 86% yield over the 2 steps.

1.7.4 *Reisman's Phenolic Oxidation Approach to Ryanodol*

These prior studies by Wood and coworkers inspired our own first generation approach toward the hydrolysis product ryanodol (**2**), wherein the oxygen-bridged D-ring was to be prepared through a phenolic oxidative dearomatization at the *ortho* position.[88] To access a model substrate, we began with the preparation of a suitably functionalized ABC tricycle from commercially available 5-iodo-2-methylphenol (**102**). A robust 7-step sequence was developed to provide ample quantities of ABC tricycle **103**. Rapid access to the tricyclic core of ryanodol was enabled by the use of a Co-mediated Pauson-Khand reaction. At this stage, the first of the two key all-carbon quaternary centers was introduced through a two-step protocol involving (1) epoxidation of the more electron rich alkene and (2) Lewis acid-catalyzed epoxide opening with silyl ketene acetal **104**. 1,2-addition of isopropylmagnesium chloride to **105** in the presence of $CeCl_3$•2LiCl[89] next delivered the isopropyl group from the α-face (**106**).

Introduction of the final three carbons of the diterpene framework was followed by conversion of the methyl ester to its acyl selenide **107**. Treatment of **107** with $(TMS)_3SiH$ and AIBN resulted in acyl radical cyclization to provide tetracyclic ketone **108**. Notably the isomeric product resulting from radical addition to C12 was *not* observed; this product is likely disfavored because of the strain associated with a *trans*-fused 5-5 ring system. Tetracycle **108** was advanced to oxidative dearomatization

substrate **109** by $NaBH(OAc)_3$ reduction of the C15 ketone and nucleophilic demethylation of the phenol. When exposed to $PhI(OAc)_2$ in hexafluoro-2-propanol (HFIP), **109** underwent clean formation of the desired *ortho*-oxidative dearomatization product **110** bearing the complete pentacyclic ryanoid carbon skeleton.



Scheme 11. *Reisman's phenolic oxidation approach to ryanodol.*

Hydroxyl-directed epoxidation with *m*-CPBA, followed by hydrogenolysis of the allylic epoxide afforded **112** (its structure unambiguously verified by X-ray crystallography).

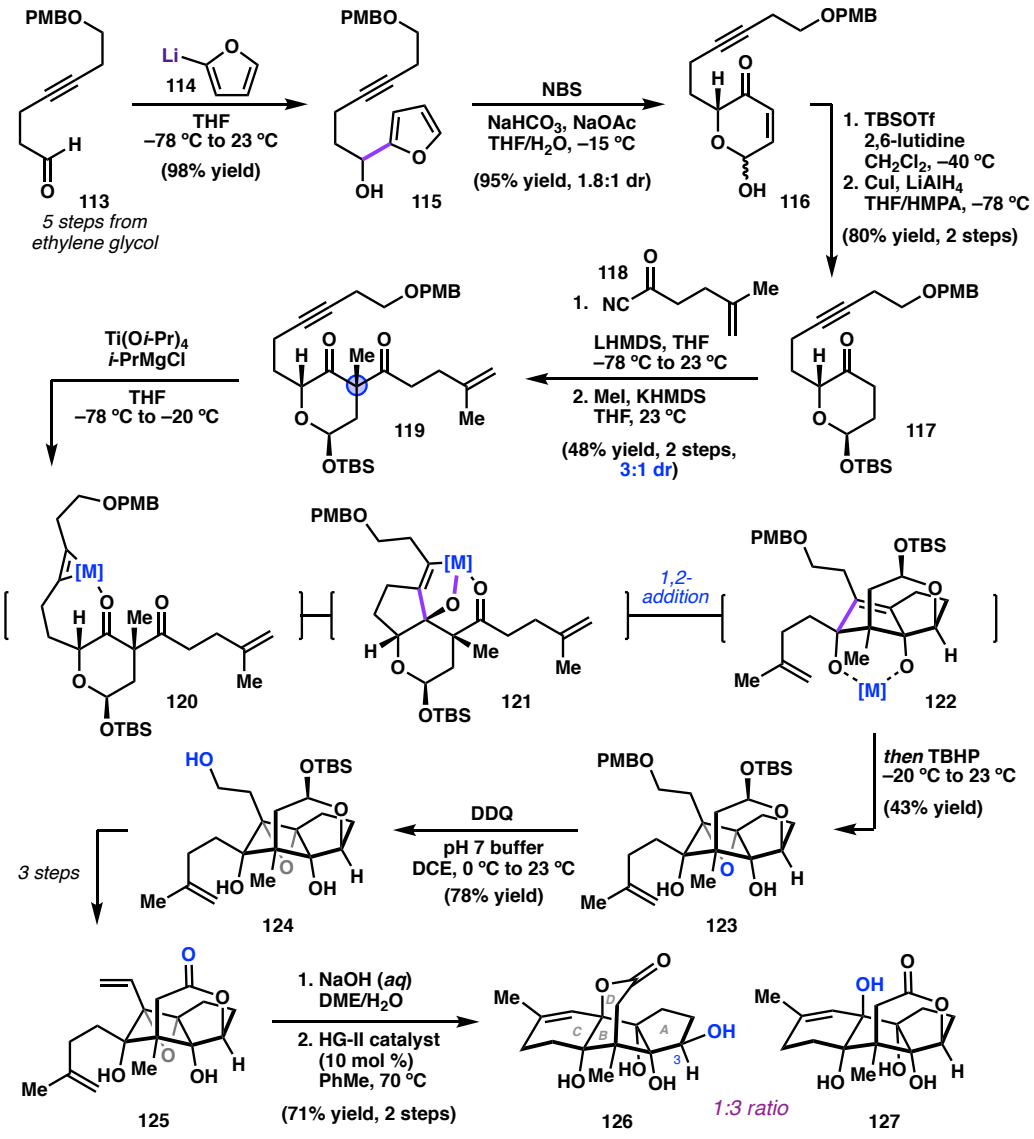
While unable to introduce the requisite oxidation at C12 and C15 for a total synthesis of ryanodol (**2**) using this approach, the information gleaned from these synthetic studies heavily guided our successful synthesis reported in 2016.

1.7.5 *Micalizio's Approach Toward Ryanodol*

The complex structure of ryanodol still continues to fascinate synthetic chemists today; very recently, Micalizio and coworkers reported a conceptually distinct approach toward the tetracyclic ABCD ring system present in ryanodol through the development of a Ti-mediated diketone-alkyne cascade annulation reaction (Scheme 12).[90] To test their methodology,[91] aldehyde **113** was first engaged with 2-lithio-furan (**114**) to generate furyl alcohol **115**. Treatment of **115** with NBS under buffered conditions induced an Achmatowicz rearrangement to generate dihydropyan **116**. Protection of the free alcohol as its TBS ether and Cu–H mediated 1,4-reduction then furnished **117**, which in turn was subjected to two sequential α-alkylations thus providing cascade substrate diketone-alkyne **119**.

In the event, when **119** was exposed to Ti(O*i*-Pr)$_4$ and *i*-PrMgCl, the Kulinkovich reaction ensued thereby producing metallacyclopropene **120**. Subsequent carbonyl addition afforded the highly functionalized oxametallacyclopentene **121**, which furthermore underwent an additional C–C bond forming event through a nucleophilic addition to afford complexed diol **122**. The latter step is presumed to be facilitated by the coordination of the distal carbonyl oxygen to the metal center. Leveraging metal-bound intermediate **122**, the team realized that the addition of TBHP at this stage could induce a final hydroxyl-directed epoxidation event to access epoxydiol **123** in 1 step from **119** in

43% yield. Impressively, the cascade reaction generated 2 new C–C bonds, 2 new rings, and installed 3 critical oxidation states from a simple precursor.



Scheme 12. *A metallacycle-mediated diketone-alkyne annulation strategy.*

To address the installation of the C-ring, the PMB group of **123** was deprotected and the product alcohol **124** was thereafter dehydrated using Grieco's selenoxide elimination. Oxidation of the hemiacetal through TBS deprotection and Ley oxidation then enabled an epoxide opening event triggered by alkaline hydrolysis of the lactone

ring. Leveraging information gleaned from the Inoue synthesis, the team completed the preparation of the anhydroryanodol framework (**126**, 18 steps) via a ring-closing metathesis. Attempts to oxidize the free C3 alcohol of tetraol **126** at this stage were reported to instead induce oxidative cleavage of the 1,2-diol. Addressing the unfunctionalized A-ring of **126** to complete a synthesis of ryanodol (**2**) will therefore require the development of a suitable protecting group scheme.

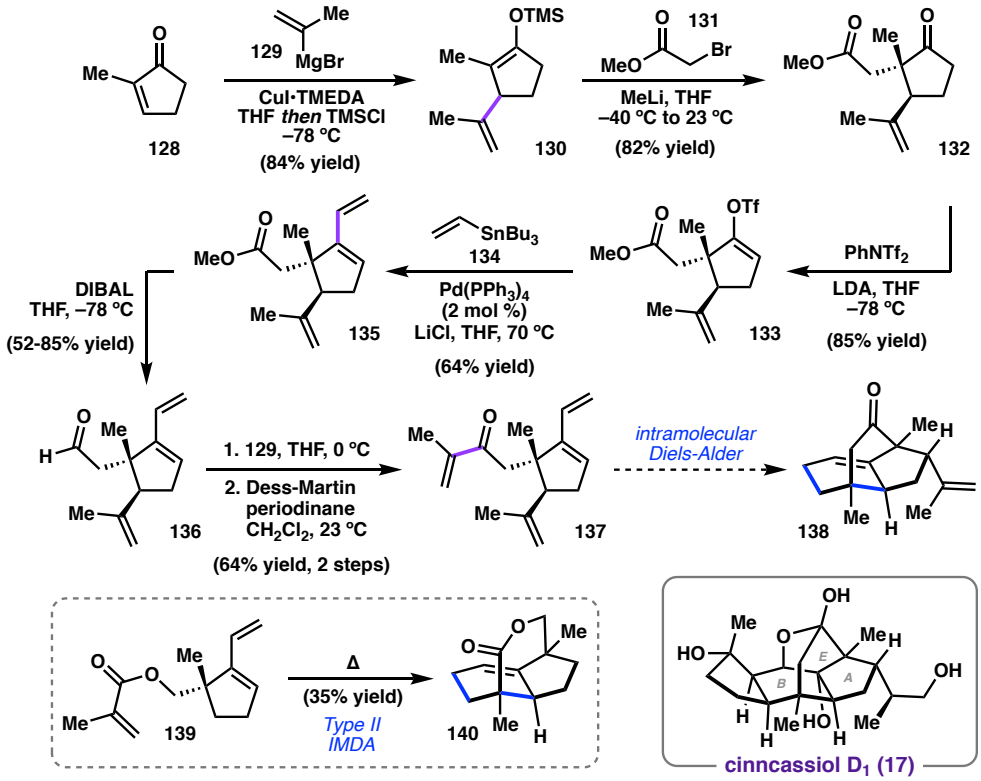
1.8 PRIOR EFFORTS TOWARD ISORYANOID DITERPENES

Less synthetic attention has been given to the isoryanoid diterpenes, and to date, no member of the family has succumbed to chemical synthesis. Two synthetic studies have been reported since their discovery, which already reveal the distinct challenges posed by the isomeric framework. The discussion of these synthetic approaches, along with our own synthetic work, will hopefully convey that efficient and concise access to the isoryanoid diterpenes demands its own unique solution.

1.8.1 *Ensley's Approach toward Cinncassiol D_1*

Prior to the coinage of the term "isoryanodane," Ensley and coworkers were drawn to the intricate structure presented by cinncassiol D_1, the first isolated member of the isoryanoid diterpene family, and elected to pursue a synthetic campaign.[92] Given the lower oxidation state of the central B-ring, their structural analysis focused on formation of the requisite C–C bonds to generate the isoryanoid framework. A type II intramolecular Diels-Alder (IMDA) reaction was sought to give rise to the central 6-membered B-ring (Scheme 13). Model studies had validated the key disconnection with

vinylic ester **139**, which succumbed to a [4+2] cycloaddition under thermal conditions. This precedent led them to access a functionalized system with the isopropyl group in place. In this vein, commercially available 2-methyl-2-cyclopenten-1-one (**128**) was first subjected to 1,4-addition conditions with isopropenylmagnesium bromide (**129**) to generate **130** after quenching the reaction mixture with TMSCl.



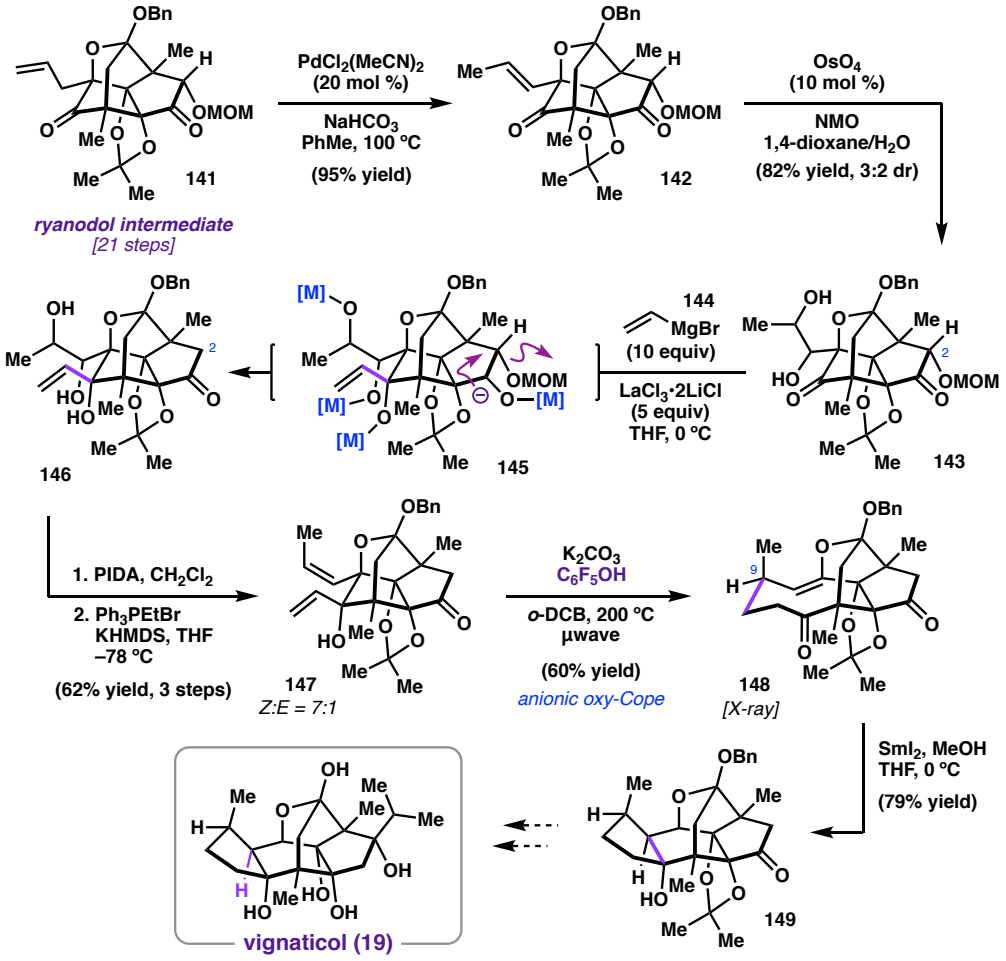
Scheme 13. *Ensley's IMDA approach to the isoryanoid diterpene cinncassiol D*$_1$.

The enol ether was deprotected with MeLi and trapped out with bromomethyl acetate (**131**) furnishing ketoester **132**. Triflation and Stille cross-coupling next provided the diene unit of the IMDA substrate. **135** was thereafter converted to dienophile **137** following a 3-step sequence. Unfortunately, under thermal conditions advanced model substrate **137** did not undergo the desired IMDA and was reported to give a complex reaction mixture which contained mostly starting material." Although a minor peak at 6

ppm was observed and hypothesized to potentially indicate the generation of **138**, further studies to validate the observation were not performed.

1.8.2 *Inoue's Approach to the Isoryanoid Diterpenes*

Recognizing the similarity between the ryanoid and isoryanoid core structure, Inoue and coworkers elected to pursue a divergent strategy and leverage an elaborated intermediate in their (+)-ryanodol route (Scheme 14).[93] Such a strategy would have to appropriately tackle the isomeric framework and the different C9 stereochemistry presented by the isoryanoid diterpenes.



Scheme 14. *Inoue's synthetic approach toward the isoryanoid diterpenes.*

To address this issue, tetracycle **141** was first subjected to alkene isomerization with catalytic $PdCl_2(MeCN)_2$. Unable to access the requisite *Z*-isomer that was necessary to address the C9 stereocenter, the alkene was oxidized with catalytic OsO_4 to generate diol **143** as a 3:2 mixture of diastereomers. At this juncture, **143** was exposed to an excess of vinylmagnesium bromide (**144**) to effect 1,2-addition into the C6 ketone. Unfortunately, clean C–C bond formation with the Grignard addition required the addition of an excess of the reagent due to competitive α-elimination at the C3 ketone, producing alcohol **146**. Undeterred by this result, glycol cleavage was induced with $PhI(OAc)_2$ and the product aldehyde was then engaged in a Wittig olefination with the ylide generated from Ph_3PEtBr to furnish *Z*-alkene isomer **147**.

Exposing the 1,5-diene **147** with microwave irradiation at elevated temperatures in the presence of K_2CO_3 and pentafluorophenol (C_6F_5OH) as an additive (the nucleophilic additive was noted to be imperative to trap out 3-chlorobenzyne generated from the elimination of HCl from *o*-DCB at these elevated temperatures) induced an anionic oxy-cope rearrangement, revealing ketone **148** harboring the correct C9 stereocenter. Finally, subjection of **148** to SmI_2 and MeOH as a protic additive led to efficient ketyl anion-mediated transannular cyclization to forge the isoryanoid pentacyclic framework (**149**). Interestingly, treatment of the same cyclization substrate **148** with Bu_3SnH and AIBN instead led to clean conversion to the ryanoid pentacyclic framework through a 6-*endo*-cyclization (with respect to C-ring formation). This divergence in reactivity was attributed to mechanistic differences between the conditions, a hypothesis that was corroborated by DFT calculations.

At 28 steps from commercially available starting materials, Inoue's synthetic approach provides insight into a potential biosynthetic relationship between the ryanoid and isoryanoid diterpenes; however, the oxidation pattern presented by late-stage intermediate **149** does not provide a straightforward pathway to any isoryanoid member isolated to date. These preliminary studies suggest that the structure of the isoryanoid diterpenes warrant innovation of a unique *de novo* route tailored to the isomeric ring system.

1.9 CONCLUDING REMARKS

Together, the ryanoid and isoryanoid diterpene natural products possess a unique subset of highly oxidized frameworks and oxidation patterns. Several outstanding questions surrounding these diterpenes remain that can uniquely be addressed through *de novo* synthesis. These questions combined with the complexity presented by their highly oxidized polycyclic structures motivated us to engage in synthetic studies to prepare these diterpenes through chemical synthesis. These synthetic studies will be discussed in detail in the following two chapters. Efficient access to these natural products remains an important goal in the field of total synthesis and stands as an important test in the current state-of-the-art of C–H oxidation technology.

1.10 NOTES AND REFERENCES

(1) Crosby, D. G. *Naturally Occurring Insecticides*. Marcel Dekker: New York, 1971.

(2) Jefferies, P. R.; Casida, J. E. Ryanoid Chemistry and Action. In *Natural and Engineered Pest Management Agents*, Hedin, P. A.; Menn, J. J.; Hollingworth, R. M., Eds. 1994; Vol. 551, p 130.

(3) Rogers, E. F.; Koniuszy, F. R.; Shavel, J.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 3086.

(4) Kelly, R. B.; Whittingham, D. J.; Wiesner, K. *Can. J. Chem.* **1951**, *29*, 905.

(5) Babin, D. R.; Findlay, J. A.; Forrest, T. P.; Fried, F.; Gotz, M.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett.* **1960**, 31.

(6) Valenta, Z.; Wiesner, K.; Babin, D. R.; Bogri, T.; Forrest, T. P.; Fried, F.; Reinshag, H. *Experientia* **1962**, *18*, 111.

(7) Babin, D. R.; Forrest, T. P.; Valenta, Z.; Wiesner, K. *Experientia* **1962**, *18*, 549.

(8) Babin, D. R. The Structures of Delphinine and Neline; Ryanodine. University of New Brunswick, 1962.

(9) Wiesner, K.; Valenta, Z.; Findlay, J. A. *Tetrahedron Lett.* **1967**, *8*, 221.

(10) Wiesner, K. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2656.

(11) Srivastava, S. N.; Przyblyska, M. *Can. J. Chem.* **1968**, *46*, 795.

(12) Srivastava, S. N.; Przybylska, M. *Acta Cryst.* **1970**, *26*, 707.

(13) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 186.

(14) Waterhouse, A. L.; Holden, I.; Casida, J. E. *J. Chem. Soc., Chem. Commun.* **1984**, 1265.

(15) Jefferies, P. R.; Toia, R. F.; Casida, J. E. *J. Nat. Prod.* **1991**, *54*, 1147.

(16) Jefferies, P. R.; Toia, R. F.; Brannigan, B.; Pessah, I.; Casida, J. E. *J. Agric. Food Chem.* **1992**, *40*, 142.

(17) Ruest, L.; Dodier, M. *Can. J. Chem.* **1996**, *74*, 2424.

(18) Ruest, L.; Berthelette, C.; Dodier, M.; Dube, L.; St-Martin, D. *Can. J. Chem.* **1999**, *77*, 12.

(19) Ruest, L.; Dodier, M.; De Seve, H.; Lessard, C.; Mongrain, P. *Can. J. Chem.* **2002**, *80*, 483.

(20) Nohara, T.; Tokubuchi, N.; Kuroiwa, M.; Nishioka, I. *Chem. Pharm. Bull.* **1980**, *28*, 2682.

(21) Yagi, A.; Tokubuchi, N.; Nohara, T.; Nonaka, G.; Nishioka, I.; Koda, A. *Chem. Pharm. Bull.* **1980**, *28*, 1432.

(22) Nohara, T.; Nishioka, I.; Tokubuchi, N.; Miyahara, K.; Kawasaki, T. *Chem. Pharm. Bull.* **1980**, *28*, 1969.

(23) Kashiwada, Y.; Nohara, T.; Tomimatsu, T.; Nishioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 2686.

(24) Nohara, T.; Kashiwada, Y.; Tomimatsu, T.; Nishioka, I. *Phytochemistry* **1982**, *21*, 2130.

(25) Nohara, T.; Kashiwada, Y.; Nishioka, I. *Phytochemistry* **1985**, *24*, 1849.

(26) Achenbach, H.; Hübner, H.; Vierling, W.; Brandt, W.; Reiter, M. *J. Nat. Prod.* **1995**, *58*, 1092.

(27) Hübner, H.; Vierling, W.; Brandt, W.; Reiter, M.; Achenbach, H. *Phytochemistry* **2001**, *57*, 285.

(28) Gonzalez-Coloma, A.; Hernandez, M. G.; Perales, A.; Fraga, B. M. *J. Chem. Ecol.* **1990**, *16*, 2723.

(29) Gonzalez-Coloma, A.; Terrero, D.; Perales, A.; Escoubas, P.; Fraga, B. M. *J. Agric. Food. Chem.* **1996**, *44*, 296.

(30) Fraga, B. M.; Terrero, D.; Gutierrez, C.; Gonzalez-Coloma, A. *Phytochemistry* **2001**, *56*, 315.

(31) Isogai, A.; Suzuki, A.; Tamura, S.; Murakoshi, S.; Ohashi, Y.; Sasada, Y. *Agric. Biol. Chem.* **1976**, *40*, 2305.

(32) Isogai, A.; Murakoshi, S.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1977**, *41*, 1779.

(33) Koshimizu, M.; Nagatomo, M.; Inoue, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 2493.

(34) Sutko, J. L.; Thompson, L. J.; Schlatterer, R. G.; Lattanzio, F. A.; Fairhurst, A. S.; Campbell, C.; Martin, S. F.; Deslongchamps, P.; Ruest, L.; Taylor, D. R. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 215.

(35) Sutko, J. L.; Airey, J. A.; Welch, W.; Ruest, L. *Pharmacol. Rev.* **1997**, *49*, 53.

(36) Rousseau, E.; Smith, J. S.; Meissner, G. *Am. J. Physiol.* **1987**, *253*, C364.

(37) Meissner, G. *Annu. Rev. Physiol.* **1994**, *56*, 485.

(38) Lattanzio, F. A.; Walterskhan, H.; Schlatterer, R. G.; Thompson, L. J.; Sutko, J. L. *Biophysical Journal* **1985**, *47*, A450.

(39) Pessah, I. N.; Waterhouse, A. L.; Casida, J. E. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 449.

(40) Lai, F. A.; Erickson, H. P.; Rousseau, E.; Liu, Q. Y.; Meissner, G. *Nature* **1988**, *331*, 315.

(41) Lanner, J. T.; Georgiou, D. K.; Joshi, A. D.; Hamilton, S. L. *Cold Spring Harb. Perspect. Biol.* **2010**, *2*.

(42) Kimlicka, L.; Van Petegem, F. *Science China Life Sciences* **2011**, *54*, 712.

(43) Wu, S. W.; Ibarra, C. A.; Malicdan, M. C. V.; Murayama, K.; Ichihara, Y.; Kikuchi, H.; Nonaka, I.; Noguchi, S.; Hayashi, Y. K.; Nishino, I. *Brain* **2006**, *129*, 1470.

(44) Rosenberg, H.; Davis, M.; James, D.; Pollock, N.; Stowell, K. *Orphanet J. Rare Dis.* **2007**, *2*.

(45) Wehrens, X. H. T.; Marks, A. R. *Mayo Clinic Proceedings* **2004**, *79*, 1367.

(46) Liu, X. P.; Betzenhauser, M. J.; Reiken, S.; Meli, A. C.; Xie, W. J.; Chen, B. X.; Arancio, O.; Marks, A. R. *Cell* **2012**, *150*, 1055.

(47) D'Adamio, L.; Castillo, P. E. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 14825.

(48) Wu, B.; Yamaguchi, H.; Lai, F. A.; Shen, J. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 15091.

(49) Belevych, A. E.; Terentyev, D.; Gyorke, S. *Novel Therapeutic Targets For Antiarrhythmic Drugs*. John Wiley & Sons, Inc.: Hoboken, NJ, 2010; p 299.

(50) Dulhunty, A. F.; Casarotto, M. G.; Beard, N. A. *Curr. Drug Targets* **2011**, *12*, 709.

(51) Turan, B.; Vassort, G. *Antioxid. Redox Signaling* **2011**, *15*, 1847.

(52) Fauconnier, J.; Roberge, S.; Saint, N.; Lacampagne, A. *Pharmacol. Ther.* **2013**, *138*, 323.

(53) Welch, W.; Ahmad, S.; Airey, J. A.; Gerzon, K.; Humerickhouse, R. A.; Besch, H. R.; Ruest, L.; Deslongchamps, P.; Sutko, J. L. *Biochemistry* **1994**, *33*, 6074.

(54) Welch, W.; Sutko, J. L.; Mitchell, K. E.; Airey, J.; Ruest, L. *Biochemistry* **1996**, *35*, 7165.

(55) Hamilton, S. L.; Serysheva, I. I. *J. Biol. Chem.* **2009**, *284*, 4047.

(56) Ramos-Franco, J.; Gomez, A. M.; Nani, A.; Liu, Y. W.; Copello, J. A.; Fill, M. *Pflugers Archiv.* **2010**, *460*, 767.

(57) Bidasee, K. R.; Besch, H. R.; Gerzon, K.; Humerickhouse, R. A. *Mol. Cell. Biochem.* **1995**, *149*, 145.

(58) Bidasee, K. R.; Xu, L.; Meissner, G.; Besch, H. R. *J. Biol. Chem.* **2003**, *278*, 14237.

(59) Fessenden, J. D.; Chen, L. L.; Wang, Y. M.; Paolini, C.; Franzini-Armstrong, C.; Allen, P. D.; Pessah, I. N. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 2865.

(60) Nohara, T.; Kashiwada, Y.; Tomimatsu, T.; Kido, M.; Tokubuchi, N.; Nishioka, I. *Tetrahedron Lett.* **1980**, *21*, 2647.

(61) Fraga, B. M.; Gonzalez-Coloma, A.; Gutierrez, C.; Terrero, D. *J. Nat. Prod.* **1997**, *60*, 880.

(62) Nohara, T.; Kashiwada, Y.; Murakami, K.; Tomimatsu, T.; Kido, M.; Yagi, A.; Nishioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 2451.

(63) Nohara, T.; Kashiwada, Y.; Tomimatsu, T.; Nishioka, I. *Phytochemistry* **1982**, *21*, 2130.

(64) Chai, X. Y.; Bai, C. C.; Shi, H. M.; Xu, Z. R.; Ren, H. Y.; Li, F. F.; Lu, Y. N.; Song, Y. L.; Tu, P. F. *Tetrahedron* **2008**, *64*, 5743.

(65) Tang, W. W.; Wei, X. Y.; Xu, H. H.; Zeng, D. Q.; Long, L. P. *Fitoterapia* **2009**, *80*, 286.

(66) Zeng, J. F.; Xue, Y. B.; Shu, P. H.; Qian, H. Q.; Sa, R. J.; Xiang, M.; Li, X. N.; Luo, Z. W.; Yao, G. M.; Zhang, Y. H. *J. Nat. Prod.* **2014**, *77*, 1948.

(67) Zhou, L.; Tuo, Y. L.; Hao, Y.; Guo, X. M.; Tang, W.; Xue, Y. B.; Zeng, J. F.; Zhou, Y.; Xiang, M.; Zuo, J. P.; Yao, G. M.; Zhang, Y. H. *Org. Lett.* **2017**, *19*, 3029.

(68) Fraga, B. M.; Terrero, D.; Bolanos, P.; Diaz, C. E. *Tetrahedron Lett.* **2017**, *58*, 2261.

(69) Wiesner, K. *Adv. Org. Chem.* **1972**, *8*, 295.

(70) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; MacLachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1979**, *57*, 3348.

(71) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 115.

(72) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 127.

(73) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 153.

(74) Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, *136*, 5916.

(75) Hagiwara, K.; Himuro, M.; Hirama, M.; Inoue, M. *Tetrahedron Lett.* **2009**, *50*, 1035.

(76) Urabe, D.; Nagatomo, M.; Hagiwara, K.; Masuda, K.; Inoue, M. *Chem. Sci.* **2013**, *4*, 1615.

(77) Hagiwara, K.; Urabe, D.; Inoue, M. *Tetrahedron Lett.* **2014**, *55*, 3817.

(78) Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1305.

(79) Masuda, K.; Nagatomo, M.; Inoue, M. *Chem. Pharm. Bull.* **2016**, *64*, 874.

(80) Nagatomo, M.; Hagiwara, K.; Masuda, K.; Koshimizu, M.; Kawamata, T.; Matsui, Y.; Urabe, D.; Inoue, M. *Chem. Eur. J.* **2016**, *22*, 222.

(81) Masuda, K.; Koshimizu, M.; Nagatomo, M.; Inoue, M. *Chem. Eur. J.* **2016**, *22*, 230.

(82) Wang, B. Photochemistry of 6-Alkenyl-2-Cyclohexenones. Synthetic Studies towards Precursors of Ryanodol. Oregon State University, 1998.

(83) Morales, C. A. Biomimetic Synthesis of (–)-Longithorone A and Synthesis of the Ryanodine Core. Harvard University, 2004.

(84) Graeber, J. K. Studies Toward the Total Synthesis of Ryanodine. Yale University, 2003.

(85) Brownlee, B. G.; Ho, P. T.; Wiesner, K. *Can. J. Chem.* **1972**, *50*, 4013.

(86) Sieburth, S. M.; Santos, E. D. *Tetrahedron Lett.* **1994**, *35*, 8127.

(87) Wood, J. L.; Graeber, J. K.; Njardarson, J. T. *Tetrahedron* **2003**, *59*, 8855.

(88) Xu, C.; Han, A.; Reisman, S. E. *Org. Lett.* **2018**, *20*, 3793.

(89) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

(90) Du, K.; Kier, M. J.; Rheingold, A. L.; Micalizio, G. C. *Org. Lett.* **2018**, *ASAP*.

(91) Kier, M. J.; Leon, R. M.; O'Rourke, N. F.; Rheingold, A. L.; Micalizio, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 12374.

(92) Sheridan, P. G. Toward the Total Synthesis of Cinncassiol D_1, A Novel Biologically Active Diterpene. Tulane University, 2005.

(93) Koshimizu, M.; Nagatomo, M.; Inoue, M. *Tetrahedron* **2018**, *74*, 3384.

Chapter 2

Total Synthesis of (+)-Ryanodine and (+)-20-Deoxyspiganthine[†]

2.1 INTRODUCTION

In 2016, our laboratory reported a concise, 15-step synthesis of (+)-ryanodol from the commercially available terpene building block (*S*)-pulegone. Key to the successful implementation of our synthetic strategy were (1) a Pauson-Khand reaction to rapidly forge the 5-5-6 ABC tricyclic ryanoid core and (2) a SeO_2-mediated Riley oxidation to oxidize the product A-ring. At the time we initiated our synthetic studies, a chemical synthesis of (+)-ryanodine was yet to be realized. As part of a broader program aimed at the development of new probe molecules for RyR function, we sought to translate our synthesis of (+)-ryanodol to a chemical synthesis of (+)-ryanodine. This chapter will describe the fruition of these synthetic efforts that have resulted in an 18 and 19-step

[†] Portions of this chapter have been reproduced from the following communication: Xu, C.; Han, A.; Virgil, S. C.; Reisman, S. E. *ACS Cent. Sci.* **2017**, *3*, 278. The research discussed was completed in collaboration with a postdoctoral scholar in our laboratory, Dr. Chen Xu.

synthesis of (+)-ryanodine and a related natural product (+)-20-deoxyspiganthine, respectively.

2.2 SYNTHETIC CHALLENGES AND PREVIOUS SYNTHETIC EFFORTS

Required for a successful synthesis of (+)-ryanodine (**1**) is the identification of a method to introduce the C3 pyrrole-2-carboxylate ester (Figure 1). While a simple and well-studied transformation that has inspired numerous creative synthetic solutions, closer inspection of the synthetic context reveals several challenges that need to be addressed. Of these challenges, perhaps most transparent is the question of chemoselectivity. In the presence of six free hydroxyl group, the C3 alcohol would require a unique solution to be engaged in a chemoselective fashion.

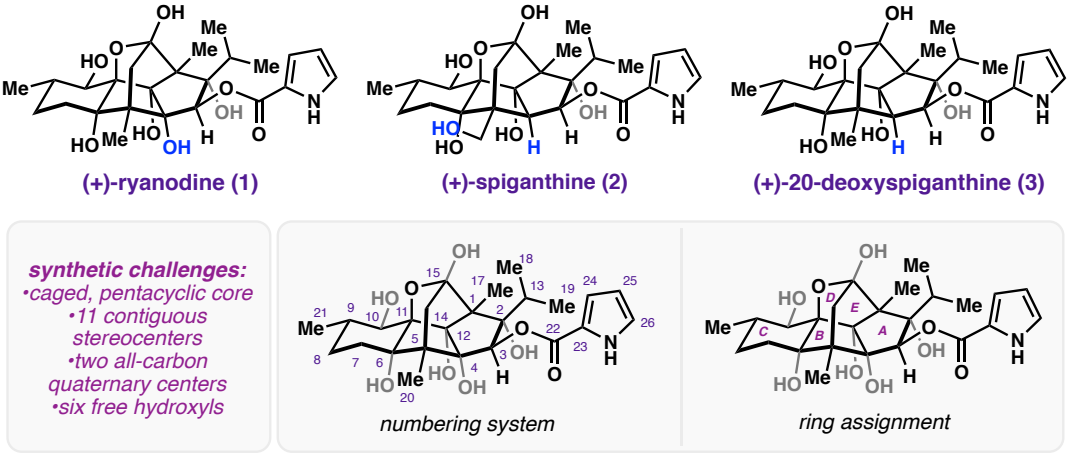


Figure 1. *Ryanodine: structure and synthetic challenges.*

This task is heightened by the steric encumbrance imposed by the pentacyclic ryanoid framework. The C3 alcohol is buried in the concave pocket of the AE ring system and furthermore flanked by an isopropyl group at C2, rendering it the most hindered of the free alcohols. Indeed, these factors combined have revealed that the C4, C10, and C12

alcohols are all more reactive than the C3 alcohol.[1-3] It was immediately apparent that a solution to the C3 pyrrole-2-carboxylate ester present in (+)-ryanodine (**1**) would require careful orchestration of a series of steps to minimize extraneous protecting group and redox manipulations.

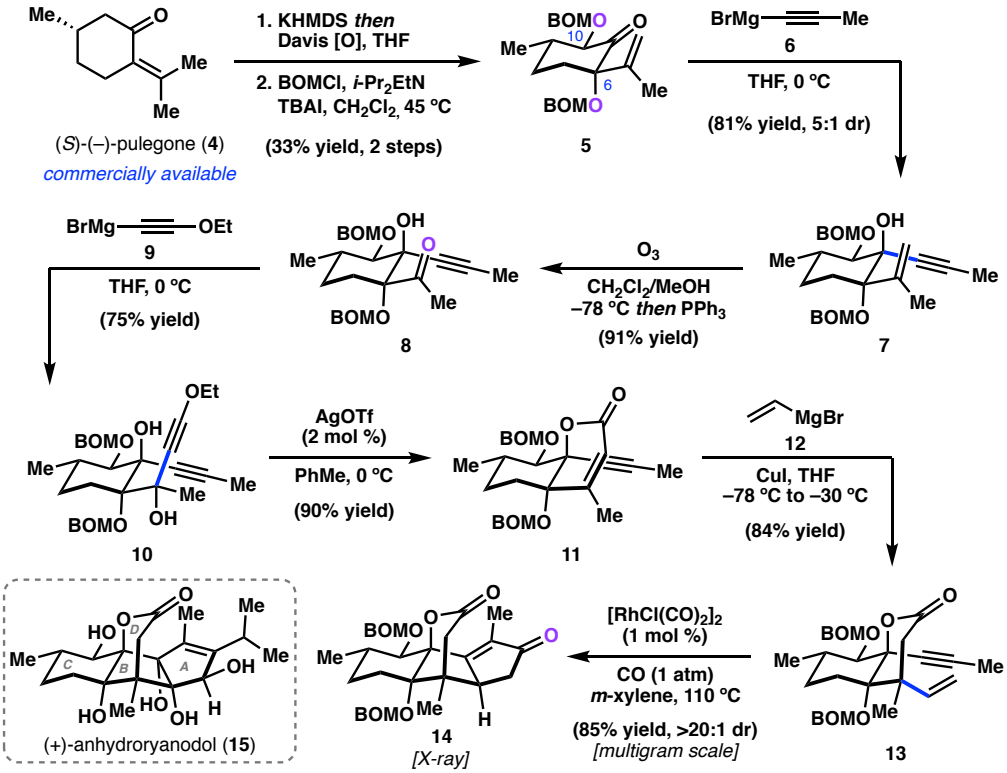
2.3 SYNTHETIC APPROACH

2.3.1 *Total Synthesis of (+)-Ryanodol*

Although our long-term objective was to prepare (+)-ryanodine (**1**), initial studies were focused on the hydrolysis product, (+)-ryanodol (**21**), to validate our synthetic strategy. Structural analysis of ryanodol identified the central bridging D and E rings as opportunities for strategic disconnections. Prior work by Deslongchamps and coworkers had established that **21** can be prepared in two steps from anhydroryanodol (**15**), establishing the viability of late-stage E-ring formation.[1, 4] Following this precedent, we reported a 13-step synthesis of anhydroryanodol from (*S*)-pulegone (**4**).[5]

In the forward sense, (*S*)-pulegone (**4**)[6] was first subjected to KHMDS and Davis oxaziridine[7] to induce oxidation at both C6 and C10 (Scheme 1). Protection of the diol as their BOM ethers provided a fully-elaborated C-ring fragment that was then subjected to 1-propynylmagensium bromide (**6**) to induce 1,2-addition. Ozonolytic cleavage of alkene **7** revealed methyl ketone **8**, primed to undergo a second 1,2-addition with the alkynyl Grignard reagent **9** derived from ethoxyacetylene and EtMgBr. The diyne **10** thus generated was next exposed to catalytic quantities of AgOTf to trigger lactonization, furnishing lactone **11**.[8] Treatment of **11** with CuI and vinylmagnesium bromide (**12**) led to productive 1,4-addition chemistry, thereby installing the first of two all-carbon

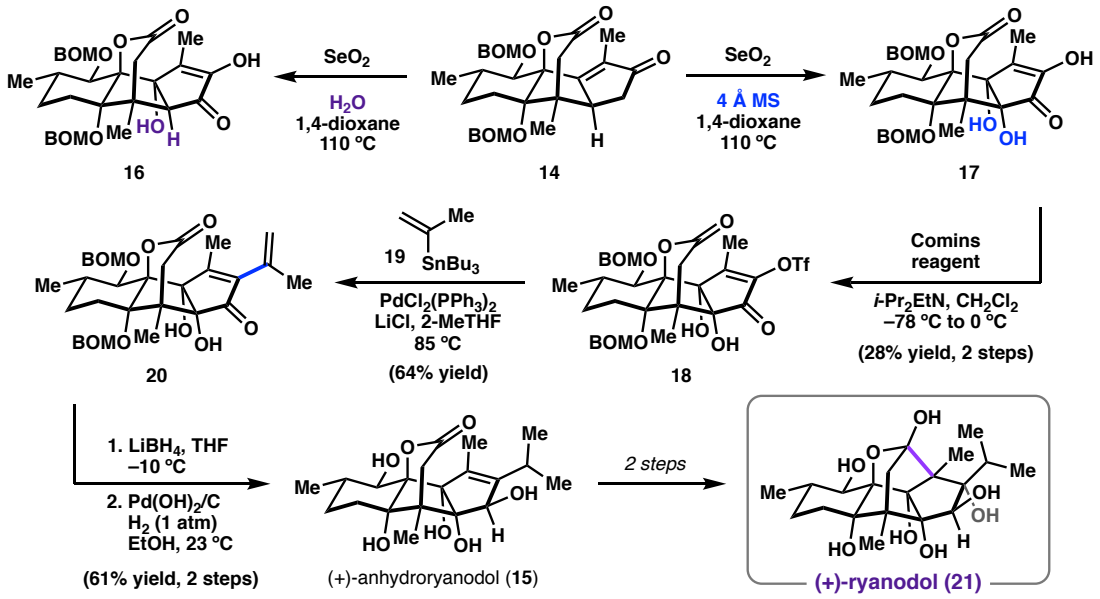
quaternary centers. Enyne **13** thereafter succumbs to a highly diastereoselective, Rh-catalyzed Pauson-Khand reaction[9] to complete the tetracyclic framework of anhydroryanodol (**15**). This concise, 8-step sequence can readily be performed on multigram scales.



Scheme 1. *8-step entry to anhydroryanodol framework from (S)-pulegone.*

At this stage, we discovered that treatment of the Pauson-Khand product **14** with SeO_2 at elevated temperature not only led to the expected Riley oxidation product, but also hydration at C12 to provide diosphenol **16**.[10-11] Further optimization of this reaction revealed that when the reaction was run under rigorously inert and anhydrous conditions, additional oxidation could be introduced to afford diosphenol **17**. This oxidation remarkably proceeds to provide three requisite oxidation states and directly introduces the A-ring oxidation pattern necessary for the total synthesis *in one step*.[12] Pressing

forward, the diosphenol **17** was converted to its triflate with Comins' reagent, and product triflate **18** was engaged in a Stille cross-coupling[13] event to introduce the final carbons of the ryanoid framework.



Scheme 2. *15-step total synthesis of (+)-ryanodol.*

With the carbon core now in place, enone **20** was reduced by the action of $LiBH_4$ to diastereoselectively generate C3 alcohol (Scheme 2). Subjection of the reduction product to $Pd(OH)_2/C$ and H_2 leads to BOM deprotection with concomitant terminal alkene reduction to complete the preparation of (+)-anhydroryanodol (**15**). In line with the Deslongchamps synthesis, we then completed a 15-step synthesis of (+)-ryanodol (**21**) by performing (1) epoxidation of the alkene with CF_3CO_3H, and (2) reductive cyclization with Li^0 and NH_3.[4] Notably, the synthesis proceeds in less than half the steps required of the Deslongchamps and Inoue routes, highlighting how strategic C–O bond construction can streamline the synthesis of highly oxidized terpenoids.

2.3.2 *Retrosynthetic Analysis of (+)-Ryanodine and (+)-20-Deoxyspiganthine*

Analysis of the previous difficulties en route to (+)-ryanodine (**1**) reported by the Deslongchamps[1, 4, 14-16] and Inoue[2-3, 17-19] teams guided our acylation strategy to complete a total synthesis. In considering how to translate our synthesis of ryanodol (**21**) to a synthesis of **1**, our guiding strategic objective was to incorporate the pyrrole-2-carboxylate ester *directly* by an esterification reaction in the final stage of the synthesis. Given the challenges encountered by others when trying to acylate **21** or appropriately protected derivatives of **21**, we decided to target the acylation of a protected derivative of (+)-anhydroryanodol (**15**) (Figure 2).[1-3] This decision was driven by the hypothesis that the C3 hydroxyl group of **15** is less sterically hindered, and by the fact that **15** presents two fewer hydroxyl groups than **21**, thereby simplifying the chemoselectivity challenge.

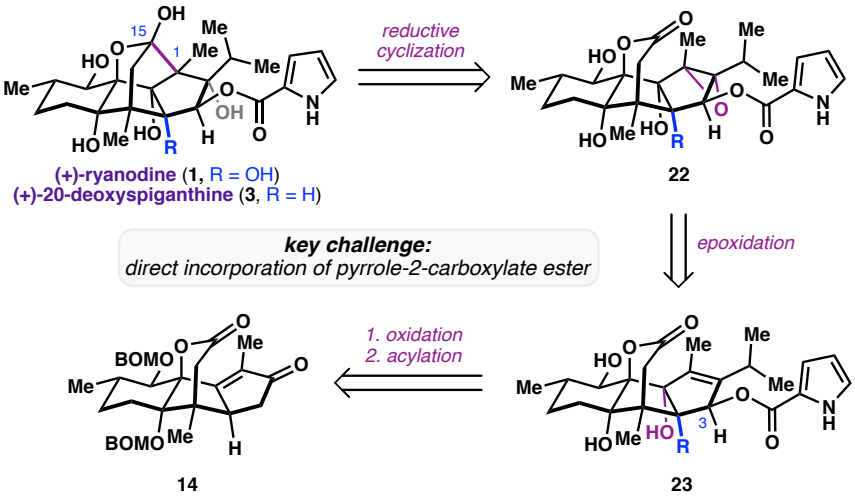


Figure 2. *Retrosynthetic analysis of (+)-ryanodine.*

Although this approach was considered advantageous from the perspective of the C3-acylation, it presents its own challenge in that the pyrrole-2-carboxylate ester would need to survive the required epoxidation of the C1–C2 alkene (**23→22**), as well as the

reductive ring closure event (**22**→**1**). The reductive cyclization of anhydroryanodol epoxide intermediates bearing C3 ester functionality (e.g. **22**) had not previously been reported. Finally, we hoped to adapt the chemistry developed for the synthesis of (+)-ryanodine to the synthesis of (+)-20-deoxyspiganthine (**3**), beginning from **14** (Figure 2), with minimal reaction reoptimization.

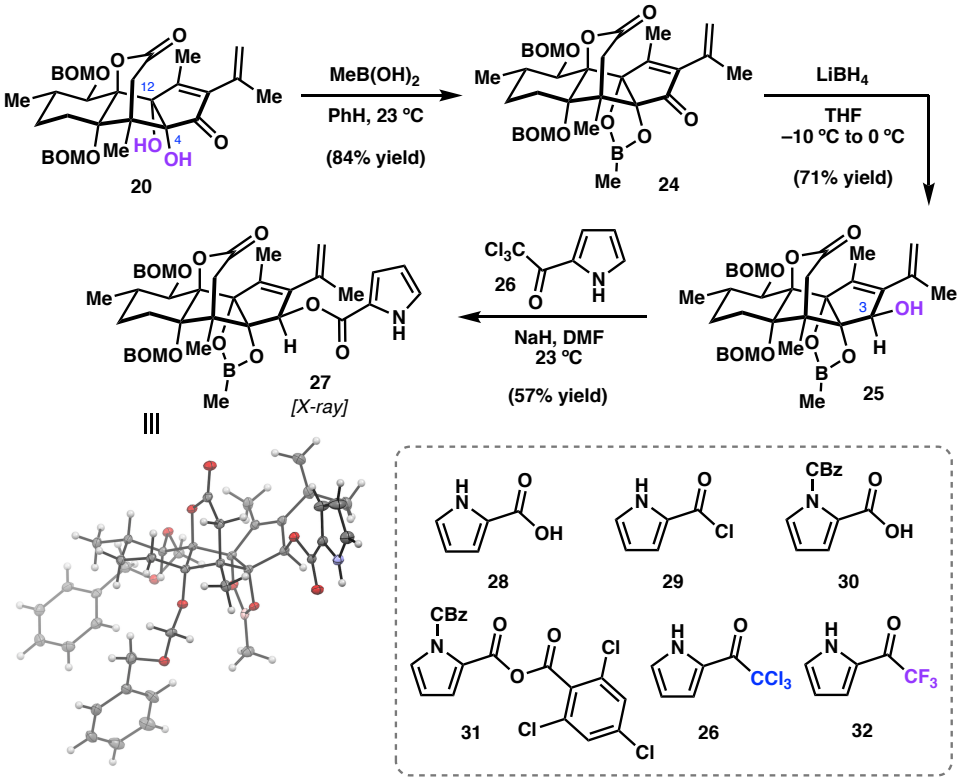
2.4 FORWARD SYNTHETIC EFFORTS

2.4.1 *Installation of the C3 Pyrrolecarboxylate Ester*

As outlined in our retrosynthetic analysis, the first goal toward completing a chemical synthesis of (+)-ryanodine was the identification of suitable conditions to effect C3-esterification with a pyrrole-2-carboxylic acid equivalent. Toward that end, Stille cross-coupling product **20**, an intermediate in our (+)-ryanodol route, was preemptively protected as its cyclic boronate ester and the protected intermediate **24** was then reduced with $LiBH_4$ to generate C3 alcohol **25**.[3, 5] The decision to protect the C4 and C12 alcohols, although tertiary, was driven by prior studies that have demonstrated their greater reactivity with acylating reagents when compared to the C3 alcohol.[1-3] While the isopropenyl group at this stage could be reduced to generate the requisite isopropyl group, the C3 alcohol of the product was found to exhibit poor reactivity when engaged with pyrrolecarboxylic acid and its derivatives.

As such, we turned to identify acylation conditions with **25**, under the presumption that the smaller steric profile of the adjacent C(sp^2) isopropenyl group (relative to isopropyl) would render the C3 alcohol more accessible. Whereas several standard acylating reagents derived from pyrrole-2-carboxylic acid (i.e. **28**-**32**) failed to deliver the

desired acylation product **27**, we were pleased to find that deprotonation of alcohol **25** with NaH at 0 ºC, followed by the addition of commercially available 2-(trichloroacetyl)pyrrole (**26**), afforded the desired pyrrole ester **27** in 57% isolated yield (structure verified by X-ray crystallography). The major side product of this reaction is an α-chloroester resulting from C14 chlorination at the lactone (see Experimental Section).

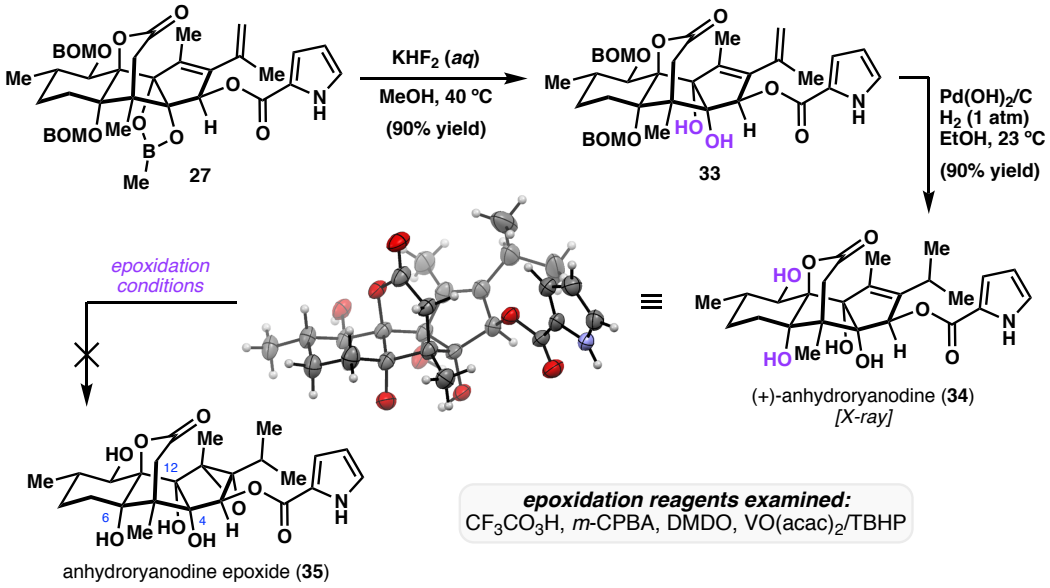


Scheme 3. *Successful acylation of C3 alcohol.*

2.4.2 *Total Synthesis of (+)-Ryanodine*

With the C3 pyrrolecarboxylate ester in place, we pressed forward to complete our synthesis of (+)-ryanodine. Acylation product **27** was advanced to anhydroryanodine (**34**) after two deprotection manipulations (Scheme 4). First, the methyl boronate of **27** was cleaved with aqueous KHF_2 in methanol to afford diol **33**, which was then subjected to

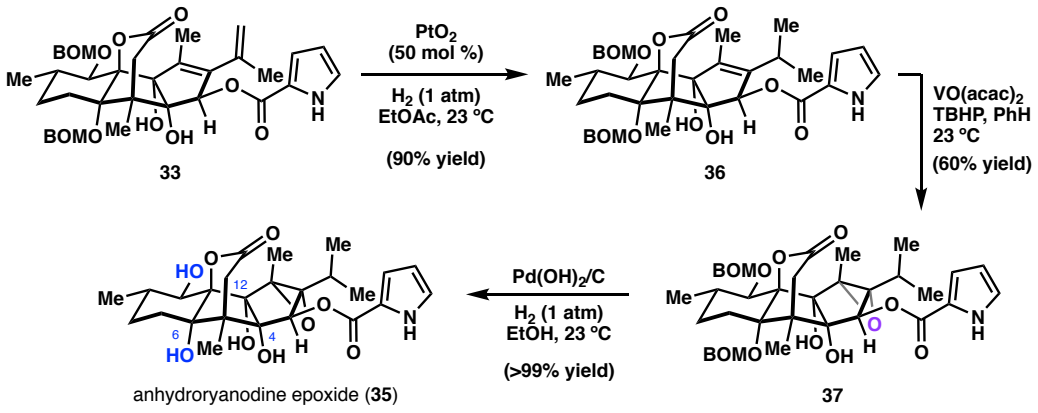
H_2 and $Pd(OH)_2/C$ to simultaneously reduce the terminal olefin and remove the BOM groups, providing **34** in 90% yield. The structure assignment of **34** was confirmed by X-ray crystallography.



Scheme 4. *Synthesis of (+)-anhydroryanodine and epoxidation attempts.*

With access to **34**, completion of the synthesis required epoxidation and reductive ring closure. Unfortunately, mild epoxidation reagents (e.g. *m*-CPBA) returned starting material, whereas more reactive reagents (e.g. CF_3CO_3H) resulted in decomposition, likely due to undesired reactivity at the pyrrole.[20] In an attempt to harness the directing ability of the proximal C4 and C12 alcohols, we turned to V-mediated epoxidation conditions; however, we were again met with the observation of no reactivity. We hypothesized that competing, non-productive coordination of vanadium by the C6, C4, and C12 alcohols was precluding formation of the active substrate-bound epoxidation species, and therefore investigated the reaction of a partially-protected intermediate. Chemoselective hydrogenation of the terminal alkene of **33** was achieved using H_2 with PtO_2 and, to our delight, exposure of **36** to $VO(acac)_2$/TBHP in benzene at room

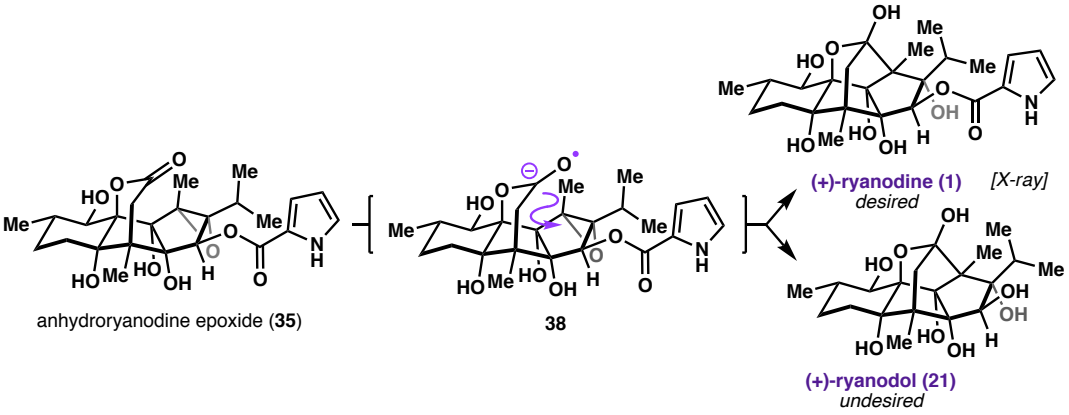
temperature delivered epoxide **37** in 60% yield (Scheme 5). The hydrogenation of diene **33** proved to be enabling for the epoxidation event, as subjecting **33** to otherwise identical V-mediated epoxidation conditions only led to trace conversion to the desired epoxide. Pressing forward, hydrogenolytic deprotection of the BOM protecting groups under previously developed conditions provided anhydroryanodine epoxide **35**.



Scheme 5. *Preparation of anhydroryanodine epoxide.*

The final step of the synthesis required formation of the C1–C15 bond through a reductive cyclization step, in analogy to the chemistry developed for the synthesis of (+)-ryanodol (**21**). Although submission of **35** to Li/NH_3 indeed affected the desired bond construction, **21** was the only product recovered under these conditions, highlighting the additional challenge presented by the lability of the ester in **35** (Figure 3). Hypothesizing that deprotonation of the pyrrole-2-carboxylate ester would render it less susceptible to cleavage by reduction or aminolysis processes, **35** was first treated with LDA (5.9 equiv), and the resulting solution was added to a mixture of Li(0) in NH_3, which provided **1** (20% isolated yield) in a 1:2 ratio with **21**. Reactions conducted with 10 equiv of LDA under otherwise identical conditions resulted in recovery of starting material, presumably due to deprotonation of the lactone, which precludes ketyl anion formation. Concerned

that formation of **21** under the Li/NH_3 conditions results in part from aminolysis of the ester, we investigated soluble single electron reductants that could be used in solvents other than liquid ammonia.



entry	conditions	SM : ryanodol : ryanodine	yield
1	Li/NH_3, THF, –78 °C	0 : 1 : 0	–
2	LDA (5.9 equiv), THF, –78 °C; then Li/NH_3, –78 °C	0 : 2 : 1	20%
3	LDA (10.0 equiv), THF, –78 °C; then Li/NH_3, –78 °C	1 : 0 : 0	–
4	SmI_2 (10.0 equiv), H_2O (100 equiv), THF, 0 °C	1 : 0 : 0	–
5	LiNap (4.5 equiv), THF, –78 °C	2 : 0 : 1	–
6	LiDBB (3.5 equiv), THF, –78 °C	1 : 0 : 4	64%

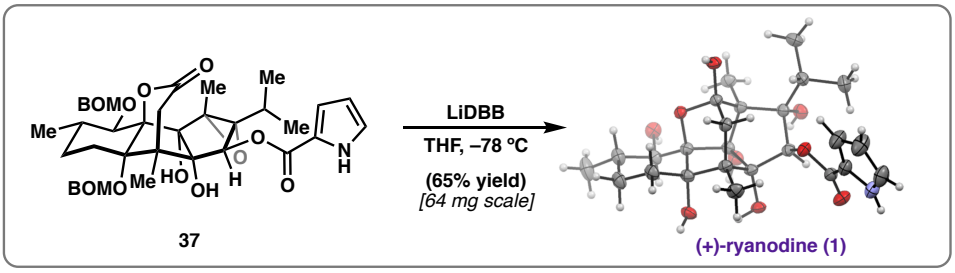


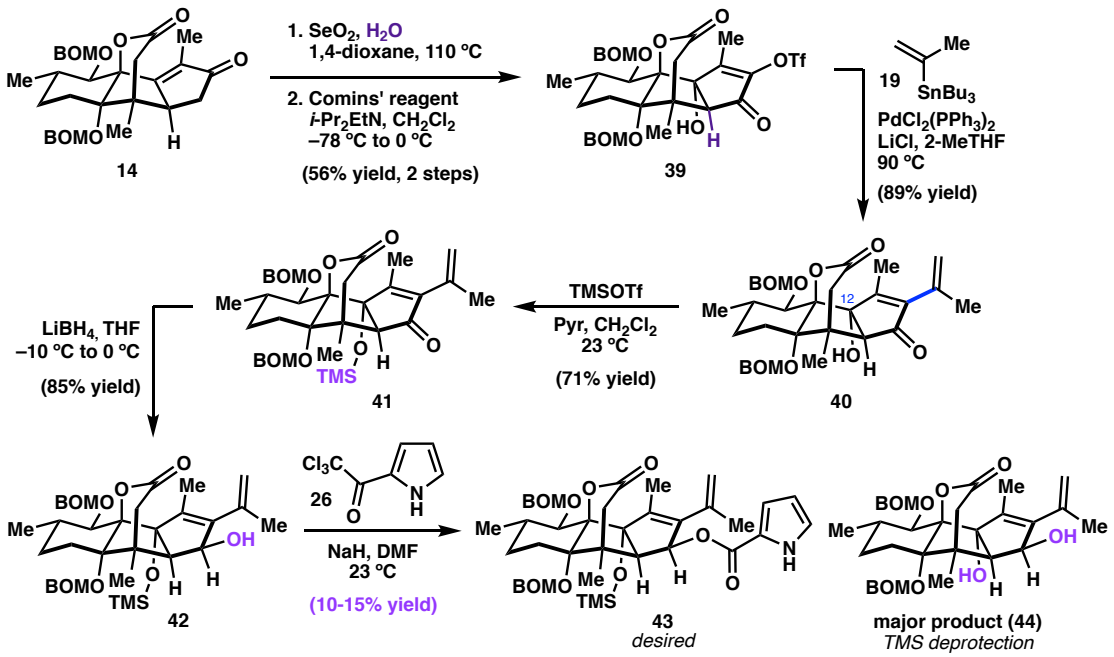
Figure 3. *Reductive cyclization optimization and 18-step synthesis.*

Gratifyingly, when lithium naphthalenide (LiNap) in THF was used, a 2:1 ratio of **35** to **1** was produced, without detectable amounts of **21** by LCMS analysis. The reaction could be further improved by employing the more reducing lithium di-*tert*-butylbiphenylide (LiDBB), which afforded **1** in 64% isolated yield.[21-22] Moreover, the step count of the synthesis could be reduced by performing the reductive ring closure on BOM protected epoxide **37**, which smoothly undergoes C–C bond formation and BOM-deprotection to

provide (+)-**1** in 65% yield. Using this 18-step route, we were able to solve the first X-ray crystal structure of the molecule.

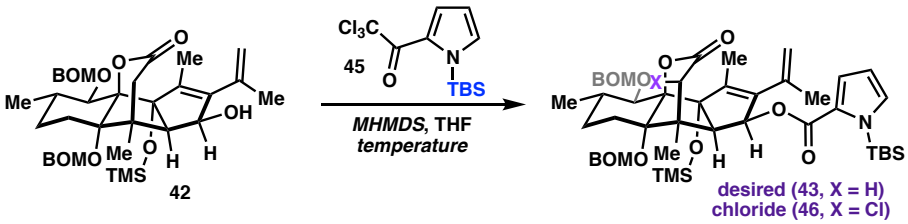
2.4.3 *Total Synthesis of (+)-20-Deoxyspiganthine*

Having completed an 18-step synthesis of (+)-ryanodine, our attention next turned to the related natural product (+)-20-deoxyspiganthine. Preliminary biological studies reported by the isolation team determined that this compound is also potent in cardiac tissue assays of RyR function.[23] Given the improved yields for the formation of **16** in the SeO_2-mediated oxidation/triflation of tetracycle **14** (Scheme 2), (+)-20-deoxyspiganthine could be an appealing starting point for the future development of RyR probe molecules. Starting with tetracycle **40** (which is prepared from **39** by Stille cross-coupling), the C12 alcohol was protected as its TMS ether and the ketone was reduced with $LiBH_4$ to give alcohol **42** (Scheme 6).



Scheme 6. *20-deoxyspiganthine acylation substrate preparation.*

Unfortunately, efforts to acylate the C3 alcohol of **42** under the previously describe conditions resulted in rapid TMS deprotection and low yields of the desired ester (10-15%). Attempts to avoid the use of the TMS protecting group were stymied by the hindered nature of the C12 alcohol: introduction of the TES ether with TESOTf under otherwise identical conditions provided <5% of the desired product, and similar results were observed in our efforts to introduce a BOM or MOM ether.



entry	base	equiv	temperature	major product	isolated yield
1	NaHMDS	1.1 equiv	–78 °C	translactonization	28% (desired)
2	LHMDS	1.1 equiv	–78 °C	SM	0%
3	KHMDS	1.1 equiv	–78 °C	SM	trace
4	NaHMDS	1.5 equiv	–60 °C	translactonization	25% (desired)
5	NaHMDS	1.5 equiv	–40 °C	translactonization	28% (desired)
6	NaHMDS	1.2 equiv	–10 °C	translactonization	20% (chloride)
7	NaHMDS	2.0 equiv	–10 °C	translactonization	18% (chloride)
8	KHMDS	2.0 equiv	–10 °C	chloride	69% (chloride)
9	KHMDS	1.2 equiv	–10 °C	chloride	20% (desired) + 45% (chloride)
10	LHMDS	2.0 equiv	–10 °C	SM	0%
11	NaH	2.0 equiv	0 °C to 23 °C	TMS deprotect.	10% (desired–TMS)
12	NaH	4.0 equiv	0 °C to 23 °C	TMS deprotect.	12% (desired–TMS)

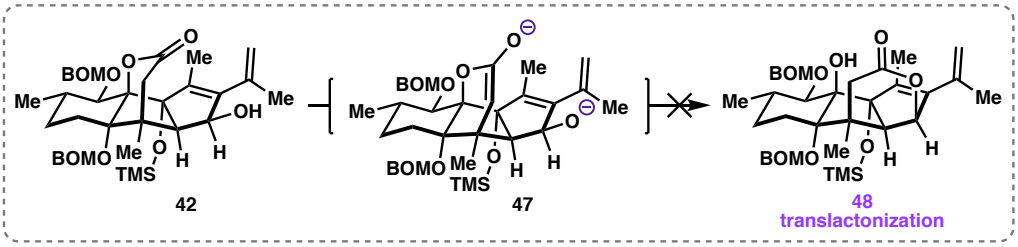
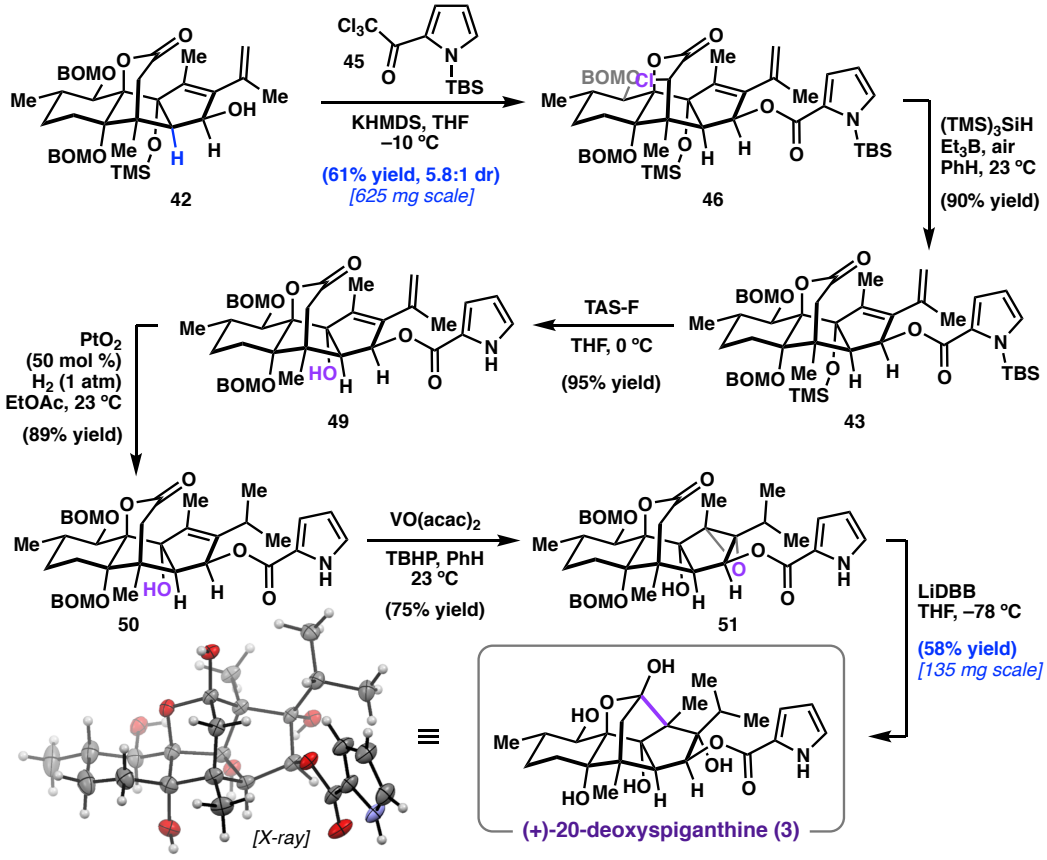


Figure 4. *Acylation optimization for 20-deoxyspiganthine*

After significant experimentation, we found that treatment of **42** with 2.0 equiv of KHMDS followed by the addition of a solution of TBS-protected pyrrole **45** provided ester **46**, which had also undergone chlorination at C15 (5.8:1 dr). The undesired chlorination reaction could, in principle, be mitigated by using less KHMDS; however,

under these conditions translactonization by the C3 alcohol precedes esterification (Figure 4). Thus, enolization of the lactone prevents translactonization, but also results in α-chlorination at temperatures required to observe good levels of reactivity.



Scheme 7. *19-step synthesis of (+)-20-deoxyspiganthine.*

Undeterred by this result, dechlorination of **46** was accomplished without complication using $(TMS)_3SiH$ and the low-temperature initiator Et_3B to give **43** (Scheme 7). Deprotection of both silyl groups was best executed with TAS-F to afford alcohol **49**; acidic conditions, as with H_2SiF_6 (*aq*) and HF, led to competitive BOM deprotection. Following this maneuver, the terminal alkene of **49** was reduced as before with PtO_2 and H_2 and hydroxyl-directed epoxidation of the remaining tetrasubstituted alkene furnished **51**. It is worth noting that unlike with diene **33** en route to (+)-

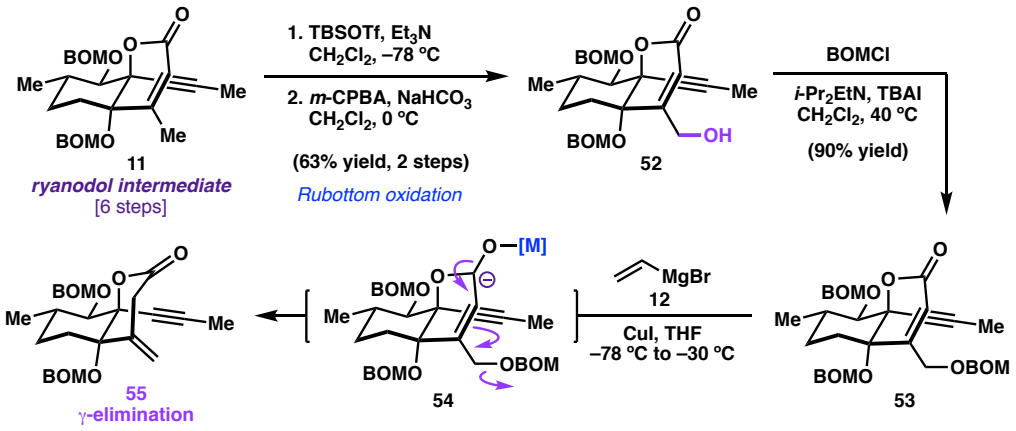
ryanodine, diene **49** *does* succumb to V-mediated epoxidation–paving the way for the generation of isopropenyl spiganthine-type analogs. Treatment of **51** with 10 equiv of freshly prepared LiDBB resulted in cyclization and deprotection of both BOM groups, affording (+)-20-deoxyspiganthine (**3**) in 58% yield. The structure of **3** was unambiguously confirmed by single crystal X-ray diffraction. At 19 steps, this is the *first* total synthesis of a spiganthine-type natural product. It is notable that with the exception of the C3-acylation reaction, no significant reoptimization was required to translate the synthesis of **1** to **3**, demonstrating the versatility of this strategy.

2.4.4 *Progress Toward the Total Synthesis of (+)-Spiganthine*

As our ryanoid program transitions to the collaborative mode, one of our primary objectives is to evaluate the oxidation state necessary to maintain effective binding to the RyR. In minimizing the number of free alcohols present, it is our belief that the scope of acylation can be maximized to fully interrogate new isoform-selective ligands to the RyR. It is with this goal in mind that we became interested in synthesizing (+)-spiganthine (**2**)–notably harboring oxidation at C20. Preliminary assays from the isolation team have demonstrated that (+)-spiganthine (**2**) shows nearly identical efficacy as (+)-ryanodine (**1**), thus the C20 oxidation appears to recover the minimal activity lost due to the reduced polarity of the A-ring in (+)-20-deoxyspiganthine (**3**).[23-24]

Recognizing that a total synthesis of **2** would hinge on the introduction of the C20 oxidation state, we began our synthetic efforts with the identification of an opportunity to readily incorporate this alcohol. Lactone **11**, an intermediate in our (+)-ryanodol route, proved to be an ideal starting point. Several methods were evaluated to perform a γ-

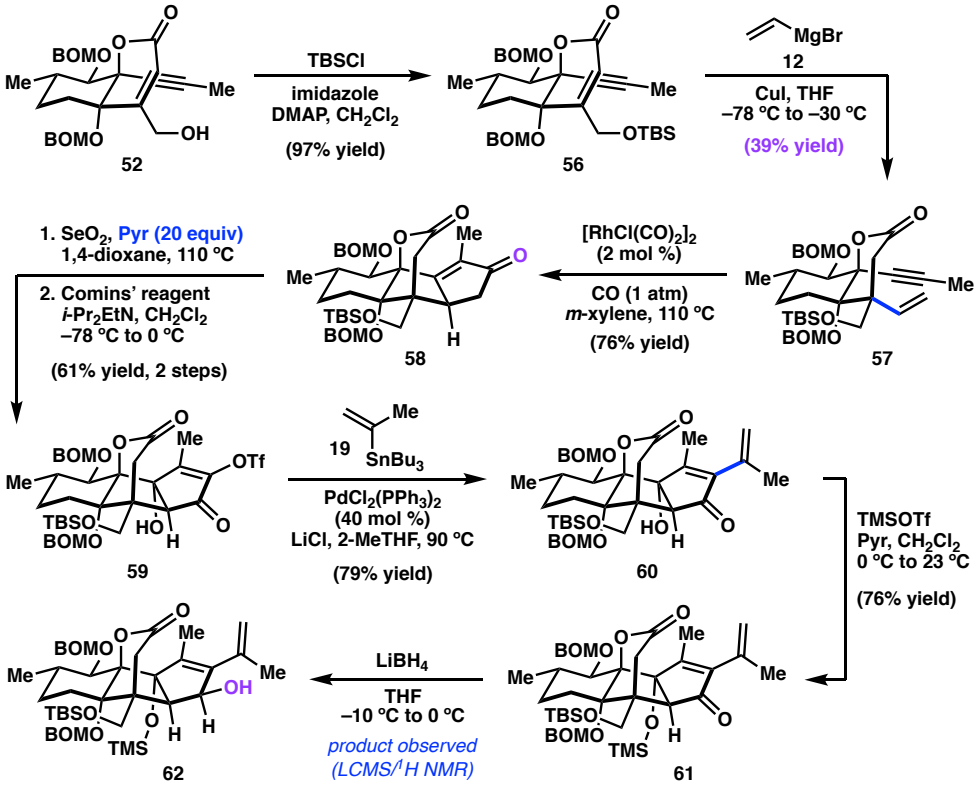
oxidation of **11** ultimately revealing an effective Rubottom oxidation protocol to generate alcohol **52** (Scheme 8). Attempts to further improve the yield of this transformation by (1) isolating and purifying the intermediate silyl ketene acetal or (2) resorting to the more stable TBDPS and TIPS silyl ketene acetal did *not* provide improved yields of **52**. While the BOM protecting group was initially conceived to be the ideal choice for the C20 free alcohol, we quickly realized that BOM ether **53** would not permit the following 1,4-addition to generate a Pauson-Khand substrate. Instead, we observed clean formation of γ-elimination product **55**. Mechanistically, this side product may arise through single electron reduction of the lactone to its ketyl anion **54**.



Scheme 8. *C20-oxidation introduction.*

We quickly discovered that the formation of **57** is highly sensitive to the protecting group choice at C20. Thus TBS protected substrate **56** provided 1,4-addition product **57** when exposed to the same conditions as was used in the conversion of lactone **11** to **13** en route to (+)-ryanodol (Scheme 9). With **57** in hand, we were pleased to find that the Pauson-Khand reaction cleanly generated tetracycle **58** with excellent diastereoselectivity. Furthermore, SeO_2-mediated oxidation of **58** and triflation provided vinyl triflate **59** without consequence. To avoid deprotection of the primary TBS ether,

pyridine was used as an additive (and buffer) for the SeO_2-mediated oxidation, in contrast to the addition of H_2O as in the case of tetracycle **14**.



Scheme 9. *Successful 1,4-addition and preparation of ABCD tetracycle.*

Vinyl triflate **59** smoothly underwent Stille cross-coupling with isopropenyl stannane **19** and the free C4 alcohol was thereafter protected as its TMS ether to generate **61**. We are now poised to begin exploring acylation chemistry and complete the first total synthesis of **2**. Again, as a testament to the versatility of this route, no reoptimization was performed in the generation of protected tetracycle **61**. Future studies to complete a total synthesis of (+)-spiganthine (**2**) will require the introduction of the pyrrole ester with the C20 oxidation state in place. A potential forward plan is outlined in Figure 5.

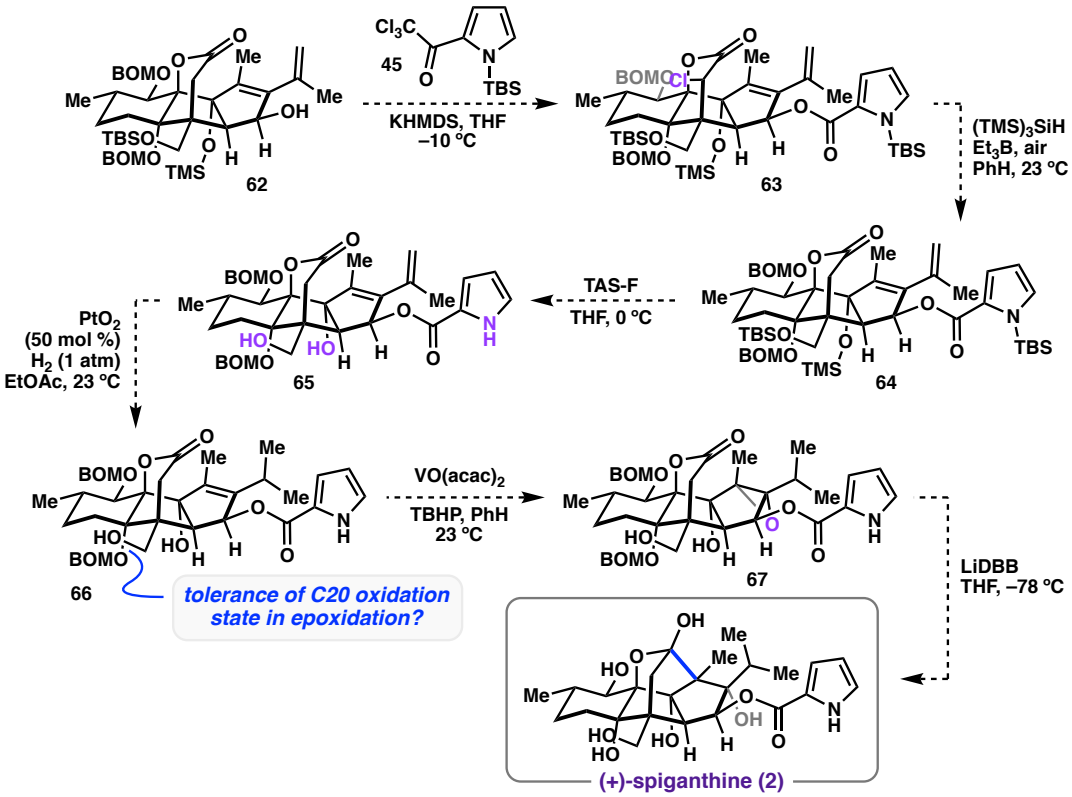


Figure 5. *Forward plan for chemical synthesis of (+)-spiganthine.*

2.5 CONCLUDING REMARKS

In summary, the chemical syntheses of (+)-ryanodine (**1**) and (+)-20-deoxyspiganthine (**3**) were achieved in 18 and 19 steps, respectively. The key features of the synthetic route include (1) a direct acylation at the hindered C3 alcohol of a protected anhydroryanodol precursor, which is a practical solution to install the crucial pyrrole-2-carboxylate ester, and (2) a LiDBB-mediated reductive cyclization to convert a protected anhydroryanodine derivative to (+)-**1**. Notably, our syntheses of (+)-ryanodine and (+)-20-deoxyspiganthine proceed in less than half the number of steps required of the previously reported route from Inoue and coworkers. We anticipate that this approach can provide access to a variety of natural and designed ryanoids, which will enable the

development of synthetic, molecular probes that can aid the study of RyR dysfunction and Ca^{2+} ion channel-based diseases.

2.6 EXPERIMENTAL SECTION

2.6.1 Materials and Methods

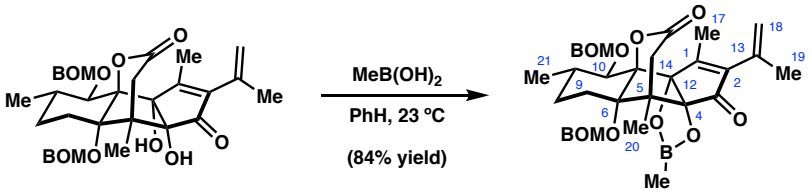
Unless otherwise stated, reactions were performed under an inert atmosphere (dry N_2 or Ar) with freshly dried solvents utilizing standard Schlenk techniques. Glassware was oven-dried at 120 °C for a minimum of four hours, or flame-dried utilizing a Bunsen burner under high vacuum. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), *N,N*-dimethylformamide (DMF), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. 2-Methyltetrahydrofuran (anhydrous, >99%, inhibitor-free) was purchased from Sigma-Aldrich and stored under argon. Methanol (HPLC grade) was purchased from Fisher Scientific. Pyridine (Pyr) was distilled from calcium hydride immediately prior to use. 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), *p*-anisaldehyde, CAM, and/or $KMnO_4$ staining. Flash column chromatography was performed 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 Avance III HD with Prodigy Cryoprobe (at 400 MHz and 101 MHz, respectively), Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26), C_6H_6 (^1H, δ = 7.16), or CD_2HOD (^1H, δ = 3.31), and $CDCl_3$ (^{13}C, δ = 77.0), C_6D_6 (^{13}C, δ = 128.0), or CD_3OD (^{13}C, δ = 49.0). Data for ^1H

NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

Reagents were purchased from commercial vendors as follows: *trans*-Dichlorobis(triphenylphosphine) palladium was purchased from Strem Chemicals and stored in a nitrogen-filled glovebox. Sodium hydride (dry, 95%), 2-(trichloroacetyl)pyrrole, solid potassium bis(trimethylsilyl)amide (KHMDS, 95%), and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F) were purchased from Sigma-Aldrich and stored in a nitrogen-filled glovebox. Platinum oxide (Adam's catalyst) and vanadyl acetylacetonate ($VO(acac)_2$) were purchased from Strem Chemicals. *Tert*-butyl hydroperoxide (TBHP, 5.5 M in decane over 4 Å MS), solid $LiBH_4$ (>95%), lithium (wire stored in mineral oil, 99.9% trace metal basis), and 4,4′-di-*tert*-butylbiphenyl (DBB) were purchased from Sigma-Aldrich.

2.6.2 Experimental Procedures

Preparation of boronate ester 24



In slight modification of a procedure[2] detailed by Inoue and coworkers, PhH (66 mL) was added to a mixture of **20** (1.06 g, 1.71 mmol, 1.0 equiv) and $MeB(OH)_2$ (1.02 g, 17.1 mmol, 10 equiv) in an oven-dried, 200 mL round-bottomed flask. The resultant mixture was concentrated *in vacuo*. This azeotropic procedure of adding PhH (66 mL) and concentrating was repeated 10 times to complete the conversion of **20** to boronate ester **24**. Purification of the crude mixture by SiO_2 flash chromatography (25% EtOAc/hexanes) afforded the desired product **24** as a white foam (920 mg, 1.43 mmol, 84% yield).

TLC (25% EtOAc/hexanes): R_f 0.40 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.30 (m, 10H, ***Ph***CH_2OCH_2O), 5.30 (p, *J* = 1.6 Hz, 1H, C_{18}), 5.25 (d, *J* = 6.5 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.09 (d, *J* = 7.0 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.05 (d, *J* = 6.6 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.90 (d, *J* = 12.0 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.86 (dt, *J* = 1.9, 1.0 Hz, 1H, C_{18}), 4.82 (d, *J* = 7.0 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.68 (d, *J* = 12.0 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.78 (d, *J* = 11.3 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.46 (d, *J* = 11.3 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.16 (d, *J* = 10.6 Hz, 1H, C_{10}), 2.53 (d, *J* = 19.8 Hz, 1H, C_{14}), 2.41 (d, *J* = 19.9 Hz, 1H, C_{14}), 2.32 (s, 3H, C_{17}), 2.21

– 2.09 (m, 1H, C_9), 1.99 (ddd, J = 14.6, 4.4, 1.9 Hz, 1H, C_7), 1.90 (q, J = 11.3 Hz, 1.5 Hz, 3H, C_{19}), 1.94 – 1.79 (m, 1H, C_8), 1.66 (dtd, J = 13.5, 4.6, 1.7 Hz, 1H, C_8), 1.61-1.52 (m, 1H, C_7), 1.31 (s, 3H, C_{20}), 1.18 (d, J = 6.5 Hz, 3H, C_{21}), 0.37 (s, 3H, BC$\boldsymbol{H}_3$).

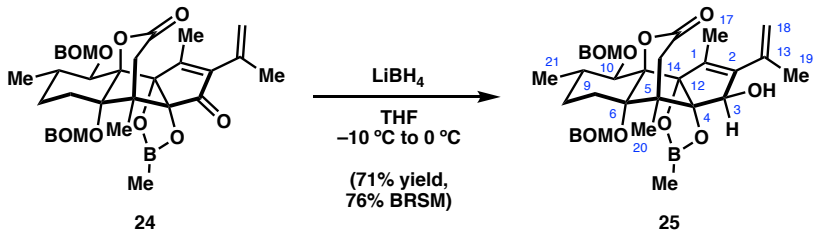
^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5 (C_3=O), 168.3 (C_1), 166.6 (C_{15}=O), 145.8 (C_2), 137.8 (C_{Ph}), 136.8 (C_{Ph}), 135.3 (C_{13}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 118.7 (C_{18}), 97.1 (C_{11}), 97.1 (C_{12}), 94.3 (C_4), 93.5 (PhCH$_2$O***C***H$_2$O), 91.0 (C_6), 90.6 (PhCH$_2$O***C***H$_2$O), 79.6 (C_{10}), 71.0 (Ph***C***H$_2$OCH$_2$O), 70.8 (Ph***C***H$_2$OCH$_2$O), 46.7 (C_5), 40.6 (C_{14}), 32.5 (C_9), 27.7 (C_8), 21.5 (C_{19}), 21.3 (C_7), 18.9 (C_{21}), 15.3 (C_{15}), 15.1 (C_{17}), –5.1 (B***C***H$_3$).

FTIR (NaCl, thin film): 2956, 2872, 1755, 1716, 1361, 1268, 1022, 1020 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+H]^+$ 643.3078, found 643.3072.

$[\alpha]_D^{25}$: +175° (c = 0.505, $CHCl_3$).

Preparation of alcohol 25



To an oven-dried, 200 mL round-bottomed flask was added enone **24** (920 mg, 1.43 mmol, 1.0 equiv) and anhydrous THF (57 mL). The solution was cooled to –10 ºC in an ice/acetone bath and solid $LiBH_4$ (156 mg, 7.16 mmol, 5.0 equiv) was added. After 1 h, a second portion of solid $LiBH_4$ (156 mg, 7.16 mmol, 5.0 equiv) was added before warming the reaction mixture to 0 ºC with an ice/water bath. Stirring was continued at 0

ºC for another 1 h before a third portion of solid $LiBH_4$ (156 mg, 7.16 mmol, 5.0 equiv) was added. The reaction was allowed to stir at 0 ºC an additional 1 h before sat. aq. NH_4Cl (40 mL) was slowly added to the reaction at 0 ºC [Caution! Vigorous evolution of H_2 gas occurs, particularly in the initial stages of addition. Careful, controlled dropwise addition is advised in order to avoid a violent reaction]. The mixture was diluted with EtOAc (40 mL), the two layers separated, and the organic layer washed with sat. aq. NH_4Cl (40 mL). The combined aqueous layers were extracted with EtOAc (2 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (30 to 40 to 50% EtOAc/hexanes) to afford recovered starting material enone **24** (61 mg, 0.095 mmol, 7% yield) and the desired alcohol **25** as a white foam (650 mg, 1.01 mmol, 71% yield, 76% BRSM).

TLC (40% EtOAc/hexanes): R_f 0.30 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 10H, ***Ph***CH_2OCH_2O), 5.25 (d, *J* = 6.8 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.23 (t, *J* = 1.7 Hz, 1H, C_{18}), 5.09 (d, *J* = 6.9 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.98 (d, *J* = 6.8 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.93 – 4.90 (m, 1H, C_3), 4.90 – 4.87 (m, 1H, C_{18}), 4.89 (d, *J* = 8.0 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.80 (d, *J* = 7.0 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.77 (d, *J* = 11.6 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.62 (d, *J* = 12.0 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.42 (d, *J* = 11.4 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.10 (d, *J* = 10.4 Hz, 1H, C_{10}), 3.79 (d, *J* = 19.9 Hz, 1H, C_{14}), 2.33 (d, *J* = 19.8 Hz, 1H, C_{14}), 2.21 – 2.10 (m, 1H, C_9), 2.08 (d, *J* = 4.4 Hz, 1H, O***H***), 1.92 (d, *J* = 2.4 Hz, 3H, C_{17}), 1.88 – 1.83 (m, 3H, C_{19}),

1.98-1.89 (m, 1H, C_7), 1.93-1.82 (m, 1H, C_8), 1.69-1.61 (m, 1H, C_8), 1.64-1.53 (m, 1H, C_7), 1.31 (s, 3H, C_{20}), 1.18 (d, J = 6.5 Hz, 3H, C_{21}), 0.33 (s, 3H, BC$\boldsymbol{H}_3$).

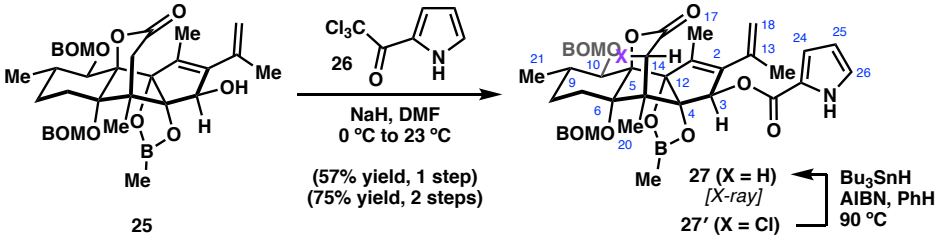
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6 (C_{15}=O), 145.8 (C_2), 138.2 (C_{13}), 138.0 (C_{Ph}), 137.1 (C_{Ph}), 135.0 (C_1), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.0 (C_{Ph}), 127.8 (C_{Ph}), 127.8 (C_{Ph}), 127.6 (C_{Ph}), 117.7 (C_{18}), 102.3 (C_{12}), 98.7 (C_4), 97.2 (PhCH$_2$O$\boldsymbol{C}$H$_2$O), 92.1 (C_6), 91.0 (C_{11}), 90.5 (PhCH$_2$O$\boldsymbol{C}$H$_2$O), 84.6 (C_3), 80.3 (C_{10}), 70.8 (Ph$\boldsymbol{C}$H$_2$OCH$_2$O), 70.6 (Ph$\boldsymbol{C}$H$_2$OCH$_2$O), 49.3 (C_5), 39.0 (C_{14}), 32.6 (C_9), 27.9 (C_8), 21.5 (C_{19}), 21.0 (C_7), 19.1 (C_{21}), 16.5 (C_{20}), 13.3 (C_{17}), –5.1 (B$\boldsymbol{C}$H$_3$).

FTIR (NaCl, thin film): 3453, 2924, 1747, 1362, 1037 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+NH_4]^+$ 662.3500, found 662.3509.

$[\alpha]_D^{25}$: +67° (c = 0.385, $CHCl_3$).

Preparation of pyrrole ester 27



An oven-dried, 50 mL round-bottomed flask was charged with NaH (95%, 51 mg, 2.0 mmol, 4.0 equiv) in a nitrogen-filled glovebox. The flask was capped with a rubber septum, removed from the glovebox and cooled to 0 ºC. Alcohol **25** (322 mg, 0.5 mmol, 1.0 equiv) in anhydrous DMF (5.0 mL) was next *rapidly* added and another portion of DMF (5.0 mL) was then used to render the transfer quantitative. The resulting reaction mixture was stirred for 30 min at 0 ºC before 2-(trichloroacetyl)pyrrole (425 mg, 2.0

mmol, 4.0 equiv) in anhydrous DMF (5.0 mL) was added dropwise via syringe. After continued stirring for 30 min at 0 ºC, the resulting dark-brown mixture was warmed to ambient temperature and stirring was continued for 48 h. The reaction was diluted with Et_2O (15 mL) and then carefully quenched with the addition of sat. aq. NH_4Cl (15 mL). The layers were separated and the organic layer was washed with H_2O (2 x 20 mL). The combined aqueous layers were extracted with Et_2O (3 x 20 mL) and the combined organic layers were then washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (15 to 20 to 25 to 30% EtOAc/hexanes) to afford pyrrole ester **27** (212 mg, 0.287 mmol, 57% yield) and chloride **27′** (69.7 mg, 0.089 mmol, 18% yield). The stereochemistry of the chloride substituted C_{14}–H was determined by nOe analysis.

An oven-dried, 50 mL Schlenk tube was charged with chloride **27′** (69.7 mg, 0.089 mmol, 1.0 equiv) and benzene (8.9 mL) under N_2. The Schlenk tube was then placed in a preheated oil bath (90 ºC) before a solution of AIBN (14.6 mg, 0.089 mmol, 1.0 equiv) and Bu_3SnH (0.178 mL, 0.178 mmol, 2.0 equiv) in benzene (8.9 mL) was added dropwise via syringe at 90 ºC. Upon complete addition, the reaction mixture was stirred for 1 h at 90 ºC, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was cooled to ambient temperature, transferred to a 50 mL round-bottomed flask and concentrated in *vacuo*. The crude residue was purified by SiO_2 flash chromatography (25% EtOAc/hexanes) to afford pyrrole ester **27**, which was combined with the pure material obtained in the previous step to give a combined 277 mg of pyrrole ester **27** (0.376 mmol, 75% combined yield).

Pyrrole ester 27:

TLC (25% EtOAc/hexanes): R_f 0.30 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H, N***H***), 7.44 – 7.29 (m, 10H, ***Ph***CH_2OCH_2O), 7.05 (td, *J* = 2.7, 1.4 Hz, 1H, C_{26}), 6.94 (ddd, *J* = 3.8, 2.4, 1.4 Hz, 1H, C_{24}), 6.32 (dt, *J* = 3.9, 2.5 Hz, 1H, C_{25}), 6.25 (q, *J* = 2.3 Hz, 1H, C_3), 5.26 (d, *J* = 6.8 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.14 (p, *J* = 1.6 Hz, 1H, C_{18}), 5.04 (d, *J* = 6.9 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.01 (d, *J* = 6.8 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.91 (d, *J* = 11.8 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.91-4.88 (m, 1H, C_{18}), 4.77 (d, *J* = 12.0 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.77 (d, *J* = 6.9 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.64 (d, *J* = 6.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.40 (d, *J* = 11.3 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.12 (d, *J* = 10.5 Hz, 1H, C_{10}), 3.57 (d, *J* = 19.8 Hz, 1H, C_{14}), 2.46 (d, *J* = 19.7 Hz, 1H, C_{14}), 2.16 (dddd, *J* = 11.6, 8.9, 6.6, 5.1 Hz, 1H, C_9), 1.98 (d, *J* = 2.5 Hz, 3H, C_{17}), 1.97-1.90 (m, 1H, C_7), 1.93-1.85 (m, 1H, C_8), 1.69-1.60 (m, 1H, C_8), 1.64-1.56 (m, 1H, C_7), 1.75 (d, *J* = 1.2 Hz, 3H, C_{19}), 1.19 (d, *J* = 6.5 Hz, 3H, C_{21}), 1.11 (s, 3H, C_{20}), 0.38 (s, 3H, $BC\boldsymbol{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C_{15}=O), 159.8 (C_{22}=O), 143.3 (C_2), 138.0 (C_{13}), 137.3 (C_{Ph}), 137.0 (C_{Ph}), 137.0 (C_1), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.0 (C_{Ph}), 127.8 (C_{Ph}), 127.6 (C_{Ph}), 124.2 (C_{26}), 121.6 (C_{23}), 117.9 (C_{18}), 116.1 (C_{24}), 110.9 (C_{25}), 102.5 (C_{12}), 98.7 (C_4), 97.2 ($PhCH_2O\boldsymbol{C}H_2O$), 92.1 ($C_6$), 91.1 ($C_{11}$), 90.5 ($PhCH_2O\boldsymbol{C}H_2O$), 83.4 ($C_3$), 80.2 ($C_{10}$), 70.9 ($Ph\boldsymbol{C}H_2OCH_2O$), 70.6 ($Ph\boldsymbol{C}H_2OCH_2O$), 49.3 ($C_5$), 39.3 ($C_{14}$), 32.6 ($C_9$), 27.9 ($C_8$), 21.1 ($C_{19}$), 21.1 ($C_7$), 19.0 ($C_{21}$), 16.2 ($C_{20}$), 13.4 ($C_{17}$), –4.9 ($B\boldsymbol{C}H_3$).

FTIR (NaCl, thin film): 3307, 2928, 1750, 1707, 1042, 1016 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+H]^+$ 738.3450, found 738.3456.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +2° (*c* = 0.630, $CHCl_3$).

Chloride 27′:

TLC (25% EtOAc/hexanes): R_f 0.45 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H, N***H***), 7.43 – 7.29 (m, 10H, ***Ph***CH_2OCH_2O), 7.07 (td, *J* = 2.7, 1.4 Hz, 1H, C_{26}), 7.00 (ddd, *J* = 3.9, 2.5, 1.4 Hz, 1H, C_{24}), 6.34 (dt, *J* = 3.8, 2.5 Hz, 1H, C_{25}), 6.30 (q, *J* = 2.4 Hz, 1H, C_3), 5.64 (s, 1H, C_{14}), 5.24 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.19 – 5.10 (m, 1H, C_{18}), 5.05 (d, *J* = 6.9 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.01 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.90 (d, *J* = 12.0 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.88 – 4.84 (m, 1H, C_{18}), 4.76 (d, *J* = 6.9 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.74 (d, 11.3 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.65 (d, *J* = 12.0 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.40 (d, *J* = 11.3 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.10 (d, *J* = 10.5 Hz, 1H, C_{10}), 2.22 – 2.10 (m, 1H, C_9), 2.09 – 2.00 (m, 2H, C_7), 1.98 (d, *J* = 2.5 Hz, 3H, C_{17}), 1.92 – 1.79 (m, 1H, C_8), 1.75 (d, *J* = 1.2 Hz, 3H, C_{19}), 1.68 (d, *J* = 1.4 Hz, 1H, C_8), 1.35 (s, 3H, C_{20}), 1.19 (d, *J* = 6.4 Hz, 3H, C_{21}), 0.39 (s, 3H, $BC\boldsymbol{H}_3$).

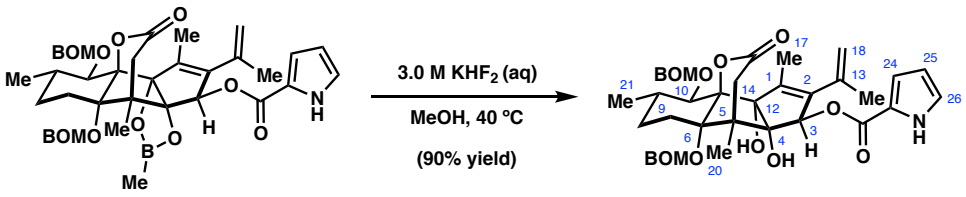
^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8 (C_{15}=O), 159.3 (C_{22}=O), 143.5 (C_2), 137.9 (C_{13}), 136.9 (C_{Ph}), 136.8 (C_{Ph}), 136.8 (C_1), 128.6 (C_{Ph}), 128.4 (C_{Ph}), 128.0 (C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 127.7 (C_{Ph}), 124.5 (C_{26}), 121.1 (C_{23}), 118.4 (C_{18}), 116.5 (C_{24}), 111.2 (C_{25}), 101.9 (C_{12}), 98.9 (C_4), 97.2 ($PhCH_2O\boldsymbol{C}H_2O$), 92.1 ($C_6$), 91.2 ($C_{11}$), 90.6 ($PhCH_2O\boldsymbol{C}H_2O$), 82.9 ($C_3$), 80.2 ($C_{10}$), 70.9 ($Ph\boldsymbol{C}H_2OCH_2O$), 70.7 ($Ph\boldsymbol{C}H_2OCH_2O$), 57.2 ($C_{14}$), 54.7 ($C_5$), 32.8 ($C_9$), 27.9 ($C_8$), 23.3 ($C_7$), 21.1 ($C_{19}$), 19.0 ($C_{21}$), 15.2 ($C_{20}$), 13.5 ($C_{17}$), –5.0 ($B\boldsymbol{C}H_3$).

FTIR (NaCl, thin film): 3326, 2947, 1758, 1710, 1361, 1154, 1044, 1015, 747 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+H]^+$ 772.3060, found 772.3066.

$[\alpha]_D^{25}$**:** –52° (*c* = 0.595, $CHCl_3$).

Preparation of diol 33



27 **33**

In slight modification of a procedure[2] detailed by Inoue and coworkers, pyrrole ester **27** (332 mg, 0.450 mmol, 1.0 equiv) was dissolved in MeOH (45 mL) and KHF_2 (3.0 M in H_2O, 3 mL, 20 equiv) was then added. The resulting solution was warmed to 40 ºC and stirring continued for 4 h at which point LCMS showed full consumption of the starting material. The reaction mixture was then cooled to ambient temperature and filtered through a plug of Na_2SO_4 (18 g) and silica gel (18 g) to remove H_2O and HF generated from KHF_2 (Note: If the reaction mixture was directly concentrated without filtration, the acidity of the reaction mixture resulted in the removal of the C_{10} BOM group), washing with EtOAc to ensure complete elution of the desired product. The filtrate was concentrated *in vacuo* and the crude residue was purified by SiO_2 flash chromatography (40% EtOAc/hexanes) to afford free diol **33** as a white foam (288 mg, 0.403 mmol, 90% yield).

TLC (40% EtOAc/hexanes): R_f 0.40 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H, N***H***), 7.45 – 7.29 (m, 10H, ***Ph***CH_2OCH_2O), 7.04 (td, *J* = 2.7, 1.4 Hz, 1H, C_{26}), 6.90 (ddd, *J* = 3.8, 2.4, 1.5 Hz, 1H, C_{24}), 6.30 (dt, *J* = 3.9, 2.5 Hz, 1H, C_{25}), 6.26 (q, *J* = 2.3 Hz, 1H, C_3), 5.19 (d, *J* = 6.3 Hz, 1H,

PhCH$_2$OC***H***$_2$O), 5.10 (p, *J* = 1.6 Hz, 1H, C$_{18}$), 4.94 (s, 2H, PhCH$_2$OC***H***$_2$O), 4.91 (d, *J* = 6.3 Hz, 1H, PhCH$_2$OC***H***$_2$O), 4.91 – 4.87 (m, 1H, C$_{18}$), 4.83 (d, *J* = 12.2 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.71(d, *J* = 8.0 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.69 (d, *J* = 8.0 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.65 (d, *J* = 12.2 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.43 (s, 1H, OH, C$_4$O***H***), 4.05 (s, 1H, C$_{12}$O***H***), 3.94 (d, *J* = 10.3 Hz, 1H, C$_{10}$), 3.42 (d, *J* = 19.8 Hz, 1H, C$_{14}$), 2.42 (d, *J* = 19.7 Hz, 1H, C$_{14}$), 2.17 – 2.03 (m, 1H, C$_9$), 1.94 (d, *J* = 2.4 Hz, 3H, C$_{17}$), 1.83 (ddd, *J* = 14.4, 4.1, 1.9 Hz, 1H, C$_8$), 1.75 (d, *J* = 1.2 Hz, 3H, C$_{19}$), 1.67 (ddt, *J* = 10.3, 4.1, 1.5 Hz, 1H, C$_7$), 1.62 – 1.52 (m, 1H, C$_8$), 1.46 (td, *J* = 12.7, 4.1 Hz, 1H, C$_7$), 1.13 (s, 3H, C$_{20}$), 1.12 (d, *J* = 5.8 Hz, 3H, C$_{21}$).

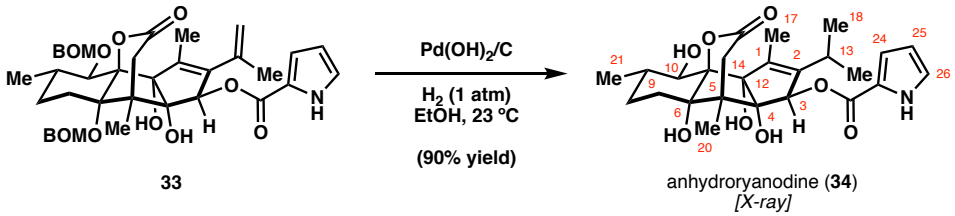
^{13}C NMR (101 MHz, CDCl$_3$): δ 168.2 (*C*$_{15}$=O), 160.4 (*C*$_{22}$=O), 140.9 (C$_2$), 138.9 (C$_{13}$), 137.7 (C$_{Ph}$), 137.4 (C$_{Ph}$), 136.6 (C$_1$), 128.7 (C$_{Ph}$), 128.4 (C$_{Ph}$), 128.4 (C$_{Ph}$), 128.2 (C$_{Ph}$), 127.7 (C$_{Ph}$), 127.7 (C$_{Ph}$), 123.9 (C$_{26}$), 121.9 (C$_{23}$), 117.4 (C$_{18}$), 115.8 (C$_{24}$), 110.7 (C$_{25}$), 97.3 (PhCH$_2$O***C***H$_2$O), 91.9 (C$_{12}$), 91.4 (C$_4$), 90.7 (C$_6$), 90.3 (PhCH$_2$O***C***H$_2$O), 88.6 (C$_{11}$), 82.9 (C$_3$), 80.6 (C$_{10}$), 71.9 (Ph***C***H$_2$OCH$_2$O), 70.5 (Ph***C***H$_2$OCH$_2$O), 49.3 (C$_5$), 39.8 (C$_{14}$), 33.2 (C$_9$), 28.1 (C$_7$), 21.1 (C$_{19}$), 21.0 (C$_8$), 18.9 (C$_{21}$), 15.9 (C$_{20}$), 13.2 (C$_{17}$).

FTIR (NaCl, thin film): 3448, 2929, 1744, 1703, 1159, 1115, 1010 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for [M+Na]$^+$ 736.3098, found 772.3099.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –70° (*c* = 0.460, CHCl$_3$).

Preparation of anhydroryanodine (34)



An oven-dried, 2 dram vial was charged with **33** (15 mg, 0.021 mmol, 1.0 equiv), $Pd(OH)_2/C$ (20 wt %, 23 mg), followed by absolute EtOH (2.1 mL). The suspension was sparged with N_2 for 3 min, then H_2 for 3 min via a three-walled balloon. The suspension was subsequently stirred for 1 h at ambient temperature under H_2, then sparged with N_2 to remove excess H_2, diluted with EtOAc (5 mL), filtered through a short pad of Celite, and concentrated *in vacuo*. Purification of the crude residue by SiO_2 flash chromatography (5% MeOH/$CHCl_3$) afforded (+)-anhydroryanodine (**34**) as a white powder (9 mg, 0.019 mmol, 90% yield).

TLC (5% MeOH/$CHCl_3$): R_f 0.35 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, CD_3OD): δ 7.09 (dd, J = 2.6, 1.5 Hz, 1H, C_{26}), 6.90 (dd, J = 3.8, 1.5 Hz, 1H, C_{24}), 6.28 (dd, J = 3.8, 2.5 Hz, 1H, C_{25}), 6.20 (q, J = 2.3 Hz, 1H, C_3), 4.03 (d, J = 10.3 Hz, 1H, C_{10}), 3.45 (d, J = 19.8 Hz, 1H, C_{14}), 2.80 (p, J = 7.1 Hz, 1H, C_{13}), 2.56 (d, J = 19.7 Hz, C_{14}, 1H), 1.89 (d, J = 2.3 Hz, 3H, C_{17}), 1.83 (td, J = 10.5, 5.8 Hz, 1H, C_9), 1.66-1.58 (m, 2H, C_7), 1.57-1.49 (m, 2H, C_8), 1.12 (d, J = 7.0 Hz, 3H, C_{19}), 1.11 (d, J = 7.0 Hz, 3H, C_{18}), 1.01 (d, J = 7.0 Hz, 3H, C_{21}), 0.99 (s, 3H, C_{20}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3 (C_{15}=O), 161.8 (C_{22}=O), 144.6 (C_2), 138.3 (C_1), 125.8 (C_{26}), 123.2 (C_{23}), 117.0 (C_{24}), 111.1 (C_{25}), 94.0 (C_{12}), 92.7 (C_4), 90.2 (C_6), 84.7

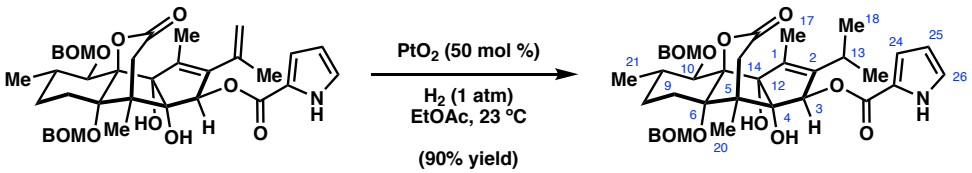
(C_3), 84.2 (C_{11}), 72.6 (C_{10}), 40.5 (C_{14}), 35.2 (C_9), 28.7 (C_7), 28.2 (C_{13}), 26.3 (C_8), 21.5 (C_{18}/ C_{19}), 19.5 (C_{21}), 18.8 (C_{18}/C_{19}), 14.3 (C_{20}), 12.4 (C_{17}).

FTIR (NaCl, thin film): 3408, 2963, 1740, 1690, 1409, 1315, 1165 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M–H]^-$ 474.2128, found 474.2112.

$[\alpha]_D^{25}$: +18° (*c* = 0.345, MeOH).

Preparation of 36



33 36

A 20 mL scintillation vial was charged with diene **33** (94 mg, 0.132 mmol, 1.0 equiv), PtO_2 (15 mg, 0.066 mmol, 0.5 equiv), followed by EtOAc (6 mL). The suspension was sparged with N_2 for 3 min, then H_2 for 3 min via a three-walled balloon. The suspension was subsequently stirred for 25 min at ambient temperature under H_2, then sparged with N_2 to remove excess H_2, diluted with EtOAc (5 mL), filtered through a short pad of Celite, and concentrated *in vacuo*. Purification of the crude residue by SiO_2 flash chromatography (40% EtOAc/hexane) afforded **36** (85 mg, 0.119 mmol, 90% yield) as a white foam.

TLC (40% EtOAc/hexanes): R_f 0.40 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H, N***H***), 7.43 – 7.29 (m, 10H, ***Ph***CH_2OCH_2O), 7.07 (td, *J* = 2.7, 1.4 Hz, 1H, C_{26}), 6.92 (ddd, *J* = 3.8, 2.4, 1.4 Hz, 1H, C_{24}), 6.33 (dt, *J* = 3.8, 2.6 Hz, 1H, C_{25}), 6.23 (q, *J* = 2.3 Hz, 1H, C_3), 5.18 (d, *J* = 6.4 Hz, 1H,

$PhCH_2OC\boldsymbol{H}_2O$), 4.92 (d, J = 6.4 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.92 (s, 2H, $PhCH_2OC\boldsymbol{H}_2O$), 4.83 (d, J = 12.2 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.71 (d, J = 12.0 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.67 (d, J = 12.0 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.65 (d, J = 12.2 Hz, 1H, $Ph\boldsymbol{CH}_2OCH_2O$), 4.39 (s, 1H, O***H***), 3.95 (s, 1H, O***H***), 3.92 (d, J = 10.4 Hz, 1H, C_{10}), 3.41 (d, J = 19.7 Hz, 1H, C_{14}), 2.80 (p, J = 7.0 Hz, 1H, C_{13}), 2.39 (d, J = 19.7 Hz, 1H, C_{14}), 2.18 – 2.03 (m, 1H, C_9), 1.91 (d, J = 2.4 Hz, 3H, C_{17}), 1.82 (dt, J = 13.2, 3.2 Hz, 1H, C_8), 1.70-1.63 (m, 1H, C_7), 1.60 – 1.51 (m, 1H, C_7), 1.46 (td, J = 12.3, 3.6 Hz, 1H, C_8), 1.13 (d, J = 7.0 Hz, 3H, C_{19}), 1.12 (d, 1.08 J = 7.0 Hz, 3H, C_{21}), 1.08 (s, 3H, C_{20}), 1.00 (d, J = 7.0 Hz, 3H, C_{18}).

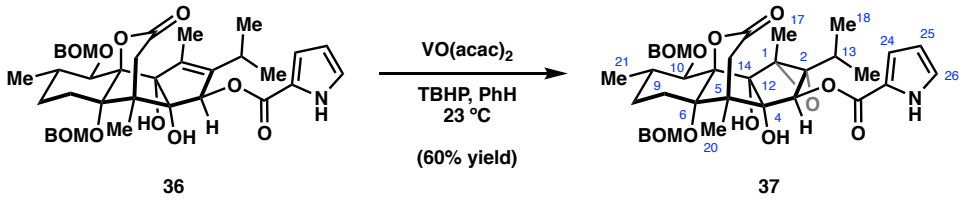
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C_{15}=O), 160.4 (C_{22}=O), 143.0 (C_2), 137.7 (C_{Ph}), 137.1 (C_{Ph}), 136.6 (C_1), 128.7 (C_{Ph}), 128.4 (C_{Ph}), 128.3 (C_{Ph}), 128.2 (C_{Ph}), 127.7 (C_{Ph}), 127.7 (C_{Ph}), 124.0 (C_{26}), 122.1 (C_{23}), 115.7 (C_{24}), 110.9 (C_{25}), 97.4 ($PhCH_2O\boldsymbol{C}H_2O$), 92.0 ($C_{12}$), 91.0 ($C_4$), 90.8 ($PhCH_2O\boldsymbol{C}H_2O$), 90.2 ($C_6$), 88.5 ($C_{11}$), 84.0 ($C_3$), 80.7 ($C_{10}$), 71.8 ($Ph\boldsymbol{C}H_2OCH_2O$), 70.5 ($Ph\boldsymbol{C}H_2OCH_2O$), 49.3 ($C_5$), 39.9 ($C_{14}$), 33.2 ($C_9$), 28.0 ($C_7$), 26.8 ($C_{13}$), 21.2 ($C_{18}$), 21.0 ($C_8$), 19.0 ($C_{19}$), 18.9 ($C_{21}$), 15.9 ($C_{20}$), 11.8 ($C_{17}$).

FTIR (NaCl, thin film): 3455, 2927, 1744, 1708, 1159, 1026 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+Na]^+$ 738.3254, found 738.3262.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$: +36° ($c$ = 0.380, $CHCl_3$).

Preparation of epoxide 37



A 50 mL, oven-dried, round-bottomed flask was charged with **36** (144 mg, 0.201 mmol, 1.0 equiv), $VO(acac)_2$ (80 mg, 0.302 mmol, 1.5 equiv) and PhH (10.1 mL). The resulting green solution was stirred at ambient temperature for 5 min prior to the dropwise addition of TBHP (5.0-5.5 M in decane, 0.2 mL, 1.01 mmol, 5.0 equiv). The resulting dark-brown solution was stirred for 2 h at ambient temperature before additional TBHP (5.0-5.5 M in decane, 0.2 mL, 1.005 mmol, 5.0 equiv) was added to the reaction mixture. Stirring was continued for 1 h until TLC analysis indicated complete consumption of starting material. The mixture was diluted with EtOAc (12 mL) and sat. aq. $Na_2S_2O_3$ (12 mL) was next slowly added. The two layers were separated, and the organic layer washed with sat. aq. $Na_2S_2O_3$ (2 x 12 mL) and sat. aq. $NaHCO_3$ (2 x 12 mL). The combined aqueous layers were extracted with EtOAc (2 x 6 mL), and the combined organic layers were washed with brine (6 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (30 to 40% EtOAc/hexanes) to afford epoxide **37** (88 mg, 0.120 mmol, 60% yield).

TLC (40% EtOAc/hexanes): R_f 0.40 (UV, *p*-anisaldehyde).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.40 (s, 1H, N***H***), 7.42 – 7.29 (m, 10H, ***Ph***CH_2OCH_2O), 7.09 (td, J = 2.8, 1.4 Hz, 1H, C_{26}), 6.93 (ddd, J = 3.8, 2.5, 1.4 Hz, 1H, C_{24}), 6.35 (dt, J = 3.7, 2.6 Hz, 1H, C_{25}), 5.76 (s, 1H, C_3), 5.19 (d, J = 6.6 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.03 (d, J

= 6.6 Hz, 1H, PhCH$_2$OC***H***$_2$O), 4.90 (d, *J* = 6.2 Hz, 1H, PhCH$_2$OC***H***$_2$O), 4.86 (d, *J* = 12.0 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.82 (d, *J* = 6.1 Hz, 1H, PhCH$_2$OC***H***$_2$O), 4.69 (d, *J* = 11.8 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.65 (d, *J* = 11.8 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.65 (d, *J* = 12.0 Hz, 1H, Ph***C*H**$_2$OCH$_2$O), 4.00 (d, *J* = 10.5 Hz, 1H, C$_{10}$), 3.98 (d, *J* = 0.7 Hz, 1H, O***H***), 3.87 (d, *J* = 20.4 Hz, 1H, C$_{14}$), 3.19 (s, 1H, O***H***), 2.56 (d, *J* = 20.3 Hz, 1H, C$_{14}$), 2.18 – 2.07 (m, 1H, C$_9$), 1.86 – 1.80 (m, 1H, C$_8$), 1.77 (dd, *J* = 13.8, 6.6 Hz, 1H, C$_{13}$), 1.71 (s, 3H, C$_{17}$), 1.71-1.64 (m, 1H, C$_7$), 1.62-1.53 (m, 1H, C$_8$), 1.57 – 1.47 (m, 1H, C$_7$), 1.22 (d, *J* = 7.4 Hz, 3H, C$_{19}$), 1.16 (d, *J* = 6.5 Hz, 3H, C$_{21}$), 1.02 (d, *J* = 7.0 Hz, 3H, C$_{18}$), 1.00 (s, 3H, C$_{20}$).

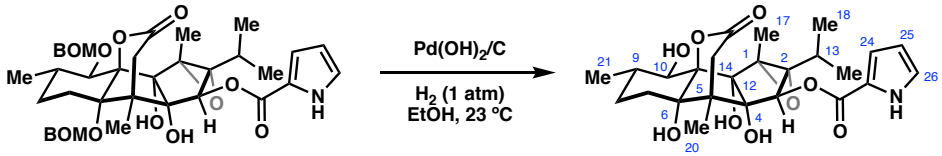
^{13}C NMR (126 MHz, CDCl$_3$): δ 168.1 (*C*$_{15}$=O), 159.3 (*C*$_{22}$=O), 137.9 (C$_{Ph}$), 136.3 (C$_{Ph}$), 128.6 (C$_{Ph}$), 128.4 (C$_{Ph}$), 128.3 (C$_{Ph}$), 128.2 (C$_{Ph}$), 127.7 (C$_{Ph}$), 127.6 (C$_{Ph}$), 124.6 (C$_{26}$), 121.5 (C$_{23}$), 115.8 (C$_{24}$), 111.0 (C$_{25}$), 97.6 (PhCH$_2$O***C***H$_2$O), 93.2 (C$_4$), 91.2 (C$_6$), 91.1 (C$_{11}$), 90.6 (C$_{12}$), 89.6 (PhCH$_2$O***C***H$_2$O), 81.3 (C$_{10}$), 81.0 (C$_3$), 76.2 (C$_1$), 74.8 (C$_2$), 71.3 (Ph***C***H$_2$OCH$_2$O), 70.6 (Ph***C***H$_2$OCH$_2$O), 50.3 (C$_5$), 38.6 (C$_{14}$), 32.6 (C$_9$), 29.4 (C$_{13}$), 27.9 (C$_7$), 20.6 (C$_8$), 18.9 (C$_{21}$), 17.6 (C$_{18}$), 17.2 (C$_{19}$), 16.3 (C$_{20}$), 14.5 (C$_{17}$).

FTIR (NaCl, thin film): 3282, 2933, 1748, 1715, 1020 cm^{-1}.

HRMS (MM:ESI–APCI) : calc'd for [M+Na]$^+$ 754.3203, found 738.3215.

$[\alpha]_D^{25}$: +40° (*c* = 0.450, CHCl$_3$).

Preparation of anhydroryanodine epoxide (35)



A 25 mL round-bottomed flask was charged with epoxide **37** (50 mg, 0.068 mmol, 1.0 equiv), $Pd(OH)_2/C$ (20 wt %, 75 mg), followed by absolute EtOH (6.8 mL). The suspension was sparged with N_2 for 3 min, then H_2 for 3 min via a three-walled balloon. The suspension was subsequently stirred for 3 h at ambient temperature under H_2, then sparged with N_2 to remove excess H_2, diluted with EtOAc (5 mL), filtered through a short pad of Celite, and concentrated *in vacuo*. The resulting white powder was used in the next step without further purification.

A sample of anhydroryanodine epoxide (**35**) was purified by preparative thin-layer chromatography (5% MeOH/$CHCl_3$) for characterization purposes.

TLC (10% MeOH/$CHCl_3$): R_f 0.50 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, CD_3OD): δ 7.12 (dd, *J* = 2.5, 1.4 Hz, 1H, C_{26}), 6.93 (dd, *J* = 3.8, 1.5 Hz, 1H, C_{24}), 6.31 (dd, *J* = 3.8, 2.5 Hz, 1H, C_{25}), 5.66 (s, 1H, C_3), 4.09 (d, *J* = 10.5 Hz, 1H, C_{10}), 3.90 (d, *J* = 20.4 Hz, 1H, C_{14}), 2.75 (d, *J* = 20.4 Hz, 1H, C_{14}), 1.91 – 1.81 (m, 1H, C_9), 1.77 (p, *J* = 7.2 Hz, 1H, C_{13}), 1.68 (s, 3H, C_{17}), 1.64 – 1.50 (m, 2H, C_8), 1.62-1.49 (m, 2H, C_7), 1.20 (d, *J* = 7.3 Hz, 3H, C_{19}), 1.11 (d, *J* = 6.4 Hz, 3H, C_{21}), 1.00 (d, *J* = 7.0 Hz, 3H, C_{18}), 0.93 (s, 3H, C_{20}).

^{13}C NMR (101 MHz, CD_3OD): δ 171.5 (C_{15}=O), 160.8 (C_{22}=O), 126.3 (C_{26}), 122.6 (C_{23}), 117.1 (C_{24}), 111.3 (C_{25}), 95.0 (C_{12}), 92.6 (C_4), 91.9 (C_{11}), 85.2 (C_6), 82.1 (C_3), 77.3

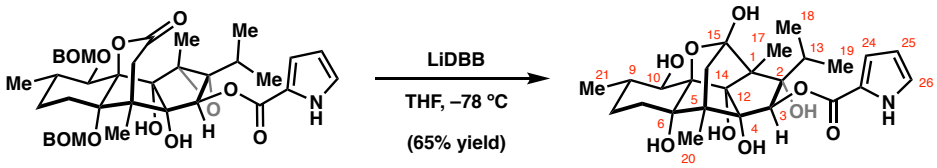
(C_1), 75.3 (C_2), 72.9 (C_{10}), 50.2 (C_5), 39.4 (C_{14}), 34.7 (C_9), 30.6 (C_{13}), 28.6 (C_8), 25.9 (C_7), 18.7 (C_{21}), 18.2 (C_{19}), 17.6 (C_{18}), 15.5 (C_{17}), 14.7 (C_{20}).

FTIR (NaCl, thin film): 3419, 2967, 1749, 1707, 1402, 1324, 1128, 1085 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M–H]^-$ 490.2083, found 490.2103.

$[\alpha]_D^{25}$**:** +18° (*c* = 0.705, MeOH).

Preparation of ryanodine (1)



Fresh LiDBB[21] was prepared according to the following procedure: An oven-dried, 25 mL Schlenk tube containing a borosilicate glass-coated magnetic stirbar was charged with 4,4′-di-*tert*-butylbiphenyl (550 mg, 2.0 mmol) and freshly cut lithium wire (14.0 mg, 2.0 mmol) (Note: Immediately prior to use, lithium wire was washed with hexanes, hammered out into a foil, and cut into several small strips). The Schlenk tube was evacuated and refilled with Ar three times before anhydrous THF (12.5 mL) was added and the resulting reaction mixture was then cooled to 0 ºC via an ice/water bath. After vigorously stirring (900-1000 rpm) at 0 ºC for 10 min, the solution became a deep-green, characteristic of the DBB radical-anion. After the reaction mixture was stirred at 0 ºC for approximately 4 h, the LiDBB solution (~0.16 M) was immediately used.

An oven-dried, 50 mL round-bottomed flask containing a borosilicate glass-coated magnetic stirbar was charged with epoxide **37** (64 mg, 0.087 mmol, 1.0 equiv) and anhydrous THF (4.3 mL) under Ar. The resulting solution was cooled to –78 ºC via a dry

ice/acetone bath. Freshly prepared LiDBB (0.16 M, 5.4 mL, 0.87 mmol, 10 equiv) was added dropwise via syringe along the side of the flask until the dark green color persisted. The deep green mixture was stirred for 0.5 h at –78 ºC and then sat. aq. NH_4Cl (10 mL) was added before the reaction mixture was warmed to ambient temperature. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (0 to 5 to 10% MeOH/$CHCl_3$) to afford ryanodine (**1**) as a white solid (28 mg, 0.057 mmol, 65% yield) (Note: The purification was made easier by first flushing with $CHCl_3$ (100 mL) until all of the excess 4,4′-di-*tert*-butylbiphenyl was removed).

TLC (10% MeOH/$CHCl_3$): R_f 0.33 (UV, *p*-anisaldehyde).

^{1}H NMR (600 MHz, CD_3OD): δ 7.04 (dd, *J* = 2.5, 1.5 Hz, 1H, C_{26}), 6.88 (dd, *J* = 3.7, 1.5 Hz, 1H, C_{24}), 6.24 (dd, *J* = 3.8, 2.5 Hz, 1H, C_{25}), 5.64 (s, 1H, C_3), 3.80 (d, *J* = 10.2 Hz, 1H, C_{10}), 2.57 (d, *J* = 13.6Hz, 1H, C_{14}), 2.27 (h, *J* = 6.8 Hz, C_{13}), 2.10 (td, *J* = 12.9, 5.2 Hz, 1H, C_7), 1.94 (d, *J* = 13.6 Hz, 1H, C_{14}), 1.85 (tdd, *J* = 10.2, 8.5, 5.6 Hz, 1H, C_9), 1.54 (dtd, *J* = 12.4, 5.2, 1.8 Hz, 1H, C_8), 1.48 (td, *J* = 13.0, 4.7 Hz, 1H, C_8), 1.40 (s, 3H, C_{17}), 1.26 (ddd, *J* = 12.7, 4.6, 2.0 Hz, 1H, C_7), 1.12 (d, *J* = 6.7 Hz, 3H, C_{19}), 1.02 (d, *J* = 6.5 Hz, 3H, C_{21}), 0.90 (s, 3H, C_{20}), 0.76 (d, *J* = 6.5 Hz, 3H, C_{18}).

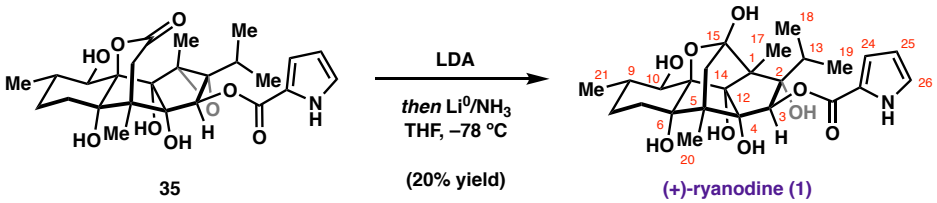
^{13}C NMR (101 MHz, CD_3OD): δ 161.8 (C_{22}=O), 125.6 (C_{26}), 123.3 (C_{23}), 117.0 (C_{24}), 110.9 (C_{25}), 102.9 (C_{15}), 96.7 (C_{12}), 92.3 (C_4), 90.8 (C_3), 87.4 (C_{11}), 86.5 (C_6), 84.3 (C_2), 72.8 (C_{10}), 65.9 (C_1), 49.6 (C_5), 41.8 (C_{14}), 35.4 (C_9), 30.9 (C_{13}), 29.3 (C_8), 26.8 (C_7), 19.5 (C_{19}), 19.0 (C_{21}), 18.9 (C_{18}), 12.6 (C_{20}), 10.2 (C_{17}).

FTIR (NaCl, thin film): 3335, 2969, 1691, 1410, 1324, 1164, 988, 750 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M–H]^-$ 492.2239, found 492.2250.

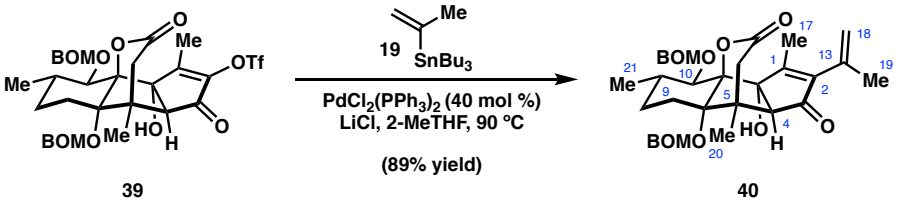
$[\alpha]_D^{25}$**:** +15° (*c* = 0.705, MeOH).

Figure 3, entry 2



An oven-dried, 1 dram vial was charged with anhydroryanodine epoxide **35** (5 mg, 0.010 mmol, 1.0 equiv) and THF (1 mL). The solution was cooled to –78 ºC via a dry ice/acetone bath before a freshly prepared solution of LDA (1.0 M in THF, 60 µL, 0.060 mmol, 5.9 equiv) was added. After 1 h of stirring at –78 ºC, the pale-yellow solution was transferred to a pre-cooled dark-blue solution of lithium (1.7 mg) in freshly distilled ammonia (3 mL) via syringe at –78 ºC and the resulting reaction mixture was stirred for 15 min. After the addition of solid ammonium chloride (50 mg), stirring was halted and the colorless reaction mixture was removed from the dry ice/acetone bath and warmed to ambient temperature over 45 min, resulting in the slow evaporation of ammonia. The residue was dissolved in water (1 mL) and extracted with $CHCl_3$ (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by preparative thin-layer chromatography (10% MeOH/$CHCl_3$) to afford ryanodine (**1**) (1 mg, 0.002 mmol, 20% yield).

Preparation of enone 22



39 **40**

In a nitrogen-filled glovebox, an oven-dried, 20 mL scintillation vial was charged with vinyl triflate **39** (302 mg, 0.425 mmol, 1.0 equiv), $PdCl_2(PPh)_3$ (119 mg, 0.170 mmol, 40 mol %), anhydrous LiCl (108 mg, 2.55 mmol, 6.0 equiv), tributyl(2-propenyl)stannane (422 mg, 1.27 mmol, 3.0 equiv), and anhydrous 2-methyltetrahydrofuran (6.4 mL). The vial was sealed with a Teflon-lined cap, and placed in a preheated heating block at 90 ºC. After 14 h, the vial was removed from the heating block and allowed to cool to ambient temperature, then sat. aq. KF (10 mL) was added. The biphasic mixture was vigorously stirred for 45 min, then diluted with EtOAc (30 mL). The two layers were separated and the organic layer washed with additional sat. aq. KF (10 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL), and the combined organic layers next washed with brine (20 mL), dried over Na_2SO_4, filtered over Celite, and concentrated *in vacuo* to afford an orange oil. Purification by SiO_2 flash chromatography (30 to 40 to 50% EtOAc/hexanes) afforded the desired product **40** as a pale yellow foam (228 mg, 0.378 mmol, 89% yield).

TLC (40% EtOAc/hexanes): R_f 0.45 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.27 (m, 10H, ***Ph***CH_2OCH_2O), 5.22 (p, J = 1.7 Hz, 1H, C_{18}), 5.07 (d, J = 5.4 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.02 (d, J = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.97 (d, J = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.84 (d, J = 5.4 Hz, 1H,

PhCH$_2$OC***H***$_2$O), 4.79 (dd, *J* = 1.9, 1.0 Hz, 1H, C$_{18}$), 4.77 (d, *J* = 12.1 Hz, 1H, PhC***H***$_2$OCH$_2$O), 4.71 (d, *J* = 12.1 Hz, 1H, PhC***H***$_2$OCH$_2$O), 4.71 (d, *J* = 12.3 Hz, 1H, PhC***H***$_2$OCH$_2$O), 4.65 (d, *J* = 12.3 Hz, 1H, PhC***H***$_2$OCH$_2$O), 4.55 (s, 1H, OH), 4.00 (d, *J* = 10.5 Hz, 1H, C$_{10}$), 2.90 (d, *J* = 1.4 Hz, 1H, C$_4$), 2.36 (d, *J* = 19.6 Hz, 1H, C$_{14}$), 2.27 (dd, *J* = 19.6, 1.6 Hz, 1H, C$_{14}$), 2.20 (s, 3H, C$_{17}$), 2.12 – 2.04 (m, 1H, C$_9$), 1.96 – 1.89 (m, 1H, C$_7$), 1.87 (t, *J* = 1.3 Hz, 3H, C$_{19}$), 1.62 (td, *J* = 7.7, 7.1, 3.1 Hz, 2H, C$_8$), 1.58 – 1.49 (m, 1H, C$_7$), 1.28 (s, 3H, C$_{20}$), 1.05 (d, *J* = 6.6 Hz, 3H, C$_{21}$).

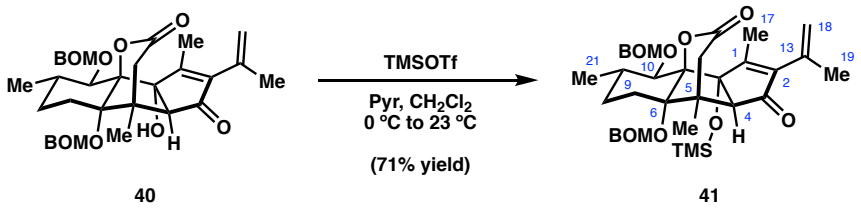
^{13}C NMR (101 MHz, CDCl$_3$): δ 204.9 (*C$_3$*=O), 169.6 (C$_1$), 167.1 (*C$_{15}$*=O), 145.9 (C$_2$), 137.0 (C$_{Ph}$), 136.8 (C$_{Ph}$), 136.3 (C$_{13}$), 128.7 (C$_{Ph}$), 128.6 (C$_{Ph}$), 128.6 (C$_{Ph}$), 128.1 (C$_{Ph}$), 128.1 (C$_{Ph}$), 128.0 (C$_{Ph}$), 127.7 (C$_{Ph}$), 117.6 (C$_{18}$), 97.0 (PhCH$_2$O***C***H$_2$O), 91.5 (C$_6$), 91.1 (C$_{11}$), 89.7 (PhCH$_2$O***C***H$_2$O), 89.3 (C$_{12}$), 79.9 (C$_{10}$), 71.0 (Ph***C***H$_2$OCH$_2$O), 70.3 (Ph***C***H$_2$OCH$_2$O), 66.0 (C$_4$), 45.4 (C$_5$), 39.2 (C$_{14}$), 33.2 (C$_9$), 27.9 (C$_8$), 21.7 (C$_{19}$), 21.1 (C$_7$), 19.9 (C$_{20}$), 18.5 (C$_{21}$), 14.6 (C$_{17}$).

FTIR (NaCl, thin film): 3387, 2928, 1748, 1698, 1027 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for [M+H]$^+$ 603.2952, found 603.2959.

$[\alpha]_D^{25}$: +100° (*c* = 0.200, CHCl$_3$).

Preparation of TMS ether 41



40 **41**

To an oven-dried, 100 mL round-bottomed flask was added enone **40** (944 mg, 1.57 mmol, 1.0 equiv), anhydrous CH_2Cl_2 (31 mL), and freshly distilled pyridine (1.27 mL, 15.7 mmol, 10 equiv). The solution was cooled to 0 ºC in an ice/water bath and TMSOTf (0.85 mL, 4.70 mmol, 3.0 equiv) was added via syringe. The ice/water bath was then removed and stirring was continued at ambient temperature. Additional portions of TMSOTf (0.85 mL, 4.70 mmol, 3.0 equiv) and pyridine (1.27 mL, 15.7 mmol, 10.0 equiv) were added every 12 h until TLC analysis indicated complete consumption of the starting material (*ca.* 36 h). The reaction mixture was next diluted with CH_2Cl_2 (15 mL) and carefully quenched with the addition of sat. aq. $NaHCO_3$ (30 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (20 to 30 to 35% EtOAc/hexanes) to afford TMS ether **41** (750 mg, 1.11 mmol, 71% yield) as a colorless foam.

TLC (30% EtOAc/hexanes): R_f 0.34 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 10H, ***Ph***CH_2OCH_2O), 5.24 (p, *J* = 1.6 Hz, 1H, C_{18}), 5.08 (d, *J* = 7.0 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 5.01 (s, 2H, $PhCH_2OC\boldsymbol{H}_2O$), 4.92 (d, *J* = 7.0 Hz, $PhCH_2OC\boldsymbol{H}_2O$), 4.84 (d, *J* = 11.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.81 (d, *J* =

10.9 Hz, PhC***H***$_2$OCH$_2$O), 4.79 (s, 1H, C$_{18}$), 4.60 (d, *J* = 11.9 Hz, 1H, PhC***H***$_2$OCH$_2$O), 4.57 (d, *J* = 10.9 Hz, 1H, PhC***H***$_2$OCH$_2$O), 4.02 (d, *J* = 10.5 Hz, 1H, C$_{10}$), 3.00 (s, 1H, C$_4$), 2.33 (d, *J* = 19.5 Hz, 1H, C$_{14}$), 2.27 (d, *J* = 19.5 Hz, 1H, C$_{14}$), 2.20 (s, 3H, C$_{17}$), 2.14 – 2.00 (m, 1H, C$_9$), 1.99 – 1.90 (m, 1H, C$_7$), 1.88 (t, *J* = 1.2 Hz, 3H, C$_{19}$), 1.78 (qd, *J* = 13.0, 4.2 Hz, 1H, C$_8$), 1.71- 1.58 (m, 1H, C$_8$), 1.56 – 1.44 (m, 1H, C$_7$), 1.22 (s, 3H, C$_{20}$), 1.15 (d, *J* = 6.5 Hz, 3H, C$_{21}$), 0.11 (s, 9H, TMS).

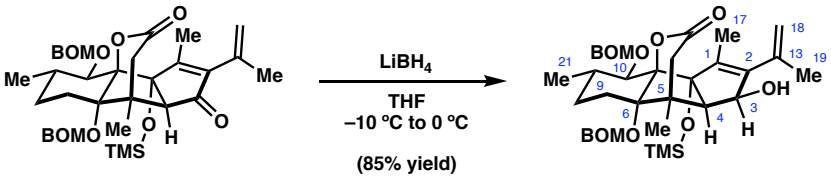
^{13}C NMR (101 MHz, CDCl$_3$): δ 205.0 (*C$_3$*=O), 170.8 (C$_1$), 167.3 (*C$_{15}$*=O), 145.6 (C$_2$), 137.9 (C$_{Ph}$), 137.0 (C$_{Ph}$), 136.1 (C$_{13}$), 128.6 (C$_{Ph}$), 128.4 (C$_{Ph}$), 128.0 (C$_{Ph}$), 127.7 (C$_{Ph}$), 127.7 (C$_{Ph}$), 127.6 (C$_{Ph}$), 117.5 (C$_{18}$), 98.1 (PhCH$_2$O***C***H$_2$O), 92.9 (C$_{11}$), 91.7 (C$_{12}$), 91.0 (C$_6$), 89.9 (PhCH$_2$O***C***H$_2$O), 81.7 (C$_{10}$), 70.5 (Ph***C***H$_2$OCH$_2$O), 65.1 (C$_4$), 46.6 (C$_5$), 39.2 (C$_{14}$), 32.9 (C$_9$), 27.9 (C$_8$), 21.5 (C$_{19}$), 21.1 (C$_7$), 20.4 (C$_{20}$), 19.0 (C$_{21}$), 14.7 (C$_{17}$), 1.9 (Si(*Me*)$_3$).

FTIR (NaCl, thin film): 2954, 1751, 1699, 1025 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for [M+H]$^+$ 675.3348, found 675.3349.

$[\alpha]_D^{25}$: +124° (*c* = 0.245, CHCl$_3$).

Preparation of alcohol 42



41 **42**

To an oven-dried, 100 mL round-bottomed flask was added enone **41** (749 mg, 1.11 mmol, 1.0 equiv) and anhydrous THF (22 mL). The solution was cooled to –10 ºC in an ice/acetone bath and solid LiBH$_4$ (121 mg, 5.55 mmol, 5.0 equiv) was added. After 1

h, a second portion of solid $LiBH_4$ (121 mg, 5.55 mmol, 5.0 equiv) was added before warming the reaction mixture to 0 ºC with an ice/water bath. Stirring was continued at 0 ºC for 1 h after which a third portion of solid $LiBH_4$ (121 mg, 5.55 mmol, 5.0 equiv) was added at 0 ºC. The reaction was allowed to stir at 0 ºC an additional 1 h before sat. aq. NH_4Cl (35 mL) was *slowly* added to the reaction. The mixture was diluted with EtOAc (15 mL), the two layers separated, and the organic layer washed with an additional portion of sat. aq. NH_4Cl (35 mL). The combined aqueous layers were extracted with EtOAc (3 x 40 mL), and the combined organic layers next dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (30 to 40 to 50% EtOAc/hexanes) to afford the desired product **42** as a colorless foam (635 mg, 0.94 mmol, 85% yield).

TLC (40% EtOAc/hexanes): R_f 0.37 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 10H, ***Ph***CH_2OCH_2O), 5.21 (p, *J* = 1.7 Hz, 1H, C_{18}), 5.22 – 5.19 (m, 1H, C_3), 5.02 (d, *J* = 6.6 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.97 (d, *J* = 7.9 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.95 (d, *J* = 7.9 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.92 (d, *J* = 6.6 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.90 (dd, *J* = 2.0, 1.0 Hz, 1H, C_{18}), 4.84 (d, *J* = 11.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.78 (d, *J* = 11.6 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.61 (d, *J* = 11.6 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.55 (d, *J* = 11.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 3.95 (d, *J* = 10.4 Hz, 1H, C_{10}), 3.33 (d, *J* = 19.6 Hz, 1H, C_{14}), 3.06 (dd, *J* = 8.0, 1.4 Hz, 1H, C_4), 2.17 (dd, *J* = 19.6, 1.4 Hz, 1H, C_{14}), 2.11 – 1.98 (m, 1H, C_9), 1.88 (t, *J* = 1.2 Hz, 3H, C_{19}), 1.89 – 1.86 (m, 1H, C_7), 1.81 (d, *J* = 2.2 Hz, 3H, C_{17}), 1.73 (d, *J* = 3.2 Hz, 1H, OH), 1.70 – 1.59 (m, 2H,

C_8), 1.56 – 1.45 (m, 1H, C_7), 1.20 (s, 3H, C_{20}), 1.14 (d, J = 6.5 Hz, 3H, C_{21}), 0.10 (s, 9H, TMS).

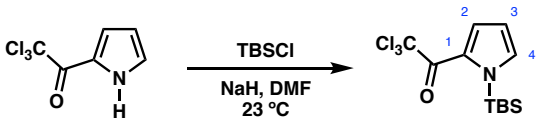
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.4 (C_{15}=O), 146.3 (C_1), 139.0 (C_2), 138.2 (C_{Ph}), 138.0 (C_{13}), 137.3 (C_{Ph}), 128.5 (C_{Ph}), 128.3 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 127.4 (C_{Ph}), 116.7 (C_{18}), 98.2 ($PhCH_2O\boldsymbol{C}H_2O$), 97.2 ($C_{12}$), 93.0 ($C_{11}$), 89.5 ($C_6$), 89.3 ($PhCH_2O\boldsymbol{C}H_2O$), 82.3 ($C_{10}$), 74.5 ($C_3$), 70.3 ($Ph\boldsymbol{C}H_2OCH_2O$), 70.1 ($Ph\boldsymbol{C}H_2OCH_2O$), 58.0 ($C_4$), 47.1 ($C_5$), 39.2 ($C_{14}$), 33.3 ($C_9$), 28.0 ($C_8$), 21.4 ($C_{19}$), 21.2 ($C_{20}$), 20.3 ($C_7$), 19.1 ($C_{21}$), 12.7 ($C_{17}$), 1.8 (Si(*Me*)$_3$).

FTIR (NaCl, thin film): 3459, 2954, 1716, 1026 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+Na]^+$ 699.3324, found 699.3325.

$[\alpha]_D^{25}$: –17° (c = 0.275, $CHCl_3$).

Preparation of TBS-protected pyrrole 45



26 (76% yield) 45

To a 100 mL, oven-dried flask was added NaH (dry, 339 mg, 14.1 mmol, 1.0 equiv) in a nitrogen-filled glovebox. The flask was capped with a rubber septum, removed from the glovebox, and anhydrous DMF (12 mL) was then added. The resulting slurry was cooled to 0 ºC in an ice/water bath and after 15 min, 2-(trichloroacetyl)pyrrole (3.0 g, 14.1 mmol, 1.0 equiv) in anhydrous DMF (12 mL) was added dropwise by cannula transfer over 10 min. [Caution! Rapid generation of H_2 gas. A vent needle was routinely used to prevent over-pressurization.] Upon complete addition, the reaction

mixture was warmed to ambient temperature and stirring was continued for another 30 min before TBSCl (2.55 g, 16.9 mmol, 1.2 equiv) in anhydrous DMF (12 mL) was added dropwise by cannula transfer over 10 min, during which time the yellow-brown solution fades to a pale pink slurry. The reaction was continued for 30 min and then diluted with Et_2O (50 mL) and carefully quenched with the addition of sat. aq. NH_4Cl (50 mL). The layers were separated and the aqueous layer next extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford an orange oil. Purification by SiO_2 flash chromatography (1 to 2 to 3% Et_2O/hexanes) afforded TBS-protected pyrrole **45** as a thick, slightly yellow oil (3.52 g, 10.8 mmol, 76% yield) that solidifies to a colorless solid upon cooling to –20 ºC.

TLC (2% Et_2O/hexanes): R_f 0.44 (UV, *p*-anisaldehyde).

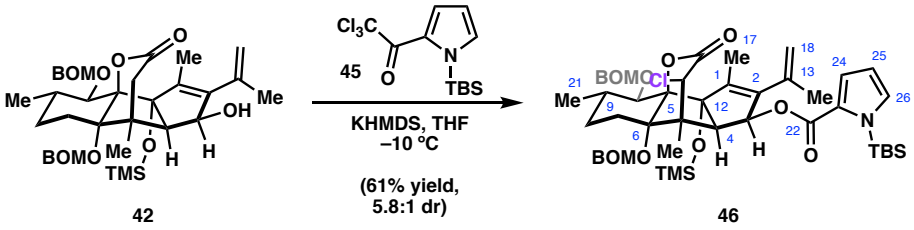
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 4.0, 1.3 Hz, 1H, C_2), 7.27 (dd, *J* = 2.5, 1.3 Hz, 1H, C_4), 6.40 (dd, *J* = 3.9, 2.5 Hz, 1H, C_3), 0.95 (s, 9H, Si(***t-Bu***)Me_2), 0.54 (s, 6H, Si(*t*-Bu)***Me***$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8 (*C*=O), 136.7 (C_4), 127.9 (C_1), 126.8 (C_2), 112.1 (C_3), 96.1 (***C***Cl_3), 27.3 (Si–C(***C***$H_3)_3$), 19.6 (Si–***C***$(CH_3)_3$), –1.4 (Si(***C***$H_3)_2$).

FTIR (NaCl, thin film): 2954, 2932, 2896, 2860, 1677 cm^{-1}.

HRMS: calc'd for $[M-H]^-$ 324.0150, found 324.0153.

Preparation of chloride 46



In a nitrogen-filled glovebox, an oven-dried, 50 mL round-bottomed flask was charged with solid KHMDS (95%, 388 mg, 1.85 mmol, 2.0 equiv). The flask was capped with a rubber septum, removed from the glovebox, and anhydrous THF (3.7 mL) was added. The resulting mixture was stirred at ambient temperature for 10-15 min to ensure complete dissolution of the solid, then cooled to –10 ºC in an ice/acetone bath and stirring continued for 15 min before adding alcohol **42** (625 mg, 0.92 mmol, 1.0 equiv) in anhydrous THF (7.0 mL) (Note: alcohol **42** was azeotroped with PhH three times immediately prior to use) dropwise via syringe before another portion of THF (1.2 mL) was used to render the transfer quantitative. The pale-yellow reaction mixture was stirred an additional 10 min at –10 ºC before TBS-protected pyrrole **45** (754 mg, 2.31 mmol, 2.5 equiv) in anhydrous THF (4.1 mL) was added dropwise via syringe (Note: pyrrole **45** was azeotroped with PhH three times immediately prior to use). The resulting dark pink-orange reaction mixture was allowed 20 min at –10 ºC then quenched with the addition of sat. aq. NH_4Cl (5 mL), warmed to ambient temperature, and diluted with EtOAc (5 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude residue by SiO_2 flash chromatography (5 to 10 to 15% EtOAc/hexanes) afforded a 5.8:1 inseparable

diastereomeric mixture of chloride **46** as a yellow-orange foam (515 mg, 0.56 mmol, 61% yield).

An analytical sample of the major diastereomer of chloride **25** was obtained by a second round of purification via SiO_2 flash chromatography (1.5% EtOAc/CH_2Cl_2). The stereochemistry of the major diastereomer of the chloride substituted C_{14}–H was determined by nOe analysis.

TLC (10% EtOAc/hexanes): R_f 0.32 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 10H, ***Ph***CH_2OCH_2O), 7.11 (s, 1H, C_{26}), 7.10 (s, 1H, C_{24}), 6.38 (dd, *J* = 7.8, 2.4 Hz, 1H, C_3), 6.30 (t, *J* = 3.1 Hz, 1H, C_{25}), 5.26 (s, 1H, C_{14}), 5.10 (s, 1H, C_{18}), 5.00 (d, *J* = 6.5 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.99 (d, *J* = 6.3 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.96 (d, J = 6.4 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.89 (d, *J* = 6.6 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.87 (dd, *J* = 1.9, 1.0 Hz, 1H, C_{18}), 4.84 (d, *J* = 11.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.76 (d, *J* = 11.5 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.62 (d, *J* = 11.5 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.58 (d, *J* = 11.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 3.96 (d, *J* = 10.4 Hz, 1H, C_{10}), 3.43 (d, *J* = 7.9 Hz, 1H, C_4), 2.04 (m, 1H, C_9), 2.00 – 1.96 (m, 2H, C_7), 1.86 (d, *J* = 2.3 Hz, 3H, C_{17}), 1.73 (s, 3H, C_{19}), 1.66 – 1.59 (m, 2H, C_8), 1.21 (s, 3H, C_{20}), 1.15 (d, *J* = 6.5 Hz, 3H, C_{21}), 0.93 (s, 9H, Si(***t-Bu***)Me_2), 0.53 (s, 3H, Si(*t*-Bu)$\boldsymbol{Me}_2$), 0.52 (s, 3H, Si(*t*-Bu)$\boldsymbol{Me}_2$), 0.17 (s, 9H, TMS).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3 (C_{15}=O), 160.0 (C_{22}=O), 145.0 (C_2), 139.4 (C_1), 138.0 (C_{Ph}), 137.4 (C_{13}), 137.1 (C_{Ph}), 133.4 (C_{24}), 128.6 (C_{Ph}), 128.4 (C_{Ph}), 128.0 (C_{Ph}), 127.8 (C_{Ph}), 127.8 (C_{Ph}), 127.5 (C_{Ph}), 127.2 (C_{23}), 121.9 (C_{26}), 117.5 (C_{18}), 111.3 (C_{25}), 98.3 ($PhCH_2O\boldsymbol{C}H_2O$), 96.6 ($C_{12}$), 94.1 ($C_{11}$), 89.5 ($PhCH_2O\boldsymbol{C}H_2O$), 88.7 ($C_6$), 82.1 ($C_{10}$),

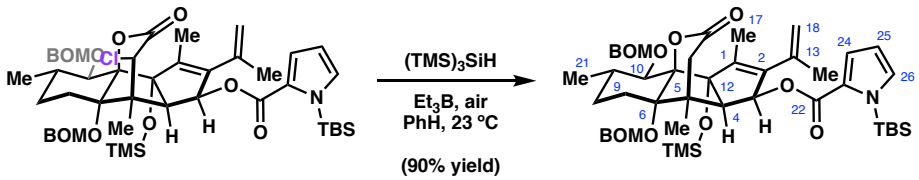
73.4 (C_3), 70.4 (Ph***C***H_2OCH_2O), 70.3 (Ph***C***H_2OCH_2O), 58.5 (C_4), 58.2 (C_{14}), 51.7 (C_5), 33.6 (C_9), 28.1 (C_8), 27.1 (Si(***t-Bu***)Me_2), 22.5 (C_7), 20.6 (C_{19}), 20.0 (C_{20}), 19.3 (Si–***C***$(CH_3)_3$), 19.1 (C_{21}), 12.9 (C_{17}), 1.8 (TMS), –1.9 (Si(*t*-Bu)***Me***$_2$), –1.9 (Si(*t*-Bu)***Me***$_2$).

FTIR (NaCl, thin film): 2953, 2930, 1754, 1715, 1262, 1150 cm^{-1}.

HRMS: calc'd for $[M+NH_4]^+$ 935.4458, found 935.4459.

$[\alpha]_D^{25}$**:** –69° (*c* = 0.840, $CHCl_3$).

Preparation of pyrrole ester 43



46 **43**

To an oven-dried, 25 mL round-bottomed flask was added chloride **46** (395 mg, 0.43 mmol, 1.0 equiv) and anhydrous PhH (8.6 mL). The solution was treated with $(TMS)_3SiH$ (0.27 mL, 0.86 mmol, 2.0 equiv) and Et_3B (1.0 M in hexanes, 0.43 mL, 0.43 mmol, 1.0 equiv) before air (4.0 mL) was slowly sparged through the reaction mixture via syringe. Stirring was continued at ambient temperature for 1 h before additional portions of $(TMS)_3SiH$ (0.27 mL, 0.86 mmol, 2.0 equiv), Et_3B (1.0 M in hexanes, 0.43 mL, 0.43 mmol, 1.0 equiv) and air (4.0 mL) were added via syringe. Stirring was then continued until TLC analysis indicated complete consumption of the starting material (*ca.* 1.5 h), during which time the reaction mixture turns dark red-orange. The reaction mixture was next concentrated *in vacuo* and the crude residue was directly purified via SiO_2 flash chromatography (15 to 20 to 25% EtOAc/hexanes) to afford pyrrole ester **43** as a yellow foam (342 mg, 0.39 mmol, 90% yield).

TLC (20% EtOAc/hexanes): R_f 0.36 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 10H, ***Ph***CH_2OCH_2O), 7.08 (dd, *J* = 9.5, 3.0 Hz, 1H, C_{26}), 7.06 (dd, *J* = 6.5, 3.1 Hz, 1H, C_{24}), 6.34 (dq, *J* = 7.9, 2.2 Hz, 1H, C_3), 6.27 (dd, *J* = 3.6, 2.6 Hz, 1H, C_{25}), 5.10 (p, *J* = 1.6 Hz, 1H, C_{18}), 4.98 (s, 2H, $PhCH_2OC\boldsymbol{H}_2O$), 4.98 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.89 (s, 1H, C_{18}), 4.88 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.85 (d, *J* = 11.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.77 (d, *J* = 11.6 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.63 (d, *J* = 11.5 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.57 (d, *J* = 11.9 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 3.97 (d, *J* = 10.3 Hz, 1H, C_{10}), 3.23 (dd, *J* = 3.6, 1.5 Hz, 1H, C_4), 3.21 (d, *J* = 19.5 Hz, 1H, C_{14}), 2.24 (dd, *J* = 19.5, 1.5 Hz, 1H, C_{14}), 2.10 – 2.01 (m, 1H, C_9), 1.87 (d, *J* = 2.3 Hz, 3H, C_{17}), 1.85 – 1.80 (m, 1H, C_7), 1.73 (s, 3H, C_{19}), 1.69 – 1.62 (m, 2H, C_8), 1.58 – 1.45 (m, 1H, C_7), 1.15 (d, *J* = 6.4 Hz, 3H, C_{21}), 0.96 (s, 3H, C_{20}), 0.93 (s, 9H, Si(***t-Bu***)Me_2), 0.52 (s, 3H, Si(*t*-Bu)$\boldsymbol{Me}_2$), 0.52 (s, 3H, Si(*t*-Bu)$\boldsymbol{Me}_2$), 0.17 (s, 9H, TMS).

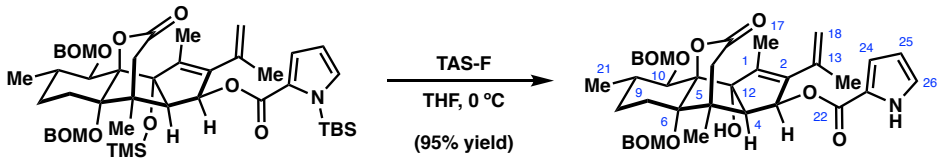
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0 (C_{15}=O), 160.4 (C_{22}=O), 144.2 (C_2), 139.0 (C_1), 138.2 (C_{Ph}), 138.0 (C_{13}), 137.2 (C_{Ph}), 133.1 (C_{26}), 128.5 (C_{Ph}), 128.3 (C_{Ph}), 127.9 (C_{23}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 127.5 (C_{Ph}), 121.6 (C_{24}), 116.9 (C_{18}), 110.9 (C_{25}), 98.2 ($PhCH_2O\boldsymbol{C}H_2O$), 97.2 ($C_{12}$), 93.0 ($C_{11}$), 89.5 ($C_6$), 89.3 ($PhCH_2O\boldsymbol{C}H_2O$), 82.3 ($C_{10}$), 74.4 ($C_3$), 70.3 ($Ph\boldsymbol{C}H_2OCH_2O$), 70.3 ($Ph\boldsymbol{C}H_2OCH_2O$), 57.4 ($C_4$), 46.9 ($C_5$), 39.0 ($C_{14}$), 33.4 ($C_9$), 28.0 ($C_8$), 27.1 (Si(***t-Bu***)$Me_2$), 20.8 ($C_{20}$), 20.7 ($C_{19}$), 20.3 ($C_7$), 19.2 (Si–$\boldsymbol{C}(CH_3)_3$), 19.1 ($C_{21}$), 12.8 ($C_{17}$), 1.8 (TMS), –1.8 (Si(*t*-Bu)$\boldsymbol{Me}_2$), –1.9 (Si(*t*-Bu)$\boldsymbol{Me}_2$).

FTIR (NaCl, thin film): 2929, 1948, 1712, 1262, 1150, 1094, 1042, 1026 cm^{-1}.

HRMS: calc'd for $[M+NH_4]^+$ 901.4849, found 901.4846.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$: –53° (*c* = 0.335, $CHCl_3$).

Preparation of alcohol 49



43 49

To an oven-dried, 25 mL round-bottomed flask was added silyl ether **43** (271 mg, 0.31 mmol, 1.0 equiv) and anhydrous THF (6.1 mL). The resulting solution was cooled to 0 ºC in an ice/water bath and stirring was continued for 15 min prior to the dropwise addition of TAS-F (253 mg, 0.92 mmol, 3.0 equiv) in a minimal amount of anhydrous DMF (1 mL) via syringe, producing a golden yellow solution (Note: TAS-F was stored and handled in a nitrogen-filled glovebox to maintain the integrity of the reagent). After 30 min at 0 ºC, an additional portion of TAS-F (169 mg, 0.61 mmol, 2.0 equiv) in a minimal amount of anhydrous DMF (0.5 mL) was added (Note: On smaller scales (<50 mg scale), a small excess of TAS-F was routinely used without issue; however, on scale-up, the reaction consistently stalled at about 50-60% conversion with the TMS group intact and required additional portions of TAS-F). Stirring at 0 ºC was continued for another 30 min, at which point TLC and LCMS analysis indicated complete consumption of the starting material. The reaction mixture was diluted with Et_2O (6 mL) and filtered through a short pad of SiO_2, washing with 65% EtOAc/hexanes until TLC analysis indicated complete elution of the desired product. The filtrate was concentrated *in vacuo* and the crude residue was purified by SiO_2 flash chromatography (30 to 40 to 50% EtOAc/hexanes) to afford alcohol **49** as a clear oil that solidifies into a white solid upon standing (203 mg, 0.259 mmol, 95% yield).

TLC (45% EtOAc/hexanes): R_f 0.43 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, C_6D_6): δ 8.77 (s, 1H, N***H***), 7.42 – 7.34 (m, 2H, ***Ph***CH_2OCH_2O), 7.30 – 7.19 (m, 4H, ***Ph***CH_2OCH_2O), 7.14 – 7.09 (m, 2H, ***Ph***CH_2OCH_2O), 7.05 – 7.00 (m, 1H, ***Ph***CH_2OCH_2O), 6.98 (td, *J* = 2.5, 1.3 Hz, 1H, C_{25}), 6.87 – 6.81 (m, 1H, C_3), 6.28 (td, *J* = 2.7, 1.4 Hz, 1H, C_{26}), 6.05 (dt, *J* = 3.7, 2.5 Hz, 1H, C_{24}), 5.29 (dd, *J* = 2.2, 1.1 Hz, 1H, C_{18}), 5.09 (t, *J* = 1.9 Hz, 1H, C_{18}), 4.93 (d, *J* = 5.4 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.70 (d, *J* = 5.5 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.63 (d, *J* = 11.8 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.54 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.52 (d, *J* = 11.8 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.45 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.35 (d, *J* = 12.4 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.35 (s, 1H, O***H***), 4.30 (d, *J* = 12.4 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.08 (d, *J* = 10.3 Hz, 1H, C_{10}), 3.51 (dd, *J* = 7.9, 1.4 Hz, 1H, C_4), 3.38 (d, *J* = 19.2 Hz, 1H, C_{14}), 2.32 (d, *J* = 2.3 Hz, 3H, C_{17}), 2.21 – 2.14 (m, 1H, C_9), 2.09 (dd, *J* = 19.2, 1.6 Hz, 1H, C_{14}), 1.71 (s, 3H, C_{18}), 1.42 (qd, *J* = 13.1, 12.7, 4.5, 1H, C_8), 1.22 – 1.15 (m, 2H, C_8/C_7), 1.13 – 1.03 (m, 1H, C_7), 0.98 (d, *J* = 6.5 Hz, 3H, C_{21}), 0.82 (s, 3H, C_{20}).

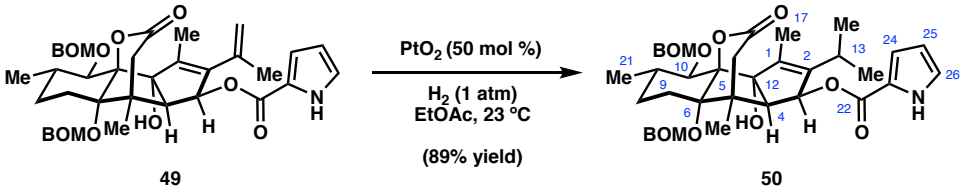
^{13}C NMR (101 MHz, C_6D_6): δ 167.8 (C_{15}=O), 160.8 (C_{22}=O), 144.2 (C_2), 139.5 (C_1), 139.0 (C_{13}), 138.3 (C_{Ph}), 137.8 (C_{Ph}), 128.8 (C_{Ph}), 128.7 (C_{Ph}), 128.4 (C_{Ph}), 128.1 (C_{Ph}), 123.8 (C_{26}), 122.6 (C_{23}), 117.1 (C_{18}), 116.0 (C_{25}), 110.7 (C_{24}), 97.8 ($PhCH_2O\boldsymbol{C}H_2O$), 95.3 ($C_{12}$), 91.4 ($C_{11}$), 90.4 ($C_6$), 89.6 ($PhCH_2O\boldsymbol{C}H_2O$), 81.8 ($C_{10}$), 76.0 ($C_3$), 70.9 ($Ph\boldsymbol{C}H_2OCH_2O$), 70.2 ($Ph\boldsymbol{C}H_2OCH_2O$), 59.4 ($C_4$), 46.5 ($C_5$), 39.8 ($C_{14}$), 33.8 ($C_9$), 28.3 ($C_8$), 21.0 ($C_{18}$), 20.2 ($C_{20}$), 20.1 ($C_7$), 18.9 ($C_{21}$), 13.2 ($C_{17}$).

