REACTION DEVELOPMENT FOR THE TOTAL SYNTHESES OF THE TERPENOID NATURAL PRODUCTS (+)-PSIGUADIAL B, (+)-RUMPHELLAONE A, AND (–)-ISODOCARPIN

Thesis by

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To my family and friends

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university, to a confident scholar, ready to enter the workforce and change the face of science. Kelsey has and continues to be my inspiration for how to be an incredible scientist and how to be a compassionate and loving person, and I know everyone who has had the pleasure of meeting and getting to know her feels the same way. Thank you for everything. I love you. And you better call me next year.

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ABSTRACT

The *de novo* synthesis of bioactive natural products provides an opportunity to learn more about the mechanism of bioactivity and to develop novel chemistry that is of interest to the synthetic community. Herein, we describe our strategy for the total synthesis of the trans-fused cyclobutane containing meroterpenoid (+)-psiguadial B. Key to this strategy was the development of a photochemical Wolff Rearrangement with asymmetric ketene aminolysis. A palladium-catalyzed C–H alkenylation is used to build structural complexity, and we use two different epimerization strategies to perform an enantiodivergent synthesis of (+)-psiguadial B.

This strategy was explored further and applied to the synthesis of chiral cyclobutanes through a 1,2-difunctionalization strategy, wherein a C–H arylation forges one carbon-carbon bond and a subsequent decarboxylative cross-coupling enables functionalization at the adjacent carbon. This strategy enabled the asymmetric total synthesis of (+)-rumphellaone A in 9 steps.

This report also highlights the work we have conducted in the development of a unified strategy for the enmein-type *ent*-kauranoid natural product, (–)-isodocarpin. We detail our investigation of a convergent cross-electrophile coupling as a means to build the core of (–)-isodocarpin. We also discuss our development of a 1,2-addition/semi-Pinacol rearrangement strategy for the preparation of all-carbon quaternary centers, which can be elaborated to enmein-type *ent*-kauranoid natural product scaffolds.

PUBLISHED CONTENT AND CONTRIBUTIONS

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   J.C.B. contributed to conception of the synthetic strategy, conducted the experiments described herein, prepared the supporting data, and participated in writing the manuscript.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
alk	alkyl
aq	aqueous
AQN	anthraquinone-1,4-diyl diether
Ar	aryl group
atm	atmosphere(s)
BiOX	bi(oxazoline)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2,2'-naphthol
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl

t-Bu	*tert*-butyl
BQ	1,4-benzoquinone
Bz	benzoyl
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
CAM	cerium ammonium molybdate
CAN	ceric ammonium nitrate
cat.	catalyst
Cbz	benzyloxycarbonyl
CD	Cinchonidine
cf.	consult or compare to (Latin: *confer*)
cis	on the same side
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
CN	Cinchonine
CoA	Coenzyme A
conc.	concentrated
conv.	conversion
Cp	cyclopentadienyl
CSA	camphor sulfonic acid

Cy	cyclohexyl
Δ	heat or difference
δ	chemical shift in ppm
d	doublet
d	deutero or dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de novo	starting from the beginning; anew
DIPEA	*N*,*N*-diisopropylethylamine
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene

dr	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
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
g	gram(s)
Grubbs-II	Grubbs' catalyst™ 2nd generation
h	hour(s)
^1H	proton
[H]	reduction
HDA	hetero-Diels–Alder

HFIP	hexafluoroisopropanol
HG-II	Hoveyda–Grubbs' catalyst™ 2nd generation
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
hv	irradiation with light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
iso	isomeric
in situ	in the reaction mixture
J	coupling constant in Hz
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LC/MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide

LED	light-emitting diode
m	multiplet or meter(s)
M	molar or molecular ion
m	*meta*
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
m/z	mass-to-charge ratio
NBS	*N*-bromosuccinimide
ND	not determined
NHC	*N*-heterocyclic carbene
nm	nanometer(s)

nM	nanomolar
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
NPh	naphthyl
Nu^-	nucleophile
o	*ortho*
o-QM	*ortho*-quinone methide
[O]	oxidation
P	peak
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PhMe	toluene
pH	hydrogen ion concentration in aqueous solution
PHAL	1,4-phthalazinediyl diether
PIFA	[bis(trifluoroacetoxy)iodo]benzene
PHOX	phosphinooxazoline
Pin	pinacol
Piv	pivaloyl

pK_a	acid dissociation constant
pm	picometer(s)
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
PyBOX	pyridine-bis(oxazoline)
PyOx	pyridine-oxazoline
PYR	2,5-diphenyl-4,6-pyrimidinediyl diether
q	quartet
QD	Quinidine
QN	Quinine
QuinOx	quinoline-oxazoline
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
rt	room temperature
s	singlet or seconds
S	sinister
sat.	saturated
SET	single-electron transfer
SFC	supercritical fluid chromatography
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
temp	temperature
terpy	2,2′:6′,2″-terpyridine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*’,*N*’-tetramethylethylenediamine

TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
TPAP	tetrapropylammonium perruthenate
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

The Total Synthesis of (+)-Psiguadial B[†]

1.1 INTRODUCTION

The leaves and fruit from the flowering plant *Psidium guajava* have long been used in traditional Chinese medicine to treat a variety of ailments and maladies.[1–5] Intrigued by this plant's medicinal properties, isolation chemists have studied the bioactive constituents, and as a result have isolated a number of bioactive natural products from this shrub.[1–3] Many of these natural products are diformyl phloroglucinol containing natural products, bearing a highly oxygenated aryl ring attached to a terpene fragment.[6–9]

Diformyl phloroglucinol meroterpenoids are a subset of this family which possess excellent medicinal properties.[3–10] These diformyl phloroglucinol containing natural

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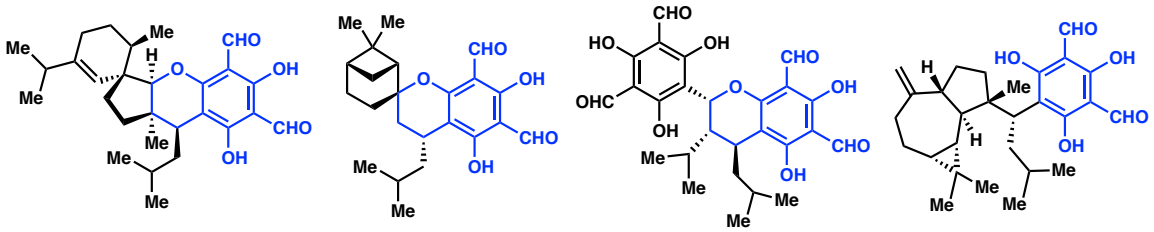
[†] Portions of this chapter were adapted from the following communication: Chapman, L. M.; Beck, J. C.; Lacker, C. R.; Wu, L.; Reisman, S. E. *The Journal of Organic Chemistry* **2018**, *83*, 6066, DOI: 10.1021/acs.joc.8b00728, copyright 2018 American Chemical Society. The research discussed in this chapter was completed in collaboration with Dr. Lauren M. Chapman, a former graduate student in the Reisman Lab and Caitlin R. Lacker, a graduate student in the Reisman Lab.

products are of particular interest to biologists and chemists alike. Biologically, these molecules are known to possess potent anti-cancer, anti-viral, and anti-microbial activities (**1-4**, Figure **1.1**).[6–11] More broadly, the phloroglucinol-containing natural products are a large class of bioactive molecules, comprising over 700 known compounds to date.[6–9] The compounds euglobal-In-3 (**1**),[8] robustadial A (**2**)[12] sideroxylonal B (**3**),[13] and macrocarpal C (**4**, Figure **1.1**),[14] are just a handful of natural products from this family that possess intriguing bioactivity against a variety of pathogens.

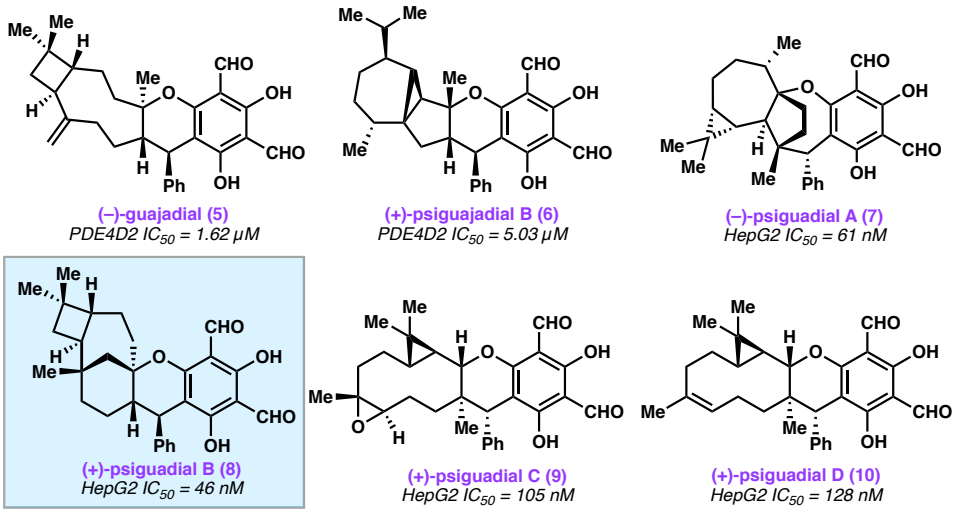
Figure 1.1. *Bioactive diformyl phloroglucinol terpenes*



More recently, four new diformyl phloroglucinol meroterpenoids, psiguadials A–D, were isolated from the leaves of the evergreen shrub, *psidium guajava* (**7–10**, Figure **1.2**).[15,16] The psiguadials are structurally unified in that they all contain a diformyl phloroglucinol subunit attached to a peripheral terpene fragment, joined through an oxygenated heterocycle and a diaryl methane moiety. The terpene fragment of each molecule contains a small, strained ring with geminal-dimethyl substitution. While each of these molecules possesses potent antiproliferative activity, we were particularly drawn to psiguadial B (**8**), as it exhibits the most potent anti-proliferative activity of the group (IC_{50} hep2G = 46 nM), and is the only member of the family containing a *trans*-fused cyclobutane ring.[15] This feature contributes to a synthetically challenging, highly strained

4,7,6 fused framework with six stereogenic centers, including one all-carbon quaternary center.

Figure 1.2. *Diformyl phloroglucinol natural products with remarkable biological activity.*

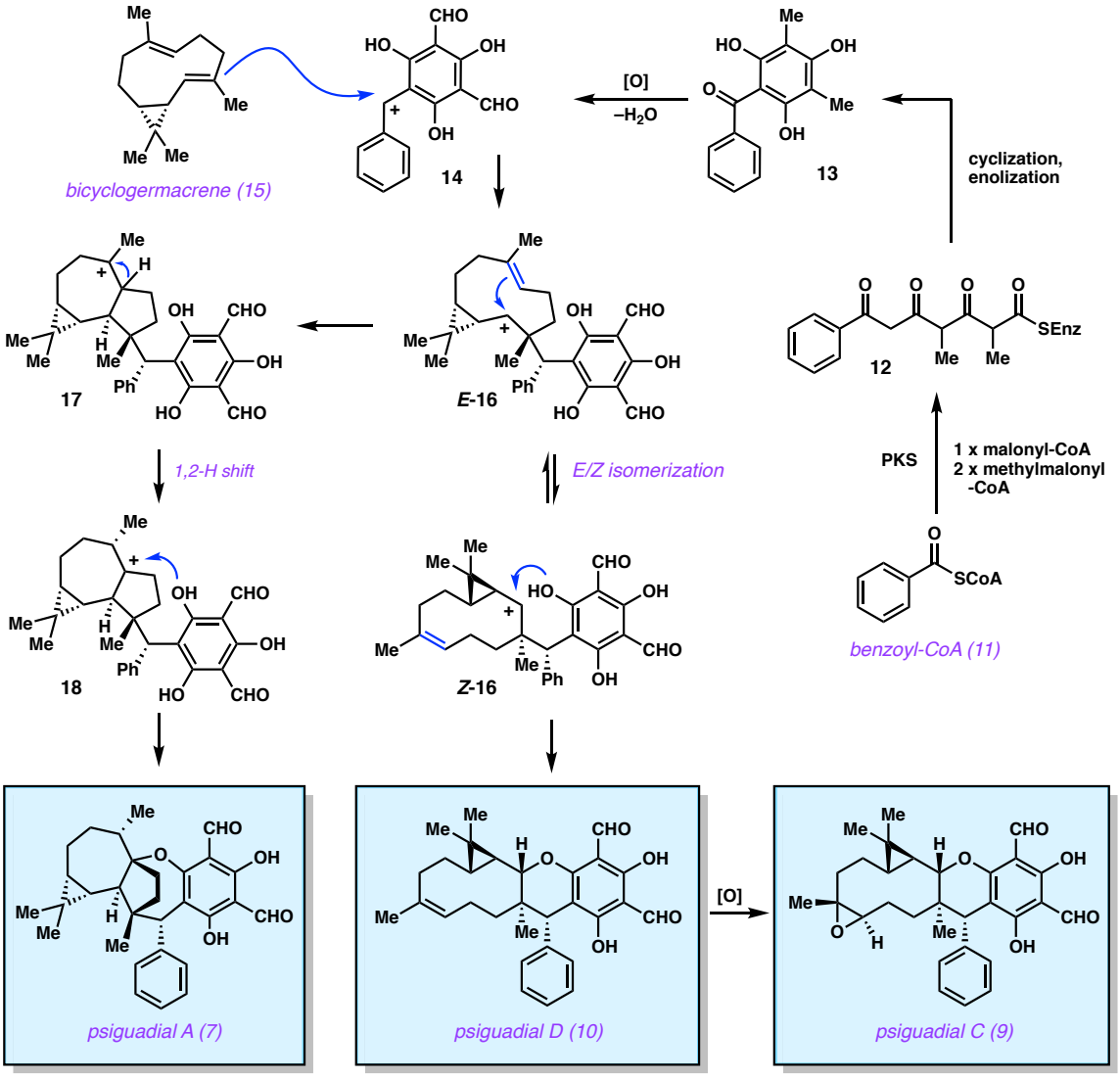


1.2 PROPOSED BIOSYNTHESIS OF THE PSIGUADIAL FAMILY

In their isolation report of psiguadials C and D (**9**–**10**), Shao et al. provided a detailed hypothesis for the biosynthesis of the psiguadial natural products.[16] They propose that synthesis of the psiguadials begins with condensation of benzoyl-CoA units to build the polyketide framework present in **7**–**10** (Scheme **1.1**). Cyclization and enolization of **12** provides diaryl ketone **13**, which is a known isolate from *Psidium guajava*. Benzylic oxidation of **13** followed by formation of the benzylic cation delivers **14**, which is thought to undergo nucleophilic capture by bicyclogermacrene (**15**). Reaction between **14** and **15** produces cyclopropylcarbinyl cation ***E*–16**, which triggers either of two cationic cyclization pathways: C-C bond formation forges the 7-5 ring system that leads to **7**, while **10** arises through isomerization of the olefin, followed by trapping of carbocation in ***Z*-16**

with the pendant phenol. Finally, **9** may be produced by oxidation of the trisubstituted olefin in **10**.

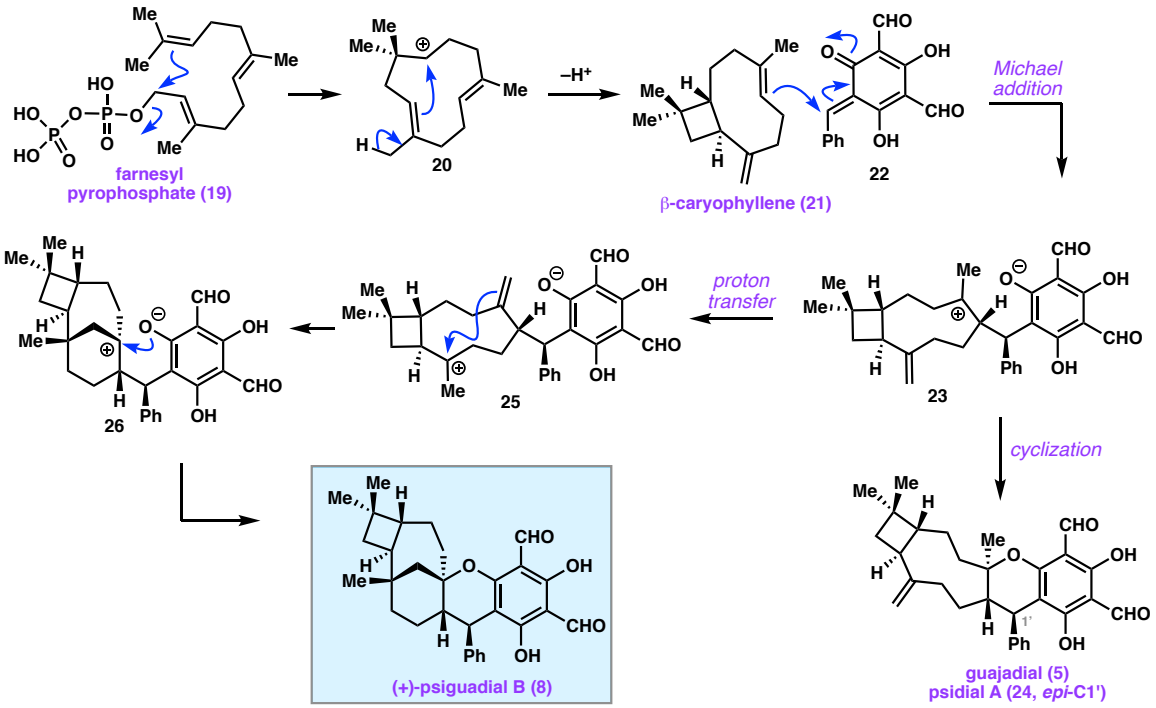
Scheme 1.1. *Proposed biosynthesis of psiguadials A, C, and D (**7**, **9**, **10**)*



An analogous cation cyclization pathway is thought to deliver **8**, from farnesyl pyrophosphate (**19**).[17,18] Intramolecular cyclization of **19** is thought to forge the 11-membered ring present in **20**. Subsequent cyclization provides β-caryophyllene (**21**), which is then thought to undergo a Michael addition with *ortho*-quinone methide (*o*-QM) **22**—likely derived from the known *P. guajava* metabolite 3,5-dimethyl-2,4,6-

trihydroxybenzophenone.[19–21] The resulting compound **23** can directly cyclize to generate **5** and **24**, or can undergo a trans-annular Prins-type cyclization to forge the central bridging ring structure. Bridgehead cation **26** is then poised to undergo cyclization to deliver **8**. Cramer[20,21] and Lee[22] have validated this biosynthetic hypothesis by semi-syntheses of **5**, **8**, and **24** from β-caryophyllene (**21**).

Scheme 1.2. *Proposed biosynthesis of (+)-psiguadial B (**8**).*



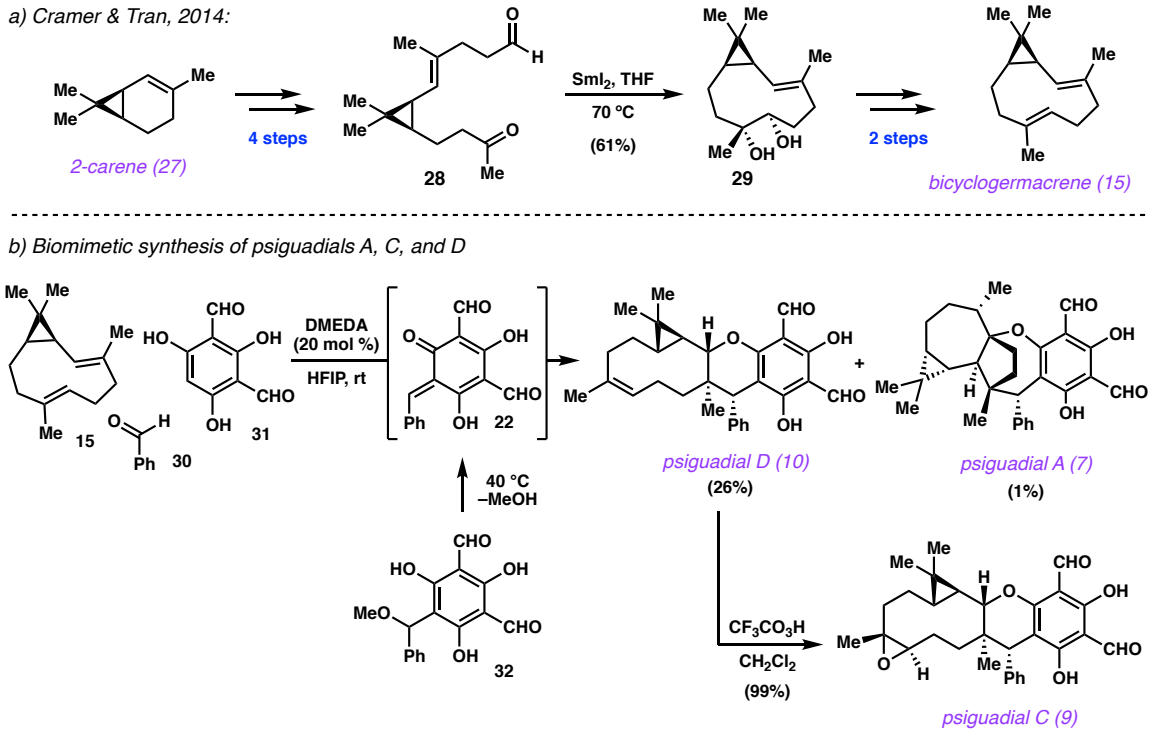
1.3 SYNTHESIS OF RELATED NATURAL PRODUCTS

1.3.1 Biomimetic Strategies for Semi-Synthesis

In 2014, Cramer and Tran were able to access bicyclogermacrene (**15**) starting from naturally occurring 2-carene (**27**) (Scheme **1.3**).[20] Four steps were required to access keto aldehyde **28**, which was poised to undergo reductive cyclization mediated by SmI_2. Further reduction provided **15**. With **15** in hand, Cramer could demonstrate that they could access psiguadials A, C, and D (**7**, **9**, and **10** respectively) through a biomimetic cyclization,

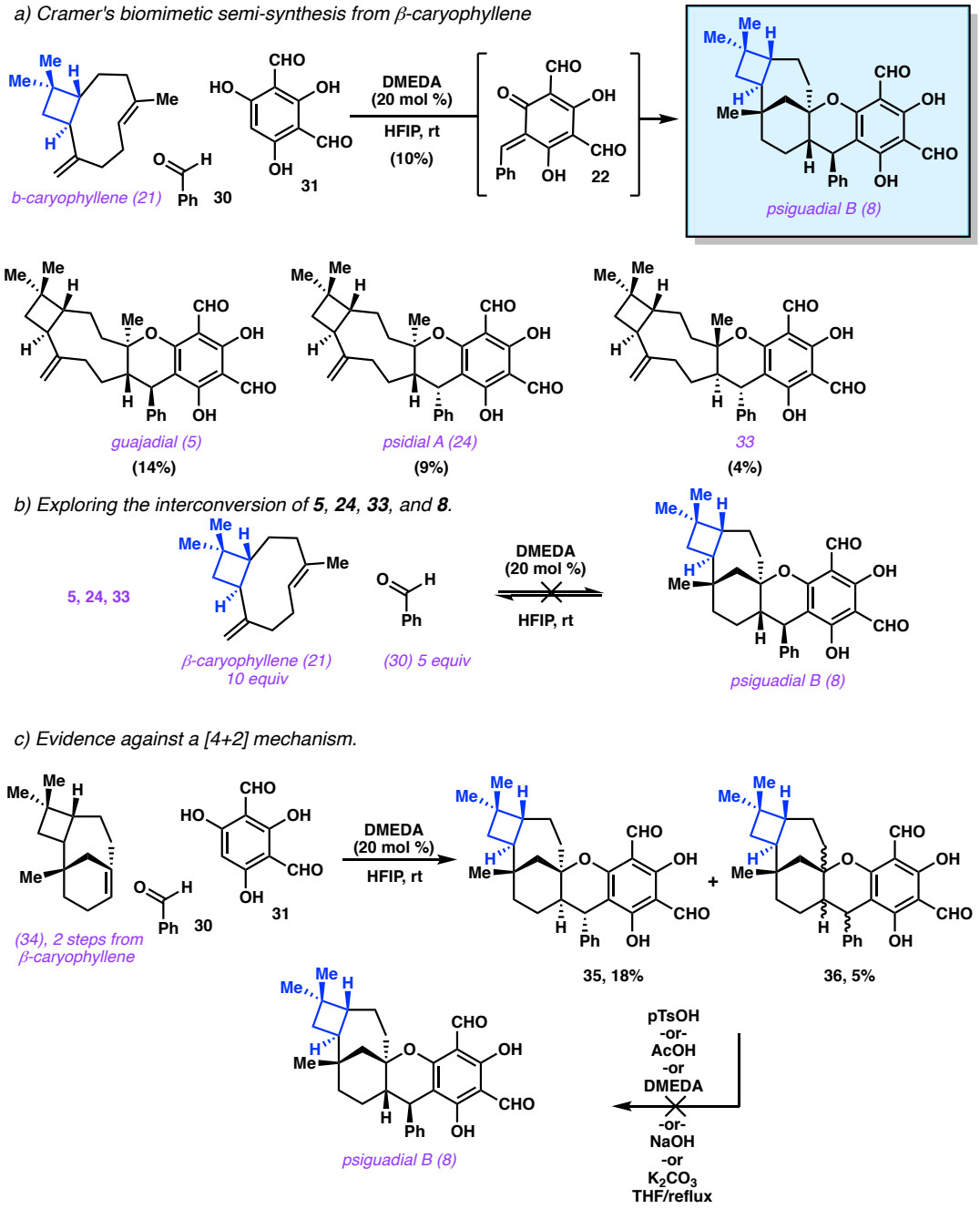
presumably through the intermediacy of **22**. Stepwise Michael addition followed by cationic rearrangement and nucleophilic capture produced **7** and **10**. Psiguadial D (**10**) could be oxidized to deliver psiguadial C (**9**).

Scheme 1.3. *Cramer's biomimetic synthesis of psiguadials A, C, and D*



More recently, Cramer and coworkers published a thorough report in which they investigated the feasibility of accessing psiguadial B (**8**) through a biomimetic cyclization cascade (Scheme **1.4**).[21] Through careful optimization, they found that treatment of **21** with three equivalents of **30** and three equivalents of **31** with catalytic DMEDA in HFIP delivered 10.4% yield of **8** in a single step. This procedure also delivers 26% yield of a mixture of **5**, **24**, and **33**. The authors demonstrate the utility of their method by performing the reaction on a 55 mmol scale. Treatment of the resulting crude mixture with ozone selectively degrades the side products, enabling clean isolation of **8**.[21]

Scheme 1.4. *Cramer's biomimetic semi-synthesis of psiguadial B*



Cramer and Tran also performed a number of calculations and mechanistic experiments to elucidate the biosynthetic formation of **8**. Their calculations indicate that the cyclization cascade is not mediated by an enzyme and that the proposed Michael

addition is exergonic and likely occurs over previously proposed Alder-ene or [4+2] reaction mechanisms. They experimentally observe that **5**, **24**, **33**, and **8** do not interconvert under the reaction conditions and that bridgehead olefin **34** does not produce **8**, solely delivering diastereomeric **35** and **36**. Any attempts to convert **35** and **36** to psiguadial B (**8**) under acid or base promoted cycloreversion were unsuccessful.

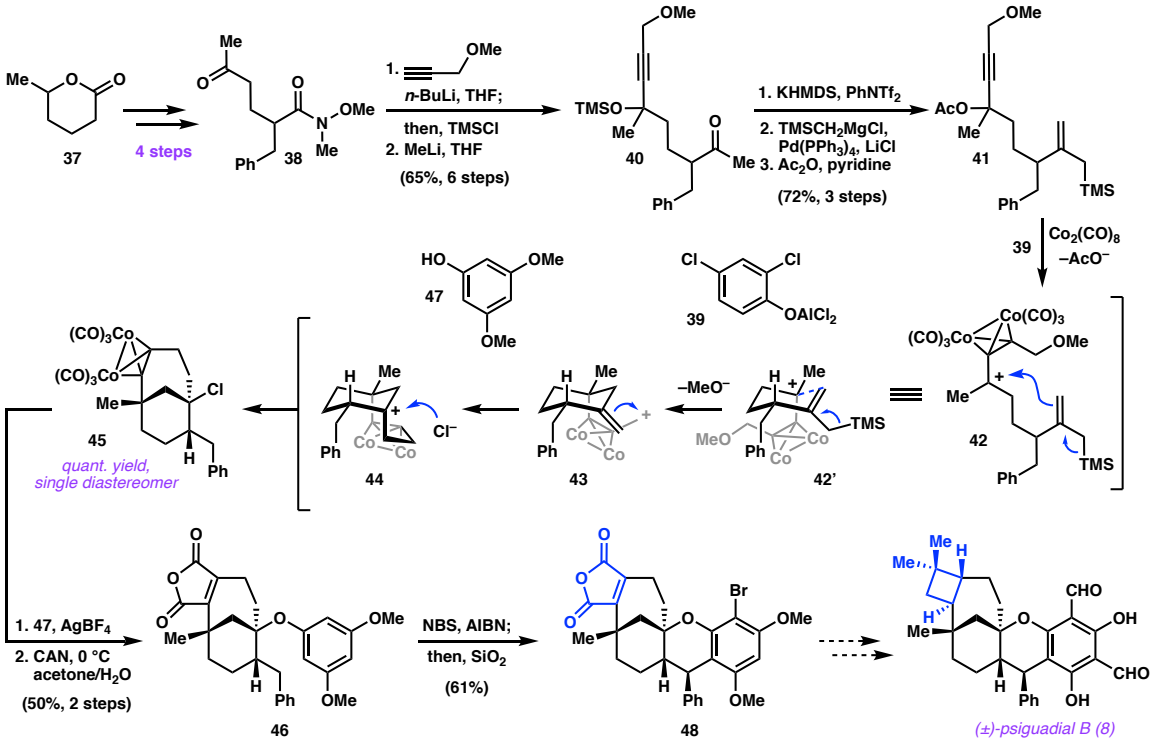
1.3.2 Total Synthesis Efforts Toward Psiguadial B

In February of 2017, Tanino and coworkers disclosed their progress toward a total synthesis of (±)-**8** (Scheme **1.5**).[23] Their synthesis commenced with commercially available lactone **37**. They were able to elaborate **37** to Weinreb amide **38** in 4 steps, which was then subjected to an alkylation protocol in which two 1,2-additions were performed to access TMS ether **40**. Generation of the corresponding enol triflate and subsequent Kumada coupling and acylation delivered **41**, their substrate for a key cyclization reaction. Treatment with $Co_2(CO)_8$ generates cation **42**, which can be intercepted by the pendant allyl silane. A subsequent ionization initiated by loss of methanol enables an isomerization and trapping with chloride to deliver **45**.

With **45** in hand, S_N1 substitution with **47** as the nucleophile followed by oxidative decomplexation of the dicobalt complex provides maleic anhydride **46** with the pendant aryl ether. At this point, benzylic functionalization mediated by NBS and AIBN followed by treatment with silica gel forges the requisite benzylic-aryl bond in **48**. While this step completes the synthesis of the core of **8**, the authors conclude their report stating that efforts to convert **48** to **8** are under way. It is important to note that the installation of the key trans-fused cyclobutane remains a challenge for the Tanino group in their current strategy. To

the best of our knowledge, the work reviewed herein constitutes the only synthetic studies toward psiguadial B (**8**).

Scheme 1.5. *Tanino's progress toward a total synthesis of (±)-psiguadial B*



1.4 A DE NOVO SYNTHETIC STRATEGY FOR THE TOTAL SYNTHESIS OF (+)-PSIGUADIAL B

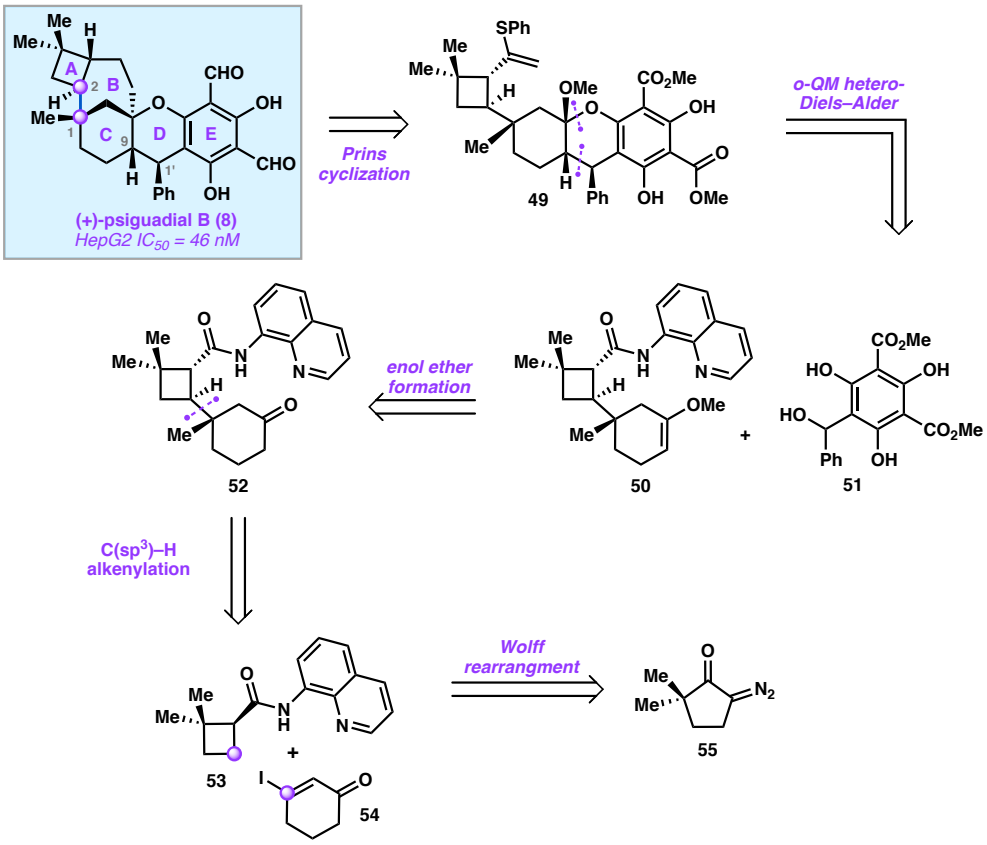
1.4.1 A [4+2] Cycloaddition Strategy

While the previously discussed semi-synthetic campaigns provide direct access to β-caryophyllene-derived natural products, we felt that an abiotic approach to the synthesis of **8** could enable the investigation of novel chemistry that could potentially be applied in broader synthetic contexts.

With this goal in mind, we turned our attention to the structure of **8** and identified a strategic disconnection through the B ring (Scheme **1.6**). We felt that scission of this

carbon-carbon bond would greatly simplify the synthesis of **8**. In the forward sense, we envisioned forming the key 7-membered ring through an intramolecular Prins cyclization between a methyl ketal and a vinyl sulfide (**49**). Although the ring closure to form this strained system was expected to be challenging, the Prins reaction has been previously used for the preparation of bridging polycycles.[24–26]

Scheme 1.6. *First generation retrosynthesis of (+)-psiguadial B*



We hypothesized that pyran **49** could be assembled through a bioinspired *ortho*-quinone methide hetero-Diels–Alder (*o*-QMHDA) reaction between enol ether **50** and an *o*-QM generated from **51**.[27] Although *o*-QMHDA reactions are widely used to construct chroman frameworks, simple acyclic enol ethers or styrenes are typically employed as dienophiles, and are used in excess to avoid *o*-QM dimerization.[28–31] In contrast, the

proposed strategy necessitates use of a functionalized cyclic enol ether, ideally as the limiting reagent. At the outset of these studies, we were unaware of any reported examples in which cyclohexanone-derived enol ethers were employed as dienophiles in *o*-QMHDA cycloadditions; thus, the proposed studies could potentially contribute a new substrate class for *o*-QMHDA reactions. Based on stereochemical analysis of reported *o*-QMHDA cycloadditions, we anticipated that the reaction would favor the desired *anti*-relationship between C1' and C9; however, whether the stereochemistry of **50** would impart the desired facial selectivity in the approach of the heterodiene was less clear.[28,29,32–34]

We envisioned preparing **50** through enolization of the corresponding ketone **52**, which we planned to access through a selective C(sp^3)–H alkenylation reaction between **53** and **54**. While **54** was known,[35] we imagined preparing **53** through a novel Wolff rearrangement with asymmetric trapping of the resulting ketene in order to set the first stereocenter present in **8**.

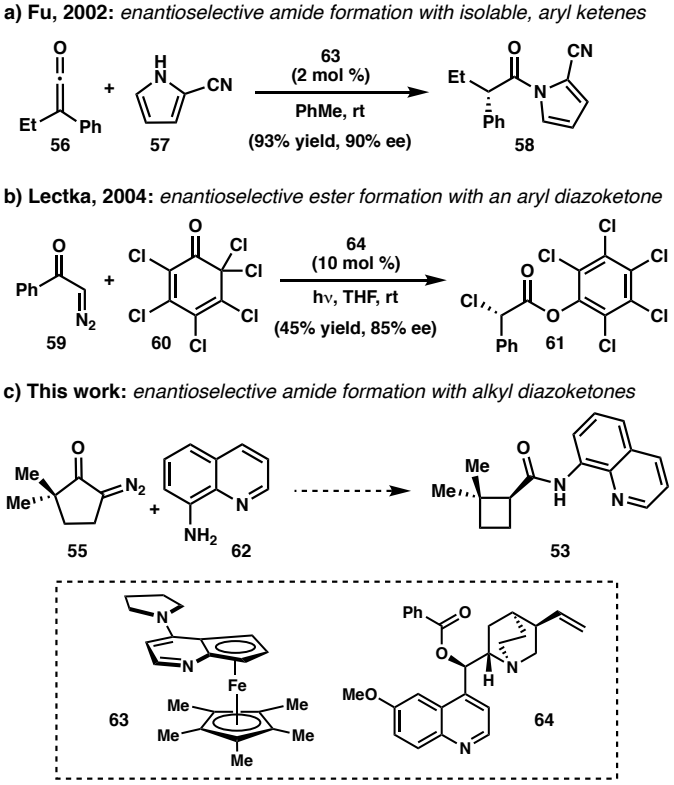
1.4.2 Development of an Asymmetric Wolff Rearrangement

A key question presented by the proposed retrosynthesis was how best to synthesize cyclobutane **53** in enantioenriched form. Elegant studies by Fu and coworkers had demonstrated that *N*-acylpyrroles can be prepared with excellent enantioselectivity from the reaction between aryl ketenes (e.g. **56**) and 2-cyanopyrrole (**57**) using chiral DMAP catalyst **63** (Scheme **1.7a**).[36,37] We hypothesized that a similar transformation could be used to prepare **53** directly from **55** by using 8-aminoquinoline (**62**) as a nucleophile in the presence of an appropriate catalyst. While there were no examples from Fu's work in which the ketene was generated *in situ* photochemically, a single example from Lectka showed

that a ketene could be generated *in situ* by a Wolff rearrangement, and engage in an enantioselective reaction (Scheme **1.7b**).[38]

Following a survey of chiral nucleophilic catalysts known to engage with ketenes,[39–41] it was discovered that irradiation of a mixture of **55** and 3 equivalents of **62** in the presence of 50 mol % (+)-cinchonine (**73**) produced **53** in 61% yield, and 79% ee (Table **1.1**, entry 1). Investigation of various solvents revealed that THF provided the

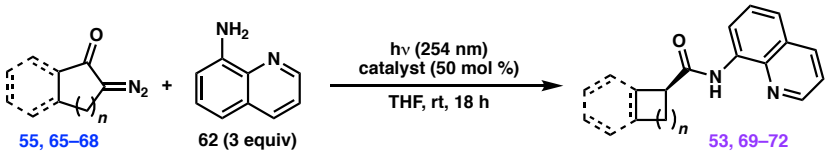
Scheme 1.7. *Enantioselective reactions with ketenes and proposed transformation*

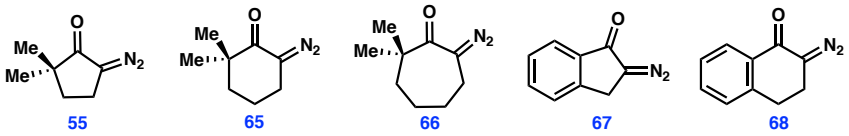


highest levels of enantioselectivity. More concentrated reaction mixtures led to lower yields, presumably due to poor light penetration as a result of the sparing solubility of **73** in THF. When scaling the reaction to quantities relevant for total synthesis (30 mmol), the catalyst loading of **73** could be reduced to 10 mol %, which provided **53** in 62% yield and

79% ee (see Scheme **1.8**). Moreover, enantiomerically pure **53** was obtained after a single recrystallization by layer diffusion.

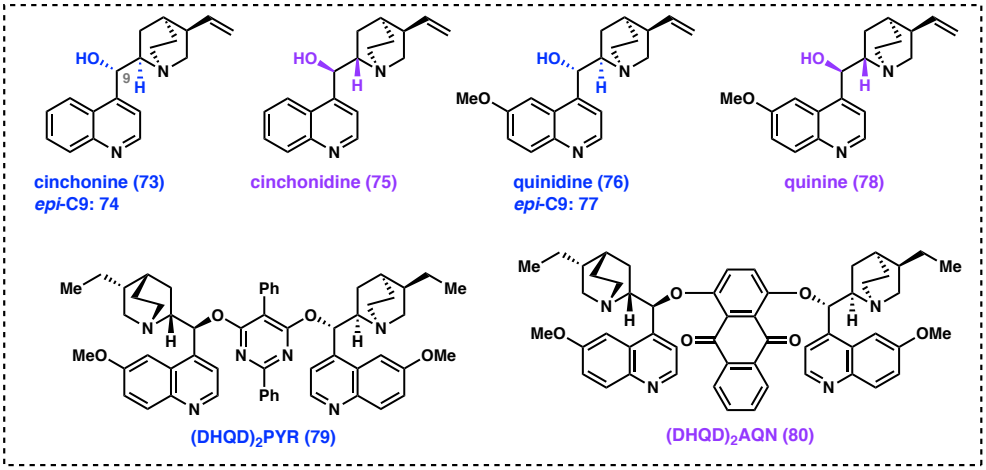
Table 1.1. *Optimization and exploration of substrate scope for tandem Wolff rearrangement/ketene addition*





catalyst	53 entry	yield[a] (%)	ee[b] (%)	69 entry	yield[a] (%)	ee[b] (%)	70 entry	yield[a] (%)	ee[b] (%)	71 entry	yield[a] (%)	ee[b] (%)	72 entry	yield[a] (%)	ee[b] (%)
73	1	61[c]	79	9	*64*	*58*	17	*49*	*64*	25	*48*	*9*	33	*54*	*35*
74	2	*50*	*24*	10	*52*	*64*	18	*60*	*7*	26	*43*	*7*	34	*65*	*42*
75	3	*64*	*–57*	11	*62*	*–22*	19	*56*	*–51*	27	*48*	*–3*	35	*38*	*–20*
76	4	*67*	*64*	12	*69*	*50*	20	59[c]	71	28	*48*	*25*	36	*42*	*23*
77	5	*58*	*48*	13	77[c]	71	21	*55*	*–39*	29	*40*	*7*	37	*61*	*41*
78	6	*65*	*–54*	14	*66*	*0*	22	*54*	*–34*	30	48	*–26*	38	*42*	*–23*
79	7	*90*	*–16*	15	*60*	*–59*	23	*65*	*–7*	31	*47*	*–5*	39	42[c]	*–75*
80	8	*50*	*53*	16	*49*	*–23*	24	*50*	*37*	32	31[c]	34	40	*35*	*–1*

[a] Reactions performed on 0.050 mmol scale and irradiated for 18 hours. Yield determined by ^{1}H NMR analysis versus an added internal standard. [b] Determined by SFC using a chiral stationary phase. [c] Reactions performed on 0.200 mmol scale and irradiated for 48 hours, isolated yield reported.



Although our total synthesis efforts focused on the preparation of **53**, we wondered if this tandem Wolff rearrangement/enantioselective addition reaction could be applied to other α-diazoketone substrates (**65**–**68**). Unfortunately, substantially lower levels of

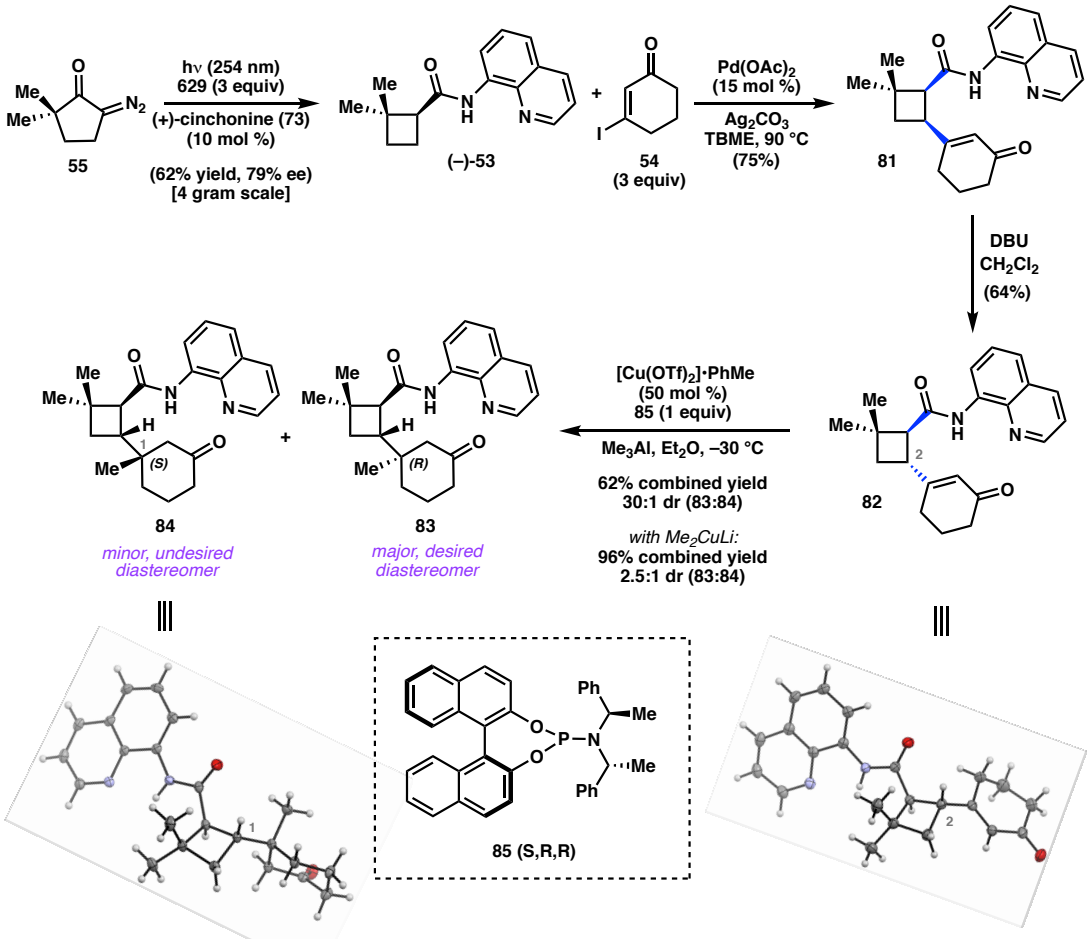
enantioinduction (9–64% ee) were observed using **73** as a catalyst with these substrates (Table **1.1**, entries 9, 17, 25, and 33). Evaluation of alternative cinchona derivatives **74**–**80** revealed that synthetically useful levels of enantioselectivity could be achieved for each substrate, depending on the catalyst. For instance, while **74**–**80** produced **53** with lower enantioinduction (16–64% ee, entries 2–8), catalysts **77** and **76** proved *optimal* for the 6- and 7-membered analogs of **55**, providing amides **69** and **70** in 71% ee (entries 13 and 20). When these reactions were conducted on preparative scale, the catalyst loading could be dropped to 20 mol %, providing cyclopentyl amide **69** (n = 2) in 81% yield and 68% ee and cyclohexyl amide **70** (n = 3) in 67% yield and 65% ee. On the other hand, benzo-fused diazoketones, **67** and **68**, performed best in the presence of dimeric cinchona catalysts **80** and **79** (entries 32 and 39). At present, a general catalyst for the tandem Wolff rearrangement/enantioselective addition of 8-aminoquinoline has not been identified, though further mechanistic investigations may inform future efforts to improve the generality of this reaction.

1.4.3 A Convergent Catalytic Alkenylation

Having identified conditions to prepare multigram quantities of **53** in enantiopure form, we were pleased to find that treatment of **53** with $Pd(OAc)_2$ (15 mol %), Ag_2CO_3, and 3 equivalents of **54** in TBME at 90 °C smoothly effected the $C(sp^3)$–H alkenylation reaction to give **81** in 75% yield on gram scale (Scheme **1.8**). Exposure of **81** to DBU furnished the requisite *trans*-cyclobutane (**82**) via selective epimerization at C2, as determined by deuterium-labeling studies. It was at this stage that single crystals of *trans*-cyclobutane **82** suitable for X-ray diffraction were obtained. Unfortunately, **82** was found to be in the incorrect enantiomeric series for elaboration to natural **8**. To our dismay, this

problem could not be circumvented by simply employing (−)-cinchonidine (**75**) in the tandem Wolff rearrangement/asymmetric ketene addition, as this *pseudoenantiomeric* catalyst afforded (+)-**53** in only 57% ee (Table 1, entry 3). Nevertheless, we elected to advance (–)-**53** in the interest of validating the key reactions in our retrosynthetic analysis as soon as possible.

Scheme 1.8. *C(sp^3)–H alkenylation and quaternary center formation via conjugate addition*

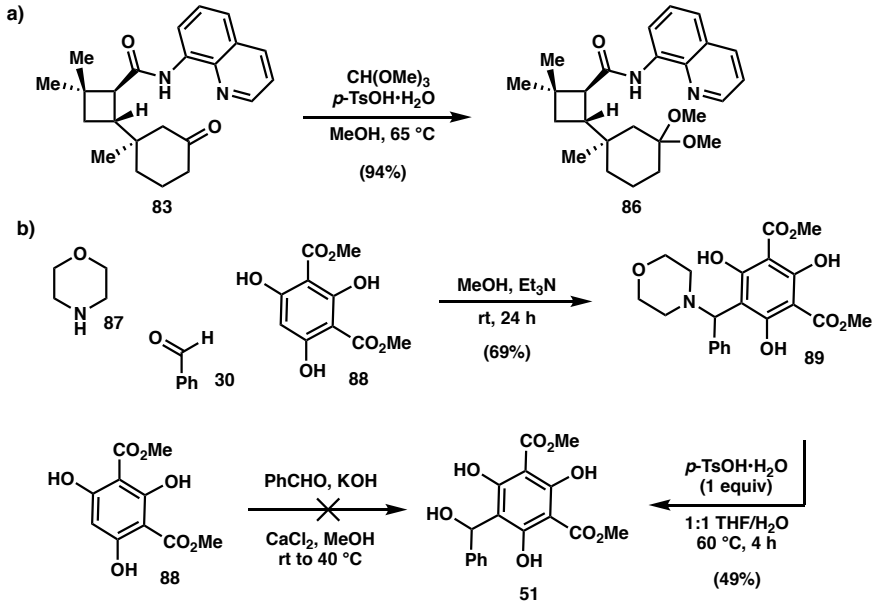


To this end, attention turned to formation of the C1 quaternary center (Scheme **1.8**). Subjection of *cis*-cyclobutane **81** to a number of standard conjugate addition conditions provided only trace yields of the corresponding product (not shown), presumably due to steric encumbrance by the proximal large aminoquinoline group. On the other hand,

treatment of *trans*-cyclobutane **82** with excess Gilman's reagent smoothly furnished **83** and **84** in near quantitative yield as a 2.5:1 mixture of diastereomers, respectively. Separation of the diastereomers by HPLC allowed single crystals of **84** to be obtained, and X-ray analysis unambiguously confirmed that the minor diastereomer (**84**) possessed the undesired (*S*) configuration of the methyl group at the C1 quaternary center, and by analogy, the major diastereomer (**83**) possessed the correct (*R*) configuration at C1.

In an effort to improve the diastereoselectivity of this transformation, we turned to asymmetric catalysis. Fortunately, application of the conditions developed by Alexakis and coworkers for copper-catalyzed conjugate addition[42,43] provided **83** in 62% yield and 30:1 dr, albeit using 50 mol % $[Cu(OTf)_2]$•PhMe and a stoichiometric equivalent of phosphoramidite ligand **85**. Presumably, the high catalyst loading is required due to the presence of the highly-coordinating 8-aminoquinolinamide, which can deactivate the catalyst or inhibit turnover.

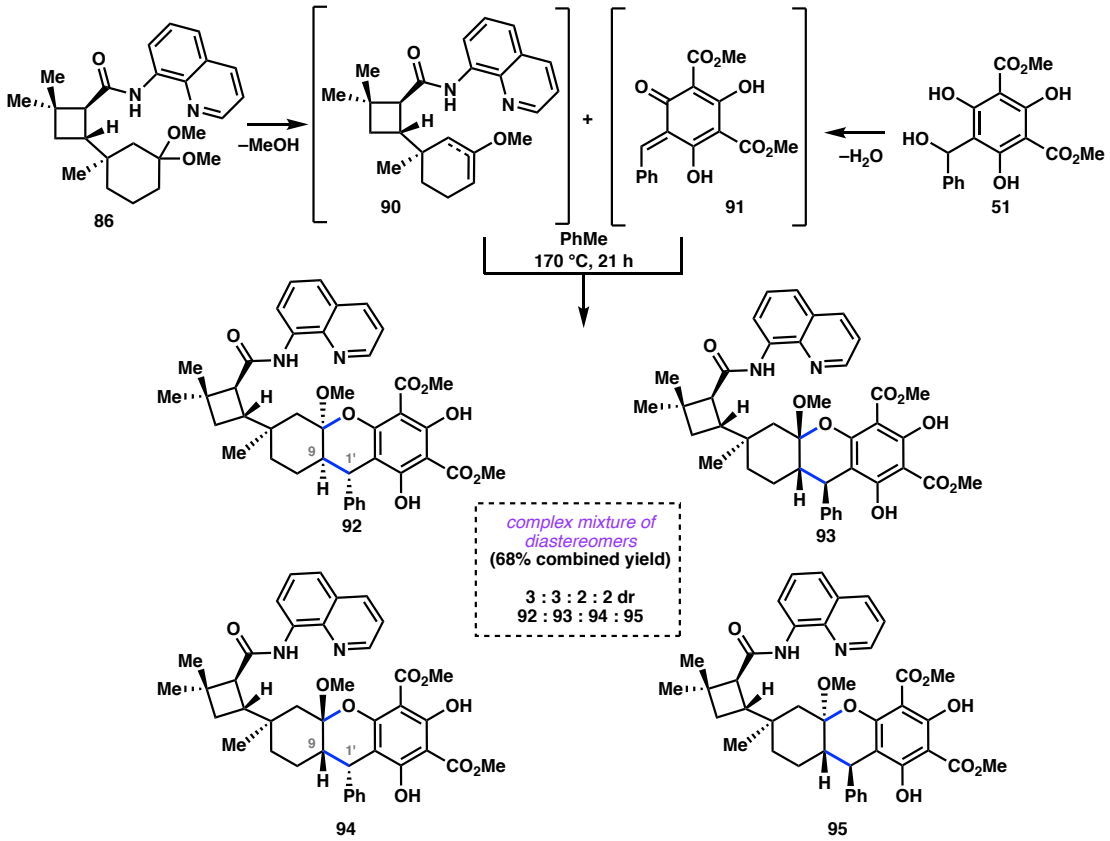
Scheme 1.9. *Synthesis of o-QMHDA cycloaddition reactants*



1.4.4 Investigation of the Key [4+2]

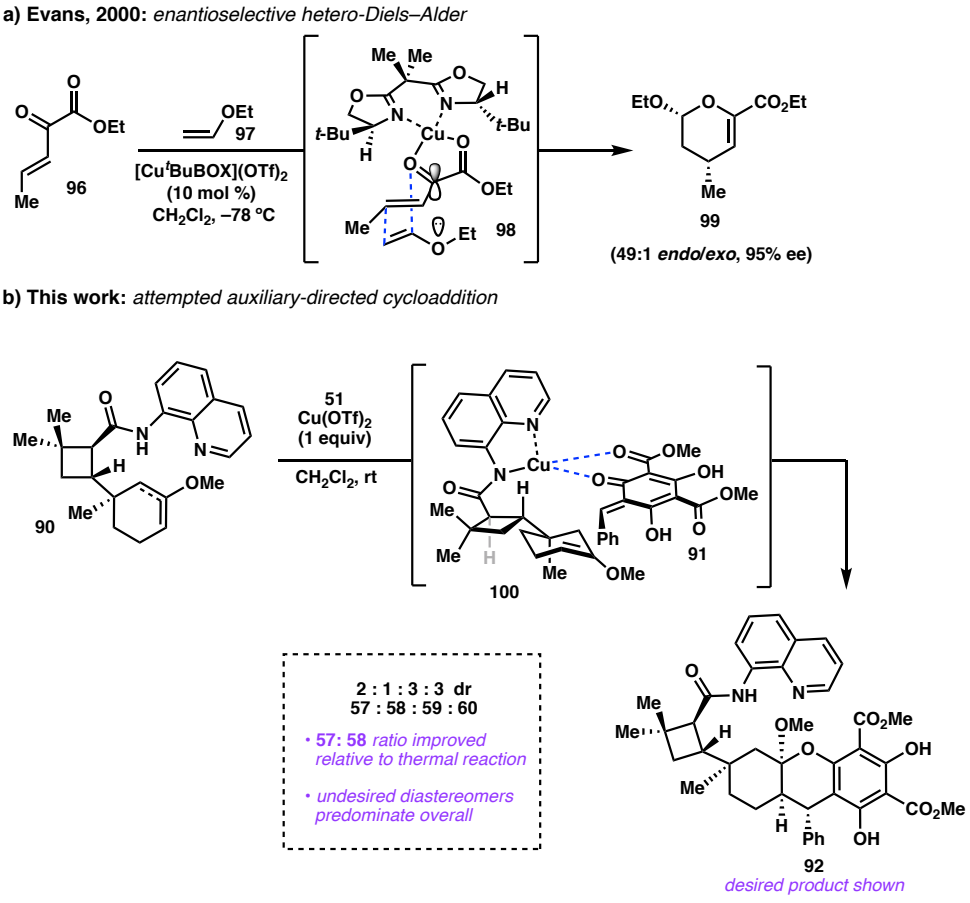
With the quaternary center secured, ketone **83** was converted to the corresponding dimethyl ketal **86** (Scheme 1.9), a precursor to the dienophile for the *o*-QMHDA reaction (*vide infra*). While phenolic aldol conditions failed to produce **51**, this acid-labile *o*-QM precursor was prepared from phloroglucinol **88**[44,45] via the morpholine adduct (**89**, Scheme 1.9b). A control experiment determined that heating of **86** to 170 °C in toluene results in thermal extrusion of methanol to afford a 1:1 mixture of enol ethers **90** (Scheme **1.10**). When a mixture of **86** and **51** was heated to 170 °C for 21 h, the cycloadduct was obtained in 68% yield, albeit as a complex mixture of diastereomers.

Scheme 1.10. *Evaluation of the thermal o-QMHDA cycloaddition*



Analytically pure samples of the four highest abundance diastereomers (**92**–**95**) were obtained by HPLC purification. Spectroscopic analysis by 2D NMR led to the assignment of **92** and **93** as the two major diastereomers, which bear the expected relative *anti* relationship between C9 and C1'. The formation of these products in a ~1:1 ratio indicates that **90** does not exert significant facial selectivity in the *o*-QMHDA reaction. The *trans*-fused isomer, **95**, presumably results from thermal equilibration of the ketal under the reaction conditions.

Scheme 1.11. *Attempted auxiliary-directed cycloaddition*



In considering how to improve the selectivity for desired diastereomer **92**, we drew inspiration from Evans' highly enantioselective inverse-demand hetero-Diels–Alder

chemistry, which proceeds via bidentate coordination of heterodienes such as **96** to a chiral Cu(II)-BOX Lewis acid catalyst (Scheme **1.11a**).[46] We envisioned that chelation of the aminoquinoline in **90** to a Cu complex could engage **91** as depicted in Scheme **1.11b**, thereby directing the *o*-QM to the top face of enol ether **90** (Scheme **1.11b**). Formation of **91** could be induced by the equivalent of triflic acid generated via complexation of $Cu(OTf)_2$ with aminoquinoline.[47,48]

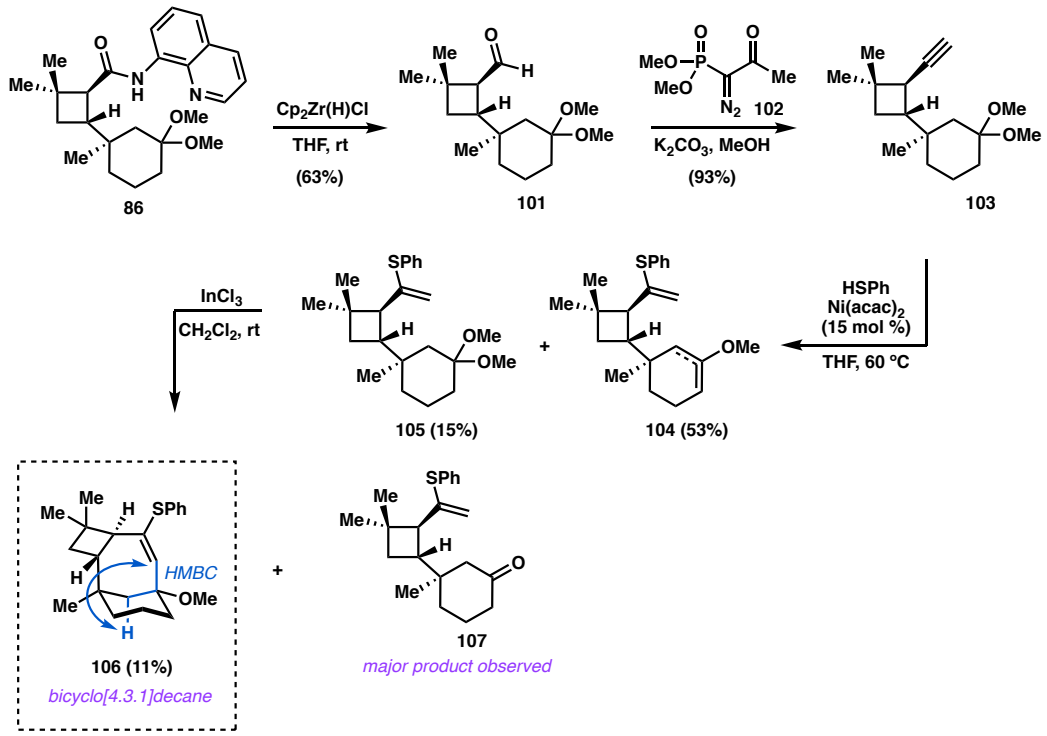
To test this hypothesis, enol ether **90** was prepared by heating in PhMe, and after exchanging the solvent for CH_2Cl_2, $Cu(OTf)_2$ and **51** were added. Analysis of the crude reaction mixture by ^1H NMR revealed that although the ratio of **92**:**93** had improved relative to the thermal reaction, significant quantities of the undesired isomers, **94** and **95**, were still formed. Moreover, this reaction suffered from lower overall yields due to rapid hydrolysis of **90** and reversion of **51** to phloroglucinol **88**. At this stage, it was clear that implementation of this strategy would require a significant investment in reaction optimization, and we felt that such an effort would only be warranted if the proposed late-stage Prins reaction were proved feasible. Thus, attention turned to assessing this key reaction in a model system.

1.4.5 Exploring a Model Prins Cyclization

To this end, the aminoquinoline auxiliary in **86** was reductively cleaved by treatment with Schwartz's reagent to furnish aldehyde **101**, which was homologated to alkyne **103** using the Ohira–Bestmann reagent (**102**) (Scheme **1.12**). Nickel-catalyzed hydrothiolation[49] proceeded with good regioselectivity to give vinyl sulfide **105** in low yield, mainly due to the facile conversion of this intermediate to a mixture of enol ethers **104** under the reaction conditions.

Unfortunately, exposure of ketal **105** to a variety of Lewis acids led to hydrolysis, yielding ketone **107** in nearly all cases. The use of $InCl_3$,[50] however, delivered the desired Prins product **106** in 11% yield. Formation of the 7-membered ring was confirmed by a key HMBC correlation between the C12 axial proton and the distinct sp^2 C7 signal at δ 140 ppm. Although the formation of the seven-membered ring through a Prins cyclization was promising, our excitement was tempered by the fact that **106** was obtained in poor yield and challenges were encountered with reproducibility. Taken together with the significant diastereoselectivity issues plaguing the *o*-QMHDA reaction, we revised our retrosynthesis.

Scheme 1.12. *Model studies toward Prins cyclization*

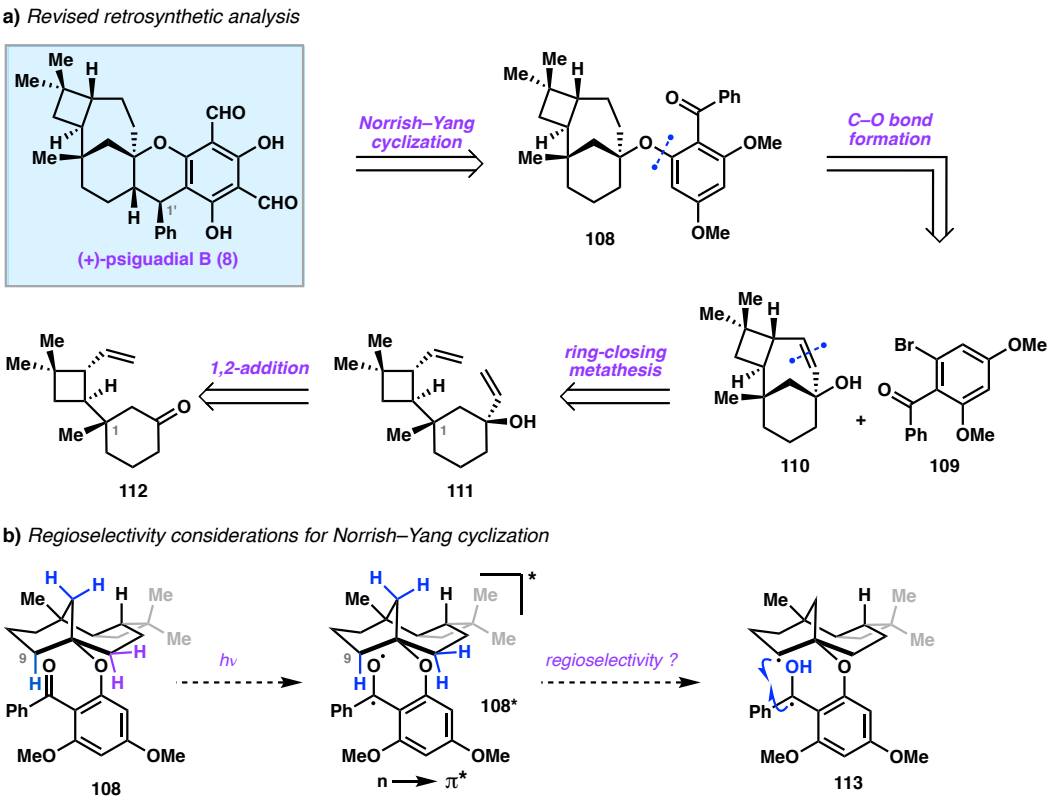


1.4.6 Second Generation Norrish-Yang Cyclization Strategy

In our revised retrosynthesis, we envisioned that the chroman substructure could be constructed via a modified Norrish–Yang cyclization,[51–53] revealing **108** as a key

intermediate (Scheme **1.13**). Benzophenones such as **108** are known to undergo photoexcitation upon irradiation with UV light to give triplet species (i.e. **108***) that can engage in Norrish type-II 1,5-hydrogen atom abstraction and subsequent radical recombination.[54–56] In the absence of any available γ or δ-hydrogens, it was hypothesized that **108*** could abstract a hydrogen atom from C9 to generate diradical **113**.[57–59] Recombination of the carbon-centered radicals would furnish the core of **8**.

Scheme 1.13. *Second generation retrosynthetic analysis*



We recognized that achieving the desired *regioselectivity* could prove challenging since the C7 and C12 methylenes in **108*** were also within range for 1,7-H–atom abstraction (Scheme 1.13b). Although the outcome of this transformation was uncertain, conformational analysis suggested that the product resulting from hydrogen atom abstraction at C9 would produce the least sterically encumbered chroman product.

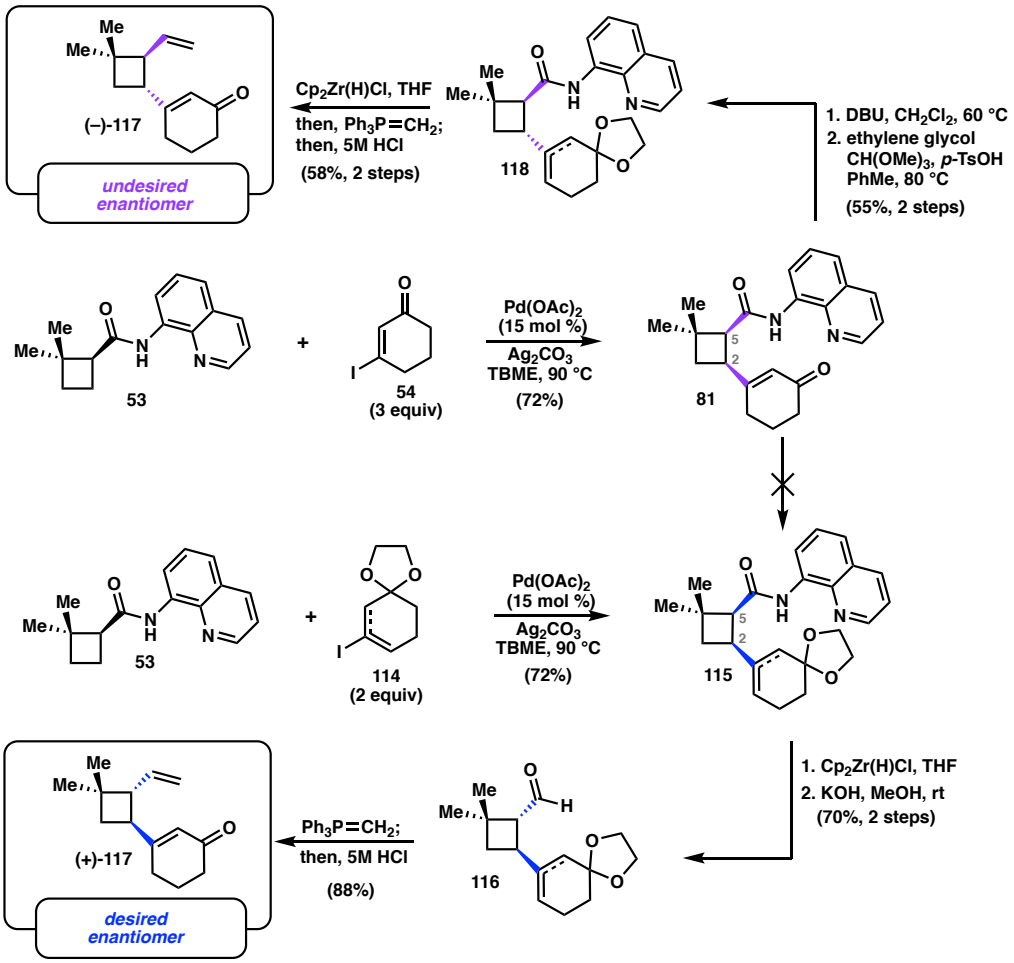
Moreover, this strategy was particularly appealing since it was expected that **108** could be assembled in an expedient and convergent fashion. Benzophenone **108** was envisioned to be accessible from tertiary alcohol **110** via an intermolecular *O*-arylation reaction with aryl bromide **109**.[60–63] We reasoned that the strained 7-membered ring in **110** could be formed by ring-closing metathesis, leading back to vinyl ketone **112**, which could in turn be synthesized from known intermediates prepared during our studies of the C(sp^3)–H alkenylation/asymmetric Wolff rearrangement.

With this revised retrosynthetic plan, we set out to prepare vinyl ketone **112**, and to also address two key challenges identified in the first generation approach: 1) to lower the catalyst loading in the conjugate addition reaction used to set the C1 quaternary center, and 2) to develop an epimerization sequence to prepare vinyl ketone **112** in the correct enantiomeric series from quinolinamide (–)-**53**. In terms of the latter challenge, we anticipated that the desired enantiomeric series could be accessed by epimerization of compounds derived from **53** (e.g. **81**) at C5 instead of C2 (Scheme **1.14**). A straightforward approach would involve disfavoring γ-deprotonation at C2 by masking the ketone of **81** in order to advance to a C5 epimerization substrate. Unfortunately, these efforts proved unfruitful, as ketalization of **81** under a variety of conditions always resulted in rapid epimerization at C2 to furnish *trans*-cyclobutane **118** in low yields.

Instead, it was recognized that **115** could be accessed directly by coupling **53** with vinyl iodide **114**. To our delight, the Pd-catalyzed coupling with vinyl iodide **114** performed even better than its enone counterpart (**54**), requiring only 2 equiv of **114** to furnish **115** in 72% yield on a gram scale. Exposure of **115** to Schwartz's reagent effected reduction to the corresponding *cis*-aldehyde, which was epimerized at C5 by treatment with

KOH in methanol to give *trans*-aldehyde **116** in 70% yield over the two steps. Gratifyingly, Wittig methylenation and hydrolysis provided (+)-**117**, the required enantiomer for synthesis of natural psiguadial B (**8**). In addition, cross-coupling of **114** eliminated a linear protection step and substantially improved the material throughput.

Scheme 1.14. *Development of enantiodivergent cross-coupling strategies*



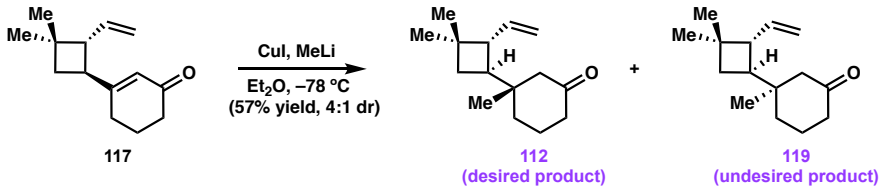
To demonstrate that either enantiomer of **117** can be prepared using a single enantiomer of organocatalyst, an alternative sequence was also developed. Epimerization of **81** to the *trans*-cyclobutane (**82**) under the previously developed conditions, followed by ketalization provided **118**. Reductive cleavage of the aminoquinoline auxiliary gave the

corresponding aldehyde (*ent*-**116**), which was telescoped through a Wittig olefination and hydrolysis as before to afford vinyl enone (−)-**117** in 58% yield over the two steps.

1.4.7 Development of a Catalytic Conjugate Addition

With the desired enantiomer of enone **117** in hand, attention turned to the installation of the C1 quaternary center using a catalytic asymmetric conjugate addition. While we were pleased we could observe high levels of the desired diastereomer using a chiral controller with substrate **82** (Scheme **1.8**), we hypothesized that high catalyst loadings were necessary because the aminoquinoline was sequestering the copper and therefore precluding catalyst turnover. After determining that we were no longer going to rely on using this moiety to direct the [4+2] reaction, we reasoned that installation of the quaternary methyl group after cleavage of the directing group could enable the development of a much more efficient conjugate addition, this time on a substrate lacking the strongly coordinating aminoquinoline.

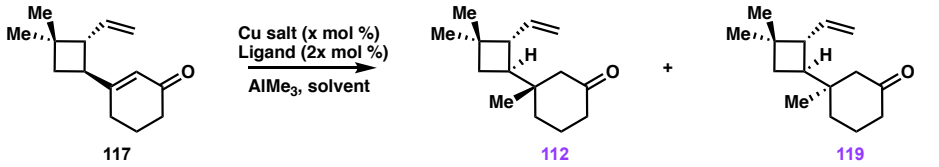
Scheme 1.15. *Assessing substrate-controlled diastereoselectivity*



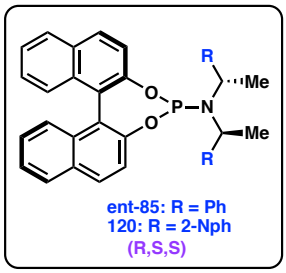
In order to assess the inherent selectivity for conjugate addition of **117**, we performed a conjugate addition of **117** using the achiral Gilman's reagent.[64] As with the original *trans*-cyclobutane **82**, we observed slight selectivity for the desired diastereomer. We hoped to enhance this intrinsic selectivity by exploring chiral copper catalysts reported by the Alexakis lab.[42,43]

Initial experiments performed to investigate our ability to *enhance* the intrinsic diastereoselectivity for the conjugate addition indicated improved diastereoselectivity, with significantly enhanced dr with the enantiomeric ligand (***ent*-85**) we had previously employed on the quinolinamidyl enone **82** (Table **1.2**, entries 1–5). We hoped that lowering the reaction temperature would restrict the conformational freedom of the sigma bond linking the cyclobutane and the cyclohexene rings and improve the dr; however, we found that the best balance of yield and diastereoselectivity was achieved at –30 ºC (Table **1.2**, entry 3). We hypothesize that the poorer reactivity observed at lower temperatures was due to decreased catalyst solubility.

Table 1.2. *Optimization and exploration a copper-catalyzed conjugate addition*



	entry	Cu source	Cu mol %	temp °C	solvent	dr (112 :119)	isolated yield
ent-85	1	CuTC	10	–30	Et_2O	9.9:1	51
	2	CuTC	15	–30	Et_2O	8.9:1	97
	3	CuTC	10	–78 to rt	Et_2O	9.9:1	62
	4	$(CuOTf)_2$·PhMe	10	–78 to –60	TBME/DME	8.7:1	75
	5	$(CuOTf)_2$·PhMe	15	–30	TBME	8.4:1	72
120	6	CuTC	10	–30	Et_2O	8.5:1	70
	7	CuTC	15	–30	Et_2O	6.9:1	95
	8	$(CuOTf)_2$·PhMe	15	–30	TBME	6.8:1	77
	9	$(CuOTf)_2$·PhMe	10	–30	Et_2O	6.9:1	86
	10	CuTC	10	–30	TBME/DME	7.2:1	84
	11	$(CuOTf)_2$·PhMe	10	–30	TBME/DME	7.1:1	82
	12	$(CuOTf)_2$·PhMe	10	–78 to –60	TBME/DME	6.5:1	85

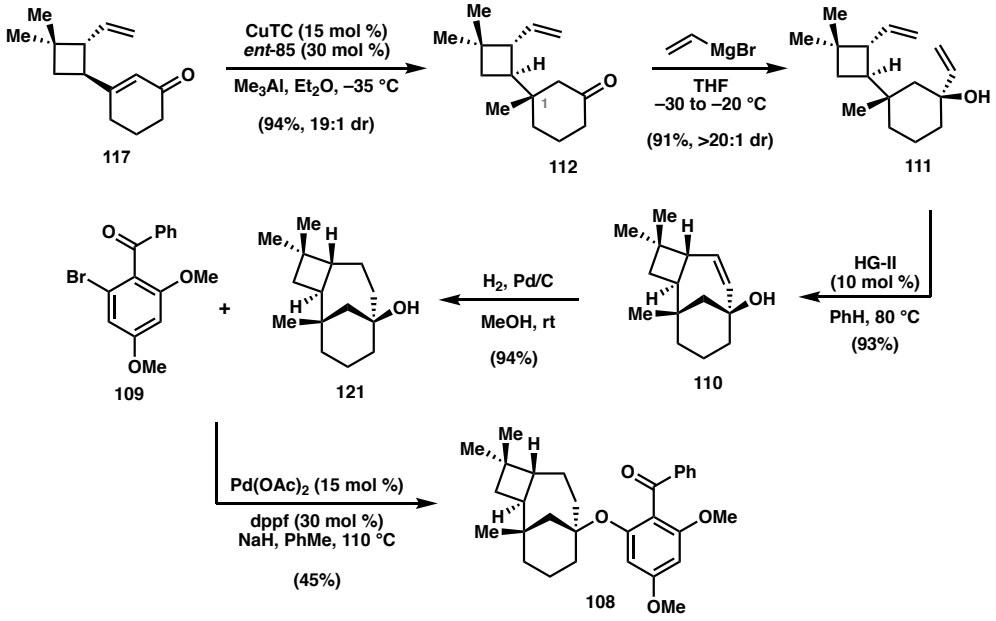


We also attempted to investigate the use of a bulkier ligand in order to further enhance the observed diastereoselectivity. We initially thought that extending the chiral information through the incorporation of a napthyl substituent would impart more diastereocontrol. Much to our surprise, the utilization of the bulkier (*R*,*S*,*S*)-configured **120**

failed to enhance the diastereoselectivity of the catalytic conjugate addition. We were unable to identify any conditions superior to the combination of CuTc and ***ent*-85** at –30 ºC, and we ultimately used these conditions to set the all carbon quaternary center for elaboration to psiguadial B (**8**).

1.4.8 Elaboration to a Norrish-Yang Substrate

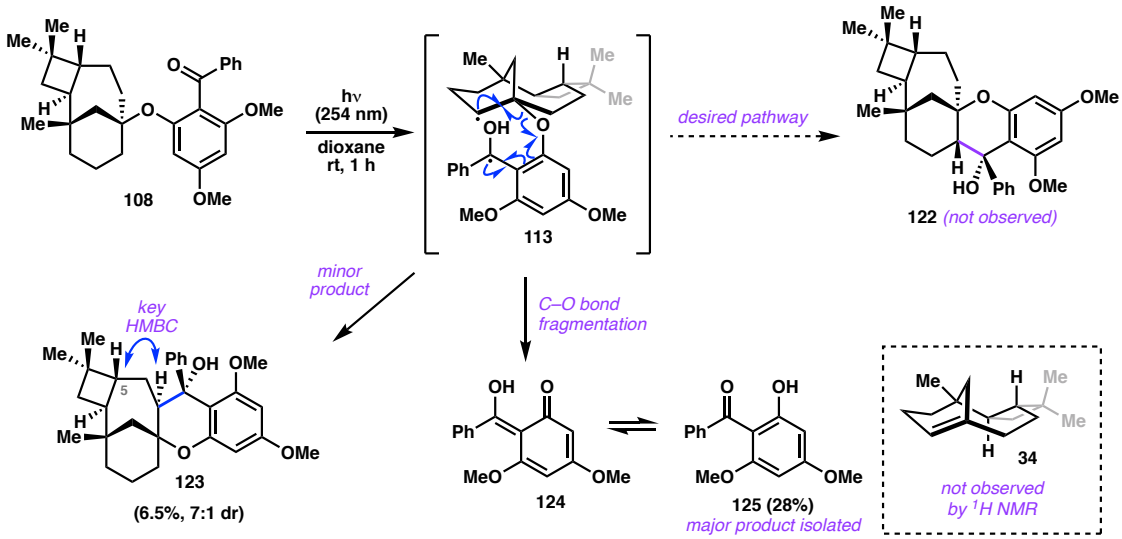
Scheme 1.16. *Elaboration to Norrish-Yang benzophenone*



Gratifyingly we were pleased to find that use of CuTC (15 mol %) in conjunction with ligand ***ent*-85** (30 mol %) provided **112** in 94% yield and 19:1 dr (Scheme **1.16**), providing superior results to what we had observed during reaction optimization. We hypothesize that this is due to improved stirring and more efficient cooling of the reaction in a flask rather than in a vial. Addition of vinyl Grignard to ketone **112** proceeded uneventfully, providing alcohol **111** in excellent yield and diastereoselectivity. Gratifyingly, exposure of **111** to second-generation Hoveyda–Grubbs catalyst at elevated temperature delivered bridged bicycle **110** in 93% yield. Subsequent hydrogenation under

standard conditions led to tertiary alcohol **121**. After some experimentation, we found that the combination of $Pd(OAc)_2$ and dppf catalyzed the intermolecular *O*-arylation between **121** and aryl bromide **109**, affording aryl ether **108** in 45% yield. Unfortunately, this transformation proved capricious, and attempts to improve the yield through further optimization were unsuccessful. Nevertheless, a sufficient amount of **108** was obtained to evaluate the key Norrish–Yang cyclization.

Scheme 1.17. *Evaluation of the Norrish-Yang cyclization*



With **108** in hand, we were poised to investigate the key Norrish-Yang cyclization event. Irradiation of **108** with 254 nm light in deoxygenated dioxane led to complete consumption of starting material within 1 hour and produced a complex mixture of new products. The formation of the undesired Norrish–Yang product **123** was confirmed by 2D NMR spectroscopy; a prominent HMBC correlation was apparent between C5 and the newly formed methine proton at C7, and several key NOE signals were consistent with the stereochemical assignment (Scheme **1.17**). Thus, while the anticipated *reactivity* was

observed, **123** results from the wrong *regioselectivity*, and was isolated in 6.5% yield—a result that would likely be difficult to substantially improve through reaction optimization.

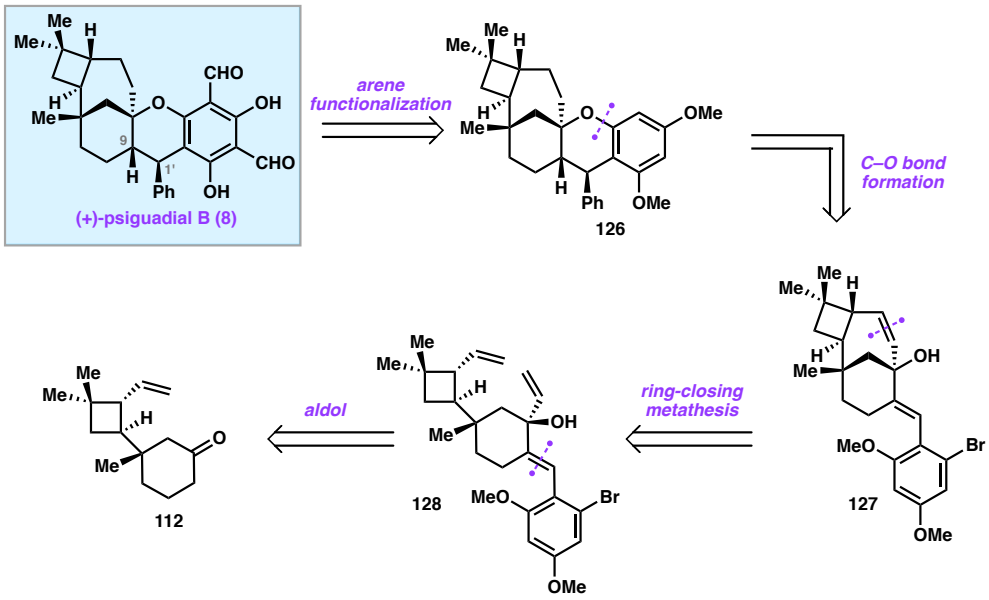
Notably, the major compound isolated from this reaction is phenol **125**, which was obtained in 28% yield. This side product presumably arises by fragmentation of diradical species **113** (or the diradical resulting from H-atom abstraction at C7), wherein C–O bond cleavage expels enol tautomer **124**; the resulting terpene-based fragment likely undergoes further decomposition, as alkene **34** or related compounds were not isolated. In an effort to investigate whether this competing pathway could be suppressed, we examined a number of different solvents and irradiation wavelengths in a model system, but observed rapid formation of phenol **125** in all cases. Having determined that the late-stage Norrish–Yang cyclization was an untenable strategy to complete the chroman core of **8**, an alternative synthetic route was devised.

1.4.9 A Third Generation Strategy

While our previous strategies were unsuccessful in delivering **8**, we were pleased to see that we had established that we could form the challenging bicyclo[4.3.1]decane through a ring-closing metathesis reaction and that we could forge a difficult O-aryl bond under transition metal catalysis. With these key findings in mind, we sought to revise our synthetic plan (Scheme **1.18**). We simplified **8** to **126** and elected to construct the C9–C1' bond at an earlier stage (Scheme **1.16**). Invoking a similar disconnection through the C–O aryl bond as in our second-generation route, it was anticipated that an *intra*molecular ring closure would prove more reliable than the challenging intermolecular arylation employed previously (see Scheme **1.16**). This bond scission revealed aryl bromide **127**, which could

be accessed using the established ring-closing metathesis, while the arene functionality at C9 could be installed via aldol condensation with vinyl ketone **112** and a suitable aldehyde.

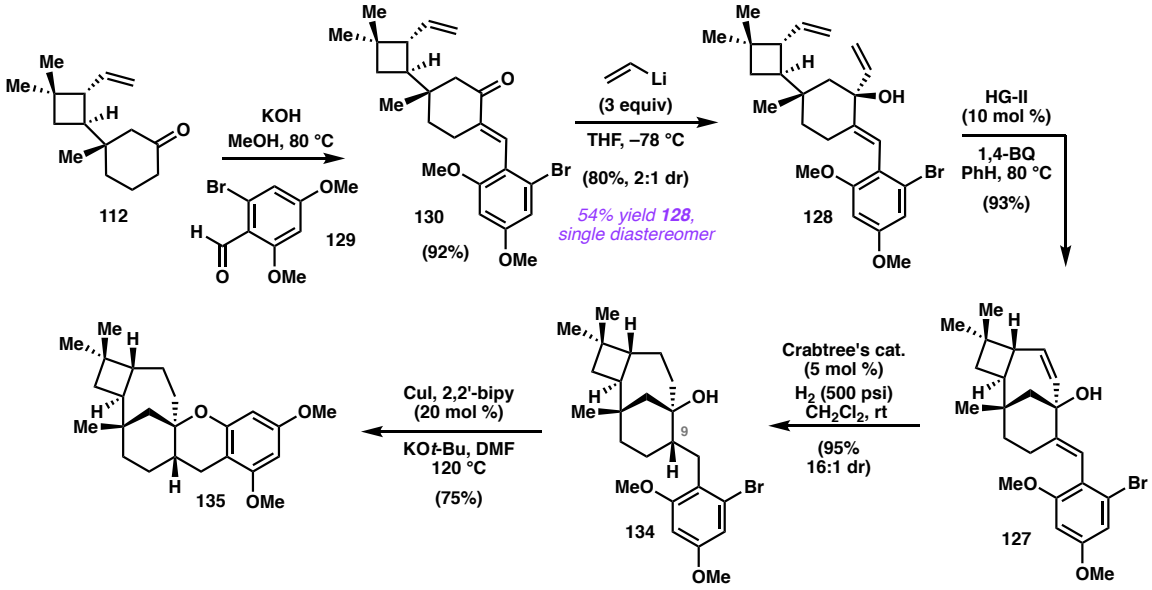
Scheme 1.18. *Our third generation retrosynthesis*



In the forward sense, a methanolic solution of vinyl ketone **112** and aldehyde **129** were treated with potassium hydroxide at elevated temperature to afford *exo*-enone **130** in 92% yield (Scheme **1.19**). In contrast to the previous system lacking substitution at C9 (i.e. **112**), 1,2-addition into this more sterically hindered ketone proved challenging. Treatment of **130** with vinyl magnesium bromide under the conditions used previously led to incomplete conversion—presumably due to competitive α-deprotonation—affording **128** (Scheme 1.20) in low yields and moderate diastereoselectivity. Attempts to improve conversion using Lewis acid activators gave higher yields of **128**, but resulted in lower levels of diastereoselectivity (<2:1). Ultimately, the desired allylic alcohol was obtained in good yield with serviceable dr by employing vinyllithium in THF at −78 °C, allowing isolation of **128** as a single diastereomer in 54% yield. The ring-closing metathesis

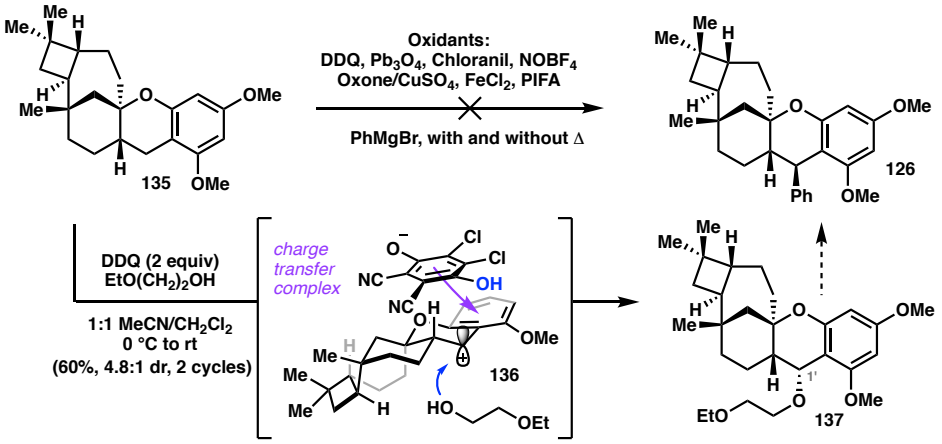
proceeded with equal efficiency on this new substrate to furnish **127** in 93% yield.

Scheme 1.19. *Synthesis of the core of (+)-psiguadial B*



With the strained sesquiterpene framework secured, both the di- and trisubstituted olefins in **127** were hydrogenated in the presence of Crabtree's catalyst, which engaged in a hydroxyl-directed reduction[65,66] to establish the C9 stereocenter with 16:1 dr, providing **134** in excellent yield. The final ring of the psiguadial framework was formed by a Cu-catalyzed intramolecular *O*-arylation reaction, furnishing pentacycle **135** in 75% yield.[67]

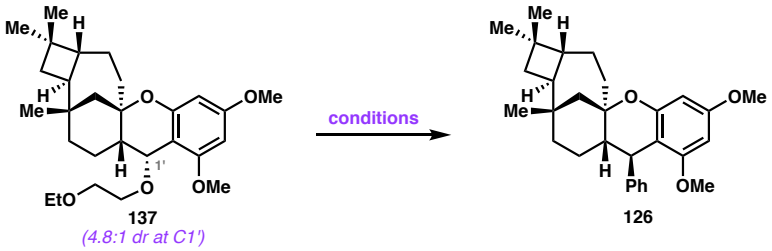
Scheme 1.20. *Attempts to install functionality at C1′*



With the successful development of a scalable and high-yielding route to **135**, the task of appending the C1' phenyl group was now at hand. Ideally, the electron rich arene in **135** would be engaged directly in a benzylic arylation reaction; a possible mechanism would involve benzylic oxidation at C1' followed by trapping with a phenyl nucleophile. Whereas a number of laboratories have shown that electron rich arenes can trap benzylic cations in simple systems,[33,68–70] it was unclear whether an electronically neutral, unsubstituted phenyl group would be sufficiently reactive to engage as the nucleophile in this type of transformation. Nonetheless, we investigated this possibility with reagents commonly used in flavonoid chemistry (e.g. DDQ,[33,70–72] Chloranil, Pb_3O_4, [30] Oxone/$CuSO_4$,[69] and $NOBF_4$[73,74]), followed by trapping with benzene, PhMgBr, or $PhB(OH)_2$, all without success (Scheme **1.20**). Efforts to apply Shi's $FeCl_2$-catalyzed benzylic dehydrogenative arylation,[75] or Muramatsu's C(sp^3)–H arylation using DDQ and PIFA[76] were also unfruitful.

Having failed to achieve a direct arylation, a stepwise protocol was employed. Oxidation with DDQ in the presence of ethoxyethanol[71,72] afforded **137**—a relatively stable product—which could be isolated in modest yields (Scheme **1.20**). The remaining mass balance of the reaction consisted of side products suspected to result from over oxidation and elimination of the benzylic ether. A survey of reaction parameters revealed that adding acetonitrile as a co-solvent led to cleaner reaction profiles, albeit at the expense of conversion. Presumably, the acetonitrile helps stabilize the intermediate benzylic cation (i.e. **136**), favoring more efficient trapping with ethoxyethanol over unproductive side reactions. Synthetically useful yields of **137** were obtained under these conditions by re-subjecting recovered **135** to the reaction conditions a second time.

Table 1.3. *Investigation of the C1′ phenylation*



137 *(4.8:1 dr at C1′)* **126**

entry	Lewis acid or catalyst	nucleophile	solvent	T (°C)	yield (dr)
1	TMSOTf	$PhB(OH)_2$	THF	–78 to 0	0
2	TMSOTf	PhMgBr	THF	–78 to 0	0
3	none	PhMgBr	PhMe	110	0
4	$Ni(dppe)Cl_2$	PhMgBr	PhMe	25	0
5	$Ni(dppe)Cl_2/MgI_2$	PhMgBr	PhMe	25	0
6	$BF_3{\cdot}OEt_2$	$PhBF_3K$	CH_2Cl_2	0 to 25	0
7	$BF_3{\cdot}OEt_2$	$PhBF_3K$	MeCN	0 to 25	0
8	$BF_3{\cdot}OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	–78 to 0	99 (1.7:1)
9	$BF_3{\cdot}OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	–78 to –45	90 (2.0:1)
10	$BF_3{\cdot}OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	–78 to –60	57 (3.3:1)

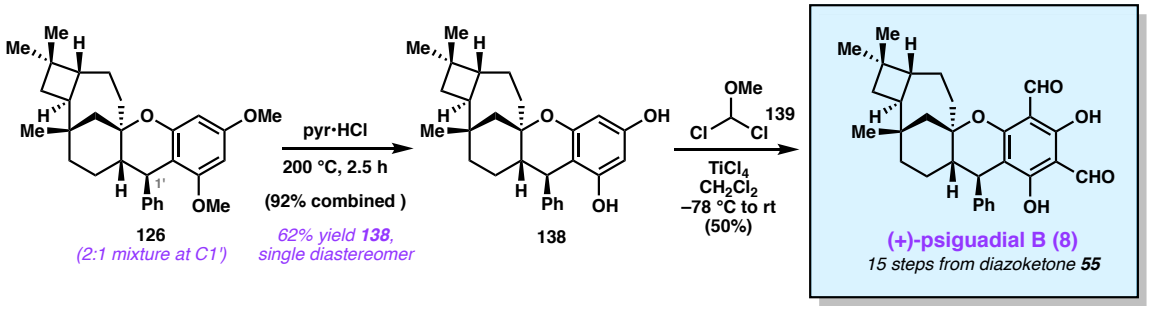
With respect to the stereochemistry at C1', **137** was isolated as a 4.8:1 mixture of diastereomers, favoring the α-disposed ether. Conformational analysis of **135** indicates that the 7-membered ring protrudes from the bottom face of the molecule, suggesting that C–O bond formation appears to proceed with contrasteric selectivity. The observed stereochemical outcome might result from an overall double inversion process that proceeds by initial association of DDQ from the less hindered top face of **135** to form a tightly bound charge-transfer complex (i.e. **136**).[31] If this complex remains closely associated, ethoxyethanol would then attack from the bottom face, thus leading to α-ether **137** as the major diastereomer.

With a functional handle installed at C1', TMSOTf was initially investigated as a Lewis acid to activate the ethoxyethyl benzyl ether, however, no phenylated product was obtained using $PhB(OH)_2$, or PhMgBr as nucleophiles (Table **1.3**, entries 1 and 2).[72] Simple heating[77] or nickel-catalyzed Kumada coupling with PhMgBr in PhMe[78–80] yielded only

eliminated products and complex reaction profiles (entries 3–5). Likewise, Bode's conditions for the addition of aryl trifluoroborates to oxonium ions, which use BF_3•OEt_2 as the Lewis acid, failed to produce **126** (entries 6 and 7).[81,82] We were therefore delighted to obtain a near quantitative yield of **126** (in 1.7:1 dr) by treating a mixture of **137** and lithium diphenylcyanocuprate with BF_3•OEt_2 (entry 8).[83,84] After some experimentation, it was found that the diastereoselectivity could be slightly improved to 2:1 by holding the reaction at –45 °C (entry 9). Although colder temperatures led to a further improvement in dr, this was accompanied by a lower yield (entry 10).

As the C1' diastereomers of **126** were inseparable by silica gel chromatography, the mixture was subjected to pyridine hydrochloride at 200 °C, which afforded the corresponding demethylated products in 92% combined yield (Scheme **1.21**). At this stage, the diastereomeric resorcinols were readily separable by column chromatography, providing **138** as a single diastereomer in 62% yield. Finally, the remaining two aryl aldehydes were simultaneously installed using Rieche formylation conditions,[85–87] delivering (+)-psiguadial B (**8**) in 50% yield. Synthetic **8** was found to be spectroscopically identical in all respects to the natural sample reported by Shao et al.[15]

Scheme 1.21. *Completion of the synthesis of (+)-psiguadial B*



1.5 CONCLUDING REMARKS

In summary, the first enantioselective total synthesis of the cytotoxic natural product, (+)-psiguadial B (**8**), was achieved in 15 steps from diazoketone **55**. The successful synthetic strategy was enabled by the implementation of a tandem photochemical Wolff rearrangement/asymmetric ketene addition reaction. Having developed a novel protocol for the enantioselective preparation of quinolinamide **53**, a variety of substrates were evaluated and conditions were identified to prepare the corresponding 5- and 6-membered ring products. *De novo* construction of the *trans*-fused cyclobutane ring in **8** was accomplished using a strategic Pd-catalyzed C(sp^3)−H alkenylation reaction, followed by one of two distinct epimerization strategies, which permit access to both enantiomers of the natural product from a single enantiomer of organocatalyst.

In the course of this work, three different synthetic routes toward (+)-psiguadial B were investigated. These studies have led to the evaluation of several challenging transformations, including 1) an *o*-QMHDA cycloaddition between a highly functionalized enol ether and a phloroglucinol-derived *o*-QM; 2) a seven-membered ring-forming Prins cyclization; and 3) a modified Norrish–Yang cyclization. Ultimately, the strained sesquiterpene core was built using a remarkably efficient ring-closing metathesis, and elaborated through a short sequence to afford the natural product in 1.3% overall yield. We believe that the development of this route to **8** may enable the synthesis of unnatural analogs of **3**, which would be difficult to access through semi-synthetic methods. Application of the key strategy concepts described herein to the synthesis of other *trans*-cyclobutane-containing natural products are currently ongoing in our laboratory.

1.6 EXPERIMENTAL SECTION

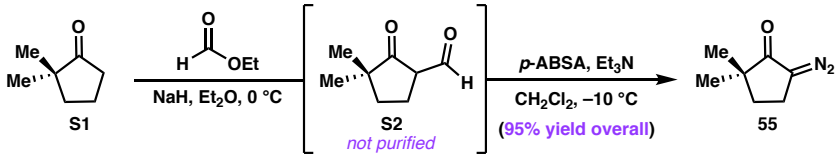
1.6.1 Materials and Methods

General Procedures. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), *tert*-butyl methyl ether (TBME), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N), N,N-diisopropylethylamine (DIPEA), and methanol (MeOH) was distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or 2,4-dinitrophenylhydrazine staining. Flash column chromatography was performed either as described by Still et al.[88] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz respectively), a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$) and $CDCl_3$ (^{13}C, $\delta = 77.1$), C_6H_5 (^1H, $\delta = 7.16$) and C_6D_6 (^{13}C, $\delta = 128$), or d_8-THF (^1H, $\delta = 3.58$) and (^{13}C, $\delta = 67.6$). 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, or obtained from the Caltech Mass Spectral Facility in fast-atom bombardment mode (FAB). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm).

1.6.2 Preparative Procedures and Spectroscopic Data

1.6.2.1 Preparation of Diazoketone Substrates



To each of two flame-dried 1 L round-bottom flasks was added NaH (60% dispersion in mineral oil, 3.17 g, 79.2 mmol, 1.20 equiv) and the atmosphere was exchanged for N_2 one time. Dry Et_2O (30.0 mL) was then added via syringe and the suspension cooled to 0 °C. Ethyl formate (12.4 mL, 152 mmol, 2.30 equiv) was then added, followed by 2,2-dimethylcyclopentanone (**S1**)[89] (7.40 g, 66.0 mmol) either neat, or as a 3.0 M solution in Et_2O. A catalytic amount of wet methanol (~100 µL) was then added and the reaction left to stir at 0 °C.[90] Upon completion, the reaction solidifies to a chunky, white solid that dissolved readily upon the addition of DI H_2O. At this point, both reaction mixtures were combined for workup: after dilution with Et_2O, the layers were separated and the aqueous layer was washed with Et_2O 3x to remove organic impurities and a small amount of unreacted starting material. The aqueous layer was then cooled to 0 °C and

acidified to pH = 3 using 5 M HCl. Et_2O was then added and the acidified aqueous layer was extracted 6x. The combined organics were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* into a 500 mL round-bottom flask.[91,92]

The crude formyl ketone **S2** was taken up in CH_2Cl_2 (132 mL) and the solution cooled to –10 °C. Triethylamine (55.2 mL, 396 mmol, 5.00 equiv) was added, followed by solid *p*-ABSA[1] (31.8 g, 132 mmol, 1.00 equiv) in three portions. The reaction was stirred for 3 hours and allowed to gradually reach 10 °C, at which point an aqueous solution of KOH (55.0 mL, 4 M) was added. Additional CH_2Cl_2 and H2O were added, the layers were separated and the aqueous layer extracted with CH_2Cl_2 until no product remains by TLC. The combined organics were dried over Mg_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (20–30% Et_2O/pentane) to afford **55** (17.4 g, 95% yield) as a bright yellow oil.

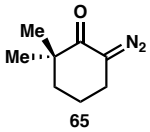
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (t, *J* = 7.0 Hz, 2H), 1.77 (t, *J* = 7.2 Hz, 2H), 1.04 (d, *J* = 1.0 Hz, 6H).; **^{1}H NMR** (400 MHz, d_8-THF) δ 2.94 (t, *J* = 7.0 Hz, 2H), 1.79 (t, *J* = 7.2 Hz, 2H), 1.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8, 56.6, 46.3, 35.7, 24.1, 21.2.; **^{13}C NMR** (101 MHz, d_8-THF) δ 203.6, 56.1, 46.9, 36.6, 24.5, 21.9.

FTIR (NaCl, thin film) 3754, 3414, 3332, 2962, 2934, 2892, 2869, 2672, 2642, 2578, 2510, 2080, 1981, 1673, 1581, 1471, 1460, 1382, 1362, 1339, 1309, 1267, 1245, 1204, 1133, 1110, 1058, 1030, 994, 977, 948, 919, 893, 780, 726, 697 cm.$^{-1}$

HRMS (MM) calc'd for $C_7H_{11}N_2O$ $[M+H]^+$ 139.0866, found 139.0860.

Diazoketones **65–68** were prepared according to the above procedure. Spectroscopic data for **67** and **68** are consistent with that reported in the literature.[93–95]



65

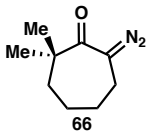
65: Yellow Oil, (1.76 g, 36% yield over 2 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.73 (m, 2H), 1.68 –1.61 (m, 2H), 1.15 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 62.6, 42.0, 37.5, 26.7, 22.9, 18.5.

FTIR (NaCl, thin film) 2943, 2864, 2082, 1626, 1472, 1449, 1381, 1342, 1317, 1275, 1261, 1220, 1201, 1162, 1122, 1044, 1011, 910, 853, 738, 658 cm.$^{-1}$

HRMS (EI) calc'd for $C_8H_{12}N_2O$ $[M]^+$ 152.0950, found 152.0956.



66

66: Yellow Oil, (400.0 mg, 26% yield over 2 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (ddt, *J* = 7.0, 4.8, 2.3 Hz, 2H), 1.75 (dt, J = 4.4, 2.8 Hz, 4H), 1.57 (ddt, *J* = 6.3, 3.4, 1.7 Hz, 2H), 1.17 (s, 6H).

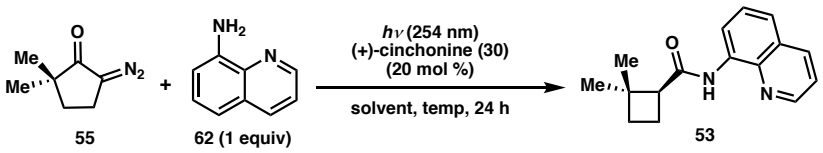
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 68.3, 47.0, 37.9, 29.5, 25.8, 25.7, 25.6.

FTIR (NaCl, thin film) 2981, 2966, 2927, 2858, 2083, 1704, 1617, 1474. 1448, 1387. 1364, 1350, 1324, 1272, 1251, 1231, 1203, 1147, 1113, 1057, 1020, 980, 953, 871, 845, 736, 656 cm.$^{-1}$

HRMS (EI) calc'd for $C_9H_{14}N_2O$ $[M]^+$ 166.1106, found 166.1095.

1.6.2.2 Small-scale screening protocol for enantioenriched amides 53, 69–72.

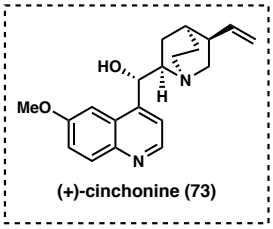
Oven-dried quartz tubes were each charged with aminoquinoline (**62**) (21.6 mg, 0.150 mmol, 3.00 equiv) and catalyst (50 mol %). Inside a N_2-filled glovebox, diazoketones **55**, **65**–**67** (0.05 mmol) were then added to each as a solution in 0.500 mL THF (excluding diazoketone **68**, which was added as a solid outside of the glovebox). The reactions were then sealed with a 19/38 rubber septum around the outside of each tube and sealed with electrical tape. The reactions were then brought out of the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp. The reactions were irradiated with stirring at room temperature for 18 hours. The reactions were then concentrated *in vacuo,* and the crude reaction mixtures were analyzed by ^{1}H NMR with an added internal standard to determine % yield. The crude residues were purified by silica gel preparative TLC (2% Et_2O/CH_2Cl_2) to provide **53, 69–72** in varying yields and enantiopurities.



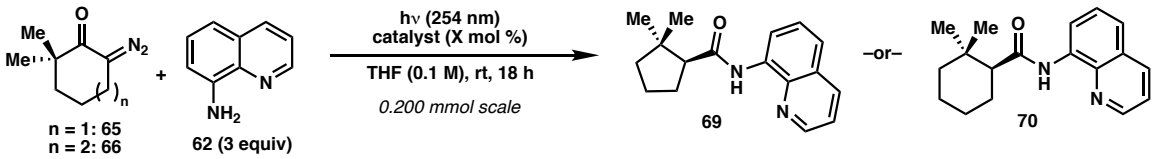
55 62 (1 equiv) 53

entry	solvent	temp °C	vessel	atm	% yield[a]	% ee[b]
1	THF	25	quartz	N_2	63	79
2	DMF	25	quartz	N_2	76	50
3	CH_2Cl_2	25	quartz	N_2	62	47
4	toluene	25	quartz	N_2	65	59
5	dioxane	25	quartz	N_2	69	79
6	MeCN	25	quartz	N_2	43	74
7	THF	0	quartz	N_2	28	79
8	THF	25	quartz	air	18	75
9	THF	25	quartz	CO	33	69
10	THF	25	vycor	N_2	29	79
11	THF	25	pyrex	N_2	20	75

[a] Determined by ^{1}H NMR via integration relative to an added internal standard, isolated yield provided in parentheses. [b] Determined by SFC using a chiral stationary phase.

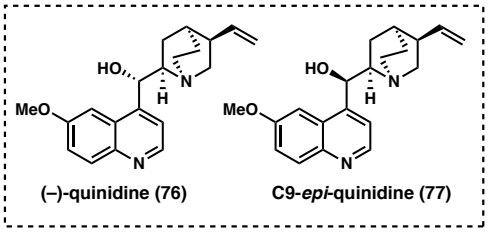


(+)-cinchonine (73)

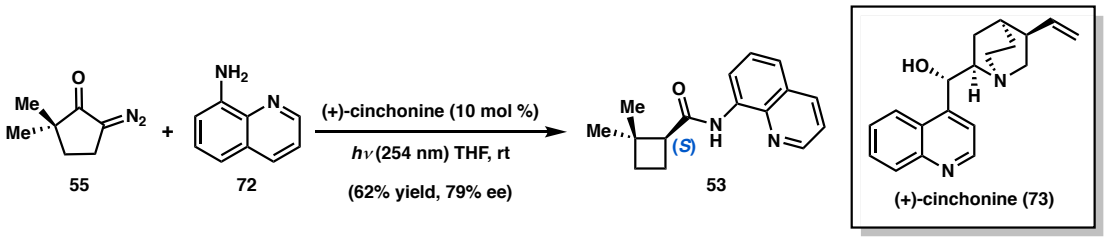


entry	diazo.	catalyst (mol %)	product	% yield[a] (isolated)	%ee[b]
1	65	77 (50)	69	78 (73)	71
2	65	77 (30)	69	73 (81)	69
3	65	77 (20)	69	84 (76)	67
4	65	77 (10)	69	82 (81)	63
5	66	76 (50)	70	57 (66)	73
6	66	76 (30)	70	66 (71)	66
7	66	76 (20)	70	66 (61)	62
8	66	76 (10)	70	62 (61)	55

[a] Determined by ^{1}H NMR via integration relative to an added internal standard, isolated yield provided in parentheses. [b] Determined by SFC using a chiral stationary phase.

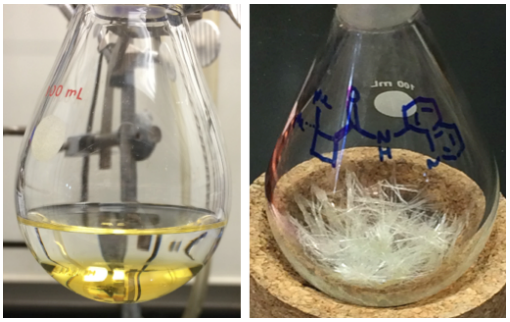


1.6.2.3 Large-scale preparation of enantioenriched amides.



To a flame-dried, 1 L quartz flask was added 8-aminoquinoline (**72**) (12.9 g, 89.5 mmol, 3.00 equiv) and (+)-cinchonine (**73**) (879 mg, 2.99 mmol, 0.100 equiv). The flask was evacuated and backfilled with N_2 three times and dry THF (600 mL) was then added via cannula. Diazoketone **55** (4.12 g, 29.8 mmol, 1.00 equiv) was added last via syringe and the reaction was irradiated with stirring using a Honeywell 254 nm lamp at room temperature. Reaction progress was monitored by TLC (72-168 hours are typically required for complete conversion on this scale, and rotation of the flask every day provided faster conversion).[96] Upon completion, the reaction mixture was concentrated *in vacuo*, the

solids were taken up in CH_2Cl_2, and the suspension filtered. The filter cake was washed with CH_2Cl_2 three times and the filtrate was concentrated *in vacuo* to give a crude residue that was purified by silica gel flash chromatography (isocratic: 6% EtOAc/hexane) to provide **53** (4.69 g, 62%) as a pale-yellow solid. The enantiomeric excess was determined to be 79% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 4.23 min, t_R (minor) = 5.64 min. $[\alpha]_D^{25.0}$ = –66.0° (c = 0.560, $CHCl_3$).



Enantioenriched cyclobutane **53** was dissolved in a minimal amount of CH_2Cl_2 in a 100 mL round-bottom flask. An equal amount of hexanes was carefully layered on top of the $CH_2Cl_2$to form a biphasic mixture. The layers were allowed to diffuse overnight to provide **53** as white needles. The supernatant was concentrated under reduced pressure and this process was repeated again to provide additional **53** (3.50 g total, 83% recovery of theoretical total of the desired enantiomer, 46% overall from **55**). Melting point: 66–68 ºC.

$[\alpha]_D^{25.0}$ = –109° (c = 0.720, $CHCl_3$).

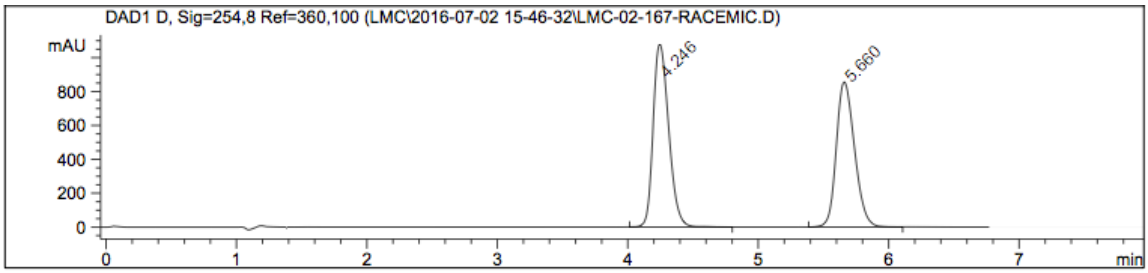
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.80 (t, *J* = 1.8 Hz, 1H), 8.79 (dd, *J* = 13.6, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52 (q, *J* = 8.2, 7.5 Hz, 1H), 7.48 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.07 (ddd, *J* = 9.1, 8.2, 0.9 Hz, 1H), 2.48 (dq, *J* = 11.4, 9.4 Hz, 1H), 2.06 (dtd, *J* = 11.6, 8.6, 3.3 Hz, 1H), 1.85 (dt, *J* = 10.8, 9.1 Hz, 1H), 1.74 (dddd, *J* = 10.7, 9.5, 3.3, 0.9 Hz, 1H), 1.39 (s, 3H), 1.14 (s, 3H).

^{13}C NMR δ 171.8, 148.3, 138.6, 136.4, 134.7, 128.1, 127.6, 121.7, 121.3, 116.4, 51.0, 40.4, 32.3, 30.9, 23.4, 17.4.

FTIR (NaCl, thin film) 3353, 3047, 2952, 2861, 1685, 1595, 1577, 1526, 1485, 1460, 1424, 1385, 1324, 1261, 1239, 1187, 1169, 1153, 825, 791,756 cm.$^{-1}$

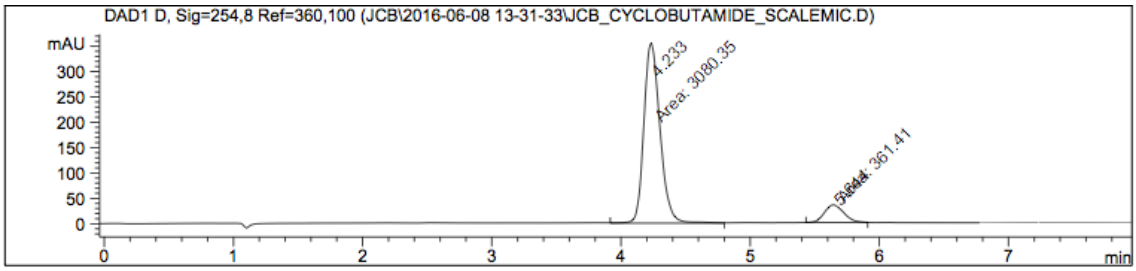
HRMS (MM) calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492, found 255.1501.

SFC data for racemic 53:



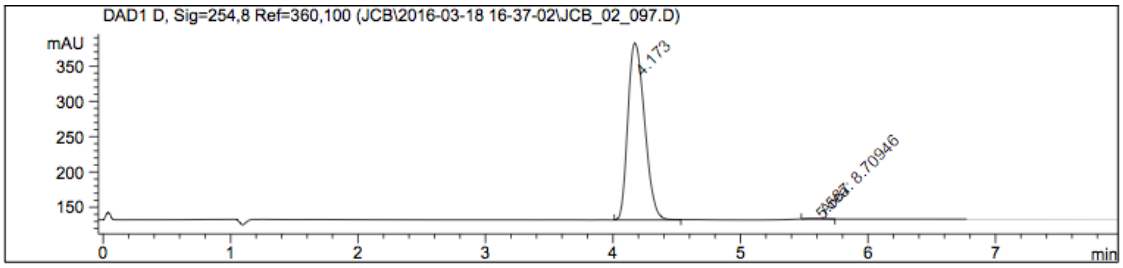
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.246	BB	0.1286	8934.03320	1078.74268	51.8271
2	5.660	BB	0.1532	8304.11426	855.84570	48.1729

Enantioenriched 53 isolated directly from reaction:

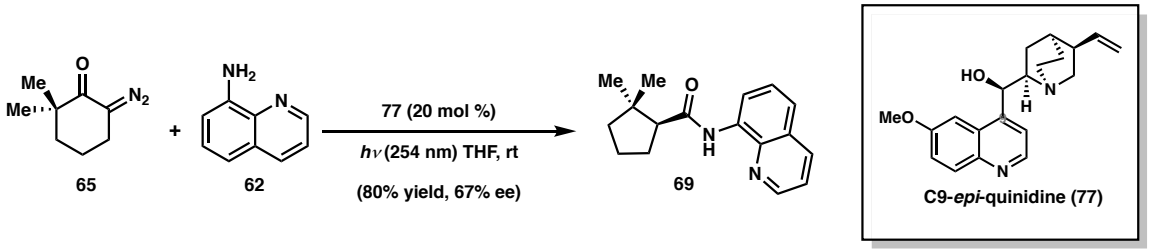


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.233	MM	0.1444	3080.35034	355.58780	89.4993
2	5.644	MM	0.1739	361.41000	34.64573	10.5007

Enantiopure 53 after a single recrystallization:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.173	BB	0.1464	2285.16455	250.58836	99.6203
2	5.587	MM	0.1518	8.70946	9.55969e-1	0.3797



0.2 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**77**) (32.5 mg, 0.100 mmol, 0.500 equiv). Diazoketone (**65**) (33.2 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 2.000 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **69** (37.5 mg, 77% yield) as a brown oil. The enantiomeric excess was determined to be 71% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 4.28 min, t_R (minor) = 5.41 min.

1.0 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with aminoquinoline (**62**) (432.5 mg, 3.000 mmol, 3.00 equiv) and (**77**) (64.9 mg, 0.200 mmol, 0.200 equiv). Diazoketone (**65**) (166.2 mg, 1.000 mmol, 1.00 equiv) was added as a solution in 2.50 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **69** (215 mg, 80% yield) as a brown oil. The enantiomeric excess was determined to be 67% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 4.28 min, t_R (minor) = 5.41 min.

$[\alpha]_D^{25.0}$ = –32.5° (c = 2.075, $CHCl_3$).

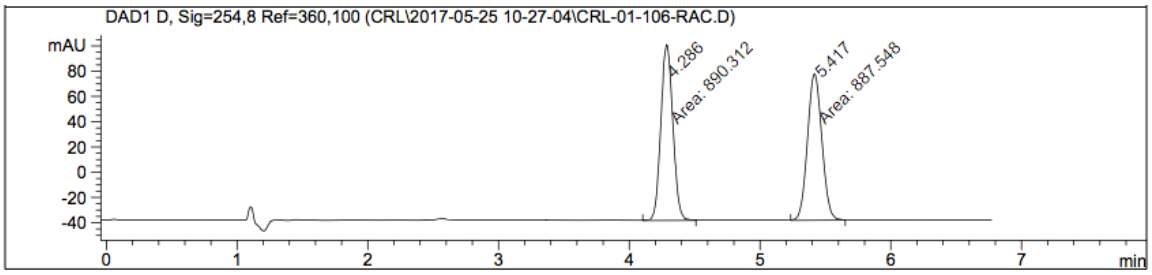
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.81 (d, *J* = 1.7 Hz, 1H), 8.80 (dd, *J* = 3.0, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.61 (t, *J* = 8.4 Hz, 1H), 2.38 – 2.22 (m, 1H), 2.02 (dtd, *J* = 13.2, 8.5, 4.4 Hz, 1H), 1.95 – 1.82 (m, 1H), 1.79 – 1.65 (m, 2H), 1.63 – 1.57 (m, 1H), 1.31 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 148.3, 138.6, 136.5, 134.8, 128.1, 127.6, 121.7, 121.3, 116.4, 58.1, 43.2, 42.1, 29.7, 27.9, 24.0, 22.5.

FTIR (NaCl, thin film) 3362, 2957, 2924, 2854, 1729, 1690, 1525, 1486, 1464, 1424, 1381, 1325, 1262, 1164, 1145, 1132, 1072, 825, 791, 720 cm.$^{-1}$

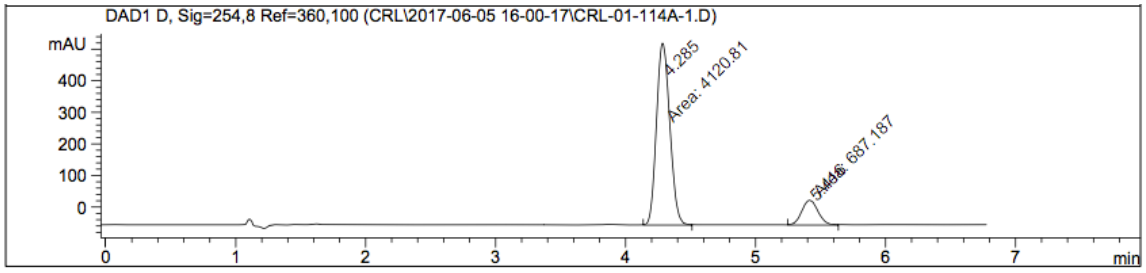
HRMS (MM) calc'd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1648, found 269.1645.

SFC data for racemic 69:



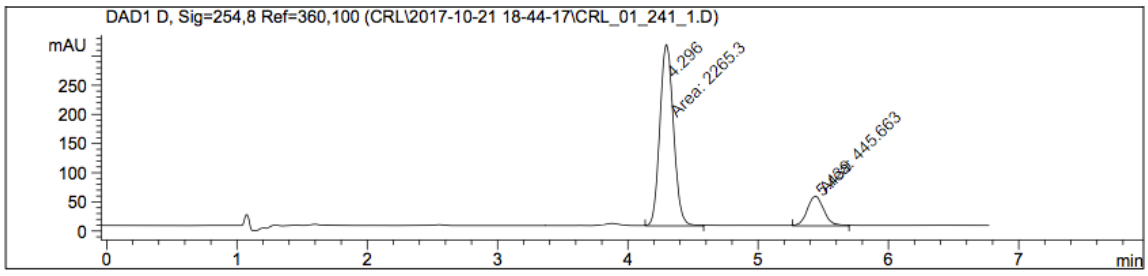
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.286	MM	0.1063	890.31165	50.0777
2	5.417	MM	0.1274	887.54810	49.9223

Enantioenriched 69:

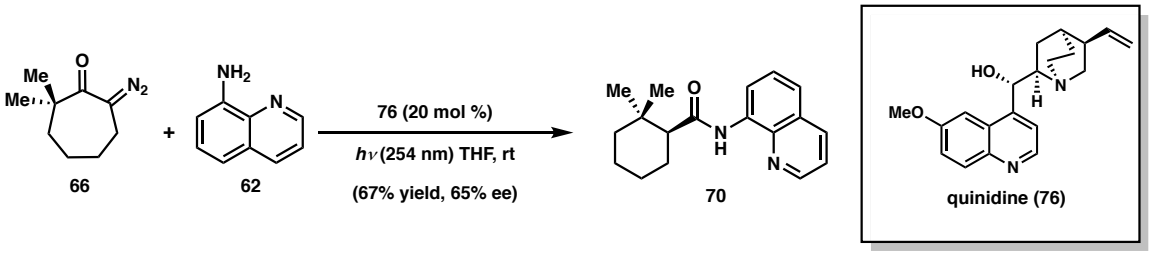


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.285	MM	0.1189	4120.80518	85.7074
2	5.416	MM	0.1449	687.18732	14.2926

Enantioenriched 69 using 20 mol % catalyst loading:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.296	MM	0.1212	2265.30225	83.5607
2	5.439	MM	0.1461	445.66309	16.4393



0.2 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with 8-aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**76**) (32.5 mg, 0.100 mmol, 0.500 equiv). Diazoketone (**66**) (31.0 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 2.00 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **70** (33.3 mg, 59% yield) as a brown oil. The enantiomeric excess was determined to be 71% by chiral SFC analysis (AD-H, 2.5 mL/min, 12% IPA in CO_2, λ = 254 nm): t_R (major) = 9.67 min, t_R (minor) = 10.34 min.

1.0 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with 8-aminoquinoline (**62**) (432.5 mg, 3.000 mmol, 3.00 equiv) and (**76**) (64.9 mg, 0.200 mmol, 0.200 equiv). Diazoketone (**66**) (152.2 mg, 1.000 mmol, 1.00 equiv) was added as a solution in 2.50 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **70** (189 mg, 67% yield) as a brown oil.

The enantiomeric excess was determined to be 65% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 9.67 min, t_R (minor) = 10.34 min. $[\alpha]_D^{25.0}$ = –17.3° (c = 1.68, $CHCl_3$).

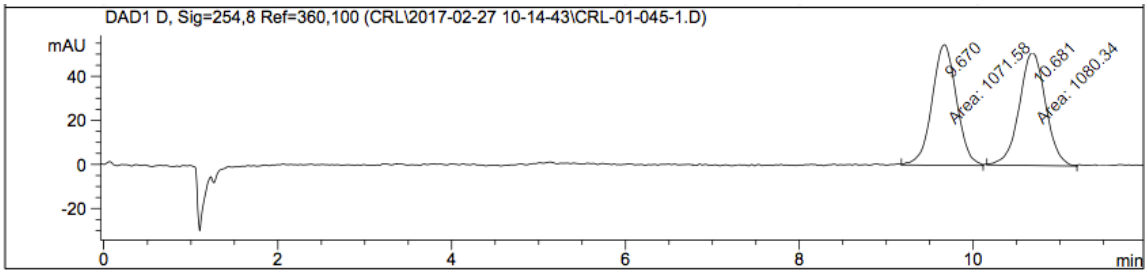
^{1}H NMR (400 MHz, CDCl3) δ 9.79 (s, 1H), 8.82 (d, *J* = 1.7 Hz, 1H), 8.80 (dd, *J* = 2.7, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.30 (dd, *J* = 11.8, 3.5 Hz, 1H), 1.99 – 1.78 (m, 3H), 1.55 – 1.47 (m, 2H), 1.39 – 1.27 (m, 3H), 1.13 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 148.3, 138.6, 136.5, 134.7, 128.1, 127.6, 121.7, 121.3, 116.5, 56.5, 41.6, 33.4, 31.5, 25.7, 25.7, 22.1, 21.2.

FTIR (NaCl, thin film) 3364, 2956, 2923, 2852, 1729, 1691, 1523, 1486, 1462, 1424, 1378, 1326, 1273, 1129, 1072, 825, 790 cm.$^{-1}$

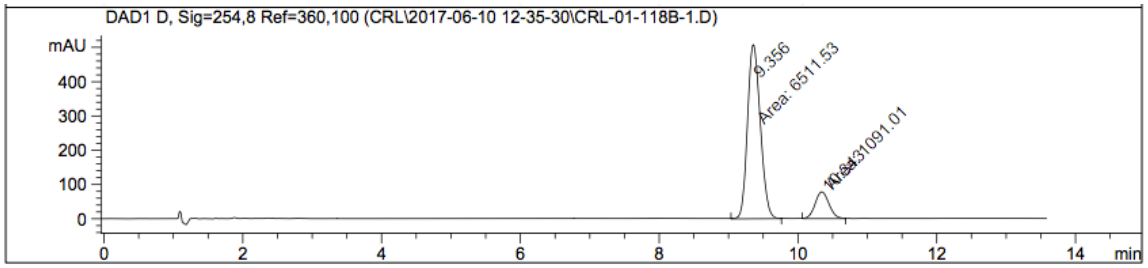
HRMS (MM) calc'd for $C_{18}H_{23}N_2O$ $[M+H]^+$ 283.1805, found 283.1796.

SFC data for racemic 70:



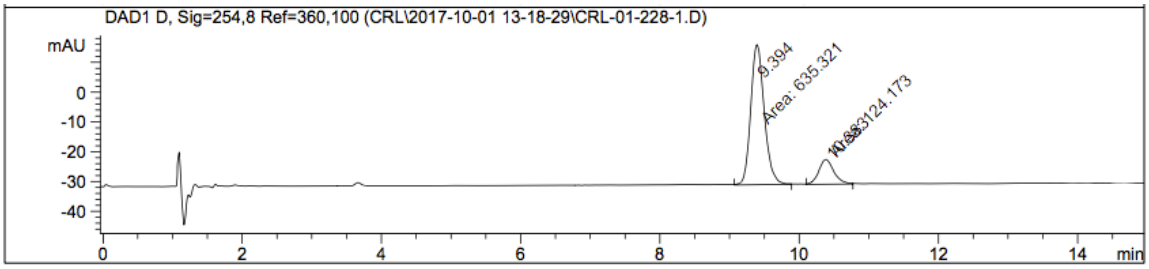
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	9.670	MM	0.3268	1071.58496	49.7965
2	10.681	MM	0.3511	1080.34424	50.2035

Enantioenriched 70:

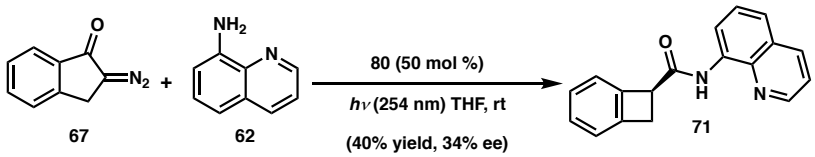


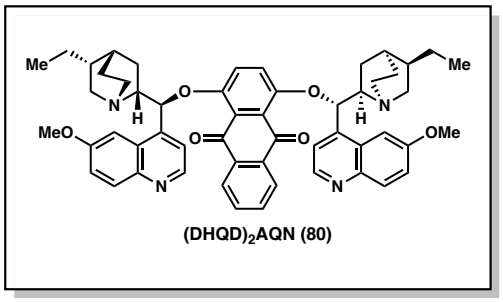
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	9.356	MM	0.2135	6511.52734	85.6494
2	10.343	MM	0.2316	1091.00696	14.3506

Enatioenriched 70 using 20 mol % catalyst loading:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	9.394	MM	0.2252	635.32117	83.6505
2	10.383	MM	0.2495	124.17338	16.3495





Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**80**) (85.7 mg, 0.100 mmol, 0.500 equiv). Diazoketone (**67**) (31.6 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 0.500 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 18 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (0–1% Et_2O/CH_2Cl_2) to afford **71** (21.9 mg, 40% yield) as a white solid. The enantiomeric excess was determined to be 34% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 5.06 min, t_R (minor) = 6.89 min.

$[\alpha]_D^{25.0}$ = –4.1° (c = 0.565, $CHCl_3$).

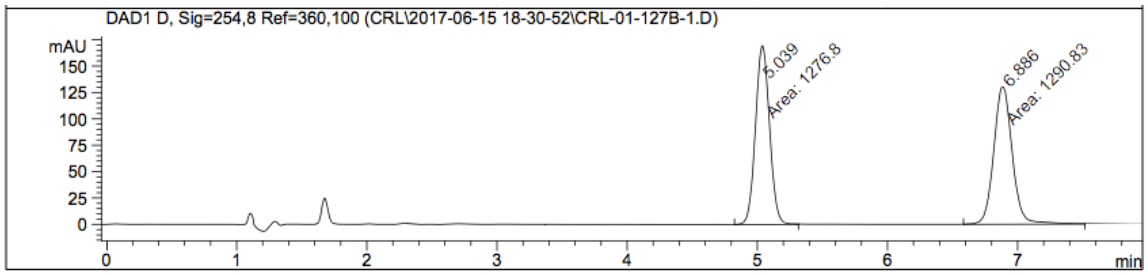
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.79 (dd, *J* = 11.5, 1.7 Hz, 1H), δ 8.78 (d, *J* = 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.50 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.38 – 7.29 (m, 2H), 7.22 – 7.16 (m, 1H), 4.56 (ddt, *J* = 5.8, 2.9, 0.8 Hz, 1H), 3.69 (ddd, *J* = 14.2, 5.7, 0.7 Hz, 1H), 3.60 (ddd, *J* = 14.2, 2.9, 0.8 Hz, 1H).

^{13}C NMR (101 MHz, CDCl3) δ 170.6, 148.4, 144.7, 142.9, 138.7, 136.4, 134.5, 128.6, 128.0, 127.8, 127.5, 123.5, 122.7, 121.7, 121.7, 116.5, 49.3, 35.2.

FTIR (NaCl, thin film) 3347, 3066, 2928, 2851, 1680, 1596, 1578, 1526, 1485, 1458, 1424, 1386, 1328, 1262, 1240, 1202, 1162, 1132, 869, 826, 791, 759, 734, 707, 679 cm.$^{-1}$

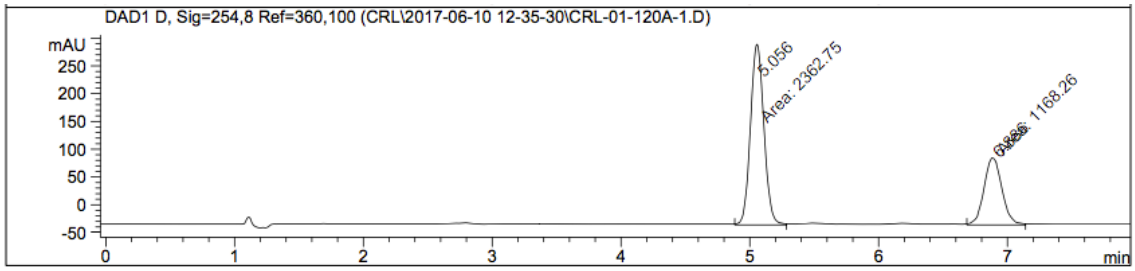
HRMS (MM) calc'd for $C_{18}H_{15}N_2O$ $[M+H]^+$ 275.1179, found 275.1178.

SFC data for racemic 71:

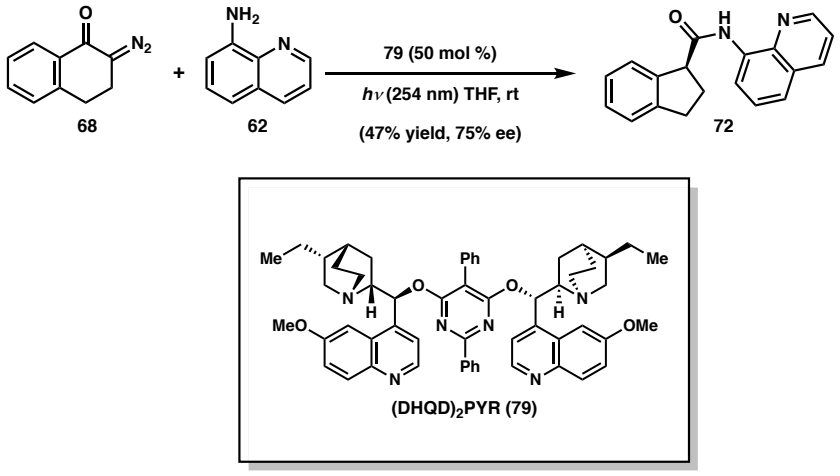


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.039	MM	0.1254	1276.80469	49.7268
2	6.886	MM	0.1641	1290.83447	50.2732

Enantioenriched 71:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.056	MM	0.1210	2362.74805	66.9143
2	6.886	MM	0.1605	1168.25940	33.0857



An oven-dried quartz tube was charged with diazoketone (**68**) (34.4 mg, 0.200 mmol, 1.00 equiv). The tube was brought into a N_2 filled glovebox, and subsequently charged with aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**79**) (88.1 mg, 0.100 mmol, 0.500 equiv). The mixture was suspended in 0.500 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (5–10% EtOAc/hexanes) to afford **72** (27.1 mg, 47% yield) as a brown oil. The enantiomeric excess was determined to be 75% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 5.73 min, t_R (minor) = 4.86 min.

$[\alpha]_D^{25.0}$ = 65.0° (c = 0.91, $CHCl_3$).

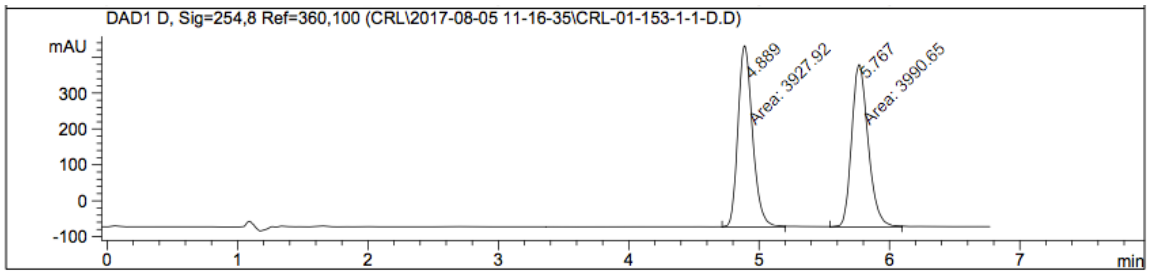
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.79 (dd, *J* = 7.1, 1.9 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.46 (m, 3H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.18 (m, 2H), 4.27 (dd, *J* = 8.4, 6.1 Hz, 1H), 3.23 (dt, *J* = 15.2, 7.4 Hz, 1H), 3.09 – 2.95 (m, 1H), 2.69 – 2.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 148.4, 144.8, 141.5, 138.7, 136.4, 134.7, 128.0, 127.9, 127.53, 126.9, 125.1, 125.0, 121.7, 121.7, 116.6, 54.0, 32.1, 30.4.

FTIR (NaCl, thin film) 3347, 2957, 2923, 2852, 1728, 1689, 1524, 1484, 1461, 1424, 1380, 1325, 1272, 1163, 1132, 1072, 826, 791, 743 cm.$^{-1}$

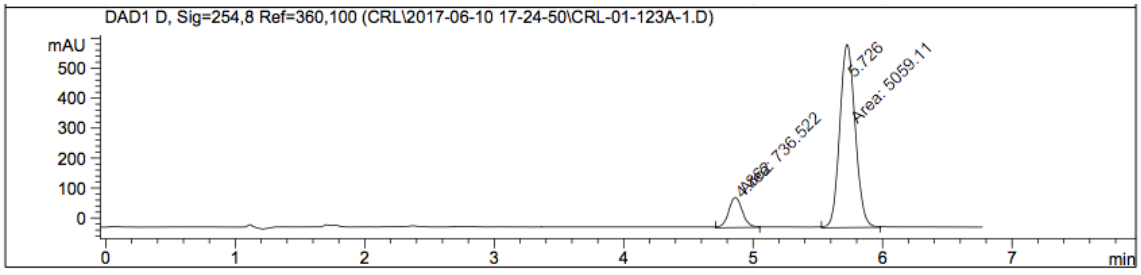
HRMS (MM) calc'd for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1335, found 289.1334.

SFC data for racemic 72:

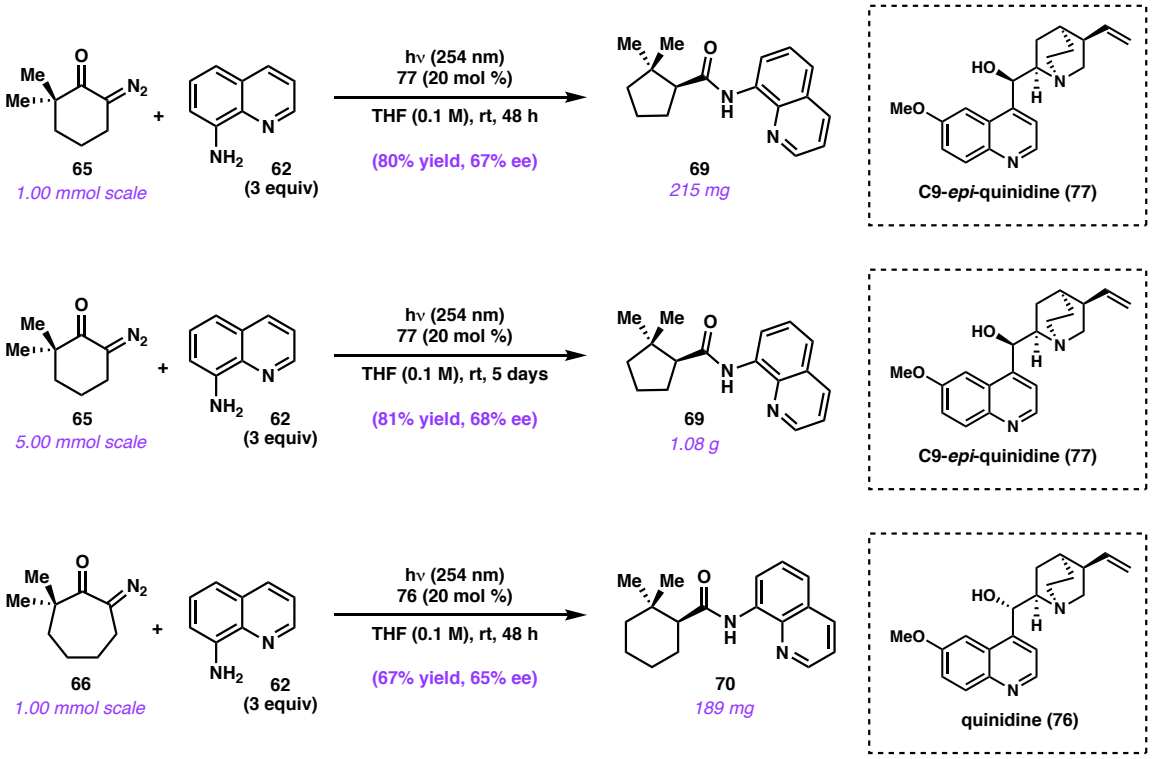


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.889	MM	0.1294	3927.92065	49.6039
2	5.767	MM	0.1468	3990.65186	50.3961

Enantioenriched 72:

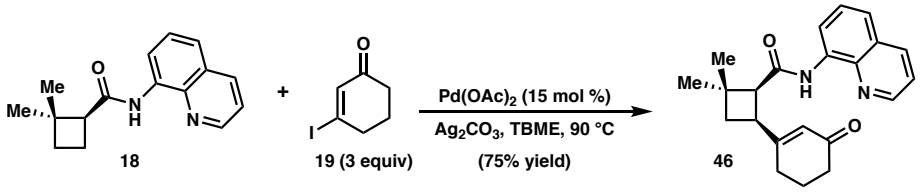


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.862	MM	0.1218	736.52246	12.7082
2	5.726	MM	0.1379	5059.11182	87.2918


Me
Me
O
N2
65
1.00 mmol scale
+
NH2
N
62
(3 equiv)
hν (254 nm)
77 (20 mol %)
THF (0.1 M), rt, 48 h
(80% yield, 67% ee)
Me
Me
O
N
H
N
69
215 mg
HO
MeO
N
H
C9-epi-quinidine (77)
65
5.00 mmol scale
62
(3 equiv)
hν (254 nm)
77 (20 mol %)
THF (0.1 M), rt, 5 days
(81% yield, 68% ee)
69
1.08 g
C9-epi-quinidine (77)
66
1.00 mmol scale
62
(3 equiv)
hν (254 nm)
76 (20 mol %)
THF (0.1 M), rt, 48 h
(67% yield, 65% ee)
70
189 mg
quinidine (76)

1.6.2.4 Synthetic Procedures Toward (+)-Psiguadial B.

Preparation of *cis*-cyclobutane 81.



To a flame-dried 150 mL pressure vessel were added cyclobutane **53** (2.87 g, 11.3 mmol), vinyl iodide (**54**)[97] (7.50 g, 33.8 mmol, 3.00 equiv), $Pd(OAc)_2$ (379 mg, 1.69 mmol, 0.150 equiv), and Ag_2CO_3 (3.11 g, 11.3 mmol, 1.00 equiv). The reagents were suspended in TBME (56.0 mL) and the vessel sealed under ambient conditions. The reaction was heated to 90 °C for 16 hours, then cooled to room temperature and filtered over a pad of celite. The filtrate was concentrated directly onto celite and purified by silica gel flash chromatography (20–40% EtOAc/hexane) to afford *cis*-cyclobutane **81** (2.95 g, 75% yield) as a pale yellow foam.

$[\alpha]_D^{25.0}$ = +84.4° (c = 0.350, $CHCl_3$).

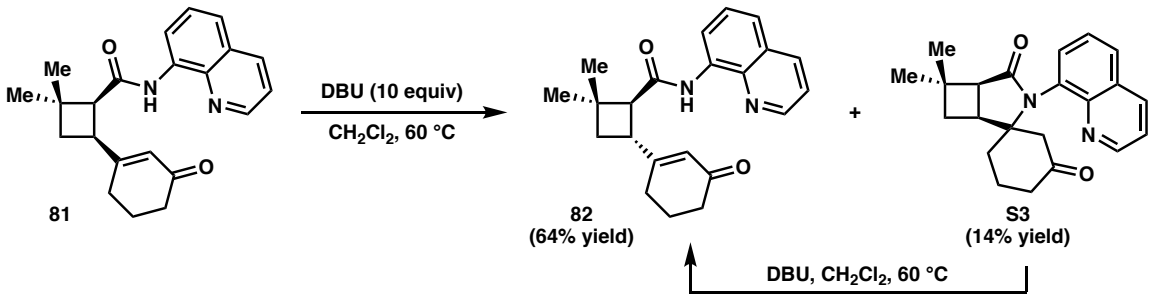
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.78 (dd, *J* = 12.4, 2.1 Hz, 1H), 8.78 (t, *J* = 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.51 (dd, *J* = 8.3, 5.0 Hz, 1H), 7.50 (d, *J* = 0.9 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.00 (q, *J* = 1.6 Hz, 1H), 3.45 (ddddd, *J* = 10.8, 8.5, 7.6, 2.1, 1.0 Hz, 1H), 3.27 (ddd, *J* = 8.8, 2.8, 0.8 Hz, 1H), 2.48 (t, *J* = 10.8 Hz, 1H), 2.31 (ddd, *J* = 7.5, 5.7, 3.5 Hz, 2H), 2.20 (qd, *J* = 6.0, 5.5, 1.1 Hz, 2H), 2.01 (ddd, *J* = 11.0, 8.3, 2.8 Hz, 1H), 1.95 – 1.84 (m, 2H), 1.46 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 170.2, 166.5, 148.3, 138.4, 136.3, 134.4, 127.9, 127.4, 124.9, 121.6, 121.5, 116.5, 56.9, 37.5, 37.5, 36.8, 35.7, 29.9, 27.8, 24.9, 22.6.

FTIR (NaCl, thin film) 3348, 2929, 2865, 1662, 1623, 1595, 1576, 1522, 1485, 1424, 1386, 1347, 1322, 1258, 1191, 1165, 1132, 827, 793 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1910.

Preparation of *trans*-cyclobutane 82 and spirolactam S3.



To a 150 mL pressure vessel were added *cis*-cyclobutane **81** (2.74 g, 7.86 mmol) and wet CH_2Cl_2 (27.5 mL). The colorless solution was treated with DBU (11.7 mL, 78.6 mmol, 10.0 equiv) and a bright yellow color was observed immediately. The vessel was sealed under ambient conditions and heated to 60 °C for 20 hours. The reaction mixture was diluted with 100 mL of water and 100 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 40% EtOAc/hexane until **81** eluted completely, then 10% MeOH/ CH_2Cl_2) to afford **82** (1.74 g, 64% yield) and **S3** (367 mg, 14% yield), each as a pale yellow solid.

Data for *trans*-cyclobutane **82**:

$[\alpha]_D^{25.0} = -129.0°$ (c = 1.43, $CHCl_3$).

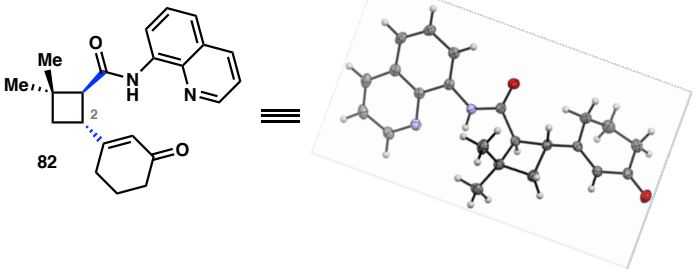
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.73 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.49 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.92 (q, *J* = 1.5 Hz, 1H), 3.58 (ddq, *J* = 18.5, 8.7, 1.6, 0.8, 0.8 Hz, 1H), 2.97 (dd, *J* = 9.8, 0.7 Hz, 1H), 2.41 – 2.29 (m, 4H), 2.05 – 1.92 (m, 3H), 1.85 (t, *J* = 10.4 Hz, 1H), 1.40 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 169.6, 167.5, 148.3, 138.3, 136.3, 134.2, 127.9, 127.3, 123.9, 121.7, 121.5, 116.3, 55.5, 37.5, 36.8, 36.4, 36.3, 30.7, 27.6, 23.1, 22.6.

FTIR (NaCl, thin film) 3344, 3046, 2952, 2865, 2246, 1669, 1623, 1595, 1577, 1526, 1485, 1461, 1424, 1323, 1346, 1326, 1292, 1253, 1191, 1161, 1133, 915, 884, 827, 792, 757,731 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1919.

XRCD: A suitable crystal of $C_{22}H_{24}N_2O_2$ (**82**) was selected for analysis. All measurements were made on a Bruker APEX-II CCD with filtered Cu-Kα radiation at a temperature of 120 K. Using Olex2, the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter, -0.04(4).



Data for spirolactam **S3**, 2.5:1 mixture of diastereomers:

$[\alpha]_D^{25.0} = -56.5°$ (c = 1.085, $CHCl_3$).

^{1}H NMR (asterisk denotes minor diast., 400 MHz, $CDCl_3$) δ 8.92 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.85* (dd, *J* = 4.1, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.13* (dd, *J* = 8.3, 1.8 Hz, 1H), 7.87 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.49 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.37* (dd, *J* = 8.3, 4.1 Hz, 1H), 3.07* (ddd, *J* = 7.3, 3.2, 0.9 Hz, 1H), 2.93 (dd, *J* = 6.0, 3.3 Hz, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 2.83 – 2.73 (m, 1H), 2.53 (dt, *J* = 13.1, 2.4 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.27 (ddq, *J* = 15.1, 11.3, 2.1 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.94 – 1.83 (m, 1H), 1.71 (dtd, *J* = 13.2, 8.6, 7.6, 3.0 Hz, 1H), 1.52 – 1.38* (m, 1H), 1.35 (s, 3H), 1.34* (s, 3H), 1.31 (s, 3H), 1.14* (s, 3H), 1.03 (td, *J* = 13.7, 4.0 Hz, 1H).

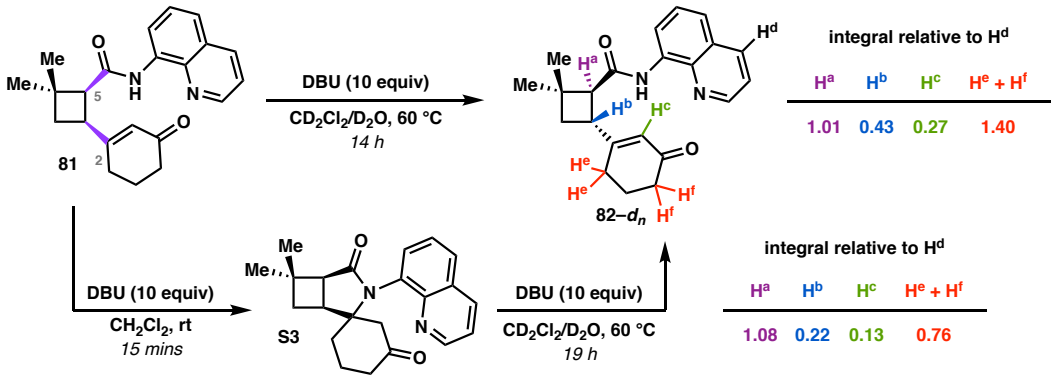
^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ 209.2, 175.5, 150.7, 146.3, 136.1, 134.2, 130.7, 129.6, 129.1, 126.2, 121.9, 69.2, 53.2, 49.9, 40.7, 35.8, 34.8, 34.1, 30.2, 29.0, 25.6, 20.1.

^{13}C NMR (minor diastereomer, 101 MHz, $CDCl_3$) δ 210.0, 175.5, 150.7, 145.6, 136.0, 134.2, 131.5, 129.6, 129.2, 126.0, 121.7, 68.9, 52.9, 49.8, 40.4, 35.0, 34.8, 34.6, 31.3, 30.0, 26.1, 20.1.

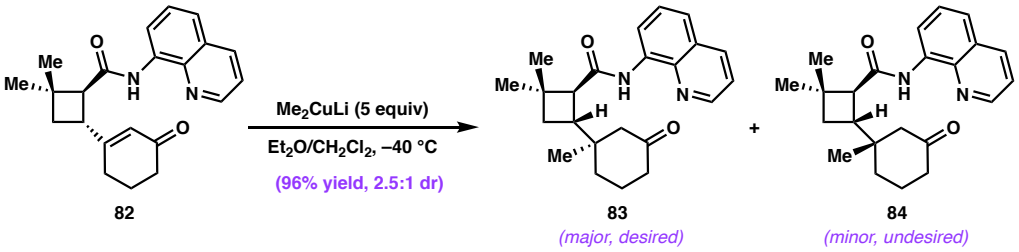
FTIR (NaCl, thin film) 3356, 3039, 2953, 2933, 2866, 1705, 1687, 1616, 1596, 1574, 1525, 1496, 1472, 1426, 1391, 1341, 1312, 1279, 1250, 1223, 1134, 1124, 1038, 1027, 905, 831, 795, 753, 664, 643 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1916.

Deuterium-labeling studies to determine site of epimerization:



Preparation of ketones 83 and 84 using Gilman's reagent.



To a flame-dried 100 mL flask was added copper (I) iodide (1.48 g, 7.75 mmol, 5.00 equiv) and Et_2O (15.5 mL). The resulting suspension was cooled to –40 °C and methyllithium (1.6 M in Et_2O; 9.68 mL, 15.5 mmol, 10 equiv) was added dropwise. The reaction mixture was stirred at –40 °C for 2 hours before **82** (540 mg, 1.55 mmol) was added dropwise as a solution in 5:2 CH_2Cl_2/Et_2O. The reaction mixture was gradually warmed to 0 °C over 4 hours, then quenched with saturated aqueous NH_4Cl (10 mL) and diluted with EtOAc. NH_4OH was added until all of the solid copper salts were sequestered and two homogenous layers remained. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 20%

EtOAc/Hexane) to afford a 2.5:1 mixture of **83** and **84** (543 mg, 96% yield), respectively as a white amorphous solid. Subsequent purification by reverse-phase HPLC using two Agilent Eclipse XDB-C8 5um 9.4 x 250 mm columns connected in series (gradient: 77–85%MeCN/H_2O) afforded analytically pure samples of each diastereomer, from which **84** was crystallized. Melting point: 80–83 ºC.

Data for minor diastereomer **84**: $[\alpha]_D^{25.0}$ = –25.5° (c = 1.50, $CHCl_3$).

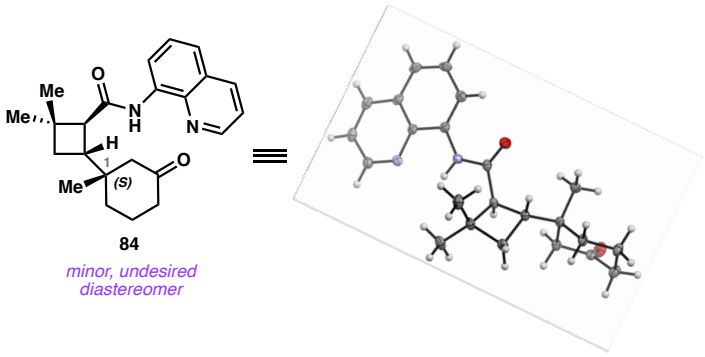
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.89 – 2.77 (m, 2H), 2.35 – 2.26 (m, 2H), 2.24 (d, *J* = 13.3 Hz, 1H), 2.09 (d, *J* = 13.4 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.88 – 1.77 (m, 1H), 1.72 – 1.61 (m, 3H), 1.55 – 1.48 (m, 1H), 1.35 (s, 3H), 1.13 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4, 170.6, 148.4, 138.5, 136.5, 134.6, 128.1, 127.6, 121.7, 121.4, 116.4, 51.5, 50.8, 41.2, 39.8, 39.6, 35.2, 34.1, 33.0, 30.8, 23.7, 22.2, 21.3.

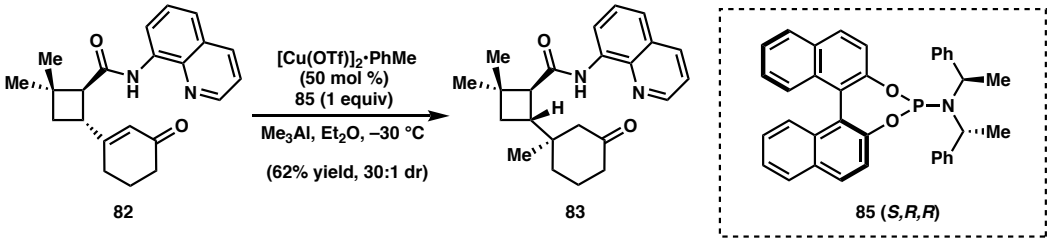
FTIR (NaCl, thin film) 3349, 3044, 2952, 2863, 1706, 1687, 1595, 1577, 1523, 1484, 1460, 1424, 1383, 1325, 1238, 1228, 1163, 827, 792 cm.$^{-1}$

HRMS (MM) calc'd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2224, found 365.2261.

XRCD: A suitable crystal of $C_{23}H_{28}N_2O_2$ (**84**) was selected for 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-Kα radiation (λ = 1.54178 Å) from a IμS HB micro-focus sealed X-ray tube. All diffractometer manipulations, including data collection, integration, and scaling were carried out using the Bruker APEXII software.



Selective preparation of ketone 83 using copper-catalyzed conjugate addition.



Inside a N_2-filled glovebox, $[Cu(OTf)]_2$•PhMe (72.4 mg, 0.140 mmol, 0.25 equiv) and (*S,R,R*) ligand **85** (302 mg, 0.560 mmol, 1.00 equiv) were added to a 25 mL flask. The reagents were suspended in Et_2O (5.60 mL) and stirred at room temperature for 30 minutes before *trans*-cyclobutane **82** (195 mg, 0.560 mmol) was added as a solid, in one portion. The reaction was sealed under N_2, removed from the glovebox and cooled to –30 °C under argon using a cryocool unit to control the temperature. Me_3Al (2.0 M in heptane; 560 µL, 1.12 mmol, 2.00 equiv) was then added dropwise, taking care to avoid an exotherm and the reaction mixture stirred vigorously at –30 °C for 16 hours. MeOH (1.00 mL) was then added to quench excess Me_3Al and then the reaction was warmed to room temperature. The mixture was diluted with EtOAc and H_2O, then the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel

flash chromatography (2% Et_2O/CH_2Cl_2 until ligand/impurities elute, then 4% Et_2O/CH_2Cl_2) to afford a 30:1 mixture of **83** and **84** (126 mg, 62% yield), as a white solid: $[\alpha]_D^{25.0} = -84.7°$ (c = 0.600, $CHCl_3$).

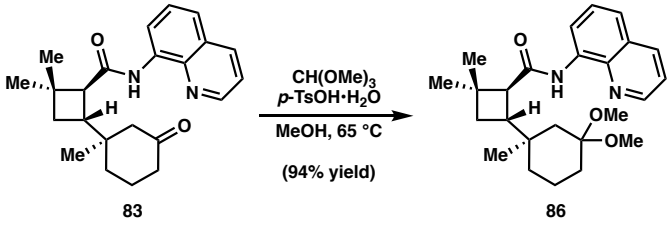
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.89 – 2.76 (m, 2H), 2.36 – 2.28 (m, 2H), 2.25 (ddd, *J* = 12.5, 6.6, 1.1 Hz, 1H), 2.04 (dt, *J* = 13.4, 2.0 Hz, 1H), 1.96 (ddq, *J* = 13.7, 7.0, 3.6 Hz, 1H), 1.81 (dtt, *J* = 13.7, 12.0, 5.0 Hz, 1H), 1.68 – 1.62 (m, 2H), 1.62 – 1.51 (m, 2H), 1.35 (s, 3H), 1.13 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4, 170.6, 148.3, 138.5, 136.5, 134.6, 128.1, 127.5, 121.7, 121.4, 116.4, 51.5, 50.4, 41.3, 40.9, 39.5, 35.2, 33.8, 32.6, 30.8, 23.7, 22.1, 20.8.

FTIR (NaCl, thin film) 3351, 3047, 2954, 2870, 1708, 1688, 1524, 1485, 1460, 1424, 1384, 1325, 1281, 1259, 1240, 1228, 1163, 919, 827, 792, 757, 732 cm.$^{-1}$

HRMS (MM) calc'd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2224, found 365.2228.

Preparation of dimethyl ketal 86.



83 86

To a flame-dried 15 mL flask was added ketone **83** (100 mg, 0.274 mmol) and dissolved in freshly distilled MeOH (2.7 mL). Trimethylorthoformate (150 μL, 1.37 mmol, 5.00 equiv) was then added, followed by *p*-toluenesulfonic acid monohydrate (2.60 mg,

0.014 mmol, 0.05 equiv). The reaction was topped with a reflux condenser and heated to 65 °C for 1 hour, then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by Florisil® flash chromatography (isocratic: 10% EtOAc/Hexane) to afford **86** (106 mg, 94% yield) as a white, foamy solid: $[\alpha]_D^{25.0}$ = –83.3° (c = 1.60, $CHCl_3$).

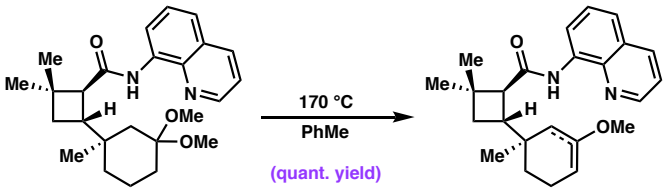
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.81 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.78 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.16 (s, 3H), 3.13 (s, 3H), 2.80 (d, *J* = 10.0 Hz, 1H), 2.69 (q, *J* = 9.7 Hz, 1H), 2.01 (ddd, *J* = 13.2, 3.5, 1.6 Hz, 1H), 1.74 (dt, *J* = 14.0, 2.4 Hz, 1H), 1.70 – 1.50 (m, 4H), 1.31 (s, 3H), 1.28 – 1.13 (m, 4H), 1.11 (s, 3H), 1.01 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 148.3, 138.5, 136.4, 134.7, 128.0, 127.6, 121.6, 121.2, 116.4, 100.8, 51.3, 47.9, 47.3, 42.3, 38.6, 34.8, 34.7, 34.0, 33.3, 32.5, 30.7, 23.9, 21.4, 18.8.

FTIR (NaCl, thin film) 3356, 3048, 2950, 2867, 2828, 1690, 1525, 1485, 1460, 1424, 1384, 1368, 1325, 1288, 1276, 1261, 1242, 1155, 1108, 1096, 1048, 946, 927, 826, 792, 756, 690, 666 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{31}N_2O_2$ $[M–OCH_3]^+$ 379.2380, found 379.2376.

Preparation of methyl enol ether 90.



86 90

(1:1 mixture of enol ethers)

To a 15 mL thick-walled, screw top pressure vessel were added dimethyl ketal **86** (59.8 mg, 0.146 mmol) and PhMe (5.0 mL). The tube sealed under a stream of N_2. The reaction was heated to 170 °C in a preheated oil bath for 3.5 hours. The reaction was then cooled to room temperature and concentrated *in vacuo* to afford **90** (55.1 mg, quantitative yield), an inseparable ~1:1 mixture of enol ether isomers, as a foamy colorless gum: $[\alpha]_D^{25.0}$ = –78.8° (c = 1.25, $CHCl_3$).

