THE DEVELOPMENT OF A SYNTHETIC STRATEGY TOWARD DIHYDROOXEPINE-CONTAINING EPIPOLYTHIODIKETOPIPERAZINES: ENANTIOSELECTIVE TOTAL SYNTHESIS OF (–)-ACETYLARANOTIN AND RELATED INVESTIGATIONS

Thesis by

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To Megan

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ABSTRACT

To the chemist, the epipolythiodiketopiperazine (ETP) fungal metabolites represent a fascinating family of natural products, not only for their unique structural elements, but also for the unusual modes by which they are hypothesized to exert their biological activities. Though efforts at the total synthesis of these molecules have led to an evolution of innovative synthetic methodologies and strategies, challenges remain—particularly with respect to acid-sensitive and highly oxygenated ETP structures, such as those containing one or more dihydrooxepine ring. As part of a broad research program targeting ETP natural products, we have developed a synthetic strategy towards dihydrooxepine-containing ETPs.

Herein, the enantioselective total synthesis of (–)-acetylaranotin is described. This represents the first total synthesis of any dihydrooxepine-containing ETP natural product. The key steps of the synthesis include an enantioselective azomethine ylide (1,3)-dipolar cycloaddition reaction to set the absolute and relative stereochemistry, a rhodium-catalyzed cycloisomerization/chloride elimination sequence to generate the dihydrooxepine moiety, and a stereoretentive diketopiperazine sulfenylation to install the epidisulfide.

Our strategy was extended to the synthesis of a small panel of epitetrathiodiketopiperazines, including the natural products SCH64877 and emethallicin C as well as analogs, which are currently being evaluated for biological activity. Furthermore, preliminary investigations into the synthesis of dihydrooxepine-containing macrocycles have been conducted, with a particular focus on the preparation of bis(*ortho*-methoxyaryl) ethers.

Finally, as part of our efforts to further explore interesting side reactions observed during synthetic studies toward acetylaranotin, a catalytic asymmetric double (1,3)-dipolar cycloaddition reaction was developed. This reaction provides access to highly substituted, enantioenriched pyrrolidizines from inexpensive, commercially available starting materials. Furthermore, the reactivity of diketopiperazine intermediates prepared *en route* to acetylaranotin toward aerobic oxidation was briefly explored.

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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 Celcius
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 = $k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, 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

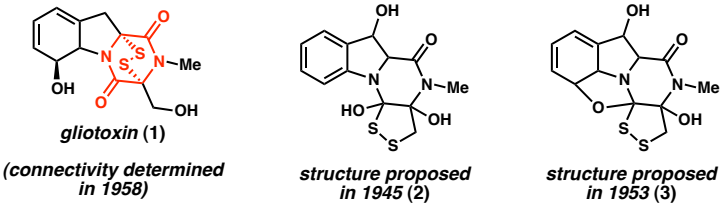
Epipolythiodiketopiperazine Natural Products

1.1 INTRODUCTION

To the chemist, the epipolythiodiketopiperazine (ETP) fungal metabolites represent a fascinating family of natural products, not only for their unique structural elements, but also for the unusual modes by which they are hypothesized to exert their biological activities.[1] Gliotoxin (**1**, see Figure 1.1) was the first of these molecules to be isolated,[2] and has been the most extensively studied: numerous manuscripts document gliotoxin's biological activities, and efforts to elucidate the details of its biosynthesis are ongoing. At the time of its isolation, the structure of gliotoxin was completely unprecedented; efforts to determine its connectivity via degradation studies and spectroscopy required collaboration between multiple research groups, and were presented over the course of thirteen separate reports.[3,4] With the subsequent discovery of a multitude of ETP subfamilies, each possessing unique structural elements peripheral to

the ETP core, the story of ETP chemistry and biology has come to beautifully exemplify the interplay between molecular structure and function.

Figure 1.1. *Gliotoxin (**1**) and previously proposed structures (**2** and **3**)*

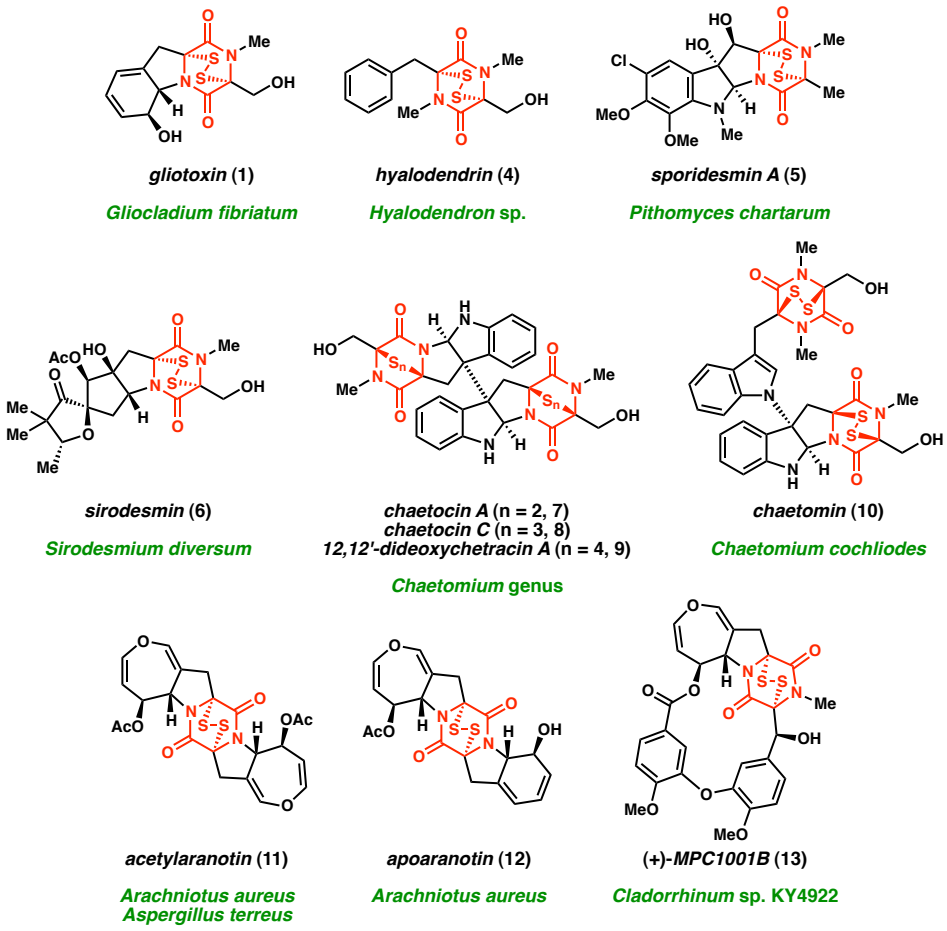


1.2 OVERVIEW OF EPIPOLYTHIODIKETOPIPERAZINE NATURAL PRODUCTS

The structural element at the core of each ETP natural product is the namesake epipolythiodiketopiperazine bicycle (Figure 1.2), comprising a diketopiperazine ring and a polysulfide linkage that bridges the two C(α)-centers. As shown in Figure 1.2, this core is found among the ETPs in combination with a variety of peripheral structures. These appendages can be as simple as the unmodified phenylalanine and serine residues of hyalodendrin (**4**)[5] to the highly oxygenated polycyclic ring system of sirodesmin (**6**).[6] As in the case of acetylaranotin (**11**),[7] some structures are C_2-symmetric about the ETP core, whereas others represent dimerization of two ETP-containing fragments adjoined at their periphery (as in **7**–**10**).[8,9] Though sub-families can roughly be designated based on structure, they are not mutually exclusive; for example, apoaranotin (**12**)[7f] possesses the cyclohexadienol monomer unit found in gliotoxin (**1**) as well as the dihydrooxepine unit found in acetylaranotin (**11**), whereas MPC1001B (**13**)[10] contains the acetylaranotin monomer unit embedded within a macrocyclic framework. Finally, the characteristic polysulfide bridge can exist as the di-, tri-, or tetrasulfide (as with **7**–**9**). Though the disulfide structures are most common, in many cases all three polysulfides are isolated

together, and the tri- and tetrasulfides are hypothesized to exert their biological activities following reduction to the disulfide (or alternatively, the dithiol) to generate the active pharmacophore.[11]

Figure 1.2. *Epipolythiodiketopiperazine natural products*



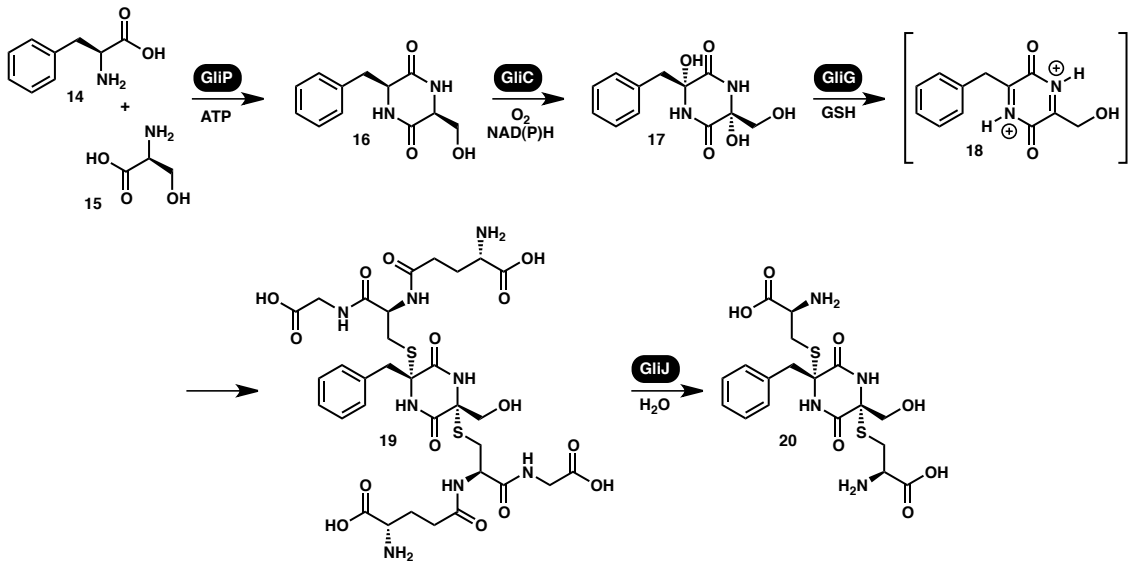
As suggested by the isolation sources listed in Figure 1.2, ETP natural products are found exclusively as secondary metabolites in fungal species. In many cases, they are hypothesized to serve as virulence and/or defense factors,[12] and generally exhibit various antimicrobial activities as well as cytotoxicity.

1.2.1 Biosynthesis

Though feeding studies have suggested that all ETP natural products derive from cyclic dipeptides,[13] and that the sulfur atoms generally derive from cysteine residues,[14] efforts to elucidate the details of biosynthetic pathway, including the associated gene clusters, have only been carried out for a few species: *Aspergillus fumigatus* (a producer of gliotoxin, **1**),[15] *Leptosphaeria maculans* (a producer of sirodesmin PL, not shown),[16] and *Aspergillus terreus* (a producer of acetylaranotin, **11**).[17] Of these investigations, the best-understood pathway to date is that for gliotoxin (**1**).

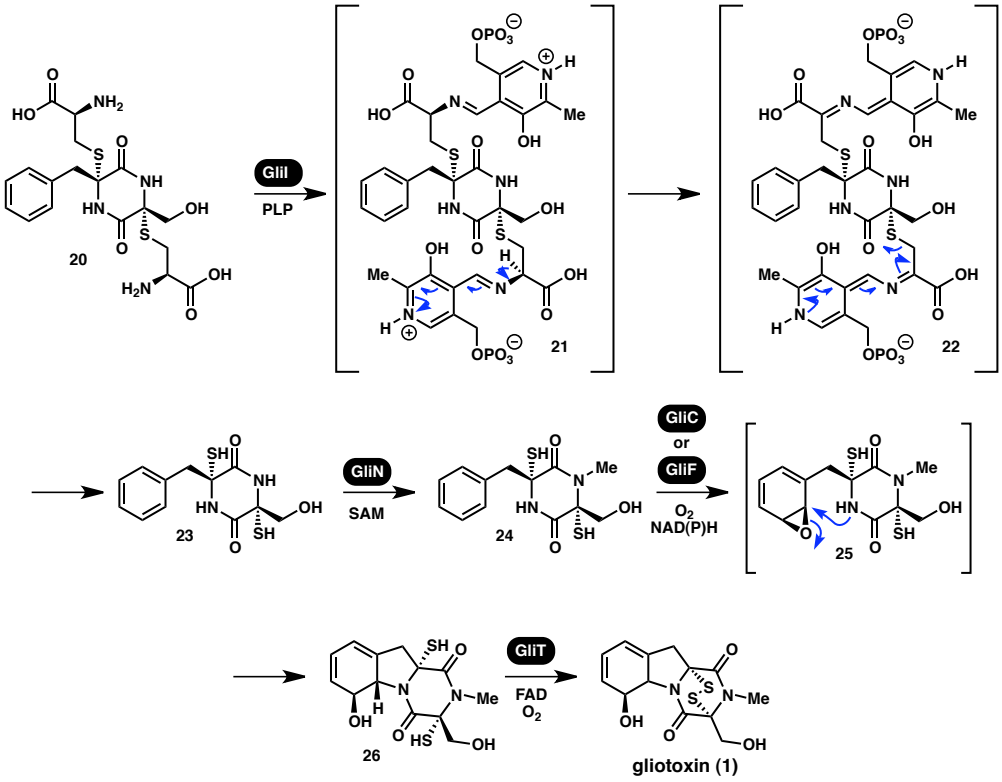
Based on a combination of feeding experiments, directed mutagenesis, and BLAST primary sequence analyses, it is proposed that gliotoxin biosynthesis begins with the synthesis of diketopiperazine **16** from phenylalanine (**14**) and serine (**15**), catalyzed by GliP, a non-ribosomal peptide synthetase (NRPS) (See Scheme 1.1).[15,18] Subsequent C–H oxidation by cytochrome P450 monooxygenase GliC then furnishes the dihydroxylated diketopiperazine **17**. The nascent hydroxyl groups are next displaced by two equivalents of glutathione (GSH), a reaction catalyzed by glutathione *S*-transferase GliG and presumed to involve the intermediacy of an iminium electrophile **18**, to afford the bis-GSH adduct **19**.[19] Hydrolytic degradation by peptidase GliJ renders the corresponding bis-Cys adduct **20**.

Scheme 1.1. *C–S bond formation during gliotoxin (**1**) biosynthesis*



C–S bond cleavage to deliver the free dithiol **23** is mediated by GliI, a homodimeric pyridoxal phosphate (PLP)-dependent carbon–sulfur lyase that is homologous to 1-aminocyclopropane-1-carboxylic acid synthases (ACCS) (Scheme 1.2).[20] Significantly, this is the first confirmed example of C–S lyase activity in the biosynthesis of a secondary metabolite. Furthermore, the absence of detectable amounts of the mono-Cys adduct during the process suggests that GliI cleaves the two C–S bonds *simultaneously*. Next, *N*-methylation is accomplished by *N*-methyltransferase GliN to afford **24**, and subsequent cytochrome P450-mediated oxidative cyclization furnishes the polycyclic cyclohexadienol ring system of the natural product, via the intermediacy of epoxide **25**.[21] Finally, the oxidase GliT promotes oxidation of the penultimate dithiol (**26**) to the disulfide, thus completing the biosynthesis of **1**.[22]

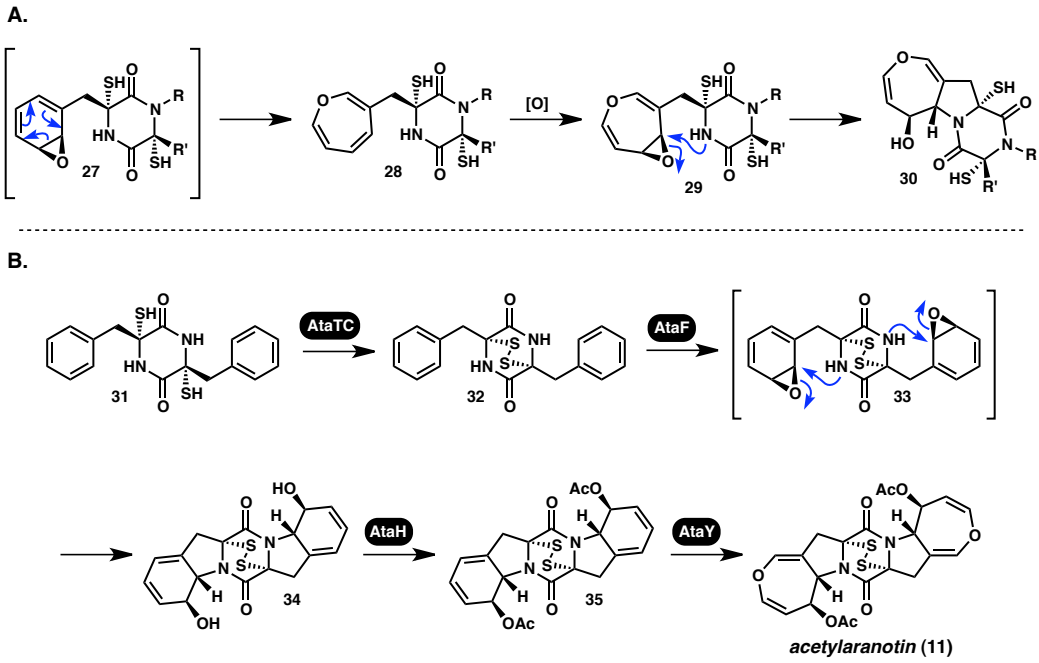
Scheme 1.2. *Completion of the biosynthesis of gliotoxin (**1**)*



Classically, the biosynthesis of acetylaranotin has been hypothesized to occur via a benzene oxide intermediate (**27**) similar to that for the biosynthesis of gliotoxin (see Scheme 1.3, part A). Whereas the diketopiperazine attacks the epoxide **25** directly to give the gliotoxin ring system, it was envisioned that epoxide **27** might instead undergo electrocyclic ring opening to afford oxepine **28**. It was proposed that subsequent oxidation to *sym*-oxepine oxide **29** followed by cyclization would furnish dihydrooxepine **30**.[7a] Recent genome-based deletion analyses reported by Wang and coworkers affirm the biogenetic relationship between gliotoxin (**1**) and acetylaranotin (**11**).[17] They propose a biosynthetic pathway similar to that outlined for **1** above (see Scheme 1.3, part B), in which cyclic dipeptide **32** undergoes cytochrome P450 AtaF-promoted oxidative cyclization to afford bis(cyclohexadienol) **34**. This intermediate is then acetylated by

acetyltransferase AtaH to furnish diacetate **35**, which undergoes sequential AtaY-mediated oxidative ring expansion to afford acetylaranotin (**11**). Feeding experiments confirmed that cyclization to provide the cyclohexadienol moiety occurs *prior* to dihydrooxepine formation, in contrast to the traditional mechanistic hypothesis.

Scheme 1.3. *Proposed biosynthetic transformations en route to acetylaranotin (**11**)*



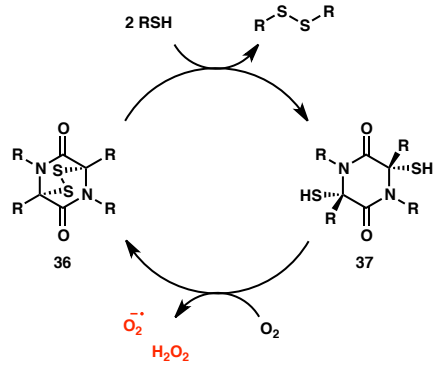
1.2.2 Biological Activity

In addition to the general antimicrobial activity mentioned above, ETPs demonstrate cytotoxicity and/or antiproliferative effects against a variety of human cancer cell lines.[10,11,23,24] Observed differences in efficacy from one agent to the next suggest a correlation between structure and specificity. Though it is generally agreed that the ETP core represents the primary pharmacophore of ETP natural products, the mechanism by which this moiety exerts its biological effects, as well as the role of peripheral structural elements, remains a topic of ongoing investigation. The two classical

hypotheses can be termed the redox cycling mechanism and the covalent modification mechanism, though recently strong evidence has been provided for a metal chelation mechanism as well.

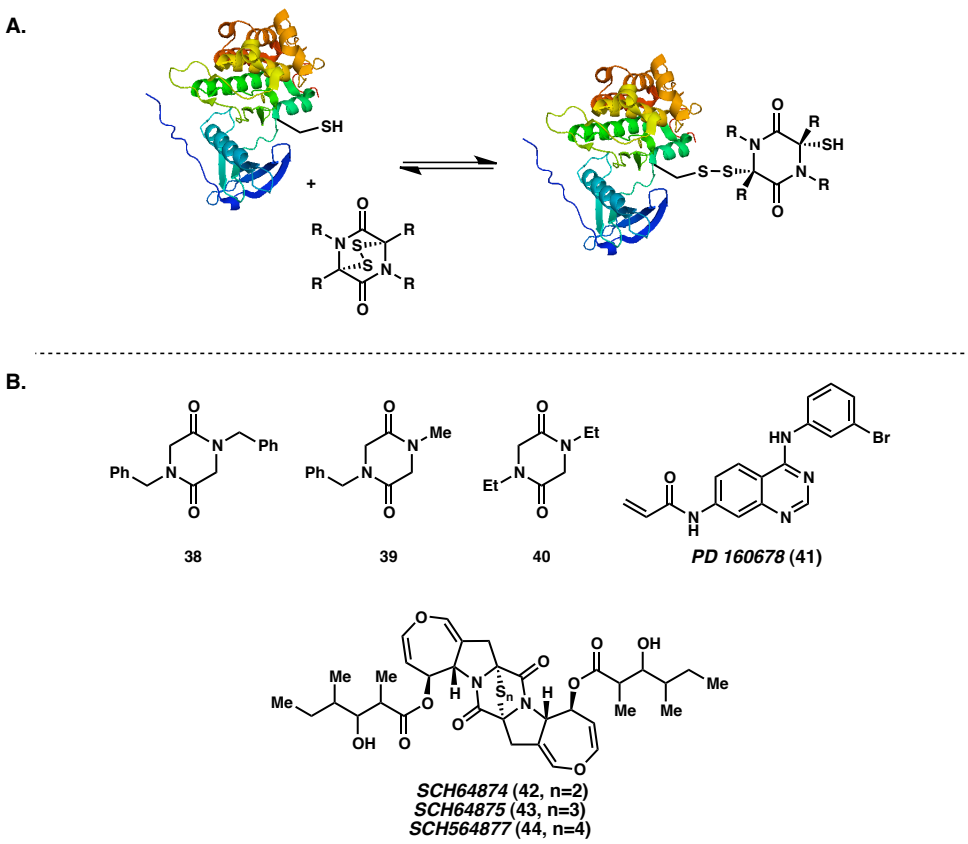
The redox cycling hypothesis states that ETP cytotoxicity is mediated by the redox activity of the highly strained disulfide moiety. Once inside the cell, the toxin (**36**) is reduced by various cellular reductants (e.g., glutathione) to the corresponding dithiol (**37**, see Figure 1.3). The increased polarity of the dithiol relative to the disulfide causes sequestration and accumulation within the cell. The dithiol's low redox potential, on the other hand, allows for reoxidation to the disulfide by molecular oxygen, resulting in the formation of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide. The resulting cycle of cellular reductant depletion and ROS generation ultimately causes cell death.[1a] It is notable that this mechanism should be minimally affected by the peripheral structure of ETP agents, aside from effects on solubility and the ability to permeate the cell membrane. In support of this mechanism is the toxicity of sporidesmin (**5**) toward erythrocytes, and that of chaetocin (**7**) toward myeloma cells, both of which have been correlated with increased cellular levels of superoxide radical.[25,26] On the other hand, the observed ability of gliotoxin (**1**) to modulate cellular calcium flux suggests that ETPs can induce oxidative stress via other, indirect pathways as well.[27]

Figure 1.3. *The redox cycling mechanism for ETP bioactivity*



Perhaps more in line with the typical mode of action for bioactive small molecules is the covalent modification hypothesis, which states that ETPs deactivate specific molecular targets by reacting with susceptible cysteine residues to form mixed disulfides (see Figure 1.4, part A). This proposal is supported by a number of *in vitro* biochemical studies; for example, gliotoxin (**1**) has been identified to form covalent adducts with alcohol dehydrogenase.[28] As a part of their investigation of the inhibition of glutaredoxin (GRx) by sporidesmin A (**5**), Mieyal and coworkers found that the synthetic ETPs **38** and **39** exhibited similar inhibitory action, whereas **40** demonstrated negligible activity (see Figure 1.4, part B).[29] Epidermal Growth Factor Receptor (EGFR), a known molecular target of fungal metabolites **42**–**44**,[30] contains an active site cysteine residue in its kinase domain that has been targeted by covalent inhibitors (such as **41**)[31] providing indirect evidence for mixed disulfide formation with the aforementioned ETPs. Though in the case of this mechanism, peripheral ETP structure would strongly influence bioactivity by contributing various secondary binding interactions between small molecule and protein target, there remains a lack of evidence for covalent adduct formation *in vivo*.

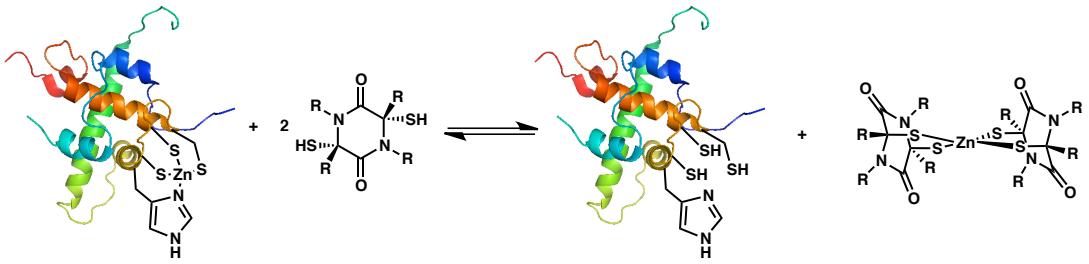
Figure 1.4. *Deactivation of molecular targets by mixed disulfide formation*



The dimeric ETPs chaetocin (**7**) and chaetomin (**10**) are known to inhibit the interaction between hypoxia inducible factor 1 (HIF-1) and the transcriptional coactivator p300, an activity with potential therapeutic potential in cancer biology.[32] In an effort to elucidate the mechanism of this inhibition and identify structure-activity relationships, Figg and coworkers investigated a small panel of ETPs, including several natural products and synthetic compounds, and found that they were all effective at blocking the binding interaction between HIF-1α and p300.[33] Using a non-denaturing ESI-MS technique, they found that in the presence of each ETP agent, structurally crucial Zn(II) ions appeared to have been removed from the HIF-1-binding domain of p300, presumably via chelation as shown in Figure 1.5. The authors have termed this the "zinc

ejection" mechanism, and although it is unclear what role peripheral ETP structure might have in determining target specificity,[34] it certainly represents a novel mode of action for small molecule inhibitors.

Figure 1.5. *Deactivation of transcriptional regulators via Zn(II) ejection*



Though evidence for each of the above mechanisms remains limited (particularly with respect to *in vivo* experiments), they represent reasonable hypotheses, and it is unlikely that they are mutually exclusive. Indeed, each ETP may exhibit some combination of these three modes of activity, and modulation of the scaffold surrounding the ETP core may ultimately allow for the tuning of this combination. As an increasing number of synthetic routes towards ETP natural products are developed, the ability to produce structural analogs and chemical probes for target pull-down will likely shed light on the mechanistic questions that remain.

1.3 PREVIOUS/CONCURRENT SYNTHETIC EFFORTS

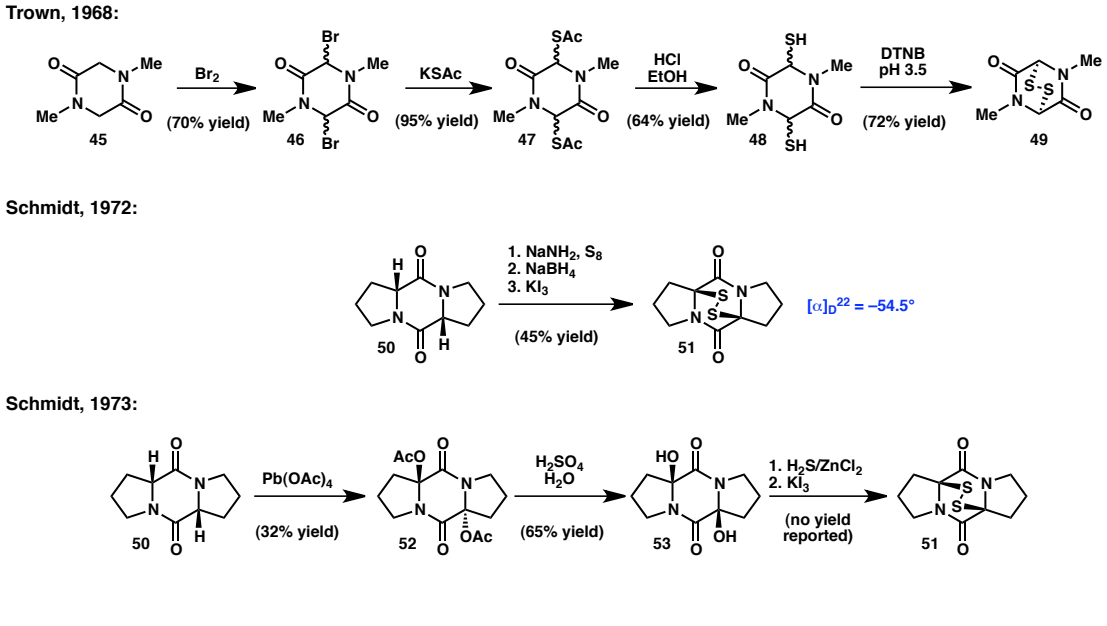
As evidenced by the abundance of degradation product literature for gliotoxin (**1**) alone, the epidithiodiketopiperazine core is quite labile. In their full account of the total synthesis of **1** and other ETP natural products, Kishi and coworkers note the particular sensitivity of the compounds to oxidative, reductive, and basic conditions.[35] Additionally, many ETPs contain *acid*-sensitive functionality. These challenges have inspired the

evolution of a variety of strategies for the protection of thiols, selective late-stage oxidation, and direct enolate sulfenylation.

1.3.1 Early Strategies for Installing the ETP Core

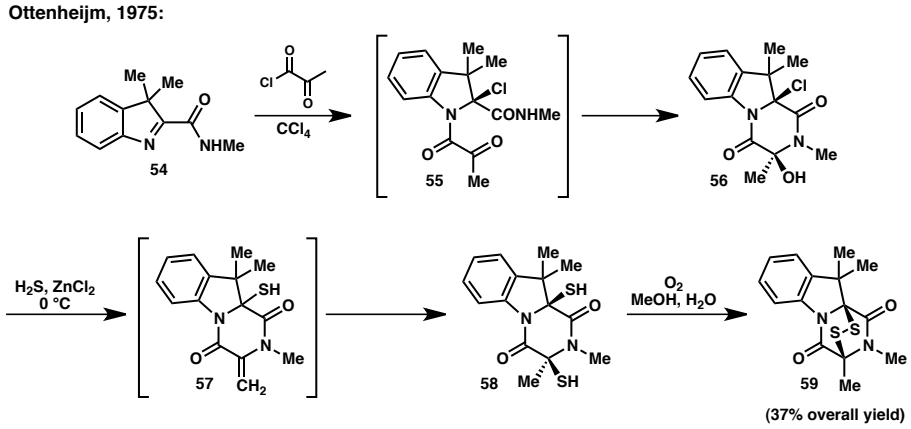
In 1968, Trown reported the first synthetic procedure for constructing the ETP core (see Scheme 1.4).[36] The sequence involved bromination of sarcosine dimer **45** with molecular bromine, followed by bromide displacement with thioacetate anion and subsequent acidic hydrolysis to afford dithiol **48**. Final oxidation with Ellman's reagent (5,5'-dithiobis(2-nitrobenzoic acid), DTNB) revealed the simple ETP bicycle **49**. Several years later, Schmidt and coworkers disclosed a strategy involving direct enolate sulfenylation; they found that they could readily sulfenylate proline dimer **50** with S_8 in the presence of $NaNH_2$, with sequential reductive and oxidative workups affording ETP **51**.[37] Notably, this process exhibits some degree of stereoretention, as **51** was shown to be optically active. The same authors later reported a procedure for converting **50** to *trans*-diacetate **52** by oxidation with $Pb(OAc)_4$.[38] This product was hydrolyzed to afford dihydroxydiketopiperazine **53**, which could be converted to ETP **51** by direct displacement by H_2S under Lewis acidic conditions, followed by oxidation with KI_3. These basic strategies continue to be used for the construction of ETPs, though their application to the synthesis of complex structures has been greatly facilitated by the development of more selective oxidants as well as robust protecting group strategies.

Scheme 1.4. *"Classical" procedures for ETP synthesis*



In 1975, Ottenheijm and coworkers reported the development of a rapid, redox manipulation-free sequence for the synthesis of ETP **59** (see Scheme 1.5).[39] Imino amide **54** was first condensed with an equivalent of pyruvoyl chloride to yield α-chloro-α'-hydroxydiketopiperazine **56**. Displacement by H_2S in the presence of $ZnCl_2$ and subsequent aerobic oxidation furnished the final ETP product (**59**).

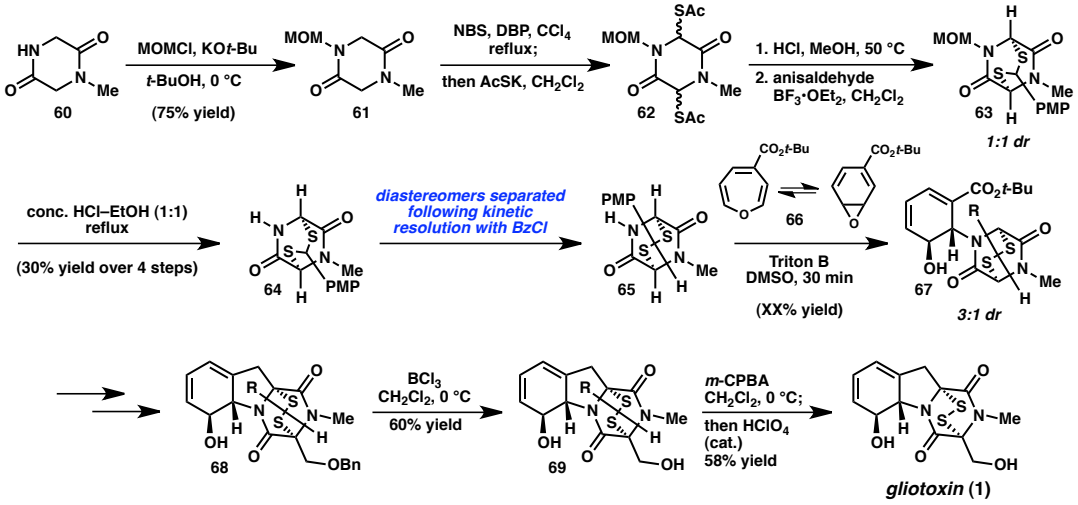
Scheme 1.5. *A "redox neutral" synthesis of ETP **59***



1.3.2 The Thioacetal Protecting Group Strategy

In order to gain synthetic access to more complex ETP structures, Kishi and coworkers developed a thioacetal protecting group strategy that allowed them to install the required C–S bonds at an early stage of a synthetic route, but reserve completion of the ETP disulfide linkage for the end of the sequence.[35,40] In their synthesis of gliotoxin (see Scheme 1.6), MOM-protected diketopiperazine **61** was advanced to *p*-anisaldehyde-derived thioacetal **64** in four steps and 30% overall yield. Following separation of diastereomers, nucleophilic addition of fragment **65** into oxepine electrophile **66** provided cyclohexadienol adduct **67** as a 3:1 mixture of diastereomers. This material was advanced to tetracycle **69**, at which point oxidation with *m*-CPBA and subsequent acidic workup revealed the ETP core of **1**.

Scheme 1.6. *Total synthesis of gliotoxin (**1**)*

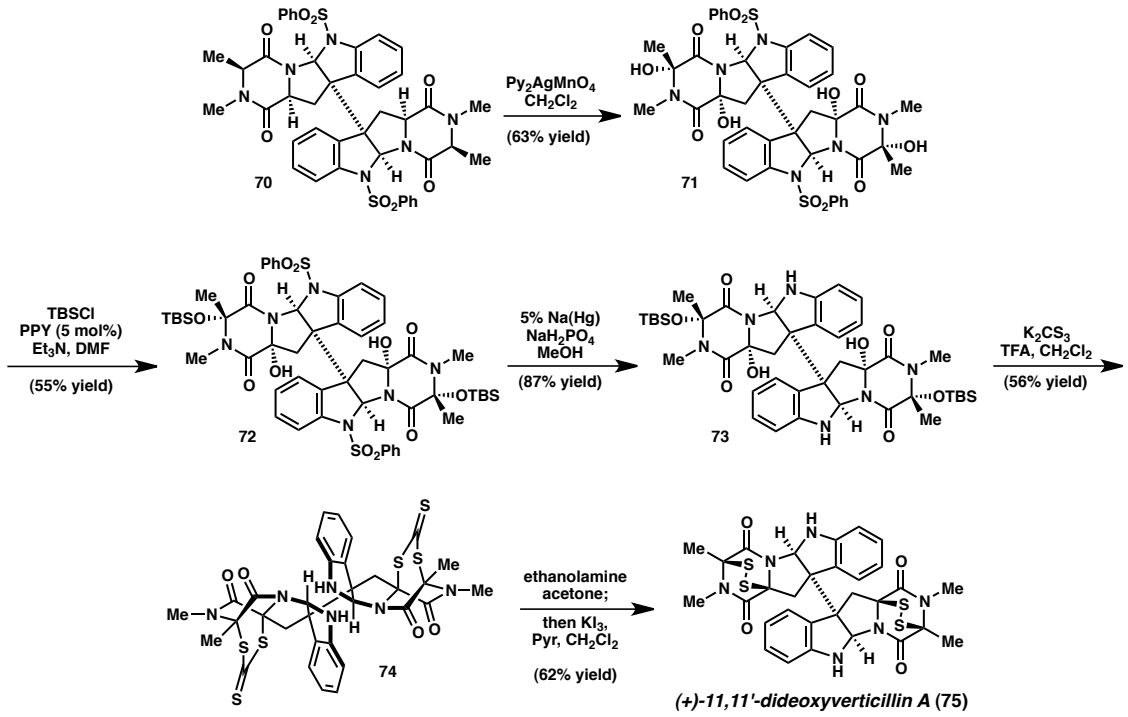


1.3.3 Recent Advances: Late Stage Oxidation/Displacement

For nearly three decades, Kishi's thioacetal protecting group strategy represented the state-of-the-art in complex ETP synthesis. Then, in 2009, Movassaghi and coworkers

reported the total synthesis of (+)-11,11'-dideoxyverticillin A (**75**).[41] This seminal effort involved the mild, stereoretentive, and late-stage oxidation of bis-diketopiperazine **70** by $[Ag(pyr)_2][MnO_4]$ to afford tetraol **71**. Following protecting group manipulation (it was noted that the free tetraol was unstable to a variety of acidic and basic conditions), nucleophilic displacement by trithiocarbonate under acidic conditions furnished bis-trithiocarbonate **74**. The natural product (**75**) was then obtained by ethanolaminolysis of the trithiocarbonate rings and KI_3-mediated oxidation of the resulting dithiol.

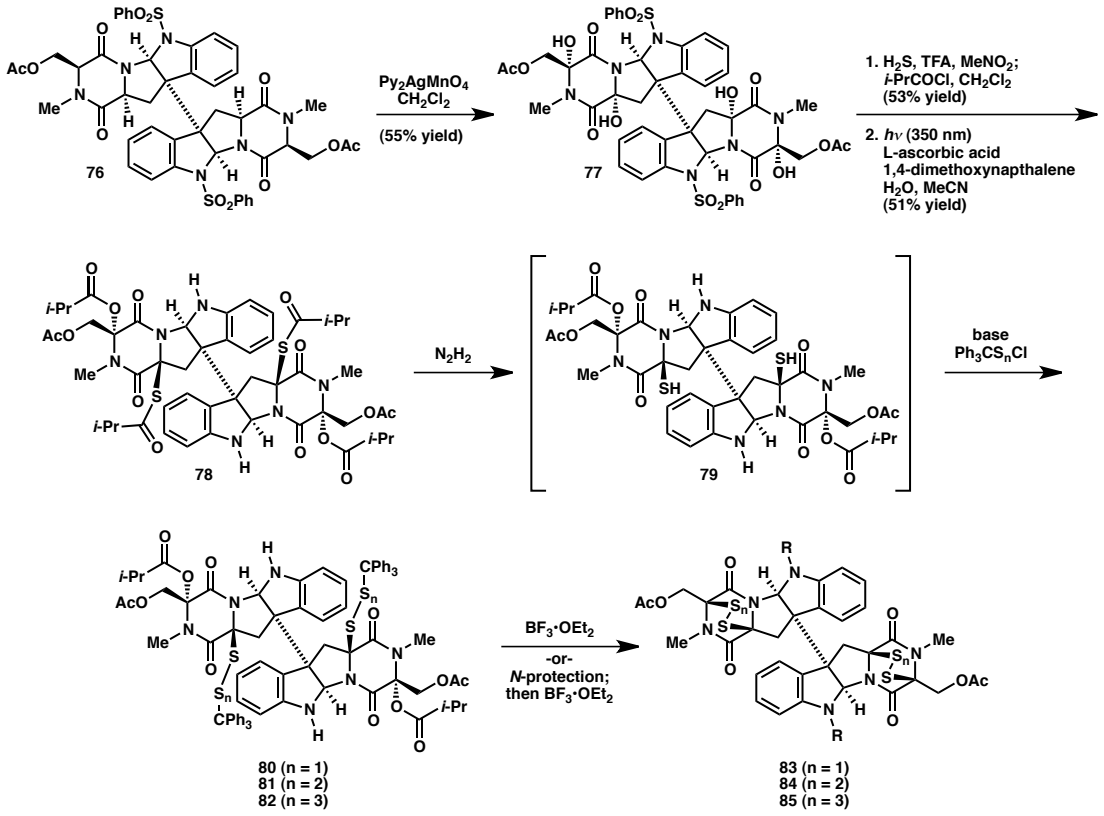
Scheme 1.7. *Total synthesis of (+)-11,11′-dideoxyverticillin A (**75**)*



In a follow-up communication, Movassaghi and Kim reported that a modification to the strategy used for the synthesis of **75** allowed for the selective preparation of related molecules as the di-, tri-, or tetrasulfide congener (see Scheme 1.8).[42] Using the conditions developed during their previous efforts, bis(diketopiperazine) **76** was oxidized to tetraol **77**. However, treatment of **77** with H_2S and TFA in $MeNO_2$ promoted thiol

installation via S_N1-type displacement at only the C(11) and C(11') positions, and subsequent exhaustive acylation afforded tetra-*iso*-butyryl intermediate **78**. Treatment with hydrazine selectively liberated the thiol groups to give intermediate **79**, which could be trapped with Ph_3CSCl, Ph_3CSSCl, or $Ph_3CSSSCl$ to afford protected disulfide **80**, trisulfide **81**, or tetrasulfide **82**, respectively. Subjection of these intermediates to BF_3•OEt_2 (following *N*-protection in the cases of **81** and **82**) resulted in cyclization of the polysulfide with concomitant loss of trityl cation to reveal the epidisulfide **83**, epitrisulfide **84**, or epitetrasulfide **85**, respectively.

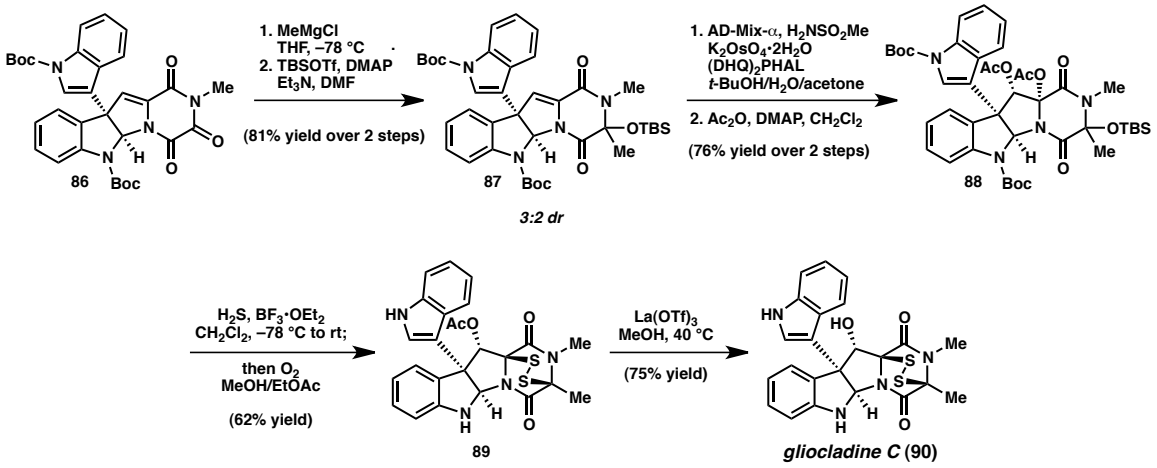
Scheme 1.8. *Selective access to epidi-, epitri-, and epitetrathiodiketopiperazines*



In 2011, Overman and coworkers reported a late-stage oxidation strategy for the synthesis of pyrroloindoline ETP natural products containing oxygenation at the C(12) position (see Scheme 1.9).[43] Reaction of triketopiperazine **86** with MeMgCl followed by

protection with TBSOTf afforded α,β-unsaturated diketopiperazine **87** as a 3:2 mixture of diastereomers. Dihydroxylation using AD-Mix-α resulted in the formation of the corresponding diol (>14:1 diastereoselectivity), which was subsequently converted to diacetate **88**. Displacement of the C(11)-hydroxyl and C(15)-siloxyl groups by H_2S was carried out in the presence of BF_3•OEt_2, and subsequent aerobic oxidation to the disulfide and deprotection of the C(12) acetate revealed gliocladine C (**90**). In a follow-up report, the authors demonstrated that this strategy could be generally applied to the total synthesis of similar ETP natural products.[23]

Scheme 1.9. *Total synthesis of gliocladine C (**90**)*



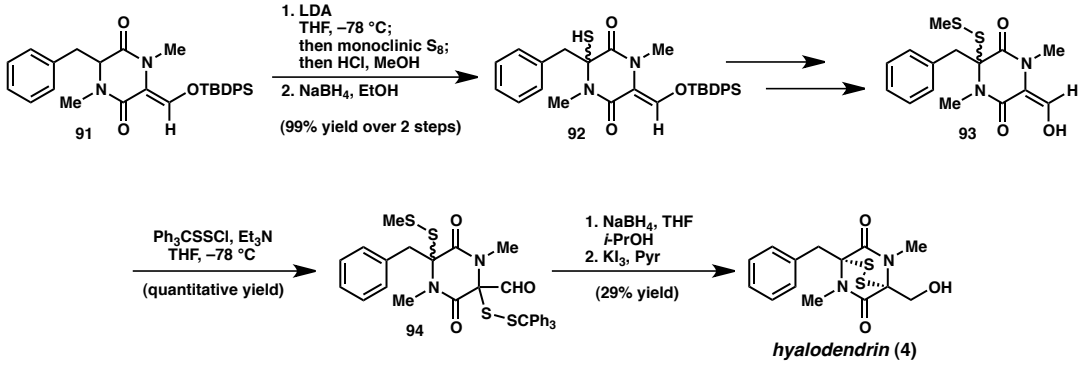
1.3.4 Recent Advances: Direct Diketopiperazine Sulfenylation

With the exception of the conditions reported by Schmidt and coworkers for the direct sulfenylation of proline dimer **50** under basic conditions, all of the examples of ETP syntheses reviewed above have involved the use of moderately to strongly acidic conditions for the displacement of various leaving groups by sulfur-containing nucleophiles. However, many natural products possess acid-labile functional groups in addition to a base- and redox-labile ETP core. Accordingly, the further development of

direct enolate sulfenylation methodologies has greatly facilitated total synthesis efforts targeting these structures.

Though the peripheral appendages of hyalodendrin (**4**) do not appear to be particularly acid-sensitive, the preparation of this natural product reported by Williams and Rastetter in 1980 constitutes one of the first examples of an enolate sulfenylation strategy in the context of natural product total synthesis (see Scheme 1.10).[44] In the first sulfenylation reaction, the lithium enolate of diketopiperazine **91** was trapped by *monoclinic* S_8 (the authors point out that the use of this form of sulfur—obtained by briefly heating the more stable orthorhombic form under vacuum—is critical to the success of the reaction), generating thiol **92**. The second sulfenylation event involved soft enolization of the more acidic α-formyl diketopiperazine **93** and subsequent trapping with Ph_3CSSCl to afford bis(disulfide) **94**. Reductive deprotection of the two disulfides followed by KI_3-mediated oxidation completed the synthesis of **4**.

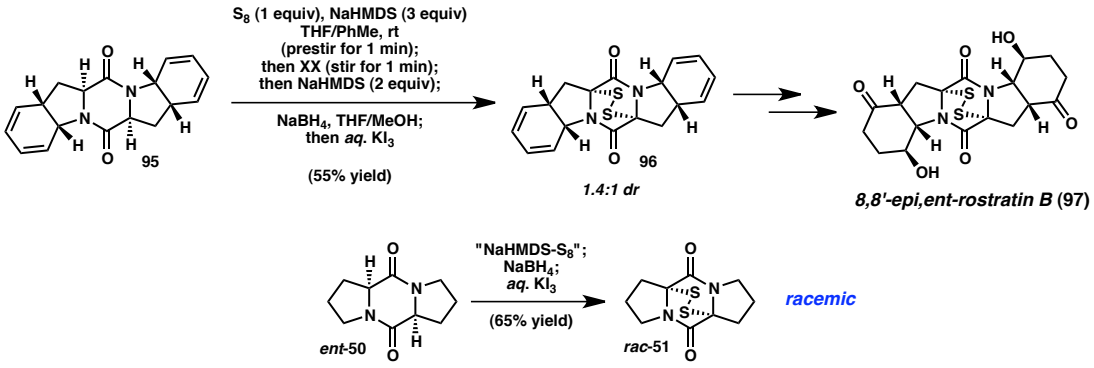
Scheme 1.10. *Enolate sulfenylation in the total synthesis of hyalodendrin (**4**)*



More recently, Nicolaou and coworkers have developed a modification to the conditions for direct enolate sulfenylation reported by Schmidt and coworkers that is better suited for complex substrates (see Scheme 1.11).[45] In their initial communication of the total synthesis of epicoccin G (not shown) and 8,8'-*epi*,*ent*-rostratin B (**97**),[45a] the

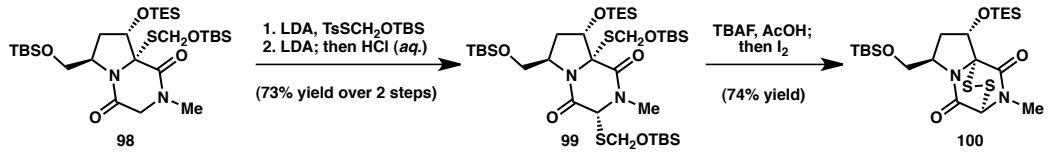
authors describe having treated diketopiperazine **95** with a reagent mixture obtained by pre-stirring one equivalent of S_8 with three equivalents of NaHMDS in THF, followed by another two equivalents of NaHMDS. The resulting crude mixture of polysulfides was then reduced to the dithiol using $NaBH_4$, and workup with *aqueous* KI_3 furnished the disulfide **96** in 55% yield as a 1.4:1 mixture of epidisulfide diastereomers. This intermediate was then advanced to **97**. In contrast with the stereoretention observed by Schmidt and coworkers, a follow-up report by Nicolaou and coworkers revealed that sulfenylation of proline dimer ***ent*-50** under the "NaHMDS-S_8" conditions results in formation of *racemic* ETP **51**.[45b]

Scheme 1.11. *Direct sulfenylation of diketopiperazines with S_8/NaHMDS*



Finally, Clive and coworkers recently reported that $TsSCH_2OTBS$ can be used to sulfenylate diketopiperazine-derived enolates to afford the *protected* thiol product.[46] As shown in Scheme 1.12, the resulting siloxymethyl thioether (e.g., **99**) can be cleaved by buffered TBAF solution, with oxidative workup providing the ETP core (e.g., **100**). Though use of this reagent has yet to be reported in the context of a total synthesis, it may prove to be quite useful for sequences in which late stage sulfenylation is desirable, but subsequent conversion to the ETP must be delayed for the duration of multiple reactions.

Scheme 1.12. *Introducing protected thiols via sulfenylation with $TsSCH_2OTBS$*



1.4 CONCLUSIONS

ETP natural products have a rich history, yet continue to stimulate the chemist. The hypothesized modes of biological activity underscore Nature's abilities to evolve diverse mechanisms for the manipulation of biological systems, and will likely inspire the development of novel therapeutic strategies. Likewise, the complex structures and biosynthetic transformations described above demonstrate that the bar set by Nature for the synthetic chemist remains high. Though efforts at the total synthesis of these molecules have led to an evolution of innovative synthetic methodologies and strategies, challenges remain—particularly with respect to acid-sensitive and highly oxygenated ETP structures. Ultimately, comprehension of the molecular processes underlying ETP bioactivity requires that these challenges be addressed.

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Chapter 2

Development of a Synthetic Strategy Towards Dihydrooxepine-Containing Epipolythiodiketopiperazine Natural Products: Enantioselective Total Synthesis of (–)-Acetylaranotin[†]

2.1 INTRODUCTION

The dihydrooxepine-containing epidithiodiketopiperazine natural product acetylaranotin (**11**) was isolated in 1968 from the two fungal species *Arachniotus aureus* and *Aspergillus terreus* (see Figure 2.1).[1] As a C_2-symmetric homodimer it is also the most simple of the dihydrooxepine-containing ETPs to be isolated in the past 45 years. Similar C_2-symmetric structures include the epitetrasulfide emethallicin C (**101**),[2] which possesses the same carbocyclic core as **11** but is adorned by (*R*)-mandelate appendages, as well as the epidisulfide SCH64874 (**42**), epitrisulfide SCH64875 (**43**), and epitetrasulfide SCH64877 (**44**),[3] which instead possess 2,4-dimethyl-3-hydroxyhexanoate appendages. Other natural products that contain the same dihydrooxepine monomer

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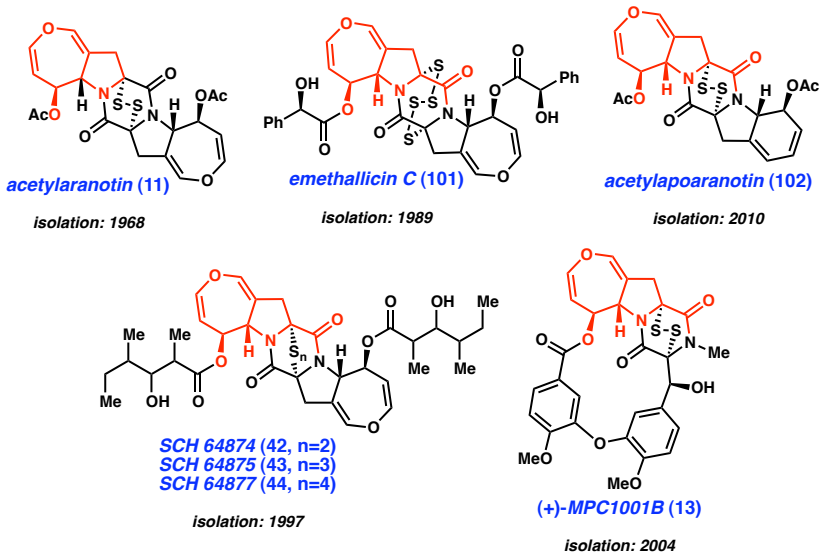
subunit include the heterodimer acetylapoaranotin (**102**)[1f, 4] and the macrocycle MPC1001B (**13**).[5]

Figure 2.1. *Dihydrooxepine-containing ETP natural products*



In the 40 years from the initial isolation of **11** until the initiation of our research program, there were no reports of any successful efforts at the total synthesis of any of the structures shown in Figure 2.1—despite several reported approaches[6]—indicating the challenge that this ETP sub-family poses to modern synthetic techniques. For this reason, as part of a broad research program targeting ETP natural products, we initially selected to pursue a synthetic strategy towards dihydrooxepine-containing ETPs.

2.1.1 Biological Activity

Though dihydrooxepine-containing ETP natural products have been found to possess a variety of therapeutically relevant biological properties, from antiviral properties to selective cytotoxicity (see Table 2.1),[2,3,4,5, 7] there have been no comprehensive studies comparing a panel of such agents against the same cellular or molecular targets. Considering that biochemical assays have suggested viral RNA

polymerases and epidermal growth factor receptor (EGFR) as molecular targets for acetylaranotin (**11**) and the SCH series (**42**–**44**), respectively, such experiments would be invaluable in the ongoing efforts to elucidate ETP mechanisms of action. For example, by comparing the effects of peripheral structure in cell viability assays to those in biochemical assays, one might gain insight into the role of these structures in the modulation of physical properties (e.g., solubility, membrane permeability) versus modulation of target-binding affinities. With this in mind, a secondary goal of our research program has been to produce such a panel of dihydrooxepine-containing agents for comprehensive biological screening.

Table 2.1. *Activities of dihydrooxepine ETPs against various cell lines and molecular targets*

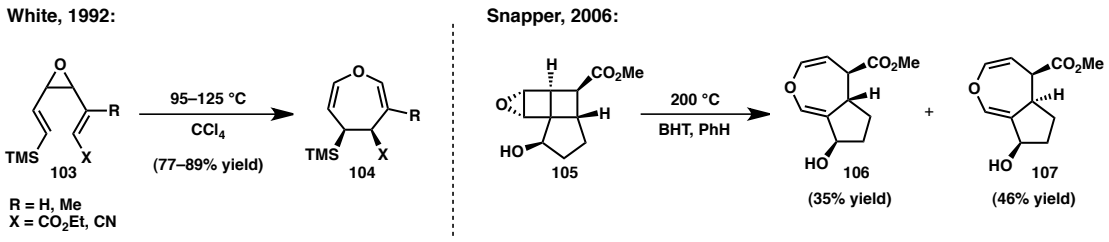
	IC_{50} (μM)	Cellular/Molecular Target
acetylaranotin (**11**)	0.20	RNA polymerase (Coxsackie A-21)
acetylaranotin (**11**)	23	A549 (human alveolar adenocarcinoma)
acetylapoaranotin (**102**)	2	"
acetylaranotin (**11**)	21.2	HCT116 (human colon cancer)
acetylapoaranotin (**102**)	13.8	"
SCH64874 (**42**)	1.4	EGFR Kinase
SCH64877 (**44**)	1.6	"
MPC1001B (**13**)	0.039	DU 145 (human prostate cancer)
emethallicin C (**101**)	1.0	Induced histamine release from mast cells

2.1.2 Previous Synthetic Approaches

The dihydrooxepine-containing ETP natural products have remained particularly challenging as the targets of modern synthetic endeavors due to their chemical lability as well as the relative dearth of methods for rapid construction of the dihydrooxepine ring itself. Indeed, at the outset of our investigations, there existed only two reported *general* methods for the synthesis of dihydrooxepine rings.

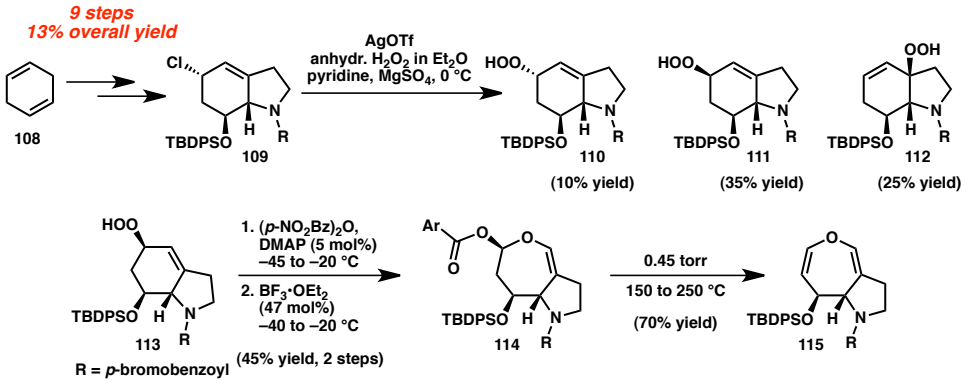
In 1992, White and coworkers reported the thermal [3,3]-sigmatropic rearrangement of divinyl epoxides **103** to give dihydrooxepines **104**.[8] More recently, Snapper and coworkers reported the thermal rearrangement of highly strained polycyclic epoxides such as **105** to give dihydrooxepines such as **106** and **107**.[9] Unfortunately, it is not apparent how either of the required precursor structures could be incorporated into a readily accessible intermediate in the context of a total synthesis of a dihydrooxepine-containing ETP.

Scheme 2.1. *General methods for constructing dihydrooxepine rings*



Because the dihydrooxepine ring is found almost exclusively in ETP natural products, most of the remaining efforts towards their synthesis have been in the context of total synthesis endeavors. Kishi and coworkers reported the synthesis of **115**, a model for the aranotin ring system (Scheme 2.2).[6e] Key to their approach was the use of the Criegee rearrangement to convert allylic hydroperoxide **113** to vinyl ether **114**,[6d] with subsequent thermal carboxylate elimination to furnish the dihydrooxepine ring. Once more, however, the authors find that the required intermediate **113** can be accessed only in low yield as a racemate, and extension of this strategy to a total synthesis does not appear to have been pursued.

Scheme 2.2. *Synthesis of model dihydrooxepine* ***115***



In reports of progress toward the macrocyclic structure of MPC1001, Clive and coworkers found that they could construct the dihydrooxepine ring of model ring system **117** by acid-promoted vinylogous lactonization of intermediate **116**, followed by selenoxide elimination to furnish the desired unsaturation.[6b,c] However, preparation of intermediate **116** requires a 26-step synthetic sequence, and advancement to the natural product using this strategy has yet to be reported.

Scheme 2.3. *Construction of dihydrooxepine model system* ***117***

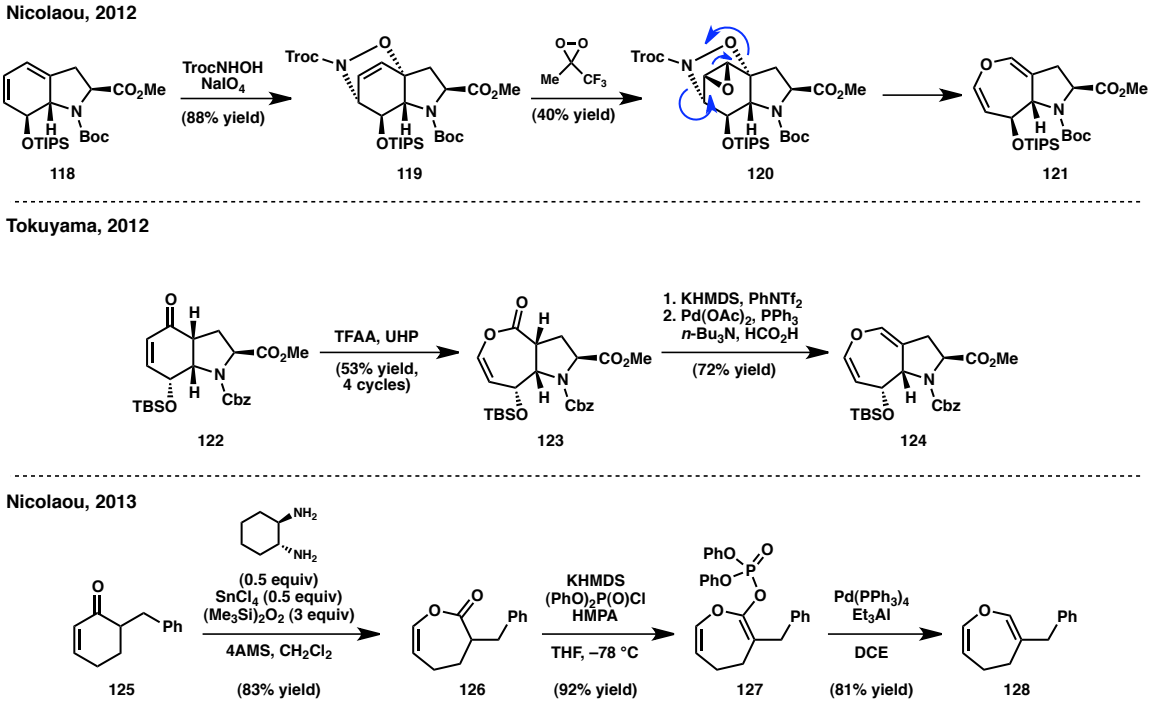
With these reports in mind, we sought to pursue a novel synthetic method for constructing the dihydrooxepine ring that would simultaneously allow for rapid access to required precursors.

2.1.3 Concurrent Synthetic Approaches

Since our initial communication of the research described in this chapter, several investigations pertaining to the synthesis of dihydrooxepine-containing ETPs have been

published. In their detailed account of the synthesis and biological evaluation of various perhydroindolone-containing ETP natural products, Nicolaou and coworkers reported the conversion of a gliotoxin-type monomer (**118**) to the acetylaranotin-type monomer (**121**) via a [4+2]/oxidation/retro [4+2] sequence as shown in Scheme 2.4.[10] Tokuyama and coworkers reported the second total synthesis of acetylaranotin (**11**) in late 2012, using a Baeyer-Villiger oxidation/vinyl triflate reduction strategy to construct the dihydrooxepine ring (**124**).[11] Shortly thereafter, Nicolaou and coworkers published an optimized general method for the synthesis of dihydrooxepines starting from cyclohexenones (e.g. **125**) via a Baeyer-Villiger/vinyl phosphate reduction sequence.[12] Such developments greatly complement the work described in this chapter, and will likely provide access to an increased diversity of structural analogs to assist in biological studies.

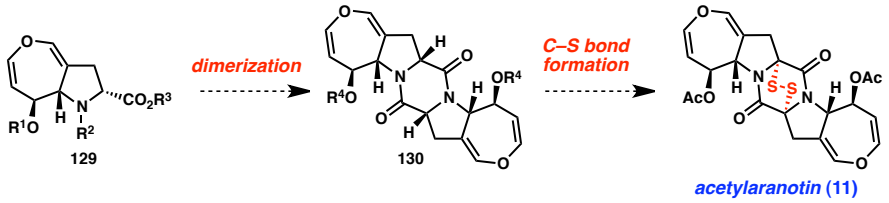
Scheme 2.4. *Recently disclosed reports pertaining to the synthesis of dihydrooxepine-containing ETPs*



2.1.4 Retrosynthetic Analysis

Our initial consideration during the planning of our synthetic approach towards dihydrooxepine-containing ETP natural products was one of target selection. We chose to initially pursue a total synthesis of the natural product acetylaranotin (**11**), with the expectation that a successful strategy for synthesis of the corresponding monomer fragment (see Figure 2.1) would ultimately allow us to target other members of the sub-family. In the present case, dimerization of such a monomer unit (**129**) would provide diketopiperazine **130** (see Scheme 2.5). We anticipated that C–S bond formation prior to dimerization might lead to opening of the pyrrolidine ring or otherwise complicate the coupling of monomer units. Accordingly, installation of the C–S bonds of the ETP was to be reserved for the final stages of the synthesis.

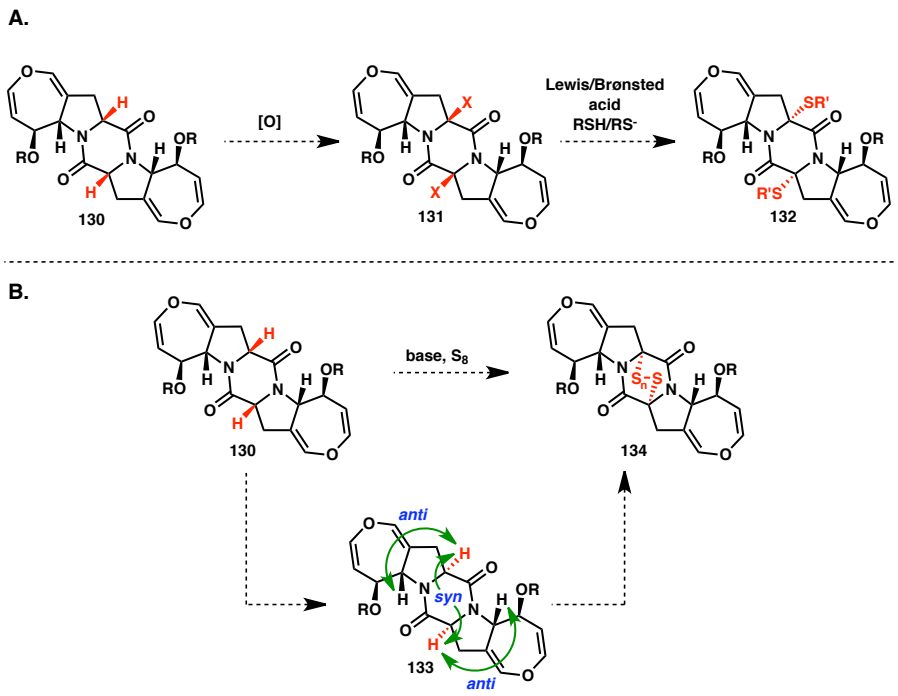
Scheme 2.5. *Endgame strategy for the synthesis of acetylaranotin (**11**)*



In considering how best to accomplish late stage C–S bond formation, a major concern was the potential instability of the dihydrooxepine ring. Embedded within this structure is a divinyl ether moiety, as well as a vinylogous acetal, both of which were expected to be sensitive to acidic as well as oxidative reaction conditions. We therefore reasoned that it would be challenging to carry out a sequence involving late stage oxidation of diketopiperazine **130** followed by displacement with sulfur-containing nucleophiles under acidic conditions (Scheme 2.6, part A), and realized that direct sulfenylation of diketopiperazine **130** under basic conditions was likely a more practical

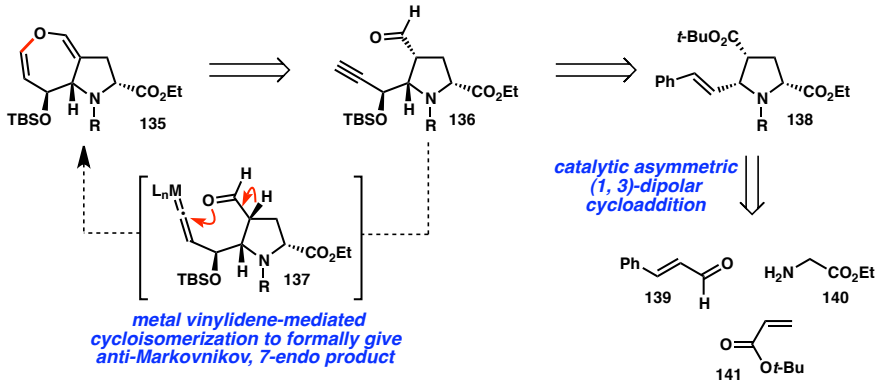
approach (Scheme 2.6, part B). It was unclear *a priori* what influence, if any, the stereochemistry of diketopiperazine **130** would have on the facial selectivity of this process. Romo and coworkers have demonstrated that for cyclo(Pro,Pro) electrophilic trapping of the kinetically generated monoenolate proceeds with retention of stereochemistry.[13] Thus, we were cognizant that it might be necessary to epimerize diketopiperazine **130** from the *syn*,*syn*,*syn* configuration to the *anti*,*syn*,*anti* diketopiperazine (**133**) prior to sulfenylation.

Scheme 2.6. *Possible strategies for C–S bond formation*



Turning our attention to construction of the acetylaranotin monomer unit **129**, we envisioned forming the C(11)–O bond (Scheme 2.7) via transition-metal catalyzed cycloisomerization of alkynyl aldehyde **136**. In turn, we anticipated that the densely functionalized pyrrolidine scaffold of this intermediate could be rapidly accessed via a (1,3)-dipolar cycloaddition between an acrylate (**141**) and a glycinate-derived imine.

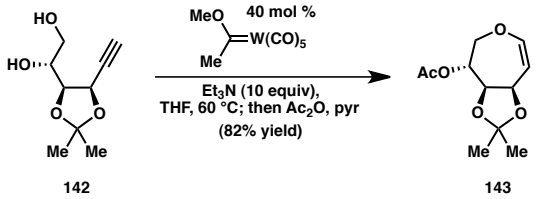
Scheme 2.7. *Retrosynthetic analysis for dihydrooxepine-containing monomer unit* ***135***



The anti-Markovnikov 7-*endo* cyclization of an aldehyde onto a terminal alkyne, as described above, is relatively unprecedented. Transition metal complexes that favor reactions of alkynes via π-activation would likely result in the undesired Markovnikov 6-*exo* cyclization. On the other hand, transition metal catalysts that promote reactions of alkynes via metal vinylidene intermediates, in which the carbon terminus is electrophilic in character,[14] were expected to provide the desired dihydrooxepine, the formal product of 7-*endo* cyclization.

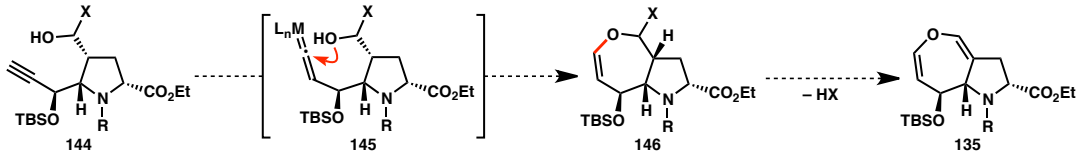
The anti-Markovnikov cyclization of primary alcohols onto terminal alkynes via metal vinylidene intermediates *is* well precedented. Complexes of transition metals belonging to groups 6 (Cr, Mo, W),[15] 8 (Ru, Os),[16] and 9 (Rh, Ir)[17] are commonly used for the catalytic synthesis of cyclic vinyl ethers (an example of 7-*endo* cyclization of an alkynyl alcohol is shown in Figure 2.8)[15d] as well as other vinylidene-mediated transformations, and we were optimistic at the outset of our investigation that the properties of such catalysts could be tuned to accomplish similar reactions with alkynyl aldehydes.

Scheme 2.8. *Tungsten-catalyzed 7-endo cycloisomerization of an alkynyl alcohol*



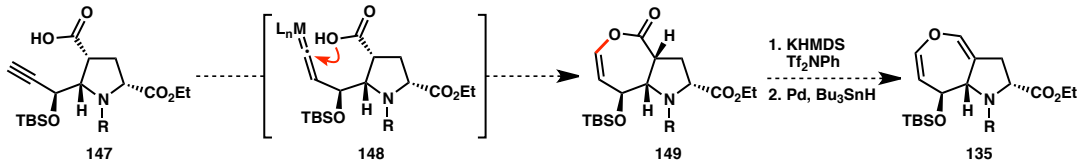
Additionally, aldehyde **136** would provide rapid access to several alternative cyclization substrates. For example, various aldehyde 1,2-adducts (**144**) could be formed via addition of HX, which could potentially demonstrate reactivity similar to alkynyl alcohols (see Scheme 2.9).[18] Subsequent elimination of HX would then furnish the desired dihydrooxepine ring (**135**).

Scheme 2.9. *Cyclization of alkynyl aldehyde 1,2-adducts followed by elimination to afford the dihydrooxepine ring*

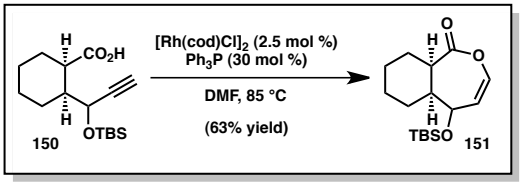


On the other hand, oxidation of the aldehyde would provide the corresponding carboxylic acid substrate (**147**, see Scheme 2.10). Such alkynyl acids have been shown to undergo cycloisomerization to give the 7-*endo* adducts, presumably via metal vinylidene intermediates.[17b,19] Conceivably, subsequent conversion of the resulting enol lactone **149** to the vinyl triflate or analogous vinyl halide surrogate would allow for palladium-mediated reduction to furnish dihydrooxepine **135**. Indeed, preliminary studies using model alkynyl carboxylic acid **150** revealed the anti-Markovnikov 7-*endo* cyclization could readily be accomplished using Rh(I) catalysis.[20]

Scheme 2.10. *Cyclization of alkynyl carboxylic acids followed by vinyl triflate reduction to afford the dihydrooxepine ring*



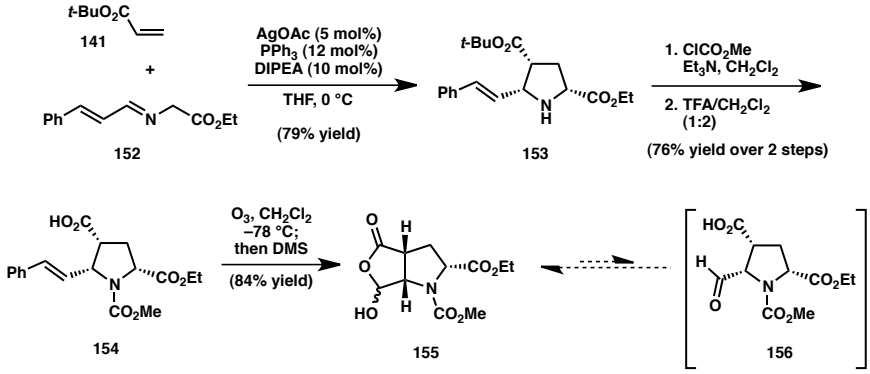
Scheme 2.11. *Rh(I)-catalyzed cycloisomerization of a model alkynyl acid (**150**)*



2.2 FORWARD SYNTHETIC EFFORTS

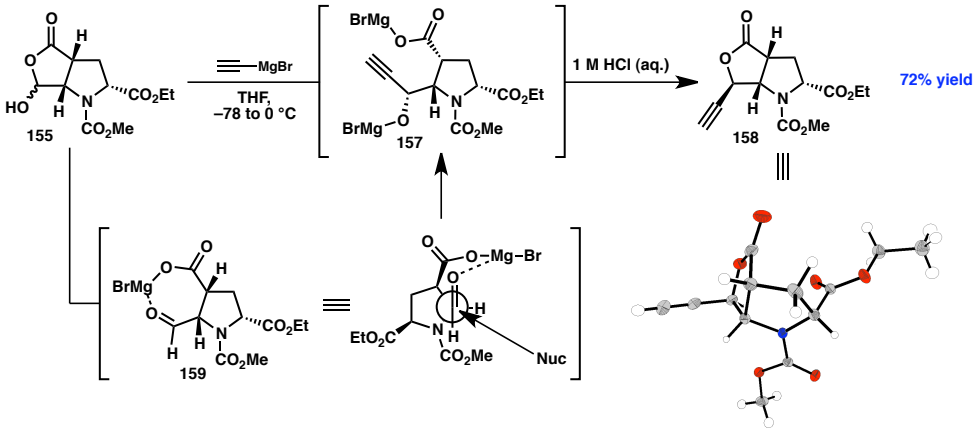
In the forward sense, our first objective was the construction of functionalized pyrrolidine scaffold **138**. To this end, racemic styrenyl pyrrolidine **153** was synthesized using a silver-catalyzed (1,3)-dipolar cycloaddition between α-imino glycinate ester **152** and *tert*-butyl acrylate (**141**, see Scheme 2.12).[21] Protection of the amine as a methyl carbamate and subsequent cleavage of the *tert*-butyl ester under acidic conditions afforded carboxylic acid **154**. Finally, ozonolytic cleavage of the styrene moiety resulted in formation of hydroxylactone **155**, which was envisioned to serve as a masked aldehyde substrate for acetylide addition, providing access to a variety of potential cycloisomerization substrates.

Scheme 2.12. *Construction of the functionalized pyrrolidine scaffold and synthesis of masked aldehyde substrate* ***155***



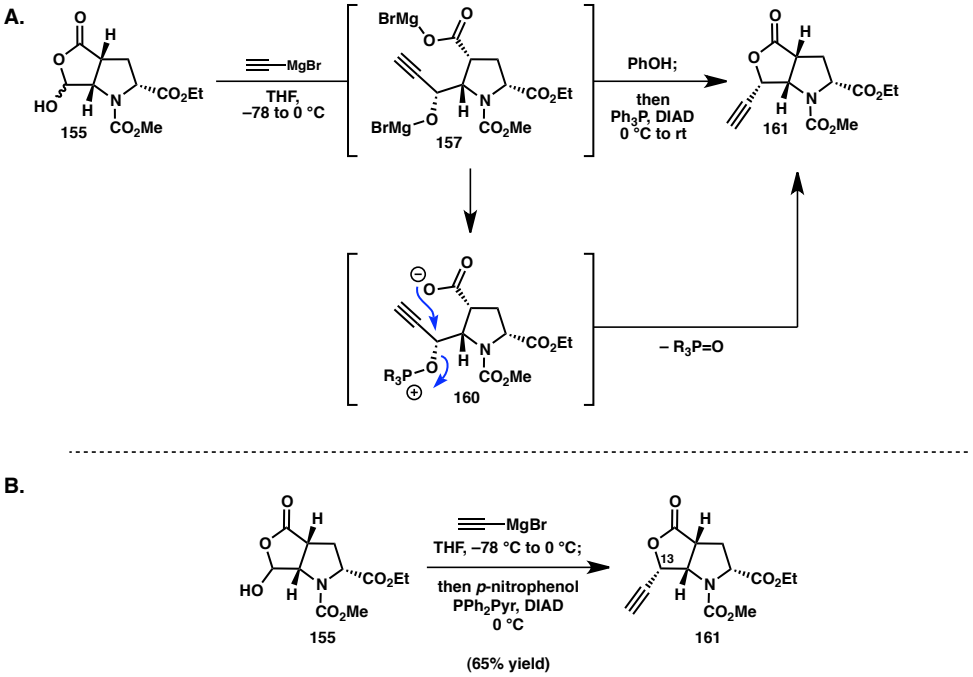
Preliminary investigation of acetylide addition to substrate **155** revealed that treatment with commercially available ethynylmagnesium bromide followed by acidic workup resulted in formation of alkynyl lactone **158** with good diastereoselectivity (Scheme 2.13). Unfortunately, single crystal X-ray diffraction revealed that **158** did not possess the desired stereochemistry at the propargylic position for advancement to the natural product. This observation can be rationalized mechanistically; initial deprotonation of hydroxylactone **155** by the first equivalent of the Grignard reagent presumably results in opening of the cyclic acetal to afford aldehyde carboxylate **159**, in which a cyclic chelation complex is formed. Approach of the nucleophile to the convex face of the resulting ring system affords propargylic alkoxide **157**, which lactonizes upon workup to provide the observed product. Unfortunately, attempts at reversing the observed selectivity by disrupting the proposed activated chelation complex (either by altering the nature of the counterion, or by using strongly coordinating additives) did not prove fruitful.

Scheme 2.13. *Diastereoselective acetylide addition to afford alkynyl lactone* ***158***



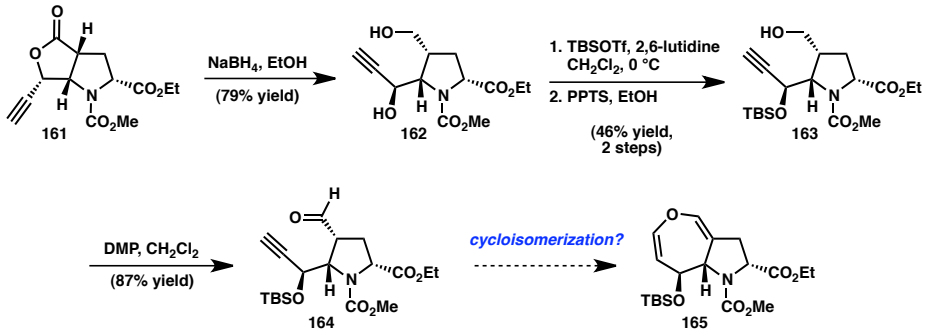
Based on the above mechanistic hypothesis, we envisioned that intermediate species **157** might be intercepted with inversion at the propargylic center via a Mitsunobu lactonization protocol.[22] Gratifyingly, it was found that quenching of the Grignard reaction with phenol, followed by addition of PPh_3 and DIAD afforded the desired epimer of the alkynyl lactone product (**161**) (see Scheme 2.14, part A). Though it was quite difficult to separate **161** from the triphenylphosphine oxide byproduct of the reaction, this purification challenge could be obviated by using *p*-nitrophenol as the quenching reagent and diphenyl 2-pyridylphosphine ($PyrPPh_2$) as the phosphine (Scheme 2.14, part B).[23]

Scheme 2.14. *Grignard addition and subsequent Mitsunobu lactonization to provide alkynyl lactone* ***161***



Conversion of alkynyl lactone **161** to the aldehyde **164** would formally require a reductive opening of the lactone ring. Unfortunately, attempts at partial reduction of lactone to give the aldehyde directly were largely unfruitful. On the other hand, it was found that lactone **161** could be reduced to diol **162** using an excess of $NaBH_4$ in ethanol. Protection of the two hydroxyl groups as TBS ethers, followed by selective deprotection with PPTS in ethanol furnished primary alcohol **163**, which was subsequently oxidized to aldehyde **164** on treatment with buffered Dess-Martin periodinane.[24] Thus, the stage was set for examination of transition metal catalysts for the direct cycloisomerization of aldehyde **164** to give dihydrooxepine **165**.

Scheme 2.15. *Advancement of lactone* ***161*** *to aldehyde* ***164***



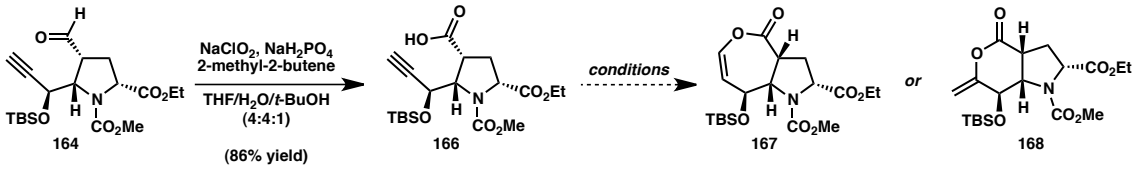
Initial attempts at cycloisomerization of substrate **164** were carried out using catalyst systems that are readily available and known to promote anti-Markovnikov cyclization of alcohols onto alkynes (as described above). In all cases, however, such conditions led either to complete decomposition or epimerization of aldehyde **164** (Table 2.2). Furthermore, experiments using gold(I) salts, which were anticipated to afford the 6-*exo* cyclization product, also demonstrated little reactivity other than slow decomposition of the starting material. Finally, cycloisomerization of several 1,2-adducts derived from aldehyde **164** (either isolated prior to cyclization or formed *in situ*) using a variety of transition metal catalysts could not be successfully accomplished.

Table 2.2. *Attempted cycloisomerization of alkynyl aldehyde* ***164***

entry	catalyst	ligand	additive	solvent, temp.	result
1	$[Rh(cod)Cl]_2$ (5 mol %)	$(p\text{-}FC_6H_4)_3P$ (60 mol %)	DIPEA	DMF, 85 °C	epimerization
2	$[Rh(cod)Cl]_2$ (5 mol %)	Ph_3P (60 mol %)	TMG	DMF, 85 °C	decomposition
3	$CpRuCl[P(p\text{-}FC_6H_4)_3]_2$ (5 mol %)	$(p\text{-}FC_6H_4)_3P$ (20 mol %)	$NaHCO_3$ $n\text{-}Bu_4NPF_6$	DMF, 85 °C	epimerization
4	$(CO)_5W{=}C(OMe)Me$ (1 equiv)	—	Et_3N	PhMe, 85 °C	decomposition
5	AuCl (30 mol %)	—	—	PhMe, 23 °C	decomposition

Encouraged by our preliminary work with model system **150**, we next chose to investigate the possibility of cycloisomerization of an alkynyl carboxylic acid substrate. To this end, aldehyde **164** was converted to carboxylic acid **166** under Pinnick oxidation conditions.[25] Surprisingly, we found that the conditions identified for cycloisomerization of model substrate **150** to **151** could not be successfully extended to substrate **166**, and in fact demonstrated no reactivity whatsoever (Table 2.3). On the other hand, Fisher carbene precatalyst $(CO)_5W{=}C(OMe)Me$ promoted only decomposition, whereas ruthenium catalysts promoted varying combinations of decomposition and Markovnikov 6-*exo* cyclization. As expected, catalysis with gold(I) salts resulted in rapid, selective formation of 6-*exo* cyclization product **168** (as confirmed by 1D and 2D ^{1}H and ^{13}C NMR spectroscopy).[26]

Table 2.3. *Synthesis and attempted cycloisomerization of alkynyl carboxylic acid* ***166***

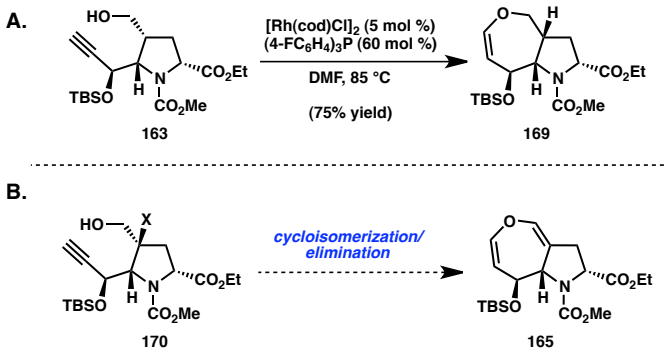


entry	catalyst	ligand	additive	solvent, temp.	result
1	$[Rh(cod)Cl]_2$ (5 mol %)	$(p\text{-}FC_6H_4)_3P$ (60 mol %)	—	DMF, 85 °C	no reaction
2	$(CO)_5W{=}C(OMe)Me$ (30 mol %)	—	Et_3N	THF 60 °C	decomposition
3	$[(p\text{-cumene})RuCl_2]_2$ (5 mol %)	$(p\text{-}FC_6H_4)_3P$ (15 mol %)	DMAP (20 mol %)	PhMe, 85 °C	6-*exo* cyclization
4	$TpRuH(PPh_3)_2$ (10 mol %)	—	—	PhMe, 85 °C	6-*exo* cyclization
5	AuCl (10 mol %)	—	—	CH_2Cl_2, 23 °C	6-*exo* cyclization

The difficulty encountered in trying to promote the desired anti-Markovnikov 6-*endo* cyclization of either the aldehyde **164** or the carboxylic acid **166** prompted us to investigate the cycloisomerization of the previous alcohol intermediate **163**. In the event,

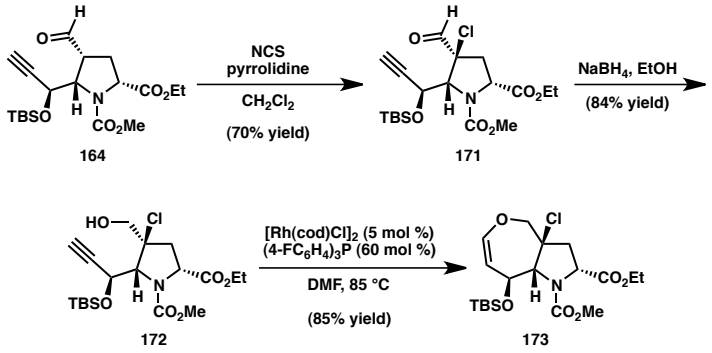
we were delighted to find that using the previously identified conditions ($[Rh(cod)Cl]_2$ and $(p\text{-}FC_6H_4)_3P$ in DMF at 85 °C), alkynyl alcohol **163** smoothly underwent 7-*endo* cycloisomerization to provide tetrahydrooxepine **169** (Scheme 2.16). While it is unclear whether the facility of cycoisomerization for this particular substrate is due to steric or geometric parameters, it is apparent that the primary alcohol **163** represents an optimal structure for cycloisomerization among the substrates investigated. Accordingly, we hypothesized that halohydrins **170** might serve as viable aldehyde surrogates by providing the favorable reactivity of the primary alcohol while possessing a suitable functional handle for subsequent conversion to the dihydrooxepine.

Scheme 2.16. *Successful cycloisomerization of alkynyl alcohol* ***163*** *and halohydrins* ***170*** *as potential aldehyde surrogates*



Aldehyde **164** was readily chlorinated by NCS in the presence of pyrrolidine to afford chloroaldehyde **171** as a single diastereomer (relative stereochemistry as shown was confirmed by NOESY spectroscopy, see Scheme 2.17). Subsequent reduction with $NaBH_4$ provided the desired chlorohydrin **172** in 59% overall yield from **164**. Chlorohydrin **172** proved to be a suitable substrate for rhodium(I)-catalyzed cycloisomerization, providing chlorotetrahydrooxepine **173** in 57% yield.

Scheme 2.17. *Synthesis and cycloisomerization of chlorohydrin* ***172***



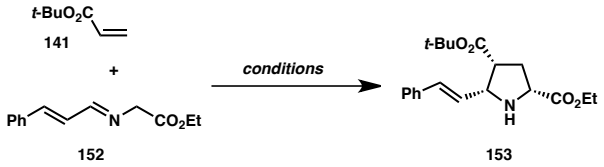
With chlorotetrahydrooxepine **173** in hand, we were very pleased to observe that treatment with DBU in DMF at elevated temperatures did in fact provide the desired dihydrooxepine ring to complete acetylaranotin monomer **165** (Table 2.4, Entry 1). However, under these conditions, **165** was isolated in only 10% yield despite proceeding to full conversion of **173**. Other strong non-ionic organic bases gave similar results, and reaction attempts employing less basic amine bases (e.g. DIPEA) or Ag(I) salts demonstrated no reactivity (Entries 2 and 3). Interestingly, we found that greatly improved yields for the reaction could be achieved using a mixture of LiCl and Li_2CO_3 in DMF at 100 °C, which provided the dihydrooxepine **165** in 50% isolated yield (Entry 4). Similar conditions have historically been used for the elimination of halides from relatively unfunctionalized molecules, and are not typically used in reactions involving structures as complex or highly oxidized as **173**.[27]

Table 2.4. *Identification of reaction conditions for elimination of HCl from chlorotetrahydrooxepine* ***173*** *to afford dihydrooxepine* ***165***

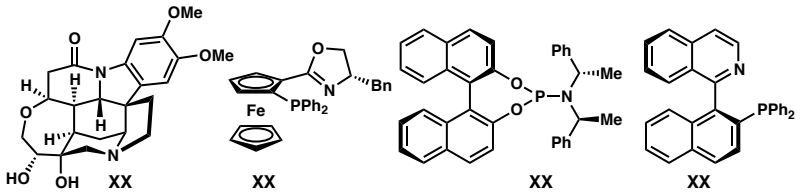
entry	base/additive	solvent, temp.	result
1	DBU	DMF, 85 °C	10% yield (no recovered SM)
2	DIPEA	DMF, 85 °C	no reaction
3	Ag(TFA), Ag_2CO_3	PhMe, 85 °C	no reaction
4	LiCl, Li_2CO_3	DMF, 100 °C	50% yield

Having accomplished a viable synthetic route towards racemic dihydrooxepine **165**, we turned our attention to the development of an enantioselective sequence. A brief survey of known catalyst systems for asymmetric (1,3)-dipolar cycloaddition reactions between alkyl acrylates and aryl glycinate imines revealed that both Ag(I)/(*S*)-QUINAP (**177**) and Cu(I)/Brucin-OL (**174**) catalyzed the reaction between **141** and **152** to give styrenyl pyrrolidine **153** in good *ee* (see Table 2.5, Entries 3 and 4).[28] Because they provided material of greater optical activity, and because Brucin-OL is substantially less expensive per mole than (*S*)-QUINAP, we opted to use the conditions in entry 4 for the preparation of **153** on scale.

Table 2.5. *Survey of catalyst systems for the enantioselective synthesis of pyrrolidine* ***153***



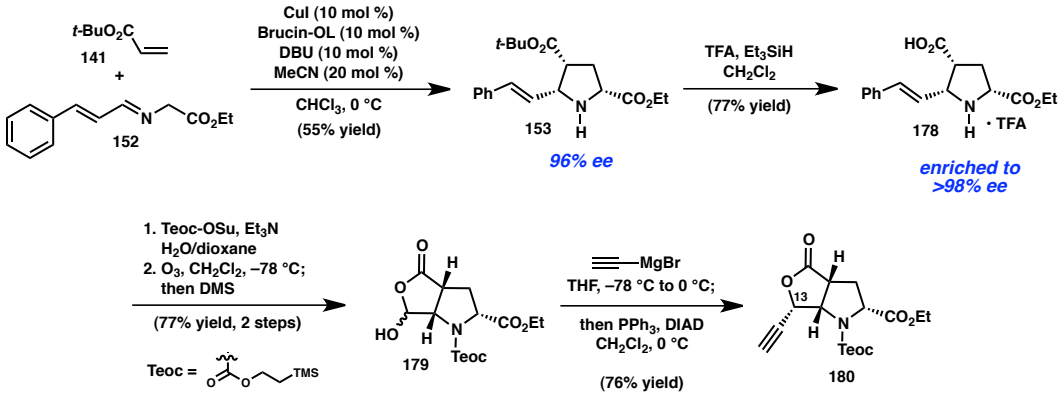
entry	catalyst/ligand/additive	solvent	temp. (°C)	yield (%)	*ee* (%)
1	$AgOAc$, **175**	Et_2O	0	53	–63
2	$AgClO_4$, **176**, DABCO	PhMe	0	59	46
3	$AgOAc$, **177**, DIPEA	THF	–45	62	90
4	CuI, **174**, DBU	$CHCl_3$	0	50	96



With access to ample quantities of pyrrolidine **153**,[29] we next reconsidered our protecting group strategy, knowing that the methyl carbamate protecting group used in our preliminary investigations was not optimal for deprotection and advancement of monomer **165** to the corresponding diketopiperazine. Ultimately, we opted to employ a trimethylsilylethyl carbamate (Teoc) protecting group, which can be removed using fluoride ion under neutral or basic conditions.[30] However, because of the acid sensitivity of this group, the order of protecting group manipulations was also modified relative to the preliminary sequence, so as to avoid subjection of the Teoc group to high concentrations of TFA. Accordingly, the *tert*-butyl ester of pyrrolidine **153** was first cleaved using TFA/Et_3SiH to afford trifluoroacetate salt **178** as a crystalline solid in 77% yield (see Scheme 2.18). Notably, the trituration procedure used to isolate this material resulted in enrichment of optical activity to >98% *ee*. Subsequent protection of the pyrrolidine nitrogen as the Teoc carbamate and ozonolytic cleavage of the styrene as

before provided hydroxylactone **179** in 77% yield over two steps. In contrast to the methyl carbamate-protected system (**155**), this substrate required an aqueous workup following reaction with ethynylmagnesium bromide in order for the subsequent Mitsunobu inversion to succeed. On the other hand, the decreased polarity of **180** versus **161** allowed for the use of Ph_3P, rather than the more expensive reagent Ph_2PPyr, without the previously encountered challenges to purification.

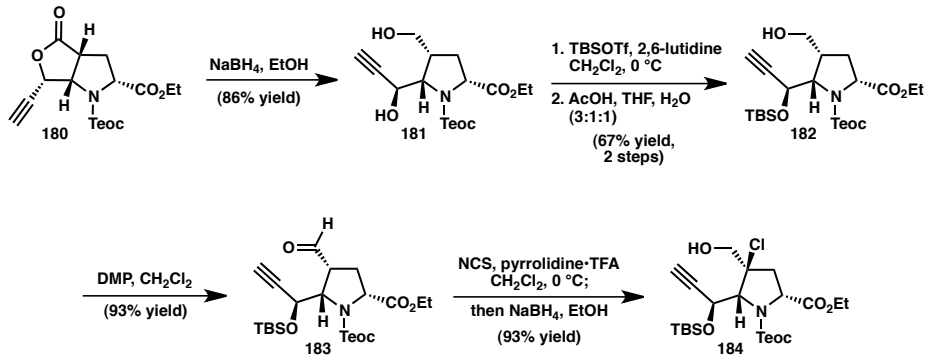
Scheme 2.18. *Synthesis of enantioenriched, Teoc-protected alkynyl lactone* ***180***



Alkynyl lactone **180** was advanced to chlorohydrin **184** using an analogous sequence to that developed for the methyl carbamate-protected variant, but with two notable exceptions (see Scheme 2.19). First, conditions employing AcOH/THF/H_2O were used to selectively cleave the primary TBS ether following treatment of **181** with TBSOTf. These conditions demonstrated substantially reduced reaction times and greater selectivity for cleavage of the primary versus the secondary silyl ether (relative to PPTS/EtOH). Additionally, pyrrolidine-mediated chlorination of Teoc-protected aldehyde **183** was sluggish and resulted in consistently low conversion regardless of reaction time. By instead using pyrrolidine•TFA complex, the reaction progressed to completion over the course of 30 h. Furthermore, isolated yields for the

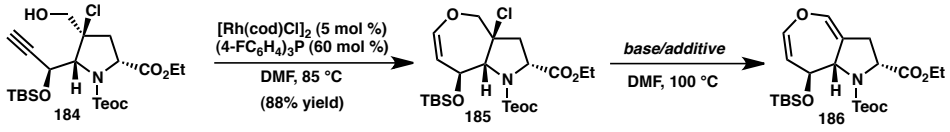
chlorination/aldehyde reduction sequence were greatly improved by performing the two processes in one flask, with no intermediate workup.

Scheme 2.19. *Advancement of alkynyl lactone* ***180*** *to chlorohydrin* ***184***



As expected, Teoc-protected chlorohydrin **184** proved to be an excellent substrate for Rh(I)-catalyzed cycloisomerization, affording chlorotetrahydrooxepine **185** in 87% yield. Though the combination of LiCl and Li_2CO_3 remained optimal for elimination of HCl from **185** to afford dihydrooxepine **186**, our curiosity about the role of each lithium salt in this reaction prompted us to perform a series of control experiments. In the absence of LiCl no reaction occurs (Table 2.6, Entry 2), whereas in the absence of Li_2CO_3 the reaction proceeds, but is accompanied by increased formation of decomposition products (Entry 3). Given that LiCl is quite soluble in DMF, whereas Li_2CO_3 is almost completely insoluble, we hypothesized that perhaps the high concentration of lithium cations in solution was critical to activation of the chloride leaving group. However, employing $LiClO_4$ rather than LiCl as the soluble source of lithium cation resulted in no reaction (Entry 4). These results suggest that the chloride ion itself is acting as a base during the elimination reaction, while the carbonate salt is simply acting as an insoluble buffer. Unfortunately, attempts to employ more basic lithium salts or more soluble carbonate salts led only to greatly increased levels of decomposition (Entries 5 and 6).

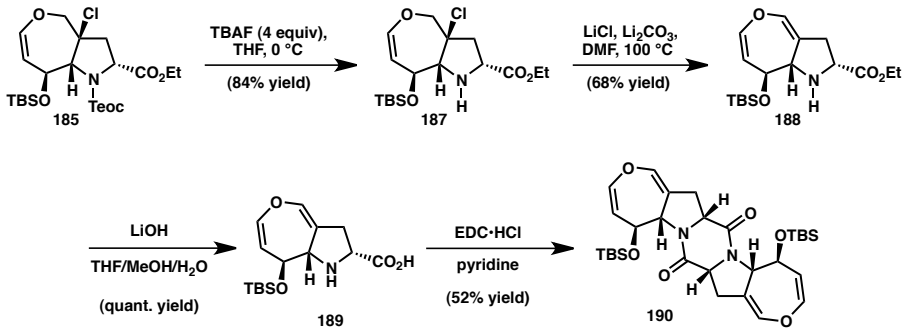
Table 2.6. *Advancement of chlorohydrin* ***184*** *to Teoc-protected dihydrooxepine monomer* ***186***



entry	base/additive	result
1	$LiCl$, Li_2CO_3	53% yield
2	Li_2CO_3	no reaction
3	$LiCl$	complex product mixture
4	$LiClO_4$, Li_2CO_3	no reaction
5	$LiOAc$, Li_2CO_3	complex product mixture
6	Cs_2CO_3	complex product mixture

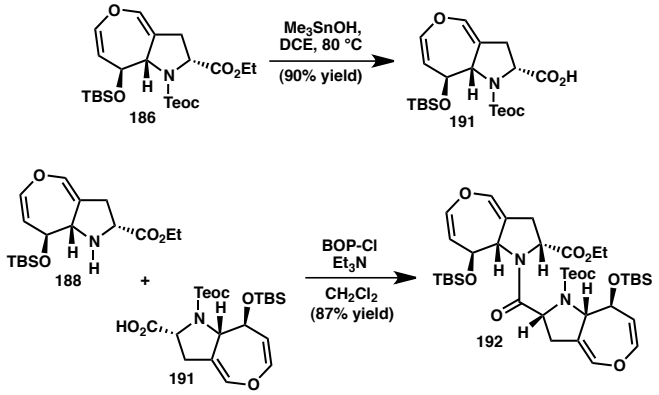
Perhaps unsurprisingly, we found it difficult to selectively cleave the Teoc protecting group from **186** in the presence of the TBS ether. In contrast, removal of the carbamate protecting group from chlorotetrahydrooxepine **185** proved to be quite facile, providing pyrrolidine **187** in 84% yield (Scheme 2.20). Furthermore, elimination of HCl from this substrate occurred in even greater yield than for the Teoc-protected substrate, affording dihydrooxepine pyrrolidine **188** in 65% yield. Subsequent saponification proceeded smoothly to provide amino acid **189**. Ultimately, it was determined that amino acid **189** could be dimerized using EDC in pyridine; however, our inability to achieve greater than 50% yield of diketopiperazine **190** under these conditions prompted us to investigate a stepwise approach, starting from two orthogonally protected monomer units.

Scheme 2.20. *Synthesis and dimerization of dihydrooxepine amino acid* ***189***



Having previously established a sequence for the preparation of pyrrolidine **188**, saponification of **186** to give the corresponding carboxylic acid component for amide coupling was required. Though the fully protected monomer unit **186** was unstable to standard saponification conditions using LiOH, the ethyl ester could be cleaved using an excess of Me_3SnOH in dichloroethane at elevated temperatures to produce carboxylic acid **191** in 90% yield. Pyrrolidine **188** and carboxylic acid **191** could be readily coupled using BOP-Cl, affording protected dipeptide **192** in excellent yield.

Scheme 2.21. *Synthesis of dipeptide* ***192***

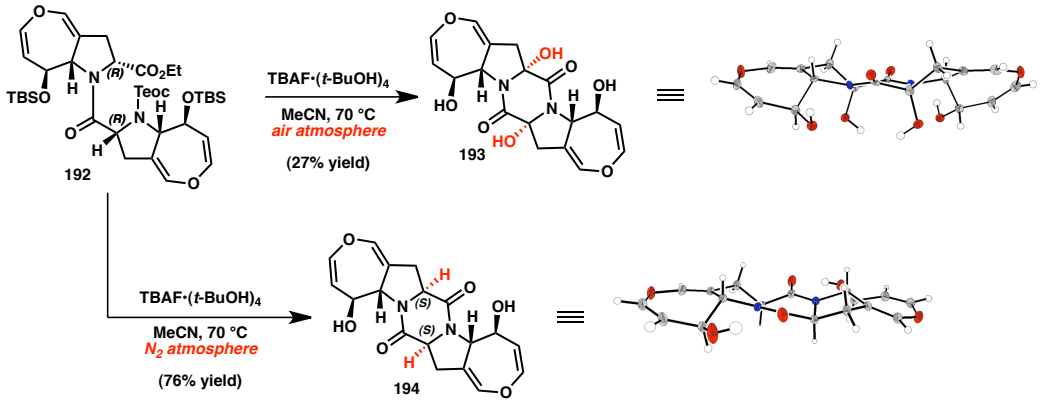


Initial attempts to deprotect dipeptide **192** using TBAF in THF resulted in various mixtures of partially or fully deprotected products. Though trace amounts of diketopiperazine were observed in the crude mixtures of some reactions, the material

recovery was consistently low. Together with the apparent instability of dihydrooxepine **186** to basic conditions, these results suggested that less basic conditions for deprotection of **192** were desirable. Unfortunately, no other fluoride sources appeared to promote the cleavage of the Teoc carbamate *at all*.

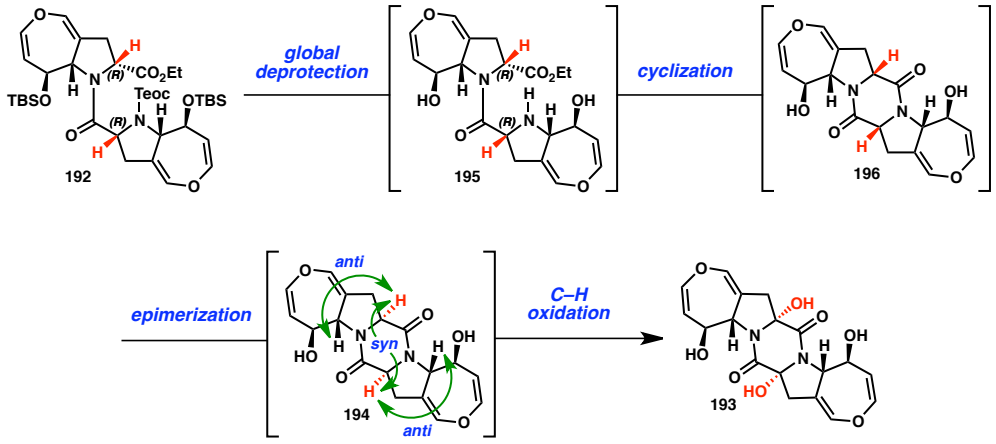
Turning our attention to attenuating the basicity of TBAF itself, we became interested in a report from Kim and coworkers, who determined that TBAF•(*t*-BuOH)$_4$ is not only substantially less hygroscopic than solid TBAF•(H$_2$O)$_3$, but also less *basic* than typical TBAF solutions.[31] We were pleased to find that treatment of dipeptide **192** with TBAF•(*t*-BuOH)$_4$ in MeCN at 70 °C effected global deprotection and cyclization to deliver a C_2-symmetric compound as the major product. Interestingly, initial characterization of this compound using standard NMR techniques and high-resolution mass spectrometry suggested that it was a *syn*-diol (**193**), the result of a double C–H oxidation process (see Scheme 2.22). On the basis of the hypothesis that the oxidant was oxygen in the ambient atmosphere, the reaction was repeated under a nitrogen atmosphere using rigorously degassed solvent, which provided diketopiperazine **194** as a single diastereomer in 76% yield. The structures of **193** and **194** were confirmed by single-crystal X-ray diffraction. Notably, the (*S*, *S*)-stereochemistry of the central diketopiperazine of **194** is the result of epimerization at both of the diketopiperazine methine positions under the cyclization conditions.

Scheme 2.22. *Unexpected aerobic oxidation and advancement of dipeptide* ***192*** *to diketopiperazine* ***194***



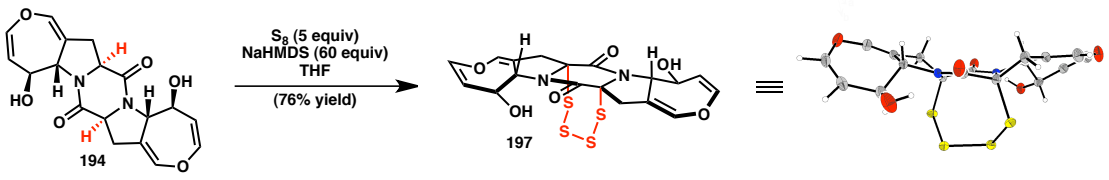
Based on a series of control experiments,[32] we hypothesize that the processes described above are proceeding via the sequence shown in Scheme 2.23. First, fluoride-promoted global desilylation of **192** provides deprotected dipeptide **195**, which cyclizes to give the expected *syn*,*syn*,*syn* diketopiperazine **196**. Subsequent epimerization to the thermodynamically favored *anti*,*syn*,*anti* configuration affords the observed diketopiperazine **194**. Under aerobic conditions, **194** then undergoes a *stereoretentive* radical-mediated C–H oxidation to afford the tetraol **193**.

Scheme 2.23. *Proposed TBAF•(t-BuOH)$_4$-promoted diketopiperazine formation/ oxidation sequence*



Though we were unable to advance oxidized product **193** to the natural product, we were nevertheless encouraged by the above results, as they suggested that an analogous sulfenylation reaction might proceed with the correct facial selectivity for C–S bond formation. After several attempts at sulfenylating diketopiperazine **194** by kinetic deprotonation with LDA followed by trapping with sulfur electrophiles (e.g. monoclinic S_8, *p*-methoxybenzyl disulfide, etc.), we found that we could obtain tetrasulfide **197** (Scheme 2.24) as the sole isolable sulfenylated product using the conditions reported by Nicolaou and coworkers (see Chapter 1).[10,33] By using the exact ratios of base to sulfur described in the literature, **197** was consistently obtained in 50% yield. However, by using a much larger excess of base relative to sulfur, the yield could be improved to 76%. Gratifyingly, single-crystal X-ray diffraction analysis revealed that oxidation had selectively occurred to give the C–S bonds in the desired orientation for advancement to the natural product.

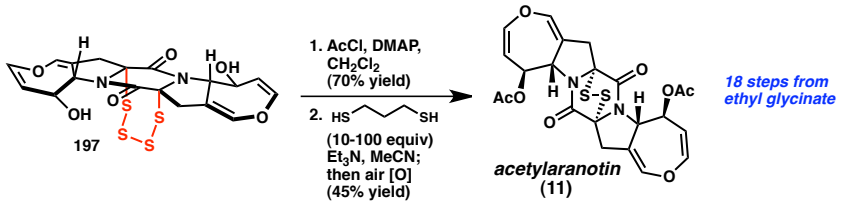
Scheme 2.X. *Sulfenylation of diketopiperazine* ***194*** *to obtain tetrasulfide* ***197***



Tetrasulfide **197** was found to be unstable to $NaBH_4$ under conditions typically used to reduce similar cyclic epipolythiodiketopiperazines. Instead, acetylation of the two peripheral hydroxyl groups furnished the diacetate, and the tetrasulfide was reduced under mild conditions using propanedithiol and Et_3N in MeCN. Aerobic oxidation of the

resulting dithiol delivered the natural product, **11**. The spectroscopic data for synthetic (–)-acetylaranotin were identical to the original isolation data.

Scheme 2.25. *Conversion of tetrasulfide **197** to acetylaranotin (**11**)*



2.3 CONCLUDING REMARKS

In conclusion, we have achieved the enantioselective total synthesis of (–)-acetylaranotin (**11**), the first total synthesis of any dihydrooxepine-containing ETP natural product, in 18 steps from inexpensive, commercially available materials. Essential to the development of this route was the successful execution of a rhodium-catalyzed cycloisomerization/chloride elimination sequence to furnish the dihydrooxepine ring and complete the monomer unit **186**. This strategy allowed us to exploit the power of an azomethine ylide (1,3)-dipolar cycloaddition reaction in order to enantio- and diastereoselectively construct the densely functionalized pyrrolidine scaffold of the requisite alkynyl alcohol substrate **184**. Notably, diketopiperazine **194** was obtained as a single diastereomer, which underwent direct sulfenylation with *complete retention of stereochemistry* to provide epitetrathiodiketopiperazine **197**. Access to monomer unit **186** has enabled the synthesis of related dihydrooxepine-containing ETP natural products and analogs, as described in Chapter 3.

2.4 EXPERIMENTAL SECTION

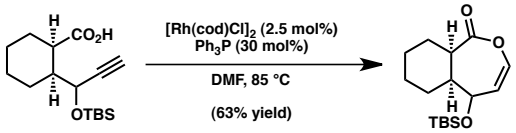
2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[34] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^{1}H, δ = 7.26), MeCN (^{1}H, δ = 1.94), or DMSO (^{1}H, δ = 2.50), and $CDCl_3$ (^{13}C, δ = 77.0), MeCN (^{13}C, δ = 118.26), or DMSO (^{13}C, δ = 40.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, 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. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm) or an Agilent Zorbax RX-SIL 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 enol lactone 151

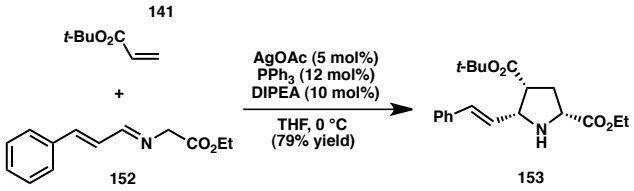


150 151

In the glove box, $[Rh(cod)Cl]_2$ (6.3 mg, 0.0127 mmol) was weighed into an oven-dried 1-dram vial. This was removed from the glove box, and charged with cycloisomerization substrate **150** (75 mg, 0.253 mmol), PPh_3 (39.9 mg, 0.152 mmol), and a magnetic stir bar. The vial was sealed with a rubber septum, and flushed with N_2. DMF (2.5 mL, dried over 4Å molecular sieves and degassed with Ar for 30 min) was then added, and the mixture was stirred until all solids had dissolved. The resulting solution was then heated to 85 °C. After 4 h, the reaction solution was cooled to rt, then transferred to a separatory funnel containing 50 mL sat. $NaHCO_3$. The mixture was extracted with Et_2O (3 x 15 mL), and the combined organic layers were washed with sat.

$NaHCO_3$ (15 mL), dried over Na_2SO_4, and concentrated to give an orange oil. The crude material was purified by flash chromatography (1→2% EtOAc/hexanes) to afford *endo*-enol lactone **151** (46.7 mg, 62% yield) as a pale yellow oil that solidifies upon standing at –20 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 5.9, 2.0 Hz, 1H), 5.45 (t, *J* = 5.1 Hz, 1H), 4.22 – 4.15 (m, 1H), 3.12 (t, *J* = 5.6 Hz, 1H), 2.15 – 1.99 (m, 3H), 1.87 (dd, *J* = 26.3, 13.1 Hz, 1H), 1.78 (app d, *J* = 12.2 Hz, 1H), 1.56 (app d, *J* = 13.7 Hz, 1H), 1.35 (tt, *J* = 13.4, 4.9 Hz, 1H), 1.20 – 1.03 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 137.6, 121.8, 72.9, 50.5, 37.7, 28.8, 27.4, 25.7, 24.9, 21.5, 17.9, -4.6, -5.0; IR (NaCl/thin film): 2934, 2897, 2856, 1764, 1645 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{16}H_{29}O_3Si$ $[M+H]^+$ 297.1881, found 297.1881.

Preparation of styrenyl pyrrolidine 153

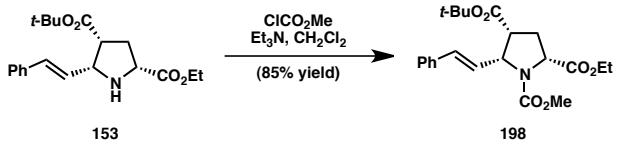


Ethyl glycinate hydrochloride (30 g) was ground together with K_2CO_3 (60 g) and several drops of brine using a mortar and pestle to give a white paste. This material was extracted with several portions of Et_2O, and the combined extracts were dried over Na_2SO_4, filtered, and concentrated to afford ethyl glycinate (~81 wt %, contains a significant amount of Et_2O) as a nearly colorless oil (a white solid—presumably the cyclic glycine dimer—forms upon prolonged storage of this material at –20 °C). An oven-dried flask equipped with a magnetic stir bar is charged with silica gel (15.0 g) then sealed with a rubber septum and flushed with N_2. THF (250 mL) is then added, and the suspension is cooled to 0 °C with stirring. The freshly prepared ethyl glycinate (81 wt %,

6.40 g, 50.0 mmol) was then added, followed by cinnamaldehyde (6.30 mL, 50.0 mmol), and the mixture was stirred at 0 °C. After 6 h, the resulting solution of imine **152** was filtered into an oven-dried flask to remove silica gel, and this flask was sealed with a rubber septum, flushed with N_2, and cooled to 0 °C.

Prior to filtration of the imine solution, an oven-dried flask equipped with a magnetic stir bar was charged with AgOAc (417 mg, 2.50 mmol) and PPh_3 (1.57 g, 6.00 mmol), then sealed with a rubber septum and flushed with N_2. The solids were dissolved in THF (250 mL) and the resulting solution was stirred for 15 min before being cooled to 0 °C. *t*-Butyl acrylate (11.0 mL, 75.0 mmol) was then added, followed by DIPEA (871 μL, 5.00 mmol). The cold imine solution was then transferred dropwise via cannula to the stirring solution of the catalyst system and dipolarophile over ~50 min. After 30 min of further stirring, the reaction solution was concentrated to an orange oil and purified by flash chromatography (14→50% EtOAc/hexanes) to afford pyrrolidine **153** (13.6 g, 79% yield) as a viscous green oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.19 (m, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.18 (dd, *J* = 15.8, 7.7 Hz, 1H), 4.29 – 4.19 (m, 2H), 4.02 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.87 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.11 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 2.51 (s, 1H), 2.37 (ddd, *J* = 13.2, 8.4, 7.8 Hz, 1H), 2.26 (ddd, *J* = 13.3, 8.2, 7.8 Hz, 1H), 1.33 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 171.6, 136.5, 131.9, 128.5, 127.6, 127.0, 126.4, 80.9, 63.9, 61.1, 59.7, 49.6, 33.0, 28.0, 14.2; IR (NaCl/thin film): 2978, 1737, 1732, 1729, 1495, 1478, 1450, 1392, 1367, 1248, 1210, 1151, 1030, 966, 847, 750, 693 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{20}H_{28}NO_4$ $[M+H]^+$ 346.2013, found 346.2006.