FTIR (NaCl, thin film): 3408, 3307, 2929, 1742, 1699, 1313, 1158, 1034 cm^{-1}.

HRMS: calc'd for $[M+NH_4]^+$ 715.3589, found 715.3589.

$[\alpha]_D^{25}$: –37° (*c* = 0.685, $CHCl_3$).

Reduction of alkene 50



49 **50**

An oven-dried, 50 mL round-bottomed flask was charged with diene **49** (225 mg, 0.32 mmol, 1.0 equiv), PtO_2 (80% w/w, 36.6 mg, 0.16 mmol, 50 mol %), and EtOAc (13 mL). The vial was capped with a rubber septum and the reaction mixture was vigorously stirred while flushing the headspace with H_2 for 5 minutes via a double-walled balloon, during which time the brown suspension turns black. The suspension was vigorously stirred under H_2 until LCMS indicated complete consumption of the starting material (*ca.* 25 min), flushed with Ar to remove excess H_2, then diluted with EtOAc (13 mL), filtered through a short pad of Celite, and concentrated *in vacuo.* Purification of the crude residue by SiO_2 flash chromatography (40 to 50% EtOAc/hexanes) afforded **50** as a clear oil that solidifies into a white solid upon standing (201 mg, 0.29 mmol, 89% yield).

TLC (45% EtOAc/hexanes): R_f 0.42 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, C_6D_6): δ 8.87 (s, 1H, N***H***), 7.42 – 7.34 (m, 2H, ***Ph***CH_2OCH_2O), 7.31 – 7.20 (m, 4H, ***Ph***CH_2OCH_2O), 7.17 – 7.08 (m, 3H, ***Ph***CH_2OCH_2O), 7.08 – 6.99 (m, 1H, ***Ph***CH_2OCH_2O), 6.98 (ddd, *J* = 3.9, 2.5, 1.5 Hz, 1H, C_{25}), 6.81 (dq, *J* = 7.9, 2.2 Hz, 1H, C_3), 6.33 (td, *J* = 2.7, 1.4 Hz, 1H, C_{26}), 6.09 (dt, *J* = 3.8, 2.5 Hz, 1H, C_{24}), 4.97 (d, *J* = 5.6 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.74 (d, J = 5.6 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.61 (d, *J* = 11.8 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.53 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.50 (d, *J* = 11.8 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.43 (d, *J* = 6.7 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.41 (d, *J* = 12.4 Hz,

1H, PhC***H***$_2$OCH$_2$O), 4.36 (d, J = 12.4 Hz, 1H, PhC***H***$_2$OCH$_2$O), 4.12 (s, 1H, O***H***), 4.07 (d, J = 10.3 Hz, 1H, C_{10}), 3.45 (dd, J = 8.0, 1.4 Hz, 1H, C_4), 3.38 (d, J = 19.2 Hz, 1H, C_{14}), 2.77 (p, J = 7.0 Hz, 1H, C_{13}), 2.23 – 2.13 (m, 1H, C_9), 2.18 (d, J = 2.3 Hz, 1H, C_{17}), 2.09 (dd, J = 19.1, 1.6 Hz, 1H, C_{14}), 1.42 (qd, J = 13.1, 4.5 Hz, 1H, C_8), 1.35 (d, J = 7.1 Hz, 3H, C_{18}), 1.21 – 1.15 (m, 2H, C_8/C_7), 1.13 – 1.02 (m, 1H, C_7), 1.00 (d, J = 6.5 Hz, 3H, C_{21}), 0.96 (d, J = 6.9 Hz, 3H, C_{19}), 0.82 (s, 3H, C_{20}).

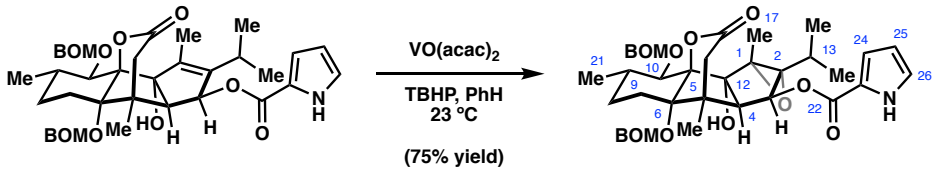
^{13}C NMR (101 MHz, C_6D_6): δ 167.5 (C_{15}=O), 160.7 (C_{22}=O), 146.0 (C_2), 138.3 (C_{Ph}), 137.9 (C_{Ph}), 137.4 (C_1), 128.8 (C_{Ph}), 128.7 (C_{Ph}), 128.4 (C_{Ph}), 123.7 (C_{26}), 122.9 (C_{23}), 115.6 (C_{25}), 110.8 (C_{24}), 97.9 (PhCH$_2$O***C***H$_2$O), 95.3 (C_{12}), 90.9 (C_6), 90.5 (C_{11}), 89.6 (PhCH$_2$O***C***H$_2$O), 82.0 (C_{10}), 77.0 (C_3), 71.0 (Ph***C***H$_2$OCH$_2$O), 70.3 (Ph***C***H$_2$OCH$_2$O), 59.3 (C_4), 46.4 (C_5), 39.7 (C_{14}), 33.8 (C_9), 28.3 (C_8), 27.6 (C_{13}), 22.0 (C_{18}), 20.2 (C_{20}), 20.1 (C_7), 19.0 (C_{19}), 18.9 (C_{21}), 11.8 (C_{17}).

FTIR (NaCl, thin film): 3417, 3306, 2962, 1934, 1743, 1699, 1158, 1026 cm^{-1}.

HRMS: calc'd for [M+Na]$^+$ 722.3300, found 722.3299.

$[\alpha]_D^{25}$: +7° (c = 0.675, $CHCl_3$).

Preparation of epoxide 51



50 **51**

To an oven-dried, 25 mL round-bottomed flask was added alcohol **50** (175 mg, 0.25 mmol, 1.0 equiv) and anhydrous PhH (5.0 mL). The solution was treated with VO(acac)$_2$ (33.2 mg, 0.13 mmol, 0.5 equiv) and then TBHP (5.5 M in decanes, 0.14 mL,

0.75 mmol, 3.0 equiv) was added via syringe along the side of the flask, during which time the green solution turns a deep red. After 30 min, additional portions of $VO(acac)_2$ (16.6 mg, 62.5 μmol, 0.25 equiv) and then TBHP (5.5 M in decanes, 0.14 mL, 0.75 mmol, 3.0 equiv) were added and stirring was continued at ambient temperature until LCMS indicated complete consumption of the starting material (*ca*. 30-45 min), at which point the reaction mixture fades to a bright orange. The reaction mixture was diluted with EtOAc (5 mL) and quenched with the addition of sat. aq. $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude residue by SiO_2 flash chromatography (35 to 45% EtOAc/hexanes) afforded epoxide **51** as an off-white foam (135 mg, 0.19 mmol, 75% yield).

TLC (45% EtOAc/hexanes): R_f 0.48 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, C_6D_6): δ 8.89 (s, 1H, N***H***), 7.38 – 7.35 (m, 4H, ***Ph***CH_2OCH_2O), 7.27 – 7.23 (m, 2H, ***Ph***CH_2OCH_2O), 7.21 – 7.16 (m, 2H, ***Ph***CH_2OCH_2O), 7.15 – 7.05 (m, 2H, ***Ph***CH_2OCH_2O), 6.96 (ddd, *J* = 3.9, 2.5, 1.4 Hz, 1H, C_{25}), 6.34 (td, *J* = 2.7, 1.4 Hz, 1H, C_{26}), 6.29 (d, *J* = 8.9 Hz, 1H, C_3), 6.09 (dt, *J* = 3.8, 2.5 Hz, C_{24}), 5.20 (d, *J* = 6.4 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.98 (d, *J* = 6.4 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.77 (d, *J* = 12.2 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.61 (d, *J* = 11.7 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.54 (d, *J* = 12.1 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.51 (d, *J* = 11.7 Hz, 1H, $PhC\boldsymbol{H}_2OCH_2O$), 4.47 (d, *J* = 6.8 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.38 (d, *J* = 6.8 Hz, 1H, $PhCH_2OC\boldsymbol{H}_2O$), 4.16 (d, *J* = 10.5 Hz, 1H, C_{10}), 3.70 (d, *J* = 19.8 Hz, 1H, C_{14}), 3.20 (s, 1H, O***H***), 3.12 (dd, *J* = 8.9, 1.6 Hz, 1H, C_4), 2.24 –

2.13 (m, 1H, C_9), 2.16 (dd, J = 19.8, 1.7 Hz, 1H, C_{14}), 1.97 (s, 3H, C_{17}), 1.74 (p, J = 7.2 Hz, 1H, C_{13}), 1.40 (d, J = 7.2 Hz, 3H, C_{18}), 1.39 – 1.30 (m, 1H, C_8), 1.24 – 1.21 (m, 1H, C_8), 1.18 (d, J = 6.5 Hz, 3H, C_{21}), 1.15 – 1.09 (m, 2H, C_7), 1.07 (d, J = 7.2 Hz, 3H, C_{19}), 0.74 (s, 3H, C_{20}).

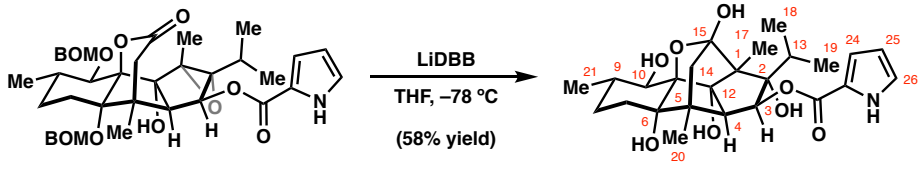
^{13}C NMR (101 MHz, C_6D_6): δ 167.8 (C_{15}=O), 160.1 (C_{22}=O), 138.8 (C_{Ph}), 138.1 (C_{Ph}), 128.7 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 127.6 (C_{Ph}), 124.6 (C_{26}), 122.1 (C_{23}), 116.0 (C_{25}), 111.0 (C_{24}), 98.0 ($PhCH_2O\boldsymbol{C}H_2O$), 91.8 ($C_{12}$), 91.7 ($C_{11}$), 90.3 ($C_6$), 88.9 ($PhCH_2O\boldsymbol{C}H_2O$), 81.8 ($C_{10}$), 80.2 ($C_2$), 76.2 ($C_1$), 73.4 ($C_3$), 70.6 ($Ph\boldsymbol{C}H_2OCH_2O$), 70.5 ($Ph\boldsymbol{C}H_2OCH_2O$), 64.2 ($C_4$), 47.7 ($C_5$), 38.9 ($C_{14}$), 33.1 ($C_9$), 30.7 ($C_{13}$), 28.4 ($C_8$), 20.5 ($C_{20}$), 19.9 ($C_7$), 19.2 ($C_{21}$), 18.0 ($C_{18}$), 17.4 ($C_{19}$), 14.6 ($C_{17}$).

FTIR (NaCl, thin film): 3305, 2964, 1747, 1705, 1026 cm^{-1}.

HRMS: calc'd for $[M+Na]^+$ 738.3249, found 738.3250.

$[\alpha]_D^{25}$: +37° (c = 0.900, $CHCl_3$).

Preparation of 20-deoxyspiganthine (3)



51

(+)-20-deoxyspiganthine (3)
[X-ray]

An oven-dried, 100 mL round-bottomed flask equipped with a borosilicate glass-coated magnetic stirbar was charged with epoxide **51** (135 mg, 0.19 mmol, 1.0 equiv) and anhydrous THF (18 mL) under Ar (Note: epoxide **51** was azeotroped with PhH three times immediately prior to use). The solution was cooled to –78 °C via a dry ice/acetone bath and stirring continued for 15 min before a freshly prepared solution of LiDBB (0.16

M, 11.8 mL, 1.89 mmol, 10 equiv) was carefully added dropwise via syringe along the side of the flask. The resulting deep green mixture was stirred for 0.5 h at –78 ºC, at which point LCMS analysis indicated complete conversion to the desired product. Sat. aq. NH_4Cl (10 mL) was carefully added before the reaction mixture was warmed to ambient temperature. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (0 to 5 to 10% MeOH/$CHCl_3$) to afford 20-deoxyspiganthine (**3**) (51.8 mg, 0.11 mmol, 58% yield) as a white powder (Note: The purification was made easier by first flushing with $CHCl_3$ (100 mL) until all of the excess 4,4′-di-*tert*-butylbiphenyl was removed).

TLC (10% MeOH/CH_2Cl_2): R_f 0.29 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, CD_3OD): δ 7.01 (dd, *J* = 2.5, 1.5 Hz, 1H, C_{26}), 6.86 (dd, *J* = 3.8, 1.5 Hz, 1H, C_{24}), 6.22 (dd, *J* = 3.8, 2.5 Hz, 1H, C_{25}), 5.65 (d, *J* = 8.5, Hz, 1H, C_3), 3.75 (d, *J* = 10.3 Hz, 1H, C_{10}), 3.23 (dd, *J* = 8.5, 1.8 Hz, 1H, C_4), 2.41 (h, *J* = 6.6 Hz, C_{13}), 2.35 (d, *J* = 13.5, 1H, C_{14}), 2.04 (td, *J* = 12.5, 5.9 Hz, 1H, C_7), 1.77 – 1.87 (m, 1H, C_9), 1.77 (dd, *J* = 13.5, 2.0 Hz, 1H, C_{14}), 1.45 – 1.58 (m, 2H, C_8), 1.37 (s, 3H, C_{17}), 1.22 (ddd, *J* =13.0, 4.3, 2.4, 1H, C_7), 1.17 (d, *J* = 6.5 Hz, 3H, C_{18}), 1.02 (d, *J* = 6.5 Hz, 3H, C_{21}), 0.84 (d, *J* = 6.4 Hz, 3H, C_{19}), 0.77 (s, 3H, C_{20}).

^{13}C NMR (101 MHz, CD_3OD): δ 161.9 (C_{22}), 125.3 (C_{26}), 123.6 (C_{23}), 116.8 (C_{24}), 110.9 (C_{25}), 103.6 (C_{15}), 97.7 (C_{12}), 86.8 (C_{11}), 86.8 (C_2), 85.2 (C_3), 84.3 (C_6), 72.8 (C_{10}),

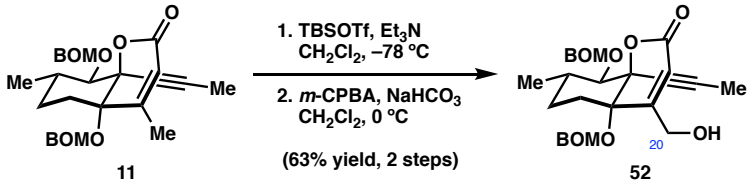
64.7 (C_1), 57.7 (C_4), 48.2 (C_5), 41.4 (C_{14}), 35.4 (C_9), 31.1 (C_{13}), 29.9 (C_8), 26.4 (C_7), 19.5 (C_{18}), 19.1 (C_{19}), 19.0 (C_{21}), 16.7 (C_{20}), 9.7 (C_{17}).

FTIR (NaCl, thin film): 3436, 2929, 1682, 1411, 1319 cm^{-1}.

HRMS: calc'd for $[M-H]^-$ 476.2290, found 476.2290.

$[\alpha]_D^{25}$**:** +6º (*c* = 0.160, MeOH).

Preparation of C20 alcohol 52



An oven-dried, 100 mL round-bottomed flask was treated with lactone **11** (538 mg, 1.10 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (22 mL). The resulting solution was cooled to –78 ºC via a dry ice/acetone bath and stirring was continued at this temperature for 15 min. Et_3N (0.76 mL, 5.48 mmol, 5.0 equiv) and then TBSOTf (0.76 mL, 3.29 mmol, 3.0 equiv) were added in sequence dropwise via syringe. The reaction was continued at –78 ºC for 1.5 h, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was treated with sat. aq. $NaHCO_3$ (10 mL), warmed to ambient temperature, diluted with CH_2Cl_2 (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The crude silyl ketene acetal was immediately redissolved in anhydrous CH_2Cl_2 (22 mL) and cooled to 0 ºC via an ice/water bath. After 15 min of continued stirring, $NaHCO_3$ (277 mg, 3.30 mmol, 3.0 equiv) was added, followed by the addition of *m*-

CPBA (77% w/w, 370 mg, 1.65 mmol, 1.5 equiv). The reaction was continued for 1 h at 0 ºC at which point TLC analysis indicated the complete consumption of the intermediate silyl ketene acetal. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and sat. aq. $NaHCO_3$ (10 mL) and sat. aq. $Na_2S_2O_3$ (5 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (50 to 60% EtOAc/hexanes) to afford C20 alcohol **52** (358 mg, 0.71 mmol, 63% yield over 2 steps) as a white solid.

TLC (50% EtOAc/hexanes): R_f 0.23 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 8H, ***Ph***CH_2OCH_2O), 7.32 – 7.27 (m, 2H, ***Ph***CH_2OCH_2O), 6.11 (s, 1H, C_{14}), 5.13 (d, J = 7.0 Hz, 1H), 5.11 (d, J = 7.3 Hz, 1H), 5.04 (d, J = 7.0 Hz, 1H), 4.90 (d, J = 7.3 Hz, 1H), 4.83 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.43 (dd, J = 16.5, 1.6 Hz, 1H, C_{20}), 4.38 (d, J = 16.5, 1.8 Hz, 1H, C_{20}), 3.70 (d, J = 9.8 Hz, 1H, C_{10}), 2.13 (dt, J = 14.8, 3.8 Hz, 1H), 2.10 – 2.04 (m, 1H), 1.79 (s, 3H, C_{17}), 1.73 (ddd, J = 14.7, 12.7, 4.2 Hz, 1H), 1.59 (dq, J = 12.8, 4.1 Hz, 1H), 1.53 – 1.39 (m, 1H), 1.13 (d, J = 6.6 Hz, 3H, C_{21}).

LRMS (APCI): calc'd for $[M+Na]^+$ 529.6, found 529.6.

^{1}H and ^{13}C NMR Comparison Tables for (+)-Ryanodine and (+)-20-Deoxyspiganthine

Table 1. Comparison of ^{1}H NMR data for (+)-Ryanodine

Proton No.	Inoue et al. Report, Synthetic (+)-Ryanodine[2] ^{1}H NMR, 400 MHz, CD_3OD ^{1}H [δ, multi., *J* (Hz)]	This Work, Synthetic (+)-Ryanodine ^{1}H NMR, 600 MHz, CD_3OD ^{1}H [δ, multi., *J* (Hz)]
1		
2		
3	5.64 (s)	5.64 (s)
4		
5		
6		
7a	1.26 (ddd, *J* = 12.7, 4.5, 2.3)	1.26 (ddd, *J* = 12.7, 4.6, 2.0)
7b	2.10 (ddd, *J* =12.7, 12.7, 5.4)	2.10 (td, *J* = 12.9, 5.2)
8a	1.46 (dddd, *J* = 13.1, 5.4, 5.4, 2.3)	1.48 (td, *J* = 13.0, 4.7)
8b	1.53 (dddd, *J* = 13.1, 5.2, 1.6)	1.54 (dtd, *J* = 12.4, 5.2, 1.8)
9	1.85 (ddqd, *J* = 13.1, 10.4, 6.8, 5.4)	1.85 (tdd, *J* = 10.2, 8.5, 5.6)
10	3.80 (d, *J* = 10.4)	3.80 (d, *J* = 10.2)
11		
12		
13	2.27 (qq, *J* = 6.8, 6.3)	2.27 (h, *J* = 6.8)
14a	1.93 (d, *J* = 13.6)	1.94 (d, *J* = 13.6)
14b	2.57 (d, *J* = 13.6)	2.57 (d, *J* = 13.6)
15		
17	1.39 (s)	1.40 (s)
18	0.76 (d, *J* = 6.3)	0.76 (d, *J* = 6.5)
19	1.12 (d, *J* = 6.8)	1.12 (d, *J* = 6.7)
20	0.90 (s)	0.90 (s)
21	1.02 (d, *J* = 6.8)	1.02 (d, *J* = 6.5)
22		
23		
24	6.88 (dd, *J* = 3.6, 1.4)	6.88 (dd, *J* = 3.7, 1.5)
25	6.24 (dd, *J* = 3.6, 2.7)	6.24 (dd, *J* = 3.8, 2.5)
26	7.04 (dd, *J* =2.7, 1.4)	7.04 (dd, *J* = 2.5, 1.5)

Table 2. Comparison of ^{13}C NMR data for (+)-Ryanodine

Carbon No.	Inoue et al. Report, Synthetic (+)-Ryanodine[2] ^{13}C NMR, 100 MHz, CD_3OD ^{13}C (δ) ppm	This Work, Synthetic (+)-Ryanodine ^{13}C NMR, 101 MHz, CD_3OD ^{13}C (δ) ppm	Chemical Shift Difference, Δδ
1	65.9	65.9	0
2	84.4	84.3	0.1
3	90.9	90.8	0.1
4	92.4	92.3	0.1
5	49.7	49.6	0.1
6	86.6	86.5	0.1
7	26.8	26.8	0
8	29.3	29.3	0
9	35.4	35.4	0
10	72.8	72.8	0
11	87.4	87.4	0
12	96.7	96.7	0
13	30.9	30.9	0
14	41.8	41.8	0
15	102.9	102.9	0
17	10.2	10.2	0
18	18.9	18.9	0
19	19.5	19.5	0
20	12.5	12.6	0.1
21	19.0	19.0	0
22	161.8	161.8	0
23	123.4	123.3	0.1
24	117.0	117.0	0
25	110.9	110.9	0
26	125.6	125.6	0

Note: The carbon assignment of C_5 by Inoue and coworkers was deduced from HMBC correlation.

Table 3. Comparison of ^{1}H NMR data for (+)-20-Deoxyspiganthine

Proton No.	Hübner et al. Report, Natural (+)-20-Deoxyspiganthine[23] ^{1}H NMR, 360 MHz, CD_3OD ^{1}H [δ, multi., *J* (Hz)]	This Work, Synthetic (+)-20-Deoxyspiganthine ^{1}H NMR, 400 MHz, CD_3OD ^{1}H [δ, multi., *J* (Hz)]
1		
2		
3	5.65 (d, *J* = 8.5)	5.65 (d, *J* = 8.5)
4	3.23 (dd, *J* = 8.5, 2)	3.23 (dd, *J* = 8.5, 1.8)
5		
6		
7a	2.04 (ddd, *J* = 13.5, 12, 6)	2.04 (td, *J* = 12.5, 5.9)
7b	1.22 (ddd, *J* = 13.5, 4.5, 4)	1.22 (ddd, *J* = 13.0, 4.3, 2.4)
8a	1.45–1.58 (m)	1.45–1.58 (m)
8b	1.45–1.58 (m)	1.45–1.58 (m)
9	1.77–1.87 (m)	1.77–1.87 (m)
10	3.75 (d, *J* = 10)	3.75 (d, *J* = 10.3)
11		
12		
13	2.41 (qq, *J* = 6.5, 6.5)	2.41 (h, *J* = 6.6)
14a	2.35 (d, *J* = 13.5)	2.35 (d, *J* = 13.5)
14b	1.77 (dd, 13.5, 2)	1.77 (dd, *J* = 13.5, 2.0)
15		
17	1.36 (s)	1.37 (s)
18	1.16 (d, *J* = 6.5)	1.17 (d, *J* = 6.4)
19	0.84 (d, *J* = 6.5)	0.84 (d, *J* = 6.5)
20	0.77 (s)	0.77 (s)
21	1.01 (d, *J* = 6.5)	1.02 (d, *J* = 6.5)
22		
23		
24	6.85 (dd, *J* = 4, 1.5)	6.86 (dd, *J* = 3.8, 1.5)
25	4.22 (dd, *J* = 4, 2.5)	6.22 (dd, *J* = 3.8, 2.5)
26	7.01 (dd, *J* = 2.5, 1.5)	7.01 (dd, *J* = 2.5, 1.5)

Note: In the isolation report, Hübner and coworkers report that $C_{25}\boldsymbol{H}$ has a ^{1}H NMR chemical shift of 4.22 ppm; however, all related ryanodines and spiganthines reported in the same paper share a $C_{25}\boldsymbol{H}$ ^{1}H NMR chemical shift between 6.22 and 6.25 ppm, as observed in our synthetic sample. This is assumed to be a typographical error made by the isolation team.

Table 4. Comparison of ^{13}C NMR data for (+)-20-Deoxyspiganthine

Carbon No.	Hübner et al. Report, Natural (+)-20-Deoxyspiganthine[23] ^{13}C NMR, 90 MHz, CD_3OD ^{13}C (δ) ppm	This Work, Synthetic (+)-20-Deoxyspiganthine ^{13}C NMR, 101 MHz, CD_3OD ^{13}C (δ) ppm	Chemical Shift Difference, Δδ
1	64.7	64.7	0
2	86.6	86.8	0.2
3	85.2	85.2	0
4	57.7	57.7	0
5	48.3	48.2	0.1
6	84.3	84.3	0
7	26.4	26.4	0
8	29.9	29.9	0
9	35.4	35.4	0
10	72.9	72.8	0.1
11	86.8	86.8	0
12	97.8	97.7	0.1
13	31.1	31.1	0
14	41.5	41.4	0.1
15	103.6	103.6	0
17	9.6	9.7	0.1
18	19.5	19.5	0
19	19.1	19.1	0
20	16.7	16.7	0
21	18.9	19.0	0.1
22	162.0	161.9	0.1
23	123.6	123.6	0
24	116.8	116.8	0
25	110.9	110.9	0
26	125.3	125.3	0

2.7 NOTES AND REFERENCES

(1) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 186.

(2) Masuda, K.; Koshimizu, M.; Nagatomo, M.; Inoue, M. *Chem. Eur. J.* **2016**, *22*, 230.

(3) Masuda, K.; Nagatomo, M.; Inoue, M. *Chem. Pharm. Bull.* **2016**, *64*, 874.

(4) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; MacLachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1979**, *57*, 3348.

(5) Chuang, K. V.; Xu, C.; Reisman, S. E. *Science* **2016**, *353*, 912.

(6) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380.

(7) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203.

(8) Egi, M.; Ota, Y.; Nishimura, Y.; Shimizu, K.; Azechi, K.; Akai, S. *Org. Lett.* **2013**, *15*, 4150.

(9) Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249.

(10) Riley, H. L.; Morley, J. F.; Friend, N. A. C. *Journal of the Chemical Society* **1932**, 1875.

(11) Sharpless, K. B.; Gordon, K. M. *J. Am. Chem. Soc.* **1976**, *98*, 300.

(12) Condakes, M. L.; Hung, K.; Harwood, S. J.; Maimone, T. J. *J. Am. Chem. Soc.* **2017**, *139*, 17783.

(13) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508.

(14) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 115.

(15) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 127.

(16) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 153.

(17) Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, *136*, 5916.

(18) Koshimizu, M.; Nagatomo, M.; Inoue, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 2493.

(19) Nagatomo, M.; Hagiwara, K.; Masuda, K.; Koshimizu, M.; Kawamata, T.; Matsui, Y.; Urabe, D.; Inoue, M. *Chem. Eur. J.* **2016**, *22*, 222.

(20) Ozonolytic cleavage of the pyrrole in (+)-ryanodine has been demonstrated with O_3 to provide a C25-aldehyde C26-formamide derivative: Waterhouse, A. L.; Pessah, I. N.; Francini, A. O.; Casida, J. E. *J. Med. Chem.* **1987**, *30*, 710.

(21) Donohoe, T. J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015.

(22) Perry, M. A.; Rychnovsky, S. D. *Nat. Prod. Rep.* **2015**, *32*, 517.

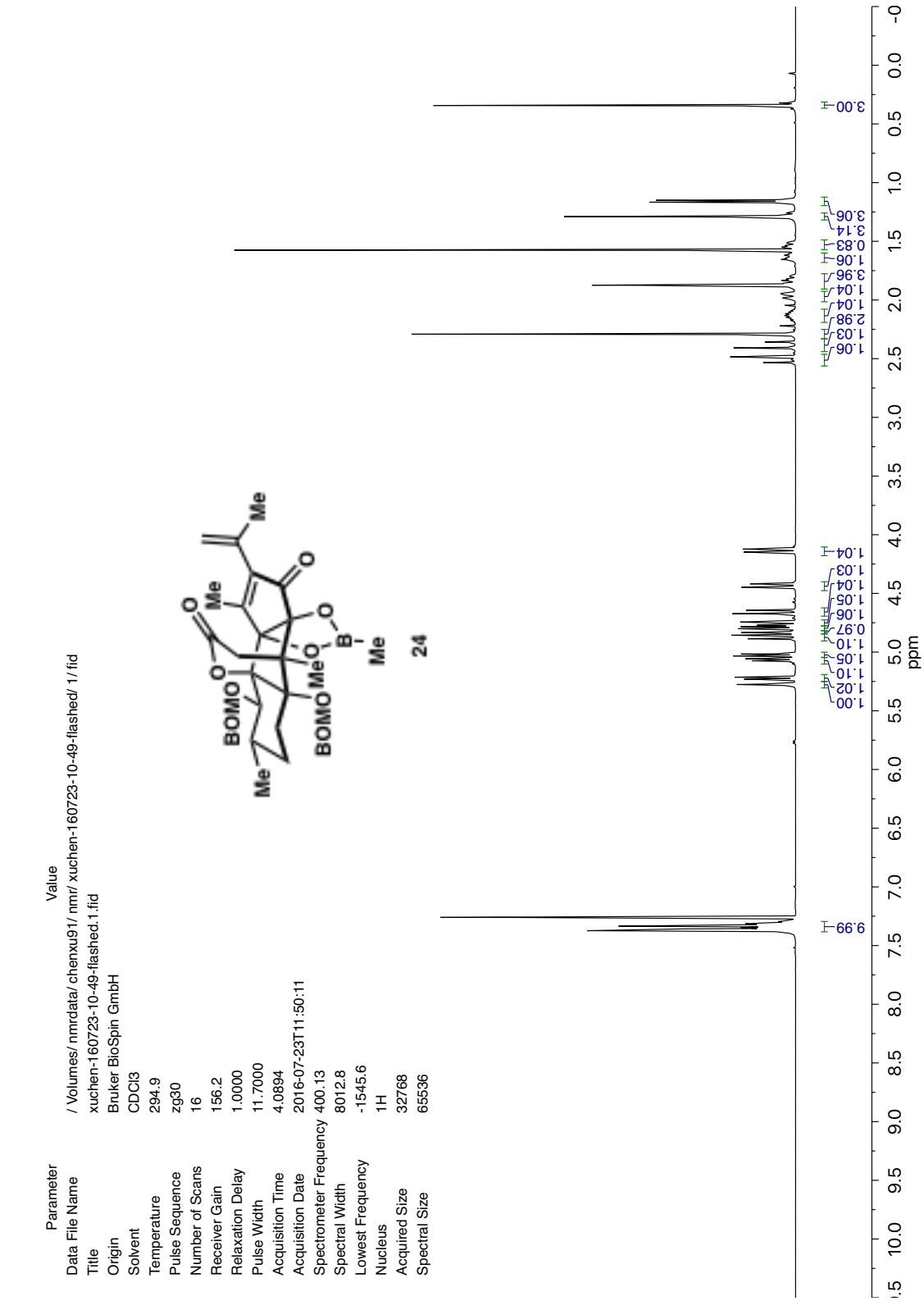
(23) Hübner, H.; Vierling, W.; Brandt, W.; Reiter, M.; Achenbach, H. *Phytochemistry* **2001**, *57*, 285.

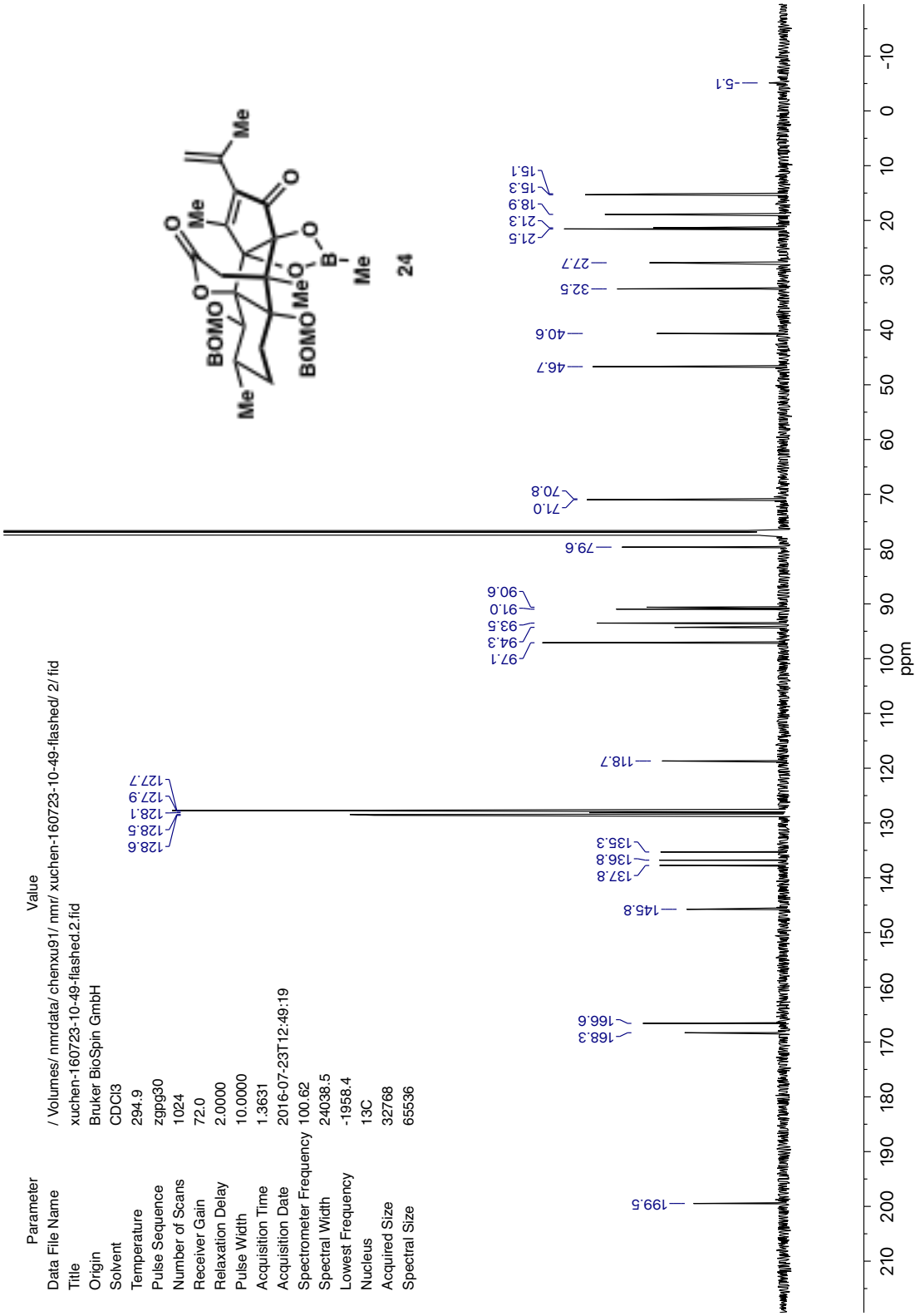
(24) Achenbach, H.; Hübner, H.; Vierling, W.; Brandt, W.; Reiter, M. *J. Nat. Prod.* **1995**, *58*, 1092.

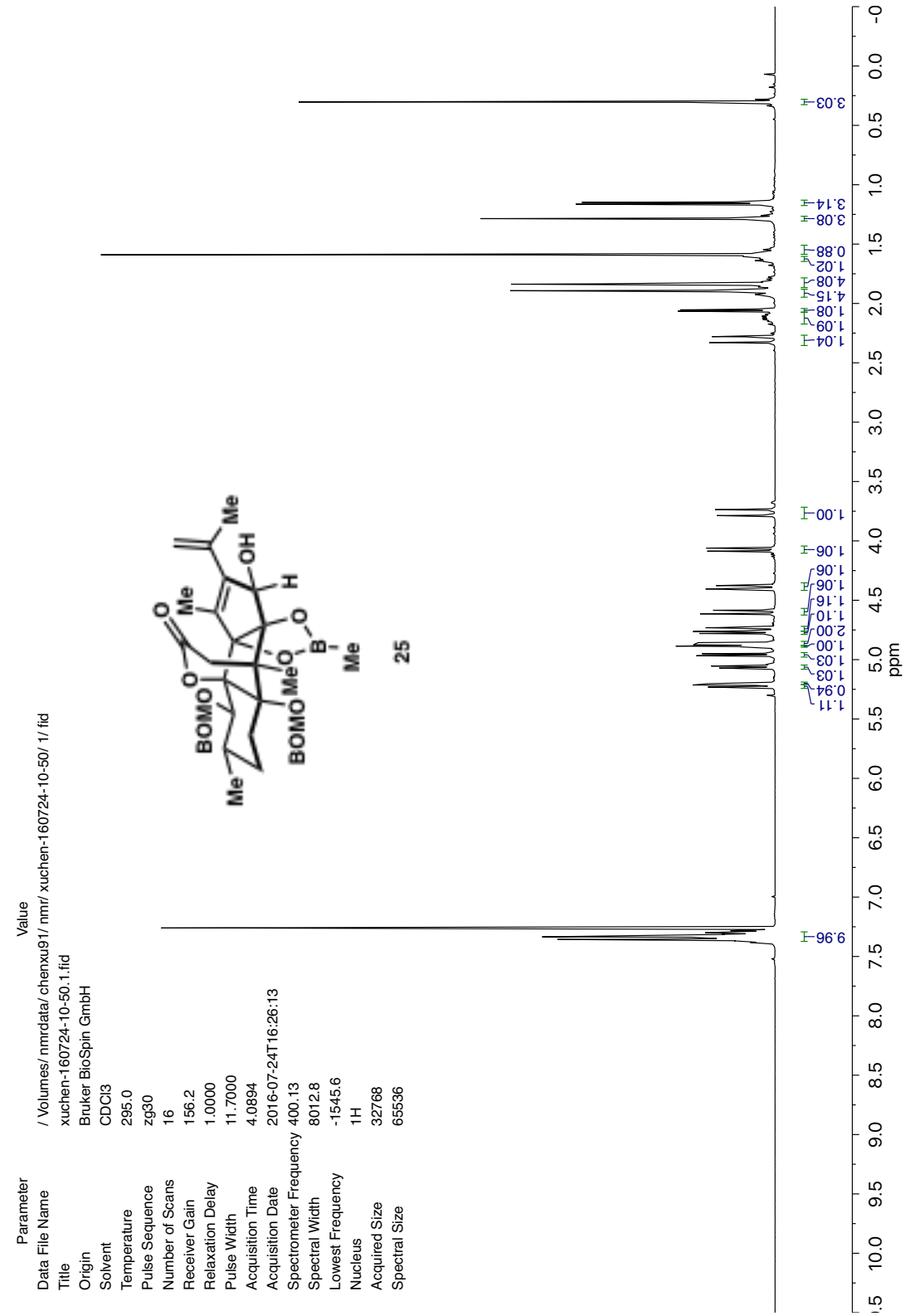
Appendix 1

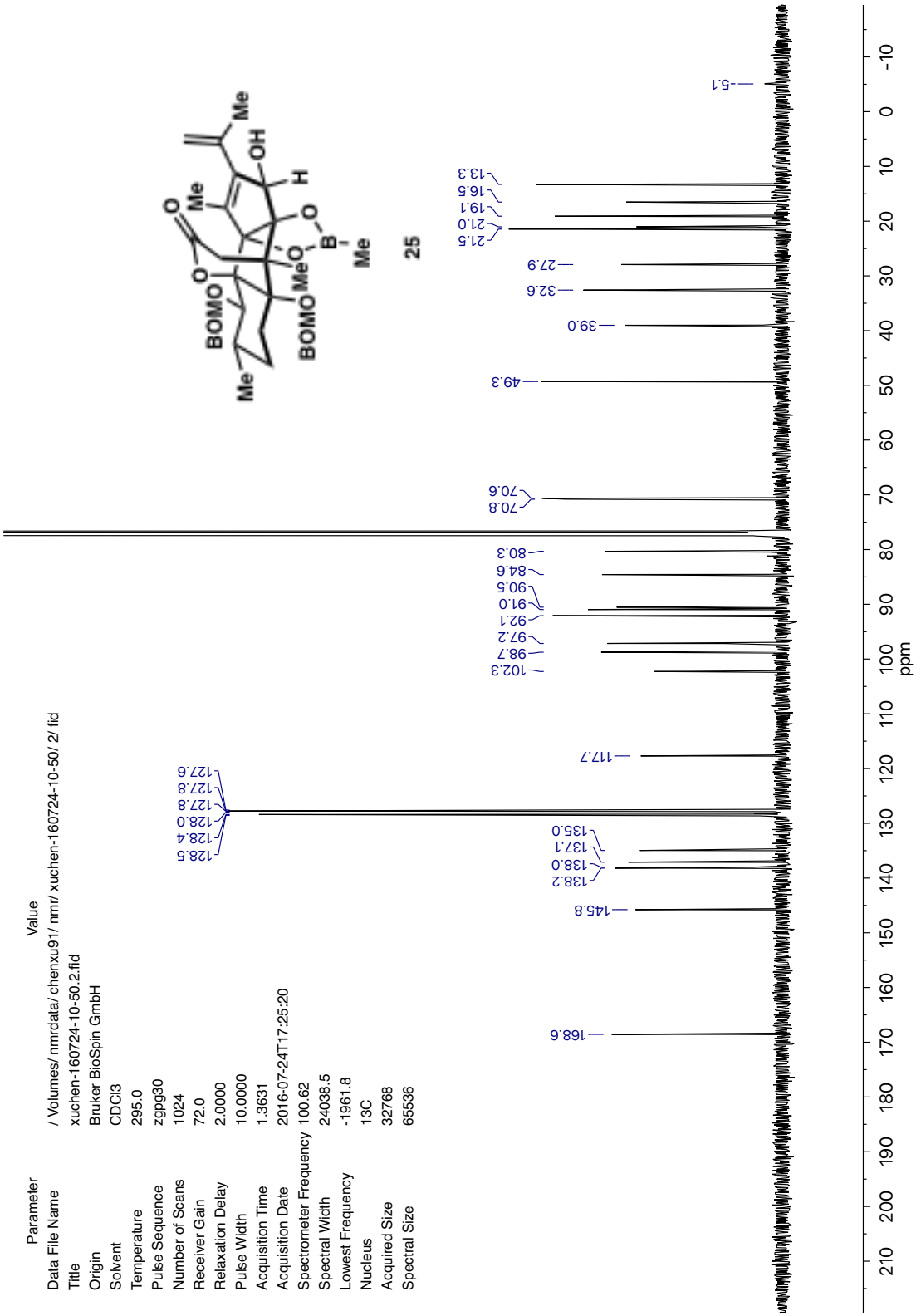
Spectra Relevant to Chapter 2:

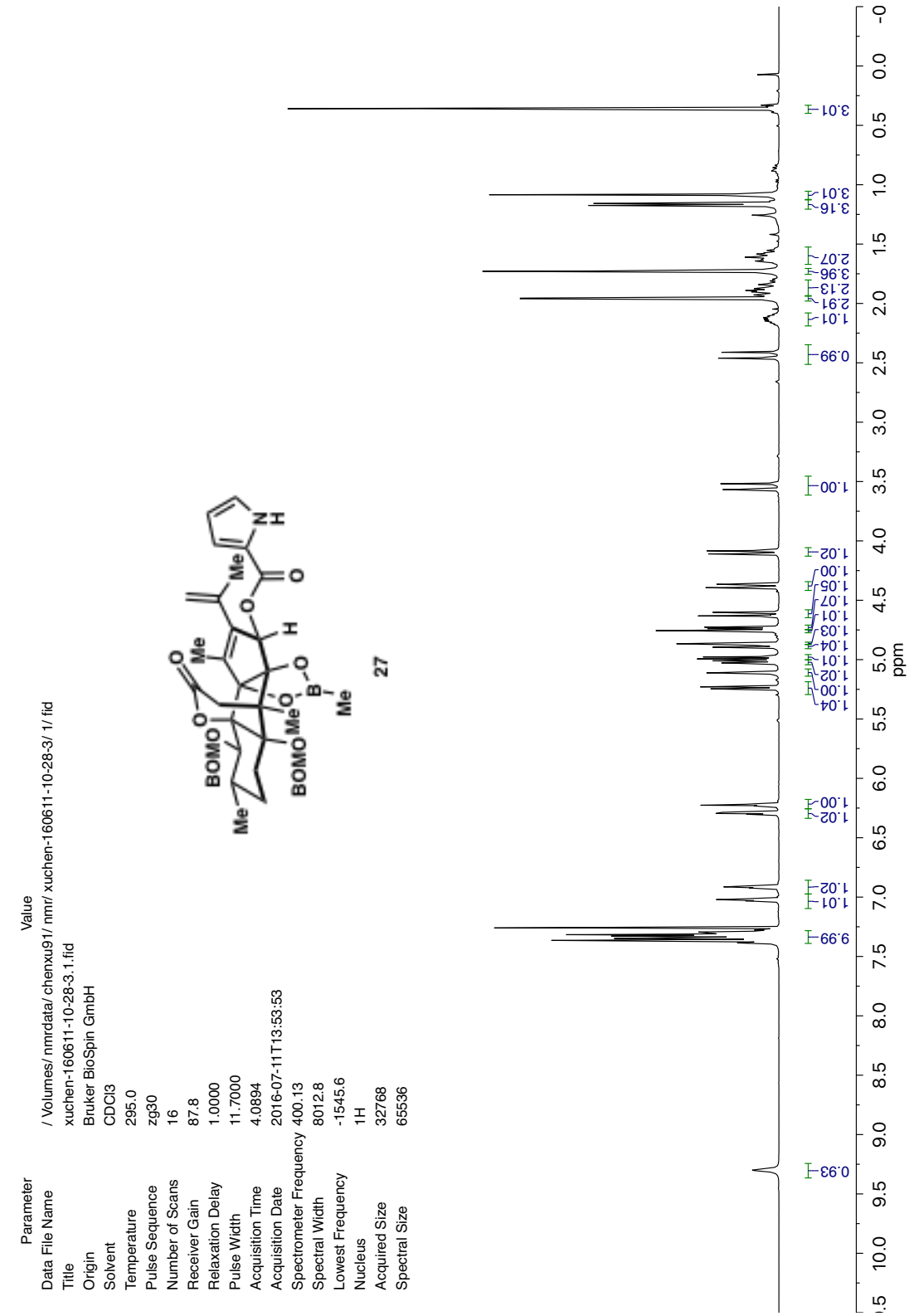
Total Synthesis of (+)-Ryanodine and (+)-20-Deoxyspiganthine

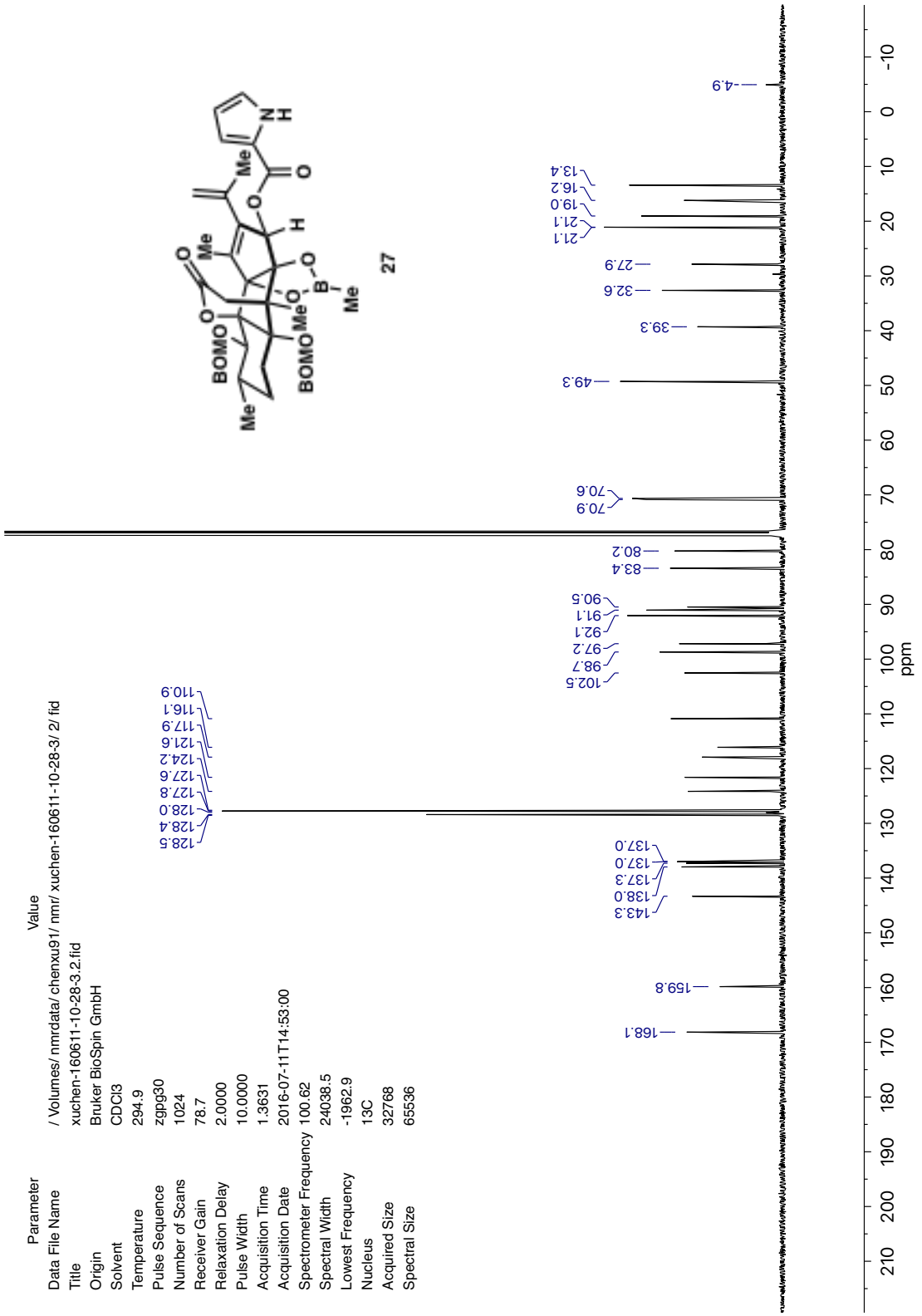

Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160723-10-49-flashed/ 1/ fid
Title xuchen-160723-10-49-flashed.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-07-23T11:50:11
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
Me
24
9.99
3.00
3.06
3.14
0.83
1.06
3.96
1.04
2.98
1.03
1.06
1.04
1.03
1.04
1.05
1.06
0.97
1.10
1.05
1.10
1.02
1.00
ppm

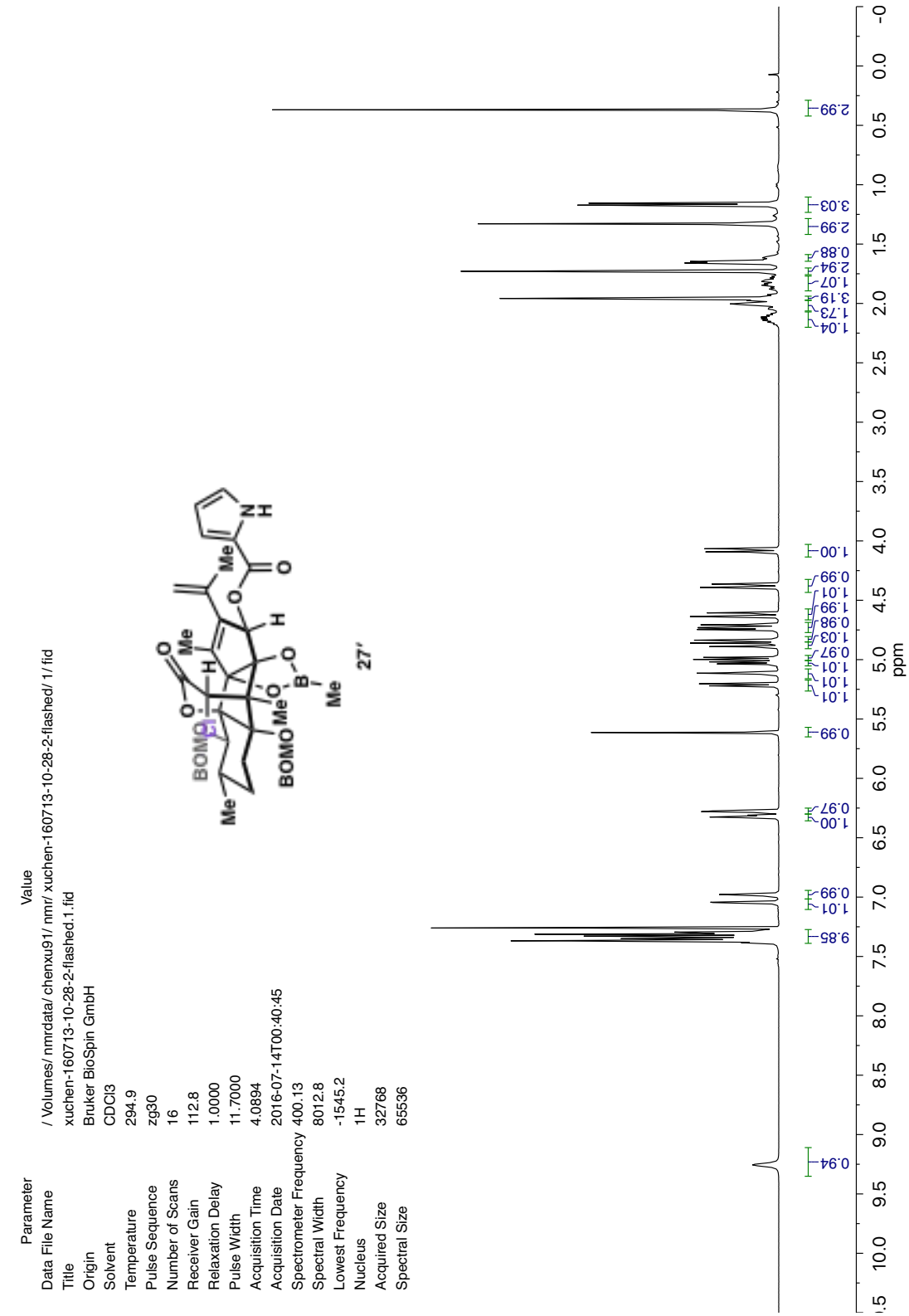

Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160723-10-49-flashed/ 2/ fid
Title xuchen-160723-10-49-flashed.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Number of Scans 1024
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-07-23T12:49:19
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1958.4
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
BOMO
Me
24
ppm

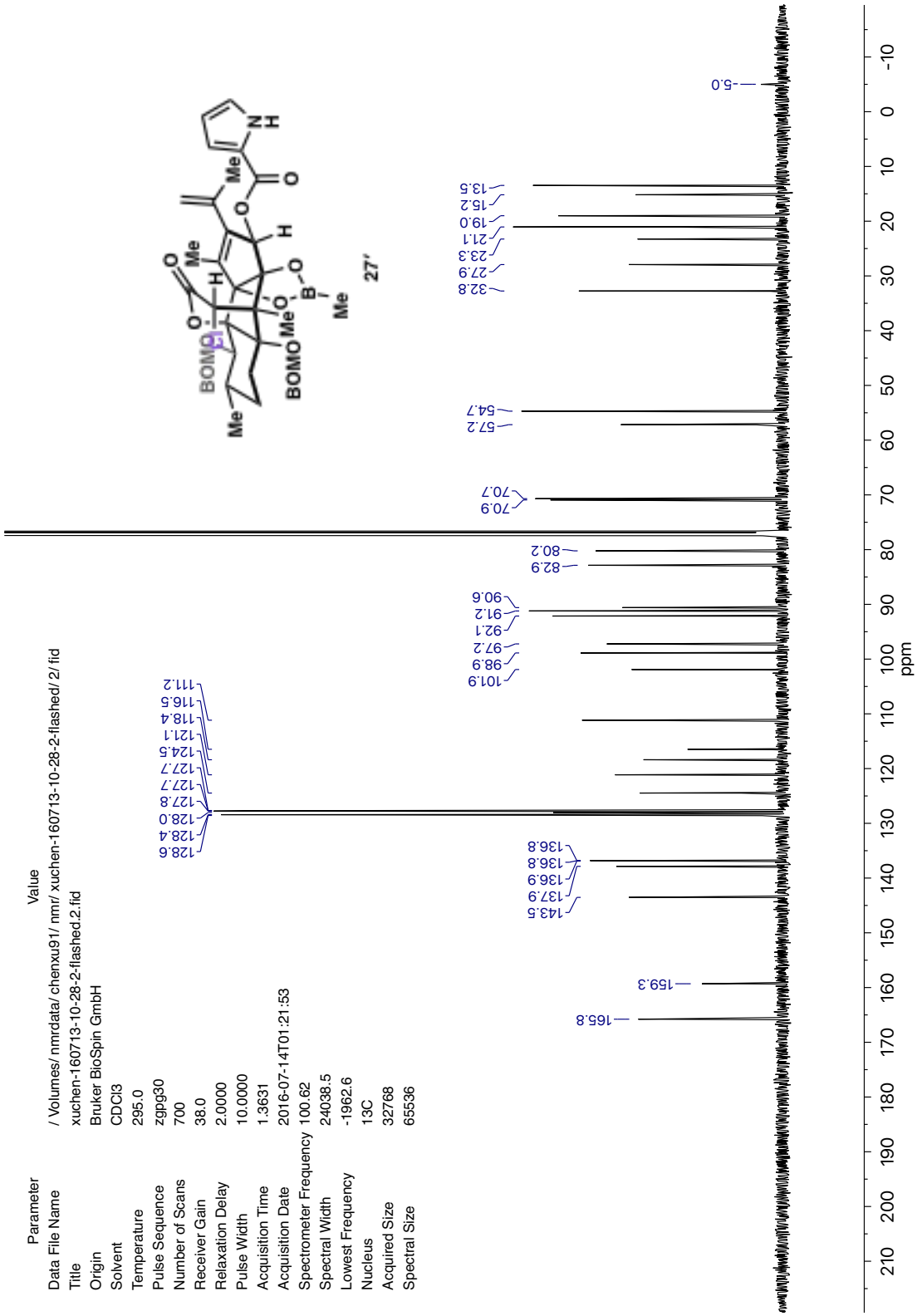

Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160724-10-50/ 1/ fid
Title xuchen-160724-10-50.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-07-24T16:26:13
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
Me
OH
H
B
25
9.96
1.00
1.06
1.06
1.06
1.16
1.10
2.00
1.00
1.03
1.03
0.94
1.11
3.03
3.14
3.08
0.88
1.02
4.08
4.15
1.08
1.09
1.04
ppm

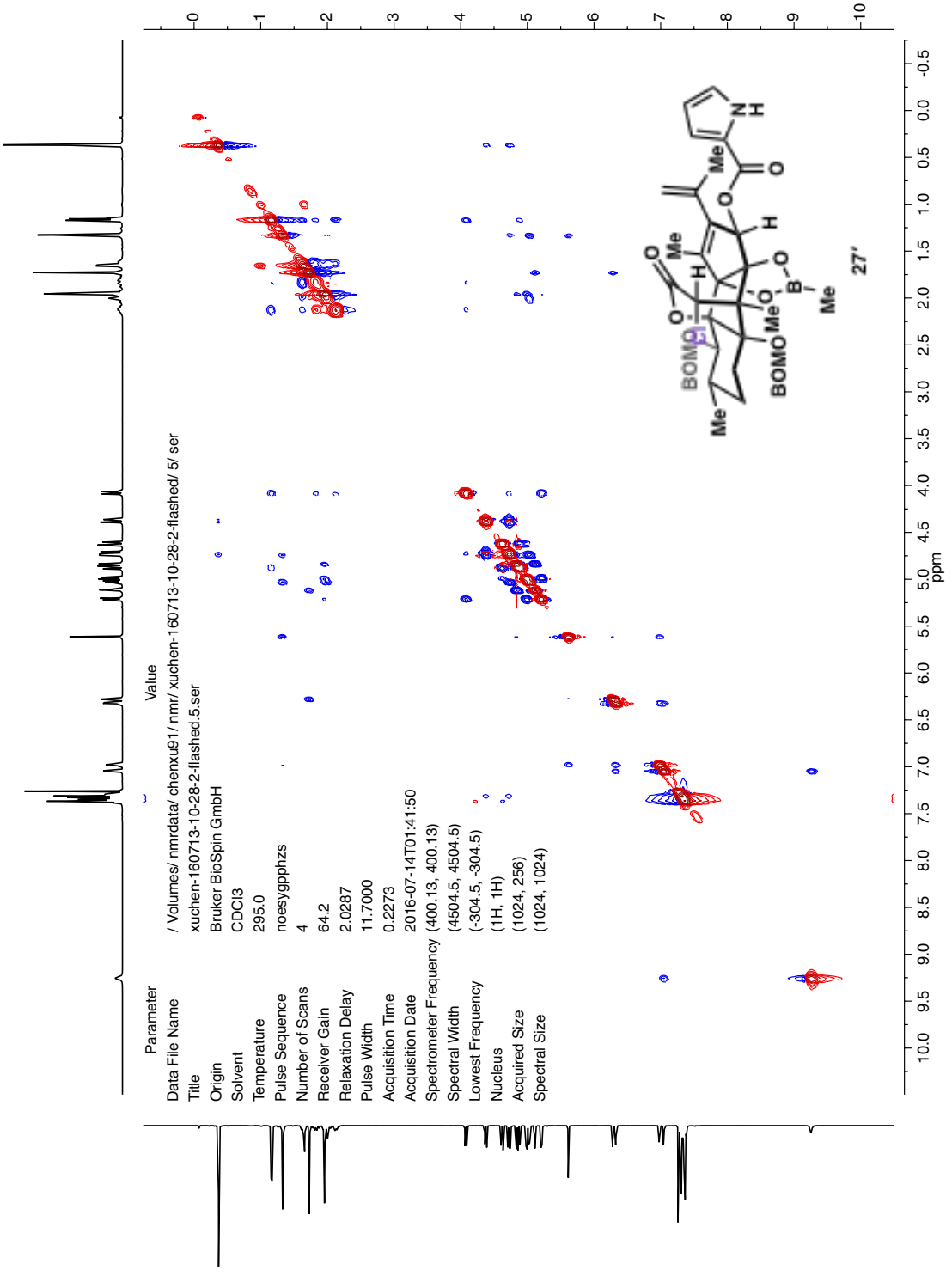

Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160724-10-50/ 2/ fid
Title xuchen-160724-10-50.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 1024
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-07-24T17:25:20
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
25
BOMO
BOMO
Me
Me
Me
Me
OH
H
O
B
Me
-5.1
13.3
16.5
19.1
21.0
21.5
27.9
32.6
39.0
49.3
70.6
70.8
80.3
84.6
90.5
91.0
92.1
97.2
98.7
102.3
117.7
127.6
127.8
127.8
127.8
128.0
128.4
128.5
135.0
137.1
138.0
138.2
145.8
168.6
ppm

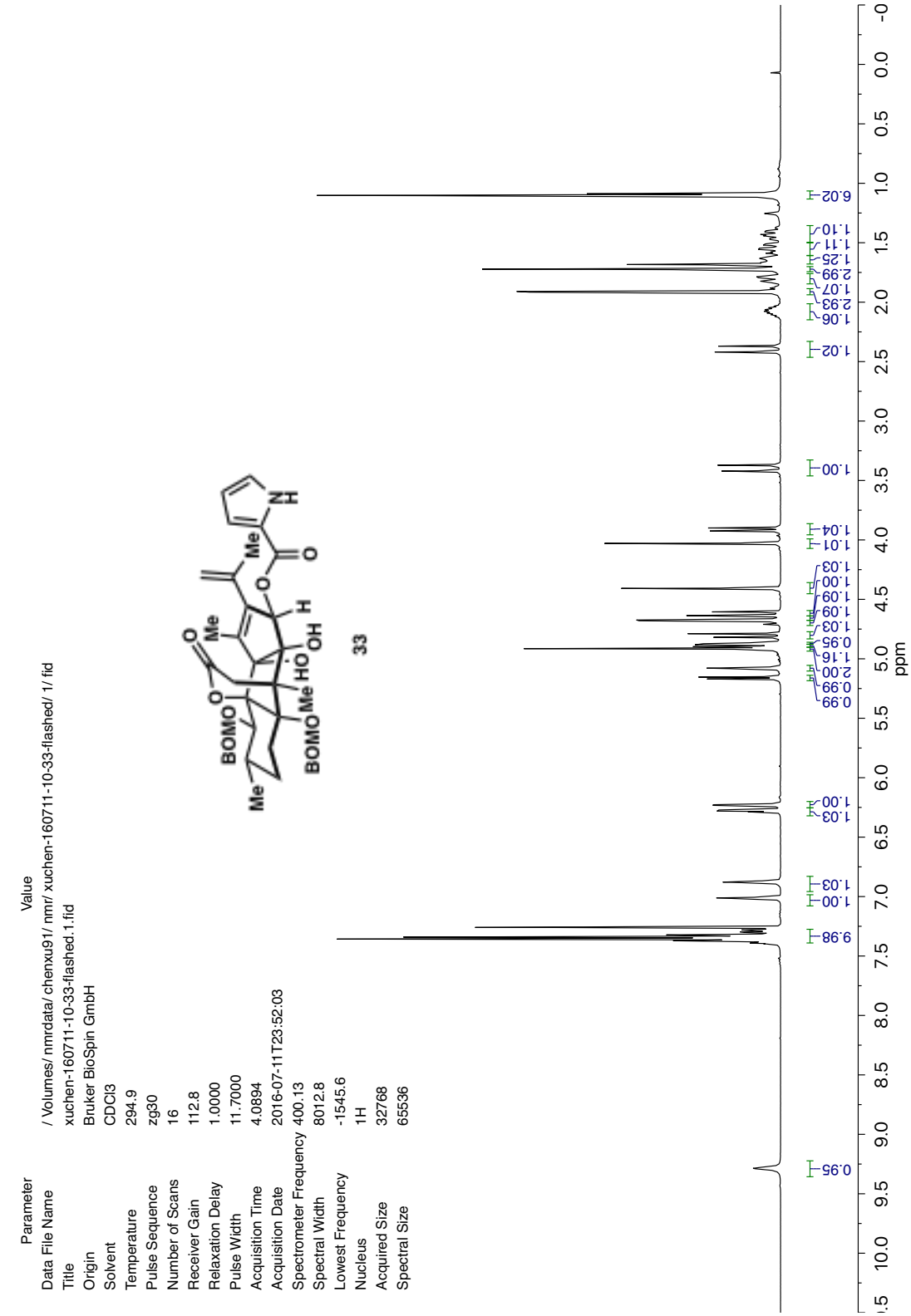

Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160611-10-28-3/ 1/ fid
Title xuchen-160611-10-28-3.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-07-11T13:53:53
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
27
ppm

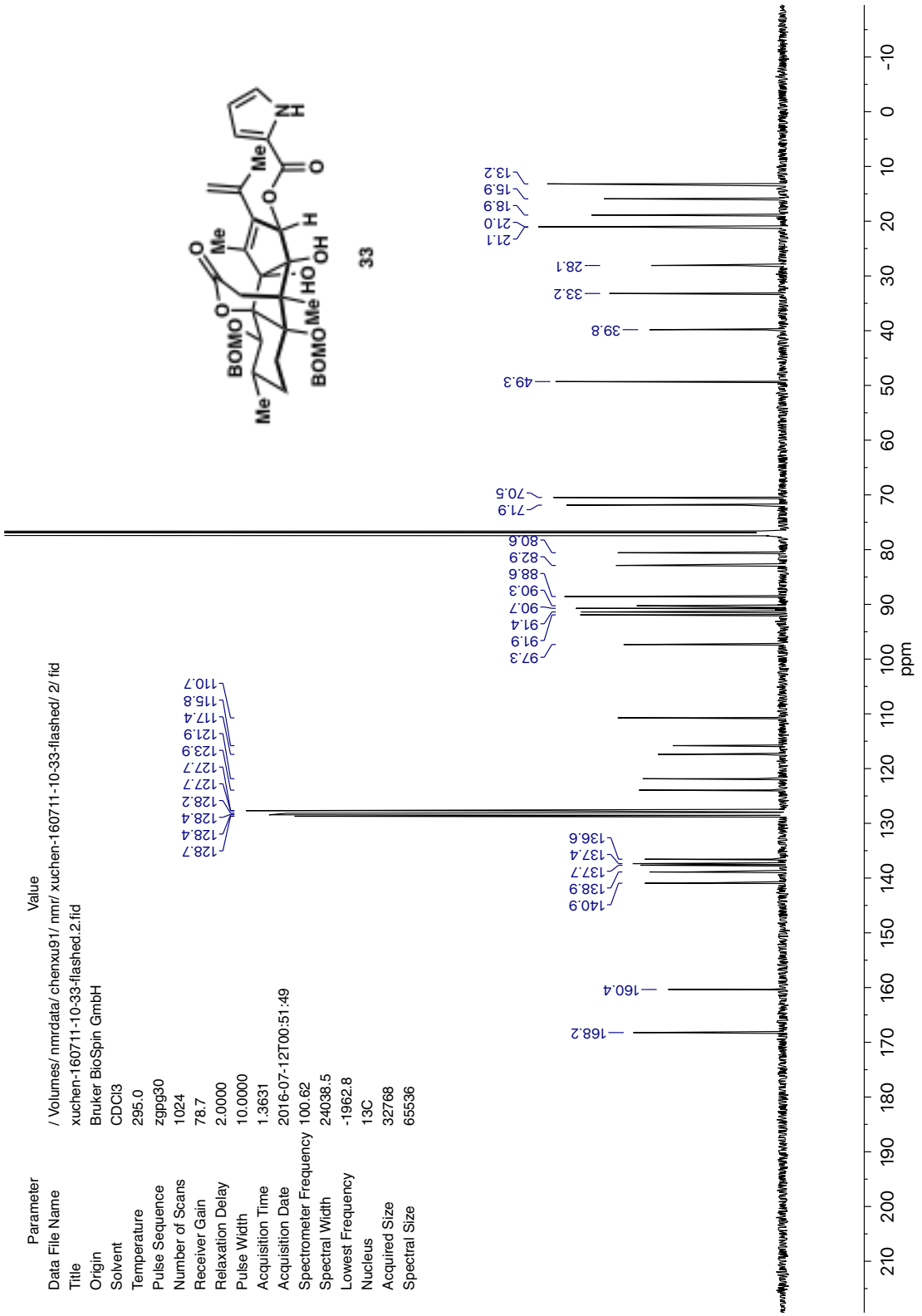

27
BOMO
BOMO
Me
Me
Me
Me
O
O
O
O
O
O
B
H
N
H
Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160611-10-28-3/ 2/ fid
Title xuchen-160611-10-28-3.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Number of Scans 1024
Receiver Gain 78.7
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-07-11T14:53:00
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1962.9
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
168.1
159.8
143.3
138.0
137.3
137.0
137.0
128.5
128.4
128.0
127.8
127.6
124.2
121.6
117.9
116.1
110.9
102.5
98.7
97.2
92.1
91.1
90.5
83.4
80.2
70.9
70.6
49.3
39.3
32.6
27.9
21.1
21.1
19.0
16.2
13.4
-4.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

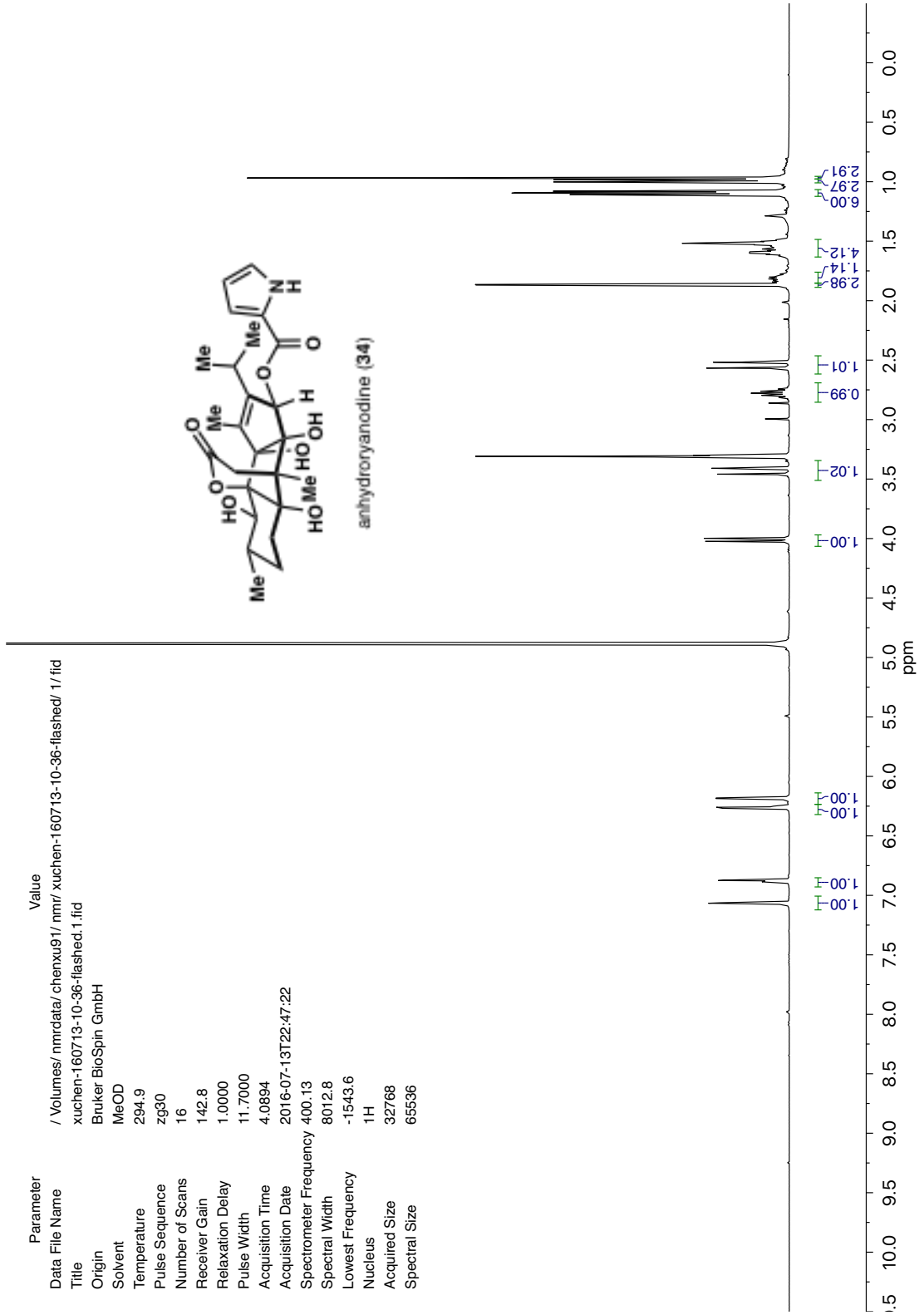

Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160713-10-28-2-flashed/ 1/ fid
Title xuchen-160713-10-28-2-flashed.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-07-14T00:40:45
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.2
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
27'
ppm

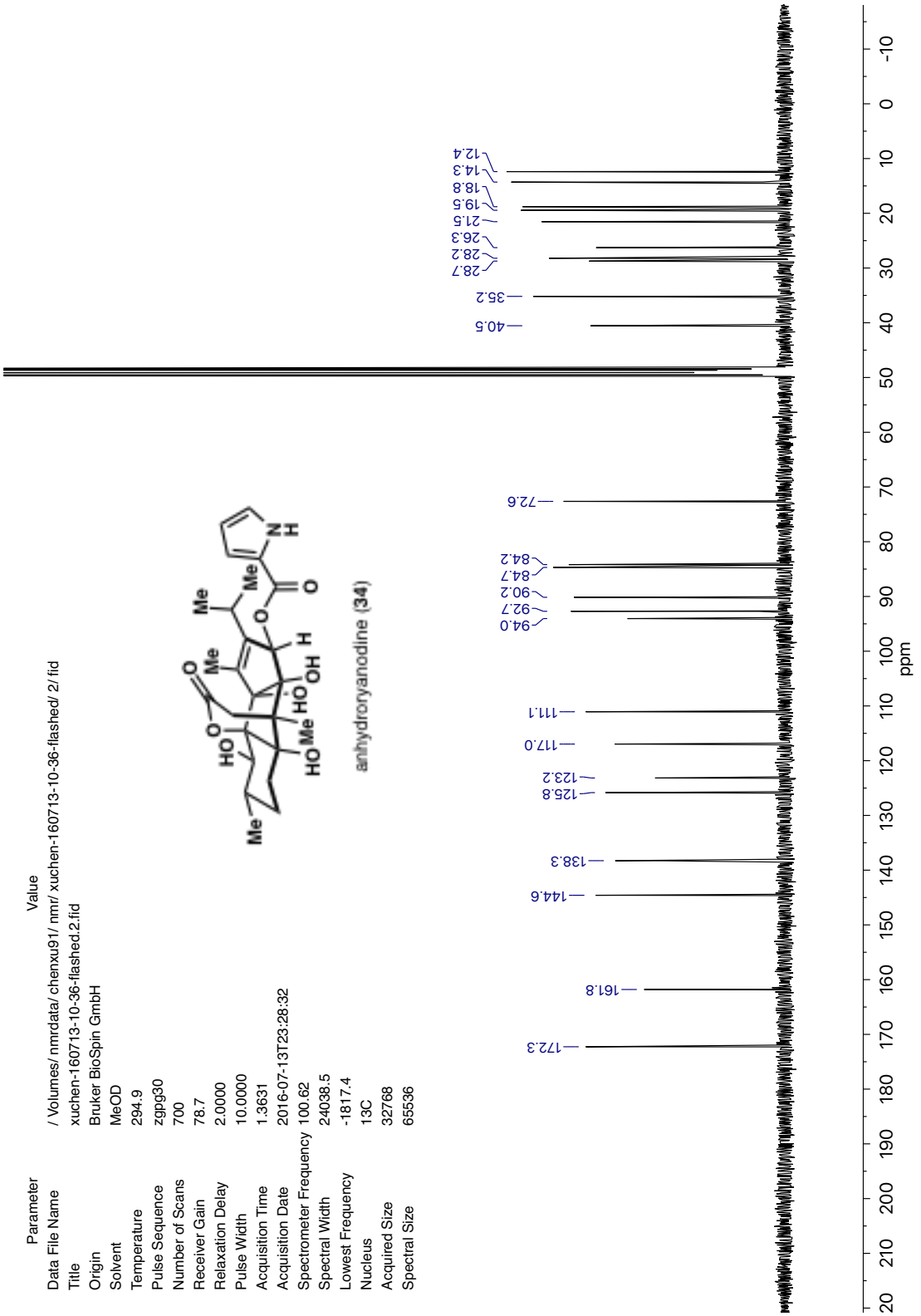

27'
BOMO
BOMO
Me
Me
Me
Me
Me
Me
O
O
O
O
O
O
H
H
N
H
B
-5.0
13.5
15.2
19.0
21.1
23.3
27.9
32.8
54.7
57.2
70.7
70.9
80.2
82.9
90.6
91.2
92.1
97.2
98.9
101.9
111.2
116.5
118.4
121.1
124.5
127.7
127.7
127.8
128.0
128.4
128.6
136.8
136.8
136.9
137.9
143.5
159.3
165.8
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160713-10-28-2-flashed/ 2/ fid
Title xuchen-160713-10-28-2-flashed.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 700
Receiver Gain 38.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-07-14T01:21:53
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1962.6
Nucleus 13C
Acquired Size 32768
Spectral Size 65536

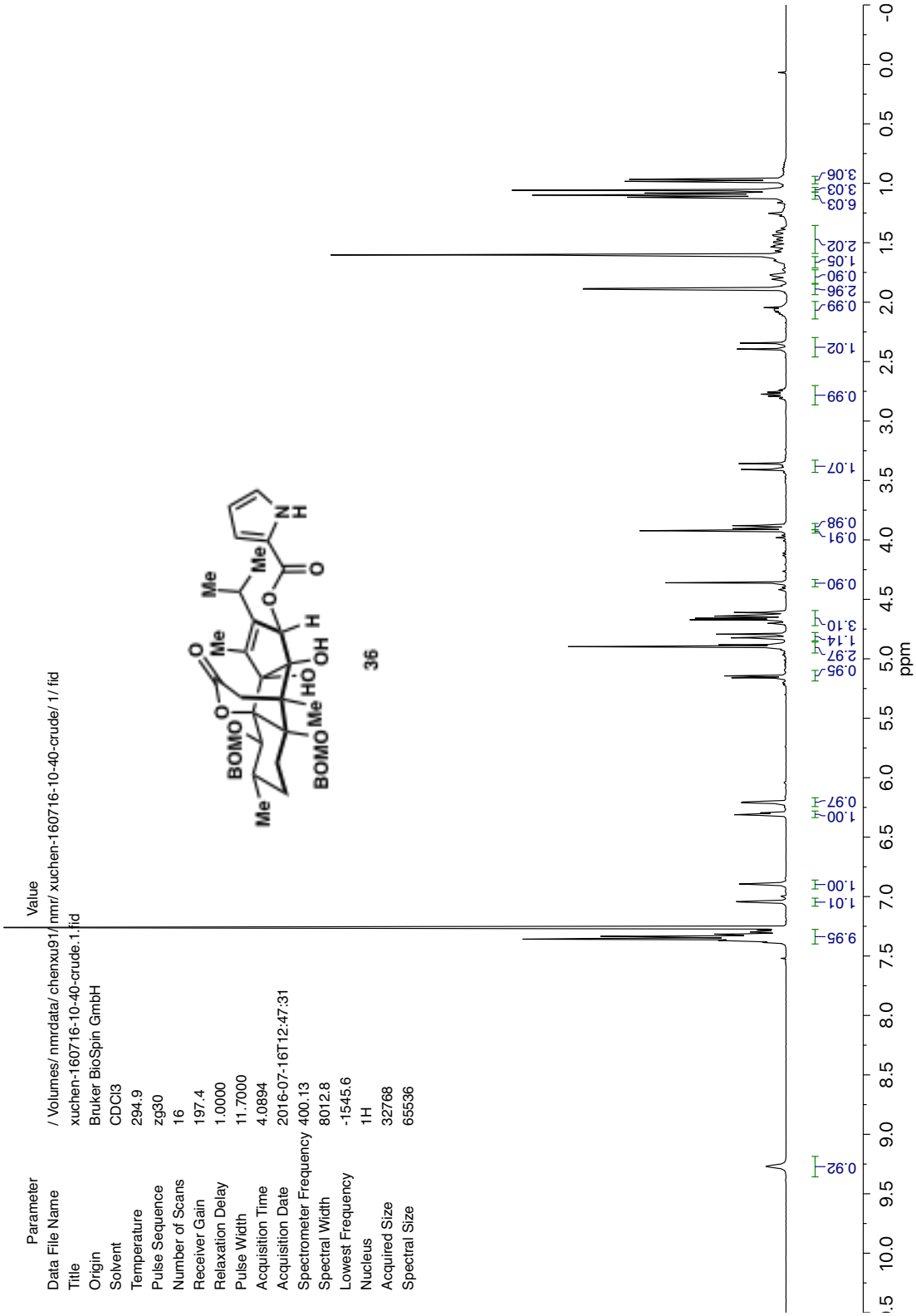

Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160713-10-28-2-flashed/ 5/ ser
Title xuchen-160713-10-28-2-flashed.5.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence noesygpphzs
Number of Scans 4
Receiver Gain 64.2
Relaxation Delay 2.0287
Pulse Width 11.7000
Acquisition Time 0.2273
Acquisition Date 2016-07-14T01:41:50
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4504.5, 4504.5)
Lowest Frequency (-304.5, -304.5)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
ppm
BOMO
BOMO
Me
Me
Me
Me
27'

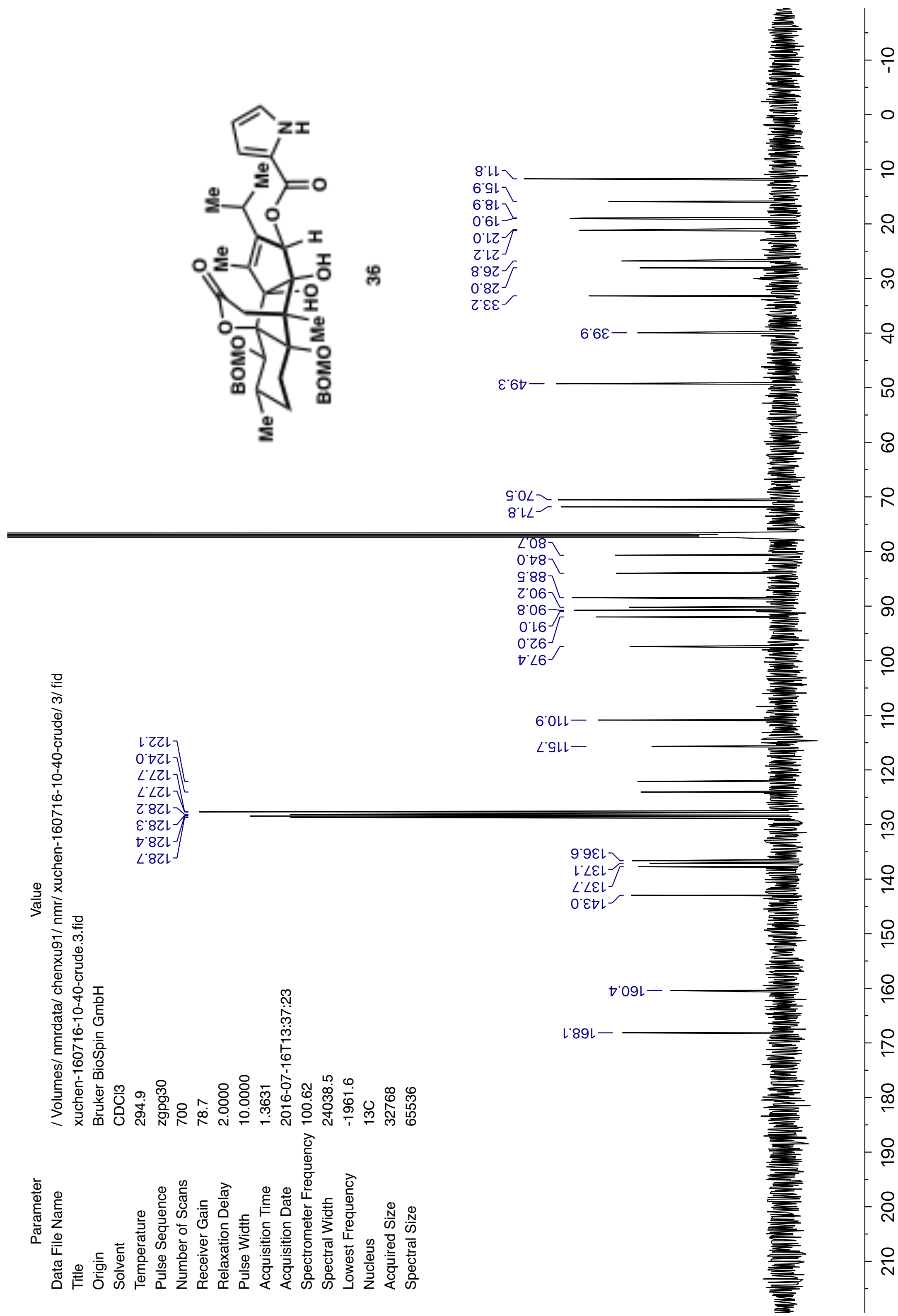

Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160711-10-33-flashed/ 1/ fid
Title xuchen-160711-10-33-flashed.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-07-11T23:52:03
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
Me
HO
OH
Me
BOMO
Me
O
33
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160711-10-33-flashed/ 2/ fid
Title xuchen-160711-10-33-flashed.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 1024
Receiver Gain 78.7
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-07-12T00:51:49
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1962.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
33
BOMO
Me
HO
OH
H
O
N
ppm

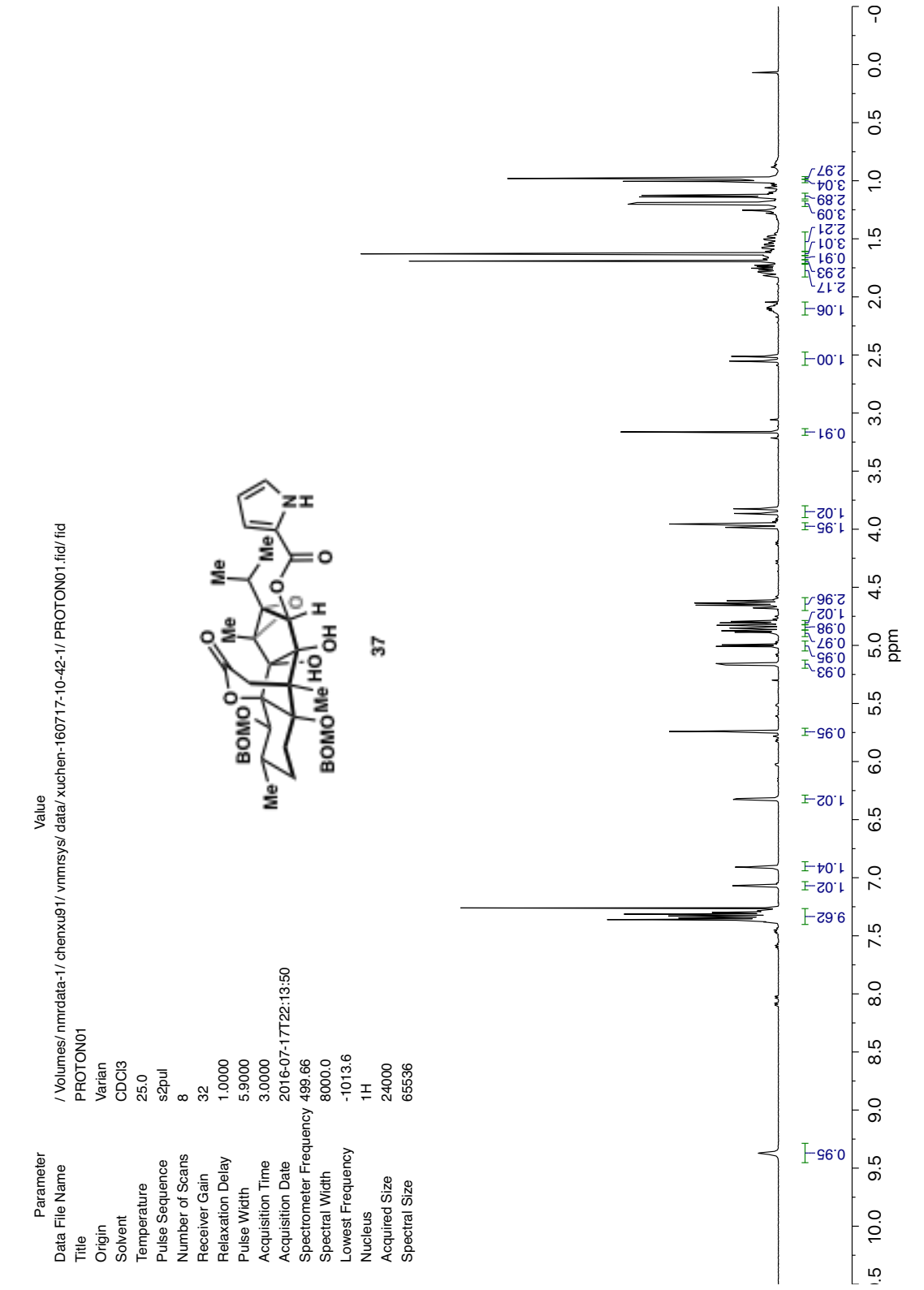

anhydroryanodine (34)
Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160713-10-36-flashed/ 1/ fid
Title xuchen-160713-10-36-flashed.1.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 294.9
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-07-13T22:47:22
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1543.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
1.00
1.00
1.00
1.00
1.00
1.02
0.99
1.01
2.98
1.14
4.12
6.00
2.97
2.91
ppm

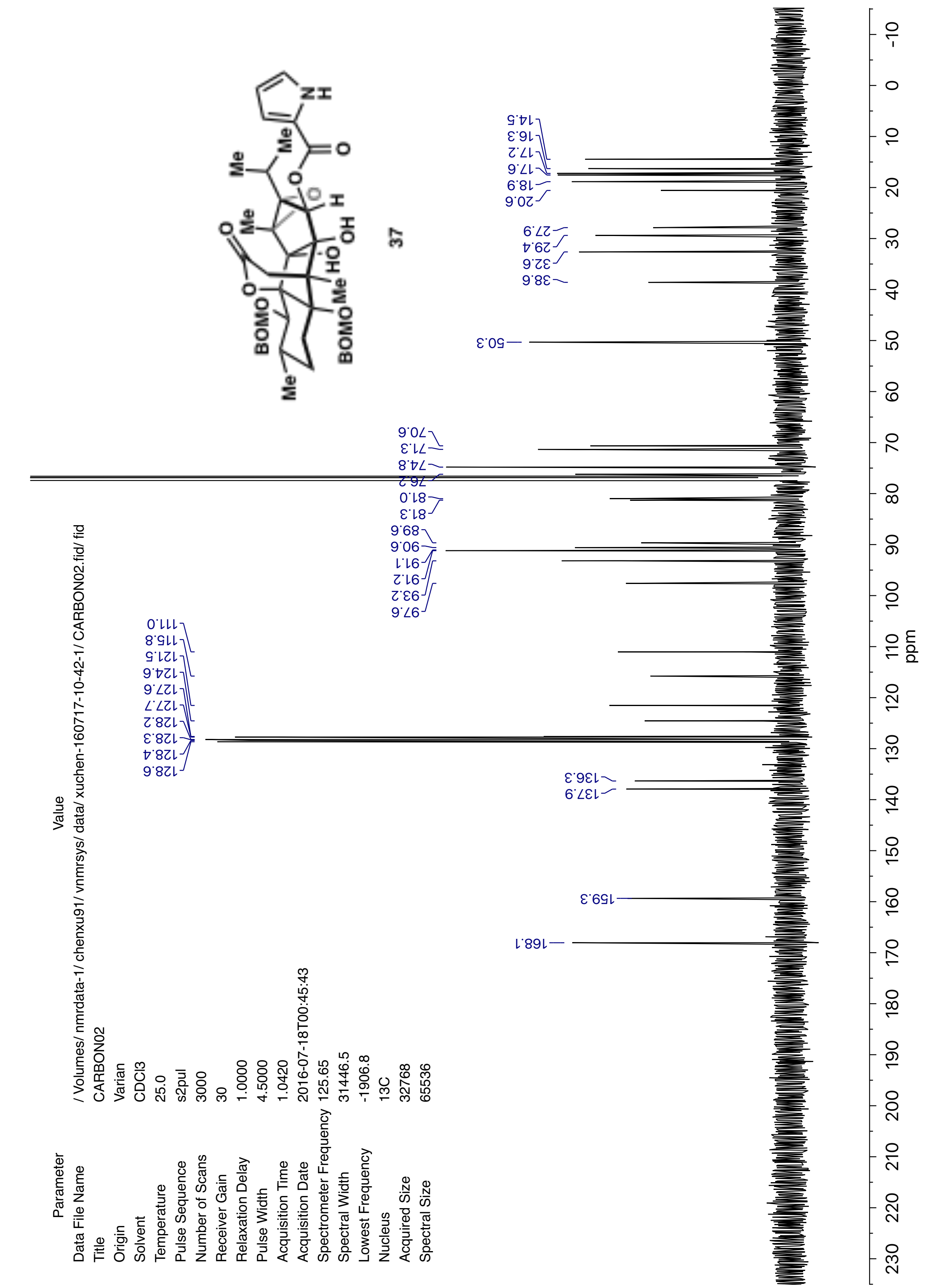

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160713-10-36-flashed/ 2/ fid
Title
xuchen-160713-10-36-flashed.2.fid
Origin
Bruker BioSpin GmbH
Solvent
MeOD
Temperature
294.9
Pulse Sequence
zgpg30
Number of Scans
700
Receiver Gain
78.7
Relaxation Delay
2.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2016-07-13T23:28:32
Spectrometer Frequency
100.62
Spectral Width
24038.5
Lowest Frequency
-1817.4
Nucleus
13C
Acquired Size
32768
Spectral Size
65536
anhydroryanodine (34)
172.3
161.8
144.6
138.3
125.8
123.2
117.0
111.1
94.0
92.7
90.2
84.7
84.2
72.6
40.5
35.2
28.7
28.2
26.3
21.5
19.5
18.8
14.3
12.4
ppm

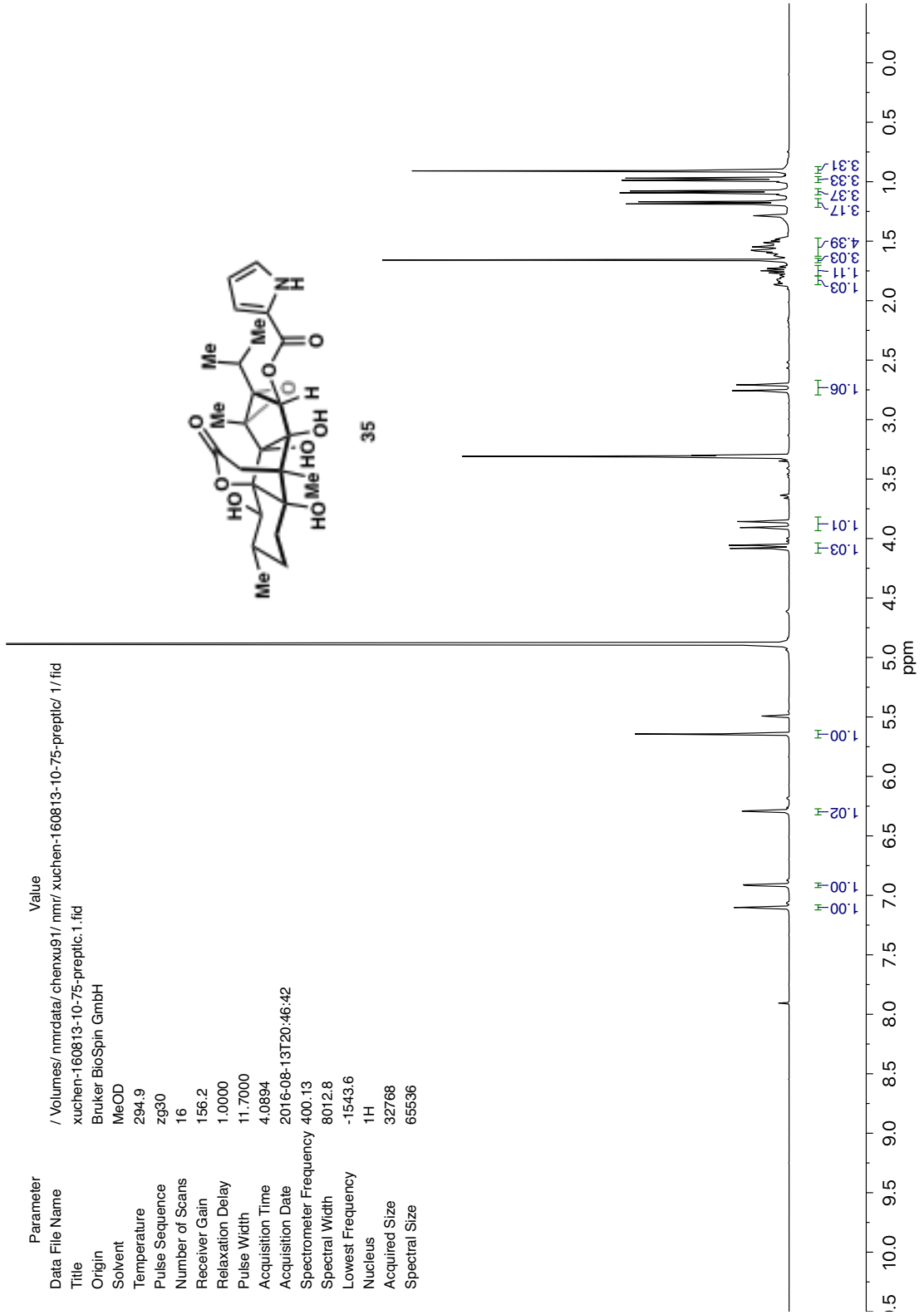

Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160716-10-40-crude/ 1/ fid
Title xuchen-160716-10-40-crude.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-07-16T12:47:31
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
Me
HO
OH
H
N
O
36
ppm

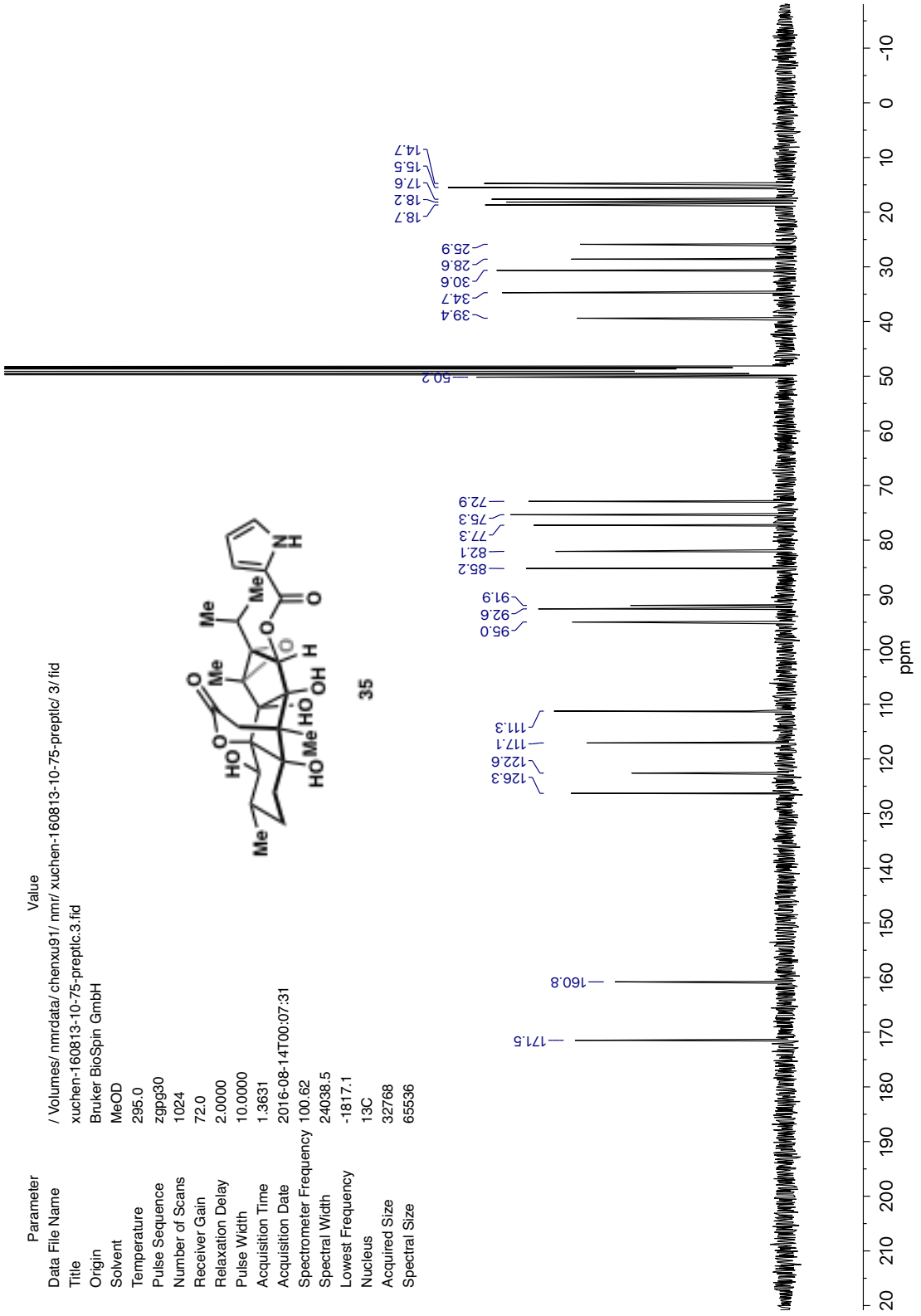


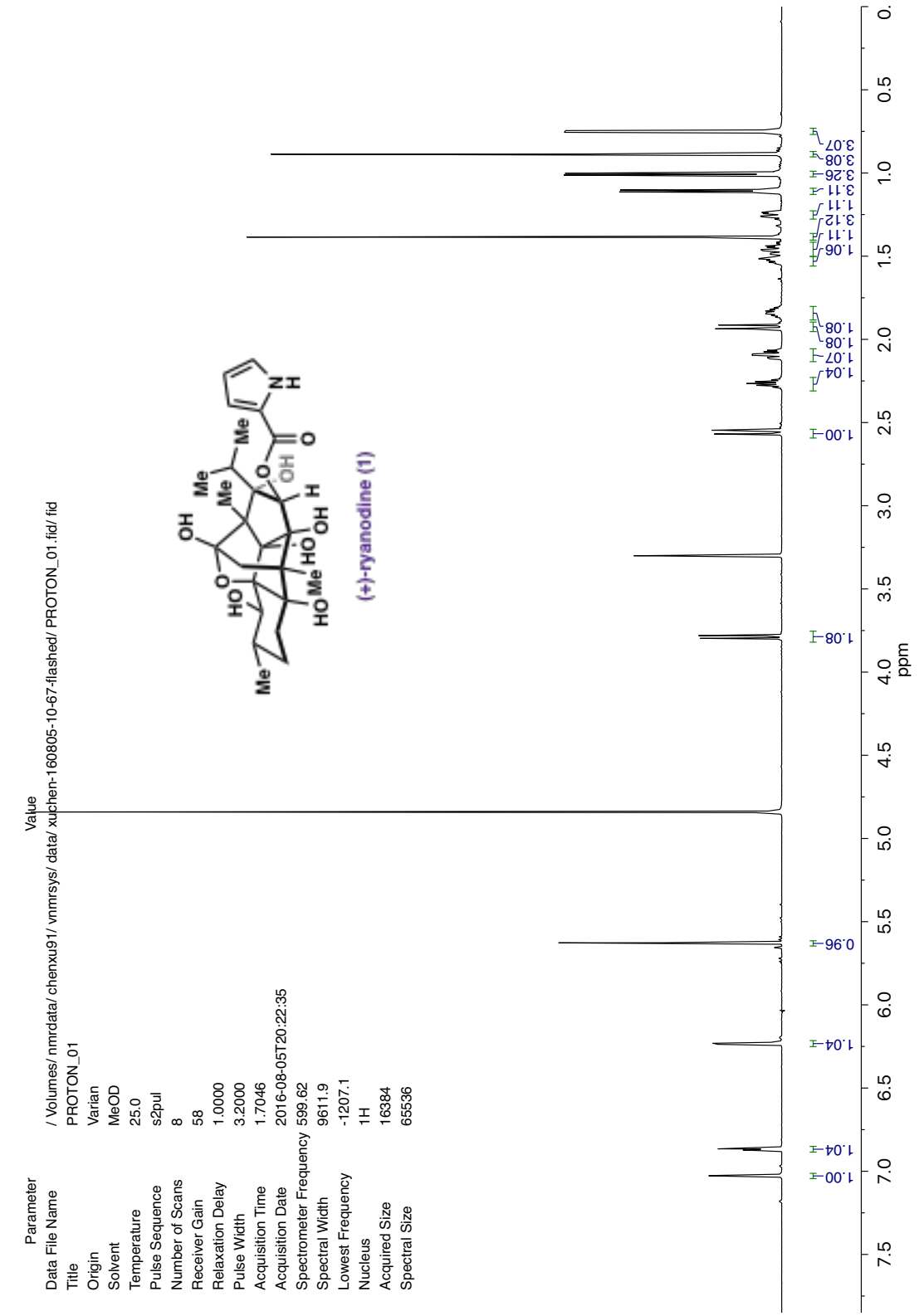
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160716-10-40-crude/ 3/ fid
Title	xuchen-160716-10-40-crude.3.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	294.9
Pulse Sequence	zgpg30
Number of Scans	700
Receiver Gain	78.7
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2016-07-16T13:37:23
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1961.6
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

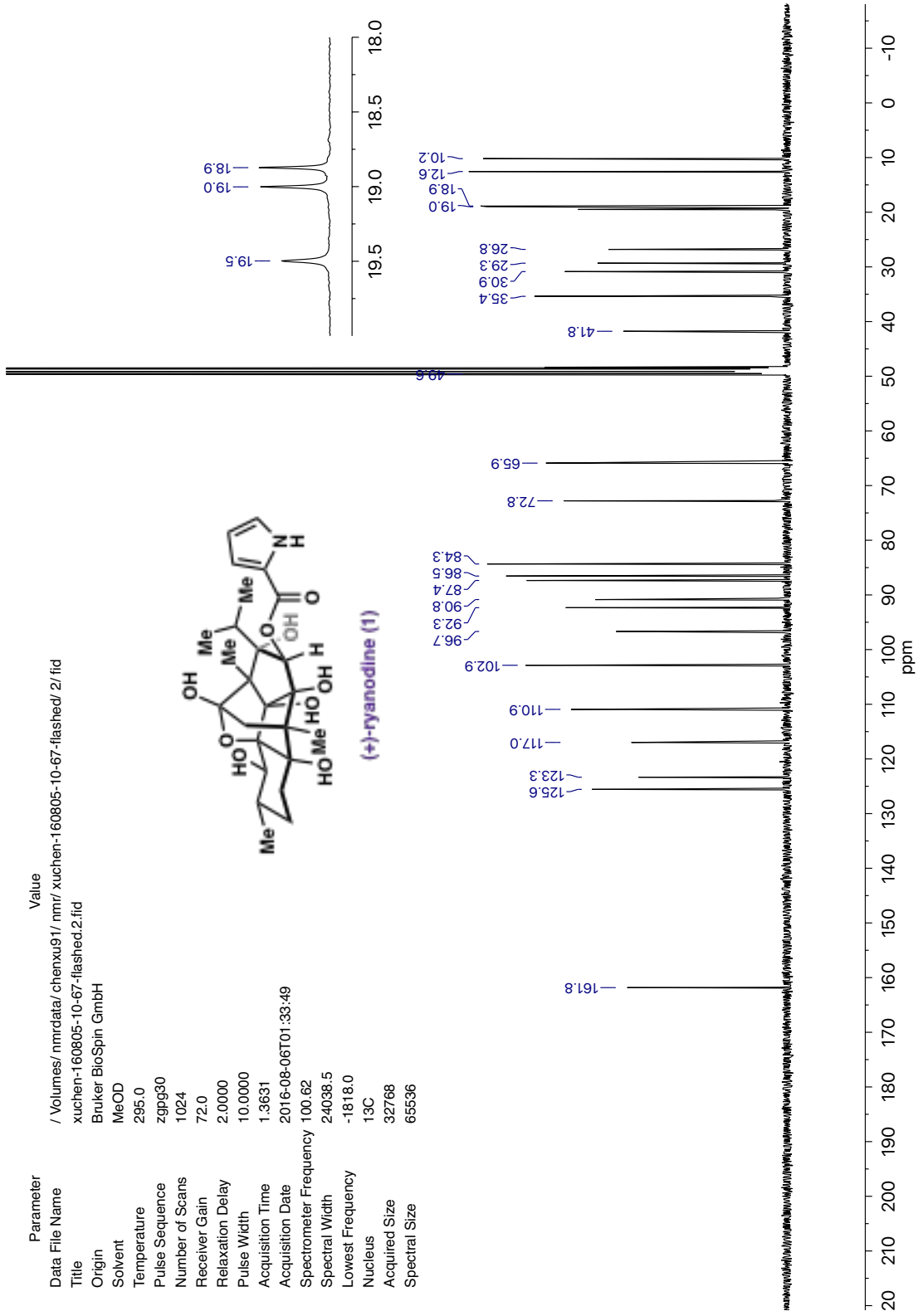

Parameter
Value
Data File Name
/ Volumes/ nmrdata-1/ chenxu91/ vnmrsys/ data/ xuchen-160717-10-42-1/ PROTON01.fid/ fid
Title
PROTON01
Origin
Varian
Solvent
CDCl3
Temperature
25.0
Pulse Sequence
s2pul
Number of Scans
8
Receiver Gain
32
Relaxation Delay
1.0000
Pulse Width
5.9000
Acquisition Time
3.0000
Acquisition Date
2016-07-17T22:13:50
Spectrometer Frequency
499.66
Spectral Width
8000.0
Lowest Frequency
-1013.6
Nucleus
1H
Acquired Size
24000
Spectral Size
65536
BOMO
BOMO
Me
Me
Me
Me
Me
HO
OH
Me
O
O
O
O
O
O
H
N
H
37
9.62
1.04
1.02
1.02
0.95
1.02
2.96
1.02
0.98
0.97
0.95
0.93
0.95
1.02
1.95
0.91
1.00
1.06
2.17
2.93
0.91
3.01
2.21
3.09
2.89
3.04
2.97
ppm

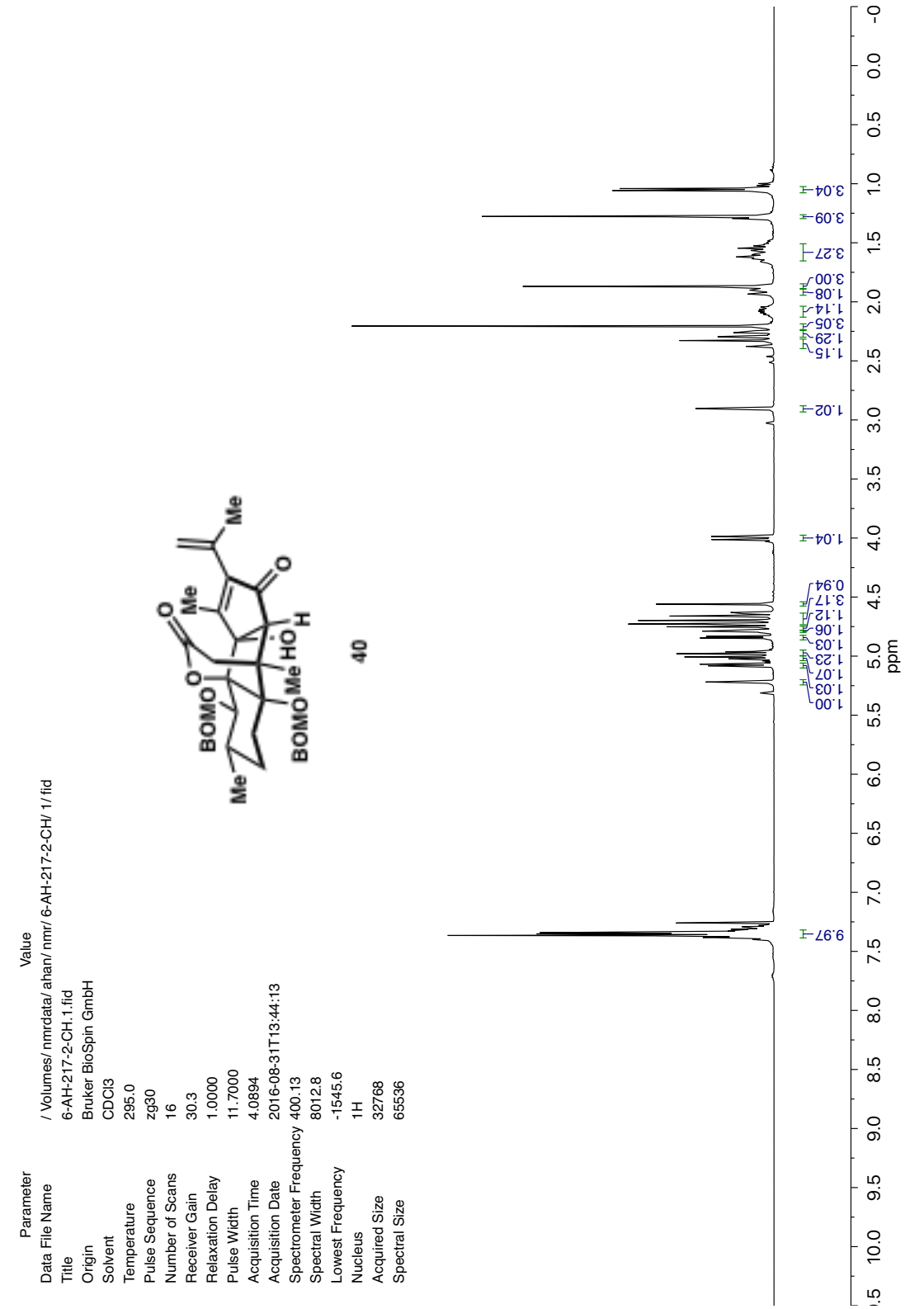

Parameter Value
Data File Name /Volumes/ nmrdata-1/ chenxu91/ vnmrsys/ data/ xuchen-160717-10-42-1/ CARBON02.fid/ fid
Title CARBON02
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 3000
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 4.5000
Acquisition Time 1.0420
Acquisition Date 2016-07-18T00:45:43
Spectrometer Frequency 125.65
Spectral Width 31446.5
Lowest Frequency -1906.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
168.1
159.3
137.9
136.3
128.6
128.4
128.3
128.2
127.7
127.6
124.6
121.5
115.8
111.0
97.6
93.2
91.2
91.1
90.6
89.6
81.3
81.0
76.2
74.8
71.3
70.6
50.3
38.6
32.6
29.4
27.9
20.6
18.9
17.6
17.2
16.3
14.5
BOMO
BOMO
Me
Me
Me
Me
Me
O
O
O
O
O
HO
OH
H
N
H
37
ppm


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160813-10-75-preptlc/ 1/ fid
Title
xuchen-160813-10-75-preptlc.1.fid
Origin
Bruker BioSpin GmbH
Solvent
MeOD
Temperature
294.9
Pulse Sequence
zg30
Number of Scans
16
Receiver Gain
156.2
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2016-08-13T20:46:42
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1543.6
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
35
1.00
1.00
1.02
1.00
1.03
1.01
1.06
1.03
1.11
3.03
4.39
3.17
3.37
3.33
3.31
ppm

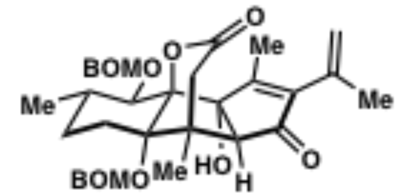

Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160813-10-75-preptlc/ 3/ fid
Title xuchen-160813-10-75-preptlc.3.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 1024
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-08-14T00:07:31
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1817.1
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
35
171.5
160.8
126.3
122.6
117.1
111.3
95.0
92.6
91.9
85.2
82.1
77.3
75.3
72.9
50.2
39.4
34.7
30.6
28.6
25.9
18.7
18.2
17.6
15.5
14.7
ppm


Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ vnmrsys/ data/ xuchen-160805-10-67-flashed/ PROTON_01.fid/ fid
Title PROTON_01
Origin Varian
Solvent MeOD
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 58
Relaxation Delay 1.0000
Pulse Width 3.2000
Acquisition Time 1.7046
Acquisition Date 2016-08-05T20:22:35
Spectrometer Frequency 599.62
Spectral Width 9611.9
Lowest Frequency -1207.1
Nucleus 1H
Acquired Size 16384
Spectral Size 65536
(+)-ryanodine (1)
ppm

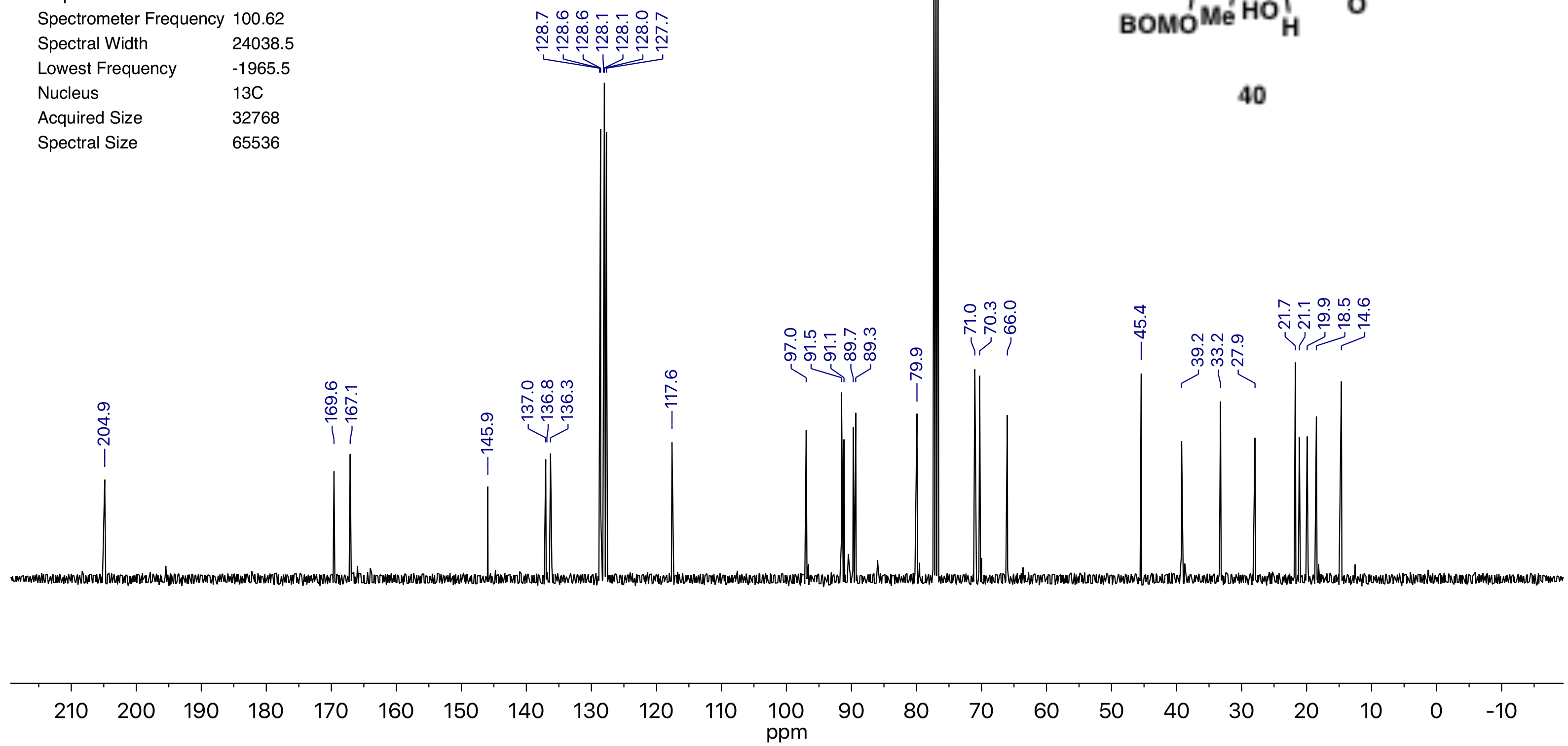

Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ xuchen-160805-10-67-flashed/ 2/ fid
Title xuchen-160805-10-67-flashed.2.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 1024
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-08-06T01:33:49
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1818.0
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
(+)-ryanodine (1)
161.8
125.6
123.3
117.0
110.9
102.9
96.7
92.3
90.8
87.4
86.5
84.3
72.8
65.9
49.6
41.8
35.4
30.9
29.3
26.8
19.0
18.9
12.6
10.2
19.5
19.0
18.9
18.5
18.0
ppm

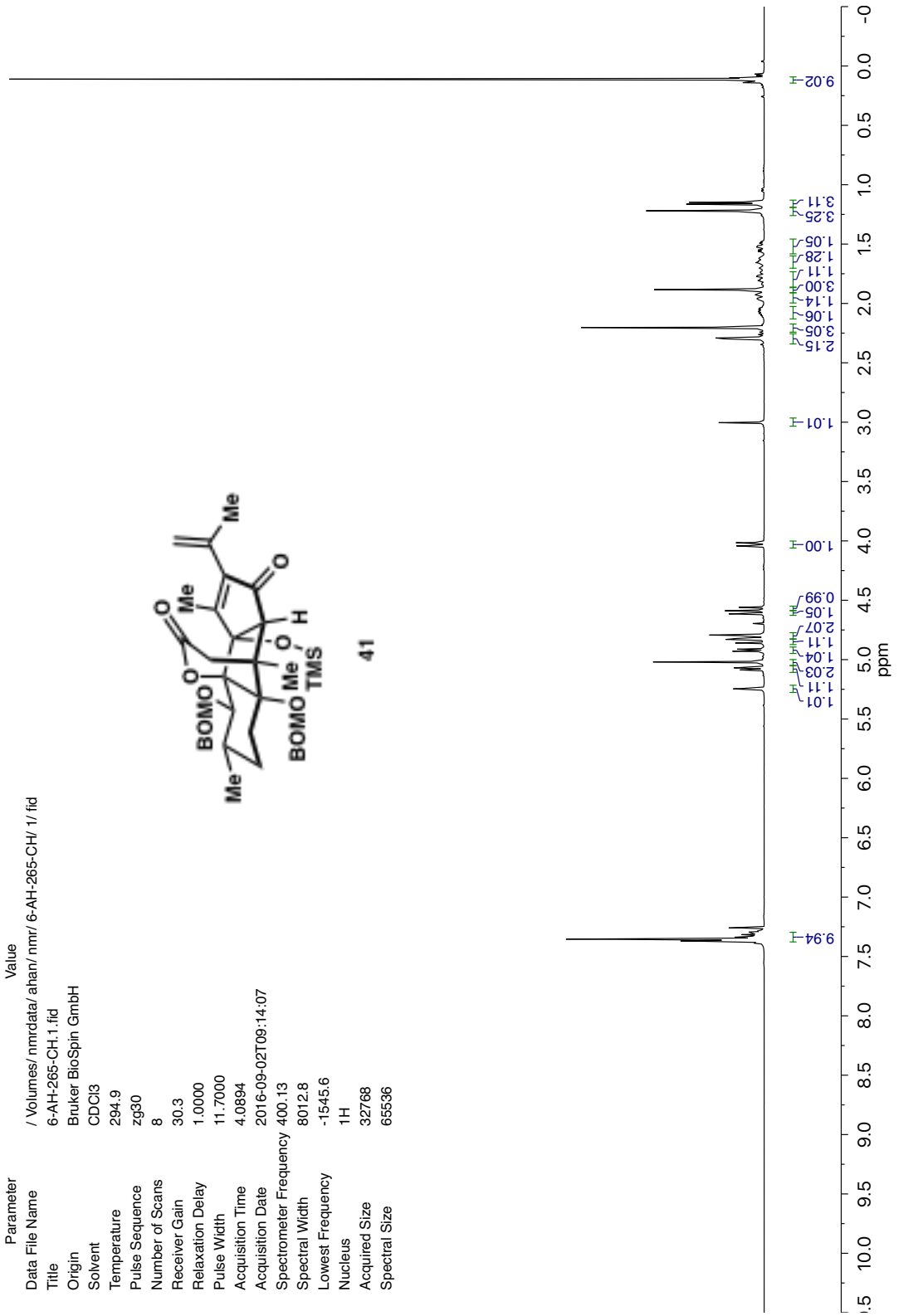

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-217-2-CH/ 1/ fid
Title
6-AH-217-2-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.0
Pulse Sequence
zg30
Number of Scans
16
Receiver Gain
30.3
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2016-08-31T13:44:13
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.6
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
BOMO
Me
Me
Me
HO
H
BOMO
40
9.97
1.00
1.03
1.07
1.23
1.03
1.06
1.12
3.17
0.94
1.04
1.02
1.15
1.29
3.05
1.14
1.08
3.00
3.27
3.09
3.04
ppm

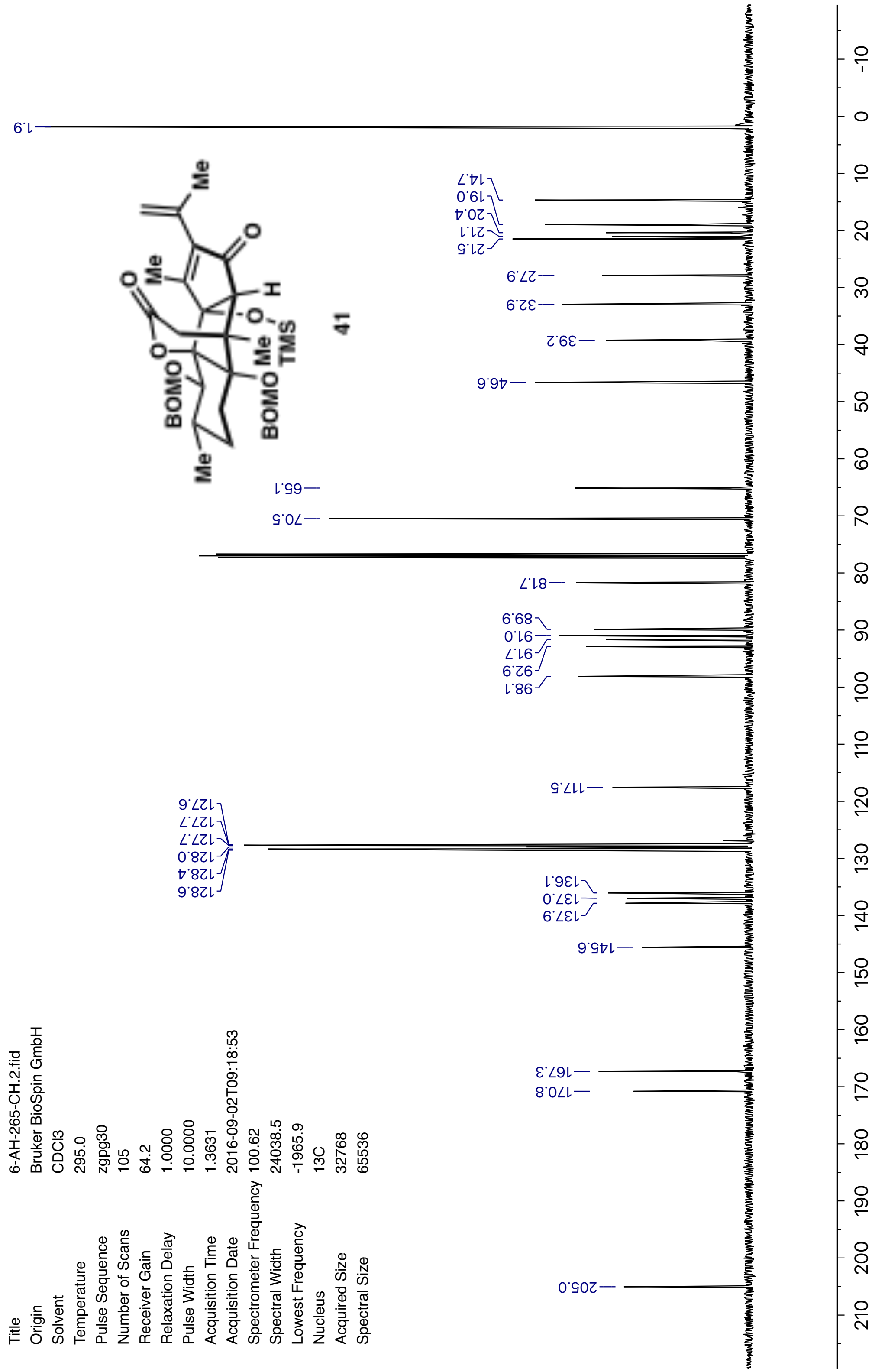
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-217-2-CH/ 2/ fid
Title	6-AH-217-2-CH.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	294.9
Pulse Sequence	zgpg30
Number of Scans	101
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2016-08-31T13:48:49
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1965.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



40

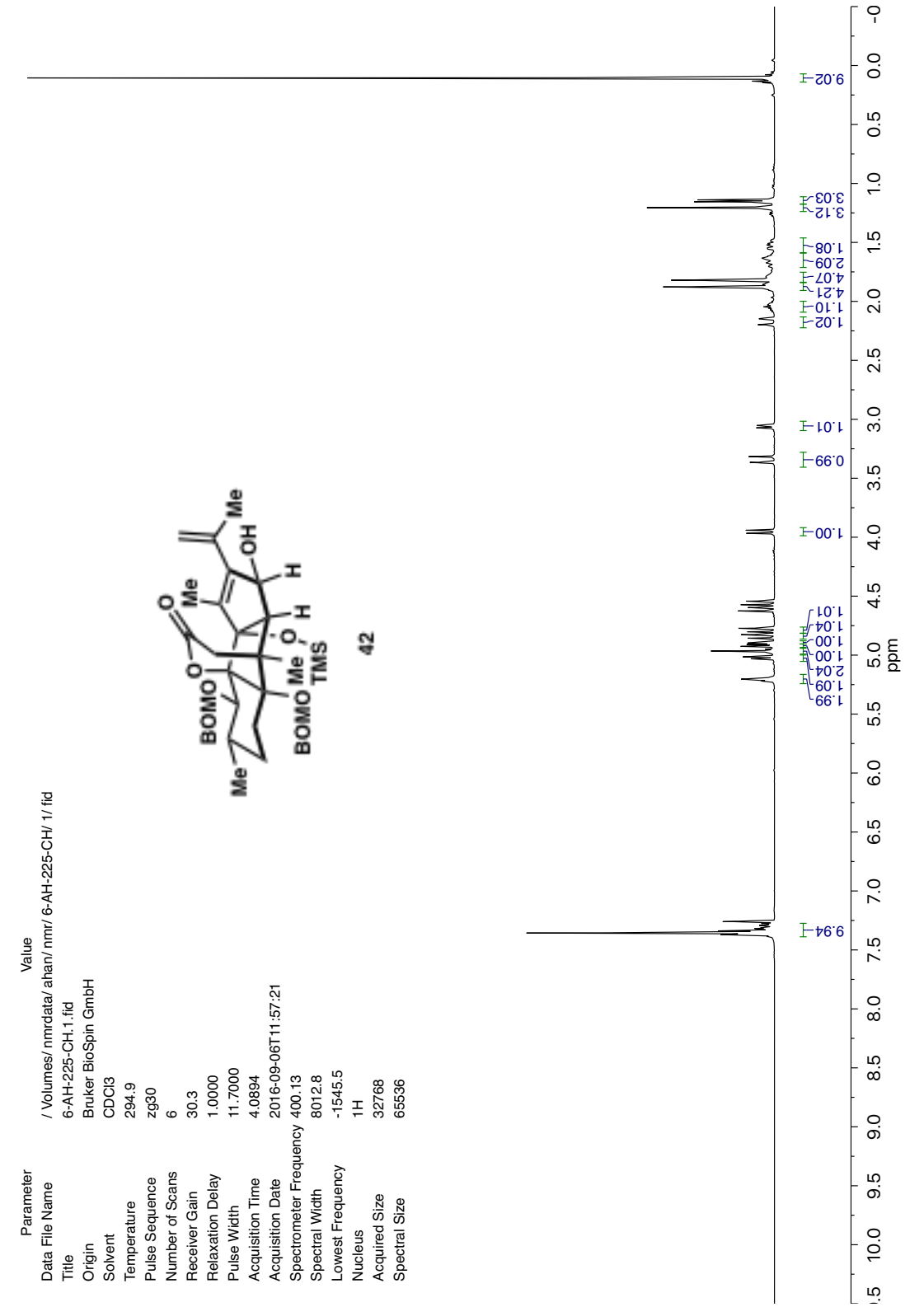


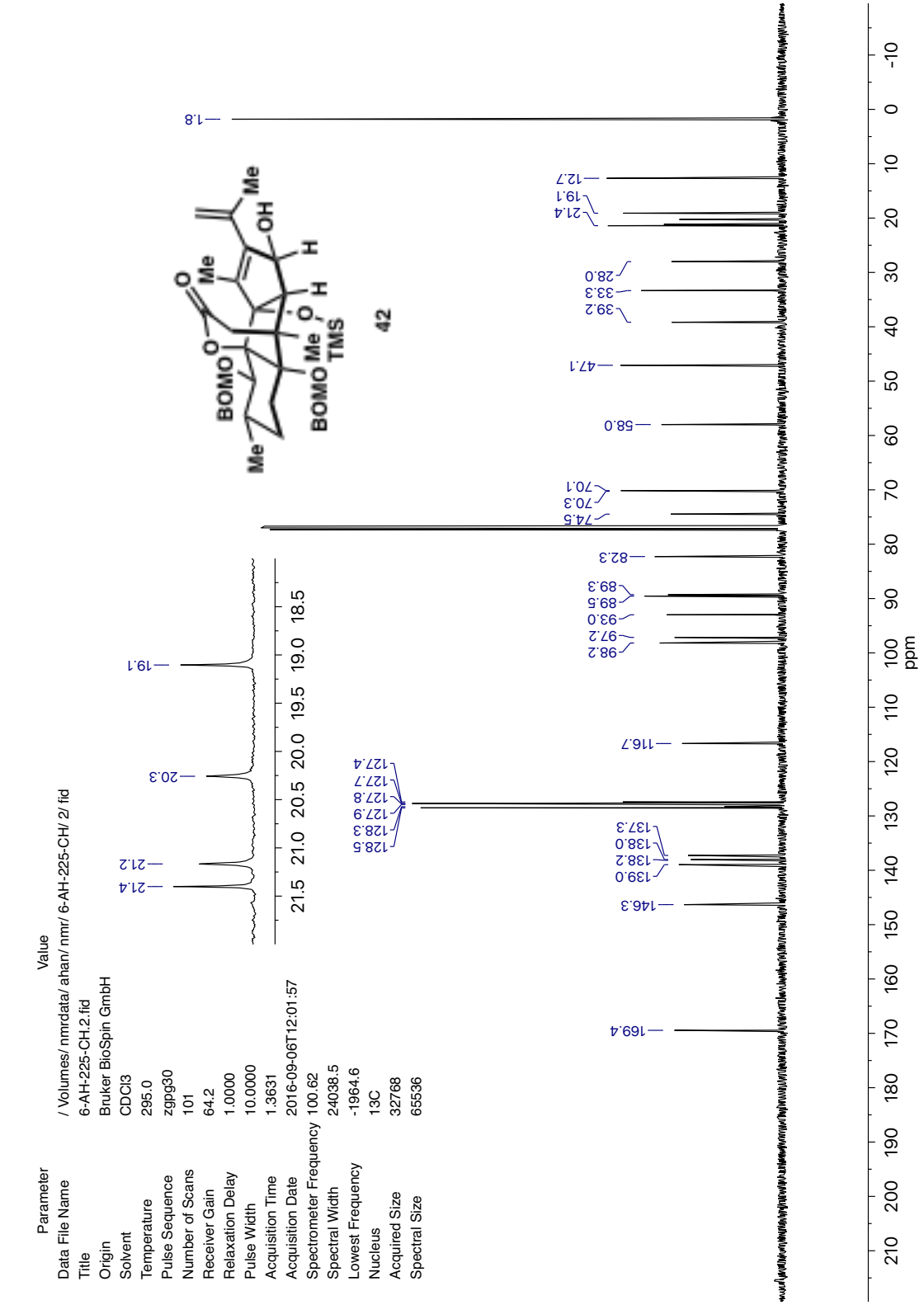

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-265-CH/ 1/ fid
Title
6-AH-265-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
294.9
Pulse Sequence
zg30
Number of Scans
8
Receiver Gain
30.3
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2016-09-02T09:14:07
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.6
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
BOMO
Me
Me
Me
BOMO
Me
TMS
H
41
9.94
1.01
1.00
0.99
1.05
2.07
1.11
1.04
2.03
1.11
1.01
9.02
3.25
3.11
1.05
1.28
1.11
3.00
1.14
1.06
3.05
2.15
ppm

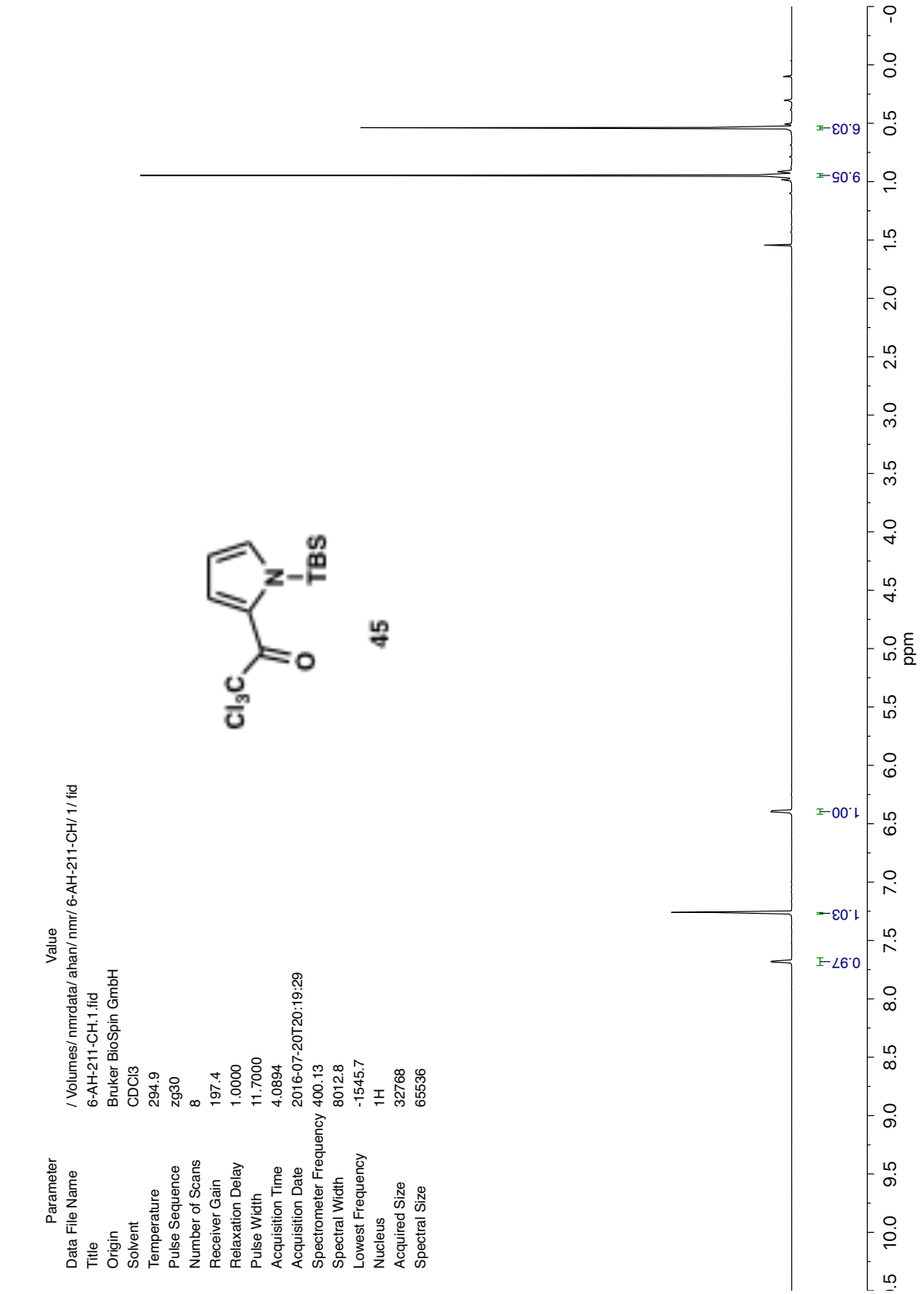


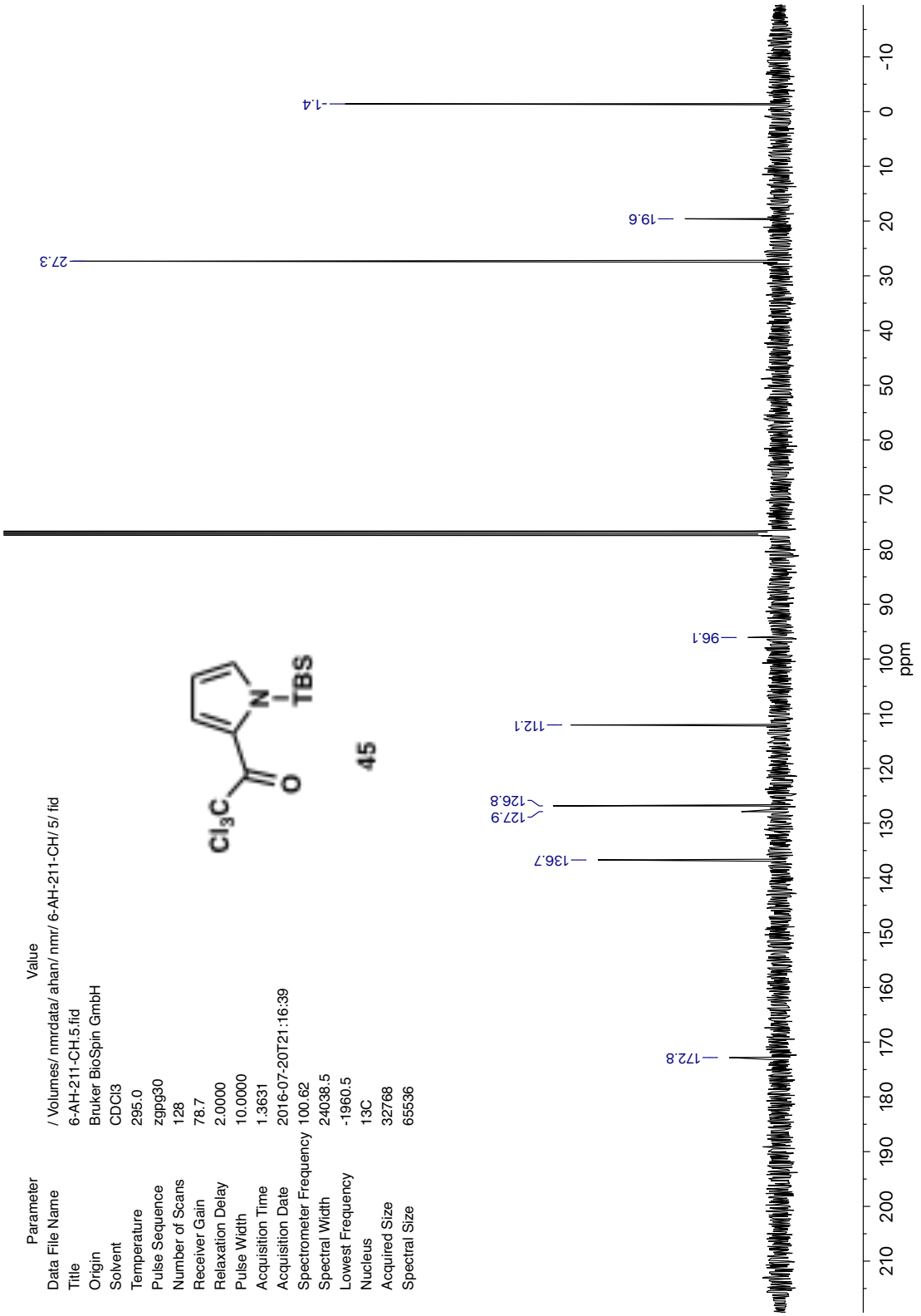
41

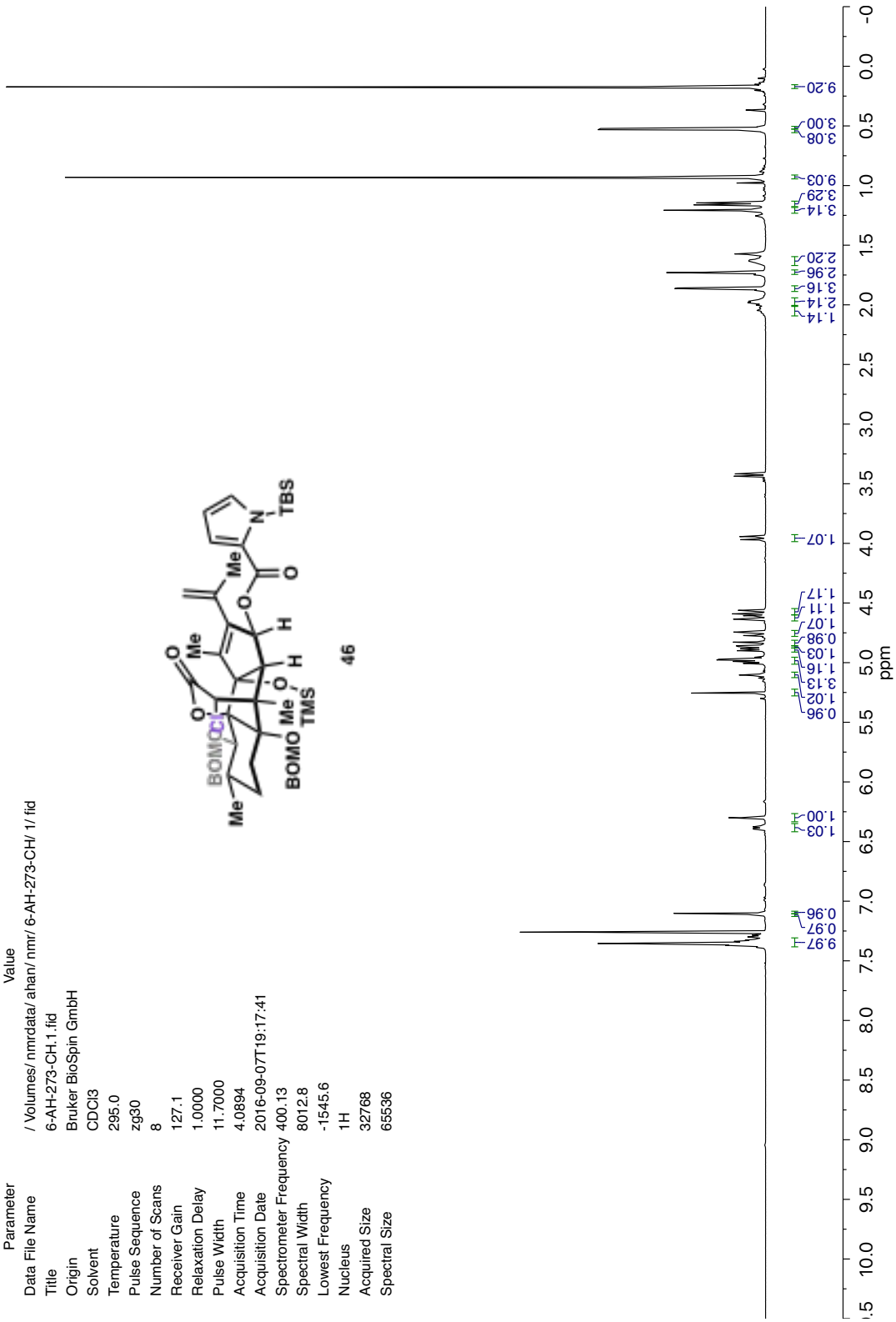
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-265-CH/ 2/ fid
Title	6-AH-265-CH.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.0
Pulse Sequence	zgpg30
Number of Scans	105
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2016-09-02T09:18:53
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1965.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

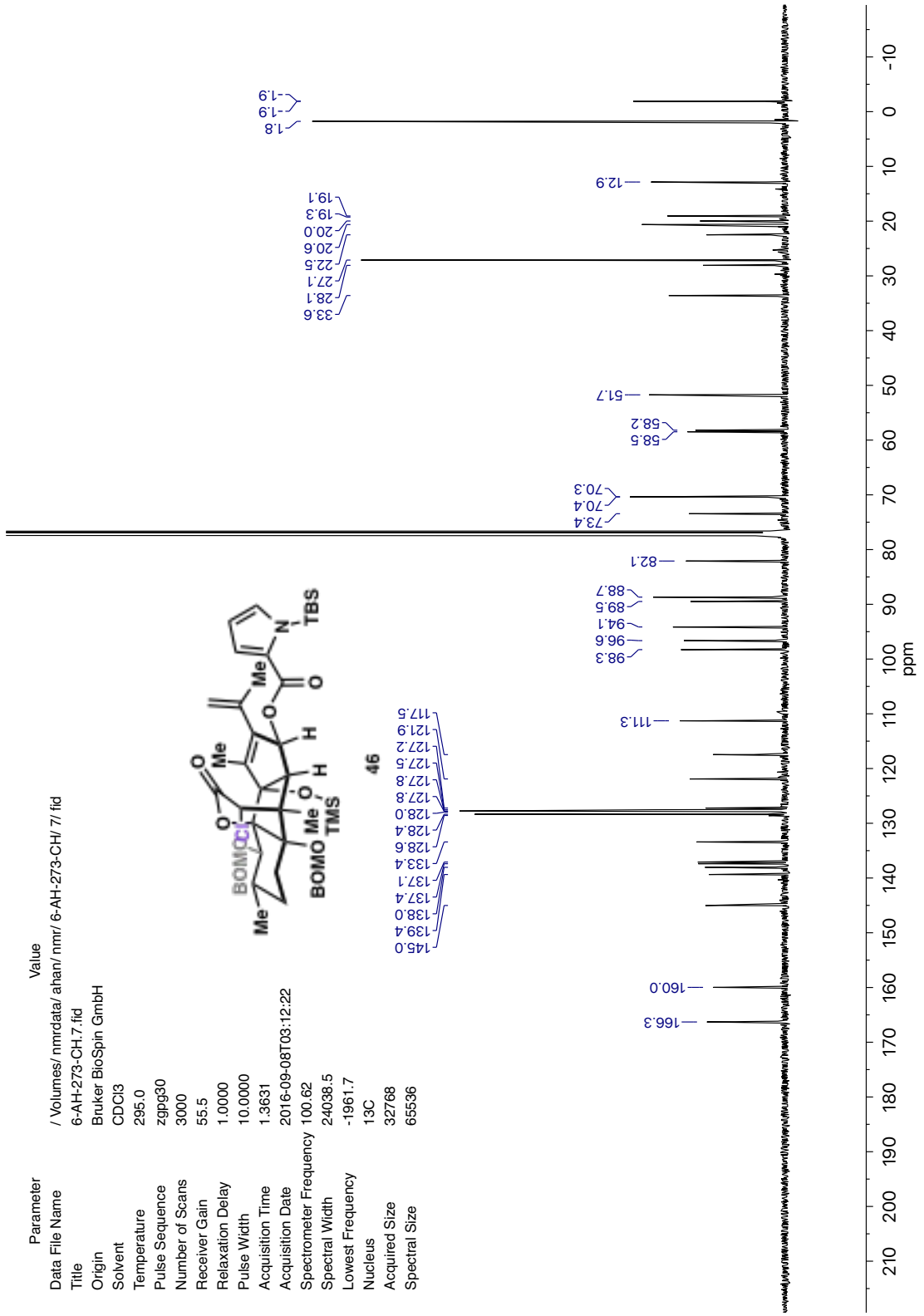

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-225-CH/ 1/ fid
Title 6-AH-225-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Number of Scans 6
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-09-06T11:57:21
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.5
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
Me
Me
OH
Me
H
H
O
O
O
Me
Me
BOMO
TMS
42
9.94
1.99
1.09
2.04
1.00
1.00
1.04
1.01
1.00
0.99
1.01
1.02
4.21
1.10
4.07
2.09
1.08
3.12
3.03
9.02
ppm

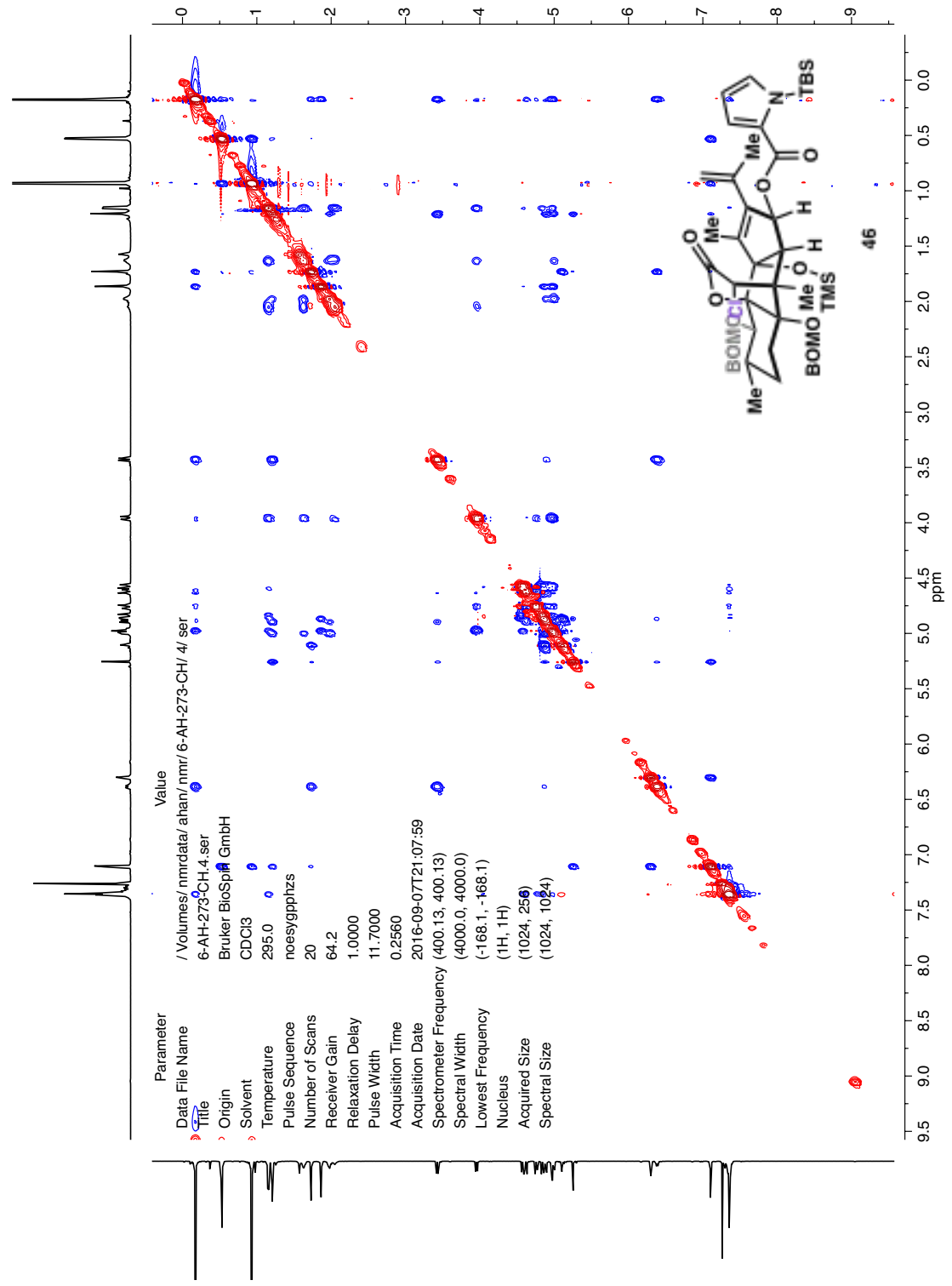

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-225-CH/ 2/ fid
Title 6-AH-225-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 101
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-09-06T12:01:57
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1964.6
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
BOMO
Me
O
Me
OH
H
H
O
Me
TMS
BOMO
Me
42
1.8
12.7
19.1
21.4
28.0
33.3
39.2
47.1
58.0
70.1
70.3
74.5
82.3
89.3
89.5
93.0
97.2
98.2
116.7
127.4
127.7
127.8
127.9
128.3
128.5
137.3
138.0
138.2
139.0
146.3
169.4
ppm

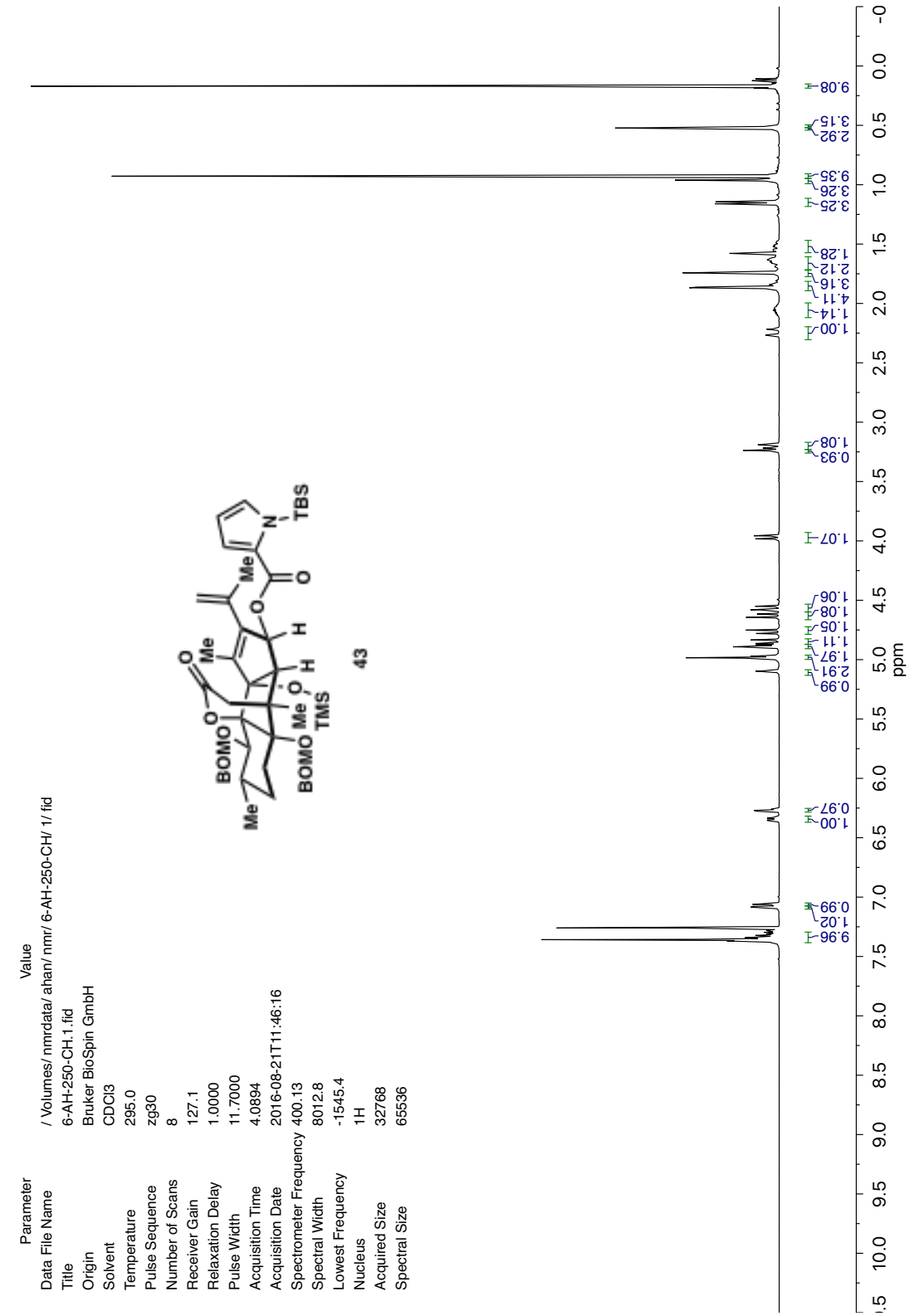

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-211-CH/ 1/ fid
Title
6-AH-211-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
294.9
Pulse Sequence
zg30
Number of Scans
8
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2016-07-20T20:19:29
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.7
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Cl3C
O
N
TBS
45
0.97
1.03
1.00
9.05
6.03
ppm

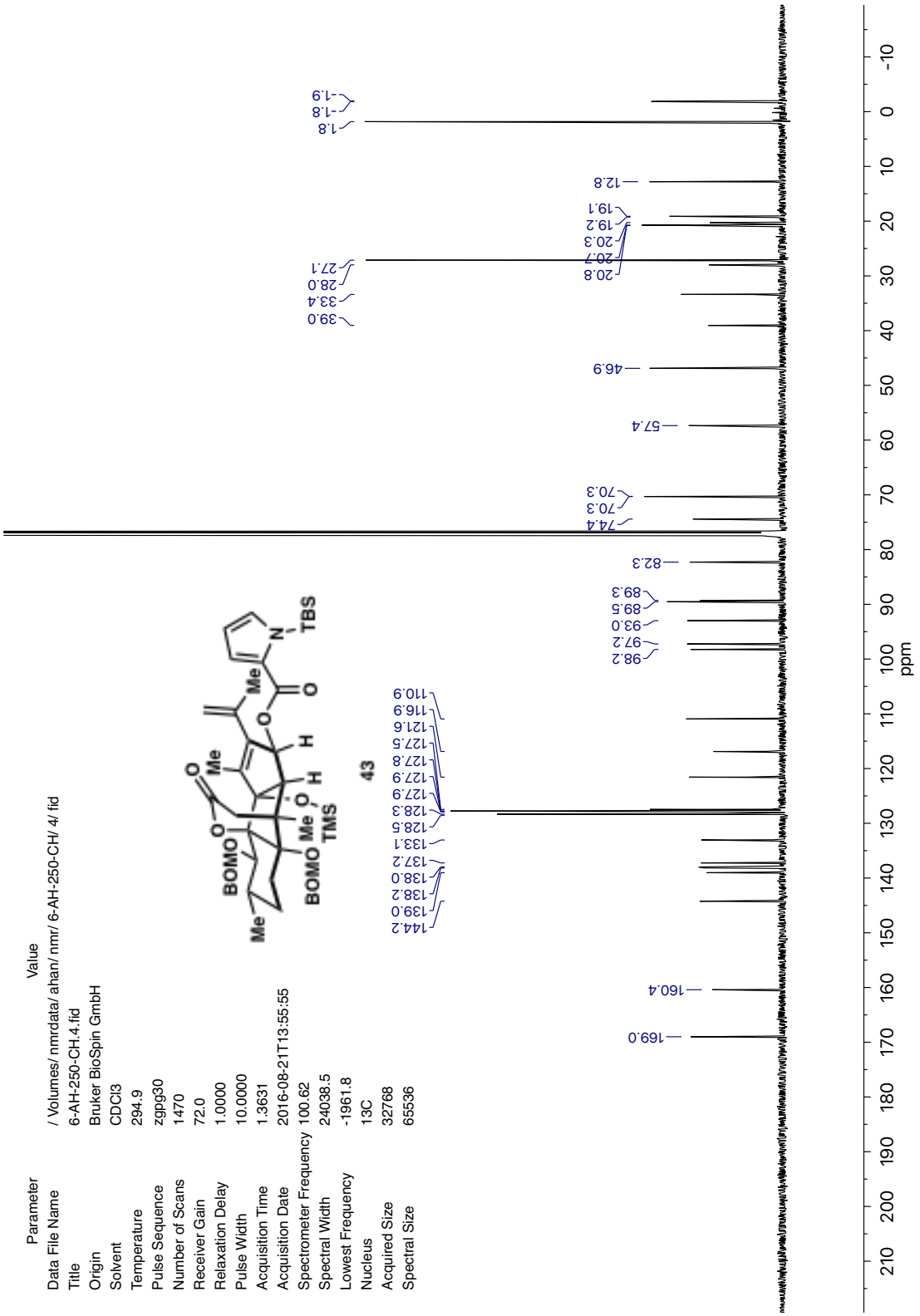

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-211-CH/ 5/ fid
Title 6-AH-211-CH.5.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 128
Receiver Gain 78.7
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-07-20T21:16:39
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1960.5
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Cl3C
O
N
TBS
45
-1.4
19.6
27.3
96.1
112.1
126.8
127.9
136.7
172.8
ppm