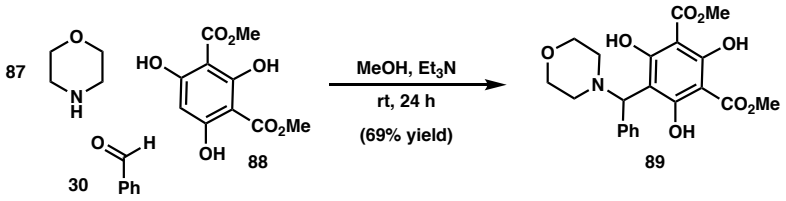
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.90 – 8.72 (m, 2H), 8.15 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.57 – 7.40 (m, 3H), 4.48 (s, 1H), 3.48 (s, 3H), 2.87 – 2.74 (m, 2H), 2.12 – 1.93 (m, 2H), 1.74 – 1.57 (m, 4H), 1.48 – 1.36 (m, 1H), 1.33 (s, 3H), 1.31 – 1.27 (m, 1H), 1.12 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 171.0, 156.3, 154.3, 148.3, 148.3, 138.6, 138.5, 136.4, 136.4, 134.8, 134.7, 128.5, 128.1, 128.1, 127.6, 126.9, 126.8, 121.7, 121.6, 121.2, 121.2, 116.4, 116.3, 99.4, 92.1, 54.1, 53.9, 52.6, 51.5, 40.9, 40.1, 36.4, 35.4, 35.2, 34.0, 33.5, 33.0, 32.6, 30.9, 30.8, 30.7, 29.9, 28.2, 26.1, 25.1, 24.1, 23.9, 21.2, 20.7, 19.5.

FTIR (NaCl, thin film) 3354, 3051, 2949, 2930, 2862, 1690, 1668, 1524, 1484, 1461, 1424, 1384, 1368, 1326, 1238, 1215, 1162, 1147, 1026, 826, 791, 756, 694 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{31}N_2O_2$ $[M+H]^+$ 379.2380, found 379.2395.

Preparation of benzhydryl morpholine 89.



To a flame-dried 100 mL round-bottom flask were added phloroglucinol **88** (1.00g, 4.13 mmol), followed by freshly distilled MeOH (41.0 mL). Benzaldehyde (**30**) (421 μL, 4.13 mmol, 1.00 equiv), morpholine (**87**) (361 μL, 4.13 mmol ,1.00 equiv), and triethylamine (576 μL, 4.13 mmol, 1.00 equiv) were then added successively via syringe and the reaction stirred at room temperature for 24 hours. The precipitate thus formed was collected by vacuum filtration and washed with MeOH (20 mL) and dried under high vacuum to afford analytically pure **89** (1.19 g, 69% yield) as a white powder.

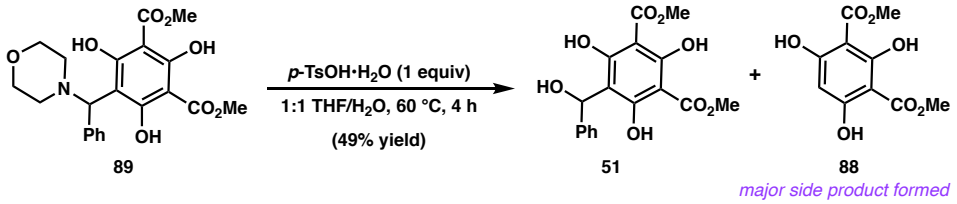
^{1}H NMR (400 MHz, $CDCl_3$) δ 15.34 (s, 1H), 13.16 (s, 1H), 12.53 (s, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.34 – 7.20 (m, 3H), 4.88 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.90 – 3.40 (br m, 4H), 3.08 (br s, 1H), 2.46 (ddd, J = 11.9, 6.2, 3.1 Hz, 2H), 2.18 (br s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 166.2, 165.6, 165.1, 138.2, 128.9, 128.4, 103.8, 96.5, 94.2, 69.0, 66.6, 52.7, 52.6.

FTIR (NaCl, thin film) 3404 (br), 3062, 3030, 2955, 2894, 2854, 2716, 2562 (br), 2252, 1953 (br), 1731, 1654, 1603, 1494, 1454, 1431, 1403, 1326, 1290, 1250, 1205, 1169, 1121, 1080, 1029, 1006, 986, 942, 915, 878, 843, 825, 808, 761, 732, 700, 648 cm.$^{-1}$

HRMS (MM) calc'd for $C_{21}H_{24}NO_8$ $[M+H]^+$ 418.1496, found 418.1515.

Preparation of fully oxidized *o*-QM precursor 51.



To a 50 mL round-bottom flask was added benzhydryl morpholine **89** (200 mg, 0.479 mmol), followed by a 1:1 mixture of THF/H_2O (9.6 mL). *p*-Toluenesulfonic acid monohydrate (91.1 mg, 0.479 mmol, 1.00 equiv) was then added in one portion and the reaction was heated to 60 °C for 4 hours. Note: it is best to monitor this reaction closely by TLC to mitigate degradation of the product to **88**, presumably via acid-mediated retro aldol. Upon completion, the reaction was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The reaction was diluted with EtOAc and the organic layer separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 5% EtOAc/CH_2Cl_2 + 0.5% AcOH, necessary to avoid streaking on the column). Fractions containing pure product were combined, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford **51** (82.0 mg, 49% yield) as a white solid.

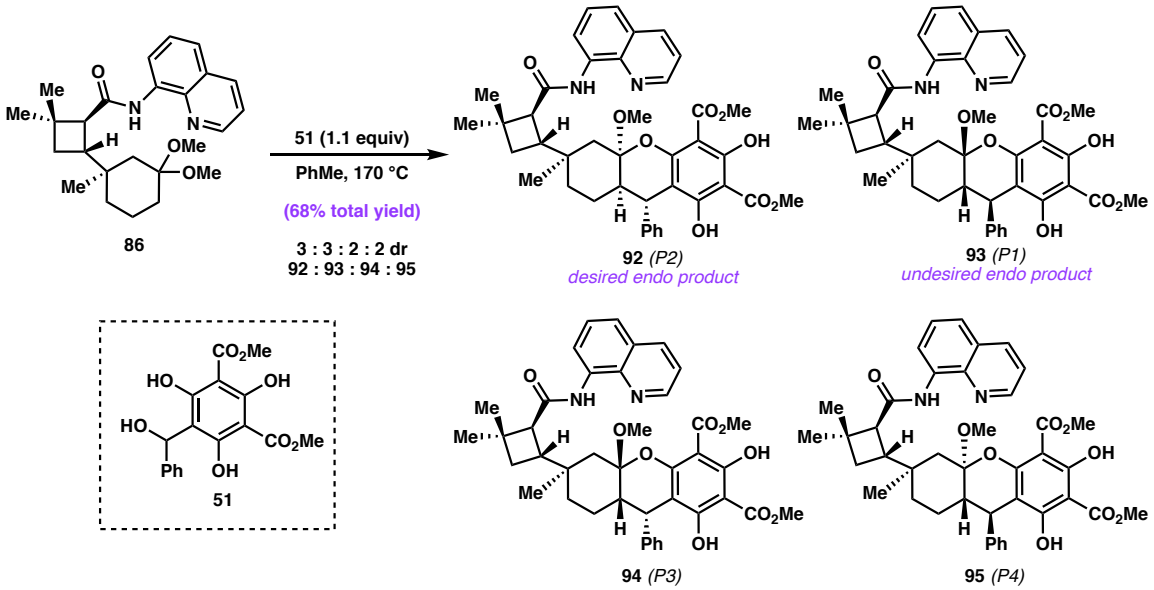
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.89 (s, 2H), 11.70 (s, 1H), 7.46 – 7.39 (m, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.26 – 7.19 (m, 1H), 6.38 – 6.23 (m, 1H), 4.09 (d, J = 11.6 Hz, 1H), 4.02 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 165.0, 164.7, 143.9, 128.2, 127.0, 125.6, 110.2, 94.5, 68.1, 53.2.

FTIR (NaCl, thin film) 3563 (br), 3357 (br), 3085, 3058, 3028, 3006, 2956, 2851, 2749 (br), 1727, 1655, 1623, 1599, 1492, 1434, 1333, 1318, 1245, 1201, 1170, 1129, 1039, 1026, 972, 909, 836, 816, 733, 698, 622 cm.$^{-1}$

HRMS (MM) calc'd for $C_{17}H_{15}O_7$ $[M–OH]^+$ 331.0812, found 331.0825.

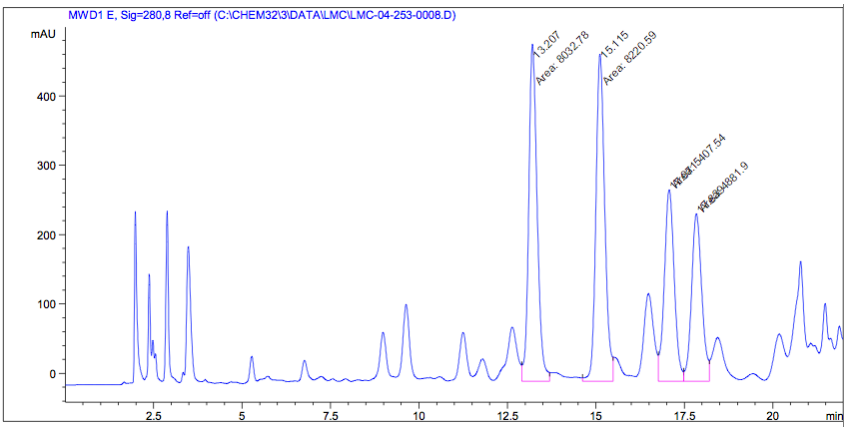
Preparation of tricyclic ketals 92–95 by thermal cycloaddition.



To a 15 mL thick-walled, screw top pressure vessel were added dimethyl ketal **86** (105 mg, 0.256 mmol) and *o*-QM precursor **51** (98.0 mg, 0.281 mmol, 1.10 equiv). PhMe (4.3 mL) was then added and the tube sealed under a stream of argon. The reaction was heated to 170 °C in a preheated oil bath for 21 hours. The reaction was then cooled to room temperature and concentrated *in vacuo*. The crude residue was first purified by silica gel flash chromatography to remove separable impurities (4% EtOAc/CH_2Cl_2 + 0.5% AcOH) to afford a complex mixture of diastereomers, including **92–95** (109 mg, 68% yield). Analytically pure samples of the four diastereomers produced in greatest abundance (i.e.

92–95) were obtained by subsequent reverse-phase HPLC purification using an Agilent XDB-C18 5 µm 30 x 250 mm column (gradient: 83–100% MeCN/H_2O).

Chromatogram from HPLC separation:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.207	MF	0.2752	8032.78027	486.56299	30.2635
2	15.115	MF	0.2903	8220.58984	472.01566	30.9711
3	17.071	MF	0.3263	5407.54297	276.19736	20.3729
4	17.839	MF	0.3366	4881.89746	241.74495	18.3925

Data for **92** (peak 2): $[\alpha]_D^{25.0} = -32.2°$ (c = 0.360, $CHCl_3$) White Solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 (s, 1H), 12.08 (s, 1H), 9.65 (s, 1H), 8.78 – 8.74 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.14 – 7.07 (m, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 3.91 (d, *J* = 7.8 Hz, 1H), 3.39 (s, 3H), 2.82 – 2.76 (m, 2H), 2.12 (s, 1H), 1.86 – 1.73 (m, 2H), 1.69 – 1.49 (m, 5H), 1.33 (s, 3H), 1.25 (d, *J* = 9.6 Hz, 1H), 1.10 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 170.8, 169.9, 166.0, 164.7, 158.9, 148.3, 145.9, 138.5, 136.5, 134.7, 128.1, 128.1, 127.8, 127.6, 126.0, 121.7, 121.3, 116.3, 104.2, 104.1, 97.1, 95.7, 52.7, 52.7, 52.2, 49.0, 44.2, 41.7, 39.9, 37.7, 35.1, 35.1, 33.9, 30.8, 28.9, 24.0, 23.5, 22.8.

FTIR (NaCl, thin film) 3412 (br), 3354 (br), 3059, 3022, 3006, 2951, 2928, 2864, 1731, 1686, 1654, 1648, 1643, 1594, 1524, 1484, 1459, 1426, 1384, 1338, 1325, 1249, 1222, 1201, 1157, 1122, 1081, 1092, 1028, 976, 945, 936, 847, 826, 792, 755, 700, 667 cm.$^{-1}$

HRMS (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3141.

Data for **93** (peak 1): $[\alpha]_D^{25.0}$ = –13.8° (c = 0.420, $CHCl_3$) White Solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (s, 1H), 11.68 (s, 1H), 9.65 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.77 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.24 – 7.16 (m, 2H), 7.16 – 7.09 (m, 1H), 7.09 – 7.02 (m, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.91 (s, 1H), 3.05 (s, 3H), 2.82 – 2.67 (m, 2H), 2.16 (dd, *J* = 12.4, 3.5 Hz, 1H), 1.98 (d, *J* = 13.8 Hz, 1H), 1.76 (dd, *J* = 13.3, 4.1 Hz, 1H), 1.70 – 1.39 (m, 6H), 1.32 (s, 3H), 1.12 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.8, 169.9, 165.0, 163.1, 157.2, 148.3, 145.6, 138.5, 136.5, 134.7, 128.1, 127.8, 127.6, 127.3, 125.6, 121.7, 121.3, 116.4, 102.4, 102.1, 99.0, 95.3, 52.8, 52.5, 51.3, 47.8, 45.3, 41.9, 41.4, 40.1, 34.7, 34.6, 32.7, 32.6, 30.8, 27.4, 23.8, 22.3.

FTIR (NaCl, thin film) 3410 (br), 3355 (br), 3055, 3021, 3000, 2950, 2864, 1734, 1686, 1654, 1643, 1599, 1524, 1484, 1460, 1426, 1384, 1336, 1326, 1279, 1247, 1225, 1163, 1142, 1093, 1063, 988, 973, 949, 841, 826, 791, 754, 698, 667 cm.$^{-1}$

HRMS (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3119.

Data for **94** (peak 3): $[\alpha]_D^{25.0}$ = –98.4° (c = 0.206, $CHCl_3$) White Solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (s, 1H), 11.61 (s, 1H), 9.64 (s, 1H), 8.82 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.76 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.57 – 7.43 (m, 3H), 7.30 (dd, *J* = 8.6, 5.1 Hz, 2H), 7.17 (s, 2H), 6.81 (s, 1H), 4.54 (d, *J* = 7.3 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.21 (s, 3H), 2.74 (q, *J* = 9.8 Hz, 2H), 2.10 (d, *J* = 13.7 Hz, 1H), 1.97 – 1.83 (m, 1H), 1.62 (d, *J* = 8.9 Hz, 2H), 1.45 (d, *J* = 13.8 Hz, 1H), 1.32 (s, 3H), 1.29 – 1.24 (m, 1H), 1.18 (d, *J* = 13.2 Hz, 1H), 1.11 (s, 3H), 1.10 – 1.06 (m, 1H), 1.04 (s, 3H), 0.76 (dd, *J* = 13.1, 3.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.9, 169.7, 164.9, 162.7, 158.0, 148.3, 142.2, 138.5, 136.5, 134.7, 128.5, 128.1, 127.7, 127.6, 125.9, 121.7, 121.3, 116.4, 104.2, 102.2, 99.3, 95.5, 52.8, 52.5, 51.3, 49.0, 43.7, 42.2, 40.3, 38.5, 34.8, 34.4, 33.0, 32.6, 30.8, 23.8, 22.1, 21.7.

FTIR (NaCl, thin film) 3408 (br), 3354 (br), 3059, 3022, 3009, 2952, 2868, 1738, 1732, 1682, 1658, 1652, 1645, 1599, 1525, 1485, 1462, 1455, 1426, 1385, 1327, 1281, 1251, 1225, 1165, 1133, 1090, 1077, 1031, 991, 946, 872, 826, 792, 755, 703 $cm.^{-1}$

HRMS (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3133.

Data for **95** (peak 4): $[\alpha]_D^{25.0} = -13.4°$ (c = 0.226, $CHCl_3$) White Solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (s, 1H), 11.23 (s, 1H), 9.66 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.76 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.22 (dd, *J* = 7.9, 6.5 Hz, 2H), 7.18 – 7.13 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.67 (d, *J* = 11.0 Hz, 1H), 3.16 (s, 3H), 2.81 – 2.66 (m, 2H), 2.10 (dd, *J* = 14.2, 1.6 Hz, 1H), 1.71 (td, *J* = 10.8, 5.3 Hz, 1H), 1.64 (dd, *J* = 9.2, 2.6 Hz, 2H), 1.56 –

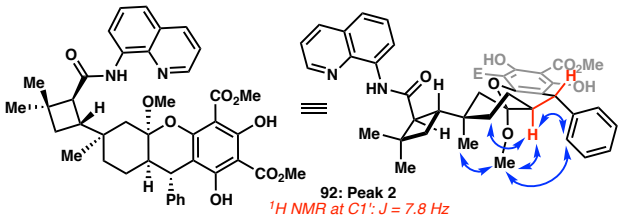
1.48 (m, 2H), 1.45 (d, J = 14.3 Hz, 1H), 1.38 – 1.32 (m, 1H), 1.31 (s, 3H), 1.21 – 1.14 (m, 1H), 1.12 (s, 3H), 1.08 (s, 3H).

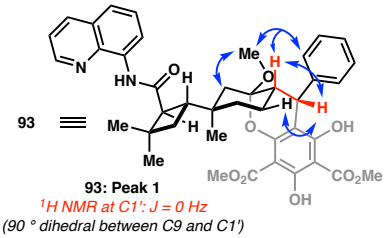
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.8, 169.5, 164.0, 162.4, 157.4, 148.3, 145.4, 138.5, 136.5, 134.7, 128.1, 128.1, 127.6, 125.9, 121.7, 121.3, 116.4, 108.0, 101.7, 99.6, 95.5, 52.7, 52.5, 51.2, 49.4, 49.0, 42.0, 41.1, 36.2, 35.3, 34.8, 33.3, 32.6, 30.8, 23.8, 22.5, 21.1.

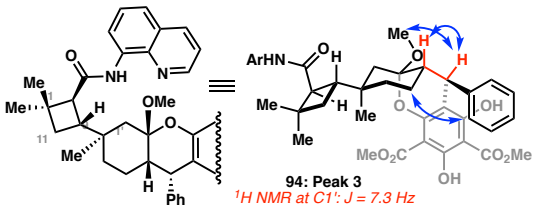
FTIR (NaCl, thin film) 3412 (br), 3354 (br), 3055, 3023, 3003, 2950, 2866, 1732, 1688, 1656, 1598, 1524, 1484, 1453, 1426, 1384, 1327, 1277, 1248, 1225, 1165, 1062, 993, 954, 925, 826, 792, 755, 702 cm.$^{-1}$

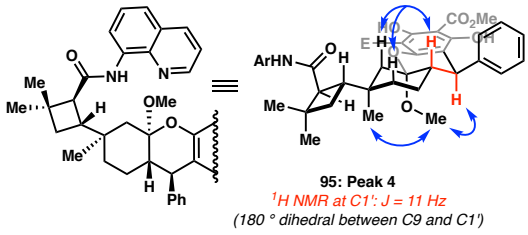
HRMS (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3139.

Summary of Key NOE correlations for stereochemical assignment of 92–95:

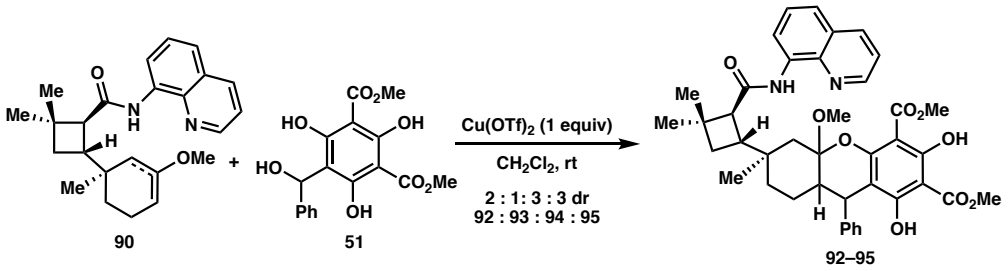






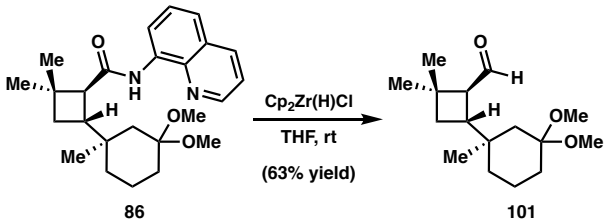


Preparation of tricyclic ketals 92–95 by $Cu(OTf)_2$-mediated cycloaddition.



Inside a N_2-filled glovebox, methyl enol ether **90** (17.0 mg, 0.045 mmol) and *o*-QM precursor **51** (16.4 mg, 0.047 mmol, 1.05 equiv) were added to a 1 dram vial and dissolved in CH_2Cl_2 (400 μL). $Cu(OTf)_2$ was then added as a solid in one portion and the reaction immediately turns a light green color, then yellow-brown within the first 5 minutes. The reaction was stirred at room temperature for 1 hour, then quenched with saturated aqueous $NaHCO_3$ and diluted with $CHCl_3$. The reaction mixture was extracted with $CHCl_3$ (3 x 1 mL) and the organics filtered through a plug of Na_2SO_4 and concentrated *in vacuo*. The crude residue was analyzed by ^1H NMR and determined to contain **92**, **93**, **94**, and **95** in an approximate ratio of 2 : 1 : 3 : 3, respectively. For spectroscopic characterization data, see above.

Preparation of aldehyde 101.



Inside a N_2-filled glovebox, Schwartz's reagent (119 mg, 0.462 mmol, 2.00 equiv) was added to a 10 mL flask and sealed under N_2. The flask was removed from the glovebox and THF (1.2 mL) was added via syringe. To the milky-white suspension was added ketal **86** (94.8 mg, 0.231mmol) as a solution in THF (1.2 mL) in a quick drip. The reaction immediately beings to turn yellow, eventually becoming a darker orange color over 1 hour, at which time the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The reaction was diluted with EtOAc and the organic layer separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 5% EtOAc/hexane + 1% Et_3N) to afford **101** (36.9 mg, 62% yield) as a pale yellow oil: $[\alpha]_D^{25.0} = -33.1°$ (c = 0.500, $CHCl_3$).

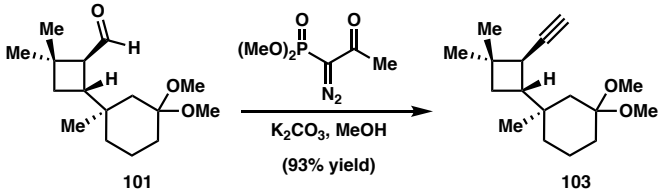
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.0 Hz, 1H), 3.14 (s, 3H), 3.09 (s, 3H), 2.64 (td, *J* = 9.7, 8.5 Hz, 1H), 2.58 (dd, *J* = 9.9, 3.0 Hz, 1H), 1.86 (ddt, *J* = 13.6, 4.2, 2.6 Hz, 1H), 1.61 (t, *J* = 10.3 Hz, 1H), 1.57 – 1.44 (m, 4H), 1.34 – 1.18 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.13 – 1.05 (m, 2H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7, 100.5, 55.2, 47.6, 47.1, 39.8, 39.3, 35.7, 34.4, 33.9, 33.0, 32.7, 31.1, 24.3, 21.7, 18.6.

FTIR (NaCl, thin film) 2952, 2868, 2828, 2705, 1713, 1461, 1383, 1368, 1341, 1288, 1262, 1246, 1180, 1166, 1110, 1098, 1048, 1009, 945, 924, 823, 828 cm.$^{-1}$

HRMS (MM) calc'd for $C_{15}H_{25}O_2$ $[M–OCH_3]^+$ 237.1849, found 237.1855.

Preparation of alkyne 103.



To a 10 mL round bottom flask were added aldehyde **101** (36.0 mg, 0.134 mmol) and K_2CO_3 (37.0 mg, 0.268 mmol, 2.00 equiv). The flask was fitted with a septum and the atmosphere exchanged 2x for N_2. Freshly distilled MeOH (1.5 mL) was then added via syringe and the solution cooled to 0 °C. Dimethyl-1-diazo-2-oxopropylphosphonate (38.6 mg, 0.201 mmol, 1.50 equiv) was weighed into a tared syringe and added dropwise to the reaction, neat. The reaction was allowed to gradually warm to room temperature and stirred for 12 hours. The reaction was then diluted with Et_2O, saturated aqueous $NaHCO_3$ was added, and the organic layer separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by Florisil® flash chromatography (isocratic: 5% Et_2O/pentane) to afford **103** (32.9 mg, 93% yield) as a pale yellow oil: $[\alpha]_D^{25.0} = –43.6°$ (c = 0.355, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.13 (s, 3H), 2.43 (dd, *J* = 10.1, 2.4 Hz, 1H), 2.16 – 2.05 (m, 2H), 2.04 – 1.93 (m, 1H), 1.69 (ddd, *J* = 13.9, 2.8, 1.8 Hz, 1H), 1.59 –

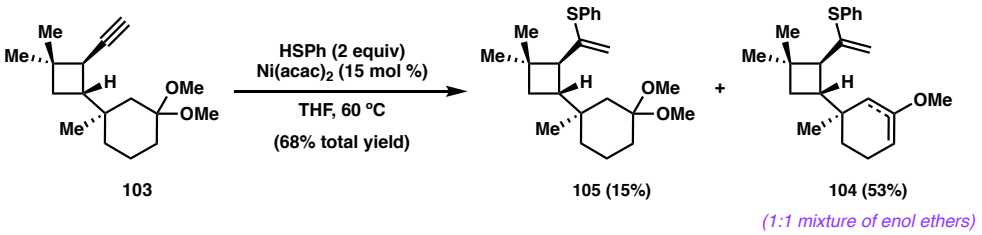
1.50 (m, 2H), 1.48 (d, J = 9.6 Hz, 2H), 1.29 – 1.17 (m, 5H), 1.16 (d, J = 2.7 Hz, 4H), 1.03 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 100.7, 85.8, 70.5, 49.1, 47.9, 47.3, 39.1, 35.2, 35.1, 34.0, 33.5, 33.2, 33.2, 29.9, 24.8, 21.1, 18.8.

FTIR (NaCl, thin film) 3310, 3263, 2953, 2866, 2828, 1459, 1383, 1364, 1342, 1323, 1288, 1266, 1243, 1180, 1157, 1106, 1094, 1048, 945, 926, 858, 830, 655, 621 cm.$^{-1}$

HRMS (MM) calc'd for $C_{16}H_{25}O_2$ $[M–OCH_3]^+$ 233.1900, found 233.1887.

Preparation of vinyl sulfides 104 and 105.



103 105 (15%) 104 (53%)

(1:1 mixture of enol ethers)

Inside a N_2-filled glovebox, THF (400 μL) was added to a 1 dram vial containing alkyne **103** (12.4 mg, 0.047 mmol), followed by $Ni(acac)_2$ as a stock solution in THF (0.10 M, 70 μL, 0.007 mmol, 0.15 equiv). The reaction was stirred for 10 minutes at room temperature before thiophenol (10 μL, 0.094 mmol, 2.00 equiv) was added neat. The reaction was sealed with a Teflon cap and heated to 60 ° C in a preheated aluminum block inside the glovebox. After 3 hours, the reaction was cooled to room temperature and diluted with CH_2Cl_2. The reaction mixture was filtered over a small pad of Celite, washed with CH_2Cl_2 until the filtrate runs colorless, and concentrated *in vacuo*. The crude residue was taken up in EtOAc and shaken with 5M NaOH (to remove excess thiophenol). The organic

layer was then filtered through a plug of Na_2SO_4, concentrated, and purified by silica gel preparative TLC (5% EtOAc/hexane + 1% Et_3N) to afford **104** (8.50 mg, 53% yield) and **105** (2.7 mg, 15% yield) each as colorless oils.

Data for ketal **105**: $[\alpha]_D^{25.0}$ = +12.3° (c = 0.115, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.36 – 7.28 (m, 3H), 5.17 (d, *J* = 1.3 Hz, 1H), 4.96 (s, 1H), 3.17 (s, 3H), 3.13 (s, 3H), 2.51 (d, *J* = 10.2 Hz, 1H), 2.26 (q, *J* = 9.7 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.65 (ddd, *J* = 13.8, 2.8, 1.6 Hz, 1H), 1.50 (ddd, *J* = 9.6, 7.0, 3.7 Hz, 2H), 1.45 – 1.39 (m, 2H), 1.21 – 1.12 (m, 4H), 1.11 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 133.8, 133.4, 129.2, 127.9, 111.6, 100.8, 49.4, 47.9, 47.3, 45.1, 39.7, 35.6, 34.8, 34.6, 33.2, 32.4, 30.6, 23.2, 21.7, 18.9.

FTIR (NaCl, thin film) 2950, 2863, 2827, 1610, 1583, 1476, 1459, 1439, 1379, 1364, 1322, 1274, 1260, 1247, 1178, 1145, 1130, 1100, 1083, 1049, 1024, 946, 926, 856, 831, 822, 747, 691 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{31}OS$ $[M–OCH_3]^+$ 343.2090, found 343.2073.

Data for enol ether **104**: $[\alpha]_D^{25.0}$ = –11.0° (c = 0.982, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 2H), 7.36 – 7.27 (m, 3H), 5.23 – 4.84 (m, 2H), 4.63 – 4.29 (m, 1H), 3.40 (s, 3H), 2.58 – 2.50 (m, 1H), 2.40 (dq, *J* = 34.9, 9.5 Hz, 1H), 2.11 – 1.91 (m, 3H), 1.64 (ddd, *J* = 15.0, 5.9, 2.4 Hz, 2H), 1.48 – 1.40 (m, 2H), 1.39 – 1.30 (m, 1H), 1.11 (d, *J* = 9.9 Hz, 3H), 1.00 (d, *J* = 2.4 Hz, 3H), 0.83 (d, *J* = 21.0 Hz, 4H).

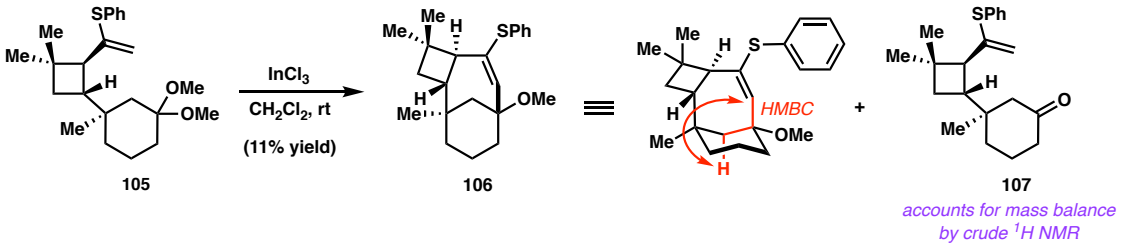
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 154.4, 146.0, 145.9, 133.8, 133.5, 133.4, 133.3, 129.2, 129.1, 127.9, 127.7, 112.3, 111.1, 100.6, 92.0, 54.1, 53.9, 50.2, 49.5, 43.5, 40.9,

37.7, 36.1, 35.1, 35.1, 34.5, 34.1, 32.9, 32.6, 31.6, 30.6, 30.5, 28.2, 25.8, 23.3, 23.2, 22.0, 20.8, 19.4.

FTIR (NaCl, thin film) 3061, 2991, 2950, 2930, 2862, 2843, 1667, 1609, 1583, 1476, 1460, 1453, 1440, 1380, 1366, 1251, 1215, 1148, 1066, 1024, 940, 817, 747, 691 $cm.^{-1}$

HRMS (MM) calc'd for $C_{22}H_{31}OS$ $[M+H]^+$ 343.2090, found 343.2087.

Preparation of bridged bicycle 106.



Inside a N_2-filled glovebox, CH_2Cl_2 was added to a 1 dram vial containing **105** (9.30 mg, 0.025 mmol), followed by $InCl_3$ (5.49 mg, 0.025 mmol, 1.00 equiv). The reaction was stirred at room temperature for 2 hours, then quenched with saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The reaction was extracted with CH_2Cl_2 (3 x 500 µL), the combined organics filtered a plug of Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (40–60% CH_2Cl_2/hexane) to afford **106** (0.900 mg, 11% yield) as a colorless oil, with the remaining mass balance accounted for by ketone **107**, as determined by crude ^{1}H NMR.

Data for bridged bicycle **66**: $[\alpha]_D^{25.0}$ = +58.2° (c = 0.053, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.30 (ddd, *J* = 8.3, 7.1, 0.8 Hz, 2H), 7.24 – 7.18 (m, 1H), 5.52 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.18 (s, 3H), 2.91 – 2.81 (m, 1H), 2.00 – 1.72 (m, 5H), 1.66 (ddd, *J* = 11.6, 6.8, 3.5 Hz, 1H), 1.44 – 1.37 (m, 2H), 1.35 (dd, *J* =

12.3, 1.7 Hz, 1H), 1.29 (m, 1H), 1.28 (s, 3H), 1.19 (dd, *J* = 14.1, 7.0 Hz, 1H), 1.00 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 139.6, 135.0, 131.7, 129.2, 127.2, 80.6, 52.4, 50.2, 49.2, 48.6, 40.1, 38.3, 36.2, 33.7, 31.3, 31.2, 28.9, 22.4, 21.2.

FTIR (NaCl, thin film) 3062, 2945, 2927, 2860, 2820, 1734, 1718, 1701, 1654, 1583, 1560, 1476, 1458, 1438, 1370, 1294, 1254, 1232, 1151, 1086, 1066, 1024, 950, 870, 840, 800, 743, 690 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{31}OS$ $[M+H]^+$ 343.2090, found 343.2077.

Data for ketone **107**: $[\alpha]_D^{25.0}$ = +31.6° (c = 0.100, $CHCl_3$).

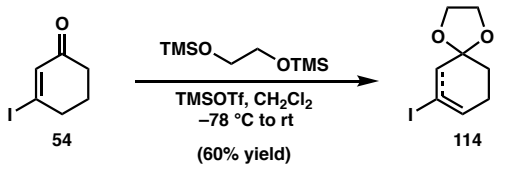
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.40 – 7.32 (m, 3H), 5.13 (d, *J* = 1.3 Hz, 1H), 4.98 (s, 1H), 2.53 (d, *J* = 10.1 Hz, 1H), 2.38 (td, *J* = 10.0, 8.9 Hz, 1H), 2.32 – 2.23 (m, 2H), 2.17 (d, *J* = 13.6 Hz, 1H), 2.02 (dt, *J* = 13.4, 1.9 Hz, 1H), 1.93 – 1.90 (m, 1H), 1.82 (dddd, *J* = 9.7, 8.1, 3.9, 2.3 Hz, 1H), 1.57 (q, *J* = 4.4 Hz, 1H), 1.49 – 1.44 (m, 1H), 1.44 – 1.33 (m, 2H), 1.16 (s, 3H), 1.03 (s, 3H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.6, 145.5, 134.1, 133.0, 129.3, 128.2, 111.4, 51.1, 49.8, 43.1, 41.3, 40.3, 35.1, 34.2, 32.5, 30.6, 23.1, 22.1, 21.8.

FTIR (NaCl, thin film) 3059, 2953, 2927, 2860, 1711, 1680, 1611, 1583, 1476, 1461, 1440, 1381, 1364, 1347, 1311, 1283, 1253, 1228, 1151, 1087, 1067, 1024, 890, 855, 749, 692 cm.$^{-1}$

HRMS (MM) calc'd for $C_{21}H_{29}OS$ $[M+H]^+$ 329.1934, found 329.1943.

Preparation of protected iodide 114.



Inside a N_2-filled glove box, a 250 mL round bottom flask was charged with TMSOTf (0.410 mL, 0.230 mmol, 0.010 equiv) and CH_2Cl_2 (20.0 mL). The flask was sealed, removed from the glove box, and placed under a N_2 atmosphere. The reaction mixture was cooled to –78 ºC, and 1,2-bistrimethylsilyloxyethane (11.0 mL, 45.0 mmol, 2.00 equiv) was added via syringe. (Note: best results were obtained when 1,2-bistrimethylsilyloxyethane was sparged with argon for 30 min prior to addition). Vinyl iodide **54** (5.00 g, 22.5 mmol, 1.00 equiv) was added to the flask dropwise as a solution in CH_2Cl_2 (20.0 mL), via cannula transfer. An additional portion of CH_2Cl_2 (5.00 mL) was used to complete the transfer. The colorless reaction mixture was allowed to stir at –78 ºC for 1 hour, at which point the reaction mixture was warmed to 0 ºC. The reaction mixture became yellow immediately upon warming and was allowed to warm to room temperature over 16 hours. The reaction mixture became dark orange and was quenched with the addition of DIPEA (11.0 mL), at which point the reaction became yellow. The mixture was poured into a separatory funnel and diluted with saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined, dried over a 1:1 mixture of anhydrous K_2CO_3 and Na_2SO_4, filtered, and concentrated to provide a yellow residue that was purified by flash silica gel chromatography (5% EtOAc, 1%

Et_3N/hexane – 20% EtOAc, 1% Et_3N/hexane) to provide **114** (3.61 g, 60% yield) as a 8:1 mixture of olefin isomers, as a pale yellow oil.

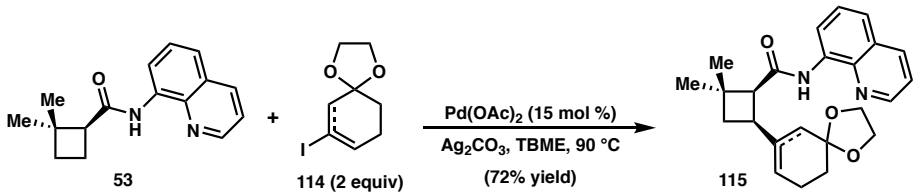
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (tt, *J* = 4.0, 1.9 Hz, 1H), 3.98 (p, *J* = 1.7 Hz, 4H), 2.72 (q, *J* = 2.3 Hz, 2H), 2.36 – 2.22 (m, 2H), 1.77 (t, *J* = 6.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 108.1, 91.1, 64.7, 49.3, 30.2, 27.5.

FTIR (NaCl, thin film) 3040, 2955, 2934, 2881, 2836, 2684, 1637, 1474, 1443, 1429, 1418, 1360, 1330, 1300, 1243, 1207, 1142, 1114, 1076, 1058, 1021, 970, 948, 889, 848, 827, 776, 738, 662 cm.$^{-1}$

HRMS (FAB) calc'd for $C_8H_{11}IO_2$ $[M]^+$ 266.9876, found 266.9888.

Preparation of *cis*-dioxolane 115.



A 100 mL, thick-walled pressure vessel was charged with $Pd(OAc)_2$ (132 mg, 0.590 mmol, 0.150 equiv), Ag_2CO_3 (1.08 g, 3.93 mmol, 1.00 equiv), and **53** (1.00 g, 3.93 mmol, 1.00 equiv). Vinyl iodide **114** (2.09 g, 7.86 mmol, 2.00 equiv) was then added to the flask as a solution in TBME (19.7 mL). The reaction vessel was sealed with a screw top under ambient conditions and heated to 90 ºC in an oil bath. The heterogeneous reaction mixture is olive green upon addition of vinyl iodide. After heating for five minutes, the reaction mixture became black. After 16 hours, the flask was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered over a pad of celite and the

filter cake was washed with CH_2Cl_2. The filtrate was concentrated, and the crude orange residue was purified by flash silica gel chromatography (30% EtOAc, 1% Et_3N/hexane–35% EtOAc, + 1% Et_3N/hexane) to provide **115** (1.11 g, 72% yield) as a white foam: $[\alpha]_D^{25.0} = -29.3°$ (c = 1.95, $CHCl_3$).

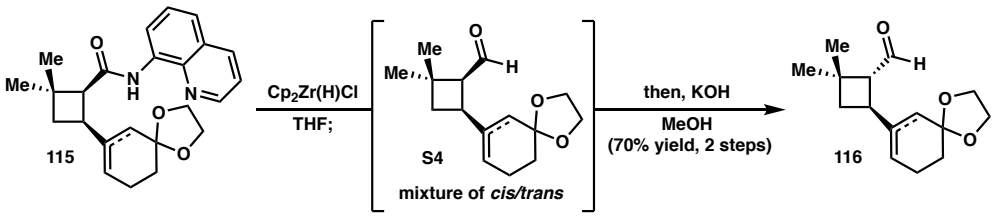
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.81 (ddd, *J* = 24.2, 7.3, 1.5 Hz, 2H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.49 (td, *J* = 8.2, 7.5, 6.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.65 (dd, *J* = 17.8, 9.1 Hz, 1H), 4.03 – 3.81 (m, 2H), 3.76 – 3.64 (m, 2H), 3.25 (q, *J* = 9.1, 8.2 Hz, 1H), 3.05 (dd, *J* = 8.7, 2.8 Hz, 1H), 2.46 (t, *J* = 10.9 Hz, 1H), 2.40 – 2.23 (m, 2H), 2.19 (dt, *J* = 16.5, 2.1 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.93 (ddd, *J* = 11.1, 8.3, 2.9 Hz, 1H), 1.71 – 1.59 (m, 1H), 1.57 – 1.48 (m, 1H), 1.40 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 147.9, 138.7, 136.3, 134.9, 134.8, 127.9, 127.5, 121.4, 121.2, 120.8, 116.6, 108.3, 64.3, 64.1, 55.9, 37.2, 37.1, 36.7, 35.4, 30.8, 30.2, 25.1, 24.4.

FTIR (NaCl, thin film) 3357, 3300, 3043, 3006, 2952, 2928, 2881, 1685, 1664, 1596, 1577, 1523, 1485, 1460, 1424, 1385, 1324, 1255, 1208, 1160, 1132, 1106, 1060, 1039, 1020, 947, 846, 826, 792, 755, 666 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{29}N_2O_3$ $[M+H]^+$ 393.2173, found 393.2183.

Preparation of *trans*-aldehyde 116.



Inside a N_2-filled glove box, a 250 mL round bottom flask was charged with Schwartz's reagent (2.30 g, 8.92 mmol, 2.06 equiv) and THF (22.3 mL). *Cis*-dioxolane **115** (1.70 g, 4.32 mmol, 1.00 equiv) was added to the flask as a solution in THF (22.3 mL). The flask was sealed, removed from the glove box and put under a N_2 atmosphere. The flask was covered with aluminum foil and allowed to stir for one hour, at which point the reaction was quenched with the addition of saturated $NaHCO_3$ solution. (Note, it is important that the quench be conducted very quickly to avoid decomposition of excess Schwartz's reagent and formation of HCl). The reaction mixture was diluted with EtOAc and the organic layer separated. The aqueous layer was filtered through a pad of celite and sand and then extracted 5x with EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide a yellow residue that was purified by flash silica gel chromatography (15% EtOAc, 1% Et_3N/hexanes) to provide **S4** (755 mg, 3.01 mmol) as a yellow oil as a 1.8:1 (*cis*/*trans*) mixture of diastereomers at C5. The oil was concentrated directly into a 200 mL round bottom flask and dissolved in wet MeOH (60.0 mL). The flask was then charged with KOH (3.36 g, 59.9 mmol, 20.0 equiv) and the mixture allowed to stir for 1 hour at room temperature. The mixture was then concentrated to a volume of ~3 mL and diluted with pH 7 buffer. A pale yellow precipitate formed upon addition of buffer. The solution was slowly acidified using dilute citric acid until pH 7 was achieved. The mixture was then poured into a separatory funnel and extracted 3x with EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide *trans*-aldehyde **116** (755 mg, 70% over 2 steps) as a mixture of olefin isomers. The yellow oil was analytically pure and used directly in the next step:

$[\alpha]_D^{25.0}$ = +35.2° (c = 0.295, $CHCl_3$). Note: it is recommended that the aldehyde be used immediately in the next step to avoid decomposition.

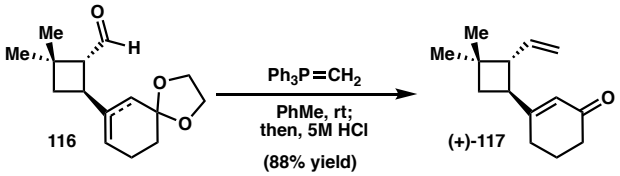
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.2 Hz, 1H), 5.37 (dt, *J* = 3.8, 1.9 Hz, 1H), 3.97 (dd, *J* = 2.5, 1.3 Hz, 4H), 3.14 (q, *J* = 9.2 Hz, 1H), 2.73 (dt, *J* = 10.0, 2.1 Hz, 1H), 2.22 (dp, *J* = 6.5, 2.1 Hz, 2H), 2.16 – 1.97 (m, 2H), 1.77 (ddd, *J* = 15.5, 9.4, 2.0 Hz, 2H), 1.69 (td, *J* = 6.5, 2.1 Hz, 2H), 1.24 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 137.1, 118.8, 108.3, 64.4, 59.5, 37.3, 37.1, 36.7, 34.3, 31.2, 30.7, 24.0, 24.0.

FTIR (NaCl, thin film) 2954, 2929, 2896, 2873, 2707, 1712, 1670, 1577, 1522, 1461,1449, 1434, 1420, 1383, 1367, 1340, 1312, 1297, 1249, 1209, 1179, 1103, 1059, 1039, 1018, 948, 846, 793 cm.$^{-1}$

HRMS (MM) calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1645.

Preparation of vinyl enone (+)-117



A 250 mL round bottom flask was charged with *trans*-aldehyde, **116** (720 mg, 2.88 mmol, 1.00 equiv). The flask was evacuated and backfilled three times with N_2 and charged with toluene (2.30 mL). The flask was then charged with freshly prepared ylide solution (36.0 mL, 0.4 M, 5.00 equiv) and the reaction mixture was allowed to stir for 30 minutes at room temperature. The reaction was quenched with the addition of saturated $NaHCO_3$ solution (10.0 mL). The organic layer was separated and the aqueous layer extracted 3x

with Et_2O. The combined organics were concentrated and dissolved in a 1:1 mixture of THF and 5M HCl (28 mL.0). The reaction mixture was allowed to stir over 16 hours, at which point the mixture was diluted with Et_2O and water. The layers were separated and the aqueous layer extracted 3x with Et_2O. The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude yellow residue was purified by flash silica gel chromatography (20–30% Et_2O/pentane) to provide (+)-**117** (520 mg, 88%) as a pale yellow oil: $[\alpha]_D^{25.0}$ = +102° (c = 0.705, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (q, *J* = 1.6 Hz, 1H), 5.81 (dddt, *J* = 16.8, 10.6, 7.9, 0.5, 0.5 Hz, 1H), 5.04 (qd, *J* = 1.9, 1.0 Hz, 1H), 5.01 (ddd, *J* = 10.8, 1.9, 1.1 Hz, 1H), 2.88 (q, *J* = 9.7, 9.1, 9.0 Hz, 1H), 2.48 (ddq, *J* = 9.8, 7.9, 1.0 Hz, 1H), 2.34 (t, *J* = 7.0, 6.5 Hz, 2H), 2.20 (qdd, *J* = 6.0, 1.5, 0.8 Hz, 2H), 1.95 (dt, *J* = 7.7, 6.1 Hz, 2H), 1.85 (ddd, *J* = 10.8, 8.3, 0.8 Hz, 1H), 1.67 (t, *J* = 10.3 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 168.8, 137.4, 123.4, 116.1, 53.8, 41.1, 37.5, 37.3, 36.0, 30.0, 27.9, 23.1, 22.6.

FTIR (NaCl, thin film) 3320, 3076, 3039, 2953, 2934, 2891, 2866, 2827, 1671, 1622, 1456, 1428, 1417, 1382, 1368, 1346, 1324, 1290, 1251, 1191, 1124, 995, 968, 942, 912, 886, 755 cm.$^{-1}$

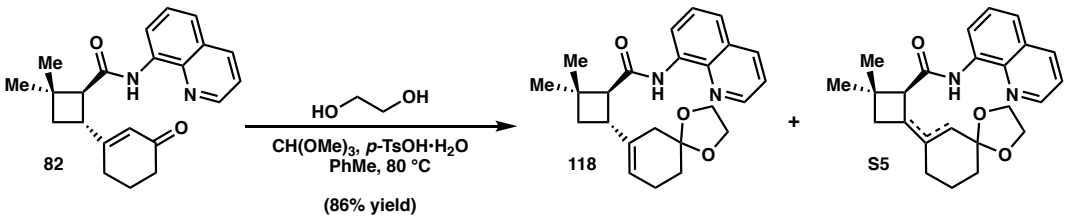
HRMS (MM) calc'd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1587, found 205.1587.

Preparation of Wittig ylide.

Inside a N_2-filled glovebox, methyltriphenylphosphonium bromide (22.2 g, 62.1 mmol) and KO*t*-Bu (7.36 g, 65.6 mmol, 1.06 equiv) were added to a flame-dried 500 mL round-bottom flask and sealed under nitrogen. The flask was brought out of the box and

dry PhMe (155 mL) was added via syringe. The flask was fitted with a reflux condenser under a stream of N_2 and heated to 110 °C for 4 hours, at which time the reaction was cooled to room temperature and the salts were allowed to settle for 3 hours before the bright yellow supernatant (~0.40 M salt-free ylide) was used for the methylenation of aldehydes **S4** and **S6** (*vide infra*).

Preparation of *trans*-dioxolanes 118 & S5.



To a flame-dried 200 mL round-bottom flask was added *trans*-cyclobutane **82** (2.59 g, 7.43 mmol) and the atmosphere was exchanged for N_2 three times. Dry PhMe (74 mL) was then added, followed by ethylene glycol (16.6 mL, 297 mmol, 40.0 equiv) and trimethyl orthoformate (2.44 mL, 22.3 mmol, 3.00 equiv) via syringe. Finally, *p*-toluenesulfonic acid monohydrate (141 mg, 0.743 mmol, 0.10 equiv) was added as a solid in one portion under a stream of N_2. The reaction mixture was heated to 80 ºC for 15 hours, at which point the reaction mixture was cooled to room temperature and quenched with a saturated solution of aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 20% EtOAc/hexane + 1% Et_3N) to afford *trans*-dioxolanes **118** and **S5** (2.50 g, 86% yield) as a partially separable mixture of

inconsequential olefin isomers. An analytically pure sample of the major dioxolane (**118**) was obtained and a representative spectrum of the mixture as used in the next step is also provided.

Data for **118** (major product, peak 1): $[\alpha]_D^{25.0}$ = –80.5° (c = 1.40, $CHCl_3$)

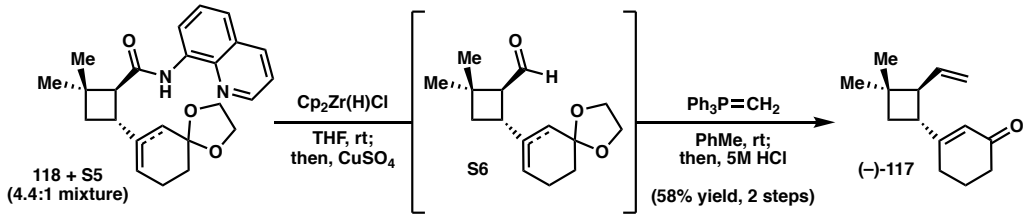
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.78 (dd, *J* = 11.0, 1.6 Hz, 1H), 8.78 (d, *J* = 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50 (dt, *J* = 15.8, 8.2, 7.5 Hz, 2H), 7.47 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.54 (dt, *J* = 3.6, 1.8 Hz, 1H), 3.96 (q, *J* = 4.4, 3.9 Hz, 4H), 3.30 (q, *J* = 9.4 Hz, 1H), 2.88 (d, *J* = 9.8 Hz, 1H), 2.25 (d, *J* = 2.8 Hz, 4H), 1.87 (dd, *J* = 10.5, 8.6 Hz, 1H), 1.81 – 1.61 (m, 3H), 1.36 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 148.2, 138.4, 137.3, 136.3, 134.6, 127.9, 127.4, 121.6, 121.2, 119.1, 116.3, 108.4, 64.4, 55.2, 36.7, 36.7, 36.4, 36.1, 30.9, 30.8, 24.1, 23.4.

FTIR (NaCl, thin film) 3350, 3046, 2952, 2929, 2893, 2839, 1686, 1596, 1578, 1525, 1485, 1460, 1424, 1383, 1368, 1326, 1248, 1209, 1161, 1102, 1059, 1021, 948, 826, 792, 756 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{29}N_2O_3$ $[M+H]^+$ 393.2173, found 393.2188.

Preparation of vinyl enone (–)-117.



Inside a N_2-filled glovebox, two flame-dried 200 mL round-bottom flasks were each charged with Schwartz's reagent (1.60 g, 6.21 mmol, 2.04 equiv) and sealed under

N_2. The flasks were removed from the glovebox and THF (15.5 mL) was added to each via syringe. To each of the milky-white suspensions was added a mixture of *trans*-dioxolanes **118** and **S5** (1.19 g, 3.04 mmol) as a solution in THF (16.0 mL) in a quick drip at room temperature. The mixtures immediately began to turn yellow, darkening to orange over the course of 1 hour, at which point the reactions were quenched with saturated aqueous $NaHCO_3$ and combined together. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed twice with 100 mL of a 0.6 M aqueous solution of $CuSO_4$ to remove the liberated 8-aminoquinoline. The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude aldehyde (**S6**, 1.70 g) was dissolved in dry PhMe (20 mL) and treated with freshly prepared ylide (80 mL, 32.0 mmol, 5.26 equiv) at room temperature. The reaction was stirred for 2 hours and monitored by TLC. Upon complete conversion, the reaction was cooled to 0 °C and quenched with 5 M HCl. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were concentrated *in vacuo* and the solvent replaced with THF (30 mL). The dioxolane was hydrolyzed by stirring vigorously with 5 M HCl for 8 hours, at which time Et_2O was added and the layers separated. The aqueous layer was extracted twice with Et_2O and the combined organics washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 30% Et_2O/hexanes) to afford vinyl enone (–)-**117** (715 mg, 58% yield over 2 steps) as a clear oil: $[\alpha]_D^{25.0} = -100°$ (c = 1.02, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (q, *J* = 1.5 Hz, 1H), 5.81 (dddt, *J* = 16.8, 10.6, 7.9, 0.5, 0.5 Hz, 1H), 5.04 (qd, *J* = 1.9, 1.0 Hz, 1H), 5.01 (ddd, *J* = 10.4, 2.0, 1.1 Hz, 1H), 2.88 (q, *J* = 9.7, 9.1, 9.0 Hz, 1H), 2.48 (ddq, *J* = 9.8, 7.9, 1.0 Hz, 1H), 2.34 (t, *J* = 7.0, 6.5 Hz, 2H),

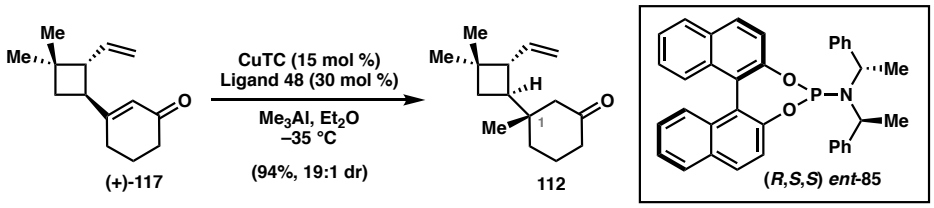
2.21 (qdd, J = 5.9, 1.5, 0.8 Hz, 2H), 1.95 (dt, J = 7.7, 6.1 Hz, 2H), 1.85 (ddd, J = 10.7, 8.3, 0.8 Hz, 1H), 1.67 (t, J = 10.4 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 168.7, 137.4, 123.4, 116.1, 53.8, 41.1, 37.5, 37.3, 36.0, 30.0, 27.9, 23.1, 22.6.

FTIR (NaCl, thin film) 3320, 3076, 3039, 2953, 2934, 2891, 2866, 2827, 1671, 1622, 1456, 1428, 1417, 1382, 1368, 1346, 1324, 1290, 1251, 1191, 1124, 995, 968, 942, 912, 886, 755 cm.$^{-1}$

HRMS (MM) calc'd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1587, found 205.1587.

Preparation of vinyl ketone 112.



Inside a N_2-filled glovebox, CuTC (105 mg, 0.551 mmol, 0.150 equiv) and ligand (*R*,*S*,*S*) *ent*-**85** (594 mg, 1.10 mmol, 0.30 equiv) were added to a flame dried 100 mL round-bottom flask. The reagents were suspended in Et_2O (18.0 mL) and stirred at room temperature for 30 minutes before vinyl enone (+)-**117** (750 mg, 3.67 mmol) was added as a solution in Et_2O (18.0 mL). The reaction was sealed under N_2, removed from the glovebox and placed under a balloon atmosphere of argon. The reaction mixture was allowed to equilibrate to –35 °C for 5 minutes using a cryocool unit to maintain the temperature. Me_3Al (2.0 M in heptane; 3.67 mL, 7.34 mmol, 2.00 equiv) was then added dropwise and the reaction stirred at –35 °C for 17 hours, at which point wet MeOH (5 mL) was slowly added to quench excess Me_3Al. The mixture was warmed to room temperature,

filtered over a plug of silica gel, and washed thoroughly with Et_2O and CH_2Cl_2 (until no product remained in eluent). The filtrate was concentrated *in vacuo* and the crude residue purified by silica gel flash chromatography (isocratic: 20% hexane/CH_2Cl_2) to afford vinyl ketone **112** (760 mg, 94% yield) as a 19:1 mixture of inseparable diastereomers at C1, colorless oil. Note: this 19:1 mixture is carried through the next three reactions, and a single diastereomer at C1 is isolable after the ring-closing metathesis: $[\alpha]_D^{25.0}$ = +37.6° (c = 1.05, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6) δ 5.68 (ddd, *J* = 16.9, 10.5, 8.6 Hz, 1H), 4.96 (qd, *J* = 2.2, 0.8 Hz, 1H), 4.93 (ddd, *J* = 11.3, 2.2, 0.8 Hz, 1H), 2.20 (ddt, *J* = 9.6, 8.6, 0.9 Hz, 1H), 2.11 (dtt, *J* = 13.9, 4.8, 1.4 Hz, 1H), 1.92 (dd, *J* = 3.3, 1.7 Hz, 2H), 1.90 – 1.79 (m, 2H), 1.50 – 1.40 (m, 2H), 1.31 – 1.21 (m, 2H), 1.21 – 1.13 (m, 1H), 0.99 (dtt, *J* = 13.4, 4.7, 4.5, 1.5, 1.1 Hz, 1H), 0.94 (s, 3H), 0.93 (s, 3H), 0.66 (s, 3H).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 17.1, 10.3, 8.7 Hz, 1H), 5.08 – 4.81 (m, 2H), 2.33 (ddd, *J* = 9.6, 8.7, 0.9 Hz, 1H), 2.30 – 2.19 (m, 2H), 2.16 (d, *J* = 13.5 Hz, 1H), 2.07 (td, *J* = 10.1, 8.5 Hz, 1H), 1.99 (dt, *J* = 13.4, 1.8 Hz, 1H), 1.90 (ddq, *J* = 14.0, 6.2, 4.7 Hz, 1H), 1.85 – 1.72 (m, 1H), 1.56 (ddd, *J* = 13.6, 11.1, 4.4 Hz, 1H), 1.51 – 1.34 (m, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H).

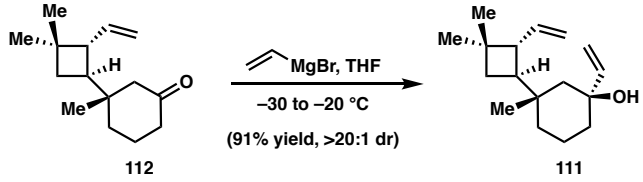
^{13}C NMR (101 MHz, C_6D_6) δ 209.3, 139.9, 115.3, 51.0, 49.5, 45.2, 41.2, 39.7, 34.7, 33.9, 32.9, 30.1, 23.7, 22.1, 21.8.

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 139.6, 115.3, 51.2, 49.5, 45.2, 41.3, 40.1, 34.8, 34.0, 33.0, 30.1, 23.7, 22.1, 21.8.

FTIR (NaCl, thin film) 3075, 2953, 2873, 1713, 1633, 1460, 1422, 1382, 1368, 1312, 1285, 1253, 1228, 1172, 1049, 995, 910 cm.$^{-1}$

HRMS (FAB) calc'd for $C_{15}H_{24}O$ $[M]^+$ 221.1900, found 221.1897.

Preparation of divinyl alcohol 111.



112 111

To a 15 mL round-bottom flask was added vinyl ketone **112** (91.0 mg, 0.413 mmol) and the atmosphere was exchanged 3x for N_2. Dry THF (4.10 mL) was then added via syringe and the reaction cooled to –30 °C using a closely monitored acetone/CO_2 bath. Vinylmagnesium bromide (2.06 mL, 1.0 M in THF, 2.06 mmol, 5.00 equiv) was then added dropwise. The reaction was maintained at –30 °C for 30 minutes, then quenched at that temperature with saturated aqueous NaH_2PO_4. The reaction mixture was diluted with Et_2O and the layers separated. The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organics were dried over Mg_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (10% EtOAc/hexane) to afford **111** (92.7 mg, 91% yield) as a colorless oil: $[\alpha]_D^{25.0}$ = +54.4° (c = 1.75, $CHCl_3$).

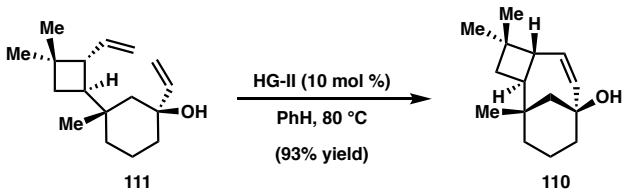
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.18 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.01 – 4.85 (m, 3H), 2.32 (t, *J* = 9.3 Hz, 1H), 1.92 (q, *J* = 9.6 Hz, 1H), 1.82 (qt, *J* = 13.5, 3.4 Hz, 1H), 1.55 (dddd, *J* = 14.0, 5.3, 3.5, 1.9 Hz, 1H), 1.48 (dq, *J* = 13.8, 3.5 Hz, 1H), 1.45 – 1.39 (m, 2H), 1.35 (dd, *J* = 13.5, 4.0 Hz, 1H), 1.31 – 1.22 (m, 3H), 1.16 – 1.11 (m, 1H), 1.11 (s, 1H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 140.6, 114.6, 110.5, 73.1, 49.0, 48.0, 45.0, 37.6, 34.6, 34.3, 33.9, 32.8, 30.1, 23.8, 22.7, 17.8.

FTIR (NaCl, thin film) 3601, 3452 (br), 3077, 2996, 2950, 2932, 2865, 1635, 1459, 1441, 1413, 1380, 1367, 1343, 1291, 1275, 1250, 1200, 1170, 1081, 1058, 994, 974, 909, 858, 846, 666 cm.$^{-1}$

HRMS (ESI) calc'd for $C_{17}H_{27}$ $[M–OH]^+$ 231.2107, found 231.2101.

Preparation of allylic alcohol 110.



A 50 mL round-bottom flask containing divinyl alcohol **111** (88.0 mg, 0.355 mmol) was pumped into a N_2-filled glovebox where Hoveyda–Grubbs second-generation catalyst (22.2 mg, 0.035 mmol, 0.100 equiv) was added. The flask was sealed under nitrogen, removed from the glovebox and dry benzene (17.7 mL) was added via syringe. The green reaction mixture was heated to 80 °C for 3.5 hours, and then cooled to room temperature. Ethyl vinyl ether was added to inactivate the catalyst and stirred for 15 minutes before the reaction mixture was concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 30% Et_2O/hexane) to afford allylic alcohol **110** (72.5 mg, 93% yield) as a pale yellow oil and a single diastereomer at C1: $[\alpha]_D^{25.0}$ = –62.9° (c = 2.67, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 10.9, 2.5 Hz, 1H), 5.15 (ddd, *J* = 11.0, 2.9, 2.2 Hz, 1H), 2.41 (dt, *J* = 11.6, 2.7 Hz, 1H), 2.09 (td, *J* = 11.5, 10.7, 7.9 Hz, 2H), 1.69 (ddd, *J*

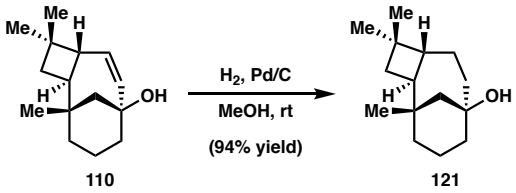
= 13.0, 3.2, 1.1 Hz, 1H), 1.64 (s, 1H), 1.63 – 1.56 (m, 2H), 1.54 – 1.41 (m, 2H), 1.34 – 1.25 (m, 2H), 1.15 (dd, *J* = 12.8, 2.2 Hz, 1H), 1.12 – 1.06 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1, 132.5, 75.1, 49.9, 45.3, 43.9, 39.0, 38.1, 37.8, 35.0, 32.6, 30.9, 26.9, 21.3, 20.2.

FTIR (NaCl, thin film) 3350 (br), 3004, 2948, 2930, 2866, 1460, 1443, 1369, 1380, 1366, 1329, 1270, 1256, 1238, 1175, 1106, 1044, 1030, 999, 973, 958, 925, 875, 864, 766, 723 $cm.^{-1}$

HRMS (MM) calc'd for $C_{15}H_{23}$ $[M–OH]^+$ 203.1794, found 203.1790.

Preparation of tertiary alcohol 121.



110 121

To a 100 mL round-bottom flask were added allylic alcohol **110** (107 mg, 0.486 mmol) and Pd/C (103 mg, 10% by weight, 0.097 mmol, 0.200 equiv). The flask was fitted with a septum and the atmosphere exchanged 1x for N_2. MeOH (9.7 mL) was then added via syringe and the reaction placed under a balloon atmosphere of H_2 (purged through a needle for 30 seconds). The reaction was stirred vigorously at room temperature for 2.5 hours, at which time the atmosphere was purged with argon. The reaction mixture was filtered over celite, washed thoroughly with Et_2O, and the filtrate concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 40%

Et_2O/pentane) to afford **121** (101 mg, 94% yield) as a colorless oil: $[\alpha]_D^{25.0}$ = +6.37° (c = 0.800, $CHCl_3$).

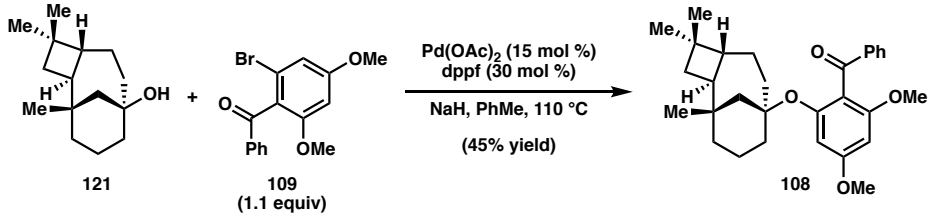
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (ddd, *J* = 11.8, 10.7, 7.9 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.78 – 1.68 (m, 3H), 1.67 (d, *J* = 0.8 Hz, 3H), 1.51 – 1.39 (m, 2H), 1.34 (dt, *J* = 3.5, 2.0 Hz, 1H), 1.33 – 1.22 (m, 4H), 1.15 – 1.04 (m, 1H), 1.02 (d, *J* = 12.8 Hz, 1H), 0.97 (s, 3H), 0.96 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 74.0, 50.2, 46.3, 40.3, 40.1, 39.7, 38.2, 36.4, 34.6, 32.8, 30.7, 27.1, 22.7, 20.9, 20.7.

FTIR (NaCl, thin film) 3368 (br), 2948, 2927, 2863, 1460, 1443, 1384, 1364, 1332, 1288, 1249, 1217, 1183, 1124, 1102, 1050, 1022, 993, 976, 936, 918, 873, 862 cm.$^{-1}$

HRMS (ESI) calc'd for $C_{15}H_{25}$ $[M–OH]^+$ 205.1951, found 205.1951.

Preparation of benzophenone 108.



Inside a N_2-filled glovebox, to a 1 dram vial containing tertiary alcohol **121** (14.4 mg, 0.065 mmol) were added $Pd(OAc)_2$ (4.36 mg, 0.019 mmol, 0.300 equiv), dppf (21.6 mg, 0.039 mmol, 0.600 equiv), and NaH (95%, 3.11 mg, 0.130 mmol, 2.00 equiv). PhMe (650 μL) was then added and the orange reaction mixture stirred at room temperature for 5 minutes before aryl bromide **109** (22.8 mg, 0.071 mmol, 1.10 equiv) was added as a solid in one portion. The reaction was sealed with a Teflon cap and heated to 110 °C in a preheated aluminum block inside the glovebox. After 13.5 hours, the reaction was cooled

to room temperature, diluted with EtOAc, and saturated aqueous Na_2HPO_4 was added. The layers were separated and the aqueous layer was extracted with EtOAc until the organic layer was colorless. The combined organics were filtered over a plug of celite and Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude residue purified by silica gel flash chromatography (isocratic: 30% hexane/CH_2Cl_2 + 1% EtOAc) to afford **108** (13.4 mg, 45% yield) as a milky white gum: $[\alpha]_D^{25.0}$ = +1.27° (c = 0.345, $CHCl_3$).

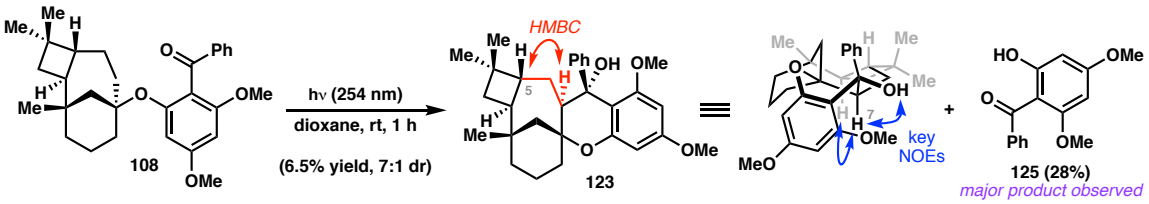
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 2H), 7.51 (tt, *J* = 7.5, 2.7 Hz, 1H), 7.44 – 7.35 (m, 2H), 6.29 (d, *J* = 2.1 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 1.90 (ddd, *J* = 12.0, 10.7, 7.9 Hz, 1H), 1.78 (d, *J* = 2.3 Hz, 1H), 1.73 (t, *J* = 6.5 Hz, 2H), 1.68 (dt, *J* = 13.0, 2.3 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.55 – 1.45 (m, 2H), 1.45 – 1.35 (m, 3H), 1.27 – 1.23 (m, 2H), 1.22 – 1.11 (m, 2H), 1.04 (d, *J* = 12.9 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 161.3, 158.7, 155.2, 138.8, 132.8, 129.6, 128.3, 116.8, 100.3, 92.5, 86.9, 55.9, 55.6, 47.6, 45.6, 39.7, 37.5, 36.8, 36.2, 36.1, 34.6, 32.7, 30.7, 27.1, 22.5, 20.9, 20.5.

FTIR (NaCl, thin film) 3059, 2948, 2930, 2861, 1671, 1601, 1582, 1458, 1451, 1438, 1420, 1364, 1335, 1312, 1266, 1216, 1199, 1157, 1138, 1107, 1052, 1015, 998, 948, 917, 843, 819, 802, 721, 702, 689 cm.$^{-1}$

HRMS (MM) calc'd for $C_{30}H_{38}NaO_4$ $[M+Na]^+$ 485.2662, found 485.2672.

Preparation of Norrish–Yang product 123



To a 13 x 100 quartz test tube was added benzophenone **108** (15.5 mg, 0.034 mmol). The tube was fitted with a 19/38 rubber septum and the atmosphere was exchanged 3 x for N_2. Rigorously degassed dioxane (4.70 mL, freeze-pump-thawed 3x) was then added via syringe and the tube was sealed with electrical tape. The reaction was then placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp and irradiated for 1 hour at room temperature. The reaction mixture was transferred to a cone-bottom flask and concentrated *in vacuo*. The crude residue was purified by silica gel preparative TLC (30% hexane/CH_2Cl_2 + 1% EtOAc) to afford **125** (2.4 mg, 28% yield) as a white solid and **123** (1.00 mg, 6.5% yield) as a colorless oil: $[\alpha]_D^{25.0}$ = +13.8° (c = 0.050, $CHCl_3$). Note: an additional ~18% yield of a complex mixture of products is also isolated as a single band. Although this mixture generally appears similar to **123** by ^{1}H NMR, definitive characterization was not achieved.

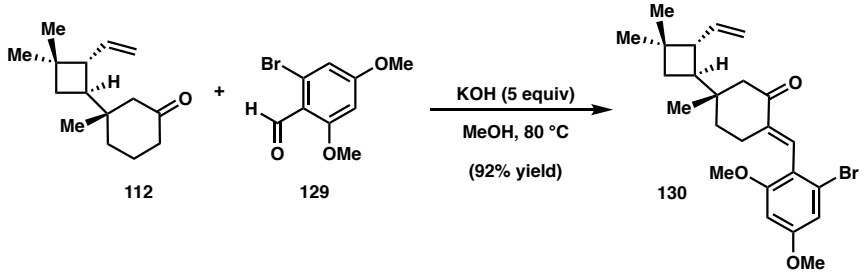
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1H), 7.24 – 7.09 (m, 4H), 6.11 (dd, *J* = 2.5, 1.1 Hz, 1H), 6.01 (dd, *J* = 2.4, 1.2 Hz, 1H), 3.95 (d, *J* = 1.1 Hz, 1H), 3.78 (d, *J* = 1.2 Hz, 3H), 3.35 (d, *J* = 1.1 Hz, 3H), 2.65 (dd, *J* = 12.7, 3.5 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.40 (t, *J* = 14.4 Hz, 1H), 2.26 (q, *J* = 10.4 Hz, 1H), 2.11 – 1.90 (m, 1H), 1.86 (d, *J* = 13.0 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.69 – 1.57 (m, 1H), 1.43 – 1.34 (m, 2H), 1.30 – 1.09 (m, 4H), 0.80 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H), 0.50 (dt, *J* = 14.5, 4.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 158.8, 154.3, 149.3, 127.4, 126.1, 125.8, 111.4, 94.2, 93.5, 80.6, 74.6, 55.6, 55.4, 48.5, 48.1, 44.0, 37.3, 36.8, 35.7, 35.5, 34.6, 33.2, 30.5, 26.4, 25.0, 20.6, 20.4.

FTIR (NaCl, thin film) 3542 (br), 3312, 3187 (br), 2960, 2924, 2854, 1738, 1726, 1710, 1666, 1614, 1592, 1492, 1462, 1453, 1445, 1423, 1376, 1366, 1351, 1332, 1261, 1215, 1203, 1150, 1112, 1045, 1020, 865, 800, 736, 702, 664 cm.$^{-1}$

HRMS (MM) calc'd for $C_{30}H_{37}O_3$ $[M–OH]^+$ 445.2737, found 445.2729.

Preparation of *exo*-enone 130.



To a 200 mL round-bottom flask were added vinyl ketone **112** (884 mg, 4.01 mmol), aryl aldehyde **129** (1.08 g, 4.41 mmol, 1.10 equiv), and KOH (1.13 g, 20.1 mmol, 5.00 equiv). Freshly distilled MeOH (40.1 mL) was then added, the flask fitted with a reflux condenser under ambient conditions and heated to 80 °C for 12 hours. At completion, the volume of MeOH was reduced *in vacuo* and the reaction quenched with a saturated solution of aqueous NH_4Cl. Et_2O was added and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash

chromatography (isocratic: 20% Et_2O/hexane) to afford *exo*-enone **130** (1.66 g, 92% yield) as an off-white solid: $[\alpha]_D^{25.0}$ = +11.4° (c = 1.08, $CHCl_3$).

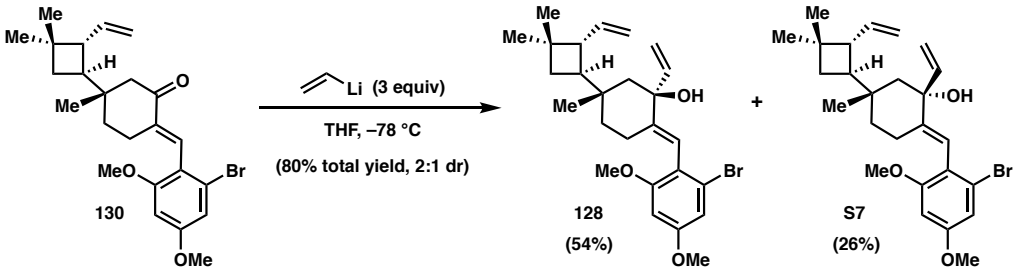
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 5.74 (ddd, *J* = 17.1, 10.3, 8.6 Hz, 1H), 4.95 (ddd, *J* = 24.7, 2.1, 0.8 Hz, 1H), 4.94 (td, *J* = 2.3, 0.8 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.44 – 2.20 (m, 5H), 2.12 (td, *J* = 10.0, 8.5 Hz, 1H), 1.55 (ddd, *J* = 13.3, 10.3, 6.0 Hz, 1H), 1.50 (ddd, *J* = 10.7, 8.4, 0.6 Hz, 1H), 1.45 (d, *J* = 10.4 Hz, 1H), 1.38 (dtd, *J* = 11.0, 5.0, 2.1 Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 160.8, 158.6, 139.6, 139.2, 130.5, 125.1, 118.7, 115.3, 109.0, 98.1, 55.8, 55.7, 50.3, 49.4, 45.0, 36.5, 34.9, 33.2, 32.5, 30.1, 24.7, 23.7, 22.6.

FTIR (NaCl, thin film) 3073, 2952, 2863, 1686, 1599, 1558, 1482, 1461, 1435, 1407, 1381, 1367, 1303, 1259, 1214, 1153, 1051, 1035, 996, 938, 911, 960, 831, 795 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{32}BrO_3$ $[M+H]^+$ 447.1529, found 447.1520.

Preparation of divinyl alcohols 128 and S7.



A 100 mL round-bottom flask was flame dried under vacuum and backfilled with N_2. Dry THF (21.2 mL) was then added, followed by freshly prepared vinyllithium as a solution in THF (8.42 mL, 0.756 M, 3.00 equiv). The solution was cooled to –78 °C and

exo-enone **130** (928 mg, 2.07 mmol) was taken up in 5.0 mL THF and added dropwise over 5 minutes. After 40 minutes, the reaction was quenched with a saturated solution of NH_4Cl and warmed to room temperature. The mixture was diluted with Et_2O and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (30% hexane/CH_2Cl_2 + 1% EtOAc until unreacted **130** and **S7** elute, then 5% EtOAc/CH_2Cl_2) to afford **128** (536 mg, 54%) as a thick, colorless oil, **S7** (260 mg, 26%) as a thick, colorless oil, and recovered **130** (164 mg, 18%).

Preparation of vinyllithium:

THF (38.0 mL) was added to a flame-dried 200 mL round-bottom flask under N_2, followed by tetravinyl tin (2.10 mL, 11.5 mmol). The solution was cooled to –78 °C and *n*-BuLi (17.3 mL, 2.5 M in hexanes, 43.3 mmol, 3.76 equiv) was added dropwise. The reaction was stirred for 20 minutes at –78 °C, then lifted out of the ice bath and allowed to warm to room temperature. The reaction was allowed to stir at room temperature for at least 2 hours before use, provides a ~0.756 M solution of vinyllithium (note: highest yields for 1,2-addition are obtained after stirring for 6 hours, at which time the mixture should be slightly milky grey in appearance).

Data for **128** (major diastereomer, peak 2): $[\alpha]_D^{25.0}$ = –23.8° (c = 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.19 (dd, *J* = 17.2, 10.6 Hz, 1H), 6.04 (d, *J* = 1.5 Hz, 1H), 5.77 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H), 5.46 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.21 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.92 (dddd, *J* = 17.0, 14.0, 2.2, 0.8 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 2.40 – 2.22 (m, 2H), 2.07 (q, *J* = 9.6 Hz, 1H),

1.92 (dt, *J* = 14.3, 4.5 Hz, 1H), 1.51 (q, *J* = 14.0, 13.3 Hz, 2H), 1.44 (d, *J* = 12.7 Hz, 1H), 1.41 (d, *J* = 9.4 Hz, 2H), 1.35 – 1.17 (m, 2H), 1.12 (s, 3H), 0.97 (d, *J* = 1.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 158.3, 146.6, 145.3, 140.5, 125.3, 120.4, 119.7, 114.8, 112.9, 108.5, 98.1, 76.1, 55.8, 55.7, 49.3, 47.0, 46.1, 34.7, 34.6, 34.4, 33.1, 30.0, 23.8, 23.4, 22.9.

FTIR (NaCl, thin film) 3424 (br) 3001, 2950, 2930, 2858, 2832, 1599, 1560, 1483, 1459, 1434, 1406, 1379, 1366, 1301, 1268, 1210, 1145, 1053, 1037, 994, 910, 879, 811 cm.$^{-1}$

HRMS (MM) calc'd for $C_{26}H_{34}BrO_2$ $[M–OH]^+$ 457.1742, found 457.1744.

Data for **S7** (minor diastereomer, peak 1): $[\alpha]_D^{25.0}$ = –34.2° (c = 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.23 (d, *J* = 1.4 Hz, 1H), 6.09 (dd, *J* = 17.4, 10.3 Hz, 1H), 5.77 (ddd, *J* = 17.2, 10.2, 8.7 Hz, 1H), 5.48 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.16 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.93 (dddd, *J* = 18.0, 15.2, 2.2, 0.8 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 2.35 (t, *J* = 9.3 Hz, 1H), 2.15 – 2.02 (m, 2H), 1.90 (dddd, *J* = 14.3, 12.8, 4.4, 1.6 Hz, 1H), 1.77 – 1.65 (m, 2H), 1.59 (d, *J* = 13.2 Hz, 1H), 1.49 – 1.41 (m, 2H), 1.34 (td, *J* = 12.8, 4.3 Hz, 1H), 1.11 (dtd, *J* = 12.6, 4.0, 1.9 Hz, 1H), 0.97 (d, *J* = 1.1 Hz, 6H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.4, 146.2, 144.9, 140.6, 125.4, 120.9, 117.9, 115.6, 114.8, 108.4, 98.1, 75.8, 55.8, 55.7, 49.6, 49.1, 46.5, 35.6, 34.9, 34.5, 33.1, 30.1, 25.0, 23.8, 22.3.

FTIR (NaCl, thin film) 3451 (br) 3073, 2998, 2951, 2934, 2858, 1630, 1560, 1560, 1482, 1461, 1434, 1406, 1380, 1366, 1301, 1266, 1211, 1150, 1038, 996, 936, 909, 884, 830, 813 cm.$^{-1}$

HRMS (MM) calc'd for $C_{26}H_{34}BrO_2$ $[M–OH]^+$ 457.1742, found 457.1744.

Preparation of allylic alcohol 127.

A 250 mL round-bottom flask containing divinyl alcohol **128** (807 mg, 1.70 mmol) was pumped into a N_2-filled glovebox where Hoveyda–Grubbs second-generation catalyst (106 mg, 0.170 mmol, 0.100 equiv) and 1,4-benzoquinone (18.4 mg, 0.170 mmol, 0.100 equiv) were added. The flask was sealed under nitrogen, removed from the glovebox, and dry benzene (85.0 mL) was added via syringe. The green reaction mixture was heated to 80 °C for 12 hours, then cooled to room temperature. Ethyl vinyl ether was added to inactivate the catalyst and stirred for 15 minutes before the reaction mixture was concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (20–30% Et_2O/hexane) to afford allylic alcohol **127** (704 mg, 93%) as a white foam and a single diastereomer at C1: $[\alpha]_D^{25.0}$ = +95.5° (c = 0.815, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.32 (d, *J* = 1.7 Hz, 1H), 5.84 (dd, *J* = 10.8, 2.4 Hz, 1H), 5.34 (ddd, *J* = 10.8, 2.8, 2.1 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.53 (dt, *J* = 11.6, 2.6 Hz, 1H), 2.37 (td, *J* = 11.2, 7.9 Hz, 1H), 2.28 (dd, *J* = 12.8, 2.3 Hz, 1H), 2.18 (dddd, *J* = 15.1, 11.0, 6.0, 1.9 Hz, 1H), 2.08 (ddd, *J* = 15.1,

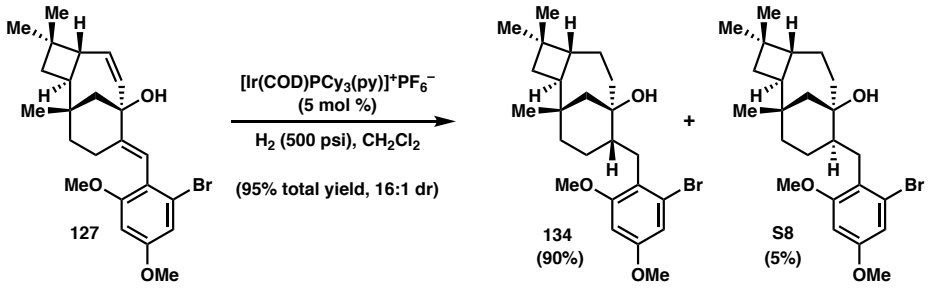
5.2, 3.6 Hz, 1H), 1.75 (s, 1H), 1.60 – 1.46 (m, 2H), 1.41 (dd, J = 12.9, 2.2 Hz, 1H), 1.37 – 1.22 (m, 2H), 1.08 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.5, 147.7, 134.6, 131.6, 125.5, 120.8, 116.3, 108.5, 98.2, 76.7, 55.9, 55.7, 50.9, 45.4, 43.4, 38.3, 37.5, 35.1, 32.3, 30.9, 26.2, 24.5, 21.5.

FTIR (NaCl, thin film) 3422 (br) 3002, 2949, 2930, 2862, 1599, 1562, 1481, 1462, 1455, 1434, 1405, 1366, 1302, 1267, 1211, 1149, 1037, 1015, 979, 938, 870, 858, 830, 813, 772, 755 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{30}BrO_2$ $[M–OH]^+$ 429.1429, found 429.1429.

Preparation of aryl bromides 134 and S8.



Inside a N_2-filled glovebox, Crabtree's catalyst (59.6 mg, 0.074 mmol, 0.05 equiv) was added to a 100 mL round-bottom flask containing allylic alcohol **127** (663 mg, 1.48 mmol). CH_2Cl_2 (14.8 mL) was added and the flask was placed inside a steel bomb, which was closed under nitrogen and brought out of the glovebox. The pressure gauge was quickly attached and all bolts on the bomb tightened with a wrench. The bomb was connected to a H_2 inlet and the vessel purged with 250 psi H_2 three times before being charged to 500 psi. The reaction was stirred at room temperature for 3 hours, at which time H_2 was vented from the reaction. CH_2Cl_2 was removed *in vacuo* and the crude residue

purified by silica gel flash chromatography (isocratic: 40% Et_2O/hexane) to afford aryl bromides **134** (599 mg, 90%) and **S8** (37.4 mg, 5%) as white, crystalline solids.

Data for **134** (major diastereomer, peak 2): $[\alpha]_D^{25.0}$ = –20.5° (c = 0.900, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 2.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.03 (dd, *J* = 13.2, 2.7 Hz, 1H), 2.61 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.08 (ddd, *J* = 11.9, 10.6, 7.9 Hz, 1H), 1.95 (ddd, *J* = 13.8, 10.4, 3.6 Hz, 1H), 1.83 (dd, *J* = 12.8, 2.6 Hz, 1H), 1.78 – 1.57 (m, 4H), 1.57 – 1.34 (m, 5H), 1.34 – 1.23 (m, 2H), 1.01 (s, 3H), 0.99 (s, 3H), 0.96 (dd, *J* = 12.9, 5.6 Hz, 2H), 0.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 158.9, 125.9, 122.8, 108.9, 98.4, 76.2, 55.9, 55.6, 51.7, 50.1, 45.4, 38.7, 38.0, 36.0, 35.0, 33.9, 33.3, 30.8, 28.5, 26.6, 26.3, 21.3, 21.0.

FTIR (NaCl, thin film) 3474 (br), 3000, 2946, 2930, 2862, 1603, 1568, 1482, 1461, 1435, 1410, 1294, 1272, 1212, 1198, 1151, 1130, 1054, 1038, 999, 937, 876, 831, 756 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{34}BrO_2$ $[M–OH]^+$ 433.1737, found 433.1685.

Data for **S8** (minor diastereomer, peak 1): $[\alpha]_D^{25.0}$ = –27.7° (c = 0.950, $CHCl_3$).

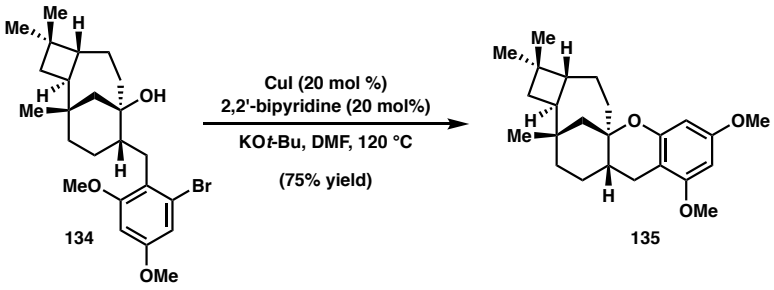
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 2.5 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.85 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.59 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.29 (dddd, *J* = 11.4, 8.0, 5.8, 3.5 Hz, 1H), 1.98 (ddd, *J* = 11.0, 9.4, 6.7 Hz, 2H), 1.80 – 1.52 (m, 4H), 1.52 – 1.37 (m, 4H), 1.37 – 1.26 (m, 4H), 1.25 (s, 1H), 0.94 (s, 6H), 0.78 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 158.5, 126.1, 123.0, 109.2, 98.3, 75.2, 55.8, 55.7, 49.3, 46.4, 45.4, 41.0, 38.5, 36.9, 36.6, 33.8, 30.5, 30.4, 29.2, 27.6, 24.2, 24.1, 21.5.

FTIR (NaCl, thin film) 3482 (br), 2998, 2945, 2928, 2859, 1690, 1648, 1602, 1567, 1482, 1459, 1435, 1409, 1381, 1364, 1294, 1273, 1211, 1198, 1154, 1134, 1051, 1039, 973, 937, 830, 809, 756.

HRMS (MM) calc'd for $C_{24}H_{35}BrO_3Na$ $[M+Na]^+$ 475.1818, found 475.1858.

Preparation of pentacycle 135.



Aryl bromide **134** (274 mg, 0.607 mmol) was added to each of two 20 mL scintillation vials and pumped inside a N_2-filled glovebox, where CuI (23.1 mg, 0.121 mmol, 0.200 equiv), 2,2'-bipyridine (18.9, 0.121 mmol, 0.200 equiv), and KO*t*-Bu (204, 1.82 mmol, 3.00 equiv) were added as solids to each. Dry DMF (6.10 mL) was then added, the reaction sealed under N_2 with a Teflon screw-cap and heated to 120 °C in a pre-heated aluminum block inside the glovebox for 3.5 hours. After cooling to room temperature, the reaction mixtures were combined and loaded directly onto a short silica gel column, pre-equilibrated with 5% Et_2O/hexane. The column was eluted with 5% Et_2O/hexane (isocratic) to afford pentacycle **135** (339 mg, 75%) as a white solid: $[\alpha]_D^{25.0}$ = +42.4° (c = 1.08, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 2.4 Hz, 1H), 6.00 (d, *J* = 2.4 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.55 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.20 – 2.03 (m, 2H), 1.97 (dd, *J* = 12.6,

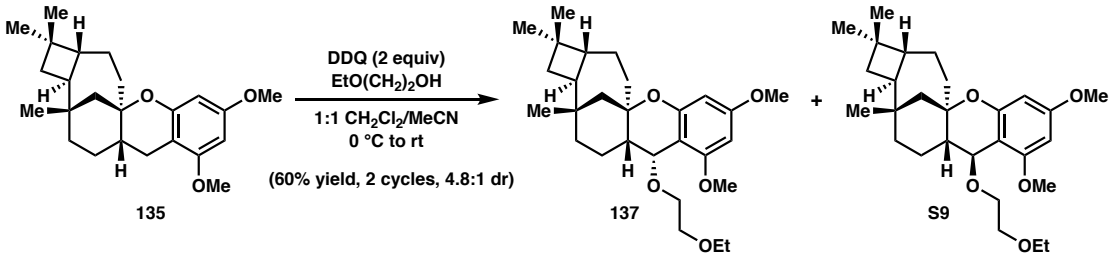
2.3 Hz, 1H), 1.77 (dddd, *J* = 18.7, 9.0, 7.4, 4.8 Hz, 2H), 1.69 – 1.55 (m, 4H), 1.52 – 1.41 (m, 3H), 1.32 (t, *J* = 10.7, 9.6 Hz, 2H), 1.32 – 1.20 (m, 1H), 1.17 (dd, *J* = 12.6, 1.1 Hz, 1H), 0.99 (s, 3H), 0.97 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 158.3, 154.4, 104.5, 94.2, 90.8, 79.9, 55.5, 55.4, 48.0, 44.3, 40.9, 38.0, 36.9, 35.6, 35.1, 33.5, 30.8, 28.4, 27.1, 26.5, 22.8, 20.9, 19.9.

FTIR (NaCl, thin film) 2995, 2945, 2928, 2862, 2843, 1617, 1589, 1494, 1460, 1420, 1363, 1288, 1215, 1201, 1186, 1164, 1145, 1108, 1074, 1054, 1033, 1008, 942, 928, 810 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{35}O_3$ $[M+H]^+$ 371.2581, found 371.2578.

Preparation of benzylic ethers 137 and S9.



To a flame-dried 25 mL round-bottom flask was added pentacycle **135** (80.0 mg, 0.216 mmol) and the atmosphere exchanged three times for argon. A 1:1 mixture of dry MeCN/CH_2Cl_2 (6.40 mL) was then added, followed by ethoxyethanol (1.54 mL) via syringe and the solution cooled to 0 °C. A previously prepared stock solution of DDQ in dry MeCN (0.860 mL, 0.508 M, 2.00 equiv) was then added dropwise. The reaction turned grey/blue immediately upon addition of DDQ and slowly turned green-blue by the end of addition. Once the addition was complete, the reaction was lifted from the ice bath and gradually warmed to room temperature. The color became an olive green-brown after 1

hour, indicating the reaction had stalled at ~50% conversion (as judged by TLC). At this point, the reaction was quenched with a saturated solution of aqueous $NaHCO_3$ and stirred vigorously for 10 minutes before the layers were separated. The aqueous layer was extracted twice more with CH_2Cl_2 and the combined organic layers were washed with one portion of DI H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography: SiO_2 was first deactivated by applying a few drops of aqueous NH_4OH (28%) to the top of a dry column and equilibrating with 100 mL of 5% Et_2O/hexane. The crude residue was then applied and eluted with fresh 5% Et_2O/hexane until unreacted **135** elutes completely, then 20% Et_2O/hexane until complete elution of second diastereomer to afford a mixture of **137** and **S9** (41.0 mg, 41% yield) as a colorless, foamy residue, and recovered starting material **135** (40.8 mg, 51%). The recovered starting material was re-subjected to the reaction conditions described above to afford additional **137** and **S9** (18.8 mg, 60% total over 2 cycles) and **135** (15.2 mg, 74% overall brsm). Analytically pure samples of **137** and **S9** were obtained by silica gel preparative TLC (30% Et_2O, 1% Et_3N/hexane) and a representative spectrum of the mixture as used in the next step is also provided.

Data for **95** (major diastereomer, peak 1): $[\alpha]_D^{25.0}$ = +43.5° (c = 0.815, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 2.4 Hz, 1H), 5.94 (d, *J* = 2.3 Hz, 1H), 4.27 (d, *J* = 3.3 Hz, 1H), 3.98 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.81 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.58 (dd, *J* = 5.9, 4.9 Hz, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 2.48 – 2.36 (m, 1H), 2.21 (qd, *J* = 14.4, 4.1 Hz, 1H), 2.10 (ddd, *J* = 12.2, 10.7, 7.9 Hz, 1H), 2.00 (dd, *J* = 12.7, 2.3 Hz, 1H), 1.79 – 1.61 (m, 3H), 1.59 – 1.41 (m, 4H), 1.42 – 1.20 (m, 4H), 1.20 (t, *J* = 7.0 Hz, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 159.7, 154.7, 106.6, 93.8, 91.2, 80.5, 72.1, 71.4, 70.5, 66.7, 55.4, 55.4, 49.3, 47.6, 46.1, 39.4, 39.3, 36.3, 34.8, 33.5, 32.4, 30.8, 26.8, 23.1, 22.3, 20.8, 15.4.

FTIR (NaCl, thin film) 2948, 2930, 2864, 1614, 1589, 1491,1462, 1438, 1424, 1365, 1353, 1332, 1320, 1287, 1215, 1202, 1189, 1166, 1148, 1109, 1053, 1033, 1005, 951, 921, 866, 811, 731, 638 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{33}O_3$ $[M–O(CH_2)_2OEt]^+$ 369.2424, found 369.2430.

Data for **S9** (minor diastereomer, peak 2): $[\alpha]_D^{25.0}$ = +29.6° (c = 0.230, $CHCl_3$).

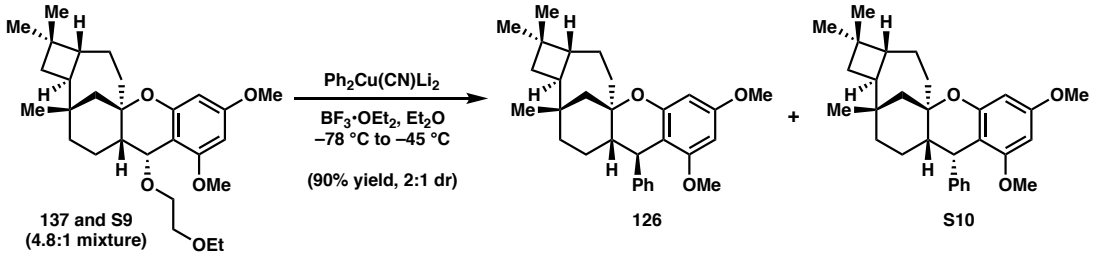
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 2.4 Hz, 1H), 5.92 (d, *J* = 2.4 Hz, 1H), 4.30 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 3H), 3.75 (ddd, *J* = 9.1, 3.0, 1.3 Hz, 1H), 3.73 (s, 3H), 3.58 – 3.45 (m, 5H), 2.24 – 2.04 (m, 2H), 1.92 (ddt, *J* = 14.7, 9.9, 3.2 Hz, 2H), 1.80 – 1.64 (m, 2H), 1.65 – 1.40 (m, 5H), 1.36 – 1.19 (m, 4H), 1.19 (t, *J* = 7.0 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 160.0, 155.9, 105.8, 94.2, 91.7, 81.7, 73.4, 70.5, 67.8, 66.7, 55.5, 55.4, 48.2, 47.2, 44.4, 37.8, 37.2, 35.6, 35.1, 33.2, 30.8, 28.4, 26.4, 23.7, 20.9, 20.4, 15.4.

FTIR (NaCl, thin film) 2947, 2934, 2864, 1613, 1587, 1490, 1459, 1438, 1421, 1364, 1349, 1312, 1288, 1267, 1245, 1216, 1202, 1147, 1107, 1054, 1034, 1002, 973, 943, 868. 812, 736, 636 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{33}O_3$ $[M–O(CH_2)_2OEt]^+$ 369.2424, found 369.2427.

Preparation of diarylmethanes 126 and S10.



A 10 mL round-bottom flask containing CuCN (11.9 mg, 0.133 mmol, 2.05 equiv) was flame-dried under vacuum. After cooling to room temperature, the flask was backfilled with argon and dry Et_2O (2.70 mL) was added via syringe. The suspension was cooled to –78 °C under argon and PhLi (0.140 mL, 1.9 M in dibutyl ether, 0.266 mmol, 4.09 equiv) was added dropwise. After stirring at –78 °C for 5 minutes, the reaction was warmed to 0 °C and stirred for an additional 30 minutes. The higher-order cuprate was then cooled back to –78 °C and the 4.8:1 mixture of benzylic ethers **137** and **S9** (30.0 mg, 0.065 mmol) was as a solution in Et_2O (1.00 mL). The reaction was stirred for 1-2 minutes before BF_3•OEt_2 (0.160 mL, 1.30 mmol, 20.0 equiv) was added dropwise via syringe. The reaction was stirred at –78 °C for 10 minutes, then quickly transferred to a pre-equilibrated bath at –55 °C, which was allowed to –50 °C over 5 minutes, then maintained at or just below –45 °C for another 30 minutes. The reaction was checked for completion by TLC, then quenched with aqueous $NaHCO_3$ and warmed to room temperature. The layers were separated and the aqueous layer extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 5% Et_2O/hexane) to afford diarylmethanes **126** and **S10**

(26.3 mg, 90%) as a 2:1 inseparable mixture, white solid: $[\alpha]_D^{25.0}$ = +2.08° (c = 1.23, $CHCl_3$).

^{1}H NMR (2:1 dr, asterisk denotes minor diastereomer, 400 MHz, $CDCl_3$) δ 7.24 – 6.96 (m, 5H), 6.10* (d, *J* = 2.4 Hz, 1H), 6.07 (d, *J* = 2.5 Hz, 1H), 6.03* (d, *J* = 2.4 Hz, 1H), 5.93 (d, *J* = 2.4 Hz, 1H), 4.10* (d, *J* = 6.4 Hz, 1H), 3.79* (s, 3H), 3.76 (s, 3H), 3.46* (s, 3H), 3.47 (d, *J* = 11.3 Hz, 1H), 3.20 (s, 3H), 2.23 – 2.06 (m, 1H), 2.00 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.93* (dd, *J* = 12.6, 2.5 Hz, 1H), 1.88 – 1.73 (m, 2H), 1.73 – 1.60 (m, 3H), 1.55 – 1.41 (m, 4H), 1.39 – 1.26 (m, 5H), 1.20 (q, *J* = 13.1, 12.1 Hz, 1H), 1.00 (s, 3H), 0.99 (s, 3H), 0.92* (s, 3H), 0.83 (s, 3H), 0.82* (s, 3H), 0.74* (s, 3H).

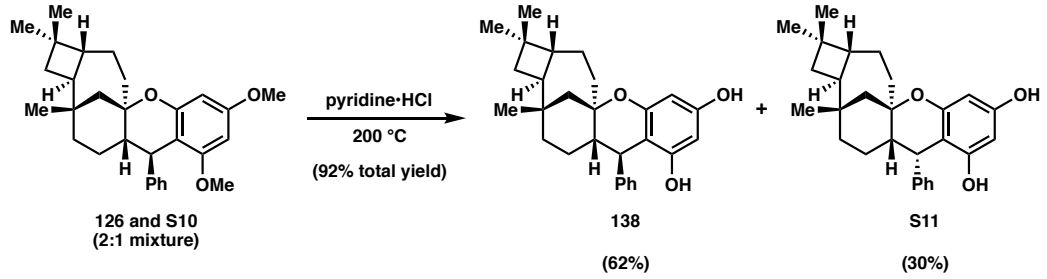
^{13}C NMR (**126**, major diastereomer, 101 MHz, $CDCl_3$) δ 160.0, 159.2, 155.2, 146.7, 129.8, 127.7, 125.4, 109.2, 94.5, 92.7, 80.4, 55.3, 55.2, 50.7, 48.1, 44.3, 41.9, 37.9, 36.9, 35.6, 35.1, 33.3, 30.8, 28.2, 26.3, 24.3, 20.9, 20.2.

^{13}C NMR (**S9**, minor diastereomer 101 MHz, $CDCl_3$) δ 160.1, 159.2, 155.1, 141.5, 128.9, 127.0, 125.5, 106.4, 94.1, 91.5, 80.7, 55.6, 55.4, 50.0, 45.8, 44.3, 39.3, 38.5, 36.7, 35.5, 35.0, 33.2, 32.7, 30.8, 26.2, 25.8, 20.9, 20.4.

FTIR (NaCl, thin film) 3081, 3059, 3025, 2998, 2948, 2934, 2864, 2843, 1614, 1588, 1490,1460, 1454, 1440, 1420, 1364, 1307, 1288, 1274, 1249, 1216, 1202, 1166, 1148, 1123, 1105, 1076, 1054, 1033, 1005, 943, 870, 811, 759, 740, 701 cm.$^{-1}$

HRMS (MM) calc'd for $C_{30}H_{39}O_3$ $[M+H]^+$ 447.2894, found 447.2905.

Preparation of resorcinols 138 and S11.



Solid pyridine•HCl (1.44 g, 12.5 mmol, 307 equiv) was weighed into each of two 2-dram vials, containing a 2:1 mixture of diarylmethanes **126** and **S10** (18.2 mg, 0.041 mmol). The vials were sealed with a Teflon screw-cap under a stream of argon and heated to 200 °C in a pre-heated aluminum block for 2.5 hours. (Note: it is important to choose a vial/heating block combination that will cover the entire volume of the solid to ensure that it stays completely melted during the course of the reaction). The reactions were cooled to room temperature, during which time the mixture solidified. The crude solids were dissolved in DI H_2O, and combined by pipetting dropwise into an Erlenmeyer flask containing a saturated solution of aqueous $NaHCO_3$. EtOAc was then added and the layers were separated. The aqueous layer was extracted three times with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 10% EtOAc, 1% AcOH/hexane) to separate resorcinols **138** and **S11**. The concentrated fractions for each diastereomer (initially a pale orange oil) were each passed through another short plug of silica gel (eluting with 20% EtOAc/heaxnes) to remove residual AcOH and remaining trace impurities to afford **138** (21.3 mg, 62%) and **S11** (10.3 mg, 30%) as white solids.

Data for **138** (major diastereomer, peak 1): $[\alpha]_D^{25.0} = -28.2°$ (c = 0.475, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 5H), 6.00 (d, *J* = 2.6 Hz, 1H), 5.88 (d, *J* = 2.6 Hz, 1H), 4.73 (s, 1H), 4.46 (s, 1H), 3.49 (d, *J* = 11.4 Hz, 1H), 2.16 (ddd, *J* = 12.3, 10.4, 7.9 Hz, 1H), 2.01 (dd, *J* = 12.8, 2.3 Hz, 1H), 1.85 – 1.58 (m, 4H), 1.54 – 1.44 (m, 2H), 1.44 – 1.30 (m, 4H), 1.28 (m, 1H), 1.18 (d, *J* = 12.9 Hz, 1H), 1.10 – 1.03 (m, 1H), 1.00 (s, 3H), 0.99 (s, 3H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 155.8, 155.4, 142.3, 128.0, 106.3, 97.7, 96.8, 80.1, 50.5, 48.1, 44.2, 41.8, 37.8, 36.9, 35.6, 35.2, 33.3, 30.8, 28.6, 26.3, 24.0, 20.9, 20.0.

FTIR (NaCl, thin film) 3511 (br), 3386 (br), 3060, 3024, 2948, 2928, 2863, 1702, 1627, 1598, 1509, 1492, 1459, 1364, 1349, 1320, 1272, 1248, 1228, 1166, 1138, 1087, 1072, 1057, 1034, 1014, 925, 869, 831, 761, 738, 703, 667, 638, 571, 516 $cm.^{-1}$

HRMS (MM) calc'd for $C_{28}H_{35}O_3$ $[M+H]^+$ 419.2581, found 419.2591.

Data for **S11** (minor diastereomer, peak 2): $[\alpha]_D^{25.0}$ = +26.7° (c = 0.180, $CHCl_3$).

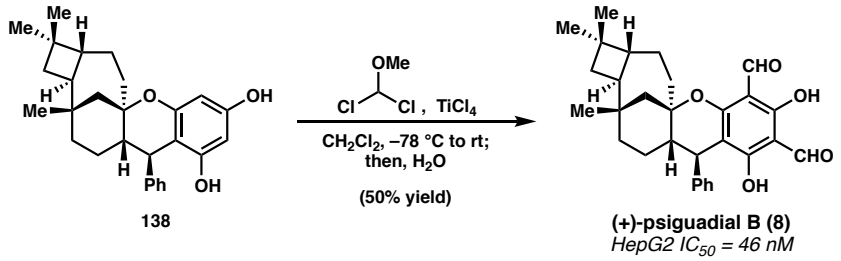
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 5H), 6.02 (d, *J* = 2.5 Hz, 1H), 5.96 (d, *J* = 2.5 Hz, 1H), 4.73 (s, 1H), 4.30 (s, 1H), 4.00 (d, *J* = 7.0 Hz, 1H), 2.16 (ddd, *J* = 12.5, 7.0, 3.9 Hz, 1H), 1.93 (dd, *J* = 12.7, 2.3 Hz, 2H), 1.79 (ddd, *J* = 12.3, 10.3, 7.8 Hz, 1H), 1.66 (ddd, *J* = 12.4, 8.7, 5.4 Hz, 1H), 1.57 – 1.43 (m, 5H), 1.39 – 1.28 (m, 4H), 1.23 – 1.12 (m, 3H), 1.09 – 0.95 (m, 2H), 0.91 (s, 3H), 0.82 (s, 3H), 0.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 155.7, 155.4, 138.6, 127.4, 104.8, 97.6, 95.9, 80.4, 49.7, 45.6, 44.2, 39.6, 38.3, 36.6, 35.4, 35.1, 33.2, 32.0, 30.8, 29.9, 26.1, 25.4, 20.8, 20.3.

FTIR (NaCl, thin film) 3385 (br), 3027, 2949, 2925, 2857, 1624, 1600, 1508, 1493, 1459, 1452, 1377, 1364, 1247, 1190, 1163, 1143, 1086, 1055, 1034, 1015, 925, 826, 761, 721, 701 $cm.^{-1}$

HRMS (MM) calc'd for $C_{28}H_{35}O_3$ $[M+H]^+$ 419.2581, 419.2595.

Preparation of (+)-psiguadial B (8).



To a 2-dram vial was added resorcinol **138** (15.4 mg, 0.037 mmol) and the atmosphere exchanged three times for N_2. CH_2Cl_2 (1.30 mL) was then added via syringe, followed by dichloromethyl methyl ether (0.083 mL, 0.920 mmol, 25.0 equiv). The solution was cooled to –78 °C and a freshly prepared stock solution of $TiCl_4$ (0.190 mL, 0.912 M in CH_2Cl_2, 0.173 mmol, 4.68 equiv) was added dropwise. The reaction immediately turned dark red. The reaction was stirred at –78 °C for 5 minutes, then warmed to room temperature and stirred for an additional 3 hours and 40 minutes. DI H_2O (2.00 mL) was then added via syringe and the reaction stirred vigorously for 15 minutes before the layers were separated. The aqueous layer was extracted five times with CH_2Cl_2 and the combined organic layers were filtered over a plug of Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 2% EtOAc/hexane + 1% AcOH) to afford (+)-psiguadial B (**8**) (8.7 mg, 50%) as an ivory solid. Note: **3** is streaky on SiO_2 and after an initial concentrated band elutes, approximately 12% of the product is contained in the following very dilute fractions. The natural product is weakly UV active, but can also be visualized by TLC using 2,4-dinitrophenylhydrazine stain.

$[\alpha]_D^{25.0}$ = +94.0° (c = 0.265, $CHCl_3$).

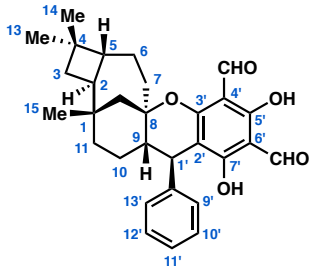
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 13.04 (s, 1H), 10.07 (s, 2H), 7.26 (dd, *J* = 14.6, 1.5 Hz, 2H), 7.23 – 7.17 (m, 1H), 7.10 (br s, 2H), 3.49 (d, *J* = 11.5 Hz, 1H), 2.20 – 2.12 (m, 1H), 2.09 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.92 (ddd, *J* = 14.9, 12.8, 4.2 Hz, 1H), 1.82 (ddd, *J* = 12.3, 8.8, 5.6 Hz, 1H), 1.73 – 1.59 (m, 3H), 1.53 – 1.44 (m, 1H), 1.49 (ddd, *J* = 11.6, 8.1, 2.9 Hz, 2H), 1.44 – 1.29 (m, 4H), 1.05 (dd, *J* = 7.6, 5.8 Hz, 1H), 1.02 (s, 3H), 1.00 (s, 3H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 191.5, 169.6, 168.5, 163.5, 143.4, 128.2, 126.2, 105.7, 104.6, 104.1, 84.1, 50.0, 47.4, 44.0, 40.4, 37.6, 36.9, 35.4, 35.1, 33.4, 30.6, 29.3, 26.1, 23.9, 20.7, 20.1.

FTIR (NaCl, thin film) 3026, 2945, 2926, 2864, 2720, 1633, 1603, 1493, 1437, 1382, 1363, 1300, 1270, 1251, 1231, 1184, 1154, 1143, 1031, 1006, 976, 926, 917, 875, 851, 840, 824, 768, 701, 636, 618, 606, 564 cm.$^{-1}$

HRMS (MM) calc'd for $C_{30}H_{35}O_5$ $[M+H]^+$ 475.2479, found 475.2487.

(+)-psiguadial B (**8**) carbon numbering as reported by Shao et al.[15]



Comparison of ^{1}H NMR spectral data for natural and synthetic (+)-psiguadial B (3).

carbon number	**Natural (+)-psiguadial B** ^{1}H NMR, 500 MHz, $CDCl_3$	**Synthetic (+)-psiguadial B** ^{1}H NMR, 400 MHz, $CDCl_3$
5'-OH	δ 13.51 (s, 1H)	δ 13.51 (s, 1H)
7'-OH	13.04 (s, 1H)	13.04 (s, 1H)
14', 15'	10.08 (s, 2H)	10.07 (s, 2H)
9', 13'	7.23 (2H)	7.26 (dd, *J* = 14.6, 1.5 Hz, 2H)
11'	7.18 (3H)	7.23 – 7.17 (m, 1H)
10', 12'	–	7.10 (br m, 2H)
1'	3.49 (d, *J* = 11.5 Hz, 1H)	3.49 (d, *J* = 11.5 Hz, 1H)
2	2.16 (1H)	2.20 – 2.12 (m, 1H)
12	2.08 (1H)	2.09 (dd, *J* = 12.7, 2.4 Hz, 1H)
7	1.93 (1H)	1.92 (ddd, *J* = 14.9, 12.8, 4.2 Hz, 1H)
5	1.82 (m, 1H)	1.82 (ddd, *J* = 12.3, 8.8, 5.6 Hz, 1H)
9	1.68 (1H)	1.73 – 1.59 (m, 3H)
6	1.65 (1H)	–
7	1.58 (m, 1H)	–
3	1.52 (1H)	1.53 – 1.44 (m, 1H)
10	1.49 (m, 2H)	1.49 (ddd, *J* = 11.6, 8.1, 2.9 Hz, 2H)
6, 11	1.41 (2H)	–
3	1.37 (1H)	1.44 – 1.29 (m, 4H)
12	1.29 (1H)	–
11	1.10 (1H)	1.05 (dd, *J* = 7.6, 5.8 Hz, 1H)
13	1.02 (s, 3H)	1.02 (s, 3H)
14	1.01 (s, 3H)	1.00 (s, 3H)
15	0.86 (s, 3H)	0.85 (s, 3H)

Comparison of ^{13}C NMR spectroscopic data for natural and synthetic (+)-psiguadial B (8).

carbon number	**Natural (+)-psiguadial B** ^{13}C NMR, 125 MHz, $CDCl_3$	**Synthetic (+)-psiguadial B** ^{13}C NMR, 101 MHz, $CDCl_3$	Δ
15'	192.3	192.3	0.0
14'	191.4	191.5	0.1
7'	169.6	169.6	0.0
5'	168.5	168.5	0.0
3'	163.5	163.5	0.0
8'	143.4	143.4	0.0
9', 11', 13'	128.2	128.2	0.0
10', 12'	126.2	126.2	0.0
2'	105.7	105.7	0.0
4'	104.6	104.6	0.0
6'	104.2	104.1	–0.1
8	84.1	84.1	0.0
9	50.0	50.0	0.0
12	47.5	47.4	–0.1
5	44.1	44.0	–0.1
1'	40.4	40.4	0.0
11	37.6	37.6	0.0
2	37.0	36.9	–0.1
3	35.5	35.4	–0.1
4	35.1	35.1	0.0
1	33.4	33.4	0.0
13	30.6	30.6	0.0
7	29.4	29.3	–0.1
15	26.1	26.1	0.0
10	23.9	23.9	0.0
14	20.7	20.7	0.0
6	20.1	20.1	0.0

1.7 NOTES AND REFERENCES

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Chapter 2

A Modular Approach to Synthesize Enantioenriched Cyclobutane Products[†]

2.1 INTRODUCTION

Having established a novel methodology for the asymmetric synthesis of **55** for application to the synthesis of (+)-psiguadial B (**8**), we wondered if we could potentially leverage this versatile building block to further explore the preparation of *trans*-fused cyclobutane containing products. The cyclobutane structural motif is present in a variety of natural products and pharmaceutical molecules (Scheme **2.1**).[1–7] Cyclobutanes are also versatile synthetic intermediates, as the ring strain inherent to these structures engenders

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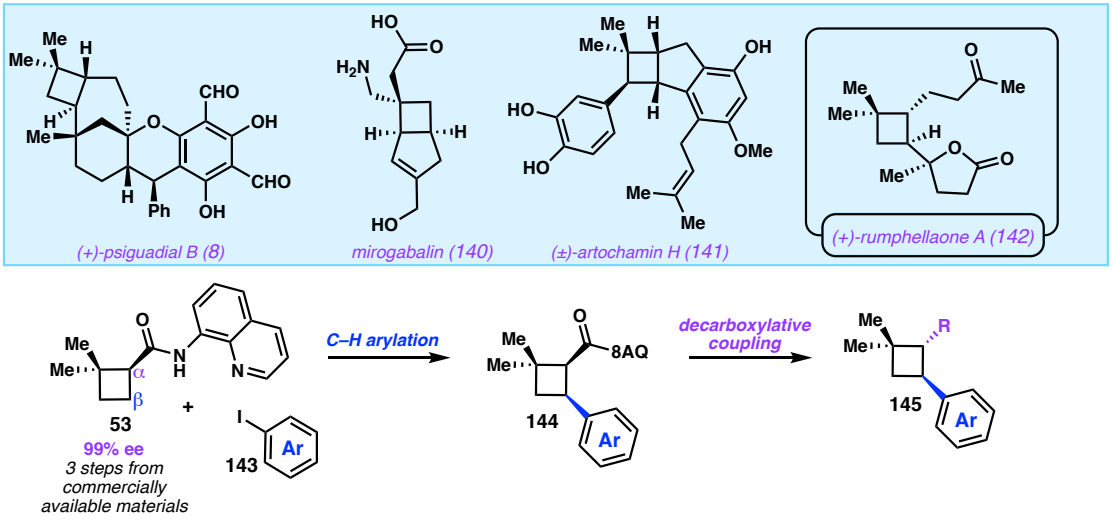
them with unique reactivity that can be leveraged in a variety of transformations to build complex frameworks. [8–11] [2+2] cycloaddition reactions represent the most extensively developed approach to construct cyclobutanes, and recent advances have given rise to elegant enantioselective reactions.[12–17] An alternative strategy is to prepare a versatile cyclobutane building block, and then use C–H functionalization or cross-coupling chemistry to elaborate the scaffold in a modular fashion.[18–27] In this latter approach, a single enantioenriched intermediate can quickly be converted to a variety of more functionalized structures.

Scheme 2.1 *Bioactive cyclobutane-containing products and our strategy for cyclobutane vicinal difunctionalization.*



We recently reported the synthesis of **8** which featured a tandem Wolff-rearrangement/asymmetric ketene addition to prepare enantioenriched 8-aminoquinolinamide **53**.[28,29] In the course of our investigation, we became acutely aware of the limitations and difficulties associated with the synthesis of functionalized cyclobutanes as well as the community's interest in more methods for their preparation.

Given the short synthesis of **53** from commercial starting materials, we became interested in further applications of this chiral building block. Specifically, we envisioned that directed C–H arylation could enable diversification at the β-position, while hydrolysis of the 8-aminoquinolinamide followed by decarboxylative radical cross-coupling could enable diversification at the α-position. Herein, we describe the development of this strategy commencing from lynchpin **53** that has enabled the synthesis of a library of vicinal difunctionalized cyclobutanes and our efforts to apply this strategy to the synthesis of **142**.

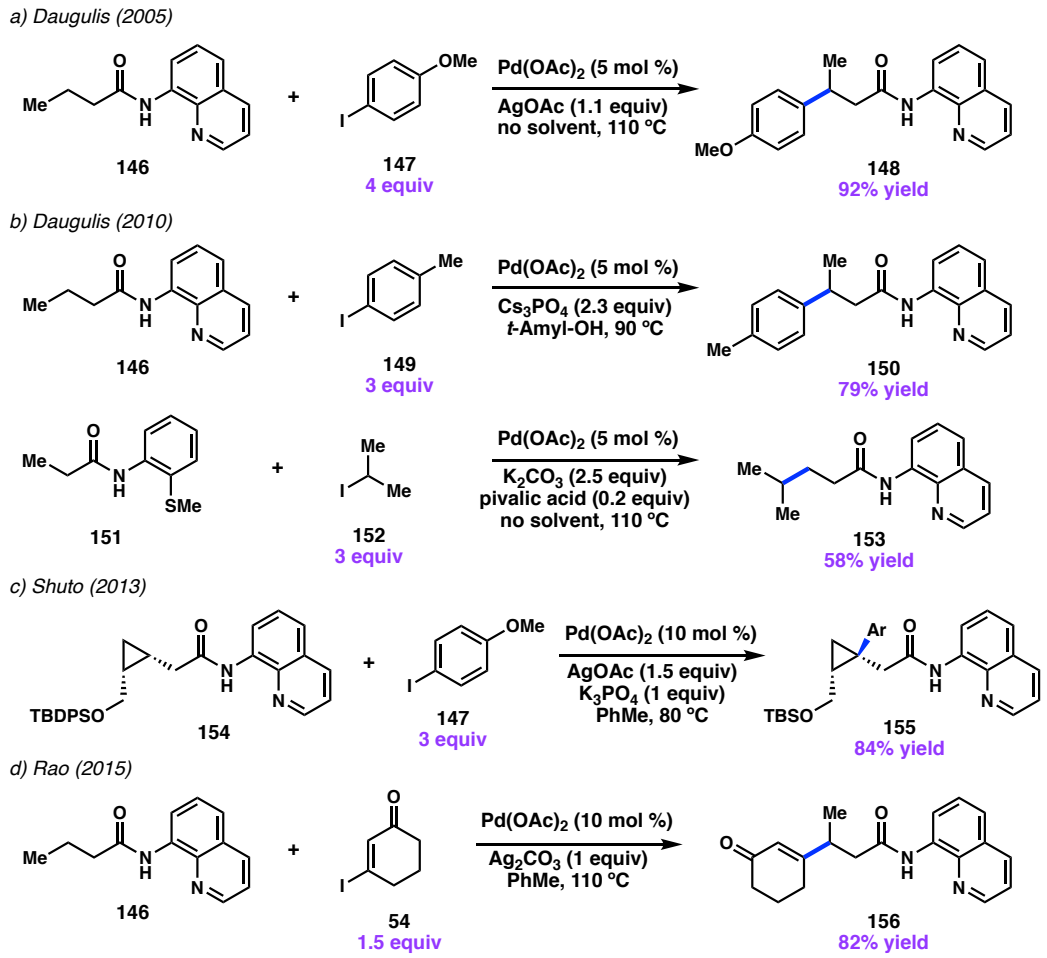
2.2 REVIEW OF AMIDE DIRECTED C(sp^3)–H ACTIVATION TO FORM C–C BONDS

At the outset of our investigation focused on the synthesis of **8**, we were intrigued by reports detailing the use of an aminoquinolinamide directing group to perform palladium-catalyzed C–H functionalization of aliphatic C–H bonds. Having developed a novel Wolff Rearrangement with asymmetric trapping of the ketene to install the quinolinamide and set the first stereocenter in a single step, we hypothesized that we could utilize this quinolinamide-directed methodology to perform functionalization of a cyclobutane.

Notably in 2005, Daugulis and co-workers reported the arylation of a C(sp^3)–H bond under palladium catalysis, utilizing aryl iodides **147** as the cross-coupling partners with silver acetate added to presumably turn over the catalyst (Scheme **2.2a**).[30] This pivotal disclosure was further expanded upon to include additional directing groups enabling C–H functionalization without the addition of stoichiometric silver salts and provided

examples of cross-coupling with additional aryl as well as alkyl iodides **152** (Scheme **2.2b**).[31]

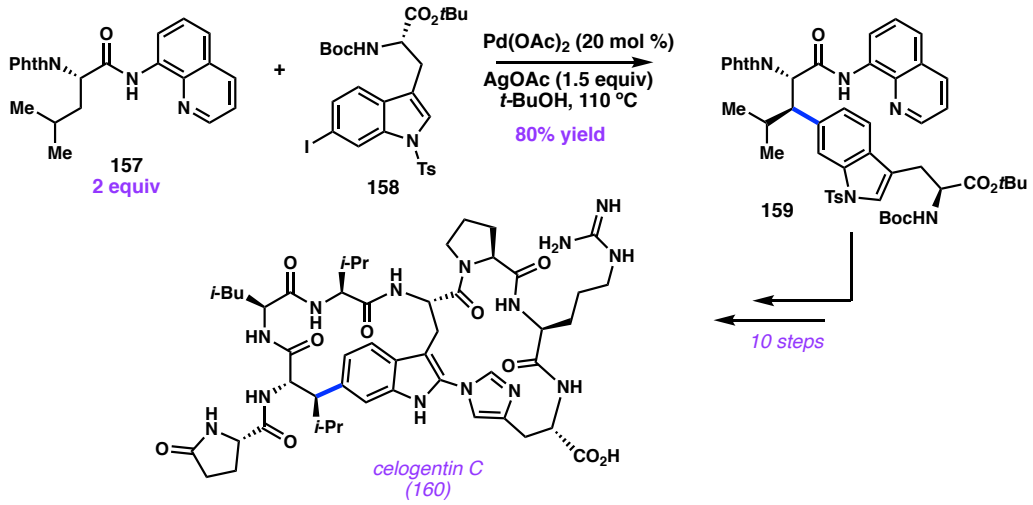
Scheme 2.2 *Precedent for aminoquinolinamide-directed C–H activation.*



We were also intrigued by an early report from the Shuto group in which they were able to activate substituted cyclopropanes utilizing the same quinolinamide directing group, forging all-carbon quaternary centers using a similar Pd(II) catalyst system (Scheme **2.2c**).[32] In their system, they were able to access all-carbon quaternary centers through activation of the tertiary cyclopropyl methine. This example demonstrated the feasibility of building sterically encumbered systems with the quinolinamide auxiliary.

Particularly notable for use in our synthesis was a disclosure from Rao and coworkers in 2015 in which they report functionalization of a methylene group with a variety of alkenyl iodides (Scheme **2.2d**).[33] We were excited to see their use of iodides such as **54** utilized in their system, as these types of unsaturated ketone products mapped on well for our synthesis of **8**.

Scheme 2.3 *Chen synthesis of celogentin C.*

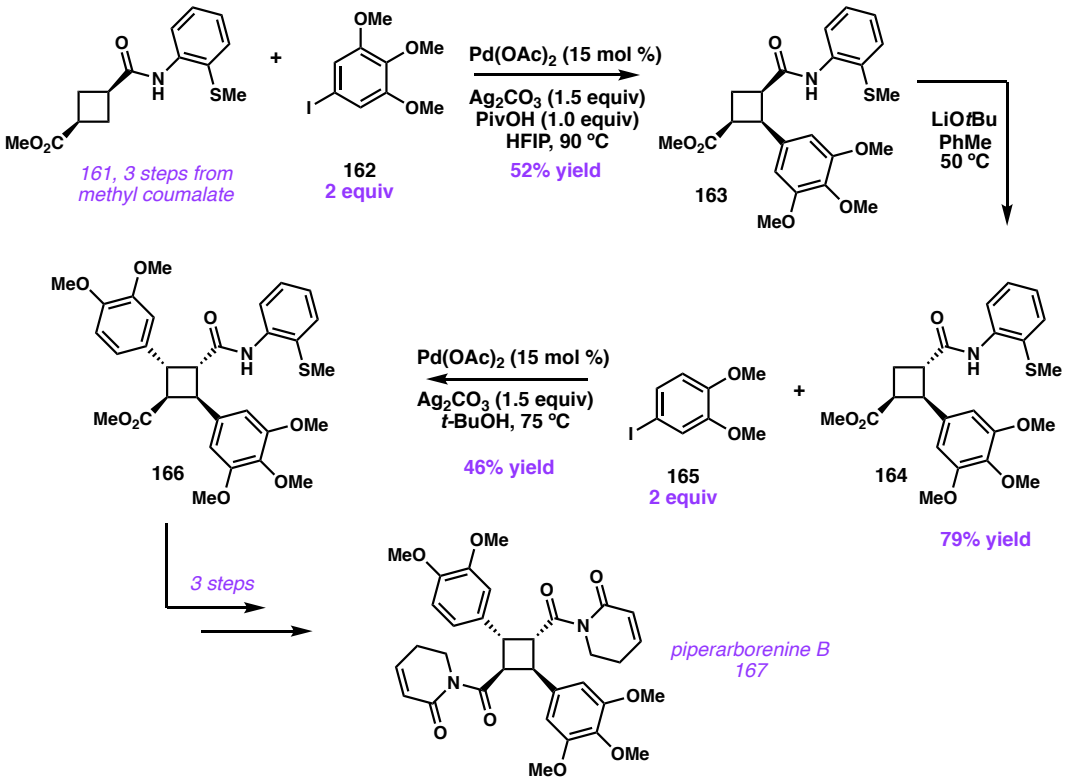


In addition to these key reports of palladium-catalyzed C–H activation methodologies, we were also aware of some examples of total syntheses of complex molecules in which a C–H bond activation strategy was employed to install functionality at an otherwise inert carbon–hydrogen bond. In 2010, the Chen group reported their total synthesis of the bicyclic peptide, celogentin C (**160**) (Scheme **2.3**).[34] Key to their strategy was a C–H activation between leucine derivative **157** bearing an 8-aminoquinolinamide and a modified tryptophan derivative **158**, selectively functionalizing **157** at the β-position. They isolated their product as single diastereomer, presumably due to the coordinating ability of the adjacent imide. It is interesting that in this particular example, the aryl iodide

158 was used as the limiting reagent, as typically the aryl iodide is used in excess. Their key indole intermediate **159** can be advanced an additional 10 steps to access the macrocyclic natural product **160**. Their synthesis elegantly leverages the intrinsic selectivity for β-functionalization of these amino quinolinamides.

A report in 2011 from the Baran lab further demonstrated the utility of C–H activation in the context of natural product total synthesis (Scheme **2.4**).[18] They were able to prepare **161** in three steps from commercially available methyl coumalate as a racemic mixture, at which point they were poised to perform their first C–H activation event.

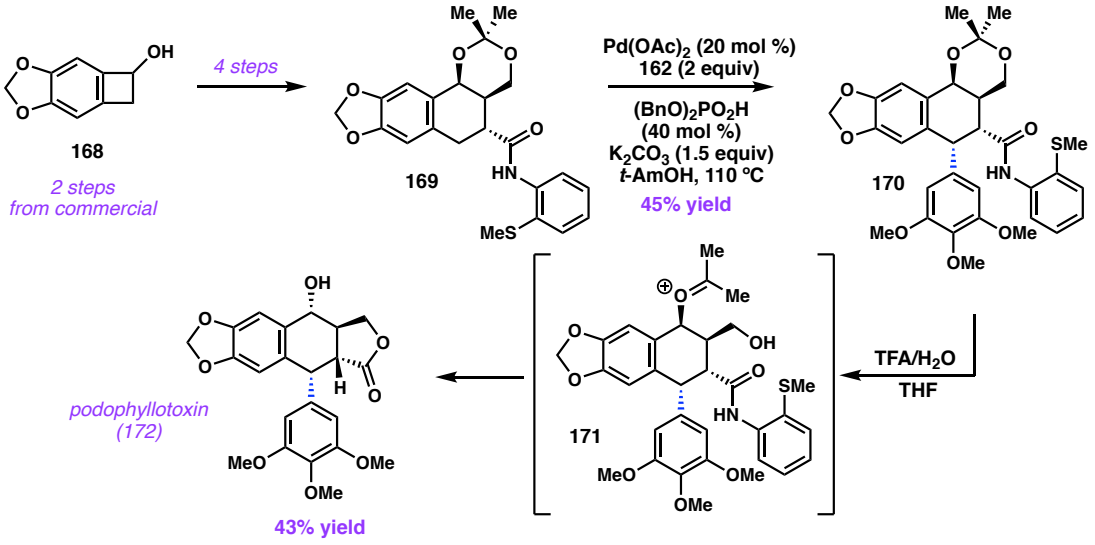
Scheme 2.4 *Baran synthesis of piperarborenine B.*



Treatment of **161** with two equivalents of aryl iodide **162** delivered modest yield of the single arylated product **163**, with all three substituents configured *cis* to one another.

Epimerization of **163** delivered **164**, which underwent a second C–H arylation reaction, this time with aryl iodide **165** as the cross-coupling partner. Arylation directed by the aminothioanisole delivered a single diastereomer of **166**, which was advanced three additional steps to provide piperarborenine B (**167**). This synthesis demonstrated the feasibility of using palladium catalysis to activate cyclobutyl methylenes in a C–H activation event. While their synthesis was limited by their use of racemic starting material, their high levels of diastereoselectivity indicated that we could generate a library of *enantioenriched* cyclobutanes by starting with a chiral cyclobutamide substrate. The Baran lab subsequently published a full paper detailing additional C–H functionalization strategies to access similar natural products.[21]

Scheme 2.5 *Maimone synthesis of podophyllotoxin.*



In 2014, the Maimone group reported a short racemic synthesis of the aryltetralin natural product, podophyllotoxin (**172**), again relying upon a key C–H activation reaction to forge a crucial C–C bond (Scheme **2.5**).[35] Their synthesis commenced with the

preparation of cyclobutanol **168**, which can be made in two steps from commercial material. Four additional steps delivered acetonide **169** containing the key aminothioanisole directing group. This substrate can undergo C–H activation with 2 equivalents of **162**, delivering **170** in modest yield. The arylated was subjected to hydrolysis of the acetonide, during which epimerization of the secondary alcohol and lactonization occured concomitantly to deliver **172**. The utility of the C–H activation is highlighted by the brevity of their synthesis, enabling the synthesis of **172** in just 7 steps from commercial material.

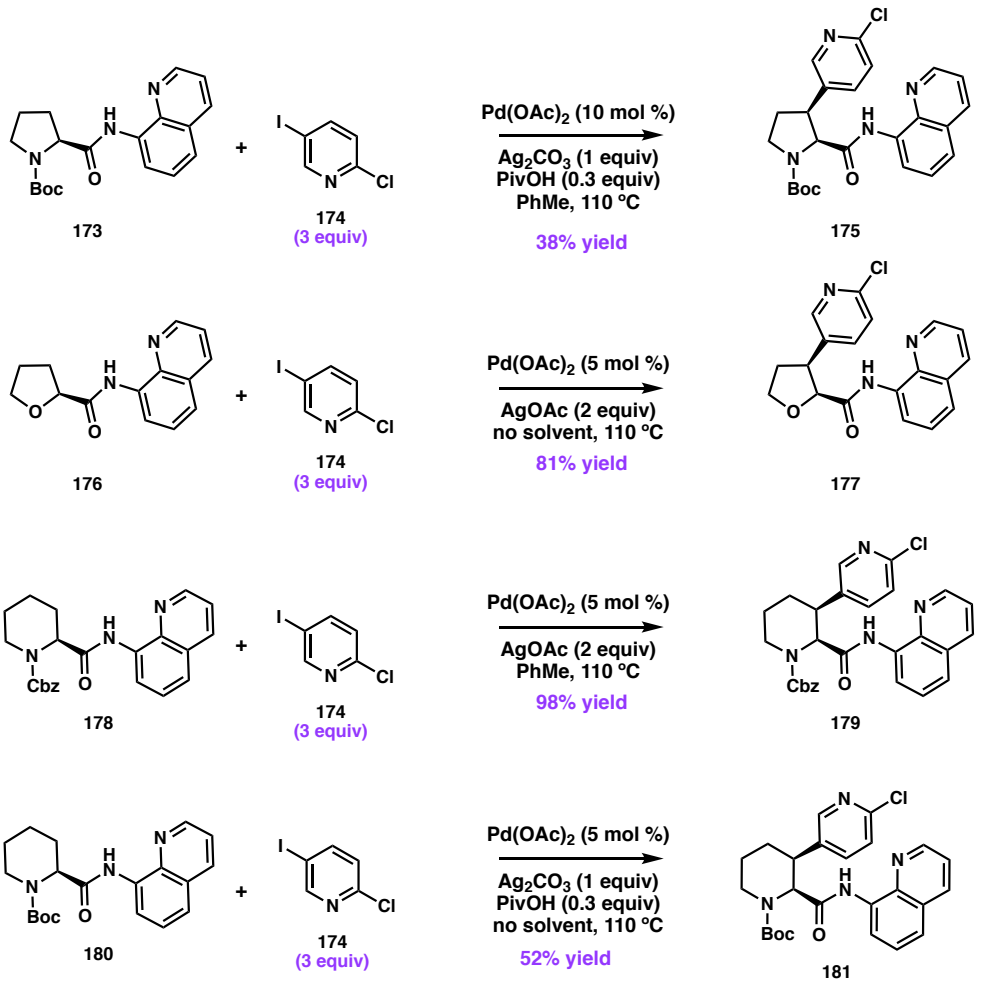
2.3 THE DEVELOPMENT OF A NOVEL C(sp^3)–H HETEROARYLATION REACTION

While C(sp^3)–H bond arylation has been explored by several groups, the corresponding *hetero*arylation reaction remains widely underdeveloped. At the outset of this investigation, we were only aware of one other report in which a heterocycle was used to direct a heteroarylation reaction.[36]

In 2016, the Bull lab published an aminoquinolinamide directed C(sp^3)–H activation reaction (Scheme **2.6**).[36] By utilizing chiral piperidines, pyrrolidines, and tetrahydrofurans, they could perform a site-selective and diastereoselective heteroarylation with 2-chloro-5-iodopyridine (**174**) as the cross-coupling partner. While they were able to achieve excellent yields of the coupled products with a Cbz-protected piperidine **178** or the tetrahydrofuran-containing quinolinamide **176**, their substrates containing Boc-protected piperidines **173** and Boc-protected pyrrolidines **180** were coupled in lower yields (Scheme

2.6). Notably, their reactions enabled the formation of enantioenriched products by starting from the chiral pool.

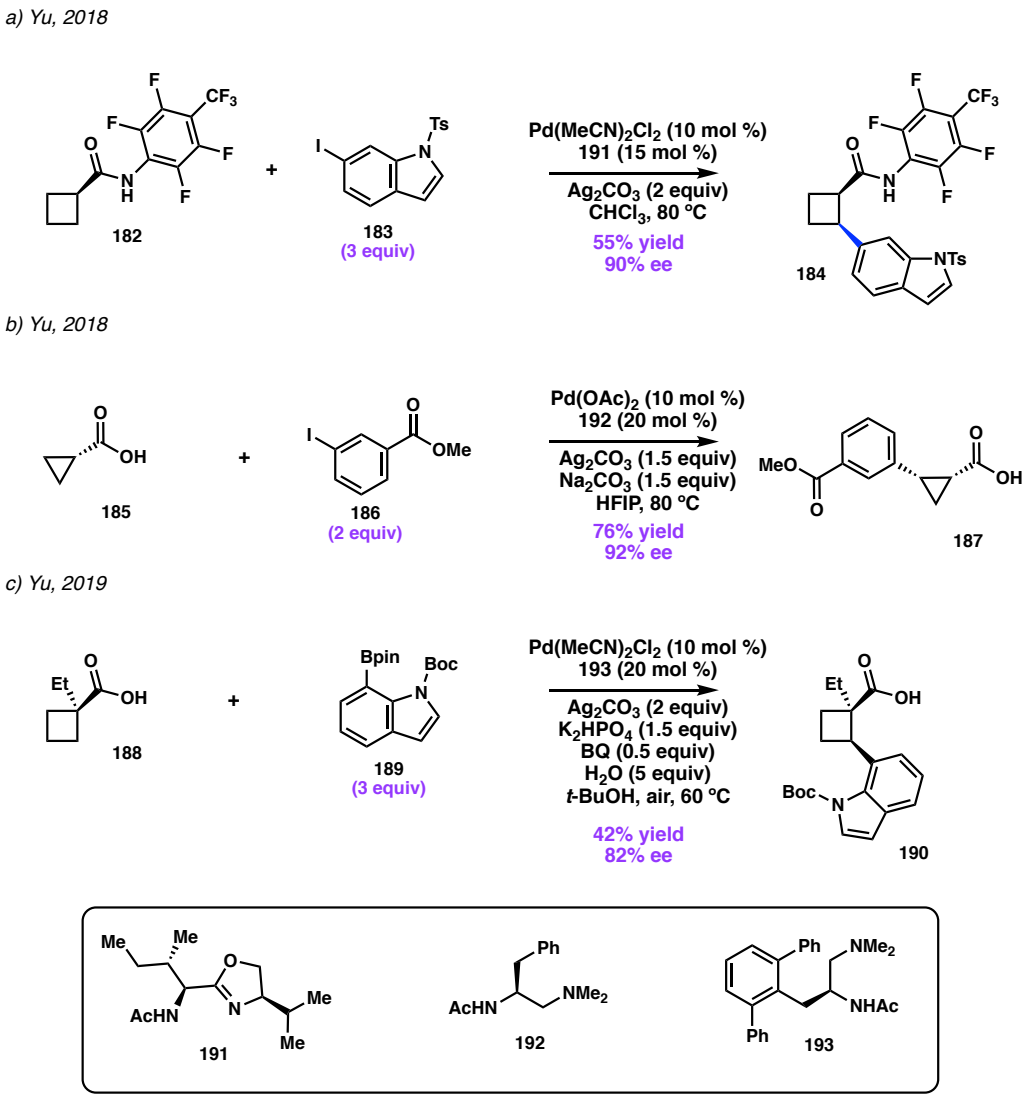
Scheme 2.6 *Bull's heteroarylation of pyrrolidines, tetrahydrofurans, and piperidines.*



During the course of our investigation, the Yu lab reported three elegant C–H activation reactions highlighting both the power of C–H activation as a strategy for the synthesis of chiral cyclic products as well as the difficulties associated with the utilization of heteroaryl moieties in cross-coupling reactions (Scheme **2.7**). In 2018, the Yu group disclosed a palladium-catalyzed C–H activation reaction between cyclobutyl carboxylic

amides **182** and aryl iodides **193** using a chiral mono-*N*-protected aminomethyl oxazoline (MPAO) ligand **191** (Scheme **2.7a**).[27] While they had previously reported the use of the related chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligands to promote cross-couplings between cyclobutyl carboxylic amides and aryl boron reagents,[22] the development of this reaction utilizing the MPAO ligand class enabled entry into a Pd(II)/Pd(IV) catalytic cycle, improving the scope of substrates tolerated in the reaction.

Scheme 2.7 *Yu's C–H activation of cyclobutanes and cyclopropanes.*



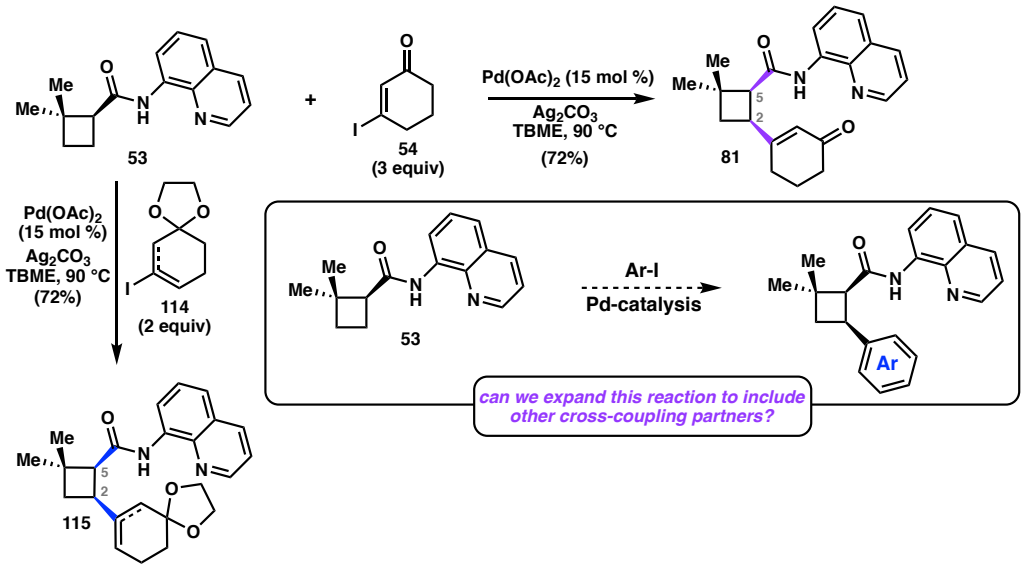
While their reaction notably enables the enantioselective arylation of cyclobutyl carboxylic amides, only two nitrogen-containing aryl iodides are employed in their reaction, both of which proceed in only modest yield.

In 2018, the Yu group reported an additional C–H activation reaction to access chiral carbocycles using carboxylic acid substrates (Scheme **2.7b**).[37] The use of free carboxylic acids in these reactions had previously been limited due to the low reactivity associated with the weak directing ability of the carboxylic acid as well as the conformationally flexibility of the acid in comparison to the rigidified amide substrates. However, this reaction was enabled by the development of the monoprotected aminoethyl amine (MPAAM) ligand class **192**, allowing for enantioselective C(sp^3)–H functionalization of free carboxylic acids **185**. While this report represents an immense achievement in the field of C–H activation, their initial report was limited to cyclopropyl carboxylic acids and did not include the cross-coupling of any nitrogen-containing heterocycles.

In early 2019, the Yu lab reported a subsequent report in which they were able to expand the breadth of their reaction to encompass the direct cross-coupling of cyclobutyl carboxylic acids **188** with aryl boronate esters **189** (Scheme **2.7c**).[38] Key to this reaction was the use of an aryl boronate rather than an aryl iodide coupling partner, presumably changing the mechanism from a Pd(II)/Pd(IV) catalytic cycle to a Pd(0)/Pd(II) catalytic cycle. They report a single cross-coupling with a heteroaryl boronate ester **189**, again highlighting the difficulties associated with using Lewis basic cross-coupling partners in directed C–H functionalization reactions.

After extensive optimization and exploration of a C–H activation for two different substrates *en route* to **8**, we hypothesized that we could expand the scope of this reaction to encompass the cross-coupling of additional electrophiles. With a robust means of preparing **53**, we became interested in identifying cross-coupling conditions that could enable the formation of a library of vicinal disubstituted cyclobutanes from our lynchpin **53** (Scheme **2.8**). We hypothesized that the efficiency with which both **54** and **114** could be coupled with **53** with excellent site- and diastereoselectivity indicated that this particular scaffold was privileged in this type of transformation and warranted further exploration.

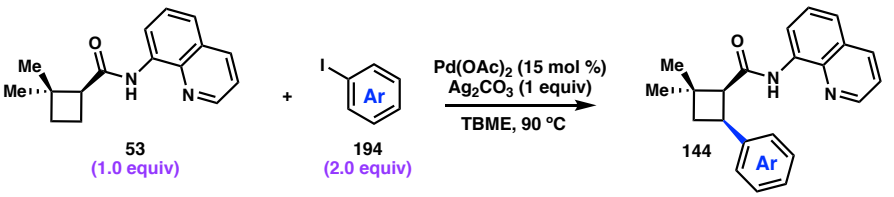
Scheme 2.8 *Our modular approach to prepare chiral disubstituted cyclobutanes.*

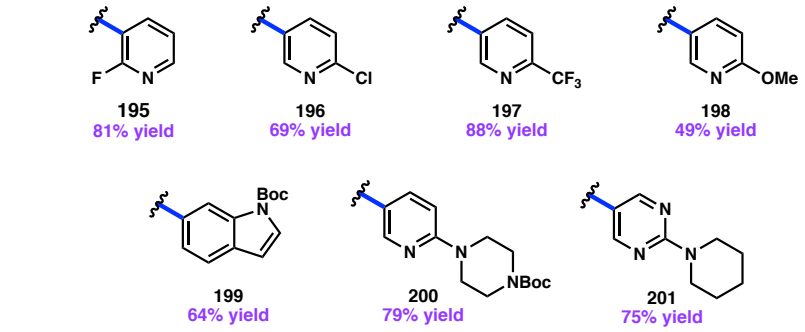


We began by investigating the scope of the directed C–H arylation of 8-aminoquinolinamide **53**, which was prepared in three steps and 99% ee from commercially available 2,2-dimethylcyclopentan-1-one.[28,29] We were pleased to see that by using our previously developed conditions [$Pd(OAc)_2$ (15 mol%), Ag_2CO_3 (1.0 equiv), aryl iodide (2.0 equiv), TBME, 90 °C], a series of heteroaryl iodides could be coupled to generate *cis*-

heteroarylated cyclobutanes (**195**–**201**) in good yields (Table **2.1**). Under these reaction conditions, we could isolate good yields of pyridine-containing cyclobutanes (**195**–**198**) with varying substitution on the arene. We were pleased to see that an indolyl iodide was a competent cross-coupling partner in this reaction (**199**) as was a piperazyl pyridine (**200**) and a piperidyl pyrimidine (**201**). We were particularly excited by products such as **200** and **201**, which contain five nitrogen atoms within the molecule.

Table 2.1. *Cyclobutamide heteroarylation*

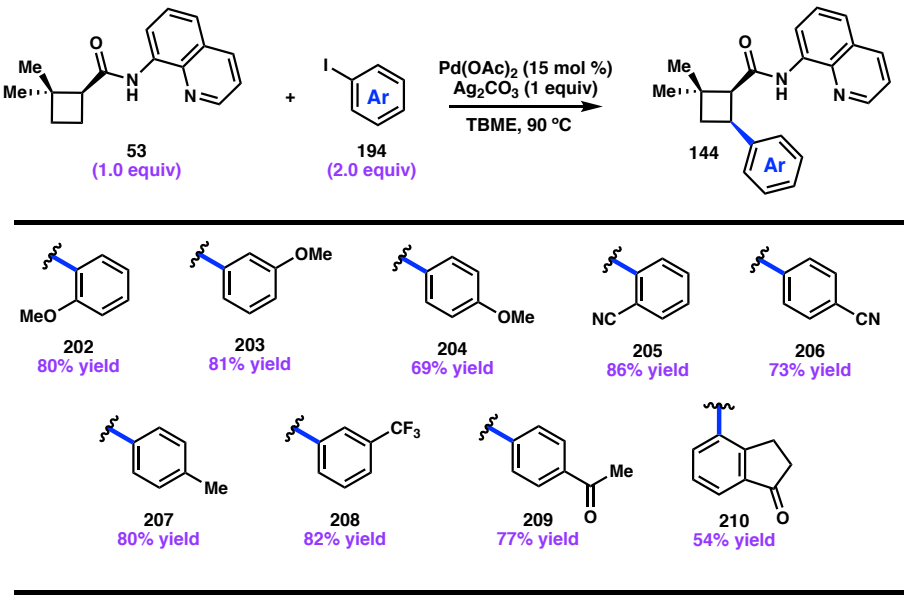




Pleased that we could incorporate heteroaryl moieties through this cross-coupling platform, we became interested in exploring the feasibility of incorporating additional aryl iodides through this reaction. Gratifyingly, we found that installation of a variety of aryl groups proceeded with high levels of yield and selectivity (Table **2.2**). This reaction tolerates aryl substitution at the *ortho*, *meta*, and *para* positions (**202**–**204**) and can tolerate

both electron withdrawing (**205**–**206**, **208**–**210**) as well as electron donating groups (**202**–**204**).

Table 2.2. *Cyclobutamide arylation*

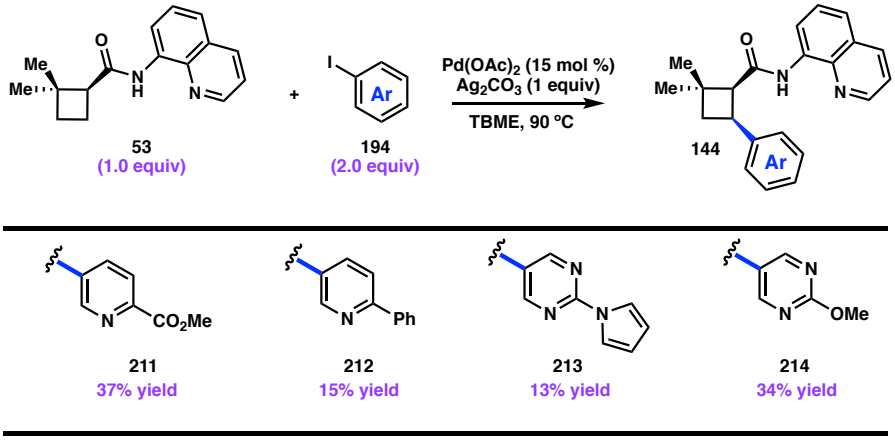


While the reaction worked with excellent efficiency and selectivity for a variety of substrates, we identified key limitations of this transformation. Unfortunately, attempts to lower the catalyst loading (7.5 mol %) or using only 1 equivalent of the aryl iodide decreased the yields by about 30% across the board. While some substrates could be adequately cross-coupled at lower temperatures, we found that 90ºC worked for most of the substrates we explored.

We also found that some substrates did not perform well in the reaction under these general reaction conditions. C–H activation reactions between **53** and pyridyl iodides with an ester at the 2-position or an aromatic ring at the 2-position performed poorly under these conditions (Table **2.3**, **211** and **212**). We also found that pyrimidine substrates with a

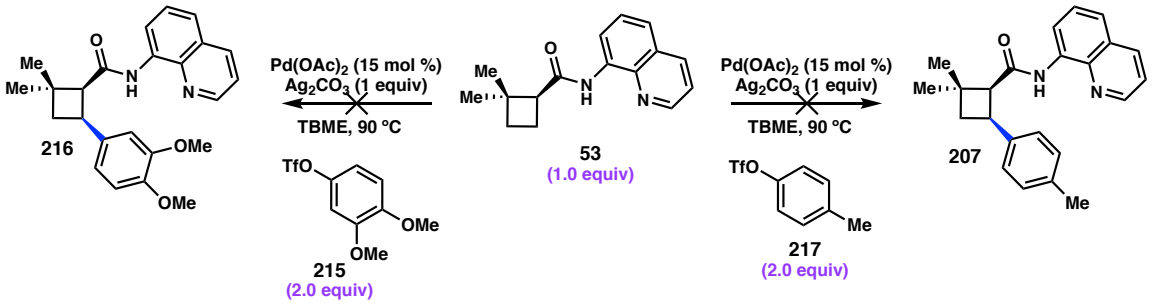
pyrrole (**213**) or a methoxy group at the 2-position (**214**) also did not work well under these reaction conditions.

Table 2.3. *Poorer performing substrates*



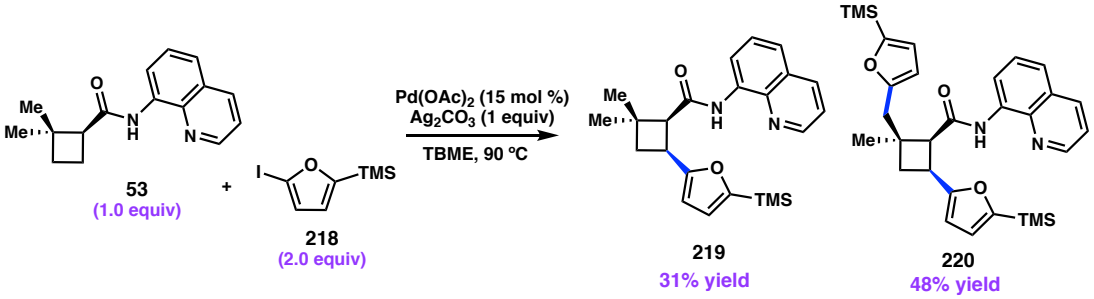
In an attempt to broaden the scope of this reaction, we investigated the feasibility of using aryl triflates as the coupling partners, as we reasoned these might be more appealing due to their ease of handling; however, under the conditions developed for the cross-coupling of aryl and heteroaryl iodides, only starting material was observed (Scheme **2.9**). Expansion of this methodology to encompass the cross-coupling of alternative classes of electrophiles was not further explored, but it would be prudent to look at additional additives as well as alternative solvents and palladium precatalysts.

Scheme 2.9 *Unsuccessful attempts to use aryl triflates in the cross-coupling reaction.*



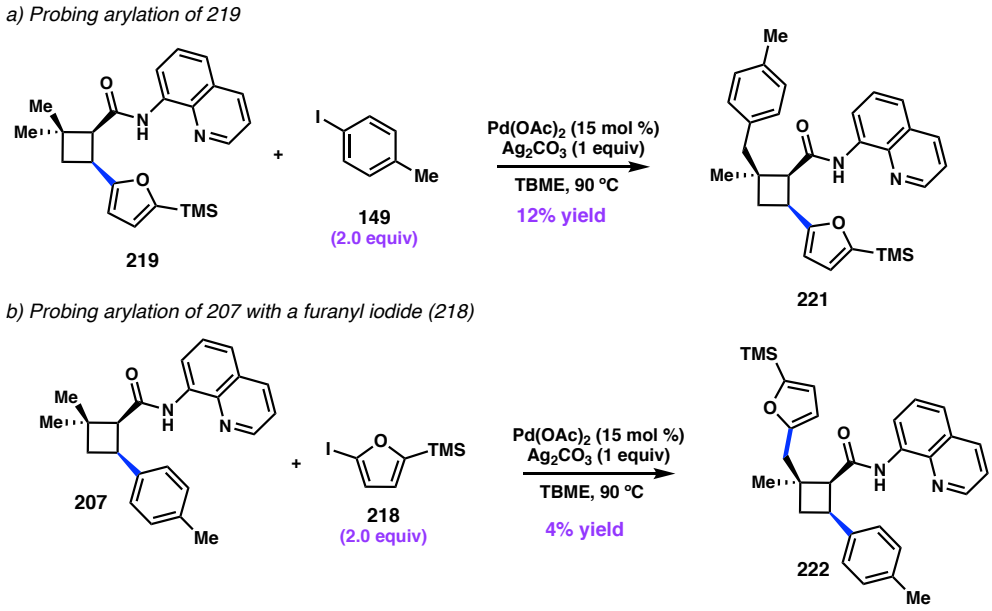
While we almost exclusively observed monofunctionalization of cyclobutane **53**, it is of note that one substrate that we investigated delivered bisarylated product. Treatment of **53** with two equivalents of **218** under the standard reaction conditions delivered significant quantities of bis-arylated product **220** (Scheme **2.10**). 2D NMR experiments indicated that the site of arylation was the beta-disposed methyl group. To the best of our knowledge, this was the only substrate that delivered any quantity of bis-arylated product under our developed reaction conditions.

Scheme 2.10 *Observed bis-arylation.*



We were perplexed by this finding—we had successfully carried out dozens of cross-couplings without observing any appreciable quantity of over-arylation. The reaction profiles were exceedingly clean, and we were often to recover unreacted **53** as well as the additional equivalent of the aryl iodide. In an attempt to better understand the nature of this bis-arylation phenomenon, we conducted a couple of experiments. We first treated **219** with **149** under the standard conditions and observed only trace over-arylation product **221** (Scheme **2.11**). We also attempted to use a different substrate with the iodofuryl cross-coupling partner **218** that had been a competent cross-coupling partner in the over-arylation reaction. Treatment of **207** with **218** under the standard conditions only delivered trace quantities of a bis-arylation product **222**.

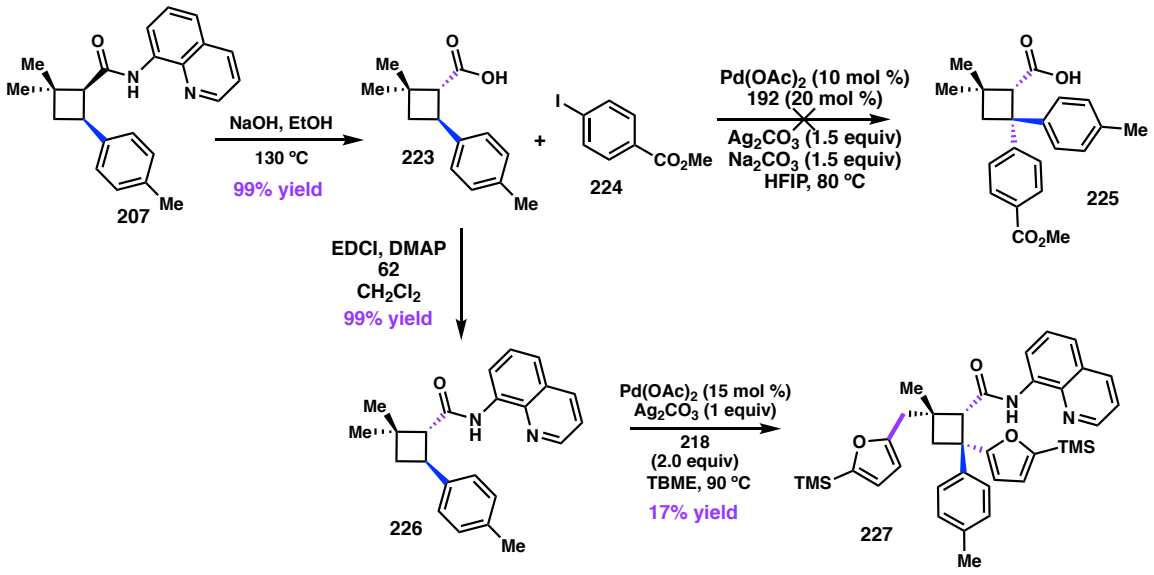
Scheme 2.11 *Probing alternative bisarylation substrates.*



To further explore the feasibility of using C–H activation to derivatize these substrates, we attempted to use Yu's C–H activation of free carboxylic acids, as we felt that the versatility of the carboxylic acid functional group could enable the introduction of additional complexity through an iterative cross-coupling approach (Scheme **2.12**). While hydrolysis of the quinolinamide **207** proceeded smoothly to deliver the *trans*-fused cyclobutanoic acid **223**, we found that this substrate was unreactive under the Yu conditions employing $Pd(OAc)_2$ and the MPAAM ligand **192** (Scheme **2.12**).[39] While the acid was unreactive, the aminoquinolinamide auxiliary could be reinstalled under canonical peptide coupling conditions, delivering **226** as the *trans*-fused cyclobutamide. To our surprise, treatment of **226** with our standard C–H activation conditions delivered a tri-arylated product **227**. While we were unsure of how synthetically useful this particular reaction would be due to the need to cleave and reinstall the auxiliary and our inability to

control or predict the bisarylation event, we were pleased to see that these scaffolds were amenable to further modulation. Satisfied with the excellent yields and diastereoselectivities we were able to observe with a variety of aryl and heteroaryl substrates, we became interested in identifying other means of modulating the cyclobutane scaffold.

Scheme 2.12 *A sequential C–H arylation strategy.*



2.4 DECARBOXYLATIVE CROSS-COUPLINGS FOR CYCLOBUTANE DIVERSIFICATION

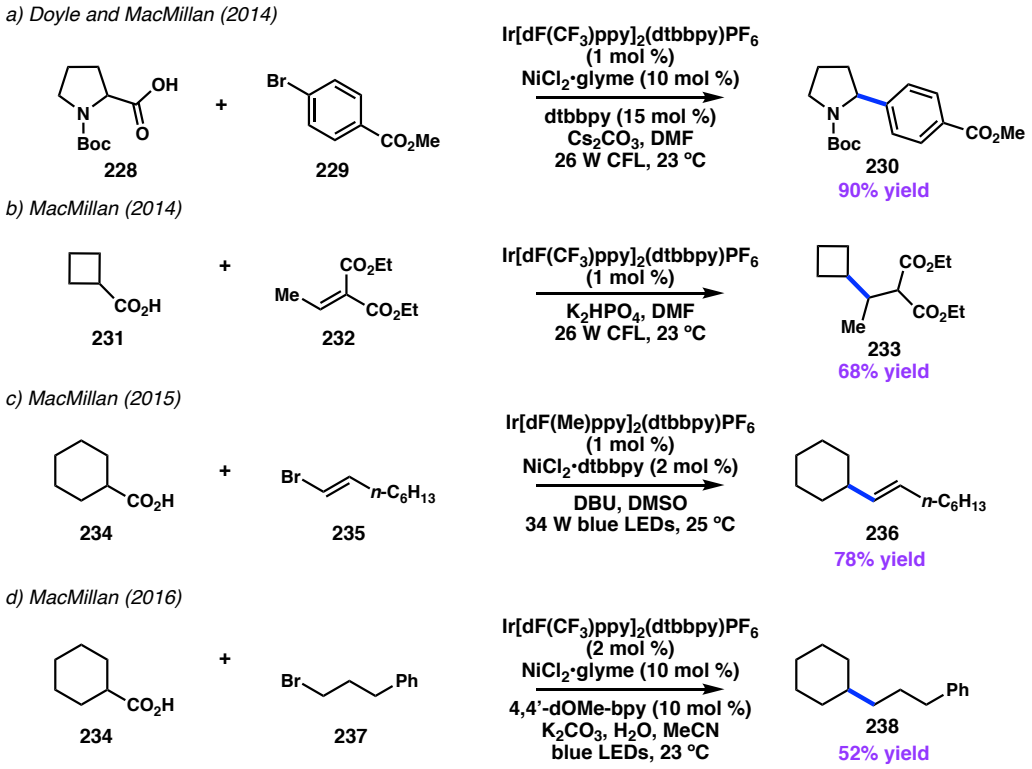
Having established the generality of the C–H arylation step, we turned our attention to diversification at the carbon bearing the 8-aminoquinolinamide. We thought that the carboxylic amide could provide a useful handle that could enable diversification of the α-carbon through either functional group interconversion or decarboxylative cross-coupling

(Scheme **2.1**). During our investigation, the Baran lab disclosed a similar strategy designed to build vicinal difunctionalization using a decarboxylative cross-coupling strategy,[23] indicating the feasibility of a decarboxylative cross-coupling approach to diversify cyclobutane products.