Preparation of methyl carbamate 198

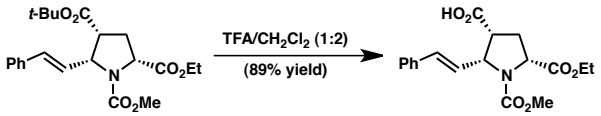


153 198

An oven-dried flask was charged with pyrrolidine **153** (667 mg, 1.93 mmol) and a magnetic stir bar, then was sealed with a rubber septum and flushed with N_2. The material was dissolved in CH_2Cl_2 (20 mL) and Et_3N (807 μL, 5.79 mmol) was added. Methyl chloroformate (224 μL, 2.90 mmol) was then added dropwise with stirring. After 1 h, the reaction was quenched with 20 mL of sat. $NaHCO_3$. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with sat. $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20% EtOAc/hexanes) to afford methyl carbamate **198** (664 mg, 85% yield) as a viscous green oil. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 7.38 – 7.33 (m, 2H*, 2H§), 7.32 – 7.24 (m, 2H*, 2H§), 7.24 – 7.17 (m, 1H*, 1H§), 6.80 (d, J = 15.7 Hz, 1H§), 6.74 (d, J = 15.7 Hz, 1H*), 6.16 (dd, J = 16.1, 8.1 Hz, 1H*), 6.14 (dd, J = 16.3, 8.5 Hz, 1H§), 4.90 (t, J = 8.0 Hz, 1H§), 4.78 (t, J = 7.9 Hz, 1H*), 4.36 – 4.19 (m, 3H*, 3H§), 3.69 (s, 3H*), 3.67 (s, 3H§), 3.24 – 3.15 (m, 1H*, 1H§), 2.49 – 2.30 (m, 2H*, 2H§), 1.36 (s, 9H*, 9H§), 1.30 (dd, J = 6.5 Hz, 6.5 Hz, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 172.1, 172.0, 168.6, 168.6, 155.2, 154.3, 136.5, 136.4, 133.8, 133.4, 128.5, 128.3, 127.8, 127.6, 126.7, 126.6, 124.7, 124.2, 81.6, 61.9, 61.3, 61.3, 61.2, 59.0, 58.7, 52.8, 52.7, 48.6, 47.8, 30.6, 29.7, 29.5, 28.1, 14.2, 14.2; IR (NaCl/thin film): 2978, 2928, 1748, 1733, 1716, 1698, 1454, 1446, 1385, 1370, 1288,

1251, 1187, 1155, 1118, 1073, 1029, 962, 843, 752 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{18}H_{22}NO_6$ $[M–C_4H_8+H]^+$ 348.1442, found 348.1453 (detected fragment has undergone elimination of *iso*-butylene from the *t*-butyl ester).

Preparation of carboxylic acid 154

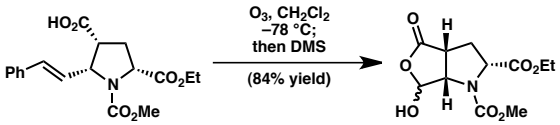


198 154

An oven-dried flask equipped with a magnetic stir bar was charged with *t*-butyl ester **198** (1.31 g, 3.25 mmol), then was sealed with a rubber septum and flushed with N_2. CH_2Cl_2 (12 mL) was then added, followed by TFA (6 mL), and the resulting solution was stirred for 10 h at room temperature. During this time, the color of the solution changed from light green to bright red. The reaction solution was concentrated under reduced pressure to give an orange-red to brown oil, which partially solidified under high vacuum. The material was purified by flash chromatography (2:1 hexanes/EtOAc with 1% AcOH) to give carboxylic acid **154** (1.00 g, 89% yield) as an orange solid. It was later found that the crude material could also be purified and the color removed by trituration with Et_2O. ^{1}H NMR (500 MHz, CD_3CN; compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 7.38 (d, *J* = 7.7 Hz, 2H*, 2H§), 7.33 (t, *J* = 7.5 Hz, 2H*, 2H§), 7.26 (t, *J* = 6.9 Hz, 1H*, 1H§), 6.79 (d, *J* = 15.8 Hz, 1H*, 1H§), 6.18 (dd, *J* = 15.8, 7.5 Hz, 1H*, 1H§), 4.80 (dt, *J* = 14.8, 7.8 Hz, 1H*, 1H§), 4.28 (dt, *J* = 10.9, 6.8 Hz, 1H*, 1H§), 4.24 – 4.15 (m, 2H*, 2H§), 3.61 (s, 3H*), 3.59 (s, 3H§), 3.36 (dq, *J* = 15.3, 8.0, 7.5 Hz, 1H*, 1H§), 2.44 (apt tt, *J* = 13.8, 7.2 Hz, 1H*, 1H§), 2.29 (q, *J* = 11.8 Hz, 1H§), 2.23 (q, *J* = 11.9 Hz, 1H*), 1.26 (t, *J* = 7.1 Hz, 3H*, 3H§); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a 1.2:1 mixture of

rotamers) δ 173.2, 173.0, 171.2, 171.2, 156.0, 155.1, 137.5, 133.6, 133.5, 129.6, 128.7, 127.3, 126.4, 126.2, 62.2, 62.0, 61.9, 61.7, 60.0, 59.6, 53.2, 53.0, 48.0, 47.3, 31.4, 30.4, 14.5; IR (NaCl/thin film): 2987, 2596, 1743, 1711, 1452, 1384, 1287, 1242, 1190, 1122, 1076, 1029, 966, 862, 833, 771, 739 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{18}H_{22}NO_6$ $[M+H]^+$ 348.1442, found 348.1444.

Preparation of hydroxylactone 155

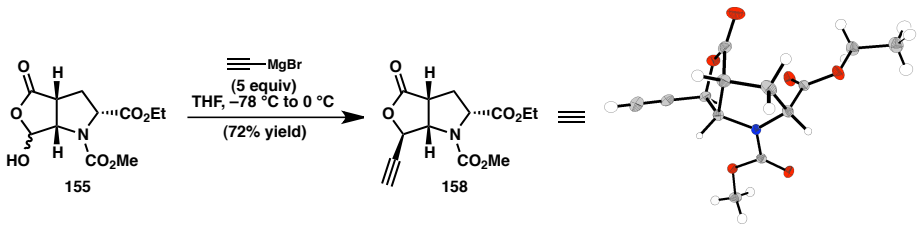


154 155

An oven-dried 3-neck flask equipped with a magnetic stir bar was charged with styrene **154** (900 mg, 2.59 mmol) and CH_2Cl_2 (26 mL). The middle neck was fitted with an adaptor for the ozone line, one of the side necks was stoppered with a punctured plastic stopper as an outlet, and the third neck was stoppered with a glass stopper. The solution was cooled to –78 °C with stirring, and O_2 was bubbled through for several minutes. O_3 was then bubbled through the solution. When the solution had turned a blue color, the O_3 was bubbled through for an additional 15 min, and then the solution and reaction vessel were purged with O_2. When the blue color had disappeared, the solution was allowed to warm to room temperature, the punctured plastic stopper was replaced with a glass stopper, and the adapter in the center neck replaced with a rubber septum. N_2 was then bubbled through the solution for 15 min to remove O_2, and DMS (7.57 mL, 104 mmol) was added. The resulting solution was allowed to stir under N_2 overnight, and then was concentrated under reduced pressure and purified by flash chromatography (50→67% EtOAc/hexanes) to afford hydroxy lactone **155** (596 mg, 84% yield) as an

extremely viscous oil. ^{1}H NMR (500 MHz, DMSO-d_6; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 7.92 (dd, J = 10.5, 6.0 Hz, 1H*, 1H§), 5.71 (d, J = 4.6 Hz, 1H*), 5.67 (d, J = 4.8 Hz, 1H§), 4.45 (t, J = 11.0 Hz, 1H*, 1H§), 4.20 (dd, J = 7.3, 3.3 Hz, 1H*, 1H§), 4.15 – 3.97 (m, 2H*, 2H§), 3.68 (s, 3H§), 3.60 (s, 3H*), 3.55 (dt, J = 15.3, 8.1 Hz, 1H*, 1H§), 2.68 – 2.53 (m, 1H*, 1H§), 2.17 (dd, J = 21.3, 13.5 Hz, 1H*, 1H§), 1.14 (t, J = 7.0 Hz, 3H*, 3H§); ^{13}C NMR (126 MHz, DMSO-d_6; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 177.6*, 177.5§, 171.8*, 171.7§, 154.6*, 154.5§, 101.9§, 101.1*, 66.0*, 65.4§, 61.6*, 61.5§, 59.6§, 59.0*, 53.5§, 53.3*, 43.5§, 42.5*, 31.7*, 30.7§, 14.2*,§; IR (NaCl/thin film): 3382, 2963, 1782, 1743, 1712, 1454, 1387, 1352, 1293, 1254, 1200, 1157, 1122, 1057, 1038, 1022, 975, 954, 933, 856, 775 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{11}H_{14}NO_7$ $[M–H]^-$ 272.0776, found 272.0733.

Preparation of alkynyl lactone 158

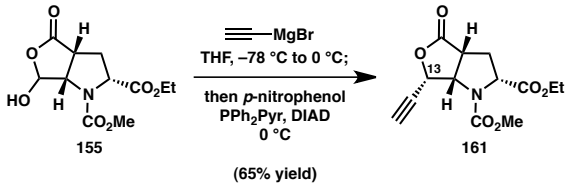


Hydroxylactone **155** (1.34 g, 4.90 mmol) was transferred to an oven-dried flask as a solution in benzene, then concentrated under reduced pressure. A magnetic stir bar was added, and the flask was sealed with a rubber septum and flushed with N_2. THF (25 mL) was added, and the resulting solution was cooled to –78 °C with stirring. Ethynylmagnesium bromide (0.5 M solution in THF, 49.0 mL, 24.5 mmol) was added

dropwise over 25 min via syringe pump (this appears to be somewhat exothermic, and the addition was paused twice during addition of the first equivalent of reagent due to violent bubbling of the dry ice bath). The resulting yellow-brown suspension was stirred for another 5 min at –78 °C, then allowed to warm to 0 °C over 25 min. During this time, the reaction contents solubilized to give a pale yellow-brown solution. The reaction was quenched with 20 mL 2 M HCl, and the THF was removed under reduced pressure. The resulting mixture was extracted with EtOAc (75 mL, then 3 x 50 mL), then saturated with NaCl and extracted again with EtOAc (50 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was stored at –20 °C overnight to allow complete lactonization, and then was purified by flash chromatography (40→75% EtOAc/hexanes) to afford alkynyl lactone **158** (993 mg, 72% yield) as a viscous oil, which could be precipitated from EtOH to form a white solid. Crystals suitable for X-ray diffraction were obtained by vapor diffusion of pentane into a saturated solution of alkynyl lactone **158** in PhMe at room temperature. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.4:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 5.42 (d, *J* = 2.0 Hz, 1H*), 5.30 (d, *J* = 1.3 Hz, 1H§), 4.68 (d, *J* = 7.8 Hz, 1H*), 4.61 (d, *J* = 7.3 Hz, 1H§), 4.58 – 4.54 (m, 1H§), 4.47 – 4.42 (m, 1H*), 4.21 – 4.08 (m, 2H*, 2H§), 3.80 (s, 3H§), 3.71 (s, 3H*), 3.44 – 3.34 (m, 1H*, 1H§), 2.71 – 2.69 (m, 1H*, 1H§), 2.62 – 2.49 (m, 2H*, 2H§), 1.24 (t, *J* = 7.1 Hz, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as mixture of rotamers) δ 176.0, 175.7, 170.9, 154.4, 154.0, 78.5, 78.4, 76.9, 73.6, 72.9, 65.3, 64.6, 62.0, 59.2, 58.8, 53.4, 53.2, 43.4, 42.4, 31.7, 30.8, 13.8; IR (NaCl/thin film): 3263, 2961, 2125, 1784, 1742, 1709, 1451, 1386, 1348, 1292, 1248,

1200, 1147, 1126, 1021, 977, 950, 773 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{13}H_{16}NO_6$ $[M+H]^+$ 282.0972, found 282.0967.

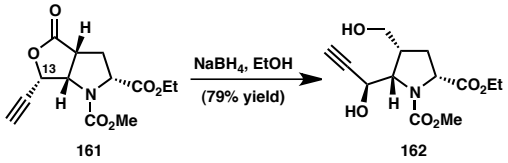
Preparation of alkynyl lactone 161



To a flame dried 250 mL round bottom flask containing hydroxylactone **155** (3.36 g, 12.3 mmol) was added 62 mL of THF and the stirred solution was cooled to –78 °C. Ethynylmagnesium bromide (0.5 M solution in THF, 123 mL, 61.5 mmol) was added via syringe pump over one hour and the solution was then allowed to stir for five minutes at –78 °C before being warmed to 0 °C and stirred for another 25 min. The reaction was then quenched with *p*-nitrophenol (10.3 g, 73.8 mmol), and allowed to stir for 10 min, resulting in a bright yellow suspension. (2-Pyridyl)diphenylphosphine (6.48 g, 24.6 mmol) was then added, and the mixture was stirred for another 10 min before DIAD (4.8 mL, 25 mmol) was added dropwise via syringe. After stirring for 28 h, the mixture was concentrated *in vacuo*, taken up in 1 M *aq*. HCl, saturated with NaCl, and extracted with EtOAc (500 mL, then 2x250 mL). The combined organic layers were then washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a dark brown-orange oil. Purification via silica gel flash chromatography (gradient elution, 1:1→1:2 hexanes–EtOAc) afforded 2.25 g of alkynyl lactone **161** (65% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 5.34 (dd, J = 5.7, 2.3 Hz, 1H§), 5.30 (dd, J = 5.7, 2.3 Hz, 1H*), 4.96 (dd, J = 8.3, 5.7 Hz, 1H§), 4.85 (dd, J =

8.1, 5.6 Hz, 1H*), 4.61 (dd, *J* = 9.4, 1.7 Hz, 1H*), 4.56 (d, *J* = 9.0 Hz, 1H§), 4.15 (apt q, *J* = 7.2 Hz, 2H*, 2H§), 3.72 (s, 3H§), 3.70 (s, 3H*), 3.41 – 3.33 (m, 1H*, 1H§), 2.68 (d, *J* = 2.3 Hz, 1H*), 2.63 (d, *J* = 2.3 Hz, 1H§), 2.58 – 2.42 (m, 2H*, 2H§), 1.29 – 1.21 (m, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 175.5§, 175.3*, 170.6*, 170.6§, 155.0§, 154.5*, 77.9§, 77.6*, 75.8*, 75.6§, 72.9*, 72.8§, 61.8§, 61.8*, 61.0§, 60.3*, 59.9*, 59.7§, 53.3§, 52.6*, 44.4*, 43.5§, 32.0§, 31.2*, 13.8*, 13.8§; IR (NaCl/thin film): 3262, 2958, 2131, 1779, 1709, 1447, 1385, 1286, 1245, 1195, 1163, 1126, 1042, 1016, 987, 920, 893, 856, 765, 733 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{13}H_{16}NO_6$ $[M+H]^+$ 282.0972, found 282.0968.

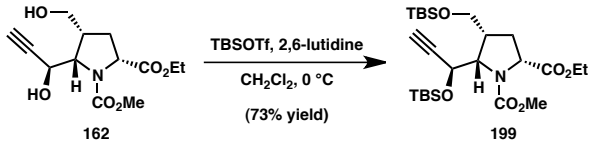
Preparation of diol 162



To a 500 mL round bottom flask containing alkynyl lactone **161** (2.04 g, 7.25 mmol) dissolved in 145 mL of EtOH, sodium borohydride (1.10 g, 29.0 mmol) was added and the reaction was stirred vigorously. Following completion of the reaction as judged by TLC (45 min), the reaction was cooled to 0 °C and quenched carefully with 60 mL of 1N *aq*. HCl. The solution was then saturated with NaCl, extracted with $CHCl_3$ (3x320 mL), then EtOAc (3x320 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification through silica gel flash chromatography (isocratic elution, 1:2 hexanes–EtOAc) afforded **162** as a colorless oil in 79% yield (1.64 g). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.2:1 mixture of

rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 4.68 (s, 1H§), 4.56 (s, 1H*), 4.44 – 4.27 (m, 2H*, 2H§), 4.27 – 4.15 (m, 2H*, 2H§), 4.03 (t, *J* = 10.7 Hz, 1H§), 3.92 (t, *J* = 10.2 Hz, 1H*), 3.81 – 3.72 (m, 1H*, 1H§), 3.69 (s, 3H*, 3H§), 2.61 (apt dp, *J* = 15.0, 7.5 Hz, 1H*, 1H§), 2.49 (s, 1H*), 2.49 (s, 1H§), 2.32 (apt dt, *J* = 12.8, 8.2 Hz, 1H*, 1H§), 2.10 (ddd, *J* = 12.1, 12.1, 12.1 Hz, 1H§), 1.99 (ddd, *J* = 11.5, 11.5, 11.5 Hz, 1H*), 1.27 (t, *J* = 7.1 Hz, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 174.7*, 173.7§, 156.0*, 155.9§, 83.1*,§, 74.8§, 74.2*, 63.3§, 62.6*, 61.9*, 61.7*, 61.7§, 61.5§, 60.8*,§, 59.3*, 59.1§, 53.1§, 52.7*, 44.4*, 43.8§, 32.0§, 30.9*, 14.0*,§; IR (NaCl/thin film): 3415, 3285, 2956, 2114, 1702, 1452, 1379, 1315, 1277, 1200, 1124, 1096, 1040, 918, 865, 819, 784, 769, 718 cm^{-1}; HRMS (ESI) calc'd for $C_{13}H_{20}NO_6$ $[M+H]^+$ 286.1285, found 286.1293.

Preparation of bis(*tert*-butyldimethylsilyl) ether 199

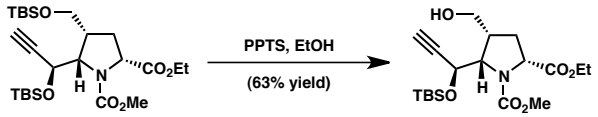


162 199

To a flame dried 250 mL round bottom flask equipped with diol **162** (1.62 g, 5.68 mmol) was added 57 mL of CH_2Cl_2 and the solution was cooled to 0 °C with stirring. Following addition of 2,6-lutidine (3.3 mL, 28 mmol), *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.3 mL, 14 mmol) was added dropwise to the reaction. Upon completion of the reaction as judged by TLC (~1 h), the reaction was quenched with a small amount of MeOH, diluted with EtOAc (180 mL), and washed with brine (180 mL). The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification through silica gel flash chromatography (isocratic elution, 6:1 hexanes–

EtOAc) afforded 2.13 g of **199** as a clear, colorless oil (73% yield). ^{1}H NMR (500 MHz, CD_3CN; compound exists as a 1:1 mixture of rotamers) δ 4.78 (s, 1H), 4.69 (s, 1H), 4.19 (t, *J* = 8.5 Hz, 2H), 4.15 – 4.00 (m, 6H), 3.91 (q, *J* = 4.9 Hz, 2H), 3.65 (s, 3H), 3.60 (s, 3H), 2.70 (s, 2H), 2.55 (dq, *J* = 14.1, 7.9 Hz, 2H), 2.45 – 2.24 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 6H), 0.90 (s, 18H), 0.90 (s, 18H), 0.15 – 0.11 (m, 12H), 0.05 (s, 12H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a 1:1 mixture of rotamers) δ 172.5, 172.1, 156.6, 118.3, 84.8, 77.2, 64.8, 64.2, 63.8, 63.0, 63.0, 63.0, 61.5, 61.4, 60.7, 60.3, 53.2, 45.5, 44.8, 34.5, 33.4, 26.4, 26.1, 19.0, 18.7, 14.7, -4.5, -5.0, -5.0; IR (NaCl/thin film): 3311, 3257, 2954, 2929, 2887, 2857, 2114, 1760, 1711, 1448, 1371, 1297, 1257, 1186, 1167, 1130, 1078, 1041, 1005, 993, 939, 838, 809, 778, 716 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{25}H_{48}NO_6Si_2$ $[M+H]^+$ 514.3015, found 514.3029.

Preparation of primary alcohol 163

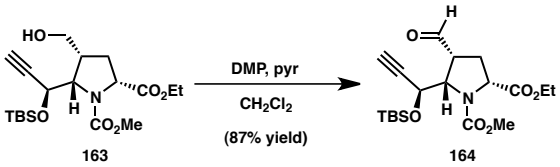


199 163

To a solution of bis(*tert*-butyldimethylsilyl) ether **199** (2.12 g, 4.13 mmol) in EtOH (41 mL) was added PPTS (1.04 g, 4.13 mmol), and the resulting solution was stirred for 14.5 h. The reaction mixture was then diluted with sat. *aq*. $NaHCO_3$ (20 mL) and brine (20 mL), then extracted with EtOAc (100 mL, then 3x50 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via silica gel flash chromatography (gradient elution, 4:1→1:2 hexanes–EtOAc) afforded **163** as a clear, colorless oil in 63% yield (1.04 g), along with 29% yield of recovered starting material (616 mg). ^{1}H NMR (500 MHz, CD_3CN; compound exists as a 1:1 mixture of rotamers) δ 4.84 (s, 1H), 4.75 (s, 1H), 4.24 – 4.16

(m, 2H), 4.16 – 4.06 (m, 6H), 3.99 (apt dd, J = 8.2, 3.7 Hz, 2H), 3.71 (apt dt, J = 11.4, 8.0 Hz, 2H), 3.65 (s, 3H), 3.60 (s, 3H), 3.07 – 2.99 (m, 2H), 2.73 (s, 2H), 2.67 – 2.55 (m, 2H), 2.31 – 2.17 (m, 4H), 1.21 (t, J = 7.2 Hz, 6H), 0.92 (s, 18H), 0.18 (s, 12H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a 1:1 mixture of rotamers) δ 172.3, 172.0, 156.5, 84.3, 77.5, 64.9, 64.2, 64.0, 63.2, 61.4, 61.4, 61.4, 60.5, 60.1, 53.1, 45.7, 45.0, 33.2, 32.2, 26.0, 18.7, 14.5, -4.8, -5.2, -5.2; IR (NaCl/thin film): 3506, 3255, 2955, 2932, 2888, 2858, 2114, 1759, 1709, 1450, 1372, 1301, 1255, 1190, 1125, 1068, 1041, 1009, 987, 939, 865, 834, 781, 715 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{19}H_{34}NO_6Si$ $[M+H]^+$ 400.2150, found 400.2148.

Preparation of aldehyde 164

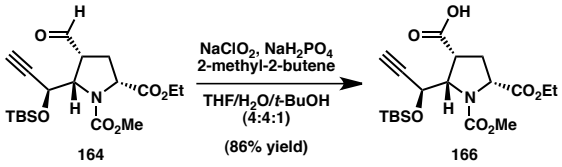


163 164

To a solution of primary alcohol **163** (1.04 g, 2.60 mmol) dissolved in 26 mL of CH_2Cl_2 (bulk solvent, not dried), was added pyridine (2.1 mL, 26 mmol), and Dess–Martin periodinane[24] (2.21 g, 5.20 mmol), and the cloudy white suspension was stirred vigorously. After 3 h, the reaction was quenched with sat. *aq*. $Na_2S_2O_3$ solution (30 mL) and sat. *aq*. $NaHCO_3$ solution (30 mL) and stirred vigorously for an additional 10 min. The layers were then separated and the aqueous layer was washed with EtOAc (2 x 100 mL). The combined organics were washed with sat. *aq*. $NaHCO_3$ solution (100 mL), then brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification through silica gel flash chromatography (isocratic elution, 3:1 hexanes–EtOAc) afforded **164** as a white amorphous solid in 87% yield (899 mg). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as

a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 10.07 (s, 1H*), 10.05 (s, 1H§), 4.96 (s, 1H*), 4.82 (s, 1H§), 4.41 – 4.32 (m, 1H*, 1H§), 4.32 – 4.25 (m, 1H*, 1H§), 4.25 – 4.12 (m, 2H*, 2H§), 3.75 (s, 3H§), 3.69 (s, 3H*), 3.15 – 3.06 (m, 1H*, 1H§), 2.91 (apt dq, J = 23.2, 12.0 Hz, 1H*, 1H§), 2.46 (s, 1H§), 2.44 (s, 1H*), 2.39 (dt, J = 14.1, 7.9 Hz, 1H*, 1H§), 1.26 (apt t, J = 7.1 Hz, 3H*, 3H§), 0.88 (s, 9H*, 9H§), 0.17 – 0.09 (m, 6H*, 6H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 198.3*, 198.2§, 170.8*, 170.5§, 155.4*, 155.2§, 82.7*, 82.4§, 76.8§, 76.4*, 64.6*, 63.9§, 62.8§, 62.0*, 61.1§, 61.0*, 59.4§, 59.1*, 53.2§, 53.1§, 53.0*, 52.4*, 30.1*, 29.0§, 25.5*,§, 18.0§, 18.0*, 14.2*, 14.2§, -5.0*,§, -5.4*, -5.5§; IR (NaCl/thin film): 3262, 2956, 2931, 2886, 2858, 2116, 1756, 1714, 1448, 1373, 1289, 1255, 1192, 1126, 1080, 1037, 1006, 987, 939, 864, 839, 780, 721 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{19}H_{32}NO_6Si$ $[M+H]^+$ 398.1993, found 398.1998.

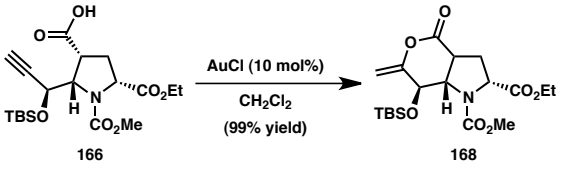
Preparation of carboxylic acid 166



Aldehyde **164** (60.0 mg, 0.151 mmol) was dissolved in a solution of 2-methyl-2-butene in THF (2.0 M, 1.2 mL, 2.4 mmol) and *tert*-butanol (0.3 mL) was added. To the resulting solution was added a solution of sodium chlorite (80 wt %, 25.7 mg, 0.227 mmol) and sodium dihydrogen phosphate monohydrate (62.5 mg, 0.453 mmol) in water (1.2 mL) via pipet with stirring. After 3 h, the reaction mixture was diluted with sat. *aq*. NH_4Cl, and extracted with EtOAc (3x4 mL). The combined organic layers were

subsequently washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (isocratic elution, 1:1 hexanes–EtOAc containing 1% AcOH) to afford carboxylic acid **166** (54.0 mg, 86% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 4.94 (s, 1H*), 4.82 (s, 1H§), 4.44 (dd, *J* = 7.8, 4.1 Hz, 1H*), 4.36 (t, *J* = 7.5 Hz, 2H§), 4.28 (t, *J* = 9.0 Hz, 1H*), 4.25 – 4.12 (m, 2H*, 2H§), 3.73 (s, 3H§), 3.70 (s, 3H*), 3.21 (dt, *J* = 13.8, 7.7 Hz, 1H*, 1H§), 2.91 (ddd, *J* = 12.2, 12.2, 12.2 Hz, 1H*), 2.84 (ddd, *J* = 12.1, 12.1, 11.8 Hz, 1H§), 2.57 – 2.47 (m, 1H*, 1H§), 2.45 (d, *J* = 2.2 Hz, 1H*, 1H§), 1.26 (t, *J* = 7.1 Hz, 3H*, 3H§), 0.88 (s, 9H*, 9H§), 0.18 – 0.10 (m, 6H*, 6H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 174.2, 173.9, 170.7, 170.4, 155.6, 81.8, 81.7, 76.1, 63.4, 63.0, 63.0, 62.6, 61.1, 58.7, 58.5, 53.0, 52.9, 45.3, 44.7, 31.6, 30.3, 25.6, 18.1, 14.2, -4.9, -5.4; IR (NaCl/thin film): 3270, 2956, 2929, 2117, 1712, 1451, 1381, 1252, 1189, 1090, 1031, 1003, 939, 891, 839, 779 cm^{-1}; HRMS (ESI) calc'd for $C_{19}H_{32}NO_7Si$ $[M+H]^+$ 414.1943, found 414.1946.

Preparation of enol lactone 168

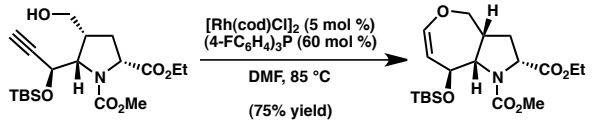


166 168

Carboxylic acid **166** (18.7 mg, 45.2 μmol) was dissolved in CH_2Cl_2 (230 μL) and AuCl (1.1 mg, 4.52 μmol) was added. The resulting solution was stirred for 5 min, then filtered through SiO_2 (eluting with 1:1 hexanes–EtOAc) and concentrated *in vacuo* to afford 18.5 mg of enol lactone **168** (99% yield). ^{1}H NMR (500 MHz, $CDCl_3$; compound

exists as a 2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 5.00 (s, 1H*), 4.91 – 4.80 (m, 1H*, 1H§), 4.71 – 4.58 (m, 1H*, 2H§), 4.42 (br s, 1H§), 4.37 (br s, 2H*), 4.20 – 4.10 (m, 2H*, 2H§), 4.07 (dd, *J* = 7.4, 3.4 Hz, 1H*, 1H§), 3.77 (s, 3H§), 3.70 (s, 3H*), 3.44 – 3.34 (m, 1H*, 1H§), 2.61 – 2.36 (m, 2H*, 2H§), 1.24 (t, *J* = 7.1 Hz, 3H*, 3H§), 0.87 (s, 9H*, 9H§), 0.18 – 0.07 (m, 6H*, 6H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 170.8, 168.9, 155.4, 153.7, 110.0, 98.5, 98.3, 69.0, 66.8, 62.4, 62.3, 61.5, 60.1, 59.8, 53.2, 53.0, 42.2, 41.0, 32.7, 32.0, 29.7, 25.6, 18.0, 14.0, -5.0, -5.1; IR (NaCl/thin film): 2955, 2929, 2857, 1757, 1718, 1669, 1448, 1375, 1260, 1217, 1192, 1131, 1087, 1044, 1003, 967, 939, 866, 839, 779 cm^{-1}; HRMS (ESI) calc'd for $C_{13}H_{18}NO_7$ $[M–C_6H_{15}OSi+H_2O]^+$ 300.1078, found 300.1086 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion and gain of water).

Preparation of tetrahydrooxepine 169

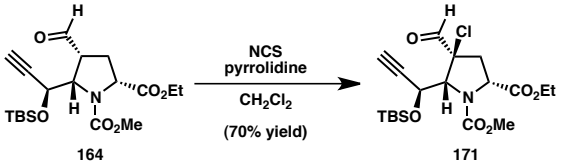


163 169

Alcohol **163** (28.7 mg, 71.8 μmol) was dissolved in dry, degassed DMF (360 μL) and transferred via syringe to a microwave vial equipped with a magnetic stir bar and sealed with a septum cap under an N_2 atmosphere. A stock solution of $[Rh(cod)Cl]_2$ (0.01 M) and $(4\text{-}FC_6H_4)_3P$ (0.12 M) in dry, degassed DMF (360 μL) was added, and the resulting solution was heated with stirring to 85 °C in an oil bath. After 22 h, the reaction mixture was cooled to rt, diluted with sat. *aq*. $NaHCO_3$, and extracted with EtOAc (5x5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*, and the resulting material was purified via silica gel flash chromatography

(gradient elution, 5:1→4:1 hexanes–EtOAc, the SiO_2 was deactivated using 0.5 % Et_3N in 5:1 hexanes–EtOAc) to afford 21.5 mg of tetrahydrooxepine **169** (75% yield) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 6.06 (s, 2H), 4.93 – 4.42 (m, 3H), 4.34 (s, 1H), 4.25 – 4.11 (m, 3H), 3.84 (dd, *J* = 12.3, 7.0 Hz, 1H), 3.68 (s, 3H), 2.75 (s, 1H), 2.38 – 1.97 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 172.1, 156.4, 155.8, 147.0, 146.4, 105.7, 104.9, 68.8, 68.5, 68.1, 67.7, 67.3, 66.6, 60.9, 60.1, 60.0, 52.6, 41.4, 40.5, 30.8, 29.9, 25.8, 17.9, 14.1, -4.7, -5.0; IR (NaCl/thin film): 3054, 2954, 2929, 2894, 2856, 1754, 1707, 1648, 1448, 1375, 1336, 1301, 1291, 1257, 1190, 1126, 1099, 1038, 1004, 939, 918, 900, 871, 837, 777 cm^{-1}; HRMS (ESI) calc'd for $C_{13}H_{18}NO_5$ $[M–C_6H_{15}OSi]^+$ 268.1180, found 268.1186 (detected fragment has undergone loss of *tert*-butyldimethylsilylanolate anion).

Preparation of chloroaldehyde 171

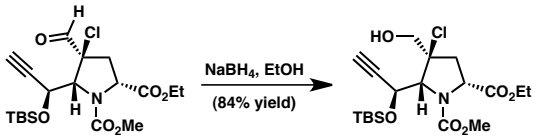


164 171

To a solution of aldehyde **164** (283 mg, 0.712 mmol) in CH_2Cl_2 (7 mL, bulk solvent, not dried) was added pyrrolidine (60 μL, 0.712 mmol) followed by *N*-chlorosuccinimide (143 mg, 1.07 mmol). The resulting solution was stirred under an air atmosphere for 2.5 h, and was subsequently quenched with sat. *aq*. $Na_2S_2O_3$. The resulting mixture was extracted with CH_2Cl_2 (8 mL, then 2x15 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via silica gel flash chromatography (gradient elution, 8:1→4:1 hexanes–EtOAc) afforded 215 mg of

chloroaldehyde **171** (70% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 9.64 (s, 1H*), 9.62 (s, 1H§), 4.92 (dd, *J* = 5.0, 2.3 Hz, 1H*), 4.79 (dd, *J* = 5.0, 2.3 Hz, 1H§), 4.66 (dd, *J* = 10.8, 7.3 Hz, 1H§), 4.58 (dd, *J* = 10.8, 7.1 Hz, 1H*), 4.48 (d, *J* = 4.5 Hz, 1H*), 4.38 (d, *J* = 4.5 Hz, 1H§), 4.27 – 4.14 (m, 2H*, 2H§), 3.78 (s, 3H§), 3.74 (s, 3H*), 3.46 (dd, *J* = 14.4, 10.8 Hz, 2H*), 3.42 (dd, *J* = 14.5, 10.9 Hz, 1H§), 2.52 – 2.43 (m, 2H*, 2H§), 1.27 (t, *J* = 7.1 Hz, 2H*, 2H§), 0.89 (s, 9H*, 9H§), 0.15 (s, 6H*, 6H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 187.7*, 187.6§, 170.1*, 169.8§, 155.5*, 155.2§, 128.9*, 128.6§, 80.9*, 80.6§, 77.7§, 77.6*, 74.3*, 73.7§, 63.0§, 62.3*, 61.4§, 61.3*, 58.3§, 58.0*, 53.3§, 53.3*, 39.0*, 37.9§, 25.5*, 25.5§, 18.0§, 18.0*, 14.2*, 14.1§, -5.0§, -5.1*, -5.5*, -5.5§; IR (NaCl/thin film): 3263, 2956, 2930, 2885, 2859, 2116, 1762, 1719, 1448, 1371, 1307, 1255, 1198, 1165, 1134, 1082, 1033, 1006, 988, 939, 860, 838, 782, 726 cm^{-1}; HRMS (ESI) calc'd for $C_{14}H_{19}ClNO_6$ $[M–C_6H_{15}OSi+MeOH]^+$ 332.0895, found 332.0900 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion and gain of methanol).

Preparation of chlorohydrin 172

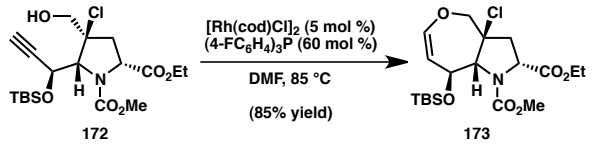


171 172

A solution of chloroaldehyde **171** (215 mg, 0.498 mmol) in EtOH (5 mL) was treated with $NaBH_4$ (75.3 mg, 1.99 mmol). After 15 min, the reaction mixture was cooled to 0 °C and slowly quenched with 1 M *aq*. HCl (15 mL). The mixture was then diluted

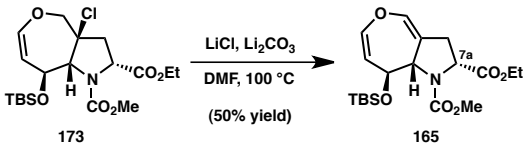
with brine (5 mL), and further saturated with solid NaCl, then extracted with $CHCl_3$ (3x15 mL) followed by EtOAc (3x15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via silica gel flash chromatography (gradient elution, 4:1→2:1 hexanes–EtOAc) afforded 182 mg of chlorohydrin **172** (84% yield) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 4.97 (dd, *J* = 4.3, 2.3 Hz, 1H*), 4.85 (dd, *J* = 4.1, 2.3 Hz, 1H§), 4.66 (dd, *J* = 10.6, 7.4 Hz, 1H§), 4.58 (dd, *J* = 10.5, 7.2 Hz, 1H*), 4.44 – 4.38 (m, 1H*, 1H§), 4.34 (dd, *J* = 4.3, 1.3 Hz, 1H*), 4.26 (dd, *J* = 4.2, 1.3 Hz, 1H§), 4.25 – 4.14 (m, 2H*, 2H§), 3.93 (dd, *J* = 12.8, 10.3 Hz, 1H*, 1H§), 3.76 (s, 3H§), 3.73 (s, 3H*), 3.54 (dd, *J* = 11.2, 3.9 Hz, 1H*), 3.45 (dd, *J* = 10.8, 4.1 Hz, 1H§), 2.88 (dd, *J* = 13.7, 10.6 Hz, 1H*), 2.85 (dd, *J* = 14.0, 10.7 Hz, 1H§), 2.57 – 2.49 (m, 2H*, 2H§), 1.26 (t, *J* = 7.2 Hz, 3H§), 1.26 (t, *J* = 7.2 Hz, 3H*), 0.94 (s, 9H*, 9H§), 0.22 (s, 3H*), 0.22 (s, 3H*), 0.20 (s, 6H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 170.6*, 170.3§, 155.6*, 155.3§, 81.7*, 81.3§, 80.3§, 79.4*, 77.2§, 76.8*, 73.3*, 72.9§, 65.8*,§, 63.9§, 63.1*, 61.2§, 61.1*, 58.5§, 58.1*, 53.2§, 53.2*, 41.0*, 39.8§, 25.6*, 25.6§, 18.1§, 18.1*, 14.2*, 14.2§, -5.1§, -5.2*, -5.4*, -5.5§; IR (NaCl/thin film): 3486, 3255, 2955, 2930, 2858, 2112, 1761, 1714, 1448, 1371, 1308, 1254, 1194, 1156, 1140, 1082, 862, 838, 782 cm^{-1}; HRMS (ESI) calc'd for $C_{19}H_{33}ClNO_6Si$ $[M+H]^+$ 434.1760, found 434.1764.

Preparation of chlorotetrahydroxepine 173



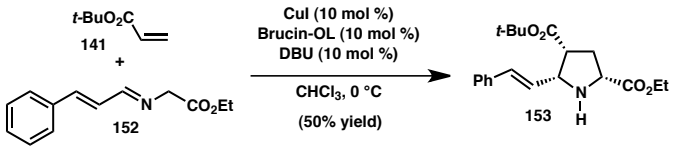
Chlorohydrin **172** (53.0 mg, 0.122 mmol) was dissolved in dry, degassed DMF (0.61 mL) and transferred via syringe to a Schlenk tube equipped with a magnetic stir bar and sealed with a septum cap under an N_2 atmosphere. A stock solution of $[Rh(cod)Cl]_2$ (0.01 M) and $(4\text{-}FC_6H_4)_3P$ (0.12 M) in dry, degassed DMF (0.61 mL) was added. The resulting yellow solution was degassed using the freeze-pump-thaw technique. The vessel was sealed and the solution frozen by submersion in a bath of liquid N_2. The vessel was then placed under vacuum for approximately five minutes before once again being sealed and allowed to thaw under static vacuum by removal from the liquid N_2 bath. This procedure was repeated twice before the head-space was finally backfilled with N_2, the vessel sealed, and the solution heated to 85 °C with stirring. After 25 h, the reaction mixture was cooled to rt, diluted with sat. *aq*. $NaHCO_3$ (10 mL), and extracted with EtOAc (5x5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*, and the resulting material was purified via silica gel flash chromatography (gradient elution, 8:1→6:1 hexanes–EtOAc) to afford 45.0 mg of chlorotetrahydrooxepine **173** (85% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 6.21 – 6.04 (m, 1H), 5.20 – 4.30 (m, 5H), 4.29 – 4.13 (m, 2H), 4.09 (d, *J* = 12.8 Hz, 1H), 3.72 (s, 3H), 2.77 – 2.42 (m, 1H), 2.52 (dd, *J* = 13.4, 7.5 Hz, 1H), 1.27 (apt q, *J* = 7.9, 7.5 Hz, 3H), 0.90 (s, 9H), 0.19 – 0.04 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 171.6, 145.7, 129.0, 128.6, 68.3, 61.3, 59.0, 58.7, 53.0, 40.4, 39.6, 25.7, 17.9, 14.2, -4.7, -5.1; IR (NaCl/thin film): 2954, 2929, 2856, 1752, 1710, 1647, 1447, 1373, 1340, 1263, 1194, 1130, 1035, 902, 871, 838, 777, 720 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{13}H_{17}ClNO_5$ $[M–C_6H_{15}OSi]^+$ 302.0790, found 302.0797.

Preparation of dihydrooxepine 165



A suspension of chlorotetrahydrooxepine **173** (8.7 mg, 20 μmol), LiCl (17.0 mg, 0.402 mmol), and Li_2CO_3 (59.4 mg, 0.804 mmol) in dry DMF (270 μL) was stirred vigorously at 100 °C for 48 h. After cooling to rt, the reaction mixture was diluted with Et_2O (to precipitate lithium salts), filtered (rinsing with EtOAc), further diluted with Et_2O, and filtered a second time. The resulting solution was concentrated *in vacuo*, then purified via silica gel flash chromatography (gradient elution, 12:1→10:1 hexanes–EtOAc) to afford 4.0 mg of dihydrooxepine **165** (50% yield) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 6.12 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.80 (br s, 1H), 4.71 (d, *J* = 8.2 Hz, 1H), 4.59 (br s, 1H), 4.42 (d, *J* = 7.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 2.95 (dd, *J* = 15.1, 9.8 Hz, 1H), 2.60 (d, *J* = 15.1 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 138.0, 135.8, 111.2 (br), 71.2 (br), 63.5, 61.2, 58.5, 52.8, 33.6 (br), 25.8, 18.0, 14.2, -4.8 (br), -5.4 (br); IR (NaCl/thin film): 2953, 2929, 2855, 1749, 1705, 1654, 1446, 1369, 1340, 1301, 1285, 1250, 1182, 1141, 1101, 1066, 1032, 970, 898, 874, 838, 771, 742 cm^{-1}; HRMS (ESI) calc'd for $C_{13}H_{16}NO_5$ [M– $C_6H_{15}OSi$]$^+$ 266.1023, found 266.1024 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion).

Enantioselective preparation of styrenyl pyrrolidine 153 (published procedure)



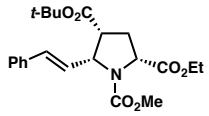
Generation of brucin-OL catalyst solution: To a flame dried 2 L three neck round bottom flask was added brucin-OL (1.50 g, 3.50 mmol) and CuI (667 mg, 3.50 mmol). The solids were then evacuated under vacuum, backfilled under N_2 atmosphere, cooled to 0 °C for 10 min, and then suspended in 74 mL of $CHCl_3$ and stirred for 24 h at 0 °C. Note: brucin-OL was prepared according to the method of Oh and co-workers.[28]

Generation of imine 152: In a separate 250 mL flame dried round bottom flask, ethyl glycinate hydrochloride (7.33 g, 52.5 mmol) and 20 g of $MgSO_4$ were suspended in 70 mL of $CHCl_3$. To the stirred suspension was added Et_3N (7.3 mL, 52 mmol) and the mixture was allowed to stir for 20 min after which *trans*-cinnamaldehyde (4.4 mL, 35 mmol) was added. After the mixture was stirred for an additional 1.5 h, the $MgSO_4$ was removed by vacuum filtration, and the resulting solution was washed with H_2O (5 x 70 mL) and 70 mL of sat. *aq*. brine solution. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting yellow-green oil was dissolved in 35 mL of $CHCl_3$ and cooled to 0 °C.

(1, 3)-Dipolar cycloaddition reaction: Following generation of the catalyst for 24 h, 1,8-diazabicycloundec-7-ene (520 μL, 3.5 mmol) was added to the brucin-OL catalyst suspension and it was allowed to stir for 15 min at 0 °C. To the resulting green solution was added *t*-butyl acrylate (7.7 mL, 53 mmol), followed by dropwise addition via cannula of the cooled solution of imine **152** in $CHCl_3$ over approximately 15 min. The brown solution was allowed to stir at 0 °C for 24 h after which the reaction was diluted with EtOAc (700 mL), washed with 5% NH_4OH solution (1 x 200 mL, followed by 2 x 100 mL), and sat. *aq*. Na_2SO_3 solution (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a brown oil. Purification through silica gel flash

chromatography (gradient elution, 9:1→1:1 hexanes–EtOAc with 0.5% Et_3N) afforded 6.07 g (50% yield) of **153** as a yellow oil. Spectroscopic data for this product were identical to those described for the corresponding racemic material; $[\alpha]_D^{25.0} = +31.1°$ (*c* = 1.15, $CHCl_3$) (96% ee, as assessed by conversion to the corresponding methyl carbamate **198**, as described above). Note: On scale up, it was found that *tert*-butylcarbonyl (Boc) protection of pyrrolidine **153** to furnish **200** resulted in less cumbersome chromatographic separations. *t*-Butyl carbamate **200** could subsequently be subjected to TFA, Et_3SiH, DCM as described to yield trifluoroacetate salt **178** (see below). Additionally, an improved cycloaddition procedure was ultimately identified (see below), which resulted in more reproducible results on large scale, and obviated the need for conversion to **200** for the purposes of purification.

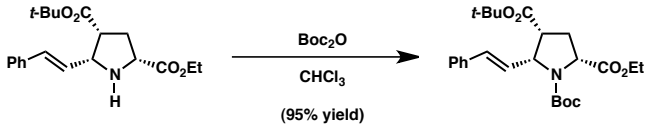
Methyl carbamate 198 (96% *ee*)



198

$[\alpha]_D^{25.0} = +21.9°$ (*c* = 0.41, $CHCl_3$); HPLC **(**Chiracel AD); 5% isopropanol/hexanes; flow rate = 1.0 mL/min; t_r (major ent.) = 15.3 min, t_r (minor ent.) = 21.4 min.

Preparation of *tert*-butyl carbamate 200

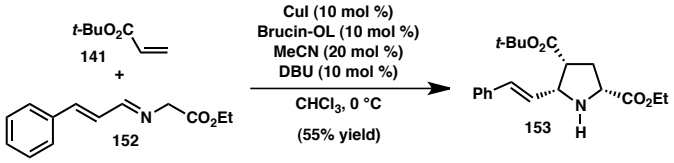


153 200

In order to achieve less cumbersome chromatographic separations and improved material purity on scale up, crude mixtures of pyrrolidine **153** were converted to *t*-butyl carbamate **200** (following initial silica gel chromatography as described above to remove

excess reagents/major impurities). Crude pyrrolidine **153** (25.0 g, 72.4 mmol) was dissolved in $CHCl_3$ (220 mL) and di-*tert*-butyl dicarbonate (17.4 g, 79.7 mmol) was added with stirring. After 1 h, the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via silica gel flash chromatography (isocratic elution, 7:1 hexanes:EtOAc) to afford *tert*-butyl carbamate **200** (30.6 g, 95% yield). Note: although attempts were made to advance crude pyrrolidine **153** directly to trifluoroacetate salt **178** in order to avoid chromatography, it was observed that the purity of **153** greatly influenced the isolated yield of **178**. On large scale, the above procedure allowed sufficiently pure material to be obtained more readily than by direct chromatography of pyrrolidine **153**. $[\alpha]_D^{25.0}$ = +28.6° (*c* = 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 7.34 (d, *J* = 7.5 Hz, 4H), 7.32 – 7.15 (m, 6H), 6.77 (d, *J* = 15.7 Hz, 1H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.14 (dd, *J* = 15.7, 8.2 Hz, 2H), 4.83 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.66 (dd, *J* = 8.2, 8.2 Hz, 1H), 4.30 – 4.13 (m, 6H), 3.24 – 3.13 (m, 2H), 2.44 – 2.29 (m, 4H), 1.40 (s, 18H), 1.34 (s, 9H), 1.34 (s, 9H), 1.32 – 1.25 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 172.5, 172.2, 168.8, 168.7, 153.7, 152.9, 146.7, 136.6, 133.4, 133.3, 128.5, 128.3, 127.5, 127.4, 126.6, 126.3, 125.1, 124.7, 85.1, 81.4, 81.4, 80.4, 80.3, 61.7, 61.2, 61.0, 59.0, 58.6, 48.3, 47.8, 30.4, 29.6, 28.3, 28.2, 28.0, 27.3, 14.2, 14.1; IR (NaCl/thin film): 2979, 2933, 1810, 1731, 1702, 1478, 1457, 1392, 1369, 1290, 1252, 1185, 1119, 1076, 960, 847, 757, 694 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{20}H_{28}NO_4$ $[M–C_4H_8–CO_2+H]^+$ 346.2013, found 346.2019 (detected fragment has undergone elimination of *iso*-butylene and CO_2 from the Boc protecting group).

Enantioselective preparation of styrenyl pyrrolidine 153 (improved procedure)



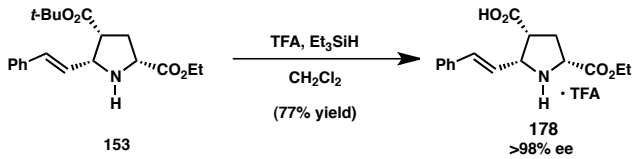
Preparation of ethyl glycinate: ethyl glycinate hydrochloride salt (29.3 g, 210 mmol) was suspended in 150 mL of DCM and 3.56 M KOH (77 mL, 273 mmol) was added with vigorous swirling. The layers were separated, and the aqueous layer was further extracted with DCM (2 x 80 mL), dried over MgSO4, and concentrated to yield 12.1 g (56% yield) of the free amine. The amine was used immediately to avoid dimerization.

Generation of imine 152: The free amine (12.1 g, 117 mmol) was dissolved in 235 mL $CHCl_3$. Silica gel (35.1 g, 0.3 g SiO_2 per mmol substrate) was added and the resulting suspension was cooled to 0 °C while open to the atmosphere. *trans*-Cinnamaldehyde (14.7 mL, 117 mmol) was added dropwise and the reaction was left to stir at 0°C for an additional 3.5 hours, during which it turned from colorless to bright yellow. The silica gel was removed via filtration and rinsed with 50 mL $CHCl_3$, and the resulting imine solution was used immediately to avoid decomposition.

(1,3)-Dipolar cycloaddition reaction: A round-bottom flasked was charged with CuI (2.23 g, 11.7 mmol), BrucinOL (5.01 g, 11.7 mmol), and 235 mL of $CHCl_3$. The resulting suspension was cooled to 0 °C under air, and MeCN (1.22 mL, 23.4 mmol) was added dropwise and with stirring. After a five minute prestir, DBU (1.75 mL, 11.7 mmol) was added and the solution was stirred vigorously for twenty minutes during which it went from a cloudy brown to a dark green. *tert*-Butyl acrylate (25.8 mL, 176 mmol) was

then added, followed by the solution of imine **152** (precooled to 0 °C and transferred via cannula over 5 min). After 5 h, the reaction mixture was loaded directly onto SiO_2 and subjected to flash chromatography (gradient elution, 5:1→1:1 hexanes–EtOAc with 0.5% Et_3N) to afford 22.4 g (55% yield) of **153** as an orange oil (97% *ee*, as assessed by conversion to the corresponding methyl carbamate **198**, as described above).

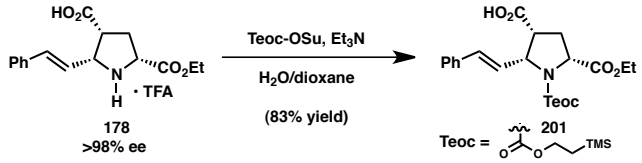
Preparation of pyrrolidinium trifluoroacetate salt 178



Pyrrolidine **153** (5.43 g, 15.7 mmol) was dissolved in 56 mL of CH_2Cl_2 in a flame dried 250 mL round bottom flask. To the solution was added Et_3SiH (12.5 mL, 78.5 mmol) followed by trifluoroacetic acid (23 mL) and the solution was allowed to stir overnight. The solution was then concentrated *in vacuo*, redissolved in $CHCl_3$ and azeotroped (3x), and subsequently azeotroped from toluene (3x). Upon further addition of toluene and $CHCl_3$, white crystals crashed out of solution and were isolated by vacuum filtration to afford **178**. The mother liquor was concentrated *in vacuo* and crystallized further from toluene and $CHCl_3$, producing additional crops of **178** (over several iterations). Further recrystallization from hot $CHCl_3$ affords 4.87 g (77% yield) of **178** as a white solid (>98% *ee*, as assessed by conversion to the methyl ester **202** following protection as the trimethylsilylethyl carbamate, as described below). Note: *t*-butyl carbamate **200** could also be subjected to the conditions described above to afford trifluoroacetate salt **178**. $[\alpha]_D^{25.0} = -63.3°$ (*c* = 0.70, $CHCl_3$); mp 108–111 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 10.34 (s, 1H), 7.42 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.38 – 7.30 (m, 3H),

6.85 (d, J = 15.8 Hz, 1H), 6.28 (dd, J = 8.9, 15.8 Hz, 1H), 4.66 – 4.60 (m, 2H), 4.20 – 4.30 (m, 2H), 3.36 (ddd, J = 7.3, 7.3, 4.2 Hz, 1H), 2.70 (ddd, J = 14.0, 10.7, 7.5 Hz, 1H), 2.54 (ddd, J = 14.0, 5.7, 4.3 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.8, 169.8, 161.8 (q, $J_{C\text{-}F}$ = 35.1 Hz), 138.9, 136.3, 129.9, 129.8, 127.8, 120.1, 117.6 (q, $J_{C\text{-}F}$ = 293.0 Hz), 65.1, 64.0, 58.9, 47.4, 31.6, 14.2; IR (NaCl/thin film): 3189, 2981, 2913, 2730, 2532, 1726, 1661, 1652, 1565, 1474, 1436, 1251, 1189, 1137, 973, 798, 746, 691 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{16}H_{20}NO_4$ [M–$C_2O_2F_3$]$^+$ 290.1387, found 290.1381 (detected cation does not include the trifluoroacetate counterion).

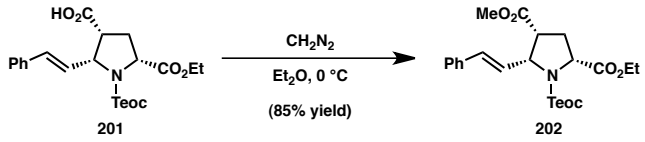
Preparation of trimethylsilylethyl carbamate 201



Trifluoroacetate salt **178** (7.93 g, 19.7 mmol) was suspended in 39 mL of H_2O and 39 mL of dioxane in a 250 mL round bottom flask. 1-[2-(Trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (7.64 g, 29.5 mmol) and Et_3N (8.2 mL, 59 mmol) were added to the stirred suspension and the reaction mixture was allowed to stir overnight. The reaction mixture was then acidified with sat. *aq*. $NaHSO_4$ solution, extracted with EtOAc (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a faint yellow oil. Purification through silica gel flash chromatography (isocratic elution, 30:1 CH_2Cl_2–MeOH) afforded 7.10 g of **201** as a colorless oil (83% yield). $[\alpha]_D^{25.0}$ = –6.0° (c = 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 7.39 – 7.31 (m, 4H), 7.28 – 7.24 (m, 1H), 6.80 (d, J = 15.8

Hz, 1H), 6.17 (dd, *J* = 15.8, 7.5 Hz, 1H), 4.80 (dd, *J* = 7.3, 7.3 Hz, 1H), 4.32 – 4.23 (m, 1H), 4.23 – 4.15 (m, 2H), 4.15 – 4.06 (m, 2H), 3.40 – 3.30 (m, 1H), 2.48 – 2.37 (m, 1H), 2.34 – 2.17 (m, 1H), 1.29 – 1.23 (m, 3H), 0.98 – 0.89 (m, 2H), 0.02 and 0.00 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 173.4, 173.1, 171.3, 171.3, 155.7, 154.9, 137.7, 133.7, 133.6, 129.7, 128.7, 127.3, 126.5, 126.4, 64.4, 64.3, 62.1, 62.0, 61.9, 61.7, 59.9, 59.7, 48.0, 47.4, 31.4, 30.4, 18.3, 14.5, –1.5, –1.5; IR (NaCl/thin film): 3059, 2982, 2954, 2900, 1745, 1705, 1668, 1404, 1349, 1284, 1250, 1186, 1114, 1075, 1061, 1038, 960, 860, 838, 740, 694 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{20}H_{28}NO_6Si$ $[M–C_2H_4+H]^+$ 406.1680, found 406.1689 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

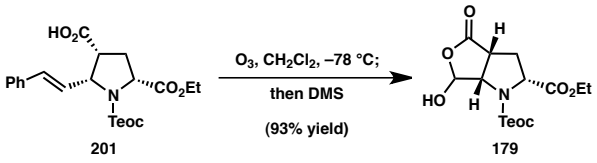
Preparation of methyl ester 202



In order to determine the extent of enantioenrichment resulting from crystallization of trifluoroacetate salt **178**, an aliquot of material was protected as the trimethylsilylethyl carbamate (**201**) as described above, then converted to methyl ester **202**. Carboxylic acid **201** (18.1 mg, 41.7 μmol) was dissolved in Et_2O (0.42 mL) and cooled to 0 °C with stirring. A solution of diazomethane in Et_2O was titrated into the reaction solution until a yellow color persisted. After 5 min, excess diazomethane was quenched by dropwise addition of AcOH (until the yellow color no longer persisted). The resulting solution was diluted with Et_2O (2 mL) and 10% aqueous K_2CO_3 (2 mL), the phases were separated, and the aqueous layer was further extracted with Et_2O (2 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*

to afford methyl ester **202** (15.9 mg, 85% yield) as a clear, colorless oil. $[\alpha]_D^{25.0} = -5.9°$ (*c* = 0.87, $CHCl_3$); ^1H NMR (500 MHz, CD_3CN; compound mixture of rotamers) δ 7.38 – 7.31 (m, 4H), 7.28 – 7.24 (m, 1H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.11 (dd, *J* = 15.8, 7.4 Hz, 1H), 4.79 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.33 – 4.24 (m, 1H), 4.24 – 4.15 (m, 2H), 4.15 – 4.06 (m, 2H), 3.59 (s, 3H), 3.43 – 3.33 (m, 1H), 2.50 – 2.39 (m, 1H), 2.37 – 2.31 (m, 1H) 1.30 – 1.22 (m, 3H), 0.98 – 0.89 (m, 2H), 0.01 and 0.00 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 173.4, 173.1, 171.2, 171.1, 155.7, 154.8, 137.6, 133.6, 133.5, 129.6, 128.8, 127.3, 126.7, 64.4, 64.3, 62.3, 62.0, 61.9, 61.8, 60.0, 59.7, 52.5, 48.3, 47.7, 31.4, 30.4, 18.3, 14.5, –1.5, –1.6; IR (NaCl/thin film): 2952, 1740, 1701, 1451, 1409, 1374, 1343, 1285, 1250, 1186, 1109, 1031, 860, 837, 750 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{21}H_{30}NO_6Si$ $[M–C_2H_4+H]^+$ 420.1837, found 420.1845 (detected fragment has undergone elimination of ethylene from the Teoc protecting group); HPLC (Chiracel OD); 5% isopropanol/hexanes; flow rate = 1.0 mL/min; t_r (major ent.) = 21.6 min, t_r (minor ent.) = 13.2 min.

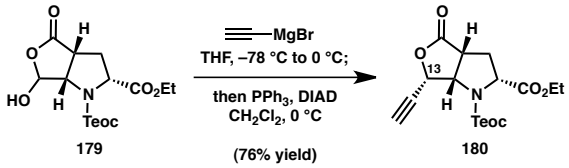
Preparation of hydroxylactone 179



A solution of styrenyl carboxylic acid **201** (1.93 g, 4.45 mmol) in 45 mL of CH_2Cl_2 was cooled to –78 °C in a flame dried three-neck round bottom flask. Ozone was bubbled through the cooled solution until the solution turned bright blue. The solution was then sparged with Oxygen (until the blue color no longer persisted), warmed to room temperature, and sparged with nitrogen for 15 min, at which point dimethylsulfide (13.1

mL, 178 mmol) was added and the solution was stirred overnight. The pale yellow solution was then concentrated *in vacuo* to afford a pale yellow oil. Purification by silica gel flash chromatography (gradient elution, 2:1→3:2 hexanes–EtOAc) afforded 1.49 g of **179** as a colorless oil (93% yield). $[\alpha]_D^{25.0}$ = –42.4° (*c* = 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO, 60 °C) δ 7.69 (s, 1H), 5.72 (s, 1H), 4.43 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.22 (d, *J* = 7.3 Hz, 1H), 4.19 – 4.10 (m, 2H), 4.12 – 3.99 (m, 2H), 3.51 (dd, *J* = 8.1, 8.1 Hz, 1H), 2.69 – 2.55 (m, 1H), 2.20 (d, *J* = 13.3 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.09 – 0.84 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (101 MHz, DMSO, 60 °C) δ 176.6, 170.9, 153.4, 101.2 (br), 100.5 (br), 65.1 (br), 64.8 (br), 63.2, 60.6, 58.7 (br), 58.5 (br), 58.4 (br), 42.8 (br), 41.8 (br), 31.0, 30.9 (br), 30.0 (br), 28.0, 21.8, 17.1 (br), 13.5, 13.4, –1.8; IR (NaCl/thin film): 3380, 2957, 2901, 1783, 1747, 1706, 1682, 1417, 1347, 1251, 1198, 1119, 1038, 944, 860, 839, 773, 696, 620 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{15}H_{24}NO_7Si$ $[M–H]^-$ 358.1328, found 358.1309.

Preparation of alkynyl lactone 180

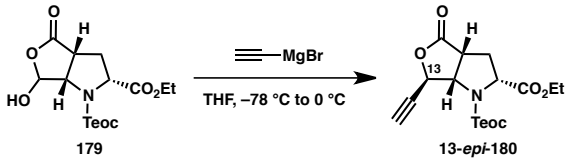


To a flame dried 250 mL round bottom flask containing hydroxylactone **179** (2.69 g, 7.48 mmol) was added 37 mL of THF and the stirred solution was cooled to –78 °C. Ethynylmagnesium bromide (0.5 M solution in THF, 75.0 mL, 37.4 mmol) was added via syringe pump over one hour and the solution was then allowed to stir for five minutes at –78 °C before being warmed to 0 °C and stirred for another 20 min. The reaction was then quenched with 20 mL of sat. *aq*. $NaHCO_3$ solution and the reaction mixture was

concentrated *in vacuo*. Following dilution with CH_2Cl_2 (500 mL) the mixture was acidified to pH = 2.5 with $Na_2HPO_4/KHSO_4$ buffer (pH = 2.5, prepared from a 10% w/v *aq*. Na_2HPO_4 solution by acidification with $KHSO_4$). The mixture was then further diluted with CH_2Cl_2 and NaCl was added to further saturate the aqueous phase. The phases were separated and the aqueous layer was washed twice with CH_2Cl_2. The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a volume of 300 mL (0.025 M solution, achieved by marking the flask for the desired volume prior to use). The solution was then cooled to 0 °C and triphenylphosphine (5.88 g, 22.4 mmol) was added and allowed to stir for 10 min. Diisopropylazodicarboxylate (3.0 mL, 15 mmol) was then added to the reaction and it was allowed to stir while warming to room temperature overnight. The orange solution was then concentrated *in vacuo* to yield an orange oil. Purification by silica gel flash chromatography (gradient elution, 3:1→1:1 hexanes–EtOAc) afforded **180** as a colorless oil in 76% yield (2.08 g). $[\alpha]_D^{25.0} = -73.0°$ (*c* = 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 5.33 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.29 (dd, *J* = 5.7, 2.0 Hz, 1H), 4.96 (dd, *J* = 8.0, 6.1 Hz, 1H), 4.85 (dd, *J* = 8.0, 6.1 Hz, 1H), 4.61 (d, *J* = 8.7 Hz, 1H), 4.56 (d, *J* = 9.0 Hz, 1H), 4.27 – 4.06 (m, 4H), 4.14 (q, *J* = 7.2 Hz, 4H), 3.40 – 3.32 (m, 2H), 2.65 (d, *J* = 2.0 Hz, 1H), 2.60 (d, *J* = 2.0 Hz, 1H), 2.56 – 2.41 (m, 4H), 1.29 – 1.19 (m, 6H), 1.04 – 0.91 (m, 4H), 0.01 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 175.5, 175.3, 170.7, 154.7, 154.3, 77.8, 77.7, 76.0, 75.8, 73.0, 72.9, 64.5, 64.3, 61.6, 61.0, 60.2, 59.8, 59.6, 44.4, 43.5, 32.0, 31.2, 17.6, 17.6, 13.8, –1.6; IR (NaCl/thin film): 3262, 2955, 2900, 2132, 1782, 1741, 1706, 1455, 1407, 1349, 1283, 1250, 1190, 1163, 1118, 1042, 1014, 978, 938, 861, 839, 765 cm^{-1}; HRMS

(Multimode-ESI/APCI) calc'd for $C_{15}H_{22}NO_6Si$ $[M–C_2H_4+H]^+$ 340.1211, found 340.1192 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of alkynyl lactone 13-*epi*-180



179 **13-*epi*-180**

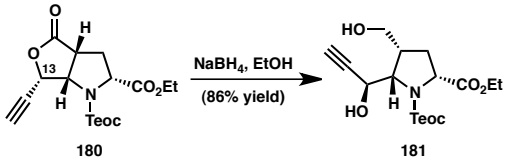
To a stirred solution of hydroxylactone **179** (12.0 mg, 33.4 μmol) in 0.17 mL of THF at –78 °C was added ethynylmagnesium bromide (0.5 M solution in THF, 0.33 mL, 0.167 mmol) dropwise. The solution was then allowed to stir for five minutes at –78 °C before being warmed to 0 °C and stirred for another 15 min. The reaction was then quenched with 0.5 mL of 1M *aq*. HCl solution and the reaction mixture was concentrated *in vacuo*. The resulting aqueous mixture was saturated with NaCl and extracted with EtOAc (5x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material (~5:1 dr by ^{1}H NMR) was purified by silica gel flash chromatography (gradient elution, 2:1→1:1 hexanes–EtOAc) to afford alkynyl lactones **13-*epi*-180** (8.5 mg, 69% yield) and **180** (1.6 mg, 13% yield). NOTE: the relative configuration of the propargylic stereocenter of **13-*epi*-180** was initially assigned by analogy to the alkynyl lactone **158**.

Alkynyl lactone 13-*epi*-180

$[\alpha]_D^{25.0} = –13.5°$ (*c* = 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 5.46 – 5.44 (m, 1H*), 5.35 – 5.33 (m, 1H§), 4.68 (d, *J* = 7.4 Hz, 1H*),

4.62 (d, J = 7.6 Hz, 1H§), 4.59 – 4.53 (m, 1H§), 4.49 – 4.42 (m, 1H*), 4.31 – 4.10 (m, 4H*, 4H§), 3.44 – 3.36 (m, 1H*, 1H§), 2.70 (d, J = 2.4 Hz, 1H§), 2.70 (d, J = 2.4 Hz, 1H*), 2.62 – 2.49 (m, 2H*, 2H§), 1.25 (t, J = 7.1 Hz, 3H*, 3H§), 1.10 – 1.04 (m, 2H§), 1.00 – 0.94 (m, 2H*), 0.06 (s, 9H§), 0.02 (s, 9H*); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 176.1, 175.8, 171.1, 171.0, 154.1, 153.7, 78.6, 78.5, 76.9, 76.8, 73.8, 73.0, 65.2, 64.9, 64.7, 64.5, 62.0, 62.0, 59.1, 58.8, 43.4, 42.4, 31.7, 30.9, 17.8, 13.8, –1.5, –1.6; IR (NaCl/thin film): 3260, 2956, 2900, 2125, 1788, 1744, 1703, 1457, 1410, 1354, 1290, 1250, 1200, 1146, 1117, 1057, 1035, 970, 941, 861, 839, 772 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{17}H_{24}NO_6Si$ $[M–H]^-$ 366.1378, found 366.1400.

Preparation of diol 181

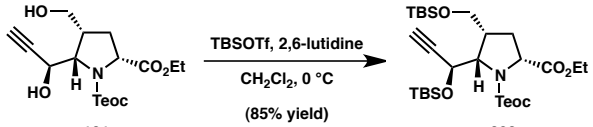


180 181

To a flame dried 500 mL round bottom flask equipped with alkynyl lactone **180** (4.84 g, 13.2 mmol) dissolved in 264 mL of EtOH, sodium borohydride (2.00 g, 52.8 mmol) was added and the reaction was stirred vigorously. Following completion of the reaction as judged by TLC (~1.75 h), the reaction was cooled to 0 °C and quenched carefully with 250 mL of 1N *aq*. HCl. The solution was then saturated with NaCl, diluted with $CHCl_3$, and extracted (1 x 500 mL, then 2 x 250 mL). The aqueous layer was then extracted with EtOAc (3 x 250 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification through silica gel flash chromatography (gradient elution, 2:1→1:1 hexanes–EtOAc) afforded **181** as a colorless

oil in 86% yield (4.20 g). $[\alpha]_D^{25.0}$ = +8.0° (*c* = 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 4.56 – 4.41 (m, 2H), 4.30 (dd, *J* = 9.8, 8.3 Hz, 1H), 4.23 – 4.05 (m, 5H), 3.93 – 3.75 (m, 1H), 3.64 (ddd, *J* = 11.2, 6.0, 6.0 Hz, 1H), 3.23 – 3.10 (m, 1H), 2.72 – 2.62 (m, 1H), 2.62 – 2.51 (m, 1H), 2.34 – 2.25 (m, 1H), 2.04 – 1.84 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.06 – 0.89 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 175.8, 175.1, 156.7, 156.4, 84.9, 75.5 (br), 75.4 (br), 65.0, 64.3 (br), 63.6 (br), 62.6 (br), 62.3 (br), 61.4, 60.6 (br), 60.2 (br), 45.3, 44.6, 33.3, 32.3, 18.3, 14.5, –1.5; IR (NaCl/thin film): 3422, 3307, 2953, 2898, 2114, 1718, 1701, 1406, 1348, 1314, 1250, 1198, 1171, 1041, 1006, 860, 838 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{15}H_{26}NO_6Si$ $[M–C_2H_4+H]^+$ 344.1524, found 344.1535 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

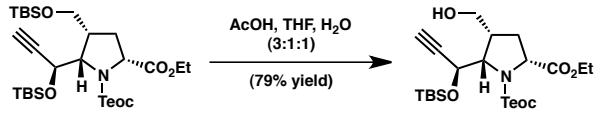
Preparation of bis(*tert*-butyldimethylsilyl) ether 203



To a flame dried 250 mL round bottom flask equipped with diol **181** (4.20 g, 11.3 mmol) was added 113 mL of CH_2Cl_2 and the solution was cooled to 0 °C with stirring. Following addition of 2,6-lutidine (6.5 mL, 56 mmol), *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.5 mL, 28 mmol) was added dropwise to the reaction. Upon completion of the reaction as judged by TLC (~1.5 h), the reaction was quenched with 3.0 mL of MeOH and 300 mL of sat. *aq*. $NaHCO_3$ solution was added. The mixture was then washed with CH_2Cl_2 (3 x 300 mL), and the organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a faint yellow oil. Purification through silica

gel flash chromatography (gradient elution, 16:1→12:1 hexanes–EtOAc) afforded 5.75 g of **203** as a colorless oil (85% yield). $[\alpha]_D^{25.0} = -11.5°$ (*c* = 1.19, $CHCl_3$); ^1H NMR (500 MHz, CD_3CN; compound exists as a 1:1 mixture of rotamers) δ 4.78 (dd, *J* = 4.2, 2.3 Hz, 1H), 4.72 (dd, *J* = 4.1, 2.2 Hz, 1H), 4.21 – 4.01 (m, 14H), 3.91 (dd, *J* = 8.0, 4.2 Hz, 1H), 3.90 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.68 (br d, *J* = 2.4 Hz, 2H), 2.61 – 2.50 (m, 2H), 2.44 – 2.25 (m, 2H), 1.22 (t, *J* = 6.7 Hz, 3H), 1.21 (t, *J* = 6.7 Hz, 3H), 1.07 – 0.97 (m, 2H), 0.91 (s, 18H), 0.90 (s, 18H), 0.95 – 0.86 (m, 2H), 0.14 (br s, 6H), 0.13 (s, 6H), 0.05 (s, 12H), 0.03 (s, 9H), 0.03 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 172.6, 172.2, 156.3, 84.9, 84.9, 77.3, 77.2, 64.7, 64.5, 64.5, 64.1, 63.9, 63.1, 61.5, 61.3, 60.7, 60.4, 45.7, 44.9, 34.6, 33.5, 26.5, 26.2, 19.1, 18.8, 18.7, 18.4, 14.7, –1.3, –4.4, –4.5, –4.8, –4.9, –4.9, –5.0; IR (NaCl/thin film): 3312, 3257, 2955, 2931, 2895, 2858, 2114, 1762, 1736, 1706, 1472, 1406, 1351, 1252, 1185, 1126, 1079, 839, 778 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{27}H_{54}NO_6Si_3$ $[M–C_2H_4+H]^+$ 572.3253, found 572.3254 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of primary alcohol 182

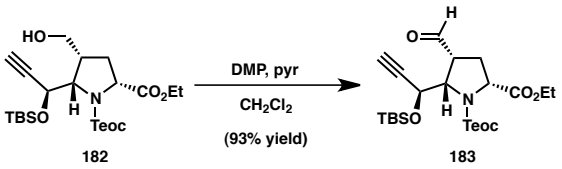


203 **182**

To a 250 mL round bottom flask equipped with bis(*tert*-butyldimethylsilyl) ether **203** (1.00 g, 1.67 mmol) was added 22 mL of a 1:1 mixture of THF:H_2O and 33 mL of acetic acid. The reaction was monitored by TLC for disappearance of starting material and conversion to mono(*tert*-butyldimethylsilyl) ether **182** (with minimal formation of

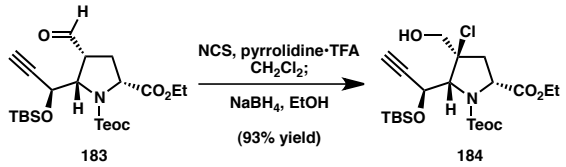
diol **181**). After 6 h, the reaction was cooled to 0 °C and quenched dropwise with 520 mL of 1N *aq*. NaOH (vigorous bubbling occurs initially) and excess sat. *aq*. $NaHCO_3$ solution until the reaction stopped bubbling. The reaction was then extracted with $CHCl_3$ (3x) followed by EtOAc (3x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification through silica gel flash chromatography (gradient elution, 16:1→1:1 hexanes–EtOAc) afforded **182** as a colorless oil in 79% yield (637 mg). $[\alpha]_D^{25.0}$ = –12.4° (*c* = 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN; compound exists as a 1:1 mixture of rotamers) δ 4.85 (dd, *J* = 3.1, 3.1 Hz, 1H), 4.77 (dd, *J* = 2.9, 2.9 Hz, 1H), 4.23 – 4.04 (m, 12H), 4.01 – 3.91 (m, 2H), 3.72 (dd, *J* = 11.5, 7.1 Hz, 2H), 3.13 (br s, 2H), 2.73 (d, *J* = 2.3 Hz, 1H), 2.72 (d, *J* = 2.3 Hz, 1H), 2.65 – 2.55 (m, 2H), 2.30 – 2.22 (m, 4H), 1.22 (t, *J* = 6.9 Hz, 3H), 1.20 (t, *J* = 6.9 Hz, 3H), 1.09 – 0.96 (m, 2H), 0.92 (s, 18H), 0.18 (s, 12H), 0.18 (s, 12H), 0.03 (s, 18H), 0.03 (s, 18H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 172.5, 172.1, 156.3, 84.5, 77.8, 77.7, 64.9, 64.6, 64.6, 64.3, 64.2, 63.4, 61.6, 61.5, 61.4, 60.6, 60.3, 46.0, 45.2, 33.4, 32.4, 26.3, 18.9, 18.8, 18.4, 14.8, –1.3, –4.4, –4.5, –4.8, –4.9; IR (NaCl/thin film): 3503, 3254, 2954, 2896, 2857, 2113, 1759, 1734, 1704, 1472, 1405, 1348, 1251, 1185, 1042, 838, 780 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{21}H_{40}NO_6Si_2$ $[M–C_2H_4+H]^+$ 458.2389, found 458.2412 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of aldehyde 183



To a 250 mL round bottom flask equipped with primary alcohol **182** (2.29 g, 4.71 mmol) dissolved in 47 mL of CH_2Cl_2 (bulk solvent, not dried), was added pyridine (3.8 mL, 47.1 mmol), and Dess–Martin periodinane[24] (4.00 g, 9.42 mmol), and the cloudy white suspension was stirred vigorously. After 3.5 h, the reaction was quenched with sat. *aq*. $Na_2S_2O_3$ solution (50 mL) and sat. *aq*. $NaHCO_3$ solution (50 mL), diluted with EtOAc (50 mL), and stirred vigorously for an additional 20 min. The layers were then separated and the aqueous layer was washed with EtOAc (3 x 100 mL). The combined organics were washed with sat. *aq*. $NaHCO_3$ solution (400 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification through silica gel flash chromatography (gradient elution, 8:1→4:1 hexanes–EtOAc) afforded **183** as a white oil in 93% yield (2.11 g). $[\alpha]_D^{25.0} = -35.2°$ (*c* = 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN; compound exists as a 1:1 mixture of rotamers) δ 9.98 (s, 1H), 9.95 (s, 1H), 4.87 (br s, 1H), 4.82 (br s, 1H), 4.33 (dd, *J* = 8.7, 4.5 Hz, 2H), 4.29 – 4.22 (m, 2H), 4.21 – 4.08 (m, 8H), 3.25 – 3.17 (m, 2H), 2.77 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 2H), 2.69 (s, 2H), 2.34 – 2.26 (m, 4H), 1.23 (t, *J* = 5.7 Hz, 3H), 1.22 (t, *J* = 5.7 Hz, 3H), 1.07 – 0.99 (m, 2H), 0.98 – 0.85 (m, 2H), 0.89 (s, 18H), 0.14 (s, 12H), 0.04 (s, 9H), 0.03 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN; compound exists as a mixture of rotamers) δ 199.4, 199.3, 172.1, 171.7, 156.2, 156.1, 83.7, 78.0, 77.9, 65.3, 64.8, 64.7, 64.6, 63.9, 63.3, 61.7, 61.6, 60.4, 60.1, 53.9, 53.2, 30.7, 29.7, 26.0, 18.8, 18.7, 18.3, 14.6, –1.5, –4.6, –4.7, –5.0, –5.0; IR (NaCl/thin film): 3262, 2954, 2930, 2897, 2857, 2116, 1758, 1706, 1472, 1405, 1348, 1251, 1188, 1079, 838, 779 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{21}H_{38}NO_6Si_2$ $[M–C_2H_4+H]^+$ 456.2232, found 456.2242 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of chlorohydrin 184

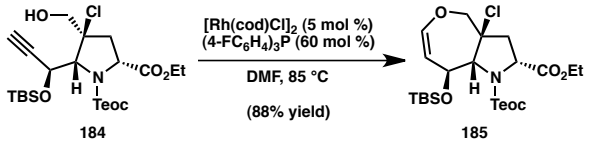


183 184

To a solution of aldehyde **183** (2.11 g, 4.36 mmol) in CH_2Cl_2 (87 mL, bulk solvent, not dried) was added pyrrolidinium trifluoroacetate (1.61 g, 8.72 mmol) followed by *N*-chlorosuccinimide (1.46 g, 10.9 mmol). The resulting solution was stirred under an air atmosphere for 30 h, and was subsequently diluted with EtOH (120 mL) and treated with $NaBH_4$ (1.65 g, 43.6 mmol). After 1.5 h, the reaction mixture was cooled to 0 °C and carefully quenched with 1M *aq*. HCl (200 mL). The resulting mixture was saturated with NaCl, then extracted with $CHCl_3$ (3 x 200 mL) followed by EtOAc (200 mL). The combined organic layers were washed with brine (400 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (gradient elution, 12:1→6:1 hexanes–EtOAc) to afford chlorohydrin **184** (2.11 g, 93% yield) as a clear, colorless oil. $[\alpha]_D^{25.0} = -8.2°$ (*c* = 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.25:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 4.96 (dd, *J* = 4.3, 2.3 Hz, 1H*), 4.85 (dd, *J* = 4.2, 2.3 Hz, 1H§), 4.64 (dd, *J* = 10.6, 7.4 Hz, 1H§), 4.56 (dd, *J* = 10.6, 7.1 Hz, 1H*), 4.38 (ddd, *J* = 13.3, 13.3, 4.1 Hz, 1H*, 1H§), 4.32 (dd, *J* = 4.4, 1.3 Hz, 1H*), 4.27 (m, 1H§), 4.26 – 4.11 (m, 3H*, 3H§), 3.96 – 3.88 (m, 1H*, 1H§), 3.53 (dd, *J* = 10.8, 4.3 Hz, 1H*), 3.42 (dd, *J* = 10.7, 4.4 Hz, 1H§), 2.90 – 2.81 (m, 1H*, 1H§), 2.55 – 2.47 (m, 2H*, 2H§), 1.25 (t, *J* = 7.0, 3H*), 1.25 (t, *J* = 7.0, 3H§), 1.04 – 0.91 (m, 2H*, 2H§), 0.93 (s, 9H*, 9H§), 0.21 (3H*), 0.21 (3H*), 0.19 (3H§), 0.19 (3H§), 0.03 (s, 9H§),

0.01 (s, 9H*); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a mixture of rotamers) δ 170.7, 170.3, 155.3, 155.1, 81.7, 81.4, 80.4, 79.5, 77.2, 76.8 (obscured by $CDCl_3$ signal, observable by acquiring spectrum in CD_2Cl_2), 73.1, 72.6, 65.8, 64.6, 64.5, 63.9, 63.1, 61.1, 61.0, 58.4, 58.1, 40.9, 39.8, 25.6, 18.0, 18.0, 17.5, 14.2, 14.1, –1.6, –1.6, –5.0, –5.2, –5.4, –5.4; IR (NaCl/thin film): 3494, 3309, 3255, 2955, 2931, 2898, 2859, 2113, 1761, 1708, 1404, 1350, 1307, 1252, 1191, 1082, 839, 781 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{21}H_{39}ClNO_6Si_2$ $[M–C_2H_4+H]^+$ 492.1999, found 492.2002 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

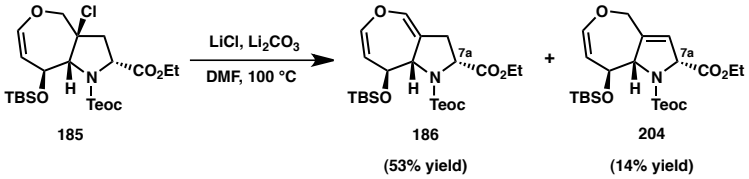
Preparation of chlorotetrahydrooxepine 185



A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with [Rh(1,5-cyclooctadiene)Cl]$_2$ (26.1 mg, 0.053 mmol, 5 mol %) and tris(4-fluorophenyl)phosphine (201 mg, 0.636 mmol, 60 mol %). An atmosphere of N_2 was established by evacuation/backfilling (three cycles) and a solution of chlorohydrin **184** (553 mg, 1.06 mmol) in dry DMF (10.6 mL, including two rinses to ensure quantitative transfer) was added via syringe. The resulting yellow solution was degassed using the freeze-pump-thaw technique. The vessel was sealed and the solution frozen by submersion in a bath of liquid N_2. The vessel was then placed under vacuum for approximately five minutes before once again being sealed and allowed to thaw under static vacuum by removal from the liquid N_2 bath. This procedure was repeated twice before the head-space was finally backfilled with N_2, the vessel sealed, and the solution heated to 85 °C with stirring. After 26 h, the reaction mixture was cooled to rt, diluted

with 50 mL sat. *aq*. $NaHCO_3$ solution, and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) followed by brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (gradient elution, 24:1→12:1 hexanes–EtOAc) to afford chlorotetrahydrooxepine **185** (483 mg, 88% yield) as a pale yellow oil. $[\alpha]_D^{25.0}$ = +91.9° (*c* = 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 6.23 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.66 (dd, *J* = 7.5, 3.7 Hz, 1H), 4.60 (d, *J* = 13.2 Hz, 1H), 4.57 – 4.49 (m, 2H), 4.41 (dd, *J* = 7.8, 1.0 Hz, 1H), 4.26 – 4.07 (m, 5H), 2.57 (ddd, *J* = 14.3, 7.6, 1.0 Hz, 1H), 2.49 (dd, *J* = 14.5, 10.0 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.04 – 0.97 (m, 2H), 0.92 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C; compound exists as a mixture of rotamers) δ 172.7, 157.3, 146.9, 109.4 (br), 77.9, 76.8 (br), 74.8, 70.0, 65.1, 62.2, 60.5, 41.5 (br), 26.6, 18.9, 18.8, 14.8, –1.1, –4.1, –4.3; IR (NaCl/thin film): 2954, 2929, 2896, 2856, 1757, 1707, 1647, 1406, 1352, 1336, 1313, 1251, 1192, 1131, 1037, 863, 837, 777 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{15}H_{23}ClNO_5Si$ $[M–C_2H_4–C_6H_{15}OSi]^+$ 360.1029, found 360.1030 (detected fragment has undergone elimination of ethylene from the Teoc protecting group, as well as loss of *tert*-butyldimethylsilanolate anion).

Preparation of dihydrooxepine 186



185 186 (53% yield) 204 (14% yield)

An oven-dried Schlenk tube was charged with a magnetic stir bar and dry LiCl (149 mg, 3.52 mmol), and its contents were flame-dried under vacuum. The headspace

was then backfilled with N_2, and Li_2CO_3 (519 mg, 7.03 mmol) was quickly added to the vessel. The tube was then evacuated and backfilled with N_2, and this procedure was repeated twice to establish an inert atmosphere. Finally, chlorotetrahydrooxepine **185** (30.5 mg, 58.6 μmol) was added as a solution in DMF (rinsing twice for a total volume of 2.3 mL), and the mixture was heated to 100 °C with vigorous stirring. After 75 h, the reaction mixture was cooled to room temperature and filtered through celite, rinsing the vessel and filter pad with EtOAc, followed by excess Et_2O. The resulting off-white suspension was again filtered through celite and concentrated *in vacuo*. This material was purified by preparative HPLC (normal phase, isochratic elution, 6% EtOAc in hexanes) to afford dihydrooxepine **186** (14.9 mg, 53% yield) and olefin isomer **204** (4.0 mg, 14% yield) as colorless oils.

Dihydrooxepine 186.

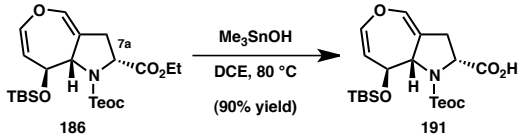
$[\alpha]_D^{25.0} = -70.5°$ (c = 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 6.37 (ddd, J = 2.5, 2.5, 1.1 Hz, 1H), 6.11 (dd, J = 8.2, 2.2 Hz, 1H), 4.81 – 4.68 (m, 2H), 4.62 (br d, J = 7.6 Hz, 1H), 4.42 (ddd, J = 7.5, 2.1, 2.1 Hz, 1H), 4.34 – 4.02 (m, 4H), 2.92 (dddd, J = 15.1, 9.8, 2.1, 2.1 Hz, 1H), 2.59 (dddd, J = 15.1, 1.6, 1.6, 1.6 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.06 – 0.98 (m, 2H), 0.91 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, 50 °C) δ 172.1, 156.3 (br), 138.0, 135.8, 114.4 (br), 111.6, 71.6, 63.9, 63.7, 61.0, 58.5, 33.9 (br), 25.9, 18.0, 17.9, 14.2, –1.5, –4.7, –5.2; IR (NaCl/thin film): 2954, 2928, 2897, 2855, 1750, 1723, 1699, 1687, 1652, 1407, 1330, 1250, 1180, 1142, 1098, 1031, 860, 837, 778 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{15}H_{22}NO_5Si$ $[M–C_2H_4–C_6H_{15}OSi]^+$ 324.1262, found 324.1267 (detected fragment has

undergone elimination of ethylene from the Teoc protecting group, as well as loss of *tert*-butyldimethylsilanolate anion).

Olefin isomer 204.

$[\alpha]_D^{25.0}$ = +121.9° (*c* = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN; 60 °C) δ 6.16 (d, *J* = 7.2, 1.2 Hz, 1H), 5.86 (br s, 1H), 5.08 (q, *J* = 1.6 Hz, 1H), 4.80 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.66 (dt, J = 5.6, 1.6 Hz, 1H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.44 – 4.38 (m, 2H), 4.28 – 4.18 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 8.4 Hz, 2H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 171.1, 146.2, 141.8, 125.9, 113.2, 73.8, 72.9, 69.0, 66.8, 64.7, 62.4, 26.7, 19.0, 18.9, 14.9, –1.1, –4.0, –4.2; IR (NaCl/thin film): 2953, 2928, 2893, 2854, 1755, 1703, 1639, 1404, 1348, 1328, 1251, 1189, 1128, 1103, 1058, 1027, 861, 836, 777 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{15}H_{22}NO_5Si$ $[M–C_2H_4–C_6H_{15}OSi]^+$ 324.1262, found 324.1264 (detected fragment has undergone elimination of ethylene from the Teoc protecting group, as well as loss of *tert*-butyldimethylsilanolate anion).

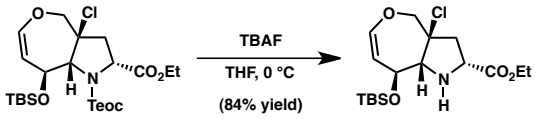
Preparation of carboxylic acid 191



To a solution of ethyl ester **186** (47.3 mg, 97.8 μmol) in DCE (1.0 mL) was added trimethyltin hydroxide (177 mg, 0.978 mmol), and the resulting solution was heated 80 °C with stirring. After 30 h, the reaction mixture was cooled to room temperature and diluted with $Na_2HPO_4/KHSO_4$ buffer (pH = 2.5, prepared from a 10% w/v *aq*. Na_2HPO_4 solution by acidification with $KHSO_4$), then extracted with EtOAc (5x). The combined

organic layers were washed with H_2O followed by brine, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (gradient elution, 40:1→20:1 CH_2Cl_2–MeOH) to afford carboxylic acid **191** (40.3 mg, 90% yield) as a white foam. $[\alpha]_D^{25.0}$ = –68.6° (*c* = 0.890, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 6.43 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 1H), 6.14 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.72 – 4.67 (m, 2H), 4.64 (dddd, *J* = 7.8, 1.8, 1.8, 1.8 Hz, 1H), 4.42 – 4.31 (m, 1H), 4.20 – 4.10 (m, 2H), 3.03 (d, *J* = 16.0 Hz, 1H), 2.91 (dddd, *J* = 15.5, 9.6, 1.7, 1.7 Hz, 1H), 1.13 – 1.01 (m, 2H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 9H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 50 °C) δ 174.7 (br), 157.5 (br), 138.5, 136.4, 114.6 (br), 111.1, 71.4, 64.8, 63.9, 58.6, 31.9 (br), 25.9, 18.0, 17.9, –1.5, –4.8, –5.1; IR (NaCl/thin film): 3088, 2954, 2928, 2897, 2855, 1750, 1722, 1684, 1652, 1418, 1336, 1250, 1180, 1142, 1101, 859, 837, 777 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{13}H_{18}NO_5Si$ [M–C_2H_4–$C_6H_{15}OSi]^+$ 296.0949, found 296.0958 (detected fragment has undergone elimination of ethylene from the Teoc protecting group, as well as loss of *tert*-butyldimethylsilanolate anion).

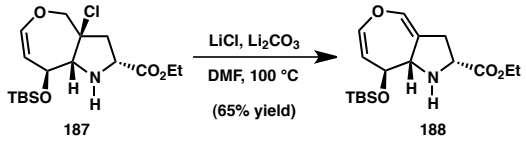
Preparation of amine 187



To a stirred solution of trimethylsilylethyl carbamate **185** (677 mg, 1.30 mmol) in THF (26 mL) at 0 °C was added a solution of TBAF (1.0 M in THF, 5.2 mL, 5.20 mmol). After 2.5 h, the solution was diluted with sat. *aq*. Na_2SO_4 solution (125 mL) and H_2O (250 mL) and extracted with EtOAc (4 x 125 mL). The combined organic layers were

washed with sat. *aq*. Na_2SO_4 solution (250 mL), H_2O (2 x 250 mL), and brine (250 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (isocratic elution, 6:1 hexanes–EtOAc) to afford pyrrolidine **187** (412 mg, 84% yield) as a pale brown oil. $[\alpha]_D^{25.0}$ **=** +117.4° (*c* = 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 7.5, 0.7 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.54 (dd, *J* = 7.4, 5.1 Hz, 1H), 4.31 (ddd, *J* = 6.9, 5.2, 0.8 Hz, 1H), 4.24 – 4.14 (m, 2H), 4.08 (d, *J* = 12.2 Hz, 2H), 3.74 (s, 1H), 2.42 (dd, *J* = 13.7, 5.9 Hz, 2H), 2.30 (dd, *J* = 13.7, 10.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 146.8, 105.5, 76.3, 74.5, 74.4, 68.5, 61.1, 58.1, 43.6, 25.7, 18.0, 14.2, –4.6, –4.9; IR (NaCl/thin film): 2954, 2929, 2886, 2856, 1741, 1646, 1472, 1286, 1252, 1192, 1138, 1088, 1057, 1035, 872, 838, 778 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{17}H_{31}ClNO_4Si$ $[M+H]^+$ 376.1705, found 376.1728.

Preparation of dihydrooxepine amine 188

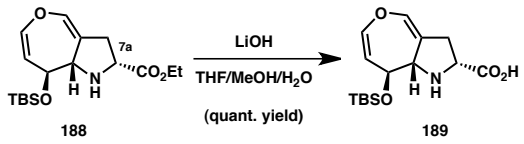


187 188

An oven-dried Schlenk tube was charged with a magnetic stir bar and dry LiCl (454 mg, 10.7 mmol), and its contents were flame-dried under vacuum. The headspace was then backfilled with N_2, and Li_2CO_3 (1.58 g, 21.4 mmol) was quickly added to the vessel. The tube was then evacuated and backfilled with N_2, and this procedure was repeated twice to establish an inert atmosphere. Finally, chlorotetrahydrooxepine **187** (67.0 mg, 0.178 mmol) was added as a solution in DMF (rinsing twice for a total volume of 7.1 mL), and the mixture was heated to 100 °C with vigorous stirring. After 48 h, the

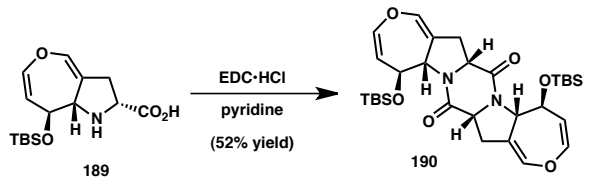
reaction mixture was cooled to room temperature and filtered through celite, rinsing the vessel and filter pad with EtOAc, followed by excess Et_2O. The resulting off-white suspension was again filtered through celite and concentrated *in vacuo*. Residual DMF was removed by distillation under high vacuum with gentle heating (water bath, 40 °C) to give the crude product as a brown oil. This material was purified by silica gel flash chromatography (isocratic elution, 8:1 hexanes–EtOAc) to afford dihydrooxepine **188** (41.1 mg) as a pale brown oil. NOTE: This material was contaminated with ~5 wt% starting material, giving a corrected yield of 65%. Material of this purity was typically used without further purification; however, analytically pure samples could be obtained with further purification by silica gel flash chromatography (gradient elution, 0→5% EtOAc–CH_2Cl_2 with 0.5% Et_3N). $[\alpha]_D^{25.0} = -28.2°$ (*c* = 1.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 1H), 6.09 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.62 (dd, *J* = 8.2, 1.8 Hz, 1H), 4.20 – 4.13 (m, 3H), 3.86 (dd, *J* = 7.7, 5.8 Hz, 1H), 3.81 (dddd, *J* = 7.2, 2.0, 2.0, 2.0 Hz, 1H), 2.85 (dddd, *J* = 14.9, 7.7, 1.7, 1.7 Hz, 1H), 2.64 (dddd, *J* = 14.9, 5.8, 1.9, 1.9 Hz, 1H), 2.74 – 2.49 (br s, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 138.5, 135.0, 115.7, 110.2, 71.7, 64.8, 60.8, 58.3, 33.8, 25.8, 18.1, 14.2, –4.5, –4.5; IR (NaCl/thin film): 3376, 2955, 2929, 2886, 2856, 1737, 1688, 1651, 1472, 1463, 1368, 1295, 1279, 1252, 1203, 1175, 1119, 1090, 1035, 1005, 882, 838, 778 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{17}H_{30}NO_4Si$ $[M+H]^+$ 340.1939, found 340.1941.

Preparation of amino acid 189



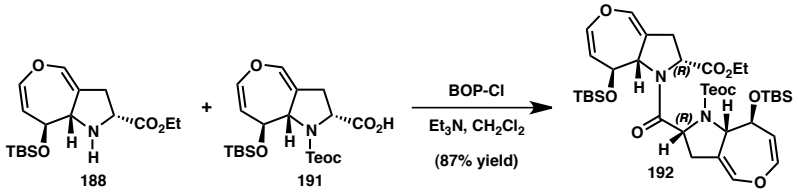
LiOH (242 mg, 10.1 mmol) was dissolved in 7 mL H_2O, and the resulting solution was added via pipet to a stirring solution of ethyl ester **188** (343 mg, 1.01 mmol) in 14 mL of THF/MeOH (1:1) under an air atmosphere. The resulting biphasic mixture was stirred vigorously for 1 h, then diluted with 100 mL sat. *aq*. Na_2HPO_4 and extracted with $CHCl_3$ (3 x 100 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated to afford 321 mg (quantitative yield) of amino acid **189** as a yellow solid. Though this material was generally used without further purification, it was found that the yellow color as well as minor impurities could be removed via trituration with THF. $[\alpha]_D^{25.0}$ = –60.5 ° (*c* = 1.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (ddd, *J* = 1.9, 1.9, 1.9 Hz, 1H), 6.13 (dd, *J* = 7.8, 2.3 Hz, 1H), 4.76 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.43 (ddd, *J* = 8.0, 2.3, 2.3 Hz, 1H), 4.22 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.10 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.09 – 2.93 (m, 2H), 0.90 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 138.8, 136.2, 110.5, 110.0, 69.2, 62.2, 57.5, 34.1, 25.8, 17.8, -4.3, -4.9; IR (NaCl/thin film): 3067, 2954, 2929, 2886, 2858, 2368, 1688, 1652, 1472, 1464, 1444, 1368, 1332, 1300, 1260, 1220, 1190, 1142, 1108, 1080, 1006, 960, 938, 872, 839, 780, 754, 724 cm^{-1}; LRMS (ESI/APCI) calc'd for $C_{15}H_{26}NO_4Si$ $[M+H]^+$ 312.2, found 312.1.

Preparation of diketopiperazine 190



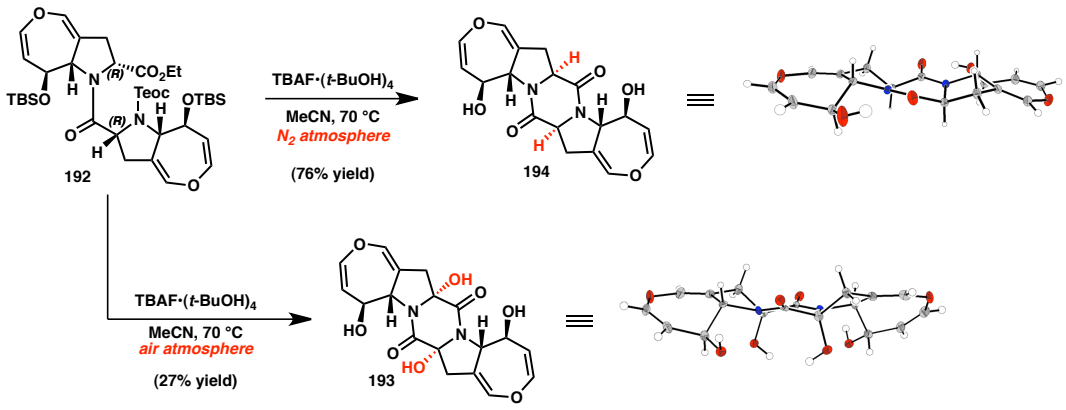
In a 1-dram vial equipped with a magnetic stir bar, amino acid **189** (40.6 mg, 0.130 mmol) was dissolved in 1.3 mL pyridine. Solid EDC•HCl (125 mg, 0.650 mmol) was then added in one portion, and the resulting suspension was stirred vigorously for 18 hours. The mixture was then diluted with H_2O, giving a yellow precipitate that was filtered off through a cotton plug and rinsed with an excess of further H_2O. The crude product was then recovered by elution through the cotton plug with CH_2Cl_2. Purification via flash chromatography (gradient elution, 2:1→1:1 hexanes–EtOAc) afforded diketopiperazine **190** (19.9 mg, 52% yield) as an off-white solid. $[\alpha]_D^{25.0}$ = –92.3 ° (*c* = 1.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 2.0, 2.0 Hz, 2H), 6.22 (dd, *J* = 8.3, 1.9 Hz, 2H), 4.68 (ddd, *J* = 8.2, 2.1, 2.1 Hz, 2H), 4.61 (dd, *J* = 8.3, 1.4 Hz, 2H), 4.25 (dd, *J* = 11.6, 7.2 Hz, 2H), 4.06 (ddd, *J* = 8.2, 1.7, 1.7 Hz, 2H), 2.94 (ddd, *J* = 15.7, 7.2, 1.0 Hz, 2H), 2.68 (dddd, *J* = 15.8, 11.8, 2.7, 2.7 Hz, 2H), 0.92 (s, 18H), 0.10 (s, 6H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 140.6, 138.2, 117.7, 109.3, 71.1, 64.0, 63.5, 29.0, 25.8, 18.1, -3.8, -4.5; IR (NaCl/thin film): 3391, 3059, 2947, 2926, 2854, 1702, 1645, 1470, 1462, 1360, 1330, 1289, 1256, 1245, 1231, 1197, 1163, 1138, 1127, 1097, 1062, 993, 980, 956, 937, 897, 860, 836, 775, 713 cm^{-1}; LRMS (ESI/APCI) calc'd for $C_{24}H_{31}N_2O_5Si$ $[M–C_6H_{15}OSi]^+$ 455.2, found 455.2 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion).

Preparation of dipeptide 192



To a stirred solution of amine **188** (59.2 mg, 0.174 mmol) and carboxylic acid **191** (73.9 mg, 0.162 mmol) in CH_2Cl_2 (1.6 mL) was added triethylamine (226 μL, 1.62 mmol) followed by BOP-Cl (206 mg, 0.810 mmol). After 24 h, the reaction mixture was diluted with sat. *aq*. $NaHCO_3$ solution and extracted with EtOAc (5x). Each organic fraction was filtered individually through a plug of SiO_2, which was then rinsed with excess EtOAc. The combined organic filtrates were concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (gradient elution, 16:1→4:1 hexanes–EtOAc) to afford dipeptide **192** (109.5 mg, 87% yield) as a white foam. $[\alpha]_D^{25.0}$ = –46.8° (*c* = 1.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 6.43 – 6.36 (m, 2H), 6.15 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.12 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.63 (s, 1H), 5.34 (d, *J* = 8.2 Hz, 1H), 5.01 (d, *J* = 9.9 Hz, 1H), 4.80 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.66 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.60 (d, *J* = 7.3 Hz, 1H), 4.50 (apt dddd, *J* = 12.3, 7.9, 2.0, 2.0 Hz, 2H), 4.28 – 4.01 (m, 4H), 2.97 – 2.87 (m, 1H), 2.87 – 2.77 (m, 1H), 2.76 – 2.68 (m, 1H), 2.67 – 2.58 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.01 (apt dd, *J* = 9.9, 8.1 Hz, 2H), 0.94 (s, 9H), 0.88 (s, 9H), 0.17 (s, 3H), 0.09 (s, 3H), 0.04 (s, 3H), 0.02 (s, 9H), –0.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 50 °C) δ 172.8, 171.7, 156.5, 138.3, 138.0, 136.0, 134.6, 116.1, 115.4, 111.1, 110.7, 71.4, 70.7, 64.6, 64.1, 63.3, 61.2, 57.1, 55.7, 34.5, 32.6, 26.3, 25.8, 18.3, 18.0, 18.0, 14.2, –1.6, –3.3, –4.7, –5.2, –5.8; IR (NaCl/thin film): 2954, 2929, 2896, 2856, 1746, 1718, 1685, 1653, 1430, 1331, 1302, 1251, 1190, 1179, 1141, 1091, 865, 837, 780 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{26}H_{33}N_2O_7Si$ $[M–C_6H_{16}OSi–C_6H_{15}OSi]^+$ 513.2052, found 513.2051 (detected fragment has undergone elimination of *tert*-butyldimethylsilanol, as well as loss of *tert*-butyldimethylsilanolate anion).

Preparation of diketopiperazine 194 (or tetraol 193)



An oven-dried Schlenk tube was charged with a magnetic stir bar, TBAF(*t*-BuOH)$_4$[31] (248 mg, 0.445 mmol), and a solution of dipeptide **192** (57.6 mg, 74.1 μmol) in dry MeCN (1.5 mL). The resulting solution was degassed using the freeze-pump-thaw technique. The vessel was sealed and the solution frozen by submersion in a bath of liquid N_2. The vessel was then placed under vacuum for ca. five minutes before once again being sealed and allowed to thaw under static vacuum by removal from the liquid N_2 bath. This procedure was repeated three times before the head-space was finally backfilled with N_2, the vessel sealed, and the solution heated to 70 °C with stirring. After 2 h and 20 min, the reaction mixture was cooled to rt, was diluted with sat. *aq*. Na_2SO_4 solution, and extracted with EtOAc (5x). Each organic fraction was passed individually through a plug of SiO_2, which was then rinsed with excess EtOAc. The combined organic filtrates were then concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (isocratic elution, 1% MeOH in 1:1 CH_2Cl_2–EtOAc) to afford diketopiperazine **194** (20.3 mg, 76% yield) as a white solid. Crystals suitable for X-ray diffraction were obtained by slow evaporation of a solution of diketopiperazine **194** in THF at ambient temperature. NOTE: It was observed that if this reaction was

performed under an air atmosphere, tetraol **193** was formed. This oxidation process displays a great degree of apparent diastereoselectivity, as no other diastereomers of the dihydroxylated product are observed in significant quantities. Tetraol **193** could be isolated as a white solid (27% yield) by preparative HPLC (reverse phase, gradient elution, 20→40% MeCN in H_2O). Crystals suitable for X-ray diffraction were obtained as follows: the material was dissolved in a minimal amount of THF and diluted with CH_2Cl_2, then benzene and *iso*-octane were sequentially layered over the resulting solution and the phases were allowed to slowly diffuse at ambient temperature.

Diketopiperazine 194

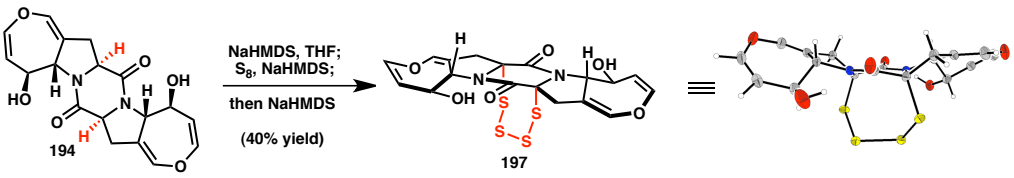
$[\alpha]_D^{25.0}$ = –624.5° (*c* = 1.01, $CHCl_3$); mp 200–222 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (ddd, *J* = 2.6, 2.6, 1.0 Hz, 2H), 6.18 (dd, *J* = 8.2, 2.3 Hz, 2H), 5.07 (s, 2H), 4.91 (dddd, *J* = 7.9, 1.7, 1.7, 1.7 Hz, 2H), 4.87 (dd, *J* = 8.2, 1.9 Hz, 2H), 4.50 – 4.44 (m, 2H), 4.35 (ddd, *J* = 7.9, 2.1 Hz, 2H), 3.01 (dddd, *J* = 14.9, 6.9, 1.2, 1.2 Hz, 2H), 2.84 (dddd, *J* = 15.1, 11.2, 2.2, 2.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 138.3, 137.8, 110.3, 109.6, 71.0, 64.1, 57.8, 33.9; IR (NaCl/thin film): 3244, 3164, 2923, 2895, 2848, 1675, 1638, 1623, 1438, 1284, 1187, 1131, 1046, 749 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{18}H_{17}N_2O_6$ $[M–H]^-$ 357.1092, found 357.1089.

Tetraol 193

^{1}H NMR (500 MHz, CD_3CN) δ 6.54 (ddd, *J* = 2.6, 2.6, 0.9 Hz, 2H), 6.25 (dd, *J* = 8.3, 2.3 Hz, 2H), 4.82 – 4.76 (m, 4H), 4.39 (ddd, *J* = 7.7, 2.2, 2.2 Hz, 2H), 2.95 (ddd, *J* = 15.4, 2.4, 2.4 Hz, 2H), 2.78 (ddd, *J* = 15.4, 1.5, 1.0 Hz, 2H); ^{13}C NMR (126 MHz, CD_3CN) δ 167.9, 139.1, 138.2, 111.2, 111.1, 87.8, 73.1, 65.0, 42.0; IR (NaCl/thin film):

3583, 3300, 2916, 2848, 1653, 1647, 1420, 1320, 1197, 1148, 1063, 1014 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{18}H_{17}N_2O_8$ $[M–H]^-$ 389.0990, found 389.0960.

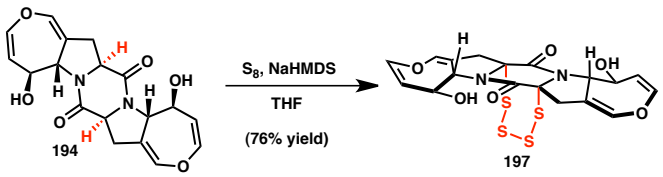
Preparation of epitetrathiodiketopiperazine 197 (published procedure)



To a stirred suspension of S_8 (22.4 mg, 87.3 μmol) in THF (5.8 mL) under a N_2 atmosphere was added a solution of NaHMDS in PhMe (0.6 M, 437 μL, 0.262 mmol) over two minutes. The S_8 solids dissolved over the course of the addition, giving initially a dark green solution that evolved to an orange-brown color towards the end of the addition. While this solution was allowed to stir for an additional one minute, a solution of NaHMDS in PhMe (0.6 M, 145 μL, 87.3 μmol) was added to a stirred solution of diketopiperazine **194** (3.13 mg, 8.73 μmol) in THF (1.0 mL) under a N_2 atmosphere. The resulting pale brown solution was then added dropwise via syringe to the previously described solution of reagents over one minute, rinsing once with THF (0.25 mL) (rinsings transferred over an additional one minute) to give a slightly opaque yellow-orange solution. After an additional one minute, a solution of NaHMDS in PhMe (0.6 M, 292 μL, 0.175 mmol) was added dropwise to the reaction mixture. After 50 min, the reaction was quenched with sat. *aq*. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (gradient elution, 3:1→3:2 hexanes–EtOAc) to afford epitetrathiodiketopiperazine **197** (1.67 mg, 40% yield) as a yellow solid. Crystals suitable for X-ray diffraction were

obtained as follows: *iso*-octane was carefully layered over a solution of epitetrathiodiketopiperazine **197** in $CHCl_3$ and the resulting phases were allowed to slowly diffuse at ambient temperature. $[\alpha]_D^{25.0} = -548.9°$ ($c = 0.135$, $CHCl_3$); mp 148–165 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, J = 2.5 Hz, 2H), 6.21 (dd, J = 8.2, 2.3 Hz, 2H), 5.02 (d, J = 7.6 Hz, 2H), 4.92 (dd, J = 8.1, 1.9 Hz, 2H), 4.73 (s, 2H), 4.49 – 4.43 (m, 2H), 3.29 (ddd, J = 16.0, 2.2 Hz, 2H), 3.03 (d, J = 16.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 138.9, 138.0, 110.4, 106.4, 74.5, 71.4, 65.4, 41.1; IR (NaCl/thin film): 3369, 2919, 2849, 1689, 1662, 1391, 1337, 1193, 1133, 1082, 1046, 748 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{18}H_{16}ClN_2O_6S_4$ $[M+Cl]^-$ 518.9585, found 518.9614.

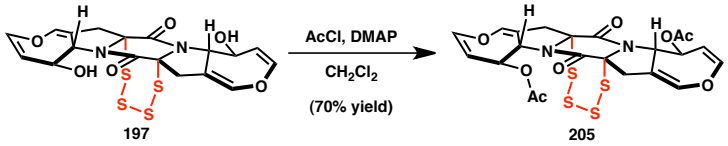
Preparation of epitetrathiodiketopiperazine 197 (improved procedure)



To a stirred suspension of S_8 (212 mg, 0.825 mmol) in THF (27 mL) under a N_2 atmosphere was added a solution of NaHMDS in PhMe (0.6 M, 16.5 mL, 9.90 mmol) over two minutes. After an additional 1 minute, a solution of diketopiperazine **194** (59.2 mg, 0.165 mmol) in 18 mL THF was added dropwise via syringe to the previously described solution of reagents over 1.5 minutes (the flask that had contained the solution of **194** was rinsed with an additional 9 mL portion of THF, which was transferred to the reaction vessel). After 50 min, the reaction was quenched with sat. *aq*. $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (gradient elution, 3:1→3:2 hexanes–EtOAc followed by

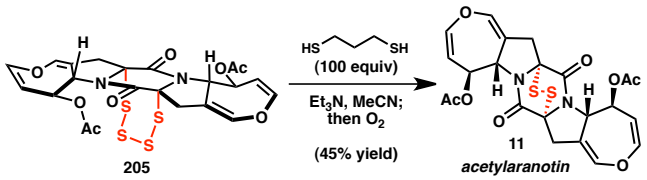
100% EtOAc) to afford epitetrathiodiketopiperazine **197** (61.0 mg, 76% yield) as a yellow solid.

Preparation of diacetate 205



To a stirred solution of diol **197** (3.11 mg, 6.43 μmol) and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (0.64 mL) at 0 °C was added acetyl chloride (6.9 μL, 97 μmol). After 10 min, the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After an additional 30 min, the reaction mixture was quenched with H_2O and extracted five times with a mixture of hexanes and EtOAc (1:1). Each organic fraction was passed individually through a plug of SiO_2, which was subsequently rinsed with excess hexanes/EtOAc. The combined filtrates were concentrated *in vacuo* to provide the crude product, which was purified by silica gel flash chromatography (gradient elution, 3:1→3:2 hexanes–EtOAc) to afford diacetate **205** (2.57 mg, 70% yield) as a yellow solid. $[\alpha]_D^{25.0} = -476.6°$ (c = 0.1285, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (ddd, J = 2.5, 2.5, 0.9 Hz, 2H), 6.27 (dd, J = 8.2, 2.4 Hz, 2H), 5.30 (ddd, J = 8.5, 2.6, 1.4 Hz, 2H), 5.20 (ddd, J = 8.4, 2.2, 2.2 Hz, 2H), 4.70 (dd, J = 8.2, 1.9 Hz, 2H), 3.36 (ddd, J = 16.4, 2.2, 2.2 Hz, 2H), 3.07 (ddd, J = 16.3, 1.2, 1.2 Hz, 2H), 2.18 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 165.7, 139.7, 138.7, 108.0, 106.0, 75.7, 71.1, 60.8, 41.7, 21.5; IR (NaCl/thin film): 2917, 2849, 1739, 1695, 1370, 1237, 1136 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{20}H_{17}N_2O_6S_4$ $[M–C_2H_3O_2]^+$ 508.9964, found 508.9961 (detected fragment has undergone loss of acetate anion).

Preparation of acetylaranotin (11)



A solution of tetrasulfide **205** (2.40 mg, 4.22 μmol) in CH_2Cl_2 (0.5 mL) was diluted with MeCN (12 mL), then treated with a solution of Et_3N in MeCN (0.2 μL, 1.4 μmol in 50 μL of MeCN), followed by propanedithiol (42 μL, 0.42 mmol). The resulting mixture was allowed to stand for 20 min, and was then washed with hexanes (5 x 8 mL, the final hexanes wash was back-extracted once with MeCN to ensure material recovery), and concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2/PhMe and loaded onto a short plug of SiO_2. Residual propanedithiol and other nonpolar impurities were eluted with 4:1 hexanes–EtOAc before the presumed dithiol intermediate was eluted with 100% EtOAc. The EtOAc fractions (~25 mL total) were combined and diluted with EtOAc (10 mL) and MeOH (70 mL), and the resulting solution was sparged with O_2 for 15 min, then allowed to stand under an O_2 atmosphere for ~6 h. The solution was then concentrated *in vacuo*, and purified by preparative HPLC (normal phase, isocratic elution, 33% EtOAc in hexanes) to afford acetylaranotin (**11**) (0.96 mg, 45% yield) as a white solid. $[\alpha]_D^{25.0}$ = –401.5° (*c* = 0.048, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 2H), 6.30 (dd, *J* = 8.2, 2.2 Hz, 2H), 5.67 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H), 5.10 (dddd, *J* = 8.4, 1.7, 1.7, 1.7 Hz, 2H), 4.60 (dd, *J* = 8.2, 1.8 Hz, 2H), 4.10 (ddd, *J* = 18.2, 2.3, 1.3 Hz, 2H), 2.98 (ddd, *J* = 18.2, 1.7, 1.7 Hz, 2H), 2.02 (s, 6H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.82 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 2H), 6.45 (dd, *J* = 8.2, 2.2 Hz, 2H), 5.42 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H), 5.02 (dddd, *J* = 8.5, 1.9, 1.4, 1.4 Hz, 2H),

4.60 (dd, *J* = 8.0, 1.8 Hz, 2H), 3.85 (ddd, *J* = 18.3, 2.5, 1.3 Hz, 2H), 3.23 (ddd, *J* = 18.3, 1.6, 1.6 Hz, 2H), 1.90 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.7, 162.3, 141.6, 139.2, 114.0, 105.4, 76.4, 70.0, 62.9, 34.1, 21.2; IR (NaCl/thin film): 2917, 2849, 1739, 1709, 1652, 1356, 1231, 1141, 1040 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{20}H_{17}N_2O_6S_2$ $[M–C_2H_3O_2]^+$ 445.0523, found 445.0522 (detected fragment has undergone loss of acetate anion).

Table 2.7. *Comparison of spectroscopic data for natural and synthetic acetylaranotin (**11**).*

^{1}H NMR Data ($CDCl_3$, data for synthetic material referenced to $CHCl_3$ at 7.26 ppm)[a]

Reported (τ)[1c]	Reported (δ)	Synthetic
3.37	6.63 (ddd, *J* = 2.3, 2.2, 1.4 Hz, 2H)	6.61 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 2H)
3.68	6.32 (dd, *J* = 7.5, 2.1 Hz, 2H)	6.30 (dd, *J* = 8.2, 2.2 Hz, 2H)
4.32	5.68 (ddd, *J* = 8.7, 2.1, 1.5 Hz, 2H)	5.67 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H)
4.91	5.09 (dddd, *J* = 8.7, 2.3, 1.4, 1.3 Hz, 2H)	5.10 (dddd, *J* = 8.4, 1.7, 1.7, 1.7 Hz, 2H)
5.37	4.63 (dd, *J* = 7.5, 1.5 Hz, 2H)	4.60 (dd, *J* = 8.2, 2.2 Hz, 2H)
5.88	4.12 (ddd, *J* = 18.0, 2.2, 1.3 Hz, 2H)	4.10 (ddd, *J* = 18.2, 2.3, 1.3 Hz, 2H)
7.03[b]	2.97 (ddd, *J* = 18.0, 1.4, 1.4 Hz, 2H)	2.98 (ddd, *J* = 18.2, 1.7, 1.7 Hz, 2H)
– [c]	– [c]	2.02 (s, 6H)

[a]Reported data was referenced to TMS as an internal standard.
[b]Reported value is 7.30 ppm, but this is assumed to be a typographical error based on the plot of the spectrum.
[c]Value not tabulated.