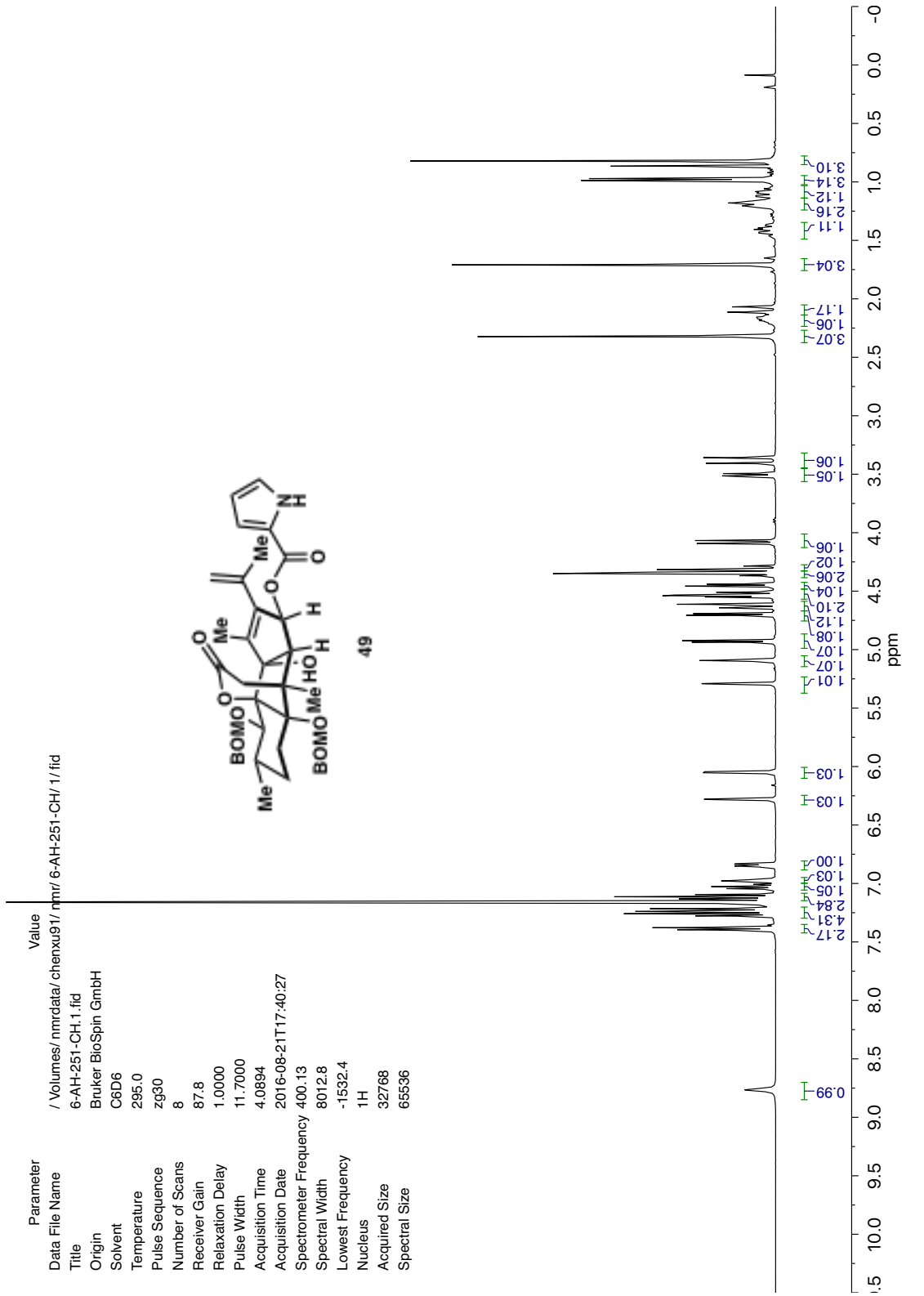

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-273-CH/ 1/ fid
Title 6-AH-273-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-09-07T19:17:41
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
TMS
TBS
46
ppm

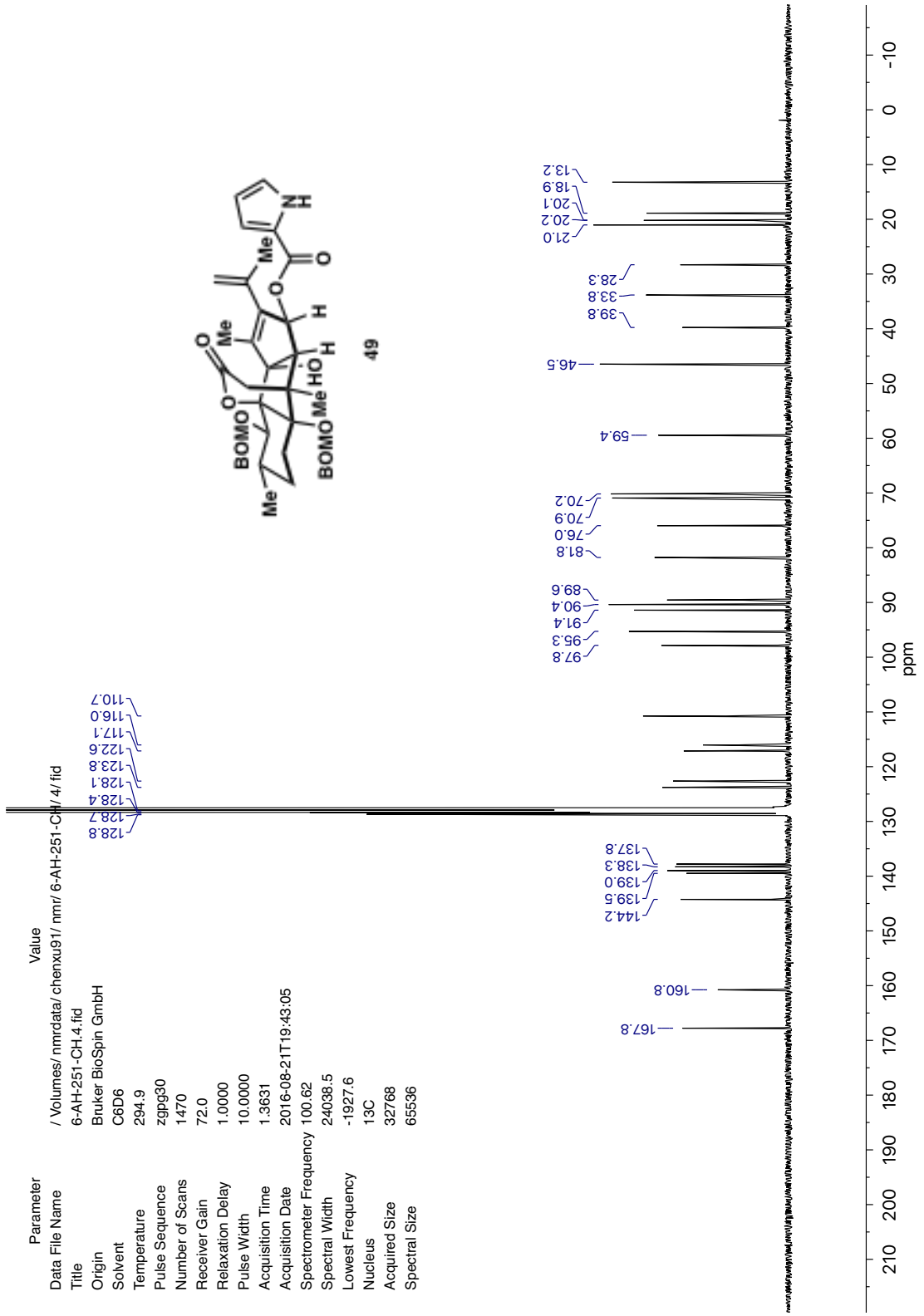

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-273-CH/ 7/ fid
Title 6-AH-273-CH.7.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 3000
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-09-08T03:12:22
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.7
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
46
BOMO
TMS
TBS
ppm

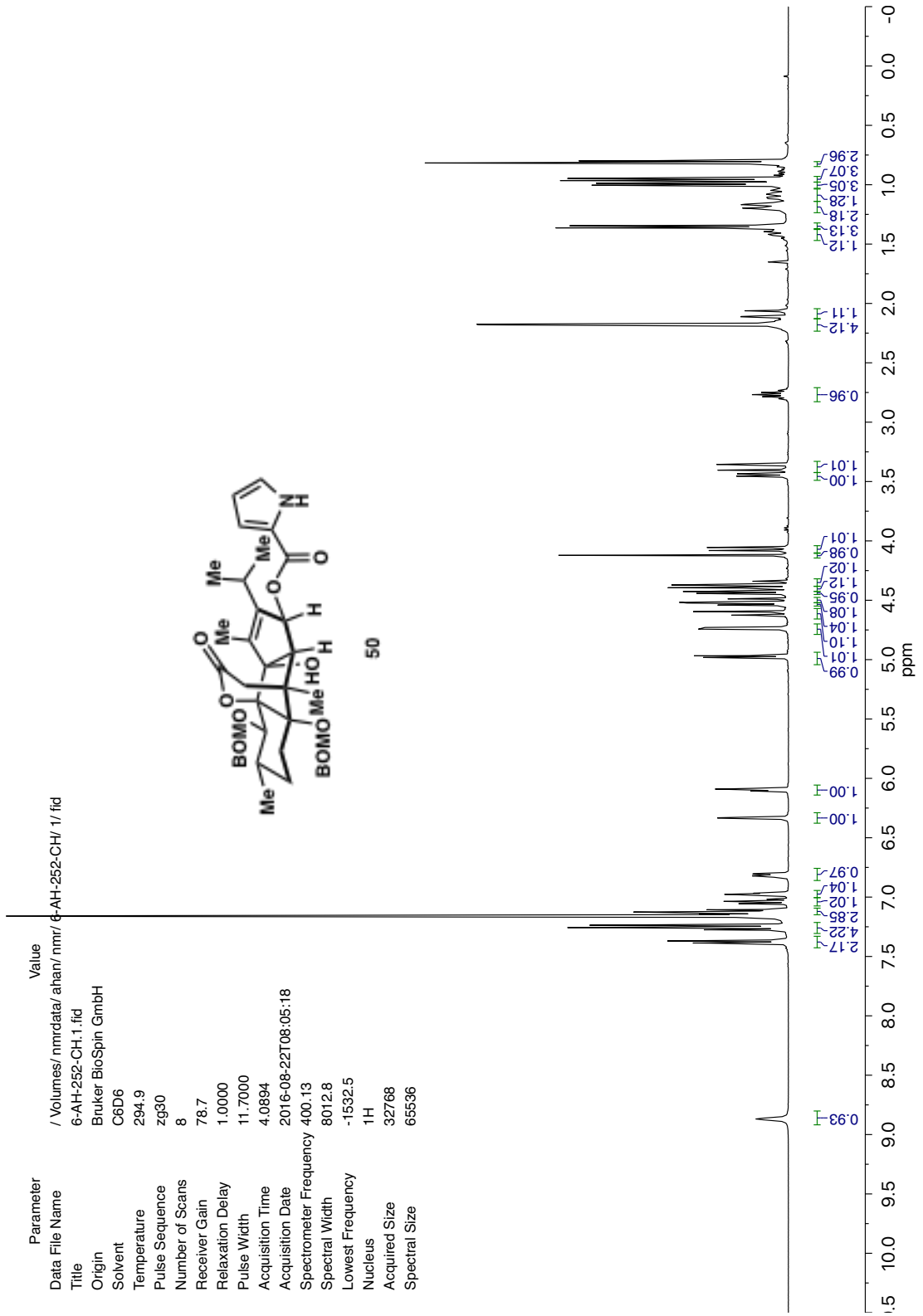

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-273-CH/ 4/ ser
Title
6-AH-273-CH.4.ser
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.0
Pulse Sequence
noesygpphzs
Number of Scans
20
Receiver Gain
64.2
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2560
Acquisition Date
2016-09-07T21:07:59
Spectrometer Frequency
(400.13, 400.13)
Spectral Width
(4000.0, 4000.0)
Lowest Frequency
(-168.1, -168.1)
Nucleus
(1H, 1H)
Acquired Size
(1024, 256)
Spectral Size
(1024, 1024)
BOMO
TMS
TBS
46
ppm

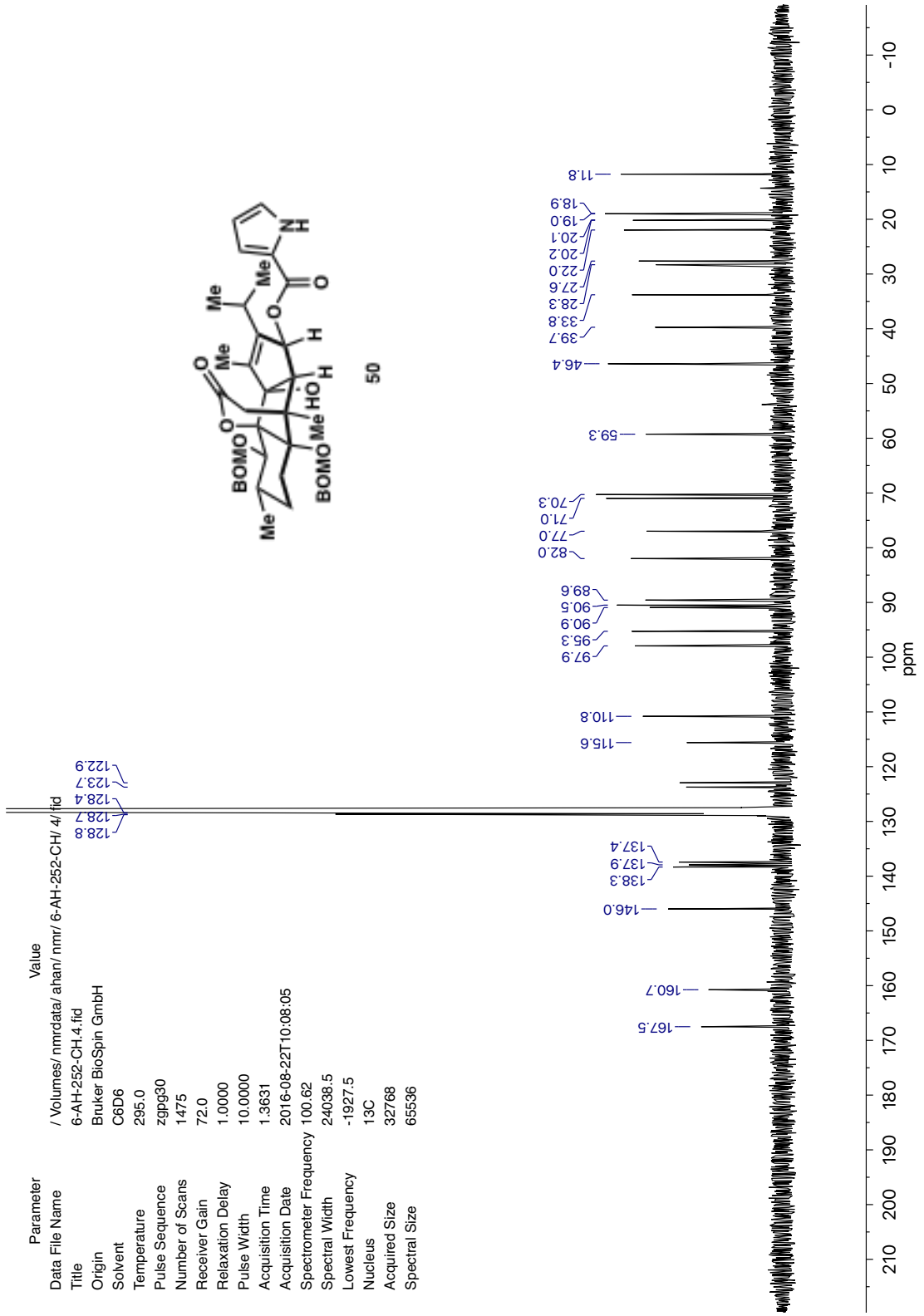

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-250-CH/ 1/ fid
Title 6-AH-250-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-08-21T11:46:16
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
Me
TBS
TMS
43
ppm

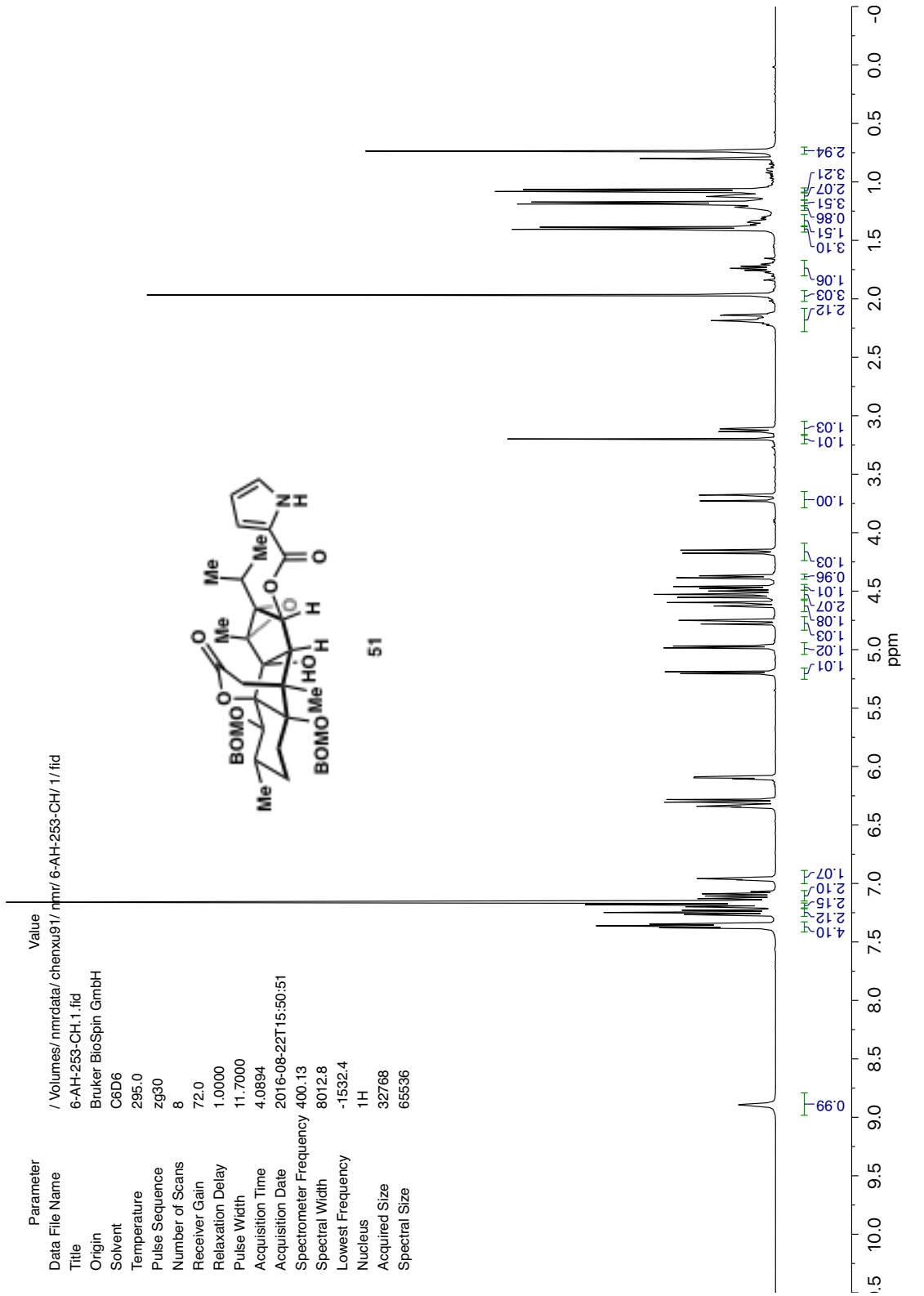

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-250-CH/ 4/ fid
Title 6-AH-250-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Number of Scans 1470
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-08-21T13:55:55
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
43
BOMO
TMS
BOMO
TBS
Me
Me
Me
O
H
H
-1.9
-1.8
1.8
12.8
19.1
19.2
20.3
20.7
20.8
27.1
28.0
33.4
39.0
46.9
57.4
70.3
70.3
74.4
82.3
89.3
89.5
93.0
97.2
98.2
110.9
116.9
121.6
127.5
127.8
127.9
127.9
128.3
128.5
133.1
137.2
138.0
138.2
139.0
144.2
160.4
169.0
ppm

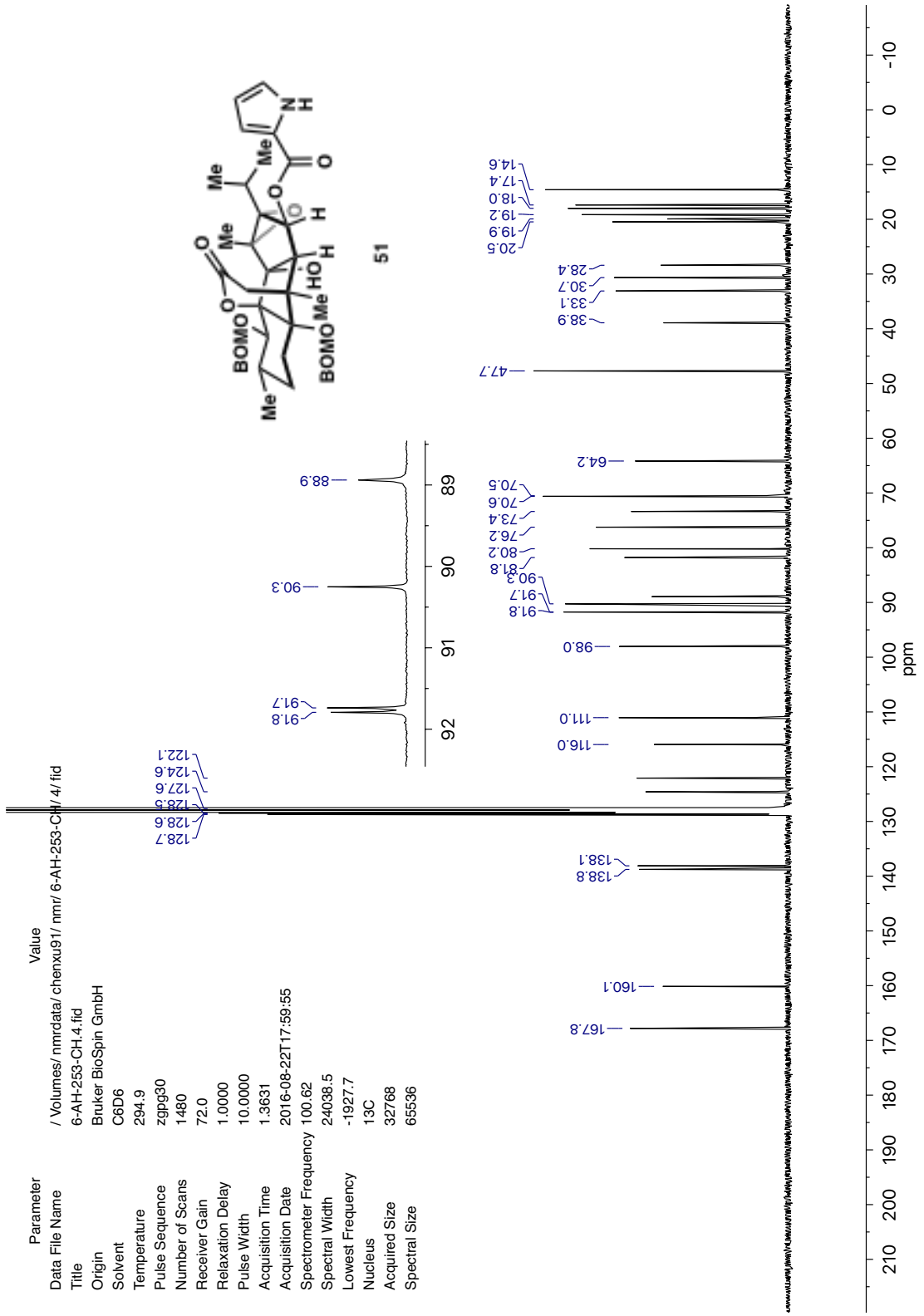

Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ 6-AH-251-CH/ 1/ fid
Title 6-AH-251-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.0
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-08-21T17:40:27
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1532.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
Me
Me
Me
HO
H
H
O
O
N
H
49
ppm

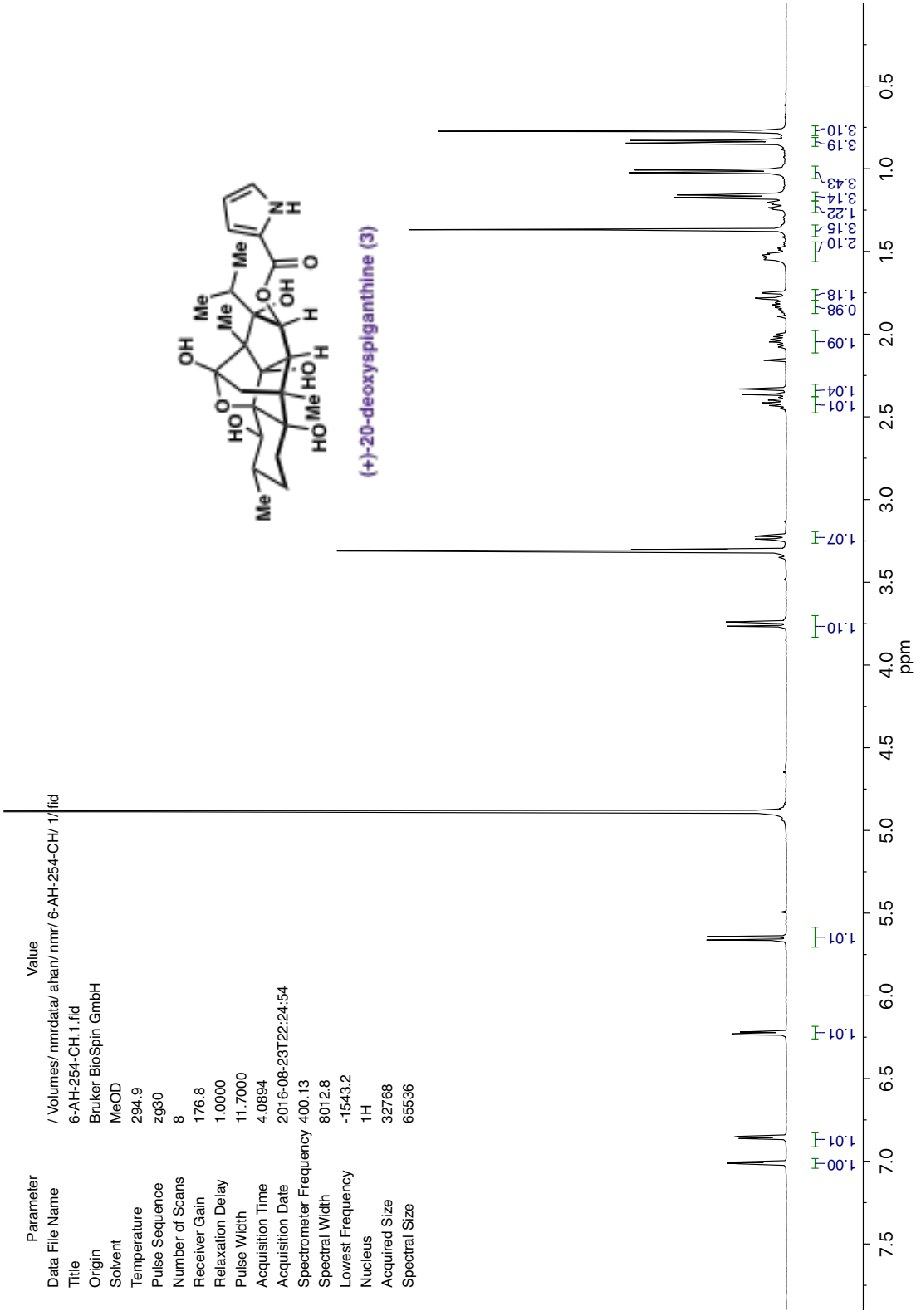

Parameter Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ 6-AH-251-CH/ 4/ fid
Title 6-AH-251-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 294.9
Pulse Sequence zgpg30
Number of Scans 1470
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-08-21T19:43:05
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.6
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
49
BOMO
BOMO
Me
Me
Me
Me
HO
H
H
O
O
O
O
N
H
128.8
128.7
128.4
128.1
123.8
122.6
117.1
116.0
110.7
167.8
160.8
144.2
139.5
139.0
138.3
137.8
97.8
95.3
91.4
90.4
89.6
81.8
76.0
70.9
70.2
59.4
46.5
39.8
33.8
28.3
21.0
20.2
20.1
18.9
13.2
ppm

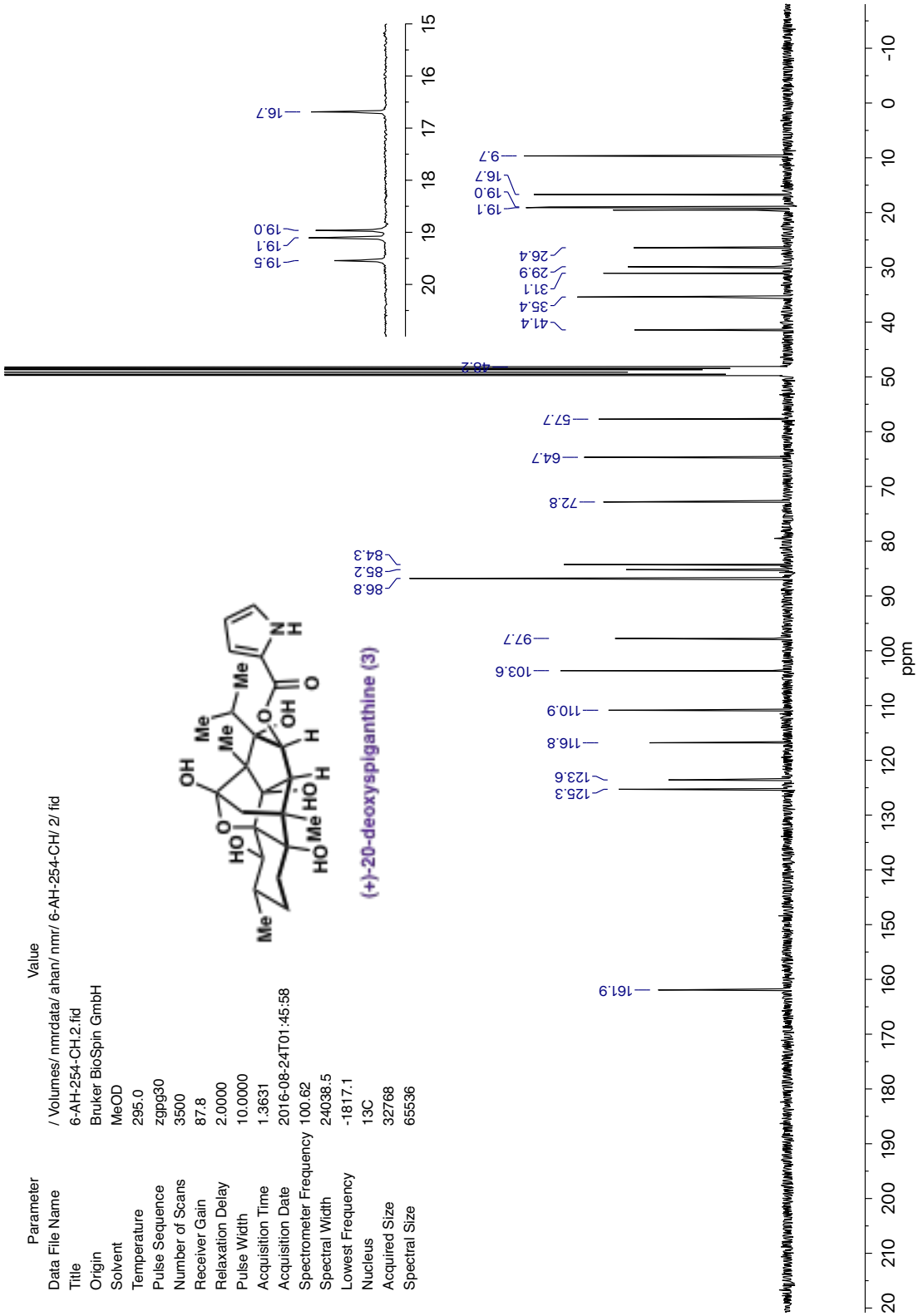

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-252-CH/ 1/ fid
Title 6-AH-252-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 294.9
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-08-22T08:05:18
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1532.5
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
50
BOMO
BOMO
Me
Me
Me
Me
Me
HO
H
H
O
O
O
O
N
H
0.93
1.00
1.00
0.97
1.04
1.02
2.85
4.22
2.17
0.99
1.01
1.10
1.04
1.08
0.95
1.12
1.02
0.98
1.01
1.00
1.01
0.96
4.12
1.11
1.12
3.13
2.18
1.28
3.05
3.07
2.96
ppm

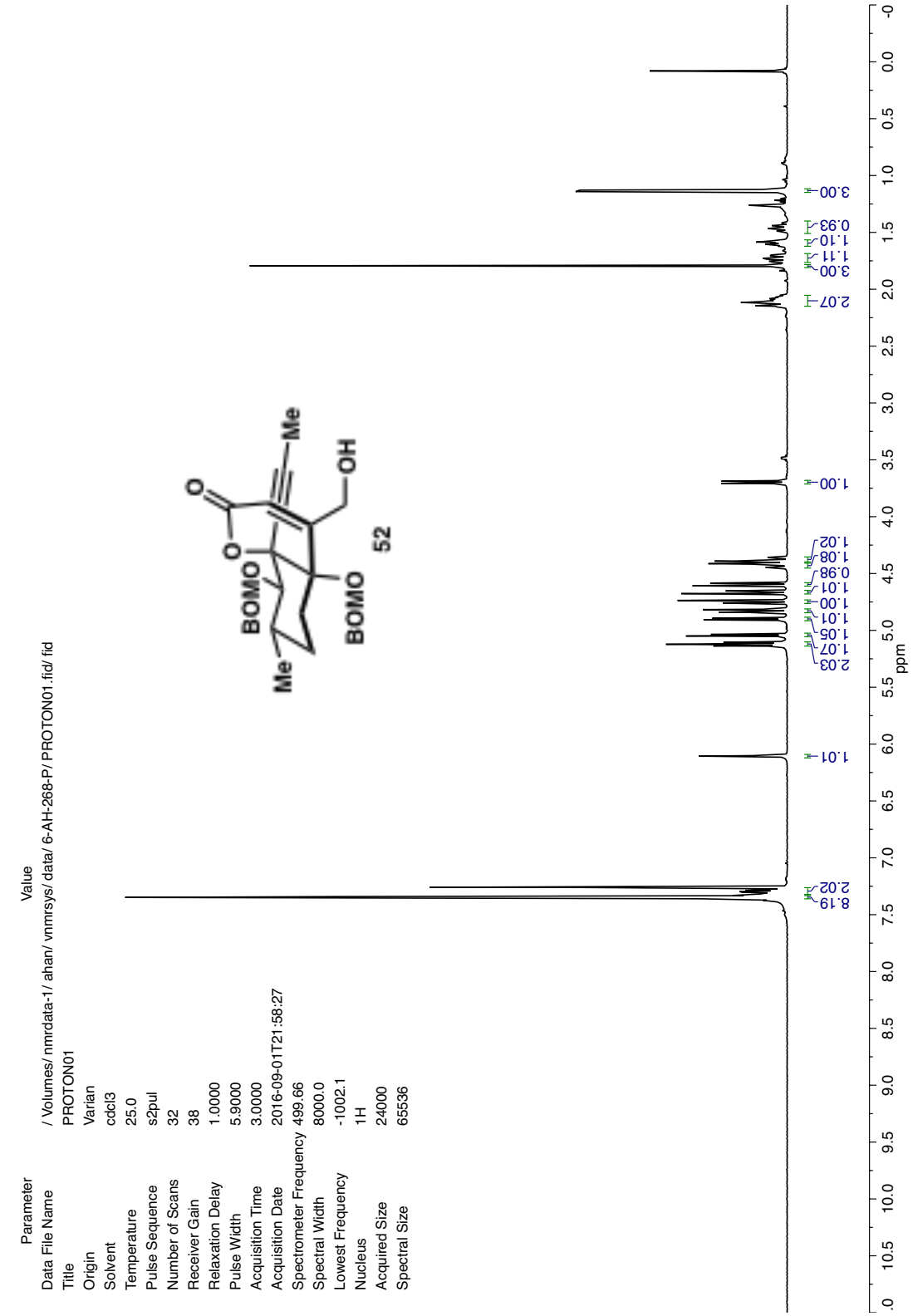

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-252-CH/ 4/ fid
Title 6-AH-252-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 1475
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-08-22T10:08:05
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.5
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
50
BOMO
BOMO
HO
Me
Me
Me
Me
Me
O
O
O
O
H
H
N
H
11.8
18.9
19.0
20.1
20.2
22.0
27.6
28.3
33.8
39.7
46.4
59.3
70.3
71.0
77.0
82.0
89.6
90.5
90.9
95.3
97.9
110.8
115.6
122.9
123.7
128.4
128.7
128.8
137.4
137.9
138.3
146.0
160.7
167.5
ppm

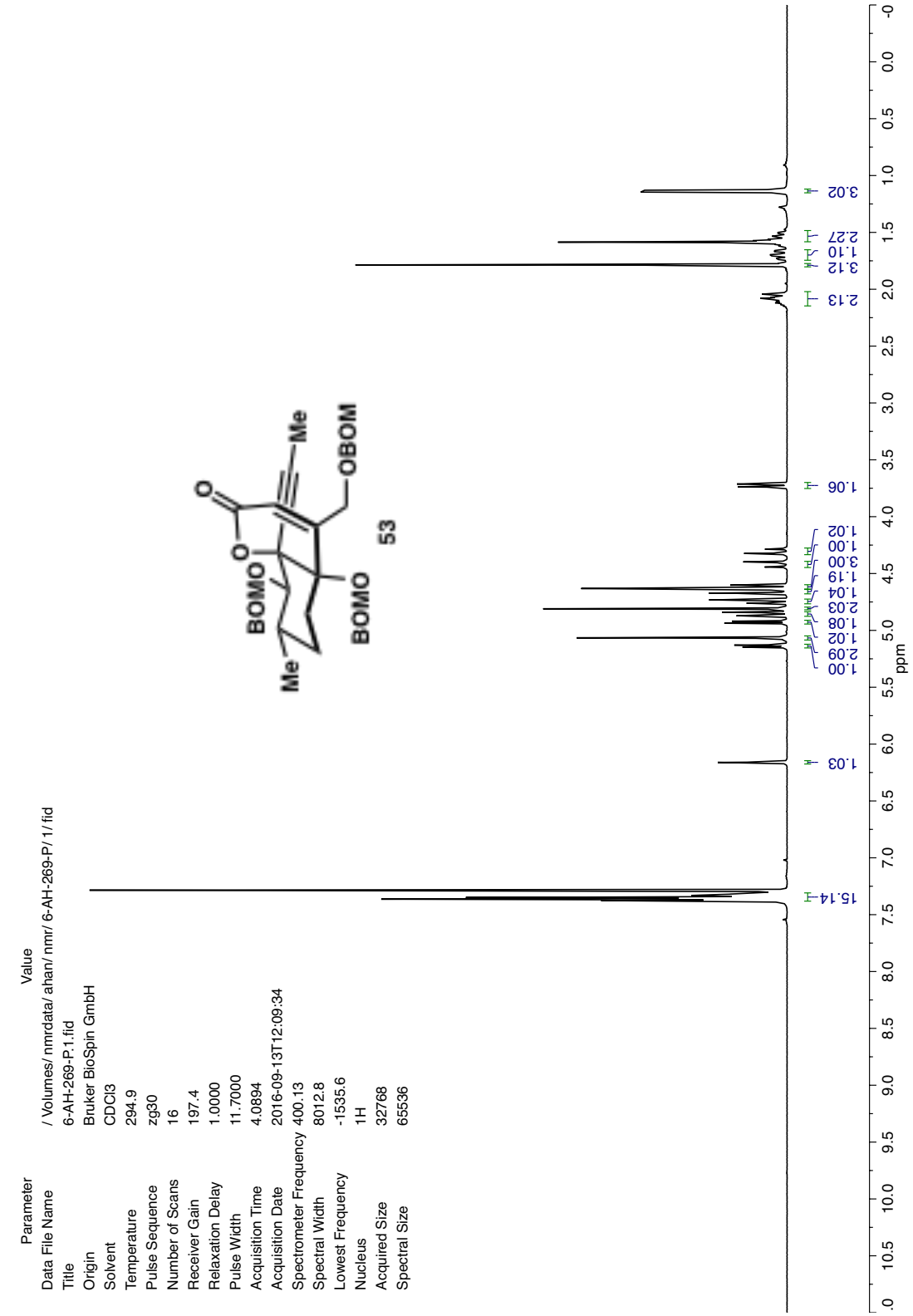

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ chenxu91/ nmr/ 6-AH-253-CH/ 1/ fid
Title
6-AH-253-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
C6D6
Temperature
295.0
Pulse Sequence
zg30
Number of Scans
8
Receiver Gain
72.0
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2016-08-22T15:50:51
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1532.4
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
51
ppm

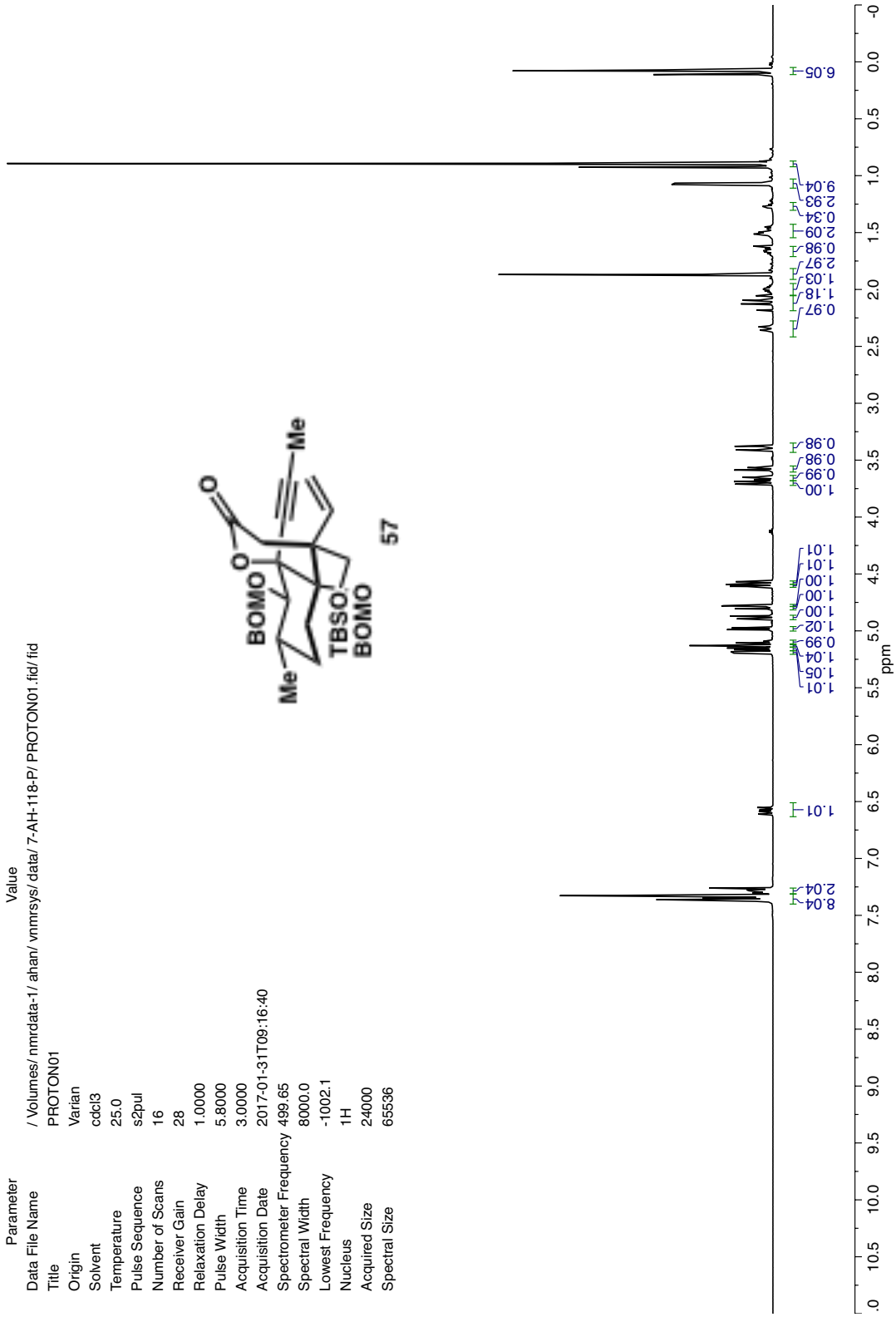

Parameter
Value
Data File Name / Volumes/ nmrdata/ chenxu91/ nmr/ 6-AH-253-CH/ 4/ fid
Title 6-AH-253-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 294.9
Pulse Sequence zgpg30
Number of Scans 1480
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-08-22T17:59:55
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.7
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
BOMO
BOMO
Me
Me
Me
Me
Me
HO
H
H
O
O
O
O
O
N
H
51
167.8
160.1
138.8
138.1
128.7
128.6
128.5
127.6
124.6
122.1
116.0
111.0
98.0
91.8
91.7
90.3
88.9
81.8
80.2
76.2
73.4
70.6
70.5
64.2
47.7
38.9
33.1
30.7
28.4
20.5
19.9
19.2
18.0
17.4
14.6
ppm

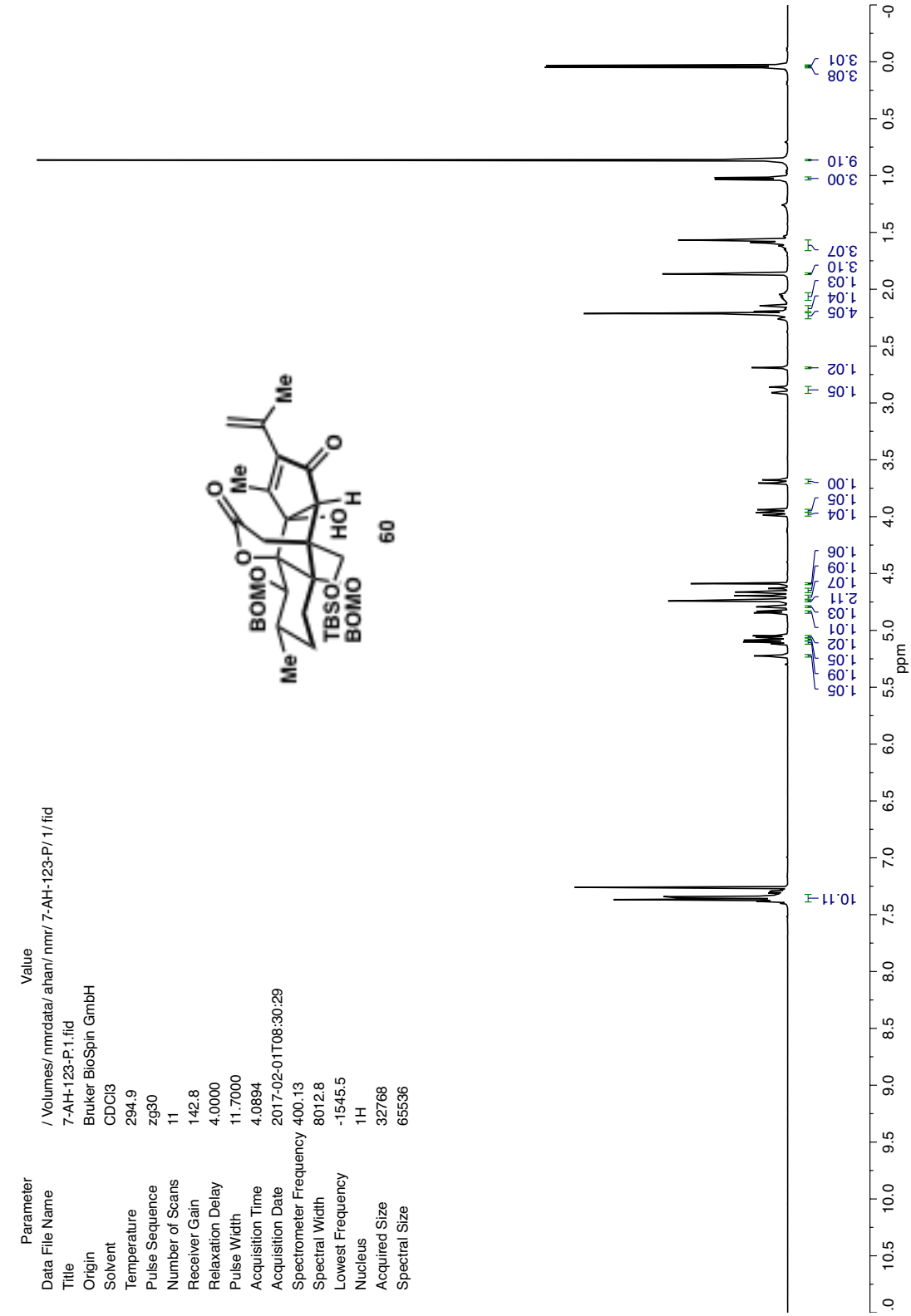

(+)-20-deoxyspiganthine (3)
Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-254-CH/ 1/fid
Title 6-AH-254-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 294.9
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 176.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-08-23T22:24:54
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1543.2
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
1.00
1.01
1.01
1.01
1.01
1.10
1.07
3.10
3.19
3.43
3.14
1.22
3.15
2.10
1.18
0.98
1.09
1.04
1.01
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
ppm

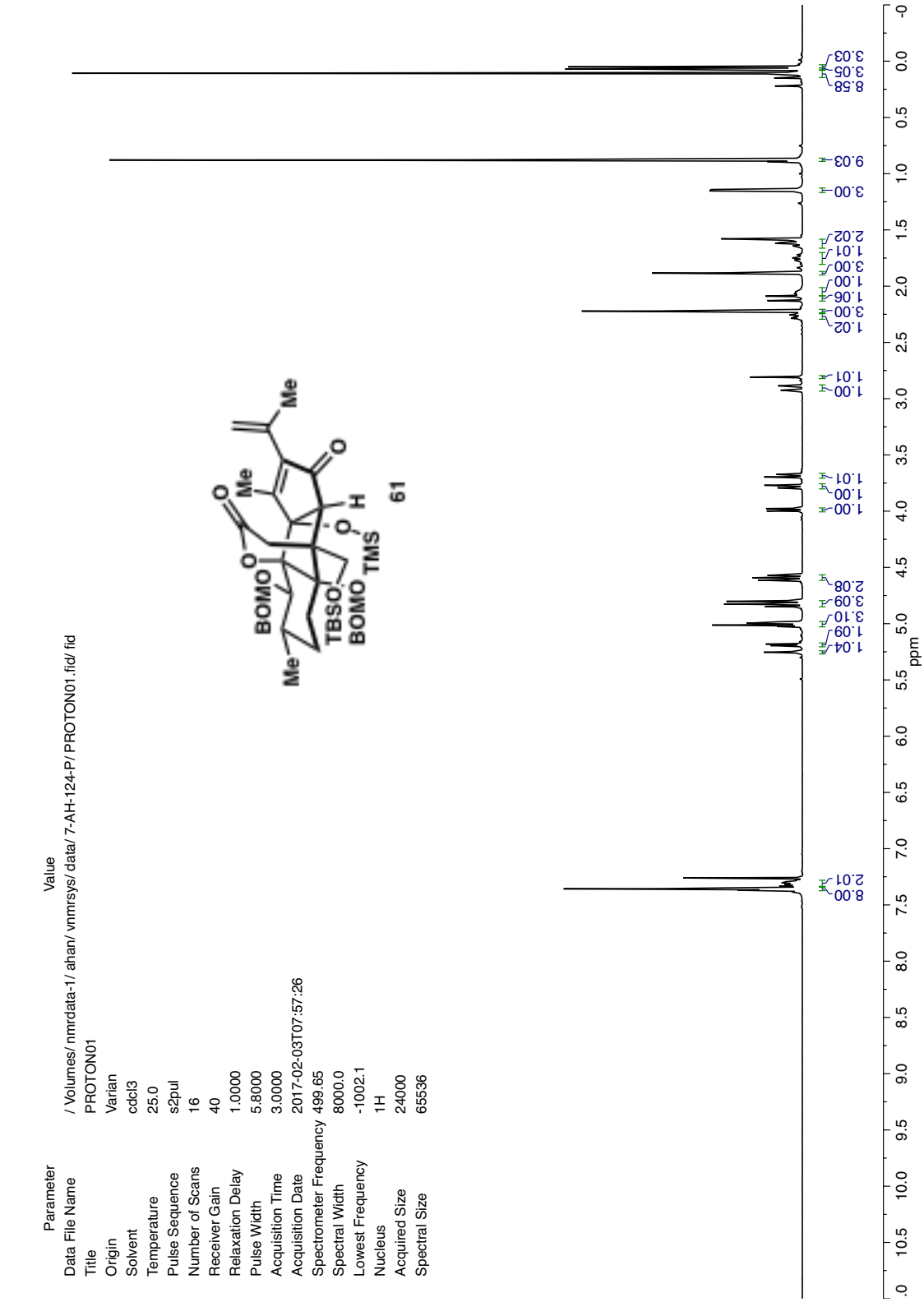

(+)-20-deoxyspiganthine (3)
Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-254-CH/ 2/ fid
Title 6-AH-254-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.0
Pulse Sequence zgpg30
Number of Scans 3500
Receiver Gain 87.8
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2016-08-24T01:45:58
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1817.1
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
16.7
19.0
19.1
19.5
9.7
16.7
19.0
19.1
26.4
29.9
31.1
35.4
41.4
48.2
57.7
64.7
72.8
84.3
85.2
86.8
97.7
103.6
110.9
116.8
123.6
125.3
161.9
ppm


Parameter Value
Data File Name / Volumes/ nmrdata-1/ ahan/ vnmrsys/ data/ 6-AH-268-P/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 32
Receiver Gain 38
Relaxation Delay 1.0000
Pulse Width 5.9000
Acquisition Time 3.0000
Acquisition Date 2016-09-01T21:58:27
Spectrometer Frequency 499.66
Spectral Width 8000.0
Lowest Frequency -1002.1
Nucleus 1H
Acquired Size 24000
Spectral Size 65536
O
O
BOMO
Me
Me
OH
BOMO
52
8.19
2.02
1.01
2.03
1.07
1.05
1.01
1.00
1.01
0.98
1.08
1.02
1.00
2.07
3.00
1.11
1.10
0.93
3.00
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-269-P/ 1/ fid
Title 6-AH-269-P1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2016-09-13T12:09:34
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1535.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
BOMO
OBOM
Me
Me
53
15.14
1.03
1.00
2.09
1.02
1.08
2.03
1.04
1.19
3.00
1.00
1.02
1.06
2.13
3.12
1.10
2.27
3.02
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata-1/ ahan/ vnmrsys/ data/ 7-AH-118-P/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 16
Receiver Gain 28
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2017-01-31T09:16:40
Spectrometer Frequency 499.65
Spectral Width 8000.0
Lowest Frequency -1002.1
Nucleus 1H
Acquired Size 24000
Spectral Size 65536
BOMO
TBSO
BOMO
Me
Me
57
8.04
2.04
1.01
1.01
1.05
1.04
0.99
1.02
1.00
1.00
1.00
1.00
1.01
1.01
1.00
0.99
0.98
0.98
6.05
9.04
2.93
0.34
2.09
0.98
2.97
1.03
1.18
0.97
ppm


Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 7-AH-123-P/ 1/ fid
Title 7-AH-123-P1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Number of Scans 11
Receiver Gain 142.8
Relaxation Delay 4.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2017-02-01T08:30:29
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.5
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
BOMO
TBSO
BOMO
Me
Me
Me
HO
H
O
O
O
60
10.11
1.05
1.09
1.05
1.02
1.03
1.01
2.11
1.07
1.09
1.06
1.04
1.05
1.00
1.05
1.02
4.05
1.04
1.03
3.10
3.07
3.00
9.10
3.08
3.01
ppm


Parameter Value
Data File Name / Volumes/ nmrdata-1/ ahan/ vnmrsys/ data/ 7-AH-124-P/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 16
Receiver Gain 40
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2017-02-03T07:57:26
Spectrometer Frequency 499.65
Spectral Width 8000.0
Lowest Frequency -1002.1
Nucleus 1H
Acquired Size 24000
Spectral Size 65536
BOMO
TBSO
BOMO
TMS
Me
Me
Me
61
8.00
2.01
1.04
1.09
3.10
3.09
2.08
1.00
1.00
1.01
1.00
1.00
1.01
1.02
3.00
1.06
1.00
3.00
1.01
2.02
3.00
9.03
8.58
3.05
3.03
ppm

Appendix 2

X-Ray Crystallography Reports Relevant to Chapter 2:

Total Synthesis of (+)-Ryanodine and (+)-20-Deoxyspiganthine

A2.1 X-RAY CRYSTAL STRUCTURE ANALYSIS

Low-temperature diffraction data (φ- and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON 100 CMOS detector with Cu-K_α radiation (λ = 1.54178 Å) from a $I_\mu S$ HB micro-focus sealed X-ray tube. All diffractometer manipulations, including data collection, integration, and scaling were carried out using the Bruker APEXII software.[1] Absorption corrections were applied using SADABS.[2] The structure was solved by intrinsic phasing using SHELXT[3] and refined against F^2 on all data by full-matrix least squares with SHELXL-2014[3] using established refinement techniques.[4] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups and hydroxyl groups). Absolute configuration was determined by anomalous dispersion.[5] Crystallographic data for **27**, **34**, **1**, and **3** can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif under CCDC deposition numbers 1508482–1508485. Graphical representation of the structures with 50% probability thermal ellipsoids was generated using Mercury visualization software.

*Table A2.1. Crystal and refinement data for compounds **27**, **34**, **1**, and **3**.*

	CX-10-028	**CX-10-036**	**CX-10-076**	**6-AH-235**
CCDC Number	1508483	1508482	1508484	1508485
Empirical formula	$C_{42}H_{48}BNO_{10}$	$C_{25}H_{33}NO_8$	$C_{33}H_{57}NO_{12}$	$C_{58}H_{90.76}N_2O_{18.38}$
Formula weight	737.62	475.52	659.79	1110.22
T (K)	100	100	200	100
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Trigonal
Space group	$P2_1$	$P2_12_12$	$P2_12_12_1$	$P3_2$
a, Å	8.7826(4)	18.9642(8)	10.9374(3)	20.8804(7)
b, Å	22.1496(10)	11.2161(4)	11.9604(3)	20.8804(7)
c, Å	10.3099(5)	13.5628(5)	27.4814(7)	11.5639(5)
α, °	90	90	90	90
β, °	109.928(2)	90	90	90
γ, °	90	90	90	120
Volume, $Å^3$	1885.50(15)	2884.87(19)	3595.00(16)	4366.3(3)
Z	2	4	4	3
d_{calc}, g/cm^3	1.299	1.095	1.219	1.267
Abs. coeff. (mm^{-1})	0.749	0.676	0.759	0.770
θ range, °	3.991 to 79.080	3.258 to 66.577	3.216 to 79.361	4.234 to 79.349
Abs. correction	Semi-empirical	Semi-empirical	Semi-empirical	Semi-empirical
GOF	1.047	1.055	1.045	1.023
R_1,[a] wR_2,[b] [I>2σ(I)]	0.0311, 0.0732	0.0563, 0.1375	0.0389, 0.1064	0.0448, 0.1071
Flack parameter	0.12(5)	0.23(12)	0.05(3)	0.07(6)
Extinction coefficient	0.00071(18)	n/a	n/a	n/a

[a] $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$. [b] $wR_2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

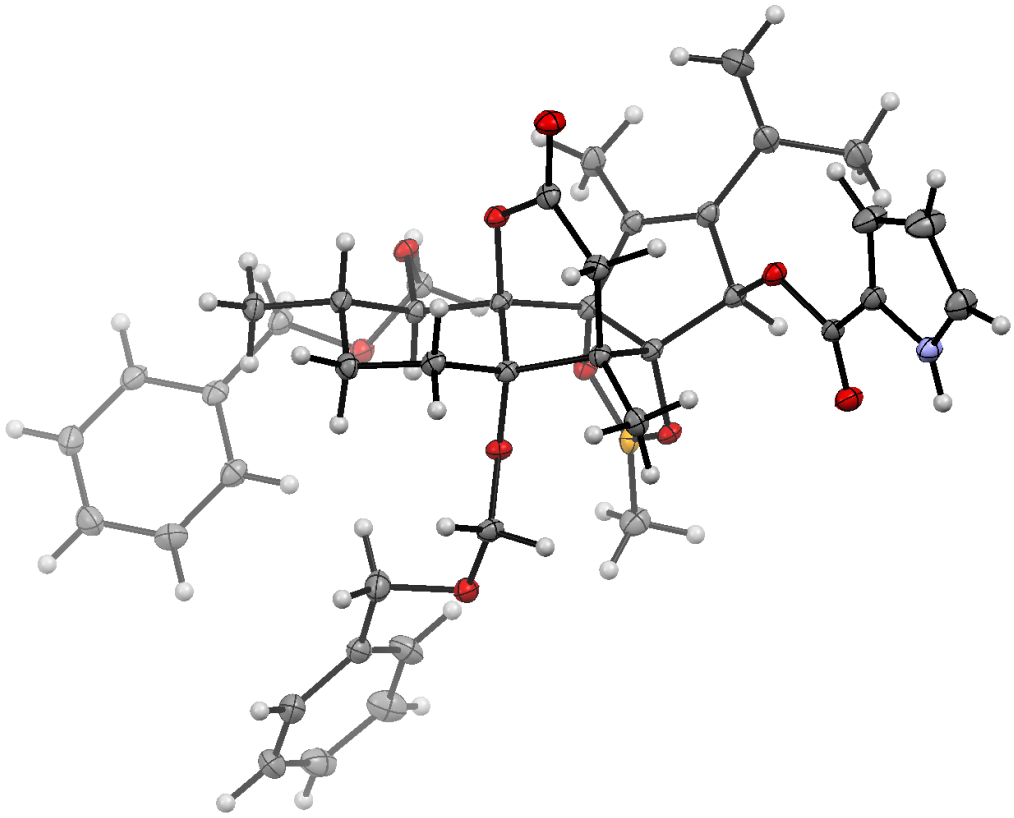


Figure A2.1. *Structure of* ***27*** *with 50% probability anisotropic displacement ellipsoids.*

Special Refinement Details for 27

Compound **27** crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = 0.12(5)).[5]

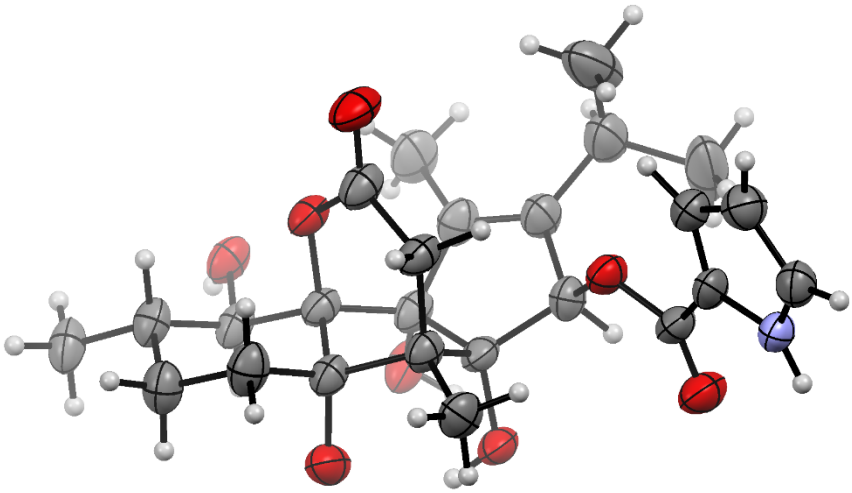


Figure A2.2. *Structure of* ***34*** *with 50% probability anisotropic displacement ellipsoids.*

Special Refinement Details for 34

Compound **34** crystallizes in the orthorhombic space group $P2_12_12$ with one molecule in the asymmetric unit. The coordinates for the hydrogen atoms bound to N1, O5, O6, O7, and O8 were located in the difference Fourier synthesis, however, refinement was unstable and they were included into the model at geometrically calculated positions and refined using a riding model. A void analysis with the program PLATON[6] revealed the presence of two large voids and the program SQUEEZE[7] was used to remove the contribution of the disordered electron density inside this void from the structure factors. Absolute configuration was determined by anomalous dispersion (Flack = 0.23(12)).[5] Bayesian statistics further confirm the absolute stereochemistry: P2(true) = 1.000, P3(true) = 0.977, P3(rac-twin) = 0.023, and P3(false) = 0.2×10^{-13}.[6]

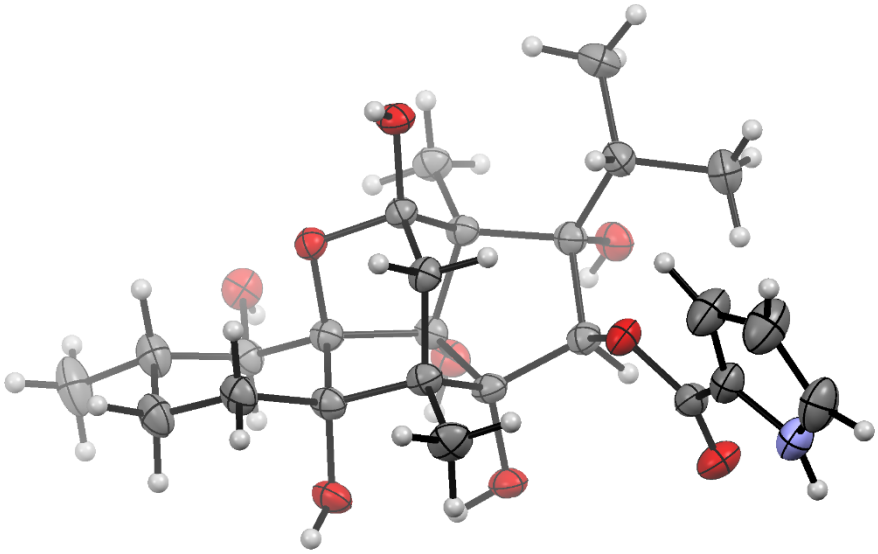


Figure A2.3. *Structure of* ***1*** *with 50% probability anisotropic displacement ellipsoids. Co-crystallized diethyl ether and water molecules are omitted for clarity.*

Special Refinement Details for 1

Compound **1** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit, along with two molecules of diethyl ether and one molecule of water. One ether molecule was disordered over multiple positions, however refinement was unstable and the disorder was not included in the model. The bond distances of all hydrogen atoms bound to O and N atoms were refined with bond restraints. Absolute configuration was determined by anomalous dispersion (Flack = 0.05(3)).[5]

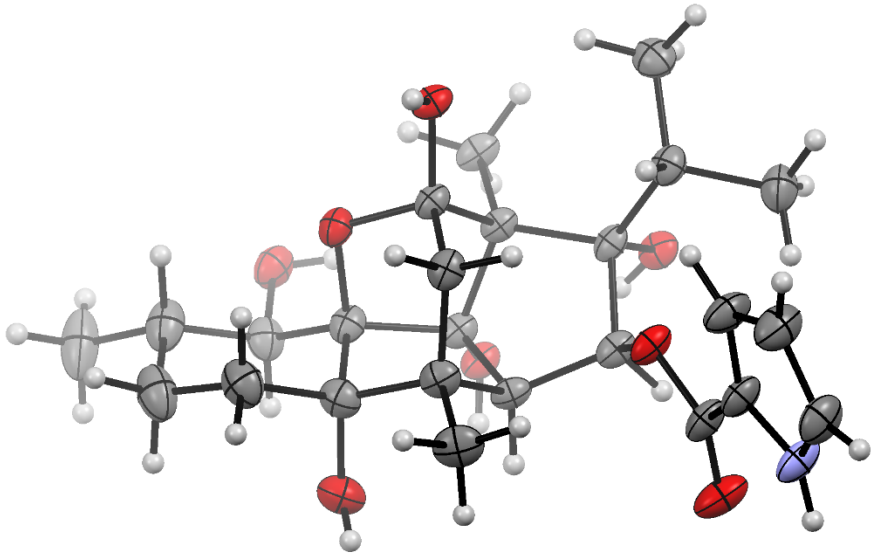


Figure A2.4. *Structure of* ***3*** *with 50% probability anisotropic displacement ellipsoids. Co-crystallized diethyl ether, water, and the second molecule of* ***3*** *are omitted for clarity.*

Special Refinement Details for 3

Compound **3** crystallizes in the trigonal space group $P3_2$ with two molecules in the asymmetric unit, along with two molecules of diethyl ether and 0.38 molecules of water. One ether molecule was disordered over multiple positions, however refinement was unstable and the disorder was not included in the model. The highest electron density maxima was modeled as a partially occupied water (0.38). The hydrogen atoms for this water molecule were not located in the difference Fourier synthesis, and were included into the model at geometrically calculated positions that fulfilled H-bonding interactions and refined using a riding model. The bond distances of all hydrogen atoms bound to O and N atoms were refined with bond restraints. No hydrogen bond acceptor was found for H7A. Absolute configuration was determined by anomalous dispersion (Flack = 0.07(6)).[5]

A2.2 REFERNCES

(1) APEX2, Version 2 User Manual, M86-E01078. Bruker Analytical X-ray Systems: Madison, WI.

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

(3) Sheldrick, G. M. *Acta Cryst.* **2008**, *64*, 112.

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

(5) Parsons, S.; Flack, H. D.; Wagner, T. *Acta Cryst.* **2013**, *69*, 249.

(6) Spek, A. L. *Acta Cryst.* **2009**, *65*, 148.

(7) Vandersluis, P.; Spek, A. L. *Acta Cryst.* **1990**, *46*, 194.

Chapter 3

Total Synthesis of the Isoryanoid Diterpene (+)-Perseanol

3.1 INTRODUCTION

Equipped with the ability to introduce the critical pyrrole-2-carboxylate ester of (+)-ryanodine, our attention next turned to the related *isoryanoid* diterpenes. Their broad spectrum of biological activity and unique polycyclic structure prompted our laboratory to initiate a synthetic campaign in 2014, with the unwavering goal of developing a concise yet modular approach. Driving our synthetic campaign was an underlying interest in unlocking the potential of the isoryanoid diterpenes to serve as ligands for the RyR, a question that could only be addressed through *de novo* synthesis. Numerous synthetic approaches were evaluated to construct the isomeric ring system presented by the isoryanoid diterpenes. This chapter will disclose the evolution of a successful fragment coupling approach for the total synthesis of the isoryanoid diterpenes, resulting in an 18-step synthesis of (+)-perseanol.

3.2 STRUCTURE AND SYNTHETIC CHALLENGES

The isomeric ring system of the isoryanoid diterpenes presented a unique set of challenges that had to be carefully addressed in considering our goal of developing a concise and modular approach. The highly caged, pentacyclic structures are decorated with at least 10 contiguous stereocenters, within which is a network of four to six free hydroxyl groups and two all-carbon quaternary centers. Stripped of the hydroxyl groups, the carbocyclic core of the isoryanoid diterpenes itself poses a critical synthetic challenge (Figure 1). The isomeric 5-6-5 ABC ring system is spanned by a two-carbon bridge forming the E-ring, and an oxygen bridge forming the medium-sized D-ring. A significant task that would need to be addressed in installing the requisite carbons of the diterpene framework is the presence of the C2 isopropyl group buried within the concave face of the AE-ring system pocket. A keen structural analysis reveals that the high level of oxidation and specific oxygen atom placement is nontrivial, with several members of the family exhibiting oxidation at every single bridgehead carbon of the central B-ring.[1-2]

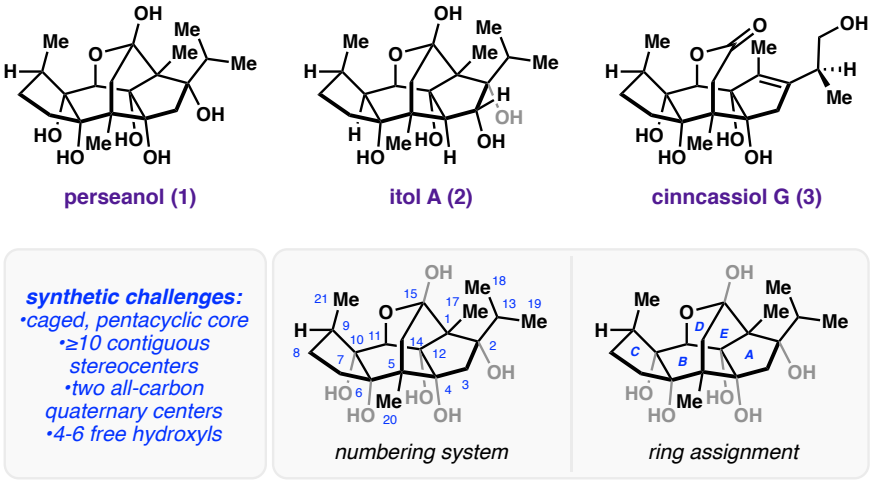
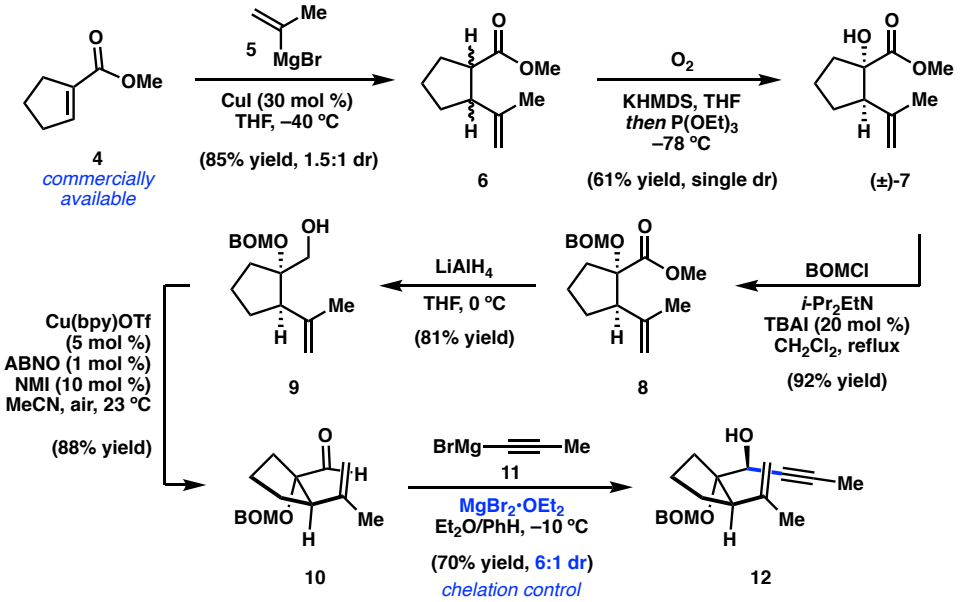


Figure 1. *Structure and synthetic challenges of the isoryanoid diterpenes.*

3.3 SYNTHETIC APPROACH

3.3.1 *Model Studies: A Pauson-Khand Disconnection*

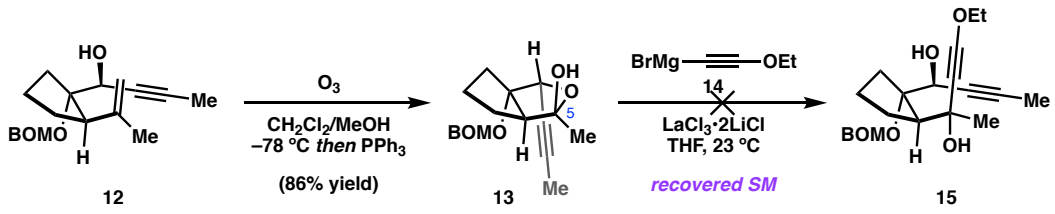
Inspired by our concise, 15-step synthesis of (+)-ryanodol, we initially sought to transpose the synthetic route to the isomeric, isoryanoid ring system.[3] To address this plan of action, we began our synthetic studies with commercially available methyl 1-cyclopentene-1-carboxylate (**4**). Cu-catalyzed 1,4-addition of isopropenylmagnesium bromide afforded known conjugate addition product **6** as an inconsequential mixture of diastereomers (Scheme 1).[4] Enolization of **6** with KHMDS was followed by exposure to O_2 and $P(OEt)_3$ to generate tertiary alcohol **7**, protected thereafter as its BOM ether **8**. Following this maneuver, the methyl ester was converted to its aldehyde **10** in a 2-step sequence involving (1) reduction to its alcohol **9** and (2) 1,2-oxidation.[5]



Scheme 1. *Preparation of a model C-ring fragment.*

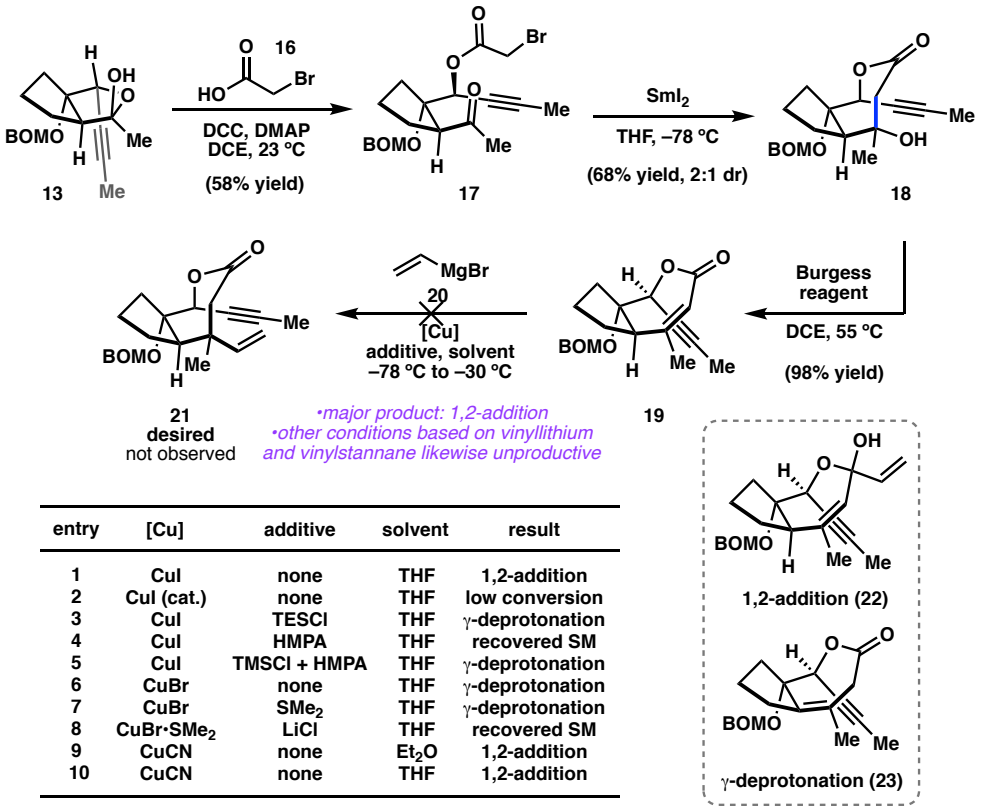
In line with our ryanodol route, aldehyde **10** was next treated with propynylmagnesium bromide (**11**) in the presence of $MgBr_2 \bullet OEt_2$ to induce chelation

controlled delivery of the nucleophile. The lone alkene present in 1,2-addition product **12** was at this stage revealed as its methyl ketone under ozonolytic conditions; however, isolation of the major product revealed the exclusive formation of stable, cyclic hemiketal **13**, a consequence of the greater conformational flexibility presented by the secondary, acyclic alcohol. As such, treatment of **13** with Grignard reagent **14** did not afford any desired 1,2-addition product **15** and instead led to recovery of the starting material. Unable to introduce this chemical information to form the central 7-membered D-ring lactone, a different lactonization method was devised.



Scheme 2. *Failure to induce 1,2-addition into C5-hemiketal.*

After screening several approaches, we discovered that hemiketal **13** succumbs to esterification at C11 when exposed to bromoacetic acid (**16**) under Steglich esterification conditions. Bromoacetate **17** was then treated with SmI_2 to induce a Reformatsky cyclization and forge the medium-sized D-ring lactone.[6] The 2:1 diastereomeric mixture of the cyclization product was finally converged to unsaturated lactone **19**, primed to undergo 1,4-addition. Yet after attempting a wide array of conditions to induce conjugate addition, we were never able to engage **19** with a vinyl cuprate. Instead, we consistently observed 1,2-addition product **22** or γ-deprotonation product **23**. In light of the failure to generate a suitable enyne precursor (**21**) for a Pauson-Khand reaction, we were forced to abandon this route and challenged with the task of reevaluating our synthetic approach to the isoryanoid diterpenes.



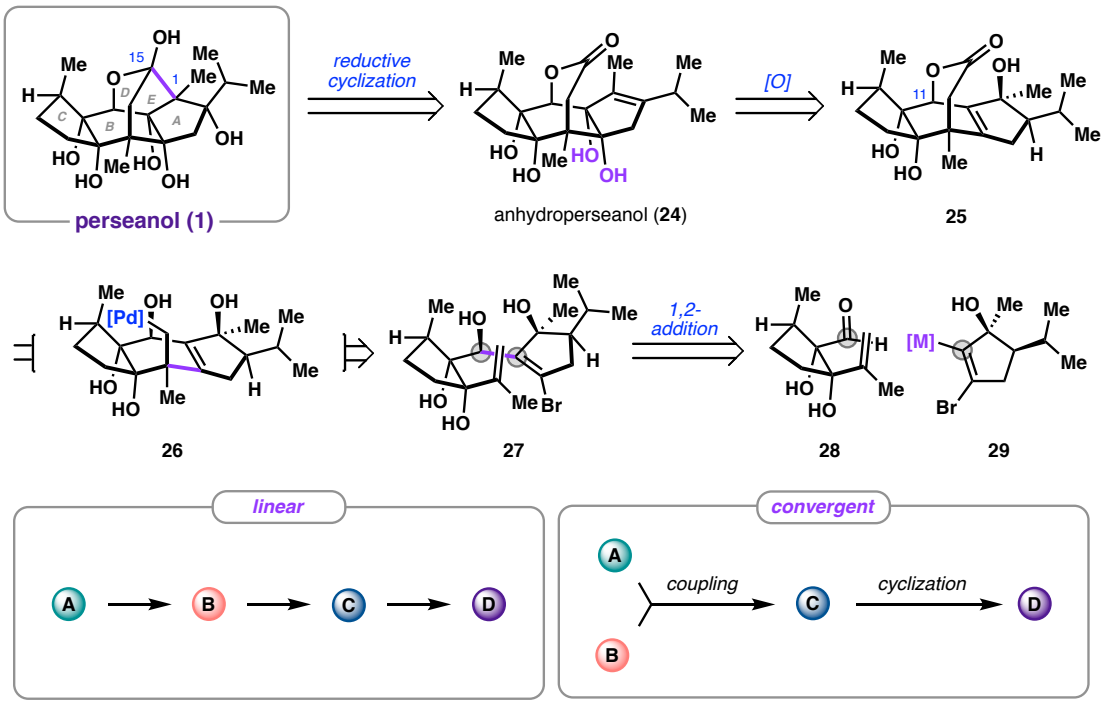
entry	[Cu]	additive	solvent	result
1	CuI	none	THF	1,2-addition
2	CuI (cat.)	none	THF	low conversion
3	CuI	TESCl	THF	γ-deprotonation
4	CuI	HMPA	THF	recovered SM
5	CuI	TMSCl + HMPA	THF	γ-deprotonation
6	CuBr	none	THF	γ-deprotonation
7	CuBr	SMe_2	THF	γ-deprotonation
8	CuBr·SMe_2	LiCl	THF	recovered SM
9	CuCN	none	Et_2O	1,2-addition
10	CuCN	none	THF	1,2-addition

Scheme 3. *Failure to induce 1,4-addition calls for a revised approach.*

3.3.2 *Retrosynthetic Analysis of the Isoryanoid Diterpenes*

In considering a revised retrosynthetic analysis of (+)-perseanol (**1**), we were compelled to approach the ABC tricyclic core in a highly convergent fashion, departing from the linear strategies that we had pursued in our ryanoid work. Such an approach was conceived to provide an unparalleled level of modularity that would enable a unifying strategy for this family of natural products.[7] Careful analysis of the ABCDE pentacyclic isoryanoid framework rendered the C1–C15 bond as a common strategic disconnection. In analogy to the conversion of anhydroryanodol to ryanodol, we sought to forge this key bond through a late-stage reductive cyclization by engaging the ketyl anion derived from a D-ring lactone with a pendant epoxide. Our isoryanoid target (+)-perseanol could

therefore be traced back to tetracycle **24**, hitherto referred to as anhydroperseanol, through an appropriately devised oxidation/reduction sequence. The AB-ring junction bridgehead diol of anhydroperseanol was further simplified and stored instead as its alkene precursor **25**. Delaying the introduction of the requisite free alcohols was conceived to avoid unnecessary protection/deprotection steps at the late stage.



Scheme 4. *Revised retrosynthetic analysis for the isoryanoid diterpene perseanol.*

In a key event, the tetracyclic framework of **25** was envisioned to be rapidly assembled in *one step* through a Pd-catalyzed Heck cyclization/carbonylation cascade from vinyl bromide **27**. Treatment of vinyl bromide **27** with a Pd-catalyst was expected to induce oxidative insertion into the polarized C–Br bond and generate an intermediate vinylpalladium species. Migratory insertion would next produce primary alkylpalladium species **26** that was presumed to be stable owing to the absence of β-hydrogens, as conferred by the formation of an all-carbon quaternary center. In the ideal scenario, the

cascade would be terminated through a cascade sequence involving (1) migratory insertion of CO and (2) capture of the resulting acylpalladium species by the secondary, C11 alcohol to generate target tetracycle **25**. Several related examples reported in the literature gave us confidence in the proposed cascade (Figure 2).[8-11]

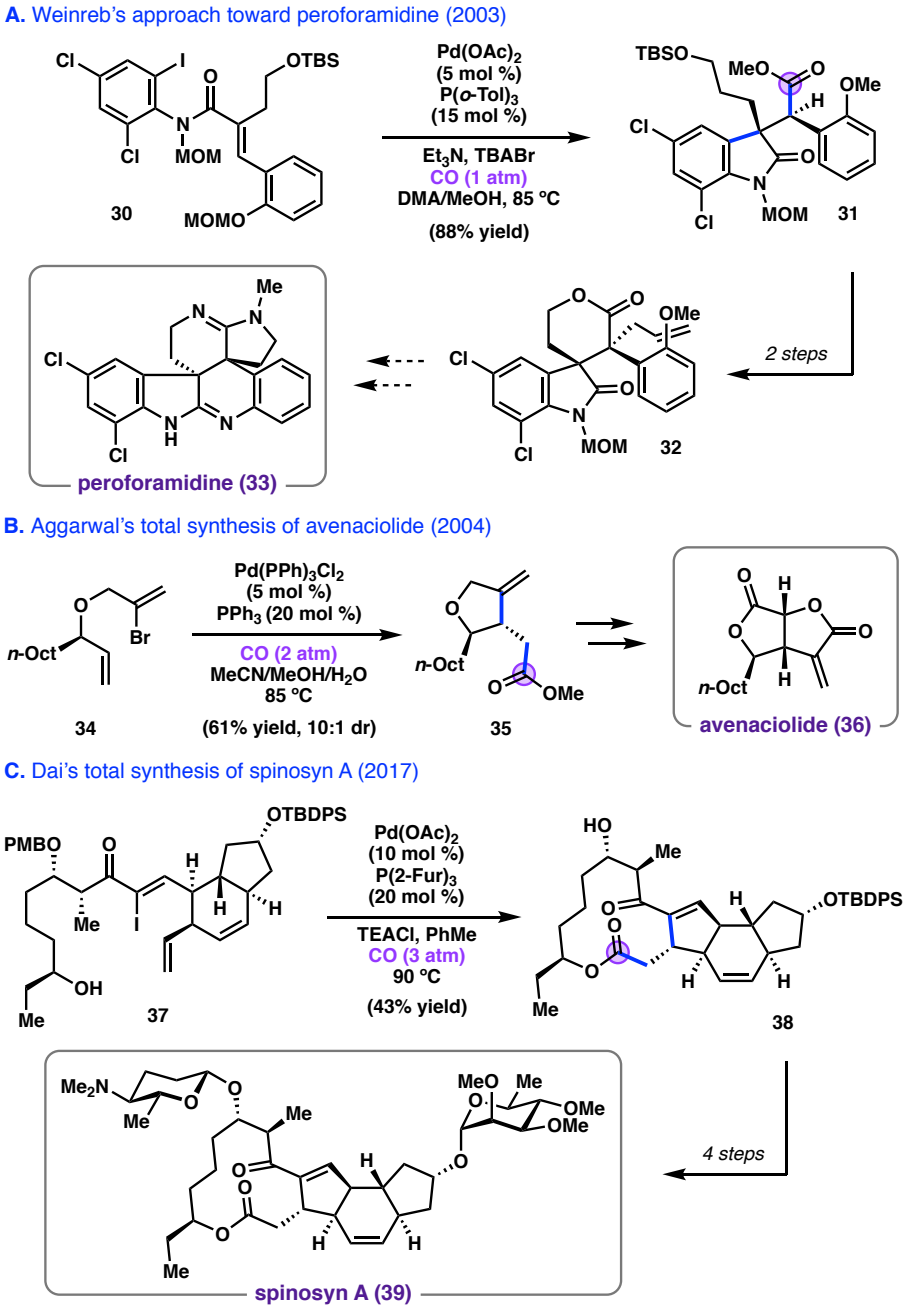


Figure 2. *Pd-catalyzed carbonylative cascades in complex molecule synthesis.*

That said, we were aware of challenges that would have to be addressed in considering the successful execution of such a cascade reaction. At the planning stage, questions regarding the relative rates of several undesired reaction pathways were raised due to seminal work from Negishi and coworkers.[12-13] These concerns were of relevance in our proposed cascade reaction due to the sterically-demanding context. The Heck cyclization would require forming an all-carbon quaternary center adjacent to a fully-substituted carbon harboring a critical oxidation state. If the rate of migratory insertion is too slow, we would expect to observe significant quantities of premature carbonylation product **42** derived from the oxidative insertion complex **40**. Even the formation of **40** warranted concern: CO forms very strong bonds with Pd(0), occupying a coordination site and stabilizing the low oxidation state through synergistic bonding; this raises the energy barrier for oxidation addition of C–X bonds, often making them turnover limiting in carbonylation catalysis.[14-17]

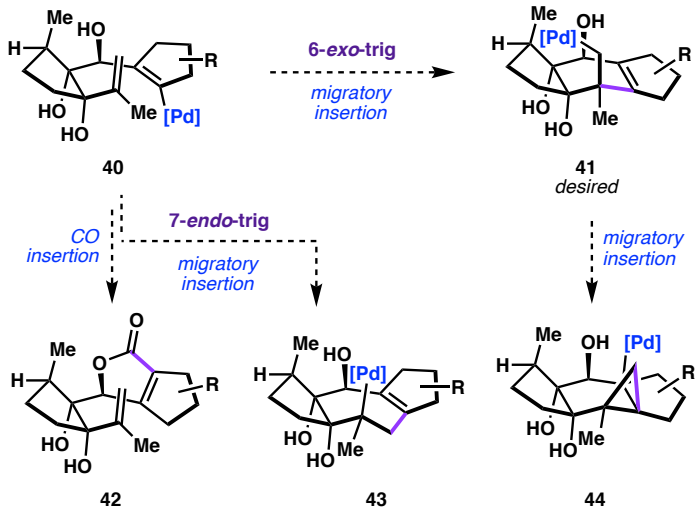


Figure 3. *Potential side reaction pathways in the proposed Pd-catalyzed cascade.*

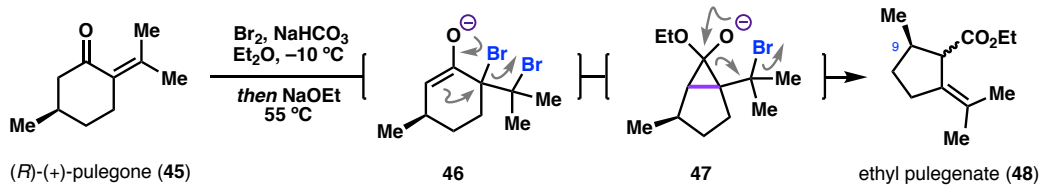
Successful migratory insertion, however, could involve two different modes of cyclization. Less of a concern was the formation of the 7-*endo* cyclization product **43**,

given that such a cyclization would result in the formation of a *tertiary* palladium alkyl species. Even if the 6-*exo* cyclization were to occur, we feared that the ensuing engagement of the primary alkylpalladium species **41** with CO in an *intermolecular* fashion may be slower than the potential *intramolecular* reaction involving a second migratory insertion to generate cyclopropane **44**. Yet as a general rule, σ-alkylpalladium complexes are thought to undergo faster CO insertion more rapidly than they insert alkenes, whereas σ-acylpalladium complexes add alkenes more rapidly than they do CO. Cognizant of the three potential side pathways available to proposed cascade substrate **40**, we required concise entry into a model system that would allow us to validate our synthetic strategy.

3.4 FORWARD SYNTHETIC EFFORTS

3.4.1 *Fragment Preparation*

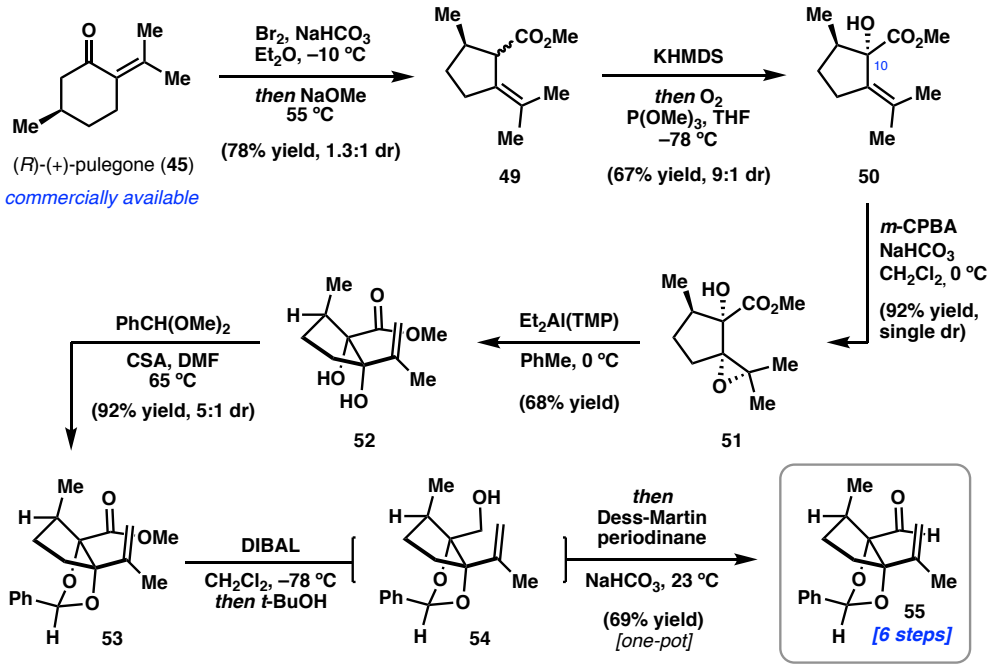
Our synthetic work on the isoryanoid diterpenes began with the preparation of a versatile C-ring fragment that would supply our evaluation of a convergent disconnection. Recognizing that (*R*)-(+)-pulegone (**45**) may serve to provide the C9 stereocenter, we commenced by performing a known 1-step ring contraction to generate methyl pulegenate (**49**) as a mixture of diastereomers.[18]



Scheme 5. *Modified 1-step conversion of (+)-pulegone to ethyl pulegenate.*

First reported in 1975 by Marx and Norman, this Favorskii reaction proceeds via the intermediacy of dibromide **46**, likewise produced as a mixture of diastereomers (Scheme 5).[19]

The resulting mixture of methyl esters **49** proved inconsequential as enolization to its potassium enolate could readily be followed by a kinetic quench with O_2 and $P(OMe)_3$, affording tertiary alcohol **50** in 9:1 dr, favoring the desired diastereomer at C10 (Scheme 6). Leveraging this synthetic handle, a peracid-mediated hydroxyl-directed epoxidation provided tetrasubstituted epoxide **51** as a single diastereomer.[20] Treatment of **51** with the aluminum amide generated from 2,2,6,6-tetramethylpiperidine (TMP) triggered a base-mediated isomerization to reveal diol **52**.[21]



Scheme 6. *Conversion of (+)-pulegone to an isoryanoid C-ring fragment.*

After an evaluation of different protecting groups for the two free alcohols, we elected to press forward with benzylidene acetal **53**, noted at the planning stage to provide options for deprotection under mild conditions.[22] Acyclic protecting group schemes led to issues

with diastereoselectivity and stability downstream. Following this protection step, the methyl ester of **53** was converted to its aldehyde **55** in a two-step protocol. The final two redox manipulations can be rendered into a one-pot transformation with the sequential addition of DIBAL and Dess-Martin periodinane, providing aldehyde **53** in a comparable 69% isolated yield.[23-24] This 6-step sequence provides ready access to a fully-elaborated C-ring fragment.

Having secured access to a C-ring fragment, our attention next turned to a suitable A-ring fragment that would enable our fragment coupling and cyclization studies. Toward that end, we took note of a report by Vidari and coworkers wherein they disclosed that iodobromocyclopentenol **56** undergoes selective lithium-halogen exchange when treated with *n*-BuLi (Figure 4).[25] Having trapped out the vinyllithium species **57**, the product vinyl bromide **58** succumbs to a second lithium-halogen exchange when treated with *t*-BuLi. This valuable dianion equivalent has remarkably yet to find strategic use in the context of complex molecule synthesis.

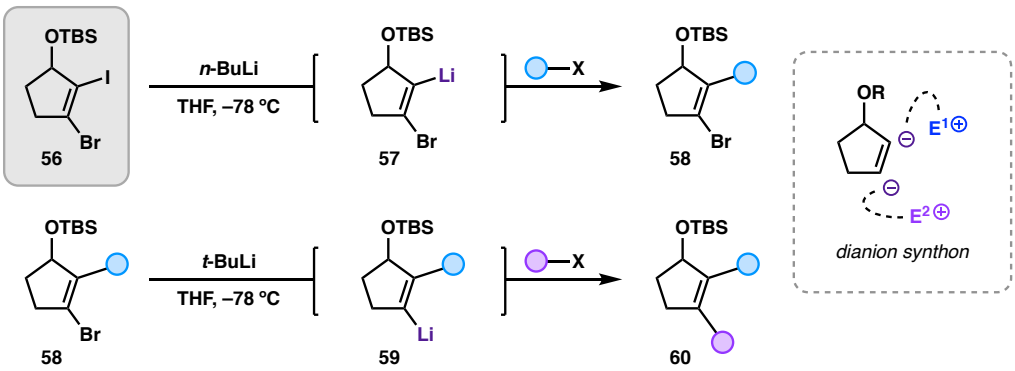
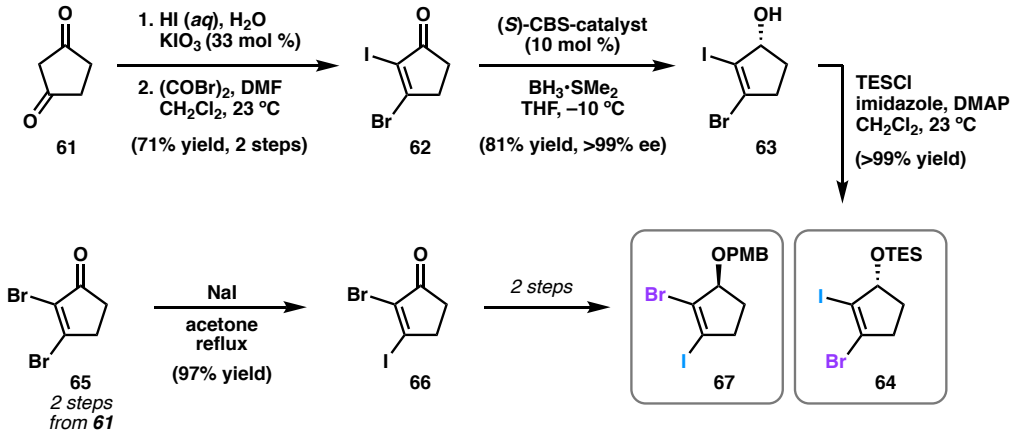


Figure 4. *A-ring fragment inspiration.*

As a starting point to evaluate our retrosynthetic analysis, both isomers of **56** were prepared in enantioenriched form from commercially available 1,3-cyclopentanedione (**61**, Scheme 7). The first isomer **64** was generated in a similar fashion to that reported by

Vidari and coworkers, beginning with an iodination of **61** with HI (*aq*) and KIO_3.[25] Treatment of the intermediate iododiketone with the Vilsmeier reagent derived from oxalyl bromide and DMF *in situ* produces iodobromocyclopentenone **62**. To render the synthesis enantioselective, we subjected **62** to CBS reduction conditions and were pleased to produce enantioenriched iodobromocyclopentenol **63** after one recrystallization. Following this 1,2-reduction, the free alcohol of **63** was protected as its TES ether under routine conditions.

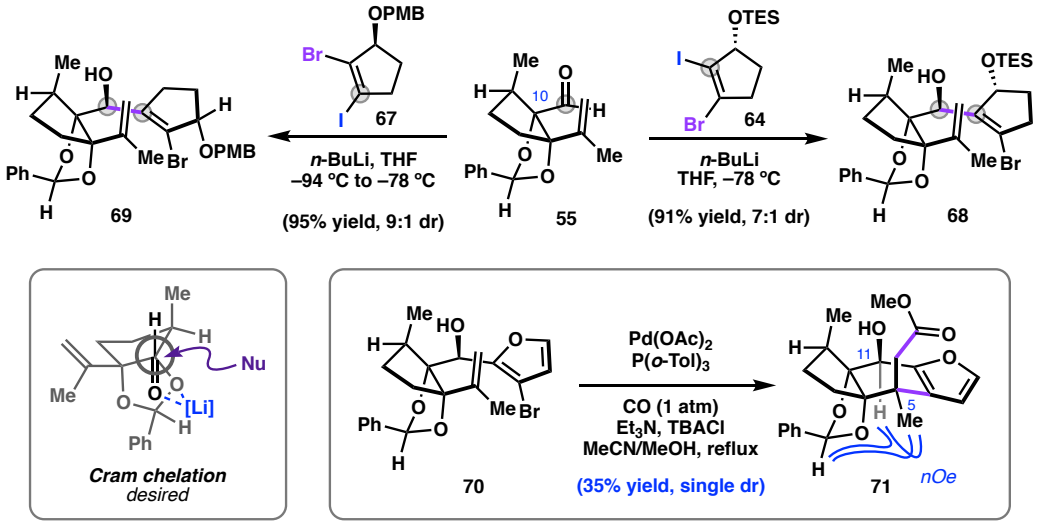


Scheme 7. *Model A-ring fragment preparation.*

The related isomer **67** was prepared from known dibromocyclopentenone **65**.[26] A Finkelstein-like exchange was induced by exposing **65** to NaI in acetone at elevated temperatures, thus leading to smooth generation of iodobromocyclopentenone **66**. In a similar fashion, **66** was subjected to CBS reduction and PMB protection to furnish enantioenriched iodobromocyclopentenol **67**. This isomer was protected as its PMB ether to concurrently investigate deprotection conditions following our fragment coupling and cyclization studies.

3.4.2 *Convergent Union and Cyclization Studies*

Having secured access to the requisite A- and C-ring fragments, we initiated synthetic studies to validate our fragment coupling approach for the isoryanoid diterpenes. Following the procedure detailed by Vidari and coworkers, iodobromocyclopentenols **64** and **67** were treated with 1.0 equiv of *n*-BuLi to induce selective Li/I exchange and the intermediate cyclopentenyllithium species was next exposed to a THF solution of C-ring fragment **55** at –78 ºC, successfully leading to 1,2-addition products **68** and **69** with good diastereoselectivity. The desired diastereomer is a product of Cram chelation controlled introduction of the cyclopentenyllithium species; presumably the 1.0 equiv of LiI generated from lithium-halogen exchange serves to form a chelate between the aldehyde and the C10 alkoxy group, enhancing the diastereoselectivity of this transformation. Attempts to further improve the dr with the addition of exogenous Lewis acidic additives (e.g. $MgBr_2 \bullet OEt_2$ and $LaCl_3 \bullet 2LiCl$) did not lead to significant enhancement.



Scheme 8. *Convergent union and preliminary carbonylation results.*

With access to 1,2-addition products **68** and **69**, we were poised to rapidly assemble the anhydroperseanol skeleton through the realization of our proposed Pd-catalyzed cascade event. Considerable efforts were dedicated to first realize a Heck cyclization/carbonylation cascade as originally proposed in Scheme 4; however, NOESY analysis of the related product **71** derived from bromofuran **70** (see Appendix 3 for more details) revealed the central B-ring adopts a boat-conformation, easily deduced by a strong nOe correlation between the C11–*H* and the C5–*Me*. Both axial substituents in turn share a strong nOe correlation with the methine of the benzylidene acetal. This conformation disposes both the C11–*OH* and the alkyl chain harboring the Pd-center in an equatorial conformation, precluding engagement in an intramolecular cyclization event. Conformational issues aside, our attempts to translate the Pd-carbonylation conditions for bromofuran **70** to vinyl bromide **68** and **69** led to TES deprotection and recovered starting material, respectively. Unable to access the lactone directly and with difficulty achieving preparative yields for the intermolecular carbonylation product, we transitioned our focus to terminating the reaction via cross-coupling chemistry (Figure 5).

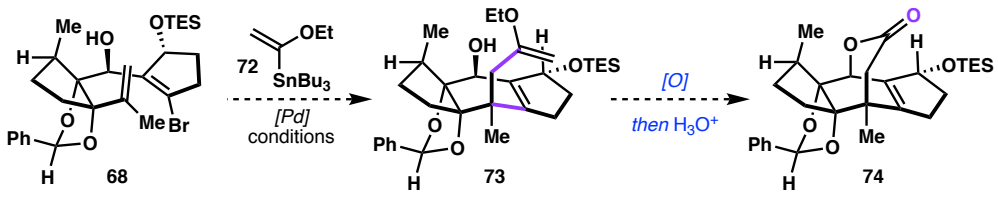


Figure 5. *Redesign of Pd-catalyzed cascade: a cross-coupling termination.*

Pd-catalyzed cascade reactions terminated via a cross-coupling event have been well explored in the literature, providing us excellent precedent for the selection of potential reagents to screen.[27-30] In choosing the appropriate nucleophile, we quickly narrowed our scope to Sn-based reagents or a Stille cross-coupling termination to avoid

(1) air and moisture-sensitive reagents that required immediate preparation and (2) nucleophiles that required activation with the addition of exogenous base additives. This decision was driven by the synthetic context, where it was easily envisioned that protecting group sensitivity and/or side reactions stemming from the functional groups present in the substrate would lead to poor yields and tedious separations. After evaluating the information required for further elaboration to the D-ring lactone, we opted to focus our efforts on a Stille cross-coupling with vinyl stannane **72**. Following successful execution of our Heck cyclization/Stille cross-coupling, it was conceived that oxidative cleavage of the terminal alkene (in the presence of the tetrasubstituted alkene) and acidic workup could induce lactonization affording tetracycle **74**.

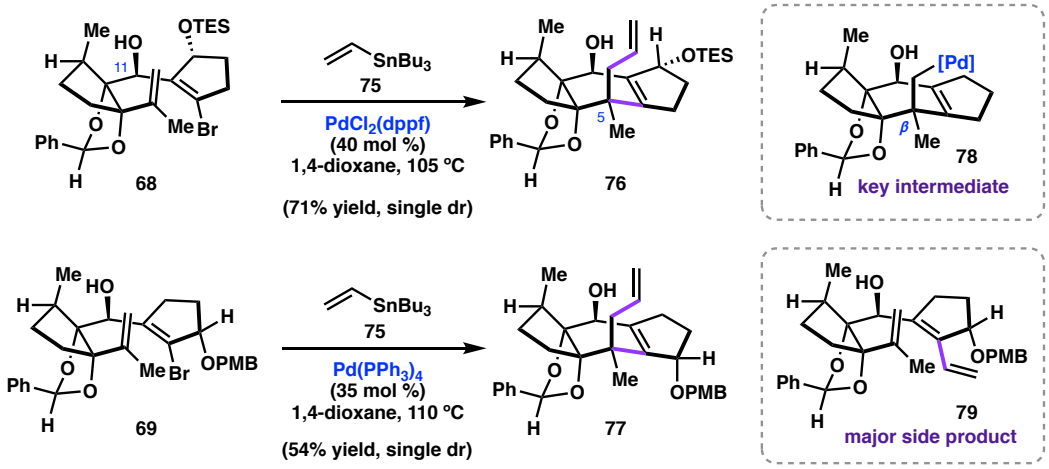
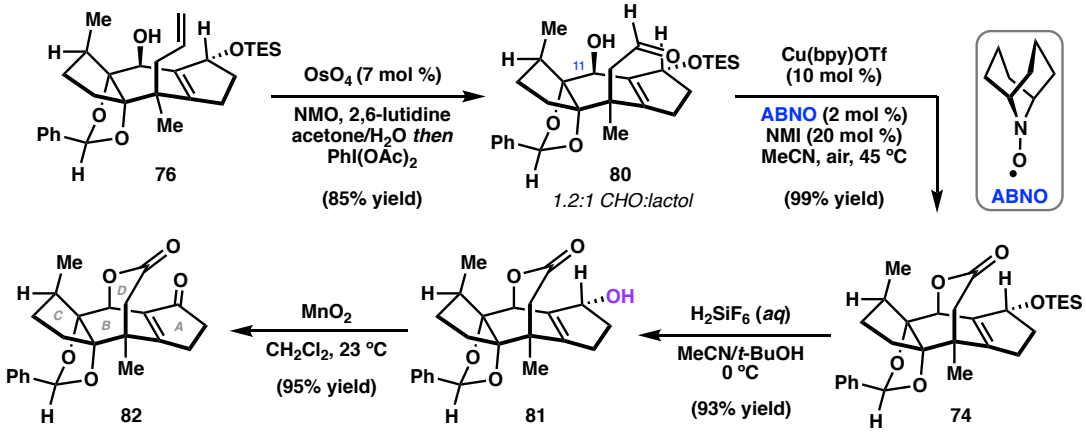


Figure 6. *A Pd-catalyzed Heck cyclization/Stille cross-coupling cascade.*

Fortuitously, we discovered that treatment of 1,2-addition product **68** with vinyl stannane **75** and $Pd(PPh_3)_4$ in DMF at elevated temperatures afforded the desired ABC tricycle **76**, that had undergone the Heck-Stille cyclization/cross-coupling cascade with exquisite diastereoselectivity. This diastereoselectivity hinged upon the C11 free alcohol, as protected variants of vinyl bromide **68** instead led to the formation of the undesired

diastereomer with selectivity as high as 7:1 dr (confirmed by NOESY analysis). Further optimization revealed that $PdCl_2$(dppf) proved to be a superior catalyst with respect to conversion, now affording our desired product in 71% isolated yield on gram scale. With the more hindered vinyl bromide **69**, $Pd(PPh_3)_4$ provided slightly improved yields by mitigating the formation of the premature cross-coupling product, diene **79**. This is perhaps a consequence of accelerated ligand exchange at Pd with monodentate ligands, which can enhance the rate of migratory insertion by (1) providing a vacant site at Pd for olefin complexation and (2) minimizing the steric demand imposed by the α-stereocenter. This selectivity for cyclization product **77** over cross-coupling product **79** could be further improved with the appropriate choice of a polar solvent. For ease of handling, 1,4-dioxane was chosen on preparative scale although amide-type solvents (e.g. DMF) proved equally as effective; however, when turning to nonpolar solvents such as α,α,α-trifluorotoluene, the cascade product is not observed and vinyl bromide **69** cleanly generates diene **79**. These details combined led us to our optimized conditions reported in Figure 6, readily executed on gram scale.



Scheme 9. *Advancement of tricycle* ***76*** *to an isoryanoid ABCD tetracycle.*

While both tricycles **76** and **77** harbor the requisite ABC framework for the isoryanoid diterpenes, it was immediately apparent that we did not require oxidation at C3 when comparing the structure of **77** to (+)-perseanol. We therefore performed our exploratory chemistry on isomer **76**. Following our synthetic plan (*vide supra*), the terminal alkene of **76** was first exposed as its aldehyde **80** via Nicolaou's modified Johnson-Lemieux oxidation conditions (Scheme 9).[31] Due to the boat conformation of the central B-ring that was deduced previously from nOe analysis of tricycle **76**, we were not surprised that aldehyde **80** prefers to remain in its open form, as opposed to its cyclized lactol (1.2:1 ratio determined via ^{1}H NMR analysis of purified material). Nevertheless, when subjecting the mixture to Stahl's Cu-catalyzed oxidative lactonization, we observed clean conversion to lactone **74** with minimal formation of the premature C11 oxidation product.[32] The slightly elevated temperatures when compared to the originally reported conditions (i.e. rt) were required to facilitate the aldehyde to lactol conformational change required of the oxidation. Access to lactone **74** marked the completion of the carbon skeleton of anhydroperseanol (**24**). **74** could be further elaborated to enone **82** following TES deprotection and oxidation of intermediate alcohol **81**.

3.4.3 *A-ring Functionalization and Reductive Cyclization Studies*

With the ABCD tetracyclic framework of the isoryanoid diterpenes in place, the final manipulations required of a successful synthesis would involve retooling the A-ring to map on to anhydroperseanol (**24**). Before addressing the introduction of the final carbons (highlighted in blue in Figure 7), we thought it prudent to develop a strategy to oxidize the tetrasubstituted alkene present in **82** to install the AB-ring junction

bridgehead diol. This decision was driven in part by the challenges we had encountered in the ryanoid system when trying to introduce the related C4 alcohol, an issue that warranted innovation in C–H oxidation technology.

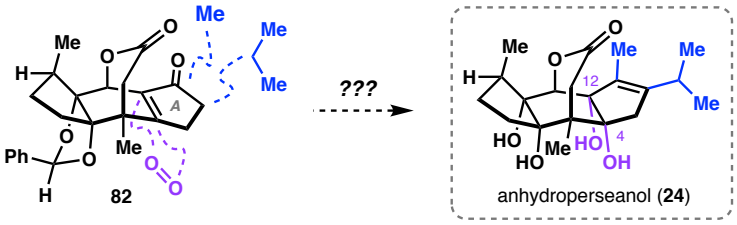
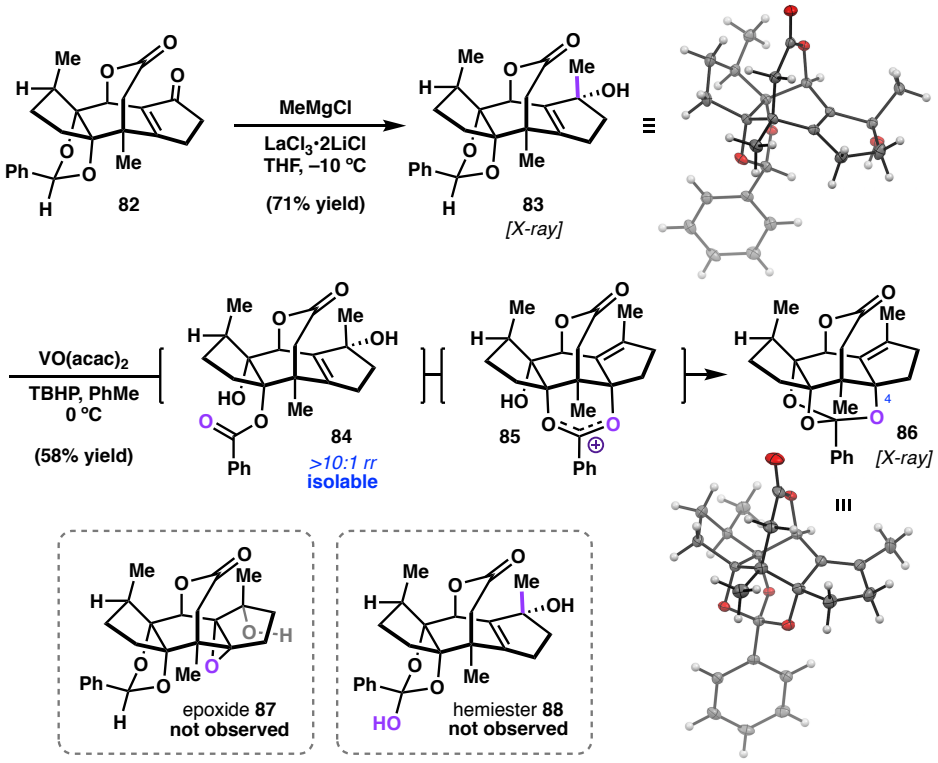


Figure 7. *Status check: comparison of* ***82*** *and anhydroperseanol.*

Thus, tetracycle **82** was first engaged with MeMgCl in the presence of $LaCl_3$•2LiCl[33] to effect 1,2-addition and generate tertiary alcohol **83** (the relative and absolute configuration were verified via X-ray crystallography). With a synthetic handle to perform hydroxyl-directed epoxidation, **83** was treated with a number of different epoxidation reagents. Unfortunately, due to the hindered nature of the alkene–imposed in part by the methine of the benzylidene acetal protecting group–we were never able to effect epoxidation under a variety of different conditions. Yet when attempting a V-mediated hydroxyl-directed epoxidation, alkene **83** underwent oxidative transposition leading to the isolation of orthobenzoate **86**, its structure verified by X-ray analysis.

Mechanistically, orthoester **86** is surmised to arise through C–H oxidation of the electron-rich methine by the V-bound substrate (Scheme 10). The isolable intermediate benzoate **84** then undergoes anchimeric assisted solvolysis to generate dioxolenium ion **85**. This 1,3-allylic transposition product is trapped in an intramolecular fashion by the C10 alcohol resulting in the formation of orthoester **86**. An alternative but related mechanistic hypothesis could involve the intermediacy of hemiester **88**, the direct product

from the proposed C–H oxidation. **88** itself may be primed to trigger the 1,3-allylic transposition to generate orthoester **86**.



Scheme 10. *Discovery of a 1,3-allylic transposition for C4 oxidation.*

It is worth noting, however, that the hemiester form of hydroxybenzoate **88** has not been isolated or observed by ^{1}H NMR, whereas **87** itself can be isolated and independently converted to orthoester **86** when treated with TFA in CH_2Cl_2 at 0 ºC.[34]

While the 1,3-allylic transposition installed an important oxidation state at C4, concerns were raised regarding the deprotection of this protecting group due to reported difficulties with a related protecting group strategy employed by Deslongchamps and coworkers in their ryanodol synthetic studies (Figure 8). The 1-step conversion of (+)-anhydroryanodol (**89**) to **90** was conceived to provide facile access to a C3 protected compound (e.g. **91**) during their relay studies en route to (+)-ryanodol.

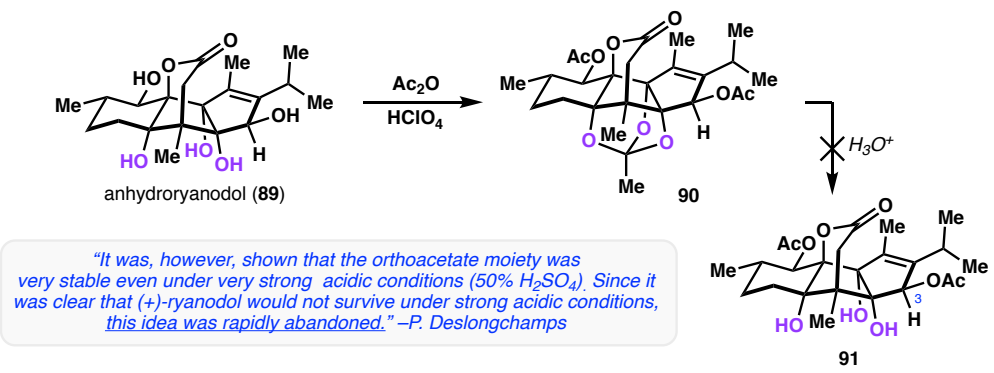
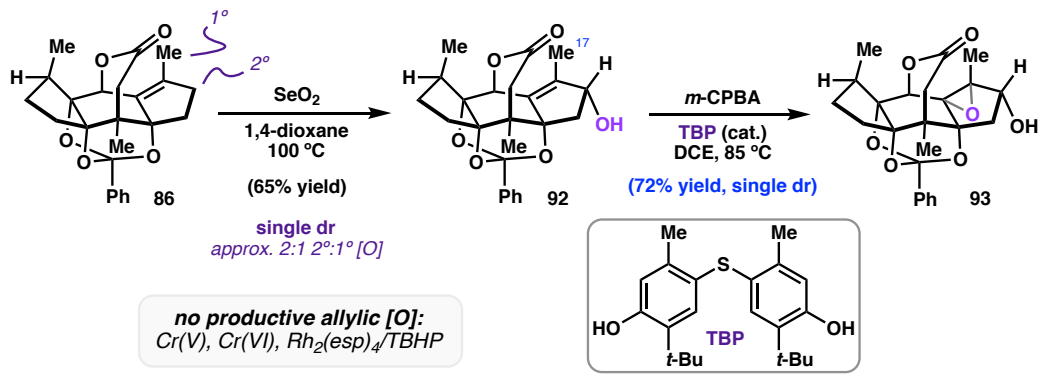


Figure 8. *Deslongchamps' anhydroryanodol orthoacetate* ***90****.*

However, **90** was noted to be remarkably stable to 50% H_2SO_4 (*aq*), and as a result "this idea was rapidly abandoned," since the natural product (+)-ryanodol itself is not stable to acid.[35] Related concerns in our system led us to complete model studies to address this issue prior to committing to this intermediate.

In the forward sense, the A-ring of orthobenzoate **86** was first oxidized with SeO_2 to produce allylic alcohol **87** (Scheme 11). The reaction proceeds with excellent diastereoselectivity resulting from introduction of the oxidant at the less-hindered convex face of the tetracyclic system; the reduced yields were a result of poor positional selectivity in the allylic oxidation. That is, we observed isolable quantities of the primary alcohol and enal derived from C17 oxidation, together comprising the remainder of the mass balance. Despite this poor overall 2:1 positional selectivity, we pressed forward to realize conditions to introduce the final A-ring oxidation state through an epoxidation of **92**. While conceivably simple, the cage-like structure imposed by the orthobenzoate proved to be a steric and/or stereoelectronic imposition, and many oxidants failed to epoxidize the alkene, instead leading to starting material decomposition or 1,2-oxidation of the allylic alcohol to its enone.



Scheme 11. *2-step oxidation sequence to access reductive cyclization substrate* ***93***.

We finally discovered that thermal conditions with *m*-CPBA (99%) as a stoichiometric oxidant proved to be successful in delivering epoxide **93**. Critical to accessing elevated temperatures with this peracid was the addition of the commercially available radical inhibitor 4,4′-thiobis-(6-*t*-Bu-3-Me-phenol) (TBP) in catalytic quantities. This additive was first reported by Kishi and coworkers to enable clean epoxidation with *m*-CPBA at high temperatures (90 ºC), and has found utility by other research groups in the context of complex molecule synthesis.[34, 36-41] In the absence of TBP, the reaction consistently stalls and the starting material succumbs to decomposition with the addition of excess peracid.

Access to epoxide **93** positioned us to test reductive cyclization conditions to complete the pentacyclic isoryanoid framework. It was not entirely apparent at the planning stage that **93** would undergo the related cyclization, given that closer inspection of the cyclization mode in demand revealed a Baldwin disfavored[42-44] 5-*endo*-tet epoxide opening to form the bridging tetrahydrofuran ring (**95→1**, Figure 9). Even viewed from the formation of the carbocyclic E-ring, the 6-*endo*-tet ring closure was viewed to be less favorable when compared to the 6-*exo*-tet ring closure of epoxide substrate **94** derived from anydroperseanol (**24**), which we had originally sought to use.

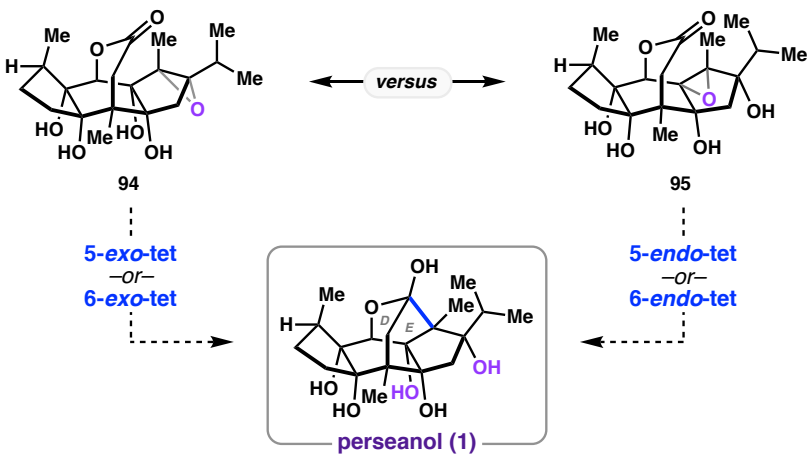
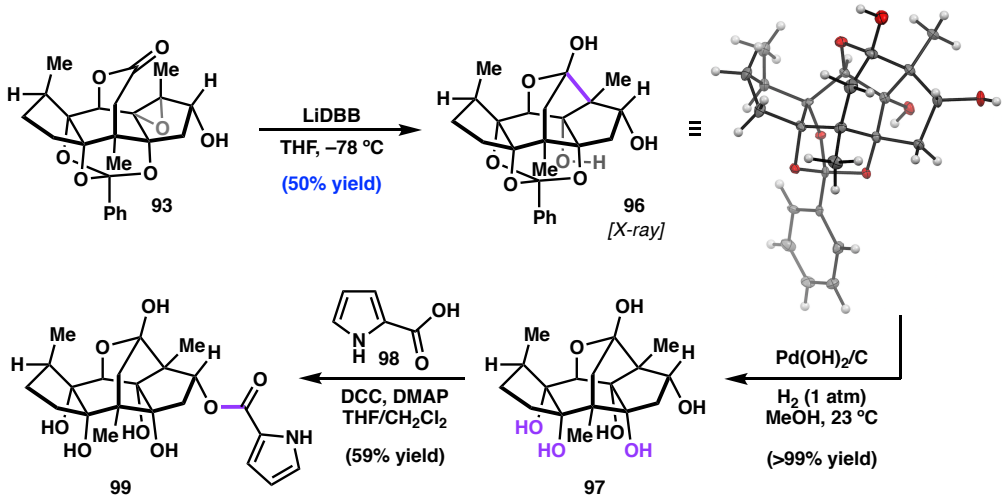


Figure 9. *Comparison of reductive cyclization substrates.*

These concerns were quickly assuaged when treatment of epoxylactone **93** with LiDBB at –78 ºC led to desired cyclized product **96** (Scheme 12).[45-46] The careful, dropwise addition of 4.0 equiv of the reactive radical anion proved necessary to avoid further decomposition of cyclized product **96**. The structure of pentacycle **96** was unambiguously verified through X-ray analysis. To address our concerns of the orthobenzoate's stability, **96** was next treated with $Pd(OH)_2/C$ under an atmosphere of H_2 following a precedent that such orthoesters could be removed by hydrogenolysis at 30 psi H_2.[47] We were pleased to find that at 1 atm of H_2 we could induce clean deprotection of the orthobenzoate to reveal pentaol **97** at ambient temperature. Notably, we found that formation of the C1–C15 bond to generate the pentacyclic isoryanoid framework was critical for hydrogenolytic deprotection to occur at 1 atm of H_2. Attempts to perform the same deprotection on tetracycle **93** do not affect hydrogenolysis, and **93** is recovered unconsumed. Other tetracycles such as **92** still harboring the alkene instead succumb to a fast π-allyl formation/reduction sequence, a consequence of the allylic acetate presented by the D-ring lactone, leaving the orthobenzoate intact.



Scheme 12. *Reductive cyclization and orthoester deprotection success.*

To begin interrogating the isoryanoid framework for the development of new candidate RyR ligands, we subjected pentaol **97** to Steglich esterification conditions with pyrrole-2-carboxylic acid (**98**) and successfully induced selective esterification at the secondary C2 alcohol to generate pyrrole ester **99** (Scheme 12).[48] No other acylation products were detected by LCMS analysis (the remainder of the mass balance is recovered starting material). We believe **99** will serve a prime starting point to begin evaluating new chemical space with the isoryanoid diterpenes.

3.4.4 *Isopropyl Introduction: Failed Attempts*

Having validated an endgame sequence to complete a total synthesis of (+)-perseanol, we moved to the critical task of introducing the isopropyl group to generate a related substrate and test our late-stage reductive cyclization approach. In this vein, tetracycle **82** was engaged with a variety of different secondary electrophiles (Figure 10). Unfortunately, we were never able to see productive reactivity under standard alkylation and aldol conditions. The base sensitivity of tetracycle **82** limited the accessible reaction

temperatures prior to observing decomposition, thus prohibiting productive reactivity with these less-reactive electrophiles.

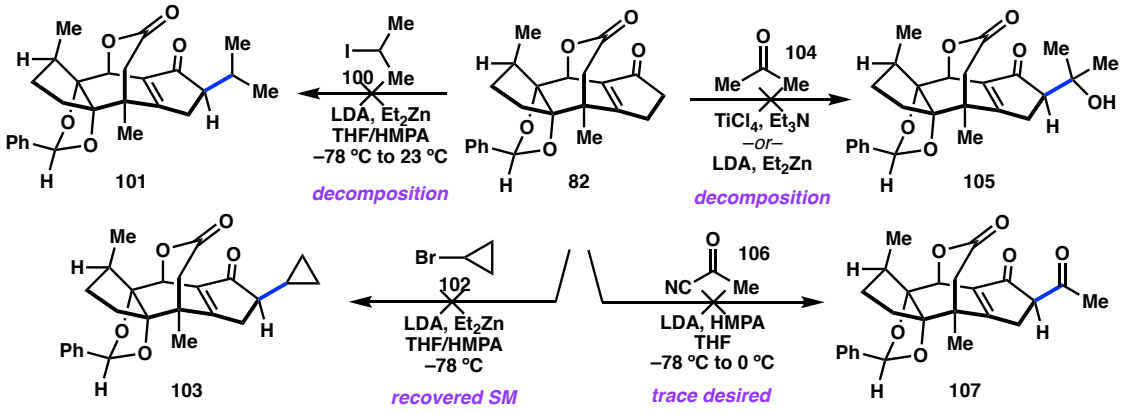
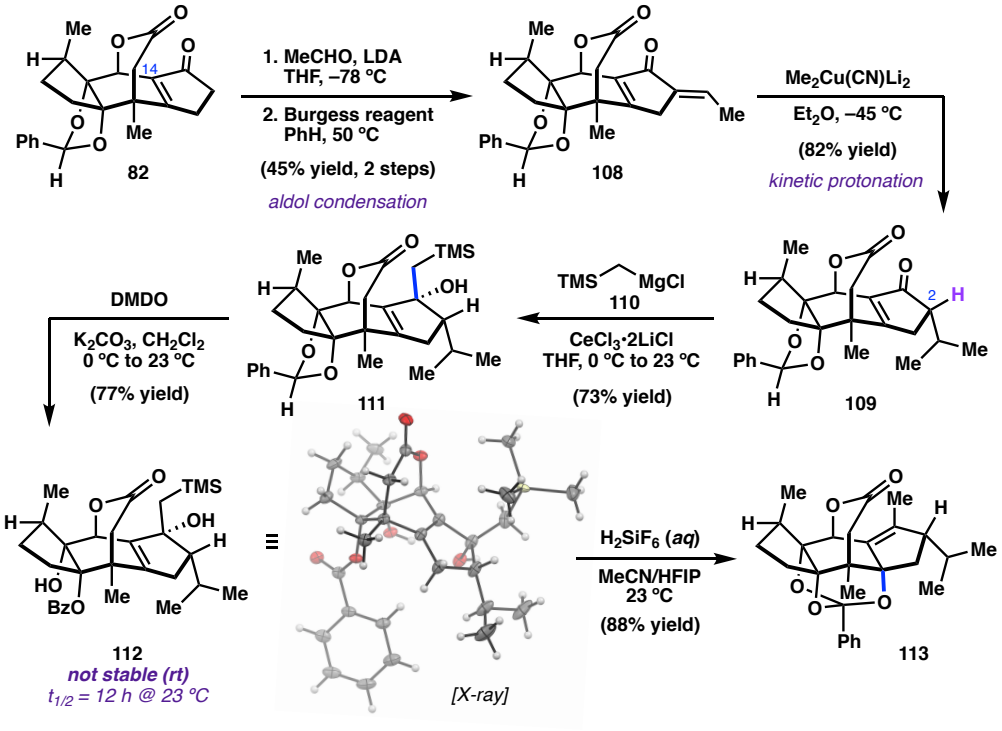


Figure 10. *Failed attempts to introduce isopropyl group.*

A solution was born by engaging the lithium enolate derived from tetracycle **82** with acetaldehyde (MeCHO) to induce an aldol reaction at –78 ºC (Scheme 13). Deuterium quenching studies revealed that the D-ring lactone does not undergo enolization under these conditions; this can be attributed to (1) poor orbital overlap between the enolizable protons and the C14 carbonyl due in part to the rigidity of **82** and (2) the strain induced from said enolization. Following successful C–C bond formation, the diastereomeric mixture of aldol adducts readily underwent dehydration by the action of Burgess reagent to generate the aldol condensation product, dienone **108**. **108** likewise proved to be remarkably base sensitive and exhibited instantaneous hydrolysis upon treatment with Et_3N, establishing an important trend: as the A-ring becomes more sp^2-hybridized, the D-ring lactone becomes more primed to undergo hydrolysis. As such, optimal yields of **108** were observed under more neutral conditions with the highly active dehydrating agent Martin Sulfurane, but the desired dienone product could not be readily

purified from the Ph_2SO byproduct without the use of preparative TLC. Thus to simplify scale-up, we pressed forward with Burgess reagent.



Scheme 13. *Successful installation of isopropyl group with undesired dr.*

The highly conjugated dienone **108** was next treated with Gilman's reagent (derived from CuCN and MeLi) to induce 1,4-addition. The intermediate lithium enolate underwent a highly facial-selective kinetic protonation to provide isopropyl ketone **109** with good diastereoselectivity (8:1 dr). Unfortunately, in comparing **109** with (+)-perseanol (**1**), the undesired diastereomer at C2 had been formed. Following a 2-step procedure, the relative and absolute configuration could be unambiguously confirmed by X-ray analysis. Prohibiting the implementation of a thermodynamic epimerization to generate the correct diastereomer was, again, the base sensitivity of **109** (Figure 11). Other strategies involving radical-mediated conditions likewise led to the recovery of the undesired C2 diastereomer. While tetracycle **82** could be elaborated to an intermediate

orthoester (**113**) harboring all of the carbons required for the isoryanoid diterpenes, the inherent selectivity imposed by the polycyclic framework prompted us to reconsider our approach.

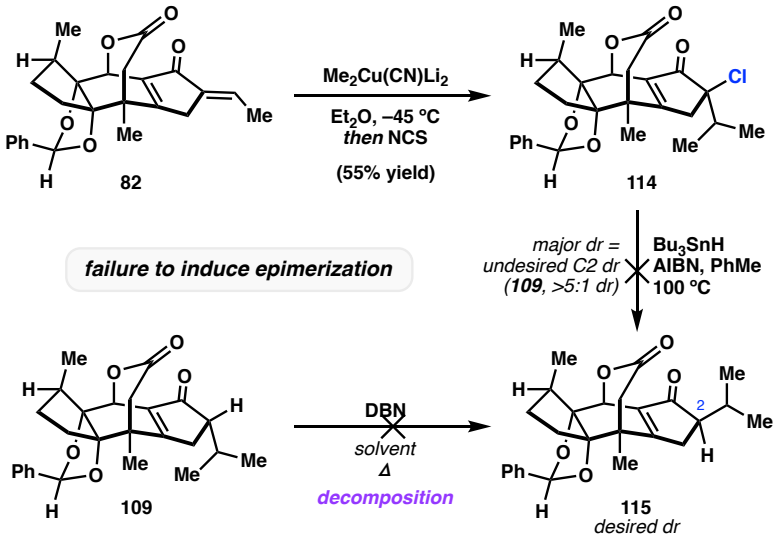


Figure 11. *Failed epimerization attempts.*

3.5 TOTAL SYNTHESIS OF (+)-PERSEANOL

3.5.1 *Revised Fragment Preparation: Maximizing Convergency*

As discussed in Section 3.4.4, a critical impediment in applying our model studies toward a total synthesis of the isoryanoid diterpene (+)-perseanol was the inability to correctly introduce the C2 isopropyl group. While several circuitous solutions could be conceived, our vision for the synthesis led us to focus our attention on the A-ring fragment that we had based all of our synthetic studies to this point. That is, we questioned whether we could introduce the desired diastereomer of the isopropyl group in a stereocontrolled fashion through a revised approach to an appropriately functionalized

A-ring fragment. We therefore sought to solve the stereochemical issues presented by the isopropyl group through the innovation of a new fragment.

Preliminary attempts to directly functionalize iodobromocyclopentenone **62** with 2-iodopropane (**100**) consistently led to faster decomposition of the starting material (Figure 12). Soft enolization of **62**, with the intention of engaging product silyl enol ether **117** under Mukaiyama aldol conditions, ultimately revealed the instability of enol ethers and enolates derived from **62** and its related triflate **62′**. These results led us to reconsider the timing of isopropyl group introduction; it appeared that the isopropyl group would need to be introduced prior to revealing the iodobromocyclopentene motif.

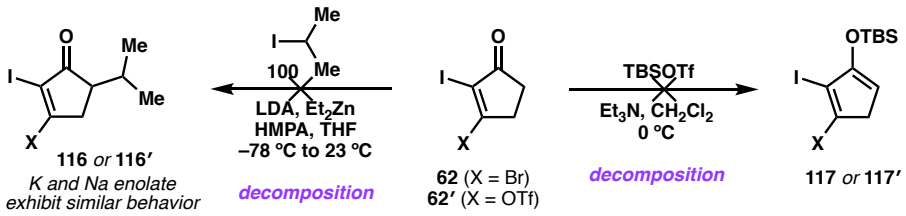
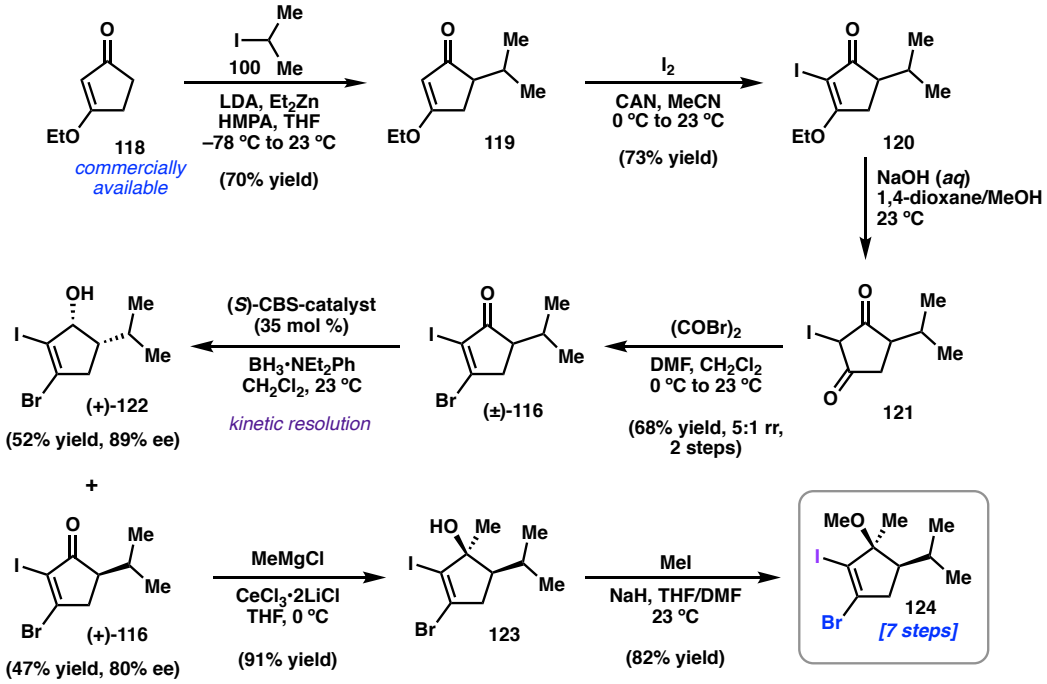


Figure 12. *Attempts to alkylate model iodobromocyclopentenone.*

Validation of this hypothesis required robust conditions to alkylate a suitable cyclopentane starting material with 2-iodopropane. Though seldom performed, we noted a similar transformation by Overman and coworkers in their fragment synthesis for (+)-guanacastapene N, the success of which hinged on the utilization of the more reactive Zn-enolate and DMPU as an additive.[49] Translating these conditions, we were successful in engaging the Zn-enolate of commercially available 3-ethoxy-2-cyclopentenone (**118**) with 2-iodopropane in the presence of HMPA as an additive (Scheme 14). This alkylation reaction requires a stable vinylogous ester: substituting the ethoxy group for a methoxy group led to an intractable decomposition mixture upon subjection to the same alkylation conditions. We knew well that the alkylation product **119** was racemic and had to be

resolved prior to engagement with the enantiopure aldehyde fragment **55** derived from (*R*)-(+)-pulegone (**45**), but for route scouting purposes we elected to press forward.



Scheme 14. *Preparation of a fully elaborated A-ring fragment.*

Having installed the isopropyl group, we required an approach to convert the vinylogous ester to its iodobromocyclopentenone. In the forward sense, **119** was first treated with I_2 in the presence of CAN to generate iodoester **120**. Hydrolysis of **120** with 1.0 N NaOH (*aq*) furnished diketone **121**, which in turn was subjected to the same Vilsmeier reagent derived from oxalyl bromide and DMF to produce (±)-**116** with good regioselectivity (confirmed at this stage by HMBC analysis). We reason that the isopropyl group guides the regioselectivity of the latter reaction through sterics. To our surprise, when (±)-**116** was exposed to CBS reduction conditions, we observed a kinetic resolution of our racemic material, thus providing recovered enriched enone (+)-**116** and enriched 1,2-reduction product (+)-**122**. The outcome can be readily rationalized by

inspecting the proposed stereochemical model (**125**): the isopropyl group is expected to reduce the rate of hydride transfer when delivered from the same face or prevent formation of the activated borohydride altogether (Figure 13).[50]

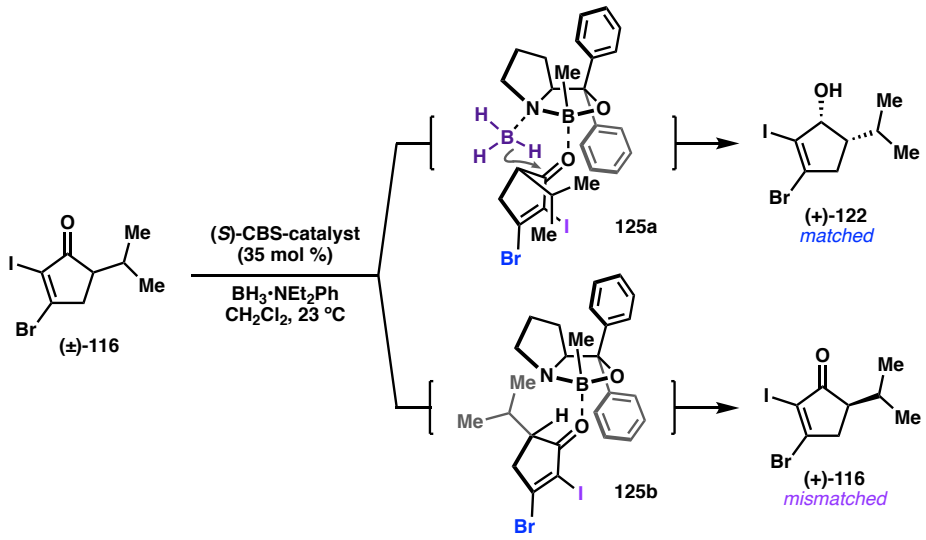


Figure 13. *Stereochemical rationale for kinetic resolution via CBS reduction.*

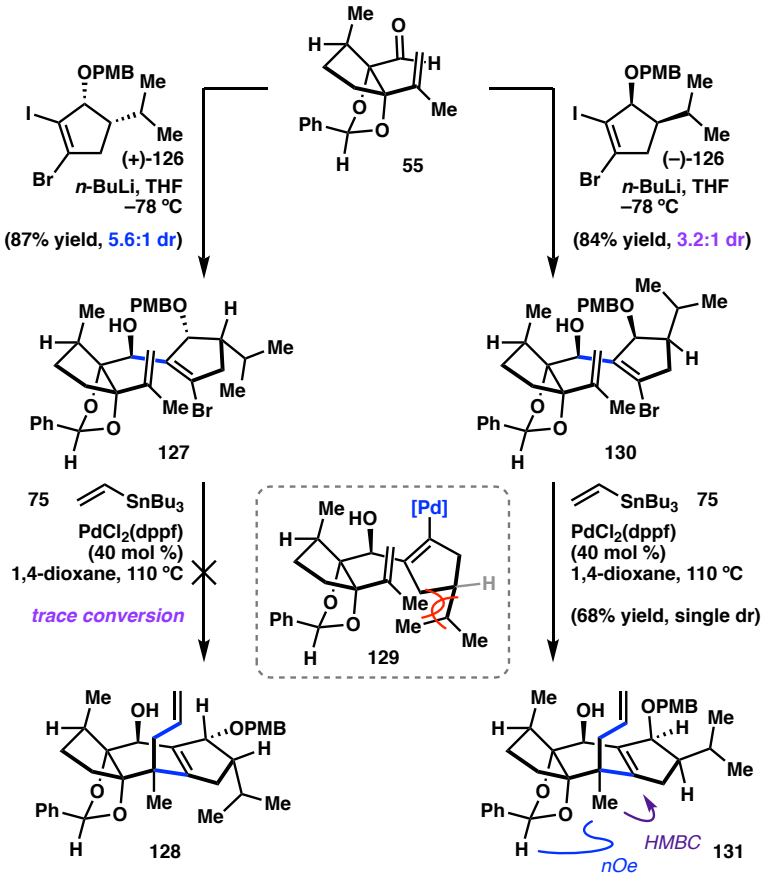
Interestingly, this phenomenon with the CBS catalyst has rarely been observed, although few isolated examples do exist in the literature.[51-53] Our optimization efforts on this resolution process have revealed several key parameters for the successful execution of this reaction: (1) nearly stoichiometric quantities of both the catalyst (35 mol %) and the BH_3 (0.9 equiv) were required to observe good conversion; (2) further catalyst modifications (e. g. *n*-Bu and MeO-CBS catalysts) led to lower conversion, albeit with comparable ee; (3) BH_3•NEt_2Ph was uniquely effective in affording excellent enantioenrichment, as other boranes either provided significantly worse ee (e.g. BH_3•SMe_2 and BH_3•THF) or low reactivity (e.g. catecholborane); (4) PhMe as the reaction solvent led to a marked rate enhancement when compared to the same reaction run in THF and CH_2Cl_2 (30 min versus 2 h versus 4 h); and (5) CH_2Cl_2 provided the best

ee of the reduction product **122**, whereas PhMe provided the best ee of recovered enone **116**.

With enriched enone (+)-**116**, the final A-ring carbon could be introduced through a 1,2-addition with MeMgCl and $CeCl_3$•2LiCl[33] and product alcohol **123** could be protected as its methyl ether under Williamson ether synthesis conditions to provide methyl ether **124** (Scheme 14). The reactivity of **124** was confirmed by engaging it with 1.0 equiv of *n*-BuLi and trapping out the intermediate vinyllithium with DMF, furnishing the expected enal (see Experimental Section). Bulkier protecting groups at oxygen prohibited lithium-halogen exchange chemistry: NOESY analysis reveals that the steric encumbrance imposed by the isopropyl group forces bulkier protecting groups (e.g. TES group) toward the vinyl iodide, leading to this reduced reactivity. With full control over the C2 stereocenter harboring the isopropyl group and proof of reactivity, we were primed to test whether these fully elaborated A-ring fragments could be used in our previously outlined fragment coupling approach.

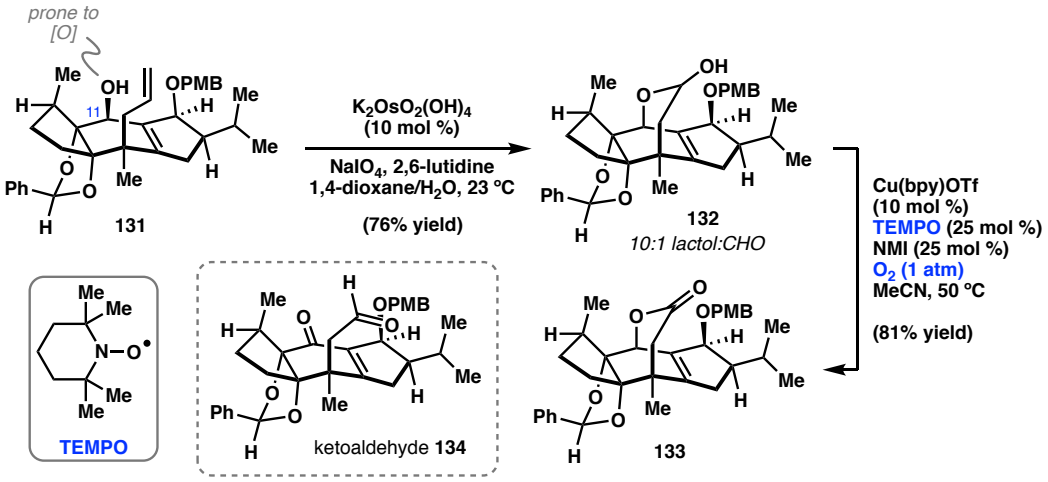
3.5.2 *Fragment Coupling and Cyclization*

To understand the scope of chemistry available to us, the PMB protected iodobromocyclopentenols (+)-**126** and its enantiomer (–)-**126** were both subjected to our previously established 1,2-addition conditions with aldehyde fragment **55** (Scheme 15). The configurational stability of the vinyllithium species generated *in situ* were confirmed by isolating the deiodinated A-ring fragment side product after aqueous workup (see Experimental Section); no halogen dance chemistry was observed and the expected deiodinated material was recovered (determined by HMBC and NOESY analysis).



Scheme. 15. *1,2-addition and cascade studies with revised A-ring fragment.*

While both nucleophiles engaged in productive C–C bond formation, we noted that the vinyllithium derived from enantiomer (+)-**126** provided slightly improved diastereoselectivity. This improvement, however, was met with low reactivity in the subsequent Pd-catalyzed cascade event. Analysis of the requisite transition state (**129**, OPMB group omitted for clarity) to access the desired C5 diastereomer reveals that the isopropyl group would encounter steric repulsion from the C-ring fragment. This demand can be relieved by instead turning to enantiomer (–)-**126**. Its 1,2-addition product **130** undergoes the Pd-catalyzed cascade *with no reoptimization* producing ABC tricycle **131** with exquisite diastereoselectivity and similar yields as before with model substrates **68** and **69**.



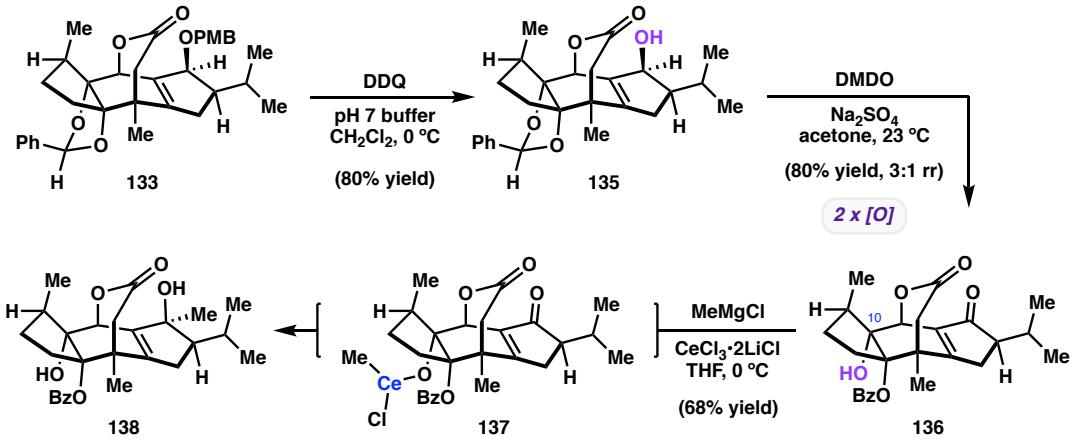
Scheme 16. *Synthesis of ABCD tetracycle* ***133*** *from tricycle* ***131***.

This result was followed by additional difficulties in translating our Johnson-Lemieux/Stahl oxidation sequence to forge the ABCD tetracycle on product **131** (Scheme 16). NOESY analysis of **131** revealed that the inclusion of the isopropyl group results in a conformational change in the central 6-membered B-ring, which now occupies a half-chair conformation. This change exposes the equatorially disposed C11 secondary alcohol to oxidation, and thus a wide array of oxidation conditions led instead to ketoaldehyde **134** as opposed to desired lactol **132**. Interestingly, the product ratio was highly dependent on the solubility of the oxidant. In light of this observation, we finally returned to the canonical Johnson-Lemieux conditions with the less soluble $NaIO_4$ as the turnover oxidant, providing us lactol **132** in good yields. To avoid the same premature oxidation of the C11 secondary alcohol, the Stahl oxidation conditions were revised; leveraging the greater steric profile of TEMPO (when compared to the previously employed nitroxyl radical, ABNO), we were able to oxidize lactol **132** to its lactone **133** with good selectivity (7:1 **133**:**134**). The successful realization of this oxidative

lactonization now secured us access to the ABCD tetracyclic skeleton of anhydroperseanol (**24**), leading us to transition to the oxidase phase of our synthesis.

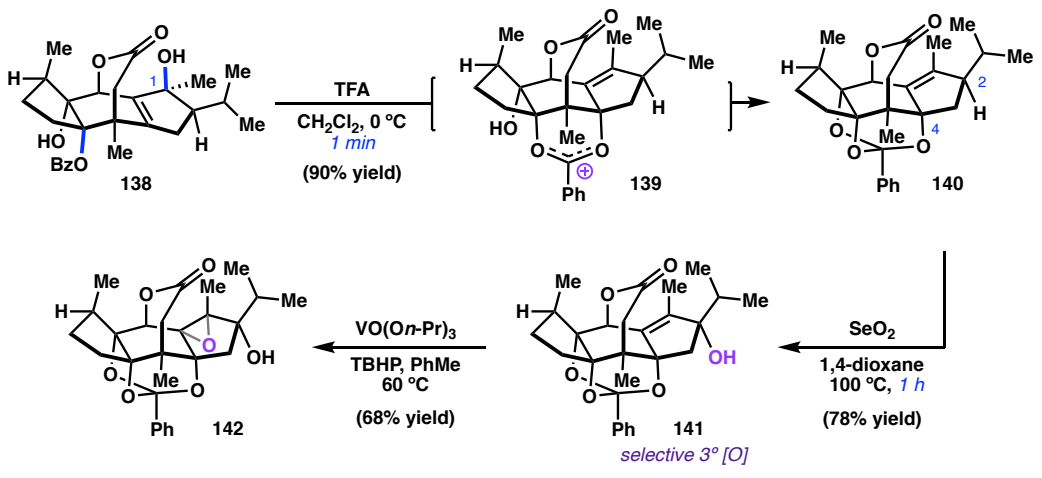
3.5.3 *Oxidase Phase and Total Synthesis*

Completion of the ABCD framework of anhydroperseanol prompted us to focus on the requisite A-ring oxidations that needed to be performed for a total synthesis of **1**. In the forward sense, tetracycle **133** was first treated with DDQ to induce PMB deprotection and generate alcohol **135** (Scheme 17). While the alcohol could be oxidized following prolonged exposure to MnO_2, we discovered that the same oxidation could be performed with freshly prepared DMDO, furthermore effecting C–H oxidation of the benzylidene acetal (3:1 rr) to provide enone **136** (major positional isomer drawn and confirmed by NOESY analysis).[54] Treatment of **136** with MeMgCl in the presence of $CeCl_3$•2LiCl prompted a 1,2-addition to afford diol **138**. The 1,2-addition occurs *anti* with respect to the isopropyl group, a feat that is perhaps aided by the formation of an ate-complex with the free C10 alcohol and consequent intramolecular delivery of the nucleophile.



Scheme 17. *Completion of isoryanoid diterpene carbon framework.*

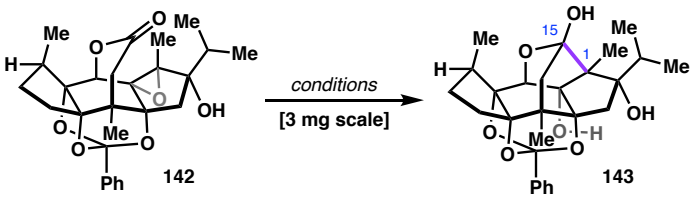
The *anti*-stereochemical relationship between the benzoate and the newly formed C1 tertiary allylic alcohol primes the substrate to undergo anchimeric assisted solvolysis (Scheme 18). Monitoring a C_6D_6 sample of **138** reveals clean conversion to orthobenzoate **140**, albeit at a slow rate (10% conversion after 12 h at RT). This process could be greatly accelerated by simply treating a CH_2Cl_2 solution of **138** with TFA at 0 ºC, inducing rapid formation of orthobenzoate **140**. With access to **140** now harboring the correct stereochemical information at C2, we could perform a SeO_2-mediated allylic oxidation to induce allylic oxidation and generate alcohol **141**. Notably, the reaction proceeds with excellent positional selectivity; no oxidation is observed at the competitive primary carbon, a side product we had observed previously in our model studies. This selectivity is best rationalized by the sterically encumbering isopropyl group occupying an equatorial position forcing the C2 methine in an axial position, primed to undergo the required ene reaction with SeO_2. The axial disposition is deduced from its unusual downfield shift in the ^{1}H NMR (δ 3.06 ppm); the observed deshielding presumably stems from a 1,3-diaxial interaction with the lone pairs of the axially disposed C4 alkoxy group.



Scheme 18. *Oxidase phase: preparation of reductive cyclization precursor* ***142****.*

Ready access to allylic alcohol **141** was met with the unwelcome discovery that epoxidation with *m*-CPBA did not provide clean conversion to epoxide **142**. Due to the prolonged reaction times that were demanded of this sterically hindered alkene, significant decomposition of the product was observed, only permitting us to isolate **142** in 20-30% yield after 2 cycles. Returning to V-mediated directed epoxidation conditions, we were able to observe clean conversion of allylic alcohol **141** to epoxide **142**; critical to the success of this transformation was the use of $VO(O\textit{n}\text{-}Pr)_3$ as the catalyst instead of the more routinely used $VO(acac)_2$. Previously noted by Nicolaou and coworkers to be a more robust epoxidation catalyst, $VO(O\textit{n}\text{-}Pr)_3$ provided us full conversion of allylic alcohol **141** to epoxide **142** whereas $VO(acac)_2$ only led to 5-10% conversion under otherwise identical conditions (even with repeated addition of $VO(acac)_2$ every 1 h, approximately 30% conversion was observed at best) .[55]

With access to epoxide **142**, the final challenges to realize our goal of completing a total synthesis of the isoryanoid diterpene (+)-perseanol were (1) reductive cyclization to forge the C1–C15 bond and complete the pentacyclic framework and (2) deprotection of the orthobenzoate leveraging the hydrogenolytic conditions we previously established in our model studies. To address the first challenge, epoxide **142** was subjected to LiDBB at –78 ºC as before; however, we were disappointingly met with a messy reaction profile with several different products forming that were consistent with degradation of the orthobenzoate via ^{1}H NMR and LCMS analysis. In light of the observed chemoselectivity issue, we elected to revisit radical anions with weaker reduction potentials than that attributed to LiDBB.[56] This short screen revealed LiNap as the optimal radical anion, allowing us to detect and isolate reductive cyclization product **143** in 17% yield.



entry	reagent	temperature	solvent	additive	ratio	yield
1	LiDBB	–78 °C	THF	–	messy	–
2	LiDBB	–20 °C	THF	–	messy	–
3	LiBiphenyl	–20 °C	THF	–	3:1 SM:desired	–
4	LiDBNap	–20 °C	THF	–	3:1 SM:desired	–
5	LiNap	–40 °C	THF	–	2:1 SM:desired	10% yield
6	LiNap	–20 °C	THF	–	2:1 SM:desired	17% yield
7	LiNap	–20 °C	THF	BMEA	6:1 SM: desired	–
8	NaNap	–20 °C	THF	–	>10:1 SM:desired	–
9	LiAnth	23 °C	THF	–	full conversion	epox. iso.
10	LiPNap	–20 °C	2-MeTHF	–	3:1 SM:desired	14% yield
11	LiPNap	10 °C	THF	–	2:1 SM:desired	14% yield
12	LiPNap	10 °C	PhH	–	2:1 SM:desired	23% yield
13	LiPNap	23 °C	PhH	–	3:1 SM:desired	13% yield
14	LiPNap	10 °C	$PhCF_3$	–	no reaction	–
15	LiPNap	–20 °C	PhMe	–	2.5:1 SM:desired	20% yield
16	SmI_2	0 °C	THF	H_2O+Et_3N	70% conversion	1,2-reduction
17	SmI_2	23 °C	THF	H_2O+Et_3N	85% conversion	1,2-reduction

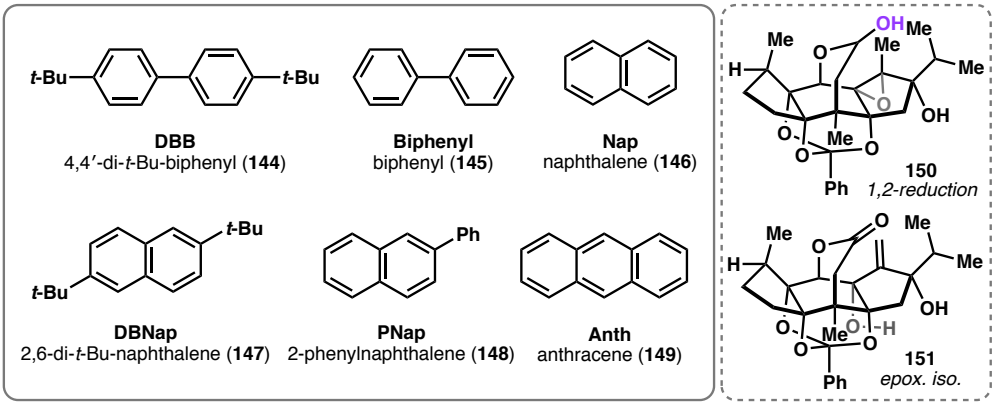
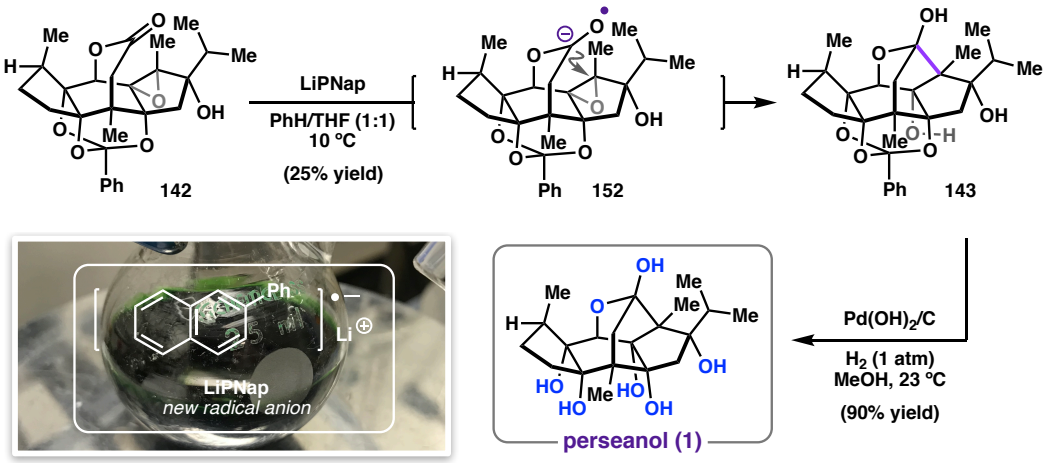


***Figure 14**. Reductive cyclization optimization.*

The reaction could be further optimized by attenuating the reduction potential of the naphthalenide radical anion. That is, the radical anion derived from 2-phenylnaphthalene (PNap) provided the desired cyclized product in 23% isolated yield when the reaction was run in PhH.[57] Other radical anions known to be far less reducing, like lithium anthracenide (LiAnth), did not lead to single electron reduction chemistry and instead led to reactivity akin to a base. Attempting to harness the unique reactivity and chemoselectivity of the SmI_2–H_2O–Et_3N reagent[58-61] likewise did not prove

successful, exclusively leading to 1,2-reduction product **150**. Optimization of this reaction is continuing in our laboratory to improve the yield and conversion of this transformation. Nevertheless, access to reductive cyclization product enabled the completion of our total synthesis upon hydrogenolytic deprotection with $Pd(OH)_2/C$ and H_2, revealing (+)-perseanol (**1**). The spectral data of our synthetic material were in full agreement with that of the natural product provided to us by Zhang and coworkers.[1-2] The synthetic route proceeds in 18 steps (LLS) from commercially available (*R*)-(+)-pulegone (**45**) and is the *first* total synthesis of an isoryanoid diterpene.



Scheme 19. *At last: total synthesis of perseanol.*

3.6 CONCLUDING REMARKS

Herein, we have disclosed a modular fragment coupling approach that has resulted in an 18-step total synthesis of the isoryanoid diterpene (+)-perseanol (**1**). Key elements of this synthesis include (1) a palladium-catalyzed Heck cyclization/Stille cross-coupling cascade to install a sterically-demanding all-carbon quaternary center, (2) the strategic manipulation of a benzylidene acetal protecting group to install the critical C4

oxidation state through a facile 1,3-allylic transposition, and (3) a Baldwin disfavored 5-*endo*-tet epoxide opening reductive cyclization to forge the pentacyclic ABCDE isoryanoid framework. We suspect the strategies disclosed herein will be broadly useful in the concise construction of related ryanoid, isoryanoid, and highly oxygenated diterpenes.