The use of carboxylic acids and redox-active esters in decarboxylative cross-coupling reactions has emerged as a powerful strategy in the construction of carbon-carbon bonds (Scheme **2.13**). In 2014, Doyle and MacMillan reported the decarboxylative cross-coupling between aliphatic carboxylic acids (**228**) and aryl bromides (**229**) under nickel/iridium dual catalysis (Scheme **2.13a**).[40] The iridium photocatalyst is thought to generate an alkyl radical which can be captured by the nickel catalyst and engaged in a nickel-catalyzed cross-coupling reaction. The MacMillan lab also reported a decarboxylative Giese-type addition, using the same iridium catalyst (Scheme **2.13b**).[41]

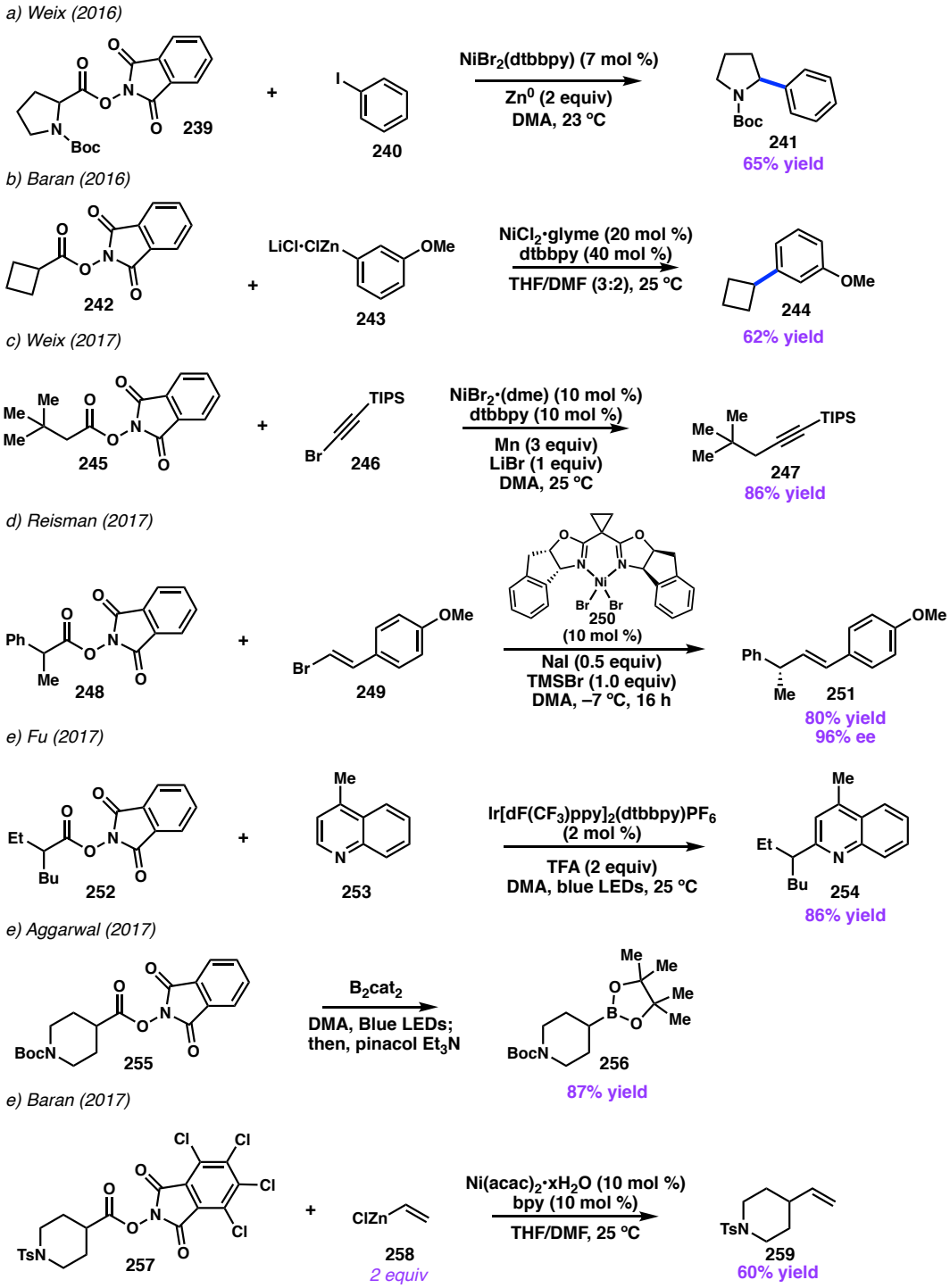
Decarboxylation of acids such as **231** is proposed to generate radical intermediates that can be trapped by a Michael acceptor (**232**) to access adducts such as **233**. The following year, MacMillan and co-workers reported a decarboxylative alkenylation reaction, using the aforementioned iridium/nickel dual-catalysis system (Scheme **2.13c**).[42] They could engage alkyl acids such as **234** in cross-coupling reactions with alkenyl bromides **235** to access cross-coupled products **236**. MacMillan later reported a decarboxylative cross-coupling between carboxylic acids **235** and alkyl bromides **237** to give adducts such as **238**, again using the combination of iridium and nickel catalysis to generate alkylated adducts (Scheme **2.13d**).[43]

Scheme 2.13 *Direct decarboxylative cross-coupling reactions of free acids.*



In addition to using the free carboxylic acids as cross-coupling partners, several groups have recently reported alkyl cross-coupling reactions using redox-active esters as substrates, enabling novel reactivity (Scheme **2.14**). In 2016, the Weix lab reported a reductive decarboxylative arylation reaction between *N*-hydroxyphthalimide (NHP) esters (**239**) and aryl iodides (**240**) to access arylated products (**241**) in good yields (Scheme **2.14a**).[44] The Baran lab has also used these NHP esters to perform a decarboxylative Negishi cross-coupling under nickel catalysis to access similar arylation products (**244**) as well as alkenylation products (**259**) (Scheme **2.14b,e**).[45,46]

Scheme 2.14 *Examples of decarboxylative couplings using NHP esters.*

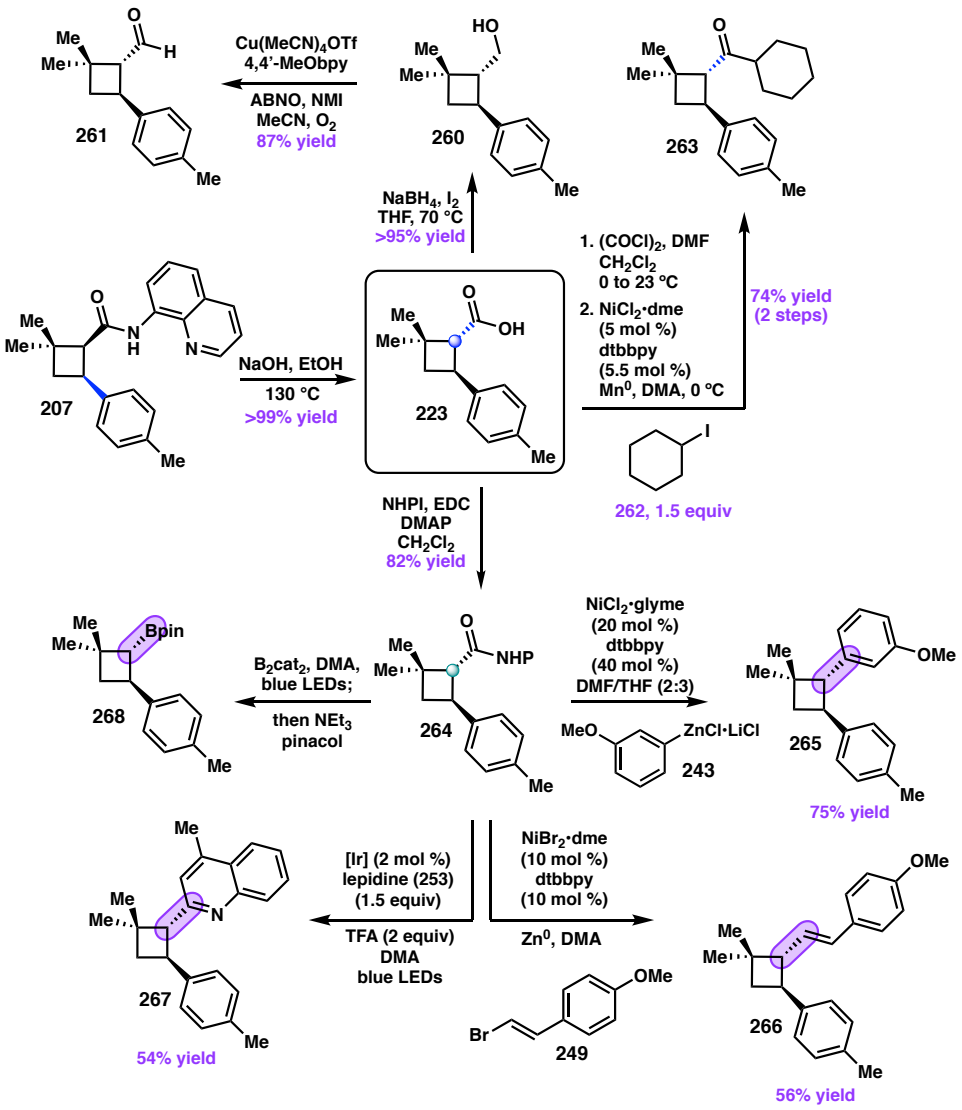


The Weix lab expanded their methodology to include the cross-coupling of alkynyl bromides (**246**), again using the NHP ester (**245**) as a versatile cross-coupling partner (Scheme **2.14c**).[47] Our lab has also explored the asymmetric cross-coupling of these NHP esters (**248**) with styrenyl bromides (**249**) to access enantioenriched benzylic styrenes (**251**) in excellent yield enantioselectivity (Scheme **2.14d**).[48] Groups have also explored activation of NHP esters using irradiation to perform additional cross-coupling reactions, including a decarboxylative Menisci reaction[49] and a decarboxylative borylation (Scheme **2.14e**).[50]

With this precedent in mind, we hypothesized that we could leverage our arylated cyclobutamide products to perform a subsequent cross-coupling reaction, further diversifying these chiral cyclobutane products (Scheme **2.1**). We were excited by the abundance of C–C bond activation strategies that had been reported, and we were eager to explore some of these methodologies with our arylation products. To this end, facile hydrolysis enabled gram-scale synthesis of **223** (Scheme **2.15**). To diversify the products through functional group interconversion, we were pleased to see that reduction of the acid to the primary alcohol **260** could be achieved by generating borane *in situ*, and the corresponding aldehyde **261** could be prepared through a Stahl oxidation.[51] Alternatively, **223** could be converted to the corresponding acid chloride and engaged in a nickel-catalyzed reductive cross-coupling with iodocyclohexane (**262**) to access ketone **263**.[52] In keeping with our goal of quickly building complex, chiral cyclobutane products, we were particularly interested in using the free carboxylic acid as a cross-coupling partner.

Unfortunately, any attempts to engage the free carboxylic acid in direct decarboxylative couplings were unsuccessful.[53]

Scheme 2.15 *Selected transformations of key acid* ***223***.



To further investigate decarboxylative coupling processes, acid **223** was subjected to EDC-mediated coupling with *N*-hydroxyphthalimide to provide NHP ester **264**. Ni-catalyzed coupling of **264** with aryl zinc chloride **243** gave *trans*-diarylcyclobutane **265** in good yield as a single diastereomer.[45] Similarly, NHP ester **264** underwent Ni-catalyzed

reductive alkenylation with styrenyl bromide **249** to furnish cyclobutane **266** in 56% yield.[44,48] Photoinduced decarboxylative Minisci type arylation of **264** under photoredox catalysis delivered quinoline **267**,[49] and borylation of **264** proceeded smoothly to afford boronic ester **268**.[50]

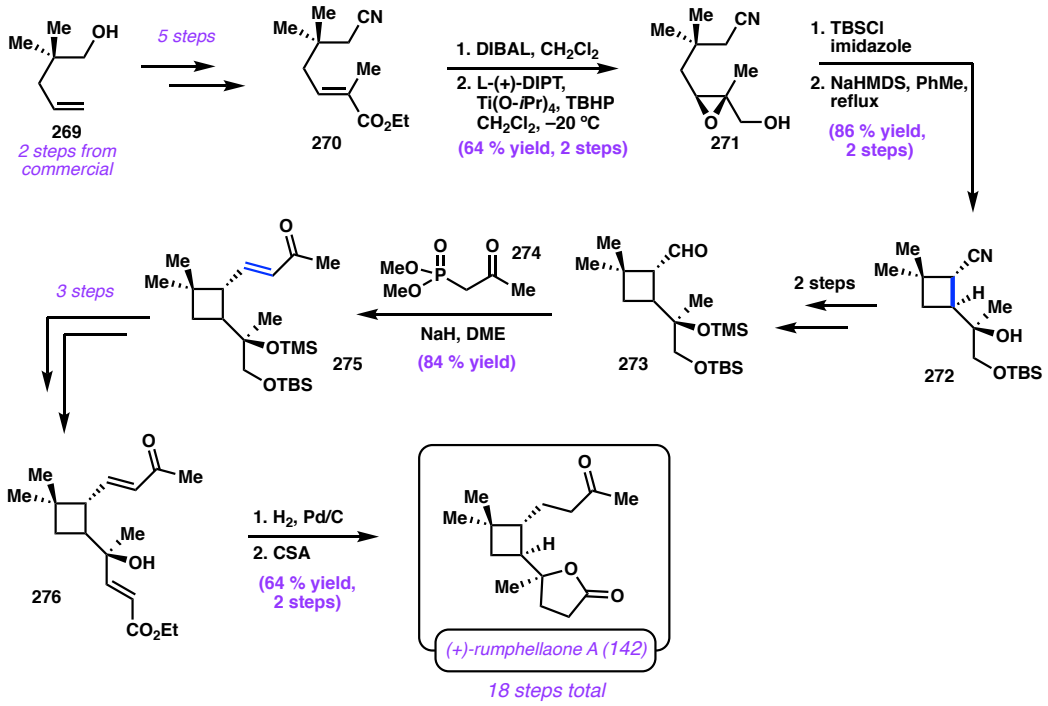
2.5 APPLICATIONS OF CYCLOBUTANE VICINAL DIFUNCTIONALIZATION: TOTAL SYNTHESIS OF (+)-RUMPEHALLONE A

To further demonstrate the utility of this cyclobutane difunctionalization strategy, we designed and executed a synthesis of the natural product (+)-rumphellaone A (**142**). (+)-Rumphellaone A (**142**) was isolated in 2010 from the gorgonian coral, *Rumphella antipathies* and possesses anti-proliferative activity against human T-cell acute lymphoblastic leukemia tumor cells.[7] Having previously targeted the *trans*-fused cyclobutane-containing natural product, (+)-psiguadial B (**8**), we felt that applying our difunctionalization strategy in a total synthesis would elegantly tie together different areas of research within our lab.

(+)-rumphellaone A (**142**) has been the target of a number of total syntheses reported to date. The Kuwahara lab reported an elegant synthesis of (+)-rumphellaone A (**142**) commencing from methyl isobutyrate (Scheme **2.16**).[54,55] Epoxy nitrile **271** can be prepared in short order, using the Sharpless epoxidation protocol to establish the first stereocenter. TBS protection followed by epoxy-nitrile cyclization in the 4-exo-tet manifold provides **272**, which can be elaborated in three

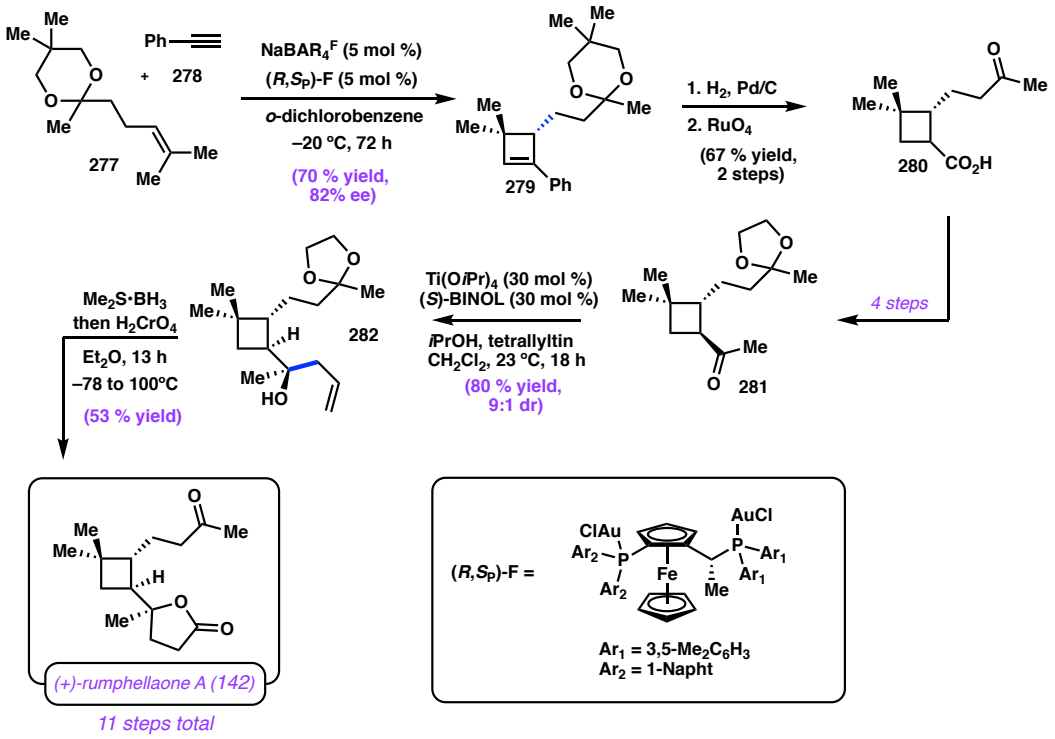
steps to enone **275**. Three additional steps delivers **276**, which can be hydrogenated and lactonized to deliver (+)-rumphellaone A (**142**) in 18 steps total.

Scheme 2.16 *Kuwahara's 2012 synthesis of (+)-rumphellaone A.*



We were also aware of a synthetic campaign from the Echavarren lab in which they were able to carry out a total synthesis of (+)-rumphellaone A (**142**) (Scheme **2.17**).[56] Their synthesis commences with an asymmetric [2+2] cycloaddition between trisubstituted olefin **277** and phenylacetylene **278** using a chiral catalyst. The cycloaddition product **279** can be hydrogenated and then oxidatively cleaved to provide ketone **280**. Four additional steps delivers **281**, which can be subjected to an asymmetric allylation reaction, using (*S*)-BINOL as the chiral controller. Hydroboration followed by an oxidation with chromic acid delivers the natural product **142**.

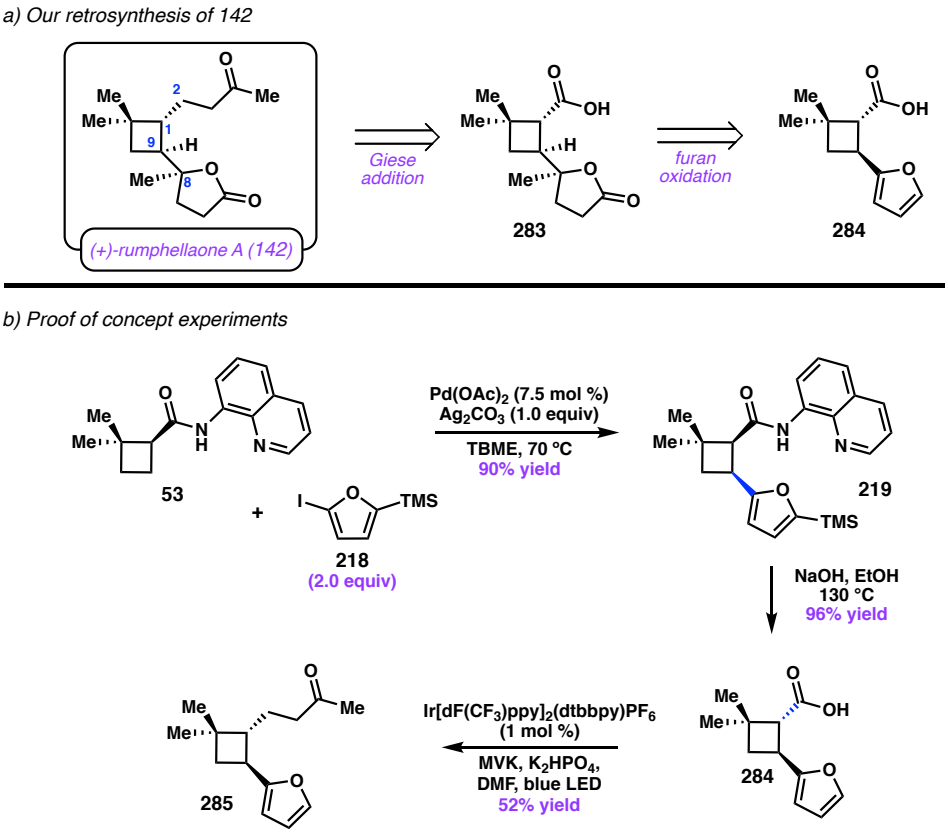
Scheme 2.17 *Echavarren's 2017 synthesis of (+)-rumphellaone A.*



While these syntheses allow for rapid access to **142**, we felt that our cyclobutane difunctionalization strategy could be applied to the synthesis of **142** and shorten the existing route to this compound. Retrosynthetically, we envisioned first disconnecting through C1–C2 bond to give **283** (Scheme **218a**); in the forward sense, the ketone fragment would be incorporated through a decarboxylative Giese addition of **284** to methyl vinyl ketone. The butenolide of **142** could derive from oxidation of furan **284**, which could be prepared from **53** by a directed C–H arylation. As a proof of concept, 8-aminoquinolinamide **53** was subjected to Pd-catalyzed C–H functionalization with furanyl iodide **218** to give *cis*-cyclobutane **219** in 90% yield (Scheme **2.18b**).[57] Hydrolysis and subsequent decarboxylative Giese

reaction with methyl vinyl ketone under photoredox catalysis provided **285** in 50% yield over two steps.

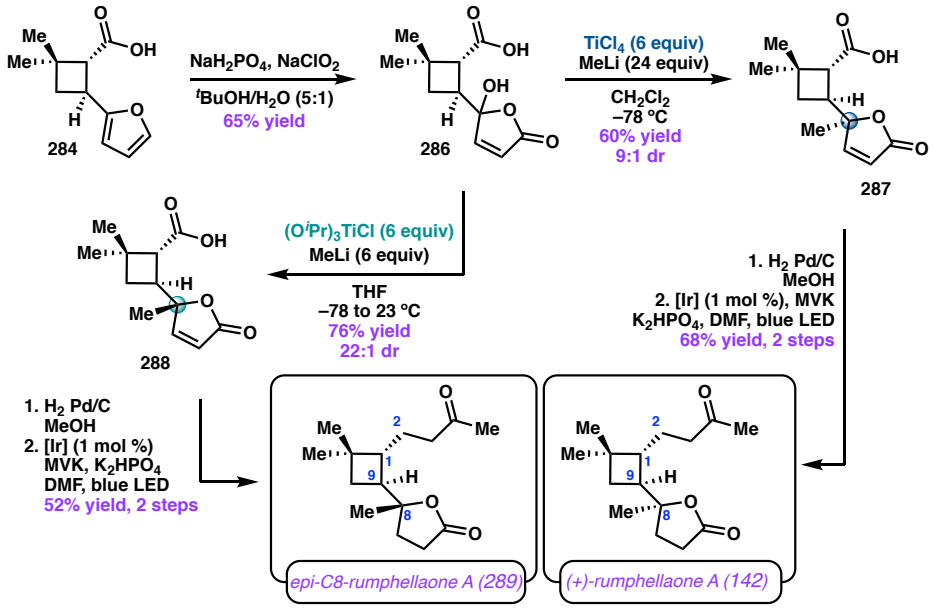
Scheme 2.18 *Our retrosynthesis of (+)-rumphellaone A and proof of concept experiments.*



Having validated the feasibility of the two key cyclobutane functionalization reactions, attention turned to the unmasking of the butenolide functionality prior to the decarboxylative Giese reaction. Treatment of **284** with sodium chlorite under buffered conditions[58] delivered 5-hydroxybutenolide **286** (Scheme **2.19**). The remaining challenge was installation of the C8 methyl substituent with the required *S*-configuration. In prior syntheses of **142**, this stereogenic center was set under the guidance of chiral catalyst

control.[54–56,59] Given that the C8 diastereomers were inseparable by column chromatography, high diastereoselectivity for this methyl addition was important.

Scheme 2.19 *A divergent methylation approach to (+)-rumphellaone A and epi-C8-rumphellaone A.*

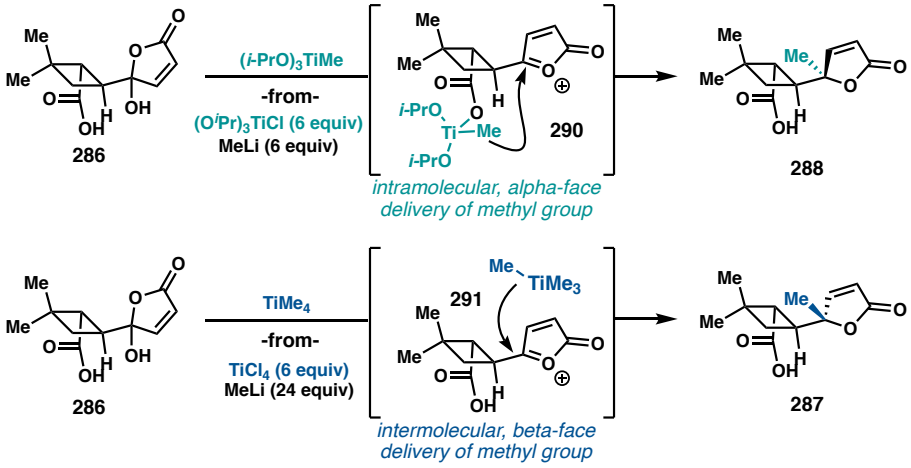


After exploring a range of conditions to effect the methylation, we were pleased to discover that either C8 diastereomer (**287** or **288**) could be prepared using the appropriate methyltitanium reagent (Scheme **2.19**). Thus, addition of **286** to a pre-formed 1:1 mixture of (^{i}PrO)$_3$TiCl and MeLi at –78 °C, with warming to 23 °C, delivered the undesired C8 diastereomer, **288**, in 76% yield and 22:1 dr.[60–62] Alternatively, addition of **286** to a –78 °C solution of Ti(Me)$_4$ in dichloromethane,[60] which was prepared *in situ* by combining MeLi and TiCl$_4$ in a 4:1 ratio, provided the desired diastereomer **287** in 60% yield and 9:1 dr.

We hypothesize that the divergent diastereoselectivity for these two reactions resulted from the different methylating reagents, (^{i}PrO)$_3$TiMe or Ti(Me)$_4$, prepared *in situ*

(Scheme **2.20**). One possible explanation is that **290** is formed by ligand exchange of the carboxylic acid of **286** with (^{i}PrO)$_3$TiMe followed by *intra*molecular delivery of the methyl nucleophile in **290**, providing **288**. Alternatively, we hypothesize that **287** results from intermolecular addition of Ti(Me)$_4$, without the assistance of chelation.

Scheme 2.20 *Stereochemical rationale for divergent methylation of 5-hydroxybutenolides.*



To complete the synthesis, **287** was reduced under standard hydrogenation conditions. Decarboxylative Giese addition to methyl vinyl ketone under the photoredox catalysis conditions we had previously investigated provided (+)-rumphellaone A (**142**) in good yield, completing the synthesis in 9 steps from commercially available material. Epimeric acid **288** could be analogously elaborated to (+)-*epi*-C8-rumphellaone A (**289**).

2.6 CONCLUDING REMARKS

Through a strategy for difunctionalization, we have demonstrated that 8-aminoquinolinamide **53** can serve as a valuable building block for the synthesis of

enantioenriched cyclobutanes. We have prepared a number of heteroarylated and arylated cyclobutane products and demonstrated that we could derivatize them through subsequent C–C bond activation-based cross-coupling reactions. We further illustrated the utility of this method in a 9-step synthesis of (+)-rumphellaone A (**142**). We anticipate that this general strategy could enable the expedient synthesis of additional natural products and other bioactive molecules.

2.7 EXPERIMENTAL SECTION

2.7.1 Materials and Methods

General Procedures. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), 1,4-dioxane, *tert*-butyl methyl ether (TBME), and toluene (PhMe) were dried by passing through activated alumina columns. Methanol (MeOH) was distilled over calcium hydride. Acetonitrile (MeCN), *tert*-butanol (*t*-BuOH), anhydrous *N,N*-dimethylformamide (DMF), anhydrous *N,N*-dimethylacetamide (DMA), chloroform ($CHCl_3$), and absolute ethanol (EtOH) were used as received from Fisher Scientific. Methyl vinyl ketone was dried over K_2CO_3 and $CaCl_2$ and then distilled immediately prior to use. K_2HPO_4 was flame-dried under vacuum and dried at 0.200 Torr overnight and stored in a dessicator. Aryl iodides were purchased from Sigma-Aldrich or Combi-Blocks or prepared according to literature procedures. $NiBr_2$•dme and $NiCl_2$•dme were purchased from Strem and stored in a N_2-filled glovebox. Zinc dust and $Pd(OAc)_2$ were purchased from Strem and stored in a dessicator. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was purchased from Oakwood chemicals and used as received. $Pd(PPh_3)_4$ and Cs_2CO_3 were

purchased from Sigma-Aldrich and stored in a N_2-filled glovebox. All other commercially obtained reagents were purchased from Sigma-Aldrich and used as received unless specifically indicated. Photochemical reactions were conducted using either Kessil A160WE blue LED lamps positioned 3–6 cm from the reactions using a computer fan to keep the reactions at ambient temperature, or 12W blue LED strips lining a beaker wrapped in aluminum foil . Yields of arylation reactions reported are an average of two runs. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel and basic alumina column chromatography was performed as described by Still et al.[63] using silica gel (particle size 0.032–0.063) purchased from Silicycle and aluminum oxide (activated, basic, Brockmann I, 58 Å pore size, powder) purchased from Sigma-Aldrich. ^{1}H and ^{13}C NMR were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Bruker Avance III HD with Prodigy cyroprobe (at 400 MHz and 101 MHz respectively). ^{19}F NMR spectra were recorded on a Varian Inova 400 (at 376 MHz). NMR data is reported relative to internal chloroform (^{1}H, $\delta = 7.26$, ^{13}C, $\delta = 77.2$) or to internal methanol (^{1}H, $\delta = 3.31$, ^{13}C, $\delta = 49.0$) and $PhCF_3$ (^{19}F, $\delta = -63.7$). Data for ^{1}H 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. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using either 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.

Specific optical rotations were recorded on a Jasco P-2000 polarimeter using a 100 mm cell.

2.7.2 Preparative Procedures and Spectroscopic Data

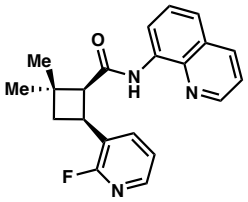
2.7.2.1 C_{sp^3}–H Arylation

General Procedure:

On the bench-top, a 2-dram vial equipped with a stir bar was charged with $Pd(OAc)_2$ (15 mol %, 0.03 mmol), Ag_2CO_3 (1 equiv, 0.2 mmol), cyclobutamide (**4**) (1 equiv, 0.2 mmol), and aryl iodide (2 equiv, 0.4 mmol). TBME (0.2 M, 1 mL) was added to the vial, then the vial was sealed with a Teflon cap and electrical tape and submerged in an oil bath at 90 °C. After approximately 5 minutes for aryl iodide substrates and 30 minutes for heteroaryl iodide substrates, the olive-green mixture became black. The reaction mixture was stirred at 90 °C additional 16 hours, at which point the vial is allowed to cool to room temperature over 15 minutes. The black reaction mixture was diluted with CH_2Cl_2 and filtered over a pad of 20 grams of tightly packed celite. The celite plug was eluted with an additional 100 mL of CH_2Cl_2. Following this, the resultant orange solution was concentrated *in vacuo* and subsequently purified by silica gel column chromatography to give the arylated cyclobutane products. (Note: some substrates required purification with basic alumina as the stationary phase).

Characterization Data for Arylation Products:

195



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 2-fluoro-3-iodopyridine (2 equiv, 89.2 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 4 mL of aqueous ammonium hydroxide (10% EtOAc/2% Et_3N/88% hexanes → 15% EtOAc/2% Et_3N/83% hexanes → 20% EtOAc/2% Et_3N/78% hexanes → 35% EtOAc/2% Et_3N/63% hexanes) to give a white foam.

Run 1: (56.1 mg, 80%), Run 2: (56.4 mg, 81%)

$\mathbf{R_f}$ = 0.22 (silica gel, 20% EtOAc/Hex, UV, p-Anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = +60.8° (c = 0.415, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 8.77 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.54 (dd, *J* = 7.0, 2.1 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.96 (ddt, *J* = 4.9, 2.0, 1.0 Hz, 1H), 7.72 (ddq, *J* = 9.9, 7.5, 1.2, 0.7 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.15 (ddd, *J* = 7.1, 4.9, 1.9 Hz, 1H), 3.99 (dtd, *J* = 11.0, 8.6, 1.1 Hz, 1H), 3.44 (ddt, *J* = 8.4, 2.5, 1.3 Hz, 1H), 2.76 (t, *J* = 10.7 Hz, 1H), 2.11 (ddd, *J* = 10.4, 8.4, 3.0 Hz, 1H), 1.53 (s, 3H), 1.19 (s, 3H).

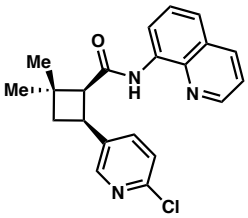
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 161.5 (d, J_{C-F} = 237 Hz), 148.2, 144.6 (d, J_{C-F} = 14.7 Hz), 139.3 (d, J_{C-F} = 6.1 Hz), 138.4, 136.3, 134.4, 127.9, 127.3, 124.2 (d, J_{C-F} = 31.2 Hz), 121.6, 121.4, 121.3 (d, J_{C-F} = 4.0 Hz), 116.4, 57.0, 36.4 (d, J_{C-F} = 14.8 Hz), 30.8, 30.7, 29.8, 25.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -71.52 (d, *J* = 10.1 Hz).

FTIR (NaCl, thin film, cm^{-1}): 3355, 3058, 2954, 2930, 2866, 1682, 1605, 1577, 1524, 1486, 1431, 1388, 1372, 1324, 1261, 1240, 1162, 1132, 1112, 826, 793, 758.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{21}H_{21}FN_3O$ $[M+H]^+$: 350.1663; found: 350.1659.

196



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-chloropyridine (2 equiv, 95.8 mg, 0.4 mmol). The crude residue was purified by column chromatography using basic alumina as the stationary phase (0 → 1% MeOH/CH_2Cl_2) to give a colorless foam.

Run 1: (50.6 mg, 69%), Run 2: (49.7 mg, 68%)

R_f = 0.24 (silica gel, 40% EtOAc/Hex, UV).

$[\alpha]_D^{25}$ = +81.1° (c = 4.3, $CHCl_3$).

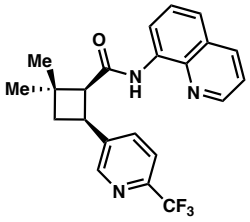
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.58 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.22 (dt, *J* = 2.6, 0.8 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.17 (d, *J* = 8.2 Hz, 1H), 3.96 (q, *J* = 11.0, 8.5 Hz, 1H), 3.38 (ddd, *J* = 8.5, 3.0, 0.8 Hz, 1H), 2.76 (t, *J* = 10.7 Hz, 1H), 2.15 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.52 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 148.8, 148.5, 148.1, 138.3, 137.7, 136.5, 136.3, 134.2, 127.9, 127.4, 123.5, 121.7, 121.6, 116.5, 57.4, 37.4, 36.3, 33.3, 29.8, 29.8, 25.0.

FTIR (NaCl, thin film, cm^{-1}): 3350, 2954, 1682, 1524, 1485, 1460, 1424, 1386, 1324, 1260, 1162, 1133, 1104, 826, 792, 755, 666.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{21}H_{21}ClN_3O$ $[M+H]^+$: 366.1368; found: 366.1370.

197



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-trifluoromethylpyridine (2 equiv, 95.8 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 5 mL of aqueous ammonium hydroxide (5% EtOAc/2% Et_3N/93% hexanes → 10% EtOAc/2% Et_3N/88% hexanes → 15% EtOAc/2% Et_3N/83% hexanes → 20% EtOAc/2% Et_3N/78% hexanes) to give a pale, yellow foam.

Run 1: (71.6 mg, 90%), Run 2: (68.2 mg, 85%)

R_f = 0.19 (silica gel, 20% EtOAc/Hex, UV).

$[\alpha]_D^{25}$ = +67.7° (c = 4.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.52 – 8.41 (m, 2H), 8.04 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.46 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.41 – 7.28 (m, 3H), 3.95 (q, *J* = 11.0, 8.5 Hz, 1H), 3.37 (ddd, *J* = 8.4, 2.9, 0.9 Hz, 1H), 2.73 (t, *J* = 10.7 Hz, 1H), 2.12 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 148.8, 148.2, 145.5 (q, J_{C-F} = 35 Hz), 141.2, 138.3, 136.5, 135.7, 134.1, 128.0, 127.4, 123.2, 121.7, 120.5, 119.9, 119.9, 119.8, 119.8, 116.5, 57.4, 37.3, 36.5, 33.7, 29.8, 25.0.

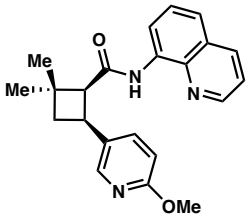
^{19}F NMR (282 MHz, $CDCl_3$): δ –68.6.

FTIR (NaCl, thin film, cm^{-1}): 3351, 2957, 1682, 1524, 1486, 1425, 1387, 1340, 1261, 1164, 1134, 1088, 1030, 826, 792, 756, 667.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{21}F_3N_3O$ $[M+H]^+$: 400.1631; found: 400.1621.

198

Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-methoxypyridine (2 equiv, 94.0 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 4 mL of aqueous ammonium hydroxide (10% EtOAc/2% Et_3N/88% hexanes → 15% EtOAc/2% Et_3N/83% hexanes → 20% EtOAc/2% Et_3N/78% hexanes → 30% EtOAc/2% Et_3N/68% hexanes) to give a white solid.



Run 1: (34.9 mg, 48%), Run 2: (36.1 mg, 50%)

R_f = 0.14 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +61.1° (c = 0.415, $CHCl_3$).

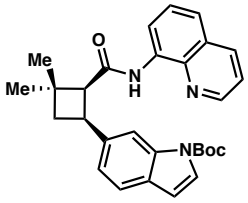
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (dd, *J* = 5.3, 3.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.01 (dt, *J* = 2.5, 0.9 Hz, 1H), 7.54 (ddd, *J* = 8.6, 2.5, 0.7 Hz, 1H), 7.46 – 7.39 (m, 3H), 6.61 (dd, *J* = 8.6, 0.7 Hz, 1H), 3.96 (qd, *J* = 11.0, 8.6, 1.1 Hz, 1H), 3.84 (s, 3H), 3.33 (ddd, *J* = 8.7, 2.9, 0.8 Hz, 1H), 2.76 (t, *J* = 10.8 Hz, 1H), 2.14 (ddd, *J* = 10.4, 8.6, 3.0 Hz, 1H), 1.51 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 162.7, 148.1, 145.3, 138.4, 138.0, 136.4, 134.5, 129.6, 128.0, 127.5, 121.6, 121.4, 116.5, 110.1, 57.6, 53.4, 37.7, 36.1, 33.4, 30.1, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3352, 2922, 2850, 2351, 1682, 1606, 1574, 1523, 1494, 1486, 1424, 1385, 1324, 1285, 1259, 1160, 1132, 1032, 826, 792, 756.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{24}N_3O_2$ $[M+H]^+$: 362.1863; found: 362.1856

199



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 6-iodo-N-Boc-indole (2 equiv, 137 mg, 0.4 mmol). The crude residue was purified by column chromatography (10% → 15% EtOAc/hexanes) to give a colorless foam.

Run 1: (56.1 mg, 60%), Run 2: (62.8 mg, 67%)

R_f = 0.36 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +114.7° (c = 5.7, $CHCl_3$).

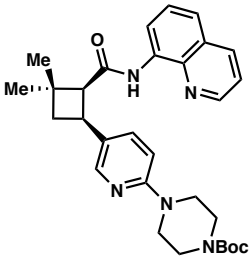
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.65 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.60 (dd, *J* = 6.3, 2.8 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.03 (s, 1H), 7.47 (d, *J* = 3.7 Hz, 1H), 7.43 – 7.32 (m, 4H), 7.09 (dt, *J* = 8.1, 1.1 Hz, 1H), 6.44 (dd, *J* = 3.7, 0.8 Hz, 1H), 4.19 (dt, *J* = 10.9, 8.6 Hz, 1H), 3.44 (dd, *J* = 8.7, 2.9 Hz, 1H), 2.85 (t, *J* = 10.7 Hz, 1H), 2.25 (ddd, *J* = 10.3, 8.6, 3.0 Hz, 1H), 1.61 (s, 9H), 1.54 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 150.0, 147.9, 138.6, 138.4, 136.3, 135.5, 134.7, 128.7, 127.9, 127.5, 125.3, 121.6, 121.5, 121.1, 120.5, 116.5, 113.4, 107.4, 83.4, 57.9, 38.2, 36.4, 35.9, 30.2, 28.3, 25.3.

FTIR (NaCl, thin film, cm^{-1}): 3358, 3008, 2954, 2929, 2866, 1730, 1686, 1618, 1578, 1523, 1485, 1424, 1386, 1370, 1338, 1253, 1214, 1151, 117, 1077, 1022, 826, 816, 756.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{29}H_{32}N_3O_3$ $[M+H]^+$: 470.2438; found: 470.2449.

200



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-(5-iodopyrin-2-yl)piperazine-1-carboxylic acid *tert*-butyl ester (2 equiv, 156 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 5 mL of aqueous ammonium hydroxide (20% EtOAc/2% Et_3N/78% hexanes → 30% EtOAc/2% Et_3N/68% hexanes → 40% EtOAc/2% Et_3N/58% hexanes) to give a pale, yellow foam.

Run 1: (79.9 mg, 77%), Run 2: (84.6 mg, 82%)

R_f = 0.27 (silica gel, 40% EtOAc/Hex, UV, *p*-anisaldehyde). $[\alpha]_D^{25}$ = +69.2° (c = 5.1, $CHCl_3$).

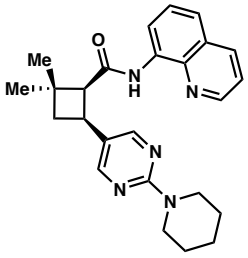
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (p, *J* = 4.4 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.06 (dt, *J* = 2.5, 0.8 Hz, 1H), 7.50 (ddd, *J* = 8.7, 2.5, 0.7 Hz, 1H), 7.46 – 7.37 (m, 3H), 6.53 (dd, *J* = 8.8, 0.8 Hz, 1H), 3.93 (dt, *J* = 11.0, 8.6 Hz, 1H), 3.45 (dd, *J* = 6.6, 3.5 Hz, 4H), 3.39 (dd, *J* = 6.3, 3.6 Hz, 4H), 3.30 (dd, *J* = 8.4, 2.9 Hz, 1H), 2.74 (t, *J* = 10.8 Hz, 1H), 2.10 (ddd, *J* = 10.4, 8.5, 2.9 Hz, 1H), 1.51 (s, 4H), 1.47 (s, 9H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 158.0, 154.9, 148.0, 146.8, 138.4, 137.0, 136.4, 134.5, 127.9, 127.4, 126.4, 121.6, 121.2, 116.4, 106.9, 79.9, 57.7, 45.5, 37.6, 35.9, 33.5, 30.1, 28.5, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3357, 3007, 2973, 2928, 2864, 2360, 1686, 1605, 1560, 1524, 1486, 1424, 1391, 1324, 1241, 1166, 1129, 1084, 1000, 934, 864, 826, 792, 756, 686, 666.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{30}H_{38}N_5O_3$ $[M+H]^+$: 516.2969; found: 516.2955.

201



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-(1-piperidinyl)pyrimidine (2 equiv, 116 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 5 mL of aqueous ammonium hydroxide (10% EtOAc/2% Et_3N/88% hexanes → 20% EtOAc/2% Et_3N/78% hexanes → 30% EtOAc/2% Et_3N/68% hexanes) to give a pale yellow foam.

Run 1: (63.0 mg, 76%), Run 2: (60.6 mg, 73%)

R_f = 0.44 (silica gel, 40% EtOAc/Hex, UV).

$[\alpha]_D^{25}$ = +83.3° (c = 3.1, $CHCl_3$).

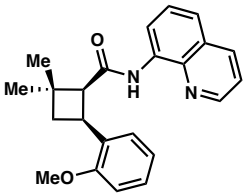
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.67 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.25 (s, 2H), 8.10 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 2H), 3.81 (dt, *J* = 11.0, 8.6 Hz, 1H), 3.67 (dd, *J* = 6.2, 4.9 Hz, 4H), 3.27 (dd, *J* = 8.6, 2.9 Hz, 1H), 2.74 (t, *J* = 10.8 Hz, 1H), 2.07 (ddd, *J* = 10.6, 8.5, 2.9 Hz, 1H), 1.60 (p, *J* = 5.5 Hz, 2H), 1.52 (qd, *J* = 5.6, 5.1, 2.3 Hz, 4H), 1.49 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 160.8, 157.1, 148.1, 138.4, 136.4, 134.5, 127.9, 127.5, 121.6, 121.3, 120.8, 116.5, 57.4, 45.0, 37.3, 36.1, 31.8, 30.0, 25.8, 25.1, 25.0.

FTIR (NaCl, thin film, cm^{-1}): 3355, 2031, 2853, 1682, 1603, 1524, 1485, 1462, 1447, 1366, 1324, 1274, 1256, 1160, 1025, 946, 826, 792, 754.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{25}H_{30}N_5O$ $[M+H]^+$: 416.2445; found: 416.2440.

202



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 2-iodoanisole (2 equiv, 93.6 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20% EtOAc/Hexanes) to give a colorless foam.

Run 1: (54.4 mg, 75%), Run 2: (61.2 mg, 84%)

R_f = 0.48 (silica gel, 30% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +84.8° (c = 3.3, $CHCl_3$).

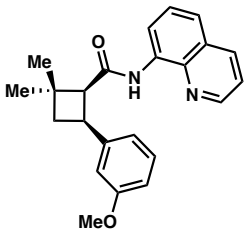
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.60 (dd, *J* = 4.9, 4.2 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.24 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.09 (dddd, *J* = 8.2, 7.4, 1.8, 0.8 Hz, 1H), 6.96 (tdd, *J* = 7.5, 1.1, 0.4 Hz, 1H), 6.61 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.09 – 3.95 (m, 1H), 3.62 (s, 3H), 3.46 (ddd, *J* = 8.6, 2.9, 0.8 Hz, 1H), 2.74 (t, *J* = 10.8 Hz, 1H), 2.13 (ddd, *J* = 10.4, 8.4, 2.9 Hz, 1H), 1.53 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.13, 157.19, 147.90, 138.41, 136.31, 134.88, 130.18, 127.92, 127.66, 127.54, 127.00, 121.45, 120.75, 120.43, 116.27, 109.43, 58.05, 55.05, 37.10, 35.89, 32.81, 30.33, 25.14.

FTIR (NaCl, thin film, cm^{-1}): 3366, 2952, 5927, 2863, 2361, 1685, 1523, 1485, 1464, 1424, 1324, 1241, 1161, 1132, 1161, 1029, 826, 792, 751.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911; found: 361.1925.

203



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 3-iodoanisole (2 equiv, 93.6 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20% EtOAc/Hexanes) to give a white solid.

Run 1: (59.0 mg, 82%), Run 2: (58.3 mg, 81%)

$\mathbf{R_f}$ = 0.36 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = +61.6° (c = 0.4, $CHCl_3$).

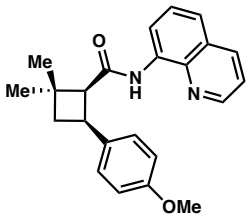
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.64 (p, *J* = 4.3 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.82 (ddt, *J* = 7.6, 1.8, 1.0 Hz, 1H), 6.77 (dt, *J* = 2.7, 1.3 Hz, 1H), 6.63 (ddt, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.03 (dtd, *J* = 11.0, 8.6, 1.1 Hz, 1H), 3.67 (s, 3H), 3.39 (ddd, *J* = 8.7, 2.9, 0.8 Hz, 1H), 2.76 (t, *J* = 10.7 Hz, 1H), 2.16 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.51 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 159.5, 148.0, 143.7, 138.4, 136.4, 134.6, 129.1, 127.9, 127.5, 121.5, 121.2, 119.1, 116.5, 112.3, 111.3, 57.7, 55.1, 37.8, 36.0, 35.8, 30.2, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3357, 2952, 2925, 1684, 1600, 1582, 1521, 1485, 1424, 1386, 1323, 1259, 1160, 1049, 878, 826, 790, 756, 694.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911; found: 361.1915.

204



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodoanisole (2 equiv, 93.6 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15% EtOAc/Hexanes) to give a white, amorphous solid.

Run 1: (47.7 mg, 66%), Run 2: (51.2 mg, 71%)

R_f = 0.23 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +59.8° (c = 1.3, $CHCl_3$).

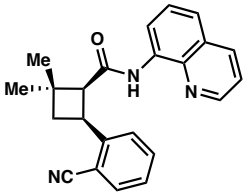
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.63 (p, *J* = 4.4 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.20 – 7.13 (m, 2H), 6.80 – 6.73 (m, 2H), 4.00 (q, *J* = 11.1, 8.6 Hz, 1H), 3.70 (s, 3H), 3.34 (ddd, *J* = 8.7, 3.0, 0.8 Hz, 1H), 2.75 (t, *J* = 10.8 Hz, 1H), 2.13 (ddd, *J* = 10.4, 8.6, 3.0 Hz, 1H), 1.51 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 157.7, 148.0, 138.4, 136.4, 134.6, 133.7, 127.9, 127.5, 121.5, 121.1, 116.5, 113.6, 57.7, 55.3, 37.9, 35.7, 35.5, 30.2, 25.2.

FTIR (NaCl, thin film, cm^{-1}): 2926, 2361, 1685, 1523, 1485, 1288, 1324, 1247, 1160, 1038, 826, 772.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911; found: 361.1921.

205



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 2-iodobenzonitrile (2 equiv, 91.8 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15% EtOAc/Hexanes) to give a pale, yellow foam.

Run 1: (57.6 mg, 81%), Run 2: (64.7 mg, 91%)

$\mathbf{R}_f$ = 0.55 (silica gel, 30% EtOAc/Hex, UV, *p*-anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = –24.4° (c = 5.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.53 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 (td, *J* = 8.0, 7.6, 1.2 Hz, 1H), 7.51 – 7.35 (m, 5H), 7.21 (tdd, *J* = 7.6, 1.3, 0.7 Hz, 1H), 4.21 (dt, *J* = 11.1, 8.3, 7.8 Hz, 1H), 3.74 (ddd, *J* = 8.3, 3.0, 0.8 Hz, 1H), 2.87 (t, *J* = 10.7 Hz, 1H), 2.16 (ddd, *J* = 10.4, 8.3, 3.1 Hz, 1H), 1.57 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 148.3, 146.9, 138.5, 136.3, 134.5, 132.6, 128.1, 127.9, 127.2, 126.3, 121.7, 121.4, 118.8, 116.3, 110.6, 57.7, 36.6, 36.1, 35.2, 29.8, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3353, 2954, 2361, 2222, 1683, 1523, 1485, 1424, 1388, 1323, 1260, 1161, 826, 791, 755, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{21}N_3O$ $[M+H]^+$: 356.1757; found: 356.1773.

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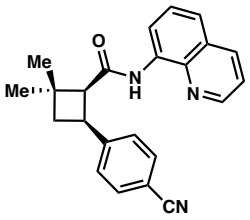


Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodobenzonitrile (2 equiv, 91.8 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20 →25 % EtOAc/Hexanes) to give a pale, yellow foam.

Run 1: (50.5 mg, 71%), Run 2: (53.3 mg, 75%)

$\mathbf{R}_f$ = 0.32 (silica gel, 30% EtOAc/Hex, UV, *p*-anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = +102.7° (c = 5.1, $CHCl_3$).

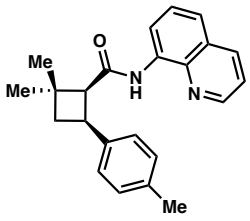
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.56 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50 (dt, *J* = 8.3, 1.8 Hz, 2H), 7.49 – 7.37 (m, 3H), 7.33 – 7.24 (m, 2H), 4.02 (dt, *J* = 10.8, 8.3 Hz, 1H), 3.43 (ddd, *J* = 8.5, 3.0, 0.8 Hz, 1H), 2.77 (t, *J* = 10.7 Hz, 1H), 2.18 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.53 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 148.4, 148.2, 138.3, 136.5, 134.2, 131.9, 128.0, 127.5, 127.3, 121.7, 121.6, 119.5, 116.5, 109.3, 57.7, 37.5, 36.1, 36.0, 29.9, 25.0.

FTIR (NaCl, thin film, cm^{-1}): 3353, 2954, 2930, 2361, 2226, 1684, 1608, 1524, 1486, 1424, 1288, 1323, 1161, 826, 792, 755, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{22}N_3O$ $[M+H]^+$: 356.1757; found: 356.1752.

207



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodotoluene (2 equiv, 87.2 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20% EtOAc/Hexanes) to give a white, amorphous solid.

Run 1: (54.1 mg, 79%), Run 2: (55.9 mg, 81%)

R_f = 0.29 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +54.2° (c = 2.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.65 (h, *J* = 4.2 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.50 – 7.36 (m, 3H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 7.4 Hz, 2H), 4.01 (td, *J* = 10.8, 8.1 Hz, 1H), 3.37 (ddd, *J* = 8.7, 2.9, 0.8 Hz,

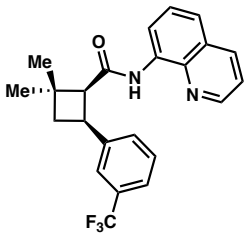
1H), 2.76 (t, *J* = 10.8 Hz, 1H), 2.24 (s, 3H), 2.14 (ddd, *J* = 10.4, 8.6, 2.9 Hz, 1H), 1.51 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 148.0, 138.7, 138.4, 136.4, 135.0, 134.7, 128.9, 127.9, 127.5, 126.7, 121.5, 121.1, 116.5, 57.7, 37.8, 35.8, 35.7, 30.2, 25.2, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 3360, 2924, 2359, 1686, 1522 1485, 1424, 1386, 1324, 1160, 826, 792.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O$ $[M+H]^+$: 345.1961; found: 345.1971.

208



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 3-iodotrifluorotoluene (2 equiv, 109.1 mg, 0.4 mmol). The crude residue was purified by column chromatography (10% EtOAc/Hexanes) to give a colorless oil.

Run 1: (67.7 mg, 85%), Run 2: (62.9 mg, 79%)

R_f = 0.23 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +47.3° (c = 3.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.57 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50 – 7.36 (m, 5H), 7.39 – 7.26 (m, 2H), 4.05 (dt, *J* = 11.0, 8.7 Hz, 1H), 3.42 (ddd, *J* = 8.6, 3.0, 0.8 Hz, 1H), 2.80 (t, *J* = 10.8 Hz, 1H), 2.20 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.53 (s, 3H), 1.23 (s, 3H).

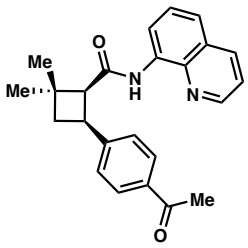
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 148.2, 143.2, 138.5, 136.6, 134.5, 130.4 (q, J_{C-F} = 32 Hz), 130.3, 128.5, 128.1, 127.6, 125.9, 123.7 (q, J_{C-F} = 3.7 Hz), 123.2, 122.8 (q, J_{C-F} = 3.8 Hz), 121.7, 121.5, 116.6, 57.8, 37.8, 36.1, 36.0, 30.2, 30.0, 25.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.50.

FTIR (NaCl, thin film, cm^{-1}): 3355, 2931, 2360, 1684, 1523, 1486, 1425, 1388, 1324, 1162, 1122, 1072, 901, 826, 793, 756, 701, 659.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{22}F_3N_2O$ $[M+H]^+$: 399.1679; found: 399.1679.

209



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodoacetophenone (2 equiv, 98.7 mg, 0.4 mmol). The crude residue was purified by column chromatography (20% EtOAc/Hexanes) to give a white, amorphous solid.

Run 1: (57.3 mg, 77%), Run 2: (56.6 mg, 76%)

R_f = 0.41 (silica gel, 40% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +95.0° (c = 3.0, $CHCl_3$).

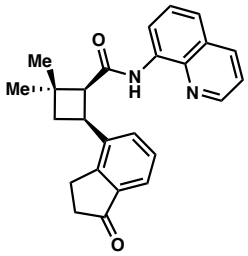
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.85 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.66 (dd, *J* = 7.1, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.51 (dd, *J* = 8.5, 4.1 Hz, 2H), 7.48 (q, *J* = 9.2, 8.2, 8.2 Hz, 1H), 7.39 – 7.33 (m, 2H), 4.12 (td, *J* = 11.3, 9.7, 8.4 Hz, 1H), 3.51 (ddd, *J* = 8.6, 2.9, 0.8 Hz, 1H), 2.88 (t, *J* = 10.7 Hz, 1H), 2.58 (s, 3H), 2.26 (ddd, *J* = 10.3, 8.5, 3.0 Hz, 1H), 1.61 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1, 170.1, 148.5, 148.1, 138.4, 136.5, 134.8, 134.4, 128.4, 128.0, 127.5, 126.7, 121.6, 121.4, 116.5, 57.8, 37.7, 36.1, 36.0, 30.0, 26.7, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3354, 2954, 2928, 2866, 1678, 1606, 1523, 1485, 1424, 1387, 1323, 1267, 1161, 956, 826, 792, 754, 657.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{24}H_{25}N_2O_2$ $[M+H]^+$: 373.1911; found: 373.1900.

210



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodo-1-indanone (2 equiv, 103.5 mg, 0.4 mmol). The crude residue was purified by column chromatography (30% EtOAc/Hexanes) to give a pale, yellow foam.

Run 1: (43.4 mg, 56%), Run 2: (39.7 mg, 52%)

R_f = 0.32 (silica gel, 40% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +2.0° (c = 5.0, $CHCl_3$).

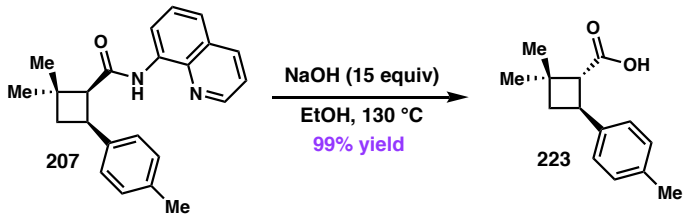
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.74 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.54 (dd, *J* = 7.1, 2.0 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 (ddt, *J* = 17.3, 7.6, 1.1 Hz, 2H), 7.46 – 7.33 (m, 4H), 4.07 (dt, *J* = 11.2, 8.4 Hz, 1H), 3.47 (ddd, *J* = 8.4, 3.0, 0.9 Hz, 1H), 3.10 (ddd, *J* = 17.1, 7.8, 3.8 Hz, 1H), 2.98 (ddd, *J* = 17.1, 7.6, 3.9 Hz, 1H), 2.92 (t, *J* = 10.8 Hz, 1H), 2.57 (dddd, *J* = 32.0, 19.4, 7.8, 3.7 Hz, 2H), 2.18 (ddd, *J* = 10.5, 8.4, 3.1 Hz, 1H), 1.58 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 170.1, 153.3, 148.1, 139.5, 138.3, 136.8, 136.5, 134.2, 132.9, 127.9, 127.5, 127.4, 121.6, 121.5, 121.4, 116.6, 57.2, 37.0, 36.5, 36.2, 34.1, 30.1, 25.2, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3353, 3012, 2954, 2927, 2866, 2359, 1709, 1587, 1523, 1485, 1425, 1386, 1324, 1265, 1162, 1055, 827, 790, 754, 666.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{25}H_{25}N_2O_2$ $[M+H]^+$: 385.1911; found: 385.1921.

2.7.2.2 Cyclobutane Derivatization



A 48 mL pressure flask was charged with *cis*-cyclobutamide **207** (693 mg, 2.01 mmol, 1.00 equiv), sodium hydroxide (1.21 g, 30.2 mmol, 15 equiv), and absolute ethanol (8.5 mL, 0.24 M). The flask was sealed and placed in a pre-heated oil bath (130 ºC) and stirred for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The crude residue was diluted with 1 M aq HCl (38 mL) and EtOAc (38 mL). The organic and aqueous layers were separated, and the organic layer was washed with 1 M HCl (2 x 38 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reddish solid was purified by silica gel flash chromatography (15 → 20% EtOAc/hexanes) to afford **223** as an off-white solid (443 mg, 99% yield).

R_f = 0.31 (silica gel, 20% EtOAc/Hexanes, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +123.6° (c = 0.28, $CHCl_3$).

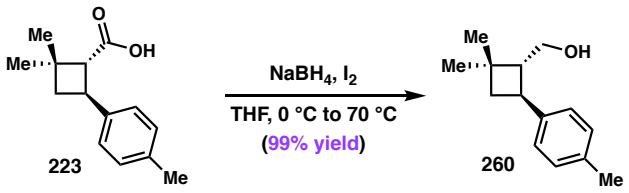
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 1.1 Hz, 4H), 3.74 (q, *J* = 9.8 Hz, 1H), 2.91 (dd, *J* = 10.0, 0.8 Hz, 1H), 2.32 (s, 3H), 2.11 (ddd, *J* = 10.9, 8.9, 0.9 Hz, 1H), 1.95 (t, *J* = 10.5 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.8, 140.7, 135.9, 129.2, 126.6, 55.2, 39.4, 36.6, 35.1, 30.6, 23.6, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 3021, 2957, 2927, 2867, 2731, 2647,1699, 1516, 1464, 1421 1370, 1281, 1238, 1162 1118, 937, 806, 716.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{22}NO_2$ $[M+NH_4]^+$: 236.1645; found: 236.1645.

Acid reduction to provide **260**.



A 2-dram vial containing a stir bar was charged with **223** (87 mg, 0.400 mmol, 1.00 equiv) and $NaBH_4$ (37.8 mg, 1.00 mmol, 2.5 equiv). The vial was then evacuated and backfilled with N_2 three times. THF (3.0 mL) was added and the reaction mixture was cooled to 0 °C. I_2 (121.8 mg, 0.480 mmol, 1.2 equiv) was then added as a solution in THF (1 mL) dropwise. The vial was then sealed with a Teflon-lined cap, placed in a pre-heated oil bath (70 ºC), and allowed to stir overnight. Once the reaction was complete, the reaction was cooled to room temperature and quenched with MeOH until bubbling stopped and the reaction mixture turned clear. The reaction mixture was concentrated, then treated with 20% KOH (4 mL) and allowed to stir for 5 h at room temperature. The aqueous layer was then extracted with EtOAc (6 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford **260** (82.2 mg, quant yield) as a white solid which was carried forward without further purification.

R_f = 0.38 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +57.0° (c = 0.42, $CHCl_3$).

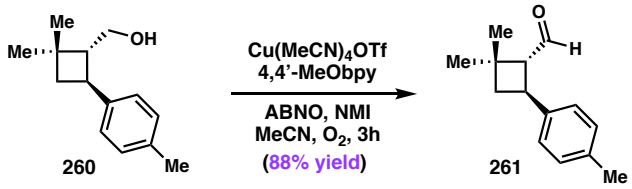
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 – 7.08 (m, 4H), 3.75 (qd, *J* = 11.0, 7.2 Hz, 2H), 3.06 (q, *J* = 9.5 Hz, 1H), 2.34 (s, 3H), 2.28 (dddd, *J* = 9.4, 8.3, 6.1, 0.7 Hz, 1H), 2.05 (ddd, *J* = 10.8, 8.7, 0.8 Hz, 1H), 1.82 (t, *J* = 10.3 Hz, 1H), 1.21 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.9, 135.6, 129.1, 126.7, 63.6, 53.9, 40.6, 37.6, 33.7, 31.4, 22.5, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3248, 2954, 2926, 2896, 2864, 1896, 1514, 1453, 1413, 1379, 1368, 1326, 1260, 1218, 1190, 1110, 1092, 1033, 1013, 812, 772.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{24}NO$ $[M+NH_4]^+$: 222.1852; found: 222.1846.

Oxidation of **260** to prepare aldehyde **261**



260 (0.400 mmol, 1.00 equiv) was dissolved in 1.2 mL MeCN in a 20 mL scintillation vial. In a separate vial, $Cu(MeCN)_4OTf$ (7.5 mg, 0.02 mmol, 0.05 equiv) and 4,4'-MeObpy (4.3 mg, 0.02 mmol, 0.05 equiv)) were dissolved in 0.4 mL MeCN and allowed to stir until the solution turned an opaque blue. To this vial was added a solution of ABNO (0.6 mg, 0.004 mmol, 0.01 equiv) and *N*-methylimidazole (3.3 mg, 0.04 mmol, 0.10 equiv) in 0.4 mL MeCN. Once the catalyst solution turned green, it was added to the reaction mixuture and allowed to stir open to air. After 3 h and 6 h, additional portions of catalyst ($Cu(MeCN)_4OTf$ (7.5 mg, 0.02 mmol, 0.05 equiv), 4,4'-MeObpy (4.3 mg, 0.02 mmol, 0.05 equiv) ABNO (0.6 mg, 0.004 mmol, 0.01 equiv), and *N*-methylimidazole (3.3

mg, 0.04 mmol, 0.10 equiv) dissolved in 0.8 mL MeCN) were added. After the addition at 6 h, the reaction vessel was sealed with a rubber septum and the reaction mixture was sparged with $O_{2(g)}$ and allowed to stir under an O_2 atmosphere for an additional 15.5 h. When the reaction was judged to be done by TLC, the reaction mixture was filtered over a short silica plug, eluting with 20% EtOAc/hexanes, and the resulting solution was concentrated *in vacuo* to give **261** as a brown oil (71.1 mg, 87% yield).

R_f = 0.69 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +62.9° (c = 1.66, $CHCl_3$).

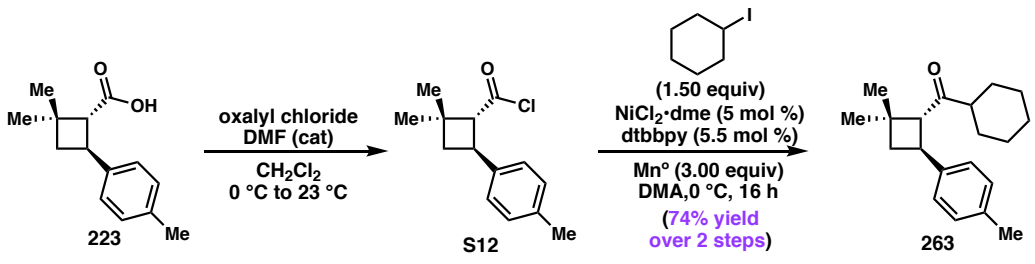
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (d, *J* = 1.6 Hz, 1H), 7.21 – 7.01 (m, 5H), 3.88 (q, *J* = 9.6 Hz, 1H), 2.97 (ddd, *J* = 9.7, 1.7, 0.9 Hz, 1H), 2.34 (s, 3H), 2.12 (ddt, *J* = 10.5, 8.9, 0.8 Hz, 1H), 2.02 (t, *J* = 10.5 Hz, 1H), 1.36 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.0, 140.8, 135.8, 129.1, 129.1, 126.5, 126.5, 62.5, 39.9, 37.5, 33.0, 31.3, 24.0, 23.6, 21.1, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3248, 2954, 2926, 2896, 2864, 1896, 1514, 1453, 1413, 1379, 1368, 1326, 1260, 1218, 1190, 1110, 1092, 1033, 1013, 812, 772.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{22}NO$ $[M+NH_4]^+$: 220.1696; found: 220.1691.

Cross-coupling to prepare cyclohexyl ketone **263**.



A 1-dram vial containing a stir bar was charged with carboxylic acid **223** (87.3 mg, 0.400 mmol, 1 equiv). The vial was sealed with a septum vial cap and tape and was evacuated and backfilled with N_2 three times. CH_2Cl_2 (0.8 mL, 0.5 M) and 2 drops DMF were added, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (0.050 mL, 0.560 mmol, 1.4 equiv) was then added dropwise. Once the addition was complete, the reaction was allowed to stir at room temperature for 1 h, at which point the solvent was removed *in vacuo* to afford acid chloride **S12** as a crude oil. **S12** was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.06 (m, 4H), 3.79 (q, *J* = 9.7 Hz, 1H), 3.29 (dd, *J* = 9.8, 0.9 Hz, 1H), 2.33 (s, 3H), 2.11 (ddd, *J* = 10.9, 9.1, 1.0 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.41 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3, 139.2, 136.5, 129.4, 126.5, 66.1, 39.0, 37.0, 30.0, 23.2, 21.2.

A flame-dried 1-dram vial containing a 2-dram stir bar (tested before to ensure it would stir) was charged with $NiCl_2$•dme (4.4 mg, 0.020 mmol, 0.05 equiv), dtbbpy (5.9 mg, 0.022 mmol, 0.055 equiv), and Mn° powder (65.9 mg, 1.20 mmol, 3.00 equiv). The vial was sealed with a septa and tape and evacuated and backfilled with N_2 three times. 0.6 mL DMA was then added, and the reaction mixture was stirred vigorously (~1300 rpm) for about 30 min. The mixture became a dark black color. The reaction mixture was then cooled to 0 °C in an ice bath. Iodocyclohexane (0.078 mL, 0.600 mmol, 1.50 equiv) was then added, followed by freshly prepared acid chloride **S12** (94.7 mg, 0.400 mmol, 1.0 equiv) dissolved in 0.8 mL DMA. The sealed vial was then placed in a cryocool set to 0 °C

and allowed to stir for 16 h. The reaction mixture was then quenched with 1.0 mL H_2O and extracted with CH_2Cl_2 (4 x 2.0 mL). The combined organic layers were filtered through a Na_2SO_4 plug and concentrated *in vacuo*. The resulting crude oil was purified by silica gel flash chromatography (0 → 5% EtOAc/hexanes) to afford **263** as a pale yellow, clear oil (84.6 mg, 74% yield over 2 steps).

R_f = 0.76 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +17.1° (c = 2.247, $CHCl_3$).

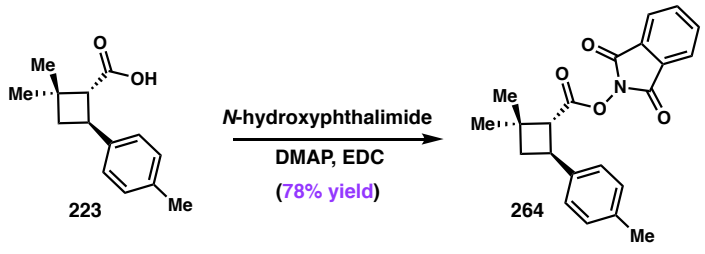
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 – 7.05 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 3.85 (q, *J* = 9.6 Hz, 1H), 3.13 (dd, *J* = 9.6, 0.8 Hz, 1H), 2.31 (s, 3H), 2.21 (tt, *J* = 11.3, 3.3 Hz, 1H), 2.02 (ddd, *J* = 10.6, 8.8, 0.8 Hz, 1H), 1.92 (t, *J* = 10.5 Hz, 1H), 1.88 – 1.62 (m, 3H), 1.44 (tdd, *J* = 13.0, 11.4, 3.6 Hz, 1H), 1.34 (s, 3H), 1.31 – 1.11 (m, 4H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.7, 141.7, 135.5, 129.1, 126.5, 60.9, 50.8, 39.1, 37.4, 33.2, 31.3, 29.6, 26.9, 26.3, 26.0, 25.5, 24.0, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3380, 3048, 3020, 2929, 2855, 1894, 1698, 1515, 1449, 1370, 1331, 1288, 1244, 1183, 1145, 1066, 1021m 994, 952, 892, 829, 805, 759.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{20}H_{32}NO$ $[M+NH_4]^+$: 302.2478; found: 302.2470.

Synthesis of NHP-ester **264**



A 20 mL vial was charged with carboxylic acid **223** (208.9 mg, 0.957 mmol, 1.00 equiv), *N*-hydroxyphthalimide (156.1 mg, 0.957 mmol, 1.00 equiv), and 4-dimethylaminopyridine (11.7 mg, 0.096 mmol, 0.10 equiv). The vial was sealed with a rubber septum and evacuated and backfilled with N_2 three times. The solids were dissolved in CH_2Cl_2 (4 mL), and then EDC (201.8 mg, 1.05 mmol, 1.10 equiv) was added as a slurry in CH_2Cl_2 (1.3 mL). The reaction mixture was allowed to stir for 23 hours at room temperature. The reaction mixture was then transferred to a flask containing EtOAc (50 mL), and the resulting solids were removed by filtration. The filtrate was concentrated *in vacuo* and the crude oil was purified by silica gel flash chromatography (15 → 40% EtOAc/hexanes) to afford **264** as a white solid (272.8 mg, 78% yield).

R_f = 0.46 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +100.5° (c = 0.42, $CHCl_3$).

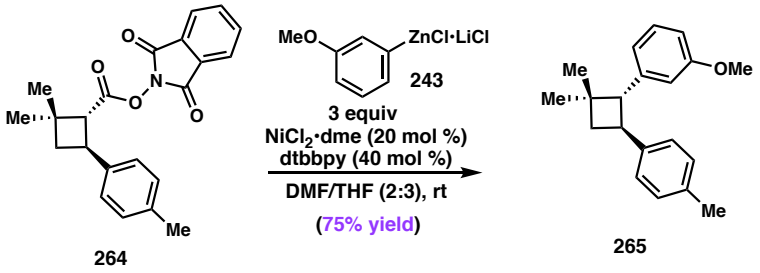
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.83 (m, 2H), 7.83 – 7.73 (m, 2H), 7.14 (s, 4H), 3.87 (q, *J* = 9.8 Hz, 1H), 3.21 (dd, *J* = 9.9, 0.9 Hz, 1H), 2.33 (s, 3H), 2.20 (ddd, *J* = 10.8, 8.9, 0.9 Hz, 1H), 2.08 (t, *J* = 10.5 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 162.2, 139.7, 136.3, 134.8, 129.3, 129.1, 126.5, 124.0, 52.5, 39.6, 37.5, 35.3, 30.5, 23.7, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 3520, 3022, 2959, 2927, 2868, 1808, 1794, 1745, 1615, 1516, 1467, 1368, 1274, 1186, 1132, 1081, 1016, 972, 878, 811, 786, 696.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{21}NO_4$ $[M+NH_4]^+$: 381.1809; found: 381.1814.

Nickel-catalyzed arylation of **264**.



A 25 mL round bottom flask was charged with **264** (109 mg, 0.300 mmol, 1.00 equiv), $NiCl_2$•dme (13.2 mg, 0.060 mmol, 0.20 equiv), and dtbbpy (32.2 mg, 0.120 mmol, 0.40 equiv). The flask was sealed with a septum and then evacuated and backfilled with argon three times. DMF was then added (3.2 mL), forming a green solution. Freshly prepared aryl zinc reagent **243** (4.8 mL, 0.90 mmol, 3.0 equiv, 0.19 M in THF) was then added and the solution turned red. The reaction was allowed to stir for 18 h, at which point the reaction was quenched with 1 M HCl (10 mL) and diluted with EtOAc (10 mL). The organic and aqueous layers were separated, and the organic layer was washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford a red oil. The crude material was then purified by silica gel flash chromatography (2.5 → 25% PhMe/hexanes) to afford **265** as a clear oil (63 mg, 75% yield).

R_f = 0.77 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +195° (c = 0.42, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.17 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.81 (ddt, *J* = 7.6, 1.7, 0.9 Hz, 1H), 6.80 – 6.71 (m, 2H), 3.79 (s, 3H), 3.32

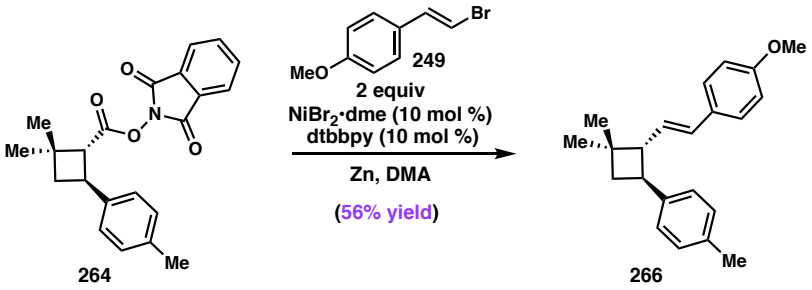
(d, J = 10.4 Hz, 1H), 2.30 (s, 3H), 2.16 (ddd, J = 10.3, 8.5, 0.7 Hz, 1H), 1.90 (t, J = 10.1 Hz, 1H), 1.28 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 142.8, 142.1, 135.5, 129.1, 129.0, 126.6, 120.0, 113.6, 111.0, 56.7, 55.2, 40.2, 37.4, 37.2, 30.9, 23.3, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3014, 2947, 2859, 1596, 1514, 1490, 1458, 1428, 1371, 1318, 1292, 1252, 1166, 1040, 832, 808, 797, 694.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{15}H_{25}O_3$ $[M+H]^+$: 281.1900; found: 281.1899.

Reductive alkenylation of **264**



A 1-dram vial containing a 2-dram stir bar was charged with NHP ester **264** (75.7 mg, 0.208 mmol, 1.00 equiv) and vinyl bromide **249** (63.9 mg, 0.300 mmol, 1.50 equiv). A separate ½-dram vial containing a stir bar was charged with dtbbpy (5.4 mg, 0.020 mmol, 0.10 equiv). Both vials were brought into a N_2 filled glovebox. The vial containing dtbbpy was charged with $NiBr_2$•dme (6.2 mg, 0.020 mmol, 0.10 equiv) and DMA (0.200 mL, 1.0 M) and allowed to stir for 10 minutes. The vial containing **264** and **249** was charged with Zn powder (25.4 mg, 0.400 mmol, 2.00 equiv). Once the catalyst solution prestir was complete, the catalyst solution was added to the reaction vial via pipette. The vial was then

sealed with a Teflon-lined cap, removed from the glovebox, placed in a pre-heated oil bath (28 °C), and allowed to stir for 15 h. Once the reaction was complete, the reaction mixture was diluted with Et_2O and passed through a short silica plug, eluting with Et_2O. The material was concentrated onto celite *in vacuo*, and the resulting powder was purified by silica gel flash chromatography (0 → 30% PhMe/hexanes) to afford **266** as a white solid (34.1 mg, 56% yield).

R_f = 0.71 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +238° (c = 1.66, $CHCl_3$).

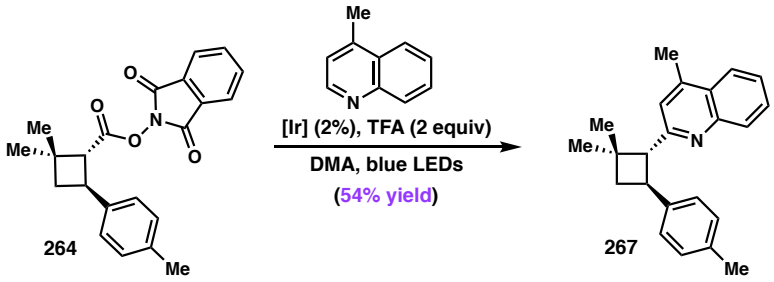
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.89 – 6.83 (m, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.22 (dd, *J* = 15.8, 7.8 Hz, 1H), 3.81 (s, 3H), 3.41 (q, J = 9.5 Hz, 1H), 2.73 (ddt, *J* = 9.5, 7.7, 0.9 Hz, 1H), 2.33 (s, 3H), 2.11 (ddd, *J* = 10.7, 8.5, 0.8 Hz, 1H), 1.87 (t, *J* = 10.3 Hz, 1H), 1.18 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9, 142.3, 135.3, 130.7, 130.0, 129.0, 128.1, 127.3, 126.6, 114.0, 55.9, 55.4, 40.0, 39.6, 36.9, 30.4, 23.6, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 2999, 2951, 2921, 2860, 1607, 1511, 1462, 1370, 1249, 1174, 1106, 1036, 966, 806.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{27}O$ $[M+H]^+$: 307.2056; found: 307.2062.

Decarboxylative heteroarylation of **264**



A flame-dried 2-dram vial was charged with NHP ester **264** (72.7, mg, 0.200 mmol, 1.00 equiv) and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.5 mg, 0.004 mmol, 0.02 equiv). The vial was evacuated and backfilled with Ar three times. DMA (2.0 mL, 0.1 M) and lepidine (43.0 mg, 0.300 mmol, 1.50 equiv) were then added, and the reaction mixture was cooled to 0 °C and sparged with Ar for 10 minutes. The reaction vial was removed from the ice bath, trifluoroacetic acid (30.6 μL, 0.400 mmol, 2.00 equiv) was added, and the reaction mixture was allowed to stir in front of a 34W blue LED lamp (~3 cm from the lamp). The reaction was monitored by TLC (20% EtOAc/hexanes). Once the reaction was complete (~4 h), the reaction was quenched with 1 mL NEt_3 and 2 mL H_2O. The aqueous layer was extracted with EtOAc (3 mL x 4), and the combined organics were washed with 1 M LiCl. The organic layer was then dried with Na_2SO_4, filtered, and concentrated onto celite *in vacuo*, and the resulting powder was purified by silica gel flash chromatography (0 → 5% EtOAc/hexanes) to afford **267** as a yellow solid (34.1 mg, 54% yield).

$\mathbf{R_f}$ = 0.76 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$\mathbf{[\alpha]_D^{25}}$ = +305° (c = 1.47, $CHCl_3$).

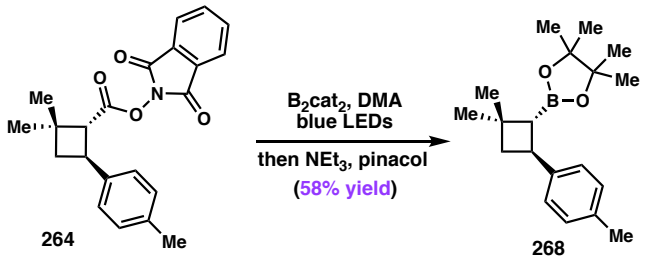
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.95 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.7, 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 3H), 4.39 (q, *J* = 9.7 Hz, 1H), 3.52 (d, *J* = 10.1 Hz, 1H), 2.67 (s, 3H), 2.30 (s, 3H), 2.20 (dd, *J* = 10.4, 8.8 Hz, 1H), 2.04 (t, *J* = 10.3 Hz, 1H), 1.39 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 148.0, 143.4, 142.6, 135.2, 130.2, 129.0, 128.9, 128.8, 128.7, 127.1, 126.9, 126.8, 125.4, 123.7, 121.7, 59.1, 39.7, 37.9, 35.4, 31.2, 23.7, 21.1, 18.9.

FTIR (NaCl, thin film, cm^{-1}): 3428, 3950, 2925, 2360, 1603, 1558, 1514, 1446, 1379, 1260, 1176, 1162, 1034, 809, 756.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{26}N$ $[M+H]^+$: 316.2060; found: 316.2063.

Decarboxylative borylation of **264**



A flame-dried 2-dram vial was charged with NHP ester **264** (72.7, mg, 0.200 mmol, 1.00 equiv) and B_2cat_2 (59.5 mg, 0.250 mmol, 1.25 equiv). The vial was evacuated and backfilled with Ar three times. DMA (2.0 mL, 0.1 M) was then added, and the reaction mixture was cooled to 0 °C and sparged with Ar for 10 minutes. The reaction vial was removed from the ice bath and suspended inside a large beaker lined with 12W blue LED

strips and covered with foil. After 21 h, pinacol (94.5 mg, 0.800 mmol, 4.00 equiv) was added as a solution in NEt_3 (700 μL, 5.04 mmol, 25.2 equiv). After 2 h, the reaction was quenched with H_2O, saturated aqueous NH_4Cl, and EtOAc. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organics were then dried with Na_2SO_4, filtered, and concentrated onto celite *in vacuo*, and the resulting powder was purified by silica gel flash chromatography (0 → 5% EtOAc/hexanes) to afford **268** as a white solid (35.1 mg, 58% yield).

R_f = 0.81 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +77.5° (c = 1.47, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 4H), 3.53 (td, *J* = 10.2, 8.2 Hz, 1H), 2.31 (s, 3H), 2.13 (ddd, *J* = 10.6, 8.2, 0.8 Hz, 1H), 2.02 (t, *J* = 10.3 Hz, 1H), 1.68 (d, *J* = 10.5 Hz, 1H), 1.26 (s, 6H), 1.24 (d, *J* = 1.1 Hz, 9H), 1.16 (s, 3H).

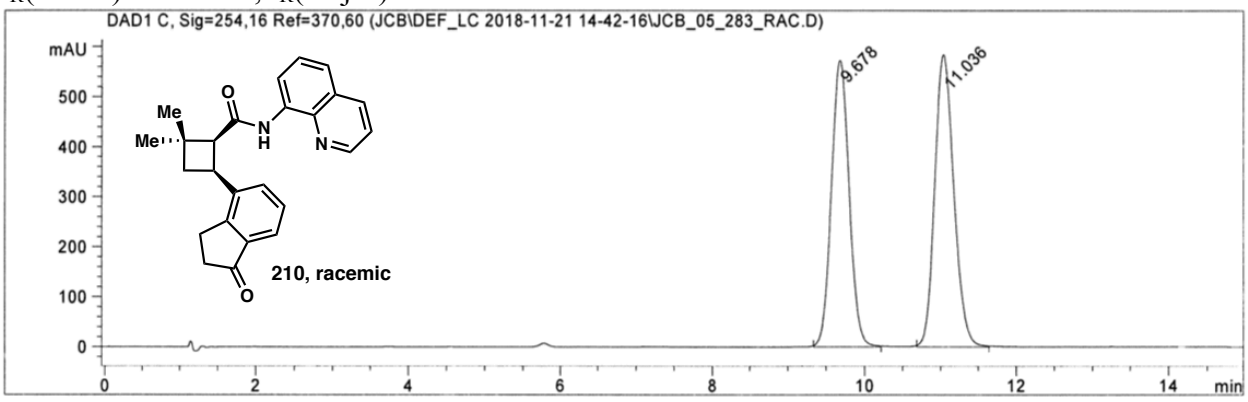
^{13}C NMR (101 MHz, $CDCl_3$): δ 144.1, 134.9, 128.9, 126.3, 83.2, 42.9, 34.3, 34.0, 32.4, 26.6, 25.3, 24.9, 21.1. (Note: the resonance from the carbon attached to the boron was not visible).

FTIR (NaCl, thin film, cm^{-1}): 3444, 2980, 2922, 2946, 2862, 2728, 1898, 1652, 1514, 1462, 1414, 1380, 1363, 1345, 1329, 1275, 1237, 1143, 1112, 1080, 1020, 967, 854, 809, 730.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{19}H_{29}BO_2Na$ $[M+Na]^+$: 323.2158; found: 323.2174.

2.7.2.3 Proof of Enantiopurity

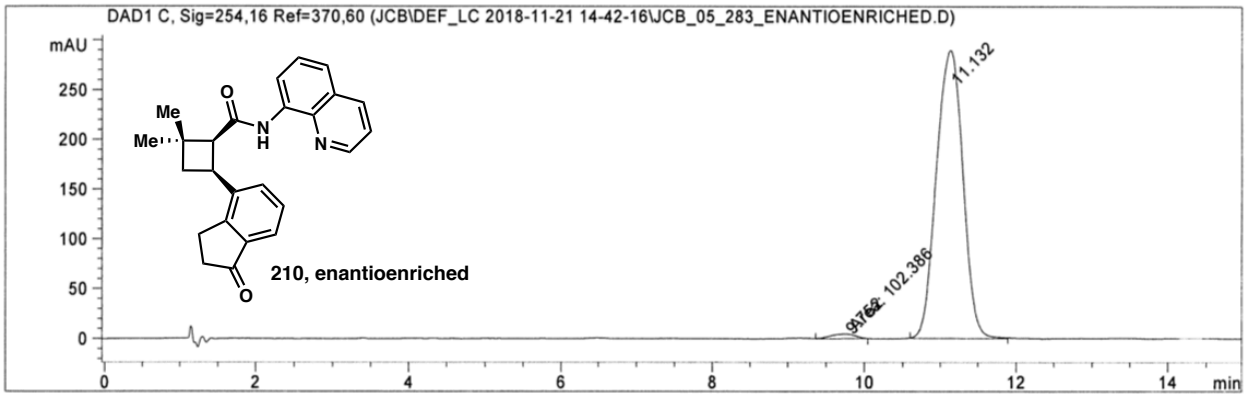
210, racemic sample. Chiral SFC: (OD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(minor) = 9.7 min, t_R(major) = 11.1 min.



Signal 1: DAD1 C, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.678	BB	0.2468	9170.02637	572.63605	47.0183
2	11.036	BB	0.2746	1.03331e4	583.59204	52.9817
Totals :				1.95031e4	1156.22809	

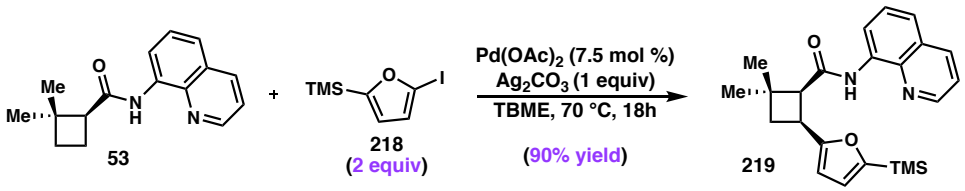
210, enantioenriched sample. Chiral SFC: (OD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(minor) = 9.7 min, t_R(major) = 11.1 min.



Signal 1: DAD1 C, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.752	MM	0.3621	102.38605	4.71307	1.4187
2	11.132	BB	0.3991	7114.58105	289.14011	98.5813
Totals :				7216.96710	293.85318	

2.7.2.4 *Total Synthesis of (+)-rumphellaone A*



A 48 mL pressure flask was charged with cyclobutamide **53** (400 mg, 1.57 mmol, 1.00 equiv), Ag_2CO_3 (434 mg, 1.57 mmol, 1.00 equiv), and $Pd(OAc)_2$ (26.5 mg, 0.118 mmol, 7.5 mol %) followed by TMS-iodofuran **218** (834 mg, 3.15 mmol, 2.00 equiv). The mixture was then suspended in TBME (8.0 mL, 0.2 M). The vessel was sealed under ambient conditions and placed in a pre-heated oil bath (70 ºC). After about 10 minutes, the olive-green mixture becomes black, and the reaction mixture is stirred for an additional 18 hours. The reaction mixture was then concentrated, diluted with toluene (3 mL), and loaded directly onto a silica gel column (0 → 20% EtOAc/hexanes) to afford **219** as a clear yellow oil (556 mg, 90% yield).

R_f = 0.56 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

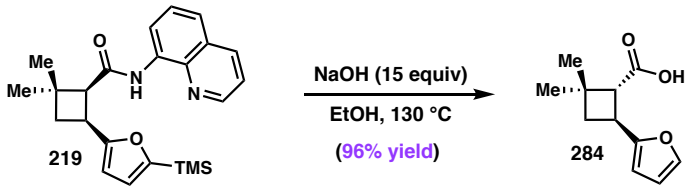
$[\alpha]_D^{25}$ = –57.2° (c = 1.22, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.68 (dd, *J* = 6.7, 2.3 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.48 – 7.39 (m, 3H), 6.48 (d, *J* = 3.1 Hz, 1H), 6.23 (dd, *J* = 3.2, 1.1 Hz, 1H), 4.07 – 3.94 (m, 1H), 3.34 (ddd, *J* = 9.0, 2.2, 0.8 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.19 (ddd, *J* = 11.0, 8.9, 2.3 Hz, 1H), 1.45 (s, 3H), 1.32 (s, 3H), -0.08 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 160.1, 158.7, 148.0, 138.5, 136.3, 134.8, 127.9, 127.6, 127.5, 121.5, 121.2, 121.1, 120.5, 120.5, 116.5, 106.8, 55.8, 38.1, 36.6, 32.3, 30.9, 30.7, 30.7, 24.9, –1.8.

FTIR (NaCl, thin film, cm^{-1}): 3360, 3109, 3049, 2954, 2866, 2613, 1944, 1878, 1687, 1595, 1578, 1522, 1485, 1424, 1385, 1324, 1249, 1161, 1131, 1009, 924, 842, 791, 757.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{29}N_2O_2Si$ $[M+H]^+$: 392.1993; found: 393.1990.



A 15 mL pressure flask was charged with *cis*-cyclobutamide **219** (532 mg, 1.36 mmol, 1.00 equiv), sodium hydroxide (813 mg, 20.33 mmol, 15 equiv), and absolute ethanol (5.7 mL, 0.24 M). The flask was sealed and placed in a pre-heated oil bath (130 ºC) and stirred for 18 h. The solvent was then concentrated *in vacuo*, and the crude residue was diluted with 1 M HCl (20 mL) and EtOAc (20 mL). The organic layer was separated and washed with 1 M HCl (2 x 20 mL). At this point, the aqueous layers should be yellow, and the organic layer should be faint brown. The combined aqueous layers were extracted with EtOAc (25 mL), and the second organic layer was washed with 1 M HCl (25 mL) until it was free of 8-aminoquinoline as indicated by TLC (usually 1-2 times). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reddish solid was purified by silica gel flash chromatography (20 → 40 % EtOAc/hexanes) to afford **284** as an off-white solid (250 mg, 96 % yield).

R_f = 0.5 (silica gel, 30% EtOAc/Hex, *p*-anisaldehyde).

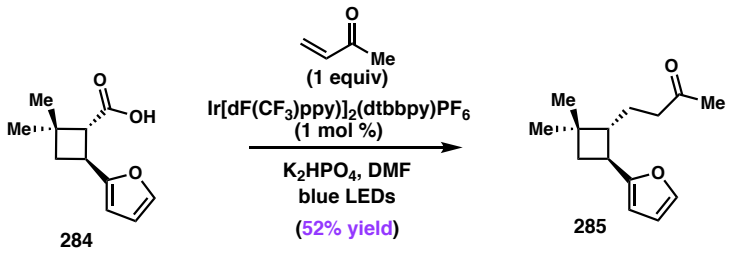
$[\alpha]_D^{25}$ = +133.0° (c = 0.85, $CHCl_3$).

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.32 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.05 (dt, *J* = 3.2, 0.8 Hz, 1H), 3.72 (q, *J* = 9.5 Hz, 1H), 3.11 – 3.02 (m, 1H), 2.12 – 1.95 (m, 2H), 1.30 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 156.6, 141.5, 110.3, 105.0, 53.2, 38.3, 36.8, 30.4, 29.2, 23.4.

FTIR (NaCl, thin film, cm^{-1}): 3119, 2993, 2956, 2869, 1722, 1682, 1604, 1506, 1461, 1411, 1390, 1371, 1276, 1224, 1208, 1175, 1161, 1104, 1067, 1008, 946, 918, 884, 850, 804, 743, 730, 695.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{11}H_{15}O_3$ $[M+H]^+$: 195.1016; found: 195.1019.



A 100 mL flame-dried, round-bottom flask was charged with carboxylic acid **284** (342 mg, 1.76 mmol, 1.00 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (19.7 mg, 0.0176 mmol, 0.01 equiv), and K_2HPO_4 (368 mg, 1.76 mmol, 1.00 equiv). The flask was evacuated and backfilled with N_2 three times. DMF (17.6 mL, 0.1 M) and freshly distilled methyl vinyl ketone (144 μL, 1.76 mmol, 1.0 equiv) were then added, and the reaction mixture was sparged with Ar for 5 minutes. The reaction flask was placed about 5 cm from a 34W blue

LED lamp and was allowed to stir at room temperature under N_2. After 42 h, the reaction was quenched with sat aq $NaHCO_3$ and extracted with EtOAc (75 mL x 3). The combined organics were then dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford the product as a crude oil, which was then purified by silica gel flash chromatography (3 → 10% EtOAc/hexanes) to afford **285** as a white solid (201 mg, 52% yield).

R_f = 0.79 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

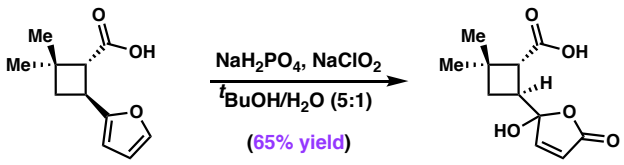
$[\alpha]_D^{25}$ = +57.8° (c = 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.97 (dt, *J* = 3.2, 0.7 Hz, 1H), 2.97 (td, *J* = 9.6, 8.5 Hz, 1H), 2.41 – 2.21 (m, 2H), 2.09 – 1.97 (m, 4H), 1.93 (ddd, *J* = 10.7, 8.5, 0.7 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.74 – 1.59 (m, 2H), 1.11 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.1, 158.9, 140.9, 110.3, 104.0, 50.4, 41.5, 39.0, 34.6, 34.3, 30.6, 30.1, 24.2, 22.3.

FTIR (NaCl, thin film, cm^{-1}): 3114, 2953, 2933, 2863, 1717, 1593, 1506, 1451, 1411, 1368, 1360, 1235, 1159, 1150, 1009, 799, 729.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{20}O_2Na$ $[M+Na]^+$: 243.1356; found: 243.1359.



A 50 mL round bottom flask was charged with carboxylic acid **284 (**200 mg, 1.03 mmol, 1.00 equiv) and was evacuated and backfilled with N_2 three times. 5:1 ^{t}BuOH/H_2O (5.2 mL, 0.2 M) was added. Once the starting material was fully dissolved, NaH_2PO_4•H_2O

(213 mg, 1.54 mmol, 1.50 equiv) was added in one portion, followed by $NaClO_2$ (349 mg, 3.09 mmol, 3.00 equiv, 80%). The suspension turned bright yellow within the first 10-15 minutes. The reaction mixture was allowed to stir 2–3 hours, at which point the yellow color dissipated and no more starting material was observed by TLC. The reaction mixture was concentrated *in vacuo*, and the resulting solids were solubilized with a mixture of EtOAc and minimal H_2O. This crude mixture was concentrated onto 4 g SiO_2. The powder was applied to a silica gel column and purified by flash silica gel chromatography (0 → 5% MeOH/CH_2Cl_2, followed by flushing with 50% MeOH/CH_2Cl_2) to afford **286** as a white solid (151 mg, 65% yield, 93% pure by qNMR).

R_f = 0.20 (silica gel, 10% MeOH/CH_2Cl_2, UV, *p*-anisaldehyde)

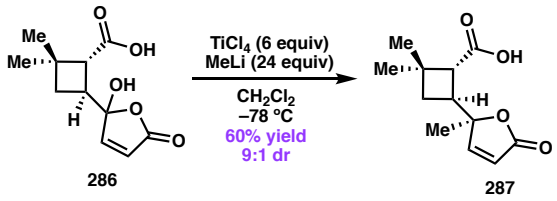
$[\alpha]_D^{25}$ +62.6° (c = 0.22, MeOH).

^{1}H NMR (400 MHz, MeOD-*d*$_4$): δ 7.27 (d, *J* = 5.9 Hz, 1H), 6.12 (d, *J* = 5.8 Hz, 1H), 2.92 (q, *J* = 9.4 Hz, 1H), 2.72 (d, *J* = 9.6 Hz, 1H), 1.80 (t, *J* = 10.3 Hz, 1H), 1.70 (dd, *J* = 11.0, 9.0 Hz, 1H), 1.20 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, MeOD-*d*$_4$): δ 175.7, 172.9, 155.7, 123.6, 51.5, 49.5, 37.8, 37.1, 36.9, 36.2, 33.7, 30.4, 30.3, 24.1, 23.7.

FTIR (NaCl, thin film, cm^{-1}): 3098, 2960, 2871, 1726, 1416, 1373, 1280, 1255, 1187, 1160, 1114, 1032, 1007, 935, 852, 829, 713.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{11}H_{16}O_5$ $[M+H]^+$: 227.0919; found: 227.0922.



A 50 mL round bottom flask was flame-dried under vacuum and then back-filled with N_2. The flask was charged with CH_2Cl_2 (5 mL) and cooled to –78 ºC, at which point, $TiCl_4$ (142 µL, 1.33 mmol, 6.00 equiv) was added. The flask was then charged with MeLi (1.5 M in Et_2O; 4.00 mL, 5.30 mmol, ~24 equiv) dropwise via syringe, until the color of the solution changed from dark brown, to bright orange, and finally to dark green. The resulting solution was stirred for 1h at –78 ºC. A flame-dried 50 mL pear-shaped (pointed) flask was charged with **286** (49.0 mg, 0.217 mmol, 1.00 equiv) and then evacuated and backfilled with N_2 three times. The substrate was dissolved in CH_2Cl_2 (23 mL) and sonicated to dissolve any particulates. The solution was cooled to –78 ºC, then added to the reaction flask via a slow cannula transfer. If the addition proceeds too quickly or the solution of starting material is not sufficiently cooled, the reaction will favor the undesired diastereomer. The flask containing **286** was rinsed with 2 mL CH_2Cl_2 to complete the transfer. The resulting mixture was allowed to stir at –78 ºC. After 4 h the reaction was quenched with 1 M HCl (20 mL), allowed to warm to 23 °C, and stirred for 30 minutes during which time the aqueous layer became blue/green. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (20 mL x 4), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (0 → 10% MeOH/CH_2Cl_2) to afford **287** as a white solid (29 mg, 9:1 dr, 60% yield).

R_f = 0.43 (silica gel, 10% MeOH/CH_2Cl_2, UV, *p*-anisaldehyde)

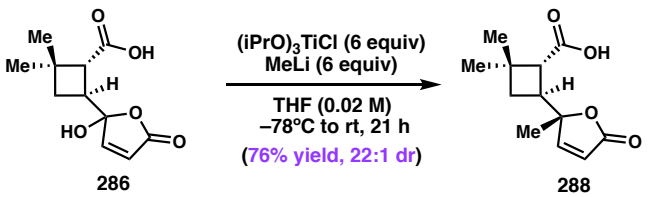
$[\alpha]_D^{25}$ = +43.0° (c = 0.46, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): 7.23 (d, *J* = 5.6 Hz, 1H), 6.01 (d, *J* = 5.6 Hz, 1H), 3.48 (s, 1H), 2.99 (dd, *J* = 9.4, 0.8 Hz, 1H), 2.92 – 2.78 (m, 1H), 1.46 – 1.41 (m, 1H), 1.39 (s, 3H), 1.35 (dd, *J* = 11.1, 9.9 Hz, 1H), 1.20 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 172.9, 172.8, 158.8, 121.1, 88.5, 49.1, 47.1, 36.4, 35.6, 35.5, 32.1, 29.9, 23.8, 21.7.

FTIR (NaCl, thin film, cm^{-1}): 3087, 2958, 2869, 1737, 1600, 1463, 1453, 1403, 1380, 1372, 1305, 1280, 1266, 1218, 1183, 1163, 1136, 1093, 1037, 961, 924, 880, 852, 824, 728, 711, 658.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{20}NO_4$ $[M+NH_4]^+$: 242.1387; found: 242.1394.



A flame-dried 50 mL round bottom flask was backfilled with N_2 and charged with THF (5 mL). The flask was cooled to –78 °C and (*i*-PrO)$_3$TiCl (1 M solution in hexanes; 1.33 mL, 1.33 mmol, 6.00 equiv) was added. MeLi (1.6 M solution in ether; 0.83 mL, 1.33 mmol, 6.00 equiv) was then added dropwise. This mixture was allowed to stir at –78 °C for 1 h. **286** (50 mg, 0.221 mmol, 1.00 equiv) was then added as a solution in THF (5.5 mL). The reaction mixture was slowly warmed to 23 °C over 21h. The reaction was then carefully quenched with 1 M HCl (11 mL) and stirred vigorously for 30 min. The organic

and aqueous layers were then separated, and the aqueous layer was extracted with EtOAc (12 mL x 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel flash chromatography (0 → 4% MeOH/CH_2Cl_2) to afford **288** (37.5 mg, 76% yield, 22:1 dr)

R_f = 0.43 (silica gel, 10% MeOH/CH_2Cl_2, UV, *p*-anisaldehyde)

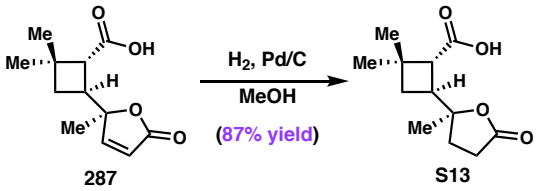
$[\alpha]_D^{25}$ = +120.4° (c = 1.20, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 5.6 Hz, 1H), 5.97 (d, *J* = 5.6 Hz, 1H), 2.79 (td, *J* = 9.9, 8.9 Hz, 1H), 2.39 (dd, *J* = 9.8, 0.8 Hz, 1H), 1.93 (t, *J* = 10.4 Hz, 1H), 1.78 (ddd, *J* = 10.8, 8.9, 1.0 Hz, 1H), 1.39 (s, 3H), 1.21 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 172.9, 159.5, 120.5, 88.4, 46.9, 36.8, 35.5, 33.5, 29.9, 23.6, 21.6.

FTIR (NaCl, thin film, cm^{-1}): 3091, 2936, 2958, 1869, 1741, 1702, 1464, 1454, 1417, 1371, 1282, 1247, 1208, 1166, 1119, 1090, 1051, 956, 912, 820, 727, 661.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{20}NO_4$ $[M+NH_4]^+$: 242.1387; found: 242.1390.



A 2-dram vial was charged with lactone **287** (29 mg, 0.129 mmol, 1.00 equiv) and Pd/C (10% by weight, 47 mg, 0.044 mmol, 0.34 equiv). The vial was then evacuated and backfilled with N_2 three times. The solids were suspended in MeOH (1.4 mL, 0.095 M), and the reaction mixture was sparged with a balloon of H_2 for 20 minutes at 0°C, at which

point the balloon was replaced with a fresh balloon, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred for 7 h under an atmosphere of H_2. Once the reaction was complete, the reaction mixture was sparged with argon for 20 minutes, diluted with EtOAc (15 mL), and filtered through celite, and concentrated *in vacuo*. The crude residue was then purified by silica gel flash chromatography (5% MeOH/CH_2Cl_2) to afford **S13** (25 mg, 88% yield) as a white solid.

R_f = 0.44 (silica gel, 10% MeOH/CH_2Cl_2, *p*-anisaldehyde)

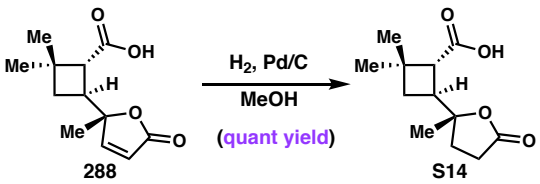
$[\alpha]_D^{25}$ = +76.3° (c = 0.72, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (d, *J* = 9.7 Hz, 1H), 2.72 (t, *J* = 9.5 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.53 (ddd, *J* = 18.2, 9.6, 5.0 Hz, 1H), 2.04 – 1.86 (m, 2H), 1.67 (s, 1H), 1.65 (s, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 177.1, 86.3, 86.3, 48.7, 39.1, 35.3, 32.6, 30.9, 29.9, 29.3, 24.0, 23.7.

FTIR (NaCl, thin film, cm^{-1}): 2958, 2934, 2869, 1773, 1736, 1702, 1459, 1420, 1382, 1369, 1283, 1248, 1166, 1142, 1077, 940, 914, 802, 646.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{22}NO_4$ $[M+NH_4]^+$: 244.1543; found: 244.1541.



288 (31.0 mg, 0.138 mmol, 1.00 equiv) was subjected to analogous conditions to afford **S14** (32.2 mg, quant yield), which was taken forward without further purification.

R_f = 0.44 (silica gel, 10% MeOH/CH_2Cl_2, *p*-Anisaldehyde)

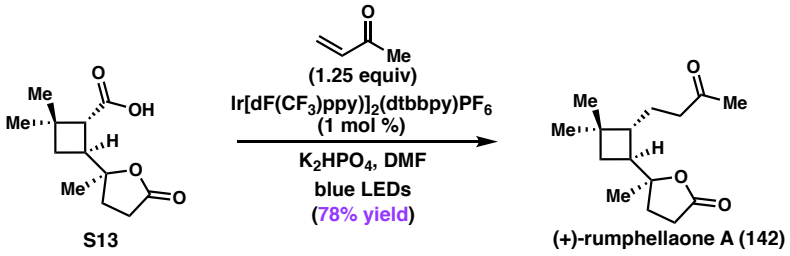
$[\alpha]_D^{25}$ = +51.2° (c = 0.53, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 – 2.56 (m, 3H), 2.50 (ddd, *J* = 18.1, 9.9, 4.9 Hz, 1H), 2.17 – 2.06 (m, 1H), 1.91 (ddd, *J* = 13.1, 10.0, 4.9 Hz, 1H), 1.81 (td, *J* = 9.8, 1.2 Hz, 1H), 1.71 (dd, *J* = 10.8, 8.0 Hz, 1H), 1.29 (s, 3H), 1.21 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 177.2, 86.5, 48.1, 39.2, 35.5, 33.6, 30.9, 29.9, 29.3, 23.9, 23.7.

FTIR (NaCl, thin film, cm^{-1}): 2958, 2869, 1770, 1738, 1732, 1704, 1699, 1463, 1422, 1383, 1369, 1283, 1245, 1222, 1165, 1138, 1075, 1002, 965, 941, 914, 802, 757, 711, 648.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{22}NO_4$ $[M+NH_4]^+$: 244.1543; found: 244.1537.



To a 2 dram vial charged with saturated lactone **S13** (16 mg, 0.0707 mmol, 1.00 equiv) was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.8 mg, 0.0007 mmol, 0.01 equiv) and K_2HPO_4 (14.8 mg, 0.0849 mmol, 1.20 equiv). The reaction vessel was evacuated and backfilled with N_2 three times. DMF (0.71 mL, 0.1 M) was then added, and the reaction mixture was cooled to 0 °C and sparged with argon for 15 minutes. Freshly distilled methyl vinyl ketone (7.2 μL, 0.0884 mmol, 1.25 equiv) was then added, and the reaction vessel was placed between two 34W blue LEDs (~5-6 cm away from each lamp) and stirred for 24 h with a small fan to keep the reactions at 23 ºC. Once complete, the reaction was diluted

with sat. aq. $NaHCO_3$ (0.8 mL) and EtOAc (0.8 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 x 1 mL). The combined organic layers were washed with 1 M LiCl (5 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude material was purified by silica gel flash chromatography (20 → 40% EtOAc/hexanes) to afford pure (+)-rumphellaone A (**142**) (15 mg, 78% yield) as a yellow solid.

R_f = 0.27 (silica gel, 40% EtOAc/Hexanes, UV, *p*-anisaldehyde)

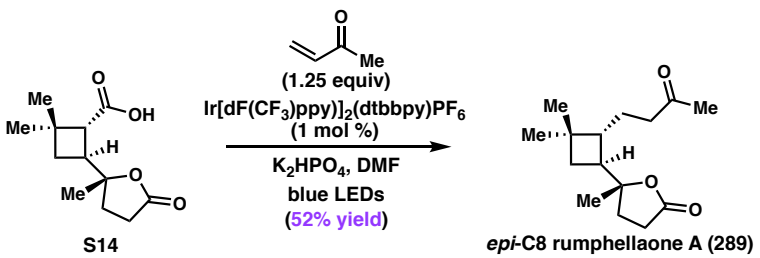
$[\alpha]_D^{25}$ = +43.4° (c = 0.35, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (ddd, *J* =18.1, 10.0, 8.9 Hz, 1H), 2.53 (ddd, *J* = 18.1, 10.0, 5.0 Hz, 1H), 2.36 (t, *J* = 7.9 Hz, 2H), 2.12 (s, 3H), 2.09 – 2.02 (m, 2H), 2.03 – 1.97 (m, 1H), 1.90 (ddd, *J* = 10.2, 9.6, 5.3 Hz, 2H), 1.88 – 1.81 (m, 1H), 1.69 – 1.61 (m, 2H), 1.57 (ddd, *J* = 10.8, 8.6, 0.8 Hz, 1H), 1.42 (t, *J* = 10.3 Hz, 1H), 1.31 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.8, 177.1, 87.4, 44.6, 44.4, 42.1, 33.7, 33.1, 31.1, 30.8, 30.1, 29.3, 25.2, 25.0, 22.6.

FTIR (NaCl, thin film, cm^{-1}): 2953, 2929, 2865, 1770, 1715, 1455, 1366, 1250, 1162, 1124, 1077, 938, 803, 645.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{15}H_{25}O_3$ $[M+H]^+$: 253.1798; found: 253.1799.



S14 (15.0 mg, 0.066 mmol, 1.00 equiv) was subjected to an analogous procedure to afford *epi*-C8-rumphellaone A (**289**) (8.1 mg, 52% yield) as a white solid.

R_f = 0.33 (silica gel, 40% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +38.5° (c = 0.41, $CHCl_3$).

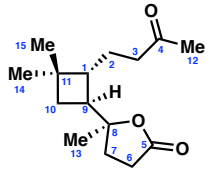
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 – 2.56 (m, 2H), 2.39 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.13 (s, 3H), 2.10 – 1.96 (m, 2H), 1.90 (ddd, *J* = 13.0, 8.8, 7.2 Hz, 1H), 1.78 (tdd, *J* = 9.2, 6.6, 0.8 Hz, 1H), 1.71 – 1.57 (m, 3H), 1.51 (t, *J* = 10.4 Hz, 1H), 1.29 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.7, 177.1, 87.3, 44.6, 44.1, 41.9, 34.5, 33.4, 31.6, 31.1, 30.2, 29.3, 25.0, 24.0, 22.6.

FTIR (NaCl, thin film, cm^{-1}): 2952, 2932, 2865, 1769, 1715, 1455, 1422, 1365, 1234, 1169, 1155, 1075, 963, 939, 801, 647.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{15}H_{25}O_3$ $[M+H]^+$: 253.1798; found: 253.1799.

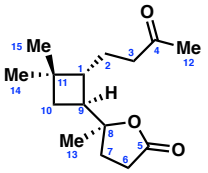
Comparison of ^{1}H NMR spectroscopic data for natural and synthetic (+)-rumphellaone A (142)



(+)-rumphellaone A (142)

Carbon Number	**Natural (+)-rumphellaone A** ^{1}H 400 MHz, $CDCl_3$	**Synthetic (+)-rumphellaone A** ^{1}H 400 MHz, $CDCl_3$
1	1.91 (ddd, *J* = 10.0, 9.2, 5.6 Hz, 2H)	1.90 (ddd, *J* = 10.2, 9.6, 5.3 Hz, 2H)
2	1.67 (m, 2H)	1.65 (m, 2H)
3	2.37 (t, *J* = 8.0 Hz, 2H)	2.36 (t, *J* = 7.9 Hz, 2H)
6α	2.63 (ddd, *J* = 18.0, 9.6, 8.8 Hz, 1H)	2.63 (ddd, *J* =18.1, 10.0, 8.9 Hz, 1H)
6β	2.54 (ddd, *J* = 18.0, 10.0, 4.8 Hz, 1H)	2.53 (ddd, *J* = 18.1, 10.0, 5.0 Hz, 1H)
7α	1.84 (m, 1H)	1.84 (m, 1H)
7β	2.01 (m, 1H)	2.01 (m, 1H)
9	2.06 (ddd, 10.4, 10.0, 10.0 Hz, 2H)	2.06 (m, 2H)
10α	1.57 (dd, *J* = 10.0, 10.0 Hz, 1H)	1.57 (ddd, *J* = 10.8, 8.6, 0.8 Hz, 1H)
10β	1.42 (dd, *J* = 10.4, 10.0 Hz, 1H))	1.42 (t, *J* = 10.3 Hz, 1H)
12	2.13 (s, 3H)	2.12 (s, 3H)
13	1.31 (s, 3H)	1.31 (s, 3H)
14	1.03 (s, 3H)	1.03 (s, 3H)
15	1.07 (s, 3H)	1.06 (s, 3H)

Comparison of ^{13}C NMR spectroscopic data for natural and synthetic (+)-rumphellaone A (142).



(+)-rumphellaone A (142)

Carbon Number	**Natural (+)-rumphellaone A** ^{13}C 100 MHz, $CDCl_3$	**Synthetic (+)-rumphellaone A** ^{13}C 101 MHz, $CDCl_3$	**Δ**
1	44.5	44.6	0.1
2	25.1	25.2	0.1
3	42.0	42.1	0.1
4	208.6	208.8	0.2
5	177.0	177.1	0.1
6	29.2	29.3	0.1
7	30.6	30.8	0.2
8	87.2	87.4	0.2
9	44.3	44.4	0.1
10	33.6	33.7	0.1
11	33.0	33.1	0.1
12	29.9	30.1	0.2
13	24.9	25.0	0.1
14	22.5	22.6	0.1
15	30.9	31.1	0.2

2.8 NOTES AND REFERENCES

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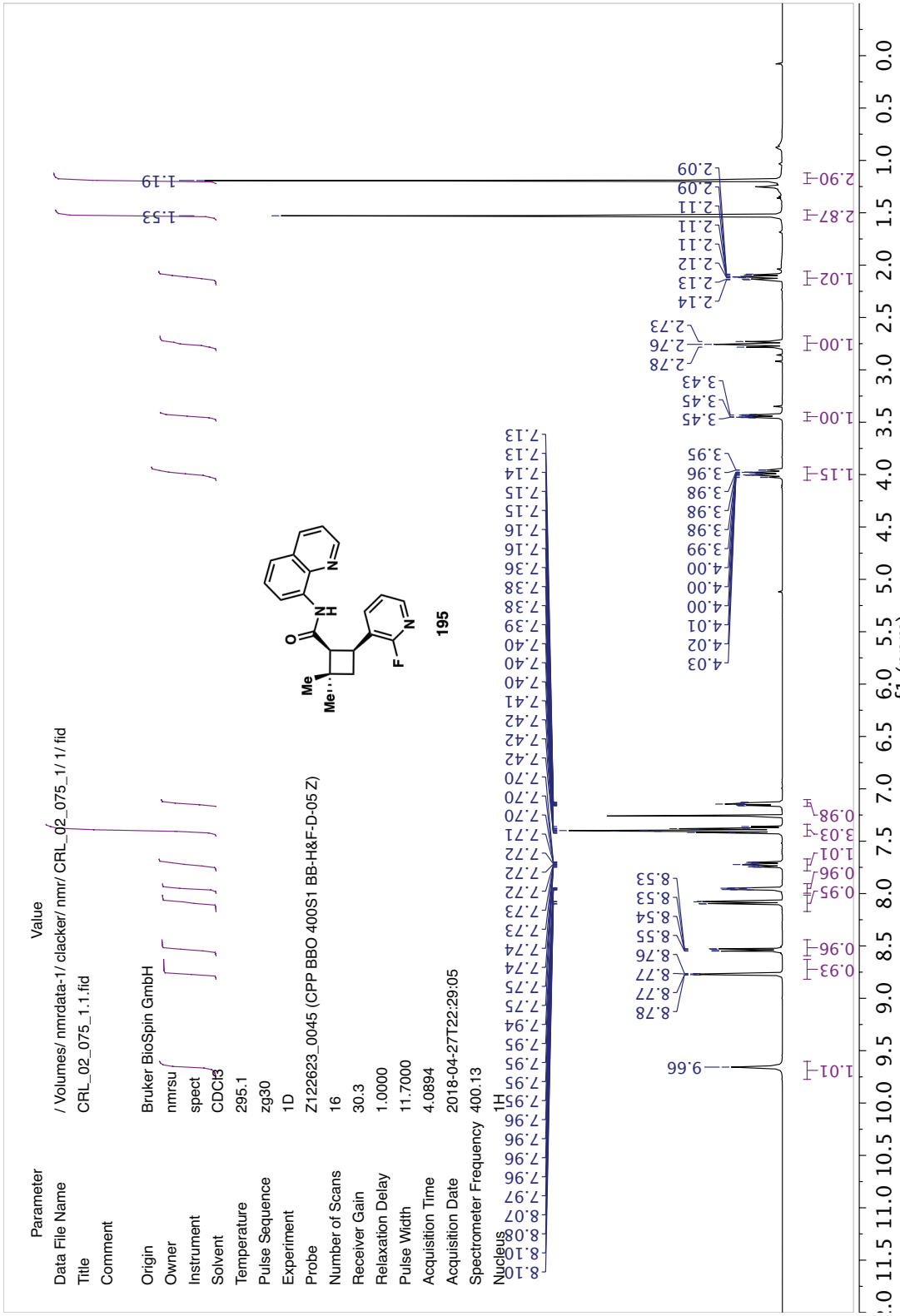
Appendix 1

Spectra Relevant to Chapter 2:

A Modular Approach to Synthesize Enantioenriched Cyclobutane Products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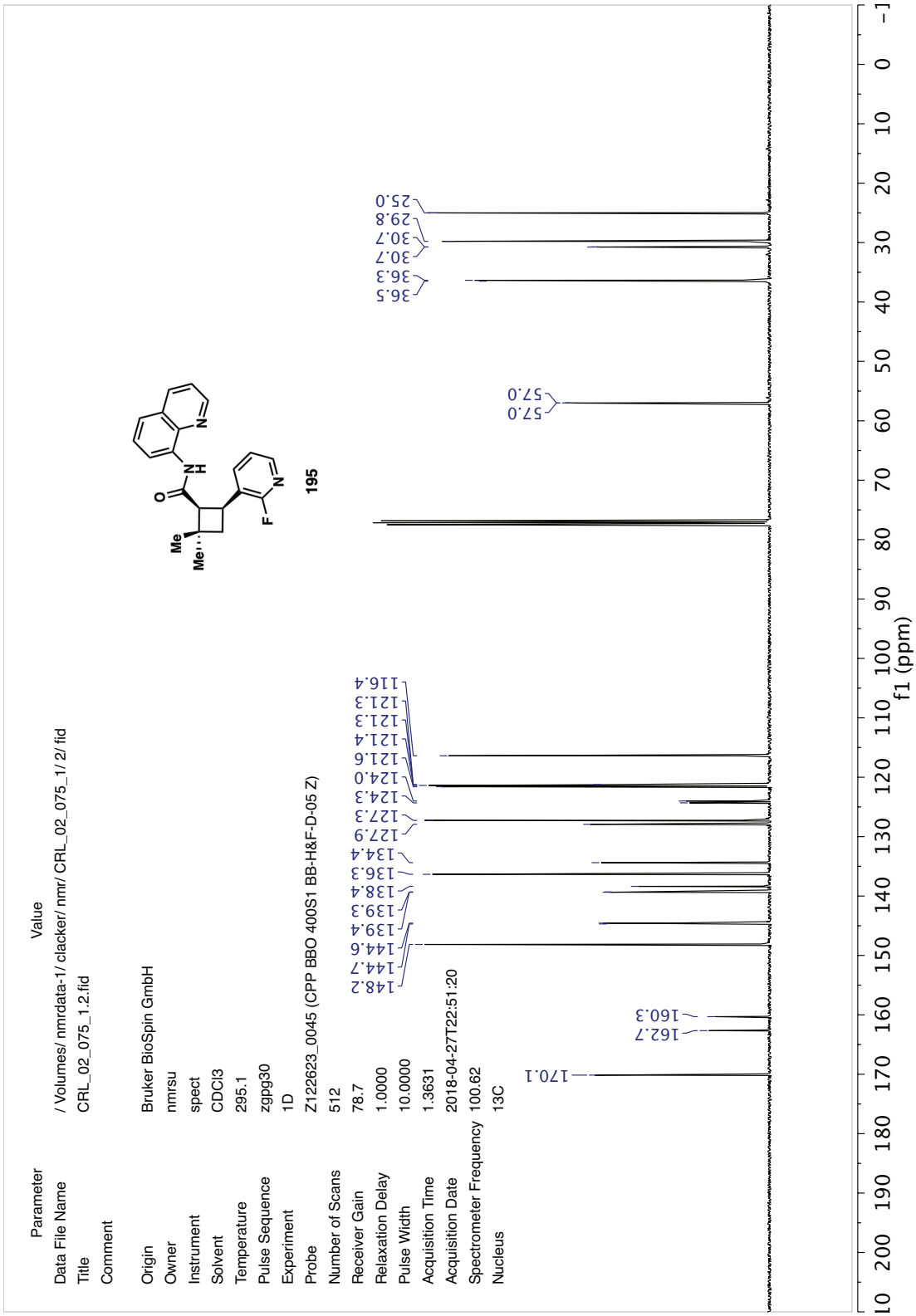
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-04-27T22:29:05
Spectrometer Frequency 400.13
Nucleus 1H
195
f1 (ppm)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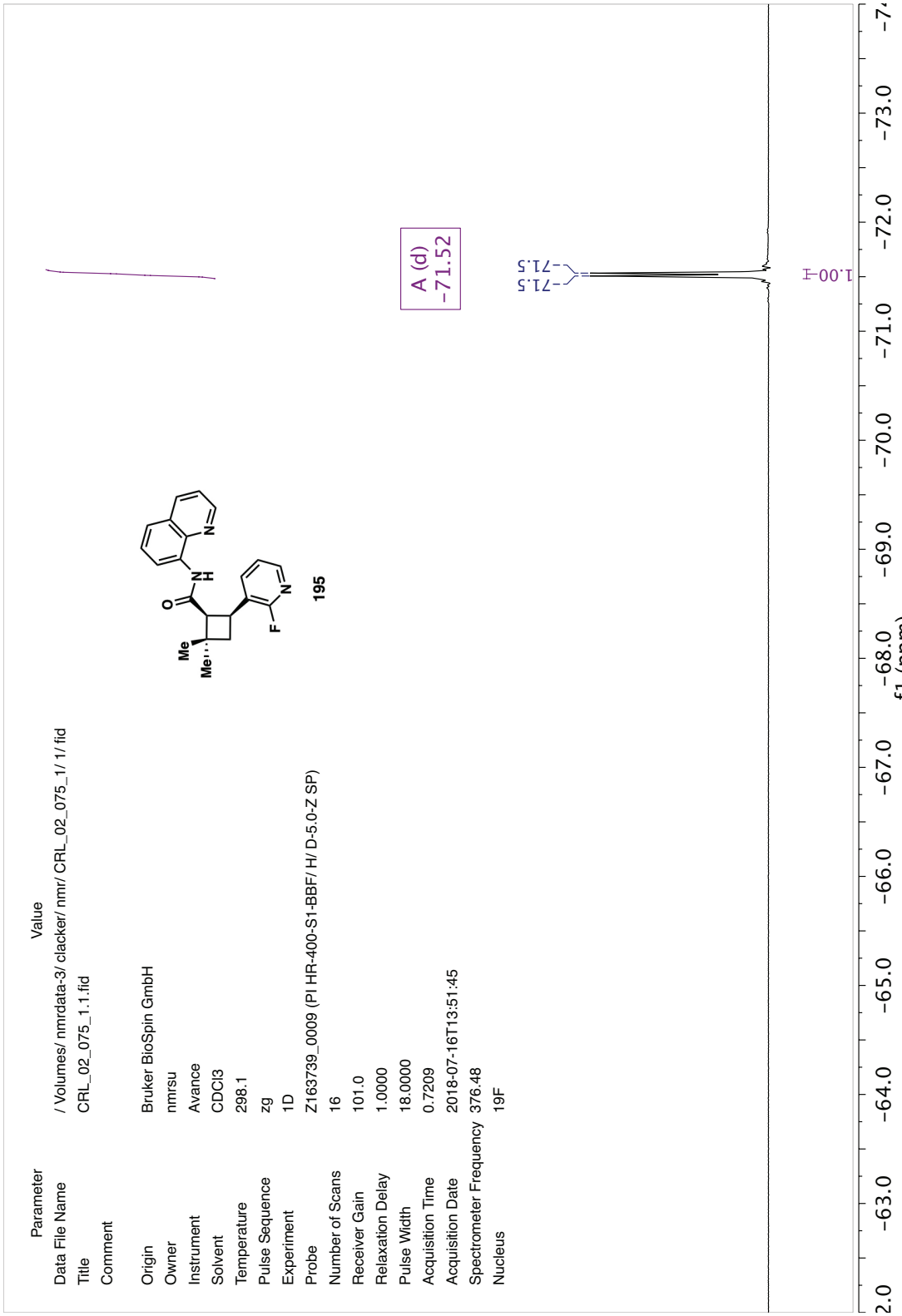
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-04-27T22:51:20
Spectrometer Frequency 100.62
Nucleus 13C
195
Me
Me
O
N
H
N
F
N
170.1
162.7
160.3
148.2
144.7
144.6
139.4
139.3
138.4
136.3
134.4
127.9
127.3
124.3
124.0
121.6
121.4
121.3
121.3
116.4
57.0
57.0
36.5
36.3
30.7
30.7
29.8
25.0
f1 (ppm)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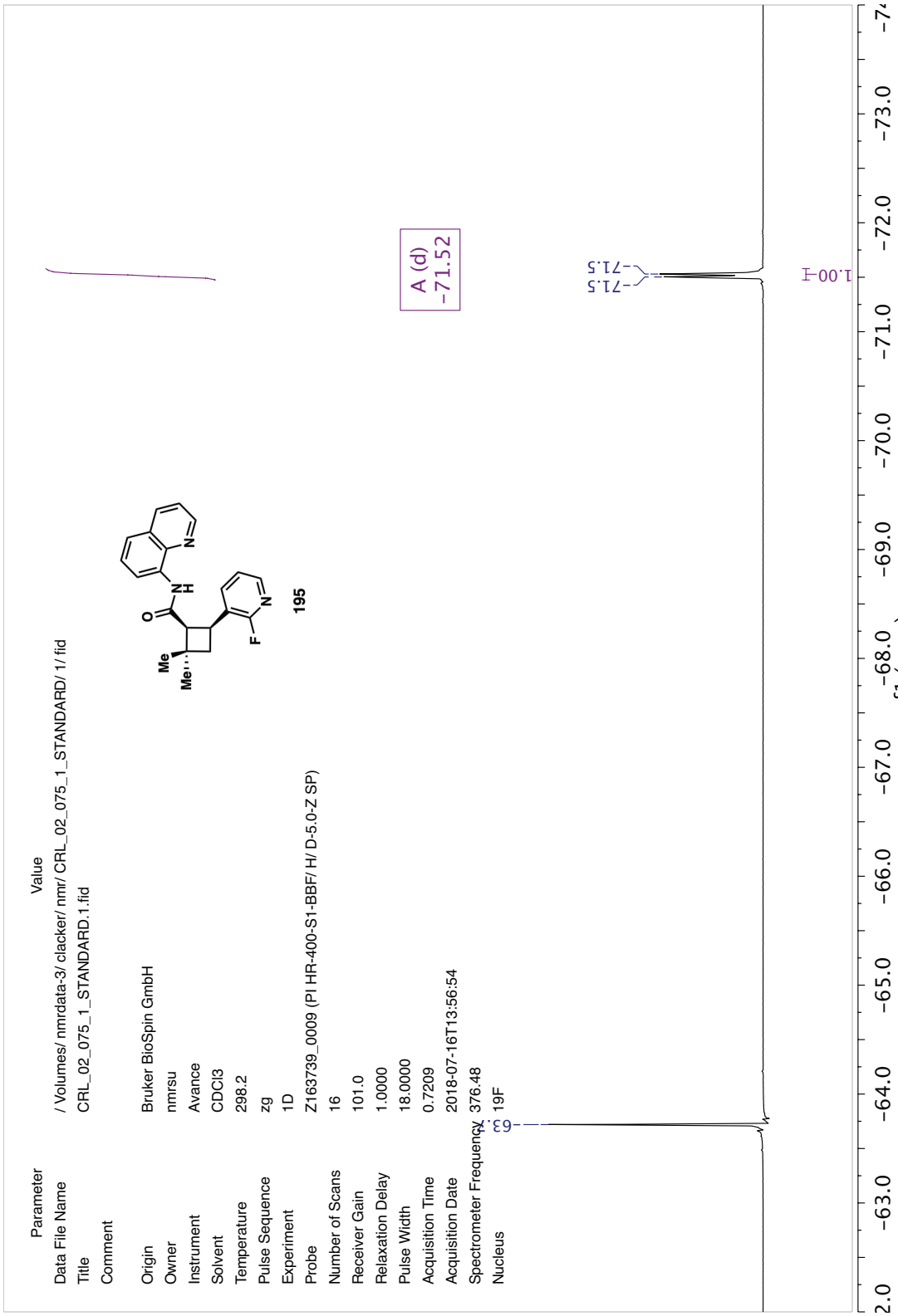
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument Avance
Solvent CDCl3
Temperature 298.1
Pulse Sequence zg
Experiment 1D
Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
Number of Scans 16
Receiver Gain 101.0
Relaxation Delay 1.0000
Pulse Width 18.0000
Acquisition Time 0.7209
Acquisition Date 2018-07-16T13:51:45
Spectrometer Frequency 376.48
Nucleus 19F
195
A (d)
-71.52
-71.5
-71.5
1.00
2.0
-63.0
-64.0
-65.0
-66.0
-67.0
-68.0
-69.0
-70.0
-71.0
-72.0
-73.0
f1 (ppm)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Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
Avance
Solvent
CDCl3
Temperature
298.2
Pulse Sequence
zg
Experiment
1D
Probe
Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
Number of Scans
16
Receiver Gain
101.0
Relaxation Delay
1.0000
Pulse Width
18.0000
Acquisition Time
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Spectrometer Frequency
376.48
Nucleus
19F
195
A (d)
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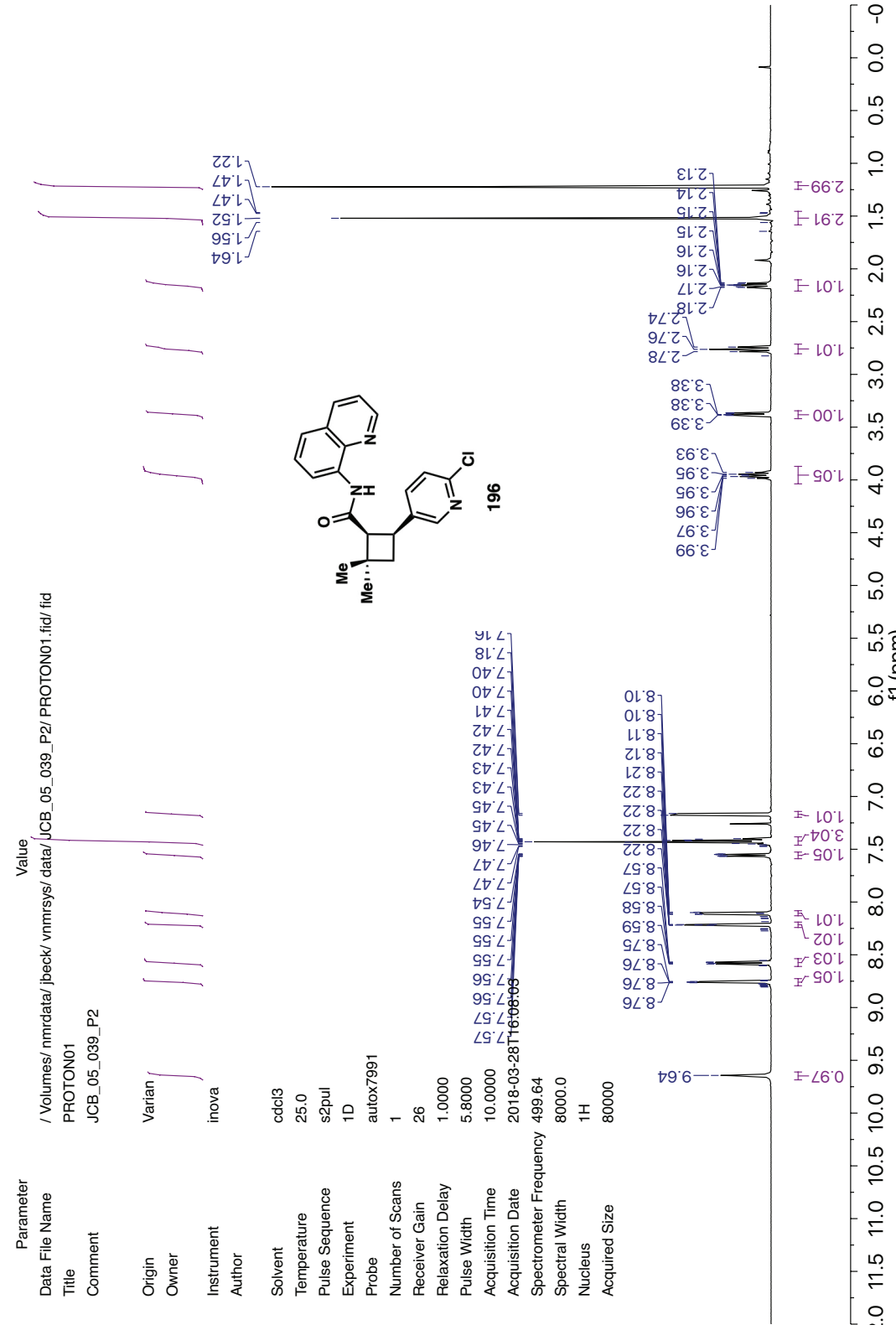
f1 (ppm)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Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe autox7991
Number of Scans 1
Receiver Gain 26
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 10.0000
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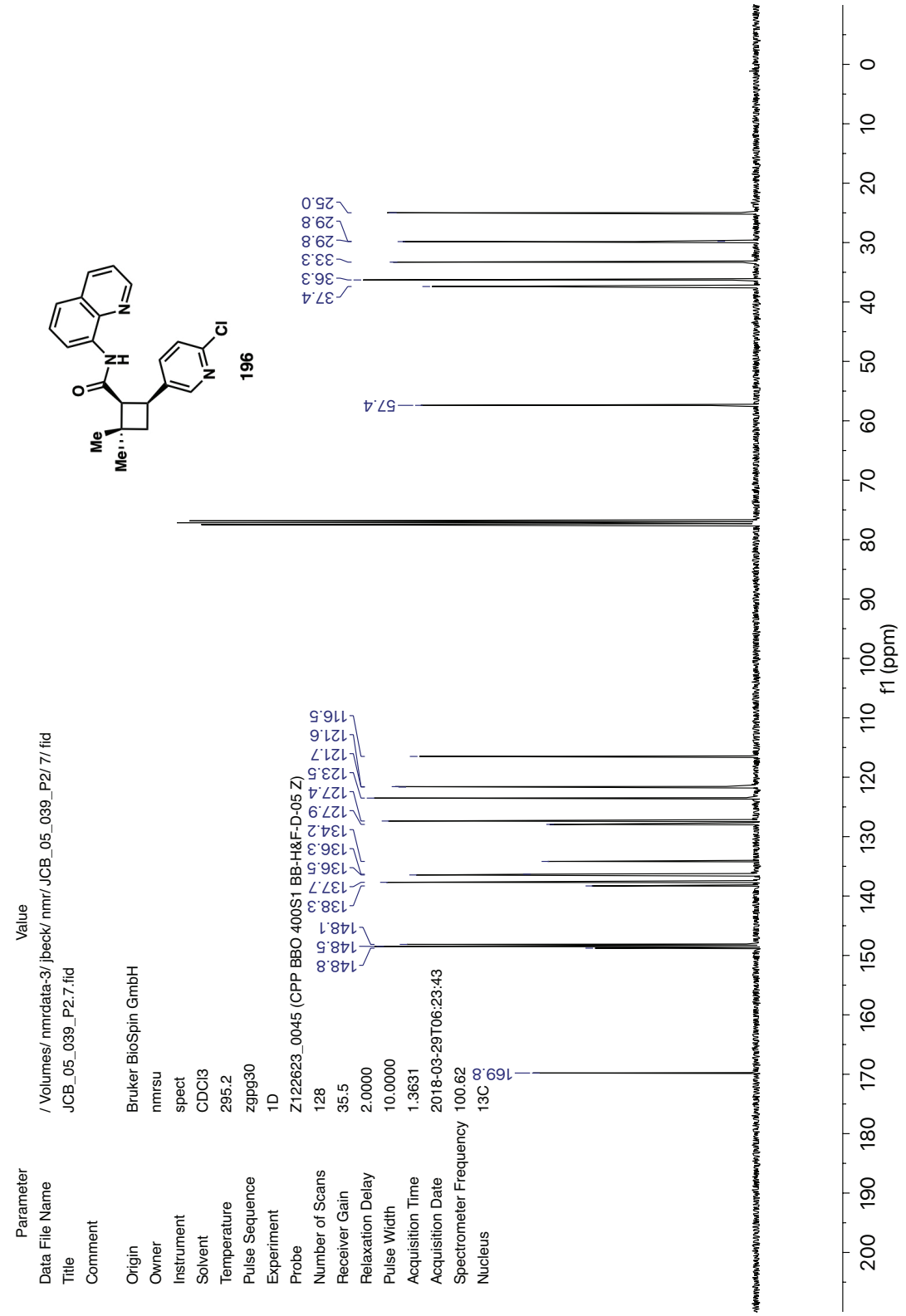
Spectrometer Frequency 499.64
Spectral Width 8000.0
Nucleus 1H
Acquired Size 80000
196
f1 (ppm)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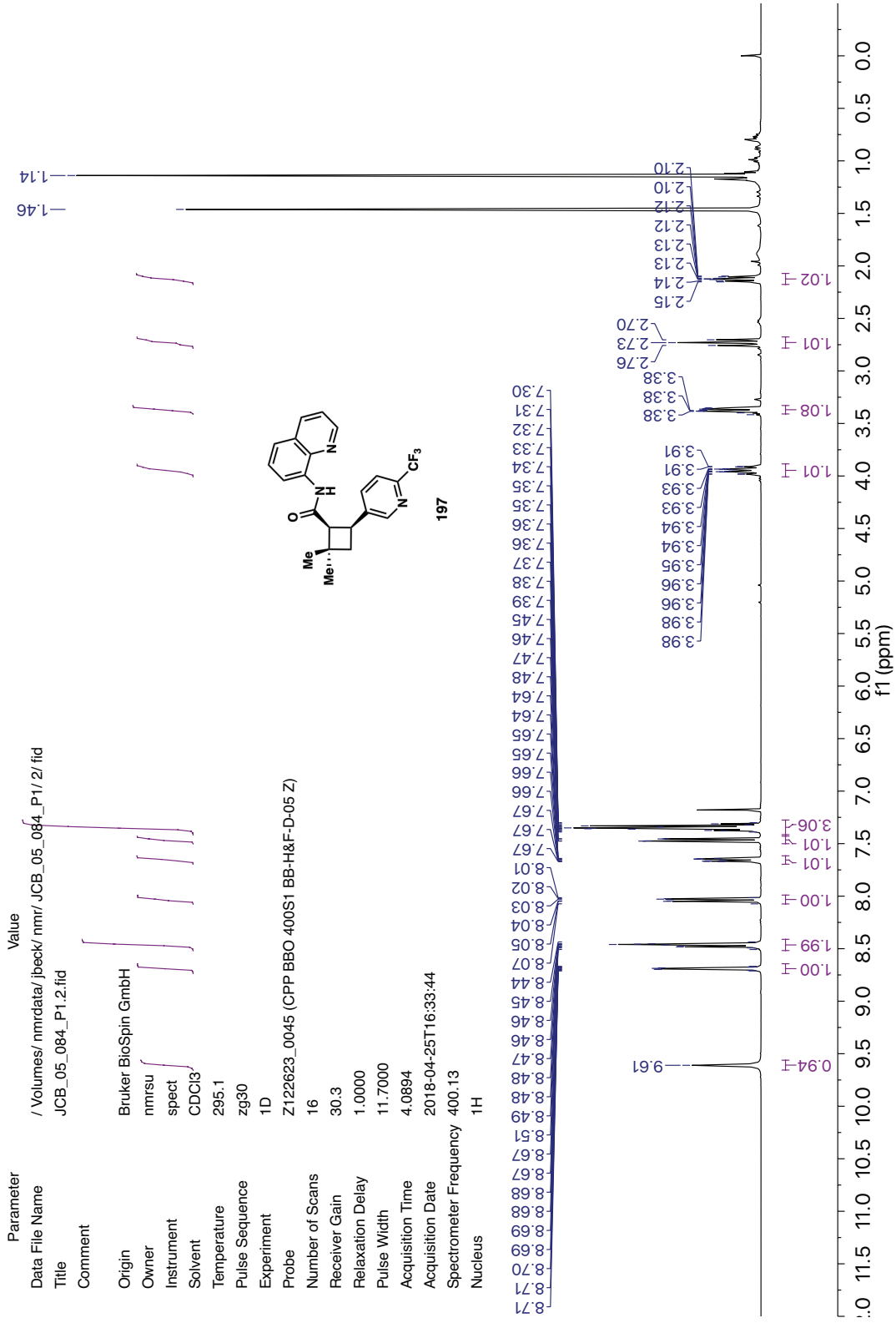
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 35.5
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-03-29T06:23:43
Spectrometer Frequency 100.62
Nucleus 13C
169.8
148.8
148.5
148.1
138.3
137.7
136.5
136.3
134.2
127.9
127.4
123.5
121.7
121.6
116.5
57.4
37.4
36.3
33.3
29.8
29.8
25.0
Me
Me
O
N
H
N
N
Cl
196
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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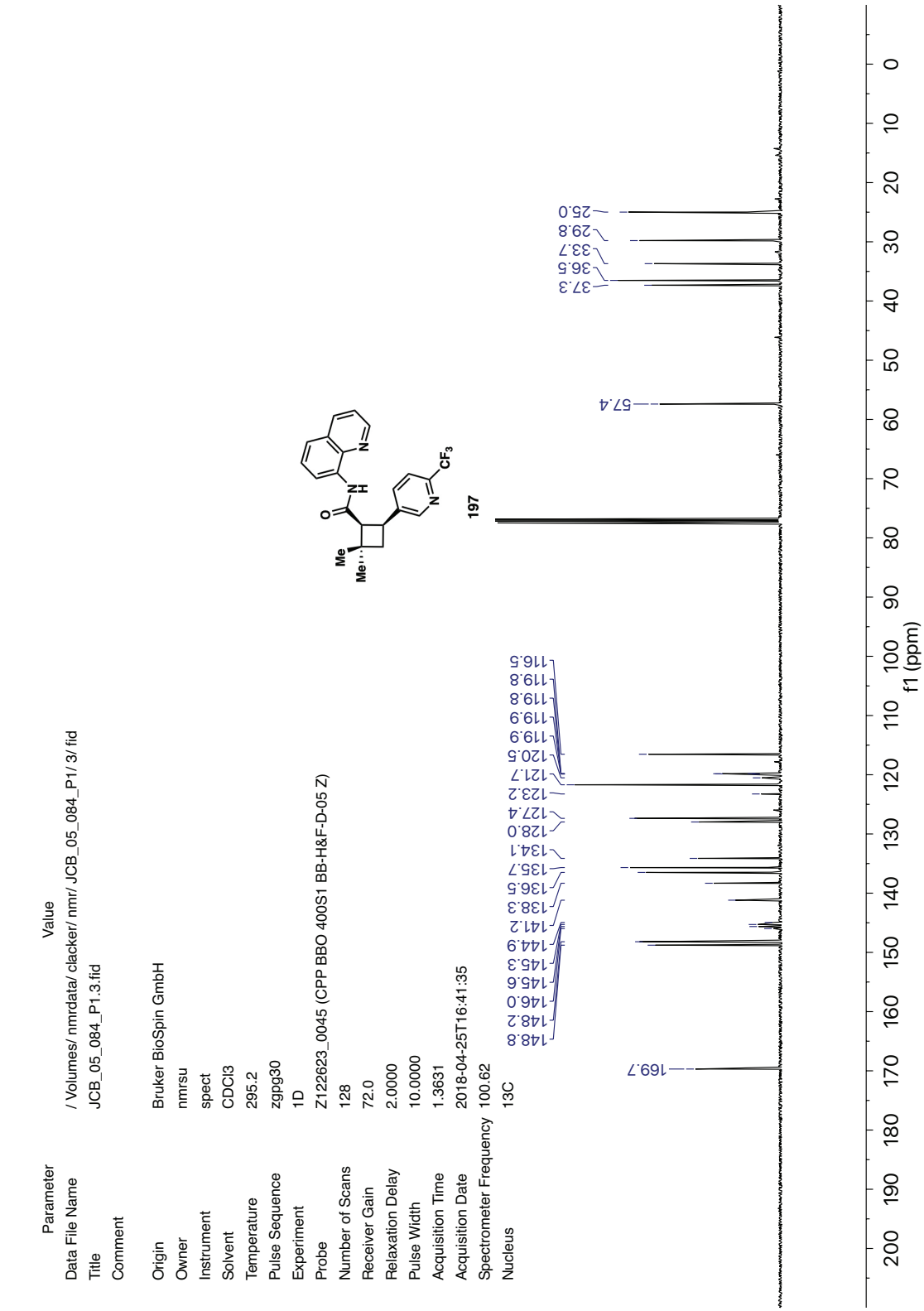
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-04-25T16:33:44
Spectrometer Frequency 400.13
Nucleus 1H
197
f1 (ppm)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Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-04-25T16:41:35
Spectrometer Frequency 100.62
Nucleus 13C
197
169.7
148.8
148.2
146.0
145.6
145.3
144.9
141.2
138.3
136.5
135.7
134.1
128.0
127.4
123.2
121.7
120.5
119.9
119.9
119.8
119.8
116.5
57.4
37.3
36.5
33.7
29.8
25.0
f1 (ppm)

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Comment	JCB_05_107_P1
Origin	Varian
Owner	
Instrument	mercury
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	ASW7284
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	6.3333
Acquisition Time	0.9856
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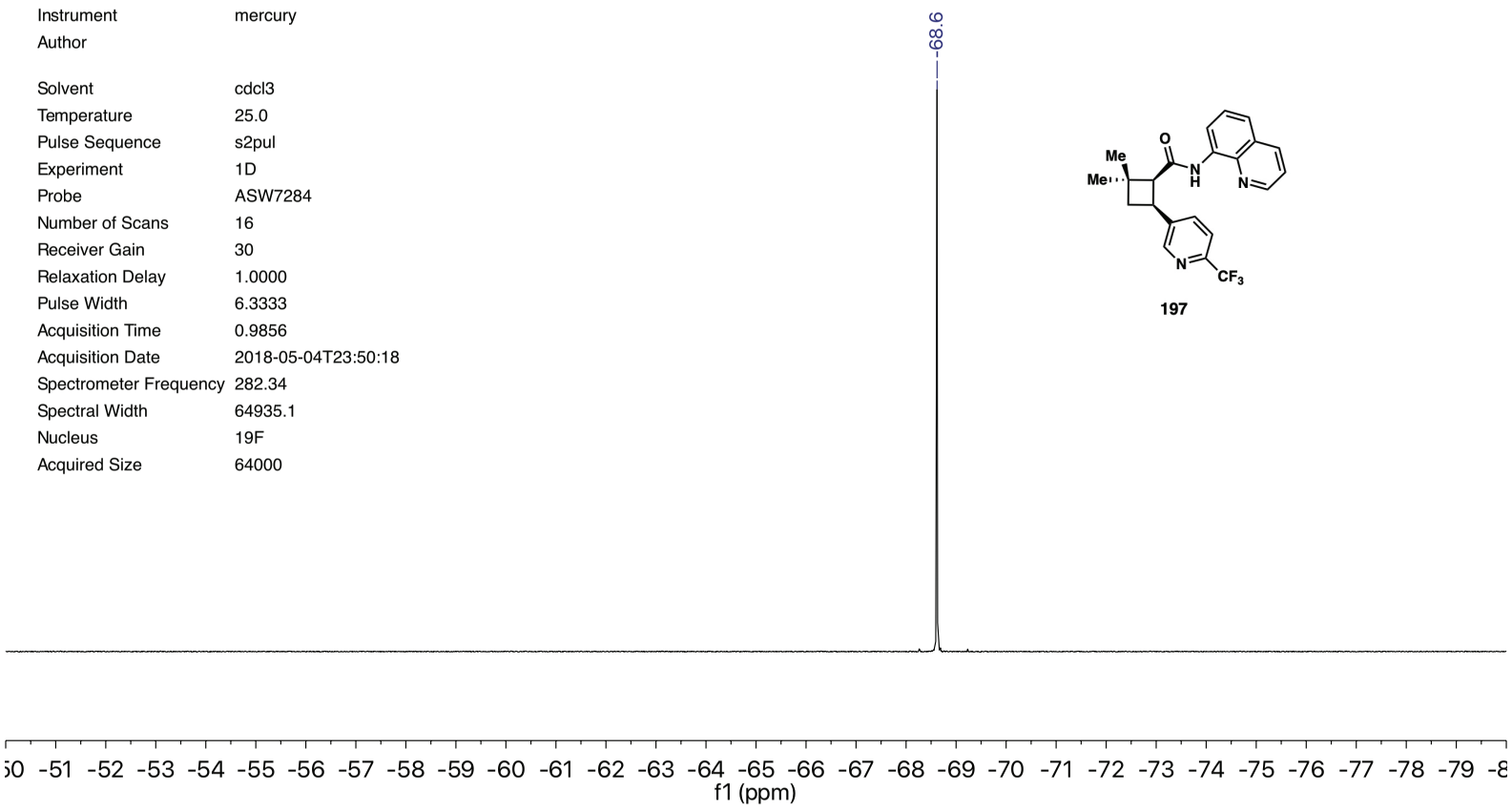
Spectrometer Frequency	282.34
Spectral Width	64935.1
Nucleus	19F
Acquired Size	64000



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Comment	JCB_05_107_19F
Origin	Varian
Owner	
Instrument	mercury
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	ASW7284
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	6.3333
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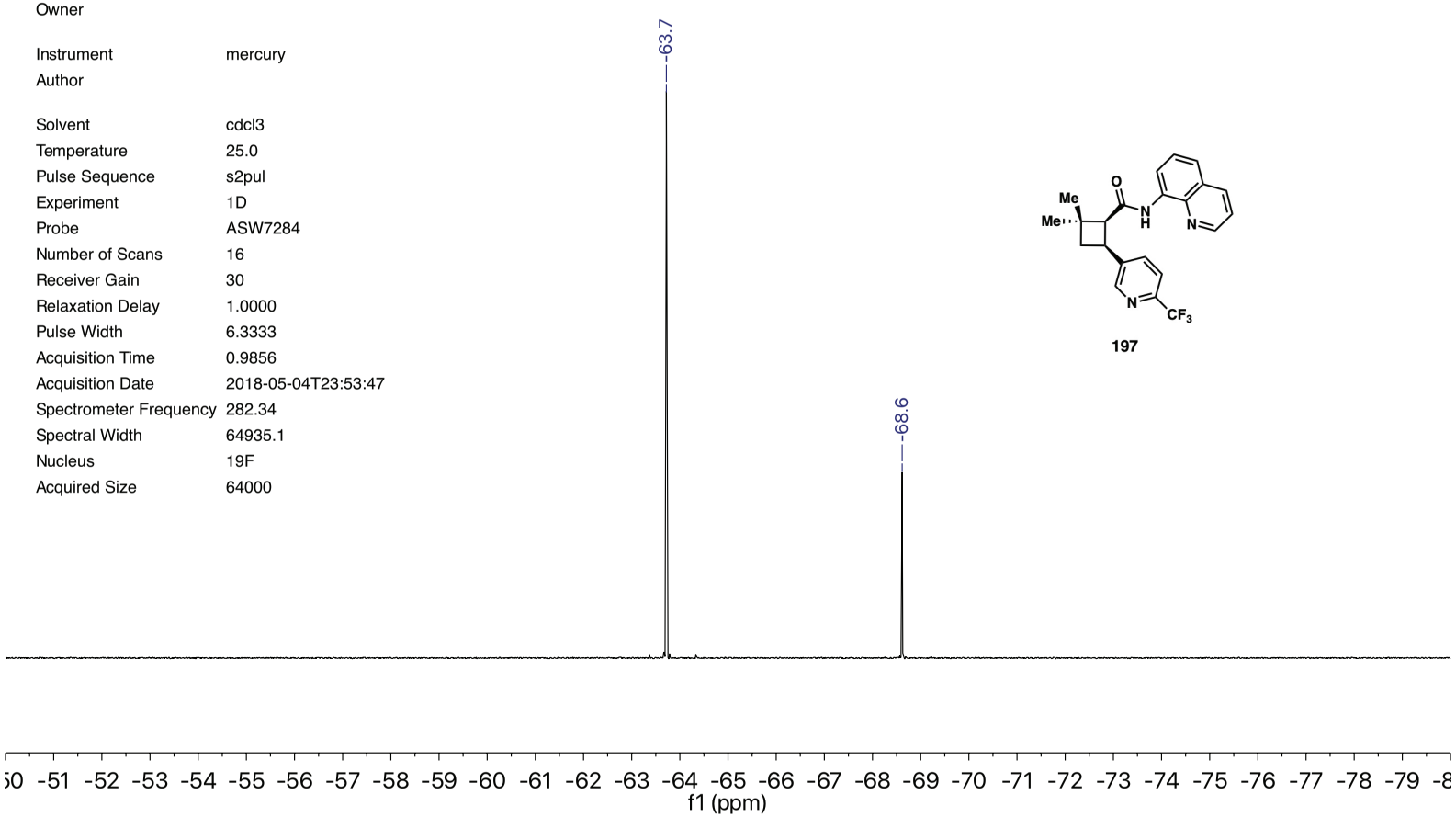
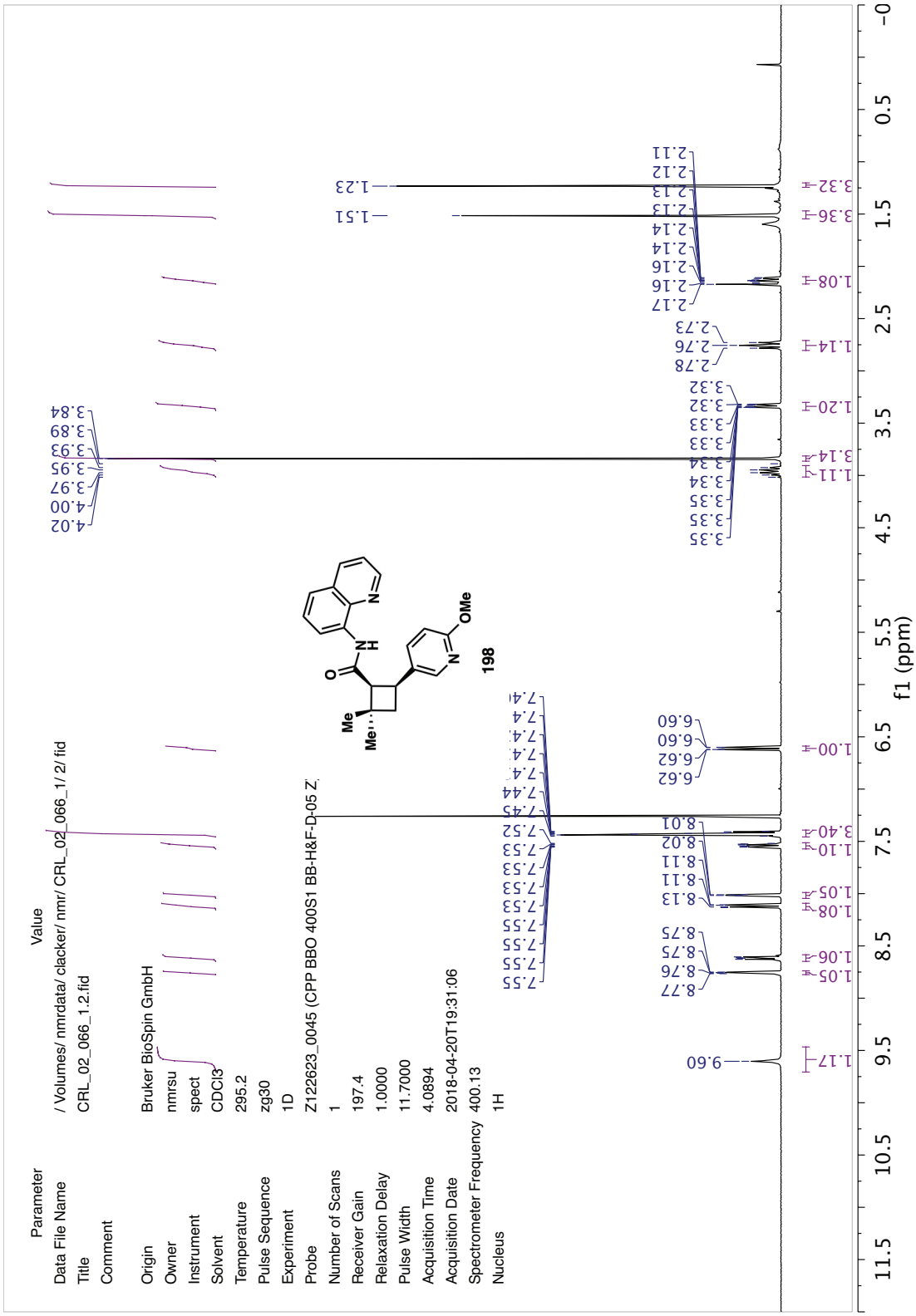
Spectral Width	64935.1
Nucleus	19F
Acquired Size	64000