^{1}H NMR Data (DMSO-d_6, data for synthetic material referenced to DMSO at 2.50 ppm)[a]

Reported[4]	Synthetic
6.82 (ddd, *J* = 2.5, 2.0, 1.5 Hz, 2H)	6.82 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 2H)
6.45 (dd, *J* = 8.0, 2.5 Hz, 2H)	6.45 (dd, *J* = 8.2, 2.2 Hz, 2H)
5.42 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H)	5.42 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H)
5.01 (br ddt, *J* = 8.5, 2.0, 1.5 Hz, 2H)	5.02 (dddd, *J* = 8.5, 1.9, 1.4, 1.4 Hz, 2H)
4.59 (dd, *J* = 8.0, 2.0 Hz, 2H)	4.60 (dd, *J* = 8.0, 1.8 Hz, 2H)
3.84 (br ddd, *J* = 18.0, 2.5, 1.5 Hz, 2H)	3.85 (ddd, *J* = 18.3, 2.5, 1.3 Hz, 2H)
3.22 (br ddd, *J* = 18.0, 1.5, 1.5 Hz, 2H)	3.23 (ddd, *J* = 18.3, 1.6, 1.6 Hz, 2H)
1.90 (s, 6H)	1.90 (s, 6H)

[a]Reference value not provided for previously reported data.

^{13}C NMR Data (DMSO-d_6, data for synthetic material referenced to DMSO-d_6 at 40.0 ppm)[a]

Reported[4]	**Synthetic**
169.7	169.7
162.3	162.3
141.6	141.6
139.2	139.2
114.0	114.0
105.4	105.4
76.4	76.4
69.9	70.0
62.9	62.9
34.1	34.1
21.2	21.2

[a]Reference value not provided for previously reported data.

2.5 NOTES AND REFERENCES

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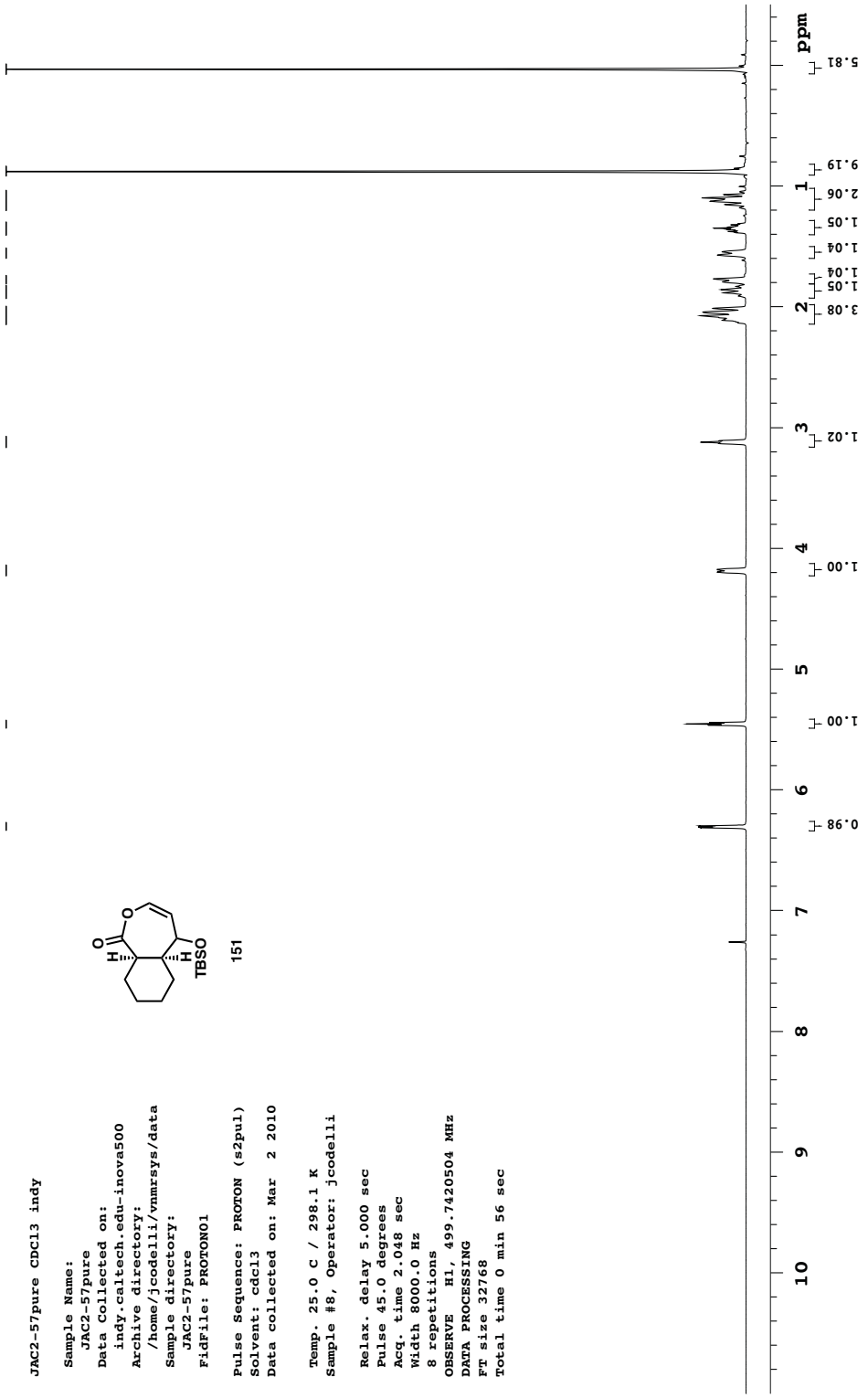
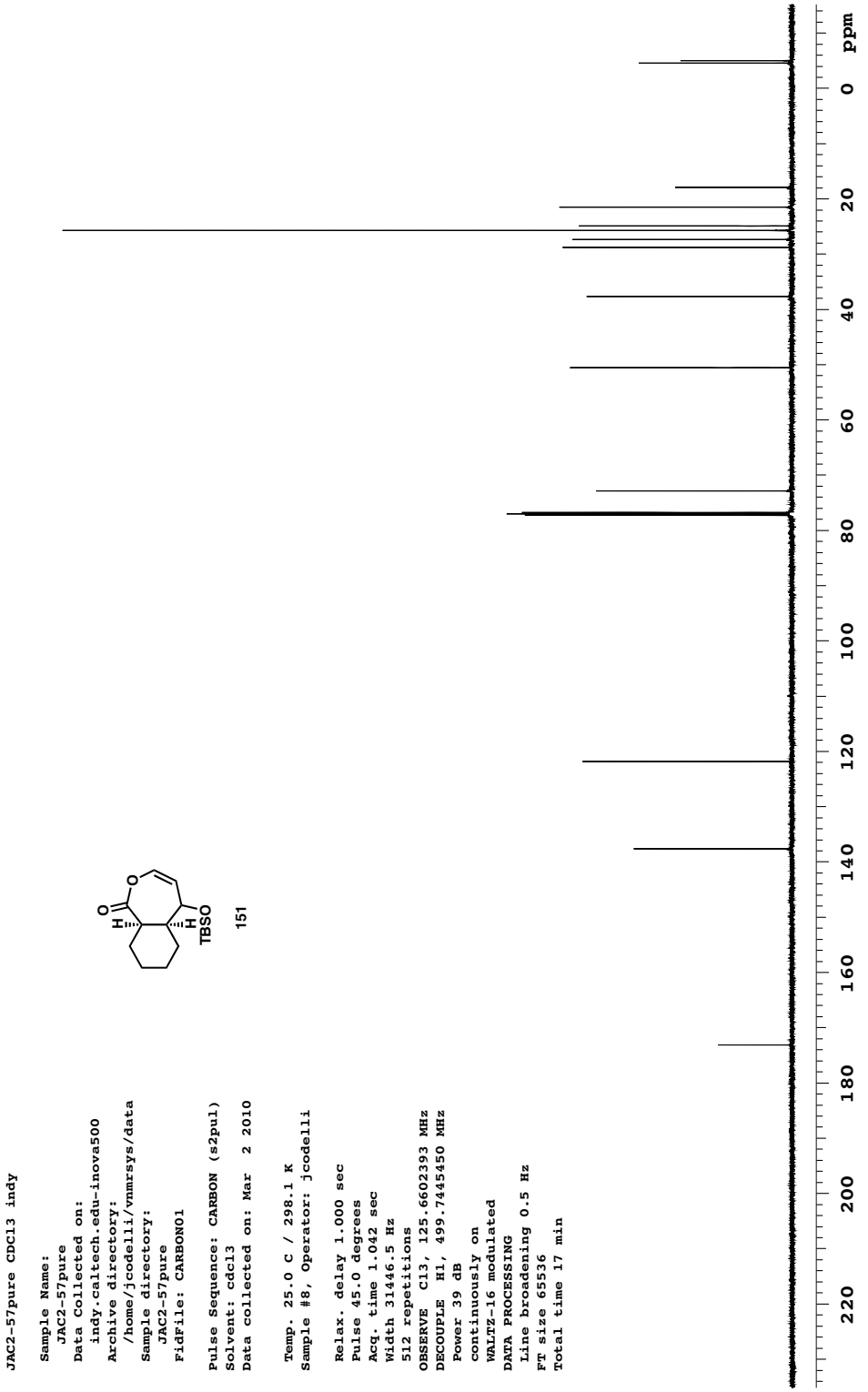
Appendix 1

Spectra Relevant to Chapter 2:
Enantioselective Total Synthesis of (–)-Acetylaranotin


JAC2-57pure CDCl3 indy
Sample Name:
JAC2-57pure
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC2-57pure
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 2 2010
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420504 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 56 sec
O
H
O
H
TBSO
151
ppm
10
9
8
7
6
5
4
3
2
1
5.81
9.19
2.06
1.05
1.04
1.04
1.05
3.08
1.02
1.00
1.00
0.98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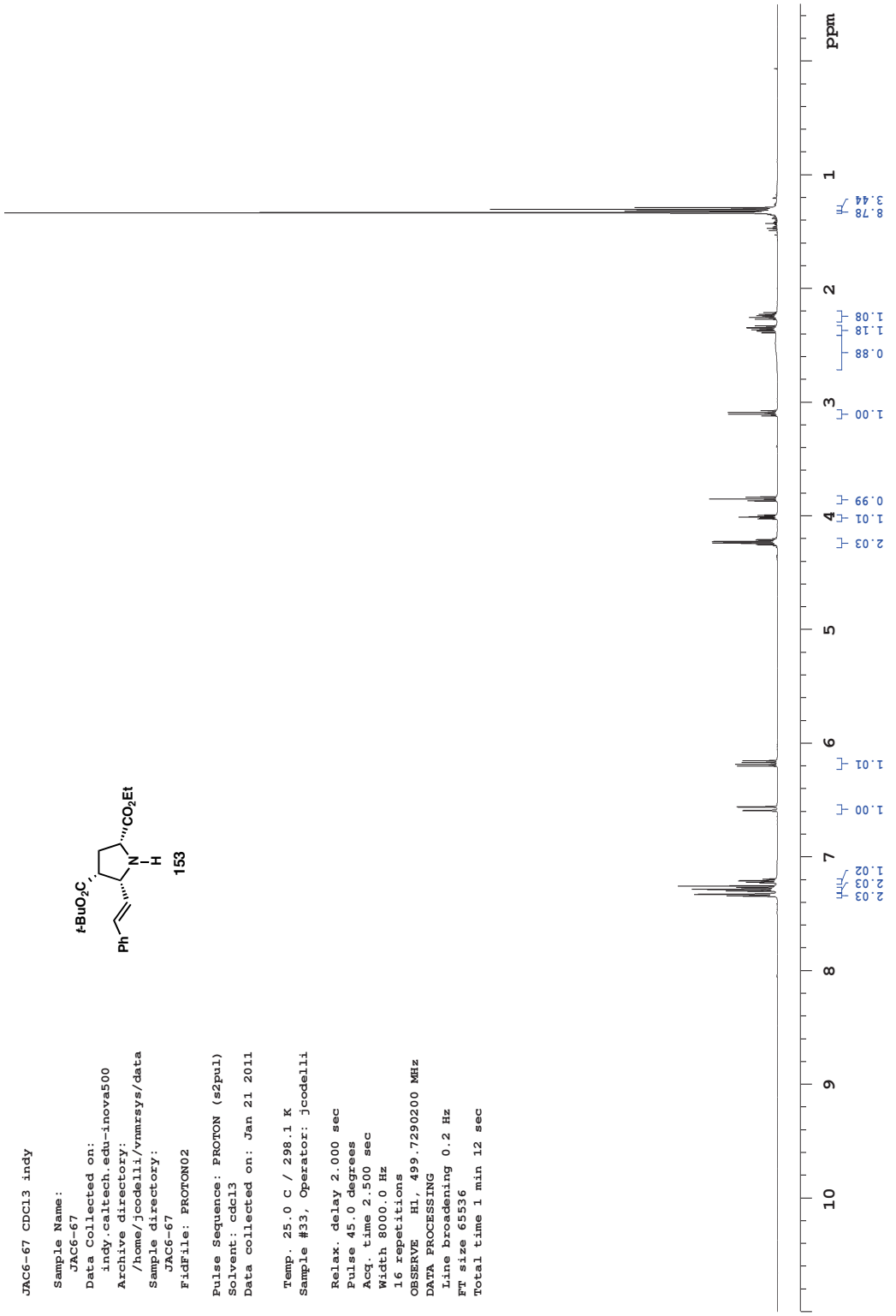
Sample Name:
JAC2-57pure
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC2-57pure
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 2 2010
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6602393 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
O
H
O
H
TBSO
151
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Archive directory:
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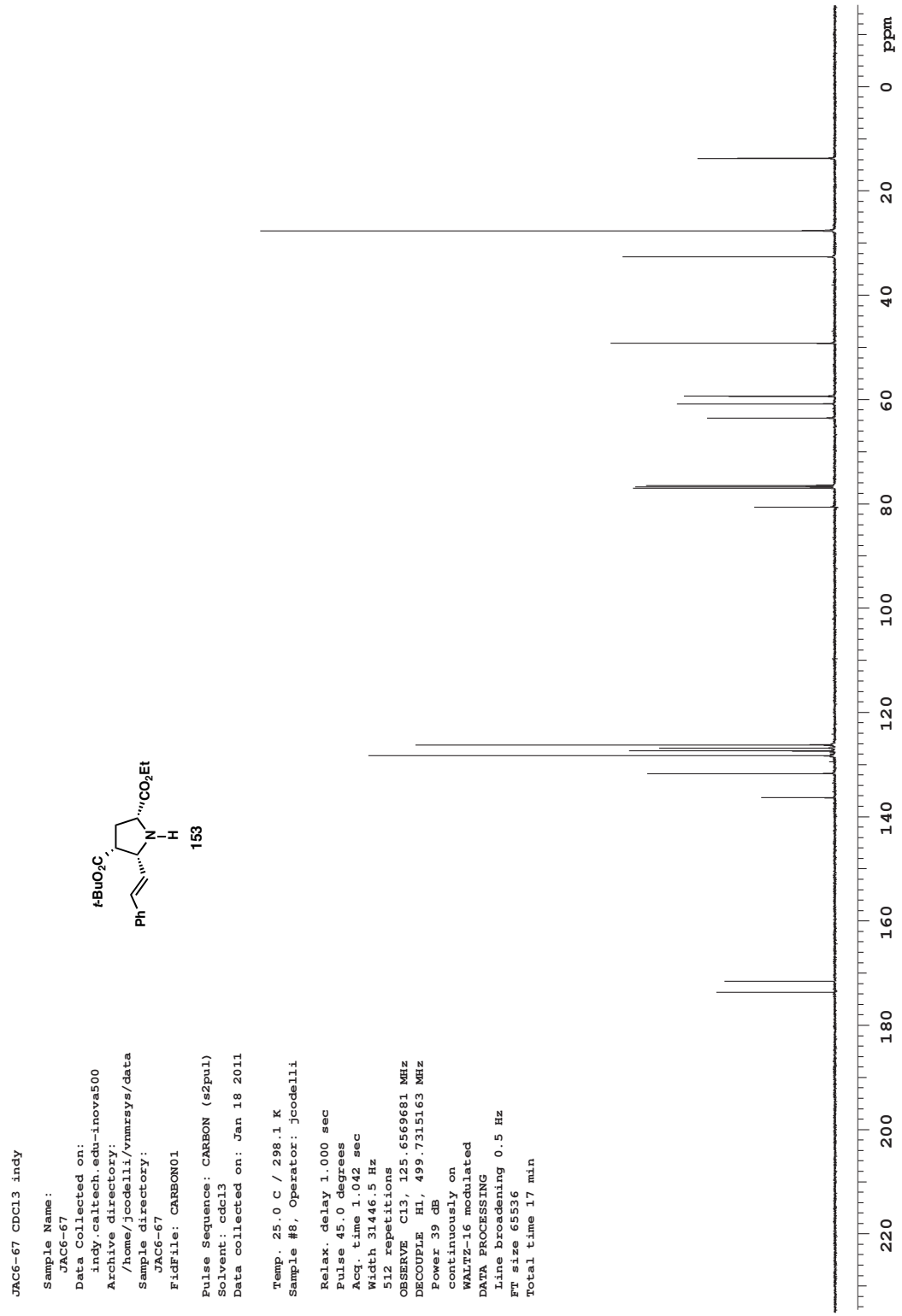
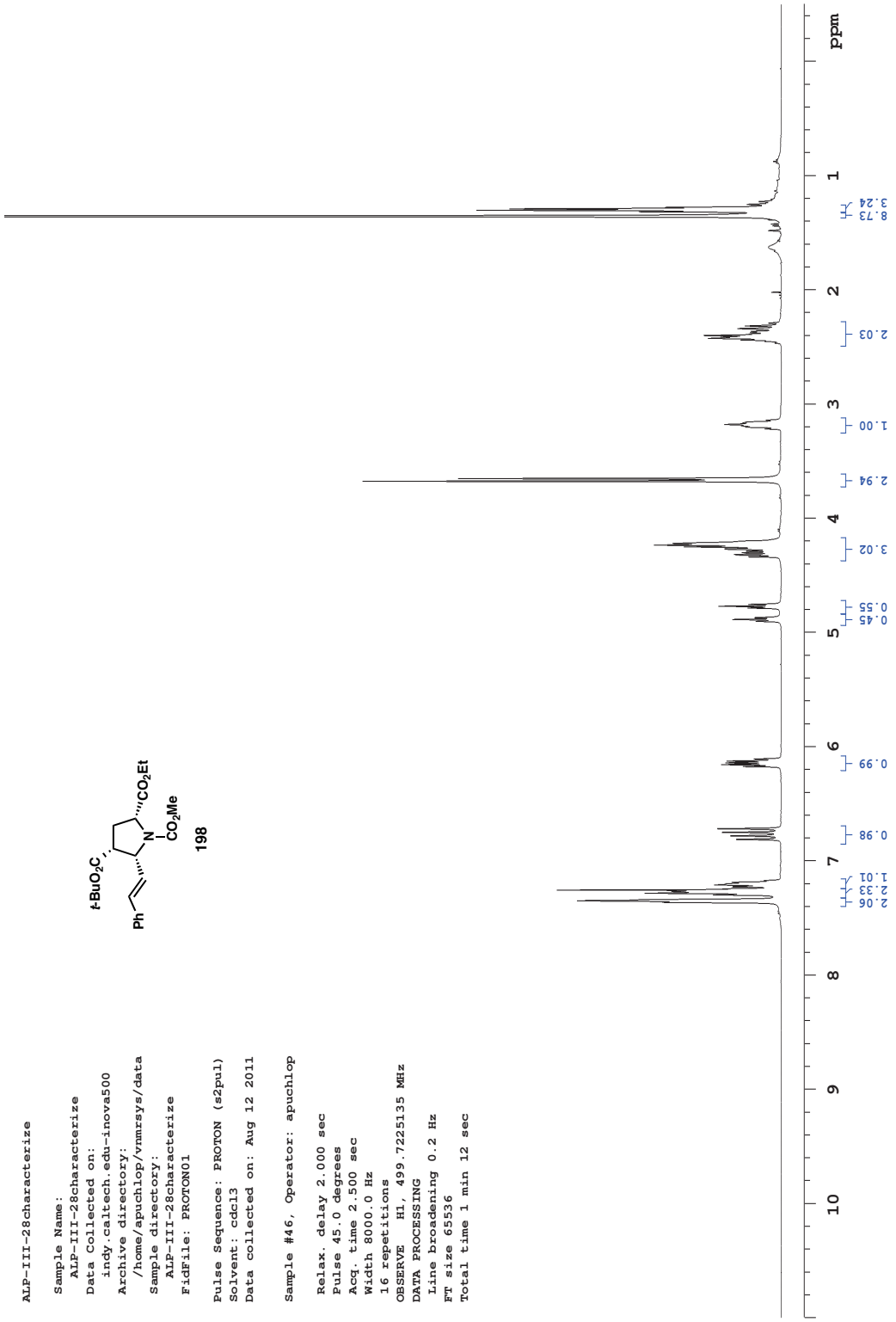
Sample directory:
JAC6-67
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
t-BuO2C
CO2Et
Ph
N
H
153
ppm
10
9
8
7
6
5
4
3
2
1
2.03
2.03
1.02
1.00
1.01
2.03
1.01
0.99
1.00
0.88
1.18
1.08
8.78
3.44


JAC6-67 CDCl3 indy
Sample Name:
JAC6-67
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-67
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 18 2011
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569681 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
t-BuO2C
CO2Et
Ph
N
H
153
220
200
180
160
140
120
100
80
60
40
20
0
ppm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ALP-III-28characterize
Data Collected on:
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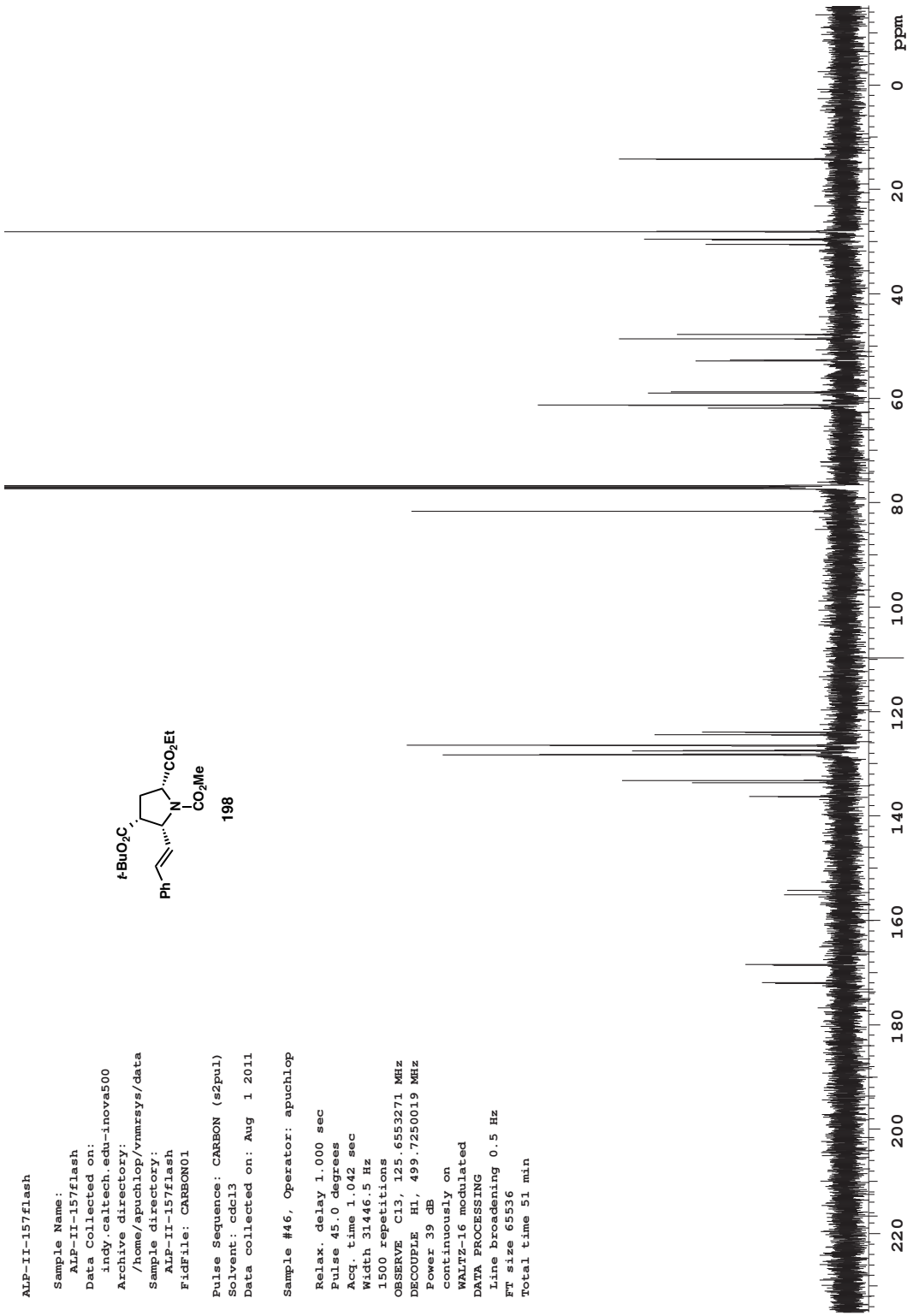
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-III-28characterize
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 12 2011
Sample #46, Operator: apuchlop
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225135 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
t-BuO2C
CO2Et
N
CO2Me
Ph
198
ppm
10
9
8
7
6
5
4
3
2
1
2.06
2.33
1.01
0.98
0.99
0.45
0.55
3.02
2.94
1.00
2.03
8.73
3.24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Sample Name:
ALP-II-157flash
Data Collected on:
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Archive directory:
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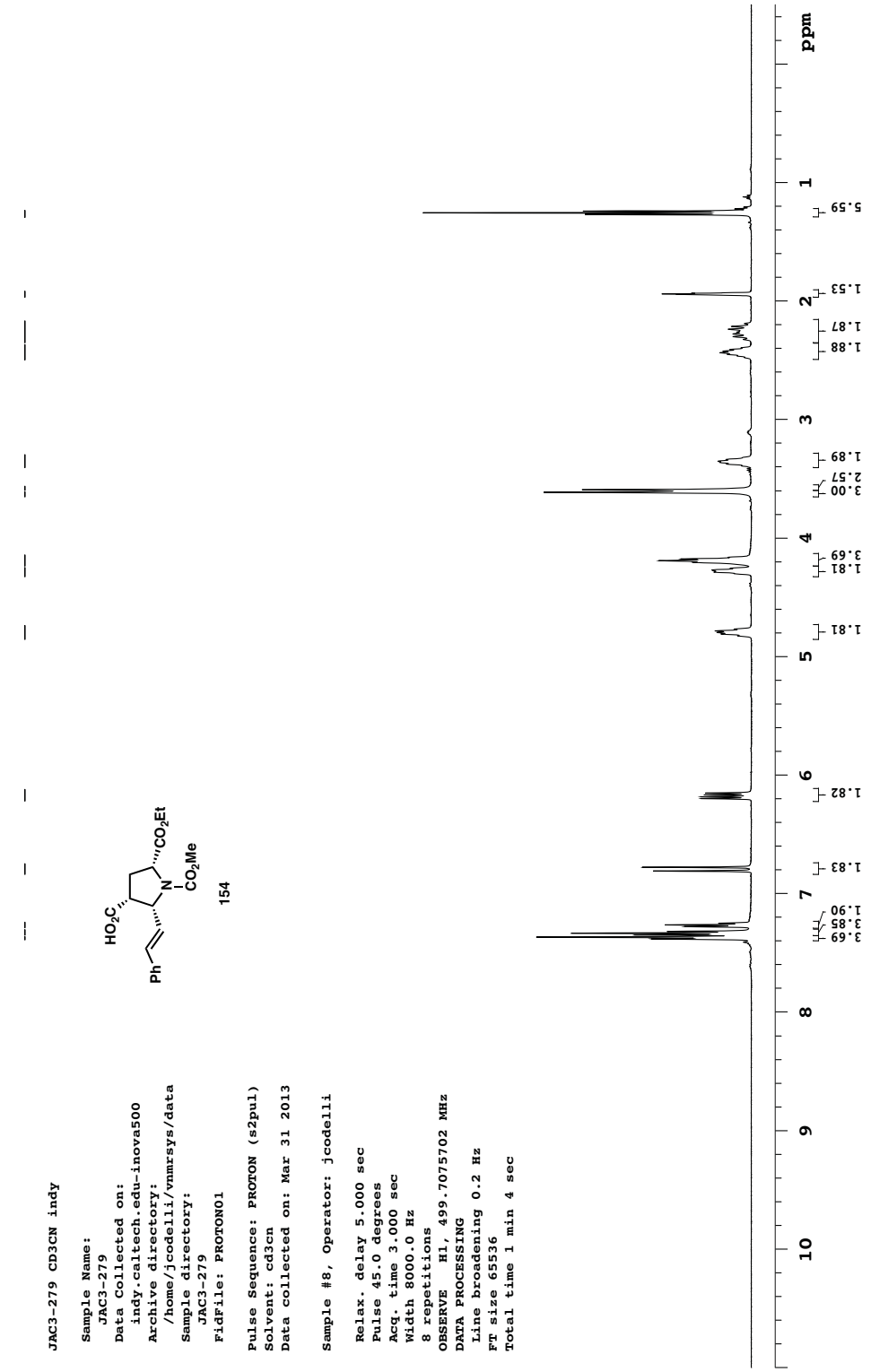
Sample directory:
ALP-II-157flash
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 1 2011
Sample #46, Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553271 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
t-BuO2C
Ph
N
CO2Et
CO2Me
198
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Sample Name:
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Data Collected on:
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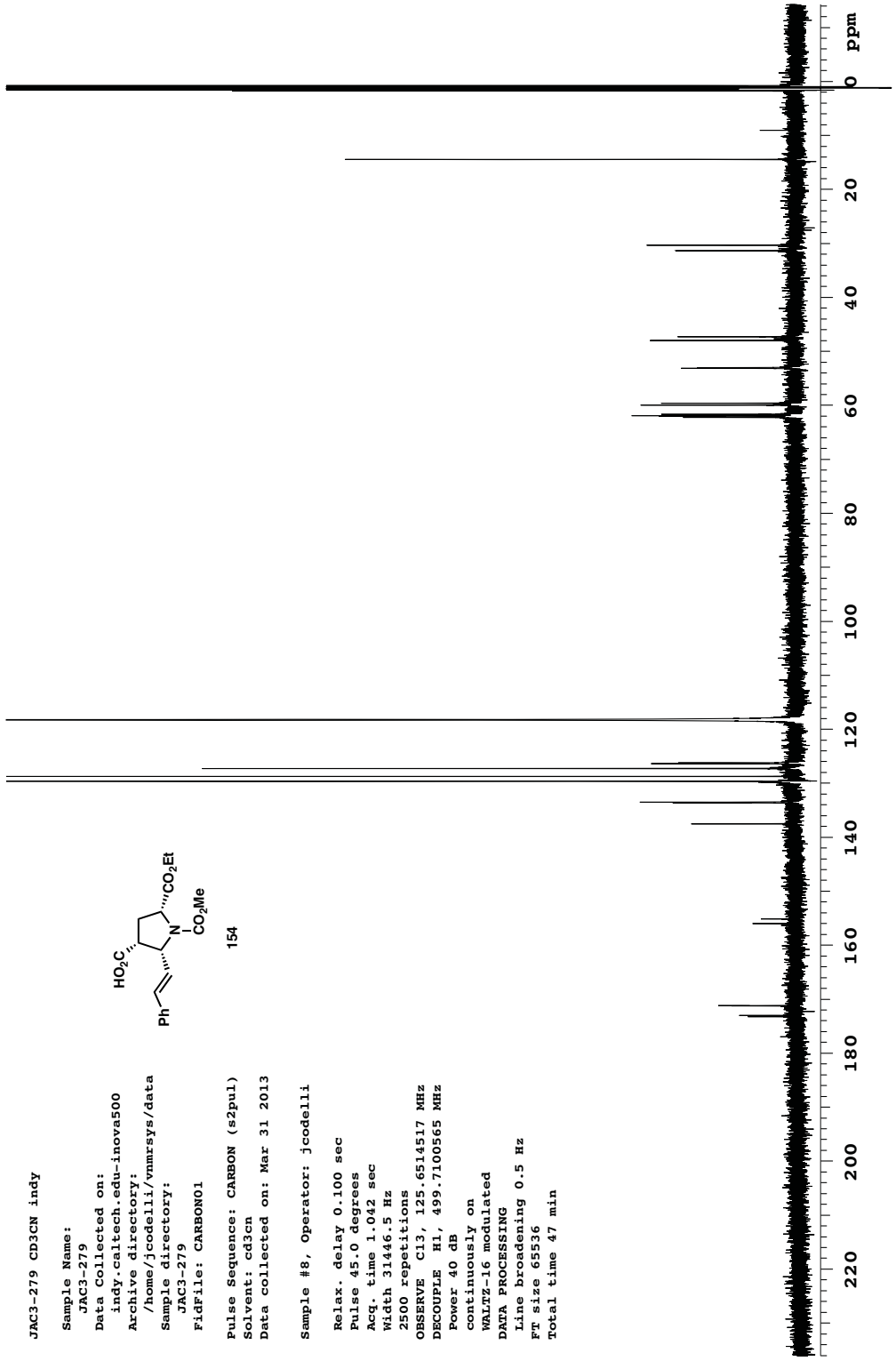
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC3-279
FidFile: PROTON01
154
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7075702 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
HO2C
CO2Et
N
CO2Me
Ph
ppm
1
2
3
4
5
6
7
8
9
10
5.59
1.53
1.88
1.87
1.89
2.57
3.00
1.81
3.69
1.81
1.82
1.83
3.69
3.85
1.90


JAC3-279 CD3CN indy
Sample Name:
JAC3-279
Data Collected on:
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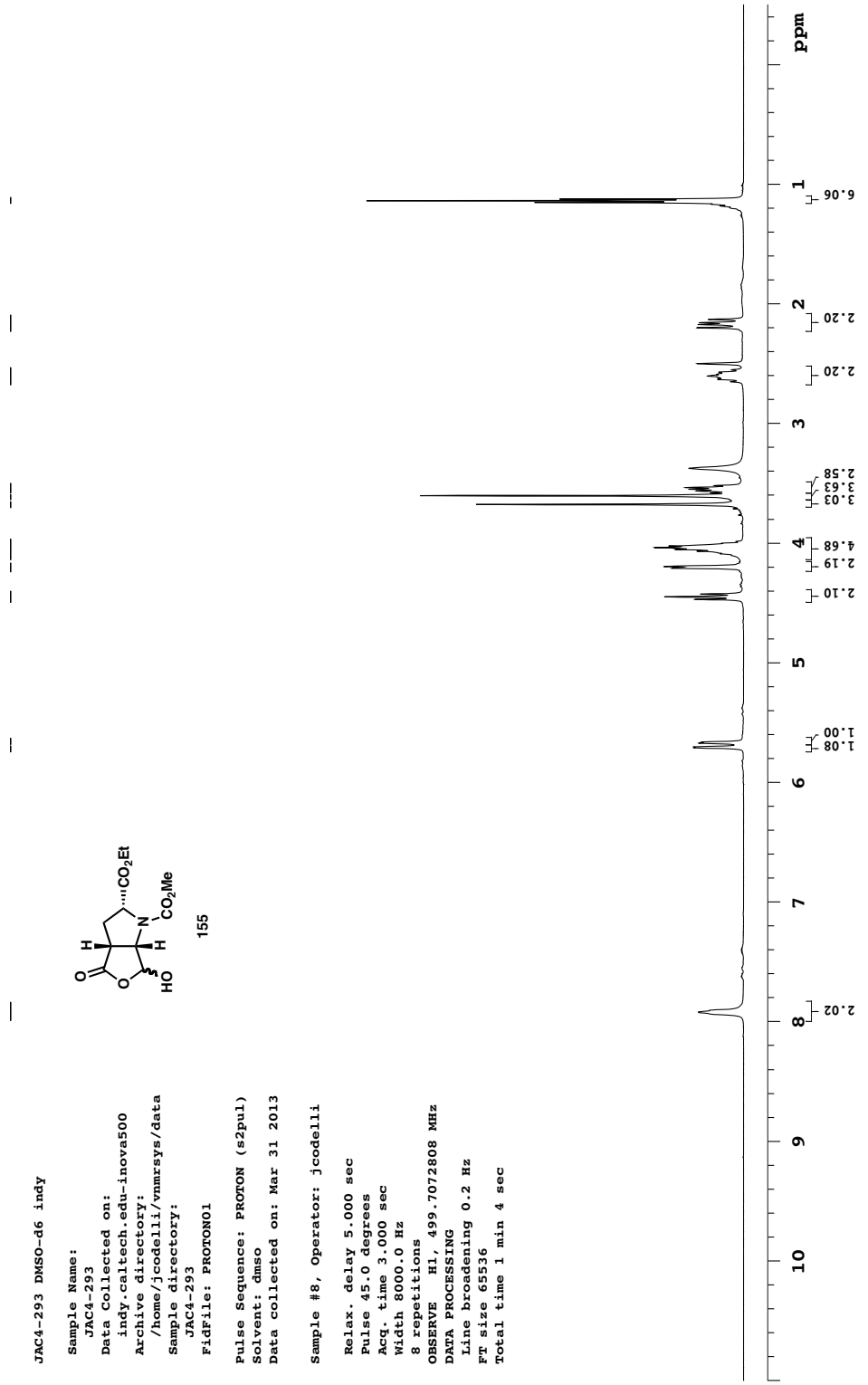
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC3-279
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 repetitions
OBSERVE C13, 125.6514517 MHz
DECOUPLE H1, 499.7100565 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 47 min
HO2C
Ph
CO2Et
N
CO2Me
154
220
200
180
160
140
120
100
80
60
40
20
0 ppm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Sample Name:
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Data Collected on:
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Archive directory:
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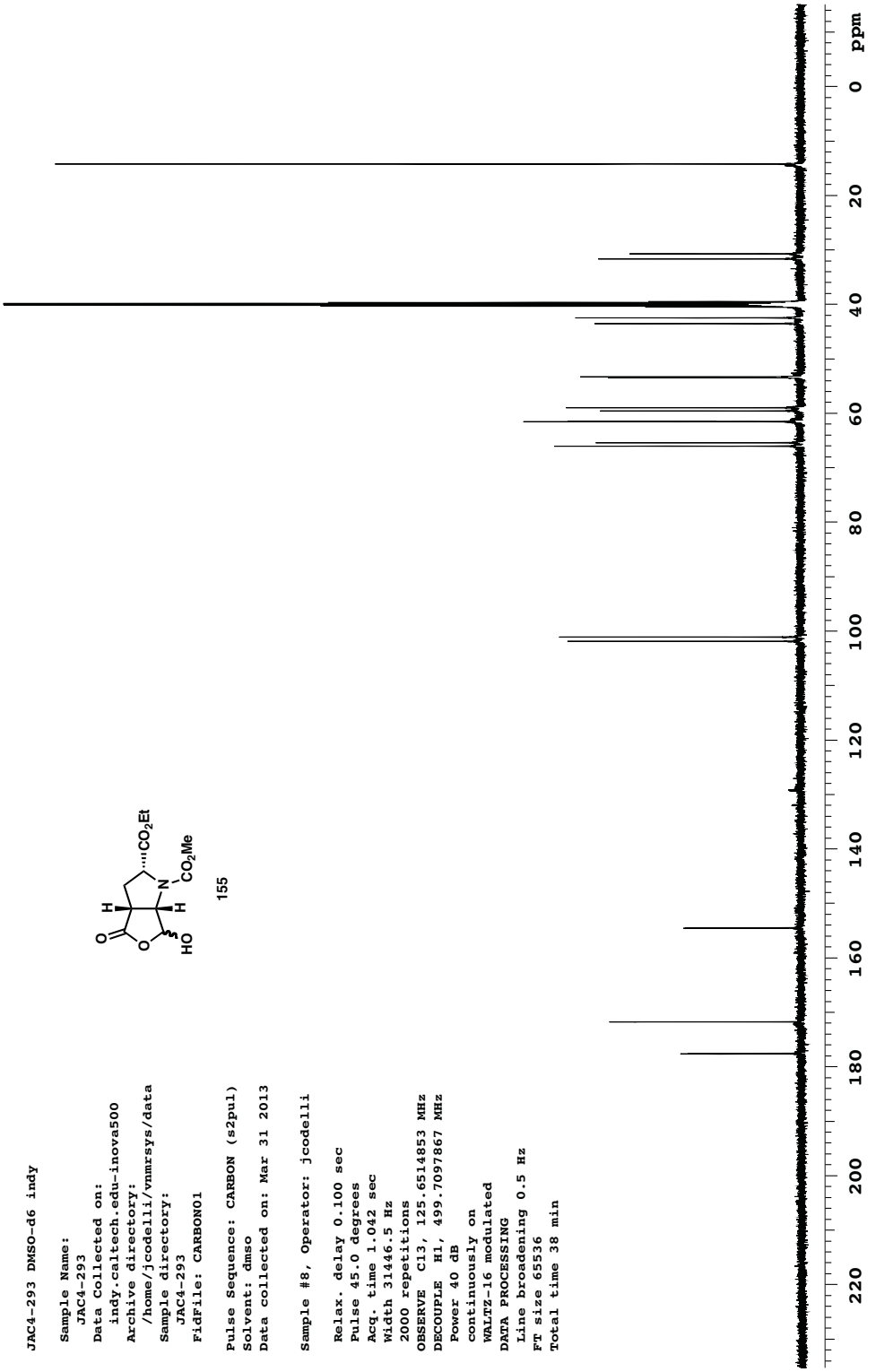
Sample directory:
JAC4-293
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7072808 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
155
ppm
6.06
2.20
2.20
2.58
3.63
3.03
4.68
2.19
2.10
1.08
1.00
2.02


JAC4-293 DMSO-d6 indy
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Data Collected on:
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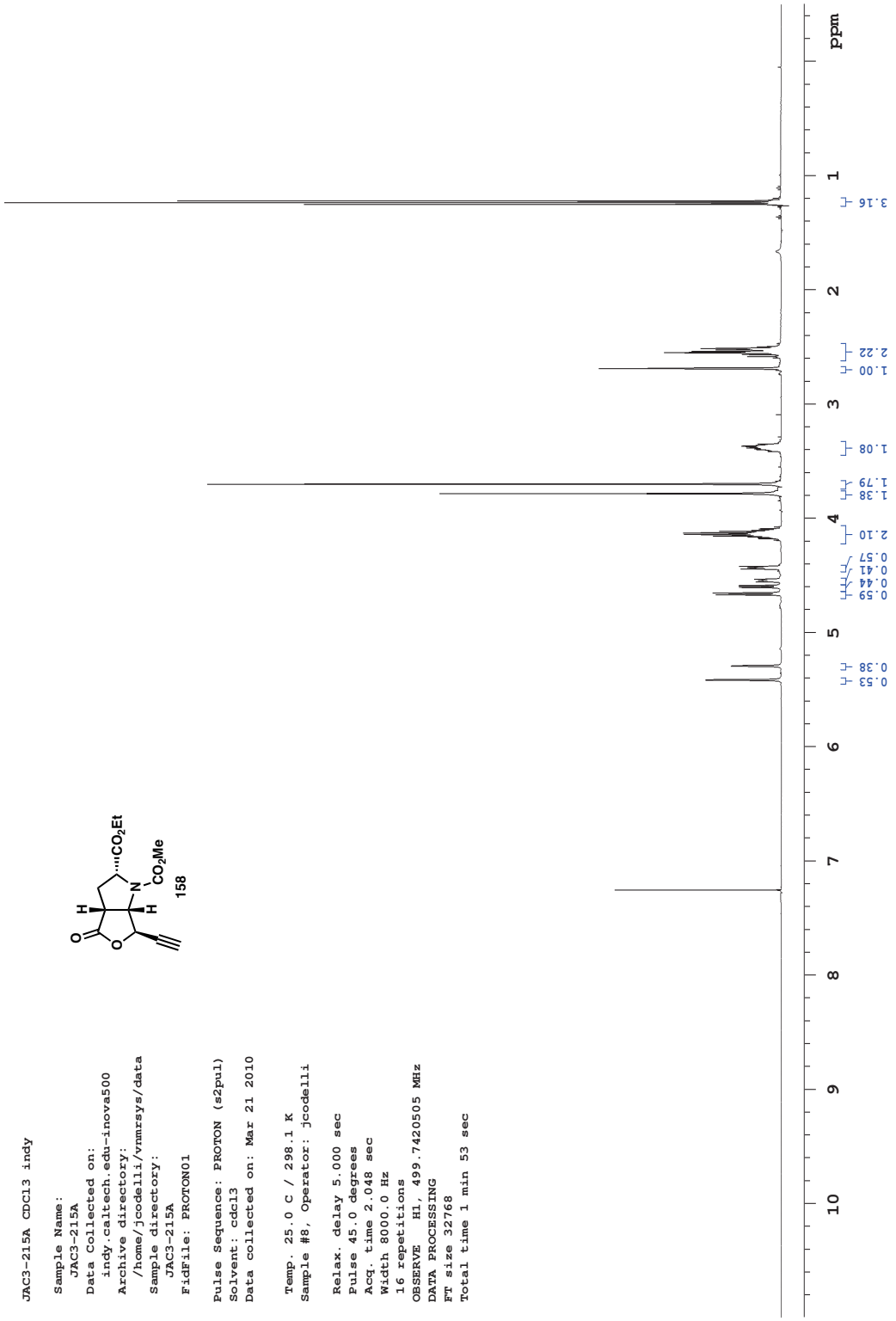
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-293
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6514853 MHz
DECOUPLE H1, 499.7097867 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min
155
220
200
180
160
140
120
100
80
60
40
20
0
ppm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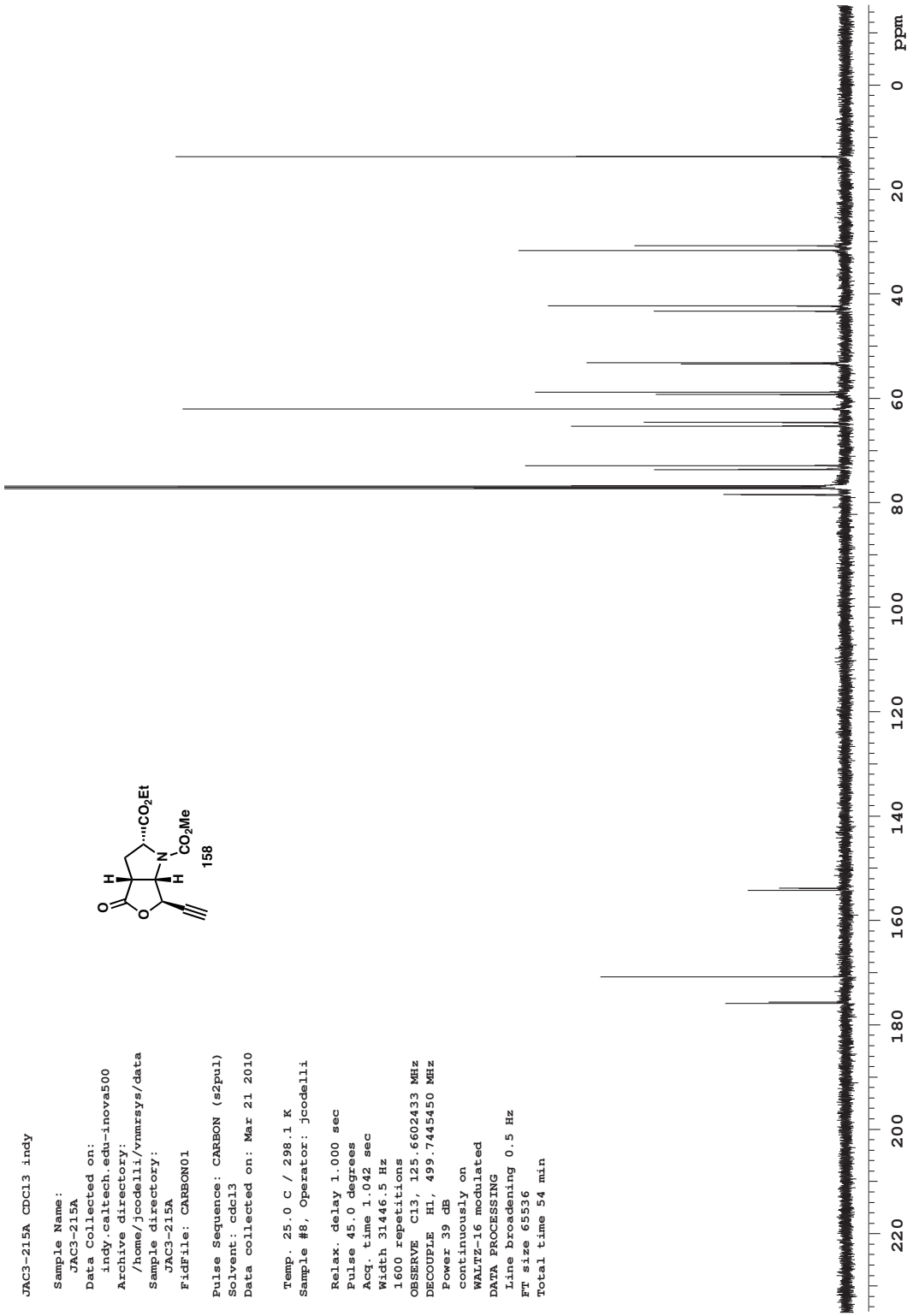
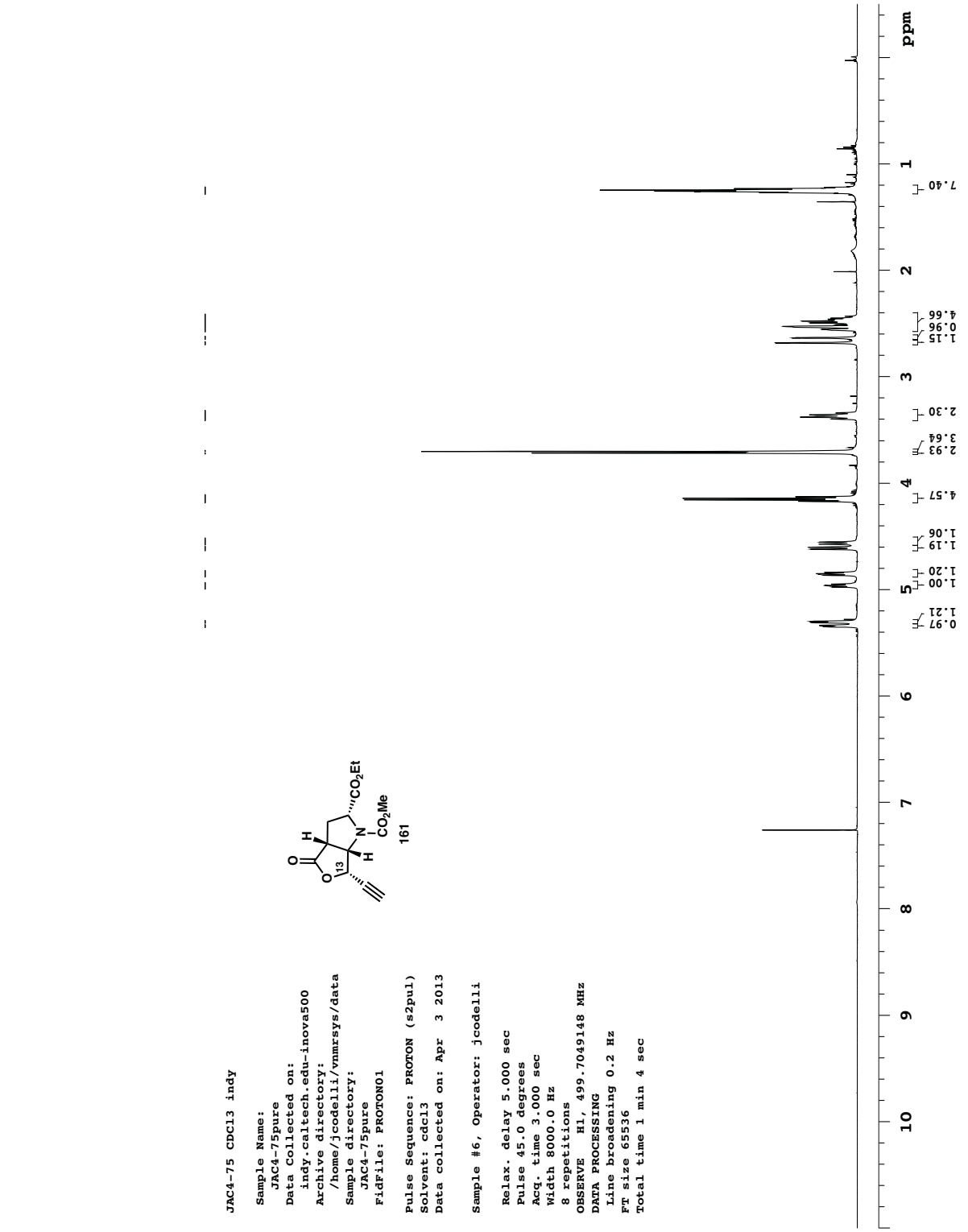
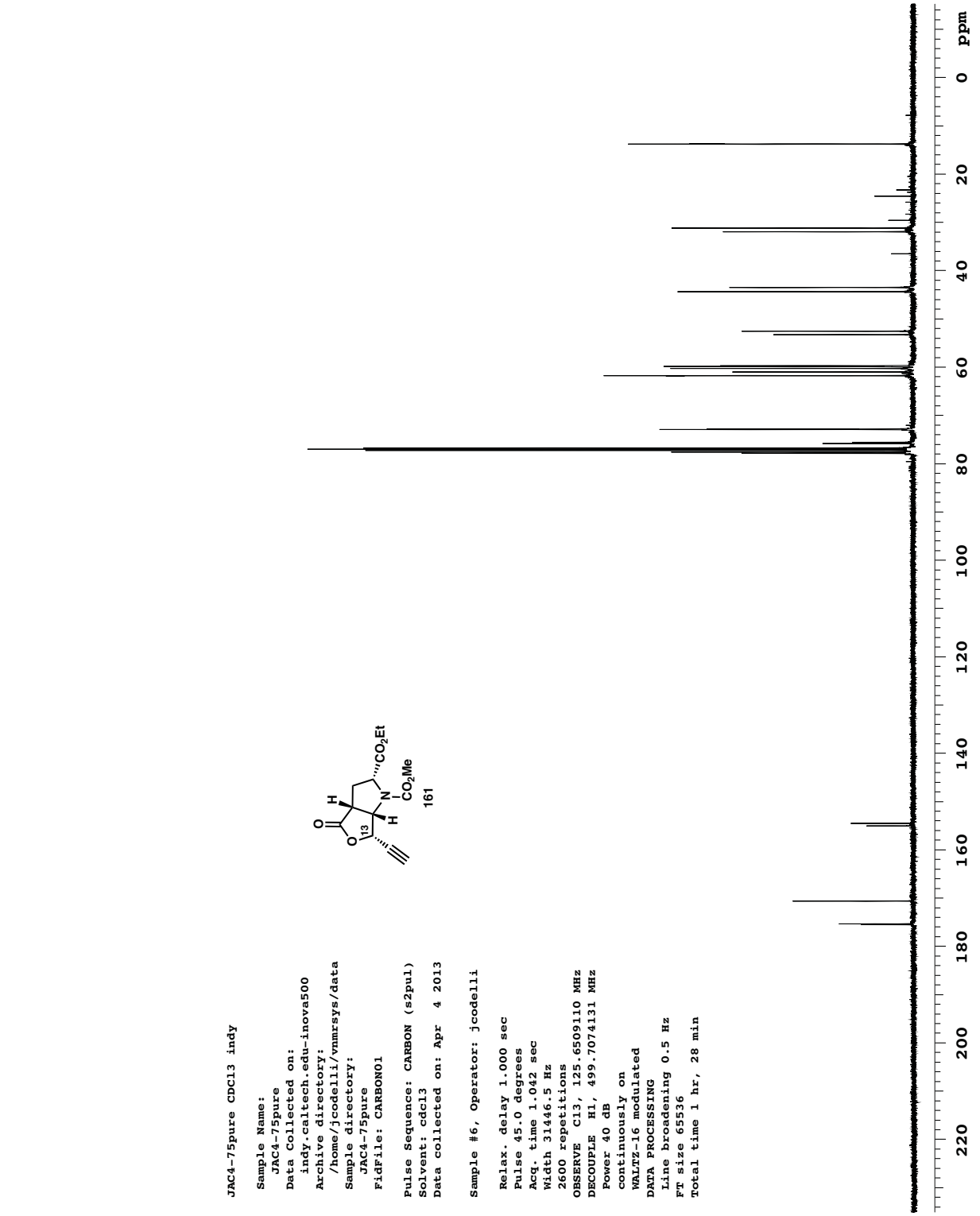
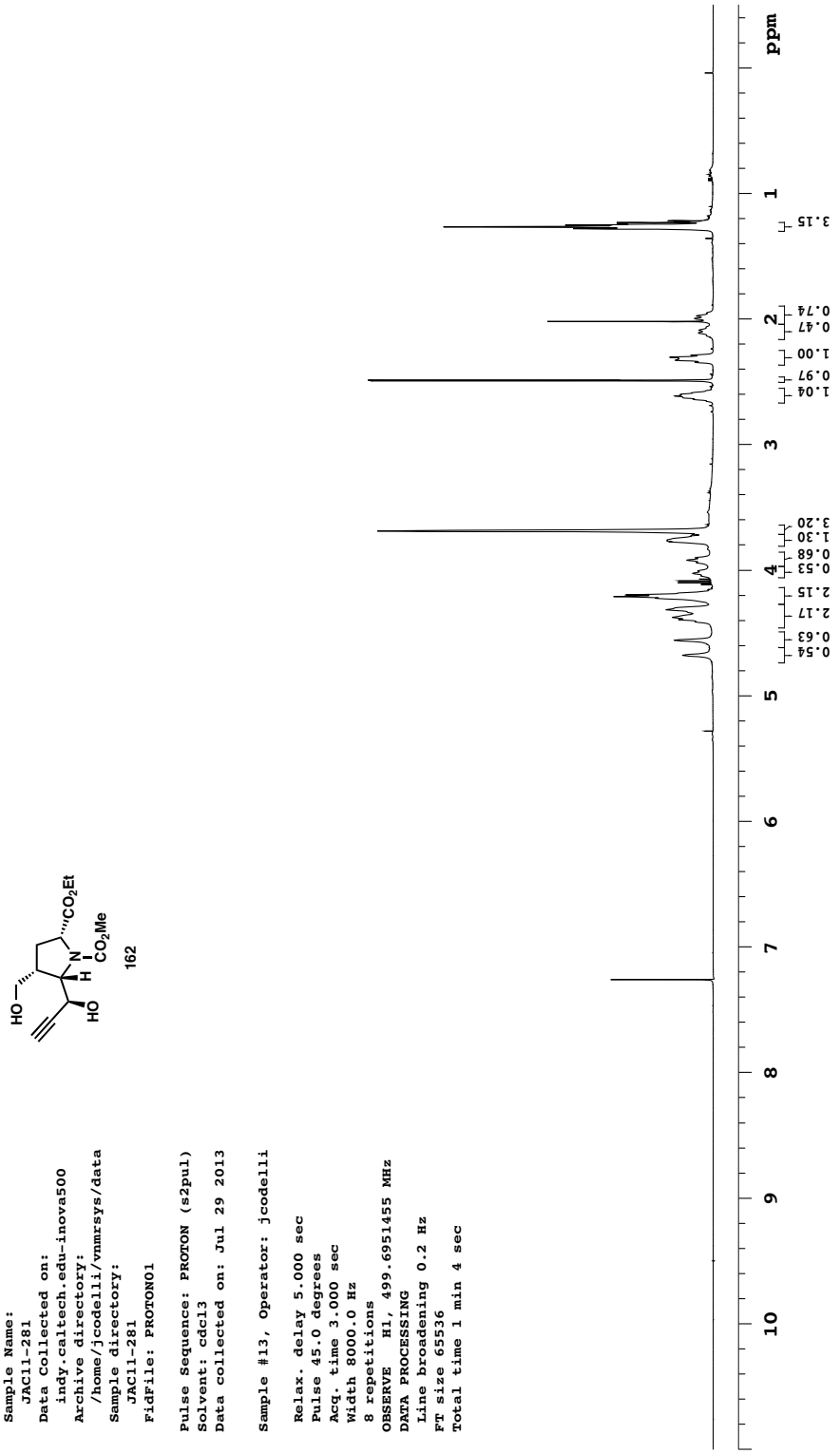
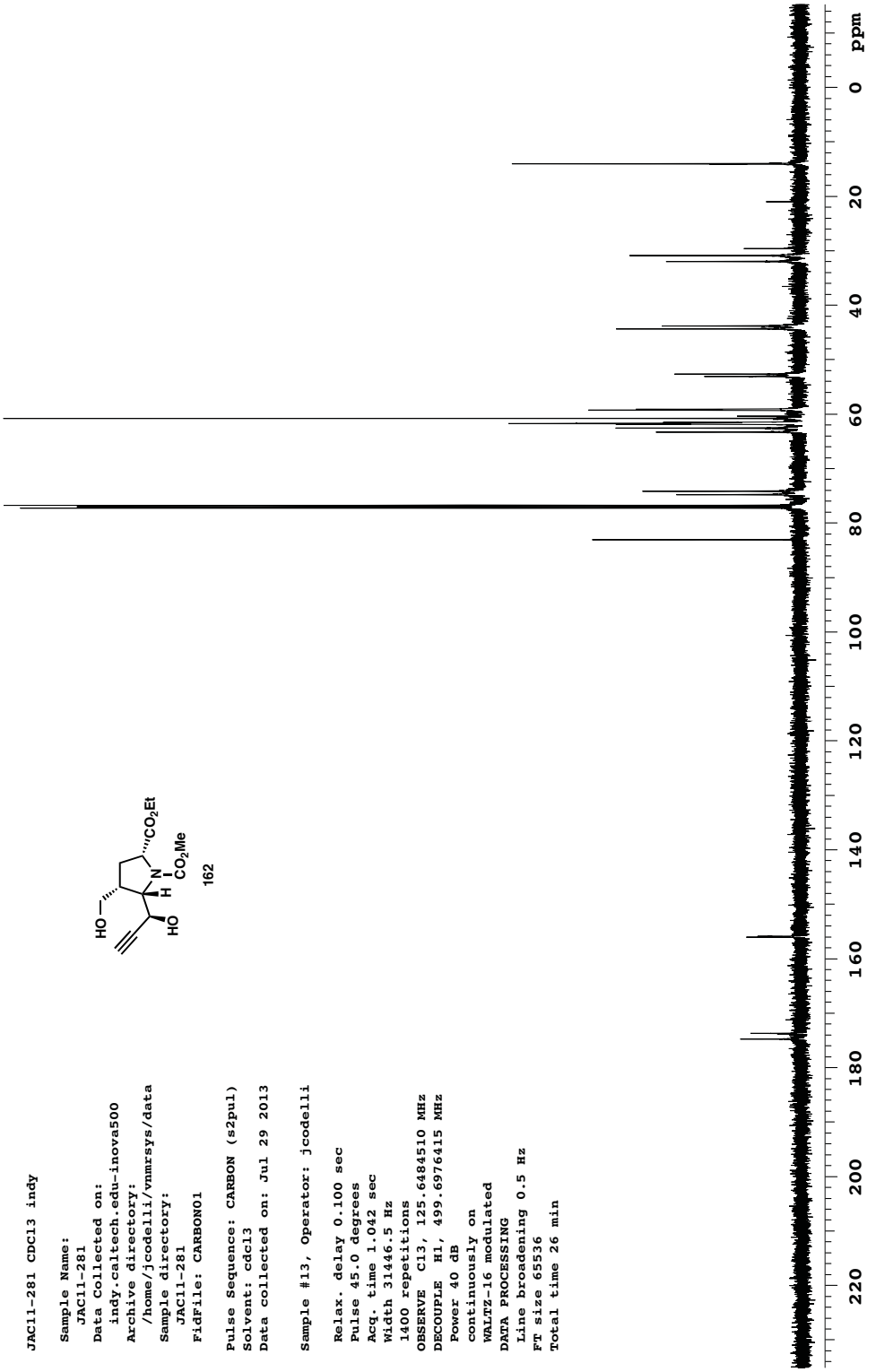
Sample Name:
JAC3-215A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC3-215A
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2010
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 53 sec
158
ppm
3.16
2.22
1.00
1.08
1.79
1.38
2.10
0.57
0.41
0.44
0.59
0.38
0.53

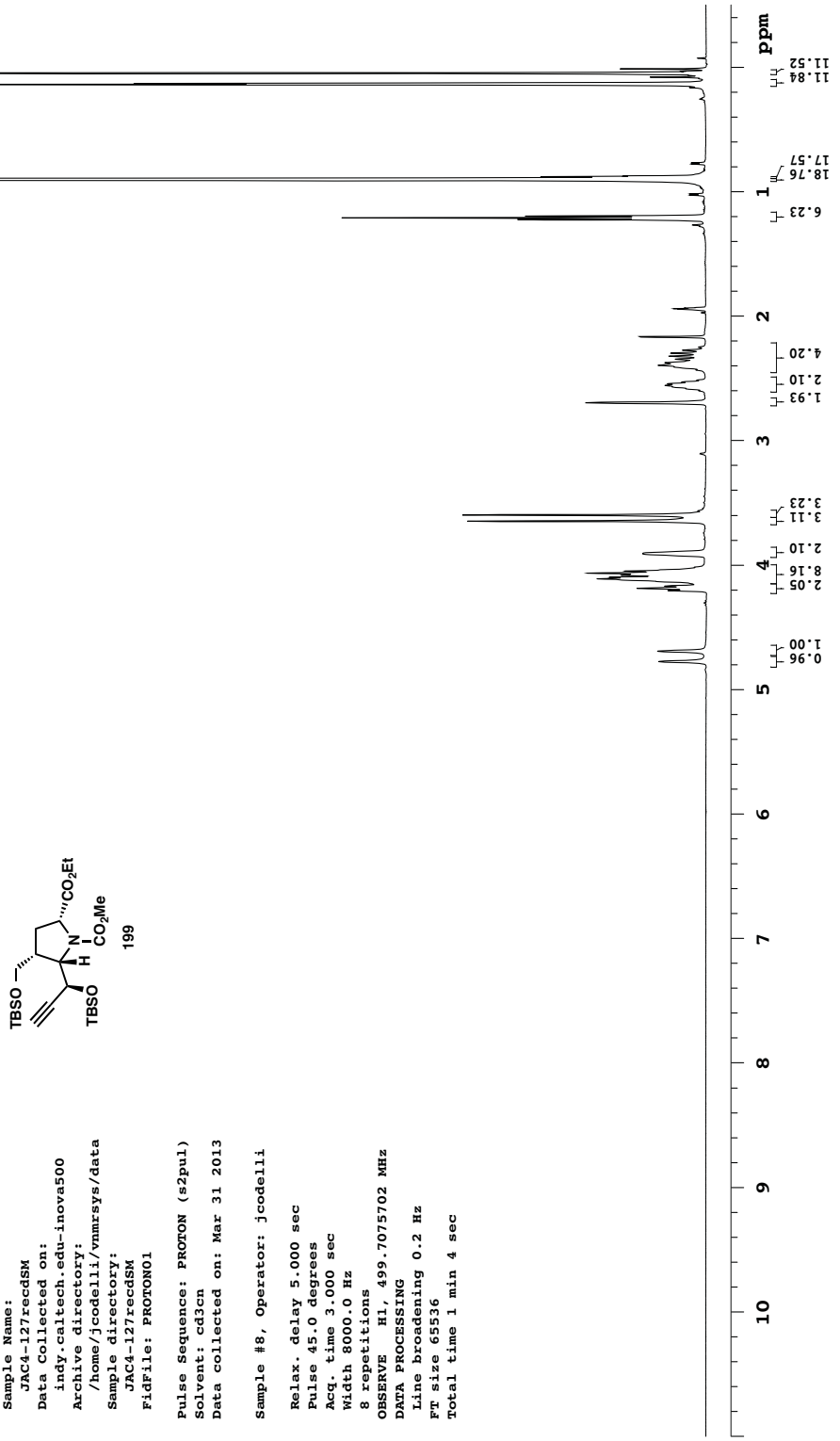

JAC3-215A CDCl3 indy
Sample Name:
JAC3-215A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC3-215A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2010
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6602433 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 54 min
CO2Et
CO2Me
158
220
200
180
160
140
120
100
80
60
40
20
0
ppm

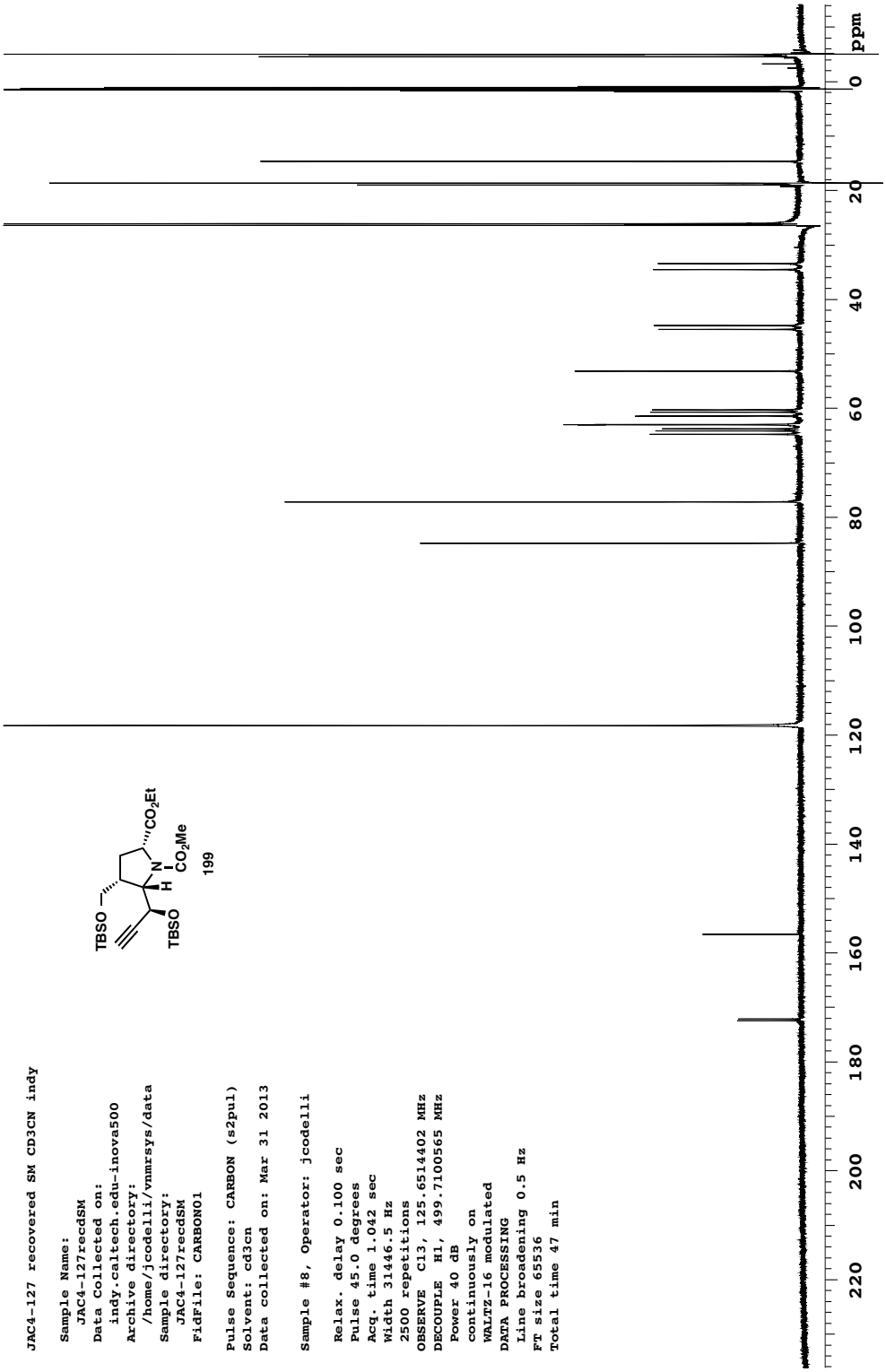

JAC4-75 CDCl3 indy
Sample Name:
JAC4-75pure
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-75pure
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2013
Sample #6, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049148 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
161
ppm
7.40
4.66
0.96
1.15
2.30
3.64
2.93
4.57
1.06
1.19
1.20
1.00
0.97
1.21

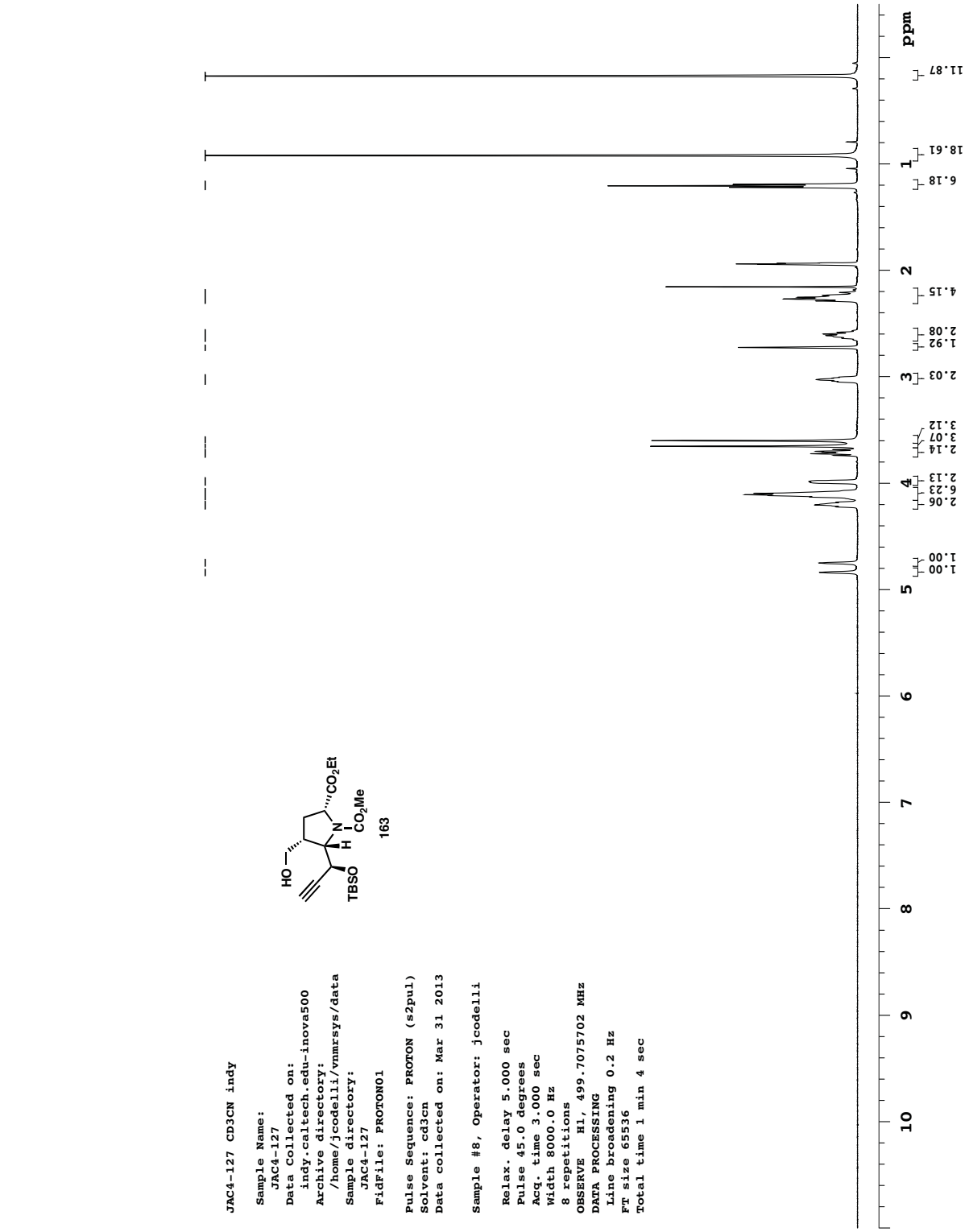

JAC4-75pure CDCl3 indy
Sample Name:
JAC4-75pure
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-75pure
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 4 2013
Sample #6, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2600 repetitions
OBSERVE C13, 125.6509110 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 1 hr, 28 min
O
H
O
13
H
N
CO2Et
CO2Me
161
220
200
180
160
140
120
100
80
60
40
20
0
ppm

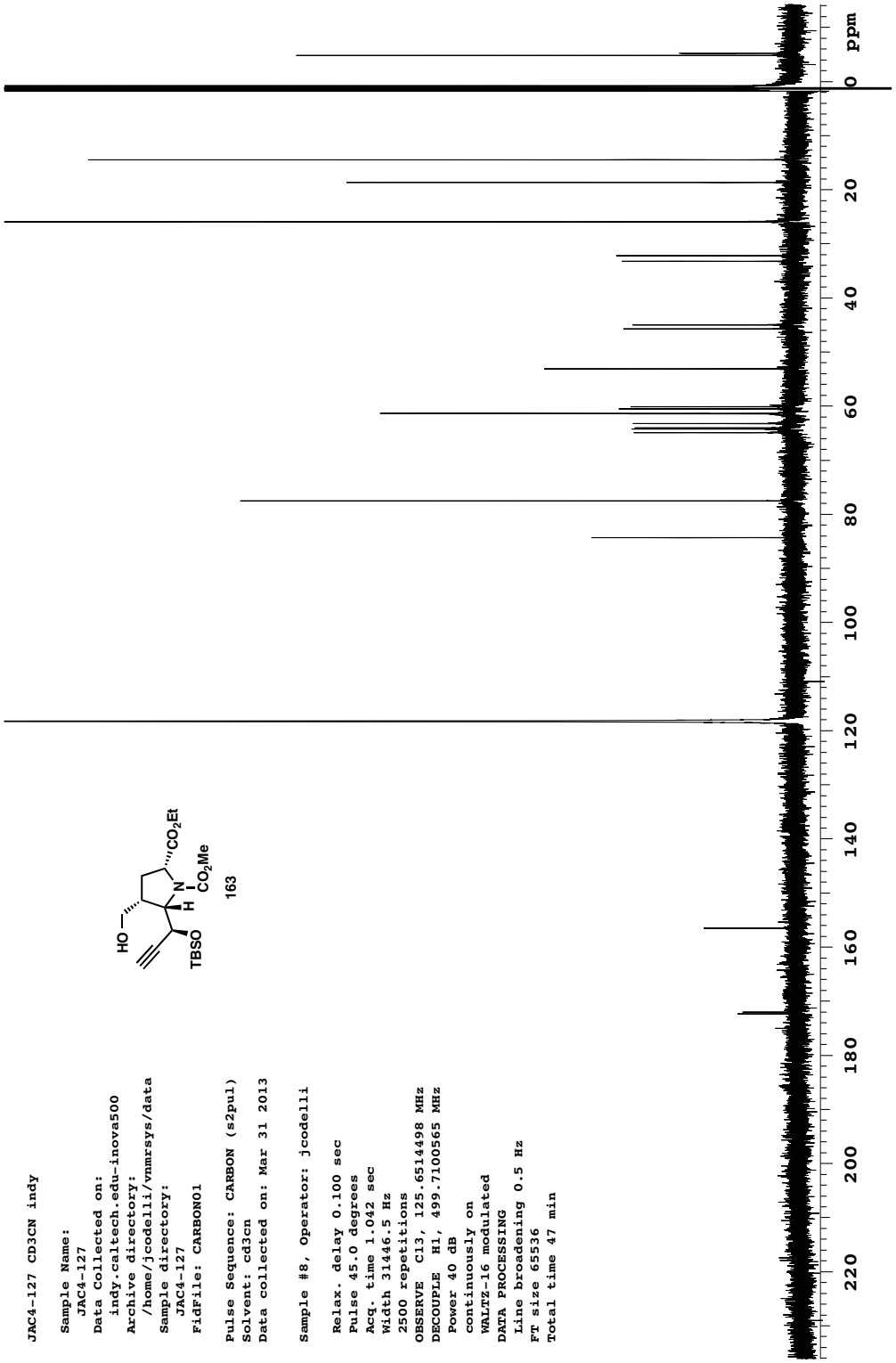

JAC11-281 CDCl3 indy
Sample Name:
JAC11-281
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-281
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 29 2013
Sample #13, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
HO
HO
N
H
CO2Et
CO2Me
162
ppm
10
9
8
7
6
5
4
3
2
1
0.54
0.63
2.17
2.15
0.53
0.68
1.30
3.20
1.04
0.97
1.00
0.47
0.74
3.15

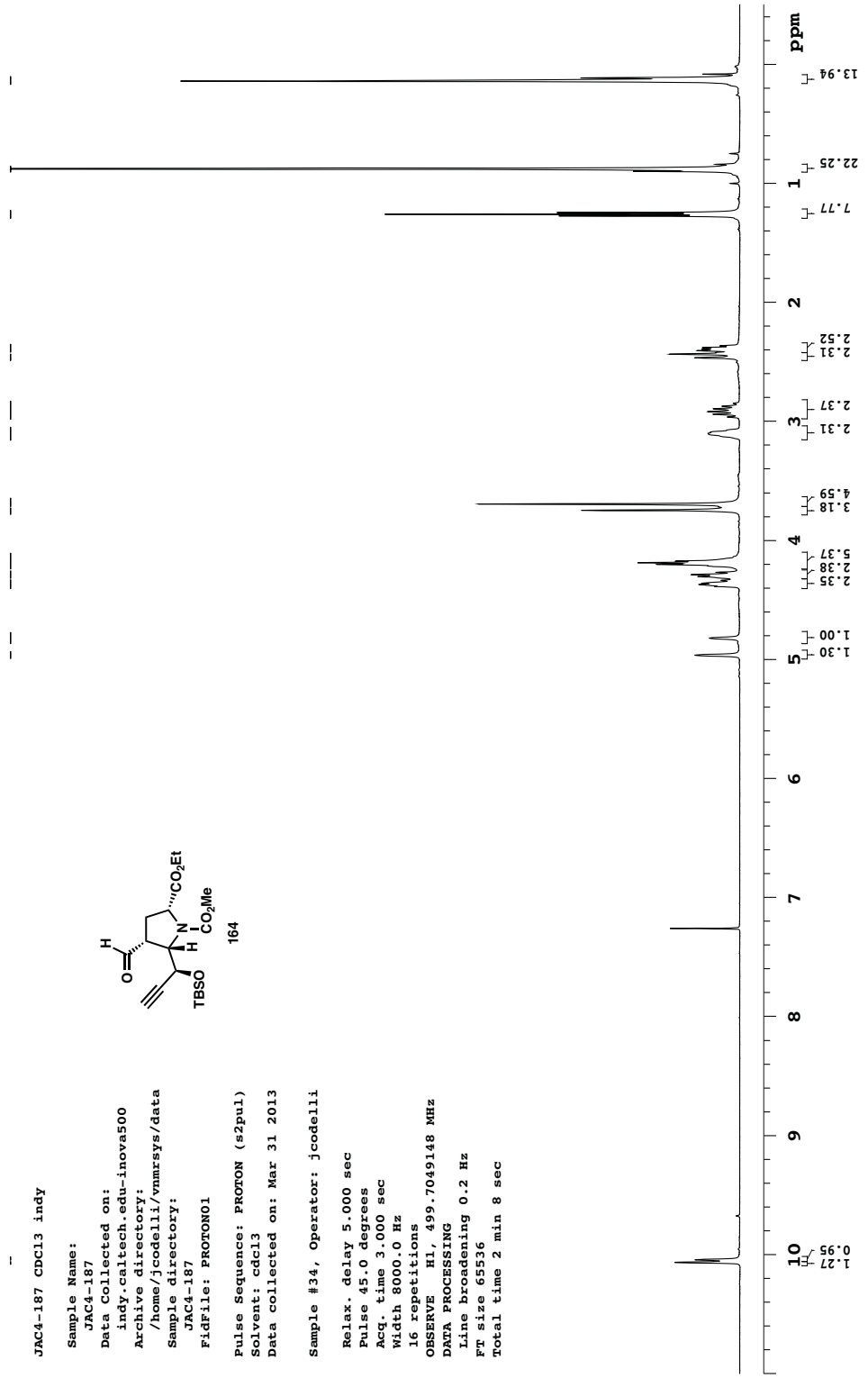

JAC11-281 CDCl3 indy
Sample Name:
JAC11-281
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-281
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 29 2013
Sample #13, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1400 repetitions
OBSERVE C13, 125.6484510 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 26 min
HO
HO
N
H
CO2Me
CO2Et
162
220
200
180
160
140
120
100
80
60
40
20
0
ppm

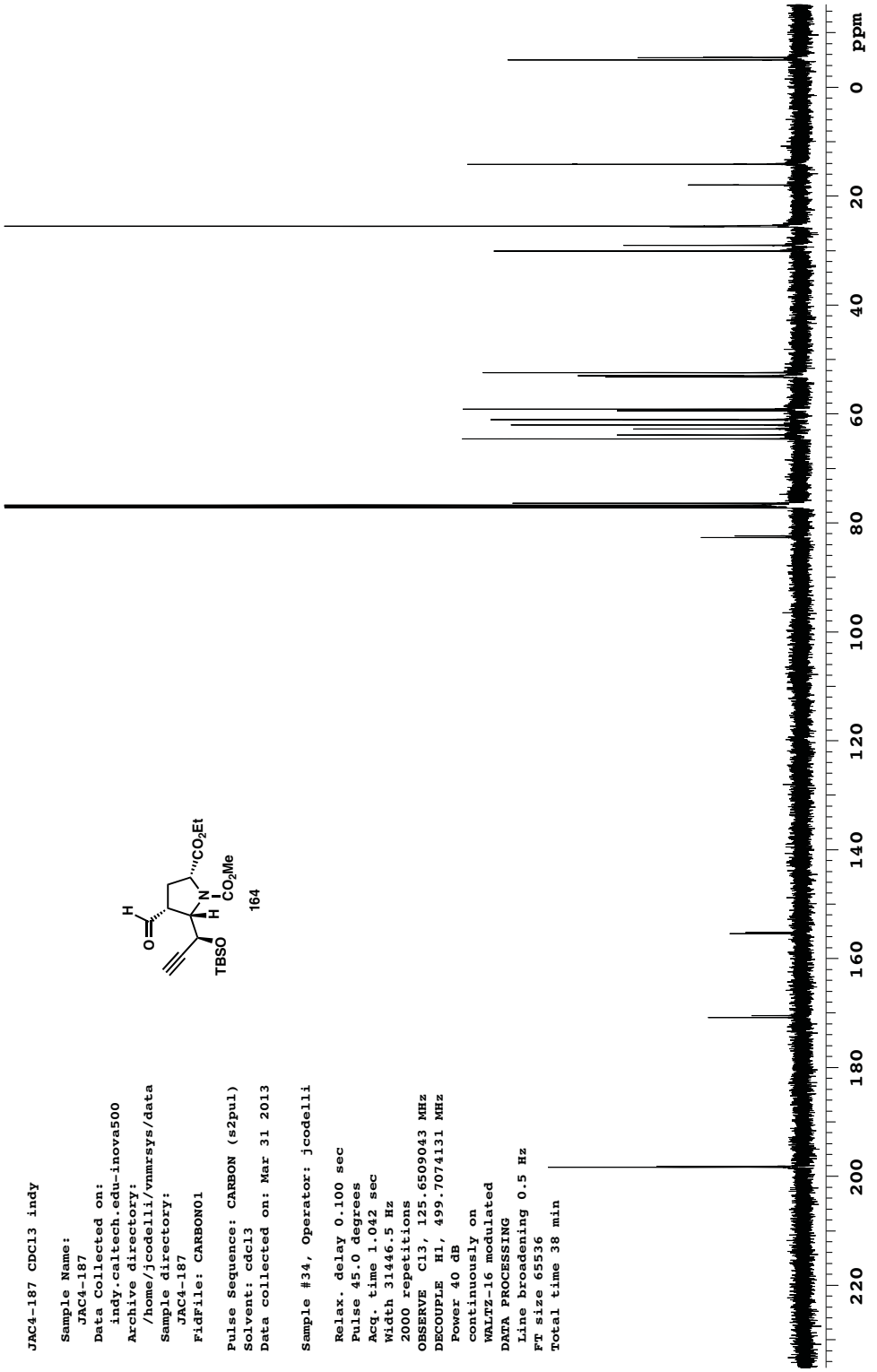

JAC4-127 recovered SM CD3CN indy
Sample Name:
JAC4-127recdSM
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-127recdSM
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7075702 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
TBSO
TBSO
CO2Et
CO2Me
199
ppm
11.84
11.52
18.76
17.57
6.23
4.20
2.10
1.93
3.11
3.23
2.10
2.05
8.16
2.10
0.96
1.00

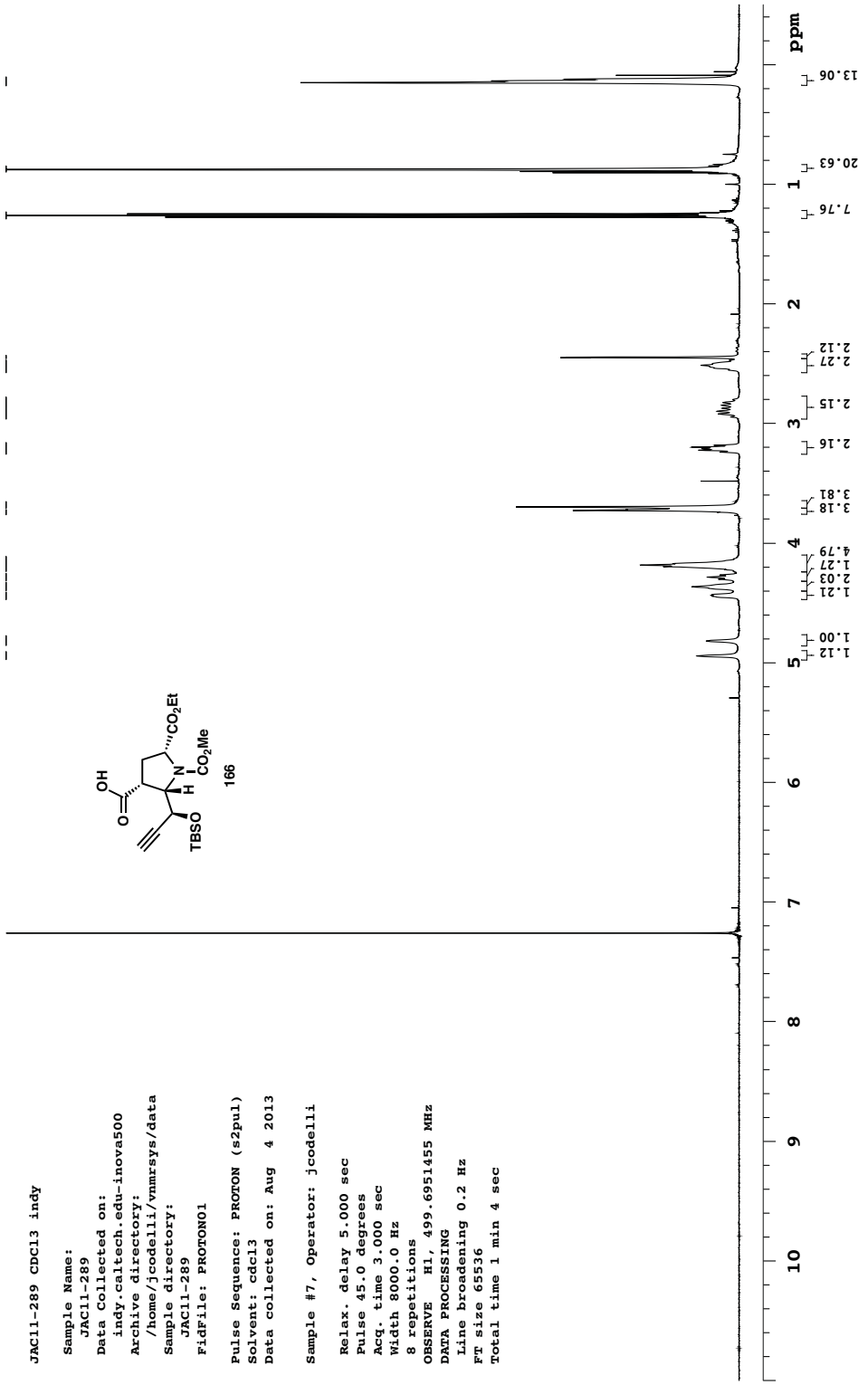

JAC4-127 recovered SM CD3CN indy
Sample Name:
JAC4-127recdSM
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-127recdSM
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 repetitions
OBSERVE C13, 125.6514402 MHz
DECOUPLE H1, 499.7100565 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 47 min
TBSO
TBSO
N
H
CO2Et
CO2Me
199
220
200
180
160
140
120
100
80
60
40
20
0
ppm

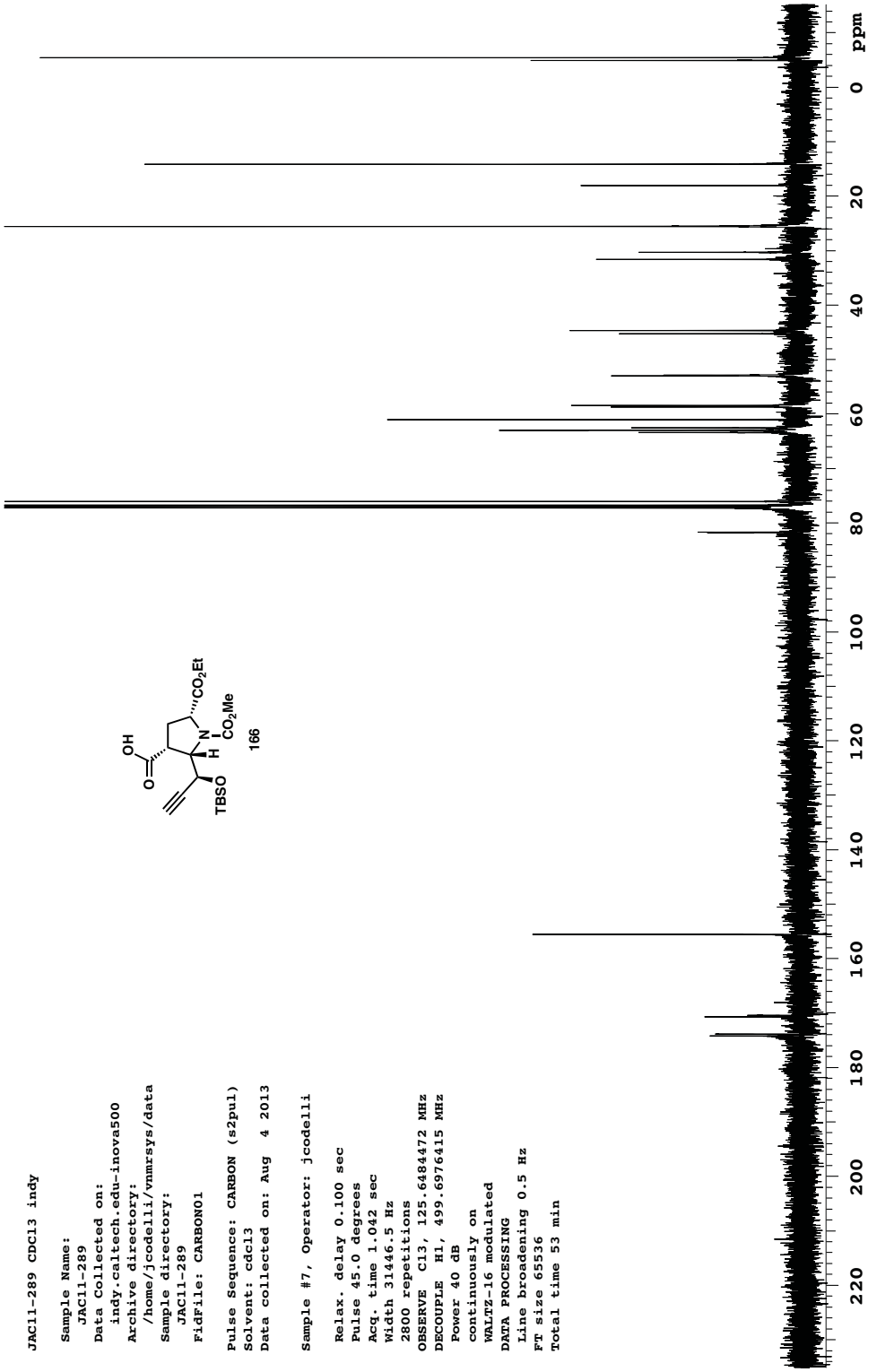

JAC4-127 CD3CN indy
Sample Name:
JAC4-127
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-127
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7075702 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
HO
TBSO
N
H
CO2Me
CO2Et
163
ppm
11.87
18.61
6.18
4.15
1.92
2.08
2.03
2.14
3.07
3.12
2.06
6.23
2.13
1.00
1.00

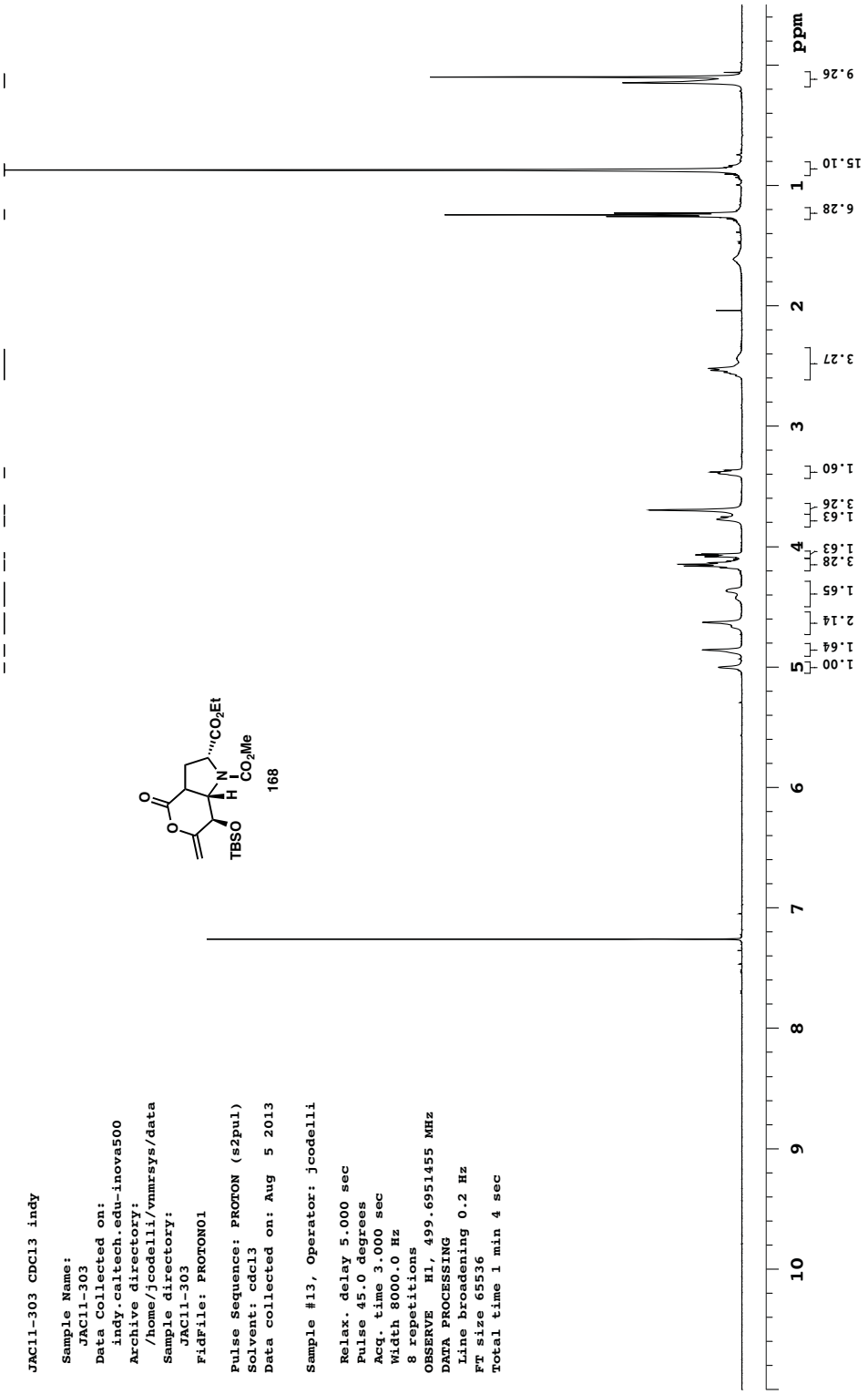

JAC4-127 CD3CN indy
Sample Name:
JAC4-127
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-127
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Mar 31 2013
Sample #8, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 repetitions
OBSERVE C13, 125.6514498 MHz
DECOUPLE H1, 499.7100565 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 47 min
HO
TBSO
CO2Et
CO2Me
163
220
200
180
160
140
120
100
80
60
40
20
0 ppm

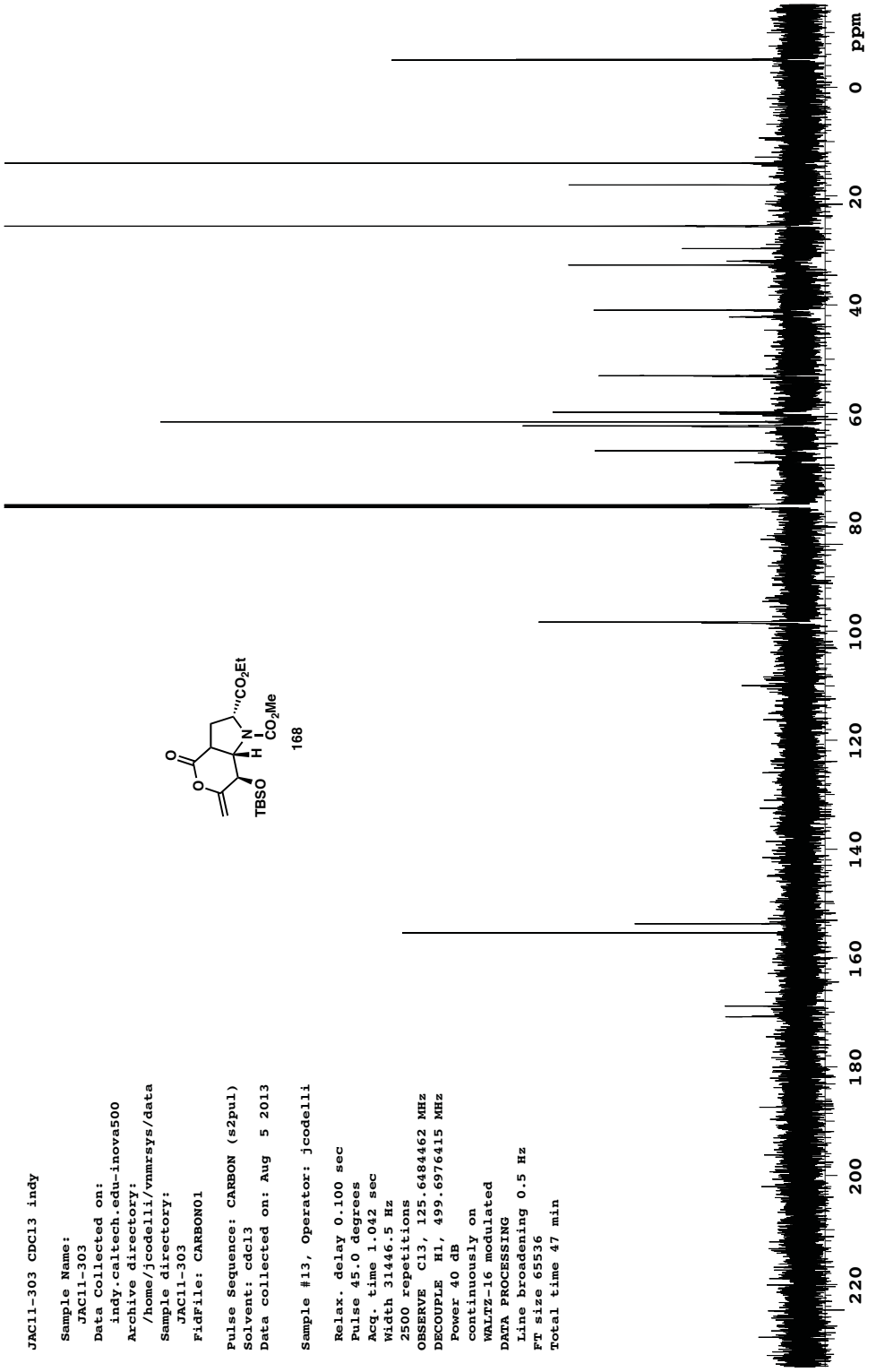

JAC4-187 CDCl3 indy
Sample Name:
JAC4-187
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-187
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 31 2013
Sample #34, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049148 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
TBSO
CO2Me
CO2Et
164
ppm
13.94
22.25
7.77
2.31
2.52
2.37
2.31
3.18
4.59
2.35
2.38
5.37
1.00
1.30
1.27
0.95

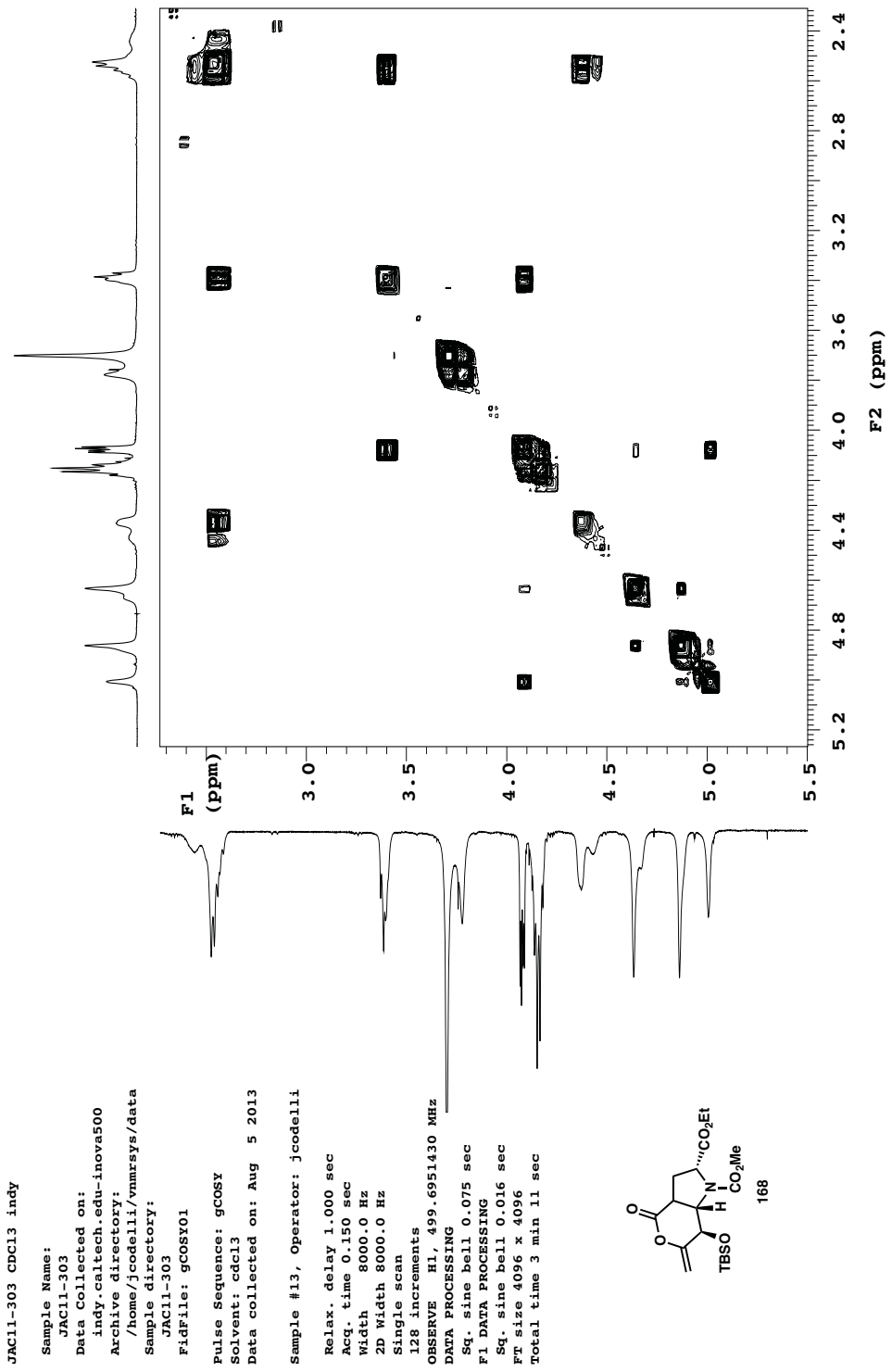

JAC4-187 CDCl3 indy
Sample Name:
JAC4-187
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-187
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 31 2013
Sample #34, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6509043 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 38 min
H
O
TBSO
N
H
CO2Et
CO2Me
164
220
200
180
160
140
120
100
80
60
40
20
0
ppm

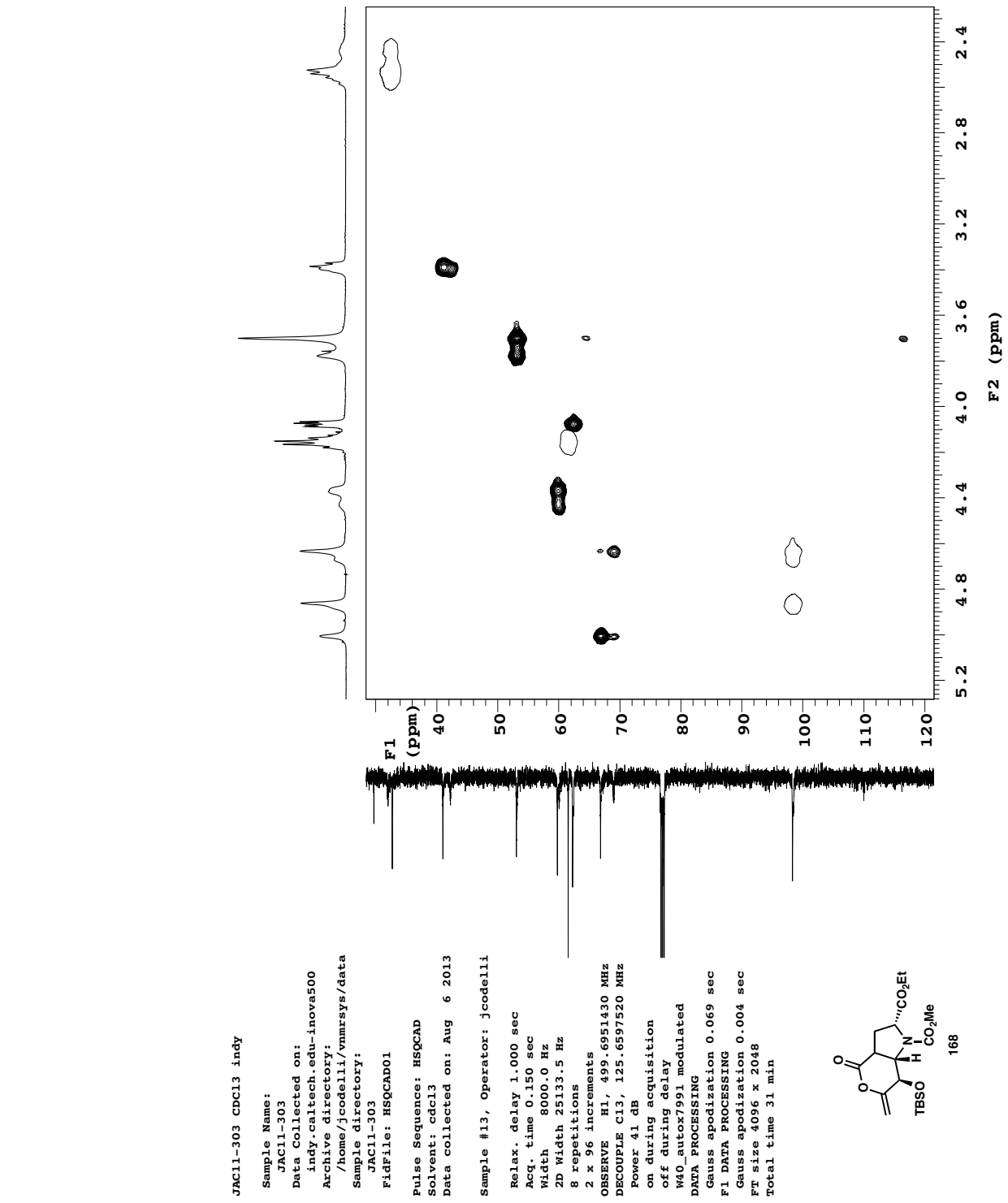

JAC11-289 CDCl3 indy
Sample Name:
JAC11-289
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-289
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
OH
O
TBSO
CO2Et
N
H
CO2Me
166
ppm
13.06
20.63
7.76
2.27
2.12
2.15
2.16
3.18
3.81
1.21
2.03
1.27
4.79
1.12
1.00

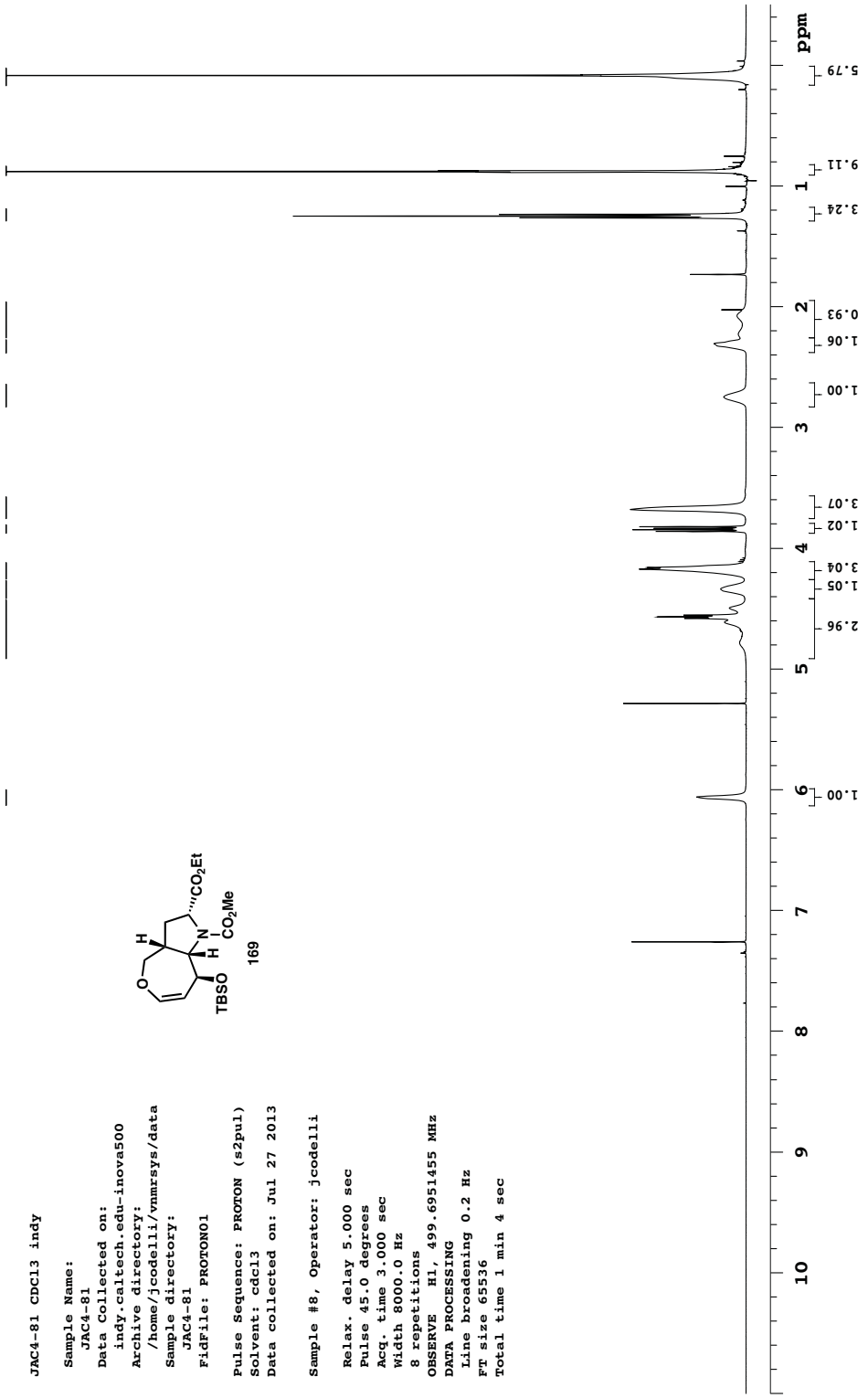

JAC11-289 CDCl3 indy
Sample Name:
JAC11-289
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-289
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2800 repetitions
OBSERVE C13, 125.6484472 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 53 min
OH
O
TBSO
N
H
CO2Me
CO2Et
166
220
200
180
160
140
120
100
80
60
40
20
0
ppm

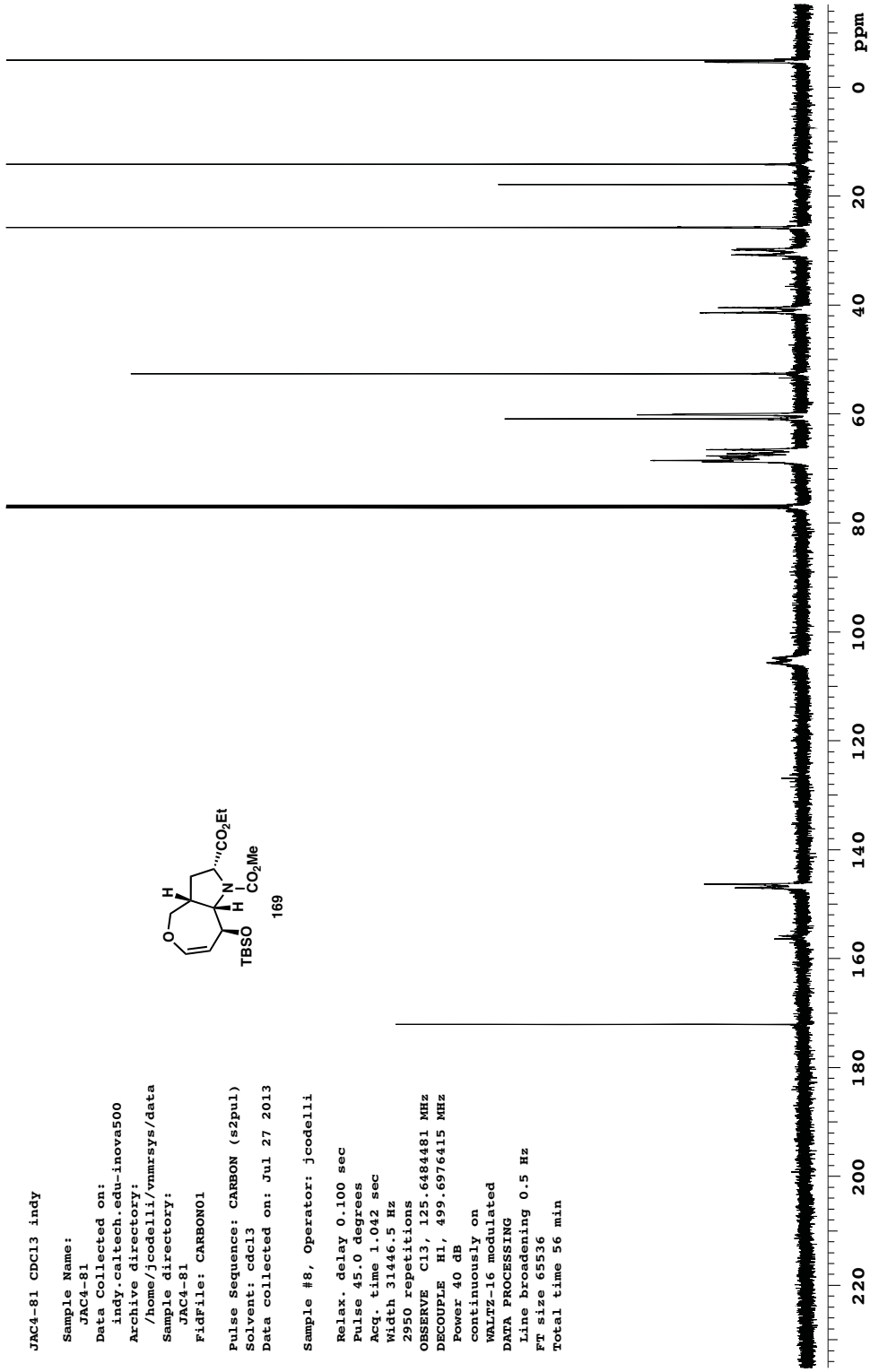

JAC11-303 CDCl3 indy
Sample Name:
JAC11-303
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-303
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2013
Sample #13, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
TBSO
CO2Et
CO2Me
168
ppm
9.26
15.10
6.28
3.27
1.60
1.63
3.26
1.63
3.28
1.65
2.14
1.64
1.00