3.7 EXPERIMENTAL SECTION

3.7.1 Materials and Methods

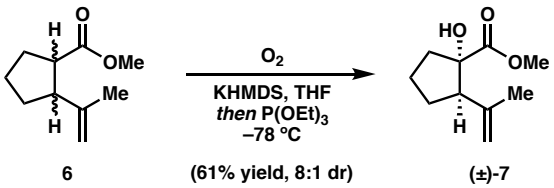
Unless otherwise stated, reactions were performed under an inert atmosphere (dry N_2 or Ar) with freshly dried solvents utilizing standard Schlenk techniques. Glassware was oven-dried at 120 °C for a minimum of four hours, or flame-dried utilizing a Bunsen burner under high vacuum. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), 1,4-dioxane, benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Methanol (HPLC grade) was purchased from Fisher Scientific. 1,2-dichloroethane (DCE), *N*,*N*-diisopropylethylamine (*i*-Pr_2EtN), and 2,2,6,6-tetramethylpiperidine (TMP) was distilled from calcium hydride prior to use and stored under argon. 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/or *p*-anisaldehyde staining. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 microns [230 to 400 mesh]) purchased from Silicycle. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy Cryoprobe (at 400 MHz and 101 MHz, respectively), Varian Inova 400 (at 400 MHz and 101 MHz, respectively), and

Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26), C_6H_6 (^1H, δ = 7.16), or CD_2HOD (^1H, δ = 3.31), and $CDCl_3$ (^{13}C, δ = 77.0), C_6D_6 (^{13}C, δ = 128.0), or CD_3OD (^{13}C, δ = 49.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

Reagents were purchased from commercial vendors as follows: (*R*)-(+)-pulegone (92%) was purchased from Acros Organics. Solid potassium bis(trimethylsilyl)amide (KHMDS, 95%) was purchased from Sigma-Aldrich and stored in a nitrogen-filled glovebox. Tetrakisacetonitrile copper(I) triflate, 2,2′-bipyridyl (≥99%), 4,4′-dimethoxy-2,2′-bipyridine, 1-methylimidazole (NMI, ≥99%), 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO), (*S*)-(–)-2-Me-CBS-oxazaborolidine, (*R*)-(+)-2-Me-CBS-oxazaborolidine, and methylmagnesium chloride (3.0 M in THF) were purchased from Sigma-Aldrich. Dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct ($PdCl_2(dppf)•CH_2Cl_2$) was purchased from Strem Chemicals and stored in a nitrogen-filled glovebox. Tributyl(vinyl)tin was purchased from Oakwood Chemical and stored in a nitrogen-filled glovebox.

3.7.2 Experimental Procedures

Preparation of hydroxyester 7



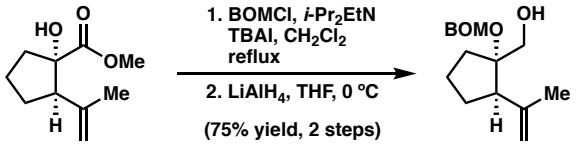
6 (61% yield, 8:1 dr) (±)-7

An oven-dried, 500 mL round-bottomed flask was charged with KHMDS (0.91 M in PhMe, 63 mL, 57.1 mmol, 1.5 equiv) and the solution was cooled to –78 ºC via a dry ice/acetone before adding methyl ester **6**[4] (6.40 g, 38.0 mmol, 1.0 equiv) in anhydrous THF (180 mL) dropwise via cannula. Upon complete addition, the reaction was continued at –78 ºC for 30 min before adding $P(OEt)_3$ (20 mL, 114 mmol, 3.0 equiv) via syringe. Next, O_2 (supplied via a double-walled balloon) was sparged through the reaction mixture until complete consumption of the starting was observed by TLC analysis (*ca.* 30 min). The reaction was quenched with the addition of sat. aq. NH_4Cl (100 mL), warmed to ambient temperature, and diluted with Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^1H NMR analysis of the crude product indicated that the reaction occurs with full consumption of the starting material in an 8:1 diastereomeric ratio. The crude residue was purified via SiO_2 flash chromatography (7.5 to 15% EtOAc/hexanes) to afford alcohol **7** (4.28 g, 23.2 mmol, 61% yield) as a colorless oil.

TLC (20% EtOAc/hexanes): R_f 0.46 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.81 (dqd, *J* = 2.2, 1.5, 0.8 Hz, 1H), 4.75 (hept, *J* = 0.8 Hz, 1H), 3.73 (s, 3H), 3.47 (s, 1H, OH), 2.69 (m, 1H), 2.26 (m, 1H), 1.97 – 1.79 (m, 5H), 1.72 (dt, *J* = 1.4, 0.7 Hz, 3H).

Preparation of alcohol 9



7 9

An oven-dried, 500 mL round-bottomed flask was charged with alcohol **7** (5.22 g, 28.3 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (250 mL). The resulting solution was cooled to 0 ºC via an ice/water bath and after 15 min of continued stirring, freshly distilled *i*-Pr_2EtN (24 mL, 170 mmol, 6.0 equiv) was added via syringe. BOMCl (14.8 mL, 85.0 mmol, 3.0 equiv) was next added dropwise via syringe at 0 ºC, immediately resulting in the generation of a white smoke. TBAI was finally added (3.14 g, 8.50 mmol, 0.3 equiv) and the flask was then warmed to ambient temperature before equipping the flask with a reflux condenser. The reaction mixture was immediately thereafter placed in a preheated oil bath at 50 ºC and left to stir for 30 h, at which point TLC analysis indicated the complete consumption of starting material. The reaction was cooled to ambient temperature, diluted with CH_2Cl_2 (50 mL), and quenched with the careful addition of sat. aq. NH_4Cl (170 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 90 mL). The combined layers were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

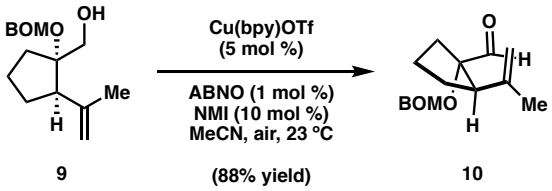
The crude residue was purified via SiO_2 flash chromatography (5 to 10% EtOAc/hexanes) to afford intermediate BOM ether **8** that was carried forward directly.

An oven-dried, 500 mL round-bottomed flask was treated with intermediate BOM ether **8** and anhydrous THF (200 mL). The solution was cooled to 0 ºC via an ice/water bath and then carefully treated with $LiAlH_4$ (3.22 g, 84.9 mmol, 3.0 equiv) in a portion-wise fashion. The resulting grey slurry was vigorously stirred for 1 h at 0 ºC, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was next *carefully* treated with EtOAc (80 mL) followed by sat. aq. Rochelle's salt (160 mL). The cooling bath was removed and the mixture was vigorously stirred overnight at ambient temperature. The resulting two layers were separated and the aqueous layer extracted with EtOAc (4 × 160 mL). The combined organic layers were washed with brine (160 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (8 to 15% EtOAc/hexanes) to afford alcohol **9** (5.87 g, 21.2 mmol, 75% yield over 2 steps) as a thick, colorless oil.

TLC (20% EtOAc/hexanes): R_f 0.36 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 5H), 4.92 (d, *J* = 7.7 Hz, 1H), 4.88 (q, *J* = 1.6 Hz, 1H), 4.85 (d, *J* = 7.7 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.78 (dt, *J* = 2.0, 1.0 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 3.59 (d, *J* = 12.2 Hz, 1H), 3.35 (m, 1H), 3.27 (br s, 1H, OH), 2.64 (m, 1H), 2.02 (m, 1H), 1.87 (s, 3H), 1.85 – 1.77 (m, 2H), 1.76 – 1.65 (m, 3H).

Preparation of aldehyde 10



9 (88% yield) 10

An oven-dried, 500 mL round-bottomed flask was charged with alcohol **9** (5.49 g, 19.9 mmol, 1.0 equiv) and anhydrous MeCN (199 mL). The solution was vigorously stirred (>700 rpm) open to air while being treated with bpy (155 mg, 1.00 mmol, 0.05 equiv), $Cu(MeCN)_4OTf$ (374 mg, 1.00 mmol, 0.05 equiv), ABNO (27.8 mg, 199 μmol, 0.01 equiv), and then NMI (158 μL, 1.99 mmol, 0.10 equiv) via microsyringe. The resulting brick-red reaction mixture was vigorously stirred exposed to air at ambient temperature until the reaction mixture turned a blue-green (*ca.* 45 min), at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was diluted with Et_2O (100 mL), and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 50% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified by SiO_2 flash chromatography (3 to 6 to 9% EtOAc/hexanes) to afford aldehyde **10** (4.80 g, 17.5 mmol, 88% yield) as a clear oil. The stereochemistry of **10** was confirmed via nOe analysis.

TLC (5% EtOAc/hexanes): R_f 0.26 (UV, *p*-anisaldehyde).

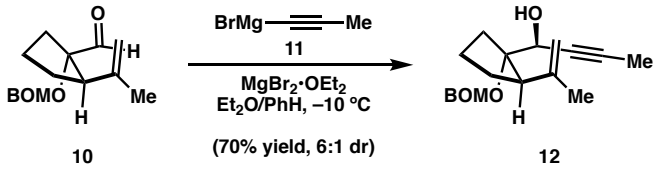
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H, CHO), 7.33 (m, 5H), 4.89 (dt, *J* = 1.9, 1.4 Hz, 1H), 4.85 (d, *J* = 7.3 Hz, 1H), 4.82 (s, 1H), 4.81 (d, *J* = 7.4 Hz, 1H), 4.75 (d, *J* = 11.9 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 2.83 (m, 1H), 2.28 (m, 1H), 1.89 – 1.66 (m, 5H), 1.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.3, 142.0, 137.3, 128.5, 128.4, 127.8, 127.7, 113.1, 92.1, 91.8, 70.1, 56.4, 29.7, 28.3, 23.4, 22.3.

FTIR (NaCl, thin film): 2957, 2876, 1728, 1645, 1454, 1376, 1022 cm^{-1}.

HRMS (FAB): calc'd for $[M+H]^+$ 275.1647, found 275.1643.

Preparation of propargyl alcohol 12



In a nitrogen-filled glovebox, an oven-dried, 200 mL round-bottomed flask was charged with $MgBr_2$•OEt_2 (1.14 g, 4.40 mmol, 1.5 equiv). The flask was capped with a rubber septum, brought out of the glovebox, and treated with aldehyde **10** (805 mg, 1.11 mmol, 1.0 equiv) in anhydrous Et_2O (53 mL) via cannula. Anhydrous PhH (5.3 mL) was added via syringe resulting in dissolution and the solution was thereafter cooled to 0 ºC via an ice/water bath. After 15 min of continued stirring, 1-propynylmagnesium bromide (0.5 M in THF, 7.63 mL, 3.81 mmol, 1.3 equiv) was added dropwise via syringe. Upon complete addition, the resulting reaction mixture was vigorously stirred at 0 ºC until TLC analysis indicated the complete consumption of starting material (*ca*. 1 h). The reaction was then quenched with the addition of sat. aq. NH_4Cl (20 mL), diluted with Et_2O (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2

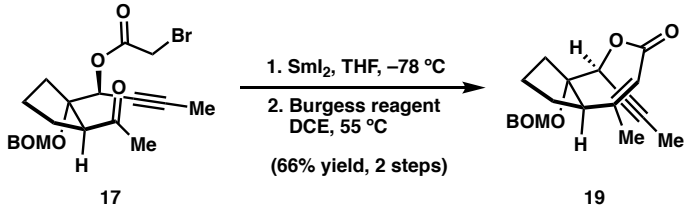
flash chromatography (15% EtOAc/hexanes) to afford propargyl alcohol **12** (646 mg, 2.05 mmol, 70% yield) as a thick, colorless oil.

TLC (15% EtOAc/hexanes): R_f 0.26 (UV, *p*-anisaldehyde).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 4H), 7.30 (m, 1H), 5.11 (d, *J* = 7.6 Hz, 1H), 4.95 (d, *J* = 7.6 Hz, 1H), 4.92 (p, *J* = 1.6 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.82 (dt, *J* = 1.9, 1.0 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.27 (dq, *J* = 7.9, 2.3 Hz, 1H), 3.73 (d, *J* = 7.9 Hz, 1H, OH), 2.75 (t, *J* = 6.4 Hz, 1H), 2.06 – 1.90 (m, 3H), 1.87 (s, 3H), 1.82 (d, *J* = 2.2 Hz, 3H), 1.81 – 1.75 (m, 2H).

LRMS (APCI): calc'd for $[M+2Na]^+$ 360.2, found 360.2.

Preparation of lactone 19



An oven-dried, 100 mL round-bottomed flask was charged with bromoacetate **17** (718 mg, 1.64 mmol, 1.0 equiv) and anhydrous THF (16 mL). The solution was cooled to –78 ºC via a dry ice/acetone bath and stirring was continued for 15 min prior to the dropwise addition of freshly prepared SmI_2 (0.1 M in THF, 33 mL, 3.28 mL, 2.0 equiv) via syringe. The reaction was continued at –78 ºC until complete consumption of the starting material was observed by TLC (*ca.* 1 h). Sat. aq. $NaHCO_3$ (12 mL) and sat. aq. Rochelle's salt (12 mL) were subsequently added and the mixture was warmed to ambient temperature, diluted with EtOAc (10 mL), and the layers separated. The aqueous

layer was extracted with EtOAc (3 × 30 mL). The combined layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (20 to 30% EtOAc/hexanes to provide an inseparable 2:1 diastereomic mixture of lactones **18** (400 mg, 1.11 mmol, 68% yield) that were carried forward without further purification.

In a nitrogen-filled glovebox, an oven-dried, 48 mL pressure flask was charged with the aforementioned lactone mixture **18** (400 mg, 1.11 mmol, 1.0 equiv) and anhydrous DCE (11 mL). The solution was next treated with Burgess reagent (346 mg, 1.45 mmol, 1.3 equiv) and the flask was then capped with a CAPFE O-ring lined cap, removed from the glovebox, and placed in preheated oil bath at 55 ºC. The reaction was allowed 3 h at 55 ºC before it was removed from the oil bath and cooled to ambient temperature. The reaction was diluted with CH_2Cl_2 (10 mL) and filtered through a pre-equilibrated SiO_2 pad layered with Na_2SO_4, washing with 70% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified by SiO_2 flash chromatography (20 to 30% EtOAc/hexanes) to afford lactone **19** (372 mg, 1.09 mmol, 98% yield) as a thick, cloudy oil.

TLC (30% EtOAc/hexanes): R_f 0.33 (UV, *p*-anisaldehyde).

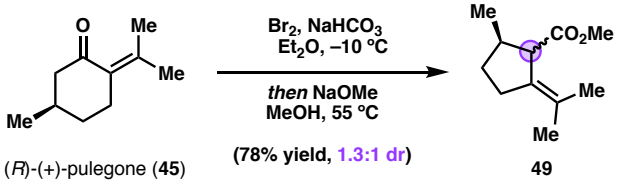
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 4H), 7.29 (m, 1H), 5.80 (p, *J* = 1.3 Hz, 1H), 5.10 (q, *J* = 2.3 Hz, 1H), 5.05 (d, *J* = 7.6 Hz, 1H), 4.99 (d, *J* = 7.6 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 2.94 (t, *J* = 8.6 Hz, 1H), 2.27 (m, 1H), 2.18 (ddd, *J* = 13.3, 7.5, 5.4 Hz, 1H), 2.06 (m, 1H), 1.95 (d, *J* = 1.2 Hz, 3H), 1.84 (d, *J* = 2.3 Hz, 3H), 1.76 – 1.67 (m, 2H), 1.47 (dq, *J* = 12.9, 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 155.3, 137.7, 128.4, 127.8, 127.7, 116.8, 90.5, 88.3, 85.6, 74.0, 70.7, 70.2, 54.8, 41.3, 34.5, 25.9, 22.2, 3.7.

FTIR (NaCl, thin film): 2958, 1707, 1438, 1380, 1274, 1057, 1024, 738 cm^{-1}.

HRMS (FAB): calc'd for $[M+H]^+$ 341.1753, found 341.1748.

Preparation of methyl pulegenate (49)



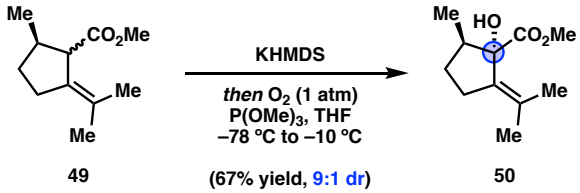
(*R*)-(+)-pulegone (**45**) **49**

According to the one-step procedure[18] of Zhang and coworkers, an oven-dried, 250 mL round-bottomed flask was charged with distilled (*R*)-(+)-pulegone (30.0 g, 197 mol, 1.0 equiv), anhydrous Et_2O (150 mL), and $NaHCO_3$ (4.97 g, 59.1 mmol, 0.3 equiv). The suspension was cooled to –10 ºC via an ice/acetone bath, then treated with Br_2 (11.1 mL, 217 mmol, 1.1 equiv) dropwise over 30 min via syringe pump. Upon complete addition, the reaction mixture was vigorously stirred for 2.5 h at –10 ºC and then transferred via cannula over 30 min to a freshly generated solution of NaOMe in MeOH–prepared from 9.96 g Na^0 (433 mmol, 2.2 equiv) and 200 mL anhydrous MeOH in an oven-dried, 1 L two-necked round-bottomed flask–at 0 ºC under Ar. The resulting white slurry was warmed to ambient temperature, then the flask was equipped with a reflux condenser and placed in a preheated oil bath at 55 ºC. The reaction mixture was stirred at

55 ºC for 4 h before cooling to ambient temperature, then further cooled to 0 ºC via an ice/water bath before diluting with Et_2O (100 mL) and quenching with the *careful* addition of sat. aq. NH_4Cl (450 mL). The mixture was warmed to ambient temperature, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined layers were washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (2.5 to 5 to 10% Et_2O/hexanes) to afford methyl pulegenate (30.1 g, 153 mmol, 78% combined yield) as an inseparable 1.3:1 diastereomeric mixture.

Spectral data of the diastereomeric mixture of methyl pulegenates matched that previously reported.[62]

Preparation of hydroxyester 50



In a nitrogen-filled glovebox, an oven-dried, 1 L round-bottomed flask was charged with solid KHMDS (95%, 21.4 g, 102 mmol, 2.0 equiv). The flask was capped with a rubber septum, removed from the glovebox, and anhydrous THF (250 mL) was added. The resulting mixture was stirred at ambient temperature for 10-15 min to ensure complete dissolution of the solids, then cooled to –78 ºC in a dry ice/acetone bath and stirring continued for 15 min before adding methyl pulegenate (10.0 g, 50.9 mmol, 1.0 equiv) in anhydrous THF (150 mL) dropwise via cannula over 30 min, before another

portion of THF (50 mL) was used to render the transfer quantitative. The bright-yellow reaction mixture was then warmed to –10 ºC via an ice/acetone bath and stirring continued for an additional 20 min, which was next cooled again to –78 ºC. The flask was then evacuated/refilled three times with O_2 supplied via a double-walled balloon, after which, in quick succession, $P(OMe)_3$ (12 mL, 102 mmol, 2.0 equiv) was added via syringe. The reaction was vigorously stirred (>650 rpm) under O_2 for 45 min at –78 ºC and then warmed to –10 ºC via an ice/acetone bath and continued stirring for 15 min, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was diluted with Et_2O (50 mL), quenched with sat. aq. NH_4Cl (200 mL) and sat. aq. $Na_2S_2O_3$ (50 mL), then warmed to ambient temperature. The layers were separated and the aqueous layer was then extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered over a short, pre-equilibrated SiO_2 pad, washing with 50% EtOAc/hexanes, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product indicated that the reaction occurs with full consumption of the starting material in a 9:1 diastereomeric ratio. Purification by SiO_2 flash chromatography (5 to 10 to 20% EtOAc/hexanes) afforded α-hydroxyester **50** as a clear oil (6.77 g, 34.1 mmol, 67% yield).

TLC (20% EtOAc/hexanes): R_f 0.44 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 2.48 – 2.37 (m, 2H), 2.20 (dt, *J* = 13.3, 6.8 Hz, 1H), 1.81 (dtd, *J* = 13.0, 6.6, 2.6 Hz, 1H), 1.65 (s, 3H), 1.63 (t, *J* = 2.1 Hz, 3H), 1.57 – 1.46 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H).

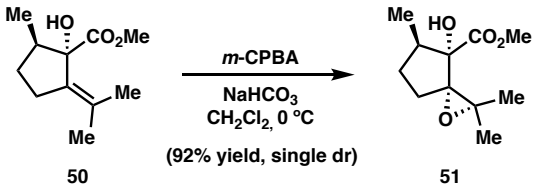
^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7, 135.9, 129.5, 83.9, 52.5, 48.4, 30.0, 29.8, 22.4, 19.5, 13.4.

FTIR (NaCl, thin film): 3516, 2953, 2874, 1719, 1459, 1437, 1371, 1313, 1236, 1178, 1146, 1117, 1063 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M-OH]^+$ 181.1223, found 181.1221.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +9° (*c* = 0.905, $CHCl_3$).

Preparation of epoxide 51



An oven dried, 500 mL round-bottomed flask was charged with alkene **50** (7.28 g, 36.7 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (180 mL). The solution was cooled to 0 ºC via an ice/water bath and then treated with $NaHCO_3$ (12.3 g, 147 mmol, 4.0 equiv) and *m*-CPBA (77% w/w, 12.3 g, 55.1 mmol, 1.5 equiv) [Note: *m*-CPBA was dried *in vacuo* for >12 h prior to use to remove H_2O]. The suspension was vigorously stirred at 0 ºC for 1 h before an additional portion of *m*-CPBA (77% w/w, 4.11 g, 18.4 mmol, 0.5 equiv) was added. Stirring was continued for an additional 1 h after which TLC analysis indicated the complete consumption of starting material. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with the addition of sat. aq. $NaHCO_3$ (100 mL) and sat. aq. $Na_2S_2O_3$ (100 mL). The resulting mixture was warmed to room temperature and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (200

mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (15 to 25 to 35% EtOAc/hexanes) to afford epoxide **51** (7.24 g, 13.9 mmol, 92% yield) as a colorless oil.

TLC (20% EtOAc/hexanes): R_f 0.23 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H), 2.94 (br s, 1H), 2.31 – 2.22 (m, 1H), 2.23 – 2.16 (m, 1H), 1.91 – 1.78 (m, 2H), 1.56 – 1.44 (m, 1H), 1.32 (s, 3H), 1.21 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H).

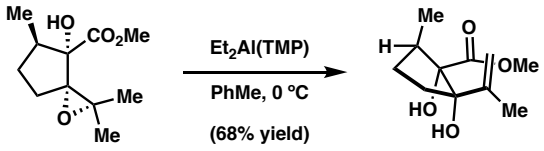
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1, 81.6, 74.1, 63.1, 51.8, 47.7, 28.9, 27.2, 22.5, 19.2, 14.1.

FTIR (NaCl, thin film): 3480, 2957, 2876, 1756, 1723, 1463, 1436, 1377, 1238, 1187, 1142, 1068, 1005 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+H]^+$ 215.1278, found 215.1281.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}} = -2°$ (c = 0.770, $CHCl_3$).

Preparation of diol 52



51 52

An oven-dried, 500 mL round-bottomed flask was charged with 2,2,6,6-tetramethylpiperidine (16 mL, 93.3 mmol, 2.5 equiv) and anhydrous PhMe (45 mL). The solution was cooled to 0 ºC via an ice/water bath and then *n*-BuLi (2.5 M in hexanes, 36 mL, 89.6 mmol, 2.4 equiv) was added dropwise via syringe. After 30 mins of continued

stirring at 0 ºC, the solution of LiTMP was treated with Et_2AlCl (1.0 M in hexanes, 90 mL, 89.6 mmol, 2.4 equiv) dropwise via syringe and stirring was continued for another 30 mins at 0 ºC affording a cloudy pale-yellow solution. Epoxide **51** (8.00 g, 37.3 mmol, 1.0 equiv) in anhydrous PhMe (45 mL) was next added dropwise via cannula over 15 min to the freshly generated slurry of $Et_2Al(TMP)$, before another portion of PhMe (15 mL) was used to render the transfer quantitative. Upon complete addition, the reaction mixture was allowed 1.5 h at 0 ºC at which time TLC analysis indicated the consumption of starting material. The reaction was quenched with the *careful* addition of sat. aq. Rochelle's salt (180 mL), diluted with EtOAc (50 mL) and warmed to ambient temperature. The mixture was next vigorously stirred until two clear layers were observed, then the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 180 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (20 to 30% EtOAc/hexanes) to afford diol **52** (5.44 g, 25.4 mmol, 68% yield) as a yellow oil.

TLC (20% EtOAc/hexanes): R_f 0.25 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89 (d, *J* = 1.0 Hz, 1H), 4.84 (s, 1H), 3.77 (d, *J* = 2.4 Hz, 3H), 3.09 (dd, *J* = 2.2, 0.6 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.45 – 2.36 (m, 1H), 2.11 – 2.01 (m, 1H), 1.90 (ddd, *J* = 14.3, 10.1, 4.2 Hz, 1H), 1.76 (dd, *J* = 1.5, 0.7 Hz, 3H), 1.54 – 1.43 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H).

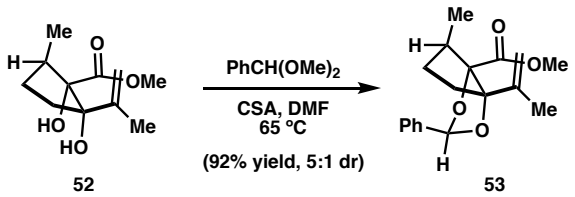
^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 146.5, 111.9, 89.5, 84.3, 52.7, 41.9, 32.9, 27.2, 19.9, 14.2.

FTIR (NaCl, thin film): 3500, 2955, 2876, 1732, 1722, 1717, 1456, 1436, 1242, 1204, 1124, 1051 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+H]^+$ 215.1278, found 215.1279.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}} = -11°$ (c = 0.560, $CHCl_3$).

Preparation of benzylidene acetal 53



An oven-dried, 200 mL round-bottomed flask was charged with diol **52** (3.85 g, 18.0 mmol, 1.0 equiv) and anhydrous DMF (110 mL). The solution was treated with benzaldehyde dimethyl acetal (8.1 mL, 53.9 mmol, 3.0 equiv) and (±)-10-camphorsulfonic acid (4.17 g, 18.0 mmol, 1.0 equiv). The flask was then equipped with a reflux condenser and the headspace was evacuated/refilled with Ar three times. The reaction mixture was placed in a preheated oil bath at 65 ºC and stirred for 24 h at which point an additional portion of benzaldehyde dimethyl acetal (2.7 mL, 18.0 mmol, 1.0 equiv) was added. After another 24 h of stirring at 65 ºC, an additional portion of benzaldehyde dimethyl acetal (2.7 mL, 18.0 mmol, 1.0 equiv) was added and the reaction was continued for another 24 h, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was cooled to ambient temperature, diluted with Et_2O (50 mL), and *carefully* quenched with sat. aq. $NaHCO_3$ (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with H_2O (80 mL), then brine (80

mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product indicated that the reaction occurs with full consumption of the starting material in a 5:1 diastereomeric ratio. Purification by SiO_2 flash chromatography (2.5 to 5 to 10% EtOAc/hexanes) afforded benzylidene acetal **53** (4.99 g, 16.5 mmol, 92% yield) as a yellow oil.

TLC (20% EtOAc/hexanes): R_f 0.70 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.52 (m, 2H), 7.39 (dt, *J* = 5.2, 1.7 Hz, 3H), 6.12 (d, *J* = 1.3 Hz, 1H), 5.14 (s, 1H), 5.04 (d, *J* = 1.4 Hz, 1H), 3.75 (s, 3H), 2.59 (q, *J* = 6.9 Hz, 1H), 2.39 – 2.21 (m, 2H), 2.13 – 2.04 (m, 1H), 1.88 (s, 3H), 1.65 (td, *J* = 6.2, 5.4, 3.9 Hz, 1H), 1.08 (dd, *J* = 7.3, 1.3 Hz, 3H).

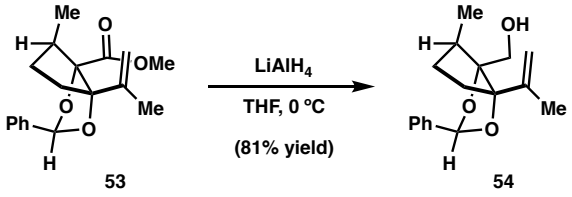
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 143.4, 136.9, 129.5, 128.4, 126.8, 113.1, 104.9, 97.6, 96.7, 51.8, 44.9, 35.0, 31.7, 20.5, 15.1.

FTIR (NaCl, thin film): 2949, 2876, 1735, 1457, 1435, 1395, 1259, 1221, 1116, 1089, 1063, 1027 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M+H]^+$ 303.1591, found 303.1598.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}} = -39°$ (*c* = 0.590, $CHCl_3$).

Preparation of alcohol 54



53 54

An oven-dried, 500 mL round-bottomed flask was treated with methyl ester **53** (5.98 g, 18.0 mmol, 1.0 equiv) and anhydrous THF (180 mL). The solution was cooled to 0 ºC via an ice/water bath and then carefully treated with $LiAlH_4$ (1.37 g, 36.0 mmol, 2.0 equiv) in a portion-wise fashion. The resulting grey slurry was vigorously stirred for 1.5 h at 0 ºC, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was next *carefully* treated with EtOAc (20 mL) followed by sat. aq. Rochelle's salt (75 mL). The cooling bath was removed and the mixture was vigorously stirred overnight at ambient temperature. The resulting two layers were separated and the aqueous layer extracted with EtOAc (4 × 80 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (10 to 20 to 30% EtOAc/hexanes) to afford alcohol **54** (4.01 g, 14.6 mmol, 81% yield) as a thick, colorless oil.

TLC (20% EtOAc/hexanes): R_f 0.22 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.53 (m, 2H), 7.45 – 7.36 (m, 3H), 5.82 (d, *J* = 1.1 Hz, 1H), 5.28 – 5.19 (m, 1H), 5.08 (t, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 12.2, 2.2 Hz, 1H), 3.76 – 3.62 (m, 1H), 2.51 (p, *J* = 7.3 Hz, 1H), 2.40 (tt, *J* = 12.8, 6.5 Hz, 1H), 2.18

(td, J = 13.5, 6.4 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.88 (dd, J = 1.5, 0.8 Hz, 3H), 1.46 (dd, J = 12.3, 6.4 Hz, 1H), 1.07 (dd, J = 7.5, 1.1 Hz, 3H).

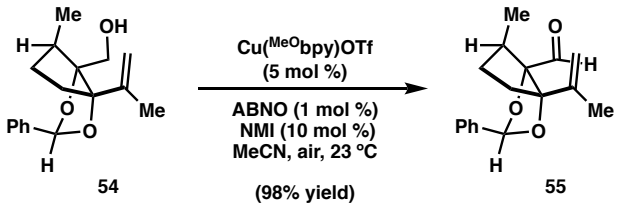
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.1, 136.4, 129.8, 128.5, 126.9, 113.2, 101.4, 97.2, 94.9, 60.7, 40.8, 36.4, 29.6, 20.7, 14.5.

FTIR (thin film, NaCl): 3465, 2962, 2876, 1460, 1453, 1397, 1310, 1220, 1125, 1088, 1061, 1027 cm^{-1}.

HRMS (MM:ESI–APCI): calc'd for $[M]^+$ 274.1563, found 274.1564.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = −17° (c = 0.895, $CHCl_3$).

Preparation of aldehyde 55



An oven-dried, 200 mL round-bottomed flask was charged with alcohol **54** (2.27 g, 8.27 mmol, 1.0 equiv) and anhydrous MeCN (83 mL). The solution was vigorously stirred (>700 rpm) open to air while being treated with ^{MeO}bpy (89 mg, 0.41 mmol, 0.05 equiv), $Cu(MeCN)_4OTf$ (156 mg, 0.41 mmol, 0.05 equiv), ABNO (11.6 mg, 82.7 μmol, 0.01 equiv), and then NMI (66 μL, 0.83 mmol, 0.10 equiv) via microsyringe. The resulting brick-red reaction mixture was vigorously stirred exposed to air at ambient temperature until the reaction mixture turned a blue-green (*ca.* 1.75 h), at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was diluted with Et_2O (40 mL), and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 50% EtOAc/hexanes. The filtrate was concentrated *in*

vacuo and the crude residue was directly purified by SiO_2 flash chromatography (5 to 7.5 to 10% EtOAc/hexanes) to afford aldehyde **55** (2.21 g, 8.10 mmol, 98% yield) as a pale yellow oil.

TLC (20% EtOAc/hexanes): R_f 0.52 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.57 (m, 2H), 7.41 (m, 3H), 5.98 (s, 1H), 5.30 (t, *J* = 0.9 Hz, 1H), 5.11 (p, *J* = 1.4 Hz, 1H), 2.56 (tddd, *J* = 8.8, 7.5, 6.4, 1.7 Hz, 1H), 2.49 – 2.34 (m, 2H), 2.05 (m, 1H), 1.87 (dd, *J* = 1.5, 0.7 Hz, 3H), 1.59 (m, 1H), 1.20 (d, *J* = 7.6 Hz, 3H).

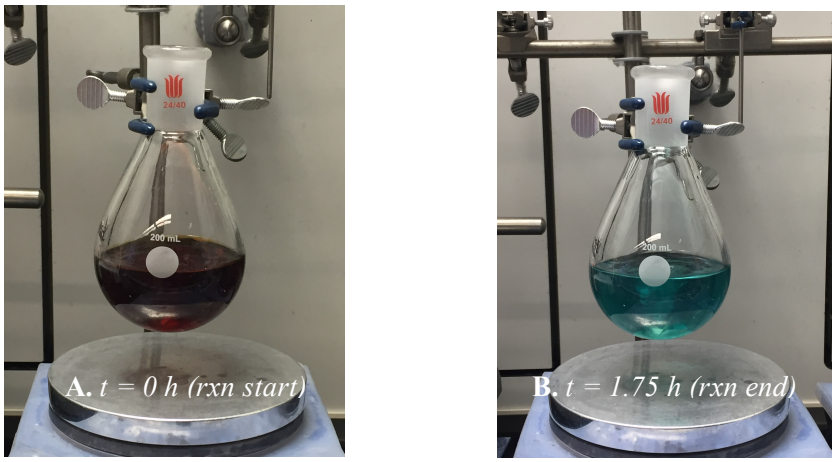
^{13}C NMR (101 MHz, $CDCl_3$): δ 200.7, 142.6, 136.2, 129.8, 128.4, 126.7, 114.5, 104.6, 97.4, 97.3, 43.5, 35.9, 31.9, 20.5, 14.5.

FTIR (NaCl, thin film): 2965, 2875, 1733, 1456, 1398, 1312, 1221, 1133, 1087, 1060, 1026 cm^{-1}.

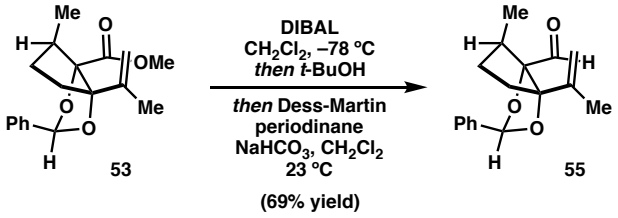
HRMS (MM:ESI–APCI): calc'd for $[M]^+$ 272.1407, found 272.1405.

$[\alpha]_D^{25} = -31°$ (*c* = 0.285, $CHCl_3$).

Figure 15. *Progression of Stahl's Cu-catalyzed aerobic oxidation of alcohol* ***54***

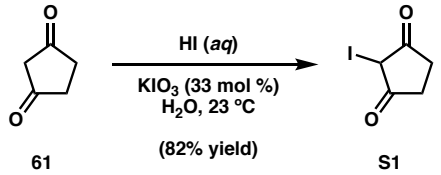


One-pot conversion of ester 53 to aldehyde 55



A flame-dried, 25 mL round-bottomed flask was charged with methyl ester **53** (44.0 mg, 146 μmol, 1.0 equiv) and anhydrous CH_2Cl_2 (4.9 mL). The resulting solution was cooled to –78 ºC via a dry ice/acetone bath and stirring was continued for 15 min prior to the dropwise addition of DIBAL (1.0 M in hexanes, 0.36 mL, 364 μmol, 2.5 equiv) via syringe. The reaction was continued at –78 ºC for 1 h at which point TLC analysis indicated the complete consumption of starting material. *Tert*-butanol (0.14 mL, 1.46 mmol, 10 equiv) was added, and the reaction was removed from the cooling bath and warmed to ambient temperature. Stirring was continued for 1 h before $NaHCO_3$ (122 mg, 1.46 mmol, 10 equiv) and Dess-Martin periodinane (216 mg, 509 μmol, 3.5 equiv) were added. The reaction was continued at ambient temperature until complete consumption of intermediate alcohol **54** was observed by TLC analysis. Sat. aq. $NaHCO_3$ (2 mL) and sat. aq. Rochelle's salt (1 mL) were added and the mixture was vigorously stirred until two clear layers were observed. The mixture was diluted with Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (4 × 5 mL) and the combined organic layers were washed with sat. aq $NaHCO_3$ (2 mL), brine (2 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via repeated SiO_2 flash chromatography (3 to 5 to 7 to 10% EtOAc/hexanes) to afford aldehyde **55** (27.3 mg, 100 μmol, 69% yield) as a pale yellow oil.

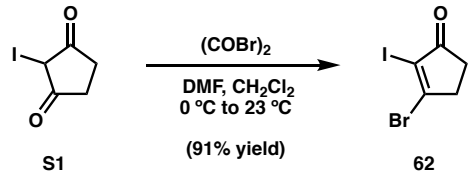
Preparation of iodocyclopentanedione S1



An oven-dried, 200 mL round-bottomed flask was charged with 1,3-cyclopentanedione (5.70 g, 58.1 mmol, 1.0 equiv) and deionized H_2O (30 mL). The resulting slurry was treated with HI (*aq*) (57% w/w, 7.8 mL, 59.3 mmol, 1.02 equiv) via syringe and then KIO_3 (4.11 g, 19.1 mmol, 0.33 equiv) in H_2O (30 mL) [Note: KIO_3 does not readily dissolve in H_2O and heating was required to affect complete dissolution] was added dropwise via cannula. Upon complete addition, the resulting mixture was vigorously stirred (950 rpm) for 15 min at ambient temperature before diluting with H_2O (30 mL) and filtering through a Büchner funnel lined with filter paper. The brown solid was washed with H_2O (3 × 125 mL), air-dried, then collected and further dried *in vacuo* (>6 h) to remove H_2O. Crude iodocyclopentanedione **XX** (11.2 g, 50.0 mmol, 86% yield) was used directly in the next step without further purification.

Spectral data of iodocyclopentanedione (**S1**) matched that previously reported.[25]

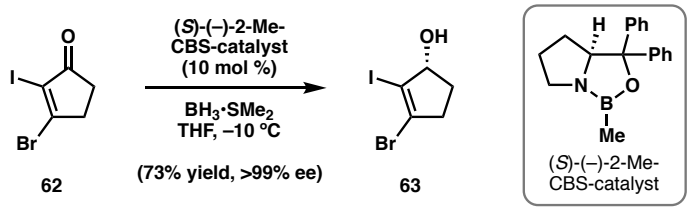
Preparation of iodobromocyclopentenone 62



An oven-dried, 250 mL round-bottomed flask was charged with iodocyclopentanedione **S1** (8.0 g, 35.7 mmol, 1.0 equiv), anhydrous CH_2Cl_2 (120 mL), and anhydrous DMF (4.2 mL, 53.6 mmol, 1.5 equiv). The slurry was cooled to 0 ºC via an ice/water bath and then treated dropwise with oxalyl bromide (4.36 mL, 46.4 mmol, 1.3 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 40 min before pouring the reaction mixture over Et_2O (120 mL) and ice-cold H_2O (60 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 120 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (60 mL), brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (20 to 30% EtOAc/hexanes) to afford iodobromocyclopentenone **62** (9.29 g, 32.4 mmol, 91% yield) as a white solid [Note: solid **62** tends to discolor over time to a pale yellow-orange; although this discoloration does not affect the subsequent step, the solid was routinely stored at –20 ºC wrapped in aluminum foil to prevent exposure from light].

Spectral data of iodobromocyclopentanone **62** matched that previously reported.[25]

Preparation of enantioenriched cyclopentenol 63



An oven-dried, 500 mL round-bottomed flask was charged with (*S*)-(–)-2-Me-CBS-oxazaborolidine (726 mg, 2.62 mmol, 0.10 equiv) and anhydrous THF (120 mL). The resulting solution was cooled to –10 ºC via an ice/acetone bath. After 15 min of continued stirring, BH_3•SMe_2 (2.0 M in THF, 19.6 mL, 26.1 mmol, 1.5 equiv) was added dropwise via syringe. The reaction mixture was stirred an additional 15 min at –10 ºC before adding cyclopentenone **62** (7.95 g, 26.2 mmol, 1.0 equiv) in anhydrous THF (100 mL) dropwise over 1 h via cannula before another portion of THF (20 mL) was used to render the transfer quantitative. Upon complete addition, the reaction mixture was continued for an additional 15 min at –10 ºC, then diluted with Et_2O (50 mL) and quenched with the *careful* addition of MeOH (20 mL) followed by 1 N NaOH (*aq*) (80 mL) [Caution! Rapid generation of H_2. A vent needle was routinely used to prevent over-pressurization.], before warming to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (25 to 35% EtOAc/hexanes) to afford cyclopentenol **63** (7.48 g, 25.9 mmol, 99% yield, 80% ee) as a white solid, that was recrystallized from 10% Et_2O/hexanes (200 mL) to afford enantioenriched cyclopentenol **63** (5.84 g, 20.2 mmol, 73% yield, >99% ee) as white needles. The ee was

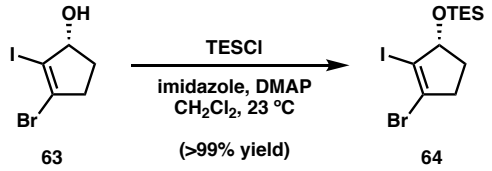
determined by SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (minor) = 4.214 min, t_R (major) = 4.570 min.

Recrystallization was performed by heating the suspension with a heat gun until complete dissolution was observed, then allowing the resulting solution to cool to ambient temperature (*ca.* 45 min). The solution was then further cooled to 0 ºC for 1-2 h to afford white needles. The Et_2O/hexanes layer was decanted, and the resulting solid was washed with ice-cold pentanes (3 × 20 mL) and then dried *in vacuo* prior to use.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +32° (*c* = 1.00, $CHCl_3$).

Spectral data of iodobromocyclopentenol **63** matched that previously reported.[25]

Preparation of TES ether 64



An oven-dried, 250 mL round-bottomed flask was charged with cyclopentenol **63** (5.75 g, 14.7 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (75 mL). The solution was treated with TESCl (4.94 mL, 29.4 mmol, 2.0 equiv), imidazole (4.01 g, 58.8 mmol, 4.0 equiv), and then DMAP (1.80 g, 14.7 mmol, 1.0 equiv) at ambient temperature. After 30 min of continued stirring, TLC analysis indicated the complete consumption of starting material and the reaction mixture was diluted with CH_2Cl_2 (25 mL) and then carefully quenched with sat. aq. NH_4Cl (100 mL). The layers were separated and the aqueous layer was

extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with brine (75 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (0 to 1 to 3% EtOAc/hexanes) to afford TES ether **64** (5.93 g, 14.7 mmol, >99% yield) as a colorless oil.

TLC (1/1% Et_2O/CH_2Cl_2/hexanes): R_f 0.34 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 (dddd, *J* = 7.4, 4.5, 2.6, 1.3 Hz, 1H), 2.81 (dddd, *J* = 16.2, 9.3, 3.6, 2.6 Hz, 1H), 2.57 (dddd, *J* = 16.1, 8.9, 5.8, 1.3 Hz, 1H), 2.39 (dddd, *J* = 13.1, 8.9, 7.5, 3.6 Hz, 1H), 1.95 (dddd, *J* = 13.0, 9.4, 5.8, 4.5 Hz, 1H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.70 – 0.64 (m, 6H).

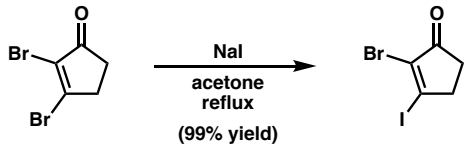
^{13}C NMR (101 MHz, $CDCl_3$): δ 133.7, 105.6, 81.3, 38.7, 33.8, 6.9, 4.9.

FTIR (NaCl, thin film): 2954, 2910, 2876, 1604, 1114, 831 cm^{-1}.

HRMS (FAB): calc'd for $[(M+H)–H_2]^+$ 402.9413, found 402.9423.

$[\alpha]_D^{25}$ = +16° (*c* = 2.09, $CHCl_3$).

Preparation of iodobromocyclopentenone 66



65 66

An oven-dried, 250 mL round-bottomed flask was charged with known dibromoenone **65**[26] (7.00 g, 29.2 mmol, 1.0 equiv), NaI (43.8 g, 292 mmol, 10 equiv), and acetone (146 mL). The flask was immediately equipped with a reflux condenser and then placed in a preheated oil bath at 68 ºC. The reaction was continued at 68 ºC

overnight (14 h) and then cooled to ambient temperature. The reaction was diluted with Et_2O (50 mL), filtered over Celite, and concentrated *in vacuo*. The filtrate was partitioned between Et_2O (200 mL) and H_2O (200 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined layers were washed with sat. aq. $Na_2S_2O_3$ (150 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (20 to 30% EtOAc/hexanes) to afford iodobromocyclopentenone **66** (8.38 g, 29.2 mmol, 99% yield) as an off-white solid.

TLC (30% EtOAc/hexanes): R_f 0.43 (UV, *p*-anisaldehyde).

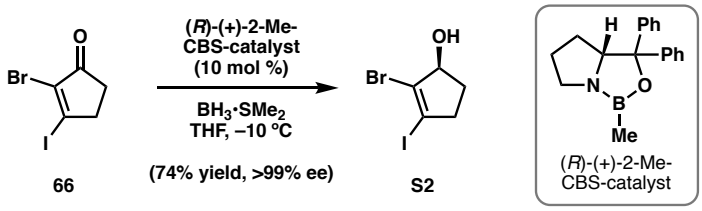
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 – 2.92 (m, 2H), 2.72 – 2.44 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.5, 137.3, 135.8, 39.8, 35.4.

FTIR (NaCl, thin film): 1694, 1557, 1237, 1203, 938, 816, 732 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 286.8563, found 286.8555.

Preparation of iodobromocyclopentenol S2



An oven-dried, 500 mL round-bottomed flask was charged with (*R*)-(+)-2-Me-CBS-oxazaborolidine (858 mg, 3.09 mmol, 0.10 equiv) and anhydrous THF (60 mL). The resulting solution was cooled to –10 ºC via an ice/acetone bath. After 15 min of continued stirring, BH_3•SMe_2 (2.0 M in THF, 23.2 mL, 46.4 mmol, 1.5 equiv) was added dropwise via syringe. The reaction mixture was stirred an additional 15 min at –10 ºC

before adding cyclopentenone **66** (8.88 g, 31.0 mmol, 1.0 equiv) in anhydrous THF (60 mL) dropwise over 1 h via cannula before another portion of THF (30 mL) was used to render the transfer quantitative. Upon complete addition, the reaction mixture was continued for an additional 15 min at –10 ºC, then diluted with Et_2O (50 mL) and quenched with the *careful* addition of MeOH (40 mL) followed by 1 N NaOH (*aq*) (90 mL) [Caution! Rapid generation of H_2. A vent needle was routinely used to prevent over-pressurization.], before warming to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 90 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (25 to 35% EtOAc/hexanes) to afford cyclopentenol **S2** (8.95 g, 31.0 mmol, 99% yield) as a white solid, which was recrystallized according to the procedure for **63** from 10% Et_2O/hexanes (200 mL) to afford enantioenriched cyclopentenol **S2** (6.60 g, 22.8 mmol, 74% yield, >99% ee) as white needles. The ee was determined by SFC analysis.

TLC (30% EtOAc/hexanes): R_f 0.41 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65 (ddddd, *J* = 7.8, 5.3, 3.9, 2.4, 1.1 Hz, 1H), 2.81 (dddd, *J* = 16.3, 9.1, 3.9, 2.5 Hz, 1H), 2.60 (dddd, *J* = 16.3, 8.9, 5.2, 1.2 Hz, 1H), 2.45 (m, 1H), 2.42 (d, *J* = 5.3 Hz, 1H, OH), 1.96 (dddd, *J* = 13.5, 9.4, 5.2, 4.3 Hz, 1H).

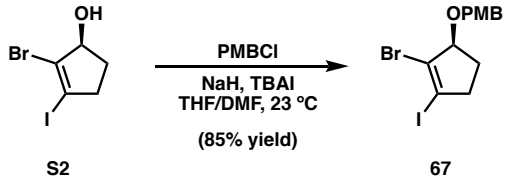
^{13}C NMR (101 MHz, $CDCl_3$): δ 134.1, 102.8, 78.2, 41.3, 33.0.

FTIR (NaCl, thin film): 3318, 2940, 1601, 1434, 1302, 1152, 1103, 1062 cm^{-1}.

HRMS (FAB): calc'd for $[(M+H)–H_2]^+$ 286.8569, found 286.8563.

$[\alpha]_D^{25}$ = –19° (*c* = 3.84, $CHCl_3$).

Preparation of PMB ether 67



S2 **67**

An oven-dried, 500 mL round-bottomed flask was charged with alcohol **S2** (7.44 g, 25.8 mmol, 1.0 equiv), anhydrous THF (65 mL), and anhydrous DMF (65 mL). The solution was cooled to 0 ºC via an ice/water bath and stirring continued for 15 min prior to the portionwise addition of NaH (60% dispersion in mineral oil, 2.06 g, 1.24 mmol, 2.0 equiv). The reaction was continued at 0 ºC for 45 min prior to the addition of PMBCl (4.5 mL, 33.5 mmol, 1.3 equiv) via syringe. The reaction was warmed to ambient temperature and then treated with TBAI (2.85 g, 7.73 mmol, 0.3 equiv). Stirring was continued at ambient temperature overnight (*ca*. 13 h) before quenching the reaction mixture with the addition of sat. aq. NH_4Cl (100 mL). The mixture was diluted with Et_2O (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via two rounds of SiO_2 flash chromatography (1st column: 50% CH_2Cl_2/hexanes; 2nd column: 7.5 to 10 to 15% EtOAc/hexanes) to afford PMB ether **67** (8.95 g, 21.9 mmol, 85% yield) as a golden yellow oil that solidified upon storage at –20 ºC. [Note: the 1st column is carefully run to remove excess PMBCl, whereas the 2nd column is run to remove any remaining side products generated from the reaction].

TLC (10% EtOAc/hexanes): R_f 0.44 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 2H), 6.88 (m, 2H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.46 (dddd, *J* = 7.8, 3.6, 2.7, 1.0 Hz, 1H), 3.81 (s, 3H), 2.81 (dddd, *J* = 16.3, 9.0, 4.7, 2.7 Hz, 1H), 2.58 (dddd, *J* = 16.3, 9.0, 4.4, 1.0 Hz, 1H), 2.31 (dddd, *J* = 13.6, 9.0, 7.8, 4.7 Hz, 1H), 2.05 (dddd, *J* = 13.5, 9.0, 4.4, 3.5 Hz, 1H).

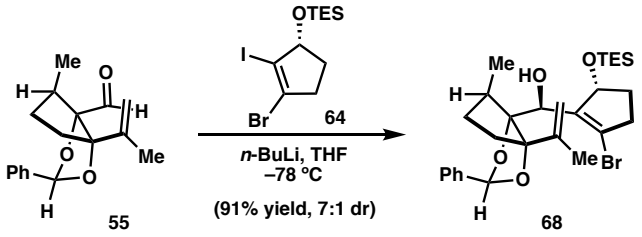
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 131.8, 130.0, 129.4, 113.8, 104.1, 84.2, 70.6, 55.3, 41.7, 31.0.

FTIR (NaCl, thin film): 2914, 1606, 1442, 1243, 1030, 814 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 425.9560, found 425.9571.

$[\alpha]_D^{25}$ = –11° (*c* = 0.460, $CHCl_3$).

Convergent union of aldehyde 55 and iodobromocyclopentenol 64



An oven-dried, 200 mL round-bottomed flask was charged with vinyl iodide **64** (2.02 g, 5.01 mmol, 1.3 equiv) and anhydrous THF (40 mL) [Note: vinyl iodide **64** was azeotroped with PhH three times immediately prior to use]. The solution was cooled to –78 ºC via a dry ice/acetone bath and stirring continued for 15 min prior to the dropwise addition of *n*-BuLi (2.5 M in hexanes, 2.0 mL, 5.01 mmol, 1.3 equiv) via syringe. Upon complete addition, the reaction mixture was stirred an additional 15 min. Aldehyde **55** (1.99 g, 3.86 mmol, 1.0 equiv) in anhydrous THF (30 mL) was added dropwise via cannula over 15 min [Note: aldehyde **55** was azeotroped with PhH three times

immediately prior to use], before another portion of THF (10 mL) was used to render the transfer quantitative. After another 30 min at –78 ºC, TLC analysis indicated the complete consumption of starting material. The reaction mixture was quenched with the addition of sat. aq. NH_4Cl (10 mL) and then warmed to ambient temperature and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product indicated that the reaction occurs with full consumption of the starting material in a 7:1 diastereomeric ratio. Purification via SiO_2 flash chromatography (3 to 5 to 9% Et_2O/hexanes) afforded alcohol **68** (1.93 g, 3.51 mmol, 91% yield) as a slightly-yellow oil.

TLC (20% Et_2O/hexanes): R_f 0.33 (UV, *p*-anisaldehyde).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (m, 2H), 7.38 (m, 3H), 6.22 (s, 1H), 5.32 (dt, *J* = 6.9, 1.8 Hz, 1H), 5.20 (p, *J* = 1.4 Hz, 1H), 5.04 (t, *J* = 1.0 Hz, 1H), 4.92 (d, *J* = 7.5 Hz, 1H), 3.76 (d, *J* = 7.5 Hz, 1H), 2.91 (dddd, *J* = 17.0, 8.2, 6.8, 2.2 Hz, 1H), 2.57 (ddd, *J* = 16.7, 9.0, 2.6 Hz, 1H), 2.42 (tt, *J* = 12.6, 6.2 Hz, 1H), 2.16 – 2.08 (m, 3H), 2.12 (dd, *J* = 1.5, 0.7 Hz, 3H), 2.01 (dd, *J* = 13.9, 6.7 Hz, 1H), 1.84 (dddd, *J* = 13.8, 8.2, 2.5, 1.6 Hz, 1H), 1.37 (dd, *J* = 12.0, 6.0 Hz, 1H), 0.93 (d, *J* = 7.4 Hz, 3H), 0.78 (t, *J* = 7.9 Hz, 9H), 0.51 – 0.37 (m, 6H).

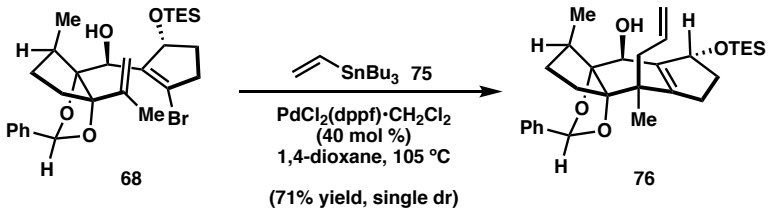
^{13}C NMR (126 MHz, $CDCl_3$): δ 148.0, 140.2, 137.9, 129.4, 128.6, 128.2, 127.1, 111.8, 105.2, 98.8, 96.6, 78.1, 71.9, 42.5, 39.9, 38.3, 32.7, 31.1, 21.1, 14.4, 6.5, 5.3.

FTIR (NaCl, thin film): 3484, 2955, 2876, 1638, 1458, 1091, 1069, 1049, 1027, 979 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 571.1850, found 571.1840.

$[\alpha]_D^{25} = -10°$ (c = 1.20, $CHCl_3$).

Preparation of ABC tricycle 76



In a nitrogen-filled glovebox, an oven-dried, 150 mL heavy-walled pressure vessel equipped with a magnetic stirbar was charged with $PdCl_2(dppf)•CH_2Cl_2$ (600 mg, 0.74 mmol, 0.40 equiv) and vinyl bromide **68** (1.01 g, 1.84 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (74 mL). The suspension was treated with tributyl(vinyl)stannane (0.97 mL, 3.31 mmol, 1.8 equiv) before the vessel was sealed with a CAPFE O-ring lined cap, removed from the glove box, and submerged in a preheated oil bath at 105 ºC. After 22 h of continued stirring at 105 ºC, the vessel was cooled to ambient temperature, diluted with Et_2O (20 mL), and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 40%/1% EtOAc/Et_3N/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified via SiO_2 flash chromatography (5/1 to 10/1% EtOAc/Et_3N/hexanes) to afford ABC tricycle **76** (638 mg, 1.30 mmol, 71% yield) as a pale-yellow oil [Note: the use of Et_3N is critical to isolate **76** without tin byproducts originating from stannane **75**]. The stereochemistry of **76** was confirmed by nOe analysis.

TLC (10% EtOAc/hexanes): R_f 0.39 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 2H), 7.37 (m, 3H), 6.02 (dddd, *J* = 16.1, 10.1, 8.1, 5.7 Hz, 1H), 5.90 (s, 1H), 5.16 – 5.01 (m, 4H), 2.68 (d, *J* = 2.2 Hz, 1H), 2.60 – 2.50 (m, 3H), 2.29 – 2.15 (m, 4H), 1.99 (dd, *J* = 13.3, 5.5 Hz, 1H), 1.75 (m, 1H), 1.65 (td, *J* = 13.4, 6.1 Hz, 1H), 1.27 (m, 1H), 1.26 (s, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.95 (d, *J* = 7.3 Hz, 3H), 0.65 (q, *J* = 7.9 Hz, 6H).

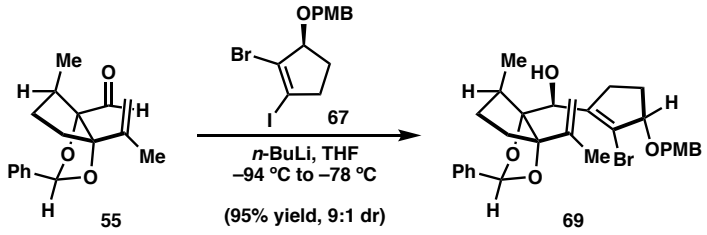
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.5, 138.0, 137.5, 135.8, 129.3, 128.3, 126.9, 116.9, 103.4, 99.8, 96.4, 77.5, 70.7, 43.5, 42.8, 41.8, 36.7, 34.1, 30.3, 30.0, 19.8, 15.2, 6.9, 5.0.

FTIR (NaCl, thin film): 3504, 2954, 2875, 1458, 1060, 1028, 1005, 914 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 519.2901, found 519.2888.

$[\alpha]_D^{25}$ = +19° (*c* = 0.795, $CHCl_3$).

Convergent union of aldehyde 55 and iodobromocyclopentenol 67



An oven-dried, 25 mL round-bottomed flask was charged with vinyl iodide **67** (127 mg, 310 μmol, 1.3 equiv) and anhydrous THF (2.0 mL) [Note: vinyl iodide **67** was azeotroped with PhH three times immediately prior to use]. The solution was cooled to –78 ºC via a dry ice/acetone bath and stirring continued for 15 min prior to the dropwise addition of *n*-BuLi (2.5 M in hexanes, 124 μL, 310 μmol, 1.3 equiv) via syringe. Upon complete addition, the reaction mixture was stirred an additional 15 min while further

cooling the cooling bath to –94 ºC via the addition of liq. N_2 Aldehyde **55** (65.0 g, 239 μmol, 1.0 equiv) in anhydrous THF (1.5 mL) was added dropwise via cannula over 15 min at –94 ºC [Note: aldehyde **55** was azeotroped with PhH three times immediately prior to use], before another portion of THF (0.5 mL) was used to render the transfer quantitative. Stirring was continued while the reaction mixture was slowly warmed to –78 ºC over 30 min, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was quenched with the addition of sat. aq. NH_4Cl (5 mL) and then warmed to ambient temperature and diluted with Et_2O (2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (7 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product indicated that the reaction occurs with full consumption of the starting material in a 9:1 diastereomeric ratio. Purification via SiO_2 flash chromatography (10 to 15 to 20% EtOAc/hexanes) afforded alcohol **69** (126 mg, 227 μmol, 95% yield) as a thick, slightly-yellow oil.

TLC (20% EtOAc/hexanes): R_f 0.42 (UV, *p*-anisaldehyde).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (m, 2H), 7.38 (m, 3H), 7.32 (m, 2H), 6.88 (m, 2H), 6.25 (s, 1H), 5.22 (s, 1H), 5.19 (t, *J* = 1.5 Hz, 1H), 4.98 (s, 1H), 4.57 (m, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 2.83 (ddt, *J* = 16.1, 9.3, 3.4 Hz, 1H), 2.55 (m, 1H), 2.33 (tt, *J* = 12.5, 6.3 Hz, 1H), 2.23 (m, 1H), 2.14 (m, 1H), 2.10 (s, 3H), 2.08 (m, 1H), 2.02 (dd, *J* = 13.8, 6.5 Hz, 1H), 1.92 (ddt, *J* = 13.8, 9.4, 4.9 Hz, 1H), 1.35 (dd, *J* = 12.1, 6.1 Hz, 1H), 0.93 (d, *J* = 7.4 Hz, 3H).

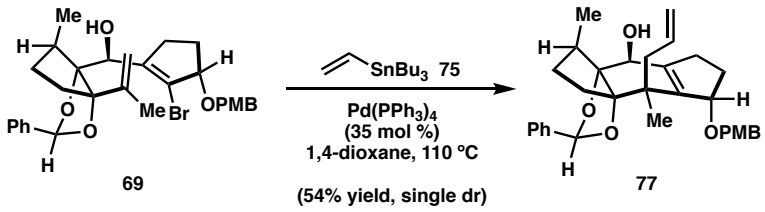
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 148.0, 144.7, 138.0, 130.3, 129.4, 128.3, 126.7, 122.8, 113.7, 112.3, 104.6, 98.3, 96.4, 84.9, 70.8, 70.1, 55.3, 42.2, 39.1, 30.8, 30.7, 28.9, 21.2, 14.1.

FTIR (NaCl, thin film): 3424, 2961, 1612, 1514, 1455, 1248, 1092, 1063, 1029 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 572.2006, found 572.1967.

$[\alpha]_D^{25}$ = +2° (*c* = 0.585, $CHCl_3$).

Preparation of ABC tricycle 77



In a nitrogen-filled glovebox, an oven-dried, 48 mL heavy-walled pressure vessel equipped with a magnetic stirbar was charged with $Pd(PPh_3)_4$ (91.0 mg, 78.8 μmol, 0.35 equiv) and vinyl bromide **69** (125 mg, 225 μmol, 1.0 equiv) in anhydrous 1,4-dioxane (23 mL). The suspension was treated with tributyl(vinyl)stannane (118 μL, 405 μmol, 1.8 equiv) before the vessel was sealed with a CAPFE O-ring lined cap, removed from the glove box, and submerged in a preheated oil bath at 110 ºC. After 24 h of continued stirring at 110 ºC, the vessel was cooled to ambient temperature, diluted with Et_2O (10 mL), and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the crude residue was redissolved in Et_2O (25 mL) and treated with sat. aq. KF (25 mL). The biphasic mixture was vigorously stirred for 15 min before separating the two layers. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined layers were washed with brine (20 mL), dried over $MgSO_4$, filtered over Celite, and concentrated *in*

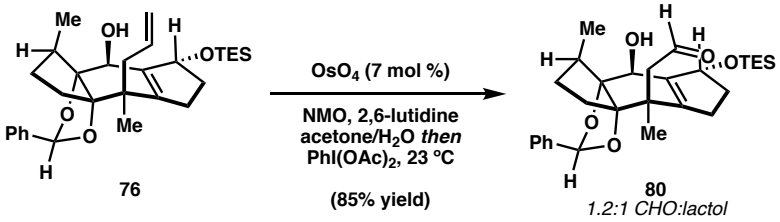
vacuo. The crude residue was purified via SiO_2 flash chromatography (5/1 to 10/1% EtOAc/Et_3N/hexanes) to afford ABC tricycle **77** (61.1 mg, 122 μmol, 54% yield) as a pale-yellow oil [Note: the use of Et_3N is critical to isolate **77** without tin byproducts originating from stannane **75**]. The stereochemistry of **77** was confirmed by nOe analysis.

TLC (20% EtOAc/hexanes): R_f 0.22 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 2H), 7.39 (m, 3H), 7.30 (m, 2H), 6.89 (m, 2H), 6.05 (dddd, *J* = 16.2, 10.3, 8.1, 5.6 Hz, 1H), 5.86 (s, 1H), 5.09 (s, 1H), 5.02 (dq, *J* = 8.8, 1.5 Hz, 1H), 4.98 (p, *J* = 1.5 Hz, 1H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 3.81 (s, 3H), 2.69 (ddt, *J* = 14.8, 7.4, 2.2 Hz, 1H), 2.59 (ddt, *J* = 17.0, 8.8, 1.9 Hz, 1H), 2.53 – 2.38 (m, 3H), 2.24 (m, 1H), 2.20 (s, 1H, OH), 2.06 (m, 1H), 1.92 (ddt, *J* = 13.9, 8.8, 6.9 Hz, 1H), 1.68 (td, *J* = 13.4, 6.1 Hz, 1H), 1.34 (m, 1H), 1.31 (s, 3H), 0.87 (d, *J* = 7.3 Hz, 3H).

LCMS (APCI): calc'd for $[M+2Na]^+$ 548.3, found 548.3.

Preparation of aldehyde 80



An oven-dried, 200 mL round-bottomed flask was charged with ABC tricycle **76** (1.73 g, 3.54 mmol, 1.0 equiv), acetone (64 mL), and deionized H_2O (6.4 mL). The solution was treated with 2,6-lutidine (1.2 mL, 10.6 mmol, 3.0 equiv) via syringe, NMO (622 mg, 5.31 mmol, 1.5 equiv), and then OsO_4 (0.05 M in PhMe, 3.5 mL, 0.18 mmol,

0.05 equiv) via syringe. The resulting reaction mixture was stirred at ambient temperature for 2 h, after which an additional portion of OsO_4 (0.05 M in PhMe, 1.4 mL, 70.8 μmol, 0.02 equiv) was added via syringe. Stirring was continued at ambient temperature until TLC analysis indicated the complete consumption of starting material (*ca.* 2 h). $PhI(OAc)_2$ (1.71 g, 5.31 mmol, 1.5 equiv) was next added as a single portion and the reaction was continued at ambient temperature for 45 min before adding sat. aq. $NaHCO_3$ (20 mL) and sat. aq. $Na_2S_2O_3$ (10 mL). The reaction mixture was diluted with Et_2O (60 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 60 mL) and the combined organic layers were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (10 to 20 to 30% EtOAc/hexanes) to afford aldehyde **80** (1.50 g, 3.01 mmol, 85% yield) as a 1.2:1 mixture with its lactol.

TLC (20% EtOAc/hexanes): R_f 0.32 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (dd, *J* = 3.3, 2.6 Hz, 1H, C***H***O), 7.55 – 7.52 (m, 2H), 7.40 – 7.36 (m, 3H), 5.95 (s, 1H), 5.17 (m, 1H), 5.12 (dt, *J* = 3.8, 1.8 Hz, 1H), 2.74 (d, *J* = 2.3 Hz, 1H), 1.47 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H), 0.99 (m, 9H), 0.66 (m, 6H).

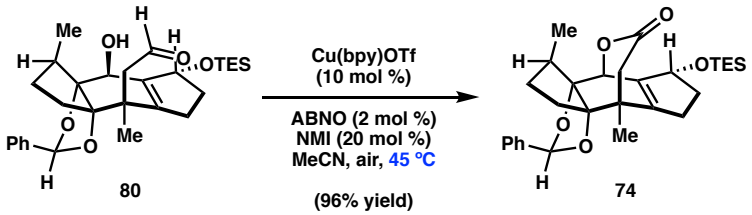
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.5, 141.5, 138.9, 136.9, 129.5, 128.3, 126.7, 103.7, 99.7, 96.1, 77.4, 70.4, 51.1, 42.9, 38.0, 34.1, 30.2, 20.8, 15.1, 6.9, 5.0.

FTIR (NaCl, thin film): 3406, 2955, 2876, 1718, 1458, 1098, 1062, 1018, 981 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 521.2694, found 521.2690.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +44° (*c* = 0.855, $CHCl_3$).

Preparation of lactone 74



An oven-dried, 200 mL round-bottomed flask was charged with aldehyde **80** (1.63 g, 3.27 mmol, 1.0 equiv) and anhydrous MeCN (33 mL). The solution was vigorously stirred (>700 rpm) open to air while being treated with bpy (61 mg, 0.33 mmol, 0.10 equiv), $Cu(MeCN)_4OTf$ (123 mg, 0.33 mmol, 0.10 equiv), ABNO (9.2 mg, 65.4 μmol, 0.02 equiv), and then NMI (52 μL, 0.65 mmol, 0.20 equiv) via microsyringe. The resulting brick-red reaction mixture was immediately submerged in a preheated oil bath at 45 ºC and vigorously stirred exposed to air until the reaction mixture turned a dark brown, at which point TLC analysis indicated the complete consumption of starting material (*ca.* 1.25 h). The reaction mixture was cooled to ambient temperature, diluted with Et_2O (30 mL), and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 60% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified by SiO_2 flash chromatography (15 to 25% EtOAc/hexanes) to afford lactone **74** (1.56 g, 3.14 mmol, 96% yield) as a white foam.

TLC (20% EtOAc/hexanes): R_f 0.35 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 5H), 5.92 (s, 1H), 5.04 (m, 1H), 5.01 (s, 1H), 2.75 (d, J = 19.4 Hz, 1H), 2.65 – 2.54 (m, 2H), 2.55 (d, J = 19.4 Hz, 1H), 2.47 – 2.34 (m, 2H), 2.21 (dddd, J = 11.7, 9.7, 6.0, 1.3 Hz, 2H), 2.03 (m, 1H), 1.85 (m, 1H), 1.44 (m,

1H), 1.31 (s, 3H), 1.27 (d, J = 7.2 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H).

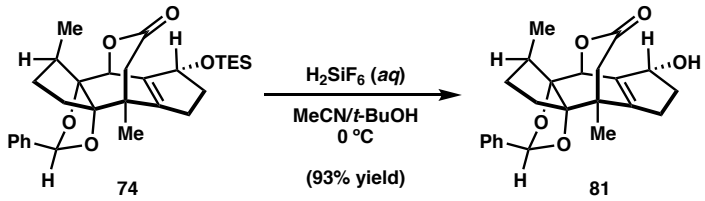
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 153.7, 140.1, 138.2, 129.3, 128.3, 126.7, 109.8, 98.1, 95.3, 76.5, 70.9, 45.1, 45.0, 40.3, 35.7, 34.6, 33.1, 29.4, 18.7, 13.2, 6.8, 4.9.

FTIR (NaCl, thin film): 2955, 2878, 1727, 1459, 1212, 1100, 1064, 1018 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 519.2537, found 519.2530.

$[\alpha]_D^{25}$ = +69° (c = 0.870, $CHCl_3$).

Preparation of alcohol 81



An oven-dried, 200 mL round-bottomed flask was charged with TES ether **74** (1.51 g, 3.04 mmol, 1.0 equiv), anhydrous MeCN (55 mL), and *t*-BuOH (6.1 mL). The solution was cooled to 0 ºC via an ice/water bath and then treated with H_2SiF_6 (*aq*) (25% w/w, 2.8 mL, 6.08 mmol, 2.0 equiv) dropwise via syringe. The reaction was stirred 15 min at 0 ºC and then quenched with sat. aq. $NaHCO_3$ (12 mL), diluted with H_2O (12 mL) and Et_2O (24 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 24 mL) and the combined organic layers were washed with brine (24 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (40 to 50 to 60% EtOAc/hexanes) to afford alcohol **81** (1.08 g, 2.83 mmol, 93% yield) as a white foam.

TLC (60% EtOAc/hexanes): R_f 0.43 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5H), 5.90 (s, 1H), 5.10 (s, 1H), 5.03 (dq, *J* = 6.8, 3.0, 2.5 Hz, 1H), 2.77 (d, *J* = 19.4 Hz, 1H), 2.69 (m, 1H), 2.58 (d, *J* = 19.4 Hz, 1H), 2.55 – 2.37 (m, 3H), 2.17 (m, 1H), 2.06 – 1.91 (m, 2H), 1.89 (d, *J* = 5.9 Hz, 1H), 1.42 (qd, *J* = 12.6, 6.9 Hz, 1H), 1.33 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H).

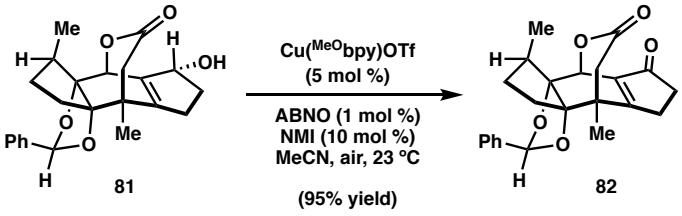
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 155.5, 139.4, 138.1, 129.4, 128.4, 126.5, 109.3, 98.4, 95.3, 76.6, 70.5, 45.1, 44.3, 40.3, 35.1, 34.0, 32.9, 29.6, 18.5, 12.9.

FTIR (NaCl, thin film): 3444, 2964, 2882, 1722, 1461, 1380, 1352, 1216, 1101, 1064, 1019, 757 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 405.1672, found 405.1657.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +69° (*c* = 0.565, $CHCl_3$).

Preparation of enone 82



An oven-dried, 100 mL round-bottomed flask was charged with alcohol **81** (1.15 g, 3.01 mmol, 1.0 equiv) and anhydrous MeCN (30 mL). The solution was vigorously stirred (>700 rpm) open to air while being treated with ^{MeO}bpy (32.5 mg, 0.15 mmol, 0.05 equiv), $Cu(MeCN)_4OTf$ (56.7 mg, 0.15 mmol, 0.05 equiv), ABNO (4.2 mg, 30.1 μmol, 0.01 equiv), and then NMI (24 μL, 0.30 mmol, 0.10 equiv) via microsyringe. The resulting brown-red reaction mixture was vigorously stirred exposed to air at ambient temperature until the reaction mixture turned a blue-green (*ca.* 1 h), at which point TLC

analysis indicated the complete consumption of starting material. The reaction mixture was diluted with Et_2O (30 mL), and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 80% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified by SiO_2 flash chromatography (40 to 50 to 60% EtOAc/hexanes) to afford enone **82** (1.09 g, 6.65 mmol, 95% yield) as a white foam.

TLC (60% EtOAc/hexanes): R_f 0.40 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 5H), 5.59 (s, 1H), 5.37 (s, 1H), 2.90 (d, *J* = 19.4 Hz, 1H), 2.82 (ddd, *J* = 7.7, 5.4, 3.2 Hz, 1H), 2.69 (d, *J* = 19.4 Hz, 1H), 2.64 (dt, *J* = 5.4, 4.0 Hz, 2H), 2.50 (m, 1H), 2.28 (ddd, *J* = 14.3, 7.1, 1.5 Hz 1H), 2.13 (dtd, *J* = 13.1, 7.2, 1.4 Hz, 1H), 2.03 (m, 1H), 1.46 (s, 3H), 1.40 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 3H).

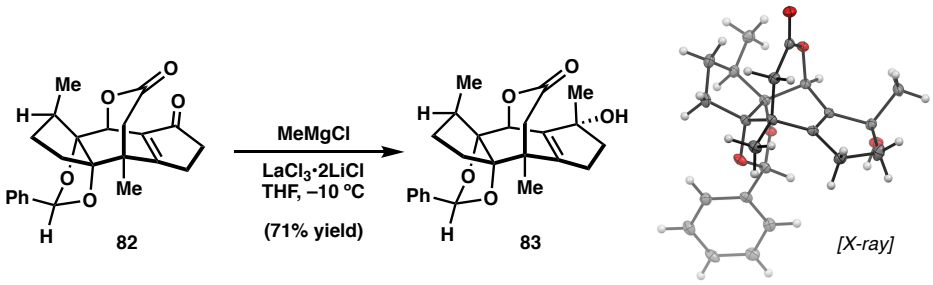
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4, 185.0, 168.7, 140.8, 138.1, 129.3, 128.4, 126.2, 108.9, 98.3, 95.4, 66.9, 44.4, 44.2, 43.0, 35.8, 34.9, 33.0, 26.3, 17.5, 12.8.

FTIR (NaCl, thin film): 2968, 2882, 1728, 1707, 1650 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 398.1962, found 398.1961.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +104° (*c* = 0.600, $CHCl_3$).

Preparation of alcohol 83



An oven-dried, 10 mL round-bottomed flask was charged with $LaCl_3$•2LiCl[33] (0.6 M in THF, 3.0 mL) via syringe and the solution was immediately cooled to 0 ºC via an ice/water bath. After 15 min of continued stirring at 0 ºC, MeMgCl (3.0 M in THF, 0.6 mL) was added dropwise via syringe. Upon complete addition, the resulting dark-yellow reaction mixture was stirred for an additional 20 min at 0 ºC affording a 0.5 M stock solution of nucleophile that was used immediately.

A separate oven-dried, 50 mL round-bottomed flask was charged with enone **82** (260 mg, 0.68 mmol, 1.0 equiv) and anhydrous THF (14 mL). The resulting solution was cooled to –10 ºC via an ice/acetone bath and after 15 min of continued stirring, the freshly prepared stock solution of nucleophile (0.5 M in THF, 2.1 mL, 1.03 mmol, 1.5 equiv) was added dropwise via syringe. Upon complete addition, the reaction was continued at –10 ºC for 30 min at which point TLC analysis indicated the complete consumption of starting material. The reaction was quenched with the addition of pH 7 buffer (2 mL) at 0 ºC and then warmed to ambient temperature. The mixture was diluted with Et_2O (10 mL) and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 80/1% EtOAc/Et_3N/hexanes. The filtrate was then concentrated *in vacuo* and directly purified via SiO_2 flash chromatography (40/1 to 50/1 to 60/1 EtOAc/Et_3N/hexanes) to afford alcohol **83** (193 mg, 0.49 mmol, 71% yield) as a white

foam. The stereochemistry of the 1,2-addition product was confirmed by nOe and X-ray analysis.

TLC (45% EtOAc/hexanes): R_f 0.35 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, C_6D_6): δ 7.43 (m, 2H), 7.12 (m, 3H), 5.96 (s, 1H), 5.01 (s, 1H), 2.44 (d, *J* = 19.2 Hz, 1H), 2.36 (m, 1H), 2.25 (d, *J* = 19.2 Hz, 1H), 2.19 (m, 1H), 1.97 (m, 1H), 1.91 (m, 1H), 1.80 (m, 1H), 1.71 (m, 2H), 1.66 (m, 1H), 1.62 (s, 1H, OH), 1.30 (m, 1H), 1.29 (s, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H).

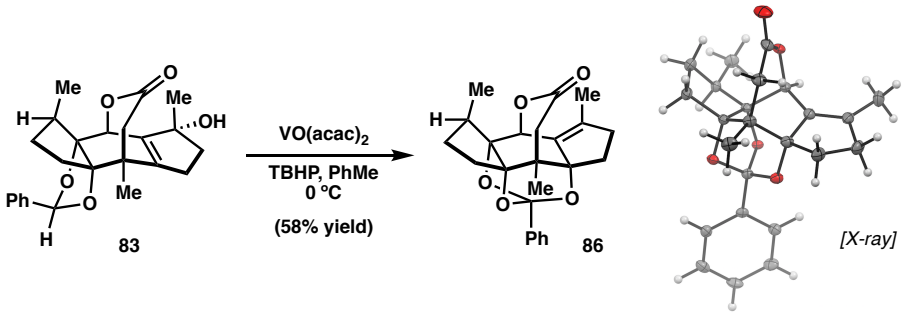
^{13}C NMR (101 MHz, C_6D_6): δ 168.8, 152.4, 142.7, 139.4, 129.2, 128.5, 126.8, 109.3, 98.6, 95.6, 82.0, 69.6, 45.3, 44.8, 40.7, 40.3, 35.2, 32.9, 28.6, 26.8, 18.3, 13.0.

FTIR (NaCl, thin film): 3445, 2964, 2882, 1723, 1714, 1456, 1351, 1217 cm^{-1}.

HRMS (ESI): calc'd for $[M–OH]^+$ 379.1864, found 379.1860.

$[\alpha]_D^{25}$ = +95° (*c* = 0.335 $CHCl_3$).

Preparation of orthobenzoate 86



An oven-dried, 50 mL round-bottomed flask was charged with alcohol **83** (192 mg, 0.48 mmol, 1.0 equiv) and anhydrous PhMe (16 mL). The solution was cooled to 0 ºC via an ice/water bath, during which time $VO(acac)_2$ (64.2 mg, 0.24 mmol, 0.5 equiv)

was added. The green solution was next treated with TBHP (5.5 M in decanes, 0.26 mL, 1.45 mmol, 3.0 equiv) dropwise via syringe. The resulting deep-red reaction was continued at 0 ºC for 1.5 h before an additional portion of $VO(acac)_2$ (64.2 mg, 0.24 mmol, 0.5 equiv) and TBHP (5.5 M in decanes, 0.26 mL, 1.45 mmol, 3.0 equiv) were added. After 1.5 h of continued stirring at 0 ºC, the reaction was deemed complete by TLC analysis and quenched with the addition of sat. aq. $NaHCO_3$ (10 mL) and sat. aq. $Na_2S_2O_3$ (5 mL). The mixture was diluted with EtOAc (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered over Celite, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (10 to 20 to 30% EtOAc/hexanes) to afford orthobenzoate **86** (110 mg, 0.28 mmol, 58% yield) as a white solid.

TLC (25% EtOAc/hexanes): R_f 0.41 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (m, 2H), 7.36 (m, 3H), 5.37 (s, 1H), 2.81 (m, 1H), 2.71 (d, *J* = 19.0 Hz, 1H), 2.62 (d, *J* = 19.0 Hz, 1H), 2.54 (m, 1H), 2.29 (dddt, *J* = 13.2, 8.5, 7.6, 2.5 Hz, 1H), 2.19 (m, 1H), 2.10 – 1.94 (m, 4H), 1.89 (s, 3H), 1.66 (m, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.23 (s, 3H).

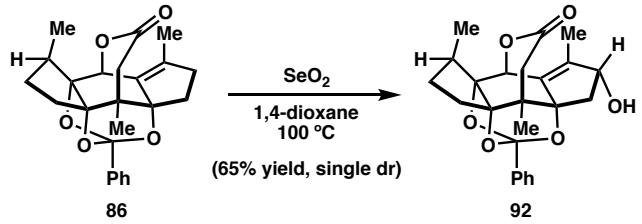
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 147.9, 135.0, 133.2, 129.6, 128.1, 126.0, 120.9, 94.4, 93.0, 91.1, 69.3, 42.1, 41.6, 39.8, 35.9, 34.1, 30.7, 28.5, 17.4, 14.4, 13.0.

FTIR (NaCl, thin film): 2963, 2880, 1731, 1688, 1456, 1355, 1193 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 395.1853, found 395.1850.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –61° (*c* = 0.650, $CHCl_3$).

Preparation of allylic alcohol 92



86 92

An oven-dried, 20 mL scintillation vial was treated with orthobenzoate **86** (129 mg, 0.33 mmol, 1.0 equiv), SeO_2 (181 mg, 1.64 mmol, 5.0 equiv), and anhydrous 1,4-dioxane (11 mL) [Note: SeO_2 was stored in a nitrogen-filled glove box to maintain the integrity of the reagent]. The vial was immediately capped with a Teflon-lined cap and placed in a preheated heating block at 100 ºC. The reaction was stirred at 100 ºC for 1.5 h at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was cooled to ambient temperature, diluted with hexanes (6 mL), and filtered over a pre-equilibrate SiO_2 plug layered with Celite, washing with EtOAc. The filtrate was concentrated *in vacuo* and the crude residue was directly purified via SiO_2 flash chromatography (10 to 20 to 30% EtOAc/CH_2Cl_2) to afford alcohol **92** (87.3 mg, 0.21 mmol, 65% yield) as an orange foam.

TLC (20% EtOAc/CH_2Cl_2): R_f 0.38 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (m, 2H), 7.38 (m, 3H), 5.37 (s, 1H), 4.44 (dd, *J* = 11.3, 6.5 Hz, 1H) 2.71 (d, *J* = 19.0 Hz, 1H), 2.56 (dp, *J* = 12.5, 7.3 Hz, 1H), 2.47 (d, *J* = 19.0 Hz, 1H), 2.25 – 2.15 (m, 2H), 2.11 – 2.01 (m, 2H), 1.98 (m, 1H), 1.98 (s, 3H), 1.71 (d, *J* = 11.4 Hz, 1H, OH), 1.65 (m, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.25 (s, 3H).

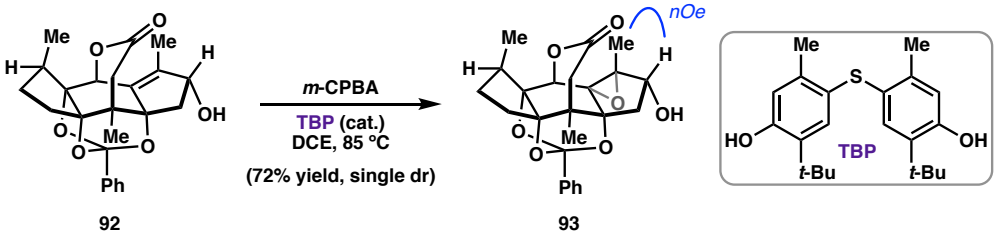
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 148.3, 137.1, 134.5, 129.9, 128.2, 125.9, 121.0, 94.3, 91.0, 90.9, 78.7, 68.8, 41.6, 41.5, 40.1, 38.7, 34.1, 28.5, 17.8, 13.0, 12.3.

FTIR (NaCl, thin film): 3437, 2964, 2881, 1732, 1452, 1380, 1353, 1196 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 411.1802, found 411.1802.

$[\alpha]_D^{25} = -81°$ ($c = 0.385$, $CHCl_3$).

Preparation of epoxyalcohol 93



An oven-dried, 20 mL scintillation vial was treated with allyl alcohol **92** (77.5 mg, 0.19 mmol, 1.0 equiv), *m*-CPBA (99%, 81.5 mg, 0.47 mmol, 2.5 equiv), and freshly distilled 1,2-DCE (6.3 mL). After complete dissolution of the peracid was observed, 4,4′-thiobis-(6-*t*-Bu-3-Me-phenol) (1.6 mg, 2 mg/100 mg) was added. The vial was immediately capped with a Teflon-lined cap and placed in a preheated heating block at 85 ºC. The reaction was stirred at 85 ºC for 4 h at which point LCMS analysis indicated the complete consumption of starting material. The reaction mixture was cooled to ambient temperature, diluted with $CHCl_3$ (6 mL), and quenched with the addition of sat. aq. $NaHCO_3$ (10 mL) and sat. aq. $Na_2S_2O_3$ (5 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (5 to 7 to 10% acetone/CH_2Cl_2) to afford epoxide **93** (58.0 mg, 0.14 mmol, 72% yield) as a glass-like film. The stereochemistry of epoxyalcohol **93** was verified by nOe analysis.

TLC (7% acetone/CH_2Cl_2): R_f 0.21 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 2H), 7.39 (m, 3H), 4.72 (s, 1H), 3.98 (ddd, *J* = 10.9, 8.8, 6.7 Hz, 1H), 2.90 (d, *J* = 19.5 Hz, 1H), 2.55 (m, 1H), 2.55 (dd, *J* = 15.7, 8.8 Hz, 1H), 2.36 (d, *J* = 19.5 Hz, 1H), 2.20 (m, 1H), 2.06 (d, *J* = 9.8 Hz, 1H), 2.04 (dd, *J* = 9.8, 3.3 Hz, 1H), 1.82 (d, *J* = 10.9 Hz, 1H, OH), 1.67 – 1.52 (m, 2H), 1.58 (s, 3H), 1.24 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 1H).

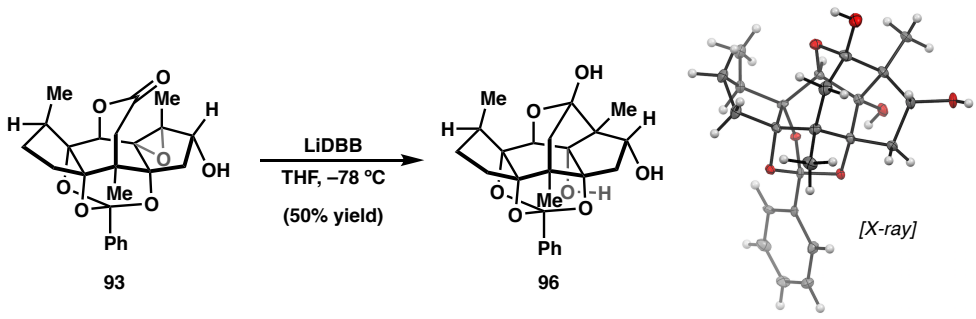
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 134.1, 129.9, 128.1, 126., 121.0, 93.8, 91.3, 84.5, 74.7, 73.4, 72.2, 70.8, 41.4, 41.2, 39.3, 38.5, 33.8, 28.3, 18.5, 14.2, 12.9.

FTIR (NaCl, thin film): 3318, 2966, 1738, 1732, 1716, 1454, 1360, 1204 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 427.1751, found 427.1750.

$[\alpha]_D^{25}$ = –134° (*c* = 0.120, $CHCl_3$).

Preparation of pentacycle 96



LiDBB[45] was prepared according to the following procedure: An oven-dried, 25 mL Schlenk tube containing a borosilicate glass-coated magnetic stirbar was charged with 4,4′-di-*tert*-butylbiphenyl (550 mg, 2.0 mmol) and freshly cut lithium wire (14.0 mg, 2.0 mmol) [Note: Immediately prior to use, lithium wire was washed with hexanes, hammered out into a foil, and cut into several small strips]. The Schlenk tube was

evacuated and refilled with Ar three times before anhydrous THF (12.5 mL) was added and the resulting reaction mixture was then cooled to 0 ºC via an ice/water bath. After vigorously stirring (900-1000 rpm) at 0 ºC for 10 min, the solution became a deep-green, characteristic of the DBB radical anion. After the reaction mixture was stirred at 0 ºC for approximately 4 h, the LiDBB solution (~0.16 M) was immediately used.

An oven-dried, 25 mL round-bottomed flask containing a borosilicate glass-coated magnetic stirbar was charged with epoxide **93** (55.8 mg, 0.13 mmol, 1.0 equiv) and anhydrous THF (9.8 mL) [Note: epoxide **93** was azeoptroped with PhH three times prior to use]. The solution was cooled to –78 ºC via a dry ice/acetone bath and stirring was continued for 15 min at this temperature prior to the dropwise addition of freshly generated LiDBB (0.16 M in THF, 3.3 mL, 0.52 mmol, 4.0 equiv). Upon complete addition, the resulting dark-orange reaction mixture was stirred for 5 min before adding sat. aq. NH_4Cl (10 mL). The mixture was warmed to ambient temperature, diluted with $CHCl_3$ (10 mL), and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (4 to 6 to 8% MeOH/$CHCl_3$) to afford pentacycle **96** (28.0 mg, 65.4 μmol, 50% yield) as an off-white foam.

TLC (8% MeOH/CH_2Cl_2): R_f 0.33 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, CD_3OD): δ 7.63 (m, 2H), 7.37 (m, 3H), 4.21 (s, 1H), 3.88 (dd, J = 7.5, 6.4 Hz, 1H), 2.62 (dd, J = 13.6, 7.5 Hz, 1H), 2.31 (dp, J = 10.0, 7.0 Hz, 1H), 2.14 (m,

1H), 2.06 (m, 1H), 2.06 (dd, J = 13.7, 6.4 Hz, 1H), 2.00 (d, J = 14.8 Hz, 1H), 1.87 – 1.71 (m, 2H), 1.63 (d, J = 14.8 Hz, 1H), 1.26 (s, 3H), 1.16 (s, 3H), 1.13 (d, J = 7.1 Hz, 3H).

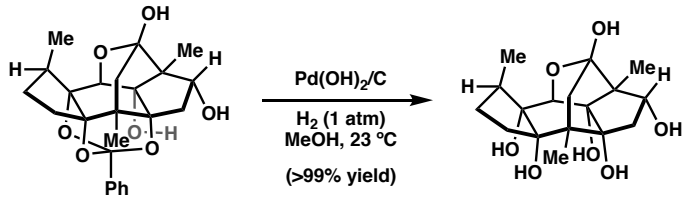
^{13}C NMR (101 MHz, CD_3OD): δ 136.8, 130.5, 128.8, 127.3, 121.8, 106.4, 96.9, 93.7, 87.3, 87.0, 76.4, 70.0, 58.4, 43.1, 42.8, 42.4, 39.7, 34.7, 29.8, 20.1, 14.1, 8.7.

FTIR (NaCl, thin film): 3418, 2938, 1462, 1453, 1350, 1026 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 451.1727, found 451.1726.

$[\alpha]_D^{25}$ = –80° (c = 0.065, $CHCl_3$).

Preparation of pentaol 97



96 97

A 20 mL scintillation vial was charged with pentacycle **96** (24.0 mg, 56.0 μmol, 1.0 equiv), $Pd(OH)_2/C$ (20 wt %, 48.0 mg), and MeOH (5.6 mL). The vial was capped with a rubber septum and the reaction mixture was vigorously stirred (1000 rpm) while flushing the headspace with H_2 for 5 minutes via a double-walled balloon. The suspension was vigorously stirred under H_2 until LCMS indicated complete consumption of the starting material (*ca.* 1 h), flushed with Ar to remove excess H_2, then diluted with CH_2Cl_2 (12 mL), filtered through a short pad of Celite, and concentrated *in vacuo.* Purification of the crude residue by SiO_2 flash chromatography (8 to 10 to 12% MeOH/$CHCl_3$) afforded pentaol **97** (19.1 mg, 55.8 μmol, >99% yield) as a white solid.

TLC (10% MeOH/CH_2Cl_2): R_f 0.11 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, CD_3OD): δ 3.83 (s, 1H), 3.66 (dd, *J* = 7.9, 5.6 Hz, 1H), 2.72 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.20 (m, 1H), 1.95 (m, 1H), 1.84 (dd, *J* = 14.5, 5.7 Hz, 1H), 1.82 (d, *J* = 14.7 Hz, 1H), 1.68 – 1.47 (m, 3H), 1.37 (d, *J* = 14.7 Hz, 1H), 1.11 (s, 3H), 1.10 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 3H).

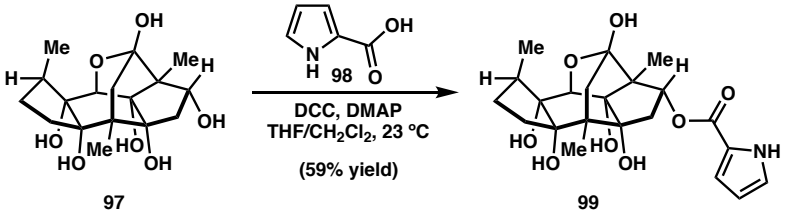
^{13}C NMR (101 MHz, CD_3OD): δ 104.5, 86.0, 85.2, 84.3, 82.0, 78.7, 70.3, 60.1, 46.9, 46.1, 44.1, 43.8, 37.4, 30.1, 18.8, 12.8, 8.9.

FTIR (NaCl, thin film): 3368, 2919, 2360, 1028 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 343.1751, found 343.1752.

$[\alpha]_D^{25}$ = –21° (*c* = 0.080, MeOH).

Preparation of pyrrole ester 99



An oven-dried, 2 dram vial was charged with pentaol **97** (10.5 mg, 30.7 μmol, 1.0 equiv), anhydrous THF (0.5 mL), and anhydrous CH_2Cl_2 (0.5 mL). The solution was next treated with pyrrole-2-carboxylic acid (6.8 mg, 61.3 μmol, 2.0 equiv), DCC (12.7 mg, 61.3 μmol, 2.0 equiv), and *then* DMAP (3.8 mg, 30.7 μmol, 1.0 equiv). The resulting reaction was left to stir at ambient temperature for 48 h at which point sat. aq. $NaHCO_3$ (2 mL) was added. The quenched reaction mixture was diluted with $CHCl_3$ (1 mL) and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 × 2 mL) and

the combined organic layers were dried over Na_2SO_4, filtered over Celite, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (5 to 7 to 9% MeOH/$CHCl_3$) to afford pyrrole ester **99** (7.9 mg, 18.1 μmol, 59% yield) as a white semi-solid.

TLC (10% MeOH/CH_2Cl_2): R_f 0.36 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, CD_3OD): δ 6.98 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.91 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.20 (dd, *J* = 3.8, 2.5 Hz, 1H), 4.97 (dd, *J* = 7.9, 5.4 Hz, 1H), 3.91 (s, 1H), 2.84 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.26 (m, 1H), 1.98 (m, 1H), 1.98 (dd, *J* = 14.7, 5.4 Hz, 1H), 1.94 (d, *J* = 14.9 Hz, 1H), 1.68 – 1.55 (m, 3H), 1.52 (d, *J* = 14.9 Hz, 1H), 1.17 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.13 (s, 3H).

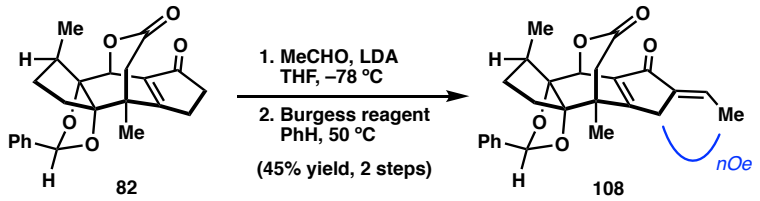
^{13}C NMR (101 MHz, CD_3OD): δ 162.2, 124.7, 123.5, 117.0, 110.8, 104.2, 86.1, 85.1, 84.7, 82.0, 78.8, 72.3, 59.9, 47.0, 44.3, 43.9, 43.8, 37.5, 30.0, 18.7, 12.8, 9.0.

FTIR (NaCl, thin film): 3401, 2929, 2853, 1641, 1451, 1409, 1319, 1169 1026 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 436.1966, found 436.1974.

$[\alpha]_D^{25}$ = –26° (*c* = 0.080, MeOH).

Preparation of dienone 108



An oven-dried, 50 mL round-bottomed flask was charged with enone **82** (233 mg, 0.61 mmol, 1.0 equiv) and anhydrous THF (12 mL). The solution was cooled to –78 ºC

via a dry ice/acetone bath and then treated with freshly prepared LDA (0.5 M in THF, 1.83 mL, 0.91 mmol, 1.5 equiv) dropwise via syringe, affording a pale-pink solution. Stirring was continued for 45 min at –78 ºC before acetaldehyde (0.21 mL, 3.66 mmol, 3.0 equiv) in anhydrous THF (0.5 mL) was added dropwise via syringe, immediately affording a pale-yellow solution [Note: acetaldehyde was stored at –20 ºC and handled in a nitrogen-filled glovebox to maintain the integrity of the reagent]. Upon complete addition, the reaction was allowed 1.5 h at –78 ºC and then quenched with the addition of pH 7 buffer (6 mL) before warming to ambient temperature. The reaction mixture was diluted with EtOAc (6 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was azeoptroped with PhH three times prior to use in the next step.

In a nitrogen-filled glovebox, an oven-dried, 20 mL scintillation vial was charged with the crude aldol adduct and anhydrous PhH (12 mL). The solution was next treated with Burgess reagent (181 mg, 0.76 mmol, 1.25 equiv) and the vial was then capped with a Teflon-lined cap, removed from the glovebox, and placed in preheated heating block at 50 ºC. The reaction was allowed 1.5 h at 50 ºC before it was removed from the heating block and cooled to ambient temperature. The reaction was diluted with CH_2Cl_2 (6 mL) and filtered through a pre-equilibrated SiO_2 pad layered with Na_2SO_4, washing with 70% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified by SiO_2 flash chromatography (30 to 40% EtOAc/hexanes) to afford dienone **108** (114 mg, 0.28 mmol, 45% yield over 2 steps, 4:1 *E*:*Z*) as a bright yellow foam. The olefin geometry of the major isomer was determined by nOe analysis.

TLC (55% EtOAc/hexanes): R_f 0.52 (UV, *p*-anisaldehyde).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (s, 5H), 6.85 (qt, *J* = 7.2, 1.7 Hz, 1H), 5.54 (s, 1H), 5.46 (s, 1H), 3.37 (ddd, *J* = 21.8, 1.8, 0.9 Hz, 1H), 3.30 (d, *J* = 21.8 Hz, 1H), 2.92 (d, *J* = 19.4 Hz, 1H), 2.69 (d, *J* = 19.4 Hz, 1H), 2.51 (dt, *J* = 12.9, 7.0 Hz, 1H), 2.29 (ddd, *J* = 14.2, 7.1, 1.5 Hz, 1H), 2.15 (dtd, *J* = 13.3, 7.3, 1.5 Hz, 1H), 2.03 (m, 1H), 1.96 (d, *J* = 7.2 Hz, 3H), 1.49 (s, 3H), 1.43 (m, 1H), 1.31 (d, *J* = 7.2 Hz, 3H).

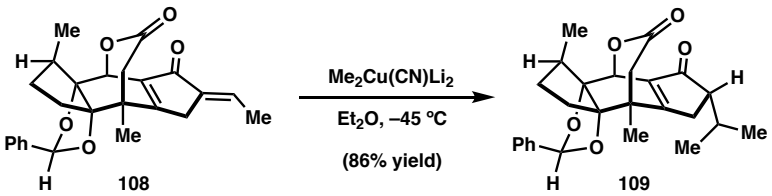
^{13}C NMR (101 MHz, $CDCl_3$): δ 189.5, 177.3, 168.8, 142.5, 138.0, 135.6, 132.7, 129.3, 128.4, 126.3, 109.0, 98.4, 95.5, 67.0, 44.6, 44.4, 42.3, 35.0, 33.0, 29.7, 17.8 15.4, 12.9.

FTIR (NaCl, thin film): 2967, 2882, 1732, 1704, 1662, 1635, 1211, 1025 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 424.2118, found 424.2121.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +61° (*c* = 0.145, $CHCl_3$).

Preparation of isopropyl ketone 109



In a nitrogen-filled glovebox, an oven-dried, 10 mL round-bottomed flask was charged with CuCN (89.6 mg, 1.00 mmol). The flask was capped with a rubber septum, removed from the glovebox, and anhydrous Et_2O (3.75 mL) was added. The resulting suspension was cooled to 0 ºC via an ice/water bath and stirring continued for 15 min prior to the dropwise addition of MeLi (1.6 M in Et_2O, 1.25 mL, 2.00 mmol) via syringe. Upon complete addition, the reaction mixture was stirred an additional 30 min at 0 ºC, resulting in a colorless, 0.2 M solution of $Me_2Cu(CN)Li_2$ in Et_2O.

A separate oven-dried, 25 mL round-bottomed flask was charged with dienone **108** (112 mg, 0.28 mmol, 1.0 equiv) in anhydrous Et_2O (9.2 mL). The solution was cooled to –45 ºC via a dry ice/MeCN bath and stirring was continued at –45 ºC for 15 min prior to the dropwise addition of $Me_2Cu(CN)Li_2$ (0.2 M in Et_2O, 0.22 mL, 0.36 mmol, 1.3 equiv) via syringe. The resulting bright-orange solution was stirred at –45 ºC for 45 min prior to the addition of sat. aq. NH_4Cl (5 mL). Stirring was continued for 5 min at –45 ºC before warming the mixture to ambient temperature. The reaction mixture was diluted with Et_2O (5 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (20 to 30% EtOAc/hexanes) to afford isopropyl ketone **109** (100 mg, 0.24 mmol, 86% yield, 8:1 dr) as a white foam. The stereochemistry of **109** was determined by nOe analysis.

TLC (50% EtOAc/hexanes): R_f 0.41 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 5H), 5.70 (s, 1H), 5.35 (s, 1H), 2.88 (d, *J* = 19.4 Hz, 1H), 2.82 (dd, *J* = 19.4, 6.4 Hz, 1H), 2.67 (d, *J* = 19.4 Hz, 1H), 2.62 (ddd, *J* = 6.4, 4.2, 2.5 Hz, 1H), 2.56 (dd, *J* = 19.4, 2.6 Hz, 1H), 2.48 – 2.39 (m, 2H), 2.27 (m, 1H), 2.09 (m, 1H), 2.00 (ddd, *J* = 14.3, 12.3, 7.6 Hz, 1H), 1.47 (s, 3H), 1.37 (m, 1H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).

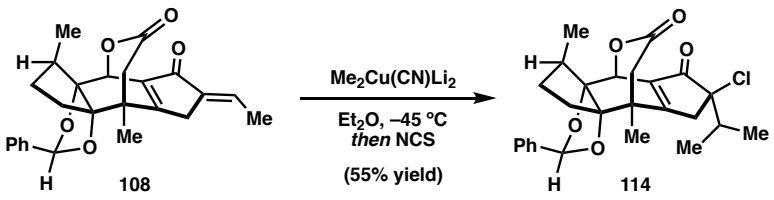
^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4, 183.9, 168.9, 140.6, 138.4, 129.2, 128.4, 126.2, 108.3, 98.1, 95.0, 66.8, 52.8, 44.3, 44.2, 42.9, 34.7, 33.0, 28.4, 20.8, 17.5, 17.3, 12.7.

FTIR (NaCl, thin film): 2959, 2882, 1729, 1702, 1460, 1211, 1109 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 440.2431, found 440.2433.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +46° (*c* = 0.225, $CHCl_3$).

Preparation of chloroketone 114



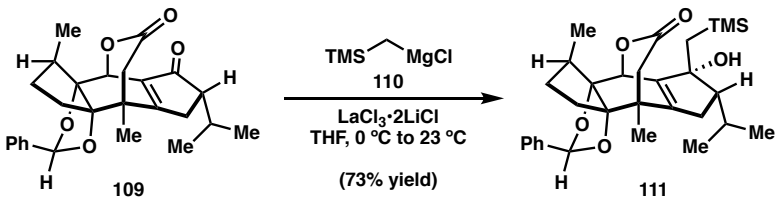
An oven-dried, 1 dram vial was charged with dienone **108** (4.0 mg, 9.84 μmol, 1.0 equiv) in anhydrous Et_2O (0.2 mL). The solution was cooled to –45 ºC via a dry ice/MeCN bath prior to the addition of freshly generated $Me_2Cu(CN)Li_2$ (0.2 M in Et_2O, 64 μL, 12.8 μmol, 1.3 equiv) via syringe. The resulting bright-orange solution was stirred at –45 ºC for 45 min prior to the addition of a freshly generate stock solution of NCS (0.5 M in THF, 30 μL, 14.8 μmol, 1.5 equiv). After 30 min of continued stirring at –45 ºC, the reaction was deemed complete by TLC and LCMS analysis and sat. aq. $NaHCO_3$ (1 mL) was added. Stirring was continued for 5 min at –45 ºC before warming the mixture to ambient temperature. The reaction mixture was diluted with EtOAc (1 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by preparative TLC (35% EtOAc/hexanes) to afford chloroketone **114** (2.5 mg, 5.49 μmol, 86% yield, >10:1 dr) as a white foam.

TLC (30% EtOAc/hexanes): R_f 0.31 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 5.72 (s, 1H), 5.38 (s, 1H), 3.14 (d, *J* = 20.1 Hz, 1H), 2.99 (d, *J* = 20.1 Hz, 1H), 2.89 (d, *J* = 19.4 Hz, 1H), 2.72 (d, *J* = 19.4 Hz, 1H), 2.46 (m, 1H), 2.38 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.27 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.46 (s, 3H), 1.32 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

LRMS (APCI): calc'd for $[M+H]^+$ 456.2, found 456.2.

Preparation of carbinol 111



An oven-dried, 10 mL round-bottomed flask was charged with $LaCl_3$•2LiCl[33] (0.6 M in THF, 3.0 mL, 1.8 mmol). The flask was cooled to 0 ºC via an ice/water bath. After 15 min of continued stirring, (trimethylsilyl)methylmagnesium chloride (0.5 M in Et_2O, 3.6 mL, 1.8 mmol) was added dropwise via syringe. Upon complete addition, the grey thick slurry was stirred for an additional 20 min at 0 ºC affording a 0.27 M stock solution that was used immediately.

A separate oven-dried, 25-mL round-bottomed flask was charged with ketone **109** (82.5 mg, 0.20 mmol, 1.0 equiv) and anhydrous THF (3.9 mL). The resulting solution was cooled to 0 ºC via an ice/water bath and after 15 min of stirring at 0 ºC, the freshly prepared stock solution of nucleophile (0.27 M in THF, 1.8 mL, 0.49 mmol, 3.0 equiv) was added dropwise via syringe. Upon complete addition, the ice/water bath was removed and stirring was continued for 0.5 h at ambient temperature prior to the addition

of an additional portion of the nucleophile (0.27 M in THF, 0.86 mL, 0.23 mmol, 1.2 equiv) via syringe at 0 ºC. After 0.5 h of continued stirring at ambient temperature, the reaction mixture was quenched with the addition of sat. aq. NH_4Cl at 0 ºC and then warmed to ambient temperature. The mixture was diluted with Et_2O and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 60/1% EtOAc/Et_3N/hexanes. The filtrate was then concentrated *in vacuo* and the crude residue was directly purified via SiO_2 flash chromatography (10/1 to 20/1% EtOAc/Et_3N/hexanes) to afford carbinol **111** (72.8 mg, 0.14 mmol, 73% yield, single dr) as an off-white solid [Note: the 1,2-addition product immediately decomposes in $CDCl_3$ and should not be stored for long periods of time].

TLC (20/1% EtOAc/Et_3N/hexanes): R_f 0.40 (UV, *p*-anisaldehyde).

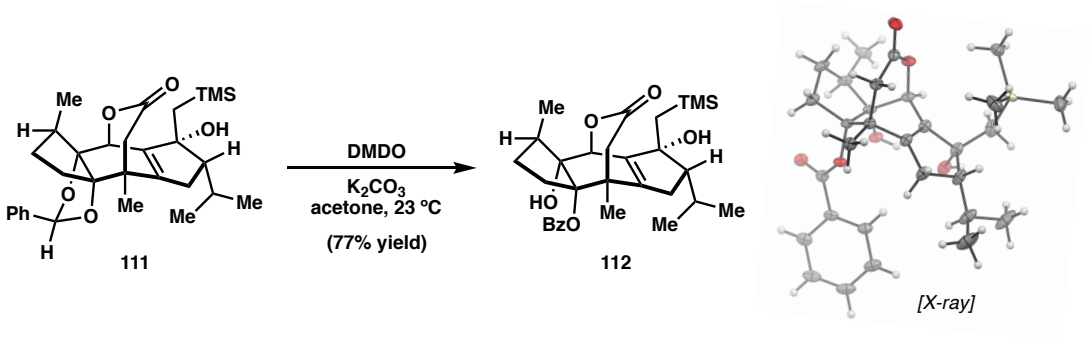
^{1}H NMR (400 MHz, C_6D_6): δ 7.43 (m, 2H), 7.11 (m, 3H), 6.00 (s, 1H), 5.03 (s, 1H), 2.49 (d, *J* = 19.2 Hz, 1H), 2.34 (d, *J* = 19.2 Hz, 1H), 2.29 (m, 1H), 2.25 (dd, *J* = 17.5, 8.3 Hz, 1H), 2.12 (dd, *J* = 17.5, 6.6 Hz, 1H), 2.10 (m, 1H), 1.97 (td, *J* = 8.0, 6.7 Hz, 1H), 1.93 (s, 1H), 1.76 – 1.68 (m, 2H), 1.59 (m, 1H), 1.55 (d, *J* = 15.0 Hz, 1H), 1.30 (m, 1H), 1.28 (d, *J* = 15.0 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 7.2 Hz, 3H), 0.99 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.13 (s, 9H).

^{13}C NMR (101 MHz, C_6D_6): δ 168.8, 151.6, 142.9, 139.5, 129.2, 128.5, 126.7, 108.8, 98.9, 95.6, 84.6, 69.9, 54.4, 45.3, 44.3, 40.2, 34.9, 34.6, 32.7, 31.5, 29.5, 23.1, 21.4, 18.2, 12.8, 0.7.

FTIR (NaCl, thin film): 3508, 2956, 1731, 1716, 1456, 1351, 1215 846 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 511.2874, found 511.2864.

Preparation of hydroxybenzoate 112



An oven-dried, 2 dram vial was charged with alcohol **111** (33.3 mg, 65.2 μmol, 1.0 equiv) and K_2CO_3 (54.1 mg, 0.39 mmol, 6.0 equiv) before adding freshly generated DMDO[63] (0.07 M in acetone, 1.9 mL, 130 μmol, 2.0 equiv) at ambient temperature [Note: the addition of K_2CO_3 is imperative for the stability of the acid-sensitive product]. The reaction was continued for 1 h with vigorous stirring (800 rpm) before an additional portion of DMDO (0.07 M in acetone, 0.93 mL, 65.2 μmol, 1.0 equiv) was added. After TLC analysis indicated the complete consumption of starting material (*ca.* 2 h), the reaction mixture was diluted with CH_2Cl_2 (2 mL) and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* and directly purified via preparative TLC (30/1% EtOAc/Et_3N/hexanes) to afford hydroxybenzoate **112** (26.4 mg, 50.2 μmol, 77% yield, >10:1 rr) as a white solid [Note: the product is used immediately as it is not stable to storage and readily undergoes elimination]. The positional selectivity of the oxidative deprotection was confirmed by X-ray analysis.

TLC (20/1% EtOAc/Et_3N/hexanes): R_f 0.17 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, C_6D_6): δ 7.99 (m, 2H), 7.05 (m, 3H), 4.76 (s, 1H), 3.27 (s, 1H, OH), 2.99 (m, 1H), 2.93 (m, 1H), 2.56 (d, J = 19.4 Hz, 1H), 2.33 – 2.24 (m, 2H), 2.28 (d,

J = 19.4 Hz, 1H), 2.02 – 1.91 (m, 2H), 1.87 (s, 1H, OH), 1.71 (dt, *J* = 13.4, 7.9 Hz, 1H), 1.58 (dd, *J* = 14.3, 7.5 Hz, 1H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 14.8 Hz, 1H), 1.15 (dddd, *J* = 13.4, 7.6 Hz, 1H), 1.09 (d, *J* = 14.8 Hz, 1H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.96 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ 168.4, 167.4, 152.4, 143.3, 132.9, 132.2, 129.7, 128.5, 97.4, 85.5, 84.7, 72.6, 53.8, 44.3, 44.1, 42.1, 34.7, 30.3, 30.0, 28.8, 27.8, 23.3, 20.8, 19.8, 12.5, 0.5.

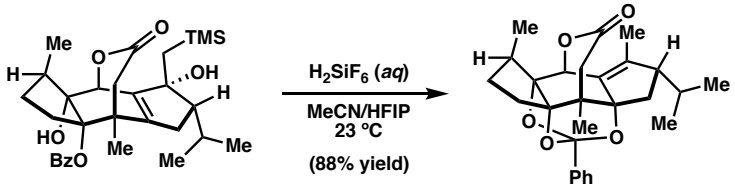
FTIR (NaCl, thin film): 3424, 2956, 1726, 1382, 1272, 1114 cm^{-1}.

LRMS (APCI): calc'd for $[M–OH]^+$ 509.3, found 509.3.

HRMS (ESI): calc'd for $[M+Na]^+$ 549.2643, found 549.2612.

$[\alpha]_D^{25}$ = +37° (*c* = 0.140, MeOH).

Preparation of orthoester 113



112 **113**

An oven-dried, 1 dram vial was charged with hydroxybenzoate **112** (3.0 mg, 5.70 μmol, 1.0 equiv), MeCN (180 μL), and HFIP (20 μL). The resulting solution was cooled to 0 ºC via an ice/water bath and stirring continued for 15 min prior to the addition of H_2SiF_6 (*aq*) (25% w/w, 8 μL, 17.1 μmol, 3.0 equiv). The reaction mixture was immediately removed from cooling bath and continued at ambient temperature until complete consumption of the starting material was observed by TLC analysis (*ca*. 20

min). Sat. aq. $NaHCO_3$ (1 mL) and EtOAc (1 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via preparative TLC (20% EtOAc/hexanes) to provide orthobenzoate **113** (2.2 mg, 5.04 μmol, 88% yield) as a white foam.

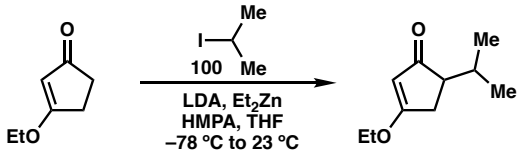
TLC (25% EtOAc/hexanes): 0.59 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (m, 2H), 7.36 (m, 3H), 5.39 (s, 1H), 2.68 (d, *J* = 18.9 Hz, 1H), 2.57 (dd, *J* = 8.6, 5.5 Hz, 1H), 2.52 (m, 1H), 2.50 (d, *J* = 18.9 Hz, 1H), 2.18 (dtd, *J* = 13.0, 7.7, 3.0 Hz, 1H), 2.10 – 1.95 (m, 4H), 1.84 (s, 3H), 1.81 (dd, *J* = 15.5, 2.3 Hz, 1H), 1.64 (ddd, *J* = 12.8, 9.8, 3.1 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.20 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): 171.1, 149.6, 135.2, 133.8, 129.5, 128.0, 125.8, 120.6, 94.3, 91.4, 90.7, 69.7, 55.0, 42.0, 41.7, 40.0, 34.1, 31.6, 28.7, 28.4, 21.8, 17.5, 17.3, 13.1, 13.0.

LRMS (APCI): calc'd for $[M+H]^+$ 437.2, found 437.2.

Preparation of isopropyl ester 119



118 **(70% yield)** **119**

An oven-dried, 500 mL round-bottomed flask was treated with freshly distilled *i*-Pr_2NH (6.4 mL, 45.6 mmol, 1.15 equiv) and anhydrous THF (45 mL). The solution was

cooled to 0 ºC via an ice/water bath and stirring was continued for 15 min prior to the dropwise addition of *n*-BuLi (2.5 M in hexanes, 17 mL, 43.6 mmol, 1.1 equiv) via syringe. Upon complete addition, the reaction was continued for 30 min to produce LDA, which was then further cooled to –78 ºC via a dry ice/acetone bath. To the cooled solution was added vinylogous ester **118** (5.00 g, 39.6 mmol, 1.0 equiv) in anhydrous THF (45 mL) dropwise via cannula over 10 min at –78 ºC. The reaction was continued at –78 ºC for 45 min prior to the dropwise addition of Et_2Zn (1.0 M in hexanes, 42 mL, 41.6 mmol, 1.05 equiv) via syringe [Note: rapid generation of ethane (*g*) is observed, care should be taken to avoid overpressurization]. The reaction was continued for 5 min at –78 ºC before adding, in quick succession, 2-iodopropane (20 mL, 198 mmol, 5.0 equiv) and anhydrous HMPA (31 mL, 178 mmol, 4.5 equiv) via syringe. The reaction flask was immediately removed from the cooling bath and stirring continued at ambient temperature overnight (*ca*. 18-20 h) at which point TLC analysis indicated the complete consumption of starting material. The reaction was recooled to 0 ºC via an ice/water bath and *carefully* quenched with sat. aq. NH_4Cl (80 mL). The mixture was warmed to ambient temperature, diluted with Et_2O (40 mL), and the layers separated. The aqueous layer was extracted with Et_2O (2 × 80 mL) and the combined organic layers were washed with sat. aq. NH_4Cl (80 mL), brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (20 to 30 to 40 to 50% EtOAc/hexanes) to afford isopropyl ester **119** (4.67 g, 27.7 mmol, 70% yield) as a yellow-orange oil.

TLC (30% EtOAc/hexanes): R_f 0.42 (UV, *p*-anisaldehyde).

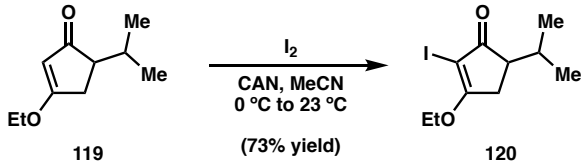
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.24 (s, 1H), 4.03 (qd, *J* = 7.1, 1.1 Hz, 2H), 2.55 (ddd, *J* = 17.2, 7.3, 1.2 Hz, 1H), 2.47 (ddd, *J* = 7.2, 4.1, 2.6 Hz, 1H), 2.35 (ddd, *J* = 17.3, 2.6, 1.1 Hz, 1H), 2.27 (pd, *J* = 6.9, 4.1 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.9, 189.3, 104.9, 67.5, 50.8, 30.3, 28.1, 20.7, 16.5, 14.1.

FTIR (NaCl, thin film): 2958, 2873, 1693, 1594, 1466, 1338, 1029 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 191.1043, found 191.1061.

Preparation of iodoester 120



An oven-dried, 500 mL round-bottomed flask was charged with vinylogous ester **119** (4.60 g, 27.3 mmol, 1.0 equiv) and anhydrous MeCN (180 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 I_2 (7.29 g, 28.7 mmol, 1.05 equiv) then CAN (15.7 g, 28.7 mmol, 1.05 equiv) in quick succession. The reaction mixture was immediately removed from the ice/water bath and the reaction was continued for 0.5 h at ambient temperature, during which time CAN slowly solubilizes resulting in a deep red-black solution. After 0.5 h, TLC analysis indicated the complete consumption of starting material. The reaction mixture was recooled to 0 ºC via an ice/water bath and *carefully* quenched with the addition of sat. aq. $Na_2S_2O_3$ (60 mL) [Note: vigorous evolution of HI is observed at the initial stages of the

quench]. The resulting biphasic mixture was diluted with EtOAc (60 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 80 mL) and the combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (20 to 35% EtOAc/hexanes) to afforded iodoester **120** (5.87 g, 20.0 mmol, 73% yield) as a yellow-orange solid.

TLC (30% EtOAc/hexanes): R_f 0.32 (UV, *p*-anisaldehyde).

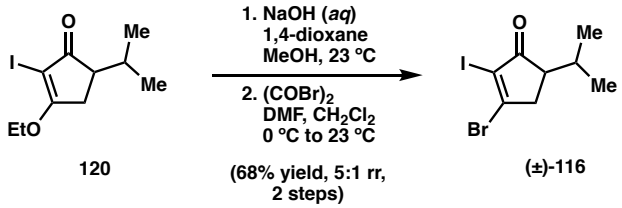
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (q, *J* = 7.1 Hz, 2H), 2.80 (dd, *J* = 17.5, 7.1 Hz, 1H), 2.65 (dd, *J* = 7.0, 4.2, 2.5 Hz, 1H), 2.54 (dd, *J* = 17.4, 2.5 Hz, 1H), 2.30 (pd, *J* = 6.9, 4.1 Hz, 1H), 1.45 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5, 188.1, 73.9, 66.5, 49.8, 29.4, 28.6, 20.2, 16.6, 15.1.

FTIR (NaCl, thin film): 2956, 1678, 1574, 1345, 1336, 1285, 1264 1046 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 317.0009, found 317.0008.

Preparation of iodobromoenone (±)-116



120 (68% yield, 5:1 rr, 2 steps) (±)-116

A 500 mL round-bottomed flask was treated with iodoester **120** (6.06 g, 20.6 mmol, 1.0 equiv), 1,4-dioxane (82 mL), MeOH (82 mL), and *then* 1.0 M NaOH (*aq*) (82 mL, 82.4 mmol, 10 equiv). The resulting deep brown reaction mixture was stirred at

ambient temperature for 3 h, at which point TLC and LCMS indicated the complete consumption of starting material. The reaction was quenched with the addition 1.0 M HCl (*aq*) (100 mL) and diluted with 10% *i*-PrOH/$CHCl_3$ (100 mL). The layers were separated and the aqueous layer was repeatedly extracted with 10% *i*-PrOH/$CHCl_3$ (100 mL) until TLC analysis of the aqueous layer indicated that absence of the intermediate diketone. The combined organic layers were washed with brine (150 mL), filtered over Celite, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (5/1 to 10/1 to 12/1% MeOH/Et_3N/$CHCl_3$) to afford intermediate iododiketone **121** as a dark brown semi-solid.

In an oven-dried, 500 mL round-bottomed flask, the intermediate iododiketone **121** was immediately taken up in anhydrous CH_2Cl_2 (200 mL) and cooled to 0 ºC via an ice/water bath. Anhydrous DMF (4.8 mL, 61.8 mmol, 3.0 equiv) was next added and stirring continued for 15 min at 0 ºC before the dropwise addition of oxalyl bromide (2.9 mL, 30.9 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 h before pouring the reaction mixture over CH_2Cl_2 (50 mL) and ice-cold H_2O (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (150 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (7.5 to 10 to 15% Et_2O/hexanes) to afford iodobromocyclopentenone (±)-**116** (4.60 g, 14.0 mmol, 68% yield) as a yellow oil that solidifies upon storage at –20 ºC. The regioselectivity was confirmed by HMBC analysis.

TLC (10% Et_2O/hexanes): R_f 0.36 (UV, $KMnO_4$).

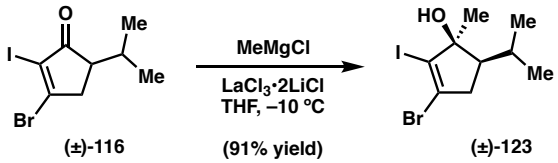
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (dd, *J* = 18.6, 7.1 Hz, 1H), 2.83 (dd, *J* = 18.6, 2.6 Hz, 1H), 2.72 (ddd, *J* = 7.0, 4.4, 2.5 Hz, 1H), 2.29 (pd, *J* = 6.9, 4.4 Hz, 1H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.0, 165.7, 108.3, 52.2, 40.5, 29.2, 20.1, 17.2.

FTIR (NaCl, thin film): 2956, 2359, 1704, 1568, 1456, 1187 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 328.9032, found 328.9024.

Preparation of alcohol 123



(±)-116 (91% yield) (±)-123

An oven-dried, 10 mL round-bottomed flask was charged with ketone **116** (50.2 mg, 0.15 mmol, 1.0 equiv) and anhydrous THF (3.1 mL). The resulting solution was treated with $LaCl_3$•2LiCl (0.6 M in THF, 0.38 mL, 0.23 mmol, 1.5 equiv) and stirring was continued at ambient temperature for 45 min prior to cooling to –10 ºC via an ice/acetone bath. After 15 min of additional stirring at –10 ºC, MeMgCl (3.0 M in THF, 66 μL, 0.20 mmol, 1.3 equiv) was added dropwise via syringe. Upon complete addition the reaction was continued at –10 ºC for 20 min before an additional portion of MeMgCl (3.0 M in THF, 33 μL, 0.10 mmol, 0.6 equiv) was added. Complete consumption of starting material was observed by TLC analysis after an additional 20 mins of stirring and the reaction mixture was thereafter quenched with the addition of sat. aq. NH_4Cl (3 mL) at –10 ºC and then warmed to ambient temperature. The mixture was diluted with Et_2O

and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 50/1% EtOAc/Et_3N/hexanes. The filtrate was then concentrated *in vacuo* and the crude residue was directly purified via SiO_2 flash chromatography (10/1 to 20/1% Et_2O/Et_3N/hexanes) to afford carbinol **123** (47.9 mg, 0.14 mmol, 91% yield) as a colorless oil.

TLC (10% Et_2O/hexanes): R_f 0.24 (UV, *p*-anisaldehyde).

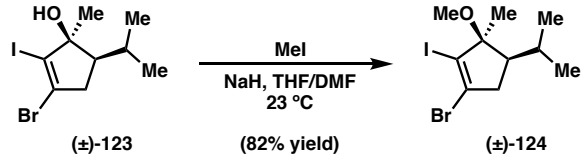
^{1}H NMR (400 MHz, C_6D_6): δ 2.26 (dd, *J* = 16.3, 8.3 Hz, 1H), 2.07 (dd, *J* = 16.3, 7.6 Hz, 1H), 1.54 (dp, *J* = 9.2, 6.6 Hz, 1H), 1.39 (m, 1H), 1.17 (s, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.83 (s, 1H, OH), 0.63 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ 133.1, 113.8, 84.1, 52.6, 44.2, 30.3, 29.5, 22.4, 21.1.

FTIR (NaCl, thin film): 3435, 2958, 2869, 1603, 1384, 1365, 1188, 1068 cm^{-1}.

HRMS (FAB): calc'd for $[(M+H)–H_2]^+$ 342.9195, found 342.9209.

Preparation of methyl ether 124



In a nitrogen-filled glovebox, an oven-dried, 10 mL round-bottomed flask was charged with NaH (dry, 10.8 mg, 452 μmol, 3.0 equiv) and anhydrous DMF (2.5 mL). The flask was capped with a rubber septum, removed from the glovebox, and cooled to 0 ºC via an ice/water bath. After 15 min of continued stirring, alcohol **123** (52.0 mg, 151 μmol, 1.0 equiv) in anhydrous THF (2.5 mL) was added dropwise via syringe. Upon complete addition, the reaction was continued at 0 ºC for 1 h before adding iodomethane

(56 μL, 904 μmol, 6.0 equiv) via microsyringe. The reaction was then removed from the cooling bath and left to stir at ambient temperature until complete consumption of starting material was observed by TLC analysis (*ca.* 3 h). The reaction was quenched with the *careful* addition of sat. aq. NH_4Cl (1 mL), diluted with Et_2O (1 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 2 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (1 to 3% EtOAc/hexanes) to afford methyl ether **124** (44.4 mg, 124 μmol, 82% yield) as a colorless oil. The relative stereochemistry was confirmed by nOe analysis.

TLC (7.5% EtOAc/hexanes): R_f 0.50 (UV, *p*-anisaldehyde).

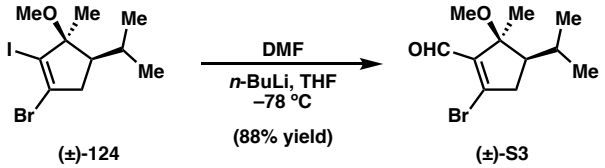
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19 (s, 3H), 2.80 (dd, *J* = 16.5, 8.2 Hz, 1H), 2.50 (dd, *J* = 16.5, 8.2 Hz, 1H), 1.97 – 1.80 (m, 2H), 1.42 (s, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 134.3, 109.6, 88.4, 53.4, 52.7, 46.8, 30.0, 29.9, 22.5, 22.2.

FTIR (NaCl, thin film): 2958, 2828, 1601, 1443, 1374, 1080 cm^{-1}.

HRMS (FAB): calc'd for $[(M+H)–H_2]^+$ 356.9351, found 356.9341.

Preparation of enal S3



(±)-124 (±)-S3

An oven-dried, 1 dram vial was charged with vinyl iodide **123** (5.8 mg, 16.2 μmol, 1.0 equiv) and anhydrous THF (0.5 mL). The resulting solution was cooled to –78 ºC via a dry ice/acetone bath and stirring was continued for 15 min prior to adding *n*-BuLi (2.5 M in hexanes, 6.5 μL, 16.2 μmol, 1.0 equiv) via microsyringe. Upon complete addition, the reaction was continued at –78 ºC for 20 min before anhydrous DMF (3.8 μL, 48.5 μmol, 3.0 equiv) was added. Complete consumption of starting material was observed by TLC analysis after an additional 15 mins of stirring at –78 ºC and the reaction mixture was thereafter quenched with the addition of sat. aq. NH_4Cl (1 mL) and then warmed to ambient temperature. The mixture was diluted with Et_2O (0.5 mL) and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 20% EtOAc/hexanes. The filtrate was then concentrated *in vacuo* and the crude residue was directly purified via preparative TLC (30% CH_2Cl_2/hexanes) to afford enal **S3** (3.7 mg, 14.2 μmol, 91% yield) as a colorless oil.

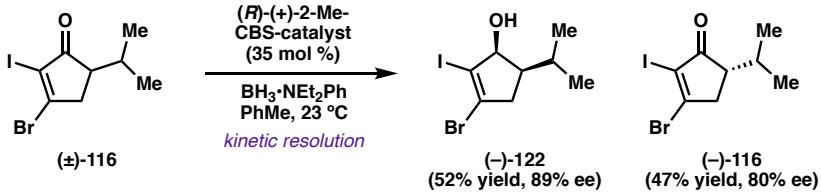
TLC (30% CH_2Cl_2/hexanes): R_f 0.27 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, C_6D_6): δ 9.99 (s, 1H), 3.06 (s, 3H), 2.33 (dd, *J* = 18.5, 9.2 Hz, 1H), 2.24 (dd, *J* = 18.5, 8.1 Hz, 1H), 1.79 (dp, *J* = 9.2, 6.7 Hz, 1H), 1.55 (s, 3H), 1.24 (td, *J* = 9.2, 8.1 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ 189.0, 148.6, 141.6, 85.8, 56.1, 52.7, 45.9, 28.6, 22.8, 22.7, 22.0.

HRMS (FAB): calc'd for $[M]^+$ 260.0412, found 260.0436.

Preparation of enriched alcohol (–)-122



An oven-dried, 10 mL round-bottomed flask was charged with (*R*)-(+)-2-Me-CBS-oxazaborolidine (29.5 mg, 106 μmol, 0.35 equiv) and anhydrous CH_2Cl_2 (2.0 mL). After 15 min of continued stirring, BH_3•NEt_2Ph (49 μL, 274 μmol, 0.9 equiv) was added dropwise via microsyringe. The reaction mixture was stirred an additional 10 min at ambient temperature before adding cyclopentenone (±)-**116** (100 mg, 304 μmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2.0 mL) dropwise over 1 h via syringe pump before another portion of CH_2Cl_2 (1.0 mL) was used to render the transfer quantitative. Upon complete addition, the reaction mixture was continued for an additional 4 h, then diluted with Et_2O (2 mL) and quenched with the *careful* addition of MeOH (0.5 mL) followed by H_2O (1.5 mL) [Caution! Rapid generation of H_2. A vent needle was routinely used to prevent over-pressurization.], before warming to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (10 to 15 to 20% Et_2O/hexanes) to afford cyclopentenol (–)-**122** (52.1 mg, 157 μmol, 52% yield) as a

white solid. The ee was determined by SFC analysis (**122:** AD-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R (minor) = 4.649 min, t_R (major) = 5.585 min; **116:** AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R (minor) = 3.312 min, t_R (major) = 3.537 min).

TLC (15% Et_2O/hexanes): R_f 0.37 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.50 (td, *J* = 6.2, 1.7 Hz, 1H), 2.60 (dd, *J* = 16.1, 7.7 Hz, 1H), 2.52 (ddd, *J* = 16.2, 8.4, 1.7 Hz, 1H), 2.00 (dddd, *J* = 10.8, 8.4, 7.8, 6.0 Hz, 1H), 1.89 (dp, *J* = 10.8, 6.4 Hz, 1H), 1.68 (d, *J* = 6.3 Hz, 1H, OH), 1.02 (d, *J* = 6.3, 3H), 0.93 (d, *J* = 6.6 Hz, 3H).

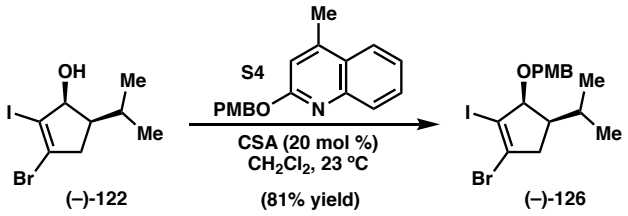
^{13}C NMR (101 MHz, $CDCl_3$): δ 136.6, 102.6, 82.1, 51.0, 42.9, 27.8, 21.4, 21.0.

FTIR (NaCl, thin film): 3330, 2956, 2869, 1598, 1241, 1096, 1065, 1011 cm^{-1}.

HRMS (ESI): calc'd for $[M]^+$ 329.9111, found 329.9116.

$[\alpha]_D^{25}$ = –11° (*c* = 1.19, $CHCl_3$).

Preparation of PMB ether (–)-126



An oven-dried, 500 mL round-bottomed flask was charged with alcohol (–)-**122** (2.66 g, 8.03 mmol, 1.0 equiv), 2-(4-methoxybenzyloxy)-4-methylquinoline[64-65] (4.49 g, 16.1 mmol, 2.0 equiv), and anhydrous CH_2Cl_2 (80 mL). The solution was treated with (±)-10-camphorsulfonic acid (373 mg, 1.61 mmol, 0.20 equiv) and the suspension was vigorously stirred at ambient temperature under Ar for 36 h. The reaction mixture was

carefully treated with sat. aq. $NaHCO_3$ (20 mL), diluted with Et_2O (80 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 40 mL) and the combined organic layers were washed with 1 N HCl (*aq*) (3 × 60 mL), brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* [Note: the 1 N HCl (*aq*) washes were deemed imperative for the efficient removal of the 2-lepidone byproduct]. The crude residue was purified via SiO_2 flash chromatography (2/2 to 3/3 to 4/4% Et_2O/CH_2Cl_2/hexanes) to afford PMB ether (–)-**126** (2.94 g, 6.51 mmol, 81% yield) as a thick colorless oil that solidifies to a white solid upon storage at –20 ºC. The stereochemistry was confirmed by nOe analysis.

TLC (15% Et_2O/hexanes): R_f 0.67 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 2H), 6.88 (m, 2H), 4.89 (d, *J* = 10.5 Hz, 1H), 4.56 (d, *J* = 10.5 Hz, 1H), 4.38 (dd, *J* = 6.0, 1.4 Hz, 1H), 3.80 (s, 3H), 2.60 (ddd, *J* = 16.2, 8.5, 1.5 Hz, 1H), 2.54 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.13 – 1.91 (m, 2H), 0.97 (d, *J* = 6.2 Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 1H).

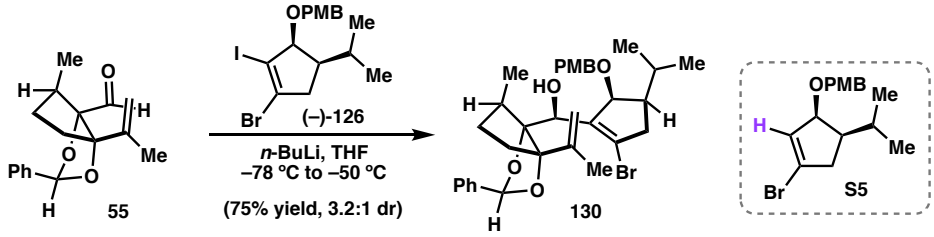
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 137.3, 130.4, 129.3, 113.8, 98.3, 88.0, 72.5, 55.3, 52.2, 43.2, 27.3, 21.5, 20.8.

FTIR (NaCl, thin film): 2956, 2869, 1614, 1514, 1248 cm^{-1}.

HRMS (ESI): calc'd for $[M+H_2O]^+$ 467.9792, found 467.9807.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –29° (*c* = 0.650, $CHCl_3$).

Convergent union of aldehyde 55 and iodobromocyclopentenol (–)-126



An oven-dried, 100 mL round-bottomed flask was charged with vinyl iodide (–)-**126** (2.24 g, 4.96 mmol, 1.25 equiv) and anhydrous THF (18 mL) [Note: vinyl iodide (–)-**126** was azeotroped with PhH three times immediately prior to use]. The solution was cooled to –78 ºC via a dry ice/acetone bath and stirring continued for 15 min prior to the dropwise addition of *n*-BuLi (2.5 M in hexanes, 2.0 mL, 4.96 mmol, 1.25 equiv) via syringe. Upon complete addition, the reaction mixture was stirred an additional 15 min. Aldehyde **55** (1.08 g, 3.97 mmol, 1.0 equiv) in anhydrous THF (18 mL) was added dropwise via cannula over 15 min [Note: aldehyde **55** was azeotroped with PhH three times immediately prior to use], before another portion of THF (3 mL) was used to render the transfer quantitative. Immediately upon complete addition of aldehyde **55**, the reaction mixture was slowly warmed to –50 ºC over 15 min and the reaction was continued at –50 ºC until TLC analysis indicated the complete consumption of starting material (*ca*. 30 min). The reaction mixture was quenched with the addition of sat. aq. NH_4Cl (10 mL) and then warmed to ambient temperature and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^1H NMR analysis of the crude product indicated that the reaction occurs with full consumption of the starting material in a 3.2:1 diastereomeric ratio. Purification via SiO_2 flash chromatography (5/5 to 10/5 to 15/5%

Et_2O/CH_2Cl_2/hexanes) afforded alcohol **130** (1.78 g, 2.97 mmol, 75% yield) as a white foam.

TLC (10/5% Et_2O/CH_2Cl_2/hexanes): R_f 0.32 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 – 7.63 (m, 2H), 7.42 – 7.36 (m, 3H), 7.05 – 6.99 (m, 2H), 6.79 – 6.74 (m, 2H), 6.37 (s, 1H), 5.32 (d, *J* = 0.8 Hz, 1H), 5.20 (t, *J* = 1.5 Hz, 1H), 4.95 (d, *J* = 4.0 Hz, 1H), 4.65 (d, *J* = 4.6 Hz, 1H), 4.46 (d, *J* = 9.6 Hz, 1H), 4.40 (d, *J* = 9.6 Hz, 1H), 3.78 (s, 3H), 2.78 (ddd, *J* = 15.8, 9.5, 0.8 Hz, 1H), 2.44 (p, *J* = 7.0 Hz, 1H), 2.39 (dd, *J* = 15.8, 7.0 Hz, 1H), 2.27 (dq, *J* = 12.3, 6.3 Hz, 1H), 2.18 – 2.12 (m, 2H), 2.11 (d, *J* = 1.1 Hz, 3H), 1.99 (dd, *J* = 13.4, 6.3 Hz, 1H), 1.87 (tdd, *J* = 9.7, 7.0, 4.6 Hz, 1H), 1.23 (dd, *J* = 11.9, 6.0 Hz, 1H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 148.1, 142.6, 138.0, 131.2, 129.7, 129.6, 129.4, 128.4, 126.9, 113.3, 112.6, 105.0, 99.1, 96.7, 80.5, 72.4, 71.3, 55.2, 55.0, 41.8, 41.4, 38.8, 30.6, 26.0, 23.0, 21.3, 14.1.

FTIR (NaCl, thin film): 3498, 2956, 2871, 1613, 1514, 1248, 1064, 1029 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 614.2476, found 614.2470.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +70° (*c* = 1.575, $CHCl_3$).

Deiodination byproduct S5:

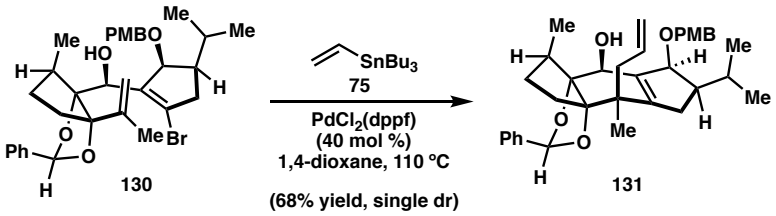
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.22 (m, 2H), 6.91 – 6.76 (m, 2H), 6.19 (td, *J* = 2.5, 1.2 Hz, 1H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.34 (d, *J* = 11.2 Hz, 1H), 4.23 (d, *J* = 5.9, 2.4, 1.6 Hz, 1H), 3.80 (s, 3H), 2.60 (dddd, *J* = 16.1, 8.4, 2.5, 1.6 Hz, 1H), 2.48 (ddd, *J* =

16.2, 7.4, 1.2 Hz, 1H), 2.09 – 1.79 (m, 2H), 0.97 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 131.5, 130.7, 129.6, 129.1, 113.7, 81.2, 70.4, 55.3, 51.9, 43.2, 27.2, 21.5, 21.3.

HRMS (ESI): calc'd for $[M+H_2O]^+$ 342.0825, found 342.0848.

Preparation of ABC tricycle 131



In a nitrogen-filled glovebox, an oven-dried, 300 mL heavy-walled pressure vessel equipped with a magnetic stirbar was charged with $PdCl_2(dppf)•CH_2Cl_2$ (880 mg, 1.08 mmol, 0.40 equiv) and vinyl bromide **130** (1.61 g, 2.69 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (135 mL). The suspension was treated with tributyl(vinyl)stannane (1.42 mL, 4.85 mmol, 1.8 equiv) before the vessel was sealed with a CAPFE O-ring lined cap, removed from the glove box, and submerged in a preheated oil bath at 110 ºC. After 24 h of continued stirring at 110 ºC, the vessel was cooled to ambient temperature, diluted with Et_2O (50 mL), and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the crude residue was redissolved in Et_2O (100 mL) and treated with sat. aq. KF (100 mL). The biphasic mixture was vigorously stirred for 15 min before separating the two layers. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined layers were washed with brine (100 mL), dried over $MgSO_4$, filtered over Celite, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash

chromatography (10/1 to 15/1 to 20/1% EtOAc/Et_3N/hexanes) to afford ABC tricycle **131** (998 mg, 1.83 mmol, 68% yield) as a pale-yellow oil [Note: the use of Et_3N is critical to isolate **131** without tin byproducts originating from stannane **75**]. The stereochemistry of **131** was confirmed by nOe analysis.

TLC (20% EtOAc/hexanes): R_f 0.54 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.36 (m, 3H), 7.29 – 7.26 (m, 2H), 6.90 – 6.82 (m, 2H), 5.90 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.66 (s, 1H), 5.12 – 4.99 (m, 2H), 4.73 (s, 1H), 4.71 (d, *J* = 10.9 Hz, 1H), 4.57 (d, *J* = 10.9 Hz, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 2.59 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.49 (h, *J* = 7.0 Hz, 1H), 2.41 – 2.23 (m, 3H), 2.21 (d, *J* = 3.5 Hz, 1H), 2.16 (m, 1H), 2.10 – 1.97 (m, 2H), 1.92 (ddd, *J* = 13.1, 7.3, 4.4 Hz, 2H), 1.52 (dd, *J* = 11.9, 6.2 Hz, 1H), 1.17 (s, 3H), 1.16 (d, *J* = 7.6 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H).

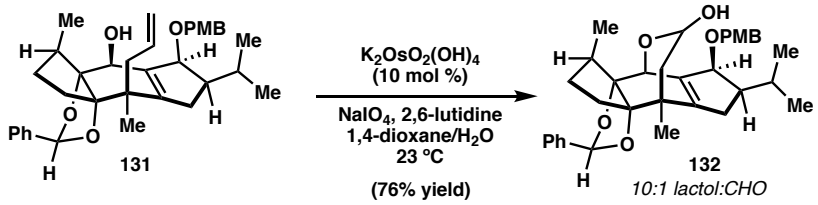
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 150.0, 137.8, 135.6, 131.2, 129.3, 129.3, 128.4, 126.9, 117.2, 113.8, 104.9, 97.8, 97.4, 86.1, 72.6, 69.6, 55.3, 51.1, 44.1, 43.9, 43.1, 35.2, 34.7, 32.9, 27.1, 22.5, 20.8, 19.9, 14.4.

FTIR (NaCl, thin film): 3480, 2954, 1613, 1514, 1458, 1248, 1031 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 567.3081, found 567.3064.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –11° (*c* = 0.565, $CHCl_3$).

Preparation of lactol 132



An oven-dried, 250 mL round-bottomed flask was charged with ABC tricycle **131** (1.84 g, 3.38 mmol, 1.0 equiv), 1,4-dioxane (61 mL), and deionized H_2O (6.8 mL). The solution was treated with 2,6-lutidine (1.6 mL, 13.5 mmol, 4.0 equiv) via syringe, $K_2OsO_2(OH)_4$ (124 mg, 0.34 mmol, 0.10 equiv), and then $NaIO_4$ (1.45 g, 6.76 mmol, 2.0 equiv). The resulting reaction mixture was vigorously stirred at ambient temperature for 1 h, after which additional deionized H_2O (54 mL) and $NaIO_4$ (723 mg, 3.38 mmol, 1.0 equiv) were added. Stirring was continued at ambient temperature until TLC analysis indicated the complete consumption of starting material (*ca.* 2 h). The reaction mixture was diluted with Et_2O (20 mL) and then treated with sat. aq. $NaHCO_3$ (40 mL) and sat. aq. $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (20 to 30% EtOAc/hexanes) to afford lactol **132** (1.40 g, 2.57 mmol, 76% yield) as a 10:1 mixture with its aldehyde.

TLC (20% EtOAc/hexanes): R_f 0.38 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.32 (m, 5H), 7.30 – 7.26 (m, 2H), 6.97 – 6.82 (m, 2H), 5.63 (s, 1H), 4.83 (s, 1H), 4.82 (m, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.38 (dd, *J* = 5.8, 1.3 Hz, 1H), 3.80 (s, 3H), 2.51 (dd, *J* = 16.8, 7.4 Hz, 1H),

2.47 – 2.38 (m, 3H), 2.23 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.10 (m, 1H), 2.04 – 1.77 (m, 5H), 1.67 (dd, *J* = 14.7, 8.8 Hz, 1H), 1.31 (d, *J* = 7.0 Hz, 3H),1.30 (s, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

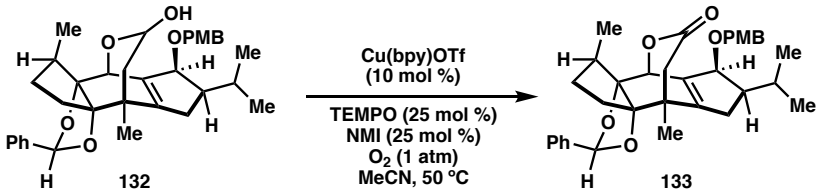
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 153.8, 138.9, 136.5, 131.1, 129.2, 129.2, 128.4, 126.7, 113.7, 110.1, 99.2, 96.6, 93.7, 84.5, 71.2, 70.0, 55.2, 53.2, 45.1, 43.7, 41.7, 36.3, 35.1, 33.6, 27.5, 21.9, 21.6, 20.5, 12.8.

FTIR (NaCl, thin film): 3444, 2956, 2873, 1613, 1514, 1248, 1026 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 564.3320, found 564.3323.

$[\alpha]_D^{25}$ = –9° (*c* = 0.590, $CHCl_3$).

Preparation of lactone 133



An oven-dried, 100 mL round-bottomed flask was charged with lactol **132** (1.29 g, 2.36 mmol, 1.0 equiv) and anhydrous MeCN (47 mL). The solution was treated with bpy (43.9 mg, 0.24 mmol, 0.10 equiv), $Cu(MeCN)_4OTf$ (88.9 mg, 0.24 mmol, 0.10 equiv), TEMPO (92.2 mg, 0.59 mmol, 0.25 equiv), and then NMI (47 μL, 0.59 mmol, 0.25 equiv) via microsyringe. The round-bottomed flask was immediately capped with a rubber septum and equipped with a double-walled O_2 balloon. The brick-red reaction was submerged in a preheated oil bath at 50 ºC and vigorously stirred (≥750 rpm) under O_2 supplied via a double-walled balloon until the reaction mixture turned a dark brown, at

which point LCMS analysis indicated the complete consumption of starting material (*ca.* 1.5 h) [Note: the starting material and product lactone are indistinguishable by TLC and thus requires the use of LCMS for reaction monitoring]. The reaction mixture was cooled to ambient temperature, diluted with Et_2O (30 mL), and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 60% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified by SiO_2 flash chromatography (25 to 35% EtOAc/hexanes) to afford lactone **133** (1.04 g, 1.91 mmol, 81% yield) as an off-white foam.

TLC (30% EtOAc/hexanes): R_f 0.71 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.34 (m, 5H), 7.32 – 7.24 (m, 2H), 6.91 – 6.82 (m, 2H), 5.65 (s, 1H), 5.06 (s, 1H), 4.64 (d, *J* = 10.5 Hz, 1H), 4.43 (d, *J* = 10.5 Hz, 1H), 4.43 (d, *J* = 6.3 Hz, 1H), 3.79 (s, 3H), 2.78 (d, *J* = 19.3 Hz, 1H), 2.68 (d, *J* = 19.3 Hz, 1H), 2.55 (dt, *J* = 13.0, 7.1 Hz, 1H), 2.49 (d, *J* = 7.9 Hz, 2H), 2.23 (m, 1H), 2.16 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.10 – 1.94 (m, 2H), 1.85 (m, 1H), 1.49 (m, 1H), 1.31 (s, 3H), 1.30 (d, *J* = 7.3 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H).

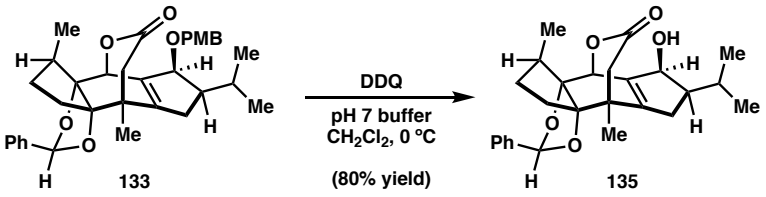
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 159.1, 157.1, 139.9, 137.9, 130.5, 129.7, 129.5, 128.5, 126.6, 113.7, 109.5, 97.8, 95.7, 83.5, 72.3, 71.1, 55.2, 53.1, 45.1, 45.0, 40.2, 35.2, 34.8, 32.9, 27.3, 21.9, 21.4, 19.1, 13.0.

FTIR (NaCl, thin film): 2958, 1727, 1514, 1249, 1034 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 567.2717, found 567.2716.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –5° (*c* = 0.475, $CHCl_3$).

Preparation of alcohol 135



An oven-dried, 100 mL round-bottomed flask was charged with PMB ether **133** (1.11 g, 2.04 mmol, 1.0 equiv), CH_2Cl_2 (55 mL), and pH 7 buffer (11 mL). The mixture was cooled to 0 ºC via an ice/water bath and stirring was continued for 15 min prior to the addition of DDQ (555 mg, 2.45 mmol, 1.2 equiv) as a single portion. The reaction mixture quickly becomes a deep green suspension and vigorous stirring (≥800 rpm) is continued for 40 min prior to the addition of another portion of DDQ (278 mg, 1.22 mmol, 0.6 equiv). The reaction was continued at 0 ºC until TLC analysis indicated the complete consumption of the starting material (*ca*. 1.5 h). Sat. aq. $NaHCO_3$ (20 mL) was added and the mixture was diluted with $CHCl_3$ (10 mL) before the layers were separated [Note: the use of $CHCl_3$ over CH_2Cl_2 proved advantageous in obtaining clear partitioning of the two layers]. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (20 to 35 to 45% EtOAc/hexanes) to afford alcohol **135** (692 mg, 1.63 mmol, 80% yield) as a white foam.

TLC (30% EtOAc/hexanes): R_f 0.24 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.33 (m, 5H), 5.65 (s, 1H), 5.13 (s, 1H), 4.72 (t, *J* = 6.1 Hz, 1H), 2.78 (d, *J* = 19.3 Hz, 1H), 2.67 (d, *J* = 19.3 Hz, 1H), 2.55 (dd, *J* = 16.8, 7.1

Hz, 1H), 2.41 (ddd, *J* = 17.1, 8.0, 1.9 Hz, 1H), 2.28 – 2.10 (m, 2H), 2.01 (m, 1H), 1.93 – 1.76 (m, 2H), 2.42 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H).

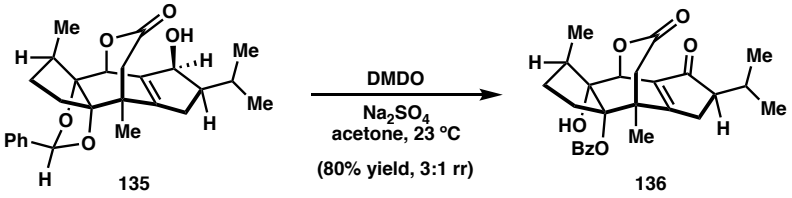
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 155.7, 140.8, 137.9, 129.5, 128.5, 126.6, 109.5, 97.9, 95.7, 77.5, 71.9, 52.2, 44.9, 44.8, 40.2, 35.3, 34.4, 33.0, 27.6, 22.0, 21.5, 19.1, 13.0.

FTIR (NaCl, thin film): 3434, 2958, 1702, 1381, 1217, 1101, 1063, 1023 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 447.2142, found 447.2144.

$[\alpha]_D^{25}$ = +51° (*c* = 0.165, $CHCl_3$).

Preparation of hydroxybenzoate 136



An oven-dried, 200 mL round-bottomed flask was charged with alcohol **135** (738 mg, 1.74 mmol, 1.0 equiv) and Na_2SO_4 (1.48 g, 0.39 mmol, 200% w/w) before adding freshly generated DMDO[63] (0.08 M in acetone, 43 mL, 3.48 mmol, 2.0 equiv) at ambient temperature. The reaction was continued for 1 h with vigorous stirring (800 rpm) before an additional portion of DMDO (0.08 M in acetone, 22 mL, 1.74 mmol, 1.0 equiv) was added. After LCMS analysis indicated the complete consumption of starting material (*ca.* 2 h), the reaction mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* and directly purified via SiO_2 flash chromatography (35 to 45 to 55% EtOAc/hexanes) to afford an inseparable regioisomeric

mixture of hydroxybenzoate **136** (610 mg, 1.39 mmol, 80% combined yield, 3:1 rr) as a white foam.

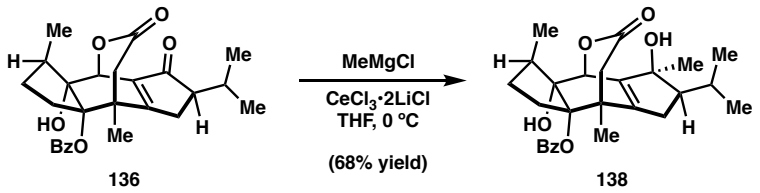
TLC (40% EtOAc/hexanes): R_f 0.37 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 5.09 (s, 1H), 3.02 (d, *J* = 19.4 Hz, 1H), 2.85 – 2.72 (m, 3H), 2.65 – 2.58 (m, 3H), 2.61 (d, *J* = 19.7 Hz, 1H), 2.32 (td, *J* = 7.0, 4.6 Hz, 1H), 2.22 (dd, *J* = 14.3, 7.7 Hz, 1H), 2.08 (m, 1H), 1.52 (s, 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.20 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H).

FTIR (NaCl, thin film): 3453, 2960, 1728, 1704, 1694, 1276, 1114 cm^{-1}.

HRMS (ESI): calc'd for $[M+NH_4]^+$ 456.2381, found 456.2377.

Preparation of diol 138



An oven-dried, 10 mL round-bottomed flask was charged with $CeCl_3$•2LiCl[33] (0.3 M in THF, 4.0 mL) via syringe and the solution was immediately cooled to 0 ºC via an ice/water bath. After 15 min of continued stirring at 0 ºC, MeMgCl (3.0 M in THF, 0.4 mL) was added dropwise via syringe. Upon complete addition, the resulting dark-yellow reaction mixture was stirred for an additional 20 min at 0 ºC affording a 0.27 M stock solution of nucleophile that was used immediately.

A separate oven-dried, 100 mL round-bottomed flask was charged with enone **136** (399 mg, 0.91 mmol, 1.0 equiv) and anhydrous THF (18 mL). The resulting solution was cooled to 0 ºC via an ice/water bath and after 15 min of continued stirring, the freshly prepared stock solution of nucleophile (0.27 M in THF, 6.7 mL, 1.82 mmol, 2.0 equiv) was added dropwise via syringe. Upon complete addition, the reaction was continued at 0 ºC for 20 min at which point TLC and LCMS analysis indicated the complete consumption of starting material. The reaction was quenched with the addition of pH 7 buffer (3.6 mL) at 0 ºC and then warmed to ambient temperature. The mixture was diluted with Et_2O (10 mL) and filtered through a pre-equilibrated SiO_2 pad layered with Celite, washing with 80/1% EtOAc/Et_3N/hexanes. The filtrate was then concentrated *in vacuo* and directly purified via SiO_2 flash chromatography (25/1 to 35/1 to 45/1 EtOAc/Et_3N/hexanes) to afford alcohol **138** (281 mg, 0.62 mmol, 68% yield) as a white foam.

TLC (40% EtOAc/hexanes): R_f 0.34 (UV, *p*-anisaldehyde).

^{1}H NMR (500 MHz, C_6D_6): δ 7.96 (d, *J* = 6.9 Hz, 2H), 7.10 – 6.99 (m, 3H), 4.85 (s, 1H), 2.75 (td, *J* = 14.6, 14.2, 7.7 Hz, 1H), 2.62 (s, 1H, OH), 2.49 (d, *J* = 19.3 Hz, 1H), 2.35 (m, 1H), 2.22 (d, *J* = 19.3 Hz, 1H), 1.73 (s, 1H, OH), 1.69 – 1.51 (m, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.17 (s, 3H), 1.09 (m, 1H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.94 (s, 3H), 0.82 (d, *J* = 6.4 Hz, 3H).

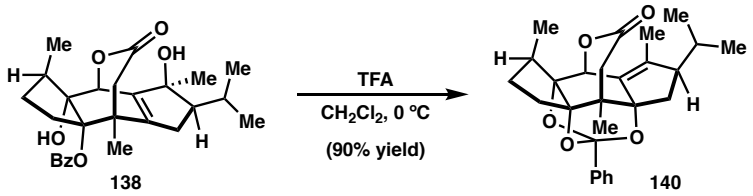
^{13}C NMR (101 MHz, C_6D_6): δ 168.4, 167.4, 148.6, 145.0 133.1, 131.9, 129.6, 128.6, 96.8, 85.5, 82.7, 71.9, 60.4, 45.0, 44.4, 41.7, 33.5, 30.0, 28.5, 22.4, 21.9, 20.3, 19.8, 12.4.

FTIR (NaCl, thin film): 3460, 2960, 2884, 1724, 1274, 1115, 1023 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 477.2248, found 477.2229.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +10° (*c* = 0.125, CH_2Cl_2).

Preparation of orthobenzoate 140



An oven-dried, 50 mL round-bottomed flask was treated with hydroxybenzoate **138** (281 mg, 0.62 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (20 mL). The resulting solution was cooled to 0 ºC via an ice/water bath and stirring was continued at this temperature for 15 min prior to the addition of TFA (0.24 mL, 3.09 mmol, 5.0 equiv) *as a single portion* via syringe. The reaction was allowed 5 min at 0 ºC, during which time the colorless reaction mixture becomes bright pink, diluted with CH_2Cl_2 (10 mL) and treated with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue could be used directly in the next step after azeotroping with anhydrous PhMe three times immediately prior to use. The crude residue was purified via SiO_2 flash chromatography (10 to 20% EtOAc/hexanes) for characterization purposes to afford orthobenzoate **140** (243 mg, 0.56 mmol, 90% yield) as a white foam.

TLC (10% EtOAc/hexanes): R_f 0.24 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.53 (m, 2H), 7.43 – 7.31 (m, 3H), 5.37 (s, 1H), 3.06 (t, *J* = 9.2 Hz, 1H), 2.71 (d, *J* = 19.0 Hz, 1H), 2.62 (d, *J* = 19.0 Hz, 1H), 2.54 (dt, *J* = 12.5, 7.2 Hz, 1H), 2.23 – 2.09 (m, 2H), 2.07 – 1.93 (m, 2H), 1.89 (dd, *J* = 14.2, 6.9 Hz, 1H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.69 (dd, *J* = 14.2, 8.2 Hz, 1H), 1.65 (m, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.25 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H).

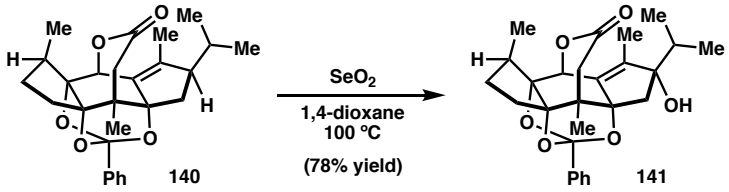
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 150.2, 135.0, 134.2, 129.6, 128.1, 126.0, 120.9, 94.5, 91.0, 91.0, 69.5, 51.9, 42.1, 41.7, 40.1, 34.1, 30.5, 28.5, 27.3, 21.1, 17.4, 15.7, 13.0, 12.6.

FTIR (NaCl, thin film): 2958, 2878, 1731, 1351, 1190 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 459.2142, found 459.2154.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –201° (*c* = 0.175, $CHCl_3$).

Preparation of alcohol 141



An oven-dried 48 mL pressure flask was charged with orthobenzoate **140** (242 mg, 0.55 mmol, 1.0 equiv), anhydrous 1,4-dioxane (18 mL), and SeO_2 (308 mg, 2.77 mmol, 5.0 equiv) [Note: SeO_2 was stored in a nitrogen-filled glove box to maintain the integrity of the reagent]. The flask was immediately capped with a CAPFE O-ring lined cap and submerged in a preheated oil bath at 100 ºC. The reaction mixture was vigorously stirred for 1 h, at which point TLC and LCMS analysis indicated the complete consumption of starting material. The pressure flask was removed from the oil bath and

cooled to ambient temperature, and the reaction mixture was diluted with Et_2O (10 mL) and filtered over a pre-equilibrated SiO_2 pad layered with Celite, washing with 80% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified via SiO_2 flash chromatography (5 to 10 to 20 to 30% EtOAc/hexanes) to afford alcohol **141** (196 mg, 0.43 mmol, 78% yield) as a yellow foam.

TLC (15% EtOAc/hexanes): R_f 0.14 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, C_6D_6): δ 7.83 – 7.65 (m, 2H), 7.14 – 7.01 (m, 3H), 5.35 (s, 1H), 2.49 (d, *J* = 18.9 Hz, 1H), 2.40 (dq, *J* = 11.7, 7.1 Hz, 1H), 2.29 (d, *J* = 18.9 Hz, 1H), 2.01 (s, 1H), 1.91 (hept, *J* = 6.8 Hz, 1H), 1.81 (m, 1H), 1.80 (d, *J* = 14.6 Hz, 1H), 1.73 – 1.63 (m, 3H), 1.67 (d, *J* = 14.7 Hz, 1H), 1.52 (s, 3H), 1.18 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.97 (s, 3H), 0.46 (d, *J* = 6.7 Hz, 3H).

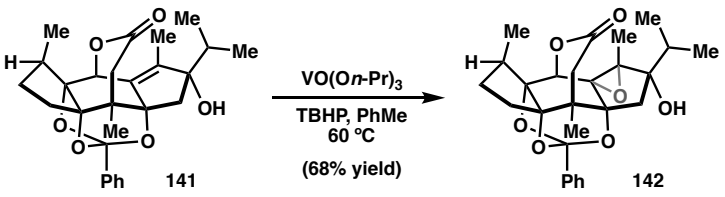
^{13}C NMR (101 MHz, C_6D_6): δ 168.8, 150.7, 137.1, 135.7, 129.8, 126.4, 121.6, 94.6, 91.3, 90.0, 87.9, 69.0, 42.0, 41.9, 39.1, 37.8, 34.3, 32.3, 28.6, 18.1, 17.6, 16.7, 13.0, 9.4.

FTIR (NaCl, thin film): 3540, 2960, 2879, 1732, 1352, 1078, 1038 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 453.2272, found 453.2271.

$[\alpha]_D^{25}$ = –161° (*c* = 0.115, CH_2Cl_2).