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Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z
Number of Scans 1
Receiver Gain 197.4
Relaxation Delay 1.0000
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Acquisition Time 4.0894
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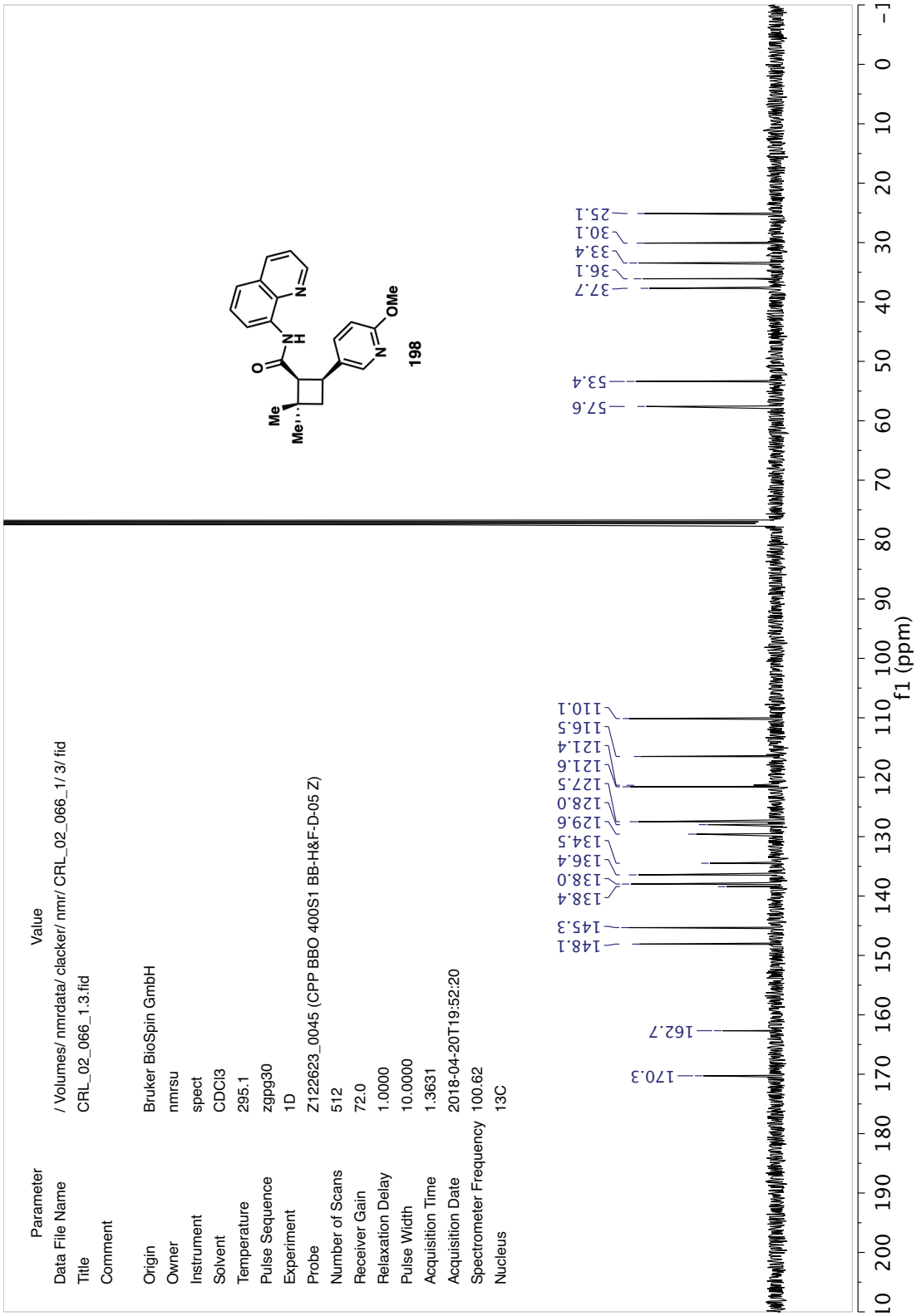
Spectrometer Frequency 400.13
Nucleus 1H
198
f1 (ppm)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Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-04-20T19:52:20
Spectrometer Frequency 100.62
Nucleus 13C
198
170.3
162.7
148.1
145.3
138.4
138.0
136.4
134.5
129.6
128.0
127.5
121.6
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110.1
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53.4
37.7
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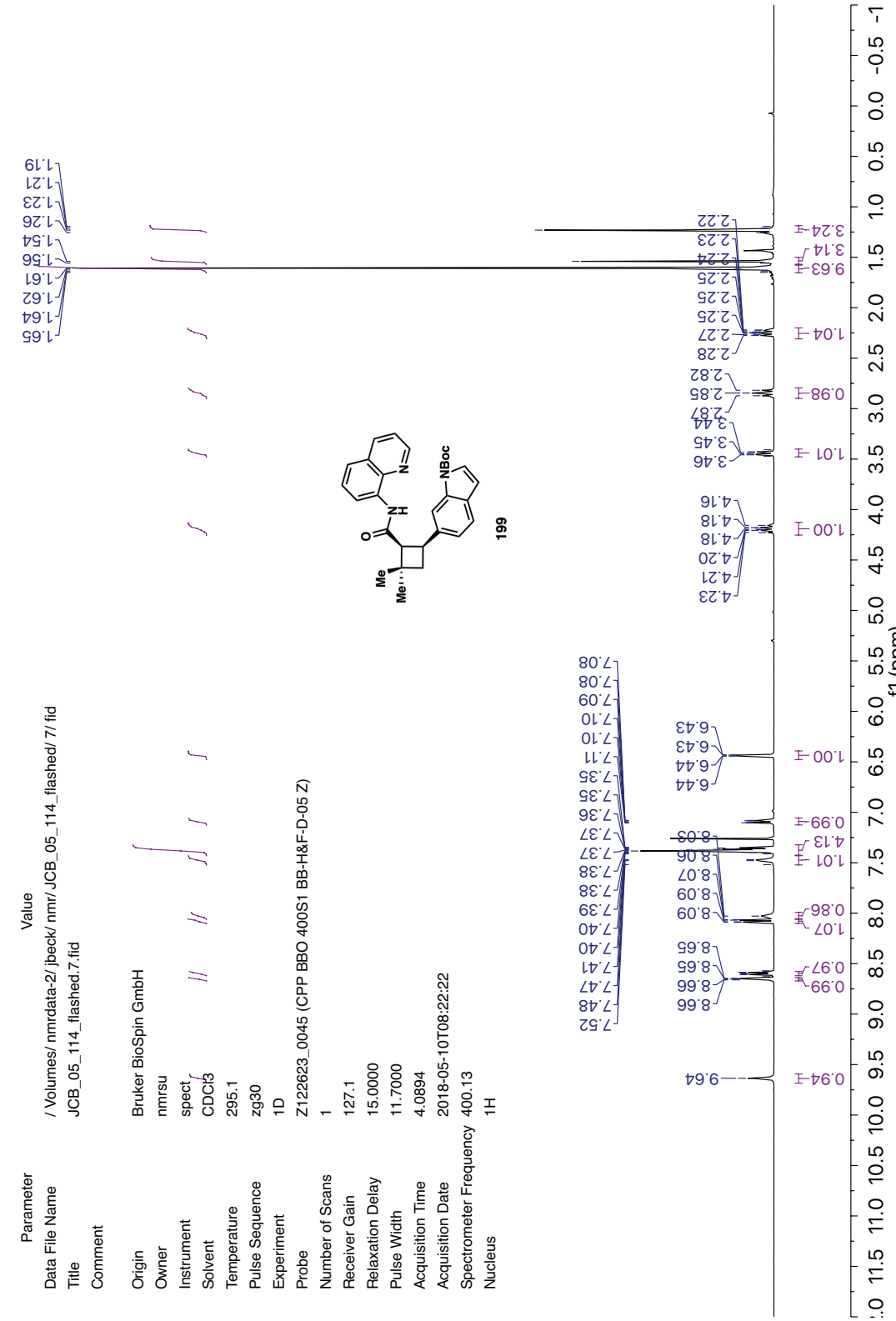
33.4
30.1
25.1
f1 (ppm)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Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 127.1
Relaxation Delay 15.0000
Pulse Width 11.7000
Acquisition Time 4.0894
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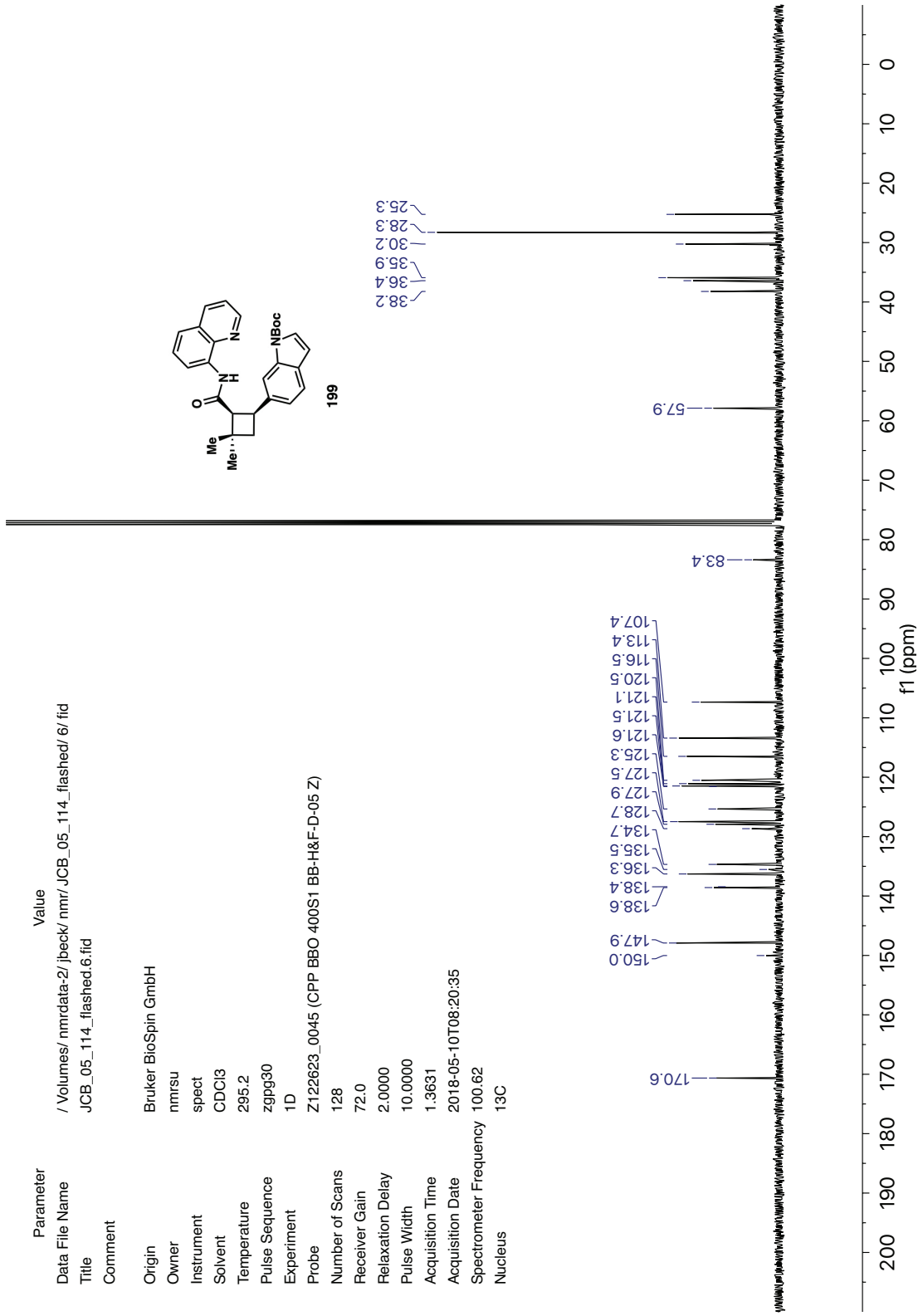
Nucleus 1H
199
f1 (ppm)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Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-05-10T08:20:35
Spectrometer Frequency 100.62
Nucleus 13C
199
Me
Me
O
N
H
N
NBoc
170.6
150.0
147.9
138.6
138.4
136.3
135.5
134.7
128.7
127.9
127.5
125.3
121.6
121.5
121.1
120.5
116.5
113.4
107.4
83.4
57.9
38.2
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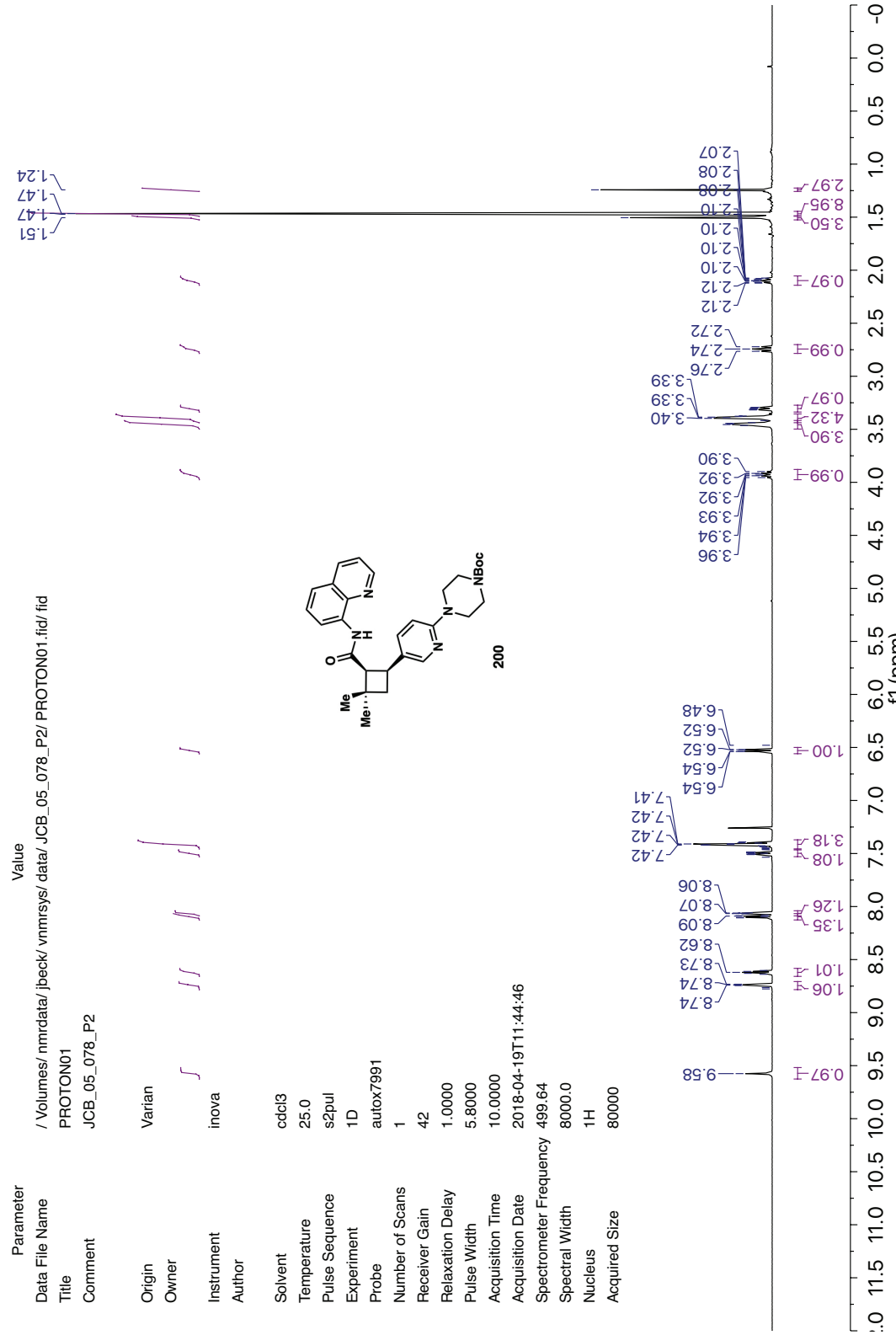
f1 (ppm)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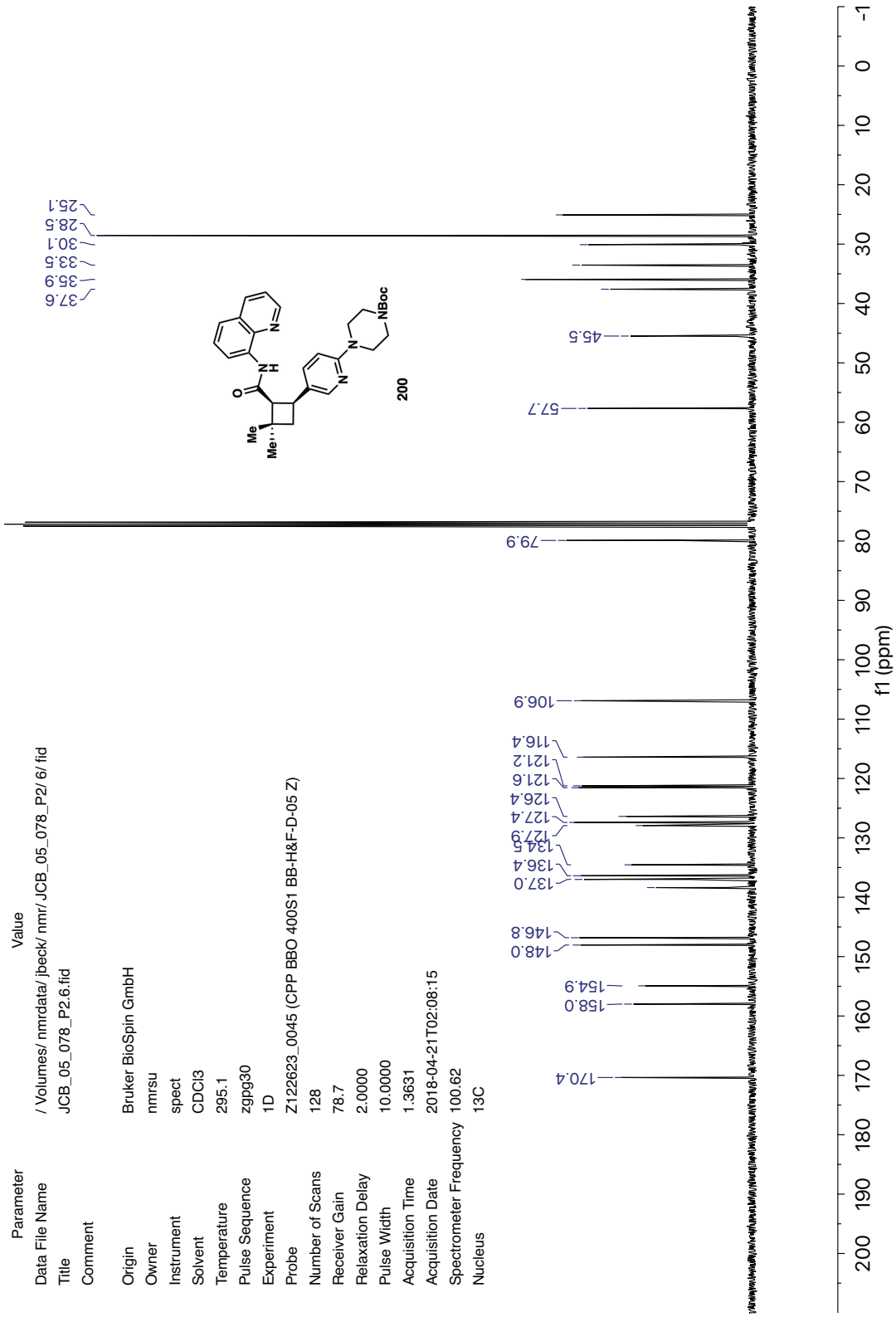
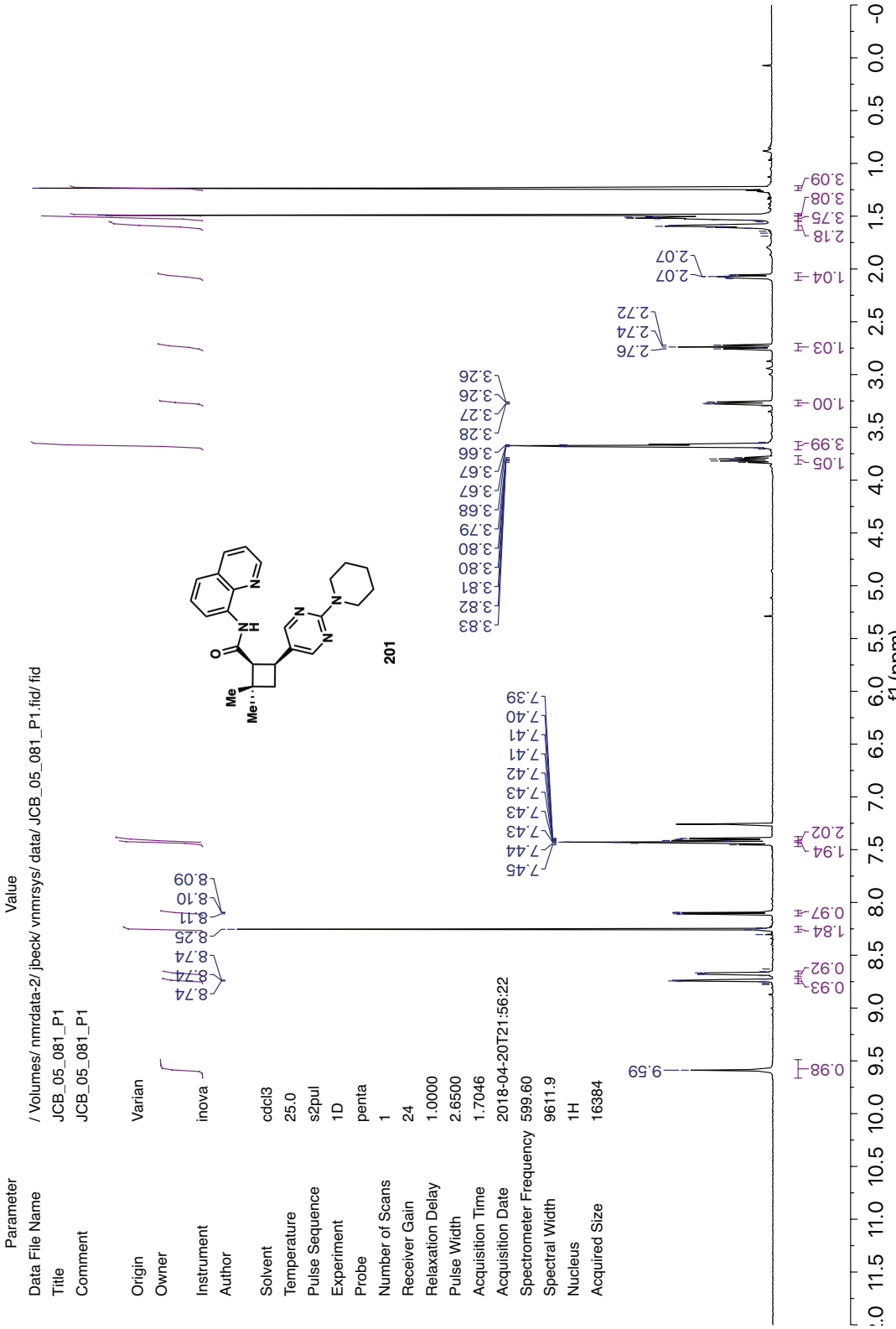
Comment JCB_05_078_P2
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe autox7991
Number of Scans 1
Receiver Gain 42
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 10.0000
Acquisition Date 2018-04-19T11:44:46
Spectrometer Frequency 499.64
Spectral Width 8000.0
Nucleus 1H
Acquired Size 80000
200
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_078_P2/ 6/ fid
Title JCB_05_078_P2.6.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 78.7
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-04-21T02:08:15
Spectrometer Frequency 100.62
Nucleus 13C
200
NBoc
Me
Me
25.1
28.5
30.1
33.5
35.9
37.6
45.5
57.7
79.9
106.9
116.4
121.2
121.6
126.4
127.4
127.9
134.5
136.4
137.0
146.8
148.0
154.9
158.0
170.4
f1 (ppm)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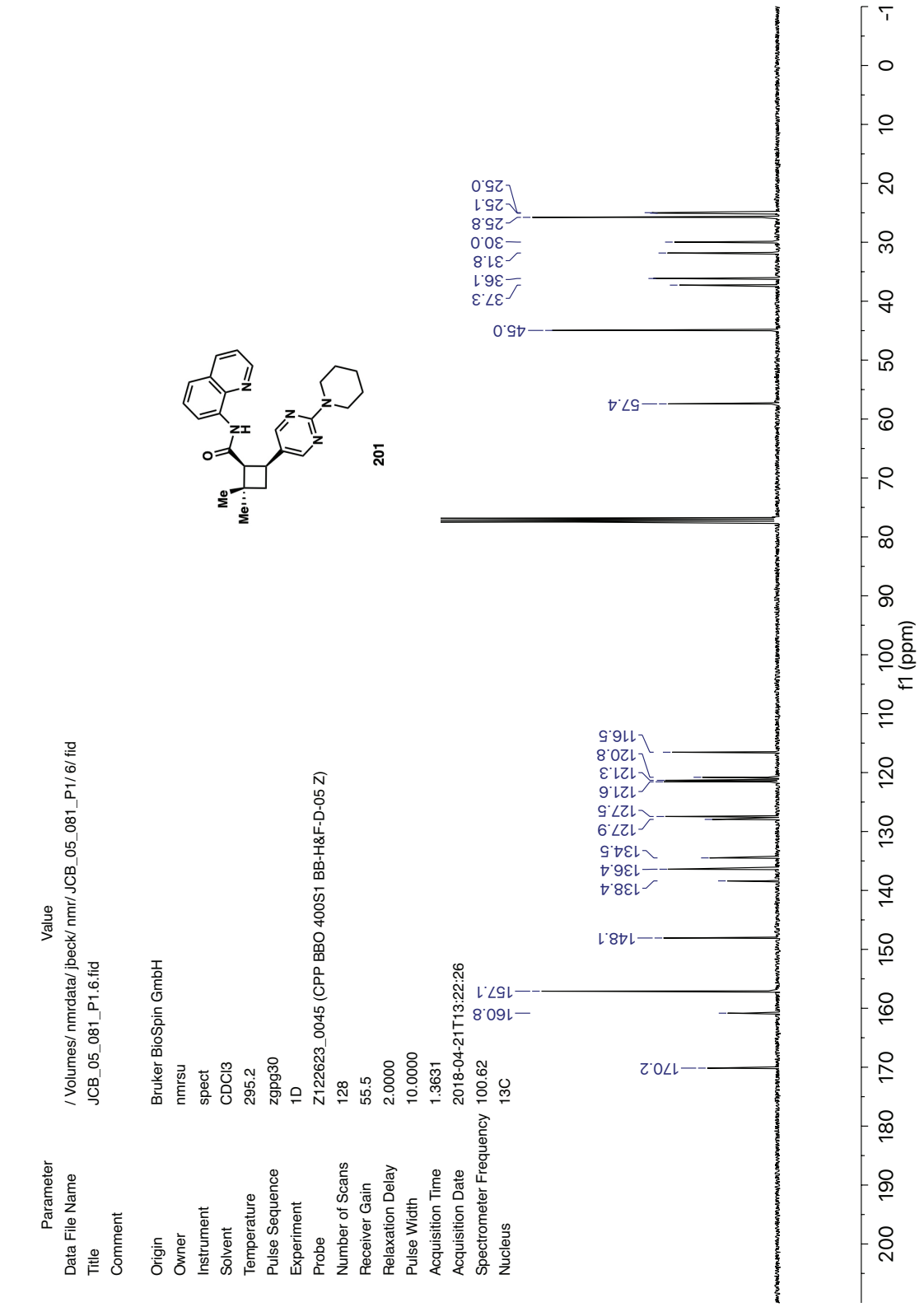
Title JCB_05_081_P1
Comment JCB_05_081_P1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 1
Receiver Gain 24
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Acquisition Date 2018-04-20T21:56:22
Spectrometer Frequency 599.60
Spectral Width 9611.9
Nucleus 1H
Acquired Size 16384
201
f1 (ppm)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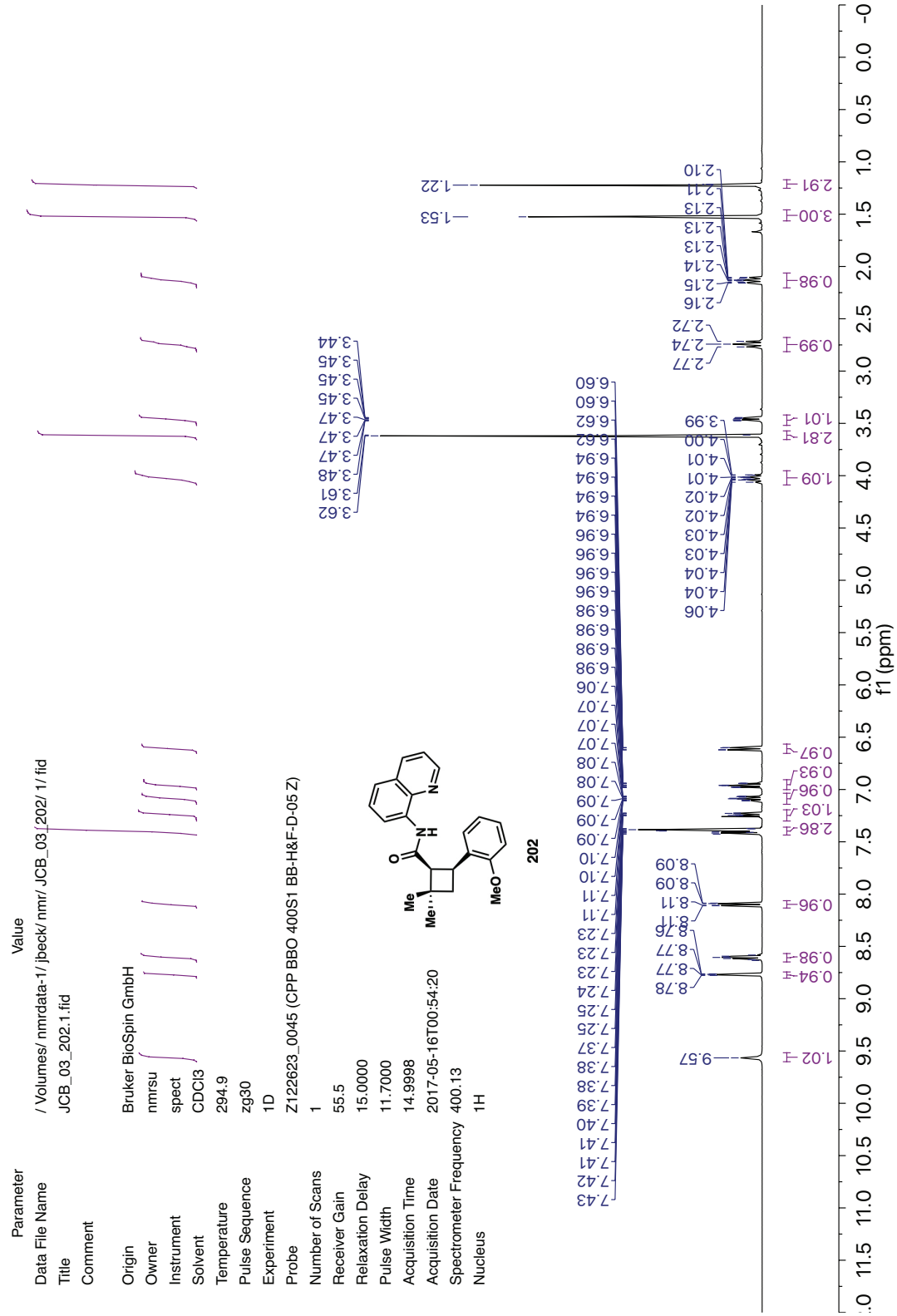
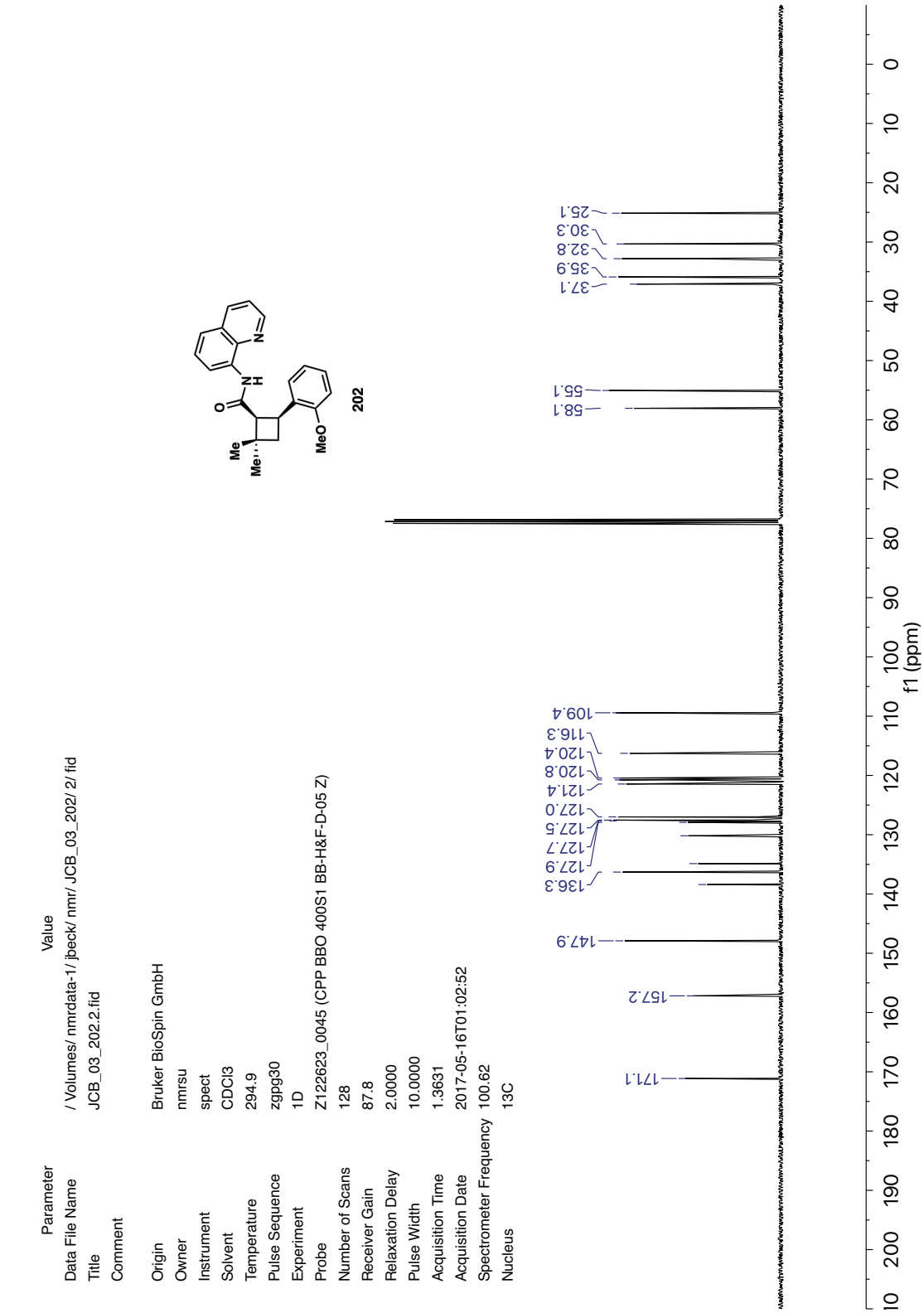
Title JCB_05_081_P1.6.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 55.5
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-04-21T13:22:26
Spectrometer Frequency 100.62
Nucleus 13C
201
170.2
160.8
157.1
148.1
138.4
136.4
134.5
127.9
127.5
121.6
121.3
120.8
116.5
57.4
45.0
37.3
36.1
31.8
30.0
25.8
25.1
25.0
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_03_202/ 1/ fid
Title JCB_03_202.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 55.5
Relaxation Delay 15.0000
Pulse Width 11.7000
Acquisition Time 14.9998
Acquisition Date 2017-05-16T00:54:20
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
MeO
202
f1 (ppm)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Value
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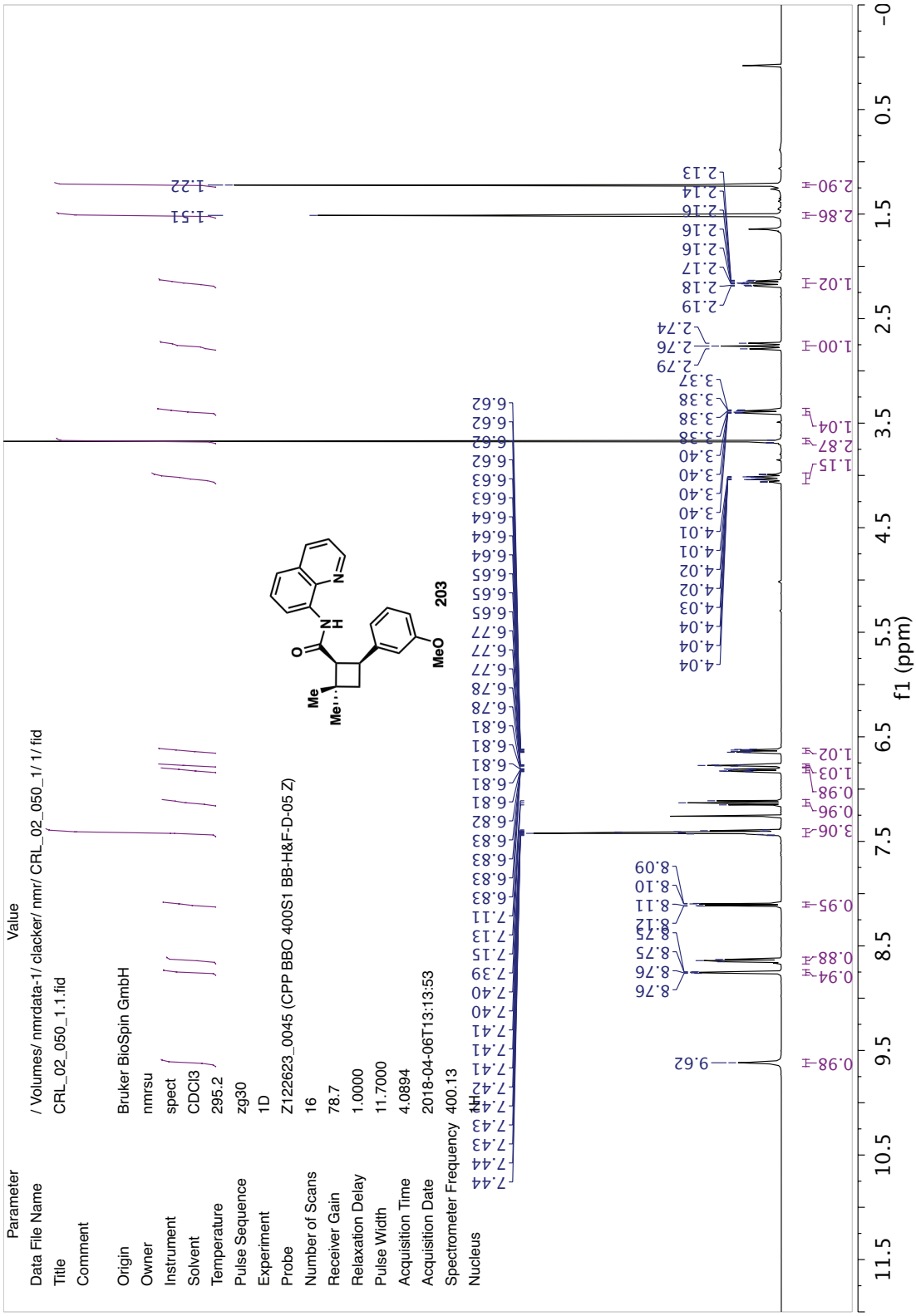
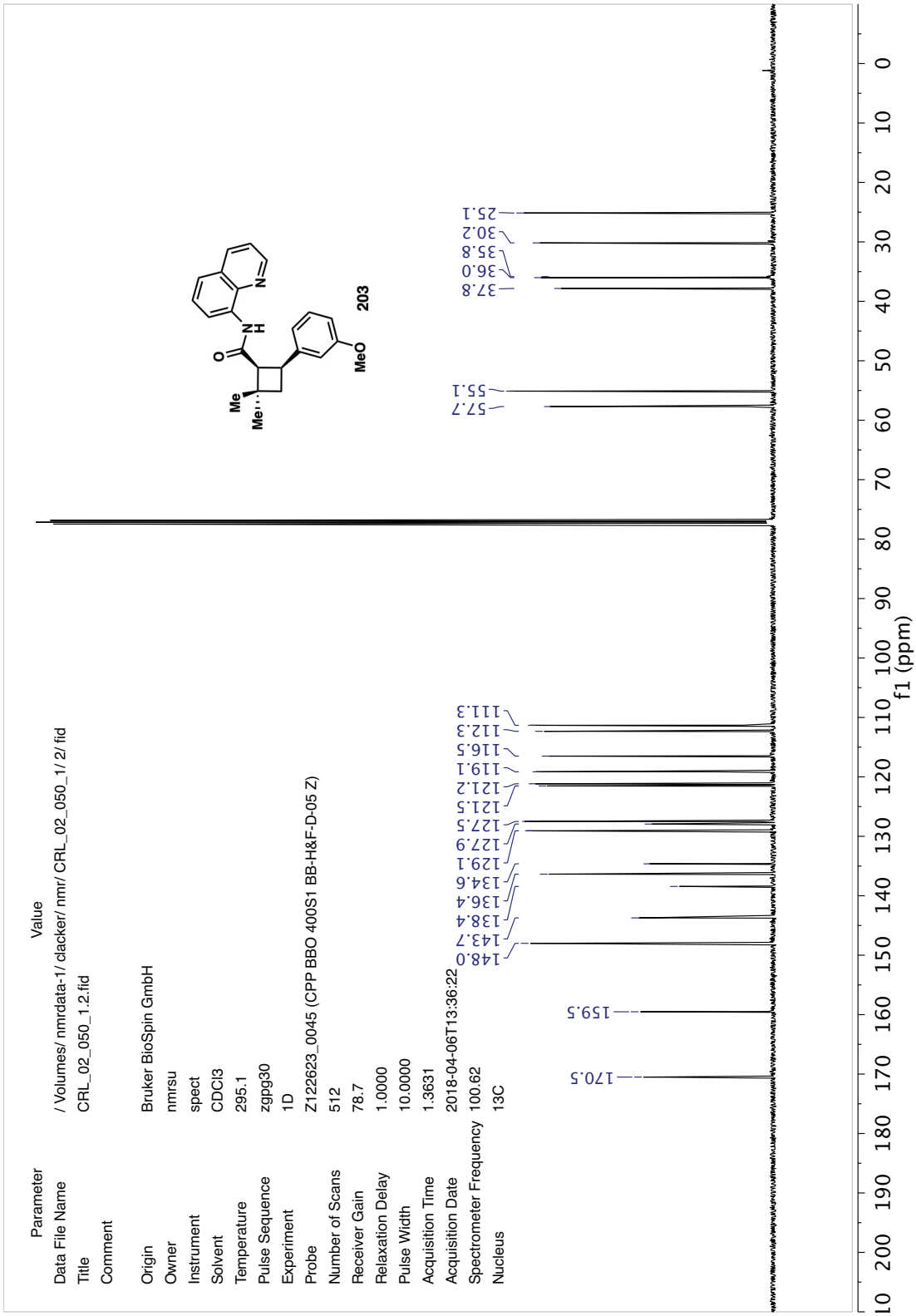
Title JCB_03_202_2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 87.8
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-05-16T01:02:52
Spectrometer Frequency 100.62
Nucleus 13C
202
Me
Me
MeO
171.1
157.2
147.9
136.3
127.9
127.7
127.5
127.0
121.4
120.8
120.4
116.3
109.4
58.1
55.1
37.1
35.9
32.8
30.3
25.1
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ clacker/ nmr/ CRL_02_050_1/ 1/ fid
Title CRL_02_050_1.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-04-06T13:13:53
Spectrometer Frequency 400.13
Nucleus 1H
203
MeO
Me
Me
f1 (ppm)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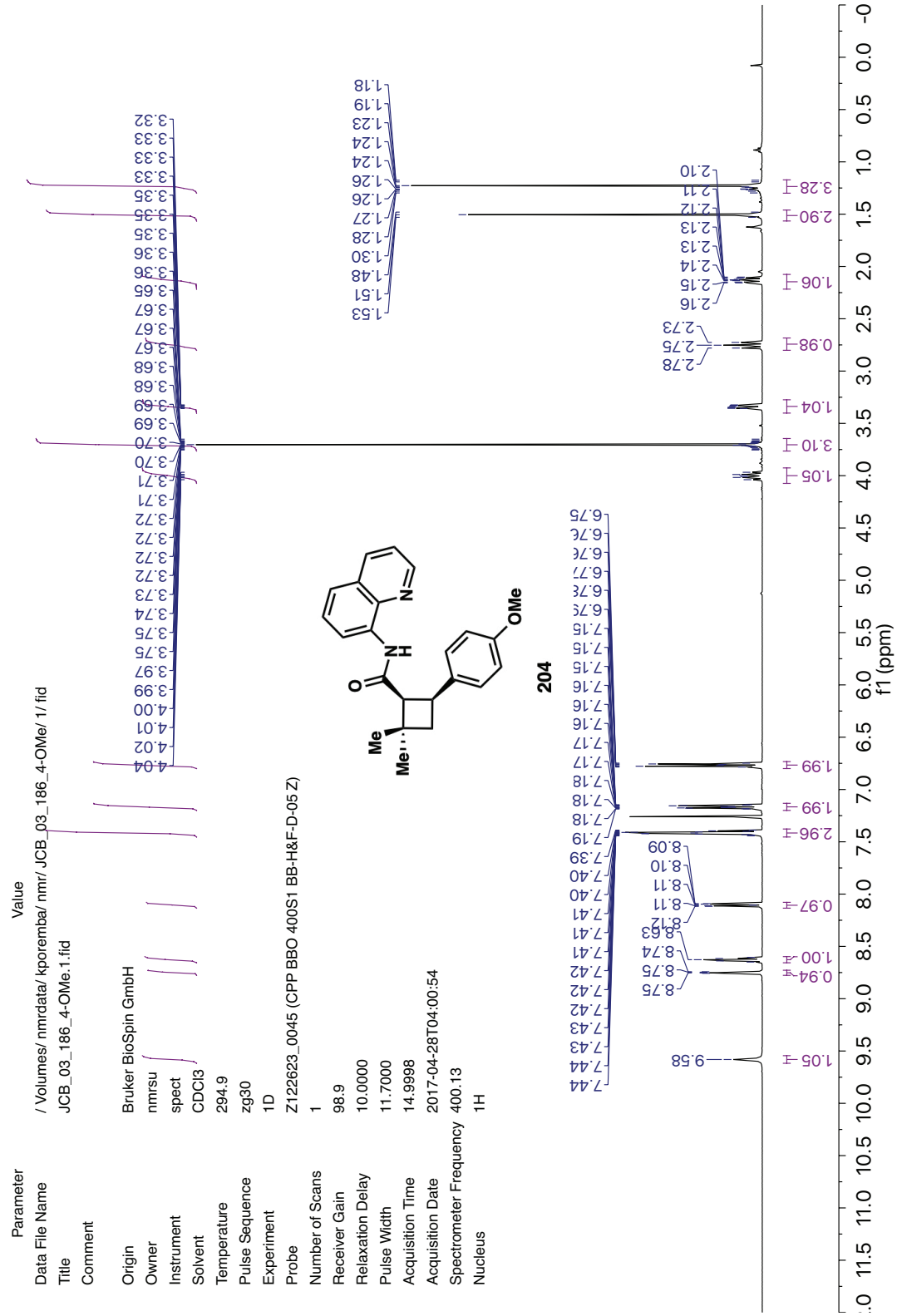
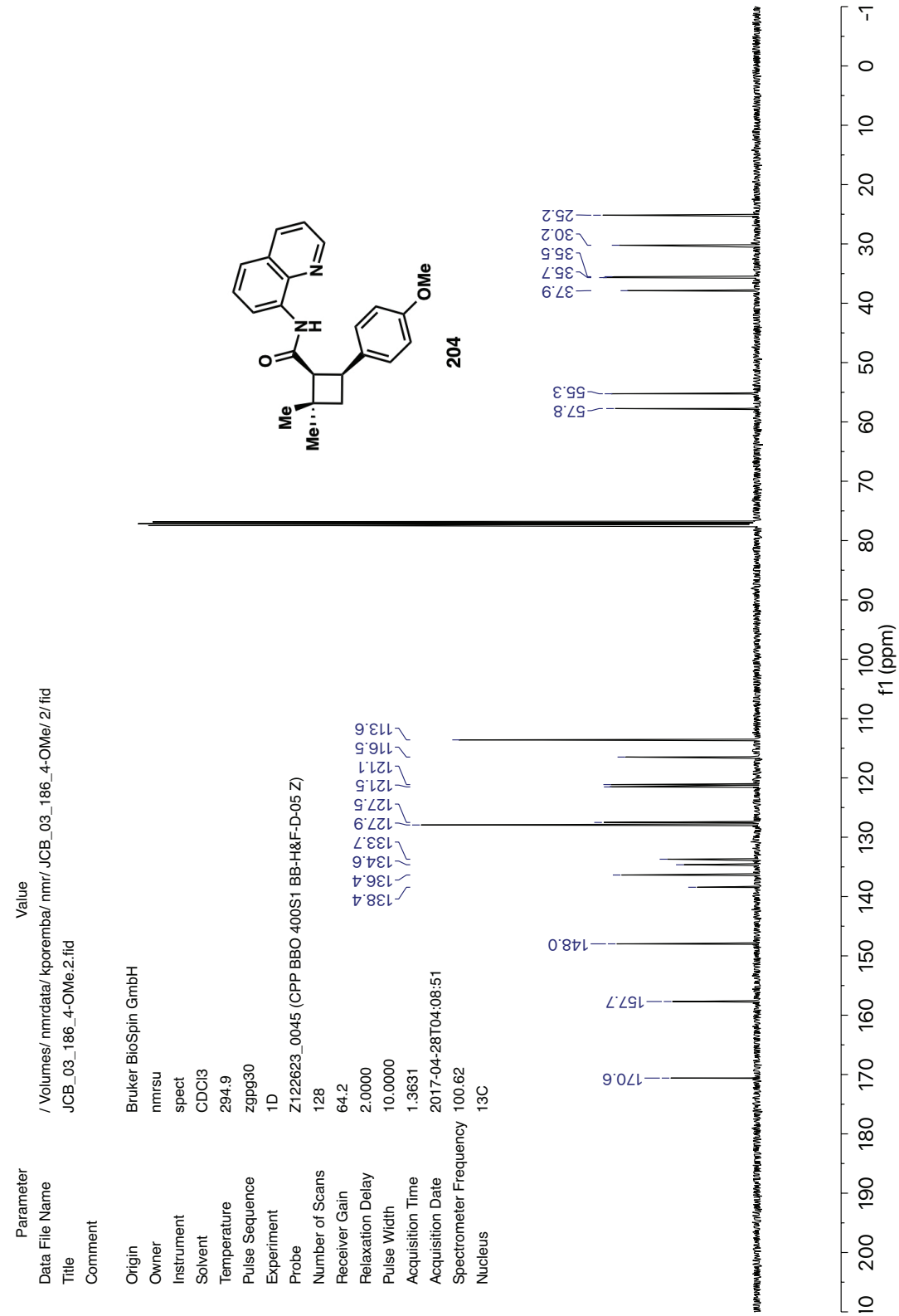
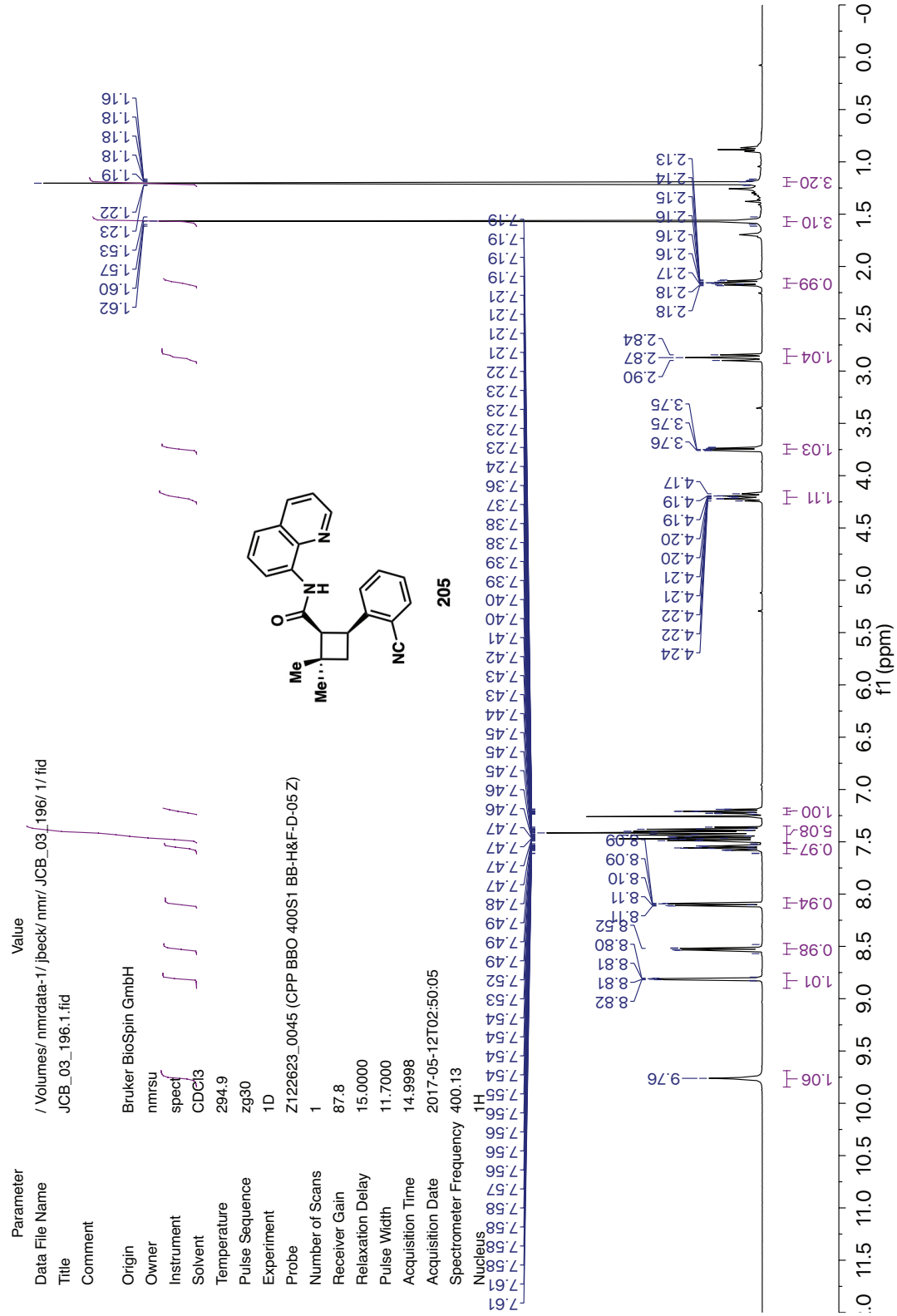
Data File Name / Volumes/ nmrdata-1/ clacker/ nmr/ CRL_02_050_1/ 2/ fid
Title CRL_02_050_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-04-06T13:36:22
Spectrometer Frequency 100.62
Nucleus 13C
170.5
159.5
148.0
143.7
138.4
136.4
134.6
129.1
127.9
127.5
121.5
121.2
119.1
116.5
112.3
111.3
57.7
55.1
37.8
36.0
35.8
30.2
25.1
Me
Me
N
H
O
MeO
203
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ kporemba/ nmr/ JCB_03_186_4-OMe/ 1/ fid
Title JCB_03_186_4-OMe.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 98.9
Relaxation Delay 10.0000
Pulse Width 11.7000
Acquisition Time 14.9998
Acquisition Date 2017-04-28T04:00:54
Spectrometer Frequency 400.13
Nucleus 1H
204
Me
Me
OMe
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ kporemba/ nmr/ JCB_03_186_4-OMe/ 2/ fid
Title JCB_03_186_4-OMe.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 64.2
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-04-28T04:08:51
Spectrometer Frequency 100.62
Nucleus 13C
204
Me
Me
O
N
H
N
OMe
170.6
157.7
148.0
138.4
136.4
134.6
133.7
127.9
127.5
121.5
121.1
116.5
113.6
57.8
55.3
37.9
35.7
35.5
30.2
25.2
f1 (ppm)


Parameter Value
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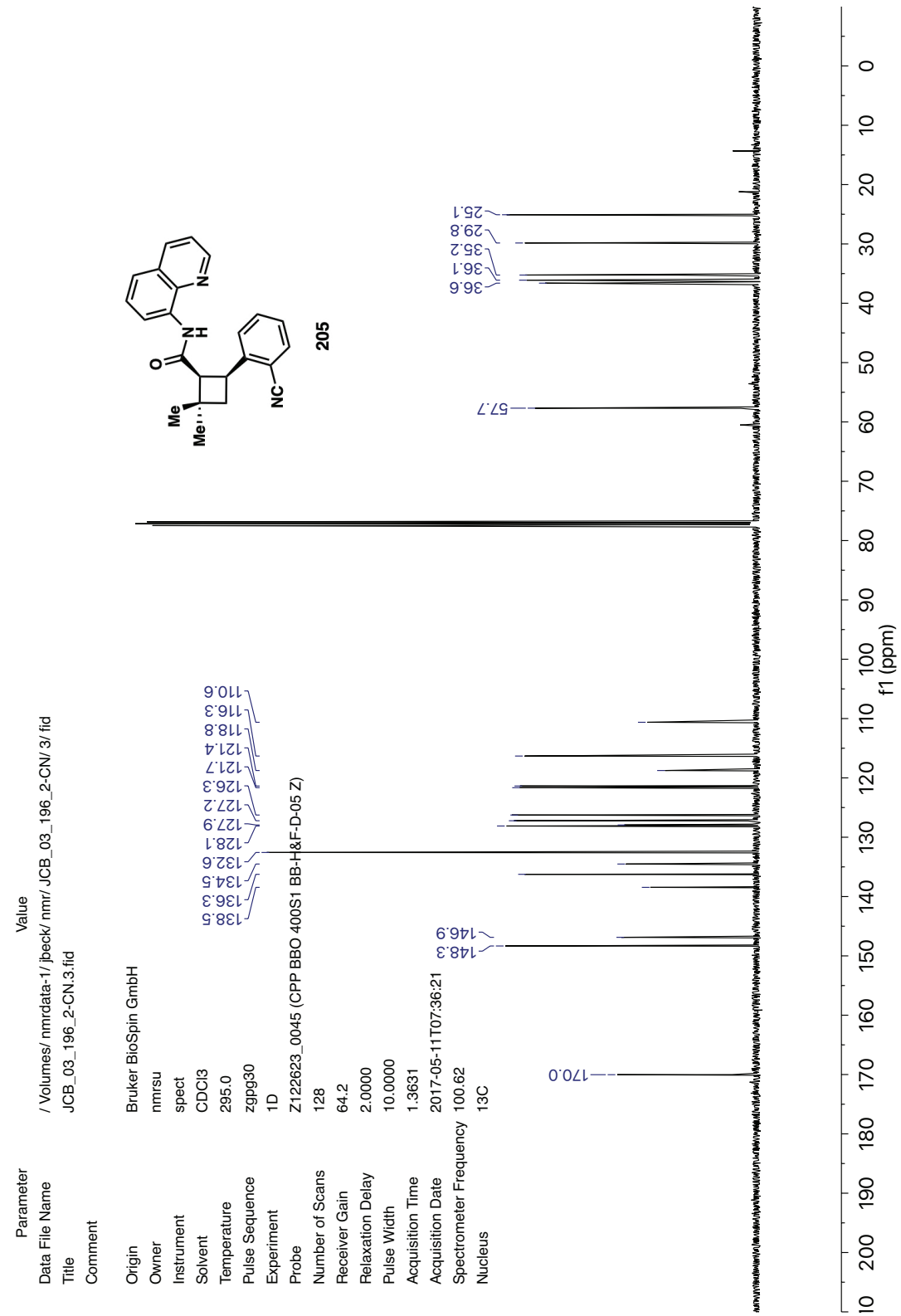
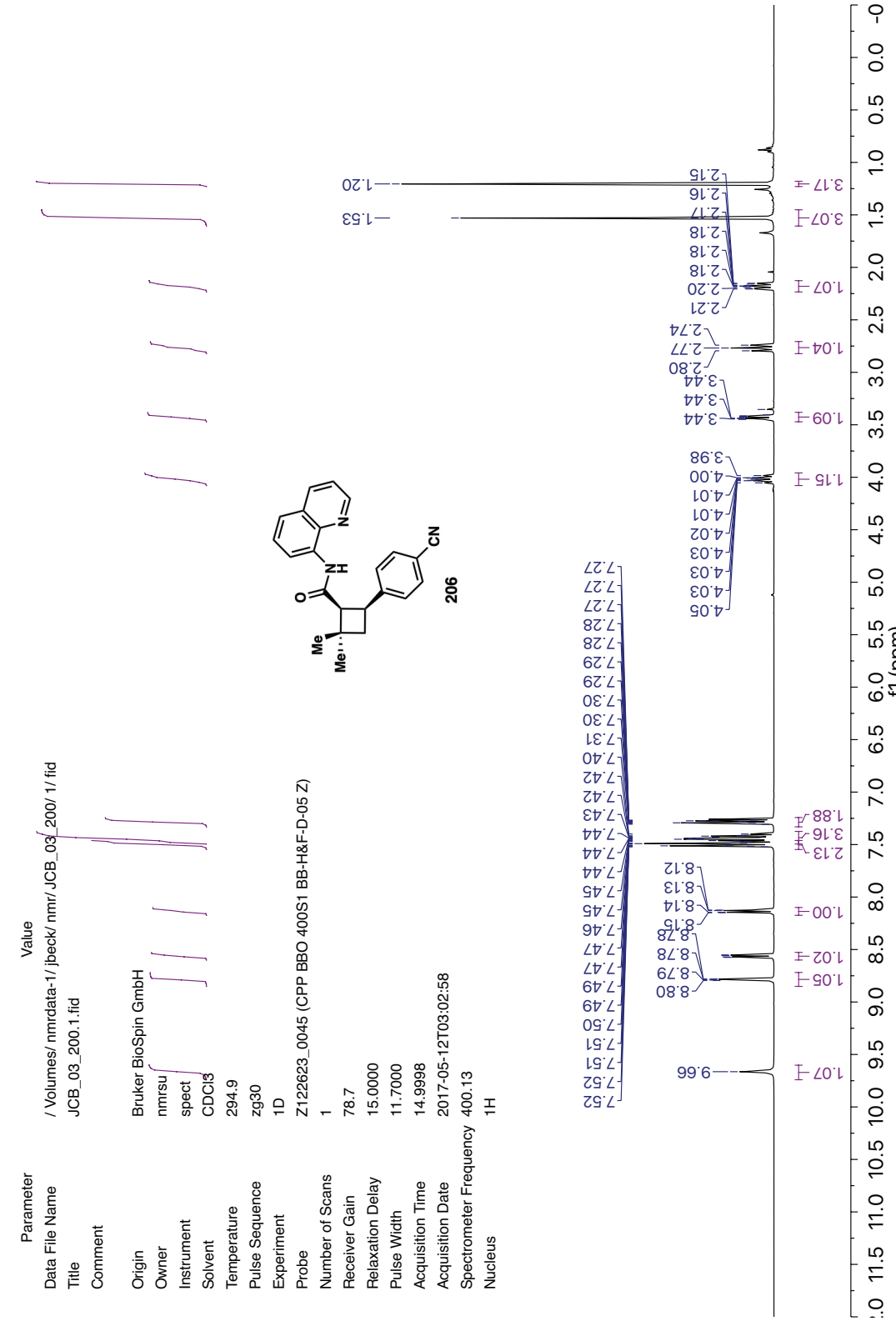
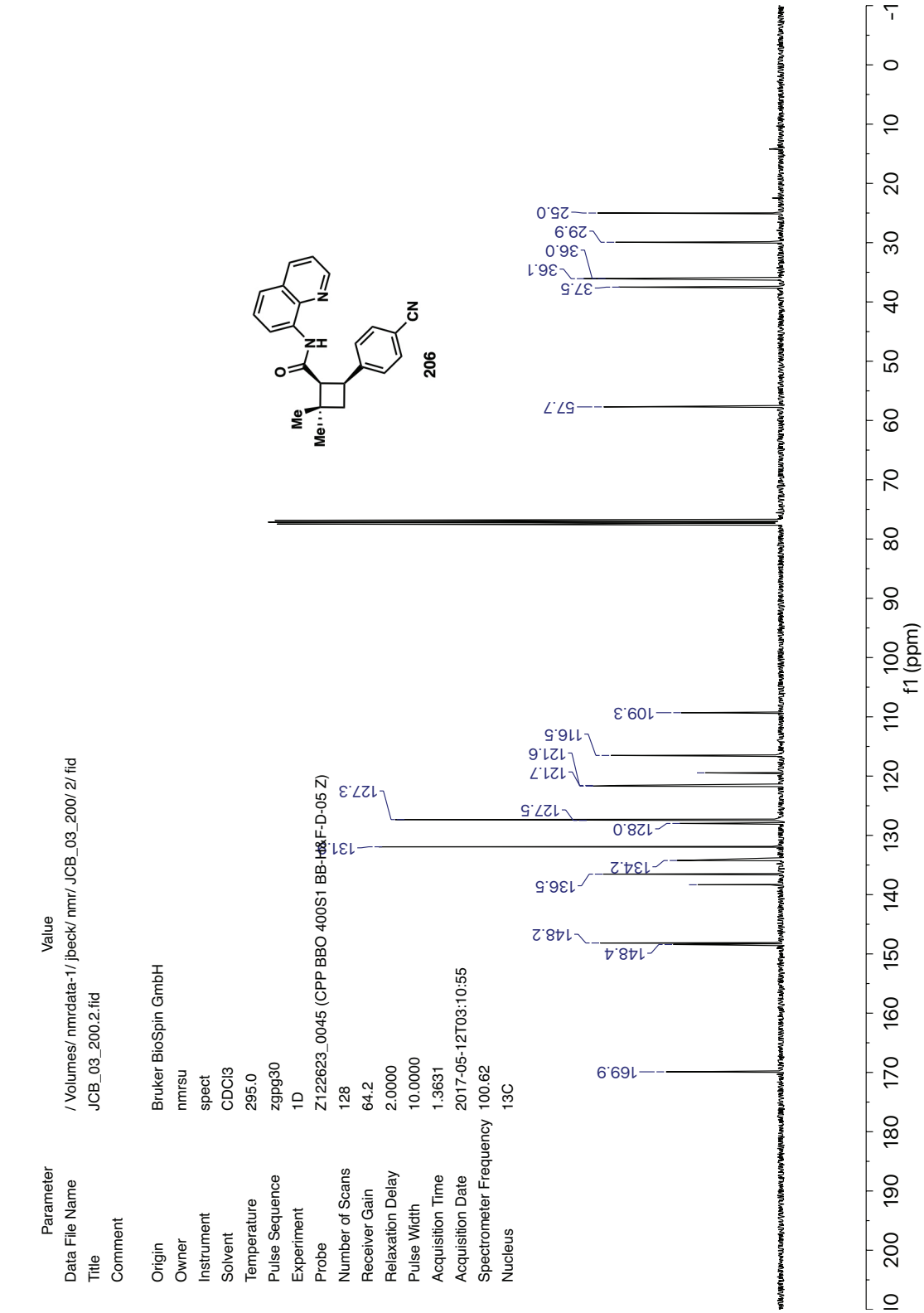
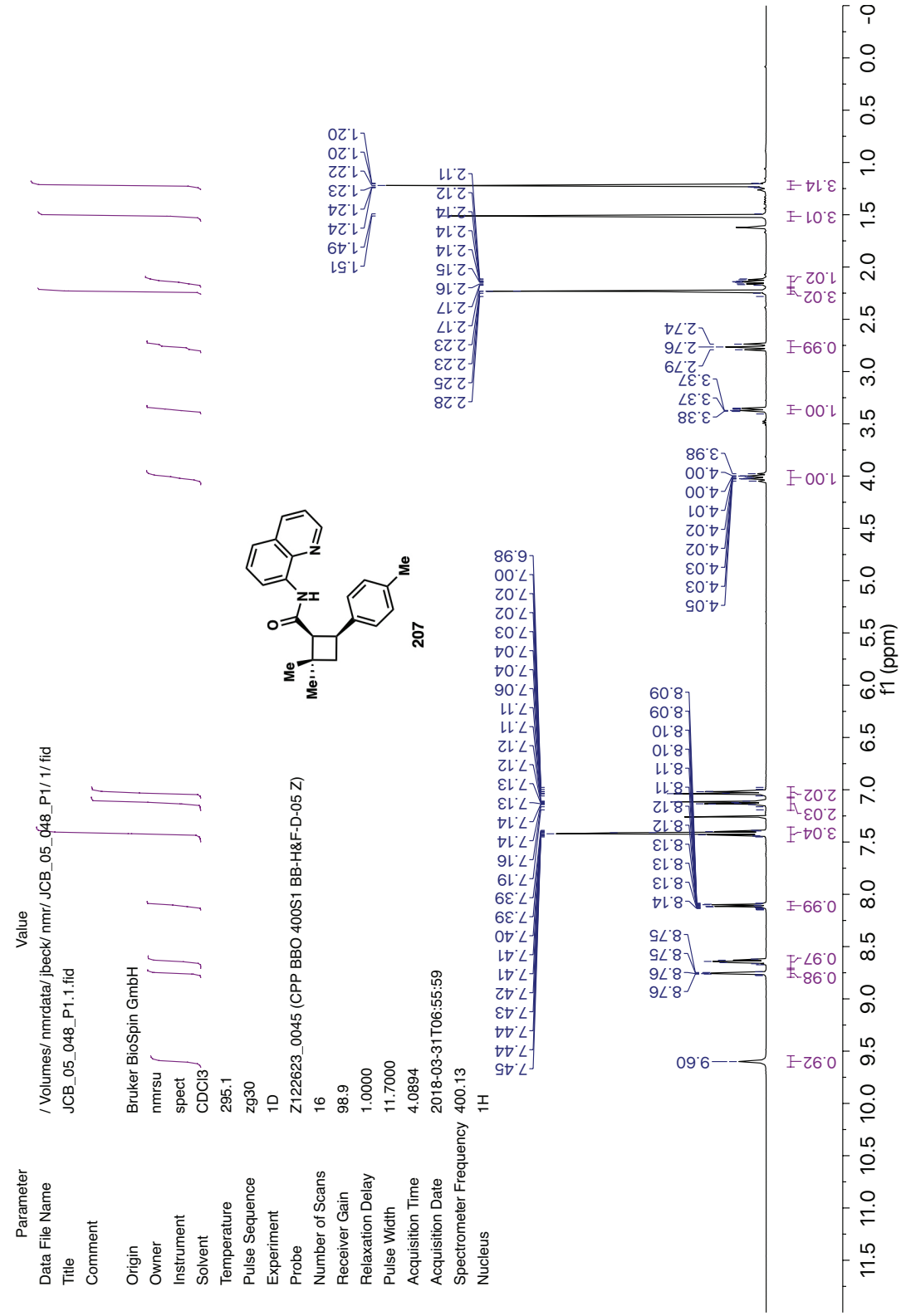
Title JCB_03_196.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 87.8
Relaxation Delay 15.0000
Pulse Width 11.7000
Acquisition Time 14.9998
Acquisition Date 2017-05-12T02:50:05
Spectrometer Frequency 400.13
Nucleus 1H
205
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_03_196_2-CN/ 3/ fid
Title JCB_03_196_2-CN.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 64.2
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-05-11T07:36:21
Spectrometer Frequency 100.62
Nucleus 13C
205
Me
Me
NC
O
N
H
N
170.0
148.3
146.9
138.5
136.3
134.5
132.6
128.1
127.9
127.2
126.3
121.7
121.4
118.8
116.3
110.6
57.7
36.6
36.1
35.2
29.8
25.1
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_03_200/ 1/ fid
Title JCB_03_200.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 78.7
Relaxation Delay 15.0000
Pulse Width 11.7000
Acquisition Time 14.9998
Acquisition Date 2017-05-12T03:02:58
Spectrometer Frequency 400.13
Nucleus 1H
206
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_03_200/ 2/ fid
Title JCB_03_200.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 64.2
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-05-12T03:10:55
Spectrometer Frequency 100.62
Nucleus 13C
206
Me
Me
O
N
H
N
CN
169.9
148.4
148.2
136.5
134.2
131.8
128.0
127.5
127.3
121.7
121.6
116.5
109.3
57.7
37.5
36.1
36.0
29.9
25.0
f1 (ppm)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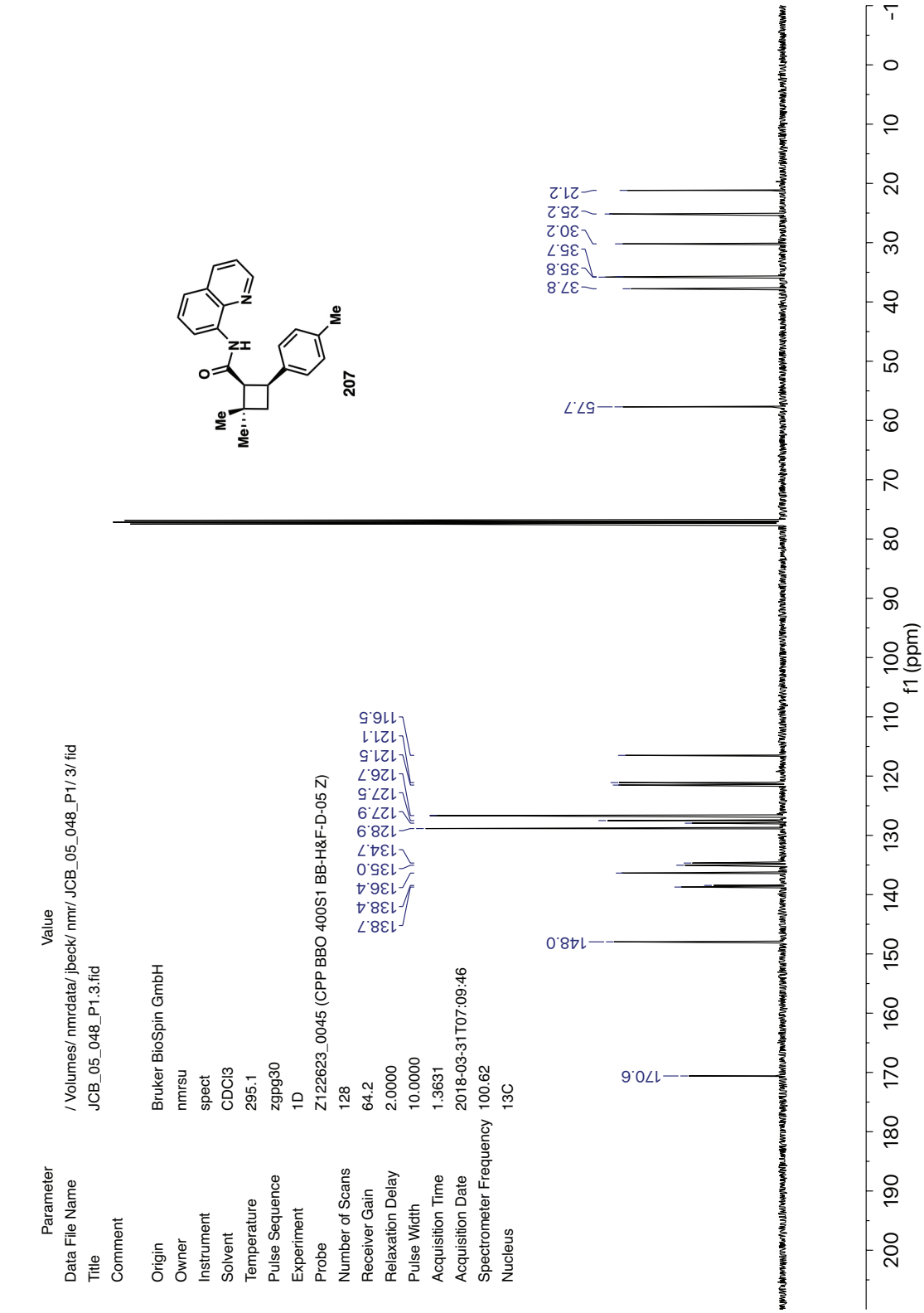
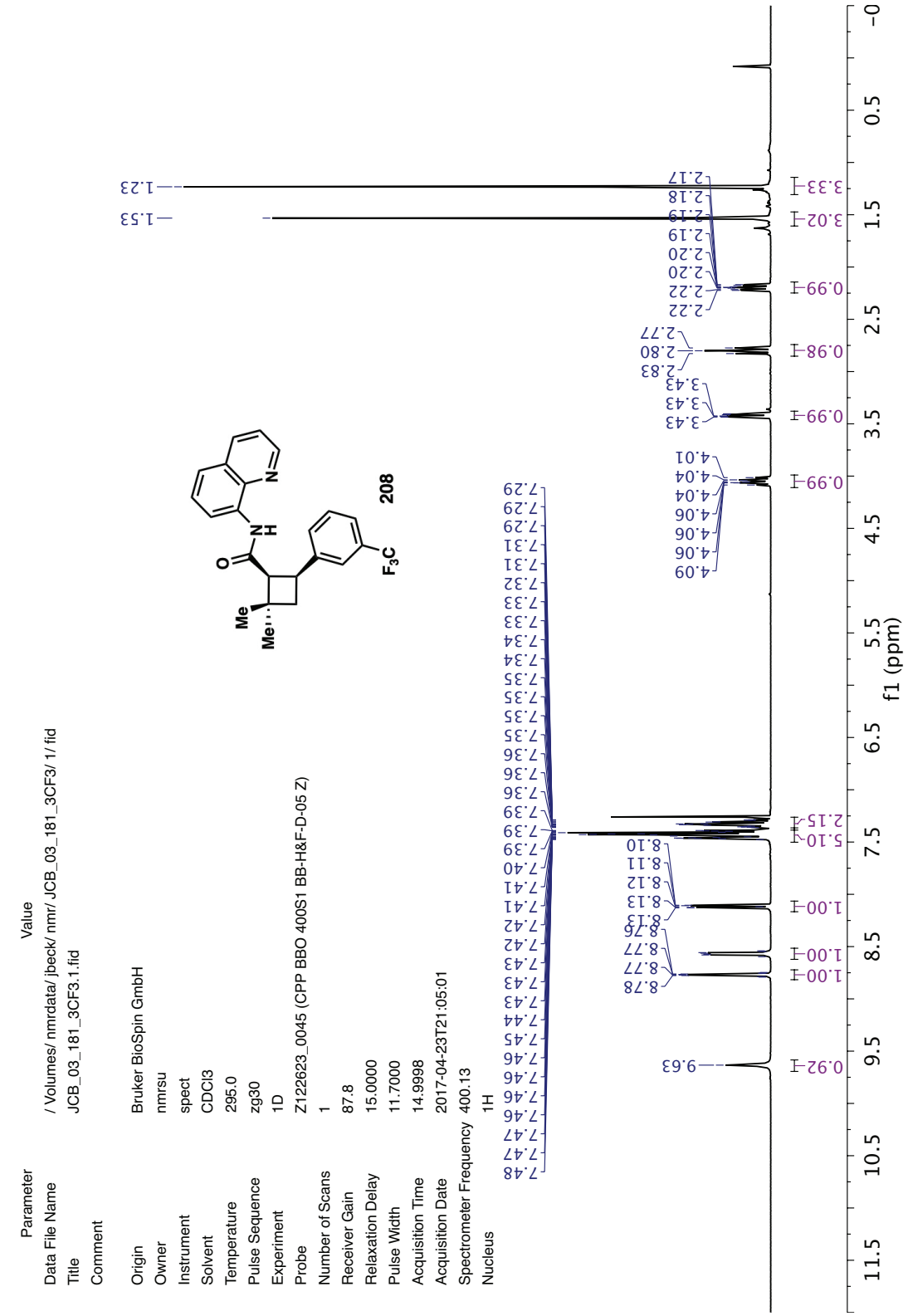
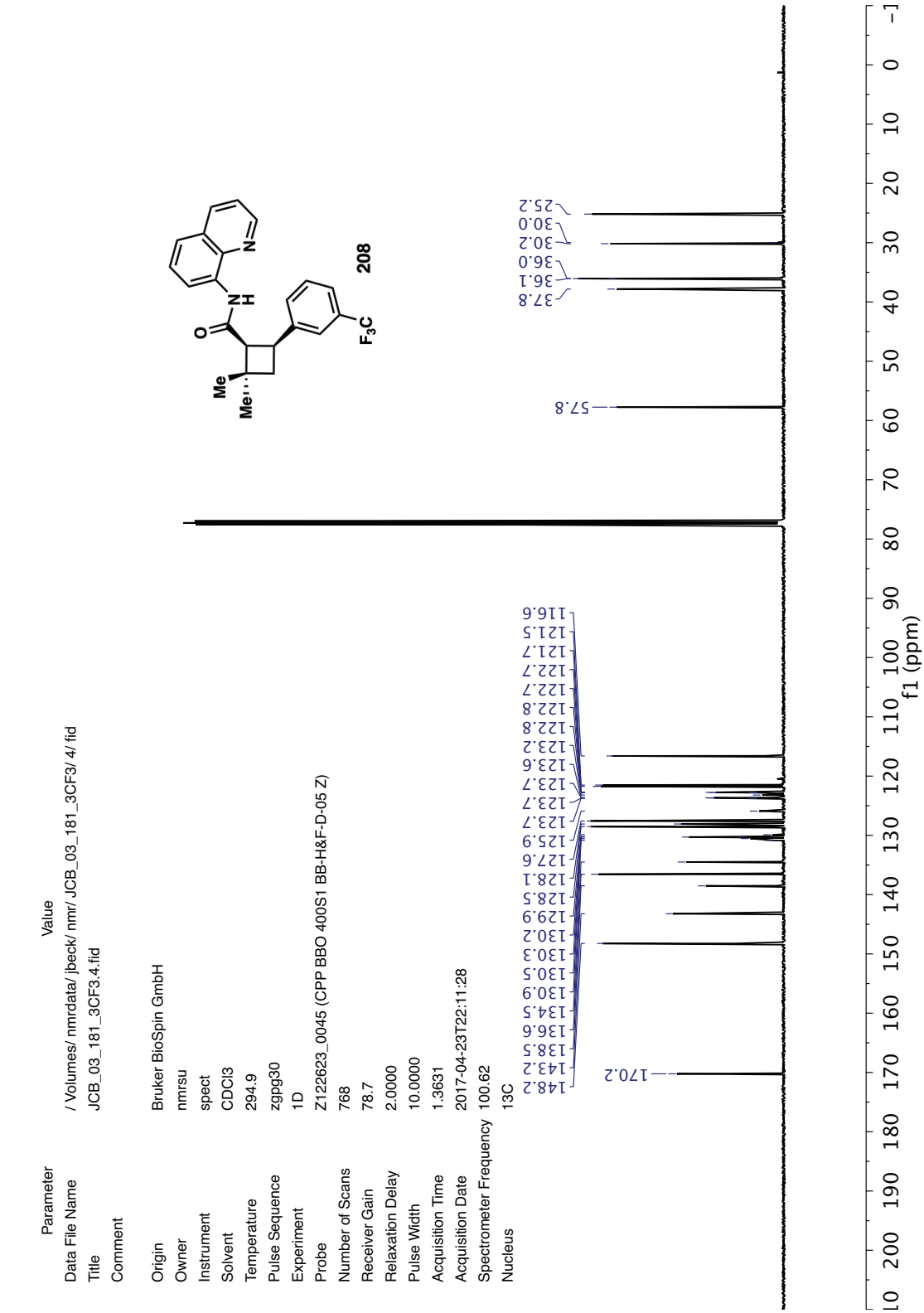
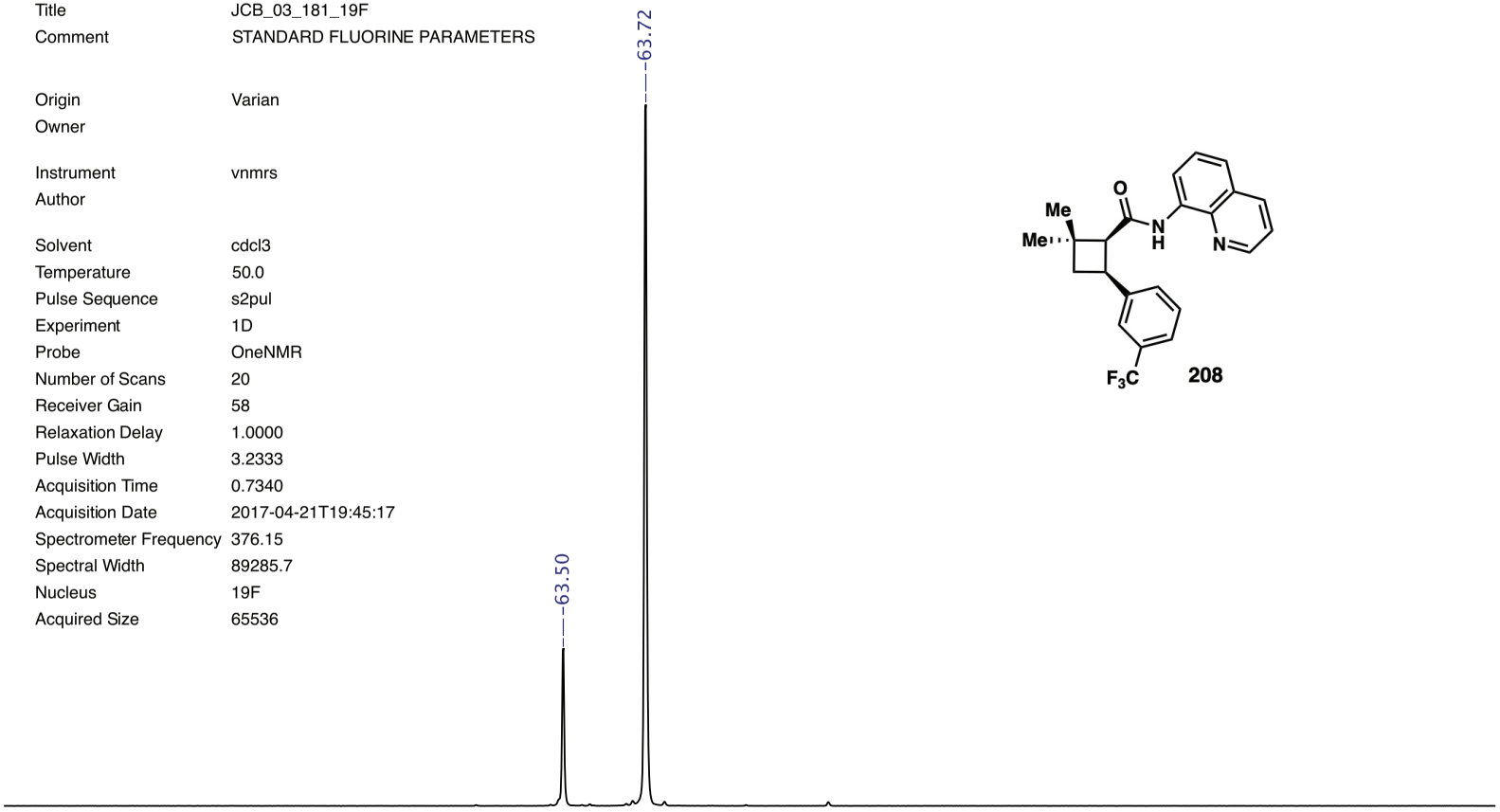
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_048_P1/ 1/ fid
Title JCB_05_048_P1.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-03-31T06:55:59
Spectrometer Frequency 400.13
Nucleus 1H
207
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_048_P1/ 3/ fid
Title JCB_05_048_P1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 64.2
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-03-31T07:09:46
Spectrometer Frequency 100.62
Nucleus 13C
207
170.6
148.0
138.7
138.4
136.4
135.0
134.7
128.9
127.9
127.5
126.7
121.5
121.1
116.5
57.7
37.8
35.8
35.7
30.2
25.2
21.2
f1 (ppm)

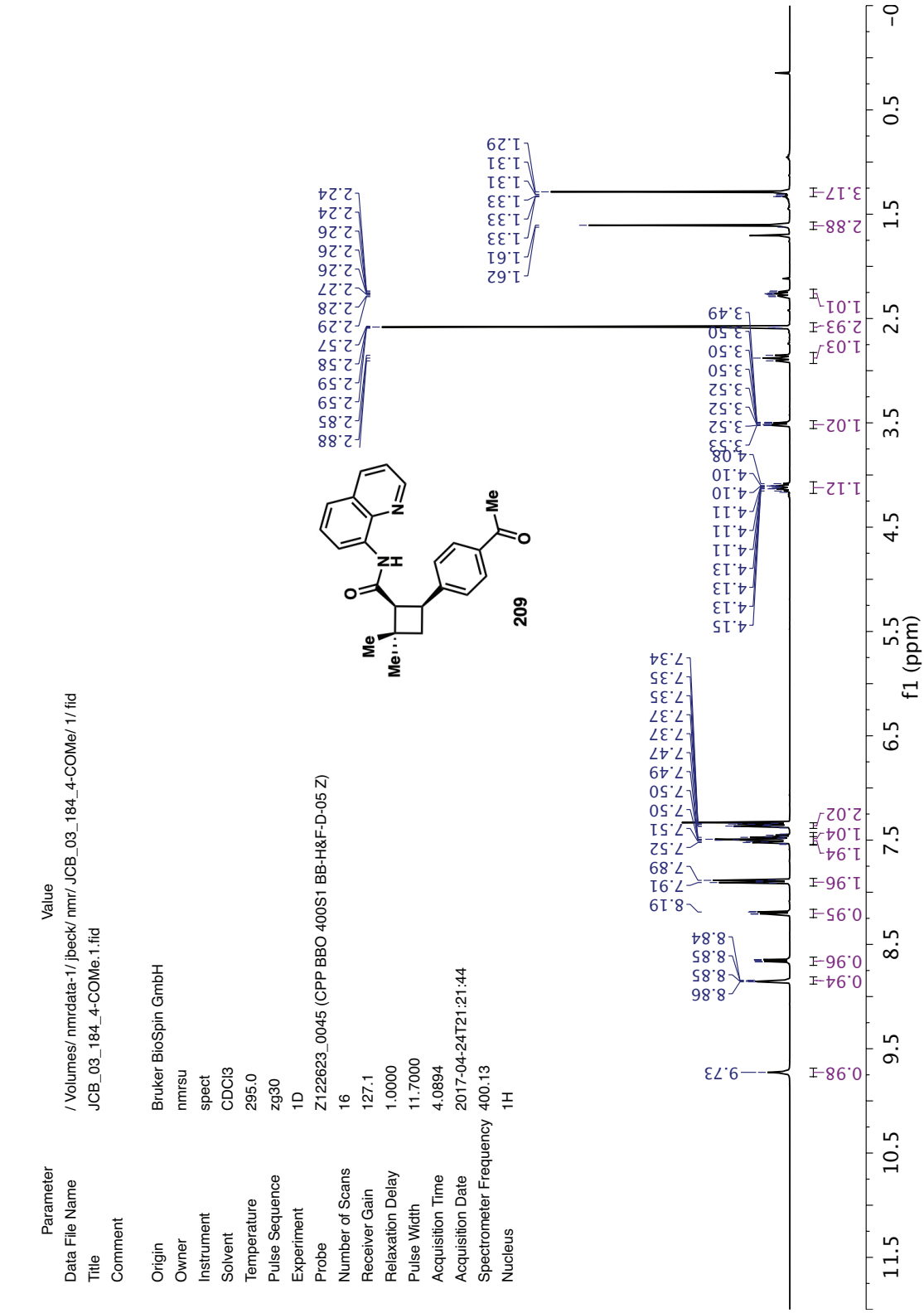

Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_03_181_3CF3/ 1/ fid
Title JCB_03_181_3CF3.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 87.8
Relaxation Delay 15.0000
Pulse Width 11.7000
Acquisition Time 14.9998
Acquisition Date 2017-04-23T21:05:01
Spectrometer Frequency 400.13
Nucleus 1H
208
f1 (ppm)

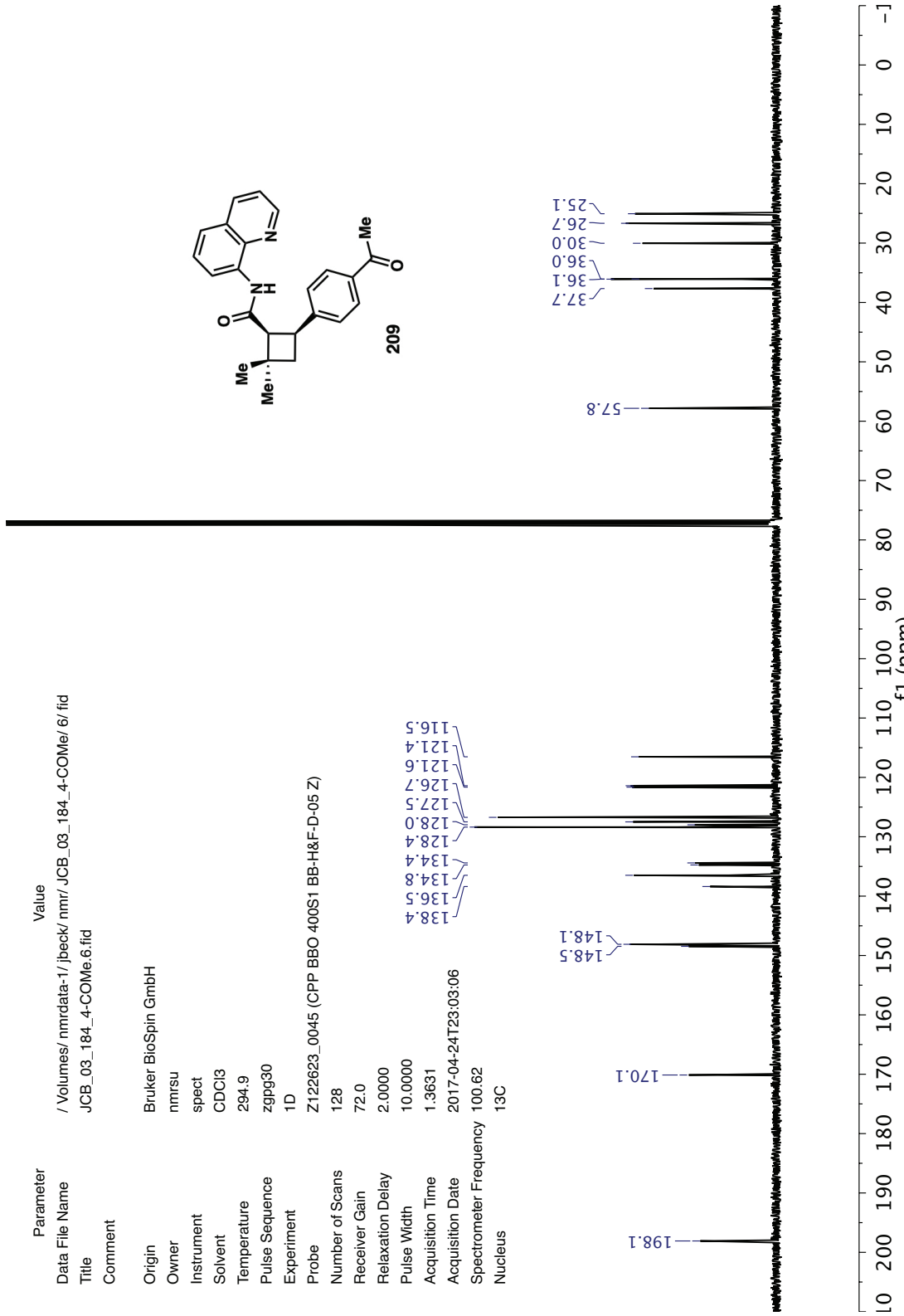

Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_03_181_3CF3/ 4/ fid
Title JCB_03_181_3CF3.4.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 768
Receiver Gain 78.7
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-04-23T22:11:28
Spectrometer Frequency 100.62
Nucleus 13C
208
f1 (ppm)

Parameter	Value
Data File Name	/ Volumes/ nmrdata-2/ jbeck/ vnmrsys/ data/ JCB_03_181_19F.fid/ fid
Title	JCB_03_181_19F
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Owner	
Instrument	vnmrs
Author	
Solvent	cdcl3
Temperature	50.0
Pulse Sequence	s2pul
Experiment	1D
Probe	OneNMR
Number of Scans	20
Receiver Gain	58
Relaxation Delay	1.0000
Pulse Width	3.2333
Acquisition Time	0.7340
Acquisition Date	2017-04-21T19:45:17
Spectrometer Frequency	376.15
Spectral Width	89285.7
Nucleus	19F
Acquired Size	65536



208


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_03_184_4-COMe/ 1/ fid
Title JCB_03_184_4-COMe.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 127.1
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2017-04-24T21:21:44
Spectrometer Frequency 400.13
Nucleus 1H
209
f1 (ppm)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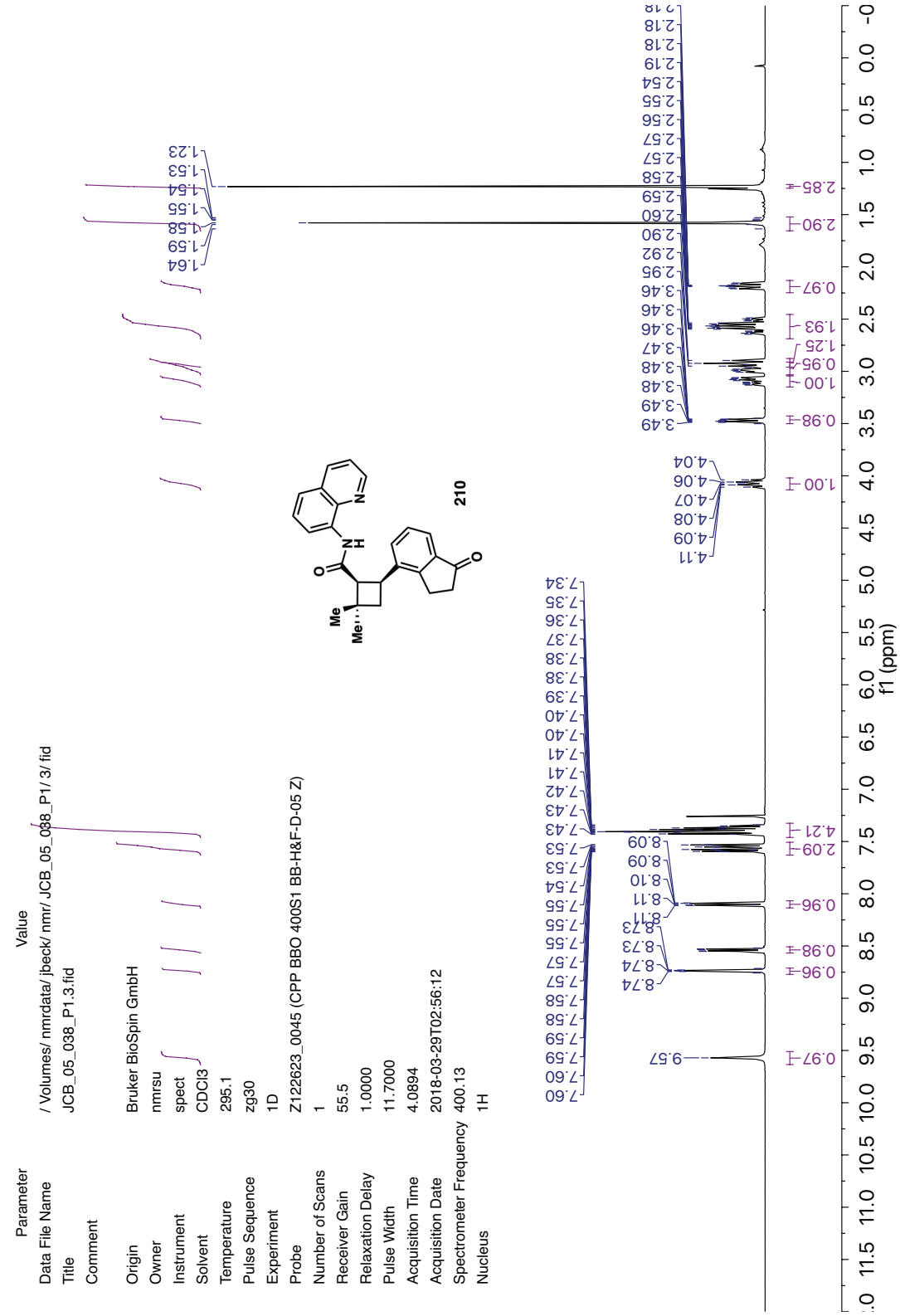
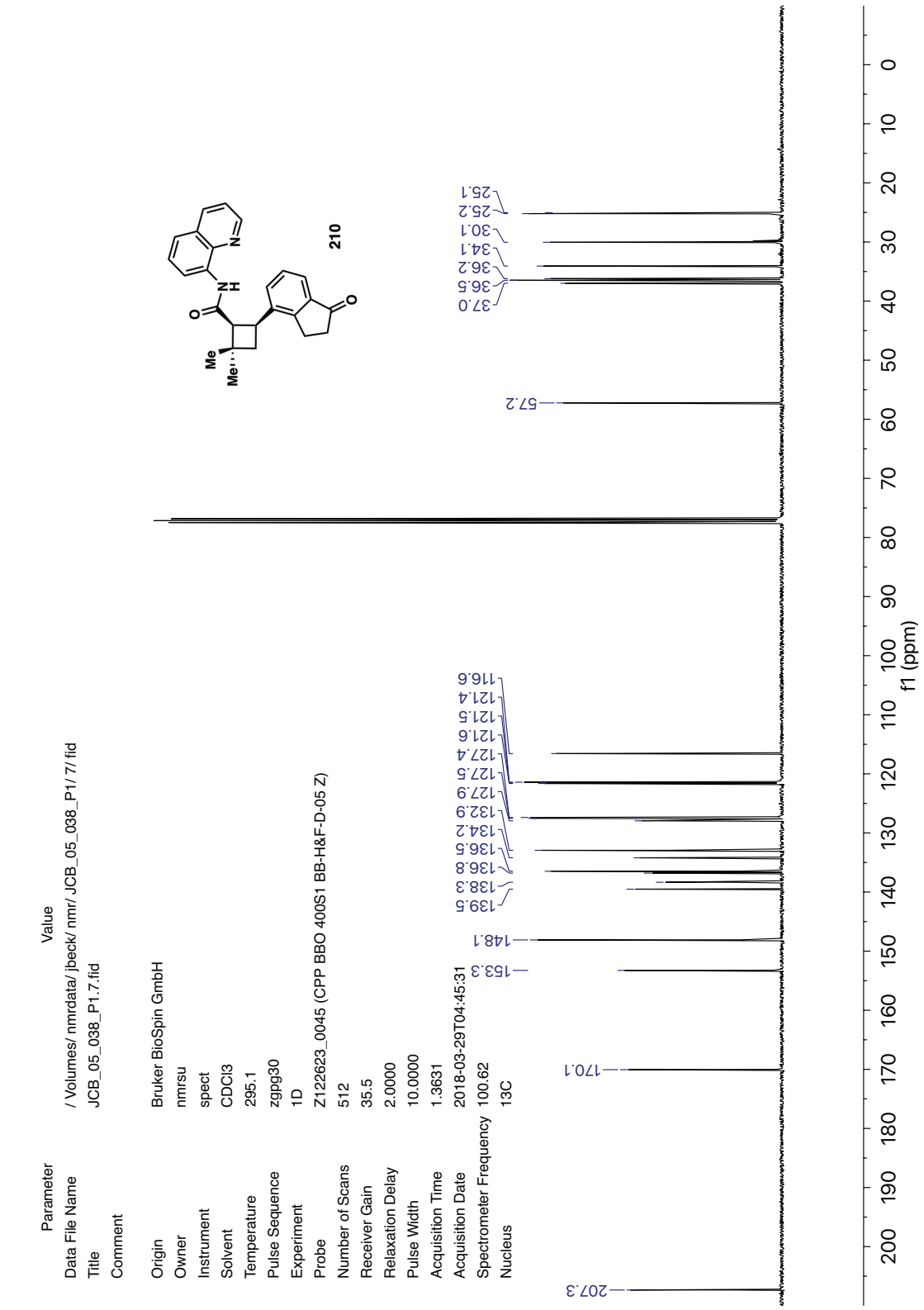
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_03_184_4-COMe/ 6/ fid
Title JCB_03_184_4-COMe.6.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 72.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-04-24T23:03:06
Spectrometer Frequency 100.62
Nucleus 13C
209
198.1
170.1
148.5
148.1
138.4
136.5
134.8
134.4
128.4
128.0
127.5
126.7
121.6
121.4
116.5
57.8
37.7
36.1
36.0
30.0
26.7
25.1
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_038_P1/ 3/ fid
Title JCB_05_038_P1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-03-29T02:56:12
Spectrometer Frequency 400.13
Nucleus 1H
210
Me
Me
f1 (ppm)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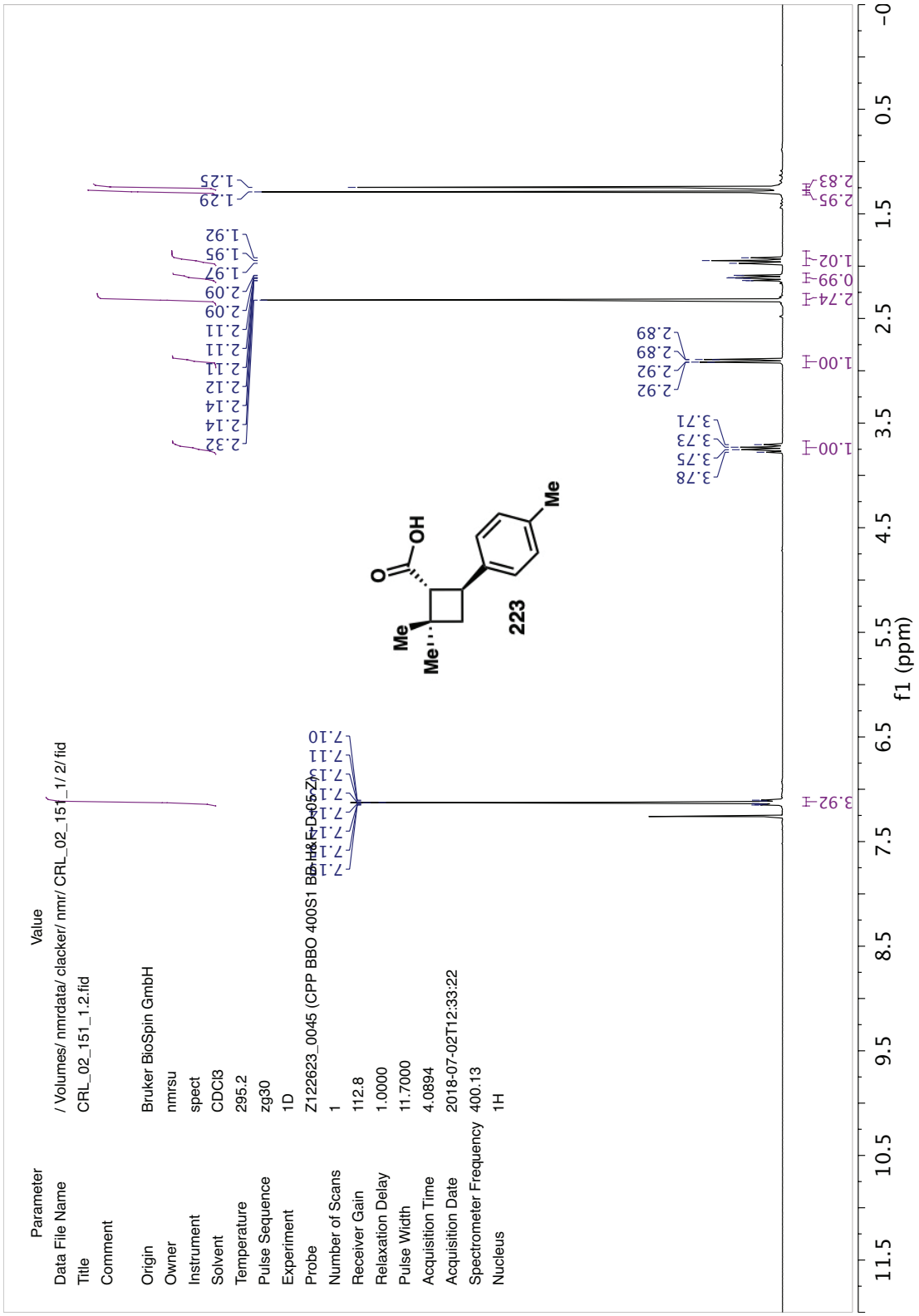
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_038_P1/ 7/ fid
Title JCB_05_038_P1.7.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 35.5
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-03-29T04:45:31
Spectrometer Frequency 100.62
Nucleus 13C
210
Me
Me
207.3
170.1
153.3
148.1
139.5
138.3
136.8
136.5
134.2
132.9
127.9
127.5
127.4
121.6
121.5
121.4
116.6
57.2
37.0
36.5
36.2
34.1
30.1
25.2
25.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Parameter
Value
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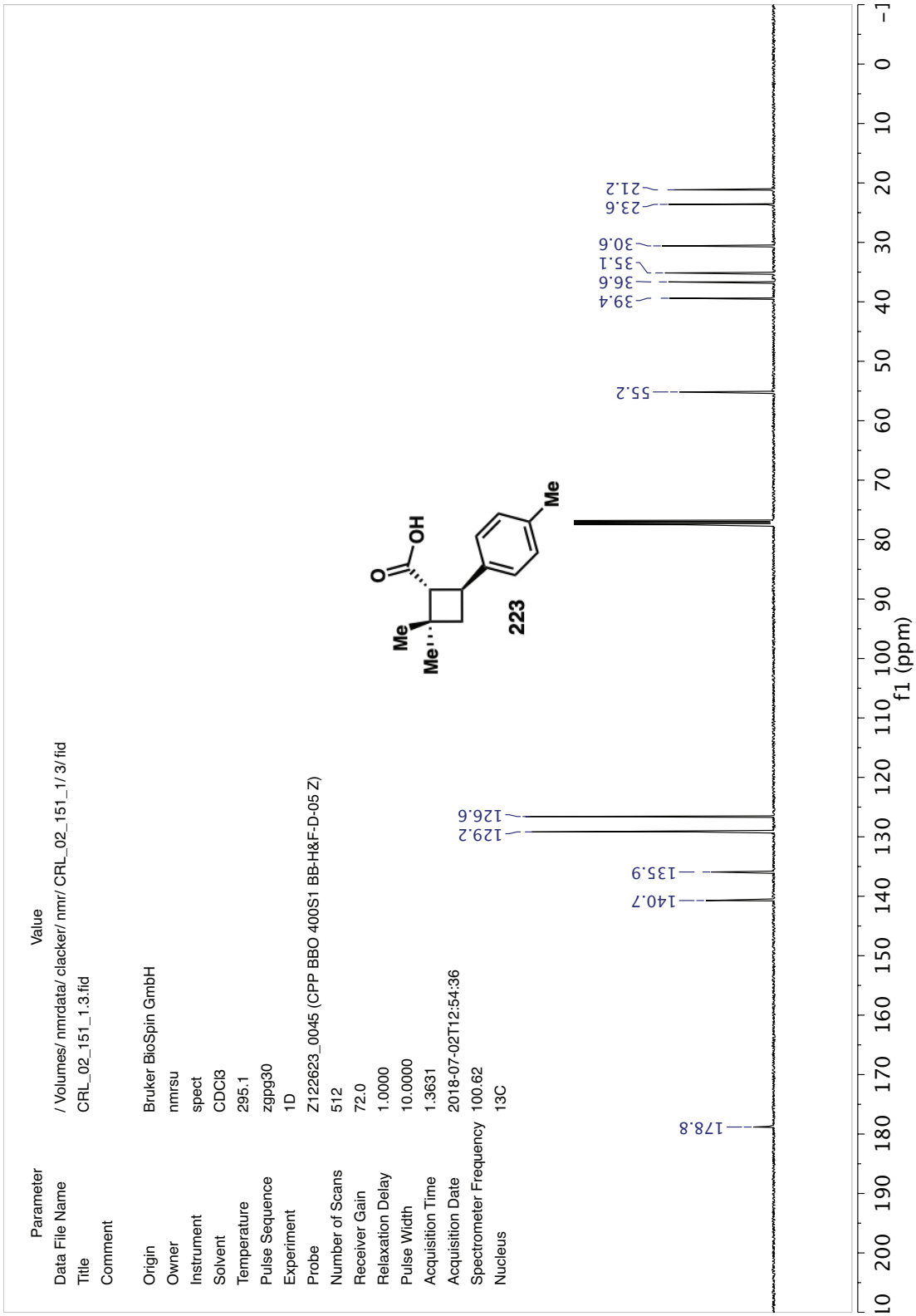
Title CRL_02_151_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05-Z)
Number of Scans 1
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-02T12:33:22
Spectrometer Frequency 400.13
Nucleus 1H
223
f1 (ppm)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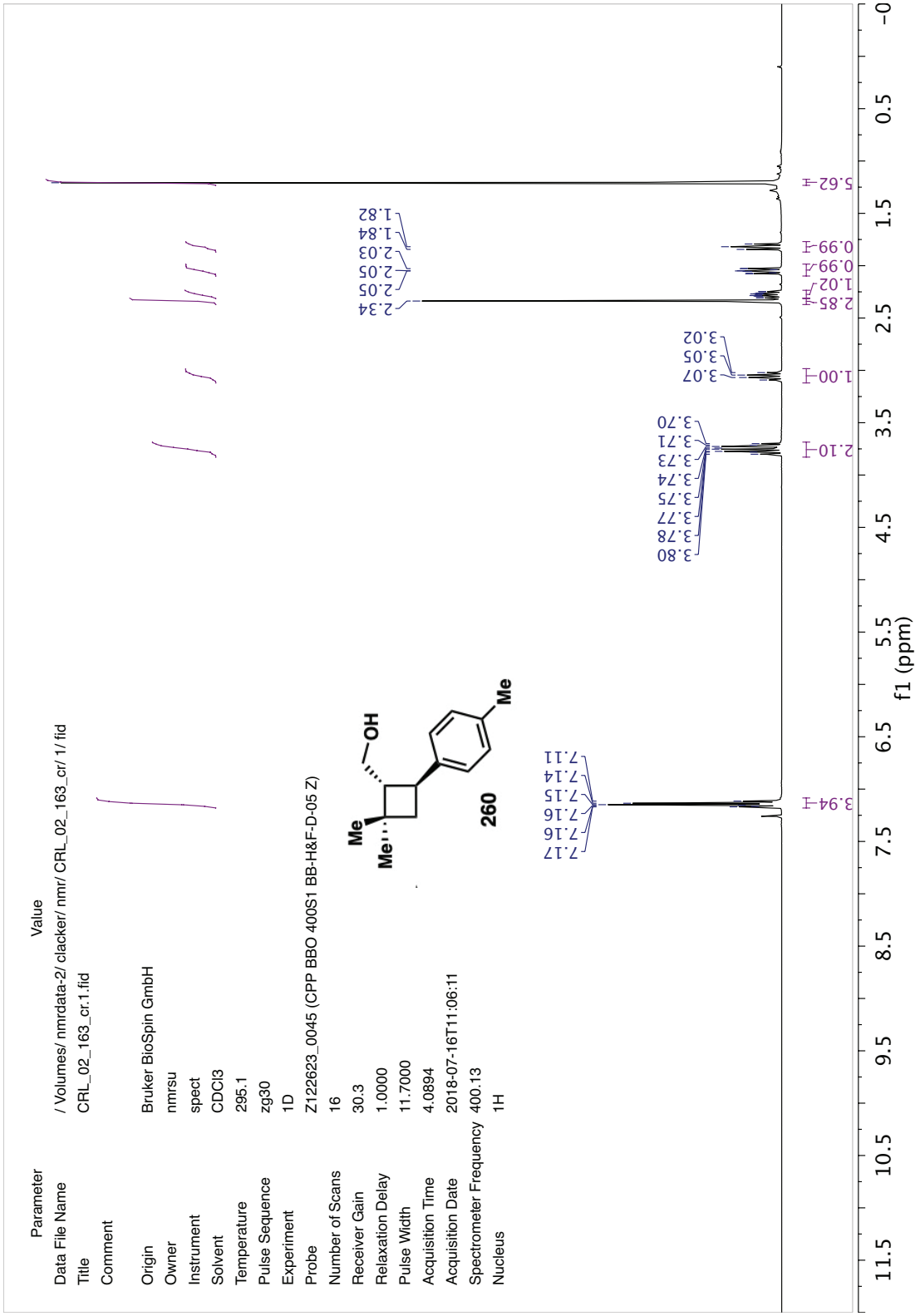
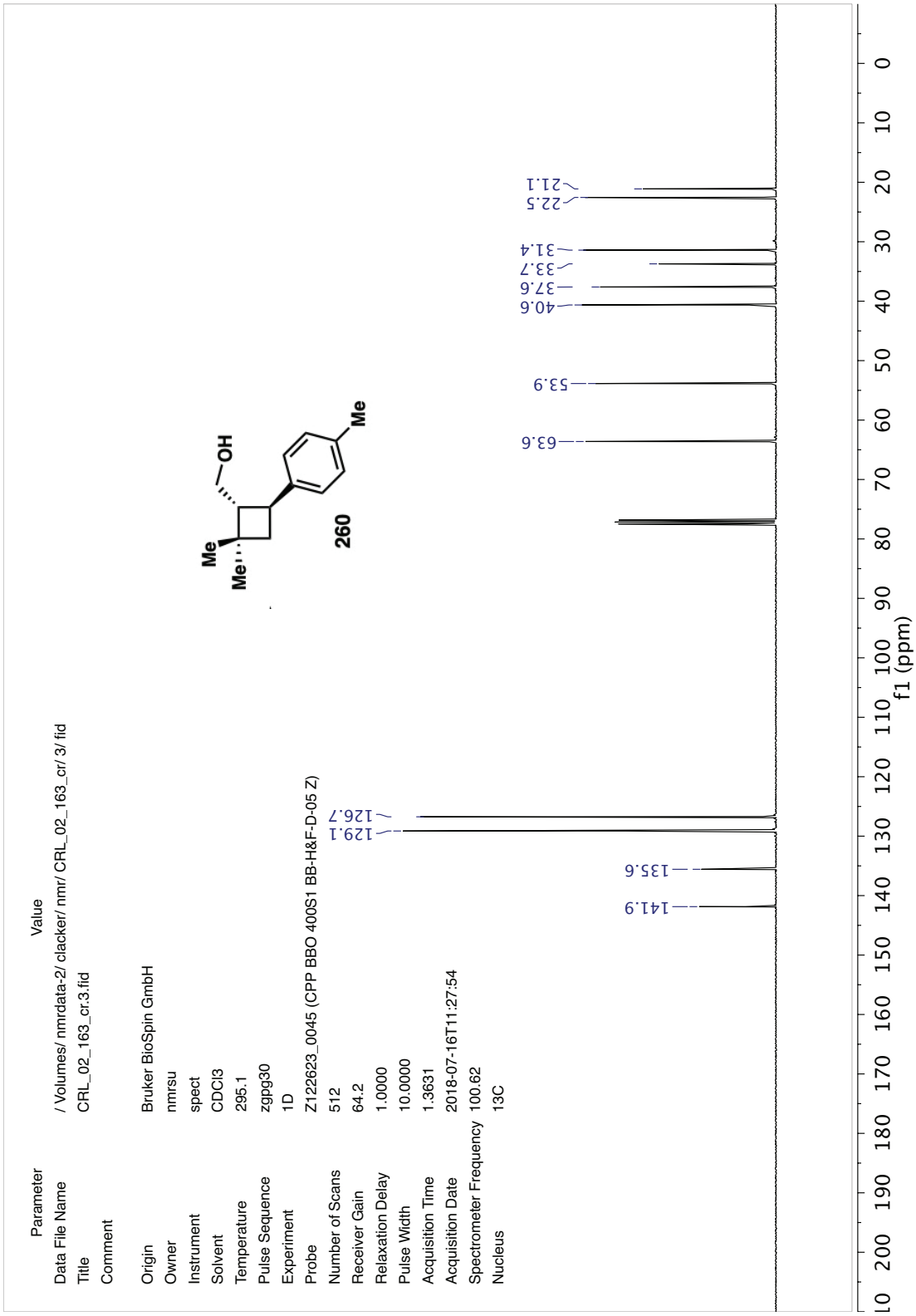
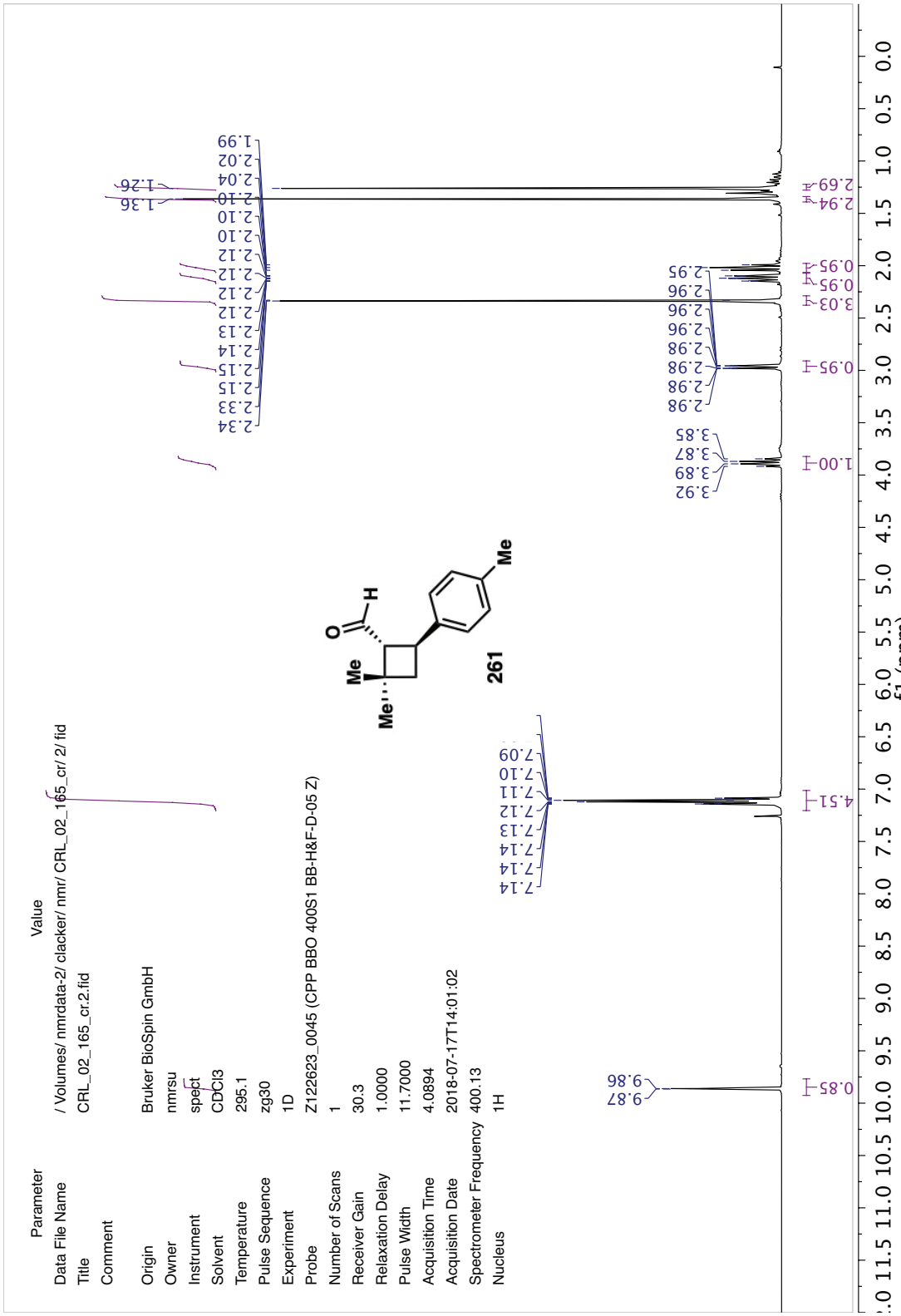
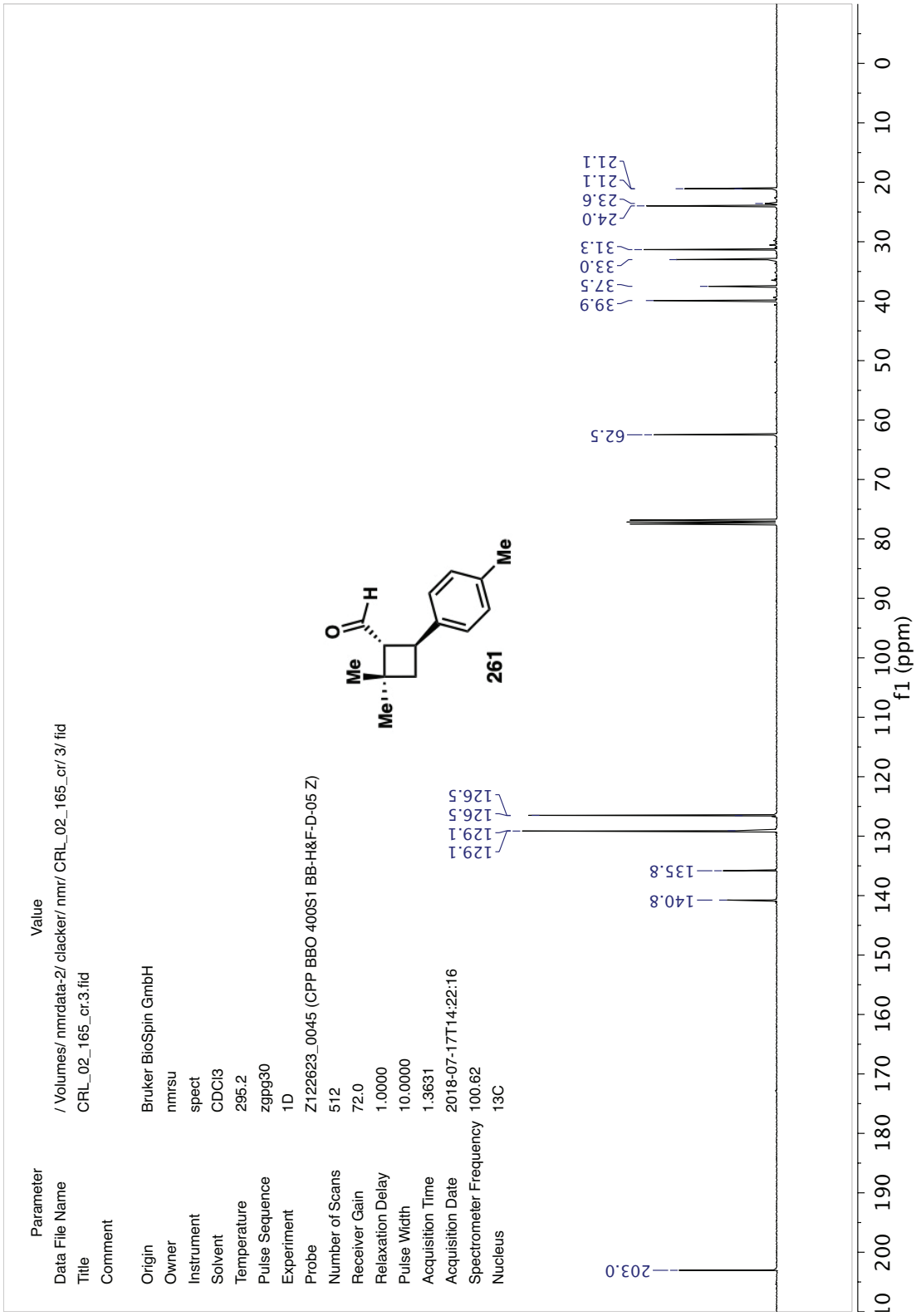
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_151_1/ 3/ fid
Title CRL_02_151_1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-02T12:54:36
Spectrometer Frequency 100.62
Nucleus 13C
178.8
140.7
135.9
129.2
126.6
55.2
39.4
36.6
35.1
30.6
23.6
21.2
Me
Me
OH
O
223
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-2/ clacker/ nmr/ CRL_02_163_cr/ 1/ fid
Title CRL_02_163_cr.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-16T11:06:11
Spectrometer Frequency 400.13
Nucleus 1H
OH
Me
Me
Me
260
7.17
7.16
7.16
7.15
7.14
7.11
3.94
3.80
3.78
3.77
3.75
3.74
3.73
3.71
3.70
3.07
3.05
3.02
2.34
2.05
2.05
2.03
1.84
1.82
5.62
0.99
0.99
1.02
2.85
1.00
2.10
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-2/ clacker/ nmr/ CRL_02_163_cr/ 3/ fid
Title CRL_02_163_cr.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-16T11:27:54
Spectrometer Frequency 100.62
Nucleus 13C
OH
Me
Me
Me
260
141.9
135.6
129.1
126.7
63.6
53.9
40.6
37.6
33.7
31.4
22.5
21.1
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-2/ clacker/ nmr/ CRL_02_165_cr/ 2/ fid
Title CRL_02_165_cr.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-17T14:01:02
Spectrometer Frequency 400.13
Nucleus 1H
261
f1 (ppm)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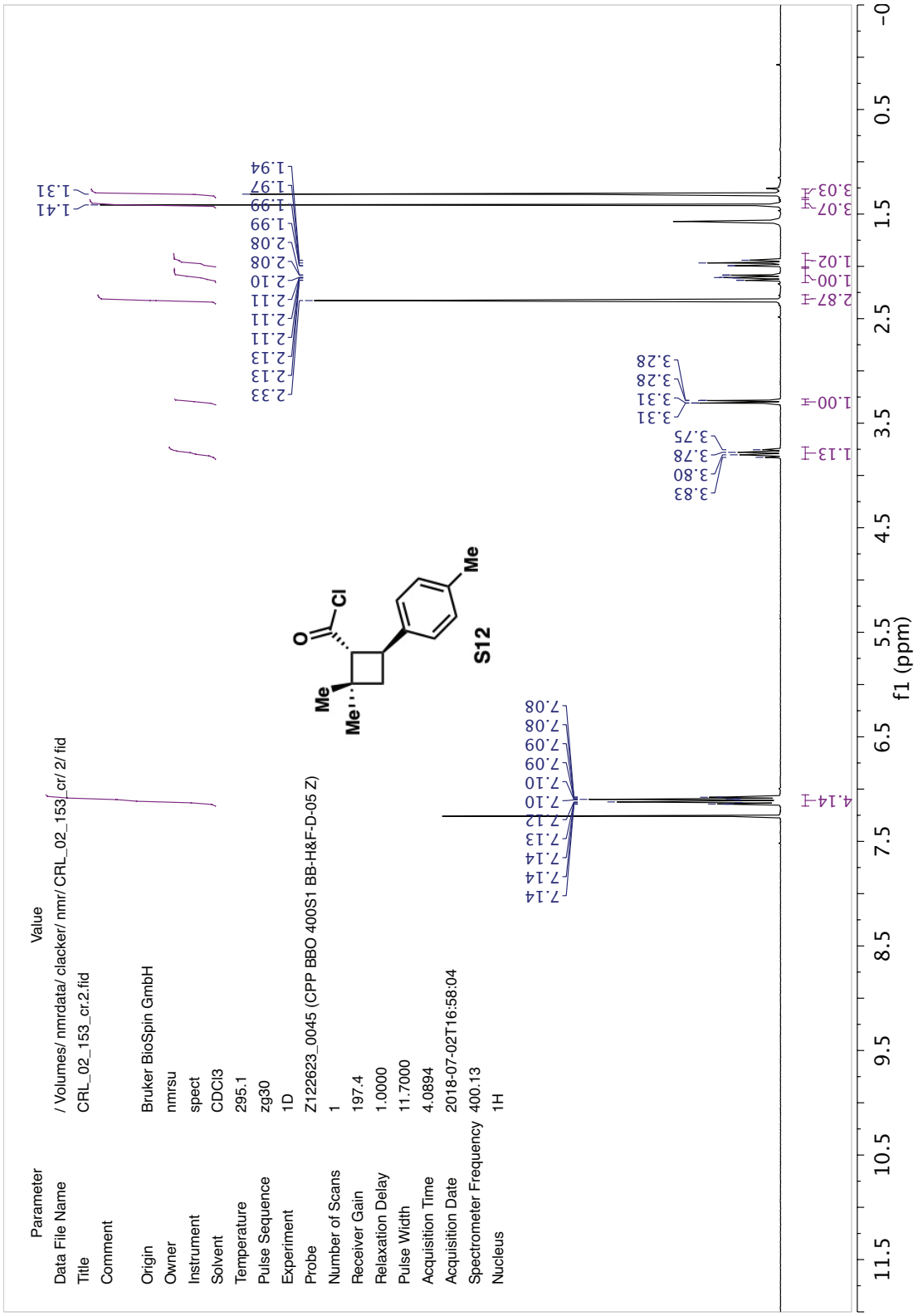
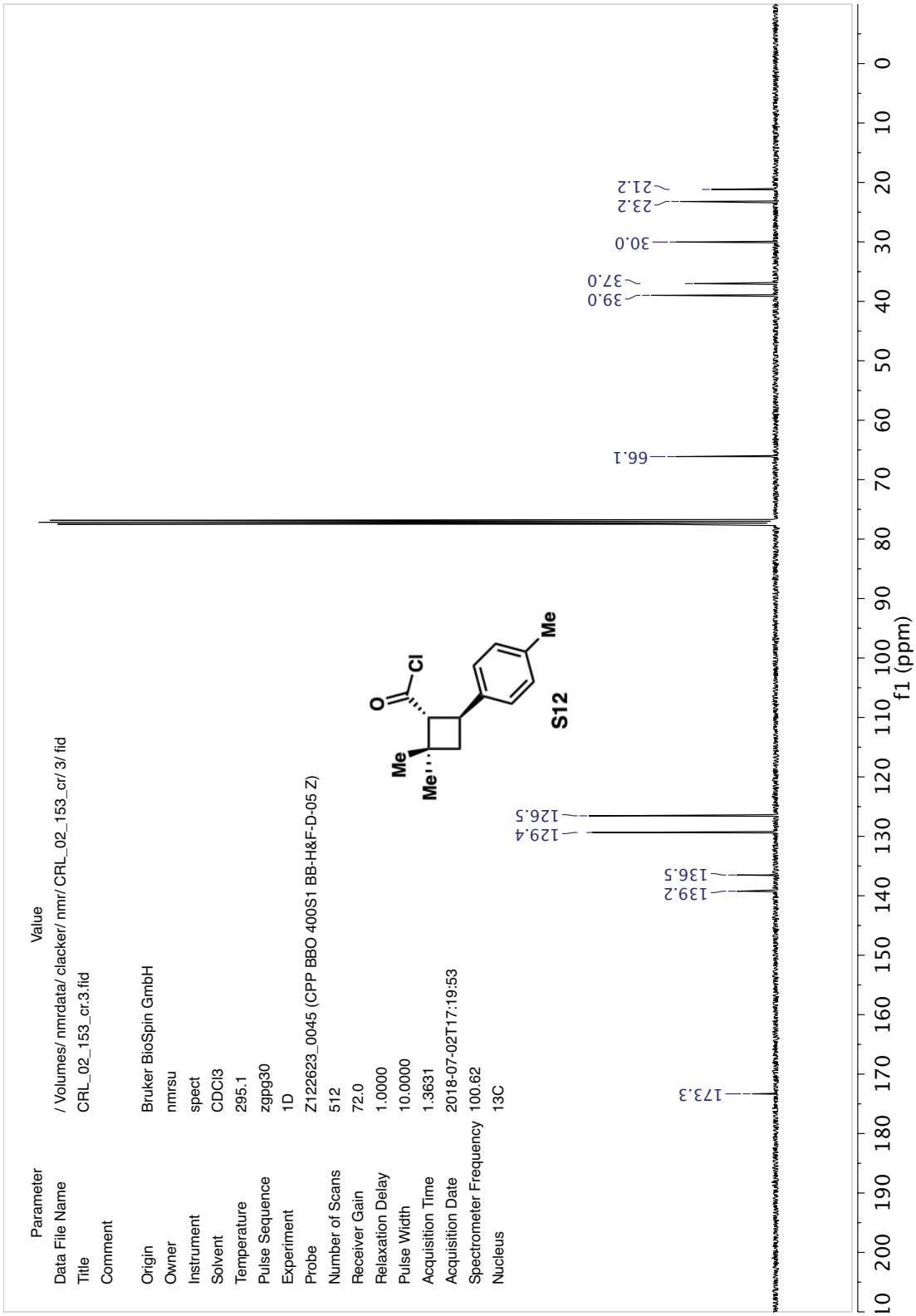
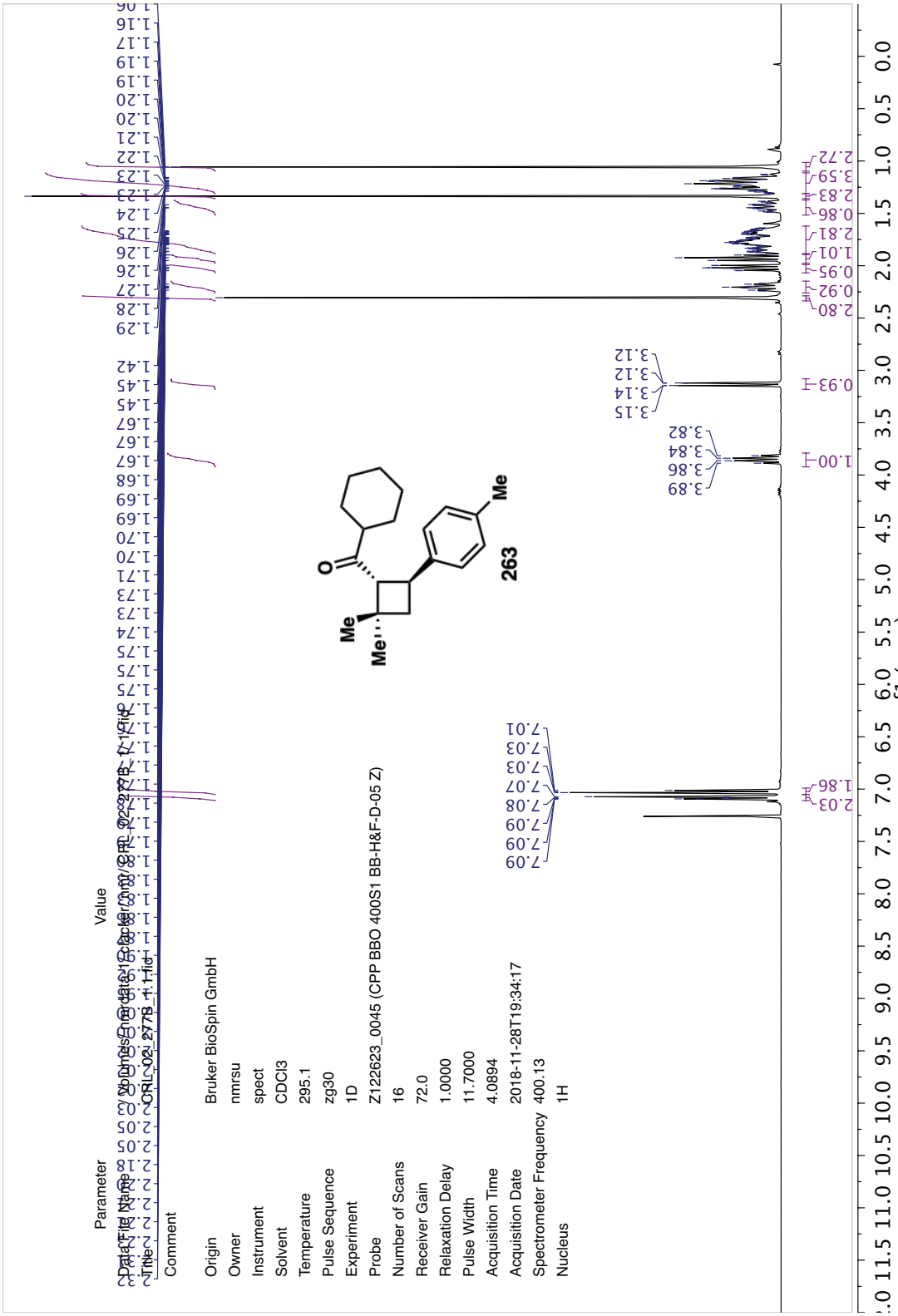
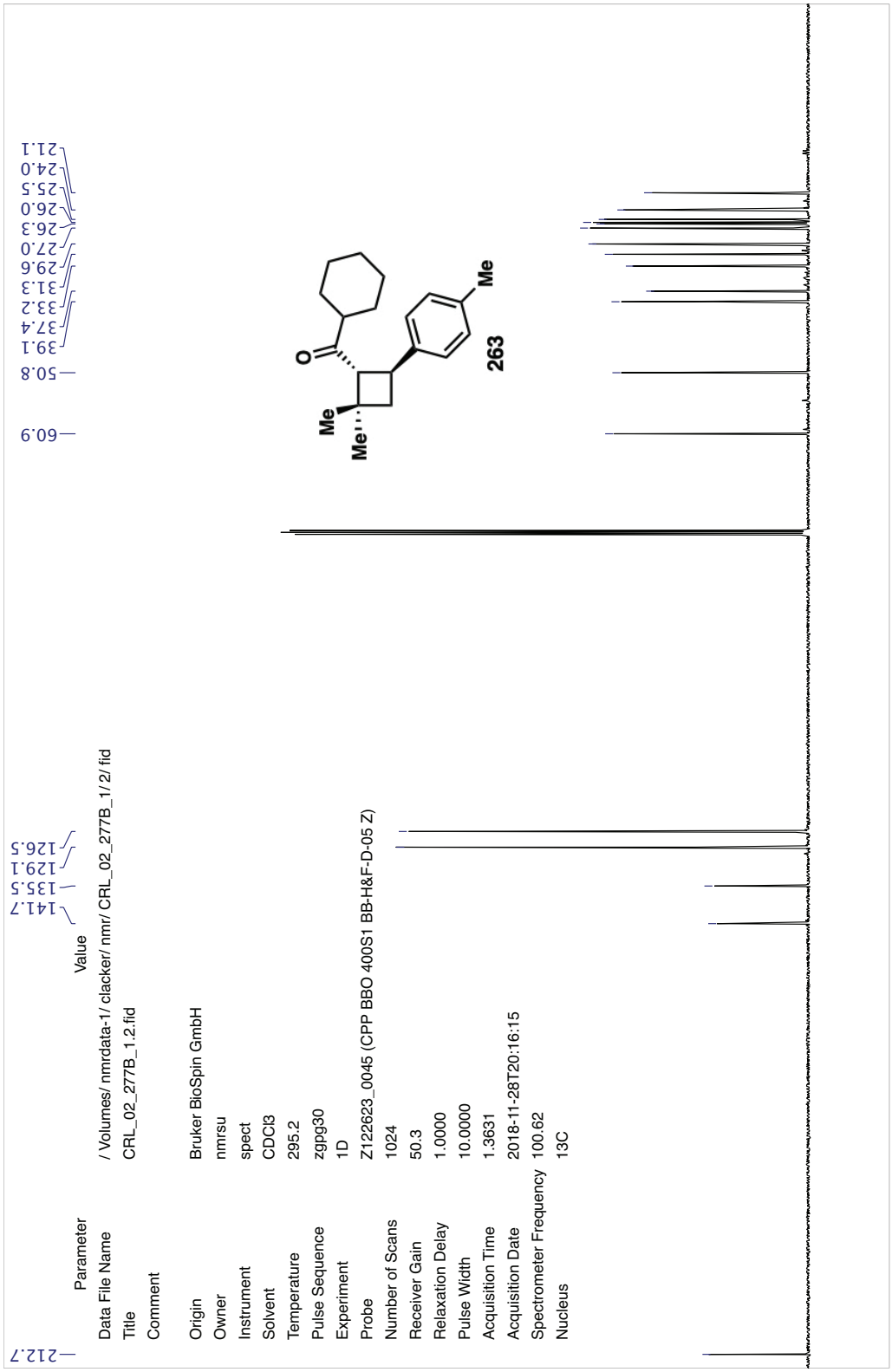
Value
Data File Name / Volumes/ nmrdata-2/ clacker/ nmr/ CRL_02_165_cr/ 3/ fid
Title CRL_02_165_cr.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-17T14:22:16
Spectrometer Frequency 100.62
Nucleus 13C
O
H
Me
Me
Me
261
203.0
140.8
135.8
129.1
129.1
126.5
126.5
62.5
39.9
37.5
33.0
31.3
24.0
23.6
21.1
21.1
f1 (ppm)

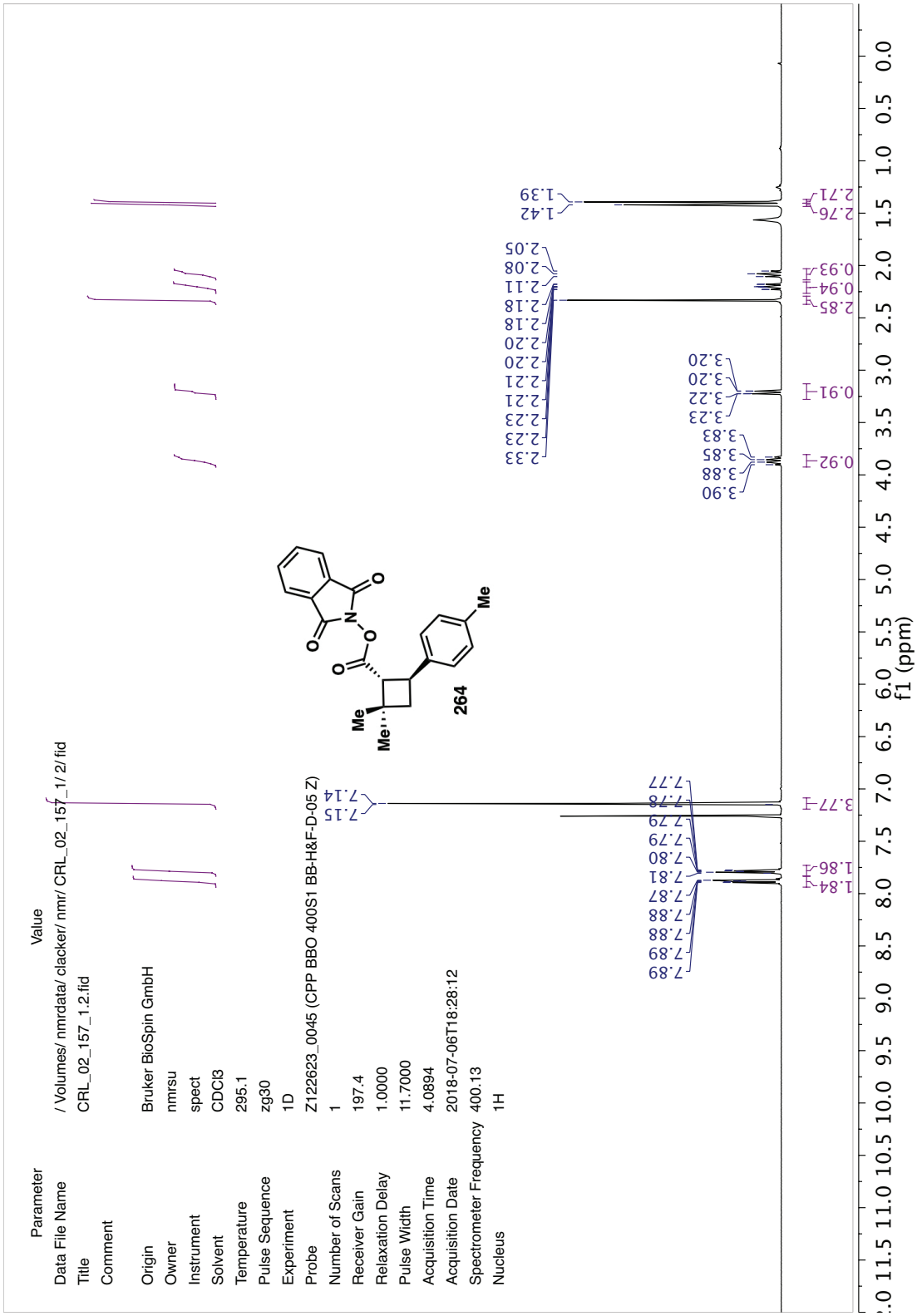

Parameter Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_153_cr/ 2/ fid
Title CRL_02_153_cr.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-02T16:58:04
Spectrometer Frequency 400.13
Nucleus 1H
S12
f1 (ppm)

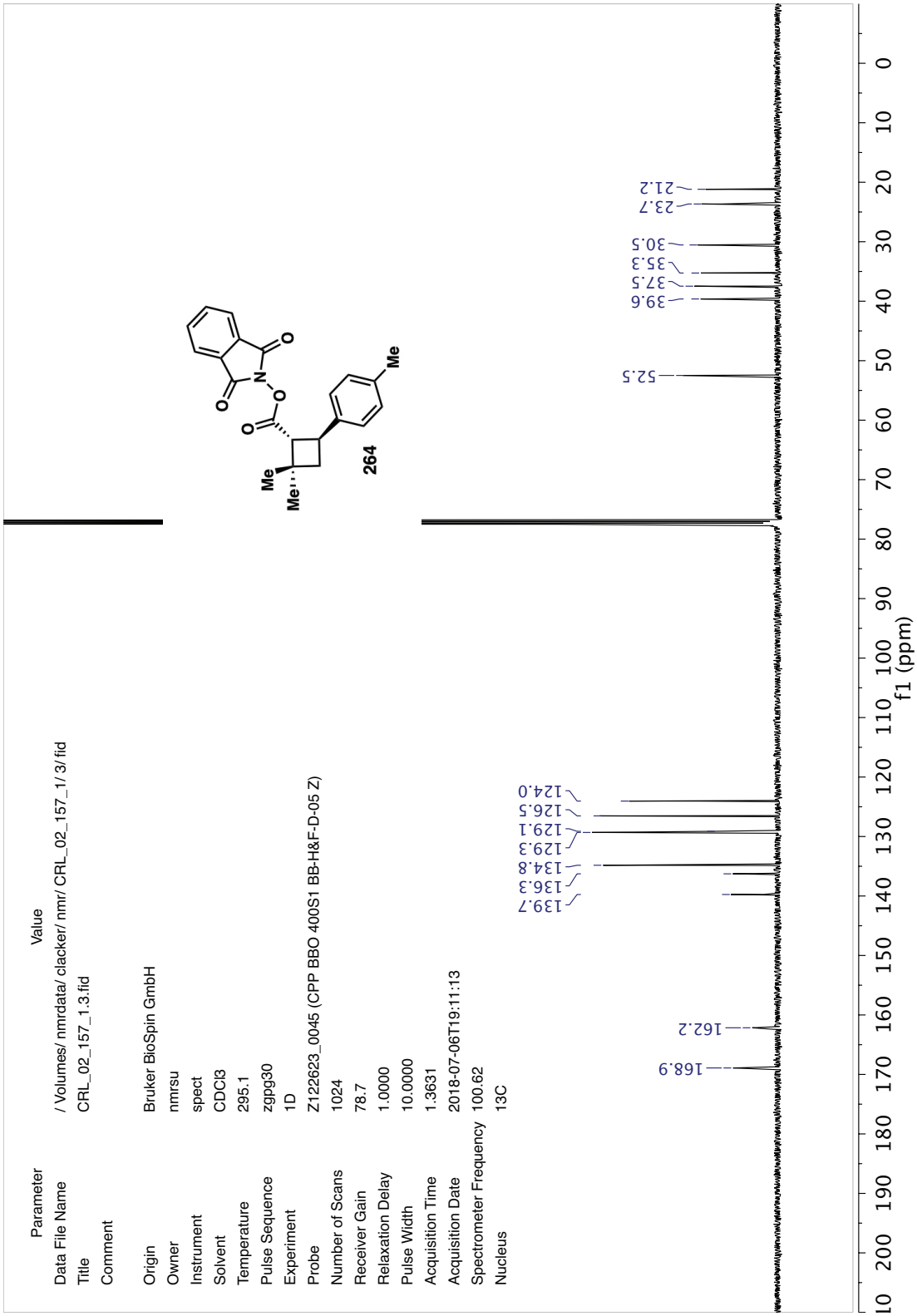

Parameter Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_153_cr/ 3/ fid
Title CRL_02_153_cr.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-02T17:19:53
Spectrometer Frequency 100.62
Nucleus 13C
173.3
139.2
136.5
129.4
126.5
66.1
39.0
37.0
30.0
23.2
21.2
Me
Me
O
Cl
S12
f1 (ppm)

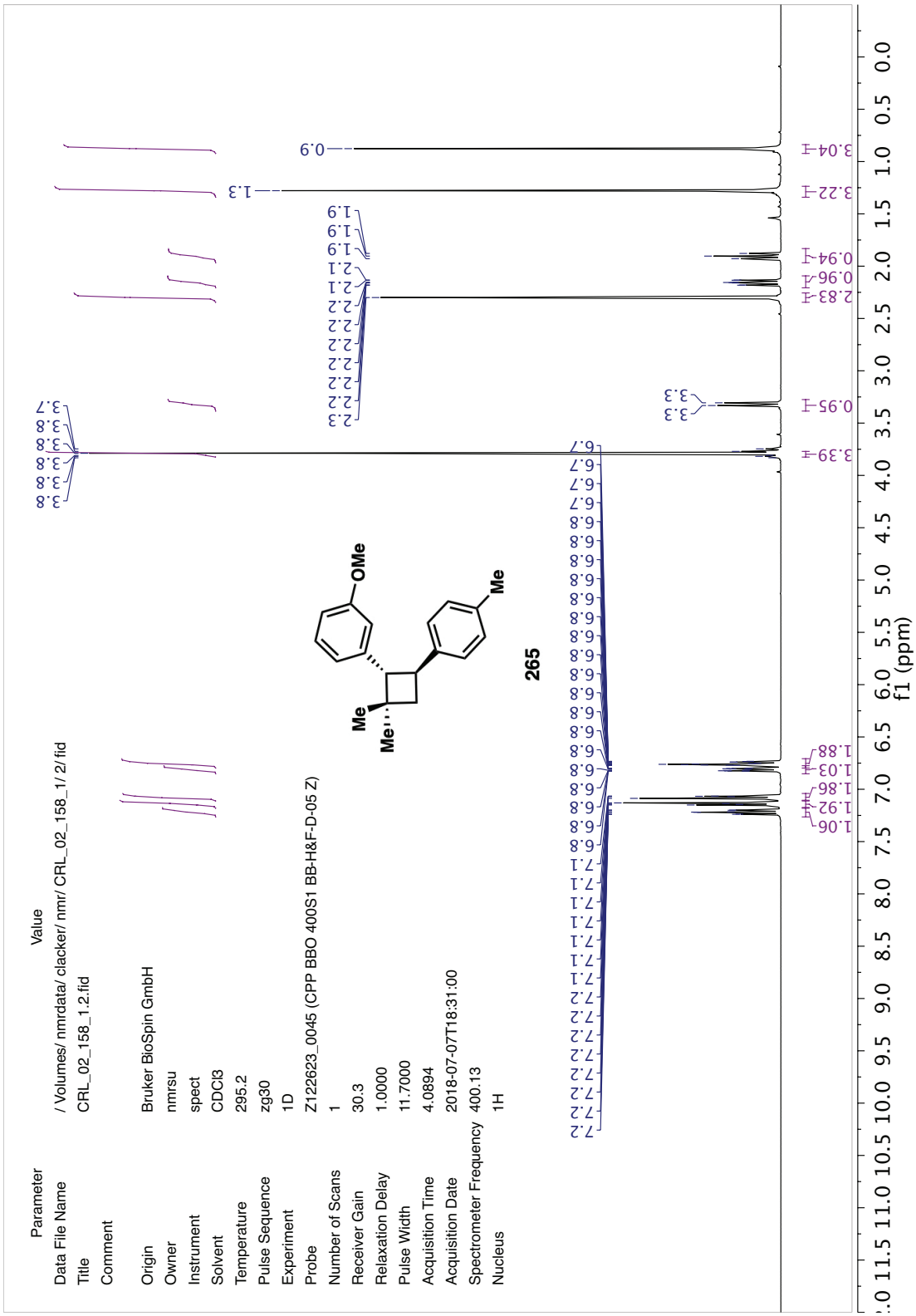

Parameter
Value
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
spect
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
16
Receiver Gain
72.0
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2018-11-28T19:34:17
Spectrometer Frequency
400.13
Nucleus
1H
Me
Me
O
Me
263
f1 (ppm)



Parameter	Value
Data File Name	/ Volumes/ nmrdata-1/ clacker/ nmr/ CRL_02_277B_1/ 2/ fid
Title	CRL_02_277B_1.2.fid
Comment	
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	1024
Receiver Gain	50.3
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-11-28T20:16:15
Spectrometer Frequency	100.62
Nucleus	13C


Parameter
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_157_1/2/fid
Title CRL_02_157_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-06T18:28:12
Spectrometer Frequency 400.13
Nucleus 1H
264
Me
Me
Me
f1 (ppm)


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ clacker/ nmr/ CRL_02_157_1/ 3/ fid
Title
CRL_02_157_1.3.fid
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
spect
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
1024
Receiver Gain
78.7
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2018-07-06T19:11:13
Spectrometer Frequency
100.62
Nucleus
13C
264
Me
Me
Me
168.9
162.2
139.7
136.3
134.8
129.3
129.1
126.5
124.0
52.5
39.6
37.5
35.3
30.5
23.7
21.2
f1 (ppm)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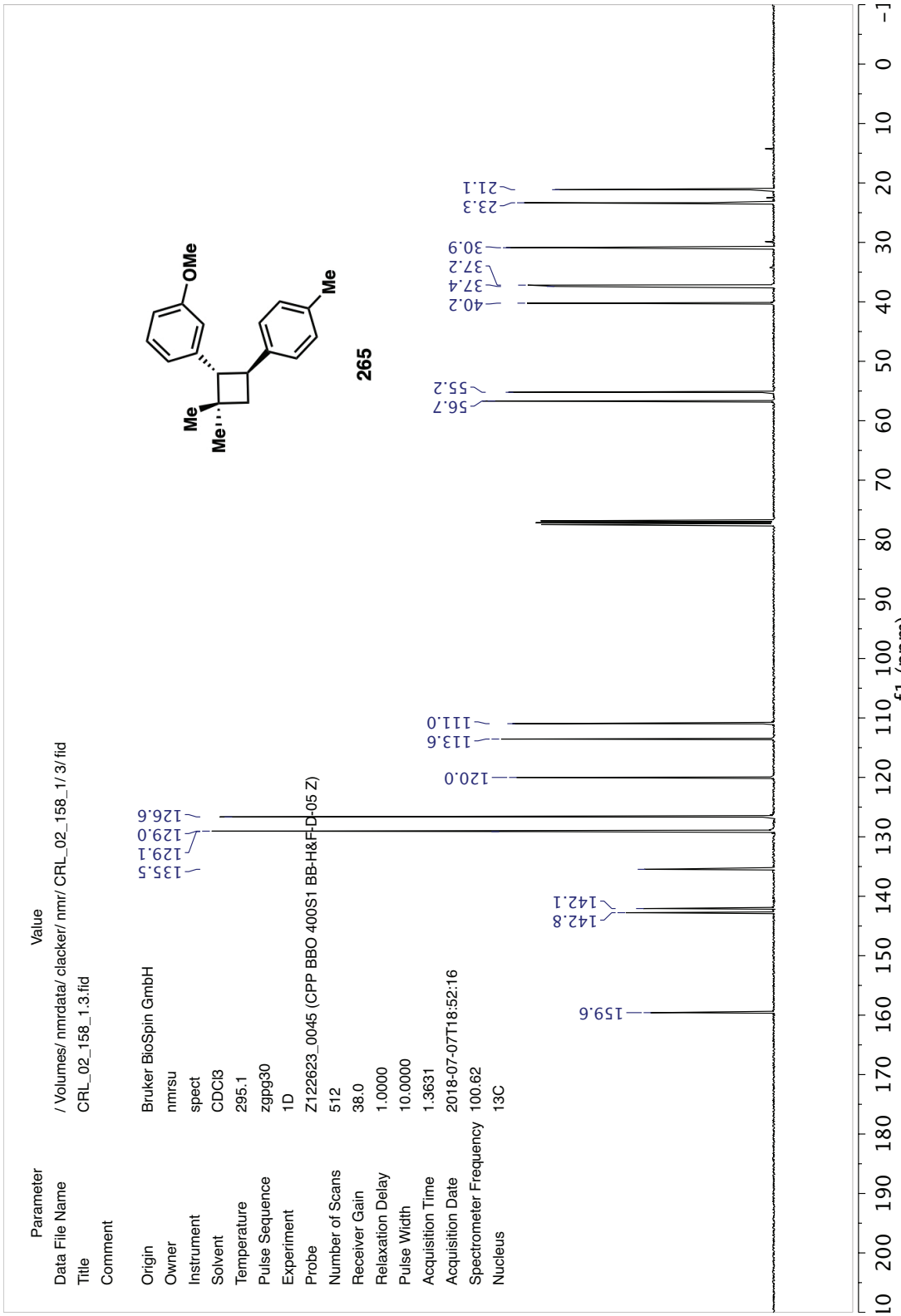
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_158_1/ 2/ fid
Title CRL_02_158_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-07T18:31:00
Spectrometer Frequency 400.13
Nucleus 1H
OMe
Me
Me
265
f1 (ppm)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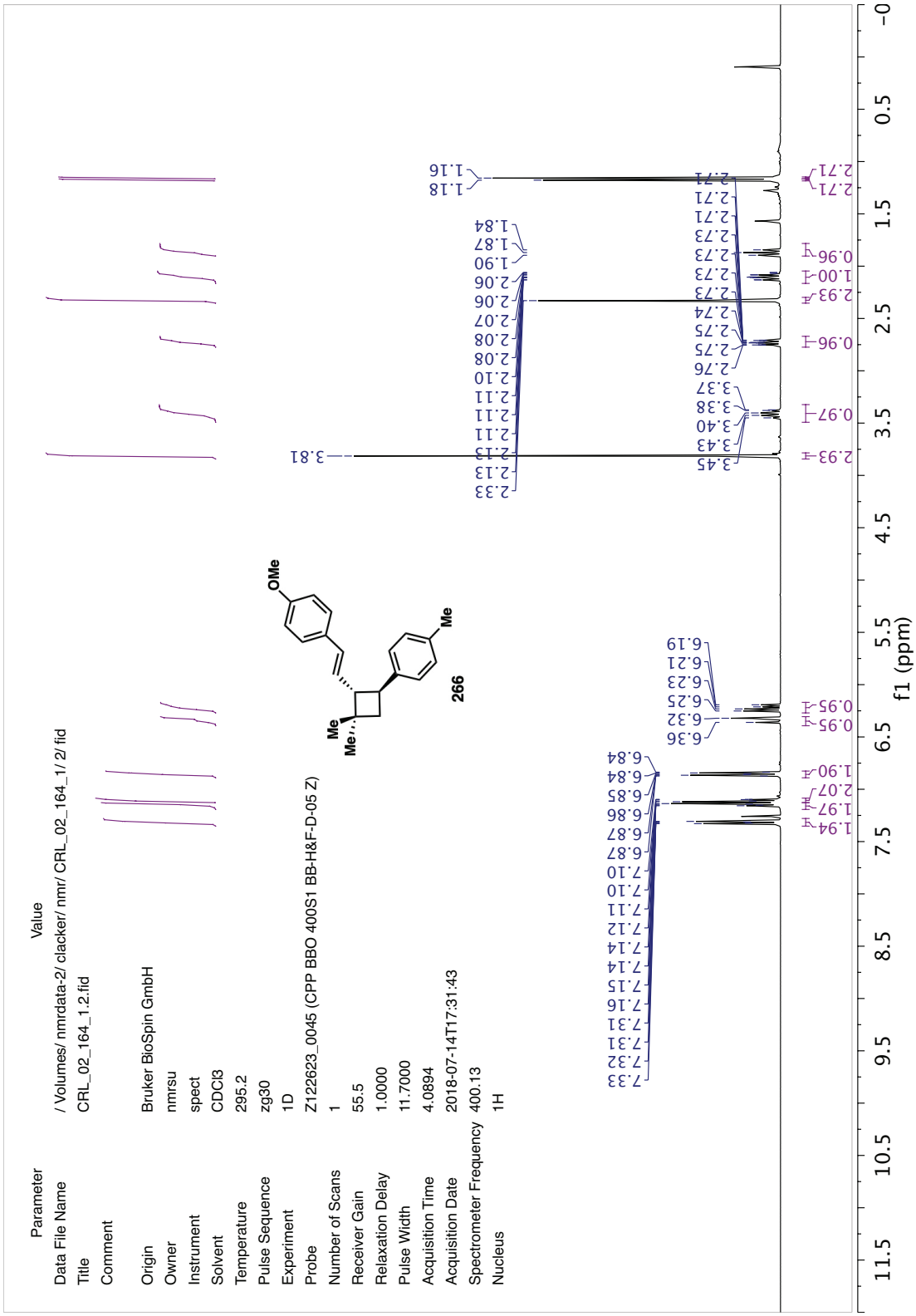
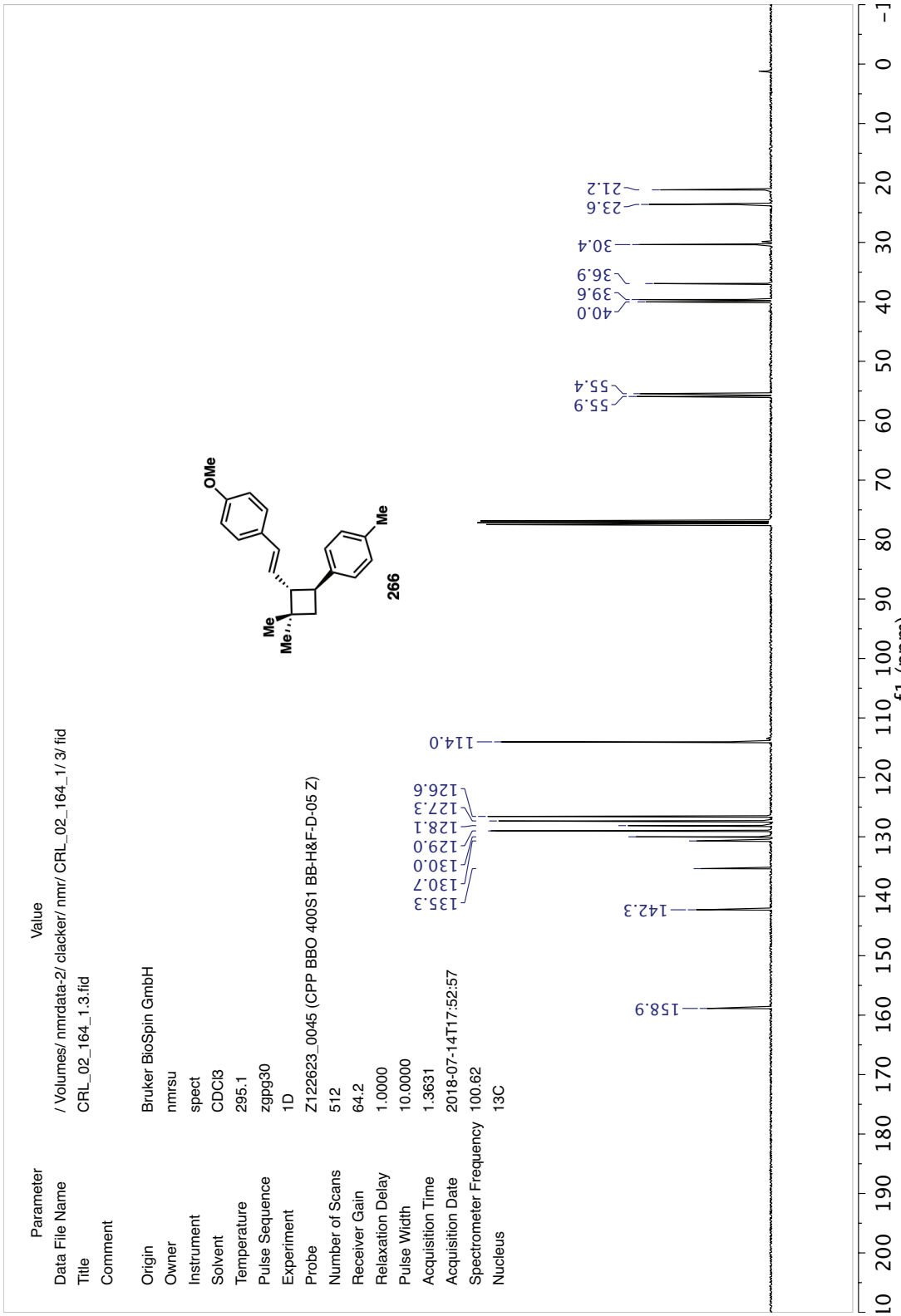
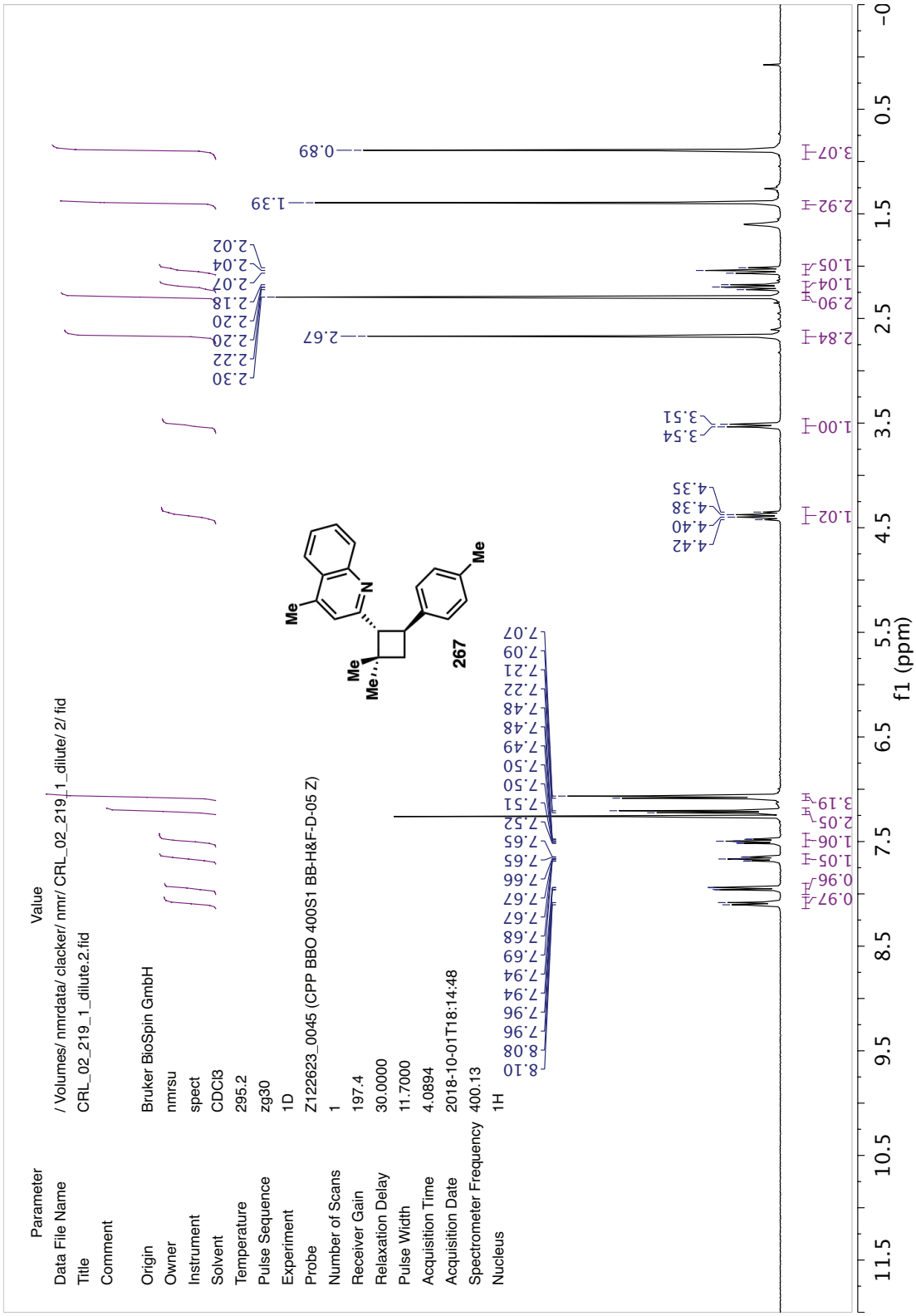
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_158_1/ 3/ fid
Title CRL_02_158_1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 38.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-07-07T18:52:16
Spectrometer Frequency 100.62
Nucleus 13C
OMe
Me
Me
Me
265
159.6
142.8
142.1
135.5
129.1
129.0
126.6
120.0
113.6
111.0
56.7
55.2
40.2
37.4
37.2
30.9
23.3
21.1
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-2/ clacker/ nmr/ CRL_02_164_1/ 2/ fid
Title CRL_02_164_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-14T17:31:43
Spectrometer Frequency 400.13
Nucleus 1H
OMe
Me
Me
Me
266
f1 (ppm)


