A UNIFIED STRATEGY TO ENT-KAURANOID NATURAL PRODUCTS: TOTAL SYNTHESES OF (–)-MAOECRYSTAL Z, (–)-TRICHORABDAL A, AND (–)-LONGIKAURIN E

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To my teachers

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ABSTRACT

The diterpenoid constituents of the *Isodon* plants have attracted reasearchers interested in both their chemical structures and biological properties for more than a half-century. In recent years, the isolations of new members displaying previously unprecedented ring systems and highly selective biological properties have piqued interest from the synthetic community in this class of natural products.

Reported herein is the first total synthesis of such a recently isolated diterpenoid, (–)-maoecrystal Z. The principal transformations implemented in this synthesis include two highly diastereoselective radical cyclization reactions: a Sm^{II}-mediated reductive cascade cyclization, which forms two rings and establishes four new stereocenters in a single step, and a Ti^{III}-mediated reductive epoxide-acrylate coupling that yields a functionalized spirolactone product, which forms a core bicycle of maoecrystal Z.

The preparation of two additional *ent*-kauranoid natural products, (–)-trichorabdal A and (–)-longikaurin E, is also described from a derivative of this key spirolactone. These syntheses are additionally enabled by the palladium-mediated oxidative cyclization reaction of a silyl ketene acetal precursor that is used to install the bridgehead all-carbon quaternary stereocenter and bicyclo[3.2.1]octane present in each natural product. These studies have established a synthetic relationship among three architecturally distinct *ent*-kaurane diterpenoids and have forged a path for the preparation of interesting unnatural *ent*-kauranoid structural analogs for more thorough biological study.

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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
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl

C	cytosine
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
Cys	cysteine
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
EDC	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide
e.g.	for example (Latin: *exempli gratia*)

EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
ETP	epipolythiodiketopiperazine
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)

i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
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
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution

pK_a	acid dissociation constant
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
Pro	proline
psi	pounds per square inch
py	pyridine
pyr	pyridine
q	quartet
R	alkyl group
R	rectus
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
s	selectivity factor = $k_{\text{rel(fast/slow)}} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl

SOD	superoxide dismutase
Su	succinimide
t	triplet
T	thymine
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
Teoc	trimethylsilylethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl

Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

Chapter 1

An Introduction to the Isodon Diterpenoids

1.1 INTRODUCTION

The *Isodon* diterpenoids are a large family of natural products isolated from the *Isodon* genus of plants, comprising more than 600 members to date.[1,2] As these plants have long been used in the folk medicine traditions of China and Japan for treatment of inflammation, gastric and respiratory infections, cancer, and other maladies, it is no surprise that many of these natural products have been found to display potent and selective biological activity, including anticancer and antibacterial properties.[3] Though investigations of the *Isodon* plants began in 1910,[4] it was the isolation of enmein (**11**)[2h–j] and its structural elucidation in 1966[5] that opened the door for more thorough studies of these plants and their bioactive constituents. In the years hence, continued studies of this genus have revealed that the vast majority of diterpenoids isolated bear carbon frameworks derived from *ent*-kaurene (**1**), though many diverse oxidation patterns and

C–C bond scissions are exhibited. For instance, maoecrystals V (**9**)[2f] and Z (**10**)[2g] are two of the most highly modified diterpenoids isolated from *Isodon* species, each possessing a unique, rearranged 6,7-*seco*-*ent*-kauranoid framework.

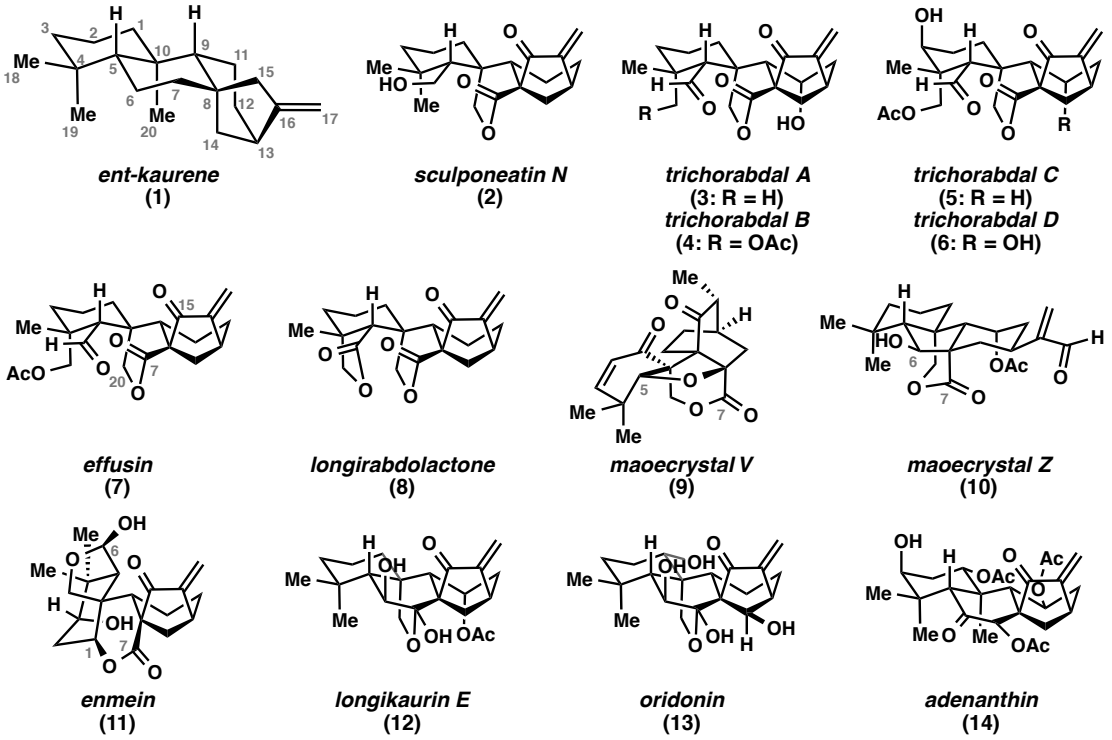


Figure 1.1. *Ent*-kaurene and selected *Isodon* diterpenoids.

Despite the multitude of *Isodon* diterpenoids isolated and characterized since the 1970s, reports of total synthesis efforts prior to 2009 are conspicuously sparse. Attention from synthetic laboratories has largely been focused on the 6,7-*seco*-*ent*-kauranoids (*e.g.*, **2**–**11**), and in the last five years, maoecrystal V (**9**) has been particularly well studied as a result of its unique structural composition and remarkable selectivity profile. Discussed herein are the strategies that have been employed to access the 6,7-*seco*-*ent*-kauranoid natural products. Additionally, a brief history detailing the isolation, structural characterization, and proposed biosynthetic pathway of this class of natural products is presented.

1.2 ISOLATION AND STRUCTURE

The earliest known studies of the *Isodon* diterpenoids are investigations by Yagi of the Japanese remedy "enmei-so," a mixture of the leaves of *I. japonicus* and *I. trichocarpa*. In a 1910 report, he detailed the isolation of a crystalline bitter principle from this remedy, termed plectranthin.[4] In 1958, independent investigations of *I. japonicus* by three Japanese research groups resulted in the isolation of enmein as the major bitter principle.[2h–j] X-ray crystallographic studies reported in 1966 confirmed the structure of enmein as a 6,7-*seco*-*ent*-kauranoid with the structure **11**.[5] Throughout the 1970s, additional *Isodon* diterpenoids bearing the "enmein-type" 1,7-lactone framework were isolated, as were other 6,7-*seco*-*ent*-kauranoids containing a spiro-fused 7,20-lactone (*e.g.*, **7**). In addition to the spirolactone, an *α,β*-unsaturated carbonyl was also found to be characteristic of many bioactive *ent*-kauranoids, frequently found as part of a bridging cyclopentanone (see **2**–**8** and **11**–**14**).

This motif has been found to be a pharmacophore important for the biological activity of the *ent*-kauranoids. For instance, Fujita reported the isolation of trichorabdals A–D[2b,c] (**3**–**6**) in 1981 and subsequently conducted limited studies on the structure-activity relationships (SAR) of various derivatives in an in vivo murine Ehrlich ascites carcinoma assay.[3b] This report and an earlier SAR study[3a] of *ent*-kauranoid derivatives for antitumor and antibacterial activity indicated that enone hydrogenation significantly weakened (**4** and **5**) or abolished (**11** and **13**) the observed bioactivity. As enones are known to react as conjugate acceptors, these findings suggest a mode of action by covalent modification.[6] Corroborating this hypothesis, adenanthin (**14**) was recently shown to exhibit anticancer activity through selective inhibition of the peroxiredoxin enzymes by covalent

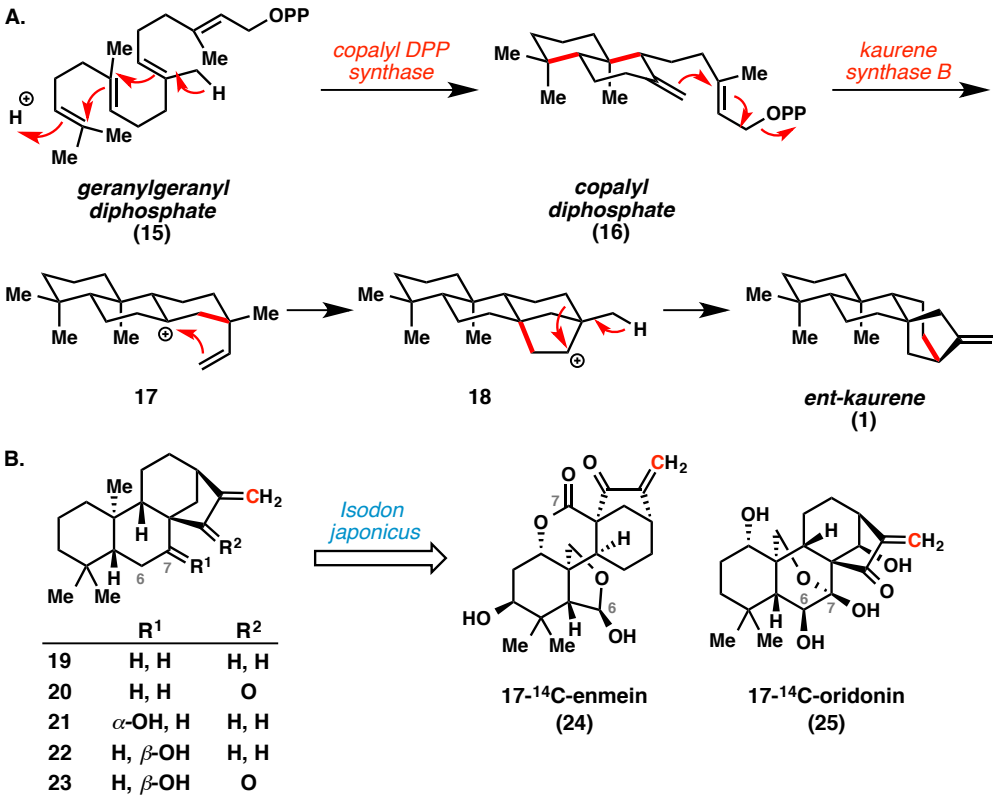
modification of a key cysteine residue; its saturated analog was likewise found to be inactive.[7] Further detailed investigations will be required in order to evaluate the biological target selectivity and elucidate the mechanism of action for other *ent*-kauranoids.

In recent years, the number of known *Isodon* diterpenoids has climbed in excess of 600, and members with novel bond cleavages and rearrangements have emerged.[1] Maoecrystals V (**9**)[2f] and Z (**10**),[2g] reported in 2004 and 2006, respectively, represent two of the most highly modified members of this family. The pentacyclic C_{19} skeleton of **9** has been excised of C6 and comprises a unique bicyclo[2.2.2]octane, three vicinal fully substituted carbons, and an ether linkage. The compact tetracyclic framework of **10**, also unprecedented among naturally occurring *ent*-kauranoids, exhibits a congested and densely functionalized central five-membered ring. The rearranged nature of **9** and **10** raises interesting questions about their biosynthetic origins.

1.3 BIOSYNTHESIS

Plant diterpenoid biosynthesis is widely established to proceed via the enzymatic cyclization of geranylgeranyl diphosphate (**15**).[8] The initial step toward *ent*-kaurene (**1**) is the cyclization of **15** by copalyl diphosphate synthase (see Figure 1.2a), giving the bicyclic copalyl diphosphate (**16**). A separate enzyme, kaurene synthase B, then transforms **16** to **1**, believed to be the ultimate progenitor of the *ent*-kauranoids. Fujita and coworkers have investigated the biosynthesis of enmein (**11**) and oridonin (**13**) by preparing a variety of oxygenated derivatives (see Figure 1.2b, **20**–**23**) of *ent*-[17-^{14}C]-kaurene (**19**) for feeding experiments with *I. japonicus*.[9] Analysis of the enmein and

oridonin isolated demonstrated some level of radiolabeling (**24** and **25**), confirmed to be localized to C17 through ozonolysis and analysis of the recovered formaldehyde. While these findings were inconclusive with respect to the probable order of oxygenations, they did support the conclusion that 6,7-*seco*-*ent*-kauranoids such as enmein (**11**) and others (Figure 1.1, **2**–**10**) arise via cleavage of oxidized *ent*-kaurene derivatives.



	R^1	R^2
19	H, H	H, H
20	H, H	O
21	α-OH, H	H, H
22	H, β-OH	H, H
23	H, β-OH	O

Figure 1.2. (a) *Ent*-kaurene biosynthesis. (b) Feeding studies. (**C** = ^{14}C isotopic label)

The biosynthetic relationships among the majority of *ent*-kauranoids can be generally summarized in terms of three transformations: oxygenation of the carbon skeleton, oxidative cleavage of the C6–C7 bond, and various skeletal rearrangements (Figure 1.3). In particular, the spiro-fused 7,20-lactone framework (*e.g.*, **27**) can be viewed as the direct product of the oxidative cleavage of the C6–C7 bond of a 7,20-epoxy-*ent*-kaurene precursor (**26**), a transformation which has been replicated in chemical synthesis.[2c,10]

However, if an α-oriented hydroxyl is present at C1 (see **30**), translactonization often occurs to afford the enmein-type 1,7-lactone (**32**). Rearrangements through retro-aldol pathways are also hypothesized: the maoecrystal Z ring system likely arises via a rearrangement paralleling that of **27** to **29**.[2g]

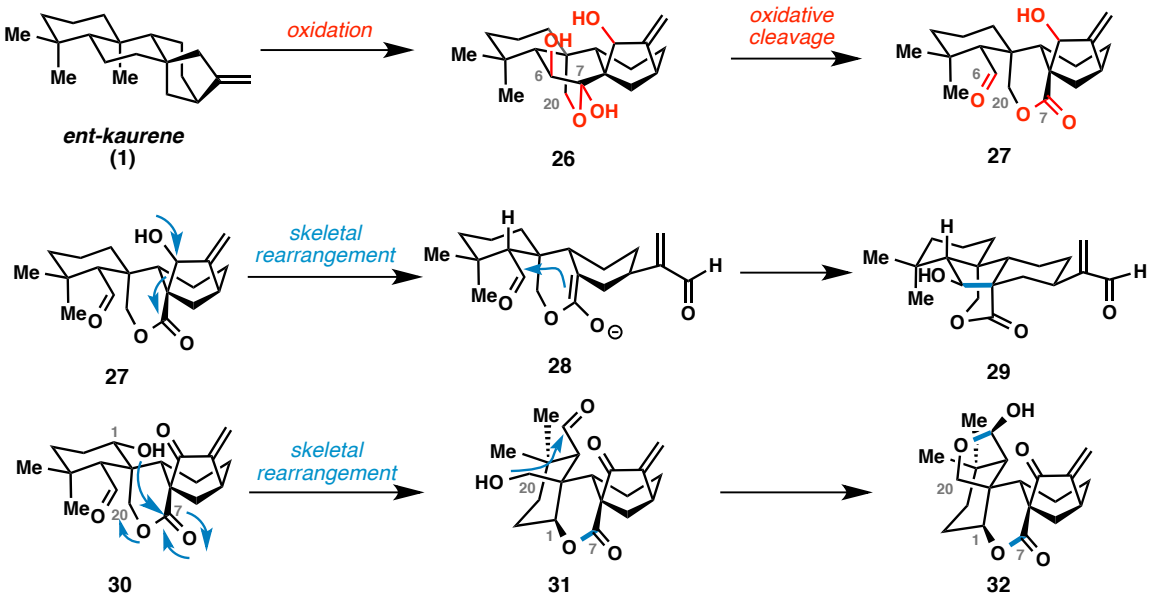


Figure 1.3. Biosynthetic oxidations, cleavages, and rearrangements of *ent*-kaurene.

1.4 PREVIOUS AND CONCURRENT SYNTHETIC EFFORTS

Prior to the elucidation of maoecrystal V (**9**) in 2004,[2f] efforts in *seco*-*ent*-kauranoid total synthesis were few and far between. Moreover, many of the racemic total syntheses reported do not provide clear entry to an enantioselective synthesis, either by asymmetric catalysis or from chiral pool starting materials. More thorough investigation of the novel biological activity displayed by members of this class requires that synthetic chemists take up this charge. The endeavors presented below are intended to highlight the history and current state of the art through the discussion of the principal transformations and strategies employed for the construction of these complex frameworks.

1.4.1 Fujita's Relay Synthesis of Enmein

As part of a larger program focused on the isolation and characterization of *Isodon* diterpenoids, Fujita and colleagues disclosed the synthetic preparation of enmein (**11**) in 1972.[11] A strategy passing through relay compound **38**, available from **11** in 14 steps, was used. Beginning with phenanthrene derivative **33**, ketone **35** is accessed in 9 steps. Formylation and thioether formation blocks C13, allowing for selective enolization and allylation of C8 to afford **36**. Following cleavage of the blocking group and ozonolysis, exposure to NaOMe affords the *ent*-kaurane framework via aldol cycliation. Moving forward, **37** is advanced through relay compound **38** to olefin **39**. The C6–C7 bond is

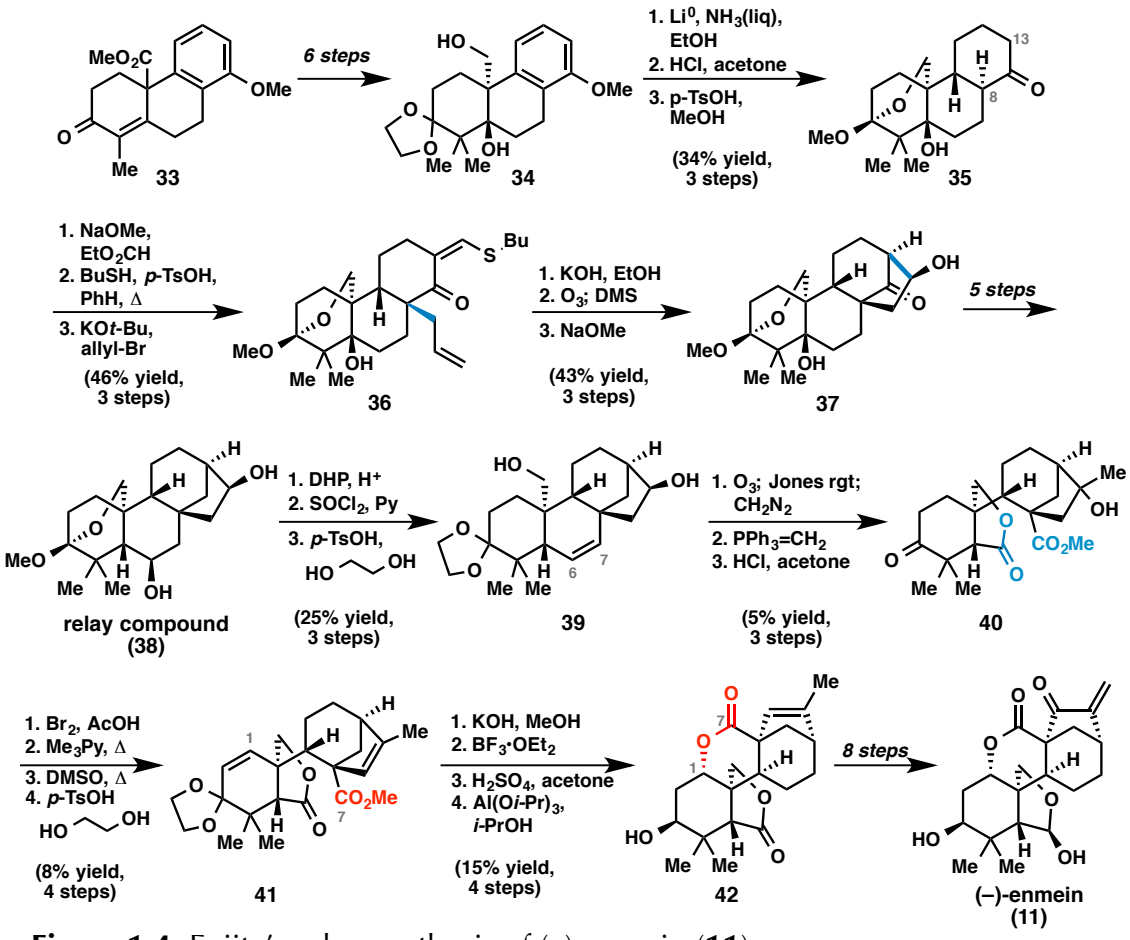


Figure 1.4. Fujita's relay synthesis of (–)-enmein (**11**).

cleaved via ozonolysis and oxidative workup to yield lactone **40**. The enmein 1,7-lactone (see **42**) is later accessed by BF_3•OEt_2-promoted intramolecular conjugate addition of the acid derived from **41**.

1.4.2 Mander's Synthesis of 15-Desoxyeffusin

Mander and colleagues disclosed the first effort toward a spirolactone-type 6,7-*seco*-*ent*-kauranoid in 1986.[12] In similar fashion to Fujita's strategy, C6–C7 oxidative cleavage of a suitably functionalized lactol precursor was envisioned to provide access to the *seco*-*ent*-kauranoid architecture of effusin (**7**).[2d]

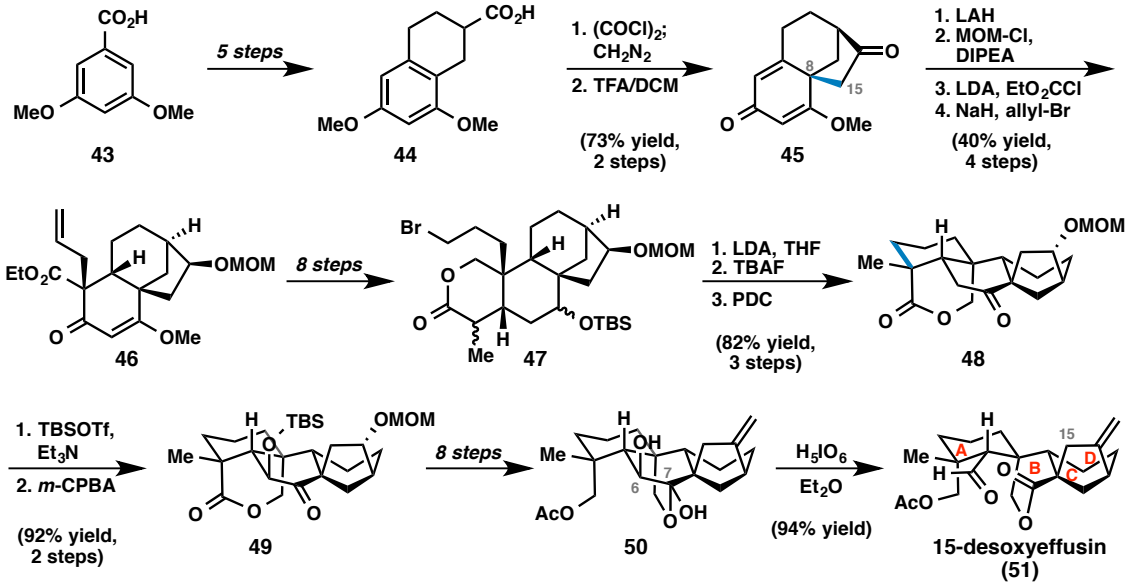


Figure 1.5. Mander's total synthesis of (±)-15-desoxyeffusin (**51**).

Beginning from 3,5-dimethoxybenzoic acid (**43**), bicyclic acid **44** is prepared in 5 steps. Acid **44** is converted to the α-diazomethylketone, which undergoes intramolecular alkylation of the aromatic ring upon treatment with trifluoroacetic acid to form the C8–C15 bond and afford bridged tricycle **45**. Exposure to LAH reduces the cyclopentanone

and delivers hydride to the *β*-face of the more electron-deficient enone to give the desired *cis*-fused 6,6-bicyclic system. Enolate alkylation and acylation install functional handles for appending the A ring in *β*-ketoester **46**, which was further advanced to lactone **47** in 8 steps.

Deprotonation of **47** with LDA resulted in cyclization to form the *ent*-kaurane framework. A sequence of protecting group and redox manipulations advanced **48** to lactol **50**, with the requisite C6 hydroxyl group for oxidative cleavage arising by Rubottom oxidation.[13] Lactol **50** was then treated with periodic acid to afford 15-desoxyeffusin (**51**) in 94% yield. The authors note that they were unable to introduce the C15 ketone by oxidation of **50** or **51** with selenium dioxide, a transformation which was successfully applied to similar gibberellin frameworks. Mander's 33-step route to **51** and a strategically similar 29-step semisynthesis of longirabdolactone (**8**)[14] would remain as the state of the art until recent efforts toward maoecrystal V (**9**).

1.4.3 Yang's Total Synthesis of Maoecrystal V

Since its structure was disclosed in 2004, **9** has quickly become the most highly targeted 6,7-*seco*-*ent*-kauranoid natural product, due to its remarkably selective cyctoxicity toward HeLa cells and complex pentacyclic architecture.[2f] To date, fifteen reports detailing efforts from nine laboratories have been published.[15,16] A 2010 communication from Yang and coworkers represents the first of three completed total syntheses of **9**.[16a]

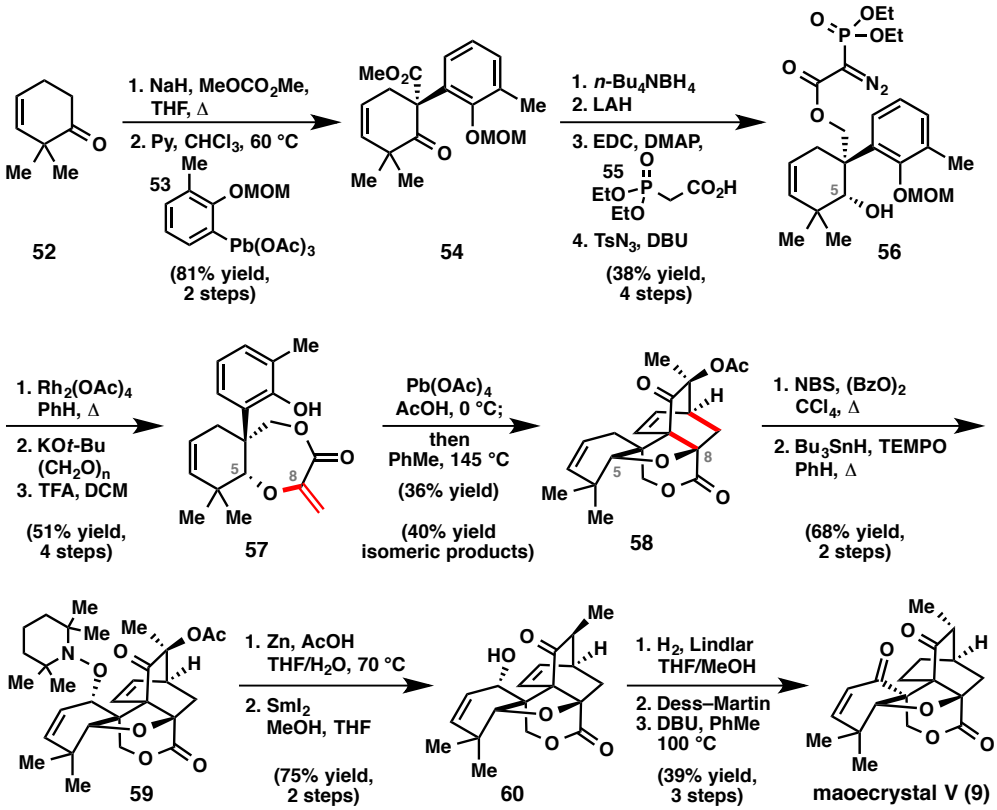


Figure 1.6. Yang's total synthesis of (±)-maoecrystal V (**9**).

Yang's strategy centers on an oxidative dearomatization/intramolecular Diels–Alder sequence used to prepare the bicyclo[2.2.2]octane and access the complete pentacyclic core. Oxidative arylation of the *β*-ketoester derived from cyclohexenone **52** by arylplumbane **53** delivers arylketone **54** in good yield. A two-step reduction sequence employing *n*-Bu_4NBH_4 followed by LAH provides the correct secondary alcohol relative stereochemistry for what will become the C5 to C8 ether bridge; the authors note that direct reduction of **54** with LAH or DIBAL provides the incorrect *β*-disposed alcohol. Following an EDC coupling of acid **55** and diazo transfer, a rhodium-catalyzed O–H bond insertion forms the second ether C–O bond. Horner–Wadsworth–Emmons olefination and cleavage of the MOM group with TFA reveals key Diels–Alder precursor **57**.

Indeed, treatment with lead tetraacetate results in oxidative dearomatization to provide an *ortho*-quinol acetate, which when heated in toluene undergoes Diels–Alder cycloaddition to deliver 36% yield of pentacycle **58**, as part of a mixture of three isomeric cycloaddition products. Pentacycle **58**, prepared in just ten steps, constitutes the framework of **9** and contains all the necessary carbons, but still requires a number of redox manipulations for conversion to the natural product. Allylic bromination and radical trapping with TEMPO are used to install necessary A ring oxygenation; N–O bond cleavage and reductive acetate removal are facilitated by zinc in AcOH and SmI_2, respectively, to yield allylic alcohol **60**. Lindlar hydrogenation, Dess–Martin oxidation, and epimerization with DBU completed the synthesis of **9**.

Though no clear entry point for asymmetry is present, the dearomatization/Diels–Alder strategy employed by Yang delivers a concise, 17-step preparation of maoecrystal V (**9**).

1.4.4 Danishefsky's Total Synthesis of Maoecrystal V

The Danishefsky laboratory has investigated multiple intramolecular Diels–Alder approaches for the synthesis of **9**.[15c,j,16b] Early attempts with functionalized model compound **61** provided undesired cycloadduct **62**, arising from improper diene facial selectivity. As the oxidation about the resulting bicyclo[2.2.2]octane of **62** was therefore incorrect for advancement to **9**, this route was abandoned.

The authors hypothesized that an achiral Diels–Alder precursor might provide a solution to the observed regioselectivity problem. Toward this end, the enolate of **63** was coupled with chloroenone **64**. Exhaustive reduction with DIBAL followed by reoxidation

of the allylic alcohol furnished enone **65**. Condensation with acyl chloride **66** and conversion to the silyl enol ether afforded Diels–Alder precursor **67**. Heating **67** in toluene effected cycloaddition as well as β-elimination of the phenyl sulfinate to reveal tetracycle **68** upon exposure to TBAF. The use of a vinyl phenyl sulfinate dienophile as a propiolate equivalent precludes the formation of isomeric products, as they converge to enantiomers upon elimination to form the olefin.

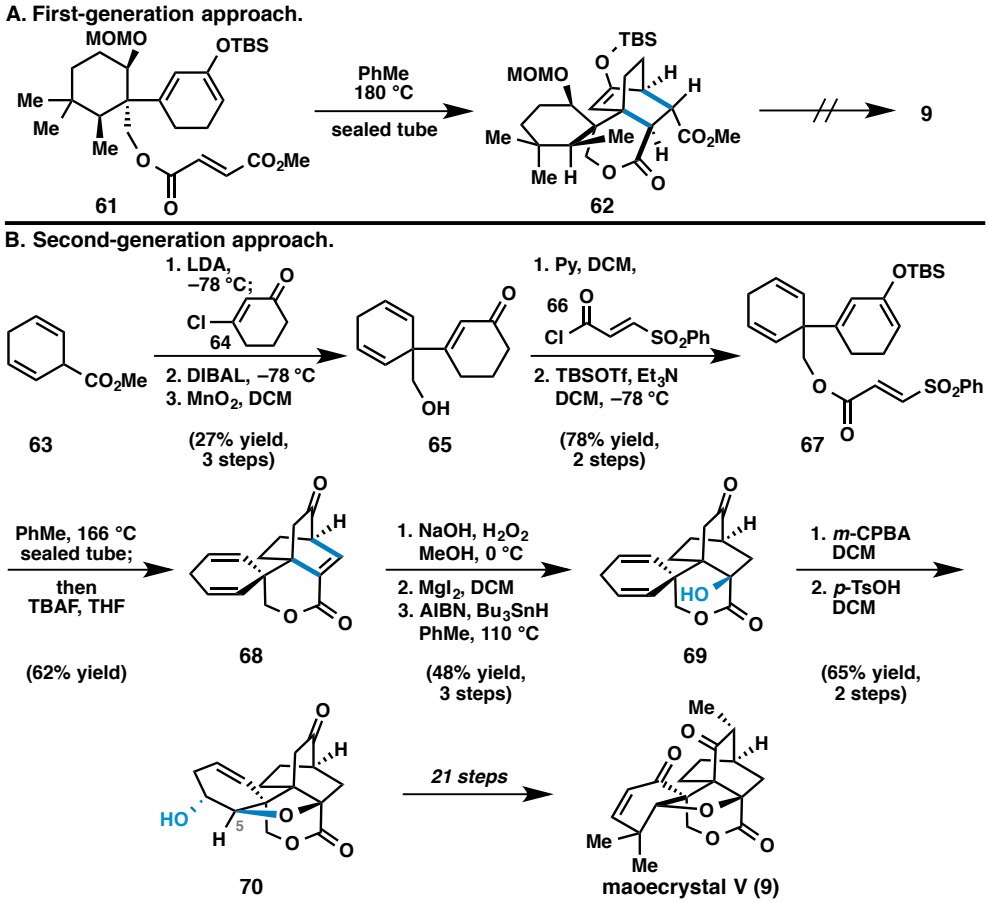


Figure 1.7. Danishefsky's total synthesis of (±)-maoecrystal V.

The authors note that the challenge in advancing **68** to **9** now lies in the differentiation of three olefins with similar levels of steric hindrance. One double bond, however, is contained within an α,β-unsaturated ester and is therefore electronically differentiated. Thus, exposure of **68** to NaOH and H_2O_2 effects chemoselective

epoxidation of the electron-deficient olefin. This epoxide can be readily converted to the iodohydrin by MgI_2, which is hydrodehalogenated under radical conditions to give tertiary alcohol **69**. The placement of the resulting alcohol now serves to activate the proximal olefin toward epoxidation by *m*-CPBA; subsequent treatment with *p*-TsOH promotes cyclization to form pentacyclic ether **70**.

With **70** in hand, Danishefsky has prepared the core of maoecrystal V (**9**), albeit epimeric at C5. The achiral precursor employed facilitates rapid preparation of the majority of the structural complexity of **9** via a single isomer of cycloadduct **68** in just six steps, further functionalized through deft use of substrate control to arrive at pentacycle **70** in eleven steps. However, due to the relative absence of substitution in **70**, a further 21 steps are required to install the enone and *gem*-dimethyl group and to properly functionalize the bicyclo[2.2.2]octane. Although **9** was prepared as a racemate, this strategy allows for the possibility of asymmetric induction during the Diels–Alder cycloaddition through the use of a chiral catalyst.

1.4.5 Zakarian's Total Synthesis of Maoecrystal V

In 2013, Zakarian and colleagues also disclosed a total synthesis of **9**.[16c] A different Diels–Alder disconnection from those employed by Yang and Danishefsky is used, employing a silyl-tethered precursor. Additionally, the lactone is constructed by a novel late-stage radical cyclization. The authors hypothesized, quite correctly, that early introduction of the tetrahydrofuran ring would likely improve stereocontrol later in the synthesis and avoid the risks of attempting ether formation on a strained polycyclic system.

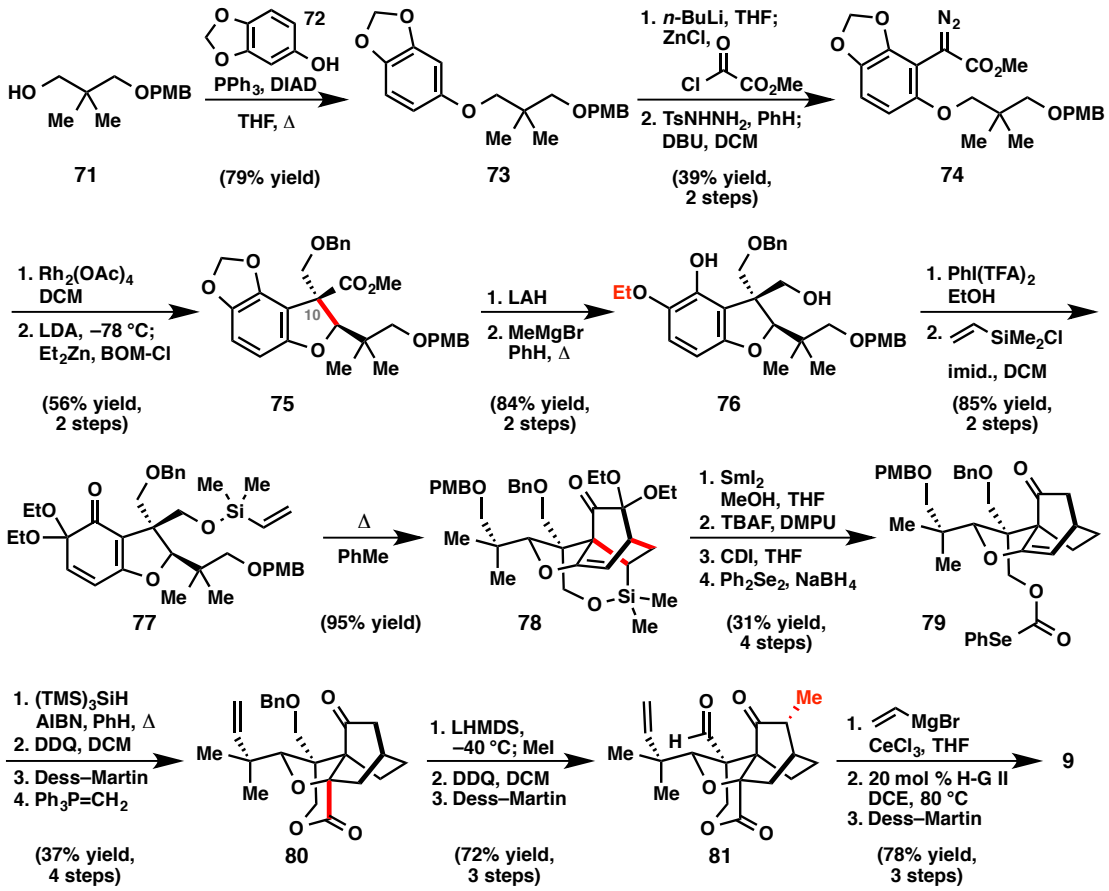


Figure 1.8. Zakarian's total synthesis of (±)-maoecrystal V (**9**).

The synthesis commenced with coupling of PMB ether **71** and sesamol (**72**) under Mitsunobu conditions.[17] Directed lithiation and acylation with methyl chlorooxoacetate followed by conversion to the *α*-diazoester using tosyl hydrazide afforded **74**. Catalytic $Rh_2(OAc)_2$ effected C–H insertion to form the furan ring, and alkylation with LDA and benzyloxymethyl chloride delivered dihydrobenzofuran **75** and the C10 all-carbon quaternary stereocenter. Moving forward, cycloaddition of *ortho*-quinone ketal **77** proceeded in refluxing toluene to form the bicyclooctane in 95% yield. Following removal of the *gem*-diethoxy substituents with SmI_2 and desilylation with TBAF, selenocarbonate **79** was accessed through successive treatment with carbonyl diimidazole (CDI) and sodium phenyl selenide.

The authors observed that only tris(trimethylsilyl)silane acted as an effective hydrogen atom donor for the desired radical cyclization, which proceeded upon exposure to AIBN. A series of functional group manipulations furnished tetracycle **80**, which was alkylated on the ketone bridge using LHMDS and iodomethane and advanced to aldehyde **81**. Vinyl Grignard addition, ring closing methathesis using Hoveyda-Grubbs II catalyst, and Dess–Martin oxidation completed the synthesis of **9**.

Zakarian's route proceeds to **9** in 24 steps, while avoiding the majority of selectivity pitfalls prevalent in Danishefsky's and Yang's strategies. Early-stage formation of the tetrahydrofuran ring proved advantageous in this regard; the authors also note that its construction via C–H insertion of diazoester **74** could potentially be rendered asymmetric through the use of chiral rhodium catalysts.

1.4.6 Zhai's Total Synthesis of Sculponeatin N

In contrast to Mander's 33-step preparation of 15-desoxyeffusin, Zhai and colleagues have recently disclosed a concise total synthesis of a quite similar 6,7-*seco*-*ent*-kauranoid, sculponeatin N (**1**).[18] Rather than employ a biomimetic oxidative cleavage, Zhai elected to pursue an intramolecular Diels–Alder for the simultaneous preparation of the B and C rings, followed by alkylation and radical cyclization to install the bridging *exo*-enone.

Beginning with known diester **82**, treatment with LDA and paraformaldehyde effects a regio- and stereoselective aldol reaction and lactonization to give bicyclic lactone **83**, which is advanced quickly to cycloaddition precursor **85**. Heating to 190 °C in a sealed tube effects the intramolecular Diels–Alder, and the authors were able to devise a one-pot

cycloaddition/protodesilation/methanolysis sequence to furnish a single *cis*-fused bicyclic product. Following TBS protection, alkylation of **86** with 2,3-dibromopropene (**87**) proceeds in good yield using LDA and HMPA to form the second quaternary center. Exposure to triethylborane and tris(trimethylsilyl)silane at room temperature results in radical cyclization to give a 68% yield of **89** along with 27% yield of the isomeric bicyclo[2.2.2]octane. Use of AIBN and tributyltin hydride on the other hand favors the undesired isomer in a 3:1 ratio. Allylic oxidation and TBS ether cleavage furnishes **2**.

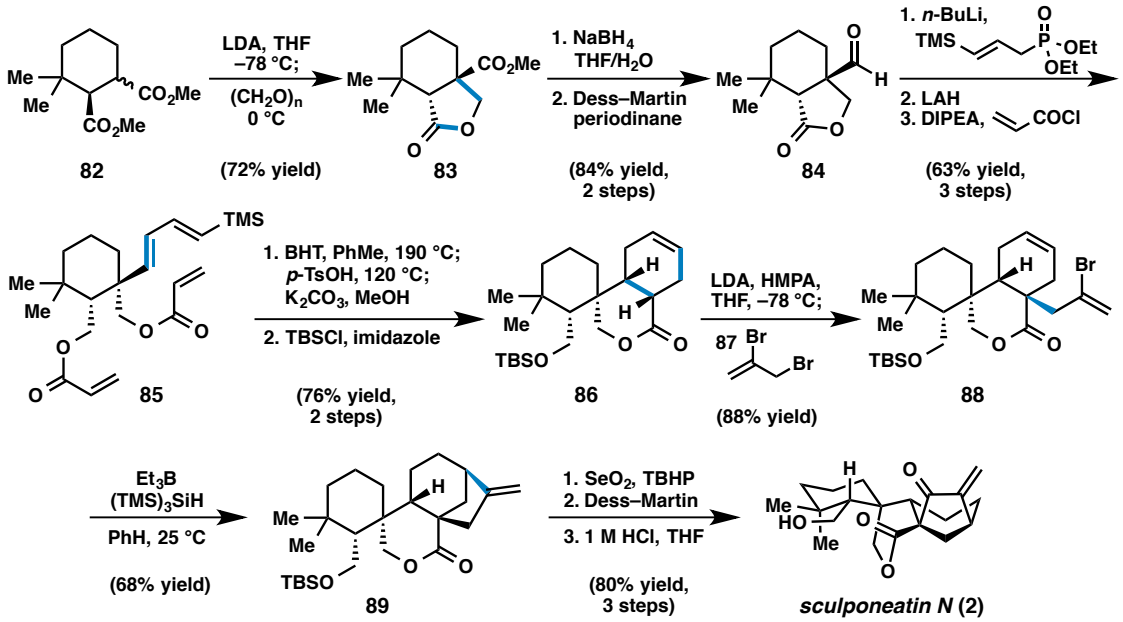


Figure 1.9. Zhai's total synthesis of (±)-sculponeatin N.

1.5 CONCLUDING REMARKS

Though the *Isodon* diterpenoids have been scantly studied by synthetic chemists for much of the last fifty years, there is renewed interest in this family of natural products brought about by the isolation of new members possessing complex and novel architectures. Improvements in synthetic methodology have enabled shorter syntheses of these targets, though asymmetric preparations and more general strategies remain out of reach. The investigation of enantioselective approaches to this class, as well as the development of new methods for the synthesis of these complex targets, will encourage and facilitate new inquiries into their biological activity.

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Chapter 2

Development of a Synthetic Strategy for Ent-Kauranoid Natural Products: Total Synthesis of (–)-Maoecrystal Z[†]

2.1 INTRODUCTION

Maoecrystal Z, isolated in 2006 by Han *et al.*,[1] is one of the most highly modified naturally occurring *ent*-kauranoids obtained from *Isodon* plants. Its compact and densely functionalized tetracyclic ring system comprises six vicinal stereogenic centers, including two all-carbon quaternary centers. Similar to many *Isodon* diterpenoids, maoecrystal Z possesses a central, spiro-fused lactone as well as an α,β-unsaturated carbonyl, a pharmacophore present in other bioactive *ent*-kauranoid natural products. Cognizant of this structural homology, we sought to develop a unified strategy that would enable access to maoecrystal Z and other distinct *ent*-kauranoid architectures. The development and execution of the first stage in our synthetic plan is discussed in detail below.

[†] Portions of this chapter were reproduced from the following communication: Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964. The research discussed was completed in collaboration with Jacob Y. Cha, a postdoctoral researcher in the Reisman Laboratory.

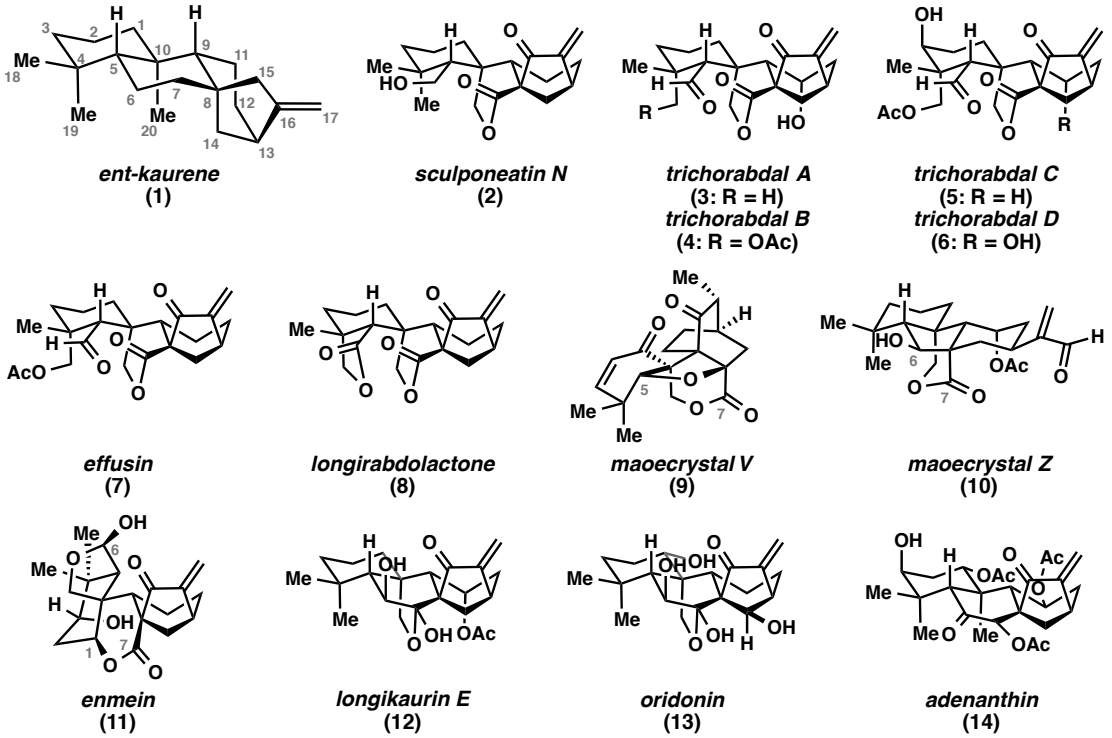


Figure 2.1. *Ent*-kaurene and selected *Isodon* diterpenoids.

2.1.1 Structure and Synthetic Challenges

The 6,7-*seco*-*ent*-kauranoids number approximately 100 out of more than 600 diterpenoids isolated from *Isodon* plants in a century of study (see Figure 2.1).[2,3] Natural products with this characteristic polycyclic framework are believed to arise through C6–C7 oxidative cleavage of a derivative of *ent*-kaurene (**1**),[4] and their structures can be further categorized into two subclasses: spiro-lactone type (7,20-lactone type, *e.g.*, **2**–**10**) and enmein type (1,7-lactone type, see **11**).[3g–i,5] Although the rearranged spiro-lactone framework of maoecrystal Z (**10**) is unique among naturally occurring diterpenoids, this ring system was previously observed during the course of isolation studies on a more representative 6,7-*seco*-*ent*-kauranoid, trichorabdal B (**4**). In a 1981 communication, Fujita and coworkers describe the treatment of **4** with dilute sodium hydroxide in

methanol, which effects a skeletal rearrangement to methyl ester **92** (see Figure 2.2), an oxidized congener of **10**.[3c] The authors proposed a mechanism of methoxide-promoted retro-Dieckmann fragmentation and subsequent aldol ring closure; a similar pathway is likely the origin of **10**.[1]

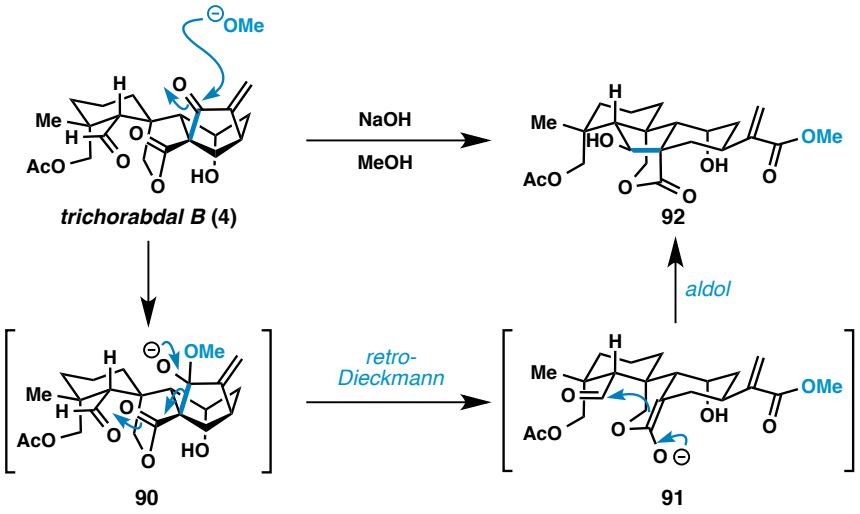


Figure 2.2. Retro-Dieckmann/aldol sequence observed by Fujita.

A principal challenge in the synthesis of maoecrystal Z (**10**) and other spiro-lactone type 6,7-*seco*-*ent*-kauranoids lies in the congested nature of the multiple vicinal stereocenters about the spiro ring junction at C10. In particular, **10** possesses two stereogenic quaternary carbons among six vicinal stereocenters adjacent to yet a third quaternary carbon. The high level of difficulty in constructing such compact, stereochemically complex architectures is evident in both recent efforts toward (±)-maoecrystal V (**9**)[6] and the few prior studies on other 6,7-*seco*-*ent*-kauranoids,[7] as discussed in the preceding chapter. Consequently, these frameworks remain formidable targets in asymmetric total synthesis.

2.1.2 Biological Activity

The known biological activities of *Isodon* diterpenoids[2] include highly selective anti-inflammatory,[8] anticancer[3f,9] and antibacterial properties.[10] Maoecrystal Z (**10**) has shown modest cytotoxicity against multiple human tumor cell lines (K562 leukemia, MCF-7 breast, and A2780 ovarian);[1] however, little is known of its molecular targets or mode of action. In contrast, the *ent*-kauranoid oridonin (**13**) has been found to act as a potent noncompetitive inhibitor of NF-κB transcriptional activity via a novel mechanism.[8] Additionally, a recent study has revealed that adenanthin (**14**) selectively inhibits two isoforms of the peroxiredoxin enzymes and also displays in vivo activity in a murine model of acute promyelocytic leukemia,[9b] suggesting that the cytotoxicity of **14** and other *ent*-kauranoids may occur by a unique target-selective mechanism. A unified strategy to access the *ent*-kauranoids maoecrystal Z (**10**), trichorabdal A (**3**) and longikaurin E (**12**) could potentially be applied to the preparation of synthetic derivatives of **12**–**14** to enable more thorough mode of action studies. Thus, an initial synthetic route toward **10** was an appealing goal.

2.1.3 Synthetic Approach

In our initial synthetic planning, we conceived of two principal retrosynthetic disconnections for the formation of the C and D rings of **10** (see Figure 2.3). Firstly, we envisioned that the five-membered C ring and the C8 all-carbon quaternary stereocenter could be constructed via an intramolecular aldol cyclization, a strategic decision guided in part by Fujita's studies on **4**,[3c] (Figure 2.2) which suggest that a precursor such as **93** would likely undergo an aldol cyclization under mild conditions to form the C ring of **10**.

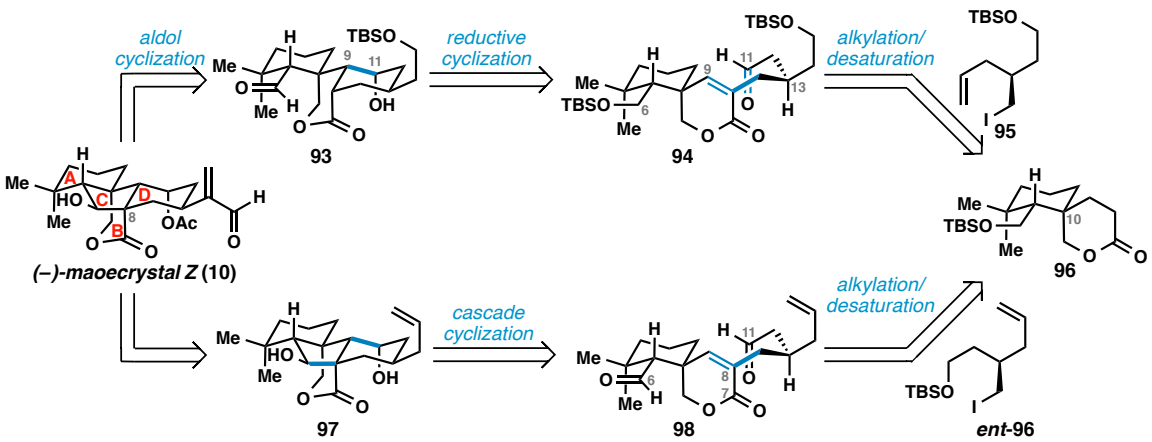


Figure 2.3. Retrosynthetic analysis for maoecrystal Z.

Secondly, it was anticipated that the six-membered D ring could be prepared from an aldehyde-enoate (*e.g.*, **94**) by a Sm-mediated ketyl-olefin reductive cyclization.[11] We hypothesized that C–C bond formation would proceed by addition of the C11 ketyl radical to the more sterically accessible enoate face, opposite to C6, which is further reinforced by the equatorially disposed siloxyethyl group of the C13 stereocenter (see **94**). Whereas this stereochemical preference was expected to result in the correct configuration at C9, the corresponding C11 alcohol configuration was difficult to predict based on conformational analysis alone. Aldehyde **94** could be convergently prepared from spirolactone **96** and alkyl iodide **95** via sequential alkylation, desaturation, and ozonolysis.

Alternate to the stepwise sequence outlined above, we recognized that it might be possible to execute both cyclizations as part of a single tandem cascade process. Recent studies by Procter and colleagues[12] have demonstrated the utility of SmI_2 for the reductive cascade cyclizations of dialdehyde substrates in order to rapidly construct polycyclic frameworks, as exemplified by their recent total synthesis of (+)-pleuromutilin.[13] In this regard, maoecrystal Z could be simplified to diol **97**, which we

hypothesized could arise from dialdehyde **98** via such a cascade. We anticipated that ketyl radical formation at the C6 aldehyde would be kinetically disfavored due to the steric encumbrance imposed by two adjacent quaternary centers; therefore, enoate addition of the C11 ketyl with desired facial selectivity (vide supra) was expected to provide the D ring. Subsequently, a second single-electron reduction would afford the C7–C8 enolate, poised to undergo aldol cyclization in accord with the precedent of Fujita's isolation studies. If the issues of chemo- and diastereoselectivity prove tractable, the proposed cascade cyclization would rapidly increase structural complexity, building two new rings and diastereoselectively setting four new stereogenic centers in a single step. Conveniently, substrates for both the stepwise and cascade approaches can be readily accessed from spirolactone **96** and either enantiomer of alkyl iodide **95**. We also expected that spirolactone **96**, possessing the C10 spirocyclic quaternary center present in many bioactive *ent*-kauranoids, would serve as a valuable synthon for efforts toward trichorabdal A (**3**) and longikaurin E (**12**) as part of a unified strategy (Figure 2.4).

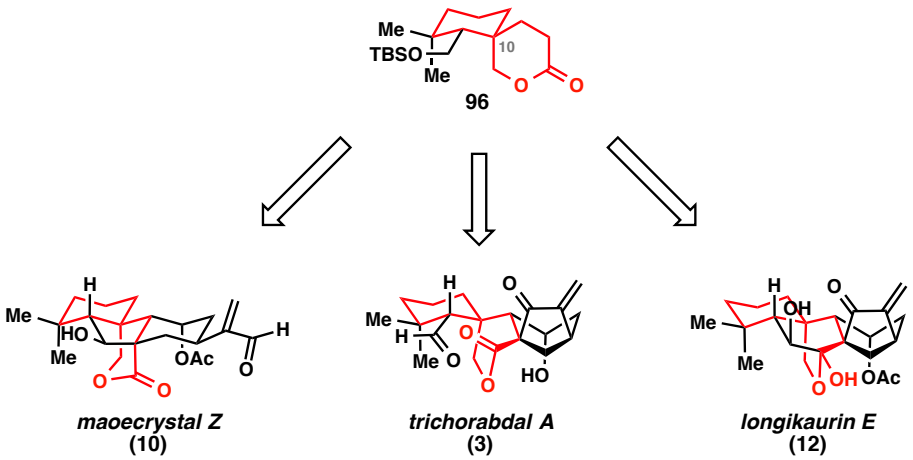


Figure 2.4. A unified strategy for *ent*-kauranoid total synthesis.

2.2 FORWARD SYNTHETIC EFFORTS

The following section describes the varied strategies explored, reactions examined, and experiments conducted in order to achieve the total synthesis of (–)-maoecrystal Z.[14]

2.2.1 Synthesis of a Common Spirolactone

In the forward sense, our initial objectives were to prepare spirolactone **96** and set the central C10 quaternary stereocenter. A known synthetic sequence employing a classical resolution with (*R*)-(–)-*α*-methylbenzylamine (**103**) was used to prepare (–)-*γ*-cyclogeraniol (**104**, Figure 2.5).[15] Protection of **104** as the *tert*-butyldimethylsilyl (TBS) ether, followed by exposure to *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded epoxide **106** as a 3:1 mixture of diastereomers. Treatment of a mixture of **106** and methyl acrylate with Gansäuer's modified conditions[16] (Table 2.1, entry 1) for the radical epoxide-olefin coupling developed by Nugent and RajanBabu[17] resulted in formation of spirolactone **96** in 28% yield. Although the yield was modest, we were delighted to find that lactone **96** was diastereomerically pure and possessed the desired stereochemical configuration at C10, as confirmed by single crystal X-ray diffraction of desilylated lactone **109** (see Figure 2.6). The major side product isolated under unoptimized conditions was allylic alcohol **108**, potentially arising from epoxide **106** via Lewis acid-promoted rearrangement or a Ti^{III}-mediated radical disproportionation process.[18]

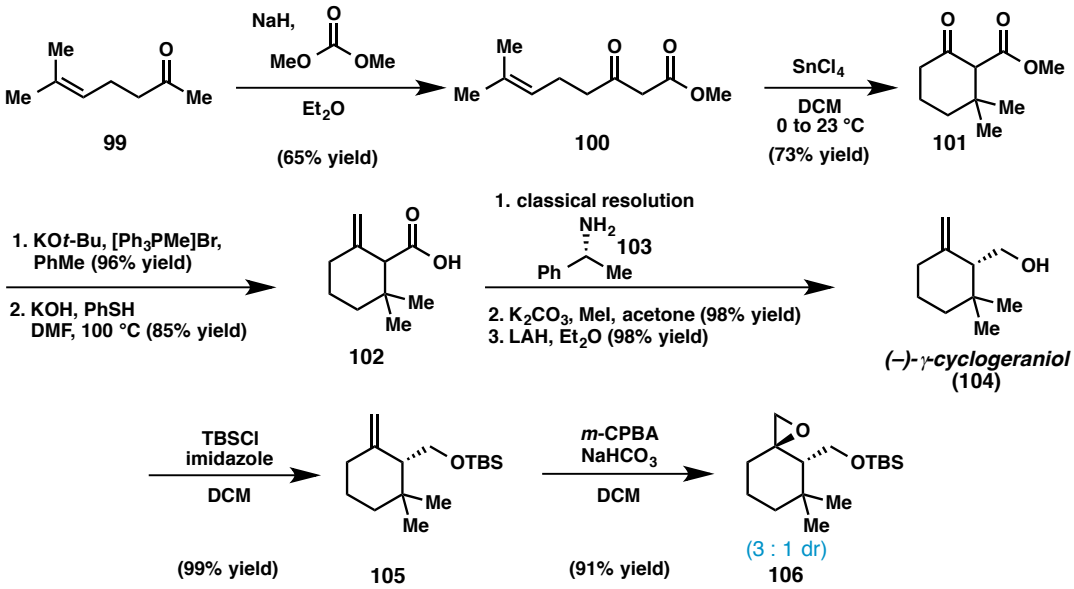
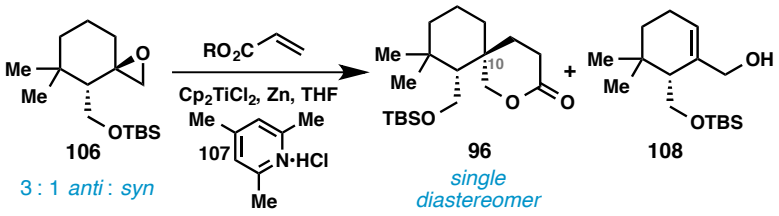


Figure 2.5. Synthesis of epoxide **106**.

Encouraged by this result, we began a survey of reaction parameters in order to obtain more synthetically useful quantities of **96**. Use of a large excess (10 equiv) of methyl acrylate and a full stoichiometric quantity of Cp_2TiCl_2 furnished **96** in 35% yield (Table 2.1, entry 2); further modest increases were realized using portionwise addition protocols for Cp_2TiCl_2 (entries 3–5). Combining a portionwise addition protocol with a more electrophilic coupling partner, 2,2,2-trifluoroethyl acrylate, enabled the isolation of lactone **96** in 76% yield (entry 6). Additionally, we were pleased to observe only a slight decrease to 74% yield when 5 equiv acrylate were used (entry 7). Under the optimized conditions, formation of allylic alcohol side product **108** was minimal. We conjecture that the poor yields observed when using methyl acrylate are due to the slow release of methanol into the reaction mixture during lactonization, resulting in coordination and inhibition of the titanium center. This effect is reduced through use of 2,2,2-trifluoroethyl acrylate and the corresponding release of more weakly coordinating trifluoroethanol.



entry	R (equiv)	Cp_2TiCl_2 equiv	Zn equiv	2,4,6-collidine•HCl (107) equiv	Yield 96 (%)[a]
1	CH_3 (3.0)	0.5	2.0	2.5	28
2	CH_3 (10.0)	2.0	3.0	5.0	35
3	CH_3 (10.0)	2.0[b]	3.0	3.0	44
4	CH_3 (10.0)	1.6[c]	3.0	3.0	61
5	CH_3 (10.0)	1.6[c]	1.5	3.0	58
6	CH_2CF_3 (10.0)	1.6[c]	1.5	3.0	76
7	CH_2CF_3 (5.0)	1.6[c]	1.5	3.0	74
8	CH_2CF_3 (3.0)	1.6[c]	1.5	3.0	62

[a]Isolated yield. [b]Added in two 1.0 equiv portions every 12 h. [c]Added in 0.2 equiv portions over 24 h.

Table 2.1. Optimization of the synthesis of spirolactone **96**.

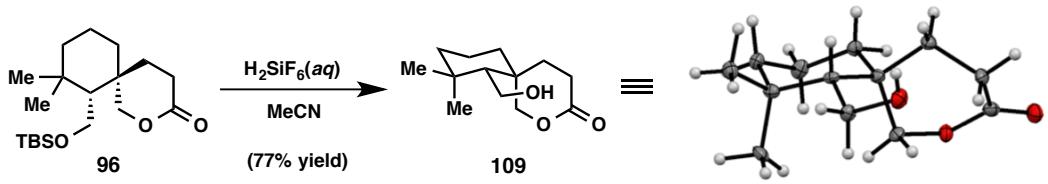


Figure 2.6. Stereochemical confirmation of spirolactone **96**.

As expected, chromatographic separation of *anti*- and *syn*-**106** and independent subjection of each to the optimized reductive coupling conditions furnished lactone **96** as a single diastereomer in 75% and 68% yield, respectively, supporting the intermediacy of radical **110** (Figure 2.7). The major diastereomer (*anti*-**106**) was also found to be consumed more quickly: when a reaction employing a 2.3:1 *anti/syn* mixture of **106** was run to 56% conversion, unreacted **106** was recovered as a 1.3:1 mixture. The high diastereoselectivity observed for this transformation is proposed to derive from approach of the acrylate partner *syn* to the C5 proton of **110**, minimizing nonbonding interactions with the adjacent siloxy and axial methyl substituents. With the initial all-carbon

quaternary stereocenter set and gram quantities of key lactone **96** in hand, we were poised to investigate its elaboration to maoecrystal Z (**10**).

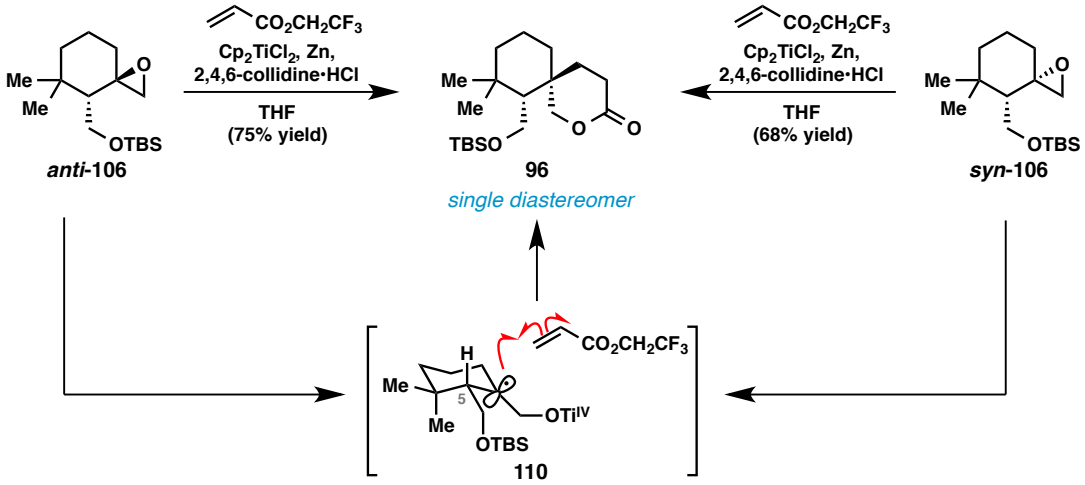


Figure 2.7. Control experiments demonstrate epoxide coupling is stereoconvergent.

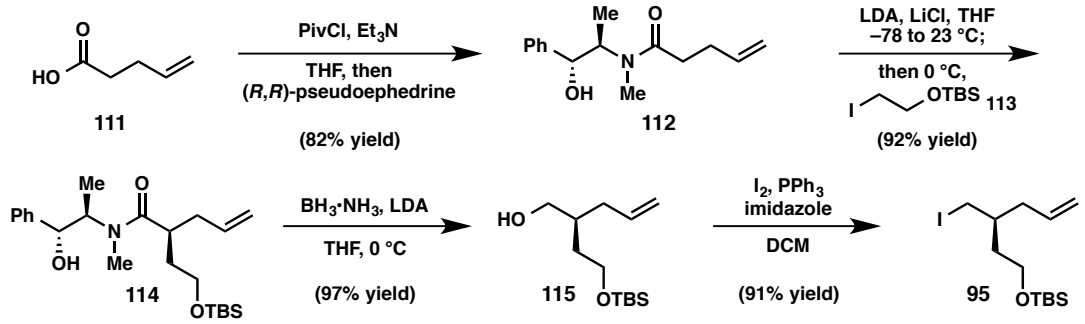


Figure 2.8. Synthesis of chiral alkyl iodide **95** via Myers alkylation protocol.

2.2.2 Pursuit of a Stepwise Cyclization

Though our ultimate ambition was to employ a Sm^{II}-mediated dialdehyde cascade cyclization to access the core of **10**, we elected to first pursue a stepwise route in order to investigate the efficiency and selectivity of each ring-forming step in isolation. Toward this end, alkyl iodide **95** was prepared according to Myers's asymmetric alkylation protocol.[19] Pent-4-enoic acid (**111**) was converted to pseudoephedrine amide **112**, which was alkylated with *tert*-butyl(2-iodoethoxy)dimethylsilane (**113**) to furnish amide **114** in

92% yield and >20:1 dr (Figure 2.8). Reductive cleavage of the auxiliary using lithium amidoborane provided the primary alcohol (**115**), readily converted to enantioenriched alkyl iodide **95** following treatment with iodine and triphenylphosphine.

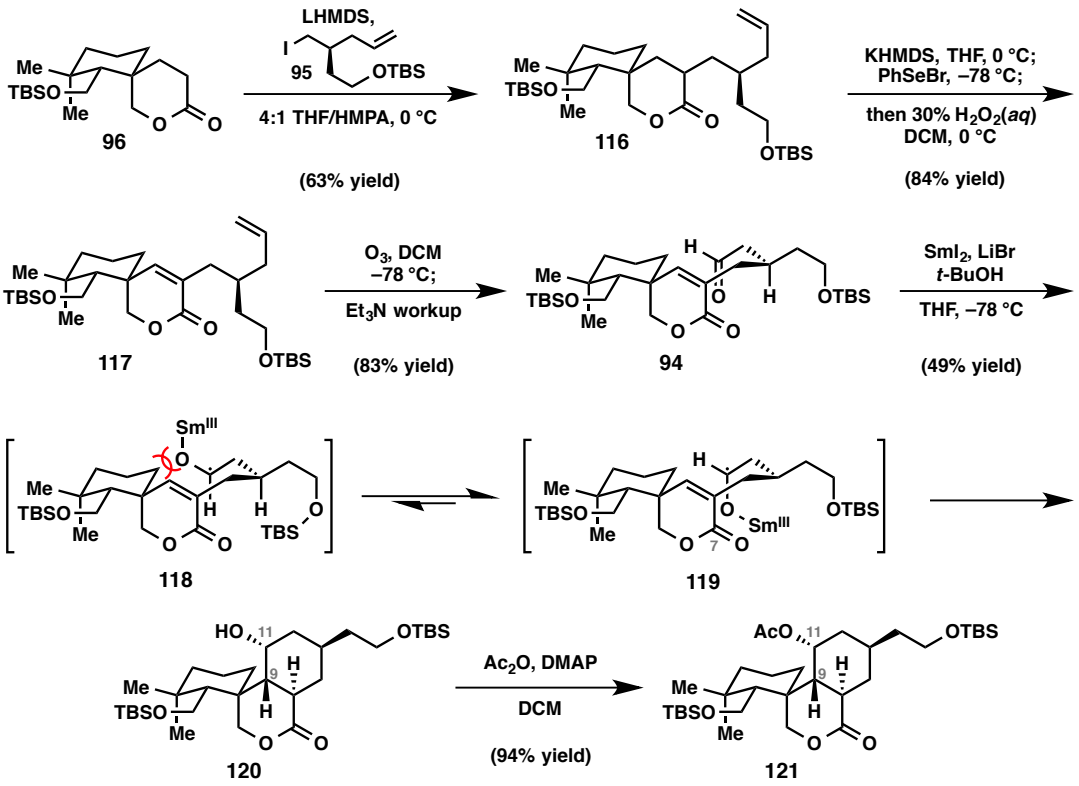


Figure 2.9. Synthesis and Sm^{II}-mediated reductive cyclization of aldehyde **94**.

Moving forward, alkylation of lactone **96** with iodide **95** proceeded upon treatment with lithium LHMDS to afford **116** in 63% yield as an inconsequential mixture of diastereomers (see Figure 2.9). The requisite desaturation of **116** was accomplished by deprotonation with KHMDS and phenylselenation at low temperature, followed by oxidation of the phenyl selenide and elimination. Alternative methods for installing the *α,β*-unsaturation, including the Saegusa–Ito protocol, [20] IBX, [21] and *N-tert*-butylphenylsulfinimidoyl chloride[22] were found to be ineffective. The terminal olefin of **117** was chemoselectively ozonolyzed to afford aldehyde **94**, the targeted ketyl-olefin

cyclization precursor.

Initial attempts to prepare tricycle **120** using SmI_2 in THF at 0 °C effected rapid decomposition of **94**, with only traces of the desired product observed by NMR analysis of the crude reaction mixture. Studies by Procter and others have demonstrated that the use of additives, especially lithium halide salts, can have dramatic effects on the outcome of reactions employing SmI_2.[23] A survey of reaction parameters revealed that the addition of LiCl or LiBr was critical for the desired reactivity. Using a tenfold excess of LiBr relative to SmI_2 and 1 equiv *tert*-butanol (*t*-BuOH) as a proton source, secondary alcohol **120** was obtained in 49% yield. Following treatment with acetic anhydride and 4-dimethylaminopyridine (DMAP), stereochemical analysis of acetate **121** by 1- and 2-D NMR techniques revealed that the configurations of the C9 and C11 stereocenters were correct for elaboration to **10** and other *ent*-kauranoids. The high selectivity for this diastereomer is proposed to result from reaction via ketyl conformation **119**. Whereas conformation **118** is destabilized by the nonbonding interaction between the Sm-ketyl and A-ring methylene, the sp^2 hybridization of C7 appears to alleviate potentially unfavorable 1,3-diaxial interactions present in conformation **119**.

Successful construction of tricycle **120** confirmed the viability of a Sm^{II}-mediated reductive cyclization as the first step in the proposed cascade. In principle, enal installation and aldol cyclization would complete the synthesis of **10**; we therefore continued to advance **121** in order to examine the requisite aldol step. Desilylation with fluorosilicic acid followed by Dess–Martin oxidation[24] furnished dialdehyde **123** (Figure 2.10). Methylenation was accomplished using Eschenmoser's salt[25] and triethylamine to yield enal **124**, isomeric to maoecrystal Z (**10**) and lacking only the C8–C6 bond.

Unfortunately, considerable experimentation with a variety of acids and bases in order to effect an intramolecular aldol cyclization did not furnish detectable quantities of **10**. NMR analysis of the crude reaction mixtures suggested that **124** had suffered undesired transesterifications or skeletal rearrangements due to competitive aldehyde enolization. Moreover, it was suspected that non-productive reactions of the enal of **124** were giving rise to additional side products. In order to more effectively probe the aldol reactivity, we chose to prepare a less functionalized aldehyde substrate.

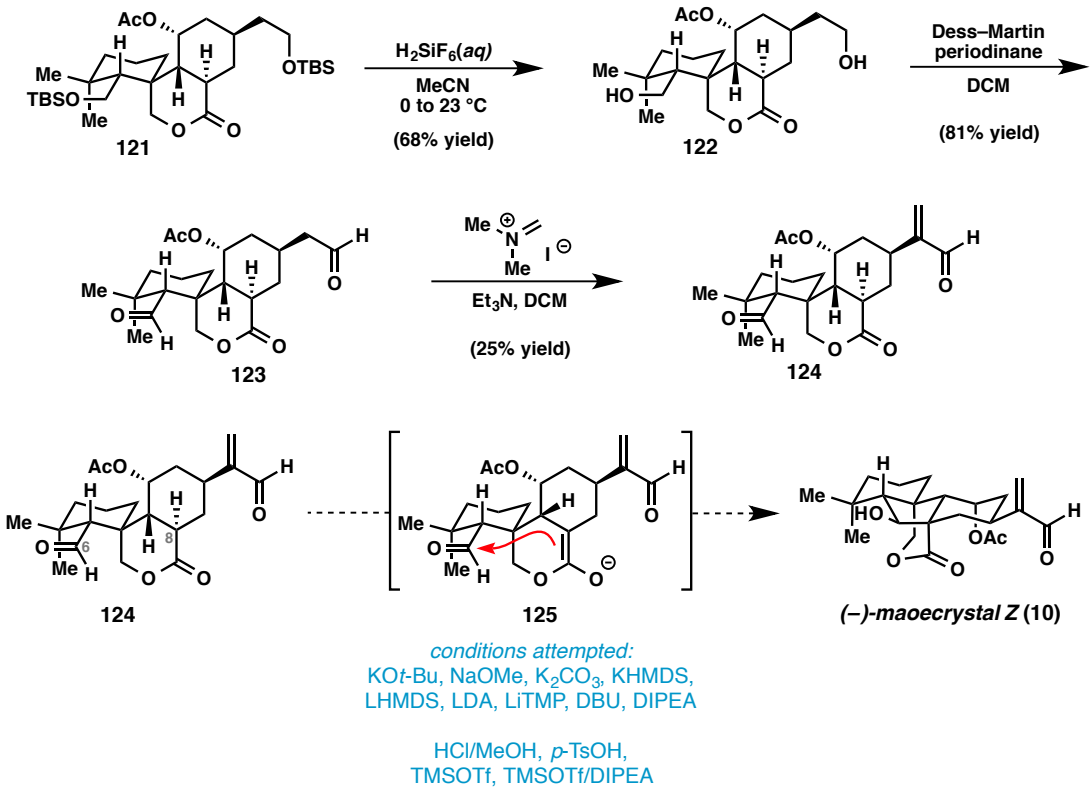


Figure 2.10. Initial efforts toward an aldol cyclization.

For this purpose, diol **122** could be selectively monosilylated using TBSCl and imidazole. TBS ether **126** was then oxidized using Dess–Martin periodinane to furnish an aldol substrate (**127**) lacking the reactive enal motif (Figure 2.11). The stereochemical configuration of this aldehyde was confirmed by single crystal X-ray diffraction. Once

again, the desired aldol cyclization (**127** to **129**) was not observed, and similar rearrangement products as observed with dial **124** were detected. The predominant reactivity pathway resulting from treatment of **127** with KHMDS at –78 °C is proposed to be aldehyde enolization resulting in skeletal rearrangement to hemiacetal **131** by the mechanism shown in Figure 2.11.[26]

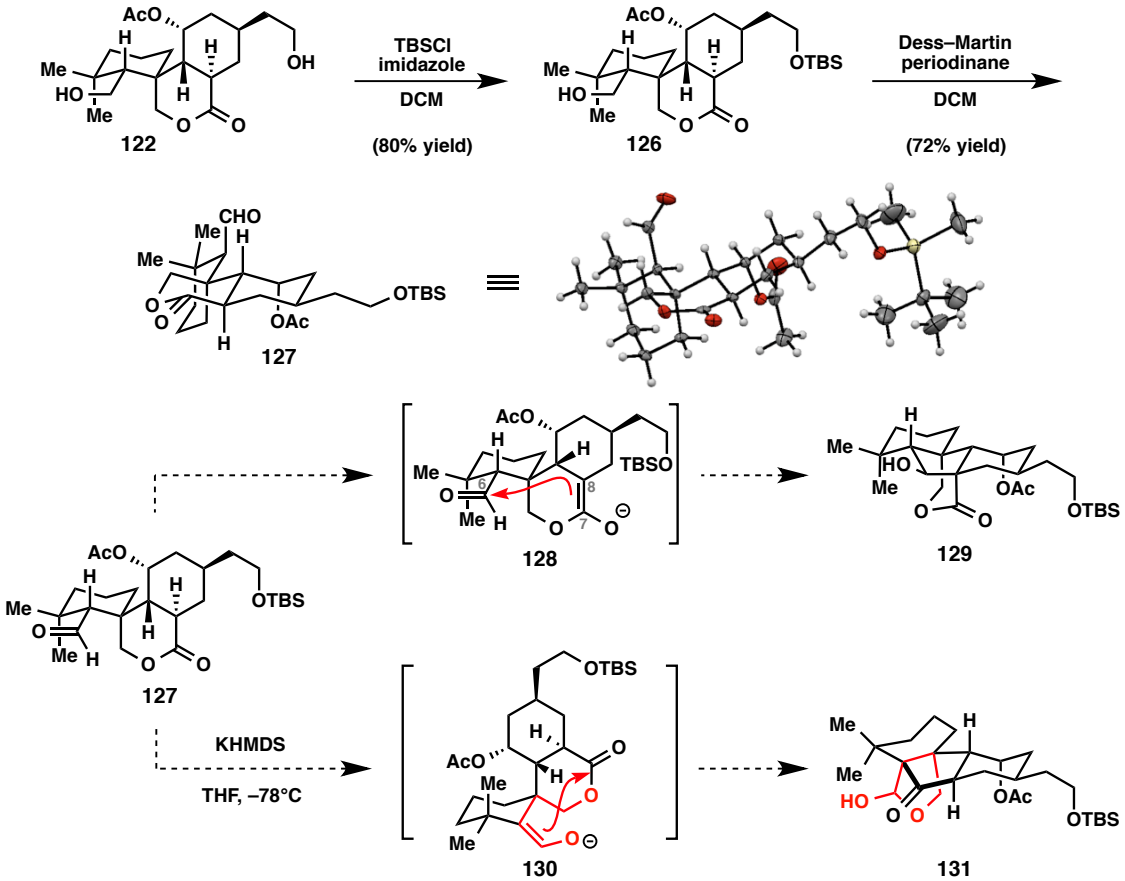


Figure 2.11. Synthesis and undesired reactivity of simplified aldol substrate **127**.

2.2.3 Synthesis of (–)-Maoecrystal Z via Cascade Cyclization

Although our continued inability to conjoin C6 and C8 was somewhat disheartening, it was recognized that the issue of enolization site selectivity is obviated in the proposed reductive cascade cyclization. We therefore turned our attention to the synthesis of a

dialdehyde cyclization substrate. Alkyl iodide *ent*-**95** was prepared from the analogous (*S*,*S*)-pseudoephedrine amide and coupled to lactone **96** as before (see Figure 2.12). Phenylselenation and selenoxide elimination followed by global desilylation and Dess–Martin oxidation furnished dialdehyde **98** in good overall yield. Thus, we were poised to investigate the crucial dialdehyde cyclization cascade.

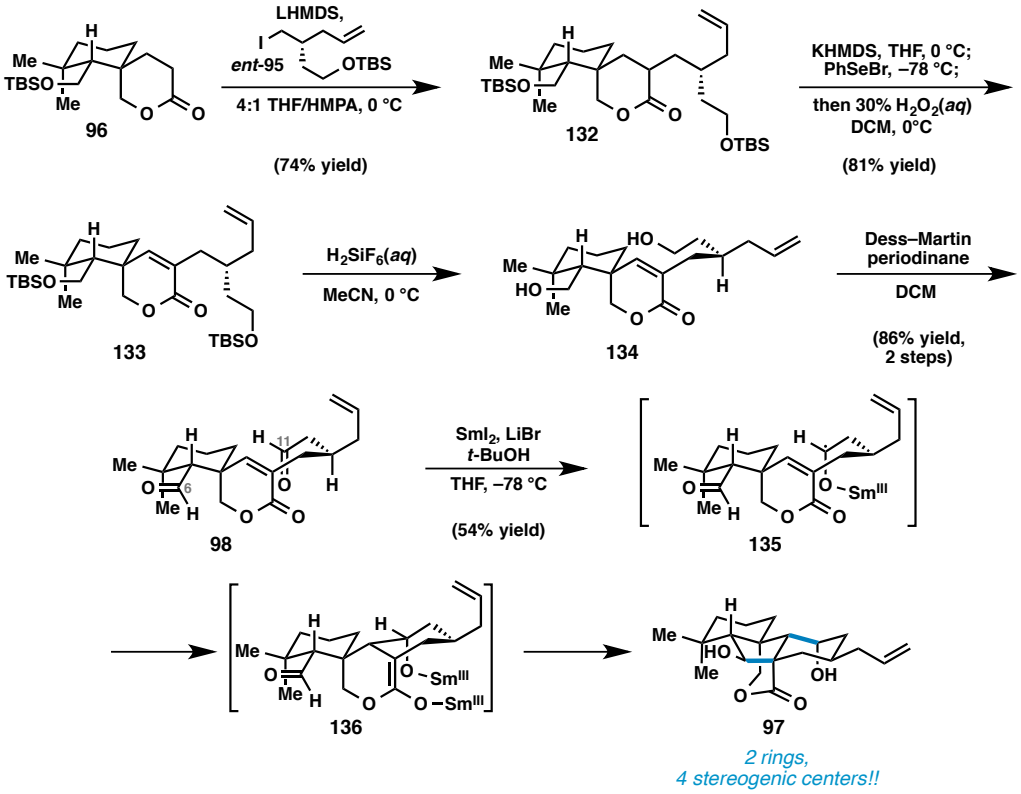


Figure 2.12. Synthesis and reductive cascade cyclization of aldehyde **98**.

In the event, treatment of **98** with SmI_2 and LiBr in the presence of *t*-BuOH at –78 °C provided tetracyclic diol **97** in 54% yield *as a single diastereomer*. Indeed, C11 ketyl radical cyclization occurs with excellent chemoselectivity and stereocontrol to form putative Sm^{III} enolate **136** following a second single electron reduction. Enolate **136** then undergoes aldol cyclization with the proximal C6 aldehyde to forge the second all-carbon quaternary stereocenter and the complete carbon skeleton of maoecrystal Z. Importantly,

all four new stereocenters possess the correct configuration for advancement to the natural product, as determined by thorough 1- and 2-D NMR analysis. In addition to the steric congestion about C6 imposed by two quaternary centers, a second explanation for the observed chemoselectivity lies in the proposed reversibility of Sm-ketyl formation from aldehydes.[23d] Though both ketyls may form, a thermodynamically favorable 6-*endo*-cyclization by the C11-ketyl (as opposed to a reversible 4-*exo*-cyclization of the C6-ketyl), followed by a second, irreversible single-electron reduction to give the Sm^{III} enolate would result in funneling of intermediates to diol **97** via aldol cyclization. The major side product of this transformation appeared to be the tricycle resulting from ketyl-olefin cyclization followed by enolate protonation.

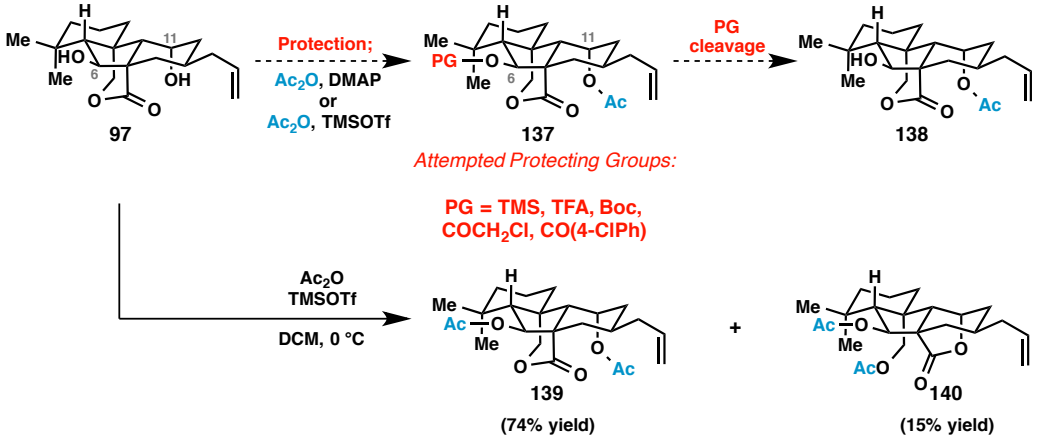


Figure 2.13. Efforts toward the acetylation of diol **97**.

With access to the core, completion of the synthesis of **10** necessitated acetylation of the C11 carbinol (see Figure 2.13) and enal installation. Unfortunately, treatment of diol **97** with acetic anhydride and DMAP effected acetylation of only the C6 carbinol, and more forcing conditions provided low yields of bis-acetate **139** and significant quantities of translactonization product **140**. Thus, several protecting groups were evaluated for a sequential protection/acetylation/deprotection scheme (see **137**, Figure 2.13). However,

use of these groups did not prove fruitful, frequently resulting in increased levels of rearrangement, low yields of **137**, or poor selectivity during protecting group removal, and often in complex mixtures. We were *in no case* able to achieve serviceable yields of **138** over the desired sequence.

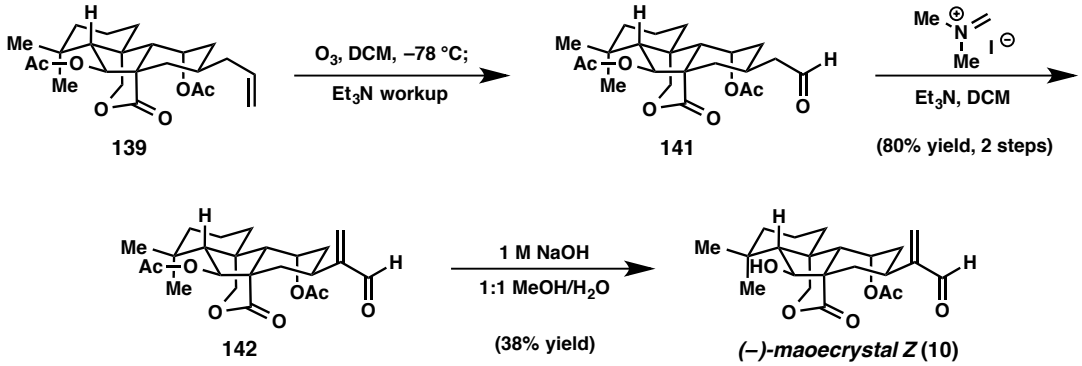


Figure 2.14. Completion of the synthesis of (–)-maoecrystal Z.

After numerous attempts to realize a selective C11 monoacetylation, we opted to advance bis-acetate **139** toward the natural product. Bis-acetylation was accomplished smoothly using Ac_2O and TMSOTf. Ozonolysis of **139** (see Figure 2.14), followed by Eschenmoser methylenation of the resulting aldehyde (**141**) provided acetyl-maoecrystal Z (**142**). A survey of conditions (Table 2.2) revealed that removal of the unneeded C6 acetate was best accomplished using sodium hydroxide in aqueous methanol, providing (–)-maoecrystal Z in 38% yield (12 steps and 4.3% overall from **104**).[27]

entry	conditions	maoecrystal Z[a]	diol	C6 acetate
1	1 M NaOH, 1:1 MeOH/H_2O	44	28	28
2	1 M NaOH, 1:4 MeOH/H_2O	20	78	2
3	1 M NaOH, EtOH	20	80	0
4	1 M NaOH, THF	0	100	0
5	Pyridine, H_2O	no reaction	--	--
6	Otera's catalyst	no reaction	--	--

[a]Relative product ratios as determined by crude ^{1}H NMR analysis.

Table 2.2. Survey of hydrolysis conditions for acetyl-maoecrystal Z (**124**).

2.3 CONCLUDING REMARKS

In summary, the first total synthesis of (–)-maoecrystal Z (**10**) is described. Essential to our strategy was the use of a Ti^{III}-mediated reductive epoxide coupling reaction for the rapid assembly of a single diastereomer of bicyclic spirolactone **96**. Early-stage construction of the A-B bicycle and central C10 all-carbon quaternary stereocenter, present in many other *ent*-kauranoid natural products, allowed later transformations to proceed in high diastereoselectivity. In a second key transformation, a Sm^{II}-mediated dialdehyde cascade cyclization furnished a single diastereomer of the tetracyclic core of **10** while simultaneously forging four of its seven stereogenic centers. The chemical transformations developed for this efficient and concise route enable the synthesis of **10** in just 12 synthetic steps from (–)-γ-cyclogeraniol (**104**) and also find broad utility in the syntheses of (–)-trichorabdal A and (–)-longikaurin E from unsaturated lactone **133**, described in Chapter 3.

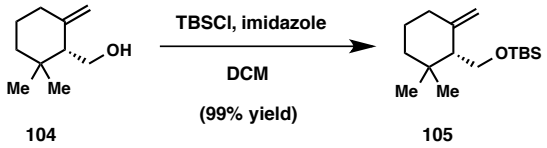
2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (DCM), and acetonitrile (MeCN) were dried by passing through activated alumina columns. Methanol (MeOH) was distilled over magnesium methoxide, Triethylamine (Et_3N) and Diisopropylamine (*i*-Pr_2NH) were distilled over calcium hydride, and hexamethylphosphoramide (HMPA) was distilled over calcium hydride under reduced pressure prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, $KMnO_4$, or CAM staining. Flash column chromatography was performed as described by Still et al.[28] using silica gel (particle size 0.032-0.063) purchased from Silicycle. 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 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), or pyridine (^1H, δ = 8.71, most downfield signal), and $CDCl_3$ (^{13}C, δ = 77.0) or pyridine (^{13}C, δ = 149.9, center peak of most downfield signal). 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. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

2.4.2 Preparative Procedures and Spectroscopic Data

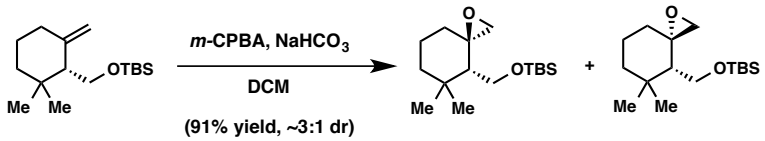
Preparation of TBS ether 105.



104 105

To a solution of (*R*)-(–)-γ-cyclogeraniol (**104**) (2.42 g, 15.7 mmol, 1.0 equiv) in DCM (150 mL) was added imidazole (2.67 g, 39.2 mmol, 2.5 equiv) then TBSCl (3.07 g, 20.4 mmol, 1.3 equiv). The resulting suspension was vigorously stirred for 1 h then diluted with H_2O (75 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 10% EtOAc/Hex) to provide TBS ether **105** (4.17 g, 99% yield). $[\alpha]_D^{25}$ = –19.6° (*c* 0.74, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.79 (m, 1H), 4.64 (m, 1H), 3.80 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.71 (dd, *J* = 10.1, 7.8 Hz, 1H), 2.17 – 2.04 (m, 2H), 1.95 (dd, *J* = 7.7, 4.8 Hz, 1H), 1.57 – 1.43 (m, 1H), 1.29 – 1.25 (m, 1H), 0.96 (s, 3H), 0.89 (s, 9H), 0.88 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.4, 109.4, 62.0, 55.9, 37.7, 34.2, 33.6, 29.0, 26.0, 25.9, 23.5, 18.3, -5.4; IR (NaCl/thin film): 2953, 2929, 2905, 2856, 1648, 1472, 1463, 1386, 1362, 1256, 1104, 888, 837, 774 cm^{-1}; HRMS (APCI+) calc'd for $C_{16}H_{33}OSi$ $[M + H]^+$ 269.2295, found 269.2293.