Preparation of epoxide 142



An oven-dried, 20 mL scintillation vial was treated with alkene **141** (104 mg, 230 μmol, 1.0 equiv) and anhydrous PhMe (7.7 mL). The resulting solution was treated with

$VO(O\textit{n}\text{-}Pr)_3$ (26 μL, 115 μmol, 0.5 equiv) via microsyringe prior to the addition of TBHP (5.5 M in decanes, 125 μL, 689 μmol, 3.0 equiv) via microsyringe. The vial was capped with a Teflon-lined cap under Ar and immediately placed in a preheated heating block at 60 ºC. The reaction was left to stir at this temperature for 14 h prior to adding an additional portion of $VO(O\textit{n}\text{-}Pr)_3$ (26 μL, 115 μmol, 0.5 equiv) and TBHP (5.5 M in decanes, 125 μL, 689 μmol, 3.0 equiv) via syringe at ambient temperature. The reaction was continued at 60 ºC for an additional 14 h at which point LCMS analysis indicated complete consumption of the starting material [Note: the starting material and product epoxide are indistinguishable by TLC and thus requires the use of LCMS for reaction monitoring]. The reaction was cooled to ambient temperature and quenched with the addition of pH 7 buffer (6 mL) and sat. aq. $Na_2S_2O_3$ (3 mL). EtOAc (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered over Celite, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (1 to 2 to 3% acetone/CH_2Cl_2) to afford epoxide **142** (73.2 mg, 156 μmol, 68% yield) as a white foam. The stereochemistry was confirmed by nOe analysis.

TLC (4% acetone/CH_2Cl_2): R_f 0.43 (UV, *p*-anisaldehyde).

^{1}H NMR (500 MHz, C_6D_6): δ 7.89 (m, 2H), 7.14 (m, 3H), 4.66 (s, 1H), 3.07 (s, 1H, OH), 2.70 (d, J = 19.6 Hz, 1H), 2.52 (d, J = 19.6 Hz, 1H), 2.30 (m, 1H), 2.14 (d, J = 16.4 Hz, 1H), 1.82 (p, J = 6.8 Hz, 1H), 1.72 (m, 1H), 1.66 – 1.54 (m, 2H), 1.57 (d, J = 16.4 Hz, 1H), 1.44 (m, 1H), 1.35 (s, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H), 0.89 (s, 3H), 0.74 (d, J = 6.8 Hz, 3H).

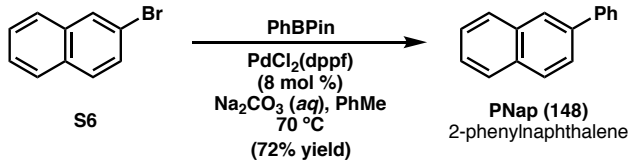
^{13}C NMR (101 MHz, C_6D_6): δ 167.8, 135.5, 129.8, 128.2, 126.5, 121.7, 93.9, 91.9, 85.0, 81.7, 76.5, 76.1, 74.8, 42.5, 41.6, 40.4, 39.6, 34.1, 33.8, 28.5, 19.6, 17.9, 17.4, 13.0, 12.9.

FTIR (NaCl, thin film): 3506, 2964, 2880, 1737, 1360, 1199 cm^{-1}.

HRMS (ESI): calc'd for $[M+Na]^+$ 491.2040, found 491.2030.

$[\alpha]_D^{25}$ = –136° (*c* = 0.185, $CHCl_3$).

Preparation of 2-phenylnaphthalene (148)

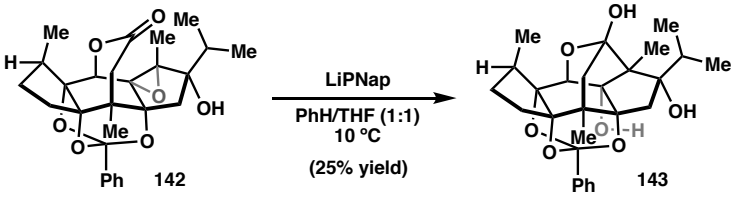


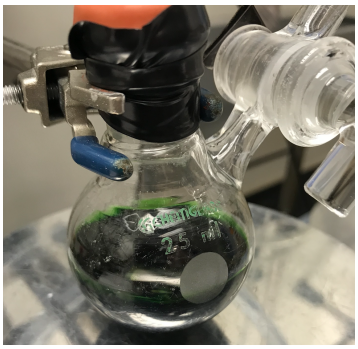
An oven-dried, 250 mL round-bottomed flask was charged with 2-bromonaphthalene (3.11 g, 15.0 mmol, 1.0 equiv), phenylboronic acid pinacol ester (6.12 g, 30.0 mmol, 2.0 equiv), and $PdCl_2$(dppf)•CH_2Cl_2 (980 mg, 1.20 mmol, 8 mol %). The flask was equipped with a rubber septum and evacuated/refilled three times with Ar. Anhydrous PhMe (100 mL) and freshly degassed 2.0 M Na_2CO_3 (*aq*) (37.5 mL, 75.0 mmol, 5.0 equiv) were subsequently added via syringe [Note: 2.0 M Na_2CO_3 (*aq*) was degassed by sparging with Ar for ≥15 min]. The biphasic mixture was immediately placed in a preheated oil bath at 70 ºC equipped with a double-walled Ar balloon and the reaction was continued at 70 ºC with vigorous stirring (≥700 rpm) until TLC analysis indicated the complete consumption of starting material (*ca*. 2 h). The reaction mixture was cooled to ambient temperature, diluted with EtOAc (40 mL), and treated with sat. aq. NH_4Cl (60 mL). The layers were separated and the aqueous layer was extracted with EtOAc (1 × 100 mL). The combined layers were washed with brine (50 mL), dried over

Na_2SO_4, filtered over Celite, and concentrated *in vacuo*. The crude residue was purified via SiO_2 flash chromatography (5% CH_2Cl_2/hexanes) to afford 2-phenylnaphthalene (2.25 g, 11.0 mmol, 72% yield) as a white solid.

Spectral data of 2-phenylnaphthalene (**148**) matched that obtained on an authentic sample purchased from Acros Organics.

Preparation of pentacycle 143





LiPNap was prepared according to the following procedure: An oven-dried, 25 mL Schlenk flask containing a borosilicate glass-coated magnetic stirbar was charged with 2-phenylnaphthalene (409 mg, 2.0 mmol) and freshly cut lithium wire (14.0 mg, 2.0 mmol) [Note: Immediately prior to use, lithium wire was washed with hexanes, hammered out into a foil, and cut into several small strips]. The Schlenk flask was evacuated and refilled with Ar three times before anhydrous THF (12.5 mL) was added and the resulting reaction mixture was vigorously stirred (900-1000 rpm) at ambient temperature for 10 min, at which point the solution becomes a deep-green. After the reaction mixture was stirred at ambient temperature for approximately 4 h, the LiPNap solution (~0.16 M) was cooled to 0 ºC via an ice/water bath and immediately used.

An oven-dried, 2 dram vial was charged with epoxide **142** (20.4 mg, 43.5 μmol, 1.0 equiv) and anhydrous PhH (1.4 mL) [Note: epoxide **142** was azeotroped with PhH three times prior to use]. The solution was cooled to +10 ºC via a dry ice/1,4-dioxane bath and stirring was continued for 15 min at this temperature prior to the dropwise addition of freshly generated LiPNap (0.16 M in THF, 1.2 mL, 196 μmol, 4.5 equiv). Upon complete addition, the resulting dark-orange reaction mixture was stirred for 5 min before adding sat. aq. $NaHCO_3$ (1 mL). The mixture was warmed to ambient temperature, diluted with $CHCl_3$ (1 mL), and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 × 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via preparative TLC (3% MeOH/CH_2Cl_2) to afford pentacycle **143** (5.1 mg, 10.8 μmol, 25% yield) as an off-white foam.

TLC (7% MeOH/CH_2Cl_2): R_f 0.30 (UV, *p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.59 (m, 2H), 7.47 – 7.33 (m, 3H), 4.25 (s, 1H), 3.19 (s, 1H, OH), 3.09 (d, *J* = 1.9 Hz, 1H, OH), 2.81 (s, 1H, OH), 2.56 (d, *J* = 15.5 Hz, 1H), 2.31 (dt, *J* = 10.5, 7.1 Hz, 1H), 2.14 – 2.04 (m, 2H), 2.11 (d, *J* = 15.6 Hz, 1H), 2.08 (d, *J* = 14.7 Hz, 1H), 1.97 (m, 1H), 1.96 (d, *J* = 14.7 Hz, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.40 (s, 3H), 1.29 (s, 3H), 1.14 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H).

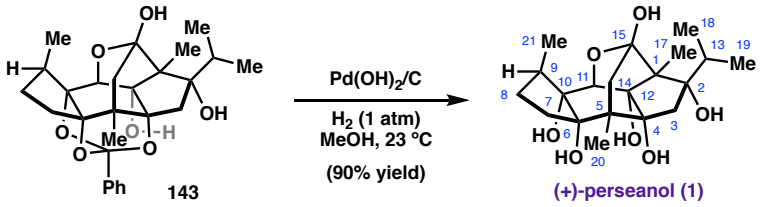
^{13}C NMR (101 MHz, $CDCl_3$): δ 134.6, 129.9, 128.2, 126.0, 120.4, 104.8, 96.0, 92.6, 88.6, 85.7, 81.0, 74.2, 60.1, 47.8, 42.1, 41.4, 39.1, 34.1, 33.3, 28.6, 20.1, 18.8, 18.6, 14.0, 9.7.

FTIR (NaCl, thin film): 3451, 2957, 2924, 1853, 1725, 1462, 1350, 1033 cm^{-1}.

HRMS (ESI): calc'd for $[M+H]^+$ 471.2377, found 471.2385.

$[\alpha]_D^{25} = -52°$ (c = 0.090, $CHCl_3$).

Preparation of perseanol (1)



An oven-dried, 2 dram vial was charged with pentacycle **143** (6.7 mg, 14.2 μmol, 1.0 equiv), $Pd(OH)_2/C$ (20 wt %, 14 mg), and MeOH (2.9 mL). The vial was capped with a rubber septum and the reaction mixture was vigorously stirred (1000 rpm) while flushing the headspace with H_2 for 5 minutes via a double-walled balloon. The suspension was vigorously stirred under H_2 until LCMS indicated complete consumption of the starting material (*ca.* 1.5 h) and then immediately diluted with CH_2Cl_2 (2 mL), filtered through a short pad of Celite, and concentrated *in vacuo*. Purification of the crude residue by SiO_2 flash chromatography (4 to 8 to 10% MeOH/$CHCl_3$) afforded (+)-perseanol (4.9 mg, 12.8 μmol, 90% yield) as a white solid.

TLC (10% MeOH/CH_2Cl_2): R_f 0.21 (*p*-anisaldehyde).

^{1}H NMR (500 MHz, CD_3OD): δ 3.82 (s, 1H, C_{11}), 2.59 (d, J = 15.8 Hz, 1H, C_3), 2.23 (m, 1H, C_7), 1.98 (dt, J = 12.7, 6.8 Hz, 1H, C_9), 1.92 (d, J = 14.7 Hz, 1H, C_{14}), 1.90 (d, J = 15.8 Hz, 1H, C_3), 1.86 (p, J = 6.7 Hz, 1H, C_{13}), 1.64 – 1.53 (m, 2H, C_8), 1.64 (d, J =

14.7 Hz, 1H, C_{14}), 1.57 (m, C_7), 1.29 (s, 3H, C_{17}), 1.13 (s, 3H, C_{20}), 1.11 (d, J = 6.9 Hz, 3H, C_{21}), 1.02 (d, J = 6.6 Hz, 3H, C_{19}), 0.97 (d, J = 6.8 Hz, 3H, C_{18}).

^{13}C NMR (101 MHz, CD_3OD): δ 104.3 (C_{15}), 89.2 (C_{12}), 85.1 (C_4), 83.1 (C_6), 82.1 (C_2), 81.6 (C_{10}), 77.7 (C_{11}), 63.0 (C_1), 52.6 (C_3), 46.9 (C_9), 45.5 (C_{14}), 44.7 (C_5), 37.5 (C_7), 35.3 (C_{13}), 30.1 (C_8), 18.9 (C_{18}), 18.9 (C_{19}), 18.5 (C_{21}), 12.8 (C_{20}), 10.7 (C_{17}).

FTIR (NaCl, thin film): 3383, 2925, 2855, 1728, 1463, 1384, 1287, 1106, 1029 cm^{-1}.

HRMS (ESI:NES): calc'd for $[M–H]^-$ 383.2075, found 383.2075.

HRMS (ESI:PES): calc'd for $[M+Na]^+$ 407.2040, found 407.2039.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +3° (c = 0.085, MeOH).

^{1}H and ^{13}C NMR Comparison Tables for (+)-Perseanol

Table 1. Comparison of ^{1}H NMR data for (+)-Perseanol

Proton No.	Zhang and coworkers Natural (+)-Perseanol ^{1}H NMR, 400 MHz, CD_3OD ^{1}H [δ, multi., *J* (Hz)]	This Work, Synthetic (+)-Perseanol ^{1}H NMR, 500 MHz, CD_3OD ^{1}H [δ, multi., *J* (Hz)]
1		
2		
3a	1.90 (d, *J* = 15.8 Hz)	1.90 (d, *J* = 15.8 Hz)
3b	2.59 (d, *J* = 15.8 Hz)	2.59 (d, *J* = 15.8 Hz)
4		
5		
6		
7a	2.22 (m)	2.23 (m)
7b	1.57 (m)	1.57 (m)
8	1.63 – 1.52 (m)	1.64 – 1.53 (m)
9	1.98 (dt, *J* = 12.9, 7.0 Hz)	1.98 (dt, *J* = 12.7, 6.9 Hz)
10		
11	3.82 (s)	3.82 (s)
12		
13	1.87 (p, *J* = 6.6 Hz)	1.86 (p, *J* = 6.7 Hz)
14a	1.64 (d, *J* = 14.6 Hz)	1.64 (d, *J* = 14.7 Hz)
14b	1.92 (d, *J* = 14.7 Hz)	1.92 (d, *J* = 14.7 Hz)
15		
17	1.30 (s)	1.29 (s)
18	0.97 (d, *J* = 6.8 Hz)	0.97 (d, *J* = 6.8 Hz)
19	1.02 (d, *J* = 6.6 Hz)	1.02 (d, *J* = 6.6 Hz)
20	1.13 (s)	1.13 (s)
21	1.11 (d, *J* = 7.0 Hz)	1.11 (d, *J* = 6.9 Hz)

Table 2. Comparison of ^{13}C NMR data for (+)-Perseanol

Carbon No.	Zhang and coworkers Natural (+)-Perseanol ^{13}C NMR, 101 MHz, CD_3OD ^{13}C (δ) ppm	This Work, Synthetic (+)-Perseanol ^{13}C NMR, 101 MHz, CD_3OD ^{13}C (δ) ppm	Chemical Shift Difference, Δδ
1	63.0	63.0	0
2	82.1	82.1	0
3	52.6	52.6	0
4	85.1	85.1	0
5	44.7	44.7	0
6	83.1	83.1	0
7	37.5	37.5	0
8	30.1	30.1	0
9	46.9	46.9	0
10	81.7	81.6	0.1
11	77.6	77.7	0.1
12	89.2	89.2	0
13	35.2	35.3	0.1
14	45.5	45.5	0
15	104.3	104.3	0
17	10.7	10.7	0
18	18.9	18.9	0
19	18.9	18.9	0
20	12.8	12.8	0
21	18.5	18.5	0

3.8 NOTES AND REFERENCES

(1) Fraga, B. M.; Gonzalez-Coloma, A.; Gutierrez, C.; Terrero, D. *J. Nat. Prod.* **1997**, *60*, 880.

(2) Zeng, J. F.; Xue, Y. B.; Shu, P. H.; Qian, H. Q.; Sa, R. J.; Xiang, M.; Li, X. N.; Luo, Z. W.; Yao, G. M.; Zhang, Y. H. *J. Nat. Prod.* **2014**, *77*, 1948.

(3) Chuang, K. V.; Xu, C.; Reisman, S. E. *Science* **2016**, *353*, 912.

(4) Sun, J. W.; Conley, M. P.; Zhang, L. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705.

(5) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742.

(6) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.

(7) Urabe, D.; Asaba, T.; Inoue, M. *Chem. Rev.* **2015**, *115*, 9207.

(8) Artman, G. D.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523.

(9) Aggarwal, V. K.; Davies, P. W.; Schmidt, A. T. *Chem. Commun.* **2004**, 1232.

(10) Bai, Y.; Shen, X. Y.; Li, Y.; Dai, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 10838.

(11) Bai, Y.; Davis, D. C.; Dai, M. J. *J. Org. Chem.* **2017**, *82*, 2319.

(12) Negishi, E.; Ma, S. M.; Amanfu, J.; Coperet, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919.

(13) Coperet, C.; Negishi, E. *Org. Lett.* **1999**, *1*, 165.

(14) Grigg, R.; Mutton, S. P. *Tetrahedron* **2010**, *66*, 5515.

(15) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.

(16) Wu, L. P.; Fang, X. J.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X. F. *ACS Catalysis* **2014**, *4*, 2977.

(17) Labinger, J. A. *Organometallics* **2015**, *34*, 4784.

(18) Shen, Y.; Li, L. B.; Pan, Z. S.; Wang, Y. L.; Li, J. D.; Wang, K. Y.; Wang, X. C.; Zhang, Y. Y.; Hu, T. H.; Zhang, Y. D. *Org. Lett.* **2015**, *17*, 5480.

(19) Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602.

(20) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(21) Yasuda, A.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1705.

(22) Willy, W. E.; Binsch, G.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 5394.

(23) Hu, P. F.; Snyder, S. A. *J. Am. Chem. Soc.* **2017**, *139*, 5007.

(24) Huang, Z. H.; Huang, J.; Qu, Y. Z.; Zhang, W. B.; Gong, J. X.; Yang, Z. *Angew. Chem. Int. Ed.* **2018**, *57*, 8744.

(25) Luparia, M.; Vadala, A.; Zanoni, G.; Vidari, G. *Org. Lett.* **2006**, *8*, 2147.

(26) Vadala, A.; Finzi, P. V.; Zanoni, G.; Vidari, G. *Eur. J. Org. Chem.* **2003**, 642.

(27) Li, C. S.; Jou, D. C.; Cheng, C. H. *Organometallics* **1993**, *12*, 3945.

(28) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65.

(29) Yang, Q. L.; Draghici, C.; Njardarson, J. T.; Li, F.; Smith, B. R.; Das, P. *Org. Biomol. Chem.* **2014**, *12*, 330.

(30) Yang, M.; Yang, X. W.; Sun, H. B.; Li, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 2851.

(31) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552.

(32) Xie, X. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2015**, *137*, 3767.

(33) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

(34) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y. S.; Xiang, J. N. *J. Am. Chem. Soc.* **2002**, *124*, 5380.

(35) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 186.

(36) Kishi, Y.; Sugiura, S.; Tanino, H.; Goto, T.; Aratani, M.; Kakoi, H.; Inoue, S.; Fukuyama, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

(37) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526.

(38) Aigner, J.; Gossinger, E.; Kahlig, H.; Menz, G.; Pflugseder, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2226.

(39) Wardrop, D. J.; Bowen, E. G. *Chem. Commun.* **2005**, 5106.

(40) Ley, S. V.; Abad-Somovilla, A.; Anderson, J. C.; Ayats, C.; Banteli, R.; Beckmann, E.; Boyer, A.; Brasca, M. G.; Brice, A.; Broughton, H. B.; Burke, B. J.; Cleator, E.; Craig, D.; Denholm, A. A.; Denton, R. M.; Durand-Reville, T.; Gobbi, L. B.; Gobel, M.; Gray, B. L.; Grossmann, R. B.; Gutteridge, C. E.; Hahn, N.; Harding, S. L.; Jennens, D. C.; Jennens, L.; Lovell, P. J.; Lovell, H. J.; de La Puente, M. L.; Kolb, H. C.; Koot, W. J.; Maslen, S. L.; McCusker, C. F.; Mattes, A.; Pape, A. R.; Pinto, A.; Santafianos, D.; Scott, J. S.; Smith, S. C.; Somers, A. Q.; Spilling, C. D.; Stelzer, F.; Toogood, P. L.; Turner, R. M.; Veitch, G. E.; Wood, A.; Zumbrunn, C. *Chem. Eur. J.* **2008**, *14*, 10683.

(41) Jeker, O. F.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3474.

(42) Baldwin, J. E. *J. C. S. Chem. Commun.* **1976**, 734.

(43) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. C. S. Chem. Commun.* **1976**, 736.

(44) Baldwin, J. E. *J. C. S. Chem. Commun.* **1976**, 738.

(45) Donohoe, T. J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015.

(46) Hill, R. R.; Rychnovsky, S. D. *J. Org. Chem.* **2016**, *81*, 10707.

(47) Murali, C.; Shashidhar, M. S.; Gopinath, C. S. *Tetrahedron* **2007**, *63*, 4149.

(48) Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 634.

(49) Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095.

(50) Helal, C. J.; Meyer, M. P. The Corey-Bakshi-Shibata Reduction: Mechanistic and Synthetic Considerations – Bifuntional Lewis Base Catalysis and Dual Activation. In *Lewis Base Catalysis in Organic Synthesis*, 1st ed.; Vedejs, E.; Denmark, S. E., Eds. Wiley-VCH: Weinheim, Germany, 2016.

(51) Bringmann, G.; Pabst, T.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E. M.; Rycroft, D. S.; Connolly, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 9127.

(52) Fehr, C.; Galindo, J.; Etter, O. *Eur. J. Org. Chem.* **2004**, 1953.

(53) Velcicky, J.; Lanver, A.; Lex, J.; Prokop, A.; Wieder, T.; Schmalz, H. G. *Chem. Eur. J.* **2004**, *10*, 5087.

(54) Mycock, D. K.; Sherlock, A. E.; Glossop, P. A.; Hayes, C. J. *Tetrahedron Lett.* **2008**, *49*, 6390.

(55) Nicolaou, K. C.; Harrison, S. T. *J. Am. Chem. Soc.* **2007**, *129*, 429.

(56) Perry, M. A.; Rychnovsky, S. D. *Nat. Prod. Rep.* **2015**, *32*, 517.

(57) Benzene as a co-solvent was recently reported to be advantageous for ketyl anion chemistry: Wolleb, H.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 10890.

(58) Szostak, M.; Collins, K. D.; Fazakerley, N. J.; Spain, M.; Procter, D. J. *Org. Biomol. Chem.* **2012**, *10*, 5820.

(59) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Org. Chem.* **2014**, *79*, 11988.

(60) Szostak, M.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 8459.

(61) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Eur. J.* **2014**, *20*, 4222.

(62) Niwa, H.; Kunitani, K.; Nagoya, T.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3094.

(63) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

(64) Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436.

(65) Stewart, C. A.; Peng, X. W.; Paquette, L. A. *Synthesis* **2008**, 433.

Appendix 3

Failed Synthetic Strategies for the Isoryanoid Diterpenes

A3.1 INTRODUCTION

The success of our synthetic route to the isoryanoid diterpene (+)-perseanol (**1**) hinged on the evaluation of several different strategies that provided us valuable insight and information on the isomeric ring system. These subtleties gleaned from failure ultimately guided our decisions on strategic bond disconnections and fragment selection. Herein, we will briefly discuss two select approaches that laid the foundation for the successful fragment coupling approach discussed in the previous chapter.

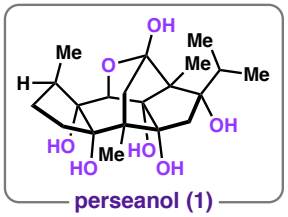
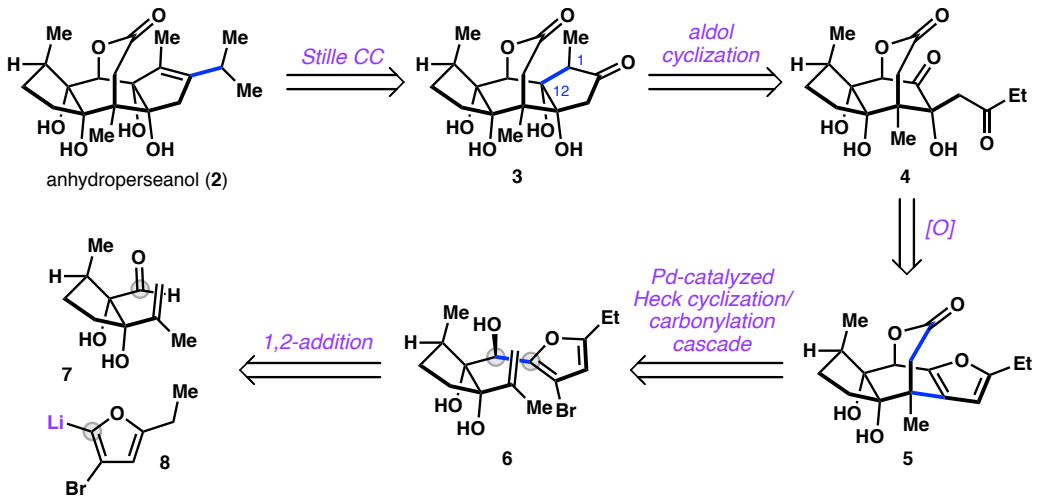


Figure 1. *The isoryanoid diterpene perseanol.*

A3.2 FURAN A-RING APPROACH

Prior to commencing our studies with vinyl bromide A-ring partners, we envisioned generating the isoryanoid A-ring with its requisite functionality from a furan surrogate (Scheme 1). In the retrosynthetic sense, this disconnection was inspired by our successful Stille cross-coupling approach to introduce the isopropyl unit of the diterpene framework. Thus anhydroperseanol (**2**) was simplified to its methyl ketone **3**. Thermodynamic enolization would generate a triflate primed to undergo cross-coupling. In making this simplification, an aldol disconnection revealed itself between the C1–C12 bond, and the requisite starting material, or 1,4-diketone **4** could be readily accessed from oxidative degradation of furan **5**. Tetracycle **5** became the testing ground for our Pd-cascade chemistry.



Scheme 1. *Furan A-ring retrosynthetic analysis.*

To begin evaluating this route, our C-ring aldehyde fragment **9** was first engaged with the 2-lithio-furan generated from commercially available 3-bromofuran (**10**, Figure 2). Deprotonation of **10** with LDA occurs selectively at the acidic C2 position; no other positional isomers are observed when the reaction is maintained at cryogenic

temperatures (–78 ºC). The 1,2-addition occurs with good yields and diastereoselectivity to afford bromofuran **11**.

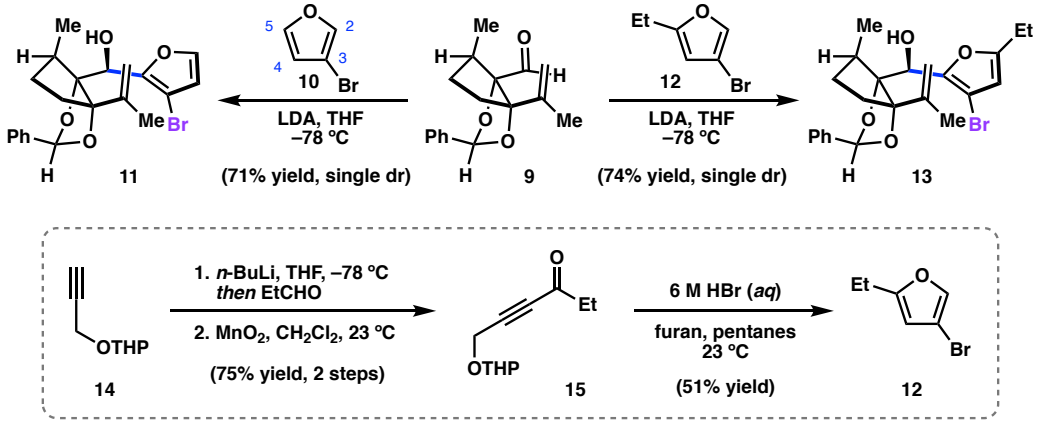


Figure 2. *Fragment coupling with 2-lithio-3-bromofuran.*

Extensive optimization led to the realization of the Pd-catalyzed Heck-Stille cascade and generation of ABC tricycle **17** (Figure 3). TBACl proved to be a critical additive to observe good levels of conversion with bromofuran **11**; the same additive with vinyl bromide substrates instead promoted direct Stille cross-coupling in favor of Heck cyclization chemistry. Notably, this same sequence could be performed with 5-ethyl-3-bromofuran (**13**) to generate advanced ABC tricycle **18** following fragment coupling and cyclization as before with no reoptimization.

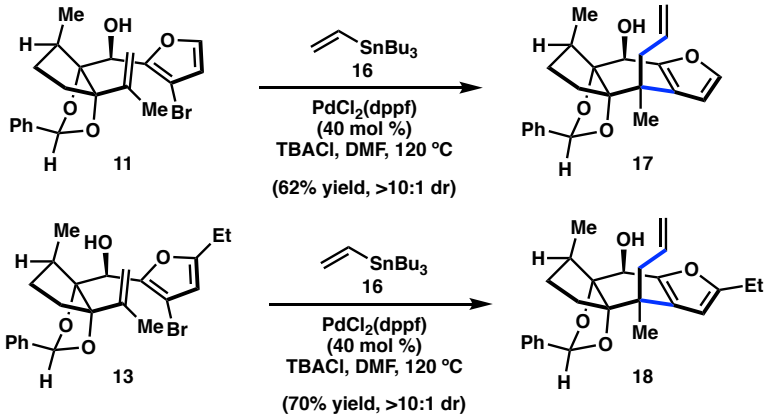
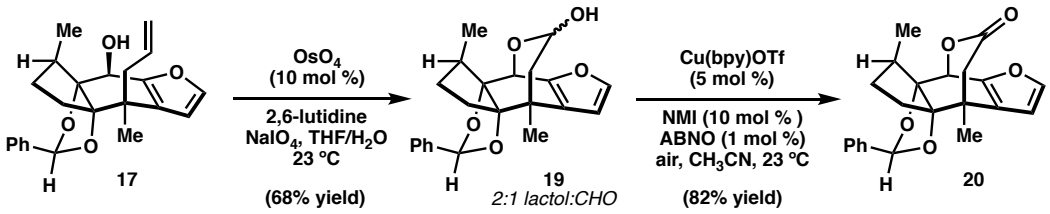


Figure 3. *Pd-catalyzed Heck-Stille cascade with bromofuran A-ring.*

With tricycles **17** and **18** in hand, we moved to address the formation of the D-ring lactone (Scheme 2). As before, Johnson-Lemieux oxidation of furan **17** provided lactol **19**. While the Stahl oxidation[1] of lactol **19** led to productive oxidation chemistry and the generation of lactone **20**, despite our best efforts, the lactol derived from the functionalized tricycle **18** proved to be resilient. Other conditions including Fetizon's reagent and TEMPO/NaOCl likewise proved unsuccessful. The subtle conformational issues derived from the simple incorporation of an ethyl group at the furan led us to abandon this approach.



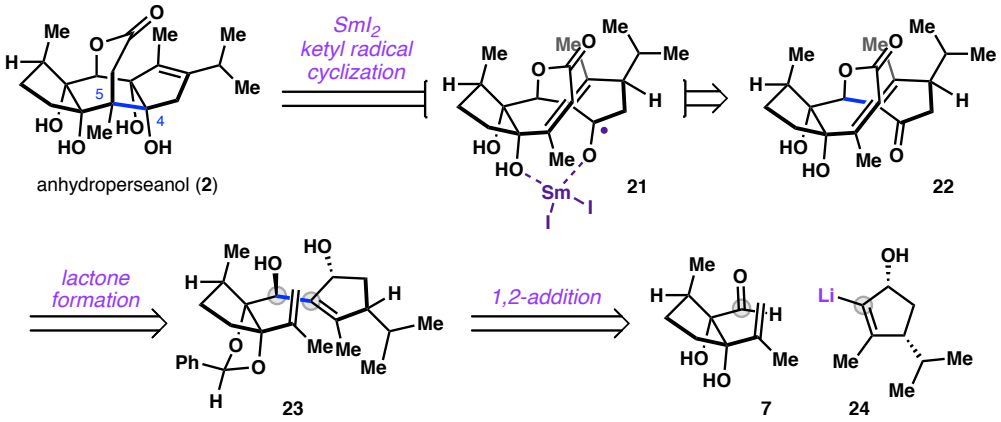
Scheme 2. *Tetracycle formation with furan A-ring.*

A3.3 SAMARIUM DIIODIDE DISCONNECTION

A3.3.1 *Retrosynthetic Analysis*

Rendering the C4–C5 bond a common strategic platform for convergent design, we become interested in the possibility of generating anhydroperseanol (**2**) through a key SmI_2 ketyl radical cyclization event (Scheme 3). Enone **22** was expected to undergo chemoselective single-electron reduction affording intermediate ketyl radical **21**. The well-reported oxophilicity of samarium was envisioned to play a key role in (1) assisting in bringing the two reacting partners into proximity and (2) guiding the sense of diastereoselectivity in this key transformation.[2] Cyclization substrate **22** could readily be simplified to 1,2-addition product **23** through a series of functional group

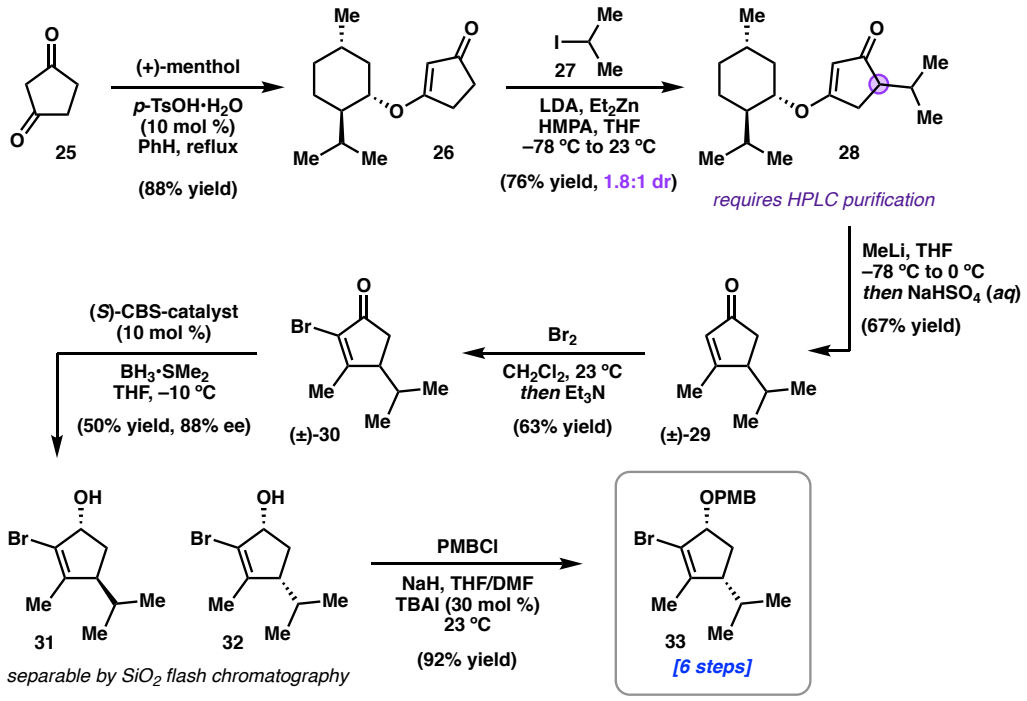
interconversions, thus requiring robust and enantioselective entry into an A-ring fragment of the type exemplified by **24**.



Scheme 3. *SmI_2 disconnection retrosynthetic analysis.*

A3.3.2 *A-ring Fragment Preparation*

A thorough investigation of the literature revealed known cyclopentenone (±)-**29**–generated in 3 steps from commercially available 1,3-cyclopentanedione (**25**)–as an ideal starting place (Scheme 4).[3] While the diastereomers of **28** were disclosed in the original report by Overman and coworkers to be separable by HPLC purification, this was deemed to be tedious and prohibitive of a scalable approach to this valuable fragment. To avoid this protocol, following bromination of (±)-**29**, we elected to perform a catalyst-controlled reduction of *rac*-bromocyclopentenone **30**, generating enriched diastereomers **31** and **32**, which are readily separable by careful SiO_2 flash chromatography.[4] Attempts to instead iodinate (±)-**29** led to α-iodination requiring the development of a highly optimized bromination procedure. Routine PMB protection of vinyl bromide **32** finally provided enriched A-ring fragment **33**, primed to undergo lithium-halogen exchange and 1,2-addition.

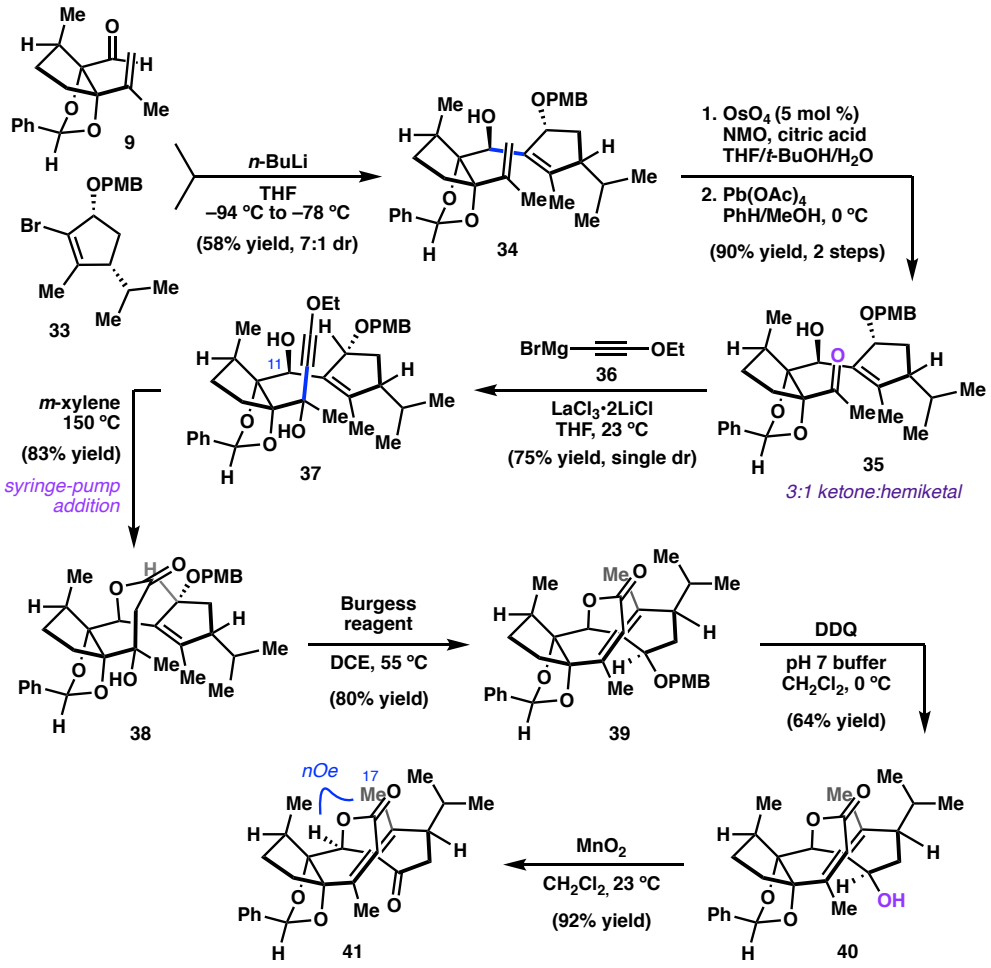


Scheme 4. *SmI_2 disconnection A-ring fragment.*

A3.3.3 *Substrate Synthesis and Evaluation of SmI_2 Disconnection*

Pressing forward, lithium-halogen exchange of bromocyclopentenol **33** with *n*-BuLi was followed by the introduction of aldehyde **9** to effect convergent union of our A and C-ring fragments (Scheme 5). The 1,1-disubstituted alkene of 1,2-addition product was next subjected to oxidative cleavage to provide methyl ketone **35**, which in turn could be converted to ethyl alkynyl ether **37** upon treatment with Grignard reagent **36** in the presence of $LaCl_3$•2LiCl.[5] Thermolysis of ether **37** in refluxing *m*-xylene generated a reactive ketene *in situ*, which succumbs to lactonization by engaging the C11 alcohol. This intramolecular nucleophilic trapping event results in the formation of D-ring lactone **38**.[6] Dehydration of the tertiary alcohol by the action of Burgess reagent was followed by PMB deprotection and oxidation to afford SmI_2 substrate, enone **41**. Promising from a

stereochemical analysis perspective was the observation of a strong nOe correlation between the C11 methine proton and the C17 methyl group, suggesting that in solution, the substrate adopts an A(1,3)-minimized conformation with the enone in good proximity with the π-system of the enoate.



Scheme 5. *Preparation of SmI_2 disconnection substrate.*

When reduced to practice, however, subjection of substrate **41** to SmI_2 with a variety of different additives consistently led to faster reduction at the D-ring lactone rather than the C4 enone, as initially predicted. Thus γ-elimination product **43** and further reduction product **44** were observed as major side products, with no observable quantities

of the desired cyclized product **42** via LCMS analysis. Recognizing the difficulty in generating the hindered C4–C5 bond with SmI_2, this approach was likewise abandoned in favor of reevaluating the A-ring fragment selection in our Pd-cascade disconnection.

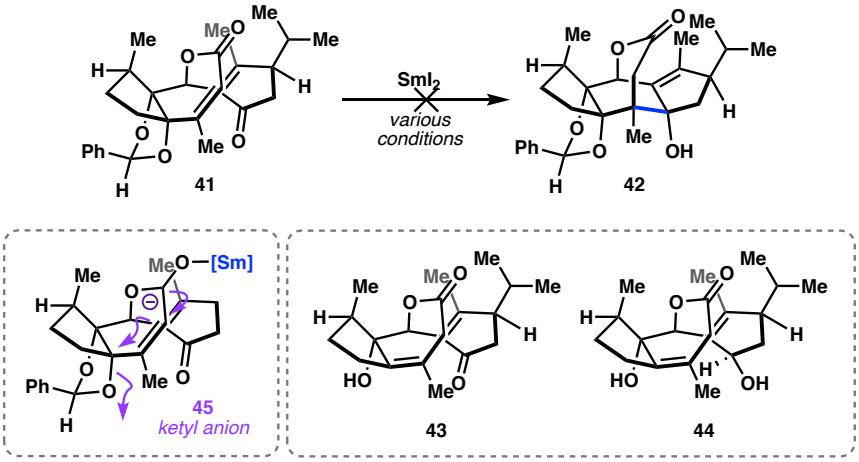


Figure 4. *Failure to induce C4-C5 bond formation via SmI_2 ketyl radical cyclization.*

A3.4 CONCLUDING REMARKS

Due to the inherent constraints of the polycyclic system of the isoryanoid diterpenes, several different approaches proved to be dead ends toward our goal of completing a synthesis of (+)-perseanol. We have disclosed two particular dead ends that provided us important information in the reevaluation and evolution of our synthetic approach. Critical concepts (in particular the Heck-Stille cascade and the catalyst-controlled reductive resolution) ultimately played a role in the successful route disclosed in the previous chapter. It is our hope that the failed approaches described in this appendix will be informative in the synthetic planning of other related ryanoids, isoryanoids, and polyhydroxylated diterpenes.

A3.5 REFERENCES

(1) Xie, X. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2015**, *137*, 3767.

(2) Procter, D. J.; Flowers, R. A.; Skrydstrup, T. *Organic Synthesis using Samarium Diiodide: A Practical Guide*. Royal Society of Chemistry: Cambridge, UK, 2009.

(3) Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095.

(4) Helal, C. J.; Meyer, M. P. The Corey-Bakshi-Shibata Reduction: Mechanistic and Synthetic Considerations – Bifuntional Lewis Base Catalysis and Dual Activation. In *Lewis Base Catalysis in Organic Synthesis*, 1st ed.; Vedejs, E.; Denmark, S. E., Eds. Wiley-VCH: Weinheim, Germany, 2016.

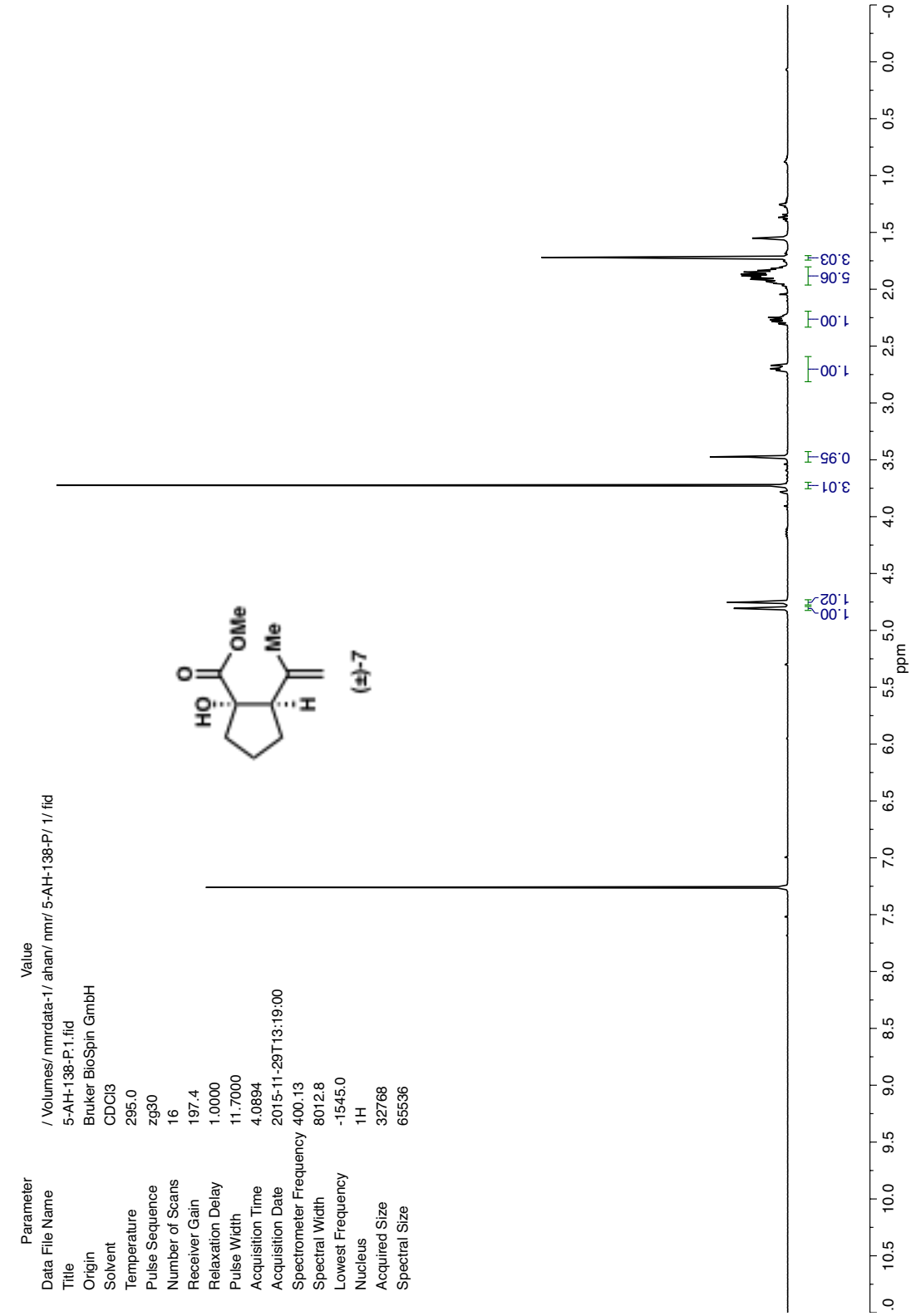
(5) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

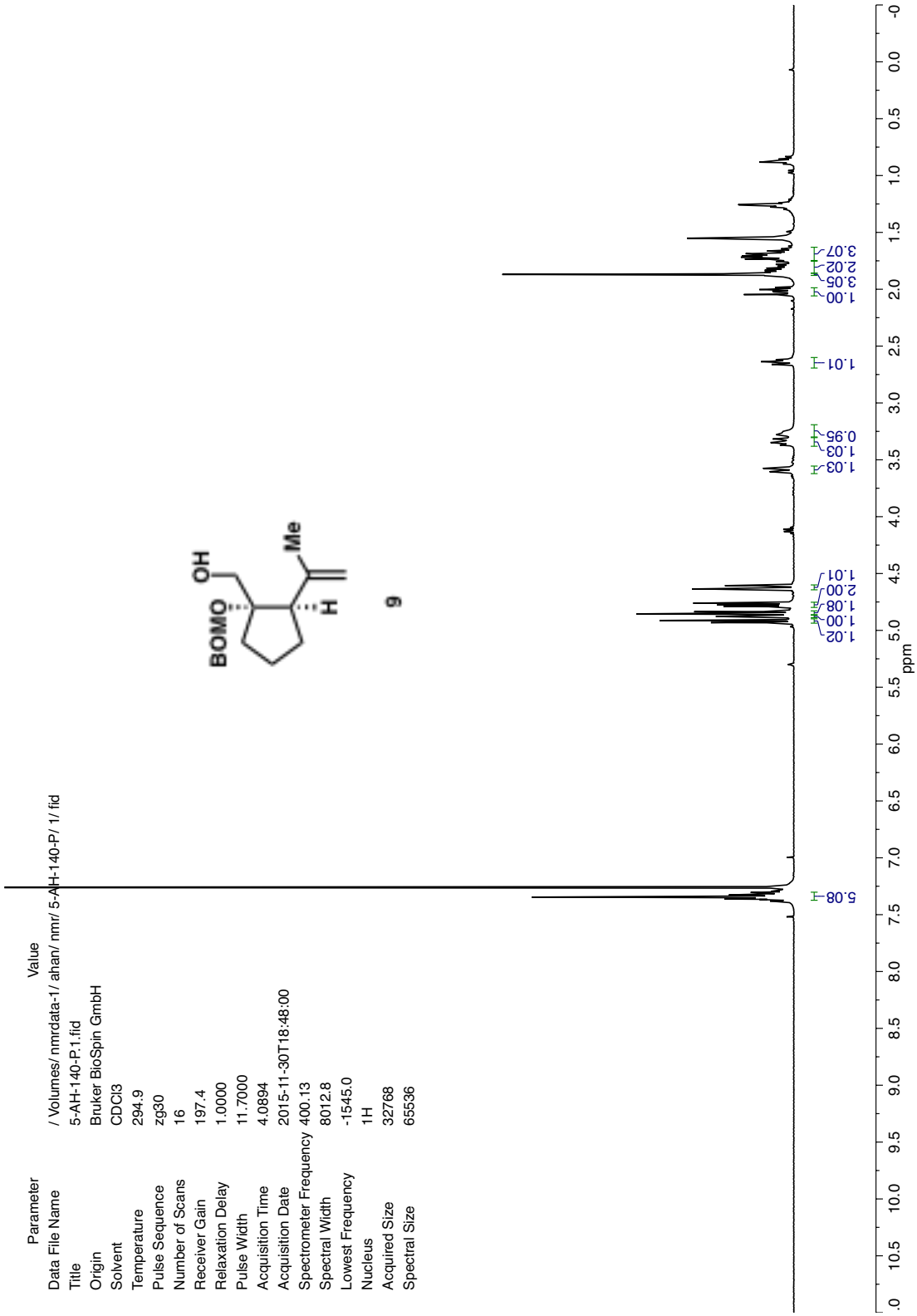
(6) Liang, L.; Ramaseshan, M.; Magee, D. I. *Tetrahedron* **1993**, *49*, 2159.

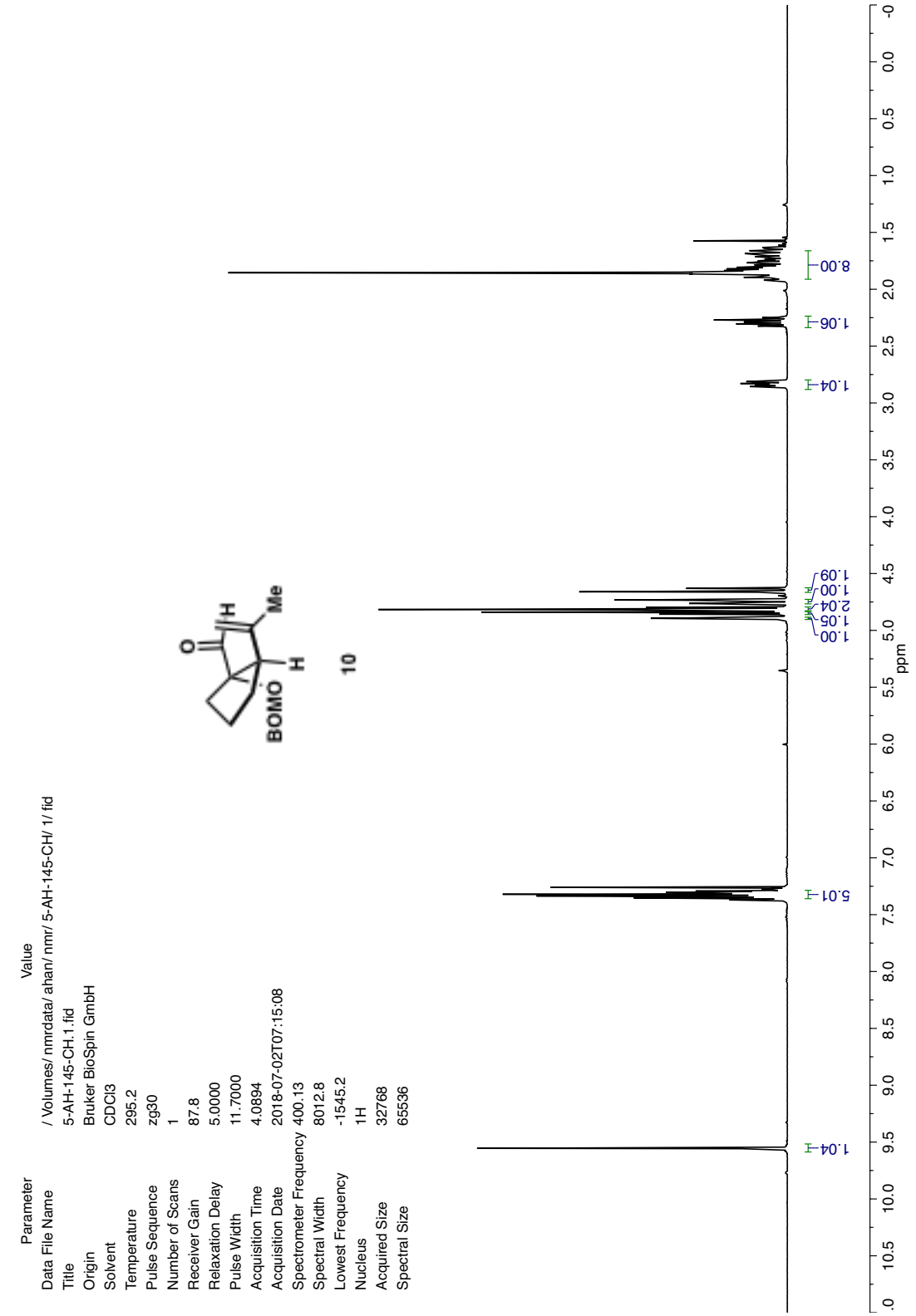
Appendix 4

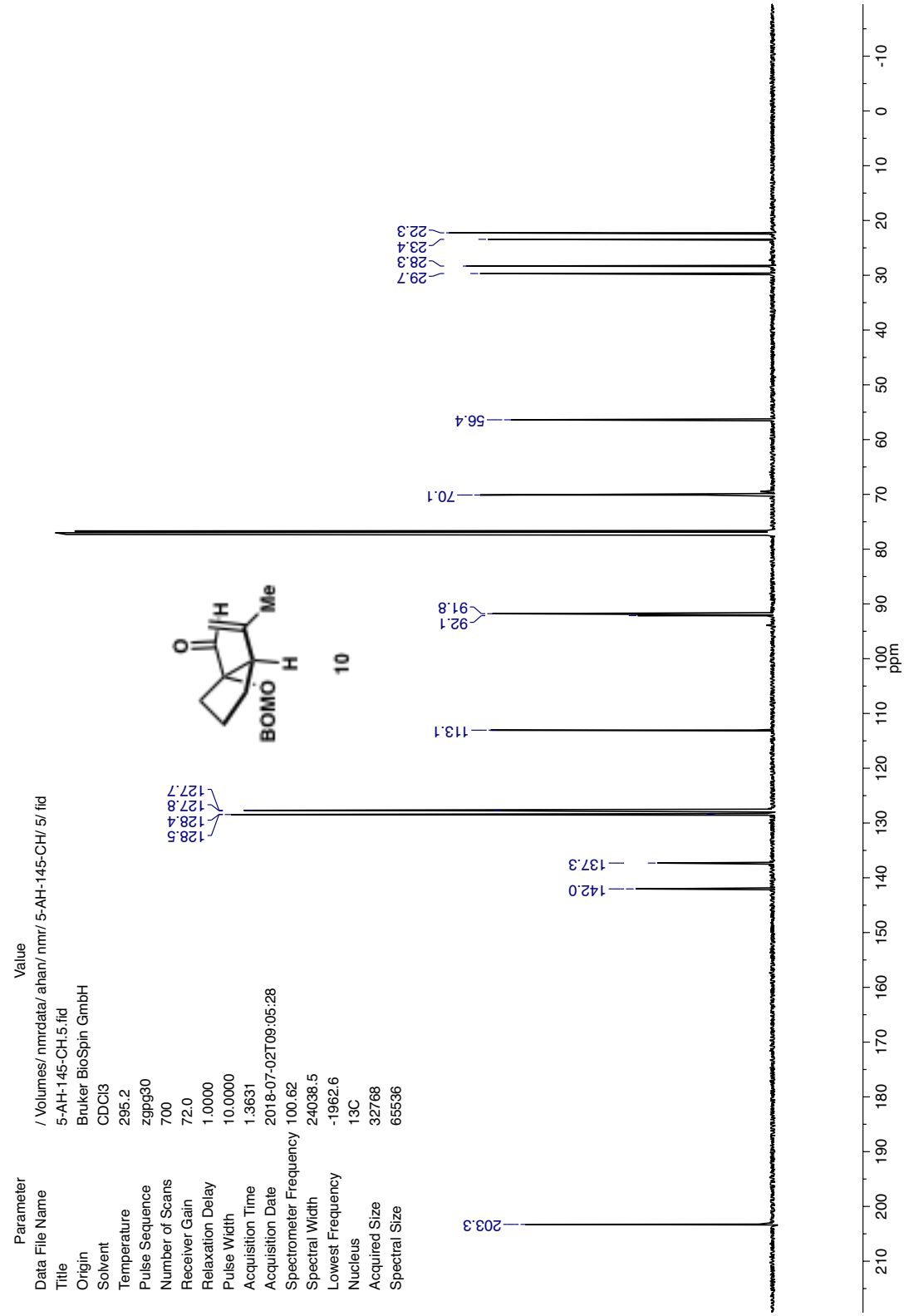
Spectra Relevant to Chapter 3:

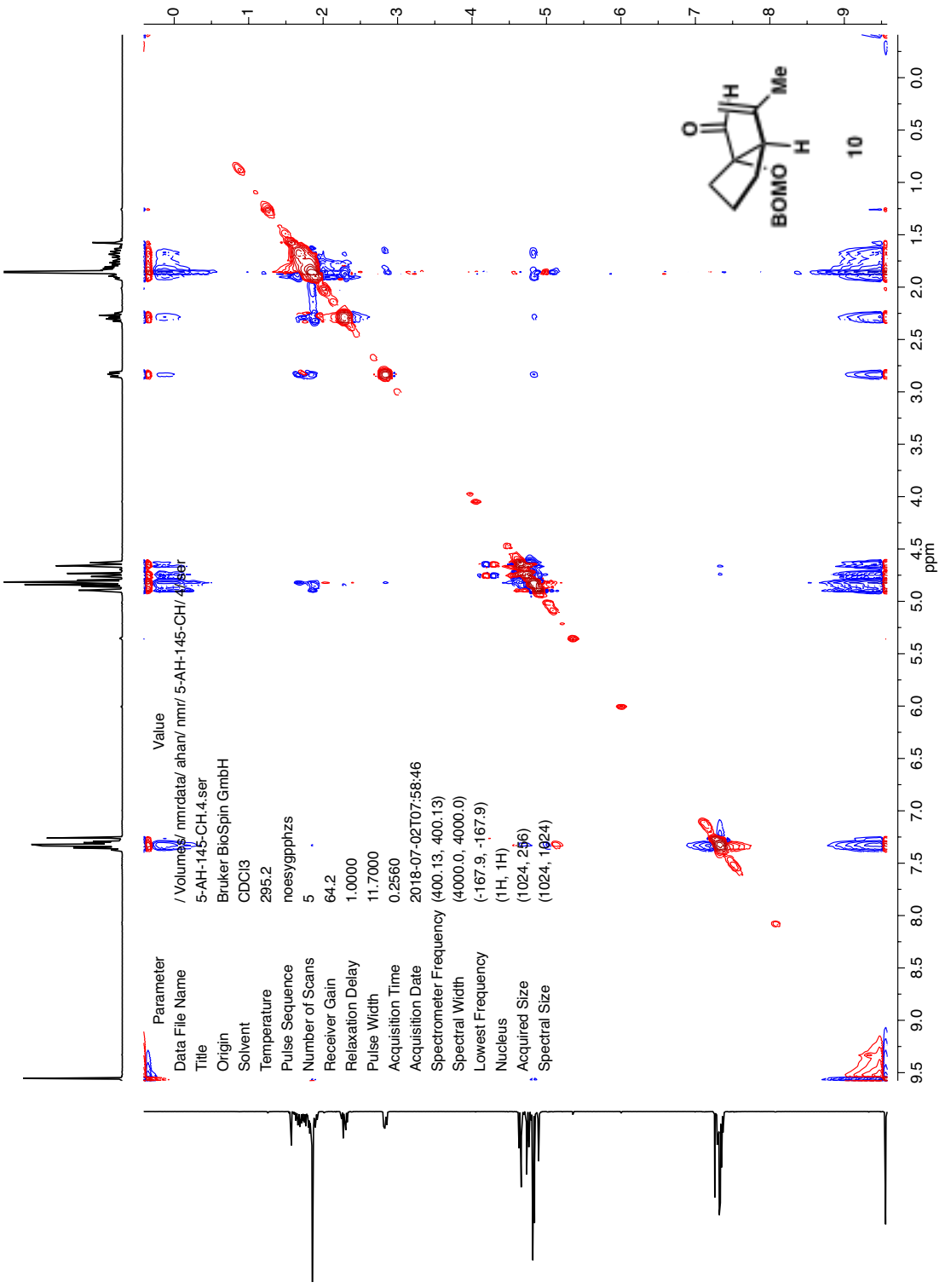
Total Synthesis of the Isoryanoid Diterpene (+)-Perseanol

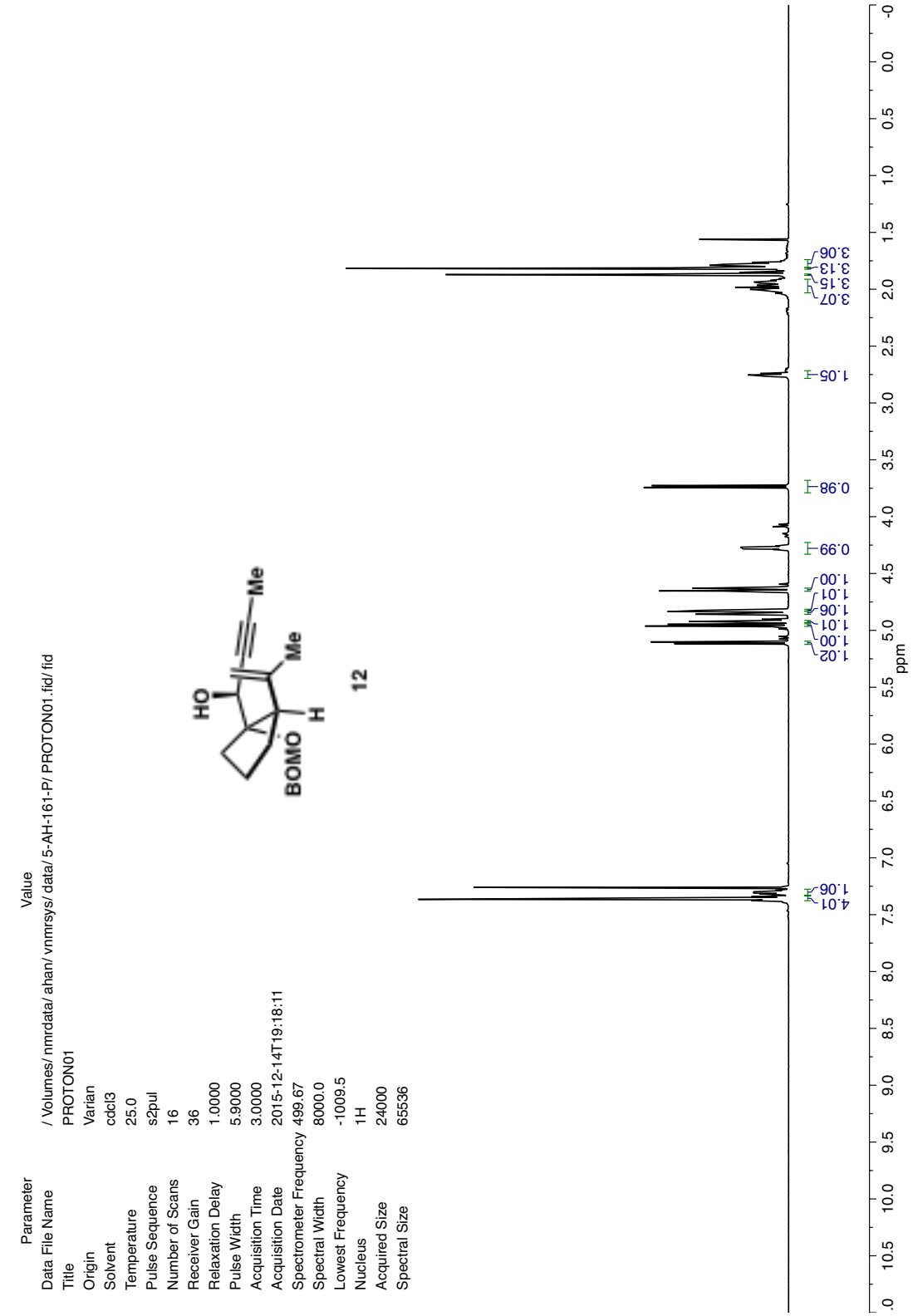

Parameter Value
Data File Name / Volumes/ nmrdata-1/ ahan/ nmr/ 5-AH-138-P/ 1/ fid
Title 5-AH-138-P1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2015-11-29T13:19:00
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.0
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
HO
O
OMe
Me
H
(±)-7
1.00
1.02
3.01
0.95
1.00
1.00
5.06
3.03
ppm

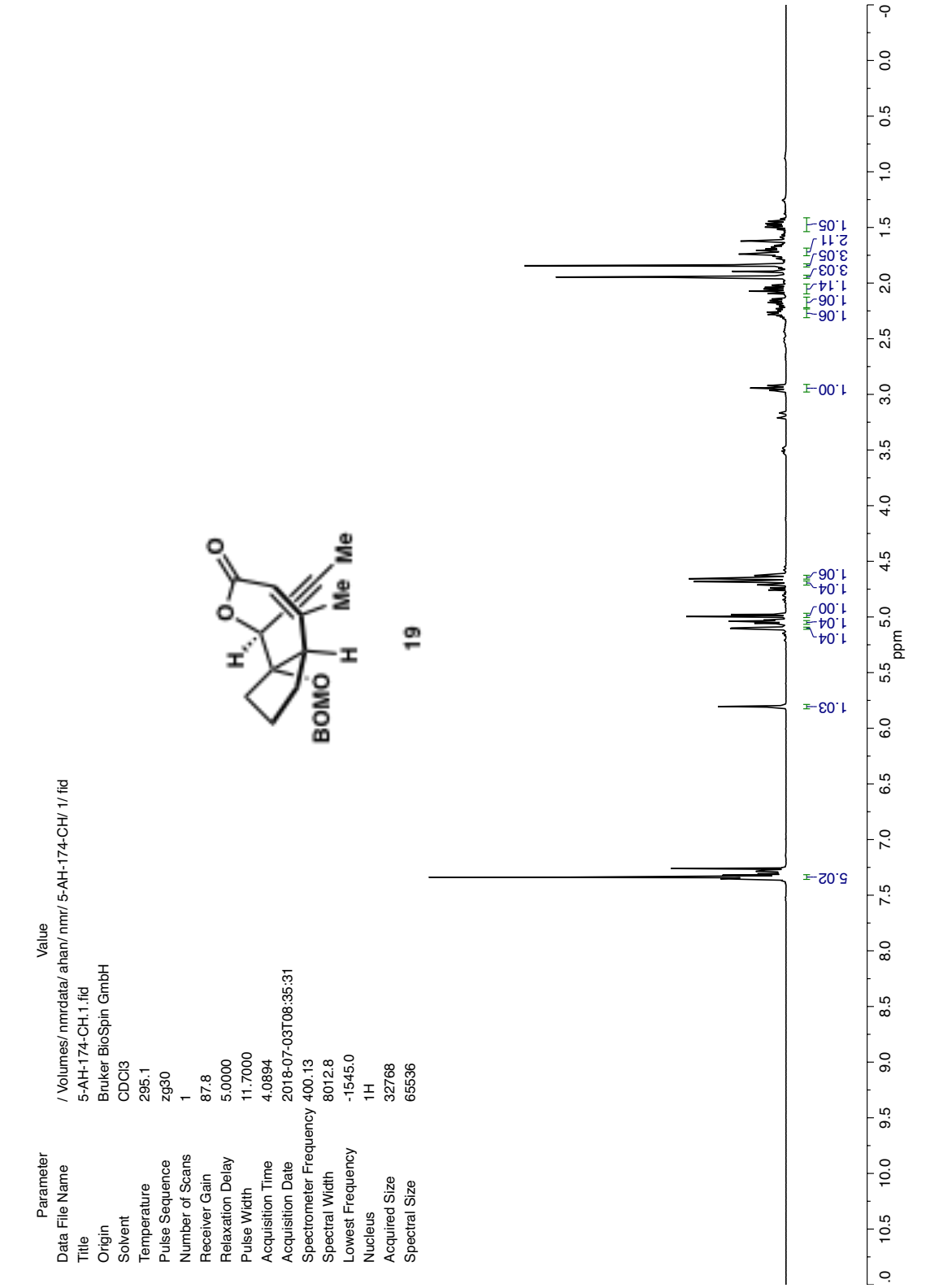

Parameter
Value
Data File Name
/ Volumes/ nmrdata-1/ ahan/ nmr/ 5-AH-140-P/ 1/ fid
Title
5-AH-140-P1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
294.9
Pulse Sequence
zg30
Number of Scans
16
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2015-11-30T18:48:00
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.0
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
OH
Me
BOMO
H
6
5.08
1.02
1.00
1.08
2.00
1.01
1.03
1.03
0.95
1.01
1.00
3.05
2.02
3.07
ppm

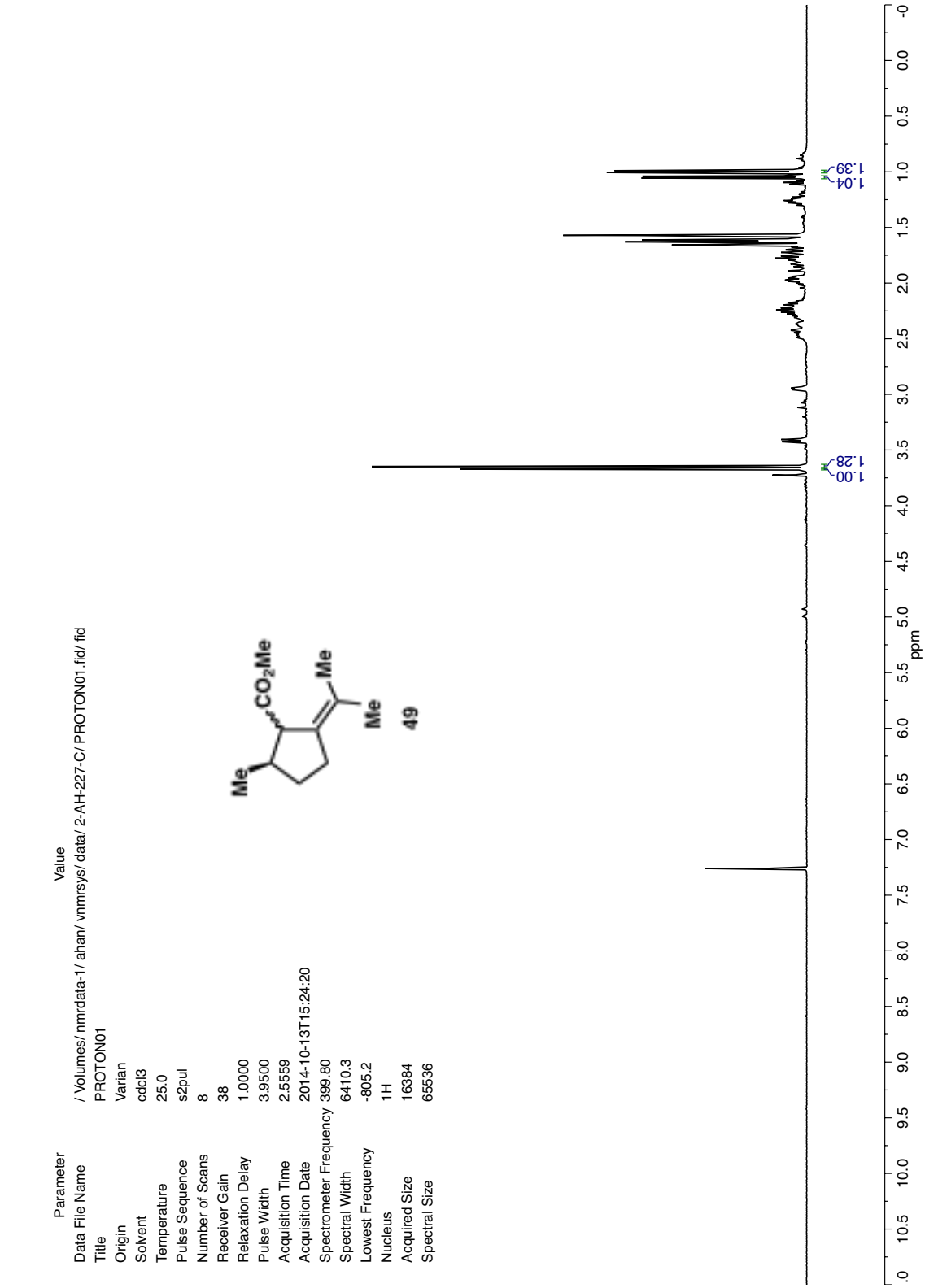

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 5-AH-145-CH/ 1/ fid
Title 5-AH-145-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 87.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-02T07:15:08
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.2
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
O
H
Me
H
BOMO
10
1.04
5.01
1.00
1.05
2.04
1.00
1.09
1.04
1.06
8.00
ppm

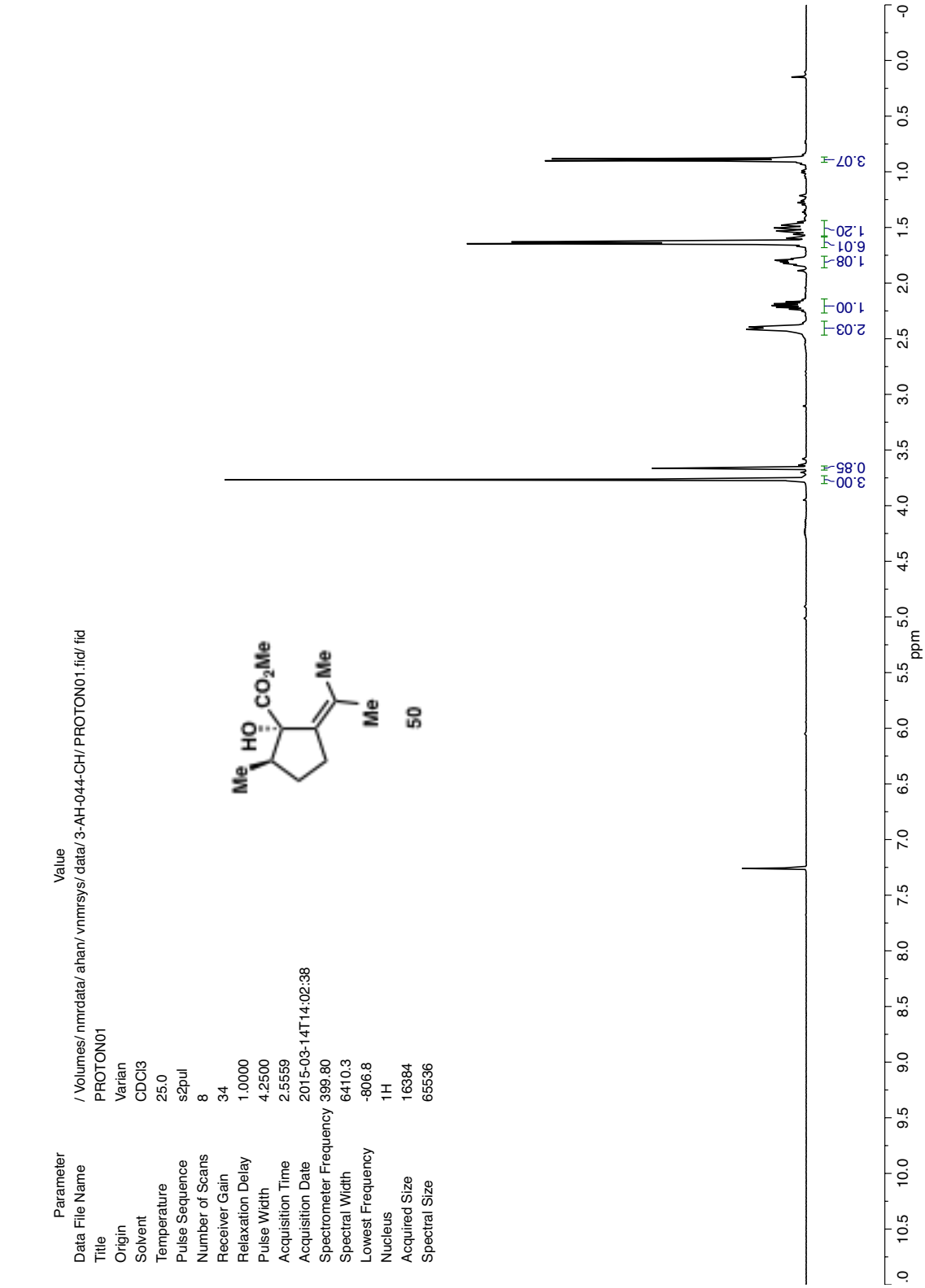

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 5-AH-145-CH/ 5/ fid
Title 5-AH-145-CH.5.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 700
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-02T09:05:28
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1962.6
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
203.3
142.0
137.3
128.5
128.4
127.8
127.7
113.1
92.1
91.8
70.1
56.4
29.7
28.3
23.4
22.3
BOMO
10
ppm

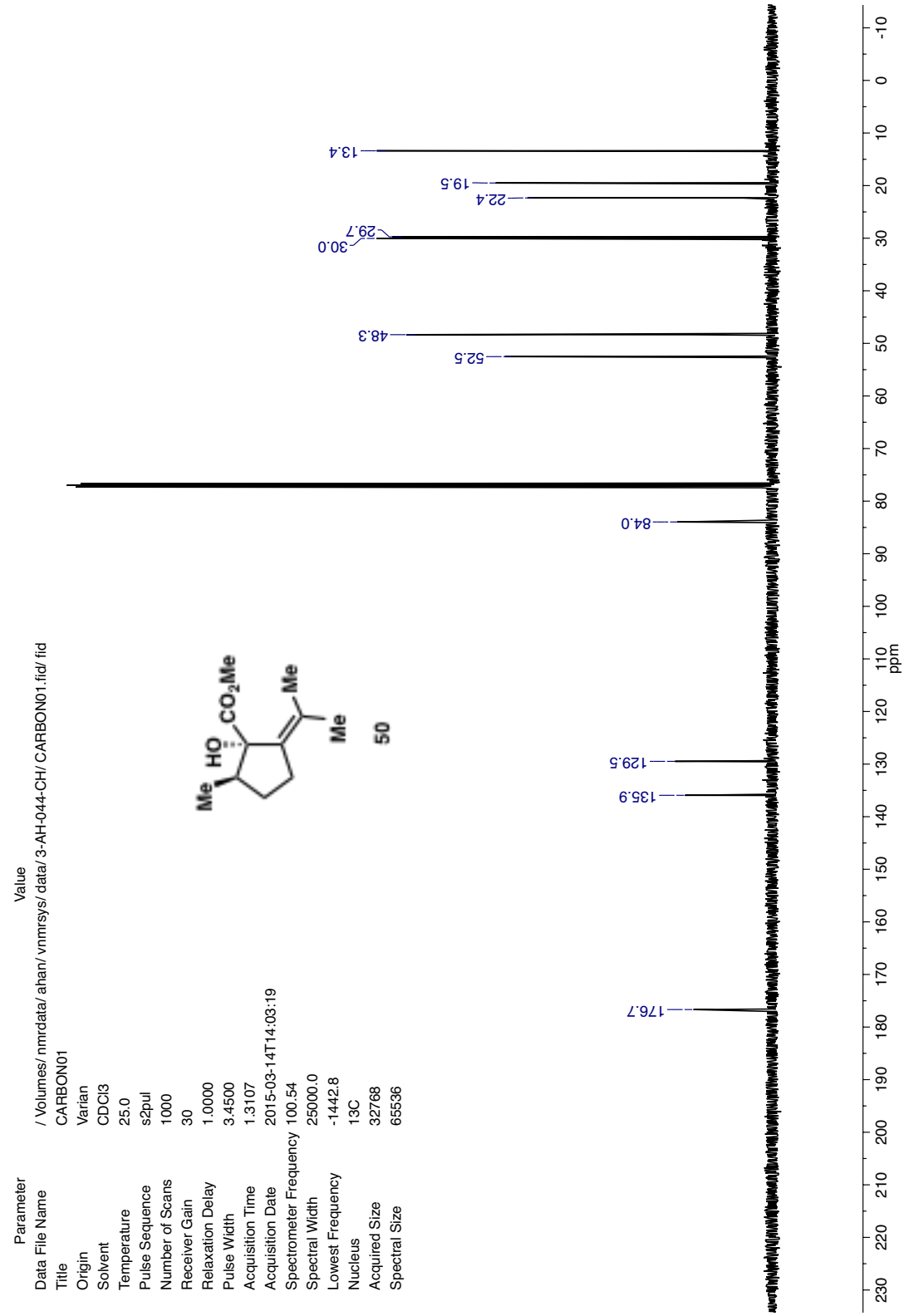

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 5-AH-145-CH/ 4/ser
Title
5-AH-145-CH.4.ser
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.2
Pulse Sequence
noesygpphzs
Number of Scans
5
Receiver Gain
64.2
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2560
Acquisition Date
2018-07-02T07:58:46
Spectrometer Frequency
(400.13, 400.13)
Spectral Width
(4000.0, 4000.0)
Lowest Frequency
(-167.9, -167.9)
Nucleus
(1H, 1H)
Acquired Size
(1024, 256)
Spectral Size
(1024, 1024)
BOMO
10
ppm

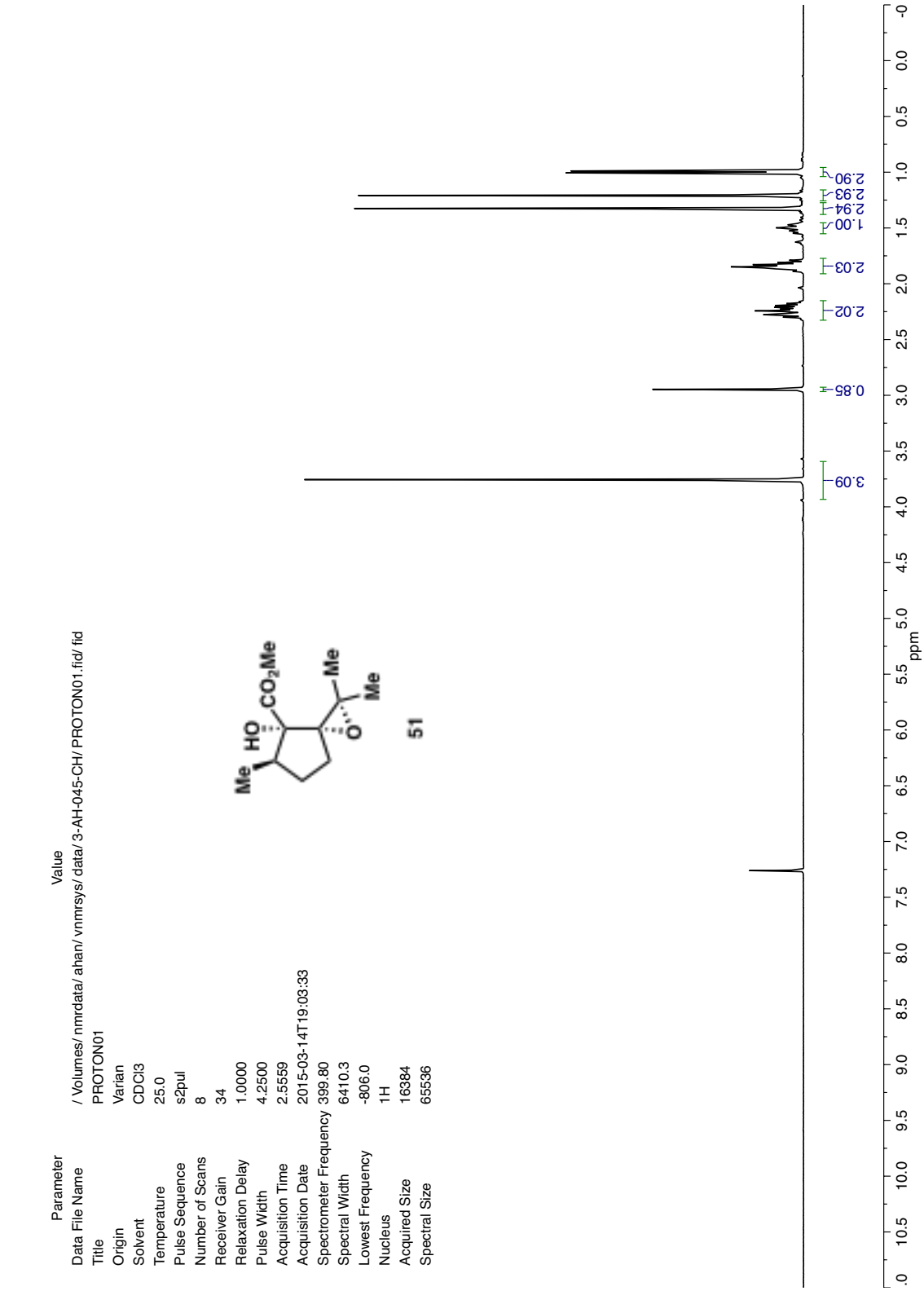

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 5-AH-161-P/ PROTON01.fid/ fid
Title
PROTON01
Origin
Varian
Solvent
cdcl3
Temperature
25.0
Pulse Sequence
s2pul
Number of Scans
16
Receiver Gain
36
Relaxation Delay
1.0000
Pulse Width
5.9000
Acquisition Time
3.0000
Acquisition Date
2015-12-14T19:18:11
Spectrometer Frequency
499.67
Spectral Width
8000.0
Lowest Frequency
-1009.5
Nucleus
1H
Acquired Size
24000
Spectral Size
65536
HO
Me
Me
H
BOMO
12
4.01
1.06
1.05
0.98
0.99
1.00
1.01
1.06
1.01
1.00
1.02
3.07
3.15
3.13
3.06
ppm

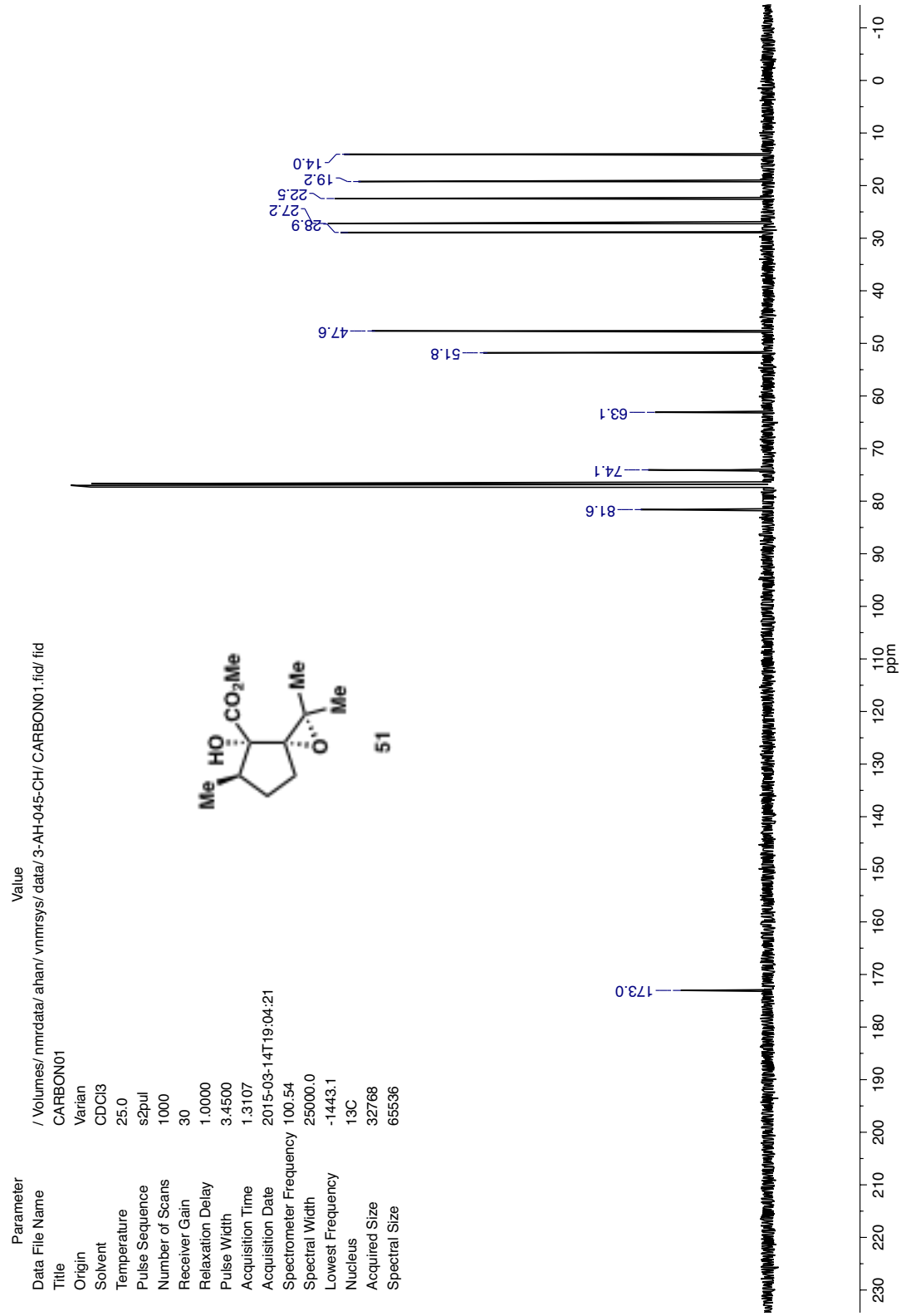

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 5-AH-174-CH/ 1/ fid
Title 5-AH-174-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 87.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-03T08:35:31
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.0
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
O
O
H
BOMO
H
Me
Me
19
5.02
1.03
1.04
1.04
1.00
1.04
1.06
1.00
1.06
1.14
3.03
3.05
2.11
1.05
ppm

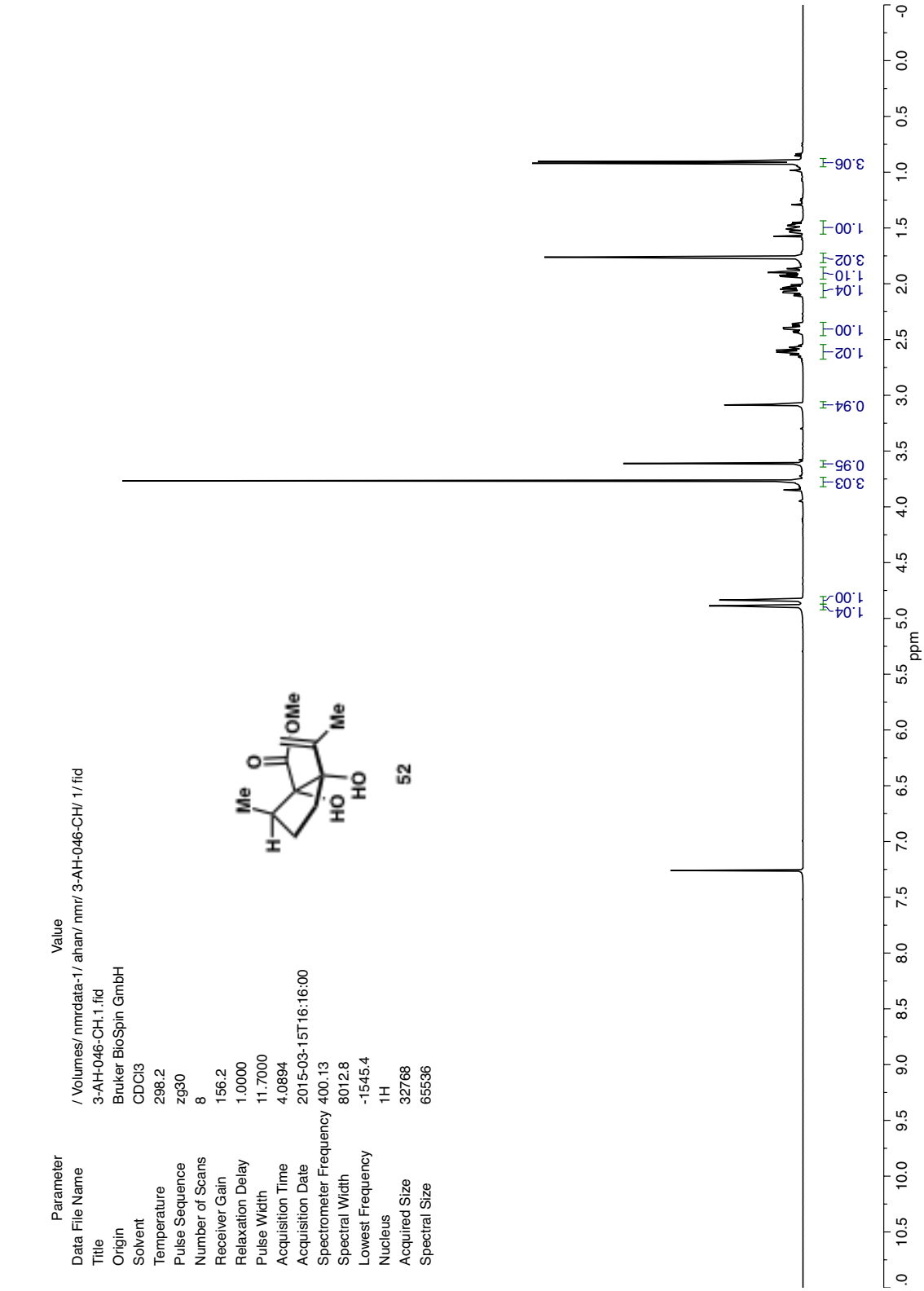

Parameter
Value
Data File Name / Volumes/ nmrdata-1/ ahan/ vnmrsys/ data/ 2-AH-227-C/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 38
Relaxation Delay 1.0000
Pulse Width 3.9500
Acquisition Time 2.5559
Acquisition Date 2014-10-13T15:24:20
Spectrometer Frequency 399.80
Spectral Width 6410.3
Lowest Frequency -805.2
Nucleus 1H
Acquired Size 16384
Spectral Size 65536
Me
CO2Me
Me
Me
49
1.00
1.28
1.04
1.39
ppm

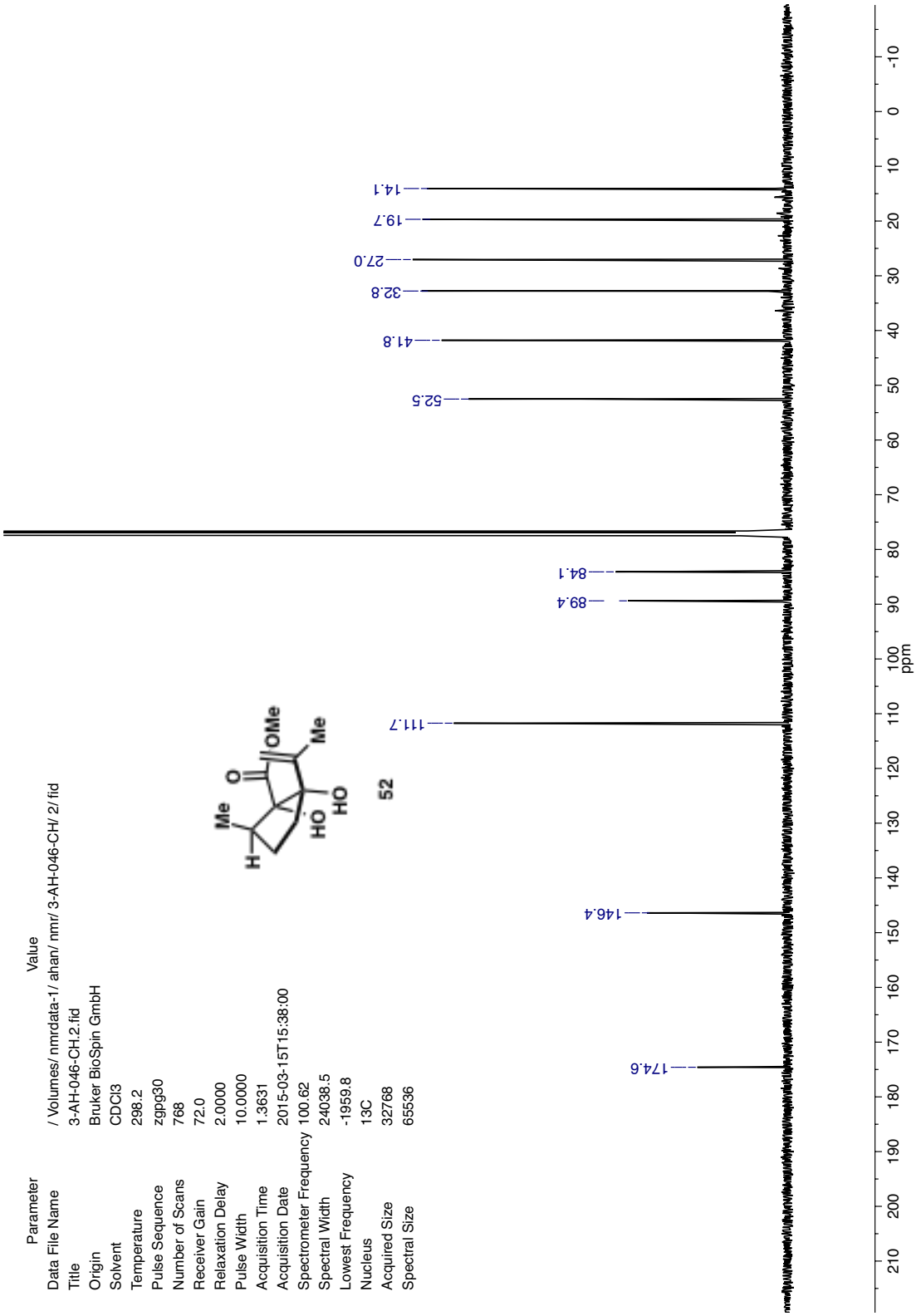

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-044-CH/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 34
Relaxation Delay 1.0000
Pulse Width 4.2500
Acquisition Time 2.5559
Acquisition Date 2015-03-14T14:02:38
Spectrometer Frequency 399.80
Spectral Width 6410.3
Lowest Frequency -806.8
Nucleus 1H
Acquired Size 16384
Spectral Size 65536
Me
HO
CO2Me
Me
Me
50
3.00
0.85
2.03
1.00
1.08
6.01
1.20
3.07
ppm

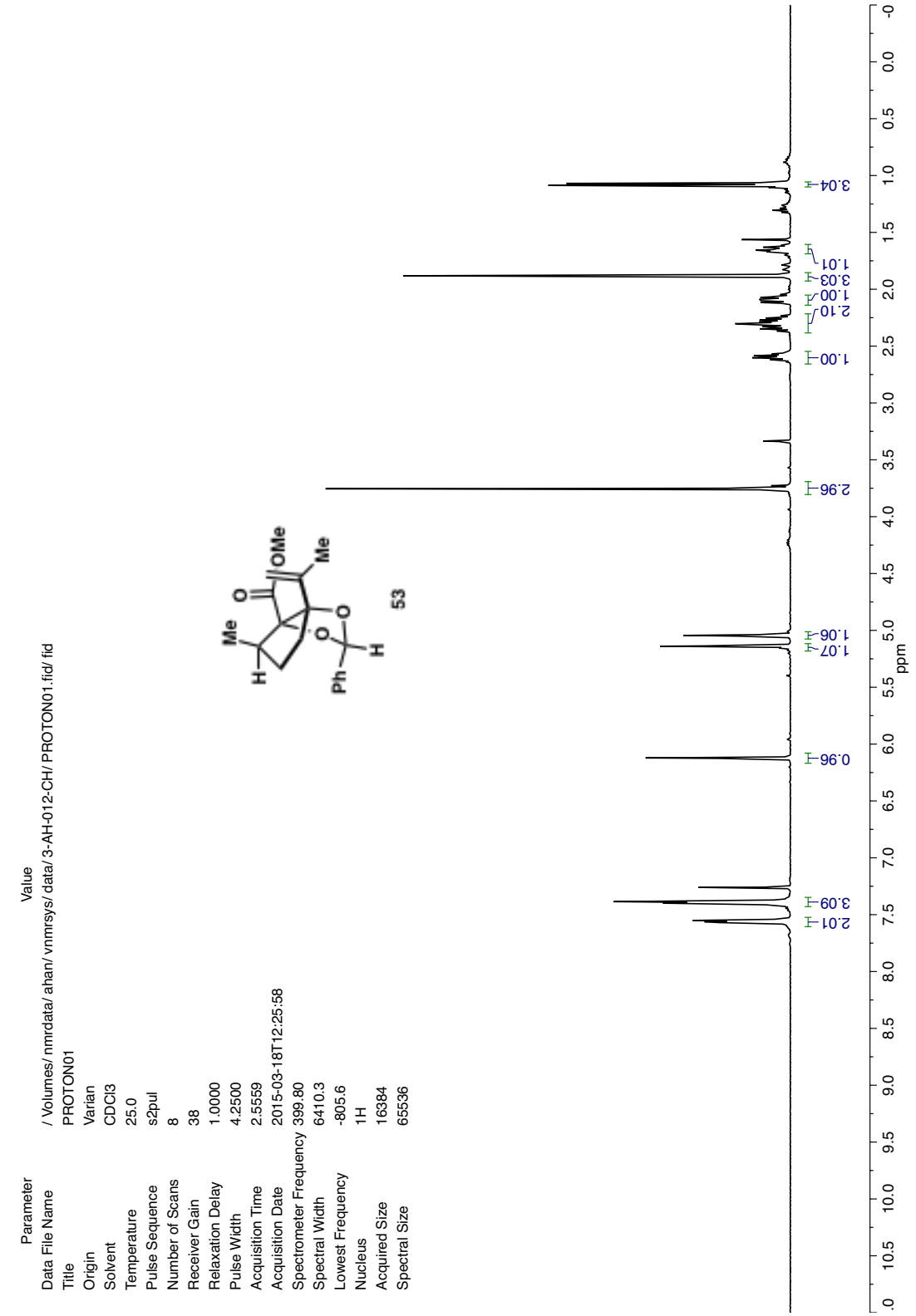

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-044-CH/ CARBON01.fid/ fid
Title CARBON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 1000
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 3.4500
Acquisition Time 1.3107
Acquisition Date 2015-03-14T14:03:19
Spectrometer Frequency 100.54
Spectral Width 25000.0
Lowest Frequency -1442.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Me
HO
CO2Me
Me
Me
50
176.7
135.9
129.5
84.0
52.5
48.3
30.0
29.7
22.4
19.5
13.4
ppm

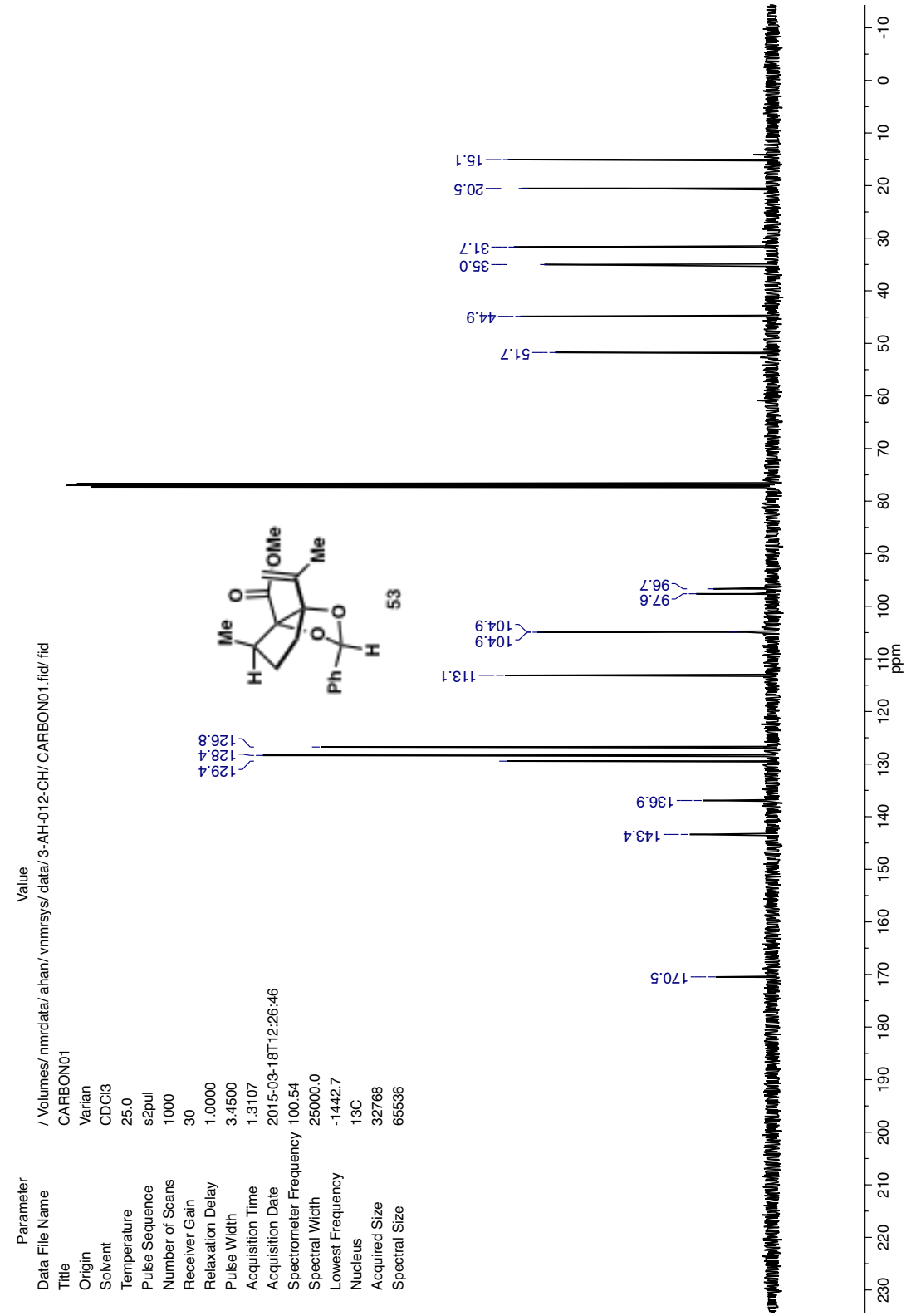

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-045-CH/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 34
Relaxation Delay 1.0000
Pulse Width 4.2500
Acquisition Time 2.5559
Acquisition Date 2015-03-14T19:03:33
Spectrometer Frequency 399.80
Spectral Width 6410.3
Lowest Frequency -806.0
Nucleus 1H
Acquired Size 16384
Spectral Size 65536
Me
HO
CO2Me
O
Me
Me
51
3.09
0.85
2.02
2.03
1.00
2.94
2.93
2.90
ppm

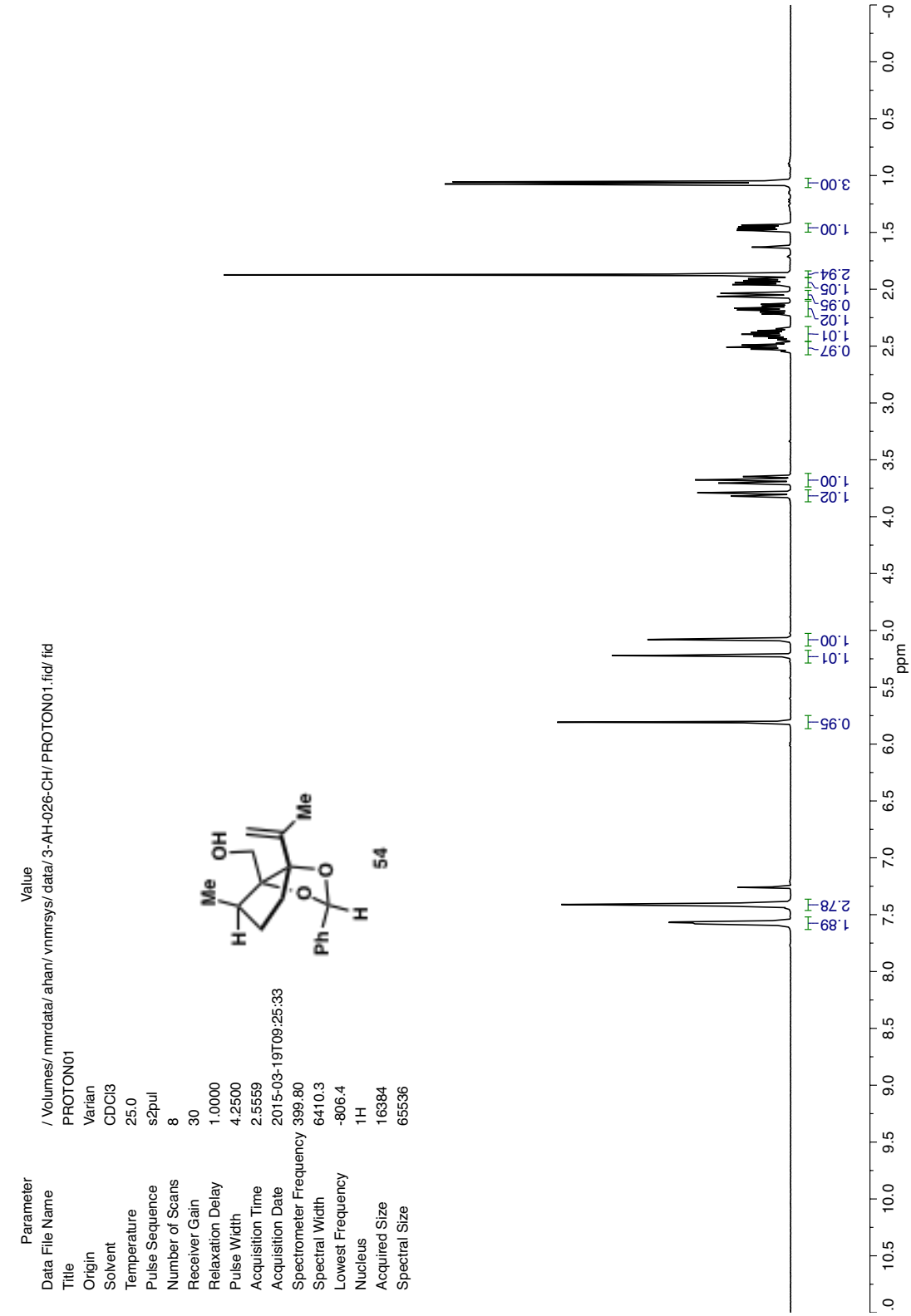

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-045-CH/ CARBON01.fid/ fid
Title CARBON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 1000
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 3.4500
Acquisition Time 1.3107
Acquisition Date 2015-03-14T19:04:21
Spectrometer Frequency 100.54
Spectral Width 25000.0
Lowest Frequency -1443.1
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Me
HO
CO2Me
O
Me
Me
51
173.0
81.6
74.1
63.1
51.8
47.6
28.9
27.2
22.5
19.2
14.0
ppm

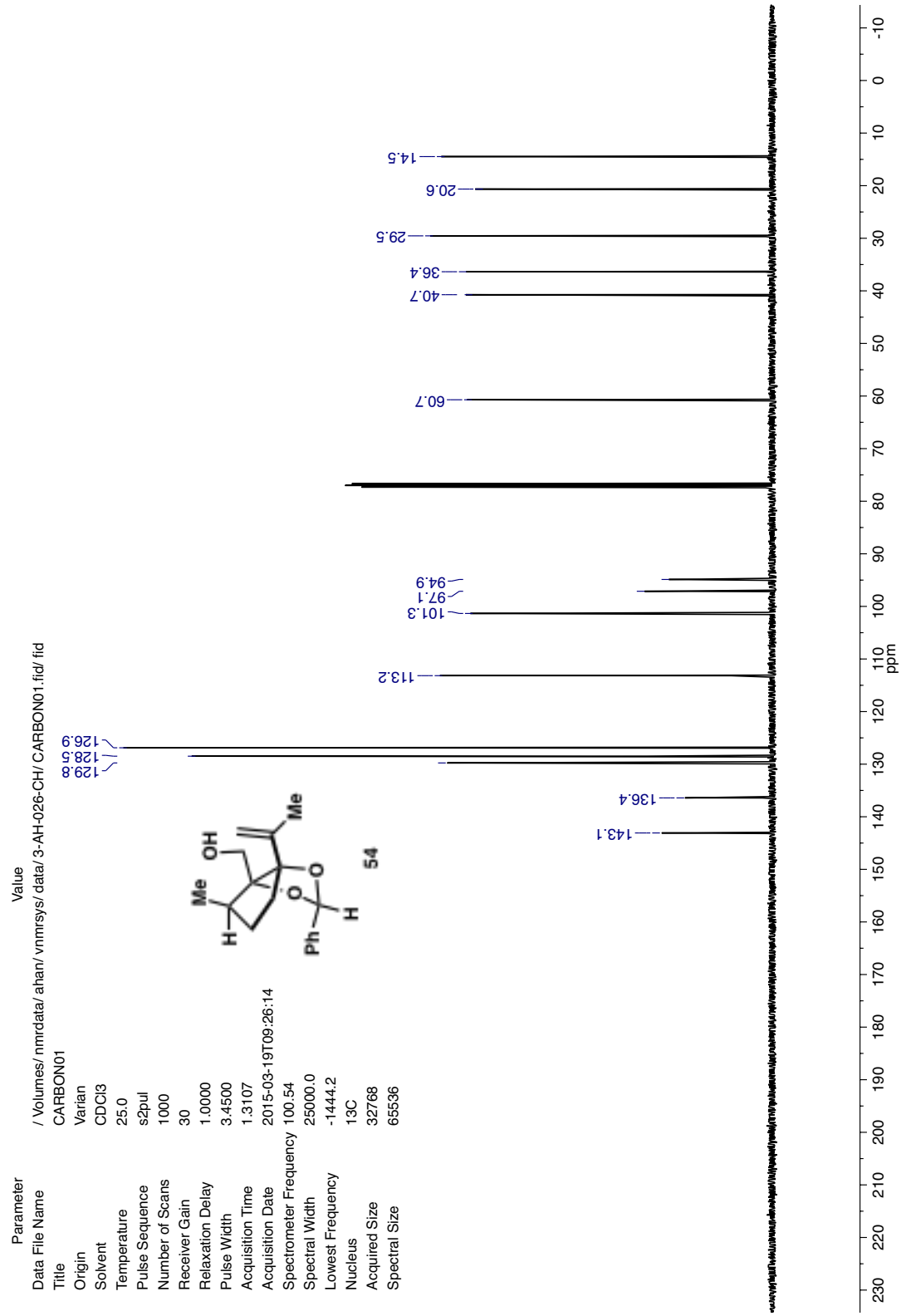

Parameter
Value
Data File Name / Volumes/ nmrdata-1/ ahan/ nmr/ 3-AH-046-CH/ 1/ fid
Title 3-AH-046-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.2
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2015-03-15T16:16:00
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
Me
O
OMe
Me
H
HO
HO
52
3.06
1.00
3.02
1.10
1.04
1.00
1.02
0.94
0.95
3.03
1.00
1.04
ppm

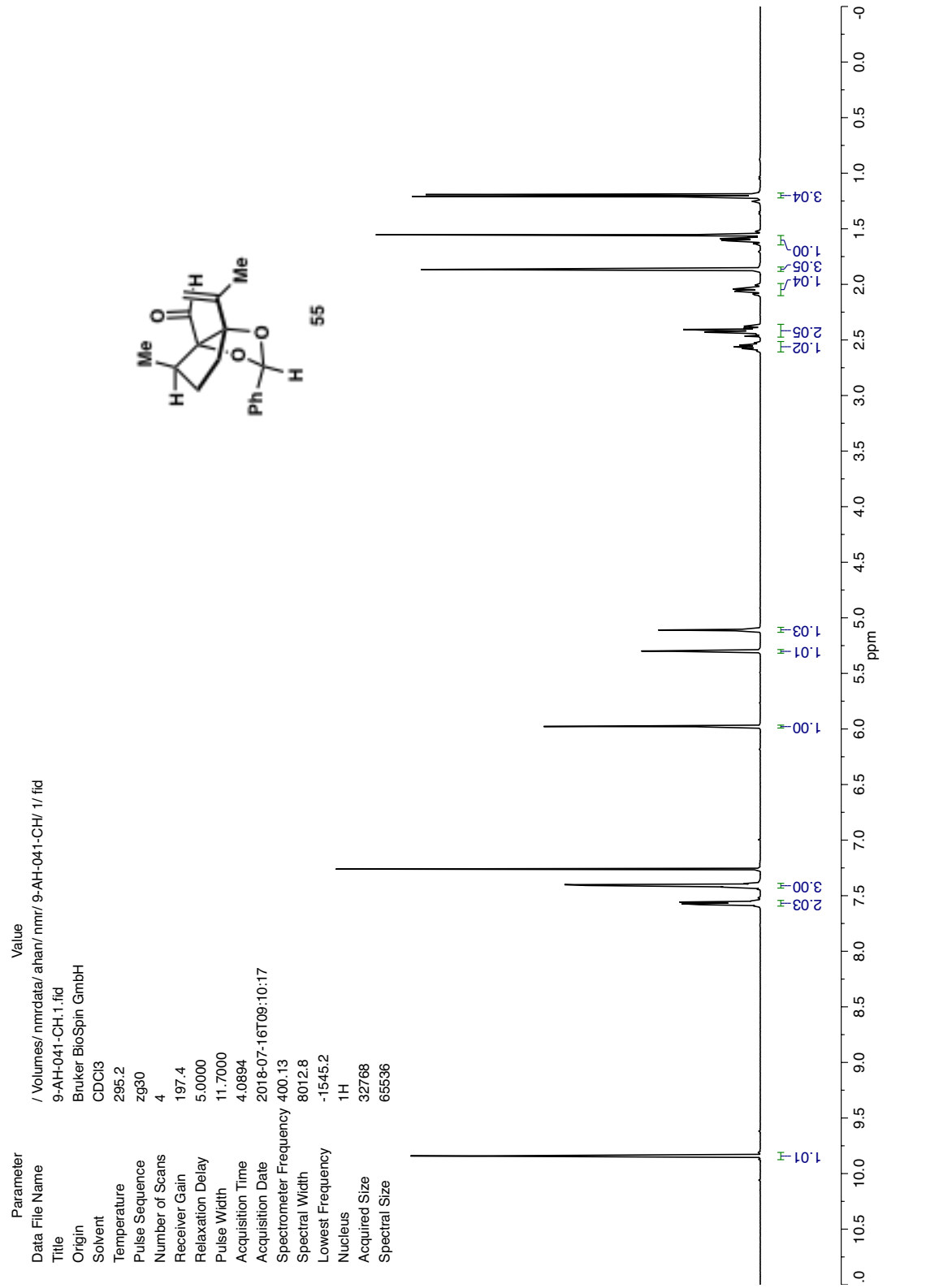

Parameter
Value
Data File Name / Volumes/ nmrdata-1/ ahan/ nmr/ 3-AH-046-CH/ 2/ fid
Title 3-AH-046-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.2
Pulse Sequence zgpg30
Number of Scans 768
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2015-03-15T15:38:00
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1959.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
52
14.1
19.7
27.0
32.8
41.8
52.5
84.1
89.4
111.7
146.4
174.6
ppm

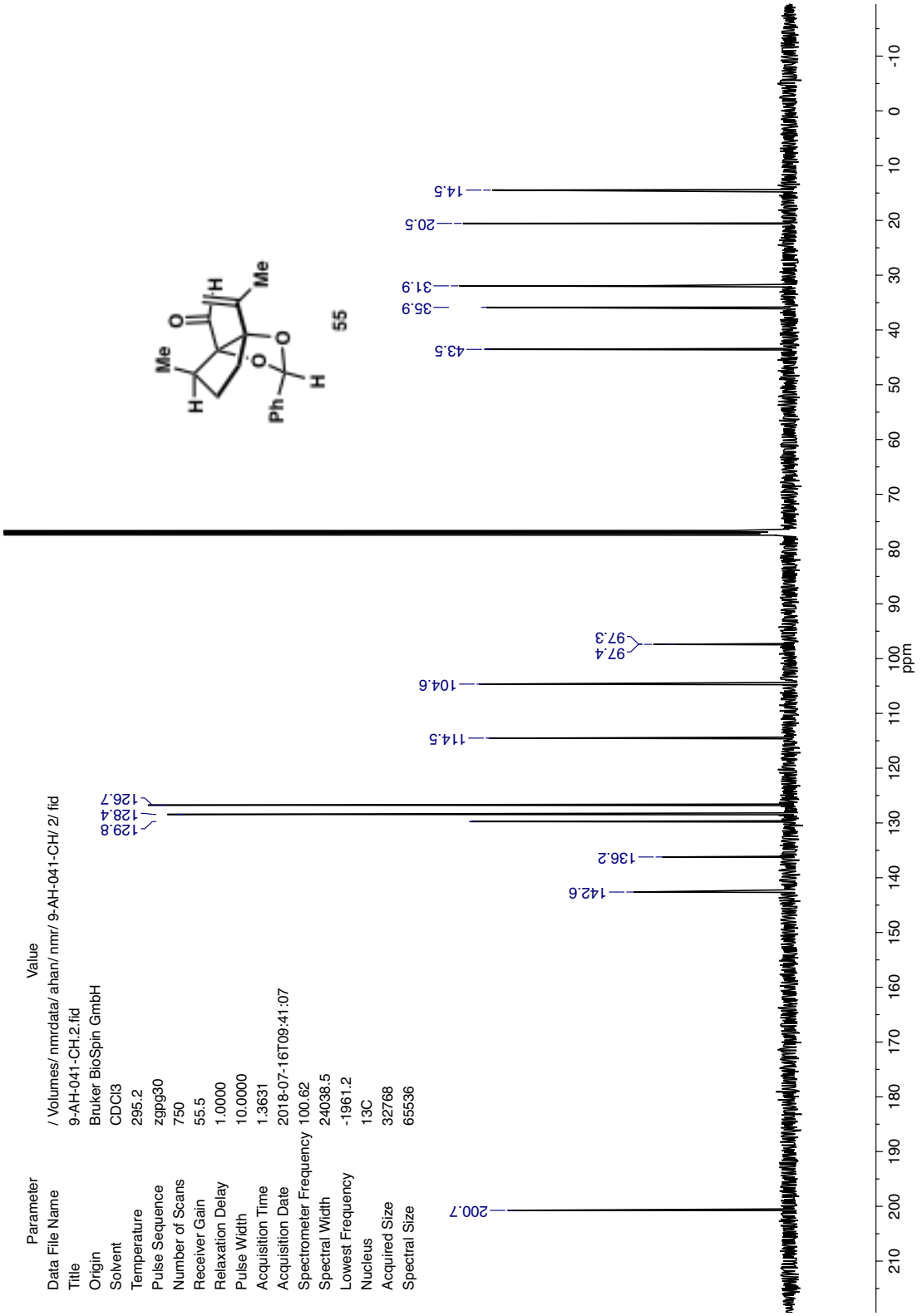

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-012-CH/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 38
Relaxation Delay 1.0000
Pulse Width 4.2500
Acquisition Time 2.5559
Acquisition Date 2015-03-18T12:25:58
Spectrometer Frequency 399.80
Spectral Width 6410.3
Lowest Frequency -805.6
Nucleus 1H
Acquired Size 16384
Spectral Size 65536
Me
O
OMe
Me
H
O
O
Ph
H
53
2.01
3.09
0.96
1.06
1.07
2.96
1.00
2.10
1.00
3.03
1.01
3.04
ppm

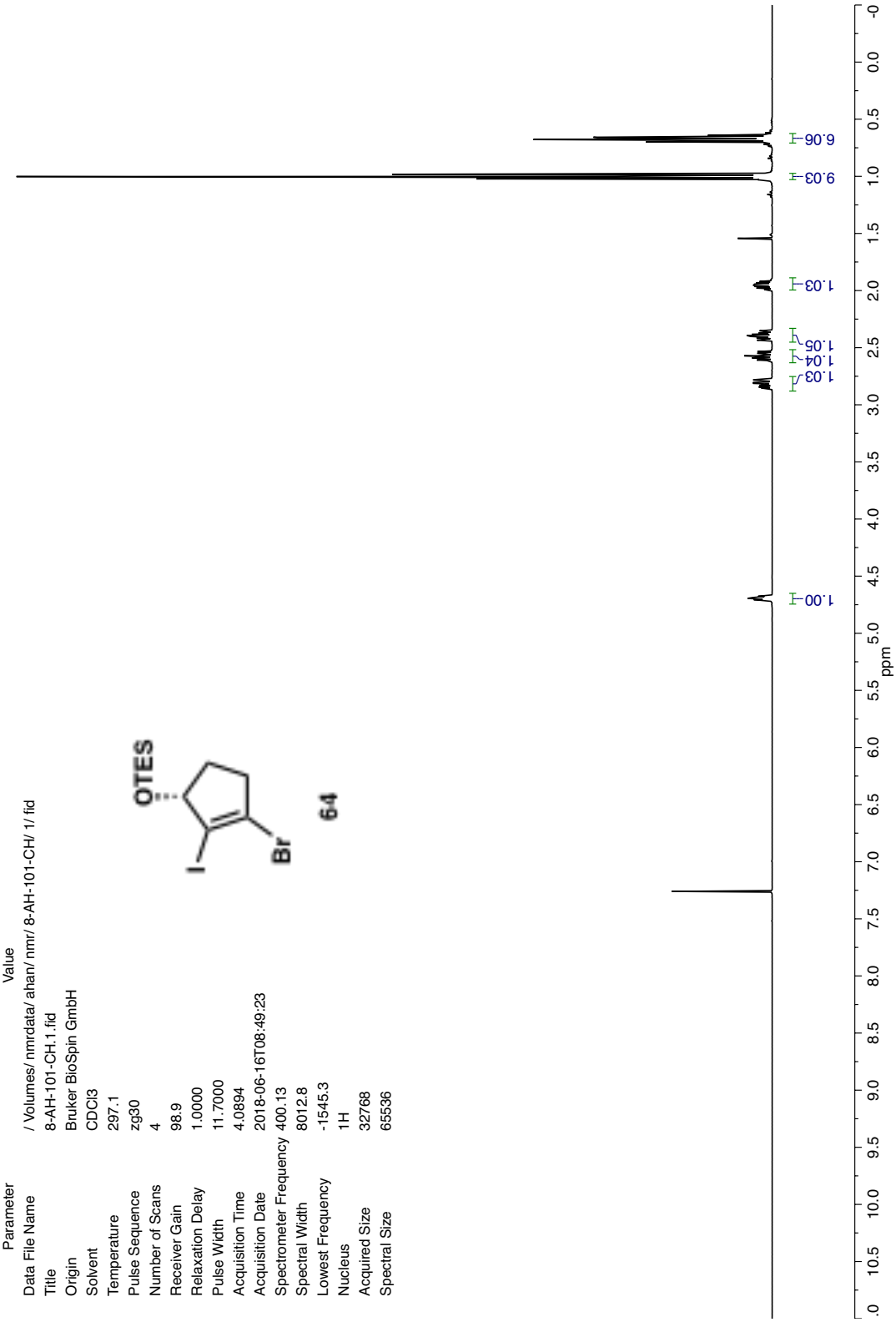

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-012-CH/ CARBON01.fid/ fid
Title CARBON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 1000
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 3.4500
Acquisition Time 1.3107
Acquisition Date 2015-03-18T12:26:46
Spectrometer Frequency 100.54
Spectral Width 25000.0
Lowest Frequency -1442.7
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
15.1
20.5
31.7
35.0
44.9
51.7
96.7
97.6
104.9
104.9
113.1
126.8
128.4
129.4
136.9
143.4
170.5
OMe
Me
Me
O
O
O
O
H
H
Ph
53
ppm

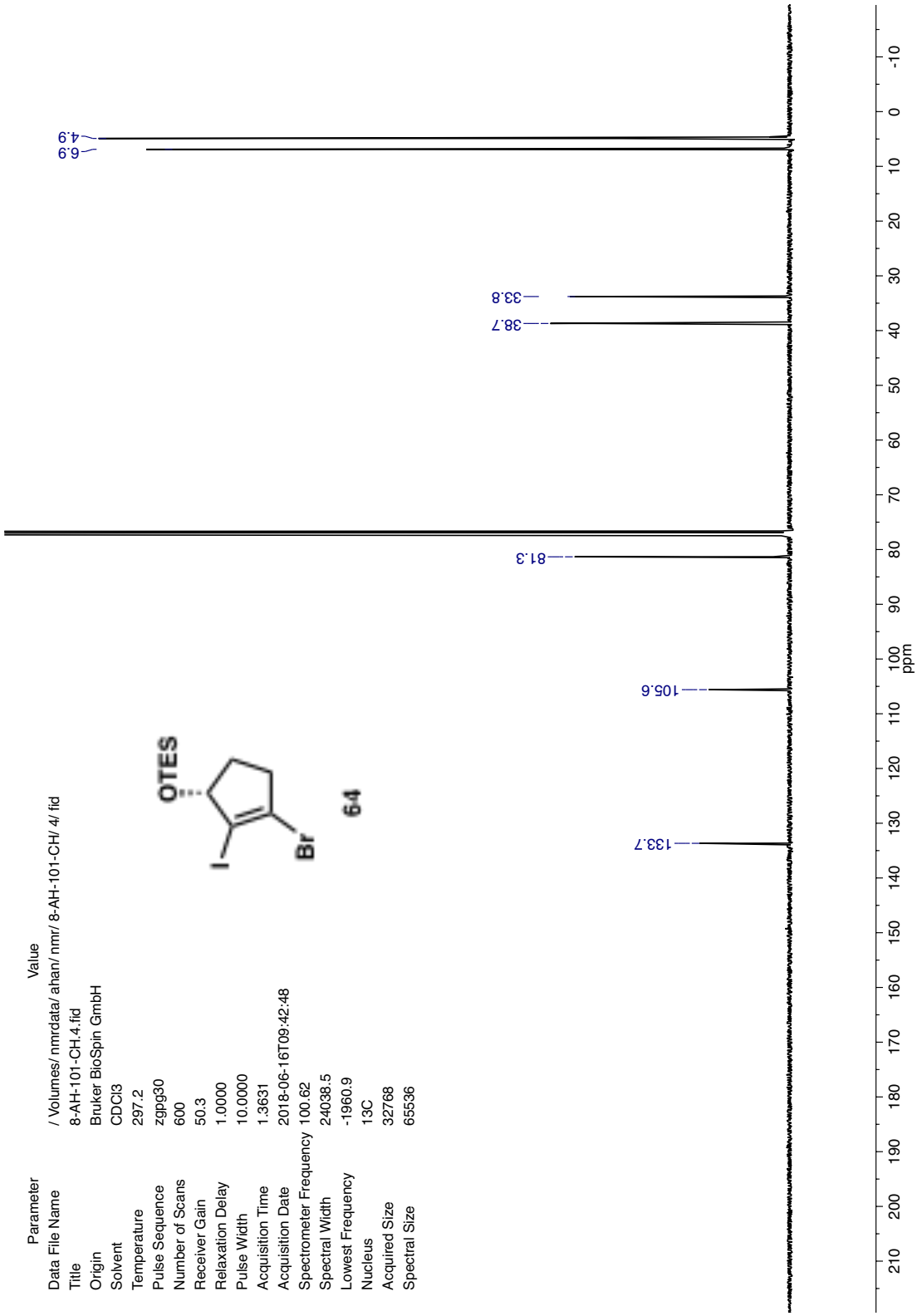

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-026-CH/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 4.2500
Acquisition Time 2.5559
Acquisition Date 2015-03-19T09:25:33
Spectrometer Frequency 399.80
Spectral Width 6410.3
Lowest Frequency -806.4
Nucleus 1H
Acquired Size 16384
Spectral Size 65536
Me
OH
H
O
O
Ph
H
Me
54
1.89
2.78
0.95
1.01
1.00
1.02
1.00
0.97
1.01
1.02
0.95
1.05
2.94
1.00
3.00
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 3-AH-026-CH/ CARBON01.fid/ fid
Title CARBON01
Origin Varian
Solvent CDCl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 1000
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 3.4500
Acquisition Time 1.3107
Acquisition Date 2015-03-19T09:26:14
Spectrometer Frequency 100.54
Spectral Width 25000.0
Lowest Frequency -1444.2
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Me
OH
Me
H
O
O
Ph
H
54
14.5
20.6
29.5
36.4
40.7
60.7
94.9
97.1
101.3
113.2
129.8
128.5
126.9
136.4
143.1
ppm

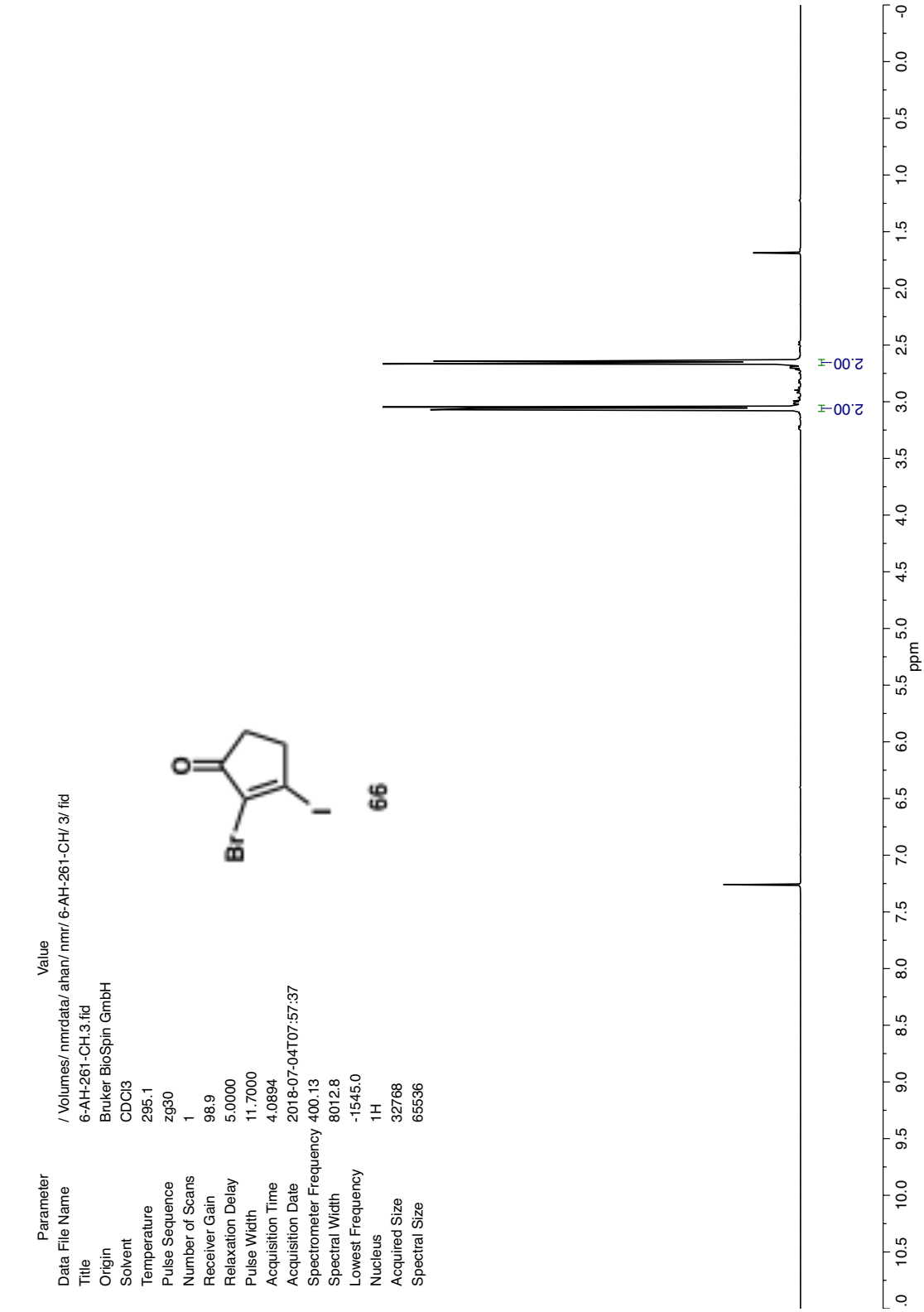

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-041-CH/ 1/ fid
Title 9-AH-041-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-16T09:10:17
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.2
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
Me
O
H
H
Me
O
O
Ph
H
55
1.01
2.03
3.00
1.00
1.03
1.01
1.00
1.02
2.05
1.04
3.05
1.00
3.04
ppm

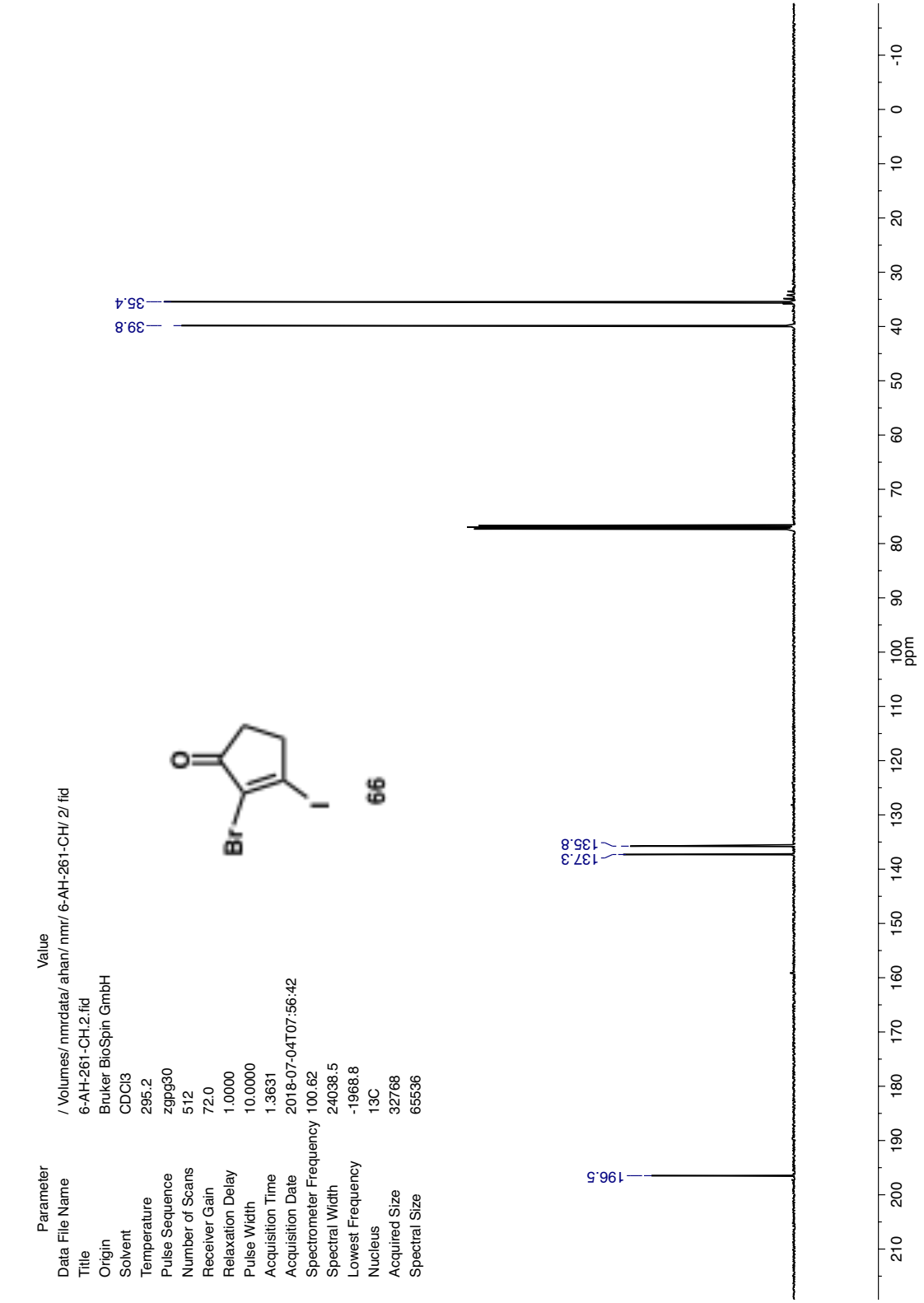

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-041-CH/ 2/ fid
Title 9-AH-041-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 750
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-16T09:41:07
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.2
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
55
Me
H
O
O
O
Ph
H
H
Me
14.5
20.5
31.9
35.9
43.5
97.3
97.4
104.6
114.5
126.7
128.4
129.8
136.2
142.6
200.7
ppm

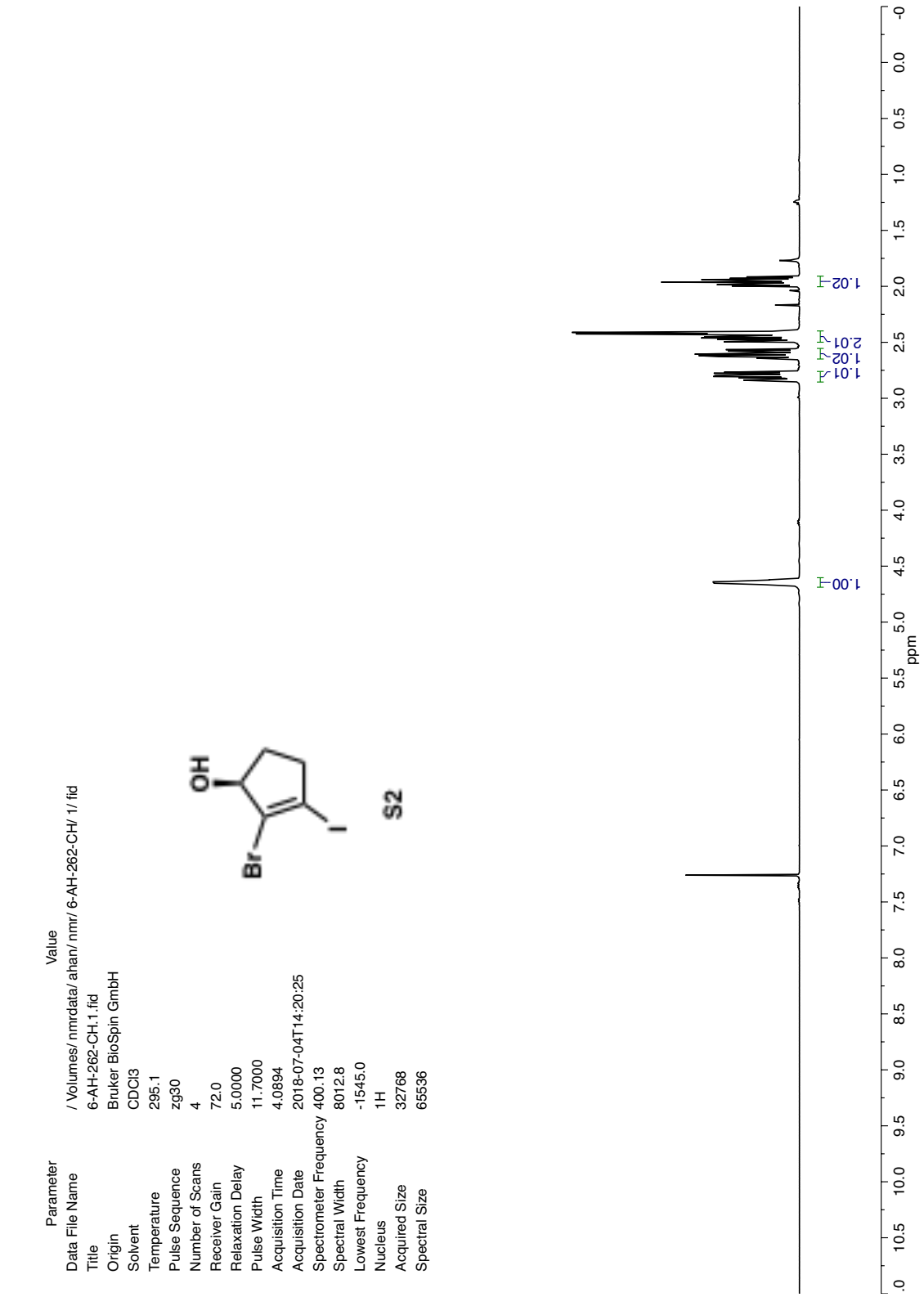

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-101-CH/ 1/ fid
Title
8-AH-101-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Pulse Sequence
zg30
Number of Scans
4
Receiver Gain
98.9
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-06-16T08:49:23
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.3
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
OTES
I
Br
64
6.06
9.03
1.03
1.05
1.04
1.03
1.00
ppm

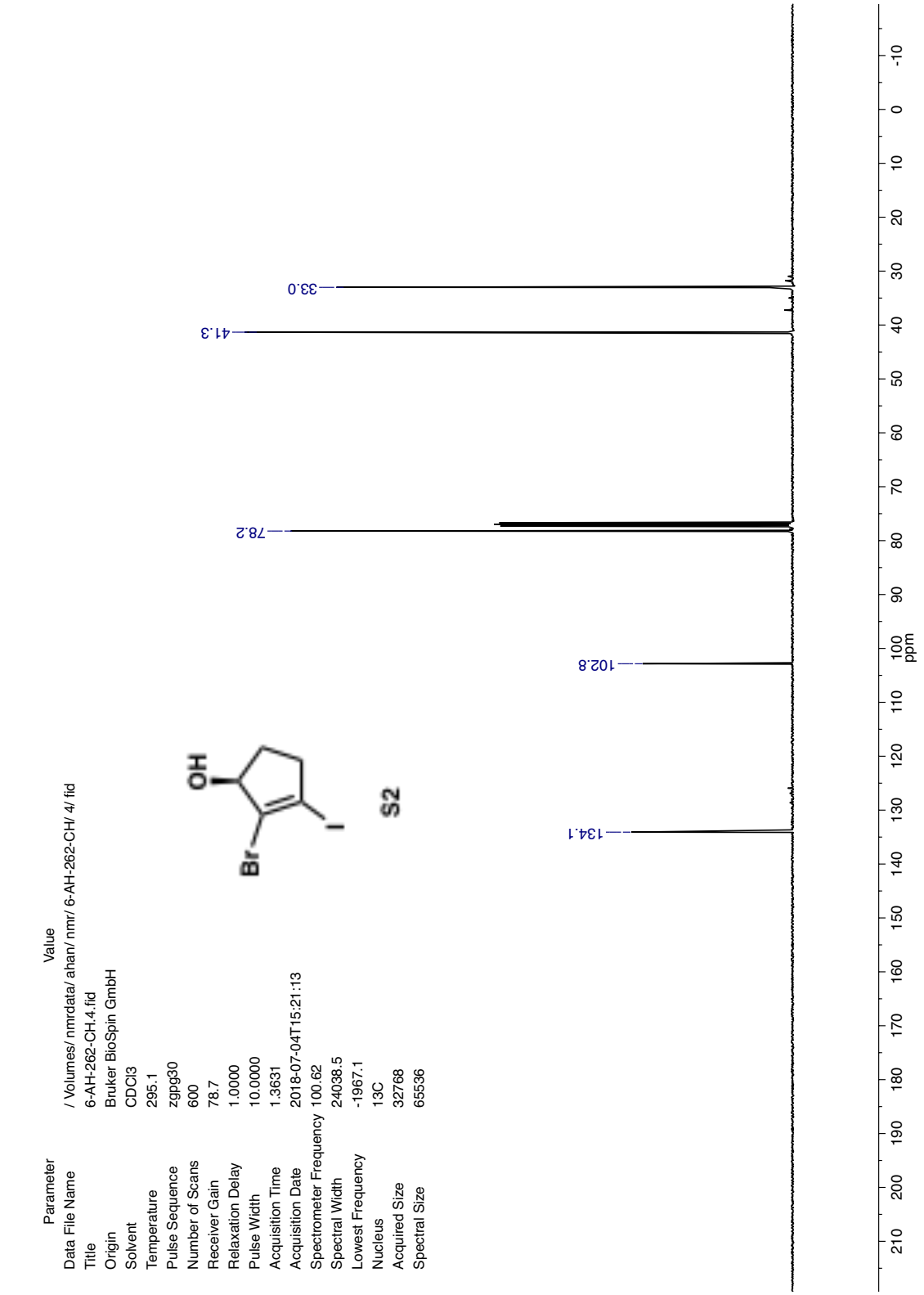


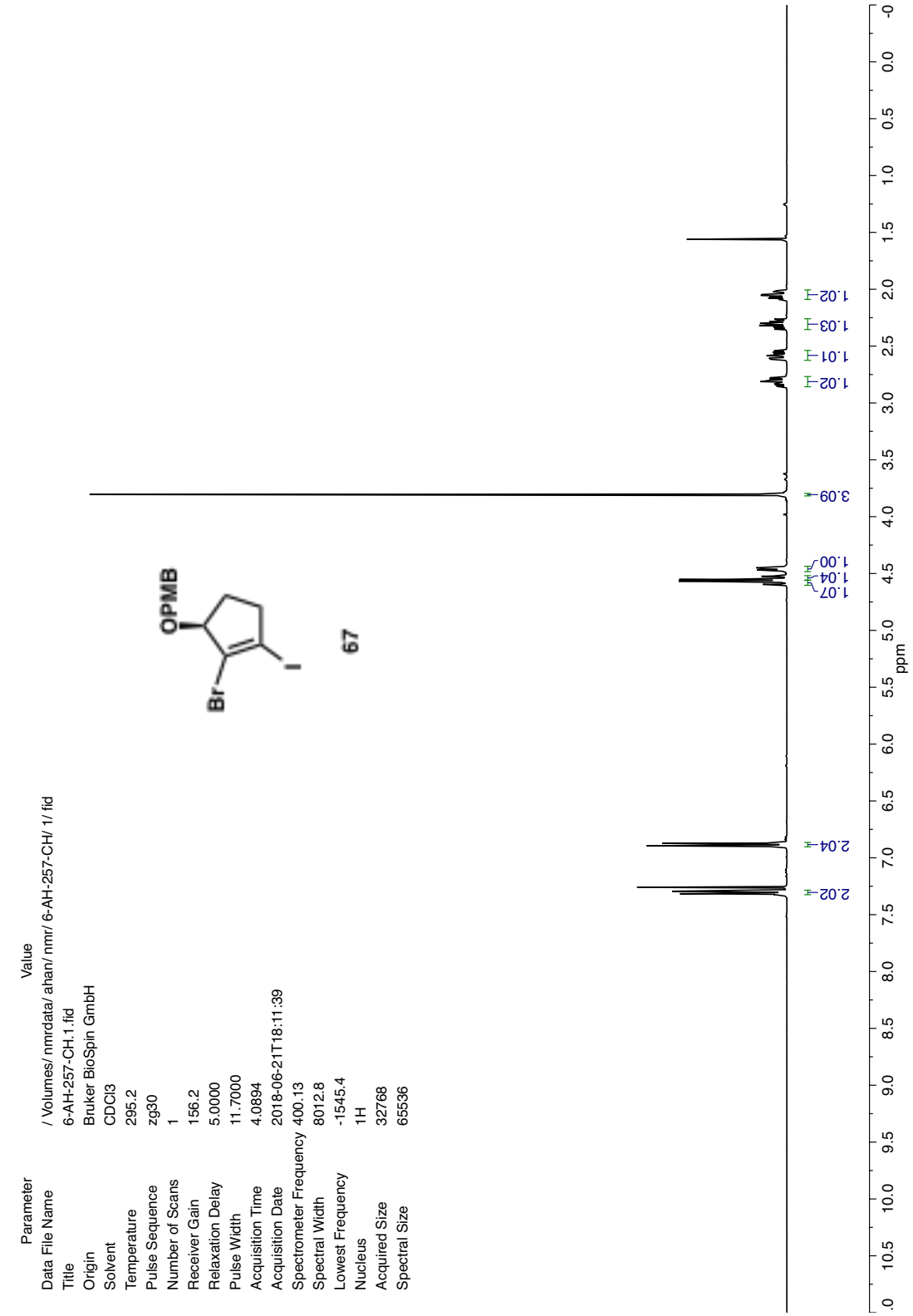
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-101-CH/ 4/ fid
Title	8-AH-101-CH.4.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Pulse Sequence	zgpg30
Number of Scans	600
Receiver Gain	50.3
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-06-16T09:42:48
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1960.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-261-CH/ 3/ fid
Title
6-AH-261-CH.3.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zg30
Number of Scans
1
Receiver Gain
98.9
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-07-04T07:57:37
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.0
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
O
Br
I
66
2.00
2.00
ppm

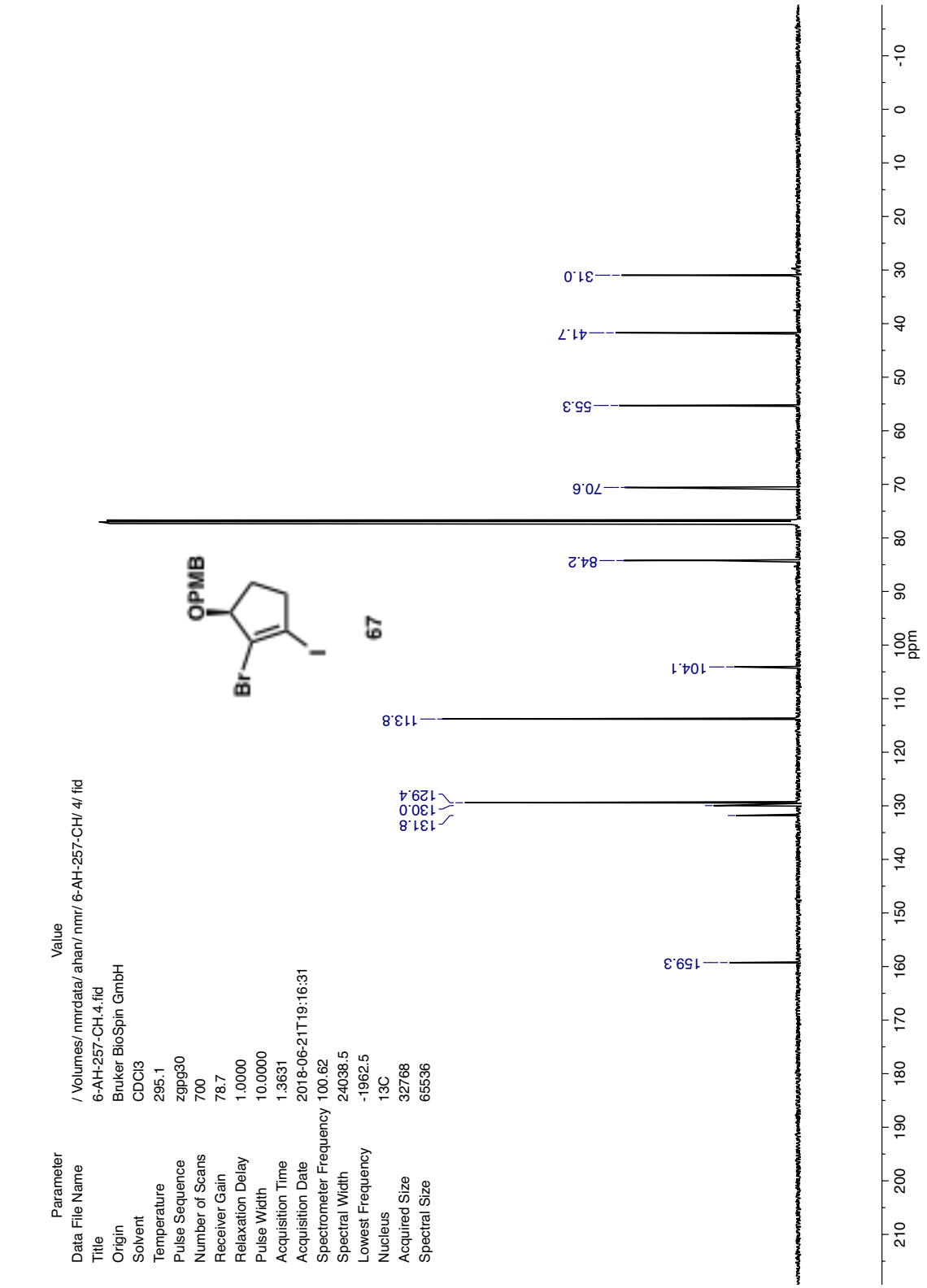

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-261-CH/ 2/ fid
Title 6-AH-261-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-04T07:56:42
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1968.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
O
Br
I
66
35.4
39.8
135.8
137.3
196.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

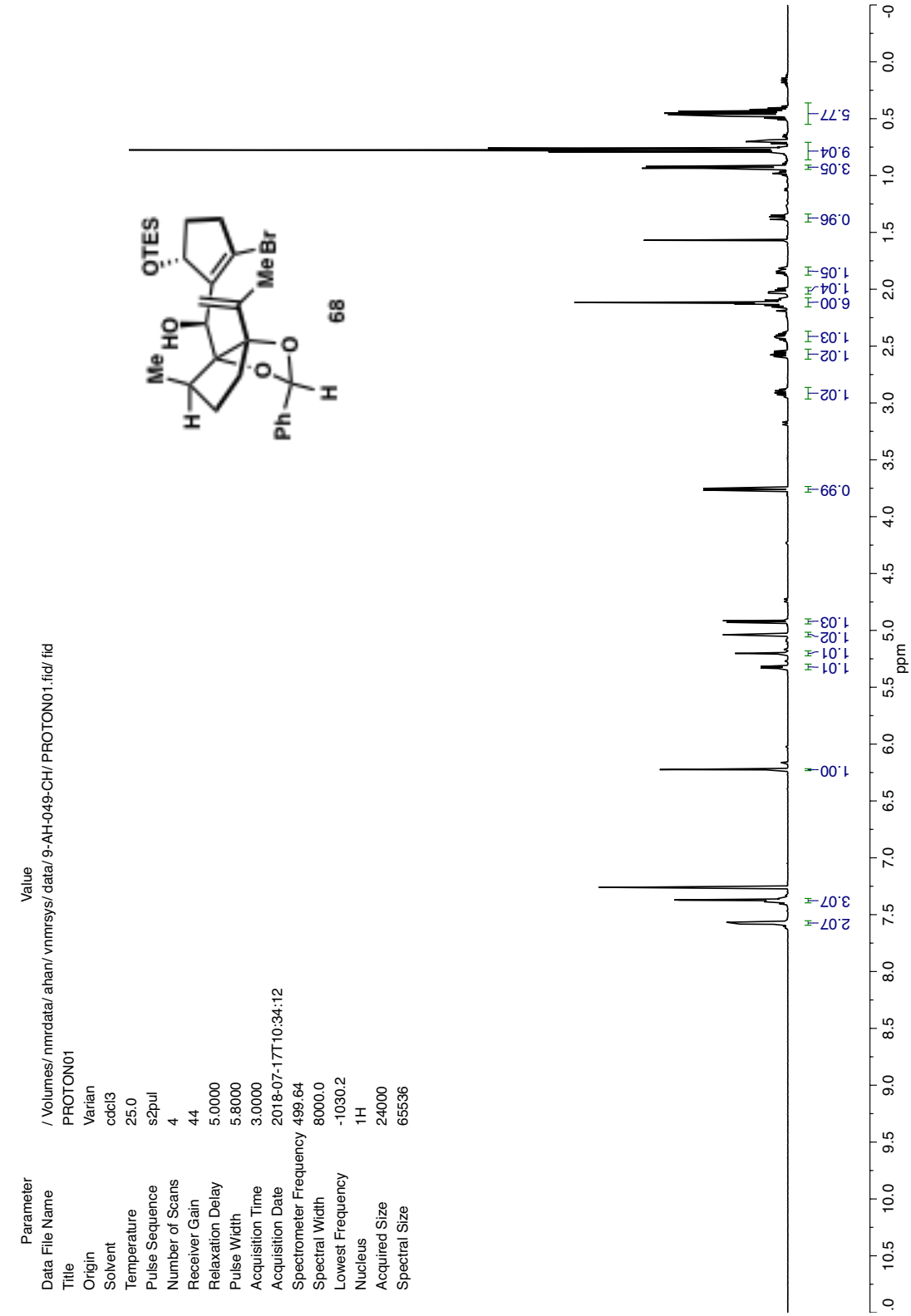

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-262-CH/ 1/ fid
Title
6-AH-262-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zg30
Number of Scans
4
Receiver Gain
72.0
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-07-04T14:20:25
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.0
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
OH
Br
I
S2
1.00
1.01
1.02
2.01
1.02
ppm


Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-262-CH/ 4/ fid
Title 6-AH-262-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 600
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-04T15:21:13
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1967.1
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
OH
Br
I
S2
33.0
41.3
78.2
102.8
134.1
ppm

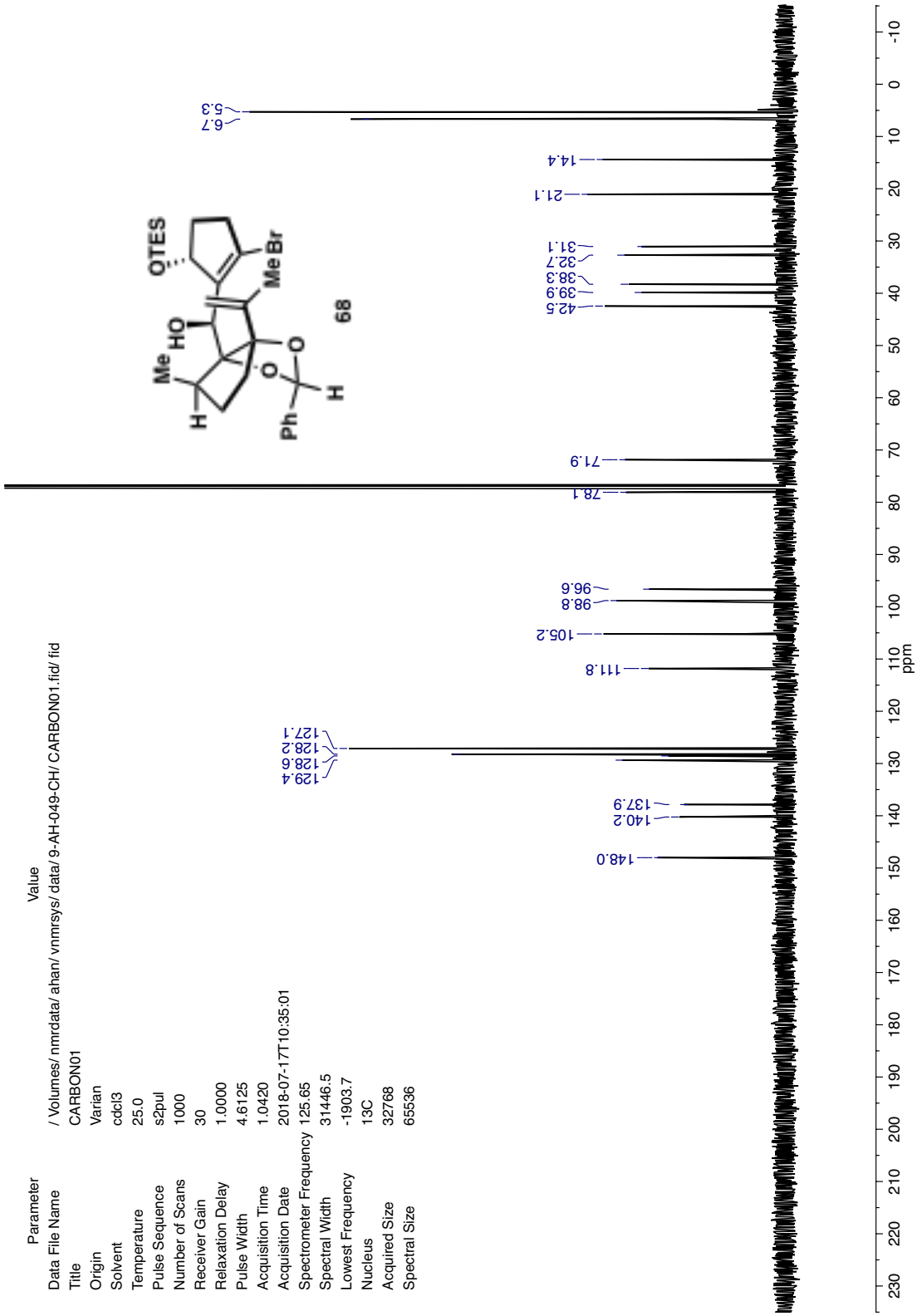


Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 6-AH-257-CH/ 1/ fid
Title	6-AH-257-CH.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Number of Scans	1
Receiver Gain	156.2
Relaxation Delay	5.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-06-21T18:11:39
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1545.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