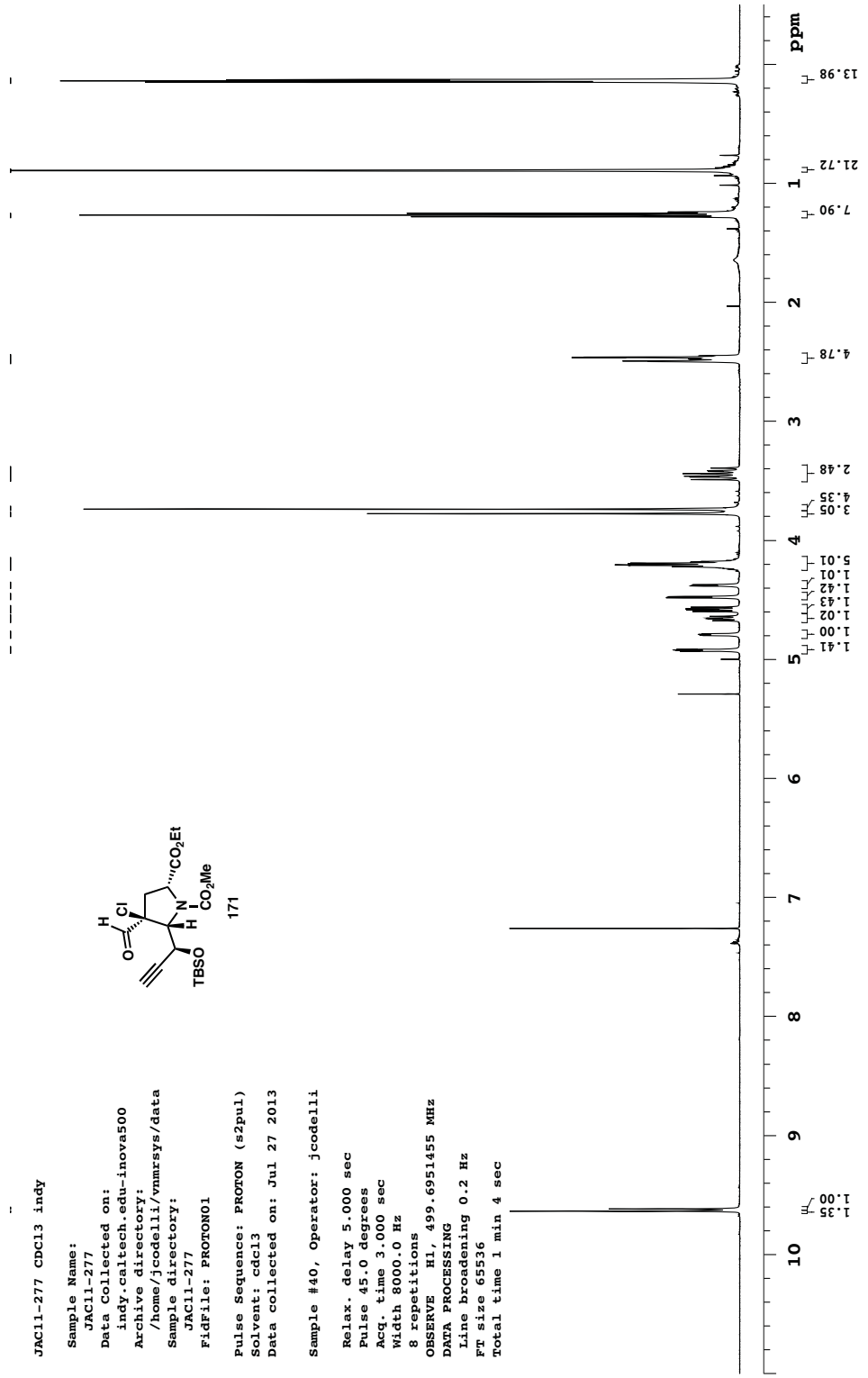

JAC11-303 CDCl3 indy
Sample Name:
JAC11-303
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-303
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2013
Sample #13, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 repetitions
OBSERVE C13, 125.6484462 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 47 min
O
O
TBSO
H
N
CO2Me
CO2Et
168
220
200
180
160
140
120
100
80
60
40
20
0
ppm

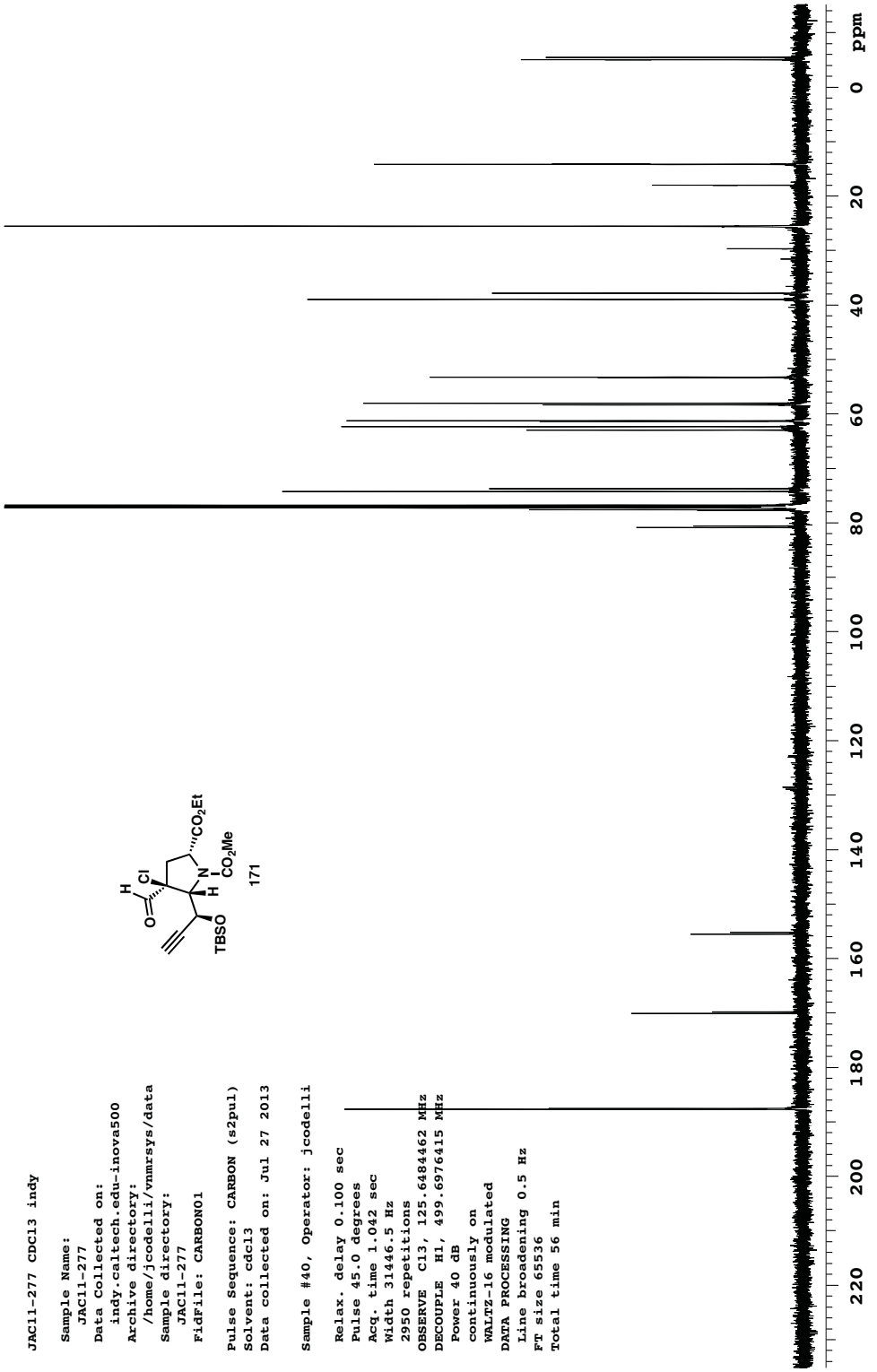

JAC11-303 CDCl3 indy
Sample Name:
JAC11-303
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-303
FidFile: gCOSY01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Aug 5 2013
Sample #13, Operator: jcodelli
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 8000.0 Hz
2D Width 8000.0 Hz
Single scan
128 increments
OBSERVE H1, 499.6951430 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.016 sec
FT size 4096 x 4096
Total time 3 min 11 sec
F1 (ppm)
F2 (ppm)
3.0
3.5
4.0
4.5
5.0
5.5
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
TBSO
CO2Et
CO2Me
168

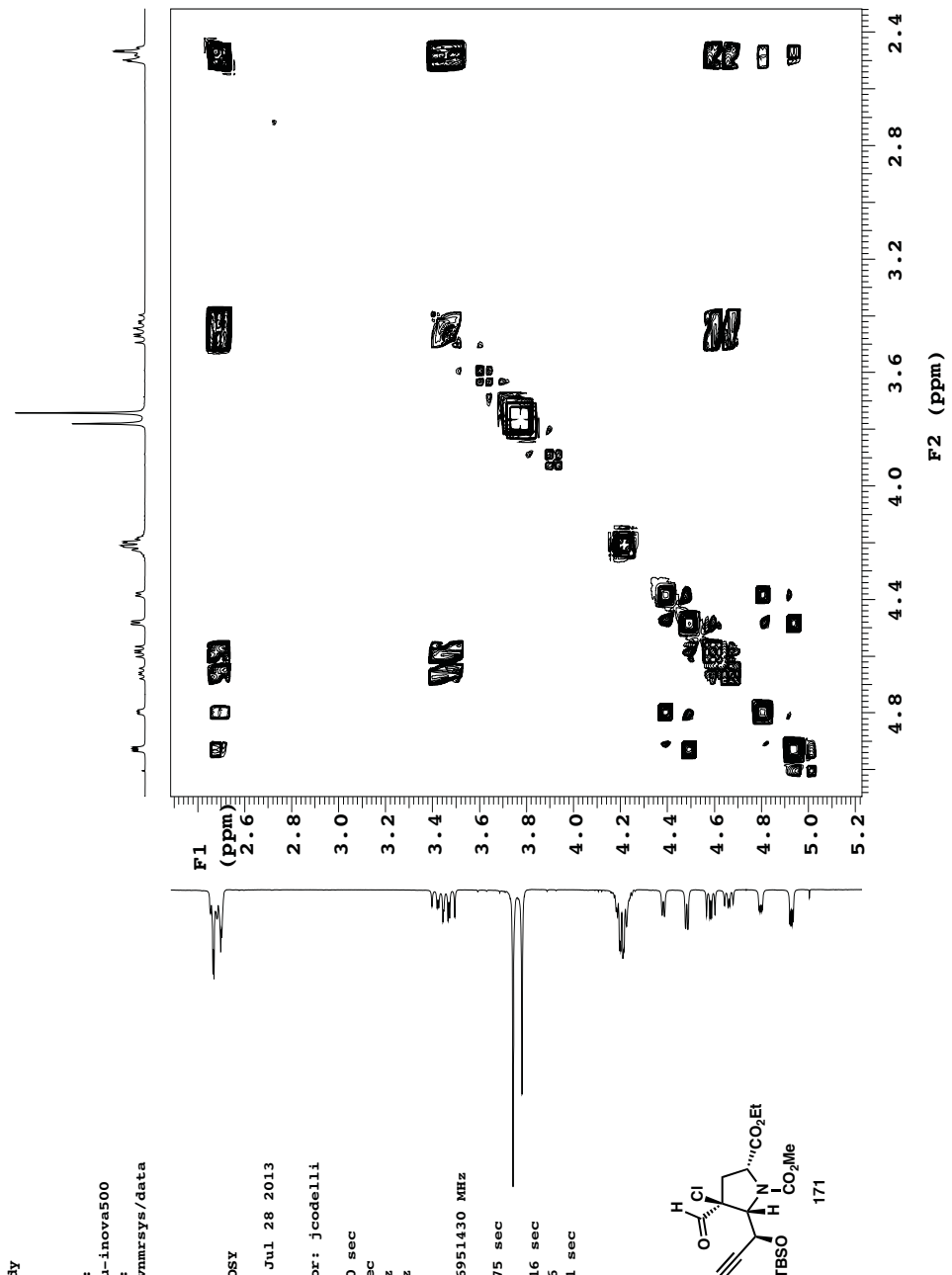

JAC11-303 CDCl3 indy
Sample Name:
JAC11-303
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-303
FidFile: HSQCAD01
Pulse Sequence: HSQCAD
Solvent: cdcl3
Data collected on: Aug 6 2013
Sample #13, Operator: jcodelli
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 8000.0 Hz
2D Width 25133.5 Hz
8 repetitions
2 x 96 increments
OBSERVE H1, 499.6951430 MHz
DECOUPLE C13, 125.6597520 MHz
Power 41 dB
on during acquisition
off during delay
W40_autox7991 modulated
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.004 sec
FT size 4096 x 2048
Total time 31 min
F1 (ppm)
F2 (ppm)
TBSO
CO2Et
CO2Me
168

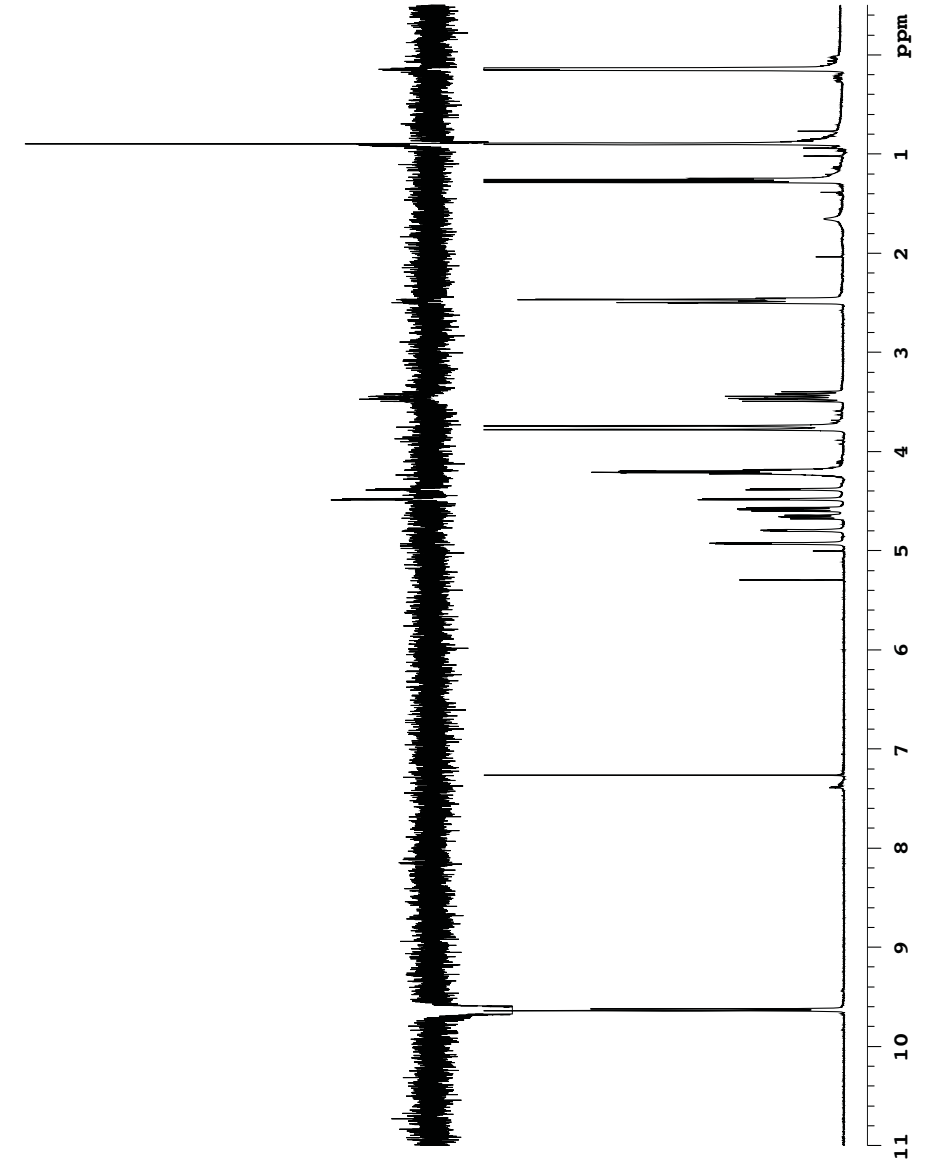

JAC4-81 CDCl3 indy
Sample Name:
JAC4-81
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-81
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2013
Sample #8, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
TBSO
CO2Et
CO2Me
169
ppm
10
9
8
7
6
5
4
3
2
1
1.00
3.07
1.02
3.04
1.05
2.96
1.00
1.06
0.93
3.24
9.11
5.79

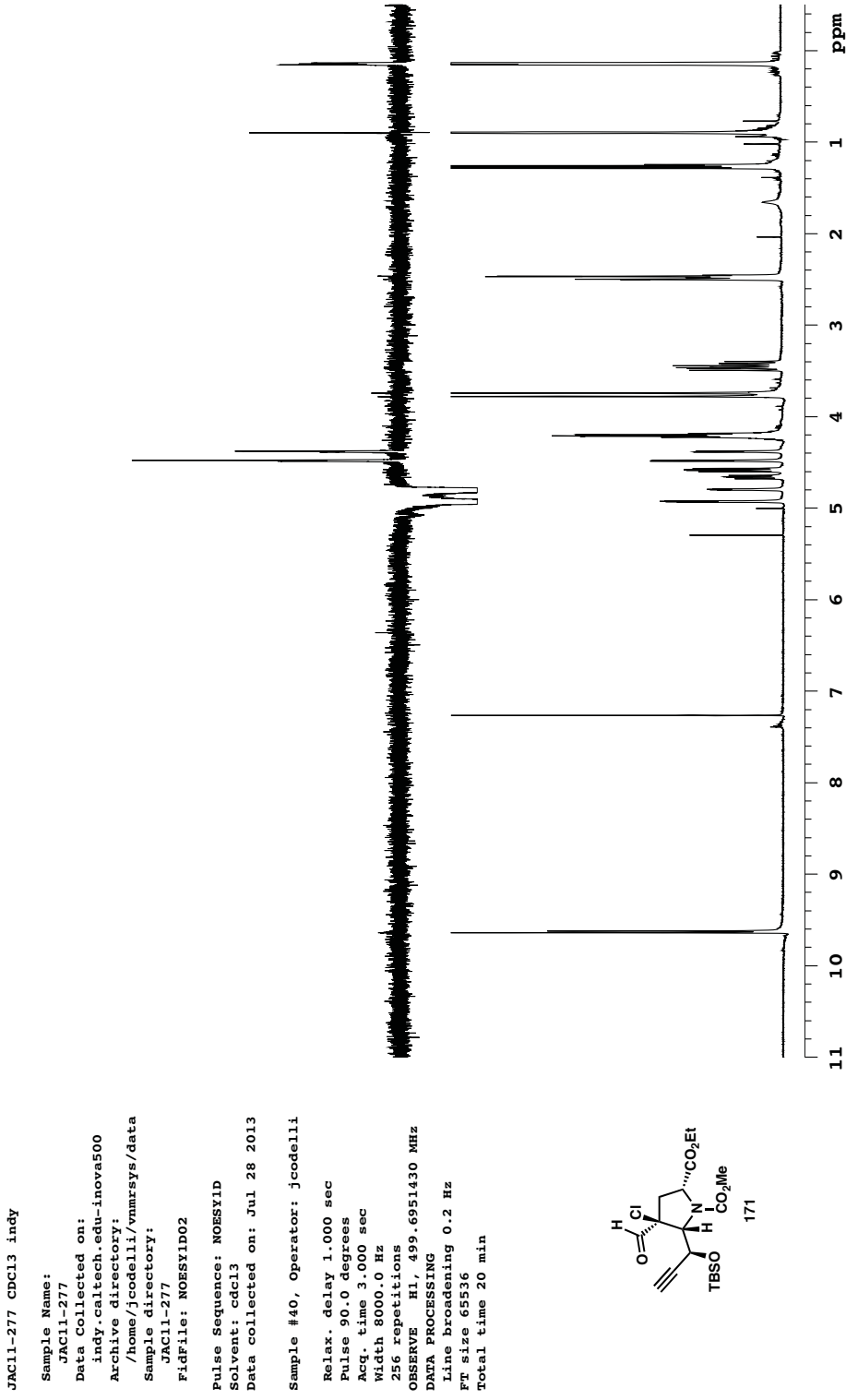

JAC4-81 CDCl3 indy
Sample Name:
JAC4-81
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC4-81
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2013
Sample #8, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 repetitions
OBSERVE C13, 125.6484481 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 56 min
TBSO
H
O
N
H
CO2Me
CO2Et
169
220
200
180
160
140
120
100
80
60
40
20
0
ppm

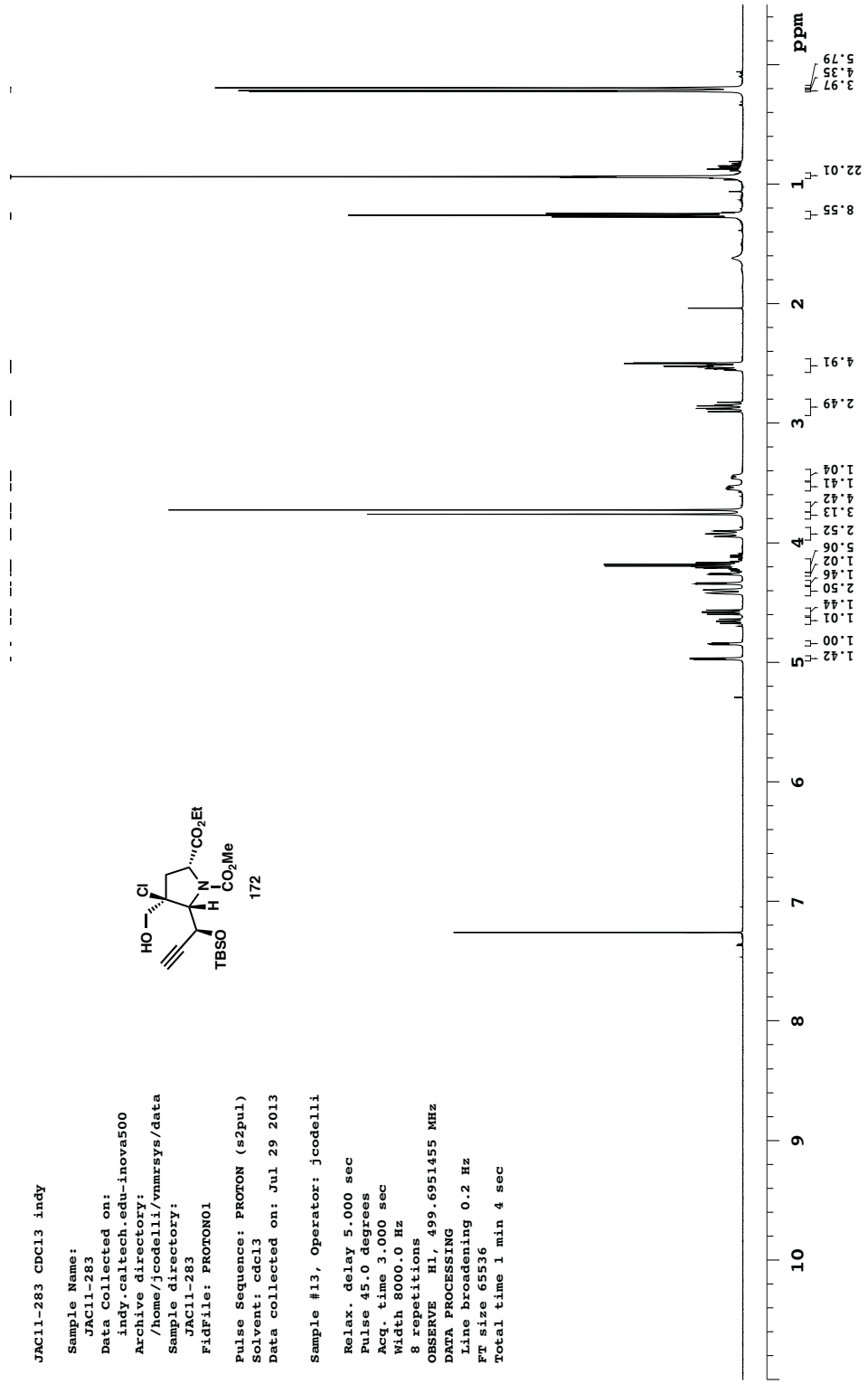

JAC11-277 CDCl3 indy
Sample Name:
JAC11-277
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-277
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2013
Sample #40, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
171
ppm
13.98
21.72
7.90
4.78
2.48
4.35
3.05
5.01
1.01
1.42
1.43
1.02
1.00
1.41
1.00
1.35

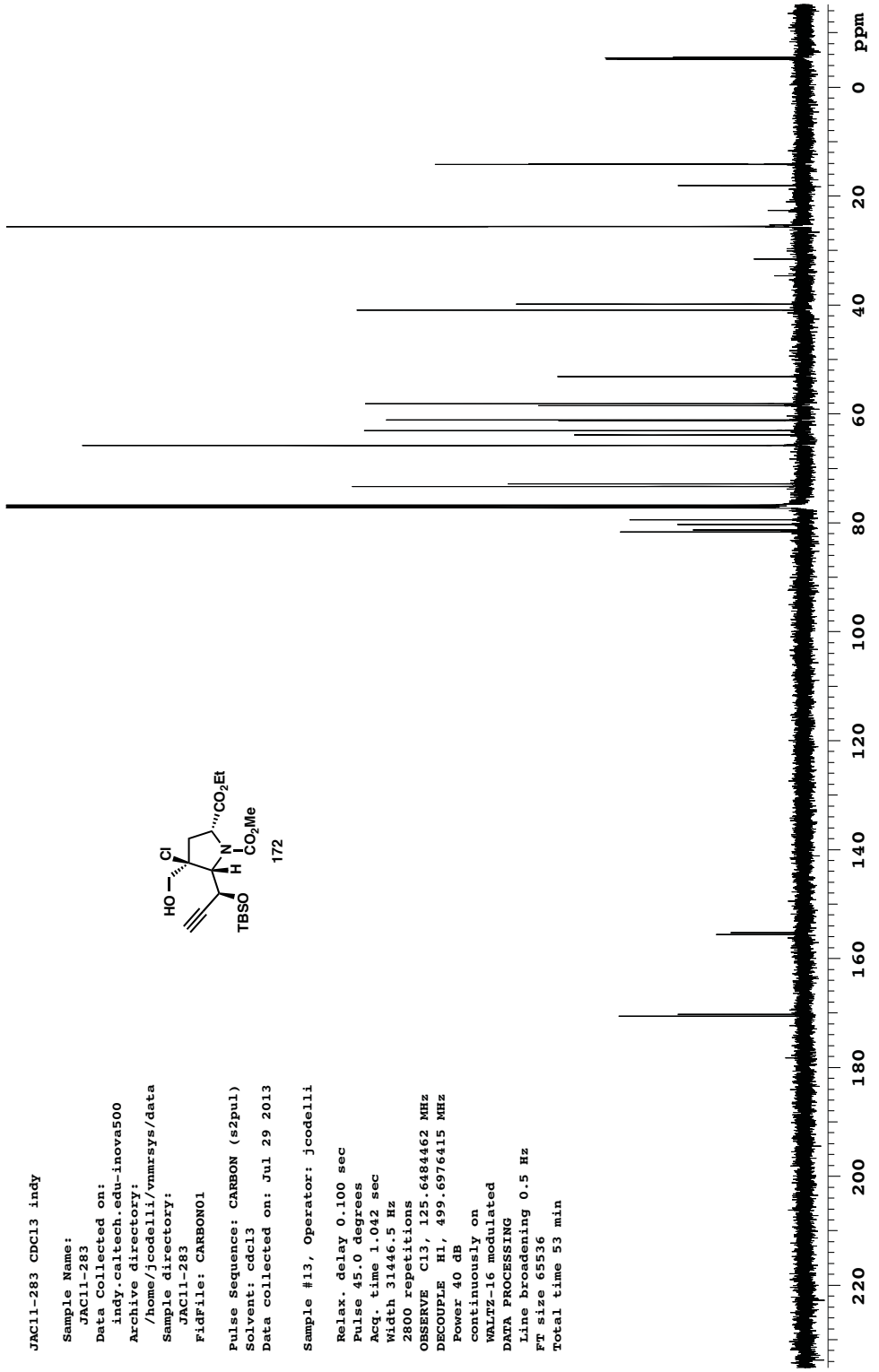

JAC11-277 CDCl3 indy
Sample Name:
JAC11-277
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-277
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2013
Sample #40, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 repetitions
OBSERVE C13, 125.6484462 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 56 min
H
Cl
O
TBSO
N
H
CO2Me
CO2Et
171
220
200
180
160
140
120
100
80
60
40
20
0
ppm

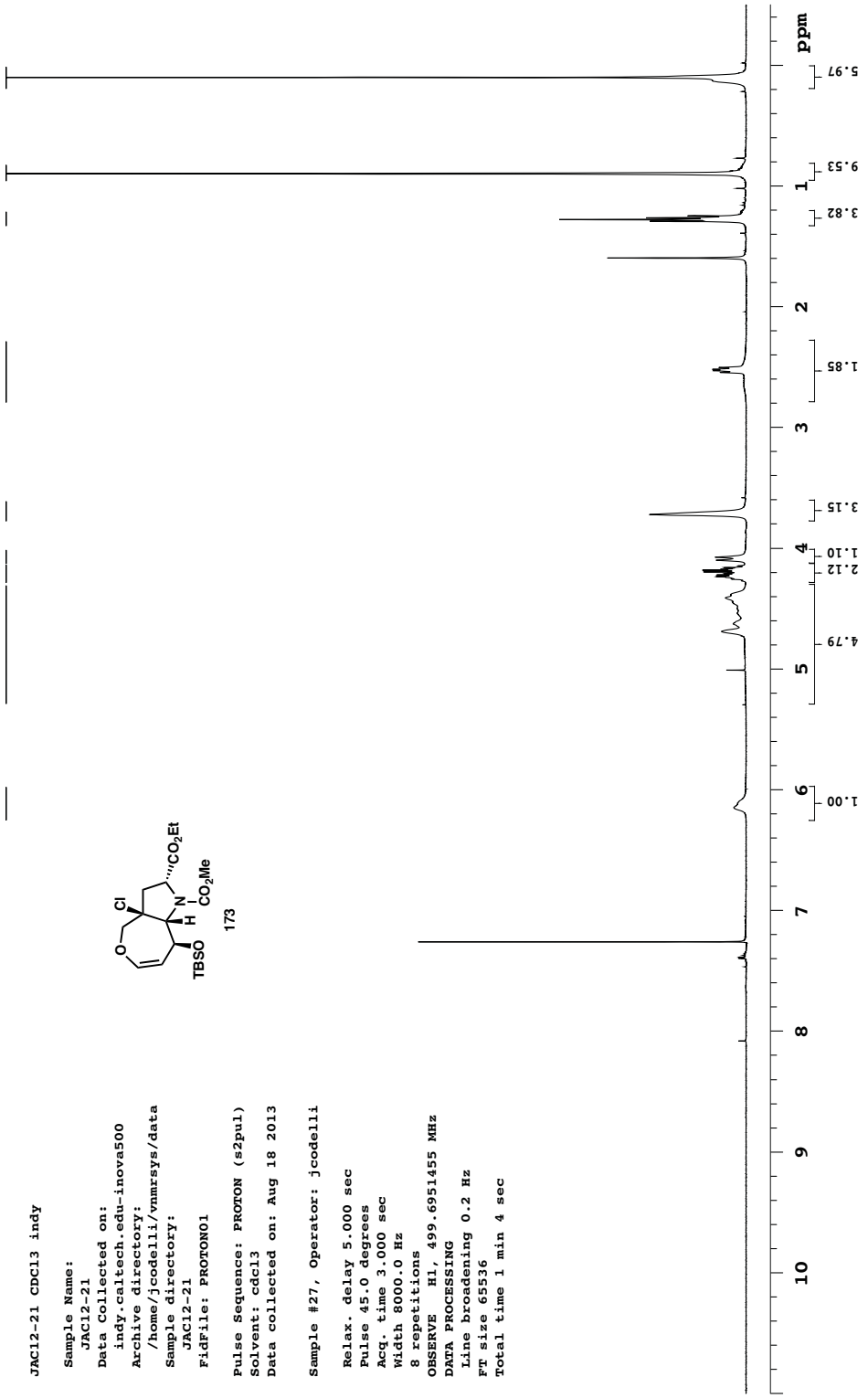

JAC11-277 CDCl3 indy
Sample Name:
JAC11-277
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-277
FidFile: gCOSY01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Jul 28 2013
Sample #40, Operator: jcodelli
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 8000.0 Hz
2D Width 8000.0 Hz
Single scan
128 increments
OBSERVE H1, 499.6951430 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.016 sec
FT size 4096 x 4096
Total time 3 min 11 sec
F1 (ppm)
F2 (ppm)
TBSO
CO2Et
CO2Me
171

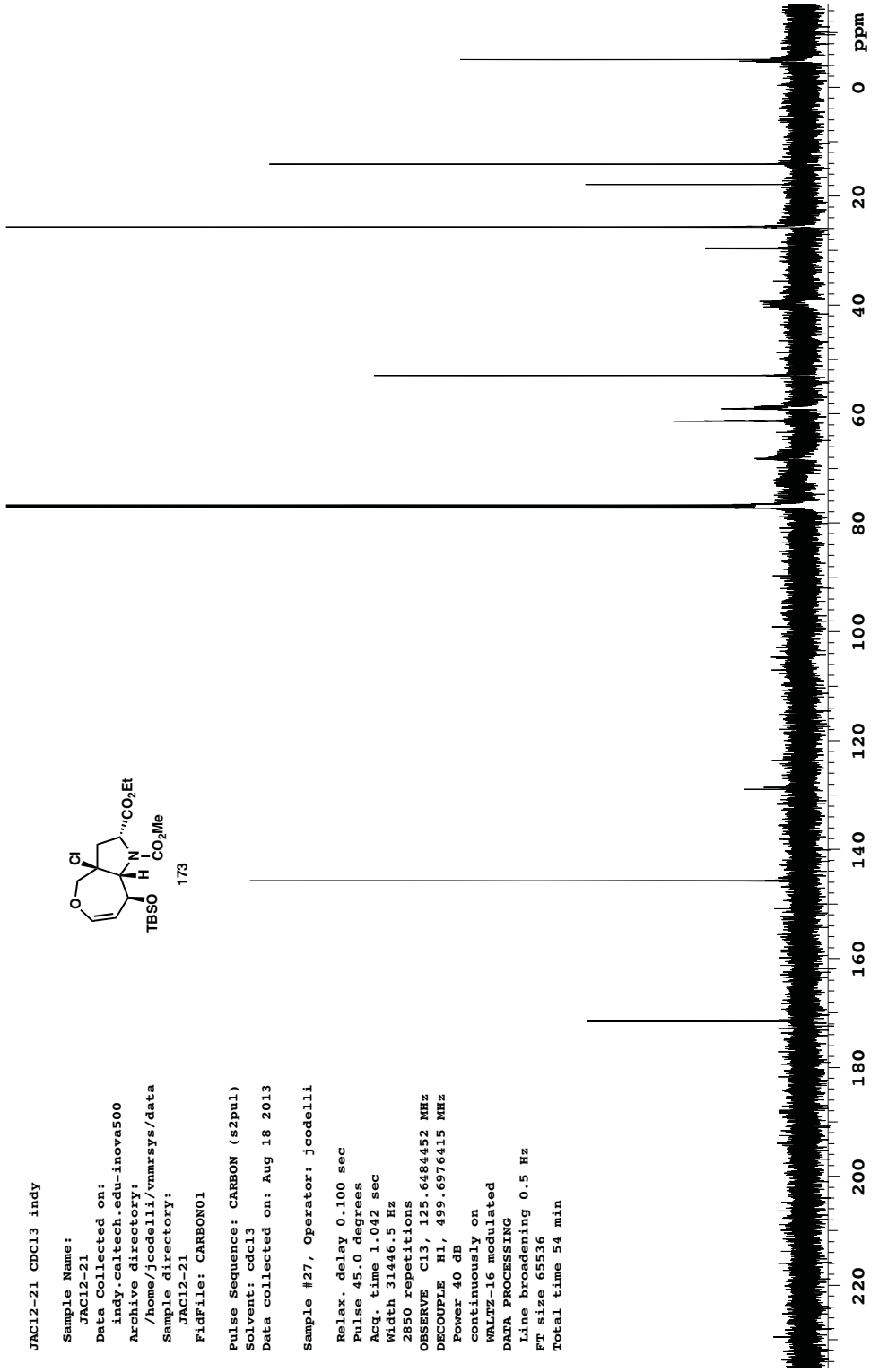

JAC11-277 CDCl3 indy
Sample Name:
JAC11-277
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-277
FidFile: NOESY1D01
Pulse Sequence: NOESY1D
Solvent: cdcl3
Data collected on: Jul 28 2013
Sample #40, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
256 repetitions
OBSERVE H1, 499.6951430 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 20 min
H
Cl
O
TBSO
N
H
CO2Et
CO2Me
171
11
10
9
8
7
6
5
4
3
2
1
ppm

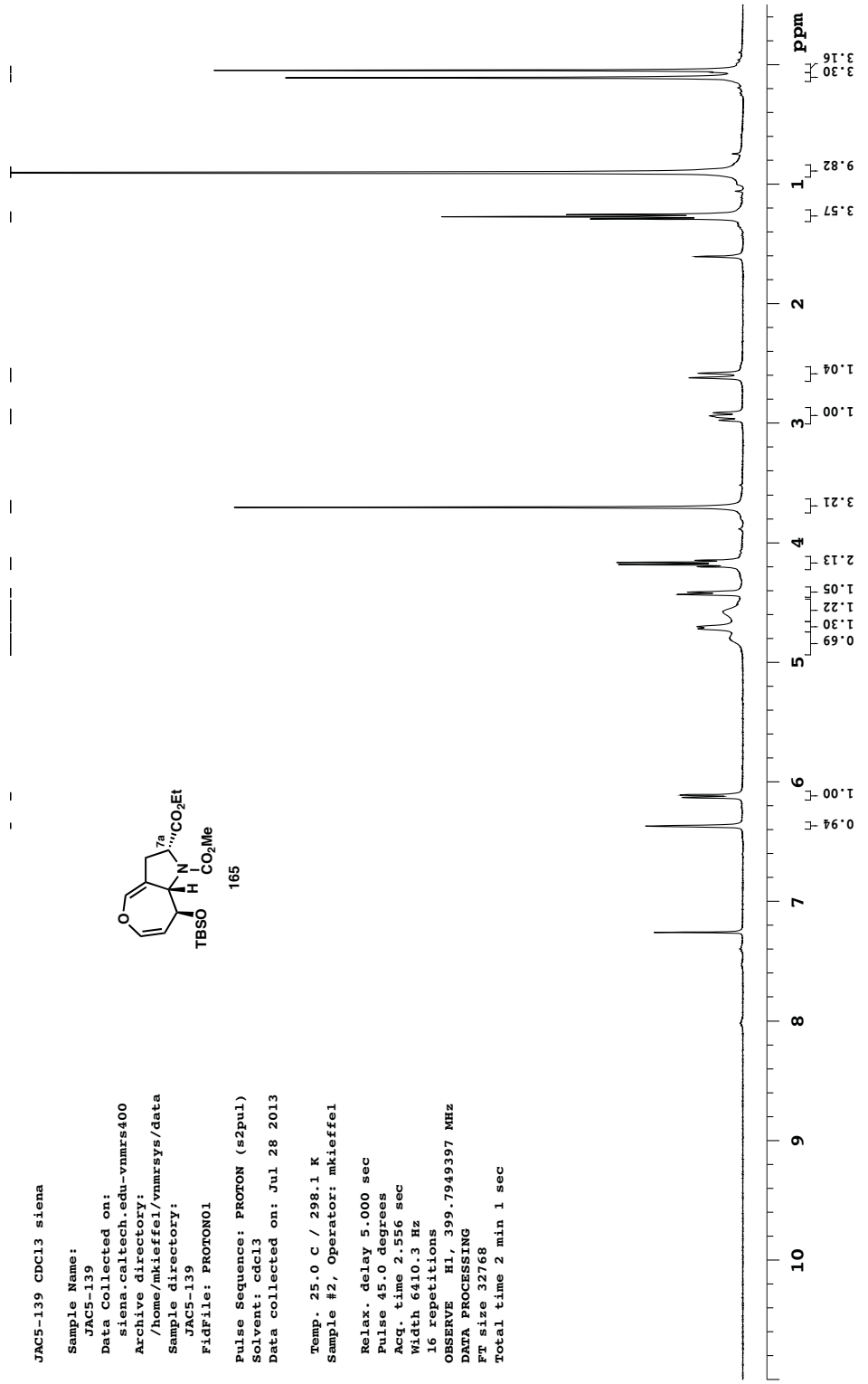

JAC11-277 CDCl3 indy
Sample Name:
JAC11-277
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-277
FidFile: NOESY1D02
Pulse Sequence: NOESY1D
Solvent: cdcl3
Data collected on: Jul 28 2013
Sample #40, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
256 repetitions
OBSERVE H1, 499.6951430 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 20 min
H
Cl
O
TBSO
N
H
CO2Et
CO2Me
171
11
10
9
8
7
6
5
4
3
2
1
ppm

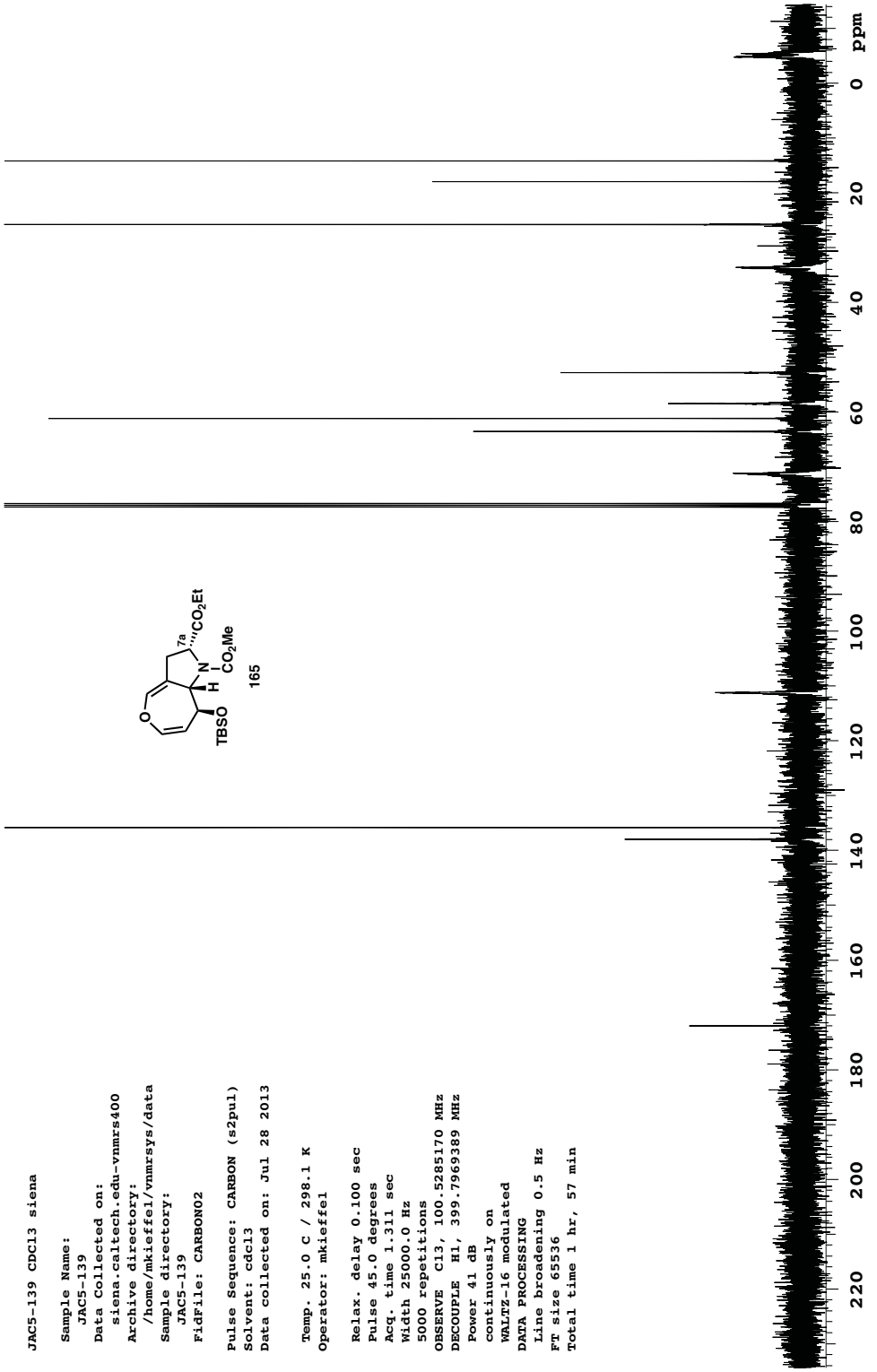

JAC11-283 CDCl3 indy
Sample Name:
JAC11-283
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-283
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 29 2013
Sample #13, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
HO
Cl
TBSO
N
H
CO2Et
CO2Me
172
ppm
10
9
8
7
6
5
4
3
2
1
1.42
1.00
1.01
1.44
2.50
1.46
1.02
5.06
2.52
3.13
4.42
1.41
1.04
2.49
4.91
8.55
22.01
3.97
4.35
5.79

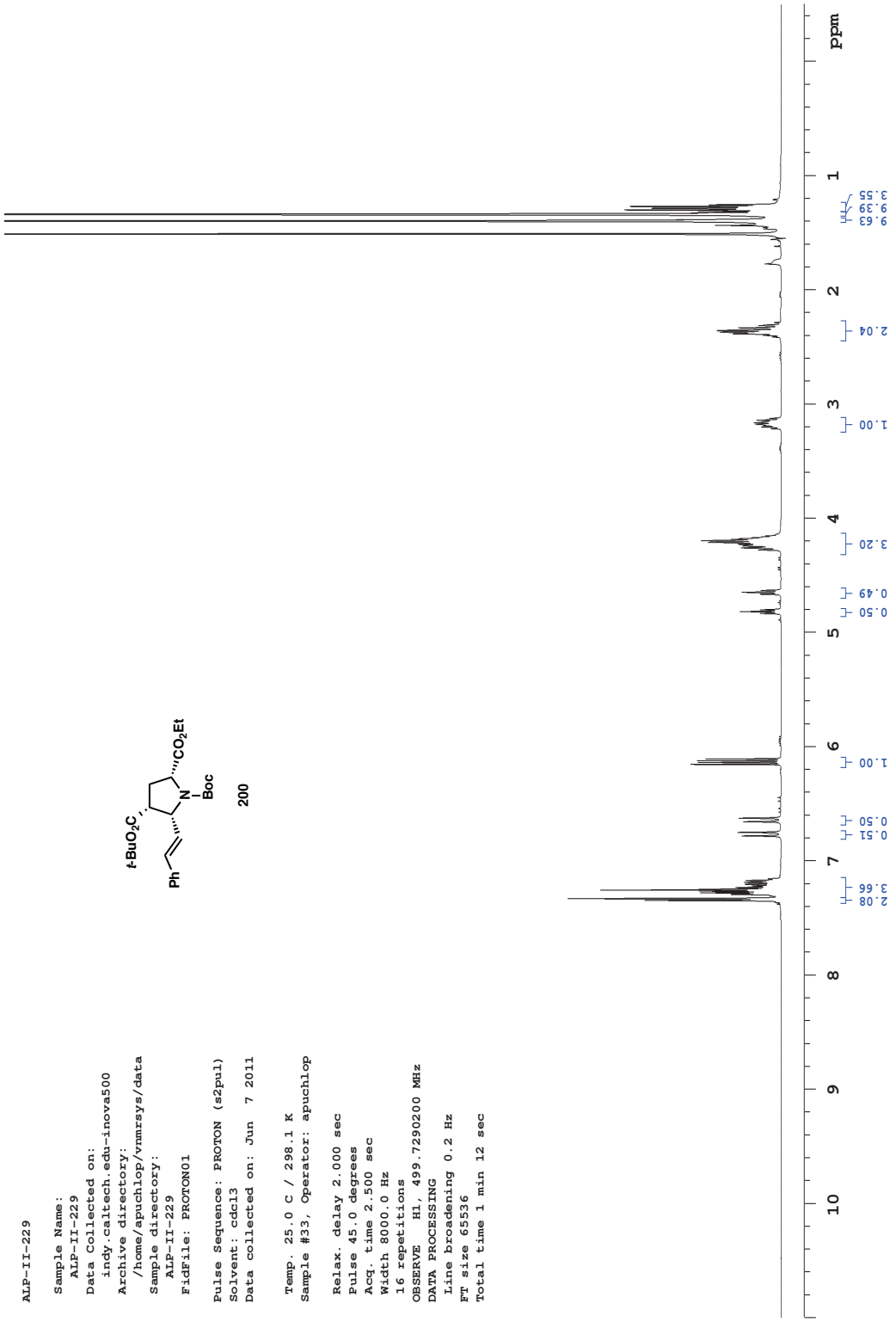

JAC11-283 CDCl3 indy
Sample Name:
JAC11-283
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-283
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 29 2013
Sample #13, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2800 repetitions
OBSERVE C13, 125.6484462 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 53 min
HO
Cl
TBSO
N
H
CO2Et
CO2Me
172
220
200
180
160
140
120
100
80
60
40
20
0
ppm

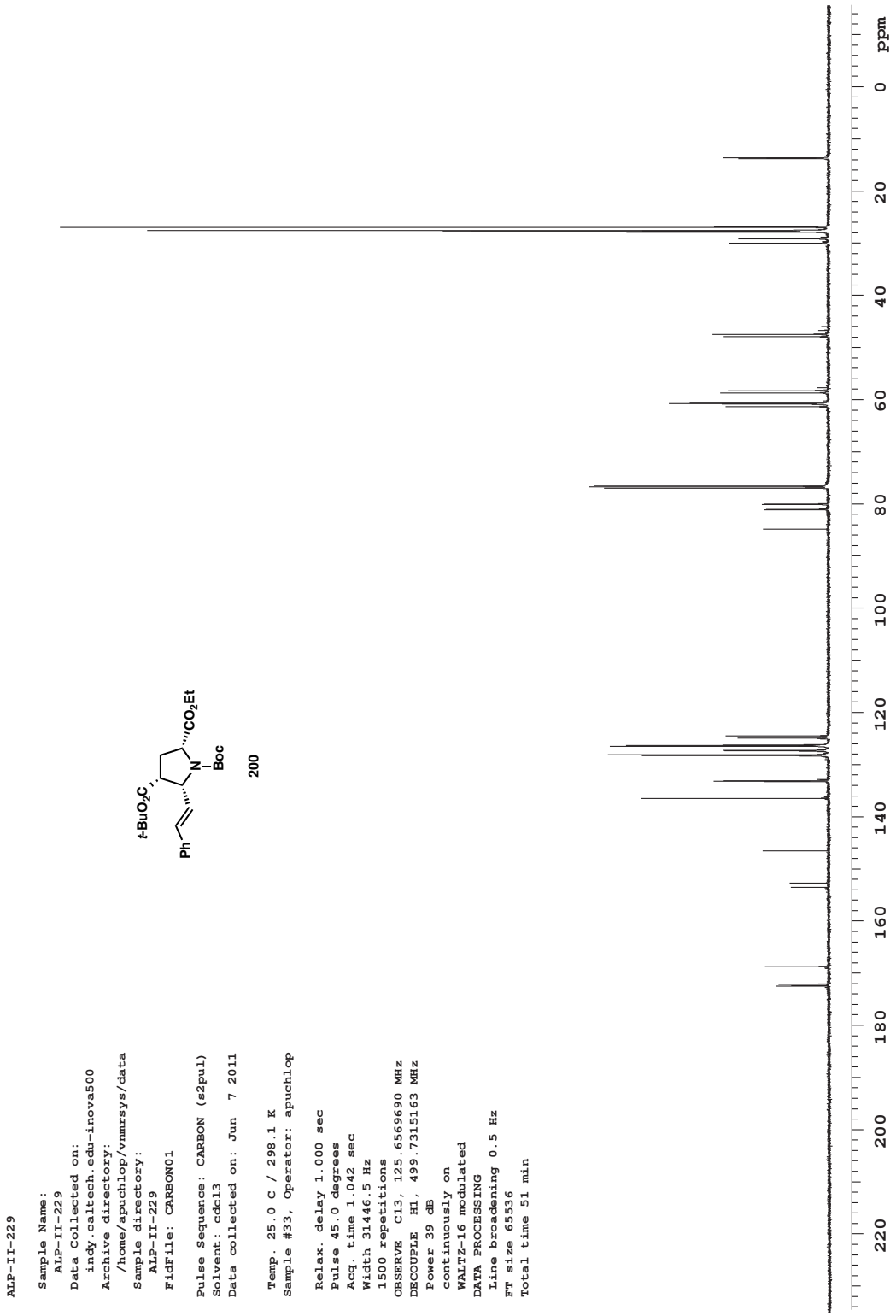

JAC12-21 CDCl3 indy
Sample Name:
JAC12-21
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-21
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 18 2013
Sample #27, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
Cl
O
N
H
TBSO
CO2Me
CO2Et
173
ppm
10
9
8
7
6
5
4
3
2
1
1.00
4.79
2.12
1.10
3.15
1.85
3.82
9.53
5.97

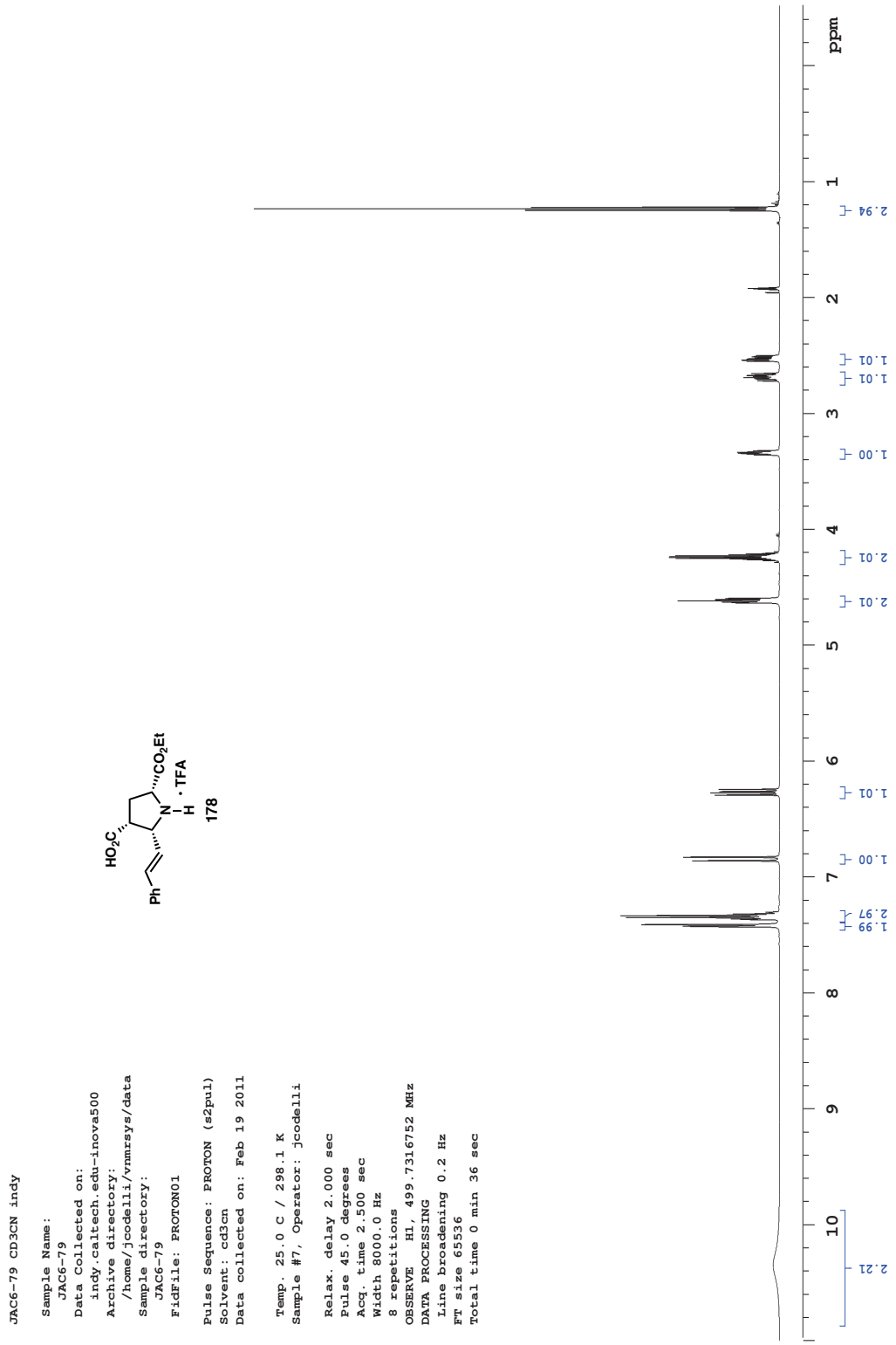

JAC12-21 CDCl3 indy
Sample Name:
JAC12-21
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-21
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 18 2013
Sample #27, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2850 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 54 min
Cl
O
TBSO
H
N
CO2Et
CO2Me
173
220
200
180
160
140
120
100
80
60
40
20
0
ppm

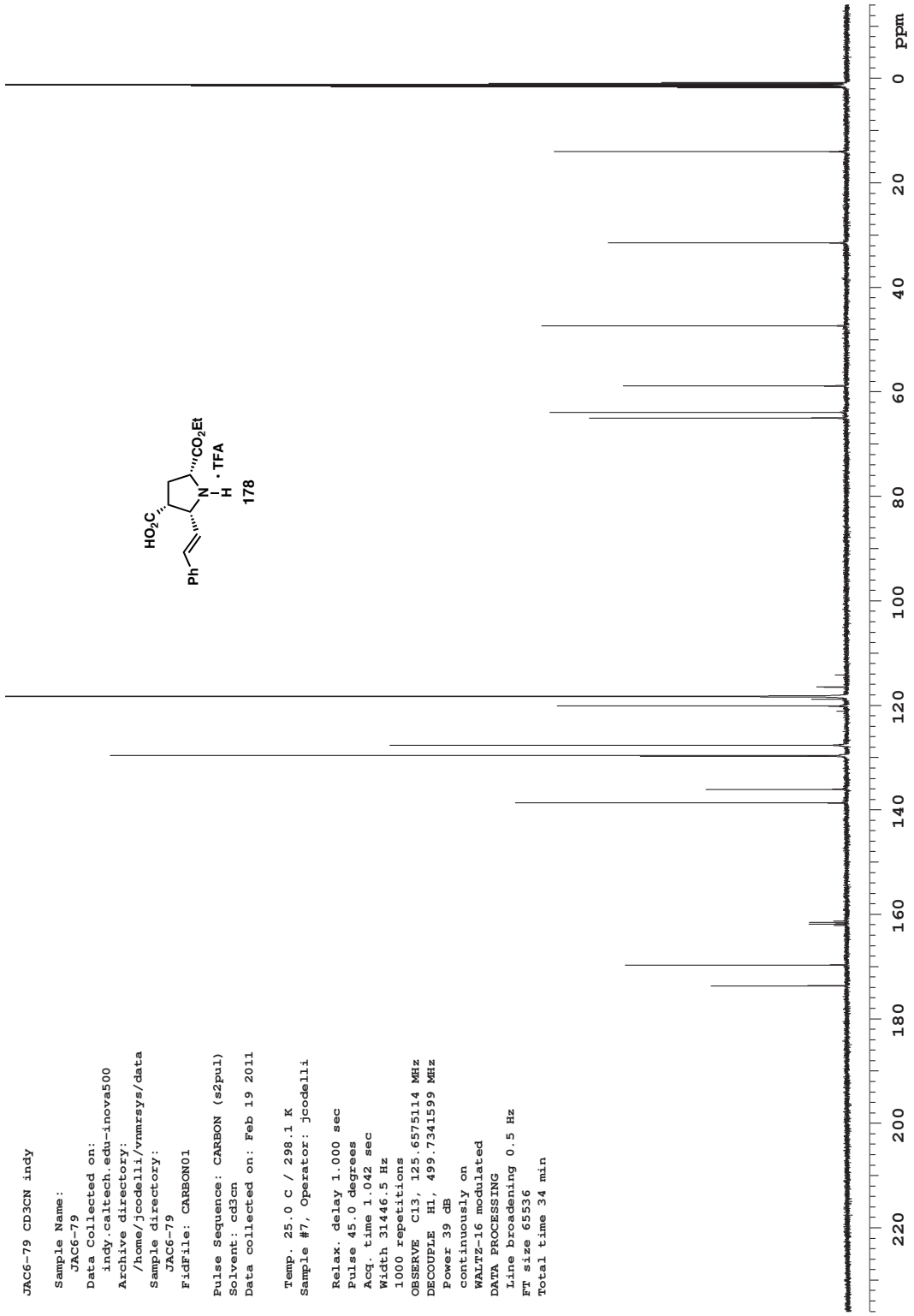

JAC5-139 CDCl3 siena
Sample Name:
JAC5-139
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/mkieffel/vnmrsys/data
Sample directory:
JAC5-139
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 28 2013
Temp. 25.0 C / 298.1 K
Sample #2, Operator: mkieffel
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7949397 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
TBSO
CO2Me
CO2Et
7a
165
ppm
3.16
3.30
9.82
3.57
1.04
1.00
3.21
2.13
1.05
1.22
1.30
0.69
1.00
0.94

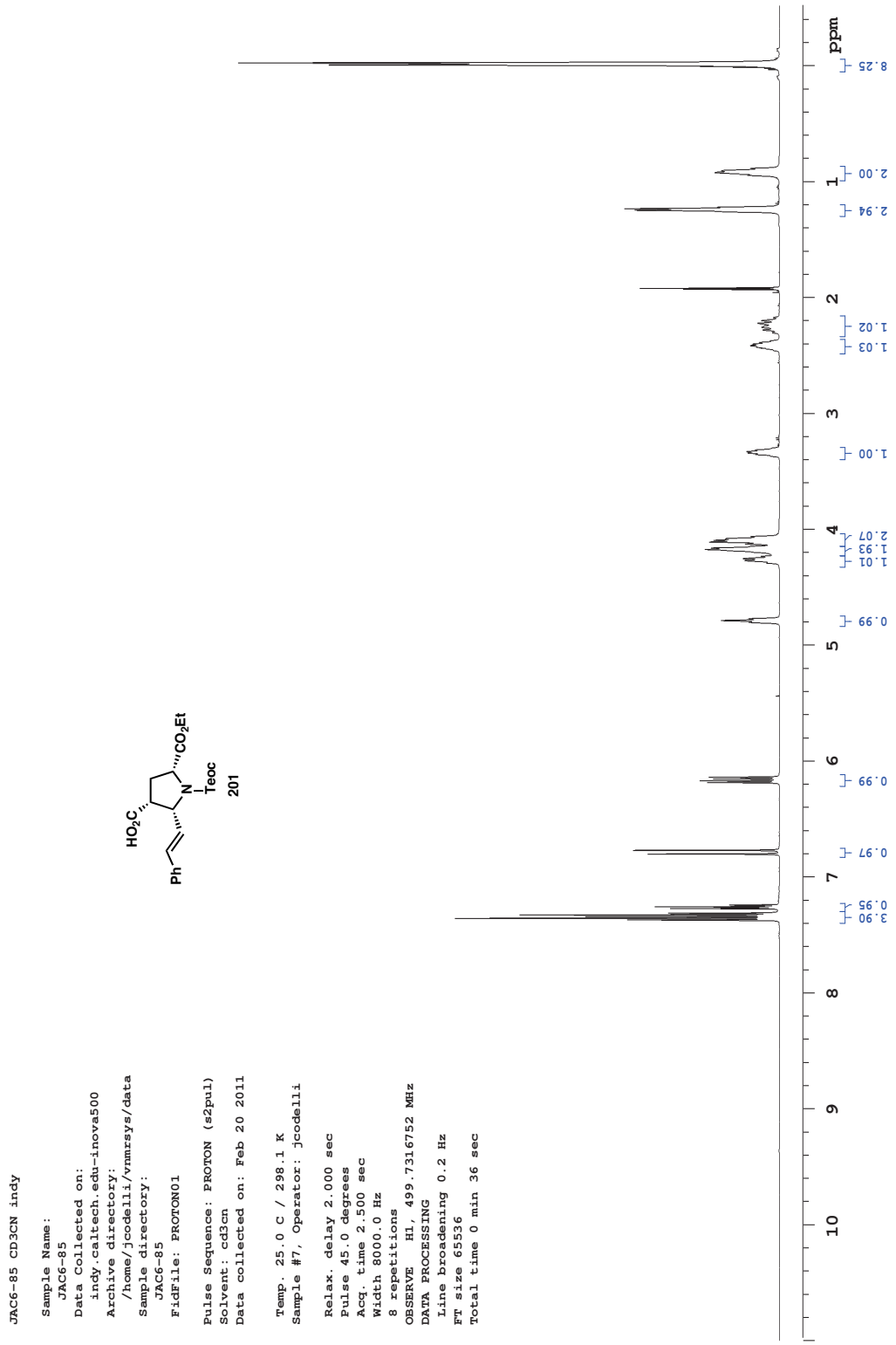

JAC5-139 CDCl3 siena
Sample Name:
JAC5-139
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/mkieffel/vnmrsys/data
Sample directory:
JAC5-139
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 28 2013
Temp. 25.0 C / 298.1 K
Operator: mkieffel
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
5000 repetitions
OBSERVE C13, 100.5285170 MHz
DECOUPLE H1, 399.7969389 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 57 min
7a
CO2Et
N
H
CO2Me
TBSO
O
165
220
200
180
160
140
120
100
80
60
40
20
0
ppm

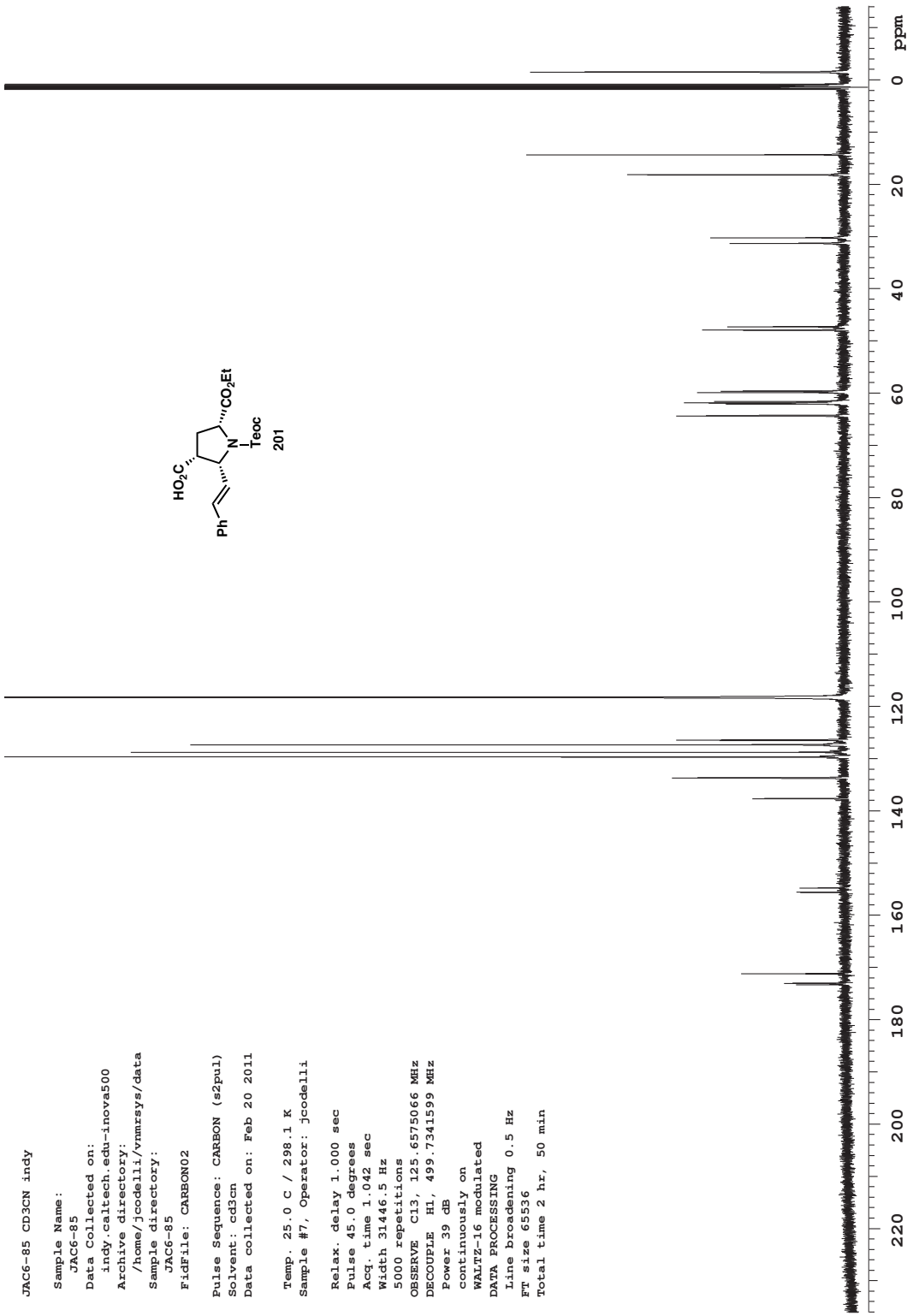

ALP-II-229
Sample Name:
ALP-II-229
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-229
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 7 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: apuchlop
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
t-BuO2C
CO2Et
N
Boc
Ph
200
ppm
1
2
3
4
5
6
7
8
9
10
3.55
9.39
9.63
2.04
1.00
3.20
0.49
0.50
1.00
0.50
0.51
3.66
2.08

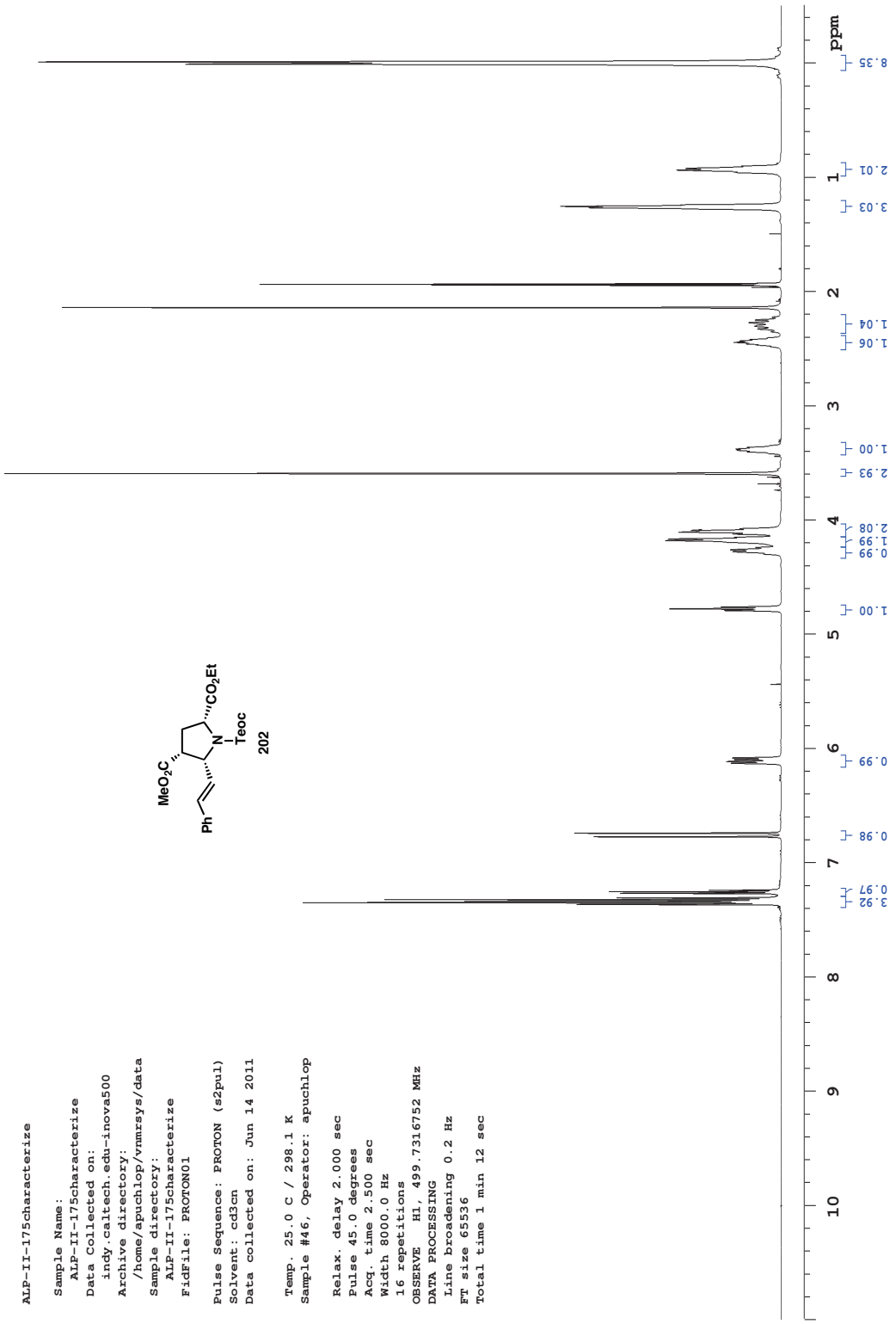

ALP-II-229
Sample Name:
ALP-II-229
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-229
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 7 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6569690 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
tBuO2C
CO2Et
N
Boc
Ph
200
220
200
180
160
140
120
100
80
60
40
20
0
ppm

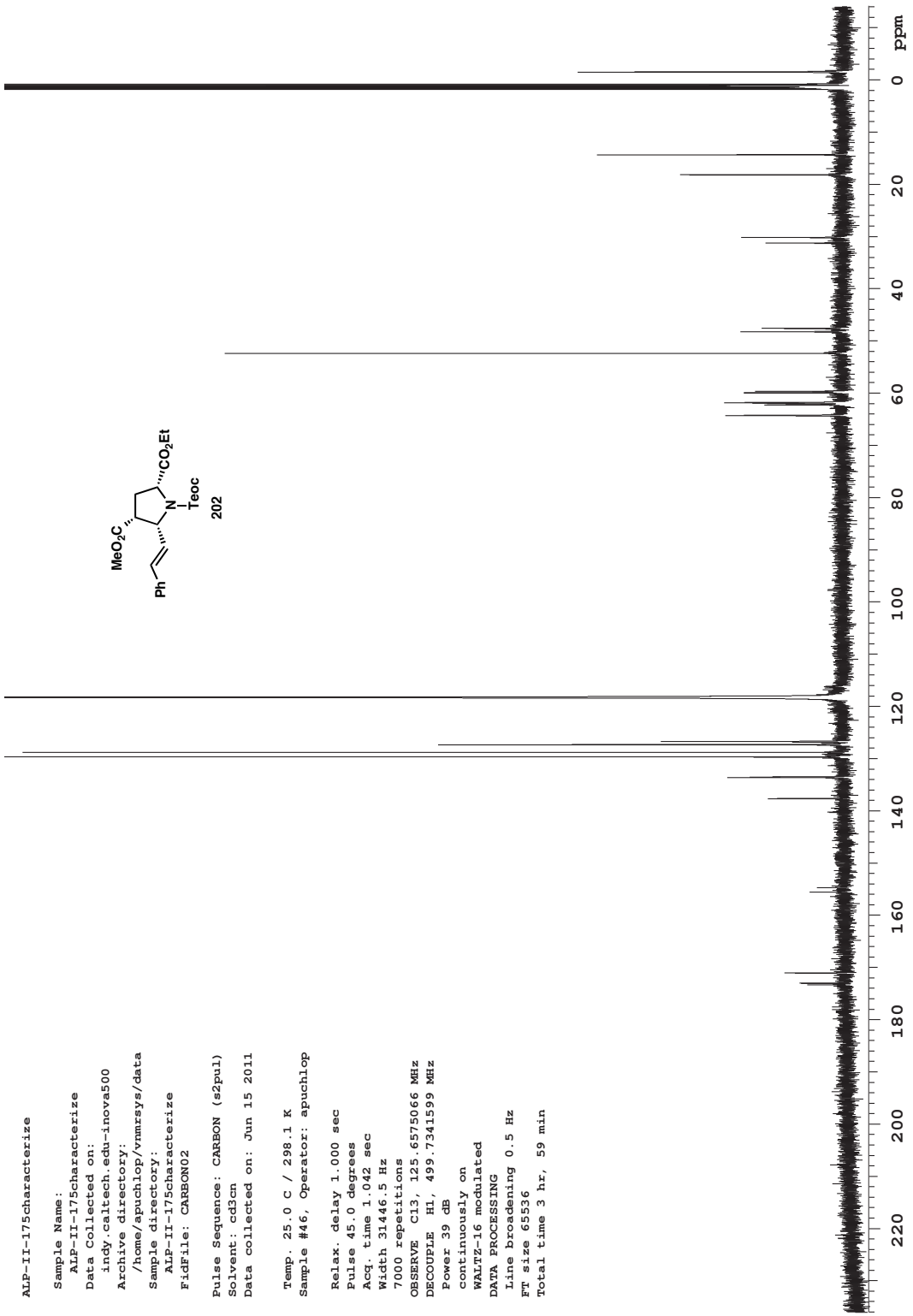

JAC6-79 CD3CN indy
Sample Name:
JAC6-79
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-79
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Feb 19 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7316752 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 36 sec
HO2C
CO2Et
Ph
N
H
· TFA
178
ppm
10
9
8
7
6
5
4
3
2
1
2.21
1.99
2.97
1.00
1.01
2.01
2.01
1.00
1.01
1.01
2.94

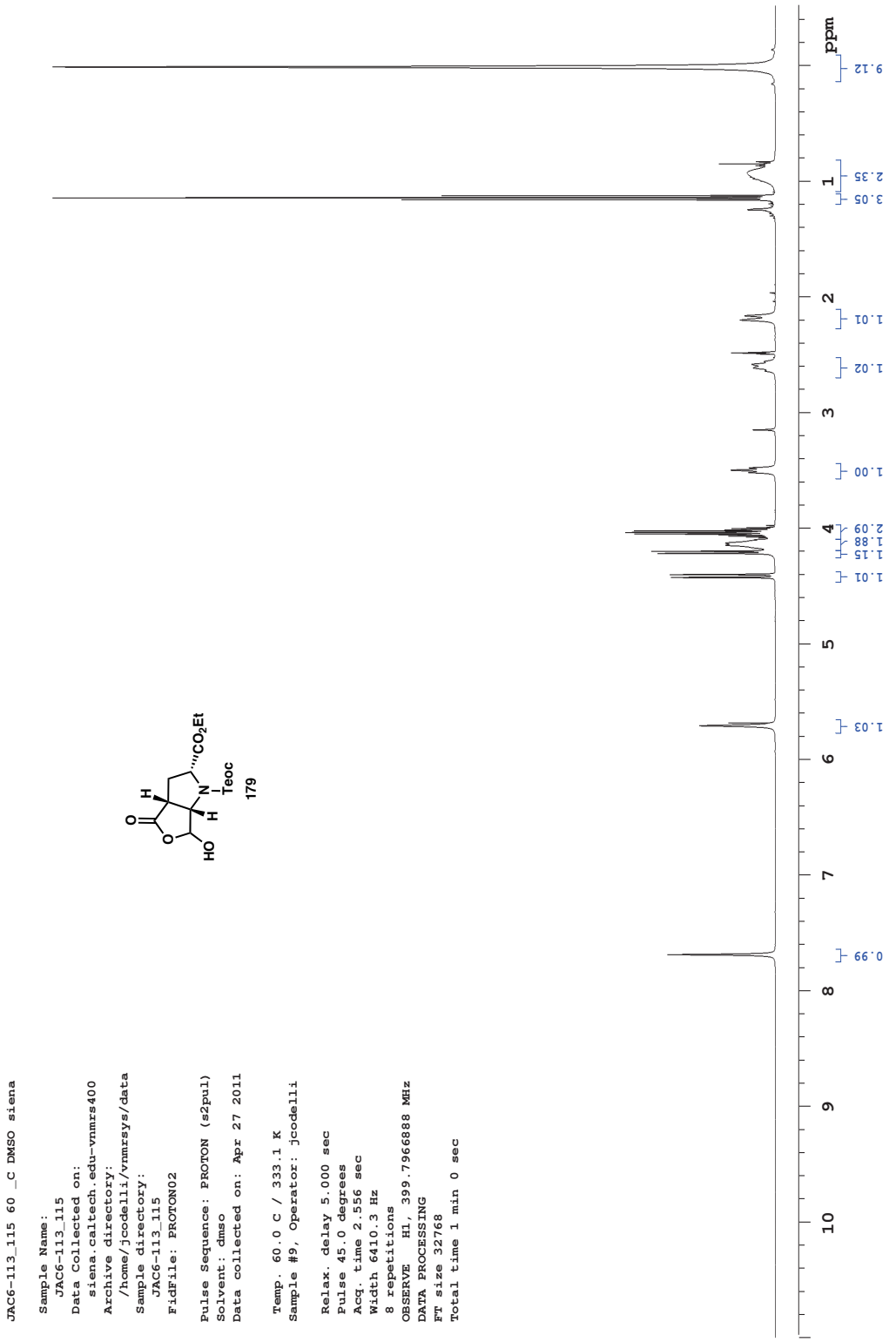

JAC6-79 CD3CN indy
Sample Name:
JAC6-79
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-79
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Feb 19 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6575114 MHz
DECOUPLE H1, 499.7341599 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
HO_2C
CO_2Et
Ph
N
H
· TFA
178
220
200
180
160
140
120
100
80
60
40
20
0
ppm

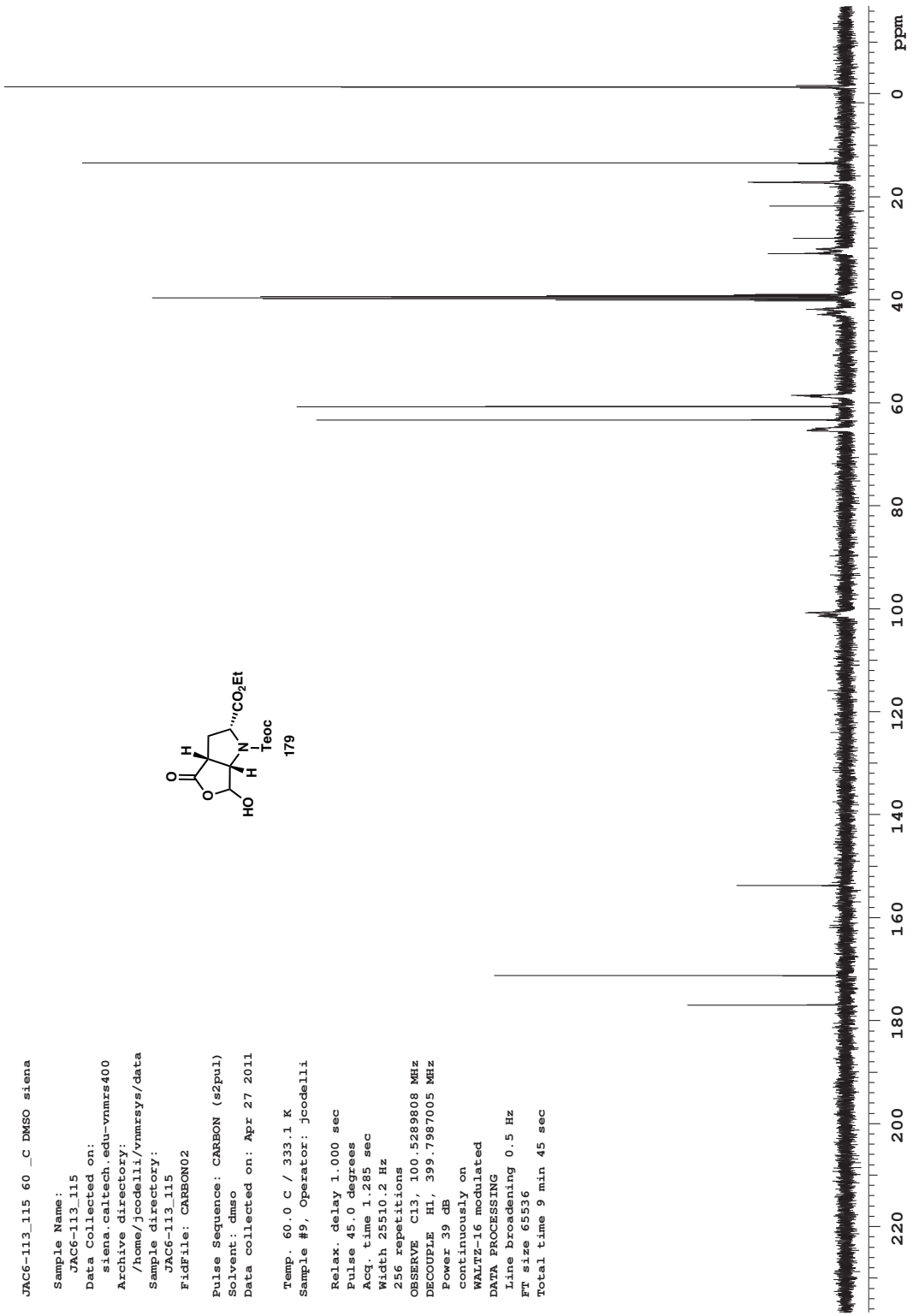

JAC6-85 CD3CN indy
Sample Name:
JAC6-85
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-85
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Feb 20 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7316752 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 36 sec
HO2C
CO2Et
N
Teoc
Ph
201
ppm
8.25
2.00
2.94
1.02
1.03
1.00
2.07
1.93
1.01
0.99
0.99
0.97
3.90
0.95

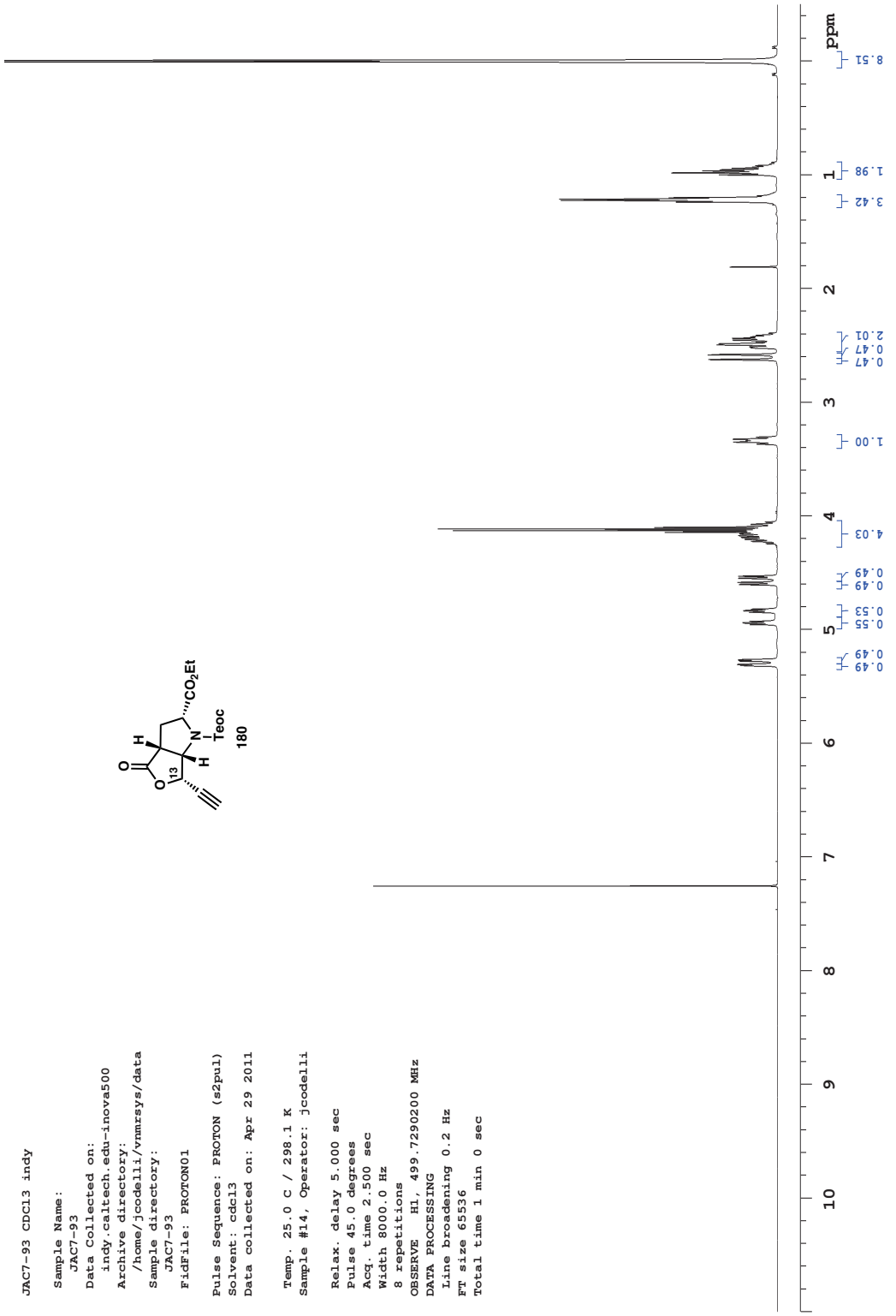

JAC6-85 CD3CN indy
Sample Name:
JAC6-85
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-85
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Feb 20 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6575066 MHz
DECOUPLE H1, 499.7341599 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 50 min
HO2C
CO2Et
N
Teoc
Ph
201
220
200
180
160
140
120
100
80
60
40
20
0
ppm

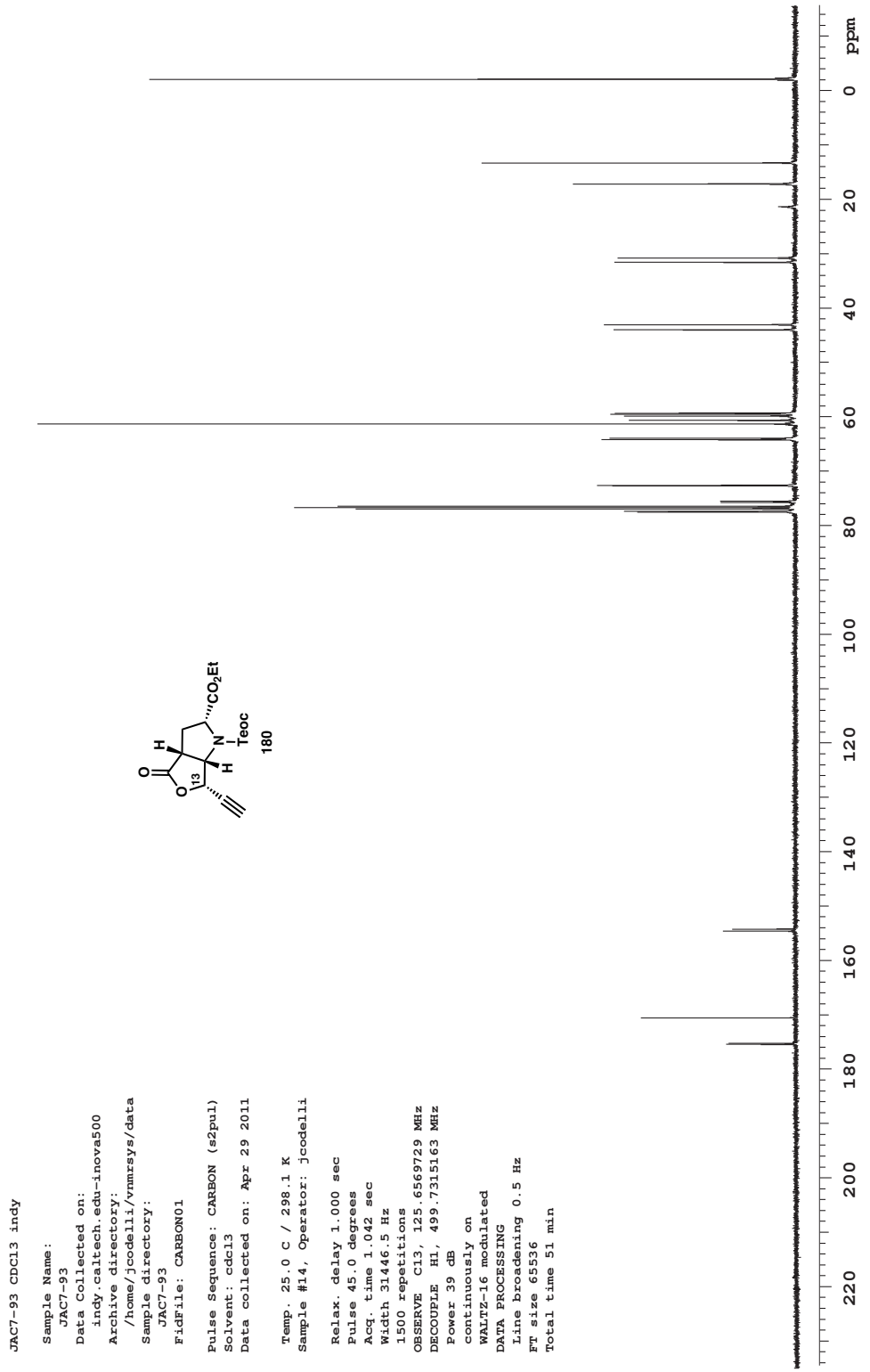

ALP-II-175characterize
Sample Name:
ALP-II-175characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-175characterize
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jun 14 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: apuchlop
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7316752 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
MeO2C
CO2Et
N
Teoc
Ph
202
ppm
8.35
2.01
3.03
1.04
1.06
1.00
2.93
0.99
1.99
2.08
1.00
0.99
0.98
0.97
3.92

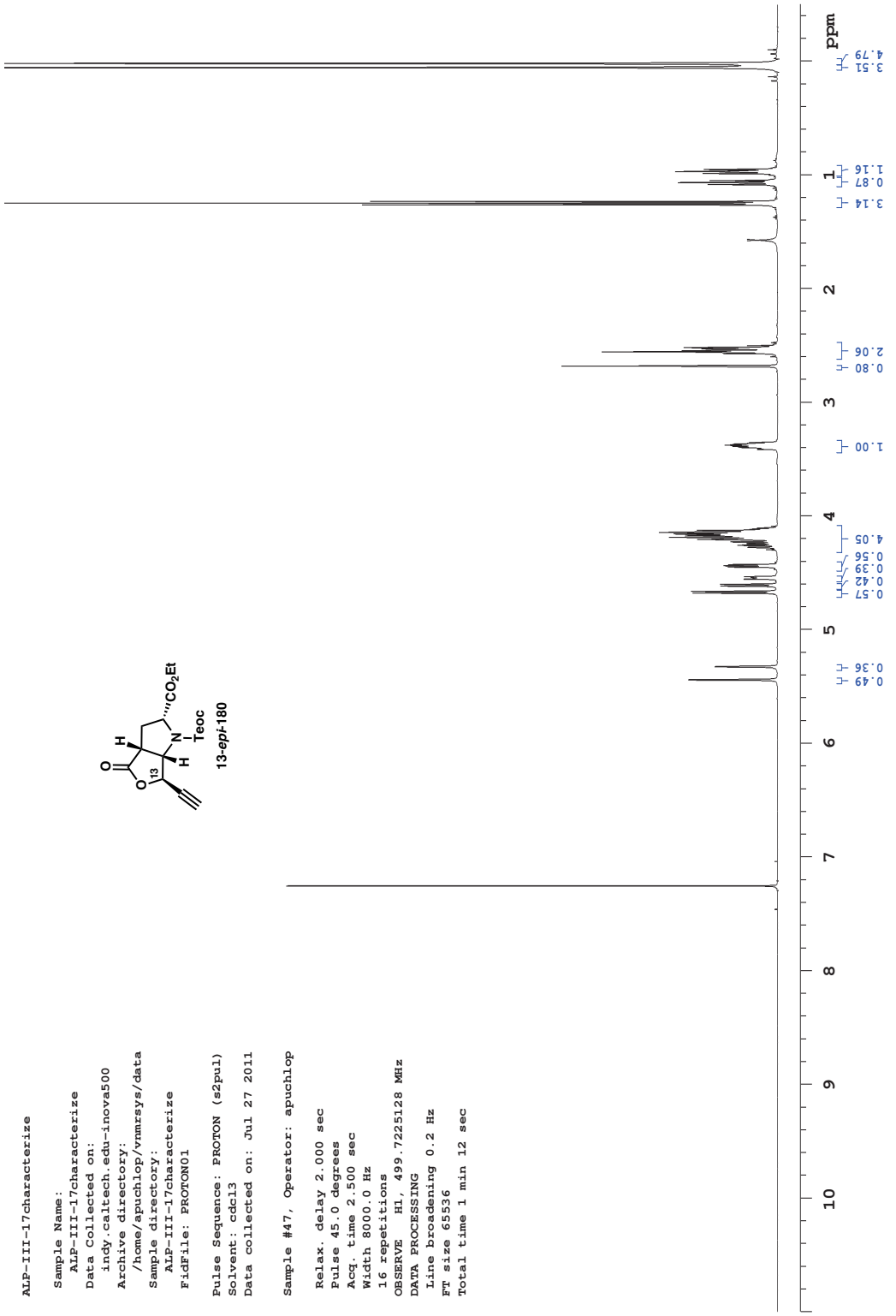

ALP-II-175characterize
Sample Name:
ALP-II-175characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-175characterize
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jun 15 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
7000 repetitions
OBSERVE C13, 125.6575066 MHz
DECOUPLE H1, 499.7341599 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 59 min
MeO2C
CO2Et
N
Teoc
Ph
202
220
200
180
160
140
120
100
80
60
40
20
0
ppm

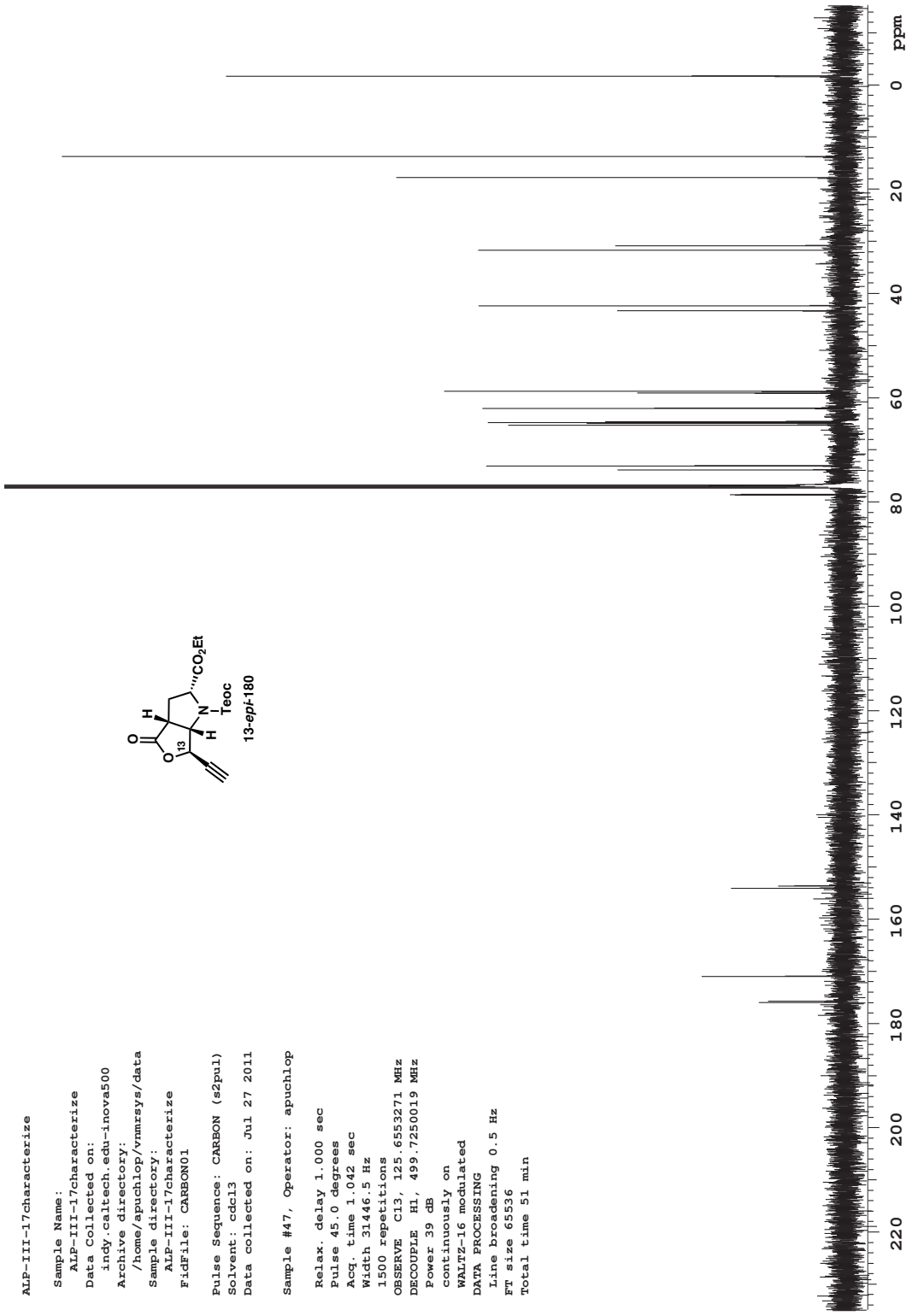

JAC6-113_115 60 _C DMSO siena
Sample Name:
JAC6-113_115
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-113_115
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Apr 27 2011
Temp. 60.0 C / 333.1 K
Sample #9, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7966888 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 0 sec
HO
O
O
H
H
N
Teoc
CO2Et
179
ppm
9.12
2.35
3.05
1.01
1.02
1.00
2.09
1.88
1.15
1.01
1.03
0.99

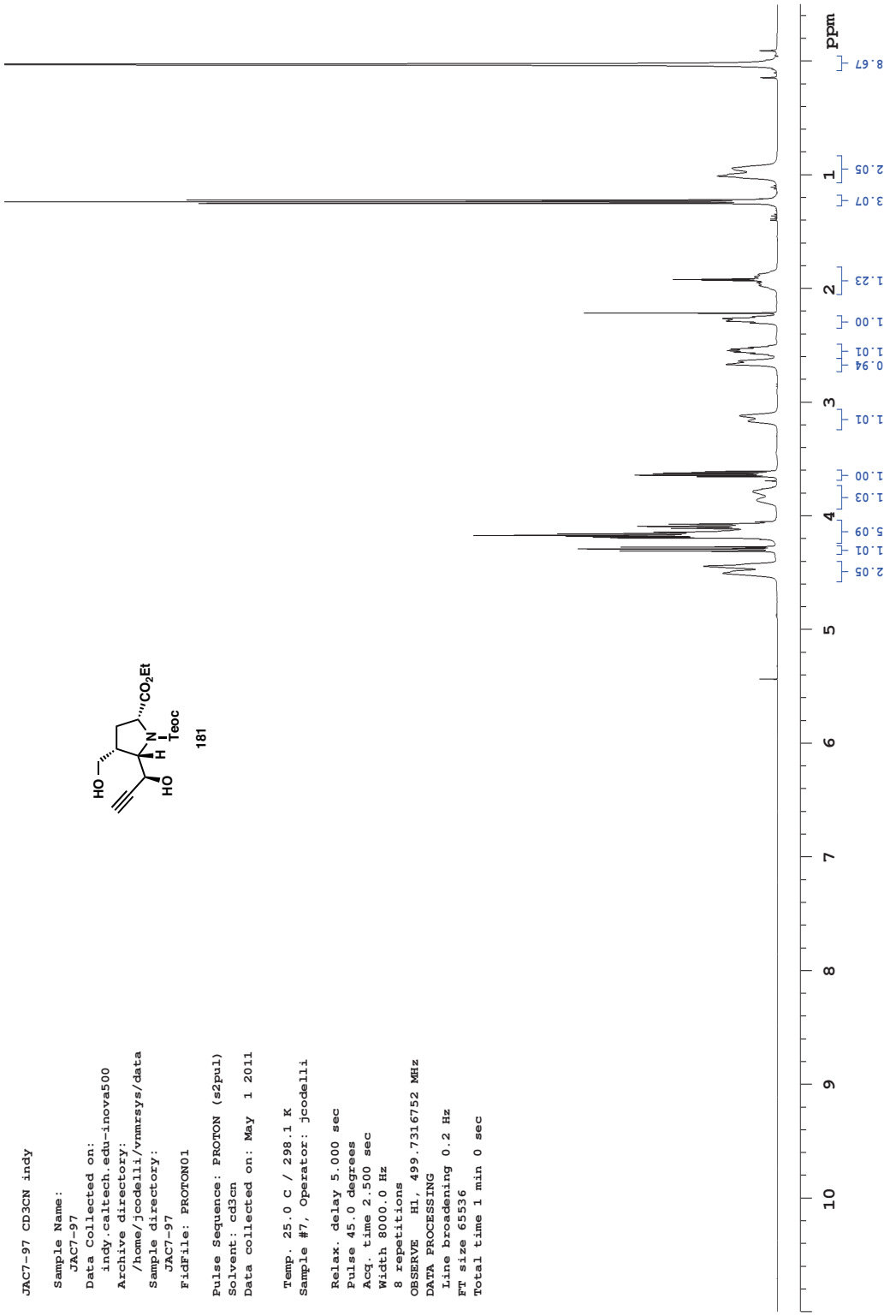

JAC6-113_115 60 _C DMSO siena
Sample Name:
JAC6-113_115
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-113_115
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Apr 27 2011
Temp. 60.0 C / 333.1 K
Sample #9, Operator: jcodalli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
256 repetitions
OBSERVE C13, 100.5289808 MHz
DECOUPLE H1, 399.7987005 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min 45 sec
O
H
O
HO
H
N
Teoc
CO2Et
179
220
200
180
160
140
120
100
80
60
40
20
0
ppm

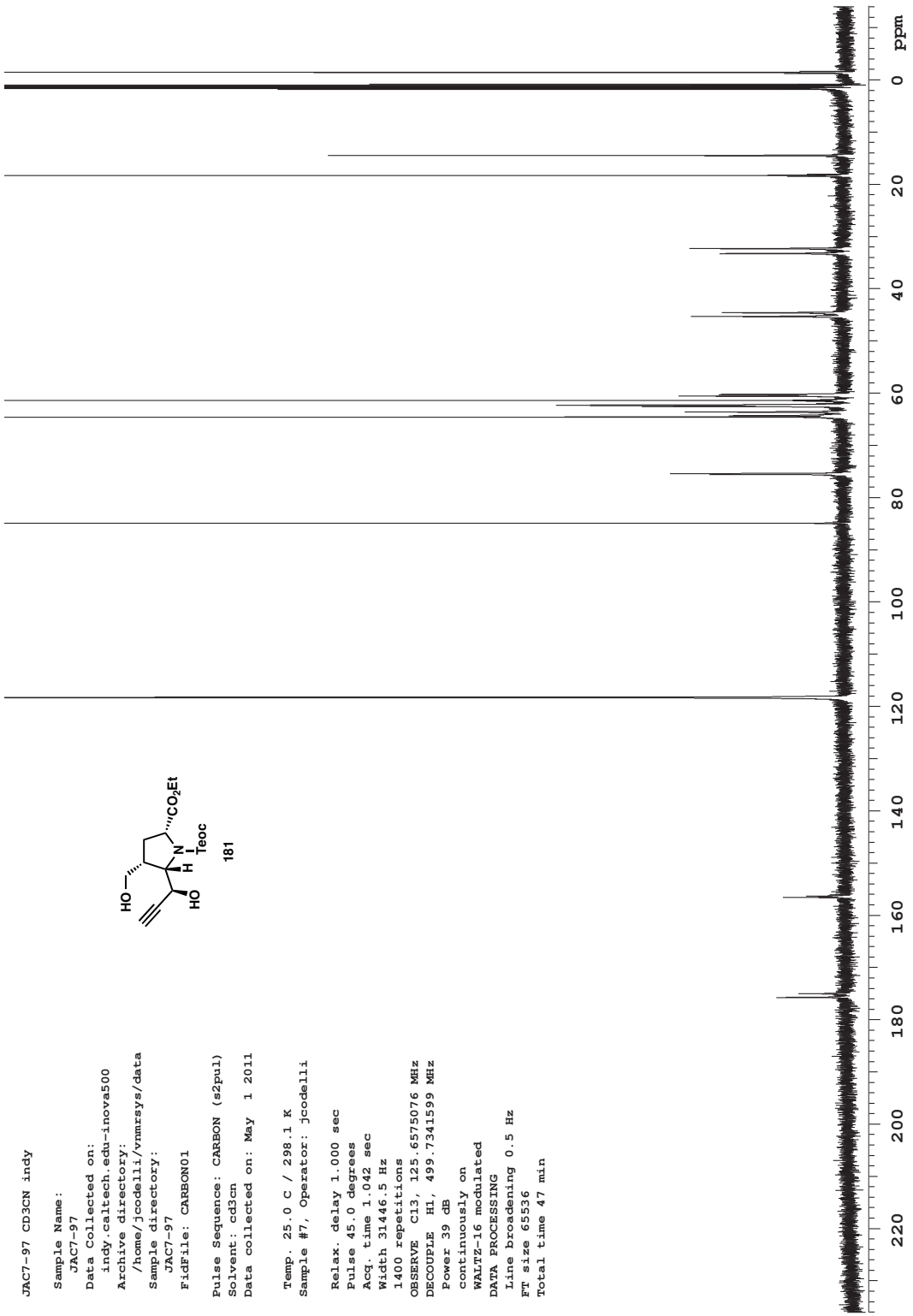

JAC7-93 CDCl3 indy
Sample Name:
JAC7-93
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-93
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 2011
Temp. 25.0 C / 298.1 K
Sample #14, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
CO2Et
Teoc
180
ppm
8.51
1.98
3.42
2.01
0.47
0.47
1.00
4.03
0.49
0.49
0.55
0.53
0.49

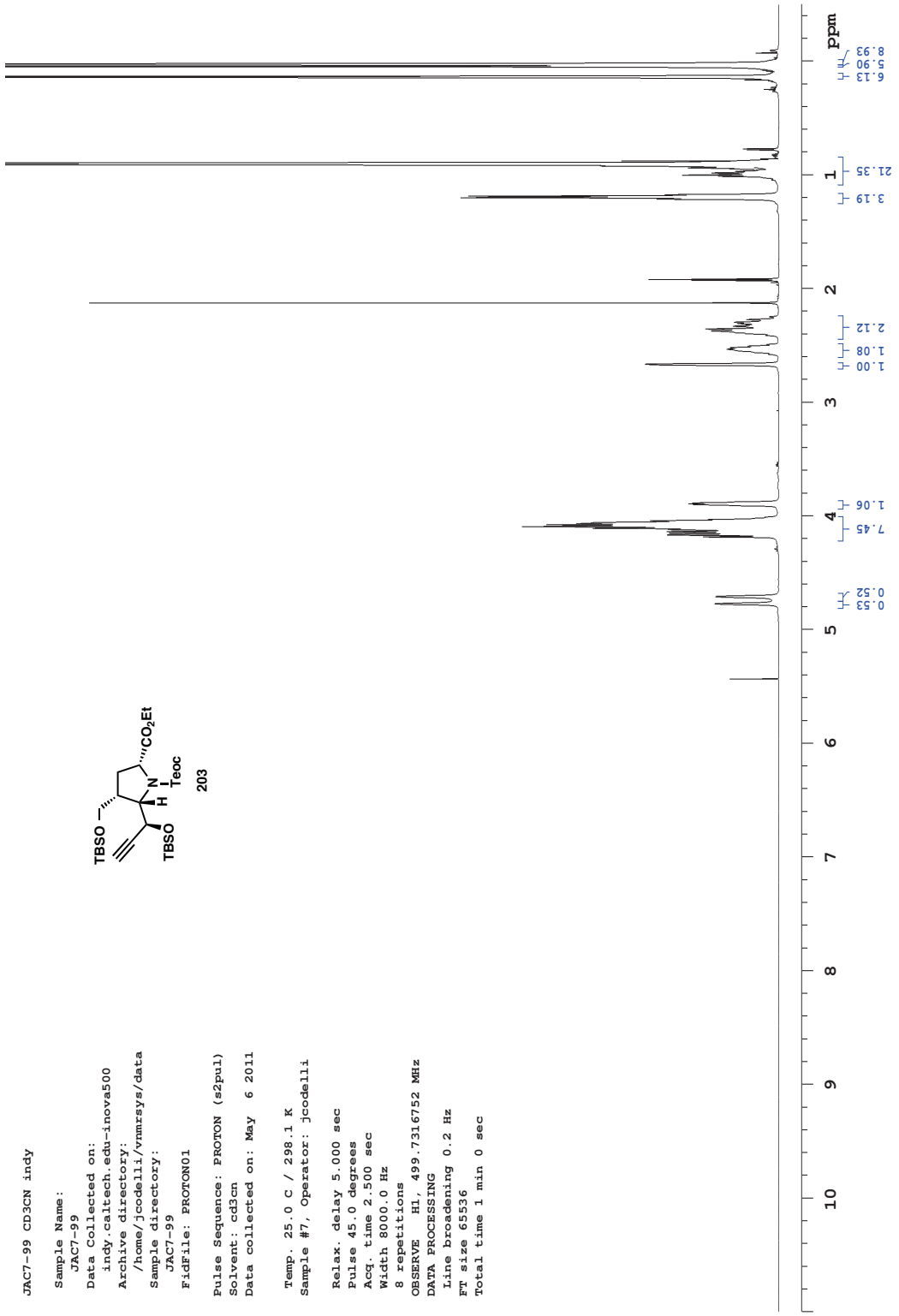

JAC7-93 CDCl3 indy
Sample Name:
JAC7-93
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-93
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 2011
Temp. 25.0 C / 298.1 K
Sample #14, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 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 51 min
O
H
O
13
H
N
Teoc
CO2Et
180
220
200
180
160
140
120
100
80
60
40
20
0
ppm

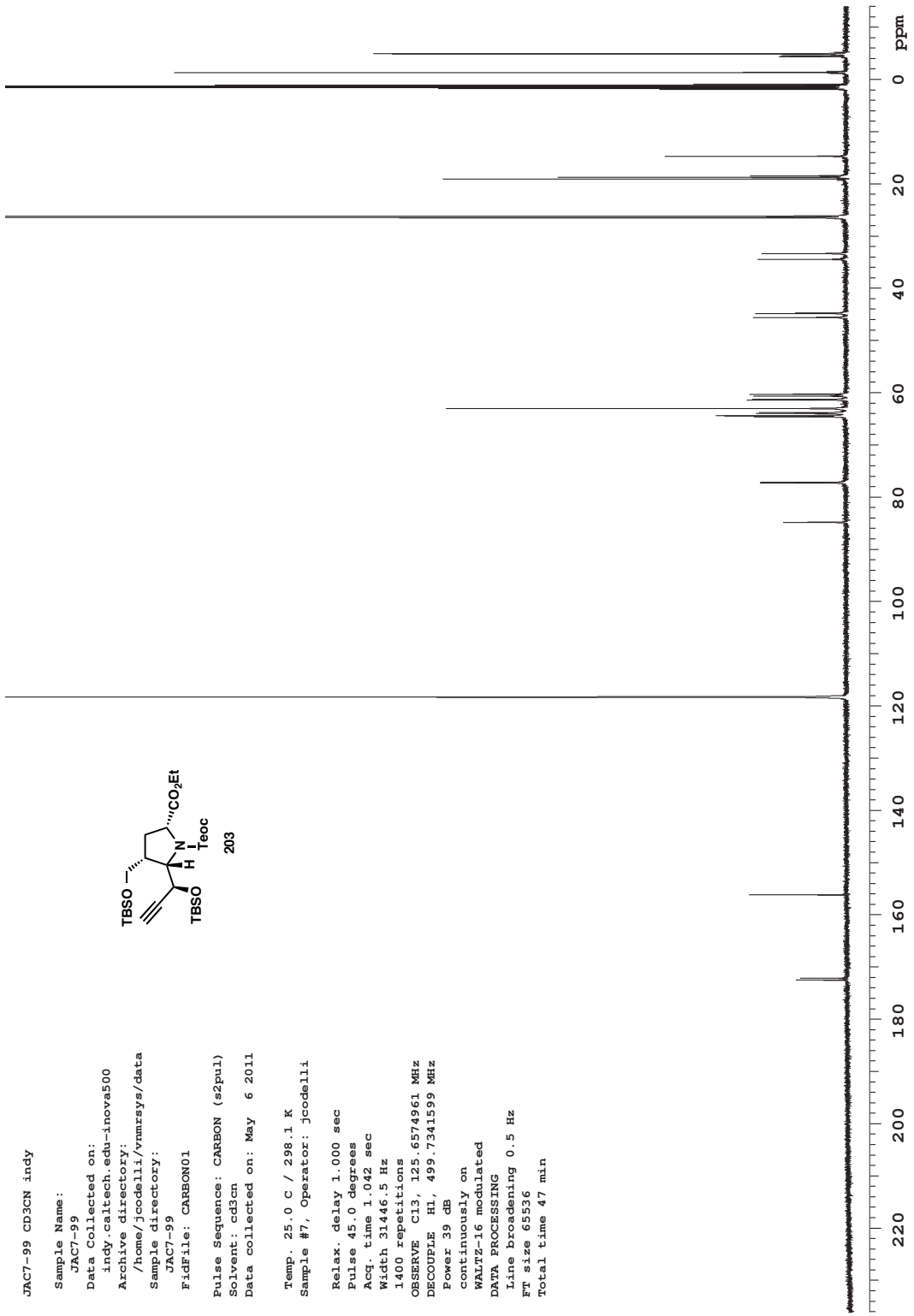

ALP-III-17characterize
Sample Name:
ALP-III-17characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-III-17characterize
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2011
Sample #47, Operator: apuchlop
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
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
13-epi-180
Teoc
ppm
4.79
3.51
3.14
1.16
0.87
2.06
0.80
1.00
4.05
0.56
0.39
0.42
0.57
0.36
0.49