Preparation of epoxide 106.



105 *anti*-106 (3:1) *syn*-106

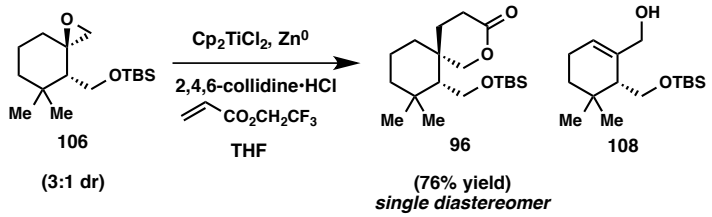
To a solution of olefin **105** (4.03 g, 15.0 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) at 0 ºC was added solid $NaHCO_3$ (6.30 g, 75.0 mmol, 5.0 equiv) then 85% *m*-CPBA (9.14 g, 45.0 mmol, 3.0 equiv). The ice bath was removed and the resulting suspension was allowed to warm to rt and stir

for an additional 1 h and then diluted with sat. $Na_2S_2O_3$ (75 mL) and sat. $NaHCO_3$ (75 mL) and stirred for 20 min. The layers were separated and the organic layer was washed with one additional portion of sat. $Na_2S_2O_3$ (75 mL) and sat. $NaHCO_3$ (75 mL). The combined aqueous extracts were then extracted with DCM (3 x 50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The resulting crude residue was chromatographed on SiO_2 (40 to 100% $CHCl_3$/Hex) to provide epoxide **106** (3.89 g, 91% combined yield).

Data for *anti*-**106**: $[\alpha]_D^{25}$ = –26.4° (*c* 1.57, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.72 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.67 (dd, *J* = 10.4, 7.3 Hz, 1H), 2.68 (d, *J* = 4.9 Hz, 1H), 2.51 (d, *J* = 4.9 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.60 – 1.56 (m, 1H), 1.45 (m, *J* = 3.9 Hz, 1H), 1.29 – 1.20 (m, 2H), 1.15 – 1.13 (m, 1H), 1.10 (s, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 61.3, 58.9, 52.2, 36.3, 34.1, 30.9, 28.6, 27.6, 25.9, 20.0, 18.1, -5.6; IR (NaCl/thin film): 2952, 2930, 2857, 1472, 1463, 1389, 1366, 1256, 1095, 837, 775 cm^{-1}; HRMS (APCI+) calc'd for $C_{16}H_{33}O_2Si$ $[M + H]^+$ 285.2244, found 285.2239.

Data for *syn*-**106**: $[\alpha]_D^{25}$ = +11.7° (*c* 1.57, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.69 (dd, *J* = 10.5, 3.4 Hz, 1H), 3.51 (dd, *J* = 10.5, 5.8 Hz, 1H), 2.80 (d, *J* = 5.1 Hz, 1H), 2.48 (d, *J* = 5.1 Hz, 1H), 1.75 – 1.67 (m, 1H), 1.60 – 1.52 (m, 3H), 1.48 – 1.41 (m, 1H), 1.29 – 1.22 (m, 2H), 1.00 (s, 3H), 0.91 (s, 3H), 0.86 (s, 9H), 0.03 (d, *J* = 2.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.8, 58.3, 54.1, 52.1, 38.4, 34.8, 33.1, 29.5, 25.9, 24.9, 20.6, 18.1, -5.40, -5.42; IR (NaCl/thin film): 2929, 2856, 1469, 1426, 1221, 1050, 836, 728 cm^{-1}; HRMS (APCI+) calc'd for $C_{16}H_{33}O_2Si$ $[M + H]^+$ 285.2244, found 285.2242.

Preparation of spirolactone 96.



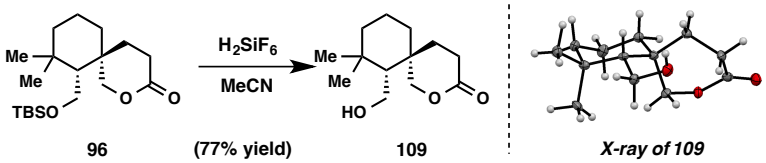
To a stirred solution of epoxide **106** (~3:1 mixture of diastereomers, 2.94 g, 10.3 mmol, 1.0 equiv) in THF (50 mL) was then added 2,4,6-collidine hydrochloride (4.89 g, 31.0 mmol, 3.0 equiv), 2,2,2-trifluoroethyl acrylate (13.1 mL, 103 mmol, 10.0 equiv), and activated zinc dust (1.01 g, 15.5 mmol, 1.5 equiv). Titanocene dichloride (513 mg, 2.06 mmol, 0.2 equiv) was then added every 3 h for 24 h (4.10 g, 16.5 mmol, 1.6 equiv overall) and then diluted with sat. NH_4Cl (50 mL) and Et_2O (30 mL). The biphasic mixture was then filtered through a small pad of Celite and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small pad of silica gel, and concentrated *in vacuo*. The resulting crude residue was chromatographed on SiO_2 (5 to 20% EtOAc/Hex) to provide spirolactone **96** (2.67 g, 76% yield).

Data for lactone **96**: $[\alpha]_D^{25}$ = +35.7° (*c* 0.975, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.43 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 3.87 – 3.81 (m, 2H), 2.57 (ddd, *J* = 16.4, 9.2, 7.0 Hz, 1H), 2.47 (dt, *J* = 16.6, 6.2 Hz, 1H), 2.34 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.96 (dtd, *J* = 13.5, 3.6, 1.5 Hz, 1H), 1.59 – 1.48 (m, 3H), 1.45 – 1.37 (m, 2H), 1.29 – 1.23 (m, 2H), 1.10 – 1.03 (m, 1H), 1.01 (s, 3H), 0.89 (s, 9H), 0.87 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 71.2, 60.4, 56.5, 42.1, 36.7, 36.3, 33.9, 33.7, 33.0, 28.6, 25.9, 23.8, 18.5, 18.0, -5.55, -5.56; IR (NaCl/thin film): 2952, 2928, 2856, 1753, 1462, 1253, 1091, 1050, 838, 776 cm^{-1}; HRMS (APCI+) calc'd for $C_{19}H_{37}O_3Si$ $[M + H]^+$ 341.2506, found 341.2494.

Data for alcohol **108**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.71 (t, *J* = 3.3 Hz, 1H), 4.16 (br dd, *J* = 12.3, 6.4 Hz, 1H), 3.93 (br dd, *J* = 12.3, 6.1 Hz, 1H), 3.90 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.57 (dd, *J* =

10.0, 8.1 Hz, 1H), 3.36 (t, *J* = 6.5 Hz, 1H), 2.08 – 1.95 (m, 3H), 1.43 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.28 (td, *J* = 13.1, 6.7 Hz, 1H), 0.95 (s, 3H), 0.91 (s, 9H), 0.88 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7, 125.1, 67.7, 64.3, 48.7, 33.8, 31.5, 28.3, 25.9, 25.0, 22.8, 18.2, -5.47, -5.50; IR (NaCl/thin film): 3351, 2954, 2928, 2857, 1472, 1388, 1361, 1256, 1135, 1105, 1056, 1034, 1006, 996, 937, 893, 882, 837, 774 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{16}H_{33}O_2Si$ $[M + H]^+$ 285.2244, found 285.2241.

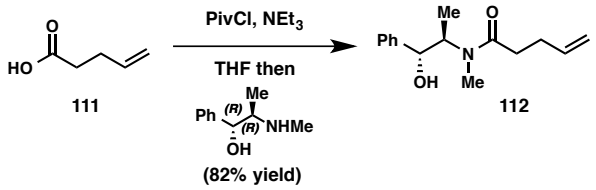
Preparation of lactone 109.



To a solution of spirolactone **96** (103 mg, 0.30 mmol, 1.0 equiv) in MeCN (4 mL) at rt was added 20-25 wt% H_2SiF_6 (0.4 mL, 0.68 mmol, 2.2 equiv). The solution was stirred until LC/MS (or TLC) indicated full consumption of starting material (30 min). The reaction mixture was diluted with sat. $NaHCO_3$ (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (50-90% EtOAc/Hex) to provide lactone **109** (53 mg, 77% yield). Crystals suitable for X-ray analysis were obtained by layering a nearly saturated solution of spirocycle **109** (53 mg) in CH_2Cl_2 (ca. 0.4 mL) with isooctane: ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.37 (dd, *J* = 11.7, 1.2 Hz, 1H), 4.27 (dd, *J* = 11.7, 1.5 Hz, 1H), 3.89 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.85 (dd, *J* = 11.5, 4.7 Hz, 1H), 2.58 (ddd, *J* = 16.8, 7.9, 7.1 Hz, 1H), 2.50 (ddd, *J* = 16.8, 7.4, 6.3 Hz, 1H), 2.36 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.57 – 1.48 (m, 2H), 1.48 – 1.40 (m, 2H), 1.35 – 1.22 (m, 2H), 1.14 – 1.06 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 173.2, 71.2, 60.4, 57.2, 41.9, 36.6, 36.3, 33.9, 33.6, 33.1, 28.4, 23.2, 18.4; IR (NaCl/thin

film): 3393, 2976, 2920, 2868, 1722, 1447, 1384, 1332, 1282, 1250, 1158, 1135, 1077, 1053, 1034, 984, 940, 833, 731 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{13}H_{23}O_3$ $[M+H]^+$ 227.1642, found 227.1640; mp = 110–111 ºC.

Preparation of Myers amide 112.



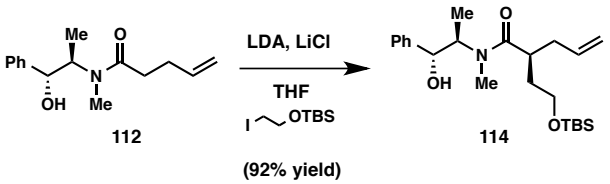
*NOTE: The enantiomeric series can similarly be prepared using (*S*,*S*)-pseudoephedrine in the following procedures (compound **111** → compound **95**) for the preparation of *ent*-**95**.

To a solution of 4-pentenoic acid (4.0 mL, 39.2 mmol, 1.0 equiv) in THF (200 mL) at 0 ºC was added Et_3N (16.3 mL, 117.6 mmol, 3.0 equiv) then pivaloyl chloride (5.8 mL, 5.7 mmol, 1.2 equiv) dropwise causing a white suspension to develop, which was then vigorously stirred for 1 h at rt. In a separate flame dried flask, (*R*,*R*)-pseudoephedrine (8.42 g, 51.0 mmol, 1.3 equiv) was dissolved in THF (200 mL) and NEt_3 (16.3 mL, 117.6 mmol, 3.0 equiv). The resulting clear solution was transferred via cannula to the solution of the mixed anhydride and stirred for 6 h at rt and then diluted with sat. $NaHCO_3$ (300 mL) and EtOAc (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The resulting crude residue was chromatographed on SiO_2 (30 to 60% EtOAc/Hex) to provide amide **112** (7.95 g, 82% yield). $[\alpha]_D^{25} = -105.6°$ (*c* 1.15, $CHCl_3$); ^1H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$): δ 7.41 – 7.21 (m, 5H), 5.92 – 5.74 (m, 1H), 5.10 – 4.92 (m, 2H), 4.61 – 4.43 (m, 2H), 4.32* (br, 1H), 3.99* (m, 1H), 3.20* (s, 1H), 2.90* (s, 3H), 2.81 (s, 3H), 2.60 – 2.49* (m, 1H), 2.49 – 2.26 (m, 4H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.97* (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (2:1 rotamer ratio, 126 MHz, $CDCl_3$): δ 174.4, 173.3, 142.3,

141.4, 137.8, 137.3, 128.5, 128.2, 128.2, 127.5, 126.8, 126.4, 115.1, 114.9, 76.3, 75.3, 58.2, 33.4, 32.8, 32.4, 29.6, 29.3, 28.9, 26.8, 15.3, 14.4; IR (NaCl/thin film): 3381, 3063, 3028, 2977, 2924, 1620, 1480, 1452, 1405, 1315, 1257, 1200, 1120, 1050, 1027, 912, 838, 758, 701 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1645, found 248.1644.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = +99.8° (*c* 0.92, $CHCl_3$).

Preparation of alkylated Myers amide 114.

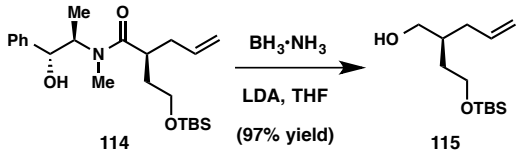


A flame-dried flask in a glove box was charged with lithium chloride (4.95 g, 116.7 mmol, 6.0 equiv) and then removed from the glove box. To this flask was then added diisopropylamine (6.3 mL, 44.7 mmol, 2.3 equiv) and THF (40 mL). The resulting suspension was cooled to –78 °C, and a solution of *n*-BuLi in hexanes (2.6 M, 15.7 mL, 40.8 mmol, 2.1 equiv) was added via cannula. The suspension was warmed briefly to 0 °C and then recooled to –78 °C. An ice-cooled solution of amide 1**12** (4.81 g, 19.5 mmol, 1.0 equiv) in THF (40 mL) was then added to the reaction flask via cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min, and at 25 °C for 5 min, and finally cooled to 0 °C, whereupon *tert*-butyl(2-iodoethoxy)dimethylsilane (8.35 g, 29.2 mmol, 1.5 equiv) in THF (20 mL) was added via cannula. The mixture was stirred at 0 °C for 15 min and then diluted with sat. NH_4Cl (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (15 to 45% EtOAc/Hex) to provide alkylated amide **114** (7.26 g, 92% yield). $[\alpha]_D^{25}$ = –53.3° (*c* 1.24, $CHCl_3$); ^1H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$): δ 7.39 – 7.21 (m,

5H), 5.80 – 5.67 (m, 1H), 5.11 – 4.93 (m, 2H), 4.59 (t, J = 6.8 Hz, 1H), 4.55 – 4.30 (m, 2H), 4.22 – 4.14* (m, 1H), 3.79 – 3.65 (m, 1H), 3.61 – 3.52 (m, 1H), 3.35 (ddd, J = 10.5, 8.6, 4.2 Hz, 1H), 3.27* (br d, J = 3.6 Hz, 1H), 3.22 – 3.11* (m, 1H), 3.04 – 2.92 (m, 1H), 2.89* (s, 3H), 2.88 (s, 3H), 2.44 – 2.31 (m, 1H), 2.24 – 2.09 (m, 2H), 1.91* (br, 1H), 1.80 – 1.71 (m, 1H), 1.70 – 1.52 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H), 0.92* (d, J = 6.8 Hz, 1H), 0.88* (s, J = 2.8 Hz, 9H), 0.85 (s, 9H), 0.07* (s, 3H), 0.06* (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (3:1 rotamer ratio, 126 MHz, $CDCl_3$): δ 177.5, 175.9, 142.3, 141.4, 135.9, 128.6, 128.2, 128.1, 127.5, 127.0, 126.3, 116.6, 76.1, 75.3, 61.8, 60.2, 58.9 (br), 58.1, 38.2, 38.0, 37.4, 36.8, 35.6, 35.5, 33.1 (br), 29.6, 26.8, 26.0, 25.8, 18.5, 18.1, 15.8, 14.4, -5.20, -5.24, -5.42, -5.44; IR (NaCl/thin film): 3391, 3064, 3029, 2955, 2928, 2856, 1619, 1472, 1452, 1409, 1305, 1256, 1100, 1083, 1052, 1005, 913, 835, 810, 775, 701 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{23}H_{40}NO_3Si$ $[M + H]^+$ 406.2772, found 406.2765.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = +46.3° (c 0.60, $CHCl_3$).

Preparation of alcohol 115.



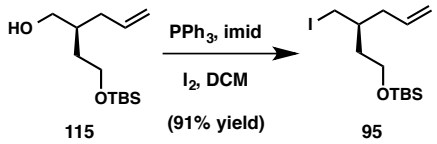
A solution of *n*-BuLi in hexanes (2.6 M, 18.9 mL, 49.0 mmol, 3.9 equiv) was added to a solution of diisopropylamine (7.4 mL, 52.8 mmol, 4.2 equiv) in THF (50 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then warmed to 0 °C, and held at that temperature for 10 min. Borane-ammonia complex (90% technical grade, 1.73 g, 50.3 mmol, 4.0 equiv) was carefully added in one portion, and the suspension was stirred at 0 °C for 15 min and then was warmed to 23 °C. After 15 min, the suspension was recooled to 0 °C. A solution of amide **114** (5.10 g, 12.6 mmol, 1.0 equiv) in THF (40 mL, followed by a 10 mL rinse) was added

via cannula. The reaction mixture was then warmed to rt, held at that temperature for 4 h, and then cooled to 0 °C where excess hydride was quenched by the careful addition of sat. NH_4Cl (100 mL). The mixture was stirred for 30 min at 0 °C and then extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (5 to 35% EtOAc/Hex) to provide alcohol **115** (2.98 g, 97% yield). $[\alpha]_D^{25}$ = –8.4° (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.81 – 5.73 (m, 1H), 5.05 – 4.99 (m, 2H), 3.78 – 3.74 (m, 1H), 3.64 (ddd, *J* = 10.5, 8.1, 3.8 Hz, 1H), 3.60 (m, 1H), 3.48 – 3.44 (m, 1H), 3.18 (d, *J* = 5.2 Hz, 1H), 2.11 (dtd, *J* = 14.0, 7.0, 1.1 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.76 – 1.71 (m, 1H), 1.70 – 1.64 (m, 1H), 1.52 (dtd, *J* = 14.5, 8.0, 4.2 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 116.2, 65.9, 61.8, 39.4, 36.4, 35.0, 25.8, 18.2, -5.48, -5.50; IR (NaCl/thin film): 3351, 2954, 2928, 2857, 1640, 1472, 1256, 1093, 835, 775 cm^{-1}; HRMS (APCI+) calc'd for $C_{13}H_{29}O_2Si$ $[M + H]^+$ 245.1931, found 245.1928.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = +10.8° (*c* 1.30, $CHCl_3$).

Conversion to the Mosher ester was accomplished by treatment of alcohol **115** (17 mg, 0.07 mmol, 1 equiv) with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (40 μL, 0.21 mmol, 3.0 equiv) and 4-DMAP (34 mg, 0.28 mmol, 4.0 equiv) in CH_2Cl_2 (2 mL) at rt for 1 h. The solution was diluted with sat. $NaHCO_3$ (2 mL) and stirred for 20 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo* to afford the corresponding crude Mosher ester in >20:1 dr (determined by ^{1}H NMR analysis of the crude reaction mixture).

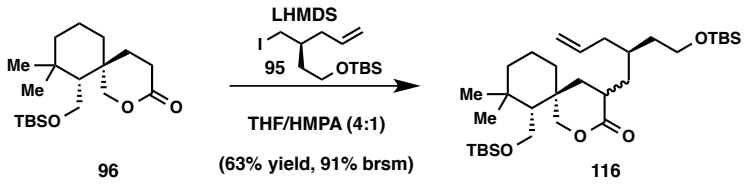
Preparation of iodide 95.



Imidazole (1.82 g, 26.8 mmol, 3.0 equiv) and I_2 (2.22 g, 8.7 mmol, 0.98 equiv) were added sequentially to a solution of PPh_3 (2.22 g, 8.5 mmol, 0.95 equiv) in CH_2Cl_2 (80 mL) at rt. A solution of alcohol **115** (2.18 g, 8.9 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added to the resulting suspension via cannula. The reaction was stirred at rt for 2 h and then diluted with sat. $Na_2S_2O_3$ (30 mL) and sat. $NaHCO_3$ (30 mL) and then stirred for 15 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0-10% EtOAc/Hex) to provide iodide **95** (2.88 g, 91% yield). $[\alpha]_D^{25}$ = +4.1° (*c* 1.215, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.71 (dddd, *J* = 17.0, 10.2, 7.6, 6.8 Hz, 1H), 5.13 (ddt, *J* = 17.0, 2.0, 1.4 Hz, 1H), 5.10 – 5.04 (m, 1H), 3.68 – 3.62 (m, 2H), 3.32 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.28 (dd, *J* = 9.8, 4.6 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.11 – 2.02 (m, 1H), 1.62 – 1.44 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.6, 117.2, 60.4, 38.6, 36.9, 35.2, 25.9, 18.3, 15.9, -5.33, -5.35; IR (NaCl/thin film): 3077, 2954, 2928, 2856, 1641, 1471, 1462, 1439, 1388, 1360, 1256, 1100, 1043, 1005, 940, 916, 835, 775, 665 cm^{-1}; HRMS (APCI+) calc'd for $C_{13}H_{27}OSi$ $[M - I]^+$ 227.1826, found 227.1824.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = –4.7° (*c* 0.565, $CHCl_3$).

Preparation of alkylated lactone 116.



96 116

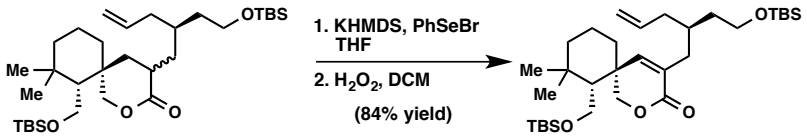
To a solution of **96** (507 mg, 1.49 mmol, 1.0 equiv) and **95** (633 mg, 1.79 mmol, 1.1 equiv) in (4:1) THF/HMPA (8 mL) at 0 °C was added a solution of LHMDS (274 mg, 1.64 mmol, 1.1 equiv) in THF (2.0 mL followed by a 1.0 mL rinse). The resulting solution was stirred for an additional 3 h at 0 °C and then diluted with sat. $NaHCO_3$ (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were washed with H_2O (3 x 40 mL) and brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (5 to 20% EtOAc/Hex) to provide alkylated lactone **116** (532 mg, 63% isolated yield) as a mixture of diastereomers and recovered **96** (140 mg).

Data for less polar diastereomer: $[\alpha]_D^{25}$ = +28.5° (*c* 0.39, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.82 – 5.72 (m, 1H), 5.07 – 4.99 (m, 2H), 4.41 – 4.33 (m, 2H), 3.88 (ddd, *J* = 24.8, 11.3, 3.6 Hz, 2H), 3.69 – 3.56 (m, 2H), 2.56 (td, *J* = 13.4, 6.8 Hz, 1H), 2.24 (dt, *J* = 15.6, 7.8 Hz, 1H), 2.08 (dd, *J* = 7.1, 5.9 Hz, 2H), 1.88 (ddd, *J* = 21.0, 14.9, 4.4 Hz, 2H), 1.82 – 1.73 (m, 1H), 1.63 – 1.36 (m, 6H), 1.24 (ddd, *J* = 10.6, 8.2, 5.3 Hz, 2H), 1.20 – 1.12 (m, 1H), 1.12 – 1.02 (m, 1H), 1.00 (s, 3H), 0.93 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (d, *J* = 3.6 Hz, 6H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.2, 136.1, 116.6, 69.1, 61.0, 60.5, 57.1, 42.3, 41.6, 38.5, 38.1, 36.6, 35.8, 34.7, 34.2, 33.1, 31.1, 26.0, 25.9, 24.2, 18.5, 18.3, 18.0, -5.29, -5.31, -5.41, -5.46; IR (NaCl/thin film) 3075, 2953, 2928, 2856, 1752, 1639, 1472, 1463, 1388, 1361, 1256, 1163, 1096, 1061, 1024, 1005, 910, 837, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M + H]^+$ 567.4259, found 567.4278.

Data for more polar diastereomer: $[\alpha]_D^{25}$ = –22.0° (*c* 1.69, $CHCl_3$); ^{1}H NMR (500 MHz;

$CDCl_3$): δ 5.78 – 5.66 (m, 1H), 5.06 – 4.95 (m, 2H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.20 (d, *J* = 11.8 Hz, 1H), 3.83 – 3.72 (m, 2H), 3.72 – 3.58 (m, 2H), 2.61 – 2.50 (m, 1H), 2.19 – 2.11 (m, 1H), 2.06 (t, *J* = 13.2 Hz, 1H), 2.01 – 1.82 (m, 3H), 1.72 – 1.18 (m, 10H), 1.18 – 1.06 (m, 1H), 1.01 (s, 3H), 0.96 – 0.78 (m, 21H), 0.06 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.3, 136.6, 116.5, 72.9, 60.7, 60.6, 55.5, 41.7, 39.8, 38.6, 37.0, 36.0, 35.8, 35.6, 34.7, 33.8, 33.1, 31.1, 26.0, 25.9, 23.8, 18.4, 18.3, 18.0, -5.27, -5.31, -5.50, -5.55; IR (NaCl/thin film): 3076, 2953, 2928, 2856, 1749, 1640, 1471, 1463, 1389, 1361, 1256, 1169, 1092, 1005, 911, 837, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M + H]^+$ 567.4259, found 567.4252.

Preparation of unsaturated lactone 117.

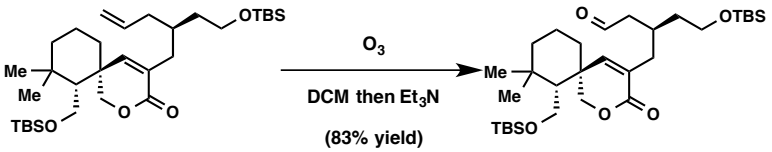


116 **117**

To a solution of KHMDS (105 mg, 0.53 mmol, 1.2 equiv) in THF (6 mL) at 0 °C was added **116** (1.5:1 mixture of diastereomers, 246 mg, 0.43 mmol, 1.0 equiv) in THF (3 mL followed by a 1 mL rinse) dropwise via cannula. The resulting clear solution was allowed to stir at 0 ºC for 30 min then at rt for 15 min. The solution was re-cooled to –78 °C, at which time, a solution of PhSeBr (114 mg, 0.48 mmol, 1.1 equiv) in THF (3 mL followed by a 1 mL wash) at –78 °C was slowly added dropwise via cannula. The resulting pale yellow solution was allowed to stir for 15 min at –78 ºC and then diluted with sat. $NaHCO_3$ (15 mL). The mixture was diluted with Et_2O (30 mL) and H_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was diluted with CH_2Cl_2 (6 mL) and cooled to 0 °C. To this was added 30 wt% H_2O_2 (0.3 mL, 2.9 mmol, 6.8 equiv) and stirred for 30 min. The reaction mixture was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer

was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (1 x 10 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 15% EtOAc/Hex) to afford unsaturated lactone **117** (206 mg, 84% yield). $[\alpha]_D^{25} = -29.2°$ (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.36 (s, 1H), 5.81 – 5.69 (m, 1H), 5.03 (br s, 1H), 5.02 – 4.98 (m, 1H), 4.47 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.36 (dd, *J* = 11.2, 1.2 Hz, 1H), 3.79 – 3.72 (m, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.19 (dd, *J* = 7.2, 0.9 Hz, 2H), 2.10 – 1.98 (m, 2H), 1.93 – 1.83 (m, 2H), 1.67 – 1.38 (m, 6H), 1.26 (td, *J* = 13.0, 3.9 Hz, 1H), 1.19 – 1.11 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H), 0.03 (d, *J* = 1.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.9, 154.2, 136.5, 127.2, 116.5, 69.8, 61.4, 61.1, 55.6, 42.1, 39.7, 37.6, 36.2, 35.1, 33.2, 33.1, 33.0, 32.9, 26.0, 25.9, 23.3, 18.4, 18.3, 18.1, -5.28, -5.31, -5.50, -5.55; IR (NaCl/thin film): 2953, 2928, 2856, 1723, 1472, 1463, 1389, 1361, 1256, 1164, 1150, 1101, 1030, 1005, 938, 837, 776, 665 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{61}O_4Si_2$ $[M + H]^+$ 565.4103, found 565.4083.

Preparation of aldehyde 94.

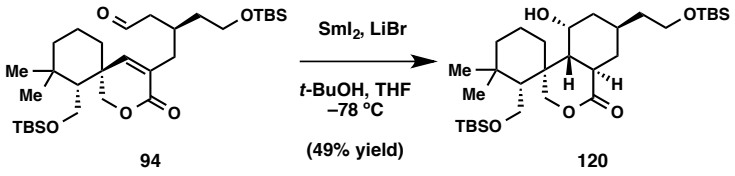


117 **94**

A solution of olefin **117** (108 mg, 0.19 mmol, 1.0 equiv) in DCM (4 mL) was cooled to –78 ºC, at which time, ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 0 setting on ozonator) until LC/MS (or TLC) indicated full consumption of starting material (ca. 20 min). The solution was purged with N_2 for 3 min then Et_3N (1.3 mL, 9.33 mmol, 50 equiv) was slowly added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred until LC/MS indicated complete conversion of the ozonide to the aldehyde (ca. 30 min), filtered through a small plug of silica gel, and concentrated *in vacuo*.

The crude residue was chromatographed on SiO_2 (5 to 25% EtOAc/Hex) to afford aldehyde **94** (90 mg, 83% yield). $[\alpha]_D^{25}$ = –29.8° (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.73 (t, *J* = 1.8, 1H), 6.40 (s, 1H), 4.48 (dd, *J* = 11.2, 1.5, 1H), 4.40 (d, *J* = 11.2, 1H), 3.80 – 3.72 (m, 2H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.49 – 2.33 (m, 4H), 2.15 (dd, *J* = 13.8, 7.5, 1H), 1.85 (br d, *J* = 13.6, 1H), 1.65 – 1.41 (m, 7H), 1.29 – 1.23 (m, 3H), 1.15 (td, *J* = 13.0, 4.2, 2H), 1.02 (s, 3H), 0.89 (s, 3H), 0.88 (d, *J* = 0.8, 9H), 0.87 (d, *J* = 0.7, 9H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.8, 164.8, 155.5, 126.1, 69.9, 61.3, 60.8, 55.5, 47.8, 42.0, 39.6, 36.9, 36.2, 33.2, 33.0, 32.9, 29.8, 26.0, 25.9, 23.3, 18.4, 18.2, 18.1, -5.37, -5.39, -5.50, -5.54; IR (NaCl/thin film): 2953, 2928, 2856, 1723, 1472, 1388, 1361, 1255, 1150, 1096, 836, 775, 665 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{31}H_{59}O_5Si_2$ $[M + H]^+$ 567.3896, found 567.3915.

Preparation of tricycle 120.

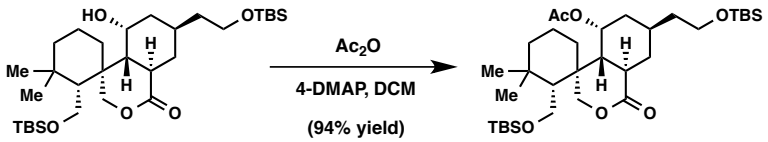


Fresh SmI_2 was prepared according to the following procedure[29]: A flame-dried flask was charged with finely ground samarium (Aldrich, 1.30 g, 8.64 mmol, 1.7 equiv) and was briefly flame-dried *in vacuo*. Once cooled, THF (50 mL) was added under argon followed by diiodoethane (1.40 g, 4.96 mmol, 1.0 equiv) with vigorous stirring for 3 h at ambient temperature. The deep blue solution (~0.1M in SmI_2) was allowed to settle for at least 10 min prior to use.

A flame-dried flask in a glove box was charged with LiBr (333 mg, 3.84 mmol, 25.0 equiv) and then removed from the glove box. A freshly prepared solution of 0.1M SmI_2 (3.84 mL, 0.384 mmol, 2.5 equiv) was then added to the flask containing LiBr and stirred until no visible white solids were apparent and a dark purple homogeneous solution emerged (ca. 5 min). The $SmBr_2$ mixture was transferred dropwise via cannula to a solution of aldehyde **94** (87 mg, 0.15 mmol,

1.0 equiv) and a solution of *t*-BuOH in THF (1.0 M, 0.15 mL, 0.15 mmol, 1.0 equiv) in THF (15 mL) at –78 °C. The reaction mixture was allowed to stir at –78 °C until LC/MS (or TLC) indicated full consumption starting material (ca. 1 h). The reaction mixture was quenched with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), and Rochelle salt (2 g), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed once with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 12% EtOAc/Hex) to afford tricycle **120** as a white foam (42.3 mg, 49% yield). $[\alpha]_D^{25}$ = –6.1° (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.57 (br s, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 3.75-3.63 (m, 4H), 2.86 (td, *J* = 12.3, 3.3 Hz, 1H), 2.47 (d, *J* = 14.6 Hz, 1H), 1.99 – 1.93 (m, 2H), 1.78 (br d, *J* = 13.6 Hz, 1H), 1.71 (t, *J* = 3.5 Hz, 1H), 1.54 – 1.39 (m, 6H), 1.30 (dd, *J* = 12.6, 4.8 Hz, 1H), 1.16 – 0.98 (m, 7H), 0.894 (s, 3H), 0.887 (s, 18 H) 0.05 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 73.3, 65.7, 60.8, 60.1, 51.7, 46.7, 42.0, 41.4, 39.6, 39.5, 35.5, 35.4, 34.2, 33.8, 27.9, 27.5, 26.0, 25.9, 23.6, 18.4, 18.3, 18.2, -5.26, -5.28, -5.46, -5.50; IR (NaCl/thin film): 3469, 2927, 2856, 1726, 1471, 1462, 1389, 1360, 1256, 1091, 836, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{31}H_{61}O_5Si_2$ $[M + H]^+$ 569.4052, found 569.4037.

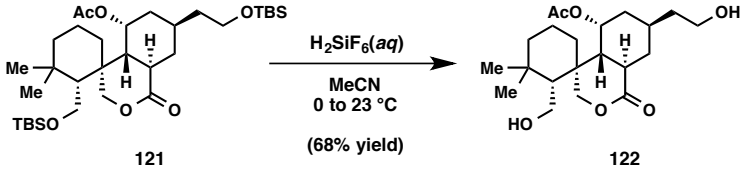
Preparation of acetate 121.



To a solution of tricycle **120** (41.9 mg, 73.6 μmol, 1.0 equiv) in DCM (3.5 mL) at rt was added Ac_2O (49 μL, 0.515 mmol, 7.0 equiv) and then 4-DMAP (45 mg, 0.37 mmol, 5.0 equiv). The solution was stirred until LC/MS (or TLC) indicated complete consumption of starting material (1.5 h), at which time, the reaction mixture was diluted with sat. $NaHCO_3$ (4 mL) and CH_2Cl_2 (2 mL) and stirred for 30 min. The layers were separated and the aqueous layer was

extracted with DCM (3 x 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7% EtOAc/Hex) to afford acetate **121** (42.1 mg, 94% yield). $[\alpha]_D^{25}$ = –19.6° (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.61 (br s, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 3.75 (qd, *J* = 10.2, 4.0 Hz, 2H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.84 (td, *J* = 12.3, 3.5 Hz, 1H), 2.49 (dd, *J* = 13.2, 2.0 Hz, 1H), 2.19 (dd, *J* = 12.8, 0.7 Hz, 1H), 2.05 (s, 3H), 1.98-1.94 (m, 2H), 1.89 – 1.78 (m, 2H), 1.60 – 1.33 (m, 7H), 1.16 (td, *J* = 12.9, 4.2 Hz, 1H), 1.10-0.99 (m, 4H), 0.899 (s, 9H), 0.881 (s, 3H), 0.876 (s, 9H), 0.07 (d, *J* = 2.3 Hz, 6H), 0.03 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 169.8, 73.1, 68.59, 60.33, 60.26, 51.4, 46.0, 42.2, 39.43, 39.36, 37.2, 36.5, 35.2, 34.1, 33.8, 30.3, 28.1, 28.0, 25.95, 25.91, 23.5, 21.6, 18.3, 18.24, -5.3, -5.42, -5.47; IR (NaCl/thin film): 2954, 2928, 2957, 1737, 1472, 1464, 1389, 1370, 1236 1089, 837, 776 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{33}H_{63}O_6Si_2$ $[M + H]^+$ 611.4158, found 611.4152.

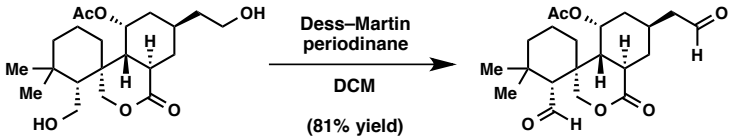
Preparation of diol 122.



To a solution of tricycle **121** (41.9 mg, 68.6 μmol) in 1.5 mL MeCN at 0 °C was added 20-25 wt% aq. H_2SiF_6 (0.20 mL, 0.34 mmol, 5.0 equiv). After stirring at 0 °C for 15 min, the ice bath was removed and the mixture allowed to warm to ambient temperature. After 60 min, sat. $NaHCO_3$ (2 mL) and EtOAc (2 mL) were carefully added. After cessation of bubbling, the layers were separated and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (50 to 100% EtOAc/Hex) to afford diol **122** as a

clear gum (17.9 mg, 68% yield). $[\alpha]_D^{25}$ = –9.1° (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.64 (dt, *J* = 3.9, 1.8 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.34 (dd, *J* = 11.6, 1.2 Hz, 1H), 3.86 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.78 (dd, *J* = 11.8, 6.5 Hz, 1H), 3.69 (t, *J* = 6.6 Hz, 2H), 2.86 (td, *J* = 12.3, 3.5 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.31 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.08 (s, 3H), 1.98 – 1.76 (m, 3H), 1.66 (dd, *J* = 6.5, 3.0 Hz, 1H), 1.57 – 1.31 (m, 8H), 1.23 – 1.07 (m, 3H), 1.05 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 170.0, 72.9, 68.8, 60.3, 60.2, 51.5, 46.2, 42.1, 39.3, 39.1, 37.2, 36.4, 34.7, 33.9, 33.8, 28.2, 28.0, 23.2, 21.7, 18.2; IR (NaCl/thin film): 3429, 2925, 2873, 1728, 1459, 1390, 1371, 1237, 1208, 1071, 1031, 967, 916, 731 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{21}H_{35}O_6$ $[M + H]^+$ 383.2428, found 383.2432.

Preparation of dialdehyde 123.

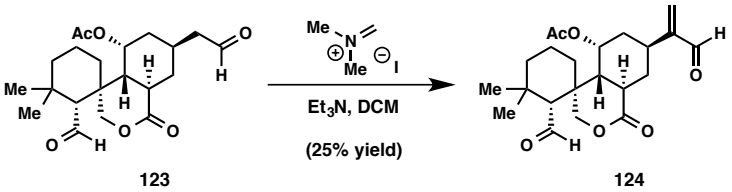


122 123

To a solution of diol **122** (12.4 mg, 32.4 μmol) in 0.7 mL DCM was added Dess–Martin periodinane (55 mg, 0.13 mmol, 4.0 equiv). After stirring for 15 min, the reaction mixture was diluted with sat. $NaHCO_3$ (1 mL) and sat. $Na_2S_2O_3$ (1 mL) and stirred vigorously until the layers became clear (ca. 20 min). The layers were then separated and the aqueous layer was extracted with DCM (3 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (33 to 50% EtOAc/Hex) to afford dialdehyde **123** (9.9 mg, 81% yield). $[\alpha]_D^{25}$ = –8.4° (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.93 (d, J = 3.9 Hz, 1H), 9.75 (t, *J* = 1.3 Hz, 1H), 5.41 (dt, *J* = 3.9, 2.1 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 2.86 (td, *J* = 12.4, 3.5 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.35 (dd, *J* = 6.1, 1.4 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.26 (d, *J* = 3.9 Hz, 1H), 2.11 (s, 3H), 2.01 (dd, *J* = 12.9, 1.9 Hz, 1H), 1.99 – 1.93 (m, 1H), 1.84 – 1.76 (m, 1H), 1.66 –

1.48 (m, 4H), 1.39 – 1.29 (m, 1H), 1.24 – 1.18 (m, 1H), 1.17 (s, 3H), 1.16 – 1.10 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 200.7, 172.3, 169.8, 71.7, 68.1, 62.3, 49.8, 45.0, 41.1, 40.6, 36.7, 36.1, 33.9, 33.6, 33.3, 27.6, 26.0, 23.3, 21.5, 18.2; IR (NaCl/thin film): 2952, 2929, 2873, 2735, 1732, 1454, 1442, 1392, 1372, 1234, 1204, 1073, 1030, 914, 836, 731 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{21}H_{31}O_6$ $[M + H]^+$ 379.2115, found 379.2107.

Preparation of enal 124.

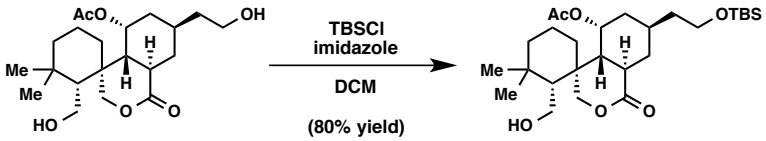


123 **124**

A solution of dialdehyde **123** (9.8 mg, 26 μmol) in 1.5 mL DCM was prepared in a glove box. *N*,*N*-dimethylmethyleneiminium iodide (48 mg, 0.26 mmol, 10 equiv) and Et_3N (55 μL, 0.39 mmol, 15 equiv) were added and the mixture was stirred for 10 h. After removal from the glovebox, the reaction mixture was diluted with sat. $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (25 to 35% EtOAc/Hex) to afford enal **124** as a white solid (2.5 mg, 25% yield). $[\alpha]_D^{25}$ = –16° (*c* 0.12, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 9.95 (d, *J* = 3.9 Hz, 1H), 9.50 (s, 1H), 6.25 (s, 1H), 6.04 (s, 1H), 5.47 (dt, *J* = 4.0, 2.1 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.43 (dq, *J* = 13.1, 3.2 Hz, 1H), 2.28 (d, *J* = 3.9 Hz, 1H), 2.14 (s, 3H), 2.10 – 2.03 (m, 1H), 2.01 (dq, *J* = 14.1, 2.9 Hz, 1H), 1.83 (dt, *J* = 13.8, 3.6 Hz, 1H), 1.66 – 1.50 (m, 3H), 1.42 – 1.20 (m, 4H), 1.18 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.4, 193.8, 172.3, 169.8, 152.5, 133.6, 71.8, 68.1, 62.4, 45.0, 41.1, 40.7, 36.4, 35.4, 33.6, 33.3, 32.6, 29.2, 27.7, 23.3, 21.6, 18.3; IR (NaCl/thin film): 2917, 2849, 1734, 1685, 1457, 1373, 1235, 1030 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{22}H_{31}O_6$ $[M + H]^+$ 391.2115,

found 391.2135.

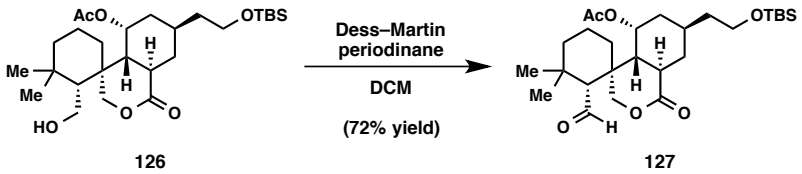
Preparation of silyl ether 126.



122 **126**

To a solution of diol **122** (13.1 mg, 34.2 µmol) in 1.0 mL DCM was added imidazole (5.8 mg, 86 µmol, 2.5 equiv) and TBSCl (5.1 mg as a solution in DCM, 0.10 mL, 34 µmol, 1.0 equiv). After stirring for 20 min, the reaction mixture was diluted with sat. $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (25 to 35% EtOAc/Hex) to afford silyl ether **126** as a clear gum (13.5 mg, 80% yield). $[\alpha]_D^{25}$ = –8.0° (*c* 0.62, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 5.63 (dt, *J* = 3.7, 2.0 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.34 (dd, *J* = 11.6, 1.3 Hz, 1H), 3.86 (dt, *J* = 11.8, 3.3 Hz, 1H), 3.79 (ddd, *J* = 11.6, 6.4, 4.9 Hz, 1H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.85 (td, *J* = 12.3, 3.5 Hz, 1H), 2.47 (dtd, *J* = 13.2, 3.7, 2.0 Hz, 1H), 2.30 (dd, *J* = 12.7, 1.6 Hz, 1H), 2.06 (s, 3H), 2.00 – 1.76 (m, 3H), 1.66 (dd, *J* = 6.5, 3.0 Hz, 1H), 1.63 (br s, 1H), 1.53 – 1.32 (m, 6H), 1.23 – 1.06 (m, 3H), 1.05 (s, 3H), 0.87 (s, 9H), 0.86 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 169.9, 72.9, 68.9, 60.3, 60.3, 51.6, 46.3, 42.1, 39.3, 39.2, 36.9, 36.5, 35.0, 33.9, 33.8, 28.2, 27.9, 25.9, 23.2, 21.6, 18.2, 18.2, -5.3, -5.3; IR (NaCl/thin film): 2952, 2927, 2856, 1733, 1472, 1462, 1388, 1370, 1237, 1206, 1099, 1034, 835, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{27}H_{49}O_6Si$ $[M + H]^+$ 497.3293, found 497.3286.

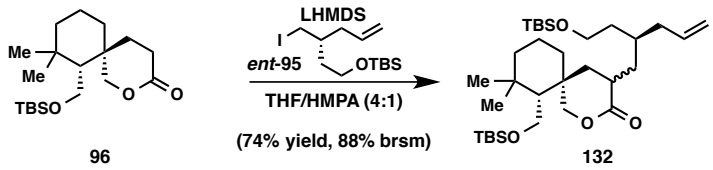
Preparation of aldehyde 127.



126 127

To a solution of silyl ether **126** (12.2 mg, 24.6 μmol) in 0.6 mL DCM was added Dess–Martin periodinane (21 mg, 49 μmol, 2.0 equiv). After stirring for 40 min, the reaction mixture was diluted with sat. $NaHCO_3$ (1 mL) and sat. $Na_2S_2O_3$ (1 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (15 to 20% EtOAc/Hex) to afford aldehyde **127** as a white solid (8.8 mg, 72% yield). Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of aldehyde **127** in Et_2O. $[\alpha]_D^{25}$ = –6.6° (*c* 0.39, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 9.94 (d, *J* = 3.9 Hz, 1H), 5.41 (dt, *J* = 3.9, 2.0 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.80 (td, *J* = 12.3, 3.4 Hz, 1H), 2.39 (dq, *J* = 13.4, 3.0 Hz, 1H), 2.30 (d, *J* = 3.8 Hz, 1H), 2.07 (s, 3H), 2.01 – 1.94 (m, 2H), 1.91 – 1.82 (m, 1H), 1.80 (dt, *J* = 13.8, 3.7 Hz, 1H), 1.65 – 1.30 (m, 6H), 1.20 (td, *J* = 13.1, 4.5 Hz, 1H), 1.16 (s, 3H), 1.11 – 1.02 (m, 5H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.2, 172.8, 169.8, 71.8, 68.6, 62.3, 60.1, 45.4, 41.1, 40.6, 39.0, 36.9, 36.3, 34.2, 33.7, 33.3, 27.6, 27.5, 25.9, 23.3, 21.5, 18.3, 18.2, –5.4 ; IR (NaCl/thin film): 2953, 2927, 2855, 1735, 1711, 1472, 1371, 1388, 1239, 1203, 1102, 1044, 834, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{27}H_{47}O_6Si$ [M + H]$^+$ 495.3136, found 495.3132. mp = 129–131 °C.

Preparation of lactone 132.



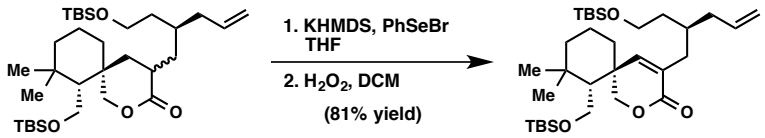
To a solution of **96** (205 mg, 0.60 mmol, 1.0 equiv) and ***ent*-95** (236 mg, 0.67 mmol, 1.1 equiv) in (4:1) THF/HMPA (3 mL) at 0 °C was added a solution of LHMDS (274 mg, 1.64 mmol, 1.1 equiv) in (4:1) THF/HMPA (2 mL followed by a 1 mL rinse). The resulting solution was stirred for an additional 3 h at 0 °C and then diluted with sat. $NaHCO_3$ (20 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with H_2O (3 x 20 mL) and brine (1 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 20% EtOAc/Hex) to provide lactone **132** (253 mg, 74% yield) as a mixture of diastereomers and recovered **96** (28 mg).

Data for less polar diastereomer: $[\alpha]_D^{25}$ = +27.6° (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 – 5.67 (m, 1H), 5.06 – 4.96 (m, 2H), 4.46 (dd, *J* = 11.6, 1.1 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 3.95 – 3.86 (m, 2H), 3.71 – 3.63 (m, 2H), 2.61 – 2.57 (m, 1H), 2.22 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.11 – 1.97 (m, 2H), 1.95 – 1.88 (m, 1H), 1.83 (ddd, *J* = 13.9, 7.7, 6.5 Hz, 1H), 1.79 – 1.69 (m, 1H), 1.64 – 1.35 (m, 5H), 1.29 – 1.16 (m, 3H), 1.11 – 1.01 (m, 2H), 1.00 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.20 – -0.09 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 136.6, 116.5, 69.2, 60.7, 60.5, 56.9, 42.4, 41.5, 38.6, 38.2, 36.1, 35.7, 34.9, 34.3, 33.0, 31.8, 26.0, 25.9, 24.3, 18.5, 18.3, 17.9, -5.31, -5.35, -5.43, -5.47; IR (NaCl/thin film): 2952, 2927, 2856, 1749, 1471, 1462, 1387, 1360, 1255, 1163, 1092, 1060, 1023, 994, 910, 836, 774 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M+H]^+$ 567.4259, found 567.4278.

Data for more polar diastereomer: $[\alpha]_D^{25}$ = –37.6° (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.8, 10.5, 7.1 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.50 (d, *J* = 11.8 Hz, 1H),

4.13 (d, *J* = 11.8 Hz, 1H), 3.83-3.75 (m, 2H), 3.62 (t, *J* = 6.8 Hz, 2H), 2.61 – 2.56 (m, 1H), 2.13 – 1.99 (m, 3H), 1.99 – 1.95 (m, 2H), 1.76 – 1.67 (m, 1H), 1.63 – 1.37 (m, 5H), 1.31 – 1.18 (m, 4H), 1.18 – 1.10 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.16 – -0.09 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 136.2, 116.6, 73.0, 61.1, 60.8, 55.1, 41.6, 40.0, 37.4, 37.2, 37.0, 36.5, 35.4, 34.8, 33.8, 33.1, 31.1, 26.0, 25.9, 18.5, 18.3, 18.0, -5.25, -5.26, -5.50, -5.55; IR (NaCl/thin film): 2952, 2927, 2856, 1751, 1471, 1462, 1387, 1360, 1255, 1168, 1151, 1094, 1062, 1005, 953, 938, 910, 836, 774 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M+H]^+$ 567.4259, found 567.4265.

Preparation of unsaturated lactone 133.

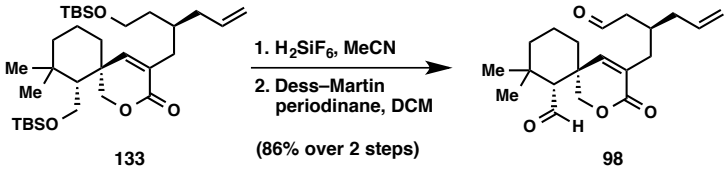


132 **133**

To a solution of KHMDS (73 mg, 0.37 mmol, 1.2 equiv) in THF (6 mL) at 0 °C was added **132** (1.5:1 mixture of diastereomers, 172 mg, 0.30 mmol, 1.0 equiv) in THF (3 mL followed by a 1 mL rinse) dropwise via cannula. The resulting clear solution was allowed to stir at 0 ºC for 30 min then at rt for 15 min. The solution was re-cooled to –78 °C, at which time, a solution of PhSeBr (79 mg, 0.33 mmol, 1.1 equiv) in THF (3 mL followed by a 1 mL wash) at –78 °C was slowly added dropwise via cannula. The resulting pale yellow solution was allowed to stir for 15 min at –78 ºC and then diluted with sat. $NaHCO_3$ (15 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was diluted with DCM (4 mL) and cooled to 0 °C. To this was added 30 wt% H_2O_2 (0.2 mL, 1.96 mmol, 6.5 equiv) and stirred for 30 min. The reaction mixture was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and

the combined organic extracts were washed with sat. $NaHCO_3$ (1 x 10 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 15% EtOAc/Hex) to afford unsaturated lactone **133** (139 mg, 81% yield). $[\alpha]_D^{25}$ = –22.7° (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.35 (s, 1H), 5.80 – 5.71 (m, 1H), 5.05-4.97 (m, 2H), 4.48 (dd, *J* = 11.2, 1.5 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 3.78 (d, *J* = 4.5 Hz, 2H), 3.64 (td, *J* = 6.9, 3.0 Hz, 2H), 2.19 (qd, *J* = 12.5, 7.2 Hz, 2H), 2.04 – 2.02 (m, 2H), 1.85 (m, 2H), 1.60 – 1.39 (m, 7H), 1.26 (td, *J* = 13.0, 3.8 Hz, 1H), 1.15 (td, *J* = 13.3, 4.1 Hz, 1H), 1.02 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (d, *J* = 0.6 Hz, 6H), 0.03 (d, *J* = 0.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 154.3, 136.5, 127.4, 116.5, 70.0, 61.5, 61.2, 55.5, 42.2, 39.8, 37.9, 36.0, 35.6, 33.3, 33.2, 33.02, 32.98, 26.0, 25.9, 23.4, 18.5, 18.3, 18.1, -5.26, -5.29, -5.53, -5.58; IR (NaCl/thin film): 2952, 2927, 2856, 1722, 1471, 1462, 1388, 1360, 1255, 1164, 1149, 1096, 1005, 909, 836, 774, 662 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{61}O_4Si_2$ $[M+H]^+$ 565.4103, found 565.4116.

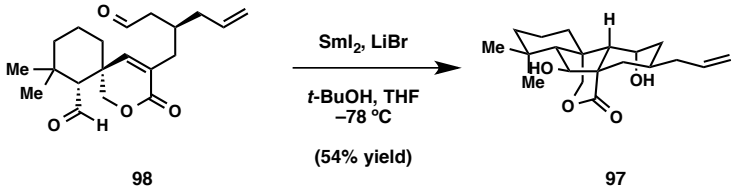
Preparation of dialdehyde 98.



To a solution of unsaturated lactone **133** (130 mg, 0.23 mmol, 1.0 equiv) in MeCN (4 mL) at 0 ºC was added 20-25 wt% H_2SiF_6 (0.5 mL, 0.85 mmol, 3.7 equiv). The solution was stirred until LC/MS (or TLC) indicated full consumption of starting material (2 h). The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The resulting crude residue was redissolved in DCM (8 mL) and cooled to 0 ºC. To the solution was added

Dess-Martin periodinane (293 mg, 0.69 mmol, 3.0 equiv), and after 2 h, an additional portion of DMP was added (293 mg, 0.69 mmol, 3.0 equiv). The solution was stirred for an additional 1 h and LC/MS had indicated full consumption of starting material. The reaction mixture was diluted with sat. $Na_2S_2O_3$ (15 mL) and sat. $NaHCO_3$ (10 mL) and stirred for 20 min. The layers were separated and the organic layer was again stirred with with sat. $Na_2S_2O_3$ (15 mL) and sat. $NaHCO_3$ (10 mL) for 20 min and the layers were separated. The organic layer was washed with H_2O (20 mL) and the combined aqueous extracts were back extracted with DCM_2 (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 35% EtOAc/Hex) to provide **98** (66 mg, 86% yield from **133**). $[\alpha]_D^{25}$ = –20.3° (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.92 (d, *J* = 3.0 Hz, 1H), 9.73 (t, *J* = 1.8 Hz, 1H), 6.32 (s, 1H), 5.78 – 5.70 (m, 1H), 5.09 – 5.03 (m, 2H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.40 (dd, *J* = 11.3, 1.4 Hz, 1H), 2.43 – 2.15 (m, 6H), 2.04 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.88 (dt, *J* = 13.7, 3.5 Hz, 1H), 1.66 (ddt, *J* = 11.3, 7.5, 3.8 Hz, 2H), 1.57 – 1.53 (m, 3H), 1.34 – 1.20 (m, 2H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 203.2, 202.6, 164.3, 151.3, 135.6, 128.2, 117.6, 70.1, 64.2, 47.4, 40.3, 39.0, 38.4, 35.5, 32.8, 32.3, 32.1, 31.8, 23.7, 18.0; IR (NaCl/thin film): 2928, 2849, 1719, 1461, 1442, 1390, 1370, 1294, 1163, 1148, 1112, 1072, 1031, 915 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{20}H_{29}O_4$ $[M+H]^+$ 333.2060, found 333.2068.

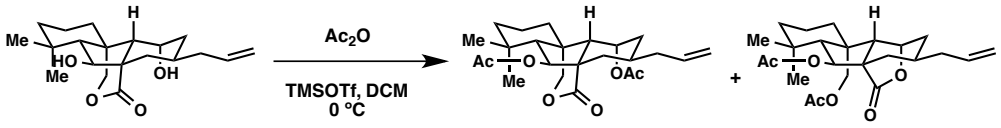
Preparation of tetracycle 97.



To a solution of dialdehyde **98** (28.0 mg, 84.2 μmol, 1.0 equiv) in THF (8 mL) was added LiBr in THF (1.0 M, 85 μL, 850 μmol, 10.1 equiv) and *t*-BuOH in THF (0.1 M, 85 μL, 85 μmol,

1.0 equiv) and the solution was cooled to –78 ºC. A separate flask was flame dried containing LiBr (219 mg, 2.52 mmol, 30 equiv) and to this was added freshly prepared 0.1 M SmI_2 (2.5 mL, 250 μmol, 3.0 equiv) and stirred for 10 min. The resulting stirring purple solution was cannulated into the dialdehyde solution and stirred for 10 min. The reaction mixture was diluted with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), H_2O (5 mL), then Rochelle salt (1.0 g) was added and then diluted with EtOAc (20 mL) and stirred for 15 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (40 to 60% MeCN/H_2O, 20 minute gradient, t_R=13.5 min) to afford tetracycle **97** (15.2 mg, 54% yield). $[\alpha]_D^{25}$ = –54.6° (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.80 (ddt, *J* = 17.1, 10.1, 7.1, 1H), 5.05 – 5.00 (m, 2H), 4.58 (dd, *J* = 11.3, 1.0, 1H), 4.52 (dd, *J* = 11.3, 2.0, 1H), 4.36 (br s, 1H), 3.97 (dd, *J* = 7.0, 4.1, 1H), 2.28 – 2.10 (m, 3H), 1.99 (m, 1H), 1.86 – 1.82 (m, 2H), 1.78 (dtd, *J* = 14.2, 3.6, 1.7, 1H), 1.62 – 1.45 (m, 6H), 1.38 (d, *J* = 7.0, 1H), 1.27 – 1.10 (m, 3H), 1.08 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 136.6, 116.3, 78.5, 74.0, 72.2, 66.1, 54.4, 51.5, 42.9, 41.6, 41.1, 41.0, 34.0, 32.7, 32.6, 32.2, 28.2, 21.3, 19.3. IR (NaCl/thin film): 3395, 2930, 2876, 1713, 1337, 1163, 1041, 913 cm^{-1}; HRMS (ESI+) calc'd for $C_{20}H_{31}O_4$ $[M + H]^+$ 335.2217, found 335.2220.

Preparation of bis-acetate 139.



97 139 (74% yield) 140 (15% yield)

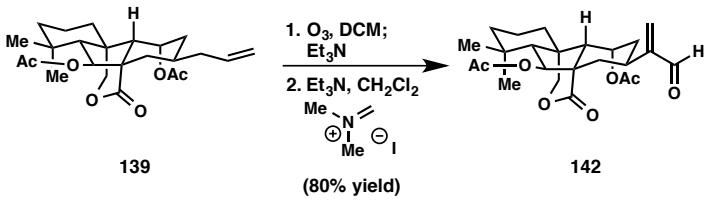
To a solution of tetracycle **97** (5.2 mg, 15.6 μmol, 1.0 equiv) in DCM (2 mL) at 0 ºC was added Ac_2O (45 μL, 476.1 μmol, 30 equiv) and TMSOTf (20 μL, 110.5 μmol, 7.1 equiv). The resulting solution was stirred at 0 ºC until LC/MS (or TLC) indicated complete consumption of starting material (5 min). The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and additional DCM (5 mL) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (50 to 75% MeCN/H_2O, 20 minute gradient, t_R=15.3 min for **139**, t_R=16.7 min for **140**) to afford bis-acetate **139** (4.8 mg, 74% yield) and γ-lactone **140** (1.0 mg, 15% yield).

Data for desired bis-acetate **139**: $[\alpha]_D^{25}$ = –106.7° (*c* 0.11, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.77-5.69 (m, 1H), 5.37 (dt, *J* = 3.5, 1.9 Hz, 1H), 5.20 (d, *J* = 7.6 Hz, 1H), 5.01-4.97 (m, 2H), 4.62 (dd, *J* = 11.9, 1.8 Hz, 1H), 3.98 (dd, *J* = 12.0, 1.0 Hz, 1H), 2.27 – 2.24 (m, 1H), 2.09 – 1.94 (m, 8H), 1.82 – 1.79 (m, 1H), 1.66 – 1.60 (m, 4H), 1.50 – 1.40 (m, 1H), 1.32 – 1.17 (m, 4H), 1.08 (s, 3H), 1.08 – 1.02 (m, 1H), 0.90 – 0.83 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 170.0, 169.4, 135.9, 116.5, 73.2, 71.4, 67.7, 62.9, 53.3, 51.3, 42.7, 41.2, 40.7, 36.4, 32.9, 32.7, 32.4, 32.2, 28.6, 21.3, 21.0, 20.8, 19.1; IR (NaCl/thin film): 2955, 1745, 1641, 1444, 1368, 1230, 1153, 1103, 1029, 920 cm^{-1}; HRMS (ESI+) calc'd for $C_{24}H_{35}O_6$ $[M + H]^+$ 419.2428, found 419.2425.

Data for translactonized acetate **140**: ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.75 (d, *J* = 10.4 Hz,

1H), 5.73 – 5.65 (m, 1H), 5.04-4.99 (m, 2H), 4.88 (d, J = 4.4 Hz, 1H), 4.18 (d, J = 12.5 Hz, 1H), 3.84 (d, J = 12.8 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.11 – 2.07 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.02-1.92 (m, 2H), 1.81 (dd, J = 12.6, 6.0 Hz, 1H), 1.74 (s, 1H), 1.68-1.51 (m, 4H), 1.51 – 1.46 (m, 1H), 1.37 – 1.32 (m, 1H), 1.21 – 1.12 (m, 2H), 1.03 (td, J = 13.0, 4.2 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 170.5, 169.7, 135.5, 116.9, 76.0, 73.2, 65.8, 63.0, 63.0, 54.7, 44.1, 41.7, 40.3, 36.7, 35.7, 35.3, 33.0, 32.8, 30.9, 21.6, 21.1, 20.9, 19.1; IR (NaCl/thin film): 2930, 2868, 1775, 1771, 1742, 1739, 1733, 1640, 1447, 1378, 1367, 1234, 1165, 1122, 1035, 937, 915 cm^{-1}; HRMS (ESI+) calc'd for $C_{24}H_{35}O_6$ $[M + H]^+$ 419.2428, found 419.2433.

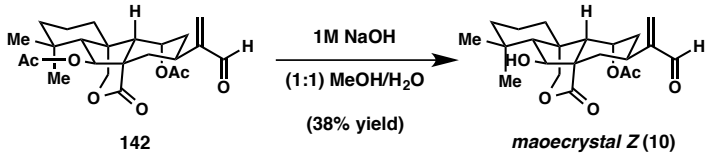
Preparation of enal 142.



A solution of bis-acetate **139** (4.8 mg, 11.5 μmol, 1.0 equiv) in DCM (2 mL) was cooled to – 78 ºC, at which time, ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 0 setting on ozonator) until LC/MS (or TLC) indicated full consumption of starting material (3 min). The solution was purged with N_2 for 3 min then Et_3N (100 μL, 717.5 μmol, 62.6 equiv) was slowly added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred until LC/MS indicated complete conversion of the ozonide to the aldehyde (30 min), filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was azeotroped with heptane and placed under high vacuum for 20 min, and then dissolved in DCM (2 mL). To this was added Et_3N (50 μL, 358.7 μmol, 31.3 equiv) and the reaction flask was then taken into a glove box. *N*,*N*-dimethylmethyleneiminium iodide (42.4 mg, 229.2 μmol, 20 equiv) was added to the solution and stirred at rt for 12 h. The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and additional DCM (5 mL). The layers

were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (40 to 60% MeCN/H_2O, 20 minute gradient, t_R=14.5 min) to afford enal **142** (4.0 mg, 80% yield from **139**). $[\alpha]_D^{25}$ = –67.9° (*c* 0.12, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.50 (d, *J* = 0.7 Hz, 1H), 6.26 (s, 1H), 6.00 (d, *J* = 1.1 Hz, 1H), 5.40 (d, *J* = 1.5 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.10 (t, *J* = 12.6 Hz, 1H), 2.22 (dt, *J* = 12.5, 1.7 Hz, 1H), 2.09 (d, *J* = 1.4 Hz, 3H), 2.05 (d, *J* = 1.5 Hz, 3H), 2.01 – 1.96 (m, 1H), 1.82 (d, *J* = 12.9 Hz, 1H), 1.77 (s, 1H), 1.66-1.44 (m, 6H), 1.31 (td, *J* = 13.2, 3.4 Hz, 1H), 1.21 (td, *J* = 13.4, 4.0 Hz, 1H), 1.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0, 172.6, 169.9, 169.4, 152.3, 134.8, 73.3, 71.5, 67.4, 62.8, 52.8, 51.1, 42.9, 41.2, 35.0, 32.9, 32.7, 32.3, 30.3, 29.8, 21.3, 21.0, 20.8, 19.1; IR (NaCl/thin film): 2958, 1737, 1680, 1367, 1225, 1158, 1031 cm^{-1}; HRMS (ESI+) calc'd for $C_{24}H_{33}O_7$ $[M + H]^+$ 433.2221, found 433.2217.

Preparation of (–)-maoecrystal Z (10).



To a suspension of enal **142** (2.9 mg, 6.7 μmol, 1.0 equiv) in 1:1 MeOH/H_2O (600 μL) at rt was added enough CH_2Cl_2 (ca. 200 μL) to afford a slightly cloudy solution. To this was added 1M NaOH (15 μL, 15 μmol, 2.2 equiv) and the solution was stirred for 1 h. An additional portion of 1M NaOH was then added (15 μL, 15 μmol, 2.2 equiv) and the solution was allowed to stir for an additional 2.5 h, at which time, LC/MS indicated complete consumption of starting material. AcOH (50 μL) was then added to neutralize the excess base. The reaction mixture was directly loaded onto a preparative reverse-phase HPLC column and purified (40 to 60% MeCN/H_2O, 20 minute gradient, t_R=8.3 min) to afford (–)-maoecrystal Z (**10**) (1.0 mg, 38% yield). $[\alpha]_D^{25} = -91.2°$ (*c* 0.05, MeOH); ^{1}H NMR (500 MHz; d_5-pyridine): δ 9.53 (s, 1H), 6.21 (s, 1H), 5.87 (s, 1H), 5.56 (td, *J* = 3.9, 2.0 Hz, 1H), 4.65 (dd, *J* = 11.8, 1.8 Hz, 1H), 4.38 (dd, *J* = 7.2, 5.5 Hz, 1H), 4.13 (dd, *J* = 12.0, 1.2 Hz, 1H), 3.61 (tt, *J* = 12.8, 3.3, 1H), 2.74 (ddd, *J* = 12.8, 3.5, 1.7 Hz, 1H), 2.23 (dtd, *J* = 13.9, 3.6, 1.8, 1H), 2.04 (t, *J* = 12.7, 1H), 2.03 (s, 3H), 1.89 (t, *J* = 2.0 1H), 1.67 (d, *J* = 6.8 Hz, 1H), 1.61 (dt, *J* = 12.9, 3.2 Hz, 1H), 1.46 (m, 1H), 1.41 (m, 1H and OH), 1.38 (m, 2H), 1.23 (s, 3H), 1.17 (m, 2H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, d_5-pyridine) δ 194.3, 175.4, 169.9, 154.2, 133.8, 73.9, 71.9, 68.4, 66.0, 53.1, 52.3, 42.7, 41.8, 36.3, 34.5, 33.0, 32.3, 31.7, 28.9, 21.3, 21.1, 19.6; IR (NaCl/thin film): 3434, 2925, 2854, 1742, 1710, 1688, 1464, 1258, 1165, 1096, 838, 777 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{31}O_6$ $[M + H]^+$ 391.2115, found 391.2112.

^{1}H NMR (500 MHz; $CDCl_3$): δ 9.52 (s, 1H), 6.30 (d, *J* = 1.0 Hz, 1H), 6.02 (s, 1H), 5.41 (td, *J* = 4.0, 2.0 Hz, 1H), 4.61 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.04 (dd, *J* = 7.1, 4.6 Hz, 1H), 4.00 (dd, *J* = 12.0, 1.2 Hz, 1H), 3.16 (tt, *J* = 12.6, 3.6, 1H), 2.30 (ddd, *J* = 12.6, 3.5, 1.8 Hz, 1H), 2.09 (s, 3H), 2.04 (dtd, *J* = 14.0, 3.5, 2.0 Hz, 1H), 1.87 (d, *J* = 4.4 Hz, -O**H**), 1.80 (dt, *J* = 13.2, 3.3, 1H), 1.74

(t, J = 2.0 Hz, 1H), 1.63 (t, J = 12.7 Hz, 1H), 1.61 (m, 2H), 1.46 (qt, J = 13.4, 3.8 Hz, 1H), 1.42 (br d, J = 6.9 Hz, 1H), 1.38 (ddd, J = 14.2, 12.9, 2.2 Hz, 1H), 1.29 (td, J = 13.2, 4.0 Hz, 1H), 1.23 (td, J = 13.5, 4.2 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H).

^{1}H NMR comparison table of maoecrystal Z (**10**)

Natural (400 MHz)			**Synthetic** (500 MHz)			Δ (ppm)
δ	mult	*J* (Hz)	δ	mult	*J* (Hz)	
9.53	s, 1H	-	9.53	s, 1H	-	0.00
6.21	s, 1H	-	6.21	s, 1H	-	0.00
5.87	s, 1H	-	5.87	s, 1H	-	0.00
5.56	br s, 1H	-	5.56	td, 1H	3.9, 2.0	0.00
4.65	d, 1H	12.0	4.65	dd, 1H	11.8, 1.8	0.00
4.35	t, 1H	7.0	4.38	dd, 1H	7.2, 5.5	+0.03
4.13	d, 1H	12.0	4.13	dd, 1H	12.0, 1.2	0.00
3.60	br t, 1H	12.4	3.61	tt, 1H	12.8, 3.3	+0.01
2.73	dd, 1H	12.8, 1.6	2.74	ddd, 1H	12.8, 3.5, 1.7	+0.01
2.22	br d, 1H	13.6	2.23	dtd, 1H	13.9, 3.6, 1.8	+0.01
2.05	m, 1H	-	2.04	t, 1H	12.7	–0.01
2.03	s, 3H	-	2.03	s, 3H	-	0.00
1.89	s, 1H	-	1.89	t, 1H	2.0	0.00
1.65	d, 1H	7.0	1.67	d, 1H	6.8	+0.02
1.61	br d, 1H	13.2	1.61	dt, 1H	12.9, 3.2	0.00
1.47	m, 1H	-	1.46	m, 1H	-	–0.01
1.43	m, 1H	-	1.41	m, 1H and OH	-	–0.02
1.37	m, 2H	-	1.38	m, 2H	-	+0.01
1.23	s, 3H	-	1.23	s, 3H	-	0.00
1.17*	m, 1H*	-	1.17*	m, 2H*	-	0.00
1.12	m, 1H	-	-	-	-	-
1.05	s, 3H	-	1.05	s, 3H	-	0.00

*We did not observe a proton at 1.12 ppm, but rather, the proton located at 1.17 ppm integrated to 2 protons.

^{13}C NMR comparison table

Natural (δ at 400 MHz)	**Synthetic** (δ at 500 MHz)	Δ (ppm)
194.5	194.3	–0.2
175.7	175.4	–0.3
170.1	169.9	–0.2
154.5	154.2	–0.3
134.0	133.8	–0.2
74.2	73.9	–0.3
72.1	71.9	–0.2
68.6	68.4	–0.2
66.3	66.0	–0.3
53.3	53.1	–0.2
52.6	52.3	–0.3
42.9	42.7	–0.2
42.1	41.8	–0.3
36.5	36.3	–0.2
34.8	34.5	–0.3
33.2	33.0	–0.2
32.5	32.3	–0.2
31.9	31.7	–0.2
29.2	28.9	–0.3
21.6	21.3	–0.3
21.4	21.1	–0.3
19.7	19.6	–0.1

Natural (δ at 400 MHz)	**Synthetic** (δ at 500 MHz)	Δ (ppm)	**Synthetic** (δ at 500 MHz)**	Δ (ppm)**
194.5	194.3	–0.2	194.5	0.0
175.7	175.4	–0.3	175.7	0.0
170.1	169.9	–0.2	170.1	0.0
154.5	154.2	–0.3	154.4	–0.1
134.0	133.8	–0.2	134.0	0.0
74.2	73.9	–0.3	74.1	–0.1
72.1	71.9	–0.2	72.1	0.0
68.6	68.4	–0.2	68.6	0.0
66.3	66.0	–0.3	66.2	–0.1
53.3	53.1	–0.2	53.3	0.0
52.6	52.3	–0.3	52.5	–0.1
42.9	42.7	–0.2	42.9	0.0
42.1	41.8	–0.3	42.1	0.0
36.5	36.3	–0.2	36.5	0.0
34.8	34.5	–0.3	34.7	–0.1
33.2	33.0	–0.2	33.2	0.0
32.5	32.3	–0.2	32.5	0.0
31.9	31.7	–0.2	31.9	0.0
29.2	28.9	–0.3	29.1	–0.1
21.6	21.3	–0.3	21.6	0.0
21.4	21.1	–0.3	21.3	–0.1
19.7	19.6	–0.1	19.8	+0.1

**Rightmost peak of the most downfield signal of C_5D_5N referenced to δ 149.9 ppm.

By referencing the rightmost peak of the most downfield signal of C_5D_5N at δ 149.9 ppm, we obtained carbon shift values that were in better agreement with the literature.

2.5 NOTES AND REFERENCES

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(26) We were unfortunately unable to isolate a clean sample of **131** but tentatively assigned its structure as the hemiacetal shown in Figure 2.11 based on crude ^{1}H NMR and LC–MS data. See Appendix 1.

(27) Spectroscopic data obtained were consistent with isolation data reported by Han and coworkers.[1]

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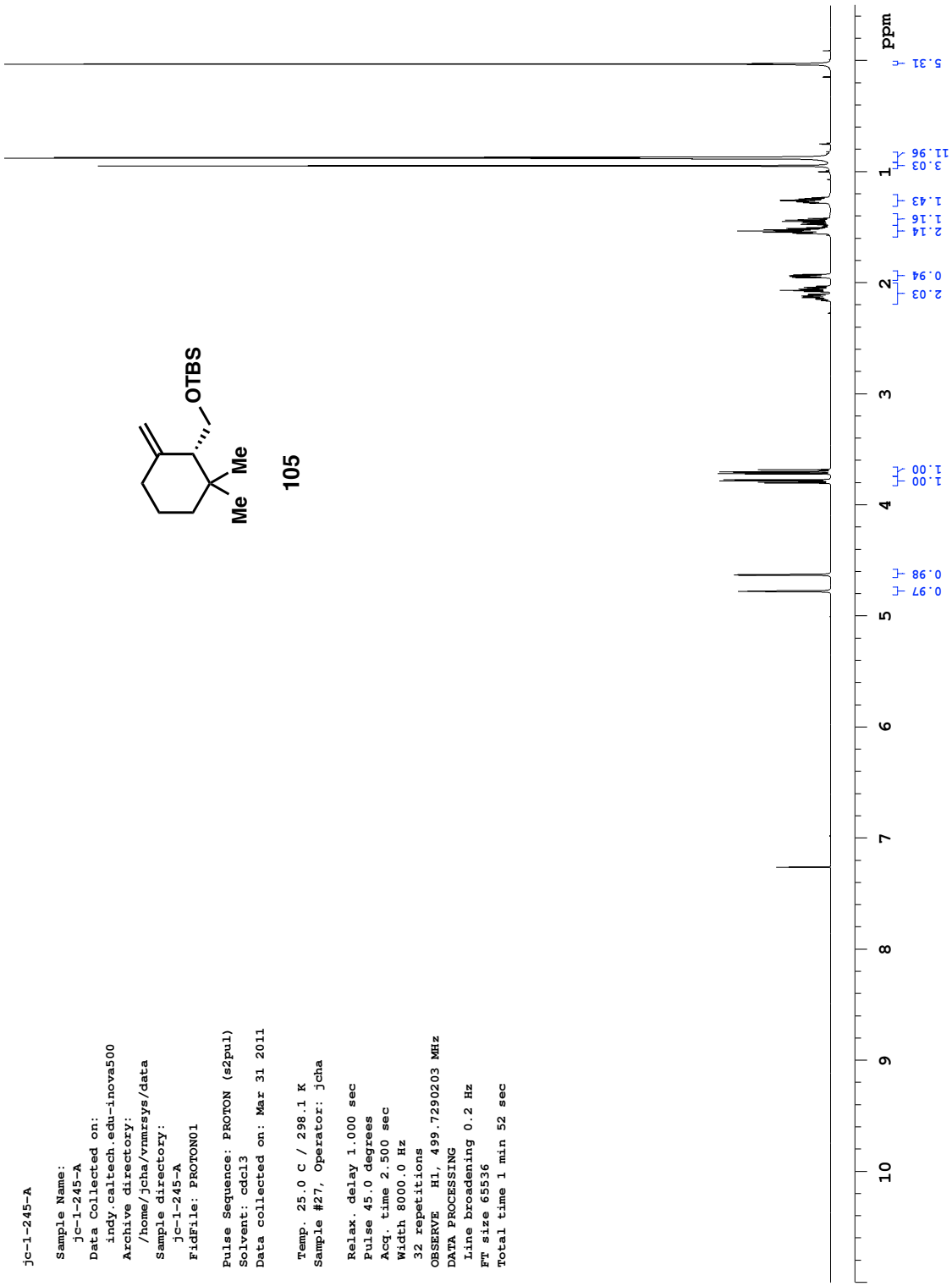
Appendix 1

Spectra Relevant to Chapter 2:
Total Synthesis of (–)-Maoecrystal Z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Sample Name:
jc-1-245-A
Data Collected on:
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Sample directory:
jc-1-245-A
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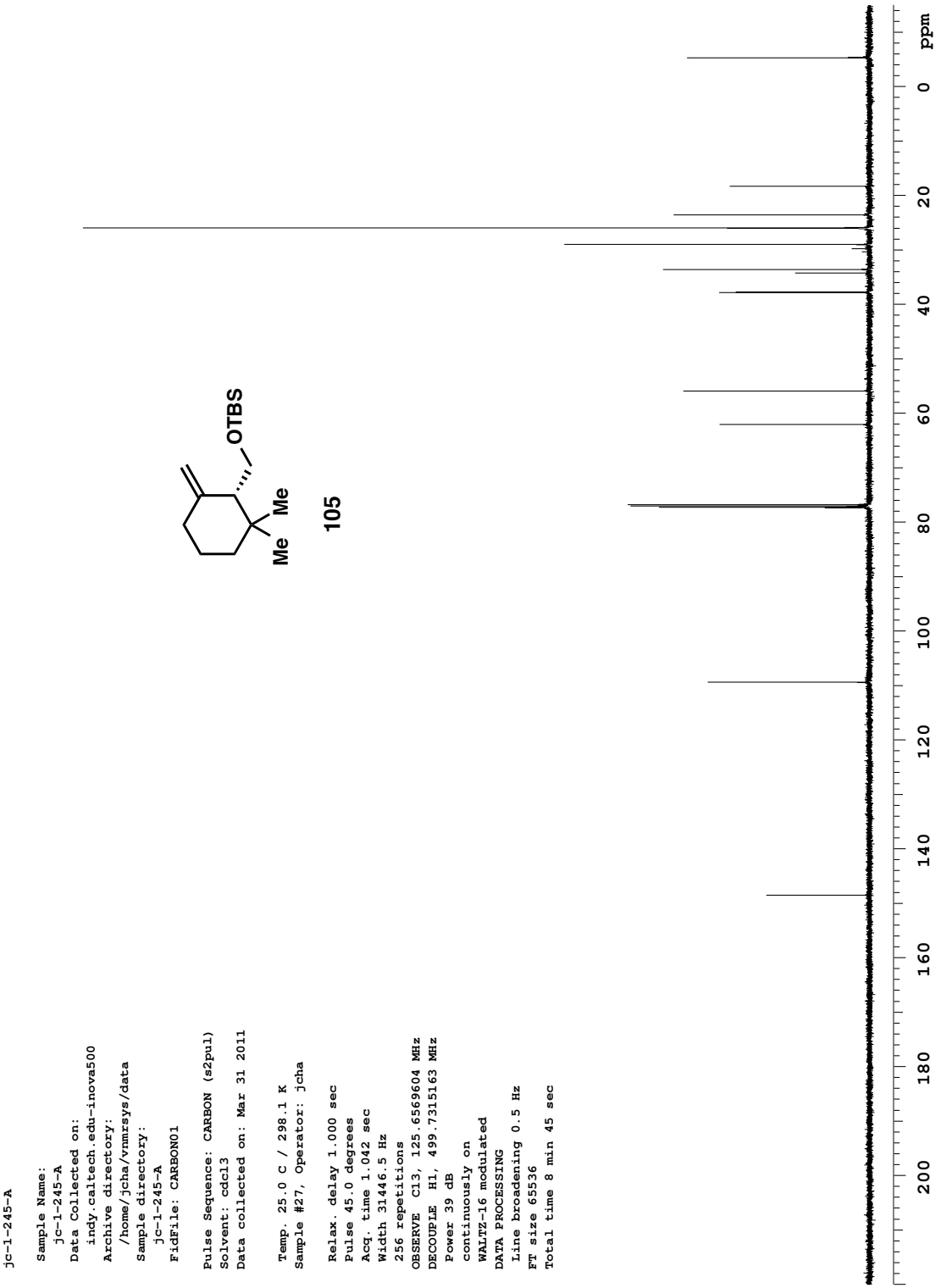
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 31 2011
Temp. 25.0 C / 298.1 K
Sample #27, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
OTBS
Me
Me
105
ppm
5.31
3.03
11.96
1.43
2.14
1.16
2.03
0.94
1.00
1.00
0.97
0.98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jc-1-245-A
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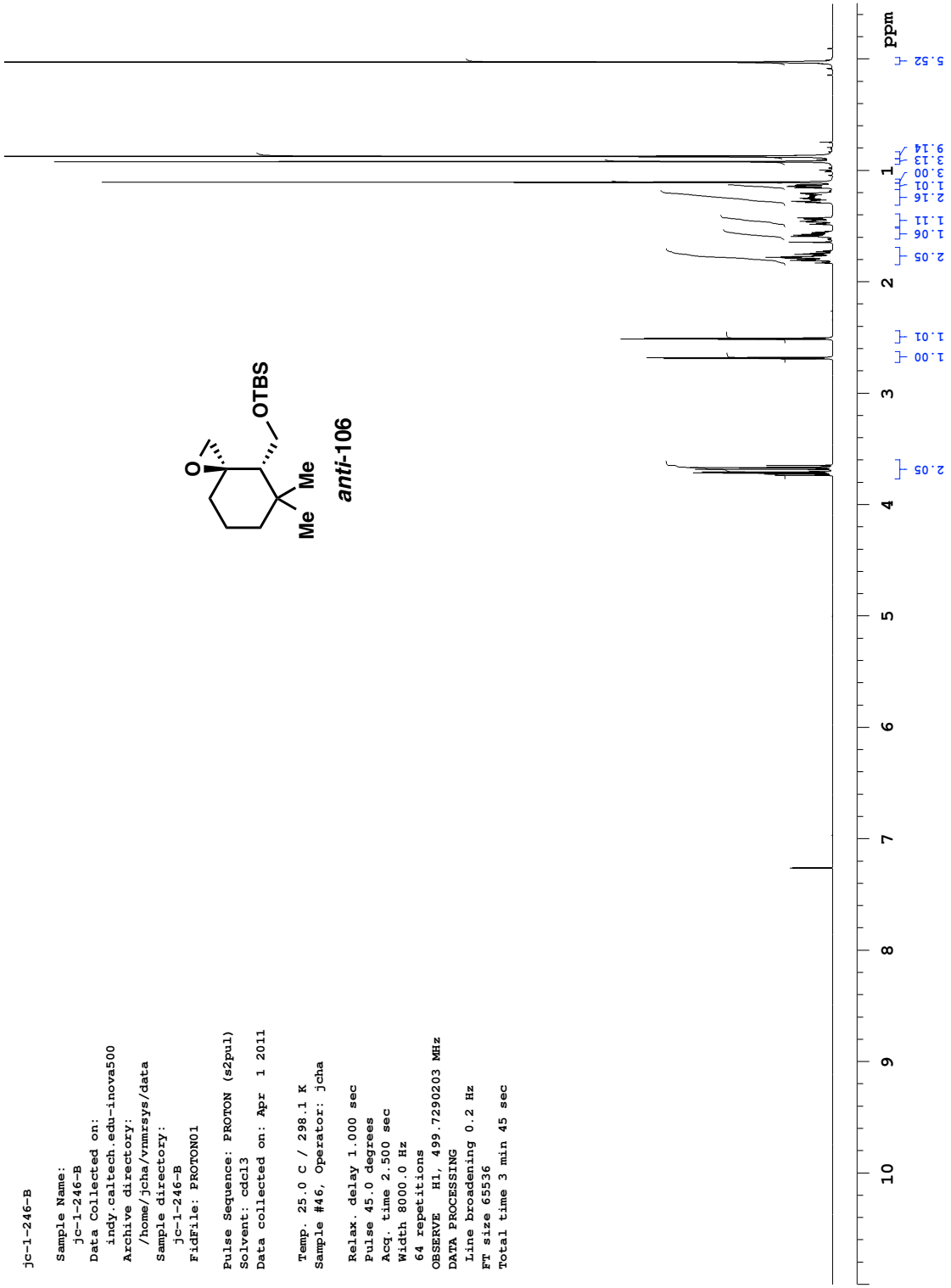
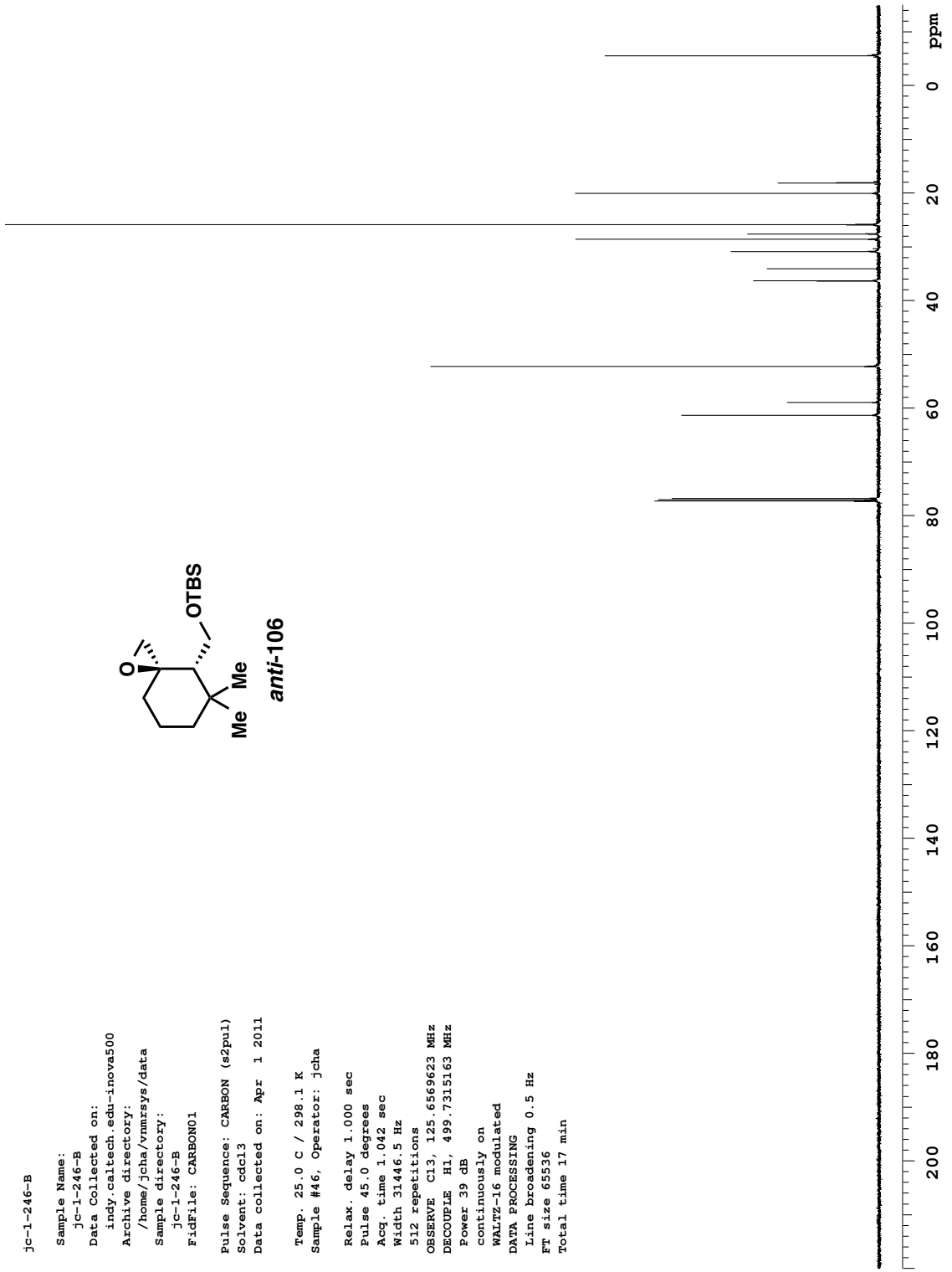
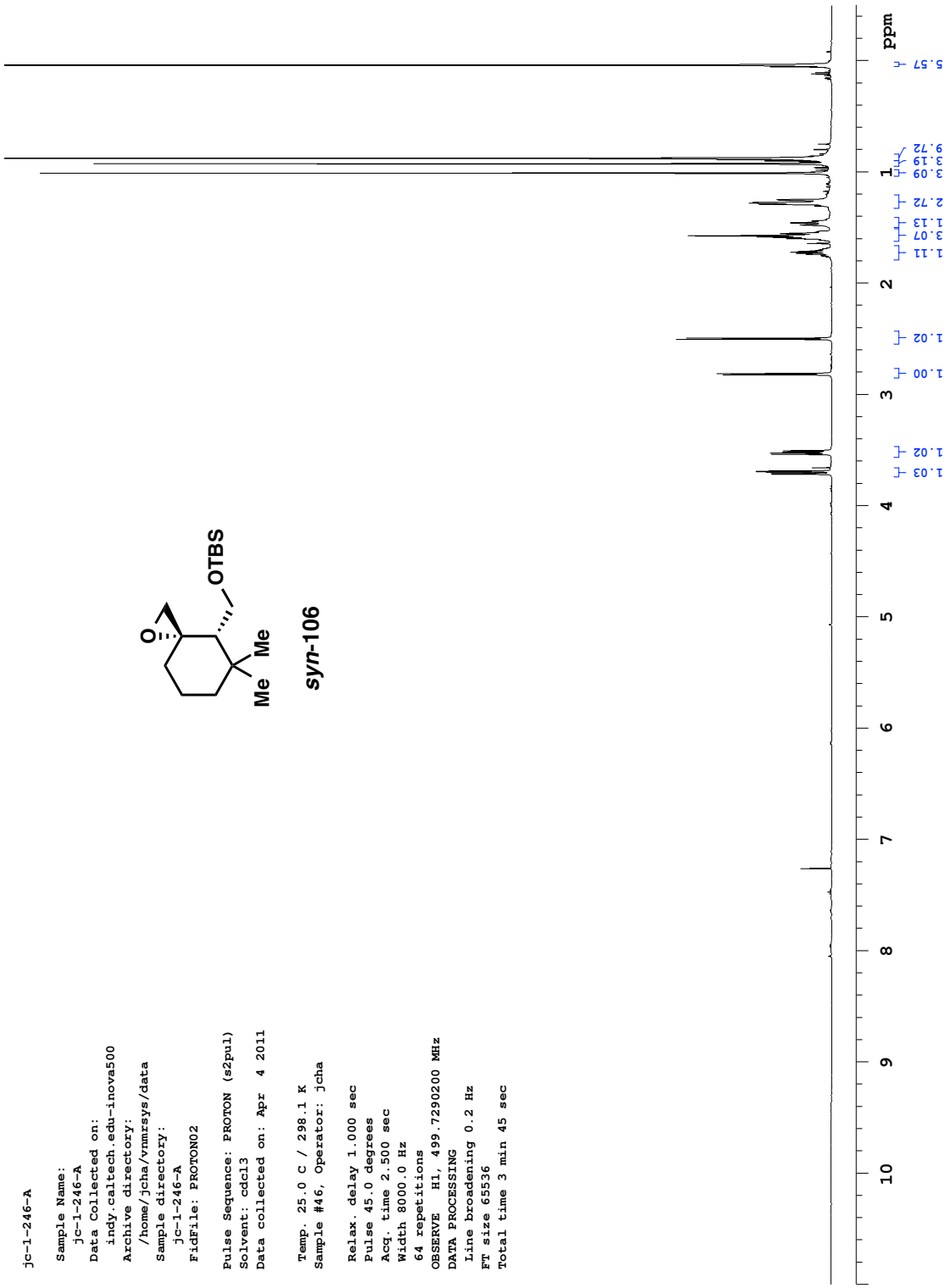
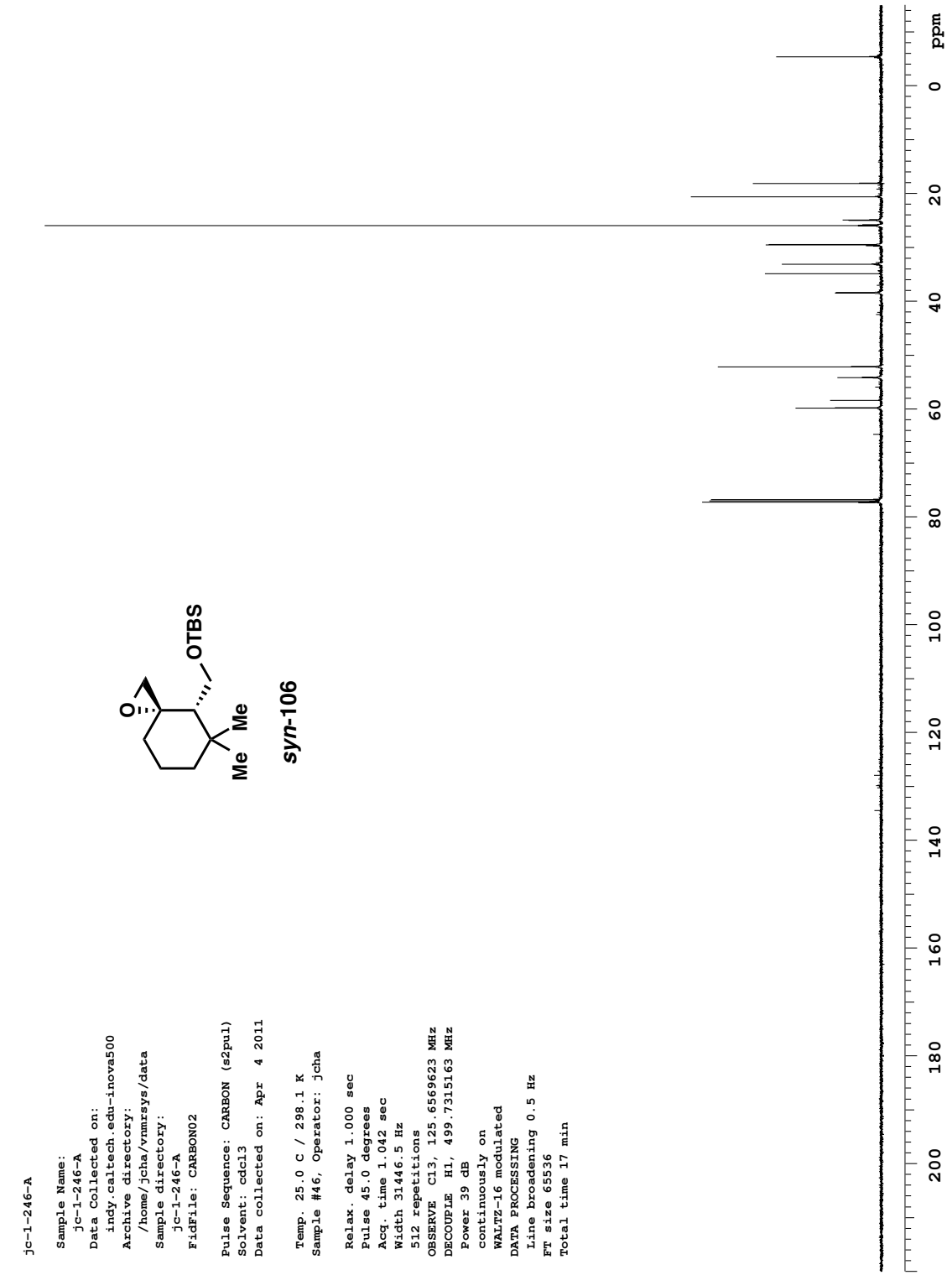
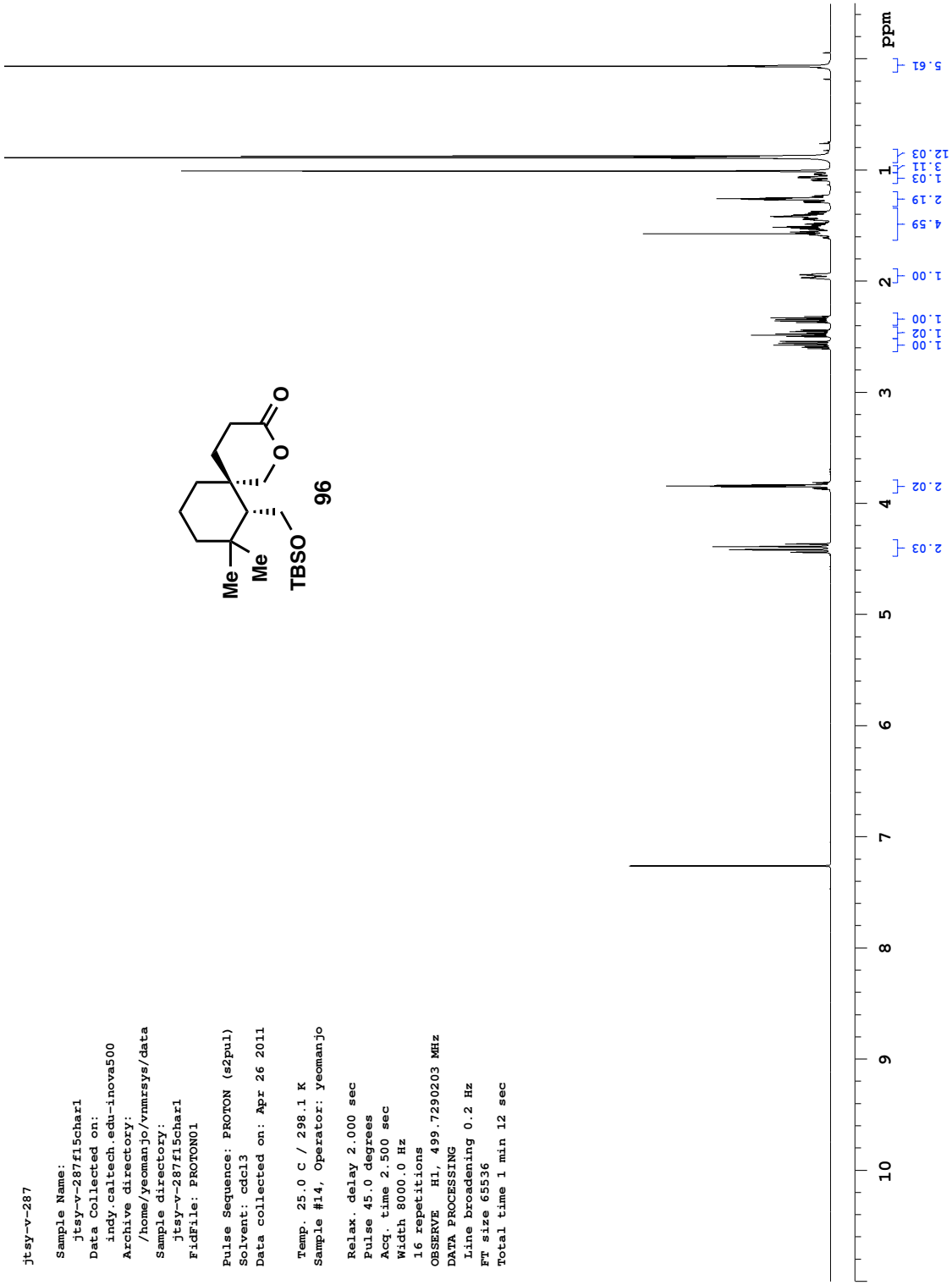
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-245-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 31 2011
Temp. 25.0 C / 298.1 K
Sample #27, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6569604 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 8 min 45 sec
OTBS
Me
Me
105
200
180
160
140
120
100
80
60
40
20
0
ppm