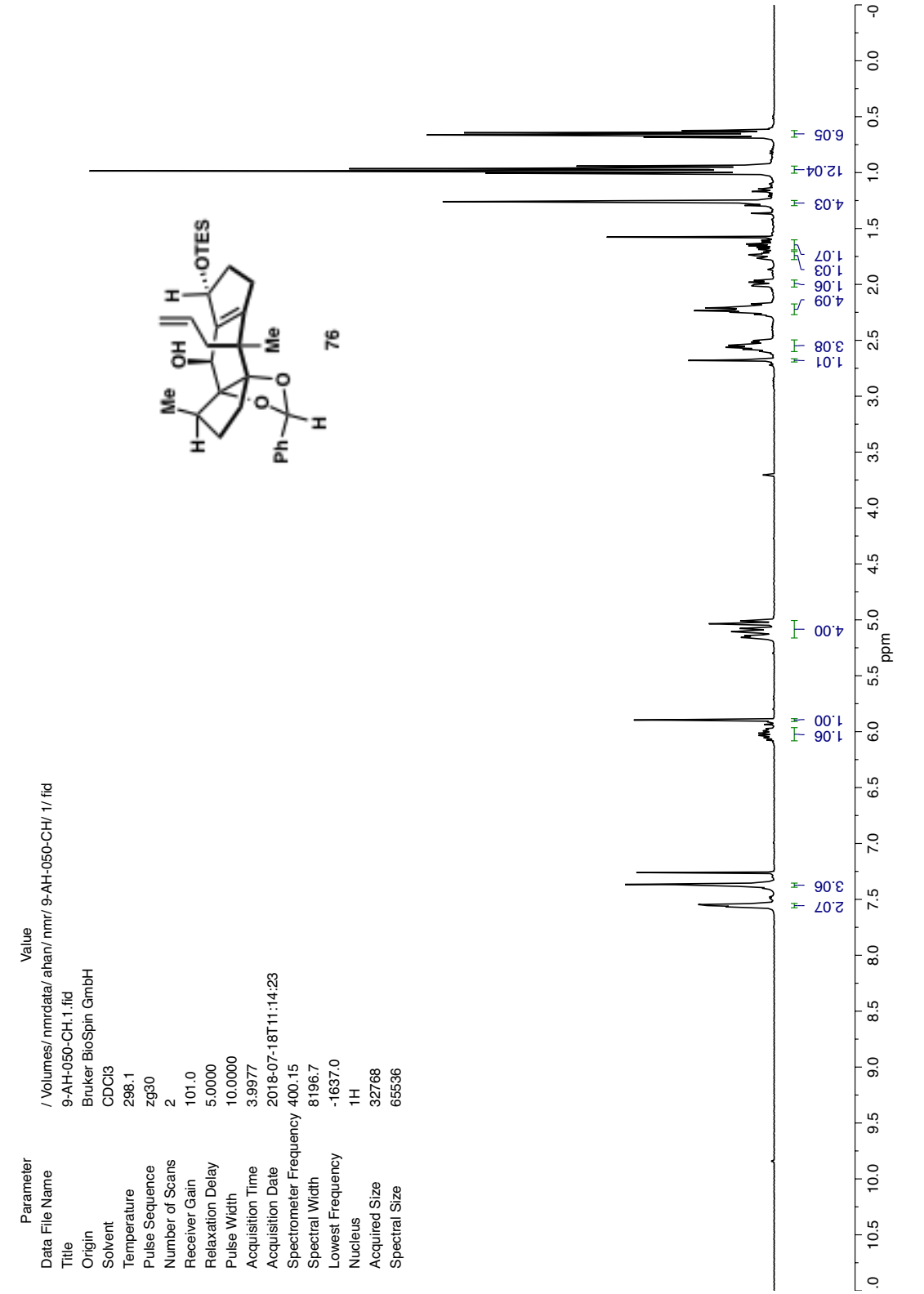

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 6-AH-257-CH/ 4/ fid
Title 6-AH-257-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 700
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-21T19:16:31
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1962.5
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
OPMB
Br
I
67
31.0
41.7
55.3
70.6
84.2
104.1
113.8
129.4
130.0
131.8
159.3
ppm

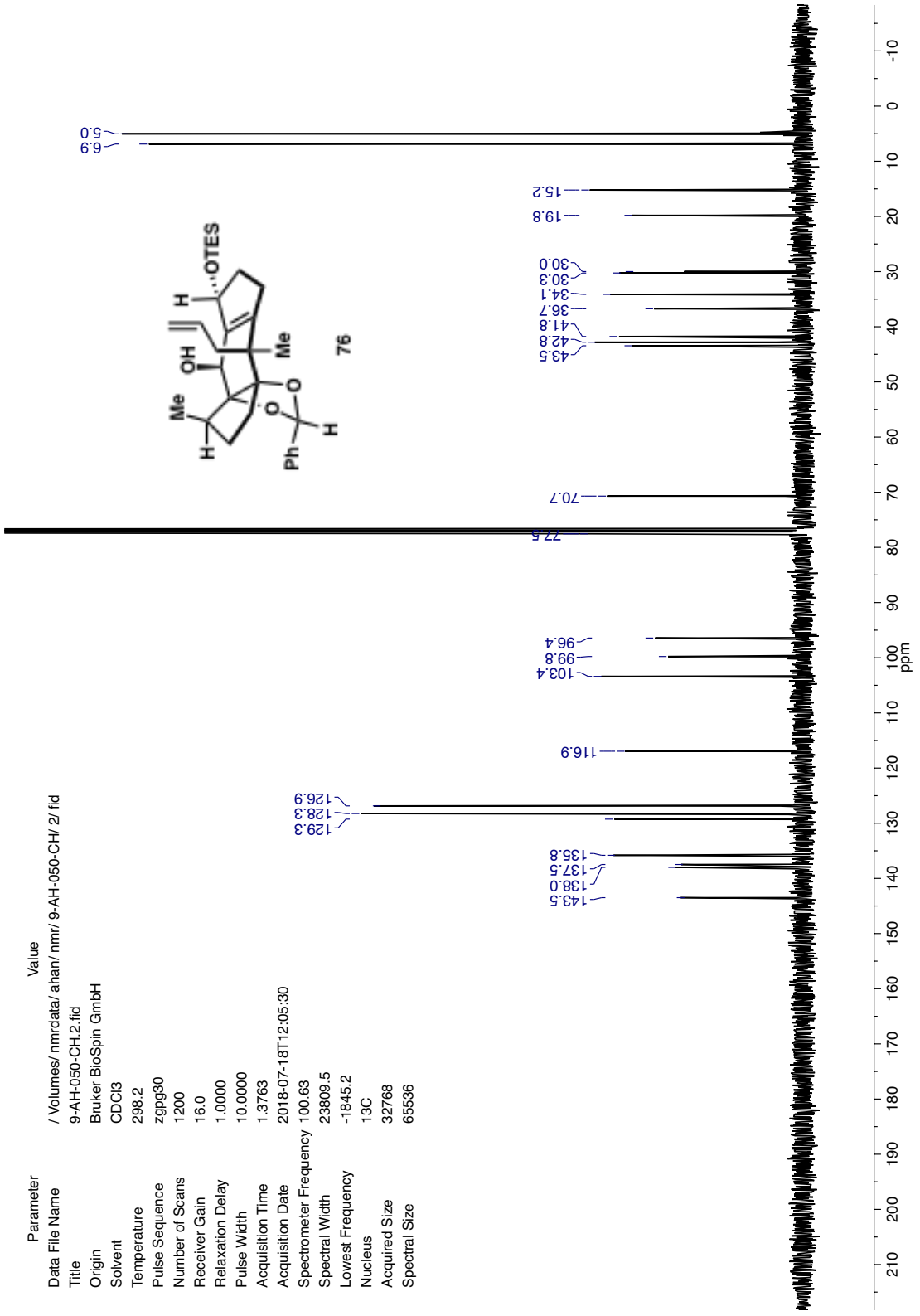


Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 9-AH-049-CH/ PROTON01.fid/ fid
Title	PROTON01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	4
Receiver Gain	44
Relaxation Delay	5.0000
Pulse Width	5.8000
Acquisition Time	3.0000
Acquisition Date	2018-07-17T10:34:12
Spectrometer Frequency	499.64
Spectral Width	8000.0
Lowest Frequency	-1030.2
Nucleus	1H
Acquired Size	24000
Spectral Size	65536

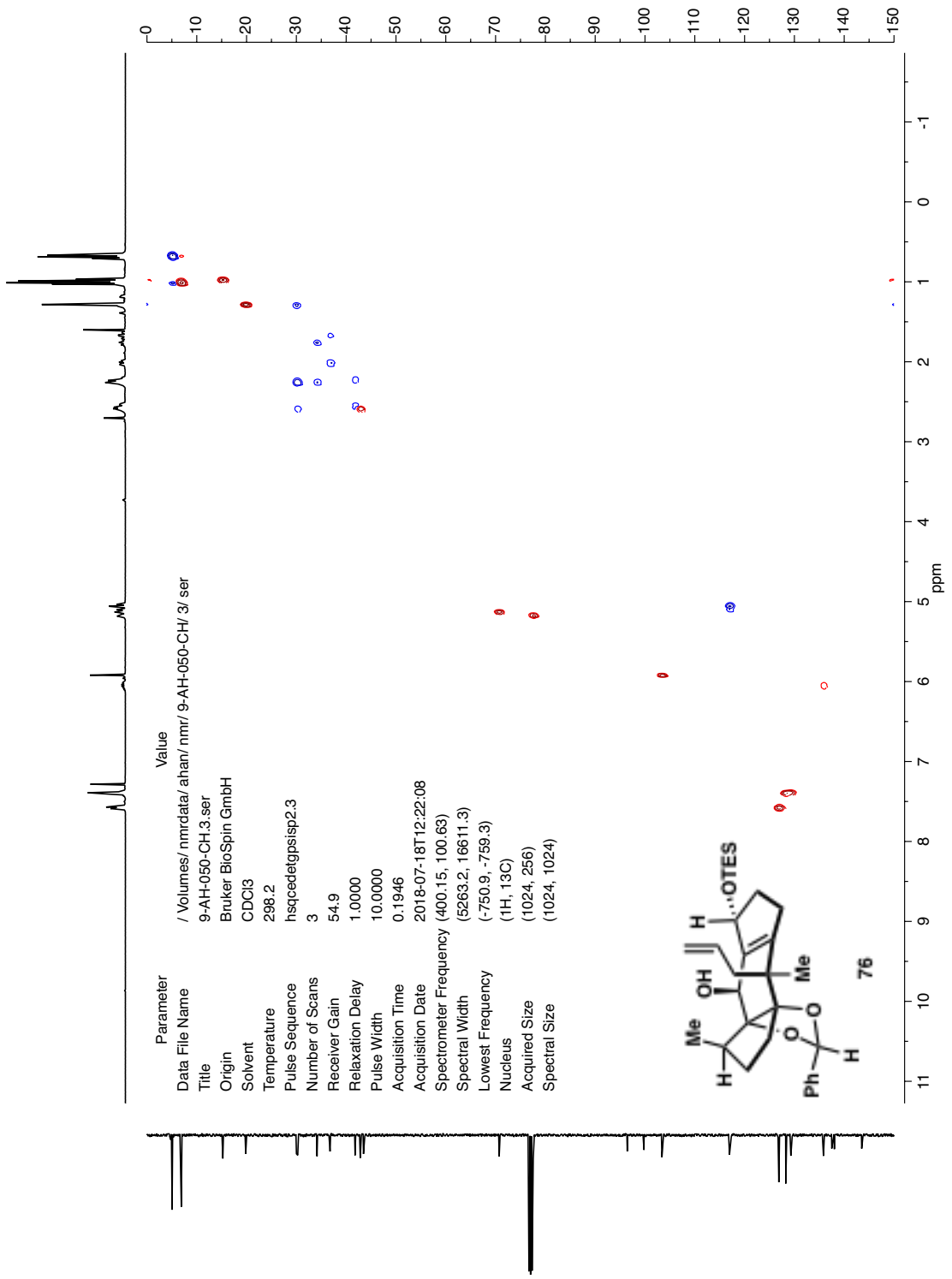


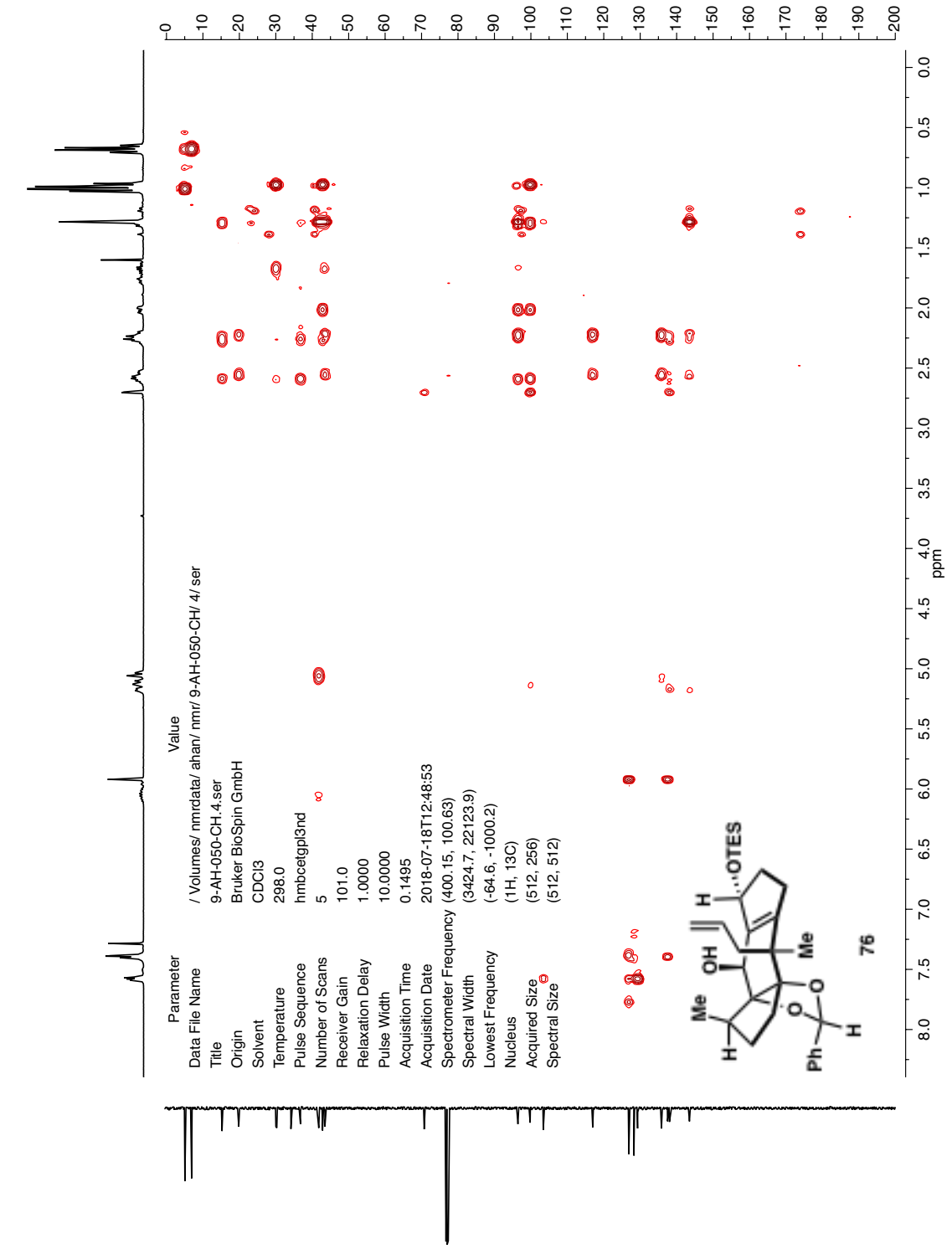
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 9-AH-049-CH/ CARBON01.fid/ fid
Title	CARBON01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	1000
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	4.6125
Acquisition Time	1.0420
Acquisition Date	2018-07-17T10:35:01
Spectrometer Frequency	125.65
Spectral Width	31446.5
Lowest Frequency	-1903.7
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

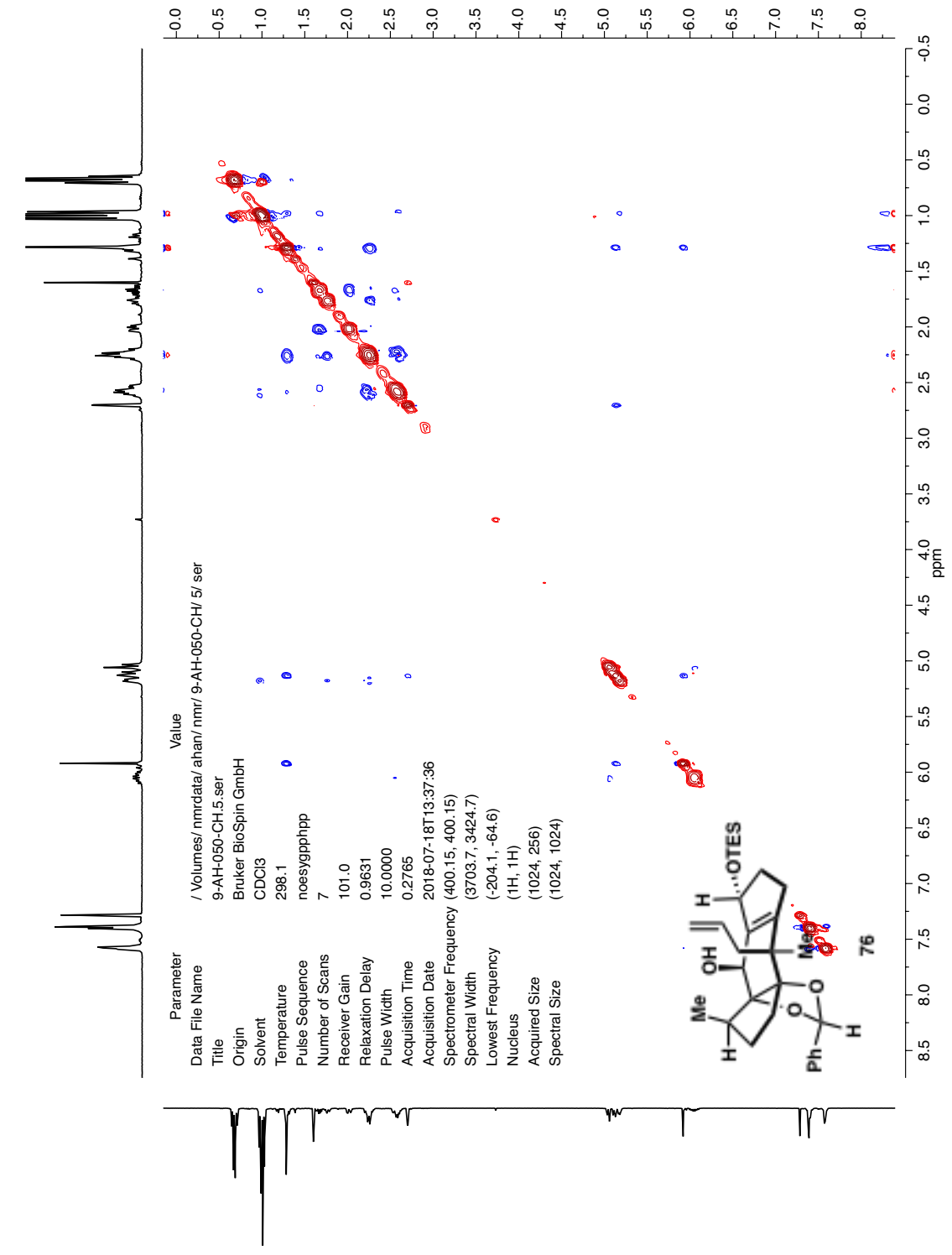

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-050-CH/ 1/ fid
Title
9-AH-050-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
298.1
Pulse Sequence
zg30
Number of Scans
2
Receiver Gain
101.0
Relaxation Delay
5.0000
Pulse Width
10.0000
Acquisition Time
3.9977
Acquisition Date
2018-07-18T11:14:23
Spectrometer Frequency
400.15
Spectral Width
8196.7
Lowest Frequency
-1637.0
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
OTES
OH
Me
Me
O
O
Ph
H
H
H
76
2.07
3.06
1.06
1.00
4.00
1.01
3.08
4.09
1.06
1.03
1.07
4.03
12.04
6.05
ppm

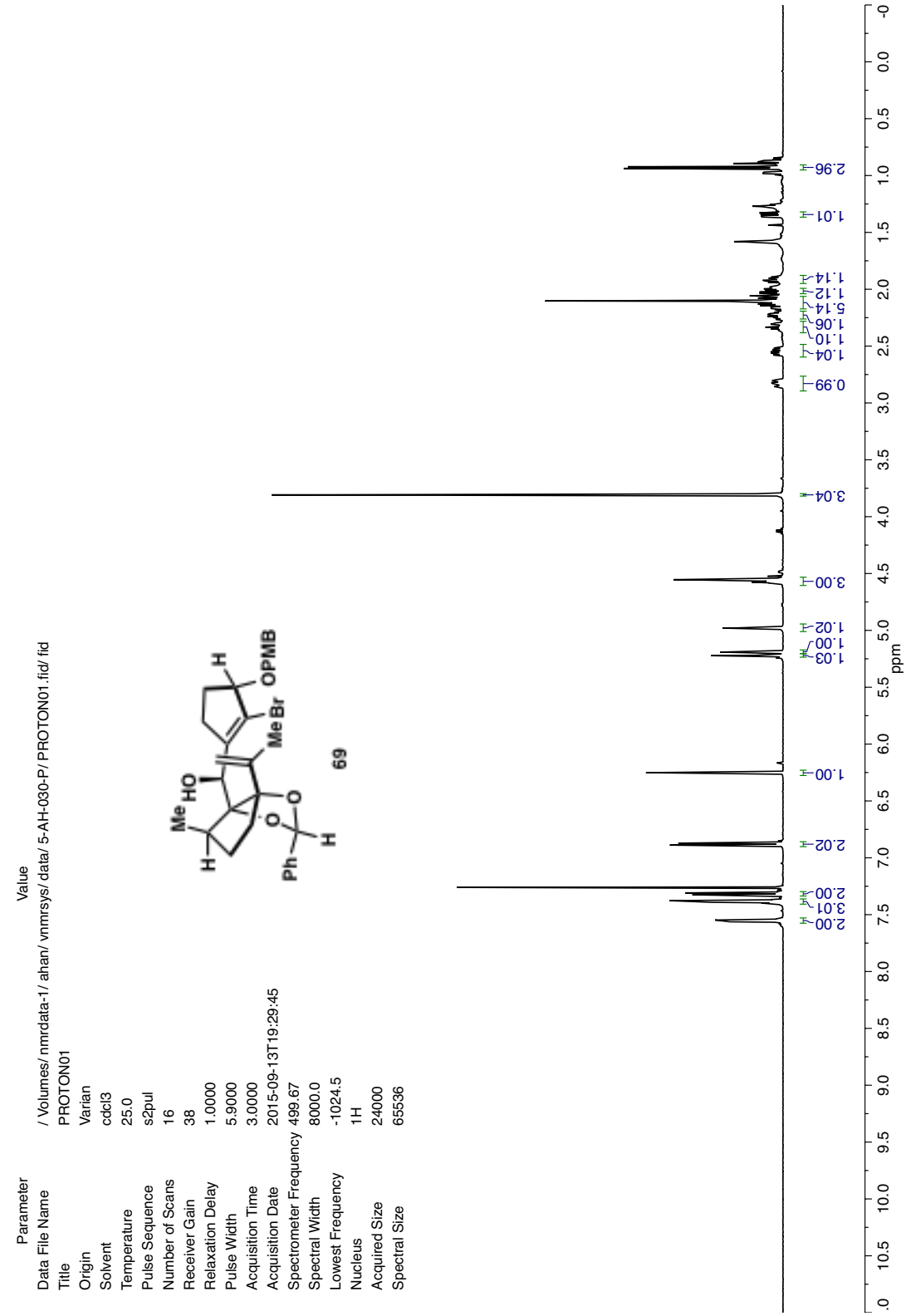


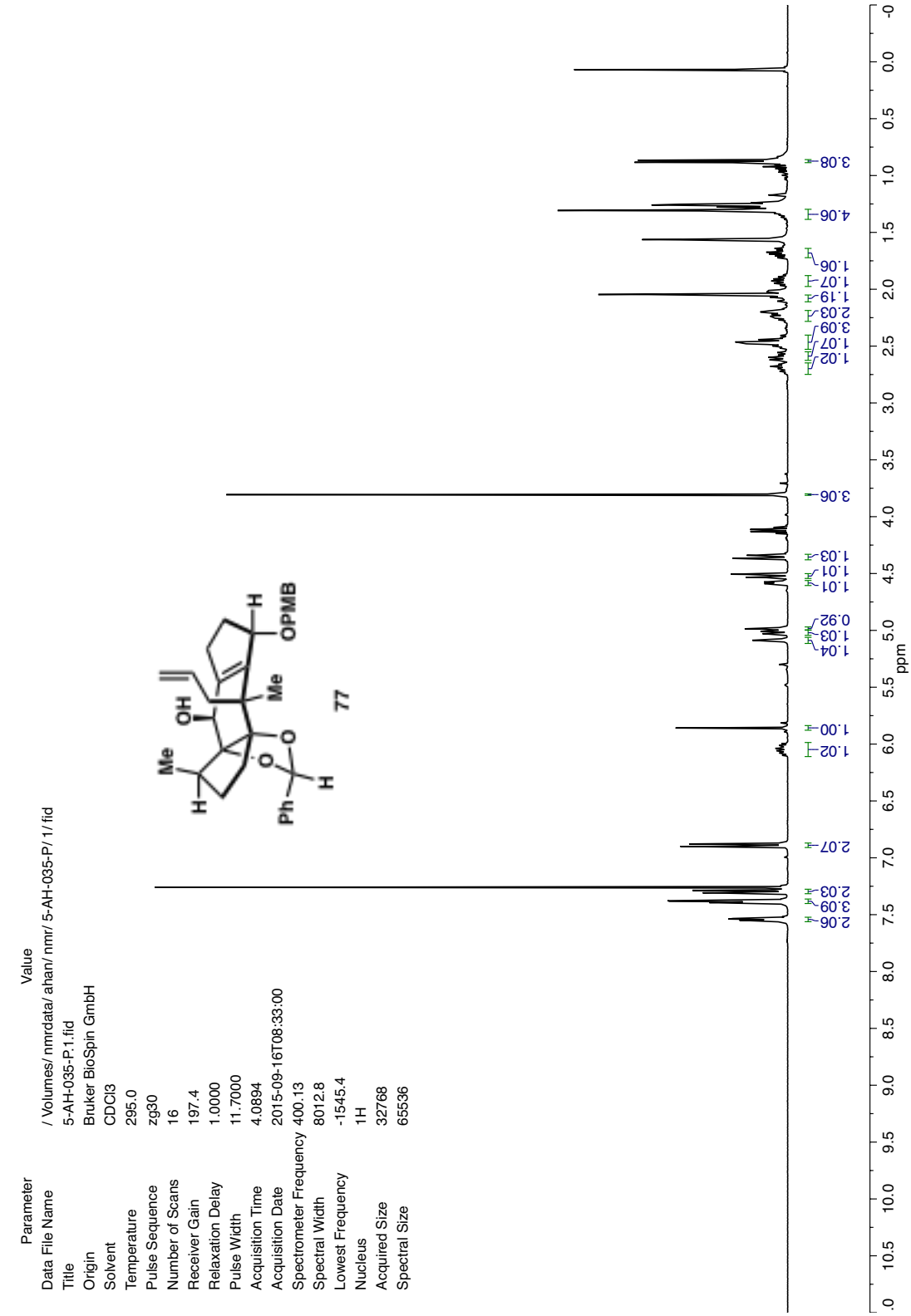
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-050-CH/ 2/ fid
Title	9-AH-050-CH.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	298.2
Pulse Sequence	zgpg30
Number of Scans	1200
Receiver Gain	16.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3763
Acquisition Date	2018-07-18T12:05:30
Spectrometer Frequency	100.63
Spectral Width	23809.5
Lowest Frequency	-1845.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

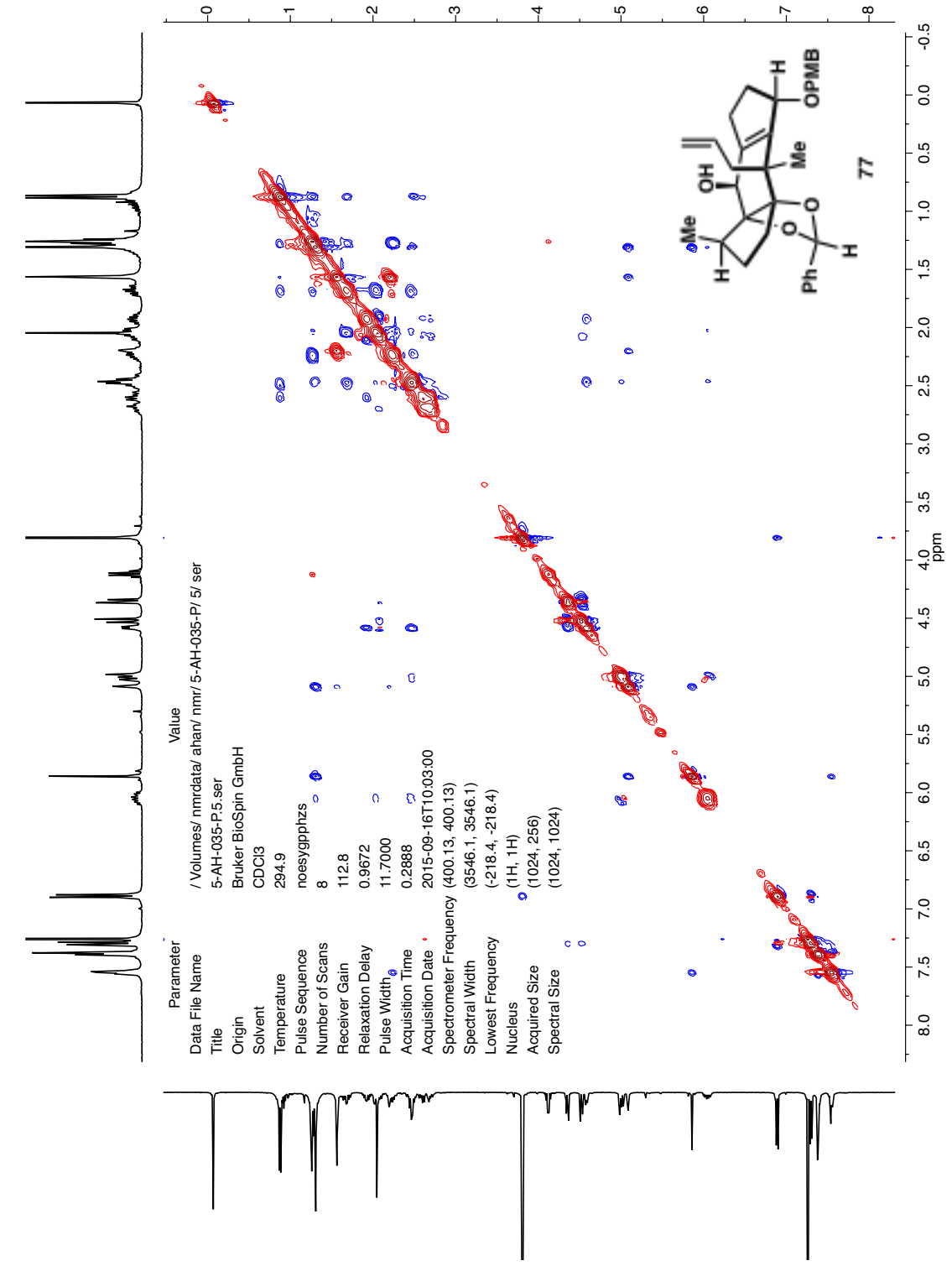

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-050-CH/ 3/ ser
Title 9-AH-050-CH.3.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.2
Pulse Sequence hsqcedetgpsisp2.3
Number of Scans 3
Receiver Gain 54.9
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 0.1946
Acquisition Date 2018-07-18T12:22:08
Spectrometer Frequency (400.15, 100.63)
Spectral Width (5263.2, 16611.3)
Lowest Frequency (-750.9, -759.3)
Nucleus (1H, 13C)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
Me
OH
H
OTES
H
Me
O
O
Ph
H
76
ppm

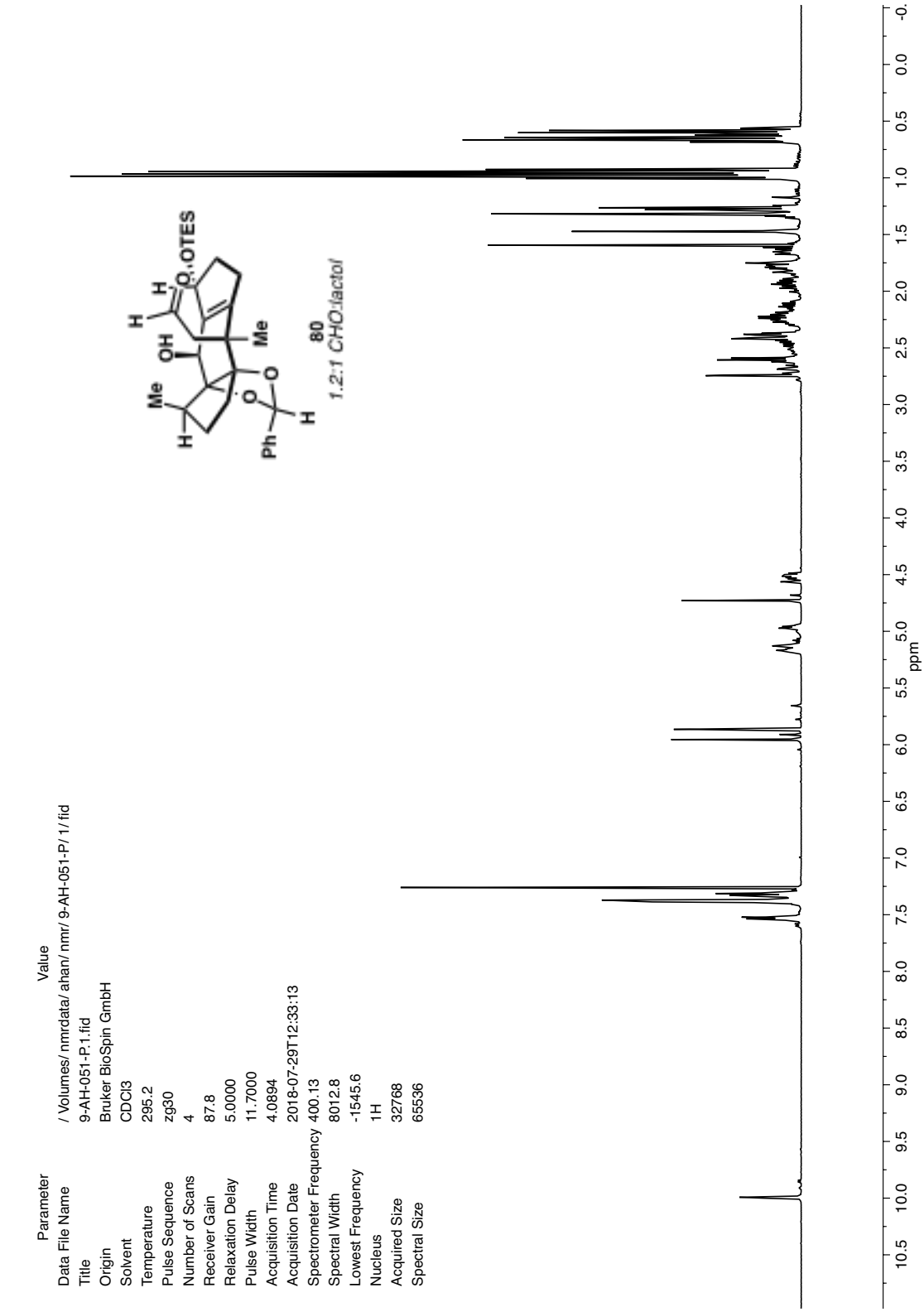

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-050-CH/ 4/ ser
Title 9-AH-050-CH.4.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.0
Pulse Sequence hmbcetgpl3nd
Number of Scans 5
Receiver Gain 101.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 0.1495
Acquisition Date 2018-07-18T12:48:53
Spectrometer Frequency (400.15, 100.63)
Spectral Width (3424.7, 22123.9)
Lowest Frequency (-64.6, -1000.2)
Nucleus (1H, 13C)
Acquired Size (512, 256)
Spectral Size (512, 512)
Me
OH
H
OTES
H
Me
O
O
Ph
H
76
ppm

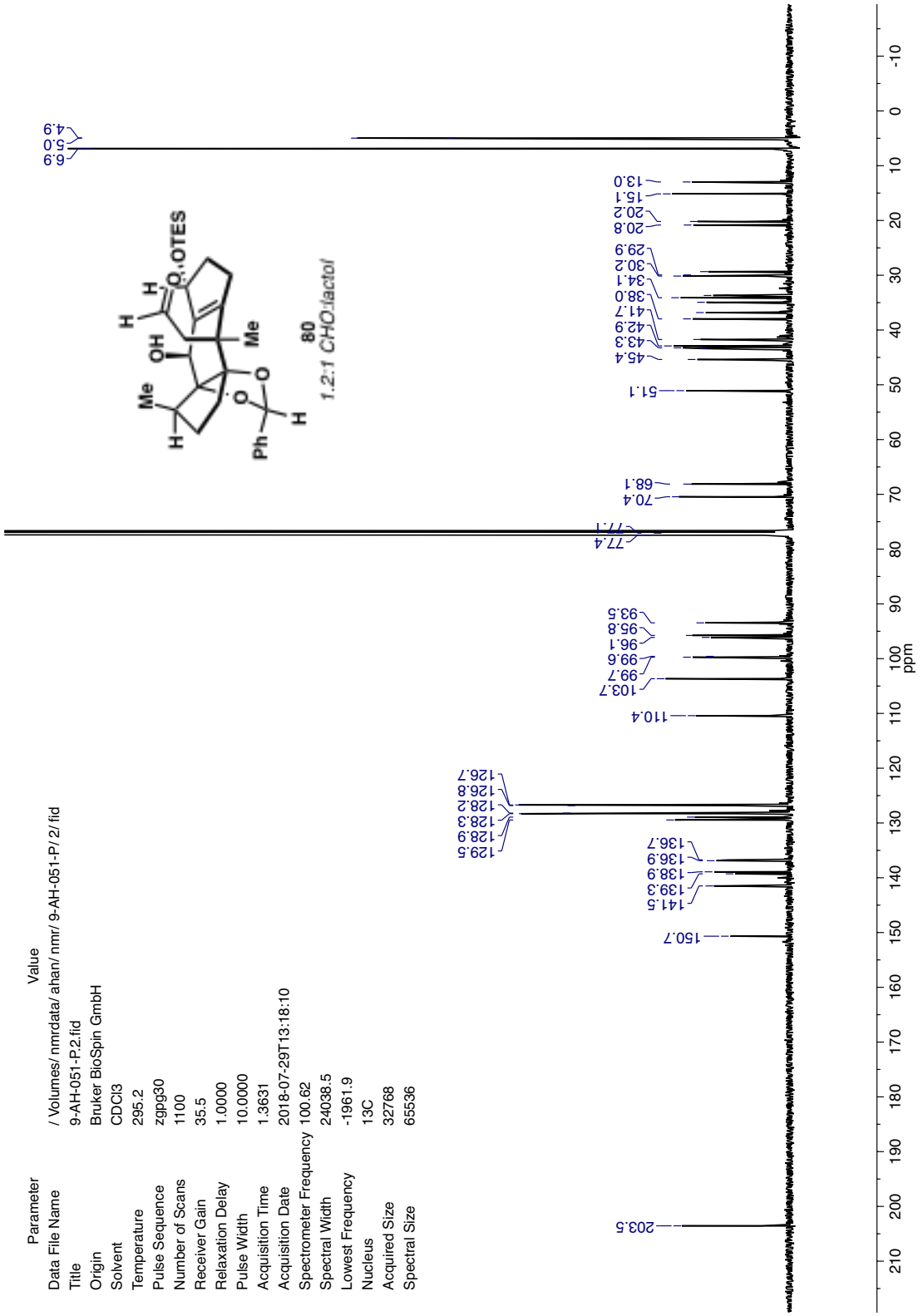

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-050-CH/ 5/ ser
Title 9-AH-050-CH.5.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.1
Pulse Sequence noesygpphpp
Number of Scans 7
Receiver Gain 101.0
Relaxation Delay 0.9631
Pulse Width 10.0000
Acquisition Time 0.2765
Acquisition Date 2018-07-18T13:37:36
Spectrometer Frequency (400.15, 400.15)
Spectral Width (3703.7, 3424.7)
Lowest Frequency (-204.1, -64.6)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
Me
OH
H
OTES
Me
H
O
O
Ph
H
76
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata-1/ ahan/ vnmrsys/ data/ 5-AH-030-P/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 16
Receiver Gain 38
Relaxation Delay 1.0000
Pulse Width 5.9000
Acquisition Time 3.0000
Acquisition Date 2015-09-13T19:29:45
Spectrometer Frequency 499.67
Spectral Width 8000.0
Lowest Frequency -1024.5
Nucleus 1H
Acquired Size 24000
Spectral Size 65536
Me
HO
H
Me Br
OPMB
O
O
Ph
H
69
2.96
1.01
1.14
1.12
5.14
1.06
1.10
1.04
0.99
3.04
3.00
1.02
1.00
1.03
1.00
2.02
2.00
3.01
2.00
ppm

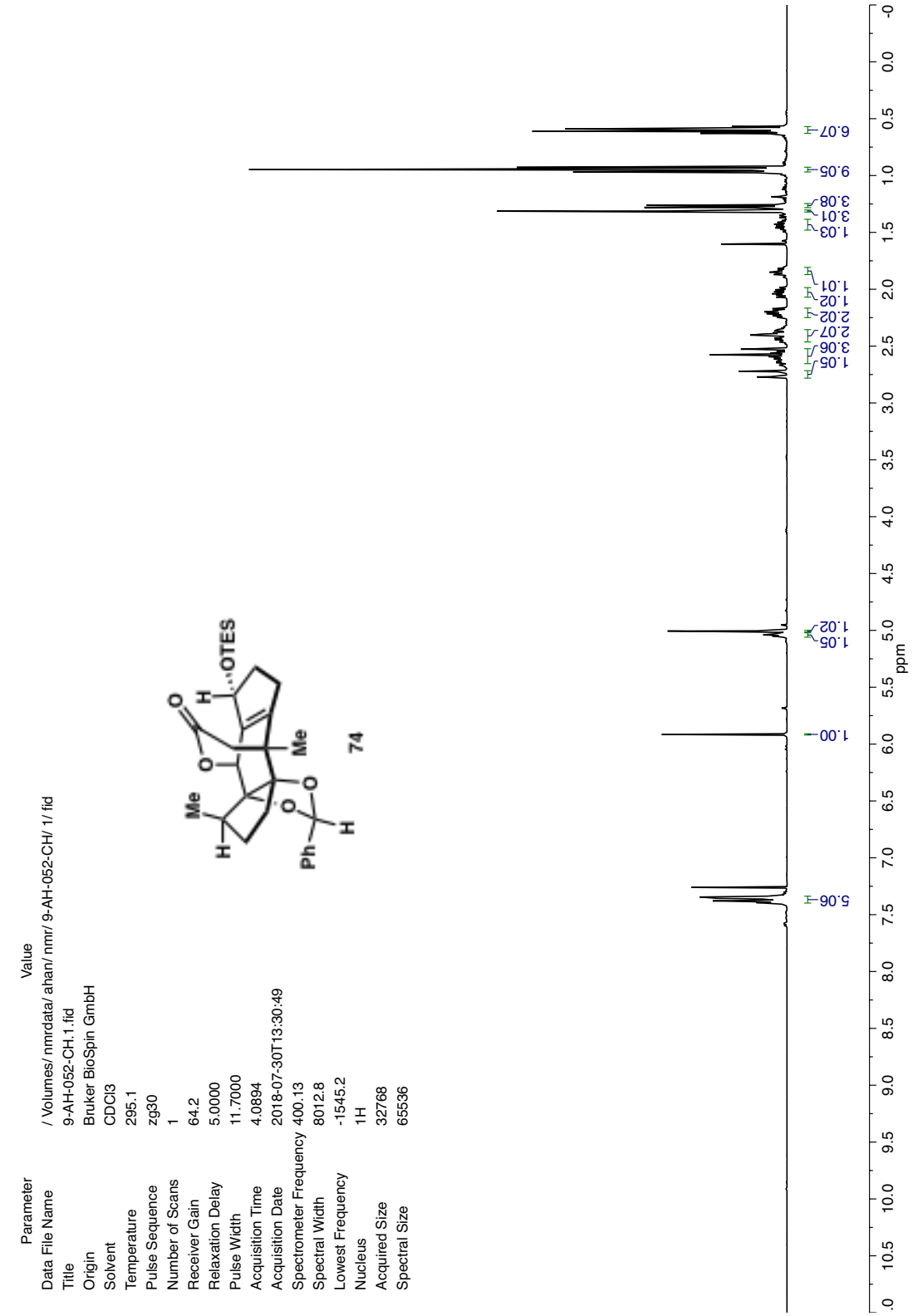

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 5-AH-035-P/ 1/ fid
Title 5-AH-035-P1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2015-09-16T08:33:00
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
Me
OH
H
O
Me
H
Ph
O
H
OPMB
77
2.06
3.09
2.03
2.07
1.02
1.00
1.04
1.03
0.92
1.01
1.01
1.03
3.06
1.02
1.07
3.09
2.03
1.19
1.07
1.06
4.06
3.08
ppm

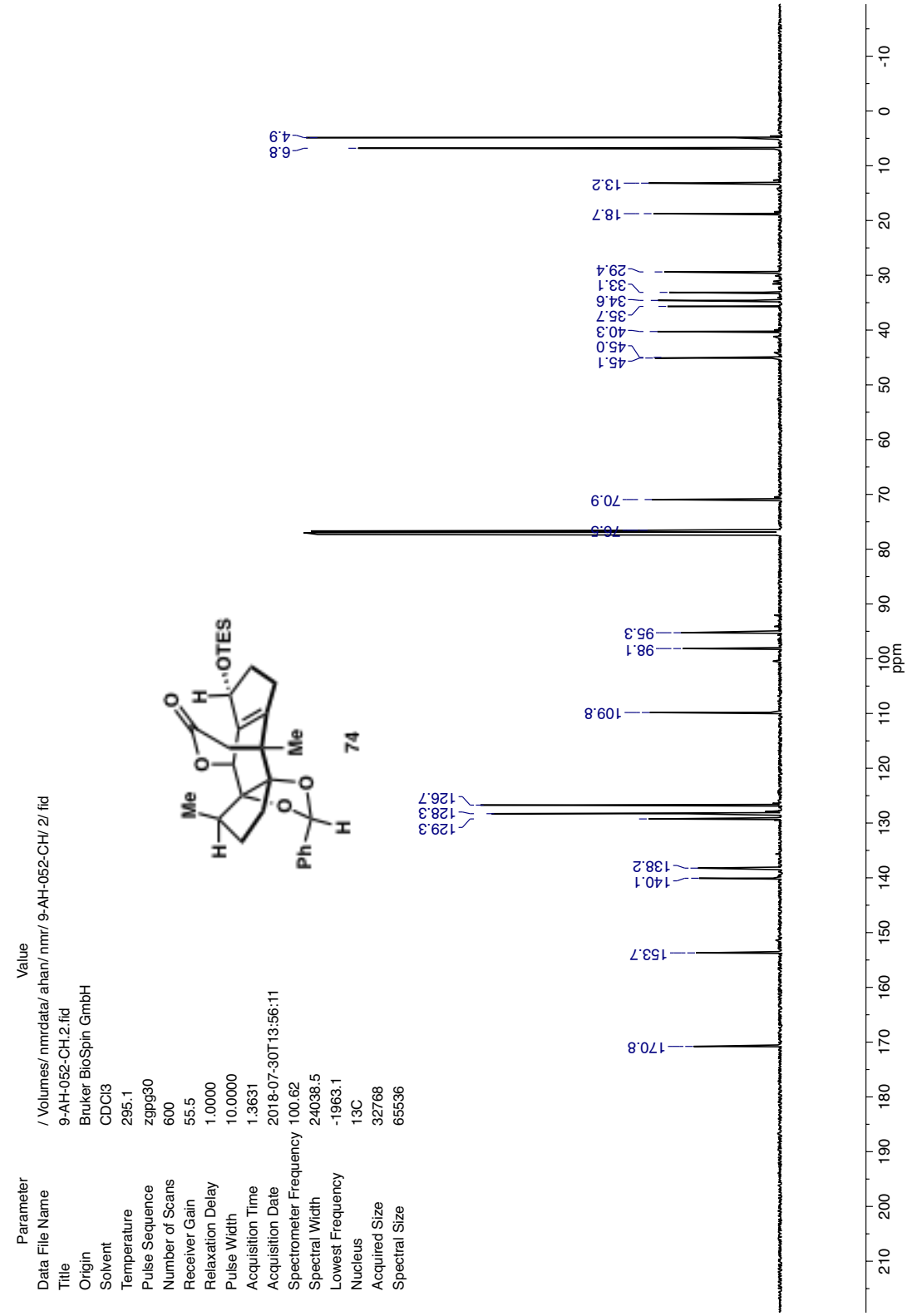

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 5-AH-035-P/ 5/ ser
Title 5-AH-035-P.5.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence noesygpphzs
Number of Scans 8
Receiver Gain 112.8
Relaxation Delay 0.9672
Pulse Width 11.7000
Acquisition Time 0.2888
Acquisition Date 2015-09-16T10:03:00
Spectrometer Frequency (400.13, 400.13)
Spectral Width (3546.1, 3546.1)
Lowest Frequency (-218.4, -218.4)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
Me
OH
Me
OPMB
H
H
O
O
Ph
H
77
ppm

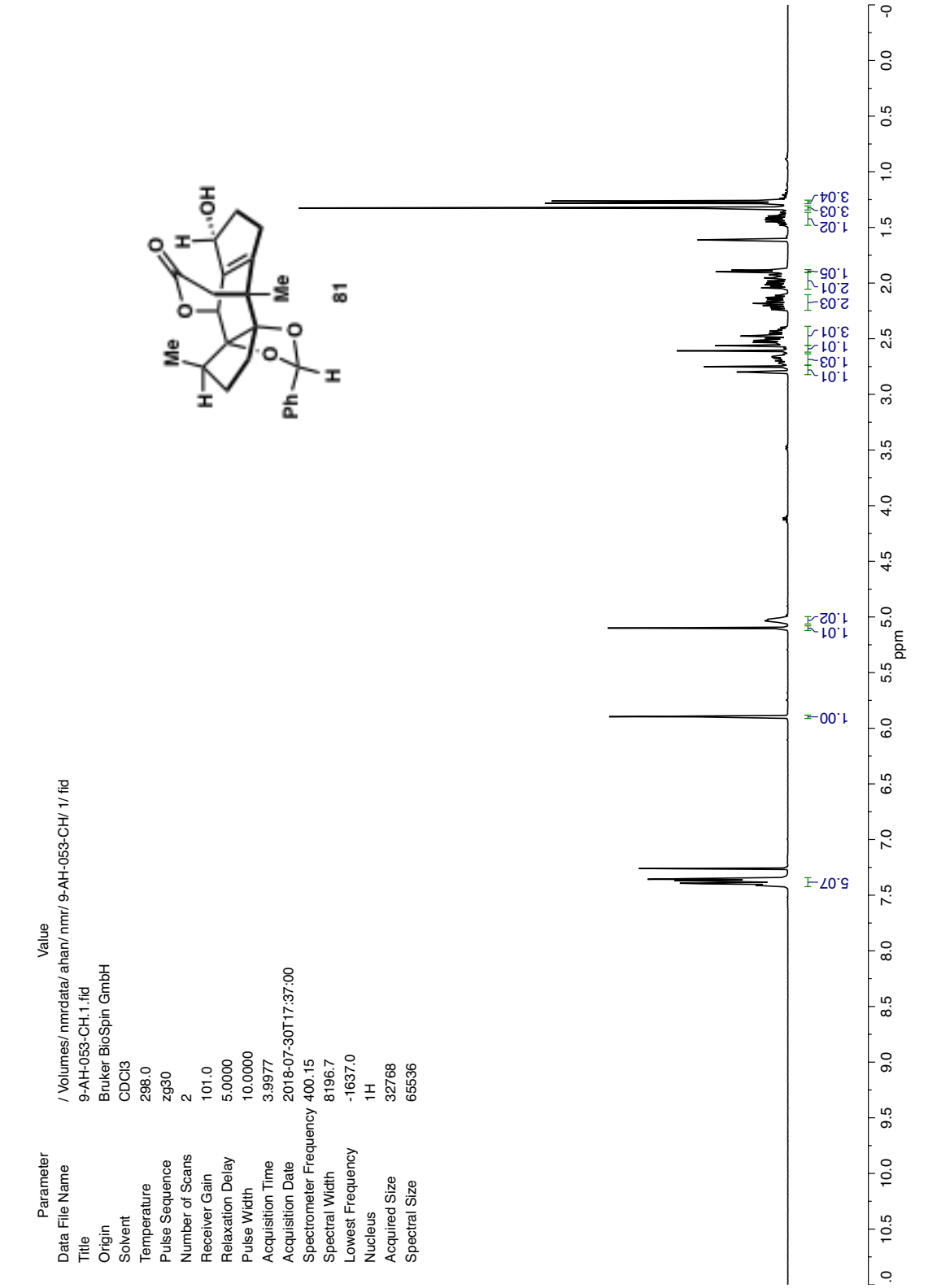

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-051-P/ 1/ fid
Title 9-AH-051-P1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 4
Receiver Gain 87.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-29T12:33:13
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
80
1.2:1 CHCl3:acetol
OTES
OH
Me
Me
Ph
H
H
H
O
O
O
10.5 10.0 9.5 9.0 8.5 8.0 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.
ppm

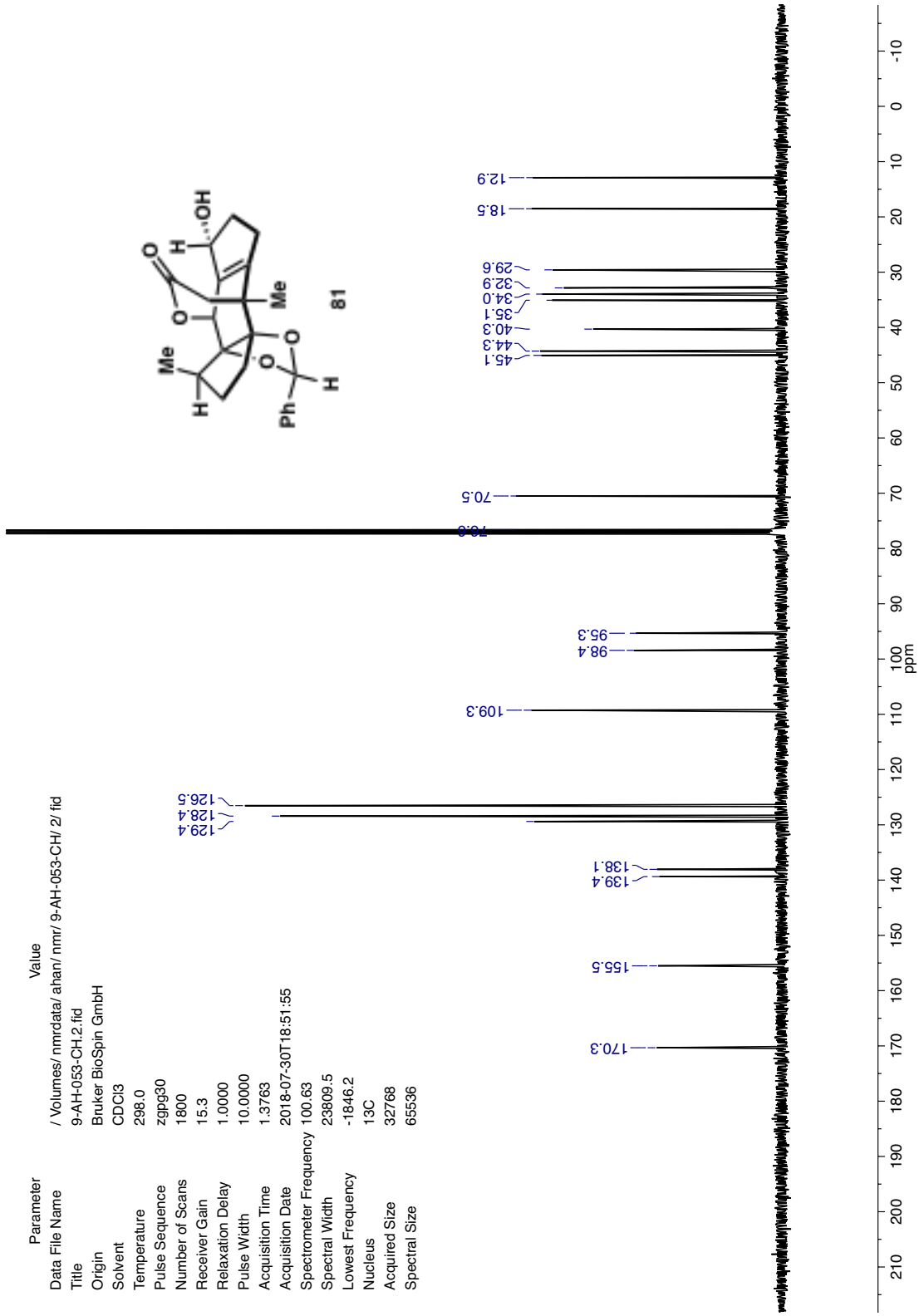


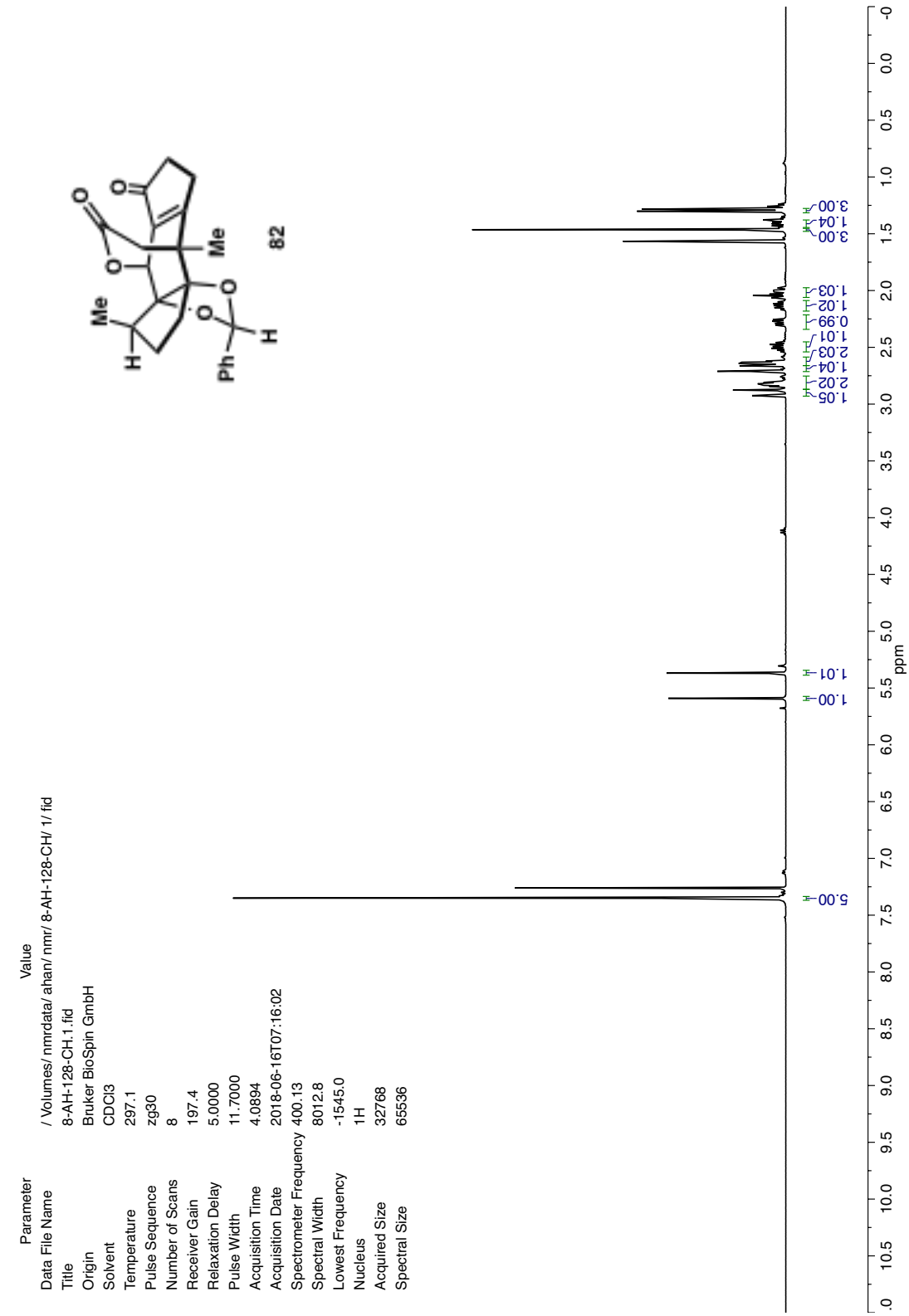
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-051-P/ 2/ fid
Title	9-AH-051-P2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Number of Scans	1100
Receiver Gain	35.5
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-07-29T13:18:10
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1961.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

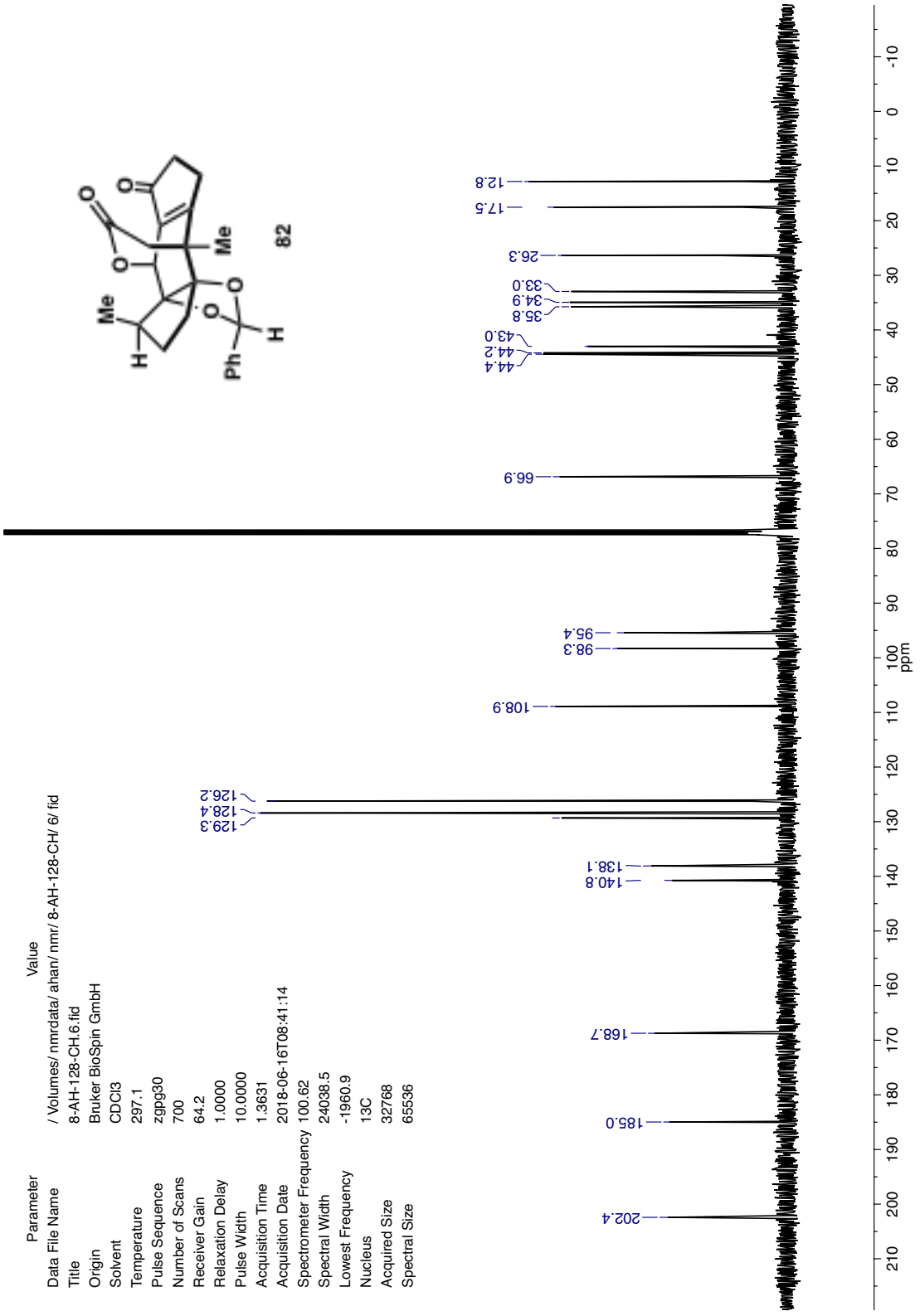

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-052-CH/ 1/ fid
Title 9-AH-052-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 64.2
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-30T13:30:49
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.2
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
OTES
Me
Me
Ph
74
5.06
1.00
1.02
1.05
6.07
9.05
3.08
3.01
1.03
1.01
1.02
2.02
2.07
3.06
1.05
ppm

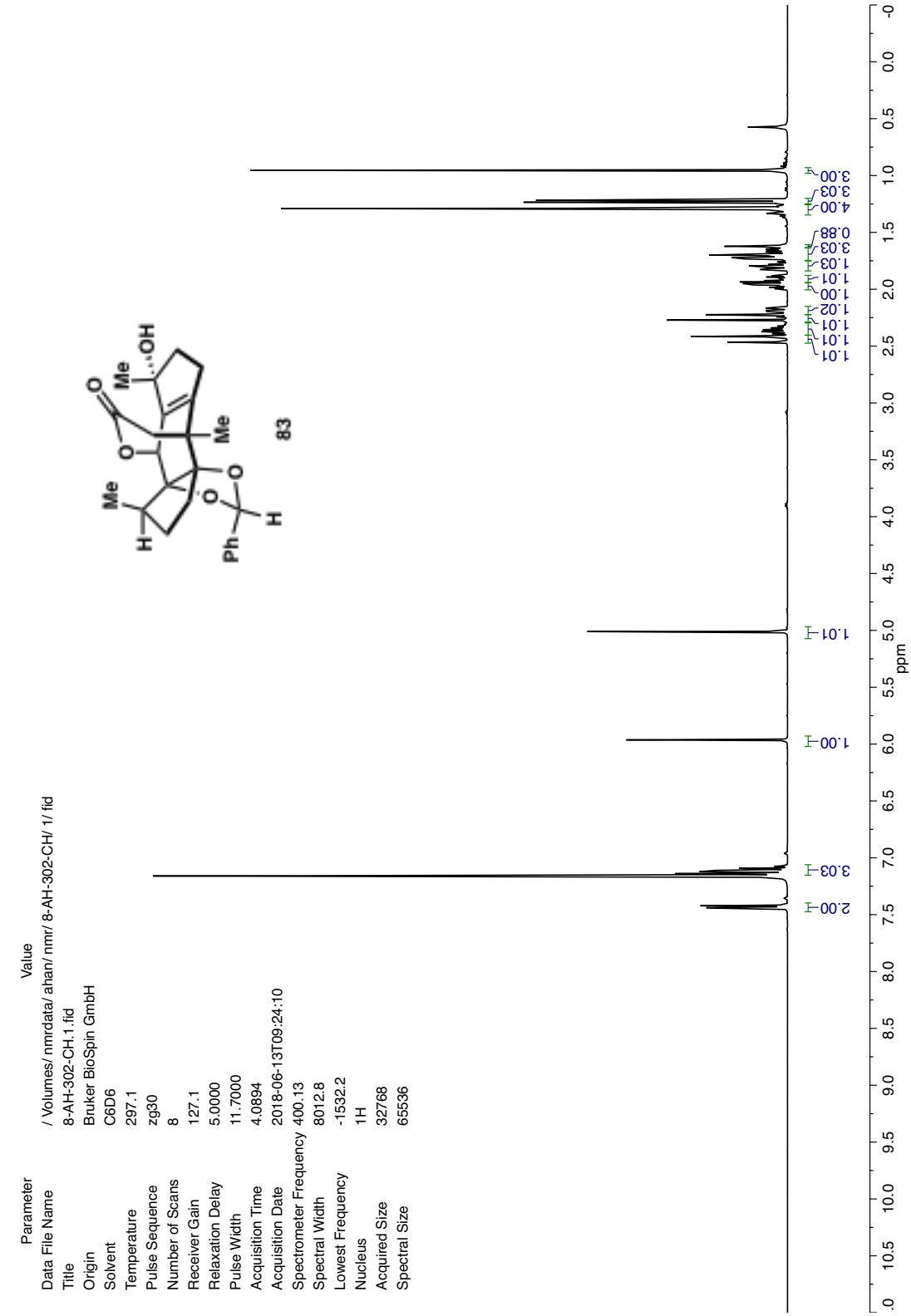

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-052-CH/ 2/ fid
Title 9-AH-052-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 600
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-30T13:56:11
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1963.1
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
OTES
Me
Me
Ph
74
4.9
6.8
13.2
18.7
29.4
33.1
34.6
35.7
40.3
45.0
45.1
70.9
76.8
95.3
98.1
109.8
126.7
128.3
129.3
138.2
140.1
153.7
170.8
ppm

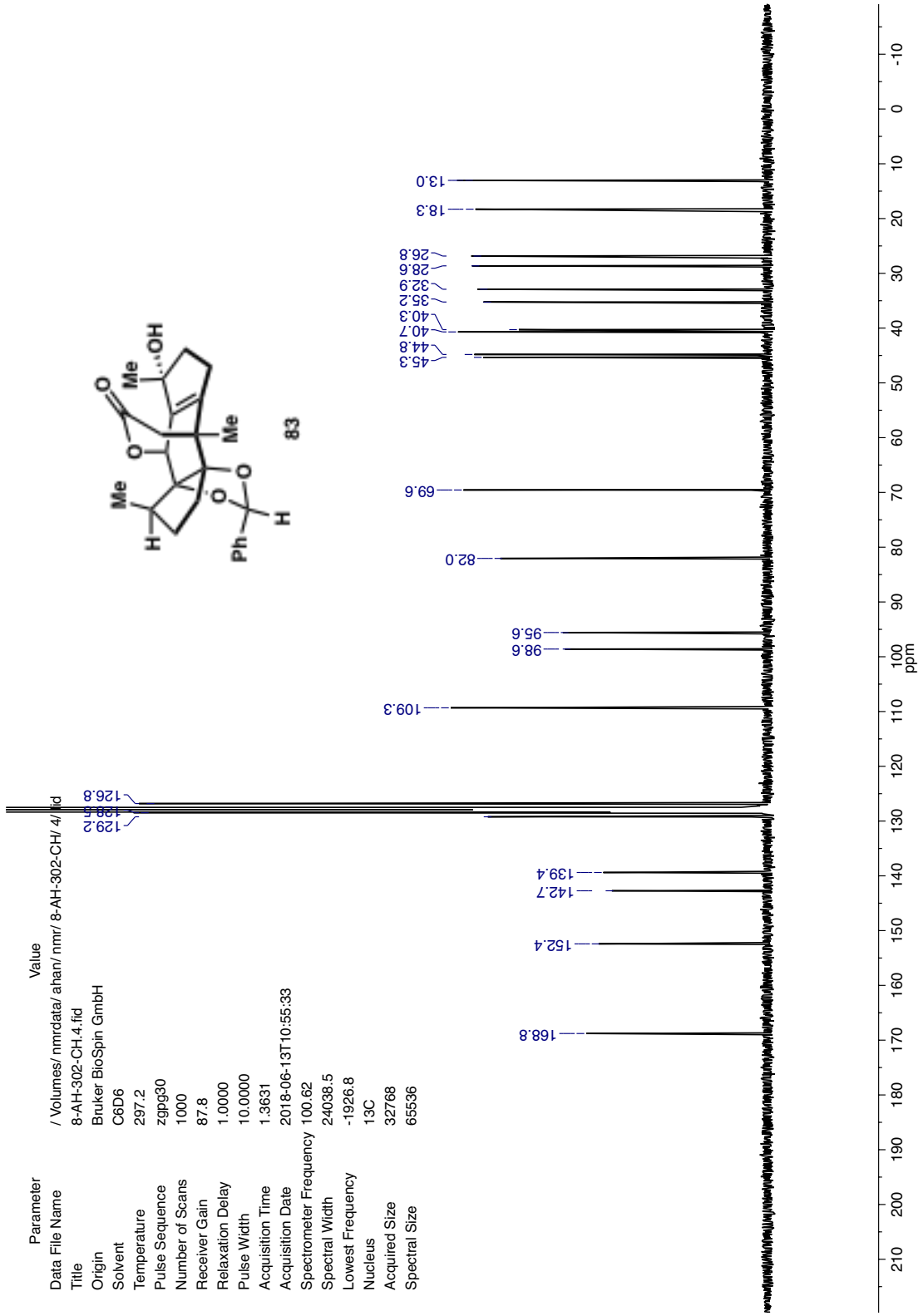

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-053-CH/ 1/ fid
Title 9-AH-053-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.0
Pulse Sequence zg30
Number of Scans 2
Receiver Gain 101.0
Relaxation Delay 5.0000
Pulse Width 10.0000
Acquisition Time 3.9977
Acquisition Date 2018-07-30T17:37:00
Spectrometer Frequency 400.15
Spectral Width 8196.7
Lowest Frequency -1637.0
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
81
Me
Me
Ph
OH
H
H
O
O
O
O
O
5.07
1.00
1.01
1.02
1.01
1.03
1.01
3.01
2.03
2.01
1.05
1.02
3.03
3.04
ppm

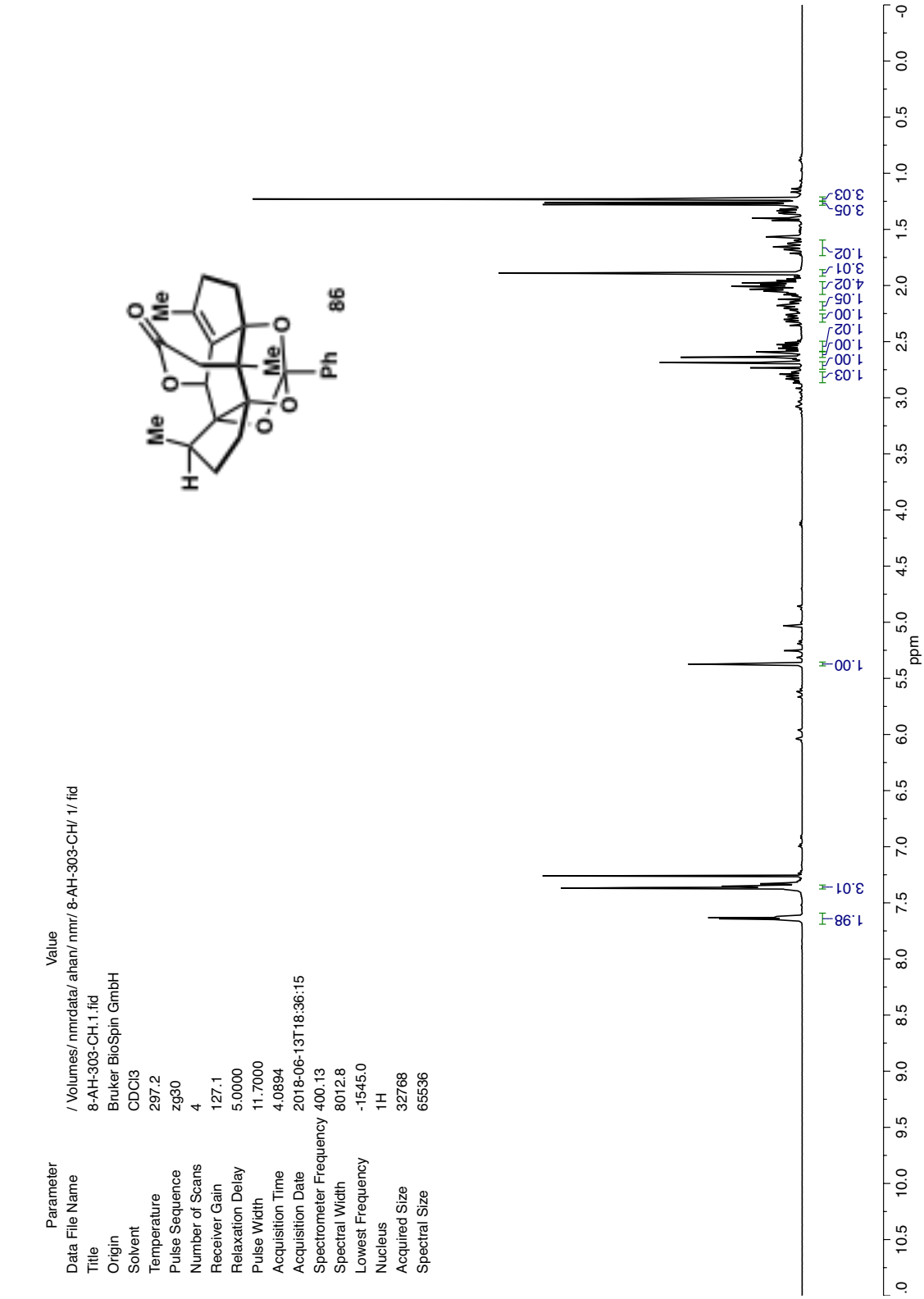

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-053-CH/ 2/ fid
Title 9-AH-053-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.0
Pulse Sequence zgpg30
Number of Scans 1800
Receiver Gain 15.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3763
Acquisition Date 2018-07-30T18:51:55
Spectrometer Frequency 100.63
Spectral Width 23809.5
Lowest Frequency -1846.2
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
12.9
18.5
29.6
32.9
34.0
35.1
40.3
44.3
45.1
70.5
76.8
95.3
98.4
109.3
126.5
128.4
129.4
138.1
139.4
155.5
170.3
81
Me
Me
Ph
OH
ppm


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-128-CH/ 1/ fid
Title
8-AH-128-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Pulse Sequence
zg30
Number of Scans
8
Receiver Gain
197.4
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-06-16T07:16:02
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.0
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Me
Me
Ph
82
5.00
1.00
1.01
3.00
1.04
3.00
1.05
2.02
1.04
2.03
1.01
0.99
1.02
1.03
ppm

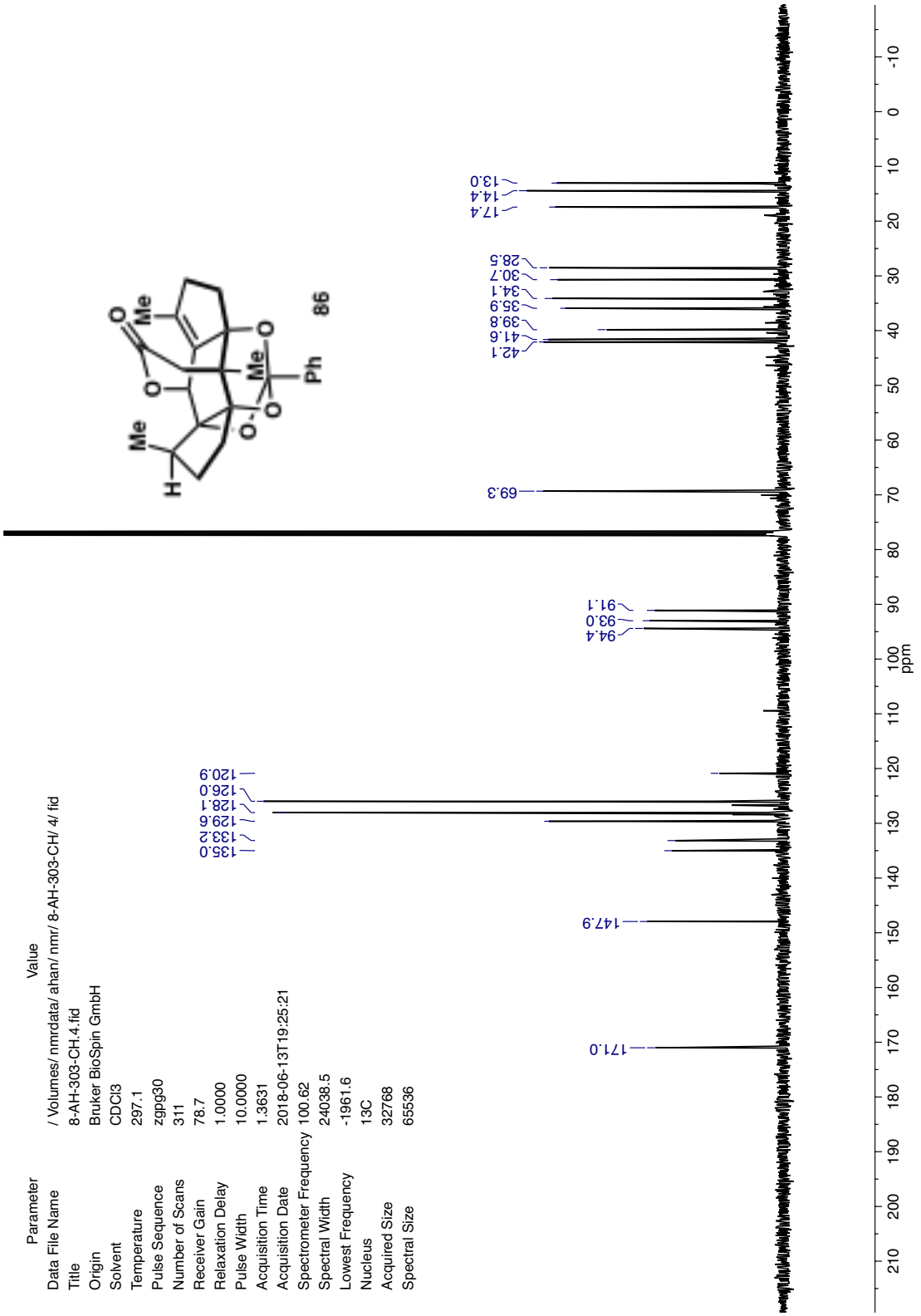

82
Me
Me
Ph
H
H
O
O
O
O
O
12.8
17.5
26.3
33.0
34.9
35.8
43.0
44.2
44.4
66.9
95.4
98.3
108.9
126.2
128.4
129.3
138.1
140.8
168.7
185.0
202.4
Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-128-CH/ 6/ fid
Title 8-AH-128-CH.6.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Pulse Sequence zgpg30
Number of Scans 700
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-16T08:41:14
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1960.9
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
ppm

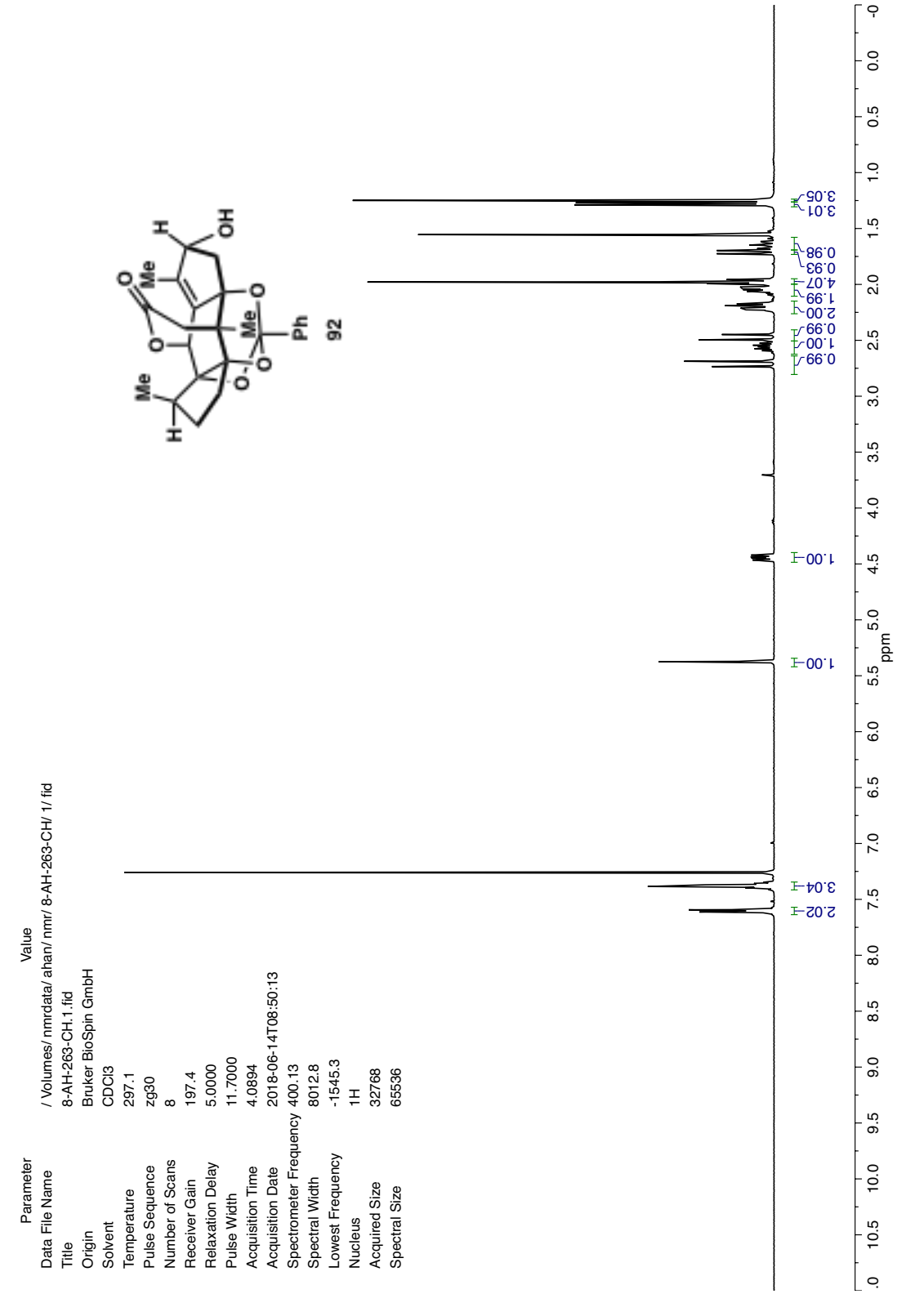

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-302-CH/ 1/ fid
Title 8-AH-302-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 297.1
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 127.1
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-13T09:24:10
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1532.2
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
Me
OH
O
Me
O
Me
O
O
H
Ph
H
83
2.00
3.03
1.00
1.01
1.01
1.01
1.01
1.02
1.00
1.01
1.03
3.03
0.88
4.00
3.03
3.00
ppm

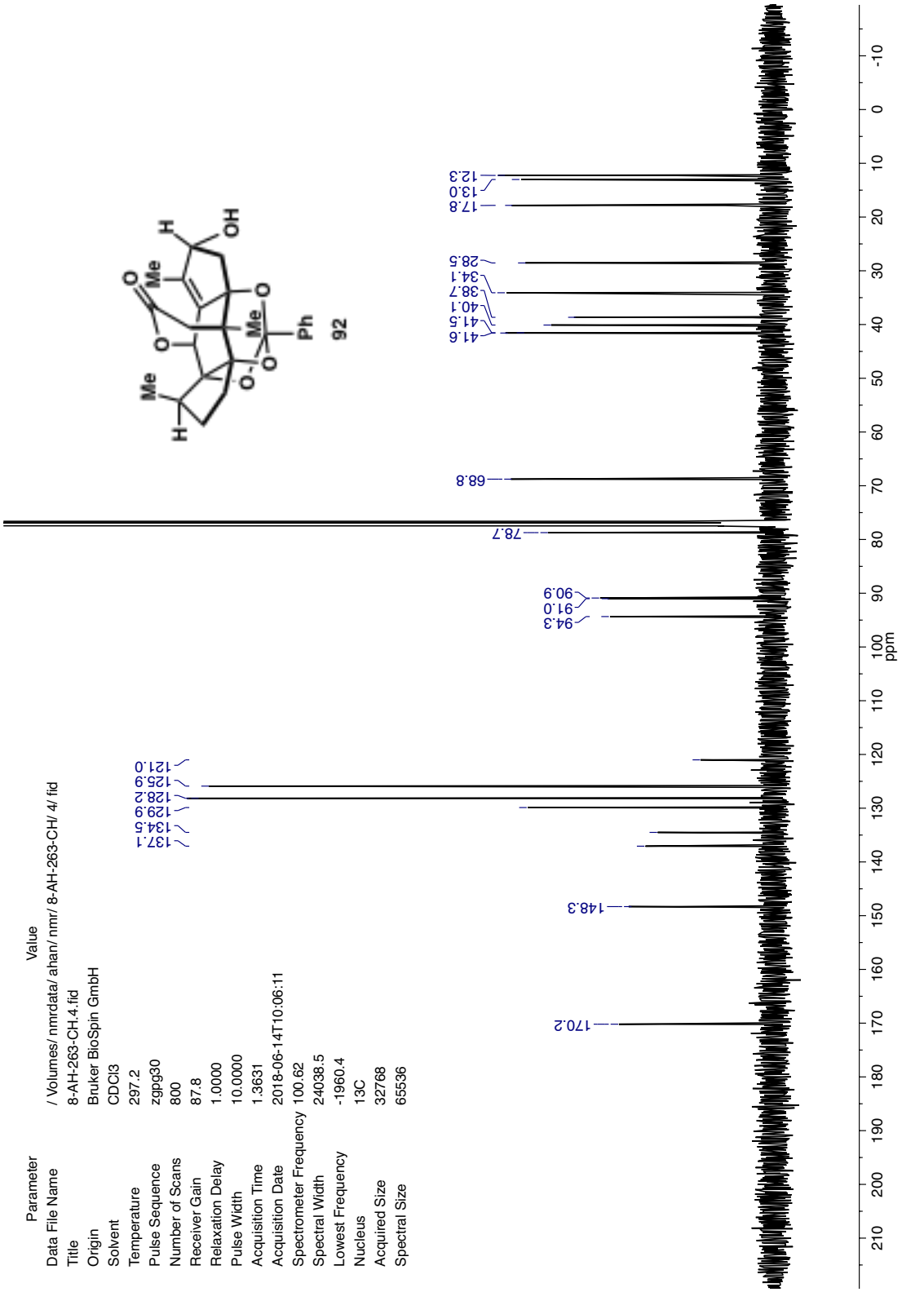

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-302-CH/ 4/ fid
Title 8-AH-302-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 297.2
Pulse Sequence zgpg30
Number of Scans 1000
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-13T10:55:33
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1926.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
83
Me
OH
O
Me
O
Me
O
O
H
Ph
H
13.0
18.3
26.8
28.6
32.9
35.2
40.3
40.7
44.8
45.3
69.6
82.0
95.6
98.6
109.3
126.8
128.6
129.2
139.4
142.7
152.4
168.8
ppm

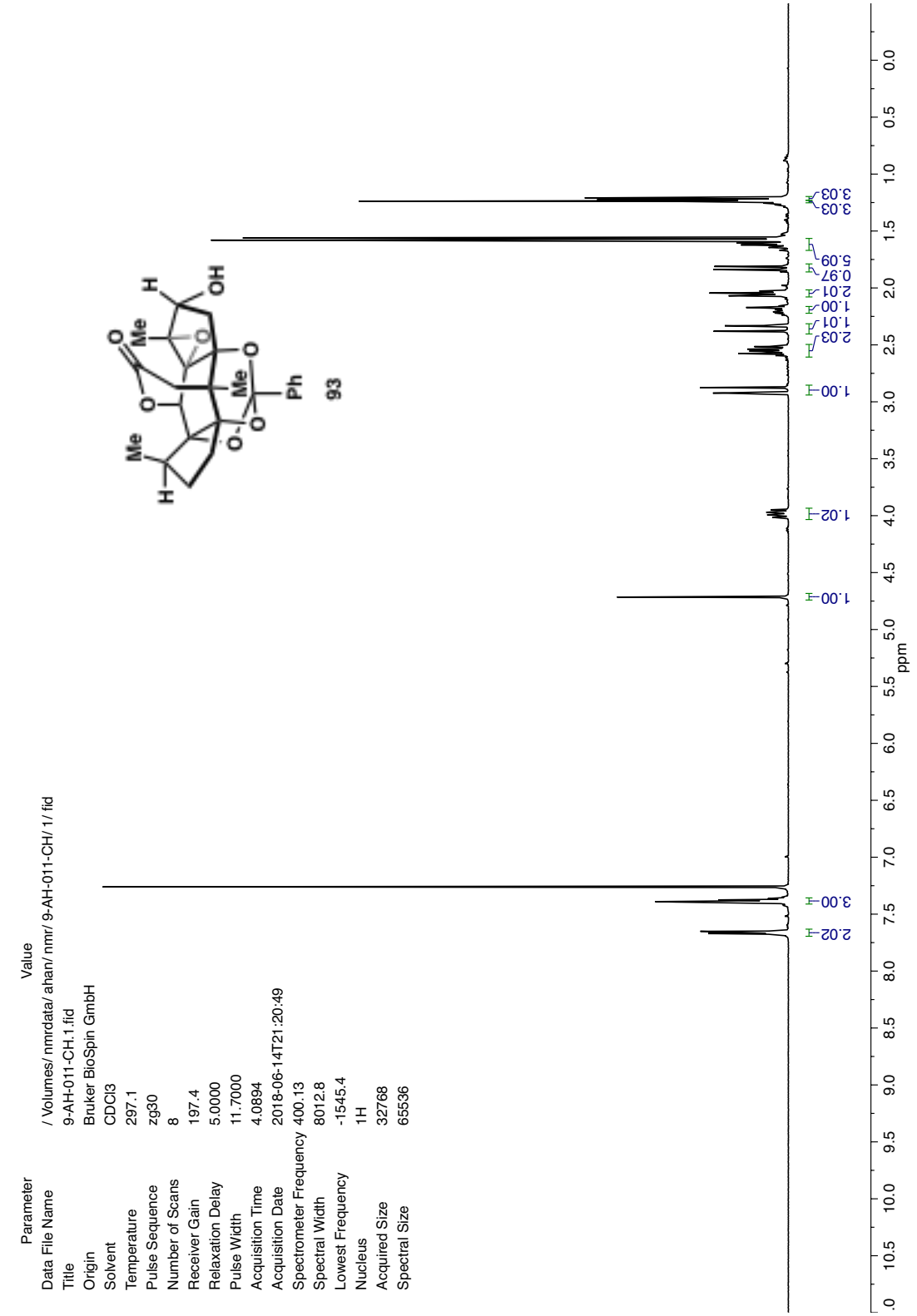


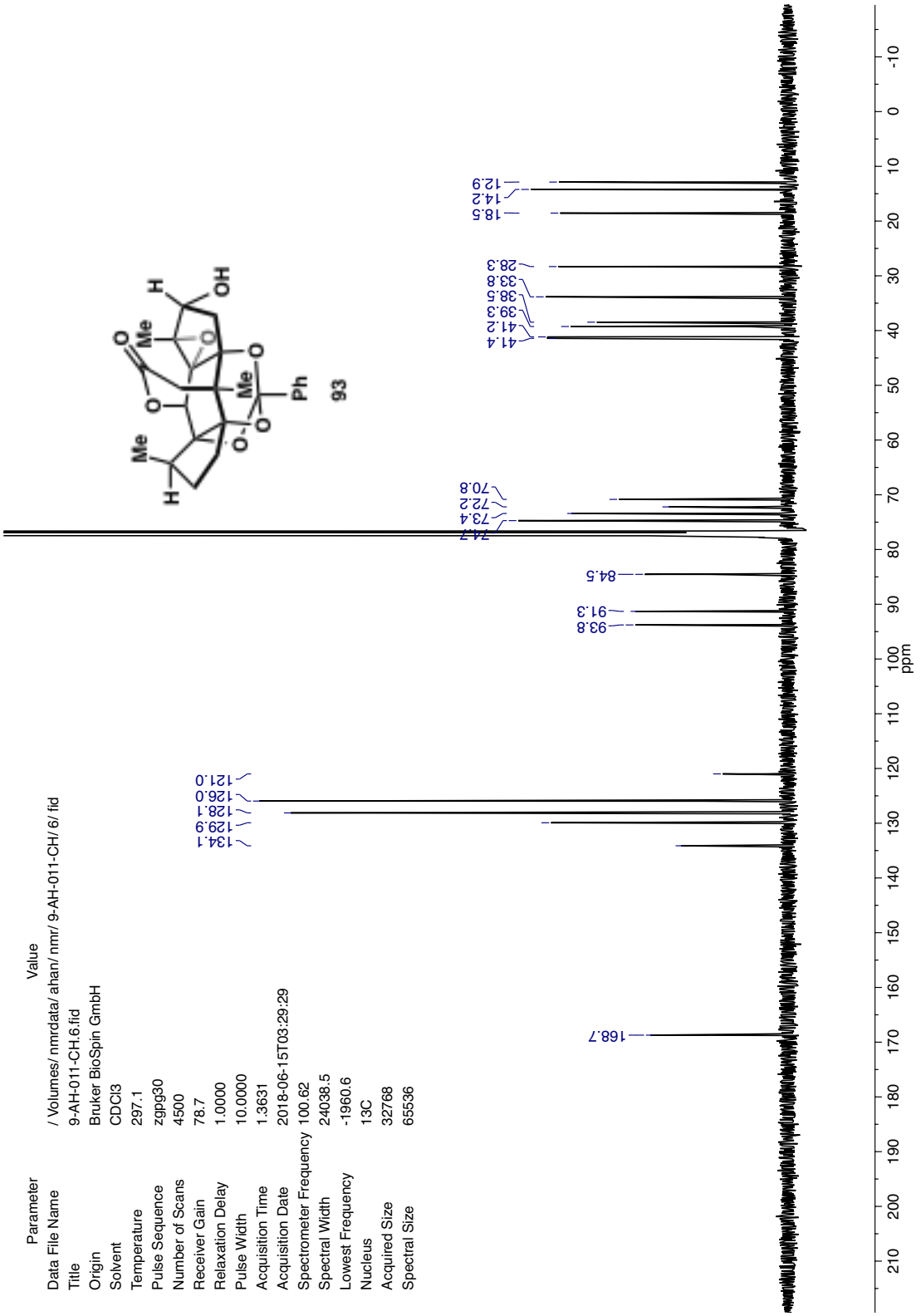
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-303-CH/ 1/ fid
Title	8-AH-303-CH.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Pulse Sequence	zg30
Number of Scans	4
Receiver Gain	127.1
Relaxation Delay	5.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-06-13T18:36:15
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1545.0
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

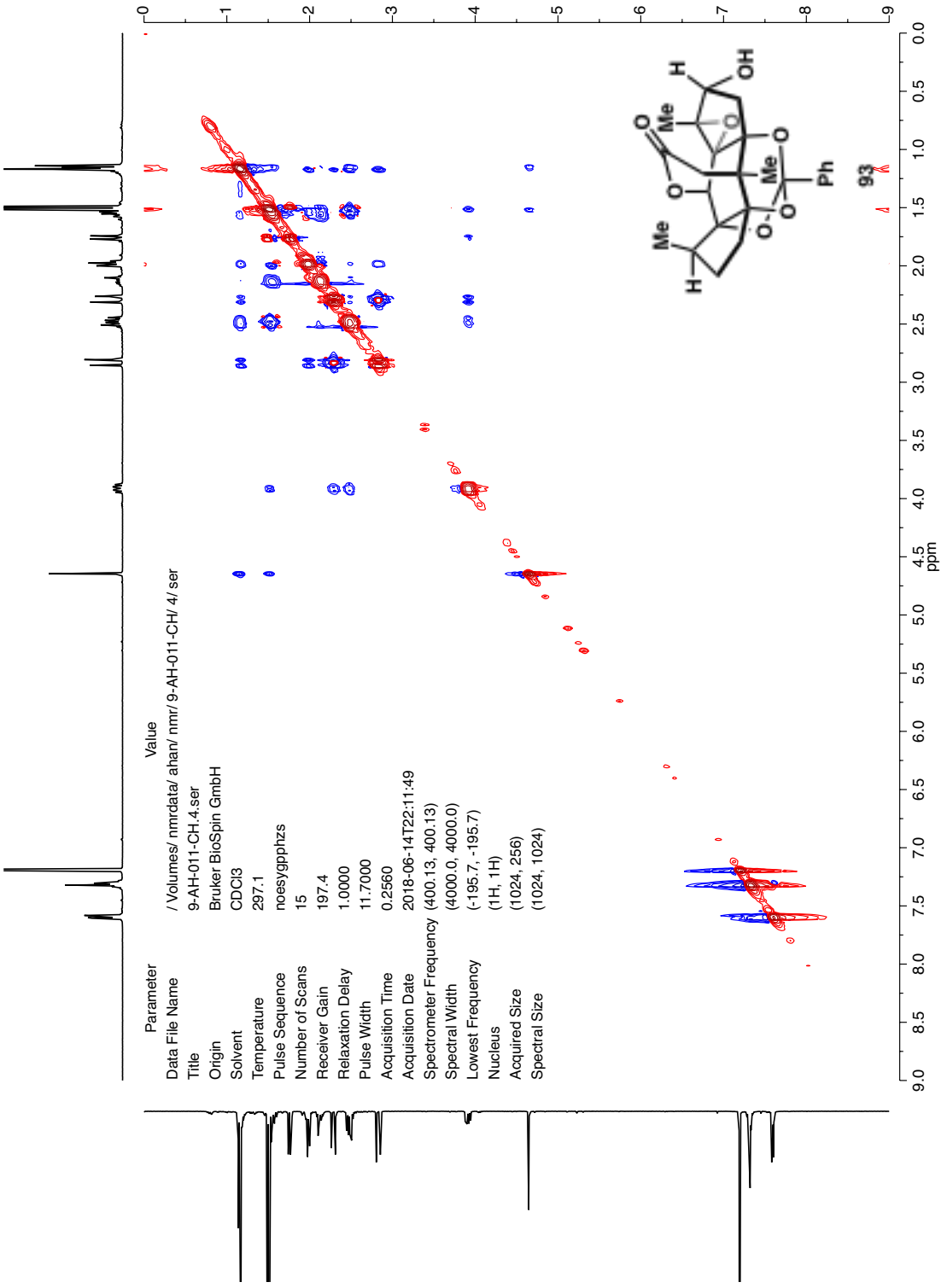

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-303-CH/ 4/ fid
Title
8-AH-303-CH.4.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
297.1
Pulse Sequence
zgpg30
Number of Scans
311
Receiver Gain
78.7
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2018-06-13T19:25:21
Spectrometer Frequency
100.62
Spectral Width
24038.5
Lowest Frequency
-1961.6
Nucleus
13C
Acquired Size
32768
Spectral Size
65536
Me
O
O
Me
H
O
O
Me
Ph
86
171.0
147.9
135.0
133.2
129.6
128.1
126.0
120.9
94.4
93.0
91.1
69.3
42.1
41.6
39.8
35.9
34.1
30.7
28.5
17.4
14.4
13.0
ppm

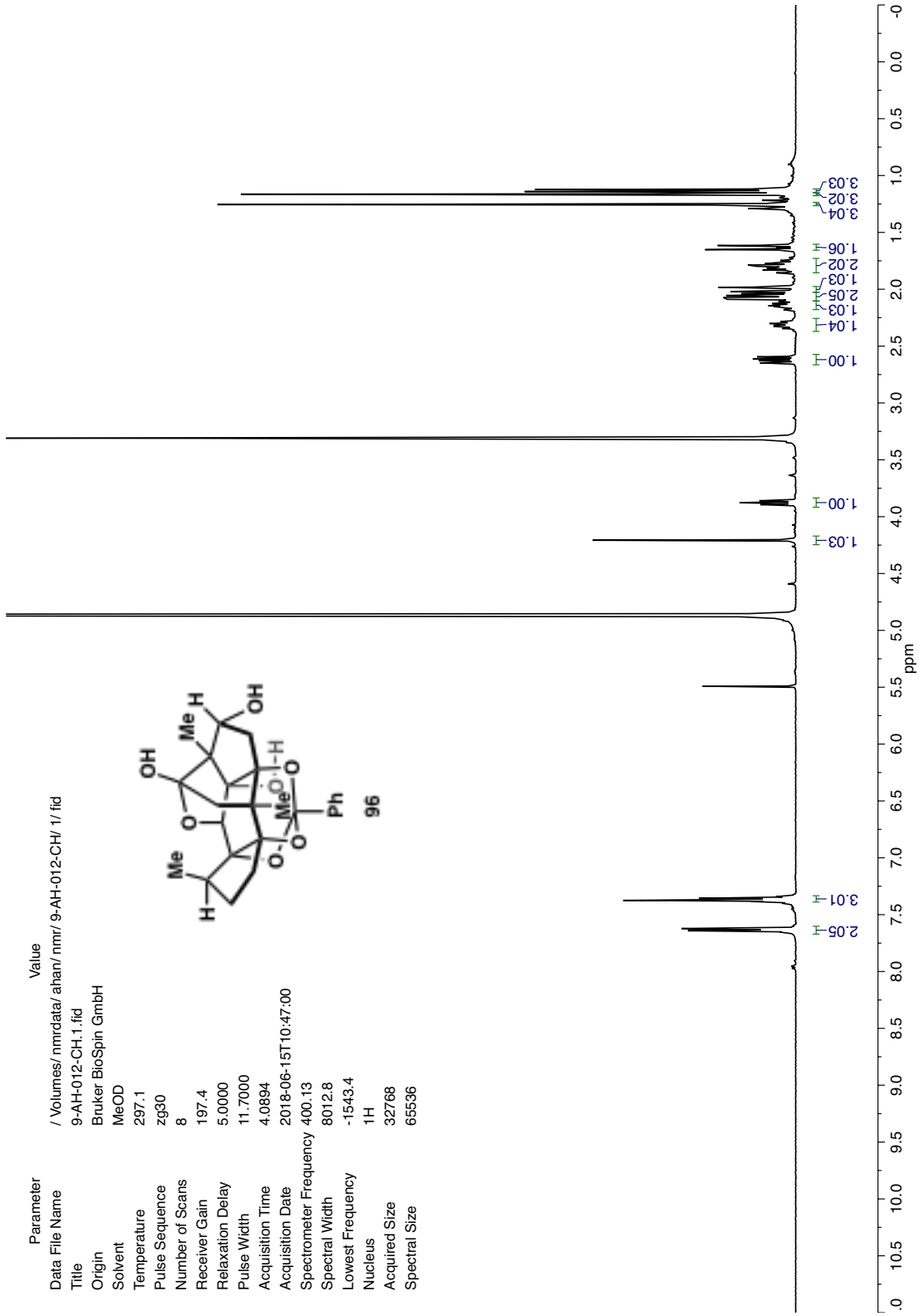

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-263-CH/ 1/ fid
Title 8-AH-263-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-14T08:50:13
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.3
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
92
2.02
3.04
1.00
1.00
1.00
0.99
1.00
0.99
2.00
1.99
4.07
0.93
0.98
3.01
3.05
ppm

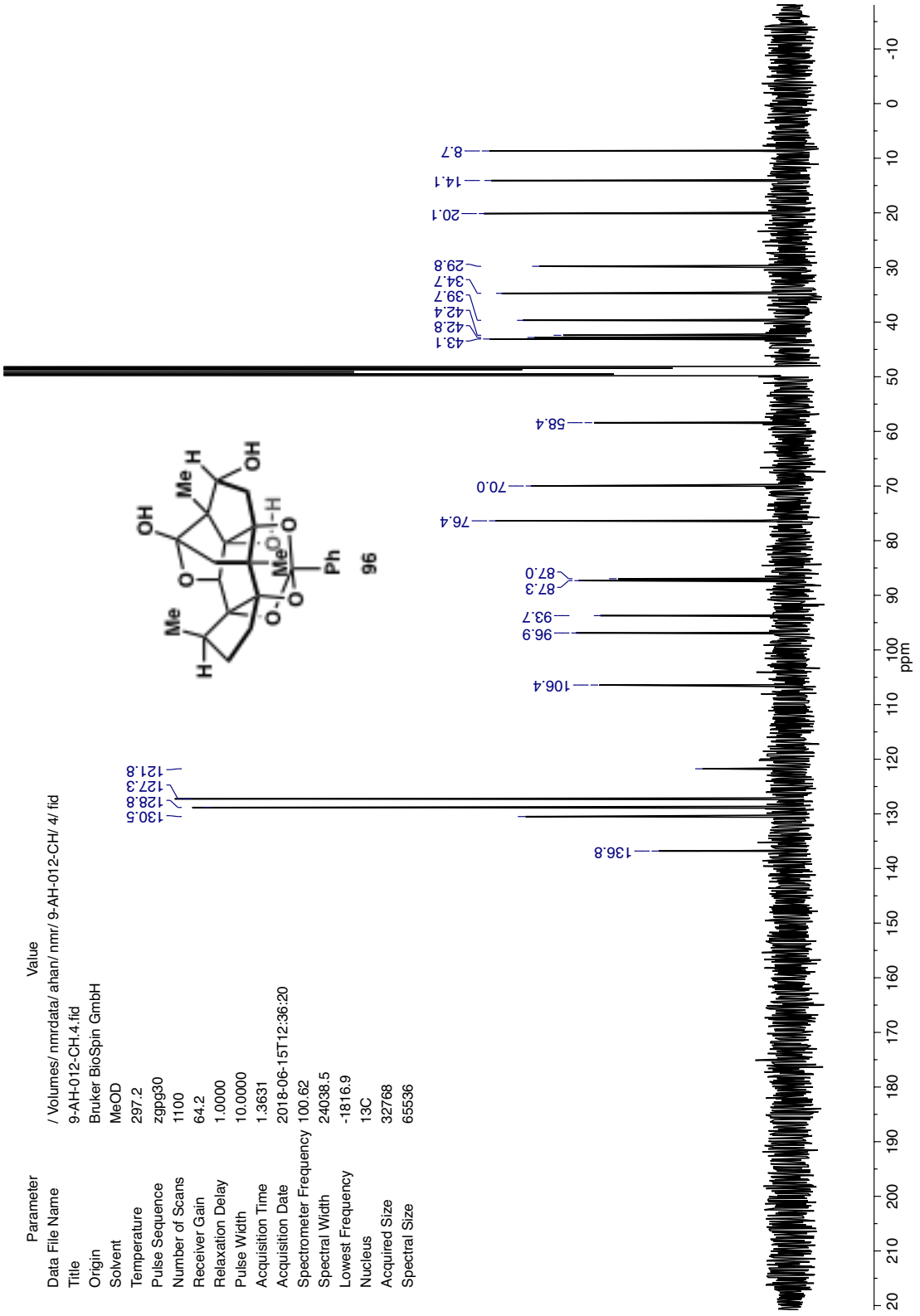

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-263-CH/ 4/ fid
Title 8-AH-263-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Pulse Sequence zgpg30
Number of Scans 800
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-14T10:06:11
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1960.4
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
92
12.3
13.0
17.8
28.5
34.1
38.7
40.1
41.5
41.6
68.8
78.7
90.9
91.0
94.3
121.0
125.9
128.2
129.9
134.5
137.1
148.3
170.2
ppm

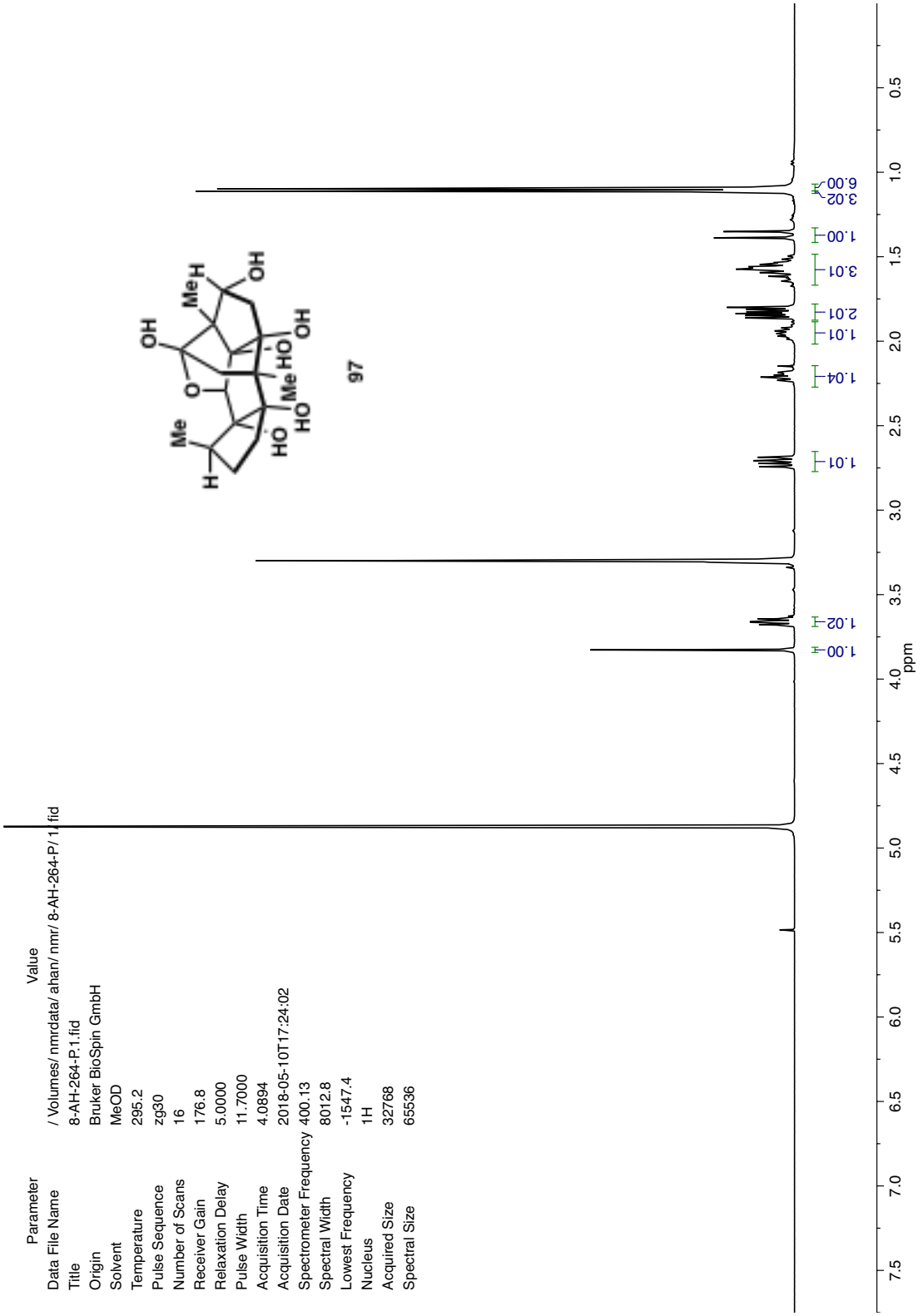

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-011-CH/ 1/ fid
Title 9-AH-011-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-14T21:20:49
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
93
3.03
3.03
5.09
0.97
2.01
1.00
1.01
2.03
1.00
1.02
1.00
3.00
2.02
ppm

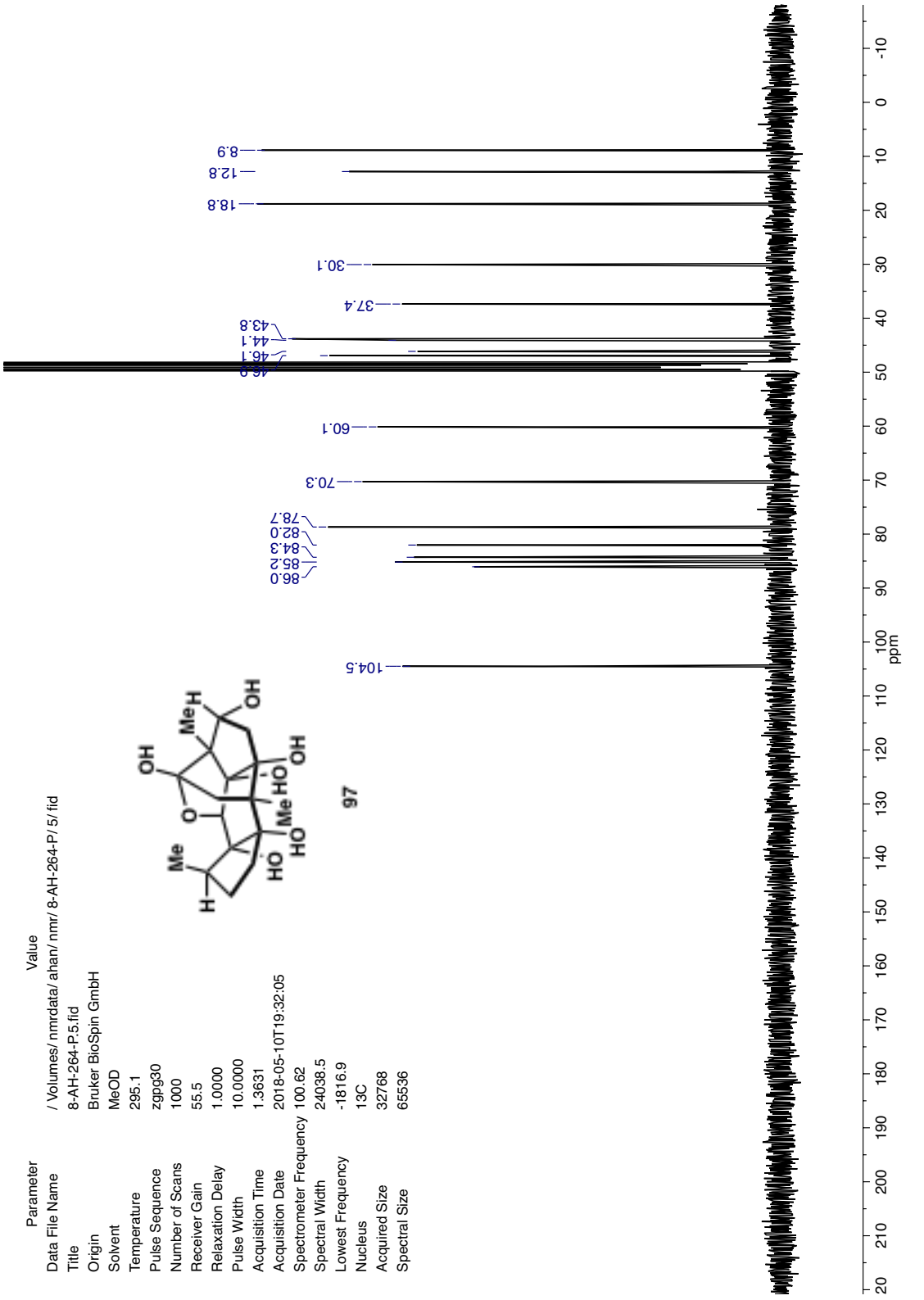

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-011-CH/ 6/ fid
Title 9-AH-011-CH.6.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Pulse Sequence zgpg30
Number of Scans 4500
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-15T03:29:29
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1960.6
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
93
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-011-CH/ 4/ ser
Title 9-AH-011-CH.4.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Pulse Sequence noesygpphzs
Number of Scans 15
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2018-06-14T22:11:49
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-195.7, -195.7)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
ppm
93

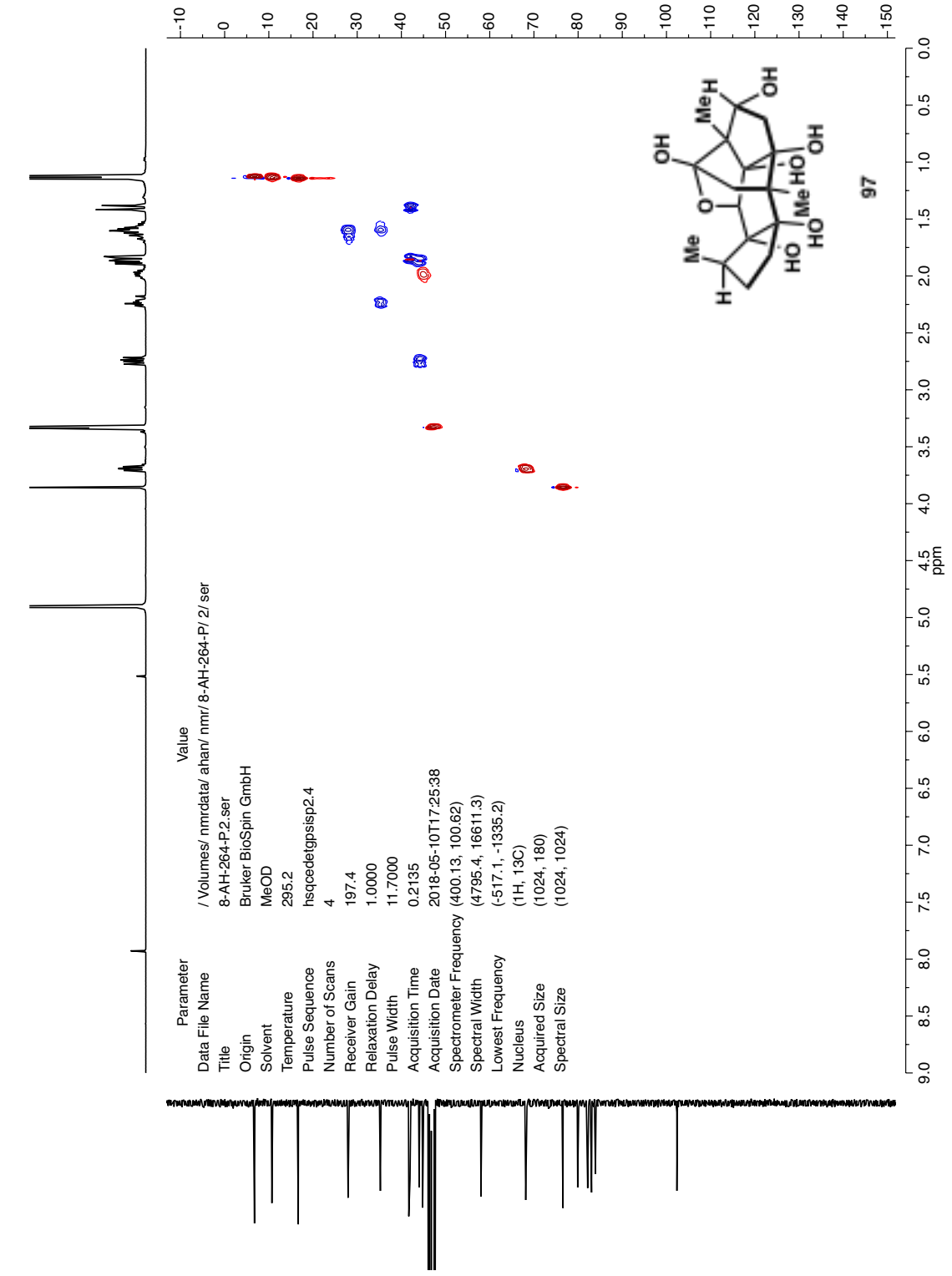

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-012-CH/ 1/ fid
Title 9-AH-012-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 297.1
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-15T10:47:00
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1543.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
OH
Me
H
OH
Me
H
O
O
O
O
Me
O
O
Ph
96
2.05
3.01
1.03
1.00
3.03
3.02
3.04
1.06
2.02
1.03
2.05
1.03
1.04
1.00
ppm

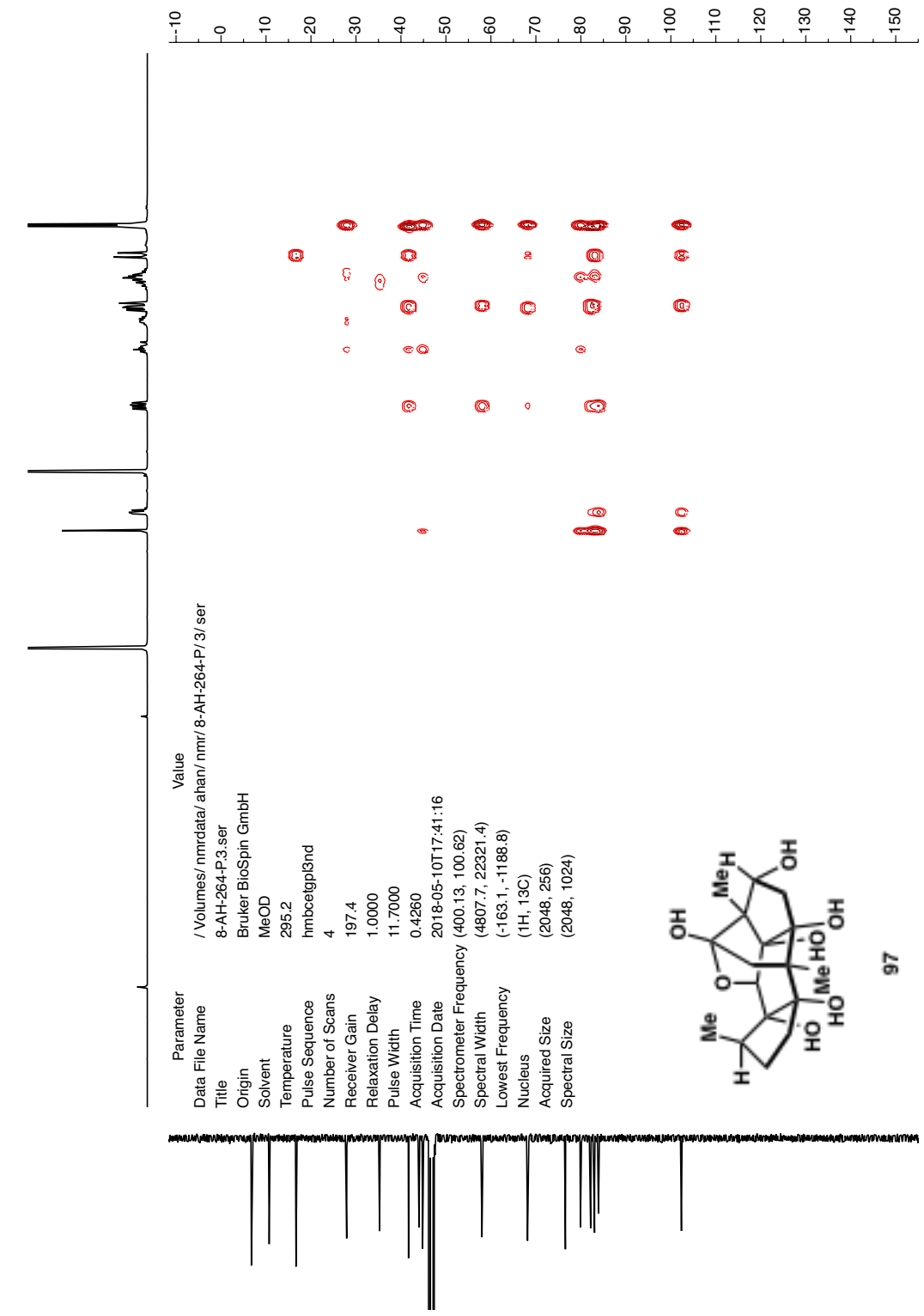

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-012-CH/ 4/ fid
Title 9-AH-012-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 297.2
Pulse Sequence zgpg30
Number of Scans 1100
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-15T12:36:20
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1816.9
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
8.7
14.1
20.1
29.8
34.7
39.7
42.4
42.8
43.1
58.4
70.0
76.4
87.0
87.3
93.7
96.9
106.4
130.5
128.8
127.3
121.8
136.8
96
ppm

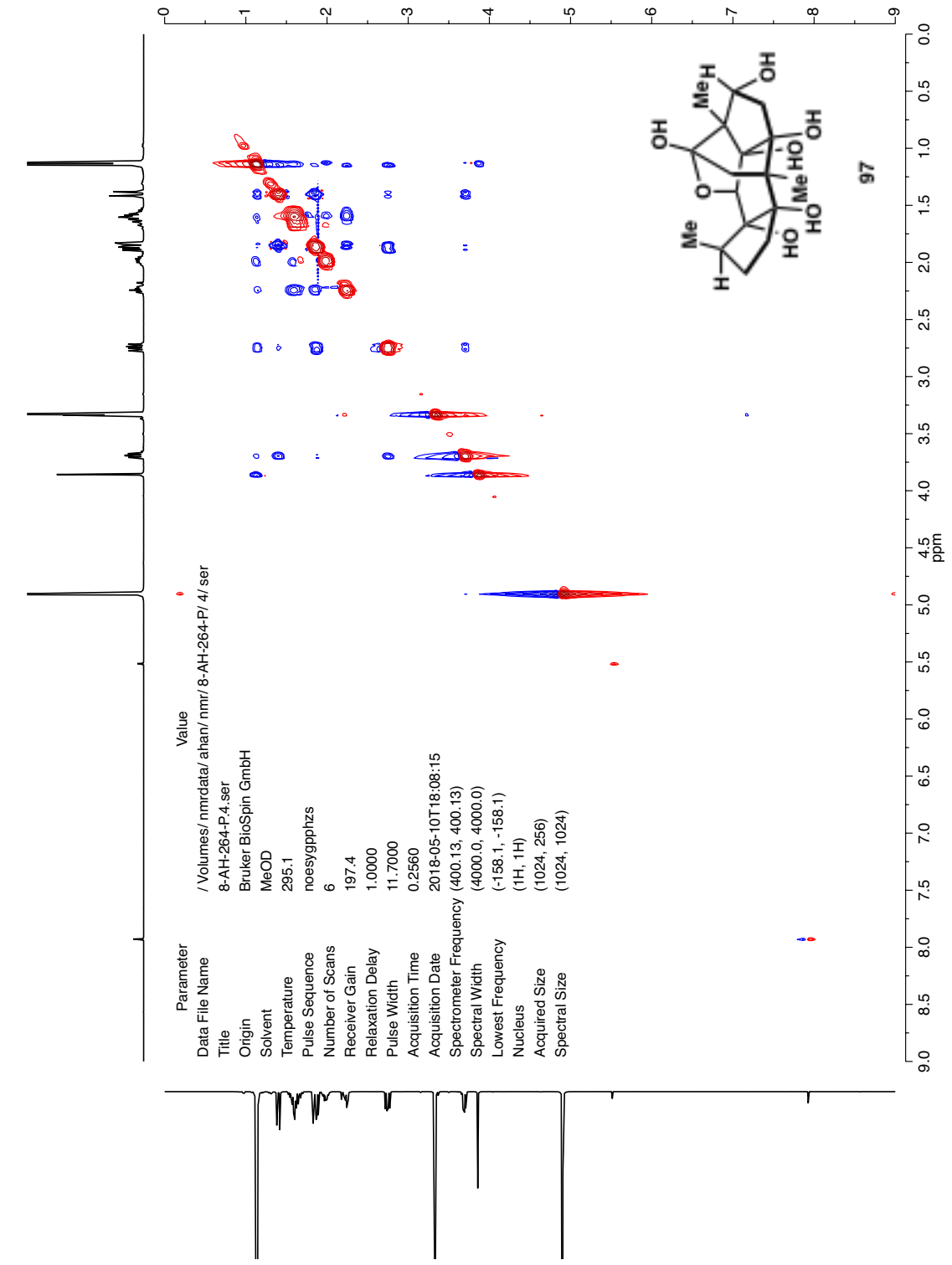

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-264-P/ 1 1 fid
Title
8-AH-264-P1.fid
Origin
Bruker BioSpin GmbH
Solvent
MeOD
Temperature
295.2
Pulse Sequence
zg30
Number of Scans
16
Receiver Gain
176.8
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-05-10T17:24:02
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1547.4
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
97
1.00
1.02
1.01
1.04
1.01
2.01
1.01
3.01
1.00
3.02
6.00
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
ppm

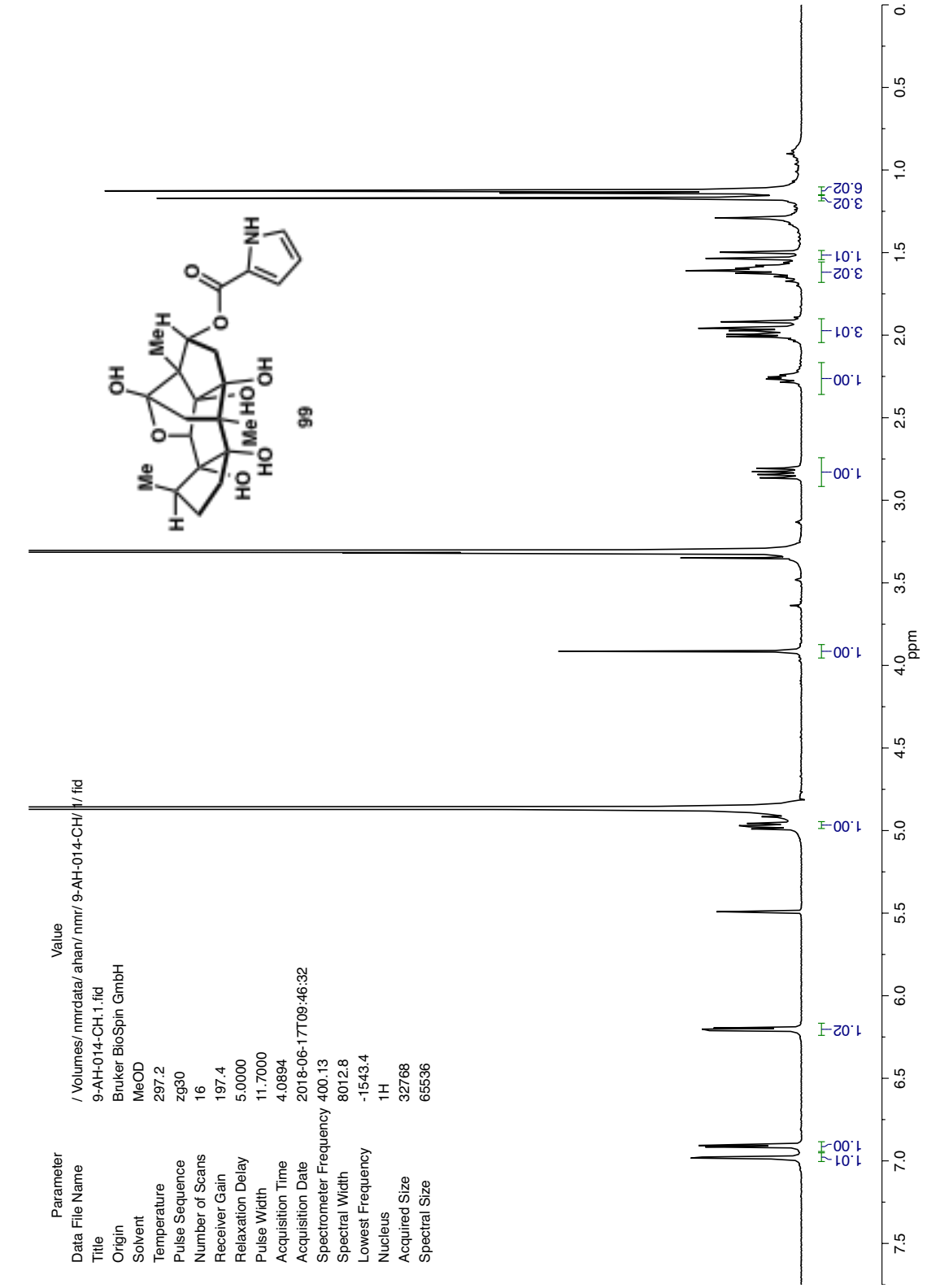


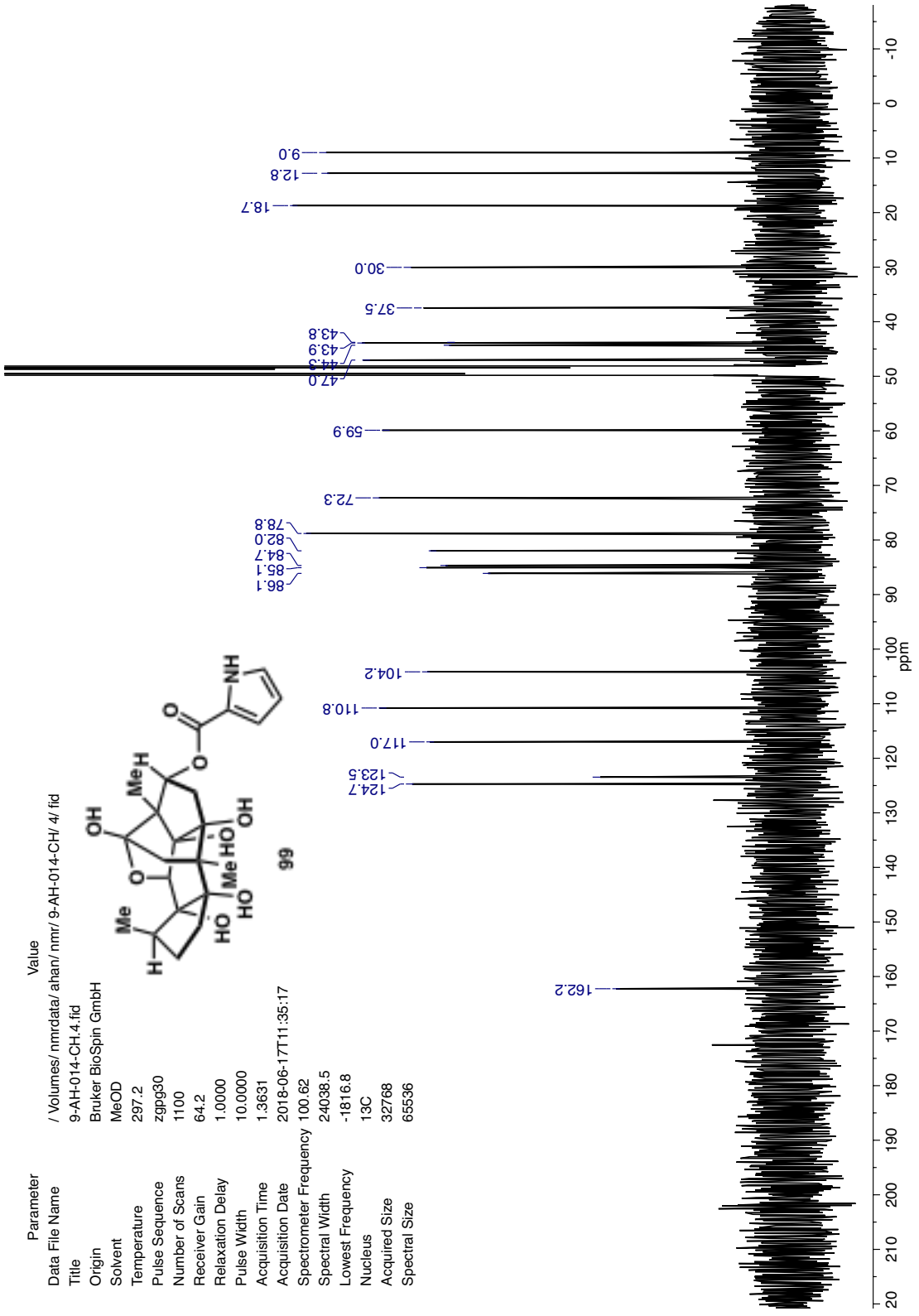
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-264-P/ 5/ fid
Title	8-AH-264-P5.fid
Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	295.1
Pulse Sequence	zgpg30
Number of Scans	1000
Receiver Gain	55.5
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-05-10T19:32:05
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1816.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

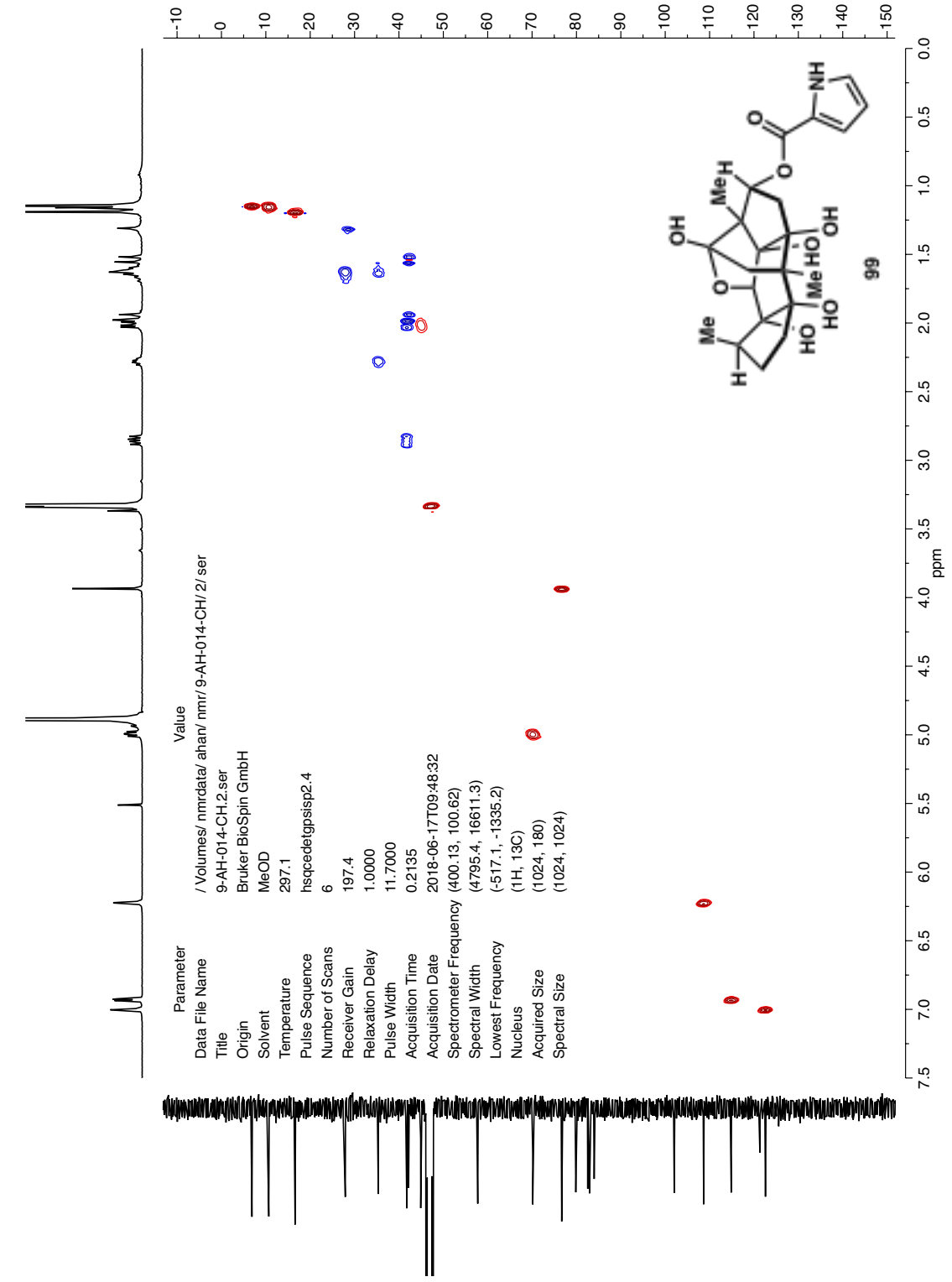

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-264-P/ 2/ ser
Title 8-AH-264-P-2.ser
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.2
Pulse Sequence hsqcedetgpsisp2.4
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2135
Acquisition Date 2018-05-10T17:25:38
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4795.4, 16611.3)
Lowest Frequency (-517.1, -1335.2)
Nucleus (1H, 13C)
Acquired Size (1024, 180)
Spectral Size (1024, 1024)
ppm
97

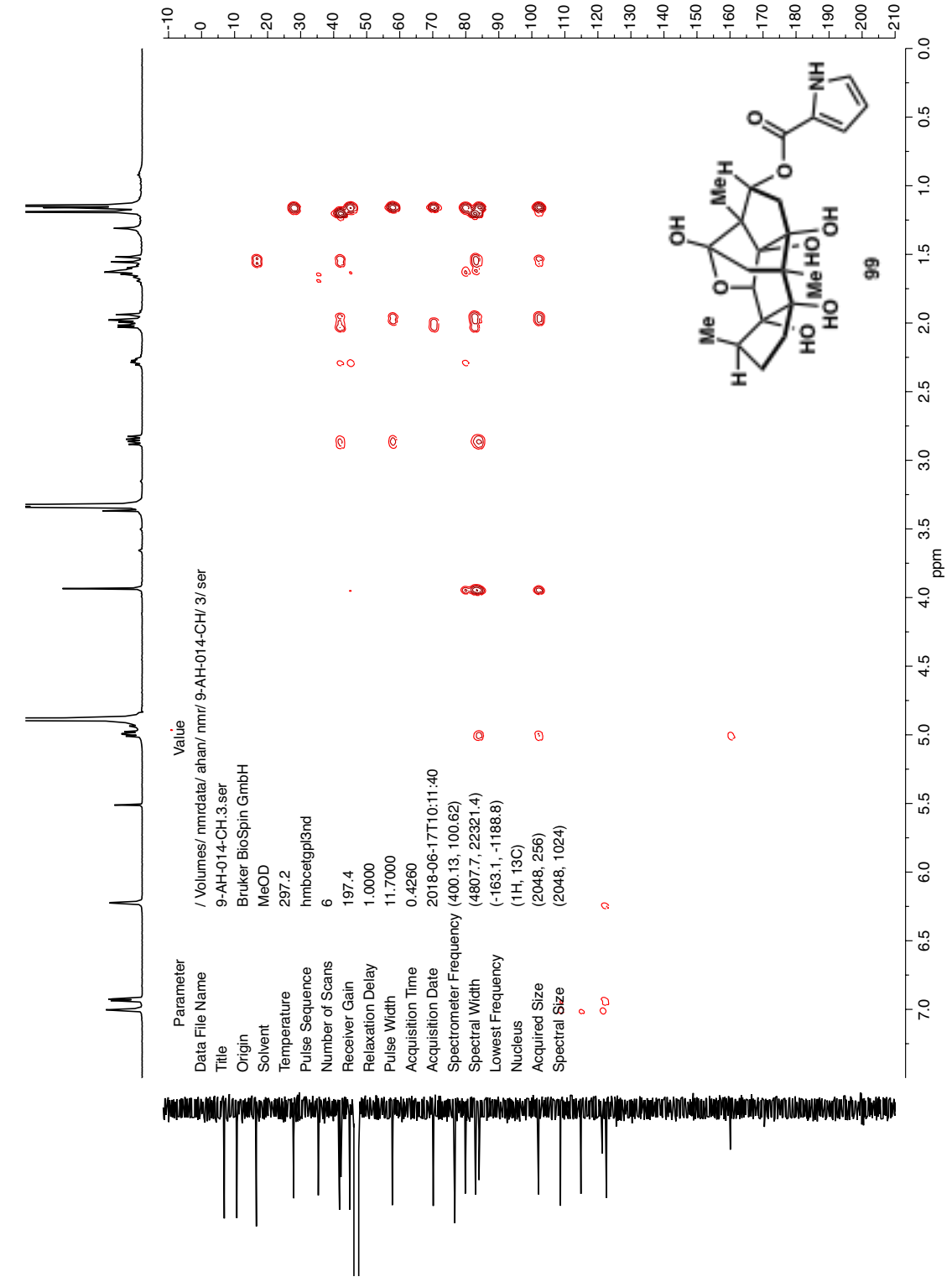

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-264-P/ 3/ ser
Title
8-AH-264-P.3.ser
Origin
Bruker BioSpin GmbH
Solvent
MeOD
Temperature
295.2
Pulse Sequence
hmbcetgpl3nd
Number of Scans
4
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.4260
Acquisition Date
2018-05-10T17:41:16
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4807.7, 22321.4)
Lowest Frequency
(-163.1, -1188.8)
Nucleus
(1H, 13C)
Acquired Size
(2048, 256)
Spectral Size
(2048, 1024)
ppm
97

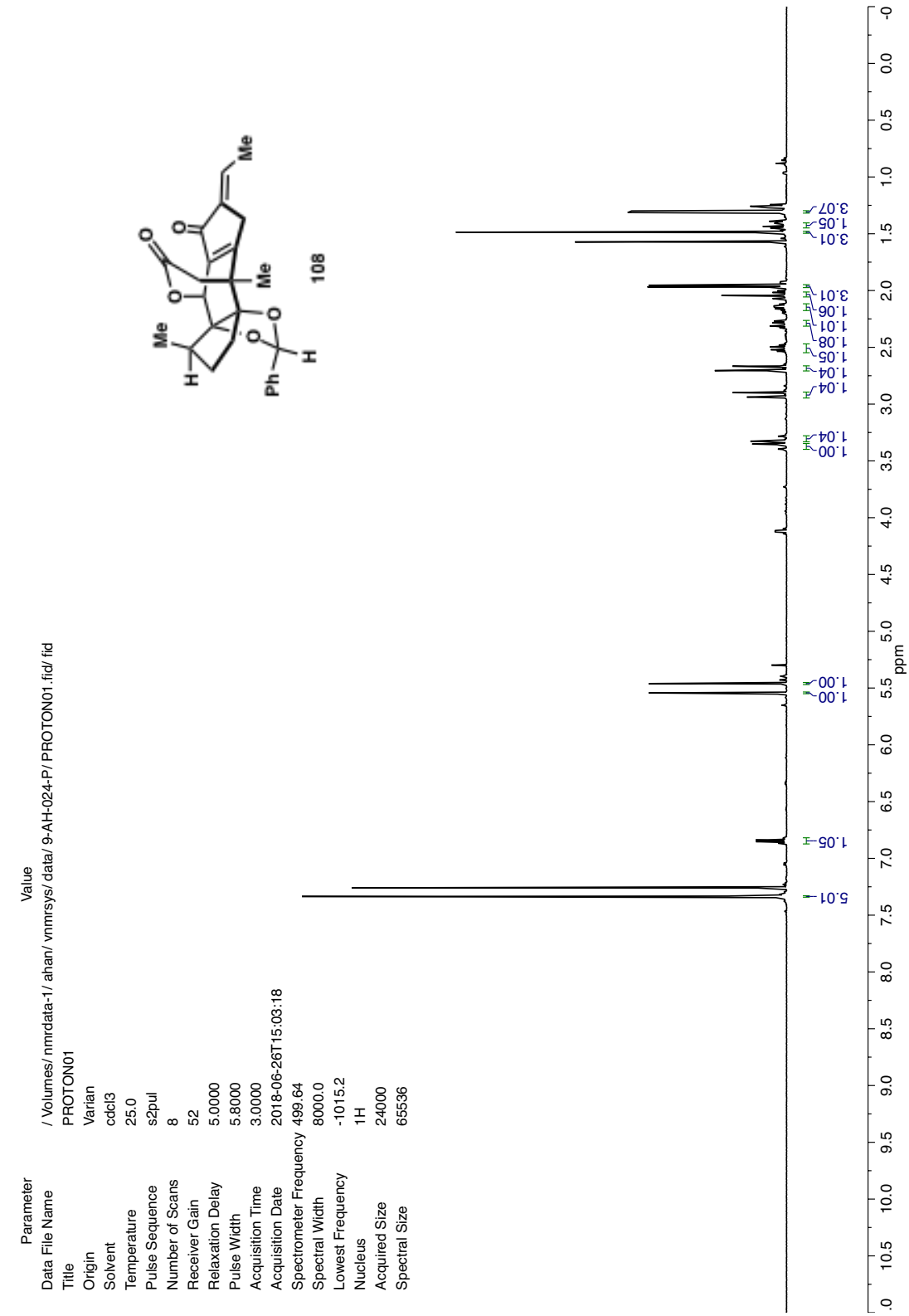

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-264-P/ 4/ ser
Title
8-AH-264-P.4.ser
Origin
Bruker BioSpin GmbH
Solvent
MeOD
Temperature
295.1
Pulse Sequence
noesygpphzs
Number of Scans
6
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2560
Acquisition Date
2018-05-10T18:08:15
Spectrometer Frequency
(400.13, 400.13)
Spectral Width
(4000.0, 4000.0)
Lowest Frequency
(-158.1, -158.1)
Nucleus
(1H, 1H)
Acquired Size
(1024, 256)
Spectral Size
(1024, 1024)
ppm
97

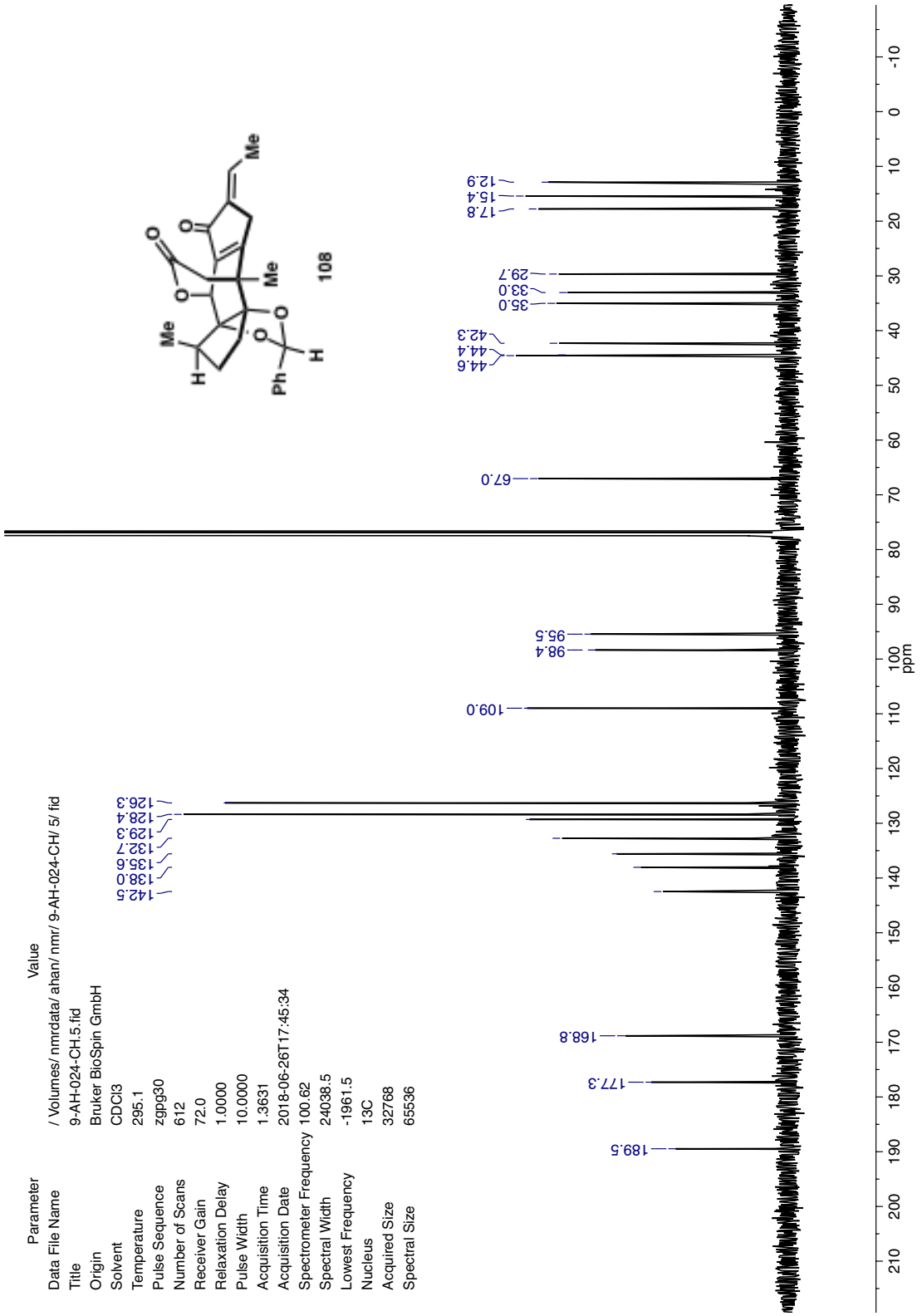

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-014-CH/ 1/ fid
Title 9-AH-014-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 297.2
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-17T09:46:32
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1543.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
99
ppm

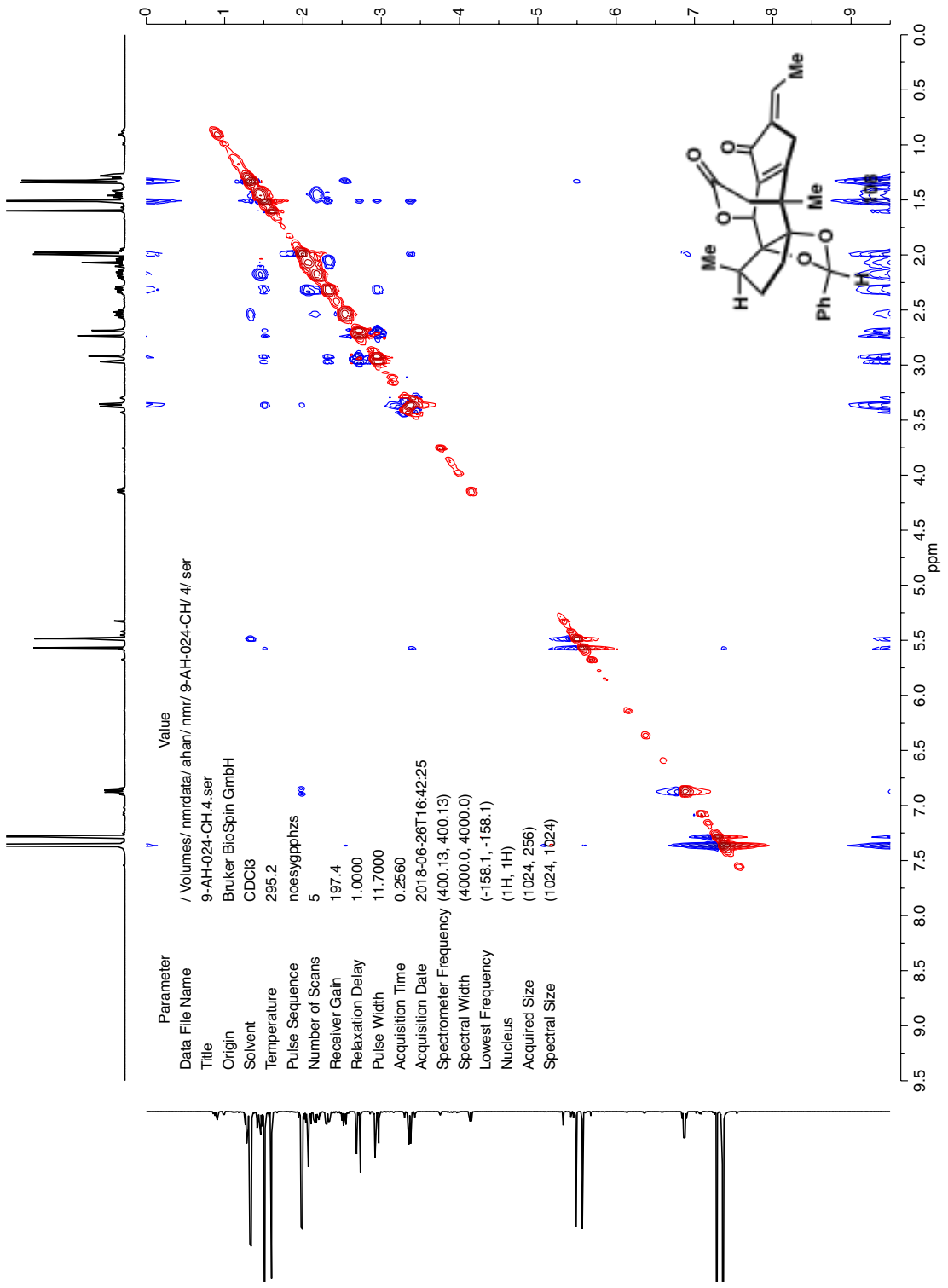

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-014-CH/ 4/ fid
Title 9-AH-014-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 297.2
Pulse Sequence zgpg30
Number of Scans 1100
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-17T11:35:17
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1816.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
99
9.0
12.8
18.7
30.0
37.5
43.8
43.9
44.3
47.0
59.9
72.3
78.8
82.0
84.7
85.1
86.1
104.2
110.8
117.0
123.5
124.7
162.2
ppm

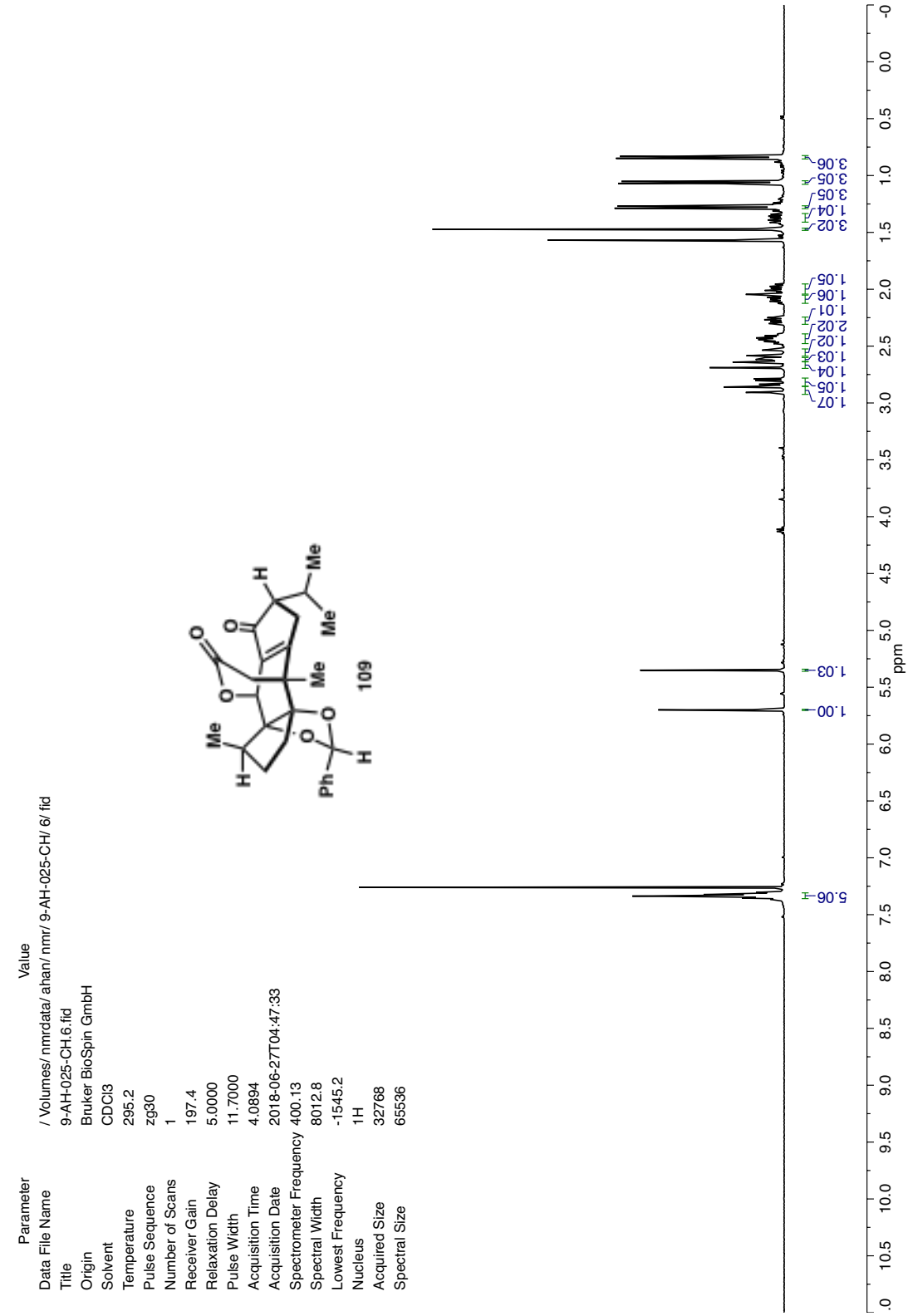

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-014-CH/ 2/ ser
Title
9-AH-014-CH.2.ser
Origin
Bruker BioSpin GmbH
Solvent
MeOD
Temperature
297.1
Pulse Sequence
hsqcedetgpsisp2.4
Number of Scans
6
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2135
Acquisition Date
2018-06-17T09:48:32
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4795.4, 16611.3)
Lowest Frequency
(-517.1, -1335.2)
Nucleus
(1H, 13C)
Acquired Size
(1024, 180)
Spectral Size
(1024, 1024)
ppm
99

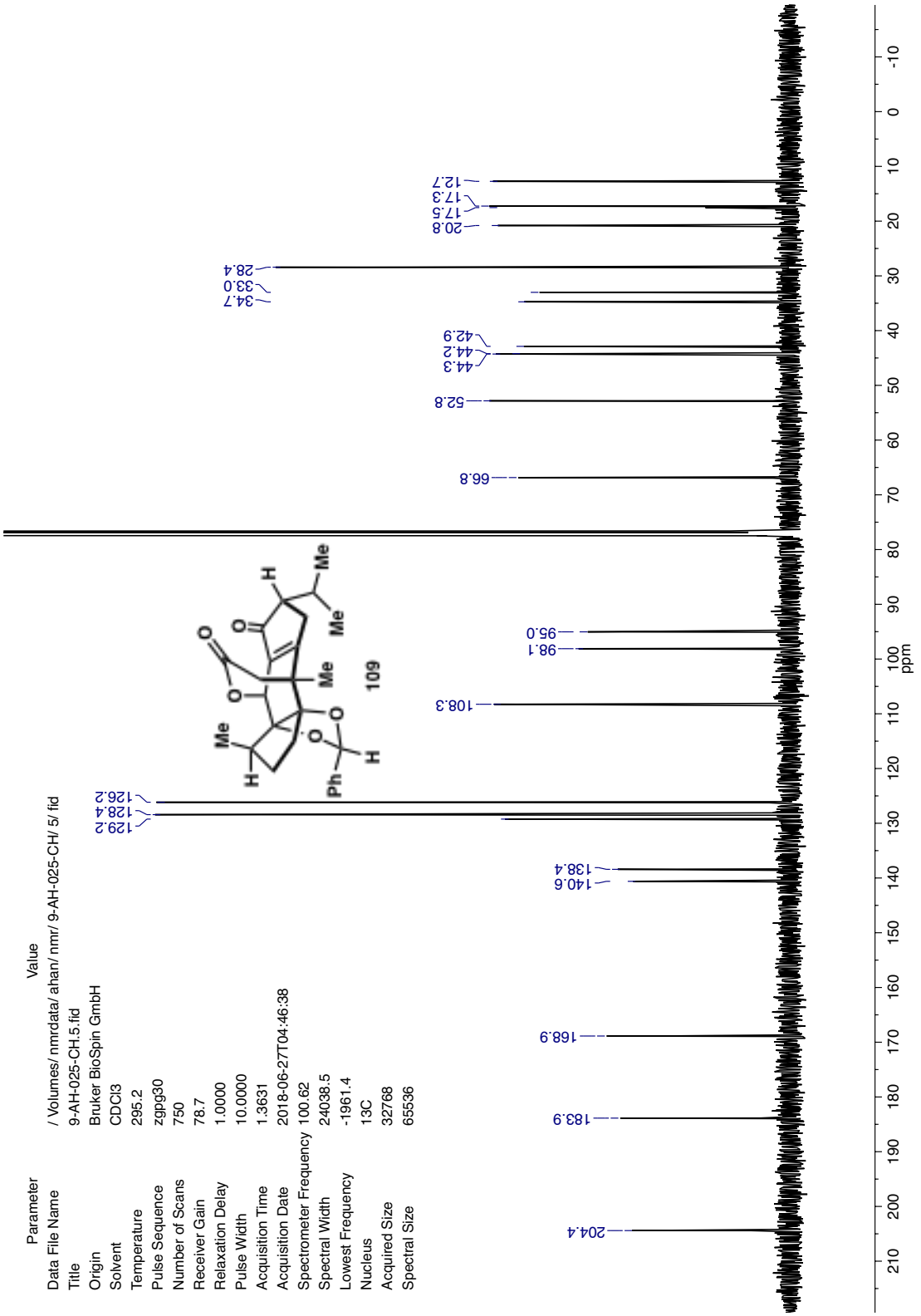

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-014-CH/ 3/ ser
Title 9-AH-014-CH.3.ser
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 297.2
Pulse Sequence hmbcetgpl3nd
Number of Scans 6
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.4260
Acquisition Date 2018-06-17T10:11:40
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4807.7, 22321.4)
Lowest Frequency (-163.1, -1188.8)
Nucleus (1H, 13C)
Acquired Size (2048, 256)
Spectral Size (2048, 1024)
ppm
99