Parameter
Value
Data File Name
/ Volumes/ nmrdata-2/ clacker/ nmr/ CRL_02_164_1/ 3/ fid
Title
CRL_02_164_1.3.fid
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
spect
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
512
Receiver Gain
64.2
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2018-07-14T17:52:57
Spectrometer Frequency
100.62
Nucleus
13C
OMe
Me
Me
Me
266
158.9
142.3
135.3
130.7
130.0
129.0
128.1
127.3
126.6
114.0
55.9
55.4
40.0
39.6
36.9
30.4
23.6
21.2
f1 (ppm)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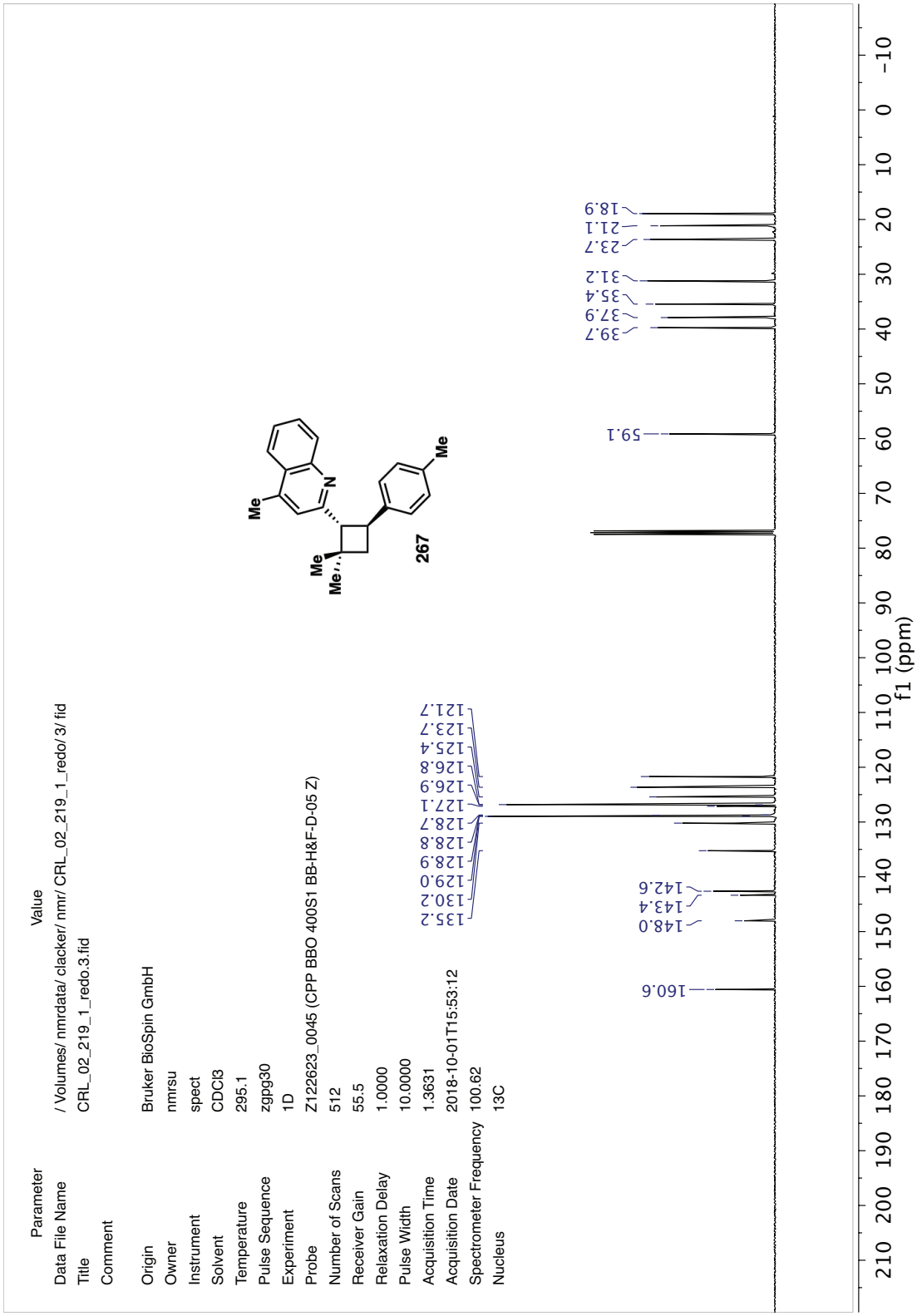
Title CRL_02_219_1_dilute.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 197.4
Relaxation Delay 30.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-10-01T18:14:48
Spectrometer Frequency 400.13
Nucleus 1H
Me
N
Me
Me
Me
267
f1 (ppm)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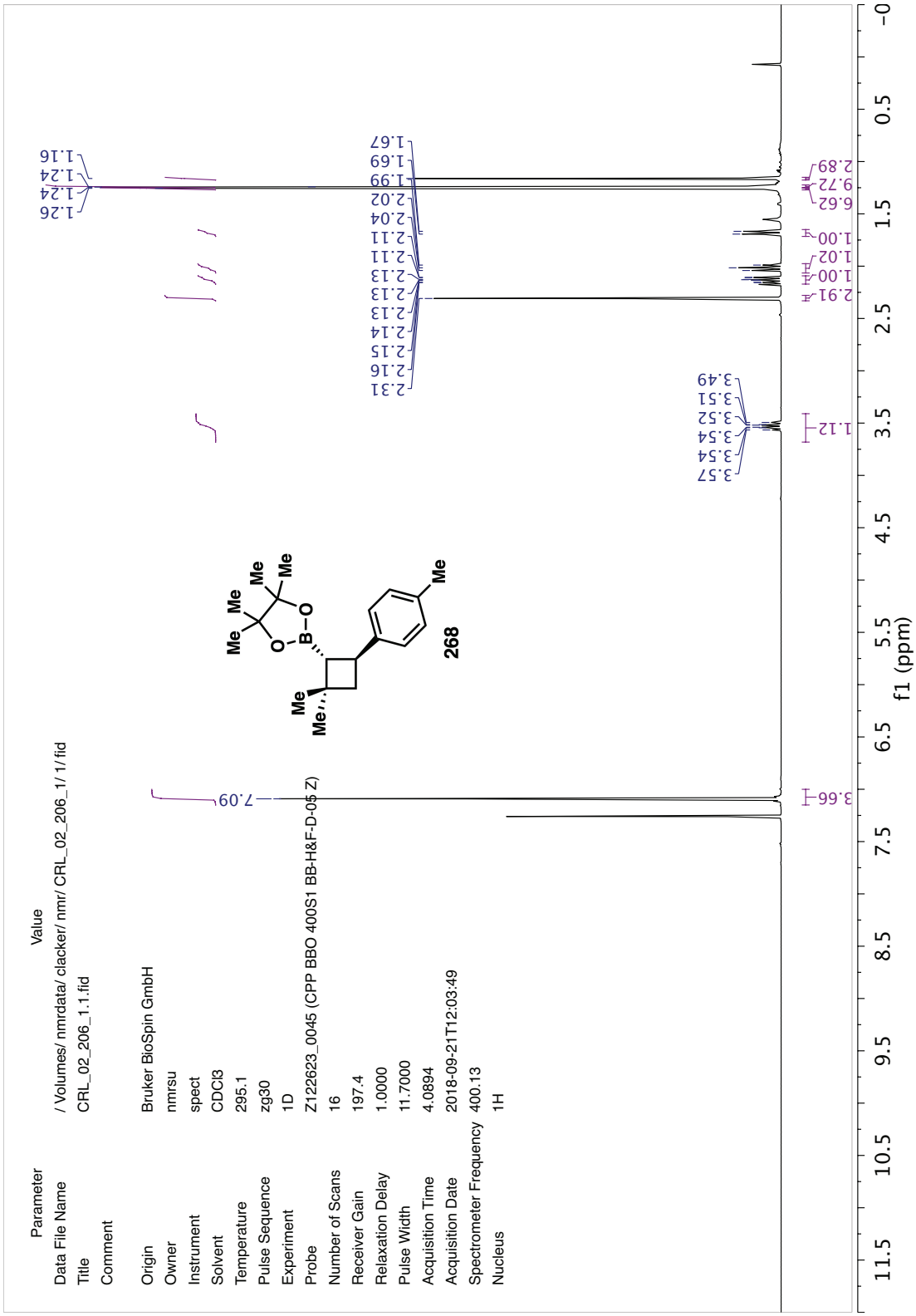
Title CRL_02_219_1_redo.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-10-01T15:53:12
Spectrometer Frequency 100.62
Nucleus 13C
Me
N
Me
Me
Me
267
160.6
148.0
143.4
142.6
135.2
130.2
129.0
128.9
128.8
128.7
127.1
126.9
126.8
125.4
123.7
121.7
59.1
39.7
37.9
35.4
31.2
23.7
21.1
18.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)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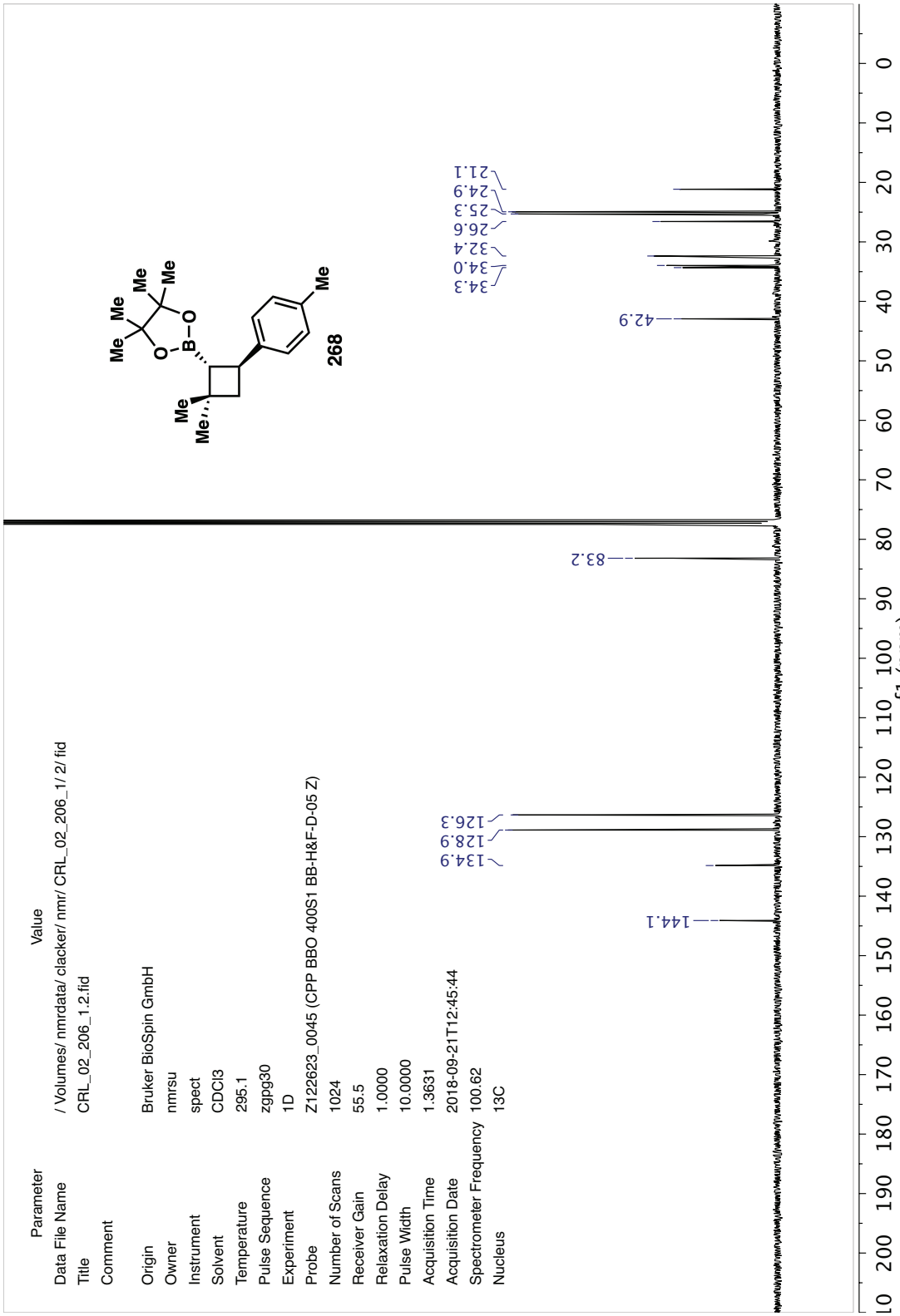
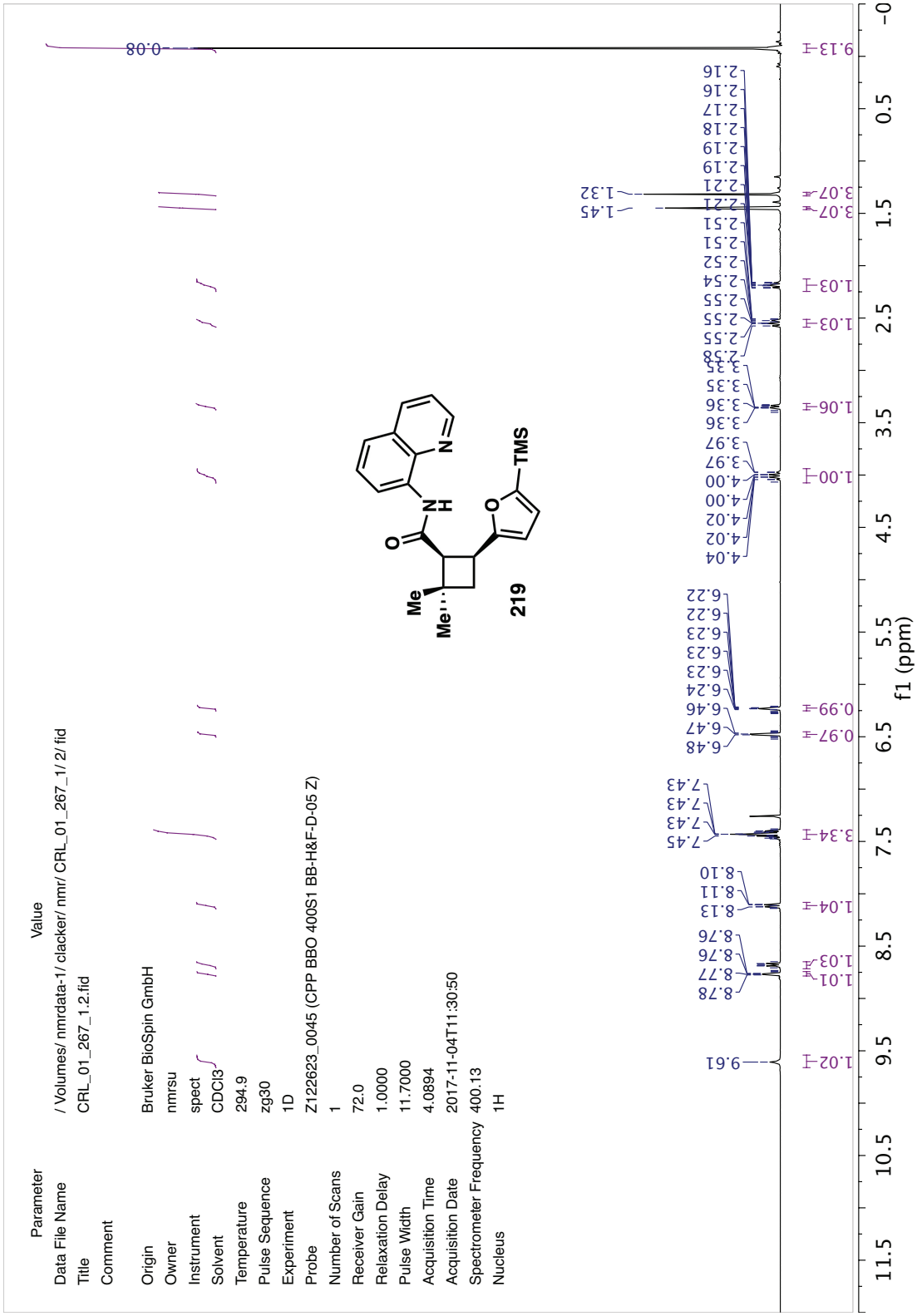
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_206_1/ 1/ fid
Title CRL_02_206_1.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-21T12:03:49
Spectrometer Frequency 400.13
Nucleus 1H
7.09
3.66
1.12
6.62
9.72
2.89
1.00
1.02
1.00
2.91
3.49
3.51
3.52
3.54
3.54
3.57
2.31
2.16
2.15
2.14
2.13
2.13
2.13
2.11
2.11
2.04
2.02
1.99
1.69
1.67
1.26
1.24
1.24
1.16
Me
Me
Me
Me
Me
O
B–O
Me
Me
268
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_206_1/ 2/ fid
Title CRL_02_206_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1024
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-21T12:45:44
Spectrometer Frequency 100.62
Nucleus 13C
Me
Me
Me
Me
Me
O
O
B
Me
Me
Me
268
144.1
134.9
128.9
126.3
83.2
42.9
34.3
34.0
32.4
26.6
25.3
24.9
21.1
f1 (ppm)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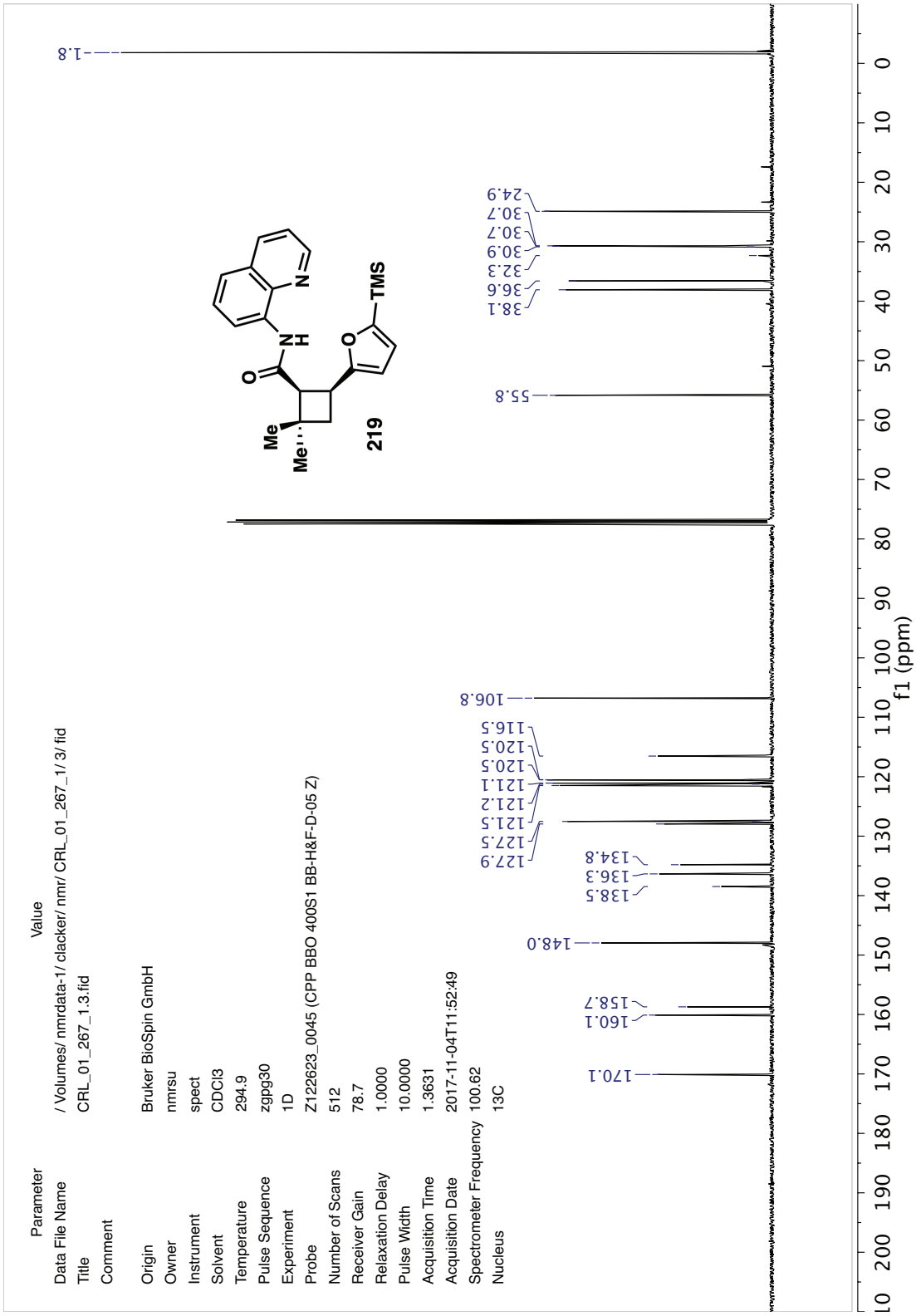
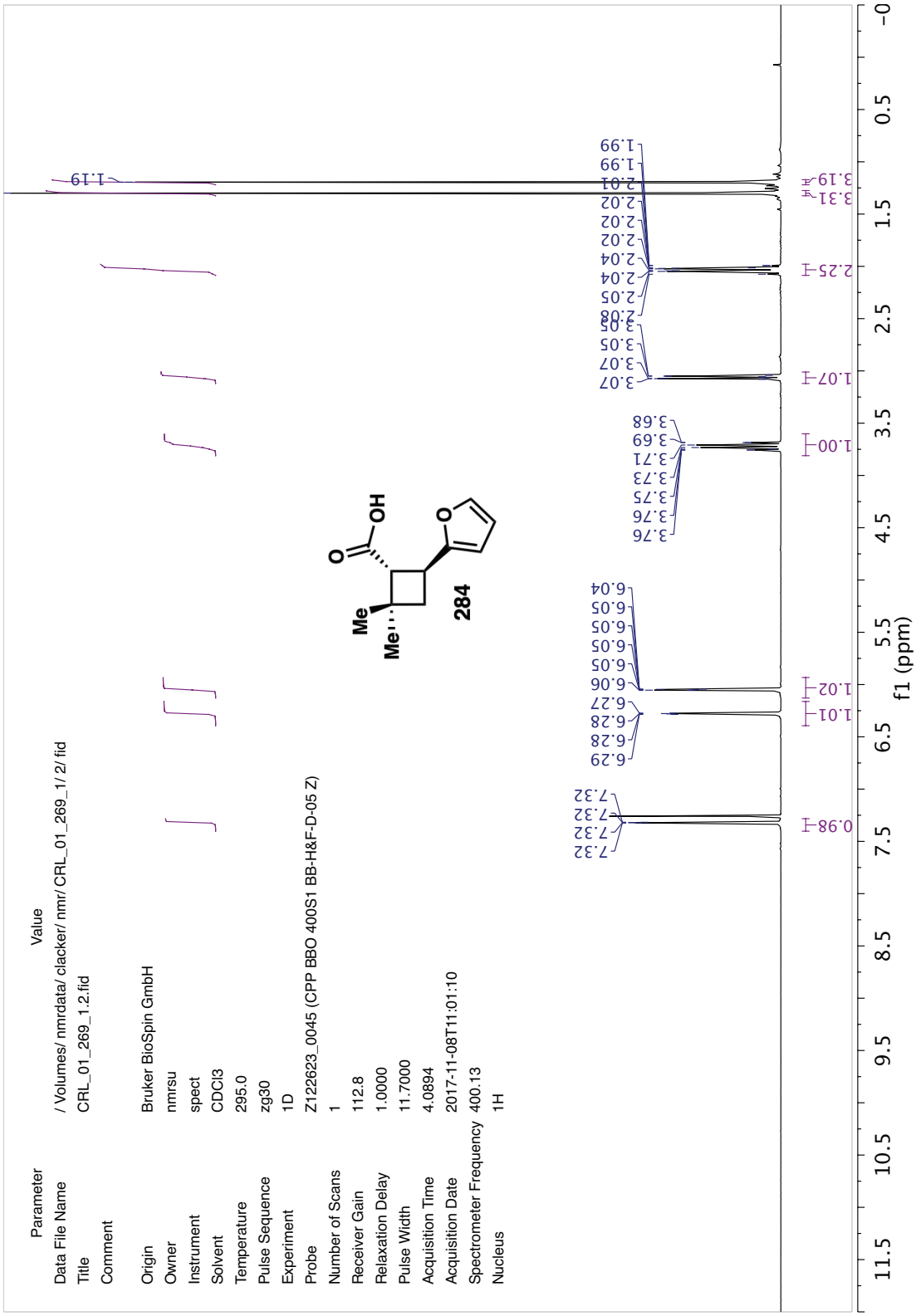
Title CRL_01_267_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2017-11-04T11:30:50
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
N
H
O
O
TMS
219
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ clacker/ nmr/ CRL_01_267_1/ 3/ fid
Title CRL_01_267_1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-11-04T11:52:49
Spectrometer Frequency 100.62
Nucleus 13C
1.8
24.9
30.7
30.7
30.9
32.3
36.6
38.1
55.8
106.8
116.5
120.5
120.5
121.1
121.2
121.5
127.5
127.9
134.8
136.3
138.5
148.0
158.7
160.1
170.1
Me
Me
O
N
H
O
TMS
N
219
f1 (ppm)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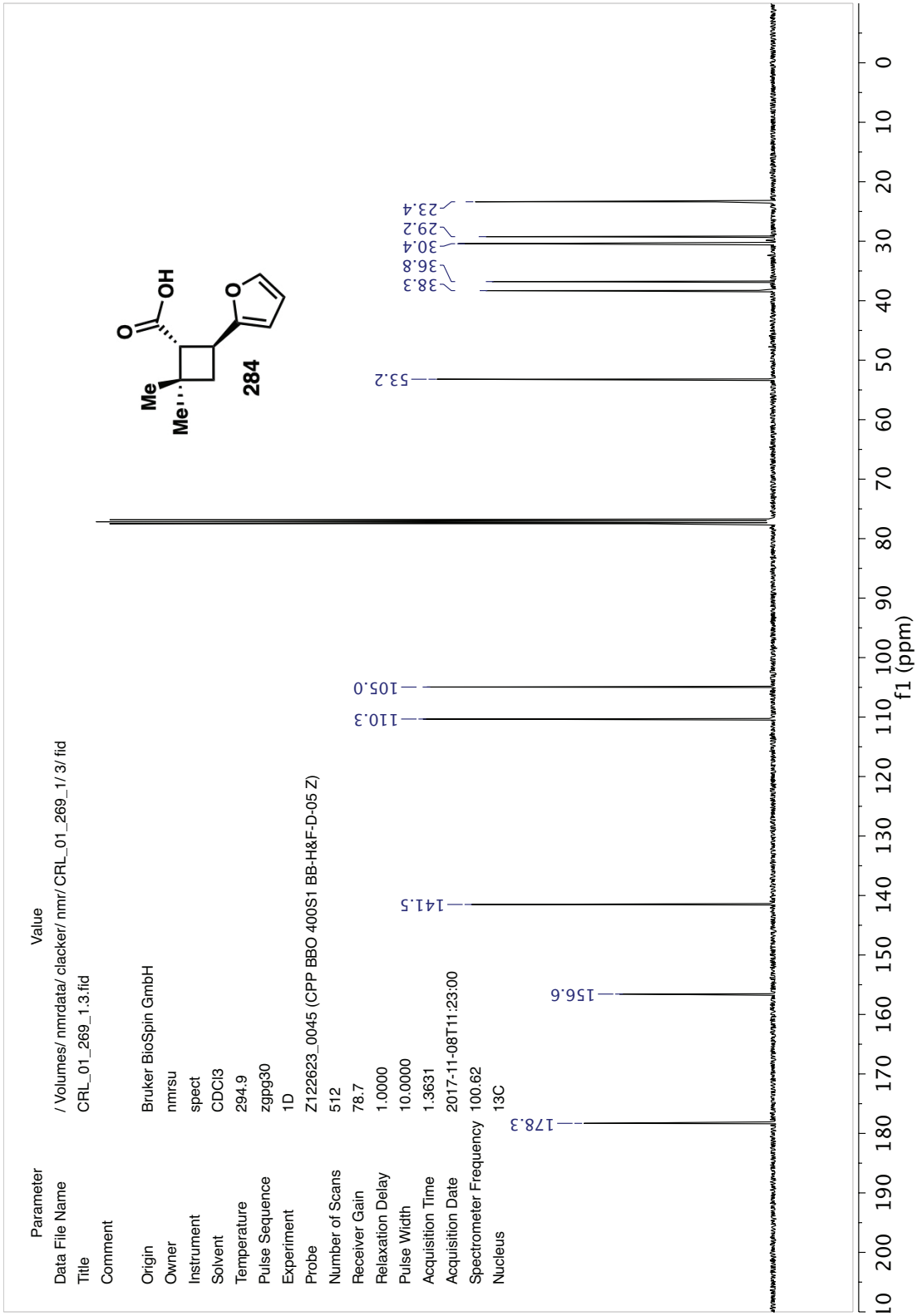
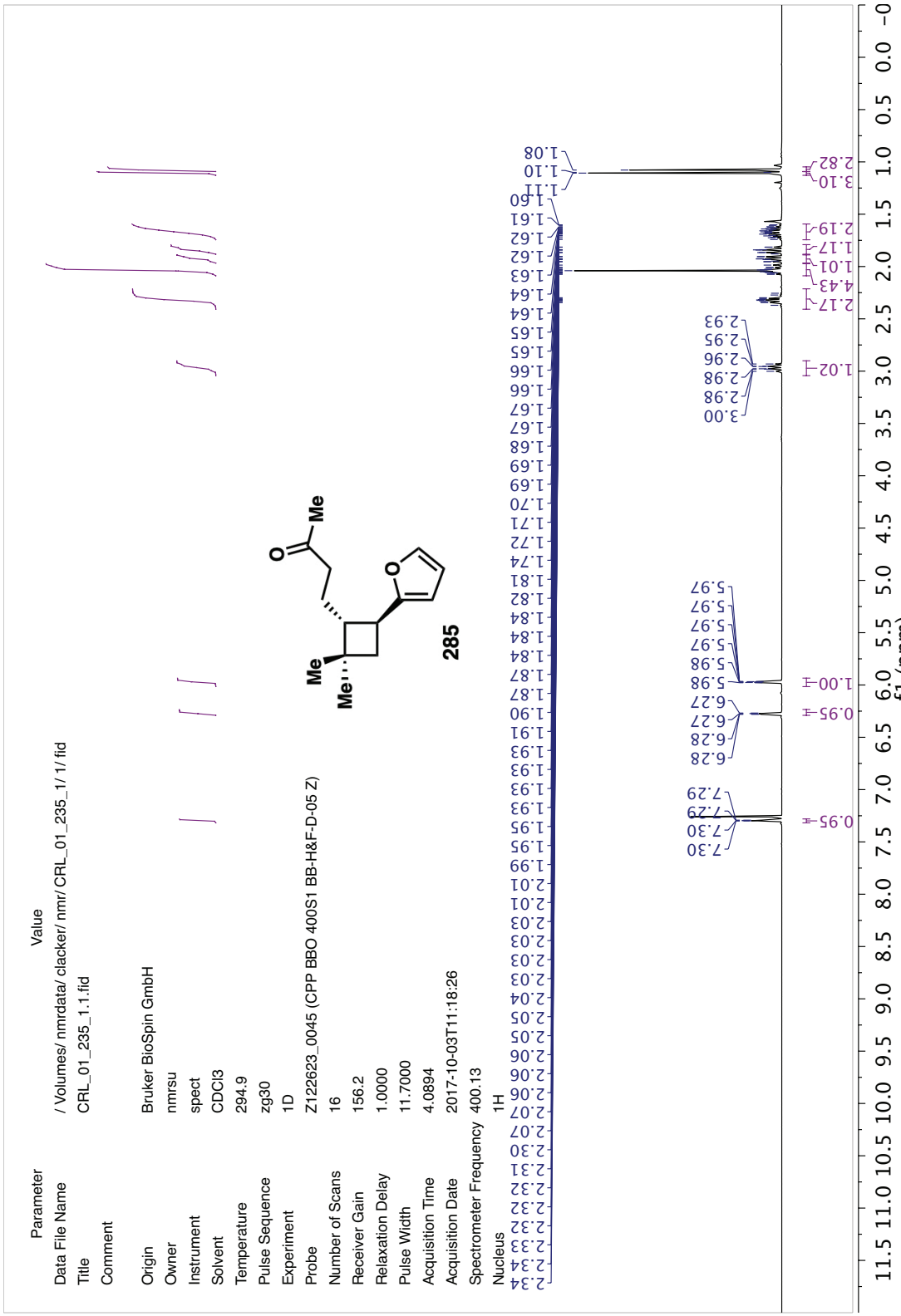
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_01_269_1/ 2/ fid
Title CRL_01_269_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.0
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2017-11-08T11:01:10
Spectrometer Frequency 400.13
Nucleus 1H
OH
O
Me
Me
O
284
f1 (ppm)


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ clacker/ nmr/ CRL_01_269_1/ 3/ fid
Title
CRL_01_269_1.3.fid
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
spect
Solvent
CDCl3
Temperature
294.9
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
512
Receiver Gain
78.7
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2017-11-08T11:23:00
Spectrometer Frequency
100.62
Nucleus
13C
178.3
156.6
141.5
110.3
105.0
53.2
38.3
36.8
30.4
29.2
23.4
Me
Me
OH
O
O
284
f1 (ppm)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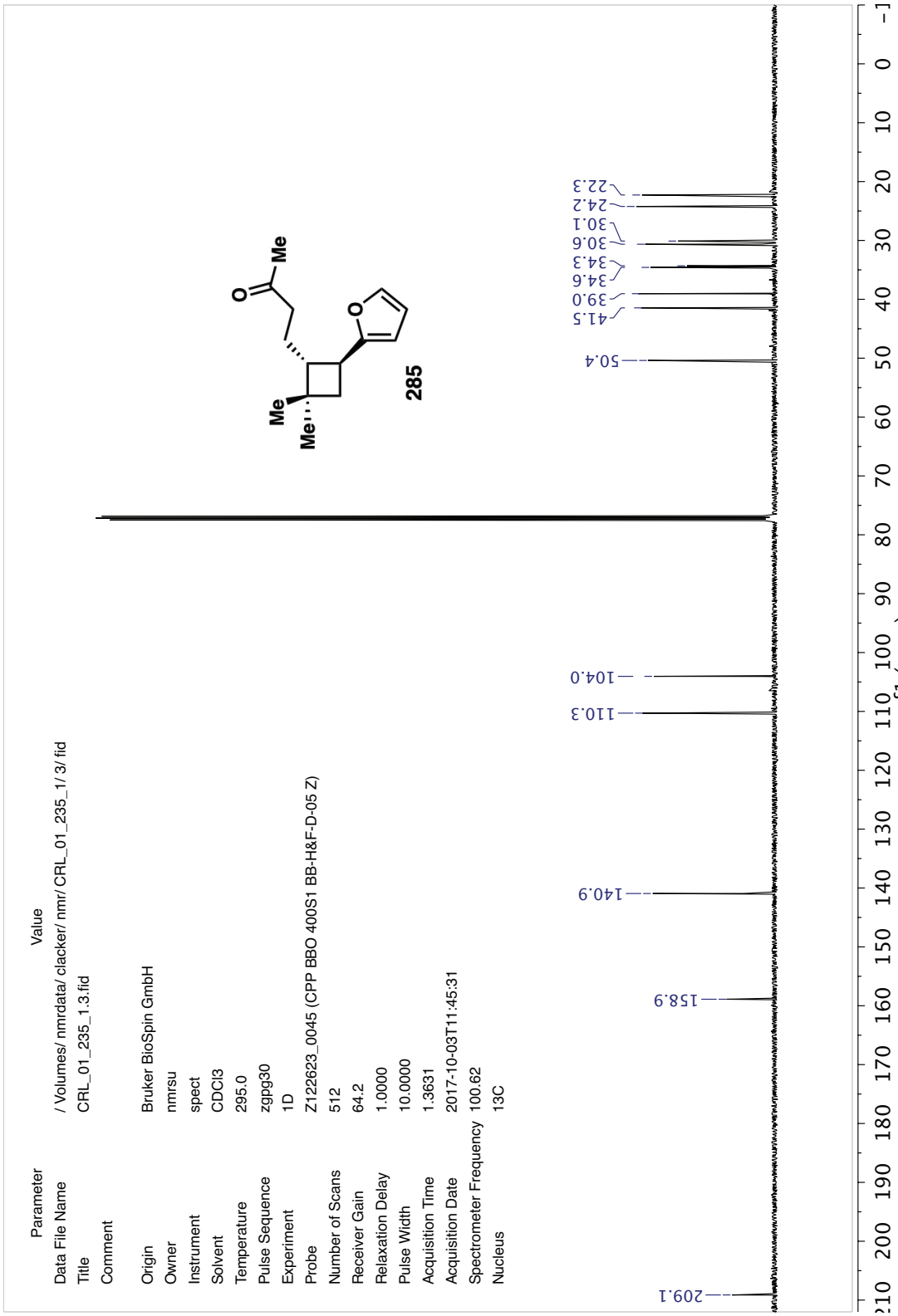
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_01_235_1/ 1/ fid
Title CRL_01_235_1.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2017-10-03T11:18:26
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
Me
O
O
285
f1 (ppm)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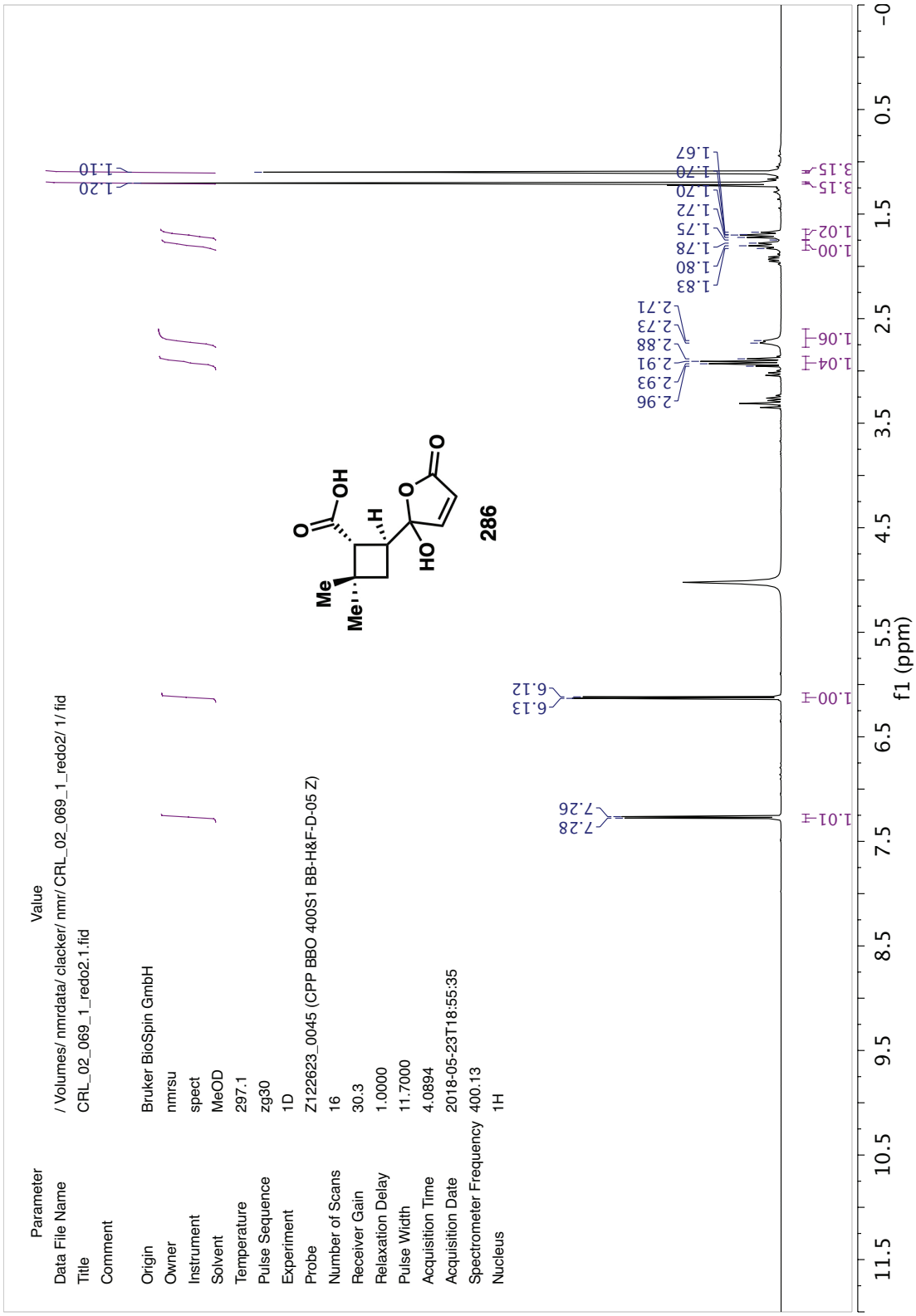
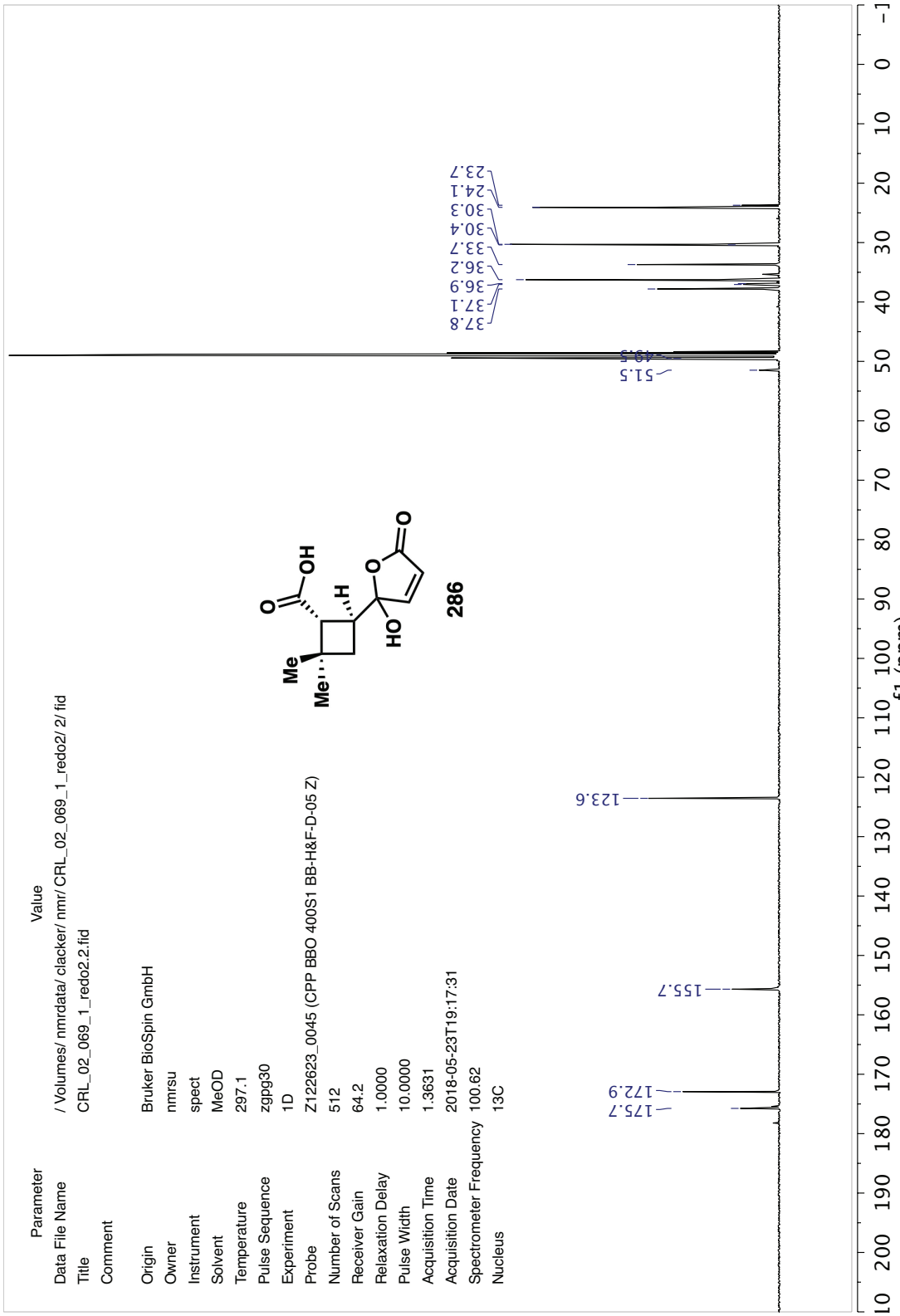
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_01_235_1/ 3/ fid
Title CRL_01_235_1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.0
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2017-10-03T11:45:31
Spectrometer Frequency 100.62
Nucleus 13C
O
Me
Me
Me
O
285
209.1
158.9
140.9
110.3
104.0
50.4
41.5
39.0
34.6
34.3
30.6
30.1
24.2
22.3
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_069_1_redo2/ 1/ fid
Title CRL_02_069_1_redo2.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent MeOD
Temperature 297.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-05-23T18:55:35
Spectrometer Frequency 400.13
Nucleus 1H
286
1.10
1.20
1.67
1.70
1.70
1.72
1.75
1.78
1.80
1.83
2.71
2.73
2.88
2.91
2.93
2.96
6.12
6.13
7.26
7.28
3.15
3.15
1.02
1.00
1.06
1.04
1.00
1.01
f1 (ppm)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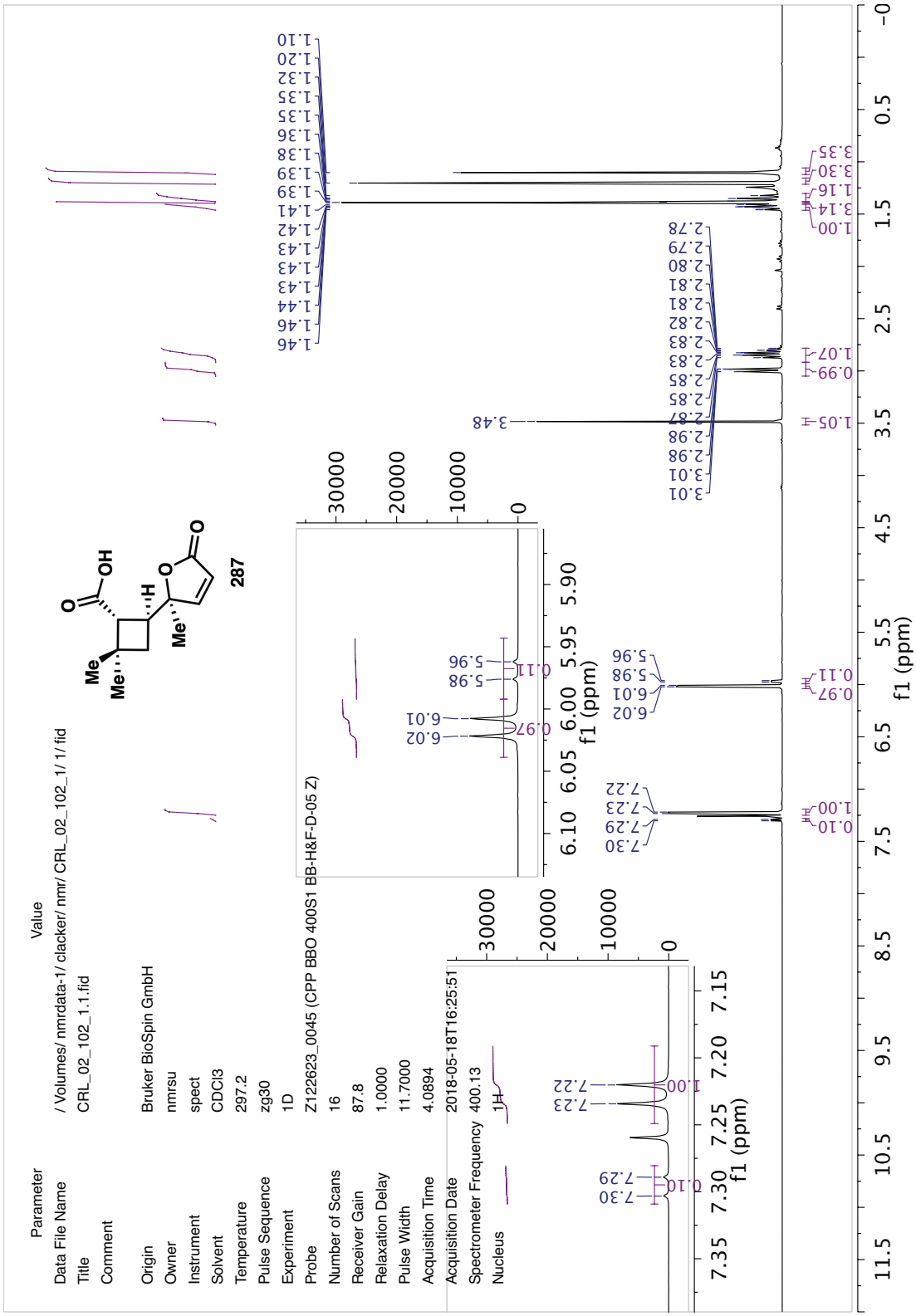
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_069_1_redo2/ 2/ fid
Title CRL_02_069_1_redo2.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent MeOD
Temperature 297.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-05-23T19:17:31
Spectrometer Frequency 100.62
Nucleus 13C
286
175.7
172.9
155.7
123.6
51.5
49.5
37.8
37.1
36.9
36.2
33.7
30.4
30.3
24.1
23.7
f1 (ppm)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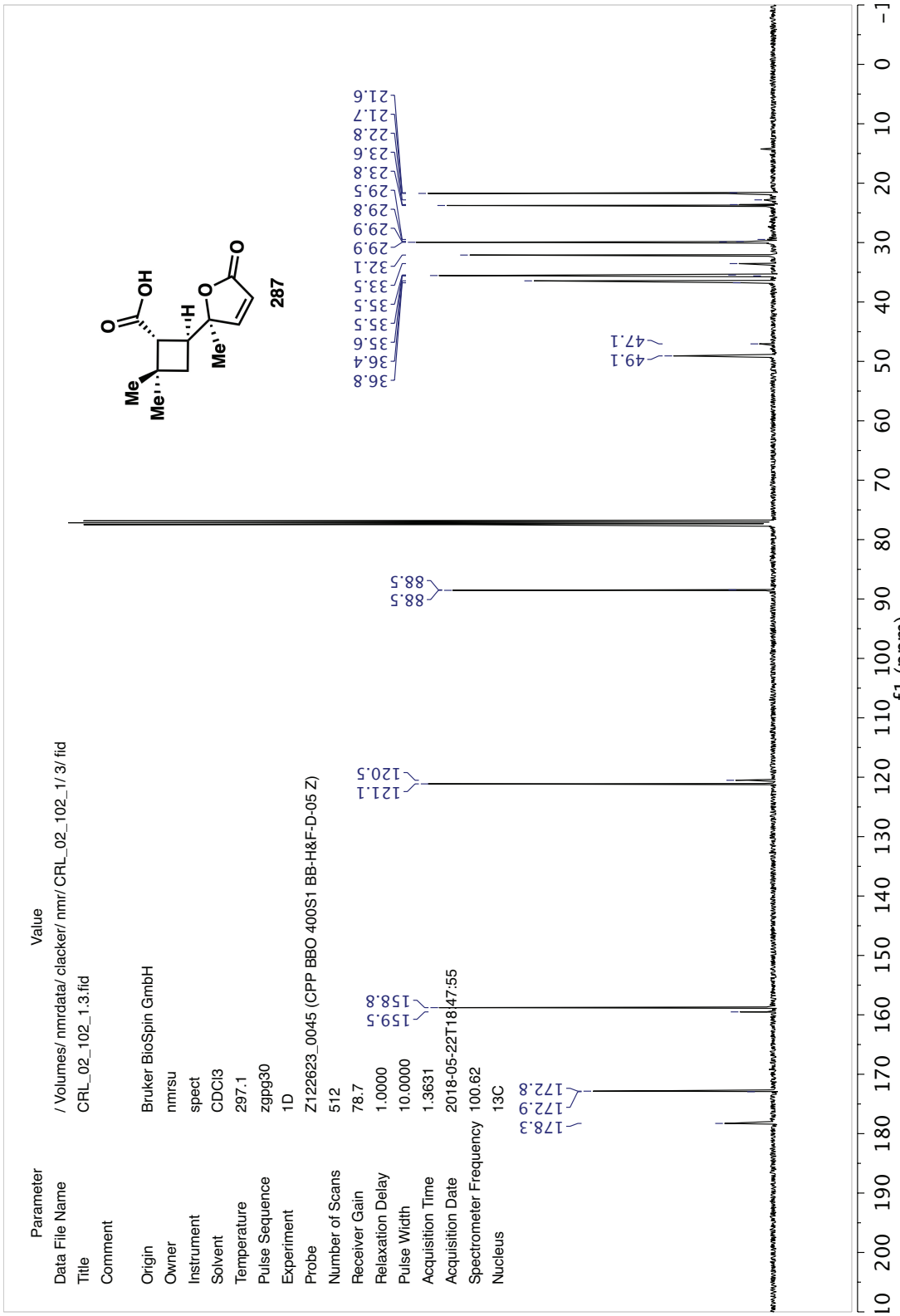
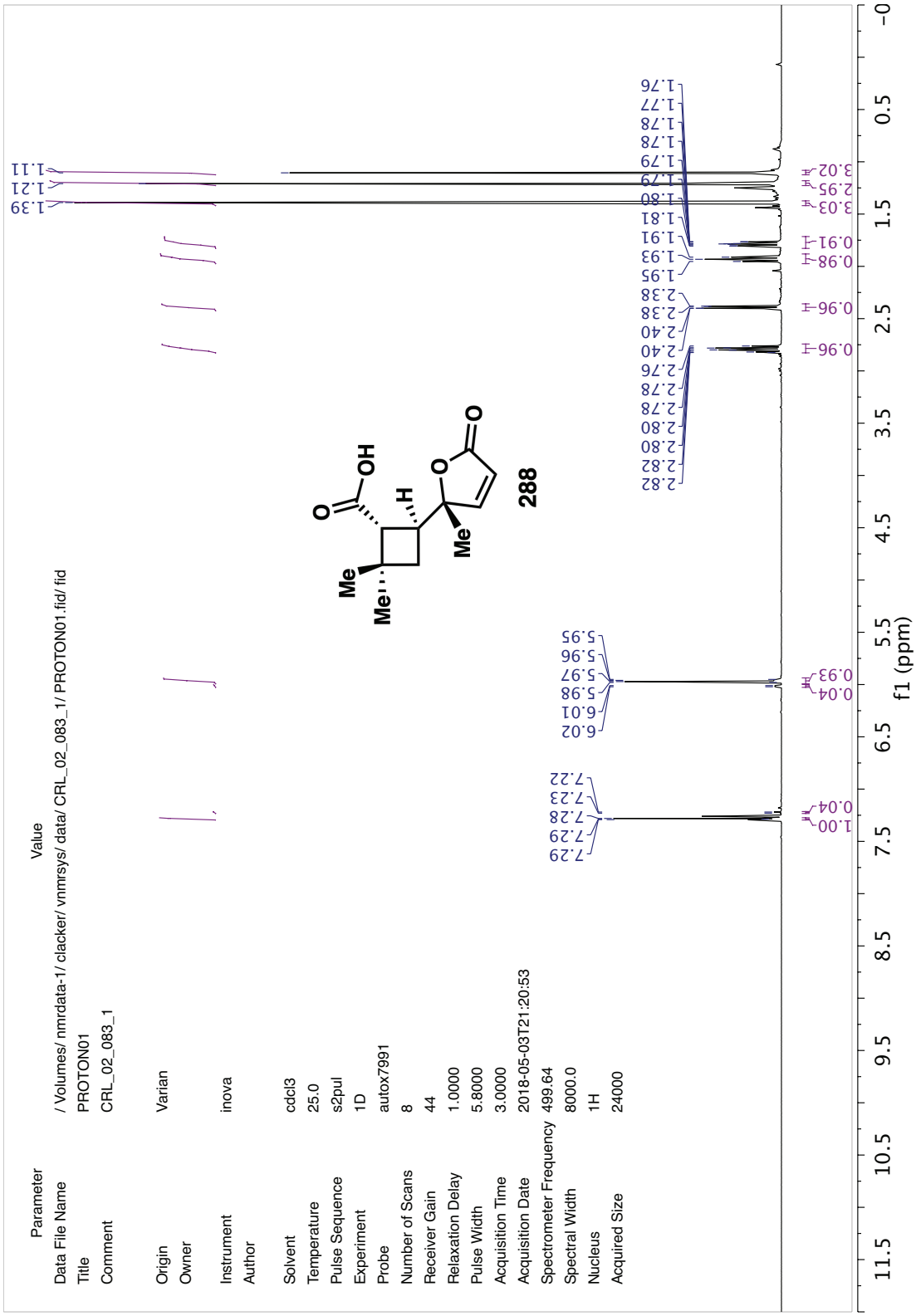
Data File Name / Volumes/ nmrdata-1/ clacker/ nmr/ CRL_02_102_1/ 1/ fid
Title CRL_02_102_1.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 297.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-05-18T16:25:51
Spectrometer Frequency 400.13
Nucleus 1H
287
f1 (ppm)


Parameter
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_102_1/ 3/ fid
Title CRL_02_102_1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 297.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-05-22T18:47:55
Spectrometer Frequency 100.62
Nucleus 13C
178.3
172.9
172.8
159.5
158.8
121.1
120.5
88.5
88.5
49.1
47.1
36.8
36.4
35.6
35.5
35.5
33.5
32.1
29.9
29.9
29.8
29.5
23.8
23.6
22.8
21.7
21.6
O
OH
Me
Me
H
O
Me
O
287
f1 (ppm)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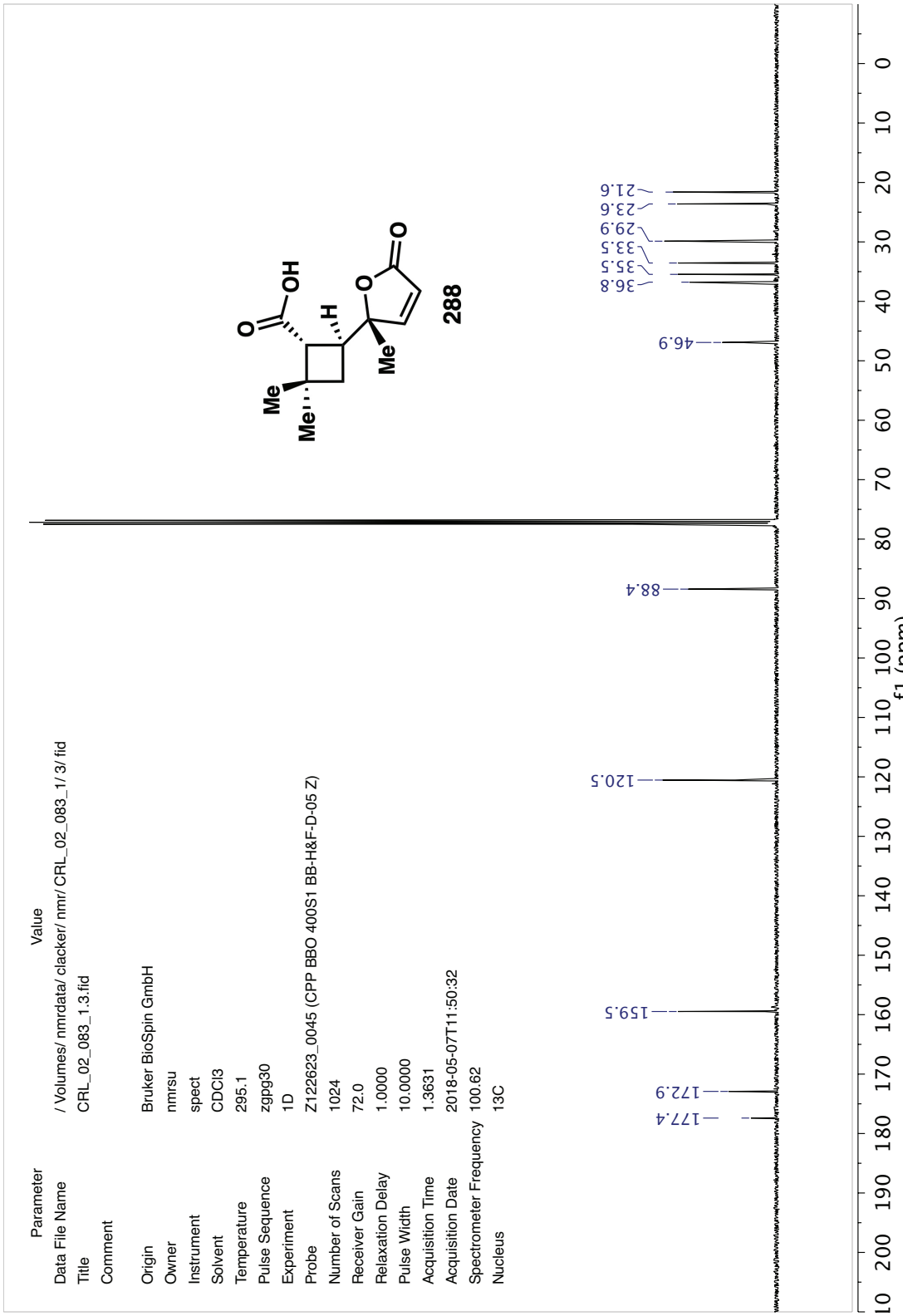
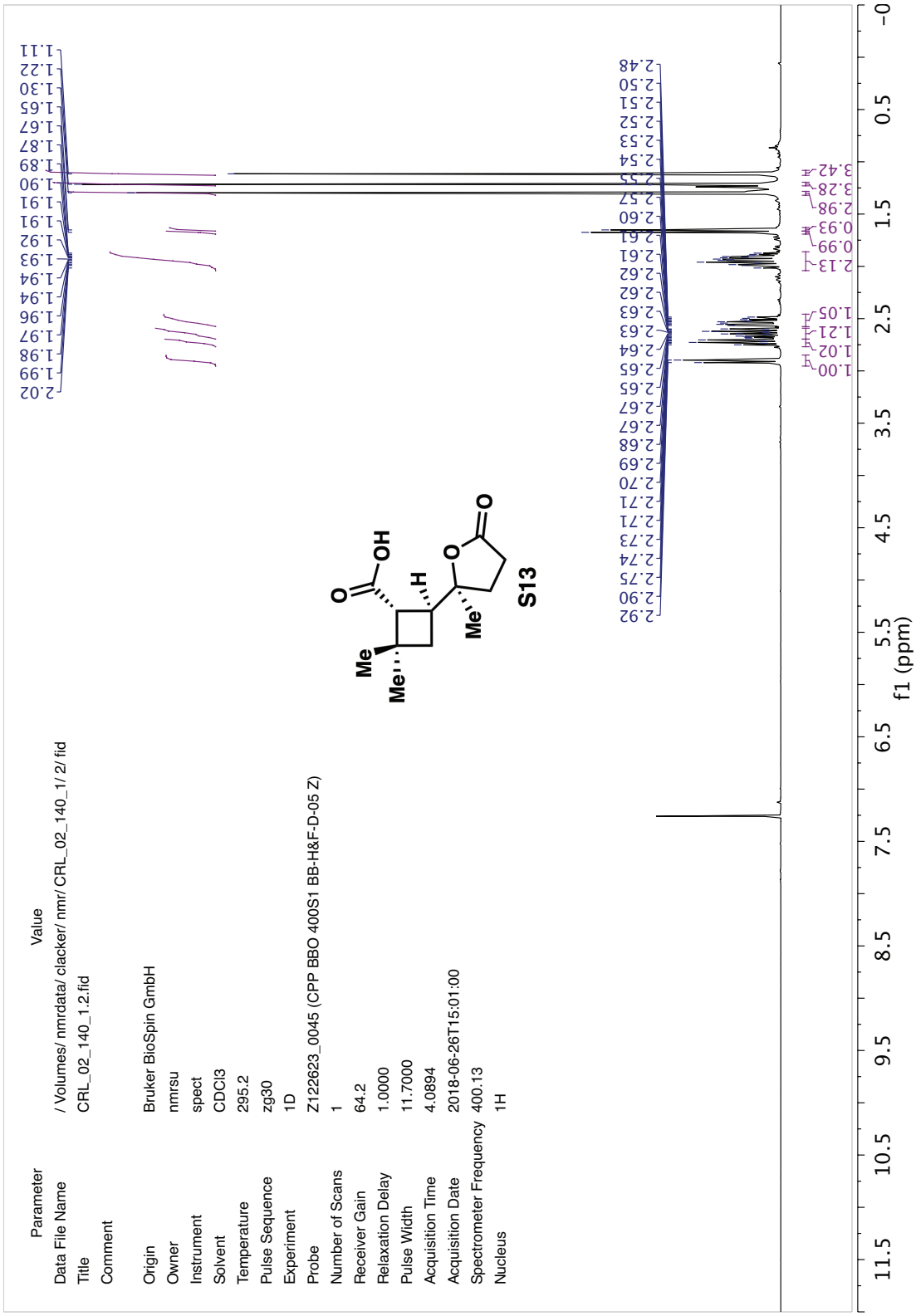
Title PROTON01
Comment CRL_02_083_1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe autox7991
Number of Scans 8
Receiver Gain 44
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2018-05-03T21:20:53
Spectrometer Frequency 499.64
Spectral Width 8000.0
Nucleus 1H
Acquired Size 24000
288
Me
Me
H
O
OH
O
O
Me
1.11
1.21
1.39
1.76
1.77
1.78
1.78
1.79
1.79
1.80
1.81
1.91
1.93
1.95
2.38
2.38
2.40
2.40
2.76
2.78
2.78
2.80
2.80
2.82
2.82
5.95
5.96
5.97
5.98
6.01
6.02
7.22
7.23
7.28
7.29
7.29
1.00
0.04
0.93
0.04
0.96
0.96
0.98
0.91
3.03
2.95
3.02
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_083_1/ 3/ fid
Title CRL_02_083_1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1024
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-05-07T11:50:32
Spectrometer Frequency 100.62
Nucleus 13C
177.4
172.9
159.5
120.5
88.4
46.9
36.8
35.5
33.5
29.9
23.6
21.6
O
OH
H
Me
Me
O
O
Me
288
f1 (ppm)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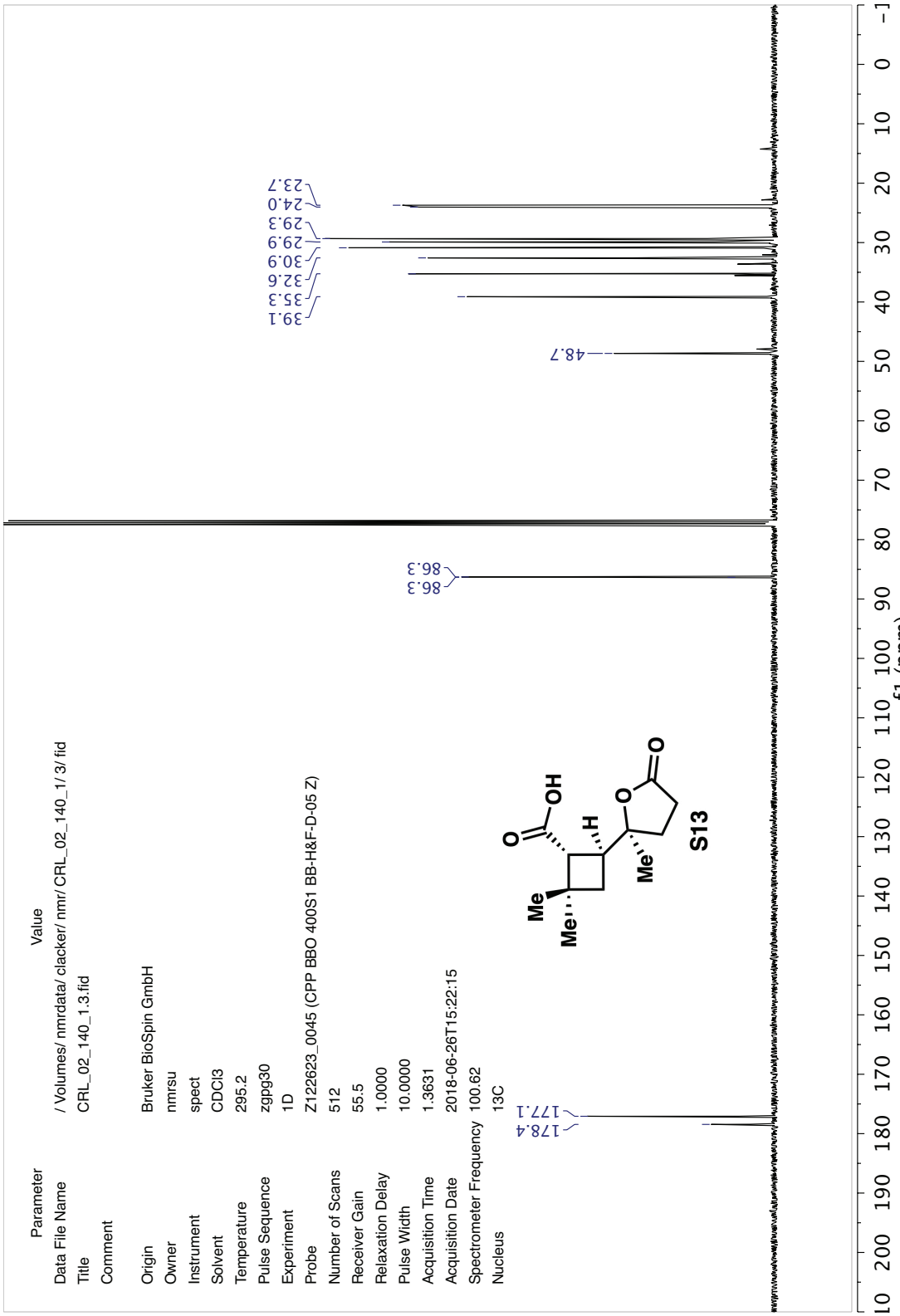
Value
Data File Name / Volumes/ nmrdata/ clacker/ nmr/ CRL_02_140_1/ 2/ fid
Title CRL_02_140_1.2.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-06-26T15:01:00
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
H
O
OH
O
O
Me
S13
f1 (ppm)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Acquisition Date 2018-06-26T15:22:15
Spectrometer Frequency 100.62
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178.4
177.1
86.3
86.3
48.7
39.1
35.3
32.6
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29.9
29.3
24.0
23.7
Me
Me
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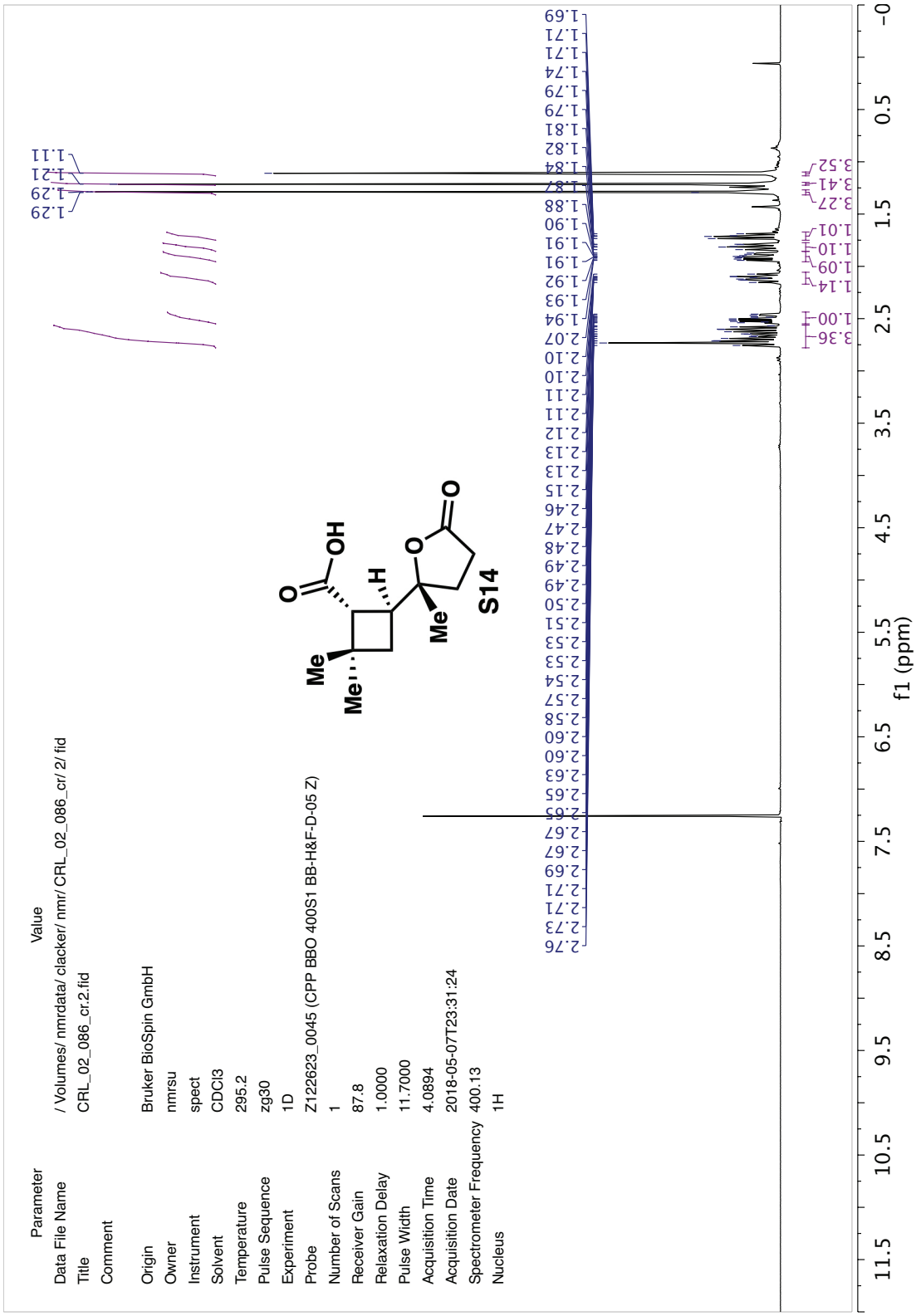
O
OH
O
O
Me
S13
f1 (ppm)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Instrument spect
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Acquisition Time 4.0894
Acquisition Date 2018-05-07T23:31:24
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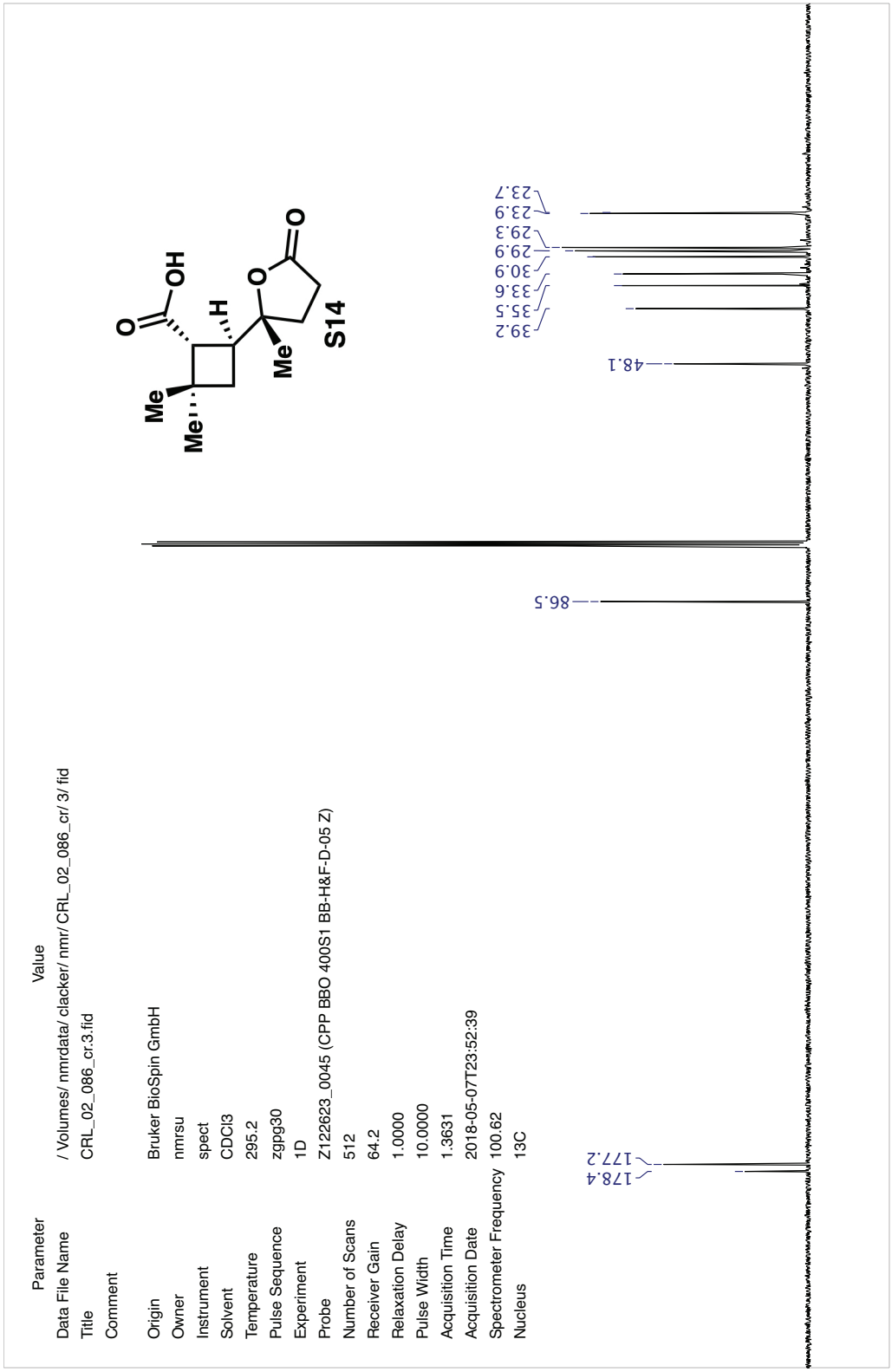
Me
H
O
OH
O
O
Me
S14
f1 (ppm)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Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
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Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
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Acquisition Date 2018-05-07T23:52:39
Spectrometer Frequency 100.62
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O
OH
Me
Me
H
O
O
Me
S14
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177.2
86.5
48.1
39.2
35.5
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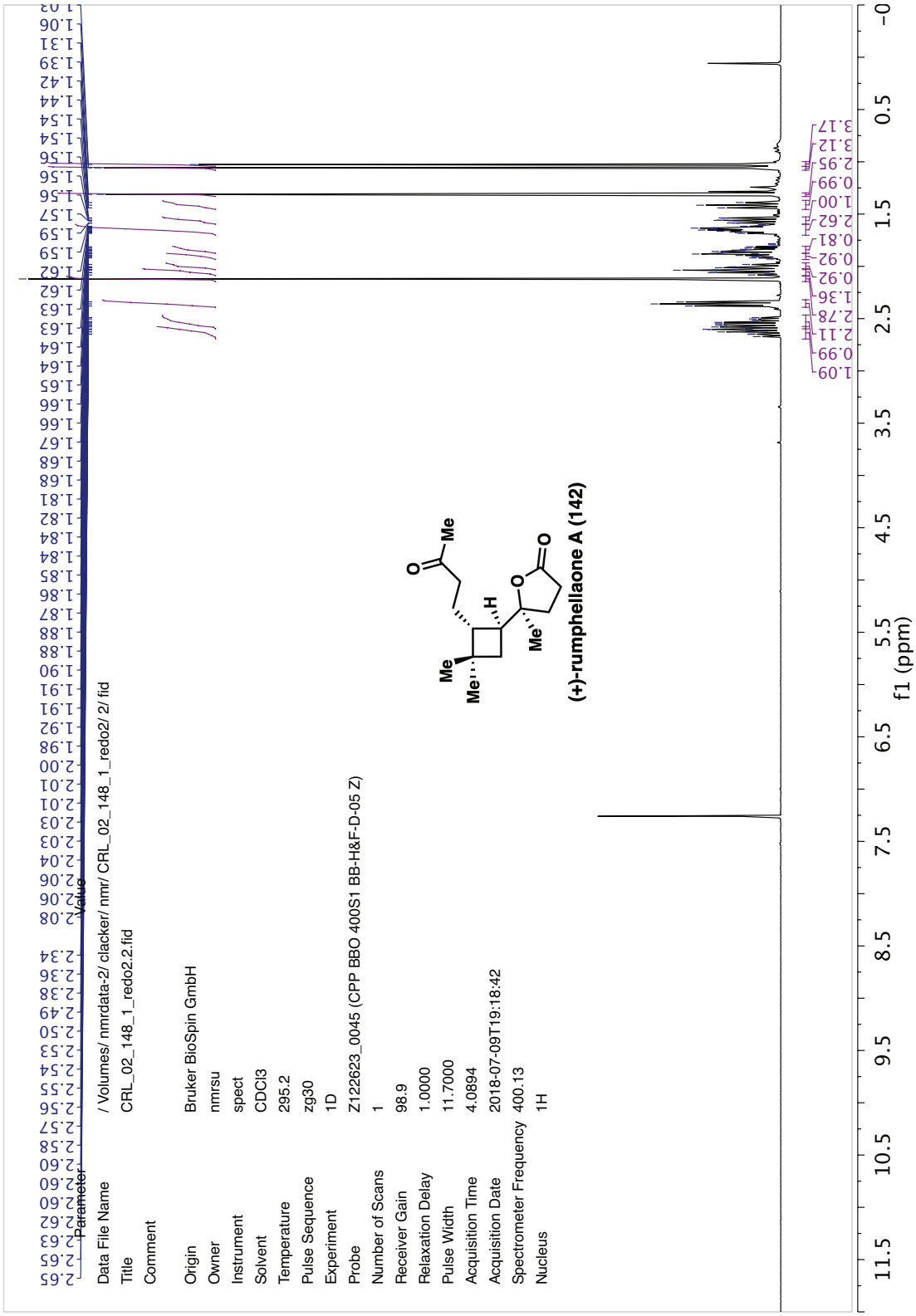
f1 (ppm)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Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
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Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-09T19:18:42
Spectrometer Frequency 400.13
Nucleus 1H
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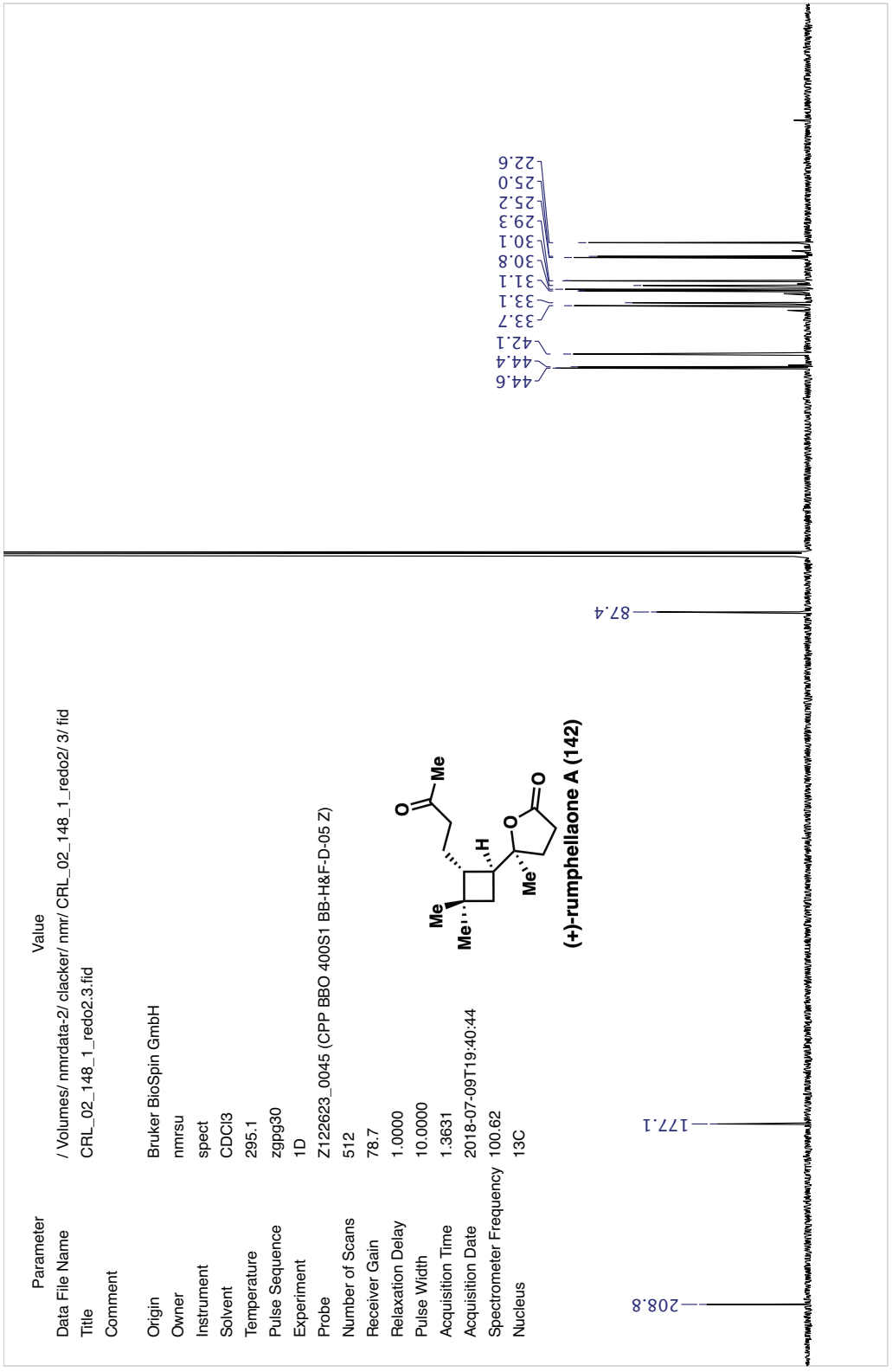
Me
H
Me
O
O
O
Me
(+)-rumphellaone A (142)
f1 (ppm)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Owner nmrsu
Instrument spect
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Pulse Sequence zgpg30
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Receiver Gain 78.7
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Pulse Width 10.0000
Acquisition Time 1.3631
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87.4
44.6
44.4
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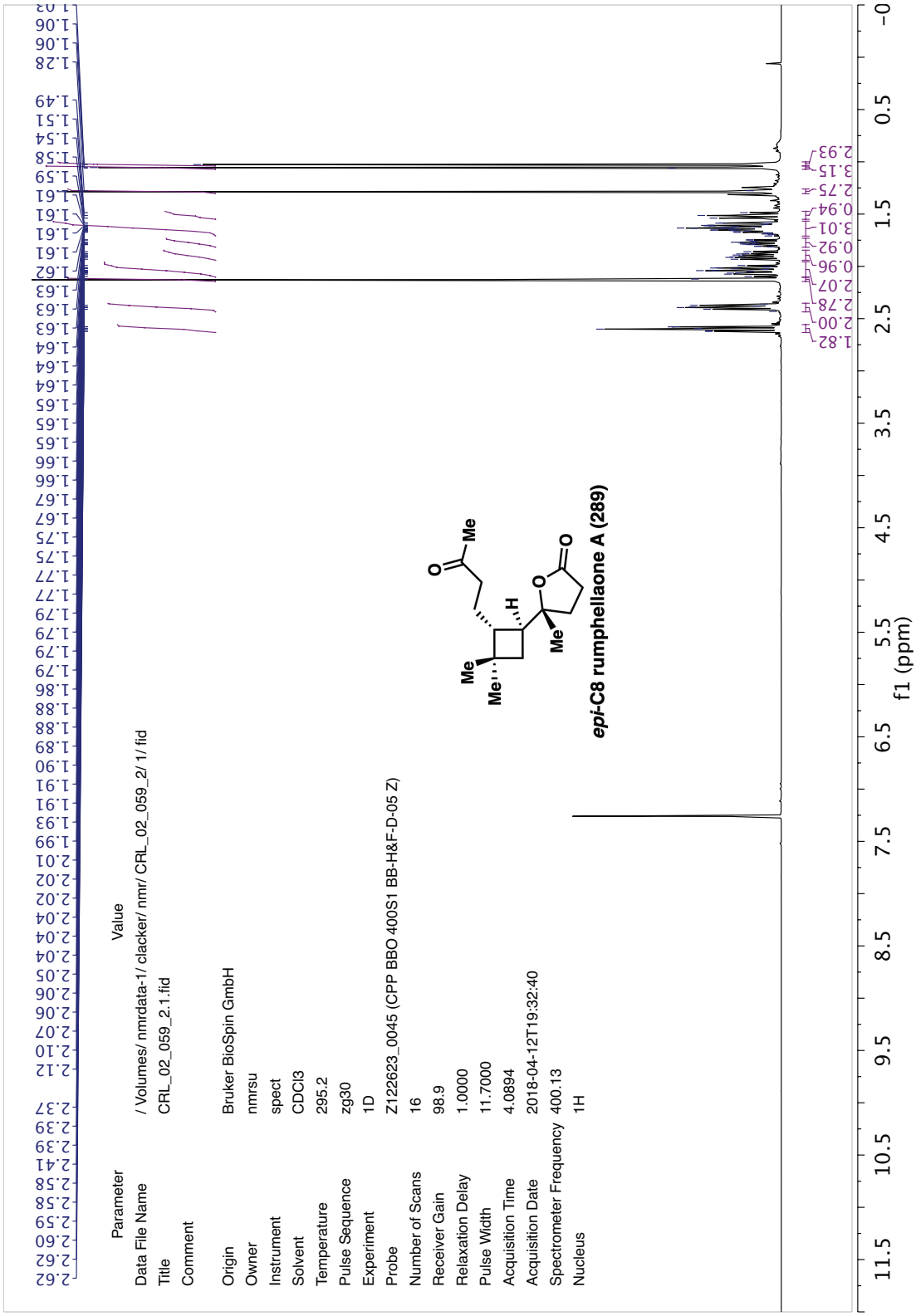
33.1
31.1
30.8
30.1
29.3
25.2
25.0
22.6
Me
Me
H
Me
O
O
O
Me
(+)-rumphellaone A (142)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)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Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
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Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 11.7000
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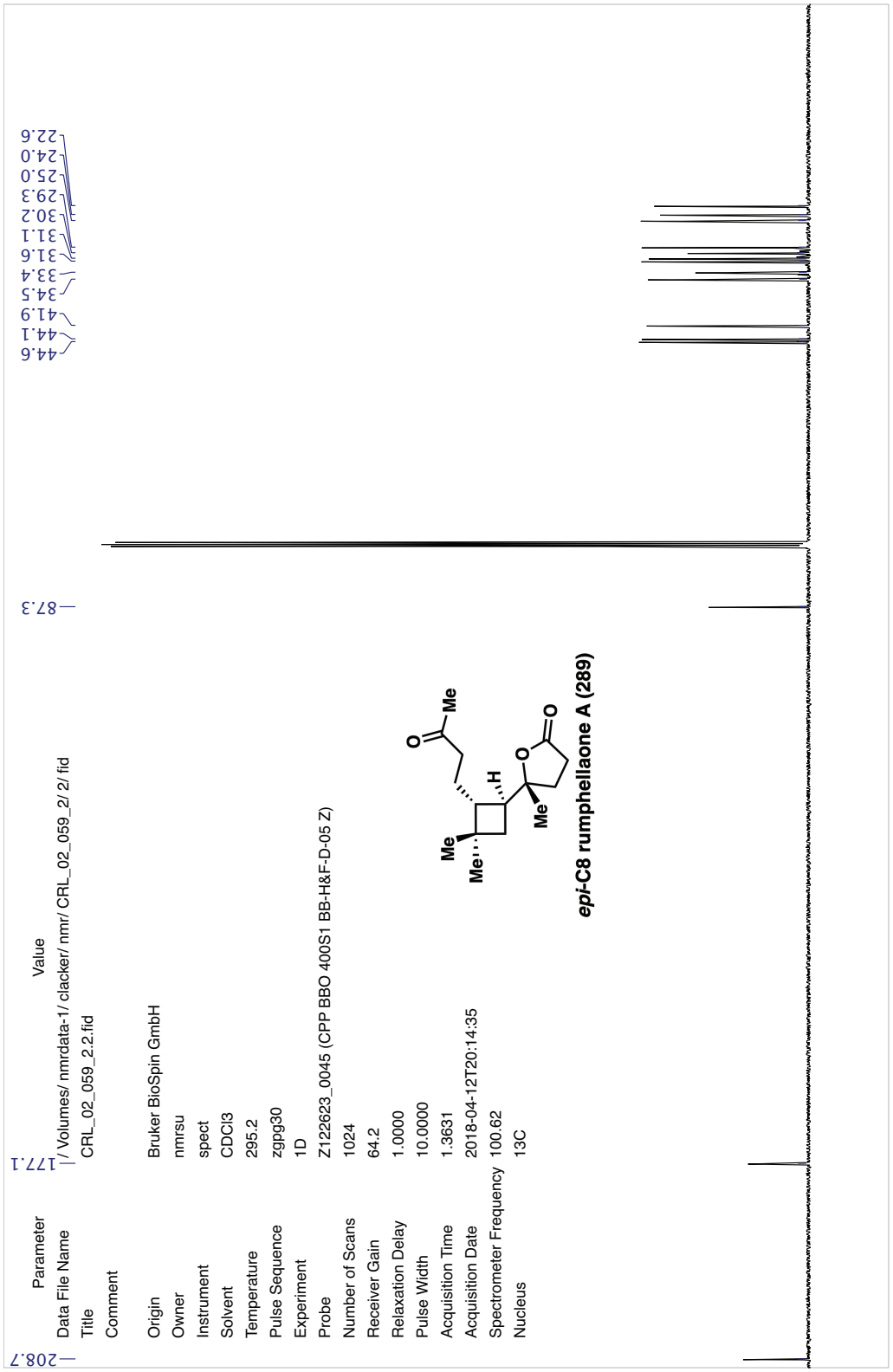
Nucleus 1H
epi-C8 rumphellaone A (289)
f1 (ppm)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Value
Data File Name
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CRL_02_059_2.2.fid
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spect
Solvent
CDCl3
Temperature
295.2
Pulse Sequence
zgpg30
Experiment
1D
Probe
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Number of Scans
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64.2
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2018-04-12T20:14:35
Spectrometer Frequency
100.62
Nucleus
13C
epi-C8 rumphellaone A (289)
208.7
177.1
87.3
44.6
44.1
41.9
34.5
33.4
31.6
31.1
30.2
29.3
25.0
24.0
22.6
f1 (ppm)

Chapter 3

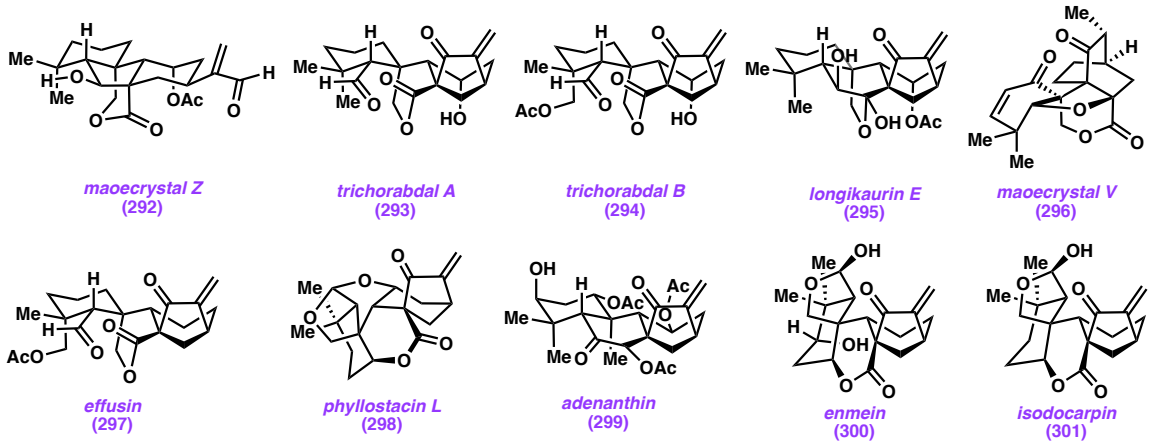
An Introduction to the Enmein-type Ent-Kauranoids

3.1 INTRODUCTION

Extracts from plants of the *Isodon* species have been used for centuries in traditional Chinese medicine.[1] In an effort to identify the bioactive chemical constituents, over 1,000 novel diterpenoids have been isolated from these plants and characterized to date.[11] Compounds such as trichorabdal A (**293**),[2] adenanthin (**299**),[3] and isodocarpin (**301**)[4] have demonstrated potent antibacterial, anti-inflammatory, and antitumor activities, and since their identification in the 1960s have become the focus of study for both chemists and biologists (Scheme **3.1**). For example, **299** was shown to selectively inhibit two isoforms of peroxiredoxin enzymes and prolong survival in murine models of acute promyelocytic leukemia.[3] *Ent*-kauranoids possessing the exocyclic enone moiety are thought to have enhanced biological activity through covalent modification of target proteins.[5] It is hypothesized that molecules in this class arise biosynthetically from common progenitors

and all contain a caged polycyclic core bearing varying oxidation patterns (Figure 1).[11] However, the wide range of biological activity in this family of natural products suggests that the stereochemical and regiochemical oxidation patterns embedded within the core of these compounds impart significant changes to their bioactivity. Despite the intriguing biological properties of these highly oxygenated terpenes, there have been few successful total syntheses of this class of natural products.

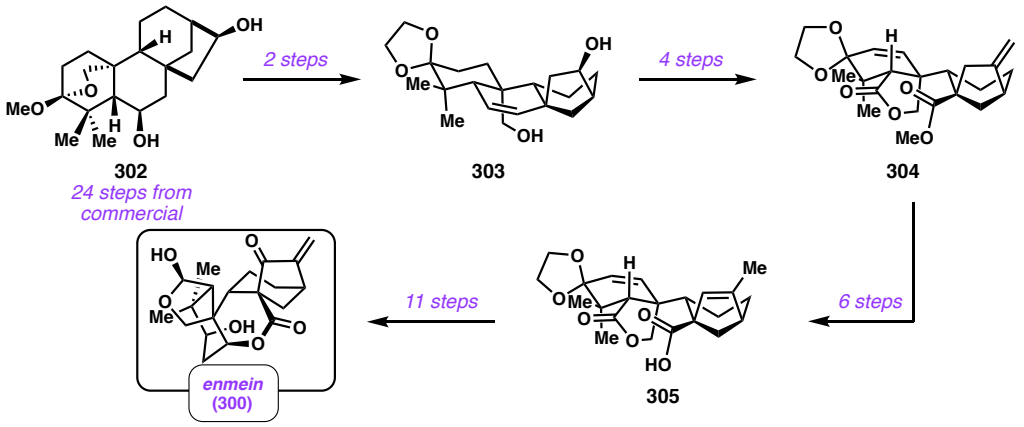
Scheme 3.1 *Representative examples of bioactive ent-kauranoids.*



3.2 PREVIOUS SYNTHESES OF RELATED NATURAL PRODUCTS

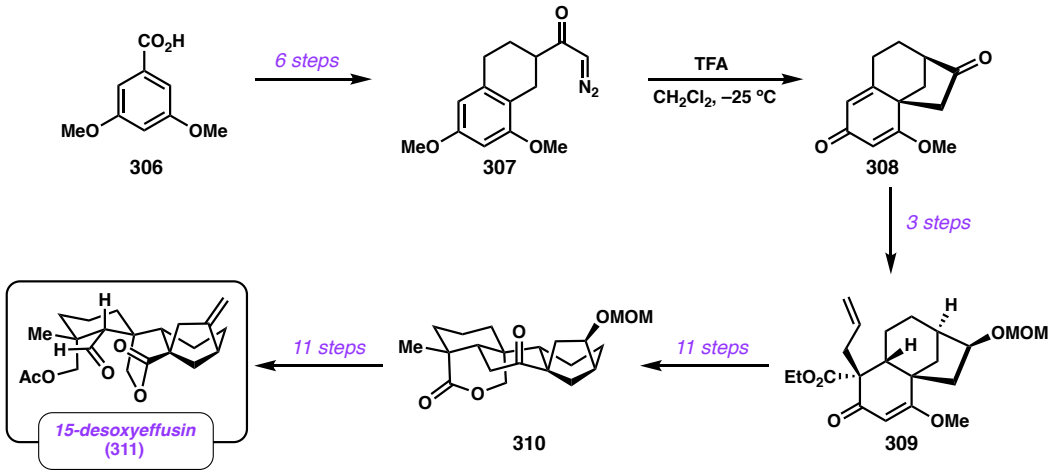
Several research groups have made contributions to the total synthesis of Isodon diterpenoids. In 1974, Fujita and coworkers disclosed a biomimetic synthesis of enmein (**300**) (Scheme **3.2**).[5–7] Diol **302** can be accessed in 24 steps from commercial material as a racemate. From diol **302**, two additional steps provides **303**. Diol **303** can be elaborated to lactone **304**, which can be derivatized to access **305** in six additional steps. From **305**, it takes the Fujita lab an additional eleven steps to finally access **300**, in a largely linear synthesis.

Scheme 3.2 *Fujita synthesis of enmein (**300**).*



Notably, their synthesis could only be rendered asymmetric through a semi-synthetic route, in which they use plant materials to isolate a single enantiomer of **302**. With enantioenriched **302**, Fujita and coworkers could carry out their established route to access enmein (**300**) as a single enantiomer.

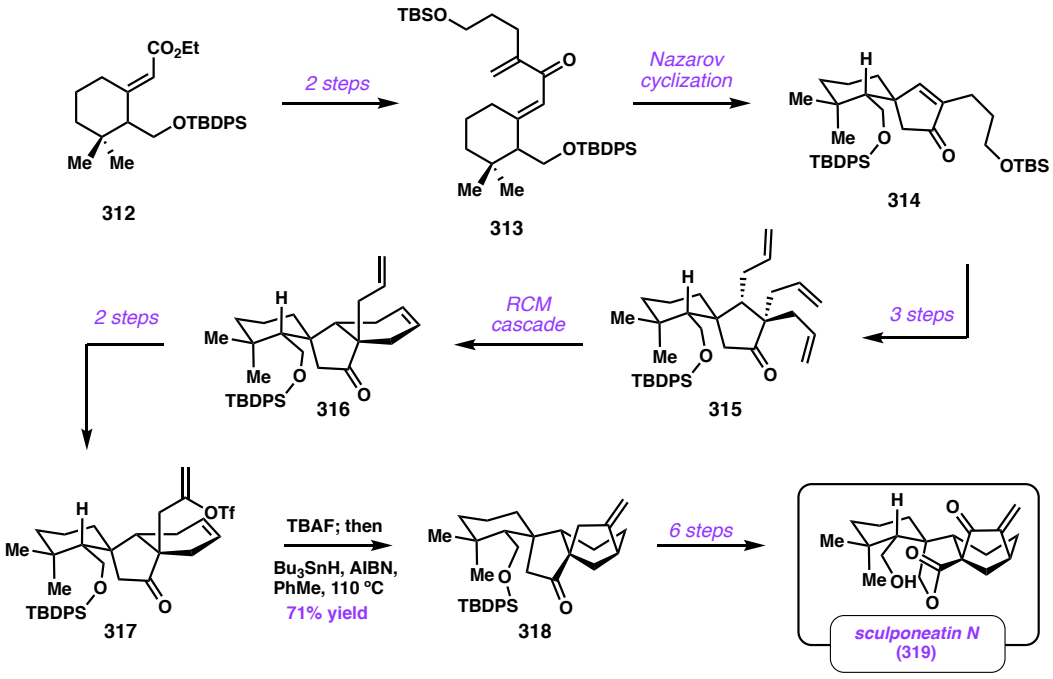
Scheme 3.3 *Mander's synthesis of 15-desoxyeffusin (**311**).*



In 1986, Mander reported a series of studies toward the total synthesis of effusin (**297**) (Scheme **3.3**).[8,9] A key intramolecular arene alkylation of α-diazoketone **307** was used to construct the bridging bicyclo[3.2.1]octane moiety present in **308**. Tricycle **308**

could be advanced three steps to build a second all-carbon quaternary center present in **309**. This vinylogous ester **309** could be elaborated to 15-desoxyeffusin (**311**) in an additional 22 steps; however, any attempts to oxidize the C15 methylene proved unsuccessful.

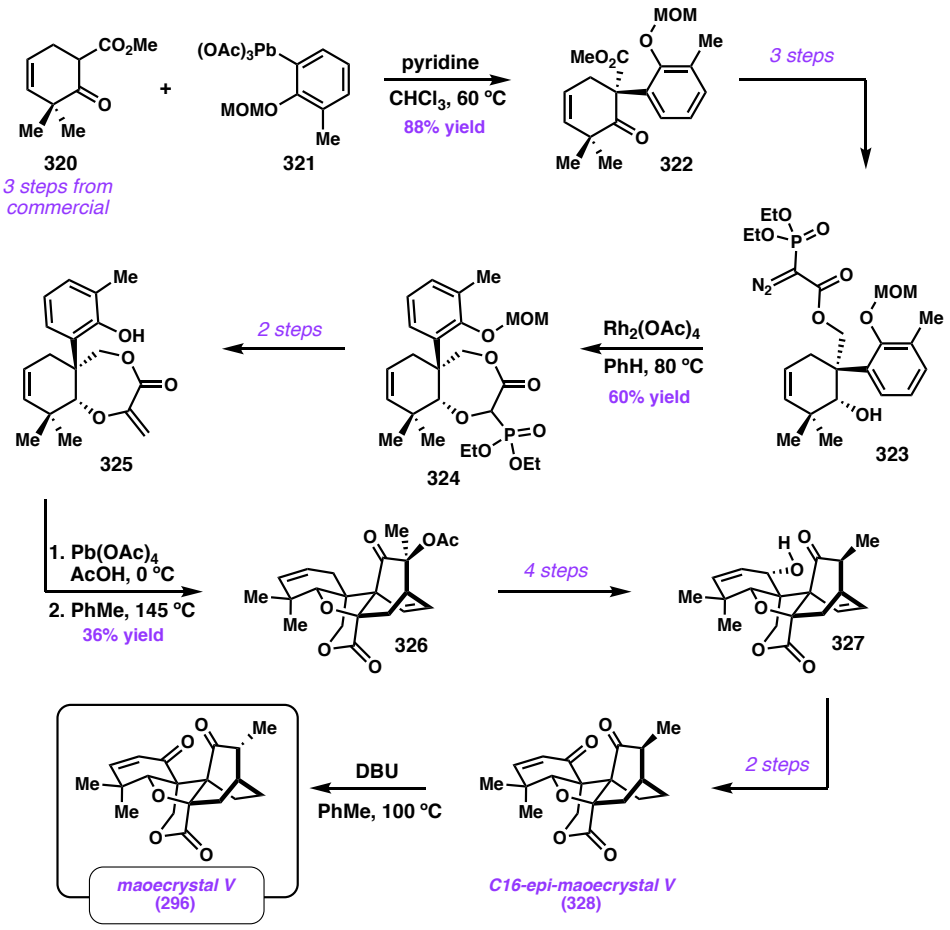
Scheme 3.4 *Thomson's synthesis of sculponeatin N (**319**).*



In 2014, the Thomson lab reported a total synthesis of sculponeatin N (**319**), starting from **312**, which can be prepared in three steps from commercial material (Scheme **3.4**).[10] Acrylate **312** can be advanced two additional steps to access diene **313**, which undergoes a key Nazarov cyclization to form the cyclopentenone moiety in **314**. Three additional steps enables the installation of three olefins present in **315**, which can be subjected to a ring closing metathesis cascade to prepare **316**. With **316** in hand, oxidation and triflation provides **317**, which is then poised to undergo elimination and a subsequent radical

cyclization to form the key [3.2.1]-bicycle of **318**. Sculponeatin N (**319**) can be accessed in six additional steps, forming **319** in 19 steps from commercial material.

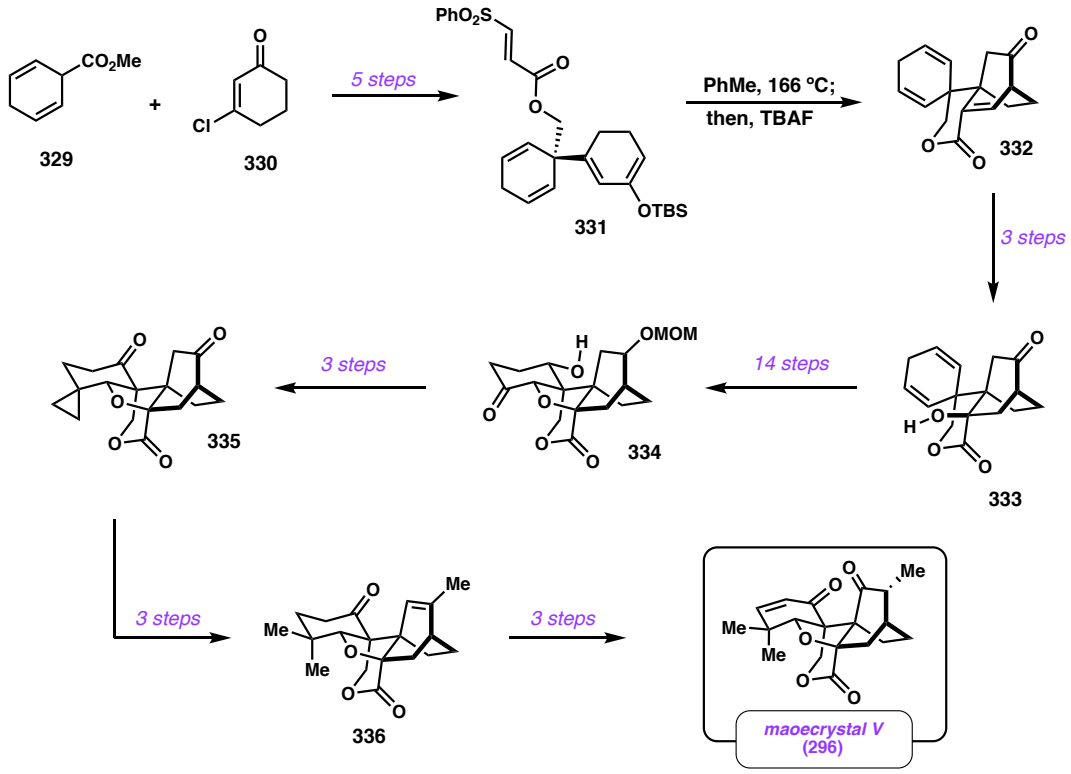
Scheme 3.5 *Yang's synthesis of maoecrystal V (**296**).*



Several research groups have targeted maoecrystal V (**296**) since its structural elucidation in 2004.[11] The first successful total synthesis of **296** was completed in 2010 by Yang and coworkers (Scheme **3.5**).[12] Their synthesis commences with b-ketoester **320**. Treatment with aryl lead reagent **321** enables an a-arylation reaction. Ketone **322** can be elaborated to diazoester **323** in two additional steps. A key intramolecular O–H insertion reaction creates the C–O bond present in **324**, which can be elaborated in two additional

steps to provide enone **325**. A Wessely oxidative acetoxylation followed by an intramolecular thermal [4+2] cycloaddition provides **326**. With the key carbon skeleton intact, Yang and co-workers are tasked with oxidative manipulation of the framework. Four steps are required to install the allylic alcohol and to remove the acetoxy group at C16 to provide **327**. From **327**, an oxidation mediated by DMP and a catalytic reduction of the bicycle produces epi-C16-maoecrystal V (**328**). A final epimerization delivers **296**.

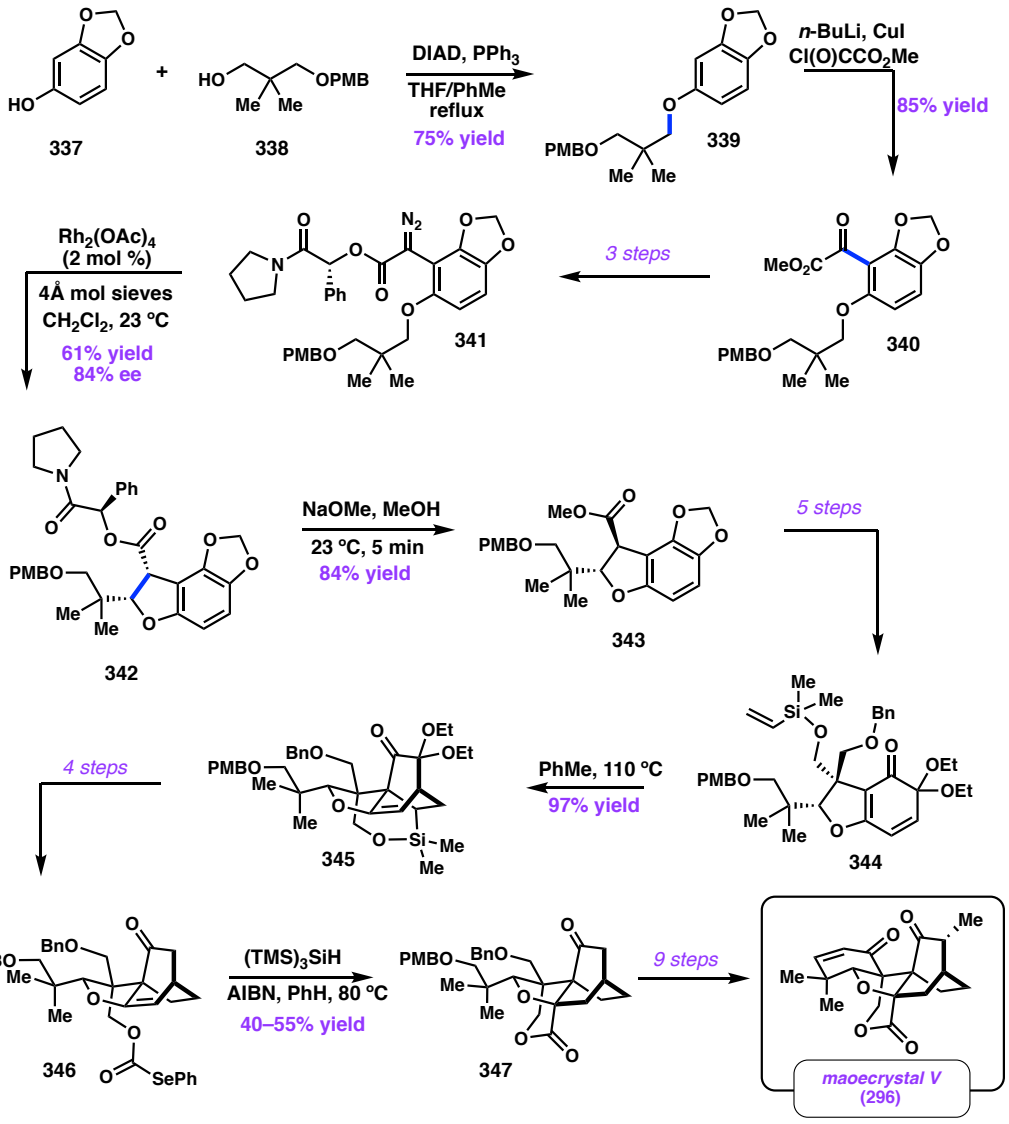
Scheme 3.6 *Danishefsky's synthesis of maoecrystal V (**296**).*



The Danishefsky lab also completed a synthesis of **296** in 2012 (Scheme **3.6**).[13] Key to their strategy was an intramolecular Diels-Alder between an unsaturated sulfone and a pendant silyl dienol ether **331**. Following elimination, they are able to establish the key carbo skeleton in **332**. From here, it takes them three steps to install the necessary

oxidation at the bridgehead and then 14 steps to deliver the central tetrahydrofuran **334**. From here, modification of A and E rings can be carried out in nine additional steps, delivering **296**.

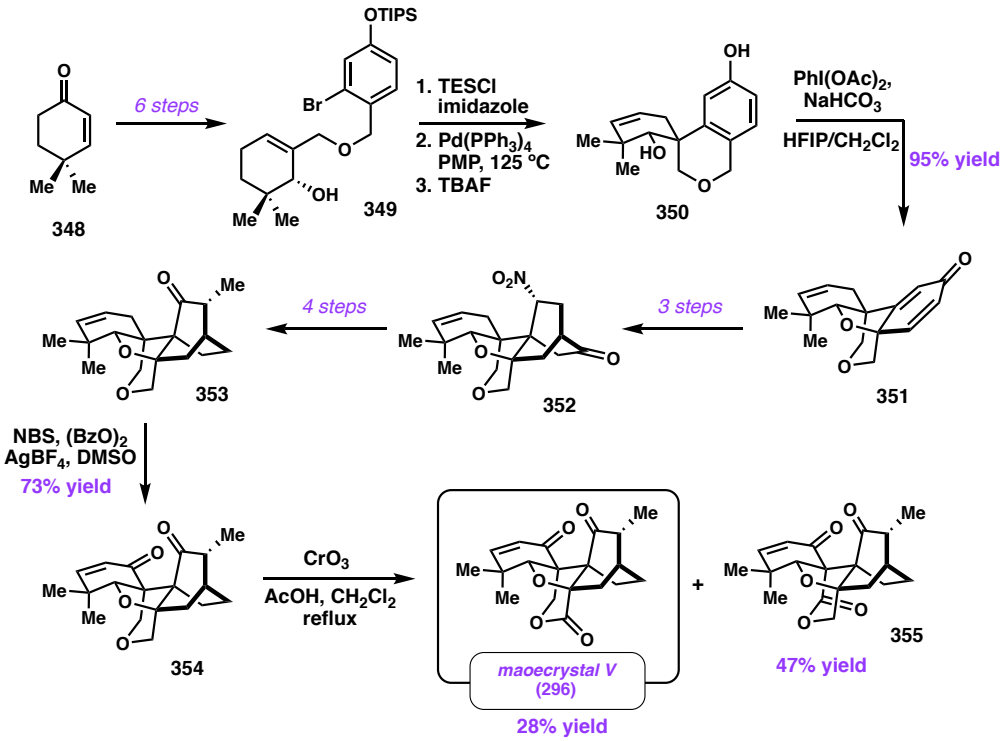
Scheme 3.7 *Zakarian's synthesis of maoecrystal V (**296**).*



The first asymmetric synthesis of **296** was reported in 2014 by Zakarian and coworkers (Scheme **3.7**).[14] Their synthesis commences with a Mitsunobu reaction between

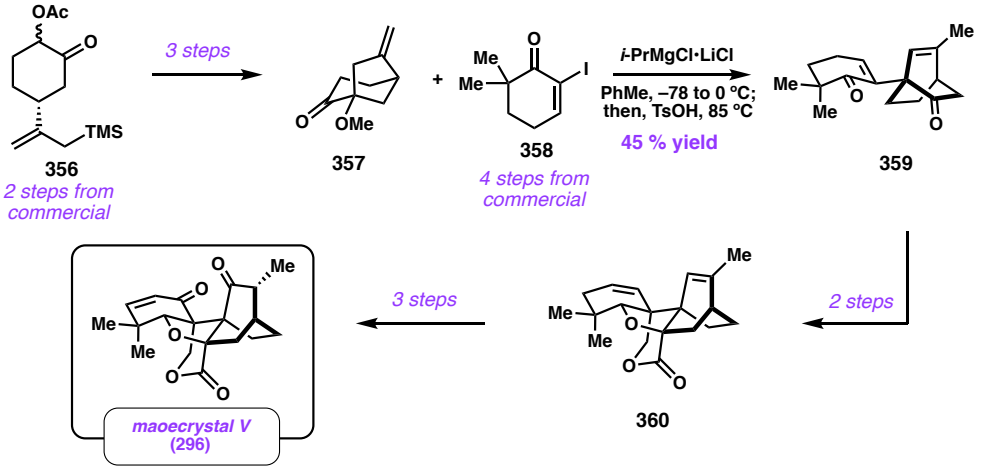
337 and **338**. They can then elaborate **339** in four additional steps, delivering key diazoester **341**. With **341** in hand, they are poised to examine their key C–H insertion reaction—they determined that using a chiral diazo mandelamide delivered their 2,3-dihydrobenzofuran in high yields with low levels of erosion of ee. Methanolysis with concomitant epimerization delivers **343**. Zakarian and coworkers are then able to elaborate **343** to vinyl silyl ether **344**, which can be subjected to a thermal, intramolecular [4+2] reaction to build the key [2.2.2]-bicycle. Cleavage of the C–Si bond along with reduction and installation of the acyl selenide delivers **346**. The key acyl selenide **346** can be subjected to a radical cyclization reaction to install the central lactone ring of **347**. Nine additional steps are required to forge the cyclohexenone A ring as well as the additional methyl group on the [2.2.2]-bicycle, furnishing **296** in 28 steps from commercial material.

Scheme 3.8 *Thomson's synthesis of maoecrystal V (**296**).*



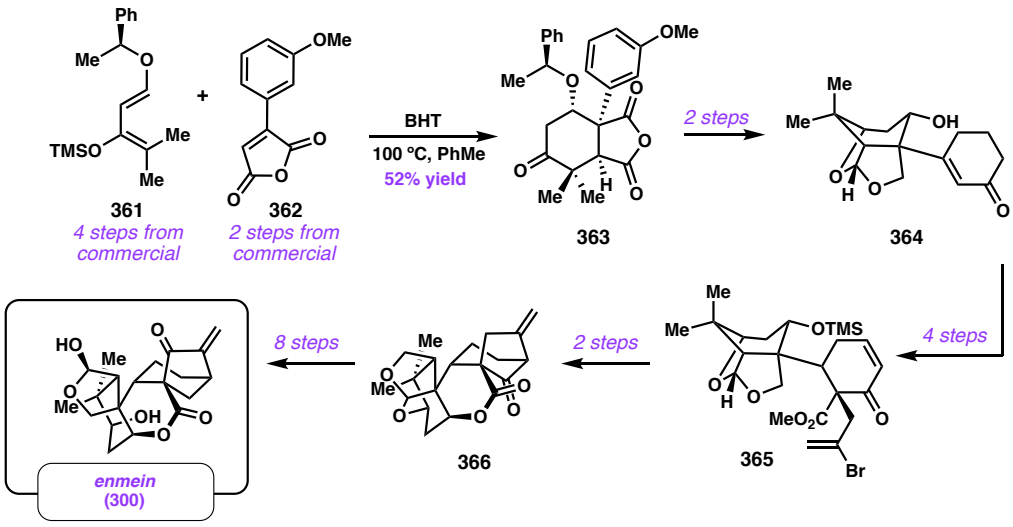
Thomson and coworkers also recently reported an asymmetric synthesis of **296** (Scheme **3.8**).[15] Their synthesis starts from 4,4-dimethylcyclohexenone (**348**). The first stereocenter is set through an asymmetric Sharpless epoxidation. The aryl bromide is subsequently installed through a TfOH promoted etherification reaction, providing **349**. At this point, a key intramolecular Heck cyclization delivers the all-carbon quaternary center of **350**. The resultant phenol is then subjected to an oxidative cyclodearomatization reaction to deliver **351**. With **351** in hand, Thomson and coworkers advance this intermediate three additional steps, including an intermolecular Diels-Alder with nitroethylene to provide **352**, building the central [2.2.2]-bicycle. With the skeletal framework assembled, they turn their attention toward oxidative manipulation of **352**. Four steps allows for reduction of the bicycle, oxidation of the nitro group and installation of the alpha-disposed methyl group to provide **353**. Allylic oxidation of **353** delivers **354**, at which point a low-yielding and poorly selective remote C–H oxidation provides a mixture of **296** and **355**.

Scheme 3.9 *Baran's synthesis of maoecrystal V (**296**).*



Baran's lab recently disclosed a convergent total synthesis of **296** (Scheme **3.9**).[16] Their route involves synthesis of a [3.2.1]-bicycle (**357**) through an intramolecular Sakurai allylation. Their key 1,2-addition is then carried out between a Grignard reagent prepared from **358** and **357**. Subsequent treatment of the 1,2-adduct with acid promotes a pinacol rearrangement to convert the [3.2.1]-bicycle to the requisite [2.2.2]-bicycle present in **359**. Two additional steps provides the key central lactone in **360**, with three additional steps required to convert **360** to **296**. Their strategy is highly convergent and vastly improved upon prior syntheses of **296**. With a robust synthetic route to access ample quantities of **296**, Baran and coworkers disappointingly observed limited biological activity against a number of cancer cell lines, despite compelling preliminary biological data reported in the literature.[11] This discovery highlights the value of total synthesis as a tool to access bioactive molecules for extensive biological study.

Scheme 3.10 *Dong's synthesis of enmein (**300**).*



During the course of our investigation, the Dong lab reported a total synthesis of enmein (**300**) (Scheme **3.10**).[17] Their synthesis commences with a convergent

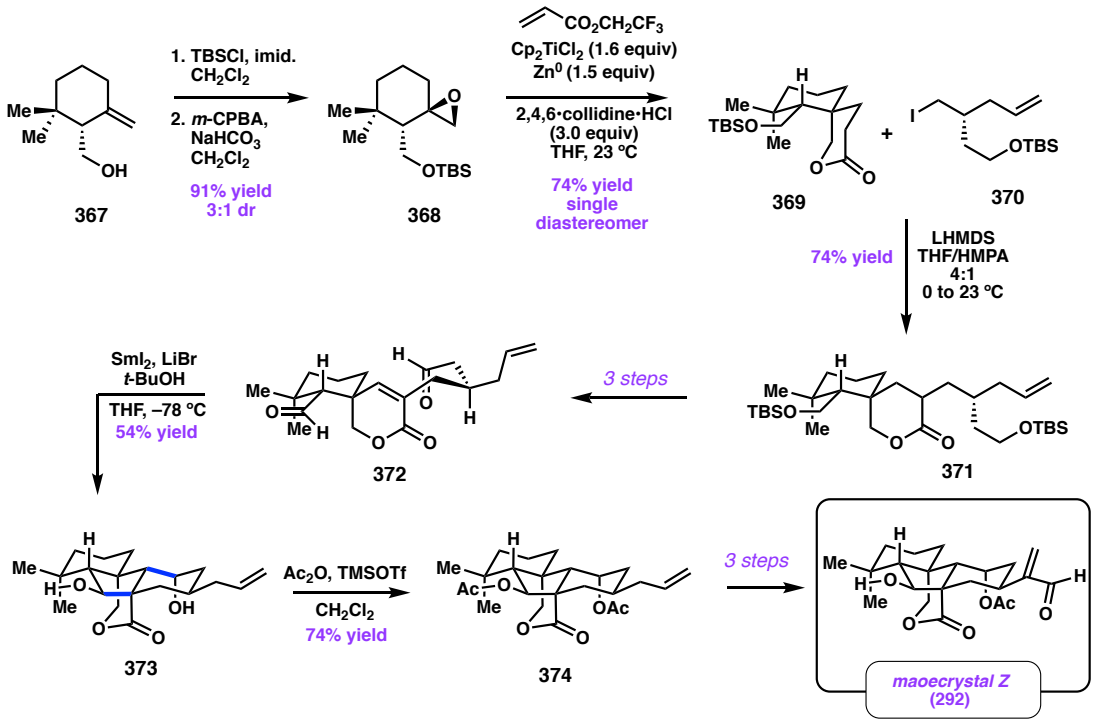
cycloaddition between **361** and **362**, delivering a single diastereomer of **363**. The stereochemistry is notably controlled by the chiral auxiliary present in **361**. Two additional steps including a Birch reduction delivers **364**, which is advanced through four steps to deliver **365**. The vinyl bromide **365** can be used as a radical precursor to close the final [3.2.1]-bicycle present in **366**. Unfortunately, manipulation of the stereochemistry and oxidation of the carboskeleton requires an additional eight steps before they can access **300**. While the end of their synthesis requires substantial functional group interconversions, this synthesis represents a vast improvement over the synthesis of **300** presented by Fujita.

3.3 THE REISMAN LAB'S APPROACH TO THE ENT-KAURANOIDS

Our lab has also worked extensively in the field of ent-kauranoid total synthesis. We felt that both the structural complexity as well as the biological activity of these natural products make them formidable targets for a total synthesis endeavor. In 2011, our lab reported a total synthesis of maoecrystal Z (**292**) commencing from γ-cyclogeraniol (**367**) (Scheme **3.11**).[18] A silylation followed by a selective epoxidation delivers **368**, a 3:1 mixture of diastereomers. Our lab determined that both diastereomers could be taken forward through an epoxide homolysis mediated by Cp_2TiCl with a Giese-type addition to trifluoroethylacrylate delivers lactone **369**. At this point, **369** could be alkylated with alkyl iodide **370**. Lactone **371** was then advanced three steps to deliver aldehyde **372**, which is poised to undergo a key reductive cyclization. Treatment with *in situ* generated $SmBr_2$ delivers a single diastereomer of tetracycle **373**, in which two key bonds have been formed. With the key carbocyclic core assembled, attention turned toward the installation of the

requisite acetates and installation of the enal moiety. Bis acylation of **373** followed by three additional steps delivers maoecrystal Z (**292**) in only 12 steps from **367**.

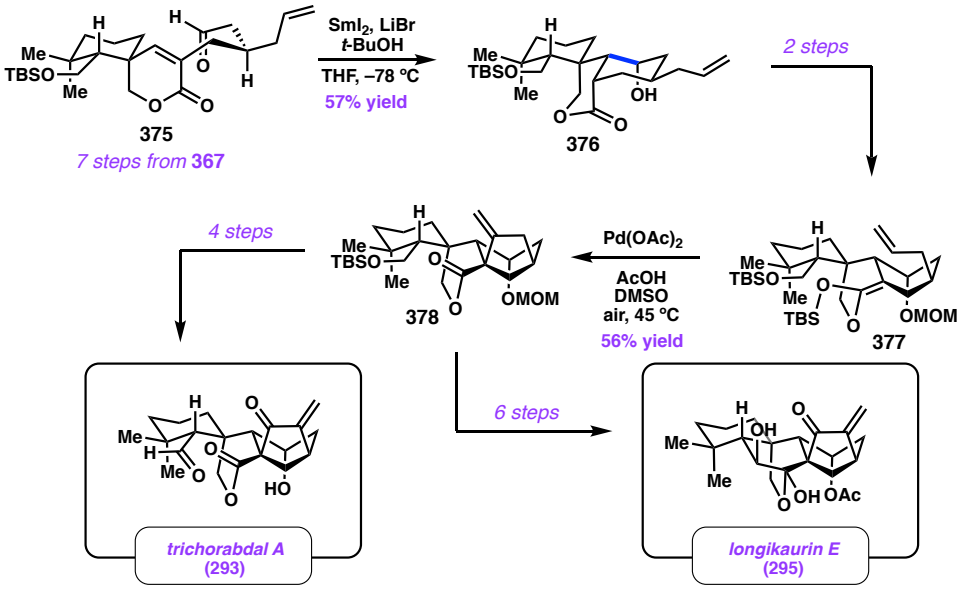
Scheme 3.11 *Reisman's synthesis of maoecrystal Z (**292**).*



Having developed a rapid and scalable approach to **292**, our lab became interested in using an analogous strategy to target other *ent*-kauranoids within this family of natural products. Again commencing from **367**, seven analogous steps delivered unsaturated lactone **375**, bearing a silyloxy group rather than an aldehyde on the cyclohexane ring (Scheme **3.12**).[19,20] From here, a reductive cyclization to forge one key bond provided **376**, again as a single diastereomer. With **376** in hand, attention turned toward the construction of the requisite [3.2.1]-bicycle present in **293** and **294**. Protection of the secondary alcohol and conversion to the corresponding silyl ketene acetal delivered **377**, which was then poised to undergo an oxidative cyclization. After substantial optimization, we found that

treatment of **377** with stoichiometric $Pd(OAc)_2$ with AcOH as an additive in DMSO in the presence of O_2 provided good yields of **378**, a key intermediate. We found that **378** could be diverted to two different natural products. Ketone **378** could be converted to **293** in four steps from commercial and could be converted to **294** in six steps from commercial, completing the synthesis.

Scheme 3.12 *Reisman's syntheses of trichorabdal A (**293**) and longikaurin E (**295**).*



3.4 CONCLUDING REMARKS

A number of groups, including our own, have been interested in the synthesis of the structurally complex ent-Kauranoid natural products. Their complex skeletal structures, dense oxidation, and promising biological activities have attracted the attention of many synthetic chemists. Many of the approaches presented thus far are highly linear and rely upon cycloaddition chemistry to build the skeletal structure. While there have been several elegant syntheses of these molecules, we feel that the complexity of these natural products

demonstrate the difficulties and shortcomings inherent in natural product total synthesis, and as such, continued synthetic campaigns will continue to be instructive and informative.

3.5 NOTES AND REFERENCES

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Chapter 4

A Cross-Coupling Approach for the Synthesis of the Enmein-Type Ent-Kauranoids[†]

4.1 INTRODUCTION

While there have been a number of elegant syntheses of ent-kauranoid natural products by our group and others, we felt that the compelling structure and promising biological activity of these natural products warranted further investigation. While there have been several creative strategies toward the synthesis of these natural products, we felt that a more convergent assembly of the kauranoid core would greatly improve upon the existing strategies. A convergent and easily diversifiable synthetic approach to these natural products will allow access to several of these highly oxygenated terpenes and enable an in-depth investigation of the structure-activity relationship (SAR).

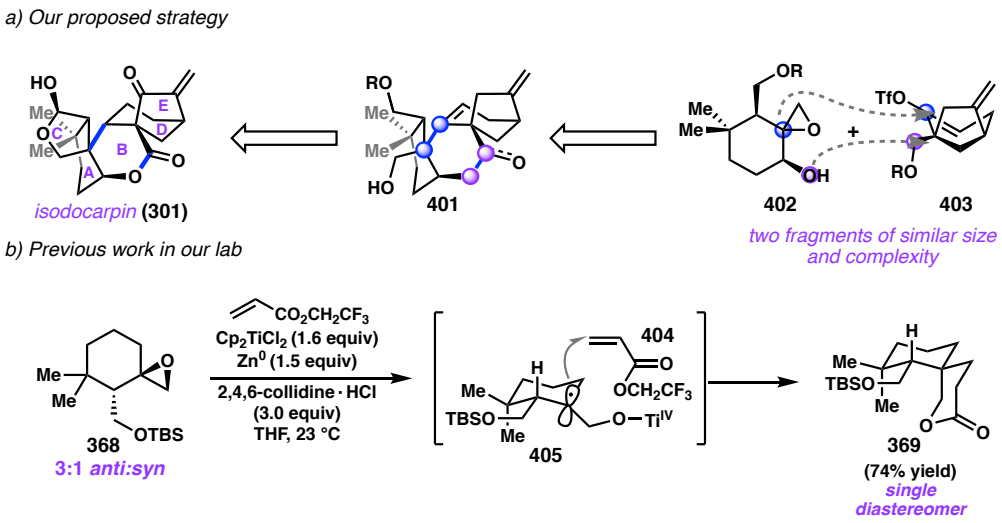
[†] The research discussed in this chapter was completed in collaboration with Kelsey E. Poremba, a graduate student in the Reisman Lab.

4.2 SYNTHETIC STRATEGY

4.2.1 Retrosynthetic Analysis

In considering the structure of the enmein-type *ent*-kauranoids (e.g. **301**), we identified the central B-ring lactone as a strategic ring forging junction for two bicyclic systems. Conceptually, we thought to cleave the molecule through the B ring, revealing two fragments of similar size and complexity (**402** & **403**) (Scheme **4.1a**). We were excited at the prospect of using an epoxy alcohol (**402**) as our A/C-ring fragment, as we felt that we could apply reductive cyclization chemistry our lab had investigated in the total syntheses of **292**, **293**, and **295** (Scheme **4.1b**).[1–3] Our lab found that reductive opening of epoxide **368**, followed by intermolecular trapping by Michael acceptor **404** could enable spirocycle formation, delivering **369** in excellent yield as a single diastereomer.

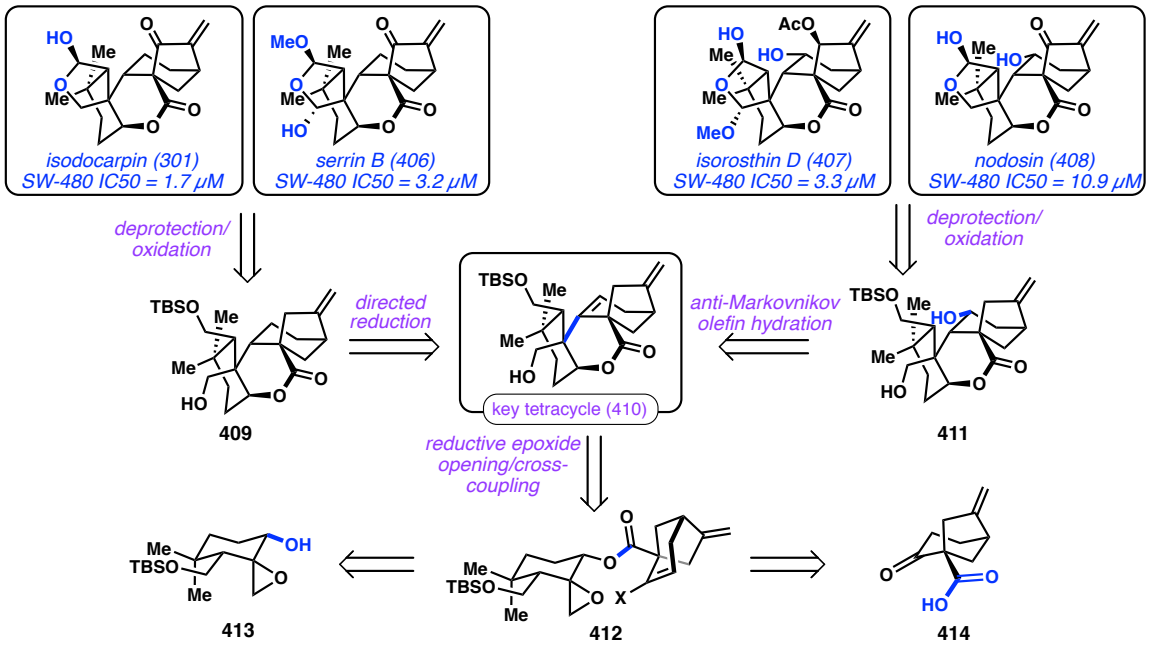
Scheme 4.1 *A simplifying convergent strategy to access **301**.*



We hypothesized that we could use a similar substrate (**402**), but instead of engaging the resulting tertiary radical in a Giese-type addition to an acrylate, use a Ni-

catalyzed intermolecular epoxide alkenylation to join the two fragments (Scheme **4.1a**). This transformation would leverage a similar carbon-centered radical intermediate our lab used in prior syntheses, but would seek to increase the convergence and modularity of the synthesis through the direct coupling of a bicyclic alkenyl triflate (**403**). In addition, this convergent coupling strategy would allow us to vary the oxidation pattern on either fragment, thereby providing modular access to other *seco-ent*-kauranoids.

Scheme 4.2 *First generation retrosynthesis of the enmein-type ent-kauranoids.*



Retrosynthetically, we envisioned that we could access four natural products through a unified strategy (Scheme **4.2**). Isodocarpin (**301**) and serrin B (**406**) could be accessed through a deprotection/oxidation sequence of lactone **409**. We hypothesized that **409** could arise from a directed reduction of the tetracycle **410**. Similarly, isorosthin D (**407**) and nodosin (**408**) could be prepared in an analogous fashion through a deprotection/oxidation sequence of diol **411**. We envisioned preparing diol **411** through an

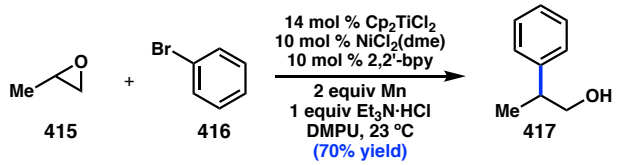
anti-Markovnikov hydration of tetracycle **410**. Disconnection of **410** through the central B-ring lactone would greatly simplify our strategy. We hypothesized that we could prepare **410** through formation of the key C–C bond (shown in blue) via an intramolecular, reductive-epoxide opening/cross-coupling reaction of **412**. The substrate for this key cyclization reaction could be obtained through ester bond formation between two appropriately functionalized building blocks: epoxy alcohol **413** and [3.2.1]-bicyclooctane **414**. While previous studies toward the synthesis of 6,7-seco-*ent*-kauranoids have relied upon linear syntheses, this convergent coupling strategy will provide an efficient and expedient preparation of these oxygenated terpenoids with a modular approach that will potentially allow for the introduction of varying functionality on each coupling fragment.

4.2.2 Reductive Cross-Coupling of Epoxides

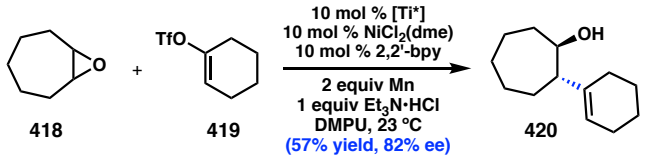
In addition to the work our lab has done in the field of reductive cross-electrophile coupling,[4–9], we were also inspired by a number of reactions reported by the Weix and Gong groups that could be explored further to achieve our desired cross-coupling. In 2014, Weix and coworkers reported a cross-coupling reaction enabled by nickel and titanium co-catalysis, providing the Markovnikov reductive arylation products between epoxides and aryl halides (Scheme **4.3a**).[10] In 2015, they expanded upon this methodology; by using a chiral titanocene, they could render this transformation asymmetric, enabling a desymmetrization of cyclic *meso*-epoxides (Scheme **4.3b**).[11] It is of note that in this reaction they were able to successfully employ alkenyl bromides and alkenyl triflates as cross-coupling partners, providing encouraging precedent for our desired transformation.

Scheme 4.3 *Precedent for desired cross-electrophile coupling.*

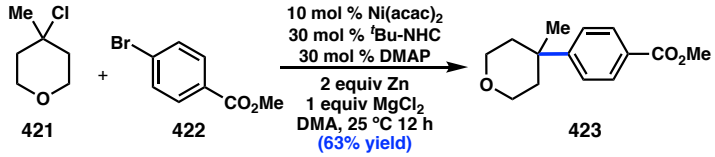
(a) Ni-catalyzed reductive cross-coupling of epoxides (Weix, 2014)



(b) Asymmetric reductive cross-coupling of epoxides (Weix, 2015)

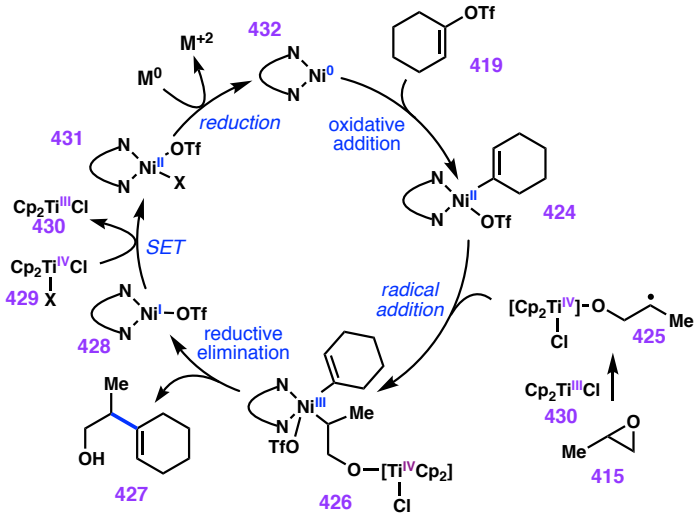


(c) Ni-catalyzed reductive cross-coupling to form quaternary centers (Gong, 2015)



Although the epoxide coupling we have proposed has not yet been employed to form quaternary centers, Gong and coworkers have demonstrated that quaternary centers can be generated through related Ni-catalyzed reductive cross-coupling reactions (Scheme **4.3c**).[12] To date, all previously reported epoxide cross-couplings have been developed on relatively simple systems, to form C–C bonds at secondary stereogenic centers, and there have been no demonstrated applications to complex natural product synthesis. Given the myriad methods for the preparation of epoxides, as well as the high levels of stereocontrol observed in the variety of epoxidation methods, we anticipate that the development of the proposed convergent fragment coupling would provide a new tool for complex natural product synthesis.

Scheme 4.4 *Mechanistic proposal for reductive cross-coupling.*



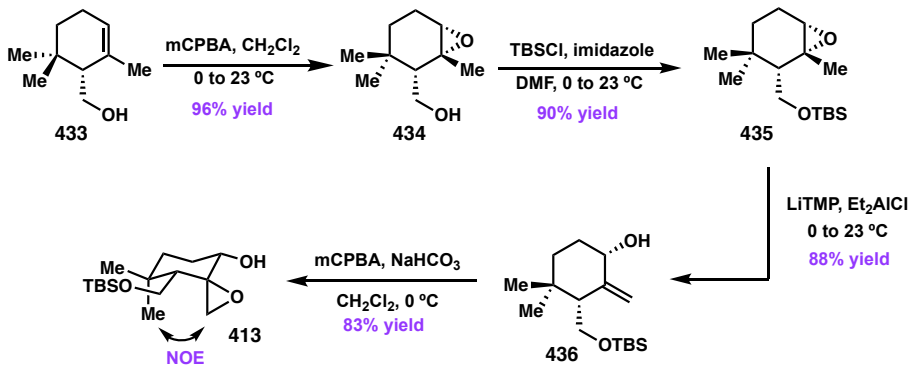
A proposed mechanism for the Ni/Ti co-catalyzed reductive cross-coupling of epoxides is shown in Scheme **4.4**. Oxidative addition of enol triflate **419** to Ni(0) provides a Ni(II) alkenyl species **424**. Ti(III) species **430** generated from the reduction of the Ti(IV) pre-catalyst by a stoichiometric metal reductant can homolytically activate epoxide **415** to deliver the more substituted carbon centered radical **425**. Addition of radical **425** to LNi(II)R_{vinyl}OTf complex **424** provides Ni(III) complex **426**, which can undergo facile reductive elimination to produce **427**. SET between the resultant LNi(I)OTf complex **428** and Cp^2Ti(IV)ClX species **429** would regenerate the active Cp_2Ti(III)X reductant **430**, as well as LNi(II)X_2 complex **431** that can undergo reduction by the stoichiometric reductant to close the catalytic cycle. Thus, productive cross-coupling requires matching of the relative rates of the enol triflate oxidative addition and the epoxide opening, such that adequate concentrations of LNi(II)R_{vinyl}OTf (**424**) and radical **425** are present to engage in a bimolecular reaction step.

4.2.3 Investigation of an Intramolecular Cross-oupling

4.2.3.1 Epoxy Alcohol Synthesis

In our preliminary studies, we developed a first-generation synthesis of epoxide **413**, shown in Scheme **4.5**. Our synthesis commenced with material from the chiral pool. Epoxidation of α-cyclogeraniol (**433**) using mCPBA as the oxidant delivered a single diastereomer of the epoxy alcohol **434**, which could be silylated under standard conditions to provide **435**.[13] Epoxide opening utilizing LiTMP and Et_2AlCl afforded allylic alcohol **436** as a single isomer. At this point, a second epoxidation using mCPBA delivered **413**, completing the synthesis of the first coupling fragment. The stereochemistry of the epoxide was determined through 2D NMR experiments. This sequence has been performed on a multi-gram scale to deliver ample quantities of enantiopure **413**.

Scheme 4.5 *Synthetic route to epoxy alcohol* ***413***.

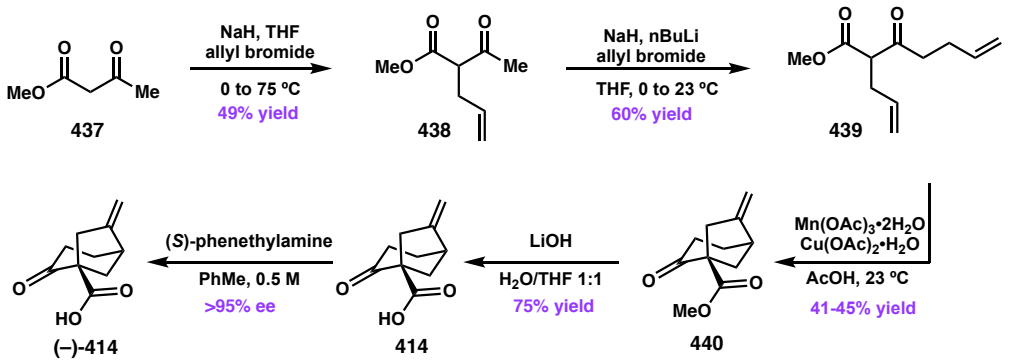


4.2.3.2 [3.2.1]-Bicyclooctanoic Acid Synthesis

With **413** in hand, we turned our attention toward the synthesis of the structurally requisite bicyclo[3.2.1]octane (**414**). While we hoped to develop an asymmetric synthesis of **414**, we were interested in rapidly probing the key step of our synthesis. To this end, we

adapted work from the Snider lab in which structurally-complex bicyclo[3.2.1]octanes could be prepared by a radical polyene cyclization (Scheme **4.6**).[14]

Scheme 4.6 *Synthesis of a bicyclo[3.2.1]octanoic acid.*



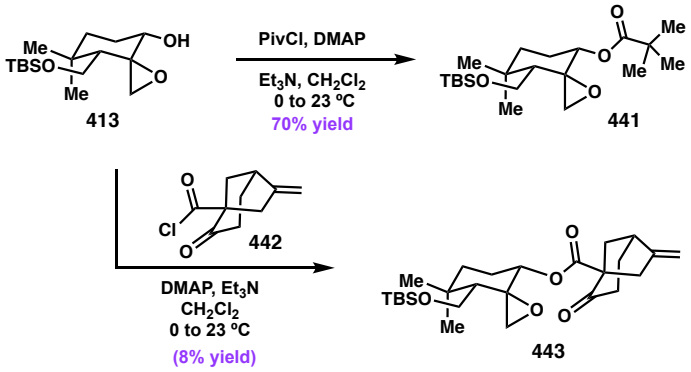
Allylation of the methylene provides methyl 2-acetylpent-4-enoate (**438**), which is subjected to a second allylation to provide **439**. Treatment of **439** with superstoichiometric amounts of $Mn(OAc)_3•2H_2O$, employing $Cu(OAc)_2•H_2O$ as the terminal oxidant, delivered **440** in moderate yield on a three-gram scale. Ester **440** could be hydrolyzed to the carboxylic acid and resolved using (*S*)-phenethylamine by sequential recrystallizations. While we were ultimately interested in preparing **414** directly through an asymmetric transformation, the route depicted in Scheme **4.6** provides rapid access to bicyclo[3.2.1]octanes of structure **414**, which could be used to determine the feasibility of the key epoxide-opening cross-coupling.

4.2.3.3 A Convergent Esterification

We were pleased to see that acylation of the epoxy alcohol **413** with a model neopentyl acyl chloride provided the pivalate ester **441** in excellent yield (Scheme **4.7**). However, attempts to perform the analogous esterification with **442**, generated from our bicyclic acid **414**, were largely unsuccessful. The reaction was plagued by low conversion,

and any attempts to increase the temperature or add additional DMAP resulted in decomposition of starting material.

Scheme 4.7 *Initial attempts at a convergent esterification.*

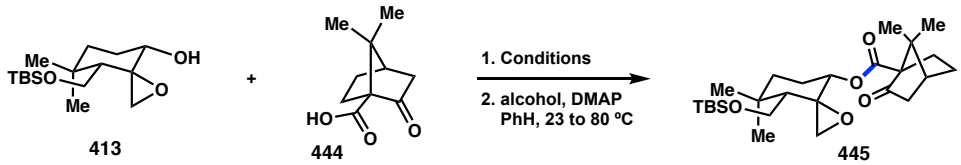


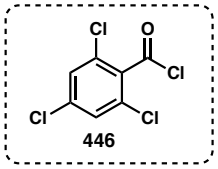
At this point, we turned our attention toward exploring alternative acylation conditions with a commercially available model system, as **414** required multiple steps and a low-yielding resolution sequence. While the use of pivaloyl chloride did not appear to be reflective of the reactivity of **442**, we thought that a bicyclic terpene could serve as a good surrogate to identify how a sterically bulky group could influence the nature of this esterification chemistry. We elected to use ketopinic acid, as we felt its steric bulk matched that present in **414** and was commercially available as a single enantiomer.

We were pleased to see that preparation of a mixed anhydride derived from the coupling of **444** with 2,4,6-trichlorobenzoyl chloride (**446**), followed by trapping with **413** delivered good yields of **445**.[15] Alternatively, treatment of **444** with 2-Me-6-NO_2-benzoic anhydride, followed by trapping with **413,**[16] also provided improved conversion to ester **445** (Table **4.1**). Formation of the mixed anhydride through the coupling of **444** and

isobutyl chloroformate (entry 3) and preparation of the acid chloride (entry 4) resulted in decomposition of starting material.

Table 4.1. *Esterification with a model system.*

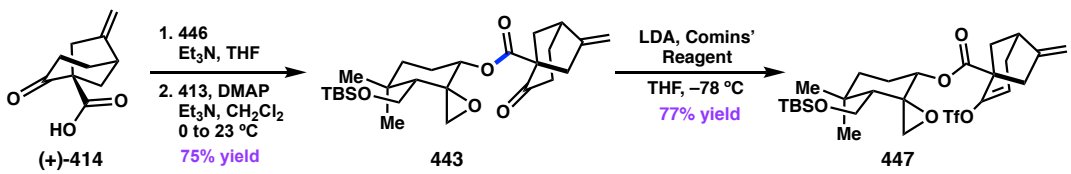




entry	conditions	result
1	446, Et_3N, THF	73% yield
2	2-Me-6-NO_2-benzoic anhydride Et_3N, THF	69% yield
3	$iBuO_2CCl$, Et_3N, THF	decomposition
4	$(COCl)_2$, DMF, PhH	decomposition

After investigating the acylation with the ketopinic acid model (**444**), we turned our attention toward testing these conditions with resolved bicyclic acid **414**. Formation of the mixed anhydride under Yamaguchi conditions, followed by treatment with **413** cleanly delivered **443** in excellent yield on a synthetically useful scale (Scheme **4.8**). We were pleased to see that not only did the esterification proceed smoothly, but conversion to the enol triflate cleanly delivered **447**.[17]

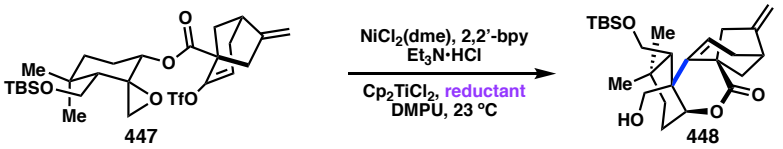
Scheme 4.8 *Preparation of an intramolecular cross-coupling substrate.*



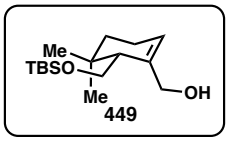
With **447** in hand, we were eager to examine the conditions reported by Weix and coworkers on our system.[10,11] We first set out to investigate how different stoichiometric reductants would influence the reactivity in this particular transformation. Unfortunately, we found that under their standard conditions with a series of different reductants, we were

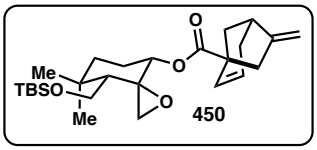
unable to isolate the desired product, **448** (Table 4.2). We observed solely protodetriflation to provide **450** with manganese as the reductant (Table **4.2**, entry 1). With other reductants, such as Zn^0 and Sm^0, we observed protodetriflation as well as allylic alcohol **449**. After careful review of these results, we hypothesized that the ester linkage may be problematic in this particular transformation.

Table 4.2. *Intramolecular cross-coupling screen.*



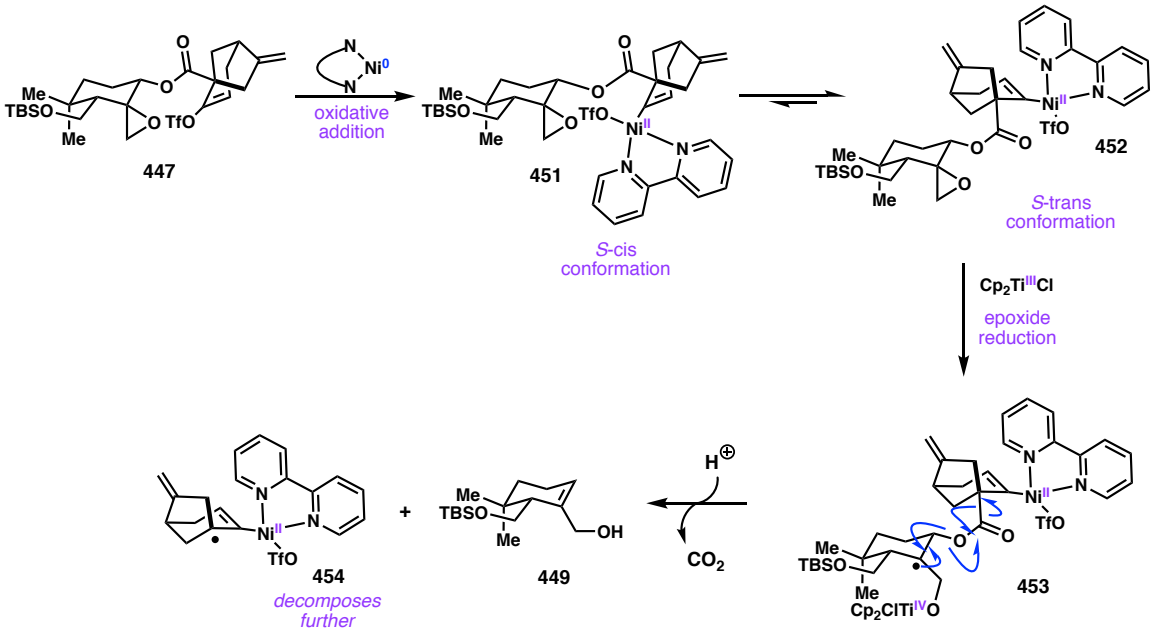
entry	reductant	result
1	Mn^0	protodetriflation
2	Zn^0	protodetriflation, 449
3	Sm^0	protodetriflation, 449
4	SmI_2	protodetriflation, 449





Our investigations indicated that our reaction was being plagued by two problems. First, while we were confident that our nickel catalyst was engaging with our enol triflate, we hypothesized that our substrate was favoring the thermodynamically favored *S*-trans conformation (**452**) rather than the *S*-cis conformation (**451**) required for radical capture of the tertiary radical generated (Scheme **4.9**). Epoxide reduction of **452**, produced radical **453**, with the radical far from the nickel center, making a radical capture process intractable. It seemed that with some reductants, while the epoxide could be successfully reduced, the resulting radical formed adjacent to the ester moiety was unstable, readily decarboxylating to provide **449** and **454**. While we were unable to isolate any side-products from the bicyclic fragment, we hypothesized that **454** could further decompose to give a handful of volatile products that would be difficult to characterize.

Scheme 4.9 *Mechanistic hypothesis for intramolecular cross-coupling.*

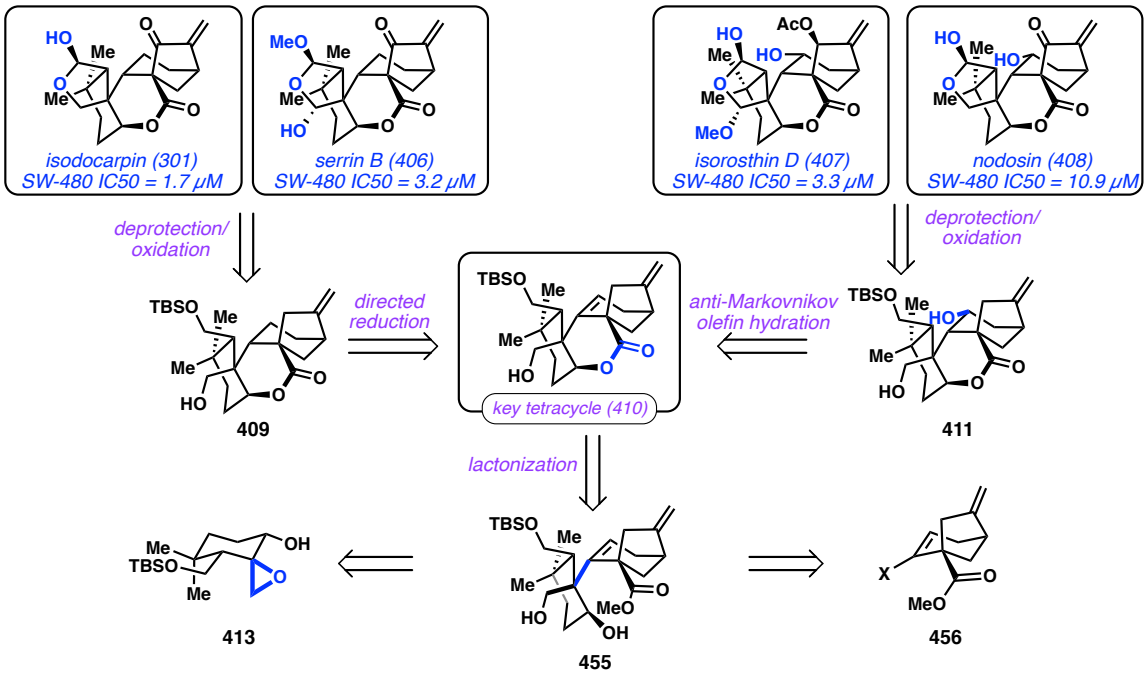


4.2.4 Investigation of an Intermolecular Cross-coupling

4.2.4.1 A Second Generation Retrosynthetic Analysis

Having identified some of the challenges associated with an intramolecular cross-coupling approach for the synthesis of the enmein-type *ent*-kauranoids, we wondered if an intermolecular approach would be more successful. We envisioned carrying out a similar endgame, where **301**, **406**, **407**, and **408** could be accessed from the same key tetracyclic intermediate **410**. However, we envisioned disconnecting through the lactone at this step, to provide diol **455** (Scheme **4.10**). At this point, formation of the all-carbon quaternary center through a convergent cross-coupling simplified the synthesis of **455** to the convergent fragment coupling of **413** and **456**. We felt that attempting this coupling in the intermolecular sense could circumvent some of the issues we encountered in the development of an intramolecular cross-coupling of **447**.

Scheme 4.10 *A second generation retrosynthesis.*



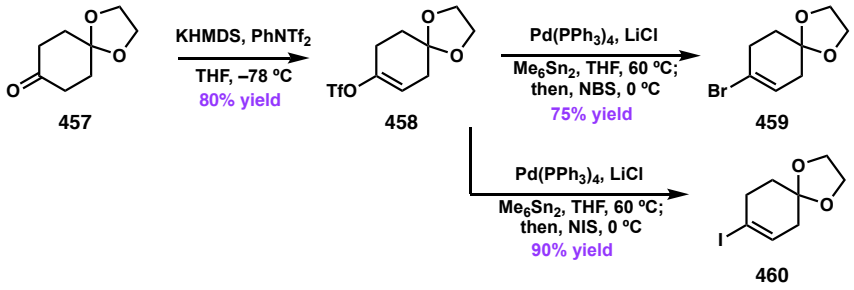
While we had already successfully completed a synthesis of epoxy alcohol **413**, we elected to begin our investigation of this key cross-coupling with a model system for the other cross-coupling partner. We were aware that this would be a difficult reaction to develop, as we knew that reductive cross-couplings with epoxides had not yet been used to generate all-carbon quaternary centers. As such, we felt it would be best to begin with a less complex system. At this point, it was unclear which alkenyl electrophiles would be most successful in the cross-coupling, so we hoped to use a more general system to explore this chemistry. We were also interested in getting preliminary reaction data as quickly as possible, and we knew that the synthesis of **416** would require additional reaction development. Additionally, **414** was only accessible in enantiopure form through a time-

intensive classical resolution, so working with a more easily accessible cross-coupling partner would be ideal.

4.2.4.2 Screening an Intermolecular Cross-coupling

We were pleased to see that we could readily access an enol triflate, alkenyl bromide, and alkenyl iodide from cyclohexanone **458** using a known Stille cross-coupling (Scheme **4.11**).[18] While Weix's reaction worked with enol triflates and alkenyl bromides (Scheme **4.3**), we were excited by the prospect of being able to carefully tune the reactivity of the alkenyl electrophile.

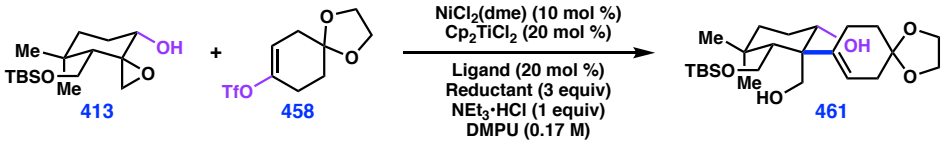
Scheme 4.11 *Synthesis of model C(sp^2) electrophiles.*

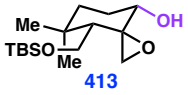
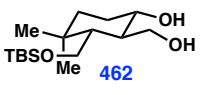
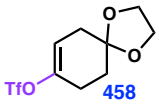
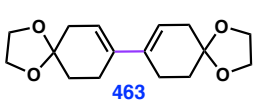


With **458** in hand, we were eager to begin exploring the feasibility of an intermolecular cross-coupling. We began our investigations using epoxy alcohol **413** and enol triflate **458** as the cross-coupling partners and explored different combinations of pyridine ligands and heterogeneous reductants (Table **4.3**). We found that when we used dtbpy, terpy, or phen as the ligand, we observed significant amounts of the epoxide reduction product **462**, regardless of which reductant was employed. Interestingly, we found that the C(sp^2) coupling partner was fully consumed with dtbpy or phen as the ligand, producing significant quantities of the divinyl side-product **463** (entries 1–2, 4–6). When terpy was used, we did not observe any divinyl production (entries 3–4). While we were

not observing any formation of **461**, we were pleased to see that under the reaction conditions we explored, we were observing engagement of both electrophiles, and so we turned our attention to exploring the more reactive alkenyl iodide (**460**) in the reaction.

Table 4.3. *Cross-coupling between an epoxy alcohol and a cyclic enol triflate.*



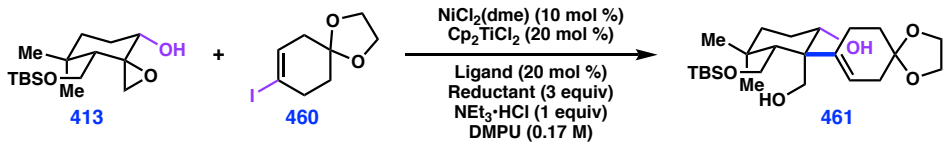
Entry	Ligand	Red.	 413	 462	 458	 463
1	dtbpy	Mn	26 %	16 %	0 %	15 %
2	dtbpy	Zn	70 %	6 %	0 %	32 %
3	terpy	Mn	17 %	18 %	19 %	0 %
4	terpy	Zn	39 %	14 %	51 %	0 %
5	phen	Mn	15 %	42 %	0 %	7 %
6	phen	Zn	64 %	31 %	0 %	61 %

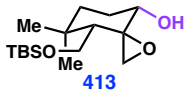
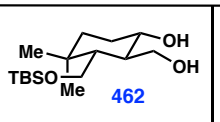
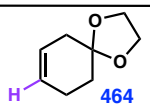
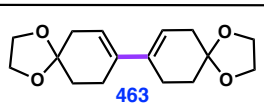
Unfortunately, we observed similar results when we used alkenyl iodide **460** as the C(sp^2) coupling partner (Table **4.4**); however, we were never able to recover the alkenyl iodide—instead our mass balance shifted toward the protodeiodinated product **464** (entries 1–6). All three ligands delivered significant quantities of the epoxide reduction product **462**, regardless of which reductant was used.