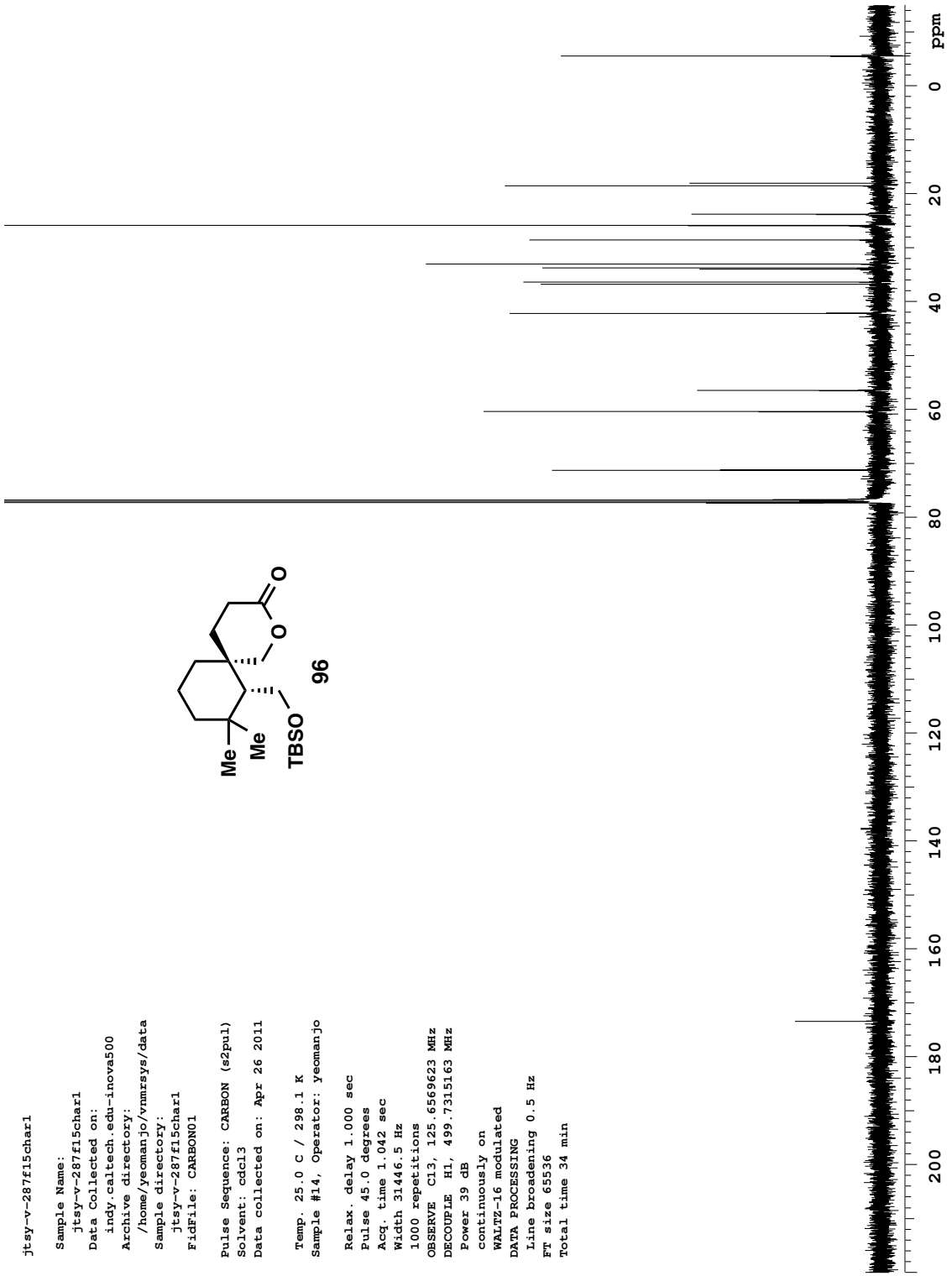

jc-1-246-B
Sample Name:
jc-1-246-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-246-B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 1 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 45 sec
OTBS
O
Me
Me
anti-106
ppm
5.52
9.14
3.13
3.00
1.01
2.16
1.06
1.11
2.05
1.00
1.01
2.05

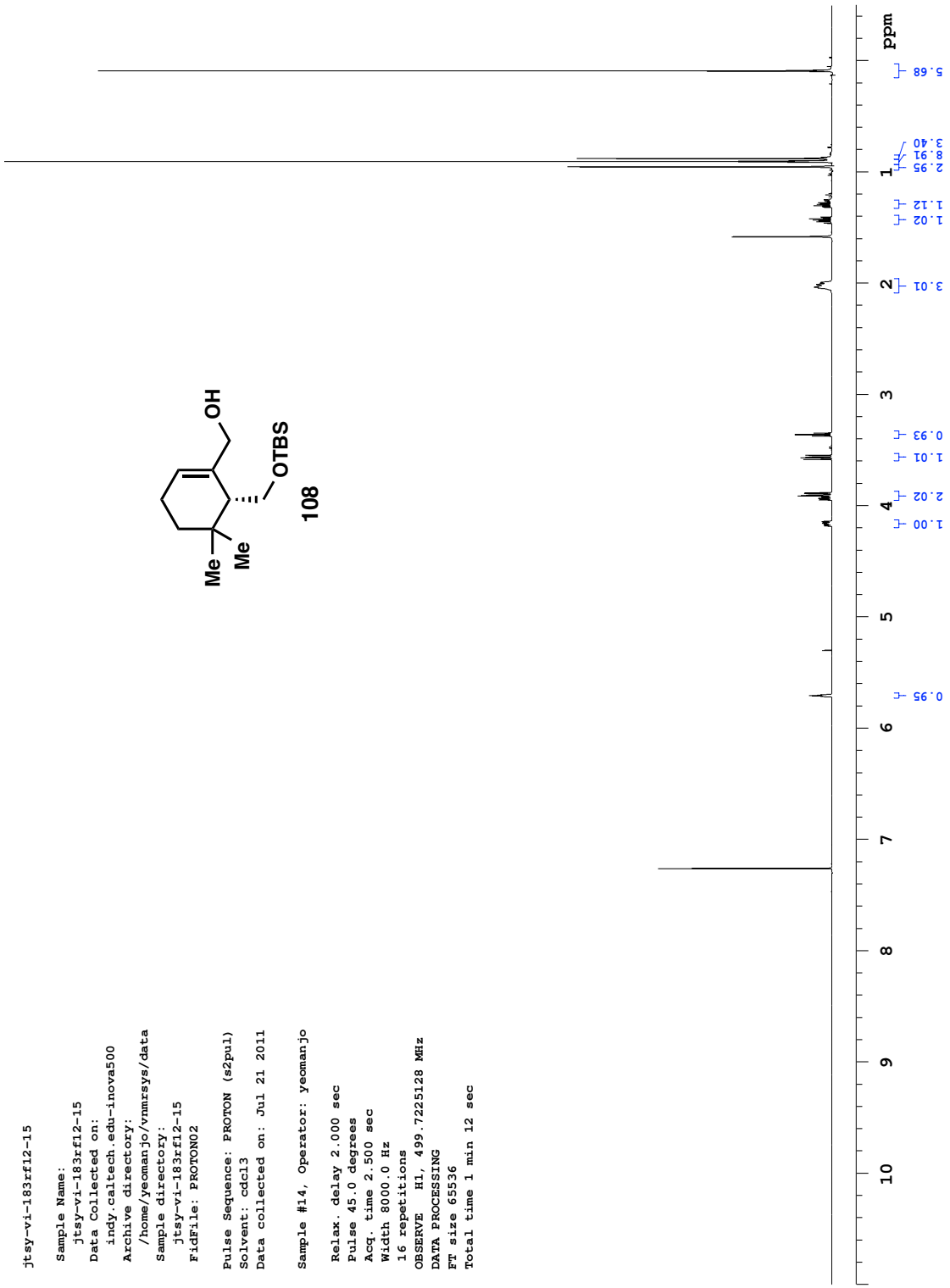

jc-1-246-B
Sample Name:
jc-1-246-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-246-B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 1 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
O
OTBS
Me Me
anti-106
200
180
160
140
120
100
80
60
40
20
0
ppm

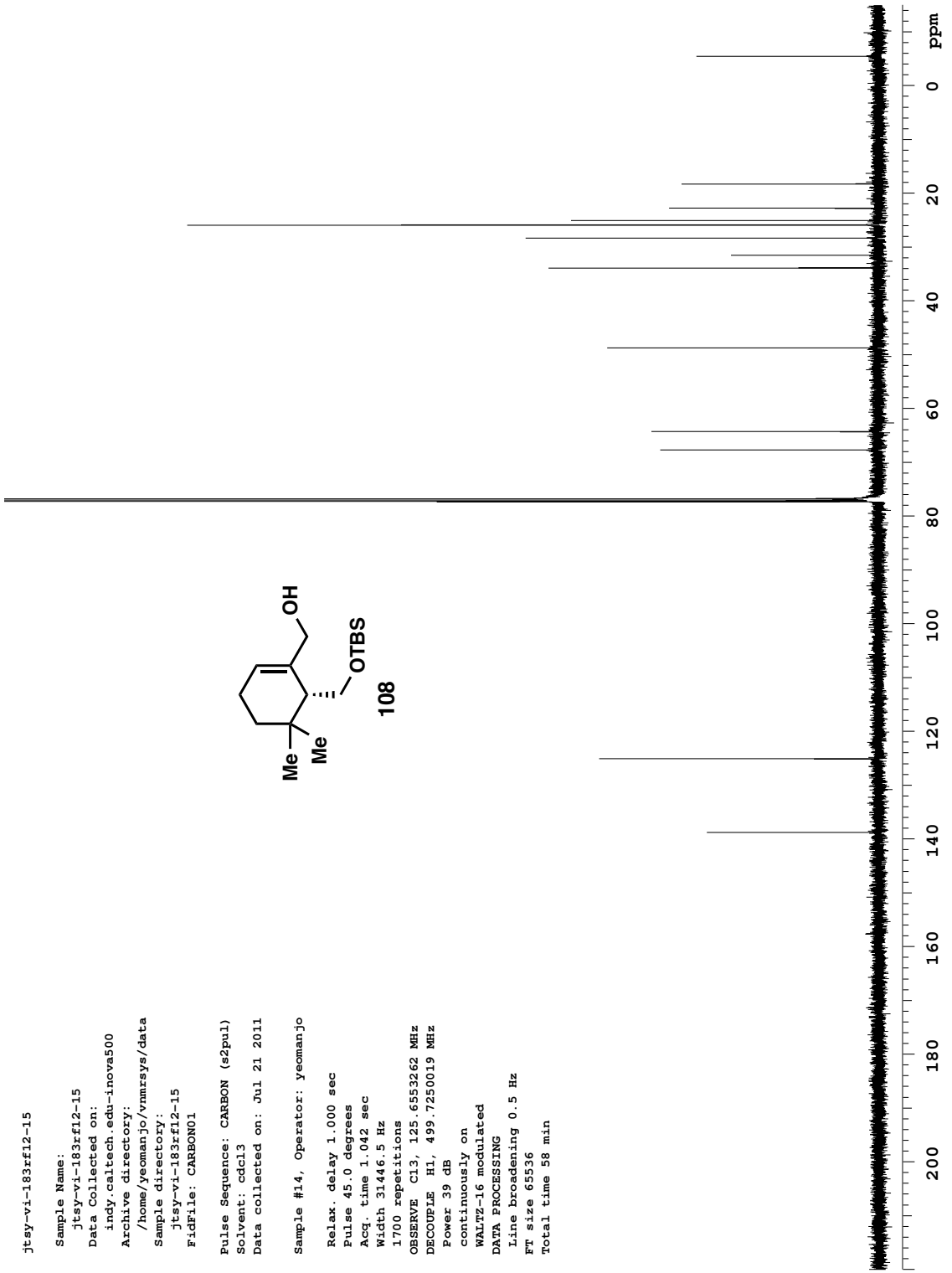

jc-1-246-A
Sample Name:
jc-1-246-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-246-A
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 4 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 45 sec
O
OTBS
Me
Me
syn-106
ppm
5.57
9.72
3.19
3.09
2.72
1.13
3.07
1.11
1.02
1.00
1.02
1.03

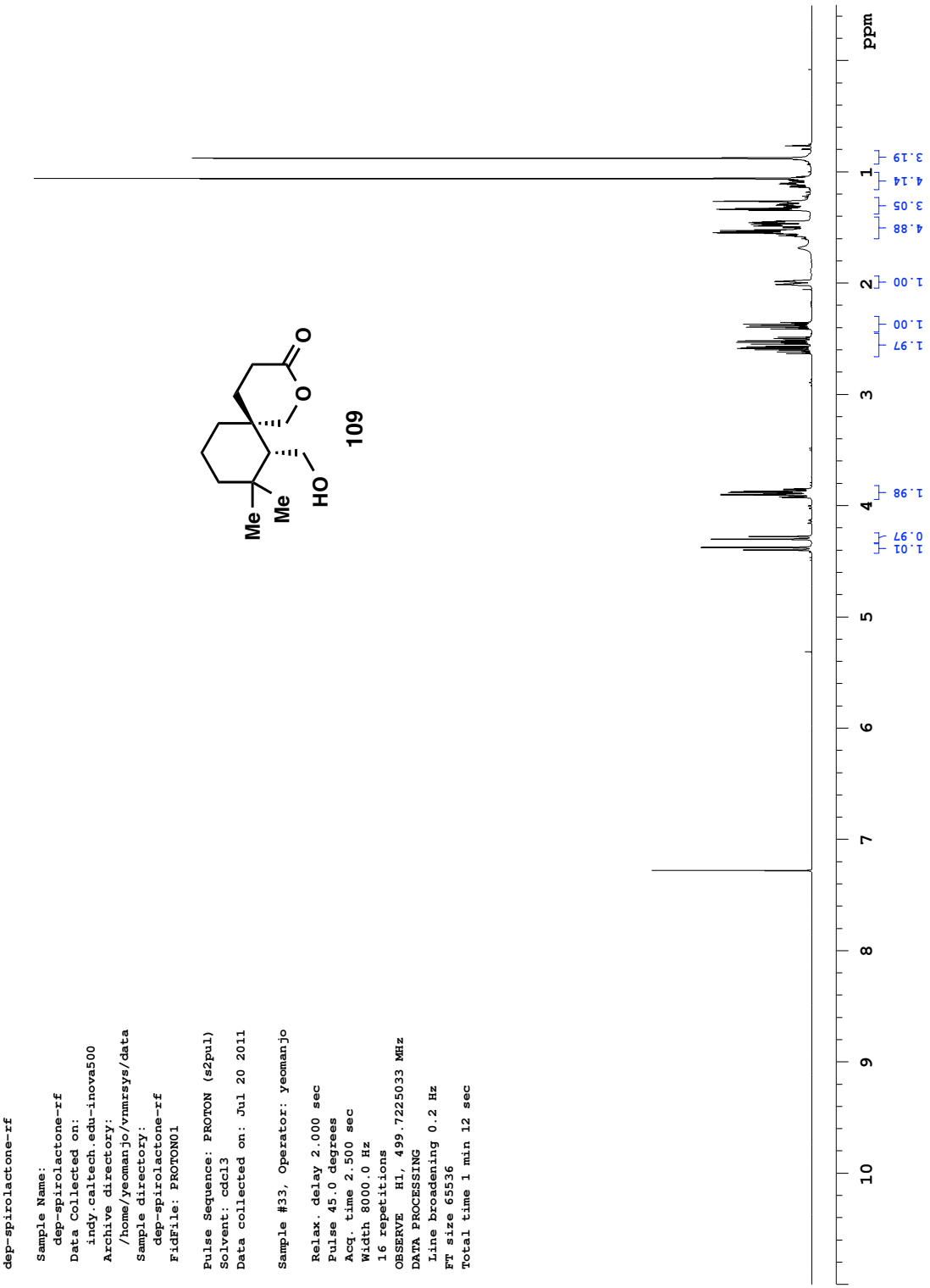

jc-1-246-A
Sample Name:
jc-1-246-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-246-A
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 4 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
OTBS
Me Me
syn-106
200
180
160
140
120
100
80
60
40
20
0
ppm

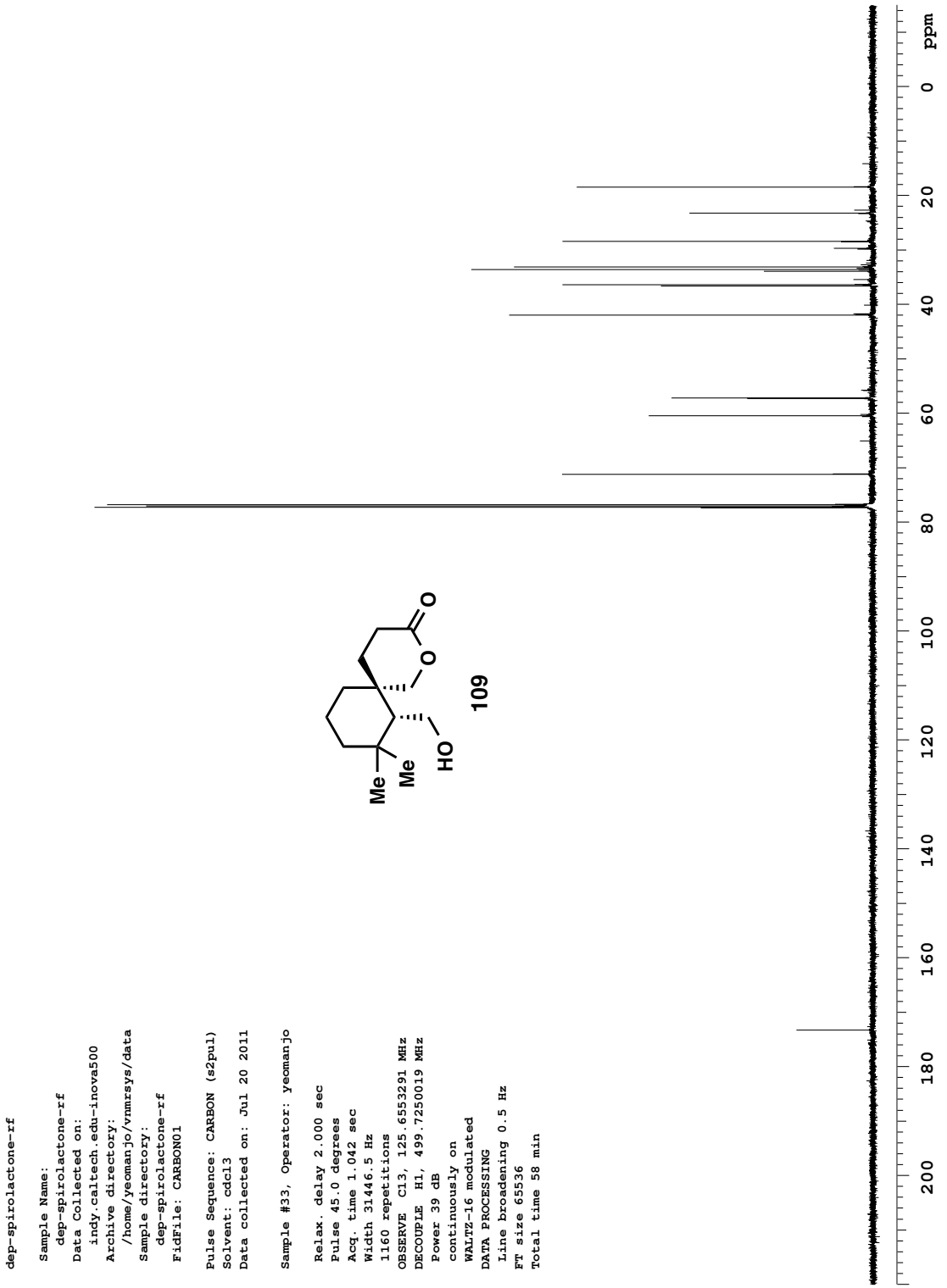

jtsy-v-287
Sample Name:
jtsy-v-287f15char1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-v-287f15char1
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 26 2011
Temp. 25.0 C / 298.1 K
Sample #14, Operator: yeomanjo
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
Me
Me
TBSO
O
O
96
ppm
5.61
12.03
3.11
1.03
2.19
4.59
1.00
1.00
1.02
1.00
2.02
2.03

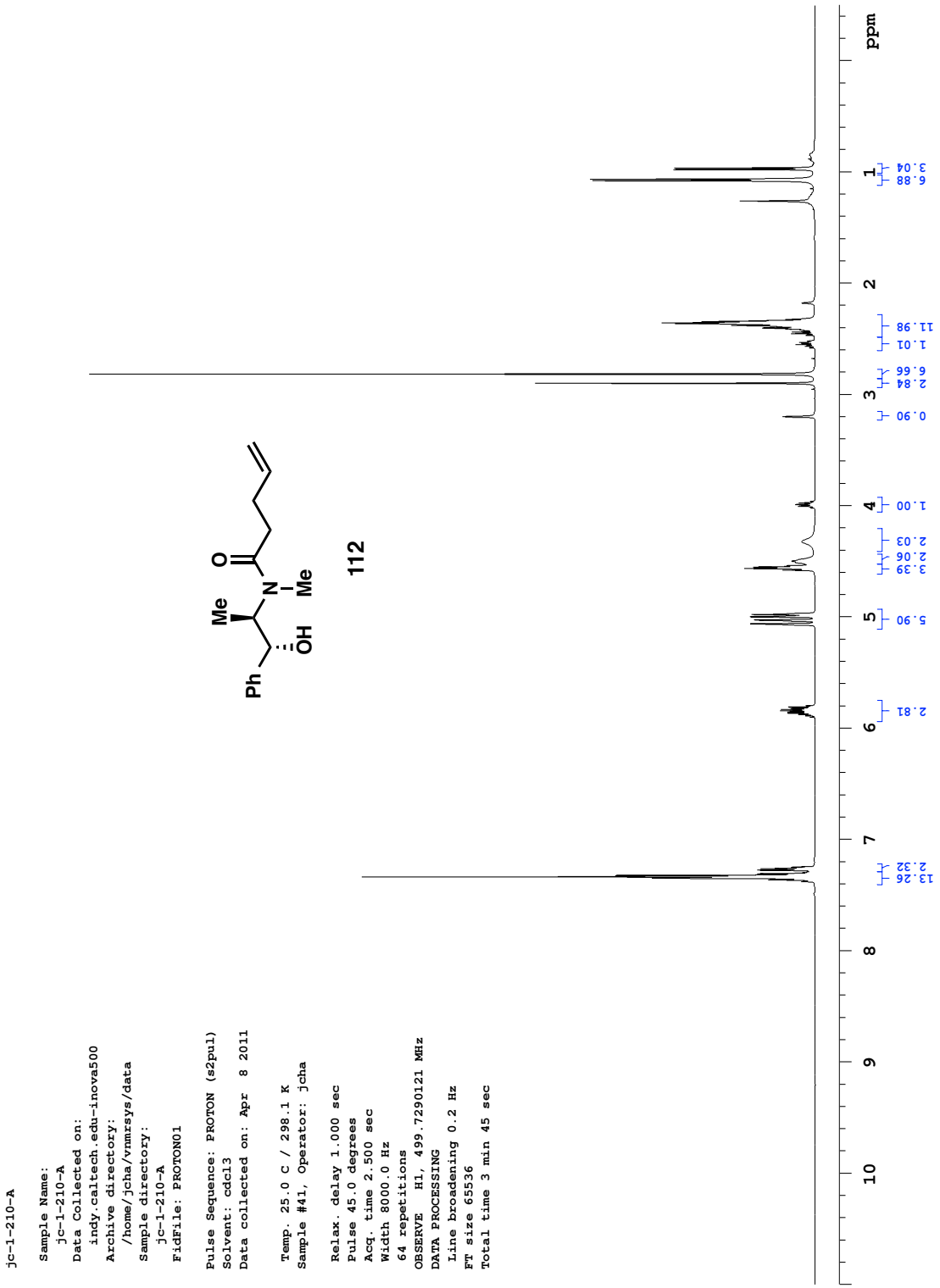

jtsy-v-287f15char1
Sample Name:
jtsy-v-287f15char1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-v-287f15char1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 26 2011
Temp. 25.0 C / 298.1 K
Sample #14, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Me
Me
TBSO
O
O
96
200
180
160
140
120
100
80
60
40
20
0
ppm

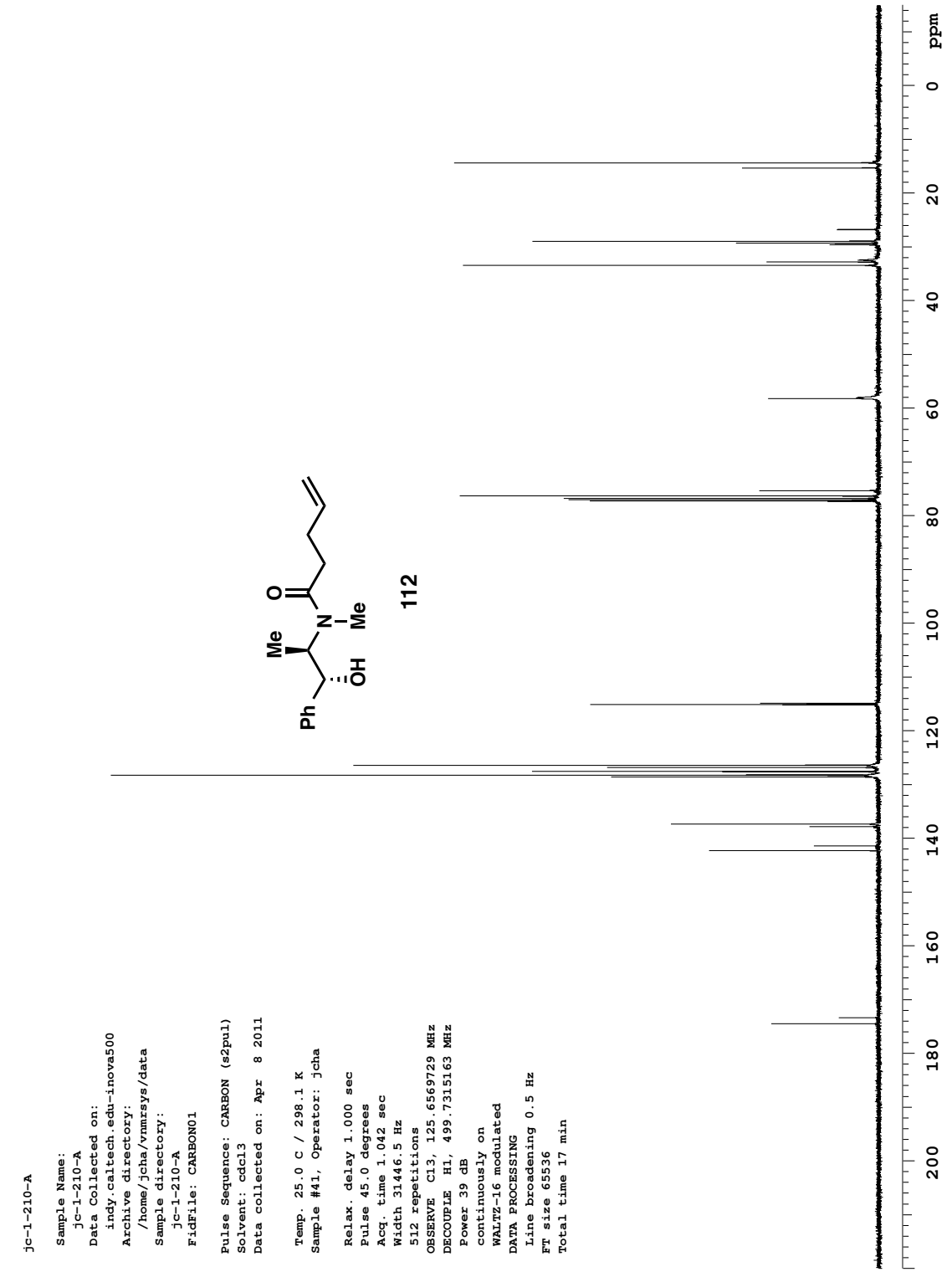

jtsy-vi-183rf12-15
Sample Name:
jtsy-vi-183rf12-15
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vi-183rf12-15
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 21 2011
Sample #14, Operator: yeomanjo
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
FT size 65536
Total time 1 min 12 sec
OH
OTBS
Me
Me
108
ppm
5.68
3.40
8.91
2.95
1.12
1.02
3.01
0.93
1.01
2.02
1.00
0.95

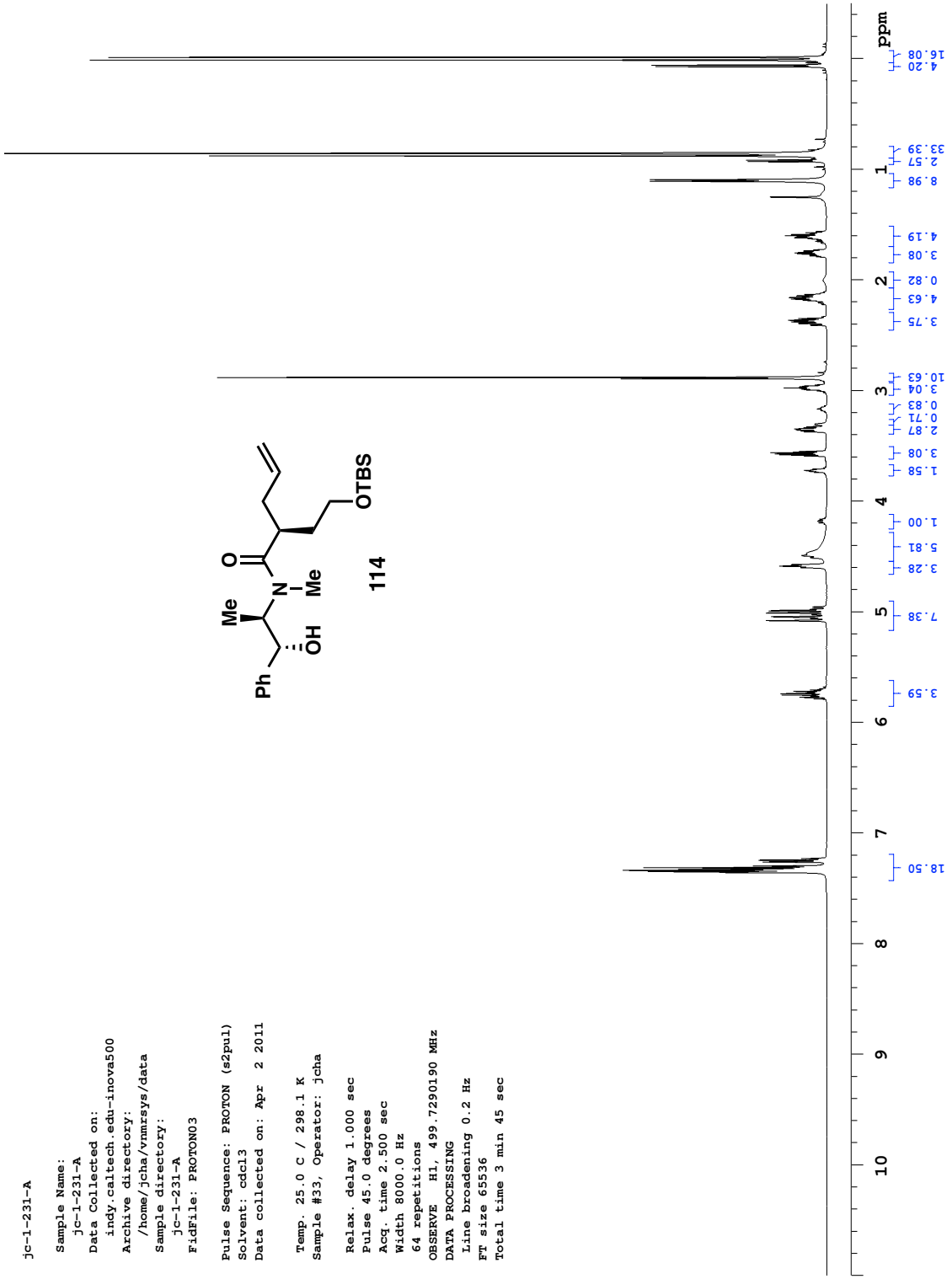

jtsy-vi-183rf12-15
Sample Name:
jtsy-vi-183rf12-15
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yecmanjo/vnmrsys/data
Sample directory:
jtsy-vi-183rf12-15
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 21 2011
Sample #14, Operator: yecmanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6553262 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
OH
OTBS
Me
Me
108
200
180
160
140
120
100
80
60
40
20
0
ppm

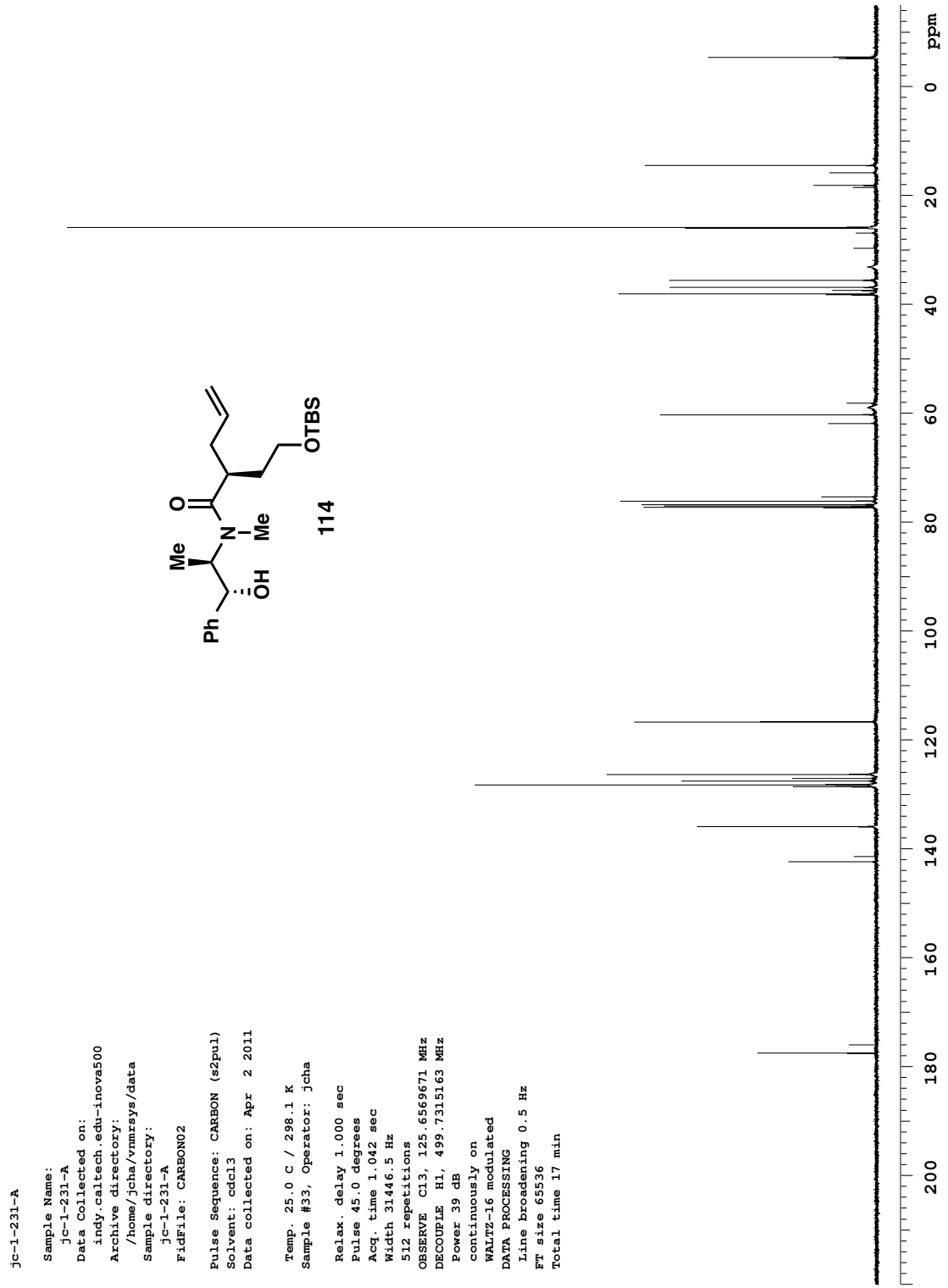

dep-spirolactone-rf
Sample Name:
dep-spirolactone-rf
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yecmanjo/vnmrsys/data
Sample directory:
dep-spirolactone-rf
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 20 2011
Sample #33, Operator: yecmanjo
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
Me
Me
HO
O
O
109
ppm
1
2
3
4
5
6
7
8
9
10
3.19
4.14
3.05
4.88
1.00
1.97
1.00
1.98
0.97
1.01

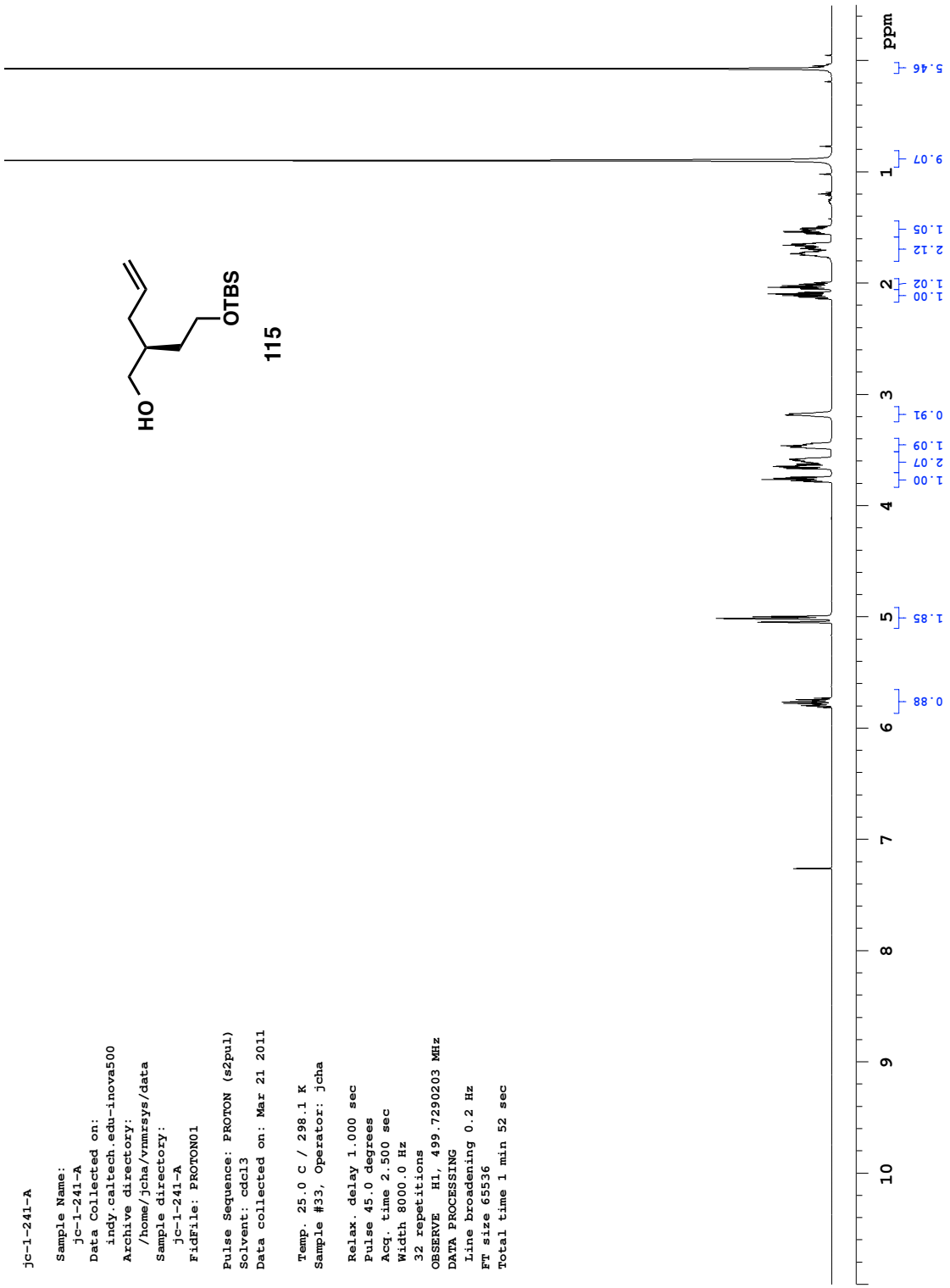

dep-spirolactone-rf
Sample Name:
dep-spirolactone-rf
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
dep-spirolactone-rf
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 20 2011
Sample #33, Operator: yeomanjo
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1160 repetitions
OBSERVE C13, 125.6553291 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
Me
Me
HO
O
O
109
200
180
160
140
120
100
80
60
40
20
0
ppm

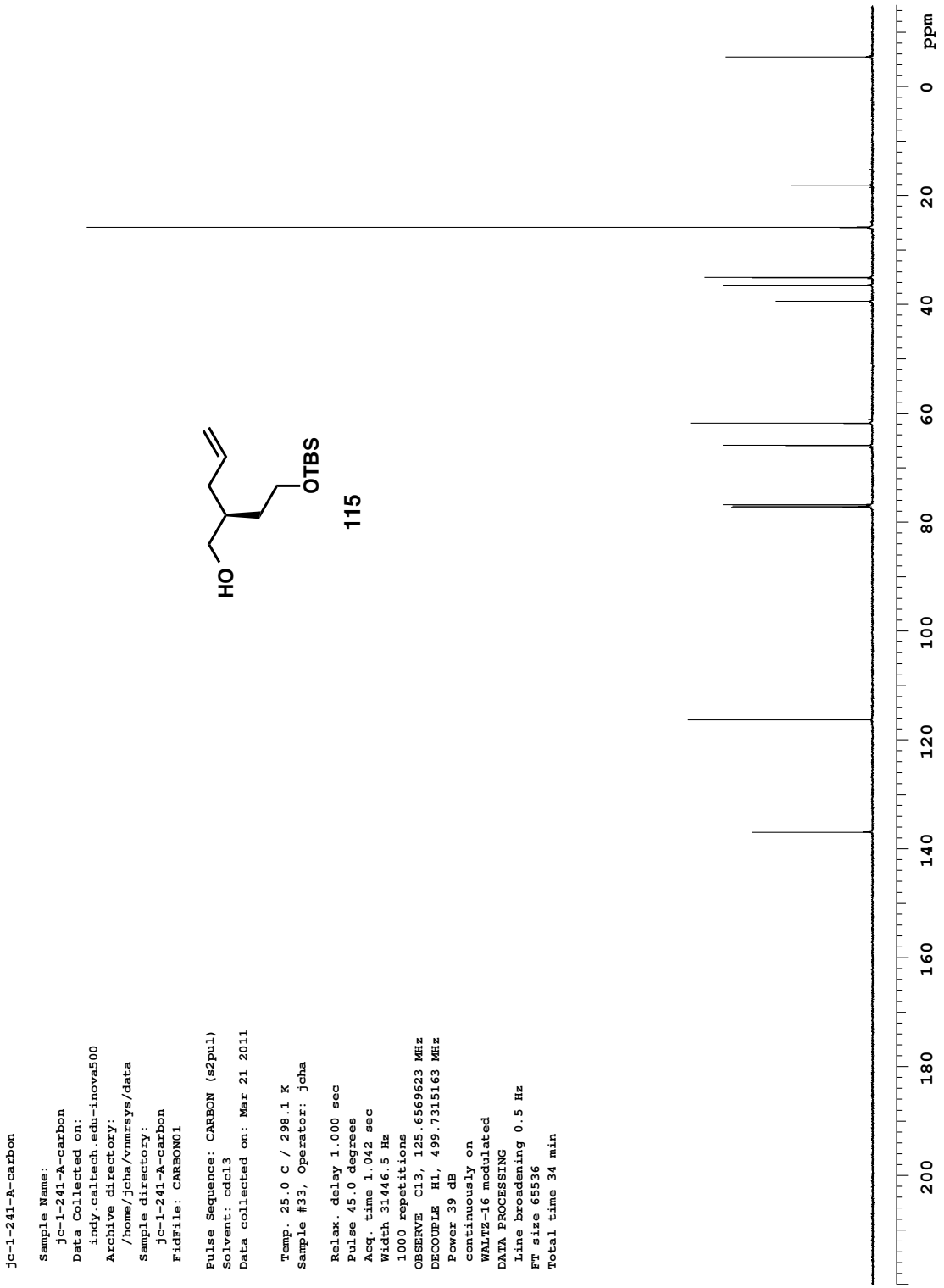

jc-1-210-A
Sample Name:
jc-1-210-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-210-A
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 8 2011
Temp. 25.0 C / 298.1 K
Sample #41, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290121 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 45 sec
Me
O
N
Me
Ph
OH
112
ppm
1
2
3
4
5
6
7
8
9
10
3.04
6.88
11.98
1.01
2.84
6.66
0.90
1.00
2.03
2.06
3.39
5.90
2.81
13.26
2.32

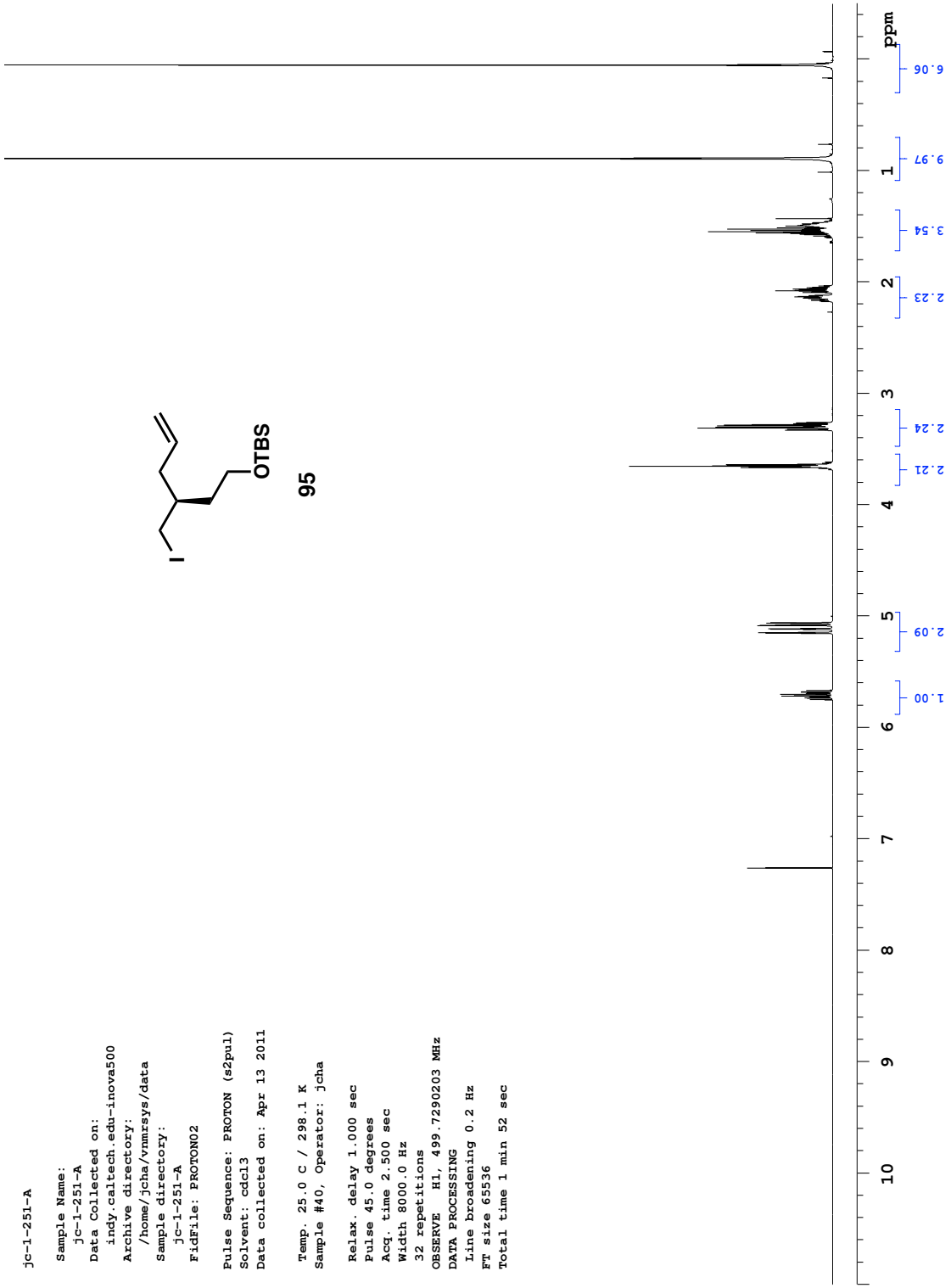

jc-1-210-A
Sample Name:
jc-1-210-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-210-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 8 2011
Temp. 25.0 C / 298.1 K
Sample #41, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569729 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
Me
O
N
Me
Ph
OH
Me
112
200
180
160
140
120
100
80
60
40
20
0
ppm

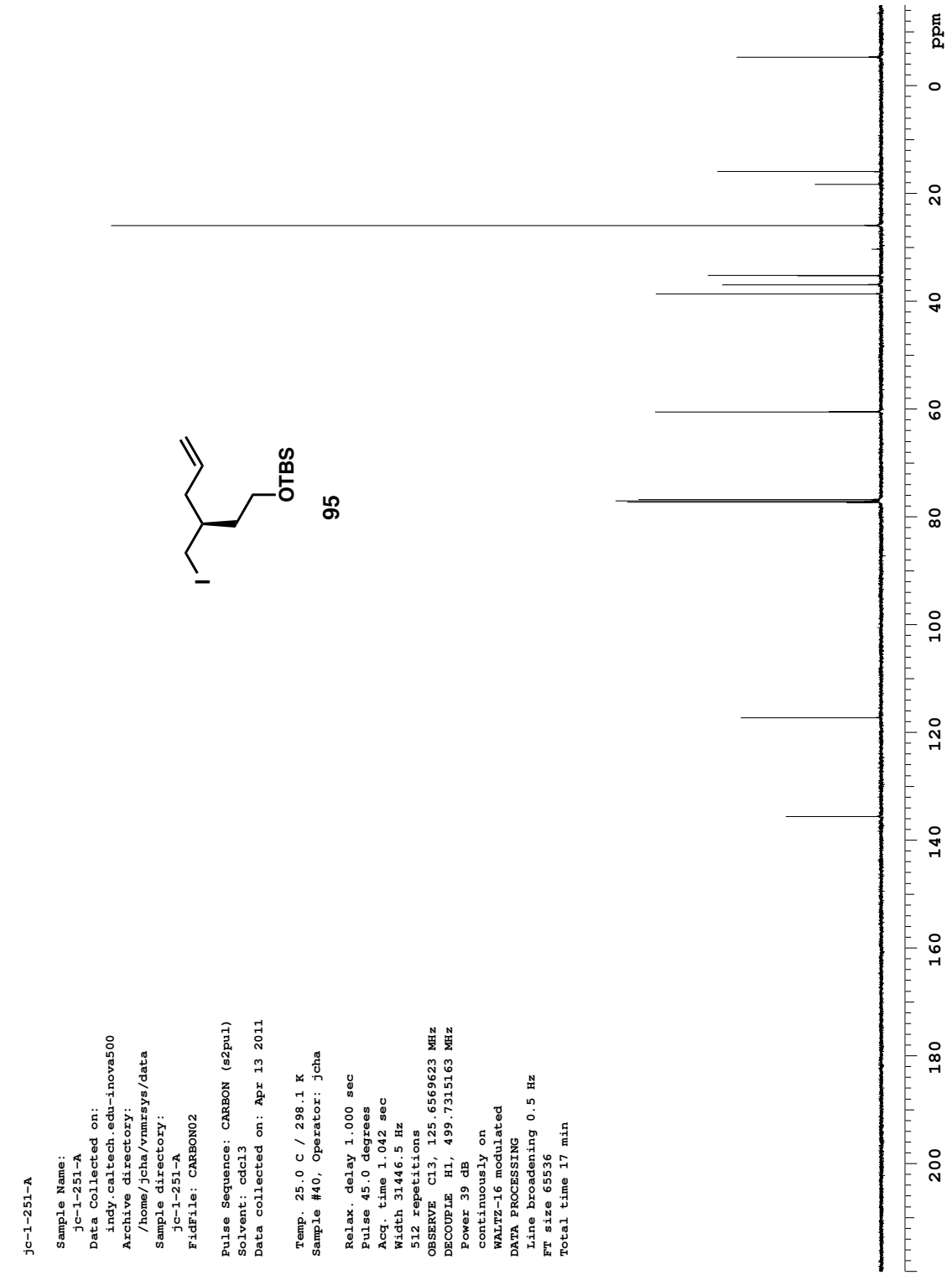

jc-1-231-A
Sample Name:
jc-1-231-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-231-A
FidFile: PROTON03
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290190 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 45 sec
Me
O
N
Me
Ph
OH
OTBS
114
ppm
4.20
16.08
2.57
33.39
8.98
4.19
3.08
0.82
4.63
3.75
3.04
10.63
0.83
0.71
2.87
3.08
1.58
1.00
5.81
3.28
7.38
3.59
18.50

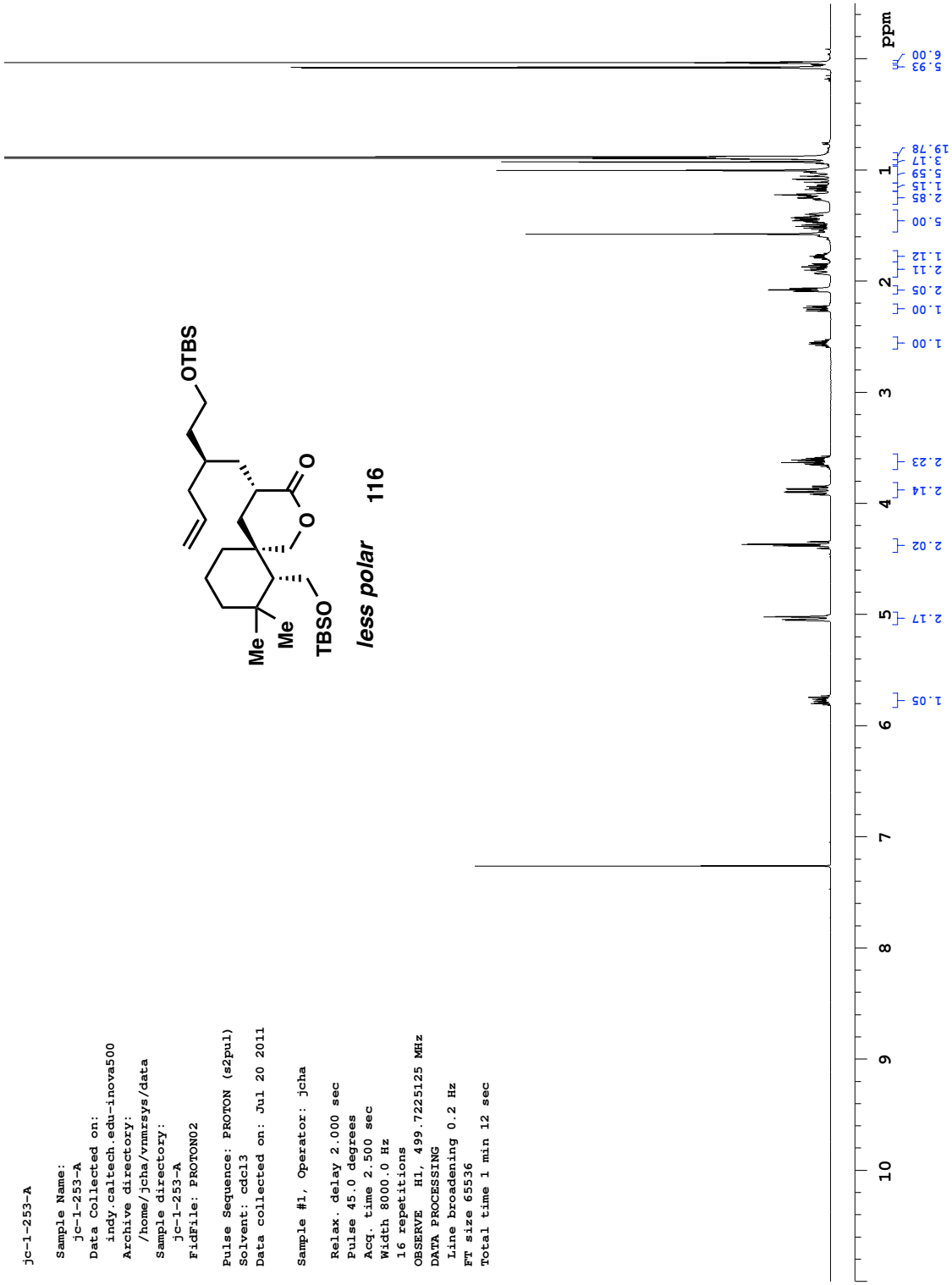

jc-1-231-A
Sample Name:
jc-1-231-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-231-A
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 2 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569671 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
Me
O
N
Me
Ph
OH
OTBS
114
200
180
160
140
120
100
80
60
40
20
0
ppm

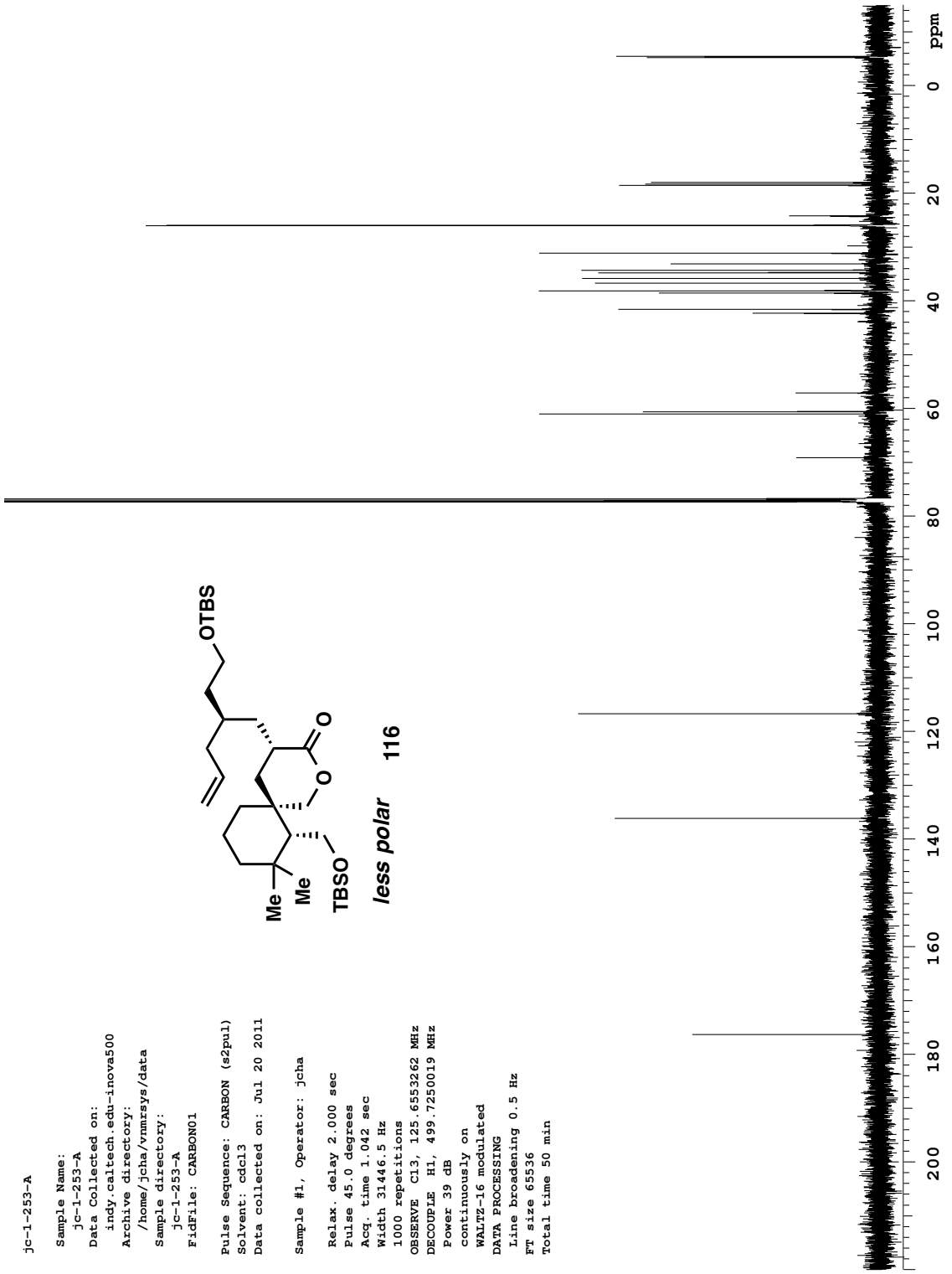

jc-1-241-A
Sample Name:
jc-1-241-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-241-A
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
HO
OTBS
115
ppm
10
9
8
7
6
5
4
3
2
1
5.46
9.07
1.05
2.12
1.00
1.02
0.91
1.09
2.07
1.00
1.85
0.88

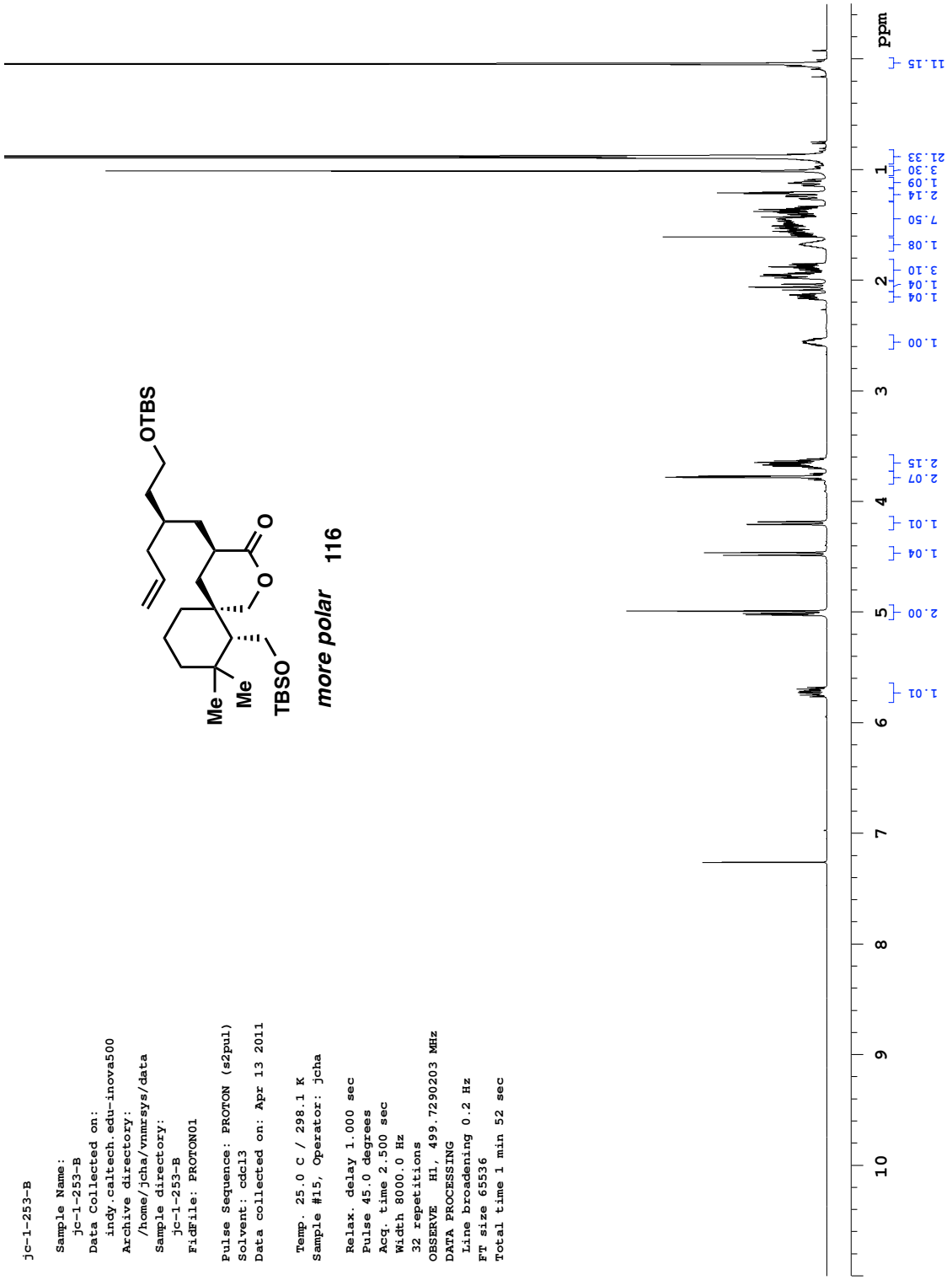

jc-1-241-A-carbon
Sample Name:
jc-1-241-A-carbon
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-241-A-carbon
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
HO
OTBS
115
200
180
160
140
120
100
80
60
40
20
0
ppm

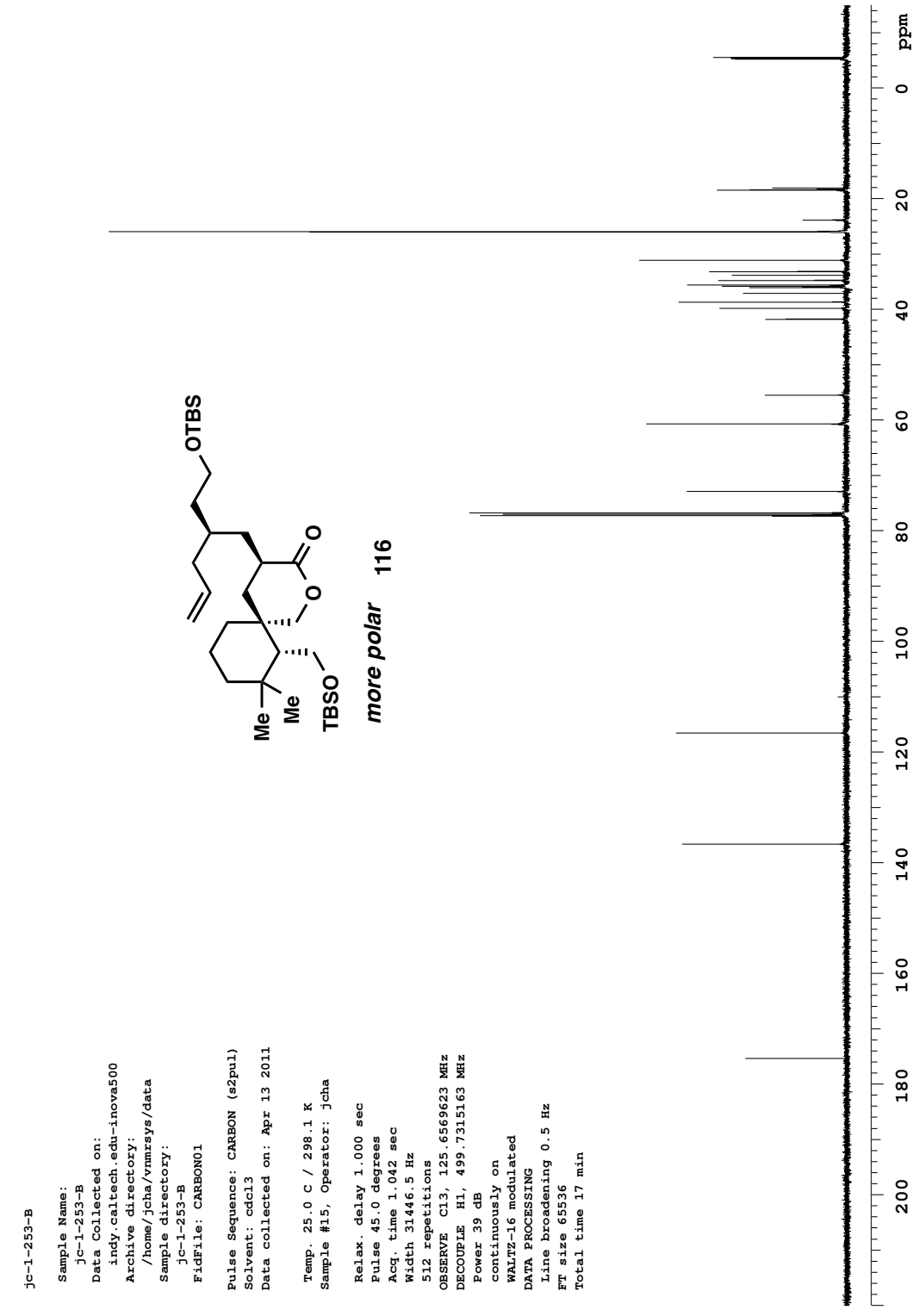

jc-1-251-A
Sample Name:
jc-1-251-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-251-A
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 13 2011
Temp. 25.0 C / 298.1 K
Sample #40, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
OTBS
I
95
ppm
6.06
9.97
3.54
2.23
2.24
2.21
2.09
1.00

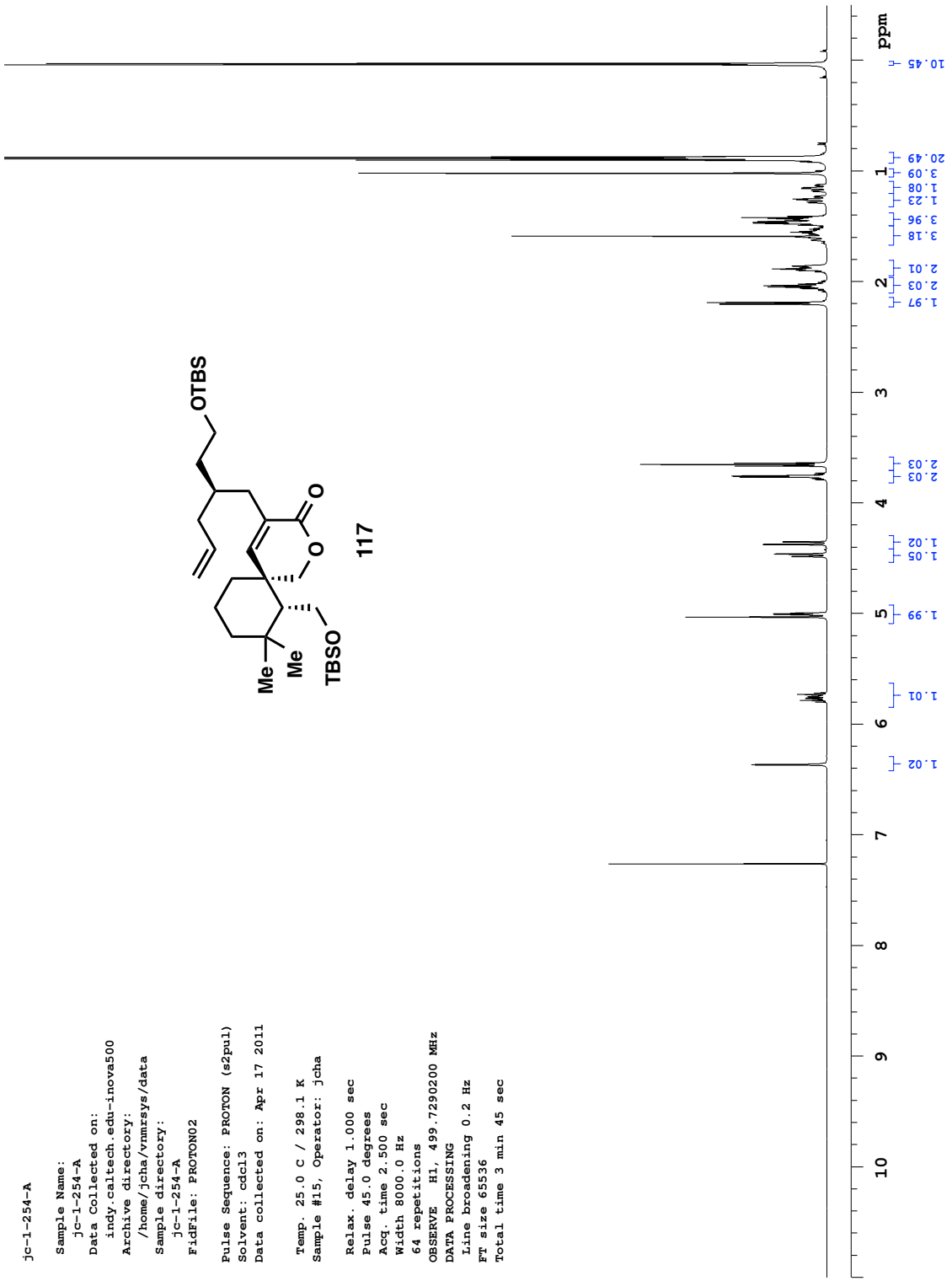

jc-1-251-A
Sample Name:
jc-1-251-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-251-A
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 13 2011
Temp. 25.0 C / 298.1 K
Sample #40, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
OTBS
I
95
200
180
160
140
120
100
80
60
40
20
0
ppm

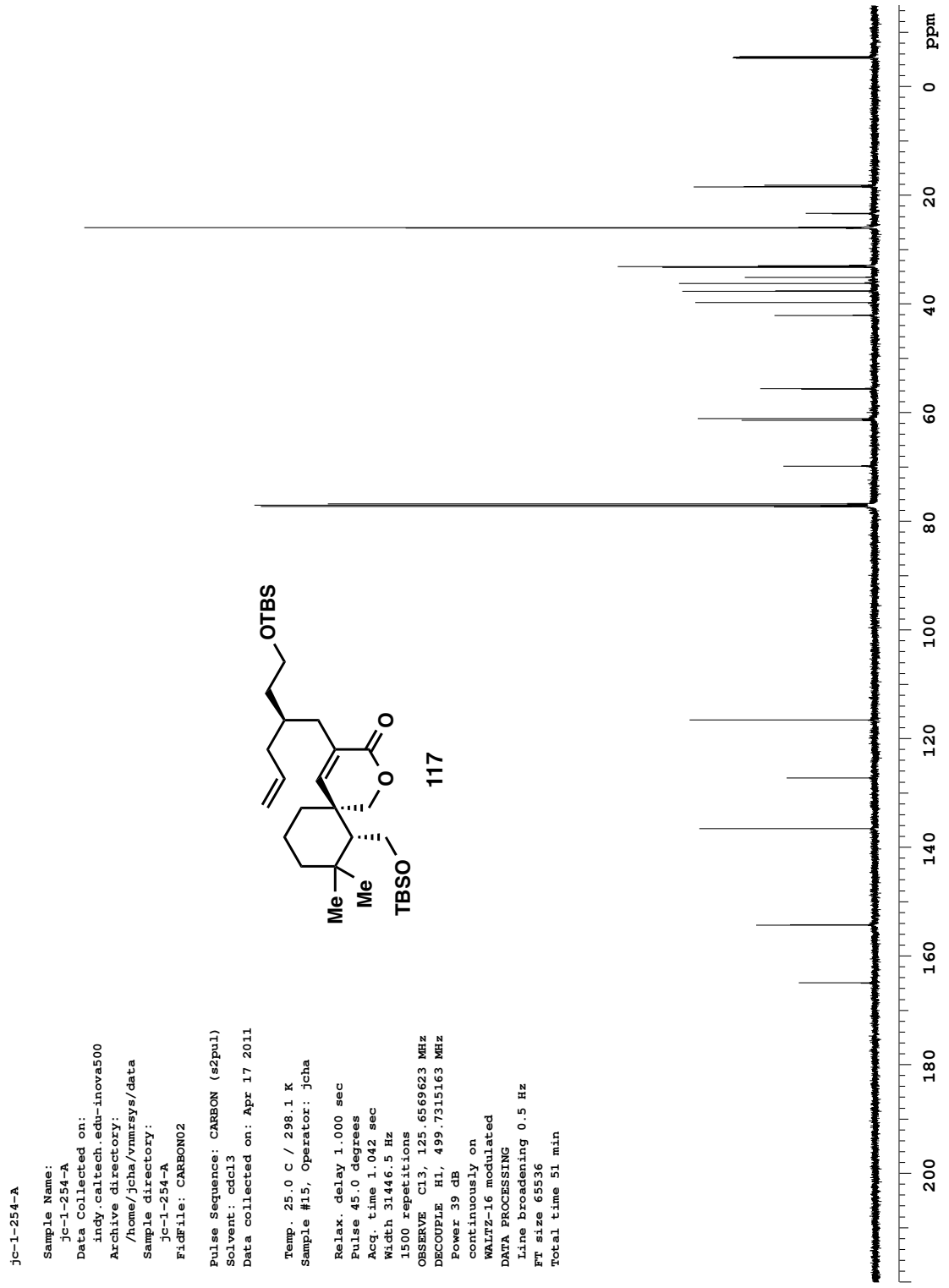

OTBS
O
O
Me
Me
TBSO
less polar
116
ppm
6.00
5.93
19.78
3.17
5.59
1.15
2.85
5.00
1.12
2.11
2.05
1.00
1.00
2.23
2.14
2.02
2.17
1.05
jc-1-253-A
Sample Name:
jc-1-253-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-253-A
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 20 2011
Sample #1, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec

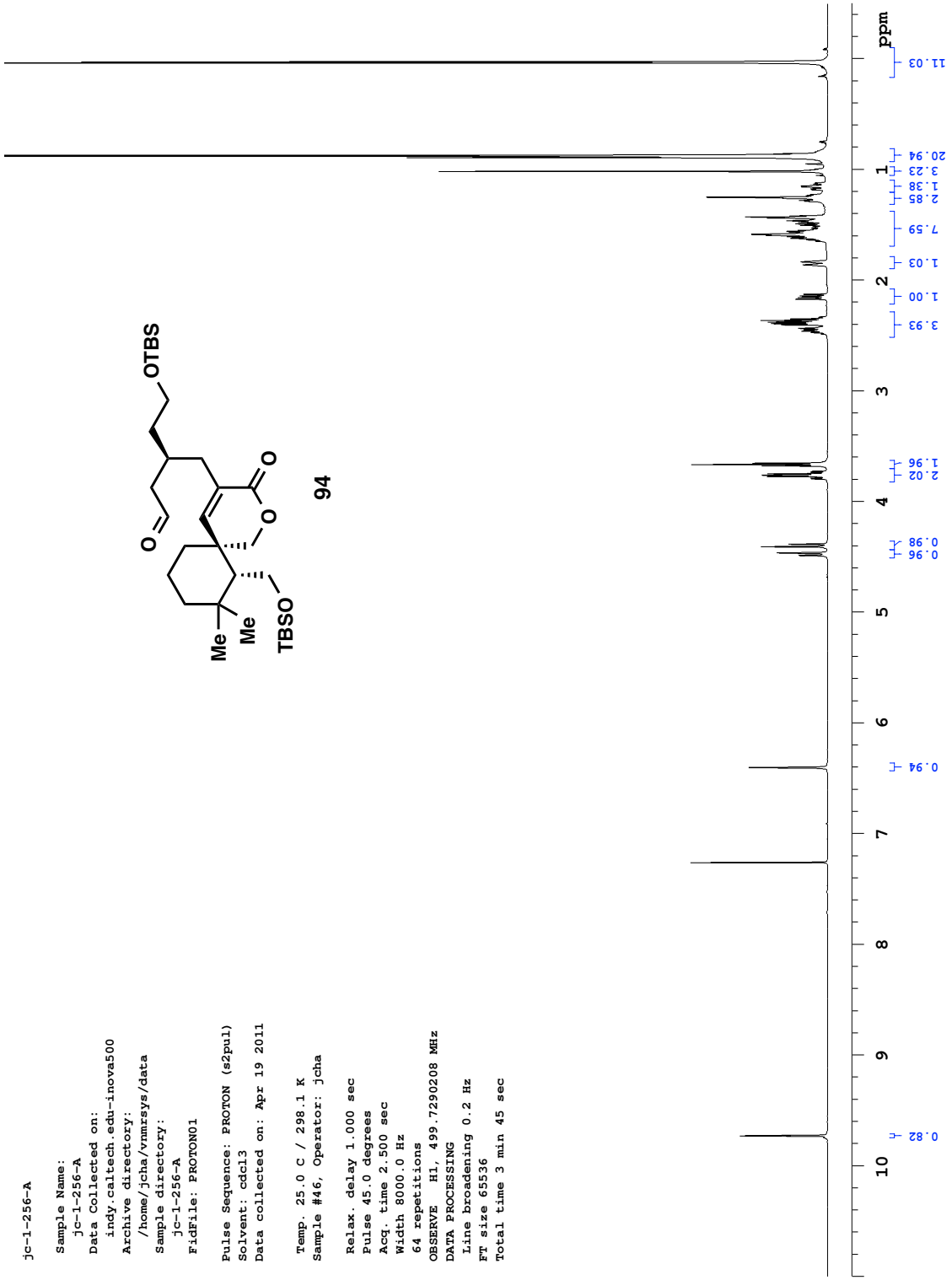

jc-1-253-A
Sample Name:
jc-1-253-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-253-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 20 2011
Sample #1, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553262 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 50 min
OTBS
Me
Me
TBSO
O
O
less polar
116
200
180
160
140
120
100
80
60
40
20
0
ppm

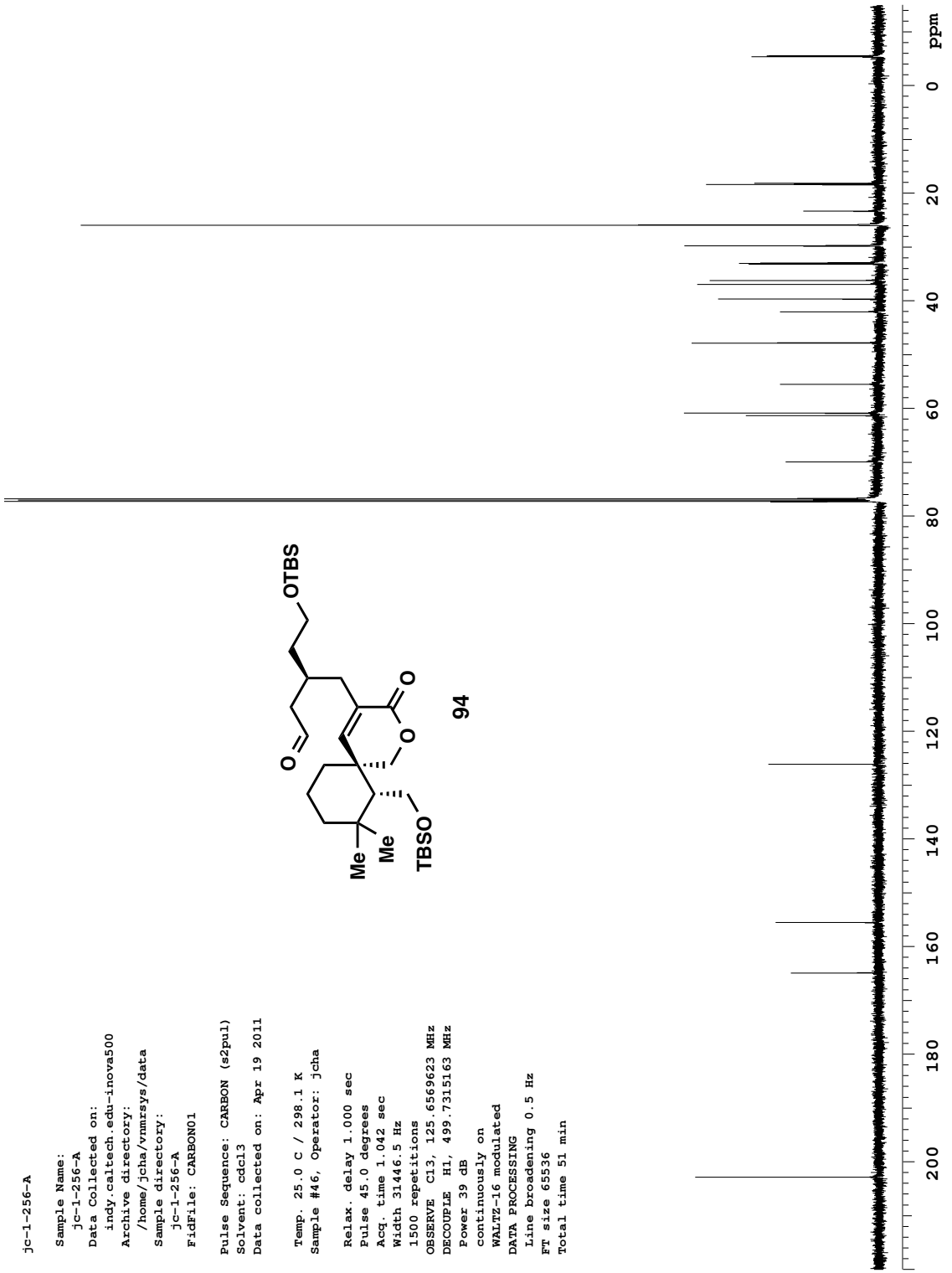

jc-1-253-B
Sample Name:
jc-1-253-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-253-B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 13 2011
Temp. 25.0 C / 298.1 K
Sample #15, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
OTBS
Me
Me
TBSO
O
O
more polar
116
ppm
11.15
21.33
3.30
1.09
2.14
7.50
1.08
3.10
1.04
1.04
1.00
2.15
2.07
1.01
1.04
2.00
1.01

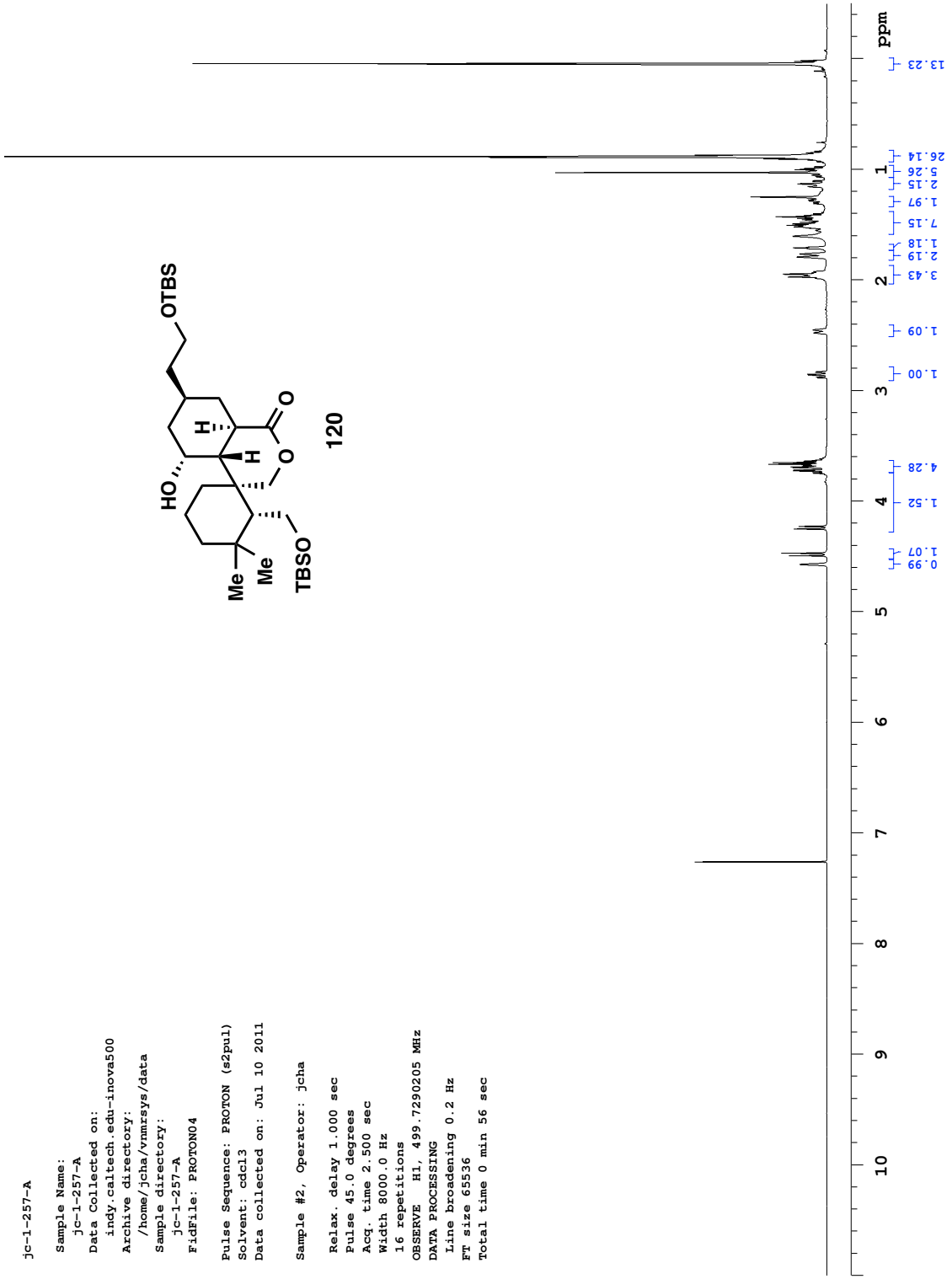

jc-1-253-B
Sample Name:
jc-1-253-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-253-B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 13 2011
Temp. 25.0 C / 298.1 K
Sample #15, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
OTBS
Me
Me
TBSO
O
O
more polar
116
200
180
160
140
120
100
80
60
40
20
0
ppm