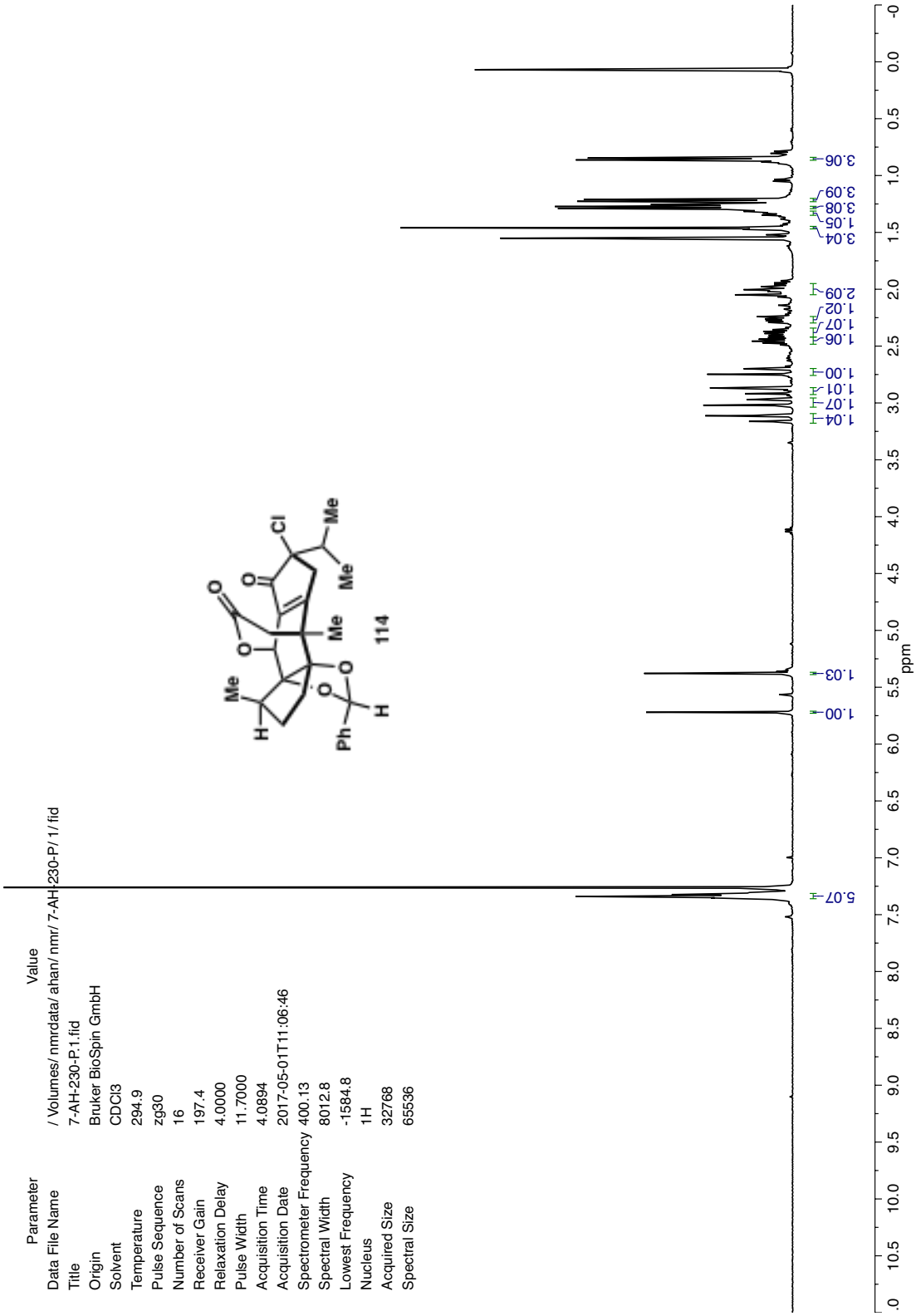

Parameter
Value
Data File Name / Volumes/ nmrdata-1/ ahan/ vnmrsys/ data/ 9-AH-024-P/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 52
Relaxation Delay 5.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2018-06-26T15:03:18
Spectrometer Frequency 499.64
Spectral Width 8000.0
Lowest Frequency -1015.2
Nucleus 1H
Acquired Size 24000
Spectral Size 65536
Me
O
O
O
Me
Me
H
O
O
Ph
H
108
5.01
1.05
1.00
1.00
1.04
1.04
1.04
1.05
1.08
1.01
1.06
3.01
3.01
1.05
3.07
ppm

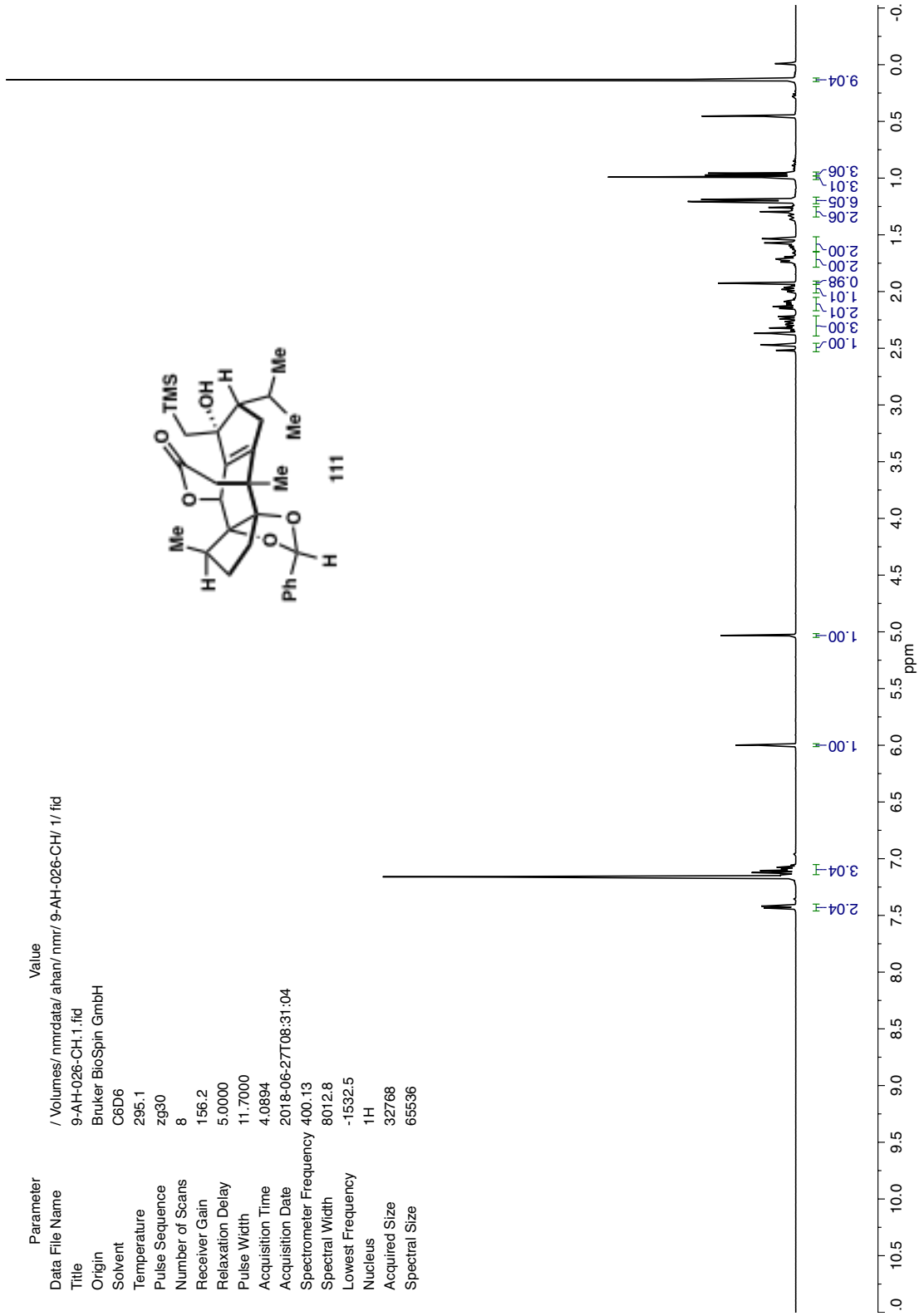

Me
O
O
O
Me
Me
O
O
H
Ph
H
108
12.9
15.4
17.8
29.7
33.0
35.0
42.3
44.4
44.6
67.0
95.5
98.4
109.0
126.3
128.4
129.3
132.7
135.6
138.0
142.5
168.8
177.3
189.5
ppm
Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-024-CH/ 5/ fid
Title 9-AH-024-CH.5.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 612
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-26T17:45:34
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.5
Nucleus 13C
Acquired Size 32768
Spectral Size 65536

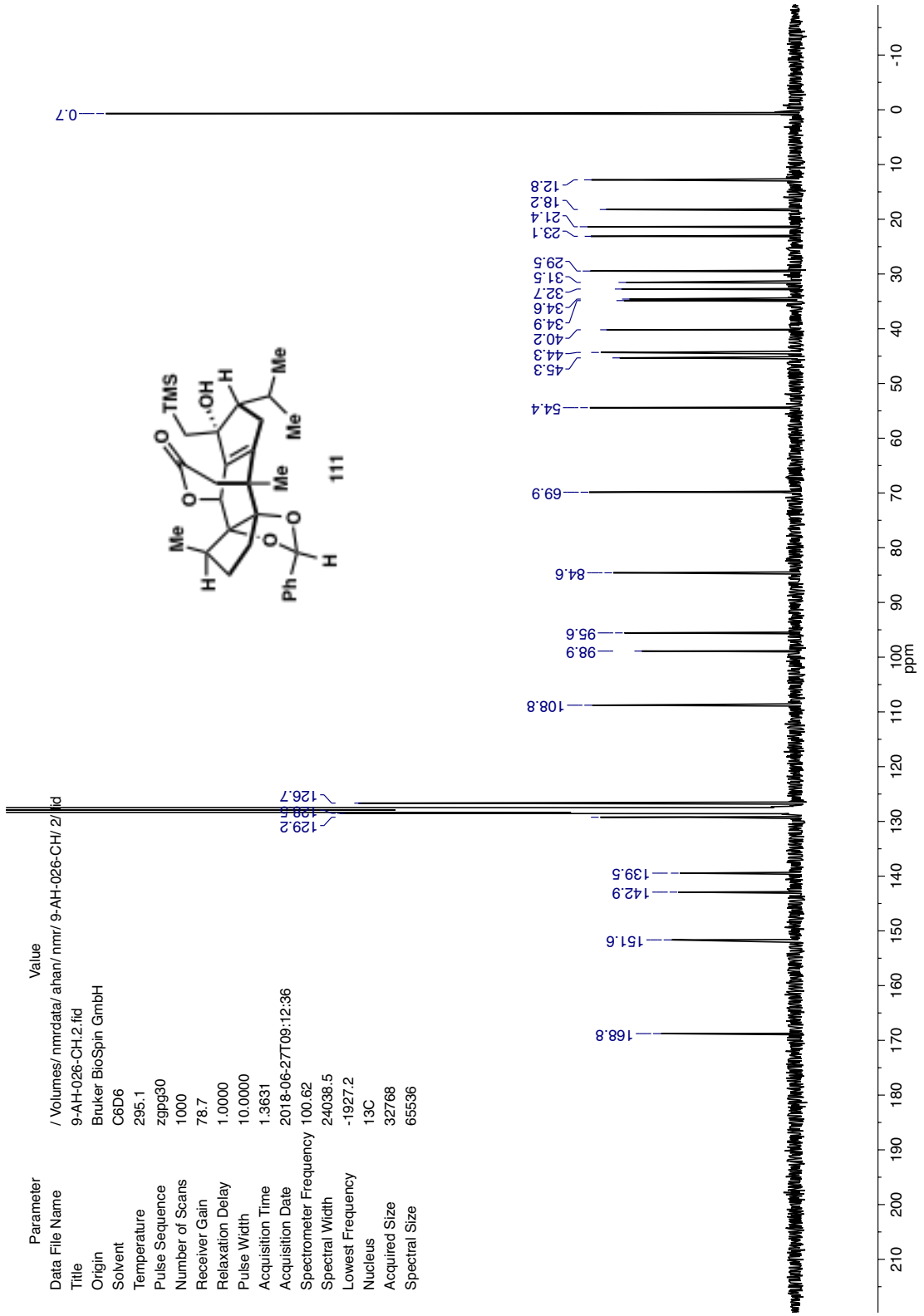

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-024-CH/ 4/ ser
Title
9-AH-024-CH.4.ser
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.2
Pulse Sequence
noesygpphzs
Number of Scans
5
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2560
Acquisition Date
2018-06-26T16:42:25
Spectrometer Frequency
(400.13, 400.13)
Spectral Width
(4000.0, 4000.0)
Lowest Frequency
(-158.1, -158.1)
Nucleus
(1H, 1H)
Acquired Size
(1024, 256)
Spectral Size
(1024, 1024)
ppm
Me
Me
Me
H
Ph
O


Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-025-CH/ 6/ fid
Title 9-AH-025-CH.6.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-27T04:47:33
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.2
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
109
5.06
1.00
1.03
3.02
1.04
3.05
3.05
3.06
1.07
1.05
1.04
1.03
1.02
2.02
1.01
1.06
1.05
ppm

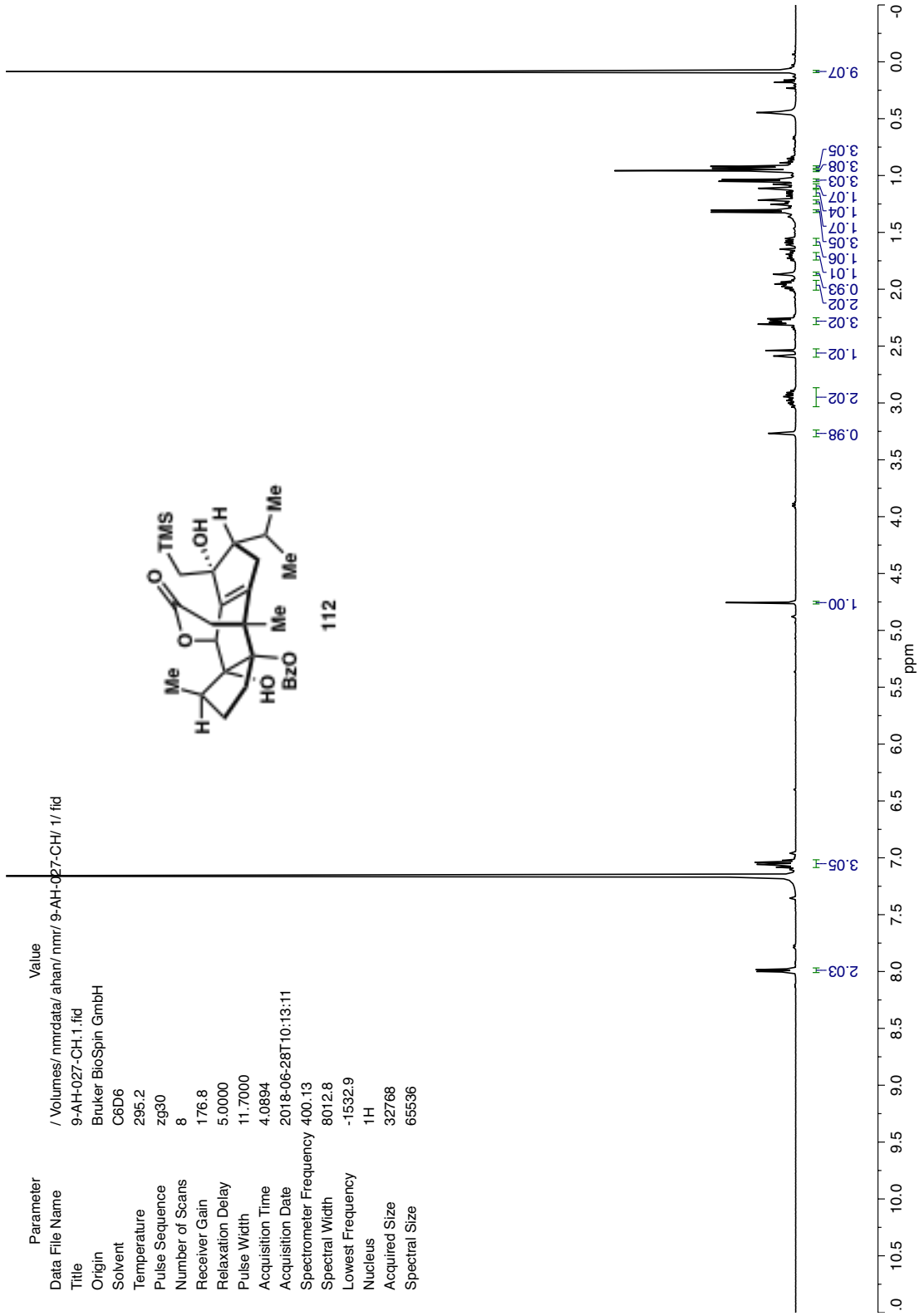

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-025-CH/ 5/ fid
Title 9-AH-025-CH.5.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 750
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-27T04:46:38
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.4
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
109
Me
Me
Me
Me
H
H
O
O
O
O
O
Ph
204.4
183.9
168.9
140.6
138.4
129.2
128.4
126.2
108.3
98.1
95.0
66.8
52.8
44.3
44.2
42.9
34.7
33.0
28.4
20.8
17.5
17.3
12.7
ppm

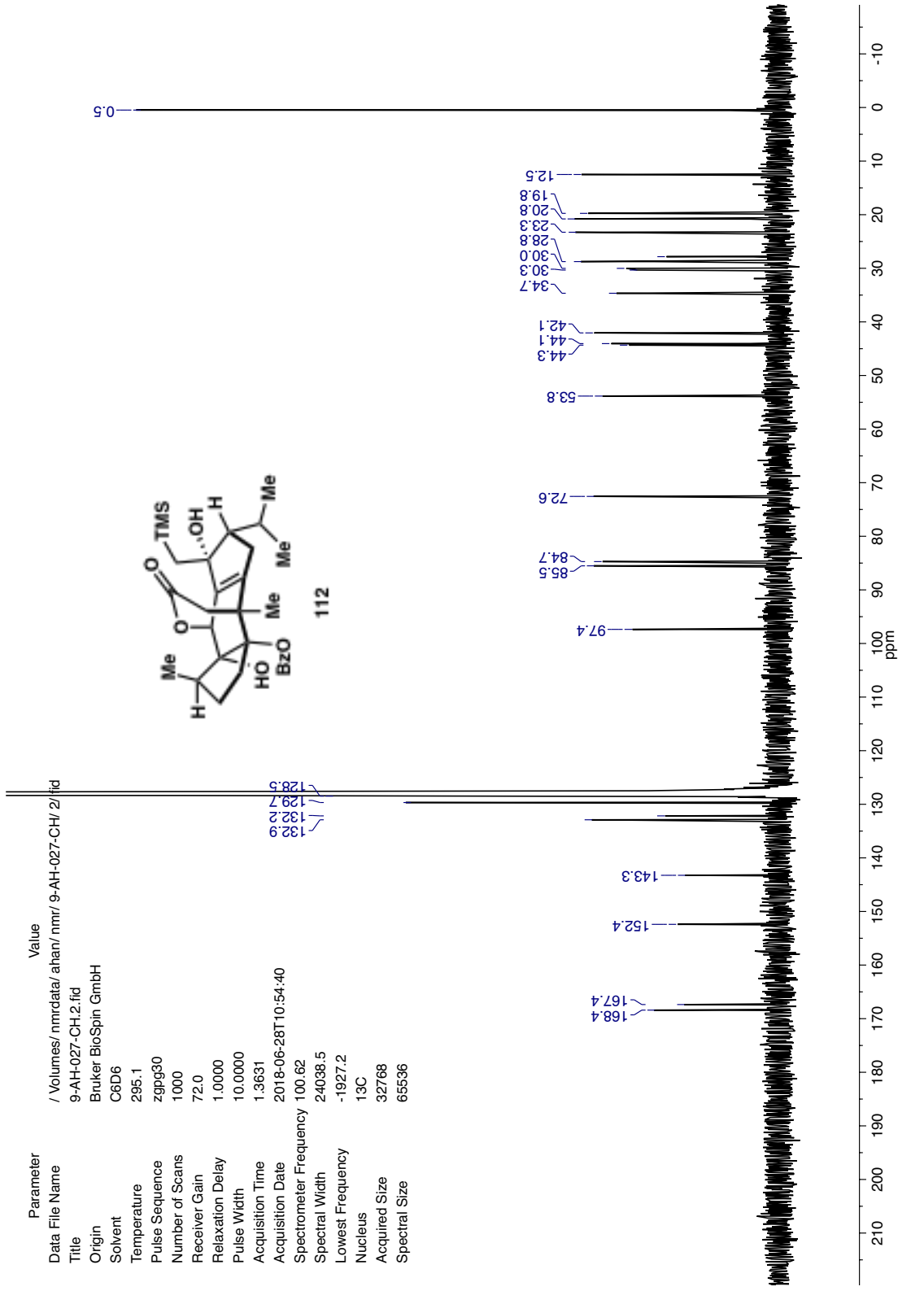

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 7-AH-230-P/ 1/ fid
Title
7-AH-230-P1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
294.9
Pulse Sequence
zg30
Number of Scans
16
Receiver Gain
197.4
Relaxation Delay
4.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2017-05-01T11:06:46
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1584.8
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Me
H
O
O
O
Ph
O
O
Me
Me
Cl
Me
H
114
5.07
1.00
1.03
1.04
1.07
1.01
1.00
1.06
1.07
1.02
2.09
3.04
1.05
3.08
3.09
3.06
ppm

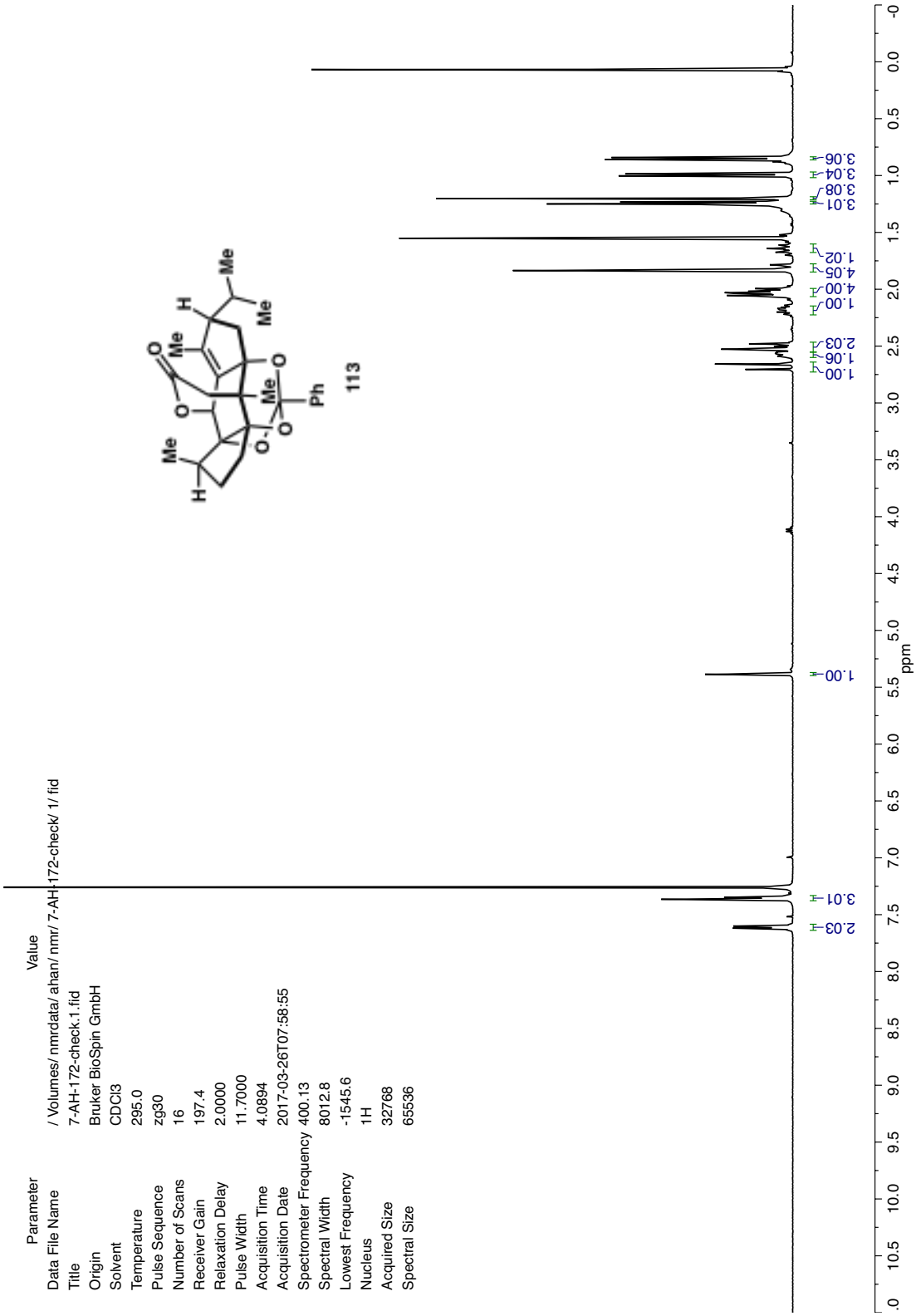

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-026-CH/ 1/ fid
Title 9-AH-026-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.1
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 156.2
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-27T08:31:04
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1532.5
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
TMS
OH
Me
Me
Me
Me
Ph
H
H
111
9.04
3.06
3.01
6.05
2.06
2.00
2.00
0.98
1.01
2.01
3.00
1.00
1.00
1.00
3.04
2.04
ppm

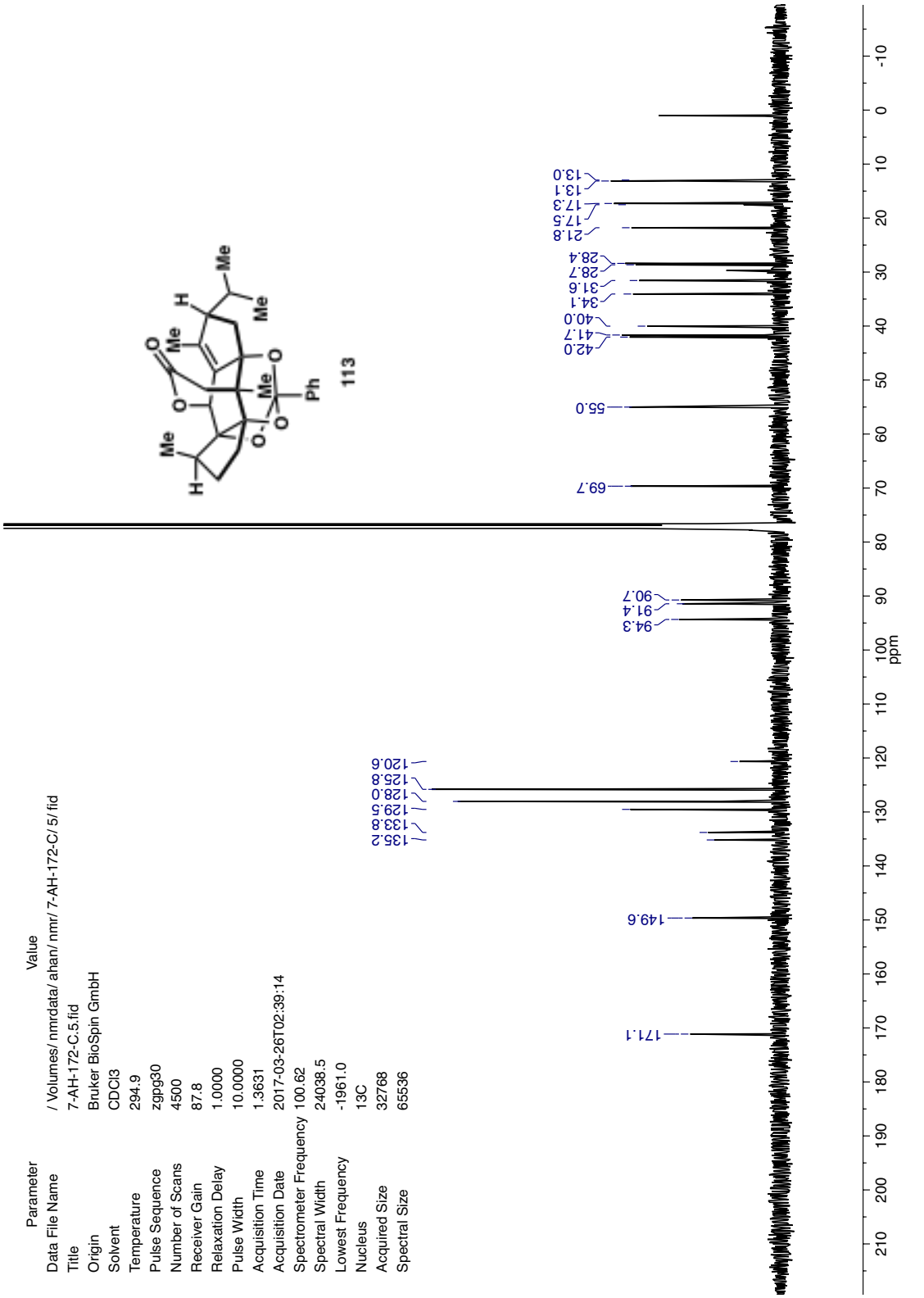


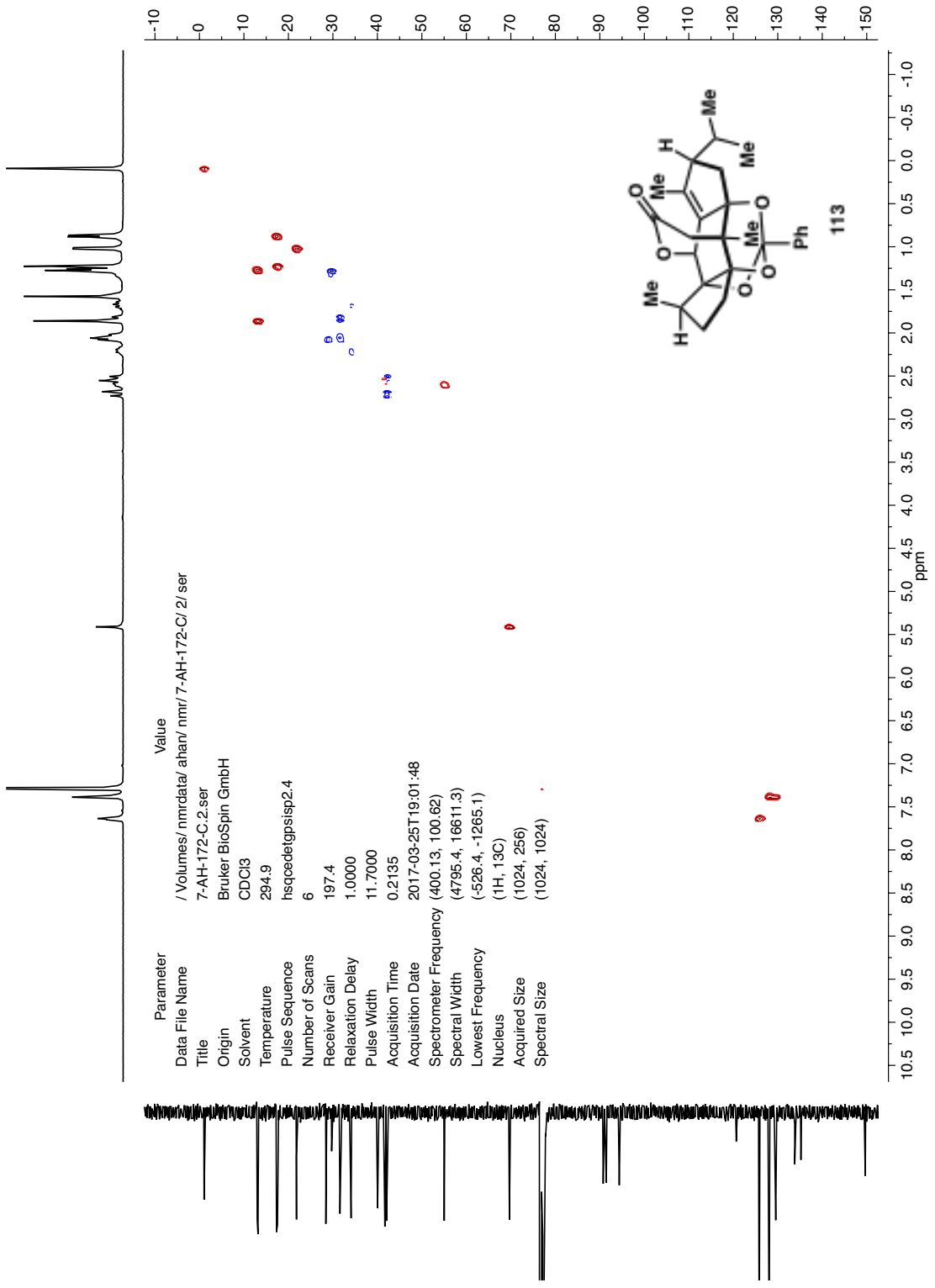
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-026-CH/ 2/ fid
Title	9-AH-026-CH.2.fid
Origin	Bruker BioSpin GmbH
Solvent	C6D6
Temperature	295.1
Pulse Sequence	zgpg30
Number of Scans	1000
Receiver Gain	78.7
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-06-27T09:12:36
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1927.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

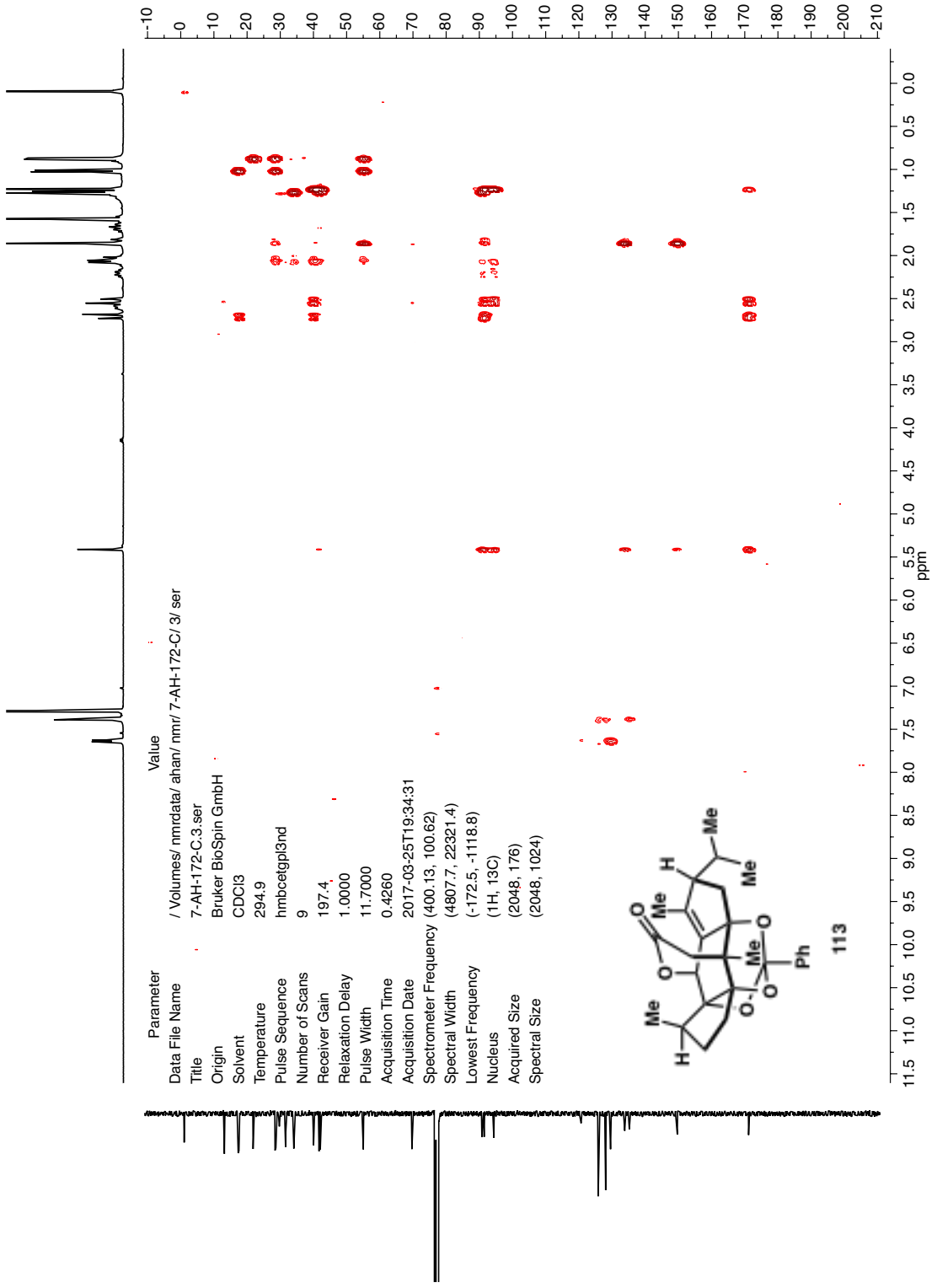

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-027-CH/ 1/ fid
Title
9-AH-027-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
C6D6
Temperature
295.2
Pulse Sequence
zg30
Number of Scans
8
Receiver Gain
176.8
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-06-28T10:13:11
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1532.9
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
TMS
OH
H
Me
Me
Me
Me
O
O
HO
BzO
H
112
9.07
3.05
3.08
3.03
1.07
1.04
1.07
3.05
1.06
1.01
2.02
0.93
3.02
1.02
2.02
0.98
1.00
3.05
2.03
ppm

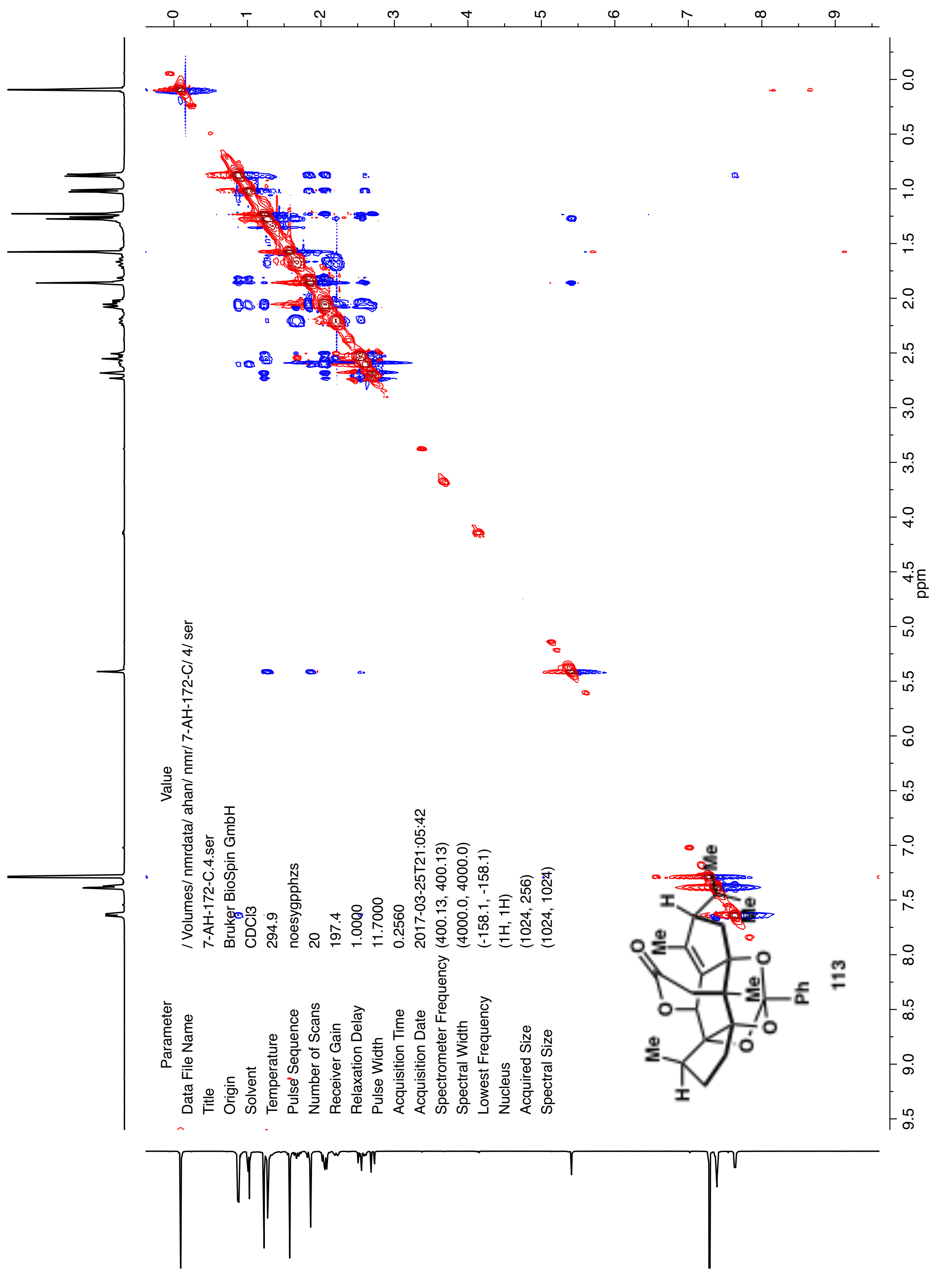

0.5
12.5
19.8
20.8
23.3
28.8
30.0
30.3
34.7
42.1
44.1
44.3
53.8
72.6
84.7
85.5
97.4
128.5
129.7
132.2
132.9
143.3
152.4
167.4
168.4
TMS
OH
H
Me
Me
O
O
Me
Me
HO
BzO
H
112
Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-027-CH/ 2/ fid
Title 9-AH-027-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 1000
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-28T10:54:40
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.2
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
ppm

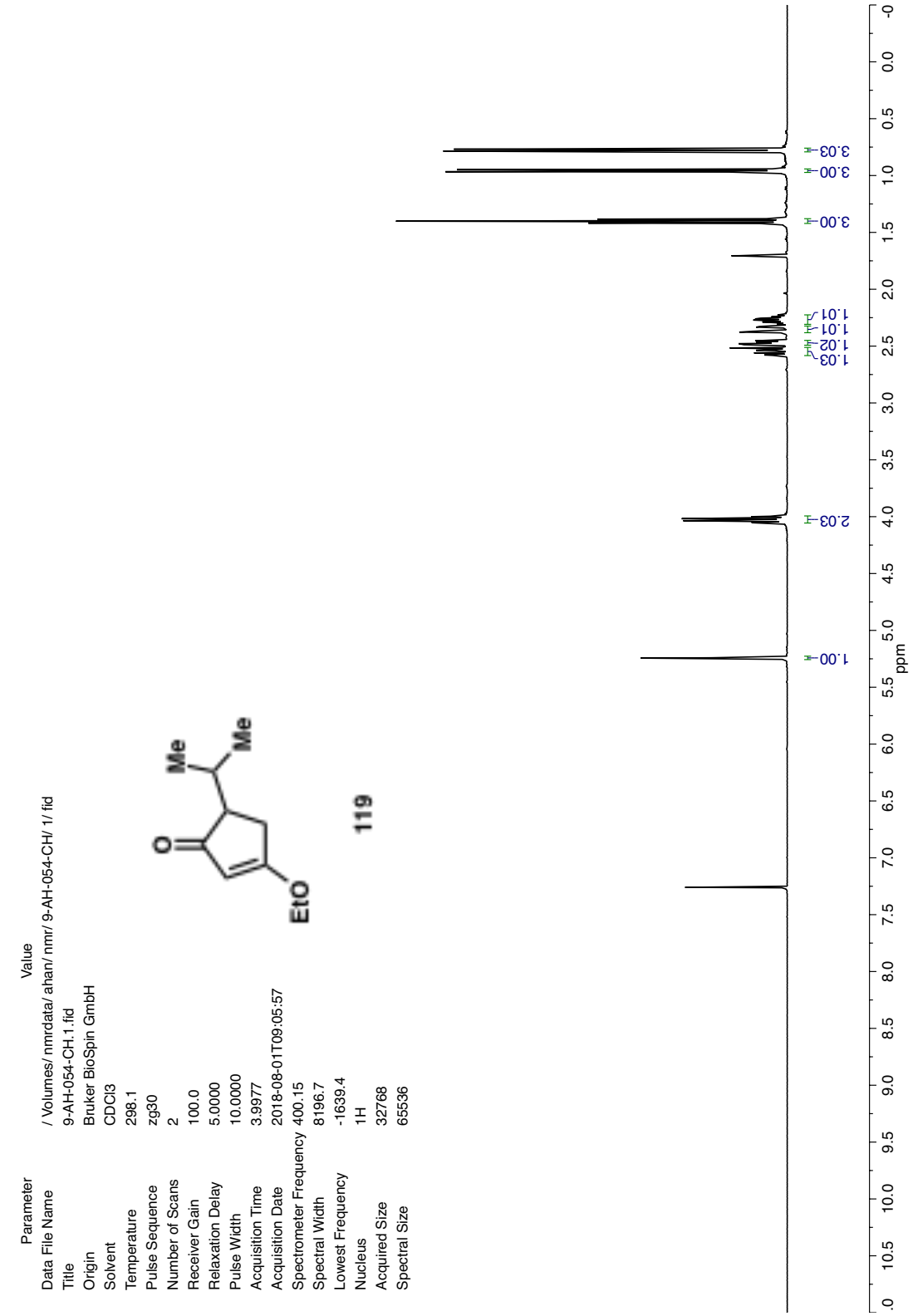

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 7-AH-172-check/ 1/ fid
Title 7-AH-172-check.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 2.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2017-03-26T07:58:55
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
113
2.03
3.01
1.00
1.00
1.06
2.03
1.00
4.00
4.05
1.02
3.01
3.08
3.04
3.06
ppm

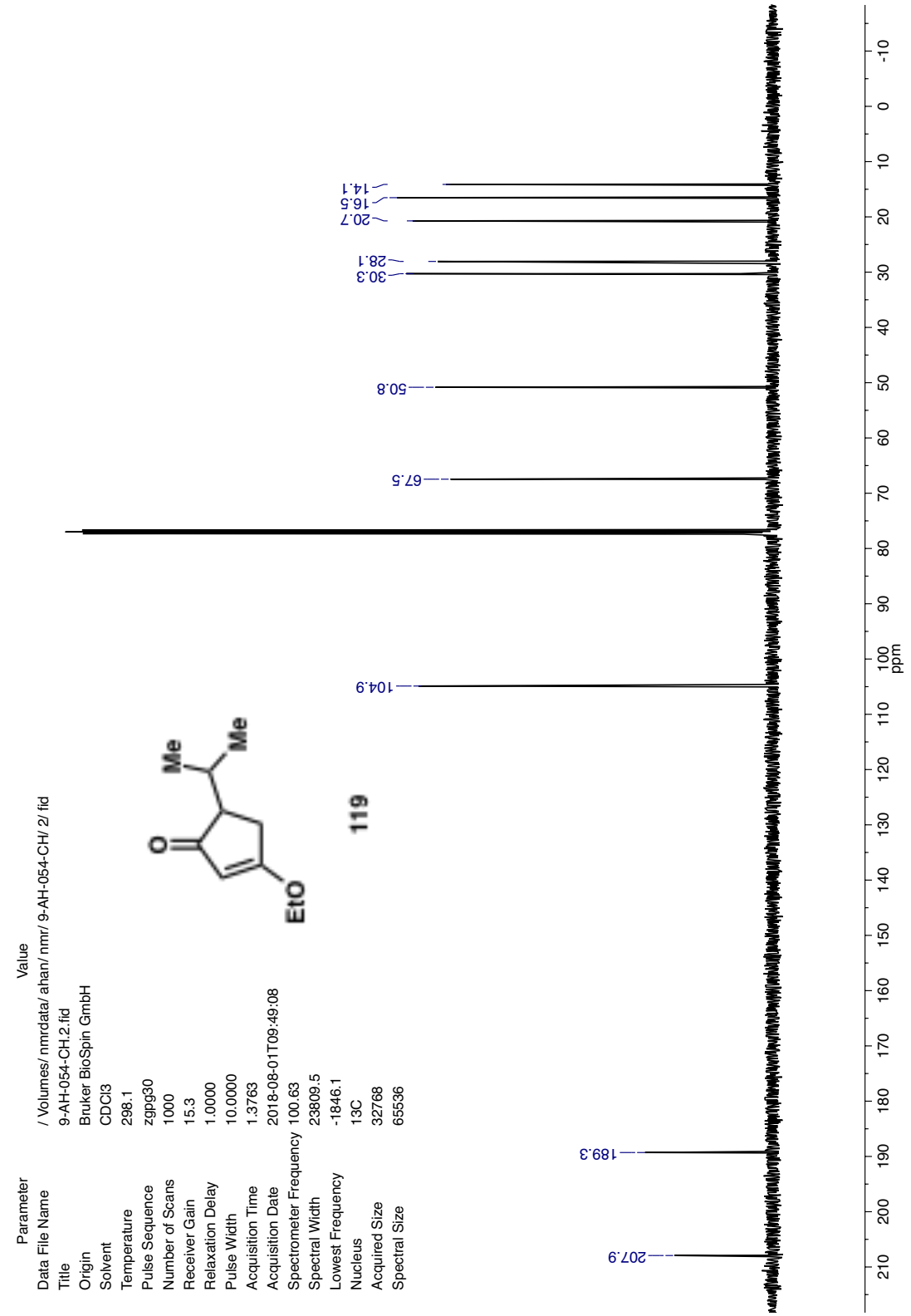

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 7-AH-172-C/ 5/ fid
Title
7-AH-172-C-5.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
294.9
Pulse Sequence
zgpg30
Number of Scans
4500
Receiver Gain
87.8
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2017-03-26T02:39:14
Spectrometer Frequency
100.62
Spectral Width
24038.5
Lowest Frequency
-1961.0
Nucleus
13C
Acquired Size
32768
Spectral Size
65536
113
171.1
149.6
135.2
133.8
129.5
128.0
125.8
120.6
94.3
91.4
90.7
69.7
55.0
42.0
41.7
40.0
34.1
31.6
28.7
28.4
21.8
17.5
17.3
13.1
13.0
ppm

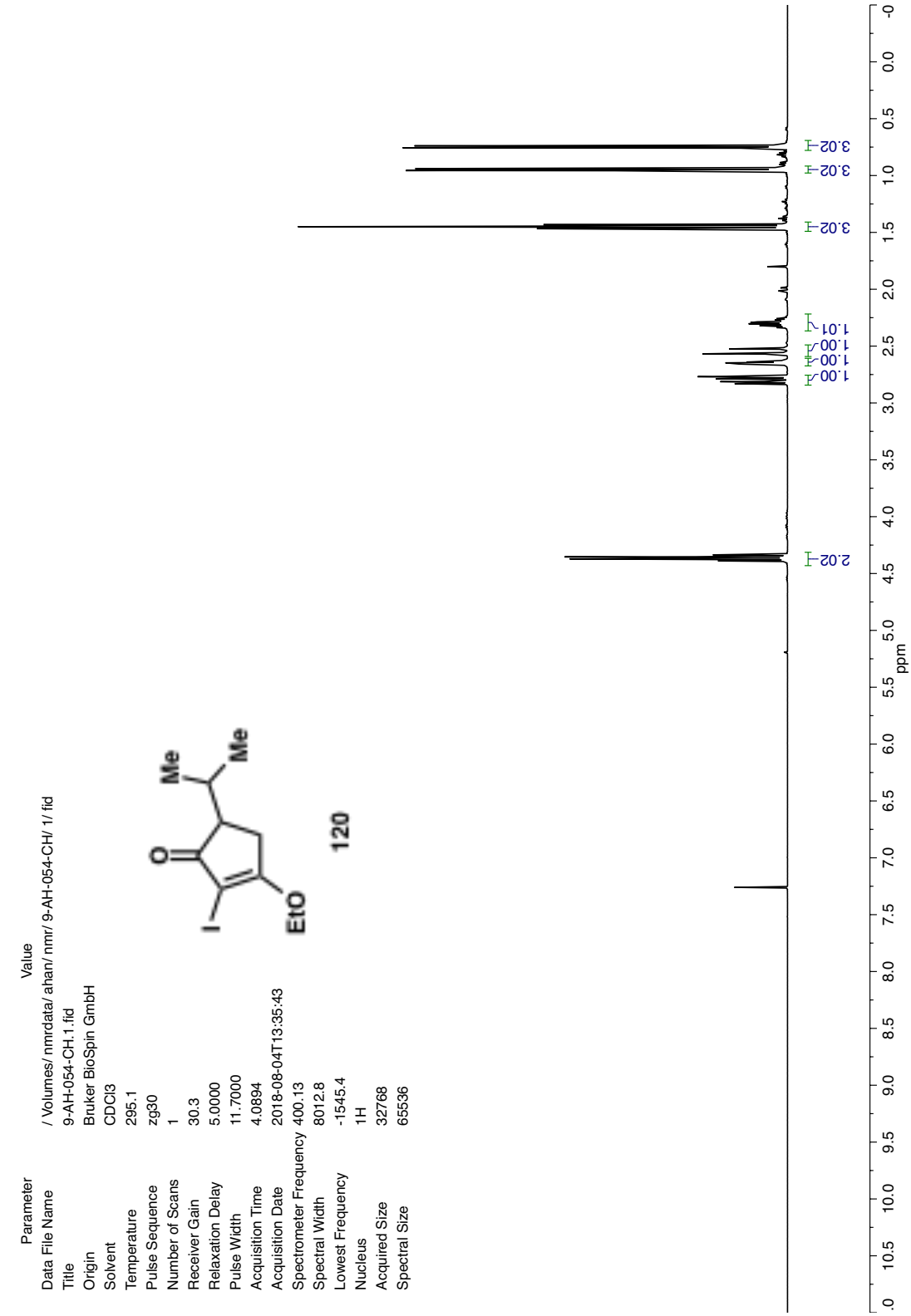

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 7-AH-172-C/ 2/ ser
Title 7-AH-172-C.2.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence hsqcedetgpsisp2.4
Number of Scans 6
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2135
Acquisition Date 2017-03-25T19:01:48
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4795.4, 16611.3)
Lowest Frequency (-526.4, -1265.1)
Nucleus (1H, 13C)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
ppm
Me
H
O
Ph
113

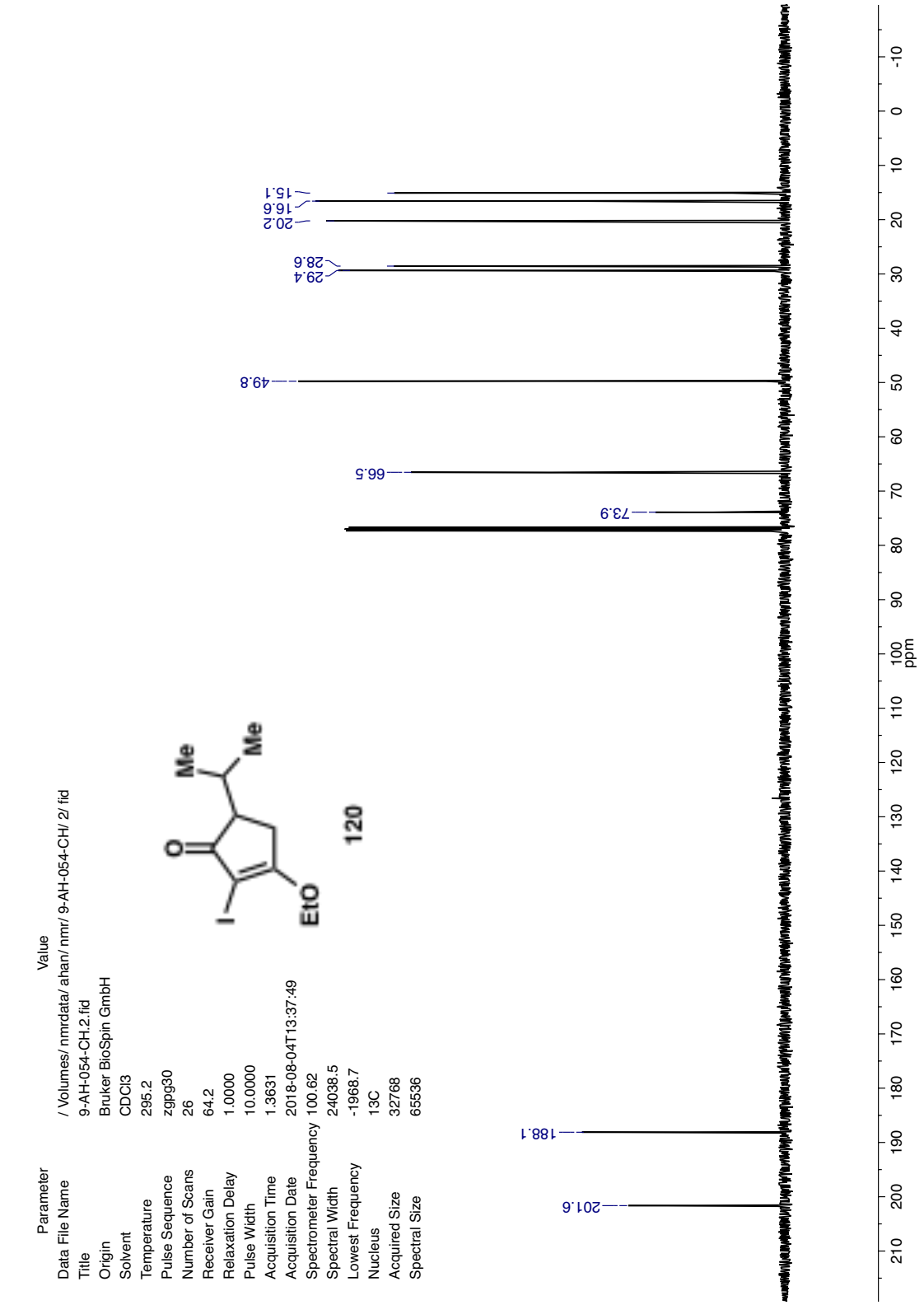

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 7-AH-172-C/ 3/ ser
Title
7-AH-172-C.3.ser
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
294.9
Pulse Sequence
hmbcetgpl3nd
Number of Scans
9
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.4260
Acquisition Date
2017-03-25T19:34:31
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4807.7, 22321.4)
Lowest Frequency
(-172.5, -1118.8)
Nucleus
(1H, 13C)
Acquired Size
(2048, 176)
Spectral Size
(2048, 1024)
Me
Me
H
Me
Me
O
O
O
O
Me
Ph
H
113
ppm

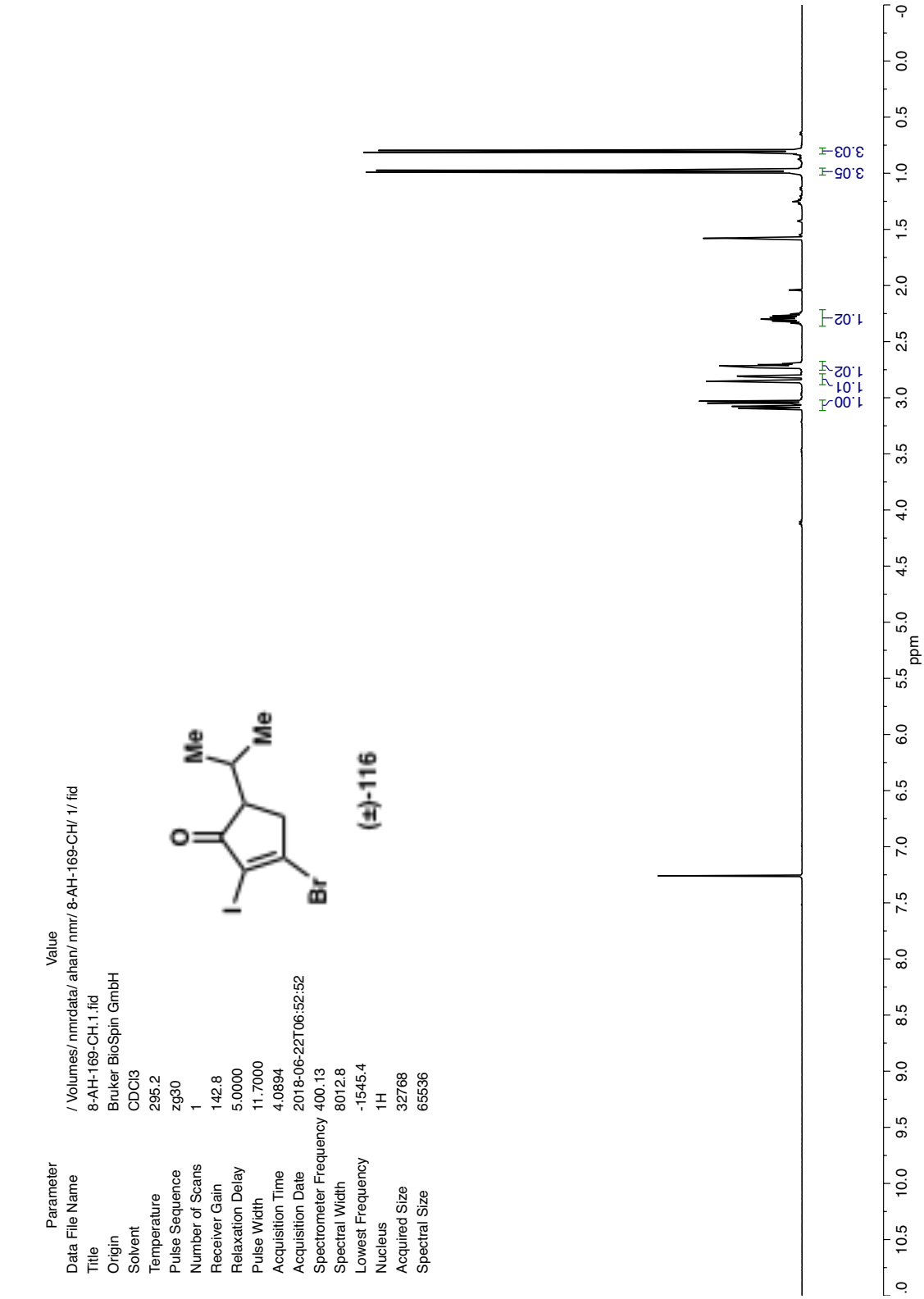

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 7-AH-172-C/ 4/ ser
Title 7-AH-172-C.4.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 294.9
Pulse Sequence noesygpphzs
Number of Scans 20
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2017-03-25T21:05:42
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-158.1, -158.1)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
ppm
113

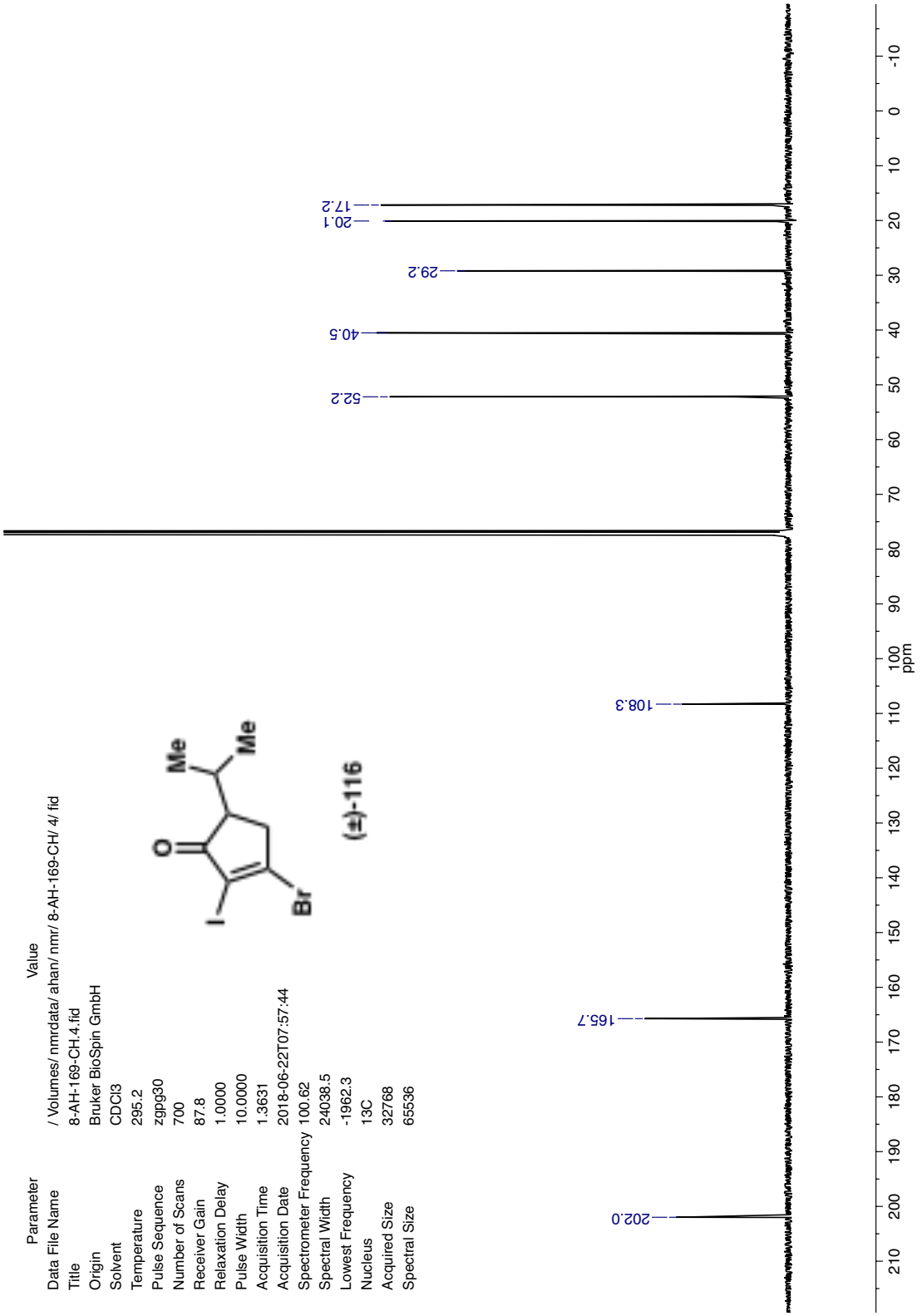

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-054-CH/ 1/ fid
Title
9-AH-054-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
298.1
Pulse Sequence
zg30
Number of Scans
2
Receiver Gain
100.0
Relaxation Delay
5.0000
Pulse Width
10.0000
Acquisition Time
3.9977
Acquisition Date
2018-08-01T09:05:57
Spectrometer Frequency
400.15
Spectral Width
8196.7
Lowest Frequency
-1639.4
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Me
Me
O
EtO
119
1.00
2.03
3.00
1.01
1.01
1.02
1.03
3.00
3.00
3.03
ppm

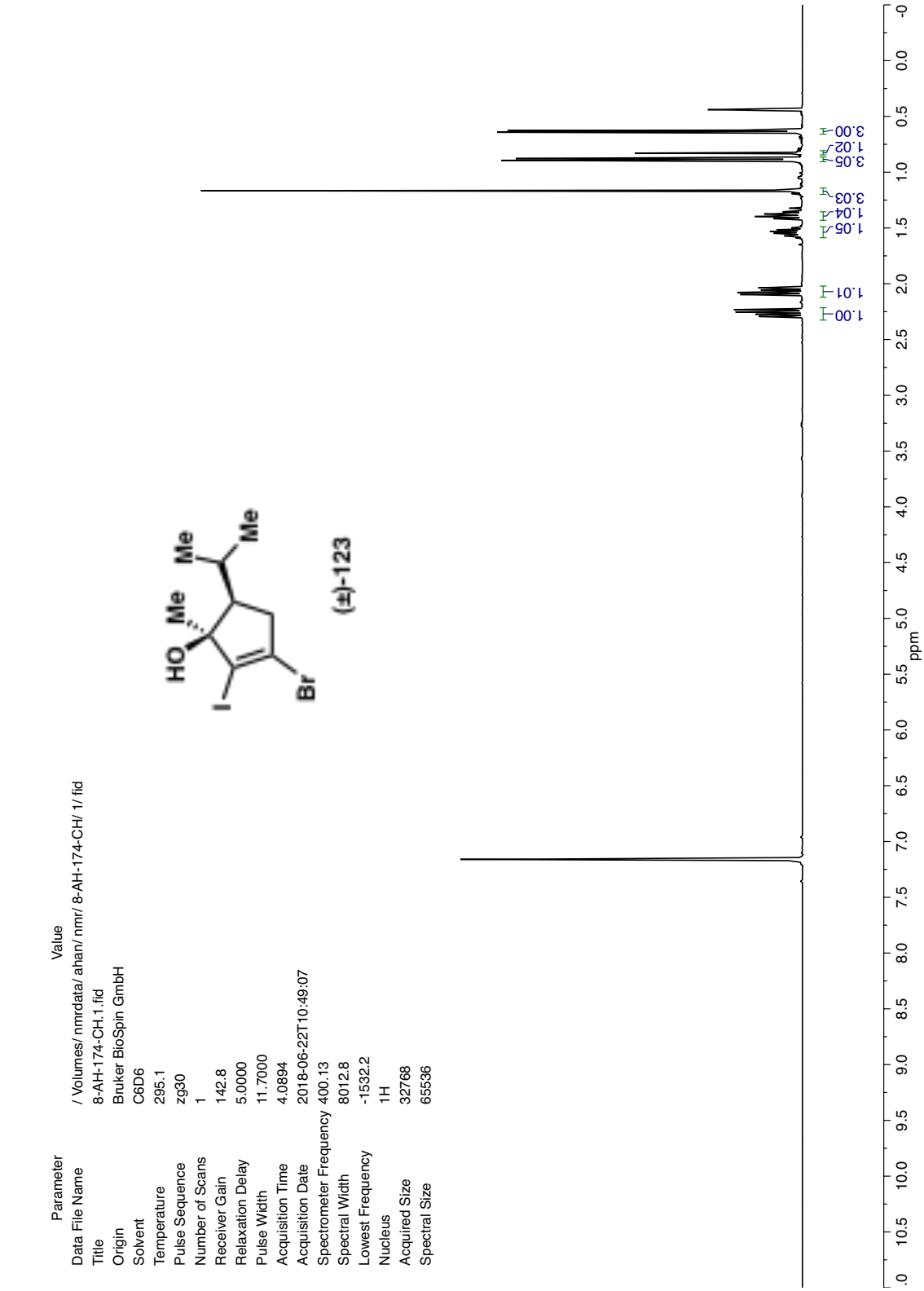

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-054-CH/ 2/ fid
Title
9-AH-054-CH.2.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
298.1
Pulse Sequence
zgpg30
Number of Scans
1000
Receiver Gain
15.3
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3763
Acquisition Date
2018-08-01T09:49:08
Spectrometer Frequency
100.63
Spectral Width
23809.5
Lowest Frequency
-1846.1
Nucleus
13C
Acquired Size
32768
Spectral Size
65536
Me
Me
O
EtO
119
207.9
189.3
104.9
67.5
50.8
30.3
28.1
20.7
16.5
14.1
ppm

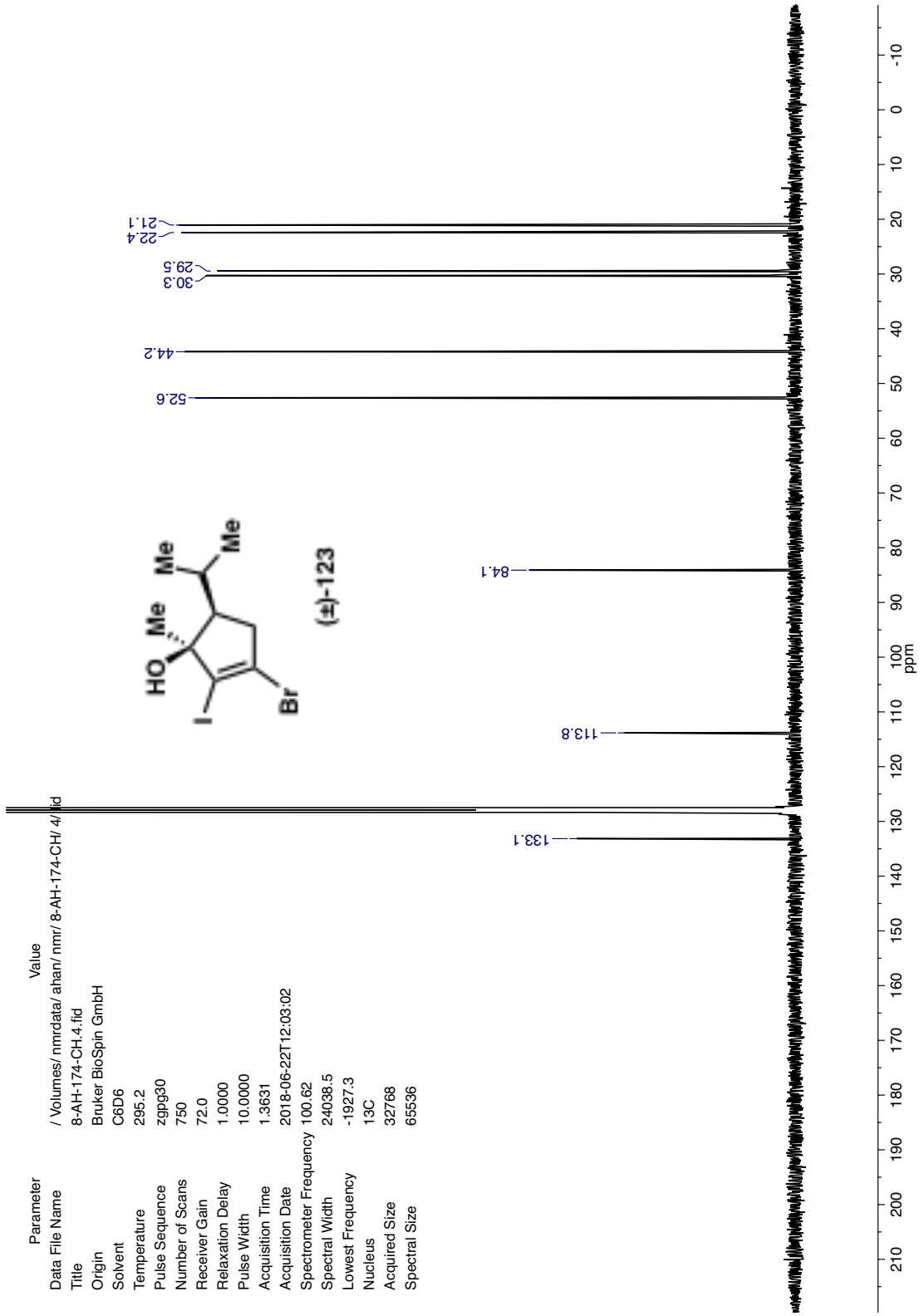

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-054-CH/ 1/ fid
Title
9-AH-054-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zg30
Number of Scans
1
Receiver Gain
30.3
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-08-04T13:35:43
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.4
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Me
Me
O
I
EtO
120
2.02
1.00
1.00
1.00
1.01
3.02
3.02
3.02
ppm

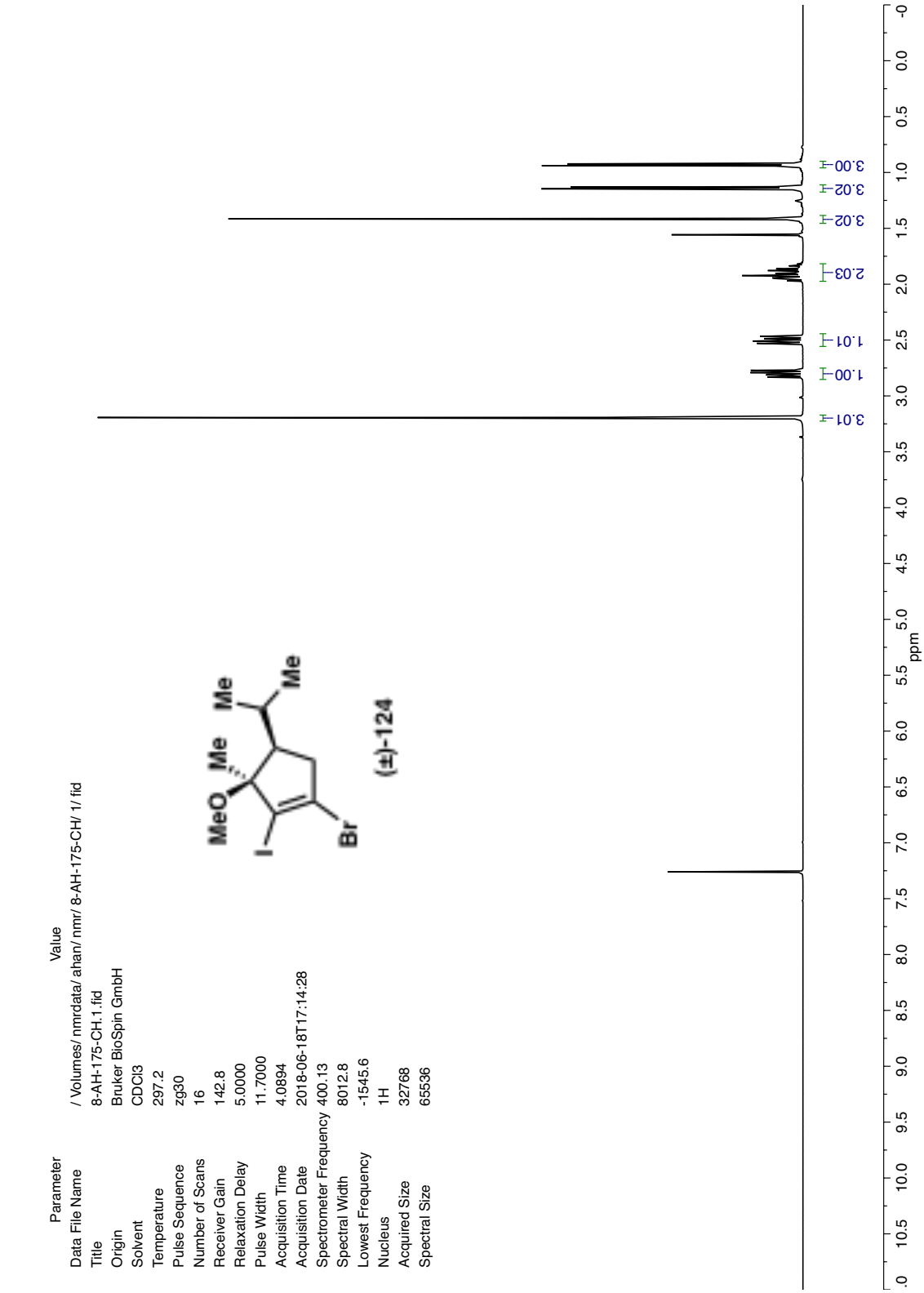

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-054-CH/ 2/ fid
Title 9-AH-054-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 26
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-08-04T13:37:49
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1968.7
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Me
Me
O
I
EtO
120
201.6
188.1
73.9
66.5
49.8
29.4
28.6
20.2
16.6
15.1
ppm

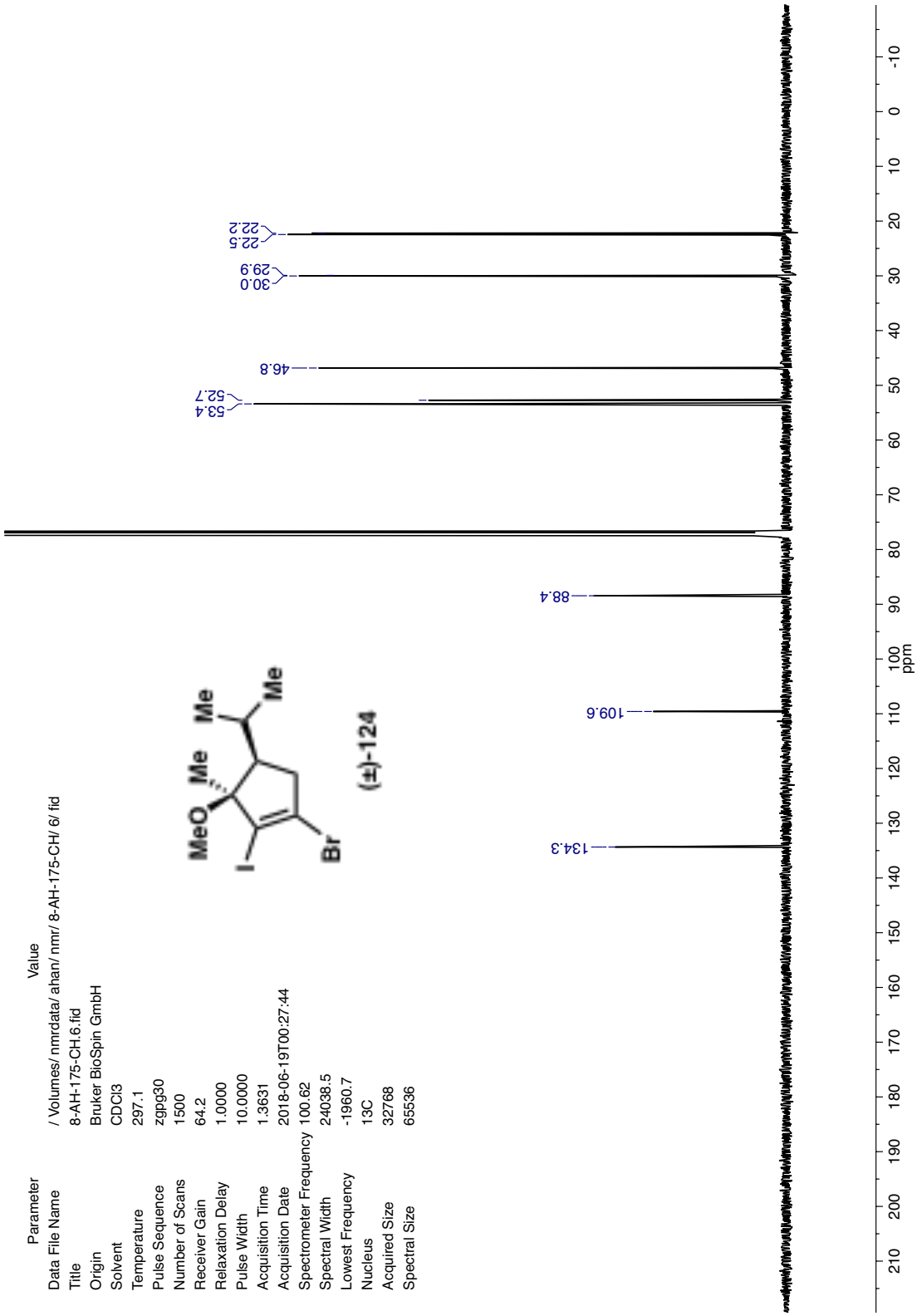

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-169-CH/ 1/ fid
Title
8-AH-169-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.2
Pulse Sequence
zg30
Number of Scans
1
Receiver Gain
142.8
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-06-22T06:52:52
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.4
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Me
Me
O
I
Br
(±)-116
3.03
3.05
1.02
1.00
1.01
1.02
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-169-CH/ 4/ fid
Title 8-AH-169-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 700
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-22T07:57:44
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1962.3
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Me
Me
O
I
Br
(±)-116
202.0
165.7
108.3
52.2
40.5
29.2
20.1
17.2
ppm

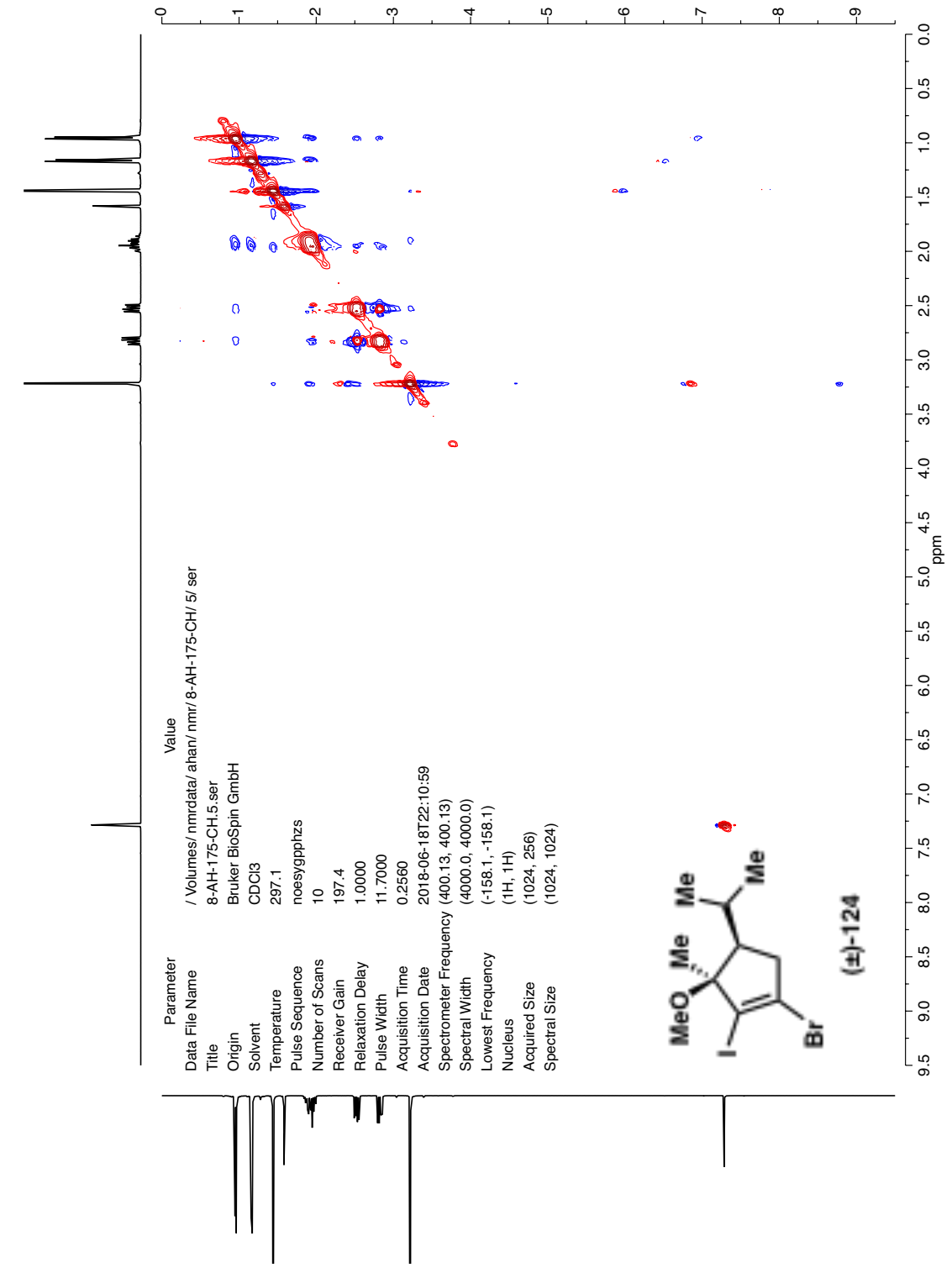

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-174-CH/ 1/ fid
Title
8-AH-174-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
C6D6
Temperature
295.1
Pulse Sequence
zg30
Number of Scans
1
Receiver Gain
142.8
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-06-22T10:49:07
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1532.2
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
HO
Me
Me
Me
I
Br
(±)-123
1.00
1.01
1.05
1.04
3.03
3.05
1.02
3.00
ppm

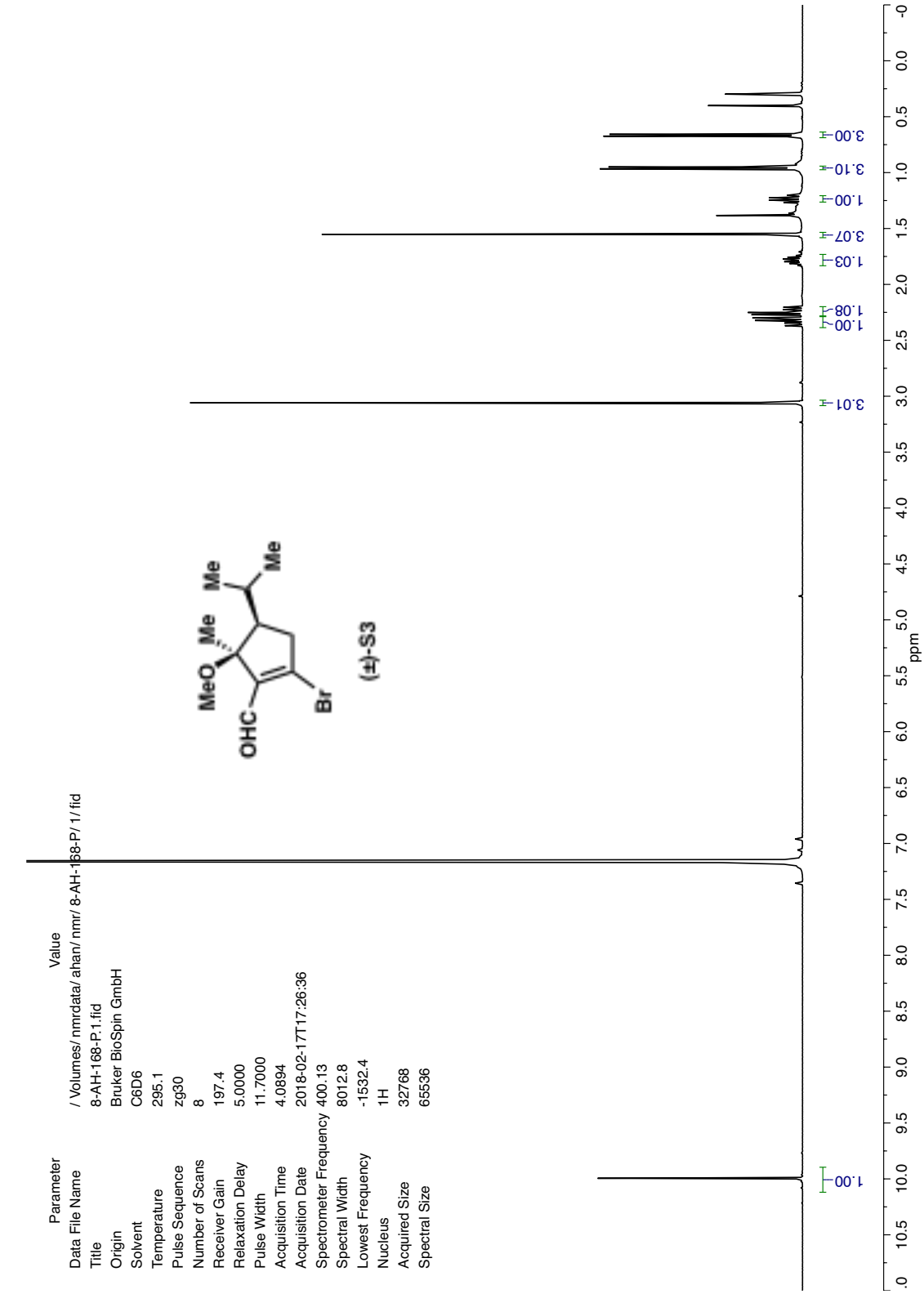

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-174-CH/ 4/ fid
Title 8-AH-174-CH.4.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 750
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-22T12:03:02
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.3
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
21.1
22.4
29.5
30.3
44.2
52.6
84.1
113.8
133.1
HO
Me
Me
Me
I
Br
(±)-123
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

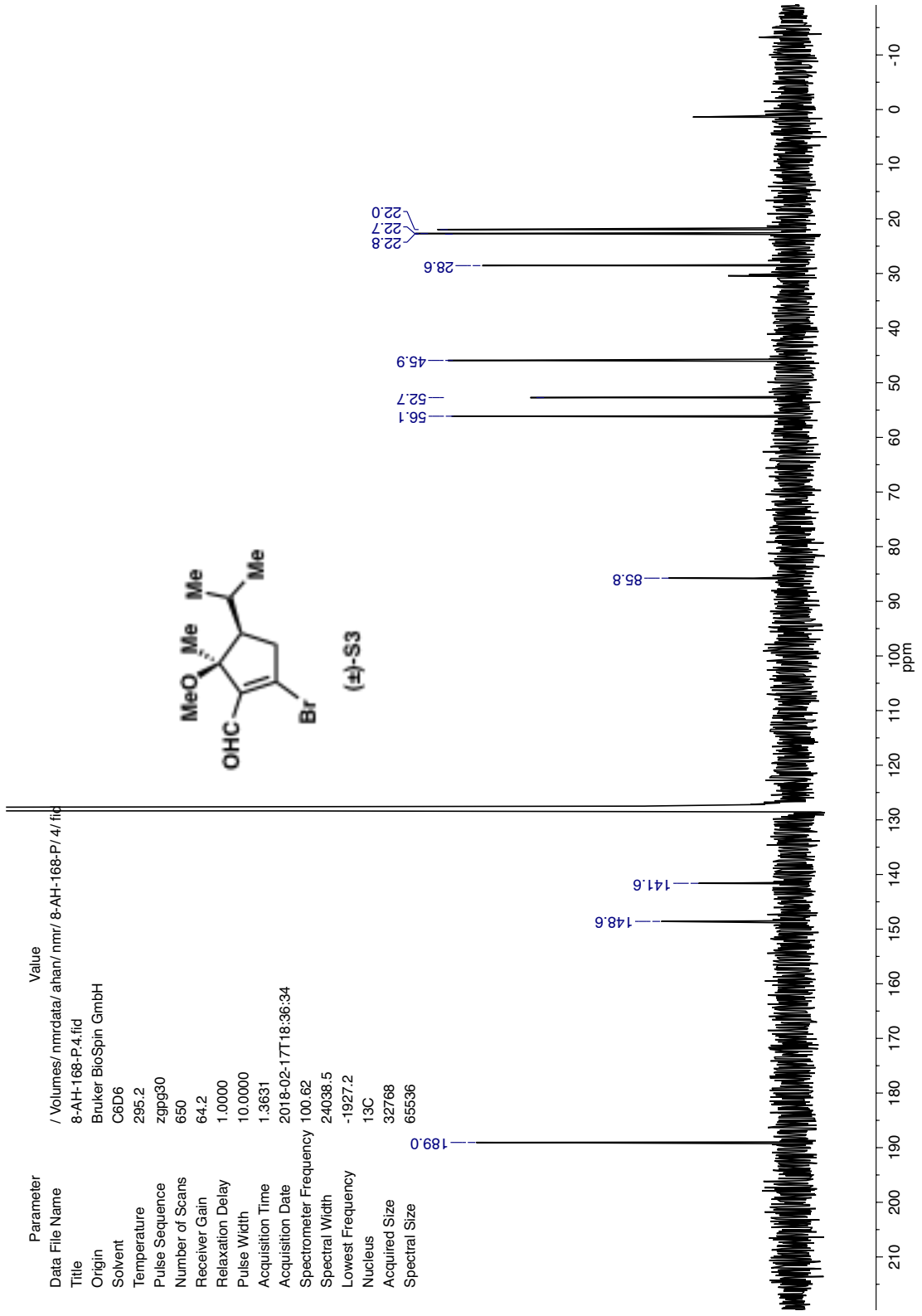

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-175-CH/ 1/ fid
Title 8-AH-175-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.2
Pulse Sequence zg30
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-18T17:14:28
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
MeO
Me
Me
Me
I
Br
(±)-124
3.01
1.00
1.01
2.03
3.02
3.02
3.00
ppm

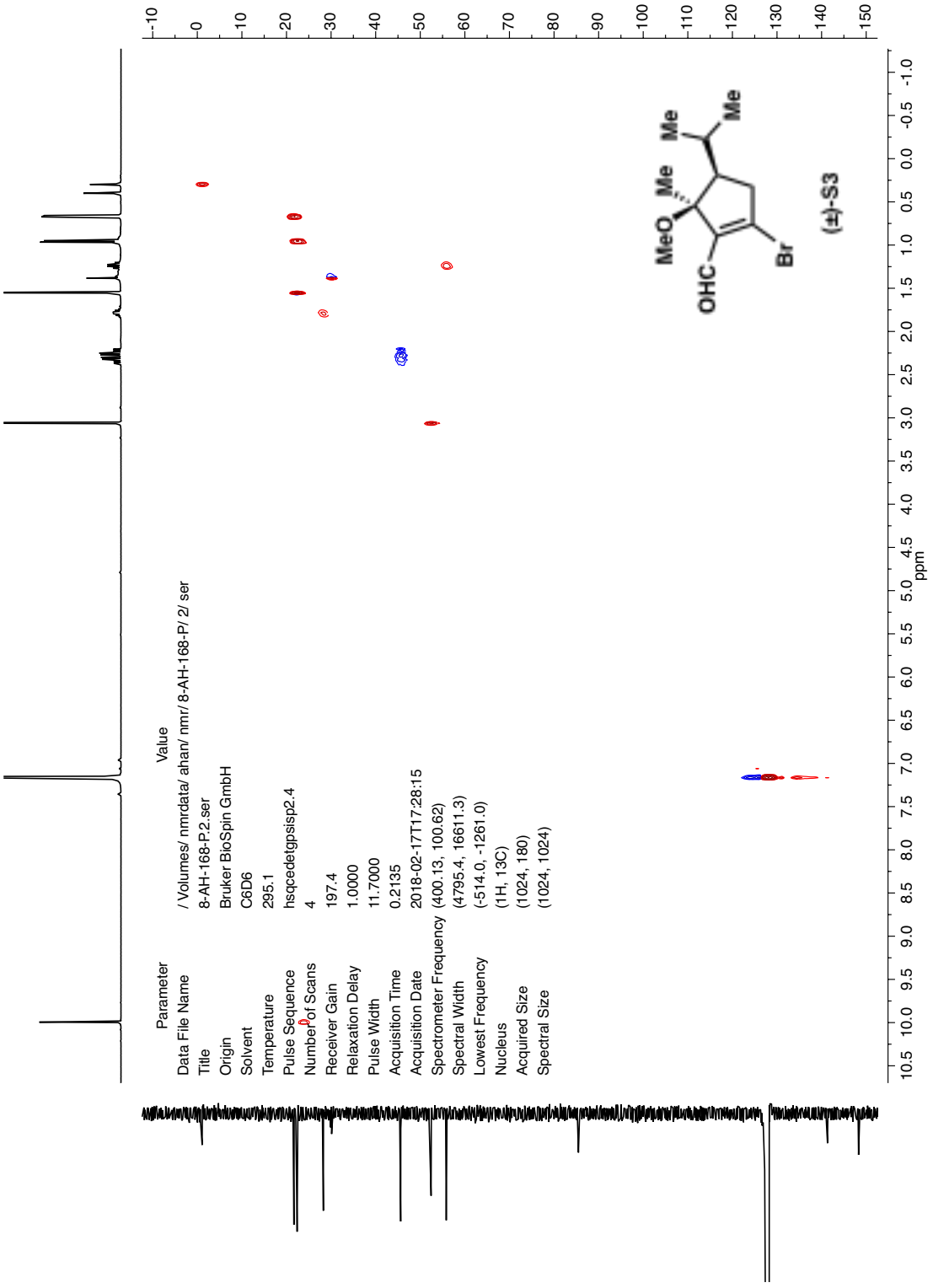


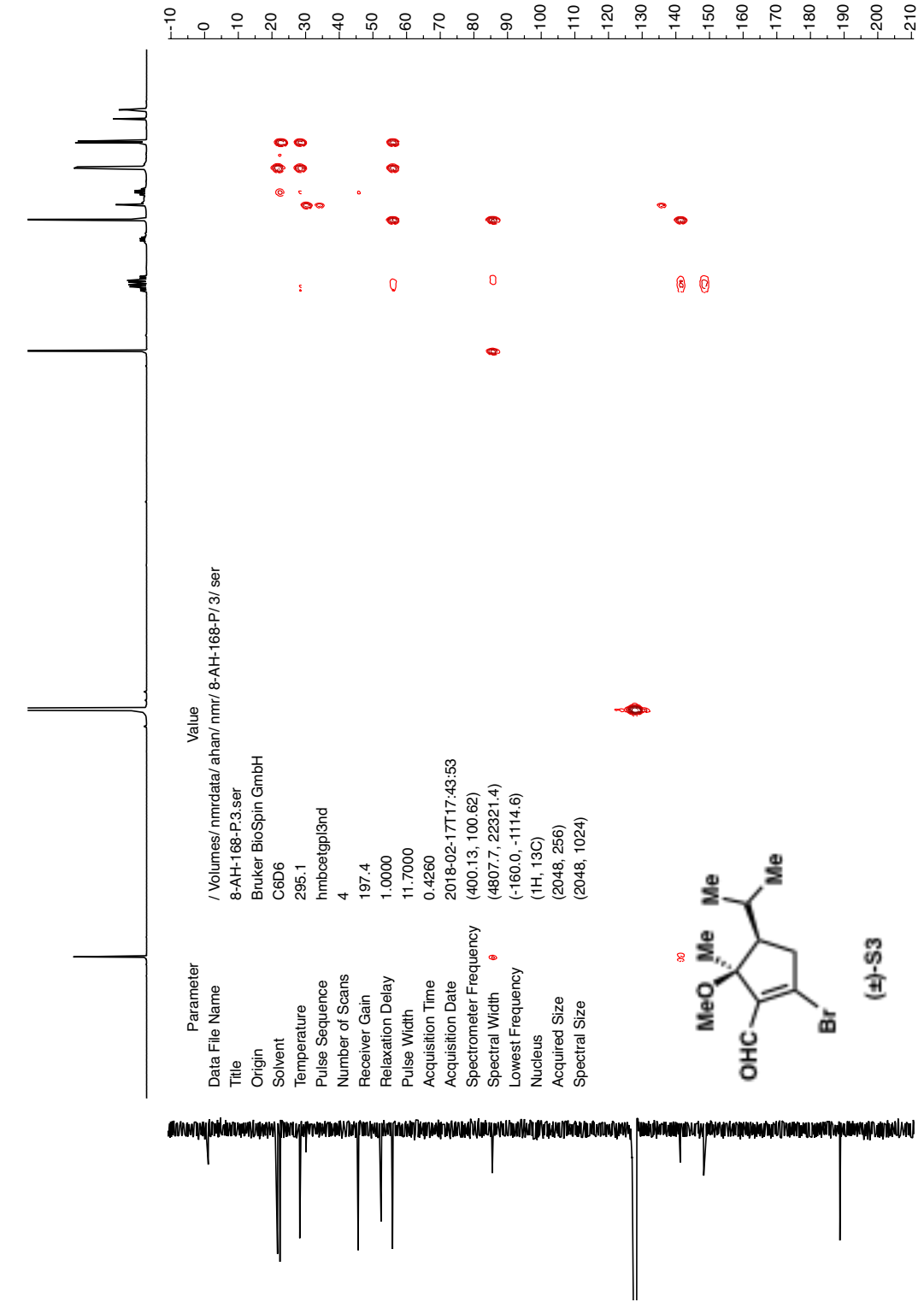
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-175-CH/ 6/ fid
Title	8-AH-175-CH.6.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Pulse Sequence	zgpg30
Number of Scans	1500
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-06-19T00:27:44
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1960.7
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

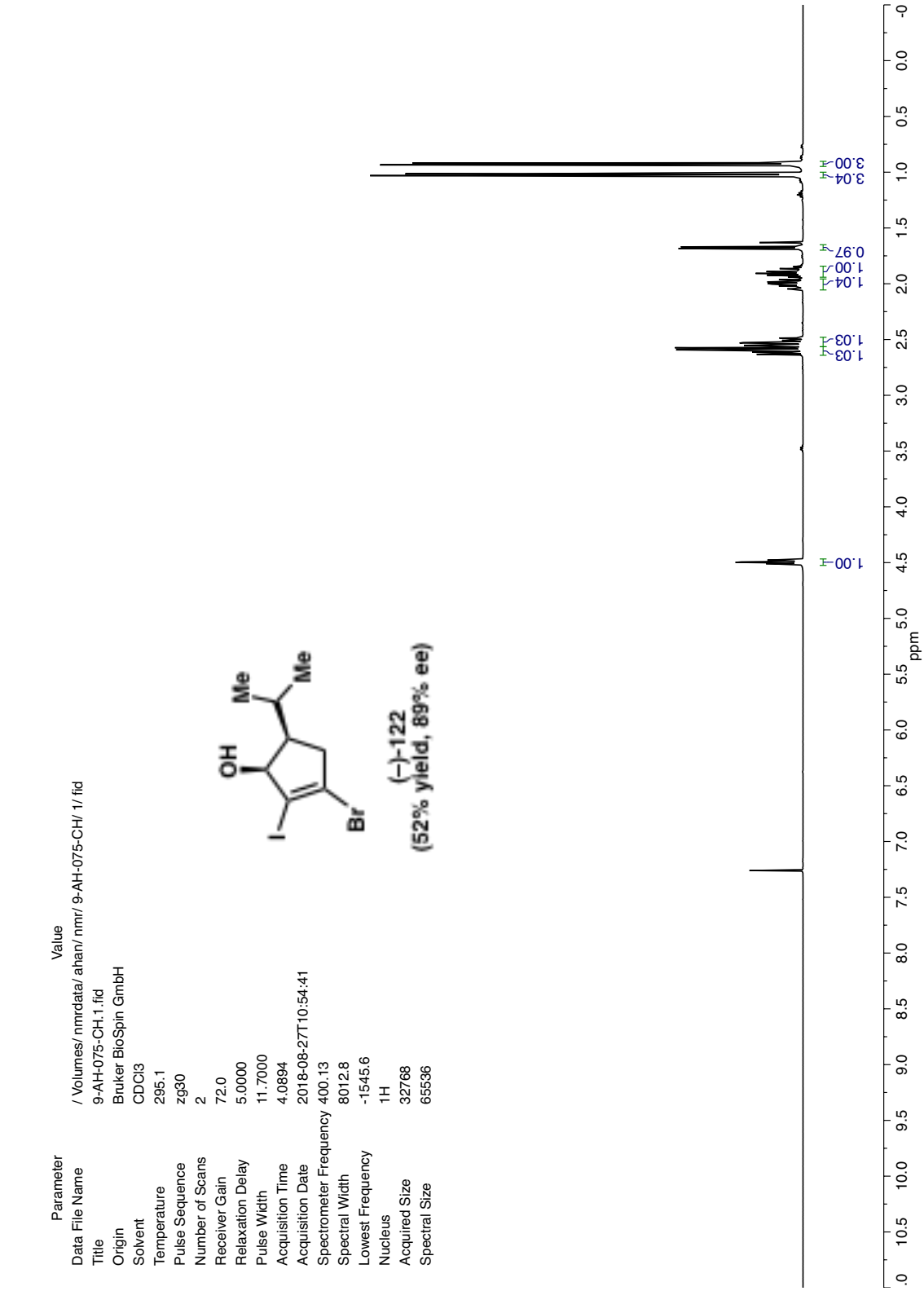

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-175-CH/ 5/ ser
Title 8-AH-175-CH.5.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Pulse Sequence noesygpphzs
Number of Scans 10
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2018-06-18T22:10:59
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-158.1, -158.1)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
MeO
Me
Me
I
Br
(±)-124
ppm

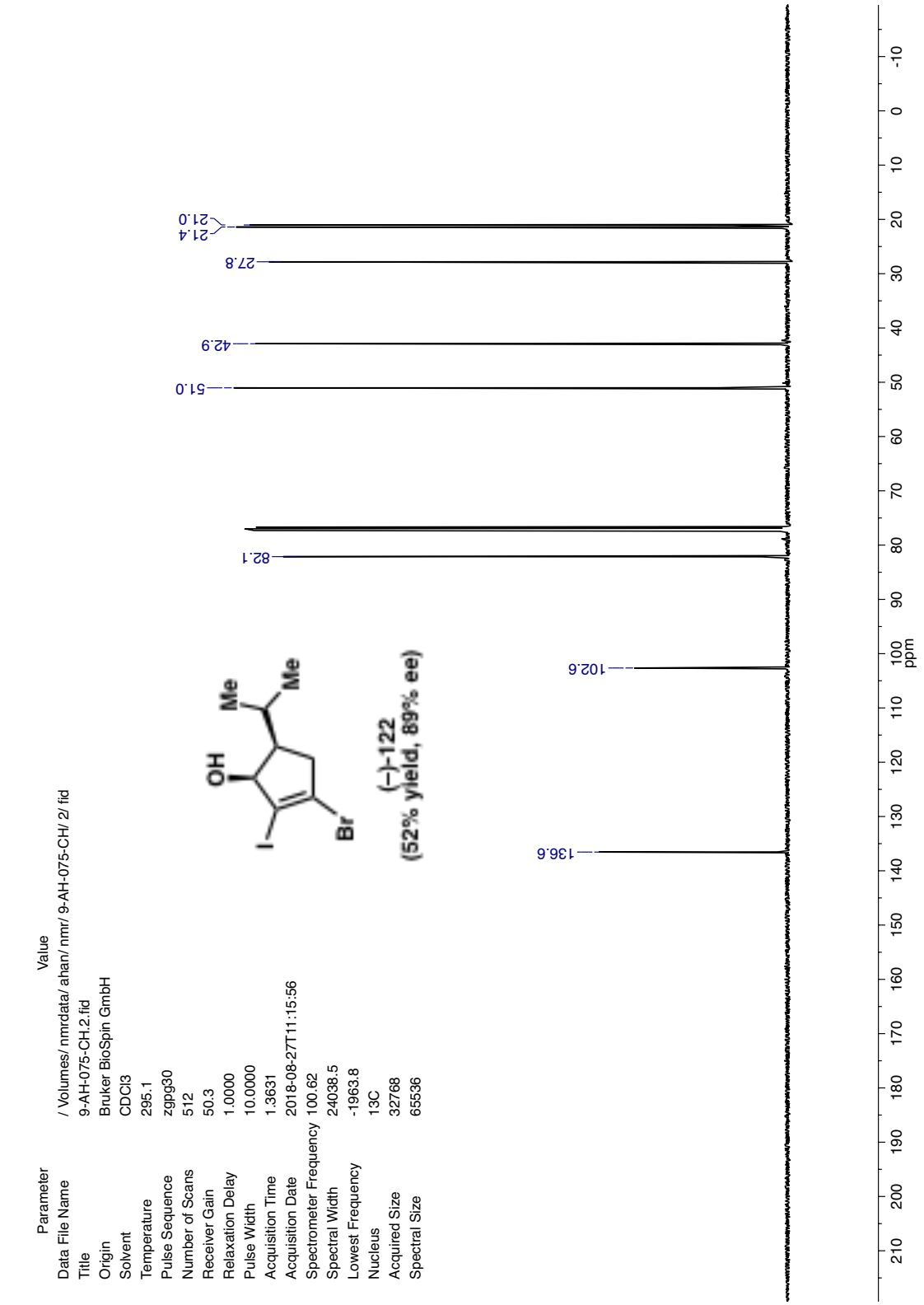

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-168-P/ 1/ fid
Title 8-AH-168-P1.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.1
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-02-17T17:26:36
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1532.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
MeO
Me
Me
Me
OHC
Br
(±)-S3
1.00
3.01
1.00
1.08
1.03
3.07
1.00
3.10
3.00
ppm

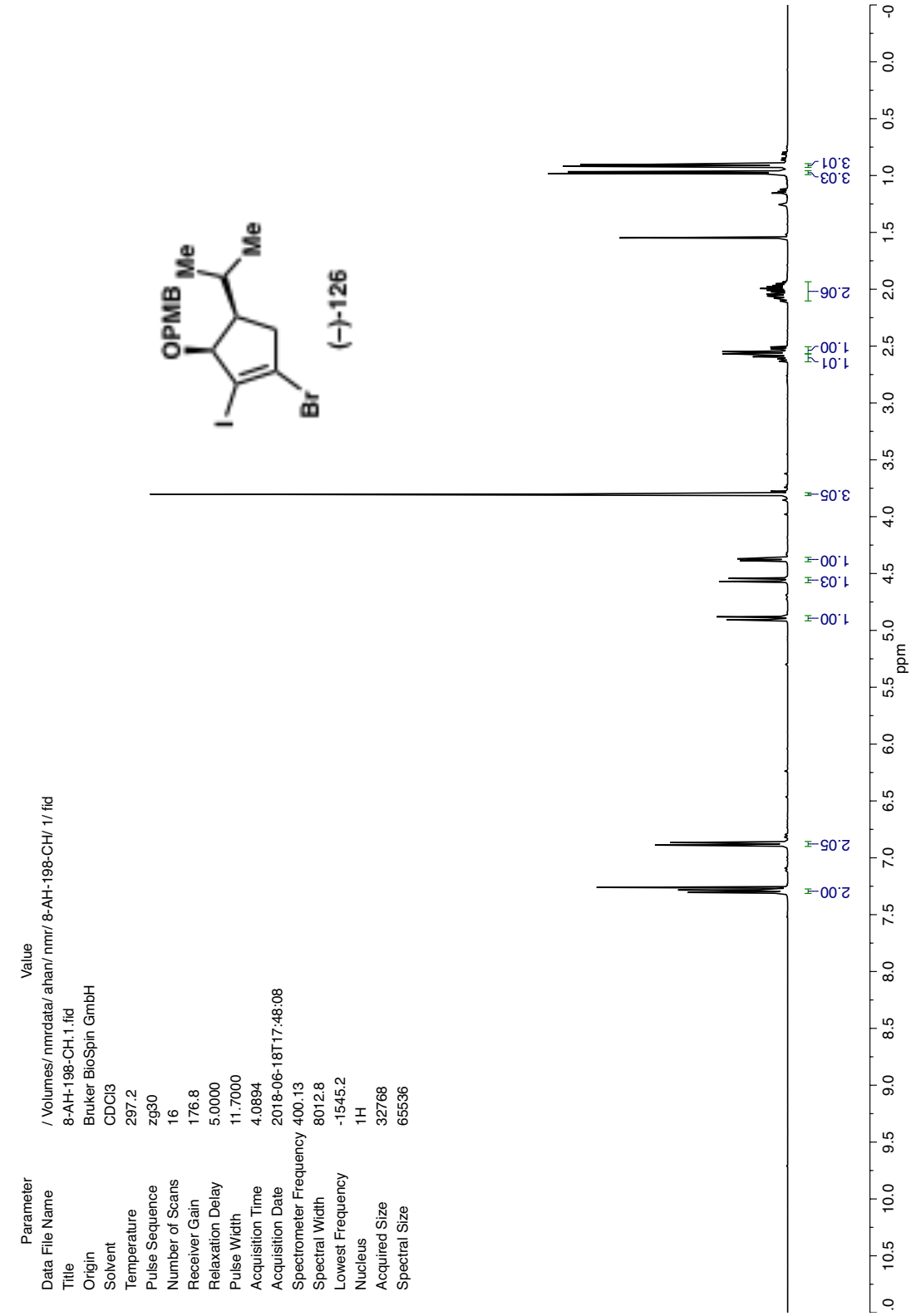

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-168-P/ 4/ fid
Title 8-AH-168-P4.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 650
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-02-17T18:36:34
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.2
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
189.0
148.6
141.6
85.8
56.1
52.7
45.9
28.6
22.8
22.7
22.0
MeO
Me
Me
Me
OHC
Br
(±)-S3
ppm


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-168-P/ 2/ ser
Title
8-AH-168-P.2.ser
Origin
Bruker BioSpin GmbH
Solvent
C6D6
Temperature
295.1
Pulse Sequence
hsqcedetgpsisp2.4
Number of Scans
4
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2135
Acquisition Date
2018-02-17T17:28:15
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4795.4, 16611.3)
Lowest Frequency
(-514.0, -1261.0)
Nucleus
(1H, 13C)
Acquired Size
(1024, 180)
Spectral Size
(1024, 1024)
MeO
Me
Me
Me
OHC
Br
(±)-S3
ppm

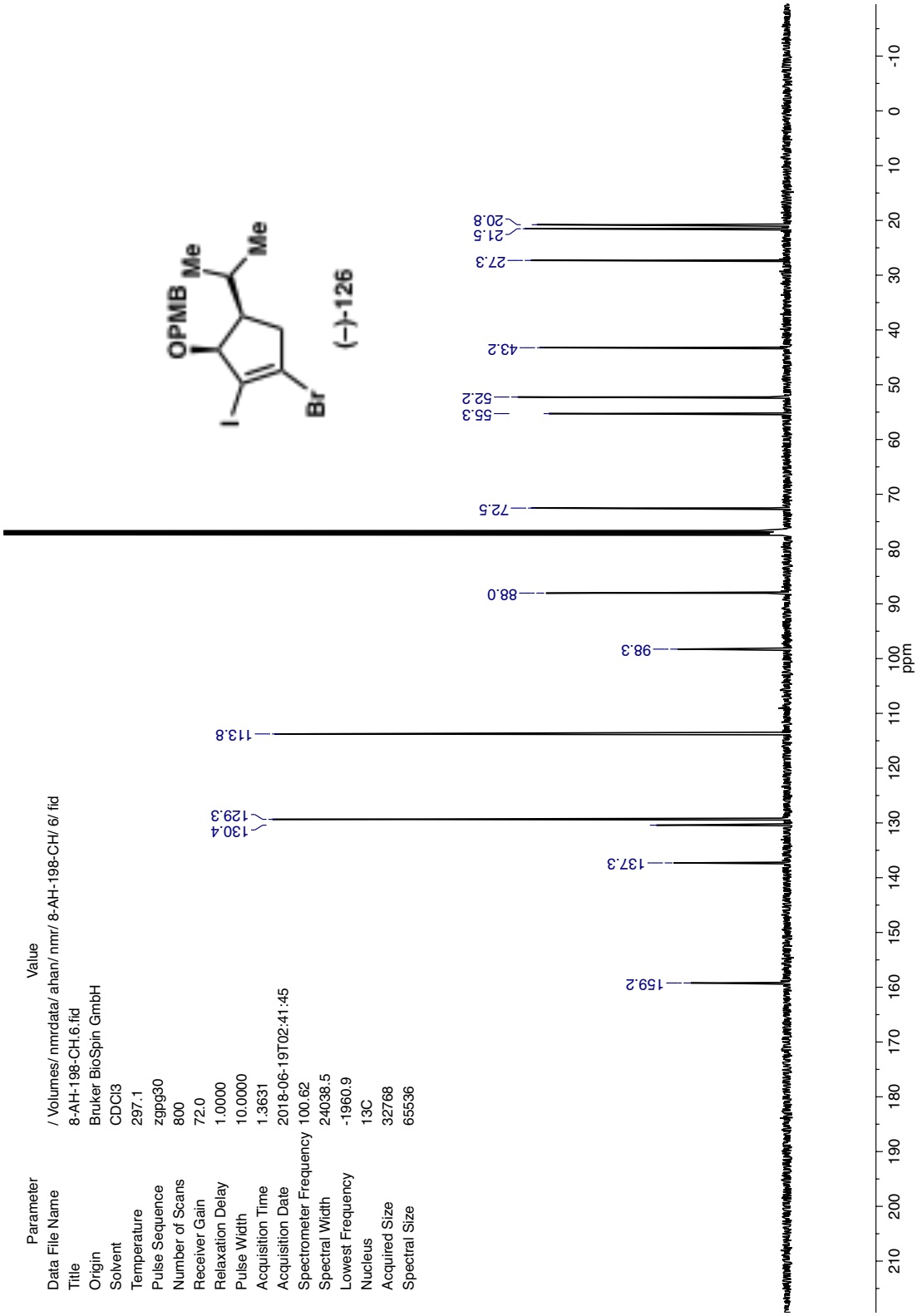

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-168-P/ 3/ ser
Title 8-AH-168-P.3.ser
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.1
Pulse Sequence hmbcetgpl3nd
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.4260
Acquisition Date 2018-02-17T17:43:53
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4807.7, 22321.4)
Lowest Frequency (-160.0, -1114.6)
Nucleus (1H, 13C)
Acquired Size (2048, 256)
Spectral Size (2048, 1024)
MeO
Me
Me
OHC
Br
(±)-S3
ppm


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-075-CH/ 1/ fid
Title
9-AH-075-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zg30
Number of Scans
2
Receiver Gain
72.0
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-08-27T10:54:41
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.6
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
OH
Me
Me
I
Br
(−)-122
(52% yield, 89% ee)
1.00
1.03
1.03
1.04
1.00
0.97
3.04
3.00
ppm

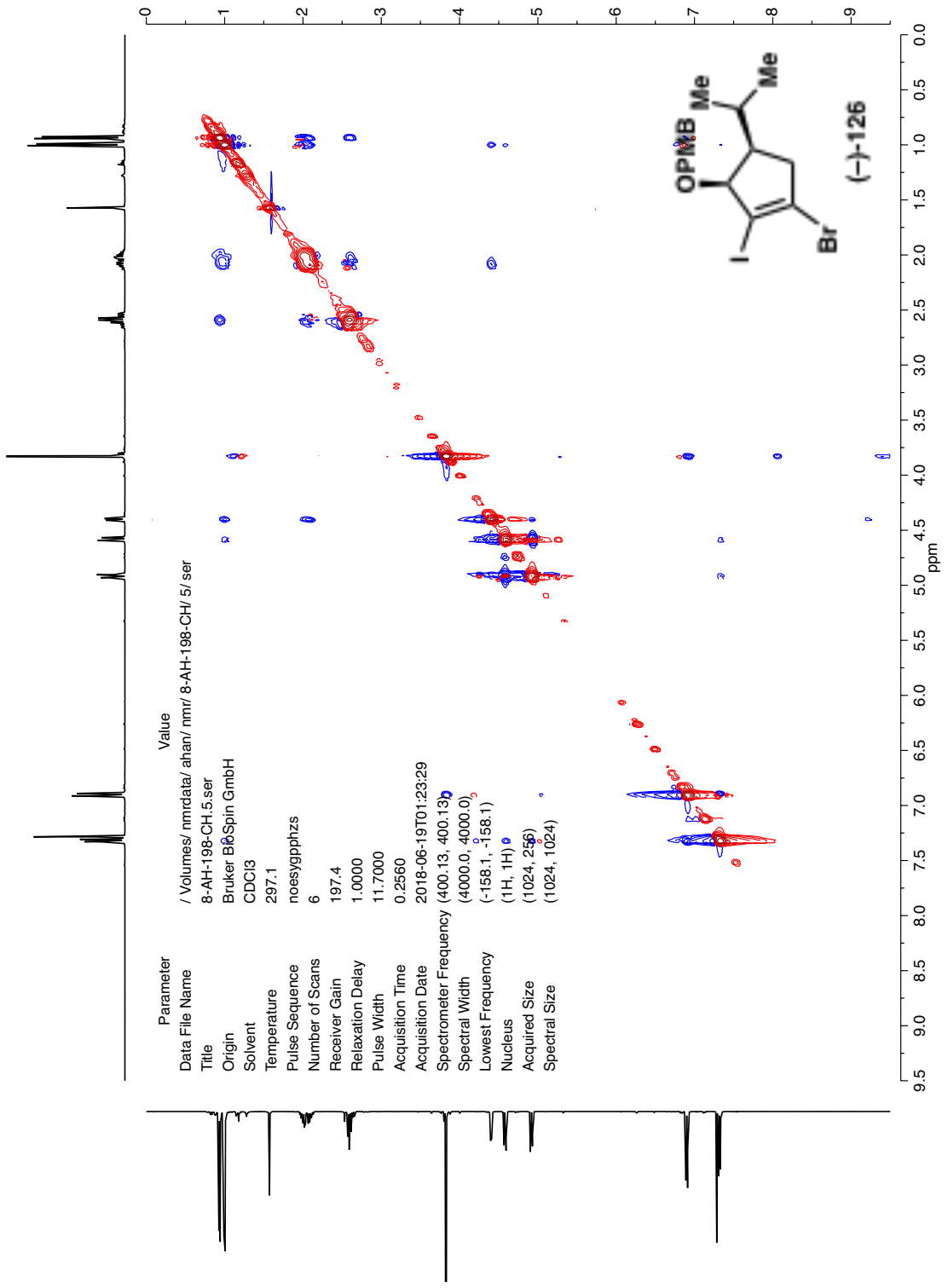

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-075-CH/ 2/ fid
Title 9-AH-075-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 512
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-08-27T11:15:56
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1963.8
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
21.4
21.0
27.8
42.9
51.0
82.1
102.6
136.6
OH
Me
Me
I
Br
(−)-122
(52% yield, 89% ee)
ppm

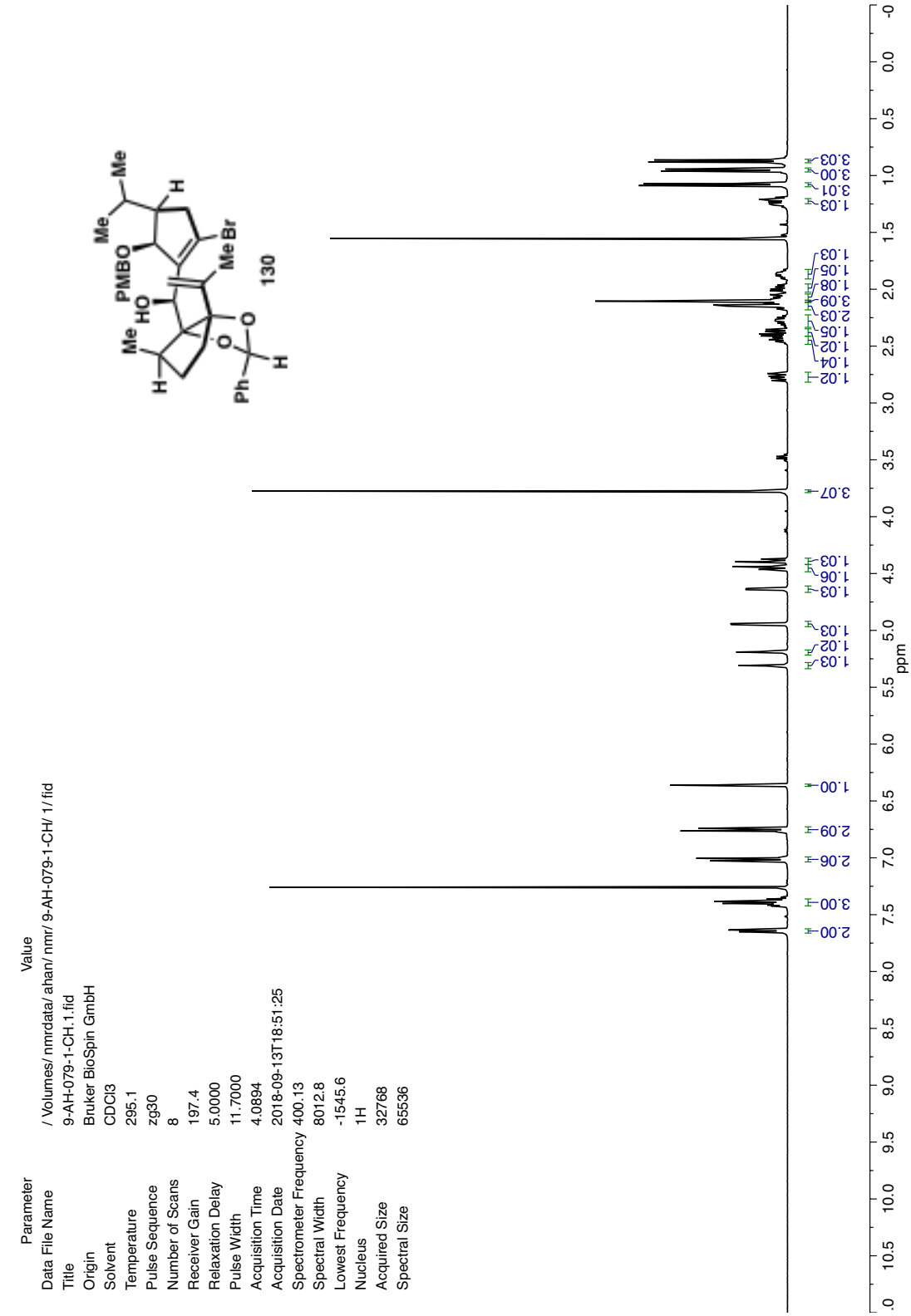


Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-198-CH/ 1/ fid
Title	8-AH-198-CH.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.2
Pulse Sequence	zg30
Number of Scans	16
Receiver Gain	176.8
Relaxation Delay	5.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-06-18T17:48:08
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1545.2
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

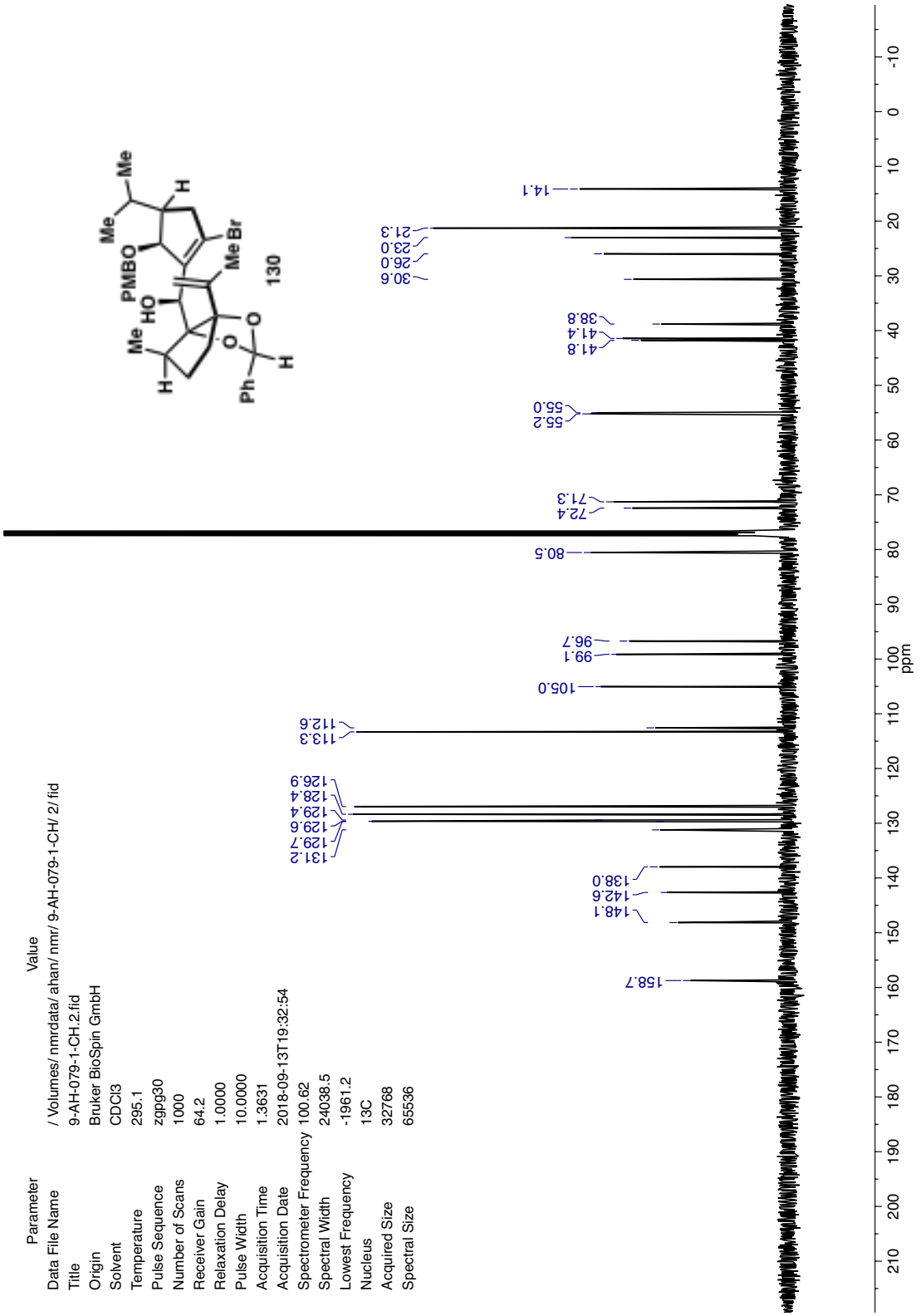


Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 8-AH-198-CH/ 6/ fid
Title	8-AH-198-CH.6.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	297.1
Pulse Sequence	zgpg30
Number of Scans	800
Receiver Gain	72.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-06-19T02:41:45
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1960.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

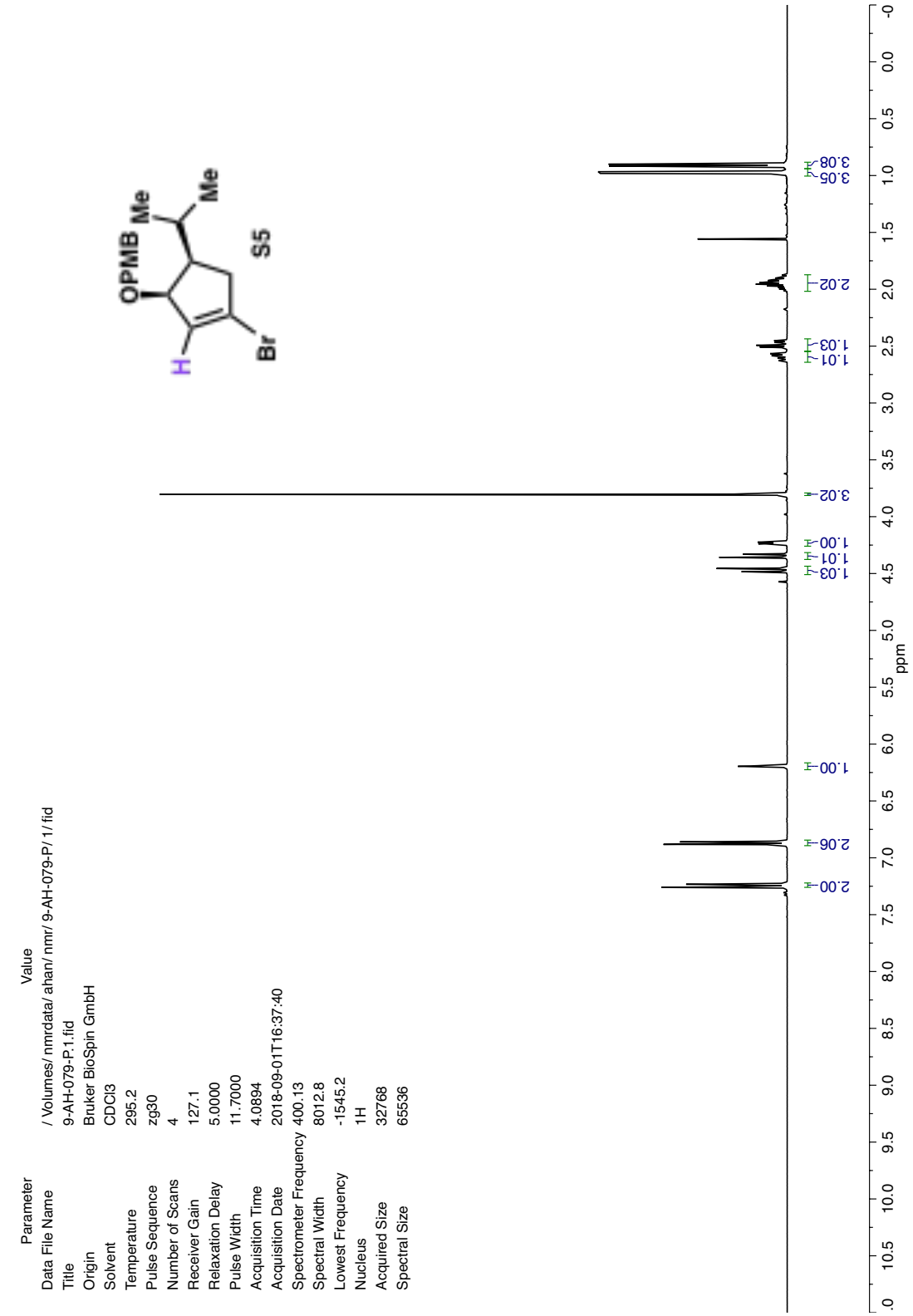

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 8-AH-198-CH/ 5/ ser
Title 8-AH-198-CH.5.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 297.1
Pulse Sequence noesygpphzs
Number of Scans 6
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2018-06-19T01:23:29
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-158.1, -158.1)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
OPMB
Me
Me
Br
I
(−)-126
ppm



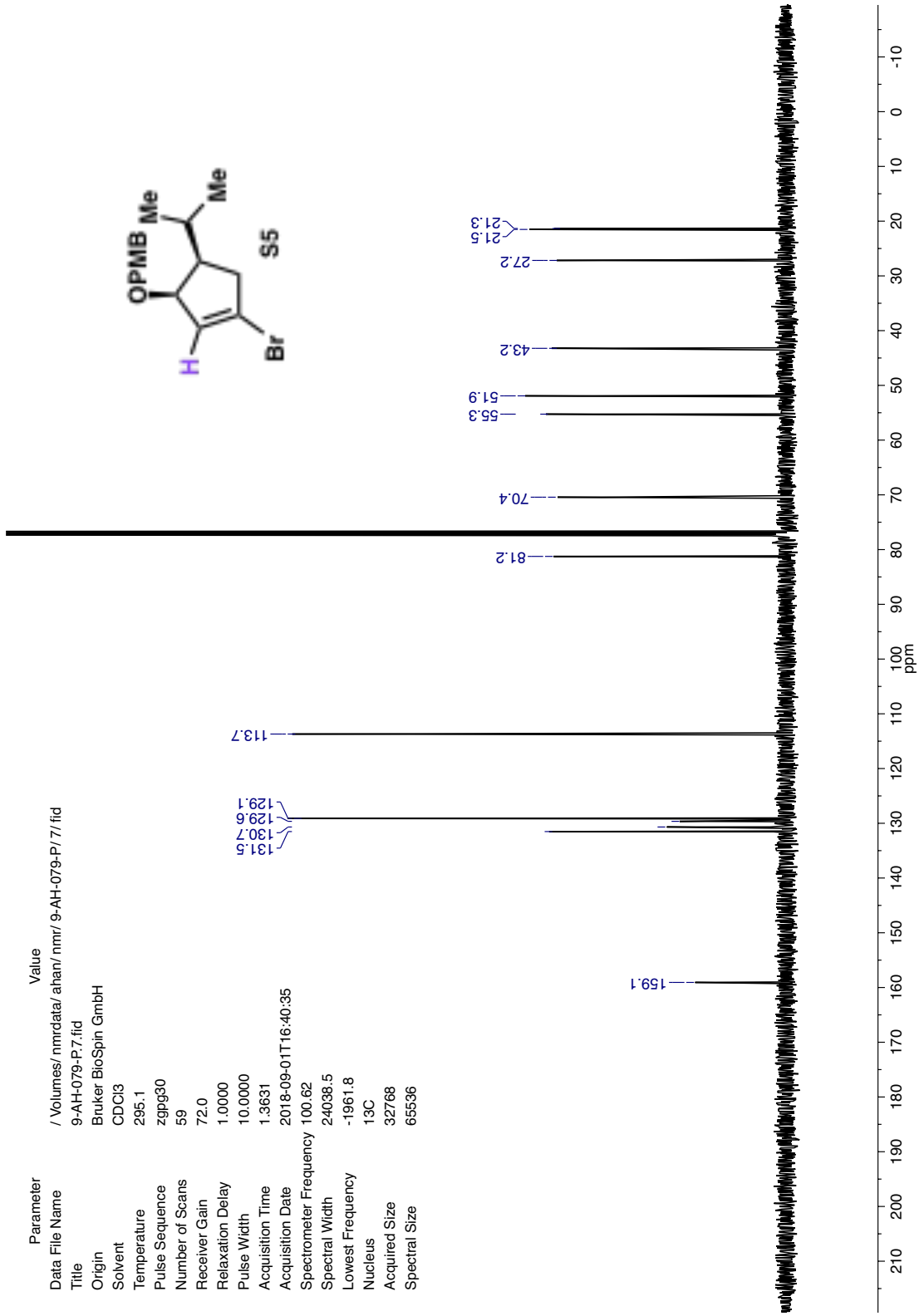
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-079-1-CH/ 1/ fid
Title	9-AH-079-1-CH.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Number of Scans	8
Receiver Gain	197.4
Relaxation Delay	5.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-09-13T18:51:25
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1545.6
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



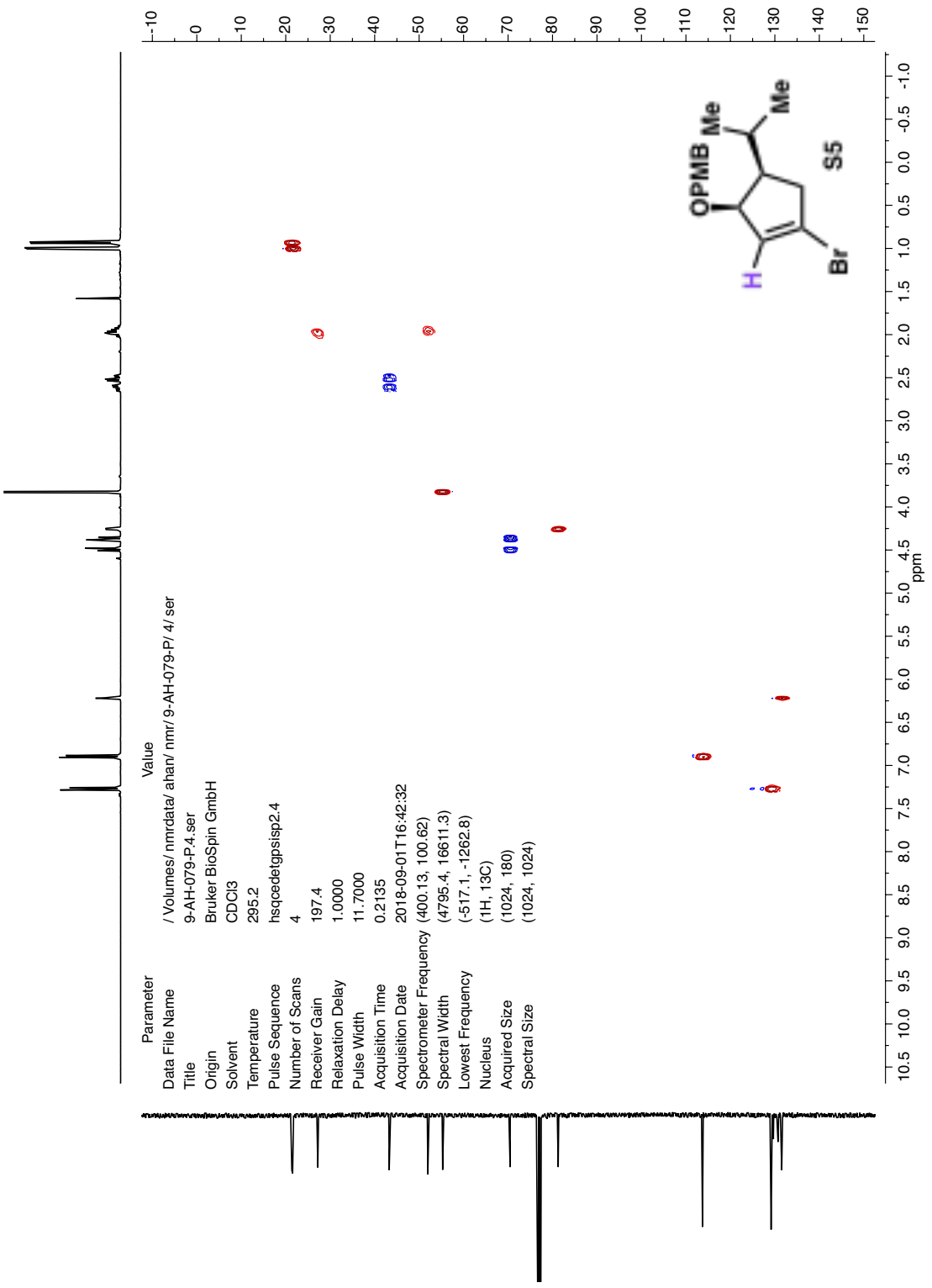
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-079-1-CH/ 2/ fid
Title	9-AH-079-1-CH.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Number of Scans	1000
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-09-13T19:32:54
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1961.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

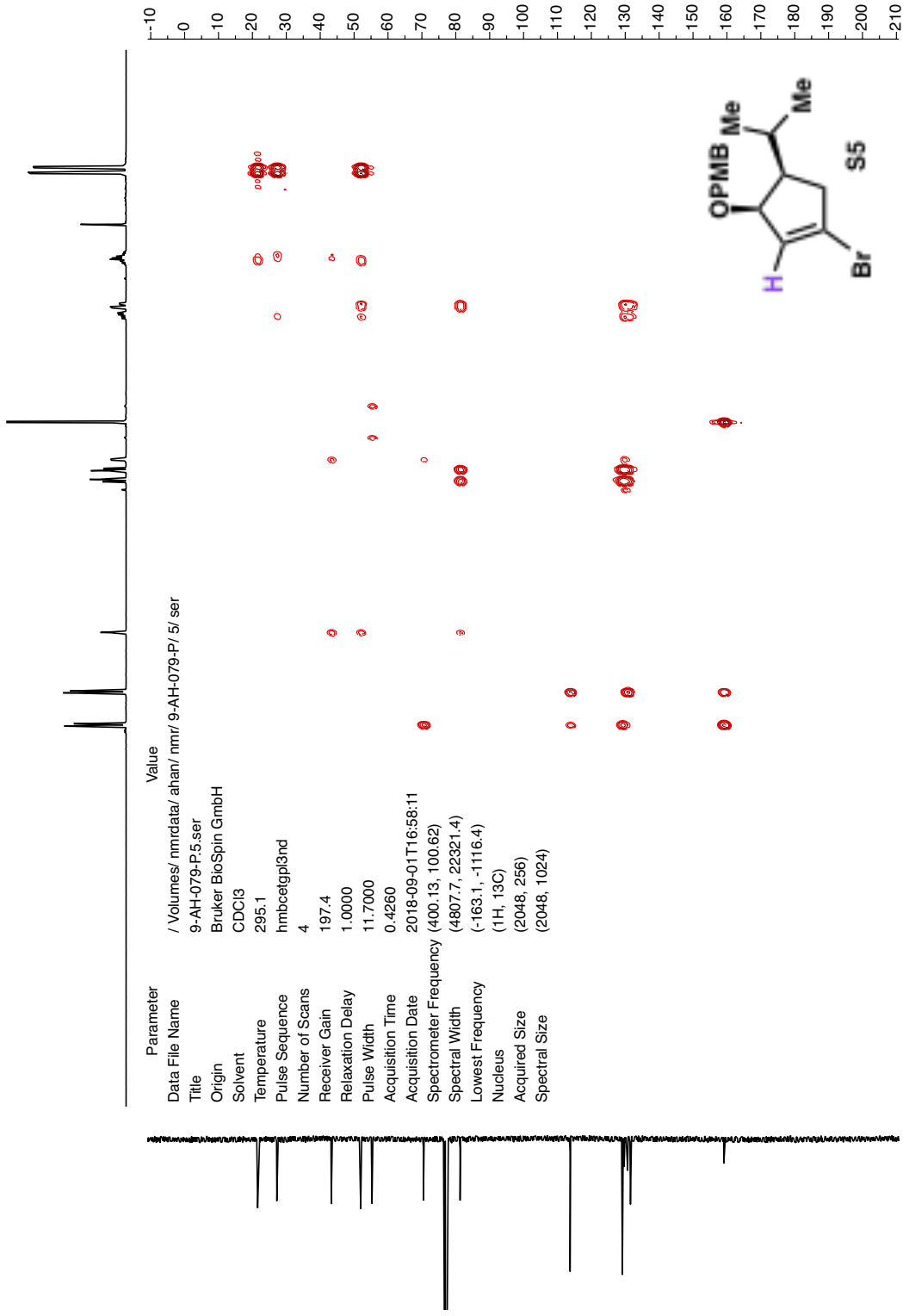


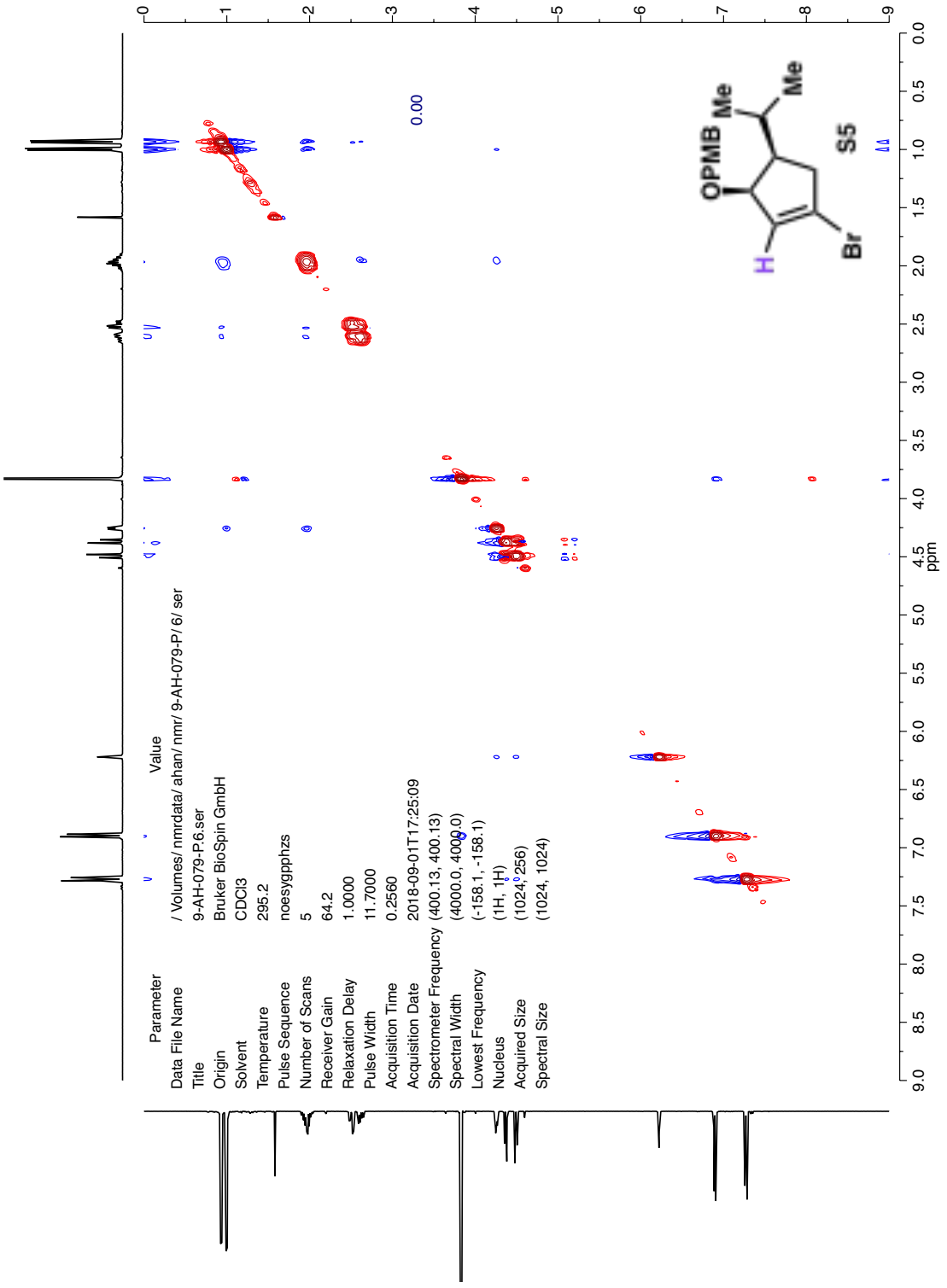
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-079-P/ 1/ fid
Title	9-AH-079-P1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Number of Scans	4
Receiver Gain	127.1
Relaxation Delay	5.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-09-01T16:37:40
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1545.2
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

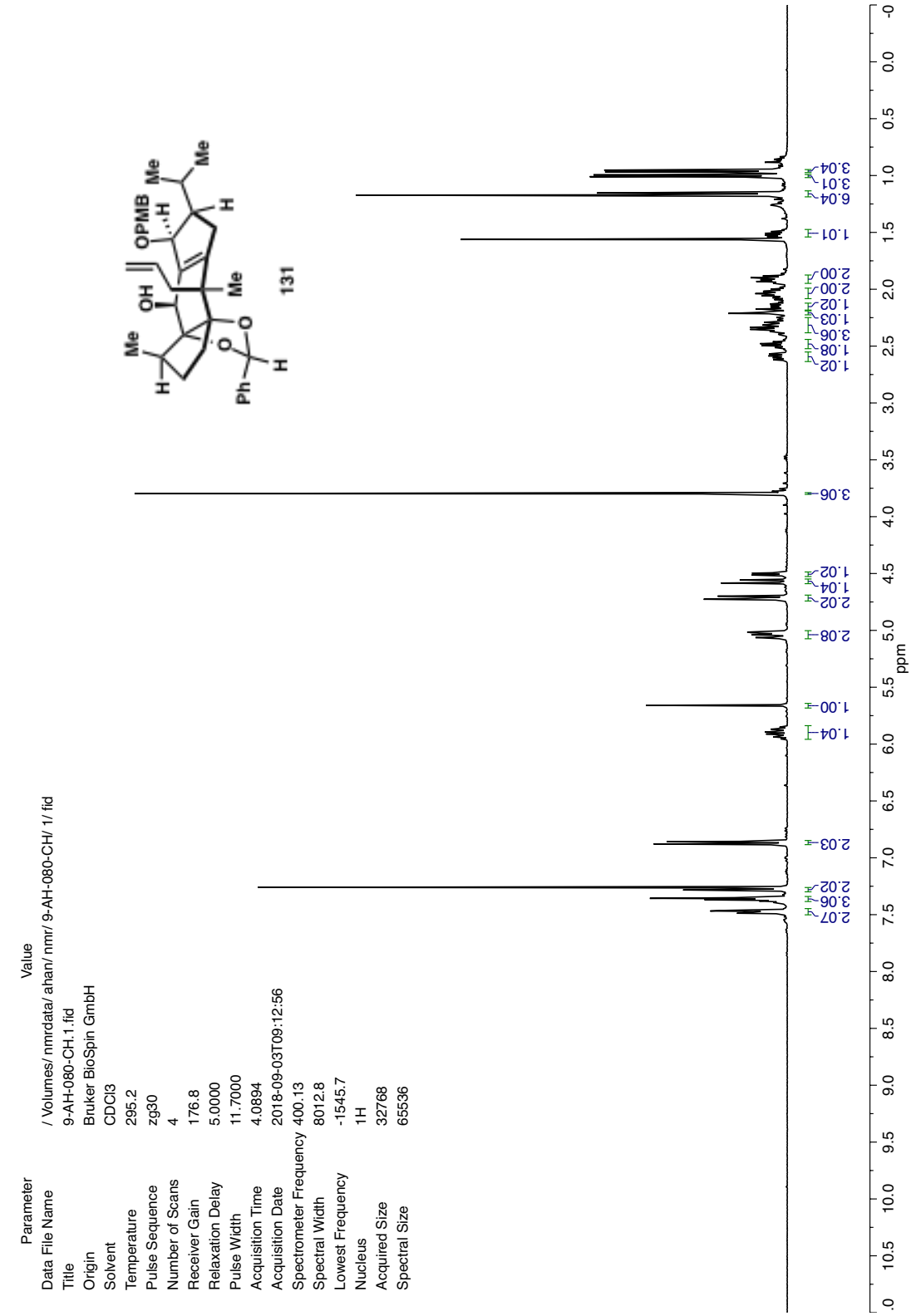


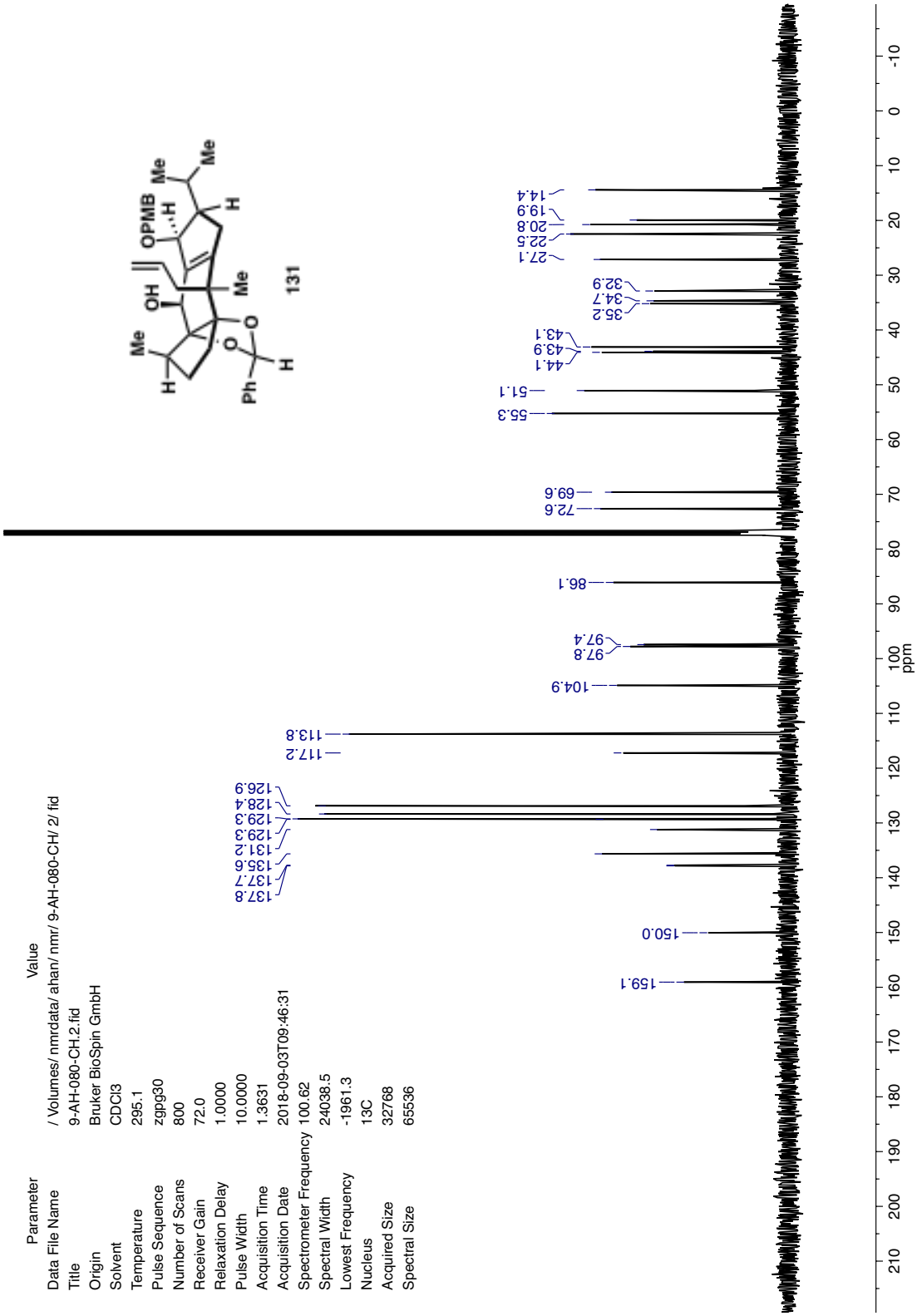
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-079-P/ 7/ fid
Title	9-AH-079-P.7.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Number of Scans	59
Receiver Gain	72.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-09-01T16:40:35
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1961.8
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

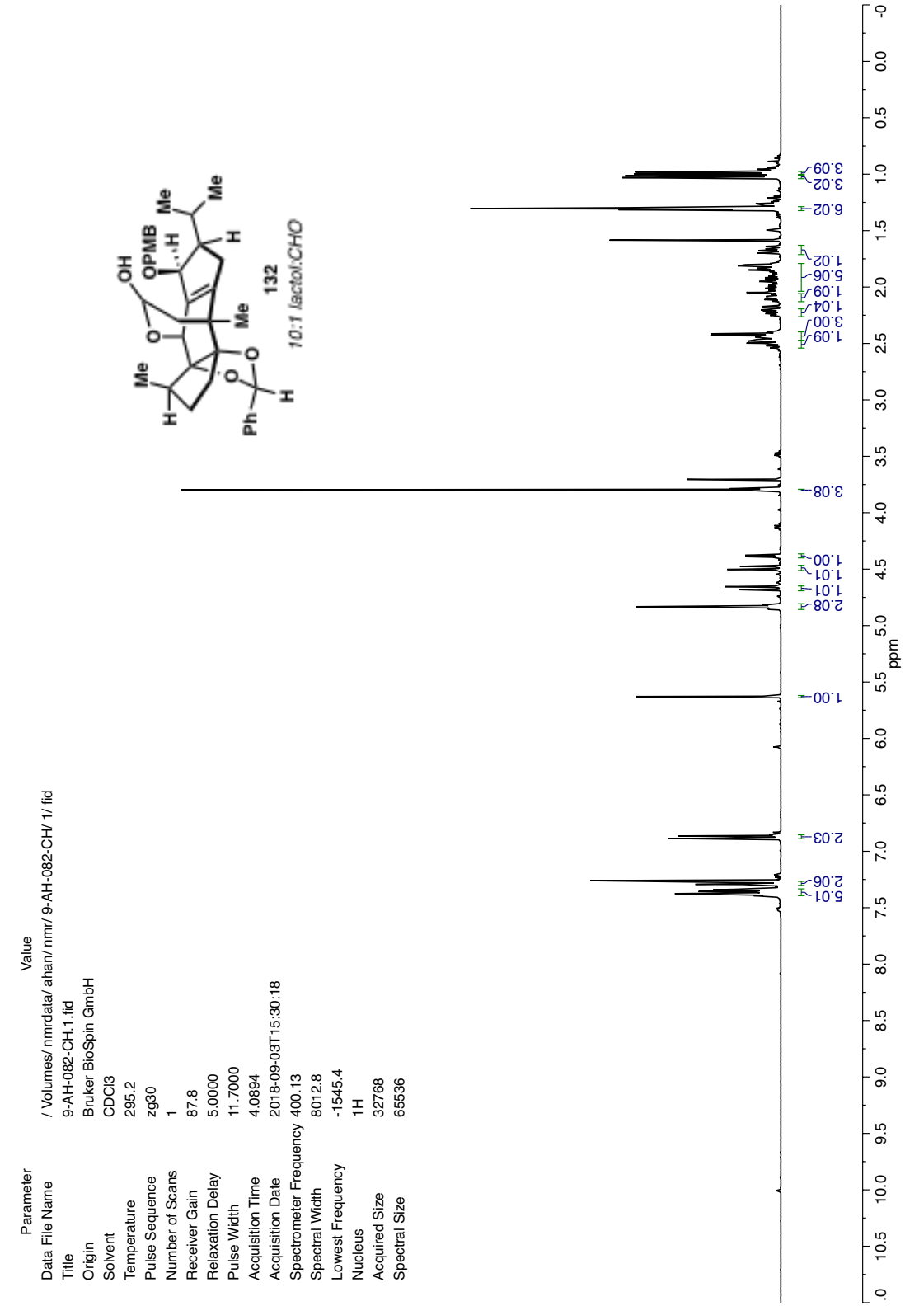

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-079-P/ 4/ ser
Title 9-AH-079-P.4.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence hsqcedetgpsisp2.4
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2135
Acquisition Date 2018-09-01T16:42:32
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4795.4, 16611.3)
Lowest Frequency (-517.1, -1262.8)
Nucleus (1H, 13C)
Acquired Size (1024, 180)
Spectral Size (1024, 1024)
OPMB
Me
Me
H
Br
S5
ppm

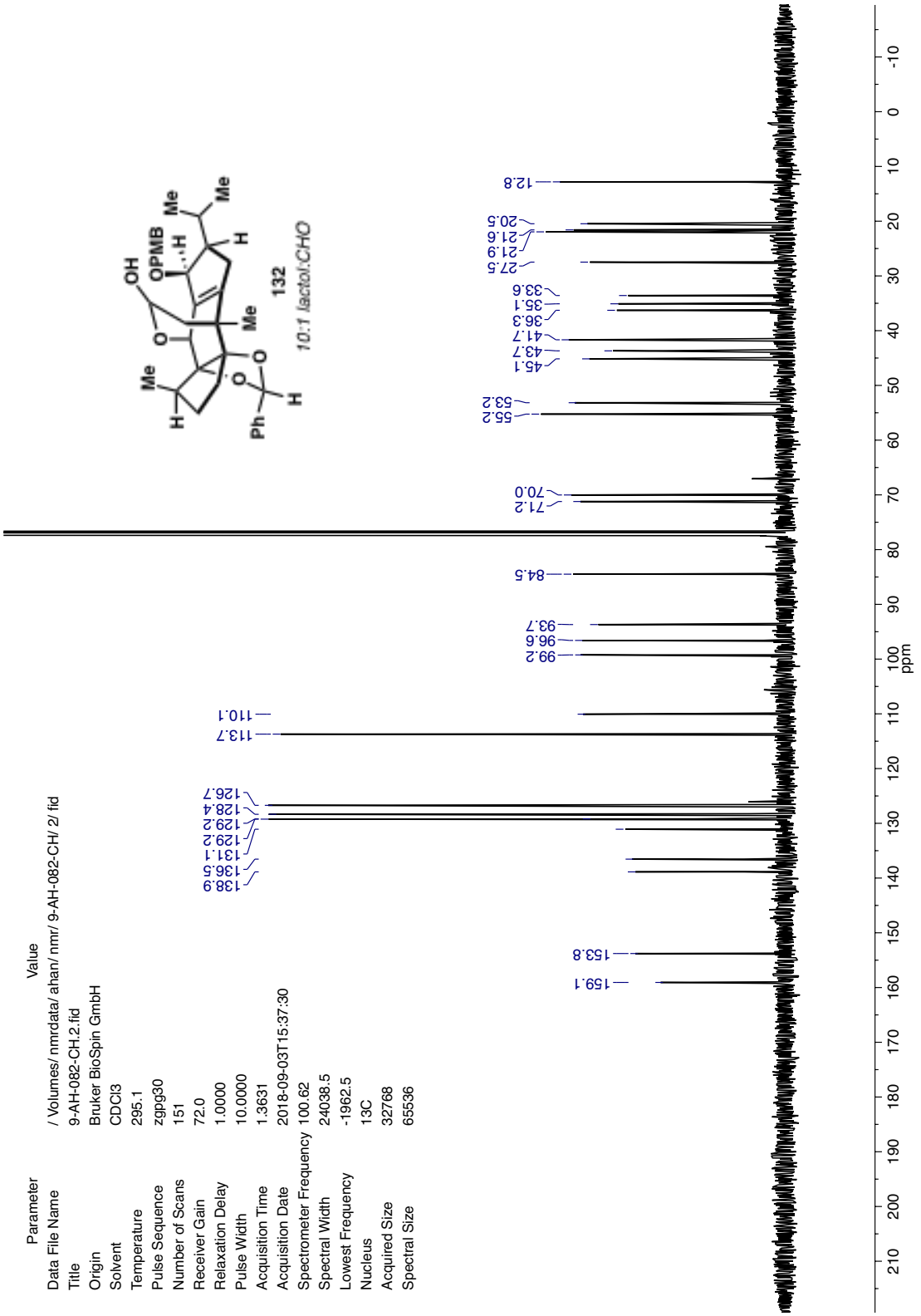

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-079-P/ 5/ ser
Title 9-AH-079-P.5.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence hmbcetgpl3nd
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.4260
Acquisition Date 2018-09-01T16:58:11
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4807.7, 22321.4)
Lowest Frequency (-163.1, -1116.4)
Nucleus (1H, 13C)
Acquired Size (2048, 256)
Spectral Size (2048, 1024)
OPMB
Me
Me
H
Br
S5
ppm