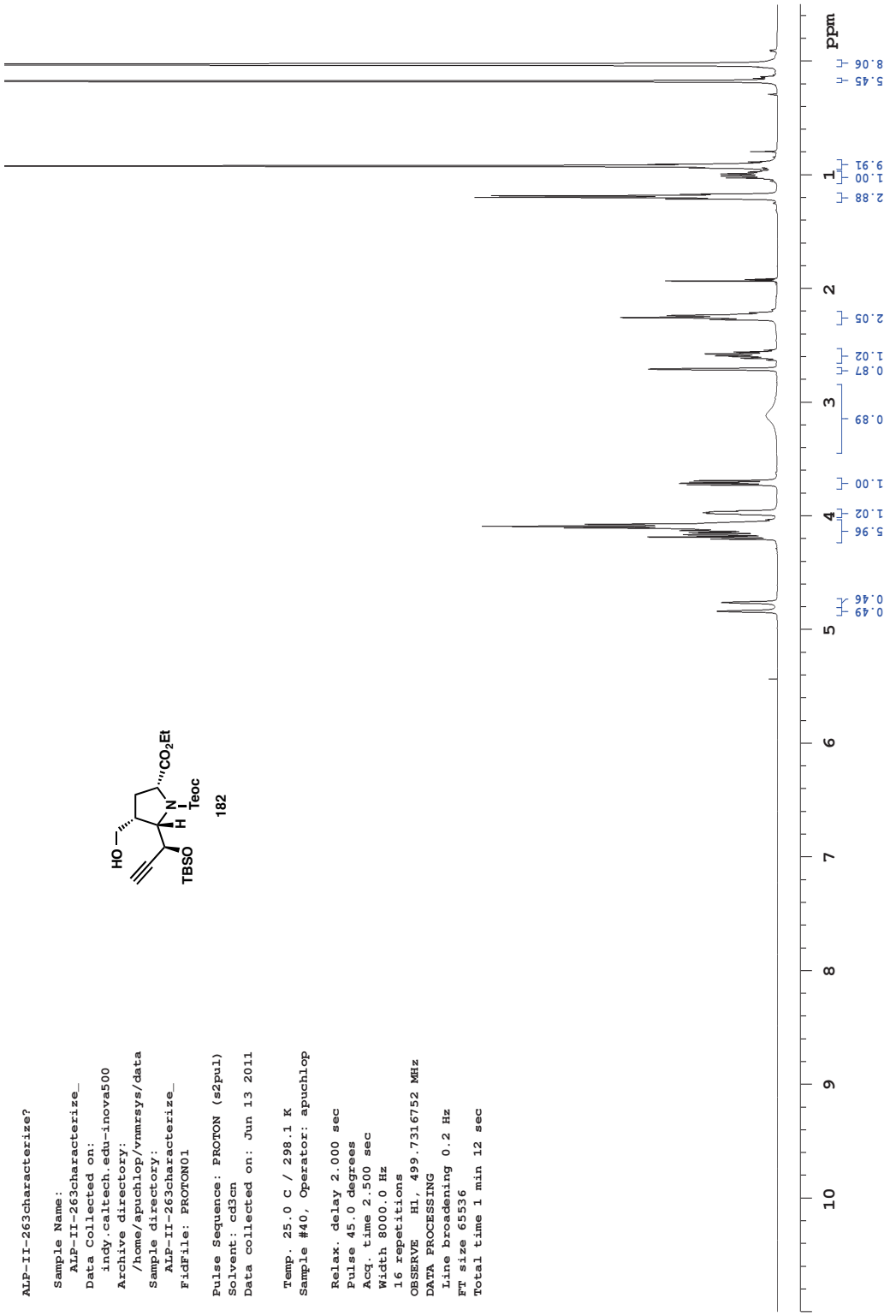

ALP-III-17characterize
Sample Name:
ALP-III-17characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-III-17characterize
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2011
Sample #47, Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 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 51 min
O
H
H
N
Teoc
CO2Et
O
O
13
13-epi-180
220
200
180
160
140
120
100
80
60
40
20
0
ppm

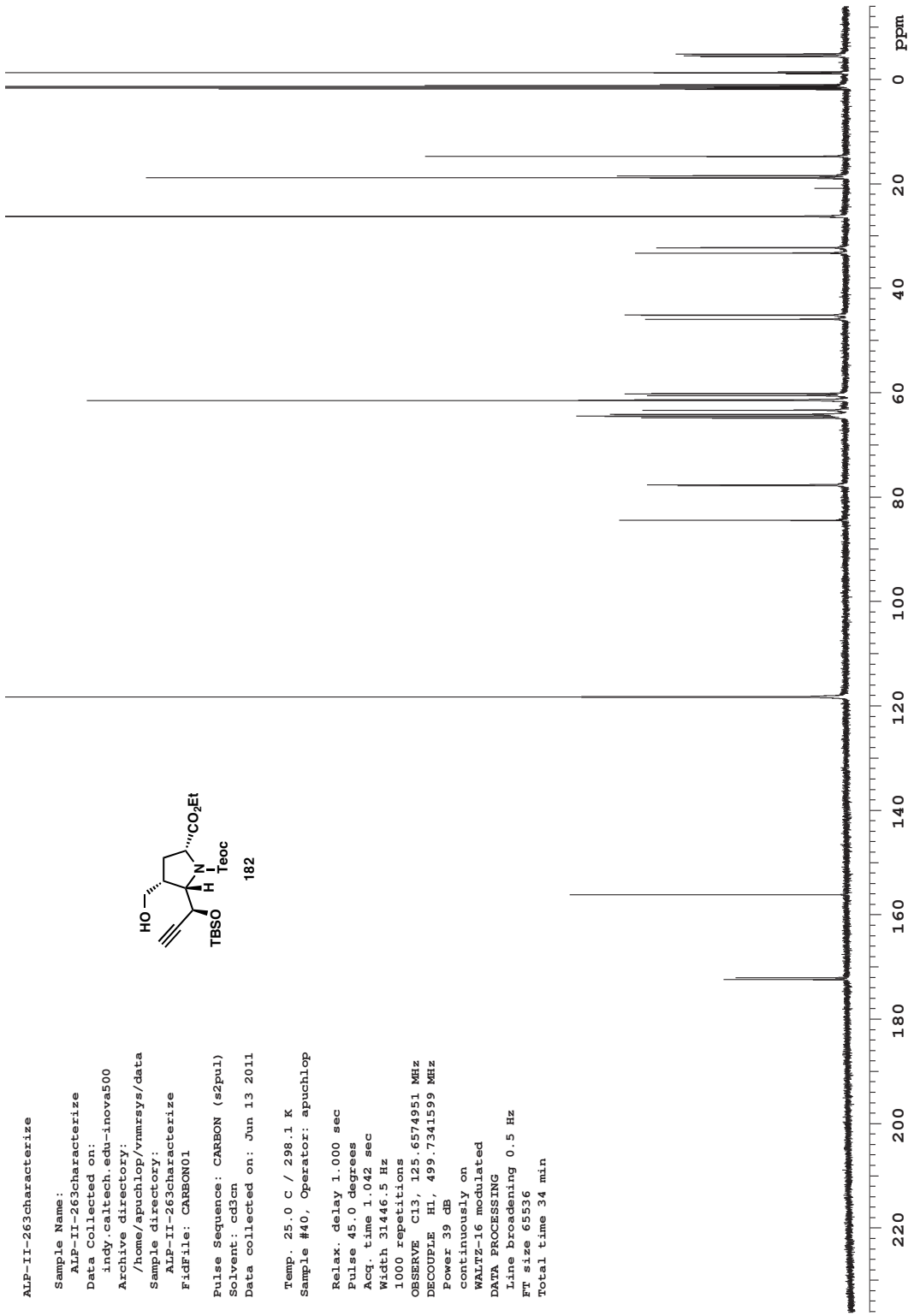

JAC7-97 CD3CN indy
Sample Name:
JAC7-97
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-97
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 1 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7316752 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
HO
HO
N
H
Teoc
CO2Et
181
ppm
10
9
8
7
6
5
4
3
2
1
8.67
2.05
3.07
1.23
1.00
0.94
1.01
1.01
1.00
1.03
5.09
1.01
2.05

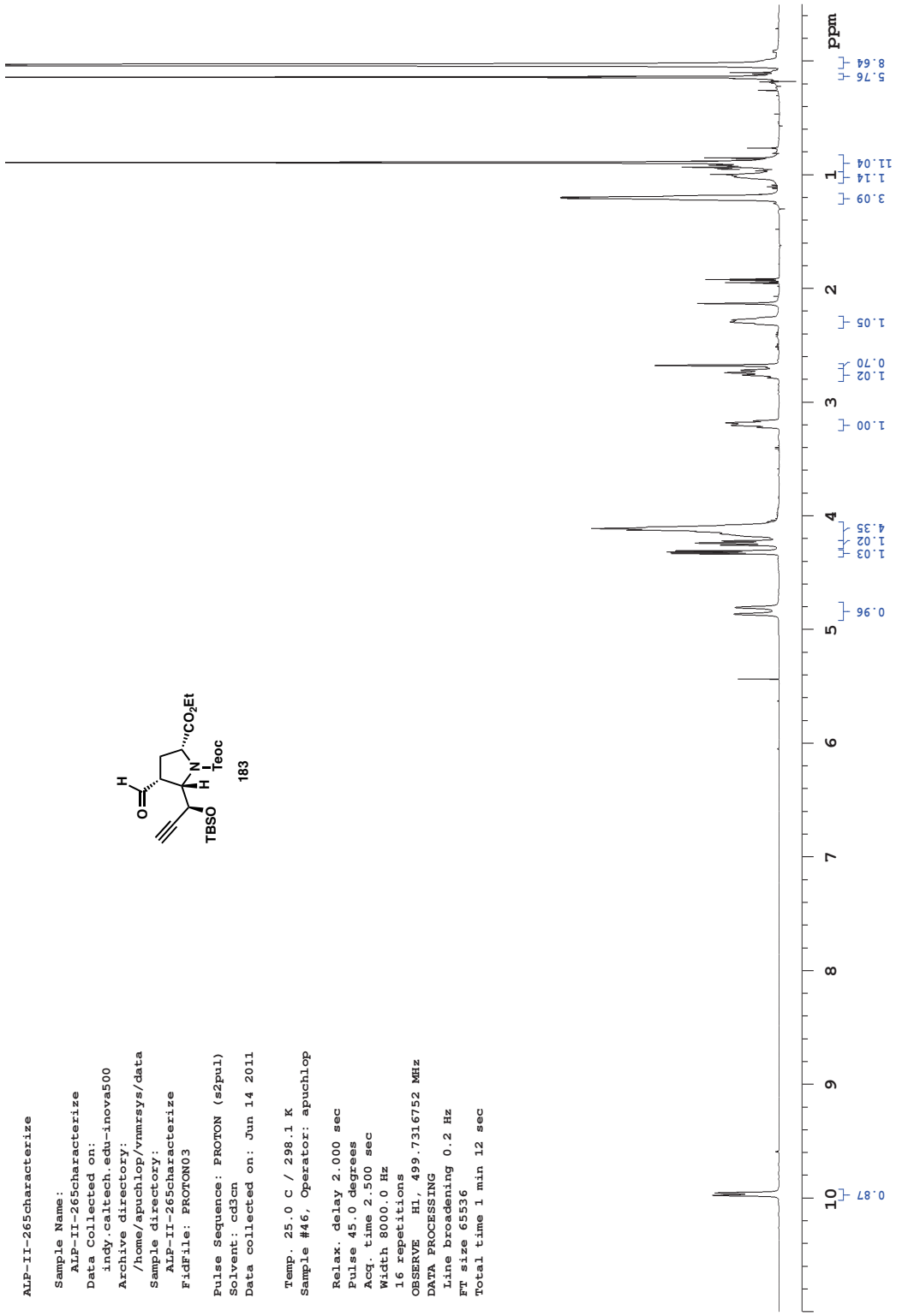

JAC7-97 CD3CN indy
Sample Name:
JAC7-97
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-97
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: May 1 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1400 repetitions
OBSERVE C13, 125.6575076 MHz
DECOUPLE H1, 499.7341599 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 47 min
HO
HO
N
H
Teoc
CO2Et
181
220
200
180
160
140
120
100
80
60
40
20
0
ppm

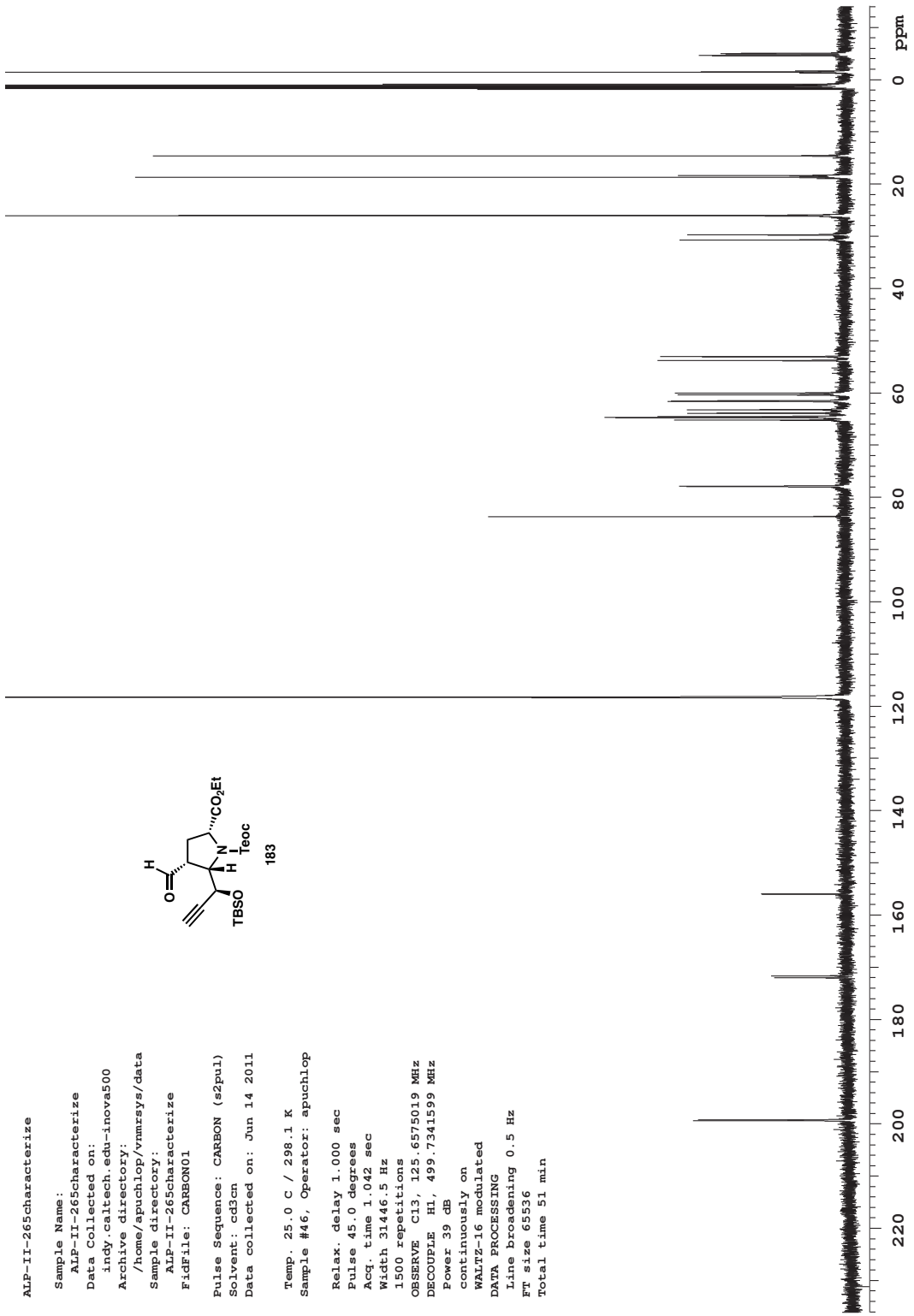

JAC7-99 CD3CN indy
Sample Name:
JAC7-99
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-99
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7316752 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
TBSO
TBSO
N
H
Teoc
CO2Et
203
ppm
10
9
8
7
6
5
4
3
2
1
8.93
5.90
6.13
21.35
3.19
2.12
1.08
1.00
1.06
7.45
0.53
0.52

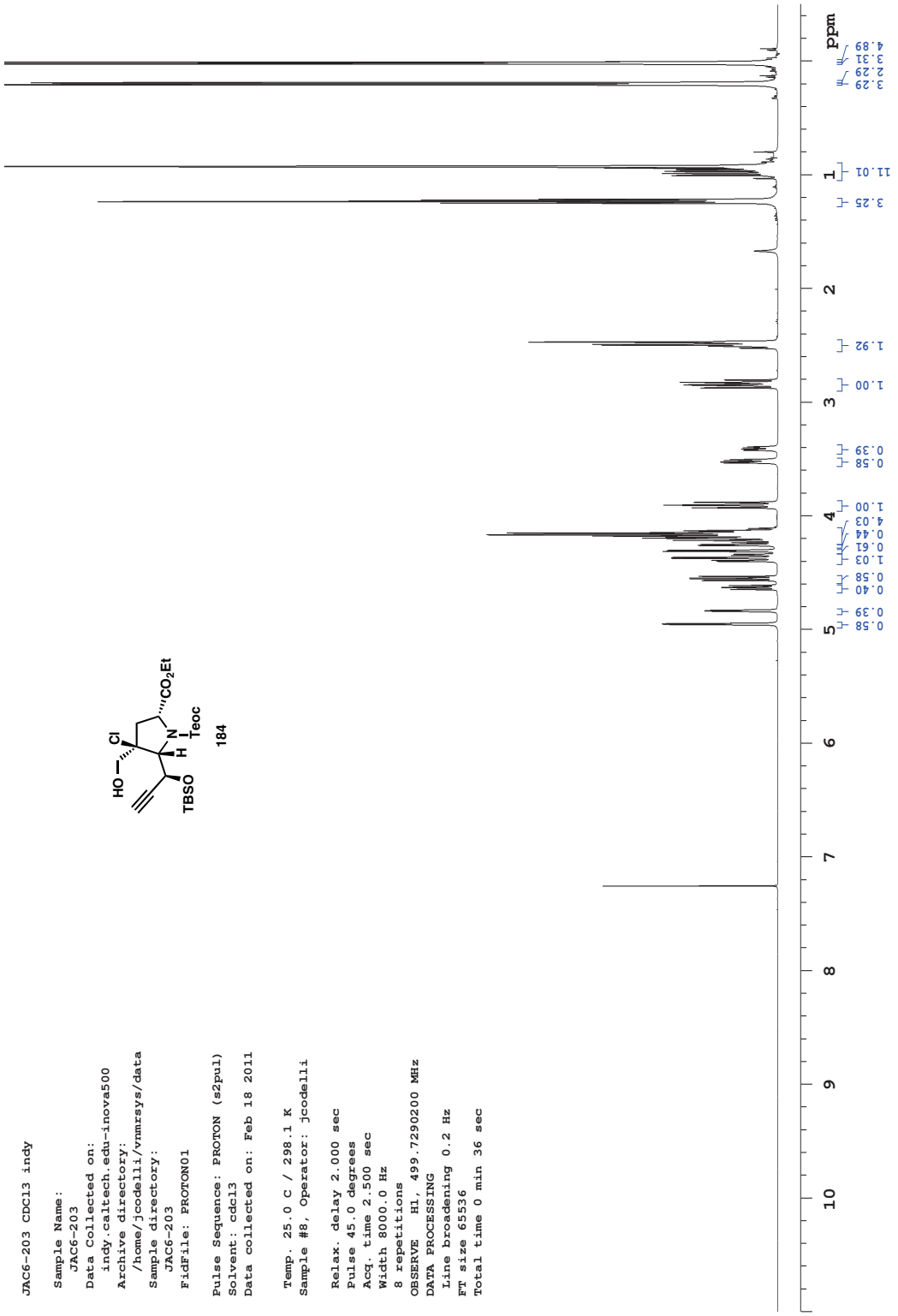

JAC7-99 CD3CN indy
Sample Name:
JAC7-99
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-99
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1400 repetitions
OBSERVE C13, 125.6574961 MHz
DECOUPLE H1, 499.7341599 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 47 min
TBSO
TBSO
N
H
Teoc
CO2Et
203
220
200
180
160
140
120
100
80
60
40
20
0
ppm

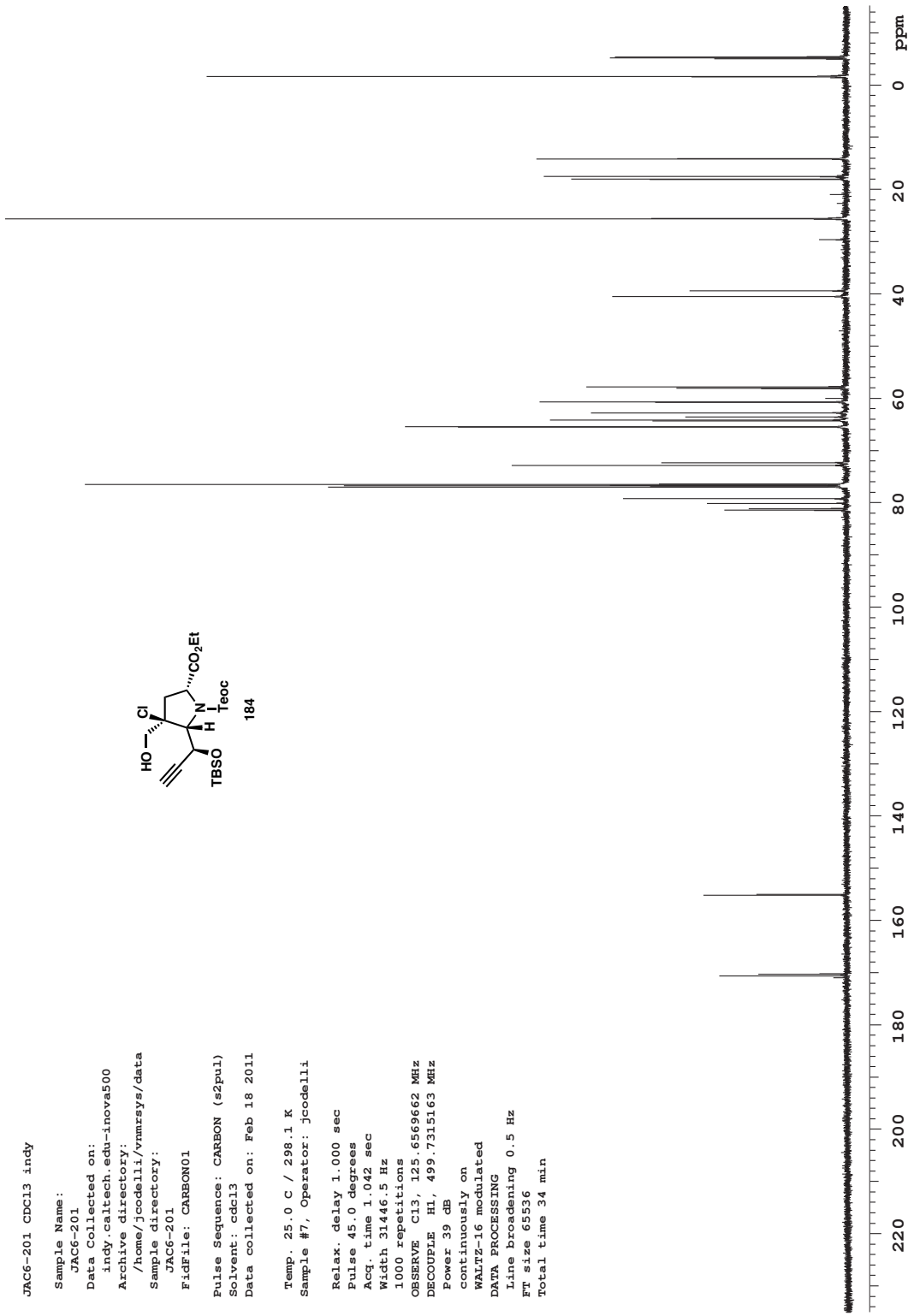

ALP-II-263characterize?
Sample Name:
ALP-II-263characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-263characterize
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jun 13 2011
Temp. 25.0 C / 298.1 K
Sample #40, Operator: apuchlop
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7316752 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
HO
TBSO
N
H
Teoc
CO2Et
182
ppm
10
9
8
7
6
5
4
3
2
1
0.49
0.46
5.96
1.02
1.00
0.89
1.02
0.87
2.05
2.88
1.00
9.91
5.45
8.06

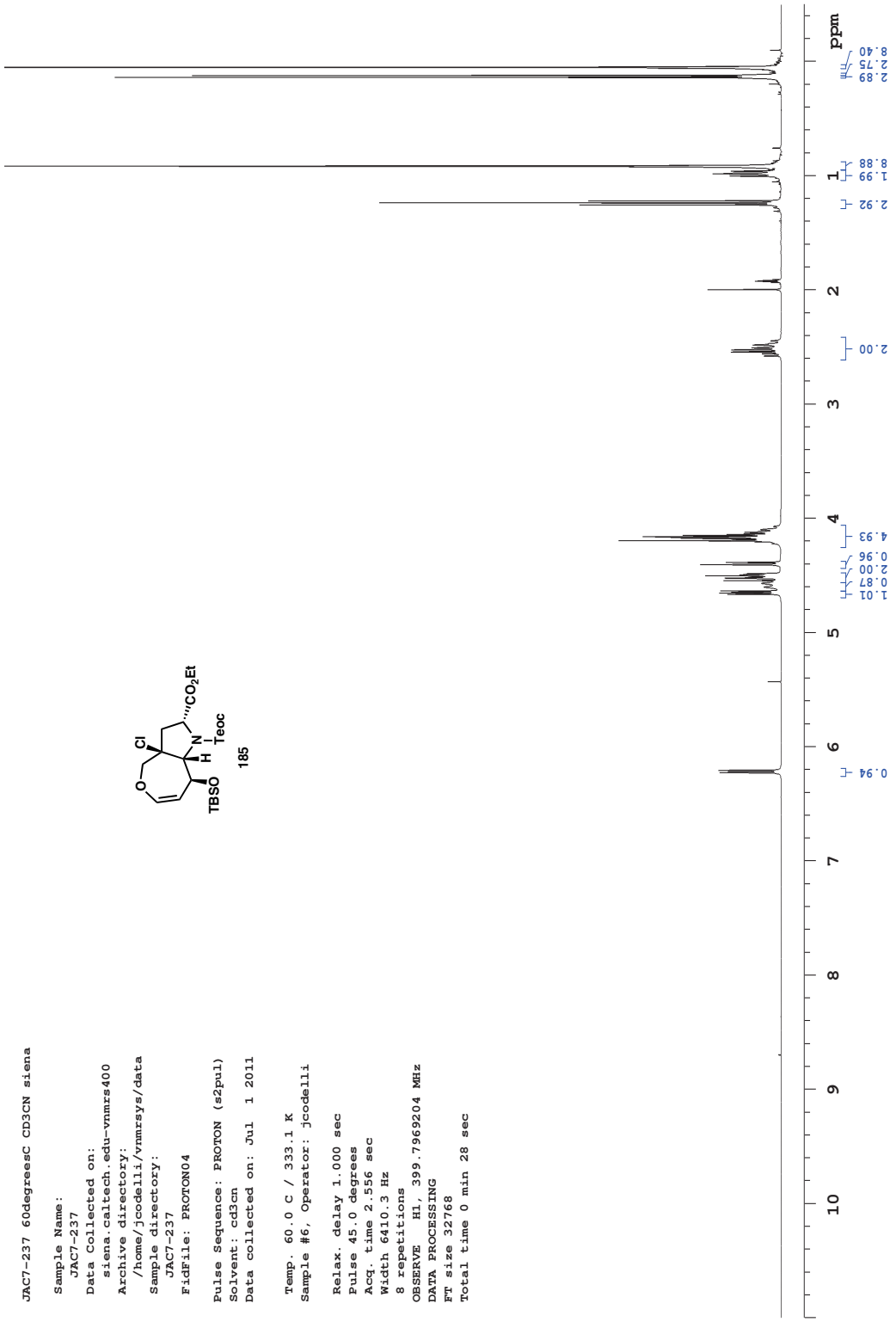

ALP-II-263characterize
Sample Name:
ALP-II-263characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-263characterize
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jun 13 2011
Temp. 25.0 C / 298.1 K
Sample #40, Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6574951 MHz
DECOUPLE H1, 499.7341599 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
HO
TBSO
N
H
Teoc
CO2Et
182
220
200
180
160
140
120
100
80
60
40
20
0
ppm

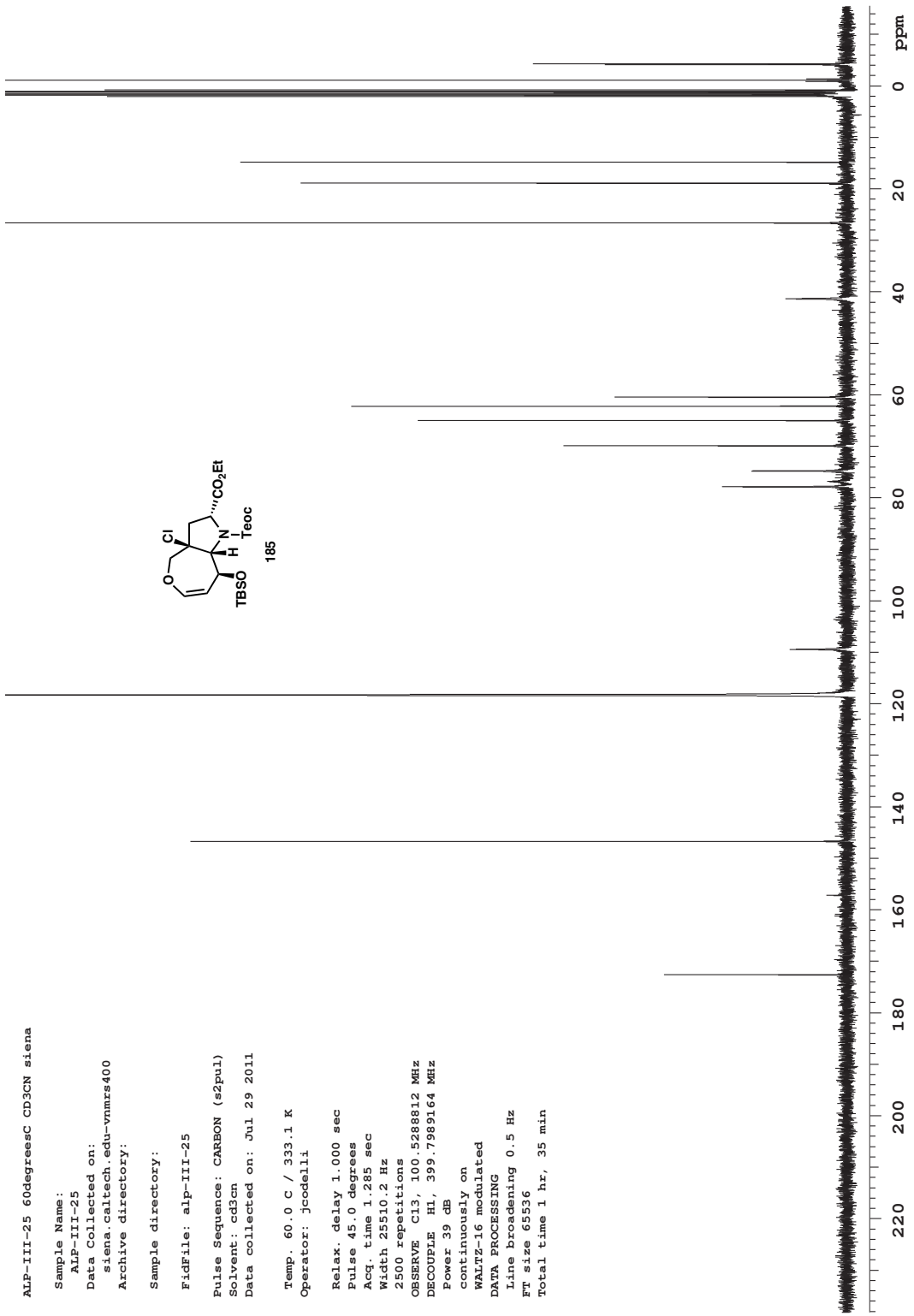

ALP-II-265characterize
Sample Name:
ALP-II-265characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-265characterize
FidFile: PROTON03
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jun 14 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: apuchlop
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7316752 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
TBSO
Teoc
183
ppm
8.64
5.76
11.04
1.14
3.09
1.05
1.02
0.70
1.00
4.35
1.02
1.03
0.96
0.87

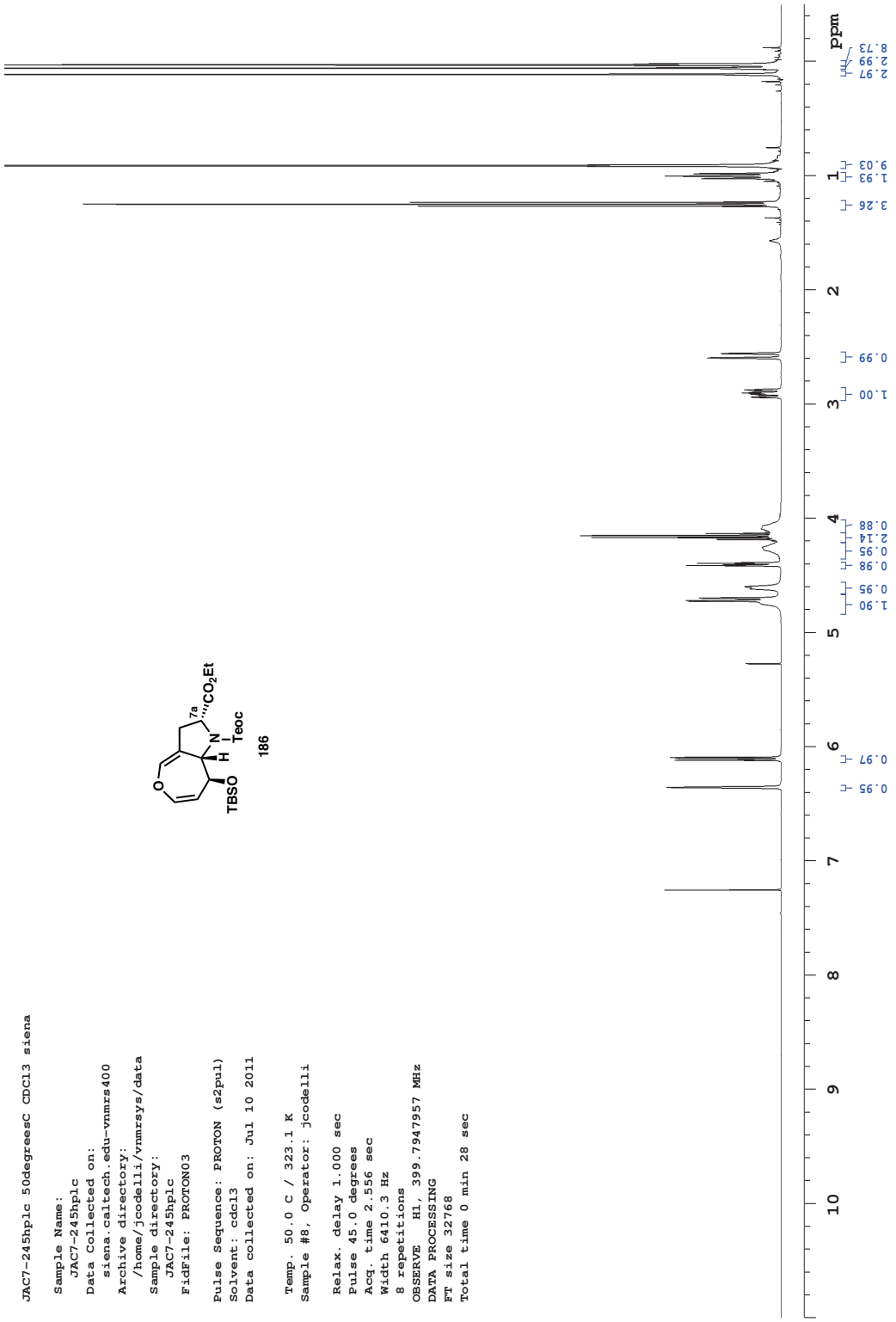

ALP-II-265characterize
Sample Name:
ALP-II-265characterize
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
ALP-II-265characterize
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jun 14 2011
Temp. 25.0 C / 298.1 K
Sample #46, Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6575019 MHz
DECOUPLE H1, 499.7341599 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
H
O
TBSO
N
H
Teoc
CO2Et
183
220
200
180
160
140
120
100
80
60
40
20
0
ppm

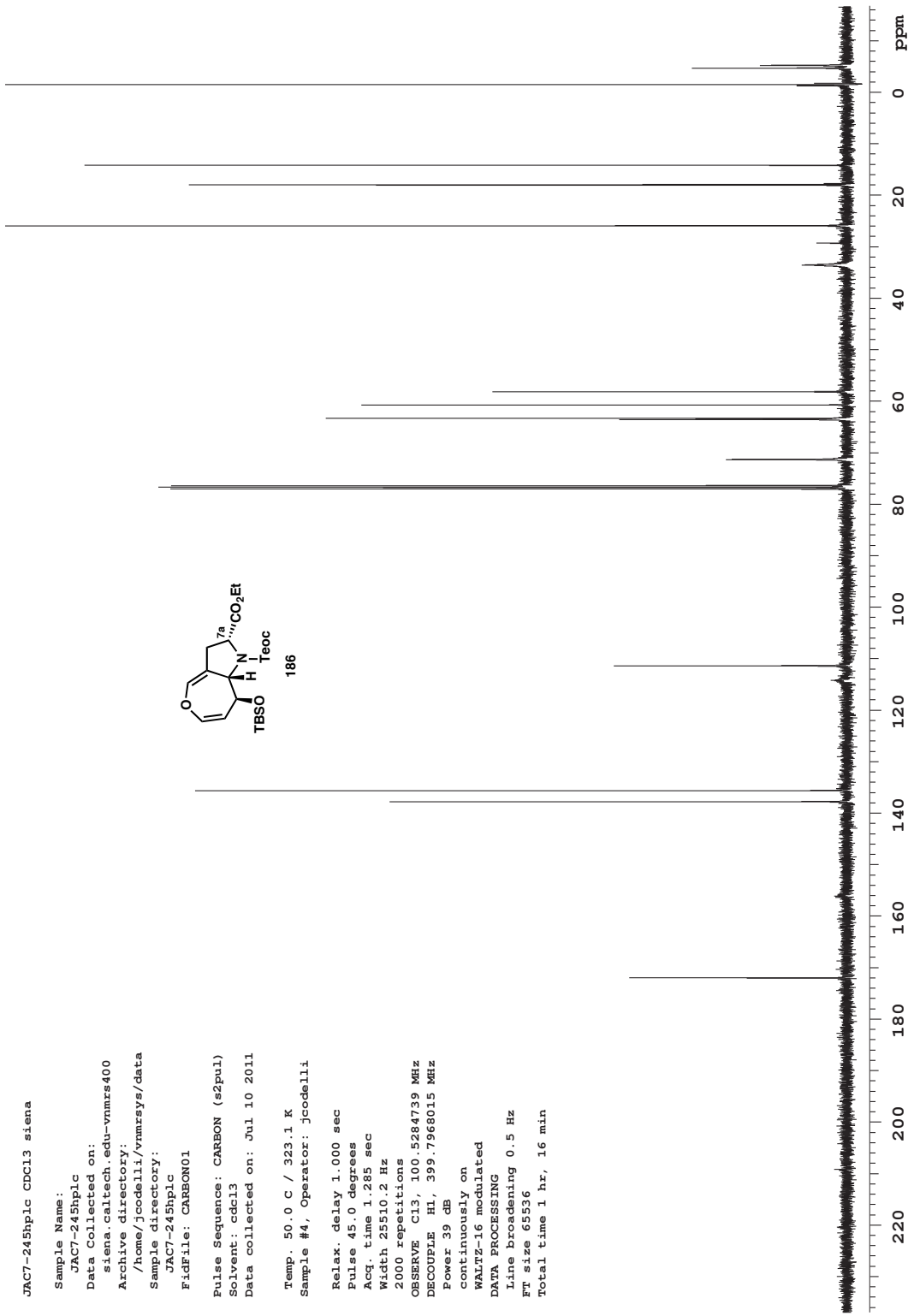

JAC6-203 CDCl3 indy
Sample Name:
JAC6-203
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-203
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 18 2011
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 36 sec
HO
Cl
TBSO
N
H
Teoc
CO2Et
184
ppm
10
9
8
7
6
5
4
3
2
1
4.89
3.31
3.29
2.29
11.01
3.25
1.92
1.00
0.58
0.39
1.00
4.03
0.44
0.61
1.03
0.40
0.58
0.39
0.58

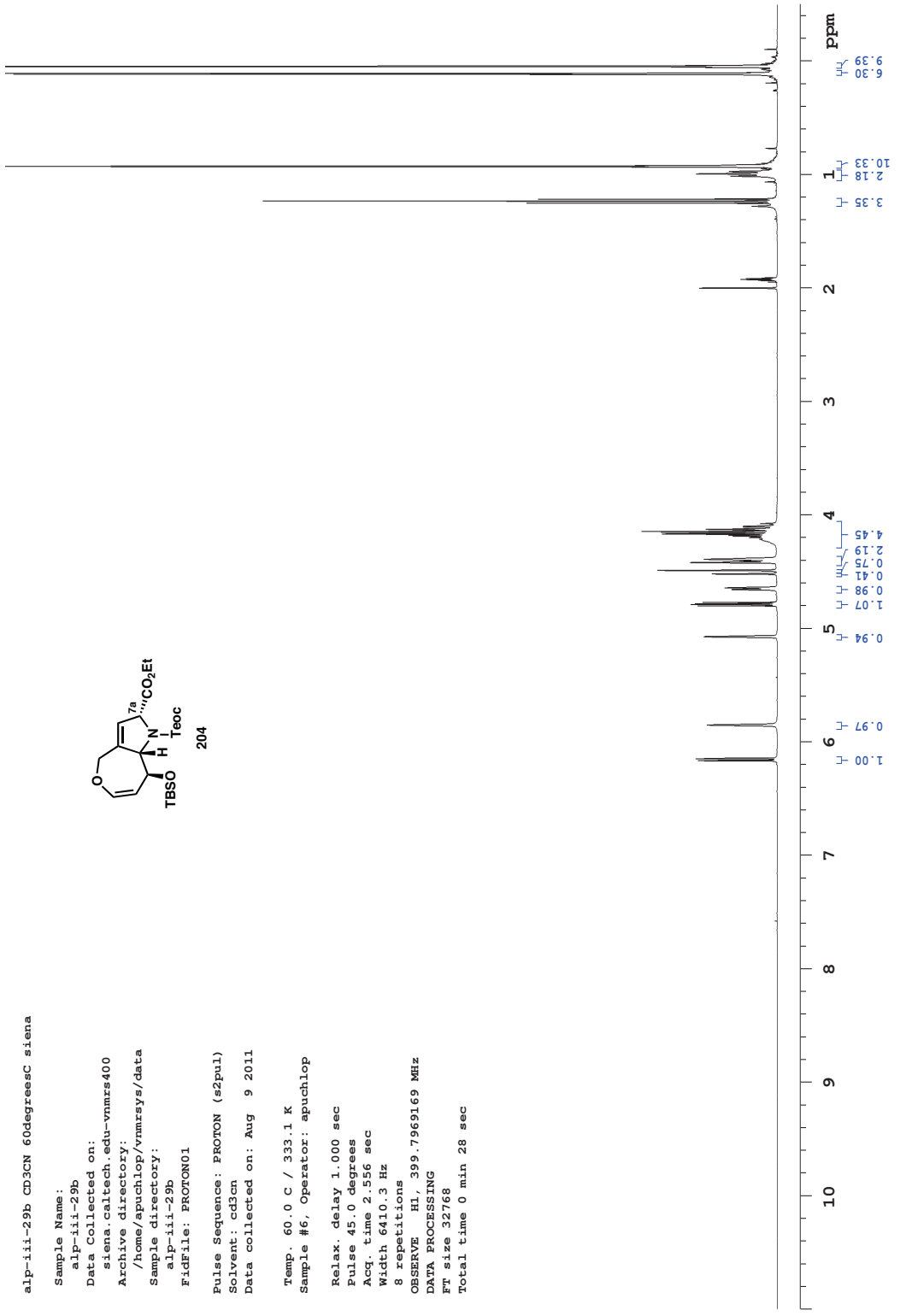

JAC6-201 CDCl3 indy
Sample Name:
JAC6-201
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC6-201
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 18 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569662 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
Cl
TBSO
N
H
Teoc
CO2Et
184
220
200
180
160
140
120
100
80
60
40
20
0
ppm

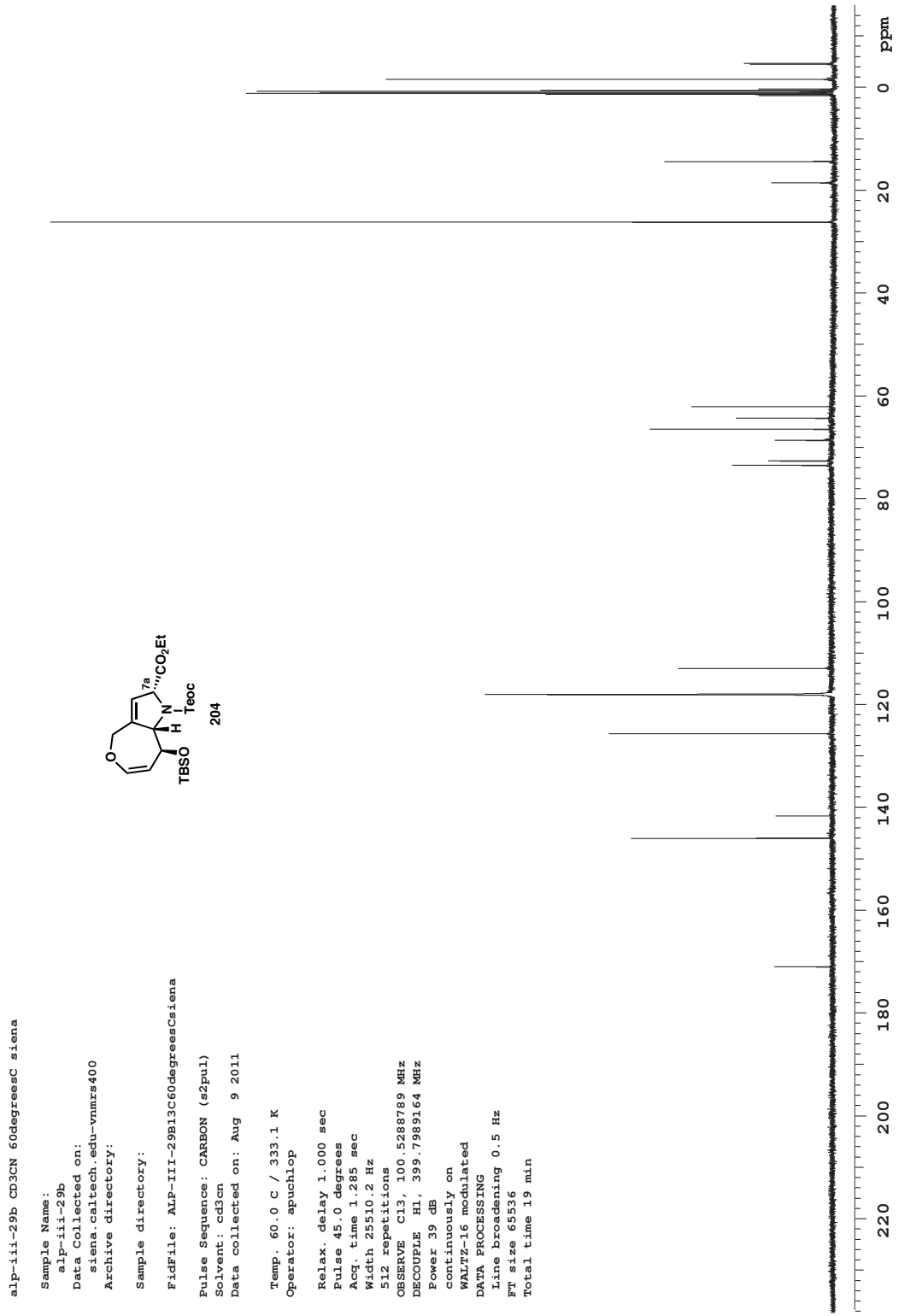

JAC7-237 60degreesC CD3CN siena
Sample Name:
JAC7-237
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-237
FidFile: PROTON04
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jul 1 2011
Temp. 60.0 C / 333.1 K
Sample #6, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7969204 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
Cl
O
TBSO
H
N
Teoc
CO2Et
185
ppm
10
9
8
7
6
5
4
3
2
1
0.94
2.92
1.99
8.88
2.89
2.75
8.40
2.00
4.93
0.96
2.00
0.87
1.01

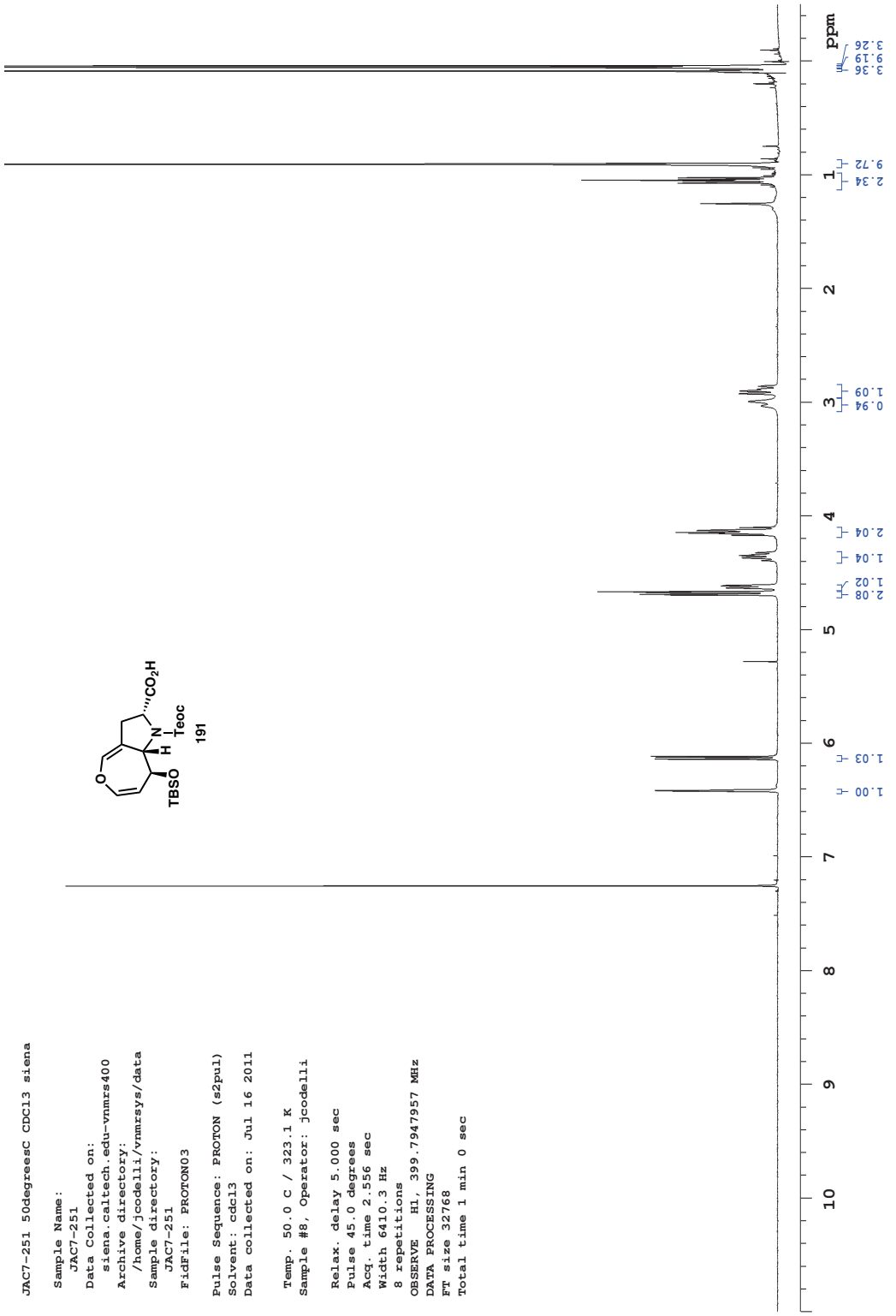

ALP-III-25 60degreesC CD3CN siena
Sample Name:
ALP-III-25
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
Sample directory:
FidFile: alp-III-25
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jul 29 2011
Temp. 60.0 C / 333.1 K
Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
2500 repetitions
OBSERVE C13, 100.5288812 MHz
DECOUPLE H1, 399.79891164 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 35 min
Cl
CO2Et
N
H
Teoc
TBSO
O
185
220
200
180
160
140
120
100
80
60
40
20
0
ppm

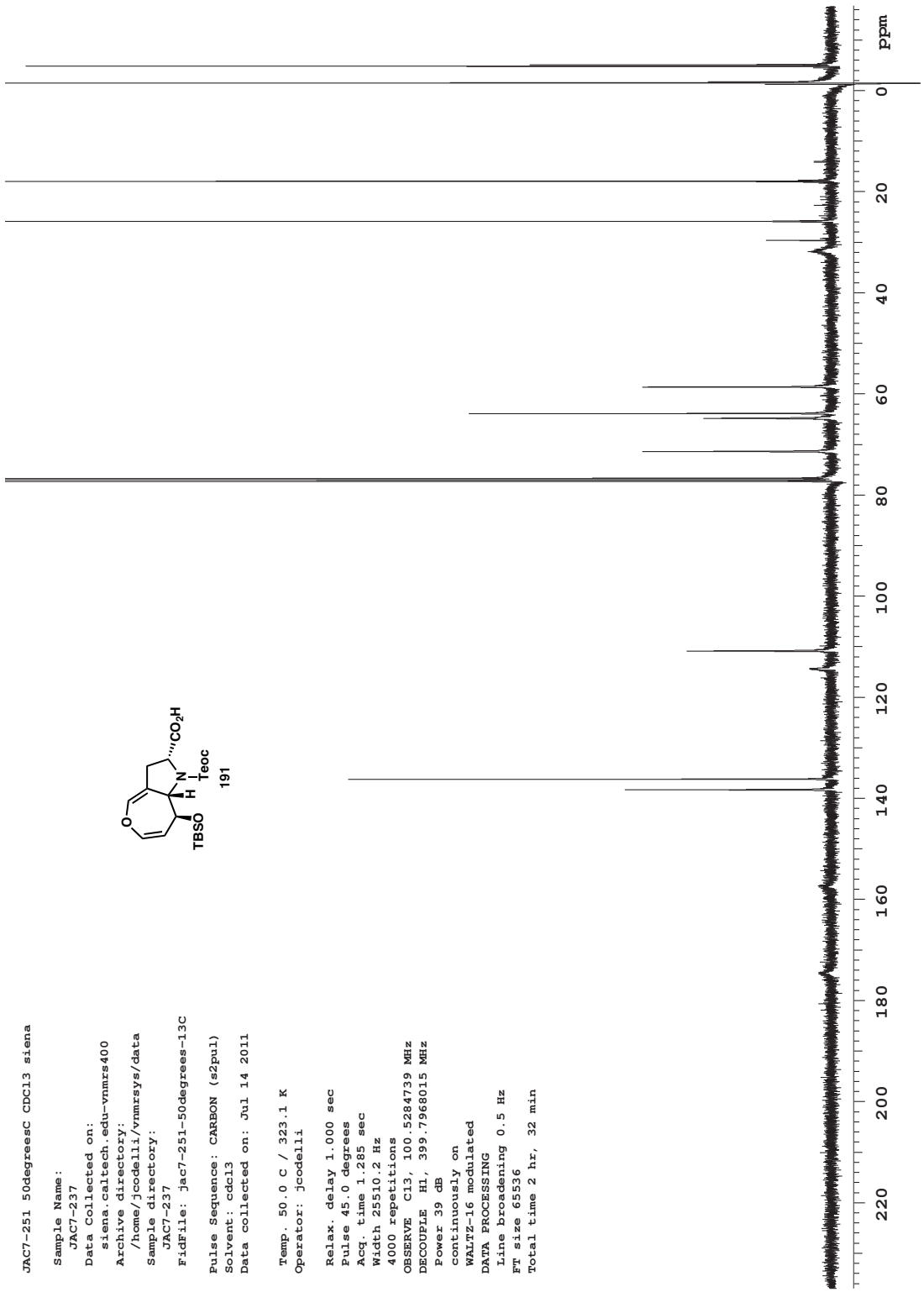

JAC7-245hp1c 50degreesC CDCl3 siena
Sample Name:
JAC7-245hp1c
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-245hp1c
FidFile: PROTON03
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 10 2011
Temp. 50.0 C / 323.1 K
Sample #8, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7947957 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
TBSO
Teoc
CO2Et
7a
186
ppm
8.73
2.99
2.97
9.03
1.93
3.26
0.99
1.00
0.88
2.14
0.95
0.98
0.95
1.90
0.97
0.95

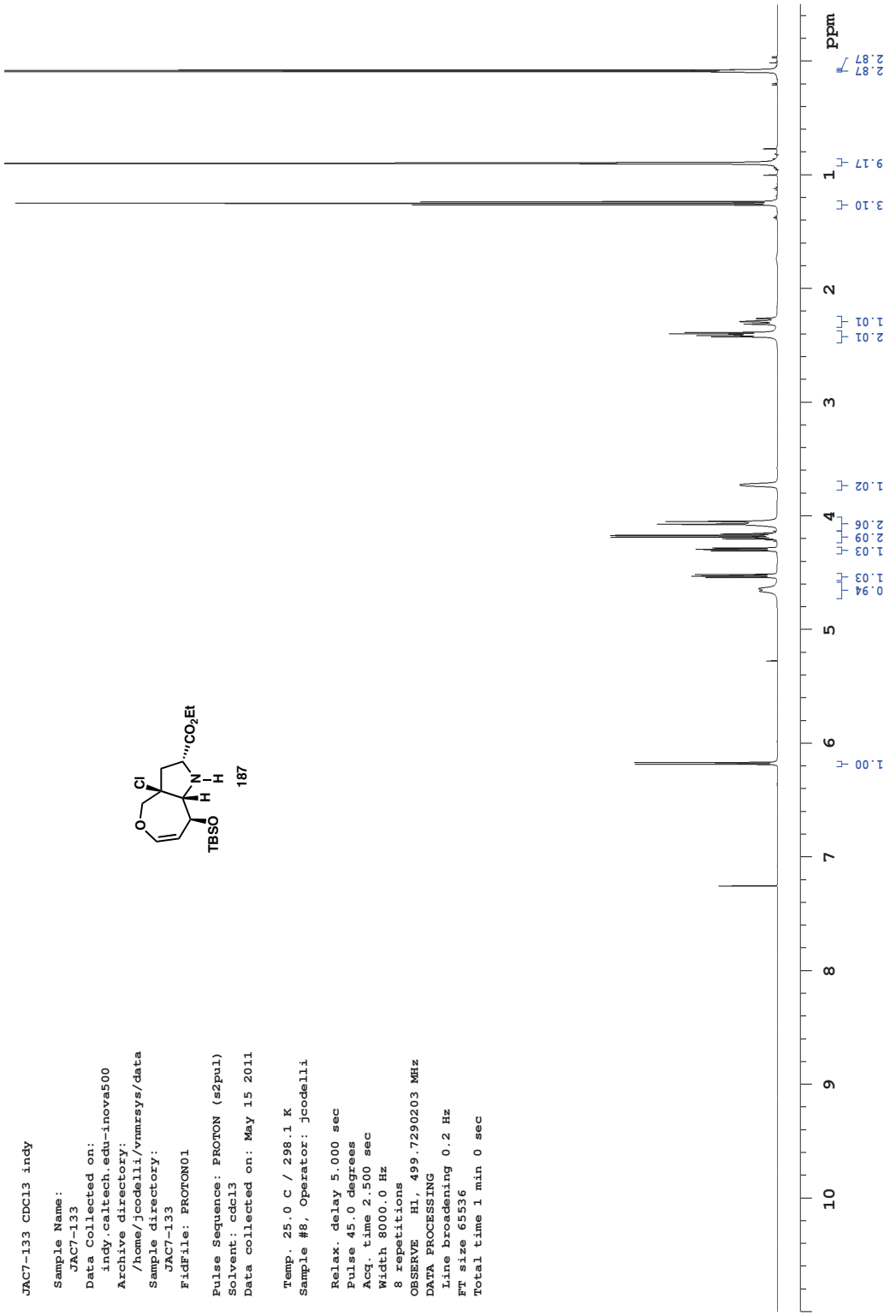

JAC7-245hp1c CDCl3 siena
Sample Name:
JAC7-245hp1c
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-245hp1c
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 10 2011
Temp. 50.0 C / 323.1 K
Sample #4, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
2000 repetitions
OBSERVE C13, 100.5284739 MHz
DECOUPLE H1, 399.7968015 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 16 min
TBSO
Teoc
CO2Et
7a
186
220
200
180
160
140
120
100
80
60
40
20
0
ppm

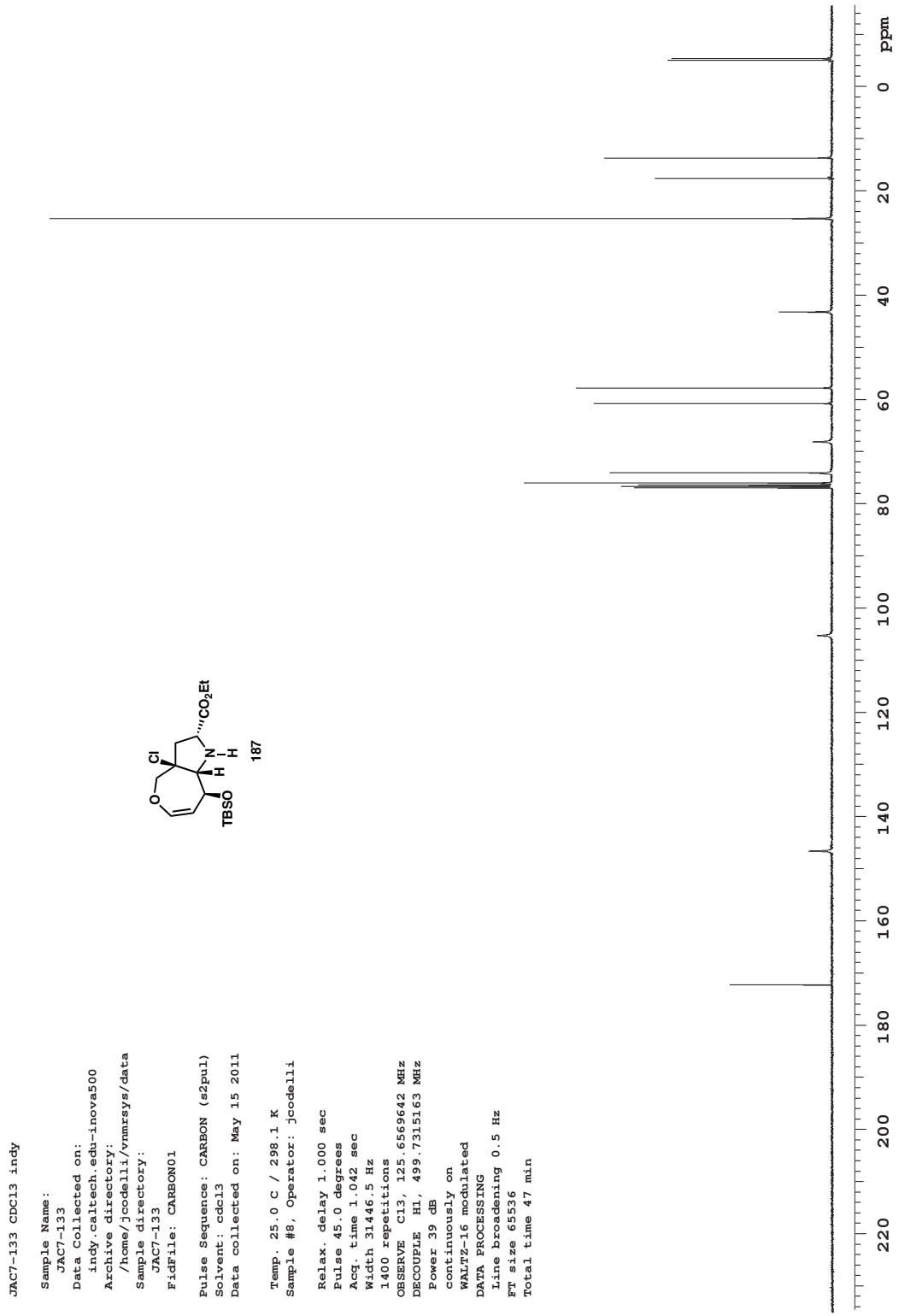

alp-iii-29b CD3CN 60degreesC siena
Sample Name:
alp-iii-29b
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/apuchlop/vnmrsys/data
Sample directory:
alp-iii-29b
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Aug 9 2011
Temp. 60.0 C / 333.1 K
Sample #6, Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7969169 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
TBSO
Teoc
7a
CO2Et
204
ppm
9.39
6.30
10.33
2.18
3.35
4.45
2.19
0.75
0.41
0.98
1.07
0.94
0.97
1.00

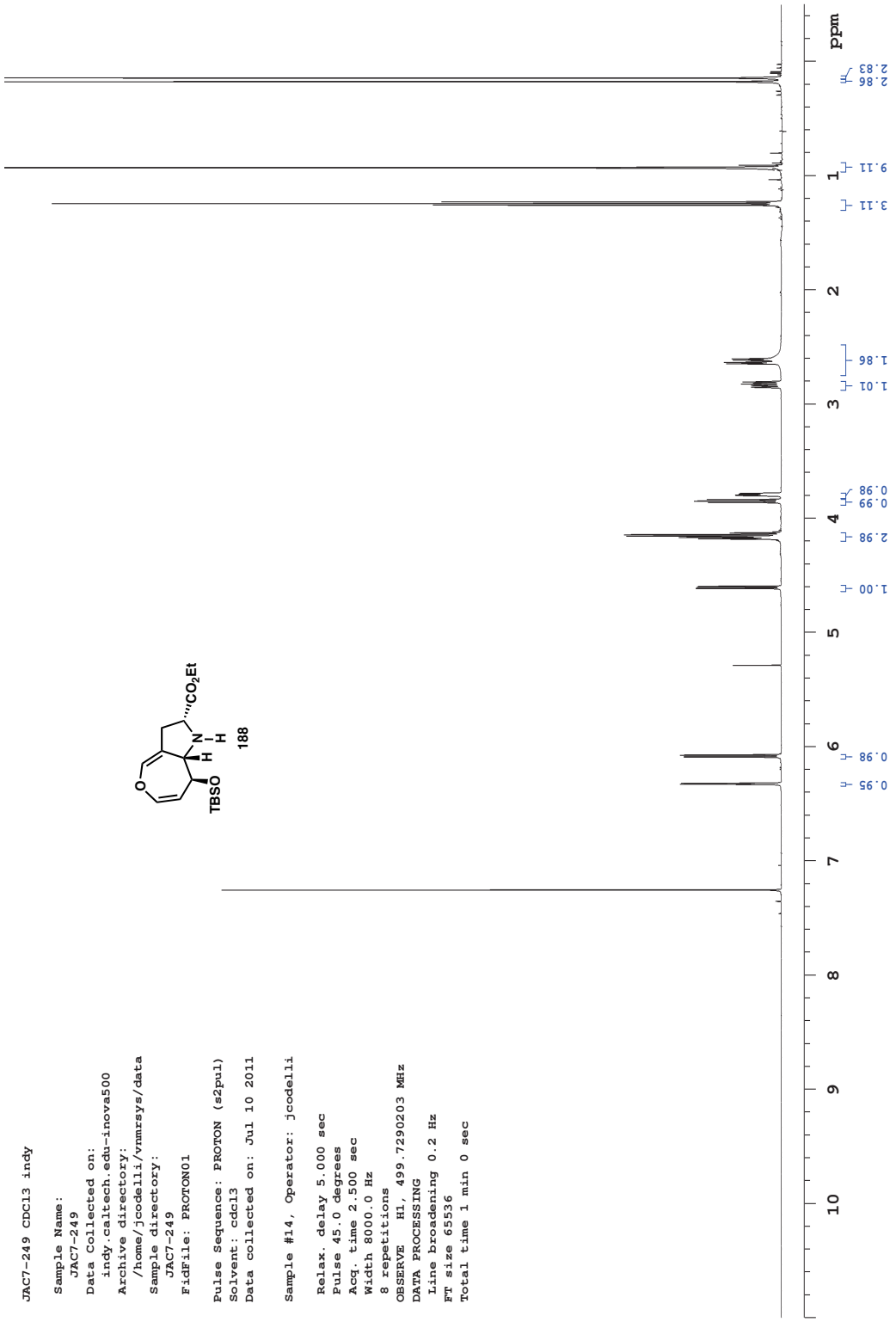

alp-iii-29b CD3CN 60degreesC siena
Sample Name:
alp-iii-29b
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
Sample directory:
FidFile: ALP-III-29B13C60degreesCsiena
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Aug 9 2011
Temp. 60.0 C / 333.1 K
Operator: apuchlop
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
512 repetitions
OBSERVE C13, 100.5288789 MHz
DECOUPLE H1, 399.7989164 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min
7a
CO2Et
N
H
Teoc
TBSO
O
204
220
200
180
160
140
120
100
80
60
40
20
0
ppm

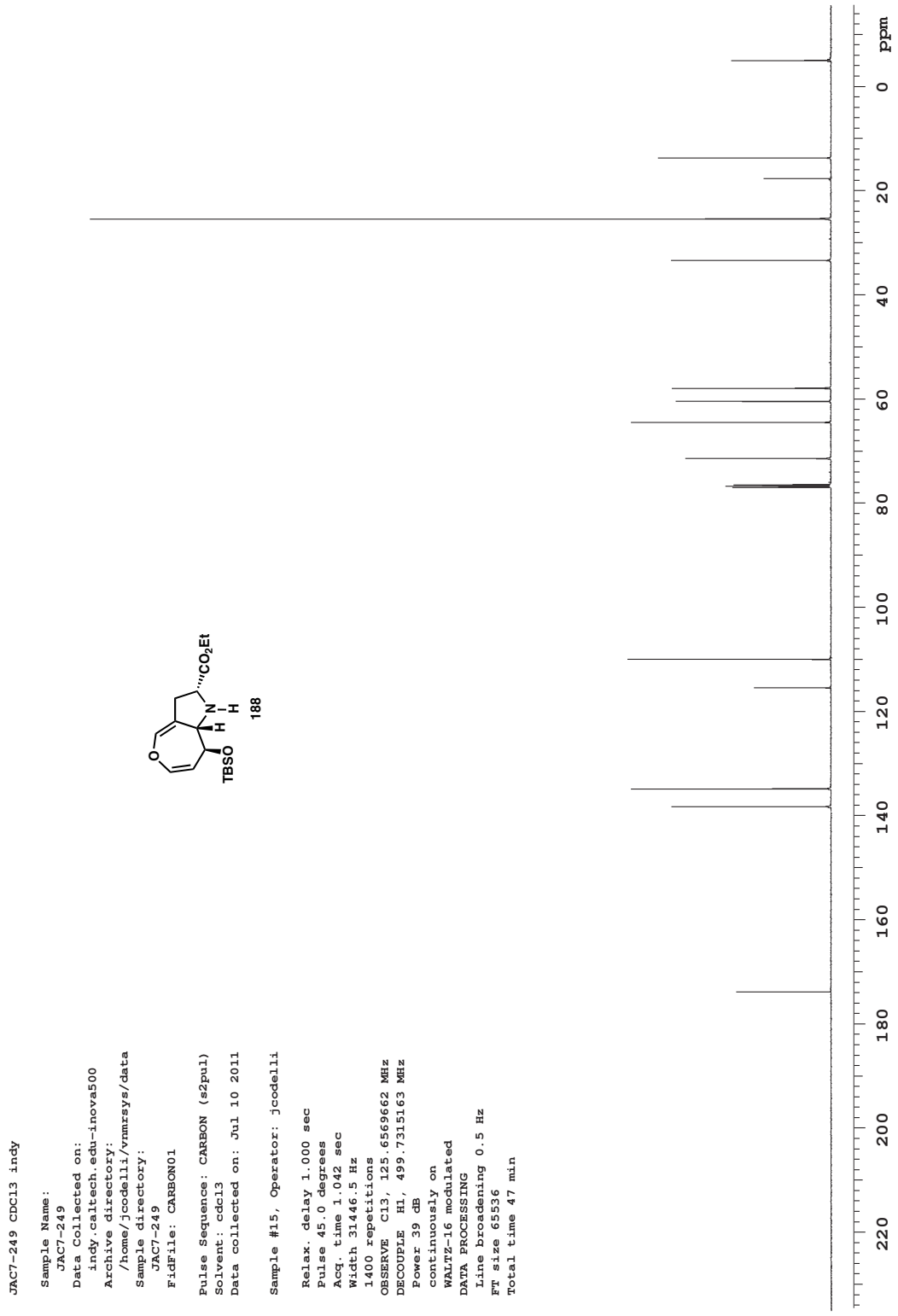

JAC7-251 50degreesC CDCl3 siena
Sample Name:
JAC7-251
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-251
FidFile: PROTON03
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 16 2011
Temp. 50.0 C / 323.1 K
Sample #8, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7947957 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 0 sec
TBSO
Teoc
191
ppm
3.36
9.19
3.26
9.72
2.34
1.09
0.94
2.04
1.04
2.08
1.02
1.03
1.00

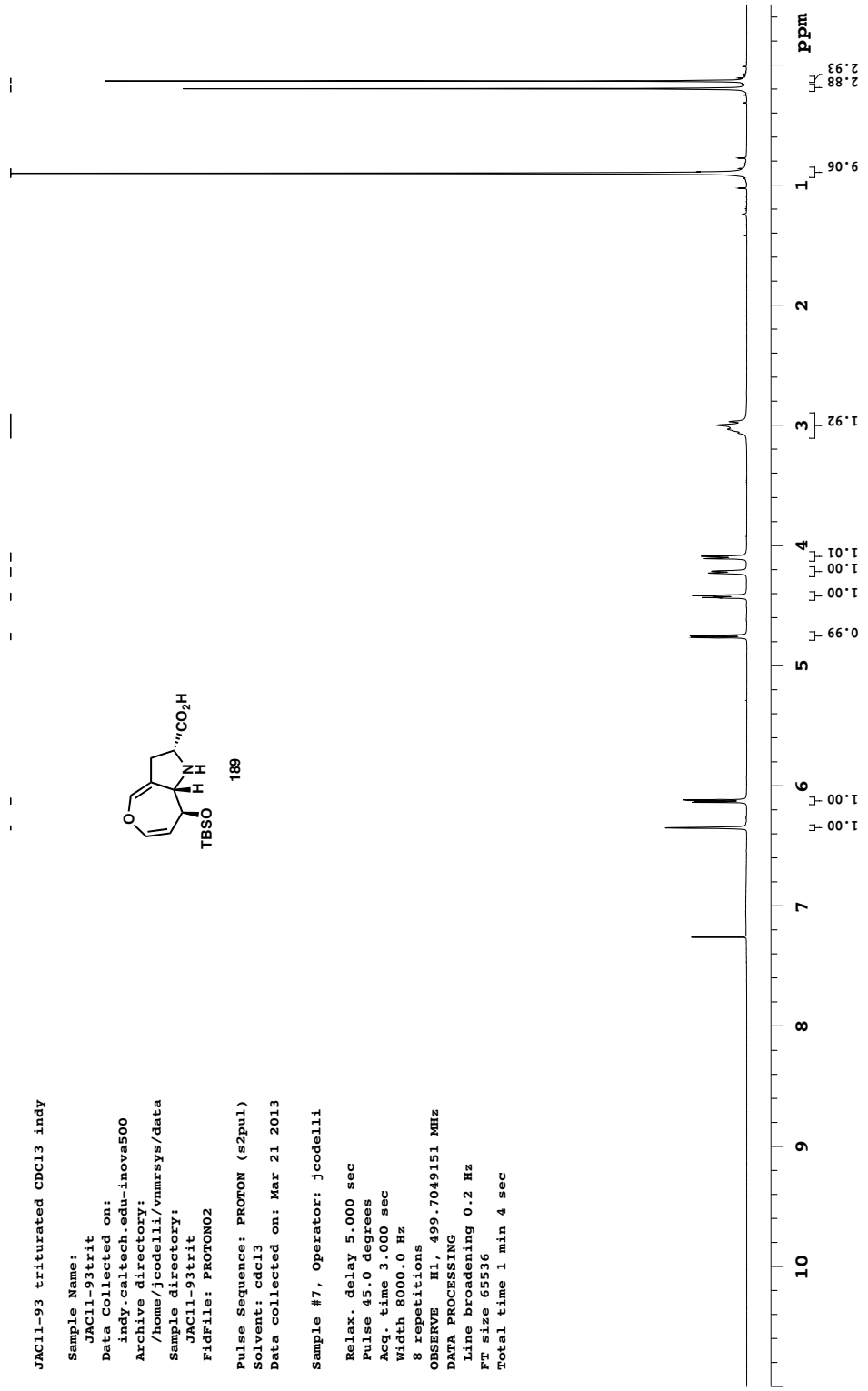

JAC7-251 50degreesC CDCl3 siena
Sample Name:
JAC7-237
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-237
FidFile: jac7-251-50degrees-13C
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 14 2011
Temp. 50.0 C / 323.1 K
Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
4000 repetitions
OBSERVE C13, 100.5284739 MHz
DECOUPLE H1, 399.7968015 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 32 min
TBSO
CO2H
N
H
Teoc
191
220
200
180
160
140
120
100
80
60
40
20
0
ppm

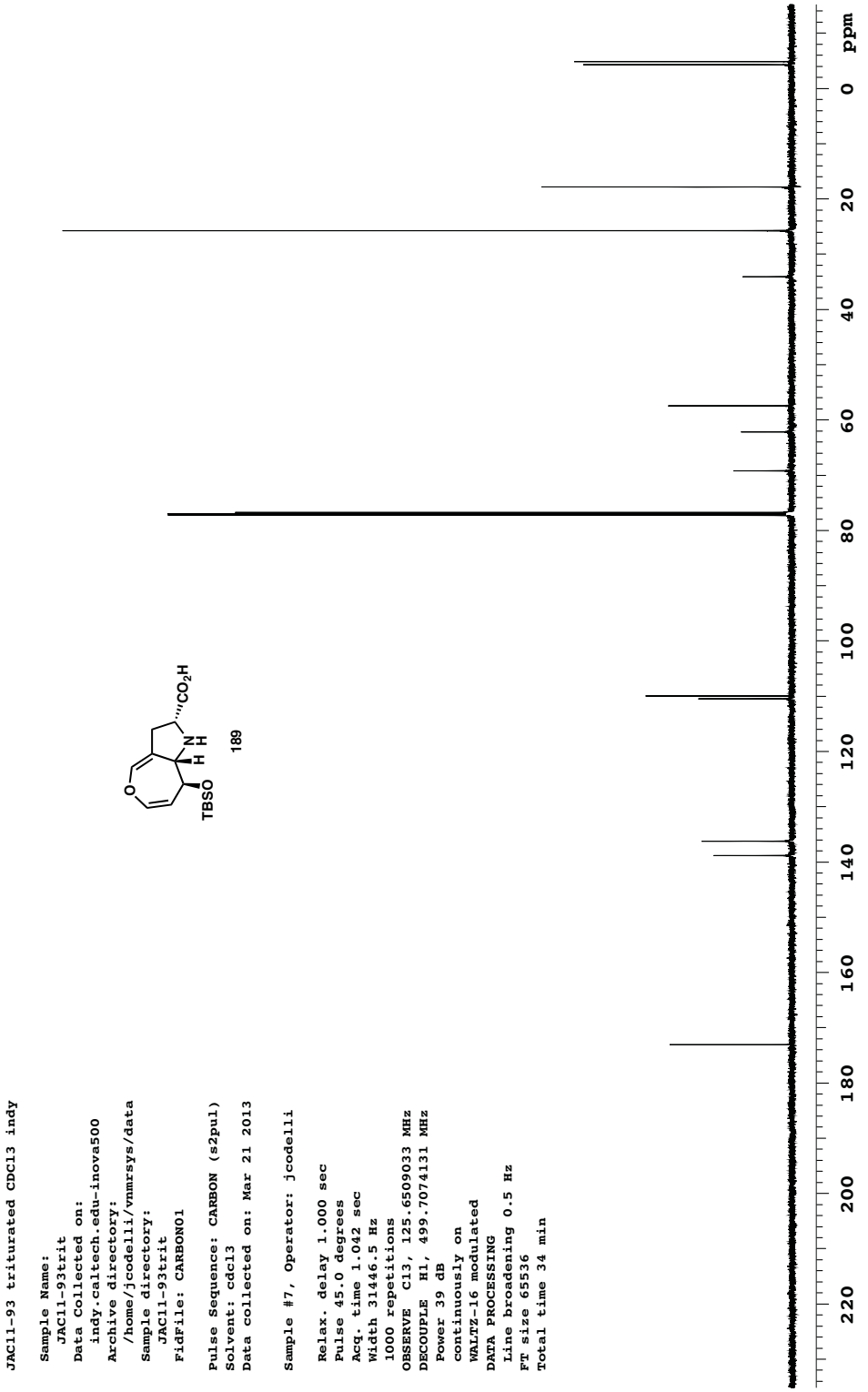

JAC7-133 CDCl3 indy
Sample Name:
JAC7-133
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-133
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 15 2011
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
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
CO2Et
Cl
N
H
H
TBSO
O
187
ppm
2.87
9.17
3.10
1.01
2.01
1.02
2.06
2.09
1.03
1.03
0.94
1.00

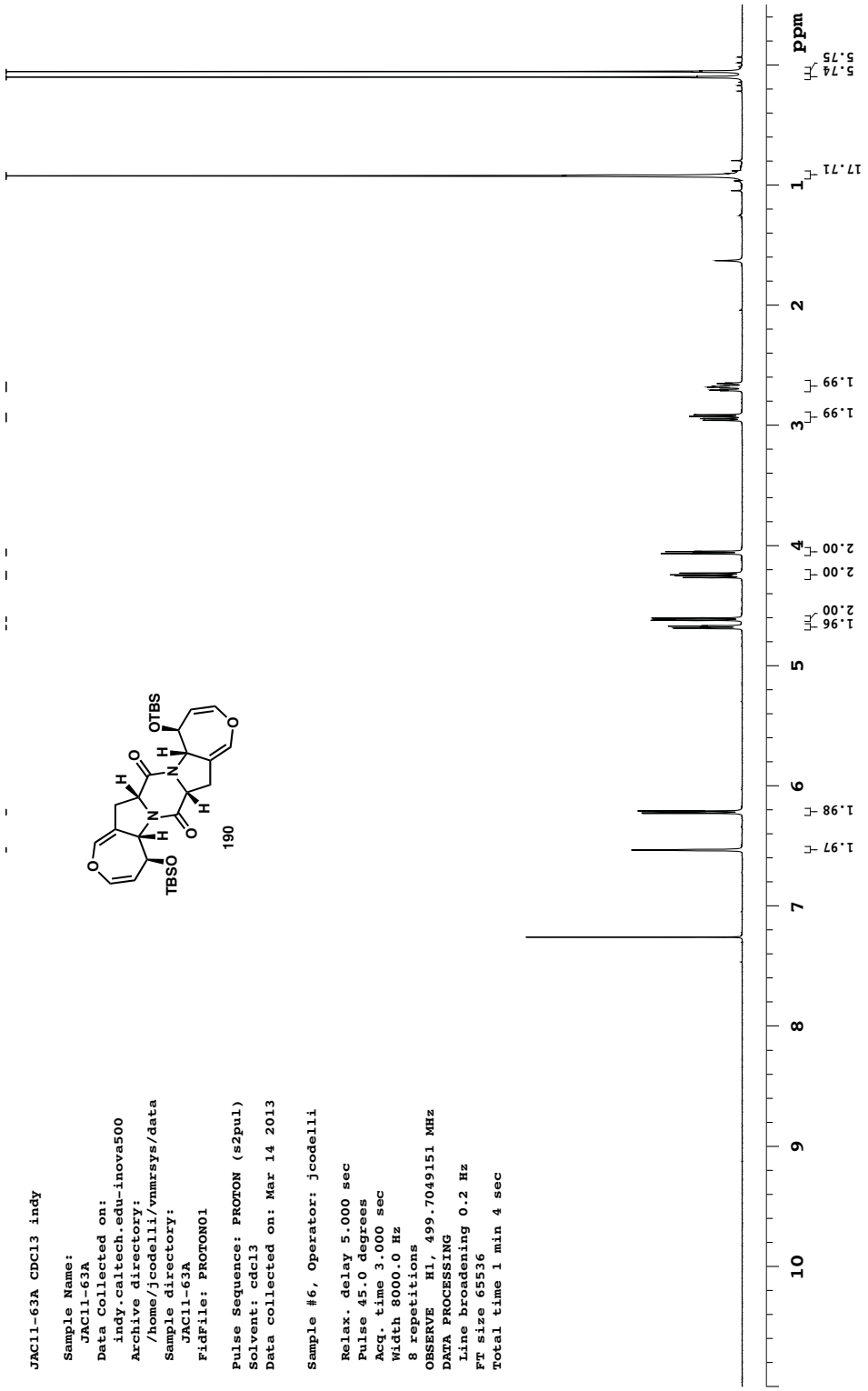

JAC7-133 CDCl3 indy
Sample Name:
JAC7-133
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-133
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 15 2011
Temp. 25.0 C / 298.1 K
Sample #8, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1400 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 47 min
Cl
CO2Et
N
H
H
O
TBSO
187
220
200
180
160
140
120
100
80
60
40
20
0
ppm

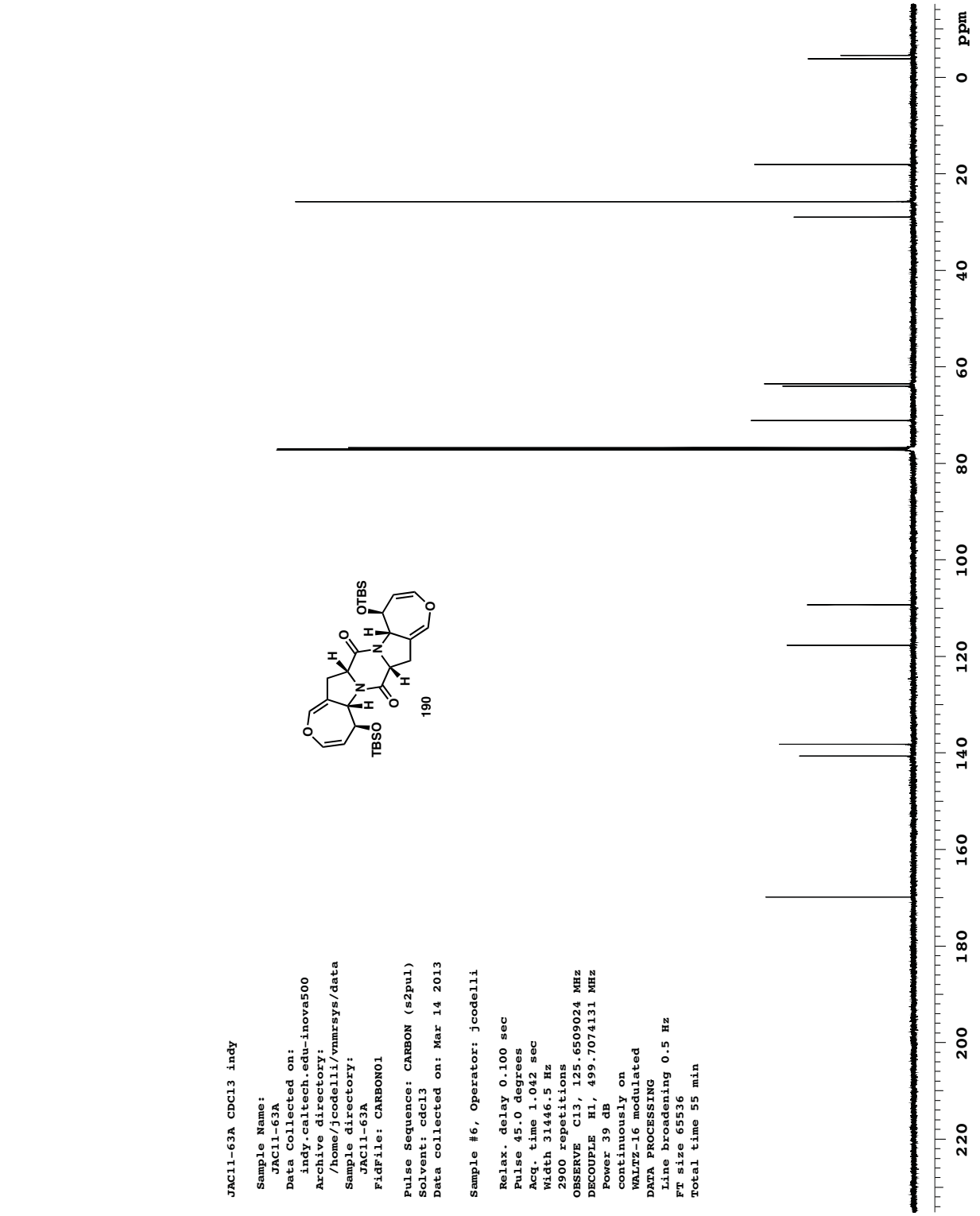

JAC7-249 CDCl3 indy
Sample Name:
JAC7-249
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-249
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 10 2011
Sample #14, Operator: jcodelli
Relax. delay 5.000 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
CO2Et
N
H
H
TBSO
O
188
ppm
2.86
2.83
9.11
3.11
1.86
1.01
0.98
0.99
2.98
1.00
0.98
0.95

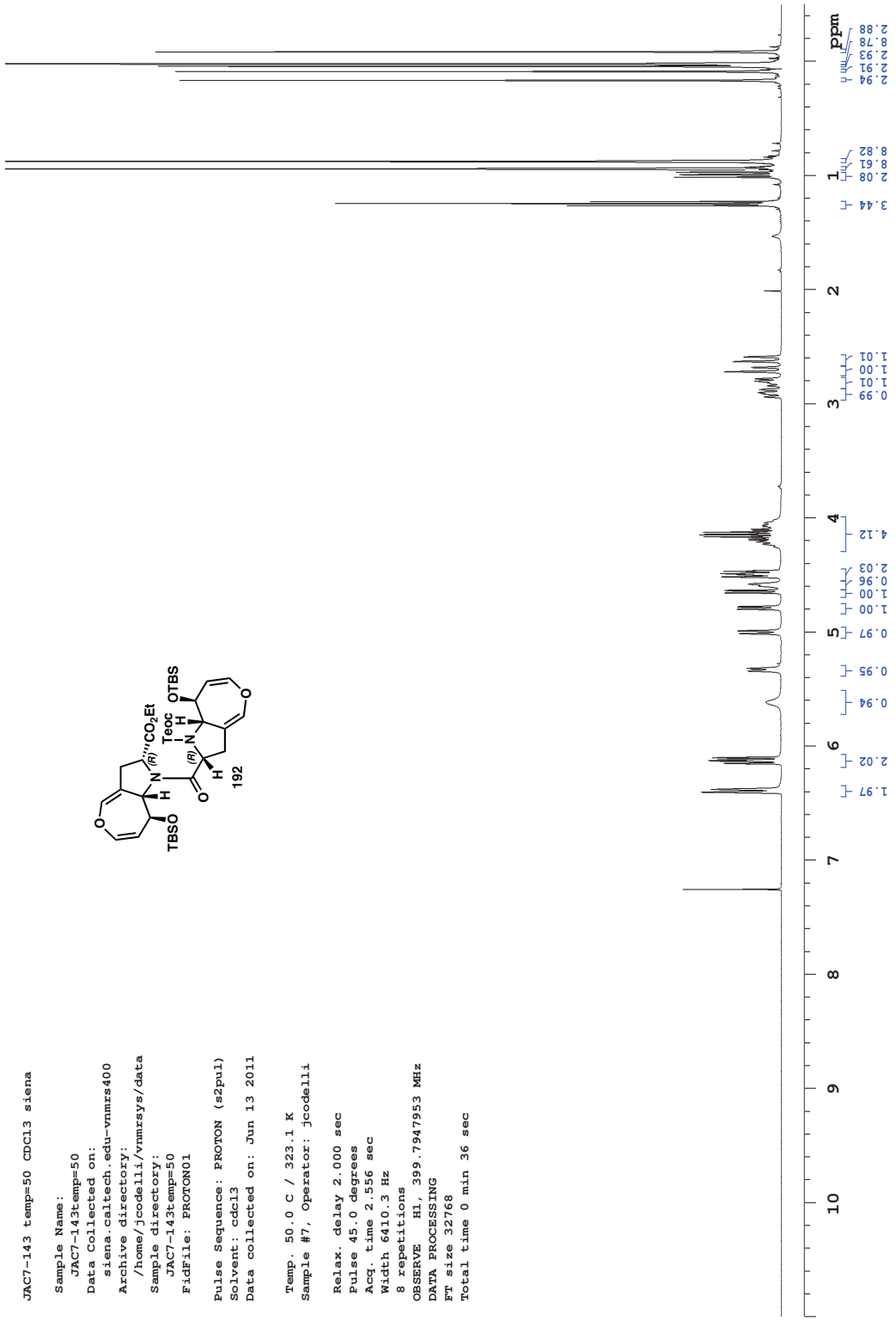

JAC7-249 CDCl3 indy
Sample Name:
JAC7-249
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-249
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 10 2011
Sample #15, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1400 repetitions
OBSERVE C13, 125.6569662 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 47 min
CO2Et
N
H
H
O
TBSO
188
220
200
180
160
140
120
100
80
60
40
20
0
ppm

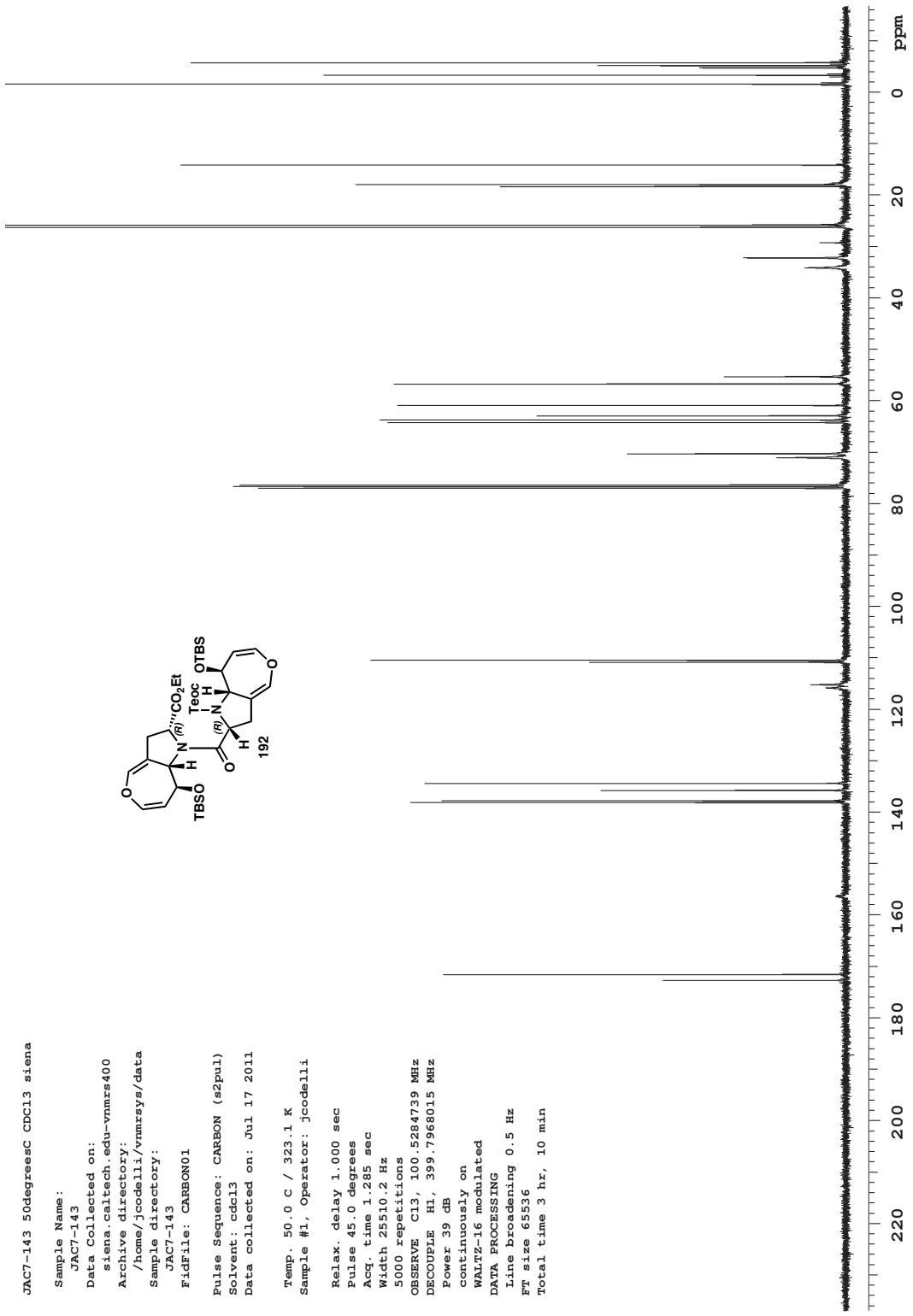

JAC11-93 triturated CDCl3 indy
Sample Name:
JAC11-93trit
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-93trit
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2013
Sample #7, Operator: jcodelli
Relax. delay 5.000 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 4 sec
CO2H
N
H H
TBSO
O
189
ppm
2.93
2.88
9.06
1.92
1.01
1.00
1.00
0.99
1.00
1.00

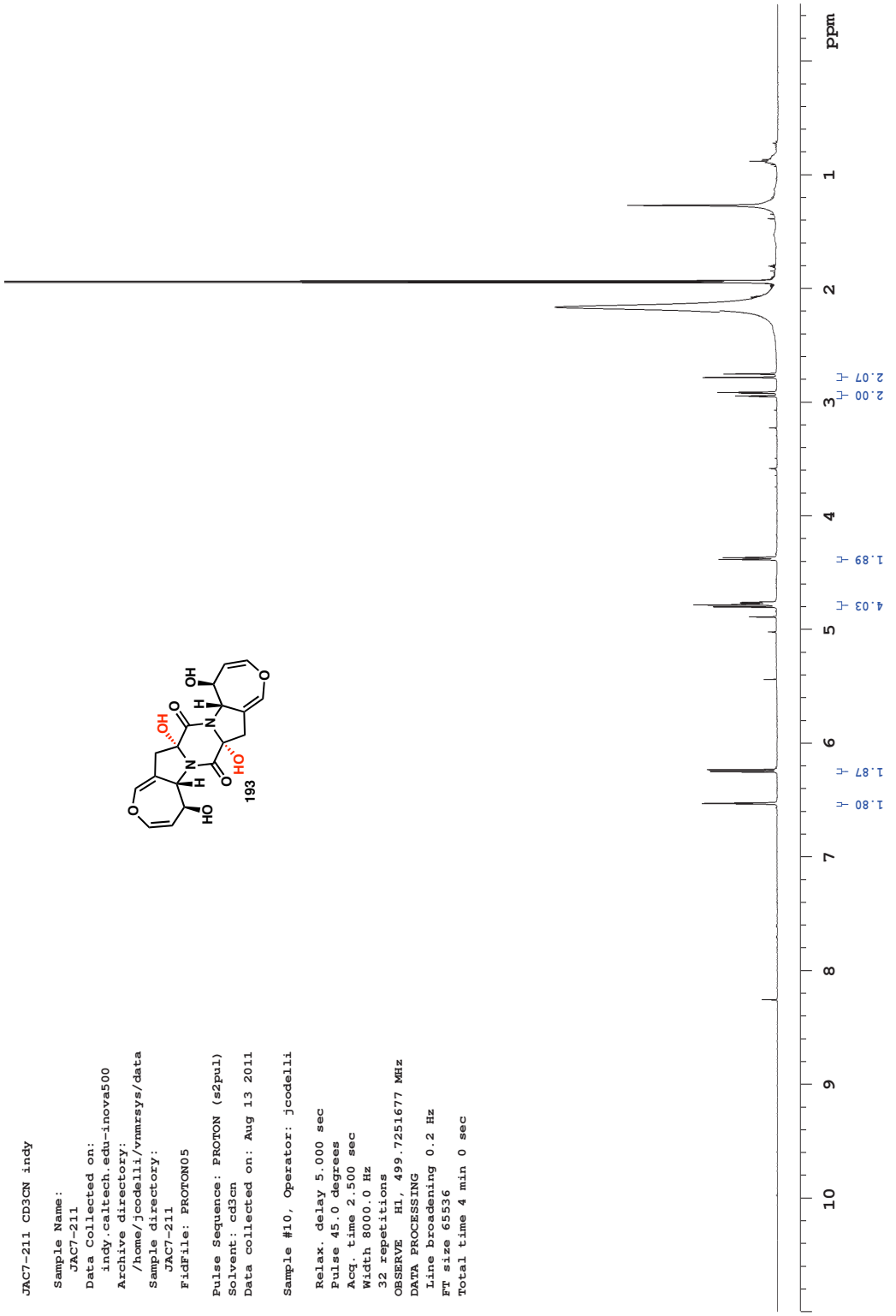

JAC11-93 triturated CDCl3 indy
Sample Name:
JAC11-93trit
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-93trit
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2013
Sample #7, Operator: jcodelli
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 0.5 Hz
FT size 65536
Total time 34 min
CO2H
N
H
H
O
TBSO
189
220
200
180
160
140
120
100
80
60
40
20
0
ppm

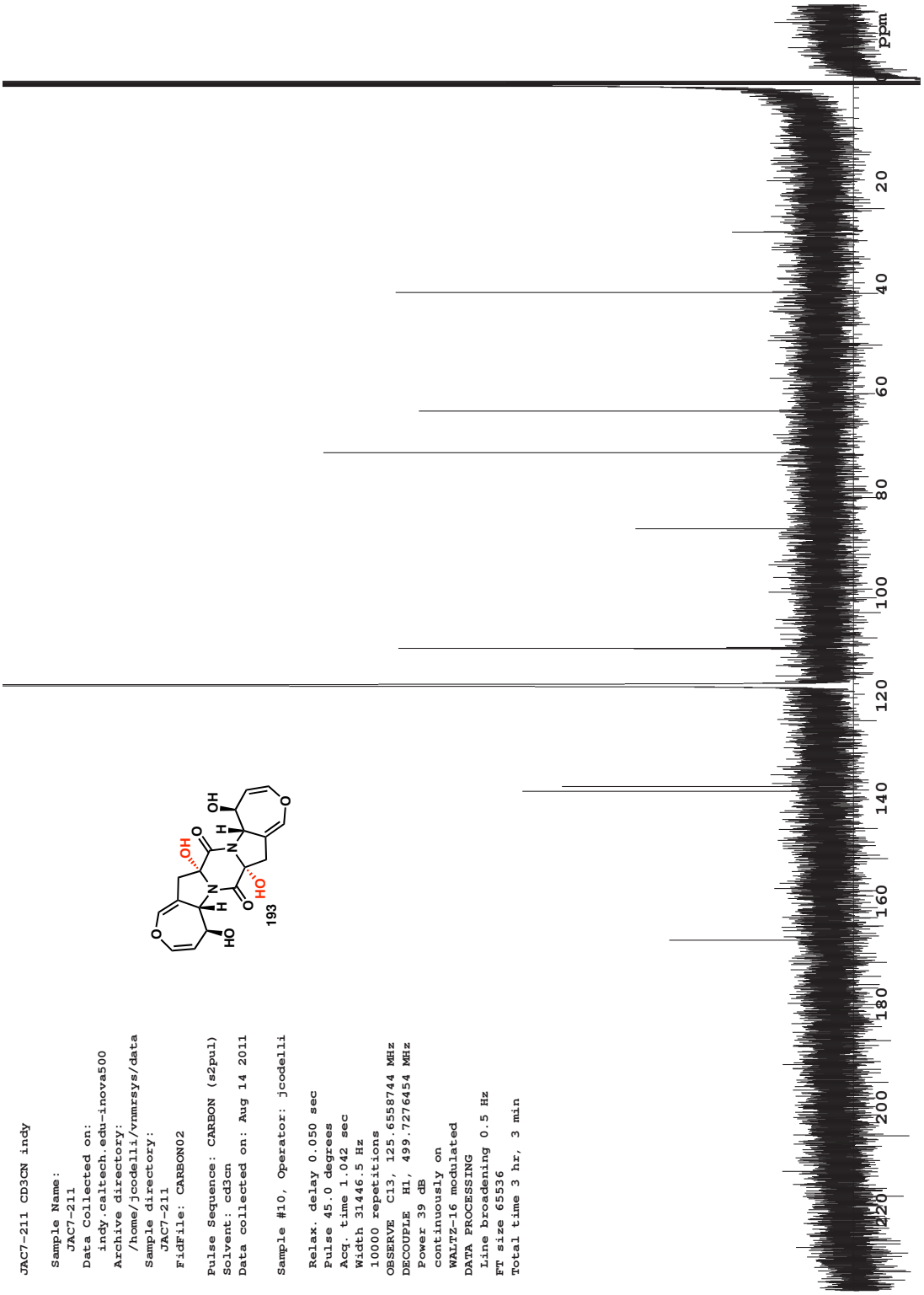

JAC11-63A CDCl3 indy
Sample Name:
JAC11-63A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-63A
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 14 2013
Sample #6, Operator: jcodelli
Relax. delay 5.000 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 4 sec
OTBS
TBSO
190
ppm
5.74
5.75
17.71
1.99
1.99
2.00
2.00
1.96
2.00
1.98
1.97

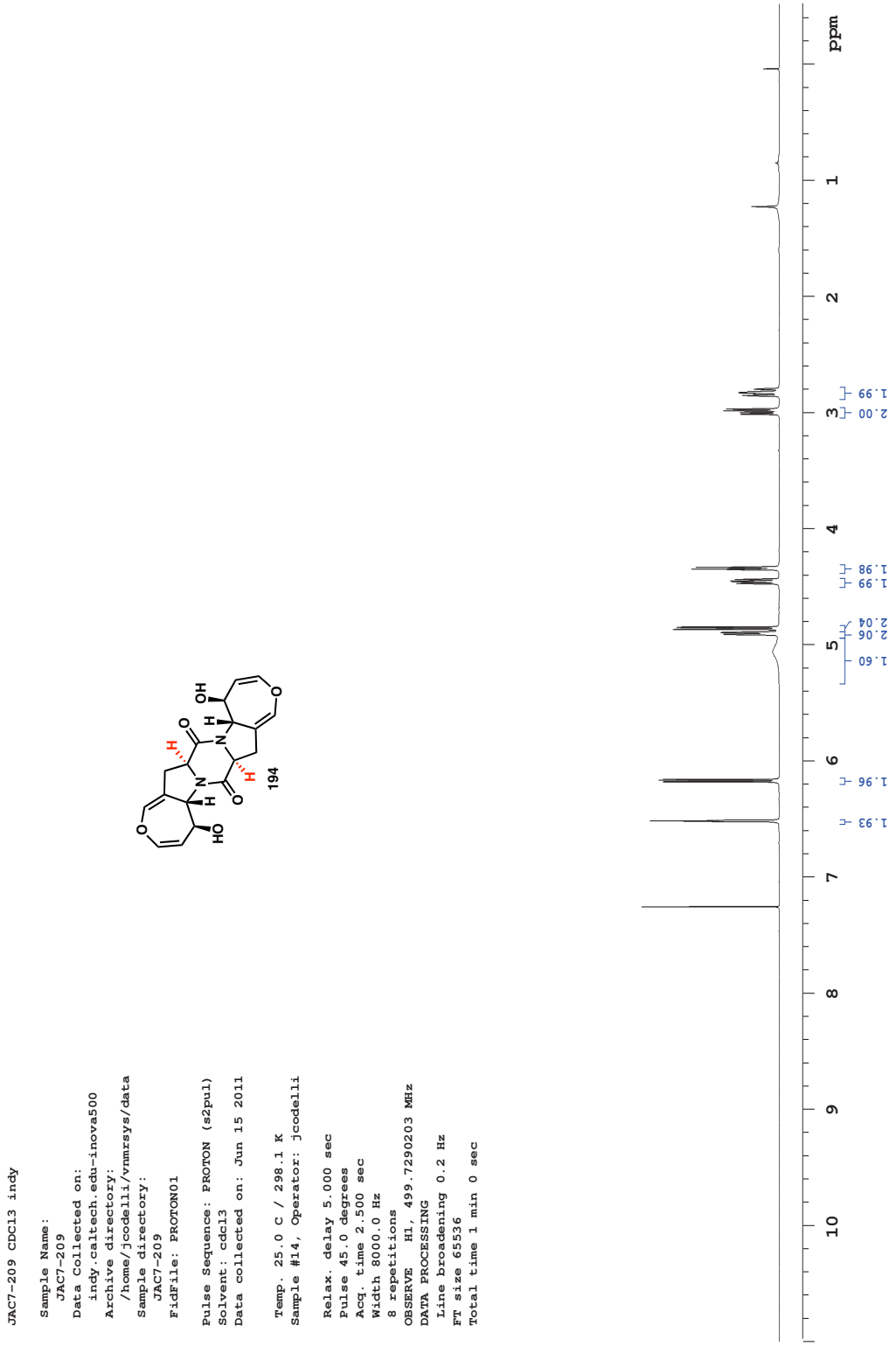

JAC11-63A CDCl3 indy
Sample Name:
JAC11-63A
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-63A
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 14 2013
Sample #6, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2900 repetitions
OBSERVE C13, 125.6509024 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 55 min
OTBS
TBSO
190
220
200
180
160
140
120
100
80
60
40
20
0
ppm

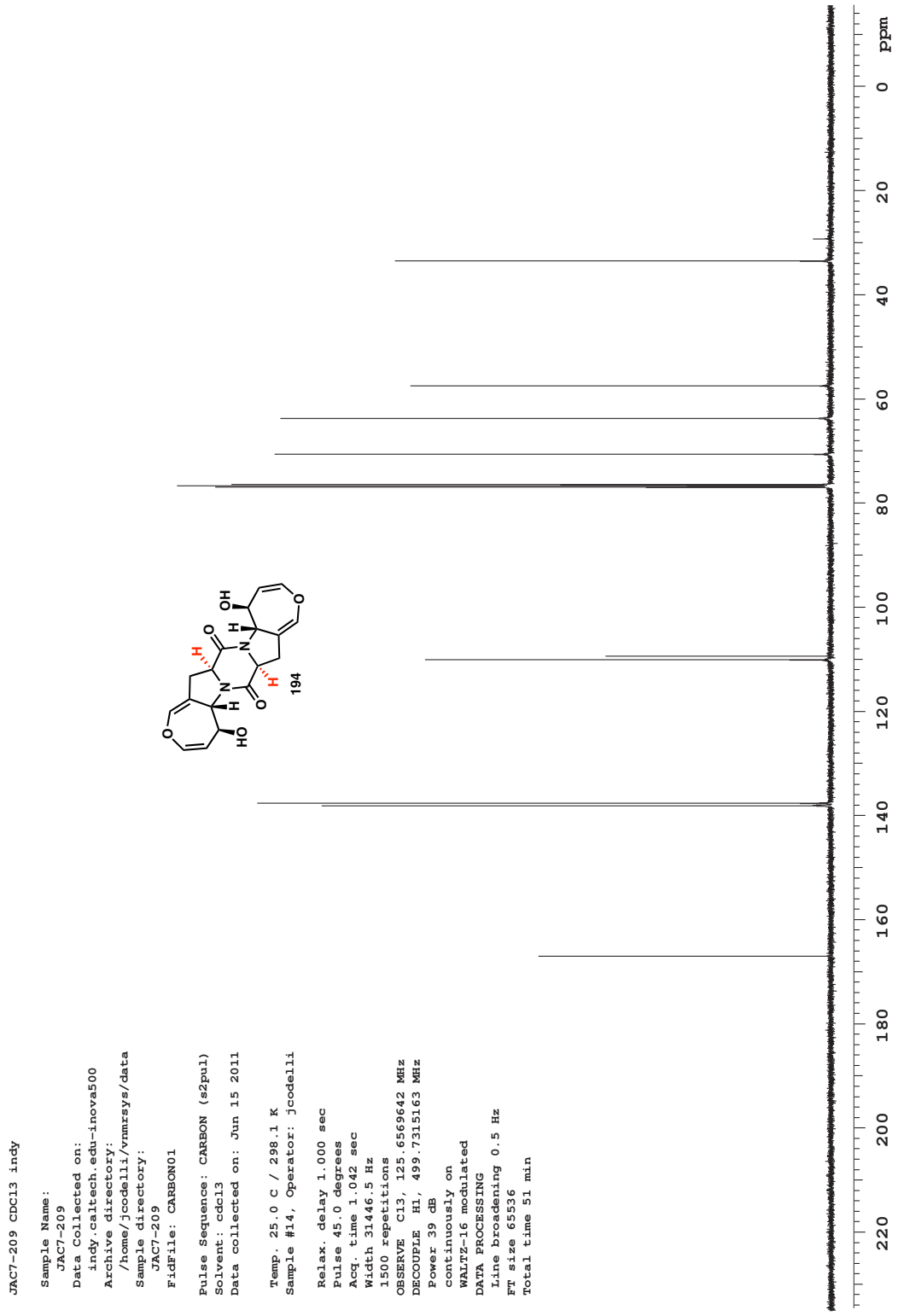

JAC7-143 temp=50 CDCl3 siena
Sample Name:
JAC7-143temp=50
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-143temp=50
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 13 2011
Temp. 50.0 C / 323.1 K
Sample #7, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7947953 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 36 sec
TBSO
OTBS
Teoc
CO2Et
192
ppm
1.97
2.02
0.94
0.95
0.97
1.00
1.00
0.96
2.03
4.12
0.99
1.01
1.00
1.01
3.44
2.08
8.61
8.82
2.94
2.91
2.93
8.78
2.88

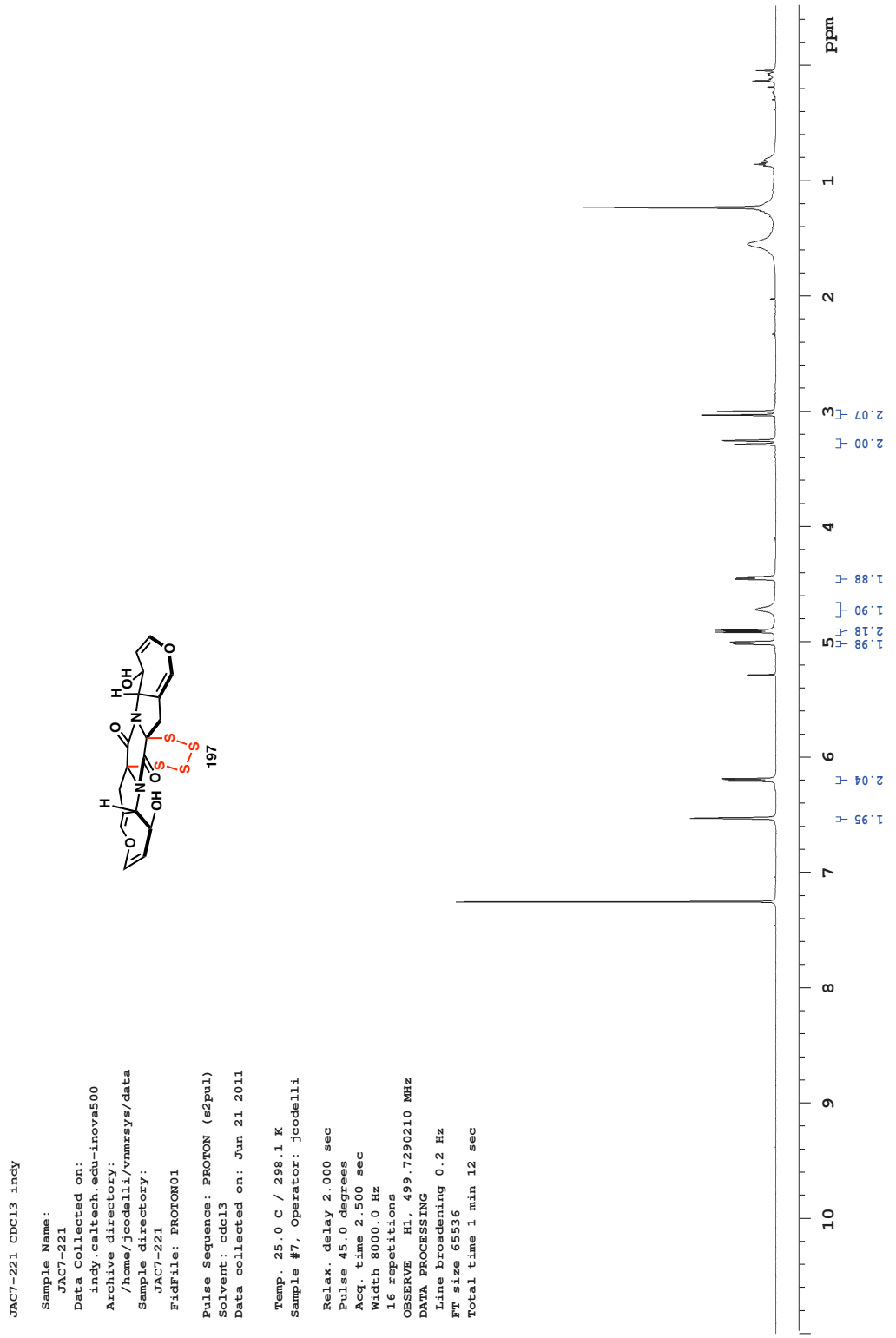

JAC7-143 50degreesC CDCl3 siena
Sample Name:
JAC7-143
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-143
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 17 2011
Temp. 50.0 C / 323.1 K
Sample #1, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
5000 repetitions
OBSERVE C13, 100.5284739 MHz
DECOUPLE H1, 399.7968015 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 10 min
TBSO
OTBS
Teoc
CO2Et
192
ppm
220
200
180
160
140
120
100
80
60
40
20
0

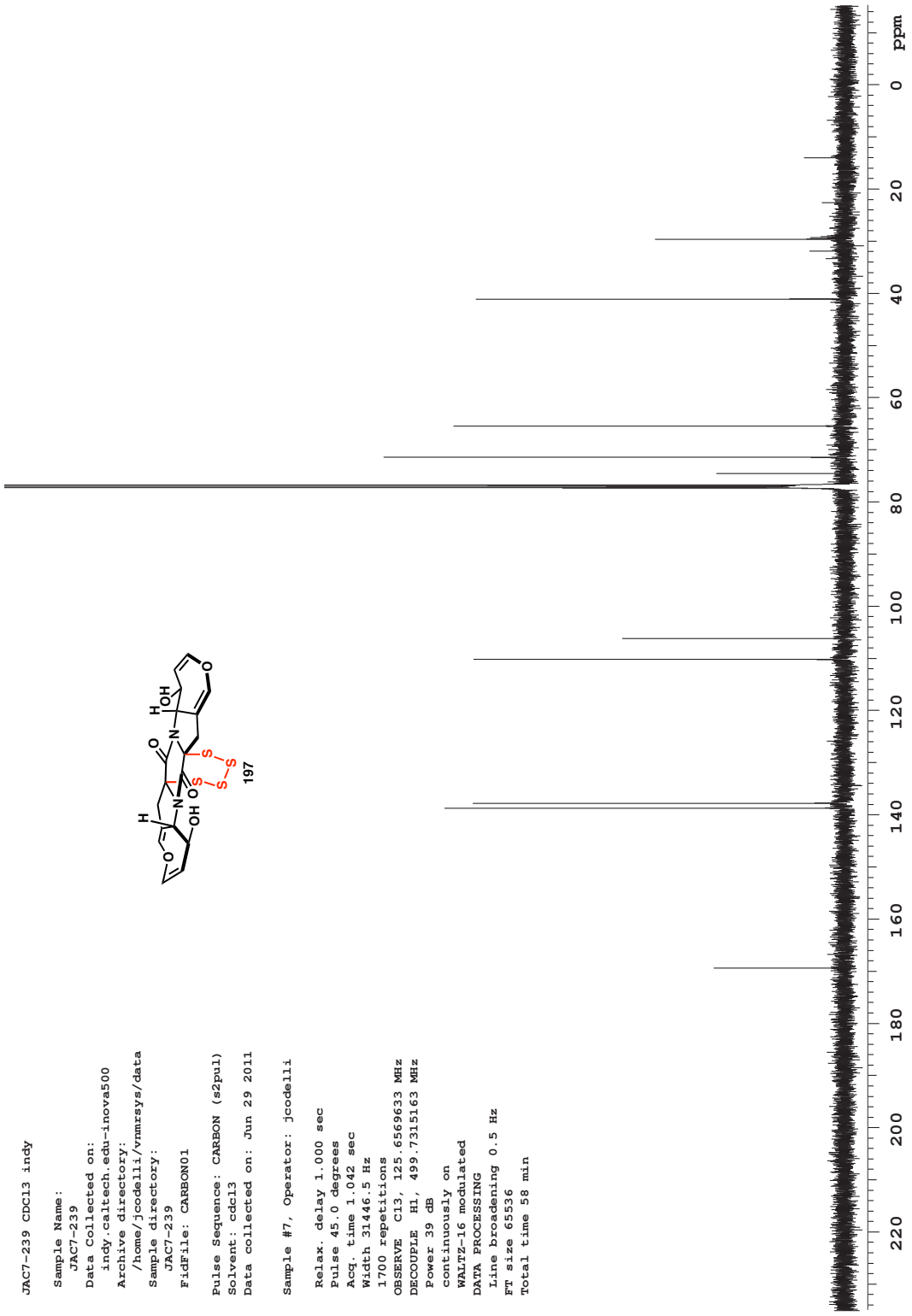

JAC7-211 CD3CN indy
Sample Name:
JAC7-211
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-211
FidFile: PROTON05
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Aug 13 2011
Sample #10, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7251677 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 0 sec
OH
O
N
H
HO
193
ppm
1
2
3
4
5
6
7
8
9
10
2.07
2.00
1.89
4.03
1.87
1.80