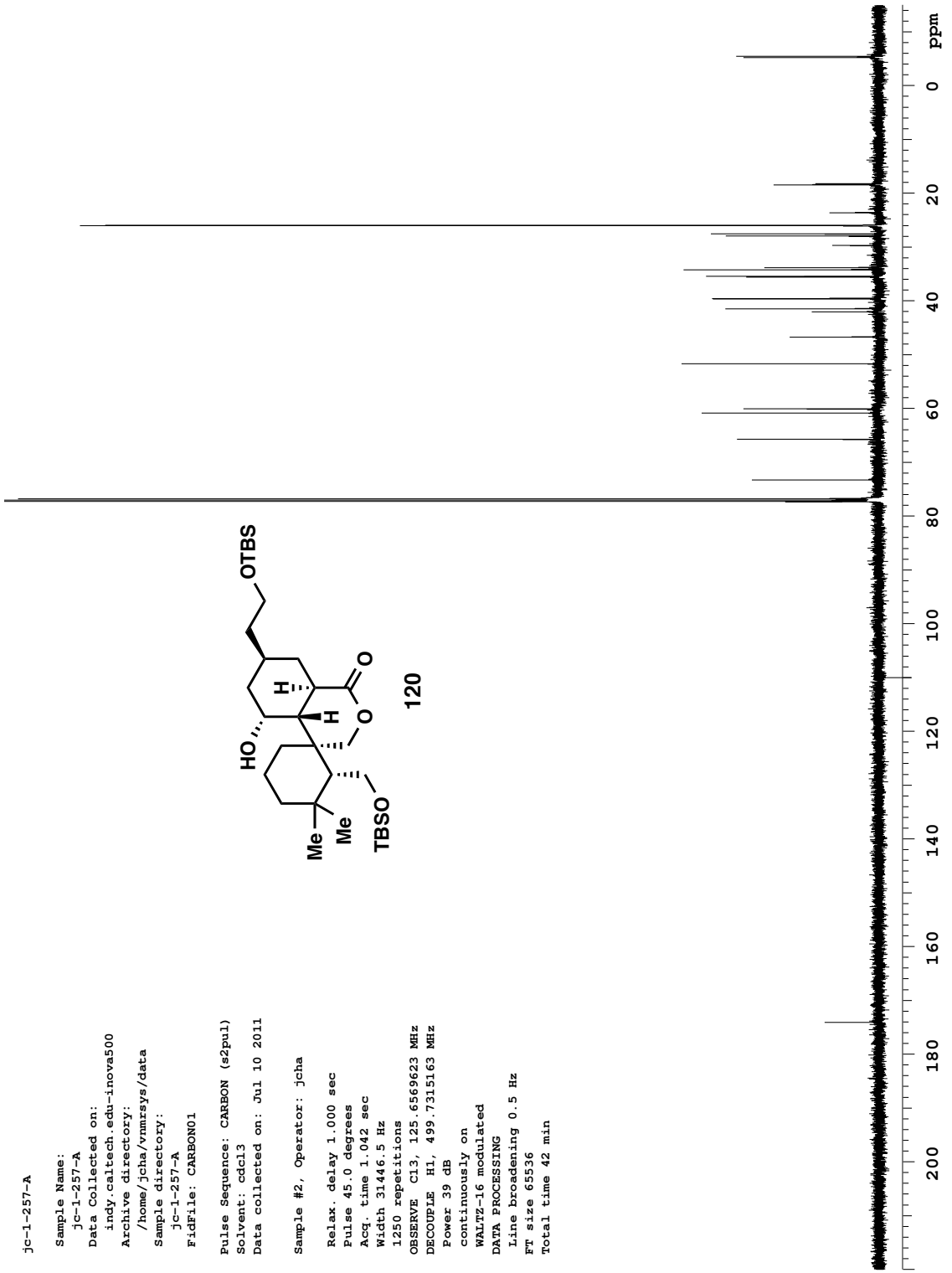

jc-1-254-A
Sample Name:
jc-1-254-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-254-A
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 17 2011
Temp. 25.0 C / 298.1 K
Sample #15, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 45 sec
OTBS
Me
Me
TBSO
O
O
117
ppm
10.45
20.49
3.09
1.08
1.23
3.18
3.96
2.01
2.03
1.97
2.03
1.02
1.05
1.99
1.01
1.02

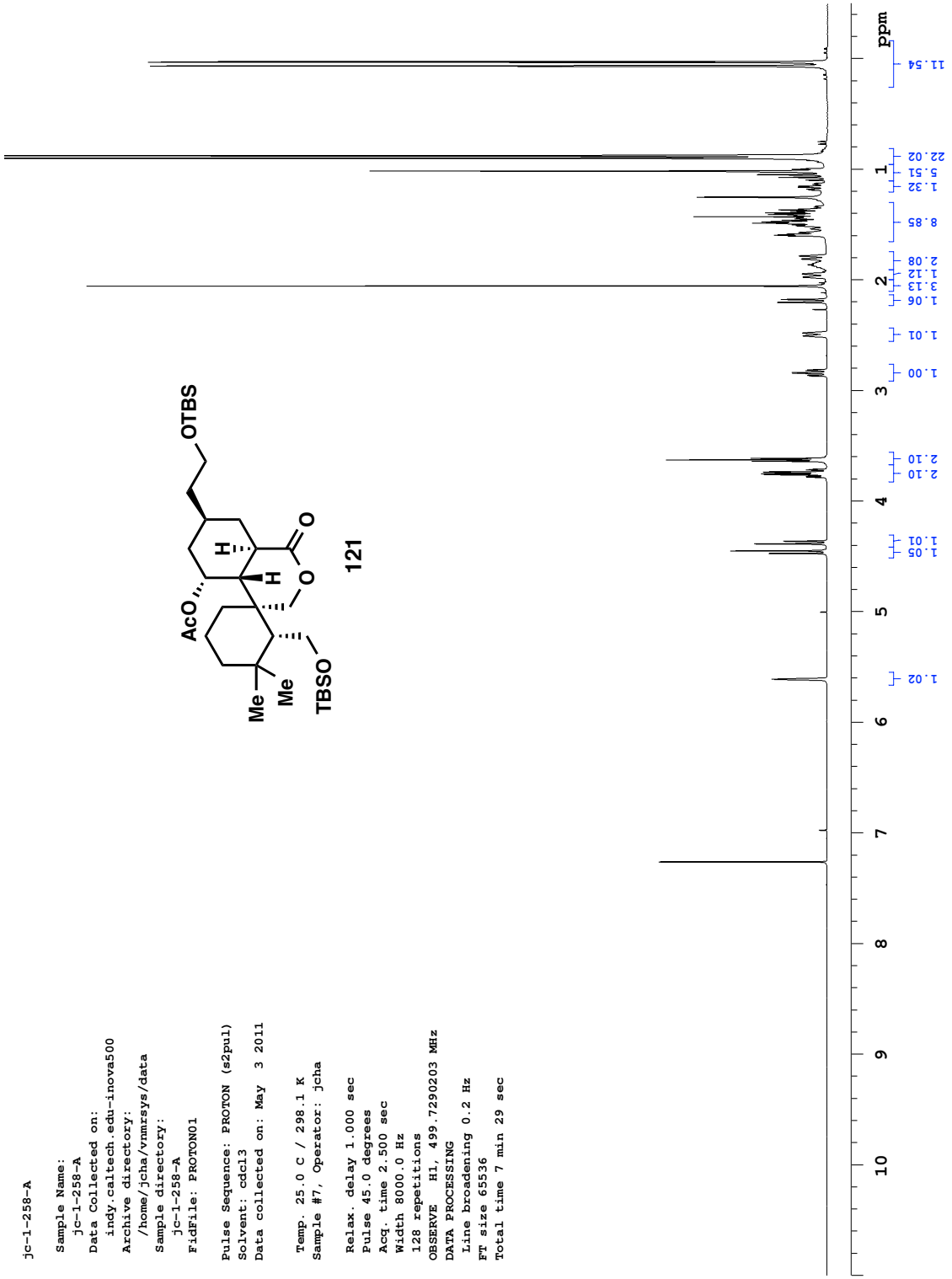

jc-1-254-A
Sample Name:
jc-1-254-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-254-A
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 17 2011
Temp. 25.0 C / 298.1 K
Sample #15, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
OTBS
Me
Me
TBSO
O
O
117
200
180
160
140
120
100
80
60
40
20
0
ppm

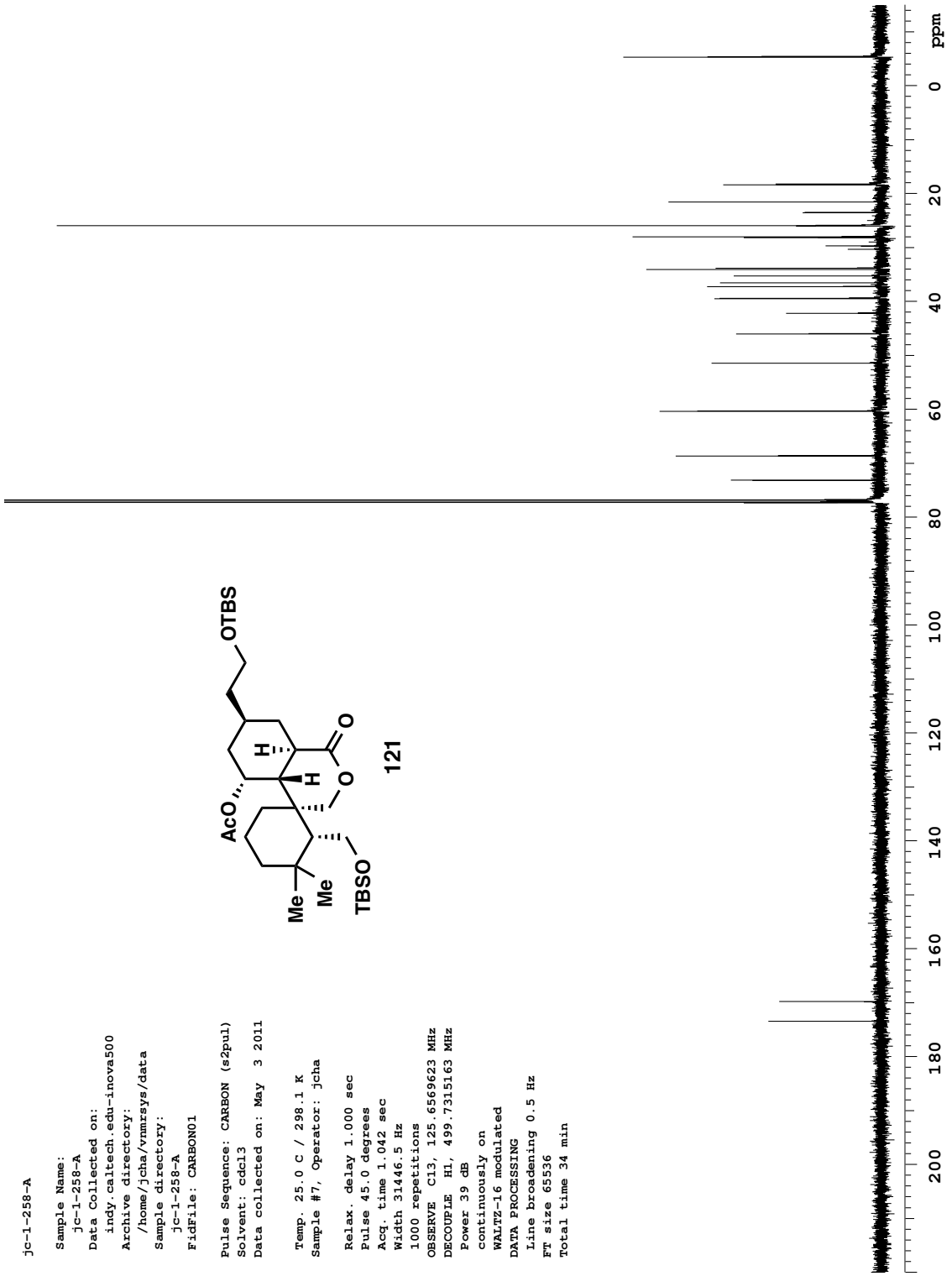

jc-1-256-A
Sample Name:
jc-1-256-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-256-A
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 19 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290208 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 45 sec
OTBS
O
O
O
Me
Me
TBSO
94
ppm
11.03
20.94
3.23
1.38
2.85
7.59
1.03
1.00
3.93
2.02
1.96
0.96
0.98
0.94
0.82

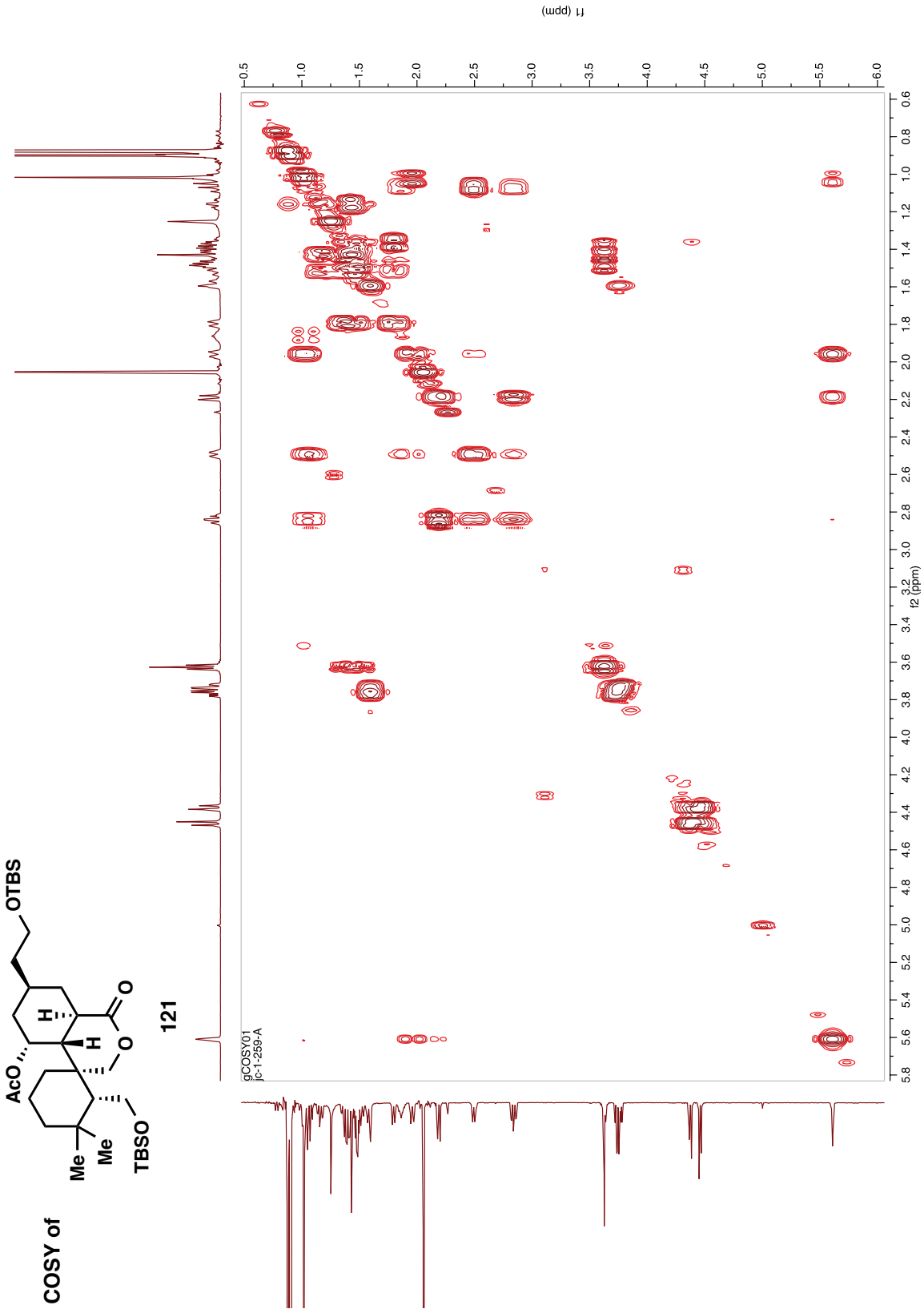

jc-1-256-A
Sample Name:
jc-1-256-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-256-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 19 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
OTBS
O
O
O
Me
Me
TBSO
94
200
180
160
140
120
100
80
60
40
20
0
ppm

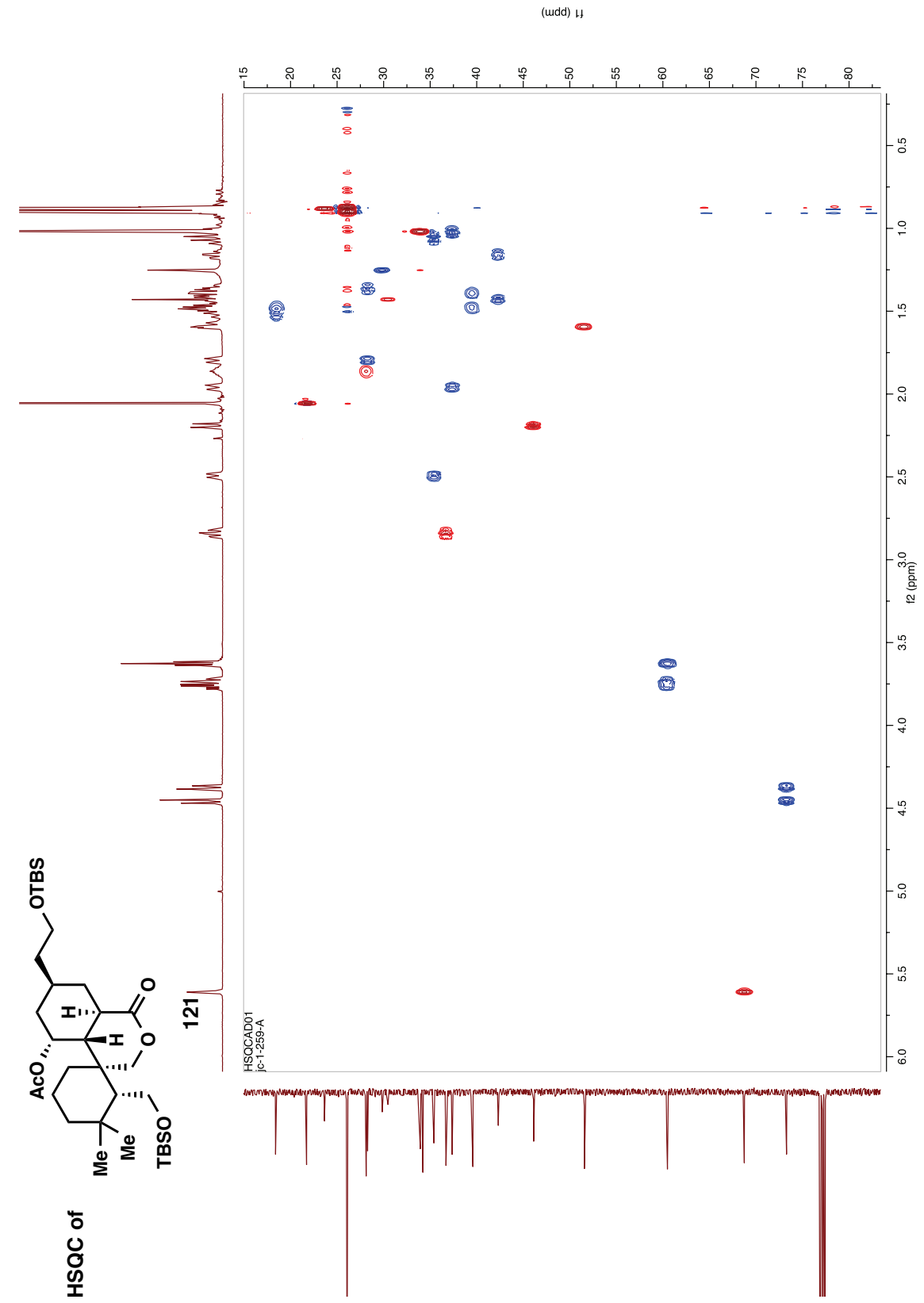

jc-1-257-A
Sample Name:
jc-1-257-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-257-A
FidFile: PROTON04
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 10 2011
Sample #2, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290205 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
OTBS
HO
H
H
O
O
Me
Me
TBSO
120
ppm
13.23
26.14
5.26
2.15
1.97
7.15
1.18
2.19
3.43
1.09
1.00
4.28
1.52
0.99
1.07

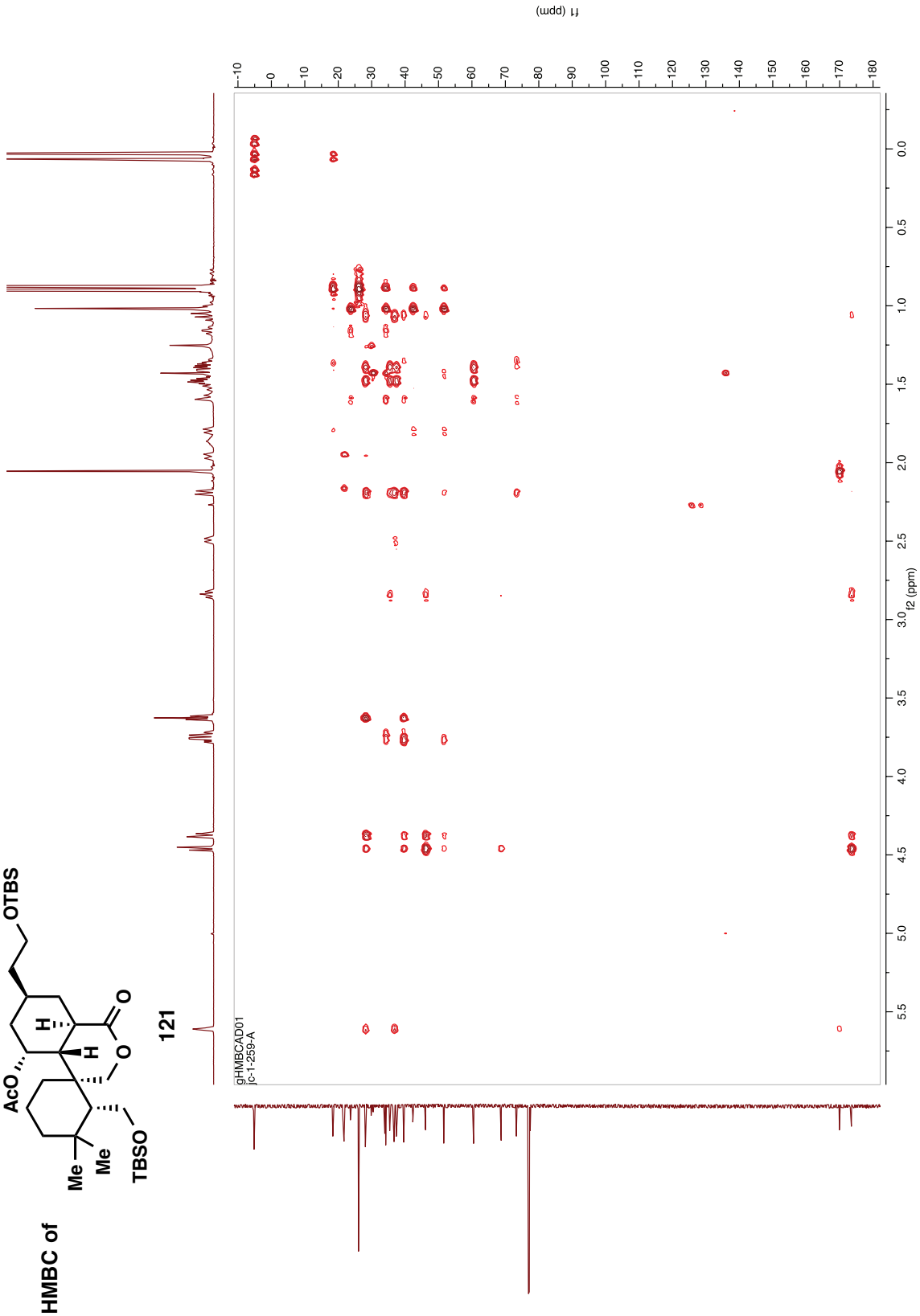

jc-1-257-A
Sample Name:
jc-1-257-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-257-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 10 2011
Sample #2, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1250 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 42 min
OTBS
HO
H
H
O
O
Me
Me
TBSO
120
200
180
160
140
120
100
80
60
40
20
0
ppm

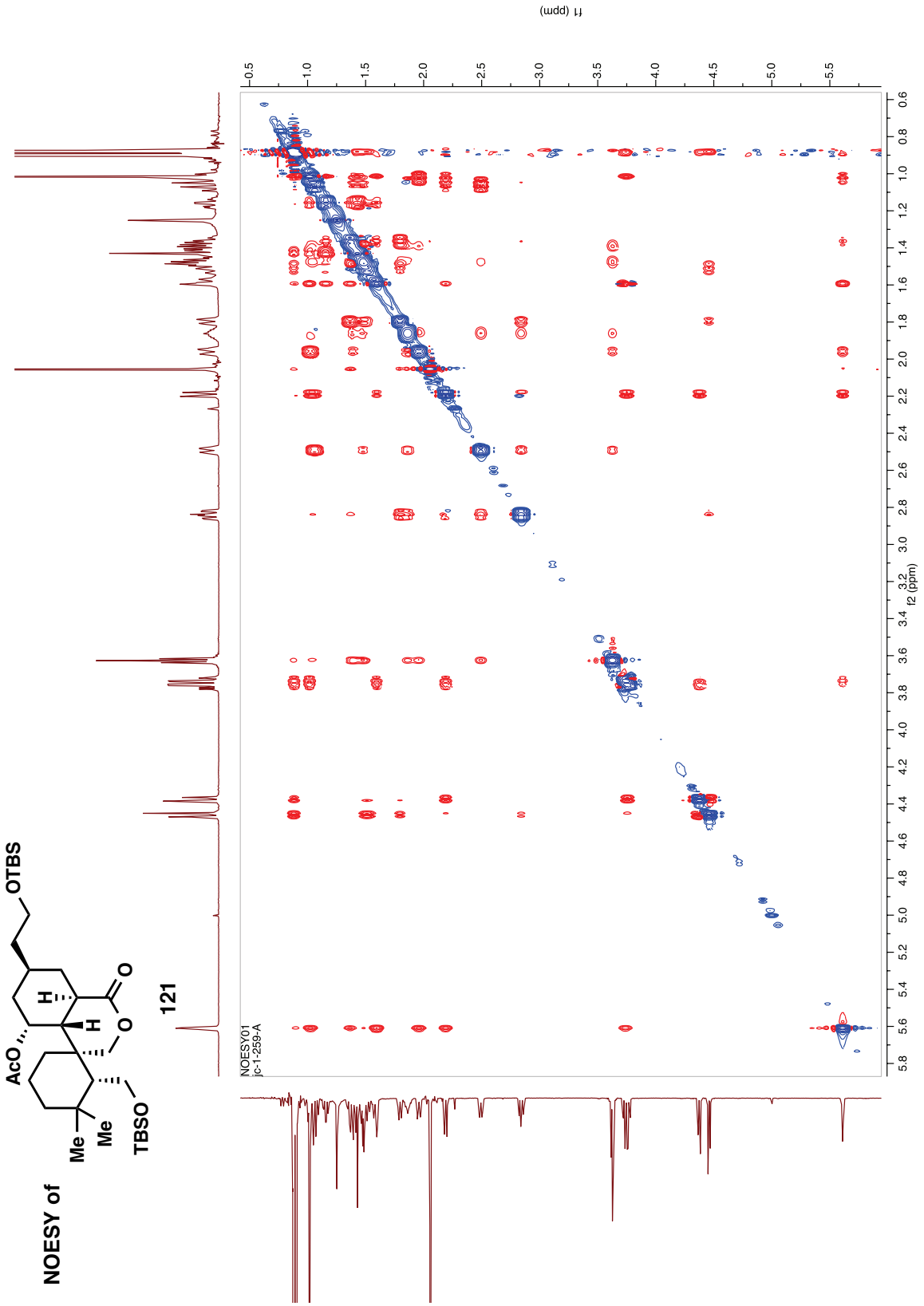

jc-1-258-A
Sample Name:
jc-1-258-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-258-A
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 3 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 7 min 29 sec
OTBS
AcO
H
H
O
O
Me
Me
TBSO
121
ppm
11.54
22.02
5.51
1.32
8.85
2.08
1.12
3.13
1.06
1.01
1.00
2.10
2.10
1.05
1.01
1.02

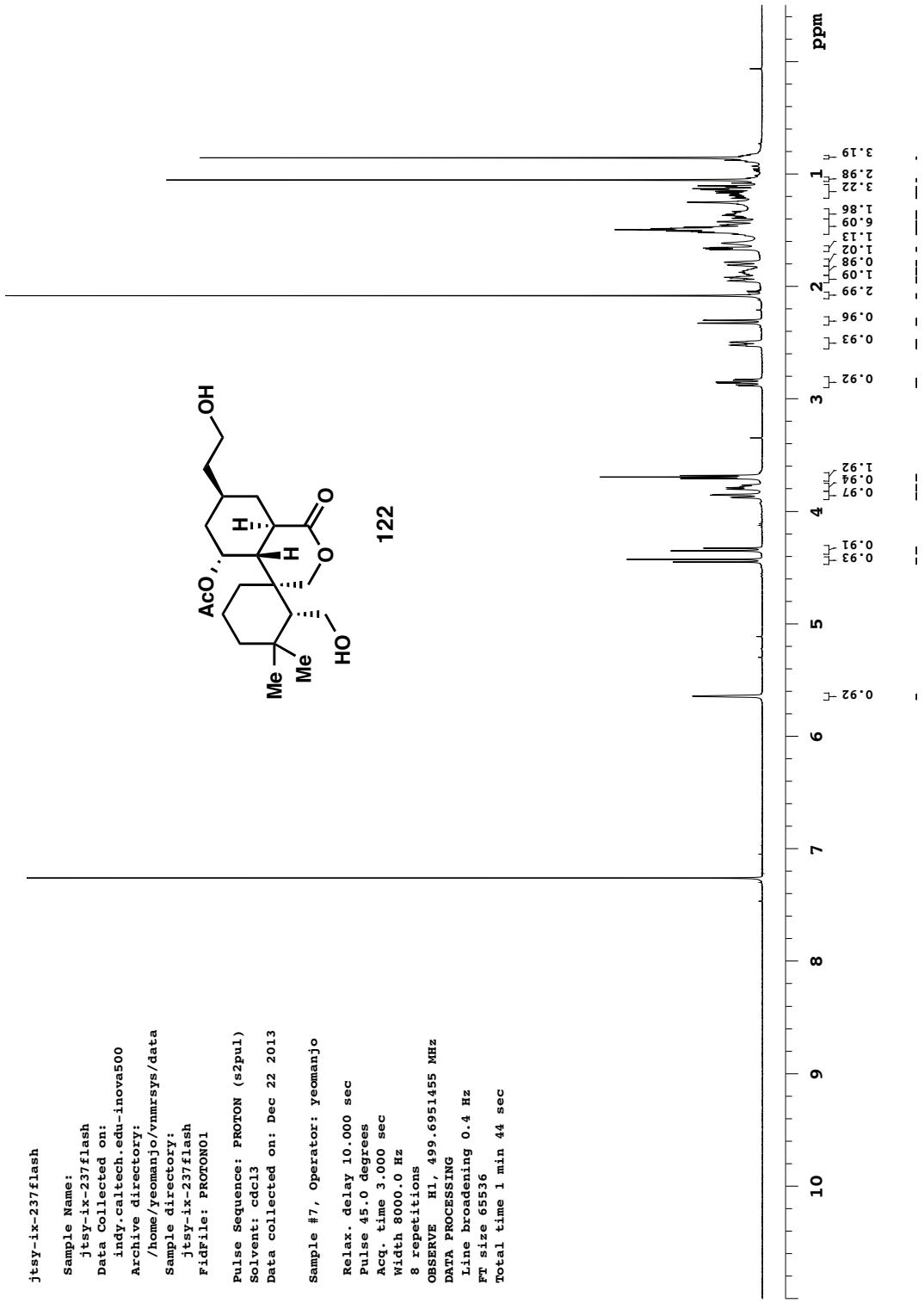

jc-1-258-A
Sample Name:
jc-1-258-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-258-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 3 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
OTBS
AcO
H
H
O
O
Me
Me
TBSO
121
200
180
160
140
120
100
80
60
40
20
0
ppm

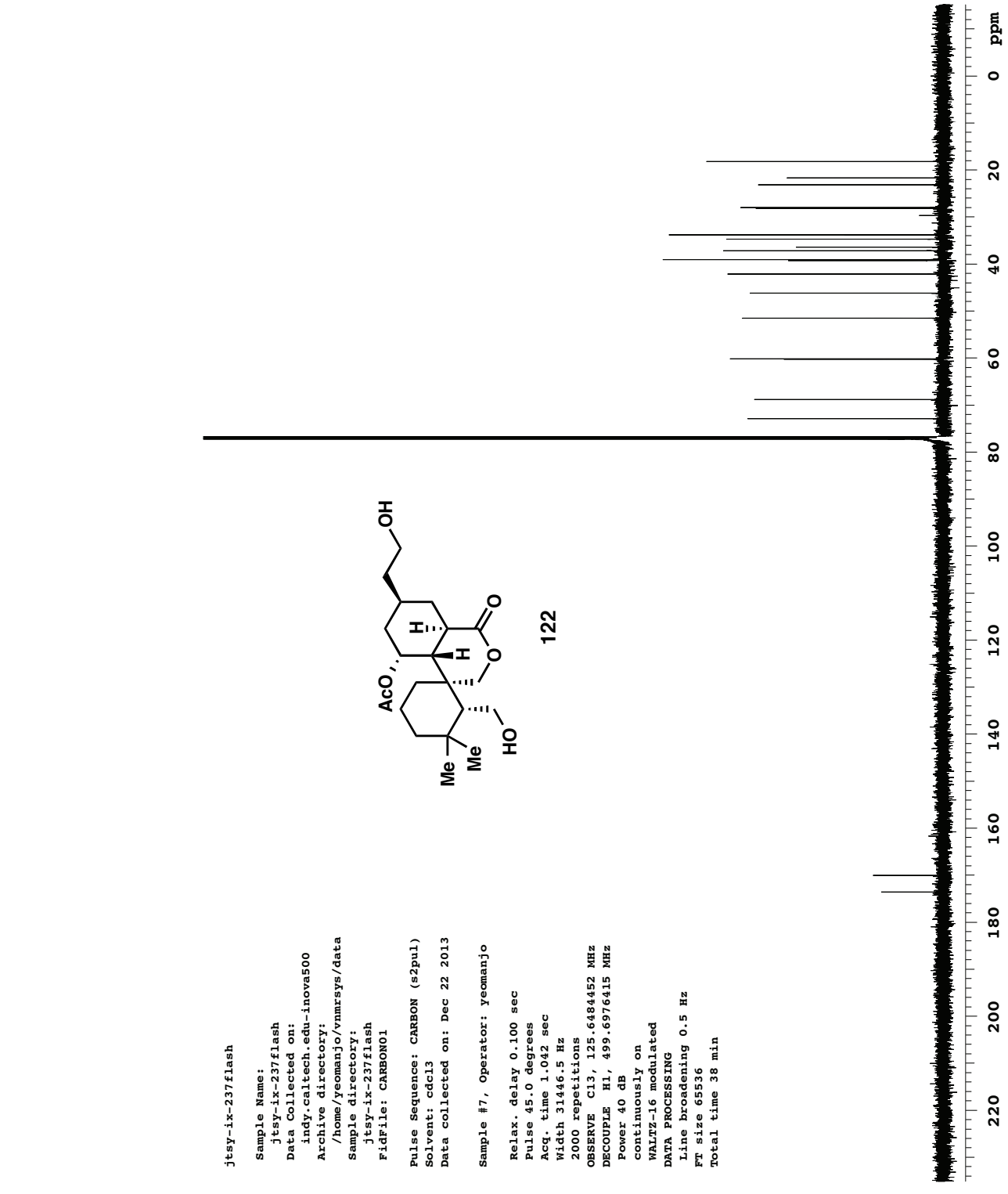

COSY of
121
AcO
OTBS
Me
Me
TBSO
gCOSY01
jc-1-259-A
f1 (ppm)
f2 (ppm)

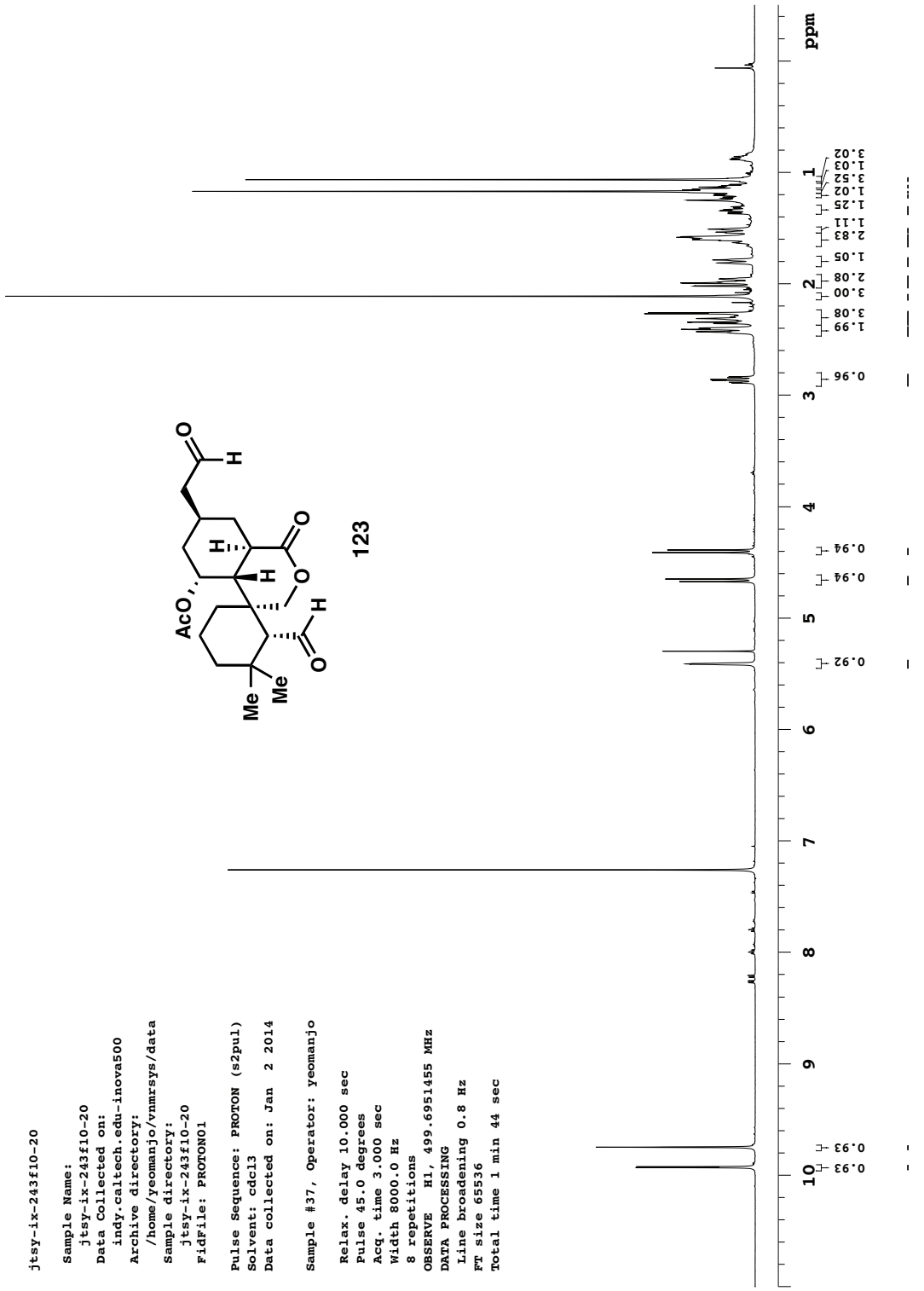

HSQC of
121
AcO
OTBS
H
H
O
O
Me
Me
TBSO
HSQCAD01
jc-1-259-A
f1 (ppm)
f2 (ppm)

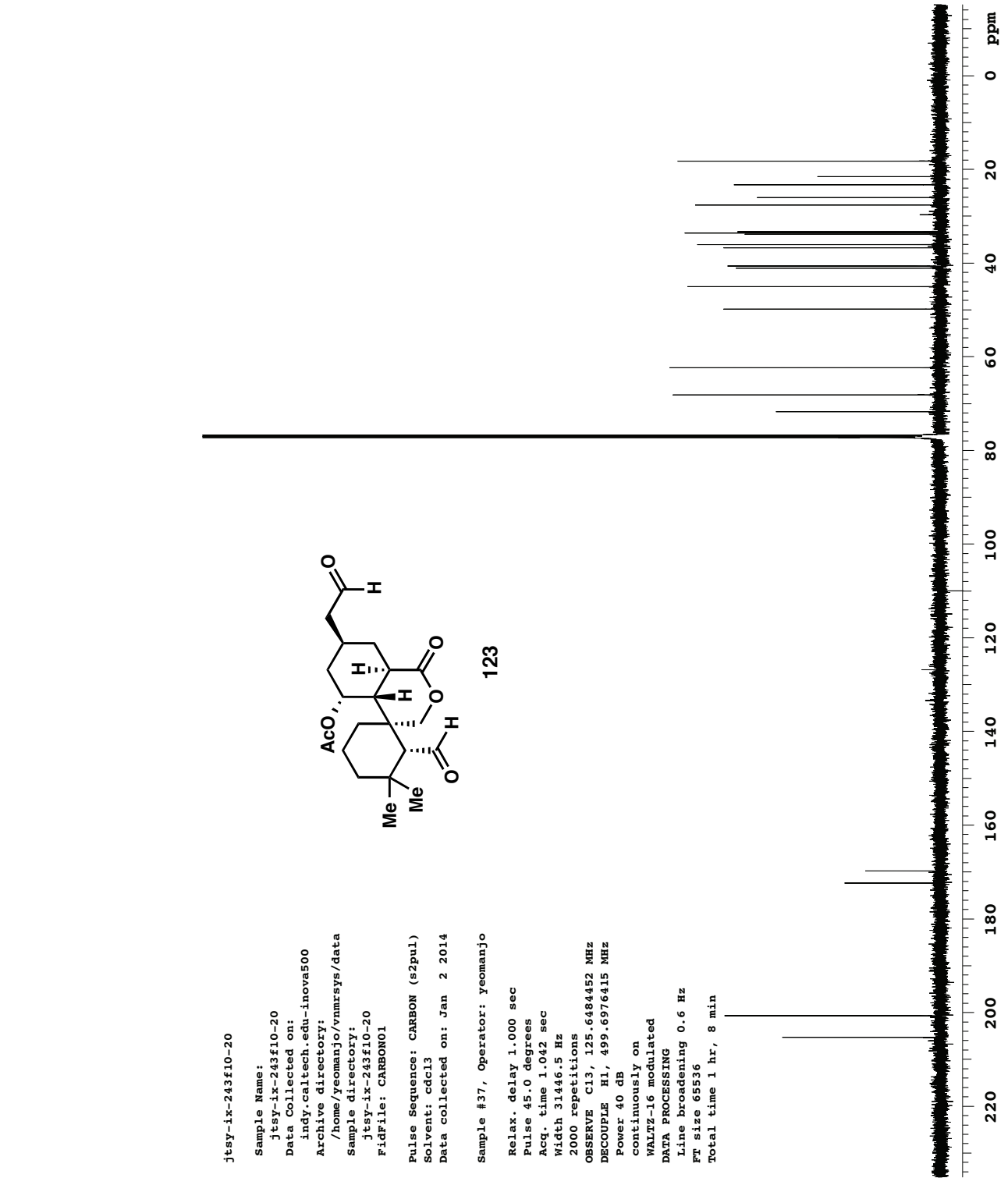

HMBC of
121
AcO
OTBS
Me
Me
TBSO
H
H
O
O
gHMBCAD01
jc-1-259-A
f1 (ppm)
f2 (ppm)

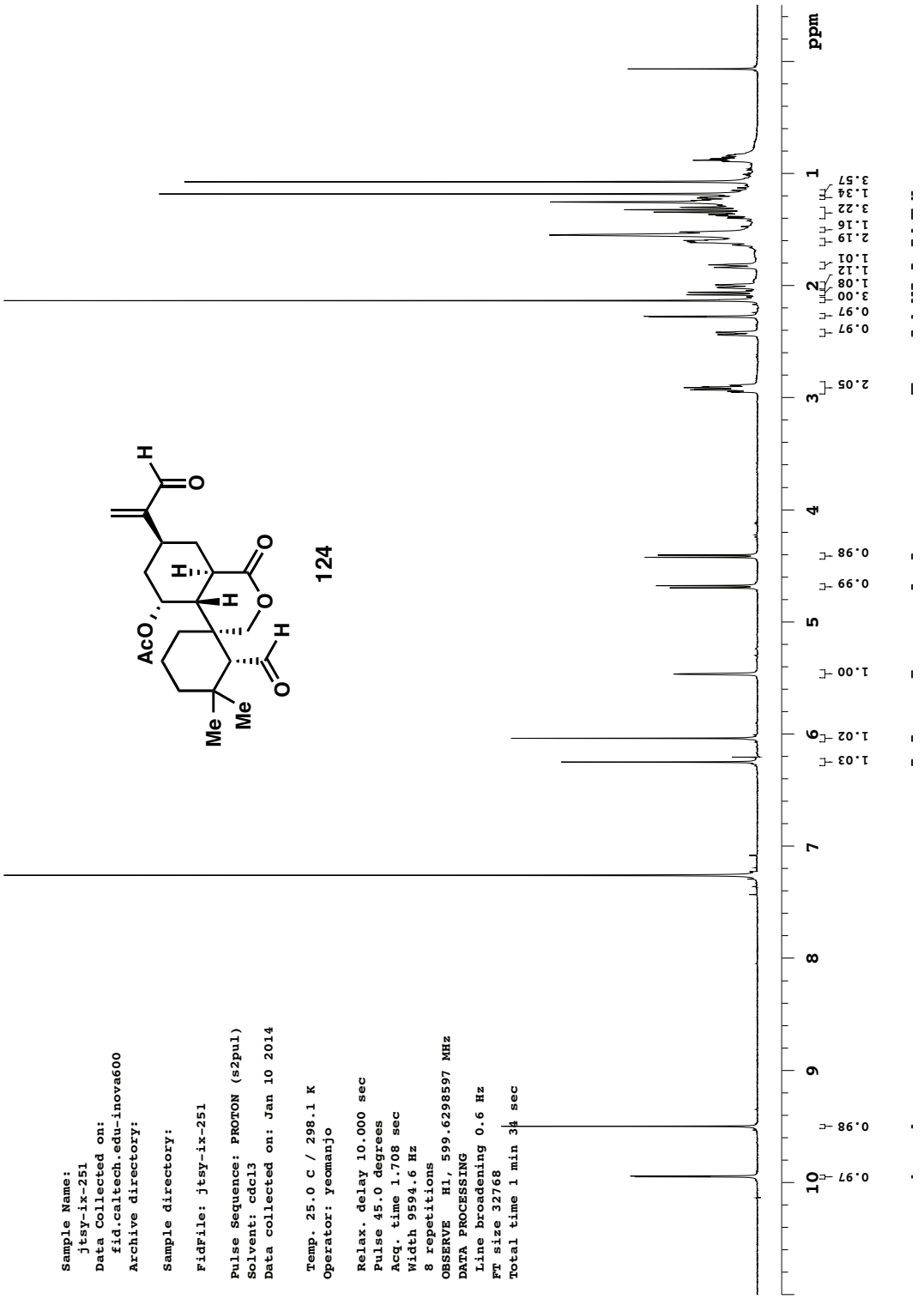

NOESY of
121
AcO
OTBS
Me
Me
TBSO
H
H
O
O
NOESY01
jc-1-259-A
f1 (ppm)
f2 (ppm)

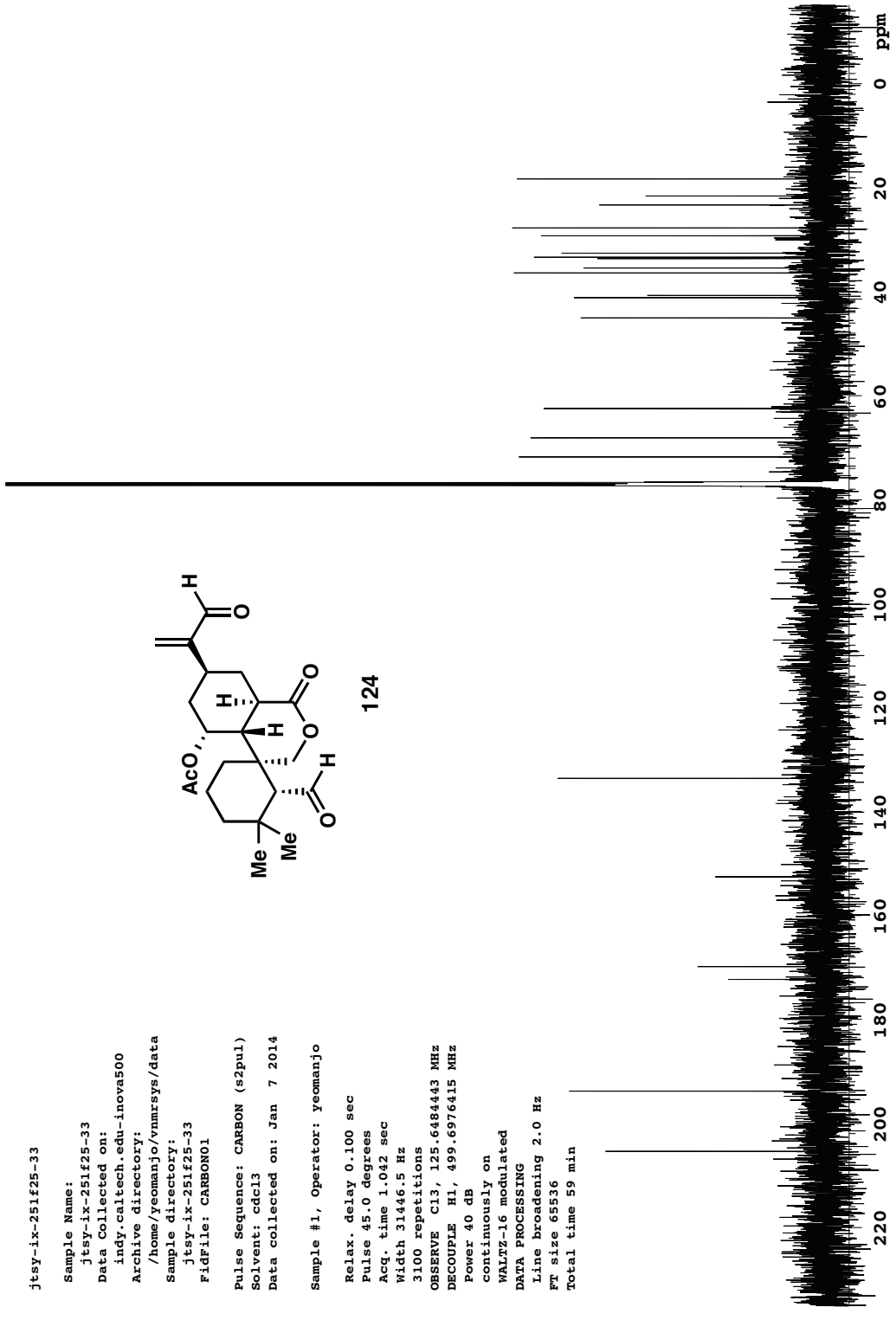

jtsy-ix-237flash
Sample Name:
jtsy-ix-237flash
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-237flash
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 22 2013
Sample #7, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6951455 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 65536
Total time 1 min 44 sec
OH
AcO
H
H
O
O
Me
Me
HO
122
ppm
0.92
0.93
0.91
0.97
0.94
1.92
0.92
0.93
0.96
2.99
1.09
0.98
1.02
1.13
6.09
1.86
3.22
2.98
3.19

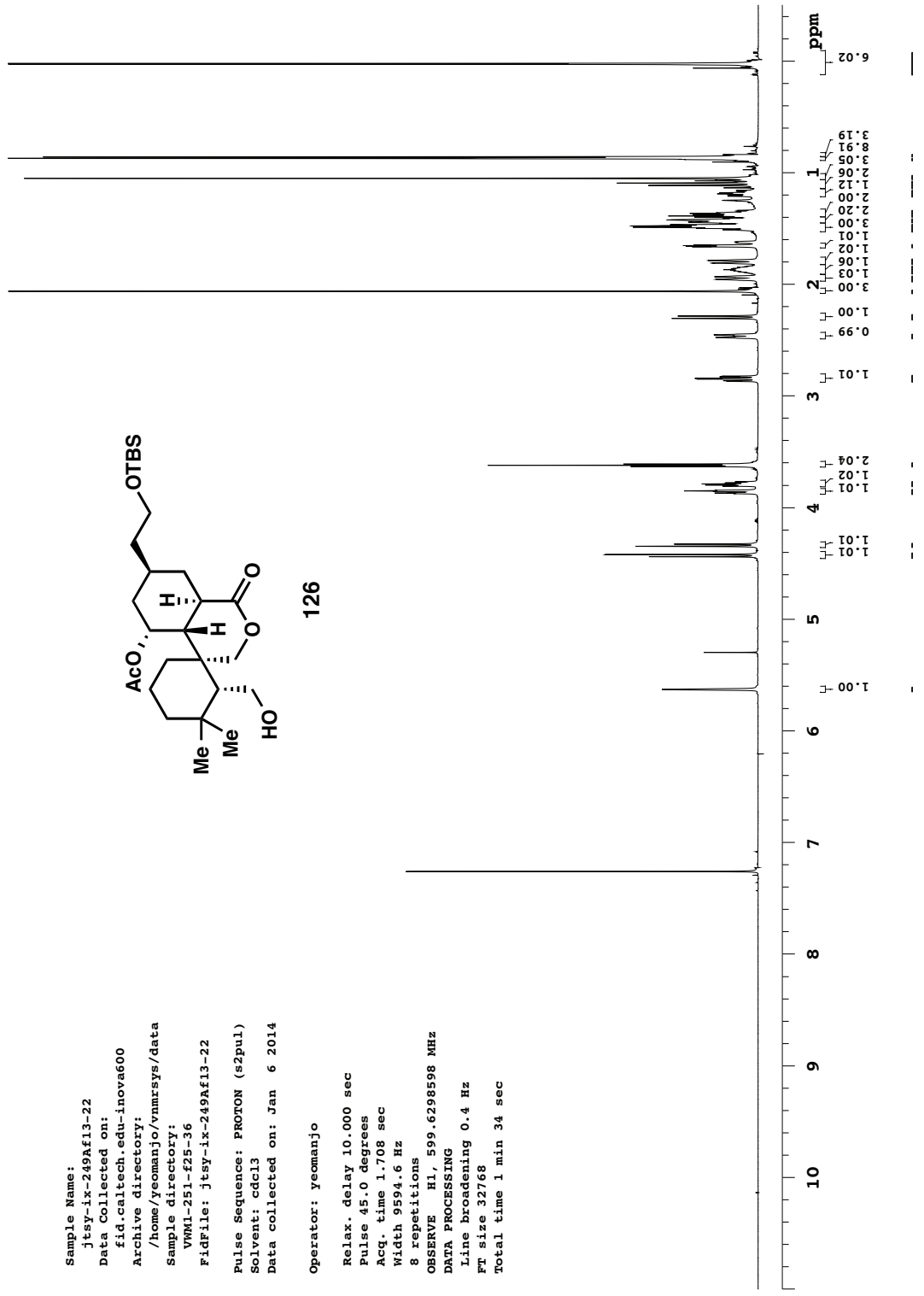

jtsy-ix-237flash
Sample Name:
jtsy-ix-237flash
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-237flash
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 22 2013
Sample #7, Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6484452 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min
OH
AcO
H
H
O
O
Me
Me
HO
122
220
200
180
160
140
120
100
80
60
40
20
0
ppm

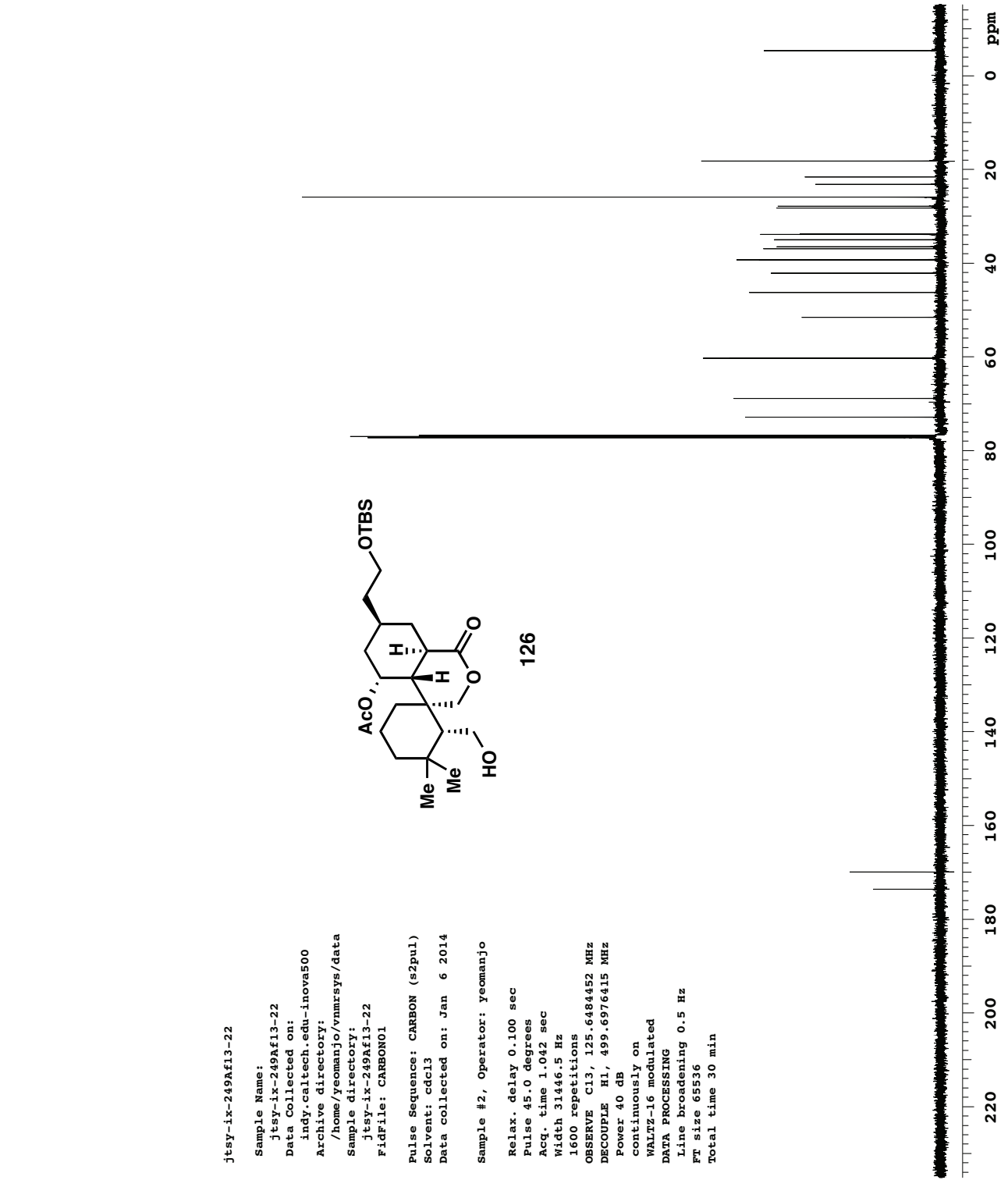

jtsy-ix-243f10-20
Sample Name:
jtsy-ix-243f10-20
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-243f10-20
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 2 2014
Sample #37, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6951455 MHz
DATA PROCESSING
Line broadening 0.8 Hz
FT size 65536
Total time 1 min 44 sec
AcO
Me
Me
123
ppm
0.93
0.93
0.92
0.94
0.94
0.96
1.99
3.08
3.00
2.08
1.05
2.83
1.11
1.25
1.02
3.52
1.03
3.02

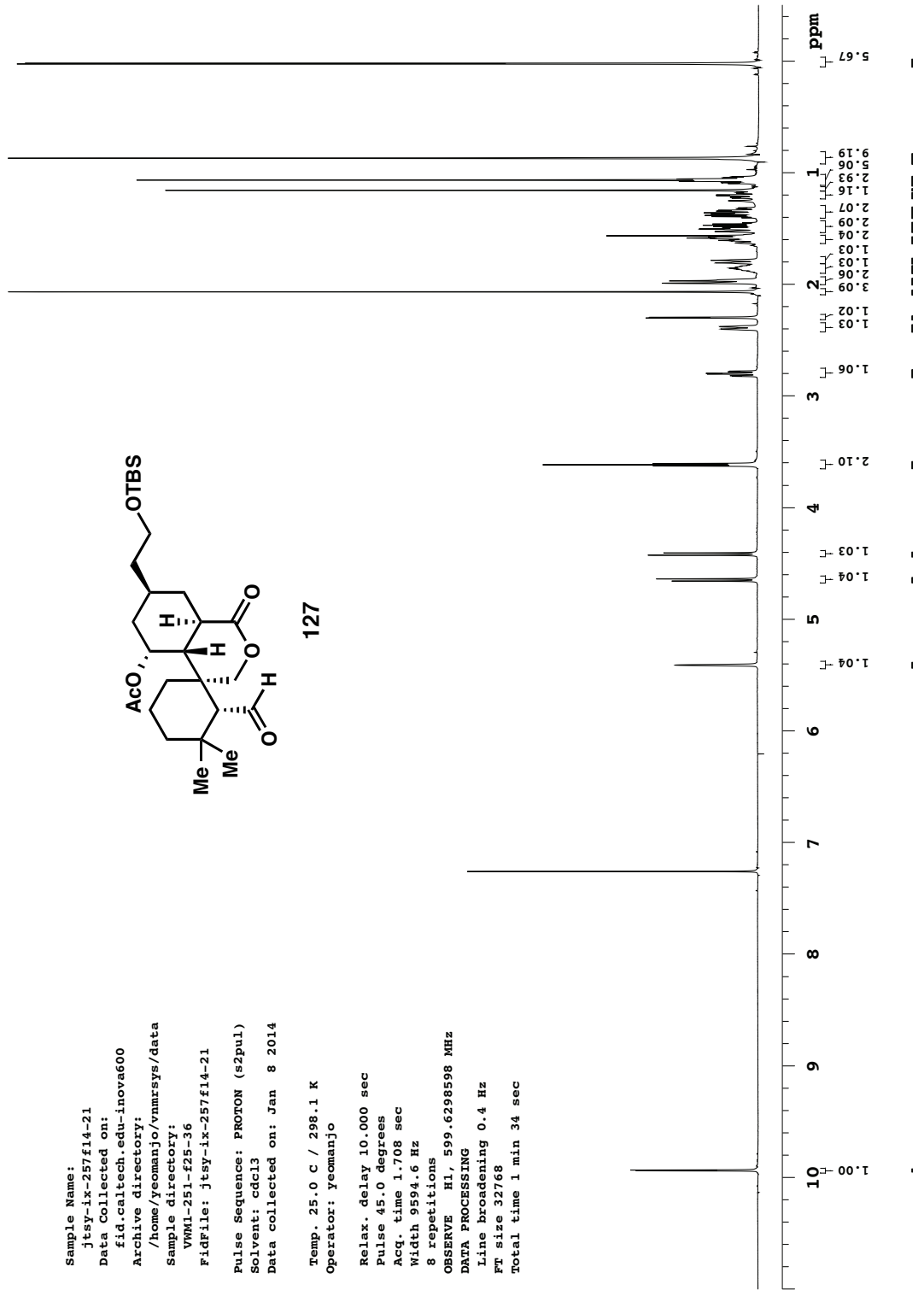

jtsy-ix-243f10-20
Sample Name:
jtsy-ix-243f10-20
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-243f10-20
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 2 2014
Sample #37, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6484452 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.6 Hz
FT size 65536
Total time 1 hr, 8 min
AcO
Me
Me
123
220
200
180
160
140
120
100
80
60
40
20
0
ppm

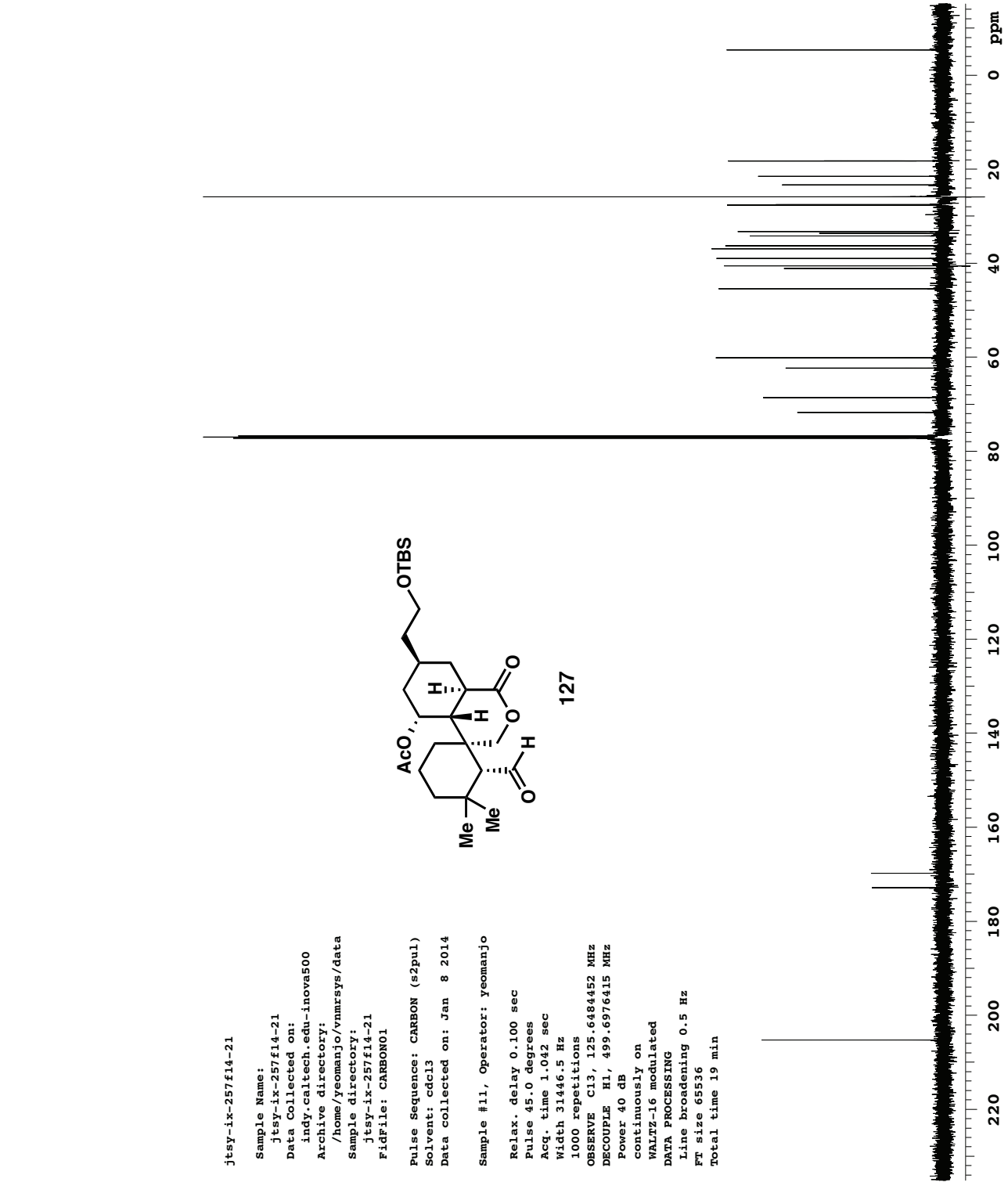

Sample Name:
jtsy-ix-251
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
Sample directory:
FidFile: jtsy-ix-251
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 10 2014
Temp. 25.0 C / 298.1 K
Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.708 sec
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6298597 MHz
DATA PROCESSING
Line broadening 0.6 Hz
FT size 32768
Total time 1 min 34 sec
AcO
Me
Me
124
ppm
0.97
0.98
1.03
1.02
1.00
0.99
0.98
2.05
0.97
3.00
1.08
1.12
1.01
2.19
1.16
3.22
1.34
3.57

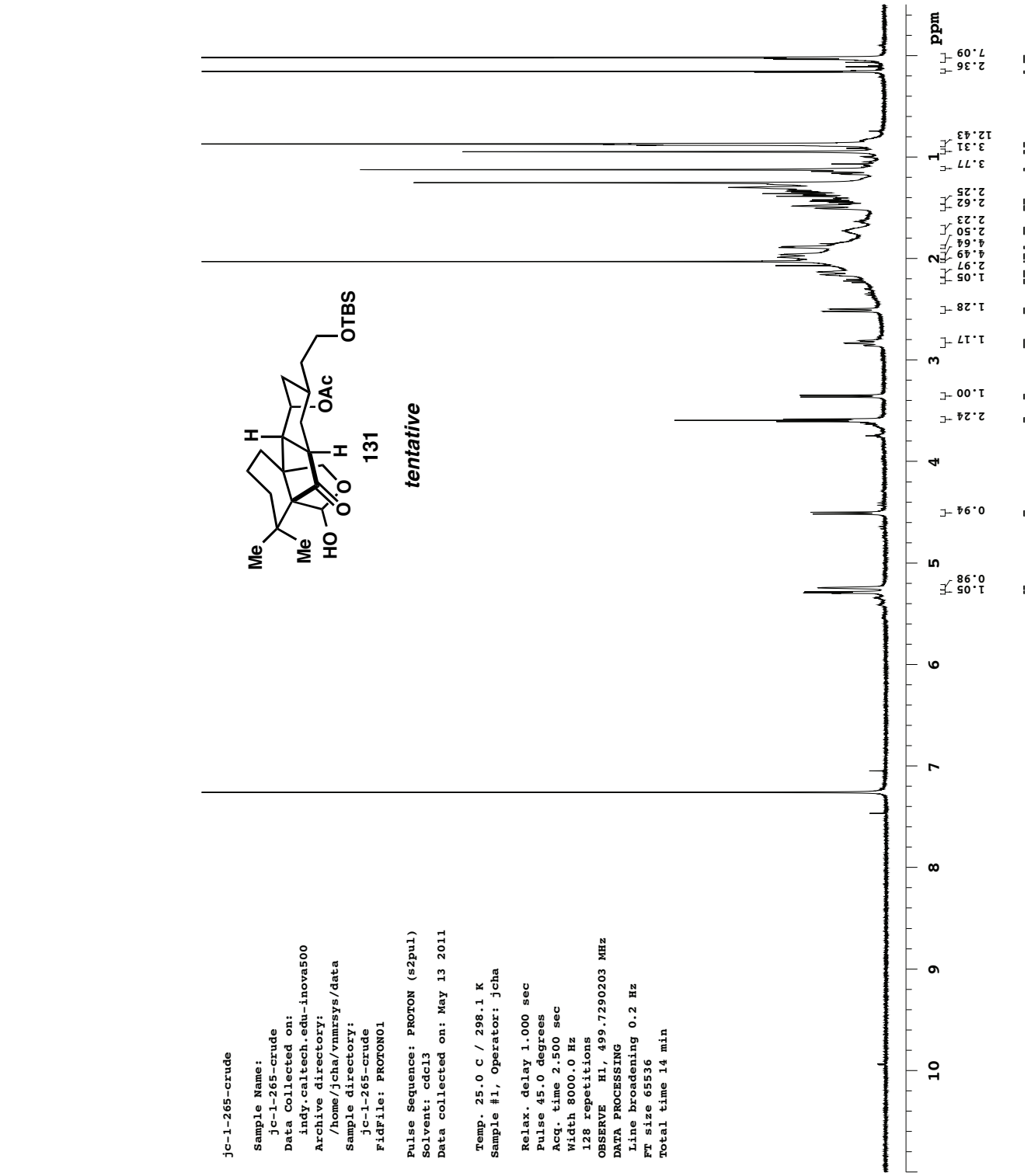

jtsy-ix-251f25-33
Sample Name:
jtsy-ix-251f25-33
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-251f25-33
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 7 2014
Sample #1, Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3100 repetitions
OBSERVE C13, 125.6484443 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 59 min
AcO
Me
Me
124
220
200
180
160
140
120
100
80
60
40
20
0
ppm

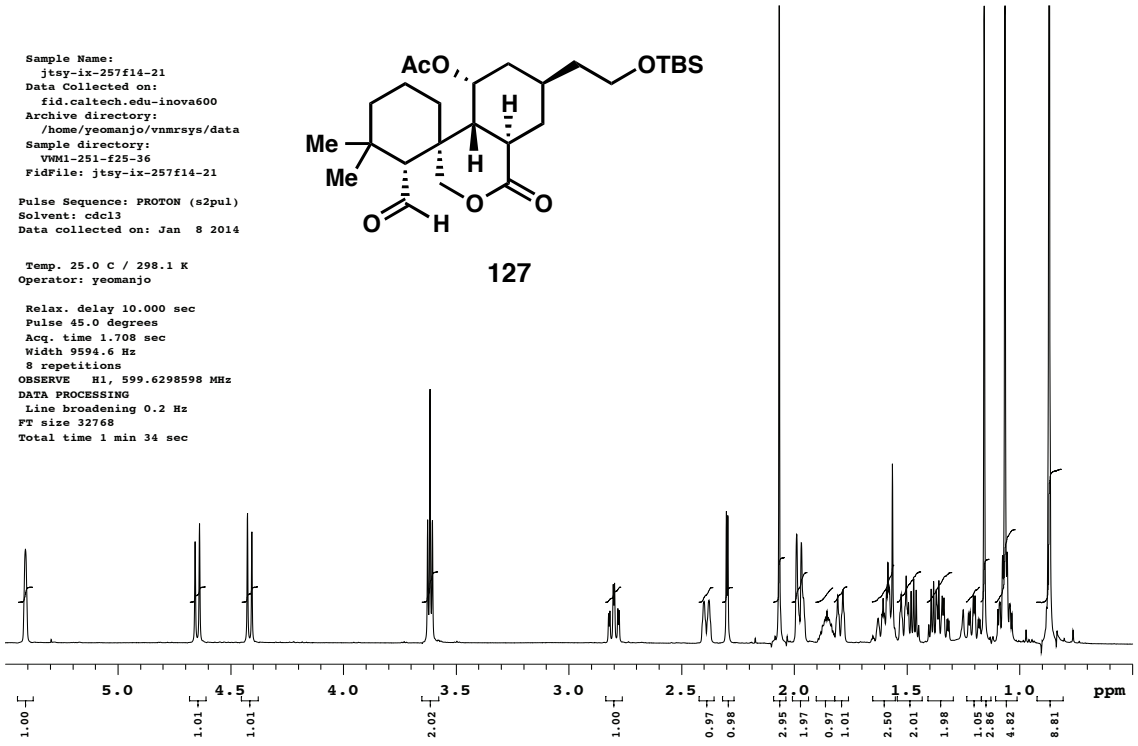

Sample Name:
jtsy-ix-249Af13-22
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
VWM1-251-f25-36
FidFile: jtsy-ix-249Af13-22
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 6 2014
Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.708 sec
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6298598 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
Total time 1 min 34 sec
OTBS
AcO
H
H
O
O
Me
Me
HO
126
ppm
10
9
8
7
6
5
4
3
2
1
1.00
1.01
1.01
1.01
1.02
2.04
1.01
0.99
1.00
3.00
1.03
1.06
1.02
1.01
3.00
2.20
2.00
1.12
2.06
3.05
8.91
3.19
6.02

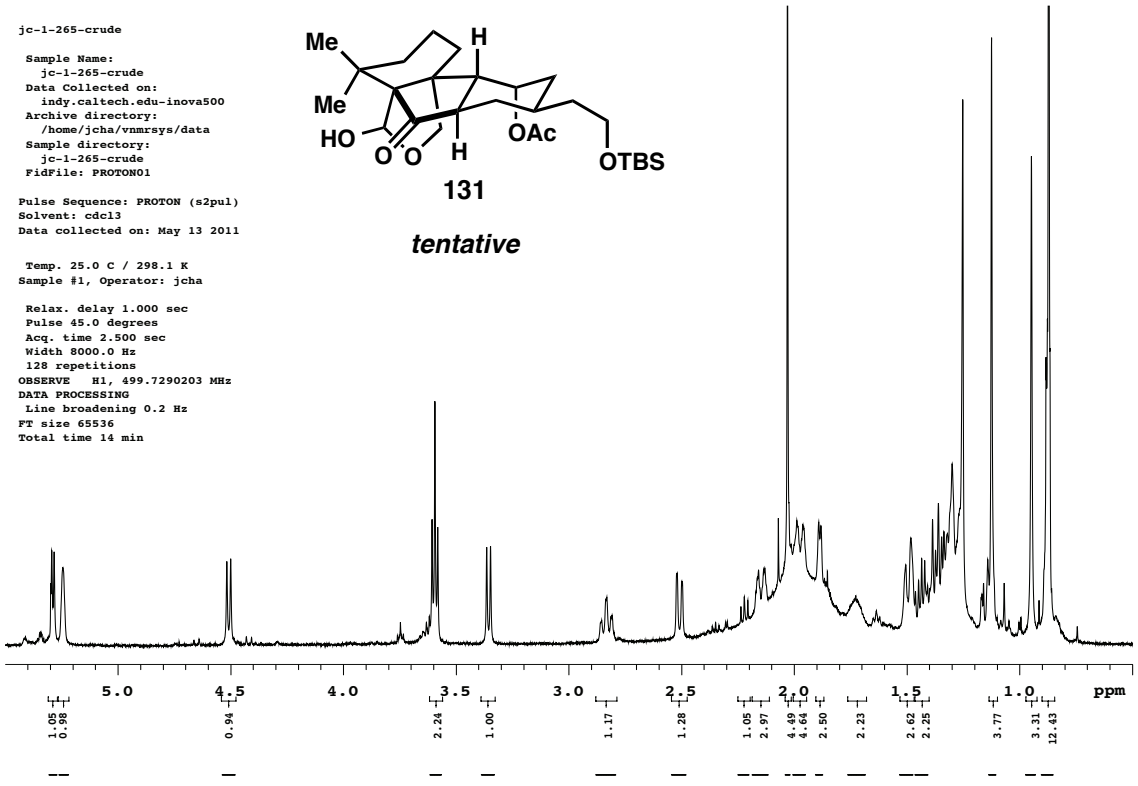

jtsy-ix-249Af13-22
Sample Name:
jtsy-ix-249Af13-22
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-249Af13-22
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 6 2014
Sample #2, Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6484452 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min
OTBS
AcO
H
H
O
O
Me
Me
HO
126
220
200
180
160
140
120
100
80
60
40
20
0
ppm

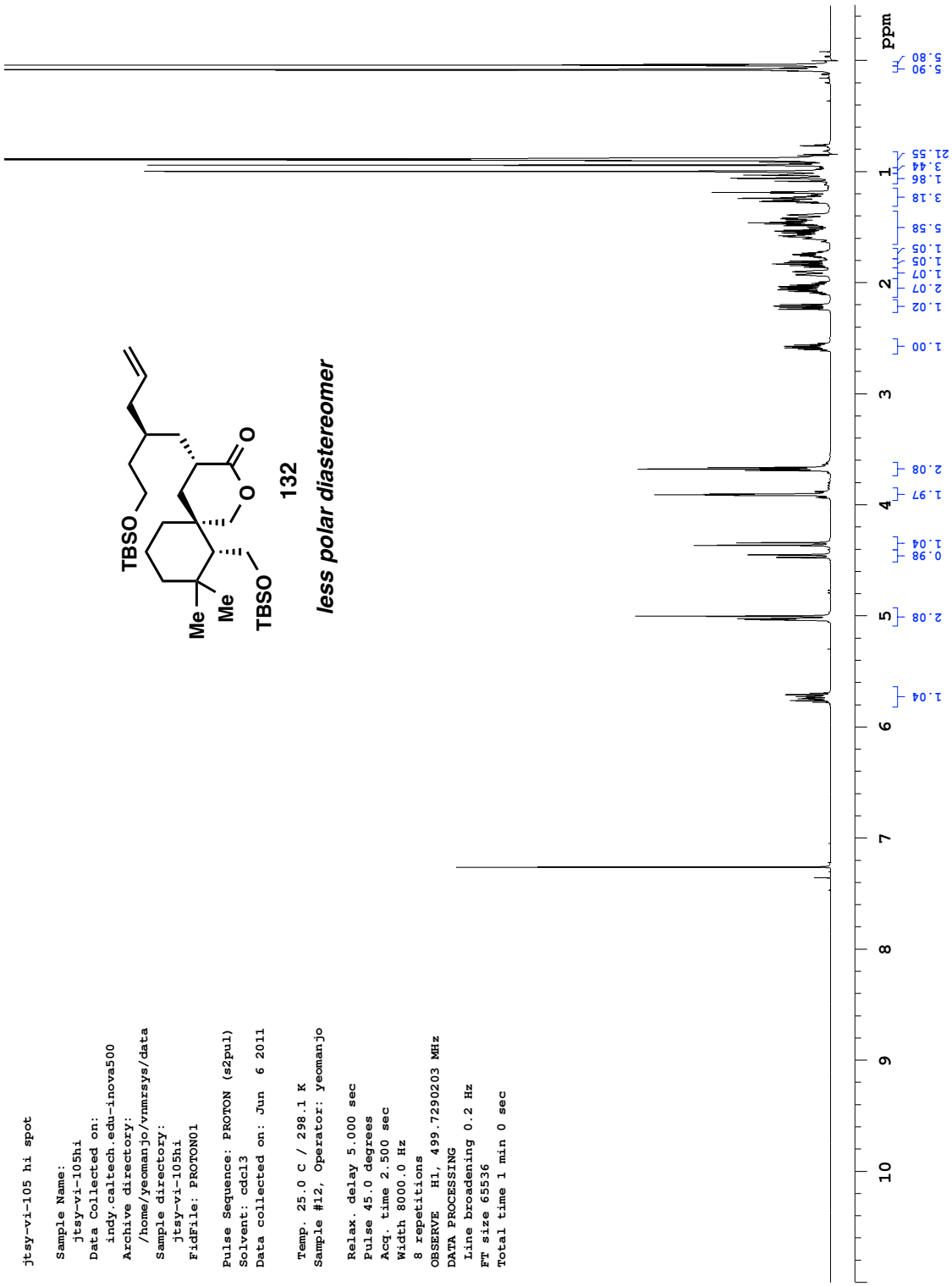

Sample Name:
jtsy-ix-257f14-21
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
VWM1-251-f25-36
FidFile: jtsy-ix-257f14-21
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 8 2014
Temp. 25.0 C / 298.1 K
Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.708 sec
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6298598 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
Total time 1 min 34 sec
OTBS
AcO
H
H
O
O
O
H
Me
Me
127
ppm
10
9
8
7
6
5
4
3
2
1
1.00
1.04
1.03
1.04
2.10
1.06
1.03
1.02
3.09
2.06
1.03
1.03
2.04
2.09
2.07
1.16
2.93
5.06
9.19
5.67

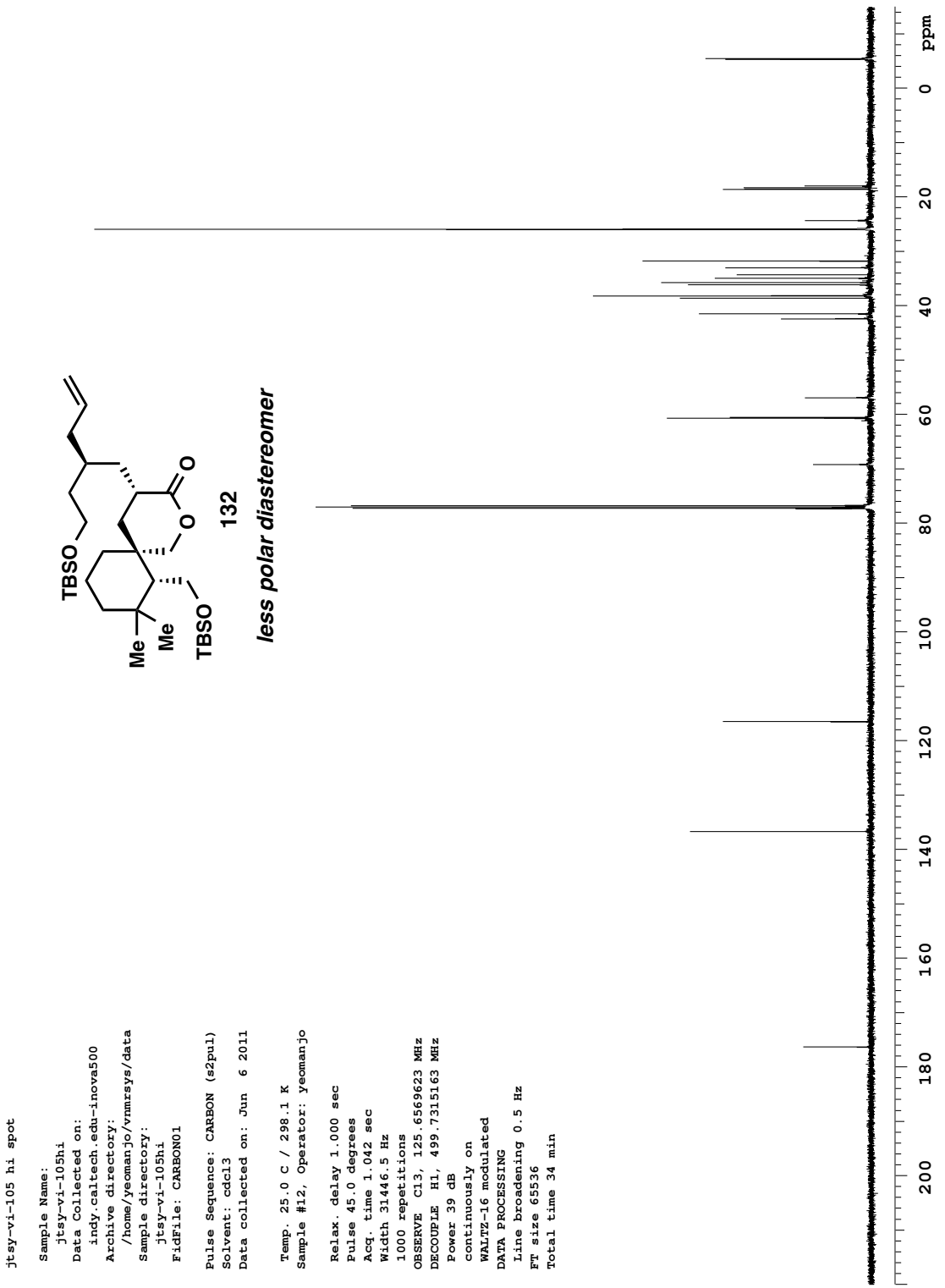

jtsy-ix-257f14-21
Sample Name:
jtsy-ix-257f14-21
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-257f14-21
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 8 2014
Sample #11, Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6484452 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min
AcO
OTBS
H
H
H
O
O
O
O
Me
Me
127
220
200
180
160
140
120
100
80
60
40
20
0
ppm

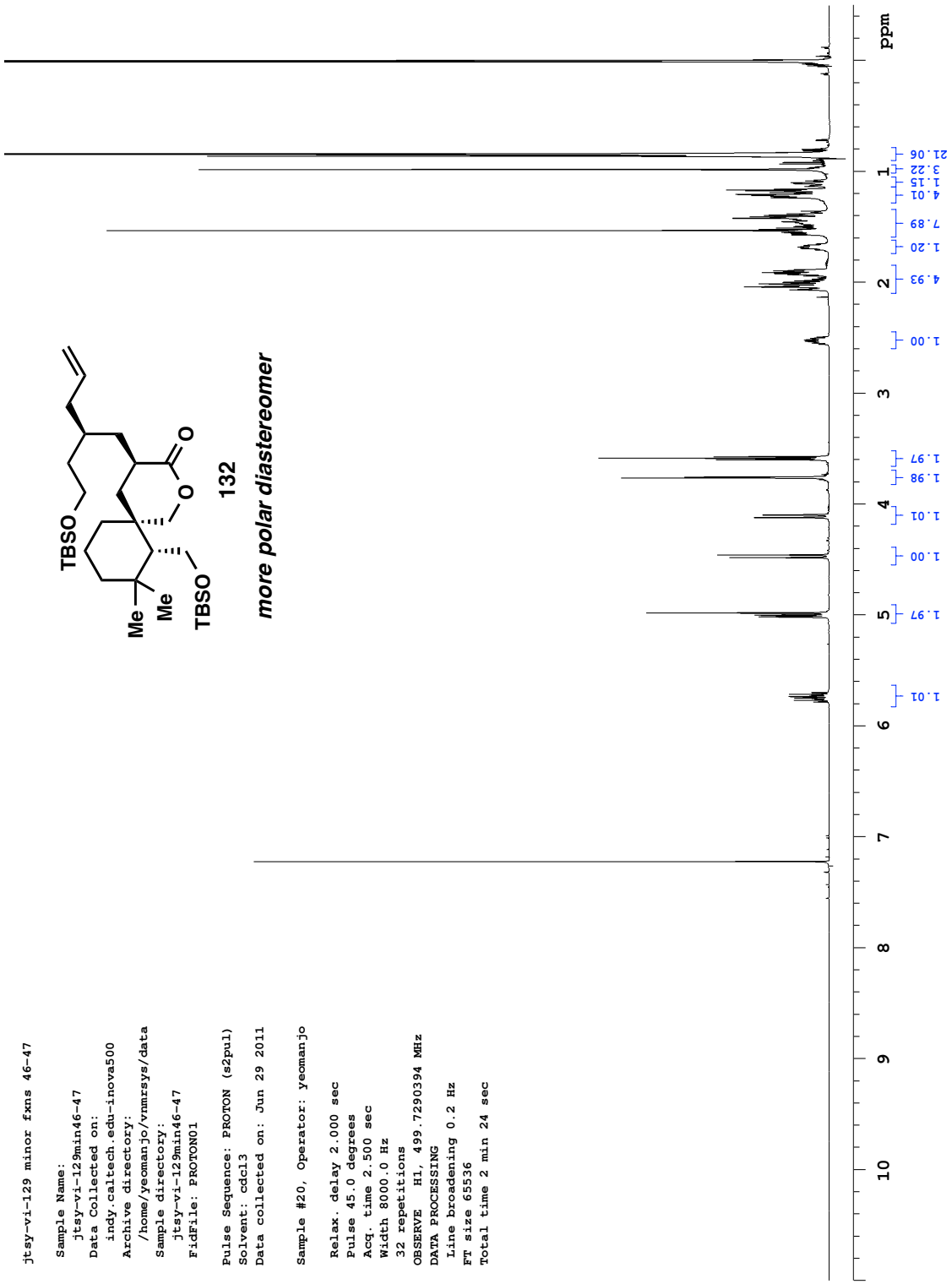

jc-1-265-crude
Sample Name:
jc-1-265-crude
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-265-crude
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 13 2011
Temp. 25.0 C / 298.1 K
Sample #1, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 14 min
Me
Me
HO
H
OAc
OTBS
131
tentative
ppm
7.09
2.36
12.43
3.31
3.77
2.25
2.62
2.23
2.50
4.64
4.49
2.97
1.05
1.28
1.17
1.00
2.24
0.94
0.98
1.05

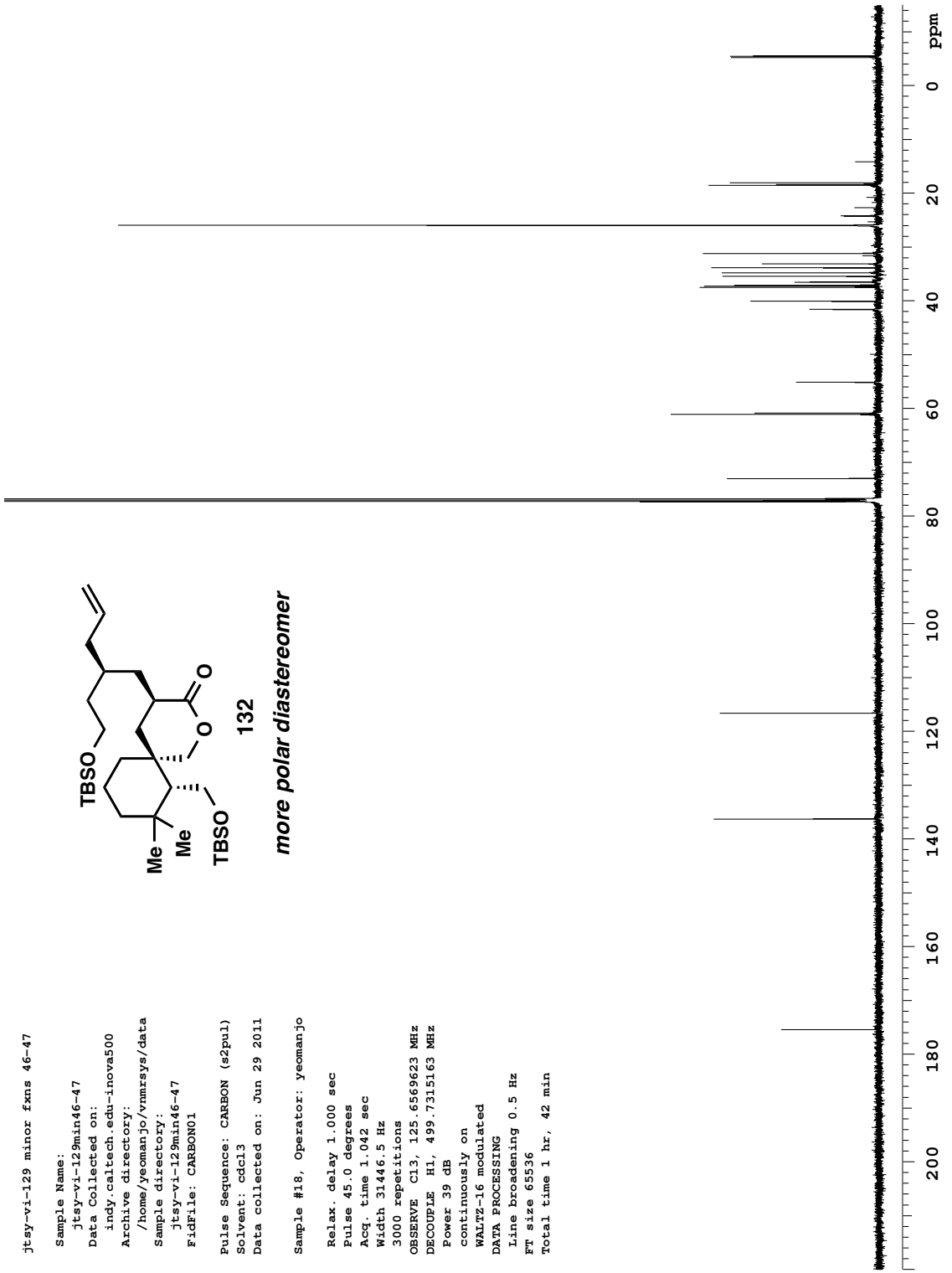

Sample Name:
jtsy-ix-257f14-21
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
VWM1-251-f25-36
FidFile: jtsy-ix-257f14-21
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 8 2014
Temp. 25.0 C / 298.1 K
Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.708 sec
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6298598 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 min 34 sec
AcO
OTBS
H
Me
Me
H
O
O
O
H
127
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.01
1.01
2.02
1.00
0.97
0.98
2.95
1.97
0.97
1.01
2.50
2.01
1.98
1.05
2.86
4.82
8.81