While Weix and coworkers had been successful with pyridine ligands, it seemed as though this class of ligands were not appropriately matched with our particular combination of epoxide and alkenyl electrophile. With this in mind, we began investigating alternative ligand classes that our lab had used in the optimization of other reductive cross-coupling reactions. We were particularly interested in modification of the nickel catalyst

through incorporation of a bis(oxazoline) ligand, as we felt a wider bite angle could facilitate the cross-coupling of more sterically-hindered electrophiles.

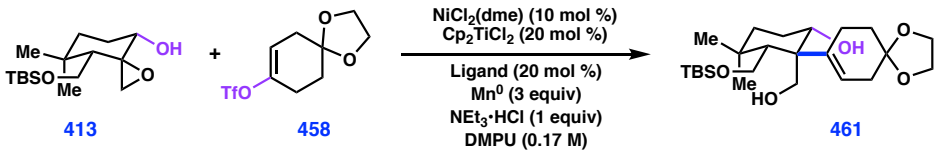
Table 4.4. *Cross-coupling between an epoxy alcohol and a cyclic enol triflate.*

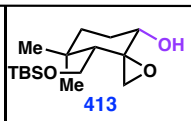
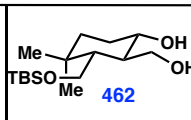
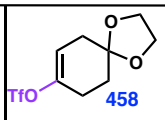
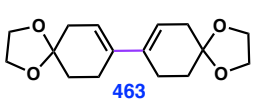


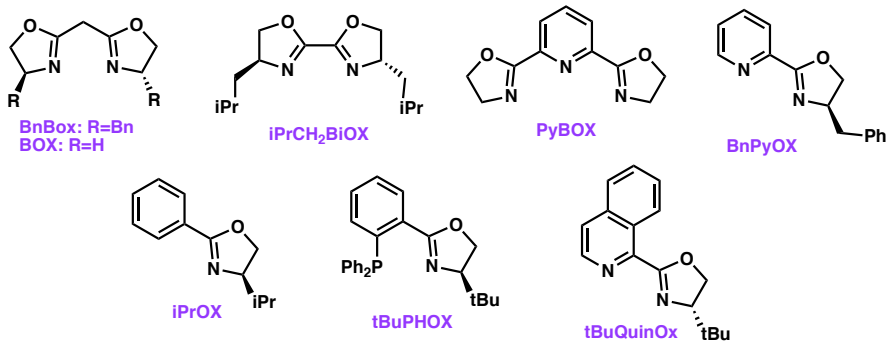
Entry	Ligand	Red.	 413	 462	 464	 463
1	dtbpy	Mn	12 %	43 %	7 %	70 %
2	dtbpy	Zn	23 %	37 %	10 %	49 %
3	terpy	Mn	28 %	13 %	30 %	0 %
4	terpy	Zn	29 %	12 %	15 %	0 %
5	phen	Mn	48 %	17 %	11 %	21 %
6	phen	Zn	66 %	3 %	5 %	20 %

With this in mind, we began exploring the intermolecular cross-coupling between **413** and enol triflate **458** with the same precatalyst, solvent, reductant, and additives reported by the Weix lab, but with a series of different oxazoline-derived ligands our lab had previously worked with. Unfortunately, none of the ligands screened delivered the desired product, and we observed similar mass-balance as we had seen previously with the pyridine ligands (Table **4.5**). All of the ligands we explored with the exception of *i*-PrOX (entry 6) and *t*-BuQuinOX (entry 8) provided the epoxide reduction product **462**. With regard to the C(sp^2) electrophile, we observed a combination of recovered starting material and divinyl (**463**) with BnBOX and BnPyOX (entries 1 and 5), only recovered starting material with PyBOX, *i*-PrOX, and *t*-BuPHOX (entries 4, 6–7), and only divinyl (**463**) with BOX and *i*-PrCH_2BiOX (entries 2–3).

Table 4.5. *Ligand screening for intermolecular cross-coupling.*

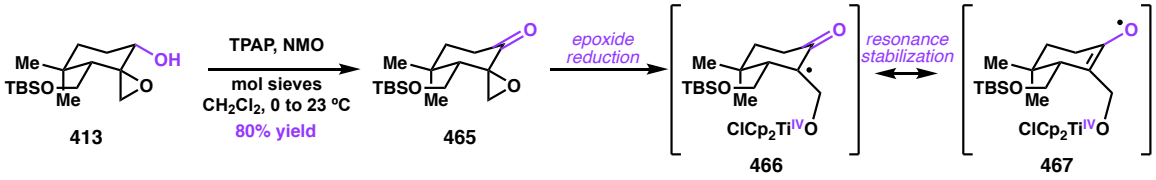


Entry	Ligand	 413	 462	 458	 463
1	BnBOX	44 %	22 %	61 %	8 %
2	BOX	25 %	43 %	0 %	22 %
3	iPrCH$_2$BiOX	62 %	11 %	0 %	38 %
4	PyBOX	45 %	26 %	71 %	0 %
5	BnPyOx	44 %	19 %	12 %	31 %
6	iPrOX	67 %	0 %	38 %	0 %
7	tBuPHOX	15 %	51 %	75 %	0 %
8	tBuQuinOx	60 %	0 %	0 %	9 %



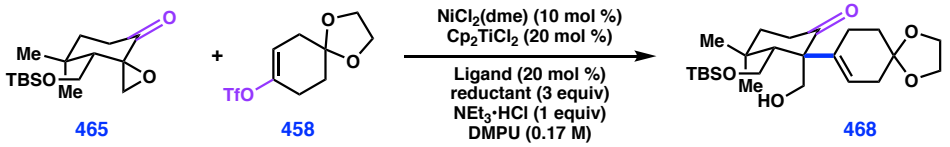
Disappointed that we did not observe the desired reactivity by tuning the employed ligand, we chose to examine the epoxide substrate. We hypothesized that the reduction product **462** was forming due to the slow radical capture by the sterically hindered nickel catalyst, resulting in a high steady state concentration of a radical intermediate, which could be reduced a second time prior to capture by the nickel. In an attempt to stabilize the radical intermediate, we prepared **465**, with an adjacent ketone that we believed could stabilize the intermediate radical species (Scheme **4.12**).

Scheme 4.12 *A resonance-stabilized intermediate.*



With a stabilized substrate in hand, we returned to the Weix conditions hoping to now observe the desired reactivity. Unfortunately, none of the pyridine ligands we tried provided the desired alkenylated product (Table **4.6**). Interestingly, we observed a new side product, which we identified as the elimination product, producing an exocyclic enone **469** in each of the reactions we examined. However, when we used the enol triflate (**458**) with the epoxy ketone (**465**) rather than the epoxy alcohol (**413**), we observed little to none of the divinyl side-product (**463**). The rest of the mass balance was starting material and decomposition.

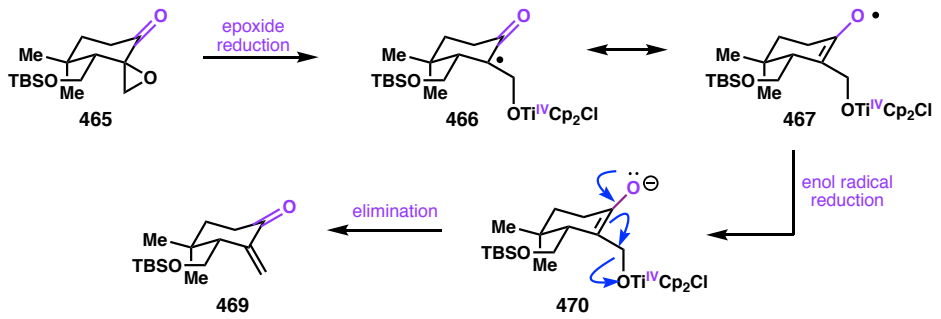
Table 4.6. *Cross-coupling between an epoxy alcohol and a cyclic enol triflate*



Entry	Ligand	Red.	465	469	458	463
1	dtbpy	Mn	53 %	11 %	81 %	0 %
2	dtbpy	Zn	31 %	23 %	23 %	0 %
3	terpy	Mn	41 %	22 %	66 %	0 %
4	terpy	Zn	59 %	21 %	54 %	0 %
5	phen	Mn	— %	— %	— %	— %
6	phen	Zn	63 %	18 %	2 %	2 %

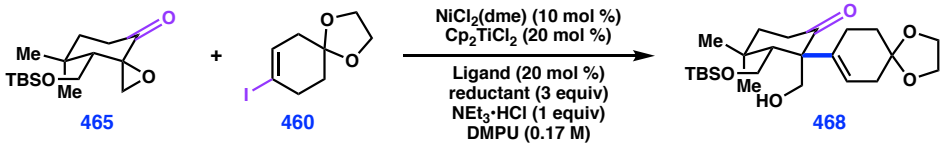
We hypothesized that while we had increased the stability of the resulting radical, enol radical reduction was outcompeting radical capture by the nickel catalyst, and instead of being reduced again and protonated, **467** was reduced to give enolate **470** and eliminated to produce **469** (Scheme **4.13**). Based on the lack of divinyl produced here, we wondered if the equivalent of hydroxide that was generated from the elimination was inhibiting the catalyst, making it difficult for the catalyst to engage with the enol triflate electrophile.

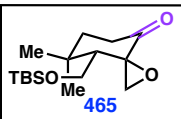
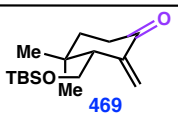
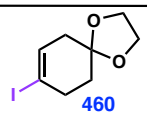
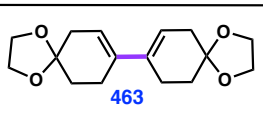
Scheme 4.13 *Hypothesized formation of side product* ***469***.



After exploring the cross-coupling between the epoxy ketone **465** and cyclic enol triflate **458**, we also looked at analogous reactions with the more reactive alkenyl iodide (**460**), hoping that by employing a more reactive cross-coupling partner, we would observe better reactivity. Unfortunately, under these conditions, we observed a very similar mass balance, with formation of enone **469** observed in each reaction (Table **4.7**). With regard to the C(sp^2) cross-coupling partner, we observed some formation of the divinyl side-product with the dtbpy ligand (entries 1–2), substantial formation of the divinyl product with the phen ligand (entries 5–6), and only alkenyl iodide with the terpy ligand (entries 3–4). With these findings, it seemed as though using an epoxide substrate designed to stabilize the intermediate radical species was not going to be a viable path forward.

Table 4.7. *Cross-coupling between an epoxy alcohol and a cyclic alkenyl iodide*

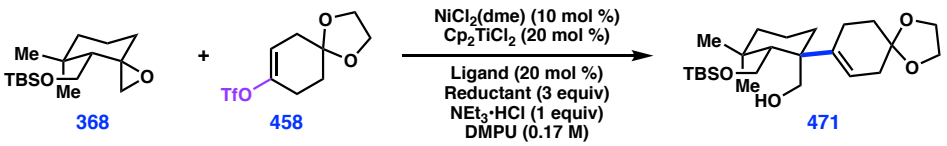


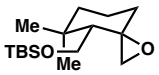
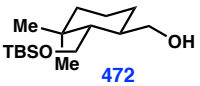
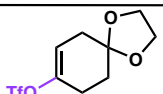
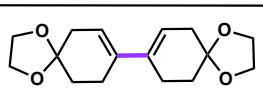
Entry	Ligand	Red.	 465	 469	 460	 463
1	dtbpy	Mn	31 %	21 %	44 %	6 %
2	dtbpy	Zn	41 %	18 %	57 %	3 %
3	terpy	Mn	43 %	25 %	75 %	0 %
4	terpy	Zn	16 %	36 %	32 %	0 %
5	phen	Mn	33 %	22 %	11 %	39 %
6	phen	Zn	28 %	23 %	0 %	49 %

Unable to produce the desired product with any of the conditions we explored, we wondered if returning to an epoxide that had been reduced *in situ* and engaged in a radical addition reaction would be instructive. In our lab's synthesis of **292**, we treated **368** with a stoichiometric reductant and trapped the resulting radical in a Giese-type addition reaction to forge an all-carbon quaternary center (Scheme **4.1b**). While the enmein-type ent-kauranoids require oxidation on the cyclohexane framework, we wondered if we could use **368** as a substrate to get a handle on some of the chemistry.

While epoxide **368** homolyzed readily with stoichiometric titanocene, we did not observe any of this reactivity under the dual-catalytic conditions (Table **4.8**). In each case, we were able to recover significant amounts of starting material, with none of the reduction product **472** observed. With regard to the C(sp^2) electrophile, we observed complete conversion to the divinyl side product **463** when we used dtbpy or phen as the ligand (entries 1–2, 5–6) and did not observe any conversion with the terpy ligand (entries 3–4).

Table 4.8. *Cross-coupling of a less oxidized epoxide with a cyclic enol triflate.*



Entry	Ligand	Red.	 368	 472	 458	 463
1	dtbpy	Mn	68 %	0 %	0 %	21 %
2	dtbpy	Zn	63 %	0 %	0 %	39 %
3	terpy	Mn	68 %	0 %	14 %	0 %
4	terpy	Zn	69 %	0 %	15 %	0 %
5	phen	Mn	83 %	0 %	0 %	36 %
6	phen	Zn	71 %	0 %	0 %	19 %

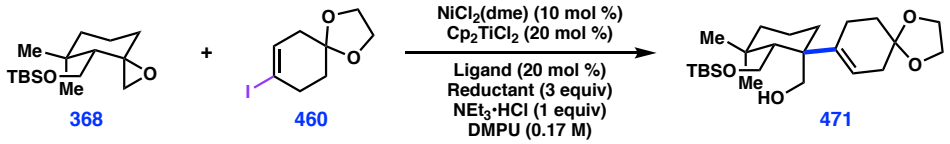
Disappointingly, we observed almost identical results with alkenyl iodide **460** in place of enol triflate **458** (Table **4.9**) with the less functionalized epoxide **368**. No conversion of the epoxide fragment to any other side product was detected under any of these conditions, and we observed analogous trends with regard to the C(sp^2) electrophile, with terpy delivering only recovered starting material (entries 3–4) and dtbpy and phen providing complete conversion to the divinyl side product (**463**) (entries 1–2, 5–6).

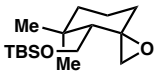
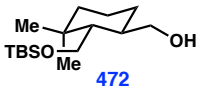
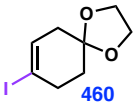
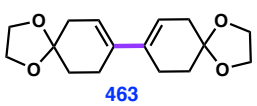
At this point, we wondered if we were using the wrong solvent for this reaction. While these reductive couplings with epoxide substrates have only been reported to react in DMPU, we decided to try additional solvents that had provided reactivity in the context of other reductive cross-couplings. We were particularly excited to try amide solvents, as we had had success using these solvents in the past and thought that these could potentially improve the desired reactivity.

We did not observe any notable reactivity with the epoxide substrate **368** in any of the solvents we tried (Table **4.10**). It seemed that as was the case in DMPU, the mass

balance with regard to the epoxide partner was just starting material. For the alkenyl cross-coupling partner, when we used MeCN or dioxane, we observed little to no conversion of the enol triflate electrophile (**458**) (entries 6 and 8). However, for each of the other solvents we explored, we saw complete conversion to the divinyl side product (**463**).

Table 4.9. *Cross-coupling of a less oxidized epoxide with a cyclic alkenyl iodide.*

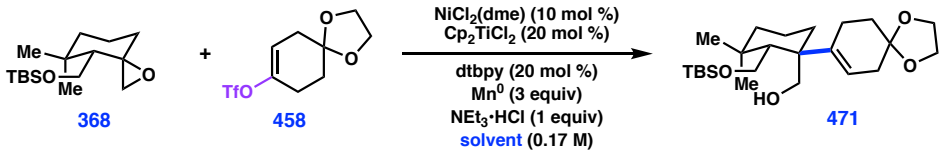


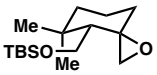
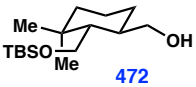
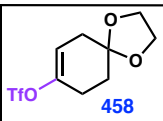
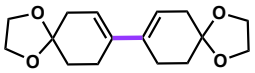
Entry	Ligand	Red.	 368	 472	 460	 463
1	dtbpy	Mn	68 %	0 %	0 %	41 %
2	dtbpy	Zn	74 %	0 %	0 %	51 %
3	terpy	Mn	75 %	0 %	54 %	0 %
4	terpy	Zn	68 %	0 %	22 %	8 %
5	phen	Mn	64 %	0 %	0 %	38 %
6	phen	Zn	51 %	0 %	0 %	41 %

While there were certainly additional solvents we could explore in hopes of fine tuning the reduction potential of the titanocene we were using, we felt we had conducted an exhaustive exploration of the Weix conditions for the substrates we were interested in coupling, so we turned our attention toward cross-electrophile conditions that had been previously employed by Gong and coworkers to forge all-carbon quaternary centers. Unlike the Weix conditions, these reactions reported by Gong used a Ni(0) precatalyst, employed $MgCl_2$ as well as a pyridine base as additives, and instead used DMA as the solvent, rather than DMPU. We were particularly excited by their use of a nickel catalyst system to build sterically encumbered all-carbon quaternary centers, as we felt this was the most significant change between our system and the reported Weix system. We hoped that

by using a nickel catalyst that had been used to construct all-carbon quaternary centers in the reductive manifold, we could potentially forge the desired carbon-carbon bond using an epoxide as one of the electrophiles.

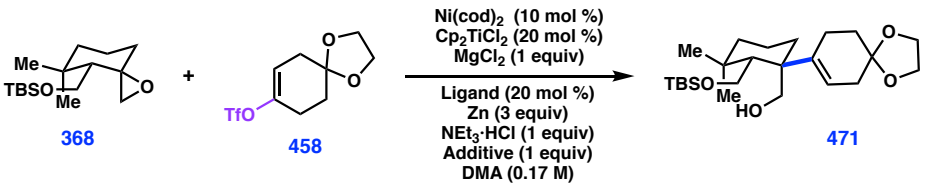
Table 4.10. *Solvent screen*

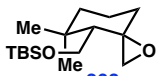
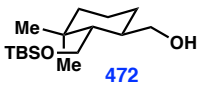
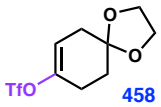
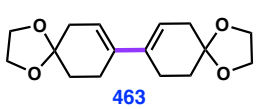


Entry	Solvent	 368	 472	 458	 463
1	DMPU	70 %	0 %	0 %	38 %
2	DMF	67 %	0 %	0 %	29 %
3	DMA	66 %	0 %	0 %	33 %
4	MeOH	68 %	0 %	0 %	25 %
5	NMP	68 %	0 %	0 %	19 %
6	MeCN	74 %	0 %	46 %	0 %
7	THF	71 %	0 %	0 %	34 %
8	Dioxane	79 %	0 %	58 %	9 %

With this precedent in mind, we investigated the feasibility of this reaction using the Gong conditions. In conducting a broad survey of some of their most applicable conditions, we explored the reaction using $Ni(cod)_2$ and both the dtbpy and IPr ligands with different pyridine-based additives. Unfortunately, we observed disappointing results, again observing little to no reactivity of the epoxide substrate **368** (Table **4.11**). Use of the IPr ligands resulted in almost complete decomposition of **458** (entries 3–4). The combination of dtbpy as a ligand and DMAP as an additive provided significant quantities of the divinyl side product **463** (entry 1), while significant starting material was observed using dtbpy as the ligand with pyridine as an additive (entry 2).

Table 4.11. *Using the Gong conditions on our system*



Entry	Ligand	Add.	 368	 472	 458	 463
1	dtbpy	DMAP	85 %	0 %	0 %	34 %
2	dtbpy	Pyr	77 %	0 %	55 %	5 %
3	IPr	DMAP	85 %	0 %	0 %	1 %
4	IPr	Pyr	95 %	0 %	0 %	2 %

4.3 CONCLUDING REMARKS

After extensive exploration of both the intramolecular as well as the intermolecular cross-electrophile couplings of epoxide-containing substrates, we concluded that while simplifying and interesting, this strategy was not going to be viable in the context of the synthesis of the enmein-type *ent*-kauranoids. With this in mind, we turned our attention toward other approaches we could employ using some of the lessons we had learned throughout this investigation.

4.4 EXPERIMENTAL SECTION

4.4.1 Materials and Methods

General Procedures. Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly dried solvents. Methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), 1,4-dioxane, *tert*-butyl methyl ether (TBME), and toluene (PhMe) were dried by passing through activated alumina columns. Methanol (MeOH) was distilled over calcium hydride. Acetonitrile

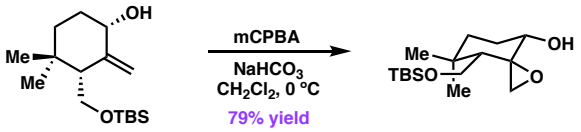
(MeCN), *tert*-butanol (*t*-BuOH), anhydrous *N,N*-dimethylformamide (DMF), anhydrous *N,N*-dimethylacetamide (DMA), chloroform ($CHCl_3$), and absolute ethanol (EtOH) were used as received from Fisher Scientific. $NiBr_2$•dme and $Ni(cod)_2$ were purchased from Strem and stored in a N_2-filled glovebox. Zinc dust and Mangenese powder were purchased from Strem and stored in a dessicator. All other commercially obtained reagents were purchased from Sigma-Aldrich and used as received unless specifically indicated. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel and basic alumina column chromatography was performed as described by Still et al.[19] using silica gel (particle size 0.032–0.063) purchased from Silicycle and aluminum oxide (activated, basic, Brockmann I, 58 Å pore size, powder) purchased from Sigma-Aldrich. ^1H and ^{13}C NMR were recorded on a Varian Inova 600 (at 600 MHz), a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Bruker Avance III HD with Prodigy cyroprobe (at 400 MHz and 101 MHz respectively). ^{19}F NMR spectra were recorded on a Varian Inova 400 (at 376 MHz). NMR data is reported relative to internal chloroform (^1H, $\delta = 7.26$, ^{13}C, $\delta = 77.2$) or to internal methanol (^1H, $\delta = 3.31$, ^{13}C, $\delta = 49.0$) and $PhCF_3$ (^{19}F, $\delta = -63.7$). 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. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using either 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. Specific optical rotations were recorded on a Jasco P-2000 polarimeter using a 100 mm cell.

4.4.2 Preparative Procedures and Spectroscopic Data

4.4.2.1 Substrate Synthesis

Preparation of epoxy alcohol **413**.



436 413

A 100 mL round bottom flask was charged with **436** (3.24 g, 11.4 mmol, 1 equiv). Then CH_2Cl_2 (57 mL, 0.2 M) was added, and the reaction mixture was cooled to 0 ºC. $NaHCO_3$ (4.783 g, 56.9 mmol, 5 equiv) was added in one portion followed by mCPBA (3.93 g, 17.1 mmol, 1.5 equiv, 75% mCPBA by weight). The reaction was allowed to stir for 2 minutes before it was quenched with saturated $Na_2S_2O_{3\,(aq)}$ (25 mL) followed by saturated $NaHCO_3$ (aq) (10 mL) and warmed to room temperature. The biphasic mixture was diluted with water (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with saturated $Na_2S_2O_{3\,(aq)}$ (100 mL), saturated $NaHCO_3$ (aq) (3 x 100 mL), then brine (100 mL). The combined organics were dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (10% EtOAc/hexanes → 15% EtOAc/hexanes) to give **413** (2.70 g, 79% yield) as an amorphous white solid.

$\mathbf{R}_f$ = 0.37 (silica gel, 20% EtOAc/Hex, CAM).

$[\alpha]_D^{23}$ = –17.5° (c = 0.65, $CHCl_3$).

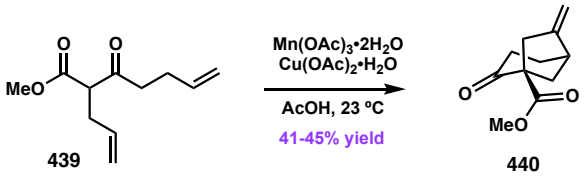
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (dd, *J* = 10.5, 3.6 Hz, 1H), 3.63 (dd, *J* = 10.6, 4.1 Hz, 1H), 3.55 – 3.39 (m, 1H), 2.91 (d, *J* = 4.8 Hz, 1H), 2.69 (d, *J* = 4.8 Hz, 1H), 2.06 – 1.91 (m, 1H), 1.73 – 1.59 (m, 2H), 1.38 – 1.24 (m, 2H), 1.08 (s, 3H), 0.99 (s, 3H), 0.93 (s, 9H), 0.08 (d, *J* = 2.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 70.8, 61.0, 50.4, 48.7, 35.1, 29.9, 29.7, 28.4, 26.0, 26.0, 24.8, 18.2, -5.4, -5.6.

FTIR (NaCl, thin film, cm^{-1}): 3430, 2929, 2856, 1472, 1257, 1084, 837, 775.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{33}O_3Si$ $[M+H]^+$: 301.2193; found: 301.2196.

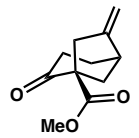
Preparation of β-ketoester **440**.



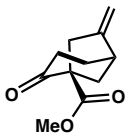
A flame-dried 250 mL round bottom flask was charged with freshly ground $Mn(OAc)_3•2H_2O$ (3 equiv, 12.3 g, 45.9 mmol) and $Cu(OAc)_2•H_2O$ (0.75 equiv, 2.29 g, 11.5 mmol). The flask was evacuated and back-filled with argon three times. The combined salts were suspended in degassed AcOH (75 mL, degassed by sparging with argon for 30 min). A separate flame-dried 50 mL pear-shaped flask was charged with **439** (3.00 g, 15.3 mmol, 1.0 equiv). This flask was evacuated and back-filled with argon three times, and then charged with degassed AcOH (12 mL, degassed by sparging with argon for 30 min). The solution of **439** was transferred to the 250 mL round bottom flask via cannula transfer

over the course of 20 minutes. The reaction mixture was allowed to stir for five hours, at which point the mixture was filtered over a pad of silica gel. The pad was washed with EtOAc (400 mL). The resulting blue solution was concentrated *in vacuo*, and then azeotroped with hexanes (3 x 100 mL) to remove some of the AcOH. The resulting blue solution was diluted with a 1:1 mixture of Et_2O/hexanes (300 mL), then washed with saturated NH_4Cl (aq) (150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (5% EtOAc/hexanes → 10% EtOAc/hexanes, increasing by 1% EtOAc every 2 column volumes) to give **440** (1.18 g, 40% yield) as an amorphous pink solid with characterization data consistent with reports from Snider and coworkers.[14]

The enantiomers of **440** could be separated by chiral preparative HPLC. (IC, 20 x 250 mm, 200 μL injections, 10 mL/min, 20% IPA in hexanes, λ = 210 nm): t_R(–) = 23.72 min, t_R(+) = 26.16 min.

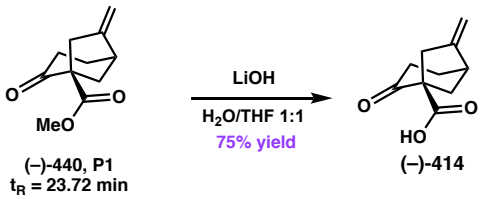


(–)-440, P1
t_R = 23.72 min
$[\alpha]_D^{23}$ = –173.0°
(c = 0.55, $CHCl_3$).



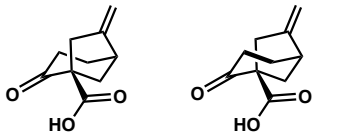
(+)-440, P2
t_R = 26.16 min
$[\alpha]_D^{23}$ = +219.5°
(c = 0.48, $CHCl_3$).

Preparation of acid **414**.



A 25 mL round bottom flask was charged with **440** (58.3 mg, 0.3 mmol, 1.0 equiv) and dissolved in THF (1 mL). The flask was submerged in an ice bath, and LiOH (22 mg, 0.9 mmol, 3.0 equiv) was added as a solution in water (1 mL). The reaction was stirred for 1.5 hours, at which point TLC indicated that no more starting material remained. The reaction was quenched with the addition of 5M HCl (600 μL). The mixture was diluted with water (3 mL) and then extracted with EtOAc (5 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (1% AcOH/1% MeOH/CH_2Cl_2 → 1% AcOH/2% MeOH/CH_2Cl_2) → 1% AcOH/3% MeOH/CH_2Cl_2 to give **414** (39.6 mg, 73% yield) as an amorphous colorless solid.

While we were able to use either (*S*) or (*R*) phenethylamine to perform a classical resolution to access each enantiomer of **414, this procedure was irreproducible. We elected to separate **440** by chiral preparative HPLC and hydrolyze each ester separately. Characterization data for each enantiomer of **414** is included below.



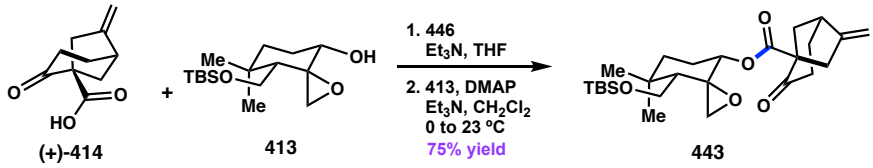
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (s, 1H), 5.09 (d, *J* = 2.2 Hz, 1H), 5.03 (s, 1H), 2.91 (dt, *J* = 18.0, 2.5 Hz, 2H), 2.71 (d, *J* = 17.7 Hz, 1H), 2.51 (ddd, *J* = 16.3, 11.5, 8.9 Hz, 1H), 2.40 (ddd, *J* = 16.3, 5.8, 2.1 Hz, 1H), 2.33 (ddd, *J* = 12.4, 5.1, 2.4 Hz, 1H), 2.03 (d, *J* = 12.2 Hz, 1H), 1.88 (ddd, *J* = 11.8, 6.1, 2.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.8, 176.2, 150.2, 108.1, 63.7, 41.7, 40.9, 39.6, 35.3, 33.4.

FTIR (NaCl, thin film, cm^{-1}): 2939, 1719, 1419, 1241, 1165, 1120, 1062, 899, 738.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{10}H_{16}NO_3$ $[M+NH_4]^+$: 198.1125; found: 198.1120.

Synthesis of ester **443**.



A 25 mL round bottom flask was charged with **(+)-414** (210 mg, 1.16 mmol, 1.0 equiv). The acid was azeotroped with PhMe (3 x 10 mL), then the flask was evacuated and back-filled with N_2 three times. The flask was then charged with THF (6 mL) and Et3N (244 μL, 1.75 mmol, 1.5 equiv). A solution of 2,4,6-trichlorobenzoyl chloride (**446**) (426 mg, 1.75 mmol, 1.5 equiv) was added as a solution in THF (3 mL) dropwise. After 3 hours, the reaction mixture was concentrated *in vacuo*, and the resulting residue was azeotroped

with PhMe (3 x 10 mL). The residue was then dried under high vacuum for five minutes, at which point **413** (350 mg, 1.16 mmol, 1 equiv) was added as a solution in benzene (3 mL), followed by DMAP (285 mg, 2.33 mmol, 2 equiv) as a solution in benzene (3 mL). The flask was then placed in a preheated oil bath and heated to 80 ºC. The mixture stirred for 1 hour, at which point the flask was removed from the oil bath and the reaction mixture allowed to cool to room temperature. The mixture quenched with the addition saturated $NaHCO_3$ (aq) (15 mL). The resulting mixture was diluted with water (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (5 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (5% EtOAc/hexanes → 6% EtOAc/hexanes) to give **443** (409 mg, 76% yield) as an amorphous, colorless solid.

R_f = 0.60 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{23}$ = +51.5° (c = 0.27, $CHCl_3$).

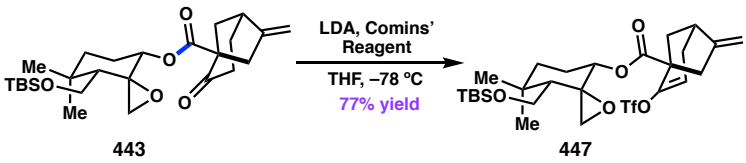
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 (d, *J* = 2.5 Hz, 1H), 5.03 (d, *J* = 2.1 Hz, 1H), 4.78 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.75 – 3.58 (m, 2H), 3.00 – 2.87 (m, 1H), 2.86 – 2.66 (m, 4H), 2.50 (ddd, *J* = 16.0, 11.9, 8.7 Hz, 1H), 2.35 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.25 (ddd, *J* = 12.4, 5.0, 2.7 Hz, 1H), 2.14 – 1.97 (m, 2H), 1.94 – 1.81 (m, 2H), 1.80 – 1.69 (m, 1H), 1.58 (d, *J* = 4.0 Hz, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 170.3, 150.3, 108.2, 73.2, 64.5, 59.9, 58.1, 51.4, 49.3, 41.6, 40.3, 38.8, 35.3, 34.7, 33.5, 29.0, 26.4, 26.0, 25.4, 18.2, -5.3, -5.4.

FTIR (NaCl, thin film, cm^{-1}): 2955, 2858, 1743, 1715, 1472, 1291, 1258, 1156, 1061, 938, 838, 776.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{26}H_{42}O_5Si$ $[M+H]^+$: 463.2874; found: 463.2868.

Synthesis of enol triflate **447**.



A 2-dram vial was charged with **443** (46.2 mg, 0.100 mmol, 1 equiv). The vial was evacuated and back-filled with nitrogen three times. The ester was dissolved in THF (500 µL) and cooled to –78 ºC. Then a solution of freshly prepared LDA (160 µL, 1.2 equiv, 0.75M) was added dropwise. The reaction was stirred at this temperature for 30 minutes, at which point Comins' reagent (45.2 mg, 0.115 mmol, 1.15 equiv) was added as a solid in one portion. After 4 hours, the reaction was warmed to room temperature and quenched by addition of water (2 mL). The mixture was diluted with saturated $NH_4Cl_{(aq)}$ (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were washed with 3M NaOH (10 mL), pushed through a plug of Na_2SO_4, and then concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 5% EtOAc/hexanes) to give **447** (45.6 mg, 77% yield) as an amorphous, colorless solid.

$\mathbf{R_f}$ = 0.63 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

$\mathbf{[\alpha]_D^{23}}$ = +10.2° (c = 2.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (dd, *J* = 4.8, 2.7 Hz, 1H), 5.12 – 4.96 (m, 2H), 4.79 (dd, *J* = 7.8, 4.4 Hz, 1H), 3.80 – 3.59 (m, 2H), 3.04 (dd, *J* = 16.4, 2.1 Hz, 1H), 2.95 (d, *J* = 4.5 Hz, 1H), 2.89 – 2.71 (m, 3H), 2.57 (ddd, *J* = 17.6, 4.3, 2.7 Hz, 1H), 2.23 – 2.10 (m, 3H), 2.11 – 1.95 (m, 1H), 1.85 – 1.67 (m, 1H), 1.54 (ddd, *J* = 13.8, 8.0, 4.1 Hz, 2H), 1.10 (s, 3H), 1.02 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H).

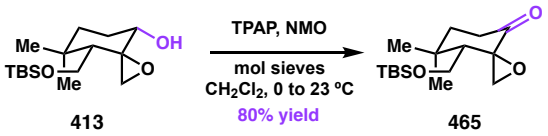
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 151.8, 149.5, 125.7, 118.0 ($J_{C–F}$ = 320 Hz) 115.9, 109.6, 73.9, 59.9, 58.1, 54.4, 51.4, 49.0, 43.6, 41.4, 39.3, 34.9, 34.7, 30.5, 29.8, 29.0, 26.2, 26.0, 18.2, -5.4, -5.5.

^{19}F NMR (282 MHz, $CDCl_3$): –73.6

FTIR (NaCl, thin film, cm^{-1}): 2929, 1743, 1420, 1292, 1236, 1213, 1164, 1143, 1079, 1046, 840, 775, 648

HRMS (ESI-TOF, *m/z*): calc'd for $C_{27}H_{45}F_3NO_7SSi$ $[M+NH_4]^+$: 612.2633; found: 612.2622.

Synthesis of epoxy ketone **465**.



A 25 mL round bottom flask was charged with 4Å molecular sieves and flame-dried under vacuum for 3 minutes. The flask was allowed to cool under vacuum, and then back-filled with nitrogen at room temperature. Epoxy alcohol **413** (150 mg, 0.5 mmol, 1.0 equiv) was added, followed by NMO (88 mg, 0.75 mmol, 1.5 equiv). The solids were dissolved in CH_2Cl_2 (2.5 mL), and then the mixture was cooled to 0 ºC. TPAP (17.6 mg,

0.05 mmol, 0.10 equiv) was added in one portion. The reaction stirred at this temperature for one hour, at which point the flask was removed from the ice bath and allowed to stir at room temperature for 30 min. The mixture was pipetted directly onto an equilibrated silica gel column and purified directly via column chromatography (hexanes → 10% EtOAc/hexanes) to give **465** (119 mg, 80% yield) as a thick, colorless oil.

$\mathbf{R_f}$ = 0.53 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (dd, *J* = 10.6, 3.1 Hz, 1H), 3.70 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.15 (d, *J* = 5.9 Hz, 1H), 2.86 (d, *J* = 5.9 Hz, 1H), 2.61 (ddd, *J* = 17.1, 8.6, 6.4 Hz, 1H), 2.48 (ddd, *J* = 17.1, 6.7, 6.2 Hz, 1H), 2.06 (ddd, *J* = 13.4, 8.6, 6.1 Hz, 1H), 1.68 (dtd, *J* = 13.3, 6.5, 1.2 Hz, 1H), 1.62 – 1.51 (m, 1H), 1.25 (s, 3H), 1.16 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.1, 61.3, 60.2, 51.9, 50.6, 37.4, 37.3, 34.4, 28.9, 28.9, 26.2, 18.5, -5.4, -5.4.

4.4.2.2 Cross-Coupling Procedure

General Procedure for Cross-Couplings:

A 1-dram vial was charged with Et_3N•HCl, ligand, and reductant (if solid). The vial was then brought into a N_2-filled glovebox. Inside the box, the vial was charged with $TiCp_2Cl_2$ and then the nickel precatalyst. The vial was then charged with substrate(s) as a solution. The vials were sealed with a Teflon cap and brought out of the glovebox. The reactions were allowed to stir overnight at room temperature at 800 rpm. After 16 hours, the reactions were diluted with 20% EtOAc/Hexanes and pushed through a 6 cm plug of

SiO2 gel, eluting with 10 mL of 20% EtOAc/Hexanes. The solvent was removed *in vacuo*, and 1,2,4,5-tetrachloro-3-nitrobenzene was added. The yields of each product were determined by ^{1}H-NMR spectroscopy.

4.5 NOTES AND REFERENCES

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(17) At the time, we were unaware of the absolute configuration of **414** we were obtaining through the chiral resolution. Unfortunately, we later discovered that these experiments were carried out using the incorrect diastereomer shown.
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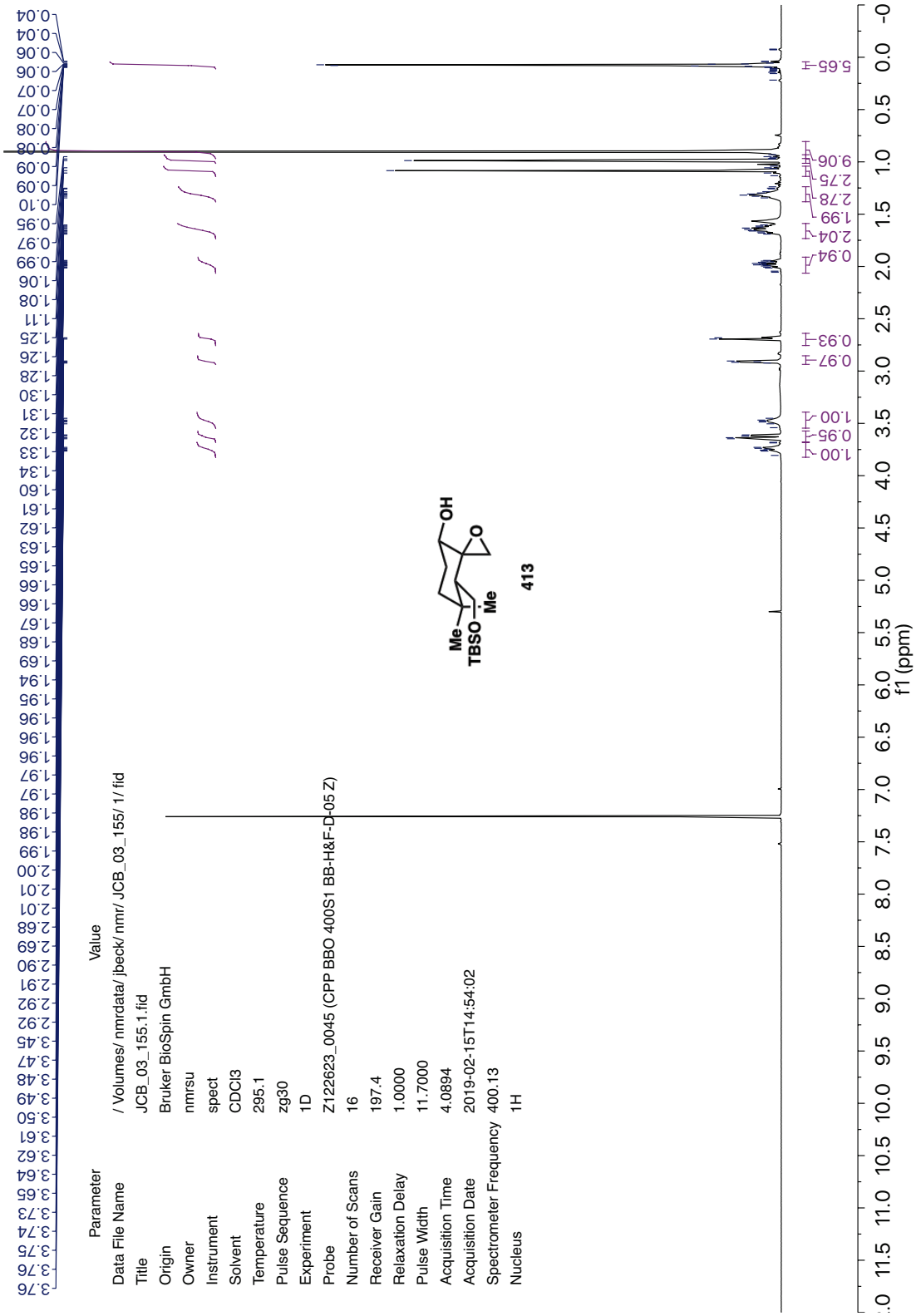
Appendix 2

Spectra Relevant to Chapter 4:

A Cross-Coupling Approach for the Synthesis of the Enmein-Type Ent-Kauranoids



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Owner	nmrsu
Instrument	spect
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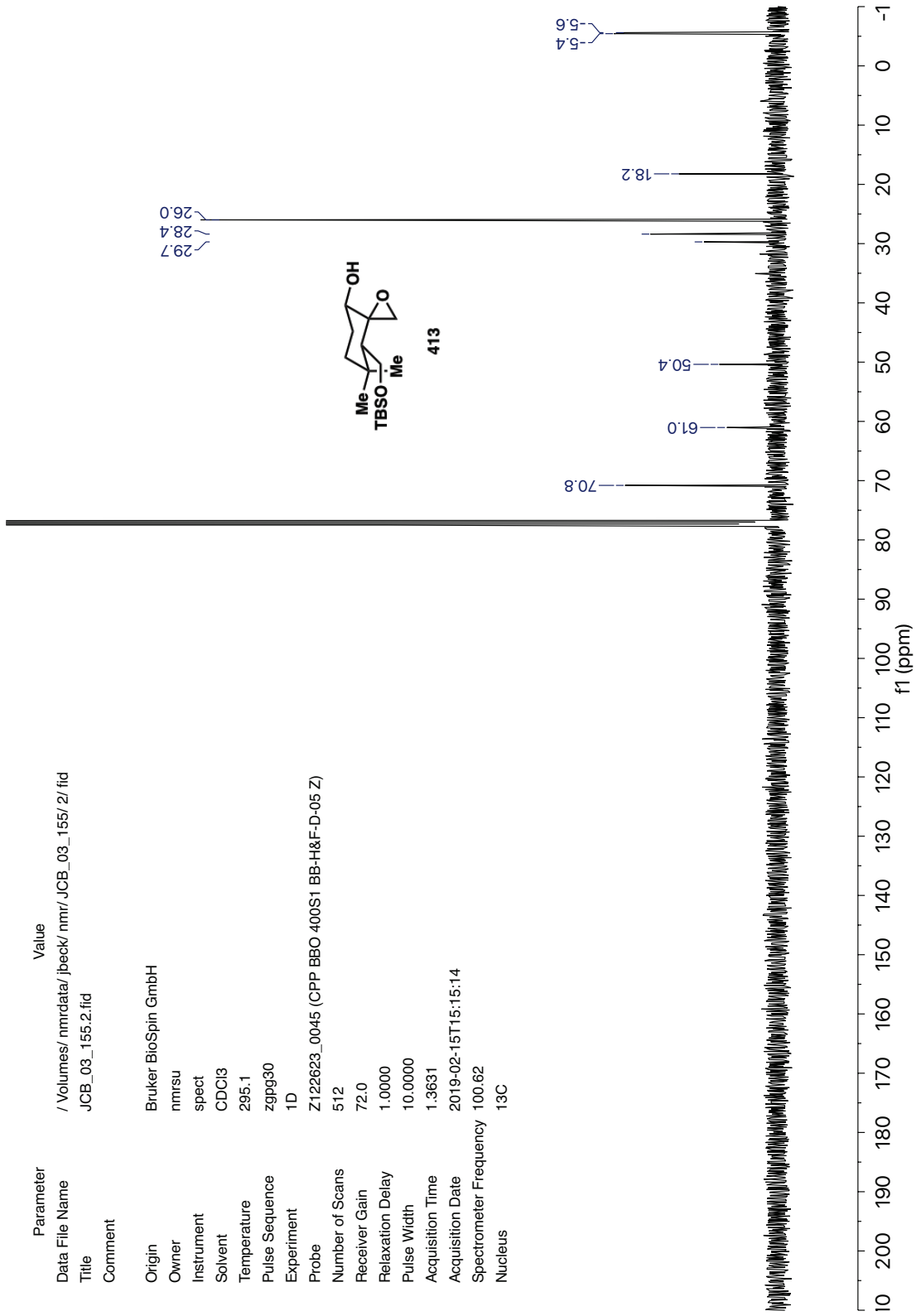
Spectrometer Frequency	400.13
Nucleus	1H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Instrument spect
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Number of Scans 512
Receiver Gain 72.0
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Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-15T15:15:14
Spectrometer Frequency 100.62
Nucleus 13C
OH
O
TBSO
Me
Me
Me
413
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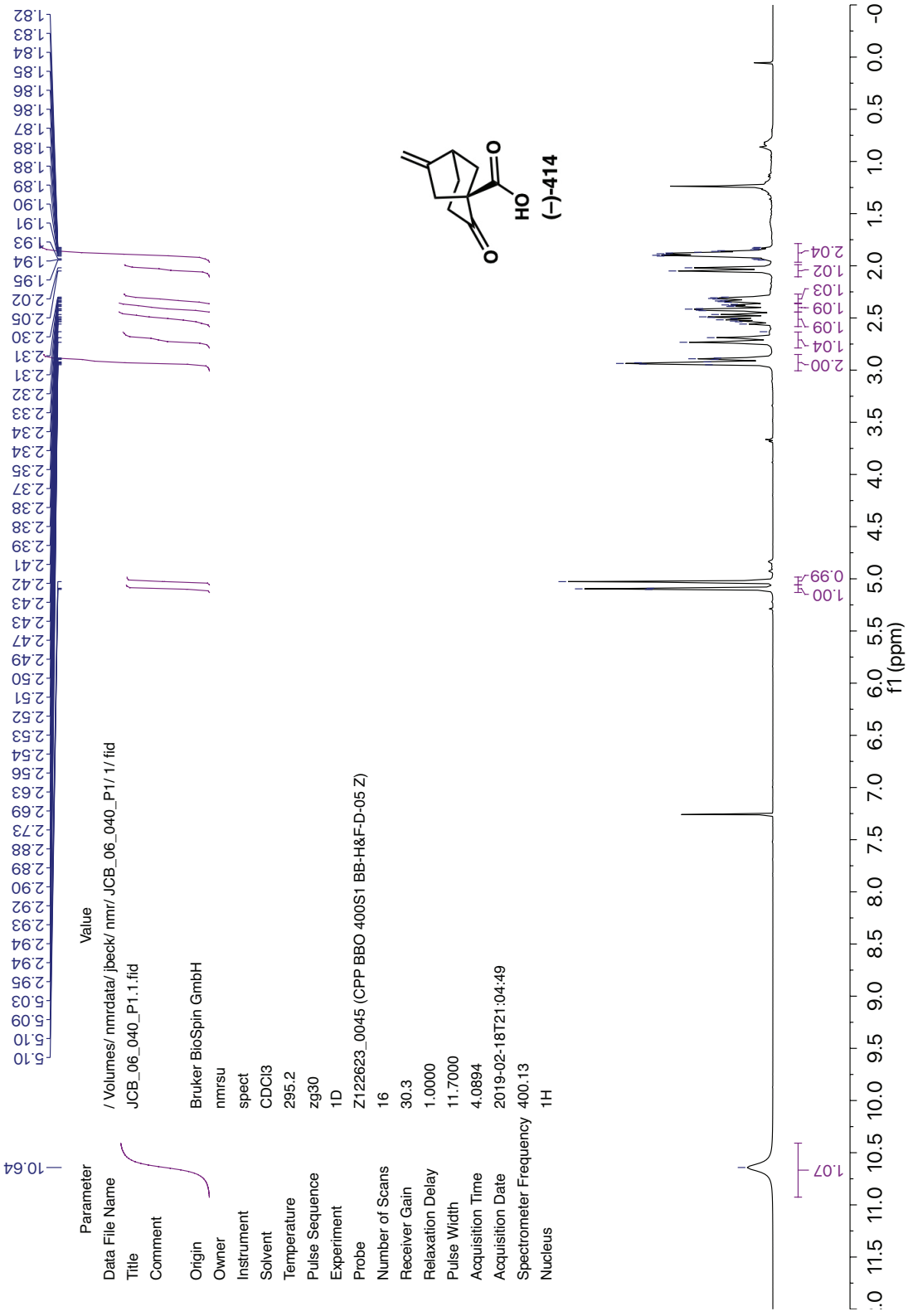
-5.6
18.2
26.0
28.4
29.7
50.4
61.0
70.8
f1 (ppm)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O
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Pulse Width 11.7000
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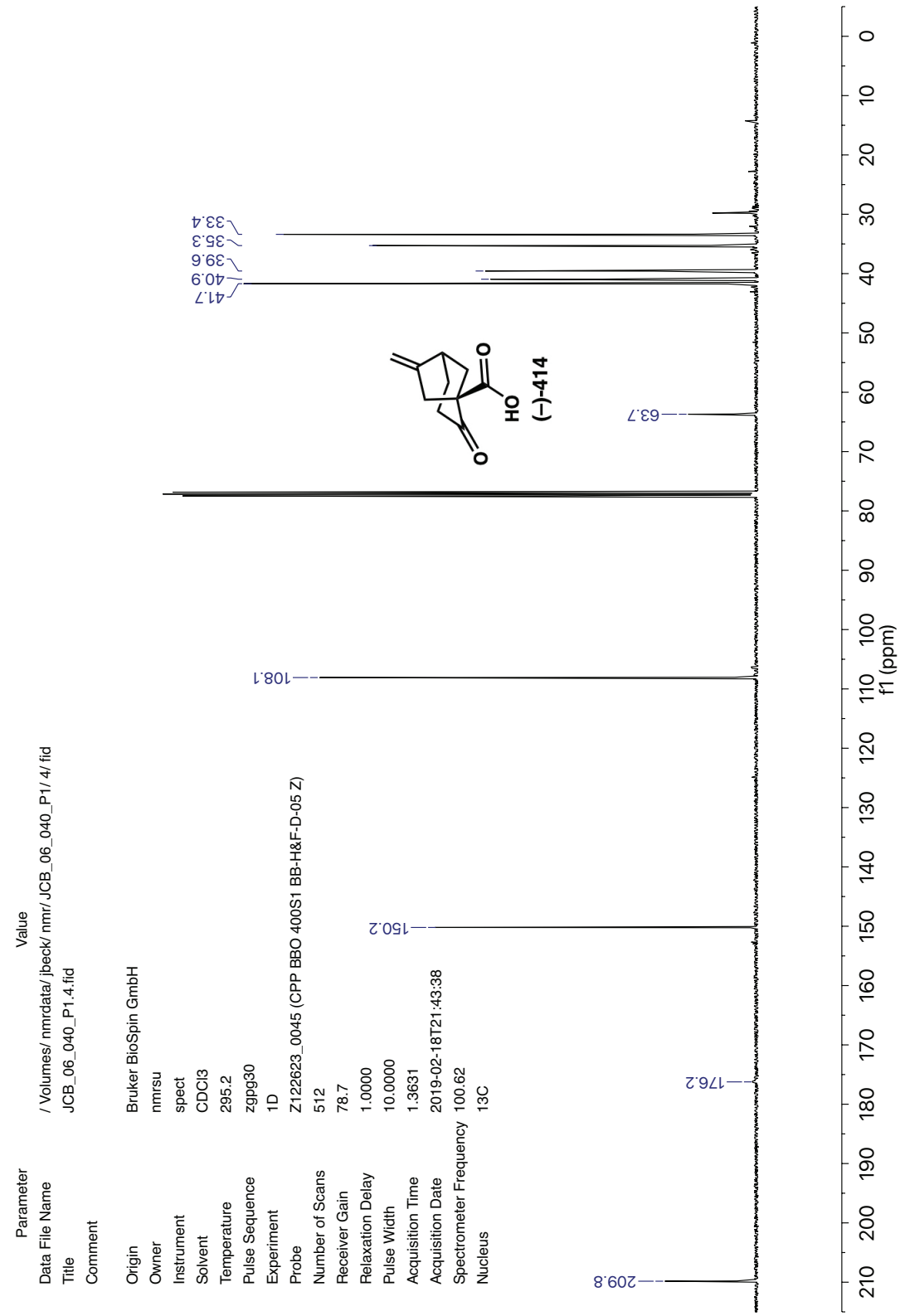
0.99
2.00
1.04
1.09
1.09
1.03
1.02
2.04
f1 (ppm)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Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-18T21:43:38
Spectrometer Frequency 100.62
Nucleus 13C
209.8
176.2
150.2
108.1
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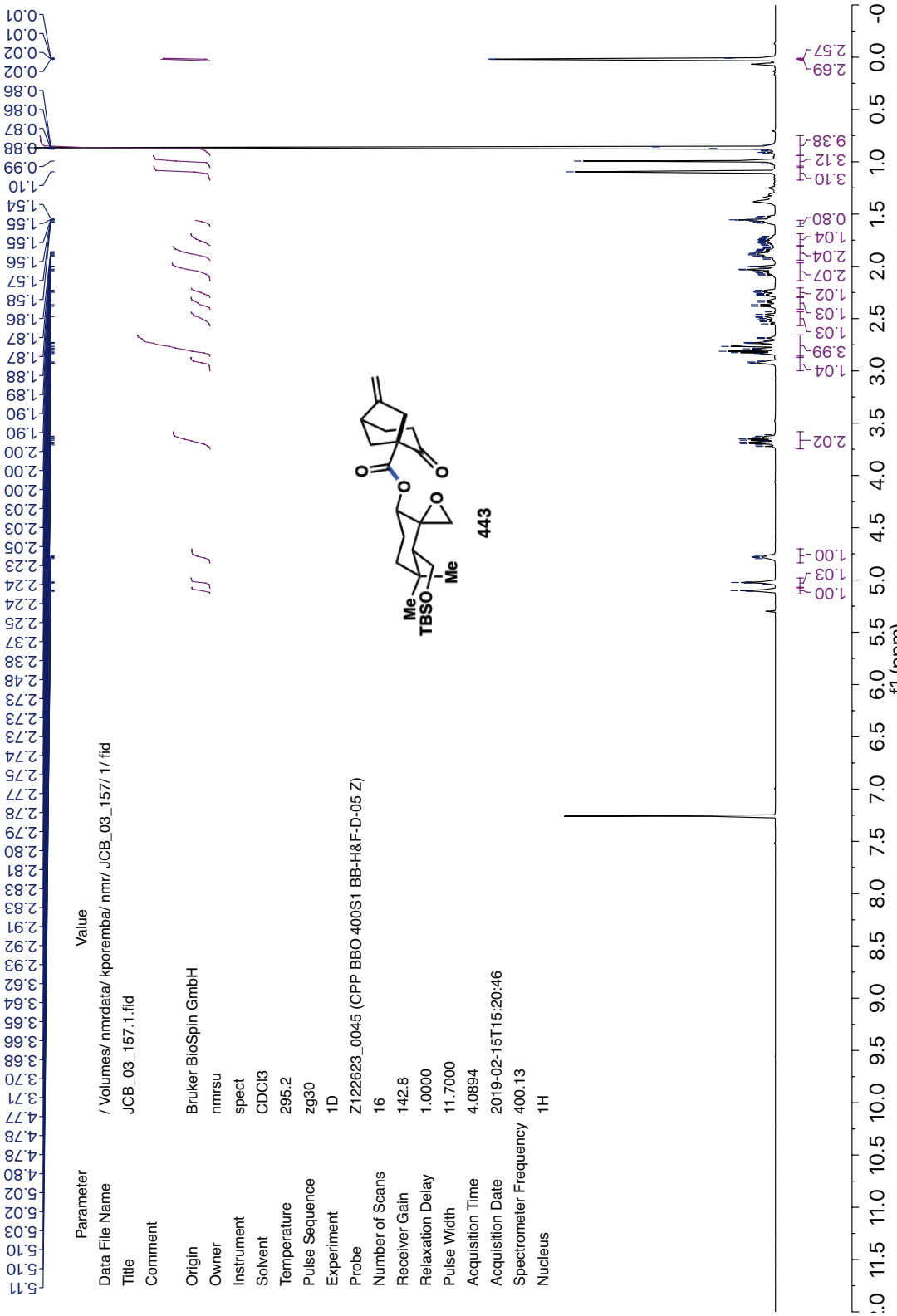
39.6
35.3
33.4
HO
O
O
(–)-414
f1 (ppm)



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Instrument	spect
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Number of Scans	16
Receiver Gain	142.8
Relaxation Delay	1.0000
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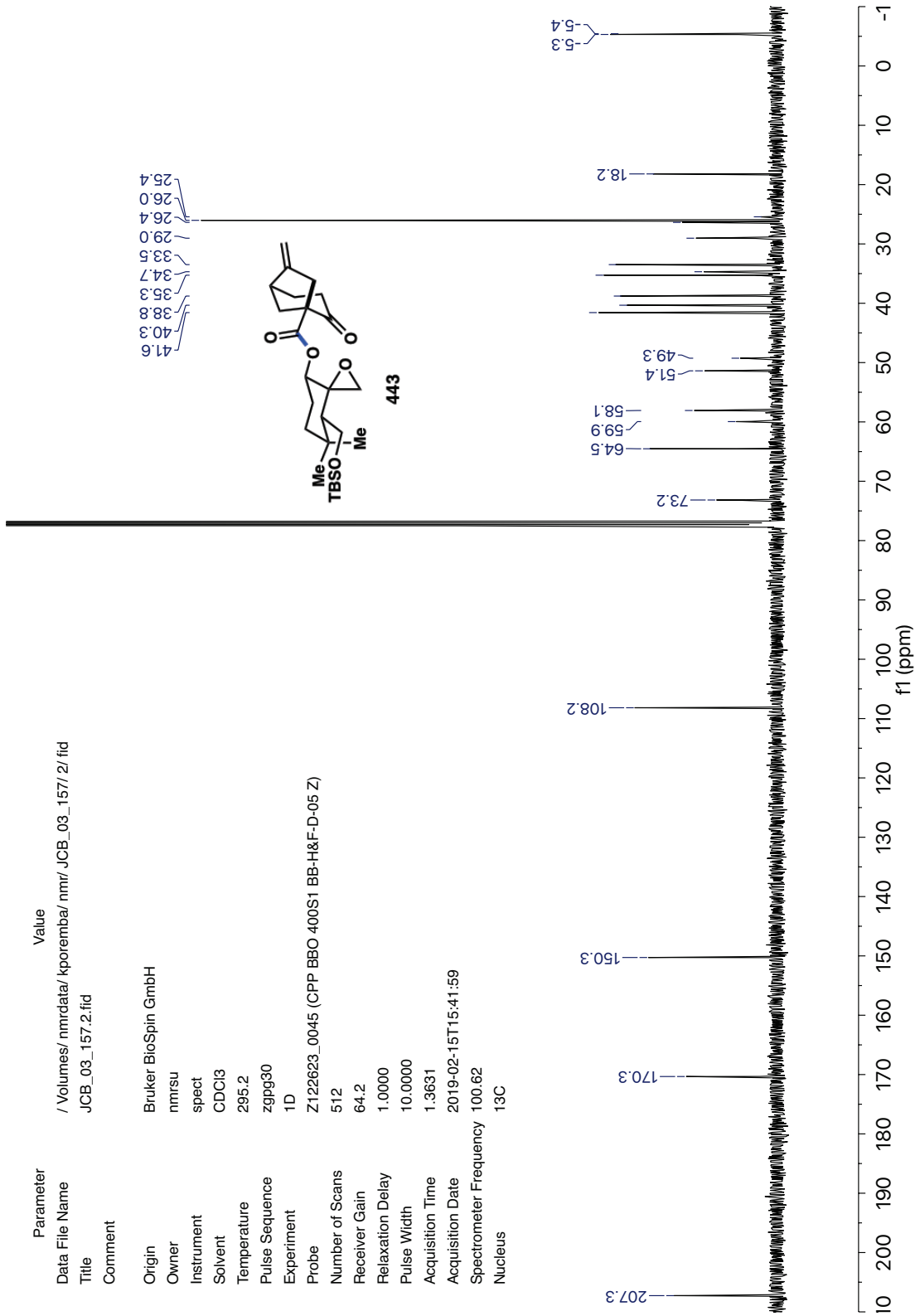
Nucleus	1H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Receiver Gain 64.2
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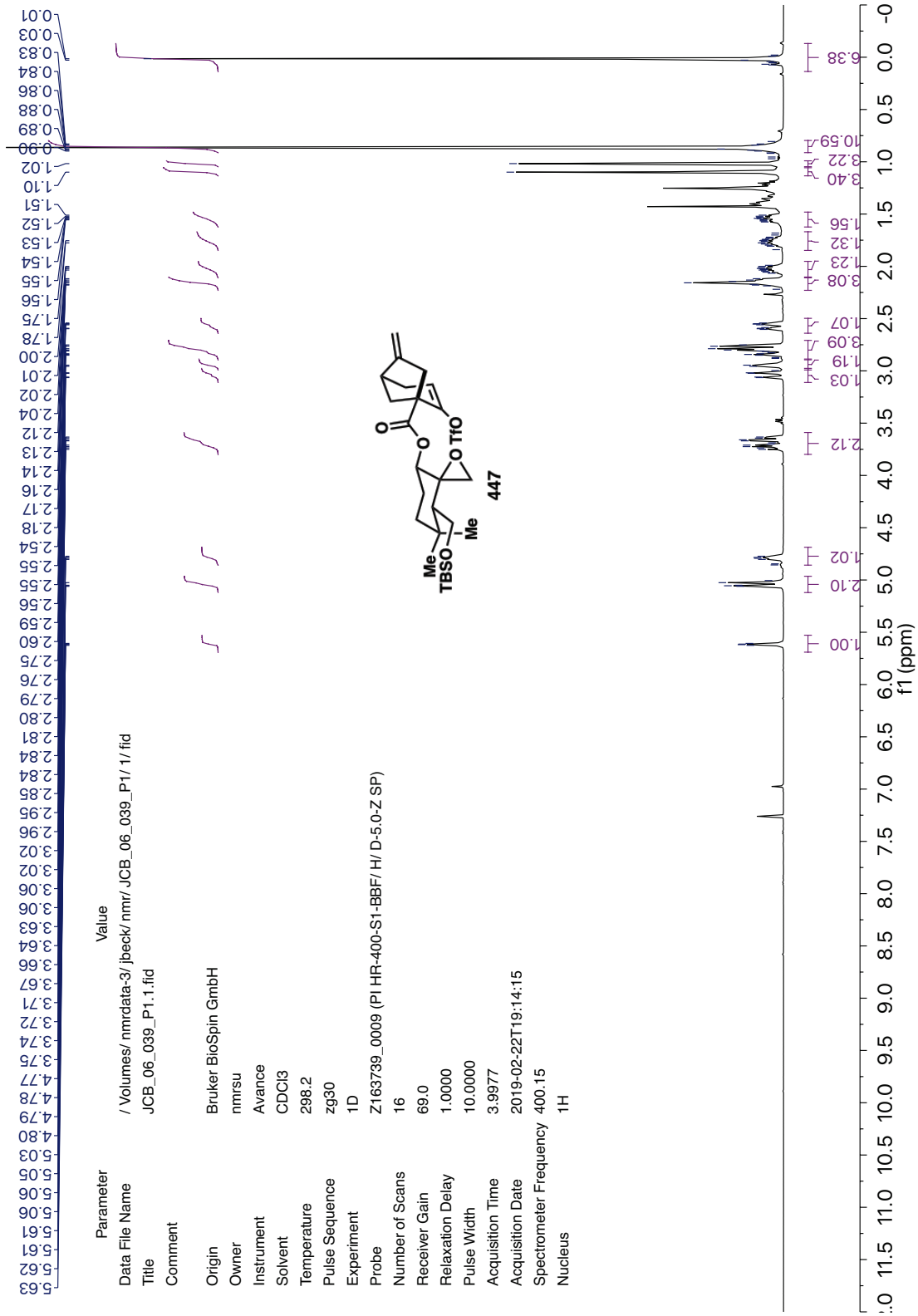
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-15T15:41:59
Spectrometer Frequency 100.62
Nucleus 13C
443
Me
TBSO
Me
207.3
170.3
150.3
108.2
73.2
64.5
59.9
58.1
51.4
49.3
41.6
40.3
38.8
35.3
34.7
33.5
29.0
26.4
26.0
25.4
18.2
-5.3
-5.4
f1 (ppm)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Solvent CDCl3
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Relaxation Delay 1.0000
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Acquisition Date 2019-02-22T19:14:15
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TBSO
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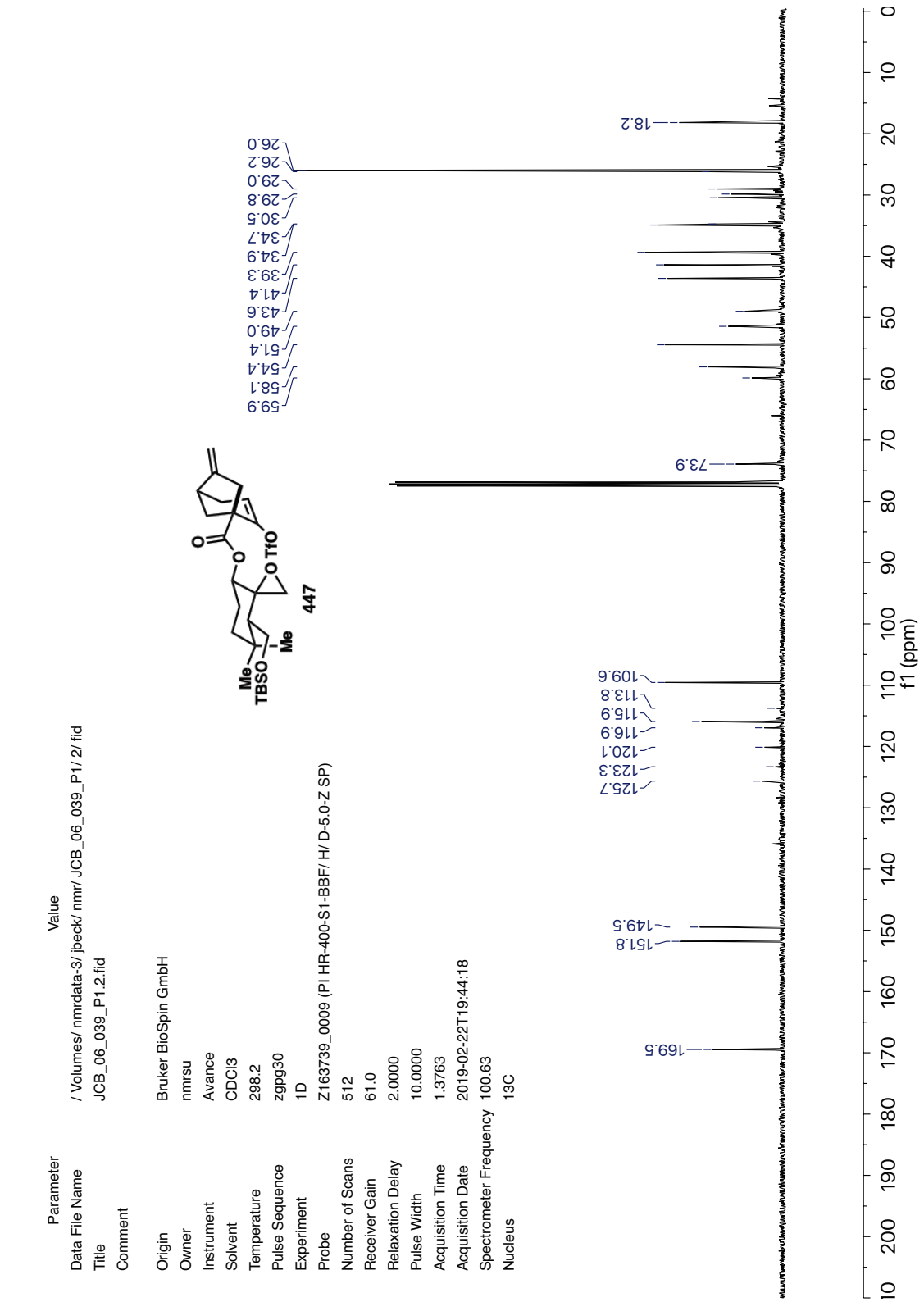
Me
O
O
O TfO
447
f1 (ppm)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Spectrometer Frequency 100.63
Nucleus 13C
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Me
TBSO
Me
O
O
O
O
TfO
169.5
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125.7
123.3
120.1
116.9
115.9
113.8
109.6
73.9
59.9
58.1
54.4
51.4
49.0
43.6
41.4
39.3
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30.5
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26.2
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f1 (ppm)

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Nucleus 19F
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-73.94
Me
TBSO
Me
O
O
O TfO
447
-66.0
-67.0
-68.0
-69.0
-70.0
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-75.0
-76.0
-77.0
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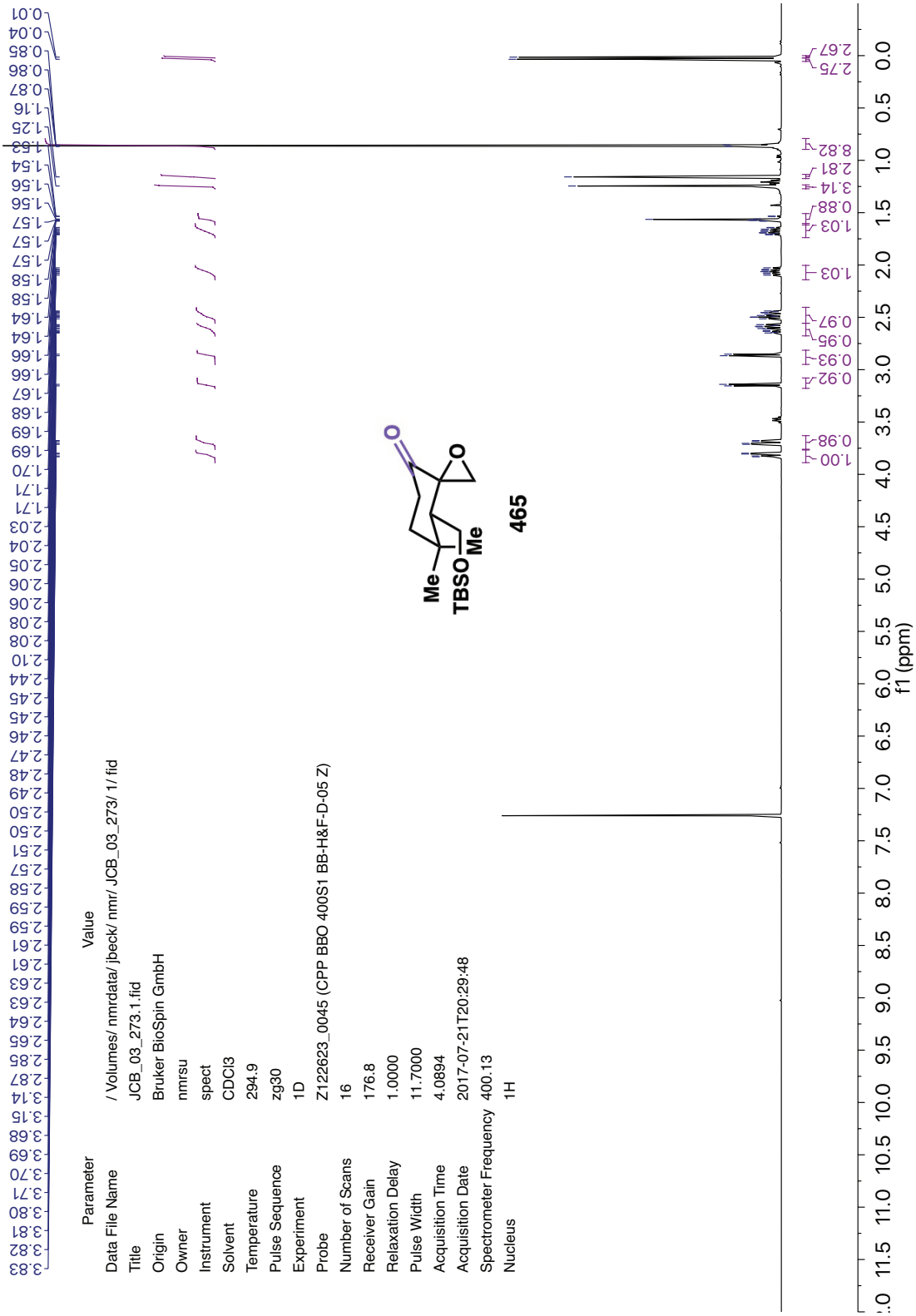
-79.0
f1 (ppm)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Instrument spect
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Pulse Sequence zg30
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Receiver Gain 176.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
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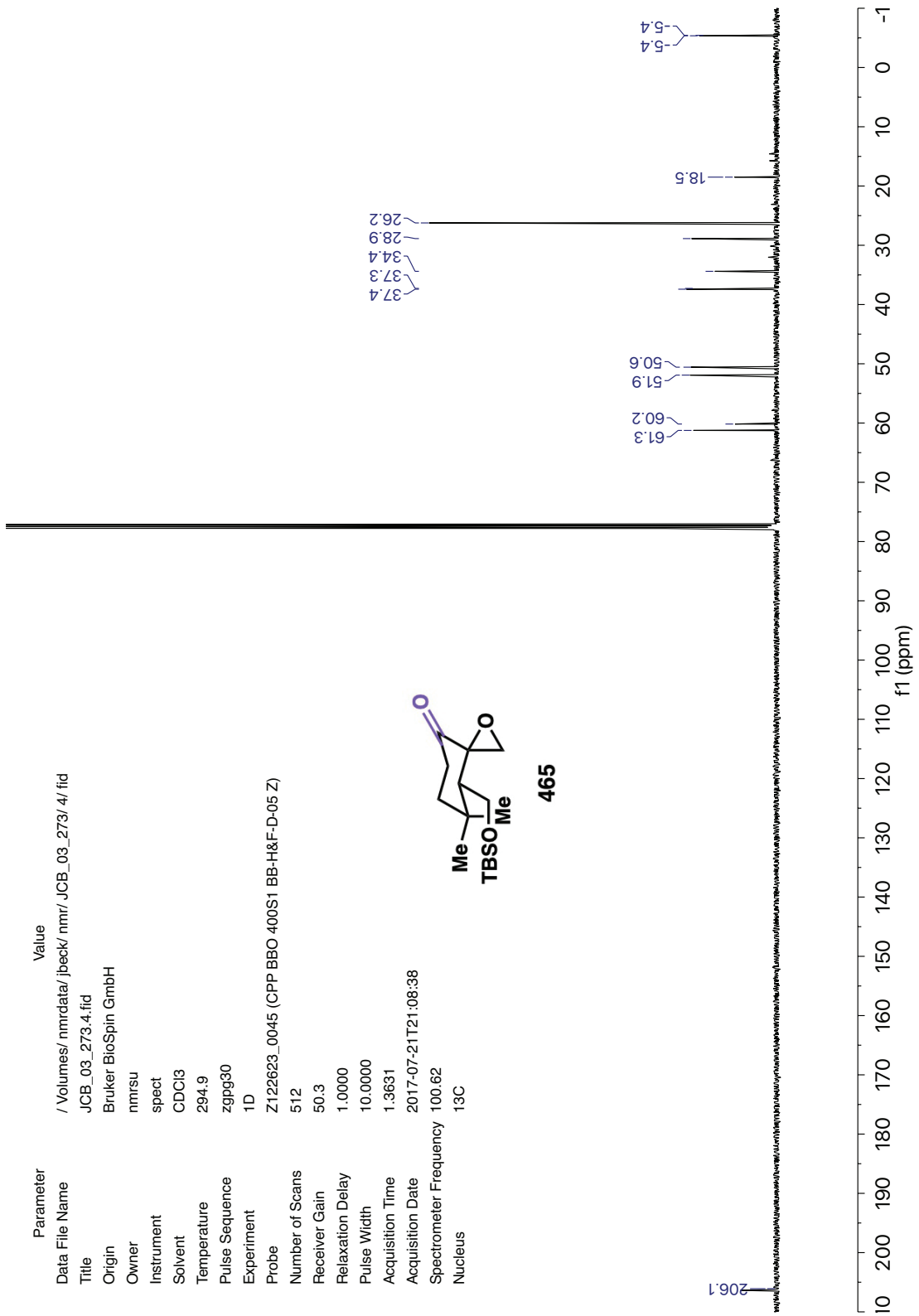
Nucleus 1H
Me
TBSO
Me
O
O
465
f1 (ppm)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Pulse Width 10.0000
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Nucleus 13C
Me
TBSO
Me
O
O
465
206.1
61.3
60.2
51.9
50.6
37.4
37.3
34.4
28.9
26.2
18.5
-5.4
-5.4
f1 (ppm)

Chapter 5

A Semi-Pinacol Approach for the Synthesis of the Enmein-Type Ent-Kauranoids

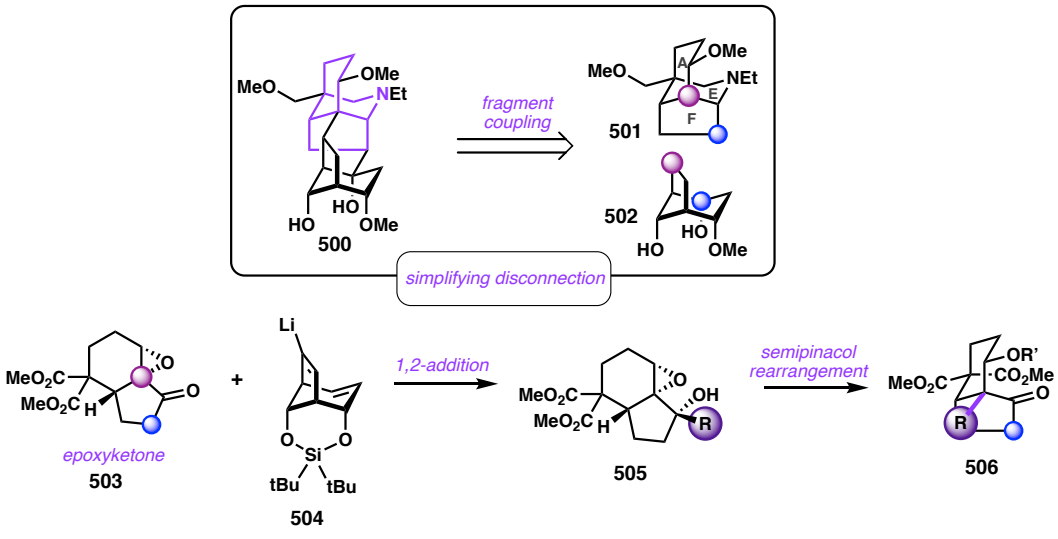
5.1 INTRODUCTION

While our first generation strategy approach focusing on construction of the enmein-type *ent*-kauranoid core through a cross-electrophile coupling was unsuccessful, we remained committed to the development of a convergent route to access **301** and related natural products. From a conceptual point of view, we felt that disconnection through the central B-ring lactone would still be the most expedient route to **301**, and we thought that we could potentially use some of the chemistry we had previously developed in our first generation route toward **301**. With this in mind, we became interested in employing a 1,2-addition/semi-Pinacol rearrangement sequence to bring together two complex fragments

and forge the key all-carbon quaternary center we had attempted to form through a convergent cross-coupling.

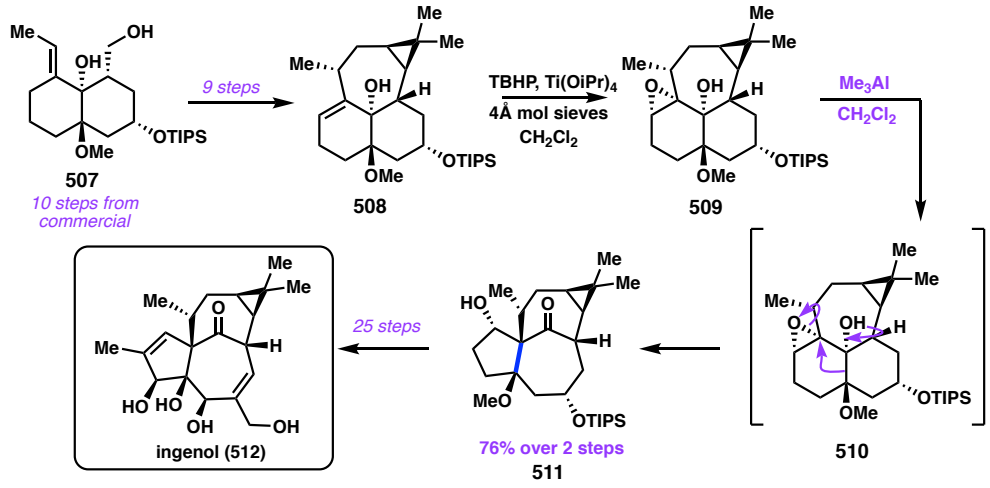
We drew inspiration from elegant work happening on the other side of the lab focused on the synthesis of the C_{19} diterpenoid alkaloids (**500**) (Scheme **5.1**). Our lab's strategy for the synthesis of these structurally analogous natural products involved a convergent fragment coupling between two complex fragments, namely epoxy ketone **503** and an alkenyl organometallic **504**. A highly selective 1,2-addition followed by subsequent semi-pinacol rearrangement delivered **505**, which maps on beautifully to the diterpenoid alkaloid core. Intrigued by this approach to forging an all-carbon quaternary center between two highly complex fragments, we wondered if we could apply a similar strategy to the synthesis of the enmein-type *ent*-kauranoids.

Scheme 5.1 *The Reisman approach to the C_{19} diterpenoid alkaloids (**500**)*



We were also aware of other salient examples of type III semi-Pinacol rearrangements in the context of complex molecule total synthesis. We were intrigued by the Tanino's group use of a type III semi-Pinacol rearrangement to forge an all-carbon quaternary center present in Ingenol (**512**) (Scheme **5.2**).[1] Epoxy alcohol **509** succumbs to a 1,2-migration upon treatment with Me_3Al. In doing so, they are able to forge an all-carbon quaternary center and build the central 5,7,7-core of the natural product. While it takes them an additional 25 steps to access ingenol (**512**), their rapid synthesis of the core is notable.

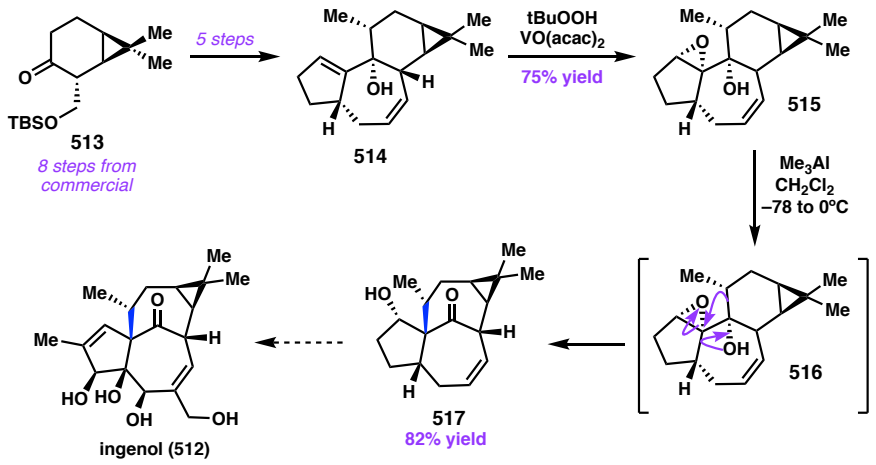
Scheme 5.2 *Tanino's synthesis of ingenol (**512**).*



The Cha lab reported a distinct strategy in the progress toward their synthesis of Ingenol (**512**), using a different type III semi-Pinacol rearrangement (Scheme **5.3**).[2,3] They first generate a 7-membered ring containing a tertiary alcohol **514**. From here, a directed epoxidation delivers **515**, which is poised to undergo a key semi-Pinacol rearrangement to forge the carbocyclic skeleton of ingenol (**512**). Treatment of **515** with Me_3Al delivers **517**,

through a highly diastereoselective semi-Pinacol rearrangement. Of note is how the stereochemistry at the epoxide controls which bond migrates. While their strategy was not successfully applied to the total synthesis of **512**, this result highlights the versatility of the semi-Pinacol rearrangement in total synthesis and is a good example of how the conformational requirements of the type III semi-Pinacol rearrangements render this transformation highly stereo- and regioselective.

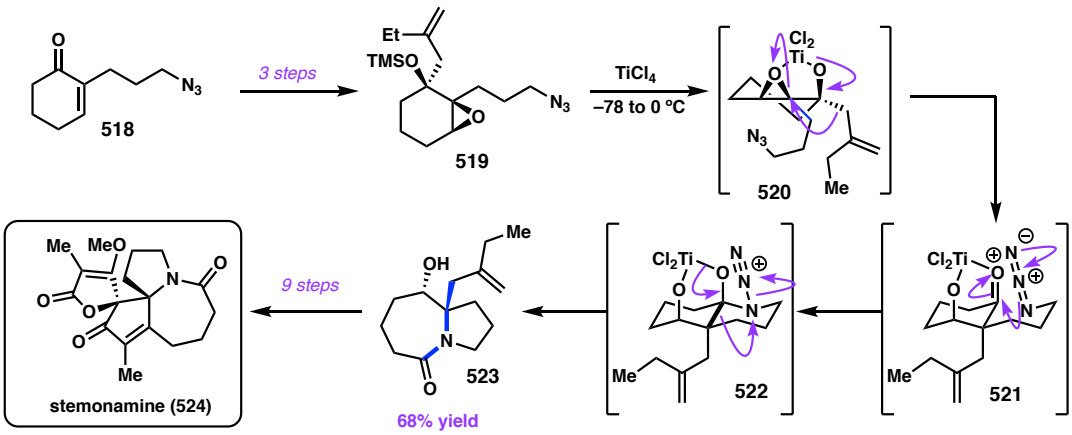
Scheme 5.3 *Cha's progress toward ingenol (**512**).*



Another elegant example of a type III semi-Pinacol rearrangement comes from the Tu lab in their impressive synthesis of stemonamine (**524**) (Scheme **5.4**).[4] Their synthesis commences from azido enone **518**, which can be elaborated in three steps to silyl protected epoxy alcohol **519**. Treatment of **519** with $TiCl_4$ initiates an impressive cascade. First, a type III semi-Pinacol rearrangement delivers **521**, forming an all-carbon quaternary center. This intermediate **521** is then poised to undergo a subsequent reaction—the pendant azide can then add into the ketone, generating a diazonium ion **522**, and a second semi-Pinacol

rearrangement forges a new carbon-nitrogen bond. This strategy uses a single Lewis acid to migrate two bonds, which is crucial in construction of the bicyclic lactam core **523**.

Scheme 5.4 *Tu's synthesis of stemonamine (**524**)*

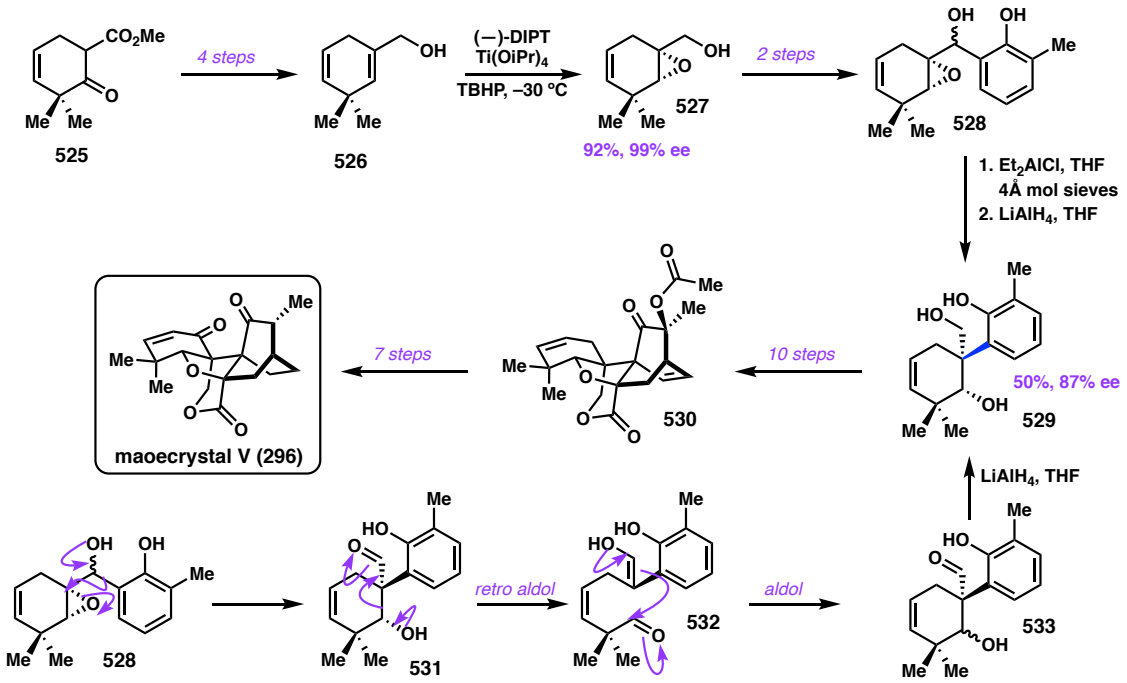


Of particular interest was a report from Yang and coworkers in their total synthesis of maoecrystal V (**296**) (Scheme **5.5**). Diene **526** can be accessed in four steps from **525**. From here, the first stereocenter can be established through a Sharpless epoxidation, giving epoxy alcohol **527** in excellent yield and enantioselectivity. Two additional steps delivers epoxy alcohol **528**, which is their substrate for a semi-Pinacol rearrangement. Treatment with diethylaluminum chloride followed by a reduction provides access to **529**; however, they observed significant erosion in enantiopurity. This is thought to occur through a retro-aldol/aldol process, wherein semi-Pinacol rearrangement delivers **531**. Hydroxy aldehyde **531** can then undergo a retro-aldol to give formyl enol **532**, which is achiral. Aldol reaction of **532** can regenerate **533**, with loss of enantiopurity.

While we were excited by this report of forging an all-carbon quaternary center in these structurally related natural products, we took note of this observed erosion of

enantiopurity. Because of this, we hypothesized that migrations of silyl protected epoxy alcohols would be better in this particular transformation, to avoid the retro-aldol/aldol reactivity.

Scheme 5.5 *Yang's synthesis of* ***296***.



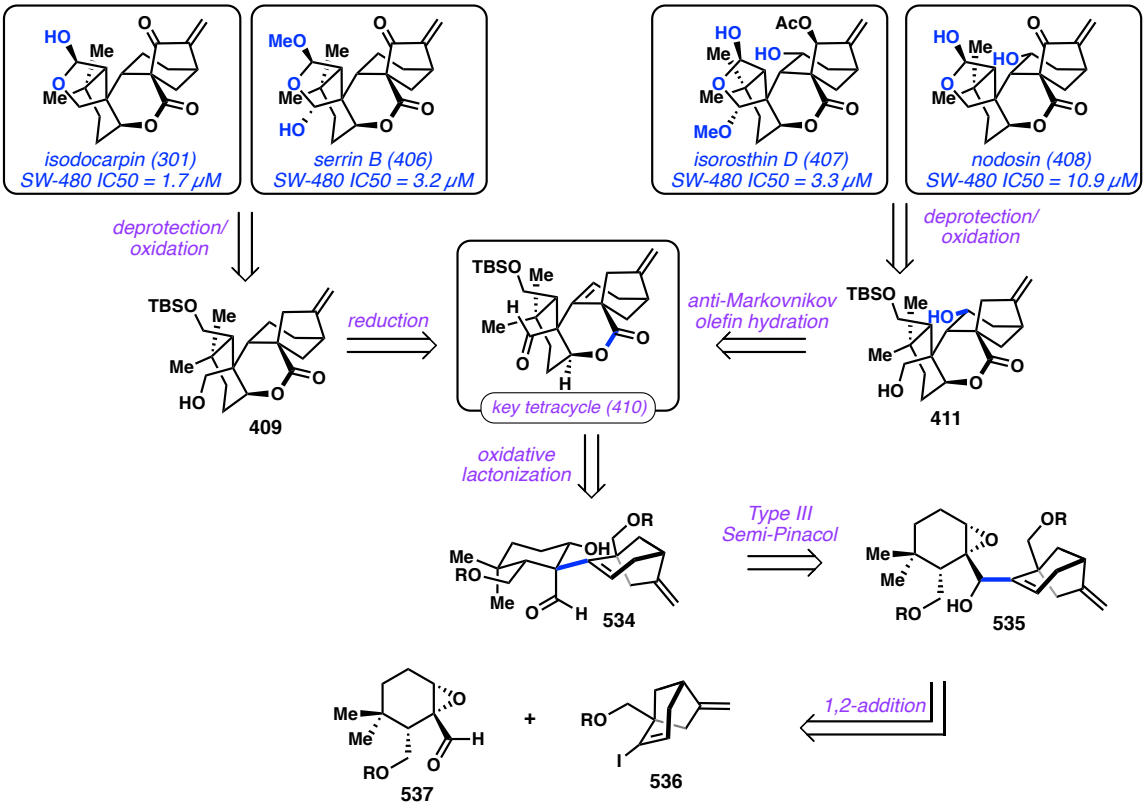
5.2 FIRST GENERATION SEMI-PINACOL STRATEGY

5.2.1 Retrosynthetic Analysis

Strategically, we felt we could access the same four natural products through a divergent strategy. Again, **301** and **406** would be accessed through a deprotection/oxidation sequence from alcohol **409** (Scheme **5.6**). This intermediate could form through a reduction of aldehyde **410**. This intermediate could also be elaborated to **407** and **408** through the intermediacy of diol **411**, making **410** a versatile intermediate. The key tetracyclic

framework could be disconnected through the lactone to reveal hydroxy aldehyde **534**, which could be elaborated to **410** in the forward sense through an oxidative lactonization.

Scheme 5.6 *Retrosynthetic analysis featuring a key semi-Pinacol rearrangement*



The synthesis of **534** could be achieved through a type III semi-Pinacol rearrangement of the corresponding epoxy alcohol **535**. We were excited at the prospect of using a semi-Pinacol rearrangement that had been analogously employed in the synthesis of the diterpenoid alkaloid core, and we were confident as this strategy had been used in our lab to construct an all-carbon quaternary center. We hoped to construct epoxy alcohol **535** through a 1,2-addition between epoxy aldehyde **537** and an organometallic reagent

derived from vinyl iodide **536**—both of which we thought we could access in short order from intermediates we had previously prepared in our first generation strategy.

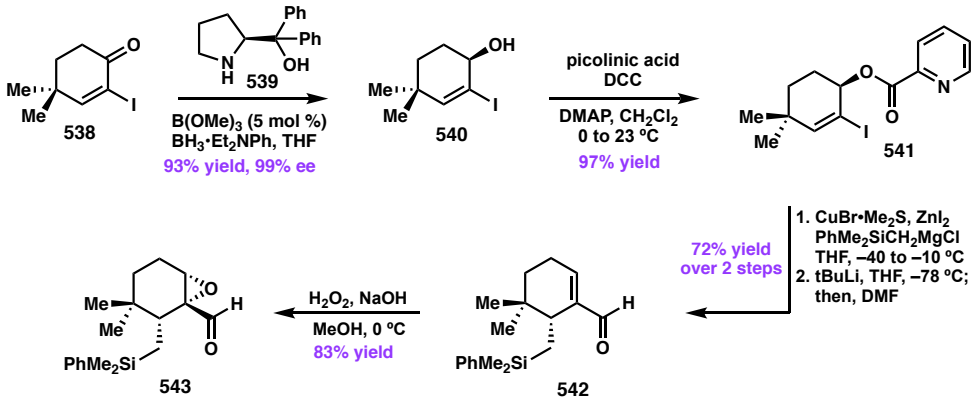
5.2.2 Epoxy Aldehyde Synthesis

In the forward sense, our synthesis of **537** commenced with the iodination of 4,4-dimethyl cyclohexenone. Treatment under reported conditions with 4-DMAP as the catalyst delivered **538** in good yield.[5] The iodoenone **538** could then be advanced through a CBS reduction, delivering excellent yield and enantiomeric excess of alcohol **540** (Scheme **5.7**).[6] With a robust means of preparing **538** and its enantiomer, we turned our attention toward installing the neopentyl stereocenter. While we had initially anticipated using a [2,3]-Wittig-Still rearrangement from the corresponding α-alkoxysilane[7] or the α-alkoxystannane[8] to carry out an anionic transposition, we were unable to achieve the desired reactivity on our system.

We turned our attention toward elegant work presented by the Knochel lab in which they were able to perform a stereoinvertive cross-coupling mediated by copper between allylic phosphonates and organozinc reagents.[9] While we were able to prepare the necessary allylic phosphonate, we didn't observe the desired reactivity under Knochel's conditions. However, we found that we could carry out an analogous reaction between an allylic picolinamide (**541**) and a silyl Grignard reagent, delivering the desired product in excellent yield.[10–12] We could then perform a standard formylation, delivering enal **542**. We were pleased to see that nucleophilic epoxidation delivered epoxy aldehyde **543** with the correct stereochemistry. While **543** was not in the correct oxidation state, we felt

confident that we could perform a late-stage Tamao-Fleming oxidation to convert silane **543** to the requisite alcohol present in **537**.[13–16]

Scheme 5.7 *A simplifying convergent strategy to access* ***543***.



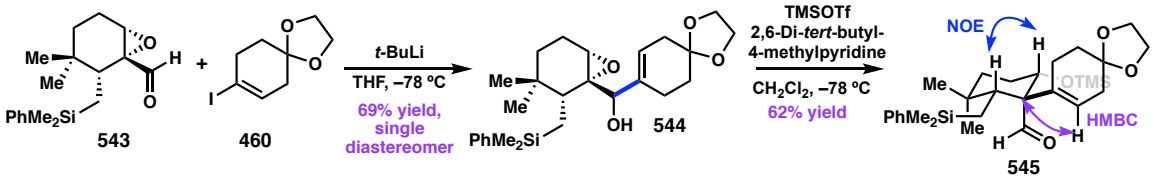
5.2.3 Model Semi-Pinacol Exploration

With a robust means of preparing **543**, we turned our attention toward ascertaining the feasibility of a semi-Pinacol reaction to install the all-carbon quaternary center. Due to the difficulties associated with the preparation of a single enantiomer of bicyclic vinyl iodides of structure **536**, we elected to first investigate a model semi-Pinacol rearrangement with other alkenyl iodides.

We were excited to see that we could generate the corresponding vinyl lithium from **460** through treatment with two equivalents of *t*-BuLi. After formation of the vinyl lithium, we found that addition into the aldehyde smoothly delivered a single diastereomer of **544** (Scheme **5.8**). While we were unsure of which diastereomer we were forming in this reaction, we were eager to begin exploring the feasibility of a 1,2-migration event. We hypothesized that either diastereomer should be able to undergo rearrangement due to the

free rotation of the acyclic alcohol. We were delighted to see that treatment of **544** with TMSOTf as the Lewis acid and 2,6-di*tert*butyl-4-methylpyridine afforded clean conversion to aldehyde **545**.

Scheme 5.8 *A monocyclic semi-Pinacol model experiment*

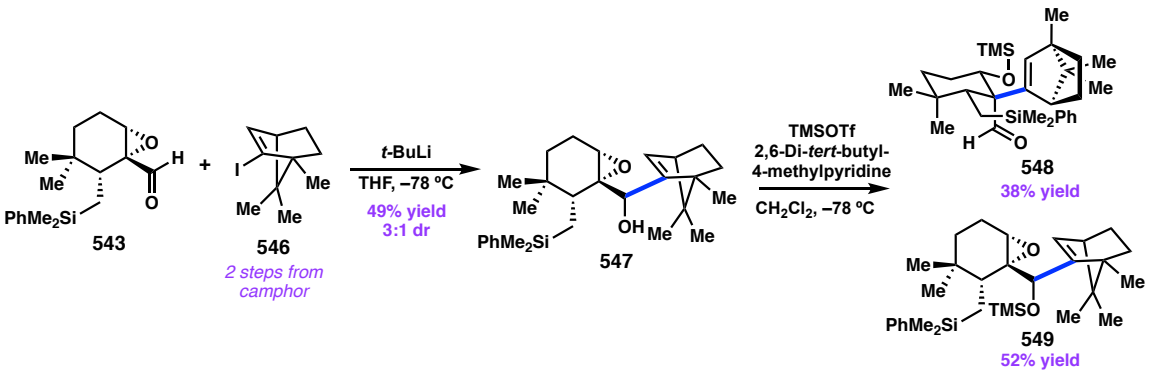


Excited by this result, we became interested in investigating the feasibility of migrating a bicyclic alkene group, which we felt would be a better model for the actual system we were looking to apply this strategy to. We hypothesized that a camphor-derived system would be a good surrogate for the steric-bulk present in **536**. We were delighted to see that preparation of **546** through the intermediacy of the corresponding hydrazone proceeded well, as reported in the literature (Scheme **5.9**).[17] As with **460**, lithium-iodine exchange proceeded smoothly. Subsequent 1,2-addition into epoxy aldehyde **543** delivered epoxy alcohol **547** as a mixture of diastereomers. While the mixture of diastereomers at this step made characterization of **547** difficult, we hypothesized that both diastereomers would be competent substrates for a 1,2-migration event and should converge to give a single diastereomer, with the stereochemistry of the product ultimately controlled by the configuration of the epoxide.

With **547** in hand, we were pleased to see that treatment with TMSOTf with 2,6-Di-*tert*-butyl-4-methylpyridine at low temperature delivered an appreciable amount of **548**.

Interestingly, the other product we identified was **549**, which could be isolated as a single diastereomer. It appeared that only a single isomer of **547** could be converted to **548** under the reaction conditions. While it is still unclear which isomer of **547** is a competent substrate for the migration, further investigation of the required stereochemistry for the migration is currently underway.

Scheme 5.9 *Migration of a camphor-derived alkene*

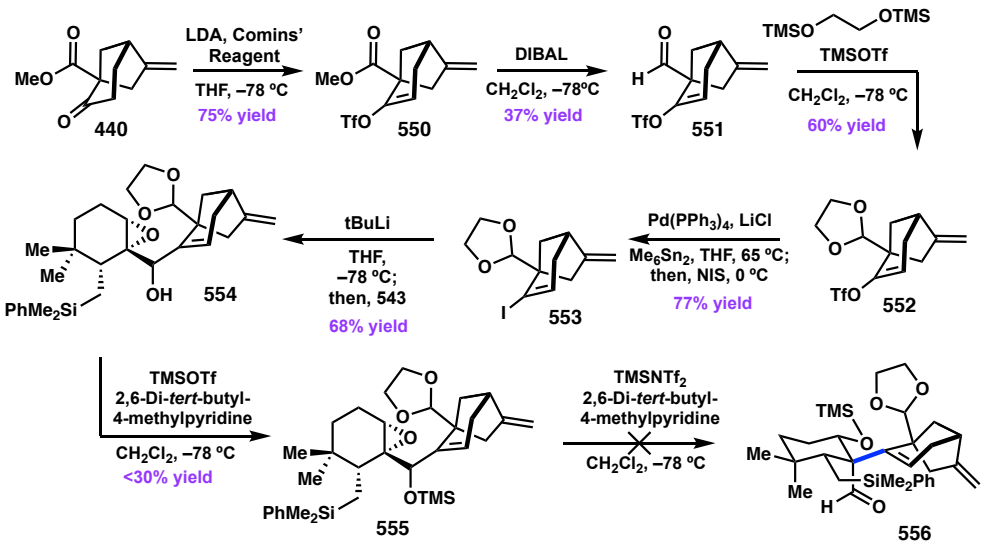


5.2.4 Semi-Pinacol Rearrangement of a [3.2.1]-bicycle.

Pleased that we could migrate a more complex alkene, we turned our attention toward applying these addition/migration conditions on a substrate that could be elaborated to **301**. Starting from **440**, which could be accessed as a single enantiomer through chiral preparative HPLC, we could form the corresponding enol triflate **550** under canonical conditions (Scheme **5.10**). From here, treatment with one equivalent of DIBAL at –78 ºC allowed us to access serviceable quantities of aldehyde **551**. While this reaction was not particularly high yielding, we felt that we could explore additional reduction conditions or a two-step protocol to access substantial quantities of the aldehyde **551**. From here,

protection of the aldehyde as its cyclic acetal followed by Stille cross-coupling with hexamethylditin and a subsequent iodination delivered **553**, which was poised to undergo 1,2-addition into our aldehyde.

Scheme 5.10 *First attempts to install and migrate a [3.2.1]-bicycle.*

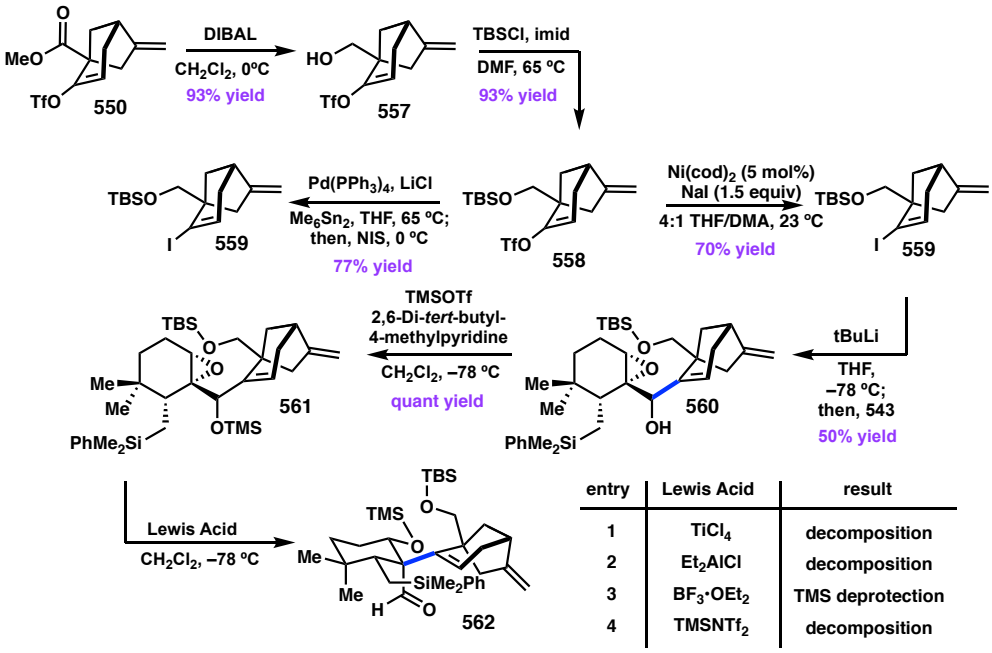


With **553** in hand, we found that 1,2-addition provided a single diastereomer of epoxy alcohol **554**, but unfortunately, treatment with the conditions that had worked on the model system only delivered low yields of TMS protected alcohol **555**. Disappointingly, treatment of **555** with $TMSNTf_2$, a stronger Lewis acid, solely resulted in decomposition. We hypothesized that the lability of the acetal protecting group was playing a role in the unwanted reactivity we observed, and so we devised a synthesis of a compound we felt would be a more robust substrate.

From **550**, we were pleased to see that treatment with three equivalents of DIBAL, this time at 0ºC delivered excellent yields of alcohol **557**, which could be silylated to give

558 (Scheme **5.11**). We hypothesized that a silyl protected alcohol **558** would be more stable under the strongly Lewis acidic conditions we knew were required to migrate large groups. From **558**, an analogous Stille reaction delivered **559**.

Scheme 5.11 *Preparation and migration of a more robust bicycle*



At this point, we had been using significant amounts of toxic hexamethylditin to convert the enol triflate (**558**) to the corresponding alkenyl iodide (**559**), and we were interested in finding a workaround that would obviate the need to use stoichiometric tin, especially on scale. With the help of Kelsey Poremba, a graduate student in the Reisman lab, we were pleased to see that under nickel catalysis, we could achieve a tin-free iodination of **558**, under very mild conditions. With iodide **559** in hand, we were then poised to investigate the key 1,2-addition/migration sequence that we had been hoping to explore. While the 1,2-addition worked well to deliver a single diastereomer of **560**,

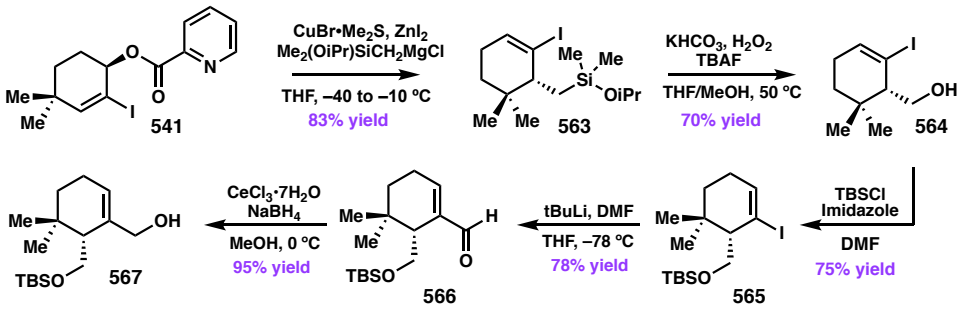
treatment with TMSOTf and 2,6-Di-*tert*-butyl-4-methylpyridine solely delivered TMS protected alcohol **561**. Further treatment of **561** with other Lewis acids provided us with either decomposition or TMS deprotection.

We hypothesized that our inability to migrate a [3.2.1]-bicyclooctane was due to the steric bulk of the adjacent silyl group. We wondered if the bulk of this group, combined with the increased bulk from the larger bicycle, limited the conformational flexibility of the cyclohexene oxide, making the necessary reactive conformation inaccessible. With this in mind, we turned our attention toward the modification of this group.

5.2.5 A Second Generation Epoxy Aldehyde

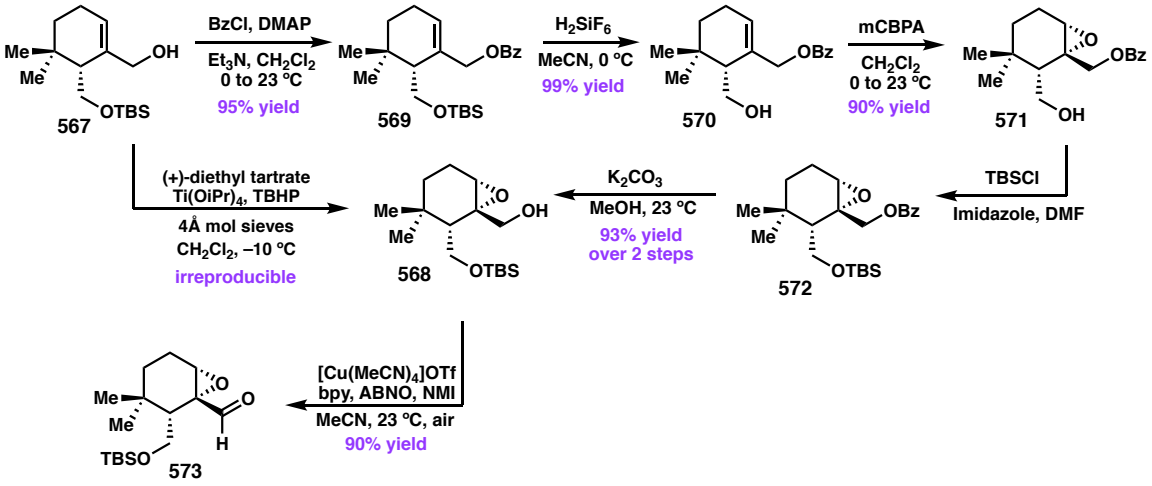
While we had initially hoped to use a Tamao-Fleming oxidation of **543** to install the necessary oxidation and modify the steric profile of the adjacent group, our attempts to functionalize the silane were unsuccessful (not shown), so we had to return to our picolinamide substrate **541** and identify a new cross-coupling partner that could enable more facile incorporation of an alcohol at this position.

Scheme 5.12 *Route to allylic alcohol* ***567****.*



Looking into the literature, it became clear that a silyl group with a hydrogen or an alkoxy group bound would be much more easily oxidized than the dimethylphenylsilyl group we had installed through the S_N2' chemistry.[13,14] From **541**, we found that we could install the more easily oxidizable silyl group and then subsequently perform a Tamao oxidation to deliver vinyl iodide **564** (Scheme **5.12**).[15,18–20] At this point, silylation of the primary alcohol, followed by formylation with DMF delivered **566**. Unfortunately, attempts to epoxidize **566** directly were met with poor levels of diastereoselectivity (not shown), so we advanced enal **566** through a Luche reduction to provide allylic alcohol **567**, which we planned to use as a substrate in a Sharpless epoxidation to access a single epoxide diastereomer.

Scheme 5.13 *Synthesis of epoxy aldehyde* ***573***.

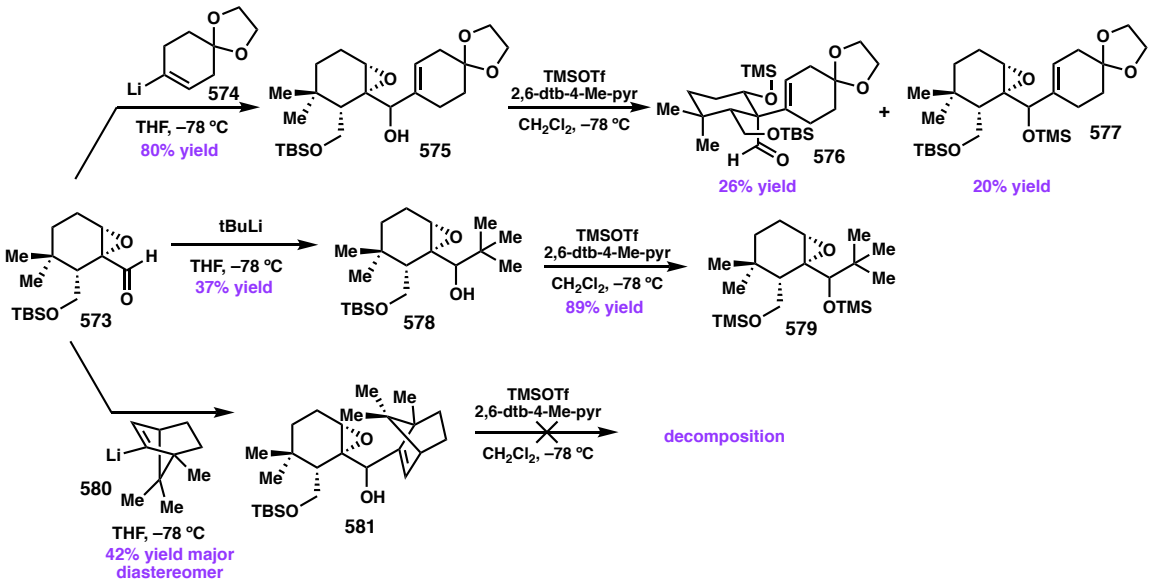


Unfortunately, subjection of **567** to standard Sharpless conditions provided inconsistent results. We found this reaction to be particularly capricious, and we found it very difficult to strike a balance between reaction temperatures that would give good

conversion and reaction temperatures that would give high levels of selectivity. In the interest in developing a scalable route to **568**, we elected to pursue a more lengthy sequence that would circumvent this persnickety reaction.

Allylic alcohol **567** could be treated with benzoyl chloride to access benzoate **569**, at which point the silyl group could be removed through treatment with H_2SiF_6. The free alcohol (**570**) could then direct an epoxidation to give **571**. This epoxy alcohol **571** could then be resilylated under standard conditions and the benzoyl group cleaved to give **568**. While this is a particularly lengthy sequence, each of the reactions proceeded in excellent yields and enabled a scalable synthesis of **568**, which could be subsequently oxidized to the corresponding epoxy aldehyde **573** under Stahl conditions.

Scheme 5.14 *Model 1,2-addition/migration sequences with epoxy aldehyde* ***573***.



With aldehyde **573** in hand, we turned our attention toward investigating the feasibility of an addition/migration sequence to set the all-carbon quaternary center. While

the 1,2-additions smoothly provided epoxy alcohols **575**, **578**, and **581**, we observed different outcomes in the semi-Pinacol step. Treatment of **575** under the TMSOTf conditions delivered a mixture of the migration product **576** and TMS protection product **577**. Interestingly, treatment of the *t*-Bu addition product under the same conditions delivered solely the TMS protection product. With a bicyclic adduct, we observed complete decomposition of **581**.

With these results, we remain interested in exploring the synthesis of [3.2.1]-bicyclooctane adducts that could undergo a semi-Pinacol rearrangement to assemble the core of **301**. In doing so, we hope to improve our synthesis of **559** to obviate the need for a preparative HPLC separation, and we feel that this investigation will enable development of catalytic reactions to assemble complex [3.2.1]-bicyclooctane structures. We are eager to explore additional Lewis acids as well as alternative additives that could promote the desired 1,2-migration with a more sterically encumbered system.

5.3 SECOND GENERATION SEMI-PINACOL STRATEGY

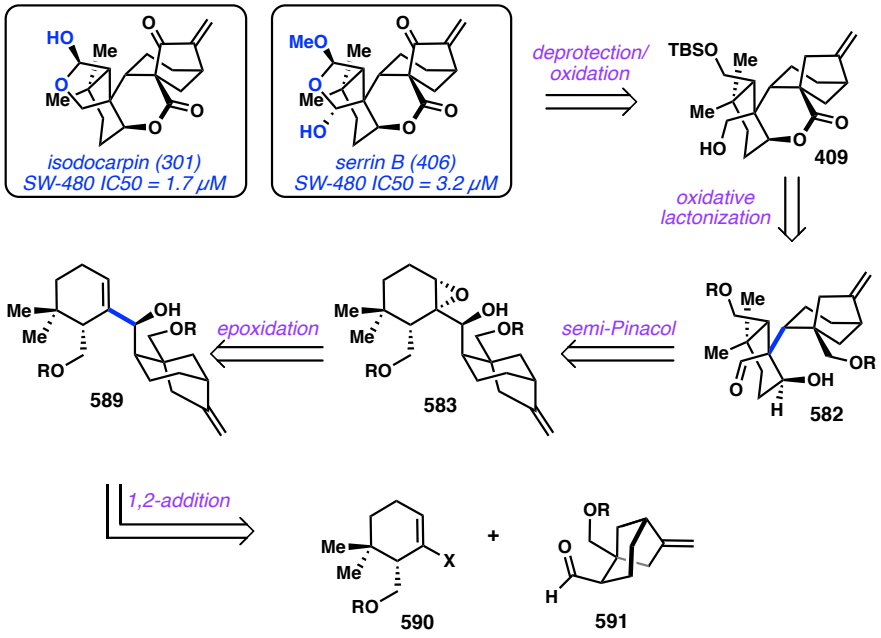
5.3.1 Retrosynthetic Analysis

While we had learned quite a bit about the migration of alkenyl groups to generate all-carbon quaternary centers through a type III semi-Pinacol rearrangement, our inability to migrate the fragment necessary for elaboration to **301** and our difficulties associated with the synthesis of a bicyclic fragment warranted a retooling of our synthetic strategy.

We wondered if we might have more success migrating a secondary alkyl group rather than an alkenyl group, and in doing so, identify a more direct route to synthesize a

bicyclic fragment. We felt we could use a similar end-game strategy to access **301** and **406** from lactone **409** (Scheme **5.15**). We felt that we could prepare lactone **409** through an oxidation/lactonization sequence from **582**, a key intermediate that contains two all-carbon quaternary centers. In **582**, the key bond shown in blue could be forged through a type III semi-Pinacol rearrangement from epoxy alcohol **583**, where the secondary alkyl group migrates to set the all-carbon quaternary center. This could be simplified to allylic alcohol **589**, which we hoped to forge through a 1,2-addition reaction between **590** and aldehyde **591**.

Scheme 5.15 *A second generation retrosynthesis of* ***301*** *and* ***406****.*



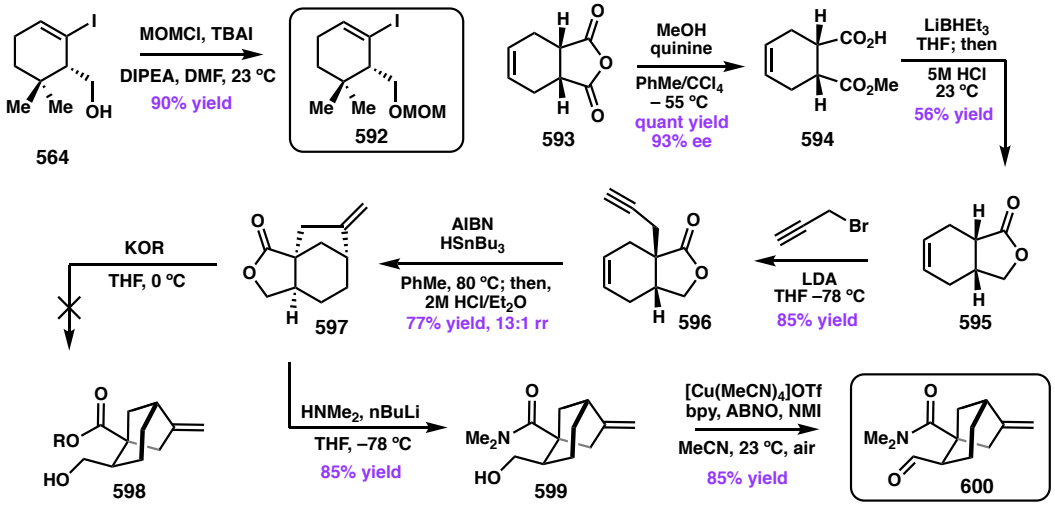
5.3.2 Fragment Synthesis

We were pleased to see that we could readily access **592** from **564**, which we had developed for our first generation route to **301** (Scheme **5.16**). For the bicyclic aldehyde

fragment, our synthesis commenced from meso anhydride **593**. A desymmetrization mediated by a cinchona alkaloid delivered half-ester **594**, which could be reduced and lactonized to give **595**, with high levels of enantioselectivity achieved in the desymmetrization step.[21] Bicyclic lactone could be propargylated to give a single diastereomer of **596**.[22] Through modification of a known procedure, we found that we could achieve high levels of selectivity for the [3.2.1]-bicyclooctane (**597**).[23] Key to the success of this strategy is the use of a bicyclic substrate—hydrolysis of the lactone prior to radical cyclization was reported to deliver significant amounts of the undesired [2.2.2]-bicyclooctane.

With the tricyclic lactone **597** in hand, we turned our attention toward the opening of the lactone. Unfortunately using a variety of alcohol nucleophiles delivered low levels of the ring opening product (**598**)—any conversion we observed seemed to be reversible and we were unable to isolate any of the hydroxy ester products. We were aware that the opening of the gamma lactone would be difficult, but we were pleased to see that lactone aminolysis delivered **599** in excellent yield.[24] While we had hoped to open the lactone to access an ester product, we were satisfied that we could get to **599**, which was in the correct oxidation state for elaboration to **301**. With **599** in hand, we found that we could use Stahl oxidation conditions to provide our key aldehyde **600**. We were concerned that we might observe epimerization to the equatorially disposed aldehyde, but it appeared that **600** was stable, so we turned our attention toward investigation of the 1,2-addition between **592** and **600**.

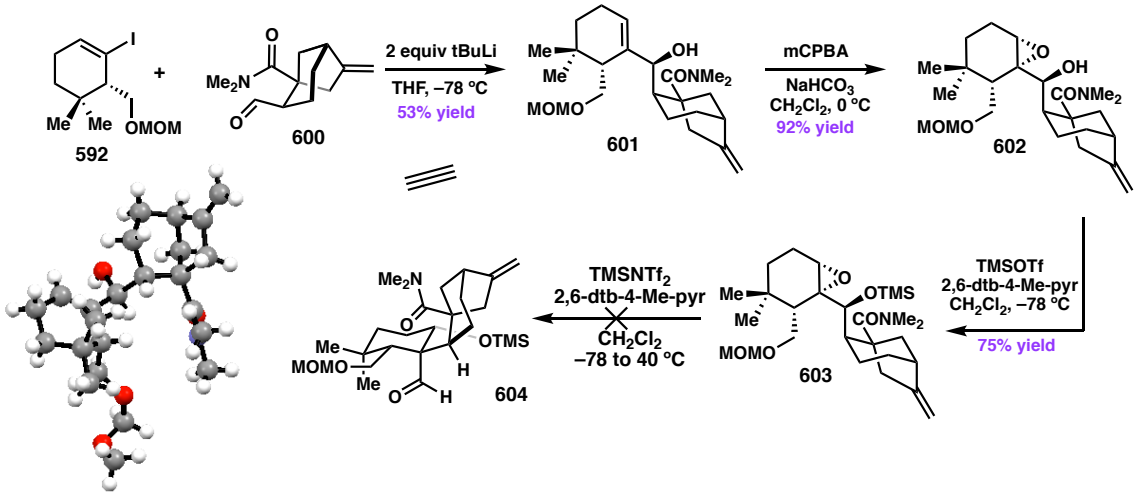
Scheme 5.16 *Synthesis of vinyl iodide* ***592*** *and aldehyde* ***600***



5.3.3 Convergent Union of a Vinyl Iodide and Bicyclic Aldehyde

Using the conditions we had previously employed for the lithiation of vinyl iodides enabled clean addition to the bicyclic aldehyde, delivering **601** as a single diastereomer (Scheme **5.17**). We were delighted to see that we could and confirm both the connectivity and stereochemistry of **601** through single crystal X-ray diffraction. This was particularly exciting, as the diastereomer formed through the 1,2-addition was the correct one needed for elaboration to the correct epoxide diastereomer. Treatment of **601** with mCPBA provided a single diastereomer of **602**, reacting through the lower-energy $A_{1,3}$-minimized conformer. With a single diastereomer of **602**, we were eager to begin exploring the feasibility of setting the all-carbon quaternary center through the envisioned semi-Pinacol rearrangement.

Scheme 5.17 *Initial 1,2-addition and semi-Pinacol results*

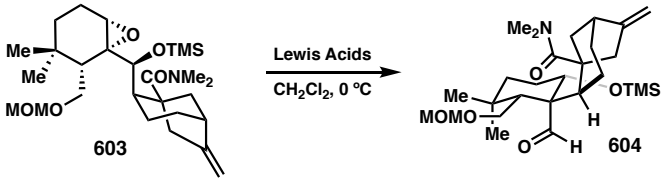


Unfortunately, treatment of **602** with TMSOTf only delivered the TMS protection product **603**. Treatment with the stronger Lewis acid solely delivered decomposition products. With a significant amount of **603** in hand, we wanted to conduct a thorough investigation of additional Lewis acids that could be used to carry out this transformation.

We began exploring a variety of Lewis acids that had previously been employed in the successful implementation of semi-Pinacol rearrangements in the literature (Table **5.1**).[1–4,25,26] Unfortunately, we had difficulty tuning the desired reactivity of the Lewis acids. Several of the Lewis acids we explored were too reactive, providing substantial decomposition (entries 1–2, 5, 11–12), while the other ones we explored only delivered recovered starting material. We hypothesized that the amide present in **603** may be intervening, enabling significant decomposition through known reactivity of amides with strong Lewis acids.[27–32] In the cases where we were only able to recover starting material, we hypothesized that the amide was sopping up the Lewis acid, preventing epoxide

activation, so we turned our attention toward the preparation of a substrate lacking a Lewis basic amide.

Table 5.1. *Screening of Lewis acids for the key semi-Pinacol rearrangement.*

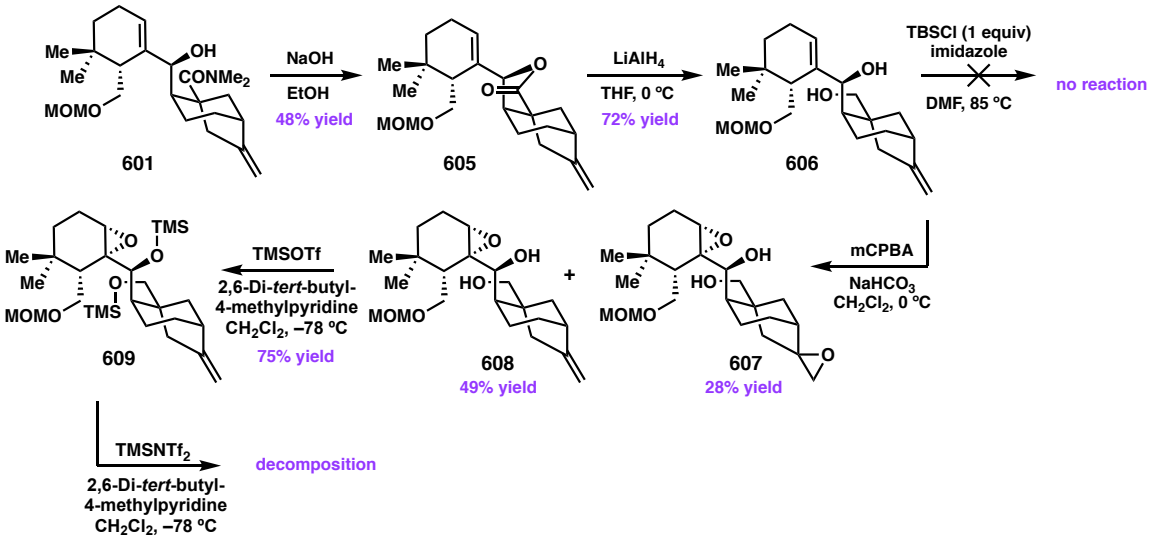


Entry	Scale	Lewis Acid	LA equiv	result
1	5 mg	$TiCl_4$	3	Decomp at 0 °C
2	5 mg	$SnCl_4$	3	Decomp at 0 °C
3	5 mg	$AlMe_3$	3	SM
4	5 mg	$Yb(OTf)_3$	3	SM
5	5 mg	HBF_4OEt_2	3	Decomp at 0 °C
6	5 mg	Et_3OBF_4	3	SM
7	5 mg	$MgBr_2$	3	SM
8	5 mg	$TiCl(OiPr)_3$	3	SM
9	5 mg	Et_2AlCl	3	SM
10	5 mg	$Zn(OTf)_2$	3	SM
11	5 mg	$BF_3{\cdot}OEt_2$	3	Decomp at 0 °C
12	5 mg	$Sc(OTf)_3$	3	Decomp at 0 °C

5.3.4 Synthesis of a Less Lewis Basic Substrate

In order to eliminate some of the issues we hypothesized were keeping us from successfully employing a semi-Pinacol rearrangement of **603**, we turned our attention toward the preparation of a substrate where some of these issues would be mitigated. We hoped to move away from a strongly Lewis basic amide and instead were interested in using a substrate with a silyl protecting group instead. In doing so, we hoped that we could still use our synthetic route to **601** and some of the knowledge we had gained in our previous chemistry.

Scheme 5.18 *Synthesis of a Diol Substrate*

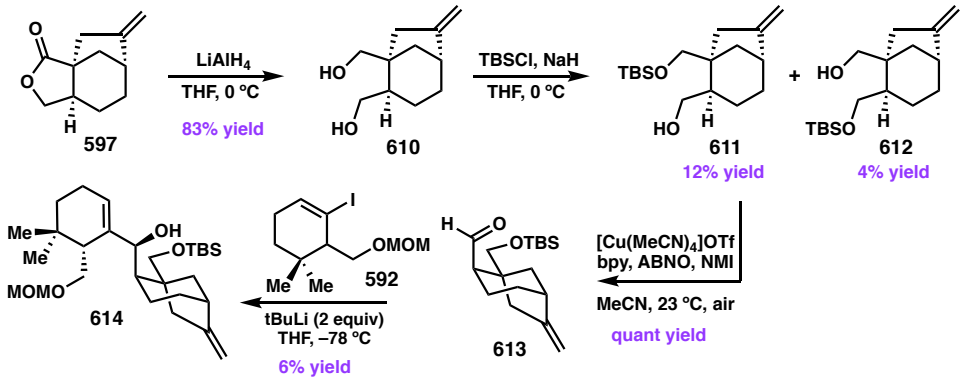


We found that treatment of **601** with NaOH in EtOH smoothly delivered lactone **605** (Scheme **5.18**). Treatment of **605** with $LiAlH_4$ delivered diol **606**. While this compound was no longer in the correct oxidation state needed for elaboration to **301**, we felt that this compound would be less problematic in the semi-Pinacol rearrangement. From **606**, silylation proved difficult, so we elected to perform an epoxidation at this stage. While we observed some over epoxidation, we could access some of the desired product upon treatment of **606** with mCPBA. Unfortunately treatment of **608** with TMSOTf resulted in low yields of **609**, and any attempts to migrate **609** under more forcing conditions solely resulted in decomposition.

We looked at trying to perform an earlier reduction. From bicyclic lactone **597**, treatment with $LiAlH_4$ delivered diol **610** (Scheme **5.19**). We were interested in discriminating between the two primary alcohols as had been previously reported;[22]

however, in our hands we observed poor selectivity for the desired product (**611**) and found it was nearly impossible to separate the two isomers. While we could obtain small quantities of the neopentyl alcohol protection product and could cleanly oxidize the remaining alcohol to the corresponding aldehyde **613**, 1,2-addition into this aldehyde proved capricious and we were unable to advance this material any further.

Scheme 5.19 *Diol Desymmetrization Strategy*



5.4 CONCLUDING REMARKS

While we have had trouble identifying conditions to enable smooth semi-Pinacol rearrangement in either the unsaturated or the saturated systems, we have learned quite a bit about the preparation of these complex fragments and how to bring them together in a robust manner. We have developed some elegant chemistry and have identified scalable approaches to both of the fragments in each iteration of our strategy. Future efforts should focus on deeper exploration of the alkenyl migration, as it seems that the preliminary results on the alkenyl model systems are more promising. Should a semi-Pinacol approach not be

realized successfully, it would be prudent to investigate other means of assembling all-carbon quaternary centers through transition-metal cross coupling.

5.5 EXPERIMENTAL DATA

5.5.1 Materials and Methods

General Procedures. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), *tert*-butyl methyl ether (TBME), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N), N,N-diisopropylethylamine (DIPEA), and methanol (MeOH) were distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, $KMnO_4$, or CAM staining. Flash column chromatography was performed either as described by Still et al.[33] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz respectively), a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150

MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.1), C_6H_5 (^1H, δ = 7.16) and C_6D_6 (^{13}C, δ = 128), or d_8-THF (^1H, δ = 3.58) and (^{13}C, δ = 67.6). 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, or obtained from the Caltech Mass Spectral Facility in fast-atom bombardment mode (FAB). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm).

5.5.2 General Procedures

General Procedure 1: 1,2-addition

A flame-dried flask was charged with alkenyl iodide (1 equiv) and evacuated and back-filled with N_2 three times. The flask was charged with THF (0.1 M) and the flask was cooled to –78 ºC, at which point, *t*-BuLi (2 equiv) was added dropwise and stirred for fivec minutes. A separate flask was charged with aldehyde (1 equiv) and evacuated and back-filled with N_2 three times. The aldehyde was dissolved in THF (0.1 M) and cooled to –78 ºC. The alkenyl lithium reagent was transferred to the aldehyde solution and the reaction

was allowed to stir for 10 minutes at –78 ºC, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$. The aqueous layer was extracted with Et_2O three times, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude residue that was purified by silica gel chromatography.

General Procedure 2: Semi-Pinacol Rearrangement

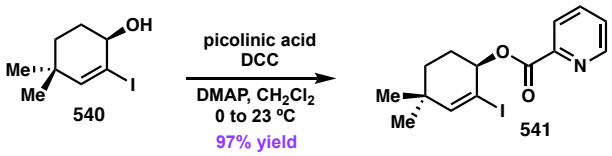
A flame-dried flask was charged with epoxy alcohol (1 equiv) and azeotroped with PhMe three times. The flask was then charged with 2,6-di-*tert*-butyl-4-methylpyridine (3 equiv) and evacuated and backfilled with N_2 three times. The solids were dissolved in CH_2Cl_2 (0.1 M) and the reaction mixture was cooled to –78 ºC. TMSOTf (2 equiv) was added as a solution in CH_2Cl_2 dropwise, and the reaction was stirred for 30 minutes at –78 ºC. The reaction was then quenched upon addition of saturated $NaHCO_{3\ (aq)}$. The mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organics were dried over Na_2SO_4 and concentrated in vacuo. The resulting crude residue was purified by silica gel chromatography.

General Procedure 3: Stille Iodination

A pressure flask was charged with enol triflate (1 equiv) then pumped into a N_2-filled glovebox. The flask was charged with LiCl (6 equiv), $Pd(PPh_3)_4$ (0.05 equiv), and THF (0.1 M). Then hexamethylditin (1 equiv) was added as a liquid directly. The flask was sealed and removed from the box. The flask was heated in an oil bath at 65 ºC for 16 hours,

at which point the flask was cooled to 0 ºC over 30 min. The flask was opened, and NIS (1.3 equiv) was added in one portion. The reaction was allowed to stir at 0 ºC for 2 hours, at which point the solvent was removed *in vacuo*. The residue was suspended in MeOH (0.2 M) and Et_2O (0.2 M). KF (5 equiv) was then added. The mixture was allowed to stir at room temperature for 4 hours, at which point the reaction mixture was filtered over a pad of Celite, eluting with Et_2O. The solvent was removed *in vacuo*, and the crude residue was purified by column chromatography.

5.5.3 Preparative Procedures and Spectroscopic Data



A flame-dried 200 mL round bottom flask was charged with 2-picolinic acid (3.22 g, 26.2 mmol, 1.1 equiv). The acid was dissolved in CH_2Cl_2 (60 mL) and the flask was cooled to 0 ºC with an ice bath. DCC (6.38 g, 30.9 mmol, 1.3 equiv) was added as a solid in one portion, followed by DMAP (1.45 g, 11.9 mmol, 0.5 equiv). The cloudy mixture stirred at 0 ºC for 30 min, at which point **540** (6.0 g, 23.8 mmol, 1 equiv) was added as a solution in CH_2Cl_2 (40 mL) dropwise via cannula over 1 hour. Once the addition was complete, the reaction was allowed to stir at 0 ºC for an additional 20 minutes. The reaction was then warmed to room temperature and stirred at 23 ºC for 4 hours, at which point TLC indicated that the reaction was complete. The suspension was filtered over a pad of celite, eluting with 300 mL of CH_2Cl_2. The solvent was removed *in vacuo* and the crude residue

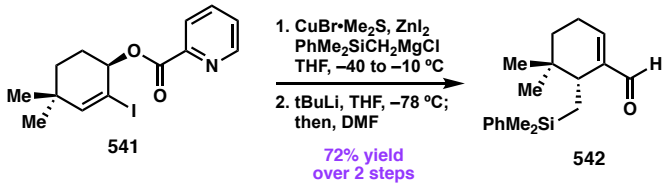
purified by column chromatography using silica gel (20% EtOAc/hexanes → 30% EtOAc/hexanes→ 40% EtOAc/hexanes) to give **541** (8.24 g, 97% yield) as an amorphous, colorless solid.

$\mathbf{R_f}$ = 0.30 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.85 (td, *J* = 7.7, 1.8 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 6.44 (d, *J* = 1.0 Hz, 1H), 5.63 (td, *J* = 5.3, 1.1 Hz, 1H), 2.20 (dddd, *J* = 14.1, 9.9, 5.1, 3.5 Hz, 1H), 2.03 (dddd, *J* = 14.1, 8.1, 5.3, 3.3 Hz, 1H), 1.68 (ddd, *J* = 13.3, 9.9, 3.3 Hz, 1H), 1.62 – 1.51 (m, 1H), 1.09 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.4, 153.4, 150.3, 148.2, 137.1, 127.0, 125.5, 93.8, 74.9, 37.4, 32.4, 28.9, 28.0, 27.1.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{16}INO_2$ $[M+H]^+$: 358.0298; found: 358.0298.



Procedure for Grignard formation:

A 250 mL round-bottom flask was charged with magnesium turnings (851 mg, 35 mmol, 6.2 equiv). The charged flask was briefly flame-dried under vacuum (1 minute or less), and allowed to cool to room temperature under vacuum. The dried magnesium was allowed to stir at 800 rpm under vacuum for one hour. The flask was then backfilled with

THF (8 mL). Chloromethylphenyldimethylsilane (4.5 mL, 25 mmol, 4.4 equiv) was added in one portion via syringe. The suspension was heated with a heat gun until the reaction began to initiate (indicated by vigorous bubbling), at which point a second portion of THF (8.7 mL) was added and the flask was submerged in an oil bath at 90 ºC. The reaction was heated at reflux for 90 minutes, at which point the flask was removed from the oil bath and cooled to room temperature. The Grignard reagent was titrated against 2-hydroxybenzaldehyde phenylhydrazone in triplicate to yield a final concentration of 1.176 M (78% yield).

A separate 100 mL round-bottom flask was pumped into a N_2-filled glovebox, where it was charged with CuBr•Me_2S (1.75 g, 8.53 mmol, 1.5 equiv) and ZnI_2 (2.73 g, 8.53 mmol, 1.5 equiv). The flask was sealed with a septum and removed from the glovebox. The flask was then charged with THF (28.5 mL) and cooled to 0 ºC. The flask was charged with freshly prepared dimethylphenylsilylmethylmagnesium chloride (see above) (14.5 mL, 17 mmol, 1.176 M, 3 equiv) via cannula. This mixture stirred for 30 minutes at 0 ºC and was then cooled to –40 ºC in a dry ice/acetone bath. Iodopicolonate **541** (2.03 g, 5.68 mmol, 1 equiv) was then added as a solution in THF (28.5 mL) via cannula. The reaction was allowed to gradually warm to –10 ºC over 90 minutes, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$ solution (30 mL). The mixture was warmed to room temperature and diluted with water (30 mL) and pentane (100 mL). The aqueous layer was extracted with pentane (3 x 100 mL), and the combined organics were then washed with saturated $NH_4Cl_{(aq)}$ solution (3 x 100 mL), water (2 x 100 mL), and brine

(100 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude residue which was taken forward without any purification.

A 100 mL round-bottom flask was charged with the crude mixture and the flask was evacuated and back-filled with N_2 three times. The residue was dissolved in THF (28.5 mL) and the flask was cooled to –78 ºC. Then *t*-BuLi (6.7 mL, 1.7M, 11.4 mmol) was added via syringe fast dropwise. The mixture immediately became bright yellow. After stirring for 5 minutes, dry DMF (3.5 mL, 45.5 mmol, 8 equiv) was added. The reaction stirred at this temperature for 10 minutes, at which point the reaction mixture was poured into a 250 mL conical flask containing a mixture of KH_2PO_4 (4.64 g, 34.1 mmol, 6 equiv) in Et_2O (45.5 mL) and water (45.5 mL) at 0 ºC. This biphasic mixture was stirred for five minutes, at which point the mixture was poured into a separatory funnel. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 2.5% EtOAc/hexanes→ 5% EtOAc/hexanes→7.5% EtOAc/hexanes) to give **542** (1.17 g, 72% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.66 (silica gel, 10% EtOAc/Hex, UV and p-anisaldehyde).

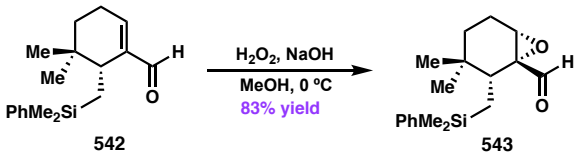
$\mathbf{[\alpha]_D^{25}}$ = +95.5° (c = 0.44, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 7.51 – 7.47 (m, 2H), 7.34 – 7.30 (m, 3H), 6.51 (t, *J* = 3.8 Hz, 1H), 2.42 (dtd, *J* = 8.0, 3.4, 1.6 Hz, 1H), 2.37 – 2.25 (m, 2H), 1.76 – 1.65 (m, 1H), 1.23 – 1.16 (m, 1H), 1.09 – 0.99 (m, 1H), 0.90 (s, 3H), 0.74 (s, 3H), 0.57 (dd, *J* = 15.0, 7.8 Hz, 1H), 0.35 – 0.31 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.2, 149.0, 148.0, 133.9, 128.7, 127.7, 127.6, 36.6, 32.3, 29.6, 28.5, 26.2, 24.7, 19.8, -1.6, -2.2.

FTIR (NaCl, thin film, cm^{-1}): 3720, 2953, 2913, 2352, 1682, 1424, 1248, 1112, 834, 818, 700.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{18}H_{30}NOSi$ $[M+NH_4]^+$: 304.2091; found: 304.2090.



A 25 mL round-bottom flask was charged with enal **542** (286 mg, 1.0 mmol, 1 equiv) and dissolved in MeOH (10 mL). The flask was cooled to 0ºC and NaOH (50 µL, 0.3 mmol, 6M, 0.3 equiv) was added. Hydrogen peroxide (134 µL, 1.3 mmol, 30 wt%, 1.3 equiv) was added and the reaction was allowed to stir for 2.5 hours at this temperature. The reaction was quenched with the addition of saturated $Na_2S_2O_{3\ (aq)}$ solution (5 mL). The mixture was diluted with water (5 mL) and then extracted with Et_2O (5 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 5% EtOAc/hexanes) to give **543** (259.6 mg, 86% yield) as a pale yellow solid.

R_f = 0.66 (silica gel, 10% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{25}$ = +2.7° (c = 1.8, $CHCl_3$).

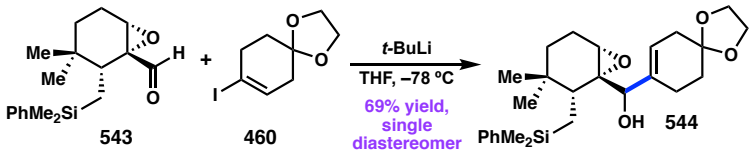
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.52 – 7.47 (m, 2H), 7.36 – 7.32 (m, 3H), 3.28 (dd, *J* = 2.7, 1.1 Hz, 1H), 2.41 (ddd, *J* = 12.2, 2.5, 1.7 Hz, 1H), 2.04 (ddt, *J* = 15.7,

5.7, 1.5 Hz, 1H), 1.89 – 1.75 (m, 1H), 1.39 (dt, *J* = 13.0, 6.7 Hz, 1H), 0.97 – 0.84 (m, 3H), 0.84 (s, 3H), 0.78 (s, 3H), 0.28 (s, 3H), 0.25 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.7, 138.9, 134.1, 129.0, 127.7, 65.3, 57.7, 33.8, 31.0, 27.8, 26.7, 26.6, 21.4, 12.9, -2.0, -2.9.

FTIR (NaCl, thin film, cm^{-1}): 2956, 1725, 1427, 1249, 1172, 1113, 881, 839, 814, 794, 729, 700.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{18}H_{30}O_2SiN$ $[M+NH_4]^+$: 320.2040; found: 320.2033.



544 was prepared according to general procedure 1 using **543** (15.0 mg, 0.05 mmol) and **470** (13.2 mg, 0.05 mmol) and purified using silica gel (20% EtOAc/hexanes isocratic) to give **542** (15.1 mg, 69% yield) as a colorless oil.

R_f = 0.38 (silica gel, 40% EtOAc/Hex, p-anisaldehyde).

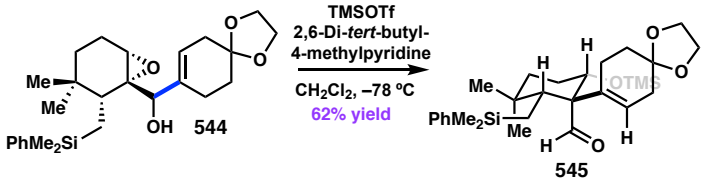
$[\alpha]_D^{25}$ = +22.1° (c = 0.27, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.49 (m, 2H), 7.42 – 7.29 (m, 3H), 5.51 (tq, *J* = 3.2, 1.4 Hz, 1H), 4.05 – 3.89 (m, 4H), 3.64 (d, *J* = 2.9 Hz, 1H), 3.16 (t, *J* = 1.9 Hz, 1H), 2.26 (dq, *J* = 4.1, 1.8 Hz, 2H), 2.06 – 1.85 (m, 3H), 1.84 – 1.63 (m, 3H), 1.61 – 1.54 (m, 1H), 1.52 (d, *J* = 3.6 Hz, 1H), 1.36 (td, *J* = 12.9, 5.7 Hz, 1H), 1.11 (dd, *J* = 16.0, 3.8 Hz, 1H), 0.82 (dd, *J* = 16.0, 7.0 Hz, 1H), 0.75 (s, 3H), 0.71 (s, 3H), 0.35 (s, 3H), 0.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.5, 136.5, 134.0, 128.8, 127.8, 120.3, 108.0, 79.1, 65.4, 64.5, 58.5, 37.1, 35.5, 31.3, 31.0, 28.5, 27.1, 27.1, 26.4, 21.8, 14.0, -1.2, -1.2.

FTIR (NaCl, thin film, cm^{-1}): 3442, 2928, 2363, 1428, 1366, 1247, 1112, 1060, 938, 907, 833, 824, 732, 699.

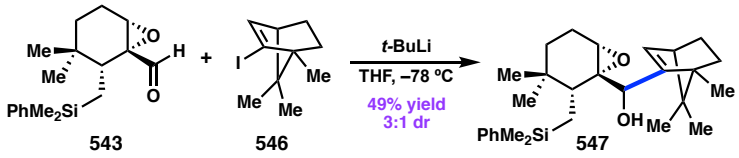
HRMS (ESI-TOF, *m/z*): calc'd for $C_{26}H_{42}NO_4Si$ $[M+NH_4]^+$: 460.2878; found: 460.2865.



545 was prepared according to general procedure 2 using **544** (13 mg, 0.03 mmol) and purified using silica gel neutralized with NH_4OH (2% EtOAc/hexanes → 3% EtOAc/hexanes→ 4% EtOAc/hexanes) to give **545** (9.3 mg, 62% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.58 – 7.47 (m, 2H), 7.32 (dp, *J* = 5.7, 1.5 Hz, 3H), 5.26 (d, *J* = 3.7 Hz, 1H), 3.94 (q, *J* = 1.2 Hz, 4H), 3.70 (d, *J* = 6.7 Hz, 1H), 2.30 – 2.19 (m, 3H), 2.06 (q, *J* = 7.5, 6.9 Hz, 1H), 1.91 – 1.55 (m, 5H), 1.43 (m, 2H), 1.31 (dd, *J* = 16.2, 1.8 Hz, 1H), 0.99 – 0.87 (m, 1H), 0.72 (s, 3H), 0.68 (s, 3H), 0.32 (s, 3H), 0.25 (s, 3H), 0.07 (s, 9H).

HRMS (ESI-TOF, *m/z*): calc'd for $C_{29}H_{47}O_4Si_2$ $[M+H]^+$: 515.3007; found: 515.2999.



547 was prepared according to general procedure 1 using **543** (30.2 mg, 0.1 mmol) and **546** (26.2 mg, 0.1 mmol) and purified using silica gel (hexanes → 5% EtOAc/hexanes→ 10% EtOAc/hexanes) to give **547** (21.6 mg, 49% yield as a 3:1 mixture of diastereomers) as a colorless solid.

$\mathbf{R_f}$ = 0.52 (silica gel, 10% EtOAc/Hex, p-anisaldehyde).

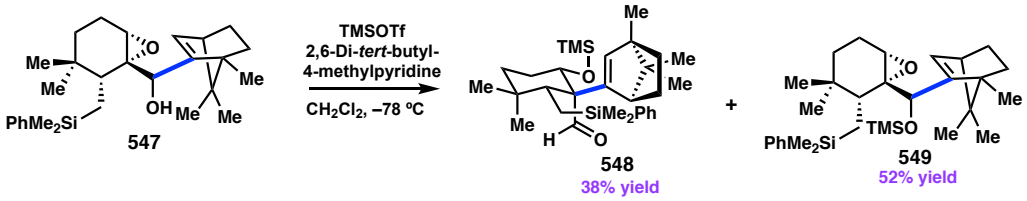
$\mathbf{[\alpha]_D^{23}}$ = +63.7° (c = 1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.52 (m, 2H), 7.35 (td, *J* = 5.0, 1.9 Hz, 3H), 5.73 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.80 (d, *J* = 1.2 Hz, 1H), 3.24 (d, *J* = 2.0 Hz, 1H), 2.25 (t, *J* = 3.4 Hz, 1H), 2.02 (ddd, *J* = 6.9, 3.0, 1.5 Hz, 1H), 1.88 (ddq, *J* = 17.1, 6.2, 1.9 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.45 – 1.30 (m, 3H), 1.29 – 1.24 (m, 1H), 1.03 (dd, *J* = 16.4, 3.1 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 3H), 0.85 – 0.76 (m, 1H), 0.74 (s, 3H), 0.70 (s, 3H), 0.70 (m, 1H) 0.68 (d, *J* = 2.2 Hz, 3H), 0.38 (d, *J* = 2.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5, 140.0, 134.0, 129.3, 129.1, 127.9, 86.6, 71.4, 66.2, 55.5, 55.4, 55.0, 51.8, 39.4, 32.2, 31.5, 28.1, 28.0, 27.0, 25.5, 21.8, 19.7, 19.7, 13.6, 12.2, -1.6, -1.9.

FTIR (NaCl, thin film, cm^{-1}): 3472, 3068, 2952, 2872, 2360, 2341, 1699, 1386, 1248, 1112, 836, 730, 701

HRMS (ESI-TOF, *m/z*): calc'd for $C_{28}H_{46}NO_2Si$ $[M+NH_4]^+$: 456.3292; found: 456.3297.



Compounds **548** and **549** were prepared according to general procedure 2, using epoxy alcohol **547** (18 mg, 0.04 mmol). The mixture was purified using silica gel (hexanes → 2% EtOAc/hexanes→ 4% EtOAc/hexanes) to provide a mixture of **548** (5.8 mg, 38% yield) and **549** (6.4 mg, 52% yield).

Characterization data for **548**:

R_f = 0.43 (silica gel, 5% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{23}$ = +6.6° (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.47 (ddd, *J* = 5.5, 4.1, 2.3 Hz, 2H), 7.31 (pd, *J* = 4.0, 3.6, 2.8 Hz, 3H), 5.70 (d, *J* = 3.6 Hz, 1H), 3.81 (t, *J* = 8.3 Hz, 1H), 2.16 (t, *J* = 3.6 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.91 – 1.83 (m, 2H), 1.74 – 1.64 (m, 1H), 1.48 – 1.39 (m, 4H), 0.94 (s, 3H), 0.89 (m, 1H), 0.79 (s, 3H), 0.72 (s, 3H), 0.70 (s, 3H), 0.64 (s, 3H), 0.34 (s, 3H), 0.21 (s, 3H), 0.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.6, 141.4, 133.9, 133.6, 128.6, 128.6, 127.8, 62.5, 58.0, 56.4, 51.1, 40.2, 36.0, 34.2, 32.9, 31.5, 30.5, 30.2, 27.6, 25.4, 22.8, 22.0, 20.9, 20.3, 14.5, 13.9, 1.4.

FTIR (NaCl, thin film, cm^{-1}): 2952, 2876, 1713, 1454, 1364, 1291, 1250, 1111, 1250, 1087, 1068, 838, 824, 674

HRMS (ESI-TOF, *m/z*): calc'd for $C_{31}H_{51}O_2Si_2$ $[M+H]^+$: 511.3422; found: 511.3430.

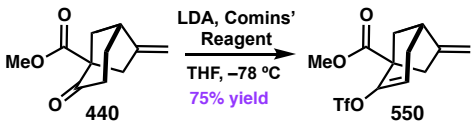
Characterization data for **549**:

$\mathbf{R_f}$ = 0.45 (silica gel, 5% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.49 (m, 2H), 7.34 (tt, *J* = 3.6, 2.3 Hz, 3H), 5.72 (dd, *J* = 3.2, 1.4 Hz, 1H), 4.19 – 4.12 (m, 1H), 3.24 (d, *J* = 1.9 Hz, 1H), 2.23 (t, *J* = 3.3 Hz, 1H), 1.90 – 1.71 (m, 4H), 1.50 – 1.42 (m, 1H), 1.40 – 1.29 (m, 2H), 1.12 (dd, *J* = 16.4, 2.1 Hz, 1H), 1.00 (s, 3H), 0.87 (m, 5H), 0.71 (d, *J* = 2.3 Hz, 6H), 0.66 (s, 3H), 0.38 (d, *J* = 3.0 Hz, 6H), 0.03 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8, 140.2, 133.8, 130.1, 128.9, 127.9, 73.4, 66.8, 56.2, 55.1, 54.9, 51.6, 40.7, 32.5, 31.5, 29.9, 28.6, 27.6, 27.4, 25.4, 21.7, 19.8, 19.7, 13.6, 12.7, 0.9, -0.9, -1.3.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{31}H_{51}O_2Si_2$ $[M+H]^+$: 511.3422; found: 511.3414.



A 2-dram vial was charged with **440** (19.4 mg, 0.1 mmol, 1 equiv). The vial was evacuated and back-filled with nitrogen three times. The ester was dissolved in THF (500 µL) and cooled to –78 ºC. Then a solution of freshly prepared LDA (160 µL, 1.2 equiv, 0.75M) was added dropwise. The reaction was stirred at this temperature for 30 minutes, at which point Comins' reagent (45.2 mg, 0.115 mmol, 1.15 equiv) was added as a solid in

one portion. After 4 hours, the reaction was warmed to room temperature and quenched by addition of water (2 mL). The mixture was diluted with saturated $NH_4Cl_{(aq)}$ (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were washed with 3M NaOH (10 mL), filtered through a plug of Na_2SO_4 and then concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 5% EtOAc/hexanes) to give **550** (23.7 mg, 73% yield) as an amorphous, colorless solid.

R_f = 0.67 (silica gel, 30% EtOAc/Hex, $KMnO_4$).

$[\alpha]_D^{22}$ = –1.3° (c = 1.0, $CHCl_3$).

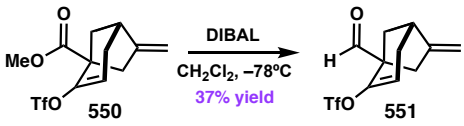
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (dd, *J* = 4.9, 2.7 Hz, 1H), 5.06 (p, *J* = 1.3 Hz, 1H), 5.04 – 5.01 (m, 1H), 3.77 (s, 3H), 3.09 – 2.93 (m, 2H), 2.88 (dt, *J* = 16.4, 2.9 Hz, 1H), 2.59 (ddd, *J* = 17.5, 4.3, 2.7 Hz, 1H), 2.25 – 2.04 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 151.9, 149.5, 118.5 (q, J_{C-F} = 320 Hz), 115.6, 109.5, 54.0, 52.6, 44.1, 41.1, 39.7, 34.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ –74.5

FTIR (NaCl, thin film, cm^{-1}): 2958, 1745, 1670, 1420, 1292, 1244, 1215, 1165, 1143, 1077, 1043, 888, 862, 605.

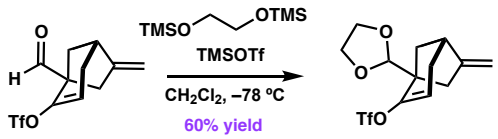
HRMS (ESI-TOF, *m/z*): calc'd for $C_{13}H_{16}F_3O_5S$ $[M+H]^+$: 327.0509; found: 327.0513.



A 25 mL round-bottom flask was charged with **550** (160 mg, 0.47 mmol, 1 equiv). The flask was evacuated and back-filled with N_2 three times, then charged with CH_2Cl_2 (4.7 mL, 0.1 M). The flask was cooled to –78 ºC, and DIBAL (84 µL, 0.47 mmol, 1 equiv) was added dropwise via syringe. The reaction stirred at –78 ºC for 20 minutes, at which point, the reaction was quenched with Rochelle's salt $_{(aq)}$ (5 mL) and warmed to room temperature. The mixture stirred vigorously for an hour, and then the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (3% EtOAc/hexanes → 20% EtOAc/hexanes) to give **551** (102 mg, 37% yield) as a colorless oil.

R_f = 0.68 (silica gel, 30% EtOAc/Hex, $KMnO_4$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.83 (d, *J* = 1.0 Hz, 1H), 5.73 (dd, *J* = 4.7, 2.8 Hz, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 3.04 (s, 1H), 2.92 (d, *J* = 16.2 Hz, 1H), 2.85 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.60 (dt, *J* = 17.7, 3.7 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.08 – 2.04 (m, 1H), 2.01 (dd, *J* = 10.9, 5.3 Hz, 1H).

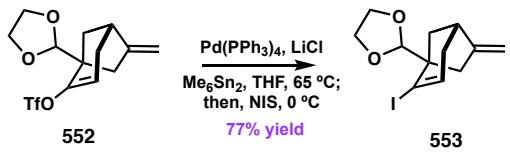


551 **552**

A 2-dram vial was charged with **551** (80 mg, 0.26 mmol, 1 equiv) and azeotroped with PhMe (3 x 1 mL). The vial was evacuated and back-filled three times with N_2. The vial was then charged with CH_2Cl_2 (2.25 mL), followed by 1,2-bistrimethysilyloxyethane (95 µL, 0.39 mmol, 1.5 equiv). The vial was cooled to –78 ºC, then TMSOTf (24 µL, 0.13 mmol) was added as a solution in CH_2Cl_2 (250 µL). The vial was allowed to warm to –20 ºC over the course of 2 hours, at which point the TLC showed complete conversion. The reaction was quenched with the addition of dry Hünig's base (500 µL). The crude mixture was concentrated *in vacuo*, and the crude residue was purified by column chromatography using silica gel (3% EtOAc/hexanes → 5% EtOAc/hexanes) to give **552** (28.1 mg, 44% yield) as a colorless oil.

R_f = 0.16 (silica gel, 5% EtOAc/Hex, $KMnO_4$).

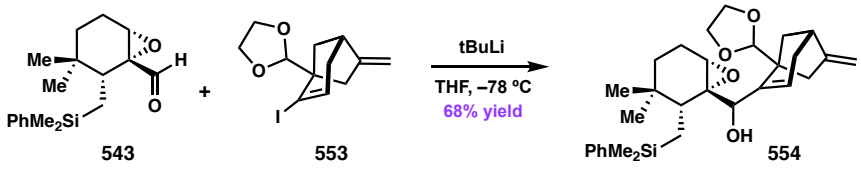
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.64 – 5.48 (m, 1H), 5.04 (dt, *J* = 2.8, 1.3 Hz, 1H), 5.01 (s, 1H), 5.00 – 4.97 (m, 1H), 4.11 – 4.06 (m, 1H), 3.98 (q, *J* = 6.8 Hz, 1H), 3.93 (td, *J* = 7.2, 5.1 Hz, 1H), 3.88 (q, *J* = 7.1 Hz, 1H), 2.96 – 2.87 (m, 2H), 2.56 – 2.49 (m, 2H), 2.17 – 2.07 (m, 1H), 1.98 (ddd, *J* = 10.9, 5.6, 1.1 Hz, 1H), 1.86 (dd, *J* = 10.9, 2.7 Hz, 1H).



Vinyl iodide **553** was prepared according to general procedure 3, using **552** (25 mg, 0.07 mmol, 1 equiv) as the substrate. The crude residue was purified by column chromatography using silica gel (2% EtOAc/hexanes → 3% EtOAc/hexanes) to give **553** (18.1 mg, 77% yield) as a colorless oil.

R_f = 0.23 (silica gel, 5% EtOAc/Hex, UV and p-anisaldehyde).

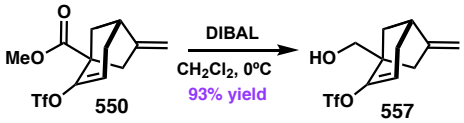
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.26 (ddd, *J* = 4.8, 2.5, 1.0 Hz, 1H), 5.11 (d, *J* = 0.7 Hz, 1H), 5.01 (ddt, *J* = 3.0, 2.0, 1.0 Hz, 1H), 4.94 (tp, *J* = 1.7, 0.8 Hz, 1H), 4.04 – 3.99 (m, 1H), 3.99 – 3.92 (m, 3H), 2.97 – 2.90 (m, 1H), 2.54 (ddd, *J* = 17.2, 4.3, 2.5 Hz, 1H), 2.50 (ddtd, *J* = 15.8, 2.7, 1.7, 1.0 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.06 (ddd, *J* = 11.0, 5.7, 1.6 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.88 (dd, *J* = 10.9, 2.5 Hz, 1H).



Epoxy alcohol **554** was prepared according to general procedure 1, using **543** (10 mg, 0.03 mmol) and **553** (11 mg, 0.03 mmol). The mixture was purified using silica gel (hexanes → 5% EtOAc/hexanes→ 10% EtOAc/hexanes) to provide **554** (11.6 mg, 69% yield).

R_f = 0.42 (silica gel, 15% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 – 7.51 (m, 2H), 7.36 – 7.29 (m, 3H), 5.71 (ddt, *J* = 4.5, 2.3, 1.0 Hz, 1H), 5.17 (s, 1H), 4.93 (ddt, *J* = 3.0, 2.0, 1.1 Hz, 1H), 4.83 (dq, *J* = 2.2, 1.3 Hz, 1H), 4.59 (d, *J* = 4.7 Hz, 1H), 3.88 – 3.81 (m, 2H), 3.76 – 3.71 (m, 1H), 3.71 – 3.65 (m, 1H), 3.30 (dd, *J* = 2.8, 1.4 Hz, 1H), 2.81 (d, *J* = 5.3 Hz, 1H), 2.53 (dt, *J* = 16.1, 2.7 Hz, 1H), 2.45 (dd, *J* = 16.1, 2.1 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.09 (ddd, *J* = 8.4, 2.3, 1.3 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.89 (ddt, *J* = 15.5, 5.6, 2.2 Hz, 1H), 1.77 (dddd, *J* = 15.5, 11.6, 6.3, 2.8 Hz, 1H), 1.45 – 1.40 (m, 1H), 1.18 – 1.11 (m, 1H), 0.92 – 0.84 (m, 1H), 0.83 (s, 3H), 0.80 – 0.71 (m, 1H), 0.67 (s, 3H), 0.37 (s, 2H), 0.36 (s, 2H).