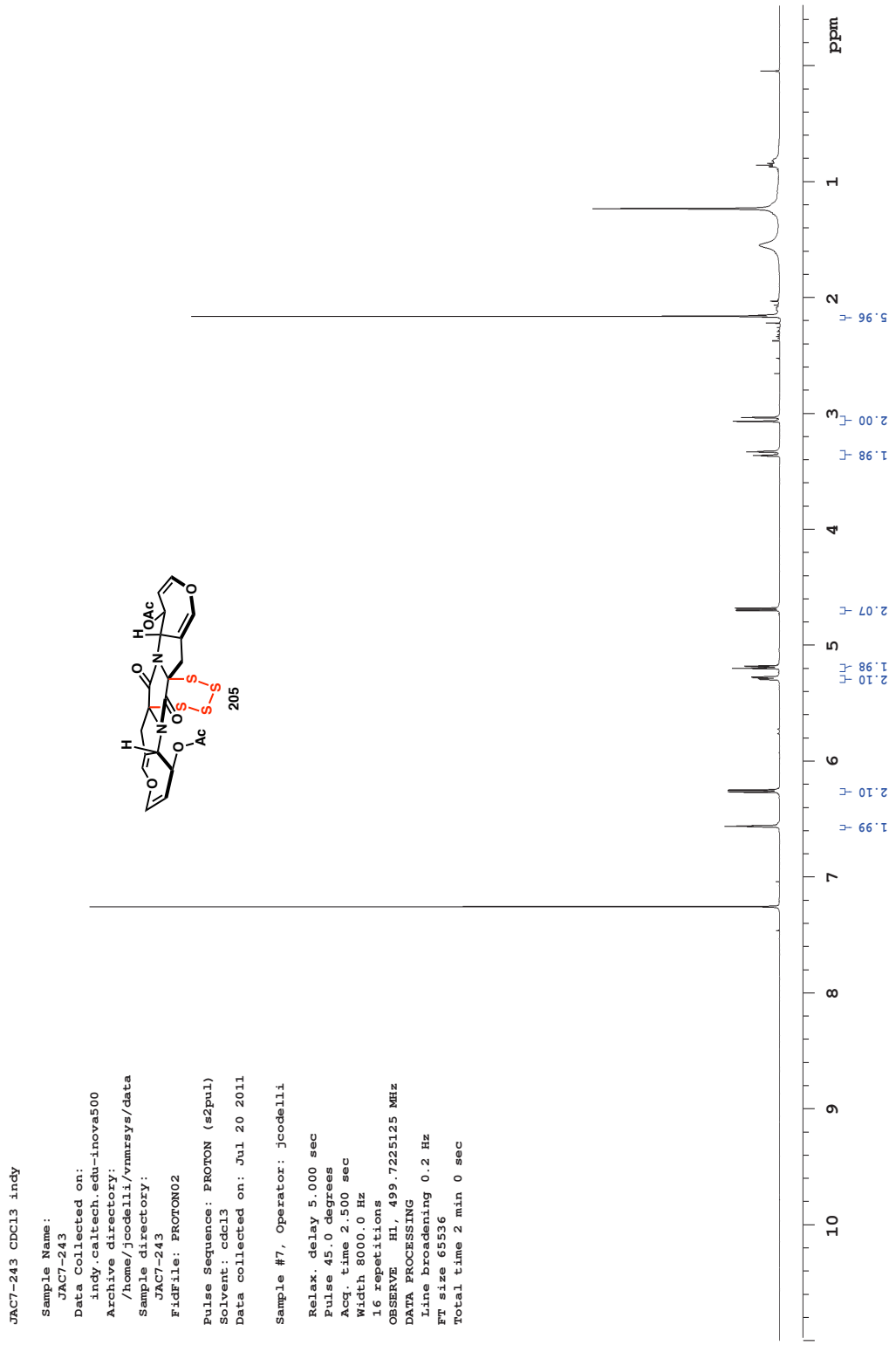

JAC7-211 CD3CN indy
Sample Name:
JAC7-211
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-211
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Aug 14 2011
Sample #10, Operator: jcodelli
Relax. delay 0.050 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
10000 repetitions
OBSERVE C13, 125.6558744 MHz
DECOUPLE H1, 499.7276454 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 3 min
OH
H
N
O
OH
O
N
H
HO
O
O
193
ppm
220
200
180
160
140
120
100
80
60
40
20

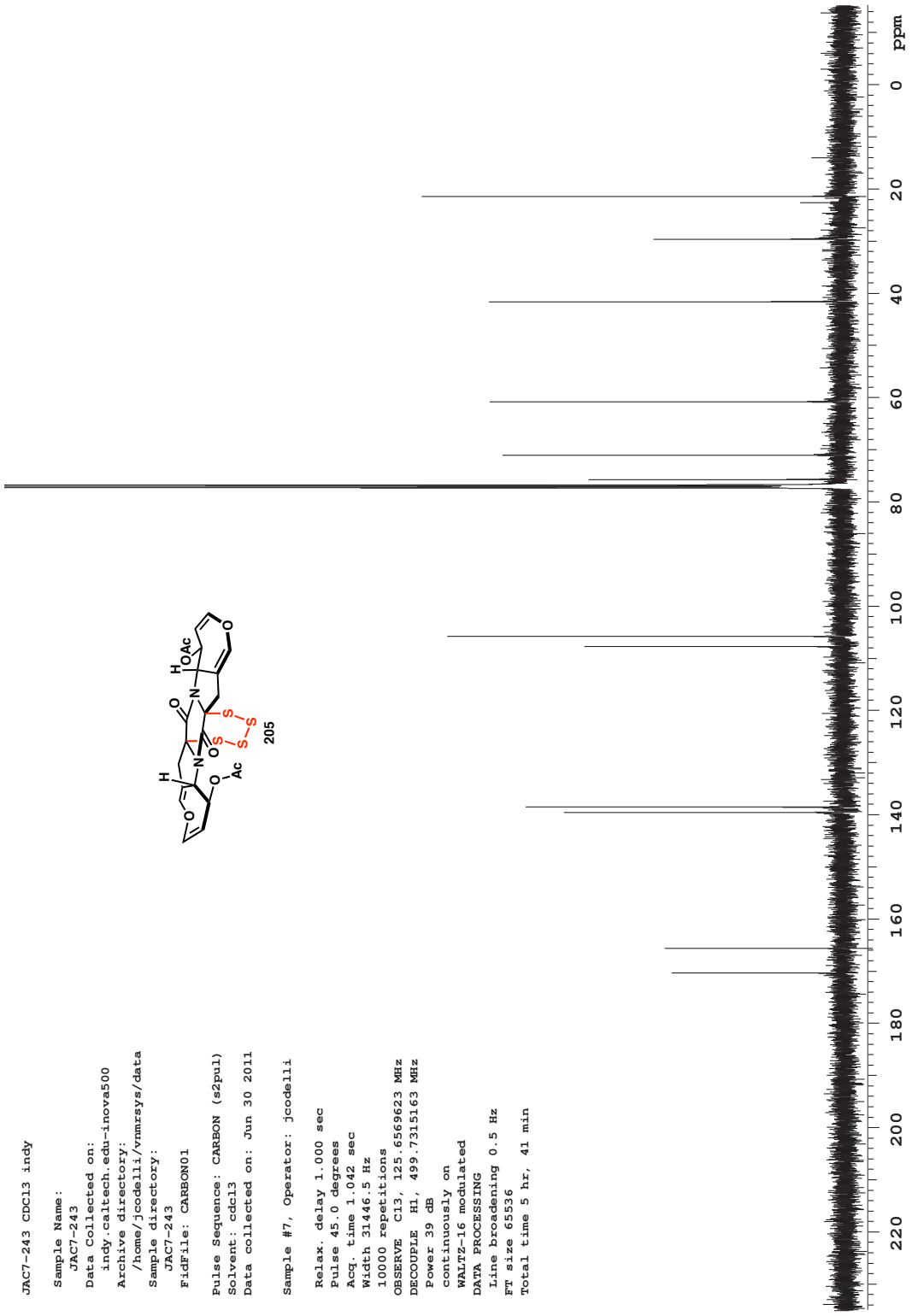

JAC7-209 CDCl3 indy
Sample Name:
JAC7-209
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-209
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 15 2011
Temp. 25.0 C / 298.1 K
Sample #14, Operator: jcodelli
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
194
ppm
1.93
1.96
1.60
2.04
2.06
1.98
1.99
2.00
1.99

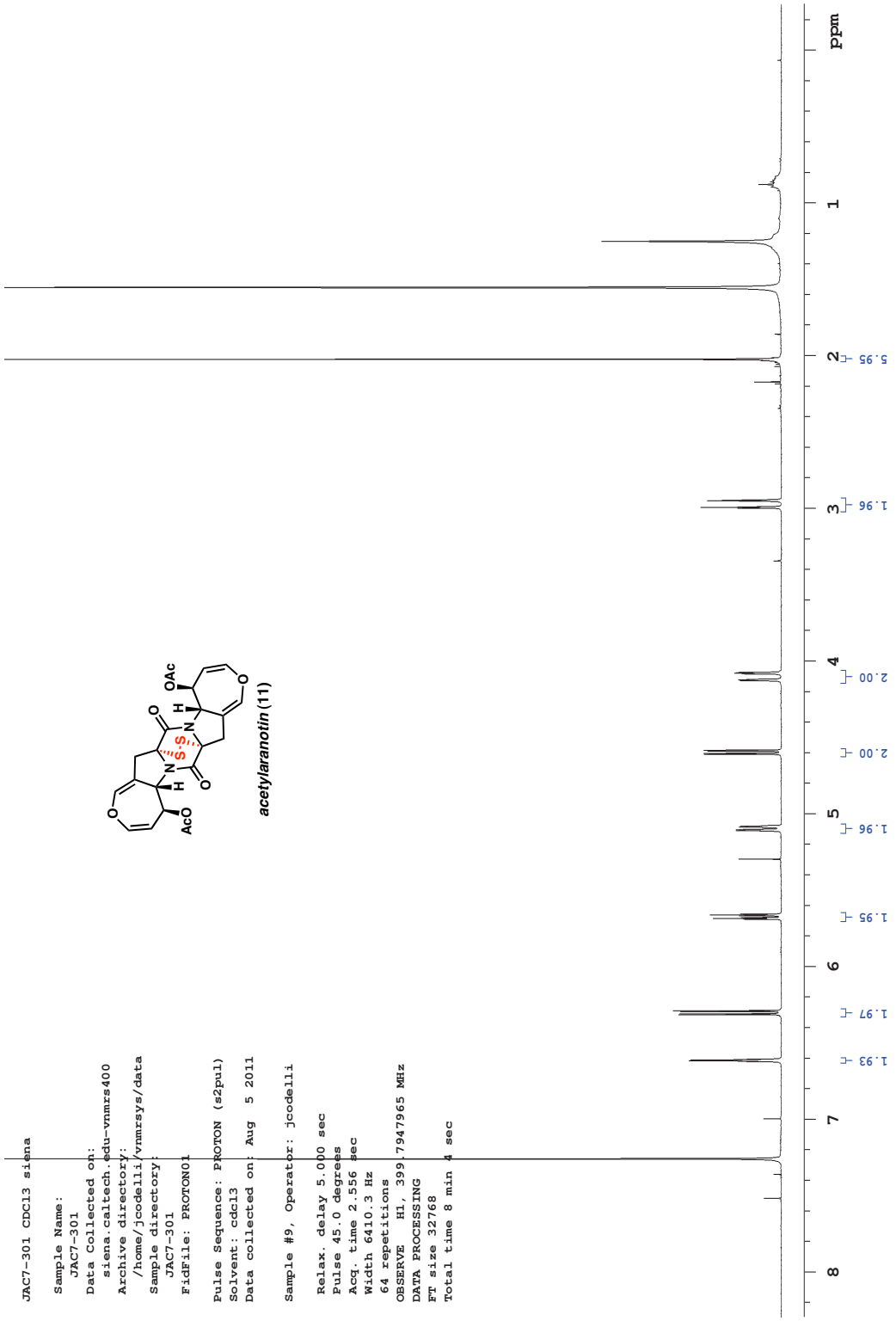

JAC7-209 CDCl3 indy
Sample Name:
JAC7-209
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-209
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 15 2011
Temp. 25.0 C / 298.1 K
Sample #14, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 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 51 min
194
220
200
180
160
140
120
100
80
60
40
20
0
ppm

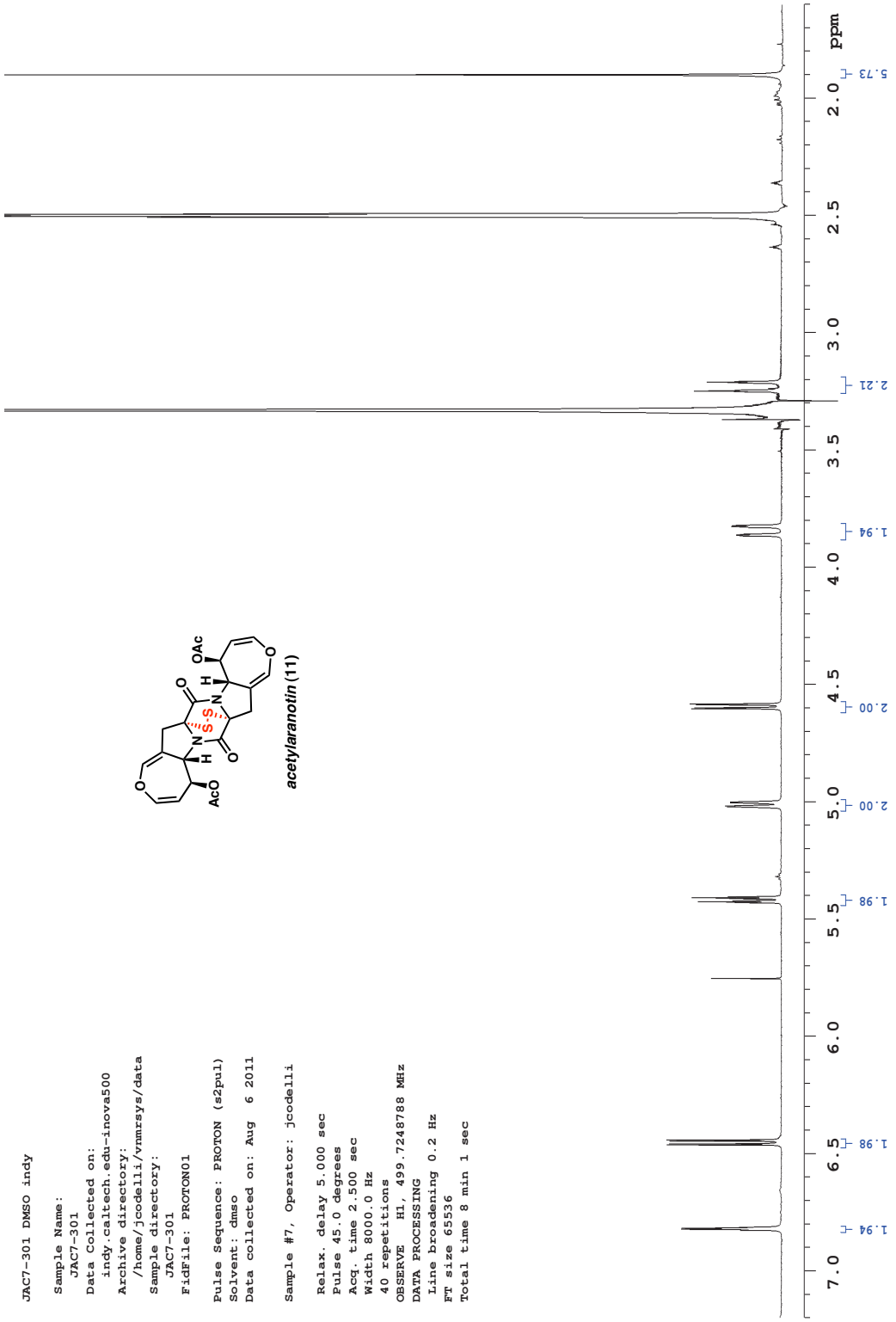

JAC7-221 CDCl3 indy
Sample Name:
JAC7-221
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-221
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 21 2011
Temp. 25.0 C / 298.1 K
Sample #7, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290210 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
197
1.95
2.04
1.98
2.18
1.90
1.88
2.00
2.07
ppm

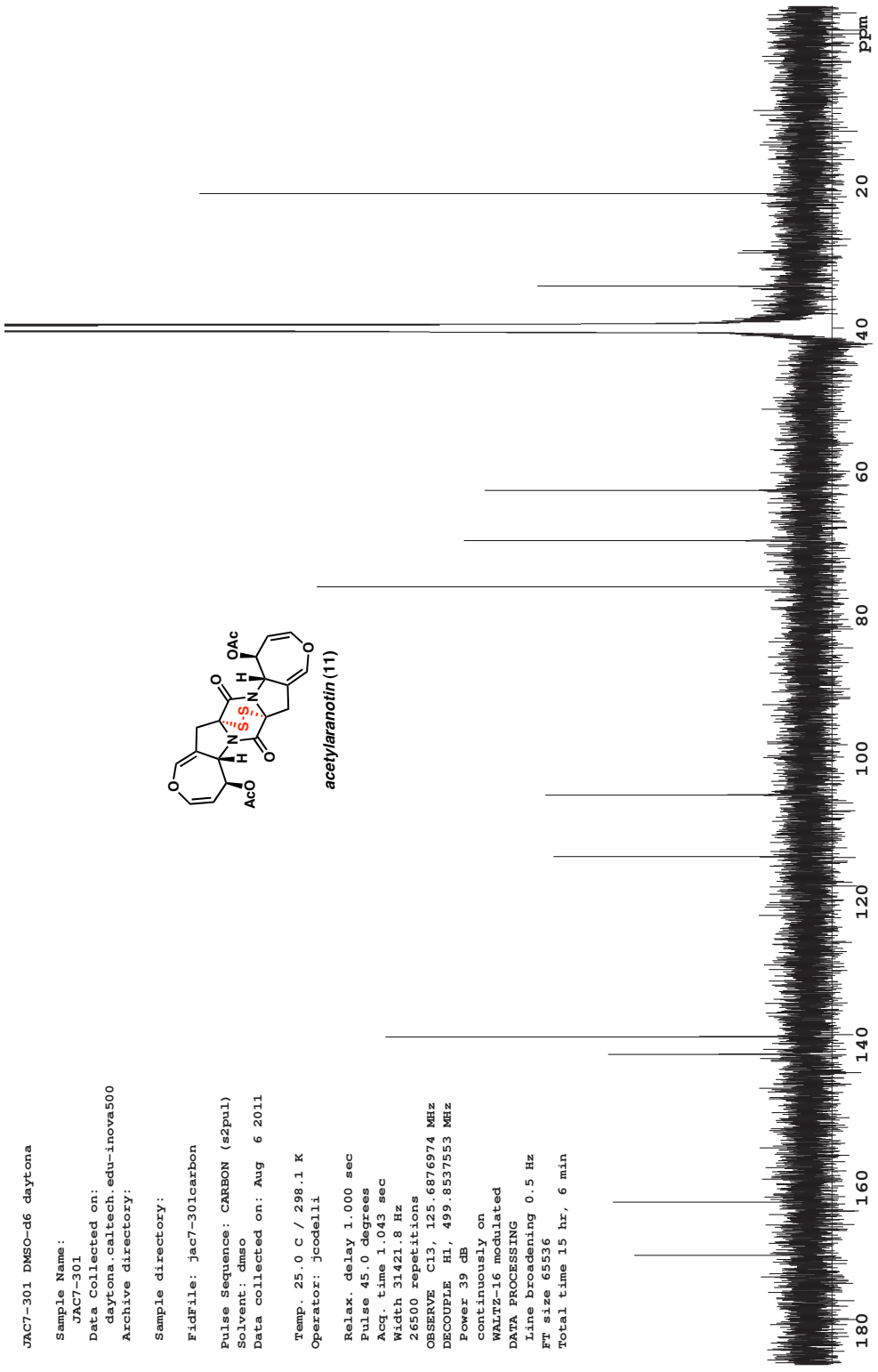

JAC7-239 CDCl3 indy
Sample Name:
JAC7-239
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-239
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 29 2011
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6569633 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 58 min
197
220
200
180
160
140
120
100
80
60
40
20
0
ppm


JAC7-243 CDCl3 indy
Sample Name:
JAC7-243
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-243
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 20 2011
Sample #7, Operator: jcodelli
Relax. delay 5.000 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 2 min 0 sec
205
5.96
2.00
1.98
2.07
2.10
1.98
2.10
1.99
ppm


JAC7-243 CDCl3 indy
Sample Name:
JAC7-243
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-243
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 30 2011
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
10000 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 5 hr, 41 min
205
220
200
180
160
140
120
100
80
60
40
20
0
ppm


JAC7-301 CDCl3 siena
Sample Name:
JAC7-301
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-301
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2011
Sample #9, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.7947965 MHz
DATA PROCESSING
FT size 32768
Total time 8 min 4 sec
OAc
AcO
acetylaranotin (11)
ppm
1
2
3
4
5
6
7
8
5.95
1.96
2.00
2.00
1.96
1.95
1.97
1.93


JAC7-301 DMSO indy
Sample Name:
JAC7-301
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC7-301
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Aug 6 2011
Sample #7, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
40 repetitions
OBSERVE H1, 499.7248788 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 8 min 1 sec
acetylaranotin (11)
OAc
AcO
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.94
1.98
2.00
2.00
1.98
1.94
2.21
5.73


JAC7-301 DMSO-d6 daytona
Sample Name:
JAC7-301
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: jac7-301carbon
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Aug 6 2011
Temp. 25.0 C / 298.1 K
Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31421.8 Hz
26500 repetitions
OBSERVE C13, 125.6876974 MHz
DECOUPLE H1, 499.8537553 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 15 hr, 6 min
OAc
AcO
acetylaranotin (11)
ppm
180
160
140
120
100
80
60
40
20

Appendix 2

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

[†] The work disclosed in this appendix for the X-ray crystallographic analysis of **158**, **193**, **194**, and **197** was completed entirely by Larry Henling and Dr. Michael Day in the Caltech X-ray crystallography lab.

A2.1 CRYSTAL STRUCTURE ANALYSIS OF ALKYNYL LACTONE 158

Figure A2.1. *Alkynyl lactone* ***158****. 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 771581.*

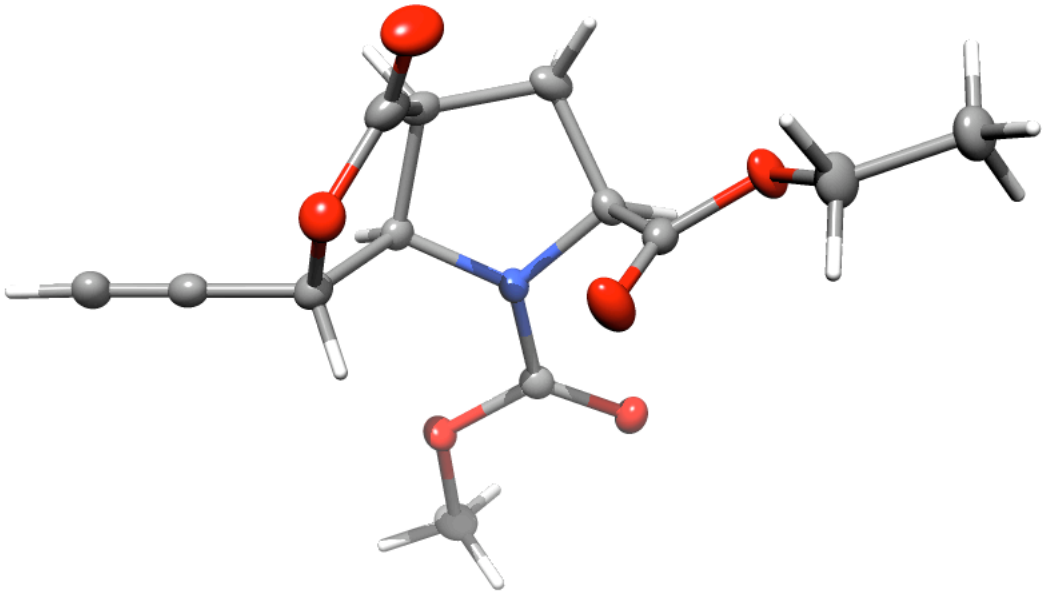


Table A2.1. *Crystal data and structure refinement for alkynyl lactone* ***158*** *(CCDC 771581).*

Empirical formula	$C_{13}H_{15}NO_6$
Formula weight	281.26
Crystallization Solvent	Toluene/pentane
Crystal Habit	Colorless
Crystal size	0.21 x 0.17 x 0.10 mm^3
Crystal color	Fragment

Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 9198 reflections used in lattice determination	2.39 to 31.03°	
Unit cell dimensions	a = 6.9163(3) Å b = 20.5882(8) Å c = 9.3847(3) Å	α= 90° β= 95.402(2)° γ = 90°
Volume	1330.39(9) $Å^3$	
Z	4	
Crystal system	Monoclinic	
Space group	P $2_1/n$	
Density (calculated)	1.404 Mg/m^3	
F(000)	592	
Data collection program	Bruker APEX2 v2009.7-0	
θ range for data collection	1.98 to 31.11°	
Completeness to θ = 31.11°	99.8 %	
Index ranges	$-9 \le h \le 10$, $-29 \le k \le 29$, $-13 \le l \le 13$	
Data collection scan type	ω scans; 10 settings	
Data reduction program	Bruker SAINT-Plus v7.66A	
Reflections collected	30667	
Independent reflections	4258 [R_{int}= 0.0413]	
Absorption coefficient	0.112 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9889 and 0.9768	

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	4258 / 0 / 241
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	2.394
Final R indices [$I>2\sigma(I)$, 3426 reflections]	R1 = 0.0424, *w*R2 = 0.0612
R indices (all data)	R1 = 0.0536, *w*R2 = 0.0618
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
Largest diff. peak and hole	0.382 and -0.339 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 alkynyl lactone* ***158*** *(CCDC 771581). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
O(1)	3264(1)	3891(1)	8422(1)	25(1)
O(2)	1757(1)	4780(1)	7535(1)	34(1)
O(3)	2341(1)	4207(1)	3372(1)	23(1)
O(4)	4388(1)	3848(1)	5210(1)	30(1)
O(5)	2648(1)	1926(1)	6592(1)	18(1)
O(6)	2464(1)	2173(1)	4217(1)	20(1)
N(1)	1720(1)	2918(1)	5876(1)	16(1)
C(1)	1757(2)	4201(1)	7692(1)	24(1)
C(2)	199(2)	3722(1)	7140(1)	20(1)
C(3)	1193(1)	3064(1)	7317(1)	16(1)
C(4)	2952(2)	3193(1)	8406(1)	20(1)
C(5)	2628(1)	2973(1)	9855(1)	21(1)
C(6)	2323(2)	2785(1)	11000(1)	27(1)
C(7)	-420(2)	3806(1)	5542(1)	22(1)
C(8)	1125(1)	3416(1)	4825(1)	18(1)
C(9)	2840(1)	3838(1)	4511(1)	18(1)
C(10)	3752(2)	4688(1)	2984(1)	26(1)
C(11)	3121(2)	4898(1)	1483(1)	28(1)
C(12)	2296(1)	2326(1)	5454(1)	16(1)
C(13)	3016(2)	1257(1)	6242(1)	24(1)

Table A2.3. *Bond lengths [Å] and angles [°] for alkynyl lactone* ***158*** *(CCDC 771581).*

O(1)-C(1)	1.3532(13)	C(1)-C(2)-H(2)	107.9(6)
O(1)-C(4)	1.4520(13)	C(3)-C(2)-H(2)	112.5(7)
O(2)-C(1)	1.2015(13)	C(7)-C(2)-H(2)	112.6(7)
O(3)-C(9)	1.3300(12)	N(1)-C(3)-C(2)	103.40(8)
O(3)-C(10)	1.4601(13)	N(1)-C(3)-C(4)	113.57(8)
O(4)-C(9)	1.2022(11)	C(2)-C(3)-C(4)	103.88(8)
O(5)-C(12)	1.3522(12)	N(1)-C(3)-H(3)	111.1(6)
O(5)-C(13)	1.4453(13)	C(2)-C(3)-H(3)	115.1(5)
O(6)-C(12)	1.2184(11)	C(4)-C(3)-H(3)	109.6(5)
N(1)-C(12)	1.3522(13)	O(1)-C(4)-C(5)	109.35(9)
N(1)-C(8)	1.4560(13)	O(1)-C(4)-C(3)	106.58(8)
N(1)-C(3)	1.4645(12)	C(5)-C(4)-C(3)	112.45(9)
C(1)-C(2)	1.5150(15)	O(1)-C(4)-H(4)	105.8(6)
C(2)-C(3)	1.5211(14)	C(5)-C(4)-H(4)	111.4(6)
C(2)-C(7)	1.5305(15)	C(3)-C(4)-H(4)	110.9(6)
C(2)-H(2)	0.969(11)	C(6)-C(5)-C(4)	178.01(12)
C(3)-C(4)	1.5368(14)	C(5)-C(6)-H(6)	177.4(7)
C(3)-H(3)	0.965(9)	C(2)-C(7)-C(8)	103.17(8)
C(4)-C(5)	1.4700(15)	C(2)-C(7)-H(7A)	113.6(6)
C(4)-H(4)	0.974(10)	C(8)-C(7)-H(7A)	111.5(6)
C(5)-C(6)	1.1802(15)	C(2)-C(7)-H(7B)	111.7(6)
C(6)-H(6)	0.976(12)	C(8)-C(7)-H(7B)	108.8(6)
C(7)-C(8)	1.5406(15)	H(7A)-C(7)-H(7B)	108.0(8)
C(7)-H(7A)	0.988(11)	N(1)-C(8)-C(9)	110.94(8)
C(7)-H(7B)	1.024(10)	N(1)-C(8)-C(7)	103.56(8)
C(8)-C(9)	1.5210(14)	C(9)-C(8)-C(7)	111.92(9)
C(8)-H(8)	0.965(10)	N(1)-C(8)-H(8)	109.3(6)
C(10)-C(11)	1.4991(16)	C(9)-C(8)-H(8)	108.3(6)
C(10)-H(10A)	0.983(11)	C(7)-C(8)-H(8)	112.8(6)
C(10)-H(10B)	1.021(12)	O(4)-C(9)-O(3)	125.37(9)
C(11)-H(11A)	1.007(13)	O(4)-C(9)-C(8)	125.13(9)
C(11)-H(11B)	1.031(13)	O(3)-C(9)-C(8)	109.47(8)
C(11)-H(11C)	0.998(11)	O(3)-C(10)-C(11)	106.74(9)
C(13)-H(13A)	1.000(11)	O(3)-C(10)-H(10A)	107.3(7)
C(13)-H(13B)	0.959(12)	C(11)-C(10)-H(10A)	112.9(7)
C(13)-H(13C)	0.975(12)	O(3)-C(10)-H(10B)	107.9(7)
		C(11)-C(10)-H(10B)	112.8(7)
C(1)-O(1)-C(4)	110.81(8)	H(10A)-C(10)-H(10B)	109.0(9)
C(9)-O(3)-C(10)	117.29(8)	C(10)-C(11)-H(11A)	110.7(7)
C(12)-O(5)-C(13)	115.07(8)	C(10)-C(11)-H(11B)	107.9(8)
C(12)-N(1)-C(8)	120.57(9)	H(11A)-C(11)-H(11B)	109.4(10)
C(12)-N(1)-C(3)	124.17(8)	C(10)-C(11)-H(11C)	110.6(7)
C(8)-N(1)-C(3)	113.68(8)	H(11A)-C(11)-H(11C)	107.0(9)
O(2)-C(1)-O(1)	121.43(10)	H(11B)-C(11)-H(11C)	111.3(10)
O(2)-C(1)-C(2)	127.79(10)	O(6)-C(12)-N(1)	124.68(10)
O(1)-C(1)-C(2)	110.78(10)	O(6)-C(12)-O(5)	124.65(10)
C(1)-C(2)-C(3)	104.06(8)	N(1)-C(12)-O(5)	110.67(9)
C(1)-C(2)-C(7)	112.68(9)	O(5)-C(13)-H(13A)	108.5(7)
C(3)-C(2)-C(7)	106.81(9)	O(5)-C(13)-H(13B)	105.3(7)

H(13A)-C(13)-H(13B)	112.0(9)
O(5)-C(13)-H(13C)	110.1(7)
H(13A)-C(13)-H(13C)	110.8(9)
H(13B)-C(13)-H(13C)	110.0(9)

Table A2.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for alkynyl lactone* ***158*** *(CCDC 771581). 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)	280(4)	222(5)	254(4)	-47(3)	-6(3)	-56(3)
O(2)	413(5)	169(5)	459(6)	-39(4)	98(4)	-32(4)
O(3)	222(4)	237(5)	239(4)	101(3)	1(3)	-57(3)
O(4)	212(4)	369(5)	298(5)	107(4)	-25(3)	-50(4)
O(5)	246(4)	132(4)	170(4)	14(3)	7(3)	15(3)
O(6)	201(4)	238(4)	153(4)	-28(3)	18(3)	7(3)
N(1)	201(4)	143(5)	136(4)	14(3)	20(3)	8(4)
C(1)	252(6)	223(7)	249(6)	-59(5)	92(5)	-10(5)
C(2)	181(5)	172(6)	241(6)	-5(5)	69(4)	14(4)
C(3)	161(5)	163(6)	158(5)	2(4)	31(4)	-5(4)
C(4)	199(5)	194(6)	196(5)	-43(5)	20(4)	-2(5)
C(5)	184(5)	235(6)	218(6)	-47(5)	-12(4)	49(5)
C(6)	226(6)	355(8)	223(6)	-7(5)	0(5)	89(5)
C(7)	187(5)	188(6)	273(6)	56(5)	24(4)	17(5)
C(8)	185(5)	169(6)	167(5)	25(4)	-6(4)	-11(4)
C(9)	216(5)	162(6)	174(5)	8(4)	43(4)	12(4)
C(10)	266(6)	260(7)	255(6)	60(5)	43(5)	-86(5)
C(11)	312(7)	288(8)	252(6)	77(6)	53(5)	-41(6)
C(12)	136(5)	162(6)	178(5)	-1(4)	4(4)	-21(4)
C(13)	297(6)	131(6)	293(7)	-11(5)	1(5)	9(5)

Table A2.5. *Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for alkynyl lactone* ***158*** *(CCDC 771581).*

	x	y	z	U_{iso}
H(2)	-877(16)	3765(5)	7724(12)	28(3)
H(3)	409(12)	2722(5)	7667(10)	11(3)
H(4)	4127(14)	3003(5)	8087(10)	17(3)
H(6)	2132(16)	2633(6)	11963(13)	48(4)
H(7A)	-460(15)	4264(6)	5225(11)	25(3)
H(7B)	-1755(15)	3605(5)	5260(11)	25(3)
H(8)	612(13)	3212(5)	3944(11)	14(3)
H(10A)	5033(17)	4477(5)	3075(12)	34(3)
H(10B)	3760(16)	5060(6)	3703(13)	37(4)
H(11A)	3197(17)	4525(7)	796(14)	48(4)
H(11B)	4040(19)	5264(7)	1218(14)	57(4)
H(11C)	1742(16)	5048(5)	1402(12)	32(3)
H(13A)	1871(16)	1088(6)	5623(12)	35(3)
H(13B)	3193(15)	1035(6)	7144(13)	34(3)
H(13C)	4195(17)	1226(6)	5752(13)	40(4)

A2.2 CRYSTAL STRUCTURE ANALYSIS OF TETRAOL 193

Figure A2.2. *Tetraol* ***193****. 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 844563.*

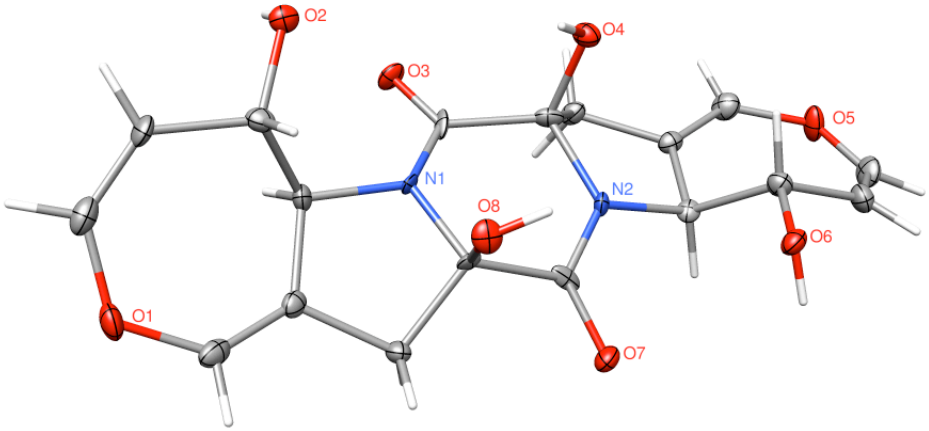
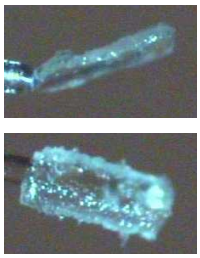


Table A2.6. *Crystal data and structure refinement for tetraol* ***193*** *(CCDC 844563).*



Empirical formula	$C_{18}H_{18}N_2O_8 \bullet 0.5(C_6H_6) \bullet H_2O$
Formula weight	447.41
Crystallization Solvent	Benzene
Crystal Habit	Blade
Crystal size	0.39 x 0.16 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 ? reflections used in lattice determination	? to ?°	
Unit cell dimensions	a = 20.744(4) Å b = 7.7389(15) Å c = 12.557(3) Å	α= 90° β= 97.41(3)° γ = 90°
Volume	1999.0(7) $Å^3$	
Z	4	
Crystal system	Monoclinic	
Space group	C 2	
Density (calculated)	1.487 Mg/m^3	
F(000)	940	
Data collection program	Bruker APEX2 v2009.7-0	
θ range for data collection	1.98 to 30.52°	
Completeness to θ = 30.52°	98.6 %	
Index ranges	$-29 \le h \le 29, 0 \le k \le 11, 0 \le l \le 17$	
Data collection scan type	ω scans; 8 settings	
Data reduction program	Bruker SAINT-Plus v7.68A	
Reflections collected	4904	
Independent reflections	4905 [R_{int}= 0.0000]	
Absorption coefficient	0.118 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7461 and 0.6457	

Table A2.6 (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	4905 / 1 / 295
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.523
Final R indices [I>2σ(I), 3856 reflections]	R1 = 0.0475, *w*R2 = 0.0570
R indices (all data)	R1 = 0.0724, *w*R2 = 0.0586
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.003
Average shift/error	0.000
Absolute structure determination	Unknown
Absolute structure parameter	0.0(15)
Largest diff. peak and hole	0.360 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.

The crystal is a twin. Below is a summary of cell_now[‡] and TWINABS results[§];

Cell for domain 1: 20.744 7.739 12.557 89.89 97.41 90.05

341 reflections within tolerance assigned to domain 1,

341 of them exclusively; 109 reflections not yet assigned to a domain

Cell for domain 2: 20.744 7.739 12.557 89.89 97.41 90.05

Rotated from first domain by 180.0 degrees about

reciprocal axis 1.000 0.000 -0.077 and real axis 1.000 0.002 0.003

[‡] cell_now v2008/2, Bruker-AXS, Madison, WI

[§] TWINABS v2008/4, Bruker-AXS, Madison, WI

319 reflections within tolerance assigned to domain 2,
107 of them exclusively; 2 reflections not yet assigned to a domain

PART 1 - Refinement of parameters to model systematic errors
4095 data (1047 unique) involve domain 1 only, mean I/sigma 7.3
4126 data (1039 unique) involve domain 2 only, mean I/sigma 7.7
12800 data (2820 unique) involve 2 domains, mean I/sigma 7.0

Table A2.7. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for tetraol* ***193*** *(CCDC 844563). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
O(1)	8553(1)	4178(3)	4236(2)	21(1)
O(2)	9325(1)	5646(3)	1137(2)	15(1)
O(3)	8215(1)	4557(4)	-488(2)	15(1)
O(4)	9086(1)	2056(3)	-1515(2)	15(1)
O(5)	7924(2)	-1604(3)	-4248(2)	21(1)
O(6)	9132(1)	-3189(3)	-1136(2)	14(1)
O(7)	8311(1)	-2039(4)	519(2)	16(1)
O(8)	9346(1)	470(3)	1510(2)	16(1)
N(1)	8556(1)	2544(4)	781(3)	10(1)
N(2)	8441(1)	-47(4)	-763(3)	11(1)
C(1)	8832(2)	5634(6)	3838(3)	21(1)
C(2)	9097(2)	5893(5)	2959(3)	18(1)
C(3)	9160(2)	4676(5)	2034(3)	15(1)
C(4)	8514(2)	3673(6)	1726(3)	15(1)
C(5)	8410(2)	2421(5)	2610(3)	14(1)
C(6)	8462(2)	2676(6)	3657(3)	17(1)
C(7)	8399(2)	3089(7)	-234(4)	14(1)
C(8)	8487(2)	1779(5)	-1118(3)	14(1)
C(9)	7949(2)	1845(5)	-2059(3)	15(1)
C(10)	7994(2)	94(5)	-2581(3)	14(1)
C(11)	7903(2)	-121(6)	-3625(3)	19(1)
C(12)	8189(2)	-3099(6)	-3834(3)	20(1)
C(13)	8577(2)	-3429(5)	-2933(3)	19(1)
C(14)	8812(2)	-2223(5)	-2026(3)	14(1)
C(15)	8243(2)	-1186(6)	-1697(3)	11(1)
C(16)	8442(2)	-553(7)	253(4)	13(1)
C(17)	8679(2)	731(5)	1142(3)	12(1)
C(18)	8300(2)	625(5)	2108(3)	14(1)
O(21)	0	3462(6)	0	17(1)
O(22)	10000	8951(5)	10000	15(1)
C(21)	9865(2)	2553(5)	5484(3)	34(1)
C(22)	9715(2)	1029(6)	5951(3)	39(1)
C(23)	9852(2)	-546(5)	5471(3)	45(1)

Table A2.8. *Bond lengths [Å] and angles [°] for tetraol* ***193*** *(CCDC 844563).*

O(1)-C(1)	1.389(5)	C(1)-C(2)-C(3)	129.7(4)
O(1)-C(6)	1.371(5)	O(2)-C(3)-C(2)	109.3(3)
O(2)-C(3)	1.432(4)	O(2)-C(3)-C(4)	110.6(3)
O(3)-C(7)	1.227(5)	C(2)-C(3)-C(4)	110.2(3)
O(4)-C(8)	1.413(4)	N(1)-C(4)-C(5)	103.8(3)
O(5)-C(11)	1.393(5)	N(1)-C(4)-C(3)	110.9(3)
O(5)-C(12)	1.355(5)	C(5)-C(4)-C(3)	109.8(3)
O(6)-C(14)	1.434(4)	C(6)-C(5)-C(18)	122.3(4)
O(7)-C(16)	1.238(5)	C(6)-C(5)-C(4)	129.5(4)
O(8)-C(17)	1.414(4)	C(18)-C(5)-C(4)	107.9(3)
N(1)-C(7)	1.342(6)	C(5)-C(6)-O(1)	130.0(4)
N(1)-C(4)	1.485(5)	O(3)-C(7)-N(1)	124.5(5)
N(1)-C(17)	1.486(5)	O(3)-C(7)-C(8)	119.1(5)
N(2)-C(16)	1.334(6)	N(1)-C(7)-C(8)	116.3(5)
N(2)-C(8)	1.489(5)	O(4)-C(8)-N(2)	110.0(3)
N(2)-C(15)	1.483(5)	O(4)-C(8)-C(9)	108.2(3)
C(1)-C(2)	1.310(5)	N(2)-C(8)-C(9)	101.3(3)
C(2)-C(3)	1.514(5)	O(4)-C(8)-C(7)	110.3(4)
C(3)-C(4)	1.553(5)	N(2)-C(8)-C(7)	113.2(4)
C(4)-C(5)	1.510(5)	C(9)-C(8)-C(7)	113.5(4)
C(5)-C(6)	1.320(5)	C(8)-C(9)-C(10)	103.1(4)
C(5)-C(18)	1.531(5)	C(11)-C(10)-C(9)	122.5(4)
C(7)-C(8)	1.531(6)	C(11)-C(10)-C(15)	129.5(4)
C(8)-C(9)	1.518(5)	C(9)-C(10)-C(15)	107.5(3)
C(9)-C(10)	1.514(5)	C(10)-C(11)-O(5)	130.9(4)
C(10)-C(11)	1.311(5)	C(13)-C(12)-O(5)	131.5(4)
C(10)-C(15)	1.527(6)	C(12)-C(13)-C(14)	129.0(4)
C(12)-C(13)	1.327(5)	O(6)-C(14)-C(13)	109.8(3)
C(13)-C(14)	1.505(5)	O(6)-C(14)-C(15)	111.1(3)
C(14)-C(15)	1.528(5)	C(13)-C(14)-C(15)	110.1(3)
C(16)-C(17)	1.528(6)	N(2)-C(15)-C(14)	112.4(3)
C(17)-C(18)	1.531(5)	N(2)-C(15)-C(10)	102.9(3)
C(21)-C(21)#1	1.403(8)	C(14)-C(15)-C(10)	110.2(3)
C(21)-C(22)	1.371(6)	O(7)-C(16)-N(2)	123.9(5)
C(22)-C(23)	1.405(6)	O(7)-C(16)-C(17)	117.9(4)
C(23)-C(23)#1	1.401(9)	N(2)-C(16)-C(17)	117.9(4)
		O(8)-C(17)-N(1)	110.9(3)
C(1)-O(1)-C(6)	122.1(3)	O(8)-C(17)-C(18)	108.3(3)
C(11)-O(5)-C(12)	121.9(3)	N(1)-C(17)-C(18)	101.9(3)
C(7)-N(1)-C(4)	122.8(4)	O(8)-C(17)-C(16)	110.8(3)
C(7)-N(1)-C(17)	126.7(4)	N(1)-C(17)-C(16)	111.4(3)
C(4)-N(1)-C(17)	109.7(3)	C(18)-C(17)-C(16)	113.2(3)
C(16)-N(2)-C(8)	125.0(4)	C(5)-C(18)-C(17)	102.3(3)
C(16)-N(2)-C(15)	123.2(4)	C(21)#1-C(21)-C(22)	120.6(3)
C(8)-N(2)-C(15)	110.4(3)	C(23)-C(22)-C(21)	119.5(4)
C(2)-C(1)-O(1)		C(23)#1-C(23)-C(22)	

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,y,-z+1

Table A2.9. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for tetraol **193** (CCDC 844563). 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)	251(17)	240(19)	131(15)	-80(14)	42(14)	-6(14)
O(2)	143(15)	152(17)	156(17)	9(13)	12(13)	-1(15)
O(3)	190(18)	78(18)	164(19)	26(14)	-25(14)	13(14)
O(4)	136(15)	179(17)	135(16)	-8(13)	22(13)	-34(14)
O(5)	286(16)	190(20)	141(14)	-62(13)	-5(16)	69(16)
O(6)	151(15)	94(16)	191(18)	-10(12)	23(13)	-17(15)
O(7)	178(18)	104(18)	180(20)	-22(14)	35(15)	-28(14)
O(8)	134(15)	179(17)	156(17)	5(13)	-20(13)	40(13)
N(1)	160(20)	29(18)	140(20)	-10(16)	54(16)	2(15)
N(2)	140(20)	75(19)	110(20)	-35(16)	30(16)	10(15)
C(1)	230(20)	150(30)	230(30)	-60(20)	-10(20)	-20(20)
C(2)	230(20)	130(20)	190(20)	-77(19)	24(19)	-70(20)
C(3)	140(20)	180(20)	140(20)	1(19)	40(18)	-40(20)
C(4)	200(30)	120(20)	130(20)	-40(20)	60(20)	0(20)
C(5)	130(20)	110(20)	170(20)	-15(19)	34(18)	8(17)
C(6)	170(20)	110(20)	240(30)	10(20)	50(20)	0(20)
C(7)	100(20)	130(30)	170(30)	-120(20)	20(20)	-40(20)
C(8)	140(20)	150(30)	130(20)	50(20)	18(18)	-20(20)
C(9)	190(20)	120(20)	130(20)	0(20)	2(18)	-29(19)
C(10)	120(20)	120(20)	160(20)	11(18)	16(18)	-10(17)
C(11)	210(20)	190(30)	170(30)	-20(20)	-10(20)	-40(20)
C(12)	220(20)	180(30)	190(30)	-90(20)	20(20)	-50(20)
C(13)	220(20)	190(30)	170(20)	-42(18)	80(20)	0(20)
C(14)	170(20)	140(20)	120(20)	5(18)	24(18)	0(20)
C(15)	70(20)	130(20)	135(19)	-10(20)	0(20)	-13(19)
C(16)	90(20)	190(30)	110(30)	70(20)	40(20)	90(20)
C(17)	190(20)	50(20)	130(20)	30(20)	36(18)	-10(20)
C(18)	180(20)	130(20)	120(20)	-4(19)	52(18)	-40(19)
O(21)	100(30)	100(30)	280(30)	0	-20(20)	0
O(22)	190(30)	120(30)	130(30)	0	10(20)	0
C(21)	280(20)	410(30)	320(30)	-60(20)	-80(20)	50(20)
C(22)	320(20)	570(30)	280(20)	80(30)	10(30)	-40(30)
C(23)	550(30)	350(30)	410(30)	90(20)	-100(30)	-20(30)

Table A2.10. *Hydrogen bonds for tetraol* ***193*** *(CCDC 844563) [Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(7)#2	0.84	1.97	2.795(4)	168.8
O(4)-H(4)...O(21)#3	0.84	1.92	2.733(3)	162.9
O(6)-H(6)...O(3)#4	0.84	1.95	2.779(4)	171.0
O(6)-H(6)...O(2)#4	0.84	2.69	2.970(3)	101.0
O(8)-H(8)...O(22)#5	0.84	1.90	2.736(3)	174.8
O(21)-H(21A)...O(2)#6	0.96	1.82	2.715(4)	153.3
O(22)-H(22A)...O(6)#7	0.84	1.92	2.712(4)	156.7

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,y,-z+1
#2 x,y+1,z
#3 x+1,y,z
#4 x,y-1,z
#5 x,y-1,z-1
#6 -x+1,y,-z
#7 x,y+1,z+1

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Figure A2.3. *Diketopiperazine* ***194****. 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 832361.*

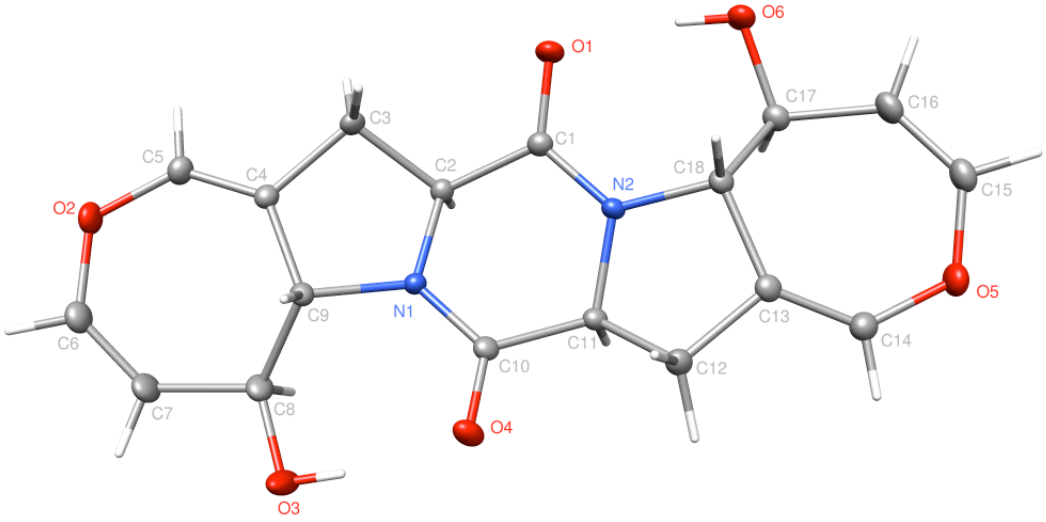


Table A2.11. *Crystal data and structure refinement for diketopiperazine* ***194*** *(CCDC 832361).*

Empirical formula	$C_{18}H_{18}N_2O_6$
Formula weight	358.34
Crystallization Solvent	THF
Crystal Habit	Block
Crystal size	0.37 x 0.37 x 0.30 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 6587 reflections used in lattice determination	2.18 to 27.57°	
Unit cell dimensions	a = 9.8372(4) Å b = 7.2818(3) Å c = 11.6037(5) Å	α= 90° β= 108.626(2)° γ = 90°
Volume	787.67(6) $Å^3$	
Z	2	
Crystal system	Monoclinic	
Space group	P 2_1	
Density (calculated)	1.511 Mg/m^3	
F(000)	376	
Data collection program	Bruker SMART v5.630	
θ range for data collection	1.85 to 42.08°	
Completeness to θ = 42.08°	97.7 %	
Index ranges	$-18 \le h \le 18$, $-13 \le k \le 13$, $-21 \le l \le 21$	
Data collection scan type	ω scans at 7 settings	
Data reduction program	Bruker SAINT-Plus v7.66A	
Reflections collected	24528	
Independent reflections	10286 [R_{int}= 0.0425]	
Absorption coefficient	0.115 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9664 and 0.9587	

Table A2.11 (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	10286 / 1 / 307
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.822
Final R indices [I>2σ(I), 8534 reflections]	R1 = 0.0456, *w*R2 = 0.0767
R indices (all data)	R1 = 0.0564, *w*R2 = 0.0781
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	Not determined
Absolute structure parameter	0.1(5)
Largest diff. peak and hole	0.524 and -0.394 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 A2.12. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for diketopiperazine* ***194*** *(CCDC 832361). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
O(1)	8348(1)	-1783(1)	4697(1)	20(1)
O(2)	6071(1)	-327(1)	9389(1)	22(1)
O(3)	5737(1)	4976(1)	7307(1)	36(1)
O(4)	6036(1)	4590(1)	5142(1)	19(1)
O(5)	9107(1)	3564(1)	885(1)	22(1)
O(6)	9445(1)	-1772(1)	2927(1)	20(1)
N(1)	7024(1)	1926(1)	6068(1)	12(1)
N(2)	8058(1)	1240(1)	4124(1)	12(1)
C(1)	8126(1)	-153(1)	4894(1)	13(1)
C(2)	8002(1)	363(1)	6130(1)	13(1)
C(3)	7351(1)	-1162(1)	6684(1)	15(1)
C(4)	6691(1)	-122(1)	7499(1)	13(1)
C(5)	6665(1)	-897(2)	8531(1)	17(1)
C(6)	5583(1)	1426(2)	9415(1)	21(1)
C(7)	5717(1)	2919(2)	8810(1)	22(1)
C(8)	6405(1)	3310(1)	7852(1)	19(1)
C(9)	6176(1)	1723(1)	6930(1)	13(1)
C(10)	6855(1)	3264(1)	5249(1)	13(1)
C(11)	7799(1)	3142(1)	4437(1)	12(1)
C(12)	7135(1)	4037(1)	3200(1)	16(1)
C(13)	7916(1)	3080(1)	2440(1)	14(1)
C(14)	8397(1)	4055(2)	1682(1)	17(1)
C(15)	9449(1)	1776(2)	741(1)	19(1)
C(16)	9583(1)	353(2)	1481(1)	19(1)
C(17)	9450(1)	160(1)	2730(1)	15(1)
C(18)	8087(1)	1087(1)	2835(1)	13(1)

Table A2.13. *Bond lengths [Å] and angles [°] for diketopiperazine* ***194*** *(CCDC 832361).*

O(1)-C(1)	1.2410(12)	C(6)-O(2)-C(5)	122.19(8)
O(2)-C(6)	1.3671(14)	C(8)-O(3)-H(3)	104.9(13)
O(2)-C(5)	1.3706(12)	C(15)-O(5)-C(14)	121.90(8)
O(3)-C(8)	1.4282(14)	C(17)-O(6)-H(6)	104.5(11)
O(3)-H(3)	0.834(15)	C(10)-N(1)-C(2)	121.93(7)
O(4)-C(10)	1.2378(12)	C(10)-N(1)-C(9)	125.25(7)
O(5)-C(15)	1.3685(13)	C(2)-N(1)-C(9)	112.58(7)
O(5)-C(14)	1.3719(12)	C(1)-N(2)-C(11)	121.51(7)
O(6)-C(17)	1.4250(13)	C(1)-N(2)-C(18)	126.34(8)
O(6)-H(6)	0.842(13)	C(11)-N(2)-C(18)	111.92(7)
N(1)-C(10)	1.3342(12)	O(1)-C(1)-N(2)	125.17(8)
N(1)-C(2)	1.4772(11)	O(1)-C(1)-C(2)	118.70(8)
N(1)-C(9)	1.5006(11)	N(2)-C(1)-C(2)	116.03(8)
N(2)-C(1)	1.3399(12)	N(1)-C(2)-C(3)	103.12(7)
N(2)-C(11)	1.4748(12)	N(1)-C(2)-C(1)	112.99(7)
N(2)-C(18)	1.5094(11)	C(3)-C(2)-C(1)	112.80(8)
C(1)-C(2)	1.5250(12)	N(1)-C(2)-H(2)	110.7(6)
C(2)-C(3)	1.5231(12)	C(3)-C(2)-H(2)	111.5(6)
C(2)-H(2)	0.998(10)	C(1)-C(2)-H(2)	105.9(6)
C(3)-C(4)	1.5107(13)	C(4)-C(3)-C(2)	102.78(7)
C(3)-H(3A)	0.960(11)	C(4)-C(3)-H(3A)	108.2(7)
C(3)-H(3B)	0.919(13)	C(2)-C(3)-H(3A)	107.4(7)
C(4)-C(5)	1.3312(13)	C(4)-C(3)-H(3B)	112.7(8)
C(4)-C(9)	1.5110(13)	C(2)-C(3)-H(3B)	111.0(8)
C(5)-H(5)	0.917(14)	H(3A)-C(3)-H(3B)	114.0(11)
C(6)-C(7)	1.3232(15)	C(5)-C(4)-C(3)	119.07(9)
C(6)-H(6A)	0.929(13)	C(5)-C(4)-C(9)	132.05(9)
C(7)-C(8)	1.5024(13)	C(3)-C(4)-C(9)	108.87(7)
C(7)-H(7)	0.935(14)	C(4)-C(5)-O(2)	131.33(10)
C(8)-C(9)	1.5415(13)	C(4)-C(5)-H(5)	117.6(8)
C(8)-H(8)	0.985(12)	O(2)-C(5)-H(5)	111.0(8)
C(9)-H(9)	0.972(11)	C(7)-C(6)-O(2)	131.33(9)
C(10)-C(11)	1.5222(12)	C(7)-C(6)-H(6A)	122.0(8)
C(11)-C(12)	1.5212(13)	O(2)-C(6)-H(6A)	106.7(8)
C(11)-H(11)	0.941(11)	C(6)-C(7)-C(8)	133.86(10)
C(12)-C(13)	1.5118(13)	C(6)-C(7)-H(7)	115.5(8)
C(12)-H(12A)	1.004(11)	C(8)-C(7)-H(7)	110.6(8)
C(12)-H(12B)	1.011(13)	O(3)-C(8)-C(7)	103.66(8)
C(13)-C(14)	1.3301(13)	O(3)-C(8)-C(9)	112.64(8)
C(13)-C(18)	1.5151(14)	C(7)-C(8)-C(9)	111.77(8)
C(14)-H(14)	0.910(13)	O(3)-C(8)-H(8)	105.1(8)
C(15)-C(16)	1.3255(15)	C(7)-C(8)-H(8)	113.9(7)
C(15)-H(15)	0.982(13)	C(9)-C(8)-H(8)	109.5(7)
C(16)-C(17)	1.5025(13)	N(1)-C(9)-C(4)	101.45(7)
C(16)-H(16)	0.958(12)	N(1)-C(9)-C(8)	113.55(7)
C(17)-C(18)	1.5405(13)	C(4)-C(9)-C(8)	114.14(8)
C(17)-H(17)	0.969(12)	N(1)-C(9)-H(9)	108.3(7)
C(18)-H(18)	0.969(12)	C(4)-C(9)-H(9)	111.6(7)

C(8)-C(9)-H(9)	107.6(7)
O(4)-C(10)-N(1)	124.78(8)
O(4)-C(10)-C(11)	119.31(8)
N(1)-C(10)-C(11)	115.86(8)
N(2)-C(11)-C(12)	103.03(7)
N(2)-C(11)-C(10)	113.26(8)
C(12)-C(11)-C(10)	113.34(7)
N(2)-C(11)-H(11)	108.7(7)
C(12)-C(11)-H(11)	110.3(7)
C(10)-C(11)-H(11)	108.1(6)
C(13)-C(12)-C(11)	101.98(8)
C(13)-C(12)-H(12A)	110.0(7)
C(11)-C(12)-H(12A)	108.1(6)
C(13)-C(12)-H(12B)	114.5(7)
C(11)-C(12)-H(12B)	112.3(7)
H(12A)-C(12)-H(12B)	109.5(10)
C(14)-C(13)-C(12)	119.65(9)
C(14)-C(13)-C(18)	133.03(9)
C(12)-C(13)-C(18)	107.08(8)
C(13)-C(14)-O(5)	132.25(10)
C(13)-C(14)-H(14)	121.0(8)
O(5)-C(14)-H(14)	106.7(8)
C(16)-C(15)-O(5)	129.93(9)
C(16)-C(15)-H(15)	119.4(8)
O(5)-C(15)-H(15)	110.7(8)
C(15)-C(16)-C(17)	132.62(10)
C(15)-C(16)-H(16)	114.5(7)
C(17)-C(16)-H(16)	112.9(7)
O(6)-C(17)-C(16)	104.65(8)
O(6)-C(17)-C(18)	111.84(8)
C(16)-C(17)-C(18)	112.40(8)
O(6)-C(17)-H(17)	108.1(7)
C(16)-C(17)-H(17)	111.9(7)
C(18)-C(17)-H(17)	107.9(7)
N(2)-C(18)-C(13)	101.13(7)
N(2)-C(18)-C(17)	113.78(7)
C(13)-C(18)-C(17)	114.32(7)
N(2)-C(18)-H(18)	105.9(7)
C(13)-C(18)-H(18)	113.6(7)
C(17)-C(18)-H(18)	107.8(7)

Table A2.14. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for diketopiperazine* ***194*** *(CCDC 832361). 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)	321(4)	98(3)	241(4)	6(3)	168(3)	39(3)
O(2)	327(4)	205(4)	204(3)	28(3)	179(3)	9(3)
O(3)	794(7)	123(4)	315(5)	22(4)	374(5)	66(4)
O(4)	269(4)	158(3)	171(3)	26(3)	99(3)	99(3)
O(5)	302(4)	203(4)	213(3)	19(3)	172(3)	7(3)
O(6)	285(4)	124(3)	235(4)	12(3)	156(3)	43(3)
N(1)	153(3)	88(3)	136(3)	10(3)	75(3)	11(3)
N(2)	169(3)	93(3)	126(3)	0(3)	70(3)	20(3)
C(1)	147(4)	114(4)	154(4)	4(3)	66(3)	9(3)
C(2)	142(4)	114(4)	140(4)	11(3)	66(3)	9(3)
C(3)	203(4)	102(4)	160(4)	25(3)	89(3)	19(3)
C(4)	157(4)	111(4)	148(4)	-7(3)	68(3)	-17(3)
C(5)	199(4)	159(4)	180(4)	21(4)	94(3)	2(4)
C(6)	266(5)	206(5)	184(4)	-18(4)	127(4)	-10(4)
C(7)	358(6)	174(5)	189(5)	-33(4)	165(4)	3(4)
C(8)	290(5)	139(4)	183(4)	-48(4)	128(4)	-44(4)
C(9)	149(4)	106(4)	141(4)	-17(3)	71(3)	-16(3)
C(10)	155(4)	111(4)	115(3)	-13(3)	46(3)	1(3)
C(11)	157(4)	100(3)	119(3)	-2(3)	52(3)	11(3)
C(12)	206(4)	134(4)	138(4)	25(3)	71(3)	45(3)
C(13)	164(4)	139(4)	113(4)	0(3)	39(3)	13(3)
C(14)	231(5)	149(4)	152(4)	7(4)	76(3)	12(4)
C(15)	216(4)	220(5)	158(4)	-17(4)	95(4)	11(4)
C(16)	223(5)	205(5)	181(4)	-23(4)	112(4)	26(4)
C(17)	157(4)	143(4)	154(4)	-6(3)	60(3)	15(3)
C(18)	152(4)	123(4)	113(3)	-9(3)	47(3)	1(3)

Table A2.15. *Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for diketopiperazine* ***194*** *(CCDC 832361).*

	x	y	z	U_{iso}
H(3)	5794(18)	4960(30)	6606(14)	51(5)
H(6)	9043(14)	-1890(20)	3463(11)	32(4)
H(2)	8996(11)	669(14)	6656(9)	3(2)
H(3A)	6590(12)	-1706(18)	6037(10)	13(3)
H(3B)	8040(13)	-1983(19)	7104(11)	21(3)
H(5)	7075(13)	-2035(19)	8718(11)	22(3)
H(6A)	5086(14)	1432(17)	9974(13)	18(3)
H(7)	5272(15)	3970(20)	8980(12)	34(4)
H(8)	7436(13)	3600(18)	8181(10)	23(3)
H(9)	5163(12)	1697(17)	6458(10)	14(3)
H(11)	8687(12)	3694(16)	4850(9)	10(3)
H(12A)	6089(12)	3711(16)	2898(10)	13(3)
H(12B)	7244(13)	5419(18)	3235(11)	17(3)
H(14)	8278(13)	5295(18)	1621(11)	19(3)
H(15)	9612(13)	1605(18)	-45(12)	22(3)
H(16)	9814(11)	-782(17)	1168(9)	13(3)
H(17)	10269(13)	679(17)	3350(11)	15(3)
H(18)	7275(12)	325(16)	2409(10)	12(3)

Table A2.16. *Hydrogen bonds for diketopiperazine* ***194*** *(CCDC 832361) [Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(4)	0.834(15)	1.809(15)	2.6365(11)	171.2(19)
O(6)-H(6)...O(1)	0.842(13)	1.775(13)	2.6082(10)	169.9(15)

A2.4. CRYSTAL STRUCTURE ANALYSIS OF TETRASULFIDE 197

Figure A2.4. *Tetrasulfide* ***197****. 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 838235.*

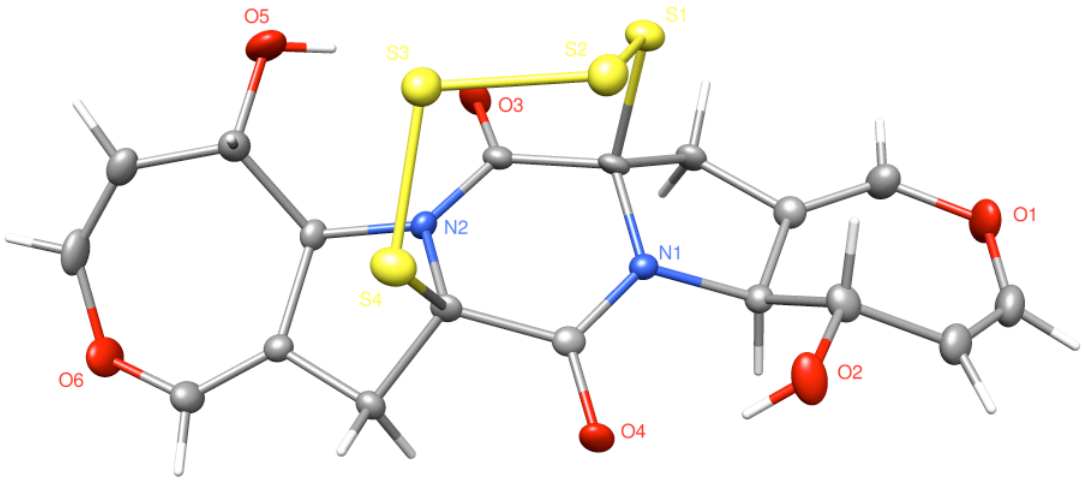
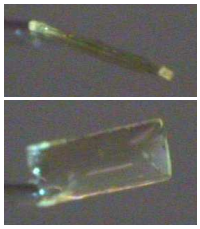


Table A2.17. *Crystal data and structure refinement for tetrasulfide* ***197*** *(CCDC 838235).*

Empirical formula	$C_{18}H_{16}N_2O_6S_4$
Formula weight	484.57
Crystallization Solvent	Chloroform/isooctane
Crystal Habit	Plate
Crystal size	0.48 x 0.20 x 0.05 mm^3
Crystal color	Light yellow



Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 9912 reflections used in lattice determination	2.61 to 29.28°	
Unit cell dimensions	a = 7.6944(3) Å b = 9.6777(3) Å c = 26.3981(9) Å	α= 90° β= 90° γ = 90°
Volume	1965.71(12) $Å^3$	
Z	4	
Crystal system	Orthorhombic	
Space group	$P\ 2_12_12_1$	
Density (calculated)	1.637 Mg/m^3	
F(000)	1000	
Data collection program	Bruker APEX2 v2009.7-0	
θ range for data collection	2.24 to 29.30°	
Completeness to θ = 29.30°	99.9 %	
Index ranges	$-10 \le h \le 10, -13 \le k \le 13, -36 \le l \le 36$	
Data collection scan type	ω scans; 9 settings	
Data reduction program	Bruker SAINT-Plus v7.68A	
Reflections collected	42286	
Independent reflections	5365 [R_{int}= 0.0472]	
Absorption coefficient	0.525 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9742 and 0.7868	

Table A2.17 (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	5365 / 0 / 273
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.797
Final R indices [$I>2\sigma(I)$, 4892 reflections]	R1 = 0.0433, *w*R2 = 0.0639
R indices (all data)	R1 = 0.0483, *w*R2 = 0.0642
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Absolute structure determination	Anomalous dispersion
Absolute structure parameter	-0.02(6)
Largest diff. peak and hole	1.078 and -0.643 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 A2.18. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for tetrasulfide* ***197*** *(CCDC 838235). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
S(1)	3450(1)	7409(1)	3420(1)	21(1)
S(2)	1537(1)	5992(1)	3477(1)	23(1)
S(3)	429(1)	6398(1)	4176(1)	23(1)
S(4)	-1817(1)	7354(1)	3987(1)	23(1)
O(1)	4095(2)	9173(2)	1605(1)	31(1)
O(2)	-845(2)	7303(2)	2186(1)	24(1)
O(3)	3157(2)	10233(2)	4085(1)	23(1)
O(4)	-2156(2)	9030(2)	2905(1)	20(1)
O(5)	2022(2)	9505(2)	5062(1)	38(1)
O(6)	-2979(2)	11716(2)	5196(1)	28(1)
N(1)	760(3)	8971(2)	3011(1)	12(1)
N(2)	315(2)	9677(2)	4025(1)	13(1)
C(1)	2554(3)	8757(3)	1390(1)	25(1)
C(2)	1178(3)	8178(3)	1600(1)	22(1)
C(3)	847(3)	7836(3)	2144(1)	19(1)
C(4)	1153(3)	9144(3)	2464(1)	14(1)
C(5)	3062(3)	9543(3)	2471(1)	17(1)
C(6)	4231(4)	9471(3)	2113(1)	24(1)
C(7)	3548(3)	9946(3)	3003(1)	17(1)
C(8)	2289(3)	9089(3)	3326(1)	14(1)
C(9)	1969(3)	9709(3)	3845(1)	15(1)
C(10)	-888(3)	9024(2)	3189(1)	14(1)
C(11)	-1150(3)	9105(3)	3753(1)	14(1)
C(12)	-2663(3)	10049(3)	3900(1)	15(1)
C(13)	-3277(3)	11166(3)	4725(1)	21(1)
C(14)	-2160(3)	10581(3)	4418(1)	15(1)
C(15)	-220(3)	10389(3)	4500(1)	14(1)
C(16)	198(3)	9562(3)	4976(1)	20(1)
C(17)	-555(3)	10219(3)	5442(1)	22(1)
C(18)	-1787(4)	11133(3)	5517(1)	24(1)

Table A2.19. *Bond lengths [Å] and angles [°] for tetrasulfide* ***197*** *(CCDC 838235).*

S(1)-C(8)	1.872(3)	C(9)-N(2)-C(15)	122.8(2)
S(1)-S(2)	2.0170(9)	C(11)-N(2)-C(15)	112.32(18)
S(2)-S(3)	2.0698(10)	C(2)-C(1)-O(1)	130.0(3)
S(3)-S(4)	2.0224(10)	C(1)-C(2)-C(3)	129.4(3)
S(4)-C(11)	1.875(3)	O(2)-C(3)-C(2)	108.4(2)
O(1)-C(6)	1.376(3)	O(2)-C(3)-C(4)	113.6(2)
O(1)-C(1)	1.374(3)	C(2)-C(3)-C(4)	108.6(2)
O(2)-C(3)	1.405(3)	N(1)-C(4)-C(5)	102.42(19)
O(3)-C(9)	1.223(3)	N(1)-C(4)-C(3)	114.2(2)
O(4)-C(10)	1.230(3)	C(5)-C(4)-C(3)	111.3(2)
O(5)-C(16)	1.423(3)	C(6)-C(5)-C(7)	121.2(2)
O(6)-C(13)	1.372(3)	C(6)-C(5)-C(4)	130.1(2)
O(6)-C(18)	1.370(3)	C(7)-C(5)-C(4)	108.4(2)
N(1)-C(10)	1.352(3)	C(5)-C(6)-O(1)	131.6(3)
N(1)-C(8)	1.444(3)	C(5)-C(7)-C(8)	102.77(19)
N(1)-C(4)	1.485(3)	N(1)-C(8)-C(9)	114.8(2)
N(2)-C(9)	1.358(3)	N(1)-C(8)-C(7)	103.82(19)
N(2)-C(11)	1.447(3)	C(9)-C(8)-C(7)	113.0(2)
N(2)-C(15)	1.488(3)	N(1)-C(8)-S(1)	113.32(17)
C(1)-C(2)	1.320(4)	C(9)-C(8)-S(1)	107.53(17)
C(2)-C(3)	1.495(3)	C(7)-C(8)-S(1)	103.97(16)
C(3)-C(4)	1.540(3)	O(3)-C(9)-N(2)	122.0(2)
C(4)-C(5)	1.519(3)	O(3)-C(9)-C(8)	120.7(2)
C(5)-C(6)	1.306(3)	N(2)-C(9)-C(8)	117.3(2)
C(5)-C(7)	1.507(3)	O(4)-C(10)-N(1)	122.2(2)
C(7)-C(8)	1.533(3)	O(4)-C(10)-C(11)	119.7(2)
C(8)-C(9)	1.517(3)	N(1)-C(10)-C(11)	118.0(2)
C(10)-C(11)	1.505(3)	N(2)-C(11)-C(10)	114.00(19)
C(11)-C(12)	1.531(3)	N(2)-C(11)-C(12)	103.76(18)
C(12)-C(14)	1.510(3)	C(10)-C(11)-C(12)	112.7(2)
C(13)-C(14)	1.310(3)	N(2)-C(11)-S(4)	113.25(16)
C(14)-C(15)	1.520(3)	C(10)-C(11)-S(4)	108.43(17)
C(15)-C(16)	1.524(3)	C(12)-C(11)-S(4)	104.34(16)
C(16)-C(17)	1.502(3)	C(14)-C(12)-C(11)	103.83(19)
C(17)-C(18)	1.312(4)	C(14)-C(13)-O(6)	128.3(2)
		C(13)-C(14)-C(12)	122.6(2)
C(8)-S(1)-S(2)	104.59(8)	C(13)-C(14)-C(15)	127.5(2)
S(1)-S(2)-S(3)	103.82(4)	C(12)-C(14)-C(15)	109.8(2)
S(4)-S(3)-S(2)	102.66(4)	N(2)-C(15)-C(14)	102.0(2)
C(11)-S(4)-S(3)	105.14(8)	N(2)-C(15)-C(16)	113.2(2)
C(6)-O(1)-C(1)	121.9(2)	C(14)-C(15)-C(16)	112.9(2)
C(13)-O(6)-C(18)	120.8(2)	O(5)-C(16)-C(17)	105.5(2)
C(10)-N(1)-C(8)	124.18(19)	O(5)-C(16)-C(15)	111.1(2)
C(10)-N(1)-C(4)	121.56(19)	C(17)-C(16)-C(15)	111.9(2)
C(8)-N(1)-C(4)	112.57(18)	C(18)-C(17)-C(16)	133.5(3)
C(9)-N(2)-C(11)	124.4(2)	C(17)-C(18)-O(6)	131.9(2)

Table A2.20. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for tetrasulfide* ***197*** *(CCDC 838235). The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	186(3)	209(4)	241(4)	12(3)	-16(3)	49(3)
S(2)	258(4)	206(4)	214(4)	7(3)	-2(3)	3(3)
S(3)	254(4)	226(4)	216(4)	20(3)	3(3)	41(3)
S(4)	192(3)	189(4)	300(4)	44(3)	3(3)	-19(3)
O(1)	225(10)	517(14)	174(11)	-12(10)	67(9)	-18(10)
O(2)	245(10)	230(11)	243(11)	-85(9)	72(8)	-102(9)
O(3)	89(9)	382(12)	205(11)	-71(9)	-4(8)	-28(9)
O(4)	94(9)	311(11)	188(10)	-50(9)	-31(8)	-3(9)
O(5)	197(11)	697(17)	243(12)	143(12)	-46(9)	85(12)
O(6)	303(11)	320(12)	208(11)	-99(9)	-6(9)	68(10)
N(1)	120(11)	120(11)	126(11)	9(9)	-11(9)	5(9)
N(2)	129(11)	156(11)	102(11)	6(9)	-9(9)	-6(9)
C(1)	319(17)	277(17)	150(15)	-33(12)	20(12)	36(14)
C(2)	267(16)	211(15)	174(15)	-59(11)	-5(12)	5(12)
C(3)	187(14)	161(14)	210(15)	-41(11)	19(11)	-9(12)
C(4)	137(13)	136(13)	133(13)	13(10)	4(10)	0(11)
C(5)	164(14)	157(13)	181(14)	20(11)	9(12)	-22(12)
C(6)	185(15)	331(17)	189(16)	12(12)	-9(12)	-21(13)
C(7)	91(13)	232(14)	183(14)	3(11)	1(11)	10(12)
C(8)	85(12)	170(13)	177(14)	-1(11)	-11(10)	41(11)
C(9)	113(13)	179(14)	165(14)	30(11)	-5(11)	34(11)
C(10)	138(13)	101(12)	170(14)	2(11)	-11(11)	-13(11)
C(11)	80(12)	172(13)	162(14)	26(11)	1(10)	-31(11)
C(12)	105(12)	179(13)	154(14)	2(11)	10(10)	-2(11)
C(13)	185(14)	244(15)	193(14)	-12(12)	-6(12)	36(13)
C(14)	130(13)	172(14)	140(14)	37(11)	-5(11)	-4(11)
C(15)	166(14)	146(13)	120(13)	-7(10)	3(11)	-9(11)
C(16)	160(14)	269(16)	168(14)	14(12)	-3(12)	20(12)
C(17)	199(14)	298(16)	149(14)	25(12)	-13(12)	-64(13)
C(18)	321(16)	273(16)	123(13)	-38(12)	29(13)	-81(15)

Chapter 3

Enantioselective Total Synthesis of C_2-Symmetric Dihydrooxepine-Containing Epipolythiodiketopiperazine Natural Products and Progress Toward MPC1001B

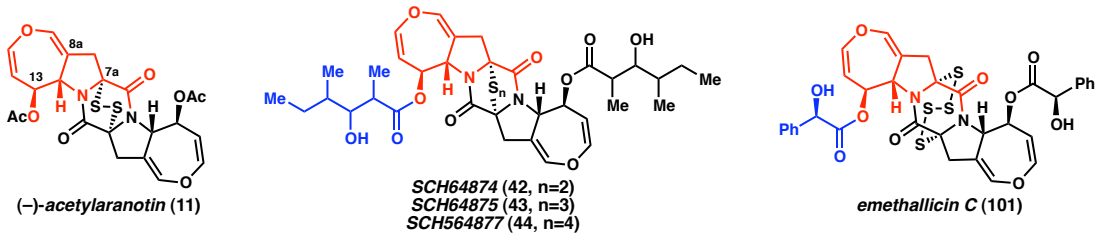
3.1 INTRODUCTION

Having completed an enantioselective total synthesis of acetylaranotin (**11**),[1] and in doing so developed a strategy towards the synthesis of dihydrooxepine-containing ETP natural products, our attention turned to the extention of this strategy to the preparation of related targets. These efforts have culminated in the synthesis of a small panel of epitetrathiodiketopiperazines, including natural products as well as analogs, which are currently being evaluated for biological activity. Furthermore, we have conducted preliminary investigations into the synthesis of dihydrooxepine-containing macrocycles, with a particular focus on the preparation of bis(*ortho*-methoxyaryl) ethers. Herein, a detailed account of these endeavors is presented.

3.2 C_2-SYMMETRIC DIHYDROOXEPINE-CONTAINING EPIPOLYTHIODIKETOPIPERAZINE NATURAL PRODUCTS

With access to tetrasulfide diol **197**, our successful completion of the total synthesis of acetylaranotin (**11**) left us well-positioned for preparation of related C_2-symmetric dihydrooxepine-containing ETP natural products, such as SCH64874 (**42**), SCH64877 (**44**),[2] and emethallicin C (**101**)[3] (see Figure 3.1). We anticipated that the successful preparation of these natural products and related unnatural analogs might allow for a more comprehensive understanding of the role of their peripheral structure in biological target specificity and/or biophysical properties. Furthermore, a better understanding of structure/activity relationships might ultimately inform the synthesis of chemical probes for molecular target validation.

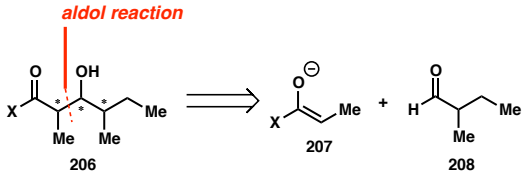
Figure 3.1. *C_2-Symmetric ETP natural products containing the dimeric aranotin core*



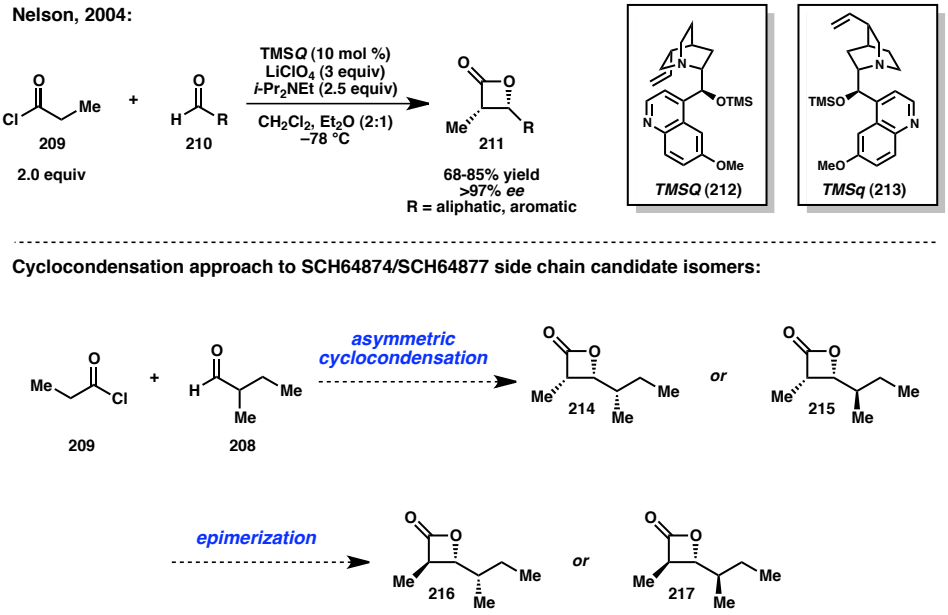
As the stereochemistry of the SCH sidechains was not disclosed in the original isolation report, we first sought to develop a divergent approach to access all eight isomers of 3-hydroxy-2,4-dimethylhexanoic acid derivatives (**206**). Classically, one might expect to form the desired stereotriad in a stereocontrolled manner using aldol chemistry (see Scheme 3.1). Nelson and coworkers have developed an enantioselective, organocatalytic cyclocondensation reaction for the preparation of β-lactones **211** from propionyl chloride (**209**) and aldehydes **210** (see Scheme 3.2),[4] which represents an

attractive variant of the aldol reaction. This transformation is appealing because in addition to possessing all of the required stereocenters, the β-lactones themselves could potentially serve as acylating agents for the formation of the various candidate isomers of SCH64874 (**42**) and SCH64877 (**44**).

Scheme 3.1. *Retrosynthetic analysis of the SCH64874 carboxylate side chain*



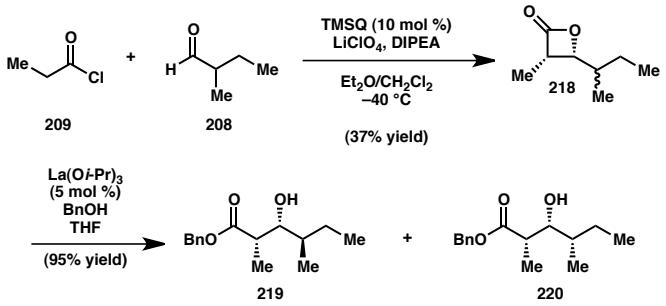
Scheme 3.2. *Enantioselective cyclocondensation reaction to provide β-lactones*



Our investigation began with the preparation of model 2,4-dimethyl-3-hydroxyhexanoate esters for spectroscopic analysis. To this end, synthetic studies commenced with the reaction between racemic 2-methylbutyraldehyde (**208**) and propionyl chloride (**209**) in the presence of quinidine-derived catalyst **212** (Scheme 3.3). The resulting mixture of enantioenriched β-lactone diastereomers (**218**) was then treated

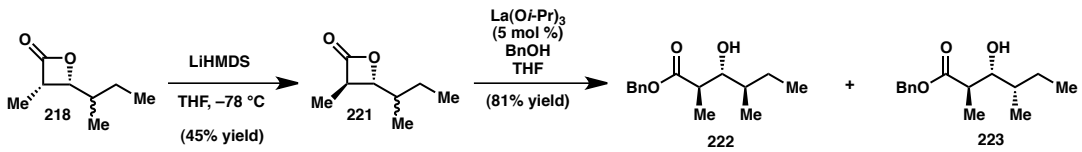
with excess benzyl alcohol in the presence of La(O*i*-Pr)$_3$ to afford the corresponding benzyl esters (**219** and **220**),[5] which could be readily separated by simple flash chromatography.

Scheme 3.3. *Synthesis of model syn,anti- and syn,syn- esters **219** and **220***



Likewise, epimerization of mixture **218** could be carried out with LiHMDS to formally give the *anti* aldol products (**221**), which could be converted to the benzyl esters **222** and **223** as before (Scheme 3.4). In this case, however, it was necessary to use preparative HPLC to separate the two diastereomers. Despite the low overall yields for these two routes, they allowed for rapid access to all four possible diastereomers of the 2,4-dimethyl-3-hydroxyhexanoate esters (**219**, **220**, **222**, and **223**) starting from inexpensive materials. Furthermore, the ability to use *either* the quinidine- or quinine-derived catalyst (**212** or **213**, respectively) provided access to either of the enantiomers of a particular ester.

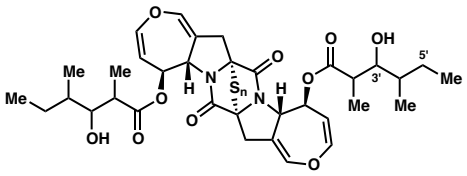
Scheme 3.4. *Synthesis of model anti,anti- and anti,syn- esters **222** and **223***

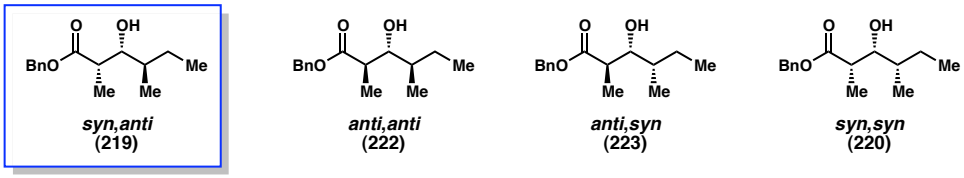


With isomers **219**, **220**, **222**, and **223** in hand, a comparison was made of their ^{1}H and ^{13}C NMR spectra to those for SCH64874 (**42**) and SCH64877 (**44**). The carboxylate

appendages shared by the natural products each contain three methine hydrogens, two methylene hydrogens, and nine methyl hydrogens. Inspection of the corresponding chemical shifts of the four benzyl esters reveals that there are three diagnostic shifts for each stereotriad: those of the β-methine (C(3')–H) and the δ-methylene (C(5')–H_a and C(5')–H_b) (see Table 3.1). As assigned by Hegde and coworkers, the chemical shift for C(3')–H is 3.72 ppm for SCH64874 (**42**) and 3.81 ppm for SCH64877 (**44**). On the other hand, the chemical shift for the down-field C(5')–H_a is 1.84 ppm (**42**) and 1.85 ppm (**44**), and that for the up-field C(5')–H_b is 1.24-1.25 ppm (**42**) and 1.13-1.10 ppm (**44**). The *anti*,*anti* diastereomer (**222**) can be ruled out, as its chemical shift for C(3')–H is too far up-field (3.39 ppm). Likewise, the chemical shift for C(5')–H_a in *anti*,*syn* diastereomer **223** is too far up-field (1.51-1.39 ppm), whereas the chemical shift for C(5')–H_b is too far down-field (1.33–1.23 ppm). Similarly, the chemical shift for C(5')–H_a in *syn*,*syn* diastereomer **220** is too far up-field (1.46-1.33 ppm). By contrast, the ^{1}H NMR data for *syn*,*anti* diastereomer **219** appear to be consistent with those of **42** and **44**. Furthermore, the ^{13}C shifts for the three methyl groups of **42** and **44** most closely match those of benzyl ester **219**. Taken together, these comparisons suggest that the SCH carboxylate side chain posseses the *syn*,*anti* configuration. Preliminary experiments revealed that the patterns described above are also observed when the individual carboxylates are coupled to the acetylaranotin core.

Table 3.1. *Comparison of relevant ^{1}H and ^{13}C NMR data for SCH64874 (**42**), SCH64877 (**44**), and model carboxylates **219**, **220**, **222**, and **223***





Important ^{1}H NMR Chemical Shifts (ppm) for 42, 44, 219, 222, 223, and 220

C#	SCH64874	SCH64877	219	222	223	220
1'	–	–	–	–	–	–
2'	2.67	2.8	2.72	2.77	2.69	2.72
3'	3.72	3.81	3.68	3.39	3.64	3.69
4'	1.49	1.5	1.50-1.41	1.44	1.51-1.39	1.46-1.33
5'	1.24-1.15	1.13-1.10	1.21-1.11	1.22-1.11	1.33-1.23	1.19-1.09
	1.84	1.85	1.77	1.62	1.51-1.39	1.46-1.33
6'	0.94	0.95	0.89	0.88	0.90	0.87
7'	1.17	1.28	1.20	1.26	1.18	1.23
8'	0.83	0.84	0.82	0.90	0.87	0.94

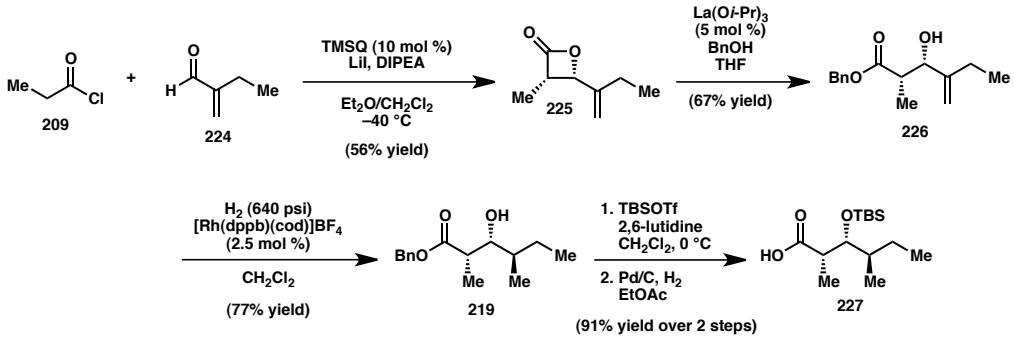
Important ^{13}C NMR Chemical Shifts (ppm) for 42, 44, 219, 222, 223, and 220

SCH64874	SCH64877	219	222	223	220
175.0	175.8	176.5	176.3	176.3	175.9
73.3	73.9	75.0	77.9	75.7	75.2
41.0	41.9	41.5	42.0	43.1	42.4
36.0	36.8	36.8	38.2	36.8	37.0
25.0	25.3	24.7	23.6	26.6	25.9
14.4	14.9	14.9	15.8	14.5	13.9
10.4	10.9	10.9	15.1	12.4	11.6
8.3	9.1	9.8	11.4	11.7	11.2

Though at this stage we were confident that we had identified the correct *relative* stereochemistry for the SCH carboxylate appendage, the question remained as to the *absolute* configuration. Furthermore, it was determined that benzyl ester **219** had only

been prepared in 60% *ee* using the sequence described above. We therefore sought to modify our sequence in such a way that it would provide not only diastereoselective access to either enantiomer of **219**, but also improved enantioselectivity. Inspired by Evans and coworkers' seminal studies on the hydroxyl-directed transformations of aldol adducts formed using chiral auxiliary technology,[6] we hypothesized that a directed hydrogenation approach might address the former challenge. Thus, in analogy to the synthesis of **219** and **220,** cyclocondensation between propionyl chloride (**209**) and 2-ethylacrolein (**224**) was carried out in the presence of quinidine-derived catalyst **212**, and the resulting β-lactone opened to give benzyl ester **226** (Scheme 3.5). Gratifyingly, at 82% ee, the optical activity of this material was substantially improved. Furthermore, directed hydrogenation using 2.5 mol % of Brown's catalyst under 640 psi of hydrogen afforded the desired hydroxy ester **219** as a 9:1 mixture of readily separable diastereomers. Alcohol **219** was converted to TBS-protected hydroxy acid **227** by a two-step sequence involving treatment with TBSOTf and 2,6-lutidine followed by hydrogenolysis of the benzyl ester. An identical sequence was employed using quinine-derived catalyst **213** to obtain ***ent*-227**.

Scheme 3.5. *Stereoselective synthesis of carboxylic acid **227***



With carboxylic acids **227** and ***ent*-227** in hand, what remained in the syntheses of the two putative SCH64877 candidates was the coupling of these fragments to the tetrasulfide diol core **197** and cleavage of the TBS ethers. Though the acid chloride derived from **227** and ***ent*-227** reacted sluggishly with **197**, it was ultimately determined that the desired ester formation could be accomplished using Yamaguchi's reagent[7] in the presence of DMAP and DIPEA in CH_2Cl_2 to afford dicarboxylate **228** (when **227** was used as the coupling partner, see Scheme 3.6). The final deprotection step was carried out using *aqueous* H_2SiF_6 in MeCN to afford a product that was found to be spectroscopically identical to SCH64877 (**44**). Synthesis of **229** (Figure 3.2) using an identical sequence but with ***ent*-227** as the coupling partner confirmed that this structure was inconsistent with the natural product.

Scheme 3.6. *Synthesis of SCH64877 (**44**)*

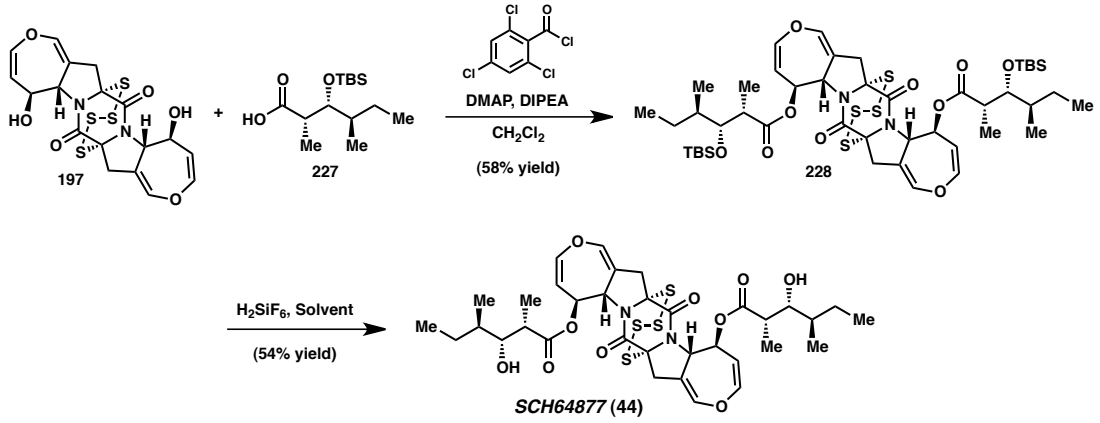
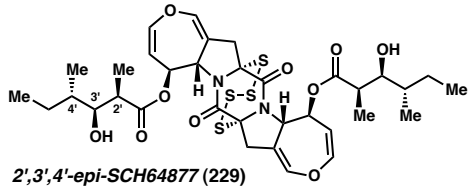
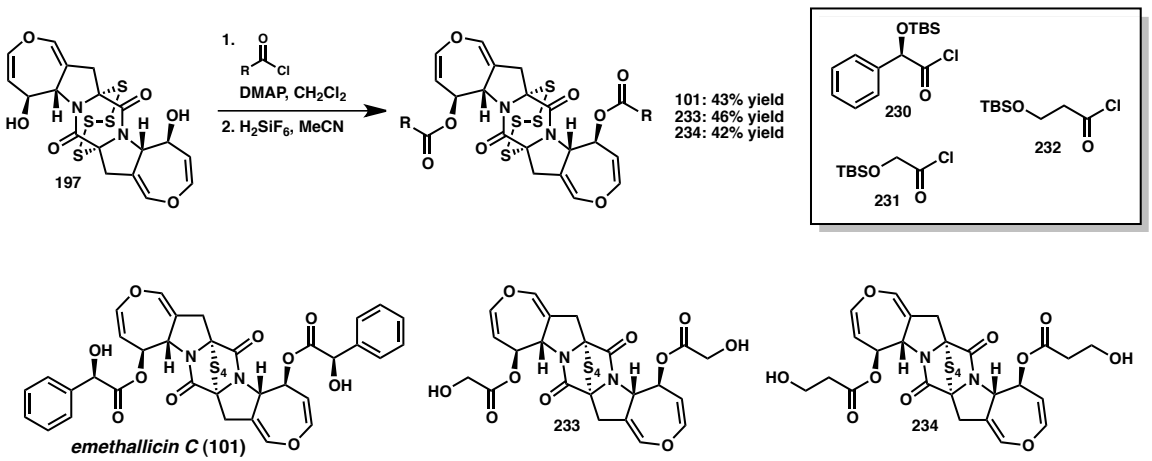


Figure 3.2. *Structure of 2′,3′,4′-epi-SCH64877 (**229**)*



Having completed a total synthesis and structural assignment of SCH64877 (**44**) (and with epimeric analog **229** in hand), we next set out to prepare emethallicin C (**101**) as well as several structural analogs, in order to complete our desired panel of epitetrathiodiketopiperazines for biological evaluation. The synthesis of emethallicin C (**101**), as well as bis(hydroxyacetate) **233** and bis(β-hydroxypropionate) **234**, could be accomplished by DMAP-promoted reaction of diol **197** with acid chlorides **230**,[8] **231**,[9] or **232**,[10] respectively, followed by subsequent removal of the TBS groups with H_2SiF_2 as described above (Scheme 3.7).

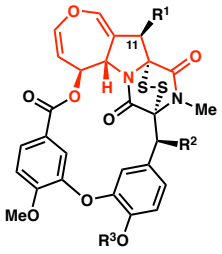
Scheme 3.7. *Synthesis of emethallicin C (**101**) and unnatural analogs **233** and **234***



3.3 MACROCYCLIC DIHYDROOXEPINE-CONTAINING EPIDITHIODIKETOPIPERAZINE NATURAL PRODUCTS

Whereas the intrinsic symmetry of molecules like acetylaranotin (**11**) and SCH84877 (**44**) simplifies their chemical synthesis, the extension of our synthetic strategy towards the macrocyclic structures of emestrin (**235**)[11] or the MPC1001 congeners (**13**, **236**, **237**, see Figure 3.3)[12] requires examination of a larger array of possible retrosynthetic disconnections.

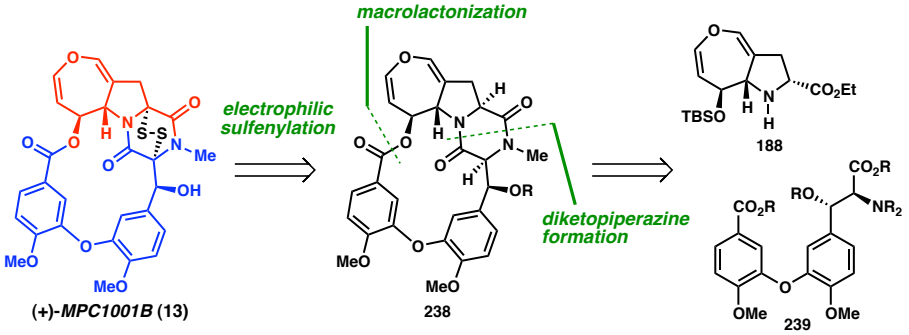
Figure 3.3. *Macrocyclic ETP natural products containing the aranotin monomer*



	R1	R2	R3
emestrin **(235)**	OH	OH	H
MPC1001 **(236)**	OH	OH	Me
MPC1001B **(13)**	**H**	**OH**	**Me**
MPC1001C **(237)**	OH	H	Me

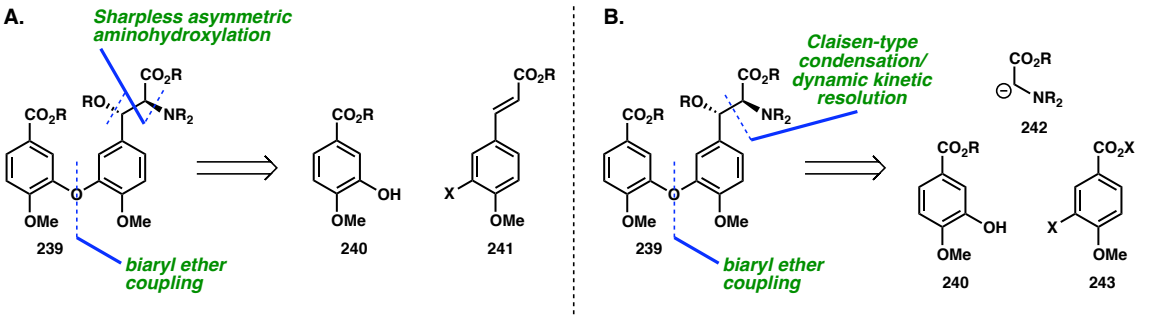
As it possesses the same oxidation pattern at C(11) as the monomer unit developed during our synthesis of C_2-symmetric dihydrooxepine-containing ETPs, our initial efforts towards accessing the macrocycles shown in Figure 3.3 have focused on MPC1001B (**13**).[13] Retrosynthetically, the most straightforward initial disconnection involves late-stage diketopiperazine sulfenylation, as in the synthesis of acetylaranotin (**11**) described in Chapter 2 (see Scheme 3.8). This would involve the intermediacy of macrocycle **238**, which can be further simplified to monomer unit **188** and biaryl ether-containing amino acid fragment **239**. The joining of these two fragments could conceivably be carried out via a stepwise diketopiperazine formation (as in Chapter 2), followed by macrolactonization.

Scheme 3.8. *Amino acid dimerization strategy for adjoining the northern and southern fragments*



Construction of biaryl ether amino acid fragment **239**[14] has been envisioned to proceed in one of two ways (see Scheme 3.9). In the first, Ullman-type coupling (or a variant thereof)[15] between a phenol **240** and halostyrene **241** would furnish the desired ether, while Sharpless asymmetric aminohydroxylation[16] would provide enantioselective access to the β-hydroxy amino acid moiety of **239**. Of course, depending on the coupling conditions employed, it might also be feasible to perform the aminohydroxylation prior to biaryl ether formation. Alternatively, the β-hydroxy amino acid moiety might be formed via condensation of a glycine-derived nucleophile **242** and carboxylic acid derivative **243** (or a biaryl ether-containing derivative), followed by dynamic kinetic resolution to obtain the desired stereochemistry at the benzylic position.[17,18]

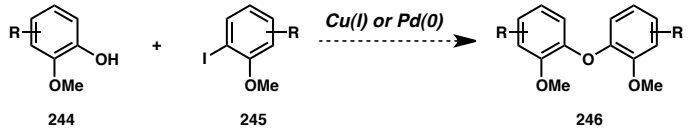
Scheme 3.9. *Strategies for constructing biaryl ether amino acid **239***



Pivotal to these or any other strategies for the synthesis of MPC1001B (**13**) is the ability to successfully carry out the biaryl ether coupling to form a bis(*ortho*-methoxyaryl) ether. There is generally a lack of literature regarding the formation of such structural motifs, and indeed our preliminary efforts in this regard were largely met with failure. Attempts at coupling *ortho*-methoxy aryl iodides with *ortho*-methoxy phenols using a variety of transition metal catalysts suffered either from negligible conversion or substrate protodehalogenation (see Scheme 3.10).[19] Likewise, attempts at Evans-Chan-

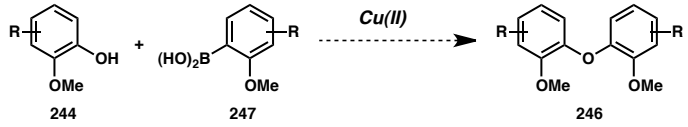
Lam-type coupling between *ortho*-methoxy aryl boronic acids and *ortho*-methoxy phenols were plagued by substrate protodeborylation.[20]

Scheme 3.10. *Unsuccessful approaches to the construction of bis(ortho-methoxyaryl) ethers (**246**)*



Conditions Attempted:

CuI, Cs_2CO_3, TMHD, DMF, 120 °C
Cu_2O, pyridine, reflux
$CuBr{\cdot}SMe_2$, K_2CO_3, pyridine, MeCN, 75 °C
CuI, picolinic acid, K_3PO_4, DMSO, 100 °C
$Pd(OAc)_2$, di(*t*-Bu)XPhos (or *t*-BuBrettPhos), K_3PO_4, PhMe, 100 °C



Conditions Attempted:

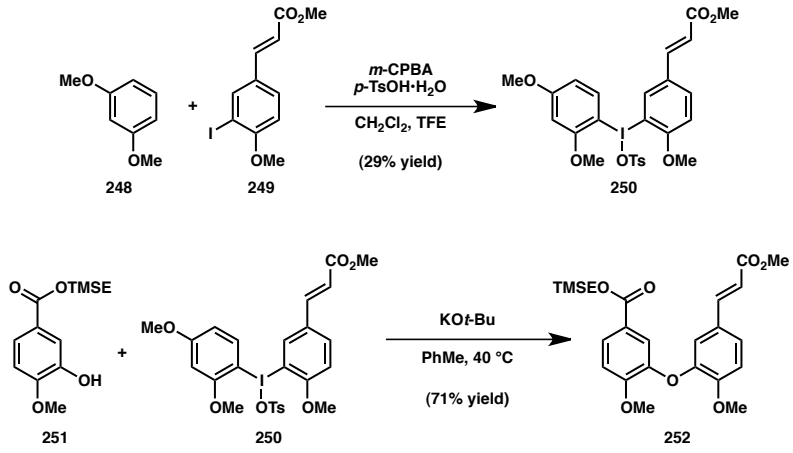
$Cu(OAc)_2$, base (Et_3N, pyridine, pyrazine, DMAP, etc.), CH_2Cl_2, 4ÅMS

Recently, diaryl iodonium salts have received much attention as highly reactive electrophiles for a variety of transition metal-mediated processes.[21] In fact, Olofsson and coworkers have demonstrated that such iodonium reagents can undergo coupling with phenols under very mild, transition metal-free conditions.[22] These reports have suggested that *para*-methoxyphenyl ligands on the I(III) center are electronically disfavored for transfer to nucleophiles. Furthermore, Pike and coworkers have demonstrated that although *ortho*-substituted aryl ligands are generally *more* favorable for transfer to nucleophiles relative to unsubstituted ligands,[23] *ortho*-methoxy ligands are the exception to this rule (being highly disfavored for transfer).[24] We therefore reasoned that an *ortho*,*para*-dimethoxyphenyl ligand might be an excellent non-transferable ligand, allowing for selective transfer of a less electron-rich *ortho*-methoxy ligand that is more

appropriately functionalized for advancement to the southern amino acid fragment of MPC1001B.

To test the above hypothesis, iodonium tosylate **250** was synthesized from aryl iodide **249** and 1,3-dimethoxybenzene (**248**) via oxidation in the presence of *m*-CPBA and *p*-TsOH•H_2O in CH_2Cl_2/TFE (see Scheme 3.11).[25] In the event, we observed that **250** readily underwent coupling with *ortho*-methoxy phenol **251** in the presence of KO*t*-Bu in PhMe at 40 °C, providing biaryl ether **252** in 69% yield. Ongoing efforts are focused on the application of this chemistry to the synthesis of MPC1001B (**13**).

Scheme 3.11. *Synthesis and biaryl ether coupling of iodonium tosylate* ***250***



3.4 CONCLUDING REMARKS

We have successfully prepared a panel of epitetrathiodiketopiperazines, which includes the natural products SCH64877 (**44**) and emethallicin C (**101**), as well as several structural analogs (**229**, **233**, **234**) and previously described intermediates (diol **197**, diacetate **205**). These efforts involved elucidation of the stereochemical configuration of the carboxylate appendages of **44**, which was accomplished via rapid synthesis of four model esters using an acid chloride/aldehyde cyclocondensation strategy. Ongoing

efforts include the biological screening of these tetrasulfides in both cell viability and biochemical assays, with the goal of comprehensively examining structure-activity relationships. Though our studies toward the synthesis of MPC1001B (**13**) and related molecules are still preliminary, further development of the biaryl ether coupling reaction described above may ultimately allow for biological investigations of macrocyclic structures as well.

3.5 EXPERIMENTAL SECTION

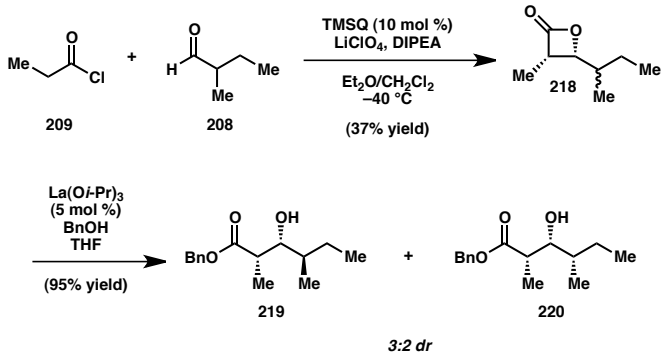
3.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. *N,N*-Diisopropylethamine (DIPEA) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[26] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^{1}H, δ = 7.26), MeCN (^{1}H, δ = 1.94), acetone (^{1}H, δ = 2.05), or DMSO (^{1}H, δ = 2.50), and $CDCl_3$ (^{13}C, δ = 77.0), MeCN (^{13}C, δ = 118.26), acetone-d_6 (^{13}C, δ = 206.26) or DMSO (^{13}C, δ = 40.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, 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. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm) or an Agilent Zorbax RX-SIL 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.

3.5.2 Preparative Procedures and Spectroscopic Data

Preparation of benzyl esters 219 and 220



Preparation of β-lactone 218: In a glovebox under an N_2 atmosphere, a flame-dried round-bottom flask equipped with a magnetic stir bar was charged with anhydrous $LiClO_4$ (4.64 g, 43.6 mmol). The vessel was then sealed with a septum cap, removed from the glovebox, and placed under a positive pressure of N_2. Et_2O (13 mL) was then added, and the mixture was stirred vigorously until the $LiClO_4$ had completely dissolved.

To this solution was added a solution of TMSQ (**212**, 525 mg, 1.32 mmol) in CH_2Cl_2 (26 mL) via syringe, and the mixture was cooled to –40 °C. DIPEA (5.53 mL, 33.0 mmol) was then added dropwise, followed by 2-methylbutyraldehyde (**208**, 1.41 mL, 13.2 mmol). Finally, a solution of propionyl chloride (**209**, 2.31 mL, 26.4 mmol) in CH_2Cl_2 (6.6 mL) was added dropwise over 6 h (using a syringe pump). The resulting solution was allowed to stir overnight at –40 °C before being diluted with Et_2O and filtered through a plug of SiO_2, eluting with excess Et_2O and concentrating to afford a crude oil. Purification via column chromatography (gradient elution, 16:1→8:1 pentanes–Et_2O) afforded β-lactone **218** (686 mg, 37% yield, mixture of diastereomers) as a clear, colorless oil.

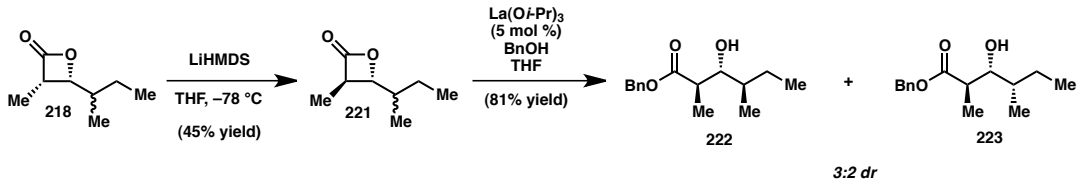
Preparation of benzyl esters 219 and 220: In a glovebox, a 20-mL scintillation vial equipped with a magnetic stir bar was charged with La(O*i*-Pr)$_3$ (29 mg, 0.092 mmol), then sealed with a septum cap, removed from the glovebox, and placed under a positive pressure of N_2. A solution of β-lactone **218** (300 mg, 2.11 mmol) and benzyl alcohol (952 μL, 9.2 mmol) in 9.2 mL of THF was then added via syringe, and the resulting mixture was stirred vigorously for 48 h. The reaction mixture was then diluted with sat. *aq*. NH_4Cl and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the resulting crude oil was purified via flash chromatography (gradient elution, 0→15% hexanes–EtOAc) to afford diastereomerically pure benzyl esters **219** (207 mg, 39% yield) and **220** (131 mg, 25% yield) as well as 164 mg (31% yield) of a 1:1 mixture of **219** and **220**.

219 (syn,anti)[27]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 5.15 (s, 2H), 3.68 (ddd, *J* = 8.4, 3.1, 3.1 Hz, 1H), 2.72 (qd, *J* = 7.2, 3.1 Hz, 1H), 2.52 (d, *J* = 3.7 Hz,

1H), 1.77 (dqd, *J* = 13.3, 7.6, 3.1 Hz, 1H), 1.50 – 1.41 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.21 – 1.11 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 135.7, 128.6, 128.3, 128.1, 75.0, 66.4, 41.5, 36.8, 24.7, 14.9, 10.9, 9.8; IR (NaCl/thin film): 3503, 3066, 3033, 2964, 2935, 2877, 1730, 1498, 1456, 1382, 1330, 1259, 1176, 1110, 1079, 1054, 1029, 971, 916, 751 cm^{-1}; HRMS (ESI) calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1642. (60% *ee*, as determined by conversion to the Mosher ester using (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride followed by NMR analysis).

220 (syn,syn): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 5.14 (s, 2H), 3.69 (ddd, *J* = 5.9, 4.7, 4.7 Hz, 1H), 2.72 (qd, *J* = 7.1, 5.3 Hz, 1H), 2.20 (d, *J* = 4.8 Hz, 1H), 1.46 – 1.33 (m, 2H), 1.23 (d, *J* = 7.1 Hz, 3H), 1.19 – 1.09 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 135.8, 128.6, 128.3, 128.1, 75.2, 66.3, 42.4, 37.0, 25.9, 13.9, 11.6, 11.2; IR (NaCl/thin film): 3497, 3066, 3034, 2963, 2935, 2877, 1730, 1498, 1456, 1380, 1336, 1261, 1167, 1109, 1052, 1028, 991, 957, 916, 752 cm^{-1}; HRMS (ESI) calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1647.

Preparation of benzyl esters 222 and 223



Preparation of β-lactone 221: In a flame-dried round-bottom flask, β-lactone **218** (193 mg, 1.36 mmol) was dissolved in 27 mL THF. The resulting solution was cooled to –78 °C with stirring and treated with LiHMDS (1.0 M solution in THF, 2.7 mL,

2.7 mmol). After 15 min, the reaction was quenched with 30 mL sat. *aq*. NH_4Cl, and allowed to warm to ambient temperature. The mixture was then extracted with Et_2O (60 mL, then 2x30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford the crude product as a clear oil. Purification via flash chromatography (gradient elution, 16:1→4:1 pentanes–Et_2O) afforded β-lactone **221** (87.8 mg, 45% yield, mixture of diastereomers) as a clear, colorless oil.

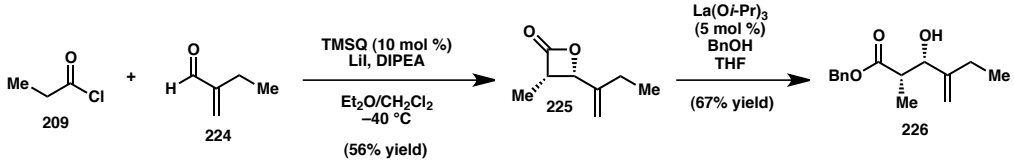
Preparation of benzyl esters 222 and 223: In a glovebox, a 20-mL scintillation vial equipped with a magnetic stir bar was charged with La(O*i*-Pr)$_3$ (9.2 mg, 0.029 mmol), then sealed with a septum cap, removed from the glovebox, and placed under a positive pressure of N_2. A solution of β-lactone **221** (82.3 mg, 0.579 mmol) and benzyl alcohol (300 μL, 2.90 mmol) in 2.9 mL of THF was then added via syringe, and the resulting mixture was stirred vigorously for 48 h. The reaction mixture was then diluted with sat. *aq*. NH_4Cl and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the resulting crude oil was purified via flash chromatography (gradient elution, 8:1→4:1 pentanes–Et_2O) to afford benzyl esters **222** and **223** (118 mg, 81% yield) as a 3:2 mixture of diastereomers. Diastereomerically pure materials could be obtained via preparative HPLC (normal phase, gradient elution, 5→7.5% EtOAc in hexanes).

222 (anti,anti)[28]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 5.15 (s, 2H), 3.39 (ddd, *J* = 8.0, 5.9, 5.9 Hz, 1H), 2.77 (qd, *J* = 7.2, 5.4 Hz, 1H), 2.58 (d, *J* = 8.1 Hz, 1H), 1.62 (dqd, *J* = 13.4, 7.5, 3.2 Hz, 1H), 1.44 (ddqd, *J* = 9.9, 6.7, 6.7, 3.3 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.22 – 1.11 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 135.7, 128.6, 128.3, 128.1, 77.9, 66.3, 42.0,

38.2, 23.6, 15.8, 15.1, 11.4; IR (NaCl/thin film): 3523, 3034, 2963, 2935, 2876, 1719, 1498, 1456, 1383, 1351, 1261, 1166, 1043, 996, 958, 750 cm^{-1}; HRMS (ESI) calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1643.

223 (anti,syn): ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 5.16 (s, 2H), 3.64 (ddd, *J* = 7.7, 6.3, 3.5 Hz, 1H), 2.69 (dq, *J* = 7.3, 7.3 Hz, 1H), 2.41 (d, *J* = 6.4 Hz, 1H), 1.51 – 1.39 (m, 2H), 1.33 – 1.23 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 135.8, 128.6, 128.3, 128.1, 75.7, 66.4, 43.1, 36.8, 26.6, 14.5, 12.4, 11.7; IR (NaCl/thin film): 3514, 3034, 2963, 2935, 2877, 1728, 1498, 1456, 1383, 1351, 1311, 1262, 1166, 1037, 991, 958, 750 cm^{-1}; HRMS (ESI) calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1642.