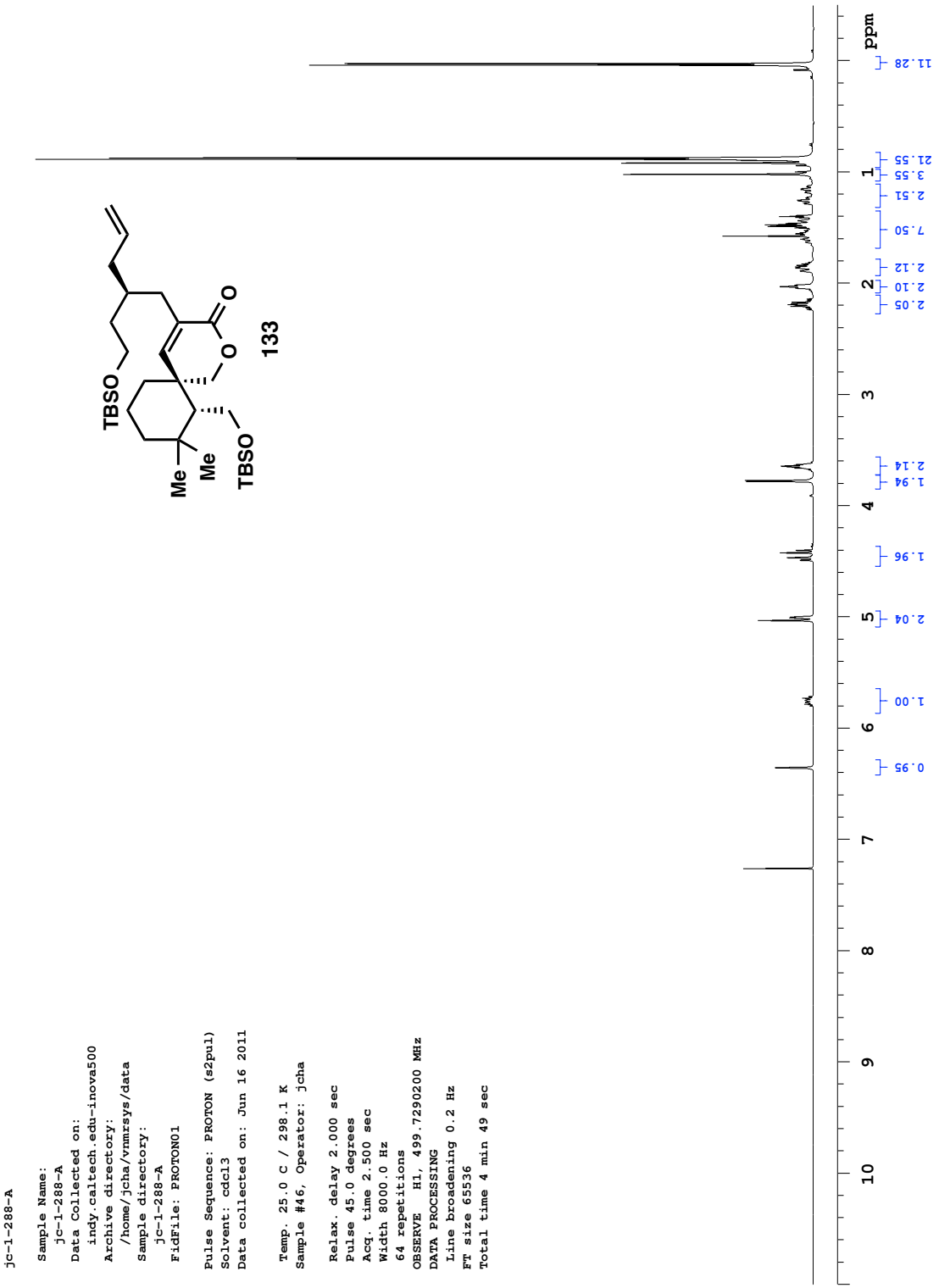

jc-1-265-crude
Sample Name:
jc-1-265-crude
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-265-crude
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 13 2011
Temp. 25.0 C / 298.1 K
Sample #1, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 14 min
Me
H
Me
HO
O
O
H
OAc
OTBS
131
tentative
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.05
0.98
0.94
2.24
1.00
1.17
1.28
1.05
2.97
4.49
4.64
2.50
2.23
2.62
2.25
3.77
3.31
12.43

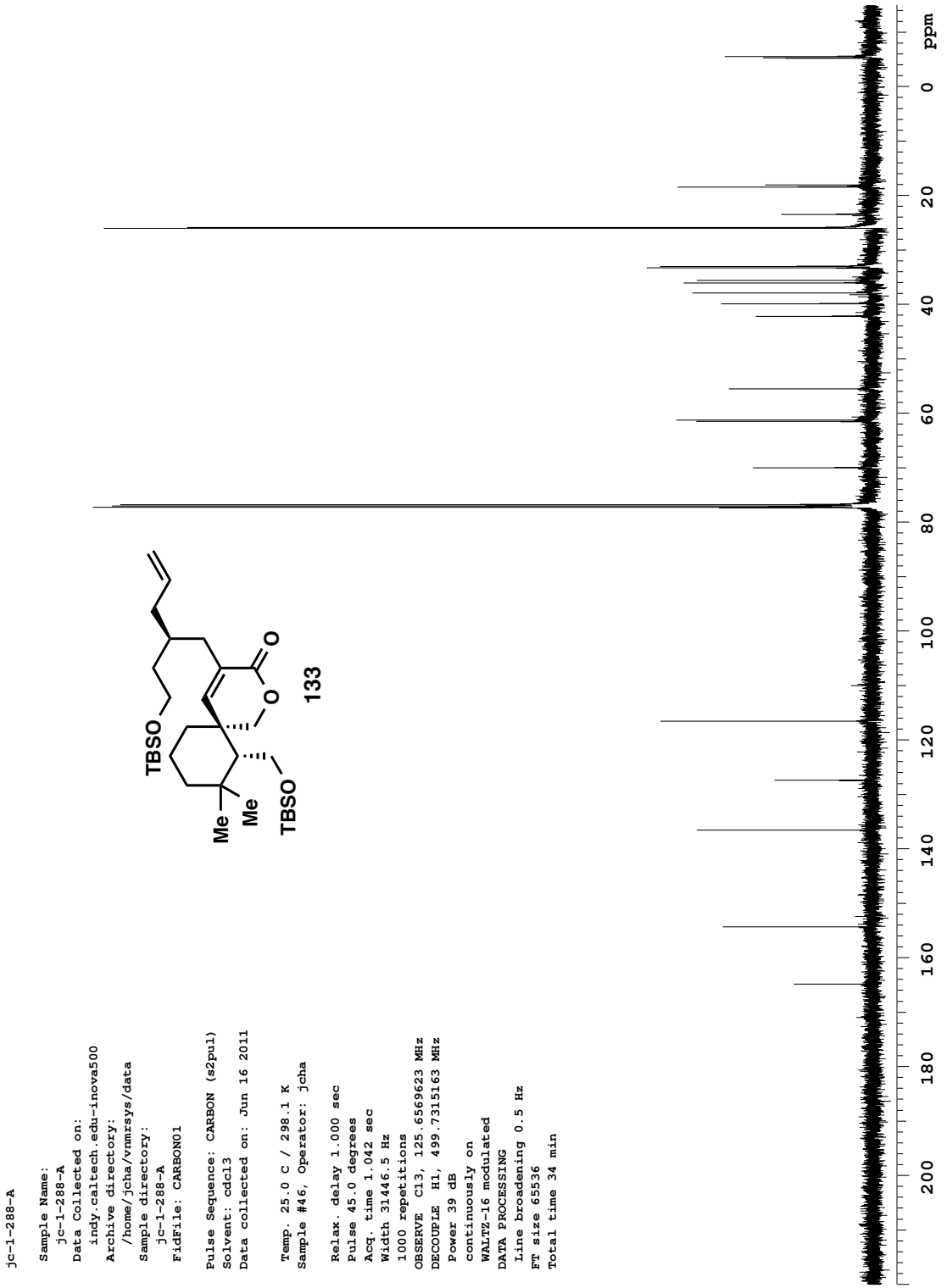

jtsy-vi-105 hi spot
Sample Name:
jtsy-vi-105hi
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vi-105hi
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 6 2011
Temp. 25.0 C / 298.1 K
Sample #12, Operator: yeomanjo
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
TBSO
Me
Me
TBSO
O
O
O
132
less polar diastereomer
ppm
10
9
8
7
6
5
4
3
2
1
5.90
5.80
21.55
3.44
1.86
3.18
5.58
1.05
1.05
1.07
2.07
1.02
1.00
2.08
1.97
0.98
1.04
2.08
1.04

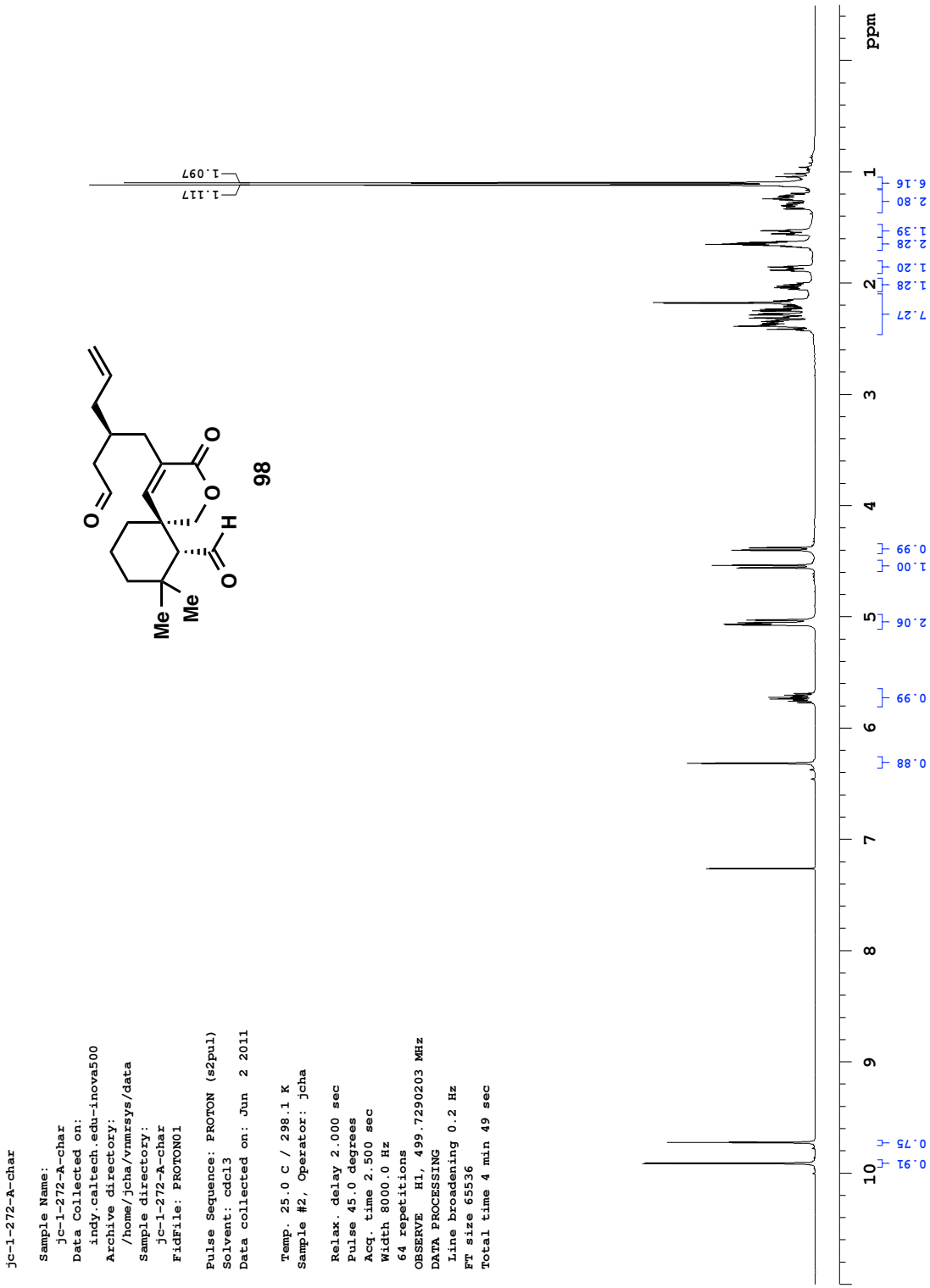

jtsy-vi-105 hi spot
Sample Name:
jtsy-vi-105hi
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vi-105hi
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 6 2011
Temp. 25.0 C / 298.1 K
Sample #12, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
TBSO
Me
Me
TBSO
O
O
132
less polar diastereomer
200
180
160
140
120
100
80
60
40
20
0
ppm

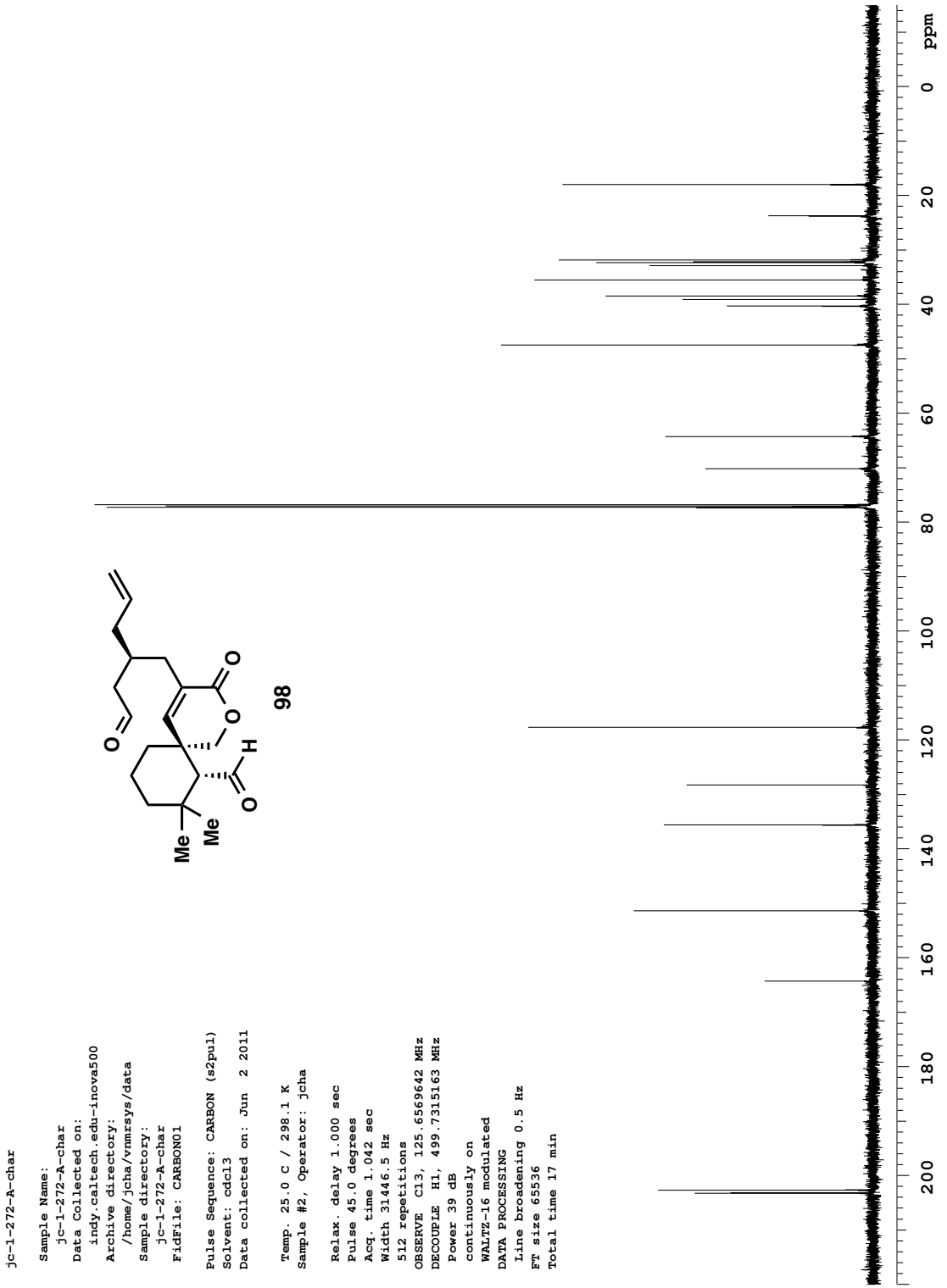

jtsy-vi-129 minor fxns 46-47
Sample Name:
jtsy-vi-129min46-47
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vi-129min46-47
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 29 2011
Sample #20, Operator: yeomanjo
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290394 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
TBSO
Me
Me
TBSO
O
O
132
more polar diastereomer
ppm
1.01
1.97
1.00
1.01
1.98
1.97
1.00
4.93
1.20
7.89
4.01
1.15
3.22
21.06

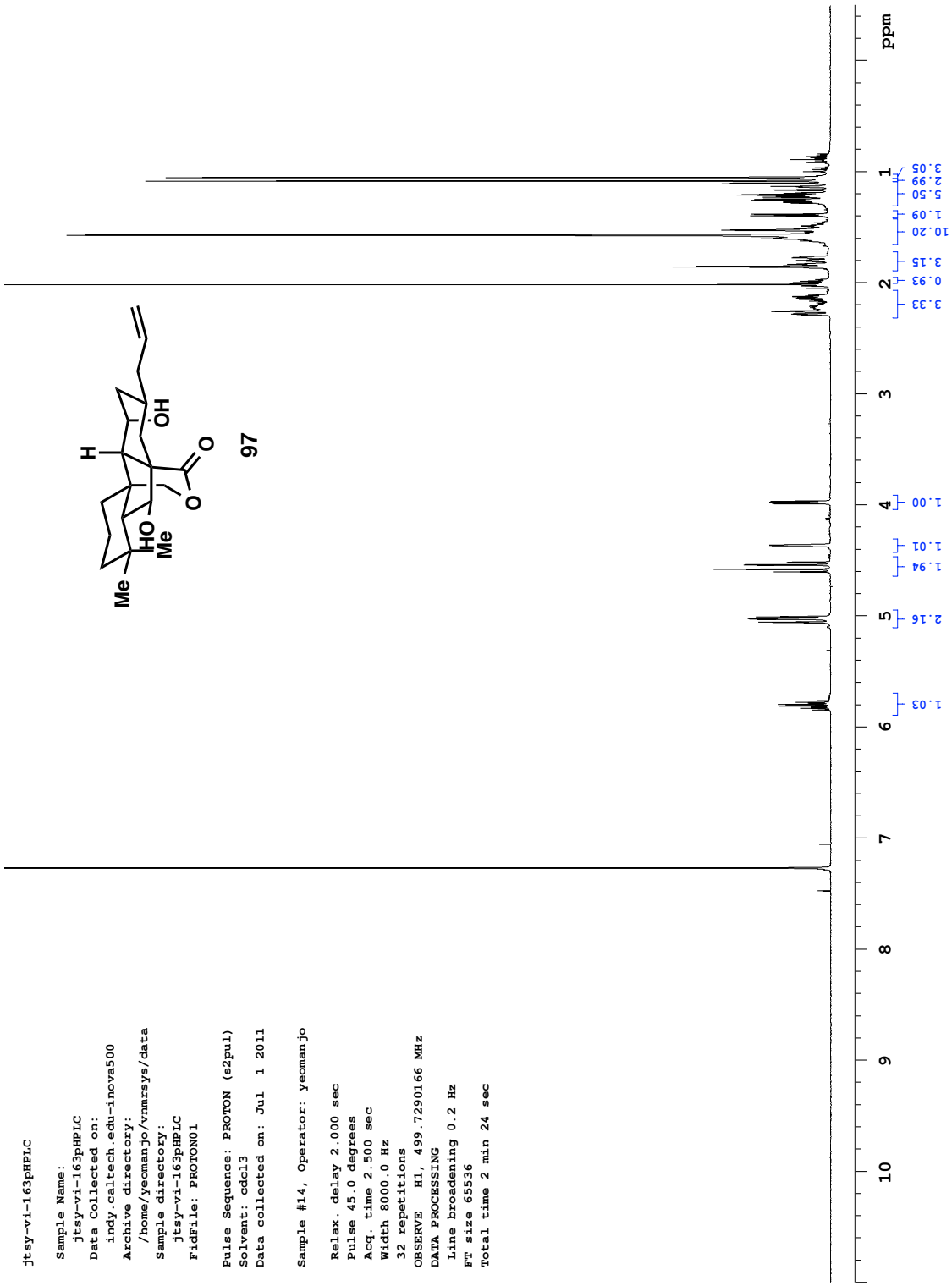

jtsy-vi-129 minor fxns 46-47
Sample Name:
jtsy-vi-129min46-47
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yecmanjo/vnmrsys/data
Sample directory:
jtsy-vi-129min46-47
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 29 2011
Sample #18, Operator: yecmanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3000 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 42 min
TBSO
Me
Me
TBSO
O
O
O
132
more polar diastereomer
200
180
160
140
120
100
80
60
40
20
0
ppm

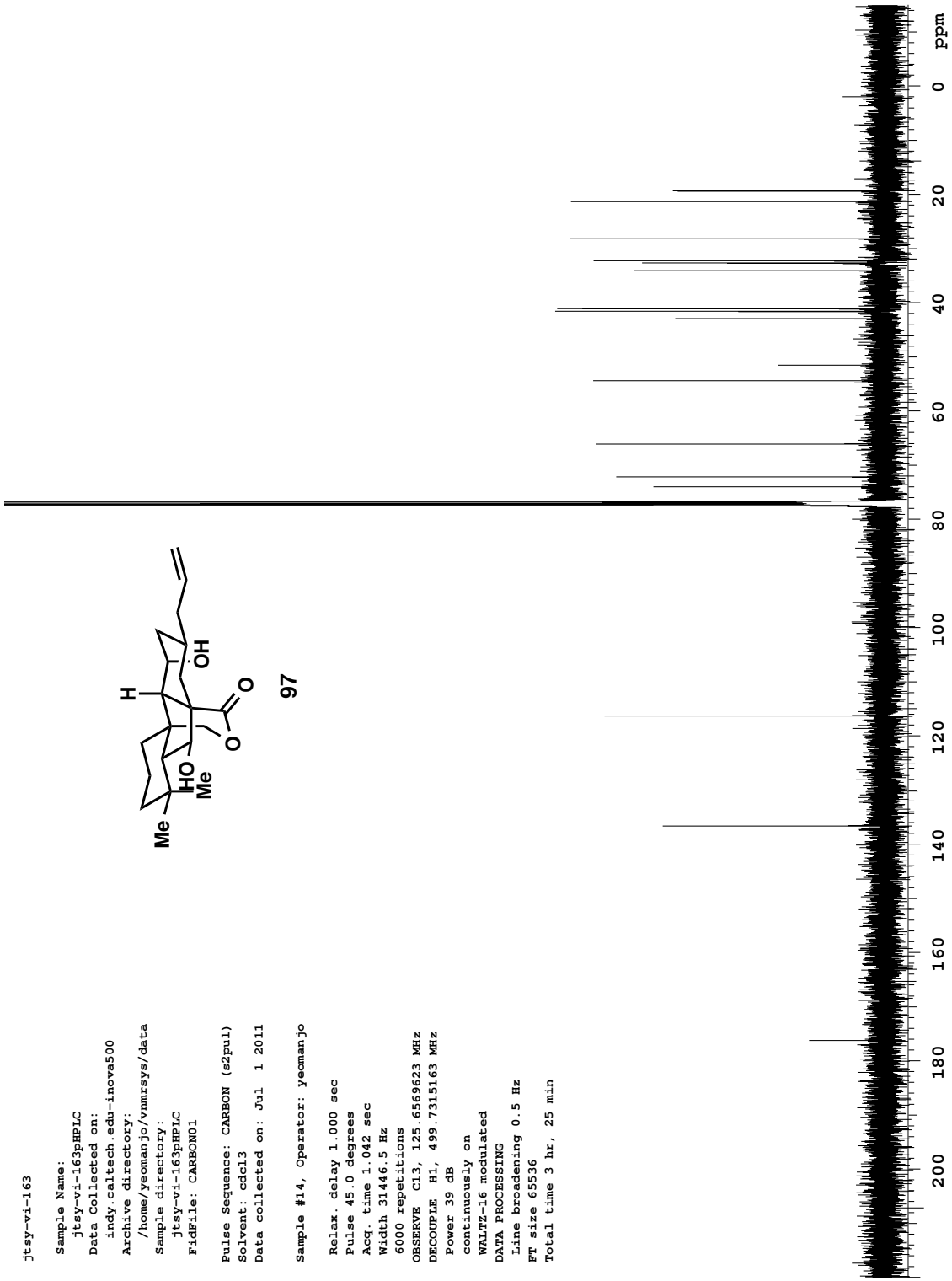

jc-1-288-A
Sample Name:
jc-1-288-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-288-A
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 16 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 49 sec
TBSO
Me
Me
TBSO
O
O
O
133
ppm
11.28
21.55
3.55
2.51
7.50
2.12
2.10
2.05
1.94
2.14
1.96
2.04
1.00
0.95

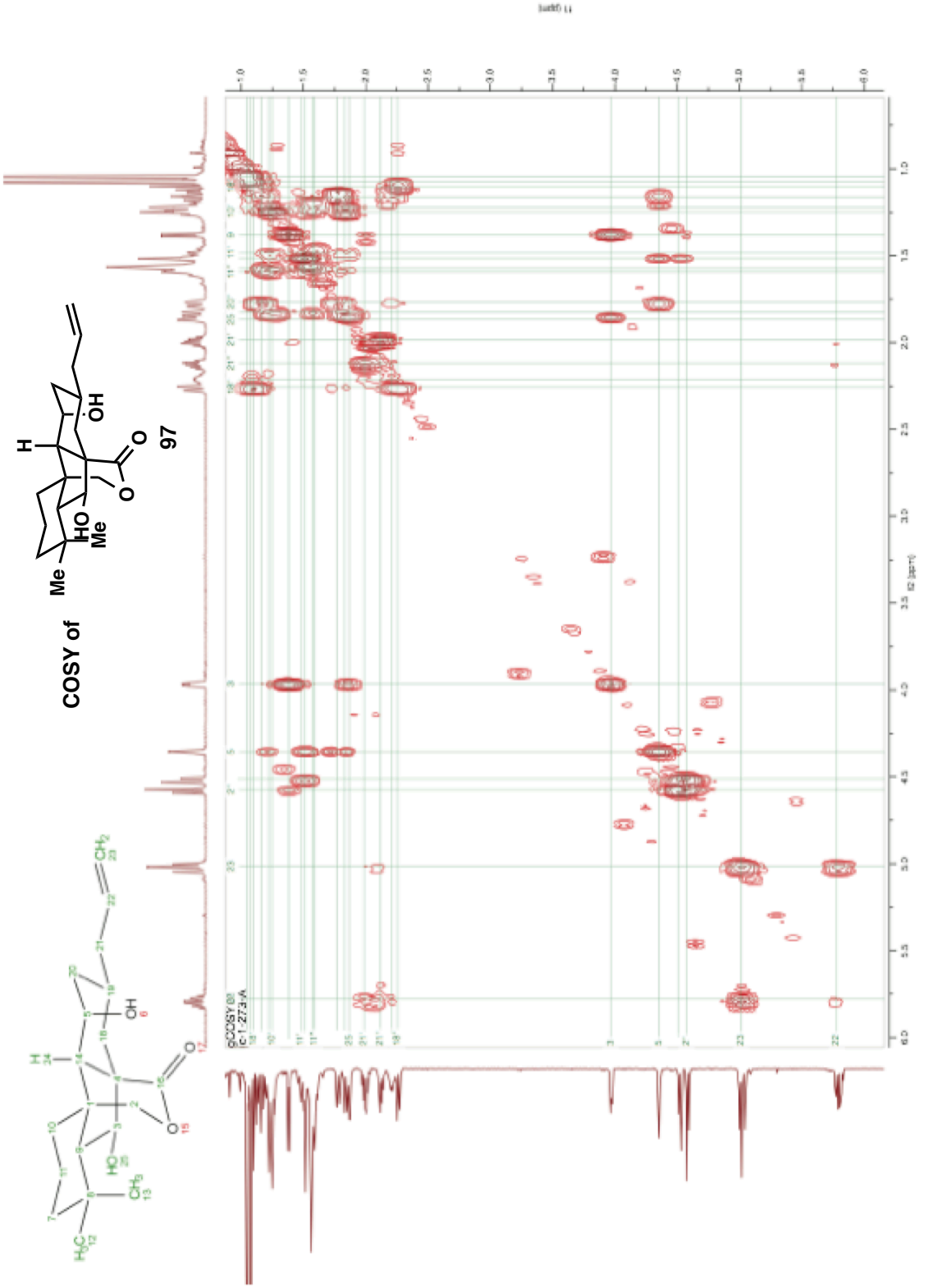

jc-1-288-A
Sample Name:
jc-1-288-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-288-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 16 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
TBSO
Me
Me
TBSO
O
O
133
200
180
160
140
120
100
80
60
40
20
0
ppm

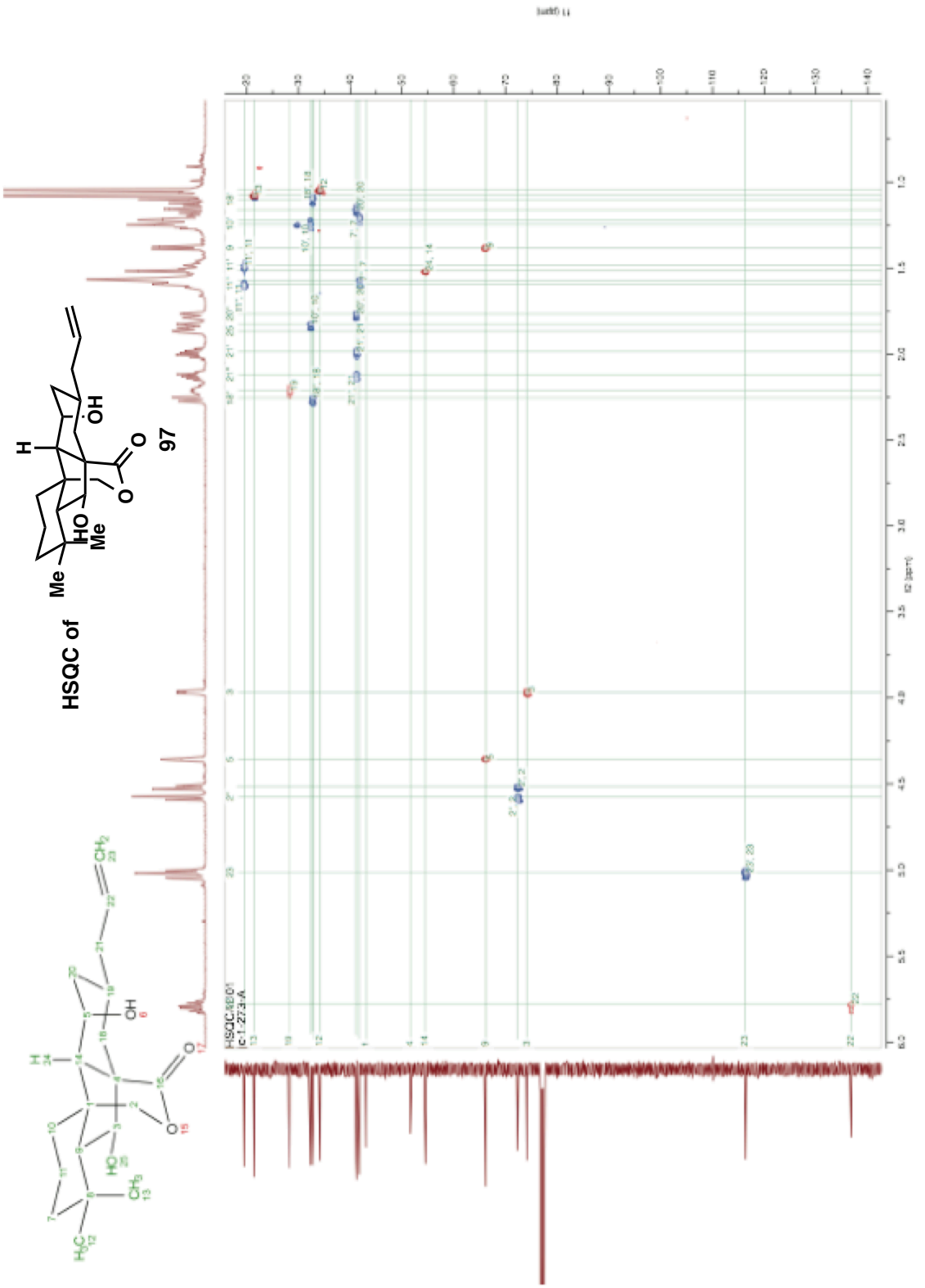

jc-1-272-A-char
Sample Name:
jc-1-272-A-char
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-272-A-char
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 2 2011
Temp. 25.0 C / 298.1 K
Sample #2, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 49 sec
98
Me
Me
O
O
O
O
H
1.117
1.097
ppm
6.16
2.80
1.39
2.28
1.20
1.28
7.27
0.99
1.00
2.06
0.99
0.88
0.75
0.91

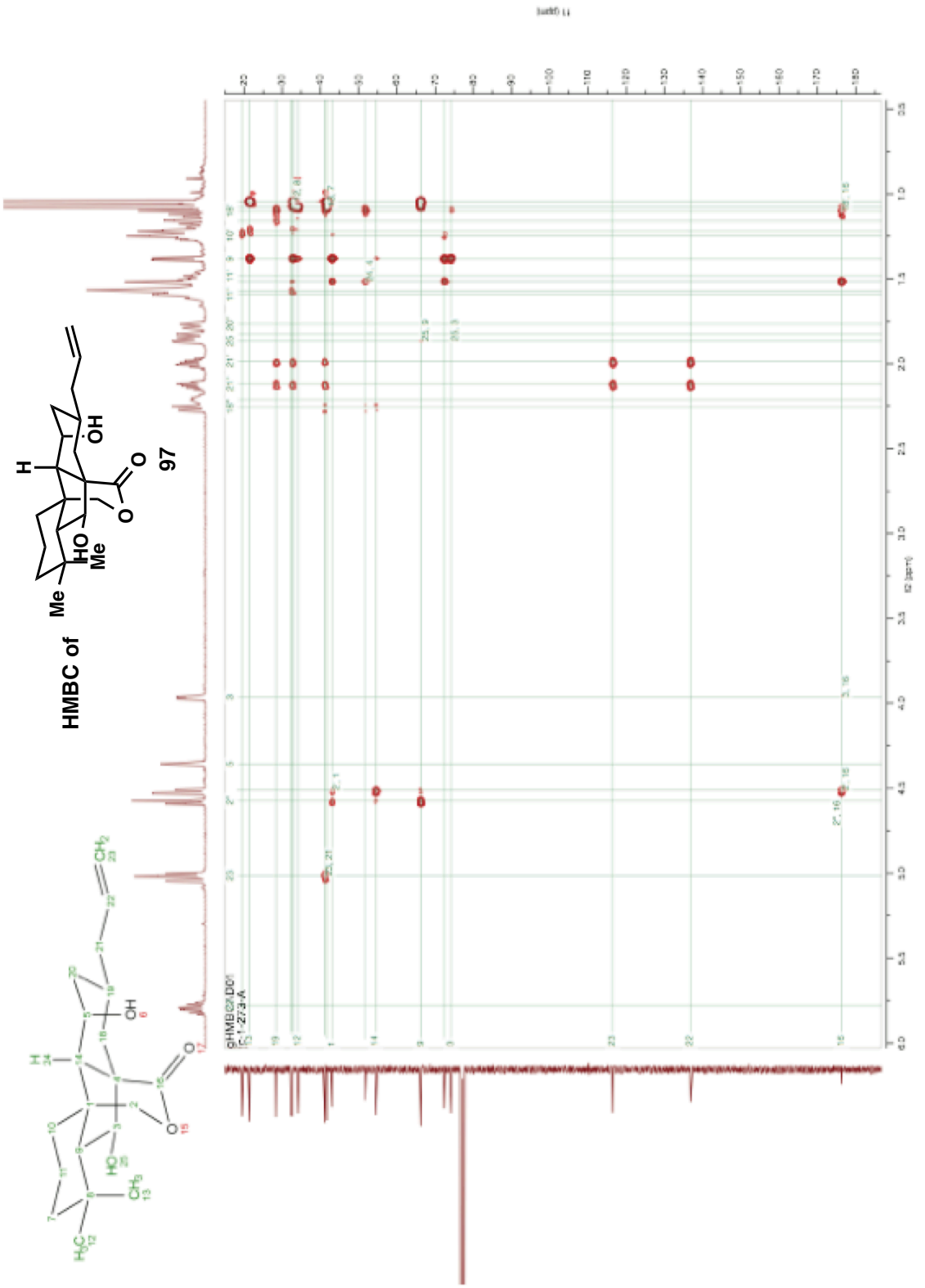

jc-1-272-A-char
Sample Name:
jc-1-272-A-char
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-272-A-char
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 2 2011
Temp. 25.0 C / 298.1 K
Sample #2, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569642 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
O
O
O
O
H
Me
Me
98
200
180
160
140
120
100
80
60
40
20
0
ppm

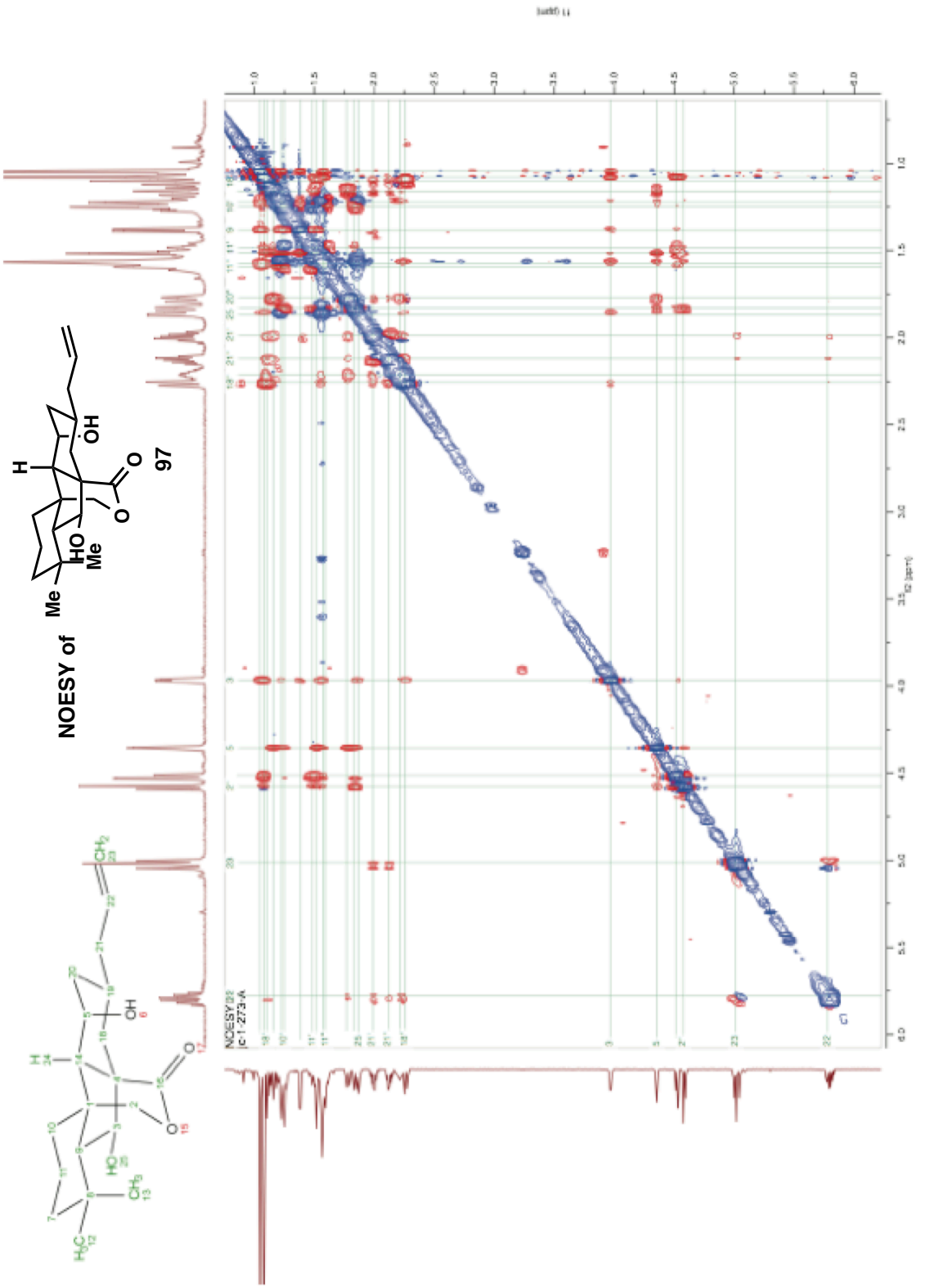

jtsy-vi-163pHPLC
Sample Name:
jtsy-vi-163pHPLC
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vi-163pHPLC
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 1 2011
Sample #14, Operator: yeomanjo
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290166 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
97
H
HO
Me
HO
Me
O
O
ppm
1
2
3
4
5
6
7
8
9
10
3.05
2.99
5.50
1.09
10.20
3.15
0.93
3.33
1.00
1.01
1.94
2.16
1.03

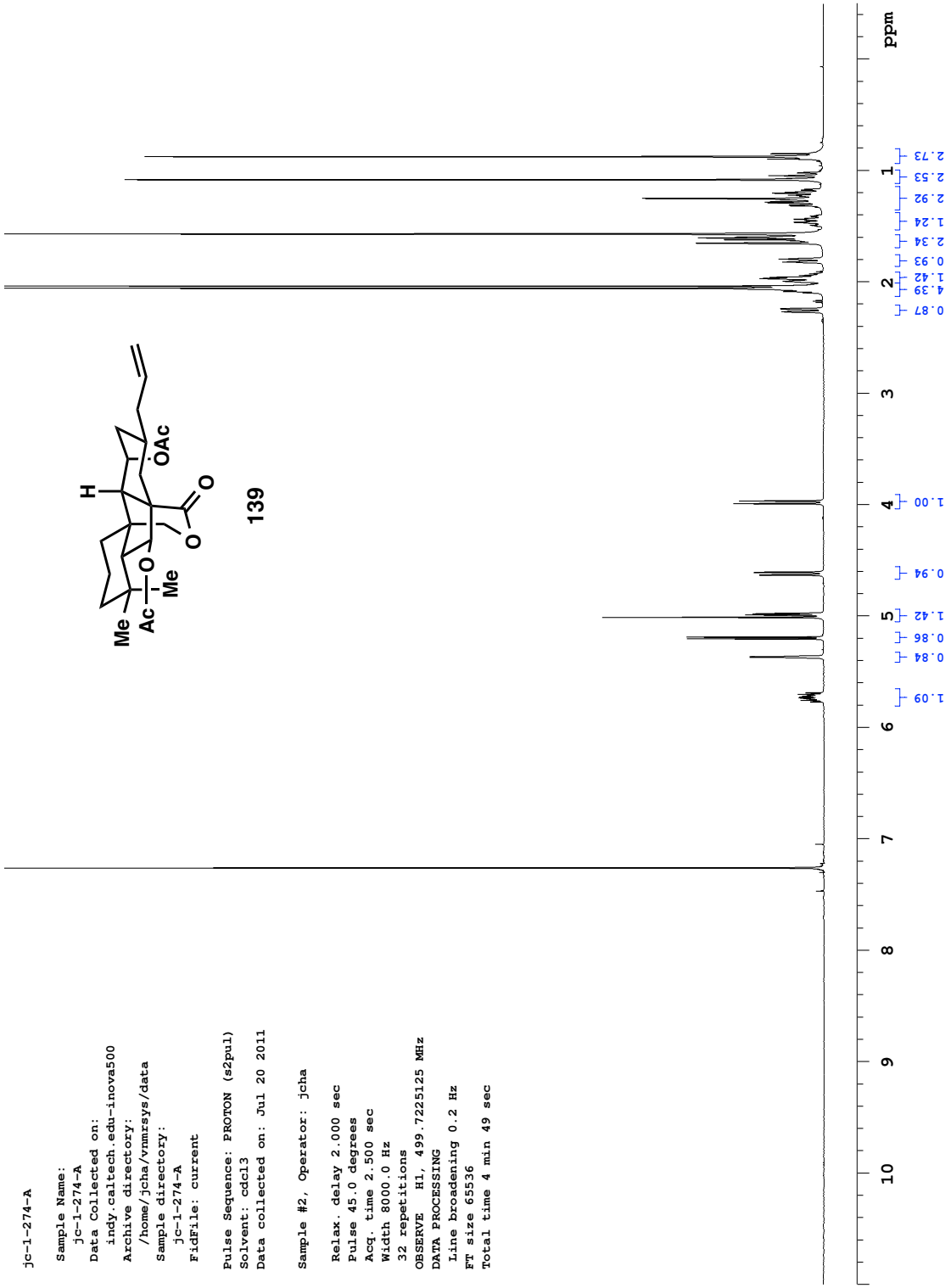

jtsy-vi-163
Sample Name:
jtsy-vi-163pHPLC
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vi-163pHPLC
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 1 2011
Sample #14, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
6000 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 25 min
H
OH
O
O
HO
Me
Me
97
200
180
160
140
120
100
80
60
40
20
0
ppm

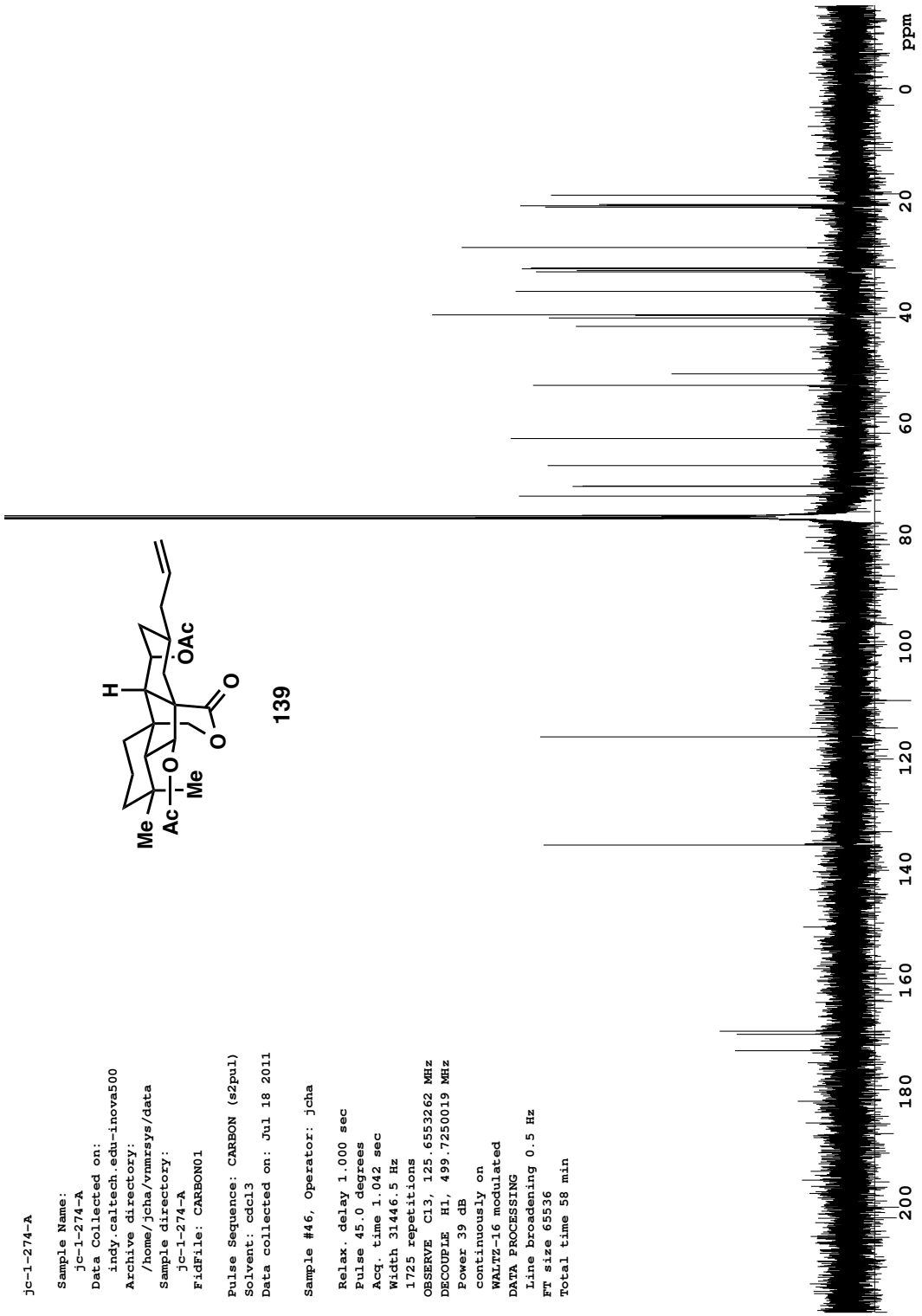

COSY of
97
H
OH
O
O
HO
Me
Me

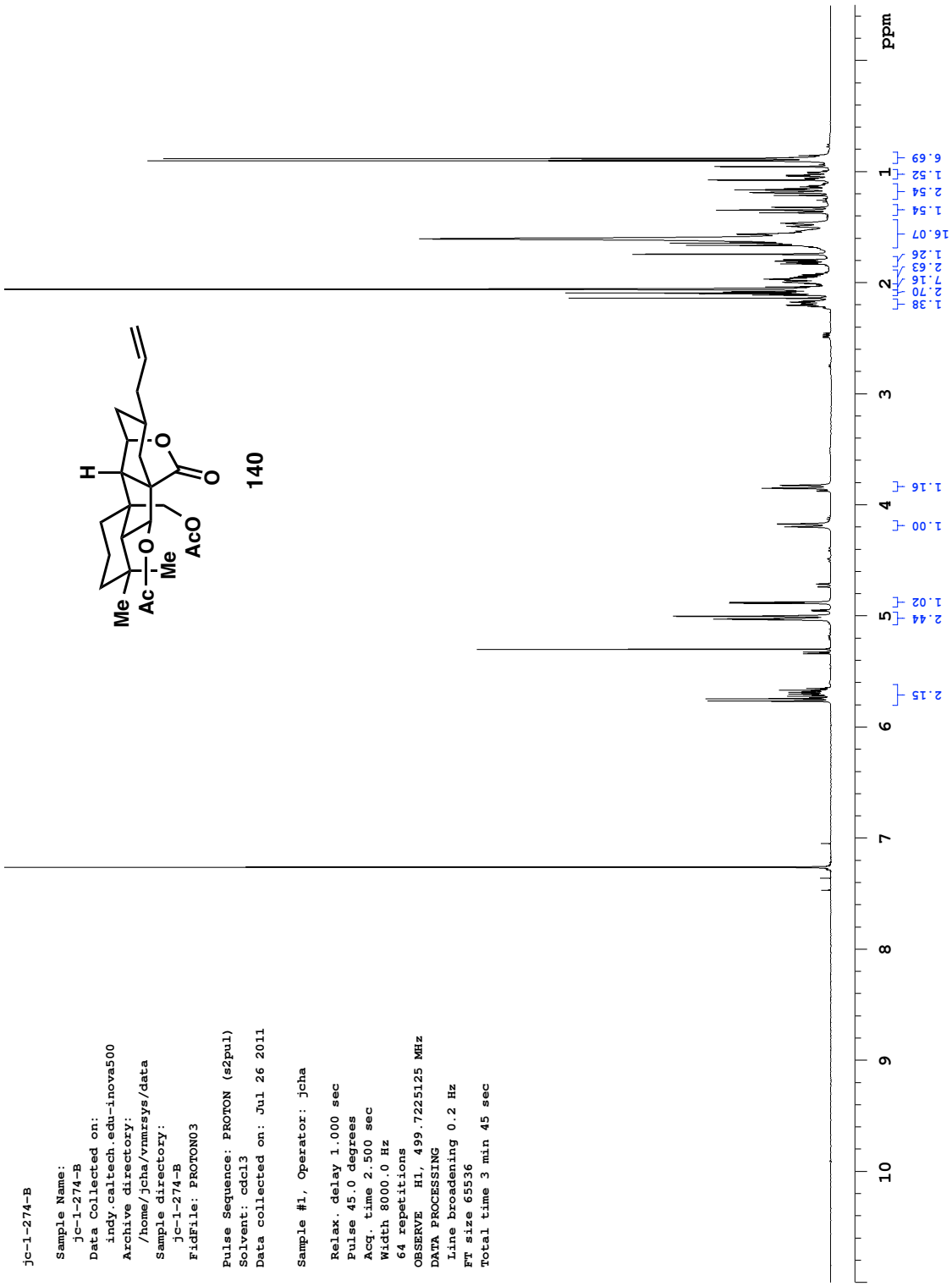

HSQC of
97
H
OH
O
O
HO
Me
Me

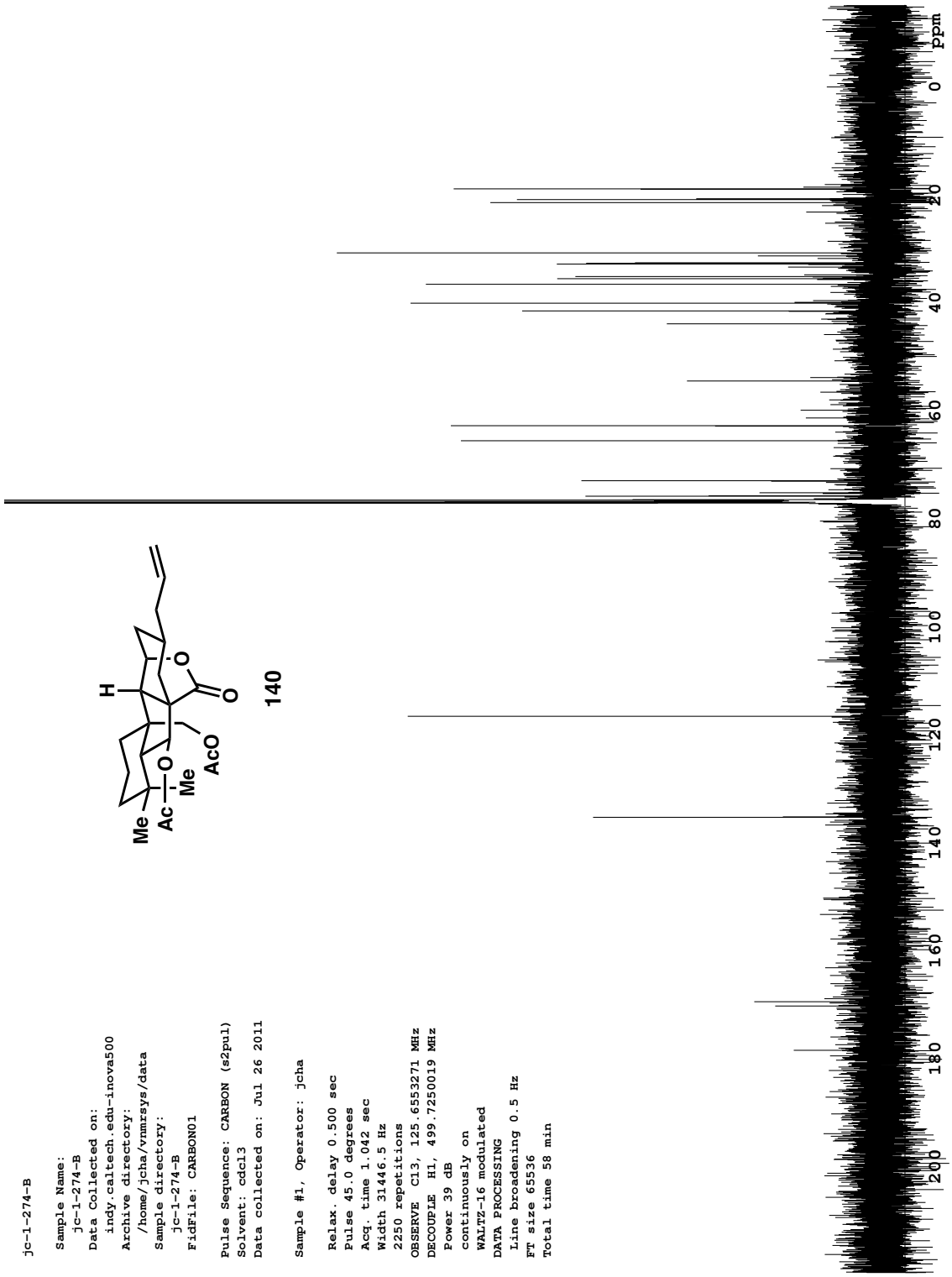

HMBC of
97
Me
HO
Me
H
OH
O
O

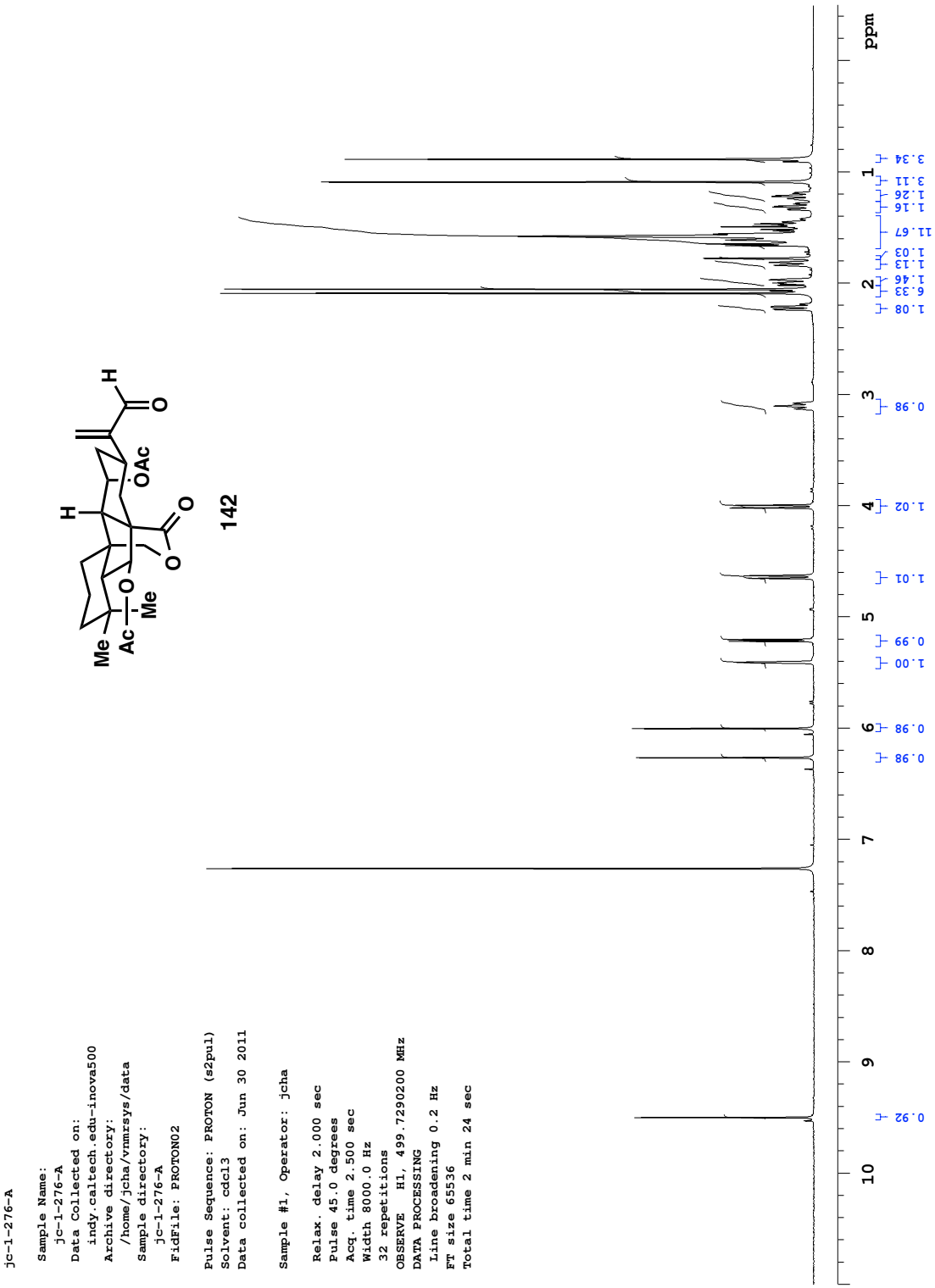

NOESY of
97
Me
HO
Me
H
OH
O
O
NOESY32
pc1-273-A

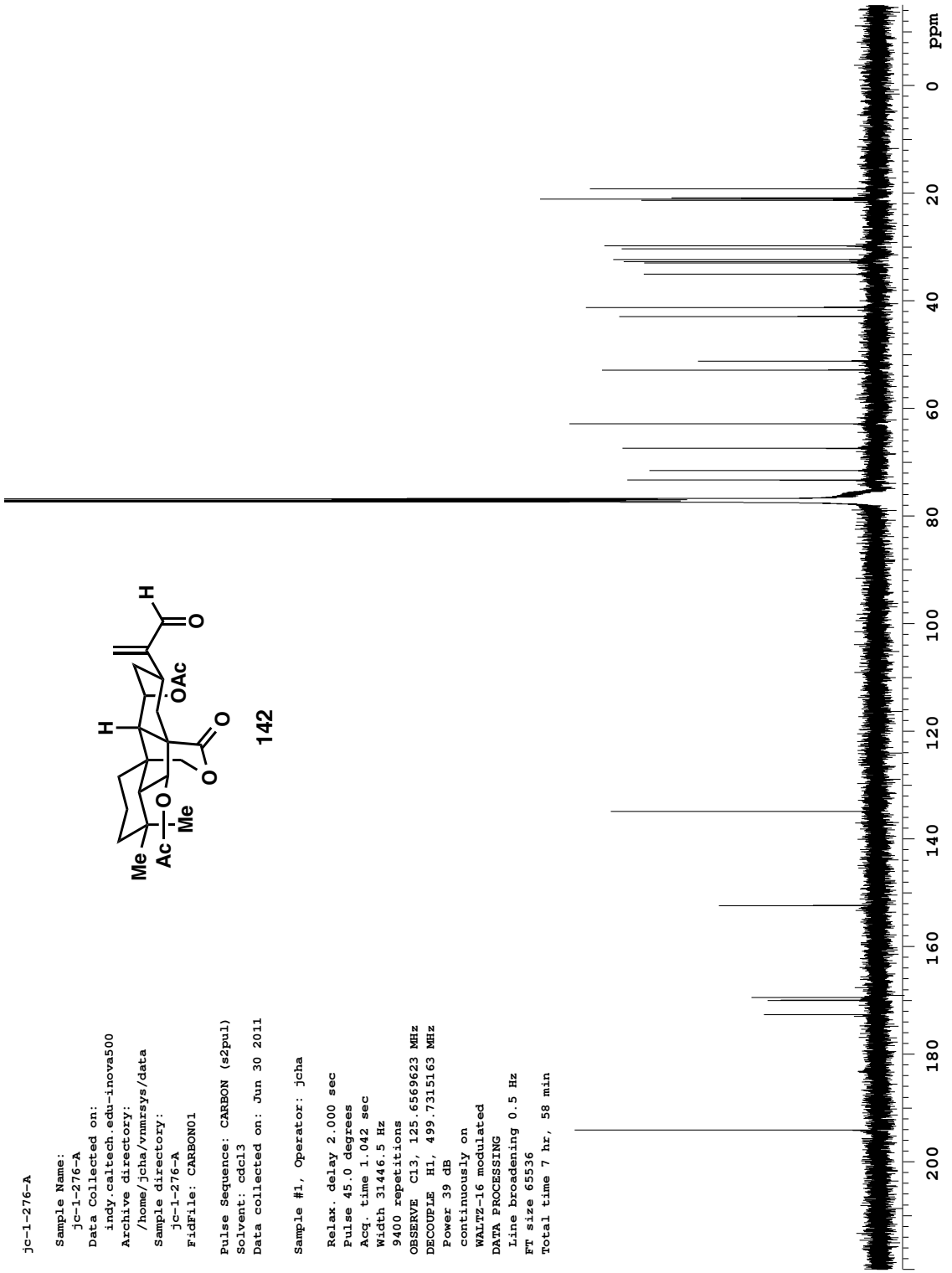

jc-1-274-A
Sample Name:
jc-1-274-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-274-A
FidFile: current
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 20 2011
Sample #2, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 49 sec
Me
Ac
O
Me
H
OAc
O
O
139
ppm
2.73
2.53
2.92
1.24
2.34
0.93
1.42
4.39
0.87
1.00
0.94
1.42
0.86
0.84
1.09

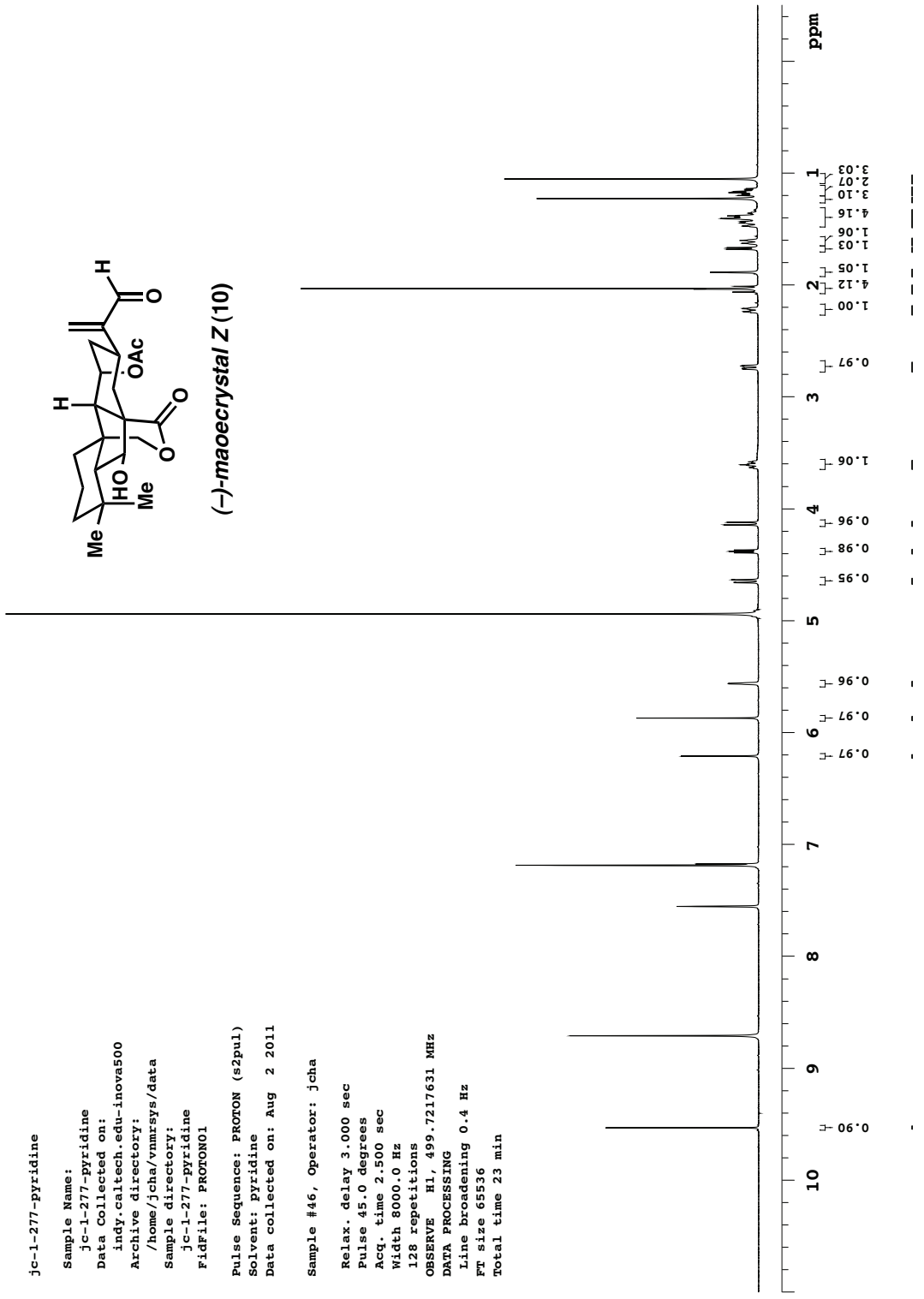

jc-1-274-A
Sample Name:
jc-1-274-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-274-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 18 2011
Sample #46, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1725 repetitions
OBSERVE C13, 125.6553262 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
H
OAc
O
O
Me
Ac
O
Me
139
200
180
160
140
120
100
80
60
40
20
0
ppm

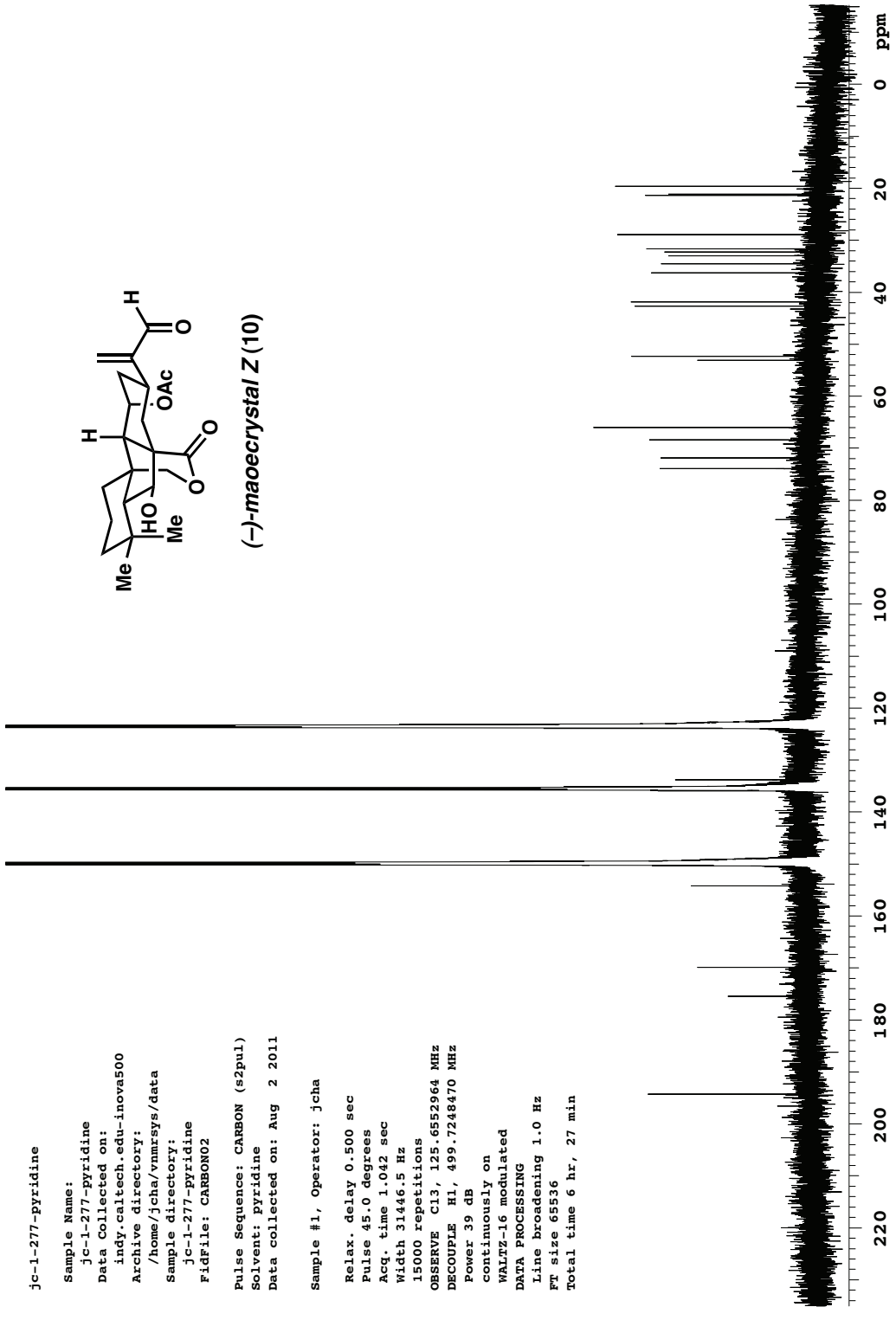

jc-1-274-B
Sample Name:
jc-1-274-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-274-B
FidFile: PROTON03
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 26 2011
Sample #1, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 45 sec
140
Me
Ac
O
Me
AcO
H
O
O
ppm
1
2
3
4
5
6
7
8
9
10
6.69
1.52
2.54
1.54
16.07
1.26
2.63
7.16
2.70
1.38
1.16
1.00
1.02
2.44
2.15

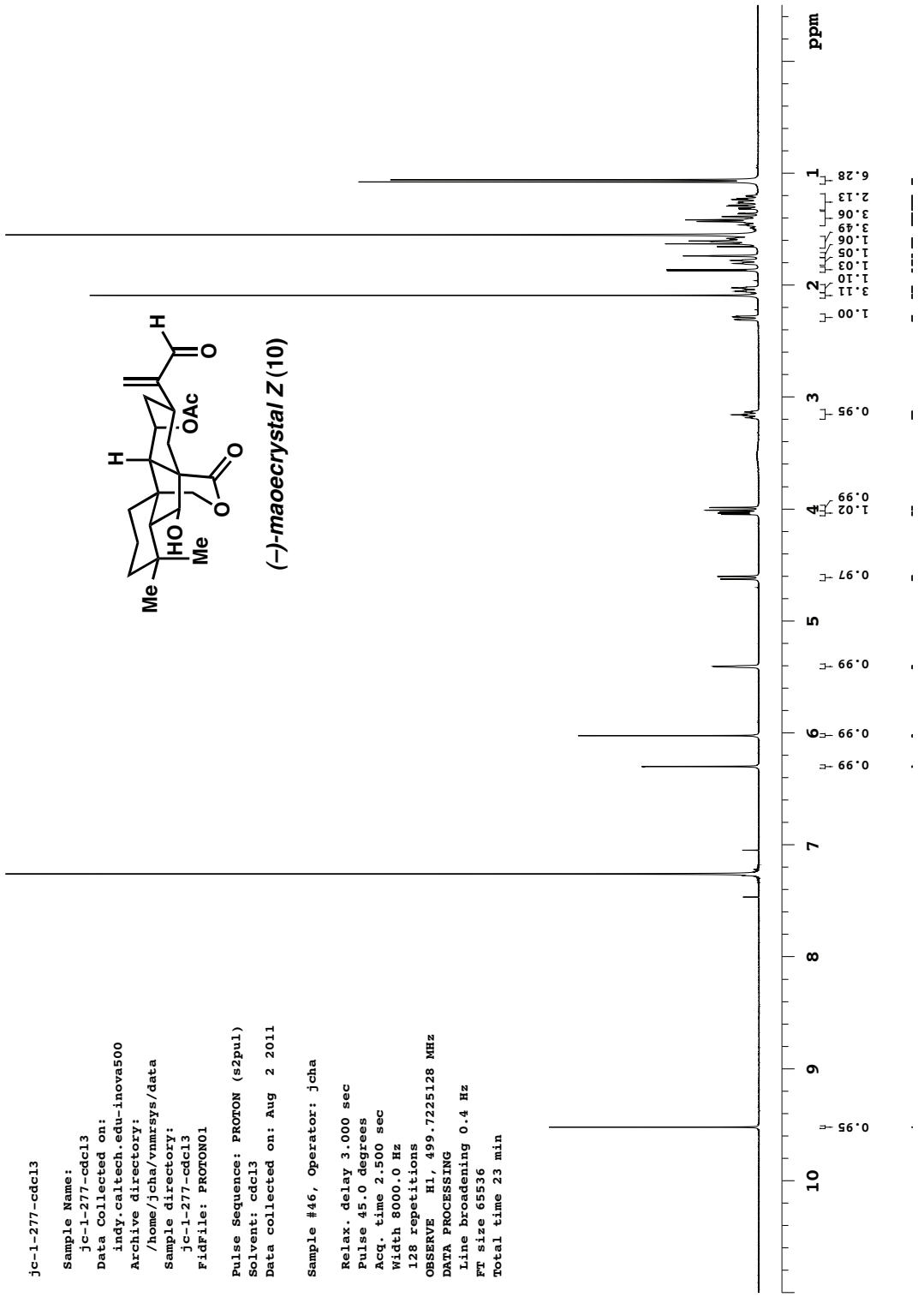

jc-1-274-B
Sample Name:
jc-1-274-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-274-B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 26 2011
Sample #1, Operator: jcha
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2250 repetitions
OBSERVE C13, 125.6553271 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
H
O
O
Me
Ac
O
Me
AcO
140
200
180
160
140
120
100
80
60
40
20
0
ppm

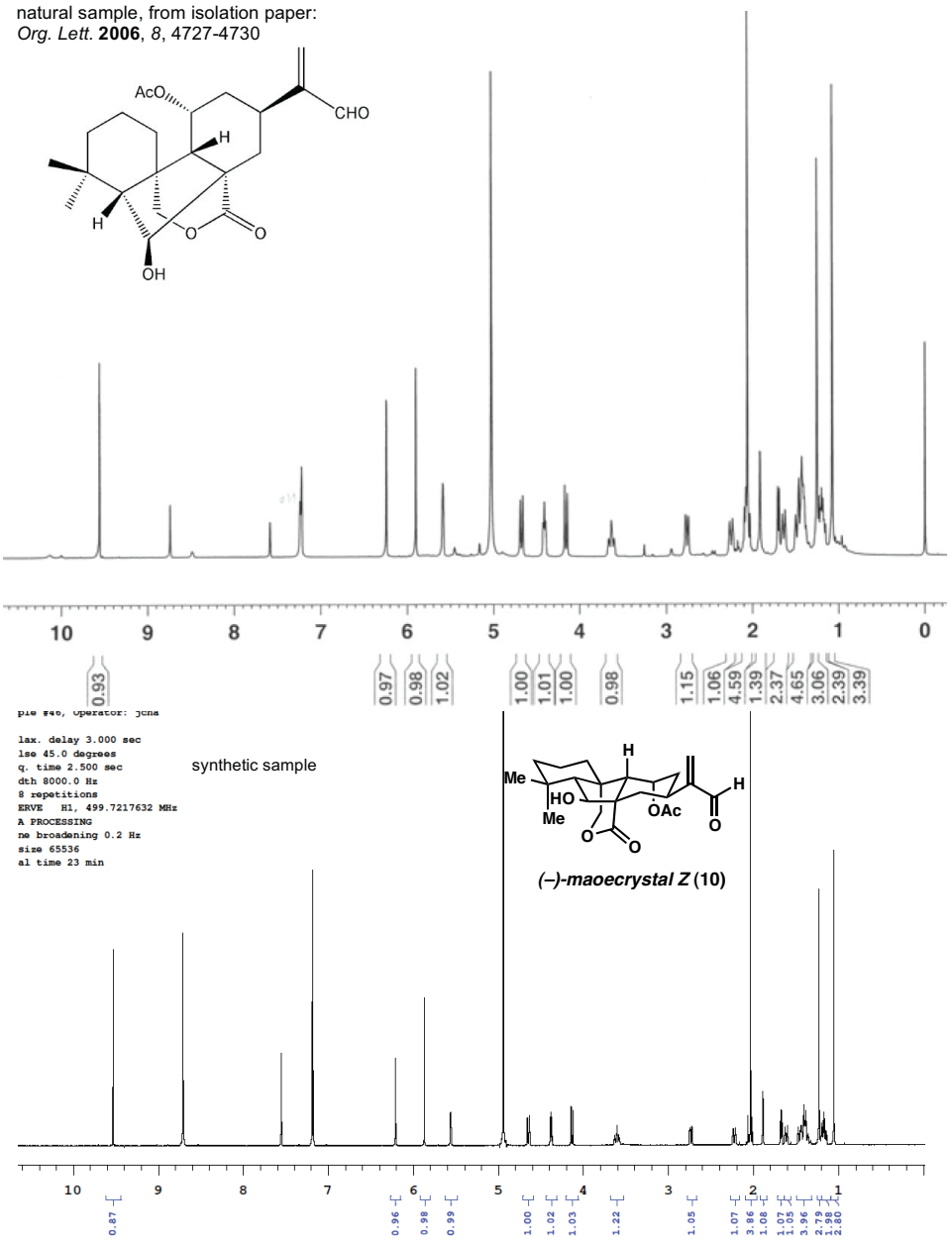

jc-1-276-A
Sample Name:
jc-1-276-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-276-A
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 30 2011
Sample #1, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
142
ppm
3.34
3.11
1.26
1.16
11.67
1.03
1.13
1.46
6.33
1.08
0.98
1.02
1.01
0.99
1.00
0.98
0.86
0.92


jc-1-276-A
Sample Name:
jc-1-276-A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-276-A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 30 2011
Sample #1, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
9400 repetitions
OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 58 min
Me
Ac
O
Me
H
OAc
O
O
O
H
O
142
200
180
160
140
120
100
80
60
40
20
0
ppm


jc-1-277-pyridine
Sample Name:
jc-1-277-pyridine
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-277-pyridine
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: pyridine
Data collected on: Aug 2 2011
Sample #46, Operator: jcha
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7217631 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 65536
Total time 23 min
(–)-maoecrystal Z (10)
Me
HO
Me
H
OAc
O
O
O
H
O
ppm
10
9
8
7
6
5
4
3
2
1
0.90
0.97
0.96
0.97
0.97
0.95
0.98
0.96
1.06
0.97
1.00
4.12
1.05
1.03
1.06
4.16
3.10
2.07
3.03


jc-1-277-pyridine
Sample Name:
jc-1-277-pyridine
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-277-pyridine
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: pyridine
Data collected on: Aug 2 2011
Sample #1, Operator: jcha
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
15000 repetitions
OBSERVE C13, 125.6552964 MHz
DECOUPLE H1, 499.7248470 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 6 hr, 27 min
H
O
OAc
O
H
O
HO
Me
Me
(–)-maoecrystal Z (10)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


jc-1-277-cdcl3
Sample Name:
jc-1-277-cdcl3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-1-277-cdcl3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 2 2011
Sample #46, Operator: jcha
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 65536
Total time 23 min
(–)-maoecrystal Z (10)
ppm
6.28
2.13
3.06
3.49
1.06
1.05
1.03
1.10
3.11
1.00
0.95
1.02
0.97
0.99
0.99
0.99
0.99
0.95


natural sample, from isolation paper:
Org. Lett. **2006**, *8*, 4727-4730
AcO
CHO
H
H
O
O
OH
10 9 8 7 6 5 4 3 2 1 0
0.93
0.97
0.98
1.02
1.00
1.01
1.00
0.98
1.15
1.06
4.59
1.39
2.37
4.65
3.06
2.39
3.39
lax. delay 3.000 sec
lse 45.0 degrees
q. time 2.500 sec
dth 8000.0 Hz
8 repetitions
ERVE H1, 499.7217632 MHz
A PROCESSING
ne broadening 0.2 Hz
size 65536
al time 23 min
synthetic sample
Me
HO
Me
H
OAc
H
O
O
(–)-maoecrystal Z (10)
10 9 8 7 6 5 4 3 2 1
0.87
0.96
0.98
0.99
1.00
1.02
1.03
1.22
1.05
1.07
3.86
1.08
1.07
1.05
3.96
2.79
2.88
2.80

Appendix 2

X-Ray Crystallography Reports Relevant to Chapter 2: Total Synthesis of (–)-Maoecrystal Z[†]

[†] The work disclosed in this appendix for the X-ray crystallographic analysis of **109** and **127** was completed entirely by Mr. Larry Henling and Dr. Michael Day in the Caltech X-ray crystallography lab.

A2.1 CRYSTAL STRUCTURE ANALYSIS OF SPIROLACTONE 109

Figure A2.1. Spirolactone **109**. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 837088.

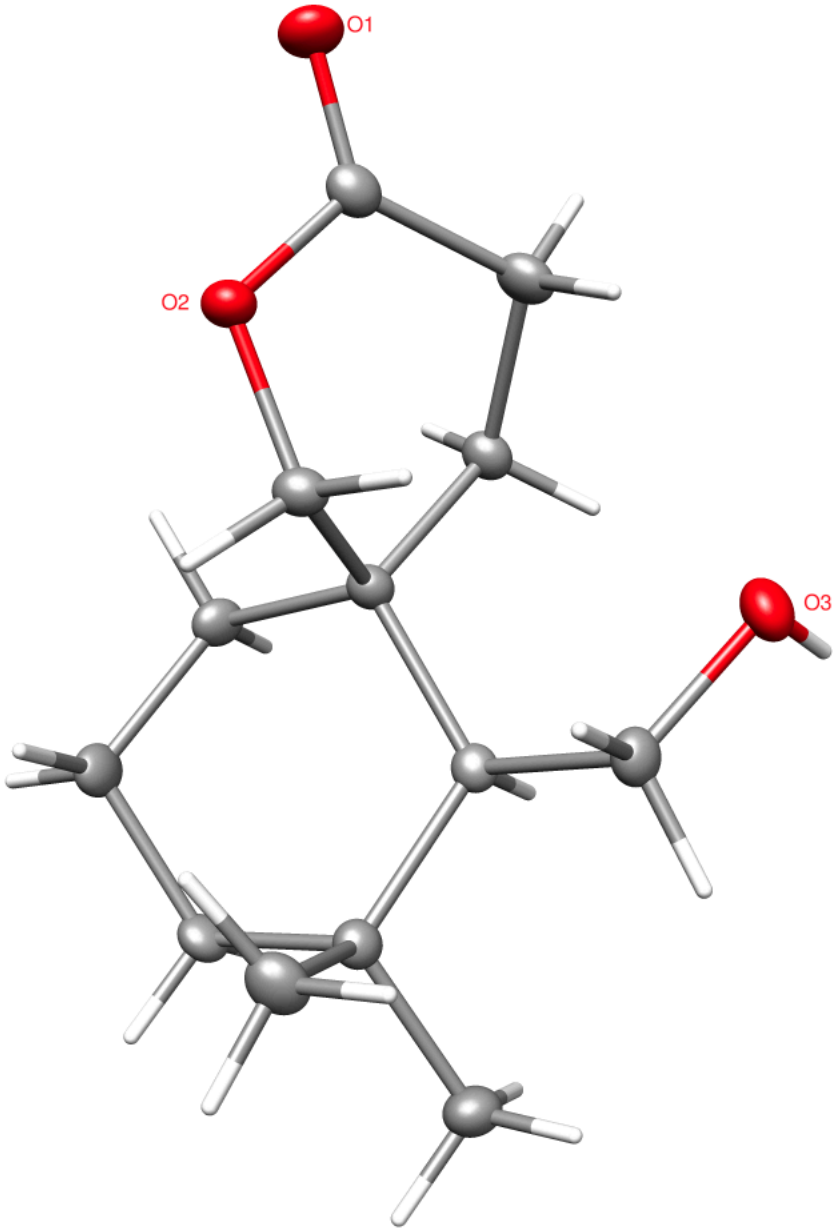


Table A2.1. Crystal data and structure refinement for spirolactone **109** (CCDC 837088).

Empirical formula	$C_{13}H_{22}O_3$
Formula weight	226.31
Crystallization Solvent	Isooctane/dichloromethane
Crystal Habit	Column
Crystal size	0.22 x 0.15 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 5677 reflections used in lattice determination	2.53 to 36.05°	
Unit cell dimensions	a = 8.3489(4) Å b = 7.3054(3) Å c = 9.9944(5) Å	α= 90° β= 105.627(3)° γ = 90°
Volume	587.05(5) $Å^3$	
Z	2	
Crystal system	Monoclinic	
Space group	P 2_1	
Density (calculated)	1.280 Mg/m^3	
F(000)	248	
Data collection program	Bruker APEX2 v2009.7-0	
θ range for data collection	2.12 to 36.35°	
Completeness to θ = 36.35°	99.6 %	
Index ranges	$-13 \leq h \leq 12$, $-12 \leq k \leq 12$, $-16 \leq l \leq 16$	
Data collection scan type	ω scans; 9 settings	
Data reduction program	Bruker SAINT-Plus v7.66A	
Reflections collected	17473	
Independent reflections	5474 [R_{int}= 0.0331]	
Absorption coefficient	0.089 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9938 and 0.9807	

Table A2.1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5474 / 1 / 233
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.709
Final R indices [I>2σ(I), 4661 reflections]	R1 = 0.0408, *w*R2 = 0.0498
R indices (all data)	R1 = 0.0512, *w*R2 = 0.0504
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Unable to reliably determine
Absolute structure parameter	-0.2(6)
Largest diff. peak and hole	0.380 and -0.314 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds

involving l.s. planes.

Table A2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for spirolactone **109** (CCDC 837088). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	6715(1)	-573(1)	7277(1)	22(1)
O(2)	4260(1)	682(1)	7046(1)	18(1)
O(3)	4941(1)	6385(1)	5917(1)	21(1)
C(1)	5908(1)	820(1)	7204(1)	17(1)
C(2)	6586(1)	2720(1)	7332(1)	18(1)
C(3)	5836(1)	3874(1)	8286(1)	16(1)
C(4)	3897(1)	3793(1)	7901(1)	13(1)
C(5)	3322(1)	2395(1)	6732(1)	16(1)
C(6)	3432(1)	3115(2)	9204(1)	16(1)
C(7)	1601(1)	3218(1)	9127(1)	19(1)
C(8)	1023(1)	5195(1)	8884(1)	16(1)
C(9)	1284(1)	6031(1)	7544(1)	14(1)
C(10)	3106(1)	5731(1)	7462(1)	13(1)
C(11)	3280(1)	6376(1)	6038(1)	17(1)
C(12)	-36(1)	5250(2)	6284(1)	20(1)
C(13)	938(1)	8103(1)	7603(1)	21(1)

Table A2.3. Bond lengths [Å] and angles [°] for spirolactone **109** (CCDC 837088).

O(1)-C(1)	1.2118(12)	C(2)-C(3)-C(4)	113.43(8)
O(2)-C(1)	1.3455(11)	C(2)-C(3)-H(3A)	108.7(7)
O(2)-C(5)	1.4640(12)	C(4)-C(3)-H(3A)	109.8(6)
O(3)-C(11)	1.4239(12)	C(2)-C(3)-H(3B)	107.5(6)
O(3)-H(3)	0.780(12)	C(4)-C(3)-H(3B)	108.2(6)
C(1)-C(2)	1.4917(14)	H(3A)-C(3)-H(3B)	109.2(8)
C(2)-C(3)	1.5280(14)	C(5)-C(4)-C(6)	109.43(8)
C(2)-H(2A)	0.972(10)	C(5)-C(4)-C(3)	107.76(8)
C(2)-H(2B)	0.946(10)	C(6)-C(4)-C(3)	106.58(7)
C(3)-C(4)	1.5608(13)	C(5)-C(4)-C(10)	111.49(7)
C(3)-H(3A)	0.954(10)	C(6)-C(4)-C(10)	110.09(8)
C(3)-H(3B)	0.966(10)	C(3)-C(4)-C(10)	111.34(8)
C(4)-C(5)	1.5288(13)	O(2)-C(5)-C(4)	111.57(7)
C(4)-C(6)	1.5377(13)	O(2)-C(5)-H(5A)	105.0(6)
C(4)-C(10)	1.5737(13)	C(4)-C(5)-H(5A)	109.2(6)
C(5)-H(5A)	0.989(11)	O(2)-C(5)-H(5B)	107.9(6)
C(5)-H(5B)	0.968(9)	C(4)-C(5)-H(5B)	111.2(6)
C(6)-C(7)	1.5115(14)	H(5A)-C(5)-H(5B)	111.8(8)
C(6)-H(6A)	0.971(10)	C(7)-C(6)-C(4)	115.05(8)
C(6)-H(6B)	0.967(10)	C(7)-C(6)-H(6A)	108.3(6)
C(7)-C(8)	1.5213(14)	C(4)-C(6)-H(6A)	108.2(6)
C(7)-H(7A)	1.022(10)	C(7)-C(6)-H(6B)	112.0(7)
C(7)-H(7B)	1.006(11)	C(4)-C(6)-H(6B)	108.1(7)
C(8)-C(9)	1.5394(13)	H(6A)-C(6)-H(6B)	104.6(8)
C(8)-H(8A)	0.974(10)	C(6)-C(7)-C(8)	109.17(9)
C(8)-H(8B)	0.921(11)	C(6)-C(7)-H(7A)	112.5(6)
C(9)-C(12)	1.5420(13)	C(8)-C(7)-H(7A)	111.7(5)
C(9)-C(13)	1.5449(14)	C(6)-C(7)-H(7B)	110.1(6)
C(9)-C(10)	1.5613(13)	C(8)-C(7)-H(7B)	108.9(6)
C(10)-C(11)	1.5425(12)	H(7A)-C(7)-H(7B)	104.2(8)
C(10)-H(10)	0.960(9)	C(7)-C(8)-C(9)	113.76(8)
C(11)-H(11A)	1.026(10)	C(7)-C(8)-H(8A)	108.8(6)
C(11)-H(11B)	1.036(10)	C(9)-C(8)-H(8A)	109.6(6)
C(12)-H(12A)	0.961(12)	C(7)-C(8)-H(8B)	111.0(6)
C(12)-H(12B)	0.960(10)	C(9)-C(8)-H(8B)	109.0(6)
C(12)-H(12C)	0.938(12)	H(8A)-C(8)-H(8B)	104.2(8)
C(13)-H(13A)	0.952(11)	C(8)-C(9)-C(12)	109.05(8)
C(13)-H(13B)	0.931(11)	C(8)-C(9)-C(13)	106.48(8)
C(13)-H(13C)	0.991(10)	C(12)-C(9)-C(13)	107.08(8)
		C(8)-C(9)-C(10)	110.98(7)
C(1)-O(2)-C(5)	115.62(8)	C(12)-C(9)-C(10)	113.40(8)
C(11)-O(3)-H(3)	105.0(10)	C(13)-C(9)-C(10)	109.54(8)
O(1)-C(1)-O(2)	118.63(9)	C(11)-C(10)-C(9)	109.93(7)
O(1)-C(1)-C(2)	125.72(9)	C(11)-C(10)-C(4)	113.29(8)
O(2)-C(1)-C(2)	115.60(9)	C(9)-C(10)-C(4)	116.95(8)
C(1)-C(2)-C(3)	110.91(9)	C(11)-C(10)-H(10)	107.4(6)
C(1)-C(2)-H(2A)	109.9(6)	C(9)-C(10)-H(10)	101.7(6)
C(3)-C(2)-H(2A)	109.8(6)	C(4)-C(10)-H(10)	106.4(5)
C(1)-C(2)-H(2B)	107.2(6)	O(3)-C(11)-C(10)	114.57(8)
C(3)-C(2)-H(2B)	111.1(6)	O(3)-C(11)-H(11A)	107.1(6)
H(2A)-C(2)-H(2B)	107.8(8)	C(10)-C(11)-H(11A)	108.5(6)

O(3)-C(11)-H(11B)	110.9(6)	H(12B)-C(12)-H(12C)	109.2(9)
C(10)-C(11)-H(11B)	108.1(5)	C(9)-C(13)-H(13A)	110.4(6)
H(11A)-C(11)-H(11B)	107.5(7)	C(9)-C(13)-H(13B)	111.3(6)
C(9)-C(12)-H(12A)	113.5(6)	H(13A)-C(13)-H(13B)	110.6(9)
C(9)-C(12)-H(12B)	108.9(6)	C(9)-C(13)-H(13C)	110.9(6)
H(12A)-C(12)-H(12B)	108.8(9)	H(13A)-C(13)-H(13C)	104.7(8)
C(9)-C(12)-H(12C)	107.1(6)	H(13B)-C(13)-H(13C)	108.8(9)
H(12A)-C(12)-H(12C)	109.2(9)		

Table A2.4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for spirolactone **109** (CCDC 837088). The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	188(4)	184(4)	282(4)	-9(3)	54(3)	43(3)
O(2)	152(4)	148(4)	242(3)	-22(3)	72(3)	9(3)
O(3)	218(4)	219(4)	233(4)	-10(3)	125(3)	-28(3)
C(1)	161(5)	199(5)	147(4)	-20(4)	55(3)	-6(4)
C(2)	125(5)	214(6)	217(5)	-39(4)	51(4)	-6(4)
C(3)	128(5)	180(5)	165(4)	-17(4)	39(3)	-9(4)
C(4)	115(5)	142(4)	132(4)	-7(3)	31(3)	3(4)
C(5)	135(5)	153(5)	174(4)	-29(4)	37(4)	5(4)
C(6)	186(5)	155(5)	139(4)	23(4)	42(4)	24(4)
C(7)	213(5)	182(5)	194(4)	39(4)	106(4)	7(4)
C(8)	153(5)	182(5)	168(4)	-19(4)	74(4)	7(4)
C(9)	143(5)	150(4)	141(4)	2(4)	40(3)	0(4)
C(10)	133(5)	131(4)	113(4)	-23(3)	29(3)	-17(4)
C(11)	184(5)	173(5)	155(4)	20(4)	62(4)	-11(4)
C(12)	136(5)	248(6)	193(5)	6(4)	11(4)	0(4)
C(13)	198(6)	177(5)	240(5)	24(4)	63(4)	38(5)

Table A2.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for spirolactone **109** (CCDC 837088).

	x	y	z	U_{iso}
H(3)	5343(16)	7264(17)	6308(13)	38(4)
H(2A)	6355(12)	3286(14)	6419(11)	18(3)
H(2B)	7754(13)	2629(13)	7687(10)	18(3)
H(3A)	6191(13)	5112(14)	8255(10)	19(3)
H(3B)	6263(12)	3407(14)	9218(11)	19(3)
H(5A)	2155(13)	2052(13)	6656(10)	16(3)
H(5B)	3458(12)	2861(13)	5863(10)	13(3)
H(6A)	4038(12)	3843(13)	9990(10)	16(3)
H(6B)	3868(13)	1889(14)	9408(11)	26(3)
H(7A)	898(12)	2361(13)	8392(10)	15(3)
H(7B)	1405(13)	2780(15)	10024(11)	28(3)
H(8A)	1609(12)	5927(15)	9680(10)	15(2)
H(8B)	-81(13)	5306(12)	8868(10)	12(3)
H(10)	3709(12)	6580(12)	8147(10)	10(3)
H(11A)	2608(12)	5509(14)	5287(10)	14(3)
H(11B)	2749(12)	7663(13)	5842(9)	14(3)
H(12A)	25(13)	3944(16)	6195(11)	27(3)
H(12B)	99(13)	5811(16)	5453(10)	20(3)
H(12C)	-1080(15)	5566(15)	6397(10)	27(3)
H(13A)	-115(13)	8302(14)	7776(10)	16(3)
H(13B)	990(13)	8688(14)	6789(11)	26(3)
H(13C)	1749(13)	8684(14)	8399(11)	22(3)

Table A2.6. Hydrogen bonds for spirolactone **109** (CCDC 837088) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(1)#1	0.780(12)	2.037(12)	2.8100(10)	171.5(13)

Symmetry transformations used to generate equivalent atoms:
#1 x,y+1,z

A2.2 CRYSTAL STRUCTURE ANALYSIS OF ALDEHYDE 127

Figure A2.2. Aldehyde **127**. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 830951.