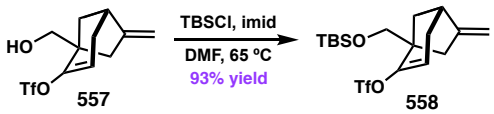
A 50 mL round-bottom flask was charged with **550** (400 mg, 1.18 mmol, 1 equiv). The flask was evacuated and back-filled with N_2 three times, then charged with CH_2Cl_2 (11.8 mL, 0.1 M). The flask was cooled to 0 ºC, and DIBAL (630 µL, 3.53 mmol, 3 equiv) was added dropwise via syringe. The reaction stirred at 0 ºC for 1 hour, at which point, the reaction was quenched with 1M HCl (4 mL) and warmed to room temperature. The mixture was diluted with water (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The crude residue was purified by column chromatography using silica gel (20% Et_2O/hexanes → 30% Et_2O/hexanes) to give **557** (343 mg, 93% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.22 (silica gel, 20% Et_2O/hexanes, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (dd, *J* = 4.6, 2.8 Hz, 1H), 5.05 (q, *J* = 1.5 Hz, 1H), 4.98 (s, 1H), 4.00 (d, *J* = 11.3 Hz, 1H), 3.61 (d, *J* = 11.3 Hz, 1H), 2.93 (d, *J* = 5.1 Hz, 1H), 2.74 (ddq, *J* = 15.9, 2.7, 1.4 Hz, 1H), 2.56 (ddd, *J* = 17.4, 4.3, 2.8 Hz, 1H), 2.27 (dt, *J* = 15.9, 2.8 Hz, 1H), 2.21 – 2.07 (m, 1H), 2.03 (dd, *J* = 11.0, 2.8 Hz, 1H), 1.85 (ddd, *J* = 11.0, 5.5, 1.1 Hz, 1H), 1.74 (s, 1H).

^{19}F NMR (282 MHz, $CDCl_3$): δ –74.3.

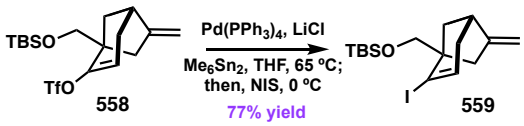


A 25 mL round-bottom flask was charged with **557** (150 mg, 0.48 mmol, 1.0 equiv) and imidazole (65 mg, 0.96 mmol, 2.0 equiv). The solids were dissolved in DMF (5 mL) and then TBSCl (87 mg, 0.576 mmol, 1.2 equiv) was added as a solid. The flask was then heated to 65 ºC and allowed to stir for 16 hours at this temperature, at which point the flask was removed from the oil bath and allowed to cool to room temperature. The reaction was quenched with the addition of water (5 mL) and then diluted with hexanes (25 mL) and additional water (20 mL). The aqueous layer was extracted with hexanes (3 x 25 mL), and the combined organics were washed with saturated $NH_4Cl_{(aq)}$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was

purified by column chromatography using silica gel (hexanes → 3% Et_2O/hexanes) to give **558** (189 mg, 93% yield) as a colorless oil.

R_f = 0.90 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

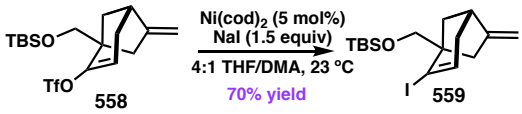
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.53 (ddd, *J* = 4.6, 2.7, 0.8 Hz, 1H), 5.03 (ddt, *J* = 2.8, 1.9, 0.9 Hz, 1H), 4.96 (tp, *J* = 1.6, 0.7 Hz, 1H), 3.90 (d, *J* = 10.1 Hz, 1H), 3.54 (d, *J* = 10.1 Hz, 1H), 2.97 – 2.83 (m, 1H), 2.74 – 2.60 (m, 1H), 2.54 (ddd, *J* = 17.2, 4.4, 2.7 Hz, 1H), 2.31 (dt, *J* = 15.8, 2.7 Hz, 1H), 2.11 (dddt, *J* = 17.4, 4.7, 2.1, 1.0 Hz, 1H), 1.97 – 1.84 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H).



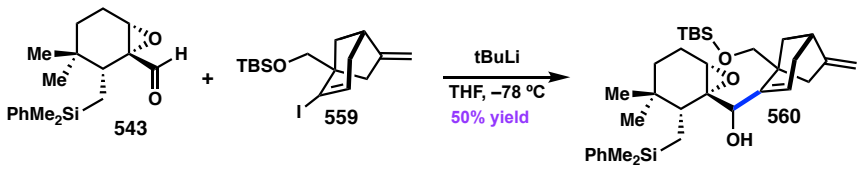
Iodide **559** could be prepared according to general procedure 3, using **558** (115 mg, 0.269 mmol, 1 equiv) as the subtrate. The mixture was purified using silica gel (hexanes) to provide **559** (83.4 mg, 77% yield).

R_f = 0.54 (silica gel, hexanes, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.22 (ddd, *J* = 4.5, 2.5, 0.9 Hz, 1H), 4.99 (ddt, *J* = 2.8, 1.8, 1.0 Hz, 1H), 4.92 (dd, *J* = 2.3, 1.2 Hz, 1H), 3.68 (d, *J* = 9.9 Hz, 1H), 3.51 (d, *J* = 9.9 Hz, 1H), 2.91 (d, *J* = 5.7 Hz, 1H), 2.52 (ddd, *J* = 17.1, 4.4, 2.5 Hz, 1H), 2.33 (dtd, *J* = 15.8, 2.6, 1.3 Hz, 1H), 2.21 (dt, *J* = 15.8, 2.8 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.89 (dd, *J* = 11.0, 2.6 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).



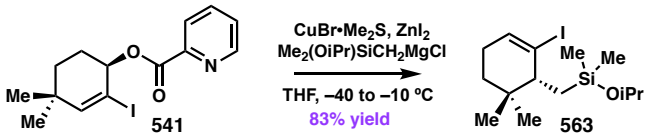
Inside a N_2-filled glovebox, a 2-dram vial was charged with $Ni(cod)_2$ (4.3 mg, 0.016 mmol, 5 mol %) and NaI (70.1 mg, 0.468 mmol, 1.5 equiv). The vial was then charged with THF (1.2 mL), DMA (0.6 mL), and enol triflate **558** (133 mg, 0.311 mmol, 1 equiv) as a solution in THF (1.2 mL). The vial was sealed and removed from the glovebox. The reaction stirred on the bench for 16 hours, at which point the reaction was quenched with the addition of water (3 mL). The mixture was diluted with additional water (5 mL) and Et_2O (5 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with water (25 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 1% Et_2O/hexanes) to give **559** (88 mg, 70% yield) as a colorless oil. See above for characterization data for **559**.



Alcohol **560** was prepared according to general procedure 1, using **543** (30.2 mg, 0.1 mmol) and **559** (40.4 mg, 0.1 mmol). The mixture was purified using silica gel (hexanes → 2.5% EtOAc/hexanes) to provide **560** (27.7 mg, 48% yield).

$\mathbf{R}_f$ = 0.87 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 – 7.49 (m, 2H), 7.39 – 7.31 (m, 3H), 5.59 (t, *J* = 3.3 Hz, 1H), 4.92 (s, 1H), 4.82 (s, 1H), 3.90 (d, *J* = 3.9 Hz, 1H), 3.80 (d, *J* = 10.0 Hz, 1H), 3.52 (d, *J* = 10.0 Hz, 1H), 3.31 (d, *J* = 2.5 Hz, 1H), 2.78 (d, *J* = 5.1 Hz, 1H), 2.45 (dt, *J* = 16.1, 2.7 Hz, 1H), 2.36 (dt, *J* = 17.3, 3.3 Hz, 1H), 2.29 (d, *J* = 15.4 Hz, 1H), 2.05 – 1.85 (m, 4H), 1.86 – 1.73 (m, 2H), 1.48 (dd, *J* = 10.7, 2.5 Hz, 1H), 1.38 (td, *J* = 12.6, 5.8 Hz, 1H), 1.05 (dd, *J* = 16.3, 2.8 Hz, 1H), 0.91 (s, 9H), 0.84 (s, 3H), 0.80 – 0.72 (m, 1H), 0.69 (s, 3H), 0.35 (d, *J* = 4.5 Hz, 6H), 0.07 (d, *J* = 10.8 Hz, 6H).



A 500 mL round-bottom flask was pumped into a N_2-filled glovebox, where it was charged with CuBr•Me_2S (3.27 g, 15.9 mmol, 1.5 equiv) and ZnI_2 (5.08 g, 15.9 mmol, 1.5 equiv). The flask was sealed with a septum and removed from the glovebox. The flask was then charged with THF (53 mL) and cooled to 0 ºC. The flask was charged with freshly prepared isopropoxydimethylsilylmethylmagnesium chloride[20] (55 mL, 31.8 mmol, 0.578 M, 3 equiv) via cannula. This mixture stirred for 30 minutes at 0 ºC and was then cooled to –40 ºC in a dry ice/acetone bath. Iodopicolonate **541** (3.78 g, 10.6 mmol, 1 equiv) was then added as a solution in THF (53 mL) via cannula. The reaction was allowed to gradually warm to –10 ºC over 3 hours, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$ solution (30 mL). The mixture was warmed to room temperature and diluted with water (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with

Et_2O (3 x 150 mL), and the combined organics were then washed with saturated $NH_4Cl_{(aq)}$ solution (200 mL), saturated $NaHCO_{3\,(aq)}$ (200 mL), water (200 mL) and brine (200 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude residue which was purified using silica gel (hexanes → 6% Et_2O/hexanes) to provide **563** (3.18 g, 83% yield).

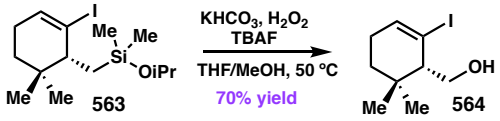
R_f = 0.90 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.15 (dd, *J* = 4.5, 3.3 Hz, 1H), 4.04 (hept, *J* = 6.0 Hz, 1H), 2.28 (dddd, *J* = 6.6, 3.7, 1.8, 0.9 Hz, 1H), 2.20 – 1.97 (m, 2H), 1.62 – 1.56 (m, 1H), 1.16 (dd, *J* = 6.1, 1.4 Hz, 6H), 1.00 (s, 3H), 0.93 (s, 3H), 0.89 – 0.79 (m, 2H), 0.21 (d, *J* = 8.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 134.9, 109.0, 65.0, 52.6, 35.3, 29.2, 28.7, 27.3, 27.2, 26.0, 20.4, 0.3, 0.0.

FTIR (NaCl, thin film, cm^{-1}): 2970, 2920, 2874, 1631, 1464, 1450, 1366, 1251, 1172, 1130, 1028, 931, 886, 838, 822.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{28}IOSi$ $[M+H]^+$: 367.0949; found: 367.0959.



A 25 mL round-bottom flask was charged with **563** (750 mg, 2.05 mmol, 1 equiv) followed by $KHCO_3$ (205 mg, 2.05 mmol, 1 equiv) and MeOH (2 mL). Then a solution of TBAF (4.1 mL, 4.09 mmol, 1 M in THF, 2 equiv) was added to the flask. At this point,

aqueous hydrogen peroxide (390 μL, 6.82 mmol, 50 wt%, 3.3 equiv) was added to the flask. The flask was added to a pre-heated oil bath at 50 ºC and left open to the atmosphere. After 90 minutes, TLC indicated complete consumption of starting material and formation of a much more polar product. The flask was removed from the oil bath and quenched with the addition of saturated $Na_2S_2O_{3\ (aq)}$ (10 mL). The mixture was diluted with Et_2O (5 mL) and the biphasic mixture was allowed to stir for an additional 30 min. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (30 mL), saturated $NaHCO_{3\ (aq)}$ (30 mL), and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude residue which was purified using silica gel (10% Et_2O/hexanes → 20% Et_2O/hexanes) to provide **564** (387 mg, 70% yield).

$\mathbf{R_f}$ = 0.57 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.59 – 6.54 (m, 1H), 3.94 (dt, *J* = 12.0, 4.1 Hz, 1H), 3.81 (ddd, *J* = 12.0, 8.7, 2.4 Hz, 1H), 2.15 – 2.08 (m, 2H), 2.02 (dh, *J* = 3.6, 1.2 Hz, 1H), 1.75 (ddd, *J* = 13.3, 10.0, 6.7 Hz, 1H), 1.30 (td, *J* = 8.5, 5.2 Hz, 2H), 1.07 (s, 4H), 1.01 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7, 100.0, 62.1, 58.6, 34.5, 31.7, 28.1, 27.9, 27.2.

HRMS (ESI-TOF, *m/z*): calc'd for $C_9H_{19}INO$ $[M+NH_4]^+$: 284.0506; found: 284.0495.

A 2-dram vial was charged with **564** (266 mg, 1.0 mmol, 1.0 equiv) and imidazole (136 mg, 2.0 mmol, 2.0 equiv). The solids were dissolved in DMF (5 mL) and then TBSCl (181 mg, 1.2 mmol, 1.2 equiv) was added as a solid. The vial was sealed and the reaction was allowed to stir at room temperature for 16 hours, at which point the reaction was quenched with the addition of water (2 mL) and then diluted with hexanes (10 mL) and additional water (5 mL). The aqueous layer was extracted with hexanes (3 x 10 mL), and the combined organics were washed with saturated $NH_4Cl_{(aq)}$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes) to give **565** (286 mg, 75% yield) as a colorless oil.

R_f = 0.90 (silica gel, 10% Et_2O/Hex, UV and p-anisaldehyde).

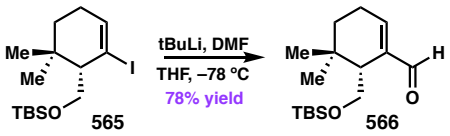
$[\alpha]_D^{24}$ = +76.8° (c = 0.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 – 6.34 (m, 1H), 3.88 – 3.71 (m, 2H), 2.17 – 1.96 (m, 2H), 1.92 (dtt, *J* = 3.7, 2.3, 1.1 Hz, 1H), 1.85 (ddd, *J* = 13.0, 10.9, 6.5 Hz, 1H), 1.22 – 1.14 (m, 1H), 1.04 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 2.1 Hz, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.1, 101.5, 62.1, 58.7, 34.6, 31.1, 28.5, 27.8, 27.2, 26.0, 18.3, -5.2, -5.2.

FTIR (NaCl, thin film, cm^{-1}): 2954, 2927, 1634, 1470, 1389, 1362, 1256, 1111, 1138, 1034, 998, 883, 837, 776.

HRMS (FAB, *m/z*): calc'd for $C_{15}H_{28}IOSi$ $[M–H]^+$: 379.0955; found: 379.0962.



A 50 mL round-bottom flask was charged with **565** (1.16 g, 3.05 mmol, 1 equiv) and the flask was evacuated and back-filled with N_2 three times. The iodide was dissolved in THF (15.2 mL) and the flask was cooled to –78 ºC. Then *t*-BuLi (4 mL, 1.5M, 6.0 mmol, 2 equiv) was added via syringe fast dropwise. The mixture immediately became bright yellow. After stirring for 5 minutes, dry DMF (1.89 mL, 24.4 mmol, 8 equiv) was added. The reaction stirred at this temperature for 10 minutes, at which point the reaction mixture was poured into a 250 mL conical flask containing a mixture of KH_2PO_4 (2.49 g, 18.3 mmol, 6 equiv) in Et_2O (24 mL) and water (24 mL) at 0 ºC. This biphasic mixture was stirred for five minutes, at which point the mixture was poured into a separatory funnel. The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 5% EtOAc/hexanes→10% EtOAc/hexanes) to give **566** (676 mg, 78% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.59 (silica gel, 10% EtOAc/Hex, UV and p-anisaldehyde).

$\mathbf{[\alpha]_D^{23}}$ = +78.8° (c = 1.5, $CHCl_3$).

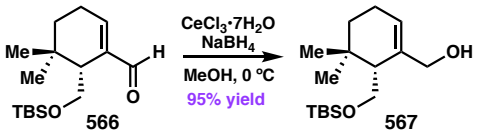
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1H), 6.88 (dd, *J* = 4.2, 3.0 Hz, 1H), 3.76 (dd, *J* = 10.5, 2.8 Hz, 1H), 3.68 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.44 – 2.26 (m, 2H), 2.28 – 2.19 (m,

2H), 2.01 (ddd, J = 13.2, 10.2, 7.1 Hz, 1H), 1.27 – 1.19 (m, 1H), 1.06 (s, 3H), 0.81 (s, 8H), 0.78 (s, 3H), -0.03 (s, 3H), -0.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.6, 153.3, 141.5, 61.9, 43.4, 32.1, 31.3, 27.8, 27.6, 25.9, 24.7, 18.2, -5.5, -5.5.

FTIR (NaCl, thin film, cm^{-1}): 2956, 2929, 2358, 1687, 1644, 1471, 1254, 1136, 1103, 1031, 996, 838, 776, 688.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{31}O_2Si$ $[M+H]^+$: 283.2088; found: 283.2094.



A 2-dram vial was charged with enal **566** (30 mg, 0.106 mmol, 1 equiv). The enal was dissolved in MeOH (350 µL) and the vial was cooled to 0 ºC. Freshly ground $CeCl_3$•$7H_2O$ (39.5 mg, 0.106 mmol, 1 equiv) was added to the vial in one portion, and the yellow mixture was allowed to stir for 10 minutes. Then $NaBH_4$ (5 mg, 0.127 mmol, 1.2 equiv) was added as a solid. The reaction stirred at 0 ºC for 30 minutes, at which point the reaction was quenched with brine (1 mL). The mixture was diluted with water (2 mL) and Et_2O (4 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (10% Et_2O/hexanes → 30% Et_2O/hexanes) to give **567** (28.6 mg, 95% yield) as a colorless oil.

R_f = 0.42 (silica gel, 15% EtOAc/Hex, p-anisaldehyde).

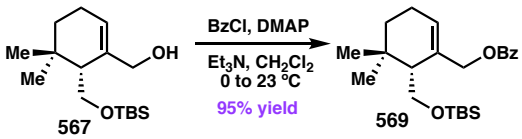
$[\alpha]_D^{24}$ = +73.4° (c = 1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (td, *J* = 3.6, 1.1 Hz, 1H), 4.25 – 4.08 (m, 1H), 4.02 – 3.82 (m, 2H), 3.56 (dd, *J* = 10.0, 8.1 Hz, 1H), 3.39 (t, *J* = 6.5 Hz, 1H), 2.12 – 1.91 (m, 3H), 1.50 – 1.36 (m, 1H), 1.35 – 1.19 (m, 1H), 0.95 (s, 3H), 0.90 (s, 9H), 0.87 (s, 3H), 0.09 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.8, 125.2, 67.8, 64.4, 48.8, 34.0, 31.6, 28.4, 26.0, 25.2, 22.9, 18.4, -5.3, -5.4.

FTIR (NaCl, thin film, cm^{-1}): 3347, 2956, 2928, 2859, 2360, 1471, 1389, 1362, 1256, 1105, 1055, 1006, 938, 892, 882, 838, 776, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{33}O_2Si$ $[M+H]^+$: 285.2250; found: 285.2238.



A 50 mL round-bottom flask was charged with alcohol **567** (300 mg, 10.5 mmol, 1 equiv) and dissolved in CH_2Cl_2 (21 mL). The flask was cooled to 0 ºC, and Et3N (1.5 mL, 10.5 mmol, 10 equiv) was added via syringe. Benzoyl chloride (366 µL, 3.15 mmol, 3 equiv) was added via syringe fast dropwise, then DMAP (65 mg, 0.528 mmol, 0.5 equiv) was added in one portion. The reaction stirred at 0 ºC for 1 hour, at which point the reaction mixture was pipetted onto a preequilibrated silica plug, eluting with 20% EtOAc/hexanes (200 mL). The volatiles were removed *in vacuo*, and the crude residue was purified by

column chromatography using silica gel (hexanes → 4% EtOAc/hexanes) to give **569** (388 mg, 95% yield) as a colorless oil.

R_f = 0.52 (silica gel, 10% EtOAc/Hex, UV and p-anisaldehyde).

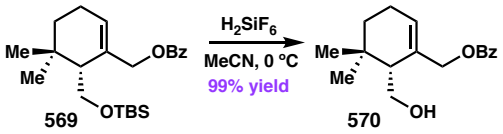
$[\alpha]_D^{22}$ = +36.1° (c = 0.73, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 5.88 (d, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 12.3 Hz, 1H), 4.75 (d, *J* = 12.3 Hz, 1H), 3.79 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.70 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.17 – 1.97 (m, 2H), 1.92 (d, *J* = 4.7 Hz, 1H), 1.68 (dt, *J* = 13.1, 8.3 Hz, 1H), 1.21 (dt, *J* = 13.2, 4.9 Hz, 1H), 1.00 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 4.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 133.3, 132.9, 130.7, 129.7, 128.5, 127.7, 68.6, 63.1, 47.9, 32.2, 31.7, 27.7, 27.6, 26.0, 23.1, 18.3, -5.3, -5.4.

FTIR (neat, cm^{-1}): 2953, 2927, 2855, 1719, 1471, 1268, 1106, 1069, 835, 774, 709.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{37}O_3Si$ $[M+H]^+$: 389.2506; found: 389.2504.



A 25 mL round-bottom flask was charged with **269** (385 mg, 0.966 mmol, 1 equiv). Acetonitrile (9.7 mL) was added to the flask, and the mixture was cooled to 0 ºC with an ice bath. H_2SiF_6 (2.3 mL, 4.82 mmol, 5 equiv, 25 wt %) was added to the flask, and the mixture was allowed to stir at 0 ºC for 4 hours, at which point TLC showed complete consumption of starting material. The reaction was quenched with the addition of saturated

$NaHCO_{3\ (aq)}$ (20 mL). The mixture was diluted with water (20 mL) and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide **570** (263 mg, 99% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.52 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

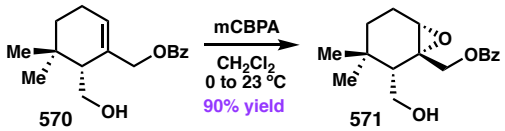
$\mathbf{[\alpha]_D^{25}}$ = +50.5° (c = 0.44, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 – 8.00 (m, 2H), 7.62 – 7.52 (m, 1H), 7.45 (dd, *J* = 8.4, 7.0 Hz, 2H), 6.01 (t, *J* = 3.7 Hz, 1H), 4.91 (dq, *J* = 12.4, 1.8 Hz, 1H), 4.75 (dd, *J* = 12.4, 1.1 Hz, 1H), 3.98 – 3.72 (m, 2H), 2.11 (ddtd, *J* = 8.4, 5.0, 3.2, 1.6 Hz, 2H), 1.88 (d, *J* = 4.1 Hz, 1H), 1.69 (dt, *J* = 13.4, 8.5 Hz, 1H), 1.57 (s, 2H), 1.25 (dtd, *J* = 13.4, 4.8, 4.3, 1.4 Hz, 1H), 1.05 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 133.2, 132.0, 130.4, 129.7, 129.5, 128.6, 68.4, 62.5, 48.5, 32.2, 31.8, 27.8, 27.6, 23.1.

FTIR (neat, cm^{-1}): 3019, 2359, 1712, 1245, 1193, 1111, 1026, 720.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1638; found: 275.1642.



A 50 mL round-bottom flask was charged with alcohol **570** (265 mg, 0.97 mmol, 1 equiv) and CH_2Cl_2 (9.7 mL) then cooled to 0 ºC. To the reaction mixture was added mCPBA (200 mg, 1.16 mmol, 1.2 equiv, 99% mCPBA) in one portion. The reaction was allowed to stir at 0 ºC for 2.5 hours, at which point TLC indicated that the starting material

had been consumed. The reaction was quenched with saturated $Na_2S_2O_{3\ (aq)}$ (8 mL) and saturated $NaHCO_{3\ (aq)}$ (4 mL). The biphasic mixture was diluted with water (5 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (30 mL), saturated $NaHCO_{3\ (aq)}$ (30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (10% EtOAc/hexanes → 25% EtOAc/hexanes) to give **571** (252 mg, 90% yield) as a colorless solid.

R_f = 0.38 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

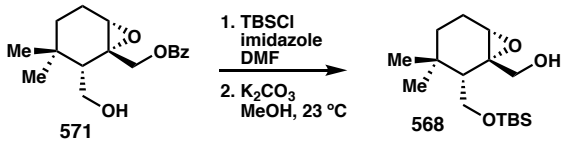
$[\alpha]_D^{22}$ = +50.5° (c = 0.44, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 7.97 (m, 2H), 7.58 (ddt, *J* = 7.9, 6.9, 1.4 Hz, 1H), 7.53 – 7.37 (m, 2H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 3.99 (dt, *J* = 11.4, 3.9 Hz, 1H), 3.92 – 3.76 (m, 1H), 3.30 (t, *J* = 1.9 Hz, 1H), 2.39 (t, *J* = 6.2 Hz, 1H), 2.02 (ddt, *J* = 15.7, 6.0, 1.6 Hz, 1H), 1.90 (dddd, *J* = 15.7, 12.4, 6.4, 2.4 Hz, 1H), 1.80 (ddd, *J* = 7.4, 4.2, 1.5 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.00 (dd, *J* = 9.1, 7.1 Hz, 1H), 0.96 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 133.4, 129.8, 129.8, 128.6, 68.1, 62.1, 59.8, 57.7, 44.2, 30.3, 28.6, 28.0, 27.2, 21.4.

FTIR (neat, cm^{-1}): 3019, 2359, 1718, 1451, 1272, 1215, 1115, 727, 712, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1591; found: 291.1577.



A 50 mL round-bottom flask was charged with **571** (240 mg, 0.826 mmol, 1 equiv) and imidazole (113 mg, 1.65 mmol, 2 equiv). The solids were dissolved in DMF (8.3 mL) and then TBSCl (150 mg, 0.99 mmol, 1.2 equiv) was added as a solid. The flask was sealed and the reaction was allowed to stir at room temperature for 16 hours, at which point the reaction was quenched with the addition of water (10 mL) and then diluted with hexanes (10 mL) and additional water (5 mL). The aqueous layer was extracted with hexanes (3 x 10 mL), and the combined organics were washed with saturated $NH_4Cl_{(aq)}$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The crude epoxy benzoate was added to a 50 mL round-bottom flask and dissolved in MeOH (14 mL). To the reaction mixture was added K_2CO_3 (1.15 g, 8.3 mmol, 12 equiv). The reaction stirred vigorously (800 rpm) for 40 minutes, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$ (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide **568** (263 mg, 93% yield over two steps) as a colorless oil.

R_f = 0.58 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{22}$ = +59.8° (c = 0.21, $CHCl_3$).

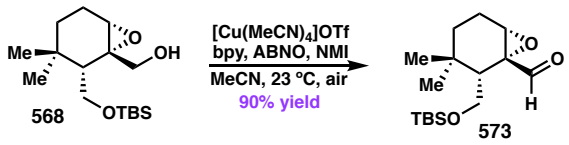
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.72 (ddd, *J* = 8.9, 4.9, 0.5 Hz, 1H), 3.62 (dd, *J* = 10.2, 8.9 Hz, 1H), 3.53 (dd, *J* = 6.2, 4.3 Hz, 1H), 3.39 (dd, *J* = 11.8,

6.1 Hz, 1H), 3.14 (t, *J* = 1.9 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.83 (dddd, *J* = 15.6, 12.1, 6.5, 2.6 Hz, 1H), 1.37 – 1.24 (m, 1H), 0.92 (s, 9H), 0.91 (s, 3H), 0.85 (s, 3H), 0.12 (d, *J* = 5.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 67.6, 61.6, 61.2, 55.8, 45.2, 30.1, 28.3, 27.7, 27.7, 26.0, 21.5, 18.5, -5.4, -5.4.

FTIR (neat, cm^{-1}): 3752, 2927, 2359, 2340, 2161, 1684, 1675, 1576, 1506, 1040, 837, 775.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{33}O_3Si$ $[M+H]^+$: 301.2193; found: 301.2195.



A 25 mL round-bottom flask was charged with epoxy alcohol **568** (160 mg, 0.533 mmol, 1 equiv) and dissolved in wet acetonitrile (11 mL). To this solution was added Stahl solution (135 μL, containing 0.2M bpy, 0.04M ABNO, and 0.4M NMI in MeCN) followed by $[Cu(MeCN)_4]OTf$ (10 mg, 0.027 mmol, 0.05 mol %). The solution was sparged with a balloon of O_2 for 10 minutes and then allowed to stir open to air for 3.5 hours. The reaction mixture was then filtered through a SiO_2 plug, eluting with 20% EtOAc/hexanes (100 mL). The volatiles were removed *in vacuo* to provide **573** (143 mg, 90% yield) as a light yellow oil.

R_f = 0.64 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

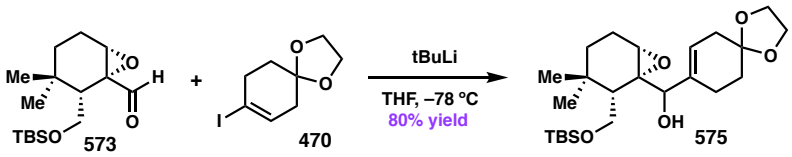
$[\alpha]_D^{22}$ = +64.1° (c = 2.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 3.68 (ddd, *J* = 8.8, 5.6, 0.6 Hz, 1H), 3.49 (dd, *J* = 11.0, 8.8 Hz, 1H), 3.41 (d, *J* = 1.9 Hz, 1H), 2.64 (ddd, *J* = 11.0, 5.5, 1.5 Hz, 1H), 2.08 (dddd, *J* = 15.5, 5.3, 2.3, 1.7 Hz, 1H), 1.87 (dddd, *J* = 15.6, 12.3, 5.8, 2.2 Hz, 1H), 1.49 – 1.36 (m, 1H), 1.01 – 0.90 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H), 0.85 (s, 9H), 0.03 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.5, 63.3, 60.5, 56.8, 42.1, 28.8, 28.6, 28.1, 27.0, 26.0, 21.3, 18.3, -5.4.

FTIR (neat, cm^{-1}): 2955, 2928, 2856, 2359, 1730, 1506, 1472, 1109, 1082, 1256, 1109, 1082, 837, 776.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{31}O_3Si$ $[M+H]^+$: 299.2037; found: 299.2030.



Epoxy alcohol **575** was prepared according to general procedure 1, using **573** (15 mg, 0.10 mmol) and **470** (26.6 mg, 0.10 mmol, 2 equiv). The mixture was purified using silica gel (10% EtOAc/hexanes → 30% EtOAc/hexanes) to provide **575** (17.5 mg, 80% yield).

R_f = 0.24 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{22}$ = +35.4° (c = 0.35, $CHCl_3$).

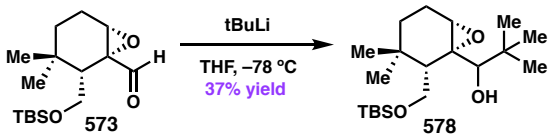
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (tq, *J* = 3.3, 1.4 Hz, 1H), 5.60 (d, *J* = 2.5 Hz, 1H), 3.94 (dd, *J* = 3.7, 1.5 Hz, 4H), 3.69 (dd, *J* = 8.7, 4.9 Hz, 1H), 3.59 (dd, *J* = 11.0, 8.7 Hz,

1H), 3.56 – 3.50 (m, 1H), 3.16 (t, *J* = 1.9 Hz, 1H), 2.40 – 2.19 (m, 3H), 2.11 (dddd, *J* = 15.9, 10.9, 5.0, 1.9 Hz, 2H), 1.98 (ddt, *J* = 15.5, 5.9, 1.6 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.74 (ddt, *J* = 8.6, 6.4, 1.1 Hz, 2H), 0.95 (s, 9H), 0.88 (qd, *J* = 7.3, 6.5, 2.5 Hz, 2H), 0.82 (s, 3H), 0.79 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.8, 121.4, 108.2, 80.1, 64.4, 64.3, 62.2, 61.7, 57.0, 41.5, 35.6, 31.3, 29.6, 28.2, 28.1, 27.5, 26.6, 26.0, 21.5, 18.5, -5.5, -5.5.

FTIR (neat, cm^{-1}): 3372, 2953, 2927, 2856, 2360, 1700, 1113, 1084, 1060, 836, 777, 733.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{24}H_{43}O_5Si$ $[M+H]^+$: 439.2874; found: 439.2854.



Alcohol **578** was prepared according to general procedure 1 with **573** (15 mg, 0.05 mmol) and *t*-BuLi (67 µL, 0.10 mmol, 1.7M, 2 equiv) as the organolithium reagent. The crude residue was purified using silica gel chromatography (hexanes → 10% EtOAc/hexanes) to provide **576** (6.8 mg, 37% yield).

R_f = 0.53 (silica gel, 10% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{22}$ = +60.6° (c = 0.30, $CHCl_3$).

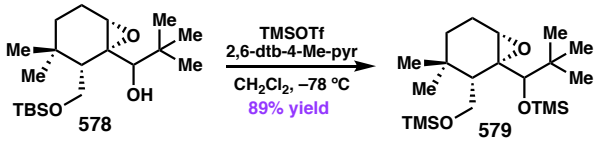
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.34 (d, *J* = 2.3 Hz, 1H), 3.73 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.66 (td, *J* = 9.5, 9.0, 1.0 Hz, 1H), 3.16 (d, *J* = 1.9 Hz, 1H), 2.75 (d, *J* = 2.1 Hz, 1H), 2.21 (ddd, *J* = 10.2, 5.0, 1.3 Hz, 1H), 1.98 (ddt, *J* = 15.5, 5.5, 2.0 Hz, 1H), 1.87 (dddd, *J* = 15.4, 12.4, 6.1, 2.2 Hz, 1H), 1.43 (d, *J* = 1.0 Hz, 1H), 1.37 (td, *J* = 12.9, 5.5 Hz, 1H), 1.02 (s,

4H), 1.00 (d, *J* = 1.0 Hz, 9H), 0.96 (d, *J* = 1.0 Hz, 9H), 0.84 (s, 3H), 0.16 (d, *J* = 2.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 85.9, 62.5, 61.8, 57.9, 43.4, 36.1, 30.6, 29.3, 28.7, 28.3, 27.4, 26.1, 21.4, 18.7.

FTIR (neat, cm^{-1}): 3360, 2929, 2858, 2359, 1388, 1069, 906, 836, 730.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{20}H_{41}O_3Si$ $[M+H]^+$: 357.2819; found: 357.2813.



Epoxide **579** was prepared according to general procedure 2, using **578** (6 mg, 0.017 mmol) as the substrate. The mixture was purified using preparative TLC (10% Et_2O/hexanes) to provide **579** (3 mg, 89% NMR yield).

R_f = 0.79 (silica gel, 20% EtOAc/Hex, UV).

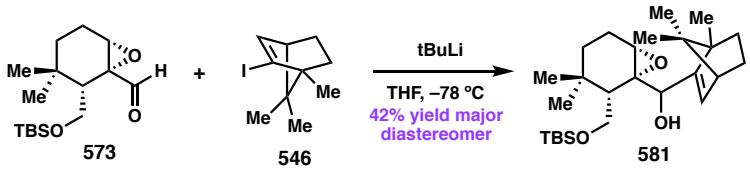
$[\alpha]_D^{23}$ = –5.1° (c = 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.53 – 3.42 (m, 1H), 2.96 (t, *J* = 2.2 Hz, 1H), 2.83 (s, 1H), 2.10 (dt, *J* = 8.0, 1.8 Hz, 1H), 1.92 – 1.79 (m, 2H), 1.47 – 1.40 (m, 3H), 0.99 (s, 3H), 0.97 (s, 9H), 0.92 (s, 3H), 0.90 – 0.81 (m, 2H), 0.16 (s, 9H), 0.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 88.7, 62.9, 62.3, 58.5, 45.2, 36.0, 31.4, 29.7, 29.4, 28.0, 27.6, 21.6, 1.0, 0.0.

FTIR (NaCl, thin film, cm^{-1}): 2922, 2362, 1382, 1035, 826, 810, 708, 683.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{20}H_{43}O_3Si_2$ $[M+H]^+$: 387.2745; found: 387.2746.

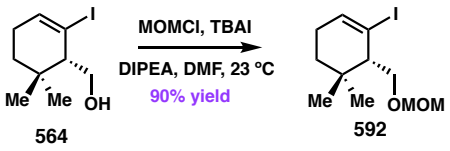


Epoxide **581** was prepared according to general procedure 1, using **573** (15 mg, 0.05 mmol) and **546** (26.2 mg, 0.10 mmol, 2 equiv). The mixture was purified using silica gel (hexanes → 5% EtOAc/hexanes) to provide **581** (17 mg, 42% NMR yield of major diastereomer).

$\mathbf{R_f}$ = 0.52 (silica gel, 20% Et_2O/Hex, p-anisaldehyde).

$\mathbf{[\alpha]_D^{23}}$ = +21.0° (c = 0.85, $CHCl_3$).

HRMS (ESI-TOF, *m/z*): calc'd for for $C_{26}H_{47}O_3Si$ $[M+H]^+$: 435.3289; found: 435.3285.



A 50 mL round-bottom flask was charged with **564** (380 mg, 1.43 mmol, 1 equiv). The flask was evacuated and backfilled with N_2 three times and then DMF (7 mL) was added via syringe. To the reaction mixture was added TBAI (264 mg, 0.71 mmol, 0.5 equiv) followed by Hünig's base (1.5 mL, 8.57 mmol, 6 equiv). The reaction was cooled to 0 ºC, at which point MOMCl (325 µL, 4.29 mmol, 3 equiv) was added dropwise via syringe. The reaction stirred at 0 ºC for 15 minutes and was then warmed to room

temperature, where it stirred for an additional 16 hours, when TLC indicated that starting material had been consumed. The reaction was quenched with the addition of 1M NaOH (10 mL). The mixture was diluted with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organics were washed with 1M NaOH (50 mL), water (50 mL), and saturated $NH_4Cl_{(aq)}$ (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (4% Et_2O/hexanes → 5% Et_2O/hexanes) to give **592** (408 mg, 90% yield) as a colorless oil.

R_f = 0.74 (silica gel, 25% Et_2O/Hex, UV and p-anisaldehyde).

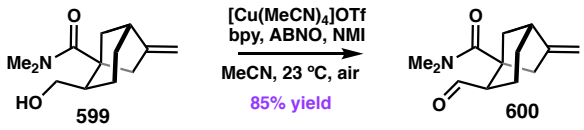
$[\alpha]_D^{22}$ = +70.2° (c = 0.42, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 – 6.41 (m, 1H), 4.68 – 4.56 (m, 2H), 3.76 – 3.66 (m, 2H), 3.39 (s, 3H), 2.14 – 2.04 (m, 3H), 1.70 (ddd, *J* = 13.2, 9.9, 7.2 Hz, 1H), 1.30 – 1.20 (m, 1H), 1.04 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.2, 100.9, 96.8, 67.5, 56.9, 55.7, 34.5, 31.2, 28.2, 27.6, 27.1.

FTIR (NaCl, thin film, cm^{-1}): 2923, 2878, 1629, 1460, 1387, 1317, 1250, 1210, 1150, 1111, 1071, 1039, 962, 917.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{11}H_{19}IO_2$ $[M–H]^+$: 309.0352; found: 309.0362.



A 2-dram vial was charged with amido alcohol **599** (8 mg, 0.358 mmol, 1 equiv) and dissolved in wet acetonitrile (700 µL). To this solution was added Stahl solution (9 µL, containing 0.2M bpy, 0.04M ABNO, and 0.4M NMI in MeCN) followed by $[Cu(MeCN)_4]OTf$ (0.7 mg, 0.0018 mmol, 0.05 mol %). The solution was allowed to stir open to air for 30 minutes. The reaction mixture was diluted with water (1 mL) and EtOAc (1 mL). The aqueous layer was extracted with EtOAc (3 x 1 mL), and the combined organics were washed with brine (3 mL), with saturated $NH_4Cl_{(aq)}$ (3 mL), and brine (3 mL). The organic layer was filtered over a plug of Na_2SO_4, and the volatiles were removed in vacuo to provide **600** (4.5 mg, 72% yield).

R_f = 0.68 (silica gel, 20% MeOH/CH_2Cl_2, I_2 and p-anisaldehyde).

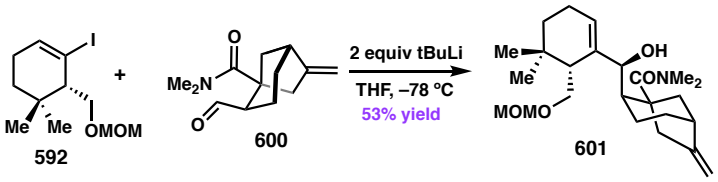
$[\alpha]_D^{22}$ = –14.7° (c = 0.42, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, *J* = 1.0 Hz, 1H), 4.94 – 4.89 (m, 1H), 4.89 – 4.85 (m, 1H), 3.06 (d, *J* = 6.0 Hz, 7H), 2.84 – 2.70 (m, 2H), 2.70 – 2.59 (m, 2H), 2.13 (dtd, *J* = 12.0, 5.9, 3.1 Hz, 2H), 1.79 – 1.64 (m, 2H), 1.64 – 1.42 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.4, 174.4, 152.8, 105.8, 53.1, 51.6, 41.7, 41.2, 39.8, 37.8, 30.3, 19.0.

FTIR (NaCl, thin film, cm^{-1}): 3480, 3421, 3239, 2938, 2210, 1714, 1618, 1412, 1045, 970, 878, 786, 660.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{13}H_{19}NO_2$ $[M+H]^+$: 222.1475; found: 222.1473.

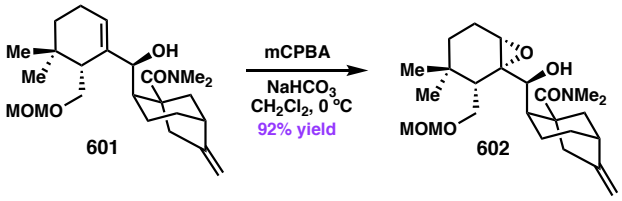


Allylic alcohol **601** was prepared according to general procedure 1, using **592** (22 mg, 0.10 mmol, 1 equiv) and **600** (31 mg, 0.10 mmol, 1 equiv). The crude residue was purified using silica gel (30% EtOAc/hexanes → 50% EtOAc/hexanes) to provide **601** (21.3 mg, 53% yield). Slow evaporation from hexanes enabled the preparation of crystals of quality that could be used for single crystal X-ray diffraction to establish connectivity (but not for publication).

$\mathbf{R}_f$ = 0.29 (silica gel, 50% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 – 5.73 (m, 1H), 4.85 (tt, *J* = 2.5, 1.0 Hz, 1H), 4.79 (d, *J* = 1.8 Hz, 1H), 4.53 (d, *J* = 1.1 Hz, 2H), 4.24 (dt, *J* = 3.3, 1.6 Hz, 1H), 3.50 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.38 – 3.28 (m, 4H), 3.08 (s, 3H), 2.93 (s, 3H), 2.63 (m, 3H), 2.59 – 2.50 (m, 1H), 2.10 – 1.99 (m, 2H), 1.89 – 1.77 (m, 4H), 1.76 (d, *J* = 5.8 Hz, 1H), 1.58 – 1.45 (m, 2H), 1.28 – 1.12 (m, 2H), 0.97 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 155.0, 141.0, 121.0, 104.3, 96.9, 73.4, 69.5, 55.7, 55.3, 46.6, 42.5, 37.9, 31.9, 31.7, 31.2, 28.5, 26.8, 22.6, 17.1.



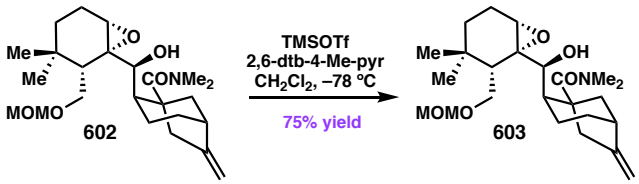
A 25 mL round-bottom flask was charged with allylic alcohol **601** (140 mg, 0.345 mmol, 1 equiv), $NaHCO_3$ (64 mg, 0.759 mmol, 2.2 equiv), and CH_2Cl_2 (6.8 mL) then cooled to 0 ºC. To the reaction mixture was added mCPBA (200 mg, 1.16 mmol, 1.2 equiv, 99% mCPBA) in one portion. The reaction was allowed to stir at 0 ºC for 15 minutes, at which point TLC indicated that the starting material had been consumed. The reaction was quenched with saturated $Na_2S_2O_{3\ (aq)}$ (15 mL). The biphasic mixture was diluted with water (5 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (30 mL), saturated $NaHCO_{3\ (aq)}$ (30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (20% EtOAc/hexanes → 60% EtOAc/hexanes) to give **602** (252 mg, 90% yield) as a colorless solid.

R_f = 0.57 (silica gel, 80% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.81 (s, 1H), 4.79 – 4.73 (m, 1H), 4.54 – 4.43 (m, 2H), 4.23 – 4.12 (m, 1H), 3.65 (d, J = 3.3 Hz, 1H), 3.35 (s, 2H), 3.24 (s, 3H), 3.21 (s, 1H), 3.04 (s, 3H), 2.79 (s, 3H), 2.71 (d, J = 17.3 Hz, 1H), 2.45 (d, J = 2.5 Hz, 1H), 2.41 (d, J = 2.6 Hz, 1H), 2.18 (s, 1H), 2.14 (d, J = 6.5 Hz, 1H), 1.91 (tq, J = 6.2, 3.8, 3.1 Hz, 1H), 1.81 (dd,

J = 15.4, 5.6 Hz, 1H), 1.78 – 1.66 (m, 1H), 1.58 (tt, *J* = 12.9, 6.0 Hz, 3H), 1.50 (d, *J* = 5.3 Hz, 2H), 1.33 – 1.25 (m, 2H), 0.83 (s, 6H).

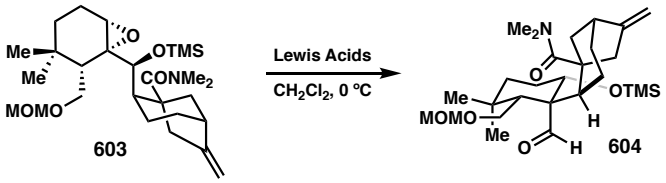
HRMS (ESI-TOF, *m/z*): calc'd for $C_{24}H_{43}N_2O_5$ $[M+NH_4]^+$: 439.3166; found: 439.3185.



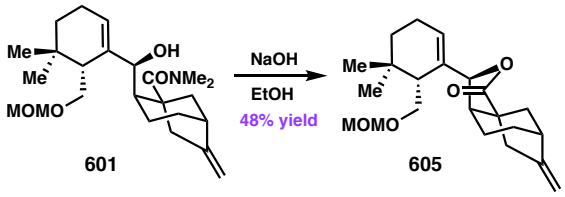
Epoxide **603** was prepared according to general procedure 2, using **602** (90 mg, 0.213 mmol) as the substrate. The mixture was purified using silica gel (10% EtOAc/Hexanes → 30% EtOAc/hexanes) to provide **603** (79.1 mg, 75% yield).

General Procedure 4: Lewis acid Screen

An oven-dried 1-dram vial was pumped into the glove box and charged with a Lewis acid (3 equiv). The vial was sealed and removed from the glovebox, then CH_2Cl_2 (100 µL) was added. The vial was cooled to 0 ºC and **603** (0.01 mmol) was added as a solution in CH_2Cl_2 (100 µL). After two hours, the mixture was filtered over a pad of silica gel eluting with 20% EtOAc/Hexanes (10 mL). The volatiles were removed *in vacuo* and analyzed by TLC and NMR.



Entry	Scale	Lewis Acid	LA equiv	result
1	5 mg	$TiCl_4$	3	Decomp at 0 °C
2	5 mg	$SnCl_4$	3	Decomp at 0 °C
3	5 mg	$AlMe_3$	3	SM
4	5 mg	$Yb(OTf)_3$	3	SM
5	5 mg	HBF_4OEt_2	3	Decomp at 0 °C
6	5 mg	Et_3OBF_4	3	SM
7	5 mg	$MgBr_2$	3	SM
8	5 mg	$TiCl(OiPr)_3$	3	SM
9	5 mg	Et_2AlCl	3	SM
10	5 mg	$Zn(OTf)_2$	3	SM
11	5 mg	$BF_3{\cdot}OEt_2$	3	Decomp at 0 °C
12	5 mg	$Sc(OTf)_3$	3	Decomp at 0 °C

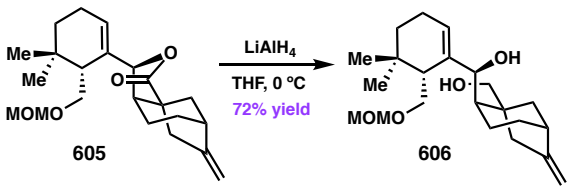


A 2-dram vial was charged with alcohol **601** (25 mg, 0.0616 mmol, 1 equiv) and then NaOH (37 mg, 0.925 mmol, 15 equiv). EtOH (600 μL) was then added and the vial was sealed with a Teflon cap. The mixture was heated to 130 ºC and stirred for 10 minutes. The vial was removed from the heating block and cooled to room temperature. 1M HCl was added (1.2 mL) and the reaction stirred for 1 hour. The mixture was then diluted with water (1 mL) and extracted with EtOAc (5 x 2 mL). The combined organics were filtered over a SiO_2 plug and the volatiles removed *in vacuo*. The crude residue was

purified by column chromatography using silica gel (5% EtOAc/hexanes → 25% EtOAc/hexanes) to give **605** (10.7 mg, 48% yield) as a colorless solid.

$\mathbf{R_f}$ = 0.69 (silica gel, 80% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.79 – 5.71 (m, 1H), 5.26 (d, *J* = 9.6 Hz, 1H), 5.00 (q, *J* = 3.6, 2.4 Hz, 1H), 4.83 (s, 1H), 4.63 – 4.52 (m, 2H), 3.67 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.36 (s, 3H), 2.80 (dt, *J* = 16.1, 2.9 Hz, 1H), 2.73 (dd, *J* = 9.1, 4.5 Hz, 1H), 2.51 (td, *J* = 10.6, 7.4 Hz, 1H), 2.28 (d, *J* = 14.0 Hz, 1H), 2.18 – 2.01 (m, 2H), 1.79 (d, *J* = 5.0 Hz, 1H), 1.73 (dd, *J* = 11.2, 2.6 Hz, 1H), 1.68 (dd, *J* = 11.2, 4.6 Hz, 1H), 1.49 (dddt, *J* = 13.5, 9.5, 6.3, 3.3 Hz, 3H), 1.39 – 1.30 (m, 1H), 1.21 (t, *J* = 7.0 Hz, 1H), 0.99 (s, 3H), 0.95 (s, 3H), 0.91 – 0.85 (m, 1H).



A 2-dram vial was charged directly with lactone **605** (10 mg, 0.027 mmol, 1 equiv). The vial was evacuated and backfilled with N_2 3 times. THF (270 µL) was added to the vial, then the reaction mixture was cooled to 0 ºC. A solution of $LiAlH_4$ (110 µL, 0.11 mmol, 1M in THF, 4 equiv) was then added to the vial, and the reaction was allowed to stir for 20 minutes at this temperature. The reaction was quenched with 1M HCl (500 µL). The aqueous layer was extracted with EtOAc (3 x 1 mL) and the combined organics were filtered over a plug of Na_2SO_4. The volatiles were removed *in vacuo*, and the crude residue

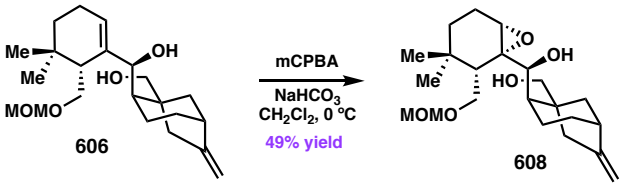
was purified by column chromatography using silica gel (20% EtOAc/hexanes → 30% EtOAc/hexanes) to give **606** (7.3 mg, 72% yield) as a colorless oil.

R_f = 0.29 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (td, *J* = 3.7, 1.4 Hz, 1H), 4.83 (ddt, *J* = 3.1, 2.3, 1.1 Hz, 1H), 4.78 (qd, *J* = 1.9, 1.0 Hz, 1H), 4.74 (s, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.76 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.41 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.36 (s, 4H), 2.75 (t, *J* = 6.4 Hz, 1H), 2.67 (d, *J* = 4.9 Hz, 1H), 2.43 (dq, *J* = 17.0, 2.3 Hz, 1H), 2.28 (dt, *J* = 17.0, 2.7 Hz, 1H), 2.08 (ddd, *J* = 17.2, 8.7, 5.7 Hz, 3H), 1.88 – 1.75 (m, 3H), 1.60 (q, *J* = 5.9 Hz, 3H), 1.52 – 1.35 (m, 3H), 0.99 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.3, 142.8, 119.8, 103.5, 96.5, 72.7, 70.9, 69.4, 55.7, 48.1, 45.7, 45.0, 43.3, 39.4, 36.2, 33.5, 31.9, 31.5, 28.4, 26.7, 22.8, 16.9.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{36}NaO_4$ $[M+Na]^+$: 387.2506; found: 387.2524



A 2-dram vial was charged with allylic alcohol **606** (10 mg, 0.0275 mmol, 1 equiv), $NaHCO_3$ (5 mg, 0.0604 mmol, 2.2 equiv), and CH_2Cl_2 (275 μL) then cooled to 0 ºC. To the reaction mixture was added mCPBA (5.2 mg, 0.0302 mmol, 1.1 equiv, 99% mCPBA) in one portion. The reaction was allowed to stir at 0 ºC for 30 minutes, at which point TLC indicated that the starting material had been consumed. The reaction was quenched with

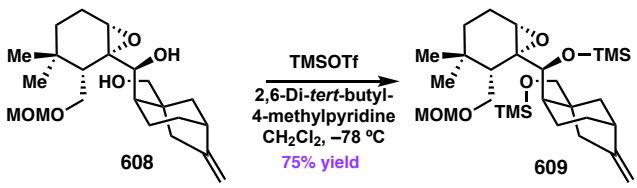
saturated $Na_2S_2O_{3\ (aq)}$ (1 mL). The biphasic mixture was diluted with water (1 mL) and CH_2Cl_2 (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (3 mL), saturated $NaHCO_{3\ (aq)}$ (3 mL), and brine (3 mL). The organic layer was filtered over a Na_2SO_4 plug and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (20% EtOAc/hexanes → 50% EtOAc/hexanes) to give **608** (5.1 mg, 49% yield) as a colorless solid.

R_f = 0.62 (silica gel, 50% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.83 (tt, *J* = 3.0, 2.3, 1.0 Hz, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.61 (d, *J* = 6.5 Hz, 1H), 4.36 (s, 1H), 4.02 (d, *J* = 11.6 Hz, 1H), 3.68 – 3.61 (m, 2H), 3.56 (d, *J* = 2.1 Hz, 1H), 3.38 (s, 3H), 3.35 (d, *J* = 11.6 Hz, 1H), 2.64 (q, *J* = 4.1 Hz, 1H), 2.44 (dq, *J* = 17.1, 2.4 Hz, 1H), 2.34 – 2.23 (m, 1H), 2.13 (s, 1H), 2.09 – 1.94 (m, 4H), 1.92 – 1.79 (m, 1H), 1.65 – 1.54 (m, 2H), 0.88 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.3, 103.5, 96.7, 70.0, 69.3, 67.1, 64.1, 55.8, 55.6, 48.1, 44.6, 43.3, 42.1, 37.6, 35.8, 33.1, 30.4, 29.9, 28.9, 27.7, 27.7, 21.3, 19.2.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{40}NO_5$ $[M+H]^+$: 398.2901; found: 398.2896.



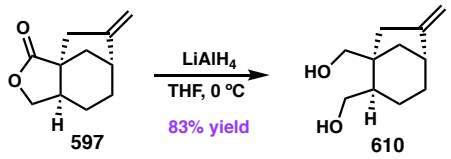
Epoxide **609** was prepared according to general procedure 2, using **608** (10 mg, 0.026 mmol) as the substrate. The mixture was purified using silica gel (2% Et_2O/hexanes → 10% Et_2O/hexanes) to provide **609** (10.3 mg, 75% yield).

$\mathbf{R_f}$ = 0.71 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.80 (s, 1H), 4.75 (s, 1H), 4.66 – 4.56 (m, 2H), 4.38 (s, 1H), 3.83 (d, *J* = 10.1 Hz, 1H), 3.59 – 3.50 (m, 2H), 3.37 (s, 3H), 3.30 (d, *J* = 2.7 Hz, 2H), 2.62 (s, 1H), 2.27 – 2.19 (m, 2H), 2.06 – 1.97 (m, 2H), 1.95 – 1.87 (m, 2H), 1.84 (dd, *J* = 10.5, 2.0 Hz, 1H), 1.76 (tdd, *J* = 15.0, 6.1, 2.1 Hz, 1H), 1.62 – 1.55 (m, 2H), 1.50 (tt, *J* = 13.4, 6.5 Hz, 1H), 1.43 – 1.31 (m, 2H), 1.12 (dd, *J* = 10.9, 5.3 Hz, 1H), 0.84 (d, *J* = 5.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 102.9, 97.0, 71.5, 68.4, 67.3, 63.1, 55.4, 52.9, 47.9, 44.5, 43.9, 41.4, 38.6, 34.6, 33.0, 30.5, 30.3, 29.9, 28.5, 28.2, 27.2, 21.4, 19.4, 1.2, –0.4.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{28}H_{52}O_5Si_2$ $[M+H]^+$: 525.3426; found: 525.3402.



A 25 mL round-bottom flask was charged directly with lactone **597** (100 mg, 0.561 mmol, 1 equiv). The flask was evacuated and backfilled with N_2 3 times. THF (5.6 mL) was added to the flask, then the reaction mixture was cooled to 0 ºC. A solution of $LiAlH_4$ (2.25 mL, 2.24 mmol, 1M in THF, 4 equiv) was then added to the flask, and the reaction

was allowed to stir for 20 minutes at this temperature. The reaction was quenched with 1M HCl (2 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were filtered over a plug of Na_2SO_4. The volatiles were removed *in vacuo* to give **610** (85.1 mg, 83% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.12 (silica gel, 50% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.85 (ddt, *J* = 3.2, 2.2, 1.0 Hz, 1H), 4.80 (d, *J* = 2.2 Hz, 1H), 4.00 (dd, *J* = 10.9, 8.5 Hz, 1H), 3.68 (d, *J* = 11.3 Hz, 1H), 3.58 (dd, *J* = 10.9, 4.2 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 2.75 (s, 1H), 2.66 (d, *J* = 5.3 Hz, 1H), 2.44 (s, 1H), 2.37 (dt, *J* = 17.1, 2.4 Hz, 1H), 2.16 (dt, *J* = 16.9, 2.7 Hz, 1H), 1.92 – 1.75 (m, 3H), 1.65 – 1.51 (m, 2H), 1.35 – 1.27 (m, 2H).

5.6 NOTES AND REFERENCES

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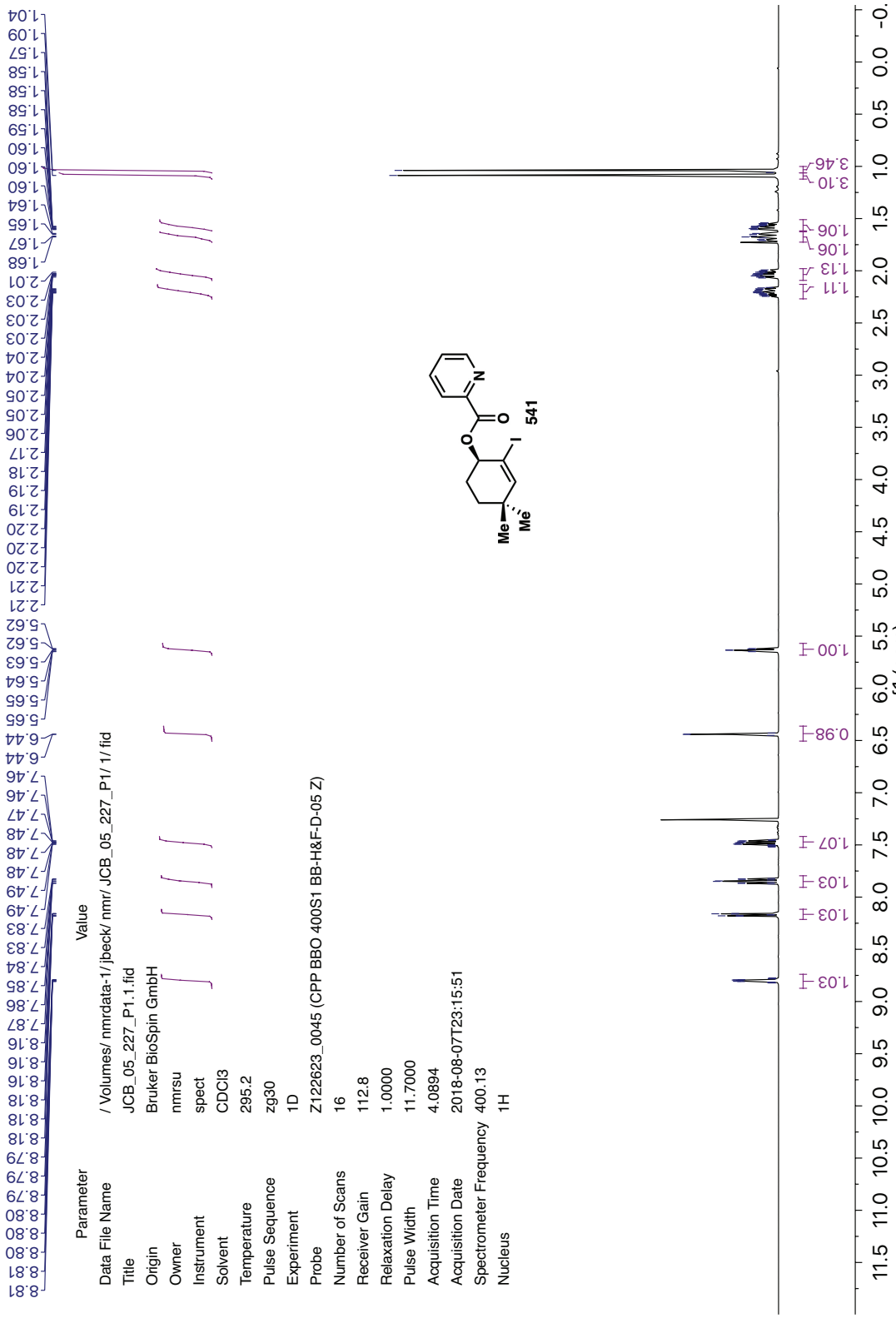
Appendix 3

Spectra Relevant to Chapter 5:

A Semi-Pinacol Approach for the Synthesis of the Enmein-Type Ent-Kauranoids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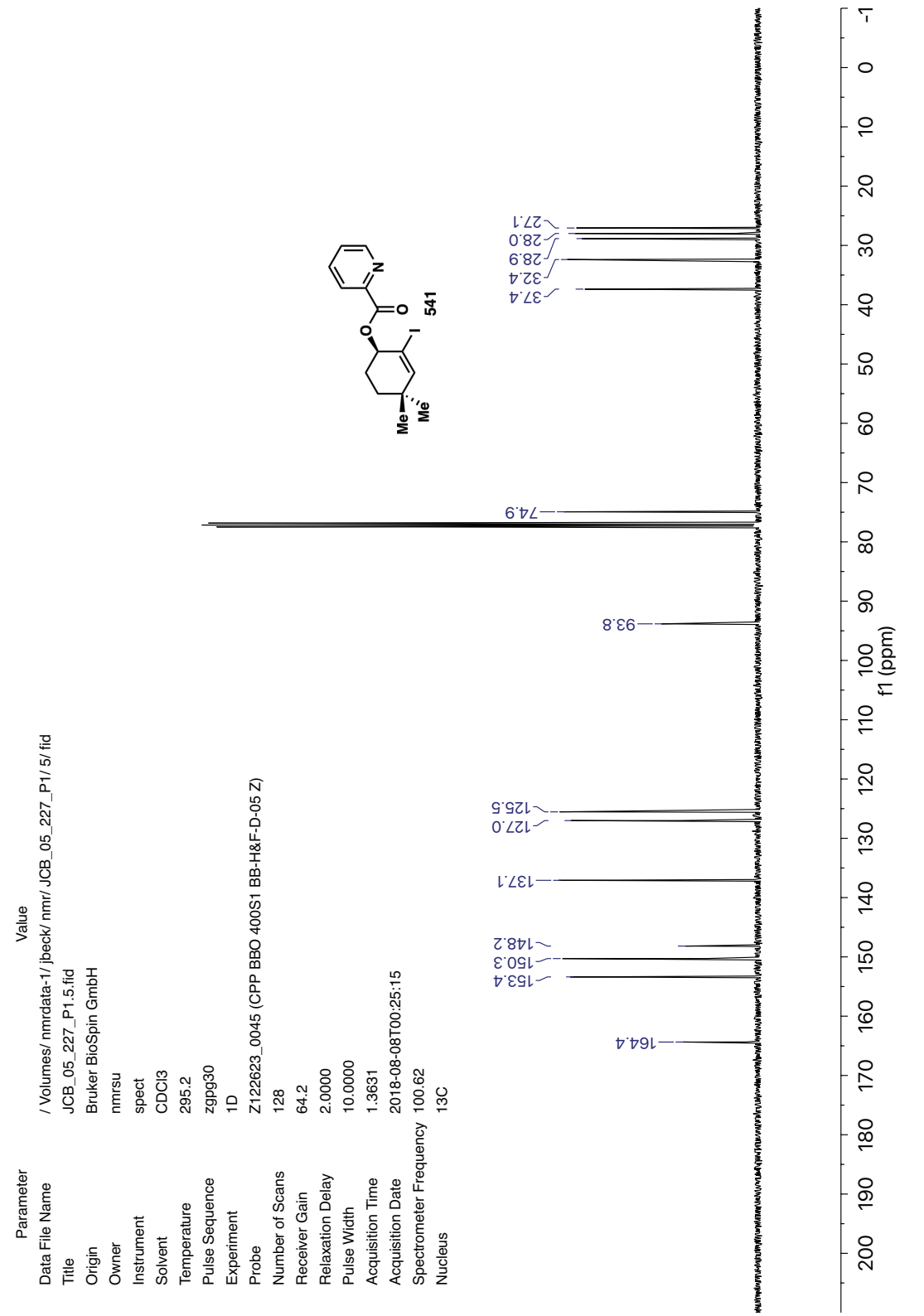
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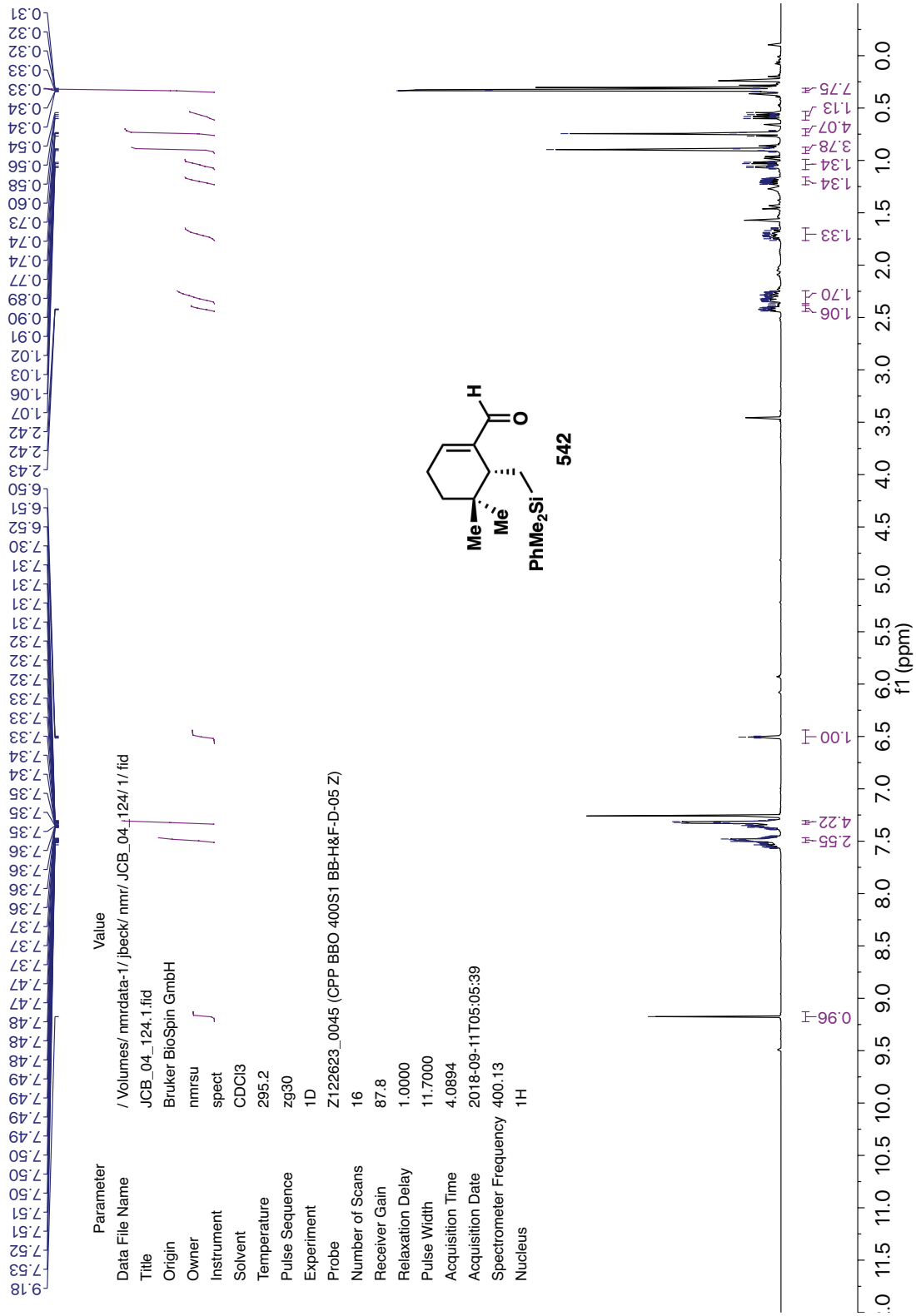
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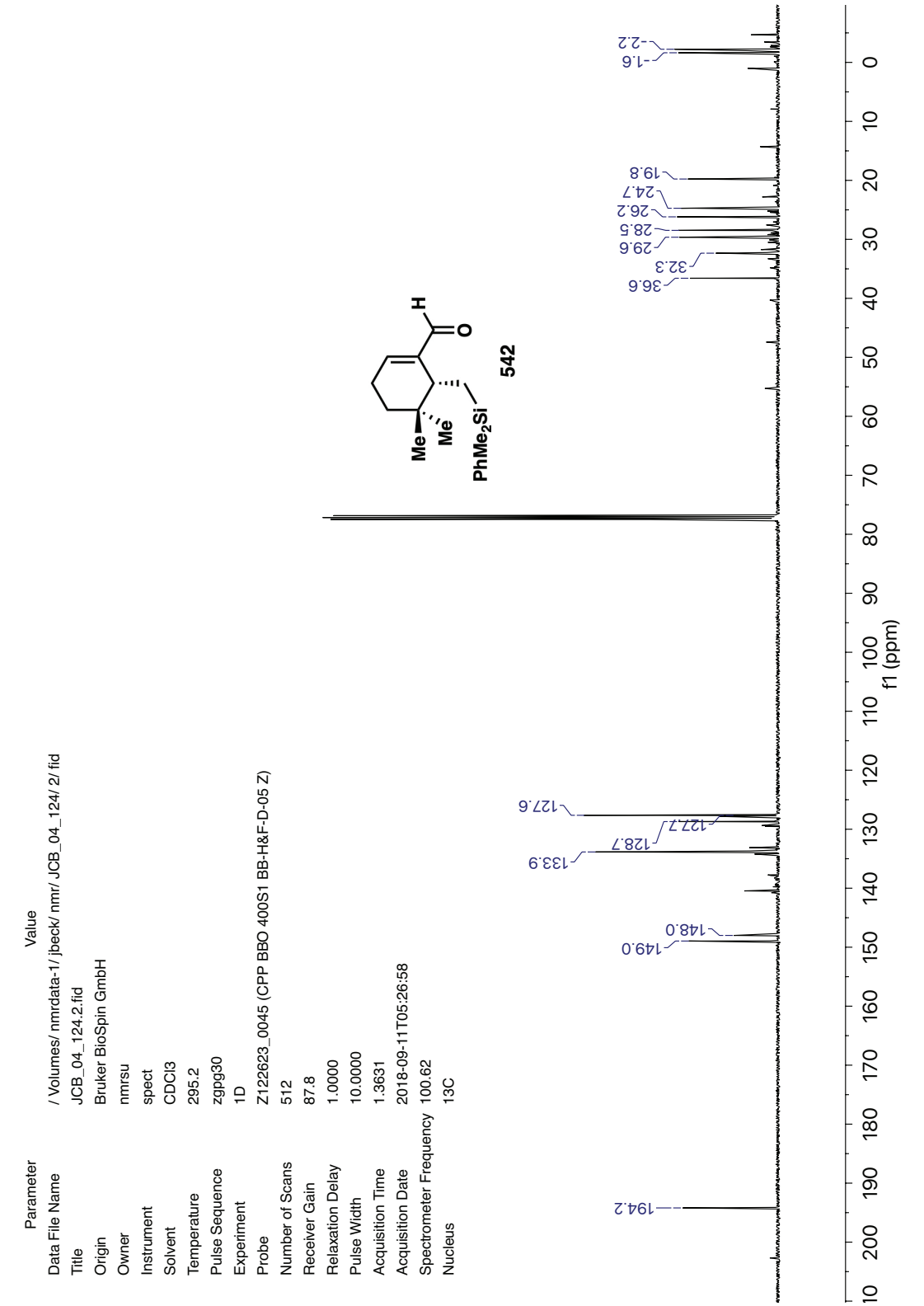
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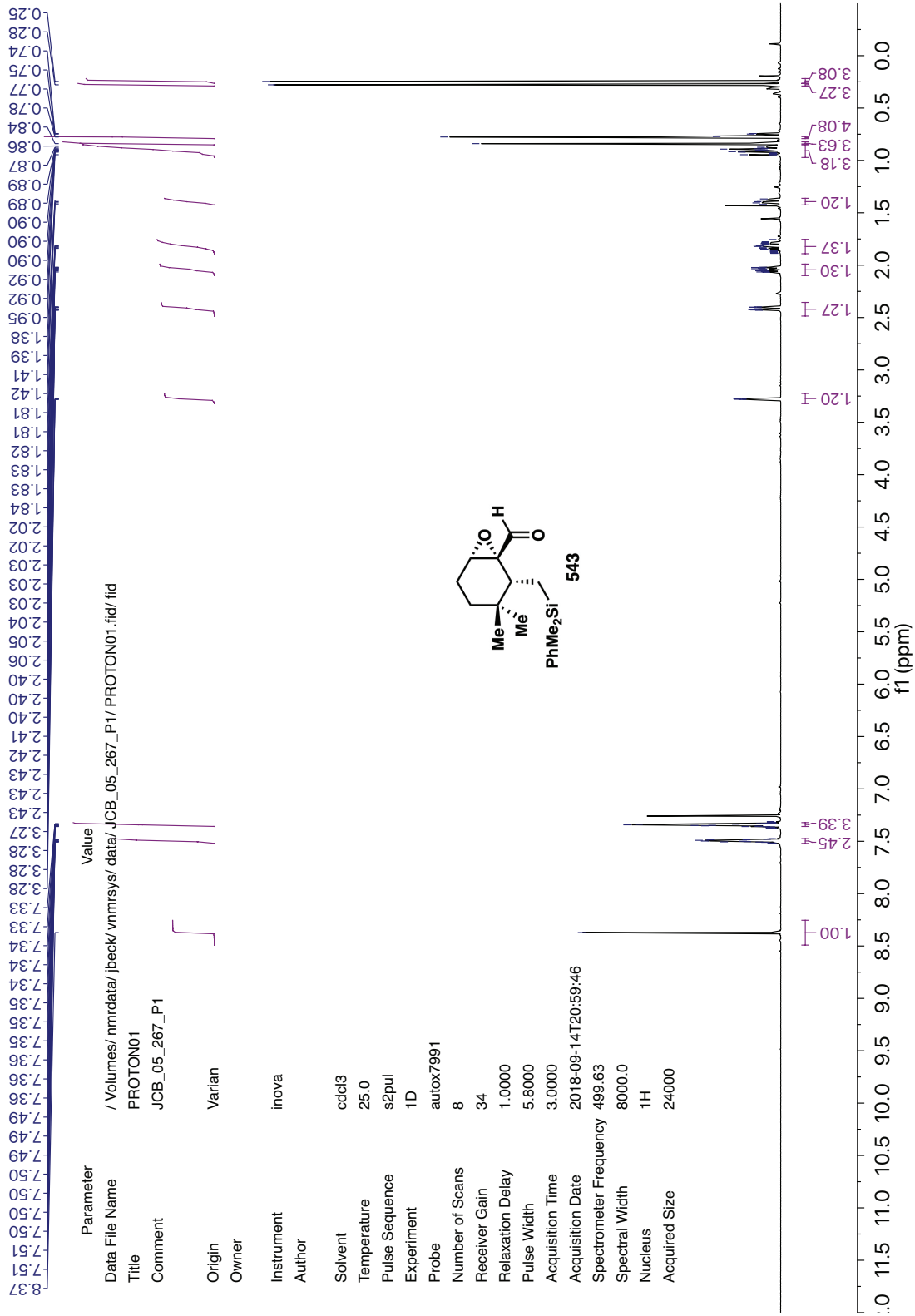
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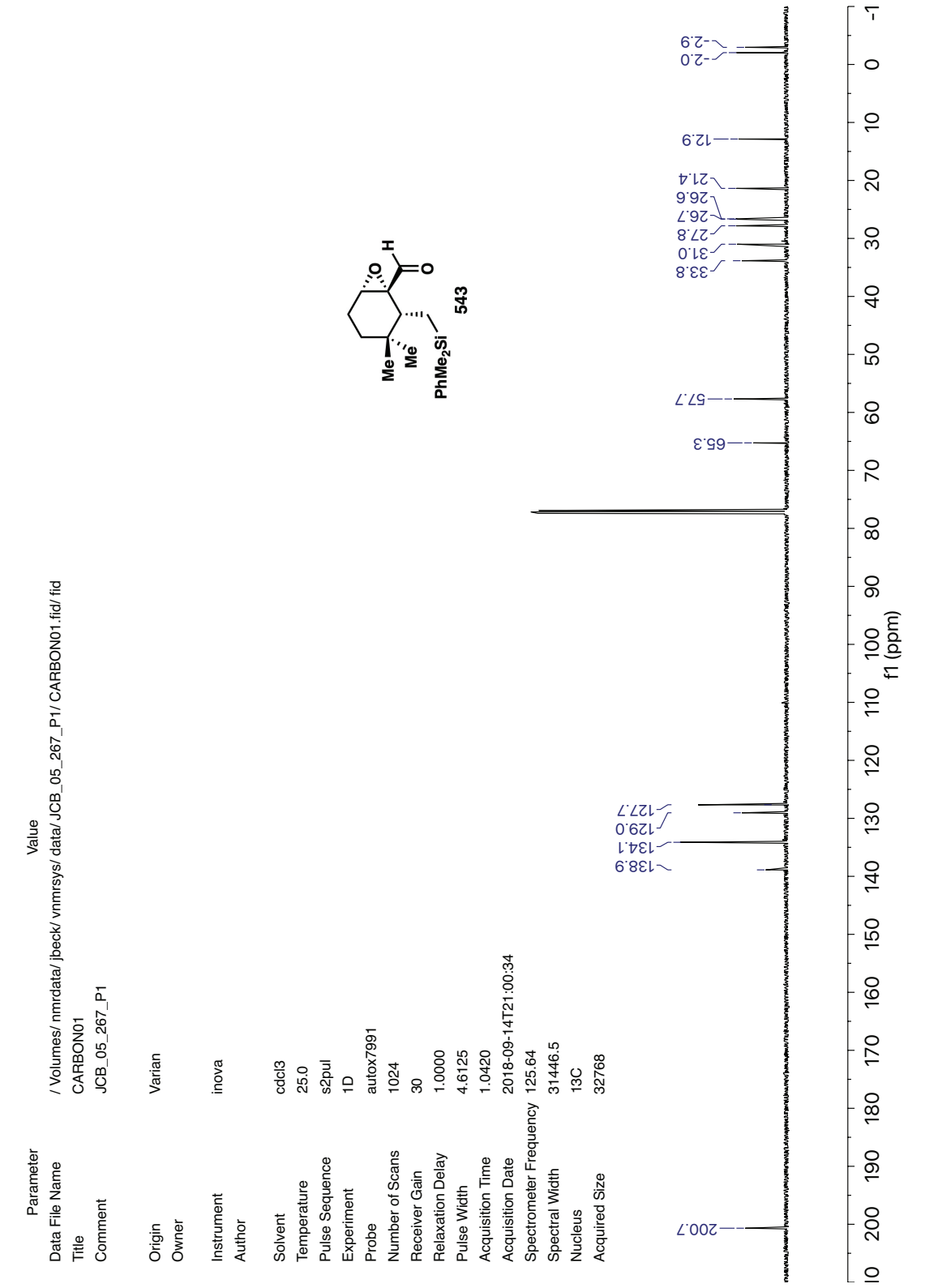
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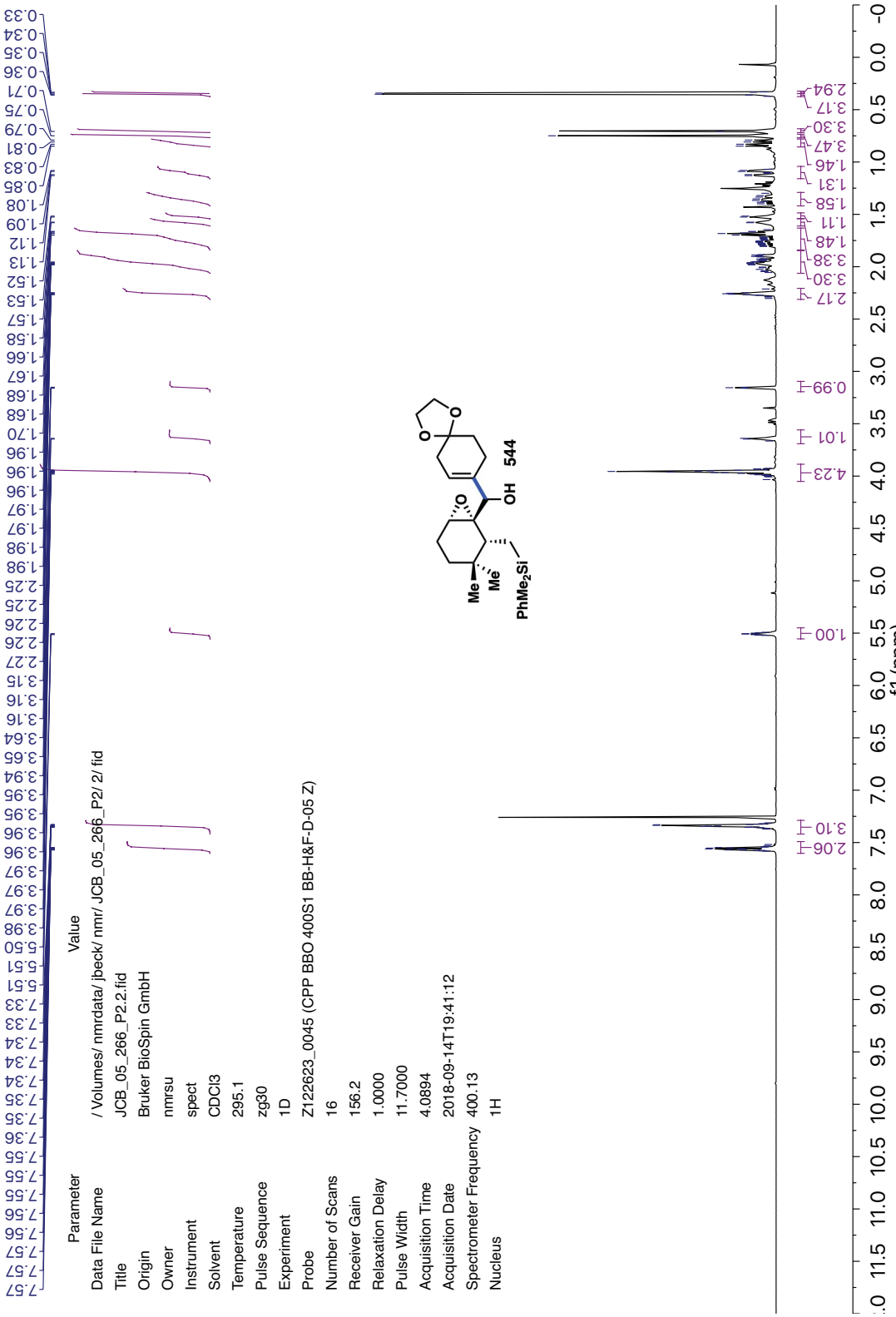
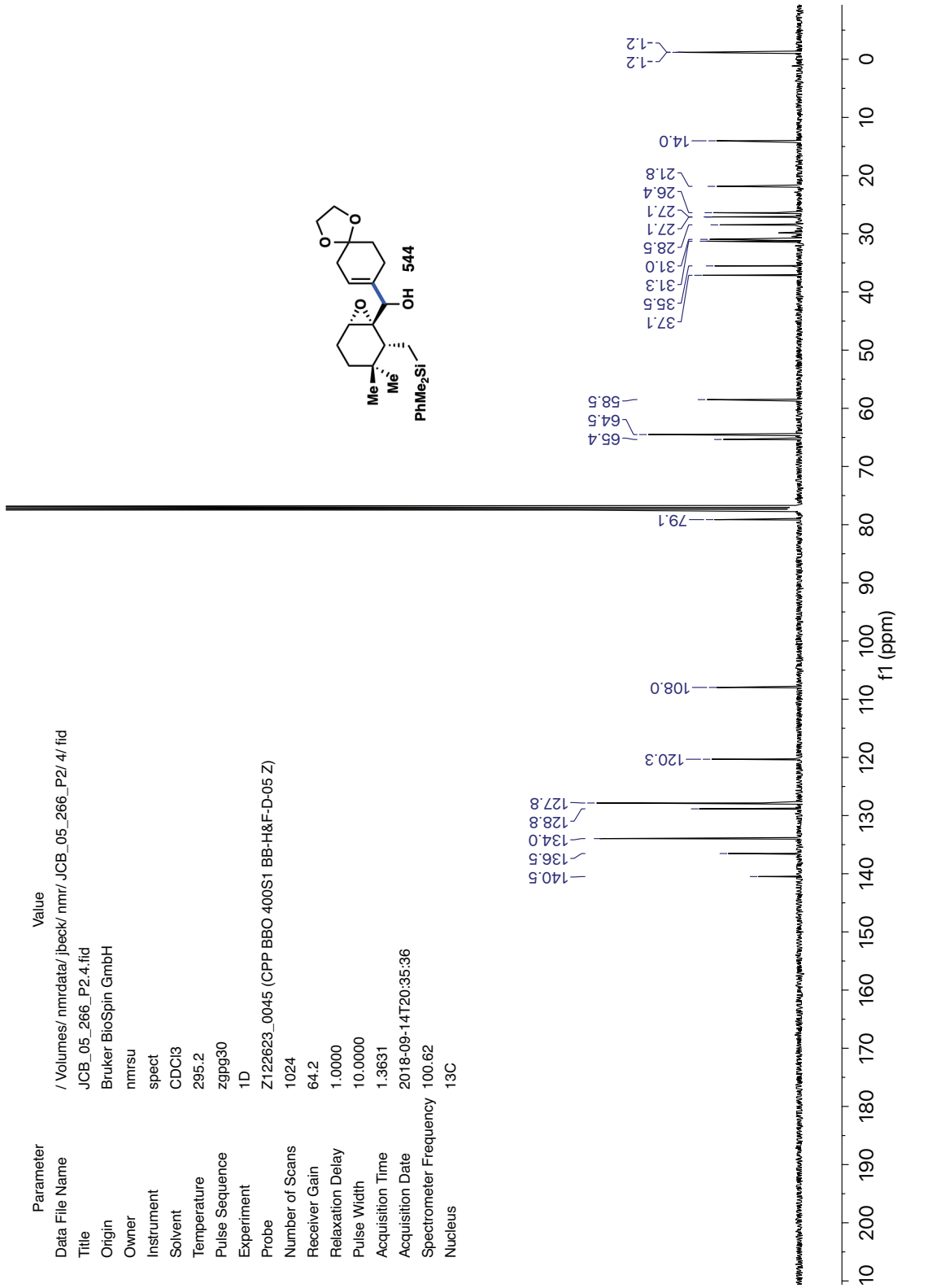
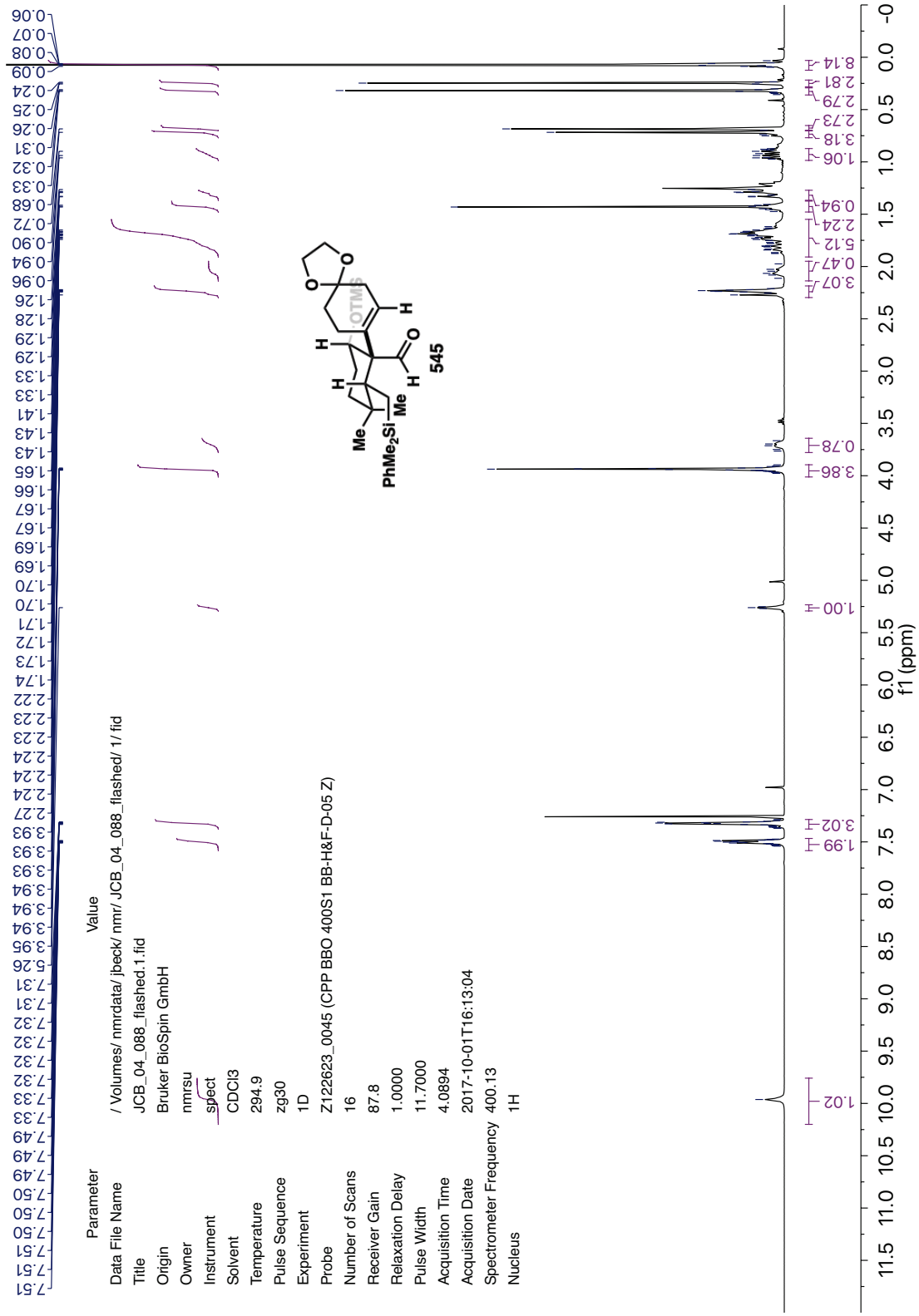
543
f1 (ppm)


544
OH
Me
Me
PhMe2Si
f1 (ppm)
Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_266_P2/ 2/ fid
Title JCB_05_266_P2.2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-14T19:41:12
Spectrometer Frequency 400.13
Nucleus 1H



Parameter	Value
Data File Name	/ Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_266_P2/ 4/ fid
Title	JCB_05_266_P2.4.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	1024
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-09-14T20:35:36
Spectrometer Frequency	100.62
Nucleus	13C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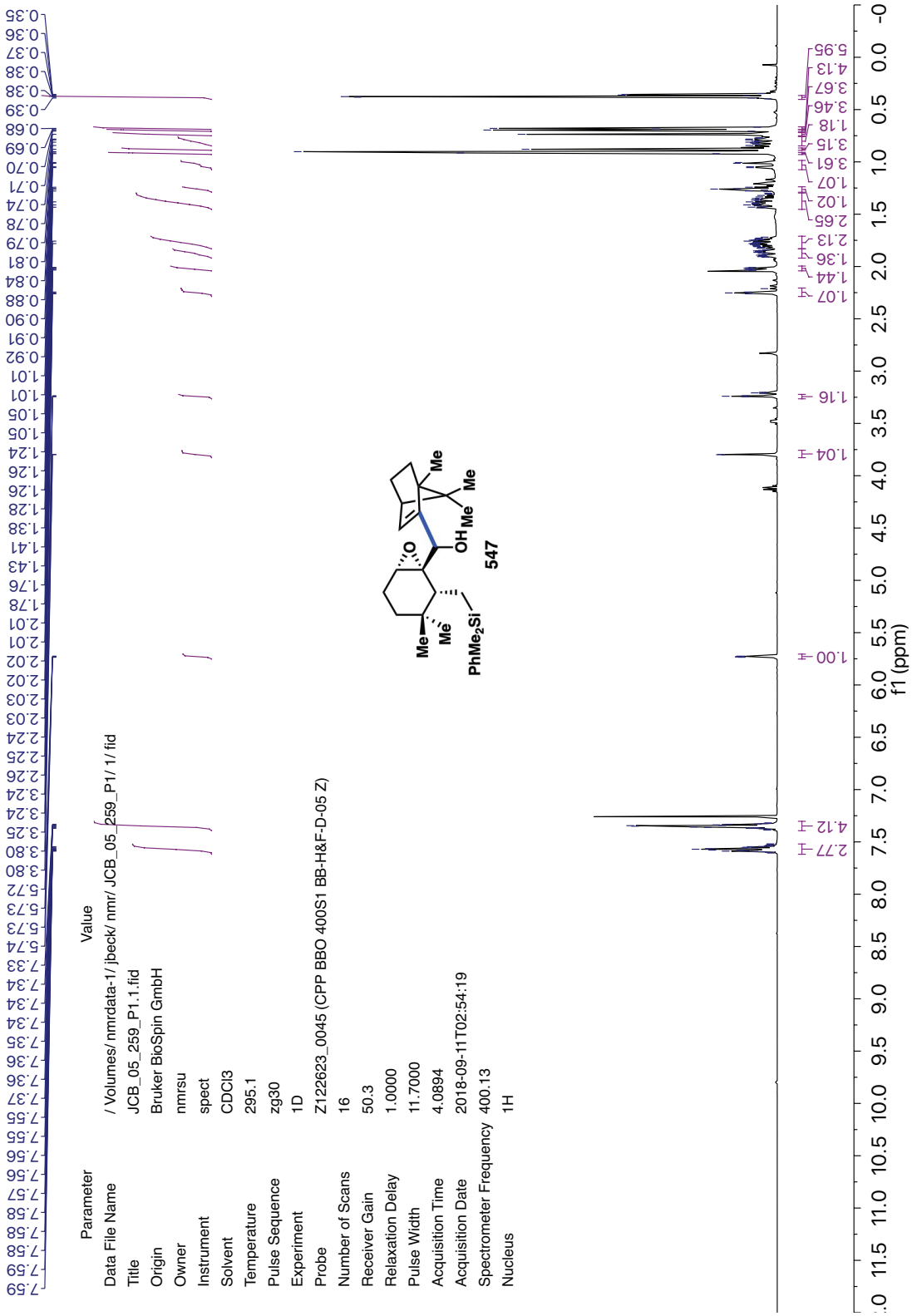
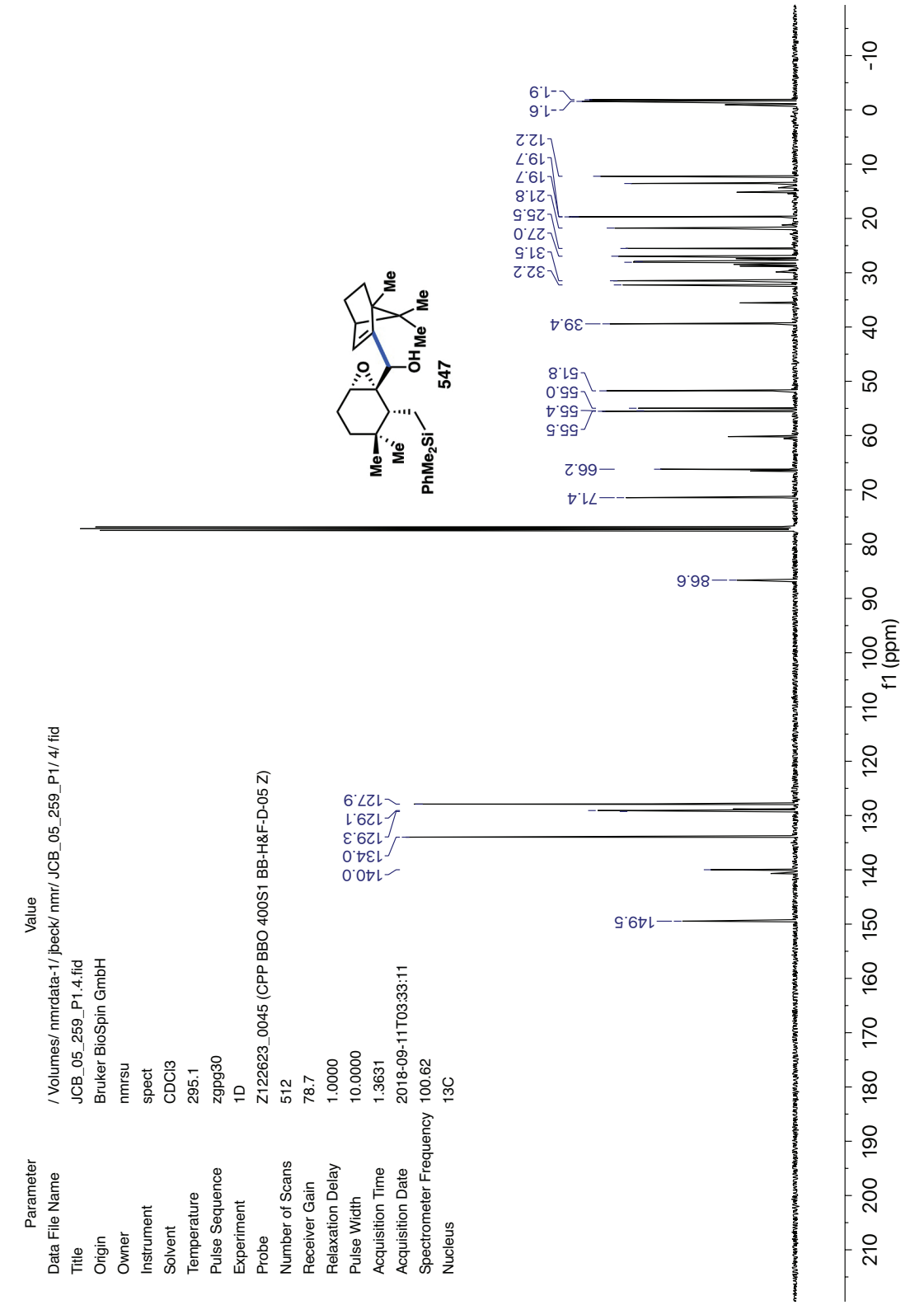
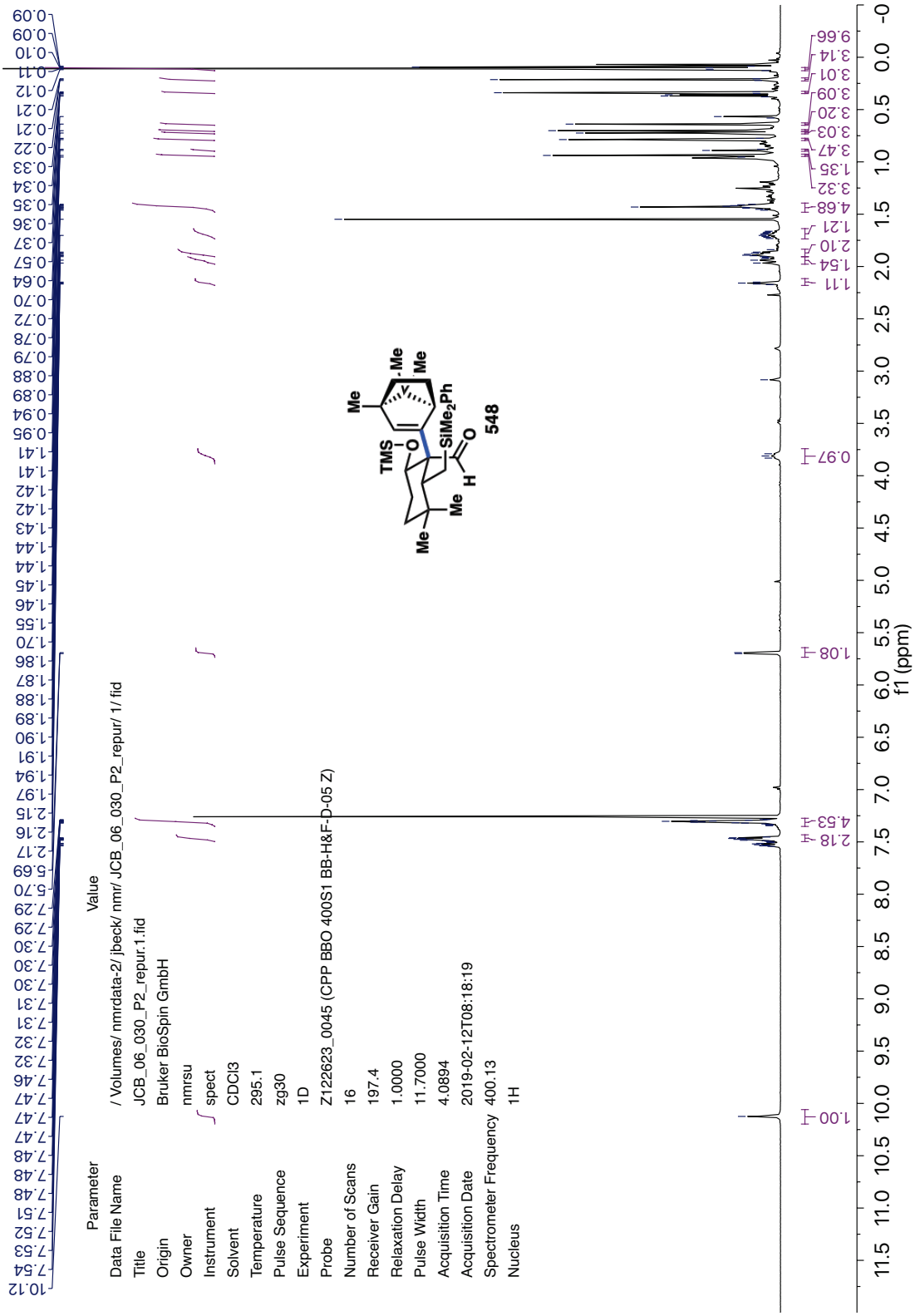
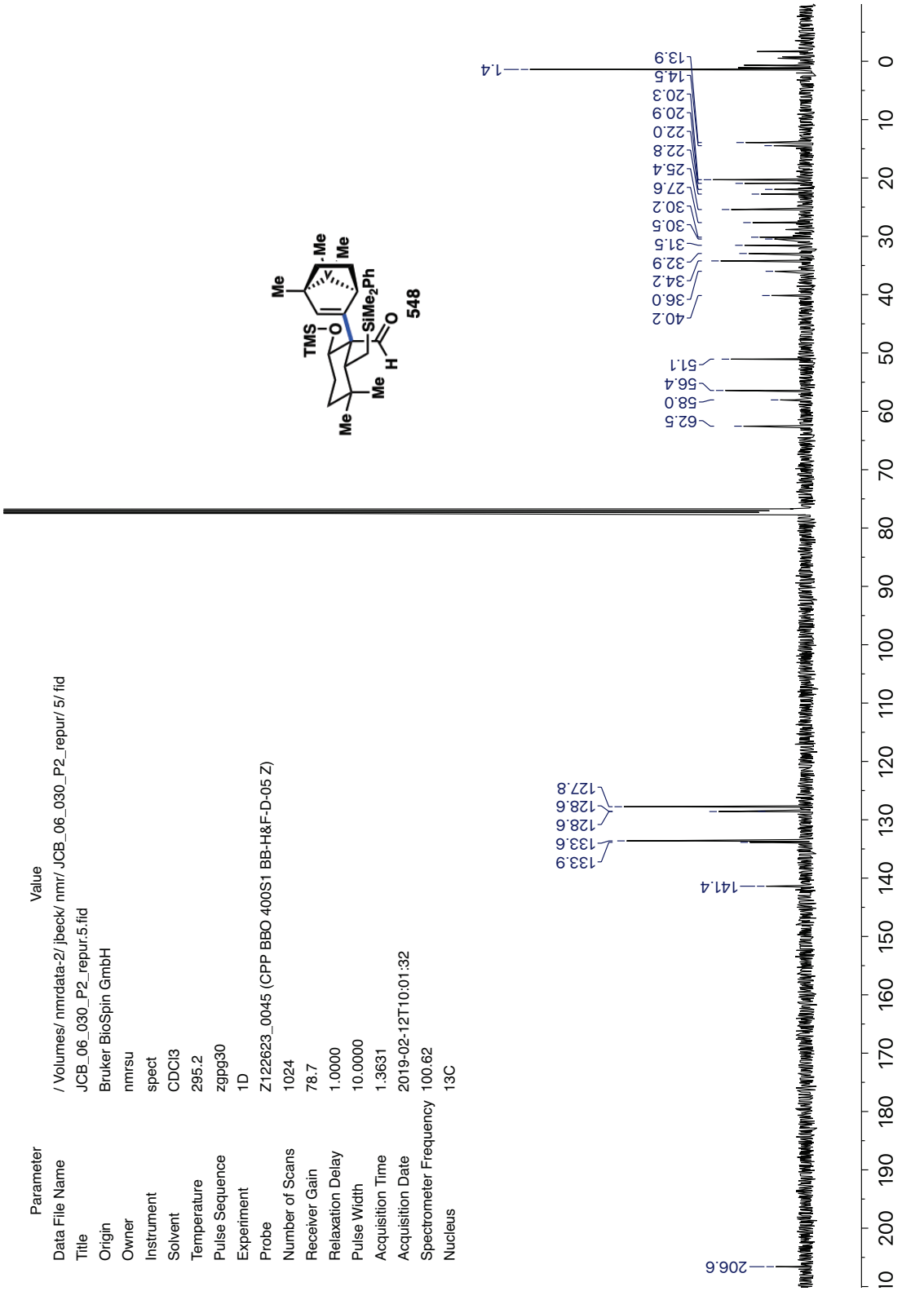
Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_04_088_flashed/ 1/ fid
Title JCB_04_088_flashed.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 294.9
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2017-10-01T16:13:04
Spectrometer Frequency 400.13
Nucleus 1H
OTMS
Me
PhMe2Si
Me
545
f1 (ppm)

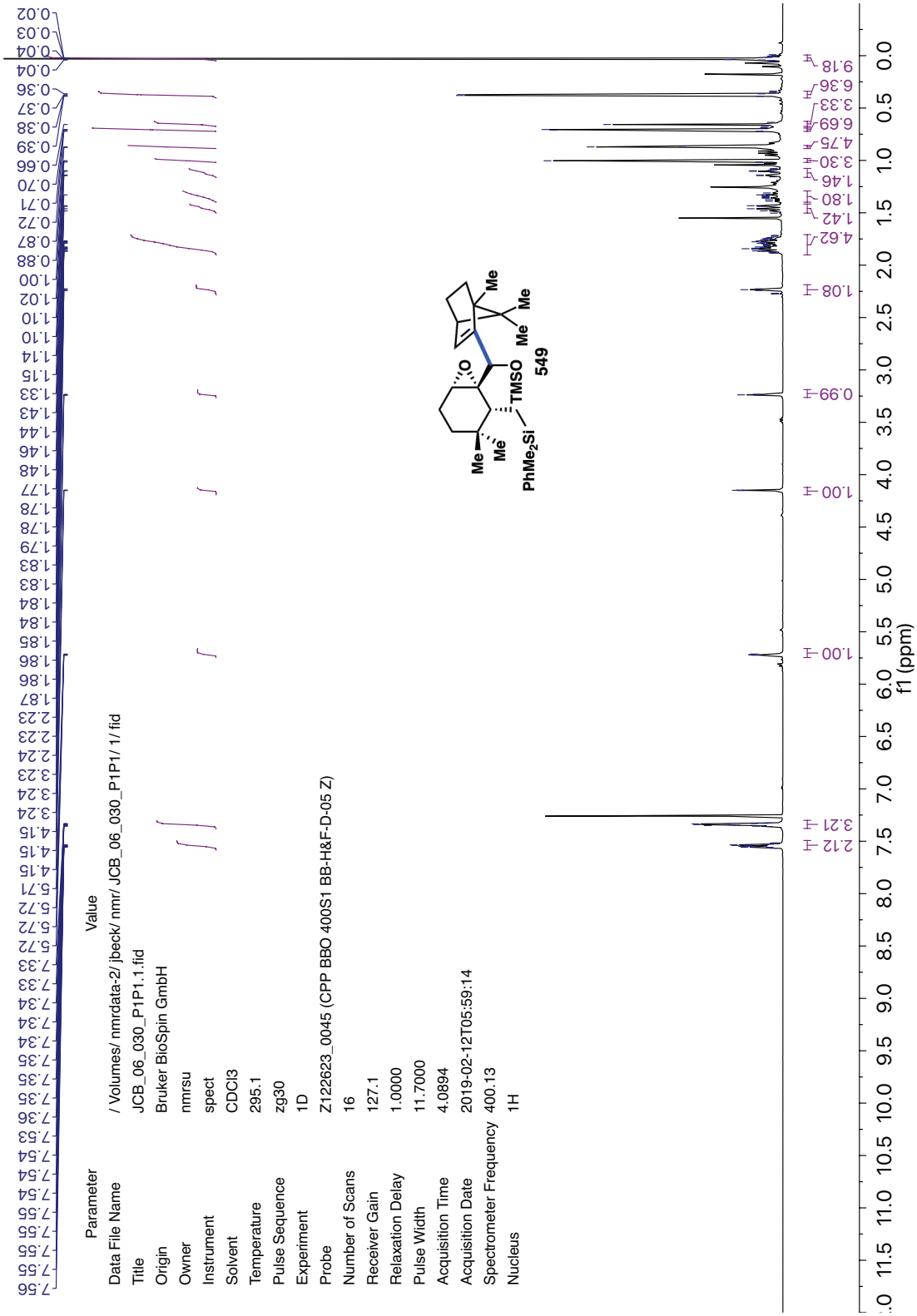

Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_259_P1/ 1/ fid
Title JCB_05_259_P1.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 50.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-11T02:54:19
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
OH Me Me
O
Me
Me
PhMe2Si
547
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_259_P1/ 4/ fid
Title JCB_05_259_P1.4.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-11T03:33:11
Spectrometer Frequency 100.62
Nucleus 13C
547
PhMe2Si
f1 (ppm)

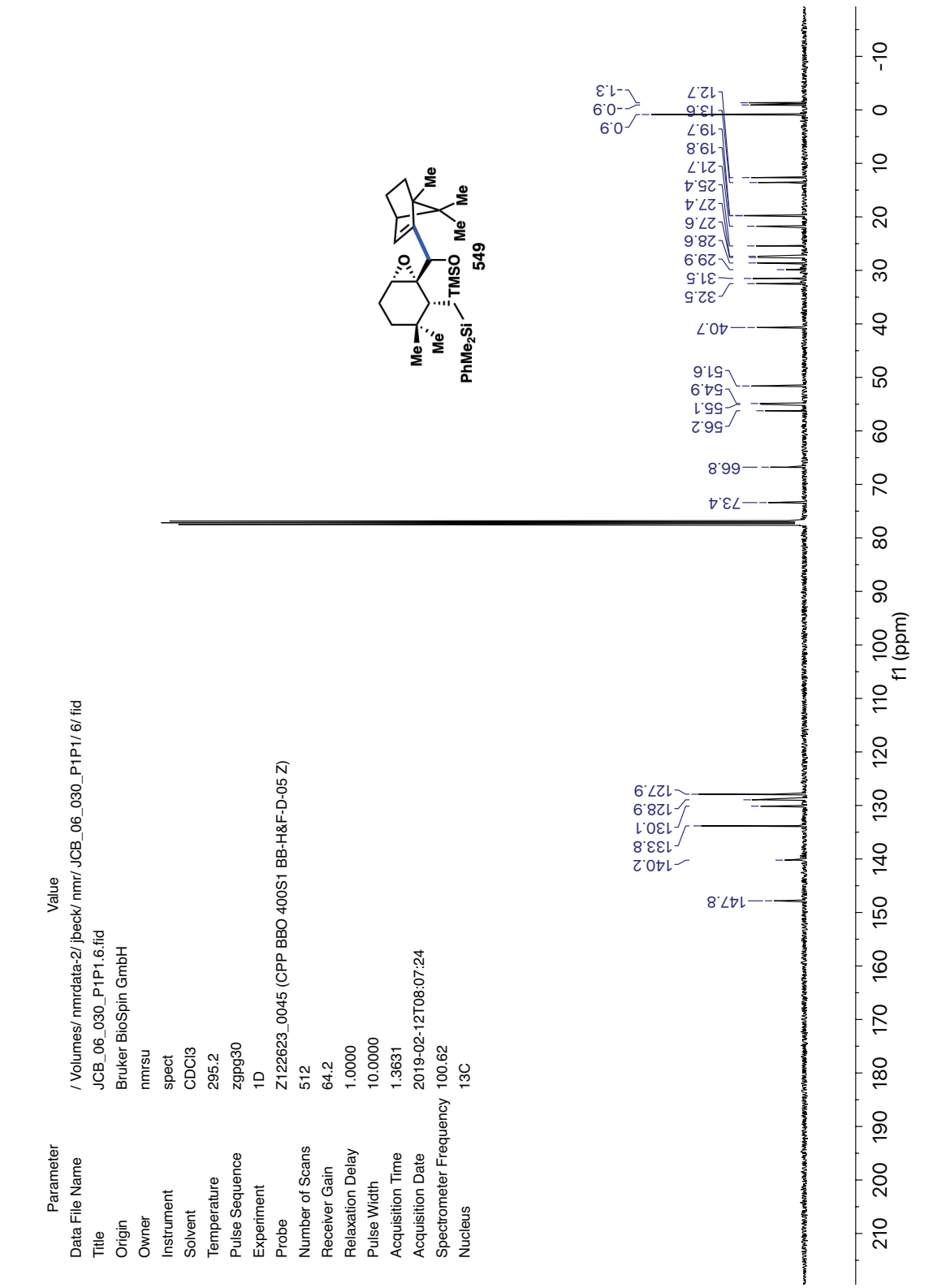


Parameter	Value
Data File Name	/ Volumes/ nmrdata-2/ jbeck/ nmr/ JCB_06_030_P2_repur/ 1/ fid
Title	JCB_06_030_P2_repur.1.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	16
Receiver Gain	197.4
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2019-02-12T08:18:19
Spectrometer Frequency	400.13
Nucleus	1H


Parameter
Value
Data File Name
/ Volumes/ nmrdata-2/ jbeck/ nmr/ JCB_06_030_P2_repur/ 5/ fid
Title
JCB_06_030_P2_repur.5.fid
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
spect
Solvent
CDCl3
Temperature
295.2
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
1024
Receiver Gain
78.7
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2019-02-12T10:01:32
Spectrometer Frequency
100.62
Nucleus
13C
548
TMS
SiMe2Ph
Me
206.6
141.4
133.9
133.6
128.6
128.6
127.8
62.5
58.0
56.4
51.1
40.2
36.0
34.2
32.9
31.5
30.5
30.2
27.6
25.4
22.8
22.0
20.9
20.3
14.5
13.9
1.4



Parameter	Value
Data File Name	/ Volumes/ nmrdata-2/ jbeck/ nmr/ JCB_06_030_P1P1/ 1/ fid
Title	JCB_06_030_P1P1.1.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2019-02-12T05:59:14
Spectrometer Frequency	400.13
Nucleus	1H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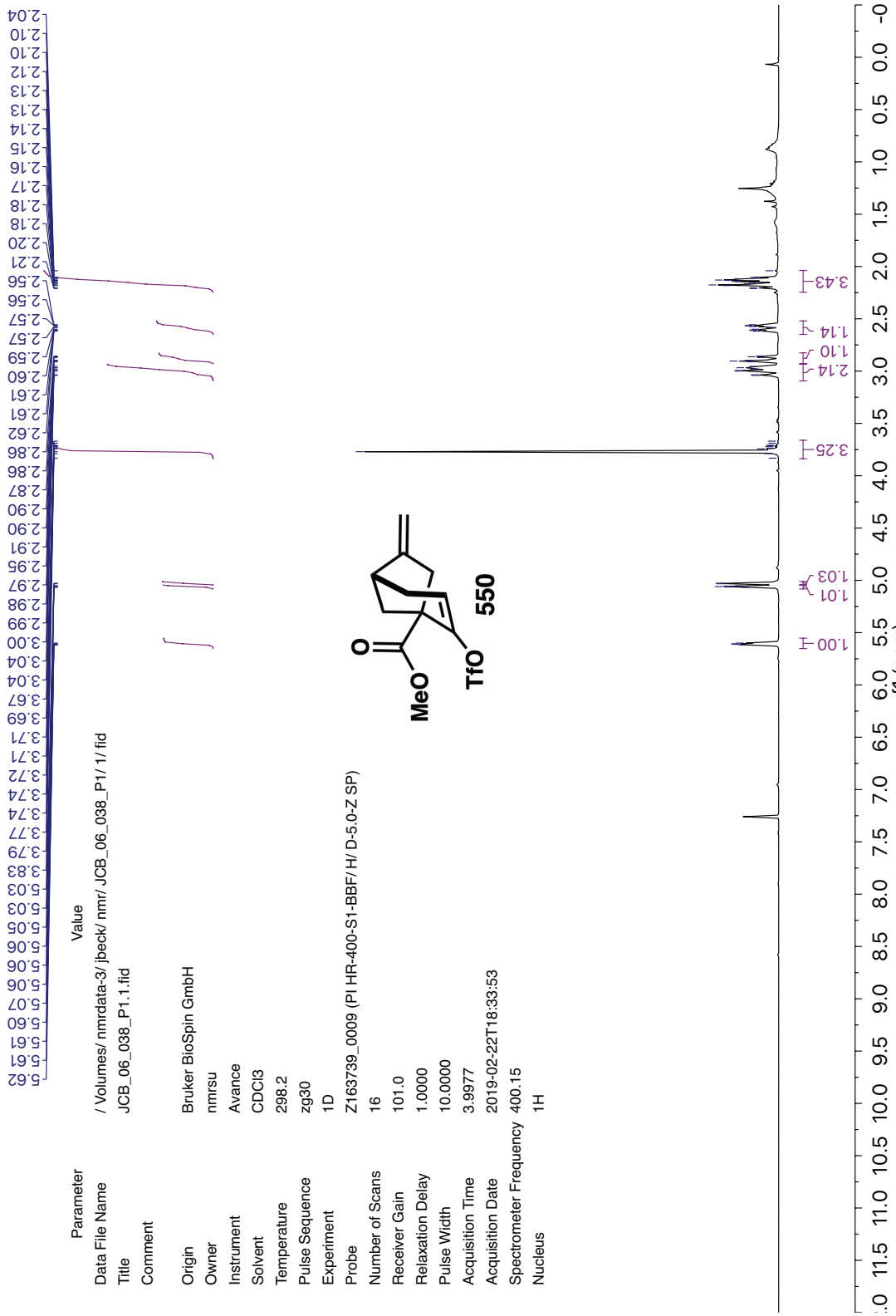
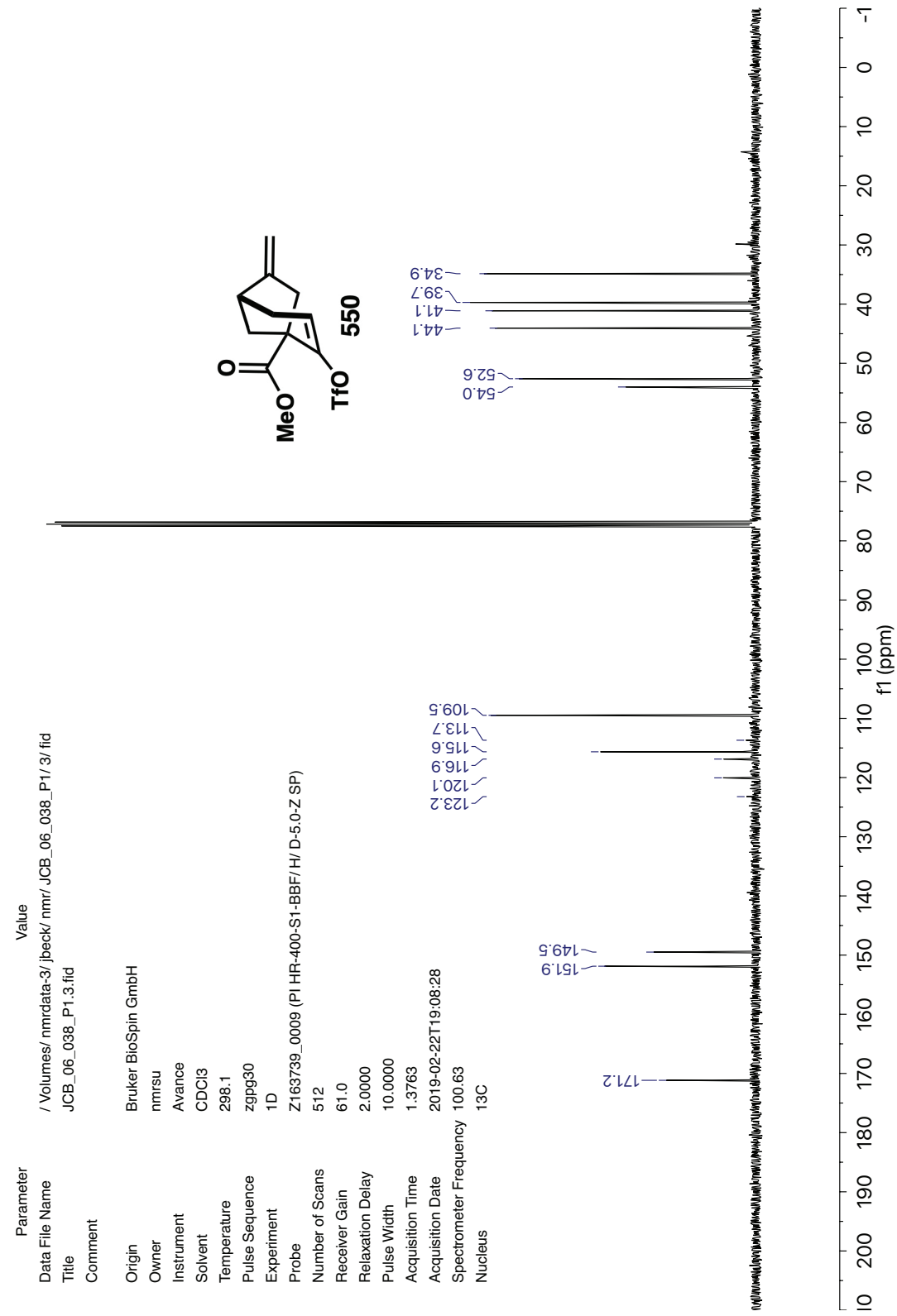
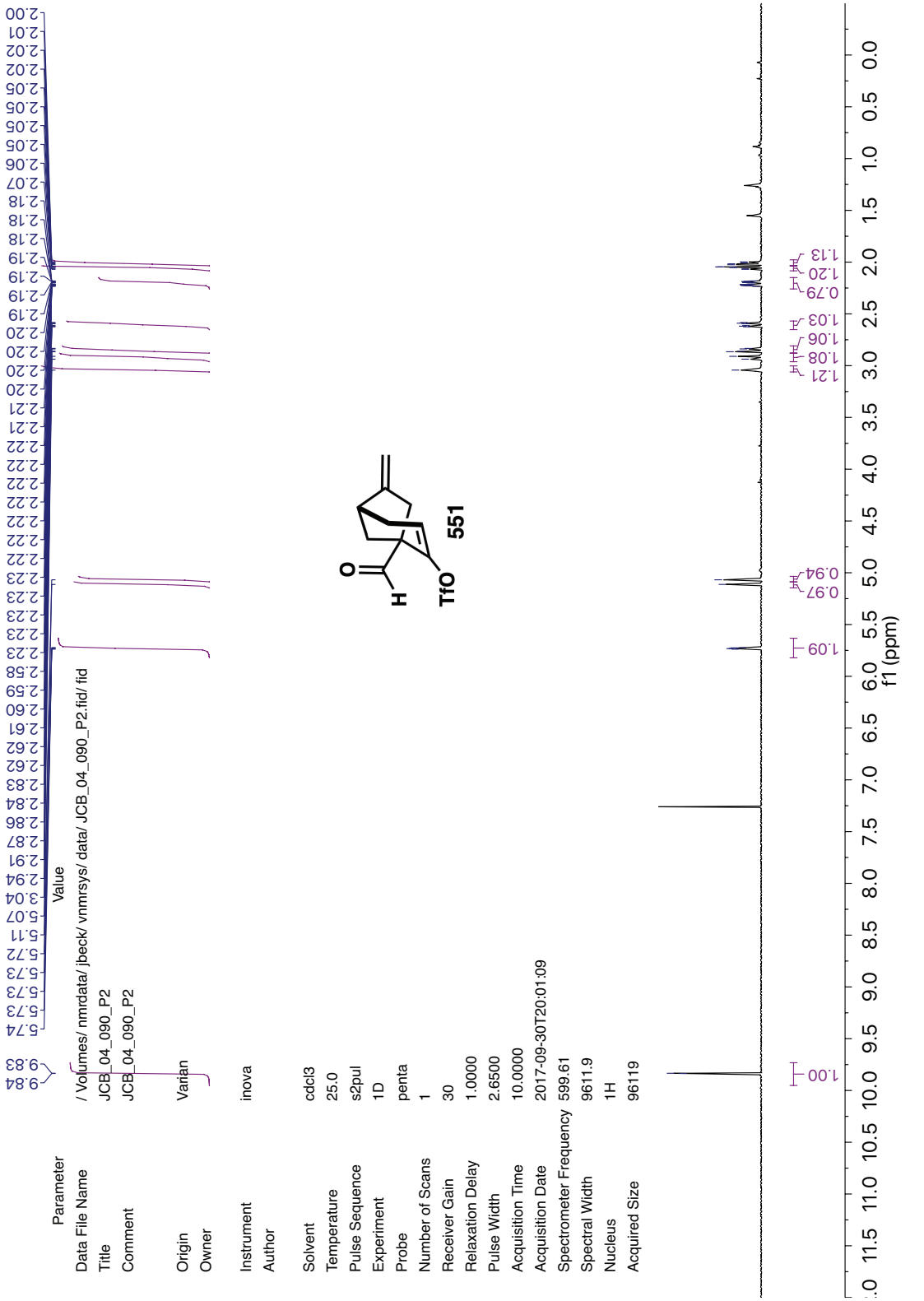
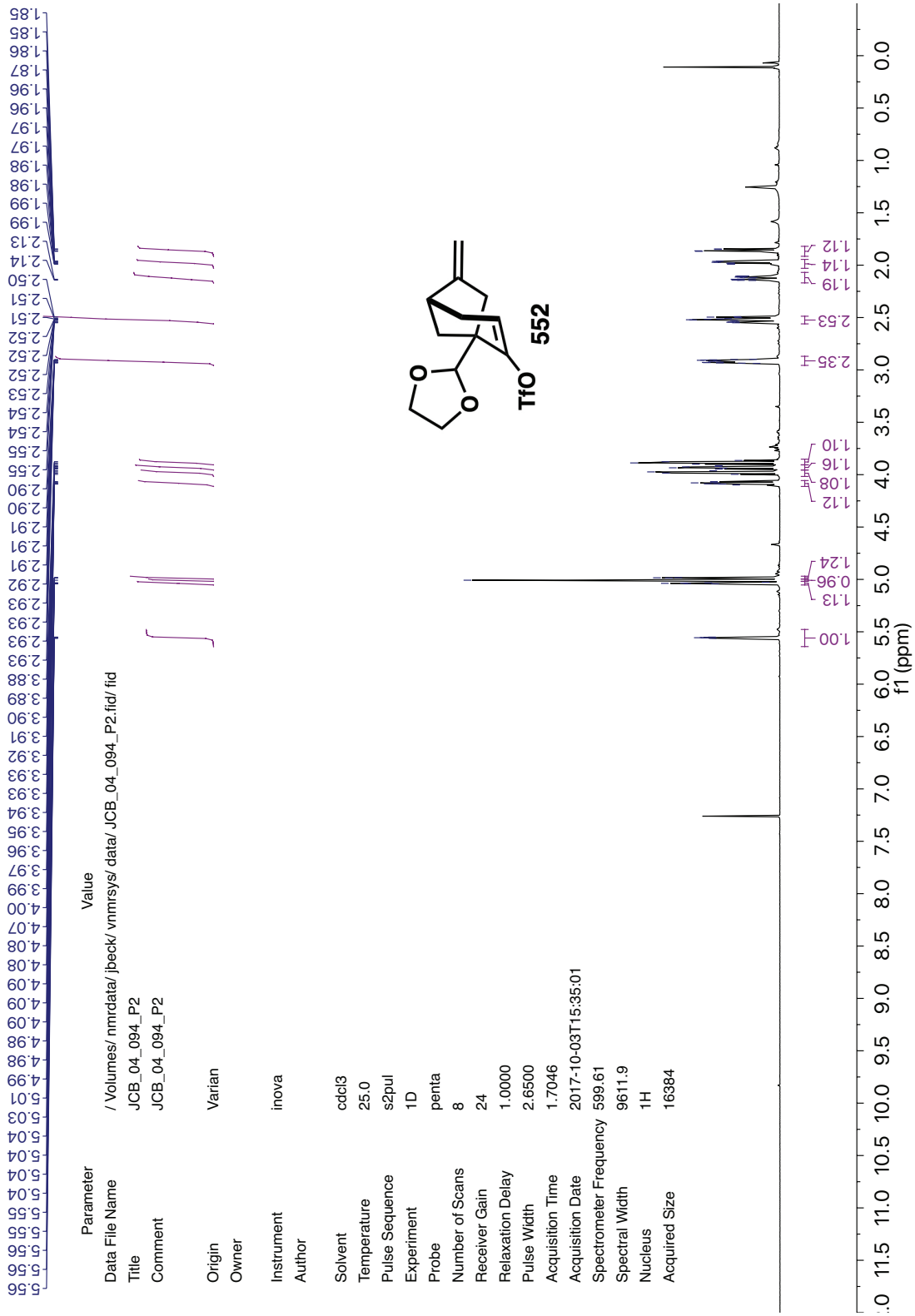
Data File Name / Volumes/ nmrdata-2/ jbeck/ nmr/ JCB_06_030_P1P1/ 6/ fid
Title JCB_06_030_P1P1.6.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-12T08:07:24
Spectrometer Frequency 100.62
Nucleus 13C
Me
Me
Me
Me
TMSO
O
PhMe2Si
549
147.8
140.2
133.8
130.1
128.9
127.9
73.4
66.8
56.2
55.1
54.9
51.6
40.7
32.5
31.5
29.9
28.6
27.6
27.4
25.4
21.7
19.8
19.7
13.6
12.7
0.9
0.9
-1.3
f1 (ppm)

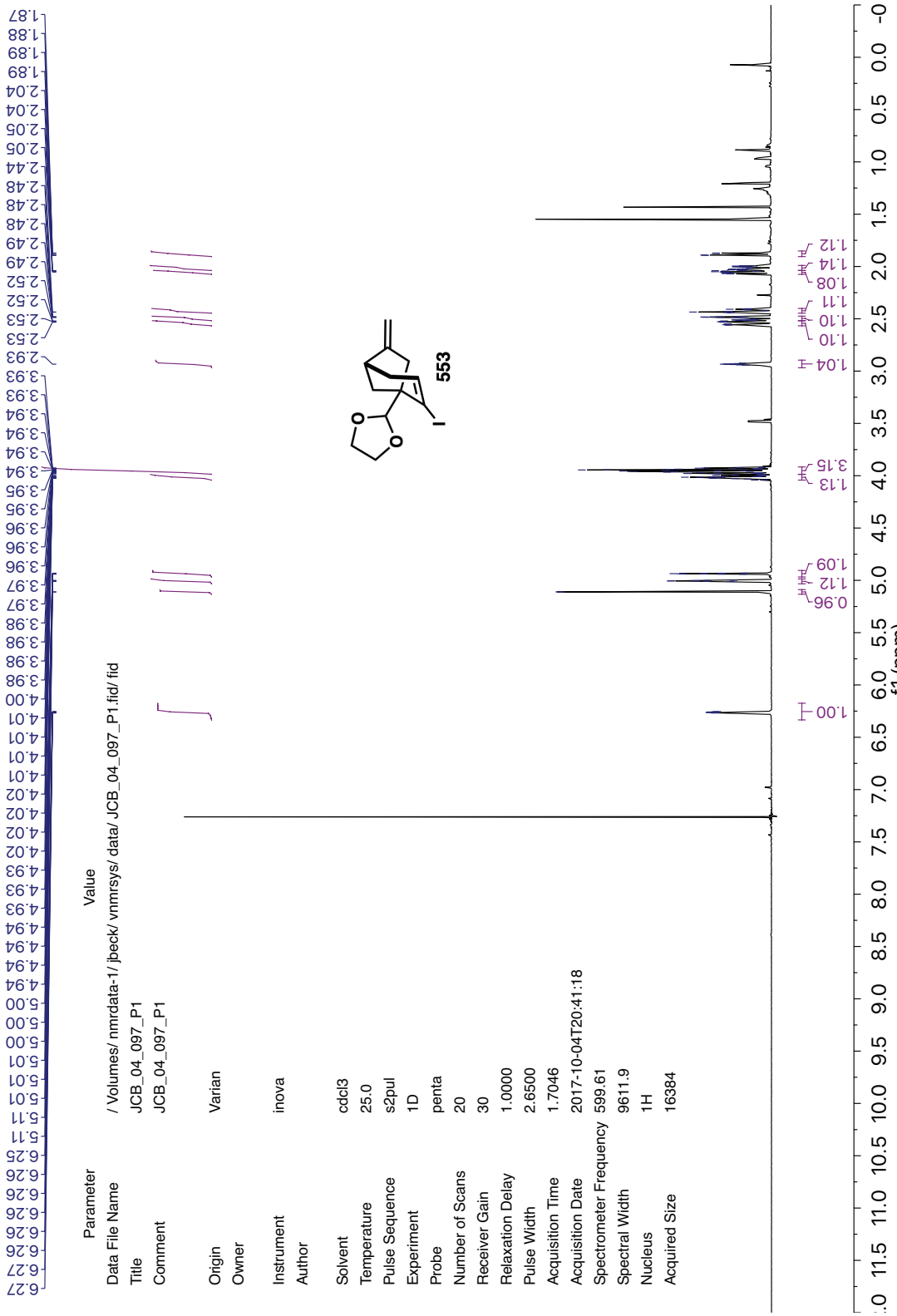

Parameter
Value
Data File Name / Volumes/ nmrdata-3/ jbeck/ nmr/ JCB_06_038_P1/ 1/ fid
Title JCB_06_038_P1.1.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument Avance
Solvent CDCl3
Temperature 298.2
Pulse Sequence zg30
Experiment 1D
Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
Number of Scans 16
Receiver Gain 101.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 3.9977
Acquisition Date 2019-02-22T18:33:53
Spectrometer Frequency 400.15
Nucleus 1H
MeO
O
TfO
550
1.00
1.03
1.01
3.25
2.14
1.10
1.14
3.43
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-3/ jbeck/ nmr/ JCB_06_038_P1/ 3/ fid
Title JCB_06_038_P1.3.fid
Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument Avance
Solvent CDCl3
Temperature 298.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
Number of Scans 512
Receiver Gain 61.0
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3763
Acquisition Date 2019-02-22T19:08:28
Spectrometer Frequency 100.63
Nucleus 13C
MeO
O
TfO
550
171.2
151.9
149.5
123.2
120.1
116.9
115.6
113.7
109.5
54.0
52.6
44.1
41.1
39.7
34.9
f1 (ppm)

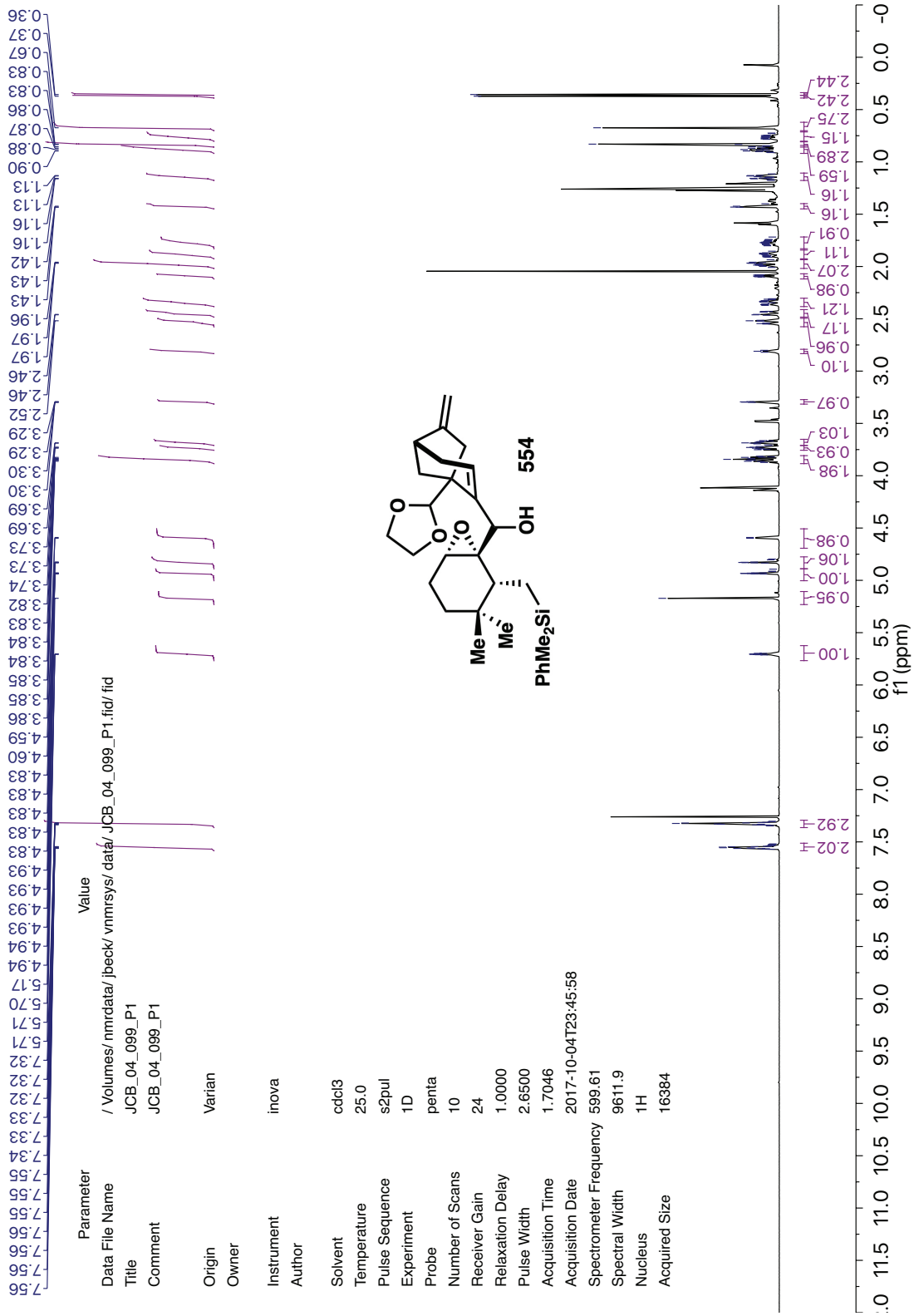
Parameter	Value
Data File Name	/ Volumes/ nmrdata-3/ jbeck/ nmr/ JCB_06_038_P1/ 2/ fid
Title	JCB_06_038_P1.2.fid
Comment	
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	Avance
Solvent	CDCl3
Temperature	298.2
Pulse Sequence	zgig
Experiment	1D
Probe	Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
Number of Scans	16
Receiver Gain	101.0
Relaxation Delay	1.0000
Pulse Width	18.0000
Acquisition Time	0.7209
Acquisition Date	2019-02-22T18:36:36
Spectrometer Frequency	376.48
Nucleus	19F


551
TfO
H
O
f1 (ppm)
Parameter
Value
Data File Name / Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_04_090_P2.fid/ fid
Title JCB_04_090_P2
Comment JCB_04_090_P2
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 1
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 10.0000
Acquisition Date 2017-09-30T20:01:09
Spectrometer Frequency 599.61
Spectral Width 9611.9
Nucleus 1H
Acquired Size 96119

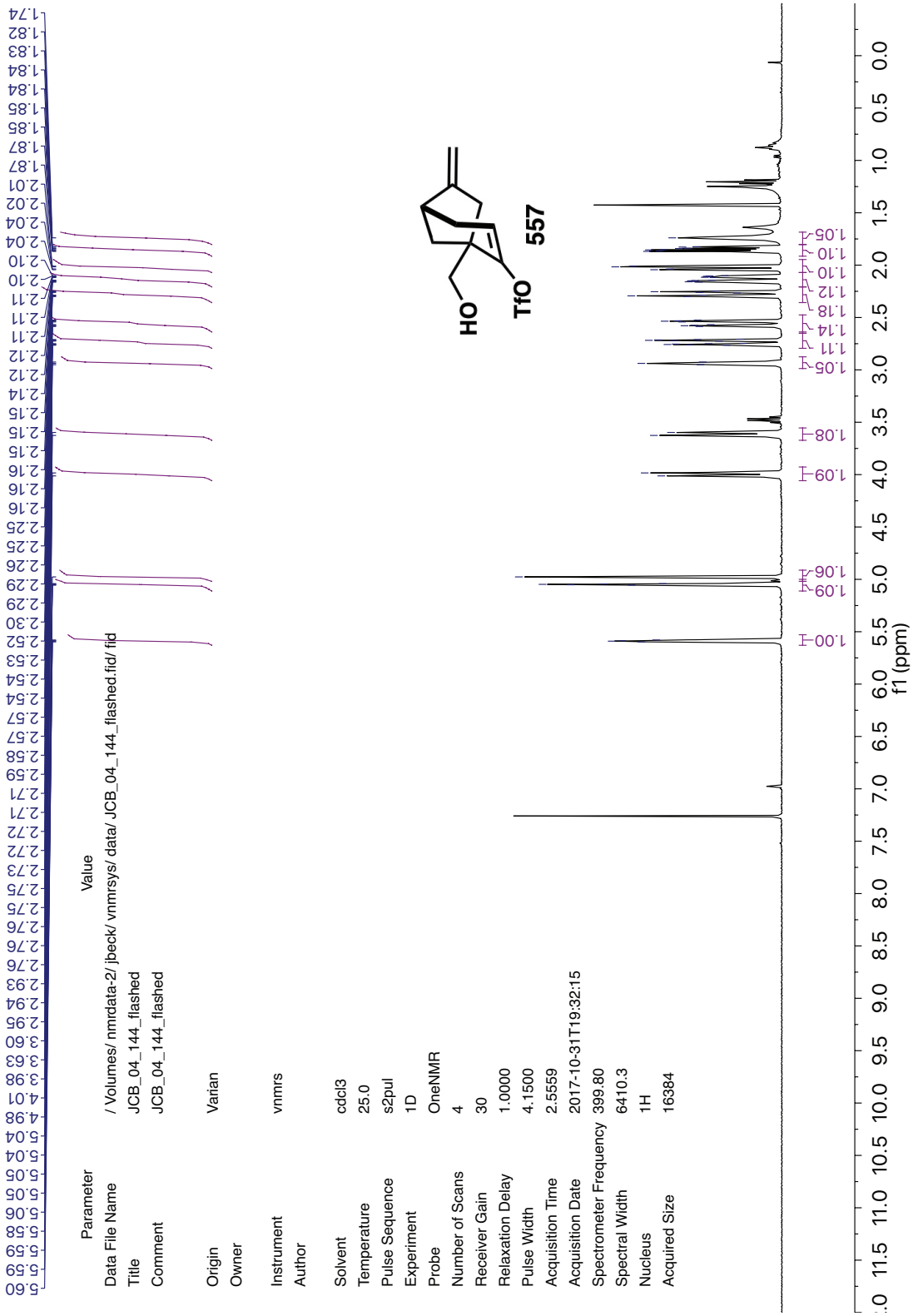

Parameter
Value
Data File Name / Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_04_094_P2.fid/ fid
Title JCB_04_094_P2
Comment JCB_04_094_P2
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 8
Receiver Gain 24
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Acquisition Date 2017-10-03T15:35:01
Spectrometer Frequency 599.61
Spectral Width 9611.9
Nucleus 1H
Acquired Size 16384
TfO
552
1.00
0.96
2.35
2.53
f1 (ppm)



Parameter	Value
Data File Name	/ Volumes/ nmrdata-1/ jbeck/ vnmrsys/ data/ JCB_04_097_P1.fid/ fid
Title	JCB_04_097_P1
Comment	JCB_04_097_P1
Origin	Varian
Owner	
Instrument	inova
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	penta
Number of Scans	20
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	2.6500
Acquisition Time	1.7046
Acquisition Date	2017-10-04T20:41:18
Spectrometer Frequency	599.61
Spectral Width	9611.9
Nucleus	1H
Acquired Size	16384

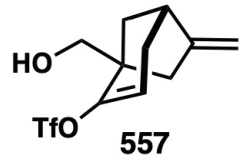


Parameter	Value
Data File Name	/ Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_04_099_P1.fid/ fid
Title	JCB_04_099_P1
Comment	JCB_04_099_P1
Origin	Varian
Owner	
Instrument	inova
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	penta
Number of Scans	10
Receiver Gain	24
Relaxation Delay	1.0000
Pulse Width	2.6500
Acquisition Time	1.7046
Acquisition Date	2017-10-04T23:45:58
Spectrometer Frequency	599.61
Spectral Width	9611.9
Nucleus	1H
Acquired Size	16384

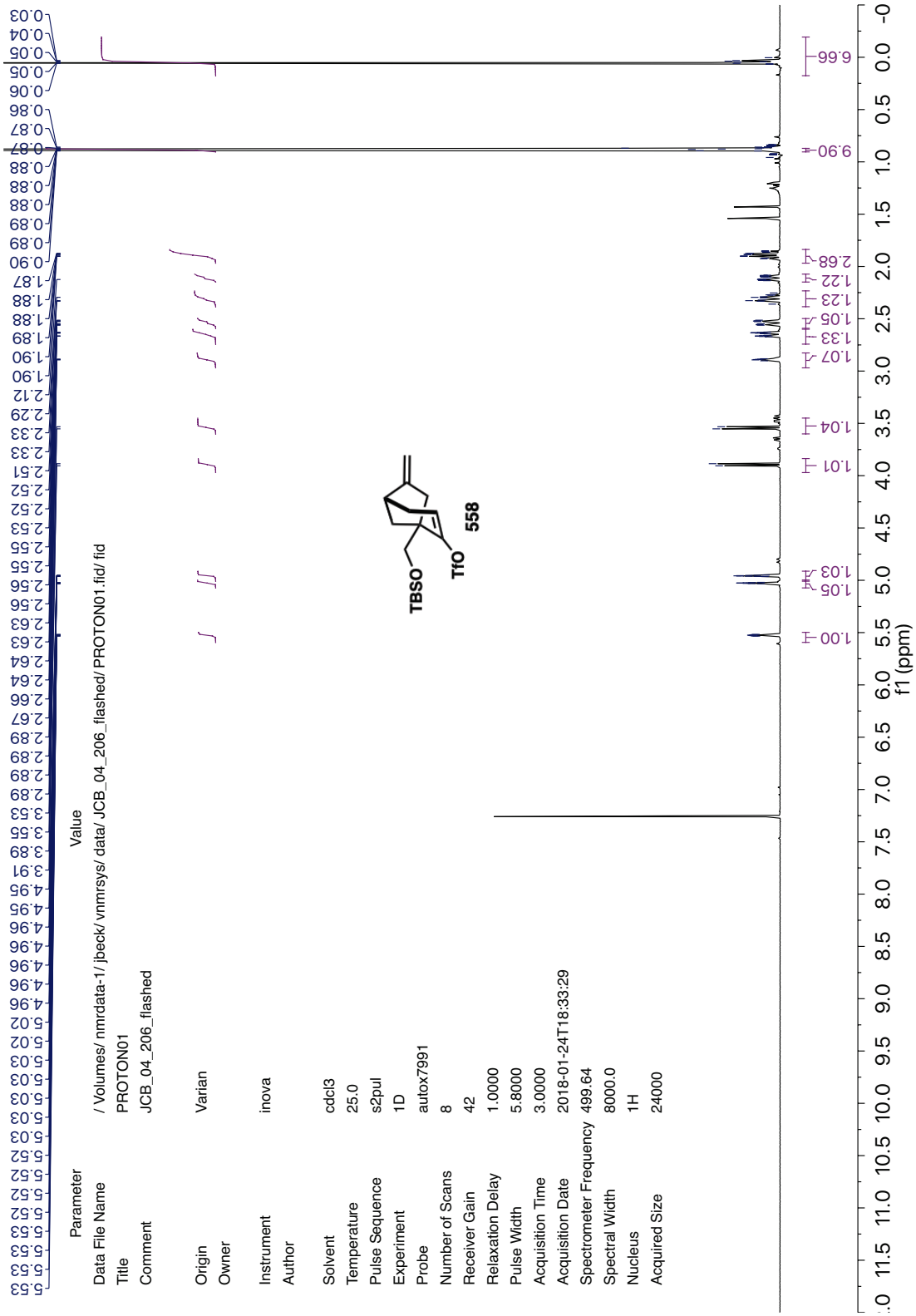

HO
TfO
557
Parameter
Value
Data File Name / Volumes/ nmrdata-2/ jbeck/ vnmrsys/ data/ JCB_04_144_flashed.fid/ fid
Title JCB_04_144_flashed
Comment JCB_04_144_flashed
Origin Varian
Owner
Instrument vnmrs
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe OneNMR
Number of Scans 4
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 4.1500
Acquisition Time 2.5559
Acquisition Date 2017-10-31T19:32:15
Spectrometer Frequency 399.80
Spectral Width 6410.3
Nucleus 1H
Acquired Size 16384
f1 (ppm)

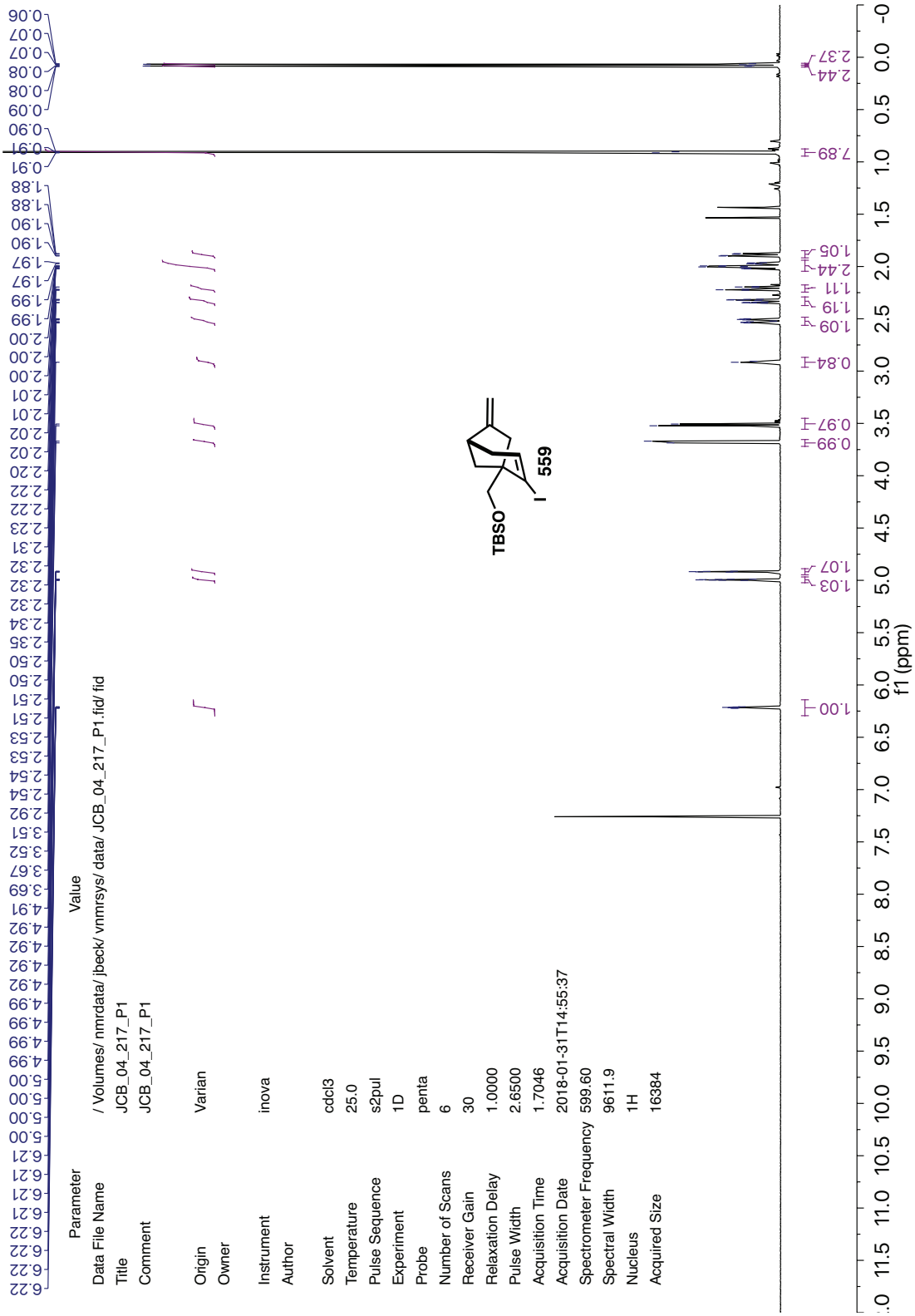
-74.28

Parameter	Value
Data File Name	/ Volumes/ nmrdata-2/ jbeck/ vnmrsys/ data/ JCB_04_144_flashed_19F.fid/ fid
Title	JCB_04_144_flashed_19F
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Owner	
Instrument	vnmrs
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	OneNMR
Number of Scans	4
Receiver Gain	54
Relaxation Delay	1.0000
Pulse Width	3.2333
Acquisition Time	0.7340
Acquisition Date	2017-10-31T19:34:30
Spectrometer Frequency	376.15
Spectral Width	89285.7
Nucleus	19F
Acquired Size	65536

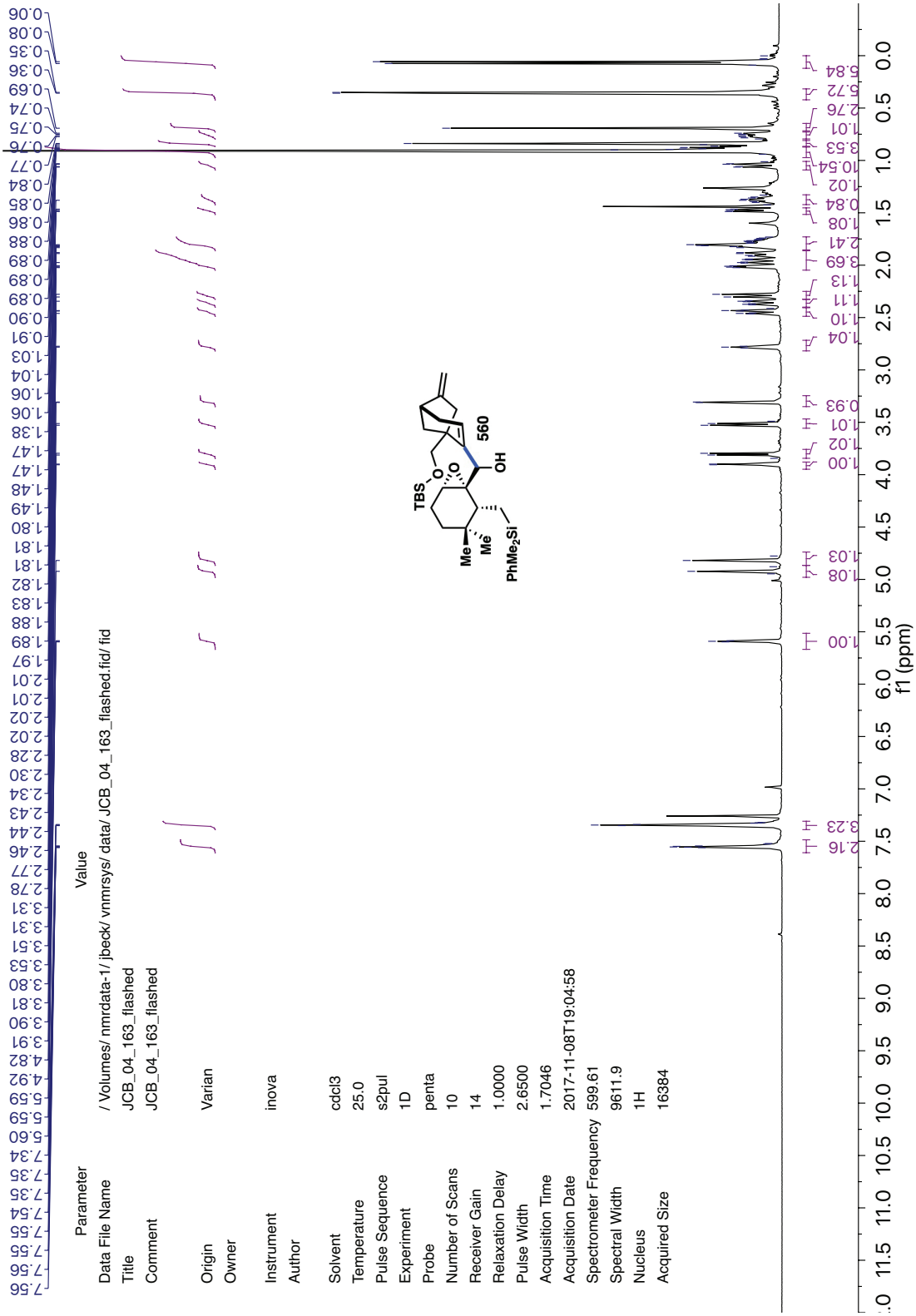


557


TBSO
TfO
558
f1 (ppm)
Parameter
Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ vnmrsys/ data/ JCB_04_206_flashed/ PROTON01.fid/ fid
Title PROTON01
Comment JCB_04_206_flashed
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe autox7991
Number of Scans 8
Receiver Gain 42
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2018-01-24T18:33:29
Spectrometer Frequency 499.64
Spectral Width 8000.0
Nucleus 1H
Acquired Size 24000



Parameter	Value
Data File Name	/ Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_04_217_P1.fid/ fid
Title	JCB_04_217_P1
Comment	JCB_04_217_P1
Origin	Varian
Owner	
Instrument	inova
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	penta
Number of Scans	6
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	2.6500
Acquisition Time	1.7046
Acquisition Date	2018-01-31T14:55:37
Spectrometer Frequency	599.60
Spectral Width	9611.9
Nucleus	1H
Acquired Size	16384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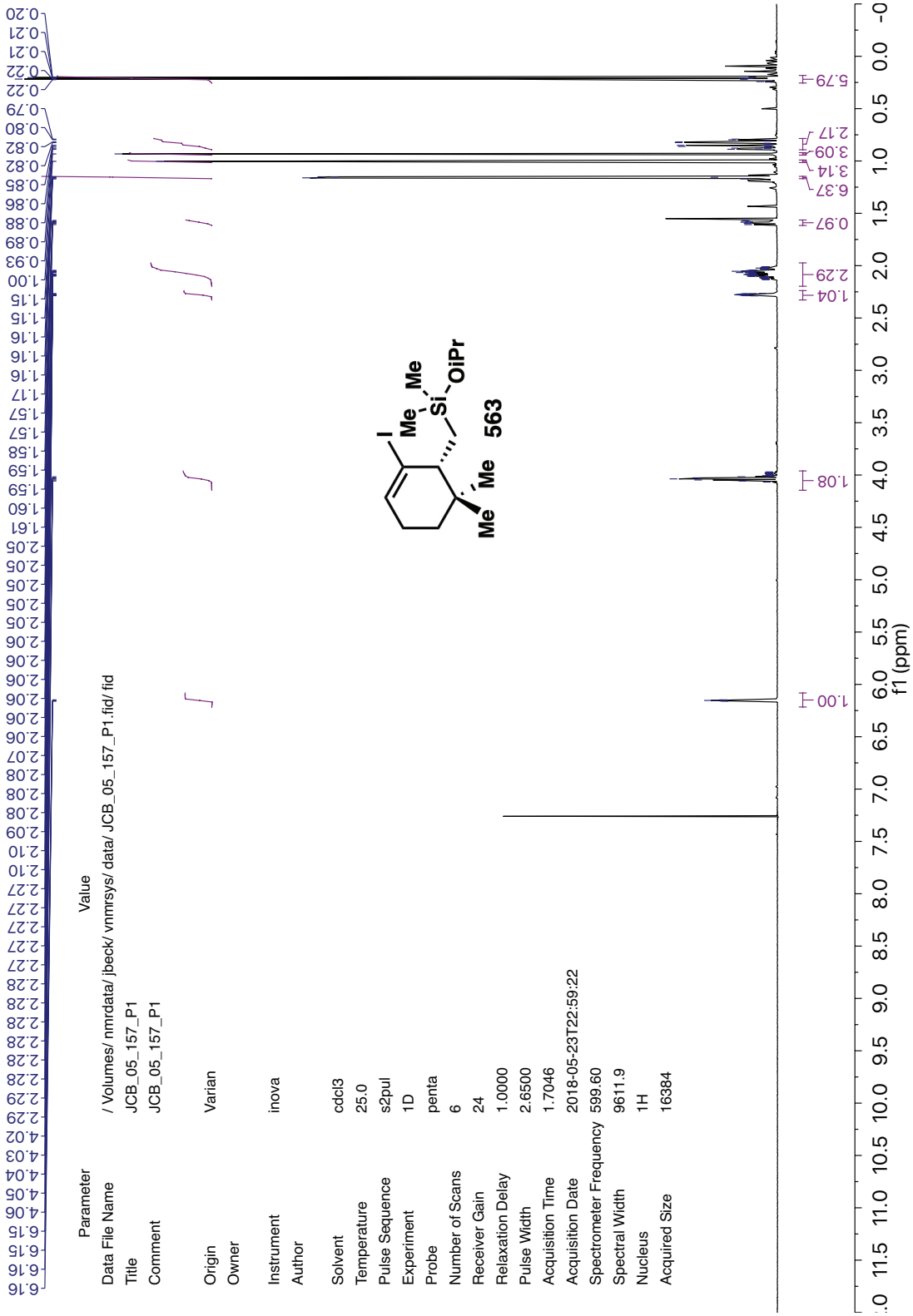
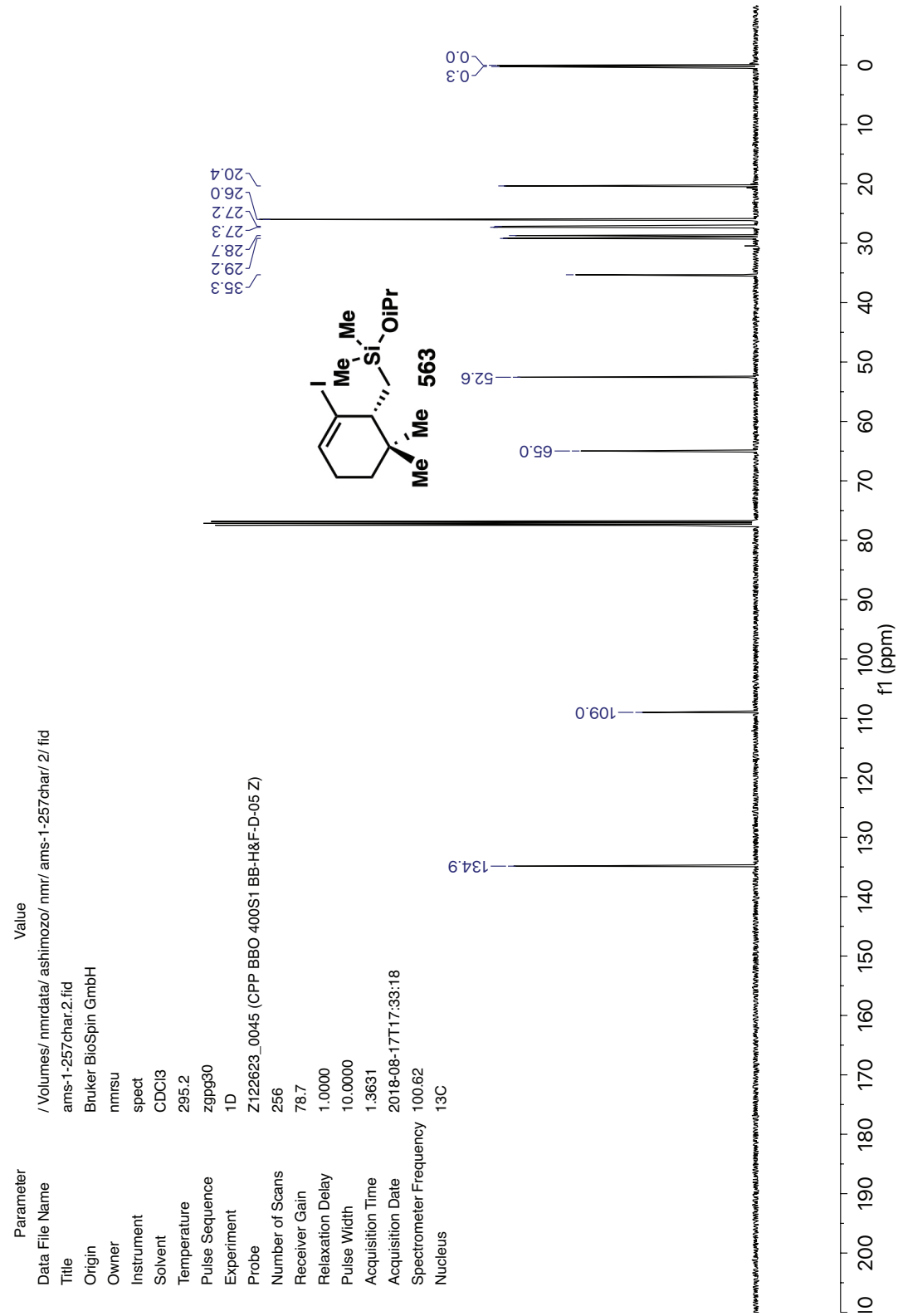
Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ vnmrsys/ data/ JCB_04_163_flashed.fid/ fid
Title JCB_04_163_flashed
Comment JCB_04_163_flashed
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 10
Receiver Gain 14
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Acquisition Date 2017-11-08T19:04:58
Spectrometer Frequency 599.61
Spectral Width 9611.9
Nucleus 1H
Acquired Size 16384
TBS
Me
Me
PhMe2Si
560
OH
f1 (ppm)