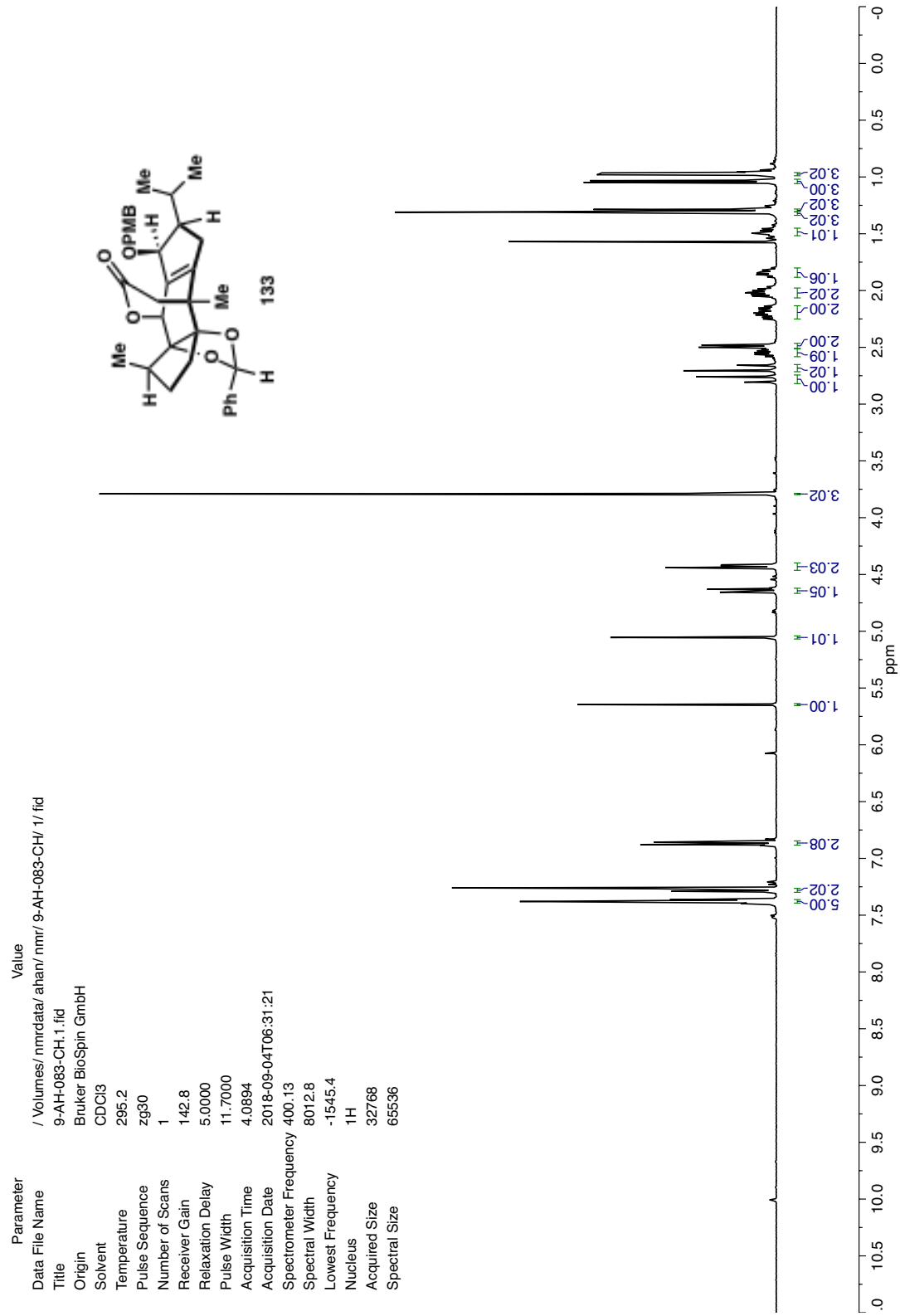

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-079-P/ 6/ ser
Title 9-AH-079-P.6.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence noesygpphzs
Number of Scans 5
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2018-09-01T17:25:09
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-158.1, -158.1)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
0.00
OPMB
Me
Me
H
Br
S5
ppm

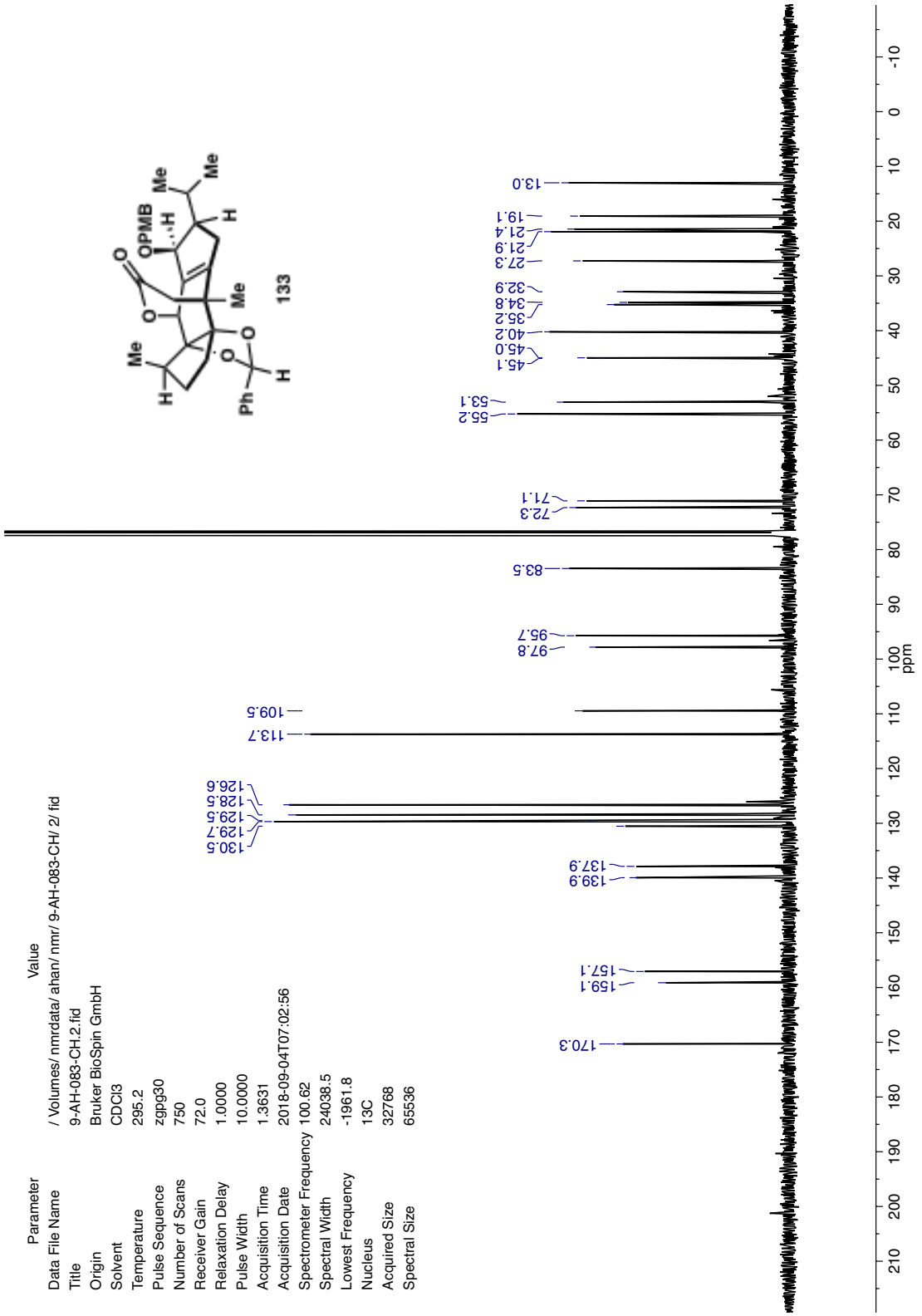

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-080-CH/ 1/ fid
Title 9-AH-080-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 4
Receiver Gain 176.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-03T09:12:56
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.7
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
OPMB
OH
Me
Ph
131
ppm

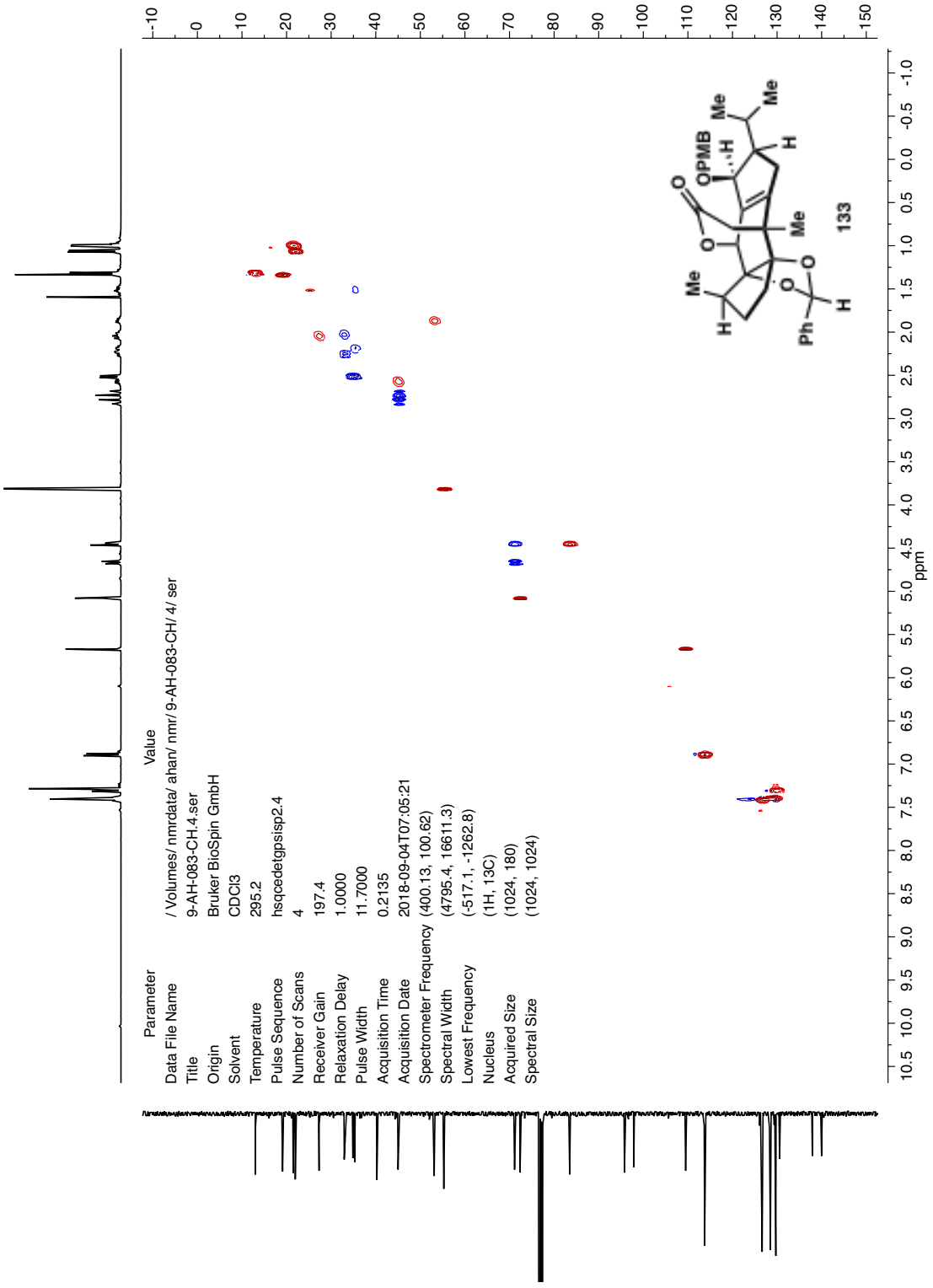

Me
Me
H
OPMB
H
OH
Me
Me
O
O
Ph
H
H
131
159.1
150.0
137.8
137.7
135.6
131.2
129.3
129.3
128.4
126.9
117.2
113.8
104.9
97.8
97.4
86.1
72.6
69.6
55.3
51.1
44.1
43.9
43.1
35.2
34.7
32.9
27.1
22.5
20.8
19.9
14.4
Value
Parameter
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-080-CH/ 2/ fid
Title 9-AH-080-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 800
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-03T09:46:31
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.3
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
ppm

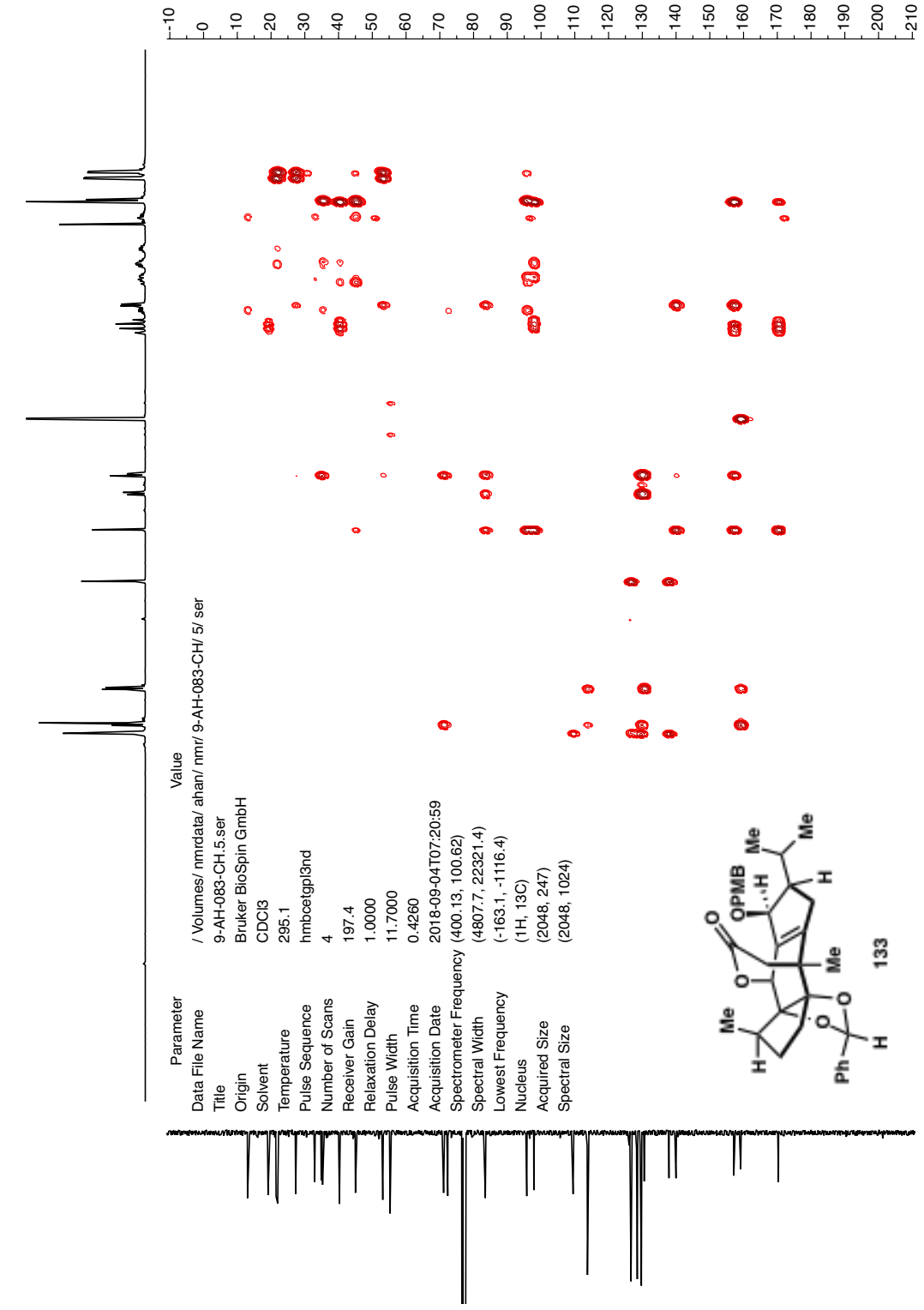

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-082-CH/ 1/ fid
Title 9-AH-082-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 87.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-03T15:30:18
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
OH
OPMB
Me
Me
Me
Me
H
H
H
O
O
O
O
Ph
132
10:1 lactol:CHO
5.01
2.06
2.03
1.00
2.08
1.01
1.01
1.00
3.08
1.00
3.00
1.04
1.09
5.06
1.02
6.02
3.02
3.09
ppm

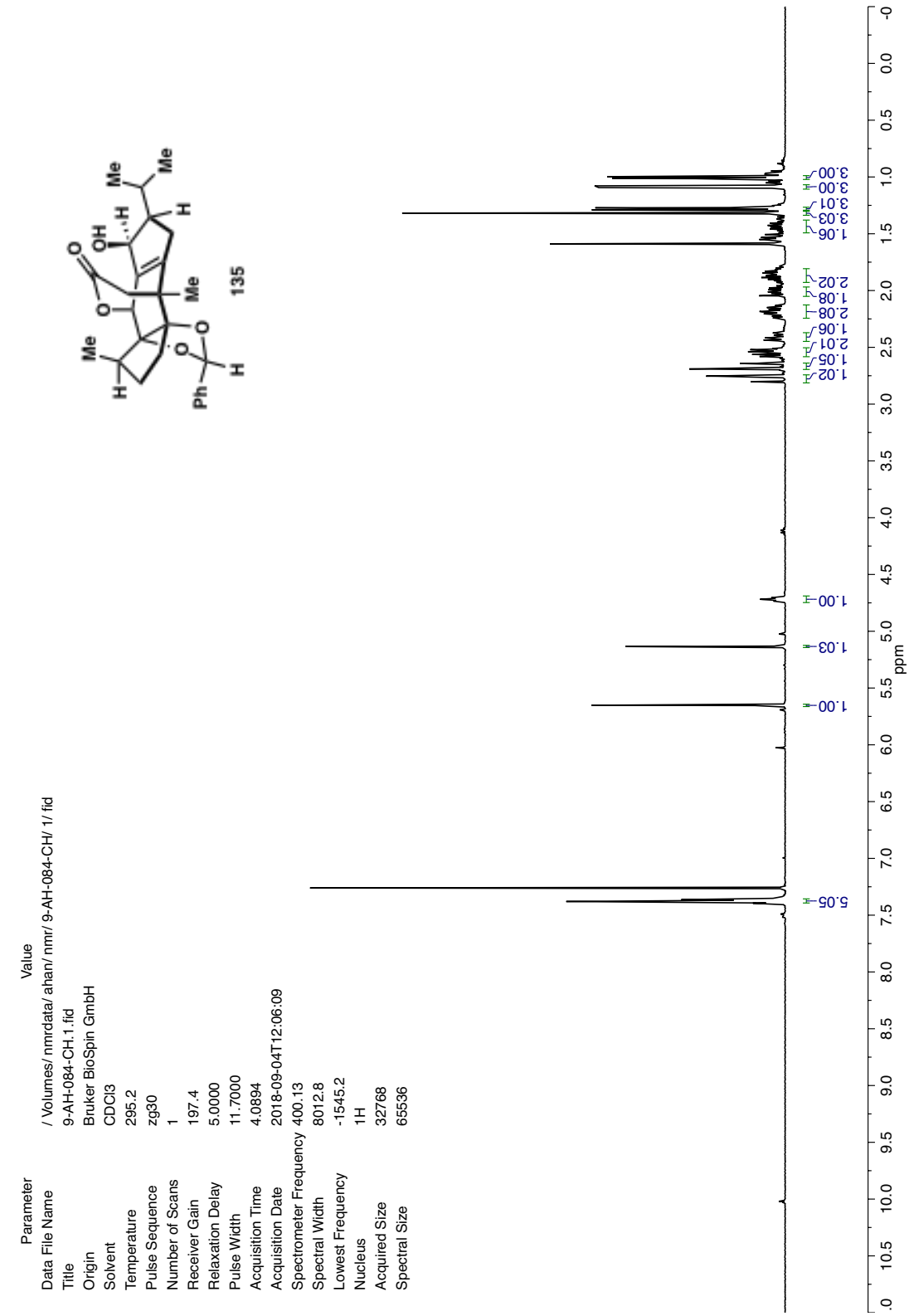

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-082-CH/ 2/ fid
Title 9-AH-082-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 151
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-03T15:37:30
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1962.5
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
OH
OPMB
Me
Me
Me
H
H
Me
O
O
O
O
Ph
H
132
10:1 lactol:CHO
12.8
20.5
21.6
21.9
27.5
33.6
35.1
36.3
41.7
43.7
45.1
53.2
55.2
70.0
71.2
84.5
93.7
96.6
99.2
110.1
113.7
126.7
128.4
129.2
129.2
131.1
136.5
138.9
153.8
159.1
ppm

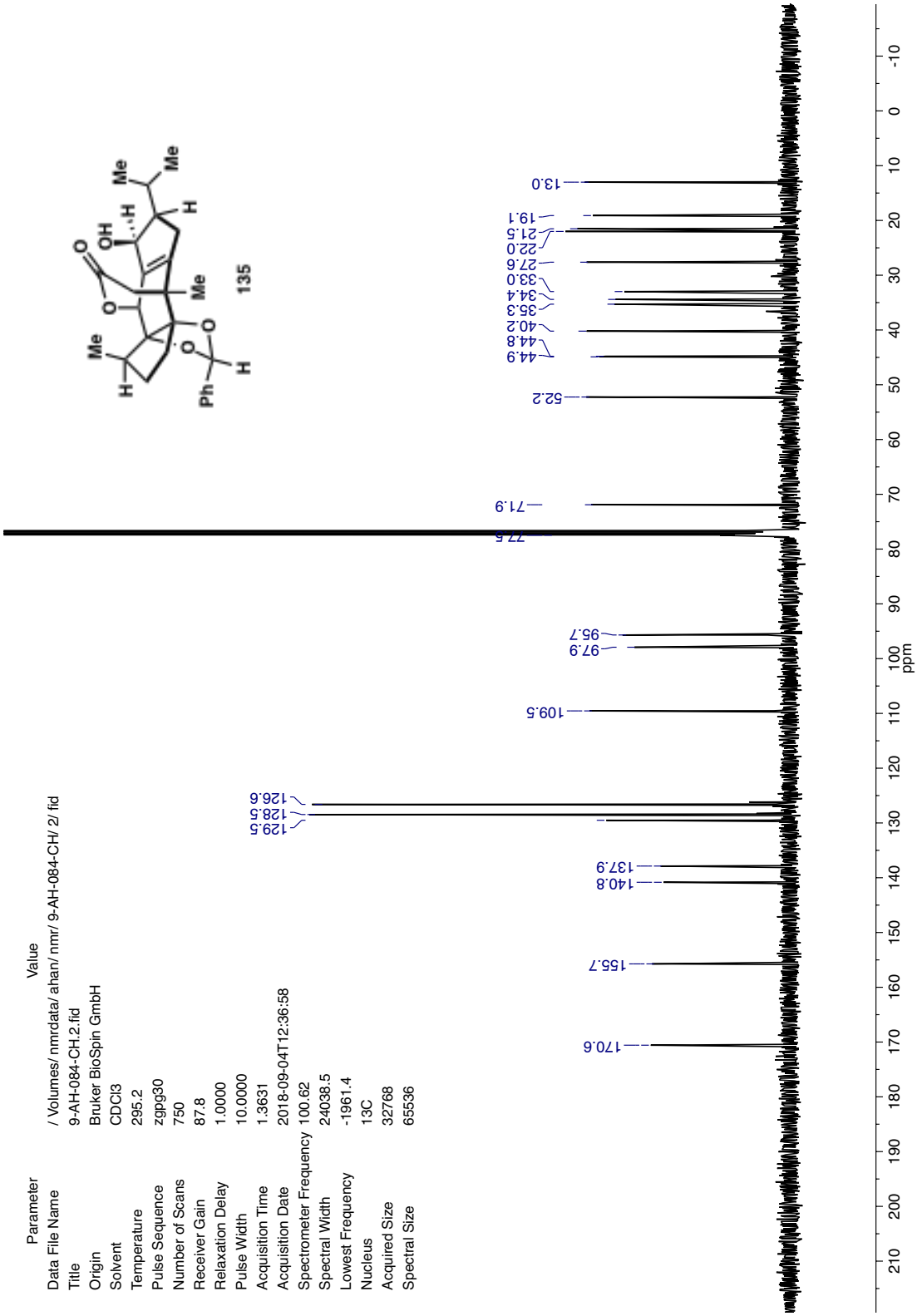

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-083-CH/ 1/ fid
Title 9-AH-083-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 142.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-04T06:31:21
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
OPMB
Me
Me
Me
Me
Ph
H
133
5.00
2.02
2.08
1.00
1.01
1.05
2.03
3.02
1.00
1.02
1.09
2.00
2.00
2.02
1.06
1.01
3.02
3.00
3.02
3.02
ppm

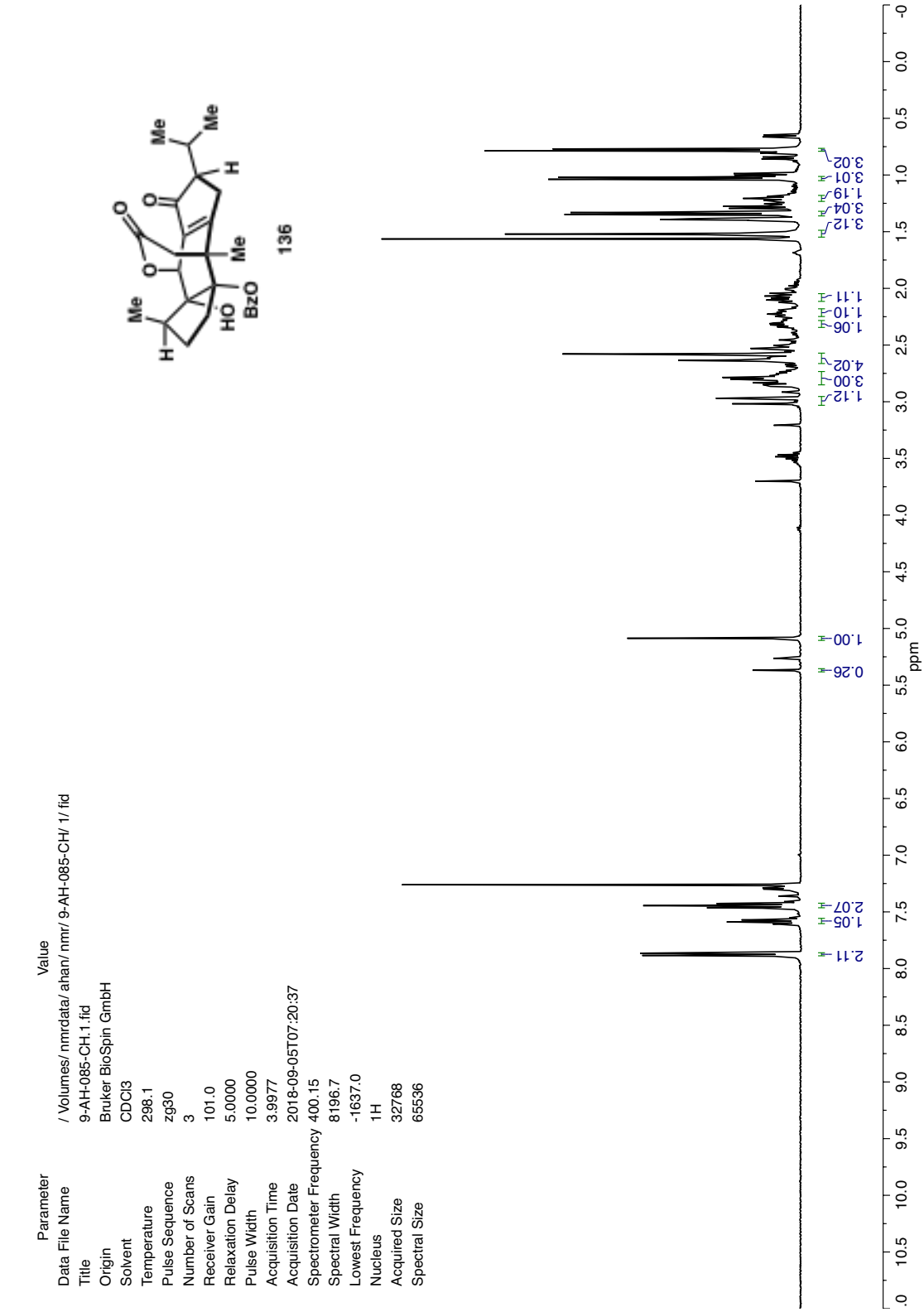

OPMB
Me
Me
Me
Me
H
H
H
O
O
O
O
O
Ph
133
13.0
19.1
21.4
21.9
27.3
32.9
34.8
35.2
40.2
45.0
45.1
53.1
55.2
71.1
72.3
83.5
95.7
97.8
109.5
113.7
126.6
128.5
129.5
129.7
130.5
137.9
139.9
157.1
159.1
170.3
Value
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-083-CH/ 2/ fid
9-AH-083-CH.2.fid
Bruker BioSpin GmbH
CDCl3
295.2
zgpg30
750
72.0
1.0000
10.0000
1.3631
2018-09-04T07:02:56
100.62
24038.5
-1961.8
13C
32768
65536
Parameter
Data File Name
Title
Origin
Solvent
Temperature
Pulse Sequence
Number of Scans
Receiver Gain
Relaxation Delay
Pulse Width
Acquisition Time
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size
ppm

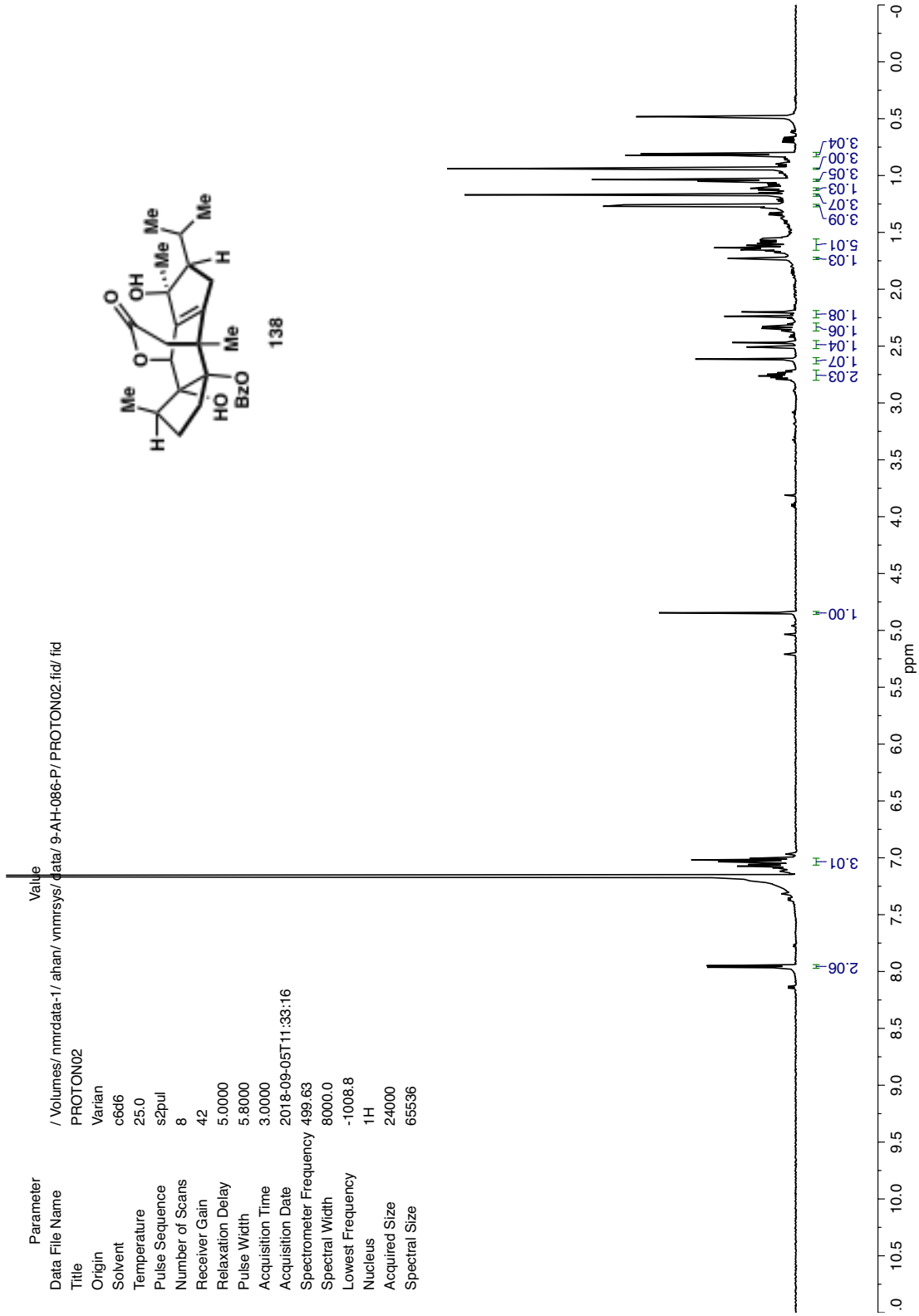

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-083-CH/ 4/ ser
Title 9-AH-083-CH.4.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence hsqcedetgpsisp2.4
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2135
Acquisition Date 2018-09-04T07:05:21
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4795.4, 16611.3)
Lowest Frequency (-517.1, -1262.8)
Nucleus (1H, 13C)
Acquired Size (1024, 180)
Spectral Size (1024, 1024)
OPMB
Me
Me
Me
Me
Ph
H
H
H
133
ppm

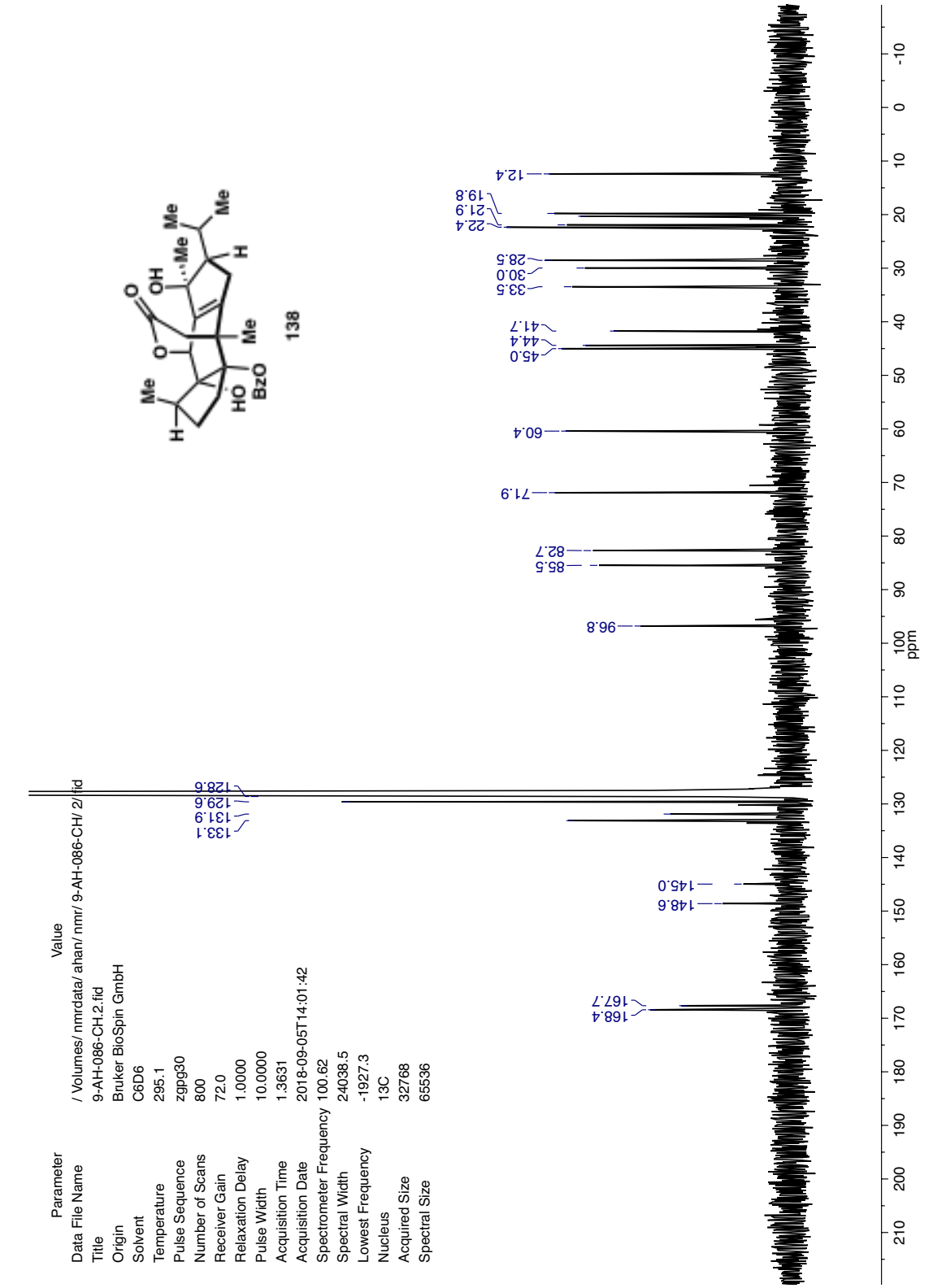

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-083-CH/ 5/ ser
Title
9-AH-083-CH.5.ser
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
hmbcetgpl3nd
Number of Scans
4
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.4260
Acquisition Date
2018-09-04T07:20:59
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4807.7, 22321.4)
Lowest Frequency
(-163.1, -1116.4)
Nucleus
(1H, 13C)
Acquired Size
(2048, 247)
Spectral Size
(2048, 1024)
OPMB
Me
Me
Me
Me
H
H
H
Ph
133
ppm

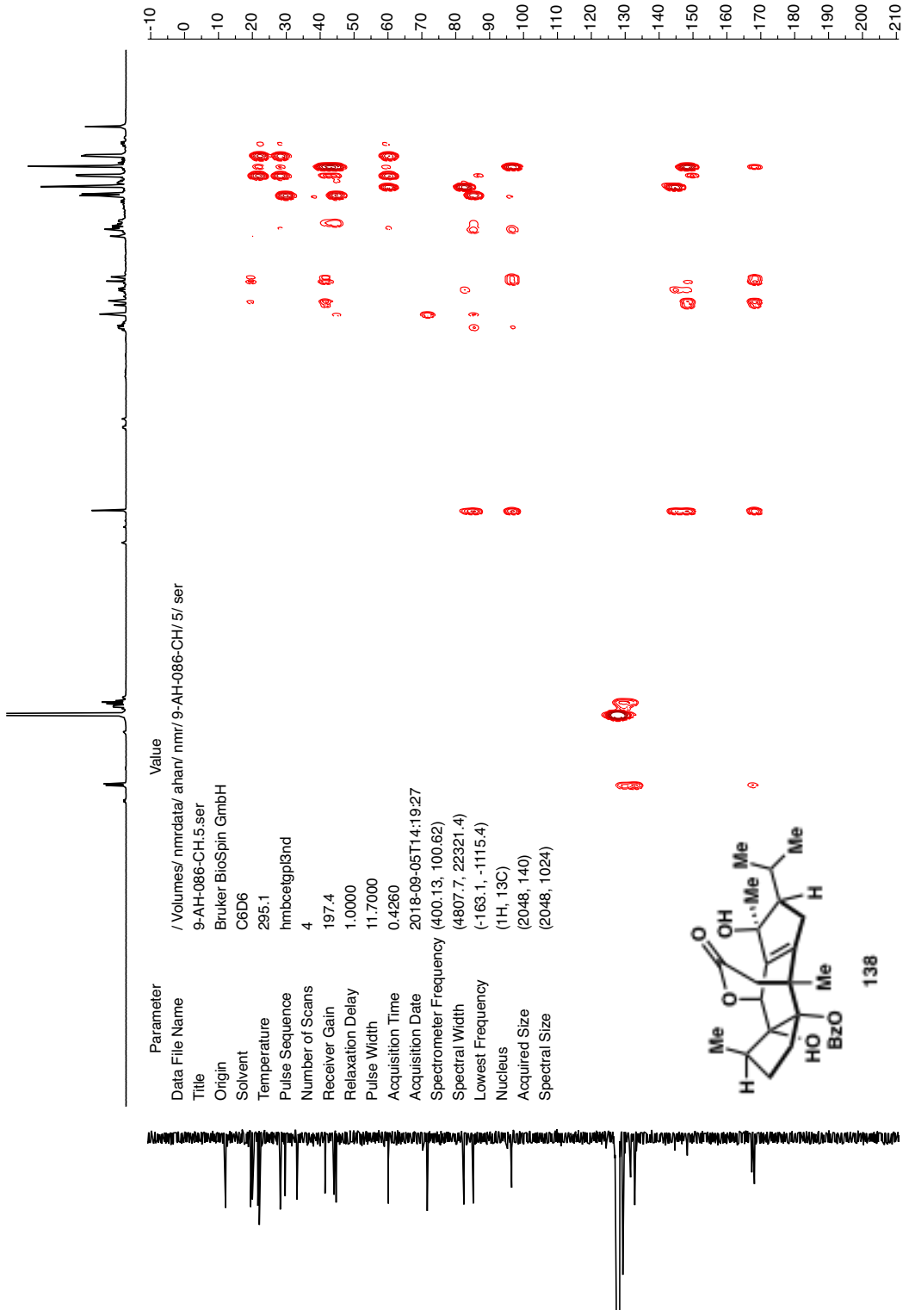

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-084-CH/ 1/ fid
Title
9-AH-084-CH.1.fid
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.2
Pulse Sequence
zg30
Number of Scans
1
Receiver Gain
197.4
Relaxation Delay
5.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-09-04T12:06:09
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.2
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Me
OH
H
Me
H
O
O
O
Me
O
Me
H
O
Ph
H
135
5.05
1.00
1.03
1.00
1.00
1.02
1.05
2.01
1.06
2.08
1.08
2.02
1.06
3.03
3.01
3.00
3.00
ppm
.0
10.5
10.0
9.5
9.0
8.5
8.0
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

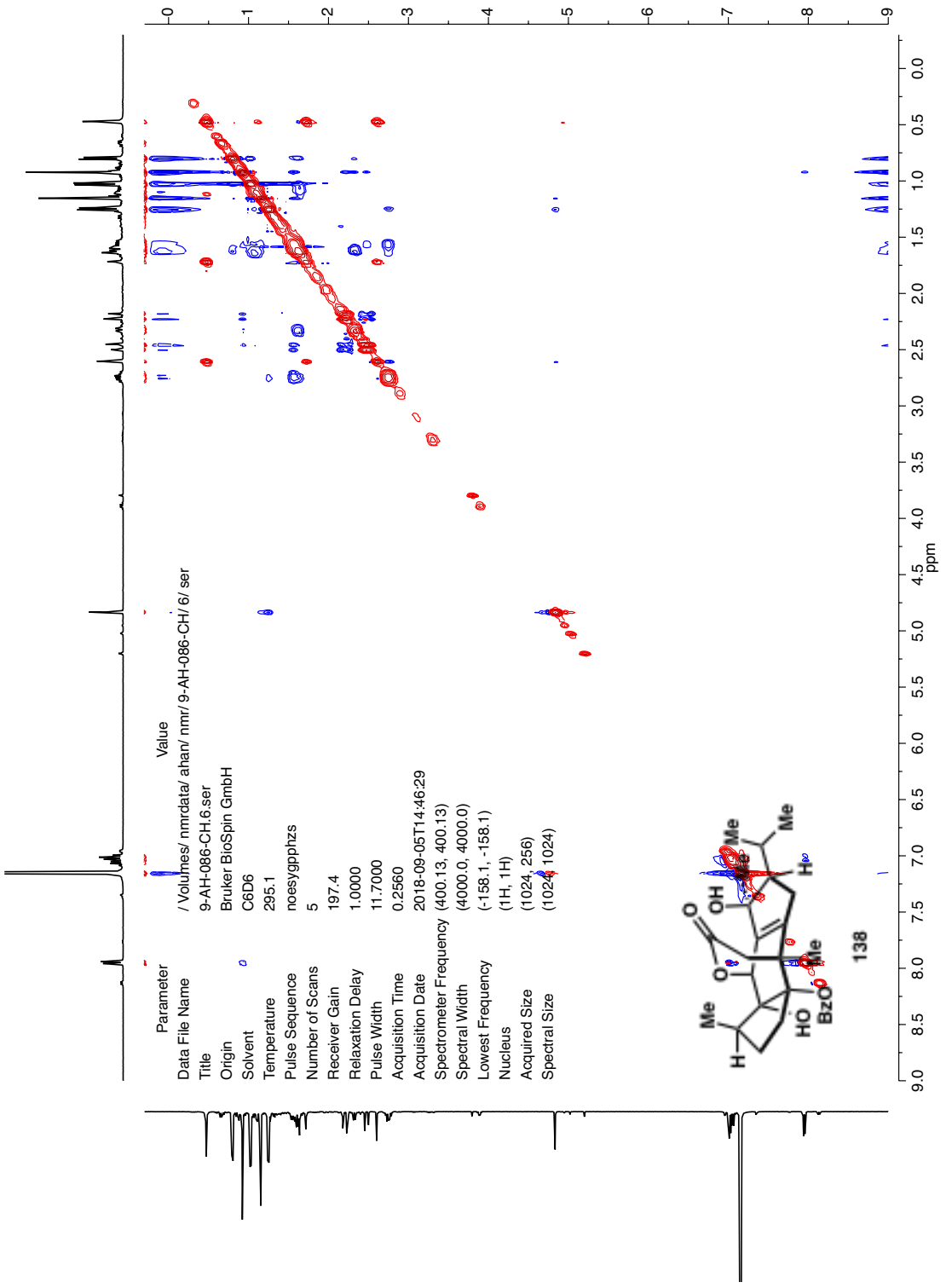

Parameter | Value
Data File Name | / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-084-CH/ 2/ fid
Title | 9-AH-084-CH.2.fid
Origin | Bruker BioSpin GmbH
Solvent | CDCl3
Temperature | 295.2
Pulse Sequence | zgpg30
Number of Scans | 750
Receiver Gain | 87.8
Relaxation Delay | 1.0000
Pulse Width | 10.0000
Acquisition Time | 1.3631
Acquisition Date | 2018-09-04T12:36:58
Spectrometer Frequency | 100.62
Spectral Width | 24038.5
Lowest Frequency | -1961.4
Nucleus | 13C
Acquired Size | 32768
Spectral Size | 65536
13.0
19.1
21.5
22.0
27.6
33.0
34.4
35.3
40.2
44.8
44.9
52.2
71.9
77.5
95.7
97.9
109.5
126.6
128.5
129.5
137.9
140.8
155.7
170.6
ppm

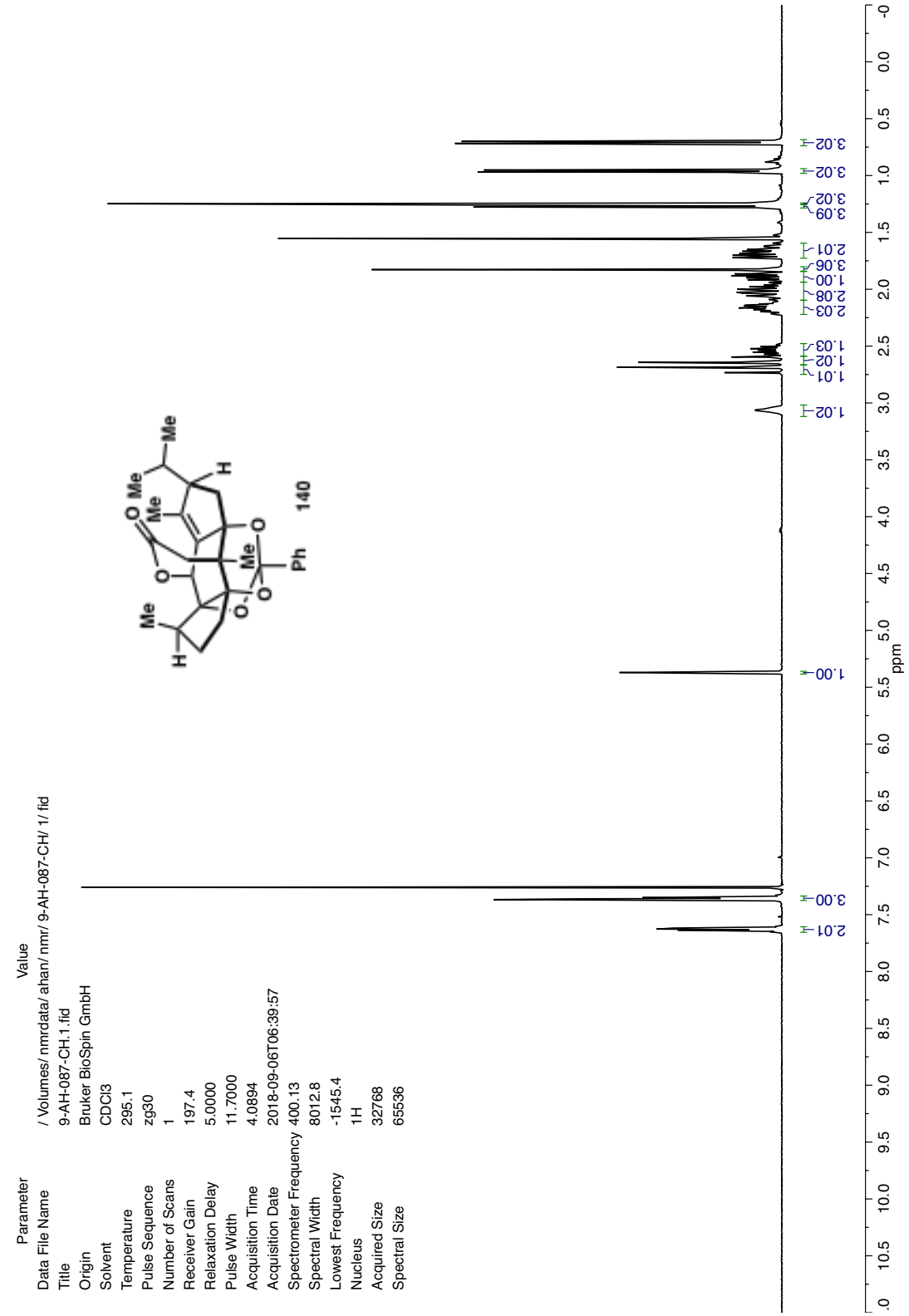

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-085-CH/ 1/ fid
Title 9-AH-085-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 298.1
Pulse Sequence zg30
Number of Scans 3
Receiver Gain 101.0
Relaxation Delay 5.0000
Pulse Width 10.0000
Acquisition Time 3.9977
Acquisition Date 2018-09-05T07:20:37
Spectrometer Frequency 400.15
Spectral Width 8196.7
Lowest Frequency -1637.0
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
Me
Me
H
O
O
O
Me
Me
HO
BzO
H
136
2.11
1.05
2.07
0.26
1.00
1.12
3.00
4.02
1.06
1.10
1.11
3.12
3.04
1.19
3.01
3.02
ppm

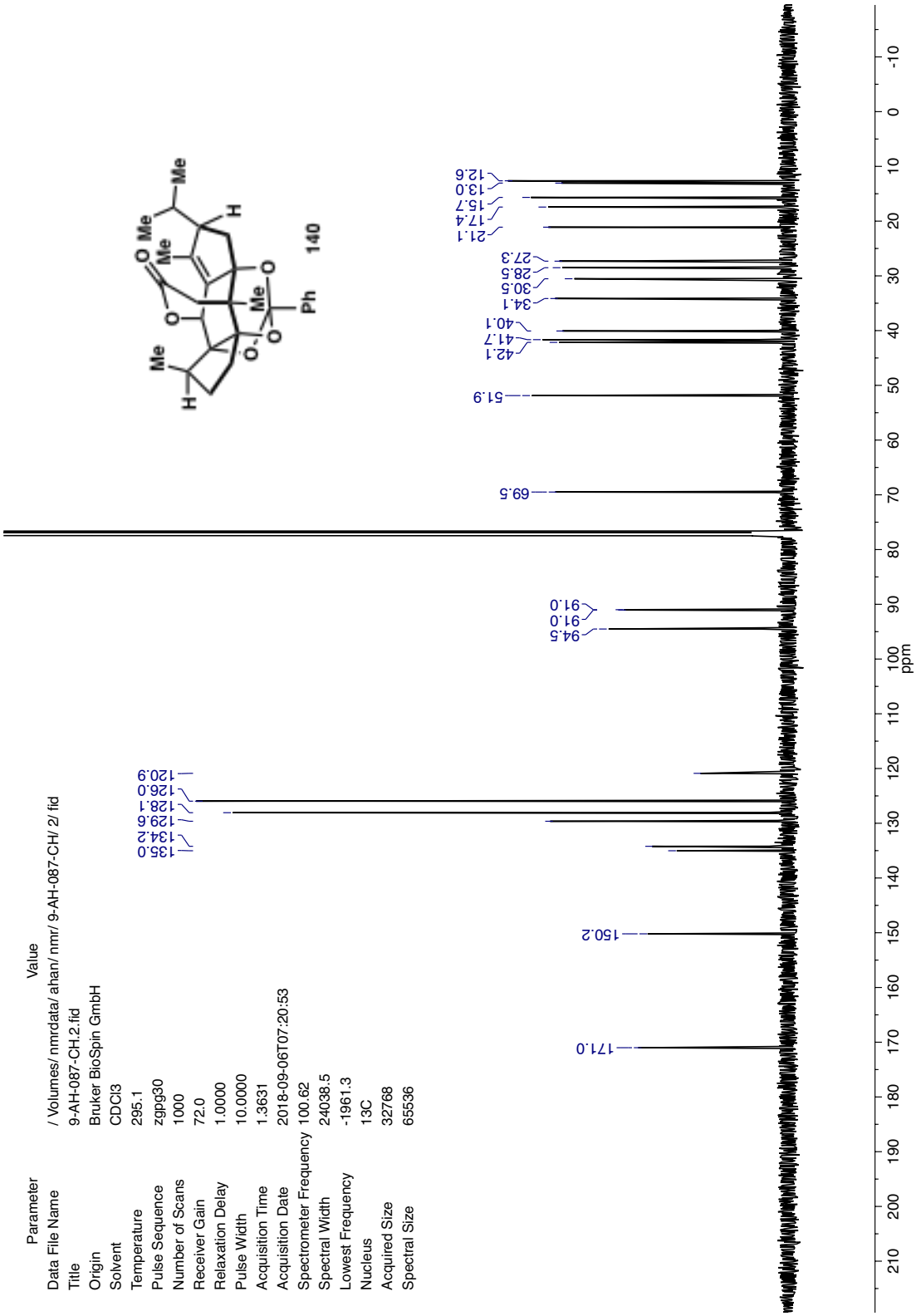

Parameter Value
Data File Name / Volumes/ nmrdata-1/ ahan/ vnmrsys/ data/ 9-AH-086-P/ PROTON02.fid/ fid
Title PROTON02
Origin Varian
Solvent c6d6
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 8
Receiver Gain 42
Relaxation Delay 5.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2018-09-05T11:33:16
Spectrometer Frequency 499.63
Spectral Width 8000.0
Lowest Frequency -1008.8
Nucleus 1H
Acquired Size 24000
Spectral Size 65536
138
2.06
3.01
1.00
2.03
1.07
1.04
1.06
1.08
1.03
5.01
3.09
3.07
1.03
3.05
3.00
3.04
ppm

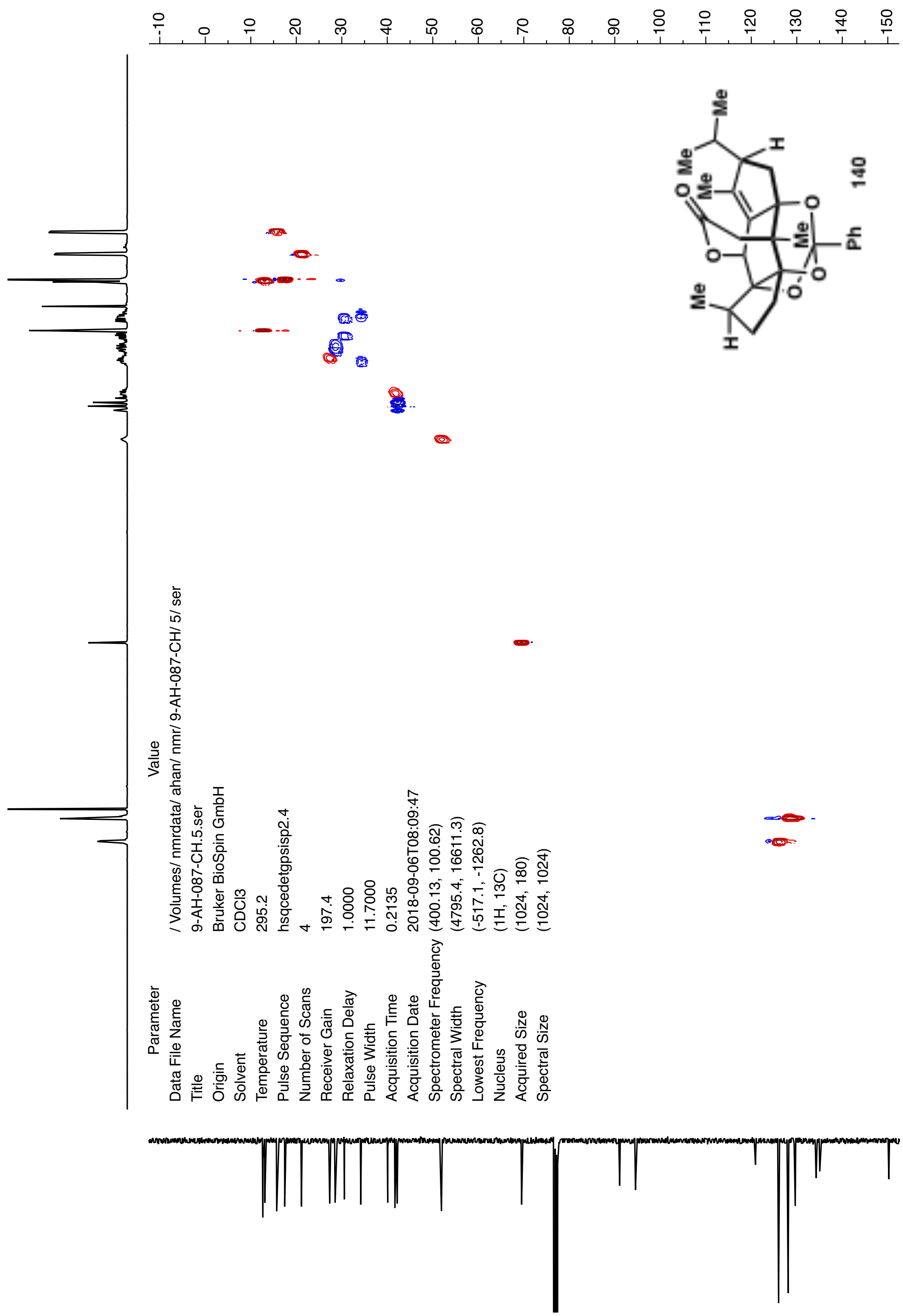

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-086-CH/ 2/ fid
Title 9-AH-086-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 800
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-05T14:01:42
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.3
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
138
12.4
19.8
21.9
22.4
28.5
30.0
33.5
41.7
44.4
45.0
60.4
71.9
82.7
85.5
96.8
128.6
129.6
131.9
133.1
145.0
148.6
167.7
168.4
ppm

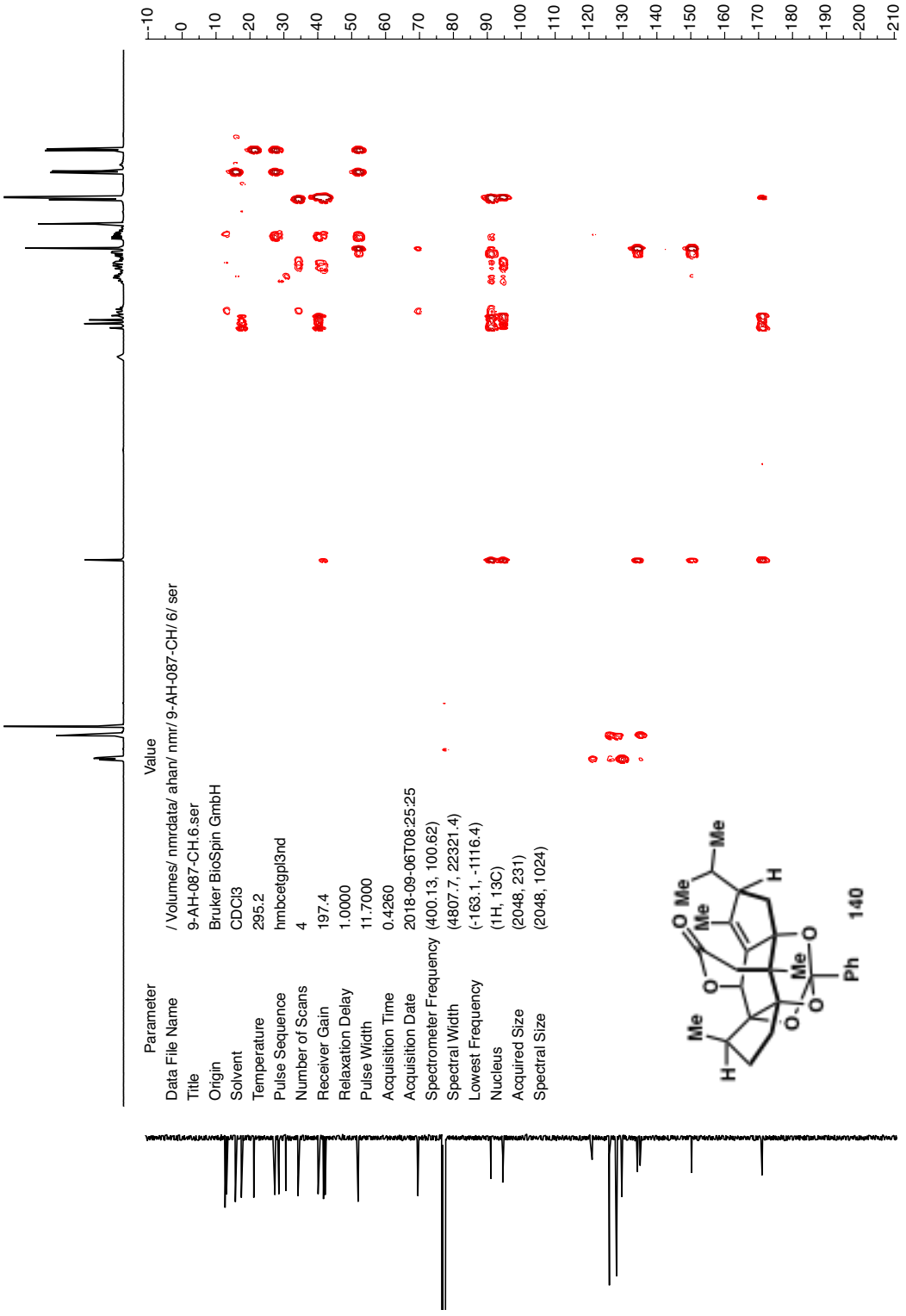

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-086-CH/ 5/ ser
Title
9-AH-086-CH.5.ser
Origin
Bruker BioSpin GmbH
Solvent
C6D6
Temperature
295.1
Pulse Sequence
hmbcetgpl3nd
Number of Scans
4
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.4260
Acquisition Date
2018-09-05T14:19:27
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4807.7, 22321.4)
Lowest Frequency
(-163.1, -1115.4)
Nucleus
(1H, 13C)
Acquired Size
(2048, 140)
Spectral Size
(2048, 1024)
Me
O
OH
Me
Me
H
Me
O
Me
HO
BzO
H
138
ppm

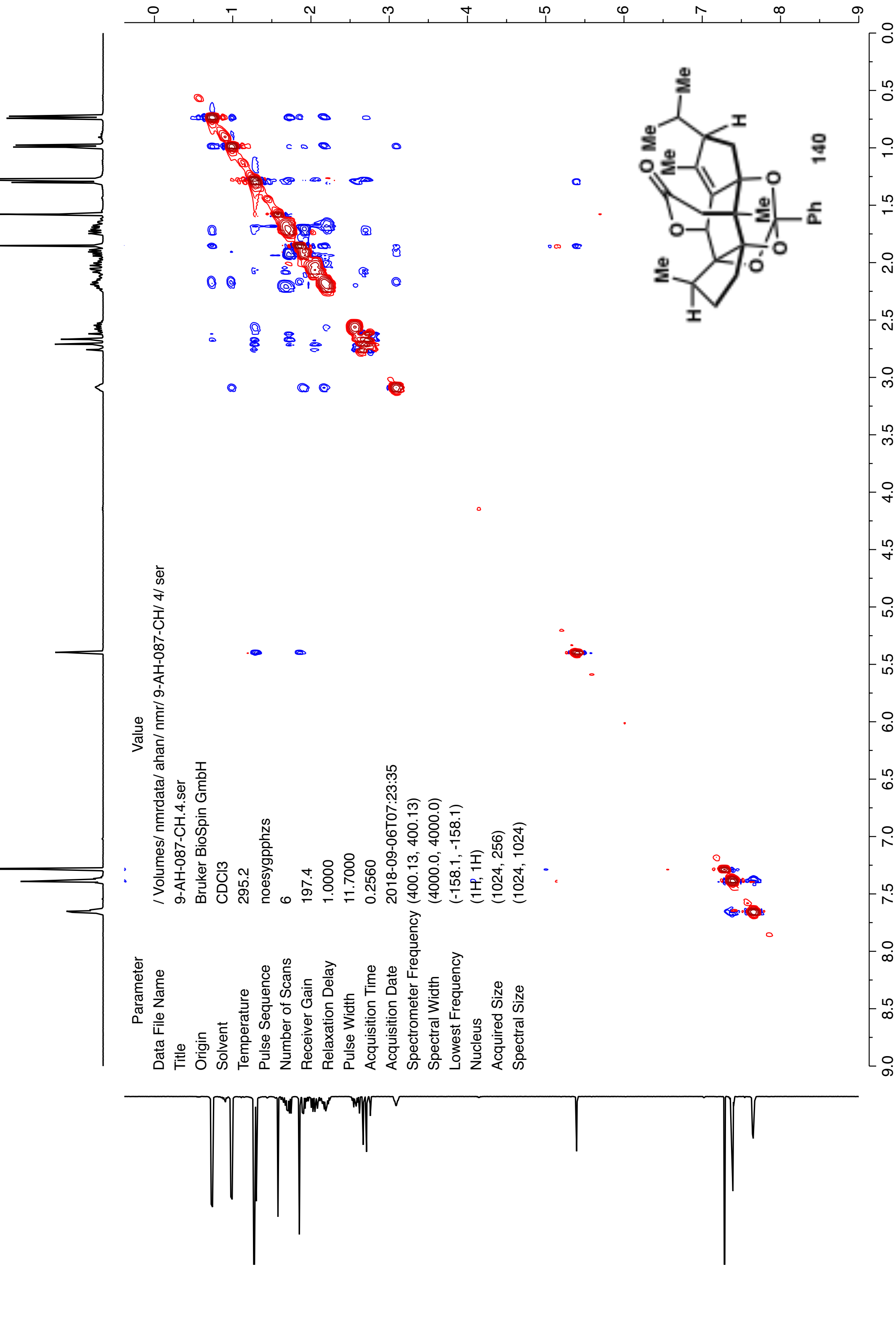

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-086-CH/ 6/ ser
Title 9-AH-086-CH.6.ser
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.1
Pulse Sequence noesygpphzs
Number of Scans 5
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2018-09-05T14:46:29
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-158.1, -158.1)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
ppm
138

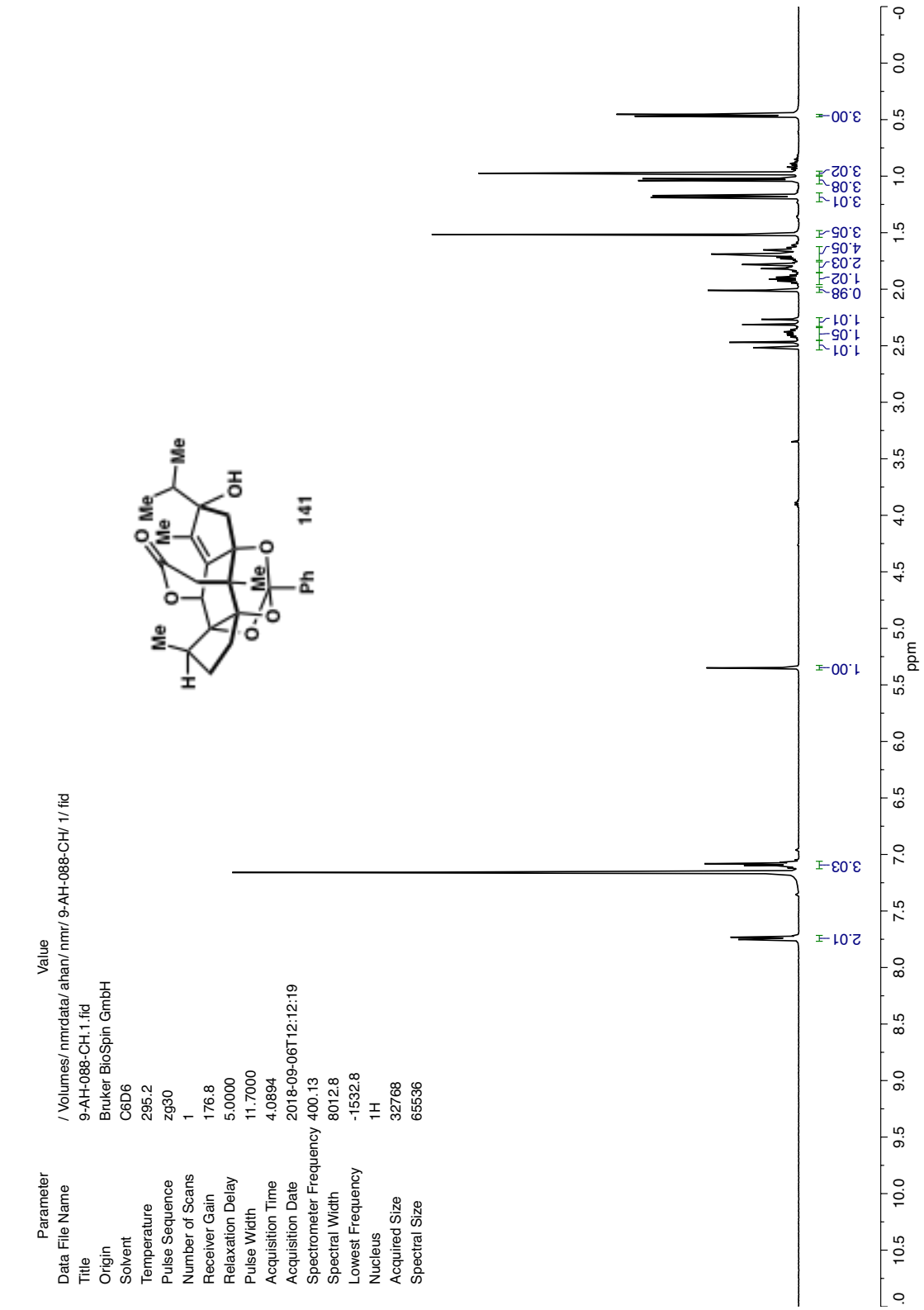

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-087-CH/ 1/ fid
Title 9-AH-087-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-06T06:39:57
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.4
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
Me
Me
Me
O
O
Me
H
H
O
O
Me
O
O
Ph
140
2.01
3.00
1.00
1.02
1.01
1.03
2.03
2.08
1.00
3.06
2.01
3.09
3.02
3.02
3.02
ppm

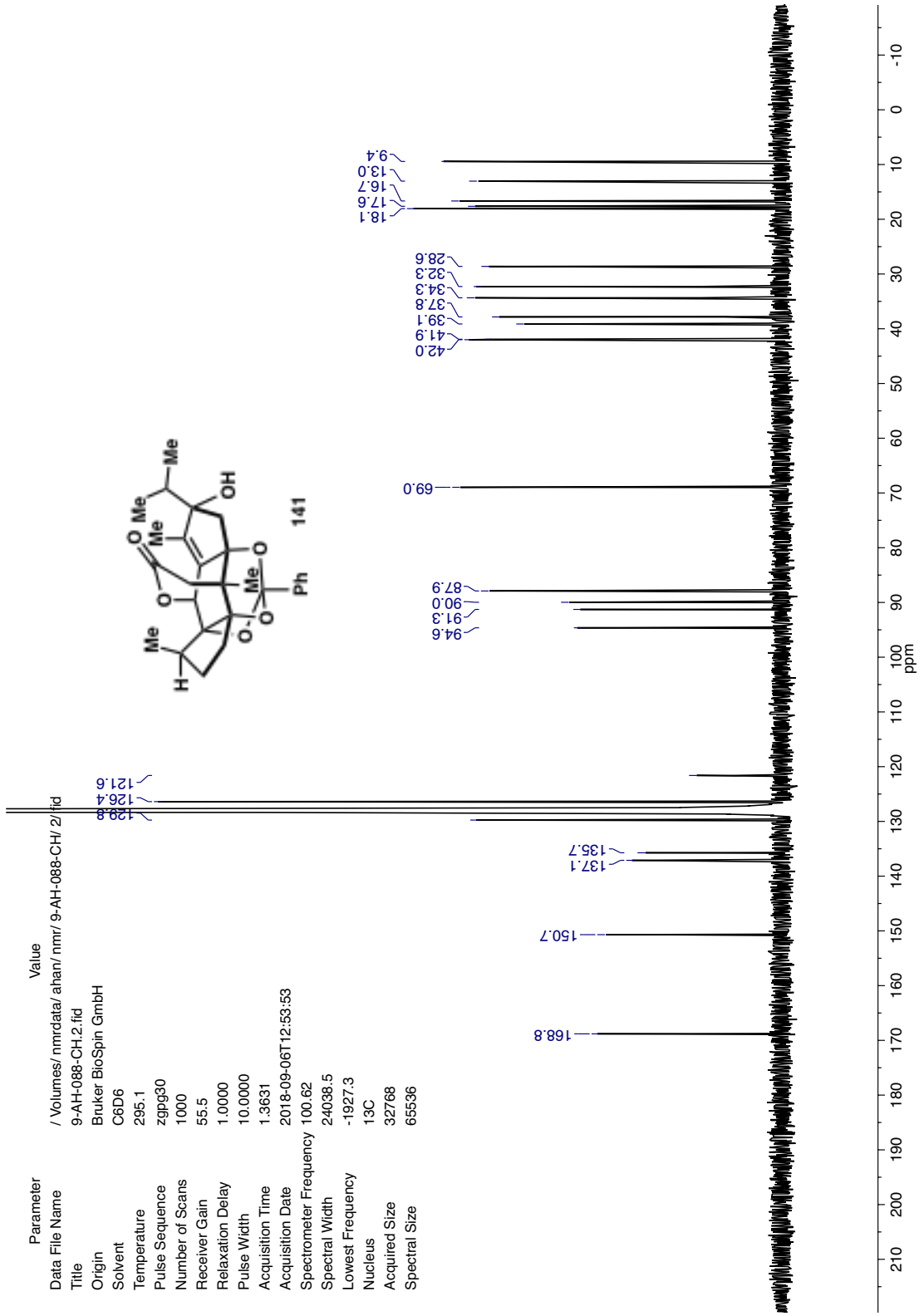

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-087-CH/ 2/ fid
Title 9-AH-087-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 1000
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-06T07:20:53
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1961.3
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Me
Me
O
Me
H
O
O
Me
O
O
Ph
Me
H
140
12.6
13.0
15.7
17.4
21.1
27.3
28.5
30.5
34.1
40.1
41.7
42.1
51.9
69.5
91.0
91.0
94.5
120.9
126.0
128.1
129.6
134.2
135.0
150.2
171.0
ppm

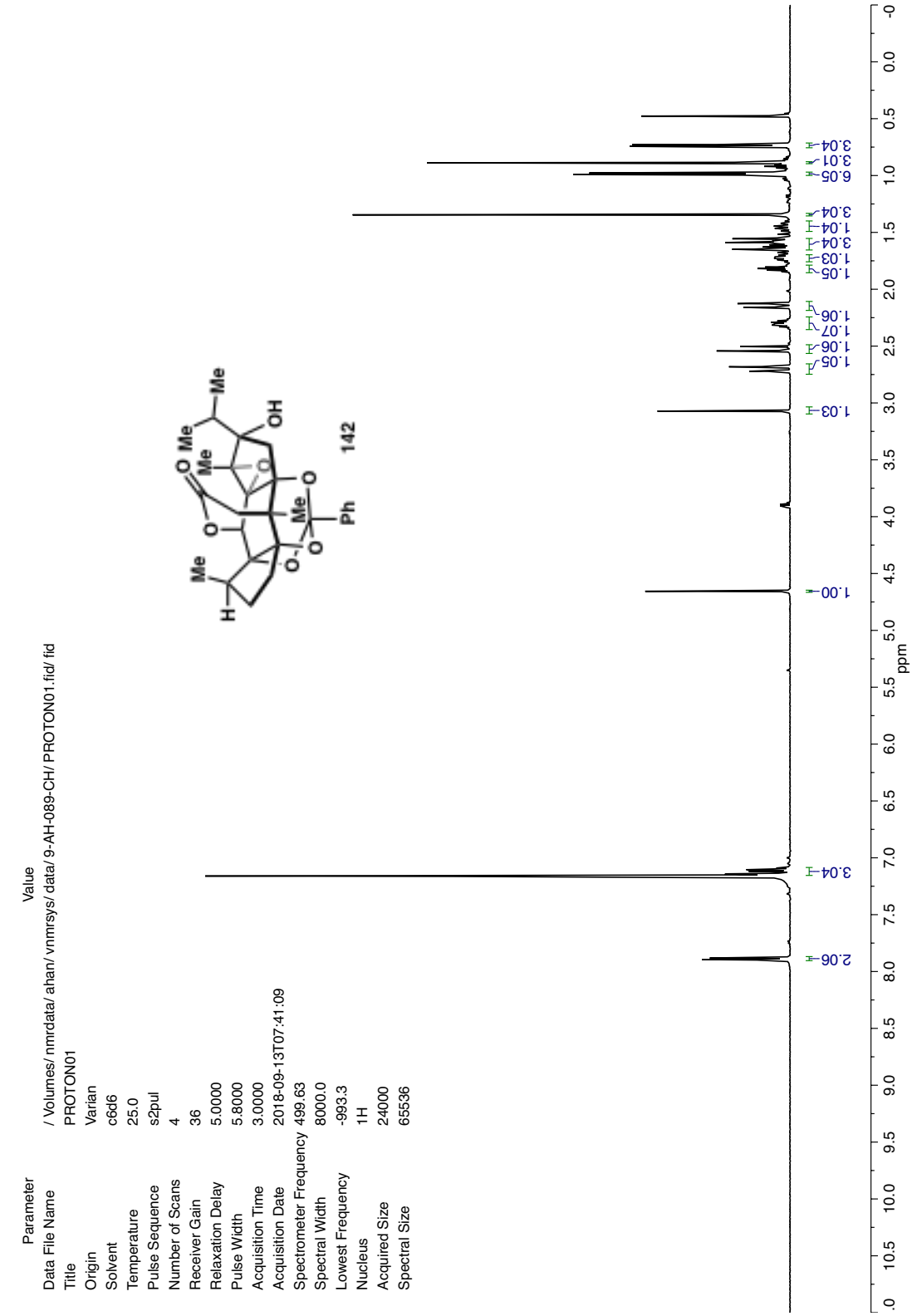

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-087-CH/ 5/ ser
Title
9-AH-087-CH.5.ser
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.2
Pulse Sequence
hsqcedetgpsisp2.4
Number of Scans
4
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2135
Acquisition Date
2018-09-06T08:09:47
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4795.4, 16611.3)
Lowest Frequency
(-517.1, -1262.8)
Nucleus
(1H, 13C)
Acquired Size
(1024, 180)
Spectral Size
(1024, 1024)
ppm
140
Me
H
O
Ph


Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-087-CH/ 6/ ser
Title 9-AH-087-CH.6.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence hmbcetgpl3nd
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.4260
Acquisition Date 2018-09-06T08:25:25
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4807.7, 22321.4)
Lowest Frequency (-163.1, -1116.4)
Nucleus (1H, 13C)
Acquired Size (2048, 231)
Spectral Size (2048, 1024)
Me
Me
O
Me
Me
H
H
O
O
Me
O
O
Ph
140
ppm

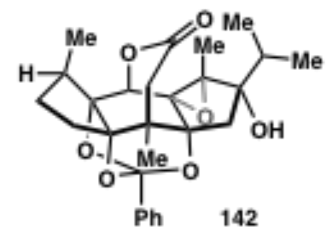

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-087-CH/ 4/ ser
Title 9-AH-087-CH.4.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence noesygpphzs
Number of Scans 6
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2018-09-06T07:23:35
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-158.1, -158.1)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
ppm
140


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-088-CH/ 1/ fid
Title 9-AH-088-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.2
Pulse Sequence zg30
Number of Scans 1
Receiver Gain 176.8
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-06T12:12:19
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1532.8
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
Me
Me
Me
OH
O
O
Me
O
O
Me
O
O
Ph
Me
H
141
2.01
3.03
1.00
1.01
1.05
0.98
1.02
2.03
4.05
3.05
3.01
3.08
3.02
3.00
ppm

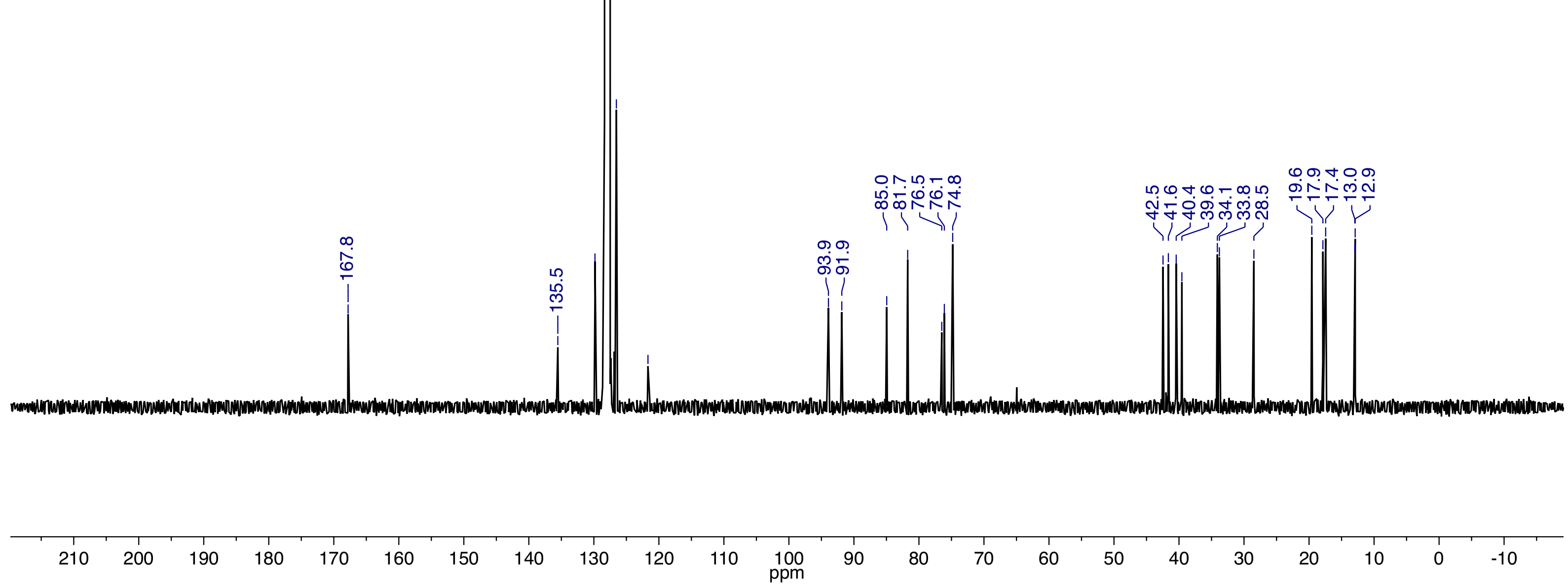

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-088-CH/ 2/ fid
Title 9-AH-088-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 1000
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-06T12:53:53
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1927.3
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
9.4
13.0
16.7
17.6
18.1
28.6
32.3
34.3
37.8
39.1
41.9
42.0
69.0
87.9
90.0
91.3
94.6
121.6
126.4
128.8
135.7
137.1
150.7
168.8
Me
Me
Me
OH
O
O
Me
O
O
Ph
Me
H
141
ppm

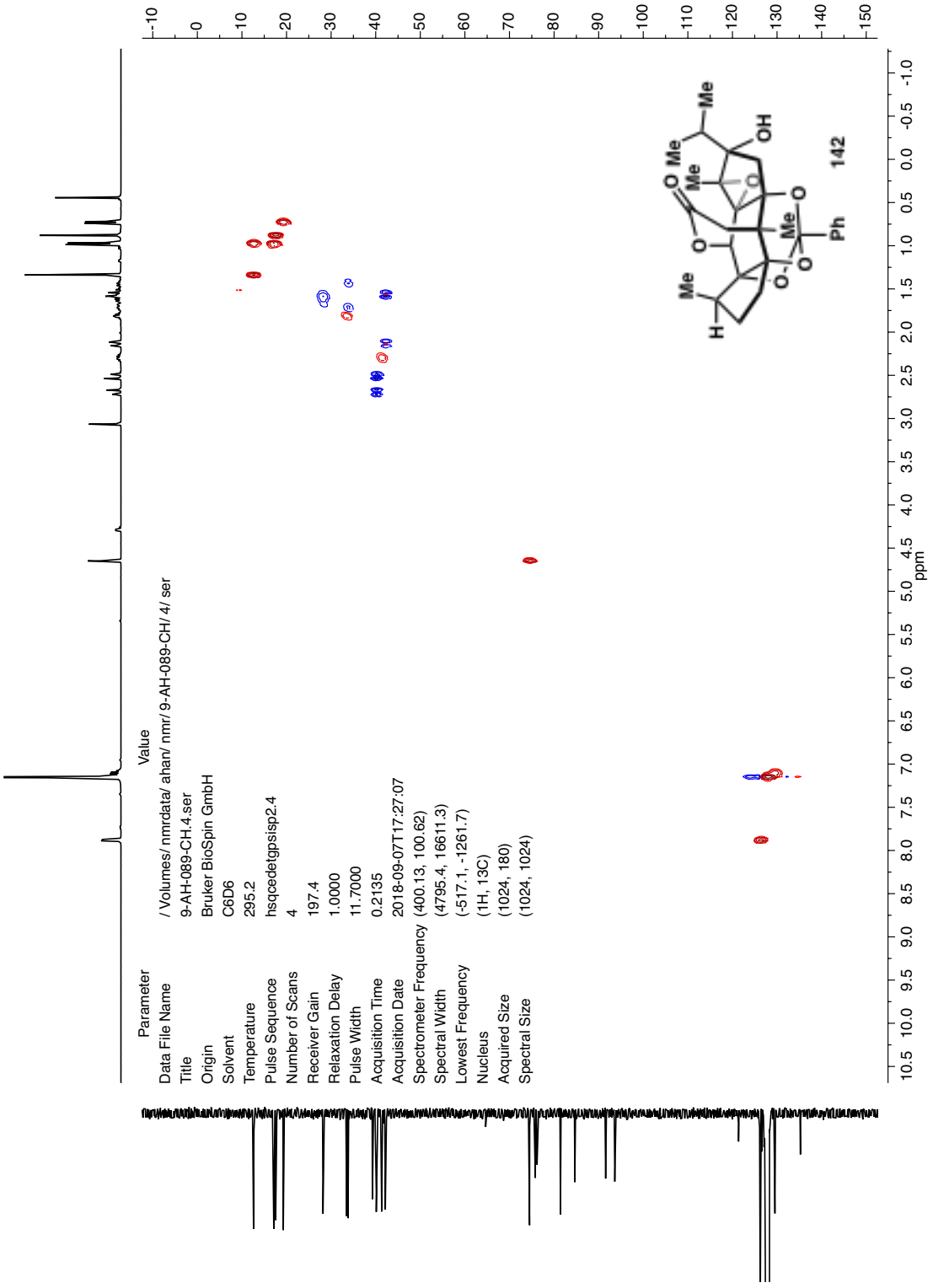

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 9-AH-089-CH/ PROTON01.fid/ fid
Title PROTON01
Origin Varian
Solvent c6d6
Temperature 25.0
Pulse Sequence s2pul
Number of Scans 4
Receiver Gain 36
Relaxation Delay 5.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2018-09-13T07:41:09
Spectrometer Frequency 499.63
Spectral Width 8000.0
Lowest Frequency -993.3
Nucleus 1H
Acquired Size 24000
Spectral Size 65536
142
2.06
3.04
1.00
1.03
1.05
1.06
1.07
1.06
1.05
3.04
1.04
3.04
1.03
1.05
6.05
3.01
3.04
ppm

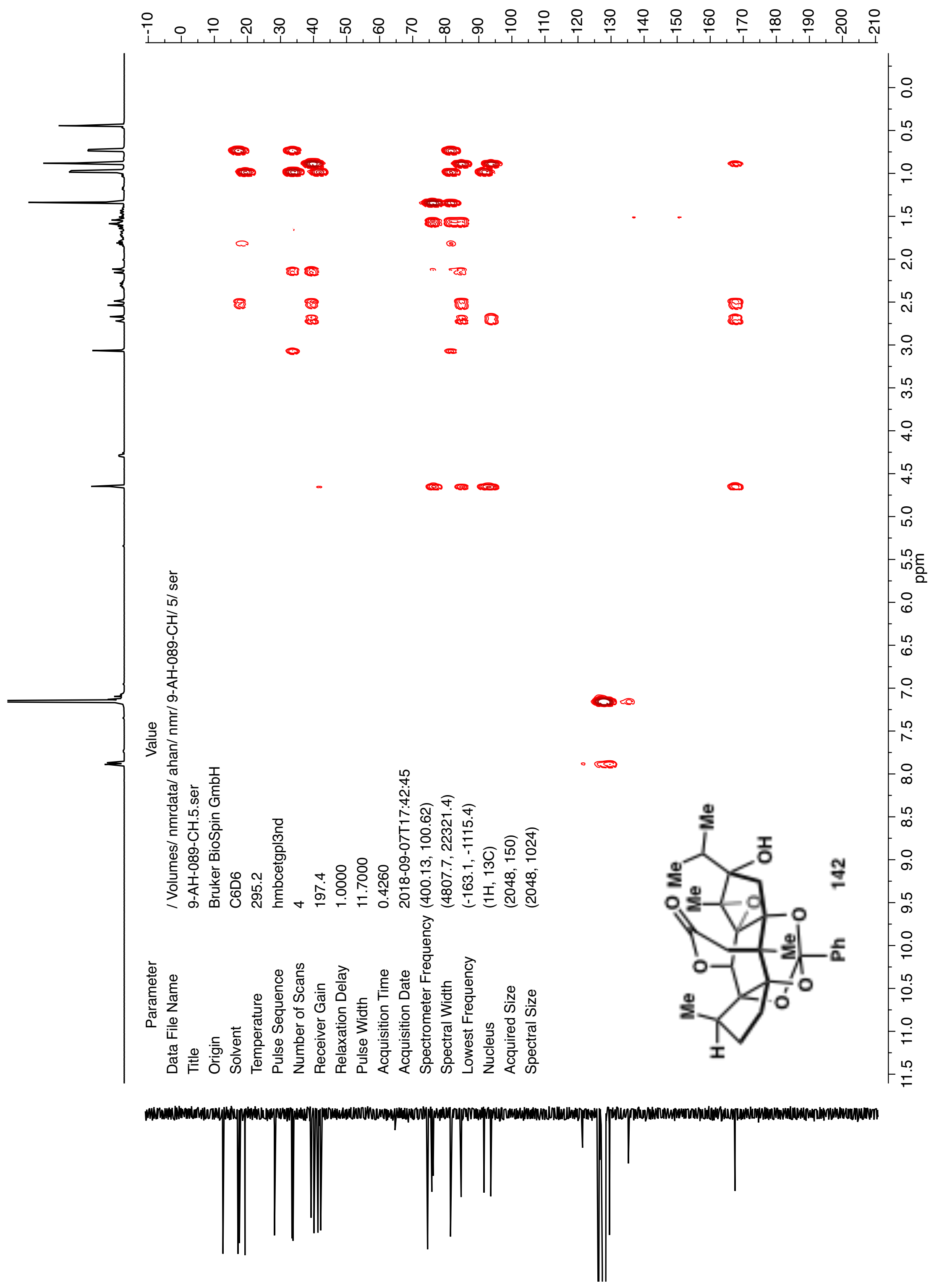
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-089-CH/ 1/ fid
Title	9-AH-089-CH.1.fid
Origin	Bruker BioSpin GmbH
Solvent	C6D6
Temperature	295.2
Pulse Sequence	zgpg30
Number of Scans	1000
Receiver Gain	55.5
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-09-07T16:45:46
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1927.3
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

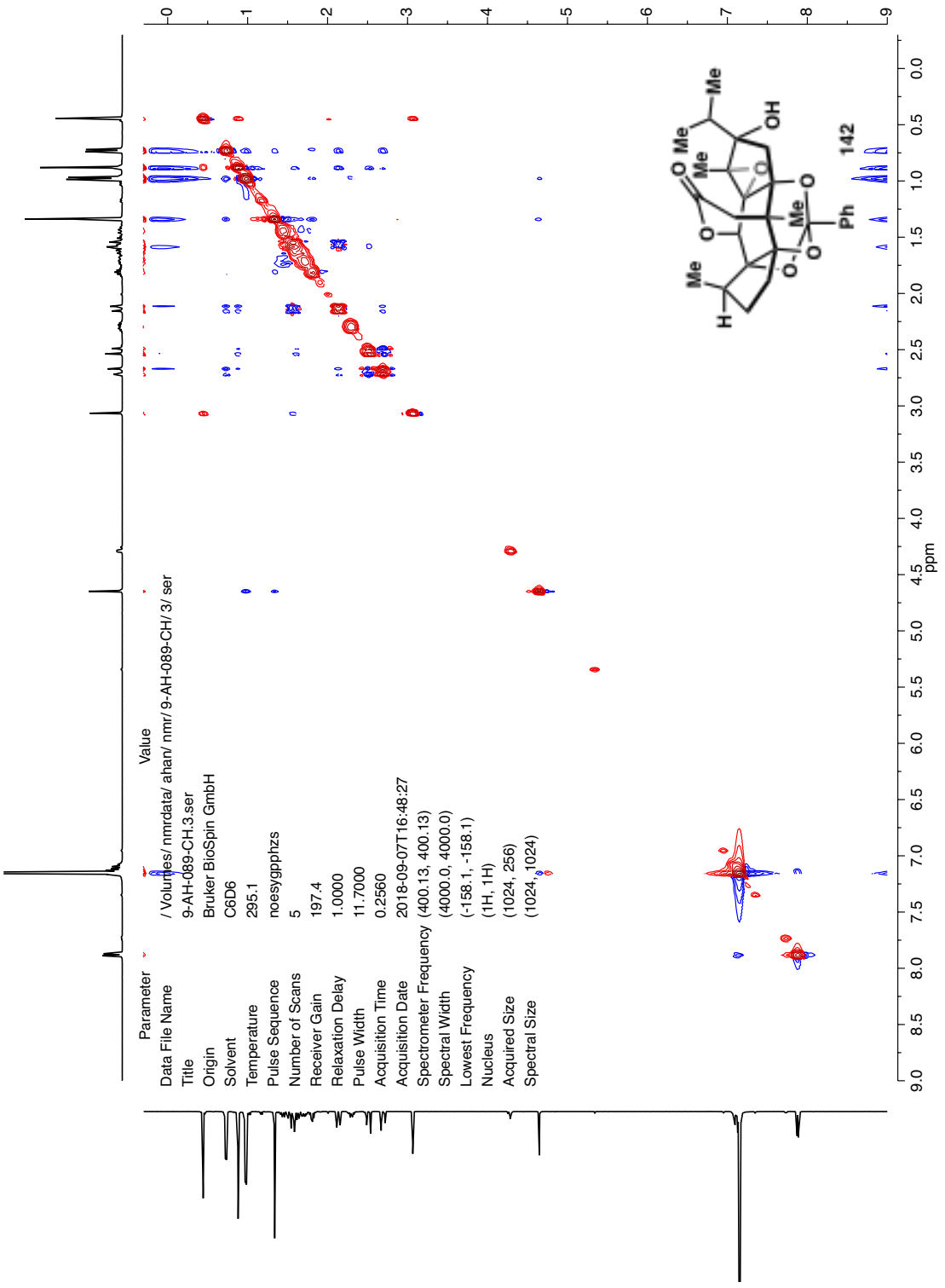


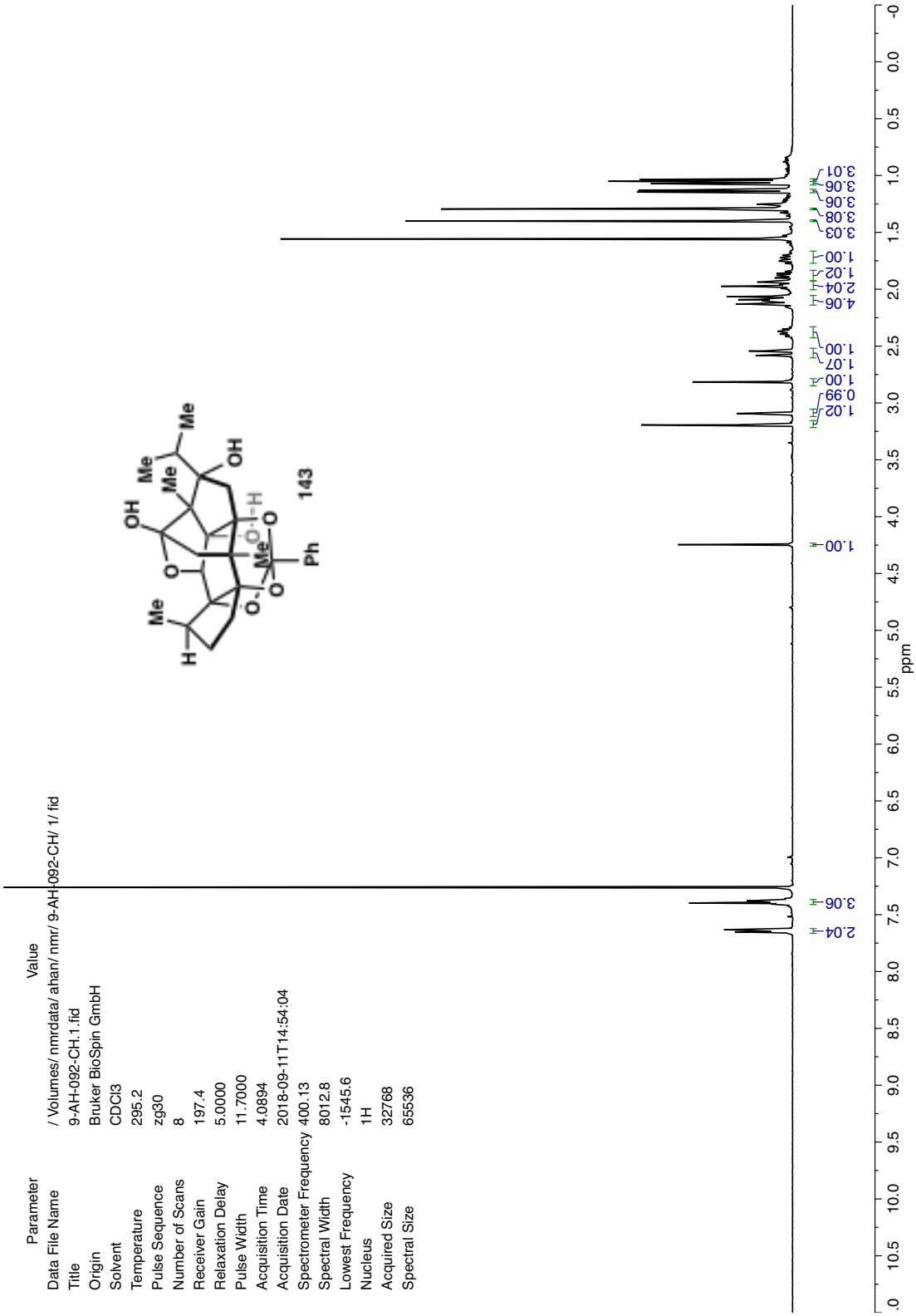
142

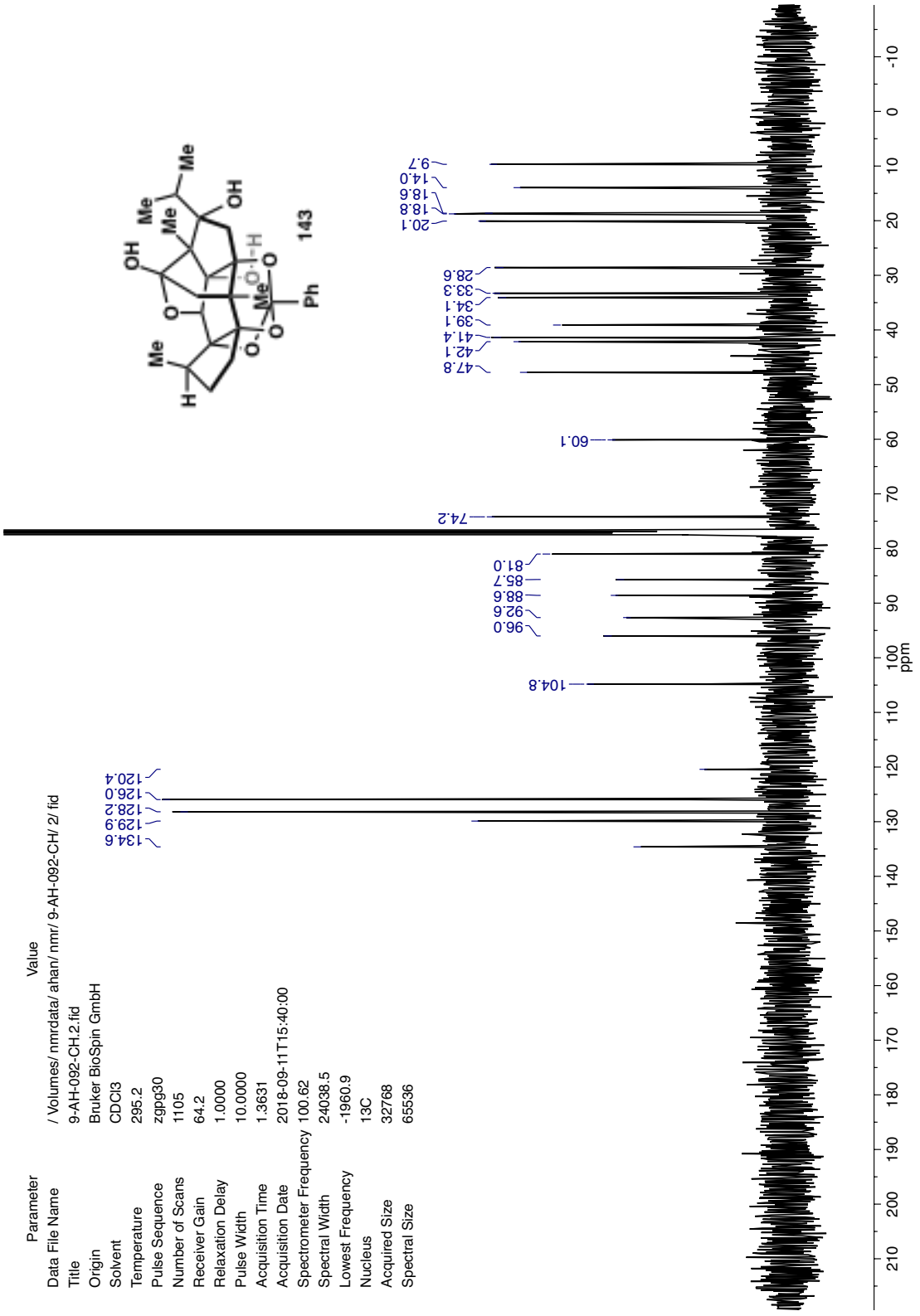


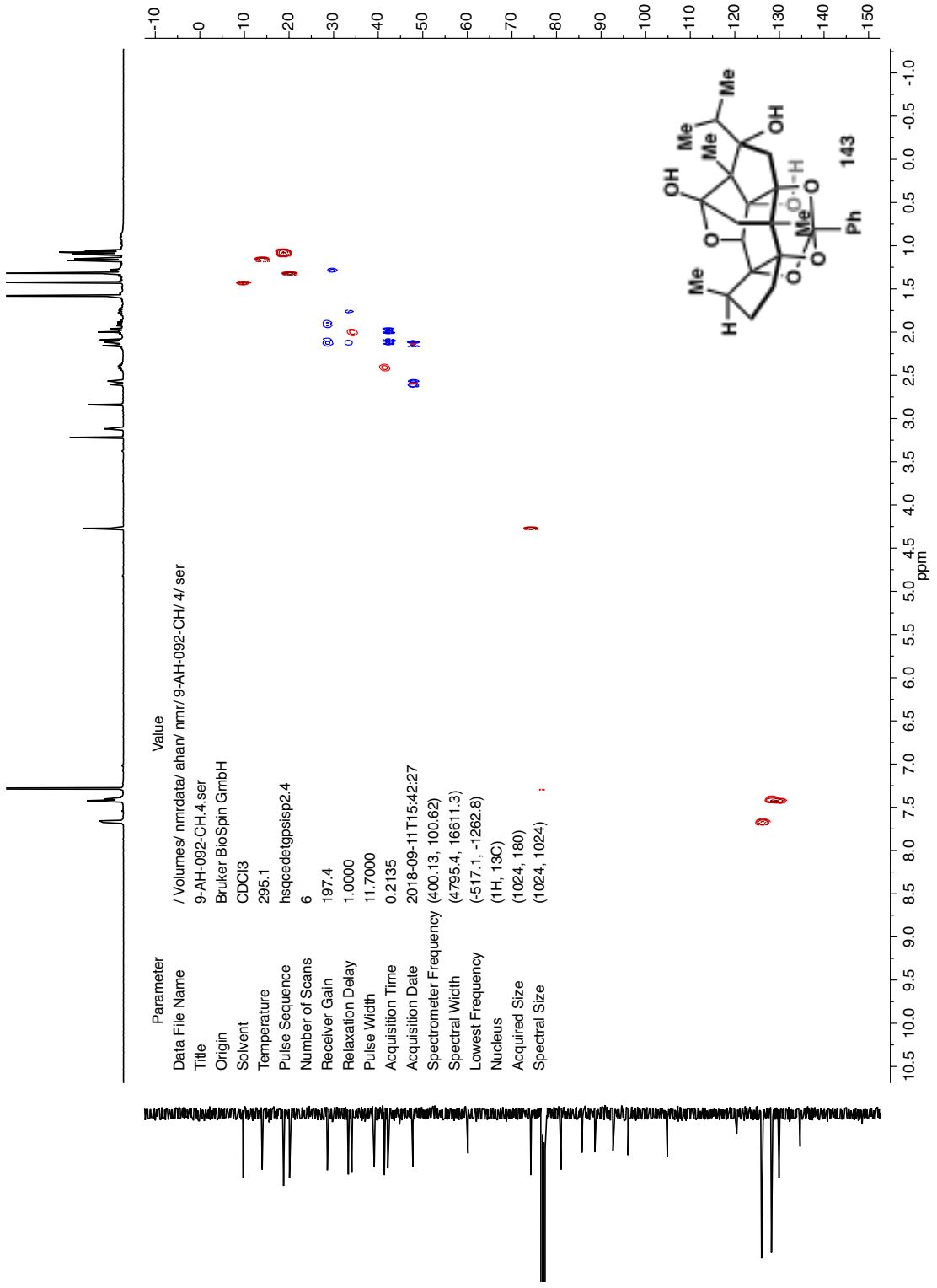

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-089-CH/ 4/ ser
Title 9-AH-089-CH.4.ser
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.2
Pulse Sequence hsqcedetgpsisp2.4
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2135
Acquisition Date 2018-09-07T17:27:07
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4795.4, 16611.3)
Lowest Frequency (-517.1, -1261.7)
Nucleus (1H, 13C)
Acquired Size (1024, 180)
Spectral Size (1024, 1024)
ppm
Me
Me
OH
O
Me
Me
O
O
O
Me
O
O
Ph
H
142

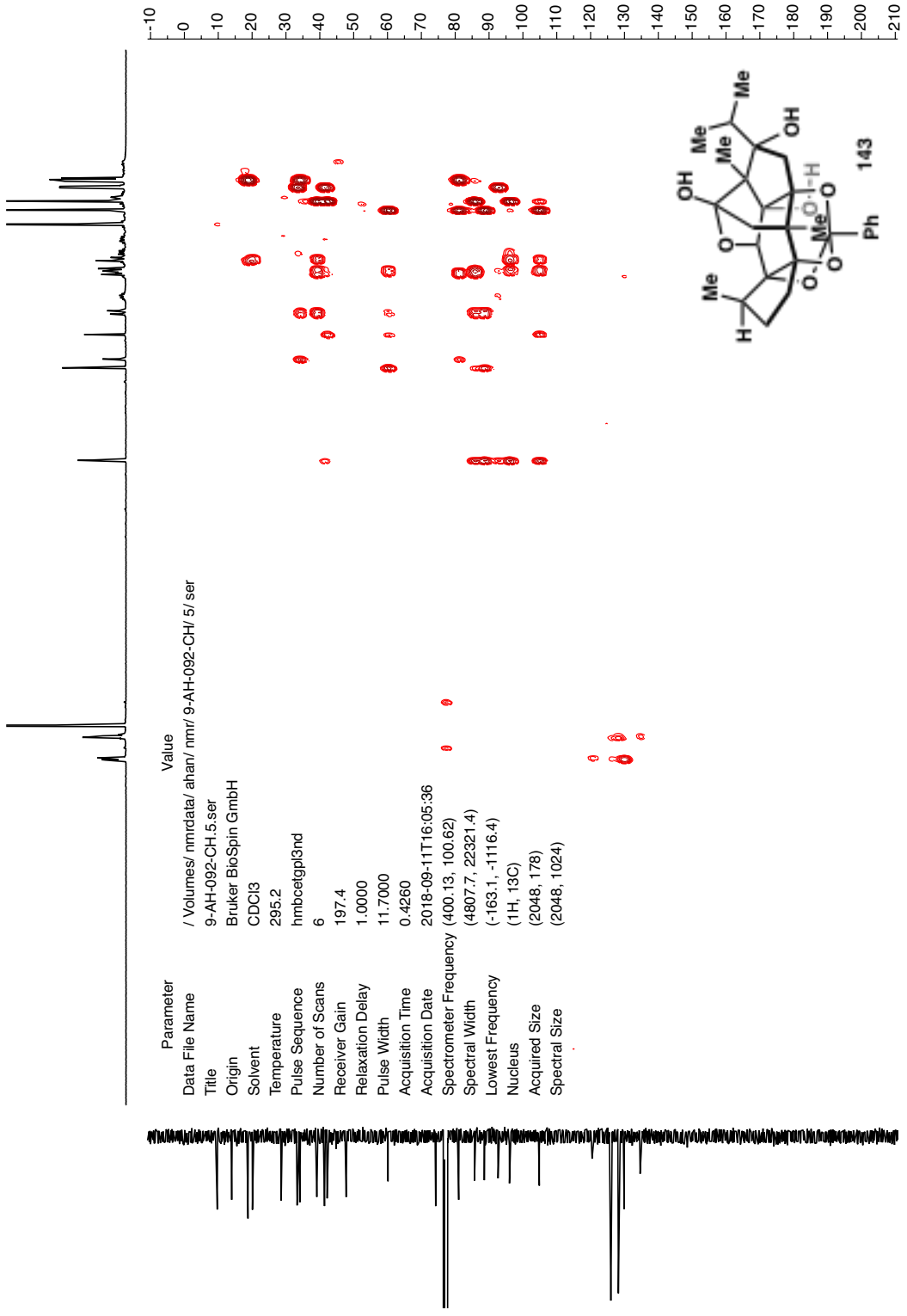

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-089-CH/ 5/ ser
Title 9-AH-089-CH.5.ser
Origin Bruker BioSpin GmbH
Solvent C6D6
Temperature 295.2
Pulse Sequence hmbcetgpl3nd
Number of Scans 4
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.4260
Acquisition Date 2018-09-07T17:42:45
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4807.7, 22321.4)
Lowest Frequency (-163.1, -1115.4)
Nucleus (1H, 13C)
Acquired Size (2048, 150)
Spectral Size (2048, 1024)
ppm
Me
H
O
Me
Me
OH
Me
Ph
142

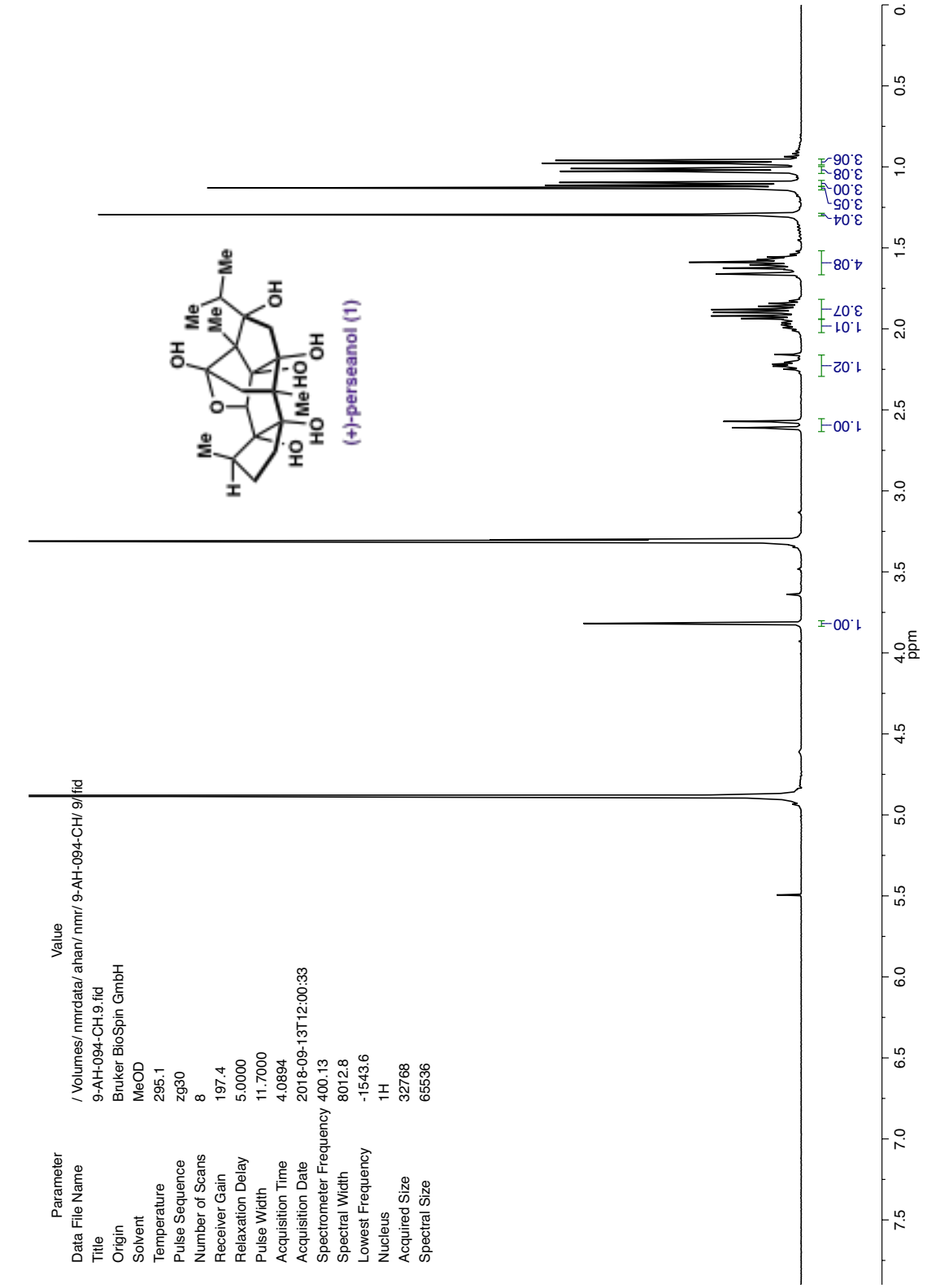

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-089-CH/ 3/ ser
Title
9-AH-089-CH.3.ser
Origin
Bruker BioSpin GmbH
Solvent
C6D6
Temperature
295.1
Pulse Sequence
noesygpphzs
Number of Scans
5
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2560
Acquisition Date
2018-09-07T16:48:27
Spectrometer Frequency
(400.13, 400.13)
Spectral Width
(4000.0, 4000.0)
Lowest Frequency
(-158.1, -158.1)
Nucleus
(1H, 1H)
Acquired Size
(1024, 256)
Spectral Size
(1024, 1024)
ppm
Me
Me
OH
O
Me
Me
O
O
Me
H
O
O
Me
O
O
Ph
142

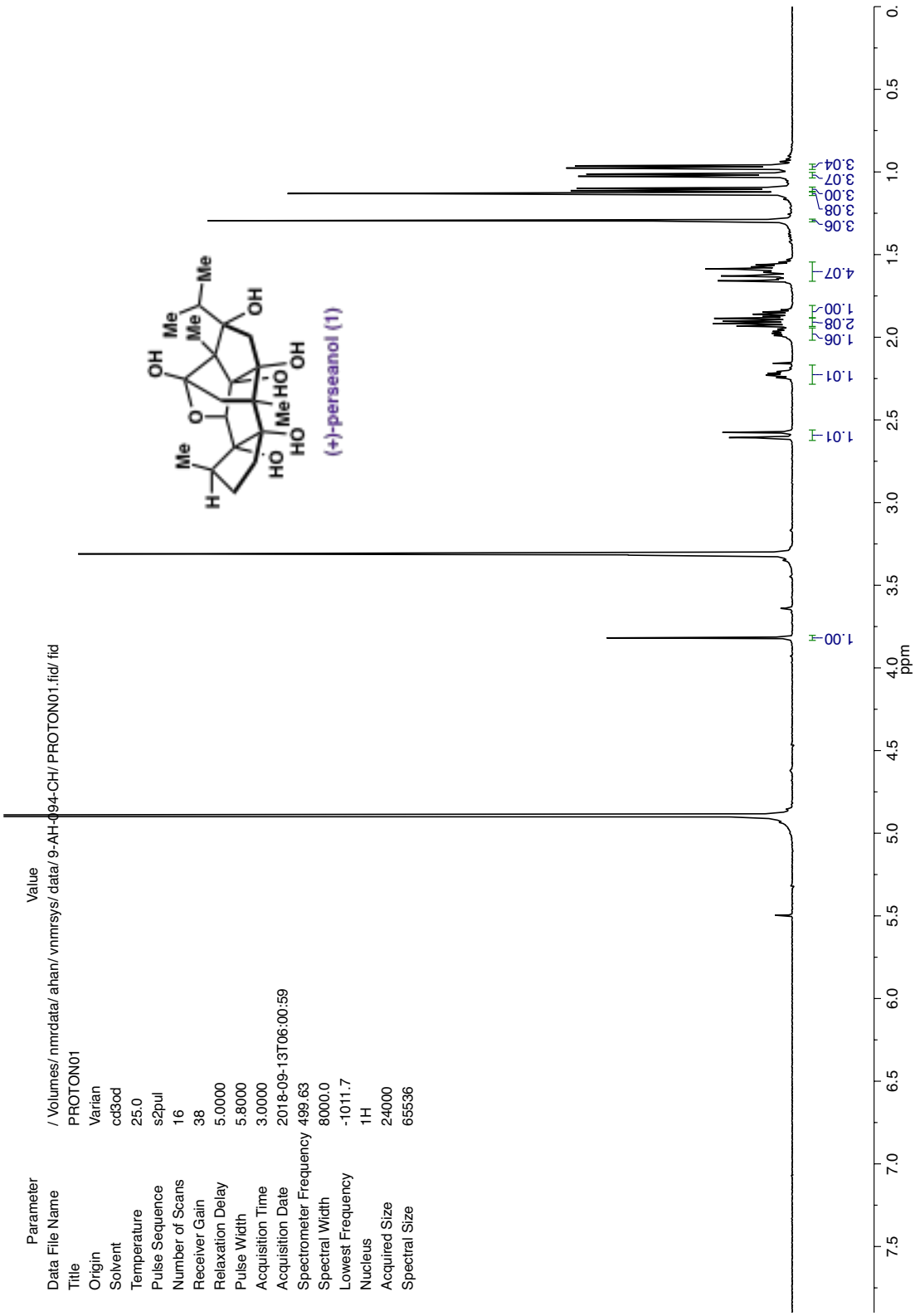

Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-092-CH/ 1/ fid
Title 9-AH-092-CH.1.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-11T14:54:04
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1545.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
OH
Me
Me
Me
OH
Me
H
O
O
O
O
Me
O
O
Ph
143
3.06
2.04
1.00
1.02
0.99
1.00
1.07
1.00
4.06
2.04
1.02
1.00
3.03
3.08
3.06
3.06
3.01
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-092-CH/ 2/ fid
Title 9-AH-092-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Number of Scans 1105
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-11T15:40:00
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1960.9
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
134.6
129.9
128.2
126.0
120.4
104.8
96.0
92.6
88.6
85.7
81.0
74.2
60.1
47.8
42.1
41.4
39.1
34.1
33.3
28.6
20.1
18.8
18.6
14.0
9.7
Me
Me
Me
Me
OH
OH
O
O
O
O
Me
O
H
Ph
143
ppm

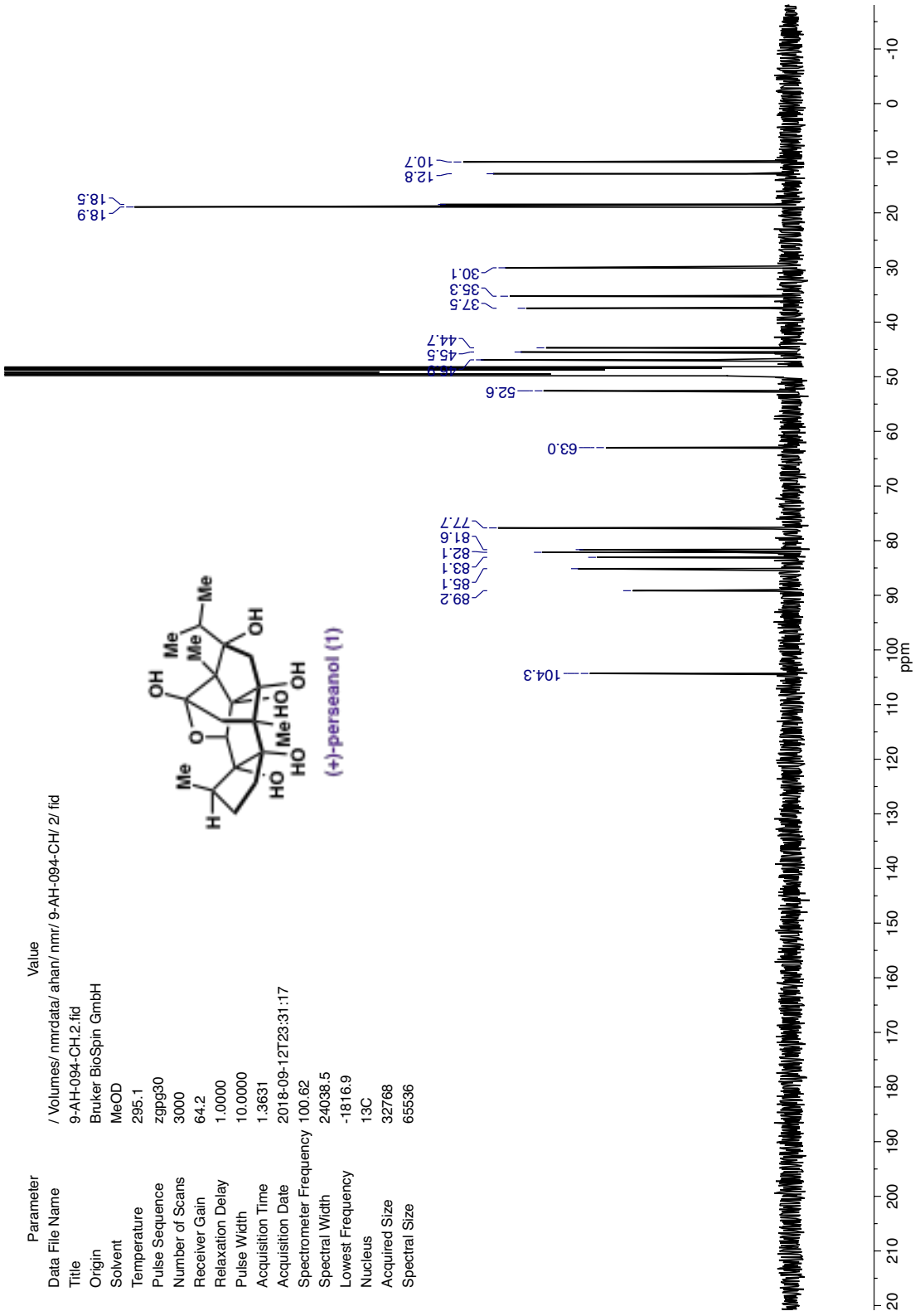

Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-092-CH/ 4/ ser
Title
9-AH-092-CH.4.ser
Origin
Bruker BioSpin GmbH
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
hsqcedetgpsisp2.4
Number of Scans
6
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.2135
Acquisition Date
2018-09-11T15:42:27
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4795.4, 16611.3)
Lowest Frequency
(-517.1, -1262.8)
Nucleus
(1H, 13C)
Acquired Size
(1024, 180)
Spectral Size
(1024, 1024)
ppm
OH
Me
Me
Me
OH
H
O
O
O
Me
O
Ph
143

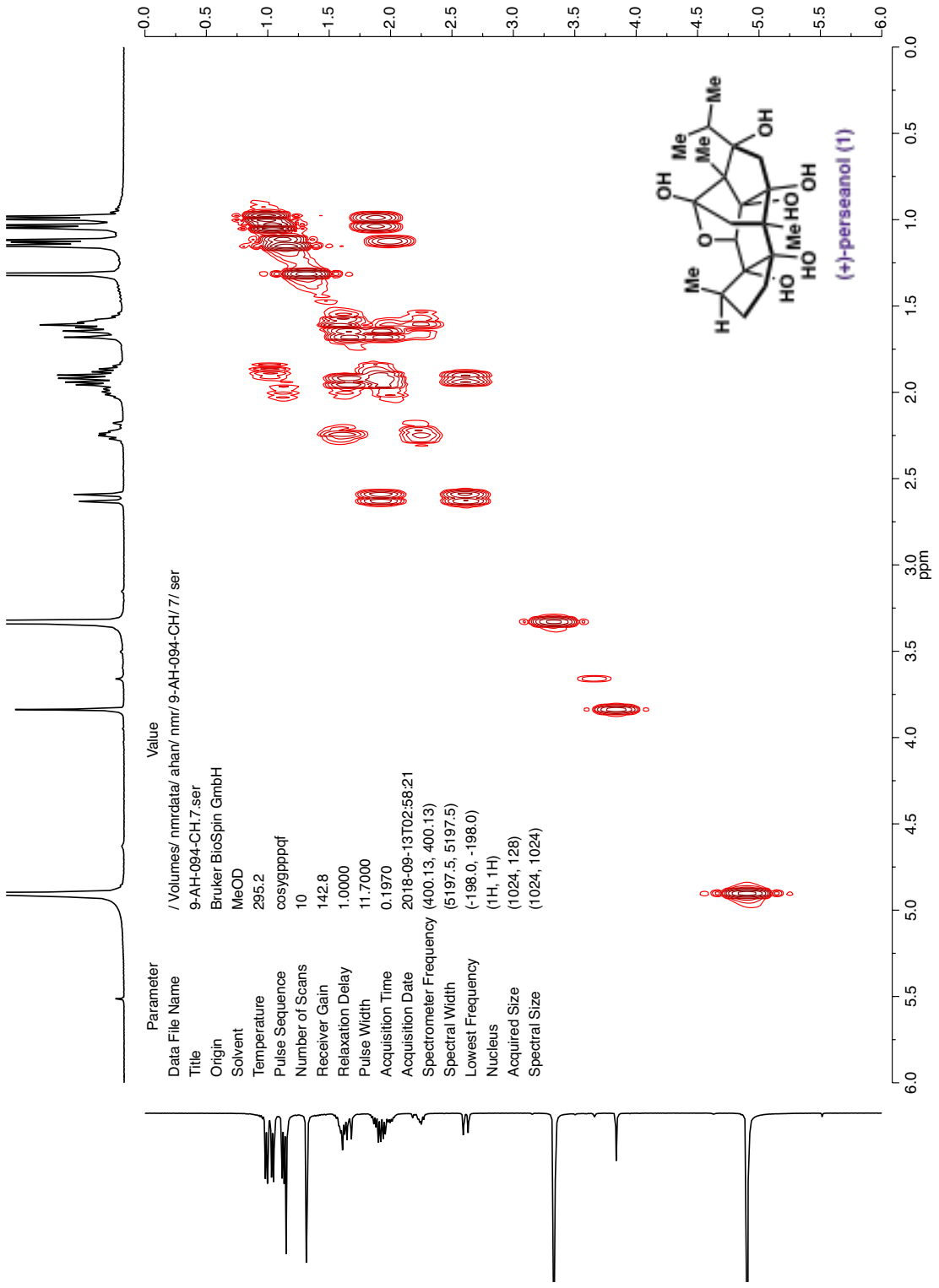

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-092-CH/ 5/ ser
Title 9-AH-092-CH.5.ser
Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 295.2
Pulse Sequence hmbcetgpl3nd
Number of Scans 6
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.4260
Acquisition Date 2018-09-11T16:05:36
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4807.7, 22321.4)
Lowest Frequency (-163.1, -1116.4)
Nucleus (1H, 13C)
Acquired Size (2048, 178)
Spectral Size (2048, 1024)
ppm
Me
OH
Me
Me
OH
Me
O
O
O
O
Me
O
Ph
143
H

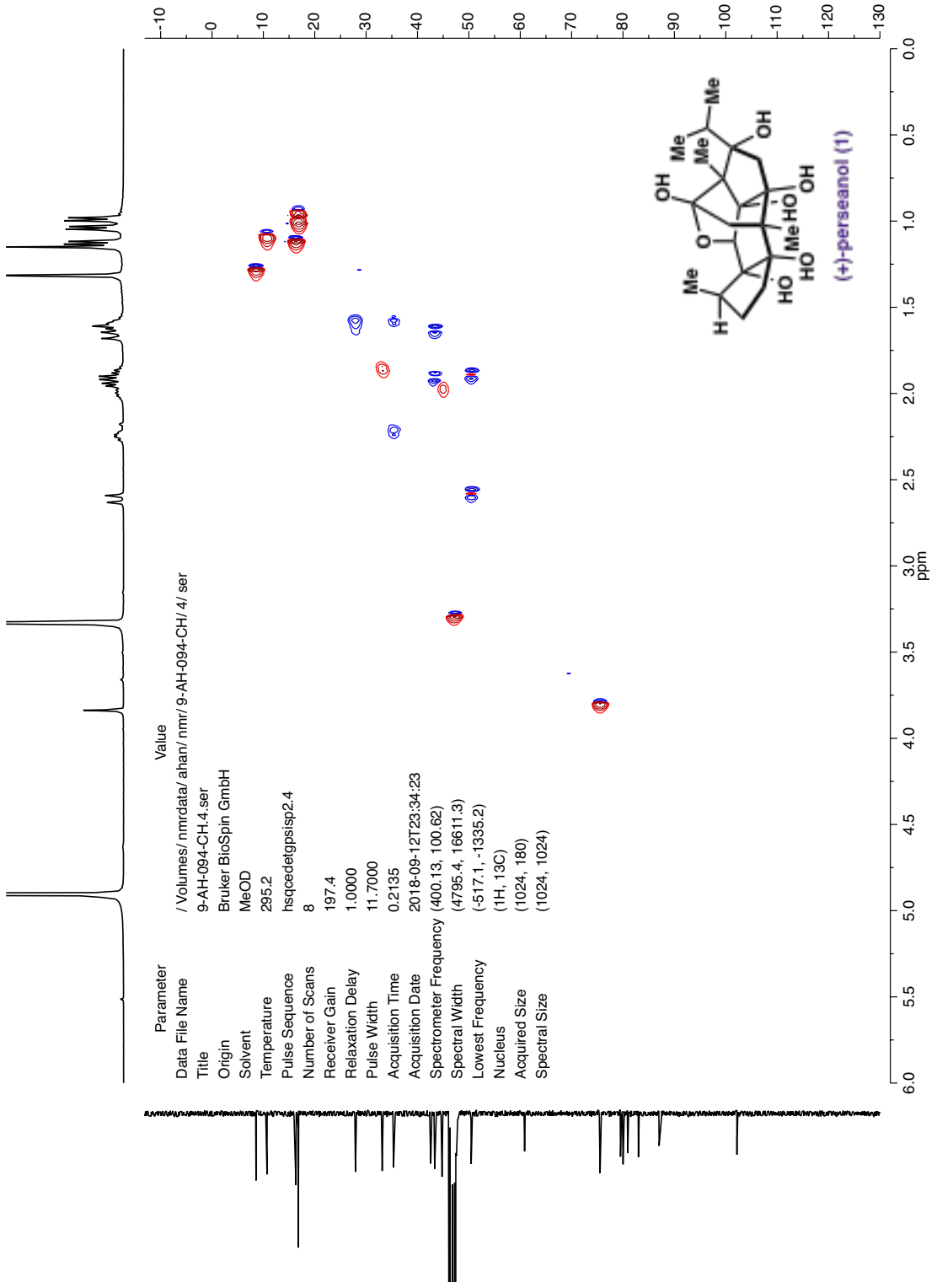

(+)-perseanol (1)
Parameter Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-094-CH/ 9/fid
Title 9-AH-094-CH.9.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.1
Pulse Sequence zg30
Number of Scans 8
Receiver Gain 197.4
Relaxation Delay 5.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-13T12:00:33
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1543.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
1.00
1.02
1.01
3.07
4.08
3.04
3.05
3.00
3.08
3.06
ppm

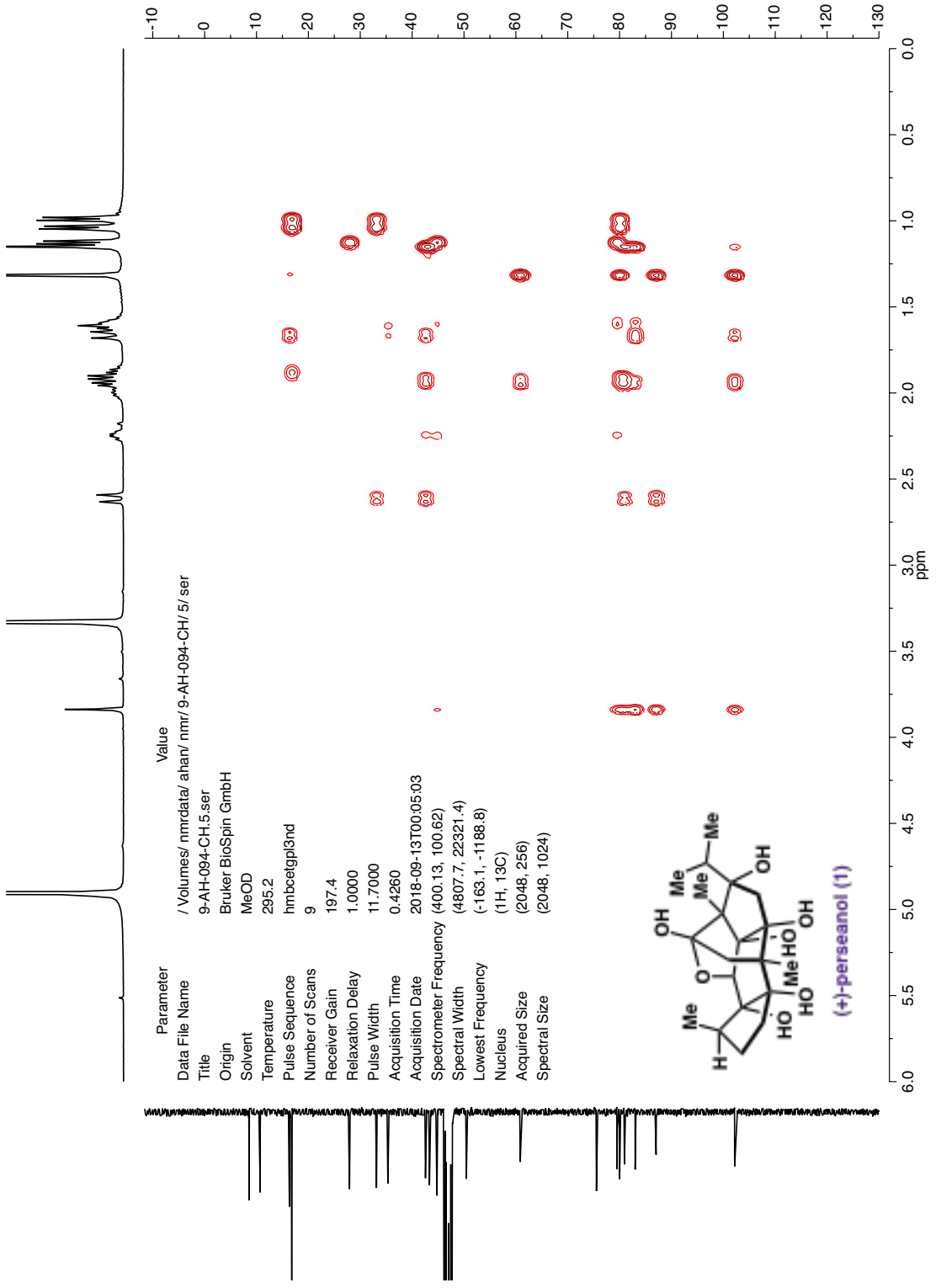


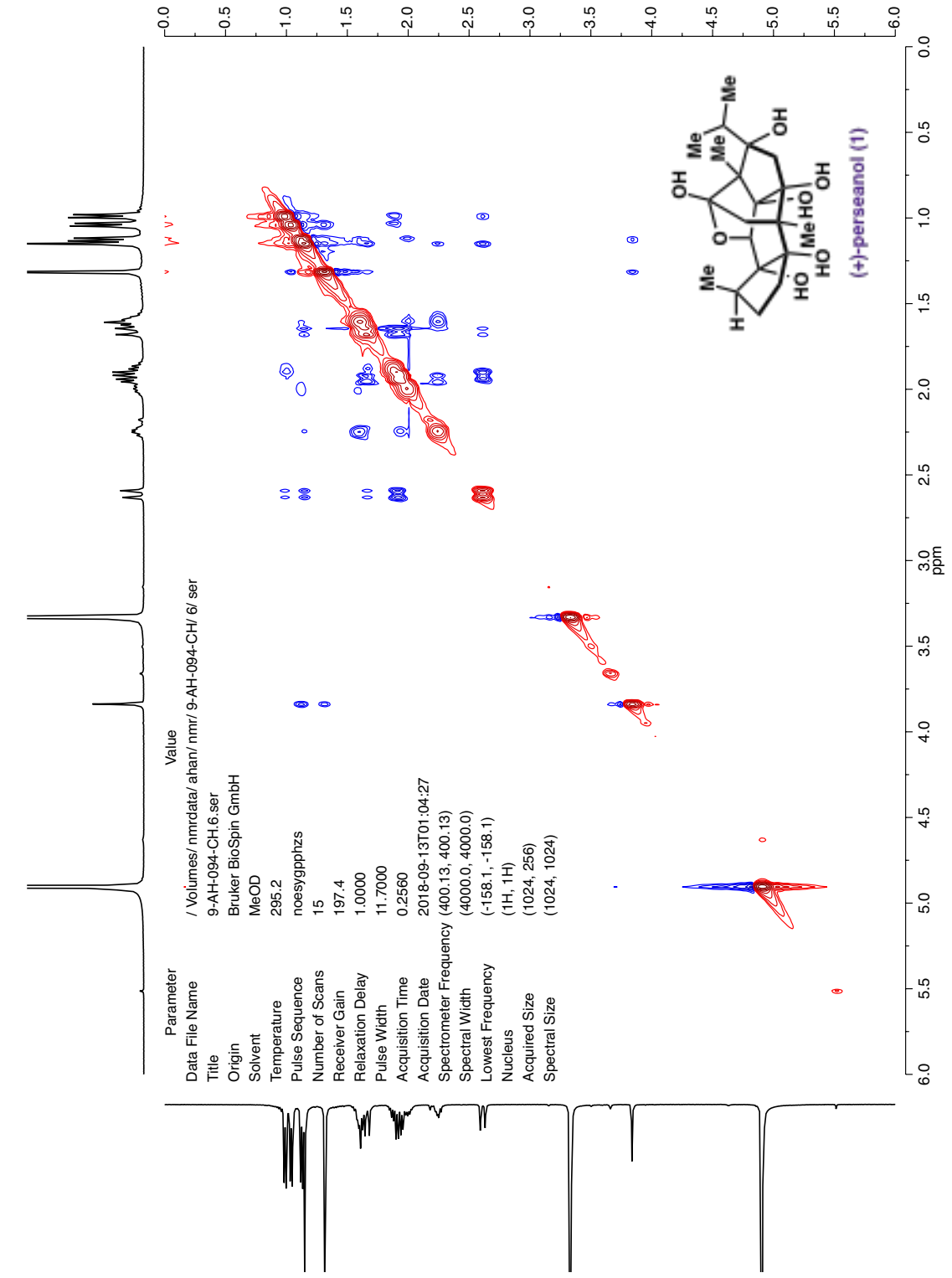
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ ahan/ vnmrsys/ data/ 9-AH-094-CH/ PROTON01.fid/ fid
Title	PROTON01
Origin	Varian
Solvent	cd3od
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	16
Receiver Gain	38
Relaxation Delay	5.0000
Pulse Width	5.8000
Acquisition Time	3.0000
Acquisition Date	2018-09-13T06:00:59
Spectrometer Frequency	499.63
Spectral Width	8000.0
Lowest Frequency	-1011.7
Nucleus	1H
Acquired Size	24000
Spectral Size	65536

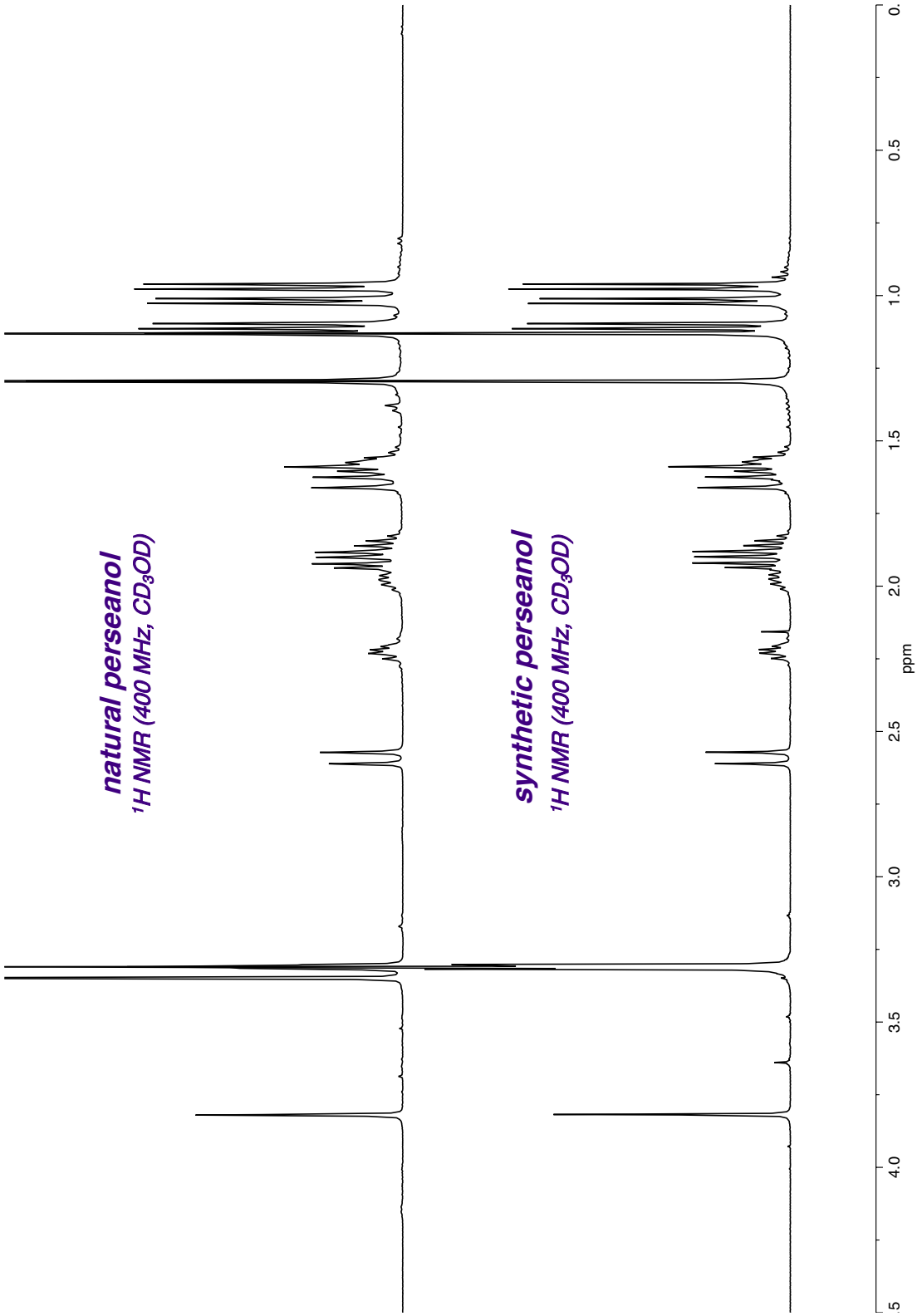

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-094-CH/ 2/ fid
Title 9-AH-094-CH.2.fid
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.1
Pulse Sequence zgpg30
Number of Scans 3000
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-12T23:31:17
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1816.9
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
(+)-perseanol (1)
10.7
12.8
18.5
18.9
30.1
35.3
37.5
44.7
45.5
52.6
63.0
77.7
81.6
82.1
83.1
85.1
89.2
104.3
ppm

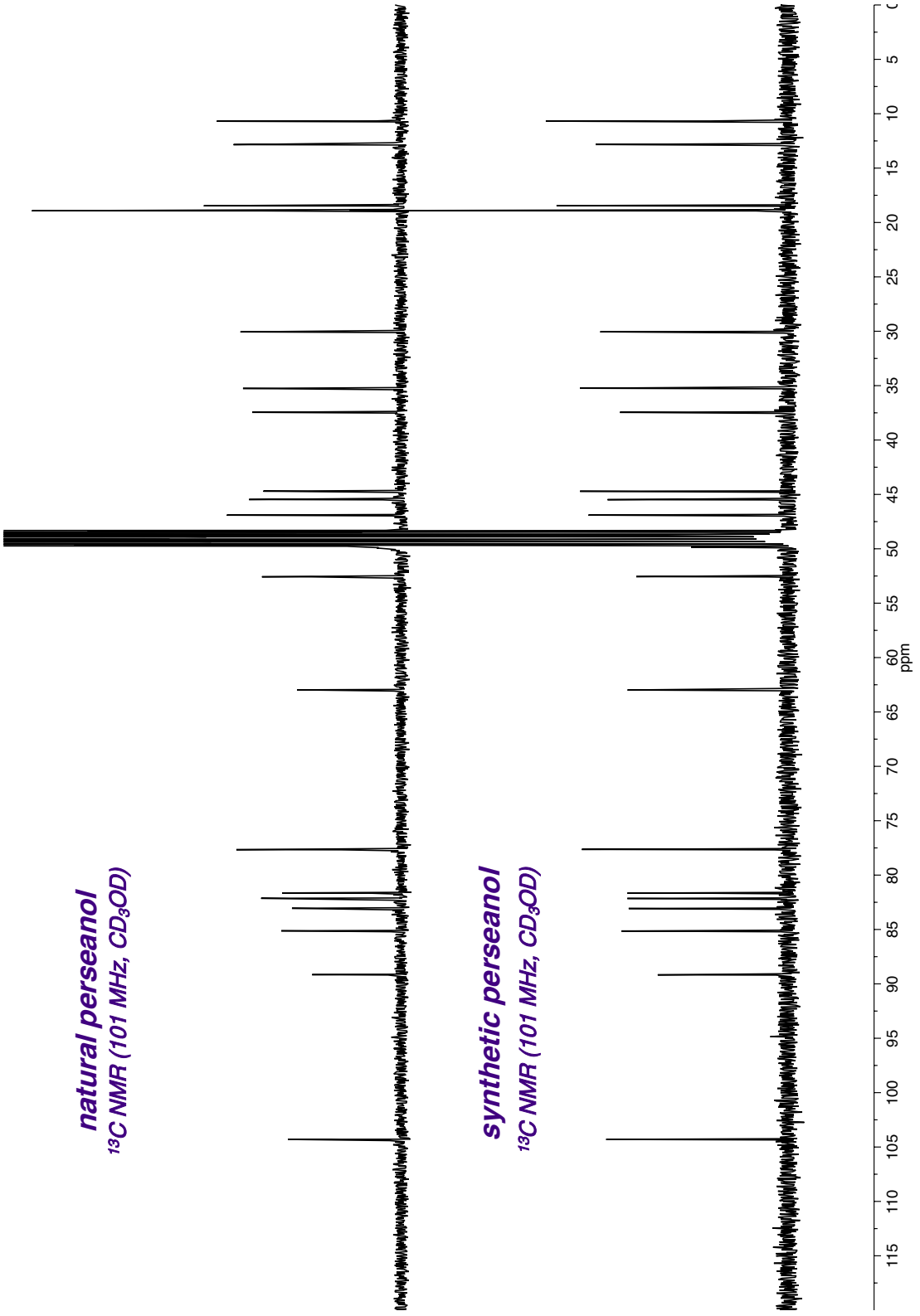

Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-094-CH/ 7/ ser
Title 9-AH-094-CH.7.ser
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.2
Pulse Sequence cosygpppqf
Number of Scans 10
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.1970
Acquisition Date 2018-09-13T02:58:21
Spectrometer Frequency (400.13, 400.13)
Spectral Width (5197.5, 5197.5)
Lowest Frequency (-198.0, -198.0)
Nucleus (1H, 1H)
Acquired Size (1024, 128)
Spectral Size (1024, 1024)
(+)-perseanol (1)
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-094-CH/ 4/ ser
Title 9-AH-094-CH4.ser
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.2
Pulse Sequence hsqcedetgpsisp2.4
Number of Scans 8
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2135
Acquisition Date 2018-09-12T23:34:23
Spectrometer Frequency (400.13, 100.62)
Spectral Width (4795.4, 16611.3)
Lowest Frequency (-517.1, -1335.2)
Nucleus (1H, 13C)
Acquired Size (1024, 180)
Spectral Size (1024, 1024)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
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
ppm
(+)-perseanol (1)


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ ahan/ nmr/ 9-AH-094-CH/ 5/ ser
Title
9-AH-094-CH.5.ser
Origin
Bruker BioSpin GmbH
Solvent
MeOD
Temperature
295.2
Pulse Sequence
hmbcetgpl3nd
Number of Scans
9
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
0.4260
Acquisition Date
2018-09-13T00:05:03
Spectrometer Frequency
(400.13, 100.62)
Spectral Width
(4807.7, 22321.4)
Lowest Frequency
(-163.1, -1188.8)
Nucleus
(1H, 13C)
Acquired Size
(2048, 256)
Spectral Size
(2048, 1024)
(+)-perseanol (1)
ppm


Parameter
Value
Data File Name / Volumes/ nmrdata/ ahan/ nmr/ 9-AH-094-CH/ 6/ ser
Title 9-AH-094-CH.6.ser
Origin Bruker BioSpin GmbH
Solvent MeOD
Temperature 295.2
Pulse Sequence noesygpphzs
Number of Scans 15
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 0.2560
Acquisition Date 2018-09-13T01:04:27
Spectrometer Frequency (400.13, 400.13)
Spectral Width (4000.0, 4000.0)
Lowest Frequency (-158.1, -158.1)
Nucleus (1H, 1H)
Acquired Size (1024, 256)
Spectral Size (1024, 1024)
(+)-perseanol (1)
ppm


natural perseanol
^{1}H NMR (400 MHz, CD_3OD)
synthetic perseanol
^{1}H NMR (400 MHz, CD_3OD)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
5
ppm


natural perseanol
^{13}C NMR (101 MHz, CD_3OD)
synthetic perseanol
^{13}C NMR (101 MHz, CD_3OD)
ppm

Appendix 5

X-Ray Crystallography Reports Relevant to Chapter 3:
Total Synthesis of the Isoryanoid Diterpene (+)-Perseanol

A5.1 X-RAY CRYSTAL STRUCTURE ANALYSIS

Low-temperature diffraction data (φ- and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to either a PHOTON 100 CMOS detector or a PHOTON II CPAD detector with Cu-K_α radiation (λ = 1.54178 Å) or Mo-K_α radiation (λ = 0.71073 Å) from a $I_\mu S$ HB micro-focus sealed X-ray tube. All diffractometer manipulations, including data collection, integration, and scaling were carried out using the Bruker APEXII software.[1] Absorption corrections were applied using SADABS.[2] The structure was solved by intrinsic phasing using SHELXT[2] and refined against F^2 on all data by full-matrix least squares with SHELXL-2014[2] using established refinement techniques.[3] All non-hydrogen atoms were refined anisotropically. Unless otherwise noted, all hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups and hydroxyl groups). Absolute configuration was determined by anomalous dispersion.[4] Graphical representation of the structures with 50% probability thermal ellipsoids was generated using Mercury visualization software.

*Table A5.1 Crystal and refinement data for compounds **83**, **86**, **96**, and **112**.*

	6-AH-294	**8-AH-130**	**8-AH-013**	**8-AH-261**
Empirical formula	$C_{24}H_{28}O_5$	$C_{24}H_{26}O_5$	$C_{30}H_{42}O_6Si$	$C_{24}H_{28}O_7$, 0.5(H_2O)
Formula weight	396.46	394.45	526.72	437.47
T (K)	100	100	100	100
Crystal system	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P12_11$	$P2_12_12_1$	$P12_11$
a, Å	8.2375(2)	8.1193(4)	10.4593(3)	12.4227(7)
b, Å	13.6626(4)	10.4443(6)	13.1370(4)	10.3715(6)
c, Å	18.0092(5)	11.5888(6)	23.0922(7)	15.5943(9)
α, °	90	90	90	90
β, °	90	95.006(2)	90	93.088(3)
γ, °	90	90	90	90
Volume, $Å^3$	2026.86(10)	978.99(9)	3172.96(16)	2006.3(2)
Z	4	2	4	4
d_{calc}, g/cm^3	1.299	1.338	1.103	1.448
Abs. coeff. (mm^{-1})	0.729	0.755	0.110	0.889
θ range, °	4.061 to 79.151	3.829 to 79.465	2.348 to 27.796	2.838 to 79.031
Abs. correction	Semi-empirical	Semi-empirical	Semi-empirical	Semi-empirical
GOF	1.039	1.024	1.079	1.086
R_1,[a] wR_2,[b] [I>2σ(I)]	0.0244, 0.0595	0.0324, 0.0860	0.0421, 0.0948	0.0609, 0.1521
Flack parameter	0.05(3)	–0.07(5)	0.06(3)	–0.01(6)
Extinction coefficient	0.0035(3)	n/a	n/a	n/a

[a] $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$. [b] $wR_2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

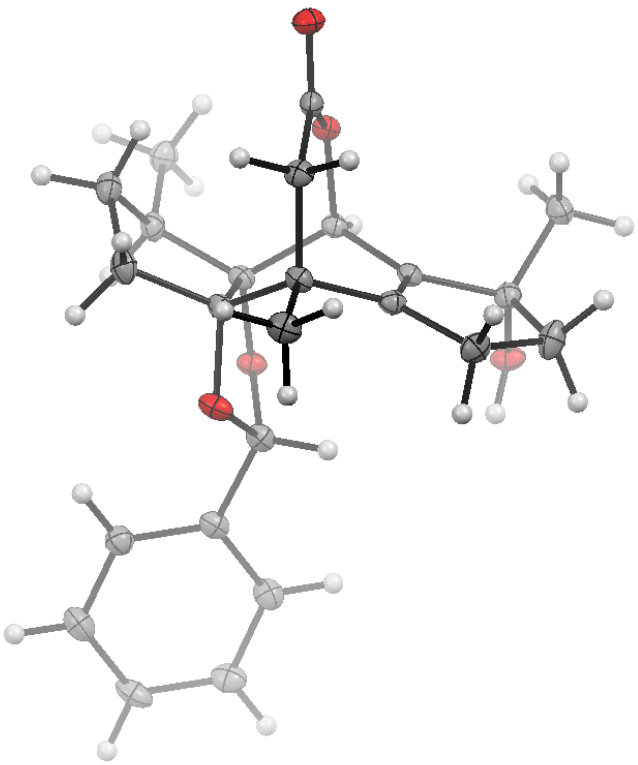


Figure A5.1. *Structure of* ***83*** *with 50% probability anisotropic displacement ellipsoids.*

Special Refinement Details for 83

Compound **83** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = 0.05(3)).[4]

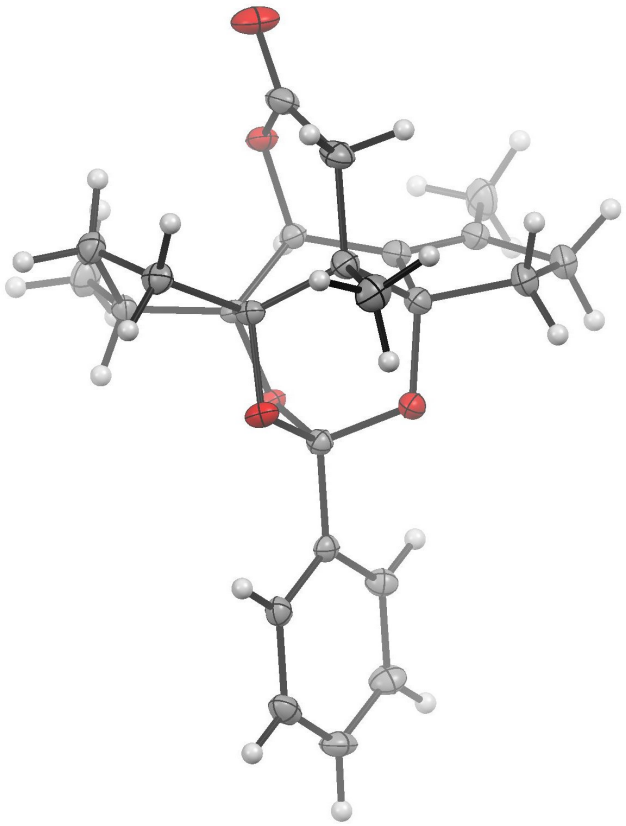


Figure A5.2. *Structure of* ***86*** *with 50% probability anisotropic displacement ellipsoids.*

Special Refinement Details for 86

Compound **86** crystallizes in the monoclinic space group $P12_11$ with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = –0.07(5)).[4]

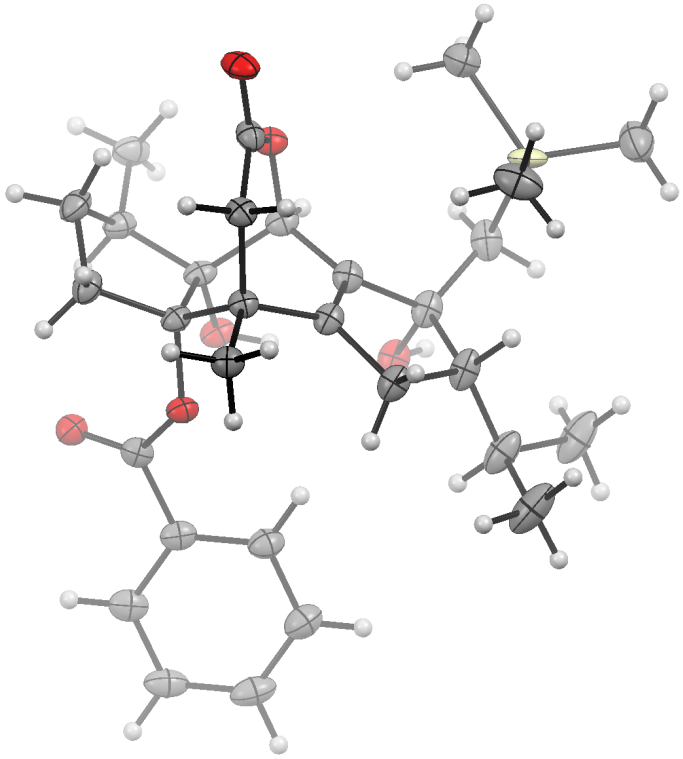


Figure A5.3. *Structure of* ***112*** *with 50% probability anisotropic displacement ellipsoids.*

Special Refinement Details for 112

Compound **112** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit. The trimethylsilyl moiety was disordered over two positions which were refined with relative populations of 60% and 40%. The coordinates for the hydrogen atoms bound to O1 and O3 were located in the difference Fourier synthesis and refined using a riding model. A void analysis with the program PLATON[5] revealed the presence of two large voids and the program SQUEEZE[6] was used to remove the contribution of the disordered electron density inside this void from the structure factors. Absolute configuration was determined by anomalous dispersion (Flack = 0.06(03)).[4] Bayesian statistics further confirm the absolute stereochemistry: P2(true) = 1.000, P3(true) = 1.000, P3(rac-twin) = $0.2x10^{-40}$, and P3(false) = $0.0x10^{0}$.

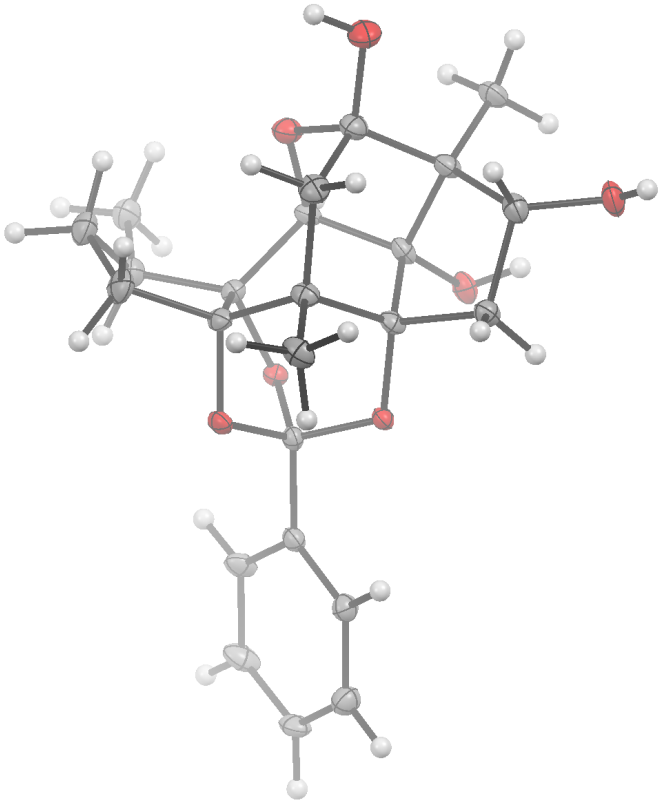


Figure A5.4. *Structure of* ***96*** *with 50% probability anisotropic displacement ellipsoids. Co-crystallized water and the second molecule of* ***96*** *are omitted for clarity.*

Special Refinement Details for 96

Compound **96** crystallizes in the monoclinic space group $P12_11$ with two molecules in the asymmetric unit along with one molecule of water. The hydrogen atoms for all hydroxyl groups and the water molecule were not located in the difference Fourier synthesis and were included into the model at geometrically calculated positions and refined using a riding model. Absolute configuration was determined by anomalous dispersion (Flack = –0.01(6)).[4]

A5.2 REFERENCES

(1) APEX2, Version 2 User Manual, M86-E01078. Bruker Analytical X-ray Systems: Madison, WI.

(2) Sheldrick, G. M. *Acta Cryst.* **2008**, *64*, 112.

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

(4) Parsons, S.; Flack, H. D.; Wagner, T. *Acta Cryst.* **2013**, *69*, 249.

(5) Spek, A. L. *Acta Cryst.* **2009**, *65*, 148.

(6) Vandersluis, P.; Spek, A. L. *Acta Cryst.* **1990**, *46*, 194.

ABOUT THE AUTHOR

Arthur Han was born on November 13th, 1990 to William and Eunjoo Han in Washington, D.C. He grew up in the neighboring Northern Virginia area, where he developed an early interest in science and mathematics. While attending Langley High School, he encountered chemistry for the first time through his coursework and Science Olympiad. His AP Chemistry teacher (and Science Olympiad coach) would ultimately forge a deep interest in chemistry that would persist to this day.

In 2013, Arthur moved to New York, NY where he earned his B.A. in chemistry at Columbia University. Having fortuitously tested out of General Chemistry, he took Organic Chemistry as a freshman with Professors Ron Breslow and Jim Leighton. His captivation for the art cemented his decision to become a chemistry major. As a result, Arthur joined Professor Jack Norton's research group to conduct undergraduate research in organometallic chemistry, focusing on the synthetic applications of metal hydrides in hydrogen atom transfer initiated radical cyclizations. Following two years of research in this arena, Arthur continued his training with Professor Samuel J. Danishefsky at the Memorial Sloan-Kettering Cancer Center. There he pursued the total synthesis of the cytotoxic anthrapyran antibiotic pluraflavin A.

Arthur thereafter moved to the California Institute of Technology to earn his doctoral degree under the direction of Professor Sarah Reisman. His research has focused on the concise total synthesis of highly oxygenated natural products, which has culminated in the first total synthesis of the isoryanoid diterpene (+)-perseanol. Following the completion of his PhD in September of 2018, he will return to the East Coast to join the Route Innovation group in Chemical and Synthetic Development at Bristol-Myers Squibb.