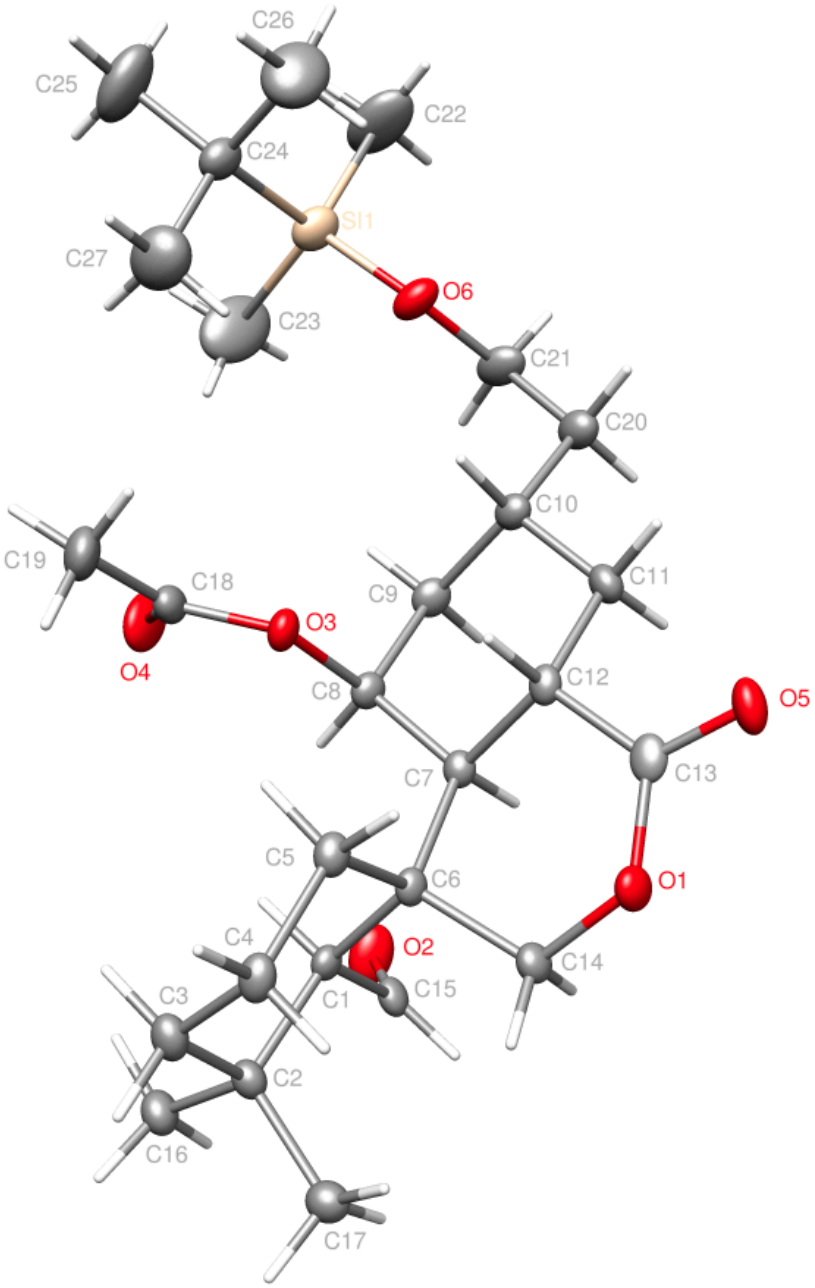
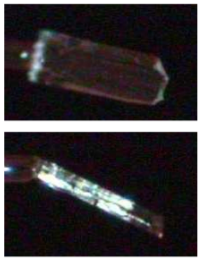


Table A2.7. Crystal data and structure refinement for aldehyde **127** (CCDC 830951).



Empirical formula	$C_{27}H_{46}O_6Si$
Formula weight	494.73
Crystallization Solvent	Ether
Crystal Habit	Plate
Crystal size	0.40 x 0.14 x 0.05 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 9883 reflections used in lattice determination	2.56 to 25.95°	
Unit cell dimensions	a = 7.0008(2) Å b = 14.2170(5) Å c = 28.7340(9) Å	α= 90° β= 90° γ = 90°
Volume	2859.91(16) $Å^3$	
Z	4	
Crystal system	Orthorhombic	
Space group	P $2_12_12_1$	
Density (calculated)	1.149 Mg/m^3	
F(000)	1080	
Data collection program	Bruker APEX2 v2009.7-0	
θ range for data collection	2.02 to 30.56°	
Completeness to θ = 30.56°	99.8 %	
Index ranges	$-10 \leq h \leq 6$, $-20 \leq k \leq 20$, $-41 \leq l \leq 39$	
Data collection scan type	ω scans; 9 settings	
Data reduction program	Bruker SAINT-Plus v7.66A	
Reflections collected	62150	
Independent reflections	8741 [R_{int}= 0.0589]	
Absorption coefficient	0.118 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7461 and 0.6633	

Table A2.7 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	8741 / 0 / 315
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.797
Final R indices [I>2σ(I), 7186 reflections]	R1 = 0.0453, *w*R2 = 0.0579
R indices (all data)	R1 = 0.0634, *w*R2 = 0.0594
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Unknown
Absolute structure parameter	0.07(7)
Largest diff. peak and hole	0.592 and -0.387 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds

involving l.s. planes.

Table A2.8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for aldehyde **127** (CCDC 830951). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Si(1)	14159(1)	5918(1)	7588(1)	29(1)
O(1)	5263(1)	6642(1)	9945(1)	20(1)
O(2)	11944(1)	5324(1)	10481(1)	33(1)
O(3)	9511(1)	4778(1)	9005(1)	19(1)
O(4)	12207(1)	3915(1)	8990(1)	38(1)
O(5)	4978(1)	7610(1)	9361(1)	23(1)
O(6)	12638(1)	6504(1)	7909(1)	27(1)
C(1)	8905(2)	4690(1)	10257(1)	15(1)
C(2)	7988(2)	3911(1)	10569(1)	18(1)
C(3)	6711(2)	3307(1)	10254(1)	21(1)
C(4)	5222(2)	3885(1)	9995(1)	20(1)
C(5)	6176(2)	4609(1)	9679(1)	18(1)
C(6)	7543(2)	5282(1)	9939(1)	14(1)
C(7)	8769(2)	5904(1)	9609(1)	15(1)
C(8)	10377(2)	5446(1)	9330(1)	16(1)
C(9)	11508(2)	6173(1)	9062(1)	20(1)
C(10)	10287(2)	6773(1)	8735(1)	19(1)
C(11)	8627(2)	7207(1)	9004(1)	19(1)
C(12)	7490(2)	6485(1)	9285(1)	16(1)
C(13)	5864(2)	6962(1)	9531(1)	18(1)
C(14)	6387(2)	5989(1)	10226(1)	18(1)
C(15)	10245(2)	5291(1)	10541(1)	18(1)
C(16)	9628(2)	3300(1)	10760(1)	24(1)
C(17)	6838(2)	4271(1)	10987(1)	23(1)
C(18)	10579(2)	4026(1)	8878(1)	24(1)
C(19)	9408(2)	3359(1)	8593(1)	34(1)
C(20)	11434(2)	7545(1)	8496(1)	25(1)
C(21)	13182(2)	7208(1)	8238(1)	29(1)
C(22)	15483(3)	6733(1)	7199(1)	63(1)
C(23)	15881(2)	5281(2)	7969(1)	68(1)
C(24)	12623(2)	5082(1)	7256(1)	28(1)
C(25)	13809(3)	4506(1)	6914(1)	66(1)
C(26)	11102(3)	5619(1)	6984(1)	62(1)
C(27)	11605(2)	4425(1)	7594(1)	56(1)

Table A2.9. Bond lengths [Å] and angles [°] for aldehyde **127** (CCDC 830951).

Si(1)-O(6)	1.6355(9)	C(15)-C(1)-C(6)	112.88(10)
Si(1)-C(22)	1.8584(17)	C(2)-C(1)-C(6)	117.75(10)
Si(1)-C(23)	1.8635(17)	C(17)-C(2)-C(3)	110.03(10)
Si(1)-C(24)	1.8647(15)	C(17)-C(2)-C(16)	107.40(10)
O(1)-C(13)	1.3433(14)	C(3)-C(2)-C(16)	109.25(10)
O(1)-C(14)	1.4589(13)	C(17)-C(2)-C(1)	115.34(10)
O(2)-C(15)	1.2024(13)	C(3)-C(2)-C(1)	107.34(10)
O(3)-C(18)	1.3539(15)	C(16)-C(2)-C(1)	107.34(10)
O(3)-C(8)	1.4648(14)	C(4)-C(3)-C(2)	112.66(11)
O(4)-C(18)	1.1946(15)	C(3)-C(4)-C(5)	110.86(10)
O(5)-C(13)	1.2125(14)	C(4)-C(5)-C(6)	113.57(10)
O(6)-C(21)	1.4286(15)	C(14)-C(6)-C(5)	109.84(9)
C(1)-C(15)	1.5095(17)	C(14)-C(6)-C(7)	104.33(10)
C(1)-C(2)	1.5634(17)	C(5)-C(6)-C(7)	113.46(10)
C(1)-C(6)	1.5654(16)	C(14)-C(6)-C(1)	111.19(10)
C(2)-C(17)	1.5346(16)	C(5)-C(6)-C(1)	109.00(10)
C(2)-C(3)	1.5335(17)	C(7)-C(6)-C(1)	108.98(9)
C(2)-C(16)	1.5411(17)	C(8)-C(7)-C(12)	109.97(9)
C(3)-C(4)	1.5223(17)	C(8)-C(7)-C(6)	119.00(11)
C(4)-C(5)	1.5269(17)	C(12)-C(7)-C(6)	110.76(9)
C(5)-C(6)	1.5472(16)	O(3)-C(8)-C(9)	109.54(9)
C(6)-C(14)	1.5310(16)	O(3)-C(8)-C(7)	107.82(9)
C(6)-C(7)	1.5545(16)	C(9)-C(8)-C(7)	111.20(10)
C(7)-C(8)	1.5272(16)	C(8)-C(9)-C(10)	113.64(10)
C(7)-C(12)	1.5333(16)	C(20)-C(10)-C(9)	112.59(10)
C(8)-C(9)	1.5131(17)	C(20)-C(10)-C(11)	109.77(11)
C(9)-C(10)	1.5287(16)	C(9)-C(10)-C(11)	109.88(10)
C(10)-C(20)	1.5253(17)	C(12)-C(11)-C(10)	113.04(10)
C(10)-C(11)	1.5266(16)	C(13)-C(12)-C(11)	109.82(10)
C(11)-C(12)	1.5286(17)	C(13)-C(12)-C(7)	113.61(10)
C(12)-C(13)	1.5021(17)	C(11)-C(12)-C(7)	112.23(9)
C(18)-C(19)	1.4975(19)	O(5)-C(13)-O(1)	117.02(11)
C(20)-C(21)	1.5089(18)	O(5)-C(13)-C(12)	122.82(12)
C(24)-C(27)	1.523(2)	O(1)-C(13)-C(12)	120.06(11)
C(24)-C(26)	1.526(2)	O(1)-C(14)-C(6)	113.88(9)
C(24)-C(25)	1.525(2)	O(2)-C(15)-C(1)	124.07(12)
		O(4)-C(18)-O(3)	124.03(13)
O(6)-Si(1)-C(22)	110.23(7)	O(4)-C(18)-C(19)	125.78(13)
O(6)-Si(1)-C(23)	109.73(7)	O(3)-C(18)-C(19)	110.17(12)
C(22)-Si(1)-C(23)	109.49(9)	C(21)-C(20)-C(10)	114.84(11)
O(6)-Si(1)-C(24)	103.71(6)	O(6)-C(21)-C(20)	109.37(10)
C(22)-Si(1)-C(24)	112.19(7)	C(27)-C(24)-C(26)	107.83(13)
C(23)-Si(1)-C(24)	111.36(8)	C(27)-C(24)-C(25)	109.58(14)
C(13)-O(1)-C(14)	122.50(9)	C(26)-C(24)-C(25)	108.56(13)
C(18)-O(3)-C(8)	117.04(9)	C(27)-C(24)-Si(1)	109.61(10)
C(21)-O(6)-Si(1)	123.77(8)	C(26)-C(24)-Si(1)	110.22(11)
C(15)-C(1)-C(2)	110.26(9)	C(25)-C(24)-Si(1)	110.97(11)

Table A2.10. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for aldehyde **127** (CCDC 830951). The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	247(2)	349(3)	278(2)	-58(2)	22(2)	4(2)
O(1)	170(5)	187(5)	247(5)	9(4)	21(4)	55(4)
O(2)	152(5)	329(6)	522(7)	-116(5)	-16(5)	-9(4)
O(3)	197(5)	142(5)	223(5)	-44(4)	13(4)	13(4)
O(4)	351(6)	327(7)	466(6)	-82(5)	-71(5)	188(5)
O(5)	211(5)	137(5)	352(5)	8(4)	-52(4)	25(4)
O(6)	278(5)	303(6)	223(5)	-96(5)	37(4)	-44(4)
C(1)	150(6)	133(6)	166(6)	-20(6)	22(5)	13(5)
C(2)	190(7)	141(7)	204(7)	16(6)	6(6)	-21(5)
C(3)	222(7)	148(7)	274(7)	5(6)	22(6)	-32(6)
C(4)	177(7)	150(7)	266(7)	-43(6)	14(6)	-36(5)
C(5)	160(7)	155(7)	216(7)	-26(6)	-17(5)	-1(5)
C(6)	122(6)	132(7)	180(6)	-14(6)	-2(5)	9(5)
C(7)	137(6)	129(6)	176(6)	-15(6)	-11(5)	-17(5)
C(8)	146(6)	166(7)	180(6)	-21(6)	6(5)	6(5)
C(9)	159(7)	215(8)	214(7)	-27(6)	15(6)	-25(5)
C(10)	231(7)	153(7)	177(6)	-25(6)	20(6)	-44(6)
C(11)	249(7)	133(7)	199(7)	18(6)	-22(6)	-5(5)
C(12)	153(6)	121(7)	192(6)	-29(6)	-23(6)	-14(5)
C(13)	143(7)	146(7)	254(7)	-48(6)	-59(6)	-34(6)
C(14)	167(7)	158(7)	200(7)	17(6)	-4(5)	23(6)
C(15)	188(7)	127(7)	215(7)	22(6)	-26(6)	14(6)
C(16)	286(8)	174(7)	264(7)	11(6)	-12(6)	-3(6)
C(17)	258(7)	213(8)	227(7)	3(6)	26(6)	-44(6)
C(18)	333(9)	164(8)	207(7)	16(6)	41(6)	64(6)
C(19)	502(10)	177(8)	340(8)	-71(7)	15(8)	13(7)
C(20)	355(8)	187(8)	221(7)	-19(6)	30(6)	-62(6)
C(21)	356(9)	283(9)	239(8)	-24(7)	79(7)	-139(7)
C(22)	701(13)	639(13)	554(11)	-180(10)	350(10)	-266(11)
C(23)	465(11)	926(16)	653(12)	-139(12)	-236(10)	253(12)
C(24)	328(8)	275(9)	231(7)	-46(7)	-3(7)	46(7)
C(25)	713(13)	542(14)	728(13)	-340(11)	146(11)	-5(11)
C(26)	682(12)	647(15)	547(11)	-108(10)	-309(10)	67(11)
C(27)	716(12)	432(12)	530(11)	-51(9)	30(10)	-201(9)

Chapter 3

Applications of a Unified Synthetic Strategy: Total Syntheses of (–)-Trichorabdal A and (–)-Longikaurin E[†]

3.1 INTRODUCTION

Having completed our initial objective, the total synthesis of maoecrystal Z, we sought access to additional distinct *ent*-kauranoid architectures. It was envisioned that a unified strategy would be a powerful tool for the synthesis of *ent*-kauranoid natural product analogs to further the exploration of novel biological properties discussed in the previous chapter. The route developed achieves the rapid synthesis of an unsaturated spirolactone intermediate, which possesses functional handles suitable for elaboration to trichorabdal A and longikaurin E. The divergent preparation of these bioactive *Isodon* diterpenoids from this key intermediate is described below.

[†] Portions of this chapter have been reproduced from the following communication: Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764. The research discussed was completed in collaboration with Victor W. Mak, a graduate student in the Reisman Laboratory.

3.1.1 Synthetic Considerations

Reported in 1982, the structure of trichorabdal A (**3**) is a prototypic 6,7-*seco*-*ent*-kauranoid (see Figure 3.1).[1] Its characteristic *exo*-methylene cyclopentanone contrasts with the acyclic enal of maoecrystal Z (**10**), though it exhibits a similar level of structural complexity. However, the structure of longikaurin E (**12**), disclosed in 1981, is that of the parent *ent*-kauranoid, with a C6–C7 bond extant.[2] In the retrosynthetic sense, we envisioned that both **3** and **12** could be accessible from *exo*-olefin **143**. To access **12**, we

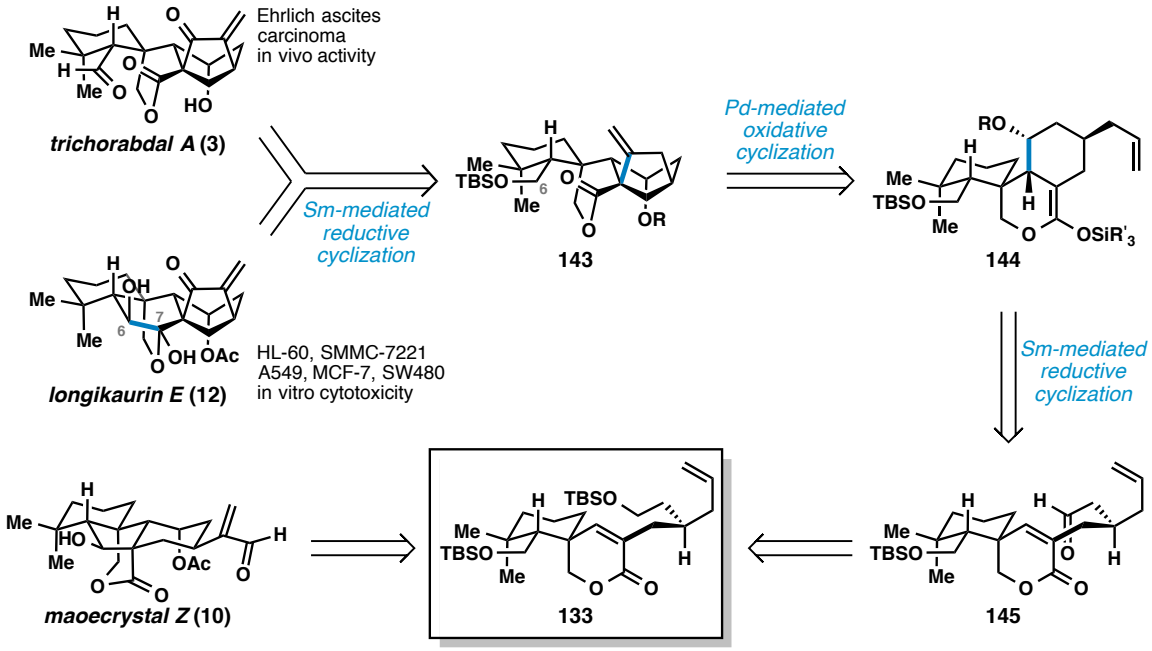


Figure 3.1. Retrosynthetic analysis for trichorabdal A (**3**) and longikaurin E (**12**).

hoped to forge the central oxabicyclo[2.2.2]octane via the reductive cyclization of a C6-aldehyde precursor.[3] In a key step, the bicyclo[3.2.1]octane motif of **143** would arise through an oxidative cyclization. Although this transformation is well established for silyl enol ethers,[4,5] we anticipated that use of a silyl ketene acetal such as **144** might prove more challenging: prior to our studies, there were no reported examples of transition metal-mediated oxidative cyclization reactions between silyl ketene acetals and simple

olefins to generate all-carbon quaternary centers.[6] Nonetheless, this disconnection was appealing as **144** could be obtained following Sm^{II}-mediated reductive cyclization of an aldehyde (**145**) derived from bis-silyl ether **133**, previously synthesized in five steps from (–)-γ-cyclogeraniol (**104**) en route to maoecrystal Z.[7]

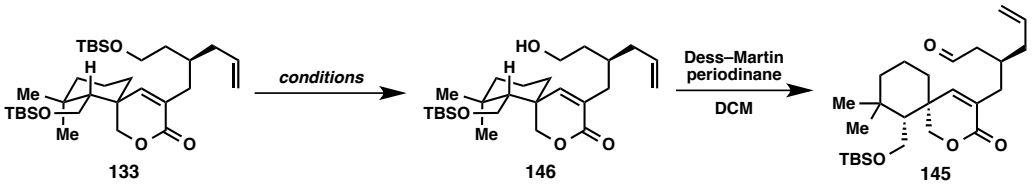
3.2 FORWARD SYNTHETIC EFFORTS

The following section describes the experiments conducted in order to achieve the total syntheses of (–)-trichorabdal A and (–)-longikaurin E.[8]

3.2.1 Development of a Key Pd^{II}-Mediated Oxidative Cyclization

As described in the retrosynthetic analysis, our initial objective was the elaboration of bis-silyl ether **133** to a suitable silyl ketene acetal substrate for the proposed oxidative cyclization reaction. Toward this end, cleavage of the more sterically accessible TBS ether could be accomplished under a variety of conditions (see Table 3.1). The use of *n*-Bu_4NHSO_4 and *p*-TsOH in methanol at 0 °C [9] (entry 3) provided optimal chemoselectivity for the desired desilylation; immediate treatment of crude alcohol **146** with Dess–Martin periodinane[10] furnished the highest yields of aldehyde **145**. Exposure of **145** to SmI_2 with LiBr and *t*-BuOH as additives effected reductive cyclization, providing a single diastereomer of tricyclic alcohol **147** in 57% yield (see Figure 3.2).[11] Protection of **147** as the methoxymethyl ether (**148**) proceeded smoothly, and subsequent deprotonation with KHMDS followed by addition of TBSCl at –78 °C delivered silyl ketene acetal **149**. Use of the MOM ether protecting group was found to be critical for silyl ketene acetal formation: use of silicon-based groups in the protection of **147** resulted

in poor yields for the ketene acetal forming step, and efforts to disilylate **147** were likewise unfruitful. As the C11 alcohol is *syn* to the enolizable proton, we hypothesize that large silyl ether groups sterically obstruct the desired deprotonation.



entry	conditions	temp (°C)	yield 145 (%)[a]
1	3:1:1 AcOH/THF/H_2O	23	68
2	4:1:1 THF/TFA/H_2O	0	55
3	*n*-Bu_4NHSO_4, *p*-TsOH, MeOH	0	77

[a]Isolated yield.

Table 3.1. Survey of conditions for selective deprotection/oxidation of **133**.

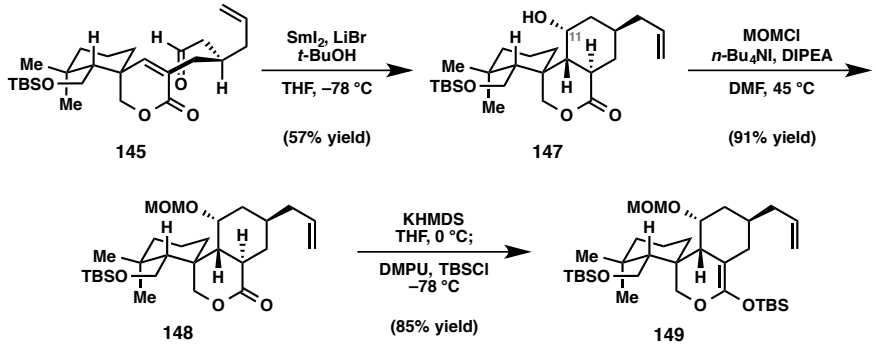
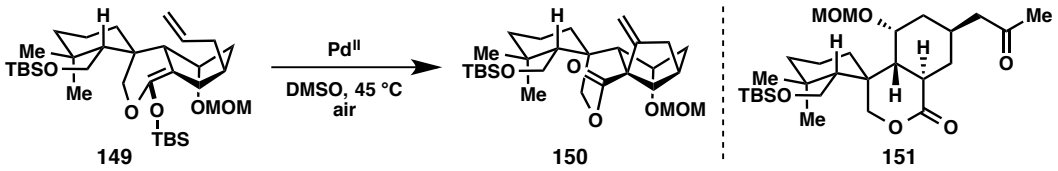


Figure 3.2. Synthesis of silyl ketene acetal **149**.

With silyl ketene acetal **149** in hand, we sought to explore the proposed oxidative cyclization to form the bicyclo[3.2.1]octane present in trichorabdal A (**3**) and longikaurin E (**12**). Upon exposure of **149** to 10 mol % $Pd(OAc)_2$ in DMSO at 45 °C under an air atmosphere, we were delighted to isolate tetracycle **150**, albeit in only 7% yield (Table 3.2, entry 1). Fortunately, the use of stoichiometric $Pd(OAc)_2$ substantially improved both conversion and the yield of **150** (entry 2), and a survey of reaction conditions was conducted. The desired transformation does proceed in MeCN at ambient temperature

(entry 3); however, an increased level of olefin isomerization side products is observed. All other solvents tested (e.g., PhMe, glyme, dioxane, *t*-BuOH, DMF) yielded only traces of **150**; other palladium sources also performed quite poorly (entries 4–6). Less coordinating counterions for palladium appear to skew the distribution of products toward that of Wacker oxidation: the major product when using $PdCl_2$ and $AgBF_4$ (entry 6) was methyl ketone **151**. No desaturated products from Saegusa–Ito-type pathways were observed.[12]



149 150 151

entry	Pd source (equiv)	additive (equiv)	yield 150 (%)[a]
1	$Pd(OAc)_2$ (0.1)	--	7
2	$Pd(OAc)_2$ (1.0)	--	35
3[b]	$Pd(OAc)_2$ (1.0)	--	28[c]
4	$Pd(TFA)_2$ (1.0)	--	19
5	$PdCl_2$ (1.0)	--	0
6	$PdCl_2$ (1.0)	$AgBF_4$ (2.0)	5[d]
7[e]	$Pd(OAc)_2$ (1.0)	H_2O (5.0)	38
8	$Pd(OAc)_2$ (1.0)	K_2CO_3 (5.0)	0
9	$Pd(OAc)_2$ (1.0)	AcOH (0.5)	56
10	$Pd(OAc)_2$ (0.1)	AcOH (0.5)	7
11	$Pd(OAc)_2$ (1.0)	AcOH (1.0)	31
12	$Pd(OAc)_2$ (1.0)	*p*-TsOH (0.5)	46
13	$Pd(OAc)_2$ (1.0)	BzOH (0.5)	32
14	$Pd(OAc)_2$ (1.0)	PivOH (0.5)	40

[a]Isolated yield. [b]Reaction conducted in MeCN at 23 °C. [c]Product isolated as an inseparable 4.3:1 mixture with an olefin isomerization side product. [d]13% yield of methyl ketone **151** was also isolated. [e]Run under a N_2 atmosphere.

Table 3.2. Reaction optimization for the formation of **150**.

High variability in both the yield and purity of **150** upon attempts to increase reaction scale beyond a few milligrams prompted an examination of the roles of adventitious water and Brønsted acid. Control experiments demonstrated that water had little effect on

product formation (entry 7), whereas the addition of bases such as K_2CO_3 inhibits the reaction (entry 8). On the other hand, the use of 0.5 equiv AcOH as an additive afforded **150** in 56% yield (entry 9) with a much cleaner reaction profile, a result reproducible on preparative scales. Neither an increased amount of AcOH, nor the use of other acids examined further improved the yield.

While the exact role of the acid additive remains unclear, we observe that formation of palladium black is strongly suppressed, a likely cause of the reduction in side product formation. In studies on a Pd^{II} catalytic system for aerobic alcohol oxidation, Sigman and colleagues observe a rate increase with the addition of AcOH, possibly due to a switch in the rate- and turnover-limiting step from *β*-hydride elimination to reoxidation.[13] In our system, there are two likely reaction pathways (Figure 3.3) to form *exo*-olefin **150**: one, olefin coordination and direct displacement by the ketene acetal nucleophile (**149** to **152**) to afford a Pd^{II}-alkyl species (**153**), releasing **150** upon *β*-hydride elimination; and two, transmetalation to afford a Pd^{II}-enolate, which may undergo a *syn*-palladation pathway via its C-bound tautomer (**155** to **153**), followed by *β*-hydride elimination to release the product (**150**). While our system does not appear to undergo catalytic turnover, limited NMR studies have suggested that olefin insertion or *β*-hydride elimination may be sluggish in our system. The addition of AcOH likely influences various equilibria and dynamic processes such as ligand exchange, transmetalation, olefin insertion, and enolate tautomerization, all of which could affect the reaction rate or mechanism. Irrespective of the role of AcOH, to the best of our knowledge, this transformation represents the first example of a Pd-mediated oxidative cyclization of a silyl ketene acetal to generate an all-carbon quaternary center.

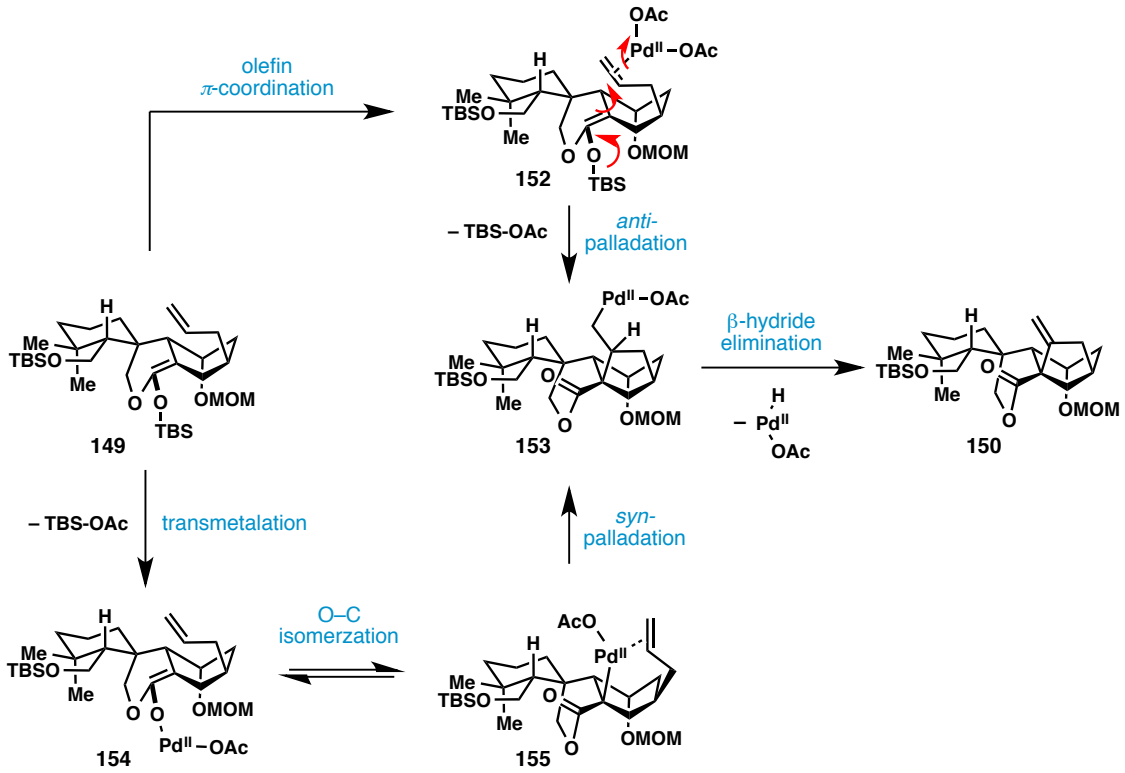
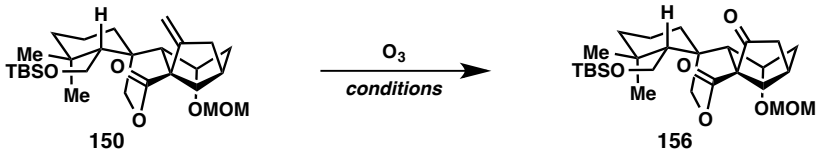


Figure 3.3. Mechanistic pathways for the formation of **150** from **149**.

3.2.2 Synthesis of (–)-Trichorabdal A

Having now established the carbon framework present in many 6,7-*seco*-*ent*-kauranoids, the remaining steps for transformation to **3** include installation of the *exo*-enone and C6 aldehyde. Initial ozonolyses of **150** employed a triethylamine workup, resulting in the isolation of only 33% yield of desired *β*-ketolactone **156**, and poor overall mass recovery (Table 3.3, entry 1). This finding suggested a marked sensitivity to base, compared with intermediates bearing the maoecrystal Z framework. A brief survey of solvents and workup parameters revealed that triphenylphosphine provided most rapid decomposition of the ozonide to ketolactone **156**. Use of triphenylphosphine supported on polystyrene for easy removal and product purification, combined with a lower reaction temperature of –94 °C increased the yield of **156** to 69% (entry 6). Notably, a further

slight increase could be realized by lowering the reaction temperature to –116 °C and switching solvents to bromoethane (entry 7).



entry	solvent	temp (°C)	workup reagent (equiv)	yield 156 (%)[a]
1	DCM	–78	Et_3N (20)	33
2	DCM	–78	Me_2S (25)	52
3	DCM	–78	thiourea (10)	51
4	DCM	–78	PPh_3 (10)	63
5	DCM	–78	PPh_3/polystyrene (10)	63
6	DCM	–94[b]	PPh_3/polystyrene (10)	69
7	EtBr	–116[c]	PPh_3/polystyrene (10)	71
8	pentane[d]	–116[c]	PPh_3/polystyrene (10)	64

[a]Isolated yield. [b]Acetone/N_2(*liq*) bath. [c]EtOH/N_2(*liq*) bath. [d]Ozonide of **150** insoluble in pentane, DCM added with workup reagents.

Table 3.3. Optimization of ozonolysis of **150**.

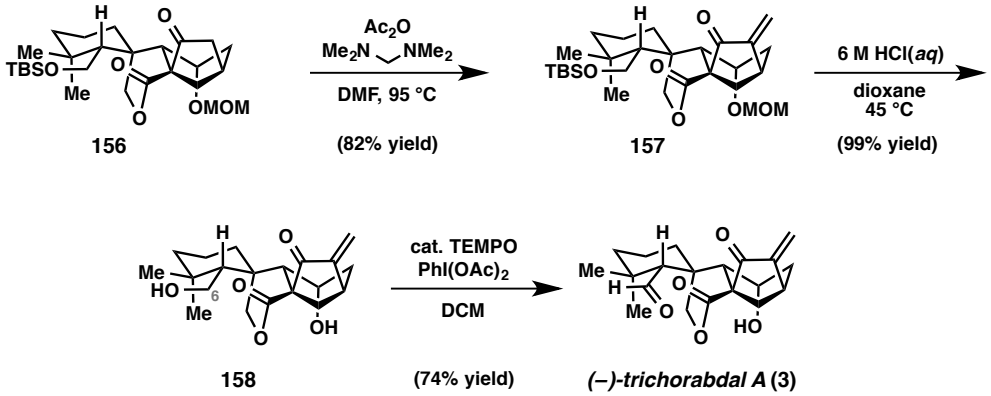


Figure 3.4. Completion of total synthesis of (–)-trichorabdal A (**3**).

Enone **157** was obtained in 82% yield upon treatment of **156** with bis(dimethylamino)methane and acetic anhydride (Figure 3.4).[14] Two-step protocols

using a strong base and Eschenmoser's salt provided significantly diminished yields of **157**. Exposure to 6 M aqueous HCl in dioxane at 45 °C smoothly effected global deprotection, and selective oxidation of the C6 primary alcohol was accomplished using catalytic TEMPO and $PhI(OAc)_2$,[15] delivering (–)-trichorabdal A (**3**).[16]

3.2.3 Synthesis of (–)-Longikaurin E

With the synthesis of **3** complete, we turned our attention to the aldehyde-lactone reductive coupling required for the synthesis of longikaurin E (**12**). Treatment of *exo*-olefin **150** with 6 M aqueous HCl in dioxane at 45 °C resulted in global deprotection to afford diol **159**; subsequent oxidation with catalytic TEMPO and $PhI(OAc)_2$ likewise proceeded smoothly (see Figure 3.5). Aldehyde **160** was acetylated using acetic anhydride and DMAP to furnish **161**, and a screen of reaction parameters for the proposed reductive cyclization was conducted.

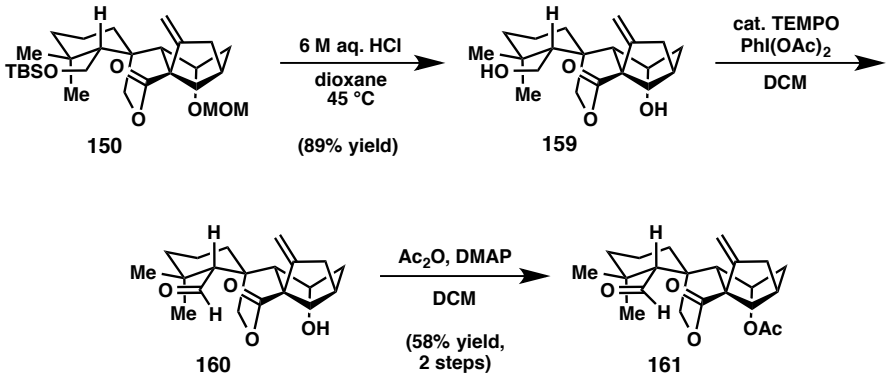
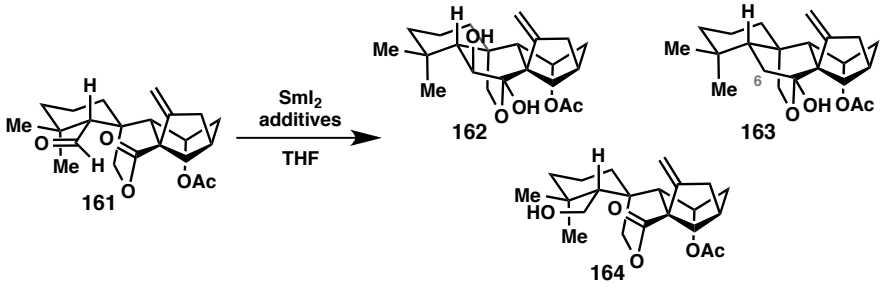


Figure 3.5. Advancement of *exo*-olefin **150** to aldehyde-lactone **161**.



entry	SmI_2 equiv	additives (equiv)	temp (°C)	yield[a] (brsm)
1	5.0	LiBr (50) *t*-BuOH (1.0)	–78	no reaction
2	5.0	HMPA (50)	–78	0%[b]
3	5.0	LiCl (50) *t*-BuOH (1.0)	0	54% **164**
4	5.0	LiBr (50) *t*-BuOH (1.0)	0	38% **164**
5	2.0	--	23	55% **162** (75%)
6	2.4	--	23	55% **162** (62%)
7[c]	5.0	*t*-BuOH (1.0)	23	72% **161**

[a]Isolated yield. [b]Complex mixture. [c]Run to full consumption of **161**.

Table 3.4. Survey of reaction paramters for conversion of **161** to **162**.

Exposure of **161** to SmI_2 with LiBr and *t*-BuOH at –78 °C (Table 3.4, entry 1) unexpectedly led to recovery of starting material. Whereas addition of HMPA effected swift decomposition of **161** (entry 2), increasing the reaction temperature to 0 °C resulted in reduction to primary alcohol **164** when employing LiCl or LiBr additives (entries 3 and 4). Gratifyingly, exclusive use of SmI_2 at ambient temperature provided the desired hydroxy-lactol (**162**) in 55% yield, along with 27% yield of recovered **161** (entry 5). Interestingly, attempting to push the reaction to full conversion did not improve the yield of **162**; instead, over-reduction to C6-deoxylactol **163** was observed (entry 7). It is presumed that warmer temperatures enable the ketyl radical intermediate to attain the necessary conformation for cyclization; omission of additives precludes competitive

over-reduction (to **164**) and α-deoxygenation (to **163**) processes, favoring cyclization product **162**. With the oxabicyclo[2.2.2]octane in hand, ozonolysis of **162** and α-methylenation under previously described conditions revealed (–)-longikaurin E (Figure 3.6).

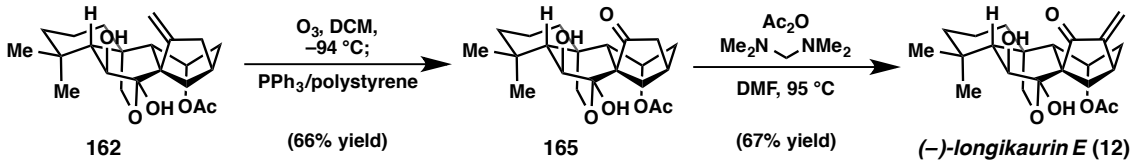


Figure 3.6. Completion of the synthesis of (–)-longikaurin E (**12**).

3.3 CONCLUDING REMARKS

In summary, a unified strategy has enabled the first total syntheses of the *ent*-kauranoid natural products (–)-trichorabdal A (**3**) and (–)-longikauin E (**12**) in 15 and 17 steps from (–)-γ-cyclogeraniol (**104**), and in 3.2% and 1.0% overall yield. Key to the success of our approach is the development of a Pd^{II}-mediated silyl ketene acetal oxidative cyclization reaction to install the bridgehead all-carbon quaternary stereocenter of **3** and **12**, and the use of a Sm^{II}-mediated reductive coupling to construct the C6–C7 bond of **12**. These transformations, taken together with those described in the previous chapter, constitute a diverging route that has established a synthetic relationship among three architecturally distinct *ent*-kaurane diterpenoids by enabling their total syntheses from one common spirolactone.

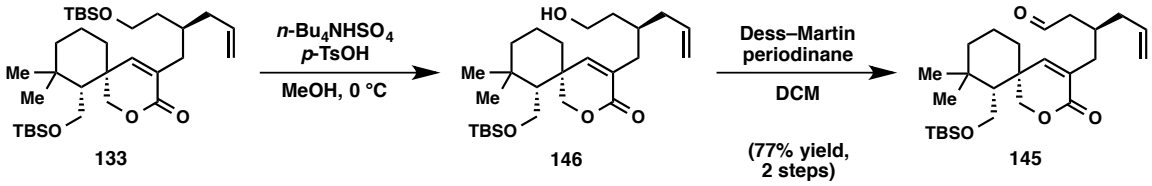
3.4 EXPERIMENTAL SECTION

3.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (DCM), and dimethylformamide (DMF) were dried by passing through activated alumina columns. Triethylamine (Et_3N) and *N*,*N*-Diisopropylethylamine (DIPEA) were distilled over calcium hydride, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and hexamethylphosphoramide (HMPA) were distilled over calcium hydride under reduced pressure, and dimethylsulfoxide (DMSO) was dried over 4ÅMS for at least 48 hours prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, $KMnO_4$, or CAM staining. Flash column chromatography was performed as described by Still et al.[17] using silica gel (particle size 0.032-0.063) purchased from Silicycle or Florisil (100-200 mesh) purchased from Sigma-Aldrich. 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 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), or pyridine (^1H, δ = 8.71, most downfield signal), and $CDCl_3$ (^{13}C, δ = 77.0) or pyridine (^{13}C, δ = 149.9, center peak of most downfield signal). 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. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm).

3.4.2 Preparative Procedures and Spectroscopic Data

Preparation of aldehyde 145.

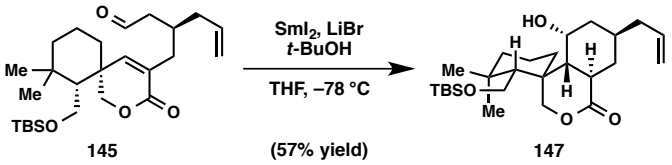


To a solution of enoate **133** (1.94 g, 3.43 mmol) in 35 mL MeOH cooled to 0 °C was added *n*-Bu_4NHSO_4 (128 mg, 0.378 mmol, 0.11 equiv) and *p*-TsOH (26 mg, 0.14 mmol, 0.04 equiv). After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with sat. $NaHCO_3$ (25 mL) and concentrated *in vacuo* to remove MeOH. The aqueous layer was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were then washed with brine (15 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide crude alcohol **146**. Crude **146** was immediately dissolved in DCM (35 mL) and Dess–Martin periodinane (2.91 g, 6.87 mmol, 2.0 equiv) was added. After stirring at ambient temperature for 30 min, sat. $NaHCO_3$ (20 mL) and sat. $Na_2S_2O_3$ (20 mL) were added and the biphasic mixture was stirred vigorously until both layers became clear (20 min). The layers were separated and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 12% EtOAc/Hex) to provide aldehyde **145** as a clear gum (1.18 g, 77% yield from **133**). $[\alpha]_D^{25}$ = –33.4° (*c* 1.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (t, *J* = 2.0 Hz, 1H), 6.39 (s, 1H), 5.78 – 5.66 (m, 1H), 5.09 – 4.99 (m, 2H), 4.48 (dd, *J* = 11.2, 1.9 Hz, 1H), 4.40 (dd, *J* = 11.2, 1.4 Hz, 1H), 3.81 – 3.71 (m, 2H), 2.48 – 2.26 (m, 4H), 2.20 – 2.10 (m, 2H), 2.01 (dt, *J* = 13.9, 7.6 Hz, 1H), 1.84 (d, *J* = 13.6 Hz, 1H), 1.69 – 1.49 (m, 2H), 1.48 – 1.39 (m, 2H), 1.25 (td, *J* = 13.0, 4.3 Hz, 1H), 1.14 (td, *J* = 13.0, 4.4 Hz, 1H), 1.01 (s, 3H), 0.89 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.5, 164.8, 155.6, 135.6, 126.2, 117.6, 69.9, 61.3, 55.5, 47.3, 42.0, 39.7, 38.6, 36.0, 33.1, 33.0, 32.8, 32.1, 25.8, 23.2, 18.3, 18.1, -5.5, -5.6; FTIR (thin film/NaCl): 3421, 3076,

2927, 2855, 2716, 1728, 1713, 1471, 1393, 1255, 1164, 1150, 1104, 1068, 995, 913, 838, 776 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{26}H_{45}O_4Si$ $[M + H]^+$ 449.3082, found 449.3067.

An analytical sample of alcohol **146** was obtained (63% yield) by SiO_2 chromatography (30% EtOAc/Hex). $[\alpha]_D^{25}$ = –44.6° (*c* 1.21, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 6.37 (s, 1H), 5.73 (dddd, *J* = 16.8, 10.4, 7.7, 6.5 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.51 (dd, *J* = 11.3, 2.1 Hz, 1H), 4.41 (dd, *J* = 11.3, 1.5 Hz, 1H), 3.83 – 3.71 (m, 3H), 3.67 (dt, *J* = 11.0, 6.4 Hz, 1H), 2.36 (ddd, *J* = 13.9, 5.6, 1.3 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.04 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.01 – 1.92 (m, 2H), 1.91 – 1.78 (m, 2H), 1.66 – 1.49 (m, 3H), 1.49 – 1.34 (m, 3H), 1.32 – 1.21 (m, 1H), 1.21 – 1.09 (m, 1H), 1.02 (s, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.2, 154.6, 136.3, 127.6, 116.8, 70.0, 61.5, 60.6, 55.6, 42.1, 40.0, 38.2, 35.7, 35.3, 33.3, 33.3, 33.0, 32.8, 25.8, 23.3, 18.4, 18.0, -5.5, -5.6; FTIR (thin film/NaCl): 3447, 3074, 2952, 2928, 2856, 1718, 1472, 1462, 1395, 1363, 1256, 1165, 1150, 1105, 1069, 995, 909, 838, 776; HRMS (MM: ESI–APCI) calc'd for $C_{26}H_{47}O_4Si$ $[M + H]^+$ 451.3238, found 451.3251.

Preparation of tricycle 147.



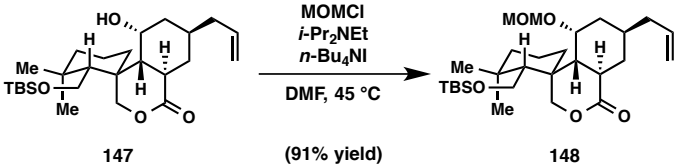
145 147

Fresh SmI_2 was prepared according to the following procedure[18]: A flame-dried flask was charged with finely ground samarium (Aldrich, 1.30 g, 8.64 mmol, 1.7 equiv) and was briefly flame-dried *in vacuo*. Once cooled, THF (50 mL) was added under argon followed by diiodoethane (1.40 g, 4.96 mmol, 1.0 equiv) with vigorous stirring for 3 h at ambient temperature. The deep blue solution (~0.1M in SmI_2) was allowed to settle for at least 10 min prior to use.

A solution of aldehyde **145** (0.676 g, 1.51 mmol) and *t*-BuOH (0.145 mL, 1.51 mmol, 1.0 equiv) in 150 mL THF was cooled to –78 °C. Inside a glovebox, a separate flame-dried flask was

charged with LiBr (3.27 g, 38 mmol, 25 equiv), removed from the glovebox, and to this flask was added freshly prepared 0.1 M SmI_2 in THF (38 mL, 3.8 mmol, 2.5 equiv) and stirred vigorously for 2 min. While stirring continued, the resulting homogenous purple solution was added to the aldehyde solution via cannula. After 45 min at –78 °C, sat. $NaHCO_3$ (60 mL), sat. $Na_2S_2O_3$ (60 mL) and Rochelle salt (10 g) were added, and the mixture was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (9 to 12% EtOAc/Hex) to afford tricycle **17** as a white foam (0.385 g, 57% yield). $[\alpha]_D^{25}$ = –11.3° (*c* 2.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 – 5.68 (m, 1H), 5.04 – 4.94 (m, 2H), 4.55 (br s, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.24 (dd, *J* = 11.5, 1.4 Hz, 1H), 3.72 (dd, *J* = 11.4, 4.1 Hz, 1H), 3.67 (dd, *J* = 11.3, 3.3 Hz, 1H), 2.85 (td, *J* = 12.3, 3.4 Hz, 1H), 2.45 (dtd, *J* = 13.2, 3.6, 2.0 Hz, 1H), 2.04 – 1.84 (m, 5H), 1.79 – 1.71 (m, 2H), 1.69 (t, *J* = 3.8 Hz, 1H), 1.56 – 1.36 (m, 4H), 1.27 (td, *J* = 12.7, 4.9 Hz, 1H), 1.09 (ddd, *J* = 14.2, 12.5, 2.2 Hz, 1H), 1.01 (s, 3H), 0.98 (t, *J* = 12.0 Hz, 1H), 0.88 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 136.2, 116.3, 73.2, 65.5, 60.0, 51.5, 46.6, 41.9, 40.9, 40.8, 39.5, 35.4, 35.1, 34.1, 33.7, 30.6, 27.8, 25.9, 23.6, 18.4, 18.1, -5.5, -5.6; FTIR (thin film/NaCl): 3461, 3075, 2927, 2856, 1716, 1471, 1463, 1394, 1362, 1256, 1220, 1064, 1046, 994, 911, 837, 776, 734 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{26}H_{47}O_4Si$ $[M + H]^+$ 451.3238, found 451.3236.

Preparation of MOM ether 148.

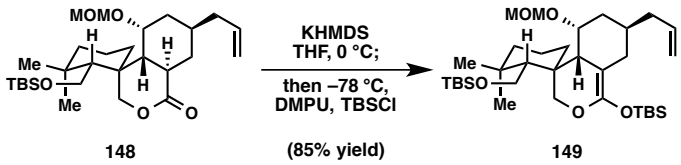


147 **(91% yield)** **148**

A solution of tricycle **147** (0.315 g, 0.699 mmol), *n*-Bu_4NI (26 mg, 70 μmol, 0.1 equiv), DIPEA (0.73 mL, 4.2 mmol, 6.0 equiv), and MOMCl (92% tech., 0.29 mL, 3.5 mmol, 5.0 equiv)

in 3.5 mL DMF was heated to 45 °C. After stirring for 6 h at 45 °C, the reaction mixture was cooled to room temperature and diluted with sat. $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7 to 9% EtOAc/Hex) to afford methoxymethyl ether **148** as a clear gum (0.315 g, 91% yield). $[\alpha]_D^{25} = -22°$ (*c* 0.76, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.81 – 5.69 (m, 1H), 5.05 – 4.98 (m, 1H), 4.98 (t, *J* = 1.2 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.37 (dt, *J* = 3.7, 1.8 Hz, 1H), 4.24 (dd, *J* = 11.4, 1.4 Hz, 1H), 3.74 (dd, *J* = 11.4, 4.1 Hz, 1H), 3.67 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.40 (s, 3H), 2.87 (td, *J* = 12.3, 3.5 Hz, 1H), 2.47 (dtd, *J* = 13.1, 3.7, 2.1 Hz, 1H), 2.09 – 1.86 (m, 5H), 1.86 – 1.72 (m, 2H), 1.69 (t, *J* = 3.7 Hz, 1H), 1.64 – 1.40 (m, 4H), 1.28 – 1.18 (m, 1H), 1.08 – 0.96 (m, 4H), 0.90 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 136.2, 116.3, 95.1, 73.3, 71.4, 59.8, 56.3, 51.4, 47.0, 42.1, 40.8, 39.6, 36.4, 36.1, 35.3, 34.1, 33.9, 31.2, 27.4, 25.9, 23.5, 18.3, 18.1, -5.5, -5.6; FTIR (thin film/NaCl): 3074, 2951, 2927, 2855, 1731, 1472, 1462, 1389, 1361, 1256, 1202, 1149, 1085, 1063, 1045, 918, 838, 776 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{28}H_{51}O_5Si$ $[M + H]^+$ 495.3500, found 495.3510.

Preparation of silyl ketene acetal 149.



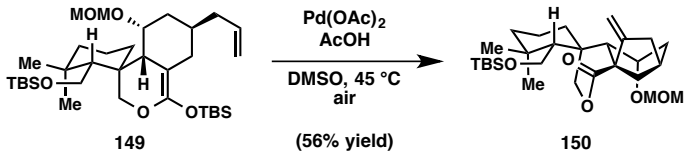
148 (85% yield) 149

*Note: 1-methyl-2-pyrrolidinone (NMP; distilled from CaH_2) can be readily substituted for DMPU affording identical product yields.

To a solution of KHMDS (0.106 g, 0.534 mmol, 2.0 equiv) in 5 mL THF cooled to 0 °C was added MOM ether **148** (0.132 g, 0.267 mmol) dropwise as a solution in THF (3 mL + 1 mL

rinse). After stirring at 0 °C for 30 min, the reaction mixture was cooled to –78 °C and DMPU (1.0 mL) was added dropwise. After stirring 5 min, TBSCl (80 mg in 1 mL THF, 0.53 mmol, 2.0 equiv) was added and cooling was maintained at –78 °C. After 1 h, the reaction mixture was warmed to 0 °C, diluted with ice-cold pentane (10 mL) and ice-cold sat. $NaHCO_3$ (5 mL). The layers were separated and the aqueous was extracted with ice-cold pentane (2 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on Florisil (3% EtOAc/Hex with 0.5% Et_3N) to afford silyl ketene acetal **149** as a clear gum (0.139 g, 85% yield). $[\alpha]_D^{25}$ = –82.6° (*c* 1.50, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.77 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.02 – 4.93 (m, 2H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.04 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.99 (d, *J* = 10.3 Hz, 1H), 3.92 (dt, *J* = 3.8, 1.8 Hz, 1H), 3.84 (dd, *J* = 10.4, 1.5 Hz, 1H), 3.81 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.36 (s, 3H), 2.69 (ddd, *J* = 13.2, 4.3, 2.1 Hz, 1H), 2.22 (s, 1H), 2.15 (dq, *J* = 13.8, 2.7 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.79 – 1.66 (m, 2H), 1.59 – 1.39 (m, 4H), 1.31 – 1.15 (m, 2H), 1.05 (s, 3H), 1.02 (s, 3H), 1.00 – 0.93 (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.5, 137.2, 115.5, 95.8, 82.8, 74.7, 71.9, 61.7, 56.3, 50.1 (br), 45.8, 41.2, 38.5 (br), 38.2, 37.7, 33.8, 33.6, 32.9, 32.8, 30.4 (br), 28.1, 26.0, 25.8, 19.5, 18.1, 18.0, -4.2, -4.4, -5.7, -5.9; FTIR (thin film/NaCl): 3075, 2952, 2929, 2857, 1713, 1472, 1463, 1361, 1250, 1166, 1150, 1099, 1047, 1035, 989, 910, 870, 839, 783 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{34}H_{65}O_5Si_2$ $[M + H]^+$ 609.4365, found 609.4354.

Preparation of tetracycle 150.

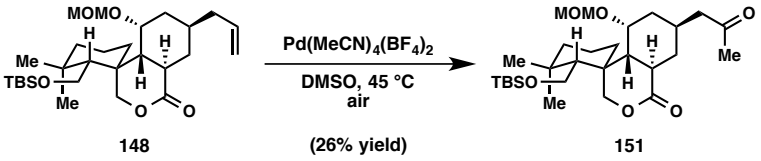


A solution of silyl ketene acetal **149** (0.139 g, 0.228 mmol), $Pd(OAc)_2$ (52 mg, 0.23 mmol, 1.0 equiv), and AcOH (6.9 mg in 0.10 mL DMSO, 0.11 mmol, 0.5 equiv) in 9 mL DMSO was heated to 45 °C in an open flask. After stirring under air for 6 h at 45 °C, the reaction mixture was cooled to room temperature, diluted with 1M HCl (10 mL) and extracted with Et_2O (4 x 6 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7 to 9% EtOAc/Hex) to afford tetracycle **150** as a clear gum (63 mg, 56% yield). $[\alpha]_D^{25}$ = +23.0° (*c* 0.305, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.98 (s, 1H), 4.94 (s, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.53 (s, 2H), 4.13 (q, *J* = 4.4 Hz, 1H), 3.79 (dd, *J* = 11.4, 5.0 Hz, 1H), 3.71 (dd, *J* = 11.7, 2.0 Hz, 1H), 3.40 (s, 3H), 2.68 (d, *J* = 5.0 Hz, 1H), 2.58 (d, *J* = 16.6 Hz, 1H), 2.47 – 2.42 (m, 2H), 2.30 – 2.22 (m, 2H), 2.19 (d, *J* = 16.3 Hz, 1H), 1.89 (dd, *J* = 11.8, 3.9 Hz, 1H), 1.78 (d, *J* = 14.0 Hz, 1H), 1.73 – 1.68 (m, 1H), 1.49 – 1.41 (m, 3H), 1.37 (dd, *J* = 14.5, 4.5 Hz, 1H), 1.30 – 1.24 (m, 1H), 1.02 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4, 157.0, 106.1, 96.0, 72.9, 71.5, 60.7, 56.1, 53.4, 52.2, 52.1, 42.9, 42.4, 41.4, 35.9, 35.8, 34.4, 34.4, 30.9, 30.6, 25.9, 23.7, 18.3, 18.2, -5.5, -5.5; FTIR (thin film/NaCl): 3583, 2926, 2853, 1739, 1464, 1388, 1252, 1232, 1147, 1082, 1046, 837, 776 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{28}H_{49}O_5Si$ $[M + H]^+$ 493.3344, found 493.3355.

Optimization of reaction parameters: General procedure for oxidative cyclization of 149 to 150 (Table 3.2).

A vial was charged with silyl ketene acetal **149** (10 mg, 16 μmol), Pd(II) salt, additive, and solvent (0.65 mL), placed under an atmosphere of O_2, N_2, or air, and heated to the desired temperature. Following the cessation of reaction progress as indicated by LC-MS or TLC analysis, the mixture was cooled to room temperature and diluted with 1M HCl (1 mL) and Et_2O (1 mL). The layers were separated and the aqueous layer was extracted further with Et_2O (3 x 0.5 mL). The combined organic extracts were washed with brine (0.5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7 to 9% EtOAc/Hex) to afford pure tetracycle **150**.

Preparation of methyl ketone 151.

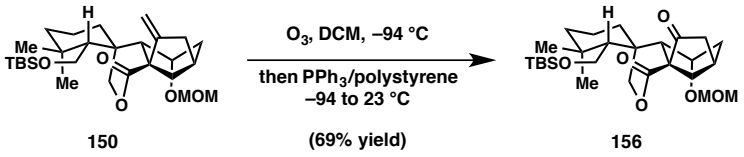


*Note: Methyl ketone **151** was initially isolated as a side product during optimization experiments for the conversion of **149** to **150** (Table 3.2, entry 6, 13% yield). Independent preparation was accomplished using the following procedure.

A solution of MOM ether **148** (16 mg, 32 μmol) and $Pd(MeCN)_4(BF_4)_2$ (14 mg, 32 μmol, 1.0 equiv) in DMSO (1.3 mL) was heated at 45 °C in an open vial. After stirring under air for 3 h, the reaction mixture was cooled to room temperature and diluted with 1M HCl (2 mL) and extracted with Et_2O (3 x 2 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 20%

EtOAc/Hex) to afford methyl ketone **151** as a clear gum (4.3 mg, 26% yield). $[\alpha]_D^{25}$ = –15° (*c* 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.76 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.37 (dt, *J* = 3.8, 1.8 Hz, 1H), 4.25 (dd, *J* = 11.4, 1.4 Hz, 1H), 3.74 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.67 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.45 (s, 3H), 2.94 (td, *J* = 12.3, 3.6 Hz, 1H), 2.46 – 2.37 (m, 2H), 2.38 – 2.23 (m, 2H), 2.13 (s, 3H), 2.09 (dq, *J* = 14.1, 3.2 Hz, 1H), 1.99 – 1.88 (m, 2H), 1.81 – 1.73 (m, 1H), 1.68 (t, *J* = 3.7 Hz, 1H), 1.59 – 1.42 (m, 4H), 1.29 – 1.19 (m, 1H), 1.11 – 1.03 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 207.5, 173.6, 95.0, 73.4, 70.7, 59.9, 56.5, 51.4, 50.1, 46.8, 42.1, 39.6, 36.3, 36.0, 35.3, 34.1, 33.9, 30.5, 27.4, 27.1, 25.9, 23.6, 18.4, 18.1, -5.5, -5.5; FTIR (thin film/NaCl): 2951, 2926, 2855, 1732, 1716, 1471, 1463, 1361, 1251, 1206, 1148, 1084, 1063, 1045, 918, 837, 776 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{28}H_{51}O_6Si$ $[M + H]^+$ 511.3449, found 511.3465.

Preparation of ketolactone 156.

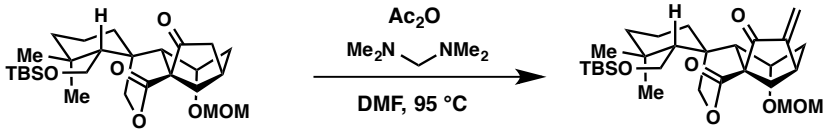


150 (69% yield) **156**

A solution of tetracycle **150** (30.0 mg, 60.9 μmol) in 6 mL DCM was cooled to –94 °C (liq. N_2/acetone) at which time ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 1 setting on ozone generator) for 10 min. The solution was purged with argon for 5 min, polystyrene-bound PPh_3 (3 mmol/g loading, 200 mg, 0.61 mmol, 10 equiv) was then added. The reaction was slowly warmed to room temperature over 30 min. After stirring for 3 h, the suspension was filtered through celite and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (15 to 20% EtOAc/Hex) to afford ketolactone **156** as a clear gum (20.9 mg, 69% yield). $[\alpha]_D^{25}$ = +8.2° (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.69 (d, *J* = 6.7

Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.27 (br s, 1H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.64 (dd, *J* = 11.7, 6.1 Hz, 1H), 3.41 (s, 3H), 2.83 (d, *J* = 10.8 Hz, 1H), 2.73 – 2.62 (m, 2H), 2.48 (ddd, *J* = 18.4, 6.9, 1.4 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.13 (dd, *J* = 18.4, 3.7 Hz, 1H), 2.07 (t, *J* = 13.1 Hz, 1H), 1.75 – 1.65 (m, 2H), 1.53 – 1.37 (m, 3H), 1.32 (dd, *J* = 15.4, 4.4 Hz, 1H), 1.29 – 1.21 (m, 1H), 1.03 (s, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 214.1, 171.3, 96.2, 72.9, 70.0, 60.4, 57.4, 56.4, 51.4, 48.2, 47.1, 43.1, 42.5, 35.2, 34.3, 34.2, 32.5, 29.1, 27.1, 25.9, 23.6, 18.2, 18.0, -5.5, -5.5; FTIR (thin film/NaCl): 2952, 2928, 2856, 1750, 1726, 1471, 1464, 1390, 1236, 1148, 1094, 1047, 959, 945, 915, 838, 778 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{27}H_{47}O_6Si$ $[M + H]^+$ 495.3136, found 495.3147.

Preparation of enone 157.

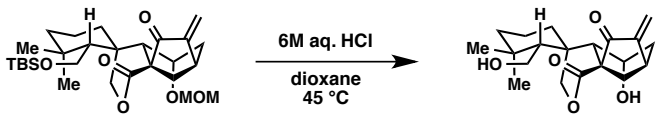


156 **157**

A solution of ketolactone **156** (19.2 mg, 38.8 μmol), bis(dimethylamino)methane (0.40 mL, 2.9 mmol, 75 equiv), acetic anhydride (0.40 mL, 4.2 mmol, 109 equiv) and 0.40 mL DMF was heated to 95 °C in a sealed vial. After stirring at 95 °C for 1 h, the reaction mixture was cooled to room temperature, diluted with sat. $NaHCO_3$ (1 mL) and extracted with DCM (3 x 1 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (0.5 mL) and brine (0.5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 15% EtOAc/Hex) to afford enone **157** as a clear gum (16.1 mg, 82% yield). $[\alpha]_D^{25}$ = +27.6° (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (s, 1H), 5.46 (s, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.24 (br s, 1H), 3.66 (d, *J* = 11.4 Hz, 1H), 3.58 (dd, *J* = 11.4, 6.1 Hz, 1H), 3.42 (s, 3H), 3.13 (ddt, *J* = 9.6, 5.0, 1.0

Hz, 1H), 2.85 (d, *J* = 12.1 Hz, 1H), 2.68 (s, 1H), 2.45 (dd, *J* = 15.2, 9.3 Hz, 1H), 2.31 (dd, *J* = 12.3, 4.7 Hz, 1H), 1.93 (t, *J* = 13.8 Hz, 1H), 1.75 (d, *J* = 14.4 Hz, 1H), 1.68 (d, *J* = 5.1 Hz, 1H), 1.58 (dd, *J* = 15.1, 4.7 Hz, 1H), 1.54 – 1.39 (m, 3H), 1.30 – 1.20 (m, 1H), 1.03 (s, 3H), 0.88 (s, 3H), 0.84 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.0, 171.3, 150.0, 118.1, 96.4, 73.0, 69.3, 60.4, 56.9, 56.4, 51.9, 48.0, 43.7, 42.5, 36.9, 34.4, 34.3, 34.3, 29.7, 29.6, 26.0, 23.7, 18.3, 18.0, -5.6, -5.6; FTIR (thin film/NaCl): 2952, 2928, 2855, 1744, 1719, 1462, 1389, 1366, 1261, 1235, 1147, 1122, 1092, 1047, 989, 932, 838, 778 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{28}H_{47}O_6Si$ $[M + H]^+$ 507.3136, found 507.3145.

Preparation of diol 158.

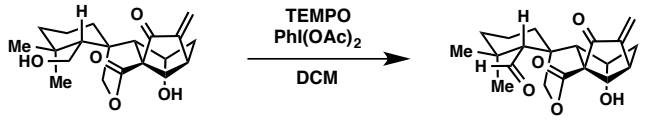


157 (99% yield) **158**

To a solution of enone **157** (16.1 mg, 31.8 μmol) in 0.90 mL dioxane was added 0.70 mL 6M HCl(*aq*), and the mixture was stirred at 45 °C. After 75 min, the reaction mixture was cooled to room temperature, carefully diluted with sat. $NaHCO_3$ (3 mL) and DCM (3 mL) and stirred until cessation of bubbling (10 min). The layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 mL) and brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (50 to 65% EtOAc/Hex) to afford diol **158** as a white solid (11.0 mg, 99% yield). $[\alpha]_D^{25}$ = +14° (*c* 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.01 (s, 1H), 5.48 (s, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.55 (br s, 1H), 4.32 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.79 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.65 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.16 (ddt, *J* = 8.8, 4.9, 1.1 Hz, 1H), 3.00 (d, *J* = 12.2 Hz, 1H), 2.65 (d, *J* = 3.2 Hz, 1H), 2.31 (ddd, *J* = 12.2, 4.8, 1.4 Hz, 1H), 2.14 (ddd, *J* = 15.1, 8.9, 1.9 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.87 – 1.79 (m, 2H), 1.76 (d, *J* = 6.1 Hz, 1H), 1.56 – 1.43 (m,

4H), 1.37 – 1.27 (m, 2H), 1.07 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 171.2, 149.7, 118.2, 69.5, 66.1, 60.1, 56.8, 51.7, 47.3, 43.4, 42.0, 34.6, 34.3, 33.9, 30.2, 30.1, 29.7, 24.0, 18.1; FTIR (thin film/NaCl): 3434, 2921, 2848, 1734, 1700, 1457, 1390, 1357, 1260, 1124, 1039, 1021, 928, 836, 749 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{20}H_{29}O_5$ $[M + H]^+$ 349.2010, found 349.2014.

Preparation of (–)-trichorabdal A (3).



158 (74% yield) *(–)-trichorabdal A* (3)

To a solution of diol **158** (11.0 mg, 31.6 μmol) in 1.6 mL DCM was added 2,2,6,6-tetramethylpiperidine 1-oxyl (1.0 mg, 6.3 μmol, 0.1 equiv) and iodobenzene diacetate (14.2 mg, 44.2 μmol, 1.4 equiv). After stirring for 3.5 h at ambient temperature, the reaction mixture was diluted with sat. $NaHCO_3$ (0.5 mL) and sat. $Na_2S_2O_3$ (0.5 mL). The layers were separated, the aqueous layer was extracted with DCM (3 x 1 mL), the combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (40 to 70% $MeCN/H_2O$, 10 minute gradient, t_R=6.8 min) to afford (–)-trichorabdal A (**3**) as a white solid (8.1 mg, 74% yield). $[\alpha]_D^{25}$ = –61° (*c* 0.12, EtOH); ^{1}H NMR (600 MHz, pyridine-d_5, at 60 °C): δ 10.06 (d, *J* = 4.3 Hz, 1H), 6.49 (s, 1H), 6.01 (s, 1H), 5.38 (s, 1H), 5.12 (d, *J* = 11.4 Hz, 1H), 4.88 – 4.64 (m, 1H), 4.65 – 4.60 (m, 1H), 3.46 (d, *J* = 11.8 Hz, 1H), 3.13 (dd, *J* = 8.9, 4.6 Hz, 1H), 2.91 (d, *J* = 4.3 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.48 – 2.38 (m, 3H), 2.04 – 1.95 (m, 1H), 1.78 (dd, *J* = 14.8, 5.0 Hz, 1H), 1.68 – 1.59 (m, 1H), 1.52 – 1.42 (m, 2H), 1.27 – 1.19 (m, 1H), 1.04 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (126 MHz, pyridine-d_5, at 60 °C): δ 205.3, 201.5, 171.1, 150.9, 117.6, 70.8, 65.0, 60.9 (br), 56.9 (br), 47.9 (br), 42.7 (br), 42.1, 40.3 (br), 35.3, 34.3, 32.4, 31.6, 28.6, 25.9 (br),

18.7; FTIR (thin film/NaCl): 3467, 2922, 2849, 1744, 1711, 1647, 1490, 1459, 1391, 1349, 1271, 1238, 1180, 1124, 1079, 1038, 1024, 928, 850, 730 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{20}H_{27}O_5$ $[M + H]^+$ 347.1853, found 347.1837.

^{1}H NMR comparison table for trichorabdal A (**3**).

Natural* [16a] (400 MHz, C_5D_5N, 40 °C) δ (ppm)	**Natural** mult	**Natural** *J* (Hz)	**Synthetic** (600 MHz, C_5D_5N, 60 °C) δ (ppm)	**Synthetic** mult	**Synthetic** *J* (Hz)	Δ (ppm)
10.03	d, 1H	3	10.06	d, 1H	4.3	+0.03
6.05	s, 1H	-	6.01	s, 1H	-	–0.04
5.35	s, 1H	-	5.38	s, 1H	-	+0.03
5.10	ABq, 1H	12	5.12	d, 1H	11.4	+0.02
4.71	ABq, 1H	12	4.72	m, 1H	-	+0.01
4.60	m, 1H	-	4.62	m, 1H	-	+0.02
3.45	d, 1H	12	3.46	d, 1H	11.8	+0.01
3.12	dd, 1H	10,4	3.13	dd, 1H	8.9, 4.6	+0.01
2.90	d, 1H	3	2.91	d, 1H	4.3	+0.01
1.00	s, 3H	-	1.04	s, 3H	-	+0.04
0.95	s, 3H	-	0.99	s, 3H	-	+0.04

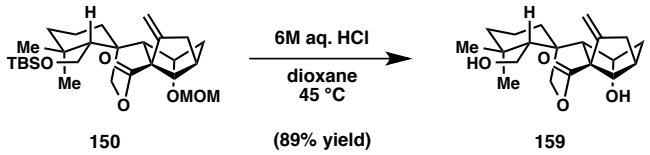
***** No further ^{1}H signals were reported.

^{13}C NMR comparison table for trichorabdal A (**3**).**

Natural[2] (100 MHz, C_5D_5N, 60 °C) δ (ppm)	**Synthetic** (126 MHz, C_5D_5N, 60 °C) δ (ppm)	Δ (ppm)
204.5	205.3	+0.8
200.7	201.5	+0.8
169.5	171.1	+0.6
150.6	150.9	+0.3
117.1	117.6	+0.5
70.7	70.8	+0.1
64.9	65.0	+0.1
60.7	60.9	+0.2
56.7	56.9	+0.2
47.8	47.9	+0.1
42.7	42.7	0.0
42.0	42.1	+0.1
40.3	40.3	0.0
35.2	35.3	+0.1
34.2	34.3	+0.1
32.3	32.4	+0.1
31.5	31.6	+0.1
28.4	28.6	+0.2
26.0	25.9	–0.1
18.6	18.7	+0.1

****** It should be noted that conformational flexibility of the natural product results in significant broadening of some carbon signals, even at elevated temperatures. For discussion of the conformational equilibria of these structures, see Osawa et al.[16c]

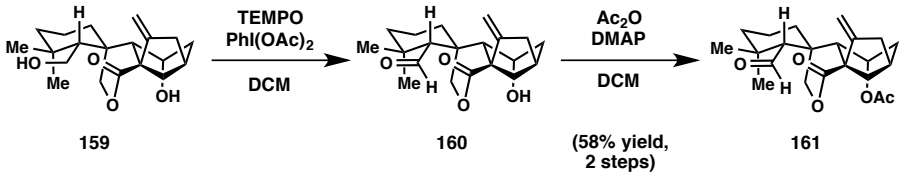
Preparation of diol 159.



150 (89% yield) **159**

To a solution of tetracycle **150** (59.2 mg, 0.120 mmol, 1.0 equiv) in 3.7 mL dioxane was added 2.8 mL 6M HCl(*aq*). The resulting solution was heated to 45 °C and stirred for 30 min. The reaction mixture was then cooled to 0 °C and diluted with sat. $NaHCO_3$ (10 mL) and DCM (10 mL) and stirred until bubbling ceased (15 min). The layers were separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (40 to 50% EtOAc/Hex) to provide diol **159** (35.9 mg, 89% yield). $[\alpha]_D^{25}$ = –28° (*c* 0.66, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 – 4.95 (m, 2 H), 4.46 (br s, 2H), 4.40 (dtd, *J* = 6.6, 5.2, 3.6 Hz, 1H), 3.87 (dt, *J* = 11.5, 4.5 Hz, 1H), 3.82 (dt, *J* = 11.5, 2.9 Hz, 1H), 2.64 (d, *J* = 5.2 Hz, 1H), 2.60 (ddt, *J* = 16.6, 5.4, 2.6 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.37 (td, *J* = 13.3, 4.3 Hz, 1H), 2.26 (br s, 1 H), 2.22 (dq, *J* = 16.2, 2.0 Hz, 1H), 1.97 (dtd, *J* = 14.2, 6.4, 1.2 Hz, 1H), 1.90 (t, *J* = 3.6 Hz, 1H), 1.88 – 1.81 (m, 3H), 1.66 (ddt, *J* = 14.2, 5.2, 1.9 Hz, 1H), 1.52 – 1.41 (m, 3H), 1.31 (ddd, *J* = 14.1, 13.1, 4.3 Hz, 1H), 1.05 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 156.1, 106.3, 71.7, 66.4, 60.6, 54.0, 53.0, 51.4, 42.5, 41.7, 40.4, 39.7, 36.5, 34.4, 34.1, 31.5, 31.4, 23.5, 18.4; FTIR (NaCl/thin film): 3246, 2929, 2872, 2848, 1734, 1459, 1388, 1353, 1298, 1242, 1087, 1044, 1023, 997, 989 cm^{-1}; HRMS (ESI+) calc'd for $C_{20}H_{31}O_4$ $[M + H]^+$ 335.2217, found 335.2228.

Preparation of acetate 161.

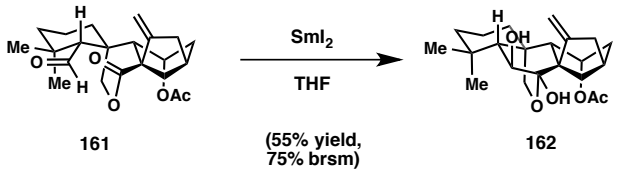


To a solution of diol **159** (35.2 mg, 0.105 mmol, 1.0 equiv) in DCM (5.3 mL) was added $PhI(OAc)_2$ (47.6 mg, 0.148 mmol, 1.4 equiv) and 2,2,6,6-tetramethylpiperidine 1-oxyl (3.3 mg, 21 μmol, 0.20 equiv). The resulting solution was stirred for 4.5 h, and then diluted with sat. $Na_2S_2O_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude aldehyde **160**. The crude residue was chromatographed on SiO_2 (25% EtOAc/Hex) to provide 25.4 mg **160** (~85% purity, contaminated with ketoaldehyde from over-oxidation). Impure **160** was dissolved in DCM (7.6 mL), and Ac_2O (36 μL, 0.38 mmol, 5.0 equiv) and DMAP (93 mg, 0.76 mmol, 10 equiv) were added. The solution was stirred at ambient temperature until TLC indicated full consumption of starting material (30 min). The reaction mixture was then diluted with sat. $NaHCO_3$ (20 mL) and DCM (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (20% EtOAc/Hex) to provide acetate **161** (22.8 mg, 58% yield from **159**). $[\alpha]_D^{25}$ = –6.9° (*c* 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.93 (d, *J* = 4.4 Hz, 1H), 5.27 (q, *J* = 5.0 Hz, 1H), 4.99 (m, 2H), 4.84 (br d, *J* = 9.3 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.46 (q, *J* = 6.1 Hz, 1H), 2.39 (d, *J* = 4.4 Hz, 1H), 2.33 – 2.17 (m, 3H), 2.07 (s, 3H), 2.01 – 1.87 (m, 3H), 1.82 – 1.67 (m, 1H), 1.66 – 1.49 (m, 3H), 1.28 – 1.16 (m, 2H), 1.14 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 205.1, 174.2, 169.7, 155.0, 107.3, 70.4, 67.7, 62.5, 53.2, 51.9, 41.9, 41.7, 40.4, 36.5, 36.1, 34.5, 33.7, 30.6, 29.6, 23.8, 21.8, 18.2; FTIR

(NaCl/thin film): 3079, 2953, 2849, 2751, 1735, 1712, 1654, 1462, 1371, 1231, 1085, 1071, 1036, 914 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{31}O_5$ $[M + H]^+$ 375.2166, found 375.2175.

An analytical sample of aldehyde **160** was obtained (65% yield) by preparative reverse phase HPLC (45% to 70% MeCN/H_2O, 10 minute gradient, t_R = 7.0 min). $[\alpha]_D^{25}$ = –65.4° (*c* 0.37, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 9.95 (d, *J* = 5.4 Hz, 1H), 4.99 (s, 1H), 4.95 (t, *J* = 2.4 Hz, 1H), 4.88 (br s, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.25 (dq, *J* = 5.4, 3.5 Hz, 1H), 2.64 (d, *J* = 5.4 Hz, 1H), 2.59 – 2.53 (m, 1H), 2.51 – 2.47 (m, 1H), 2.46 – 2.35 (m, 2H), 2.17 (dq, *J* = 16.3, 2.0 Hz, 1H), 2.00 (d, *J* = 3.0 Hz, 1H), 1.96 (dt, *J* = 13.5, 6.6 Hz, 1H), 1.90 – 1.82 (m, 2H), 1.63 – 1.54 (m, 4H), 1.50 (dt, *J* = 13.2, 3.5 Hz, 1H), 1.31 (m, 1H), 1.18 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.6, 174.9, 155.5, 107.6, 71.3, 66.0, 63.4, 53.5, 53.5, 41.9, 41.2, 40.6, 39.5, 36.2, 34.4, 33.6, 31.4, 29.9, 23.6, 18.4; FTIR (NaCl/thin film): 3467, 2990, 2946, 2844, 2717, 1718, 1653, 1465, 1390, 1280, 1233, 1201, 1117, 1088, 1025, 881 cm^{-1}; HRMS (ESI+) calc'd for $C_{20}H_{29}O_4$ $[M + H]^+$ 333.2060, found 333.2070.

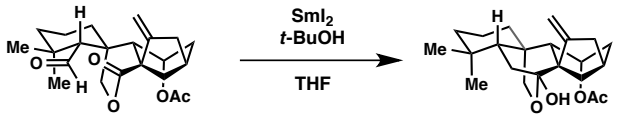
Preparation of hydroxylactol 162.



161 (55% yield, 75% brsm) **162**

To a solution of **161** (4.4 mg, 12 μmol, 1.0 equiv) in THF (0.27 mL) was added freshly prepared 0.1 M SmI_2 (0.23 mL, 23 μmol, 2.0 equiv). The solution was stirred until the reaction turned from blue to green (ca. 1.5 h). The reaction mixture was then diluted with sat. $NaHCO_3$ (1 mL), sat. $Na_2S_2O_3$ (1 mL), and DCM (2 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 2 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (17% to 25% EtOAc/Hex) to provide recovered **161** (1.2 mg, 27% yield) and hydroxylactol **162** (2.4 mg, 55% yield). $[\alpha]_D^{25}$ = –47.2° (*c* 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 – 6.14 (m, 1H), 5.14 (ddd, *J* = 5.8, 4.1, 1.9 Hz, 1H), 5.11 (dd, *J* = 2.6, 1.2 Hz, 1H), 4.23 (dd, *J* = 9.1, 1.9 Hz, 1H), 4.10 (dd, *J* = 9.1, 1.8 Hz, 1H), 4.03 (dd, *J* = 7.3, 1.9 Hz, 1H), 2.59 (s, 1H), 2.50 – 2.42 (m, 2H), 2.40 (d, *J* = 1.9 Hz, 1H), 2.29 (dt, *J* = 8.9, 4.2 Hz, 1H), 2.17 – 2.09 (m, 2H), 2.06 (s, 3H), 1.75 (dt, *J* = 5.7, 1.5 Hz, 1H), 1.67 (dd, *J* = 11.7, 3.6 Hz, 1H), 1.51 – 1.41 (m, 3H), 1.39 – 1.32 (m, 3H), 1.27 – 1.22 (m, 2H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 155.2, 113.0, 97.5, 75.4, 69.3, 69.1, 62.0, 57.3, 53.7, 46.7, 41.3, 37.2, 34.4, 34.2, 34.0, 33.6, 29.9, 27.2, 22.6, 22.0, 18.5; FTIR (NaCl/thin film): 3436, 2927, 2851, 1733, 1648, 1443, 1376, 1264, 1237, 1210, 1073, 1029 cm^{-1}; HRMS (ESI+) calc'd for $C_{20}H_{29}O_3$ $[M - OAc]^+$ 317.2111, found 317.2119.

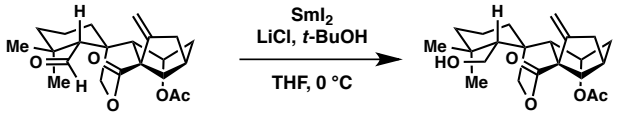
Preparation of lactol 163.



161 **(72% yield)** **163**

To a solution of aldehyde **161** (5.0 mg, 13 μmol, 1.0 equiv) in THF (1.3 mL) was added *t*-BuOH (1.3 μL, 13 μmol, 1.0 equiv) and freshly prepared 0.1 M SmI_2 (0.67 mL, 67 μmol, 5.0 equiv) dropwise over 1 min. The resulting solution was stirred until the reaction turned from blue to green (ca. 6 h), and then diluted with sat. $NaHCO_3$ (5 mL), sat. $Na_2S_2O_3$ (5 mL), and DCM (10 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (25% to 33% EtOAc/Hex) to provide lactol **163** (3.6 mg, 72% yield). $[\alpha]_D^{25}$ = –135° (*c* 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.18 (dd, *J* = 2.7, 1.5 Hz, 1H), 5.14 (td, *J* = 6.0, 1.6 Hz, 1H), 4.92 – 4.90 (m, 1H), 4.23 (s, 2H), 2.60 (dd, *J* = 13.9, 11.1 Hz, 1H), 2.56 (ddt, *J* = 15.6, 5.1, 2.3 Hz, 1H), 2.41 (s, 1H), 2.40 (ddt, *J* = 11.9, 3.2, 1.0 Hz, 1H), 2.29 (dt, *J* = 9.6, 4.7 Hz, 1H), 2.15 (ddt, *J* = 15.7, 9.5, 1.3 Hz, 1H), 2.12 (ddt, *J* = 15.7, 3.0, 1.5 Hz, 1H), 2.06 (s, 3H), 1.91 (dd, *J* = 14.0, 8.6 Hz, 1H), 1.64 (ddt, *J* = 11.6, 4.0, 1.0 Hz, 1H), 1.58 (d, *J* = 5.3 Hz, 1H), 1.52 – 1.47 (m, 2H), 1.45 – 1.32 (m, 3H), 1.29 (dtd, *J* = 13.7, 3.3, 1.5 Hz, 1H), 1.19 (td, *J* = 13.4, 5.1 Hz, 1H), 1.11 (td, *J* = 12.7, 4.0 Hz, 1H), 1.10 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1, 156.7, 105.5, 97.3, 69.1, 68.8, 61.1, 53.4, 49.2, 45.3, 40.8, 37.3, 36.0, 33.9, 33.7, 32.7, 32.0, 30.4, 27.1, 22.0, 21.1, 18.6; FTIR (NaCl/thin film): 3402, 2929, 1729, 1646, 1444, 1366, 1236, 1210, 1182, 1101, 1044, 915 cm^{-1}; HRMS (ESI+) calc'd for $C_{20}H_{29}O_2$ $[M - OAc]^+$ 301.2162, found 301.2164.

Preparation of primary alcohol 164.



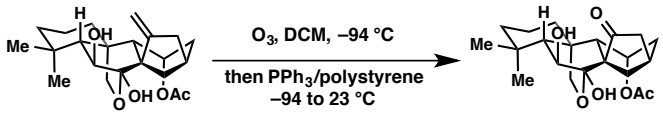
161 (54% yield) **164**

Freshly prepared 0.1 M SmI_2 (0.17 mL, 17 μmol, 5.0 equiv) was added directly to a vial charged with LiCl (7.2 mg, 170 μmol, 50 equiv) and stirred until the solution had turned emerald green and all solids were dissolved (< 10 min). The resulting solution was added dropwise via cannula into a solution of aldehyde **161** (1.3 mg, 3.5 μmol, 1.0 equiv) and a solution of *t*-BuOH in THF (0.01 M, 0.35 mL, 3.5 μmol, 1.0 equiv) stirring at 0 °C. Stirring continued until the reaction turned yellow (35 min). The reaction mixture was diluted with sat. $NaHCO_3$ (1 mL), sat. $Na_2S_2O_3$ (1 mL), and H_2O (0.5 mL), then Rochelle salt (100 mg) and EtOAc (2 mL) were added. The layers were separated, and the aqueous layer extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (20 to 25% EtOAc/Hex) to afford alcohol **164** (0.7 mg, 54% yield). $[\alpha]_D^{25} = -7.5°$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.47 (ddd, *J* = 5.4, 4.5, 3.4 Hz, 1H), 4.96 (t, *J* = 2.4 Hz, 1H), 4.90 (t, *J* = 1.9 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.82 (d, *J* = 11.8 Hz, 1H), 3.73 (dt, *J* = 10.9, 4.7 Hz, 1H), 2.81 (d, *J* = 4.3 Hz, 1H), 2.65 (ddt, *J* = 16.8, 5.8, 2.7 Hz, 1H), 2.45 (q, *J* = 6.8 Hz, 1H), 2.36 (dd, *J* = 11.9, 2.7 Hz, 1H), 2.24 (dq, *J* = 16.9, 2.2 Hz, 1H), 2.08 – 2.02 (m, 1H), 2.07 (s, 3H), 1.99 (dd, *J* = 12.2, 4.8 Hz, 1H), 1.86 (d, *J* = 13.6 Hz, 1H), 1.67 – 1.57 (m, 2H), 1.53 – 1.45 (m, 4H), 1.28 – 1.24 (m, 1H), 1.19 (td, *J* = 14.3, 5.3 Hz, 1H), 1.05 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 170.1, 156.5, 105.2, 70.4, 68.0, 60.3, 53.3, 52.4, 51.2, 42.8, 42.4, 40.9, 37.4, 35.8, 34.3, 34.2, 30.2, 30.0, 23.7, 21.9, 18.1; IR (NaCl/thin film): 3463, 2951, 2925, 2868, 2848, 1737, 1729, 1651, 1460, 1447, 1388, 1372, 1233, 1181, 1083, 1021 cm^{-1}; HRMS (ESI+) calc'd for $C_{20}H_{29}O_3$ $[M - OAc]^+$ 317.2117, found 317.2105.

General procedure for reductive cyclization of aldehyde 161 (Table 3.4).

To a flask charged with aldehyde **161** (1.3 mg, 3.5 μmol, 1.0 equiv) was added one of the following: 0.35 mL THF; 0.35 mL 10 mM *t*-BuOH /THF solution (3.5 μmol, 1.0 equiv); 0.35 mL THF and 30 uL HMPA (0.175 mmol, 50 equiv) and maintained at the indicated temperature. Inside a glove box, an oven-dried vial was charged with LiCl or LiBr (170 μmol, 50 equiv) or naught, and removed from the glove box, or not. Freshly prepared 0.1 M SmI_2 was added directly to the reaction vessel dropwise, or to the vial containing LiX, which was stirred for 1–10 min until all solids were dissolved, and the resulting solution then added dropwise via cannula to the reaction vessel. Following addition of SmI_2 or SmI_2/LiX, the reaction was allowed to stir at the indicated temperature until the appearance of a yellow solution (35–55 min). At this point, the reaction was diluted with sat. NaHCO (1 mL), sat. $Na_2S_2O_3$ (1 mL), and H_2O (0.5 mL), and Rochelle salt (100 mg) and EtOAc (2 mL) were added. The layers were separated, and the aqueous extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (17% to 33% EtOAc/Hex) to afford hydroxylactol **162**, lactol **163**, primary alcohol **164**, or recovered aldehyde **161**.