Me
Me
Si
OiPr
I
Me
Me
563
Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_05_157_P1.fid/ fid
Title JCB_05_157_P1
Comment JCB_05_157_P1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 6
Receiver Gain 24
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Acquisition Date 2018-05-23T22:59:22
Spectrometer Frequency 599.60
Spectral Width 9611.9
Nucleus 1H
Acquired Size 16384
5.79
2.17
3.09
3.14
6.37
0.97
2.29
1.04
1.08
1.00
f1 (ppm)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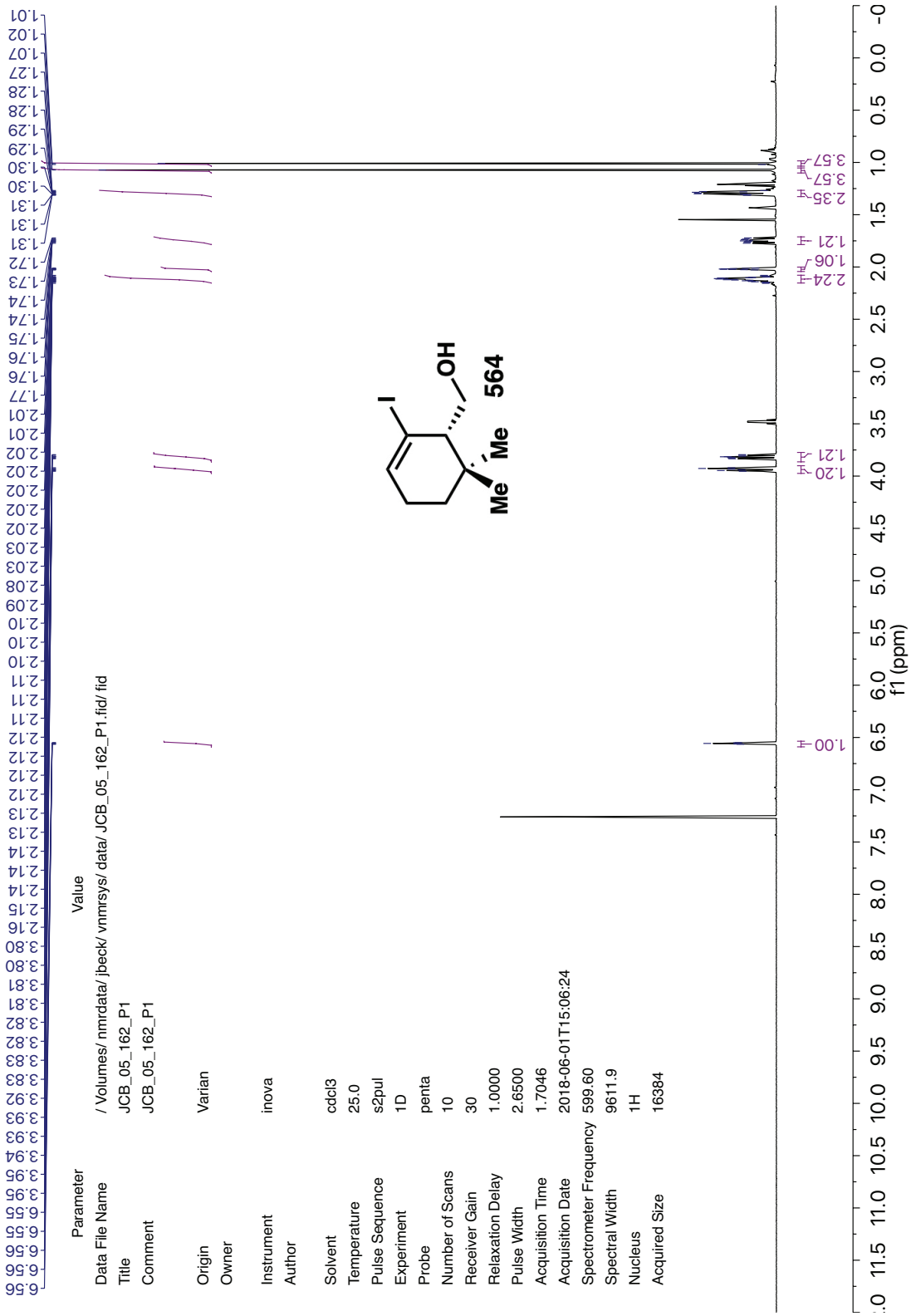
Data File Name / Volumes/ nmrdata/ ashimozo/ nmr/ ams-1-257char/ 2/ fid
Title ams-1-257char.2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 256
Receiver Gain 78.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-08-17T17:33:18
Spectrometer Frequency 100.62
Nucleus 13C
134.9
109.0
65.0
52.6
35.3
29.2
28.7
27.3
27.2
26.0
20.4
0.3
0.0
I
Me
Me
Si
OiPr
Me
Me
563
f1 (ppm)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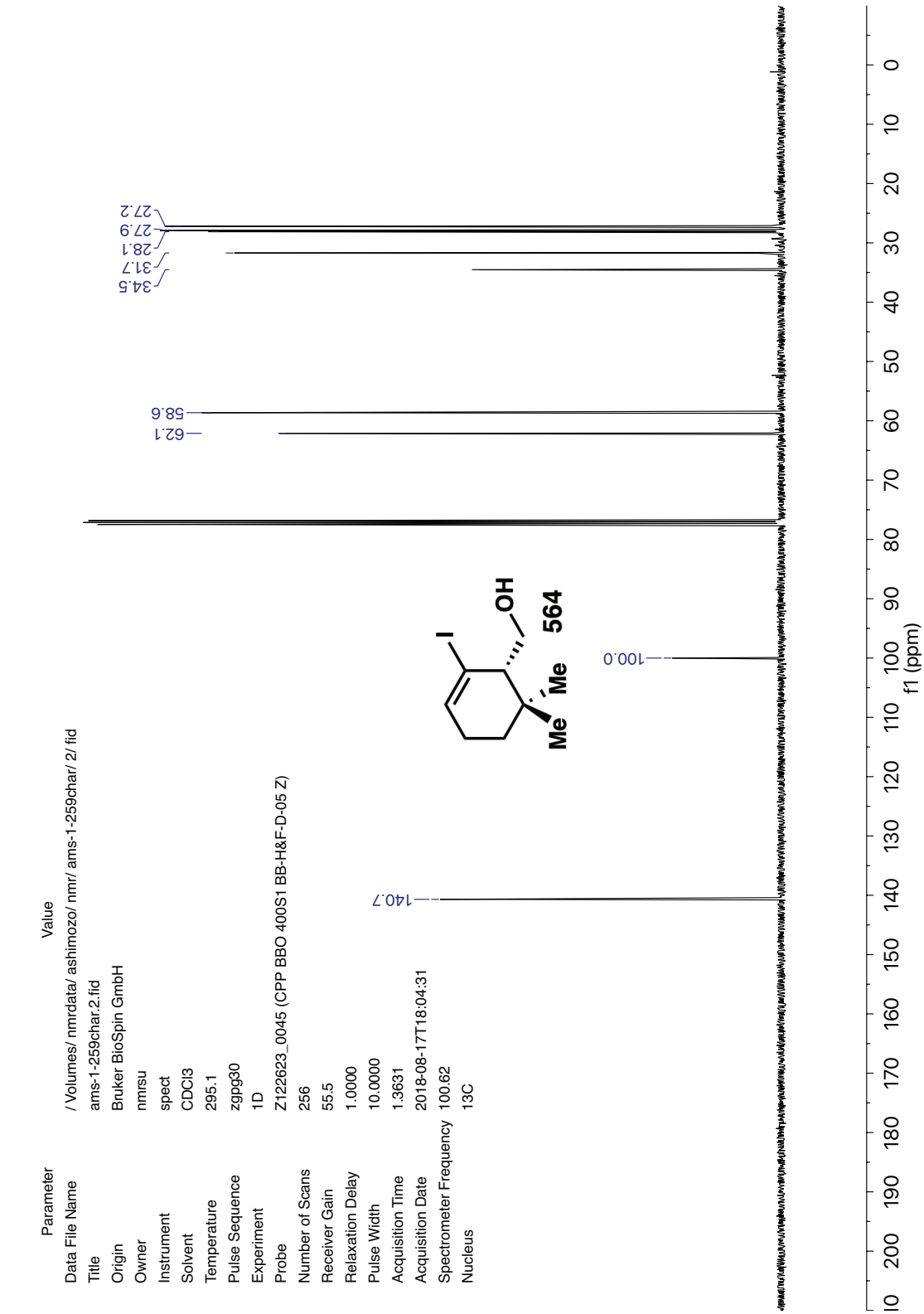
Value
Data File Name / Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_05_162_P1.fid/ fid
Title JCB_05_162_P1
Comment JCB_05_162_P1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 10
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Acquisition Date 2018-06-01T15:06:24
Spectrometer Frequency 599.60
Spectral Width 9611.9
Nucleus 1H
Acquired Size 16384
I
OH
Me
Me
564
1.00
1.20
1.21
2.24
1.06
1.21
2.35
3.57
3.57
f1 (ppm)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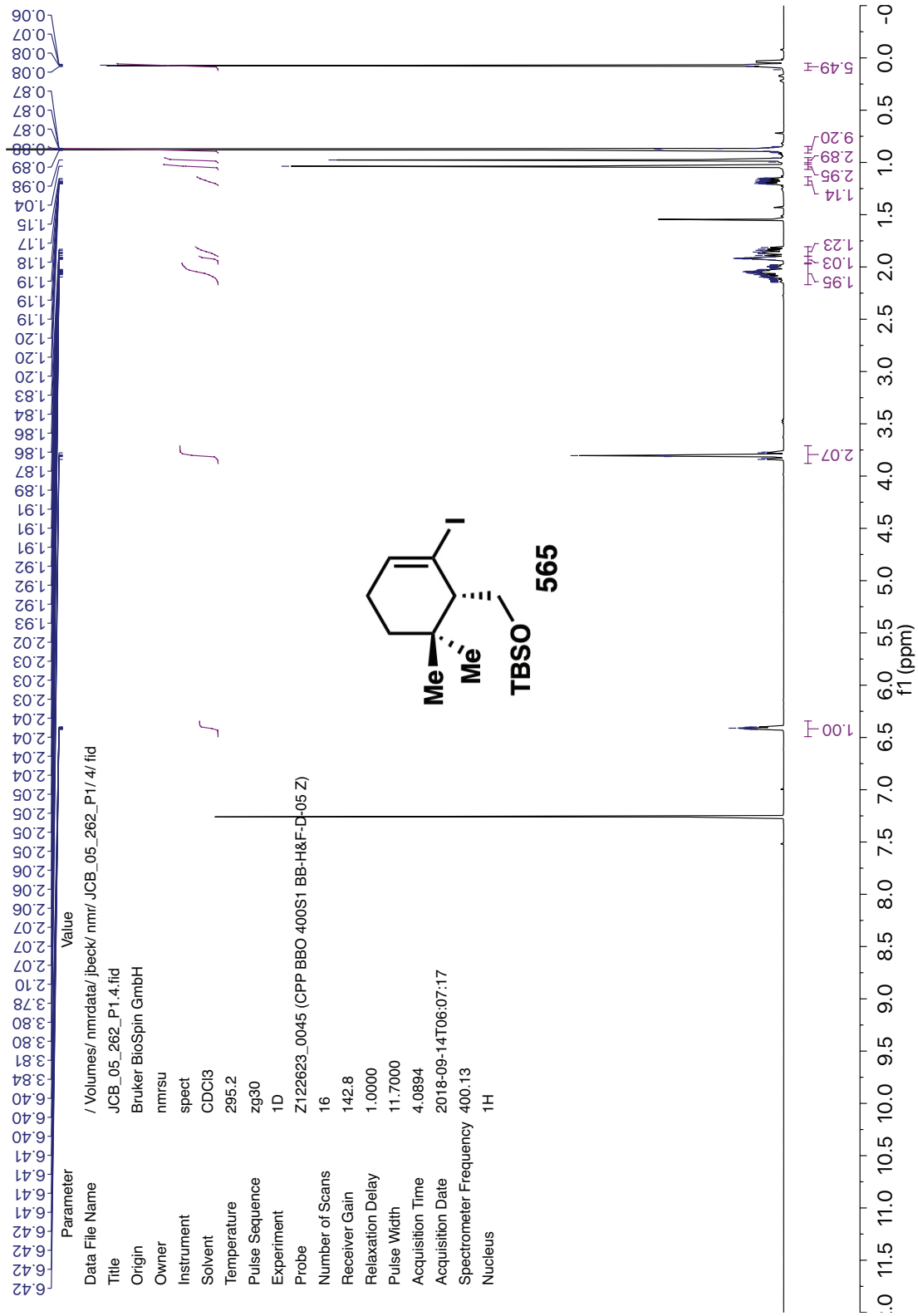
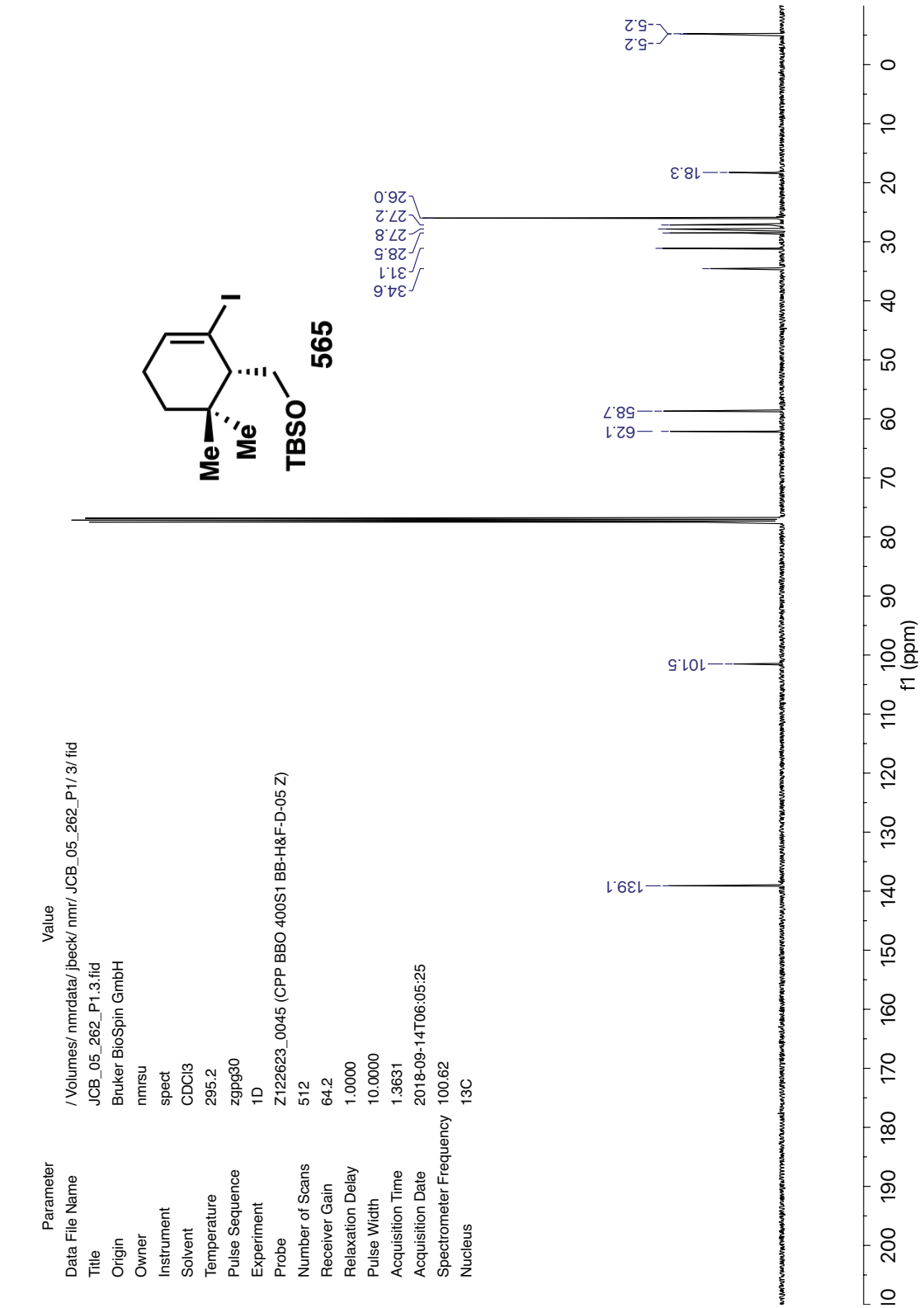
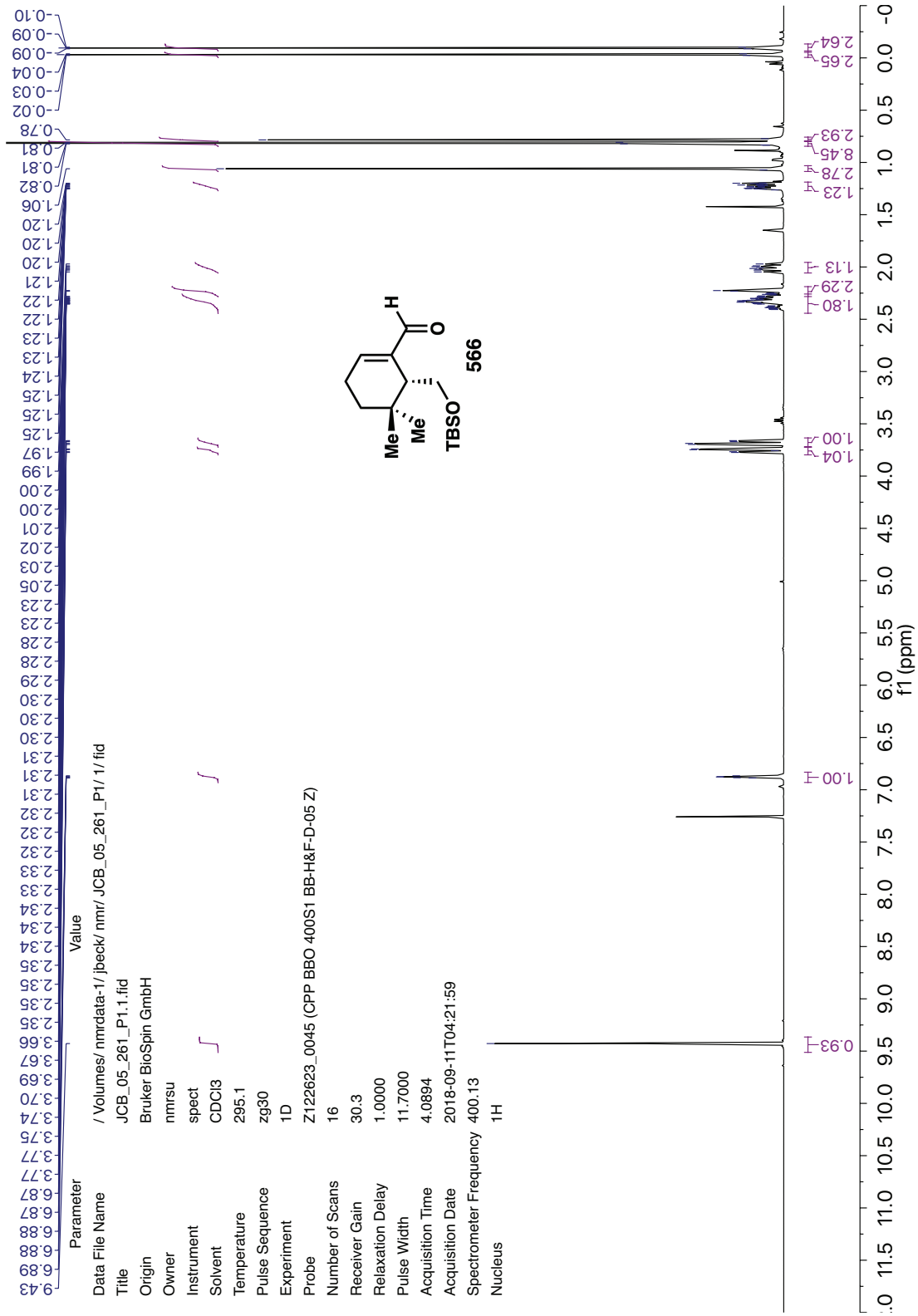
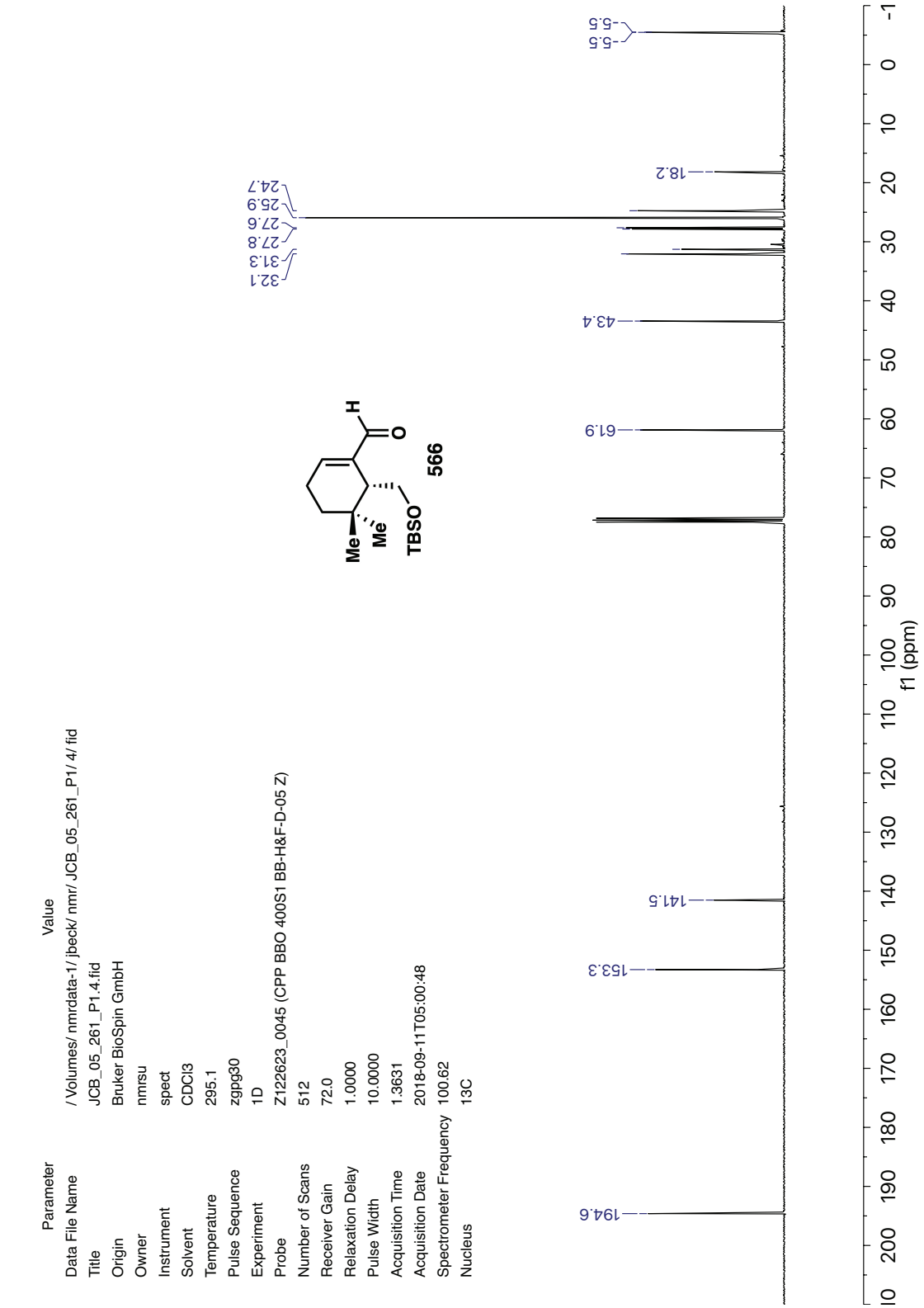
Data File Name / Volumes/ nmrdata/ ashimozo/ nmr/ ams-1-259char/ 2/ fid
Title ams-1-259char.2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 256
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-08-17T18:04:31
Spectrometer Frequency 100.62
Nucleus 13C
140.7
100.0
62.1
58.6
34.5
31.7
28.1
27.9
27.2
I
OH
Me
Me
564
f1 (ppm)

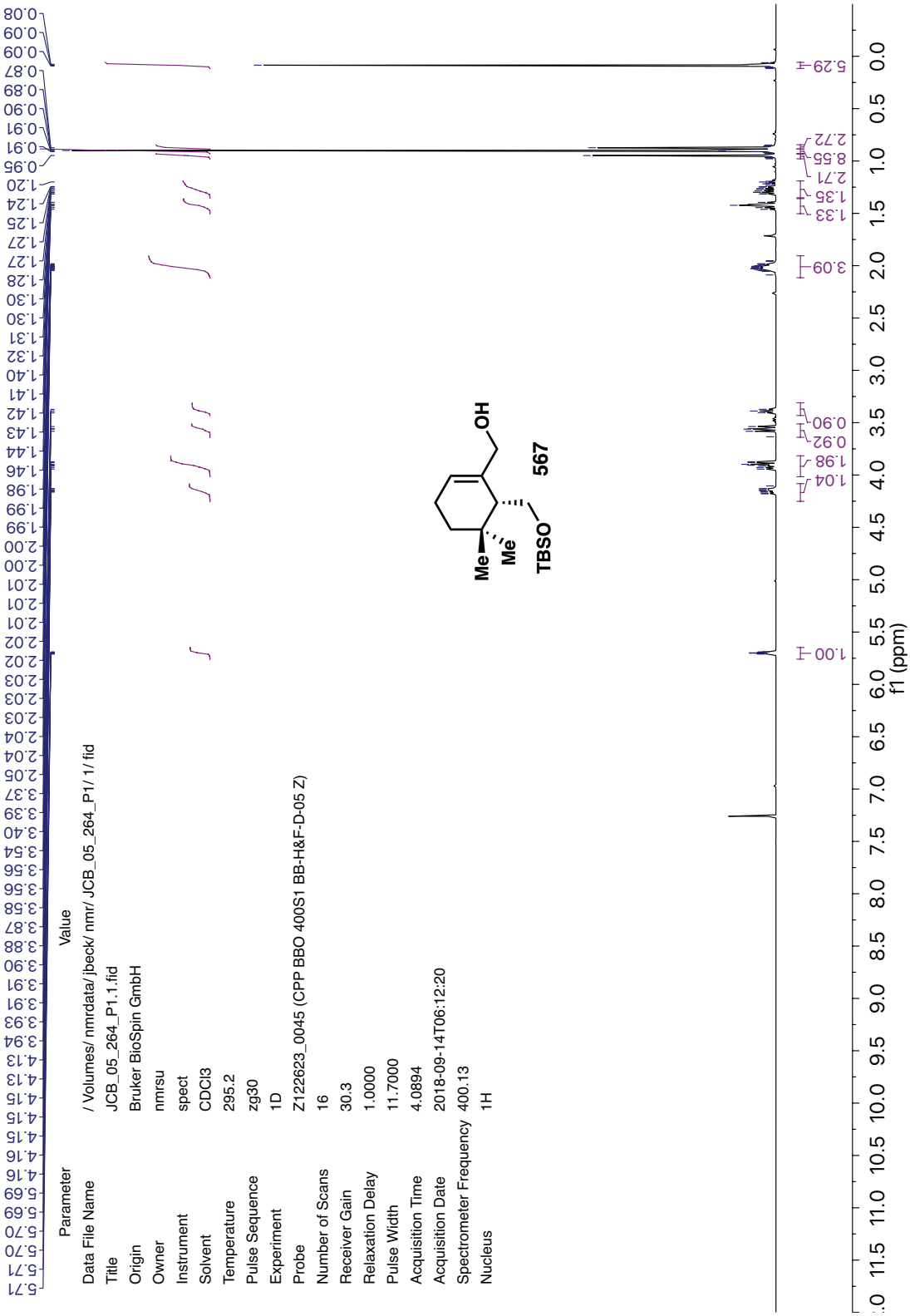

Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_262_P1/ 4/ fid
Title JCB_05_262_P1.4.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-14T06:07:17
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
TBSO
I
565
f1 (ppm)



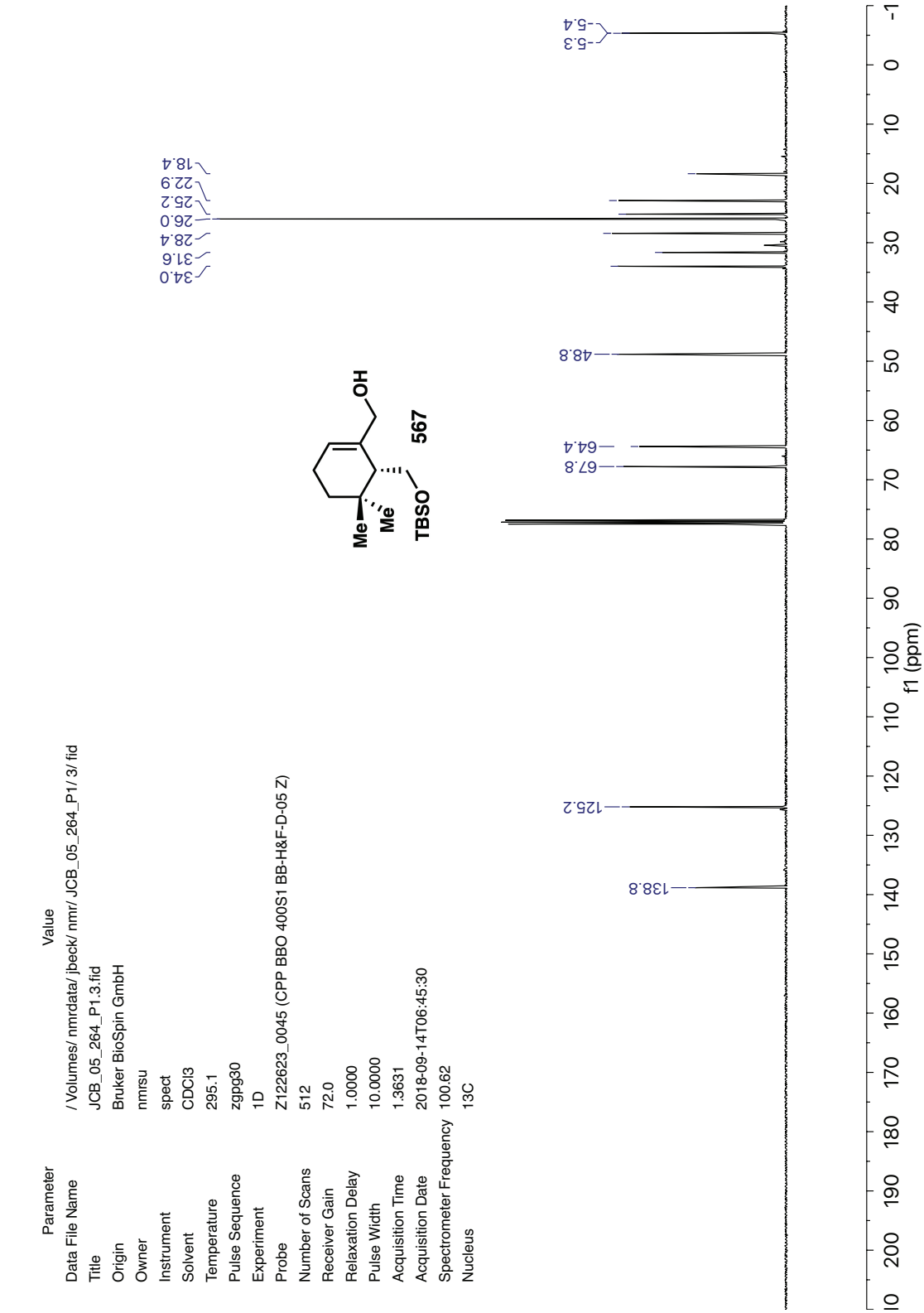
Parameter	Value
Data File Name	/ Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_262_P1/ 3/ fid
Title	JCB_05_262_P1.3.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	512
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-09-14T06:05:25
Spectrometer Frequency	100.62
Nucleus	13C

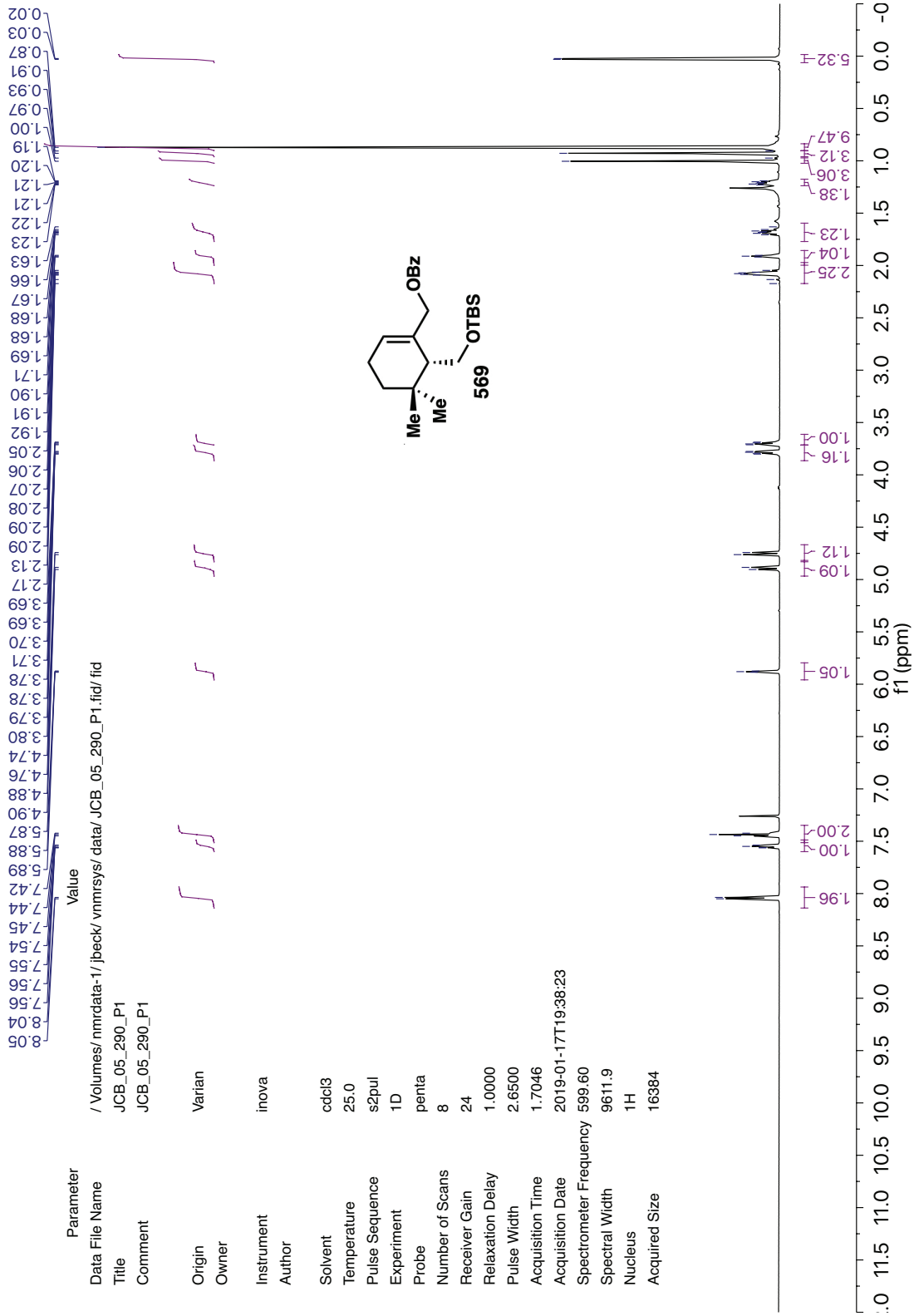

Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_261_P1/ 1/ fid
Title JCB_05_261_P1.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 30.3
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-09-11T04:21:59
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
TBSO
H
O
566
2.64
2.65
2.93
8.45
2.78
1.23
1.13
2.29
1.80
1.04
1.00
1.00
0.93
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_261_P1/ 4/ fid
Title JCB_05_261_P1.4.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-11T05:00:48
Spectrometer Frequency 100.62
Nucleus 13C
194.6
153.3
141.5
61.9
43.4
32.1
31.3
27.8
27.6
25.9
24.7
18.2
-5.5
-5.5
Me
Me
TBSO
O
H
566
f1 (ppm)

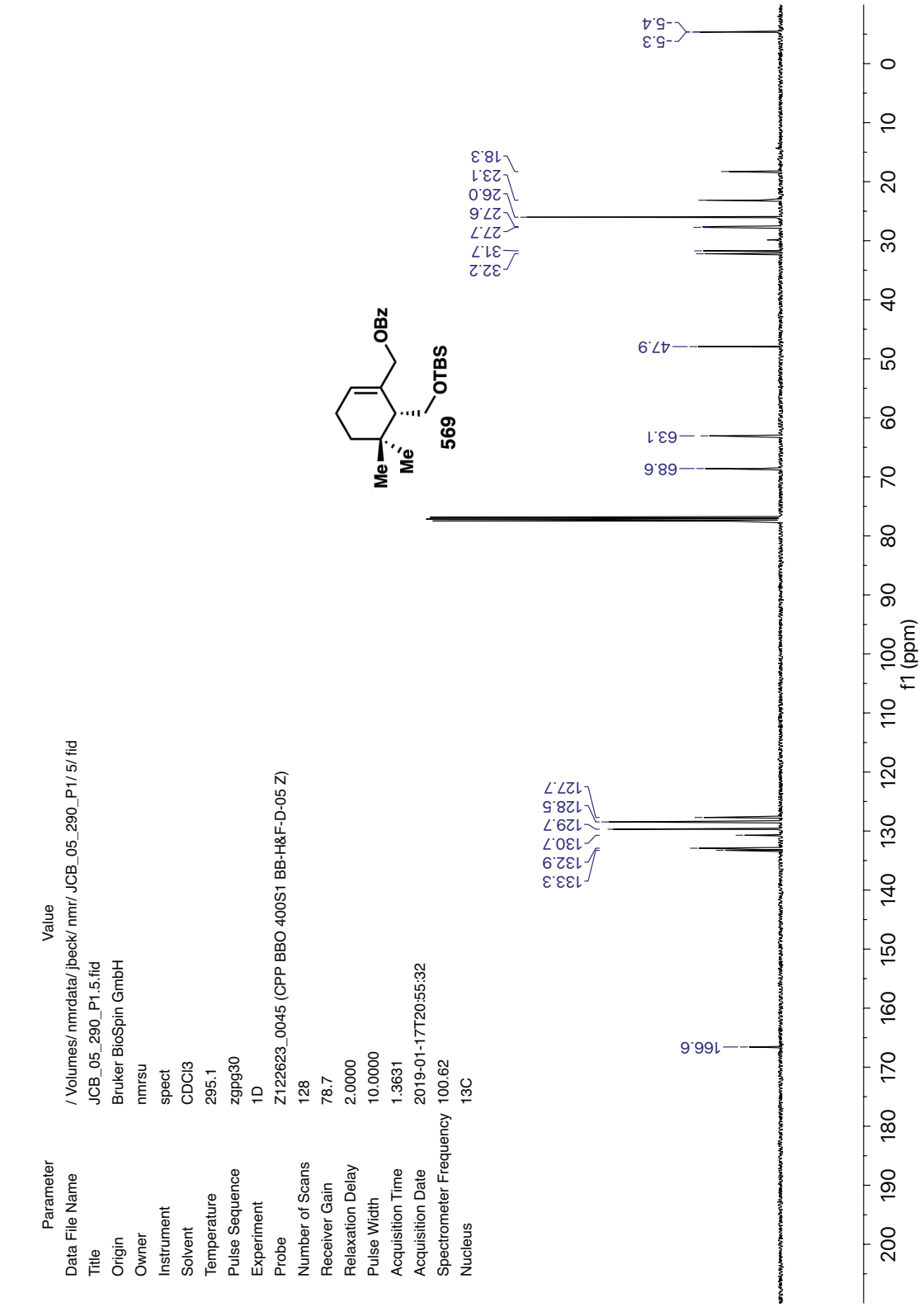


Parameter	Value
Data File Name	/ Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_264_P1/ 1/ fid
Title	JCB_05_264_P1.1.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	16
Receiver Gain	30.3
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-09-14T06:12:20
Spectrometer Frequency	400.13
Nucleus	1H


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_264_P1/ 3/ fid
Title JCB_05_264_P1.3.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-09-14T06:45:30
Spectrometer Frequency 100.62
Nucleus 13C
OH
Me
Me
TBSO
567
-5.3
-5.4
18.4
22.9
25.2
26.0
28.4
31.6
34.0
48.8
64.4
67.8
125.2
138.8
f1 (ppm)



Parameter	Value
Data File Name	/ Volumes/ nmrdata-1/ jbeck/ vnmrsys/ data/ JCB_05_290_P1.fid/ fid
Title	JCB_05_290_P1
Comment	JCB_05_290_P1
Origin	Varian
Owner	
Instrument	inova
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	penta
Number of Scans	8
Receiver Gain	24
Relaxation Delay	1.0000
Pulse Width	2.6500
Acquisition Time	1.7046
Acquisition Date	2019-01-17T19:38:23
Spectrometer Frequency	599.60
Spectral Width	9611.9
Nucleus	1H
Acquired Size	16384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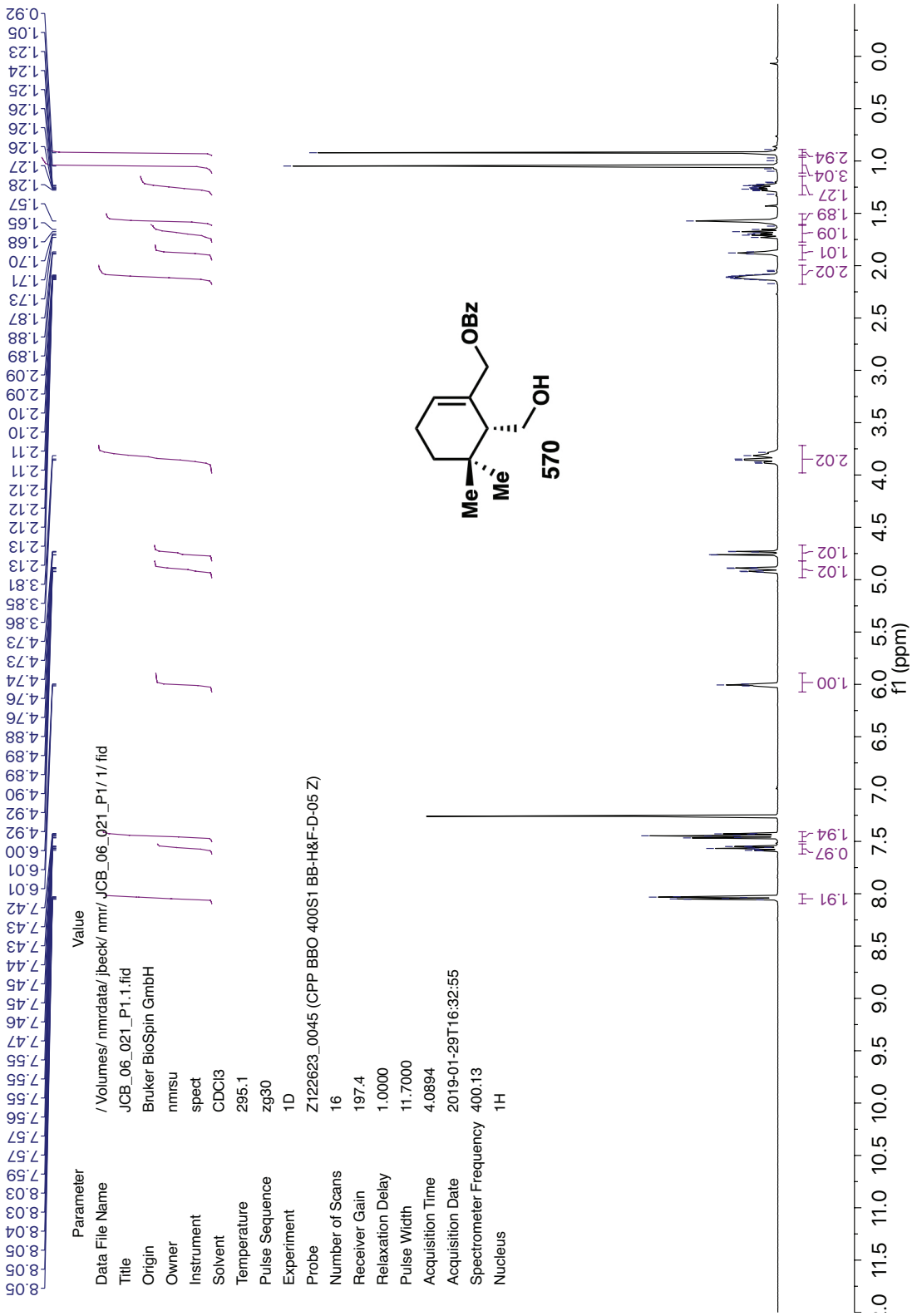
Title JCB_05_290_P1.5.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 128
Receiver Gain 78.7
Relaxation Delay 2.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-01-17T20:55:32
Spectrometer Frequency 100.62
Nucleus 13C
OBz
OTBS
Me
Me
569
166.6
133.3
132.9
130.7
129.7
128.5
127.7
68.6
63.1
47.9
32.2
31.7
27.7
27.6
26.0
23.1
18.3
-5.3
-5.4
f1 (ppm)


OBz
OH
Me
Me
570
f1 (ppm)
Parameter Value
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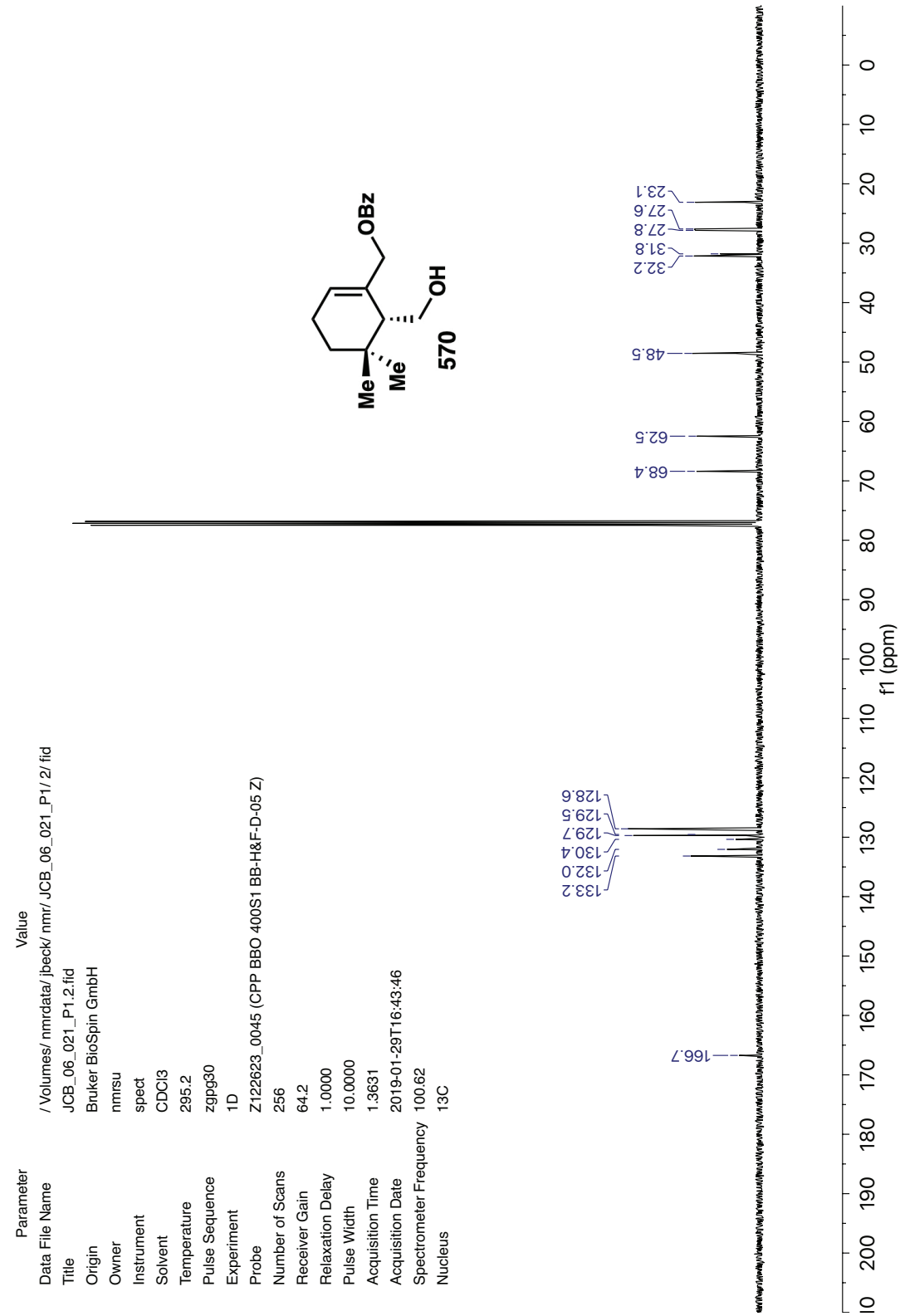
Title JCB_06_021_P1.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2019-01-29T16:32:55
Spectrometer Frequency 400.13
Nucleus 1H


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_06_021_P1/ 2/ fid
Title JCB_06_021_P1.2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 256
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-01-29T16:43:46
Spectrometer Frequency 100.62
Nucleus 13C
OBz
OH
Me
Me
570
166.7
133.2
132.0
130.4
129.7
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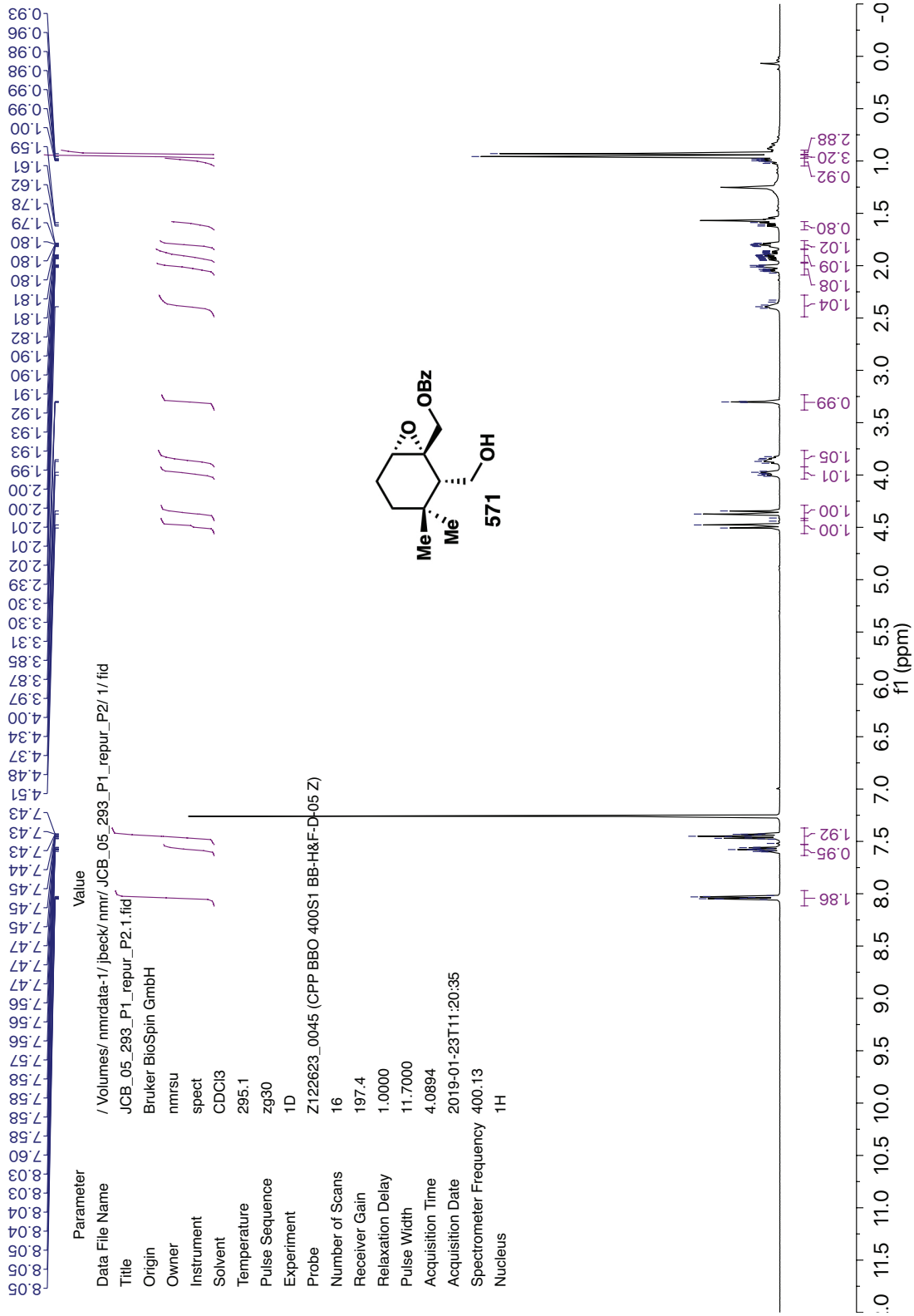
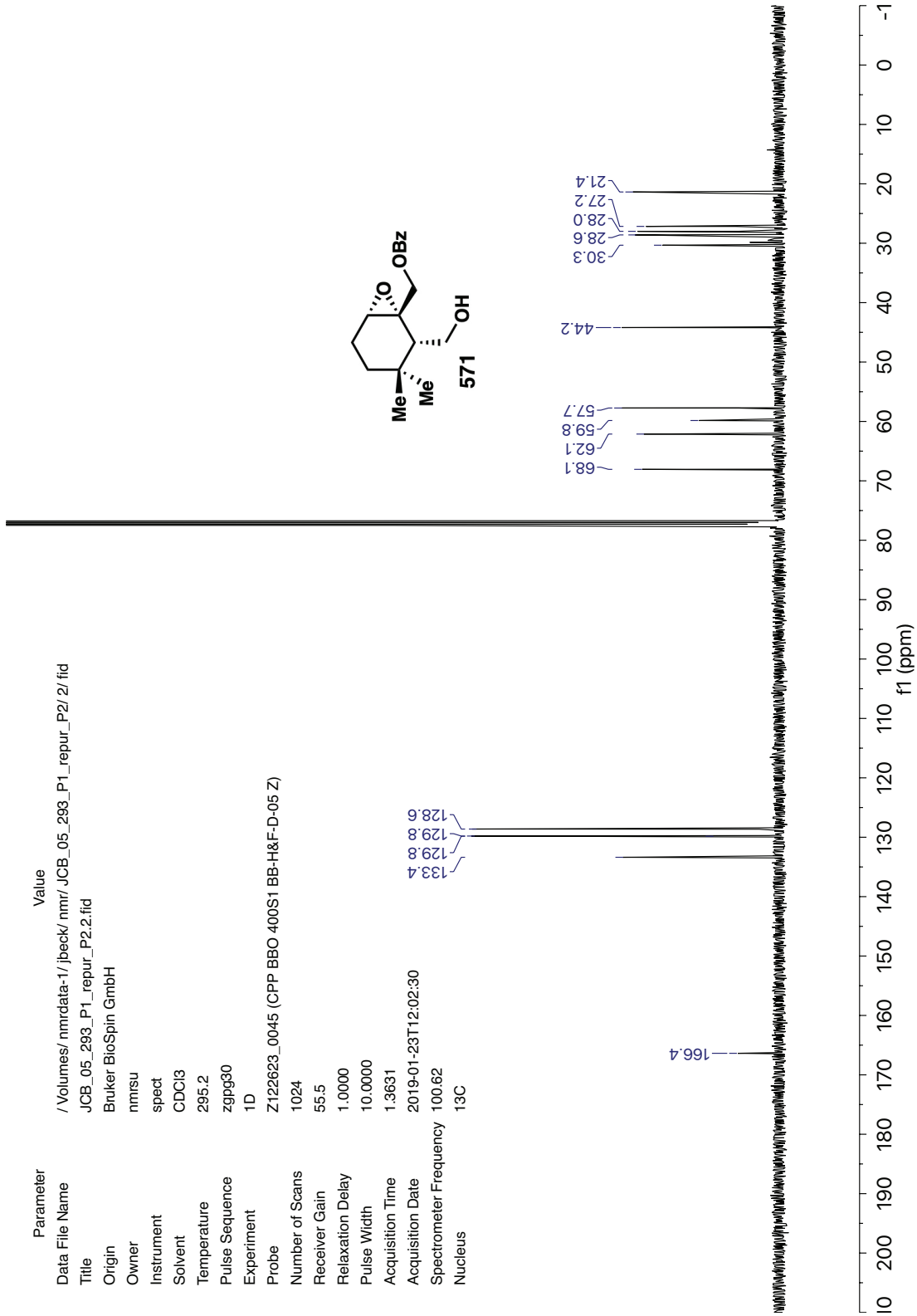
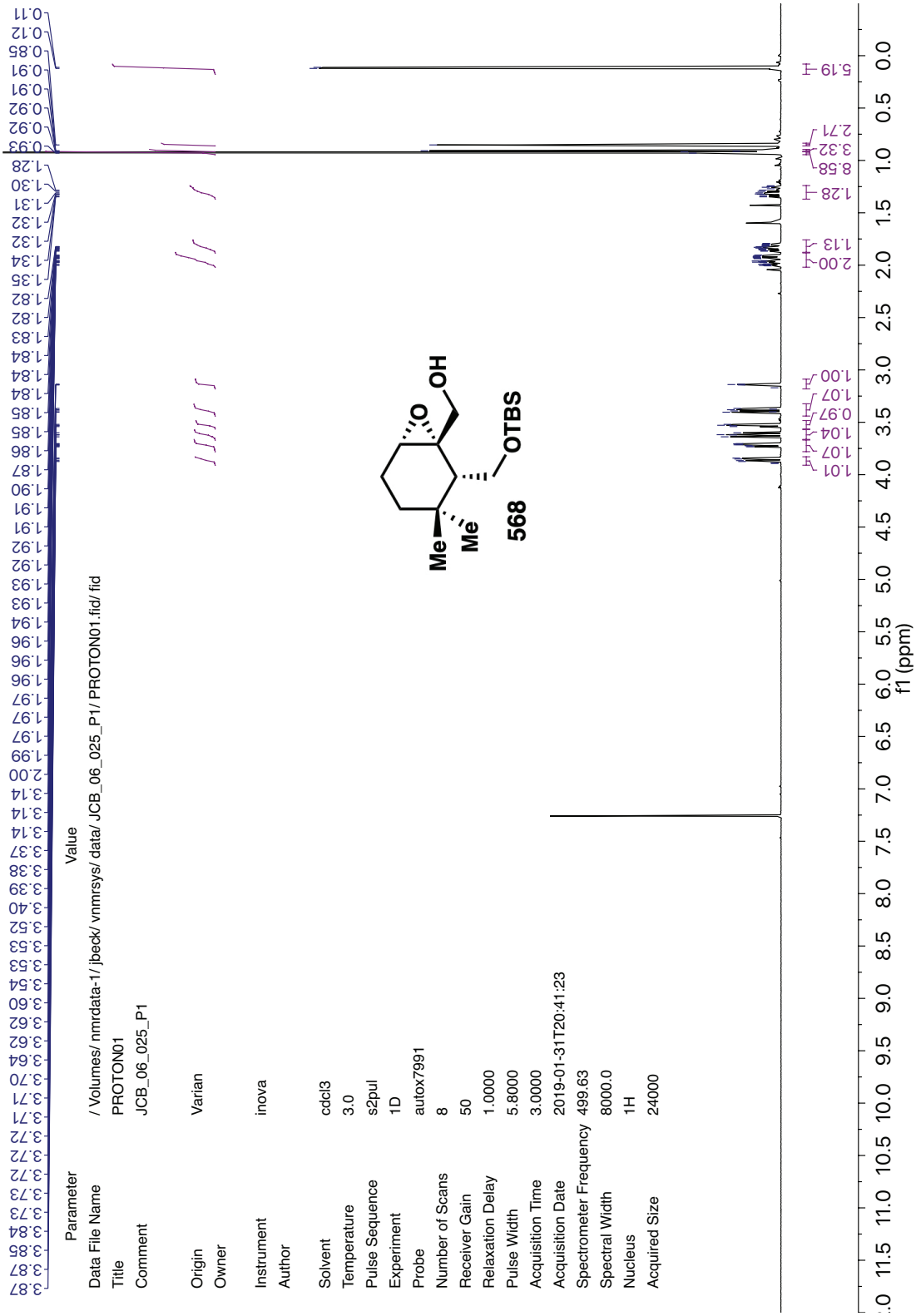
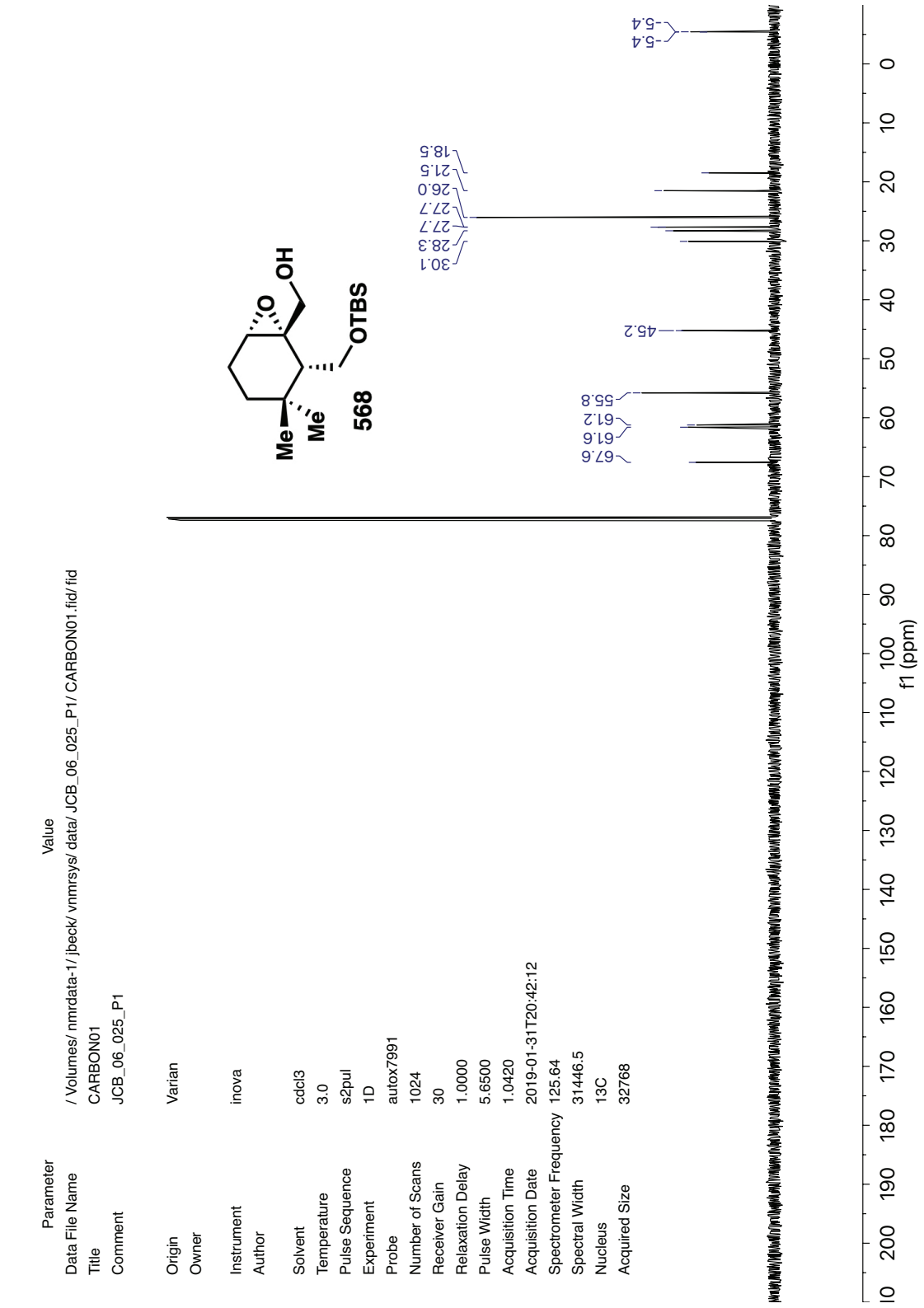
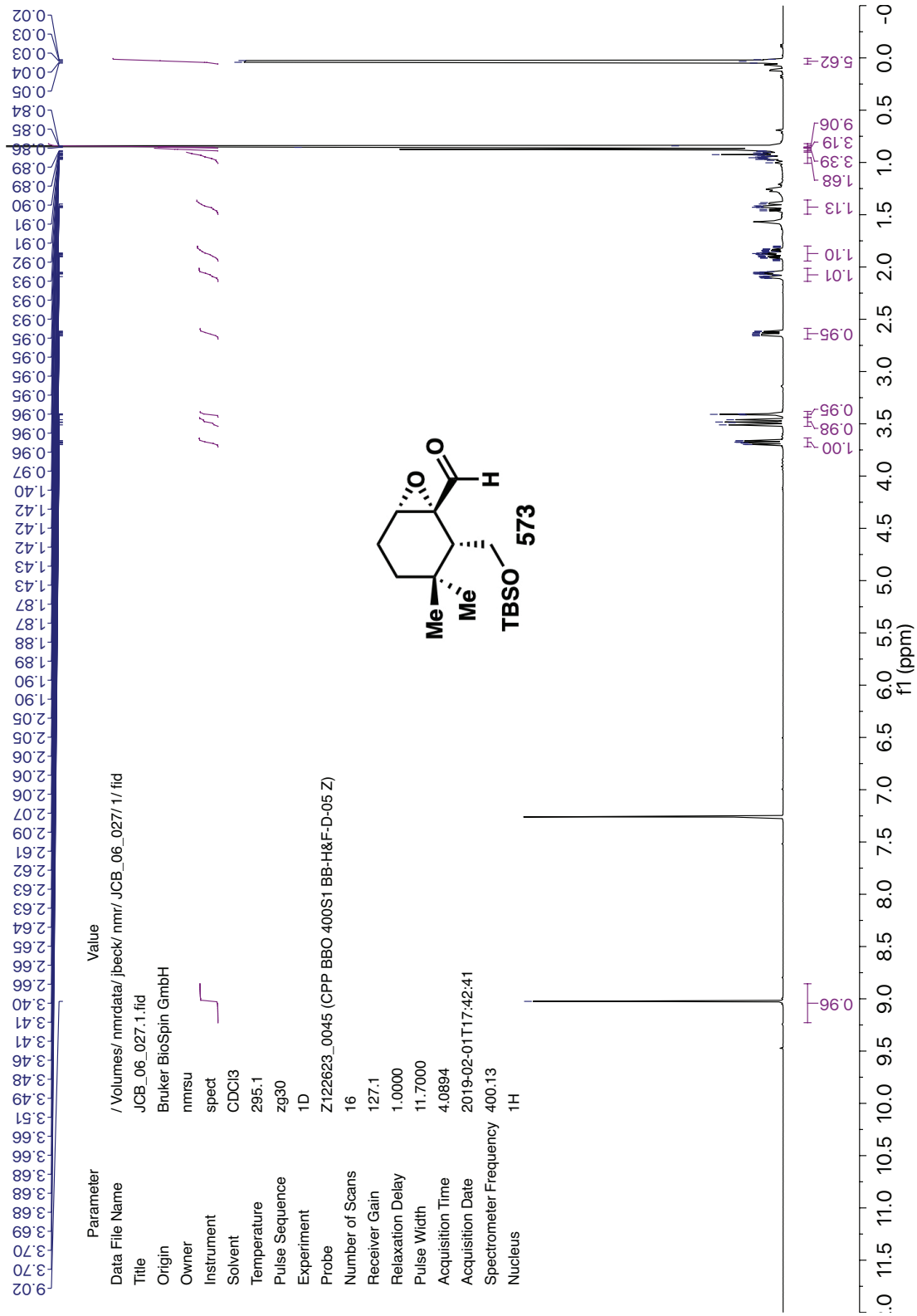
31.8
27.8
27.6
23.1
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_293_P1_repur_P2/ 1/ fid
Title JCB_05_293_P1_repur_P2.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2019-01-23T11:20:35
Spectrometer Frequency 400.13
Nucleus 1H
OBz
O
OH
Me
Me
571
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_293_P1_repur_P2/ 2/ fid
Title JCB_05_293_P1_repur_P2.2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1024
Receiver Gain 55.5
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-01-23T12:02:30
Spectrometer Frequency 100.62
Nucleus 13C
OBz
O
OH
Me
Me
571
166.4
133.4
129.8
129.8
128.6
68.1
62.1
59.8
57.7
44.2
30.3
28.6
28.0
27.2
21.4
f1 (ppm)


Parameter
Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ vnmrsys/ data/ JCB_06_025_P1/ PROTON01.fid/ fid
Title PROTON01
Comment JCB_06_025_P1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 3.0
Pulse Sequence s2pul
Experiment 1D
Probe autox7991
Number of Scans 8
Receiver Gain 50
Relaxation Delay 1.0000
Pulse Width 5.8000
Acquisition Time 3.0000
Acquisition Date 2019-01-31T20:41:23
Spectrometer Frequency 499.63
Spectral Width 8000.0
Nucleus 1H
Acquired Size 24000
OH
O
OTBS
Me
Me
568
5.19
2.71
3.32
8.58
1.28
1.13
2.00
1.01
1.07
1.04
0.97
1.07
1.00
f1 (ppm)


Parameter
Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ vnmrsys/ data/ JCB_06_025_P1/ CARBON01.fid/ fid
Title CARBON01
Comment JCB_06_025_P1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 3.0
Pulse Sequence s2pul
Experiment 1D
Probe autox7991
Number of Scans 1024
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 5.6500
Acquisition Time 1.0420
Acquisition Date 2019-01-31T20:42:12
Spectrometer Frequency 125.64
Spectral Width 31446.5
Nucleus 13C
Acquired Size 32768
568
Me
Me
OTBS
OH
O
-5.4
-5.4
18.5
21.5
26.0
27.7
27.7
28.3
30.1
45.2
55.8
61.2
61.6
67.6
f1 (ppm)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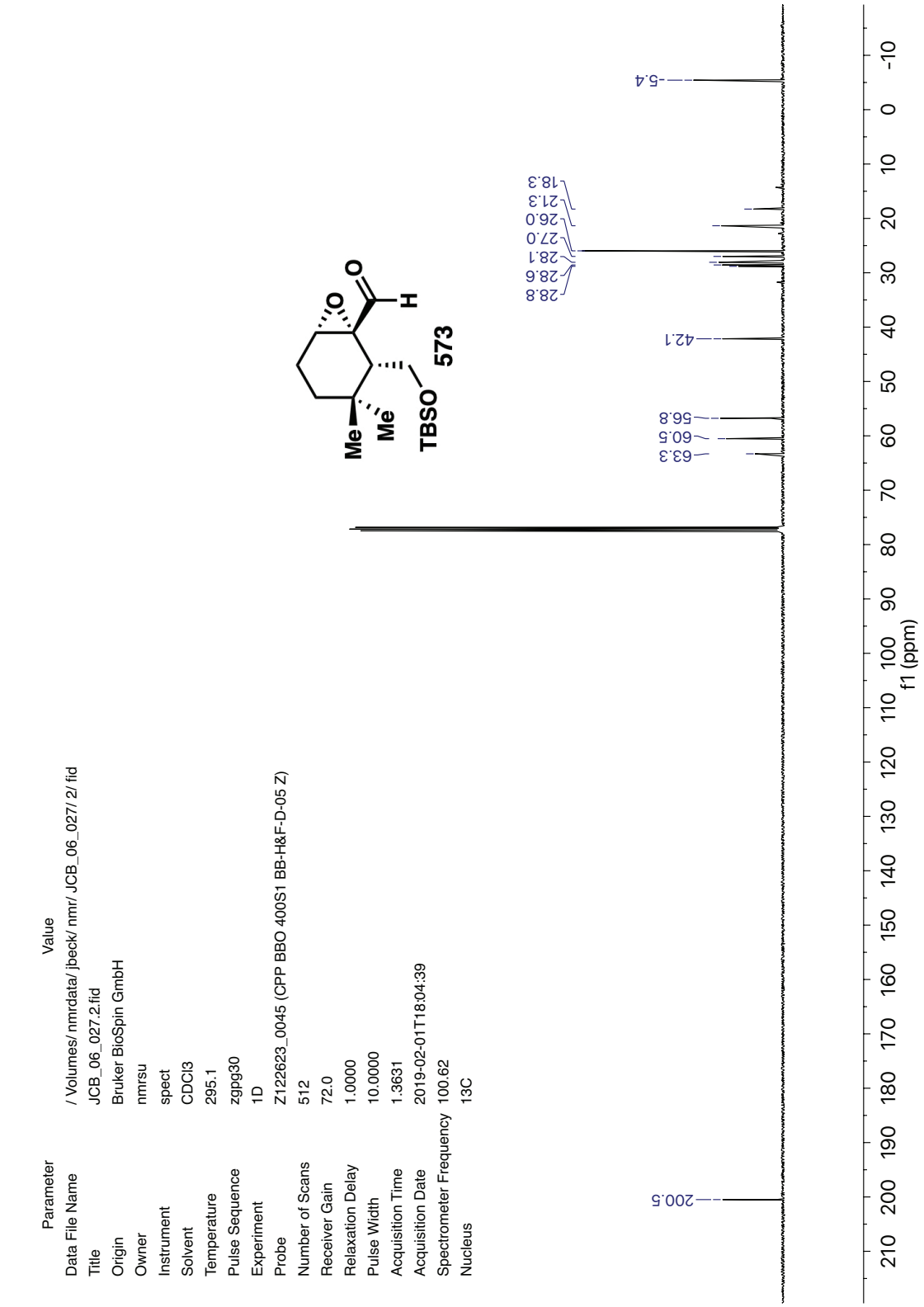
Data File Name
/ Volumes/ nmrdata/ jbeck/ nmr/ JCB_06_027/ 1/ fid
Title
JCB_06_027.1.fid
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
spect
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
16
Receiver Gain
127.1
Relaxation Delay
1.0000
Pulse Width
11.7000
Acquisition Time
4.0894
Acquisition Date
2019-02-01T17:42:41
Spectrometer Frequency
400.13
Nucleus
1H
Me
Me
TBSO
573
O
O
H
f1 (ppm)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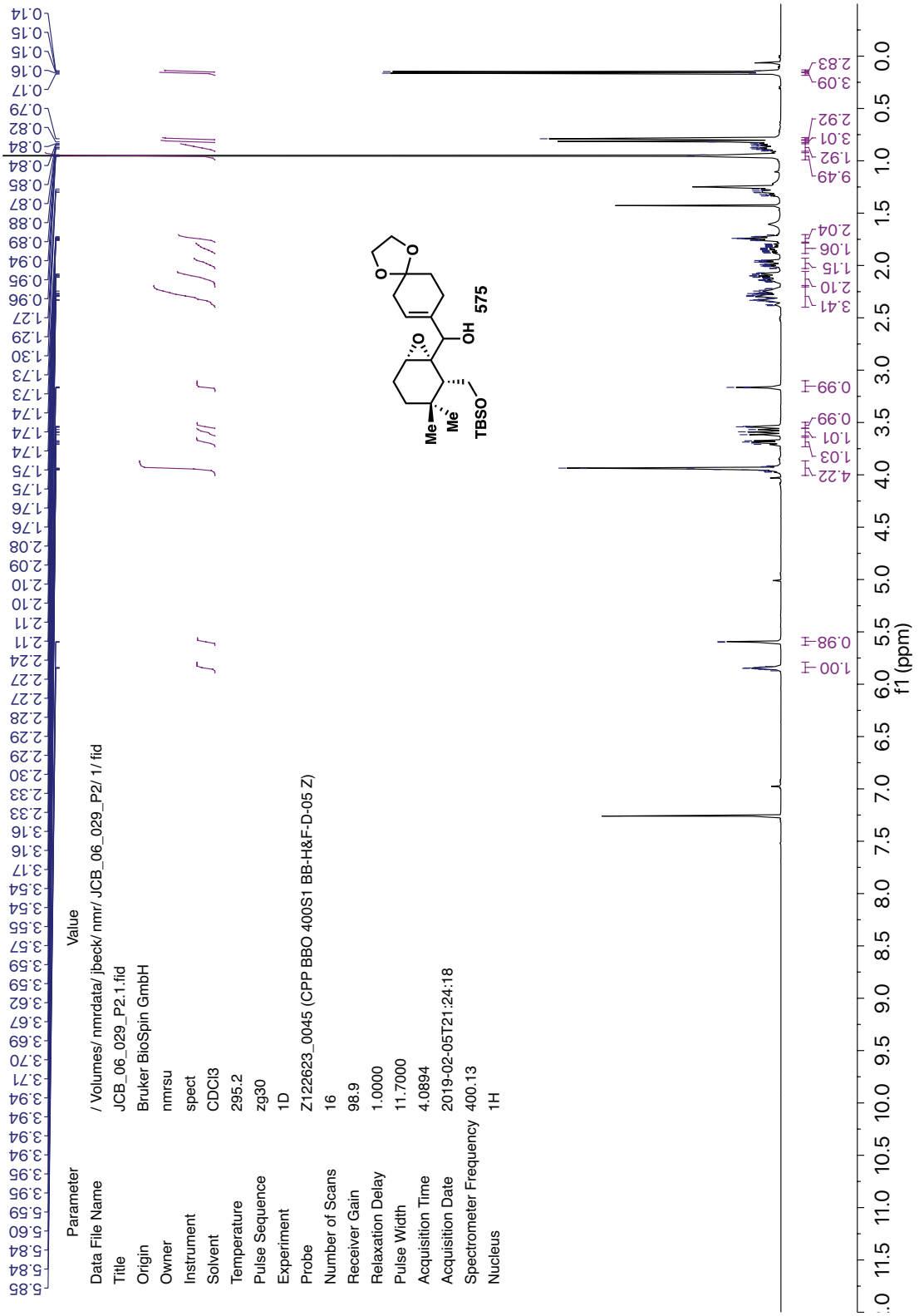
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_06_027/ 2/ fid
Title JCB_06_027.2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-01T18:04:39
Spectrometer Frequency 100.62
Nucleus 13C
200.5
63.3
60.5
56.8
42.1
28.8
28.6
28.1
27.0
26.0
21.3
18.3
-5.4
Me
Me
TBSO
573
O
O
H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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Value
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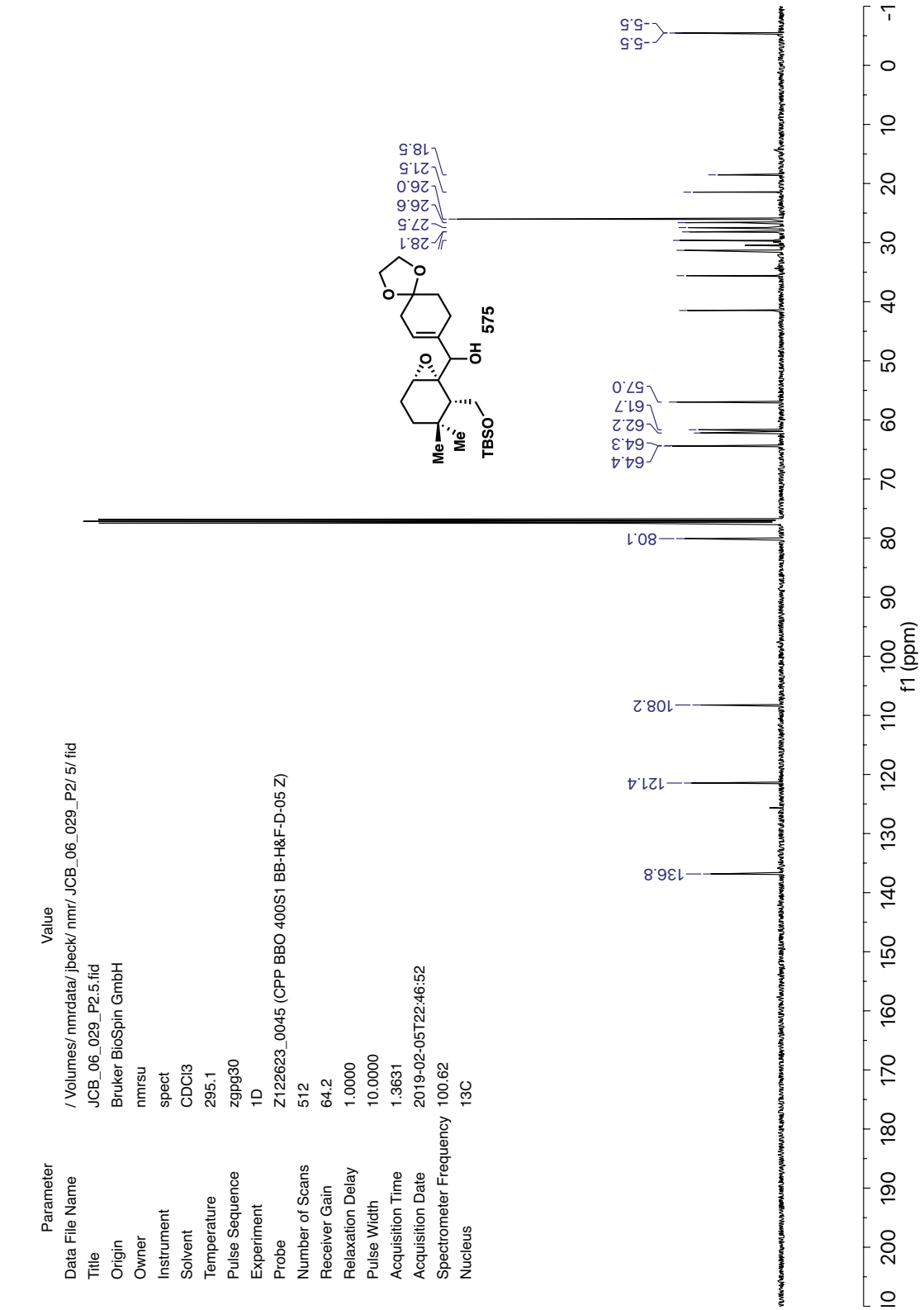
Title JCB_06_029_P2.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2019-02-05T21:24:18
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
TBSO
OH
575
f1 (ppm)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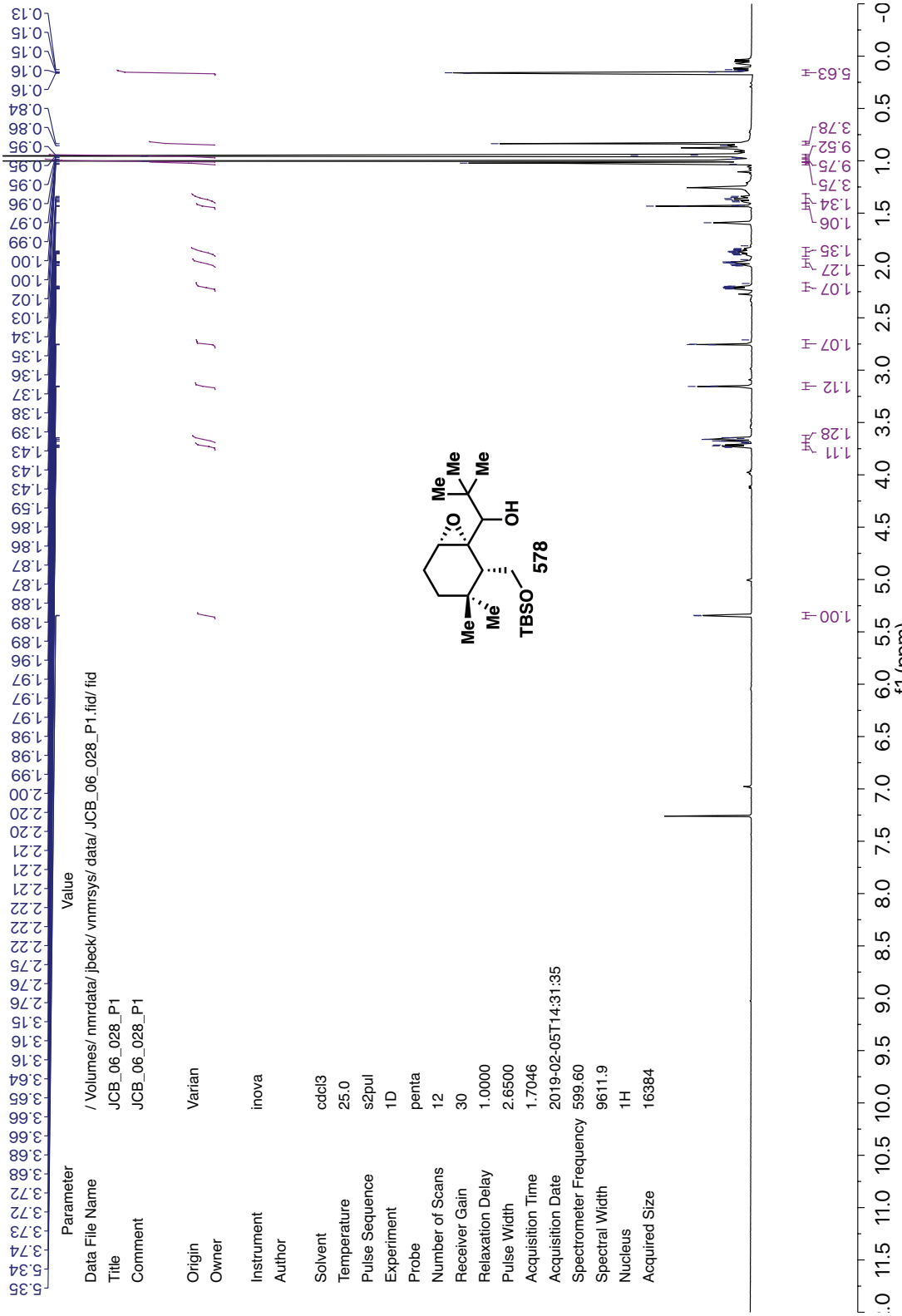
Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_06_029_P2/ 5/ fid
Title JCB_06_029_P2.5.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-05T22:46:52
Spectrometer Frequency 100.62
Nucleus 13C
-5.5
-5.5
64.4
64.3
62.2
61.7
57.0
80.1
108.2
121.4
136.8
28.1
27.5
26.6
26.0
21.5
18.5
Me
Me
TBSO
OH
575
f1 (ppm)



Parameter	Value
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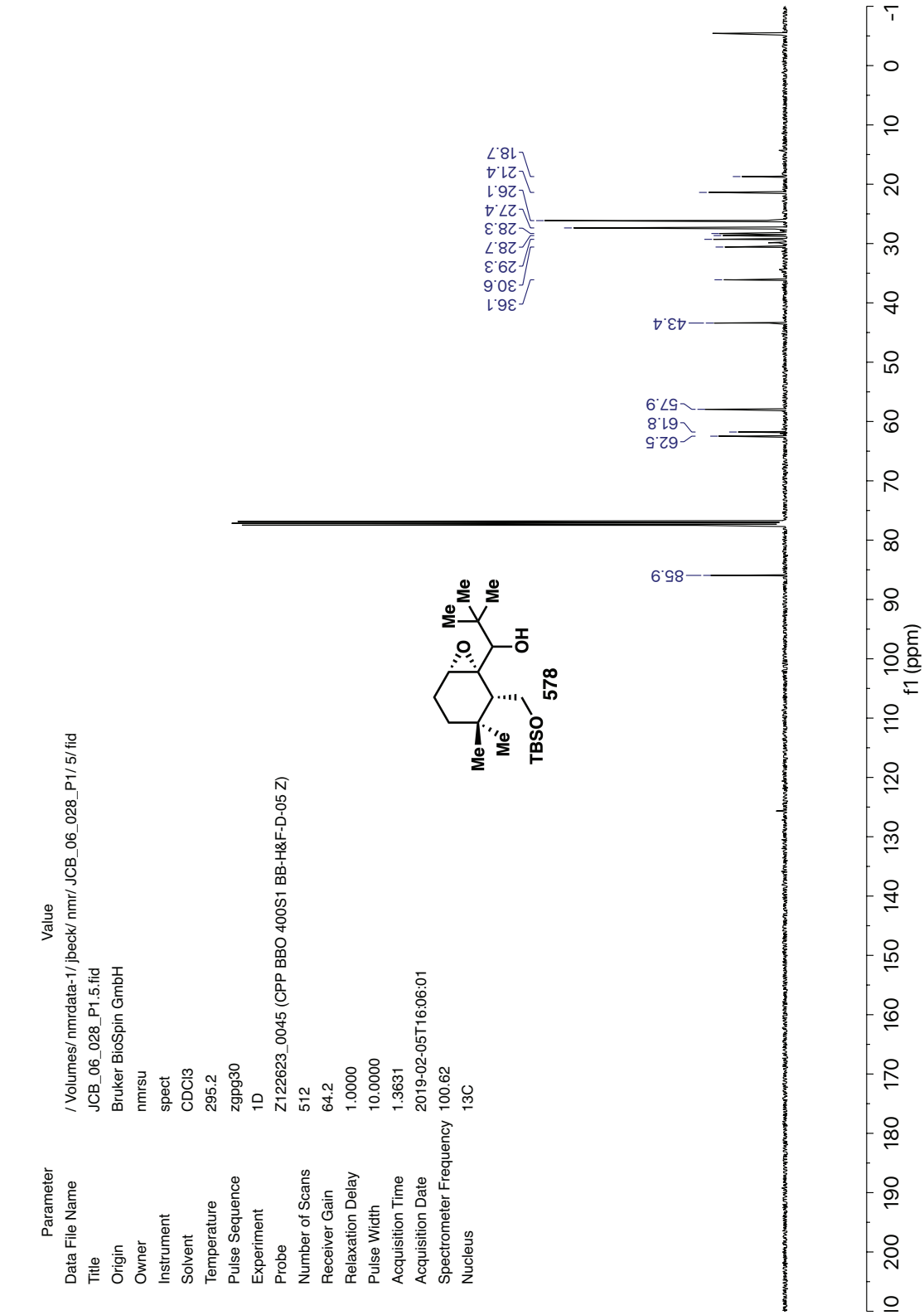
Title	JCB_06_028_P1
Comment	JCB_06_028_P1
Origin	Varian
Owner	
Instrument	inova
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	penta
Number of Scans	12
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	2.6500
Acquisition Time	1.7046
Acquisition Date	2019-02-05T14:31:35
Spectrometer Frequency	599.60
Spectral Width	9611.9
Nucleus	1H
Acquired Size	16384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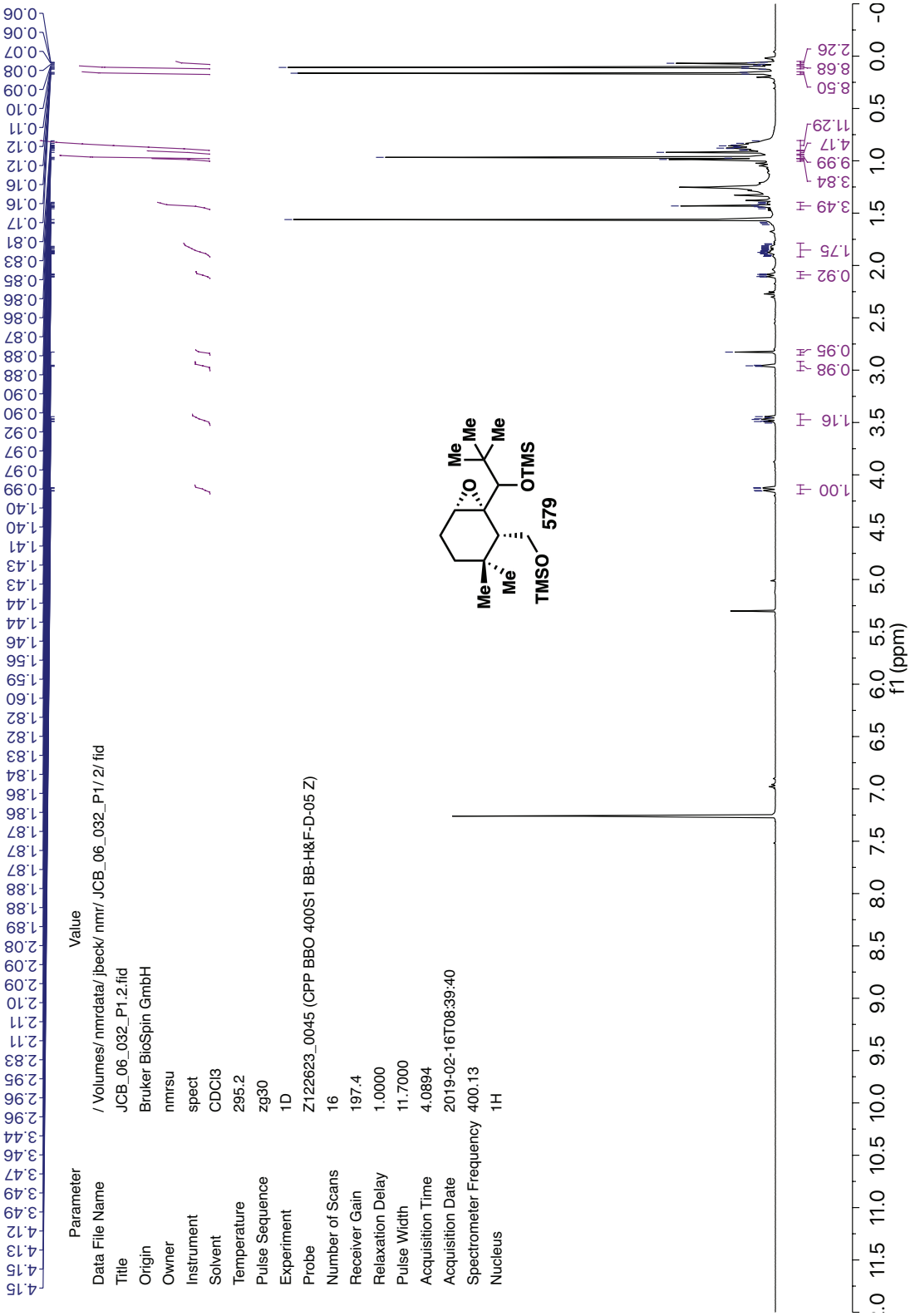
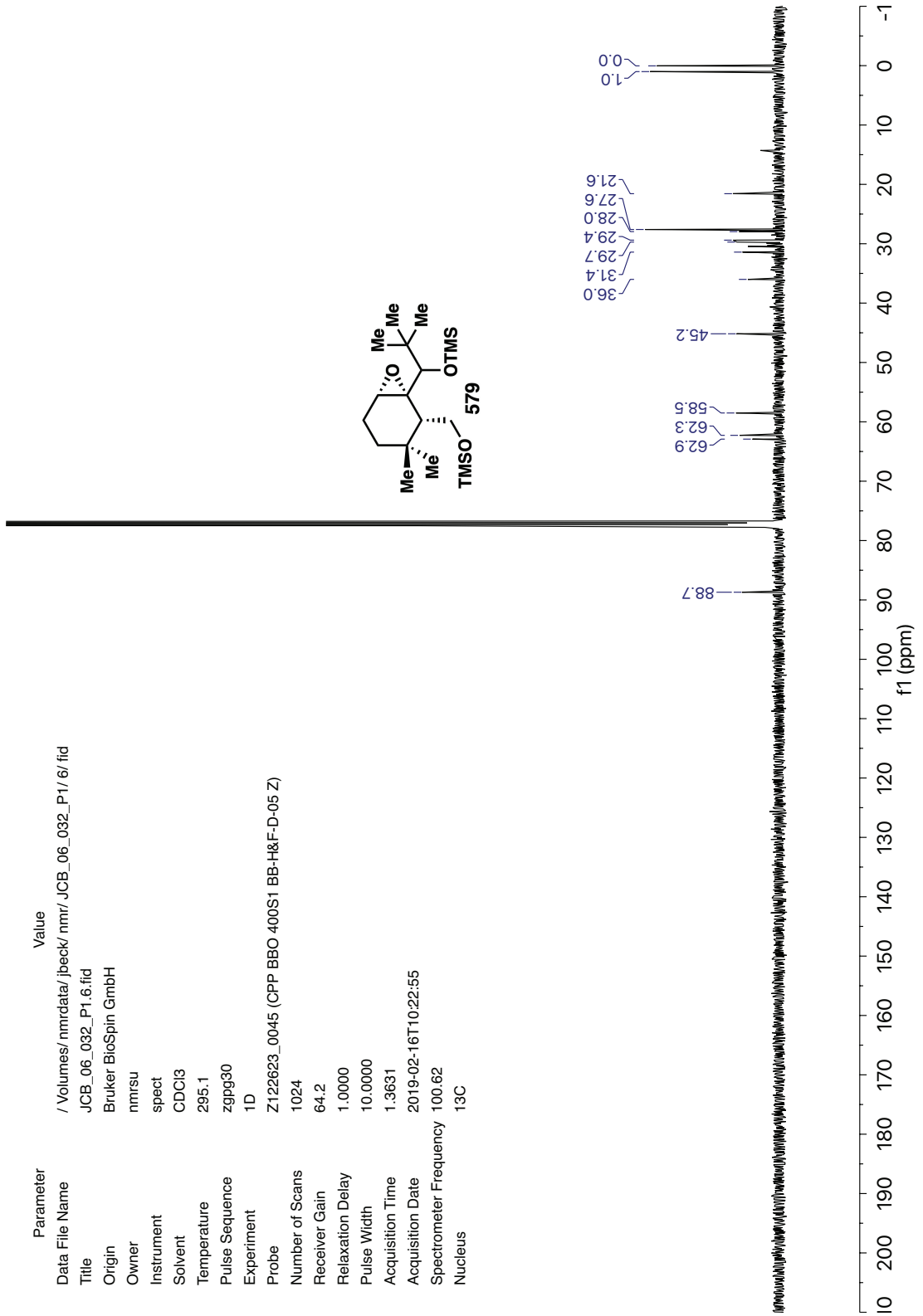
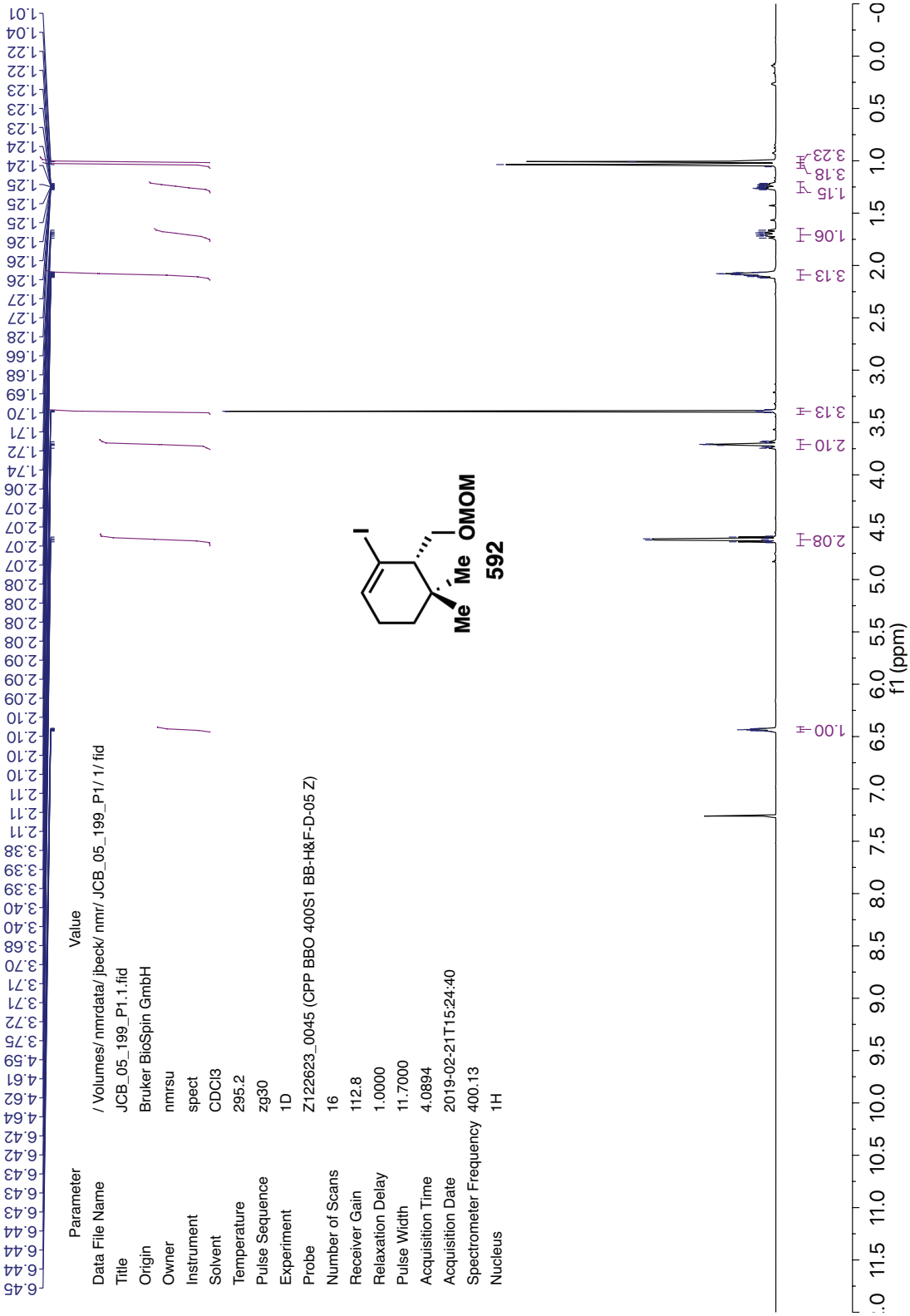
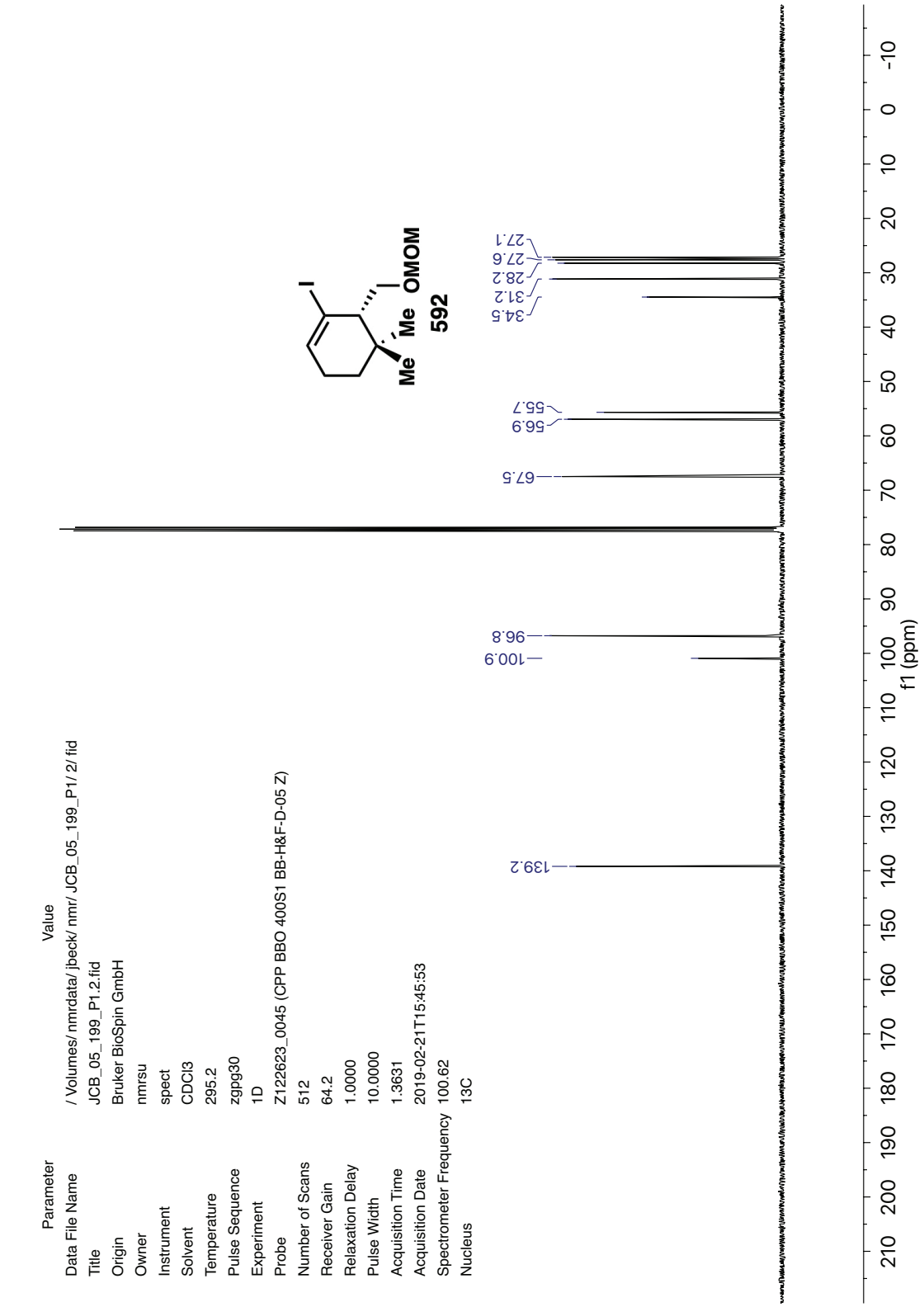
Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_06_028_P1/ 5/ fid
Title JCB_06_028_P1.5.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-05T16:06:01
Spectrometer Frequency 100.62
Nucleus 13C
Me
Me
Me
O
OH
Me
Me
TBSO
578
85.9
62.5
61.8
57.9
43.4
36.1
30.6
29.3
28.7
28.3
27.4
26.1
21.4
18.7
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_06_032_P1/ 2/ fid
Title JCB_06_032_P1.2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2019-02-16T08:39:40
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
Me
O
OTMS
Me
Me
TMSO
579
1.00
1.16
0.98
0.95
0.92
1.75
3.49
3.84
9.99
4.17
11.29
8.50
8.68
2.26
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_06_032_P1/ 6/ fid
Title JCB_06_032_P1.6.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1024
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-16T10:22:55
Spectrometer Frequency 100.62
Nucleus 13C
Me
Me
Me
O
OTMS
Me
Me
TMSO
579
88.7
62.9
62.3
58.5
45.2
36.0
31.4
29.7
29.4
28.0
27.6
21.6
1.0
0.0
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_199_P1/ 1/ fid
Title JCB_05_199_P1.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 112.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2019-02-21T15:24:40
Spectrometer Frequency 400.13
Nucleus 1H
Me Me OMOM
592
1.00
2.08
2.10
3.13
3.13
1.06
3.13
1.15
3.18
3.23
f1 (ppm)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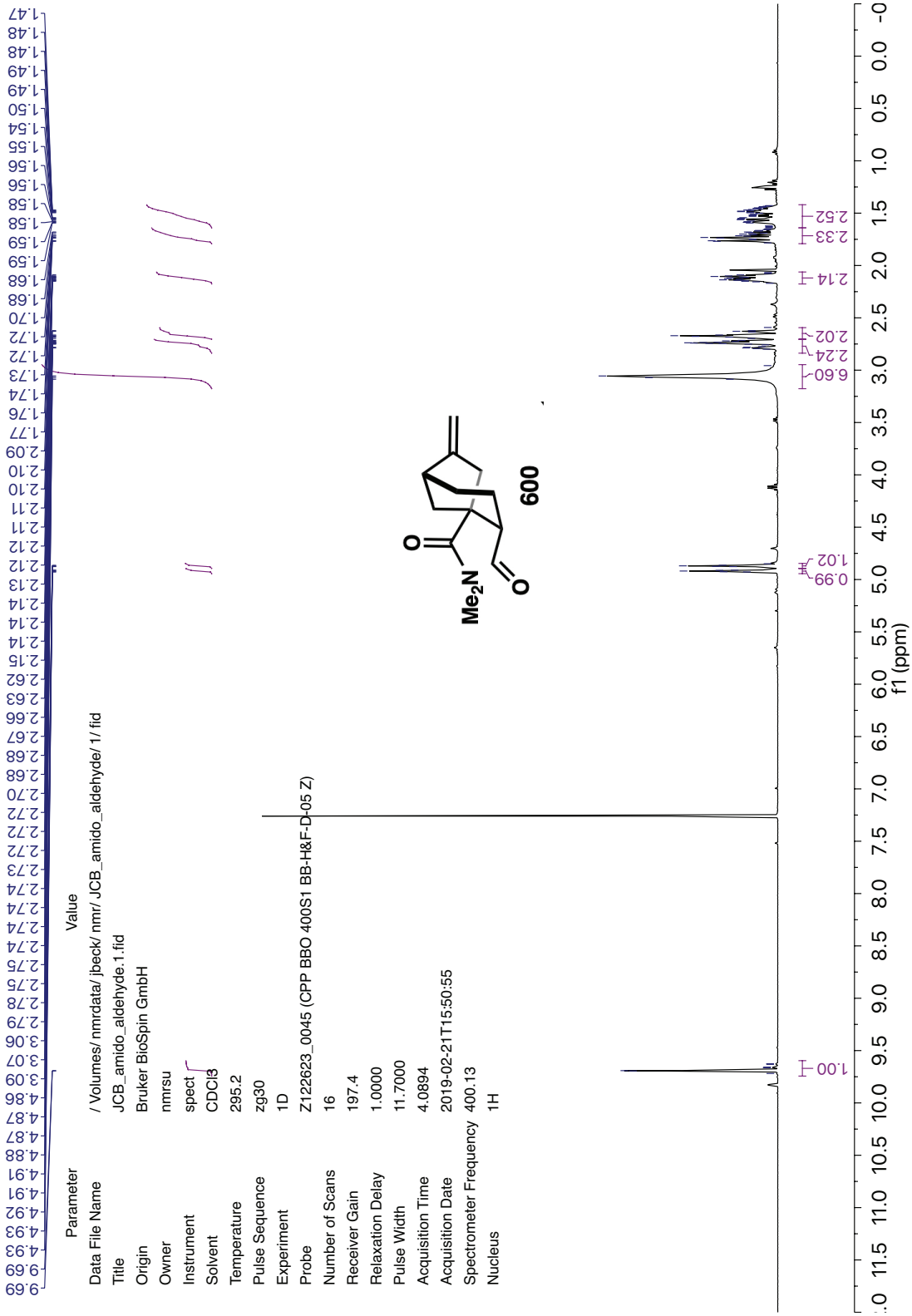
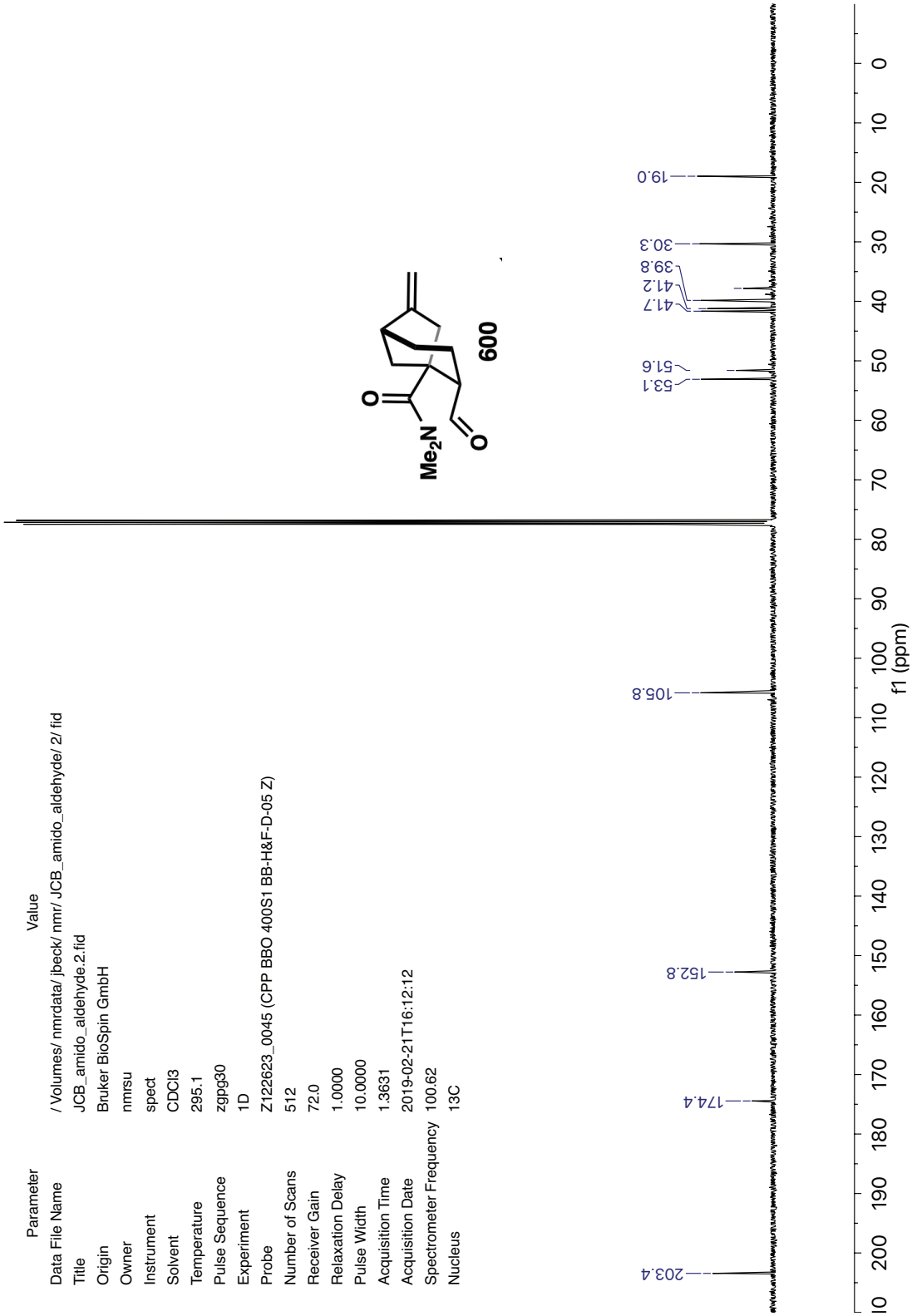
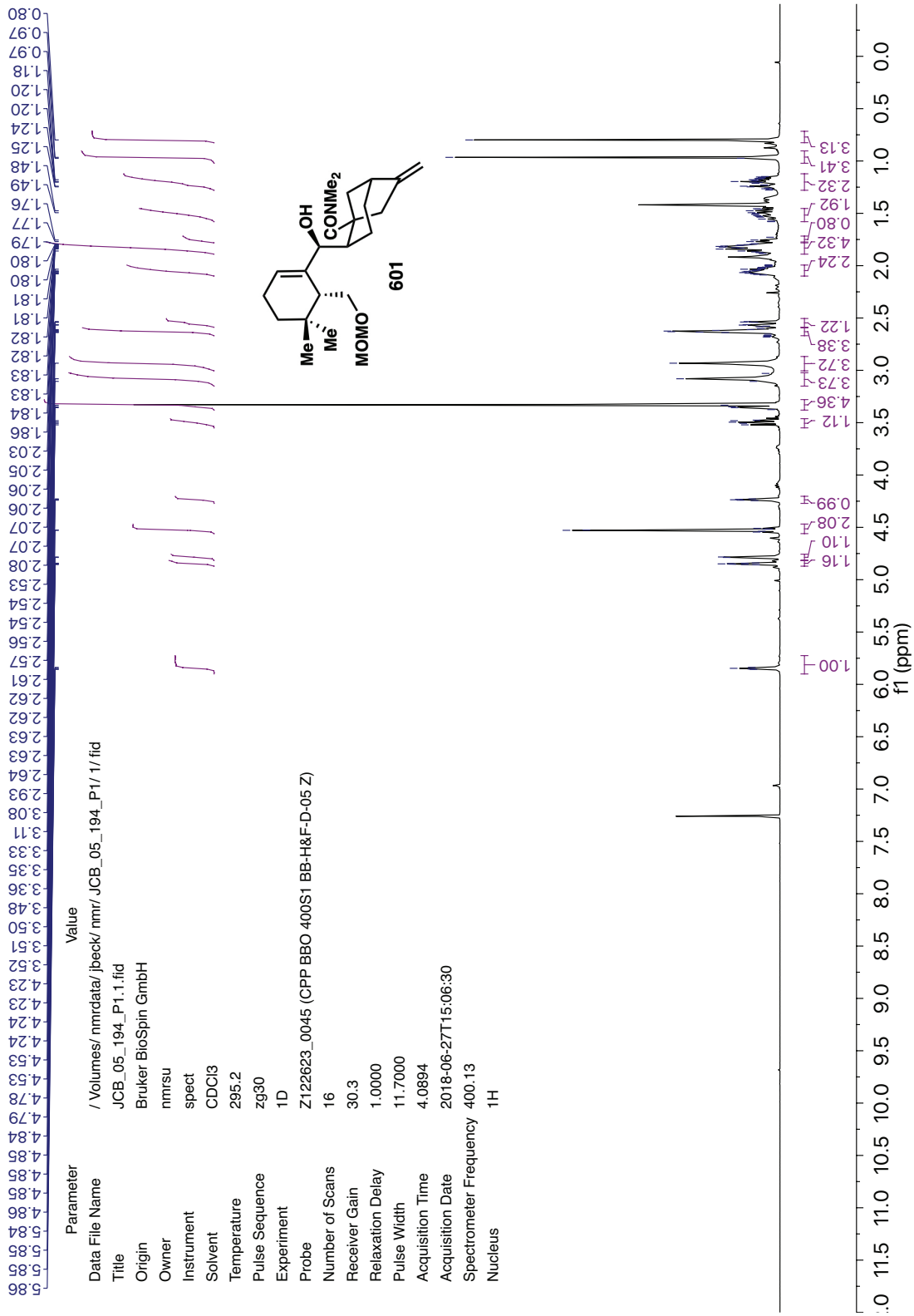
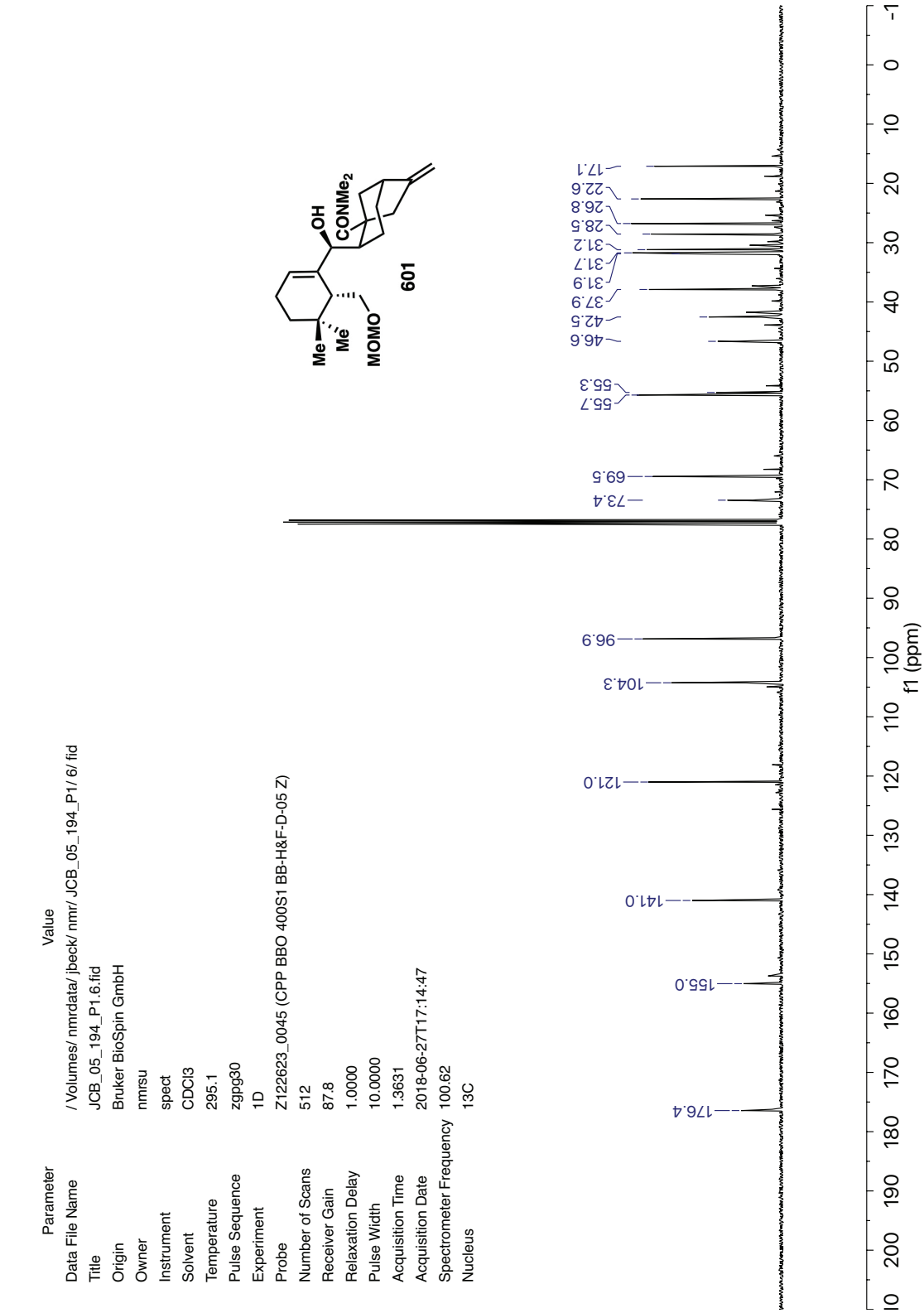
Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_199_P1/ 2/ fid
Title JCB_05_199_P1:2.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2019-02-21T15:45:53
Spectrometer Frequency 100.62
Nucleus 13C
139.2
100.9
96.8
67.5
56.9
55.7
34.5
31.2
28.2
27.6
27.1
Me
Me
OMOM
I
592
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Parameter
Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_amido_aldehyde/ 1/ fid
Title JCB_amido_aldehyde.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 197.4
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2019-02-21T15:50:55
Spectrometer Frequency 400.13
Nucleus 1H
Me2N
O
O
600
1.00
0.99
1.02
6.60
2.24
2.02
2.14
2.33
2.52
f1 (ppm)


Parameter
Value
Data File Name
/ Volumes/ nmrdata/ jbeck/ nmr/ JCB_amido_aldehyde/ 2/ fid
Title
JCB_amido_aldehyde.2.fid
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Instrument
spect
Solvent
CDCl3
Temperature
295.1
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
512
Receiver Gain
72.0
Relaxation Delay
1.0000
Pulse Width
10.0000
Acquisition Time
1.3631
Acquisition Date
2019-02-21T16:12:12
Spectrometer Frequency
100.62
Nucleus
13C
203.4
174.4
152.8
105.8
53.1
51.6
41.7
41.2
39.8
30.3
19.0
Me2N
O
O
600
f1 (ppm)



Parameter	Value
Data File Name	/ Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_194_P1/ 1/ fid
Title	JCB_05_194_P1.1.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	16
Receiver Gain	30.3
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-06-27T15:06:30
Spectrometer Frequency	400.13
Nucleus	1H


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_194_P1/ 6/ fid
Title JCB_05_194_P1.6.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 87.8
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-06-27T17:14:47
Spectrometer Frequency 100.62
Nucleus 13C
OH
CONMe2
Me
Me
MOMO
601
176.4
155.0
141.0
121.0
104.3
96.9
73.4
69.5
55.7
55.3
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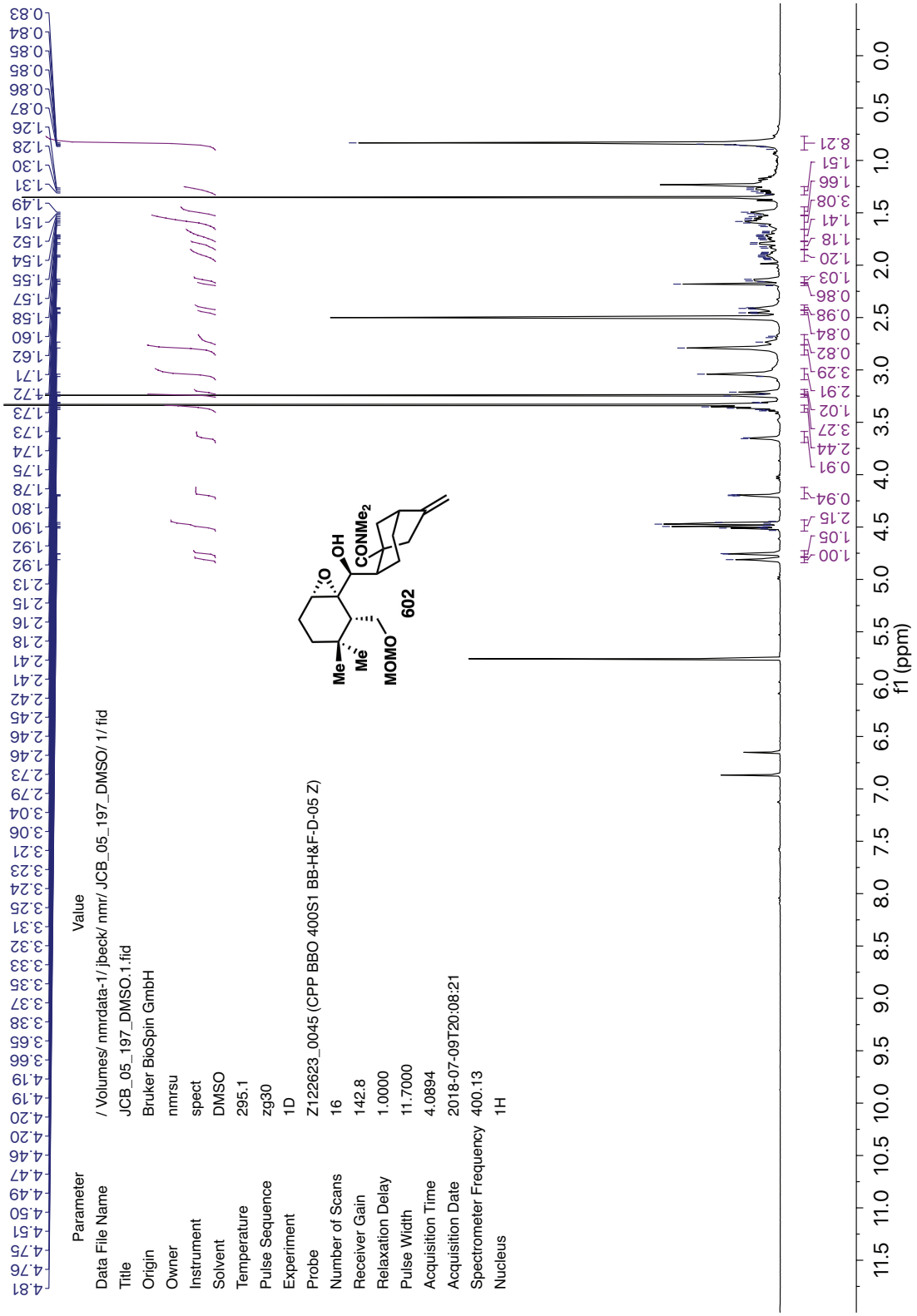
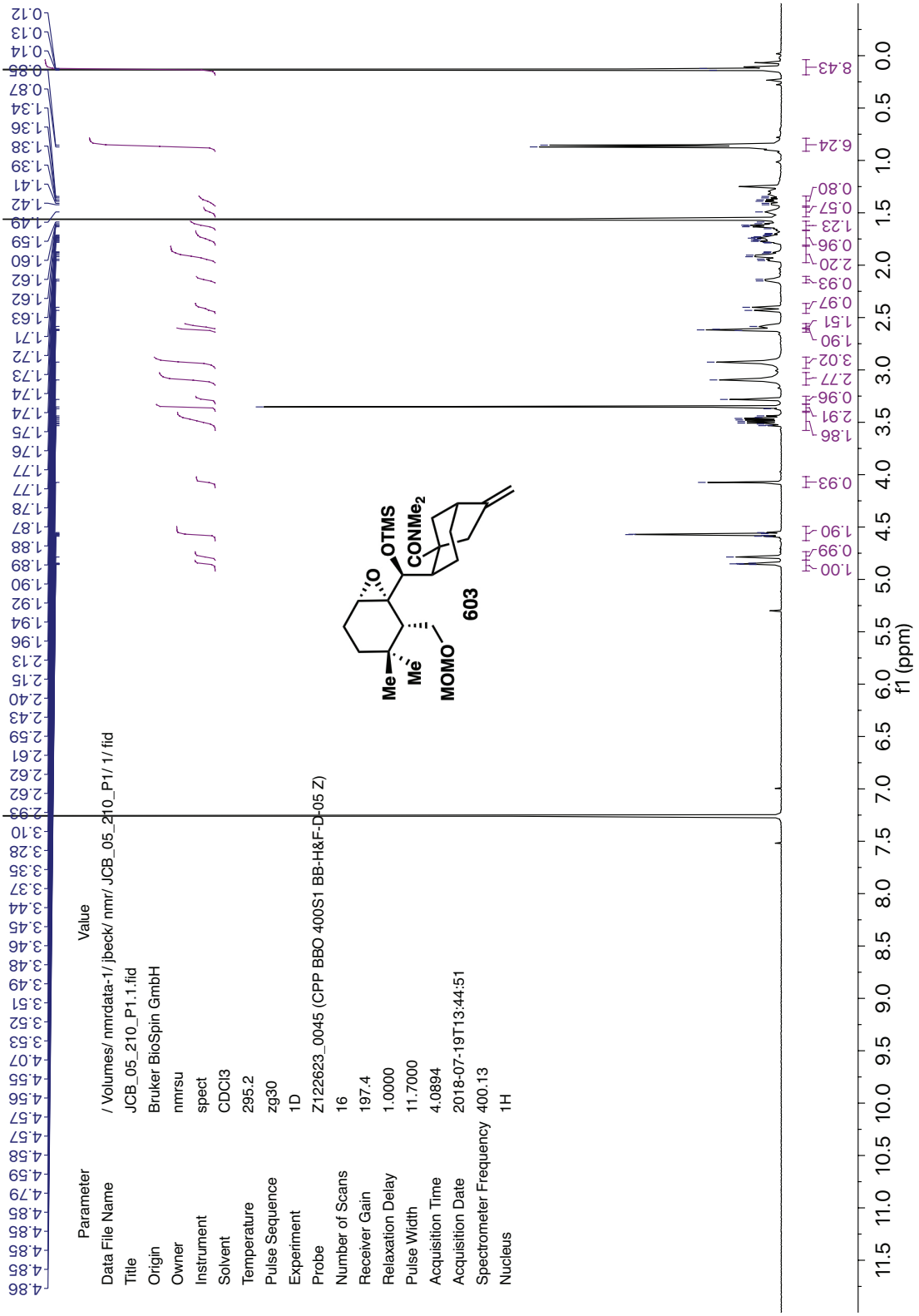
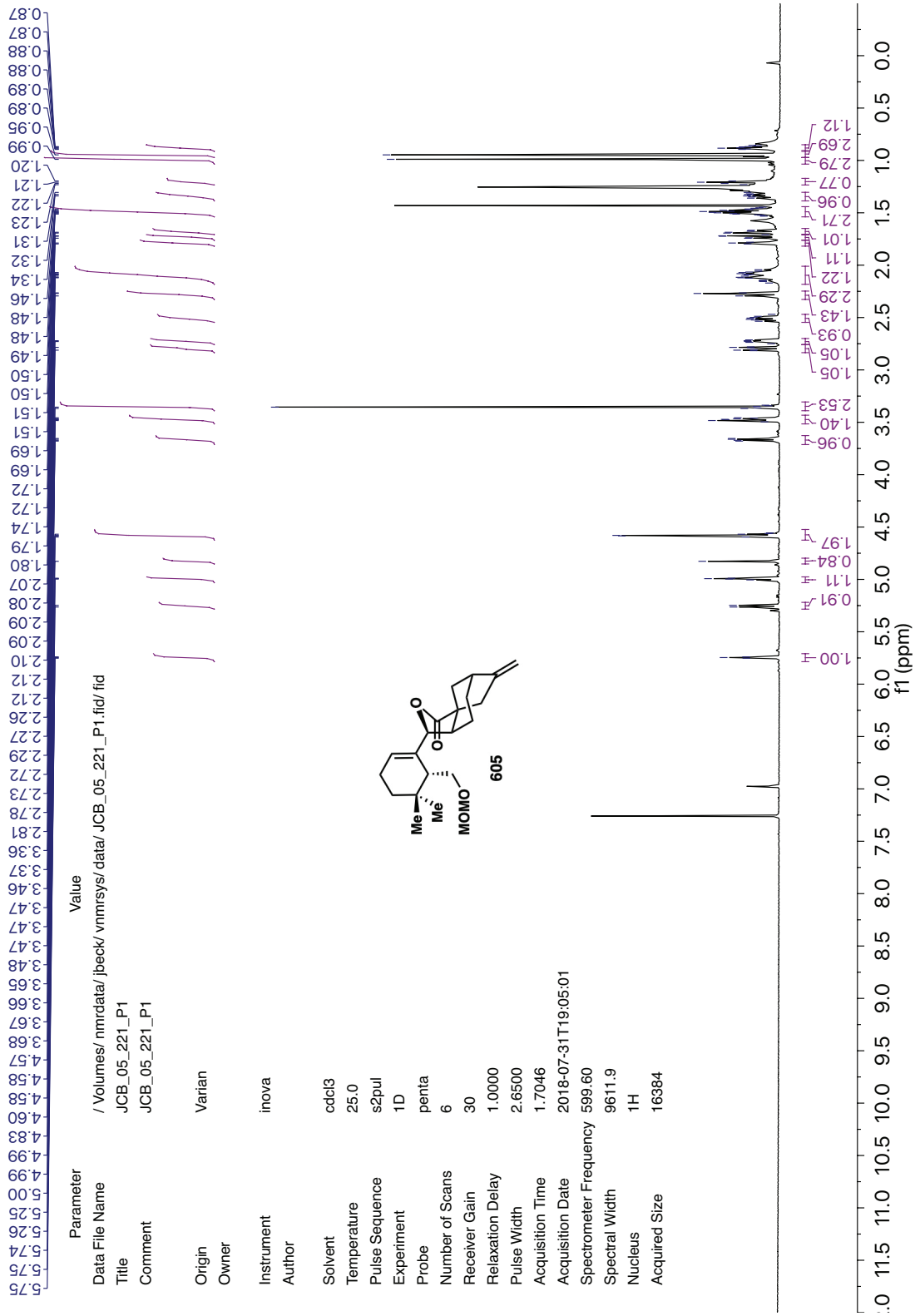
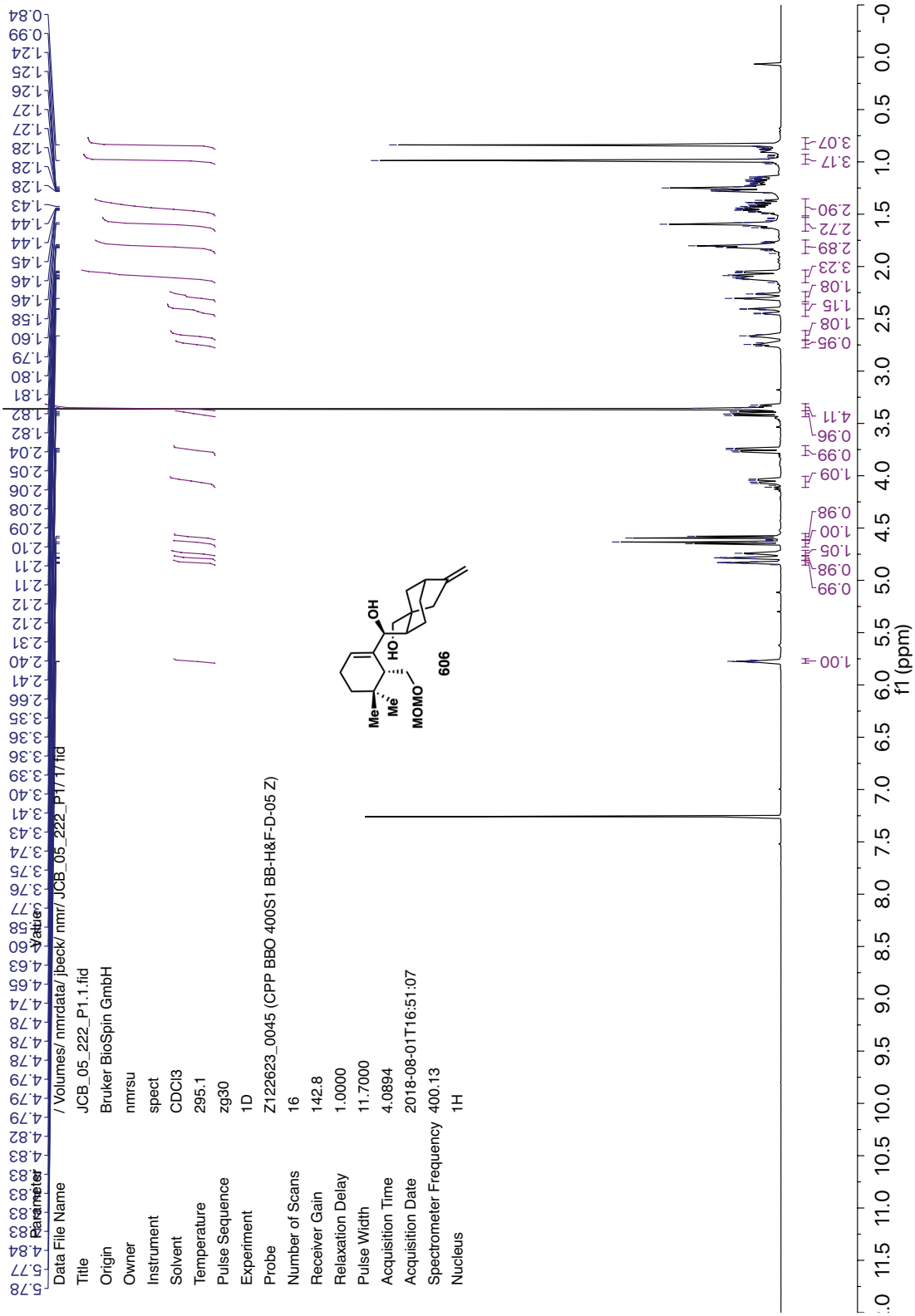
37.9
31.9
31.7
31.2
28.5
26.8
22.6
17.1
f1 (ppm)

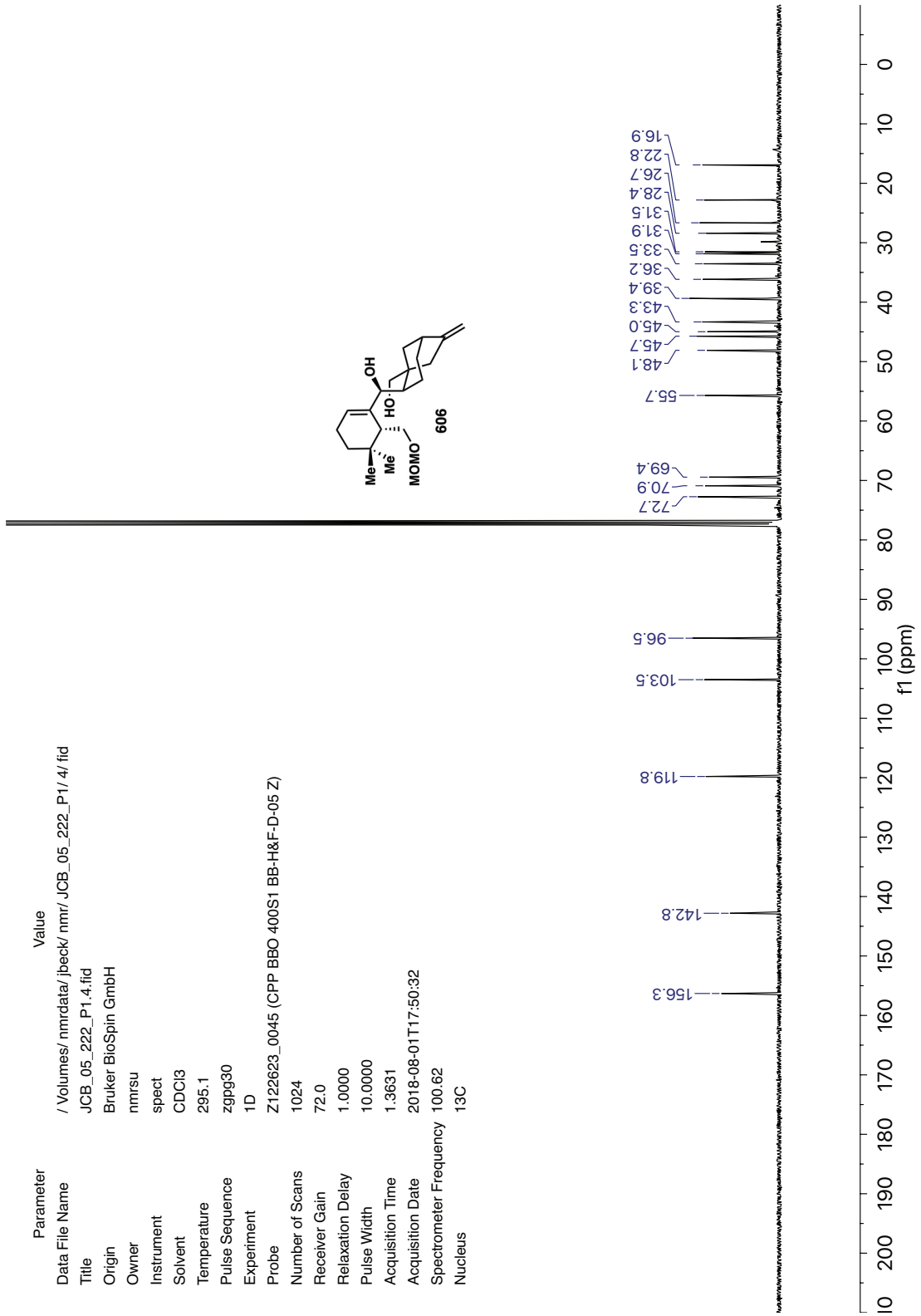

Parameter Value
Data File Name / Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_197_DMSO/ 1/ fid
Title JCB_05_197_DMSO.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent DMSO
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-07-09T20:08:21
Spectrometer Frequency 400.13
Nucleus 1H
602
f1 (ppm)

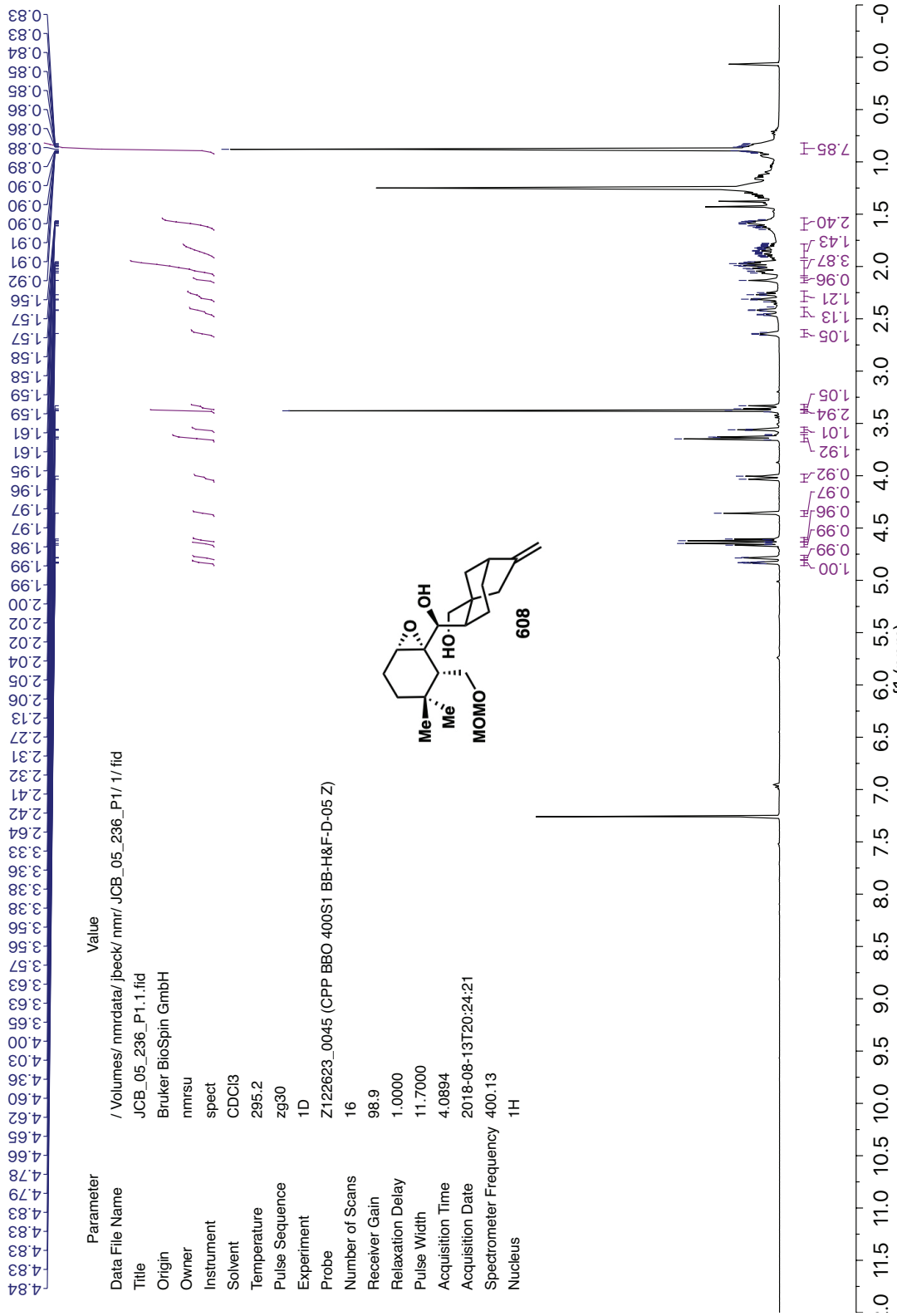


Parameter	Value
Data File Name	/ Volumes/ nmrdata-1/ jbeck/ nmr/ JCB_05_210_P1/ 1/ fid
Title	JCB_05_210_P1.1.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	16
Receiver Gain	197.4
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Acquisition Date	2018-07-19T13:44:51
Spectrometer Frequency	400.13
Nucleus	1H


Parameter
Value
Data File Name / Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_05_221_P1.fid/ fid
Title JCB_05_221_P1
Comment JCB_05_221_P1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 6
Receiver Gain 30
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 1.7046
Acquisition Date 2018-07-31T19:05:01
Spectrometer Frequency 599.60
Spectral Width 9611.9
Nucleus 1H
Acquired Size 16384
Me
Me
MOMO
O
O
605
f1 (ppm)


Parameter Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_222_P1/ 1/ fid
Title JCB_05_222_P1.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 142.8
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-08-01T16:51:07
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
HO
OH
MOMO
606
f1 (ppm)


Parameter
Value
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_222_P1/ 4/ fid
Title JCB_05_222_P1.4.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1024
Receiver Gain 72.0
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-08-01T17:50:32
Spectrometer Frequency 100.62
Nucleus 13C
156.3
142.8
119.8
103.5
96.5
72.7
70.9
69.4
55.7
48.1
45.7
45.0
43.3
39.4
36.2
33.5
31.9
31.5
28.4
26.7
22.8
16.9
OH
HO
Me
Me
MOMO
606
f1 (ppm)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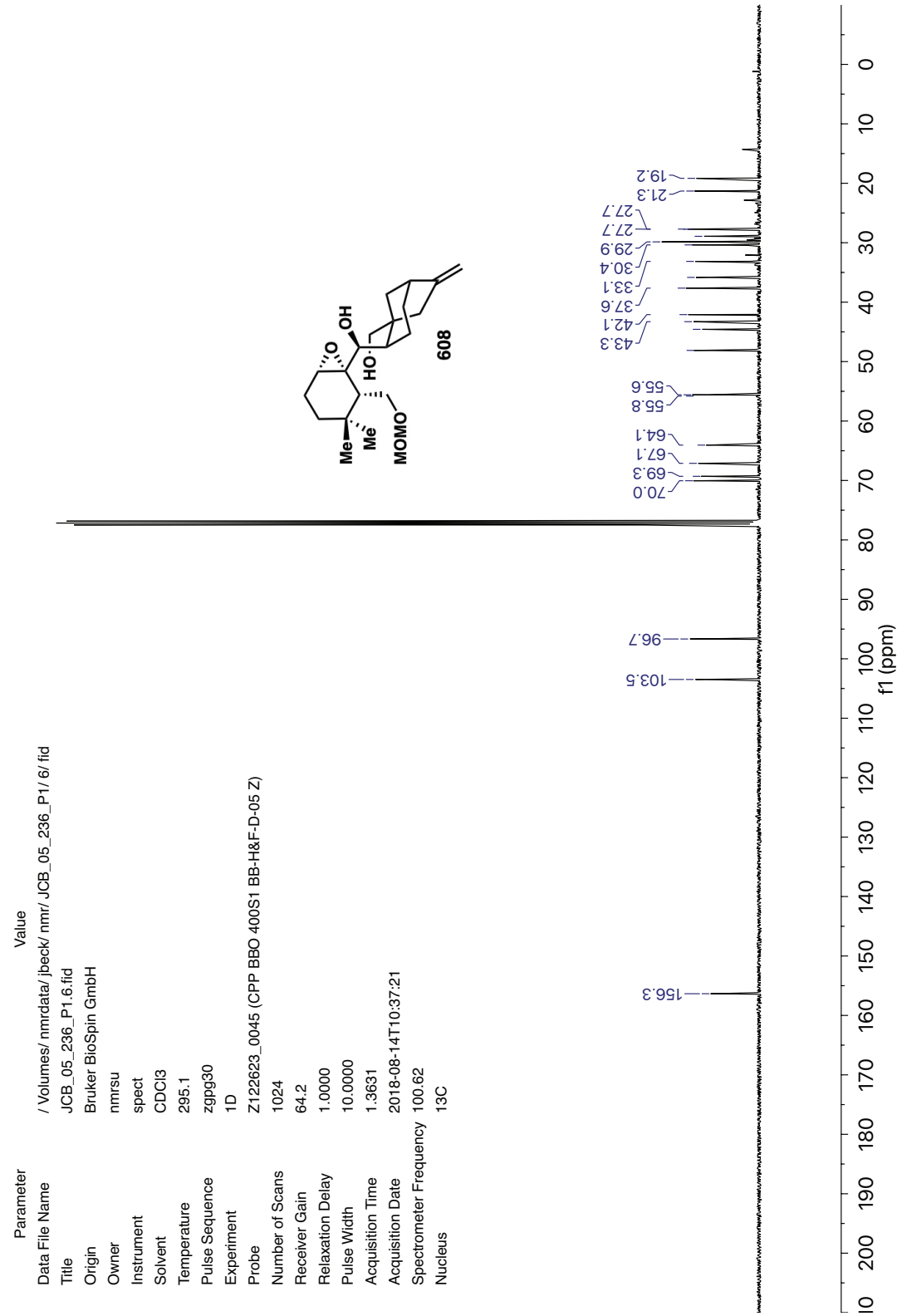
Data File Name / Volumes/ nmrdata/ jbeck/ nmr/ JCB_05_236_P1/ 1/ fid
Title JCB_05_236_P1.1.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 16
Receiver Gain 98.9
Relaxation Delay 1.0000
Pulse Width 11.7000
Acquisition Time 4.0894
Acquisition Date 2018-08-13T20:24:21
Spectrometer Frequency 400.13
Nucleus 1H
Me
Me
MOMO
HO
OH
O
608
7.85
2.40
1.43
3.87
0.96
1.21
1.13
1.05
2.94
1.05
1.92
1.01
0.92
0.97
0.96
0.99
1.00
f1 (ppm)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Title JCB_05_236_P1.6.fid
Origin Bruker BioSpin GmbH
Owner nmrsu
Instrument spect
Solvent CDCl3
Temperature 295.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1024
Receiver Gain 64.2
Relaxation Delay 1.0000
Pulse Width 10.0000
Acquisition Time 1.3631
Acquisition Date 2018-08-14T10:37:21
Spectrometer Frequency 100.62
Nucleus 13C
608
Me
Me
MOMO
HO
OH
O
156.3
103.5
96.7
70.0
69.3
67.1
64.1
55.8
55.6
43.3
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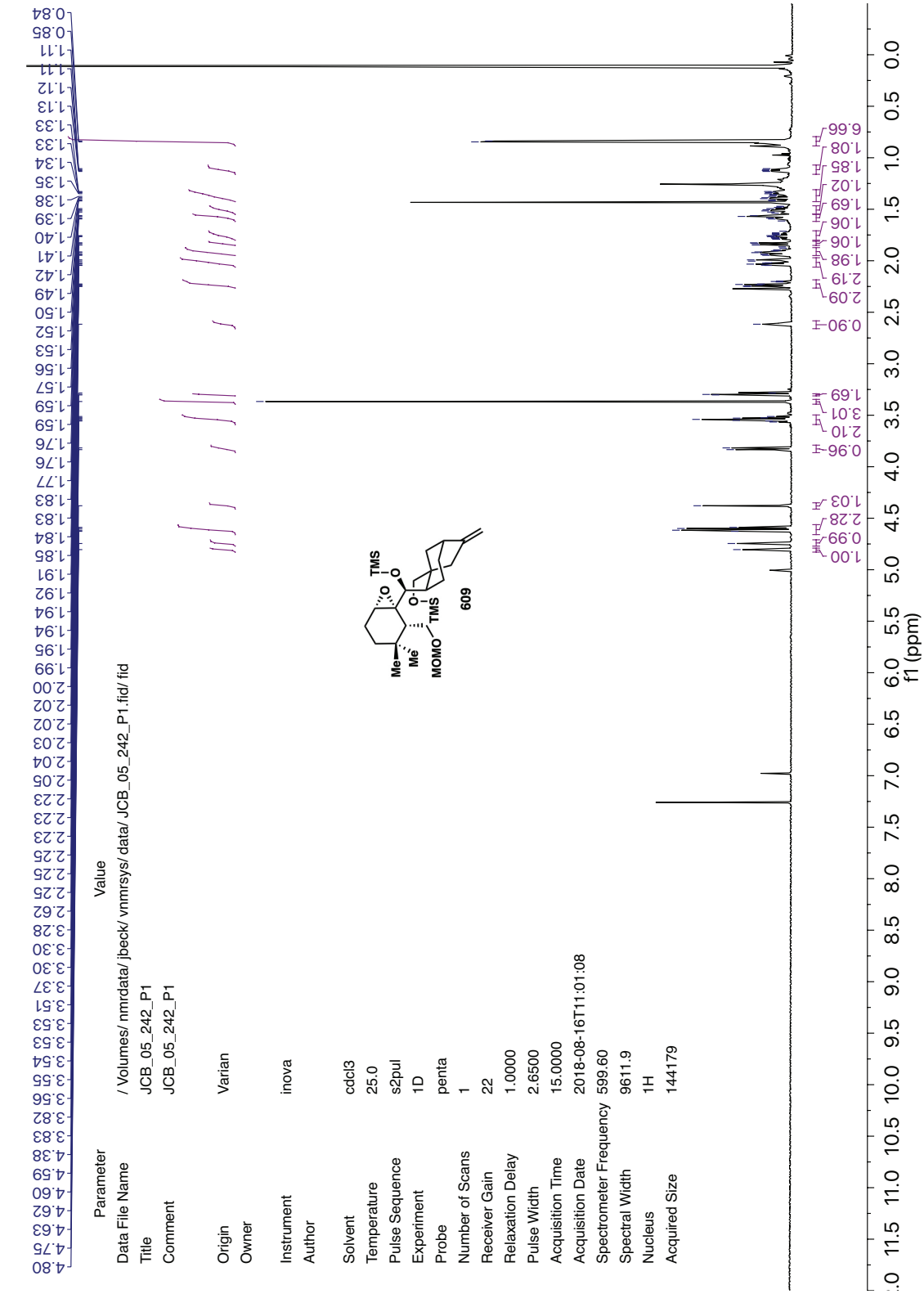
27.7
27.7
21.3
19.2
f1 (ppm)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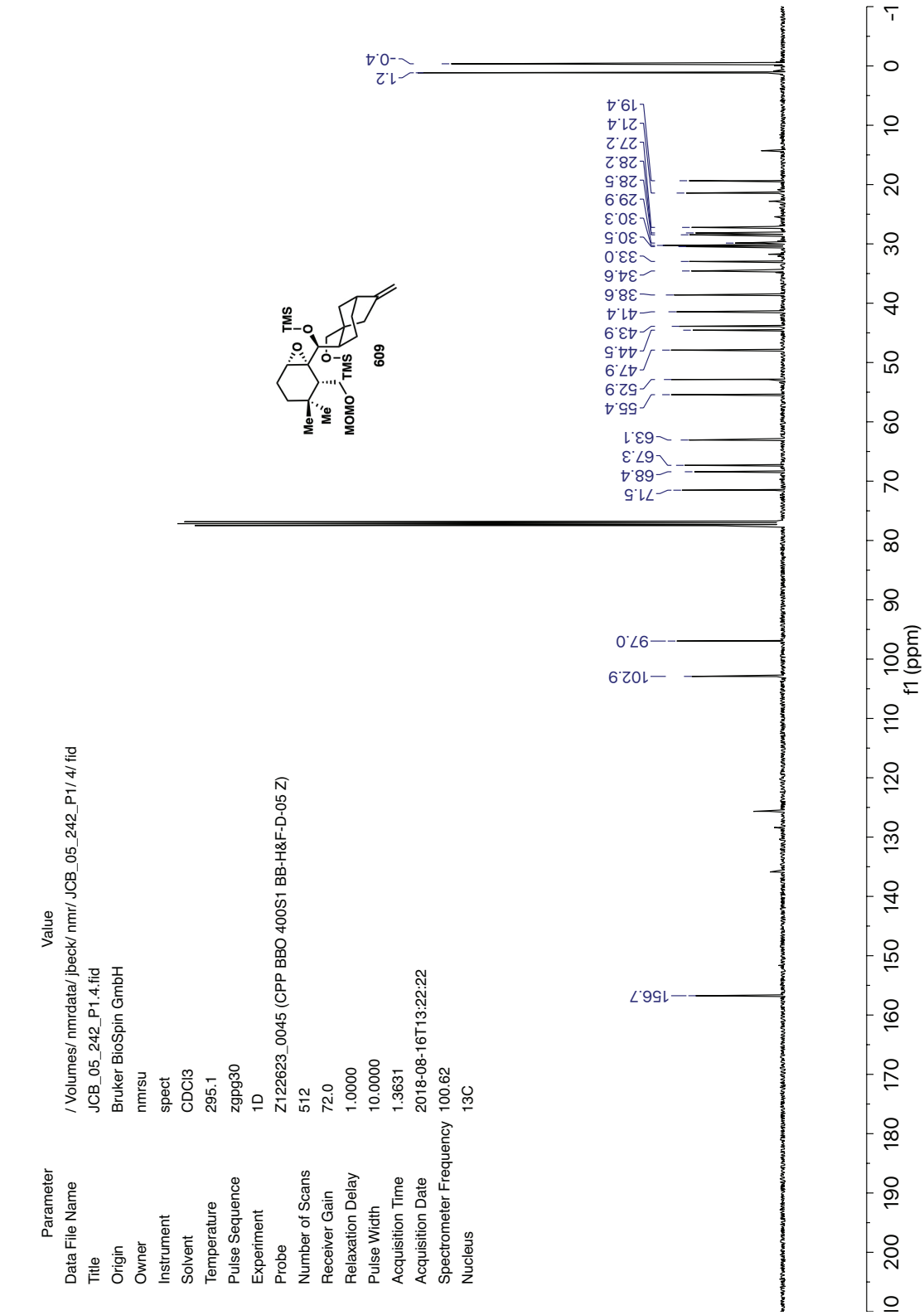
Title JCB_05_242_P1
Comment JCB_05_242_P1
Origin Varian
Owner
Instrument inova
Author
Solvent cdcl3
Temperature 25.0
Pulse Sequence s2pul
Experiment 1D
Probe penta
Number of Scans 1
Receiver Gain 22
Relaxation Delay 1.0000
Pulse Width 2.6500
Acquisition Time 15.0000
Acquisition Date 2018-08-16T11:01:08
Spectrometer Frequency 599.60
Spectral Width 9611.9
Nucleus 1H
Acquired Size 144179
TMS
O
O
O
Me
Me
MOMO
TMS
609
f1 (ppm)



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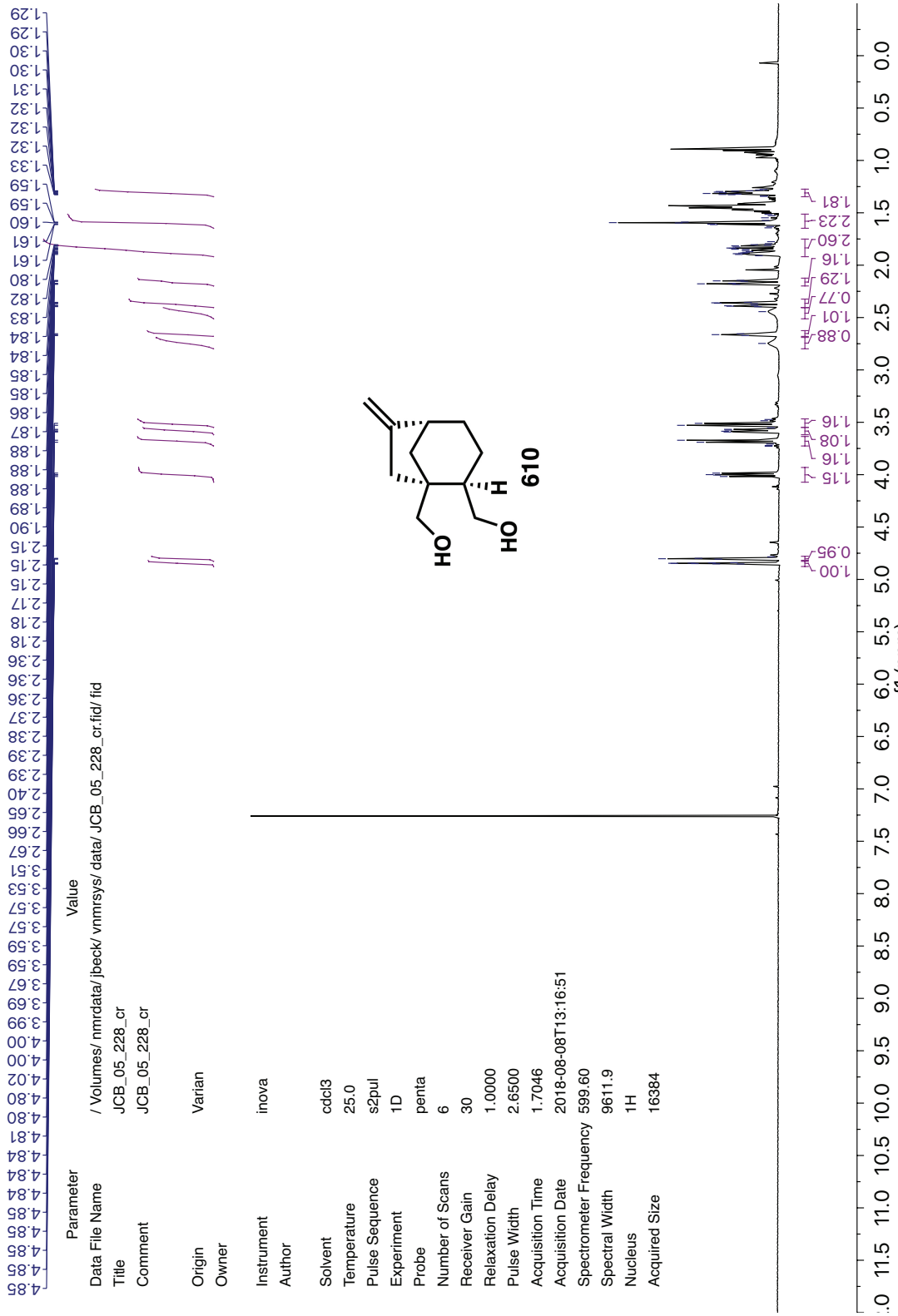
Title	JCB_05_242_P1.4.fid
Origin	Bruker BioSpin GmbH
Owner	nmrsu
Instrument	spect
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Acquisition Date	2018-08-16T13:22:22
Spectrometer Frequency	100.62
Nucleus	13C



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Data File Name	/ Volumes/ nmrdata/ jbeck/ vnmrsys/ data/ JCB_05_228_cr.fid/ fid
Title	JCB_05_228_cr
Comment	JCB_05_228_cr
Origin	Varian
Owner	
Instrument	inova
Author	
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Probe	penta
Number of Scans	6
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	2.6500
Acquisition Time	1.7046
Acquisition Date	2018-08-08T13:16:51
Spectrometer Frequency	599.60
Spectral Width	9611.9
Nucleus	1H
Acquired Size	16384

ABOUT THE AUTHOR

Jordan Casey Beck was born on September 30, 1992 to Donna Sanders and Jeff Beck in Santa Monica, CA. He grew up in the Mar Vista neighborhood of Los Angeles, graduating from Venice High School in 2010 as valedictorian and reigning prom king. Jordan then attended Brown University in Providence, Rhode Island. While Jordan began his undergraduate career as a premed student, his passion for science propelled him to study organic chemistry. He performed research with Professor Amit Basu and worked on the development of a methodology for selective galactoside functionalization.

After receiving his B.S. in Chemical Biology from Brown in 2014, Jordan returned home to California and enrolled at the California Institute of Technology in Pasadena to pursue a PhD in organic chemistry. He joined the lab of Professor Sarah Reisman, working on the total synthesis of bioactive terpenoid natural products. Following graduation from Caltech in 2019, Jordan will begin a career in consulting, working for the Boston Consulting Group in the Los Angeles office. In his free time, Jordan enjoys exploring new restaurants, lap swimming, and drinking red wine with friends.