Preparation of benzyl ester 226



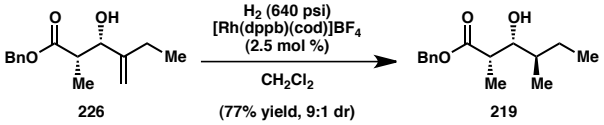
Preparation of β-lactone 225: In a glovebox under an N_2 atmosphere, a flame-dried round-bottom flask equipped with a magnetic stir bar was charged with anhydrous LiI (402 mg, 3.00 mmol). The vessel was then sealed with a septum cap, removed from the glovebox, and placed under a positive pressure of N_2. To the flask was added a solution of TMSQ (**212**, 59 mg, 0.150 mmol) in 4.7 mL CH_2Cl_2, followed by 0.53 mL Et_2O. The resulting mixture was stirred vigorously until all of the LiI had dissolved, and then cooled to –40 °C. DIPEA (628 μL, 3.75 mmol) was then added dropwise, followed by 2-ethylacrolein (**224**, 85 wt%, 173 μL, 1.5 mmol). Finally, a solution of propionyl chloride (**209**, 328 μL, 3.75 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over 2 h

(using a syringe pump). The resulting solution was allowed to stir for an additional 3 h before being diluted with Et_2O and filtered through a plug of SiO_2, eluting with excess Et_2O and concentrating to afford a crude oil. Purification via column chromatography (gradient elution, 24:1→8:1 pentanes–Et_2O) afforded β-lactone **225** (149 mg, corrected for Et_2O contamination to 117 mg, 56% yield) as a clear, colorless, and volatile oil.

Preparation of benzyl ester 226: In a glovebox, a 20-mL scintillation vial equipped with a magnetic stir bar was charged with La(O*i*-Pr)$_3$ (13 mg, 0.042 mmol), then sealed with a septum cap, removed from the glovebox, and placed under a positive pressure of N_2. A solution of β-lactone **225** (117 mg, 0.835 mmol) and benzyl alcohol (433 μL, 4.18 mmol) in 4.2 mL of THF was then added via syringe, and the resulting mixture was stirred vigorously for 1.5 h. The reaction mixture was then diluted with sat. *aq*. NH_4Cl and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the resulting crude oil was purified via flash chromatography (gradient elution, 12:1→6:1 hexanes–EtOAc) to afford benzyl ester **226** (139 mg, 67% yield) as a clear, colorless oil. $[\alpha]_D^{25.0} = -14.1°$ (*c* = 1.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.12 (dddd, *J* = 1.3, 1.3, 1.3, 1.3 Hz, 1H), 4.95 (dddd, *J* = 1.5, 1.5, 1.5, 1.5 Hz, 1H), 4.48 (d, *J* = 3.6 Hz, 1H), 2.73 (qd, *J* = 7.2, 4.0 Hz, 1H), 2.43 (s, 1H), 2.07 – 1.90 (m, 2H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 149.6, 135.7, 128.6, 128.3, 128.2, 109.7, 74.1, 66.5, 42.5, 25.0, 12.1, 10.3; IR (NaCl/thin film): 3488, 3090, 3066, 3034, 2967, 2939, 2880, 1734, 1648, 1498, 1456, 1382, 1340, 1257, 1213, 1174, 1123, 1081, 1063, 1028, 991, 955, 904, 752 cm^{-1}; HRMS (ESI) calc'd for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1485, found 249.1489. (82% *ee*, as determined by conversion

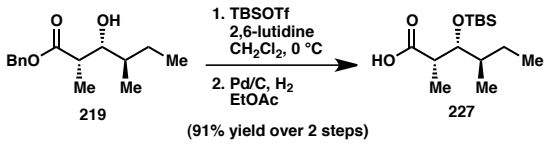
to the Mosher ester using (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride followed by NMR analysis). The opposite enantiomer (***ent*-226)** was prepared via an analogous sequence using TMSq (**213**) as the cyclocondensation catalyst. $[\alpha]_D^{25.0}$ = +14.6 ° (*c* = 1.38, $CHCl_3$).

Diastereoselective preparation of benzyl ester 219



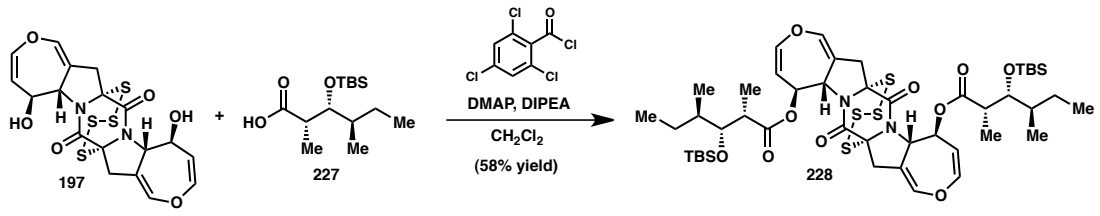
In a glovebox under a N_2 atmosphere, a stainless steel autoclave lined with a glass insert and equipped with a magnetic stir bar was charged with a solution of allylic alcohol **226** (66.7 mg, 0.269 mmol) and $[Rh(dppb)(cod)]BF_4$ (4.9 mg, 6.76 μmol) in 9.7 mL CH_2Cl_2. The apparatus was then sealed, removed from the glovebox, and connected to a high-pressure hydrogen inlet. The vessel was pressurized to 200 psi with H_2, then carefully vented, and this process was repeated once more before pressurizing to a final H_2 pressure of 640 psi. The reaction was allowed to proceed with stirring behind a blast shield for 22 h, at which time it was carefully vented, and the reaction mixture was filtered through a plug of SiO_2, eluting with 1:1 hexanes–EtOAc. Purification of the resulting crude mixture (9:1 dr) via flash chromatography (gradient elution, 0→15% EtOAc in hexanes) afforded benzyl ester **219** (52.1 mg, 77% yield) as a clear, colorless oil. $[\alpha]_D^{25.0}$ = –4.38 ° (*c* = 1.30, $CHCl_3$). ***Ent*-219** : $[\alpha]_D^{25.0}$ = +4.20° (*c* = 0.997, $CHCl_3$).

Preparation of carboxylic acid 227



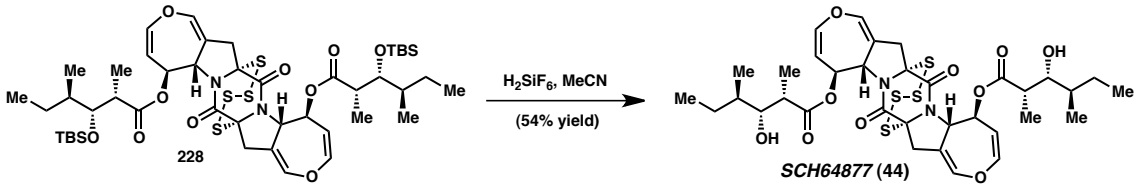
A solution of benzyl ester **219** (51.6 mg, 0.206 mmol) in 4.1 mL of CH_2Cl_2 was cooled to 0 °C with stirring under a N_2 atmosphere. 2,6-lutidine (72 μL, 0.62 mmol) was then added followed by TBSOTf (71 μL, 0.31 mmol). After 2 h, the reaction mixture was quenched with a small amount of MeOH, diluted with sat. *aq*. $NaHCO_3$, and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude intermediate was then dissolved in 4.1 mL EtOAc and Pd/C (10 wt % Pd, 28.4 mg) was added. The resulting suspension was sealed with a septum cap, and the headspace purged with N_2. After 5 min, the headspace was purged with H_2 (for 5 min), and then left under a balloon of H_2 for 1 h. The headspace was once more purged with N_2, and the reaction mixture was filtered through celite, rinsing with excess EtOAc, and concentrated to afford carboxylic acid **227** (51.6 mg, 91% yield) as a clear, colorless oil. $[\alpha]_D^{25.0}$ = +4.31 ° (*c* = 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.48 (s, 1H), 3.92 (dd, *J* = 4.9, 4.9 Hz, 1H), 2.63 (qd, *J* = 7.0, 4.7 Hz, 1H), 1.58 – 1.46 (m, 2H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.14 – 1.02 (m, 1H), 0.92 – 0.86 (m, 15H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.8, 76.7, 42.6, 40.1, 26.0, 24.9, 18.3, 15.3, 12.0, 11.9, -4.3, -4.3; IR (NaCl/thin film): 2959, 2930, 2883, 2858, 1708, 1472, 1463, 1412, 1383, 1361, 1283, 1252, 1117, 1091, 1059, 1020, 1005, 938, 894, 836, 810, 774 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{14}H_{29}O_3Si$ $[M–H]^-$ 273.1891, found 273.1893. ***Ent*-227**: $[\alpha]_D^{25.0}$ = –5.78 ° (*c* = 0.960, $CHCl_3$).

Preparation of bis(*tert*-butyldimethylsilyl) SCH64877 (228)



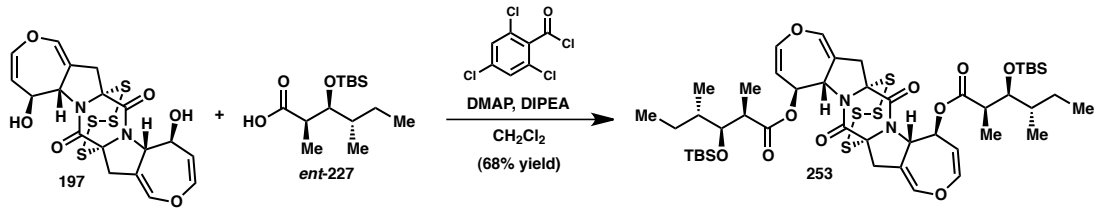
In a 1-dram vial, carboxylic acid **227** (52.4 mg, 0.191 mmol) was dissolved in a stock solution of DIPEA (43.2 μL, 0.248 mmol) in CH_2Cl_2 (0.48 mL), solid DMAP (117 mg, 0.955 mmol) was added, and the mixture was swirled until homogeneous. A stock solution of Yamaguchi's reagent (35.8 μL, 0.229 mmol) in CH_2Cl_2 (0.48 mL) was then added, and the resulting mixture was swirled until homogeneous and allowed to sit. After 10 min, the resulting acylating solution was added to a 1-dram vial containing a magnetic stir bar and solid diol **197** (18.5 mg, 0.0382 mmol). The resulting solution was capped and stirred for 20 h. The reaction mixture was then diluted with sat. *aq*. $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, then filtered through SiO_2, eluting with 3:1 hexanes–EtOAc. The resulting crude material was purified via flash chromatography (gradient elution, 8:1→4:1 hexanes–EtOAc) to afford dicarboxylate **228** (22.0 mg, 58% yield) as a white, amorphous solid. $[\alpha]_D^{25.0} = -306$ ° (*c* = 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (dd, *J* = 2.1, 2.1 Hz, 2H), 6.26 (dd, *J* = 8.2, 2.3 Hz, 2H), 5.29 (dddd, *J* = 8.5, 1.8, 1.8, 1.8 Hz, 2H), 5.19 (ddd, *J* = 8.5, 2.2, 2.2 Hz, 2H), 4.60 (dd, *J* = 8.2, 2.0 Hz, 2H), 4.12 (dd, *J* = 4.5, 4.5 Hz, 2H), 3.36 (ddd, *J* = 16.5, 2.2, 2.2 Hz, 2H), 3.06 (d, *J* = 16.3 Hz, 2H), 2.70 (qd, *J* = 7.2, 4.5 Hz, 2H), 1.56 – 1.45 (m, 4H), 1.30 (d, *J* = 7.2 Hz, 6H), 1.17 – 1.07 (m, 2H), 0.97 – 0.80 (m, 30H), 0.10 (s, 6H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 165.3, 139.6, 138.6, 108.2, 106.1, 75.6, 74.7, 70.9, 60.8, 42.8, 41.7, 40.6, 26.1, 25.0, 18.4, 15.7, 12.7, 12.1, -3.9, -4.3; IR (NaCl/thin film): 3369, 2957, 2928, 2855, 1731, 1698, 1462, 1366, 1343, 1302, 1276, 1250, 1235, 1213, 1185, 1136, 1117, 1093, 1055, 971, 938, 895, 863, 836, 815, 774, 737, 721 cm^{-1}; HRMS (ESI) calc'd for $C_{32}H_{43}N_2O_7S_4Si$ $[M–C_{14}H_{29}O_3Si]^+$ 723.1717, found 723.1717 (detected fragment has undergone loss of one of the carboxylate side chains).

Preparation of SCH64877 (44)



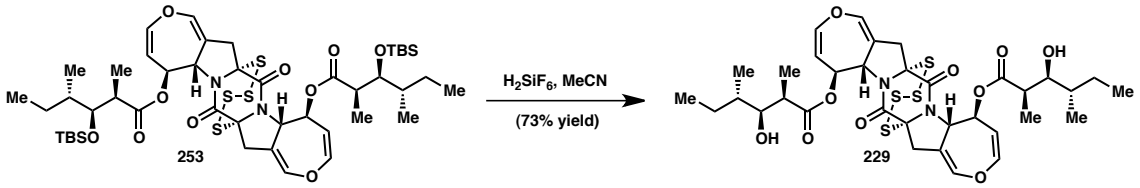
A 1-dram vial equipped with a magnetic stir bar was charged with bis(*tert*-butyldimethylsilylether) **228** (22.0 mg, 0.0221 mmol), followed by MeCN (2 mL) and H_2SiF_6 (20-25 wt % *aq*. solution, 100 μL). The resulting suspension was stirred vigorously (with occasional shaking to ensure exposure of material to the reaction medium) for 24 h, then quenched with sat. *aq*. $NaHCO_3$, and extracted with EtOAc (5x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The material was then purified via preparative HPLC (reverse phase, gradient elution, 60→95% MeCN in H_2O) to afford SCH64877 (**44**, 9.2 mg, 54% yield) as a white, amorphous solid. $[\alpha]_D^{25.0}$ = –411 ° (*c* = 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 1.8, 1.8 Hz, 2H), 6.28 (dd, *J* = 8.4, 1.9 Hz, 2H), 5.30 (s, 4H), 4.59 (dd, *J* = 8.3, 1.2 Hz, 2H), 3.81 (ddd, *J* = 9.5, 2.1, 2.1 Hz, 2H), 3.37 (ddd, *J* = 16.4, 2.5, 1.2 Hz, 2H), 3.11 (d, *J* = 16.7 Hz, 2H), 3.06 (d, *J* = 3.4 Hz, 2H), 2.79 (qd, *J* = 7.2, 1.8 Hz, 2H), 1.84 (dqd, *J* = 13.5, 7.6, 3.1 Hz, 2H), 1.56 – 1.47 (m, 2H), 1.27 (d, *J* = 7.3 Hz, 6H), 1.25 – 1.16 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 6H), 0.85 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 165.9, 139.9, 138.9, 108.0, 105.8, 75.4, 73.9, 70.9, 60.9, 41.9, 41.5, 36.7, 25.3, 14.9, 10.8, 9.1; IR (NaCl/thin film): 3529, 2962, 2929, 2874, 1719, 1693, 1457, 1370, 1343, 1301, 1279, 1243, 1183, 1136, 1052, 972, 739, 722 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{34}H_{44}ClN_2O_{10}S_4$ $[M+Cl]^-$ 803.1573, found 803.1574.

Preparation of bis(*tert*-butyldimethylsilyl) 2',3',4'-*epi*-SCH64877 (253)



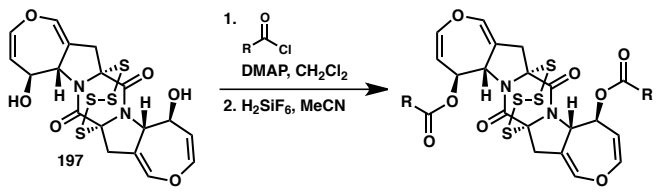
Following an analogous procedure to that for the conversion of **197** to **228**, coupling of diol **197** (9.27 mg, 0.0192 mmol) and carboxylic acid ***ent*-227** (26.3 mg, 0.0960 mmol) afforded dicarboxylate **253** (13.1 mg, 68% yield) as a white, amorphous solid. $[\alpha]_D^{25.0}$ = –336 ° (*c* = 0.655, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (ddd, *J* = 2.5, 2.5, 1.3 Hz, 2H), 6.26 (dd, *J* = 8.3, 2.2 Hz, 2H), 5.31 – 5.26 (m, 2H), 5.22 (ddd, *J* = 8.4, 2.1, 2.1 Hz, 2H), 4.60 (dd, *J* = 8.2, 1.9 Hz, 2H), 3.96 (dd, *J* = 6.0, 3.9 Hz, 2H), 3.35 (ddd, *J* = 16.5, 2.2, 2.2 Hz, 2H), 3.05 (ddd, *J* = 16.4, 1.2, 1.2 Hz, 2H), 2.75 (dd, *J* = 7.2, 6.0 Hz, 2H), 1.63 – 1.53 (m, 2H), 1.53 – 1.44 (m, 2H), 1.26 (d, *J* = 7.0 Hz, 6H), 1.18 – 1.07 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 6H), 0.91 (t, *J* = 7.3 Hz, 6H), 0.90 (s, 18H), 0.08 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 165.4, 139.7, 138.7, 108.3, 105.9, 76.5, 75.5, 70.7, 61.0, 42.7, 41.7, 40.8, 26.1, 24.5, 18.4, 15.9, 13.8, 12.3, -3.8, -3.9; IR (NaCl/thin film): 3364, 2957, 2929, 2881, 2856, 1721, 1697, 1463, 1372, 1348, 1305, 1278, 1235, 1212, 1186, 1138, 1109, 1061, 1005, 973, 866, 835, 815, 775, 738, 718 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{32}H_{43}N_2O_7S_4Si$ $[M–C_{14}H_{29}O_3Si]^+$ 723.1717, found 723.1714 (detected fragment has undergone loss of one of the carboxylate side chains).

Preparation of 2',3',4'-*epi*-SCH64877 (229)



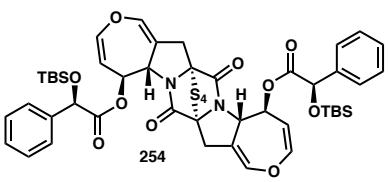
Following an analogous procedure to that for the conversion of **228** to **44**, deprotection of bis(*tert*-butyldimethylsilyl) ether **253** (13.1 mg, 0.0131 mmol) afforded 2',3',4'-*epi*-SCH64877 (**229**, 7.4 mg, 73% yield) as a pale yellow, amorphous solid. $[\alpha]_D^{25.0} = -357$ ° (*c* = 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (ddd, *J* = 2.5, 2.5, 0.9 Hz, 2H), 6.27 (dd, *J* = 8.3, 2.3 Hz, 2H), 5.32 (dddd, *J* = 8.5, 2.8, 1.7, 1.7 Hz, 2H), 5.24 (ddd, *J* = 8.5, 2.1, 2.1 Hz, 2H), 4.61 (dd, *J* = 8.2, 1.9 Hz, 2H), 3.84 (d, *J* = 8.8 Hz, 2H), 3.37 (ddd, *J* = 16.5, 2.2, 2.2 Hz, 2H), 3.08 (ddd, *J* = 16.6, 1.2, 1.2 Hz, 2H), 2.77 (qd, *J* = 7.2, 2.3 Hz, 2H), 2.73 (br s, 2H), 1.82 (dqd, *J* = 13.4, 7.5, 3.2 Hz, 2H), 1.55 – 1.46 (m, 2H), 1.27 (d, *J* = 7.2 Hz, 6H), 1.29 – 1.16 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 6H), 0.86 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 165.8, 139.8, 138.9, 108.0, 105.9, 75.5, 74.0, 71.0, 60.9, 42.1, 41.5, 37.1, 25.2, 15.1, 11.0, 9.5; IR (NaCl/thin film): 3503, 2962, 2929, 2874, 1726, 1695, 1457, 1369, 1344, 1301, 1279, 1184, 1135, 971, 738, 723 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{34}H_{44}ClN_2O_{10}S_4$ $[M+Cl]^-$ 803.1573, found 803.1563.

Typical procedure for the acylation of diol 197 using carboxylic acid chloride reagents



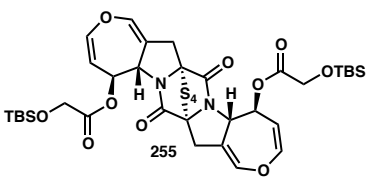
To a solution of diol **197** (8.74 mg, 0.0181 mmol) and DMAP (33.2 mg, 0.272 mmol) in 0.9 mL CH_2Cl_2 was added 0.9 mL (~0.181 mmol) of a stock solution of acid chloride **230** (0.320 mmol in 1.5 mL CH_2Cl_2). The resulting solution was stirred for 40 min, then diluted with sat. *aq*. $NaHCO_3$ and extracted with CH_2Cl_2 (3x). Each organic layer was individually passed through a plug of SiO_2, which was then flushed with excess 1:1 hexanes–EtOAc, and the resulting filtrate concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 4:1→2:1 hexanes–EtOAc) afforded dicarboxylate **254** (10.4 mg, 59% yield) as a white, amorphous solid.

Bis(*tert*-butyldimethylsilyl) emethallicin C (254)



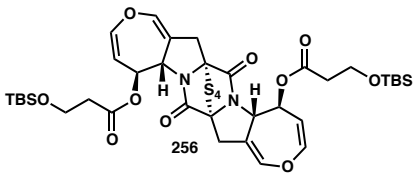
$[\alpha]_D^{25.0}$ = –307 ° (*c* = 0.520, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 4H), 7.39 – 7.34 (m, 4H), 7.32 – 7.28 (m, 2H), 6.55 (dd, *J* = 1.8, 1.8 Hz, 2H), 6.08 (dd, *J* = 8.2, 1.8 Hz, 2H), 5.34 (s, 2H), 5.27 – 5.20 (m, 4H), 4.16 (dd, *J* = 8.2, 1.4 Hz, 2H), 3.38 (ddd, *J* = 16.3, 2.5, 1.4 Hz, 2H), 3.13 (ddd, *J* = 16.3, 1.1, 1.1 Hz, 2H), 0.93 (s, 18H), 0.15 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 165.5, 139.7, 139.0, 138.7, 128.2, 128.0, 127.0, 108.0, 105.5, 75.7, 74.1, 71.2, 60.6, 41.7, 25.8, 18.4, -4.7, -4.7; IR (NaCl/thin film): 3369, 3066, 3033, 2952, 2927, 2855, 1752, 1696, 1659, 1472, 1364, 1341, 1301, 1252, 1174, 1134, 1073, 1006, 971, 907, 865, 837, 779, 729 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{46}H_{56}ClN_2O_{10}S_4Si_2$ $[M+Cl]^-$ 1015.2050, found 1015.2078.

Bis[α-(*tert*-butyldimethylsiloxy)acetate] 255



Following the procedure described above for the conversion of **197** to **254**, coupling of diol **197** (8.74 mg, 0.0181 mmol) and acid chloride **231** (0.181 mmol) afforded dicarboxylate **255** (10.0 mg, 67% yield). $[\alpha]_D^{25.0}$ = –262 ° (*c* = 0.500, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (ddd, *J* = 2.5, 2.5, 0.9 Hz, 2H), 6.27 (dd, *J* = 8.2, 2.2 Hz, 2H), 5.29 – 5.26 (m, 2H), 5.24 (ddd, *J* = 8.4, 2.0, 2.0 Hz, 2H), 4.69 (dd, *J* = 8.2, 1.8 Hz, 2H), 4.40 (d, *J* = 17.4 Hz, 2H), 4.35 (d, *J* = 17.4 Hz, 2H), 3.34 (ddd, *J* = 16.4, 2.2, 2.2 Hz, 2H), 3.06 (ddd, *J* = 16.3, 1.1, 1.1 Hz, 2H), 0.93 (s, 18H), 0.14 (s, 6H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 165.7, 139.8, 138.8, 107.8, 105.7, 75.7, 71.2, 62.0, 60.8, 41.6, 25.8, 18.5, -5.2, -5.3; IR (NaCl/thin film): 3583, 2952, 2928, 2855, 1762, 1693, 1472, 1437, 1363, 1342, 1302, 1253, 1185, 1134, 1006, 838, 781 cm^{-1}; HRMS (ESI) calc'd for $C_{34}H_{48}ClN_2O_{10}S_4Si_2$ $[M+Cl]^-$ 863.1424, found 863.1452.

Bis[β-(*tert*-butyldimethylsiloxy)propionate] 256



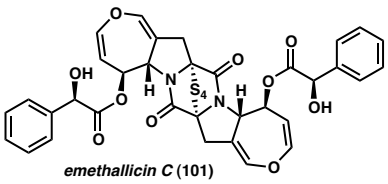
Following the procedure described above for the conversion of **197** to **254**, coupling of diol **197** (8.74 mg, 0.0181 mmol) and acid chloride **232** (0.181 mmol) afforded dicarboxylate **256** (9.0 mg, 58% yield). $[\alpha]_D^{25.0}$ = –343 ° (*c* = 0.450, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (ddd, *J* = 2.5, 2.5, 0.9 Hz, 2H), 6.25 (dd, *J* = 8.2, 2.3 Hz, 2H), 5.29 (dddd, *J* = 8.5, 2.9, 1.7, 1.7 Hz, 2H), 5.22 (ddd, *J* = 8.4, 2.1, 2.1 Hz, 2H), 4.68 (dd, *J* = 8.0, 1.8 Hz, 2H), 3.97 (apt qt, *J* = 10.2, 6.6 Hz, 4H), 3.35 (ddd, *J* = 16.4, 2.2, 2.2 Hz, 2H), 3.05 (ddd, *J* = 16.4, 1.2, 1.2 Hz, 2H), 2.72 – 2.59 (m, 4H), 0.89 (s, 18H), 0.08 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 165.6, 139.6, 138.7, 108.1,

106.1, 75.6, 70.9, 60.8, 58.7, 41.6, 38.4, 25.9, 18.3, -5.3, -5.3; IR (NaCl/thin film): 3583, 3369, 2952, 2927, 2854, 1734, 1696, 1473, 1364, 1343, 1302, 1255, 1181, 1137, 1099, 1064, 1006, 971, 939, 836, 812, 778, 723 cm^{-1}; HRMS (ESI) calc'd for $C_{36}H_{52}ClN_2O_{10}S_4Si_2$ $[M+Cl]^-$ 891.1737, found 891.1745.

Typical procedure for the preparation of bis(hydroxycarboxylates) 101, 233, and 234

A 1-dram vial equipped with a magnetic stir bar was charged with bis(*tert*-butyldimethylsilylether) **254** (10.4 mg, 0.0106 mmol), followed by MeCN (1 mL) and H_2SiF_6 (20-25 wt % *aq*. Solution, 50 μL). The resulting suspension was stirred vigorously (with occasional shaking to ensure exposure of material to the reaction medium) for 17 h, then quenched with sat. *aq*. $NaHCO_3$, and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The material was then purified via preparative TLC (2:1 PhMe–acetone) to afford emethallicin C (**101**, 5.8 mg, 73% yield) as a pale yellow, amorphous solid.

Emethallicin C (101)

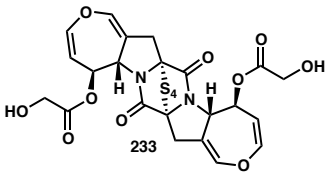


emethallicin C (101)

$[\alpha]_D^{25.0}$ = –316 ° (*c* = 0.19, $CHCl_3$); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.68 – 7.65 (m, 4H), 7.41 – 7.37 (m, 4H), 7.35 – 7.30 (m, 2H), 6.78 (ddd, *J* = 2.5, 2.5, 1.0 Hz, 2H), 6.33 (dd, *J* = 8.2, 2.2 Hz, 2H), 5.36 (d, *J* = 4.8 Hz, 2H), 5.25 (dddd, *J* = 8.6, 2.8, 1.5, 1.5 Hz, 2H), 5.20 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H), 4.90 (d, *J* = 5.4 Hz, 2H), 4.41 (dd, *J* = 8.2, 1.8 Hz, 2H), 3.57 (ddd, *J* = 16.4, 2.6, 1.7 Hz, 2H), 3.21 (ddd, *J* = 16.3, 1.2, 1.2 Hz, 2H); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 172.7, 167.0, 141.2, 140.2, 139.4, 129.1, 128.8, 127.9, 110.6, 105.9, 77.4, 74.1, 72.6, 62.0, 41.8; IR (NaCl/thin film): 3429, 2918, 2850, 1729,

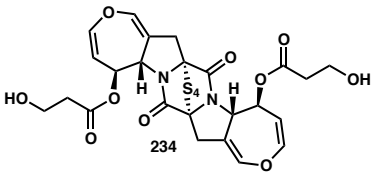
1683, 1373, 1344, 1235, 1185, 1137, 1090, 1069, 1015, 968, 861, 815, 722 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{34}H_{28}ClN_2O_{10}S_4$ $[M+Cl]^-$ 787.0321, found 787.0298.

Bis(α-hydroxyacetate) 233



Following the procedure described above for the conversion of **254** to **101**, deprotection of bis(*tert*-butyldimethylsilylether) **255** (10.0 mg, 0.0121 mmol) afforded bis(hydroxyacetate) analog **233** (5.0 mg, 69% yield). $[\alpha]_D^{25.0}$ = –462 ° (*c* = 0.25, acetone); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.78 (ddd, *J* = 2.5, 2.5, 0.9 Hz, 2H), 6.42 (dd, *J* = 8.2, 2.2 Hz, 2H), 5.23 (dddd, *J* = 8.5, 2.6, 1.5, 1.5 Hz, 2H), 5.20 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H), 4.76 (dd, *J* = 8.2, 1.7 Hz, 2H), 4.21 (d, *J* = 6.0 Hz, 4H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.51 (ddd, *J* = 16.4, 2.6, 1.7 Hz, 2H), 3.13 (ddd, *J* = 16.3, 1.2, 1.2 Hz, 2H); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 172.6, 167.0, 140.9, 139.4, 110.5, 106.5, 77.4, 72.0, 62.1, 61.9, 41.8; IR (NaCl/thin film): 3306, 2916, 2849, 1743, 1689, 1374, 1344, 1303, 1235, 1186, 1137, 1095, 816, 723 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{22}H_{20}ClN_2O_{10}S_4$ $[M+Cl]^-$ 634.9695, found 634.9686.

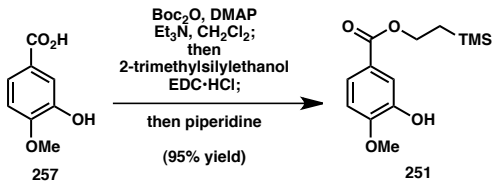
Bis(β-hydroxypropionate) 234



Following the procedure described above for the conversion of **254** to **101**, deprotection of bis(*tert*-butyldimethylsilylether) **256** (9.0 mg, 0.0105 mmol) afforded bis(hydroxypropionate) analog **234** (4.8 mg, 73% yield). $[\alpha]_D^{25.0}$ = –404 ° (*c* = 0.24, acetone); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.77 (ddd, *J* = 2.5, 2.5, 0.9 Hz, 2H), 6.39 (dd, *J* = 8.2, 2.3 Hz, 2H), 5.28 – 5.23 (m, 2H), 5.19 (ddd, *J* = 8.5, 2.1, 2.1 Hz, 2H), 4.72 (dd, *J* = 8.1, 1.9 Hz, 2H), 3.95 – 3.83 (m, 4H), 3.75 (t, *J* = 5.8 Hz, 2H), 3.52 (ddd, *J*

= 16.3, 2.1, 2.1 Hz, 2H), 3.12 (ddd, *J* = 16.4, 1.2, 1.2 Hz, 2H), 2.61 (t, *J* = 6.1 Hz, 4H); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 171.9, 166.9, 140.7, 139.3, 110.8, 107.1, 77.3, 71.7, 62.0, 58.3, 41.8, 39.4; IR (NaCl/thin film): 3368, 2916, 2848, 1726, 1686, 1560, 1369, 1302, 1235, 1186, 1136, 1043, 815, 723 cm^{-1}; HRMS (Multimode-ESI/APCI) calc'd for $C_{24}H_{24}ClN_2O_{10}S_4$ $[M+Cl]^-$ 663.0008, found 662.9992.

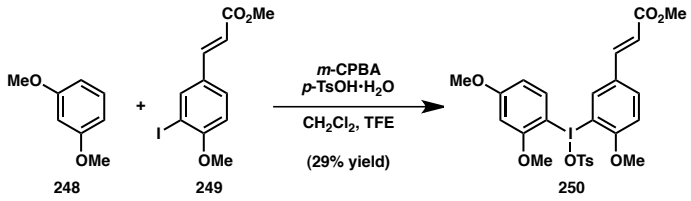
Preparation of (trimethylsilyl)ethyl ester 251



To a solution of *iso*-vanillic acid (**257**, 500 mg, 2.97 mmol) and DMAP (72.6 mg, 0.594 mmol) in 3.0 mL CH_2Cl_2 were added Et_3N (414 μL, 2.97 mmol) and Boc_2O (1.57 mL, 6.83 mmol). NOTE: the resulting mixture effervesced for ~10 min. After 2 h, 2-(trimethylsilyl)ethanol (1.28 mL, 8.91 mmol) was added (resulting in slight effervescence). After 45 min, EDC•HCl (569 mg, 2.97 mmol) was added. After 6 h, piperidine (22 mL, 223 mmol) was added. After 1.5 h, the reaction mixture was diluted with EtOAc (100 mL), then washed with 1 M HCl (2x100 mL), H_2O (100 mL), and brine (100 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo* (under high vacuum until most of the piperidine had evaporated). Purification via flash chromatography (gradient elution, 8:1→4:1 hexanes–EtOAc) afforded (trimethylsilyl)ethyl ester **251** (756 mg, 95% yield) as a white, amorphous solid with a melting point close to ambient temperature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.76 (s, 1H), 4.40 – 4.35 (m, 2H), 3.92 (s, 3H), 1.13 – 1.08 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.46, 150.24, 145.14,

123.81, 122.60, 115.50, 109.75, 62.98, 55.95, 17.34, -1.47; IR (NaCl/thin film): 3414, 2953, 2898, 2844, 1710, 1616, 1591, 1512, 1457, 1442, 1379, 1352, 1283, 1251, 1220, 1182, 1126, 1093, 1026, 965, 952, 860, 838, 763 cm^{-1}; HRMS (ESI) calc'd for $C_{11}H_{17}O_4Si$ $[M–C_2H_4+H]^+$ 241.0891, found 241.0896.

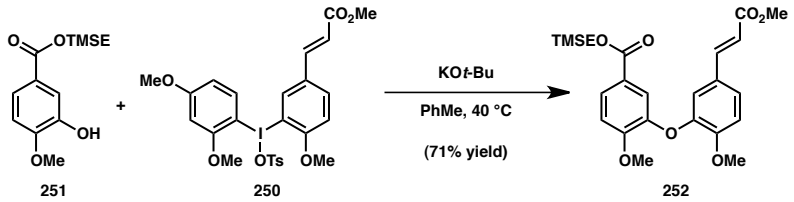
Preparation of λ^3-iodane 250



A 1-dram vial equipped with a magnetic stir bar was charged with aryl iodide **249** (50 mg, 0.16 mmol), *m*-CPBA (85 wt %, 32 mg, 0.16 mmol), *p*-TsOH•H_2O (30 mg, 0.16 mmol), and 0.62 mL of CH_2Cl_2/TFE (1:1). To the resulting solution was added 1,3-dimethoxybenzene (**248**, 21 μL, 0.16 mmol) with stirring. After 3 h, the reaction mixture was concentrated *in vacuo* to give a dark brown residue. The residue was dissolved in acetone (~1 mL), then added dropwise via pipet to a vigorously stirring volume of Et_2O (~30 mL). The resulting precipitate was filtered off to afford λ^3-iodane **250** (28 mg, 29% yield) as a pale purple solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 1H), 7.63 – 7.57 (m, 3H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 16.0 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.54 – 6.50 (m, 2H), 6.22 (d, *J* = 16.0 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 165.4, 158.6, 157.6, 142.7, 141.9, 139.3, 139.0, 133.7, 132.7, 130.2, 128.4, 126.0, 117.9, 112.3, 108.7, 104.6, 99.9, 91.4, 57.2, 56.9, 55.9, 51.8, 21.3; IR (NaCl/thin film): 3459, 2946, 2847, 1714, 1632, 1595, 1580, 1493, 1459, 1437, 1399, 1319, 1284, 1264, 1212, 1173, 1136, 1120, 1032, 1009, 816, 730 cm^{-1}; HRMS (ESI) calc'd for $C_{19}H_{20}IO_5$

$[M–C_7H_7O_3S]^+$ 455.0350, found 455.0371 (detected fragment does not include the *para*-toluenesulfonate ligand).

Preparation of diaryl ether 252



To a solution of phenol **251** (5.3 mg, 0.020 mmol) in 0.25 mL PhMe was added KO*t*-Bu (1.0 M in THF, 22 μL, 0.022 mmol), and the resulting mixture was stirred for 15 min. Solid iodane **250** (15 mg, 0.024 mmol) was then added, and the mixture was heated to 40 °C. After 3 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated, and the resulting crude material was purified by flash chromatography (gradient elution, 8:1→4:1 hexanes–EtOAc) to afford biaryl ether **252** (6.5 mg, 71% yield) as a white, amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.5, 2.1 Hz, 1H), 7.54 (d, J = 15.9 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 8.5, 2.0 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.98 (s, 1H), 6.98 (d, J = 10.0 Hz, 1H), 6.17 (d, J = 15.9 Hz, 1H), 4.37 – 4.32 (m, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.76 (s, 3H), 1.09 – 1.03 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 166.0, 154.2, 152.3, 145.7, 145.0, 144.1, 127.5, 126.5, 125.2, 123.5, 119.8, 117.5, 115.9, 112.4, 111.5, 63.1, 56.1, 56.0, 51.6, 17.3, -1.5; IR (NaCl/thin film): 3400, 2952, 2840, 1712, 1636, 1607, 1573, 1511, 1430, 1378, 1266, 1219, 1175, 1124, 1094, 1025, 980, 946, 859, 838, 765 cm^{-1}; HRMS (ESI) calc'd for $C_{18}H_{15}O_6$ $[M–C_3H_9Si–CH_3O–C_2H_4+H]^+$ 327.0863, found 327.0870 (detected fragment

has undergone loss of trimethylsilyl cation, ethylene, and methoxide anion and gain of H^+).

Table 3.2. *Comparison of spectroscopic data for natural and synthetic SCH64877 (44)*

^{1}H NMR Data ($CDCl_3$, data for synthetic material referenced to $CHCl_3$ at 7.26 ppm)

Reported chemical shift (δ)[2]	**Synthetic**	**Δ**
3.28[a] (dd, *J* = 15, 1 Hz, 2H)	3.37 (ddd, *J* = 16.4, 2.5, 1.2 Hz, 2H)	+0.09
3.11 (d, *J* = 15 Hz, 2H)	3.11 (d, *J* = 16.7 Hz, 2H)	0
5.30 (s, 2H)	5.30 (s, 2H)	0
5.30 (s, 2H)	5.30 (s, 2H)	0
4.6 (d, *J* = 10 Hz, 2H)	4.59 (dd, *J* = 8.3, 1.2 Hz, 2H)	–0.01
6.28 (d, *J* = 8 Hz, 2H)	6.28 (dd, *J* = 8.4, 1.9 Hz, 2H)	0
6.60 (s, 2H))	6.58 (dd, *J* = 1.8, 1.8 Hz, 2H)	–0.02
2.8 (dq[b], *J* = 8, 2 Hz, 2H)	2.79 (qd, *J* = 7.2, 1.8 Hz, 2H)	–0.01
3.81 (dd, *J* = 10, 1 Hz, 2H)	3.81 (ddd, *J* = 9.5, 2.1, 2.1 Hz, 2H)	0
1.5 (m, 2H)	1.56 – 1.47 (m, 2H)	+0.02
1.13-1.10[c] (m, 2H)	1.25 – 1.16 (m, 2H)	+0.09
1.85 (dq, *J* = 8, 2 Hz, 2H)	1.84 (dqd, *J* = 13.5, 7.6, 3.1 Hz, 2H)	–0.01
0.95 (t, *J* = 8 Hz, 6H)	0.92 (t, *J* = 7.5 Hz, 6H)	–0.03
1.28 (d, *J* = 8 Hz, 6H)	1.27 (d, *J* = 7.3 Hz, 6H)	–0.01
0.84 (d, *J* = 8 Hz, 6H)	0.85 (d, *J* = 6.8 Hz, 6H)	+0.01

[a] This is suspected to be a typographical error. [b] This is suspected to be a typographical error, based on the reported *J* value for the C(7') methyl group. [c]This is suspected to be a typographical error, based on the reported chemical shift for SCH64874 (**42**).

^{13}C NMR Data ($CDCl_3$, data for synthetic material referenced to $CDCl_3$ at 77.0 ppm)

Reported chemical shift (δ)[2]	**Synthetic**	**Δ**
165.9	165.9	0
75.5	75.4	–0.1
41.5	41.5	0
108.0	108.0	0
61.0	60.9	–0.1
70.9	70.9	0
105.8	105.8	0
139.9	139.9	0
138.9	138.9	0
175.8	175.8	0
41.9	41.9	0
73.9	73.9	0
36.8	36.7	–0.1
25.3	25.3	0
10.9	10.8	–0.1
9.1	9.1	0
14.9	14.9	0

Table 3.3. *Comparison of spectroscopic data for natural and synthetic emethallicin C (**101**)*

^{1}H NMR Data (acetone-d_6, data for synthetic material referenced to acetone-d_5 at 2.05 ppm)

Reported chemical shift (δ)[3]	**Synthetic**
3.212 (d, *J* = 16.4 Hz, 2H)	3.21 (ddd, *J* = 16.3, 1.2, 1.2 Hz, 2H)
3.566 (ddd, *J* = 16.4, 2.5, 2.0 Hz, 2H)	3.57 (ddd, *J* = 16.4, 2.6, 1.7 Hz, 2H)
4.409 (dd, *J* = 8.2, 1.7 Hz, 2H)	4.41 (dd, *J* = 8.2, 1.8 Hz, 2H)
4.873 (d, *J* = 5.6 Hz, 2H)	4.90 (d, *J* = 5.4 Hz, 2H)
5.202 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H)	5.20 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H)
5.256 (ddd, *J* = 8.5, 2.2, 1.7 Hz, 2H)	5.25 (dddd, *J* = 8.6, 2.8, 1.5, 1.5 Hz, 2H)
5.362 (d, *J* = 5.6 Hz, 2H)	5.36 (d, *J* = 4.8 Hz, 2H)
6.332 (dd, *J* = 8.2, 2.2 Hz, 2H)	6.33 (dd, *J* = 8.2, 2.2 Hz, 2H)
6.780 (dd, *J* = 2.5, 2.0 Hz, 2H)	6.78 (ddd, *J* = 2.5, 2.5, 1.0 Hz, 2H)
7.325 (br t, *J* = 7.3 Hz, 2H)	7.35 – 7.30 (m, 2H)
7.391 (br t, *J* = 7.3 Hz, 4H)	7.41 – 7.37 (m, 4H)
7.667 (br d, *J* = 7.3 Hz, 4H)	7.68 – 7.65 (m, 4H)

3.6 NOTES AND REFERENCES

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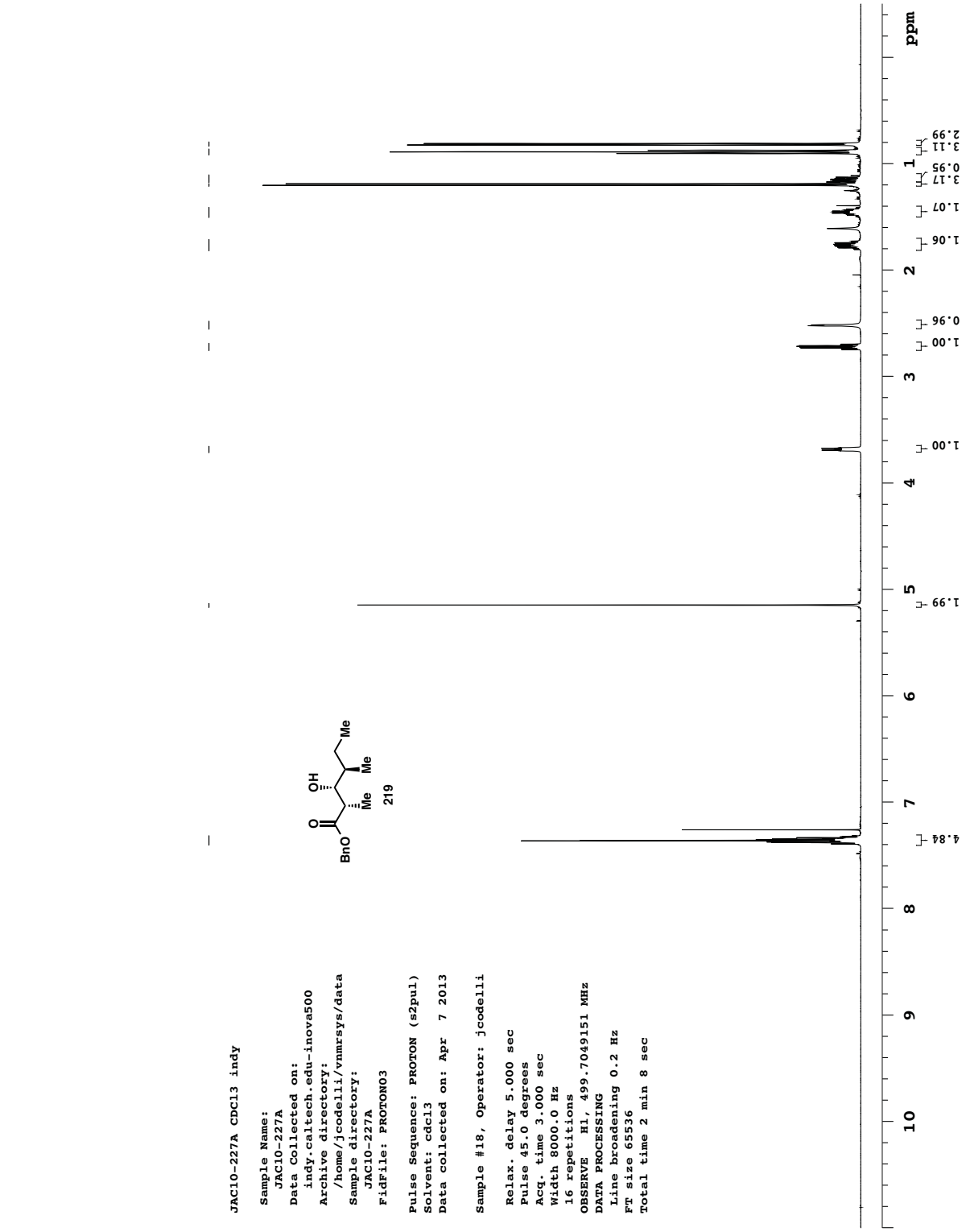
(28) Relative stereochemistry was determined by DBU-promoted epimerization of ***ent*-219**, which afforded a mixture of ***ent*-219** and ***ent*-222**.

Appendix 3

Spectra Relevant to Chapter 3:
C_2-Symmetric Dihydrooxepine-Containing ETPs and MPC1001B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Sample directory:
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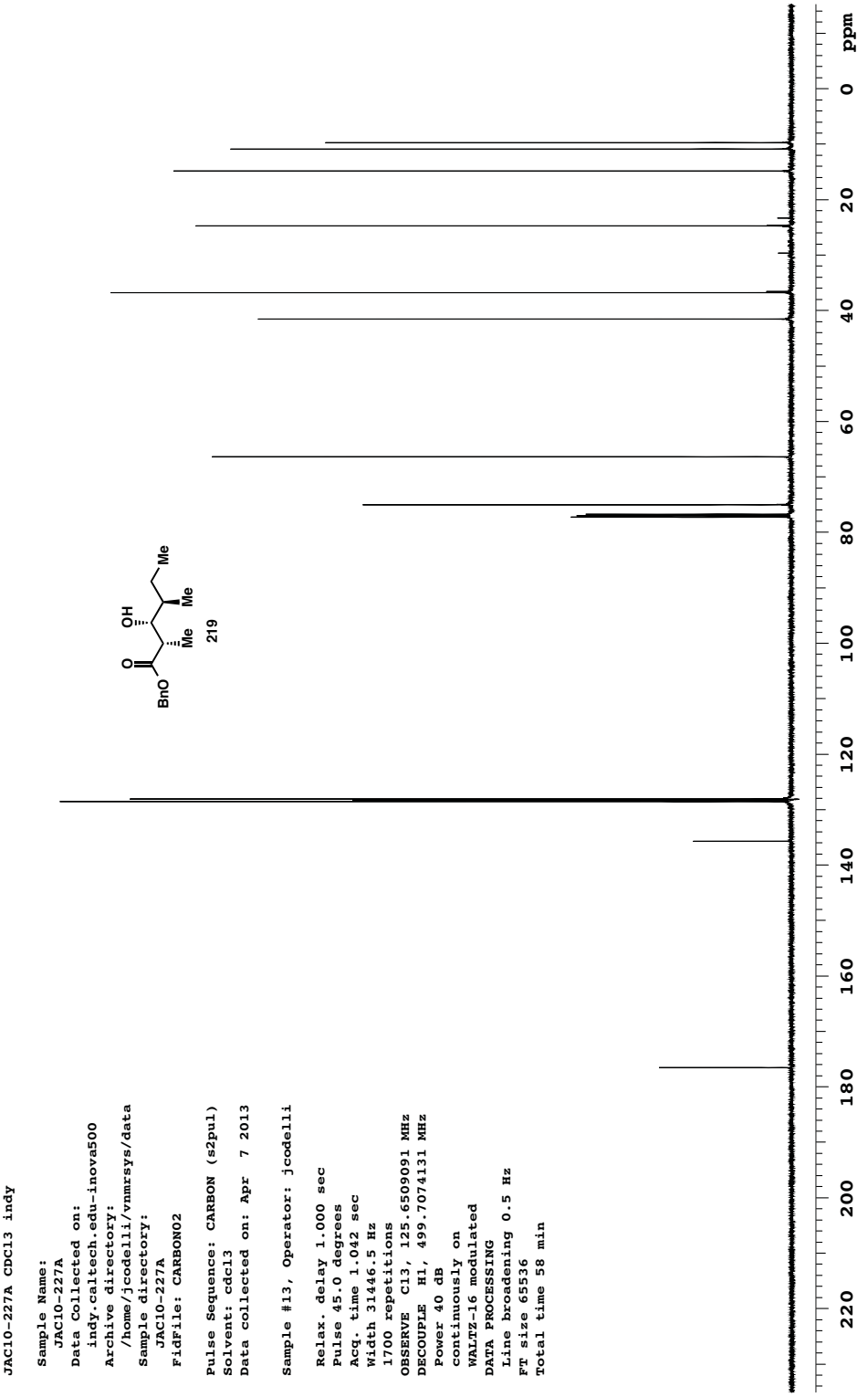
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 7 2013
Sample #18, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
OH
O
BnO
Me
Me
Me
219
ppm
10
9
8
7
6
5
4
3
2
1
4.84
1.99
1.00
0.96
1.00
1.06
1.07
3.17
0.95
3.11
2.99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Archive directory:
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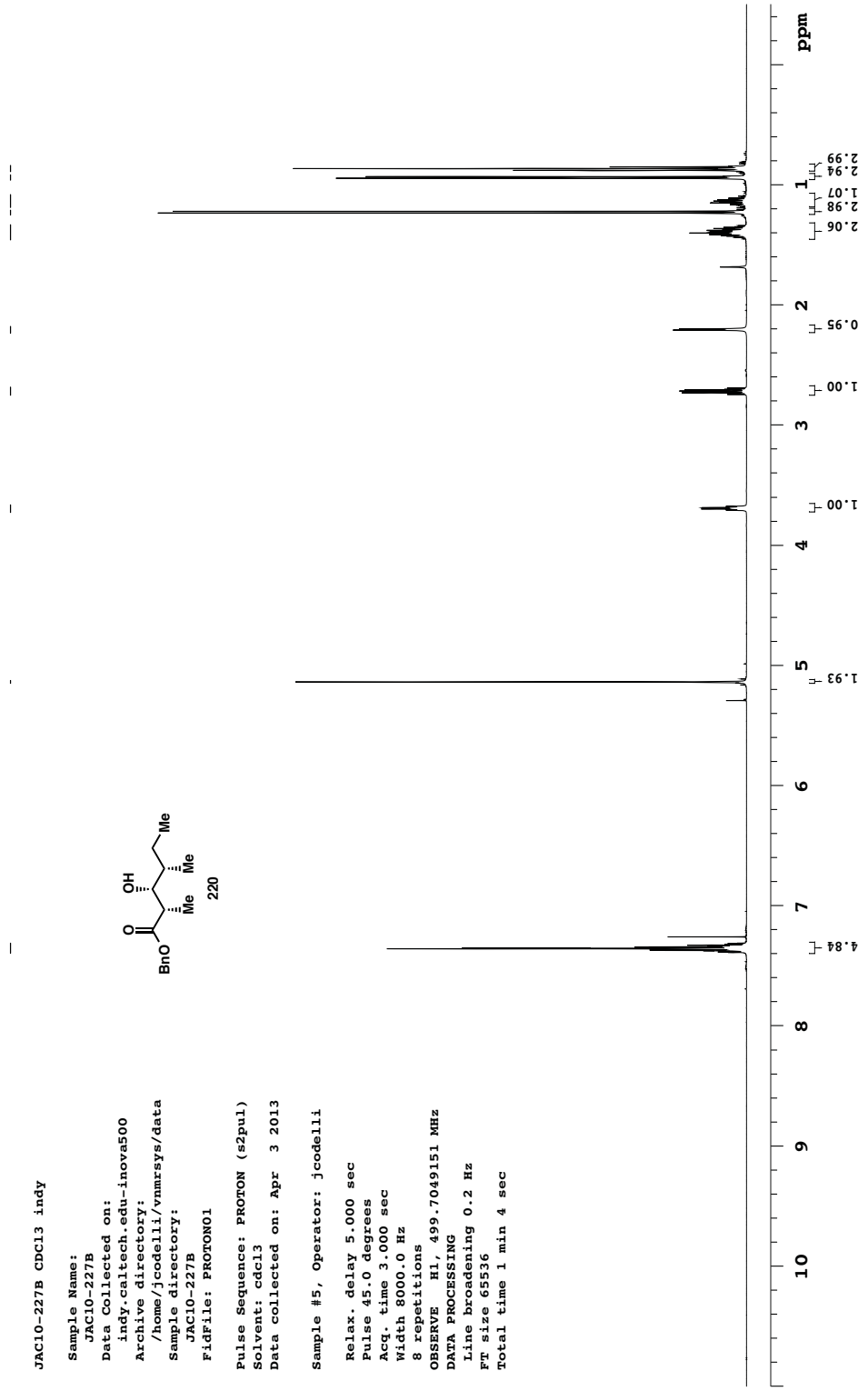
Sample directory:
JAC10-227A
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 7 2013
Sample #13, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6509091 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
BnO
O
OH
Me
Me
Me
219
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Sample directory:
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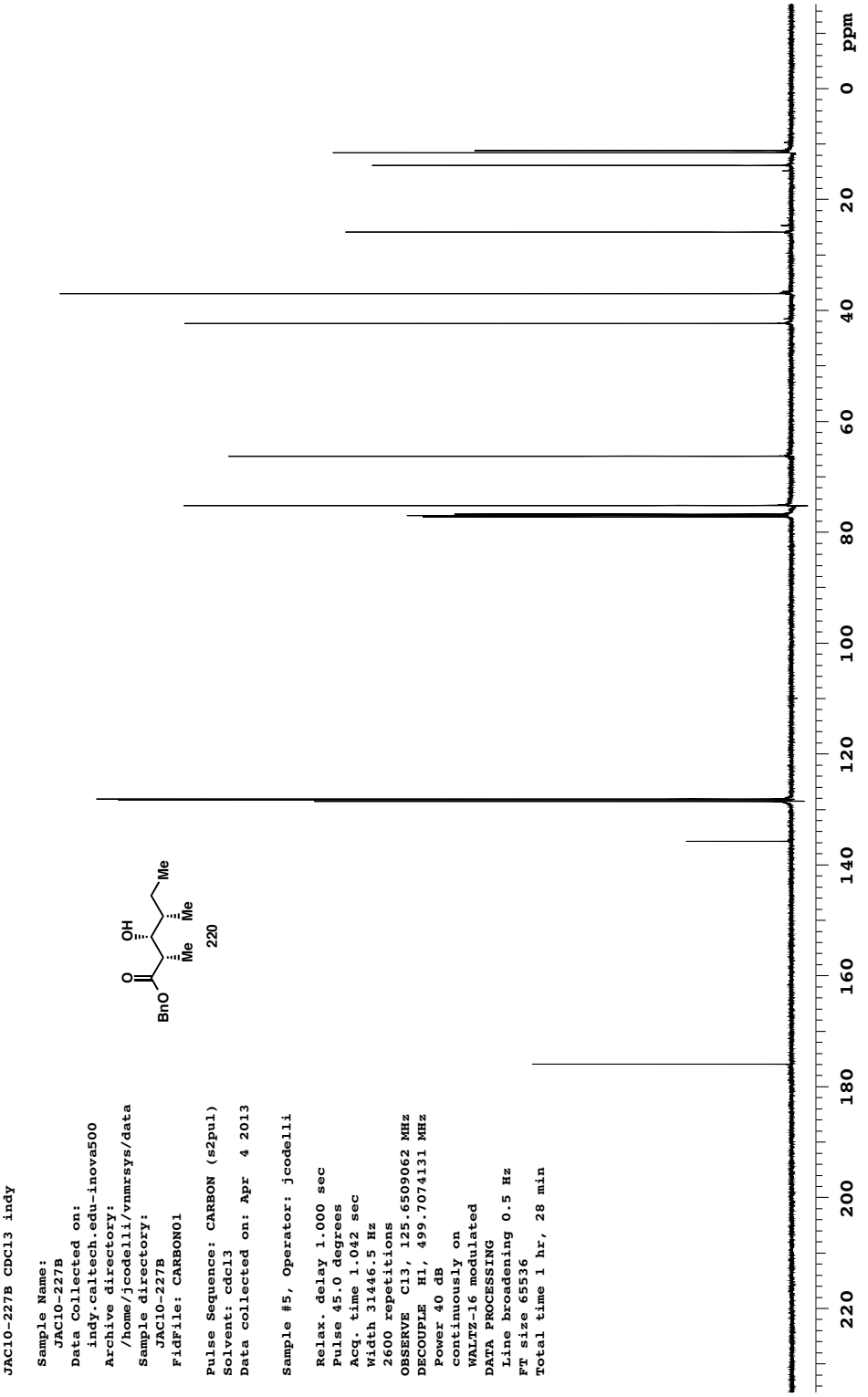
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2013
Sample #5, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
OH
O
BnO
Me
Me
Me
220
ppm
10
9
8
7
6
5
4
3
2
1
4.84
1.93
1.00
1.00
0.95
2.06
2.98
1.07
2.94
2.99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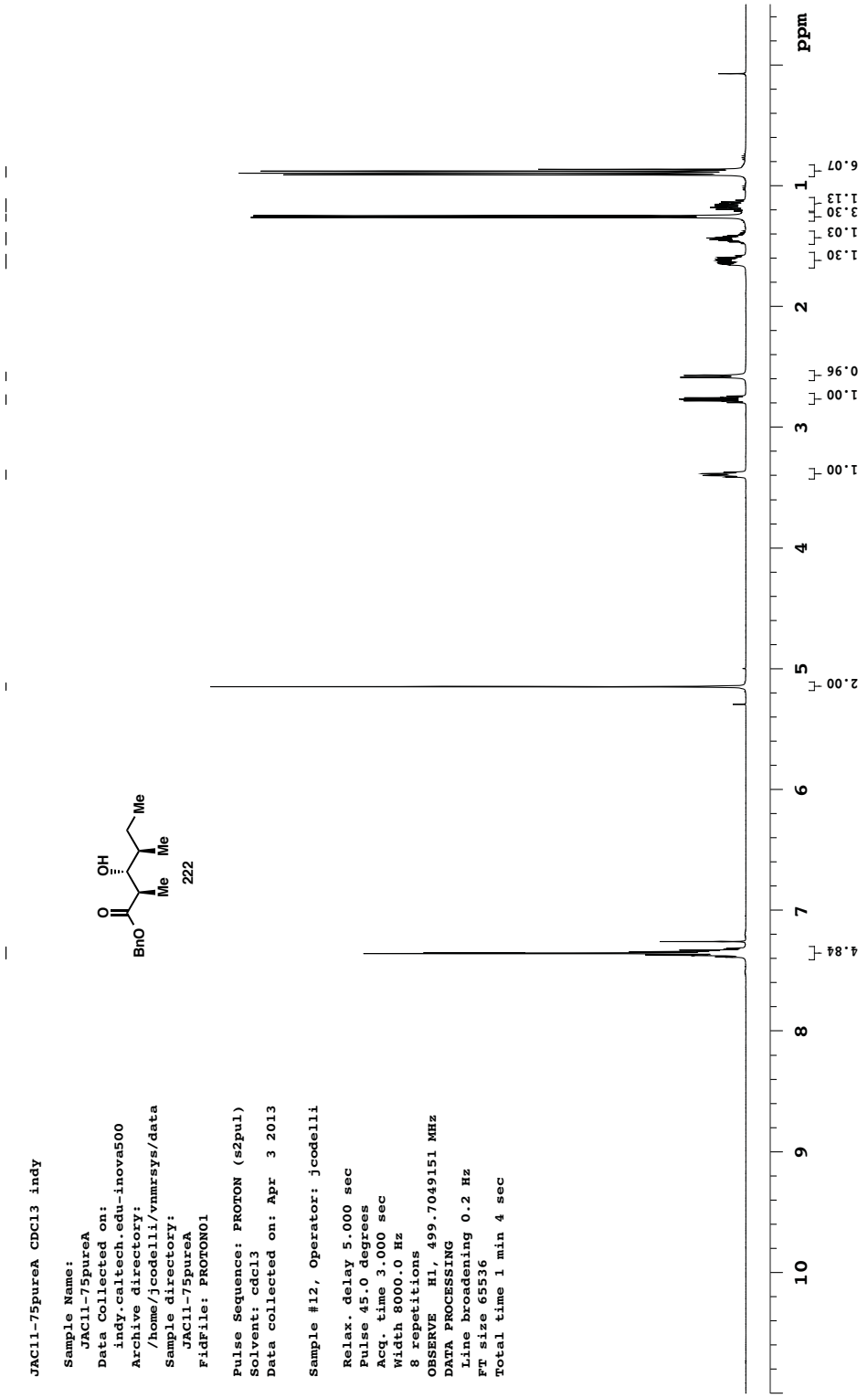
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 4 2013
Sample #5, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2600 repetitions
OBSERVE C13, 125.6509062 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 28 min
OH
O
BnO
Me
Me
Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Archive directory:
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Sample directory:
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FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2013
Sample #12, Operator: jcodelli
Relax. delay 5.000 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 4 sec
OH
O
BnO
Me
Me
Me
222
ppm
10
9
8
7
6
5
4
3
2
1
4.84
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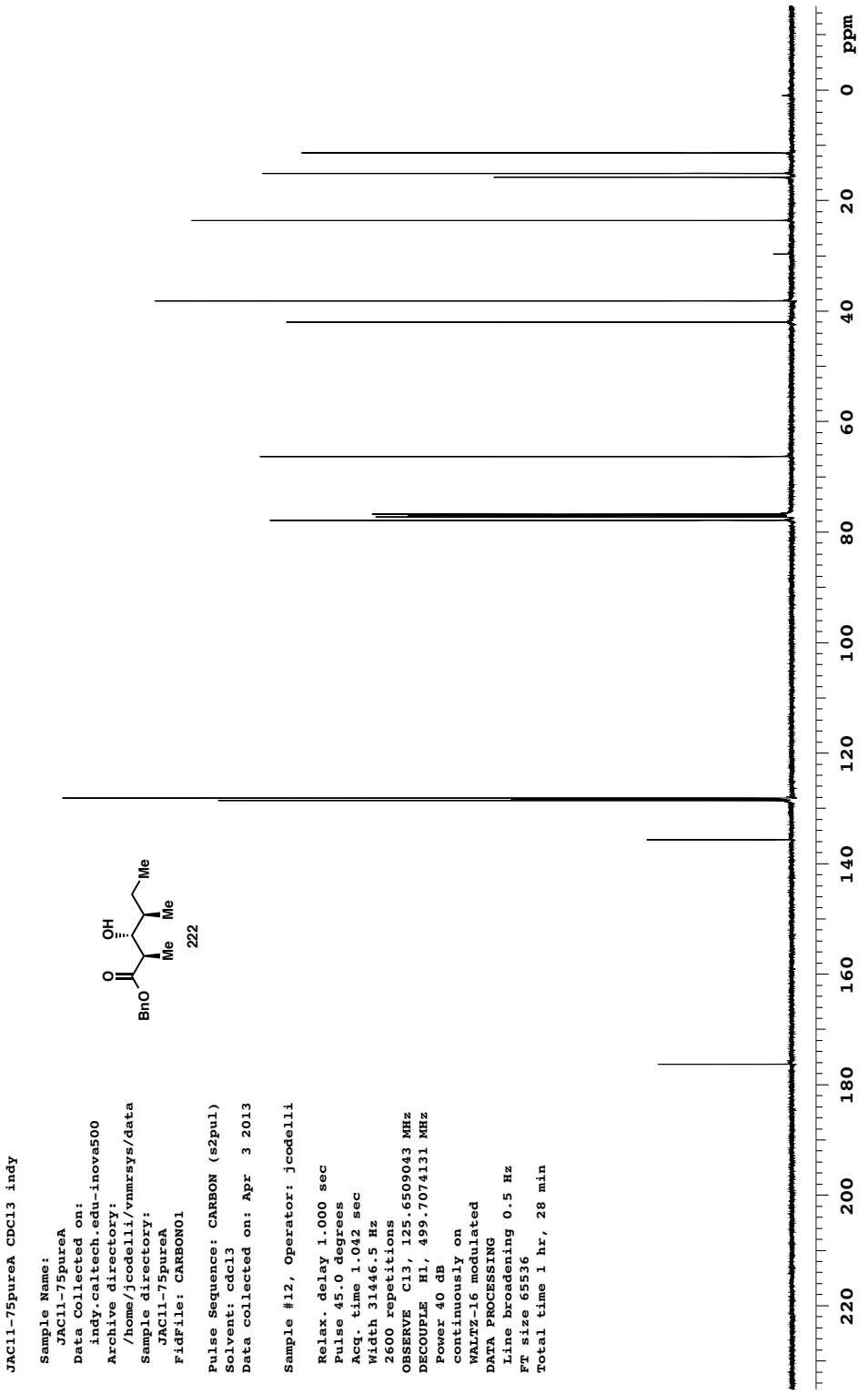
1.00
1.00
0.96
1.00
1.30
1.03
3.30
1.13
6.07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Archive directory:
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Sample directory:
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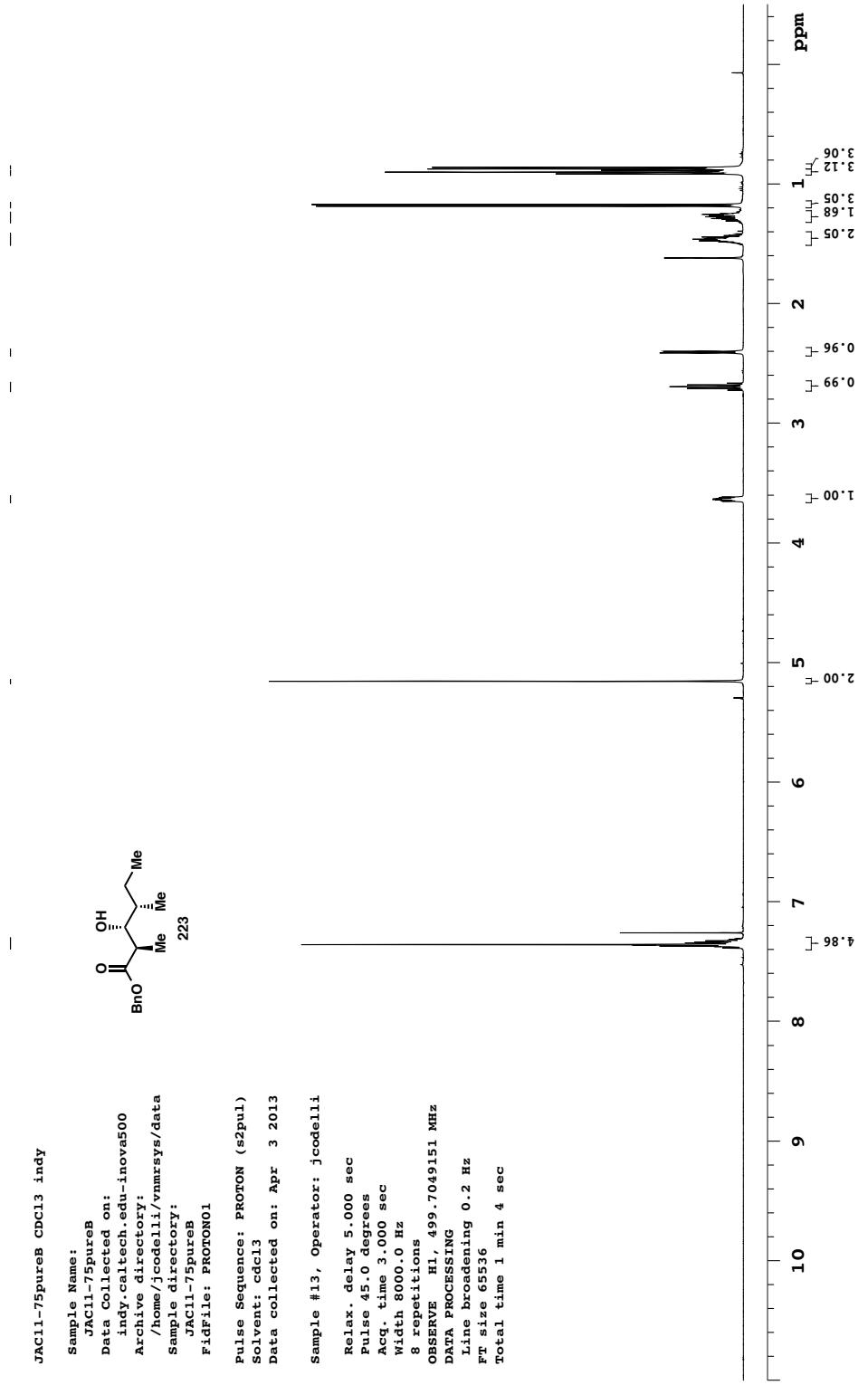
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2013
Sample #12, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2600 repetitions
OBSERVE C13, 125.6509043 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 28 min
BnO
O
OH
Me
Me
Me
222
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Archive directory:
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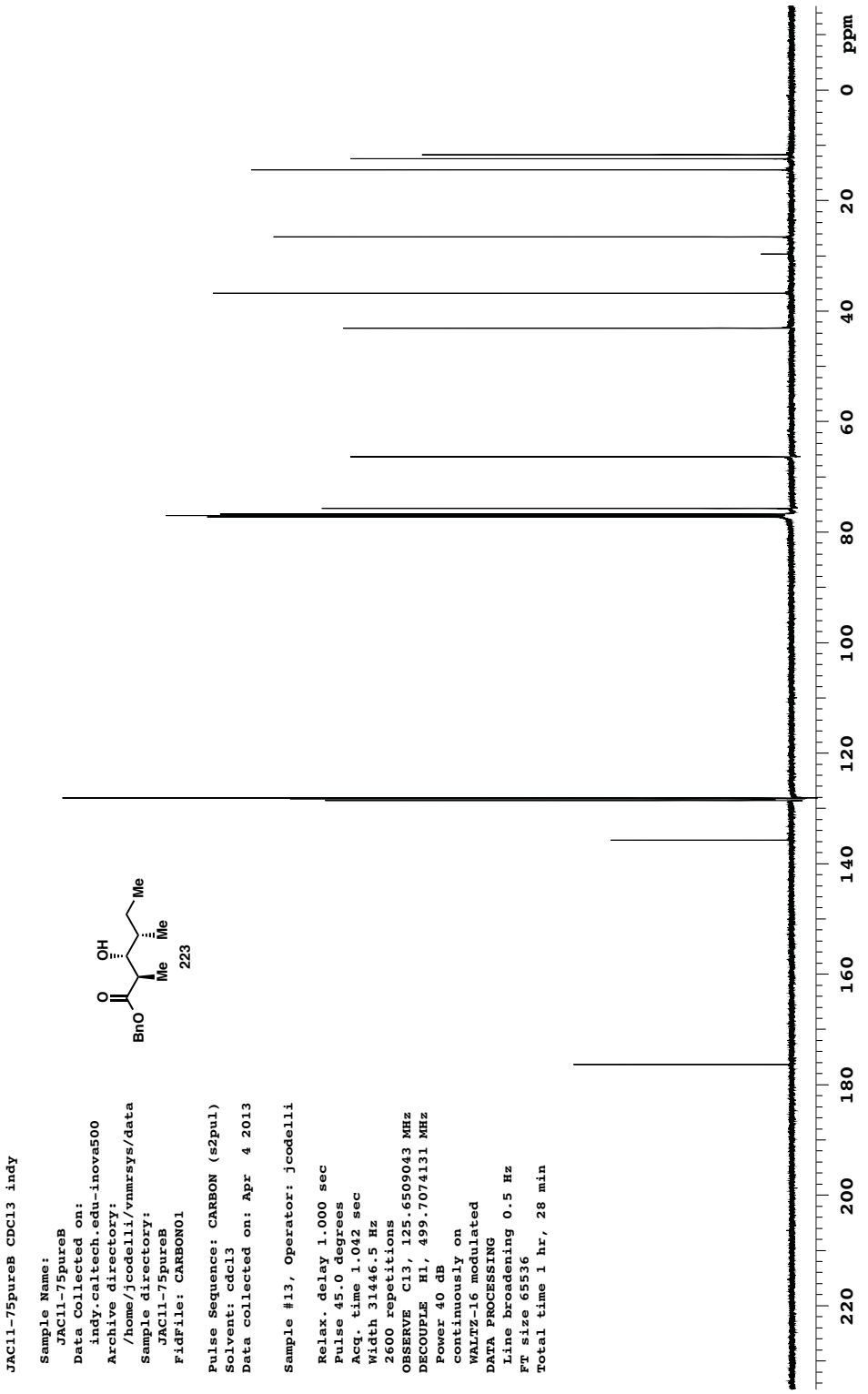
Sample directory:
JAC11-75pureB
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2013
Sample #13, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
OH
O
BnO
Me
Me
Me
223
ppm
4.86
2.00
1.00
0.99
0.96
2.05
1.68
3.05
3.12
3.06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Archive directory:
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Sample directory:
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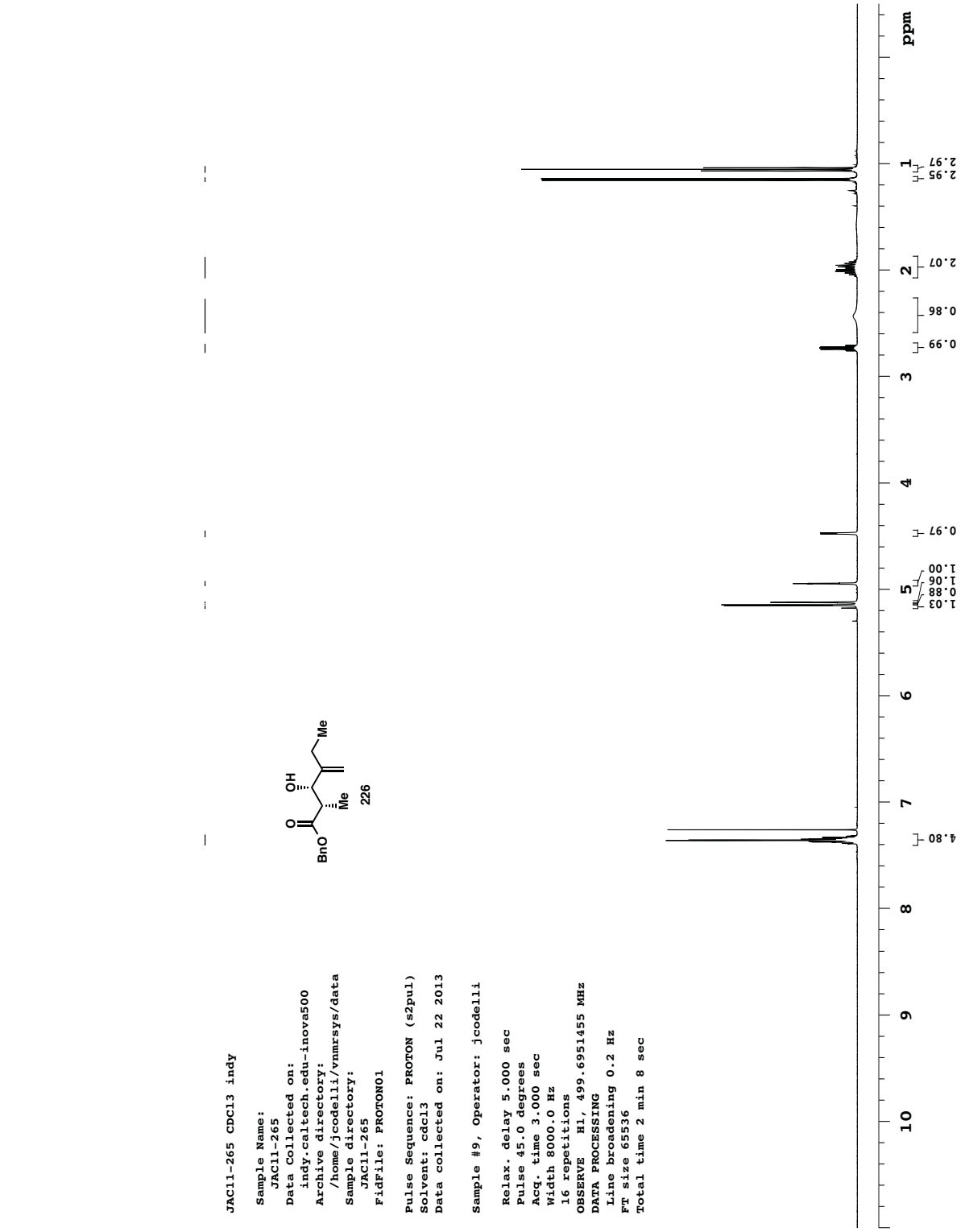
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 4 2013
Sample #13, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2600 repetitions
OBSERVE C13, 125.6509043 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 28 min
OH
O
BnO
Me
Me
Me
223
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 22 2013
Sample #9, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6951455 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
OH
Me
O
Me
BnO
226
ppm
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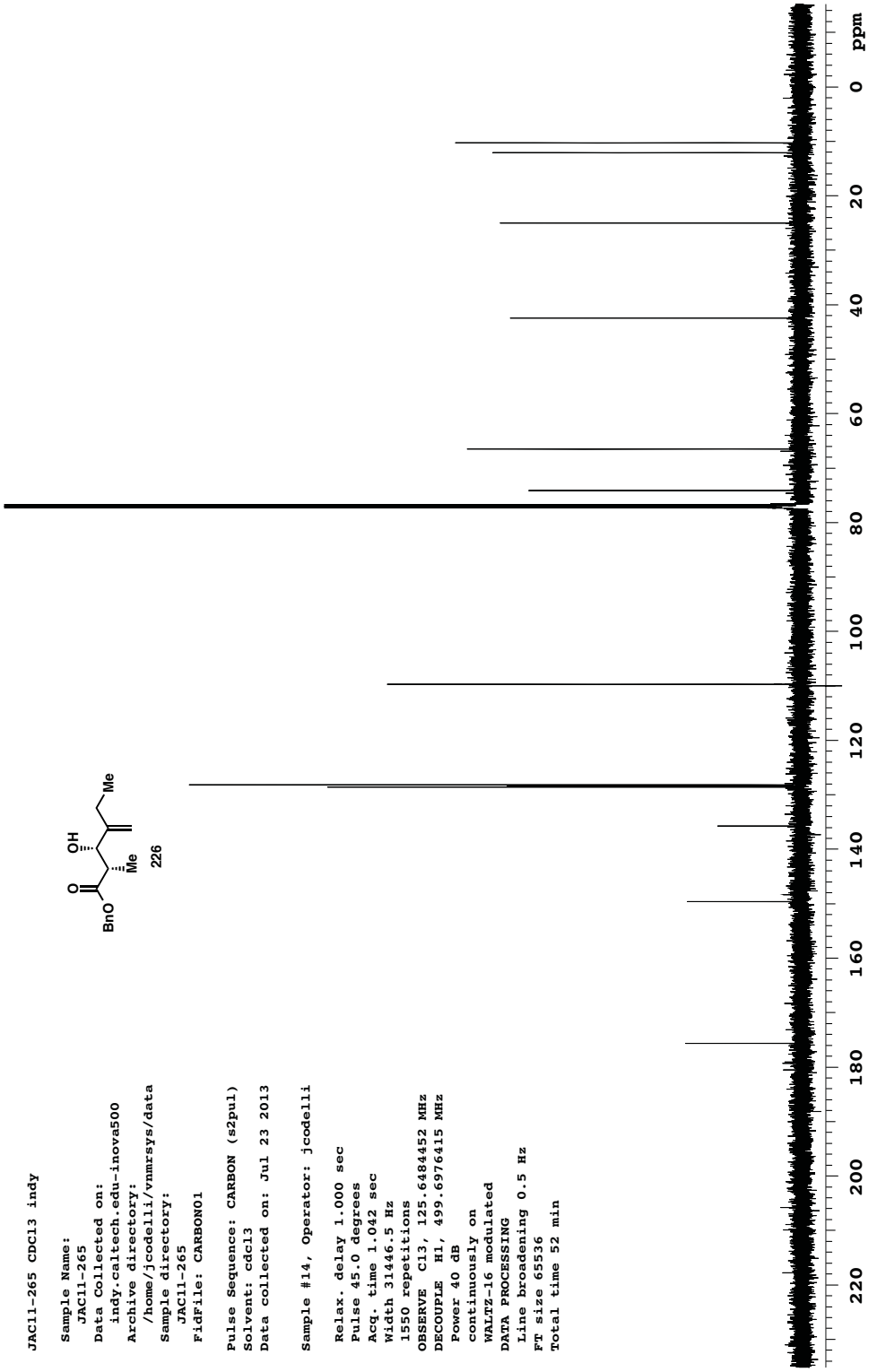
2.95
2.07
0.98
0.99
0.97
1.03
0.88
1.06
1.00
4.80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Archive directory:
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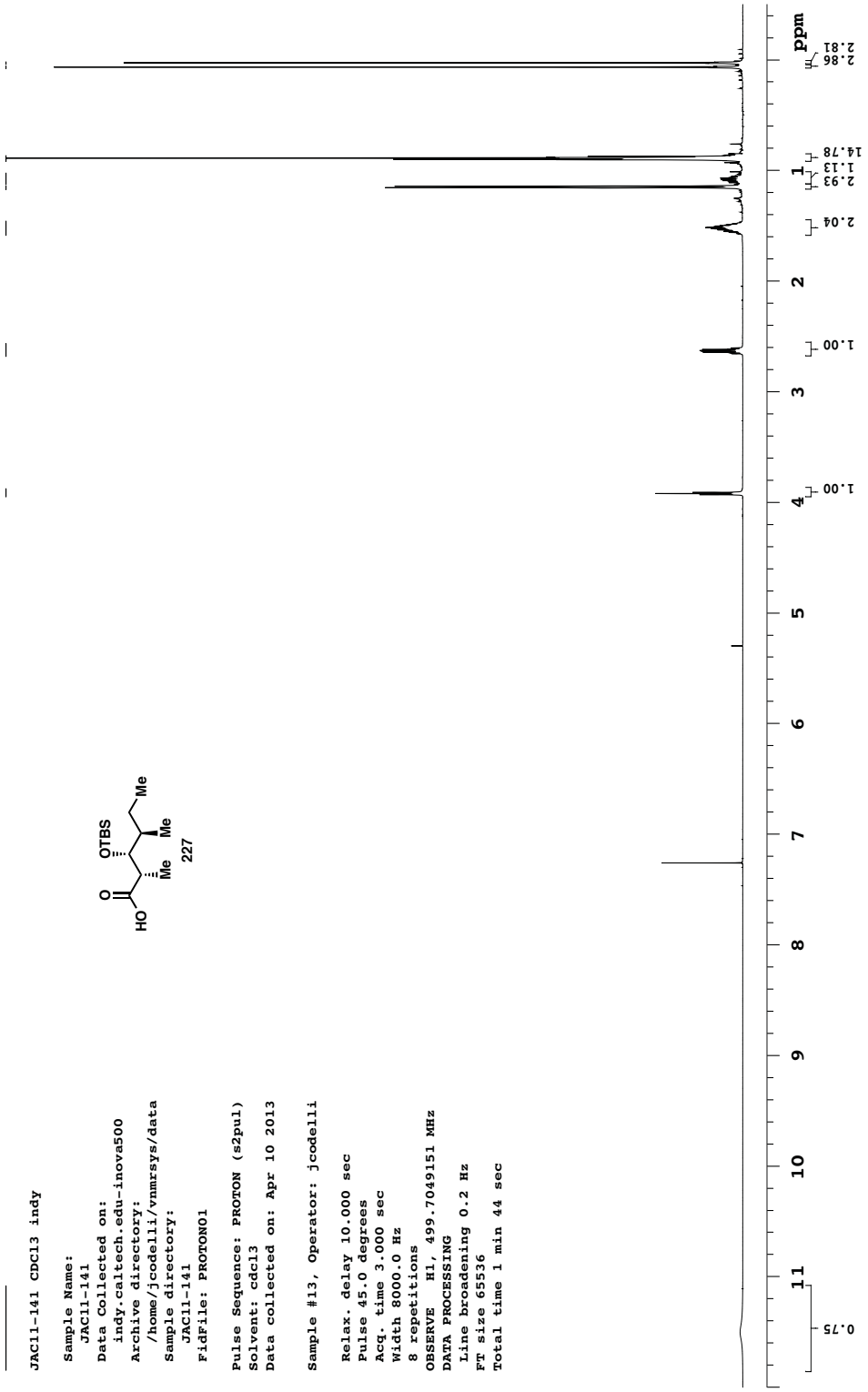
Sample directory:
JAC11-265
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 23 2013
Sample #14, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1550 repetitions
OBSERVE C13, 125.6484452 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 52 min
OH
Me
O
Me
BnO
226
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Data Collected on:
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Archive directory:
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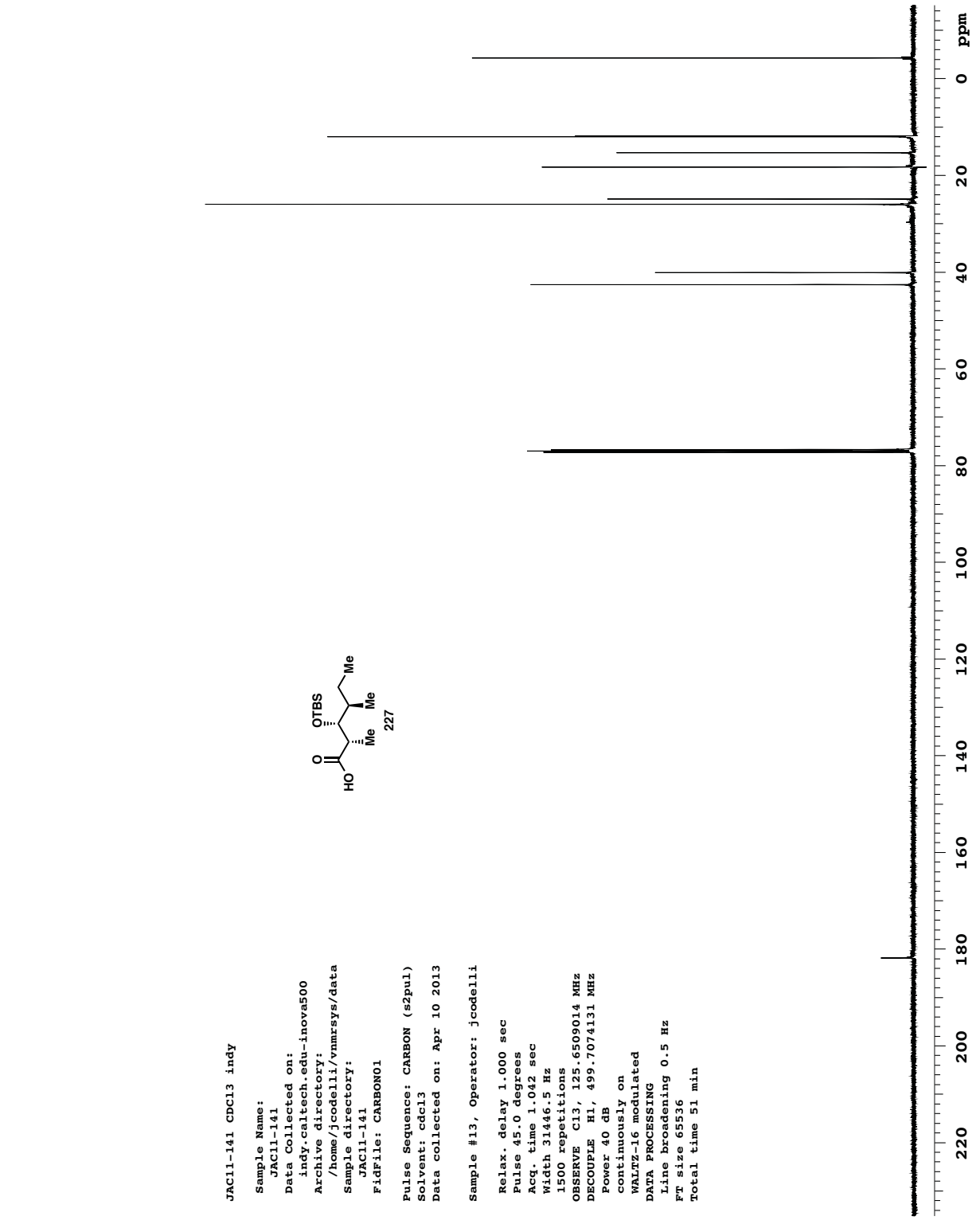
Sample directory:
JAC11-141
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 10 2013
Sample #13, Operator: jcodelli
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 44 sec
OTBS
Me
Me
Me
O
HO
227
ppm
2.86
2.81
14.78
1.13
2.93
2.04
1.00
1.00
0.75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Archive directory:
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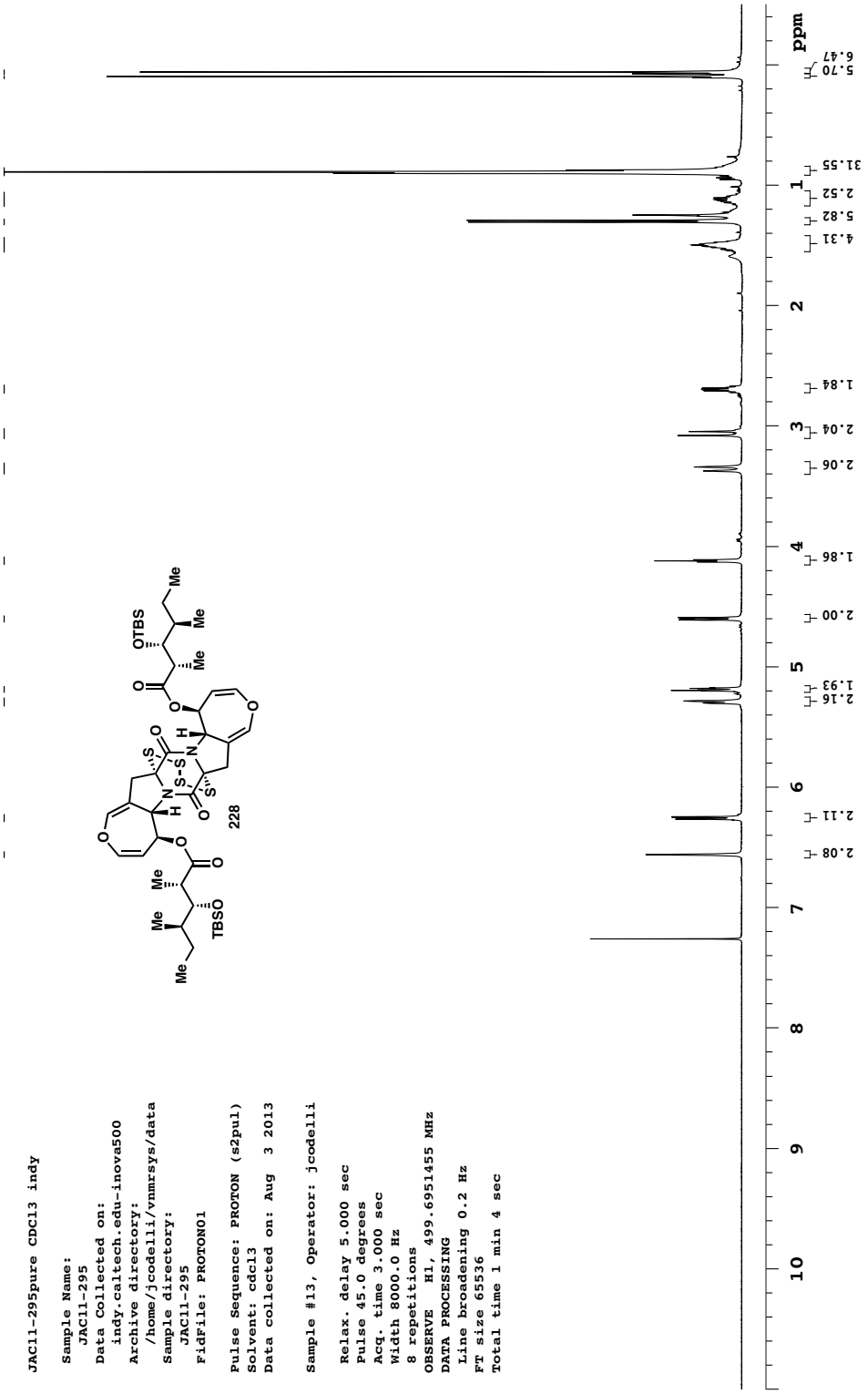
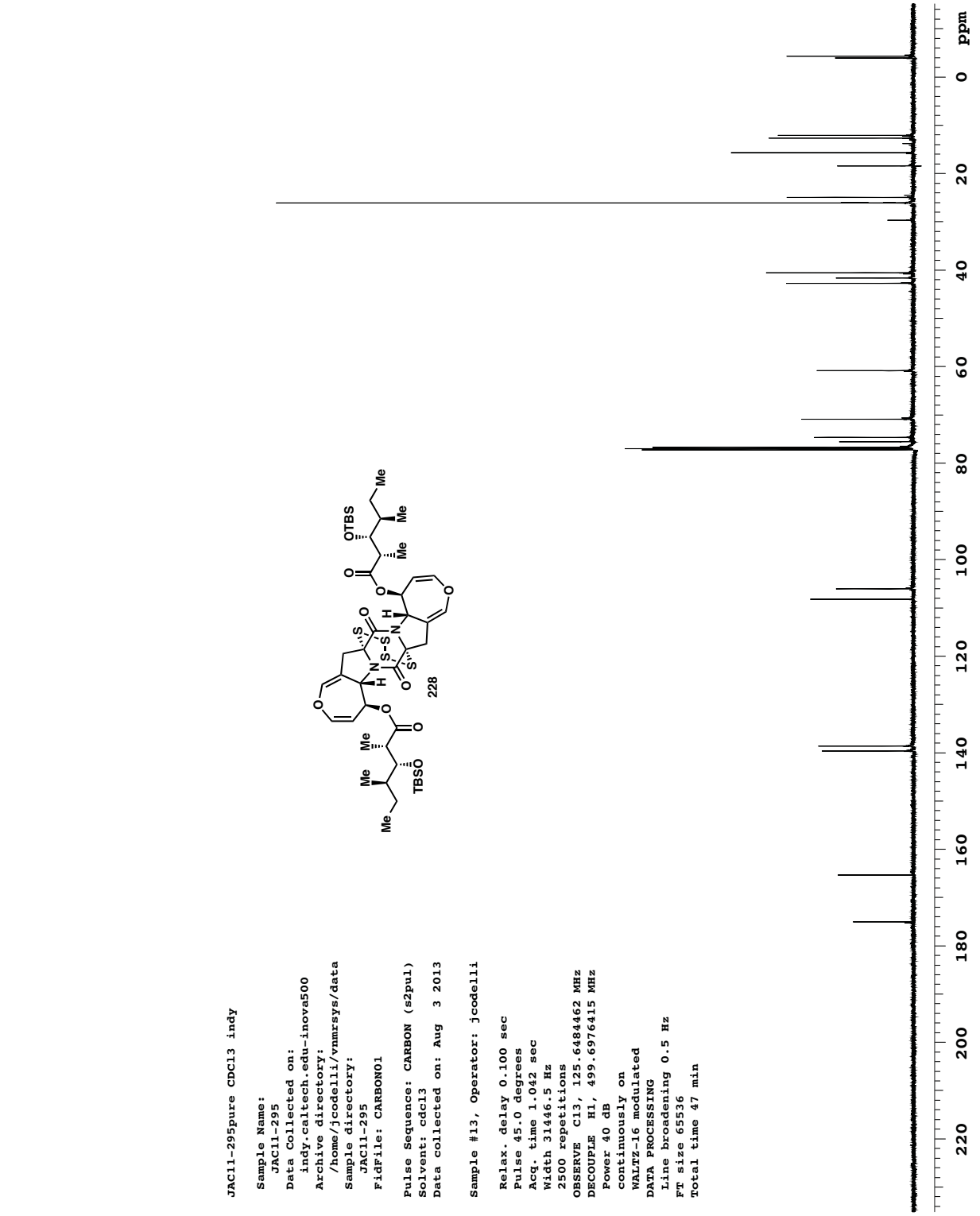
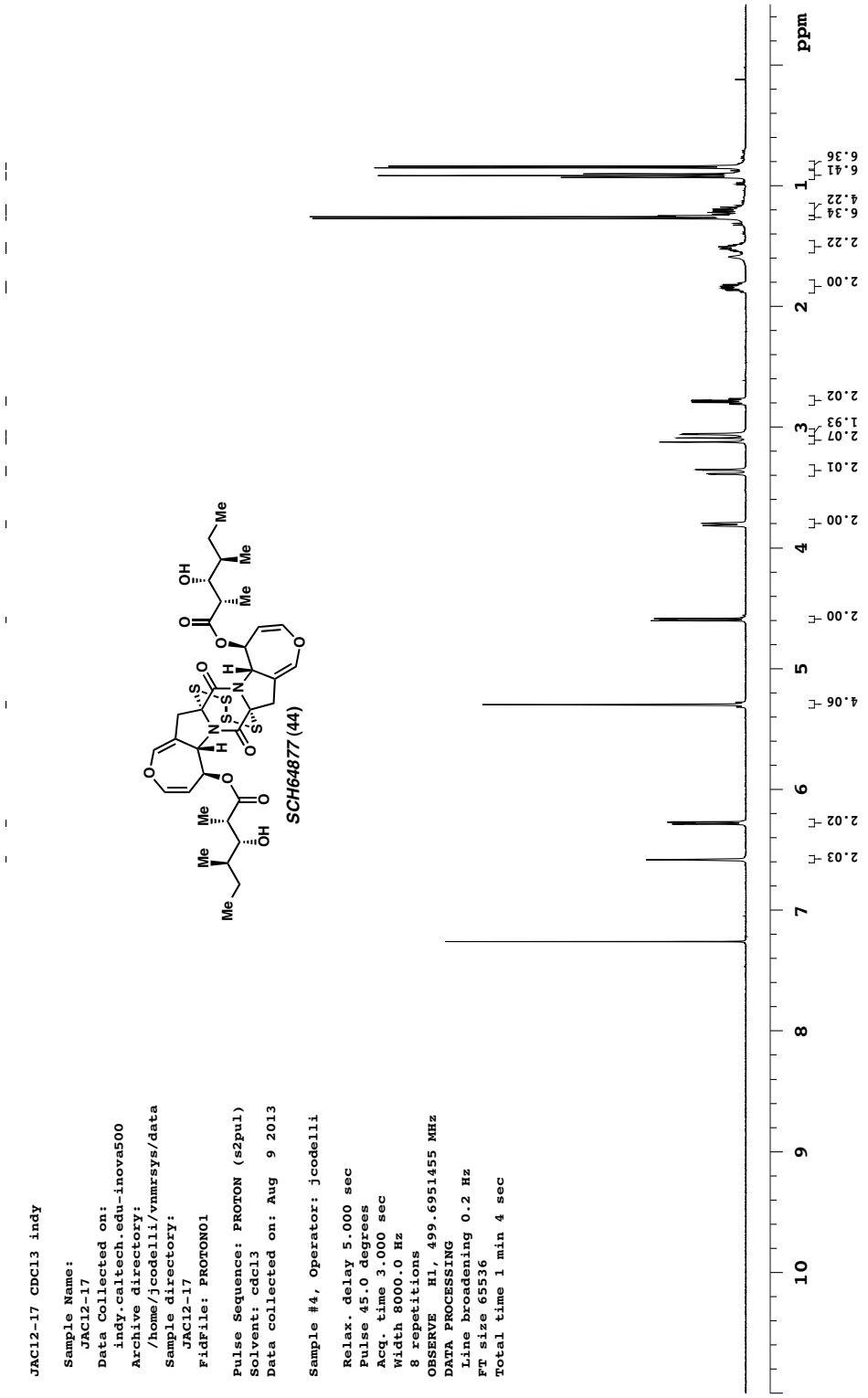
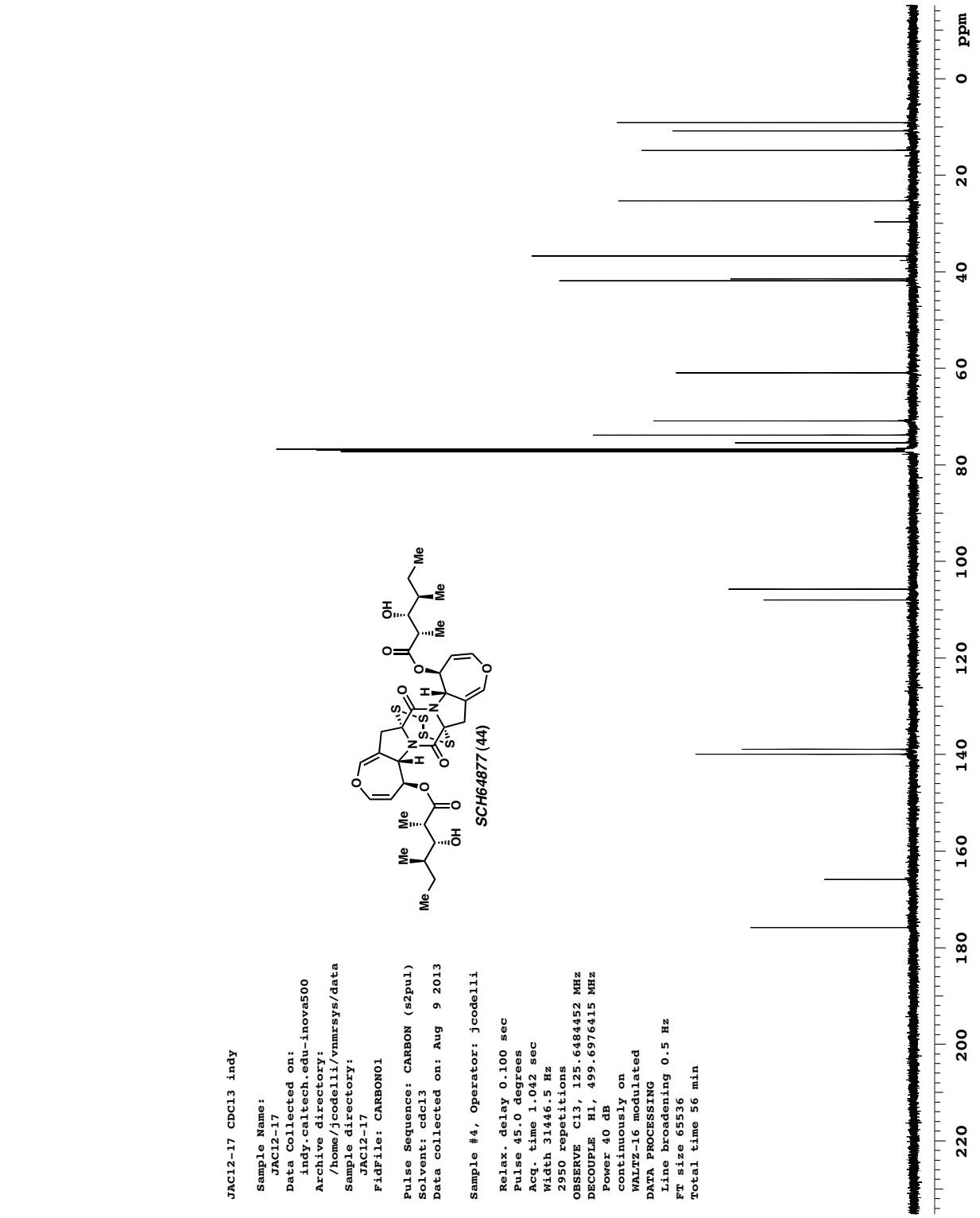
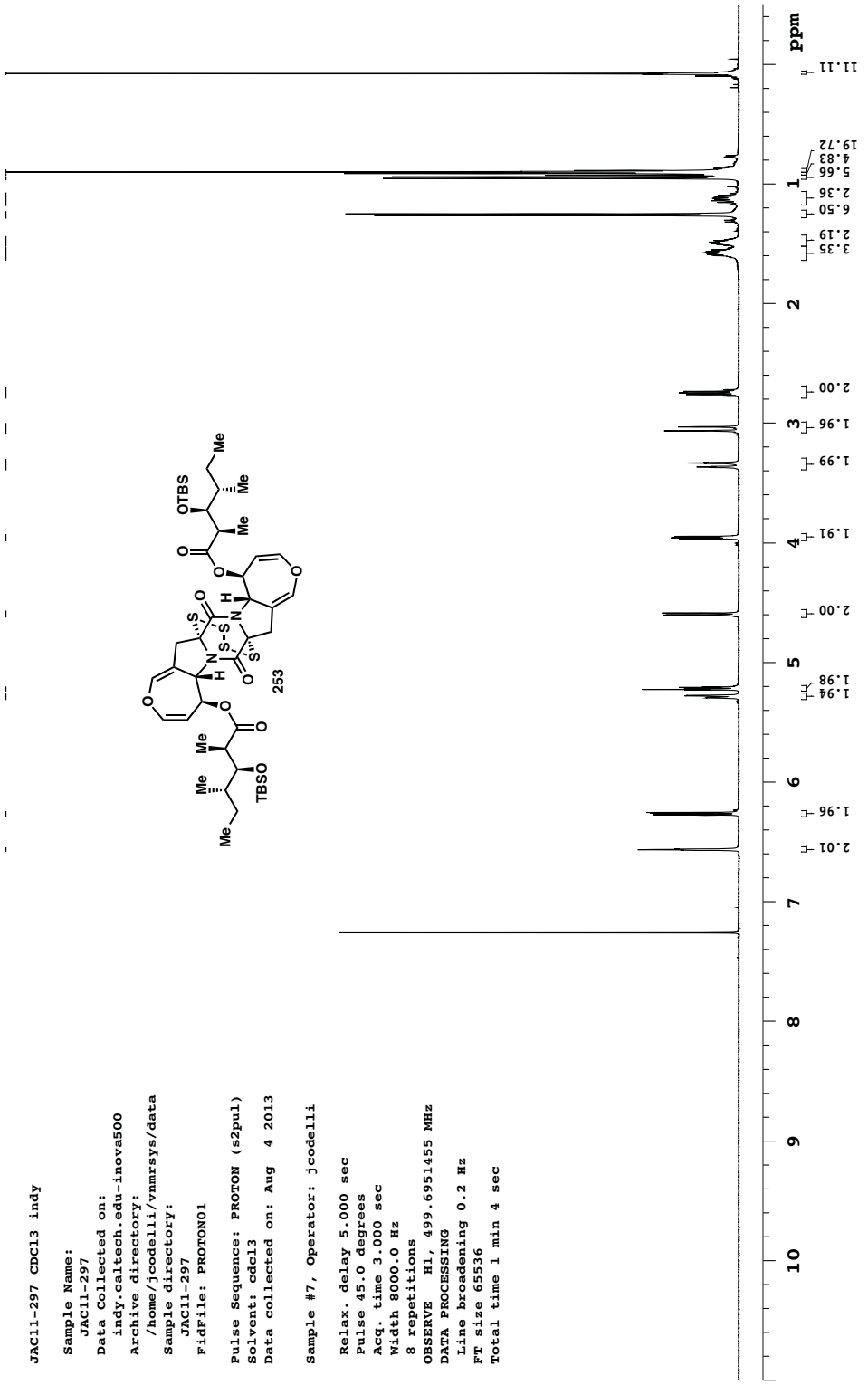
Sample directory:
JAC11-141
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 10 2013
Sample #13, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6509014 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
O
OTBS
HO
Me
Me
Me
227
220
200
180
160
140
120
100
80
60
40
20
0
ppm

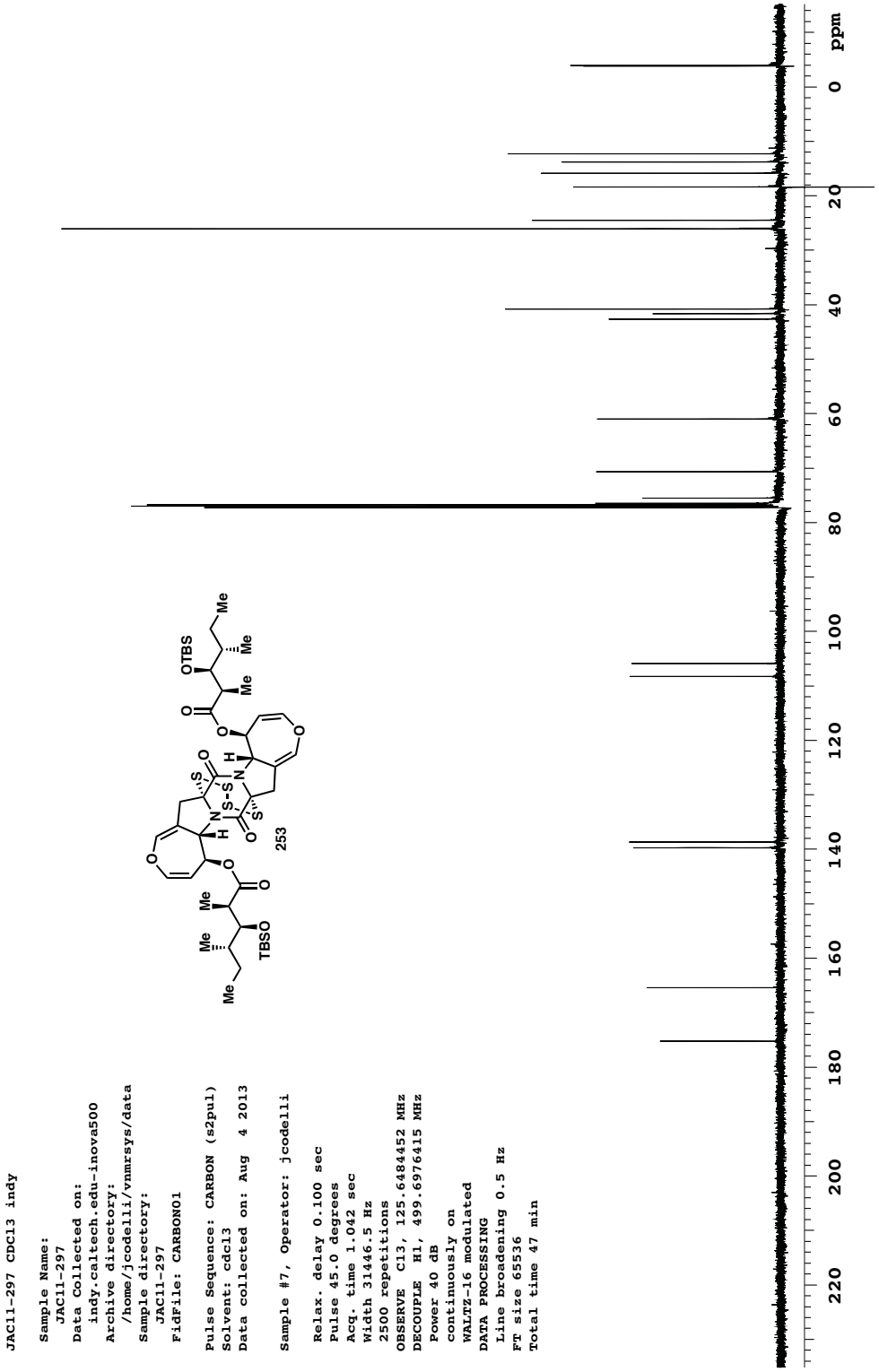

JAC11-295pure CDCl3 indy
Sample Name:
JAC11-295
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-295
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 3 2013
Sample #13, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
OTBS
TBSO
Me
O
S
N
H
228
ppm
10
9
8
7
6
5
4
3
2
1
5.70
6.47
31.55
2.52
5.82
4.31
1.84
2.04
2.06
1.86
2.00
2.16
1.93
2.11
2.08

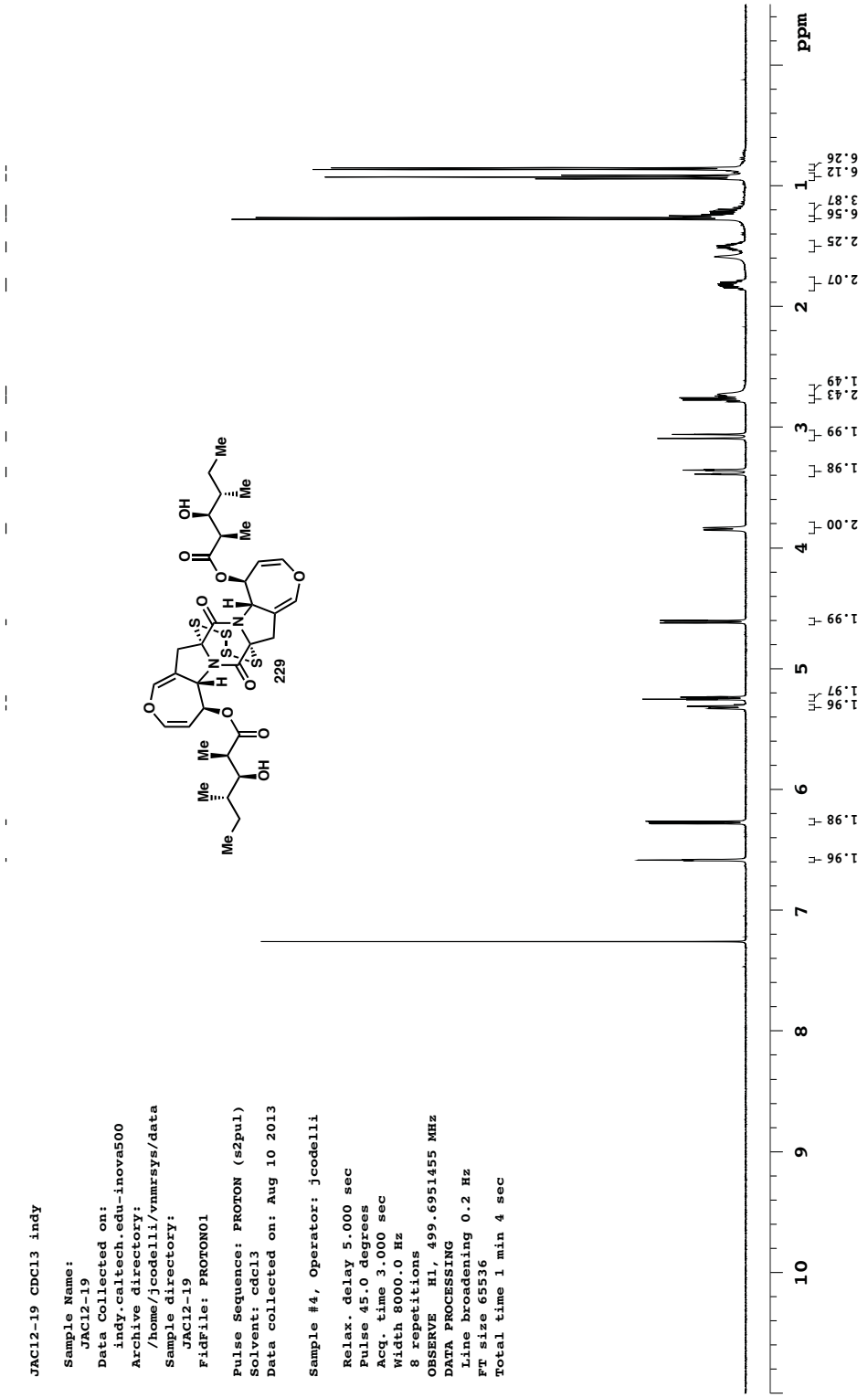

JAC11-295pure CDCl3 indy
Sample Name:
JAC11-295
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-295
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 3 2013
Sample #13, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 repetitions
OBSERVE C13, 125.6484462 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 47 min
OTBS
TBSO
228
220
200
180
160
140
120
100
80
60
40
20
0
ppm

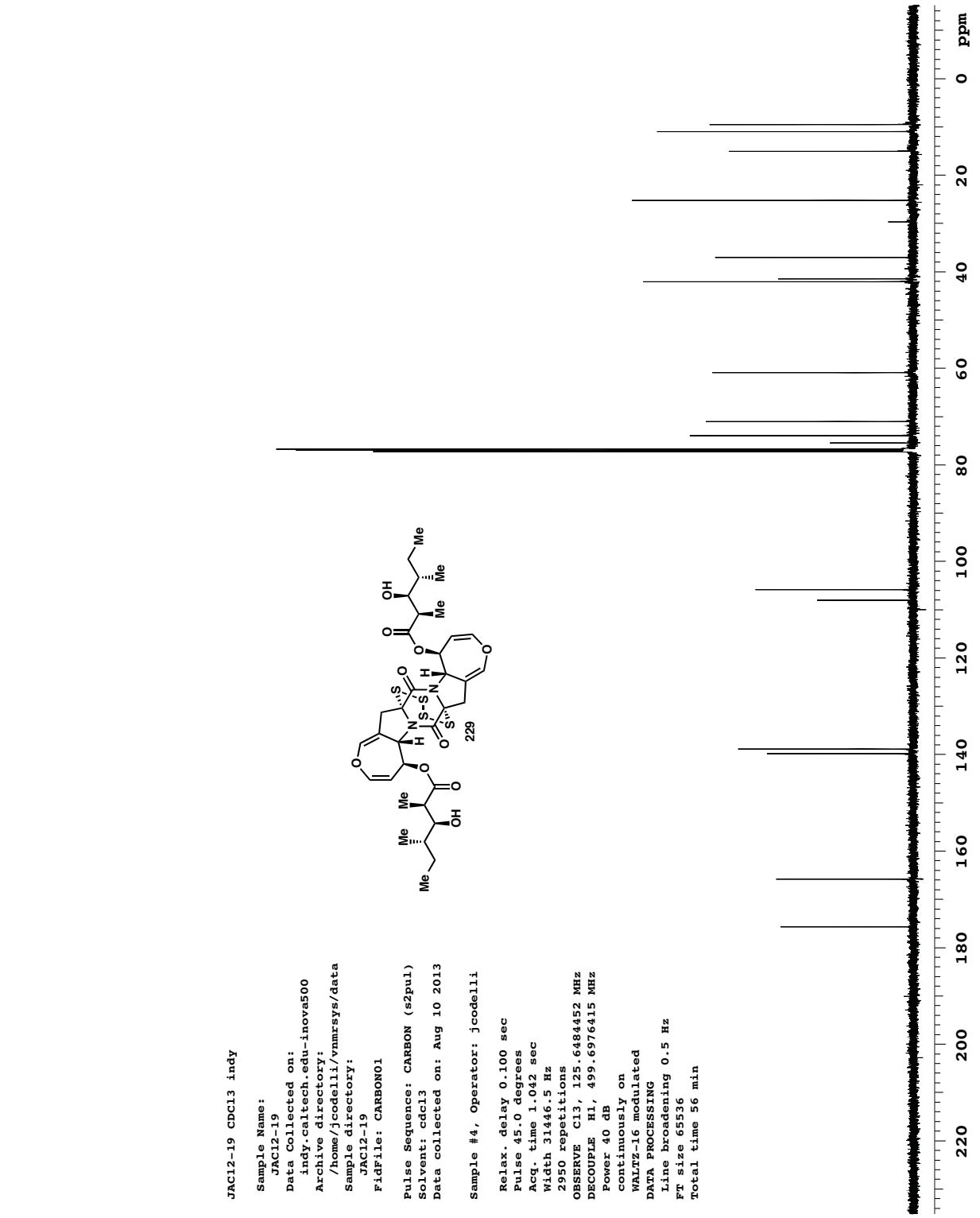

JAC12-17 CDCl3 indy
Sample Name:
JAC12-17
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-17
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 9 2013
Sample #4, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
SCH64877 (44)
ppm
6.41
6.36
6.34
4.22
2.22
2.00
2.02
1.93
2.07
2.01
2.00
2.00
4.06
2.02
2.03