Preparation of ketolactol 165.

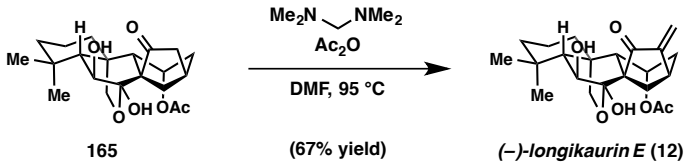


162 **(66% yield)** **165**

A solution of lactol **162** (4.4 mg, 12 μmol, 1.0 equiv) in DCM (2 mL) was cooled to –94 °C (liq. N_2/acetone), and ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 1 setting on ozone generator) for 10 min. The solution was purged with argon for 10 min, and then polystyrene-bound PPh_3 (3 mmol/g loading, 39 mg, 0.12 mmol, 10 equiv) was added. After 25

min, the reaction was warmed to 0 °C and stirred for 30 min, and finally warmed to room temperature and stirred for an additional 30 min. The solution was filtered through a pad of celite and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (33% EtOAc/Hex) to afford ketolactol **165** (2.9 mg, 66% yield). $[\alpha]_D^{25}$ = –86° (*c* 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 (d, *J* = 12.0 Hz, 1H), 5.24 (td, *J* = 4.9, 1.4 Hz, 1H), 4.16 (dd, *J* = 9.4, 1.9 Hz, 1H), 4.09 (dd, *J* = 9.3, 1.7 Hz, 1H), 3.79 (dd, *J* = 12.0, 7.5 Hz, 1H), 3.53 (s, 1H), 2.71 (ddd, *J* = 12.4, 4.0, 1.3 Hz, 1H), 2.70 – 2.65 (m, 1H), 2.50 (ddd, *J* = 18.7, 7.1, 1.6 Hz, 1H), 2.30 – 2.24 (m, 2H), 2.18 (dd, *J* = 18.6, 4.0 Hz, 1H), 2.10 (s, 3H), 1.59 (dd, *J* = 4.9, 1.2 Hz, 1H), 1.54 – 1.42 (m, 3H), 1.38 – 1.33 (m, 2H), 1.26 – 1.21 (m, 3H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 222.7, 169.7, 94.8, 74.7, 68.9, 68.1, 59.6, 58.8, 53.6, 49.3, 41.3, 36.9, 35.9, 33.9, 33.7, 30.6, 29.1, 25.9, 22.5, 21.9, 18.3; FTIR (NaCl/thin film): 3338, 2924, 2870, 1728, 1446, 1373, 1306, 1238, 1212, 1061, 1021, 939 cm^{-1}; HRMS (ESI+) calc'd for $C_{21}H_{31}O_6$ $[M + H]^+$ 379.2115, found 379.2123.

Preparation of (–)-longikaurin E (12).



To a solution of **165** (2.6 mg, 6.9 μmol, 1.0 equiv) in DMF (0.23 mL) was added bis(dimethylamino) methane (0.23 mL, 1.7 mmol, 240 equiv) and Ac_2O (0.23 mL, 2.1 mmol, 300 equiv), and the resulting mixture was stirred at 95 °C for 45 min in a sealed vial. After cooling to room temperature, the solution was diluted with 1M HCl (2 mL) and extracted with Et_2O (3 x 4 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (33% EtOAc/Hex) to afford (–)-longikaurin E (**12**) (1.8 mg, 67% yield). $[\alpha]_D^{25}$ = –51° (*c* 0.30, C_5H_5N); $[\alpha]_D^{25}$ = –39° (*c* 0.17, $CHCl_3$); ^{1}H NMR

(500 MHz, $CDCl_3$): δ 6.00 (t, *J* = 0.9 Hz, 1H), 5.84 (d, *J* = 12.0 Hz, 1H), 5.47 (t, *J* = 0.8 Hz, 1H), 5.27 (ddd, *J* = 5.5, 4.5, 1.1 Hz, 1H), 4.13 (dd, *J* = 9.3, 1.4 Hz, 1H), 4.10 (dd, *J* = 9.3, 1.9 Hz, 1H), 3.87 (dd, *J* = 12.0, 8.1 Hz, 1H), 3.53 (s, 1H), 3.13 (dd, *J* = 9.4, 4.7 Hz, 1H), 2.71 (dd, *J* = 12.3, 0.8 Hz, 1H), 2.31 (ddd, *J* = 16.2, 9.3, 1.0 Hz, 1H), 2.21 (ddd, *J* = 12.2, 4.6, 1.2 Hz, 1H), 2.11 (s, 3H), 1.79 (ddt, *J* =16.0, 5.5, 1.1 Hz, 1H), 1.62 (d, *J* = 4.0 Hz, 1H), 1.51 – 1.42 (m, 2H), 1.39 – 1.33 (m, 2H), 1.32 – 1.20 (m, 3H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 208.4, 169.7, 151.7, 118.5, 95.0, 74.8, 69.1, 68.0, 58.5, 58.5, 53.7, 41.4, 38.0, 37.1, 34.1, 33.7, 33.6, 31.3, 26.3, 22.8, 21.9, 18.4; FTIR (NaCl/thin film): 3270, 2953, 2918, 2854, 1727, 1714, 1644, 1504, 1372, 1373, 1264, 1241, 1167, 1057, 940 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{31}O_6$ $[M + H]^+$ 391.2115, found 391.2125.

^{1}H NMR comparison table for longikaurin E (**12**).

Natural*[2a] ($CDCl_3$) δ (ppm)	**Natural** mult	**Natural** *J* (Hz)	**Synthetic** ($CDCl_3$, 500 MHz) δ (ppm)	**Synthetic** mult	**Synthetic** *J* (Hz)	Δ (ppm)
5.26	dd, 1H	4.5, 4.5	5.27	ddd, 1H	5.5, 4.5, 1.1	+0.01
4.11	br s, 2H	-	4.13 4.10	dd, 1H dd, 1H	9.3, 1.4 9.3, 1.9	-
3.91	dd, 1H	12, 8	3.87	dd, 1H	12.0, 8.1	–0.04
2.09	s, 3H	-	2.11	s, 3H	-	+0.02
1.71 – 1.88	m**	-	1.79	ddt, 1H	16.0, 5.5, 1.1	-
1.62	m**	-	1.62	d, 1H	4.0	0.00
1.25	m**	-	1.20 – 1.32	m, 3H	-	-
1.14	s, 3H	-	1.15	s, 3H	-	+0.01
1.12	s, 3H	-	1.13	s, 3H	-	+0.01

^{13}C NMR comparison table for longikaurin E (**12**).

Natural*[2a] ($CDCl_3$) δ (ppm)	**Synthetic** ($CDCl_3$, 126 MHz) δ (ppm)	Δ (ppm)
208.4	208.4	0.0
169.6	169.7	+0.1
151.7	151.7	0.0
118.2	118.5	+0.3
95.0	95.0	0.0
74.5	74.8	+0.3
68.9	69.1	+0.2
68.1	68.0	–0.1

* No further ^{1}H or ^{13}C signals were reported.
** Integrations not reported.

3.5 NOTES AND REFERENCES

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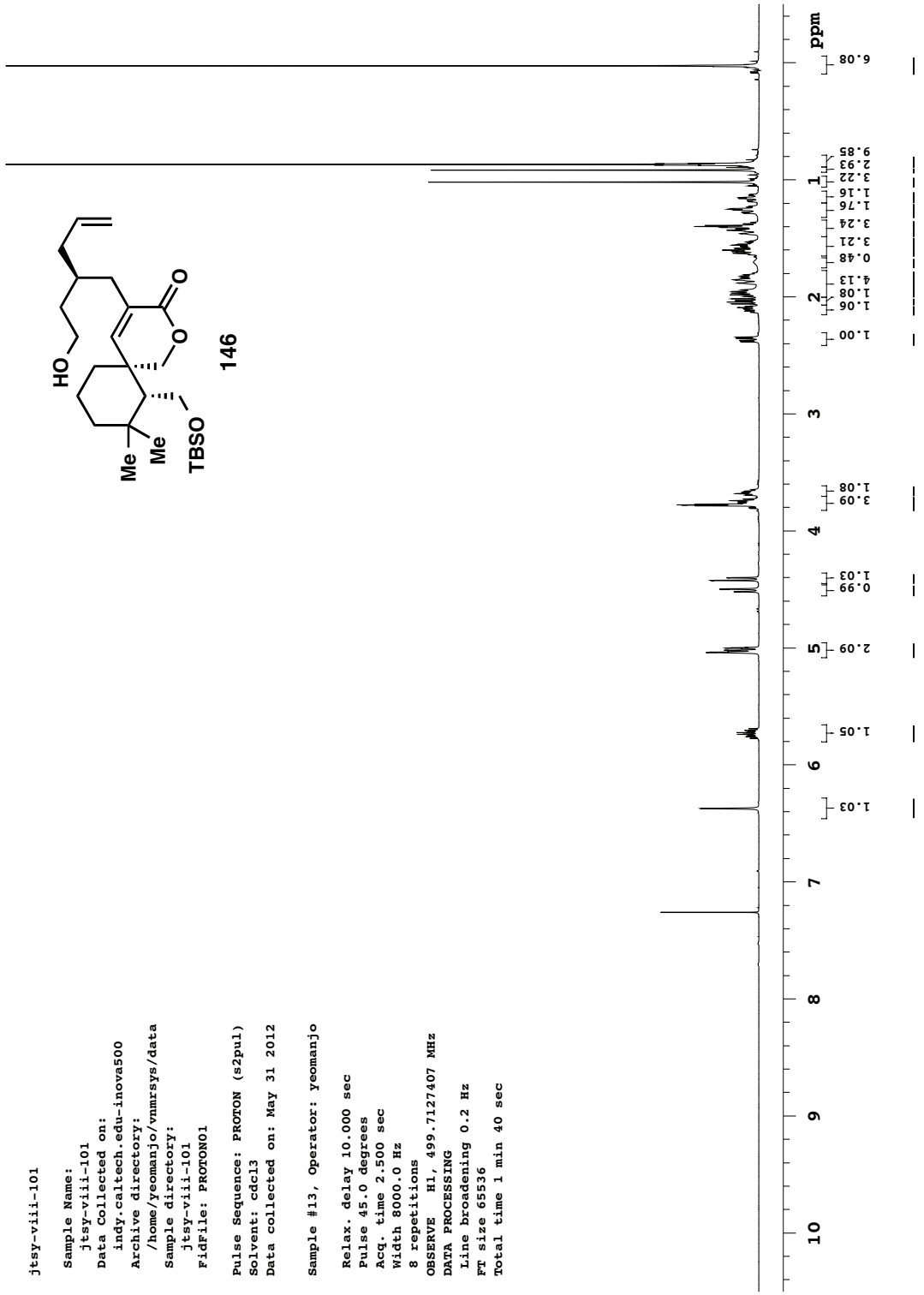
Appendix 3

Spectra Relevant to Chapter 3:
Total Syntheses of (–)-Trichorabdal A and (–)-Longikaurin E


jtsy-viii-101
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jtsy-viii-101
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-viii-101
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 31 2012
Sample #13, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127407 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 40 sec
HO
Me
Me
TBSO
O
O
146
ppm
10
9
8
7
6
5
4
3
2
1
1.03
1.05
2.09
0.99
1.03
3.09
1.08
1.00
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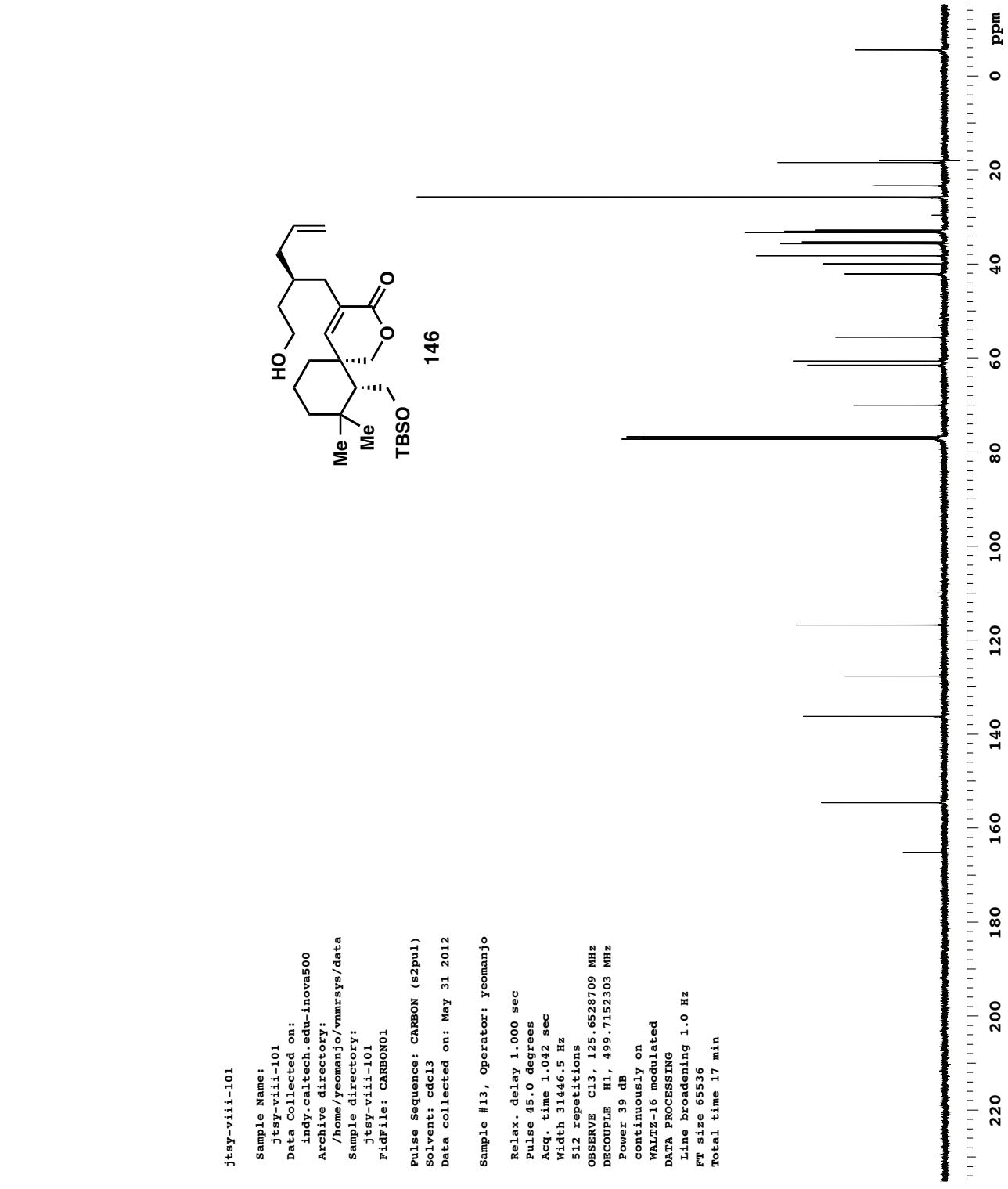
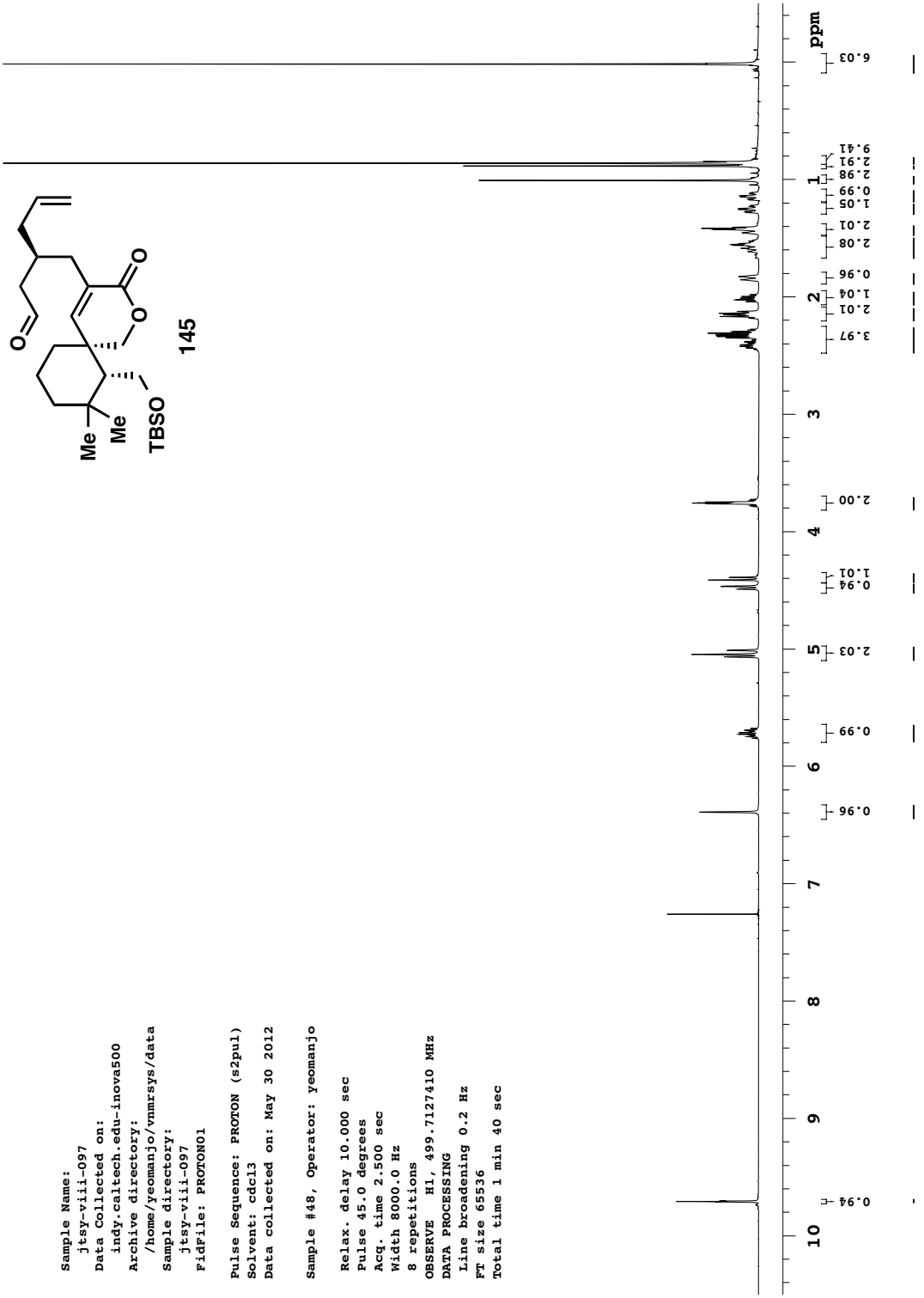
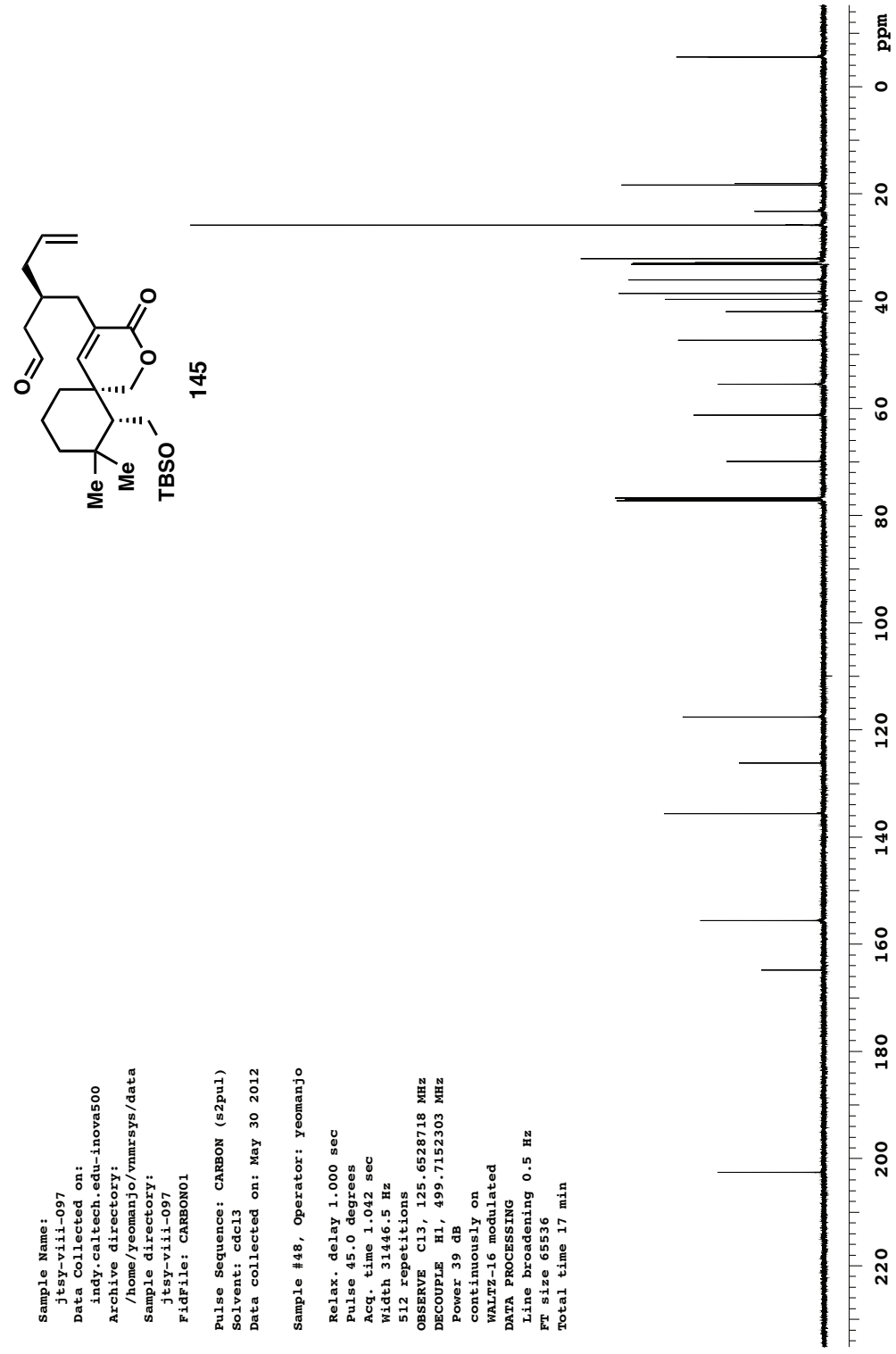
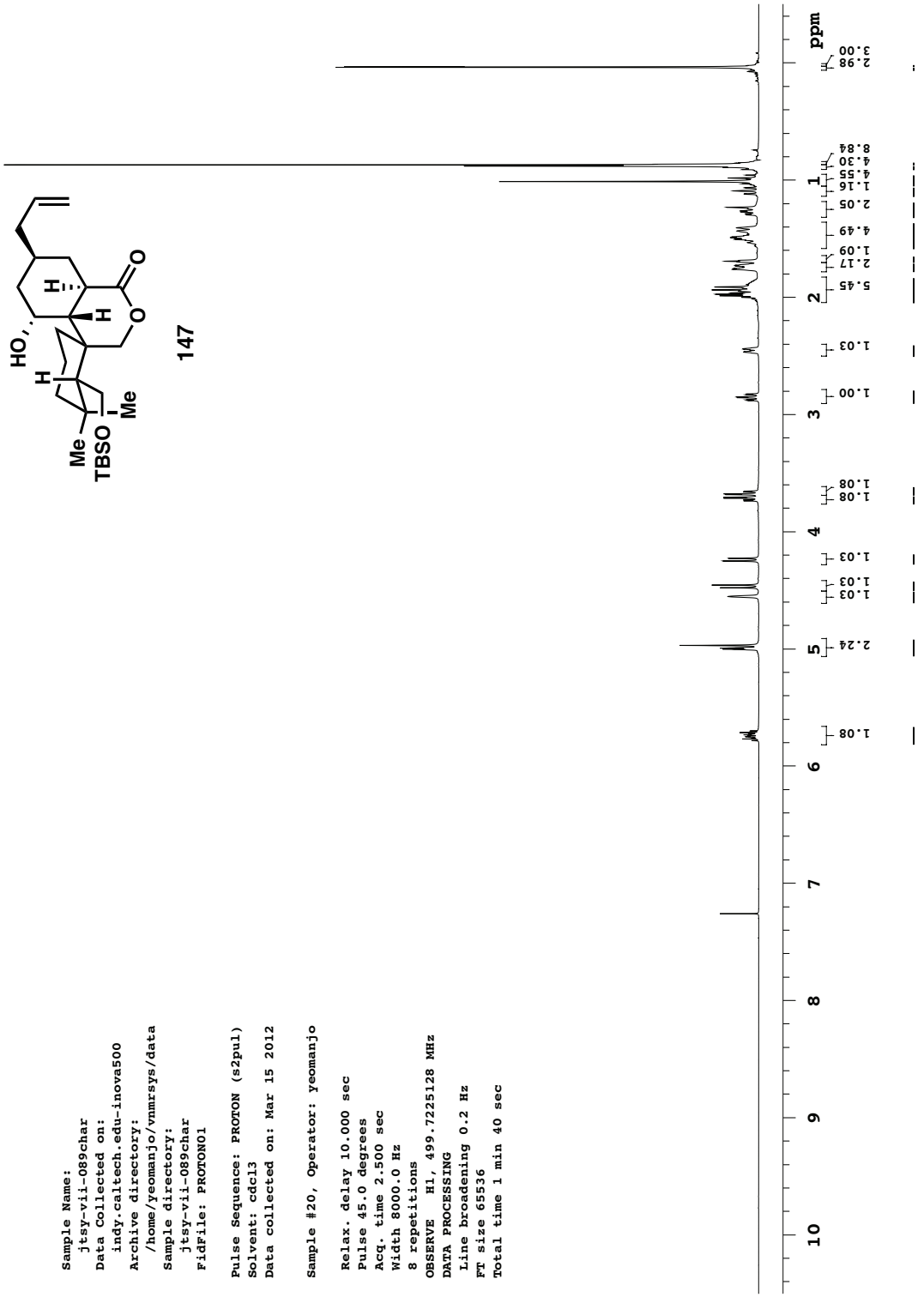
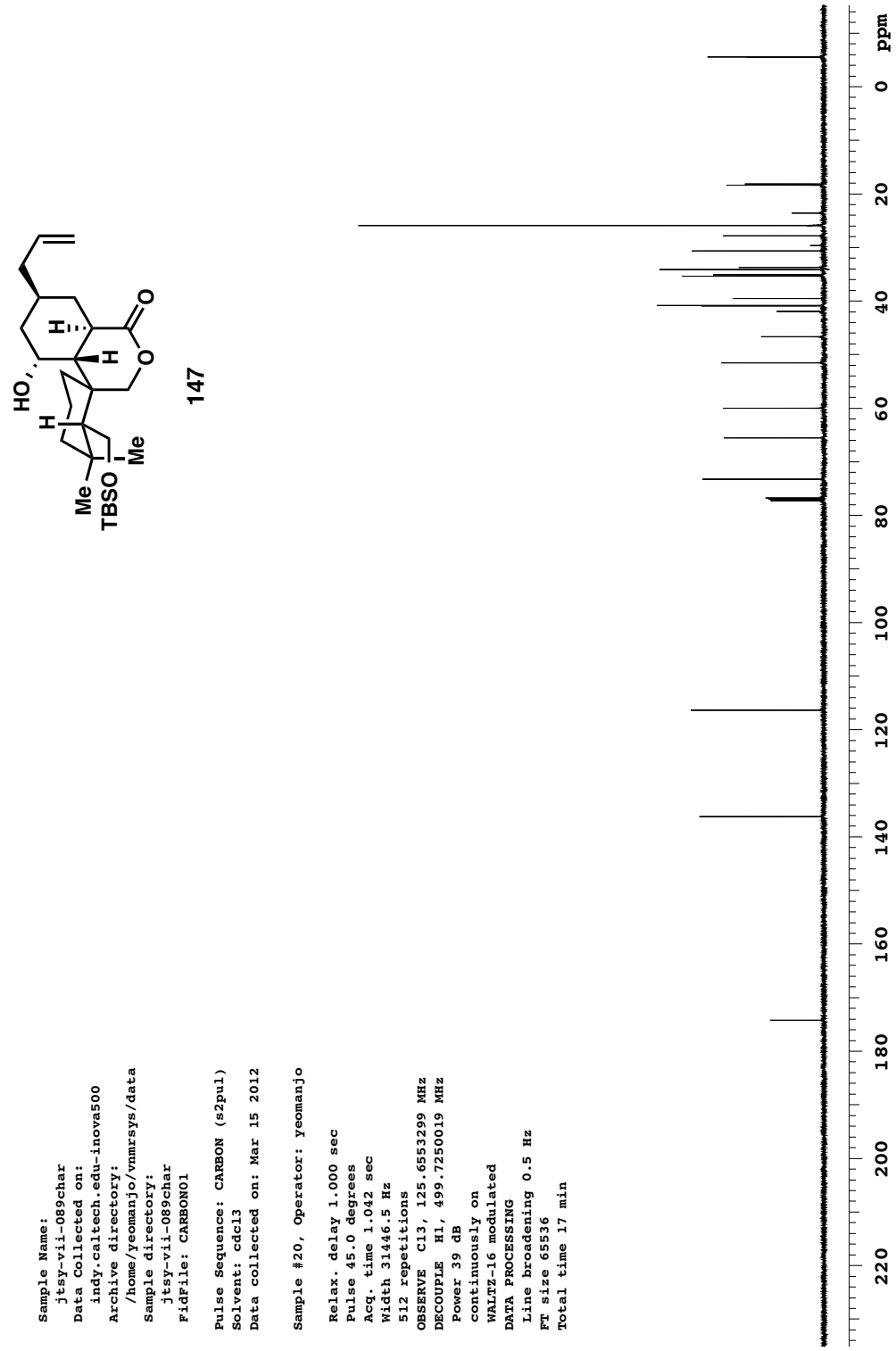
6.08

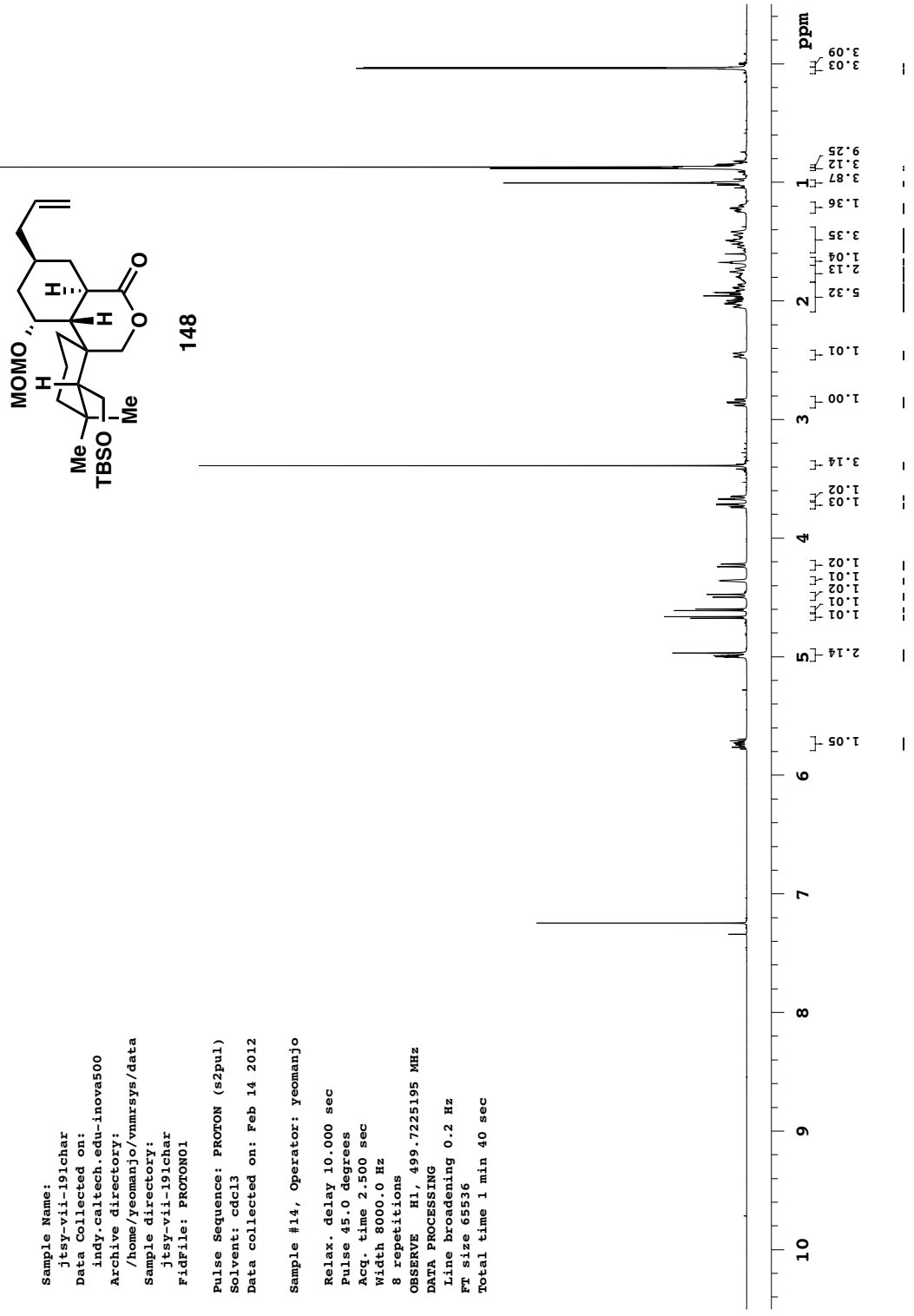

jtsy-viii-101
Sample Name:
jtsy-viii-101
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-viii-101
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 31 2012
Sample #13, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528709 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 17 min
HO
O
O
Me
Me
TBSO
146
220
200
180
160
140
120
100
80
60
40
20
0
ppm

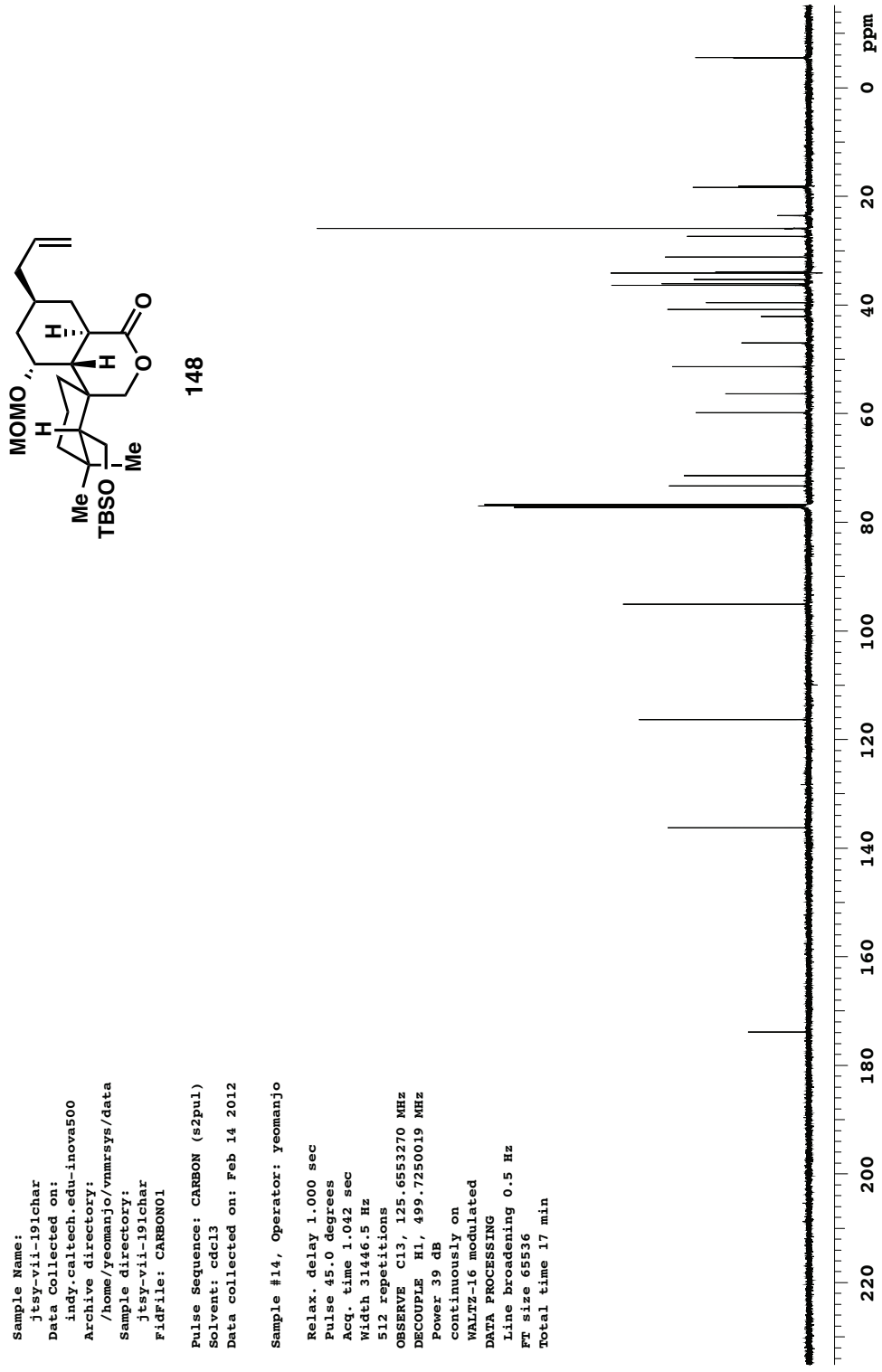

Sample Name:
jtsy-viii-097
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-viii-097
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 30 2012
Sample #48, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 40 sec
Me
Me
TBSO
145
ppm


Sample Name:
jtsy-viii-097
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-viii-097
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 30 2012
Sample #48, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528718 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
O
O
O
Me
Me
TBSO
145
220
200
180
160
140
120
100
80
60
40
20
0
ppm

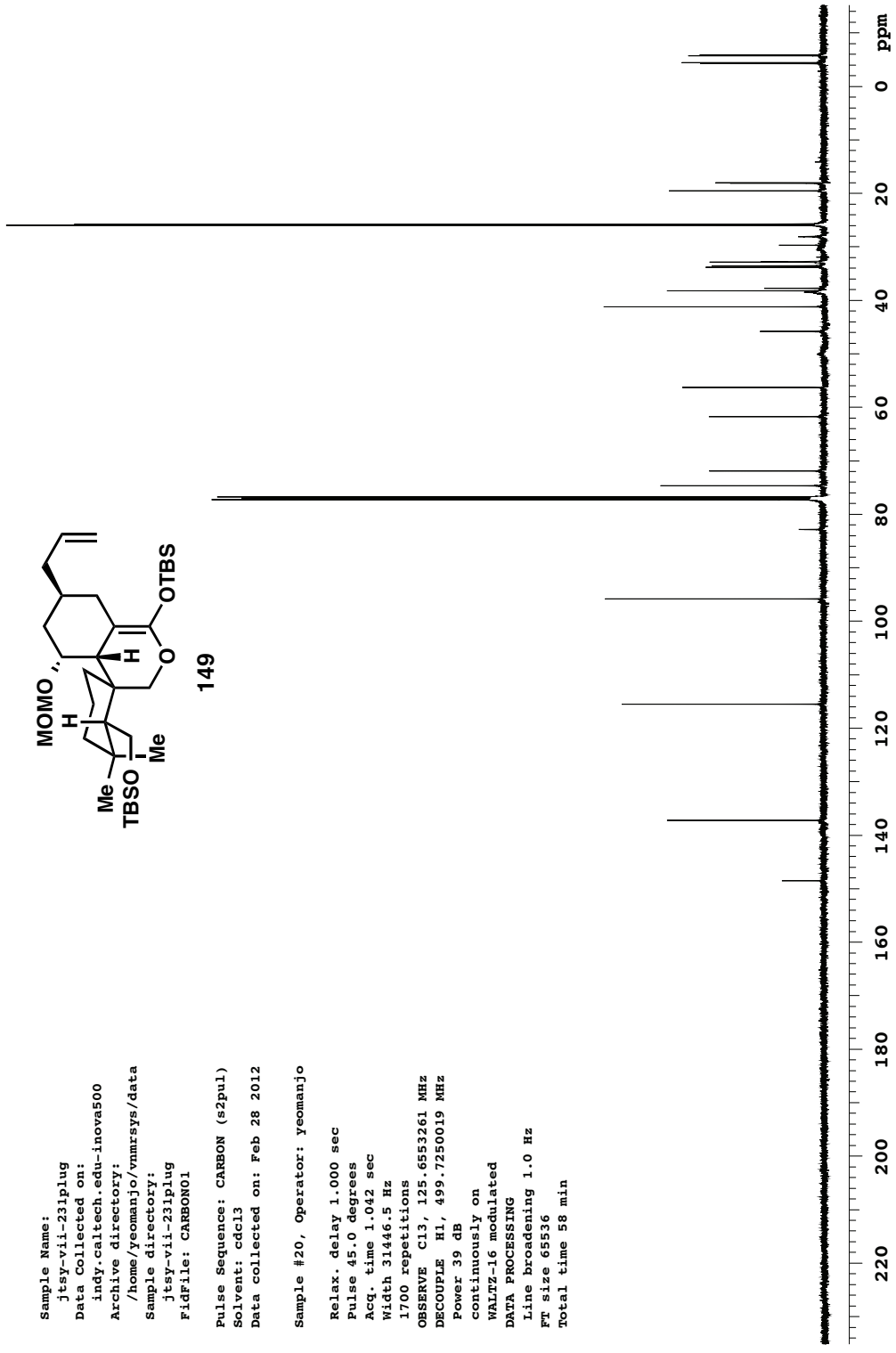

HO
H
H
O
O
Me
TBSO
Me
147
Sample Name:
jtsy-vii-089char
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vii-089char
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 15 2012
Sample #20, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 40 sec
ppm
10
9
8
7
6
5
4
3
2
1
1.08
2.24
1.03
1.03
1.03
1.08
1.08
1.00
1.03
5.45
2.17
1.09
4.49
2.05
1.16
4.55
4.30
8.84
2.98
3.00

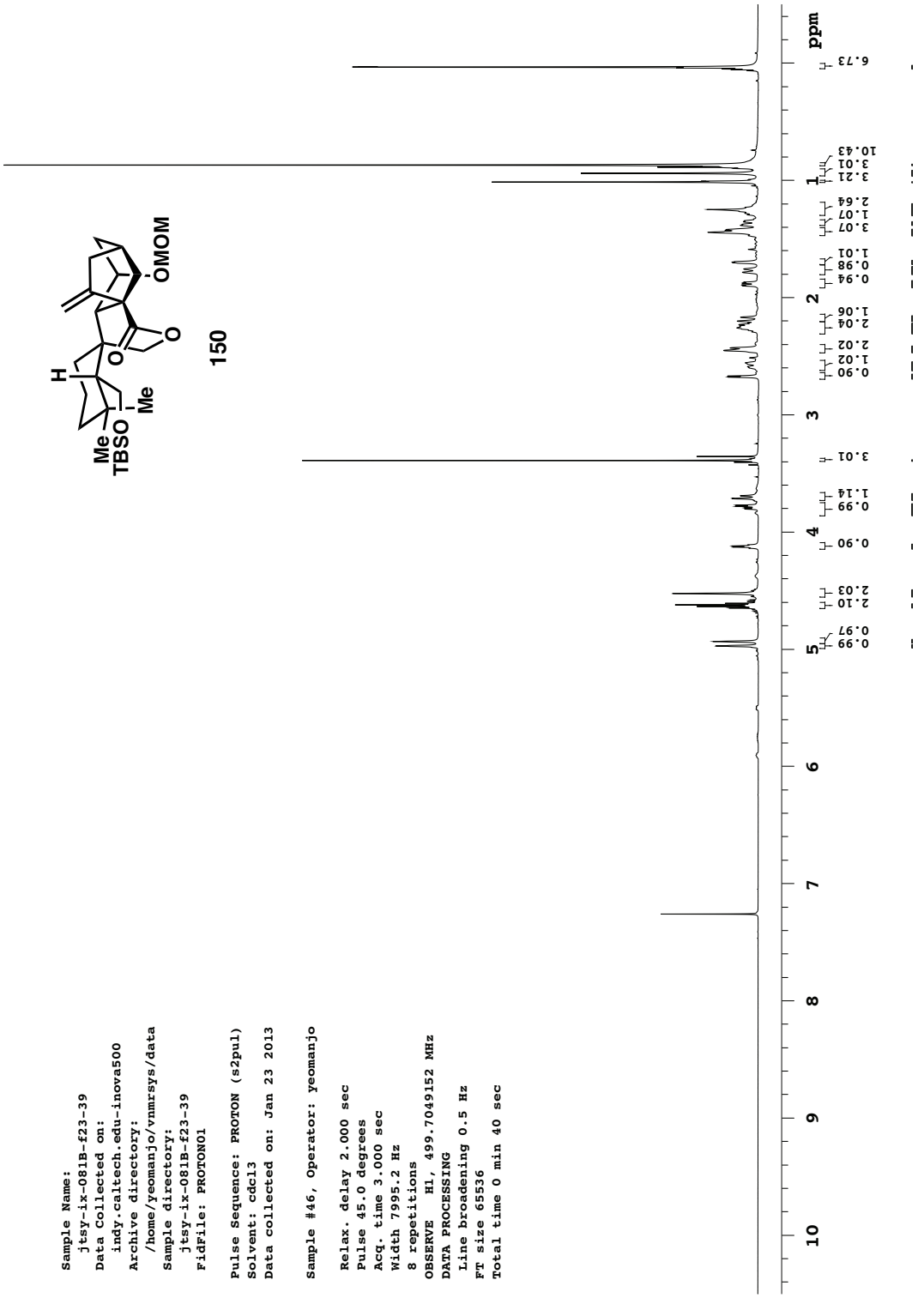

Sample Name:
jtsy-vii-089char
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vii-089char
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 15 2012
Sample #20, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553299 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
HO
H
H
H
O
O
Me
TBSO
Me
147
220
200
180
160
140
120
100
80
60
40
20
0
ppm

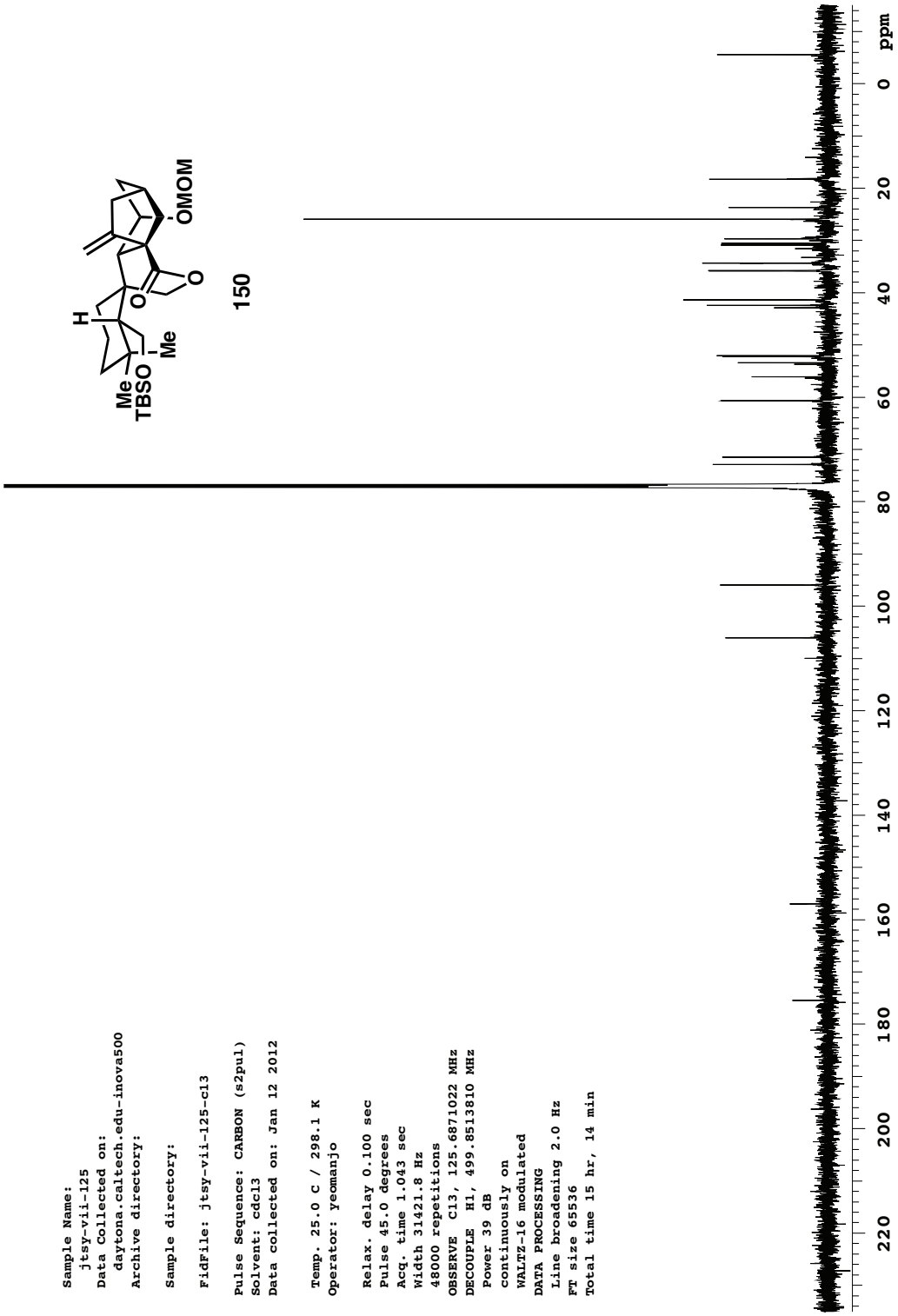

Sample Name:
jtsy-vii-191char
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vii-191char
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 14 2012
Sample #14, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225195 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 40 sec
MOMO
H
Me
TBSO
Me
H
H
O
O
148
ppm
10
9
8
7
6
5
4
3
2
1
1.05
2.14
1.01
1.01
1.02
1.01
1.02
1.02
1.03
3.14
1.00
1.01
5.32
2.13
1.04
3.35
1.36
3.87
3.12
9.25
3.03
3.09

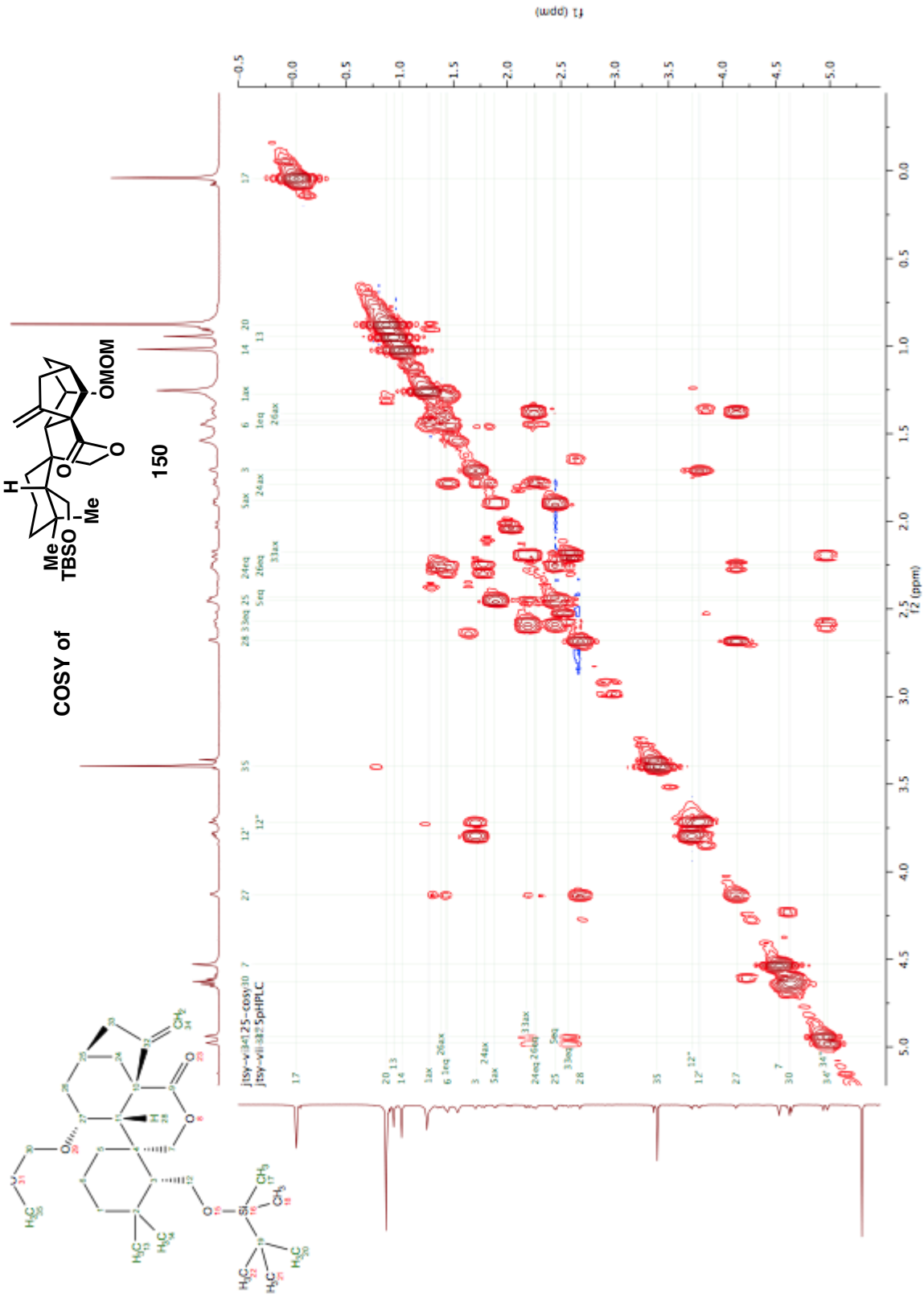

Sample Name:
jtsy-vii-191char
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vii-191char
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 14 2012
Sample #14, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553270 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
MOMO
H
Me
TBSO
Me
H
H
O
O
148
220
200
180
160
140
120
100
80
60
40
20
0
ppm

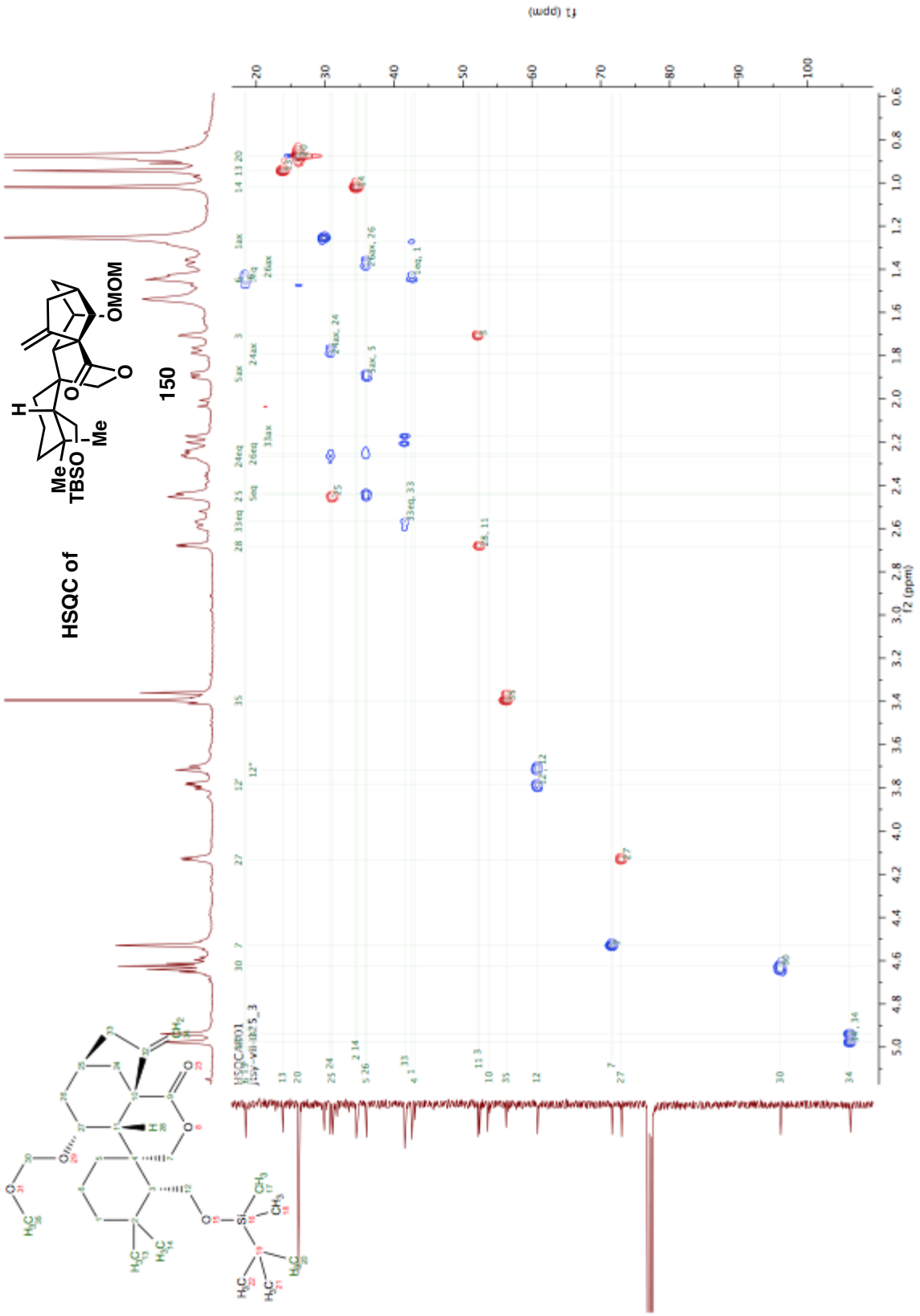

MOMO
H
Me
TBSO
Me
H
O
OTBS
149
Sample Name:
jtsy-vii-231plug
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vii-231plug
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 28 2012
Sample #20, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 40 sec
ppm
10
9
8
7
6
5
4
3
2
1
1.01
2.00
0.98
0.98
0.91
1.00
0.97
1.95
2.93
0.92
0.88
0.95
1.93
1.89
3.84
4.37
2.99
3.68
9.37
10.19
5.77
2.76
3.40

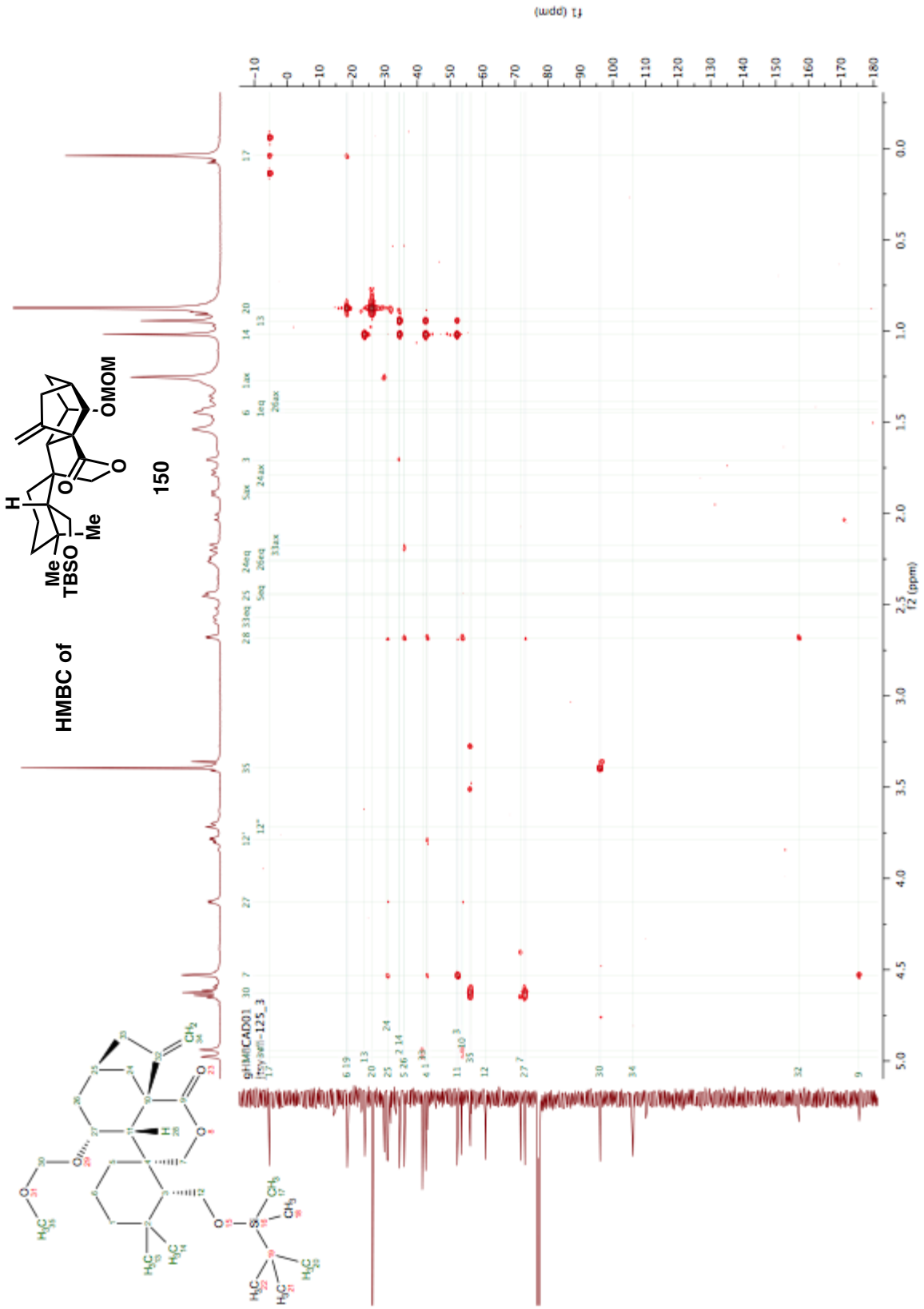

Sample Name:
jtsy-vii-231plug
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-vii-231plug
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 28 2012
Sample #20, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6553261 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 58 min
MOMO
H
Me
TBSO
Me
H
O
OTBS
149
220
200
180
160
140
120
100
80
60
40
20
0
ppm

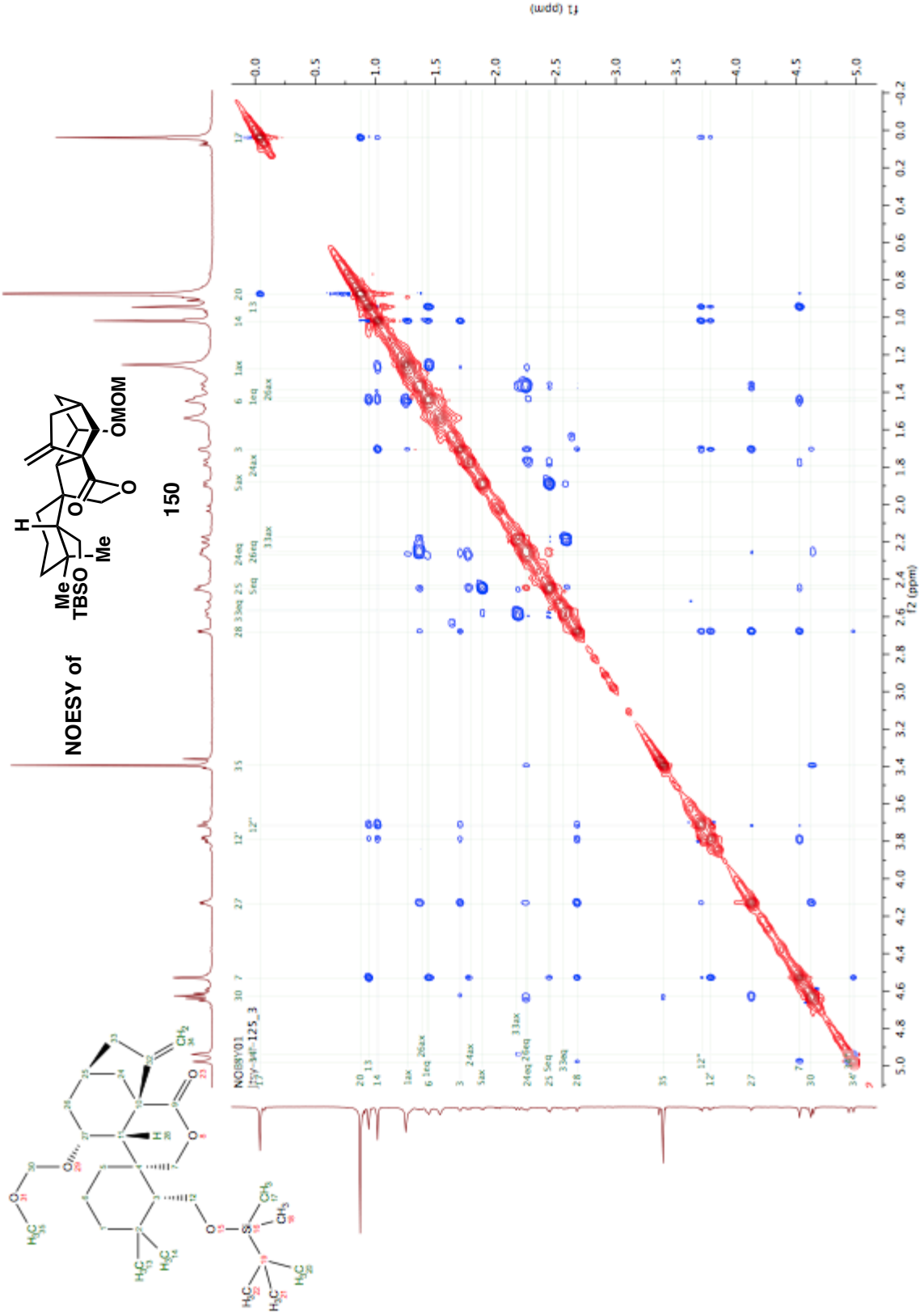

Sample Name:
jtsy-ix-081B-f23-39
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-081B-f23-39
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 23 2013
Sample #46, Operator: yeomanjo
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7995.2 Hz
8 repetitions
OBSERVE H1, 499.7049152 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 0 min 40 sec
H
Me
TBSO
Me
O
O
OMOM
150
ppm
10.43
3.21
3.01
3.07
1.07
2.64
0.94
0.98
1.01
0.90
1.02
2.02
2.04
1.06
3.01
0.90
0.99
1.14
2.10
2.03
0.99
0.97
6.73

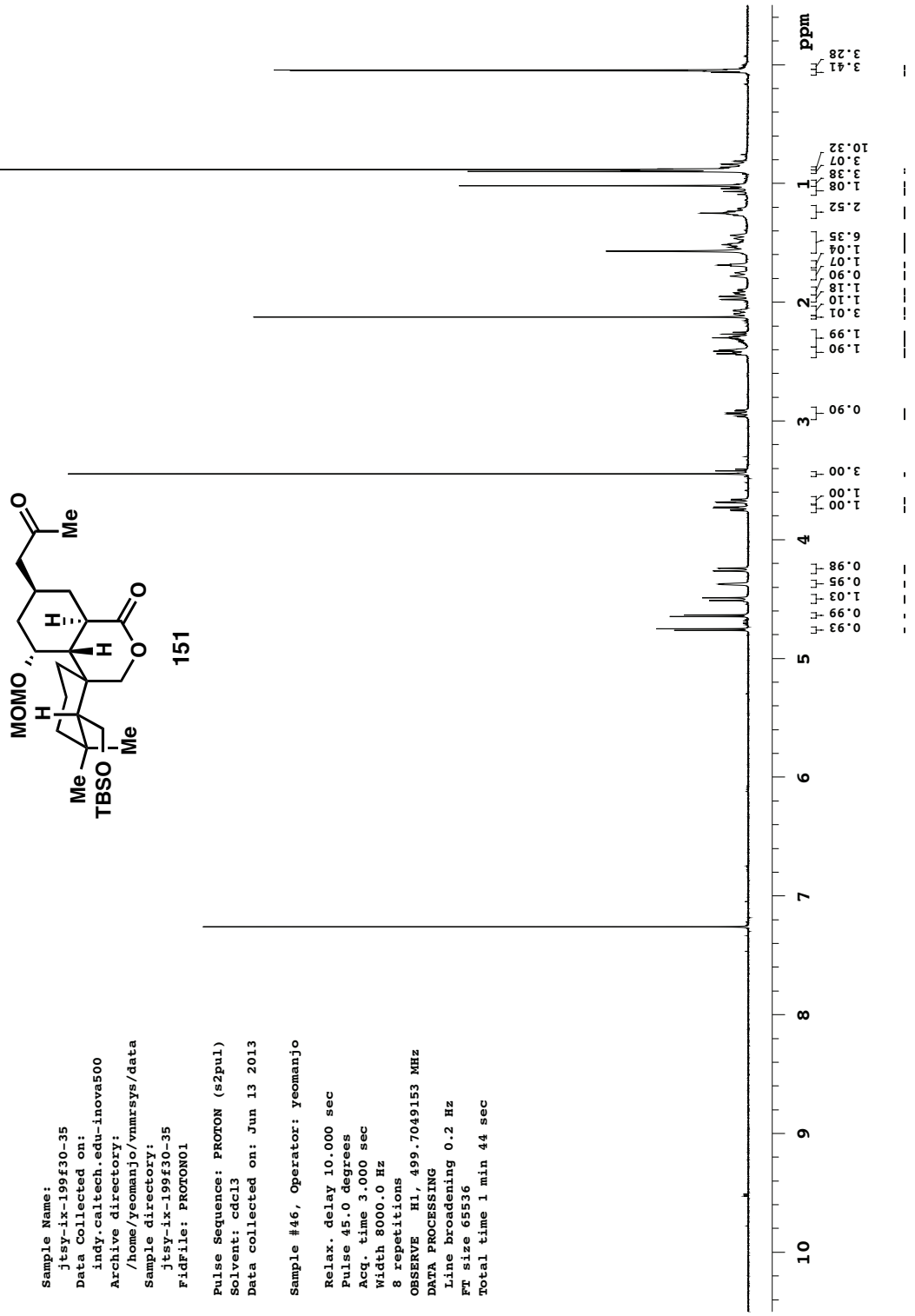

Sample Name:
jtsy-vii-125
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: jtsy-vii-125-c13
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 12 2012
Temp. 25.0 C / 298.1 K
Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31421.8 Hz
48000 repetitions
OBSERVE C13, 125.6871022 MHz
DECOUPLE H1, 499.8513810 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 15 hr, 14 min
Me
TBSO
Me
H
O
O
OMOM
150
220
200
180
160
140
120
100
80
60
40
20
0
ppm

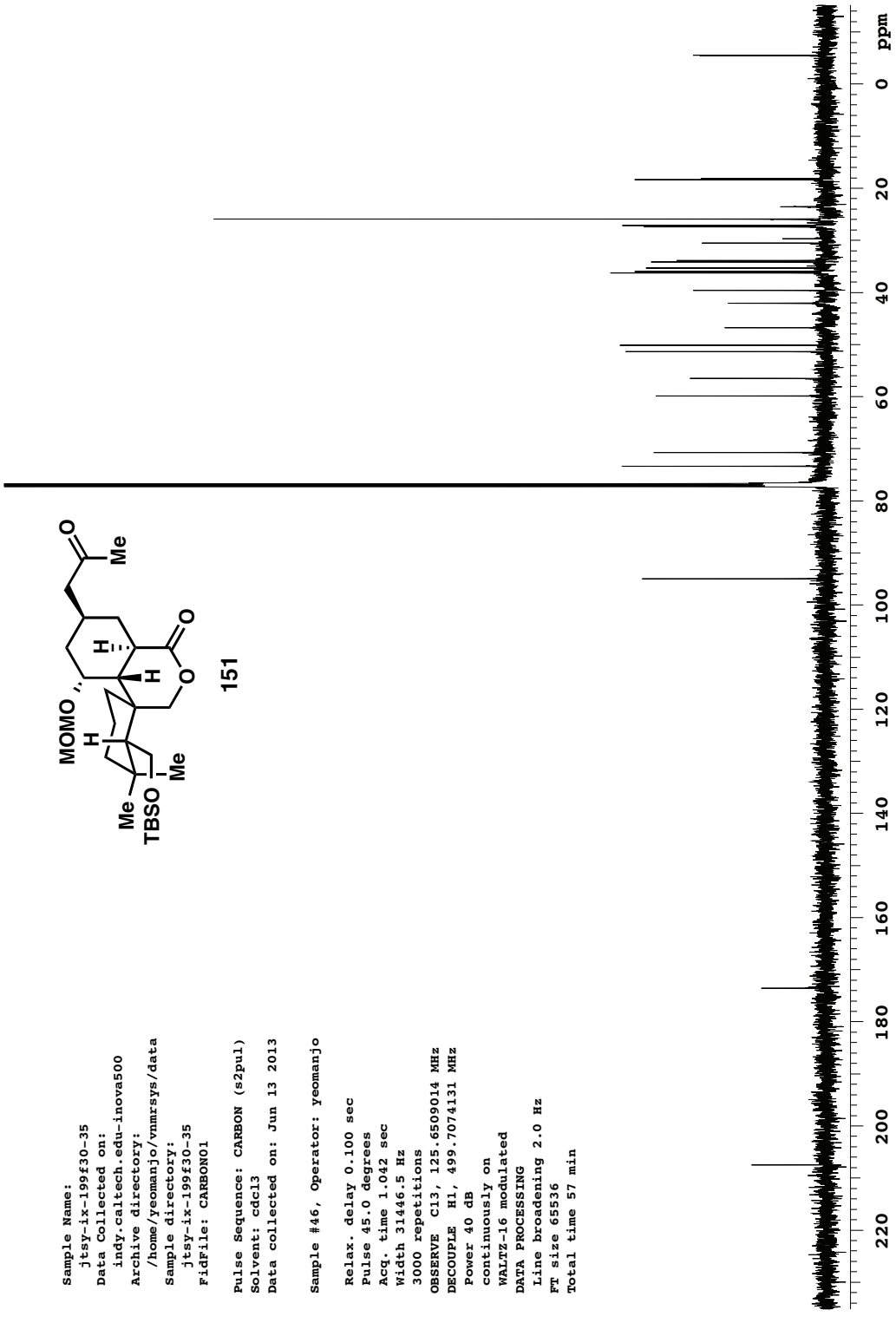

COSY of
150
OMOM
Me
TBSO
Me
H
O
O
f1 (ppm)
f2 (ppm)

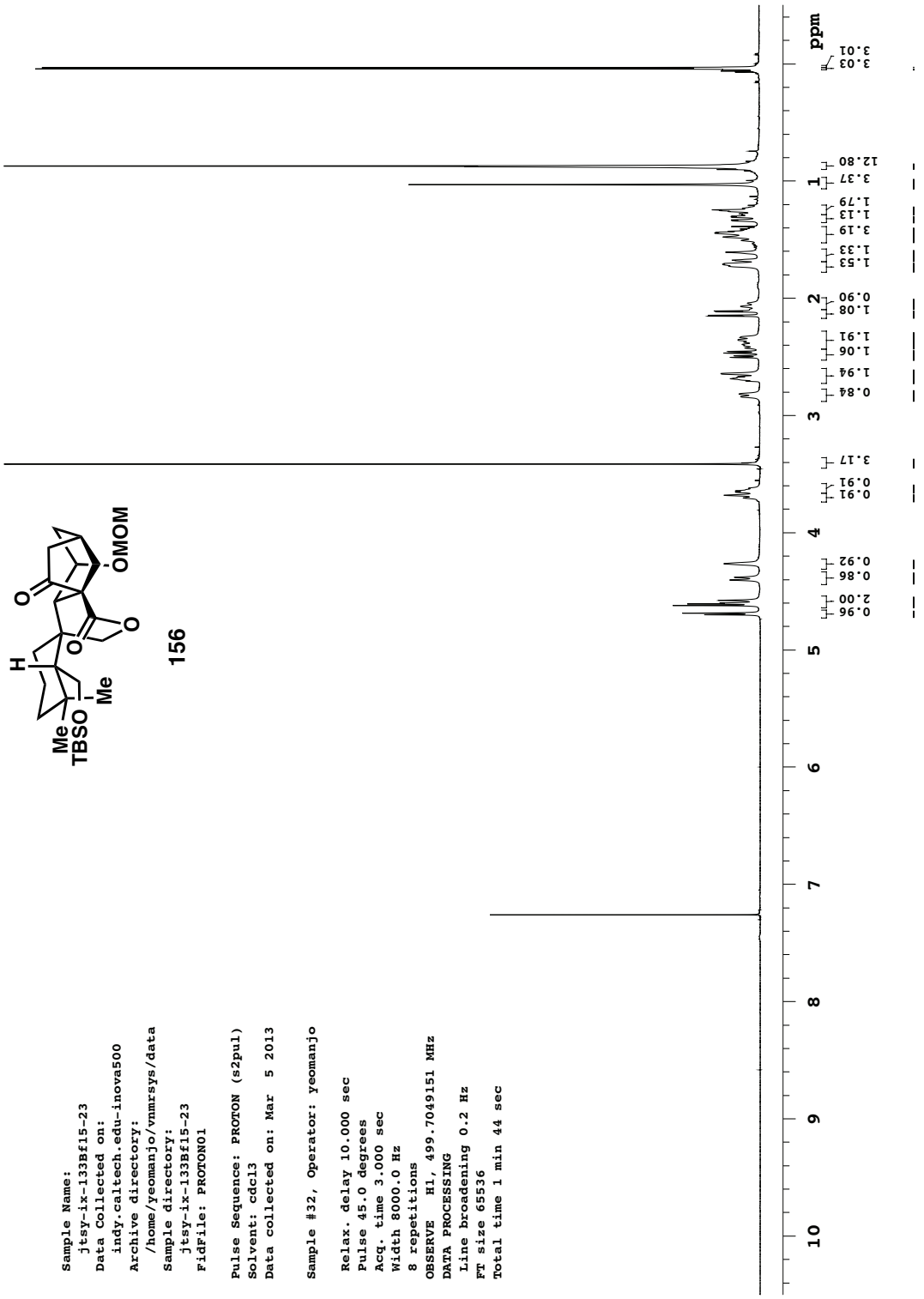

HSQC of
150
OMOM
Me
TBSO
Me
H
O
O
f1 (ppm)
f2 (ppm)

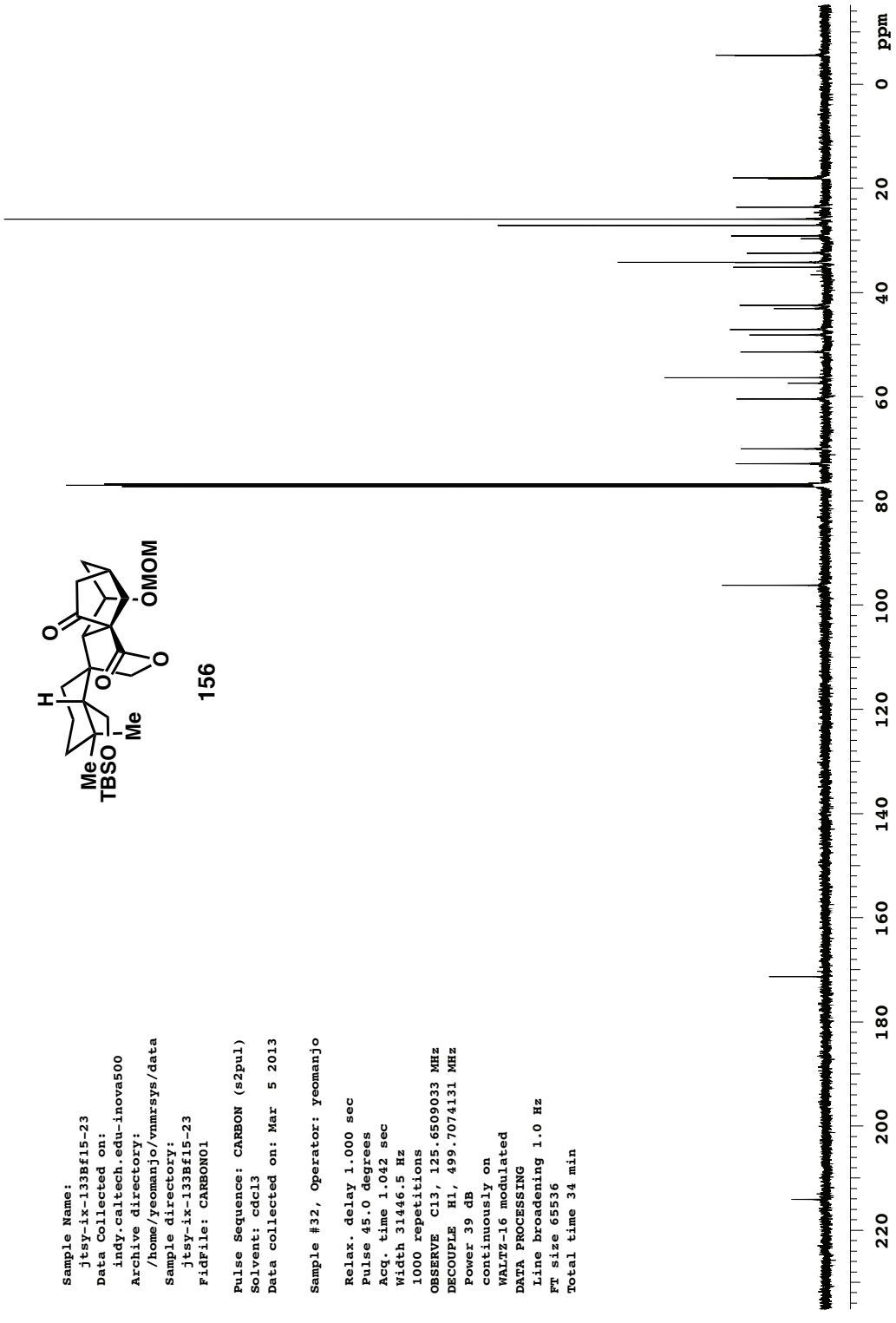

HMBC of
150
OMOM
TBSO
Me
Me
H
O
O
f1 (ppm)
f2 (ppm)

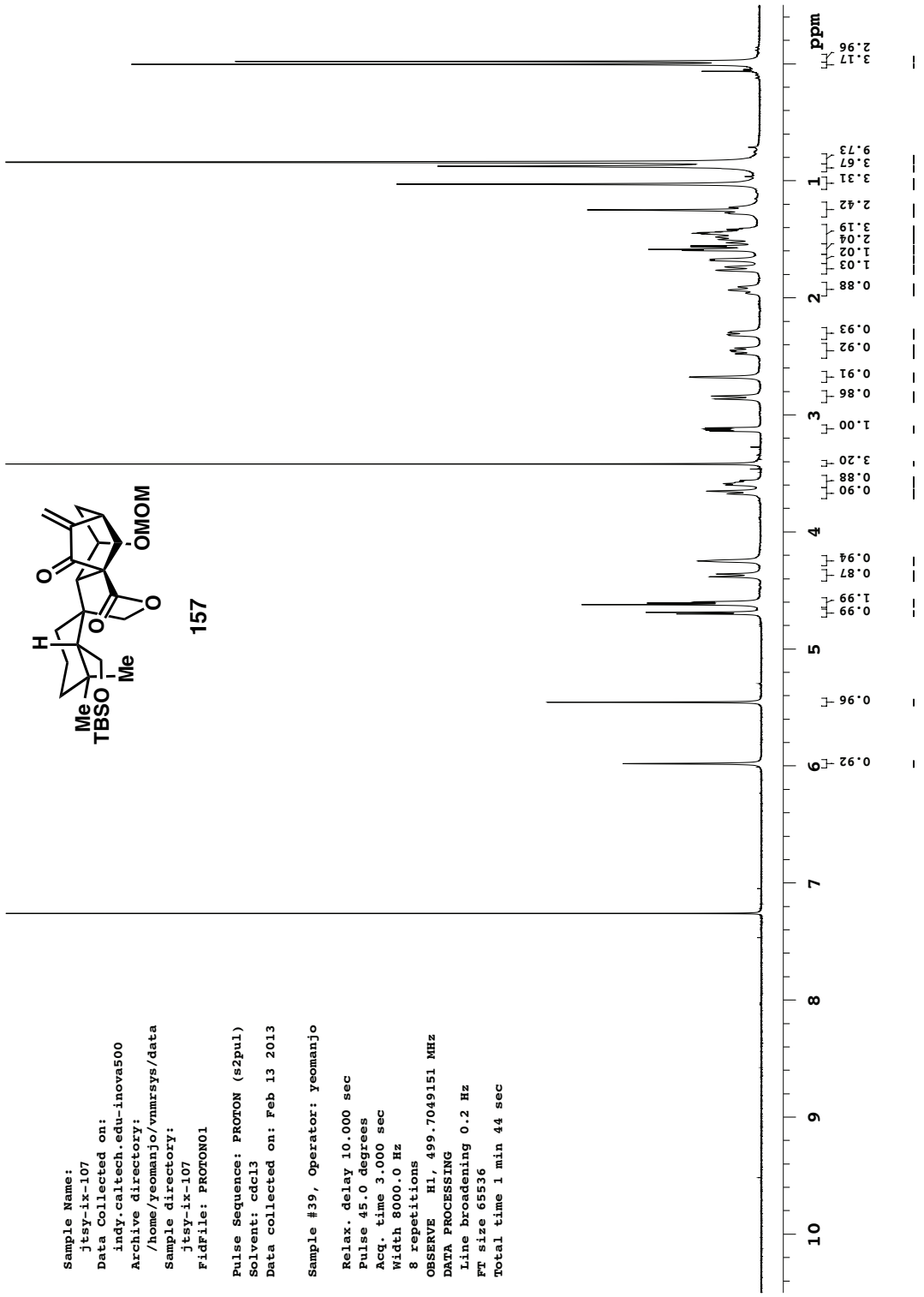

NOESY of
150
OMOM
Me
TBSO
Me
H
O
O
f1 (ppm)
f2 (ppm)

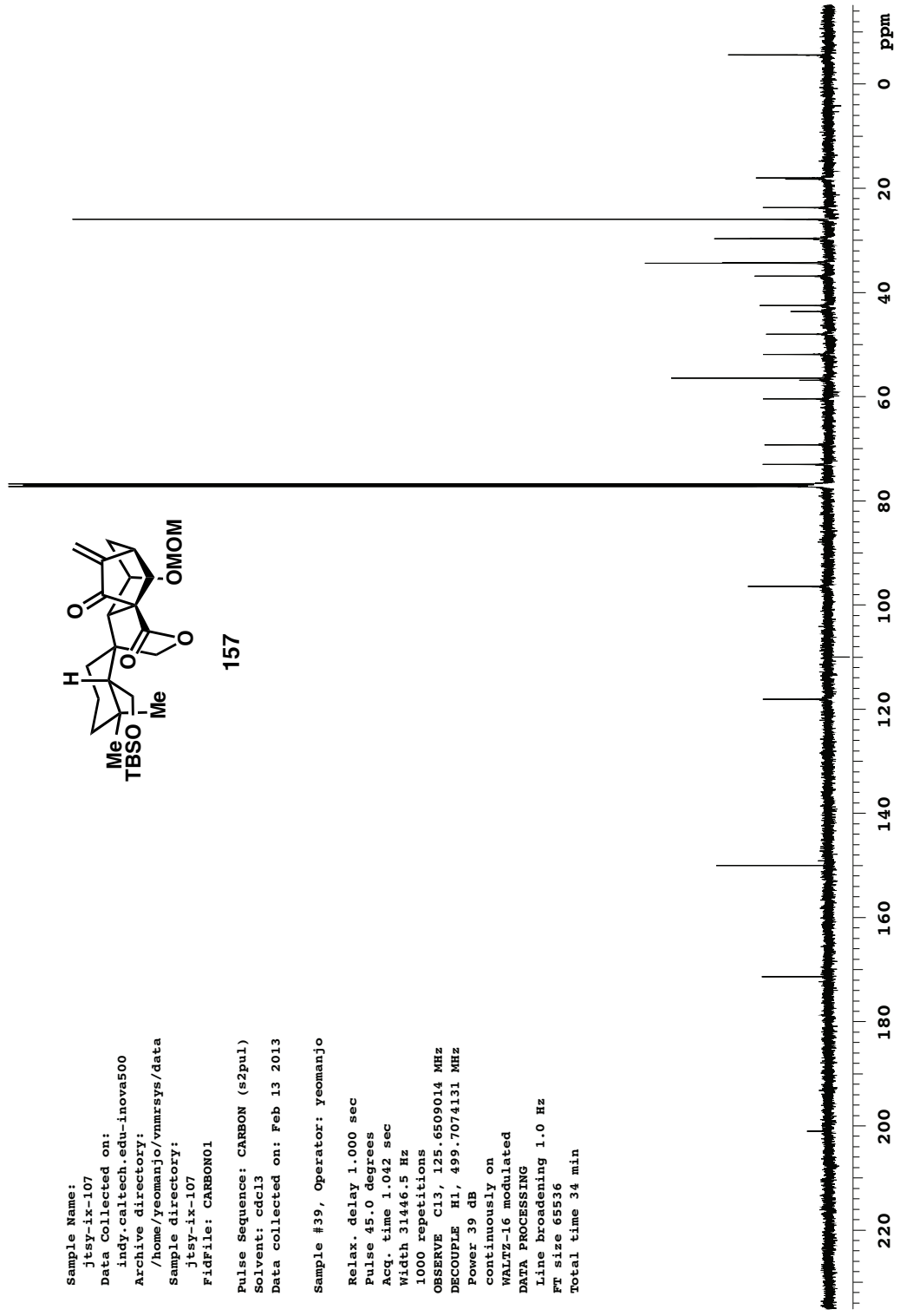

Sample Name:
jtsy-ix-199f30-35
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-199f30-35
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 13 2013
Sample #46, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049153 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 44 sec
MOMO
TBSO
Me
Me
Me
H
H
H
O
O
O
O
151
ppm
10
9
8
7
6
5
4
3
2
1
0.93
0.99
1.03
0.95
0.98
1.00
1.00
3.00
0.90
1.90
1.99
3.01
1.10
1.18
0.90
1.07
1.04
6.35
2.52
1.08
3.38
3.07
10.32
3.41
3.28

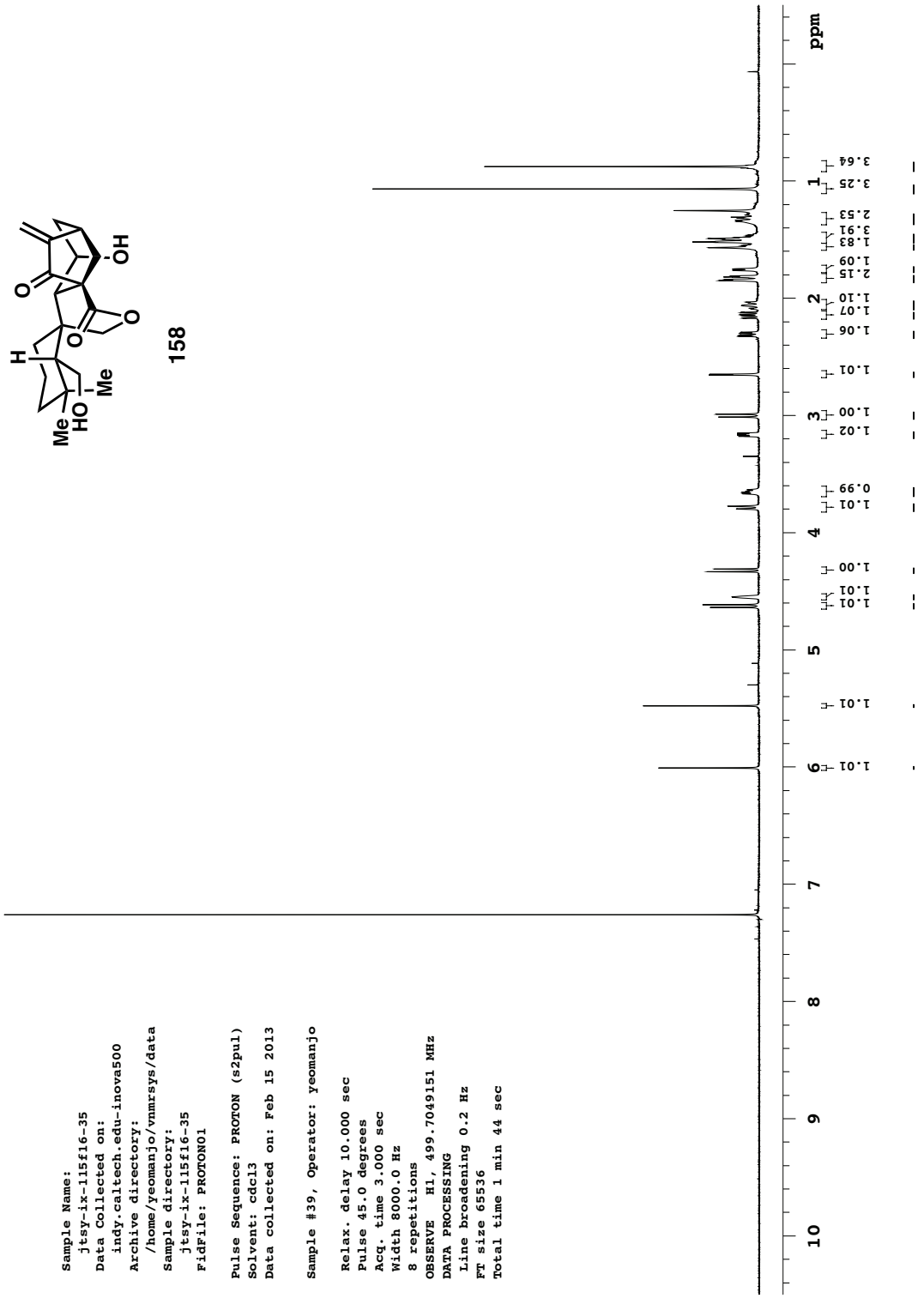

Sample Name:
jtsy-ix-199f30-35
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-199f30-35
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 13 2013
Sample #46, Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3000 repetitions
OBSERVE C13, 125.6509014 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 57 min
MOMO
H
Me
TBSO
Me
H
H
O
O
O
Me
151
220
200
180
160
140
120
100
80
60
40
20
0
ppm

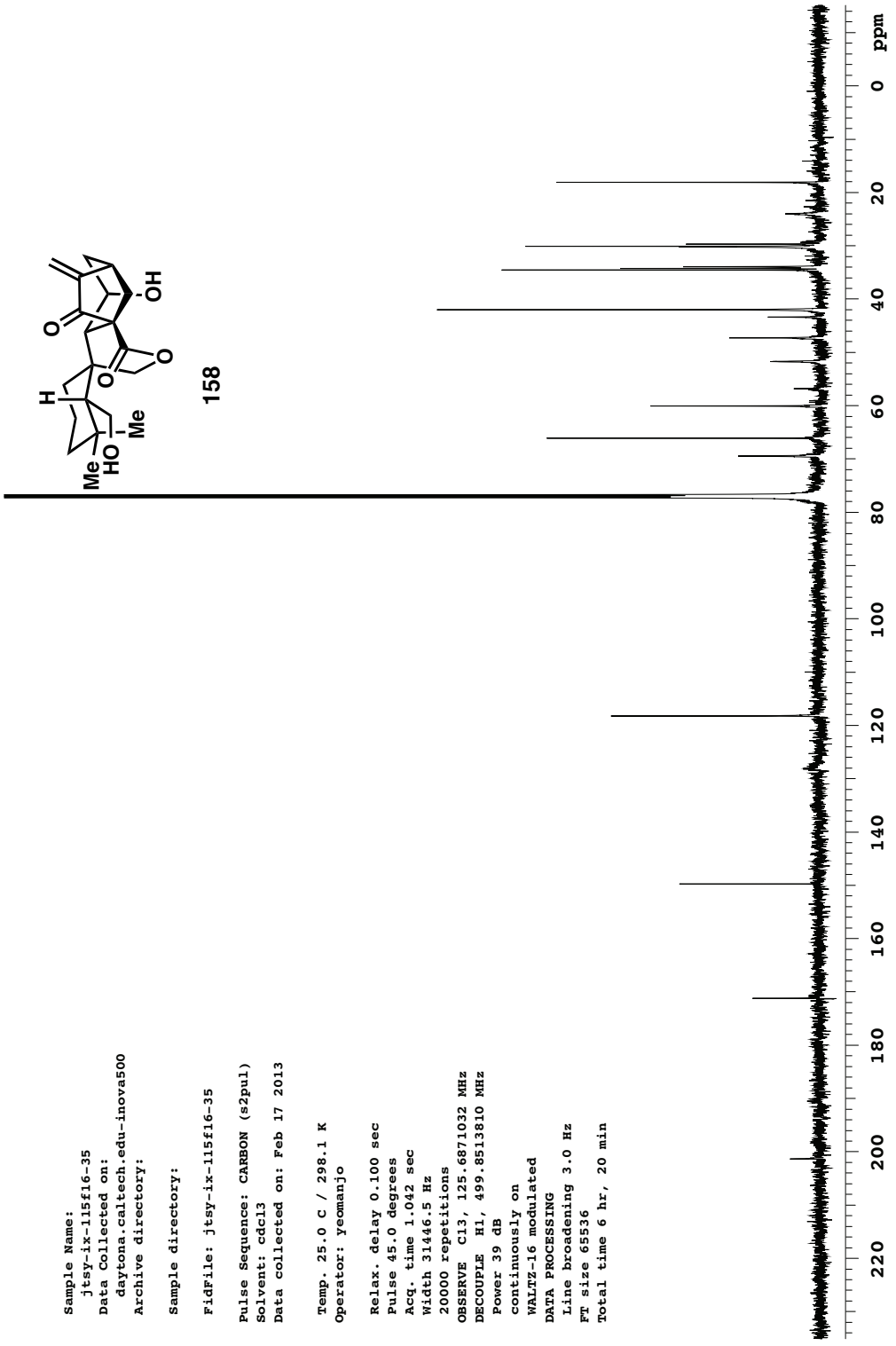

Sample Name:
jtsy-ix-133Bf15-23
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-133Bf15-23
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 5 2013
Sample #32, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 44 sec
Me
TBSO
H
Me
O
O
O
O
OMOM
156
ppm
0.96
2.00
0.86
0.92
0.91
0.91
3.17
0.84
1.94
1.06
1.91
1.08
0.90
1.53
1.33
3.19
1.13
1.79
3.37
12.80
3.03
3.01

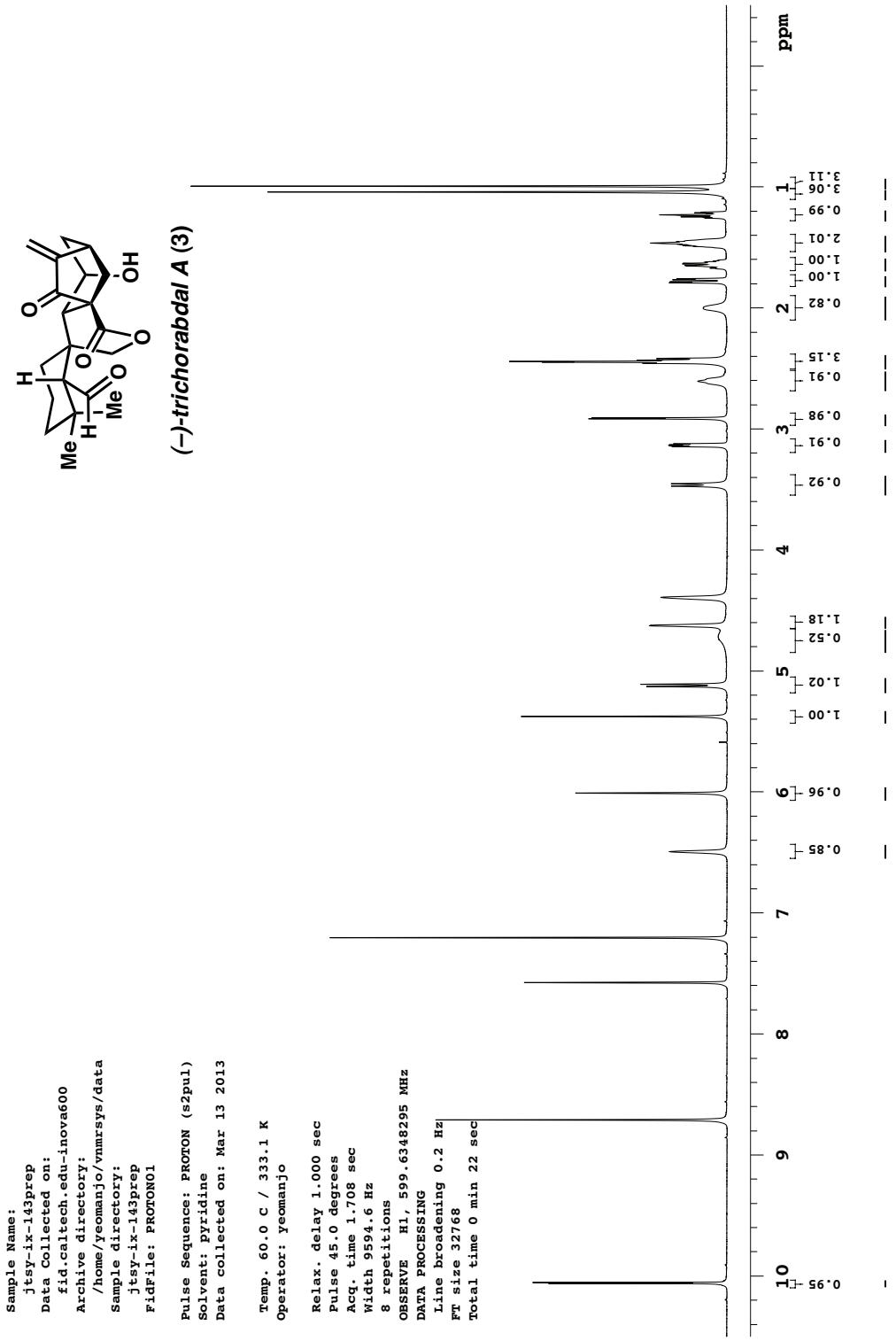

Sample Name:
jtsy-ix-133Bf15-23
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-133Bf15-23
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 5 2013
Sample #32, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6509033 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 34 min
H
Me
TBSO
Me
O
O
O
OMOM
156
220
200
180
160
140
120
100
80
60
40
20
0
ppm

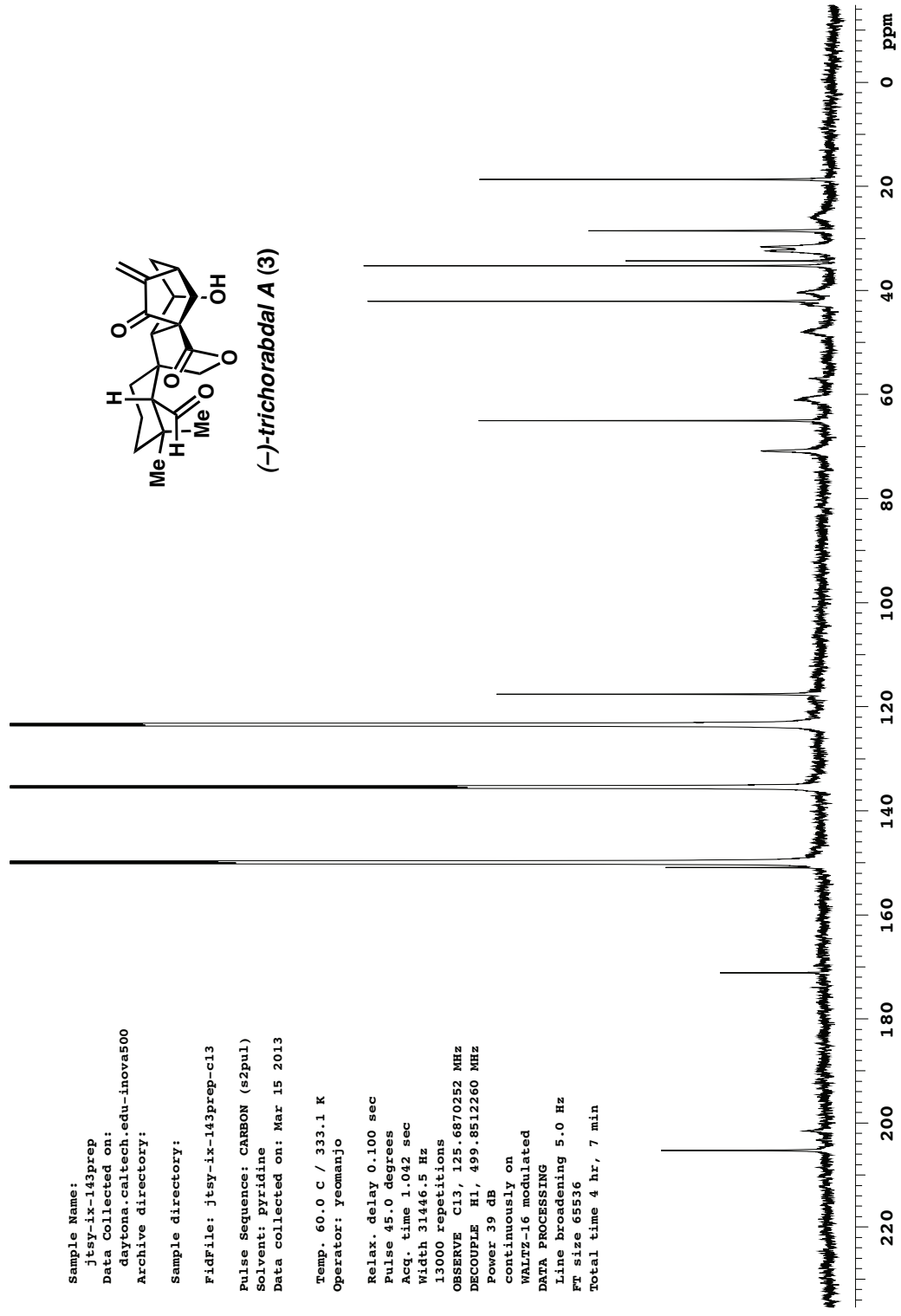

Sample Name:
jtsy-ix-107
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-107
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 13 2013
Sample #39, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 44 sec
OMOM
Me
TBSO
Me
H
O
O
O
157
ppm

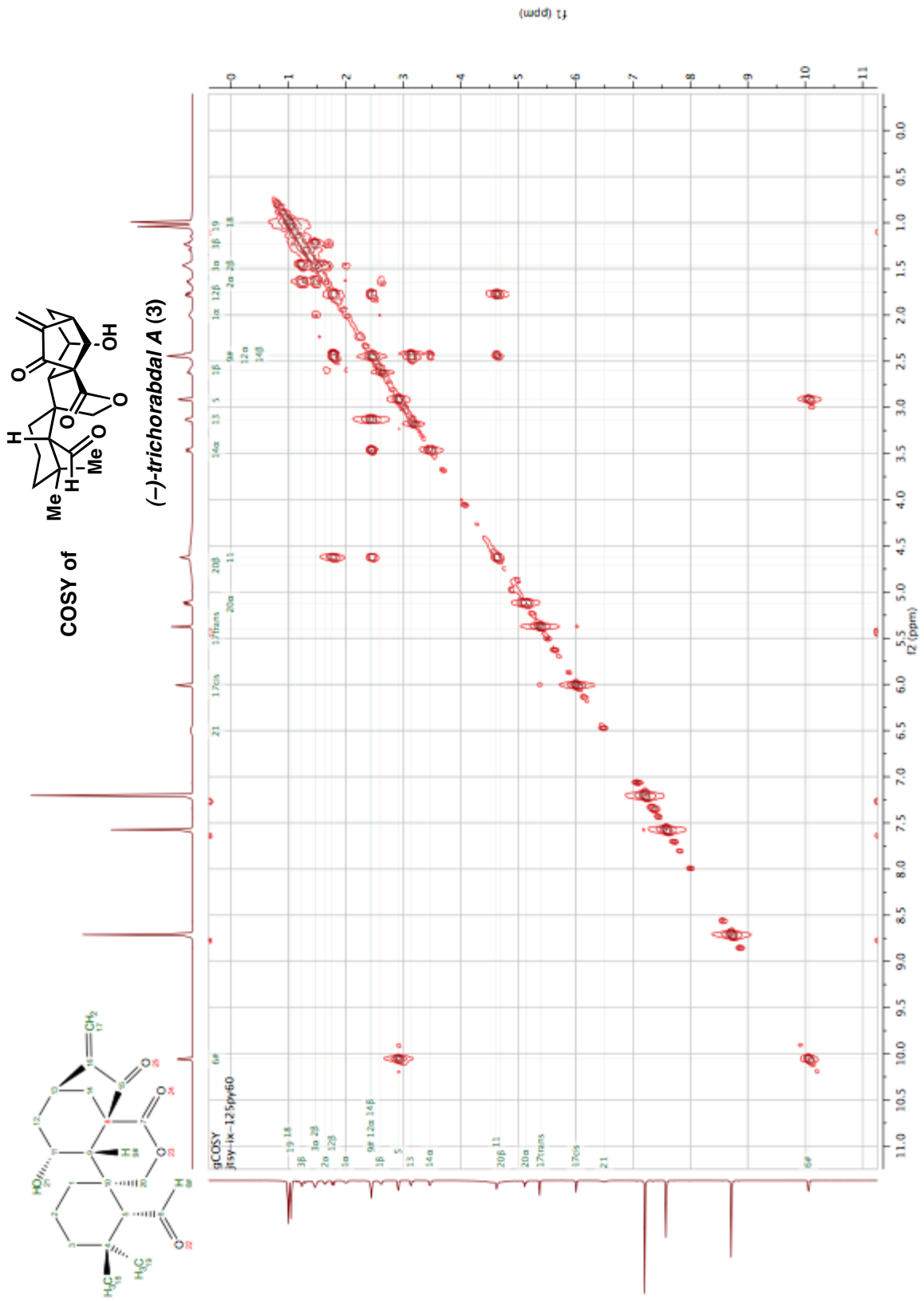

Sample Name:
jtsy-ix-107
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-107
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 13 2013
Sample #39, Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6509014 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 34 min
H
Me
TBSO
Me
O
O
O
OMOM
157
220
200
180
160
140
120
100
80
60
40
20
0
ppm

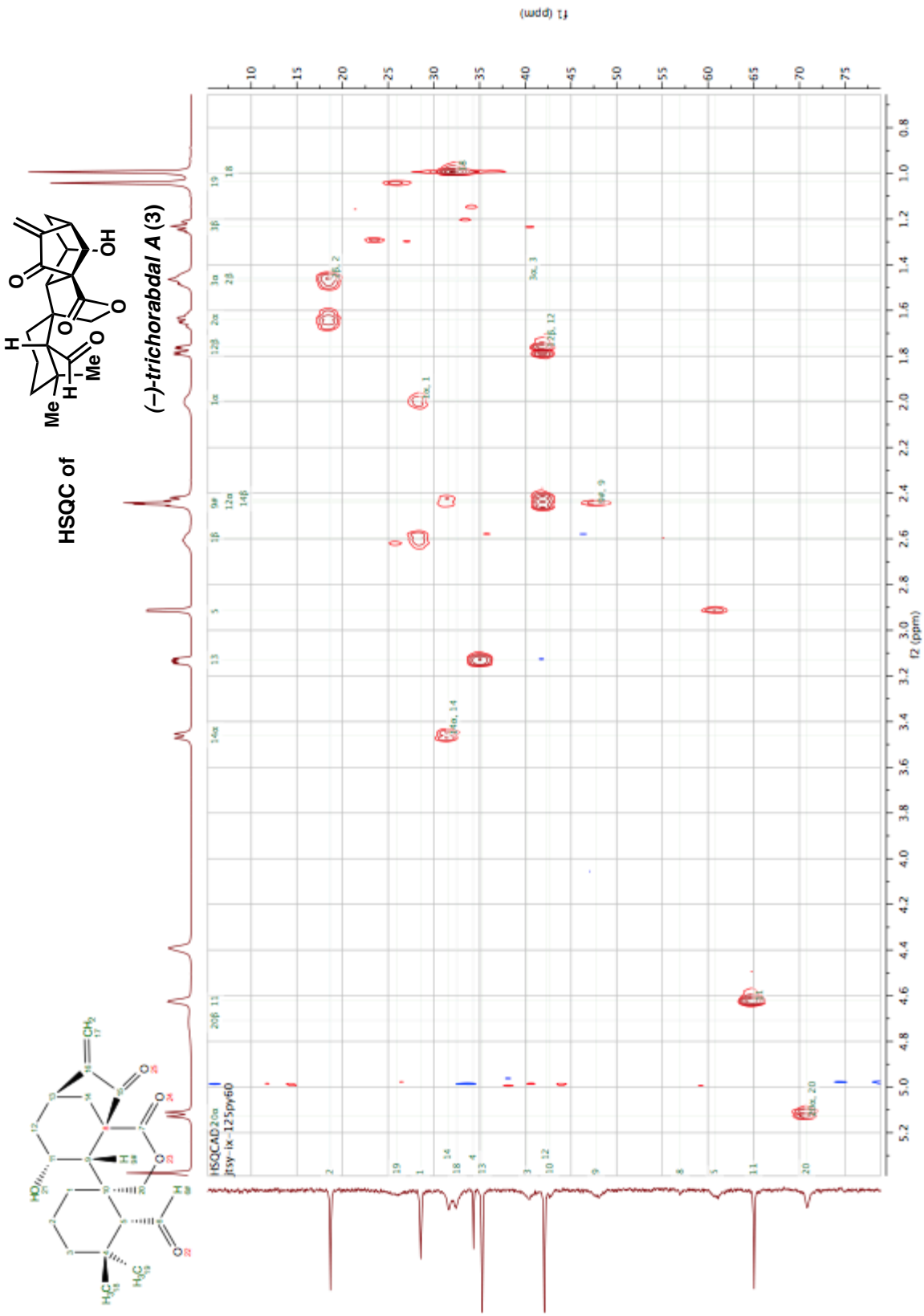

158
Sample Name:
jtsy-ix-115f16-35
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-115f16-35
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 15 2013
Sample #39, Operator: yeomanjo
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 44 sec
ppm
10
9
8
7
6
5
4
3
2
1
1.01
1.01
1.00
1.01
0.99
1.01
1.02
1.00
1.01
1.06
1.07
1.10
2.15
1.09
1.83
3.91
2.53
3.25
3.64

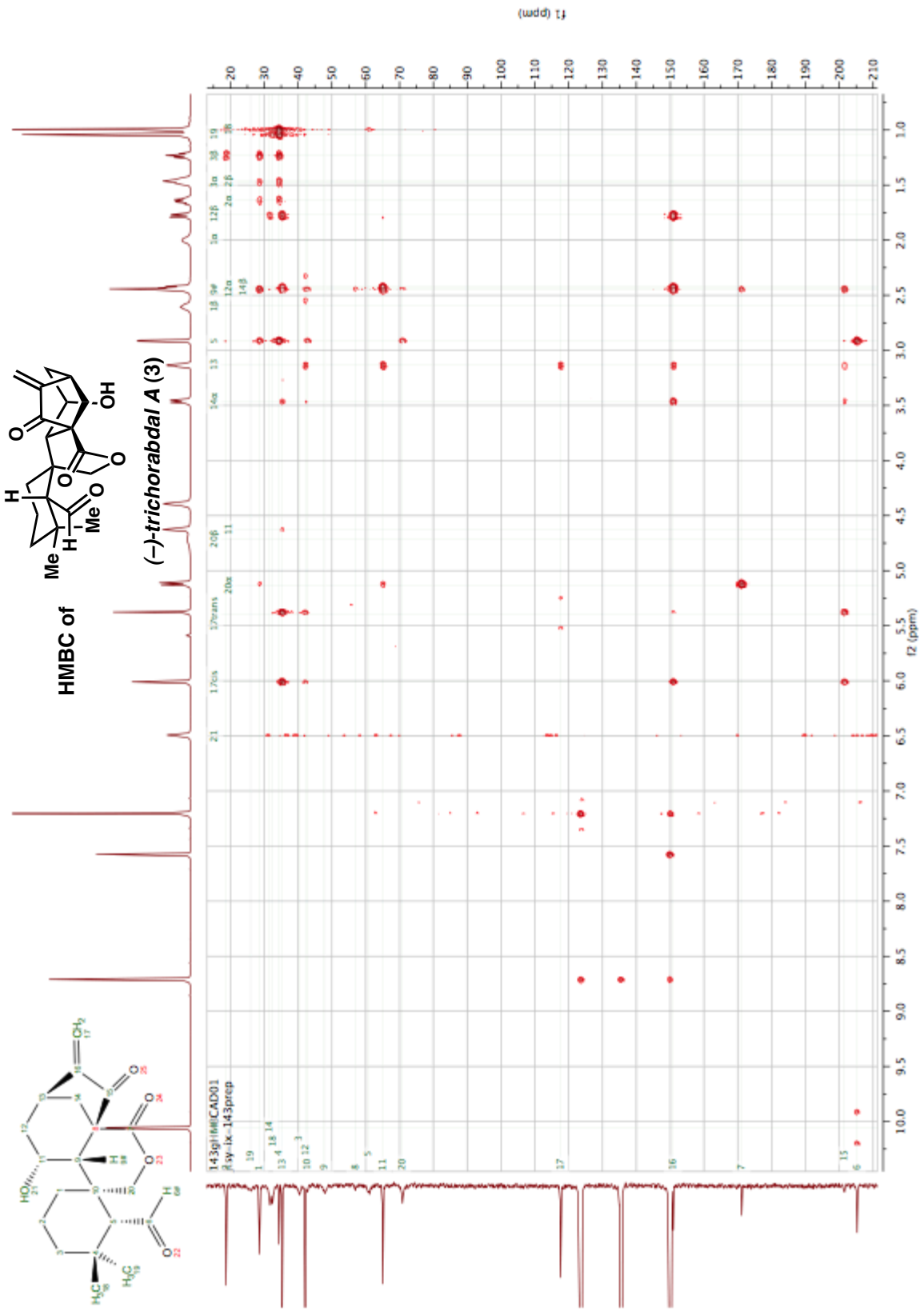

Sample Name:
jtsy-ix-115f16-35
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: jtsy-ix-115f16-35
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 17 2013
Temp. 25.0 C / 298.1 K
Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
20000 repetitions
OBSERVE C13, 125.6871032 MHz
DECOUPLE H1, 499.8513810 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 6 hr, 20 min
158
Me
HO
Me
H
O
O
O
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

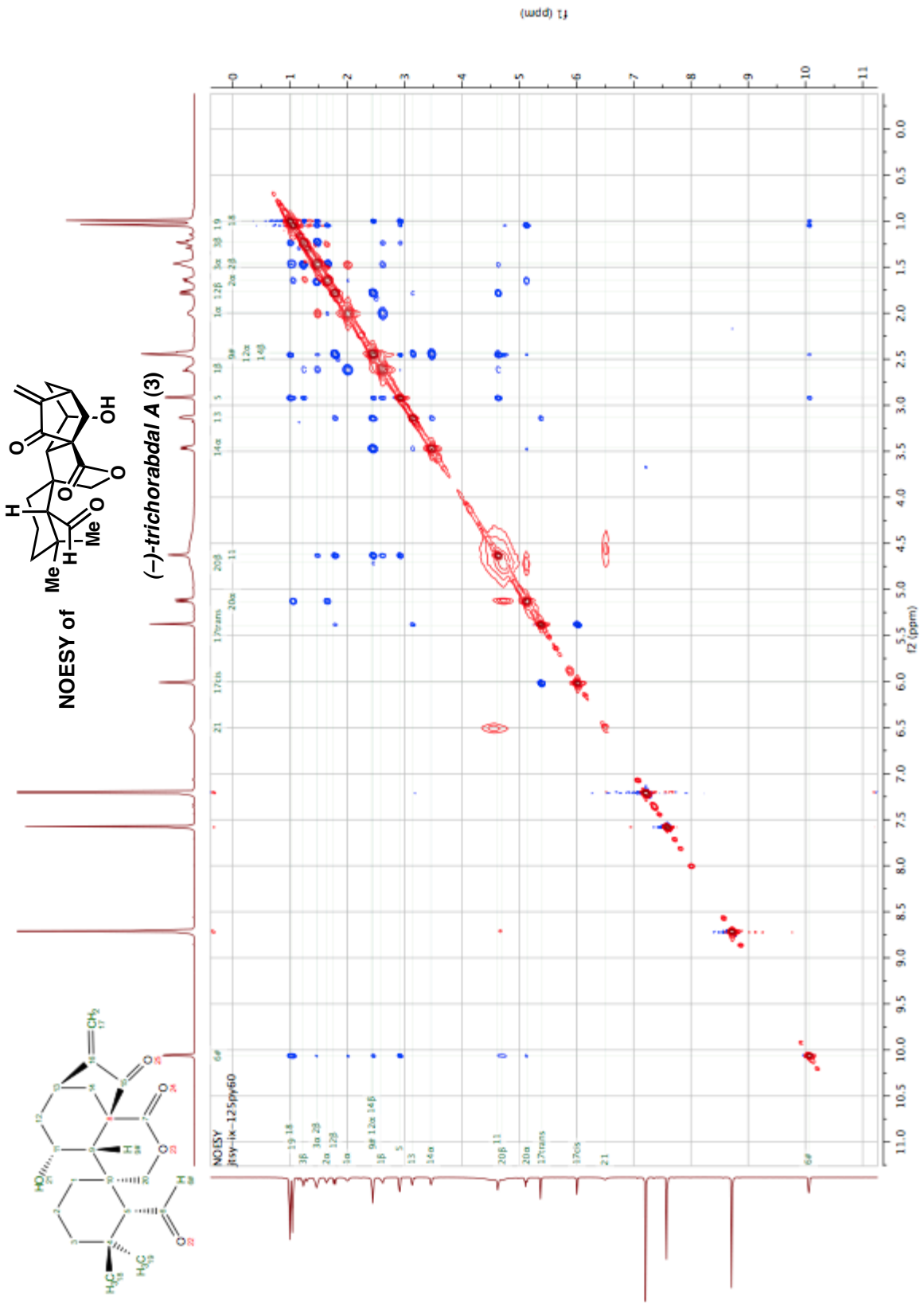

Sample Name:
jtsy-ix-143prep
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
/home/yeomanjo/vnmrsys/data
Sample directory:
jtsy-ix-143prep
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: pyridine
Data collected on: Mar 13 2013
Temp. 60.0 C / 333.1 K
Operator: yeomanjo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.708 sec
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6348295 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min 22 sec
(–)-trichorabdal A (3)
ppm
0.95
0.85
0.96
1.00
1.02
0.52
1.18
0.92
0.91
0.98
0.91
3.15
0.82
1.00
1.00
2.01
0.99
3.06
3.11

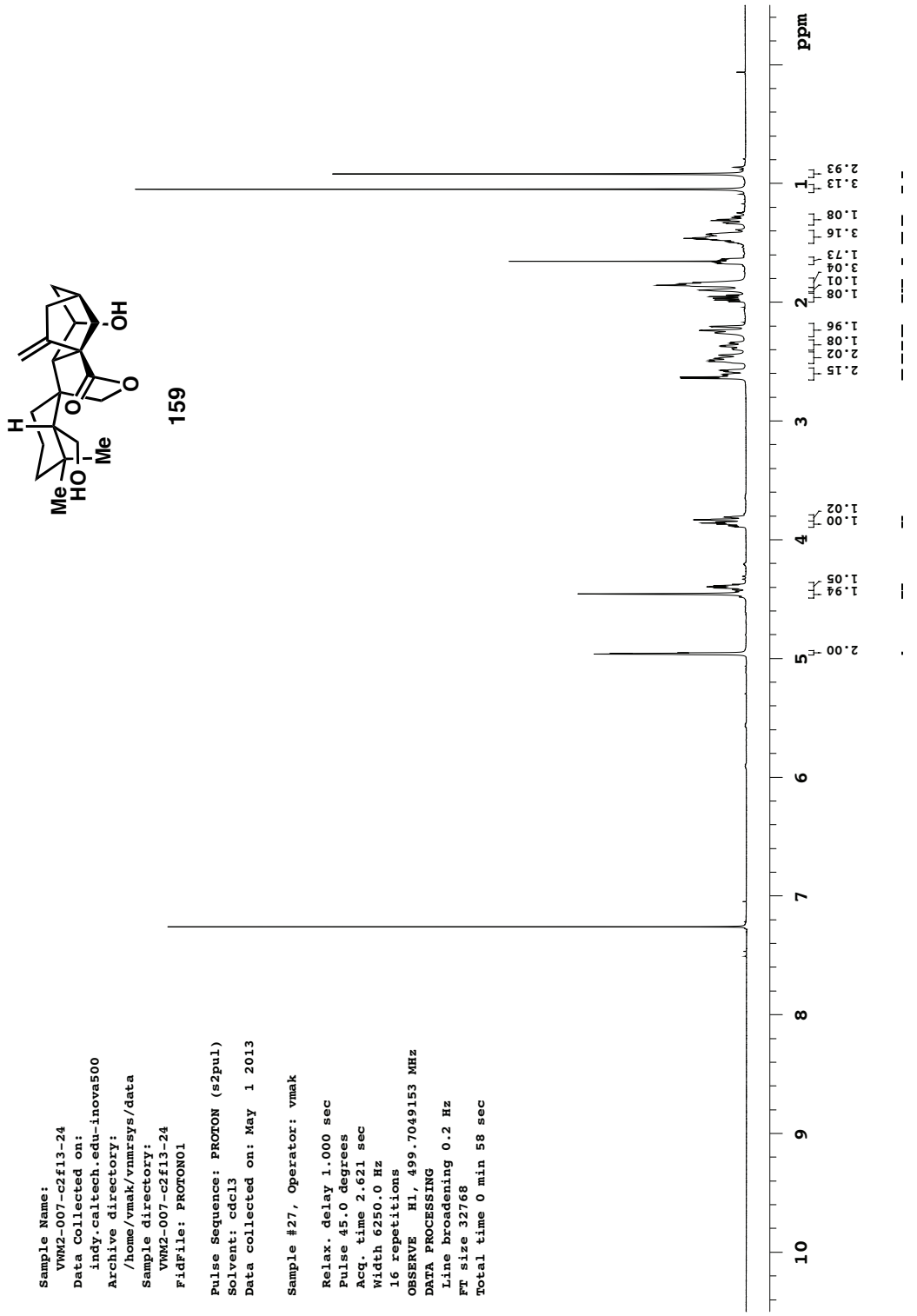

Sample Name:
jtsy-ix-143prep
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: jtsy-ix-143prep-c13
Pulse Sequence: CARBON (s2pul)
Solvent: pyridine
Data collected on: Mar 15 2013
Temp. 60.0 C / 333.1 K
Operator: yeomanjo
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13000 repetitions
OBSERVE C13, 125.6870252 MHz
DECOUPLE H1, 499.8512260 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 4 hr, 7 min
Me
H
Me
O
O
O
O
H
OH
(–)-trichorabdal A (3)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

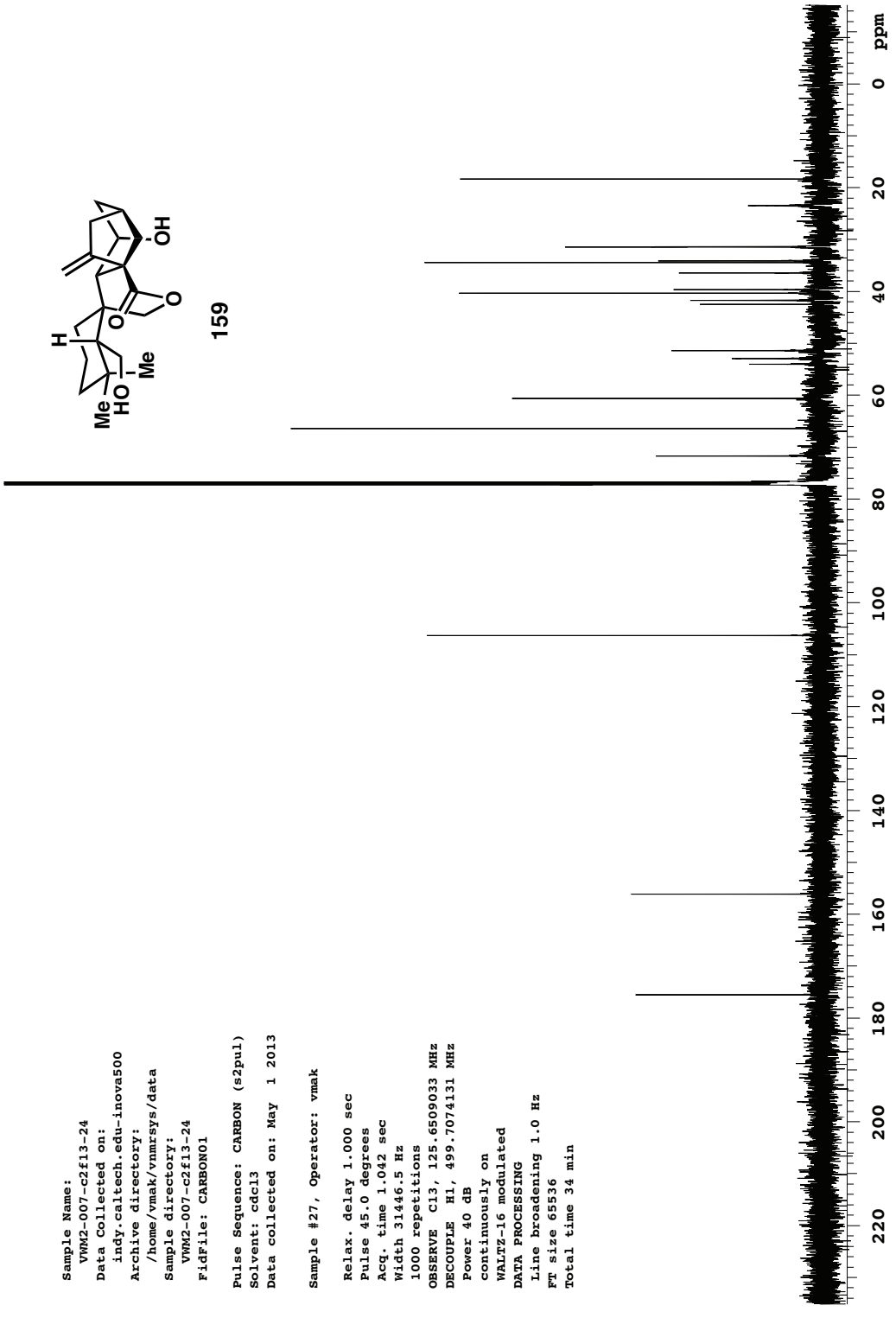

COSY of
(–)-trichorabdal A (3)
gCOSY
jtsy-ix-125phy60
f1 (ppm)
f2 (ppm)

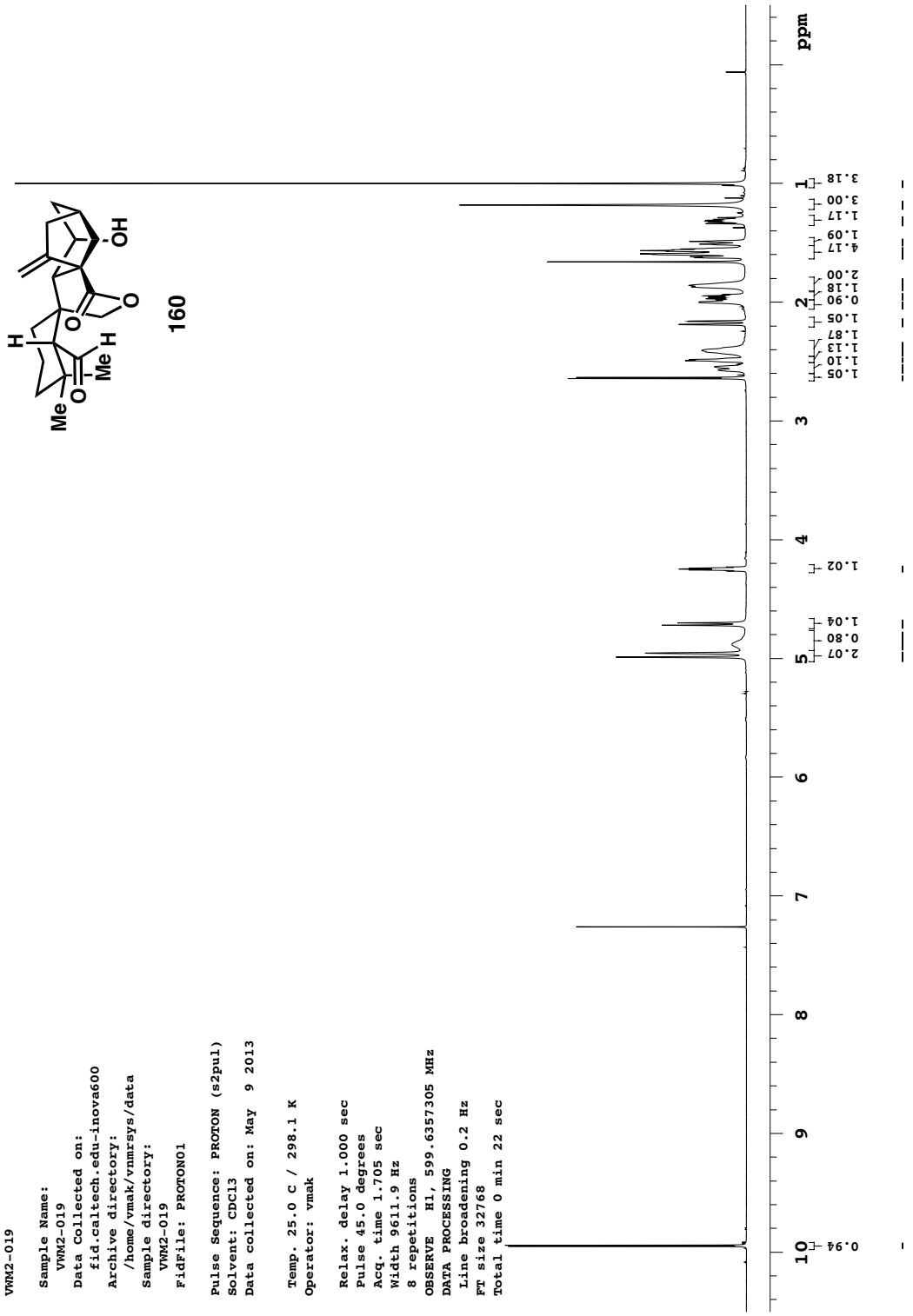

HSQC of
(–)-trichorabdal A (3)
f1 (ppm)
f2 (ppm)

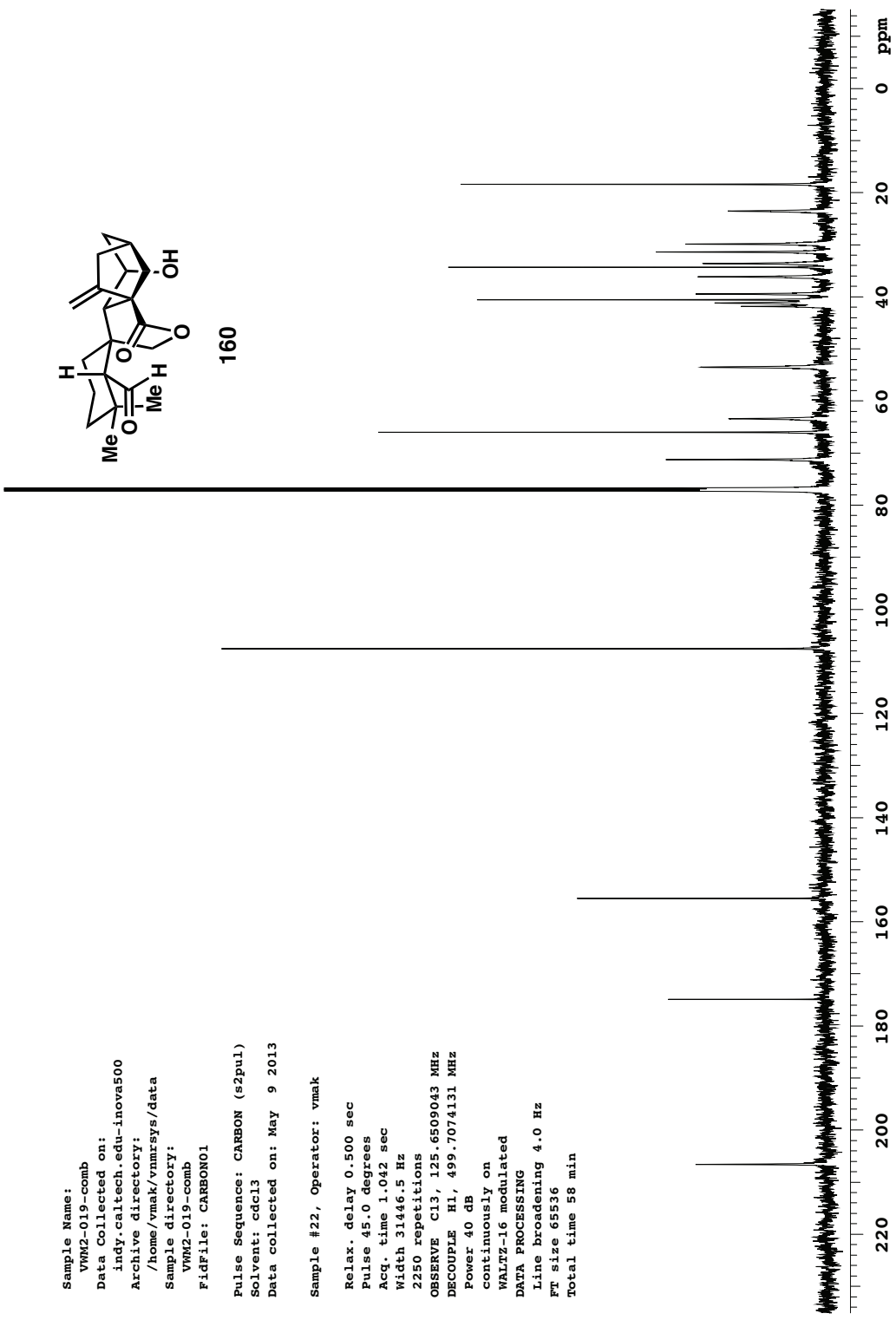

HMBC of
(–)-trichorabdal A (3)
OH
O
O
O
H
Me
O
Me
H
f1 (ppm)
f2 (ppm)

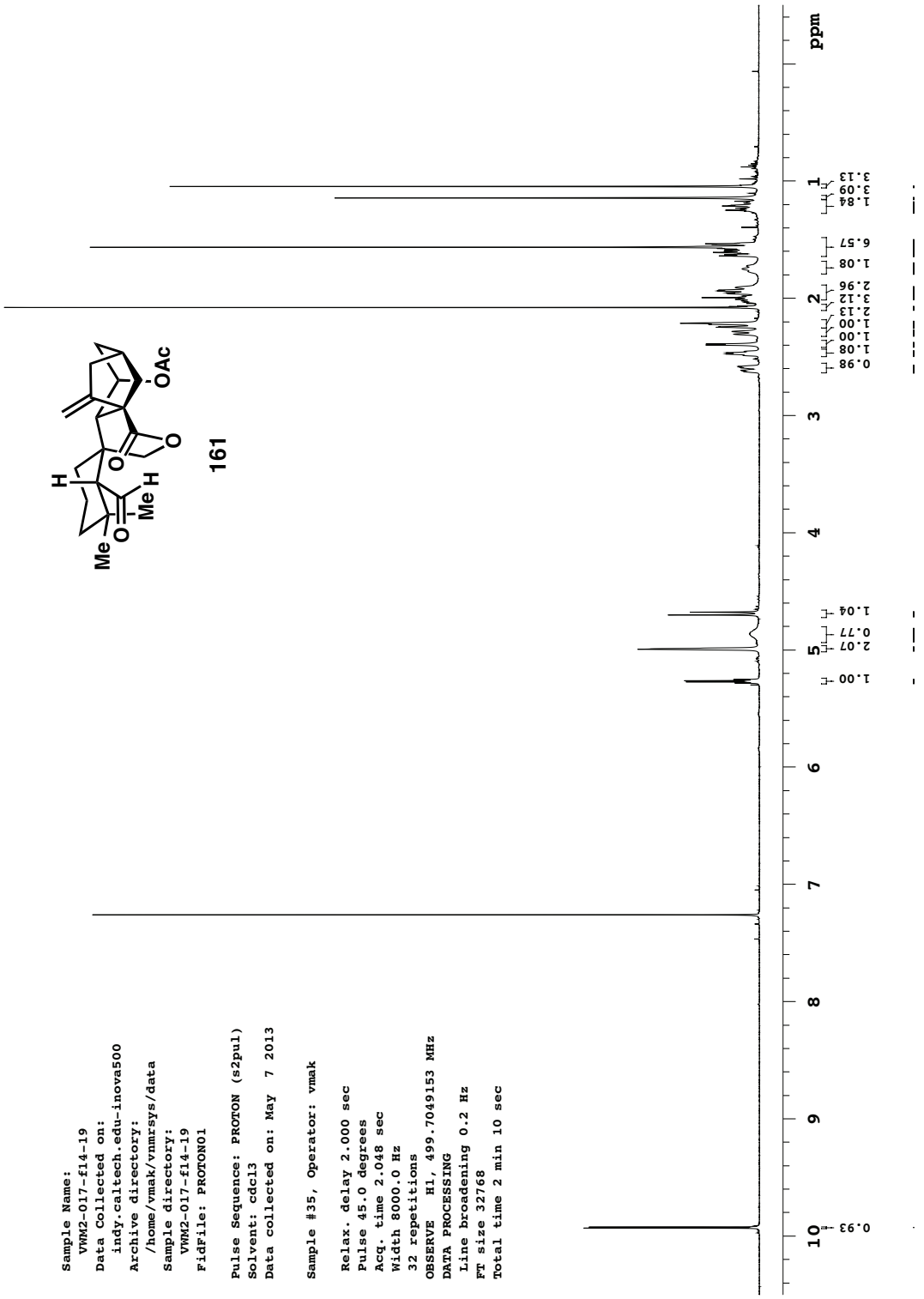

NOESY of
(–)-trichorabdal A (3)
NOESY
jtsy-ix-125py60
f1 (ppm)
f2 (ppm)

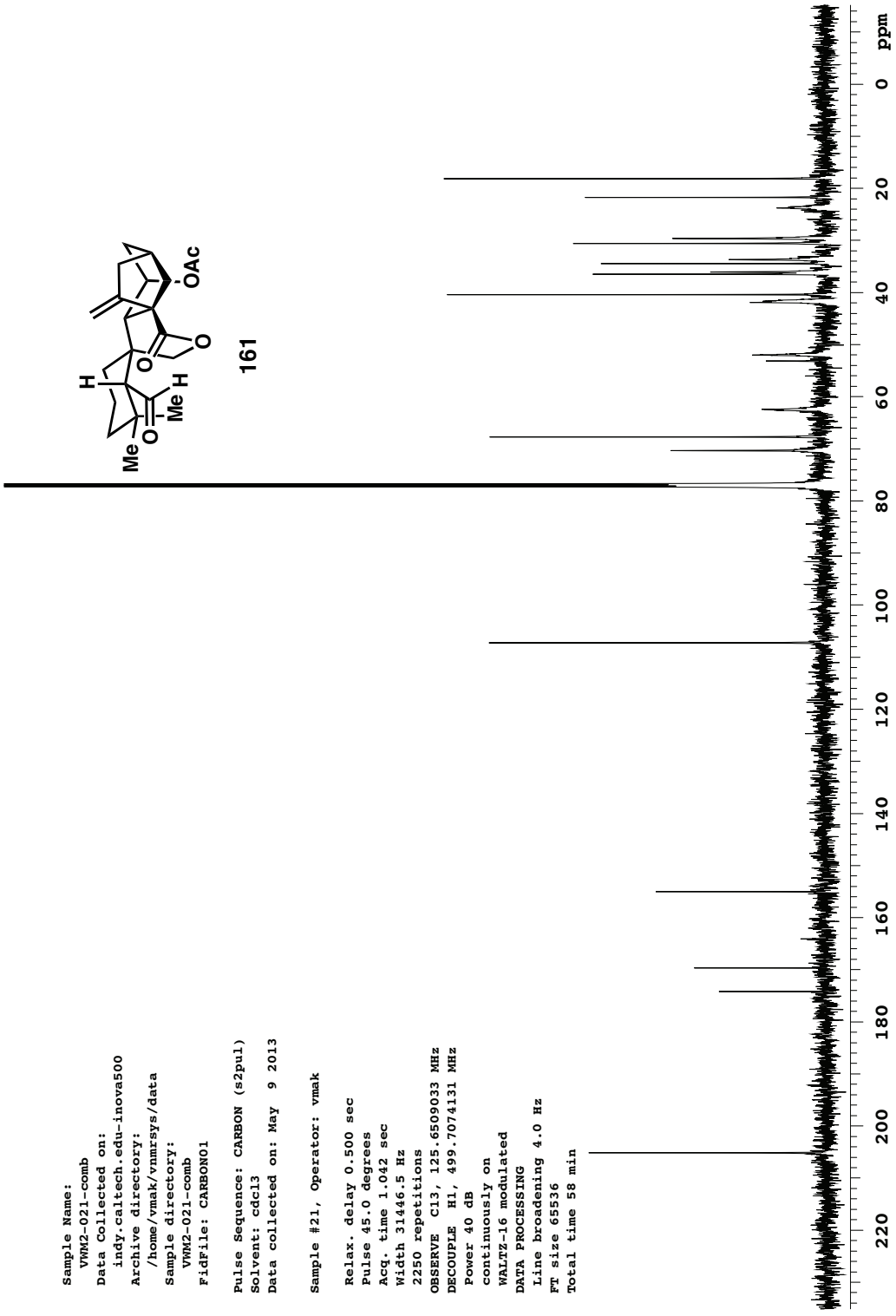

Sample Name:
VWM2-007-c2f13-24
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-007-c2f13-24
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 1 2013
Sample #27, Operator: vmak
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.621 sec
Width 6250.0 Hz
16 repetitions
OBSERVE H1, 499.7049153 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min 58 sec
159
Me
HO
Me
H
O
O
OH
ppm
10
9
8
7
6
5
4
3
2
1
2.00
1.94
1.05
1.00
1.02
2.15
2.02
1.08
1.96
1.08
1.01
3.04
1.73
3.16
1.08
3.13
2.93

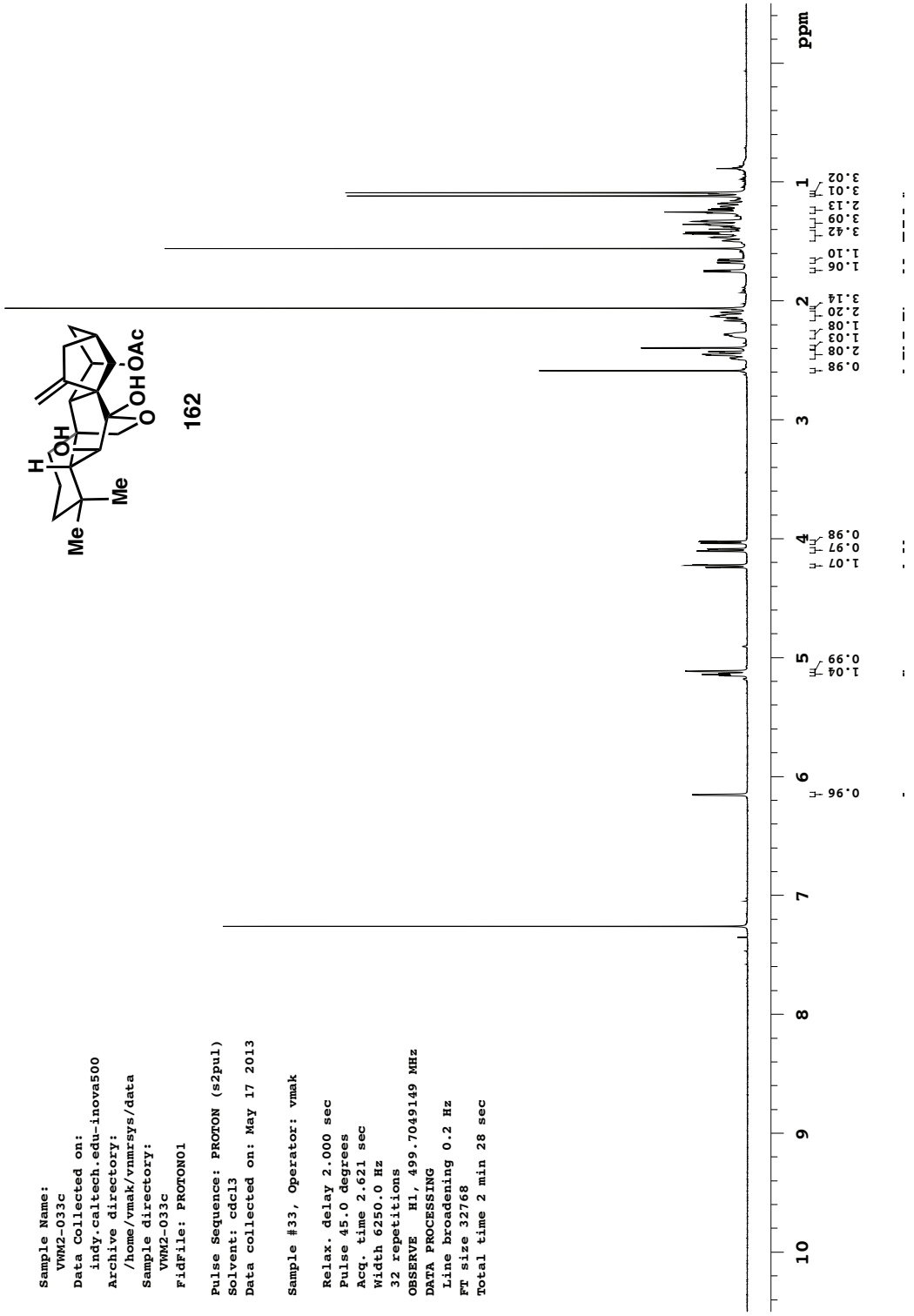

Sample Name:
VWM2-007-c2f13-24
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-007-c2f13-24
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 1 2013
Sample #27, Operator: vmak
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6509033 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 34 min
H
Me
HO
Me
O
O
OH
159
220
200
180
160
140
120
100
80
60
40
20
0
ppm

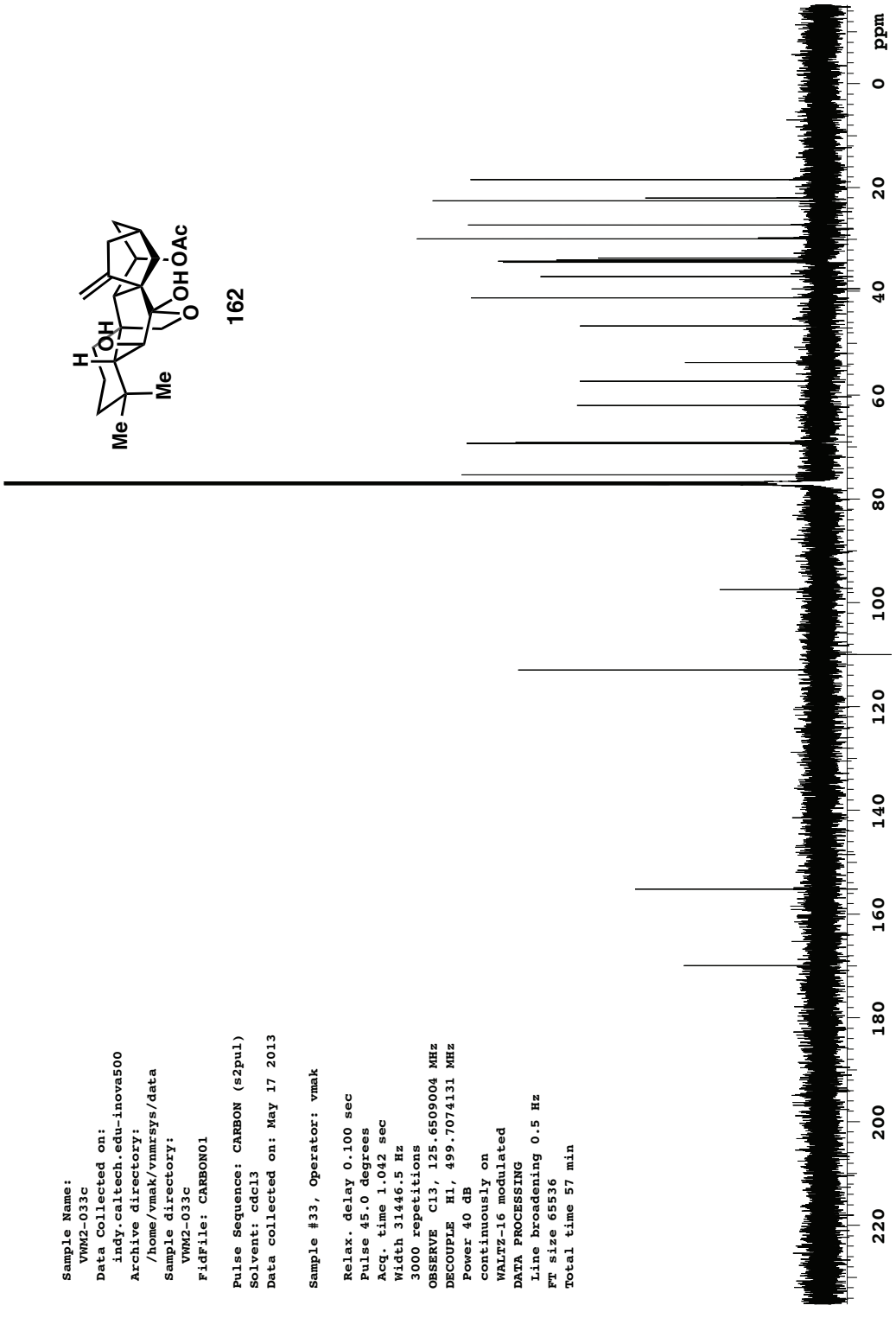

VWM2-019
Sample Name:
VWM2-019
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-019
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: CDCl3
Data collected on: May 9 2013
Temp. 25.0 C / 298.1 K
Operator: vmak
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.705 sec
Width 9611.9 Hz
8 repetitions
OBSERVE H1, 599.6357305 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min 22 sec
160
Me
H
Me
H
OH
O
O
O
ppm
10
9
8
7
6
5
4
3
2
1
0.94
2.07
0.80
1.04
1.02
1.05
1.10
1.13
1.87
1.05
0.90
1.18
2.00
4.17
1.09
1.17
3.00
3.18

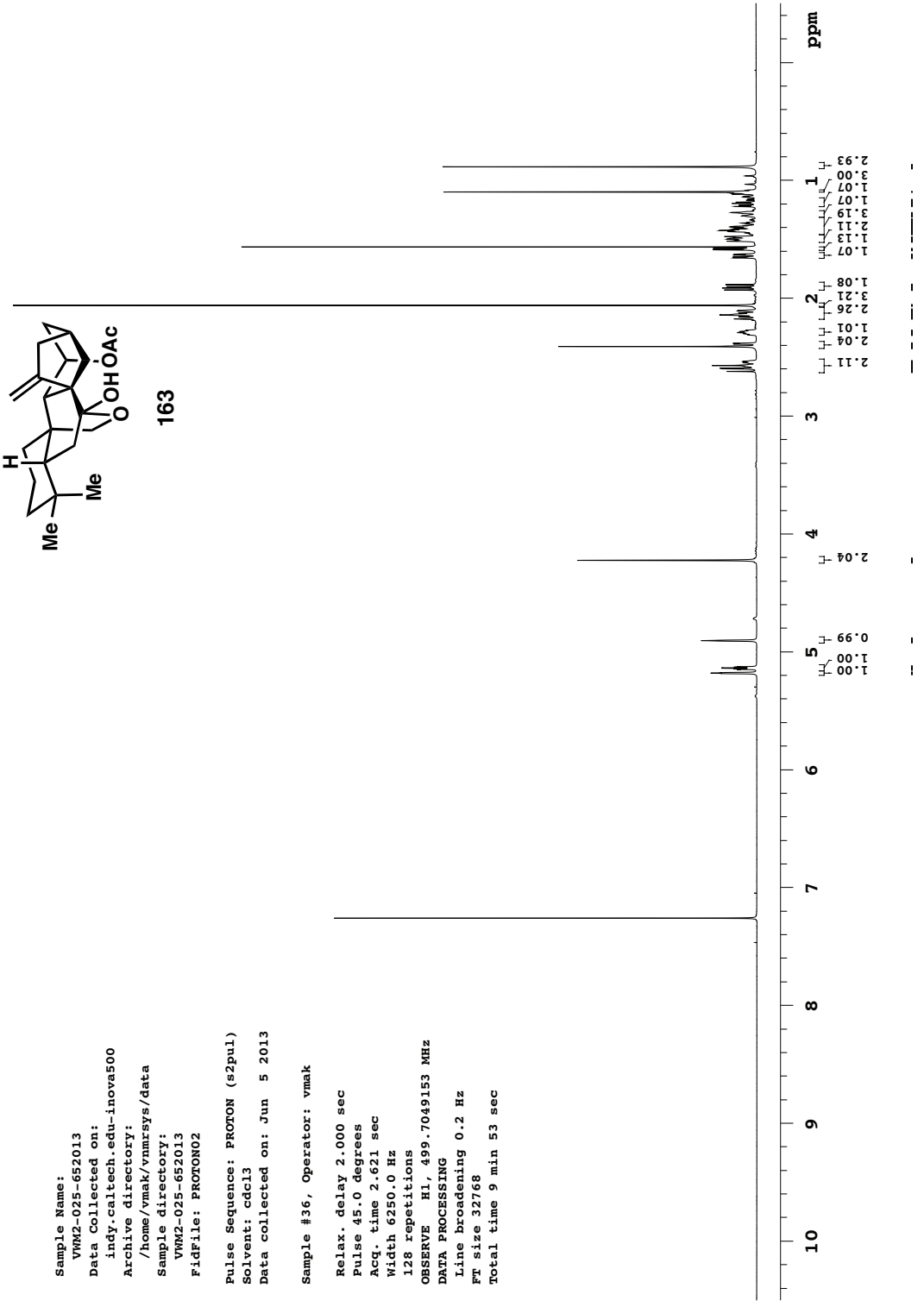

Sample Name:
VWM2-019-comb
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vnmrsys/data
Sample directory:
VWM2-019-comb
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 9 2013
Sample #22, Operator: vmak
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2250 repetitions
OBSERVE C13, 125.6509043 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 65536
Total time 58 min
160
Me
O
Me
H
H
O
O
O
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

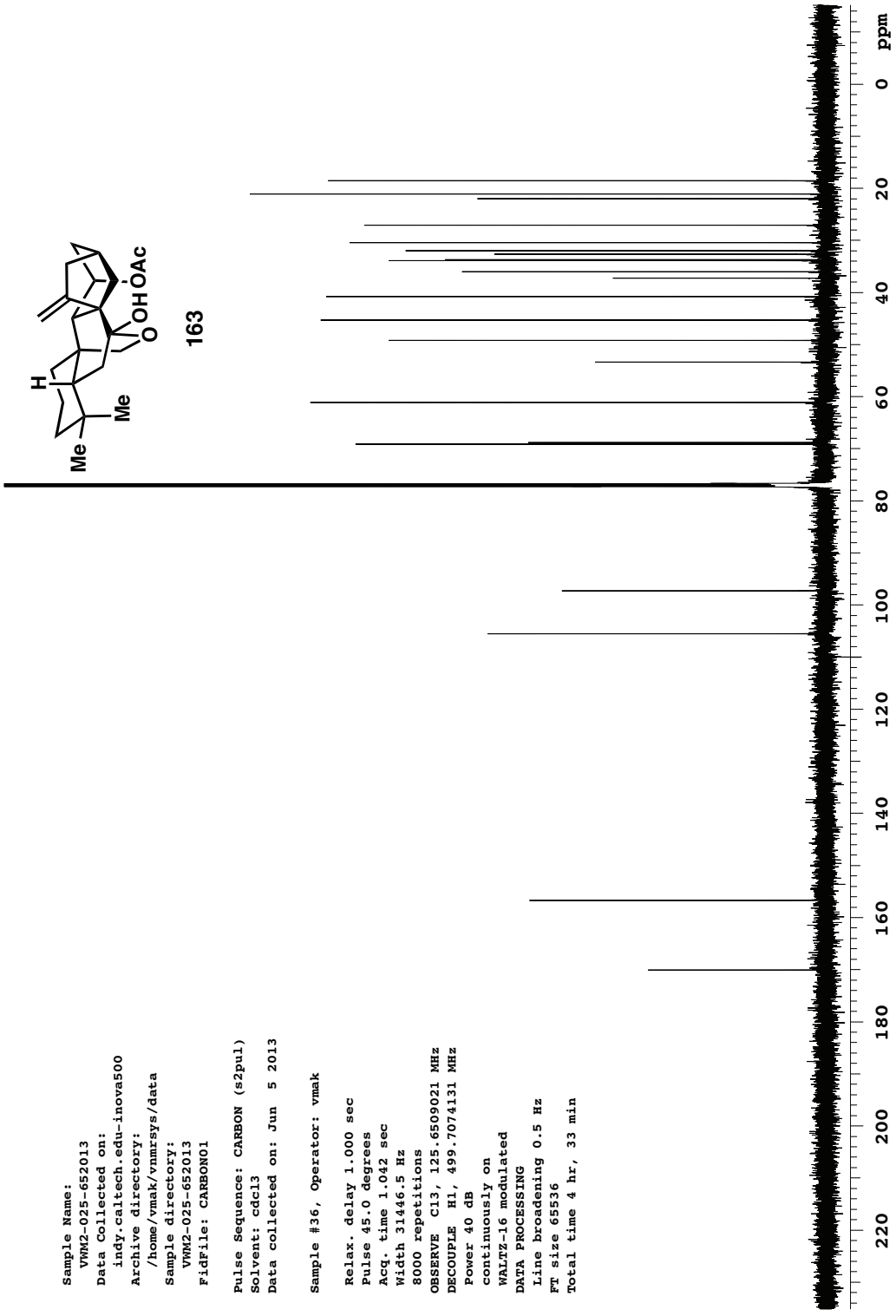

Sample Name:
VWM2-017-f14-19
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-017-f14-19
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 7 2013
Sample #35, Operator: vmak
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7049153 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 2 min 10 sec
OAc
O
O
O
H
Me H
Me
O
161
ppm
0.93
1.00
2.07
0.77
1.04
0.98
1.08
1.00
1.00
2.13
3.12
2.96
1.08
6.57
1.84
3.09
3.13

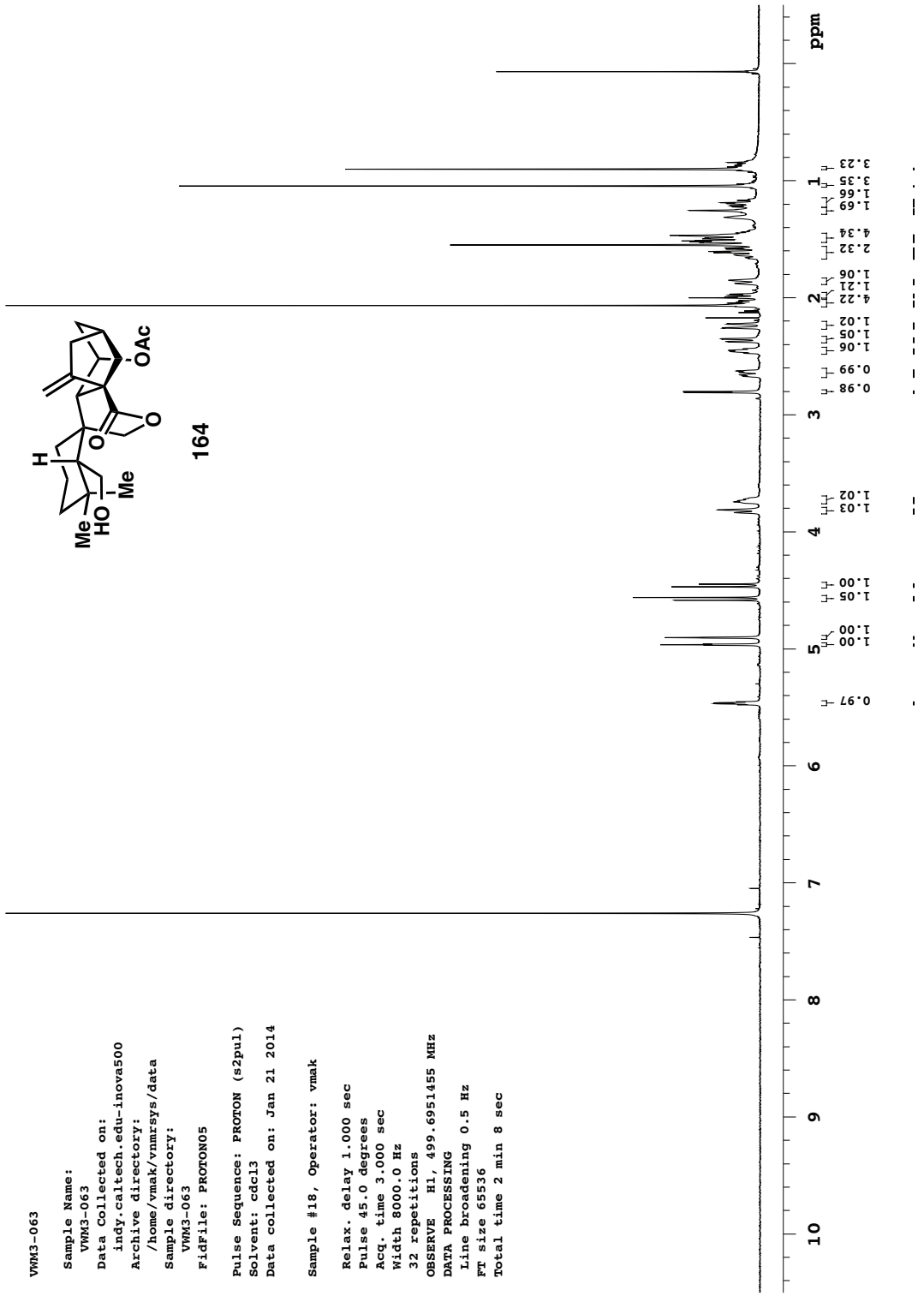

Sample Name:
VWM2-021-comb
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-021-comb
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 9 2013
Sample #21, Operator: vmak
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2250 repetitions
OBSERVE C13, 125.6509033 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 65536
Total time 58 min
OAc
Me
Me
H
H
O
O
O
O
161
220
200
180
160
140
120
100
80
60
40
20
0
ppm

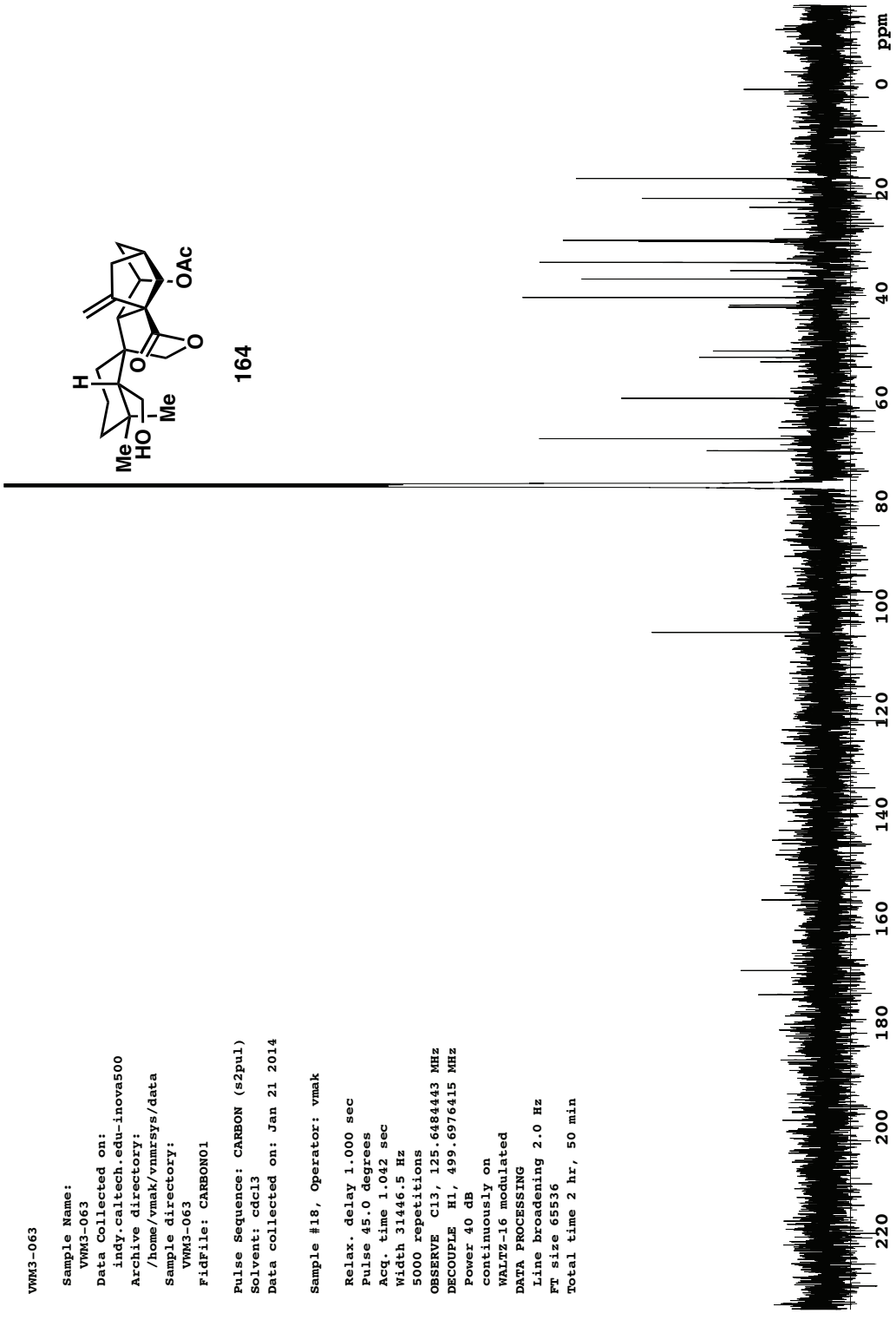

Sample Name:
VWM2-033c
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-033c
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 17 2013
Sample #33, Operator: vmak
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.621 sec
Width 6250.0 Hz
32 repetitions
OBSERVE H1, 499.7049149 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 2 min 28 sec
H
OH
Me
Me
O
OH
OAc
162
ppm
10
9
8
7
6
5
4
3
2
1
0.96
1.04
0.99
1.07
0.97
0.98
0.98
2.08
1.03
1.08
2.20
3.14
1.06
1.10
3.42
3.09
2.13
3.01
3.02

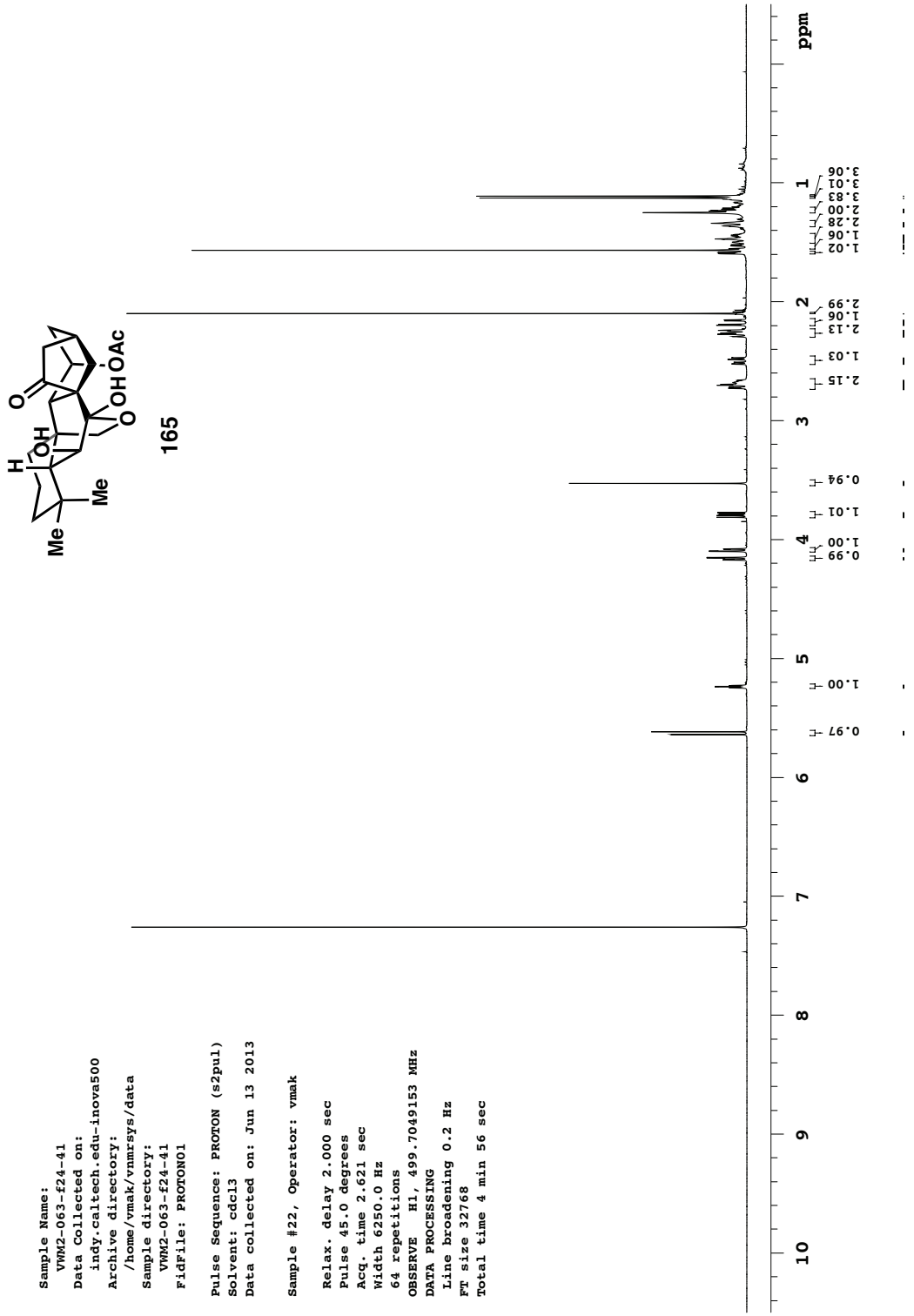

Sample Name:
VWM2-033c
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-033c
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 17 2013
Sample #33, Operator: vmak
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3000 repetitions
OBSERVE C13, 125.6509004 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 57 min
H
OH
Me
Me
O
OH
OAc
162
220
200
180
160
140
120
100
80
60
40
20
0
ppm

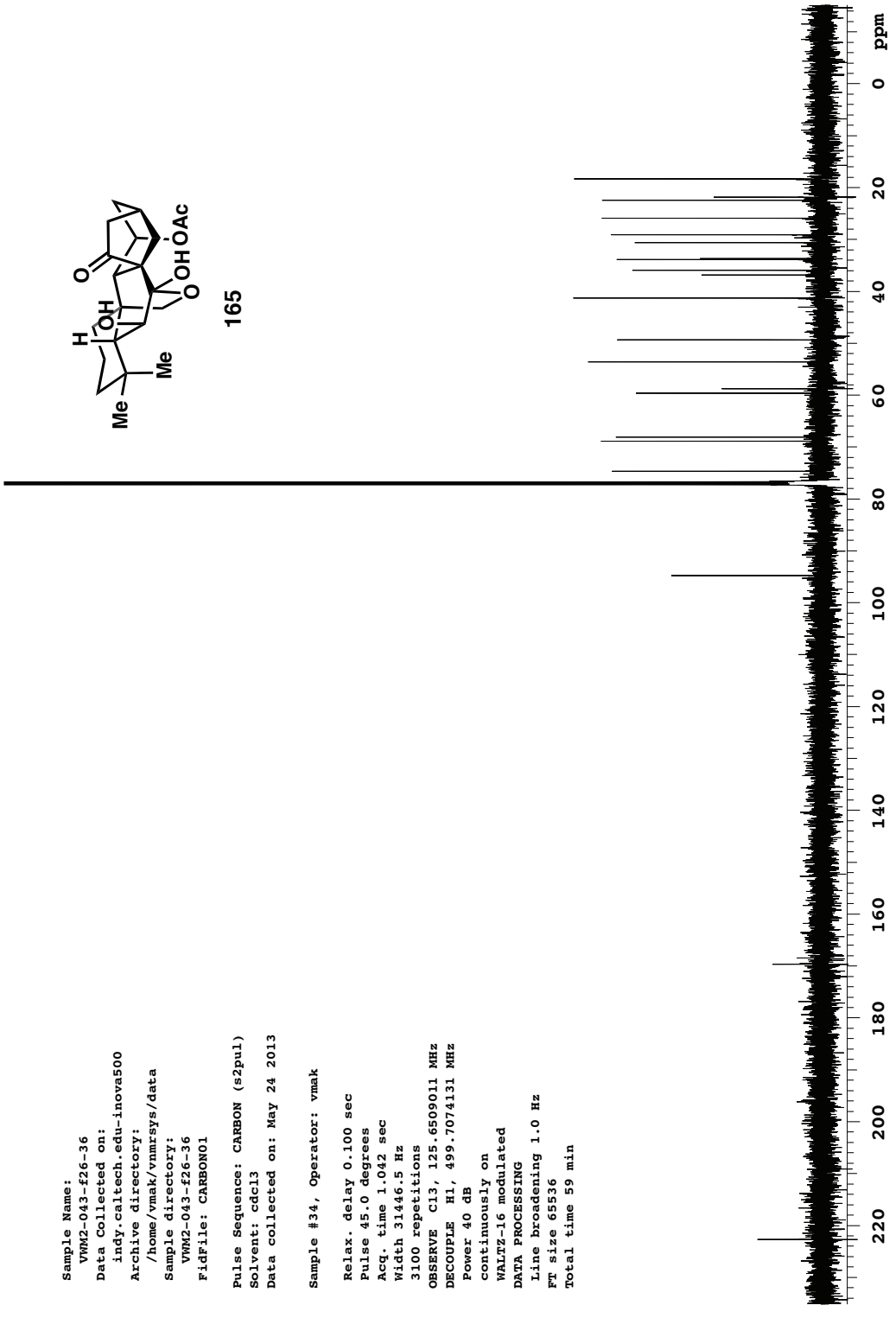

Sample Name:
VWM2-025-652013
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vnmrsys/data
Sample directory:
VWM2-025-652013
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2013
Sample #36, Operator: vmak
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.621 sec
Width 6250.0 Hz
128 repetitions
OBSERVE H1, 499.7049153 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 9 min 53 sec
Me
Me
H
OH
OAc
O
163
ppm
10
9
8
7
6
5
4
3
2
1
1.00
0.99
2.04
2.11
1.00
2.04
1.01
2.26
3.21
1.08
1.07
1.13
2.11
3.19
1.07
1.07
3.00
2.93

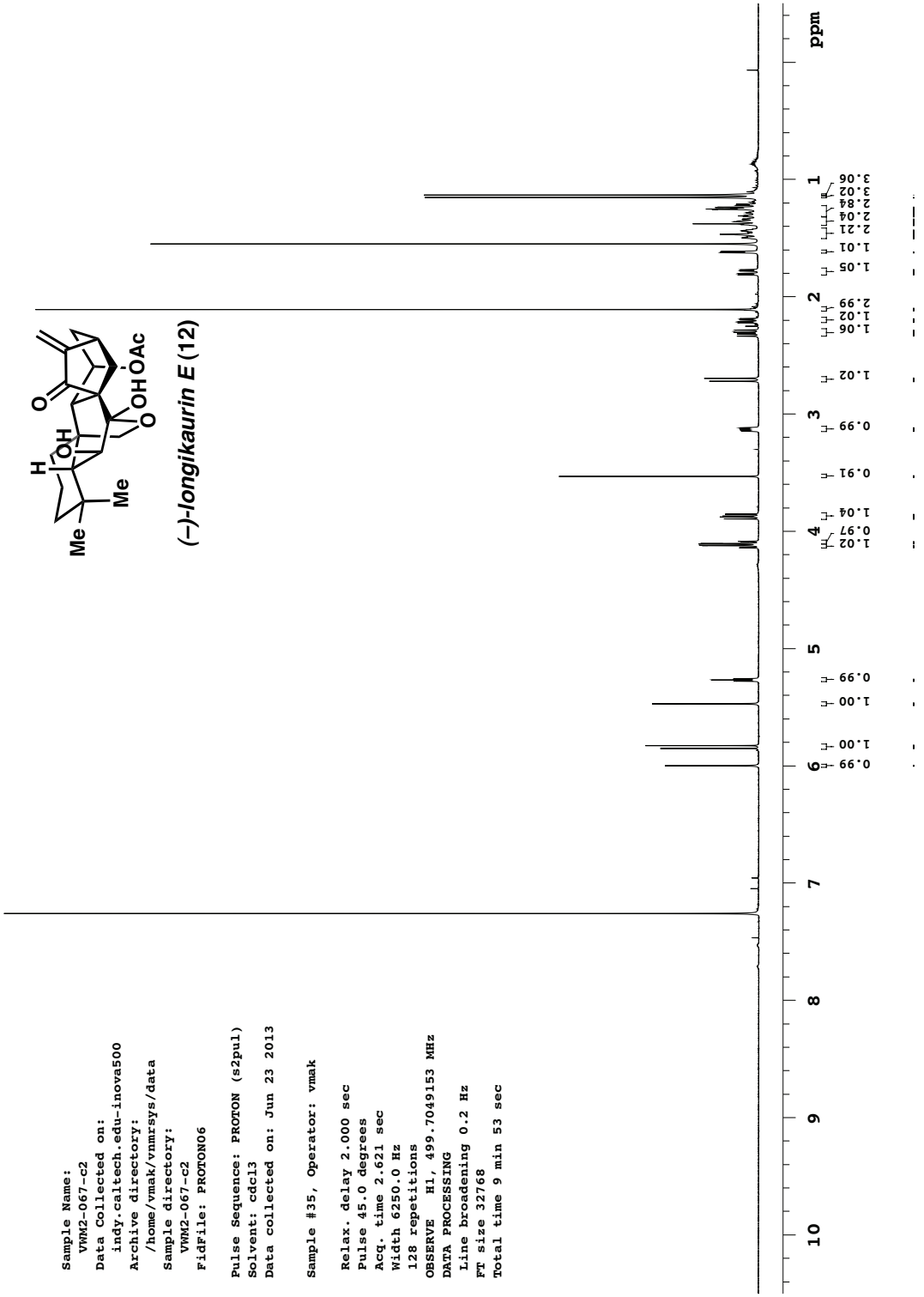

Sample Name:
VWM2-025-652013
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-025-652013
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2013
Sample #36, Operator: vmak
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
8000 repetitions
OBSERVE C13, 125.6509021 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 4 hr, 33 min
Me
Me
H
OH
OAc
163
220
200
180
160
140
120
100
80
60
40
20
0
ppm

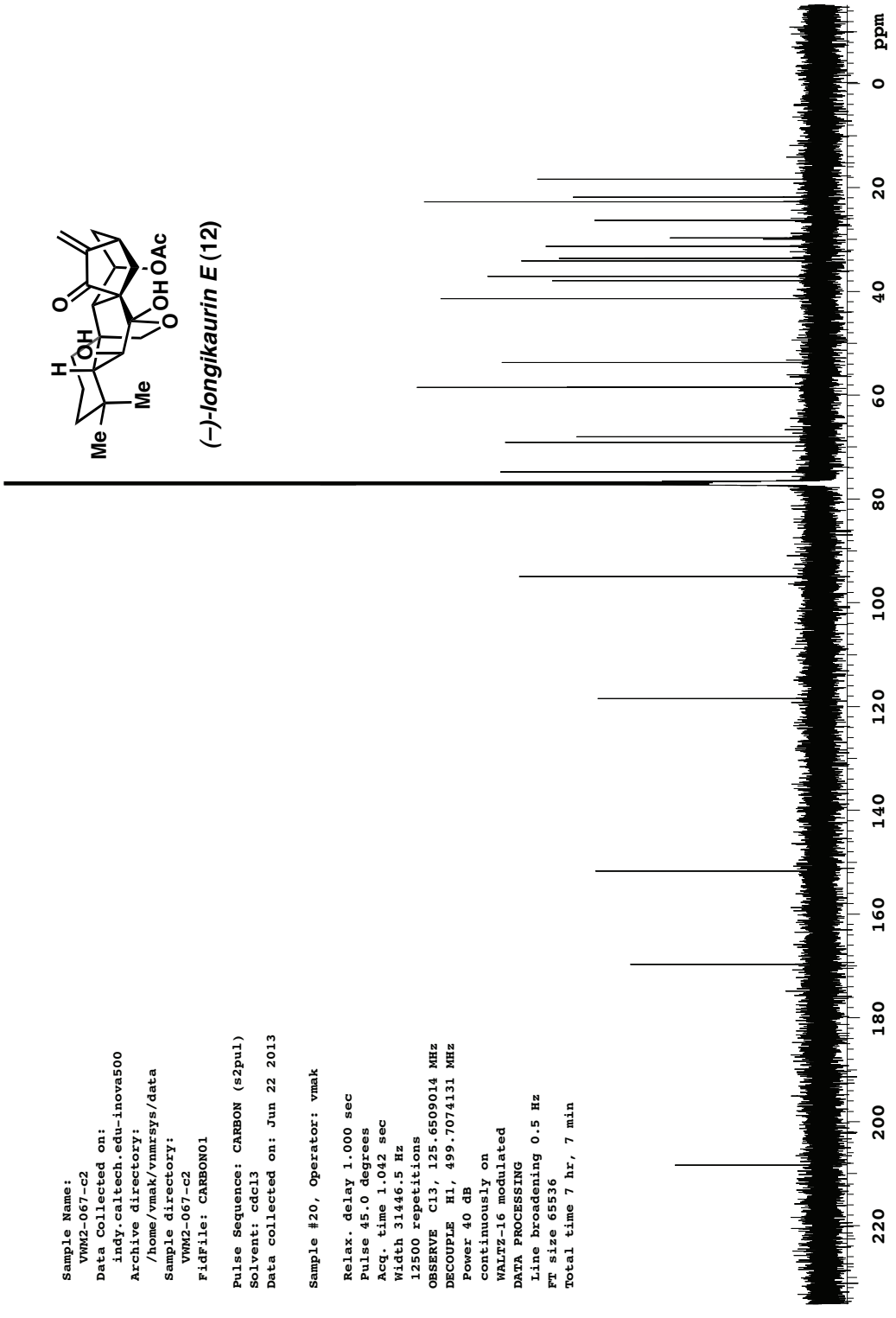

VWM3-063
Sample Name:
VWM3-063
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM3-063
FidFile: PROTON05
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2014
Sample #18, Operator: vmak
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.6951455 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 min 8 sec
Me
HO
Me
H
O
O
OAc
164
ppm
0.97
1.00
1.05
1.00
1.03
1.02
0.98
0.99
1.06
1.05
1.02
4.22
1.21
1.06
2.32
4.34
1.69
1.66
3.35
3.23


VWM3-063
Sample Name:
VWM3-063
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM3-063
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2014
Sample #18, Operator: vmak
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6484443 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 2 hr, 50 min
H
Me
HO
Me
O
O
OAc
164
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Sample Name:
VWM2-063-f24-41
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-063-f24-41
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 13 2013
Sample #22, Operator: vmak
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.621 sec
Width 6250.0 Hz
64 repetitions
OBSERVE H1, 499.7049153 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 4 min 56 sec
Me
Me
OH
H
O
OH
OAc
165
ppm
1.02
1.06
2.28
2.00
3.83
3.01
3.06
2.13
1.06
2.99
1.03
2.15
0.94
1.01
0.99
1.00
1.00
0.97


Sample Name:
VWM2-043-f26-36
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-043-f26-36
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 24 2013
Sample #34, Operator: vmak
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3100 repetitions
OBSERVE C13, 125.6509011 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 59 min
H
OH
O
OH
OAc
Me
Me
165
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Sample Name:
VWM2-067-c2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-067-c2
FidFile: PROTON06
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 23 2013
Sample #35, Operator: vmak
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.621 sec
Width 6250.0 Hz
128 repetitions
OBSERVE H1, 499.7049153 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 9 min 53 sec
(–)-longikaurin E (12)
ppm


Sample Name:
VWM2-067-c2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/vmak/vnmrsys/data
Sample directory:
VWM2-067-c2
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 22 2013
Sample #20, Operator: vmak
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
12500 repetitions
OBSERVE C13, 125.6509014 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 7 min
(–)-longikaurin E (12)
Me
Me
H
OH
O
OH
OAc
220
200
180
160
140
120
100
80
60
40
20
0
ppm

ABOUT THE AUTHOR

John Thomas Schafer Yeoman was born on Thanksgiving Day, November 27, 1986, in Iowa City, Iowa to parents Diane Schafer-Yeoman and Thomas Yeoman. John spent all of his childhood living in the small town of Monticello, Iowa, where he attended the Monticello Community Schools, took piano lessons and was active in the school's music and drama programs. He recalls interest in the sciences from an early age and a desire to understand the workings of the world around him.

Upon graduating as valedictorian of his high school class of 91 students, he attended Grinnell College in the bustling metropolis of Grinnell, Iowa. A lifelong musician and music lover, John was an active member of the student-led male a cappella group, the G-Tones, and arranged songs for a few of their performances. While taking organic chemistry classes with Prof. James Lindberg, he decided to pursue a chemistry major and conducted undergraduate research.

Following completion of his undergraduate degree in 2008, John moved to Southern California in order to fulfill his dream of appearing as a Jeopardy quiz show contestant while engaging in doctoral studies under the supervision of Prof. Sarah Reisman at the California Institute of Technology, in Pasadena. His work in her laboratory focused on the development of synthetic strategies toward bioactive terpenoids including maoecrystal Z, trichorabdal A, and longikaurin E, for which he earned a Ph.D. In the spring of 2014, John will move to Cambridge, Massachussetts, where he will join the medicinal chemistry research group at Amgen.