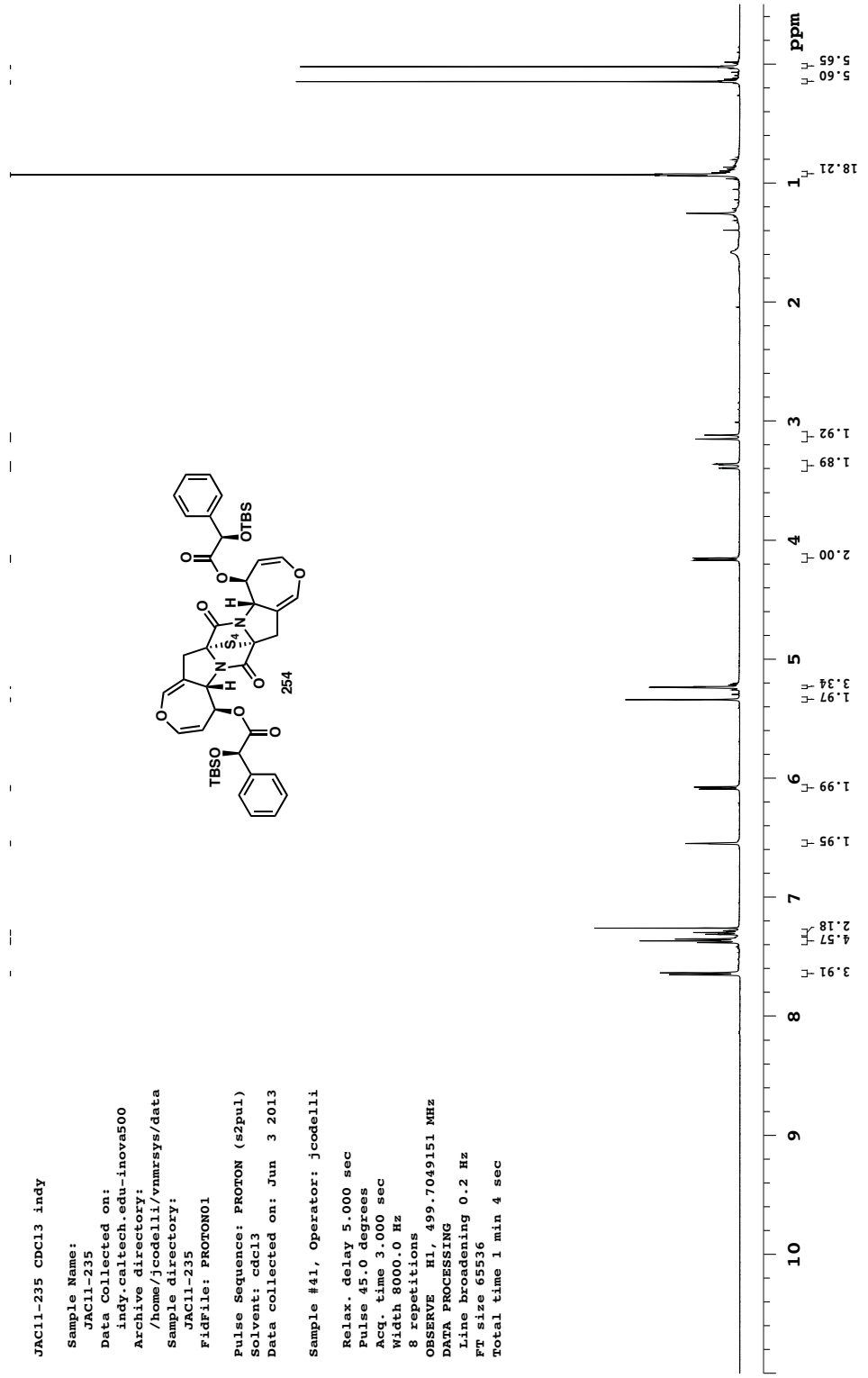

JAC12-17 CDCl3 indy
Sample Name:
JAC12-17
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-17
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 9 2013
Sample #4, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 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 56 min
SCH64877 (44)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

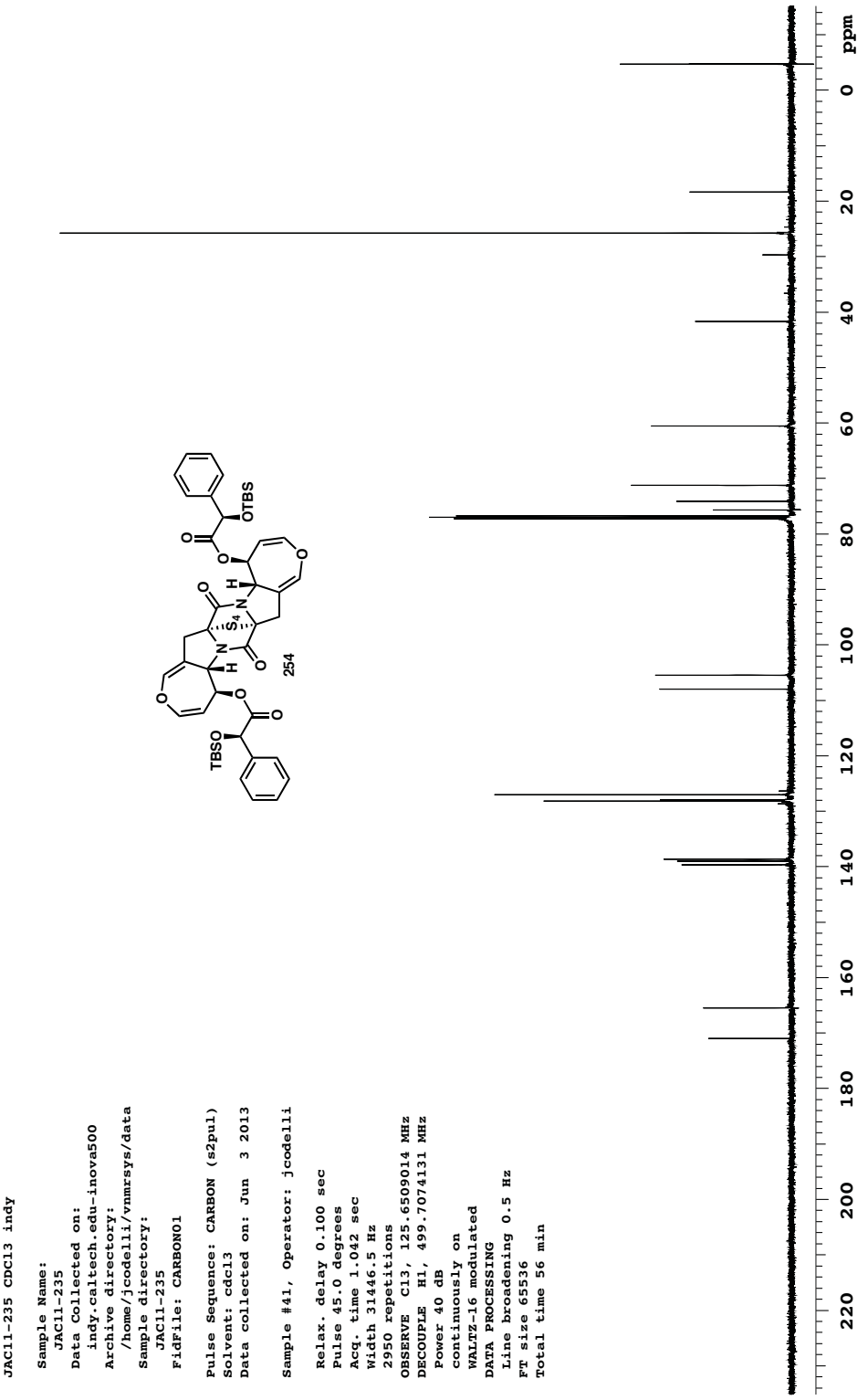

JAC11-297 CDCl3 indy
Sample Name:
JAC11-297
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-297
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
253
ppm
11.11
19.72
4.83
5.66
2.36
6.50
2.19
3.35
2.00
1.96
1.99
1.91
2.00
1.94
1.98
1.96
2.01

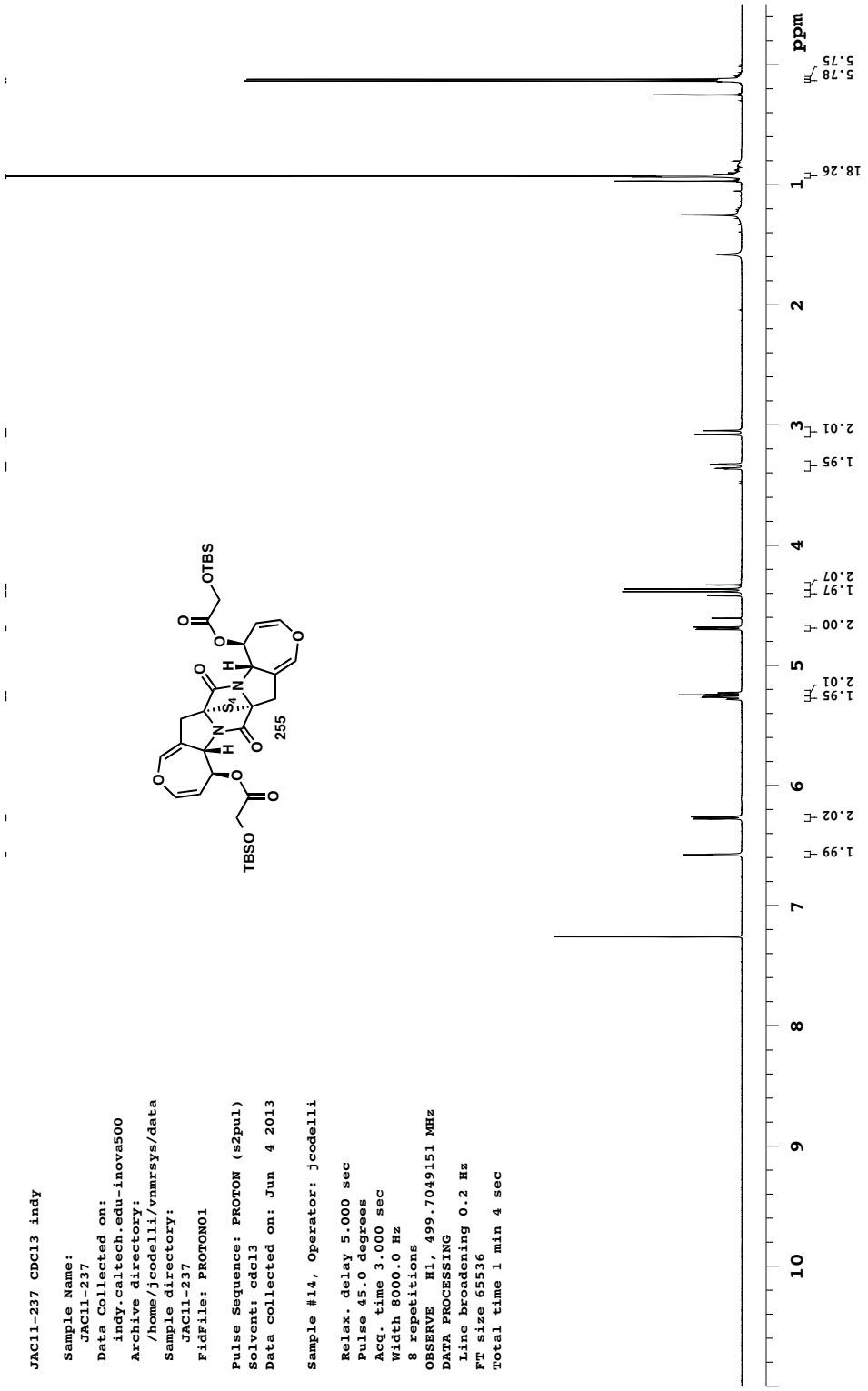

JAC11-297 CDCl3 indy
Sample Name:
JAC11-297
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-297
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 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 47 min
OTBS
TBSO
253
220
200
180
160
140
120
100
80
60
40
20
0
ppm

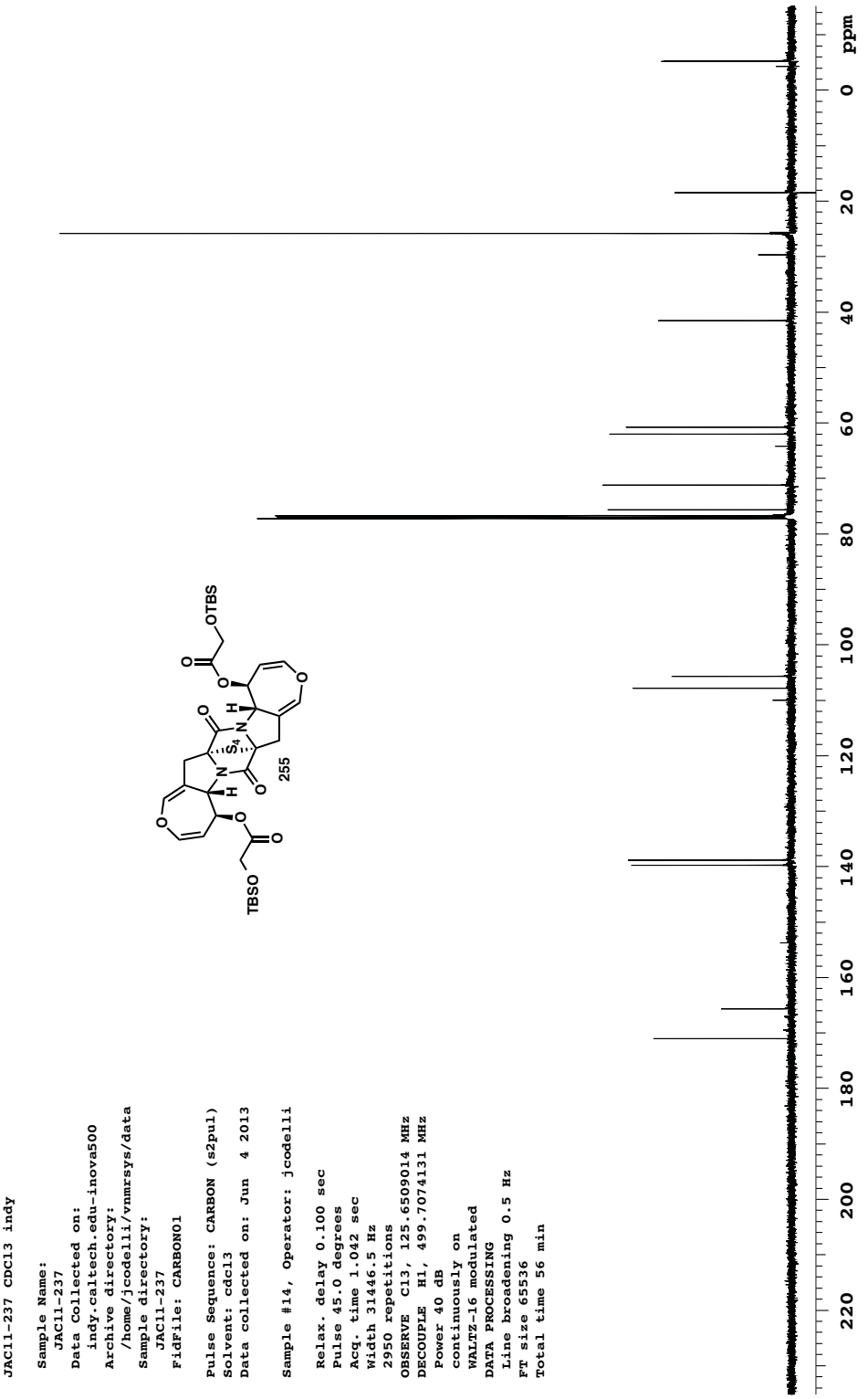

JAC12-19 CDCl3 indy
Sample Name:
JAC12-19
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-19
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 10 2013
Sample #4, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
229
ppm
10
9
8
7
6
5
4
3
2
1
1.96
1.98
1.96
1.97
1.99
2.00
1.98
1.99
2.43
1.49
2.07
2.25
6.56
3.87
6.12
6.26

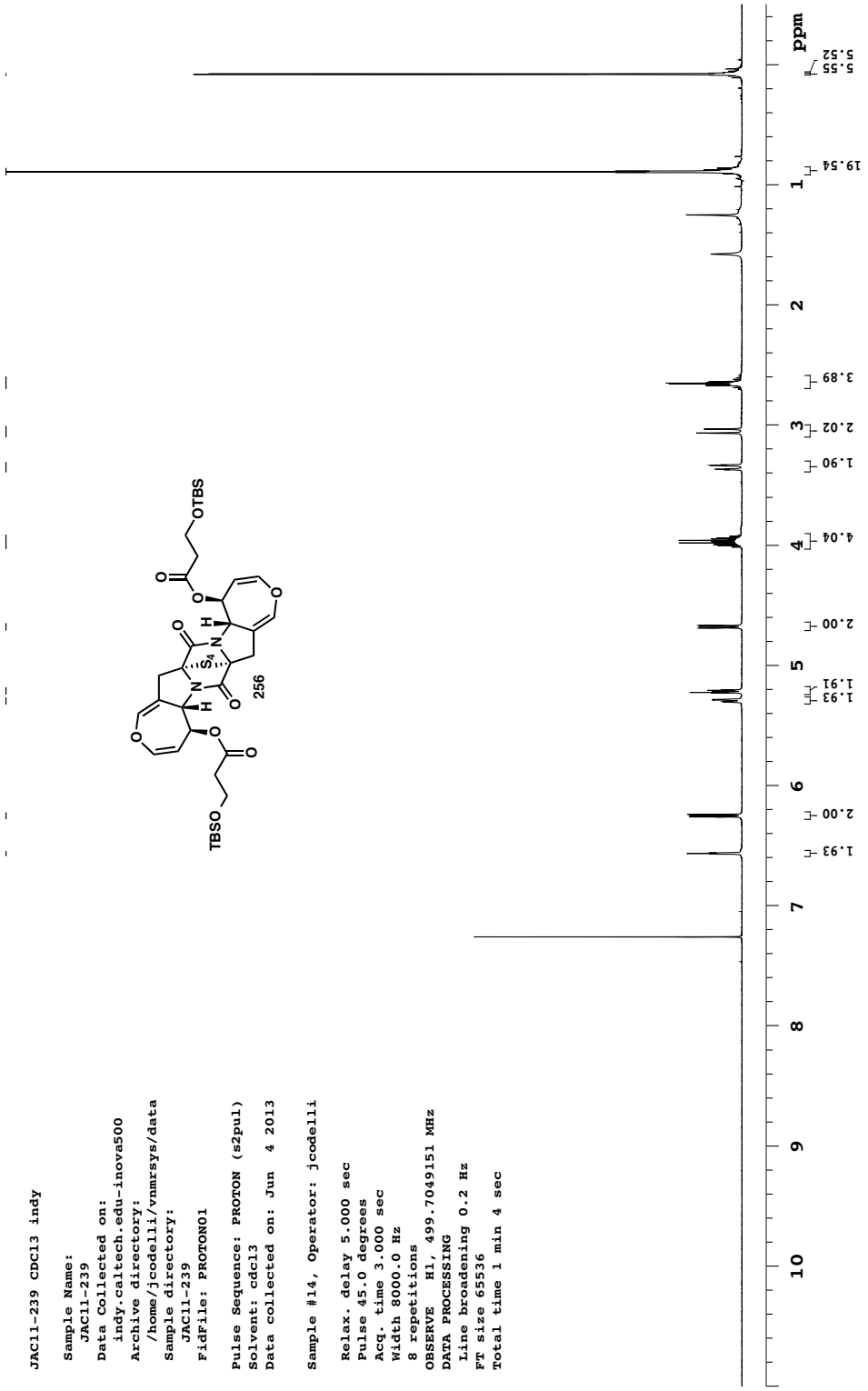

JAC12-19 CDCl3 indy
Sample Name:
JAC12-19
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-19
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 10 2013
Sample #4, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 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 56 min
229
220
200
180
160
140
120
100
80
60
40
20
0
ppm

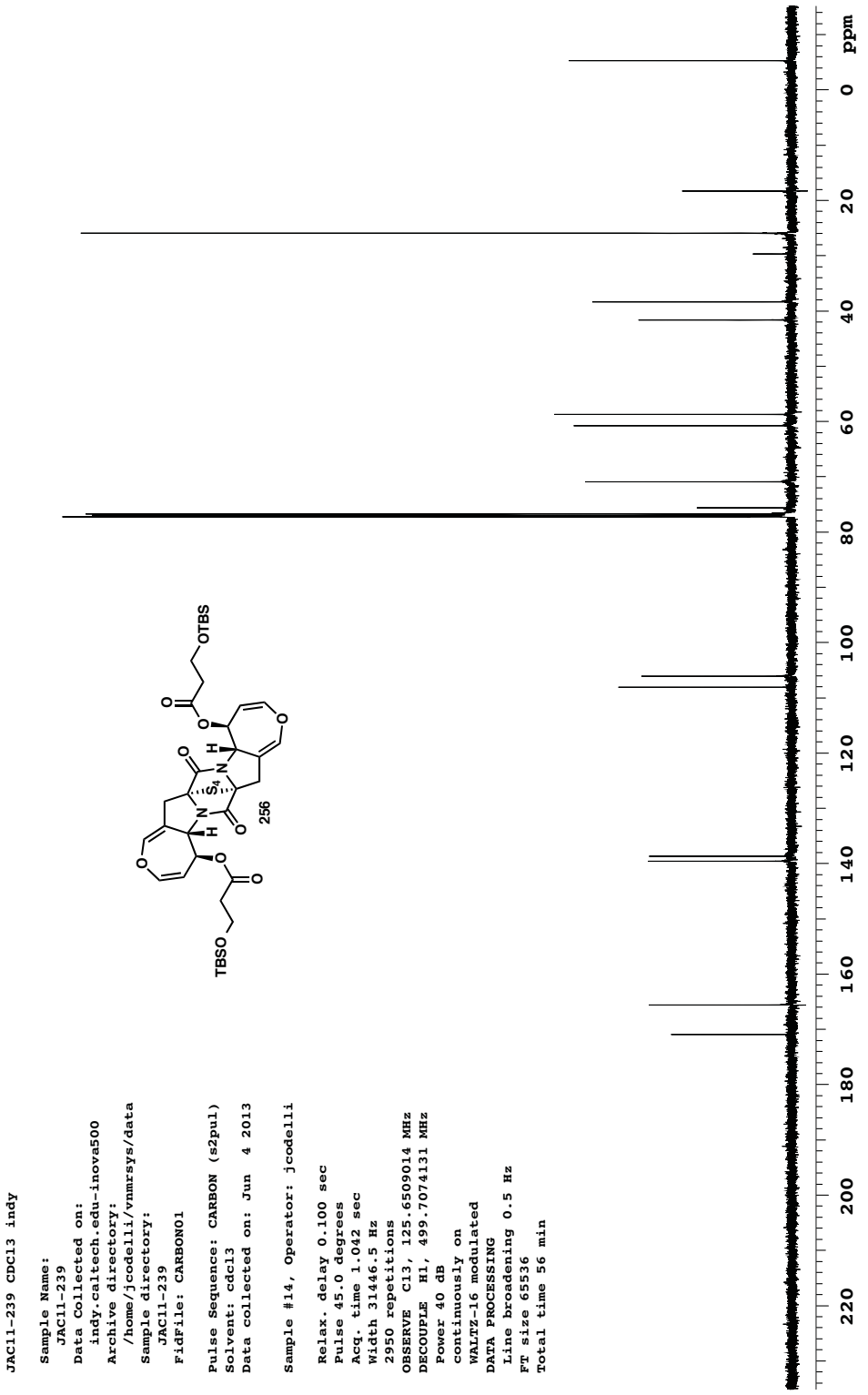

JAC11-235 CDCl3 indy
Sample Name:
JAC11-235
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-235
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 3 2013
Sample #41, Operator: jcodelli
Relax. delay 5.000 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 4 sec
OTBS
TBSO
254
ppm
10
9
8
7
6
5
4
3
2
1
5.65
5.60
18.21
1.92
1.89
2.00
1.97
3.34
1.99
1.95
4.57
2.18
3.91

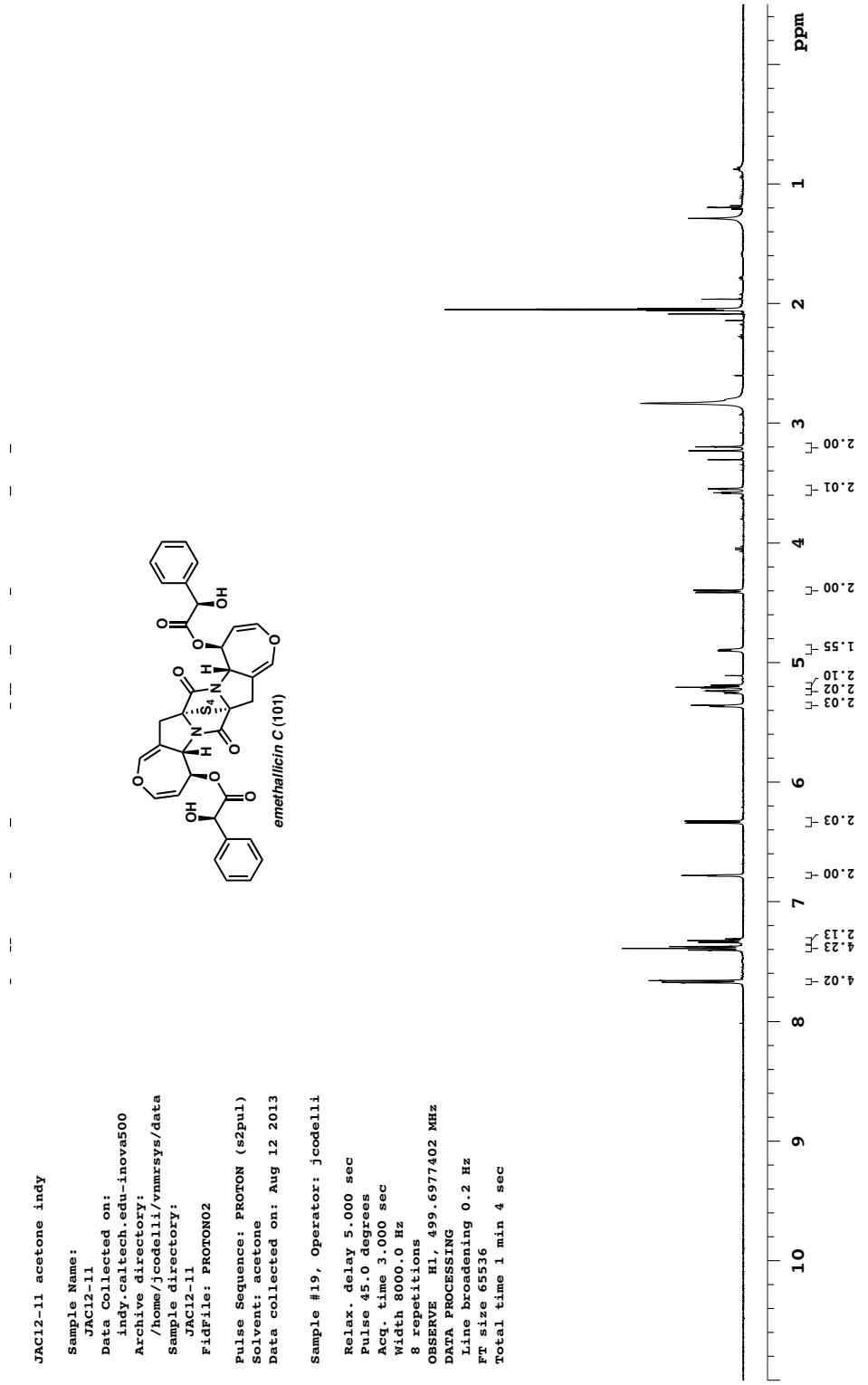

JAC11-235 CDCl3 indy
Sample Name:
JAC11-235
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-235
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 3 2013
Sample #41, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 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 56 min
TBSO
OTBS
254
220
200
180
160
140
120
100
80
60
40
20
0
ppm

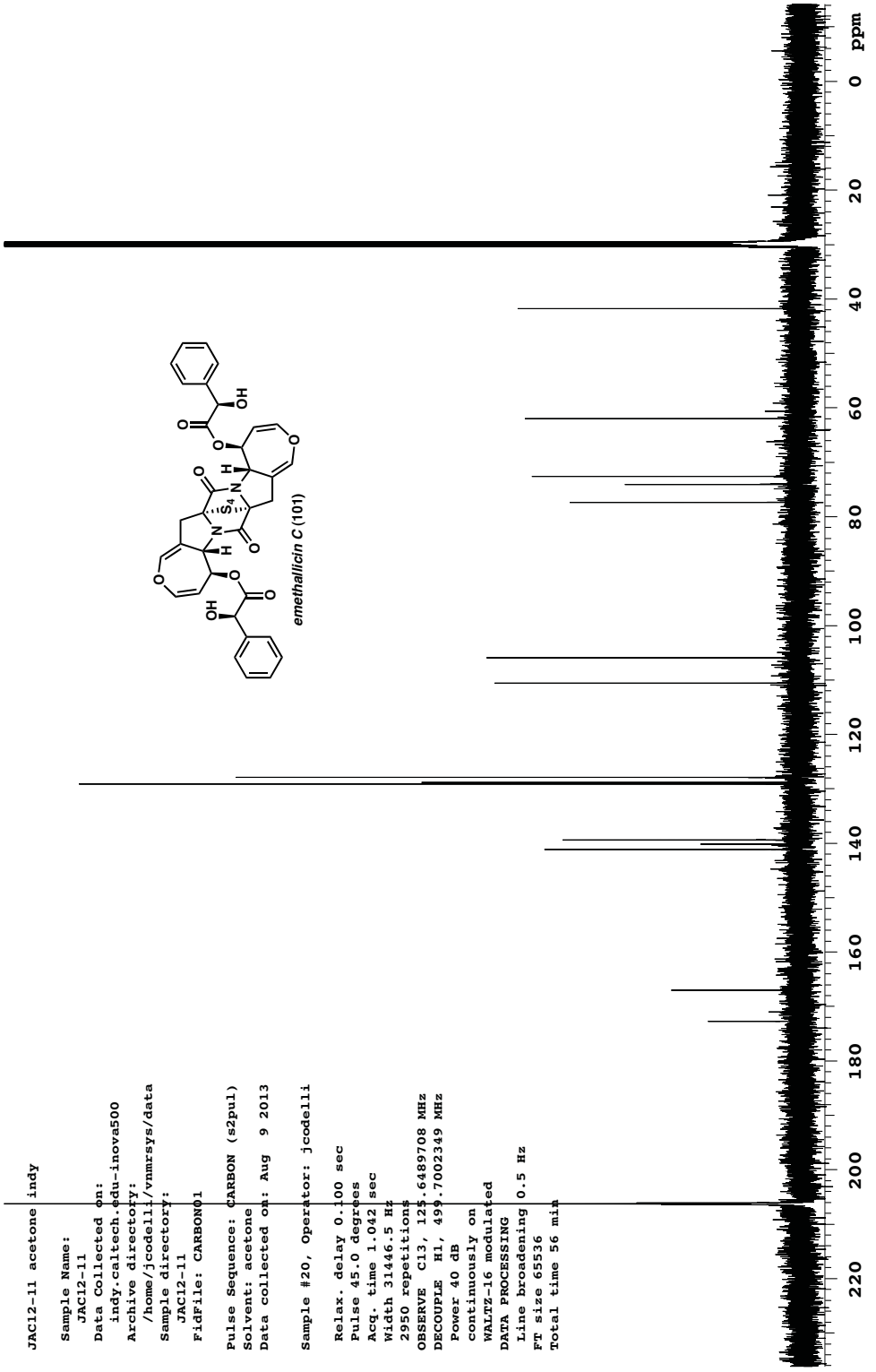

JAC11-237 CDCl3 indy
Sample Name:
JAC11-237
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-237
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 4 2013
Sample #14, Operator: jcodelli
Relax. delay 5.000 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 4 sec
OTBS
TBSO
255
ppm
5.78
5.75
18.26
2.01
1.95
1.97
2.07
2.00
1.95
2.01
2.02
1.99

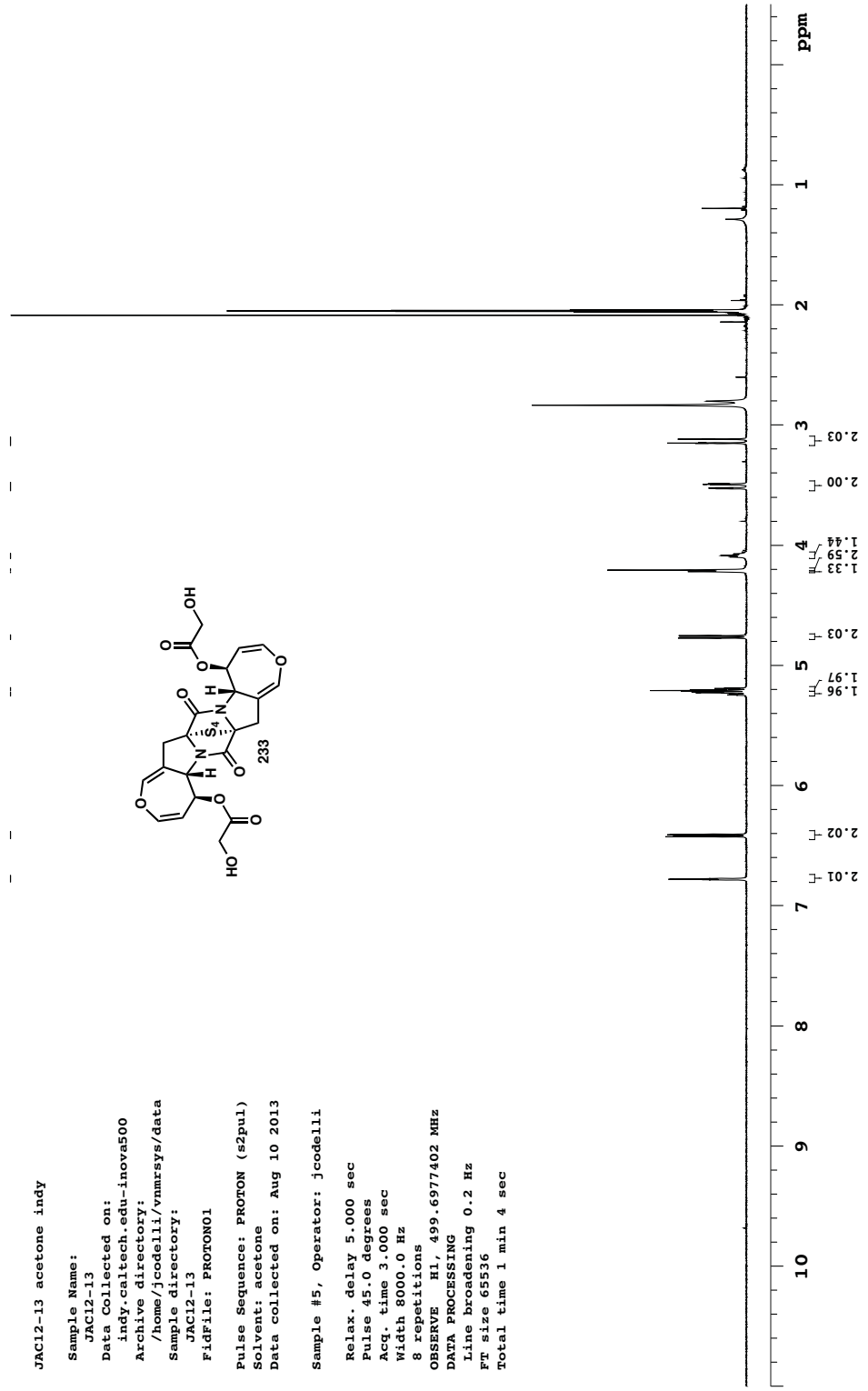

JAC11-237 CDCl3 indy
Sample Name:
JAC11-237
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-237
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 4 2013
Sample #14, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 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 56 min
OTBS
TBSO
255
220
200
180
160
140
120
100
80
60
40
20
0
ppm

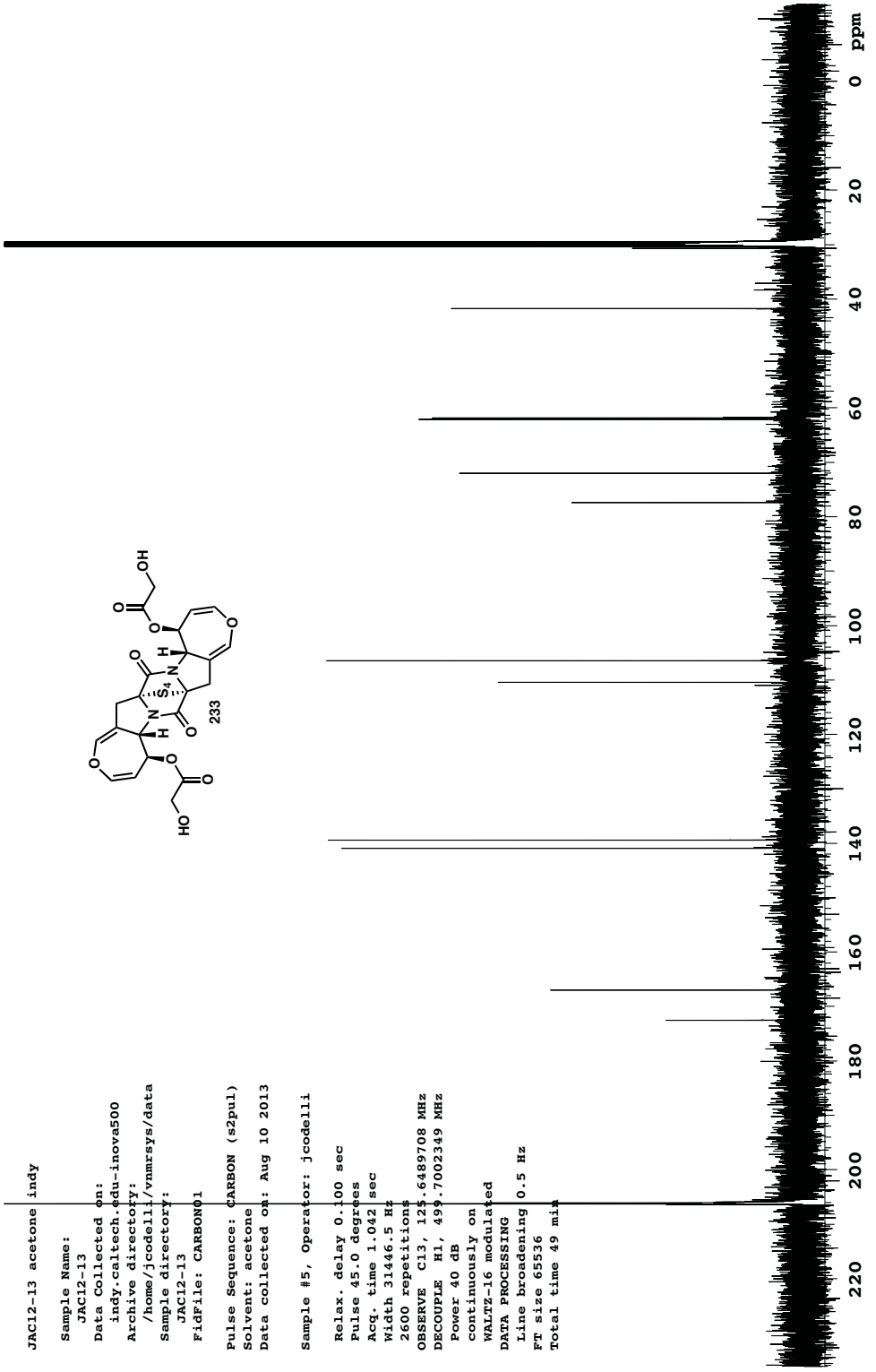

JAC11-239 CDCl3 indy
Sample Name:
JAC11-239
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-239
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 4 2013
Sample #14, Operator: jcodelli
Relax. delay 5.000 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 4 sec
OTBS
TBSO
256
ppm
5.55
5.52
19.54
3.89
2.02
1.90
4.04
2.00
1.93
1.91
2.00
1.93

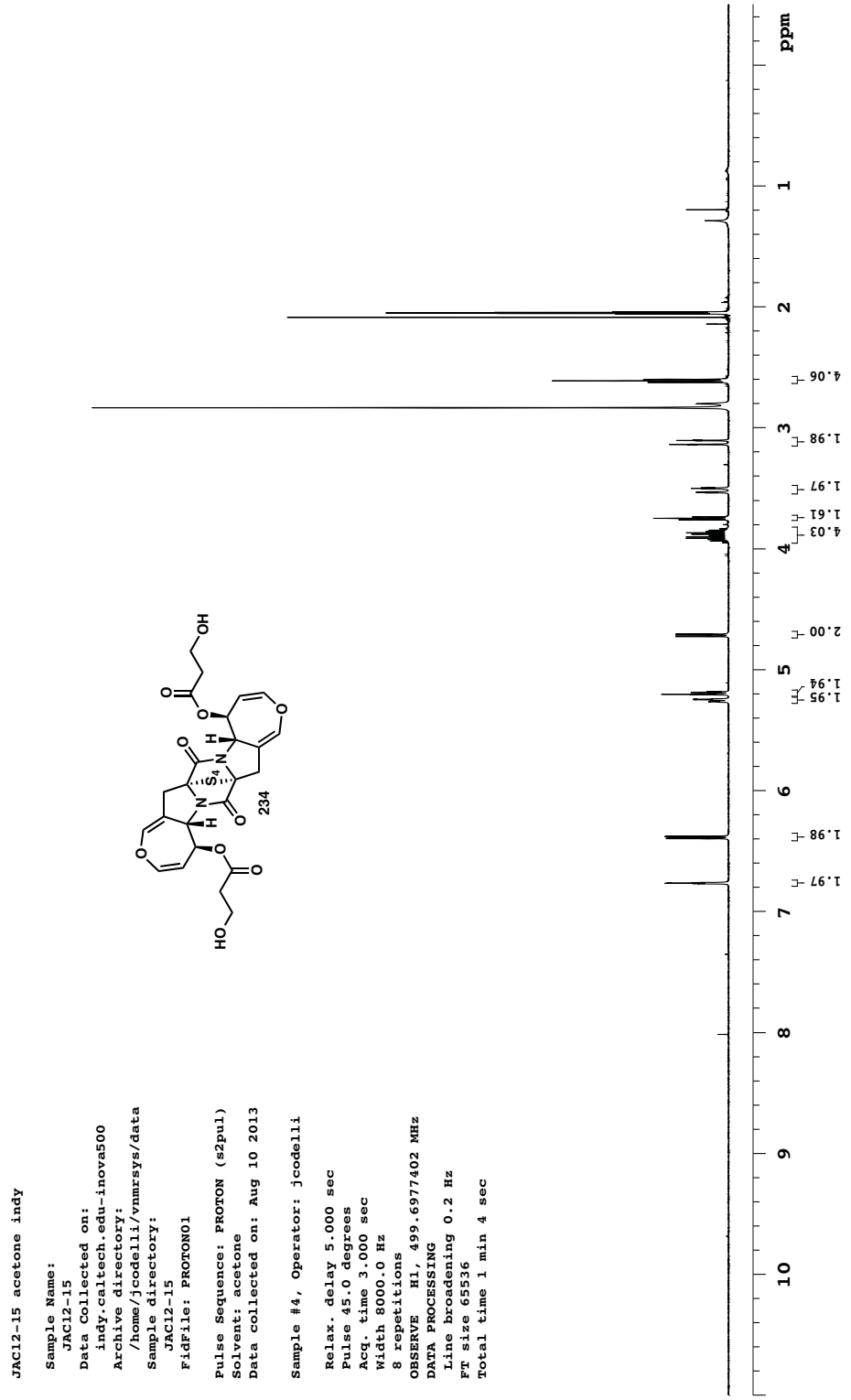

JAC11-239 CDCl3 indy
Sample Name:
JAC11-239
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-239
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 4 2013
Sample #14, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 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 56 min
OTBS
TBSO
256
220
200
180
160
140
120
100
80
60
40
20
0
ppm


JAC12-11 acetone indy
Sample Name:
JAC12-11
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-11
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: acetone
Data collected on: Aug 12 2013
Sample #19, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6977402 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
emethallicin C (101)
ppm
4.02
4.23
2.13
2.00
2.03
2.00
2.03
2.10
2.02
1.55
2.00
2.01
2.00


JAC12-11 acetone indy
Sample Name:
JAC12-11
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-11
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: acetone
Data collected on: Aug 9 2013
Sample #20, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 repetitions
OBSERVE C13, 125.6489708 MHz
DECOUPLE H1, 499.7002349 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
emethallicin C (101)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


JAC12-13 acetone indy
Sample Name:
JAC12-13
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-13
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: acetone
Data collected on: Aug 10 2013
Sample #5, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6977402 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
233
2.01
2.02
2.03
1.96
1.97
2.03
1.33
2.59
1.44
2.00
2.03
ppm


JAC12-13 acetone indy
Sample Name:
JAC12-13
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC12-13
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: acetone
Data collected on: Aug 10 2013
Sample #5, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2600 repetitions
OBSERVE C13, 125.6489708 MHz
DECOUPLE H1, 499.7002349 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 49 min
OH
HO
233
220
200
180
160
140
120
100
80
60
40
20
0 ppm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/home/jcodelli/vnmrsys/data
Sample directory:
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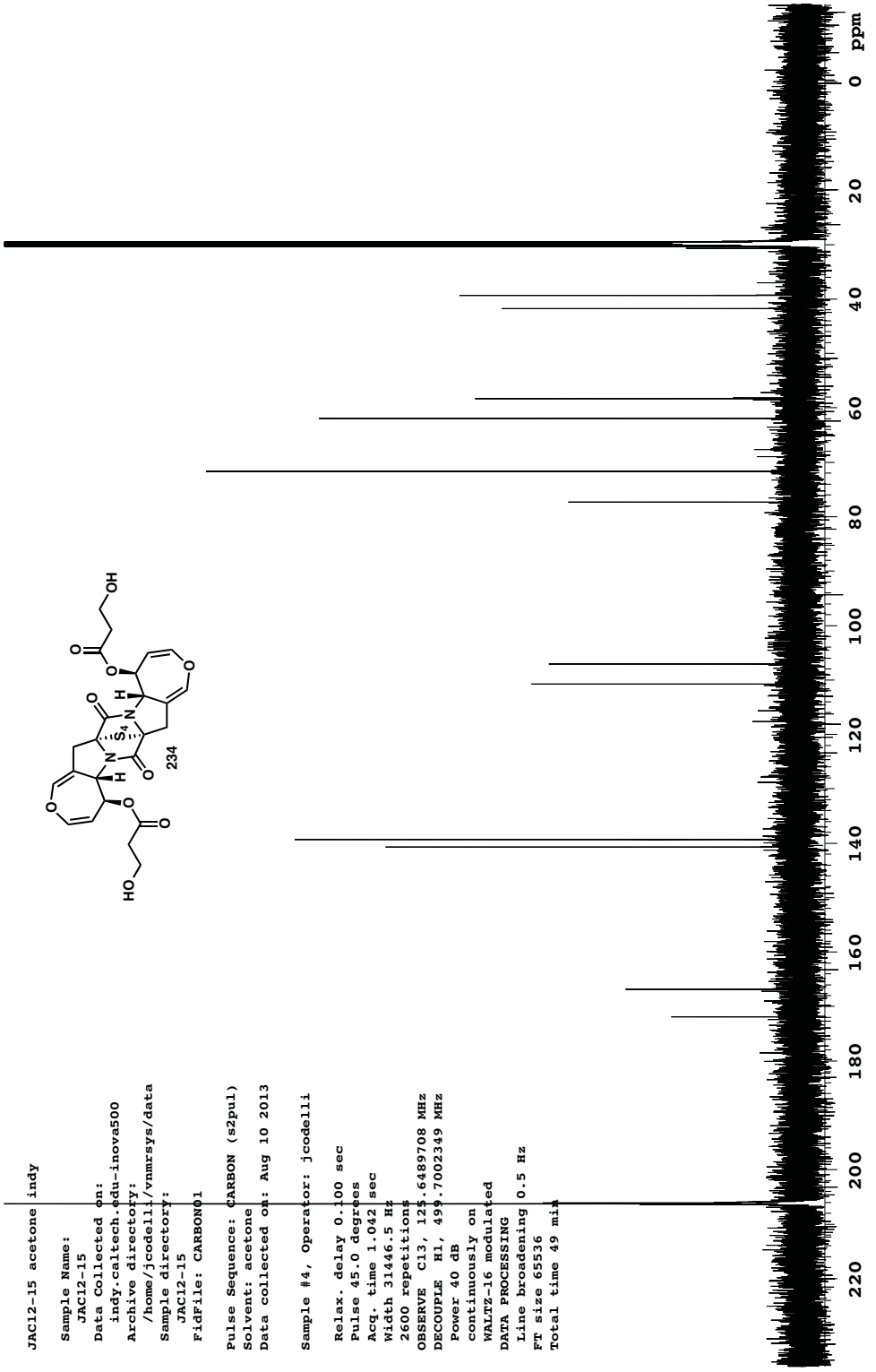
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: acetone
Data collected on: Aug 10 2013
Sample #4, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6977402 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
234
4.06
1.98
1.97
1.61
4.03
2.00
1.95
1.94
1.98
1.97
ppm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Data Collected on:
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Sample directory:
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Pulse Sequence: CARBON (s2pul)
Solvent: acetone
Data collected on: Aug 10 2013
Sample #4, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2600 repetitions
OBSERVE C13, 125.6489708 MHz
DECOUPLE H1, 499.7002349 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 49 min
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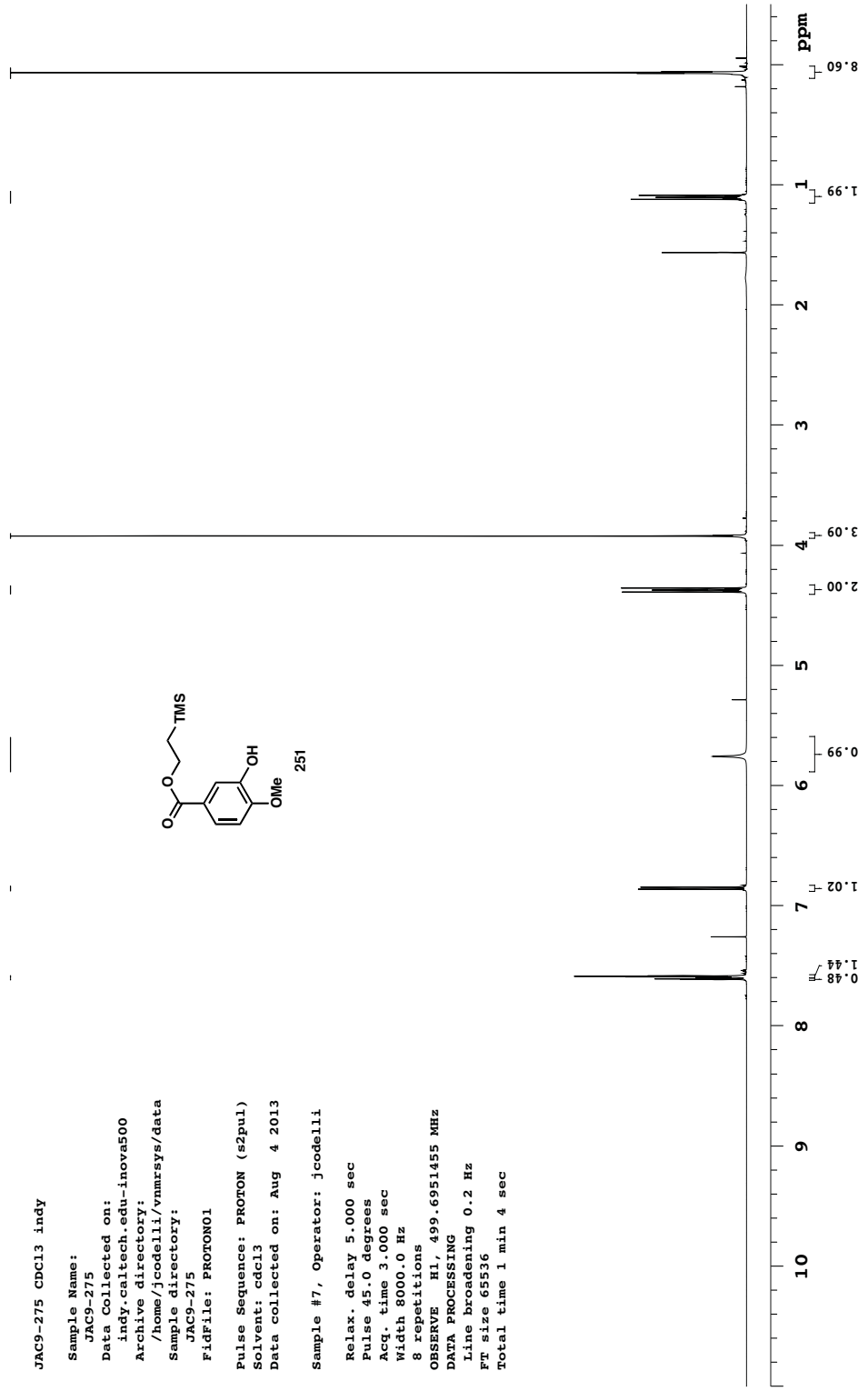
HO
234
220
200
180
160
140
120
100
80
60
40
20
0 ppm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Archive directory:
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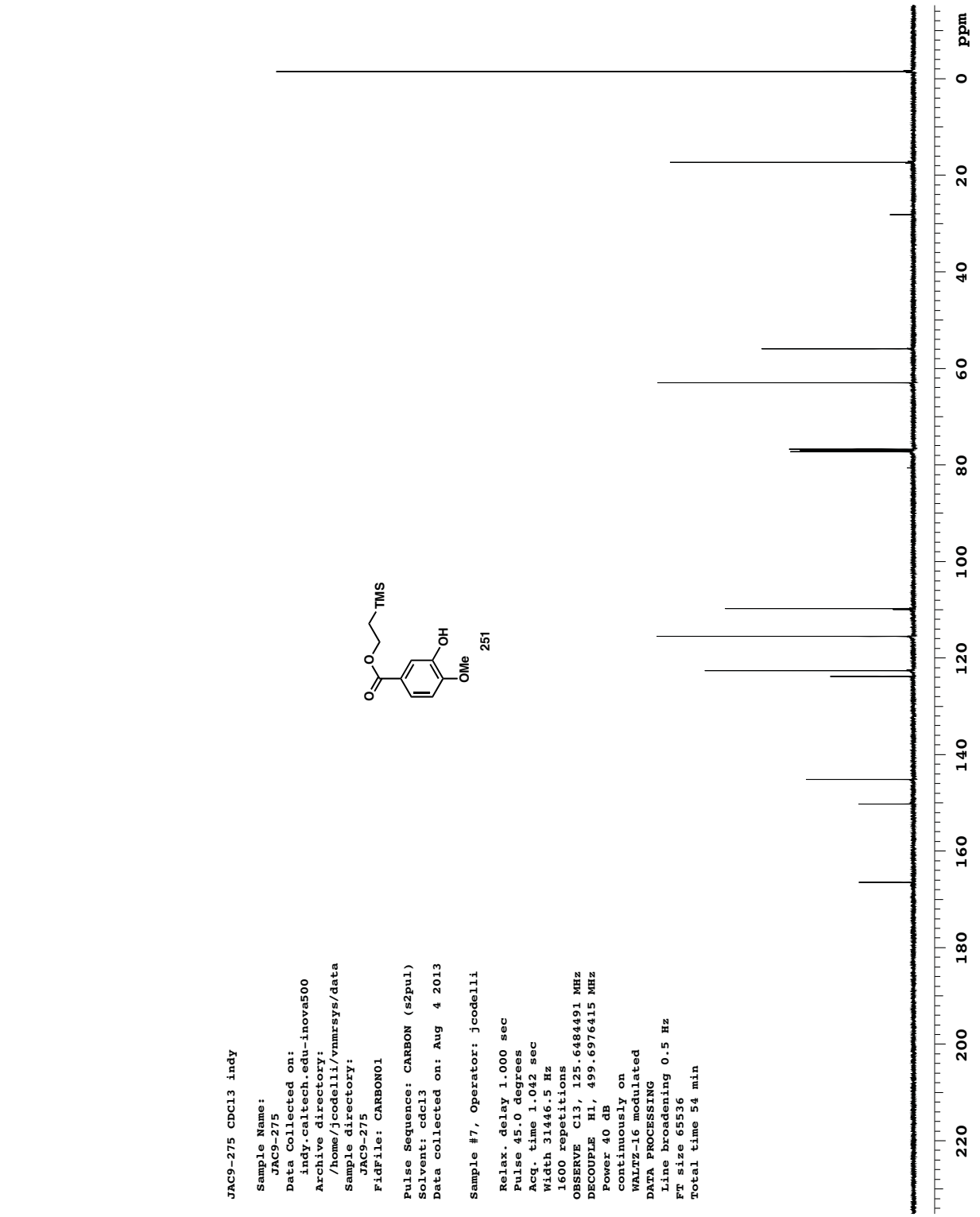
Sample directory:
JAC9-275
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6951455 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
TMS
OH
OMe
O
O
251
ppm
8.60
1.99
3.09
2.00
0.99
1.02
0.48
1.44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Data Collected on:
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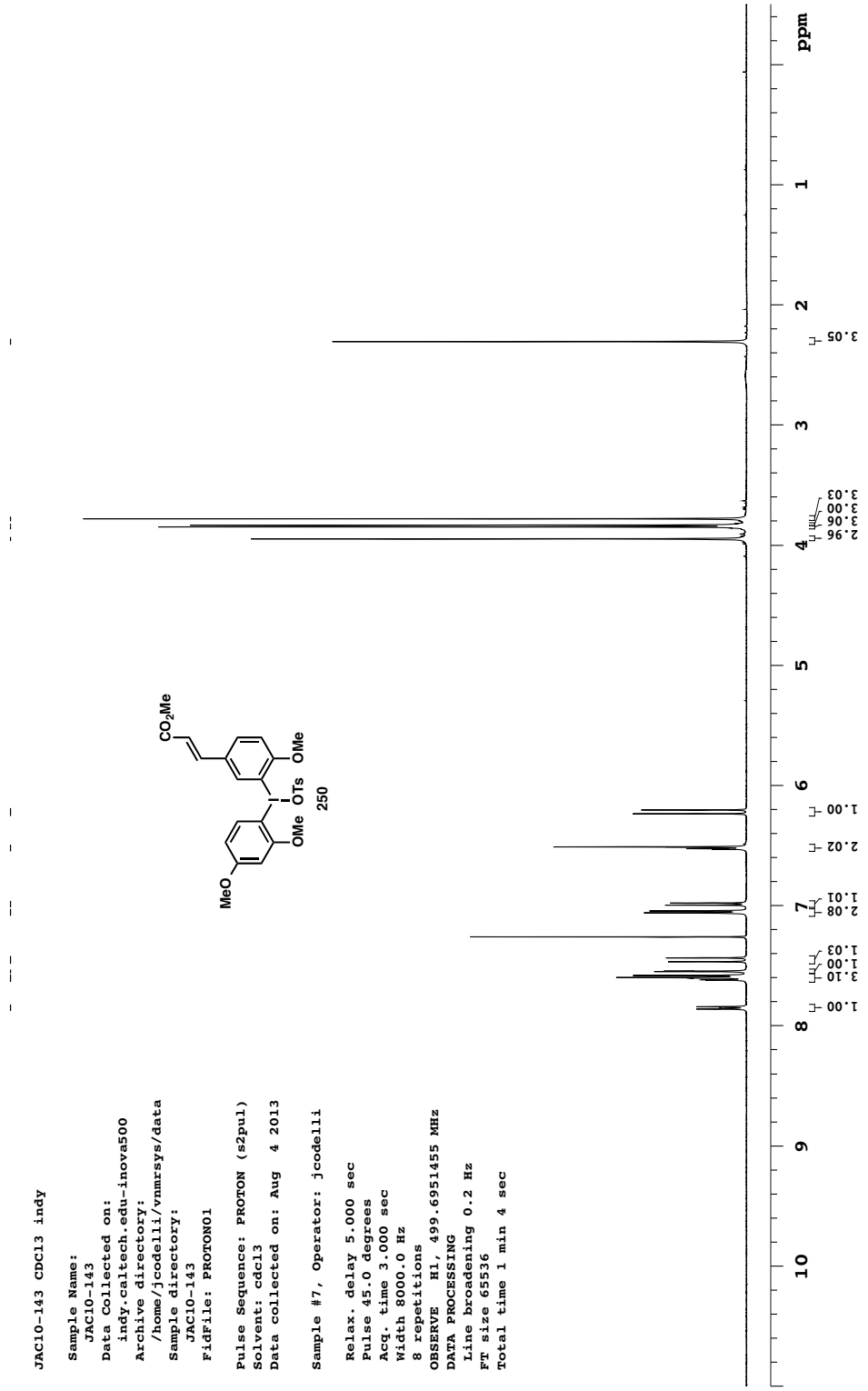
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC9-275
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6484491 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 54 min
TMS
O
O
OH
OMe
251
220
200
180
160
140
120
100
80
60
40
20
0
ppm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Data Collected on:
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Archive directory:
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Sample directory:
JAC10-143
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 5.000 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 0.2 Hz
FT size 65536
Total time 1 min 4 sec
CO2Me
OMe
OTs
OMe
MeO
250
ppm
1.00
3.10
1.00
1.03
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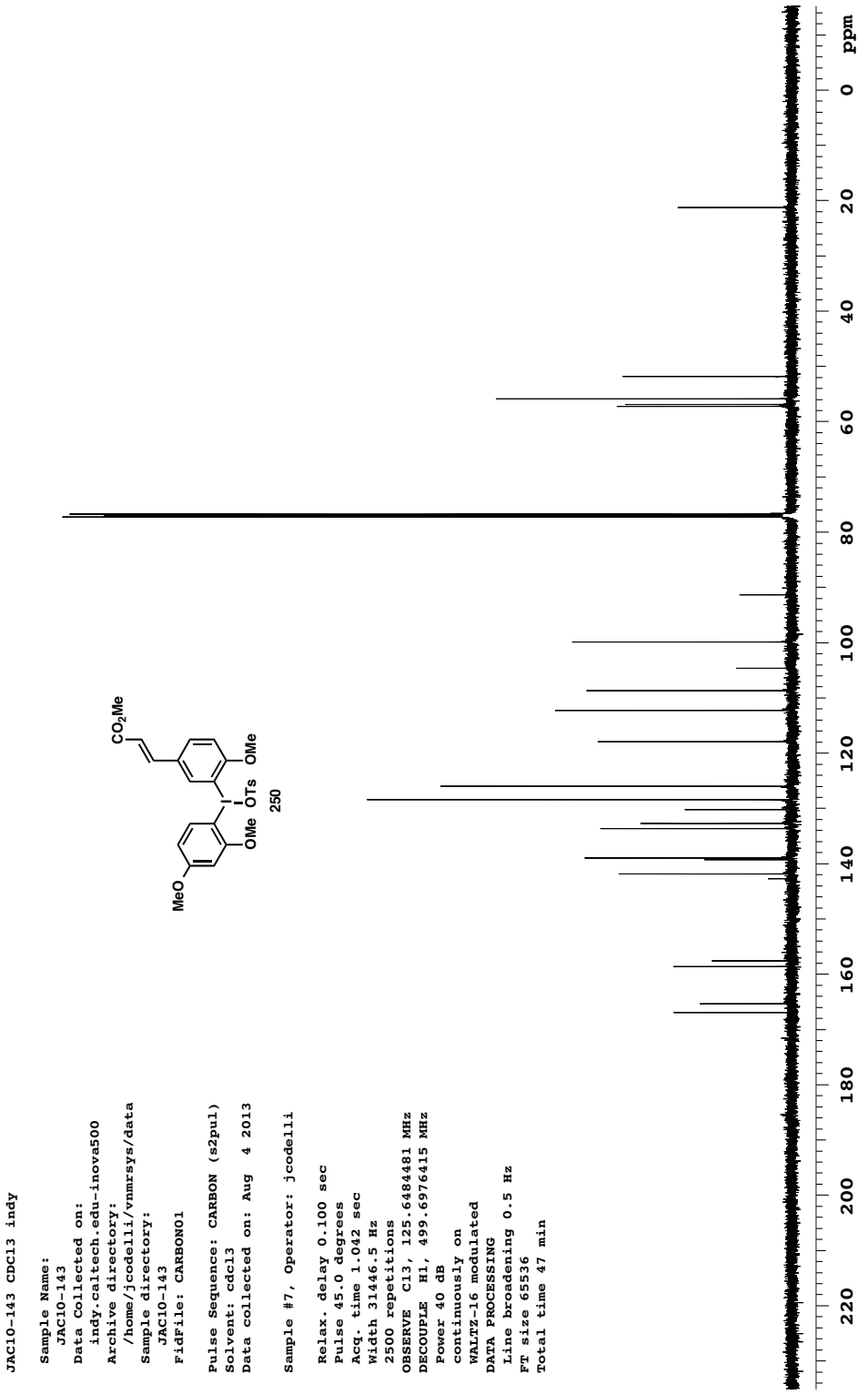
2.02
1.00
2.96
3.06
3.00
3.03
3.05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Sample Name:
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Data Collected on:
indy.caltech.edu-inova500
Archive directory:
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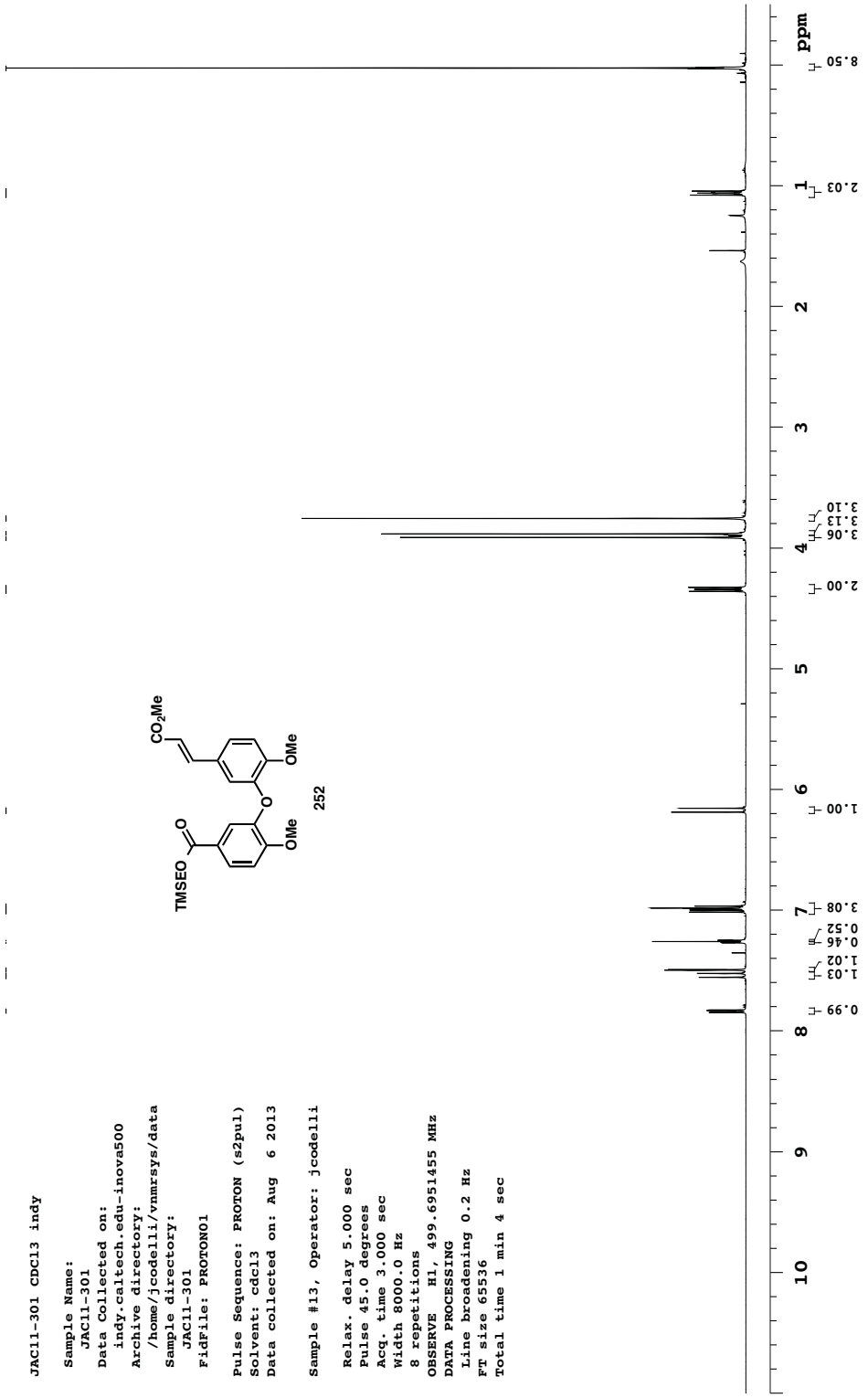
Sample directory:
JAC10-143
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2013
Sample #7, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 repetitions
OBSERVE C13, 125.6484481 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 47 min
CO2Me
OMe
OTs
OMe
MeO
250
220
200
180
160
140
120
100
80
60
40
20
0
ppm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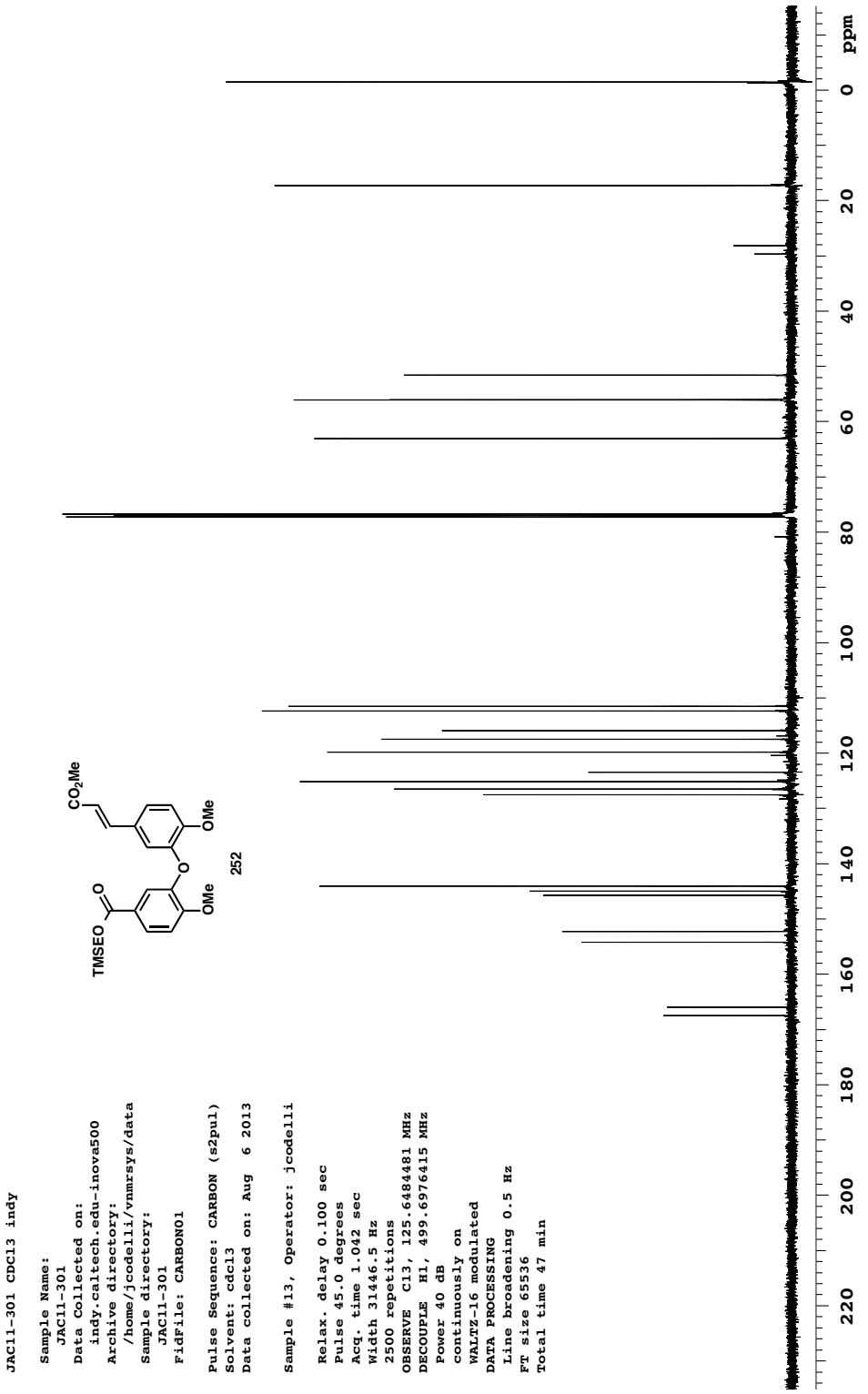
Sample Name:
JAC11-301
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-301
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 6 2013
Sample #13, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6951455 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
CO2Me
OMe
OMe
TMSEO
O
O
252
ppm
8.50
2.03
3.06
3.13
3.10
2.00
1.00
3.08
0.52
0.46
1.02
1.03
0.99


JAC11-301 CDCl3 indy
Sample Name:
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Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-301
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 6 2013
Sample #13, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2500 repetitions
OBSERVE C13, 125.6484481 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 47 min
TMSEO
O
OMe
O
OMe
CO2Me
252
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Chapter 4

Further Investigation of Side Reactions[†]

4.1 INTRODUCTION

One of the goals of any total synthesis research program is the discovery and development of new chemical reactions. This can occur either via the design of a novel transformation with a particular structural target in mind, *or* via the serendipitous observation of unintended yet interesting reactivity. Our synthetic studies toward acetylaranotin (**11**) required the development of several key transformations, such as the chlorohydrin cycloisomerization/elimination sequence for constructing the dihydrooxepine ring (see Chapter 2).[1] Furthermore, we observed several notable side reactions over the course of our efforts; in addition to the fluoride-promoted C–H oxidation mentioned in Chapter 2, we also observed a cascade cycloaddition process during our optimization of the enantioselective (1,3)-dipolar cycloaddition (1,3-DCA)

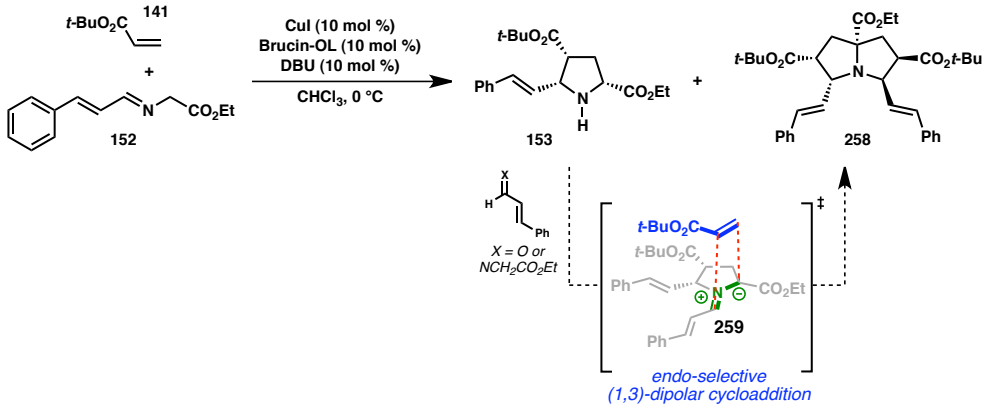
[†] Part of this chapter was published as the following communication: Lim, A. D.; Codelli, J. A.; Reisman, S. E. *Chem. Sci.* **2013**, *4*, 650. The research discussed in this chapter was completed in collaboration with Andrew D. Lim, a graduate student in the Reisman Lab.

that initiates our synthetic route. Though these reactions were not productive with respect to our total synthesis efforts, our curiosity prompted the further investigation of their scope and mechanism.

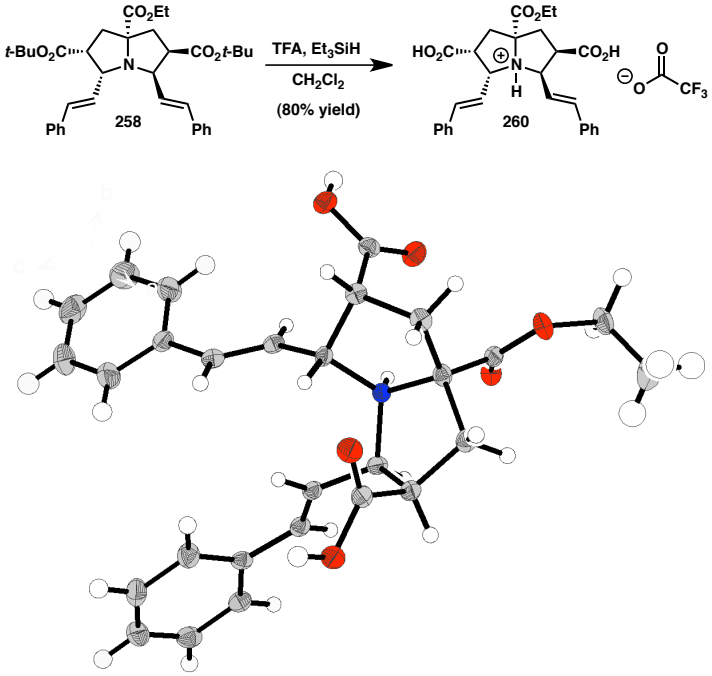
4.2 AN ENANTIOSELECTIVE CASCADE CYCLOADDITION PROCESS TO FORM HIGHLY SUBSTITUTED PYRROLIZIDINES

During studies aimed at optimizing the (1,3)-dipolar cycloaddition reaction utilized to prepare pyrrolidine **153** for the synthesis of acetylaranotin, we observed that under sub-optimal conditions the reaction stalls and a significant amount of pyrrolizidine **258** is isolated (Scheme 4.1). The structure of **258** was confirmed by single-crystal X-ray diffraction analysis of the corresponding TFA salt **260** (Scheme 4.2). We hypothesized that this product was being formed via a second (1,3)-dipolar cycloaddition, in which the initial pyrrolidine product **153** condenses with an equivalent of cinnamaldehyde or cinnamaldimine **152** to give ylide **259**, which then undergoes further reaction with *tert*-butyl acrylate to produce the final product (**258**).[2,3]

Scheme 4.1. *Observed formation of pyrrolizidine* ***258*** *during optimization of the Cu-catalyzed 1,3-dipolar cycloaddition*

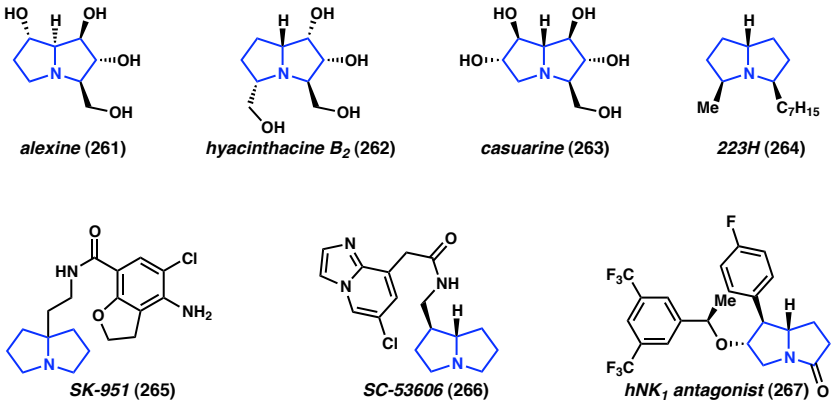


Scheme 4.2. *Formation and X-ray crystal structure of TFA salt* ***260***



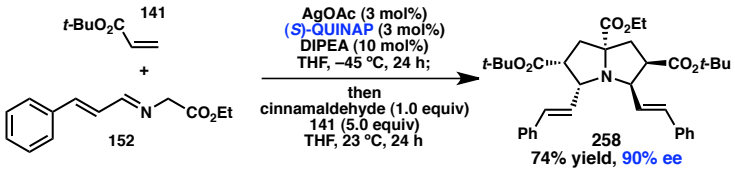
Given the presence of the pyrrolizidine ring system in a variety of bioactive natural products and pharmaceutical agents (see Figure 4.1),[4] as well as the general lack of methods for the rapid enantioselective preparation of highly substituted pyrrolizidine derivatives,[5] we sought to further develop this reaction, investigate its scope, and explore the subsequent reactivity of the resulting products.

Figure 4.1. *Pyrrolizidine-containing natural products and pharmaceutical agents*



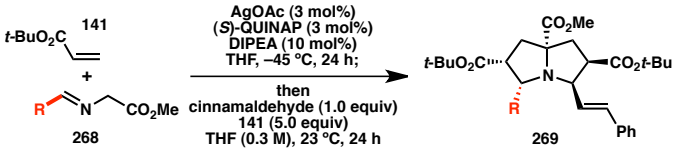
In our initial survey of conditions for the enantioselective (1,3)-dipolar cycloaddition reaction to produce pyrrolidine **153**,[6,7] we had identified the CuI/Brucin-OL catalyst system[8] as optimal for the scalable preparation of **153**. On the other hand, the operational simplicity of the AgOAc/(*S*)-QUINAP catalyst conditions[9] prompted us to use this system for investigations of pyrrolizidine formation.[10] Following preliminary experimentation, we were pleased to find that treatment of a mixture of cinnamaldehyde-derived α-imino ester **152**, AgOAc (3 mol %), QUINAP (3 mol %) and DIPEA (10 mol %) with *tert*-butyl acrylate (**141**, 1.5 equiv) in THF at –45 °C for 24 h, followed by addition of cinnamaldehyde (1.0 equiv) and additional **141** (5.0 equiv) with warming to 23 °C provided pyrrolizidine **258** in 74% yield and 90% *ee* (Scheme 4.3).[11,12] Notably, warmer temperatures are required for the second (1,3)-DCA, which proceeds very slowly at –45 °C. It is important that imine **152** is consumed before the reagents are added for the second cycloaddition; if **152** remains, it reacts rapidly and less selectively with *tert*-butyl acrylate upon warming to give **153**,[13] which can lead to the isolation of pyrrolizidine **258** in reduced *ee*.

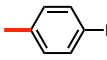
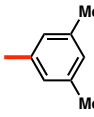
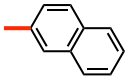
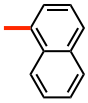
Scheme 4.3. *Optimized conditions for preparation of pyrrolizidine* ***258***



With conditions in hand to prepare pyrrolizidine **258** in good yield and high *ee*, attention turned to evaluating the substrate scope of the reaction (Table 4.1). A variety of substituted aryl aldehyde-derived α-imino esters **268** furnished the corresponding pyrrolizidines **269** in good yields with high enantioselectivity. Substitution at the *ortho*-, *meta*-, and *para*-positions of the arene with both electron-donating and electron-withdrawing substituents is well-tolerated. In particular, α-imino esters bearing electron-withdrawing aryl substituents provide the pyrrolizidine products with uniformly high levels of enantioselectivity (Table 4.1, **269f–j, 269m–o**). Notably, the α-imino ester derived from pyridine 3-carboxaldehyde is a suitable substrate, providing pyridyl-substituted pyrrolizidine **269r** in good yield and good *ee* (Entry 18). Alternatively, the 2-pyridyl α-imino ester provided pyrrolizidine **269s** in low yield and modest *ee* (Entry 19). It is possible that the proximal nitrogen results in an alternative binding mode between the azomethine ylide and the catalyst, decreasing the enantioselectivity during the first (1,3)-DCA.[14] In addition, the pyrrolidine intermediate or the pyrrolizidine product (**269s**) might bind to and inhibit the silver catalyst.

Table 4.1. *Substrate scope for catalytic asymmetric synthesis of highly substituted pyrrolizidines: α-imino ester*



entry		R	yield[a] (%)	ee[b] (%)
1	269a		90	91
2	269b		91	91
3[c]	269c		83	88
4[c]	269d		82	92
5[c]	269e		78	88
6	269f		87	93
7	269g		91	95
8	269h		89	92
9	269i		70	96
10	269j		80	96
11[d]	269k		86	90
12	269l		72	90
13	269m		87	94
14	269n		89	93
15	269o		82	92
16[d]	269p		76	92
17[c]	269q		84	93
18	269r		90	90
19	269s		33	44

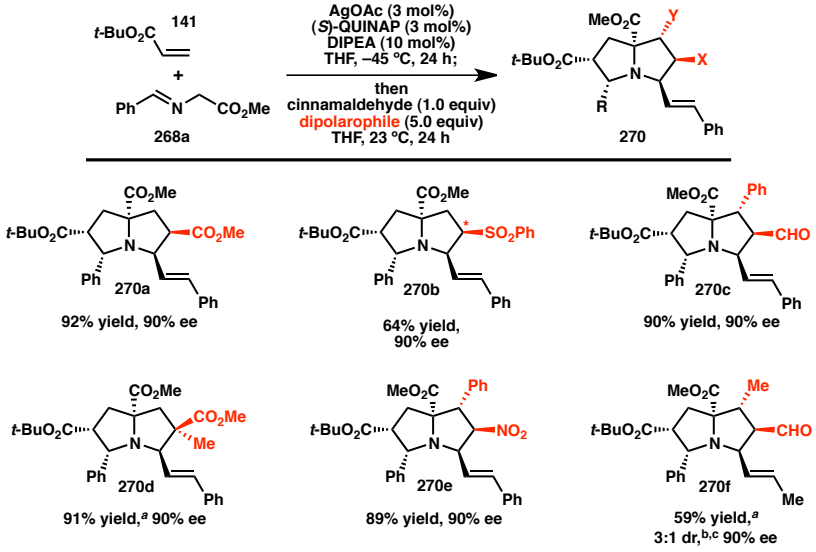
[a] Isolated yield. [b] Determined by SFC using chiral stationary phase. [c] 6 mol % each AgOAc and (*S*)-QUINAP were employed. [d] 6 mol % each AgOAc and (*S*)-QUINAP were employed at 0.1 M reaction concentration.

In some cases, the pyrrolizidine products were obtained in lower *ee* using our standard reaction conditions (e.g. compounds **269c–e**, **269q**).[15] It was determined that for these α-iminoesters, the first (1,3)-DCA proceeds slowly relative to the more electron-poor substrates; we reasoned that the remaining imine reacts with lower enantioselectively upon warming, which ultimately results in the formation of the pyrrolizidine with reduced *ee*. We hypothesized that increasing the catalyst loading should ensure complete consumption of the α-imino ester prior to warming the reaction for the second (1,3)-DCA. This hypothesis proved to be true; using 6 mol % each of AgOAc and (*S*)-QUINAP, pyrrolizidines **269c–e** and **269q** were obtained in good yields and high ee (Table 4.1, Entries 3, 5, 11 and 17). Alternatively, the solubility of *p*-

methoxy and 2-naphthyl α-iminoesters **268k** and **268p** was poor under our standard conditions; for these substrates the best results were obtained by lowering the overall reaction concentration (to 0.1 M versus 0.3 M) and increasing the catalyst loading to 6 mol %.

A variety of dipolarophiles can be used for the second (1,3)-DCA (Table 4.2). For example, use of *E*-1-nitro-2-phenylethylene as the second dipolarophile provides pyrrolizidine **270e** in 89% yield and 90% *ee*. This compound contains six stereogenic centers and is isolated as a *single* diastereomer. Use of methyl methacrylate provides pyrrolizidine **270d**, which contains an all-carbon quaternary center, in 91% yield and 90% ee.

Table 4.2. *Substrate scope for catalytic asymmetric synthesis of highly substituted pyrrolizidines: second dipolarophile*



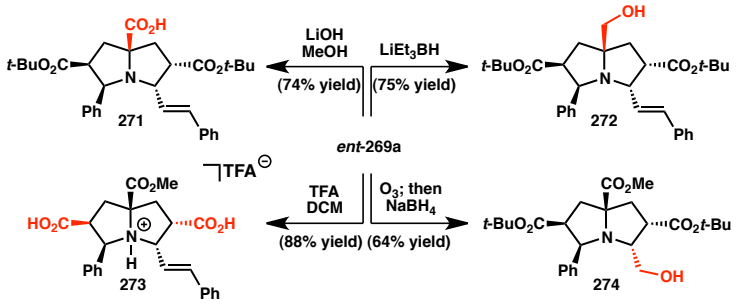
[a] 10.0 equivs of dipolarophile were used. [b] For this reaction, crotonaldehyde was used instead of cinnamaldehyde. [c] Refers to *endo*/*exo* selectivity of the second (1,3)-DCA reaction.

Interestingly, α,β-unsaturated aldehydes appear to be uniquely well suited for generating the pyrrolidine-derived azomethine ylide for the second (1,3)-DCA. Attempts

to employ aryl aldehydes (e.g. benzaldehyde) or alkyl aldehydes (e.g. 2-ethylbuytraldehyde) for the second (1,3)-DCA failed to provide the pyrrolizidine products in synthetically useful yields (see Experimental Section). We believe this unique reactivity of α,β-unsaturated aldehydes explains why standard catalytic, asymmetric (1,3)-DCAs are not plagued by unwanted pyrrolizidine formation, since α-imino esters derived from enals are rarely employed in methods development.

Using benzaldehyde-derived α-imino ester **268a**, the catalytic asymmetric (1,3)-DCA cascade reaction has been conducted on gram-scale, providing pyrrolizidine ***ent*-269a**[16] in 89% yield and slightly diminished *ee* (87%).[17] Importantly, this compound can be selectively modified to give several intermediates capable of further derivitazation (Scheme 4.4). For example, the more reactive and accessible methyl ester of ***ent*-269a** can be selectively saponified using LiOH or reduced using $LiEt_3BH$ to give carboxylic acid **271** or alcohol **272**, respectively. Alternatively, the *tert*-butyl esters can be cleaved upon treatment with trifluoroacetic acid (TFA) to give dicarboxylic acid **273**. Finally, the styrene of ***ent*-269a** can be ozonolytically cleaved and reduced *in situ* to provide amino alcohol **274** in 64% yield. Thus, each of the functional groups of ***ent*-269a** can be chemoselectively modified.

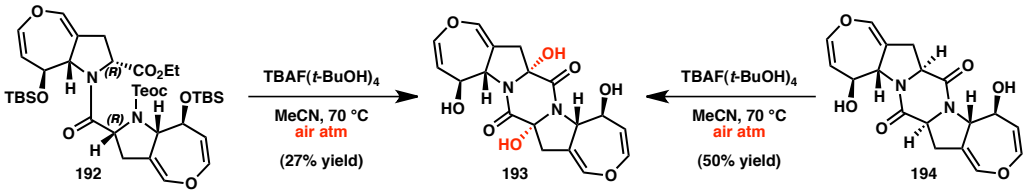
Scheme 4.4. *Selective derivatization of pyrrolizidine* ***ent-269a***



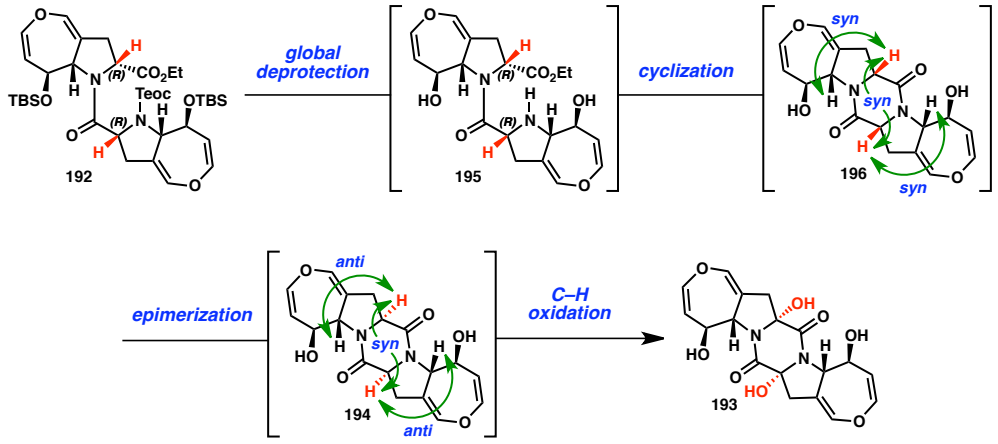
4.3 DIKETOPIPERAZINE OXIDATION AND STEREOCHEMISTRY

During studies aimed at the preparation of diketopiperazine **194** for the synthesis of acetylaranotin (**11**), we observed the formation of tetraol **193** when dipeptide **192** was treated with TBAF•(*t*-BuOH)$_4$ in MeCN at 70 °C under an *air* atmosphere (see Scheme 4.5, also see Chapter 2).[18] Furthermore, isolation of diketopiperazine **194** and resubjection to the above aerobic conditions provided the same oxidation product **193**. Based on these results, we tentatively proposed the mechanistic hypothesis shown in Scheme 4.6. First, fluoride-promoted global desilylation of **192** provides deprotected dipeptide **195**, which cyclizes to give the expected *syn*,*syn*,*syn* diketopiperazine **196**. Subsequent epimerization to the *anti*,*syn*,*anti* configuration affords the observed diketopiperazine **194**. Finally, *stereoretentive* aerobic oxidation of **194** then furnishes the tetraol **193**.

Scheme 4.5. *Formation of dihydroxylated diketopiperazine **193***



Scheme 4.6. *Proposed TBAF•(t-BuOH)$_4$-promoted diketopiperazine formation/ oxidation sequence*

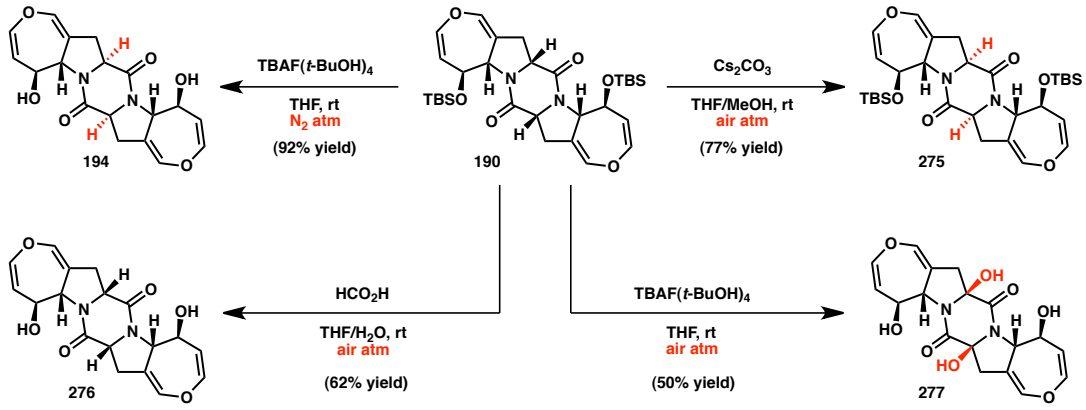


Such O_2-mediated α-oxidations are typically carried out using very strong, ionic bases (e.g. KO*t*-Bu or NaHMDS),[19,20,21] although a recent report from Buckley and coworkers supports the hypothesis that the fluoride ion may play some role in the oxidizing capability of our system.[22] Furthermore, the fact that no hydroperoxide intermediates or *anti*,*anti*,*syn* products are observed suggests that each oxygen atom on a single diketopiperazine ring may originate from a single molecule of O_2, via a sequence involving initial intermolecular oxidation of the first C–H bond by O_2 followed by intramolecular oxidation of the second C–H bond by the resulting peroxide radical.

In an effort to further elucidate the nature of this oxidation process and better-understand its stereochemical outcome, control experiments were carried out using TBS-protected *syn*,*syn*,*syn* diketopiperazine **190** (see Scheme 4.7). Diketopiperazine **190** could be epimerized *with* or *without* concomitant cleavage of the TBS ethers, by treatment with TBAF•(*t*-BuOH)$_4$ in THF under an inert atmosphere at ambient temperature or Cs_2CO_3 in THF/MeOH at ambient temperature to furnish diketopiperazines **194** or **275**, respectively. This suggests that for both the bis-TBS-protected and unprotected diketopiperazine, the thermodynamic preference is for the *anti*,*syn*,*anti* configuration. However, we were surprised to find that in the presence of ambient air atmosphere, diketopiperazine **190** undergoes TBAF•(*t*-BuOH)$_4$-promoted deprotection with concomitant *stereoretentive* C–H oxidation to afford *syn*,*syn*,*syn* oxidation product **277**! This suggests that the TBAF•(*t*-BuOH)$_4$-promoted oxidation is stereospecific, and unlikely to involve enol intermediates, given that no epimerization occurs prior to oxidation. Finally, it was observed that the unepimerized, unprotected diketopiperazine **276** could be obtained by subjection of **190**

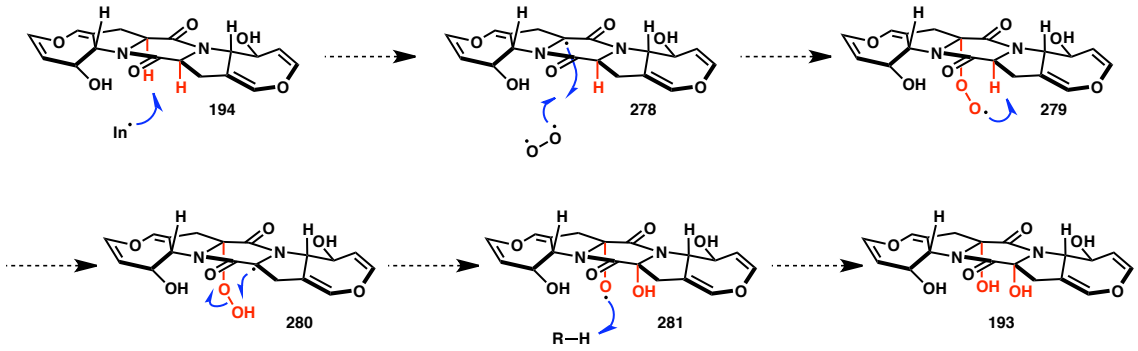
to HCO_2H in THF/H_2O, and future control experiments will seek to determine the stereochemical outcome of dihydroxylation or sulfenylation of this substrate.

Scheme 4.7. *Manipulation of diketopiperazine oxidation and stereochemistry*



Taken together, the above observations suggest the mechanism for oxidation of diketopiperazine **194** could be as shown in Scheme 4.8. Intermolecular hydrogen radical abstraction from **194** occurs to afford radical species **278**, which reacts with triplet O_2 to provide peroxide radical **279**. Subsequent intramolecular hydrogen radical abstraction affords diketopiperazine radical **280**, which undergoes intramolecular S_H2-type displacement to afford alkoxy radical **281**. Final intermolecular hydrogen radical abstraction from another molecule of **194** or some propagating (or terminating) species R–H furnishes the oxidized product (**193**). Unfortunately, preliminary efforts aimed at applying these conditions to simpler diketopiperazines as a general method for C–H oxidation have proven unfruitful.

Scheme 4.8. *Proposed mechanism for aerobic oxidation of diketopiperazine* ***194***



4.4 CONCLUDING REMARKS

In conclusion, a catalytic asymmetric double (1,3)-dipolar cycloaddition reaction has been developed, as part of our efforts to further explore interesting side reactions observed during synthetic studies toward acetylaranotin (**11**). This reaction provides access to highly substituted, enantioenriched pyrrolidizines from inexpensive, commercially available starting materials. Depending on which of the second dipolarophiles are employed, pyrrolizidines containing as many as six stereogenic centers have been prepared with high levels of enantio- and diastereoselectivity. We expect that this reaction could be of use for the preparation of natural product analogues of new lead compounds for pharmaceutical studies.

Likewise, a series of control experiments allowed us to probe the mechanism of the aerobic oxidation of diketopiperazine **194**. Though we were unable to develop this transformation into a general reaction methodology, future studies of related complex diketopiperazines may allow for the identification of structural parameters required for oxidation to occur.

4.5 EXPERIMENTAL SECTION

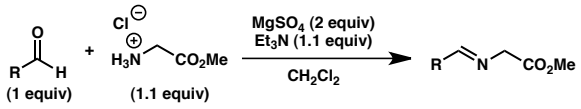
4.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) and *N*,*N*-diisopropylethylamine (DIPEA) were distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[23] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^{1}H, δ = 7.26), MeCN-d_2 (^{1}H, δ = 1.94), or acetone-d_5 (^{1}H, δ = 2.05), and $CDCl_3$ (^{13}C, δ = 77.0), CD_3CN (^{13}C, δ = 118.26), DMSO-d_6 (^{13}C, δ = 39.52). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, 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. Analytical SFC was performed with a Mettler SFC supercritical CO2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm) with visualization at 254 nm. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

4.5.2 Preparative Procedures and Spectroscopic Data

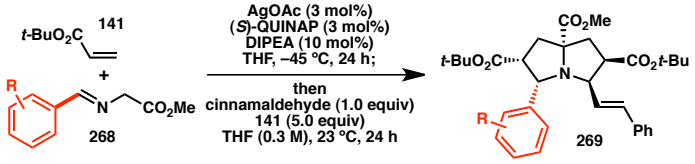
General procedure 1 for the synthesis of α-iminoesters 152, 268a-s



The α-iminoesters were prepared according to the procedure reported by Longmire et al.[24] To a suspension of the glycine methyl (or ethyl) ester hydrochloride (1.1 equiv) and magnesium sulfate (2.0 equiv) in methylene chloride was added triethylamine (1.1 equiv). This solution was stirred at room temperature for 1 h before the aldehyde (1.0 equiv) was added. After stirring at room temperature overnight, magnesium sulfate was filtered off and washed with methylene chloride. The filtrate was washed with distilled water (5x) and then with brine, dried over magnesium sulfate, filtered, and concentrated to afford the α-iminoesters. The crude iminoesters could be used directly for the cycloaddition reactions. The reactions reported above were performed on the scale of

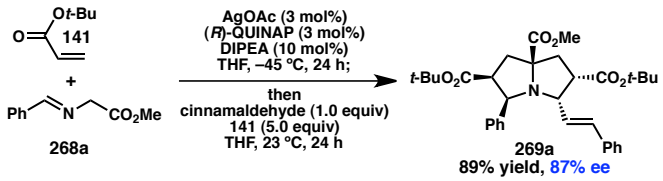
1.0–4.0 g of aldehydes at 0.5 M concentration. **NOTE:** Formation of α-iminoester **152** was allowed to proceed for 1.5 h rather than overnight in order to avoid decomposition.

General procedure 2 for the synthesis of pyrrolizidines 269a-s



Silver(I) acetate (1.0 equiv) and (*S*)-QUINAP (1.0 equiv) were added to a vial. Tetrahydrofuran was then introduced, and this solution was stirred at room temperature for 1 h to make a stock solution of 0.009 M silver(I)/(*S*)-QUINAP catalyst. Silver(I) acetate/(*S*)-QUINAP catalyst solution (0.03 equiv) followed by the dipolarophile (*t*-Bu Acrylate; 1.5 equiv) and Hünig's base (0.1 equiv) were added to the α-iminoester (1.0 equiv) at -45 °C in the glovebox. The final concentration of the α-iminoester was 0.3 M. After stirring for 24 hours, the reaction was allowed to warm to room temperature and taken out of the glovebox. Dipolarophile (5 equiv) and then cinnamaldehyde (1 equiv) were added. After stirring for 24 hours, the reaction was quenched with a tetrahydrofuran solution of acetic acid (1.1 equiv) and concentrated directly. The reactions were performed on a scale of 20–80 mg of the iminoester.

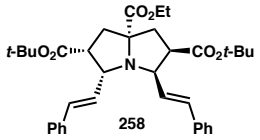
Gram-scale procedure for the preparation of pyrrolizidine *ent*-269a



18.8 mg silver (I) acetate (0.113 mmol) and 49.4 mg (*R*)-QUINAP (0.112 mmol) were added to a vial. Tetrahydrofuran (12.5 mL) was then introduced, and this solution

was stirred at room temperature for 1 h to make a stock solution of 0.009 M silver(I)/(*R*)-QUINAP catalyst. Silver(I) acetate/(*R*)-QUINAP catalyst solution (10 mL, 0.09 mmol) followed by the 0.66 ml *t*-butyl acrylate (4.5 mmol) and 52 μl Hünig's base (0.30 mmol) were added to 532 mg of α-iminoester **268a** (3.00 mmol) at -45 ºC. The final concentration of the α-iminoester was 0.3 M. After stirring for 24 hours, the reaction was allowed to warm to room temperature. 2.2 ml *t*-butyl acrylate (15 mmol) and then 380 μl cinnamaldehyde (3.0 mmol) were added. After stirring for 24 hours, the reaction was quenched with 2 mL of a tetrahydrofuran solution of acetic acid (10:1 v/v) and concentrated directly. The crude reaction mixture was purified by silica gel column chromatography (5→20% ethyl acetate in hexanes) to obtain 1.46 g pyrrolizidine **269a** in 89% yield and 87% ee.

(2*R*,3*R*,5*R*,6*R*)-2,6-di-*tert*-butyl-7a-ethyl-3,5-di((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (258)

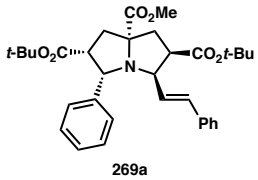


258

According to the general procedure pyrrolizidine **258** was obtained as a light yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 73% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 4% IPA in CO_2, λ = 254 nm): t_R (major) = 5.2 min, t_R (minor) = 6.6 min. $[\alpha]_D^{25}$ = –109.5° (c = 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.36 (m, 2H), 7.35 – 7.23 (m, 7H), 7.19 – 7.15 (m, 1H), 6.63 (d, *J* = 15.5 Hz, 1H), 6.53 (d, *J* = 15.5 Hz, 1H), 6.20 (dd, *J* = 15.6, 7.7 Hz, 1H), 6.06 (dd, *J* = 15.5, 10.6 Hz, 1H), 4.30 (dd, *J* = 10.6, 7.6 Hz, 1H), 4.27 – 4.16 (m, 3H), 3.45 (ddd, *J* = 13.3, 7.6, 6.0 Hz, 1H), 3.08 (dt, *J* = 10.3, 7.7 Hz, 1H), 2.78 (dd, *J* = 13.5, 10.3 Hz, 1H), 2.49 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.17 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.11 (t, *J* = 13.0 Hz, 1H),

1.31 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 9H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.2, 170.5, 170.1, 137.1, 136.4, 136.2, 131.2, 128.6, 128.3, 128.2, 127.9, 127.1, 126.7, 126.4, 125.2, 80.8, 80.8, 75.5, 67.1, 64.4, 61.2, 50.8, 49.6, 37.4, 36.6, 28.1, 28.0, 14.3; FTIR (NaCl, thin film) 2978, 2932, 1727, 1495, 1477, 1449, 1392, 1367, 1257, 1152, 1029, 968, 848, 754 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 588.3320, found 588.3284.

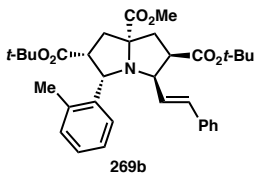
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269a)



269a

According to the general procedure pyrrolizidine **269a** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 90% yield and 91% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (major) = 6.1 min, t_R (minor) = 7.2 min. $[\alpha]_D^{25}$ = –103.3° (c = 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.30 – 7.24 (m, 6H), 7.21-7.10 (m, 2H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.02 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.78 (d, *J* = 8.3 Hz, 1H), 4.19 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.79 (s, 3H), 3.61 (ddd, *J* = 12.1, 7.5, 6.5 Hz, 1H), 3.39 (td, *J* = 7.9, 3.8 Hz, 1H), 2.99 (dd, *J* = 13.2, 3.8 Hz, 1H), 2.37 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.29 (dd, *J* = 19.1, 6.4 Hz, 1H), 2.12 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.26 (s, 9H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.1, 171.0, 170.9, 141.1, 136.4, 135.3, 128.5, 127.9, 127.8, 127.7, 126.7, 126.5, 126.3, 80.7, 80.2, 76.8, 65.2, 65.0, 52.9, 52.2, 51.3, 39.1, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 2977, 1726, 1493, 1453, 1391, 1367, 1293, 1255, 1204, 1151, 1094, 968, 845, 746 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 548.3007, found 548.3040.

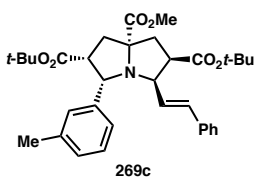
(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-((*E*)-styryl)-5-(*o*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269b)



269b

According to the general procedure pyrrolizidine **269b** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 91% yield and 89% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 10.0 min, t_R (minor) = 11.5 min. $[\alpha]_D^{25}$ = –84.443° (c = 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.15 (m, 6H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.22 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.93 (d, *J* = 8.2 Hz, 1H), 4.10 (dd, *J* = 10.2, 7.6 Hz, 1H), 3.82 (s, 3H), 3.65 (ddd, *J* = 13.5, 7.4, 0.8 Hz, 1H), 3.50 (t, *J* = 8.0 Hz, 1H), 3.05 (d, *J* = 13.1 Hz, 1H), 2.40 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.35 (t, *J* = 12.8 Hz, 1H), 2.09 (dd, *J* = 13.1, 7.7 Hz, 1H), 1.28 (s, 9H), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.37, 171.20, 170.72, 138.66, 136.50, 135.55, 135.03, 129.21, 128.41, 127.58, 126.78, 126.48, 126.35, 125.89, 80.61, 79.95, 77.25, 77.00, 76.75, 76.22, 64.01, 61.95, 52.14, 51.32, 50.98, 39.80, 39.23, 27.99, 27.47, 27.21, 19.14; FTIR (NaCl, thin film) 2976, 1727, 1479, 1458, 1392, 1367, 1294, 1256, 1199, 1151, 1097, 1034, 967, 844, 749 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3163, found 574.3159.

(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-((*E*)-styryl)-5-(*m*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269c)

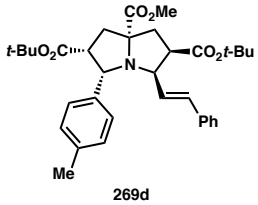


269c

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **269c** was obtained as a white foam

after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 76% yield and 88% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 9.8 min, t_R (minor) = 11.4 min. $[\alpha]_D^{25}$ = -236.413° (c = 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 – 7.09 (m, 7H), 6.98 (d, *J* = 7.4 Hz, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.05 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.76 (d, *J* = 8.3 Hz, 1H), 4.22 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.81 (s, 3H), 3.61 (ddd, *J* = 12.2, 7.5, 6.5 Hz, 1H), 3.38 (td, *J* = 7.9, 4.3 Hz, 1H), 3.00 (dd, *J* = 13.3, 4.3 Hz, 1H), 2.39 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.30 (s, 3H), 2.14 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.29 (s, 9H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.1, 171.0, 170.9, 141.0, 137.0, 136.5, 135.3, 128.6, 128.5, 127.8, 127.7, 127.4, 126.5, 126.3, 125.0, 80.7, 80.1, 76.6, 65.2, 65.2, 52.8, 52.2, 51.1, 39.0, 38.9, 28.0, 27.4, 21.5; FTIR (NaCl, thin film) 2978, 2930, 1732, 1606, 1456, 1367, 1256, 1152, 1099, 1038, 969, 846, 740 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3163, found 562.3163.

(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-((*E*)-styryl)-5-(*p*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269d)

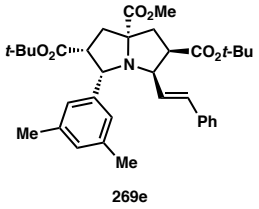


269d

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **269d** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 92% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (minor) = 10.2 min, t_R (major) = 11.3 min. $[\alpha]_D^{25}$ = -178.7° (c = 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 – 7.19 (m, 7H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.04 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.21 (dd, *J* = 10.2, 7.7 Hz, 1H), 3.81 (d, *J* = 0.7 Hz, 1H), 3.62 (dt, *J* =

13.2, 6.9 Hz, 1H), 3.38 (td, *J* = 8.1, 4.0 Hz, 1H), 3.00 (dd, *J* = 13.3, 4.0 Hz, 1H), 2.38 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.30 (s, 1H), 2.13 (dd, *J* = 13.3, 7.6 Hz, 1H), 1.28 (s, 1H), 1.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.1, 171.0, 170.9, 138.0, 136.5, 136.1, 135.2, 128.4, 128.4, 127.8, 127.7, 126.5, 126.4, 80.7, 80.1, 76.6, 65.1, 64.9, 52.9, 52.2, 51.2, 39.0, 28.0, 27.4, 21.0; FTIR (NaCl, thin film) 2977, 1727, 1512, 1495, 1477, 1457, 1367, 1151, 968, 848, 748 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3163, found 562.3170.

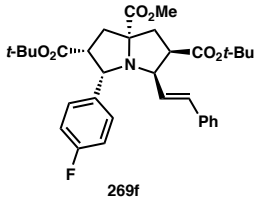
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(3,5-dimethylphenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269e)



269e

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **269e** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 78% yield and 88% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 5% IPA in CO2, λ = 254 nm): t_R (minor) = 9.0 min, t_R (major) = 10.5 min. $[\alpha]_D^{25}$ = -120.032° (c = 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 – 7.22 (m, 6H), 6.97 (s, 1H), 6.80 (s, 1H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.06 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.72 (d, *J* = 8.3 Hz, 1H), 4.22 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.82 (s, 1H), 3.61 (ddd, *J* = 12.3, 7.5, 6.5 Hz, 1H), 3.35 (td, *J* = 7.9, 4.8 Hz, 1H), 2.99 (dd, *J* = 13.3, 4.8 Hz, 1H), 2.39 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.33 – 2.26 (m, 1H), 2.26 (s, 1H), 2.13 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.29 (s, 9H), 1.00 (s, 9H).; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.09, 170.91, 170.86, 140.95, 136.89, 136.49, 135.28, 128.44, 128.29, 127.65, 126.53, 126.30, 125.68, 80.68, 80.02, 76.62, 65.34, 65.28, 52.66, 52.16, 51.04, 38.98, 38.69, 28.03, 27.38, 21.35; FTIR (NaCl, thin film) 2977, 1728, 1603, 1456, 1391, 1366, 1152, 968, 847, 747 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 576.3320, found 576.3318.

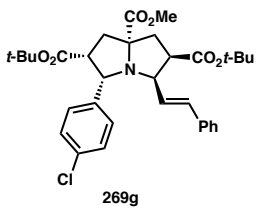
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(4-fluorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269f)



269f

According to the general procedure pyrrolizidine **269f** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 87% yield and 93% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 4% IPA in CO2, λ = 254 nm): t_R (minor) = 7.8 min, t_R (major) = 9.7 min. $[\alpha]_D^{25}$ = -40.596° (c = 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 – 7.36 (m, 2H), 7.30 – 7.26 (m, 2H), 7.24 – 7.20 (m, 3H), 6.93 (t, *J* = 8.8 Hz, 2H), 6.29 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.76 (d, *J* = 8.2 Hz, 1H), 4.15 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.79 (s, 3H), 3.59 (ddd, *J* = 12.2, 7.5, 6.5 Hz, 1H), 3.36 (td, *J* = 7.8, 3.4 Hz, 1H), 2.36 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.11 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.27 (s, 9H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.0, 170.9, 170.8, 162.9, 160.9, 136.7, 136.7, 136.3, 135.3, 129.5, 129.4, 128.5, 127.8, 126.5, 126.1, 114.6, 114.4, 80.7, 80.3, 76.6, 64.7, 64.4, 53.0, 52.2, 51.3, 39.2, 39.0, 28.0, 27.5; FTIR (NaCl, thin film) 3435, 2978, 2931, 1726, 1603, 1507, 1457, 1392, 1367, 1153, 846, 754 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 566.2912, found 566.2909.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(4-chlorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269g)

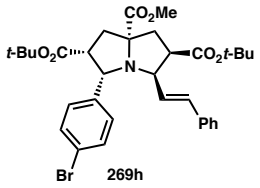


269g

According to the general procedure pyrrolizidine **269g** was obtained as a yellow oil after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 91% yield and 95% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in

CO2, λ = 254 nm): t_R (major) = 6.2 min, t_R (minor) = 8.1 min. $[\alpha]_D^{25}$ = -476.013° (c = 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.17 (m, 7H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.01 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.77 (d, *J* = 8.2 Hz, 1H), 4.16 (dd, *J* = 10.2, 7.7 Hz, 1H), 3.78 (s, 3H), 3.62 (dt, *J* = 12.3, 6.9 Hz, 1H), 3.38 (td, *J* = 7.9, 2.9 Hz, 1H), 2.99 (dd, *J* = 13.2, 2.7 Hz, 1H), 2.40 – 2.26 (m, 1H), 2.12 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.27 (s, 9H), 1.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.8, 170.7, 170.5, 139.5, 136.1, 135.2, 132.2, 129.2, 128.4, 127.7, 127.7, 126.3, 126.0, 80.6, 80.2, 76.5, 64.5, 64.3, 52.9, 52.1, 51.2, 39.2, 38.9, 27.9, 27.3; FTIR (NaCl, thin film) 3431, 2977, 2932, 1727, 1489, 1456, 1292, 1151, 1088, 1014, 847, 750 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 582.2617, found 582.2611.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(4-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269h)

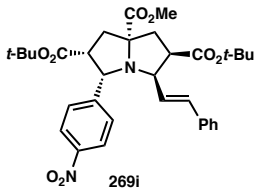


269h

According to the general procedure pyrrolizidine **269h** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 89% yield and 92% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 3% IPA in CO2, λ = 254 nm): t_R (major) = 6.1 min, t_R (minor) = 8.0 min. $[\alpha]_D^{25}$ = -59.159° (c = 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 – 7.36 (m, 2H), 7.35 – 7.27 (m, 4H), 7.27 – 7.22 (m, 3H), 6.31 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.75 (d, *J* = 8.2 Hz, 1H), 4.16 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.80 (s, 3H), 3.62 (ddd, *J* = 12.3, 7.4, 6.5 Hz, 1H), 3.38 (td, *J* = 7.8, 3.1 Hz, 1H), 2.99 (dd, *J* = 13.2, 3.1 Hz, 1H), 2.38 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.11 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.28 (s, 9H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) 177.0, 170.9, 170.7, 140.2, 136.2, 135.4, 130.8, 129.8,

128.5, 127.8, 126.5, 126.1, 120.4, 80.8, 80.4, 76.6, 64.7, 64.5, 53.0, 52.2, 51.3, 39.4, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 3447, 2978, 2932, 1728, 1586, 1456, 1393, 1368, 1257, 1151, 1011, 845, 739 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 626.2112, found 626.2096.

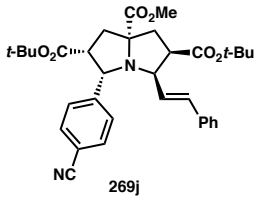
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(4-nitrophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269i)



269i

According to the general procedure pyrrolizidine **269i** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 70% yield and 96% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO2, λ = 254 nm): t_R (major) = 3.8 min, t_R (minor) = 5.2 min. $[\alpha]_D^{25}$ = -101.586° (c = 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.31 – 7.19 (m, 5H), 6.27 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.88 (d, *J* = 8.2 Hz, 1H), 4.16 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.81 (s, 3H), 3.65 (ddd, *J* = 12.2, 7.4, 6.8 Hz, 1H), 3.47 (td, *J* = 7.9, 2.6 Hz, 1H), 3.03 (dd, *J* = 13.2, 2.6 Hz, 1H), 2.38 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.37 – 2.29 (m, 1H), 2.16 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.28 (s, 9H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.7, 170.5, 170.5, 149.2, 146.9, 135.9, 135.7, 128.8, 128.5, 128.0, 126.4, 125.6, 123.0, 80.9, 80.7, 76.7, 64.6, 64.4, 53.1, 52.3, 51.3, 39.6, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 2978, 1727, 1598, 1522, 1457, 1392, 1367, 1346, 1294, 1249, 1199, 1151, 850, 745 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 593.2857, found 593.2854.

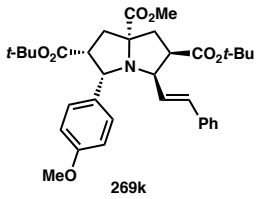
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(4-cyanophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269j)



269j

According to the general procedure pyrrolizidine **269j** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 80% yield and 96% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 4% IPA in CO2, λ = 254 nm): t_R (major) = 5.7 min, t_R (minor) = 7.1 min. $[\alpha]_D^{25}$ = –57.101° (c = 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 – 7.53 (m, 4H), 7.31 – 7.19 (m, 5H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.84 (d, *J* = 8.2 Hz, 1H), 4.14 (dt, *J* = 7.1, 5.9 Hz, 1H), 3.79 (s, 3H), 3.67 – 3.57 (m, 1H), 3.44 (td, *J* = 7.9, 2.7 Hz, 1H), 3.01 (dd, *J* = 13.2, 2.6 Hz, 1H), 2.38 (dd, *J* = 13.2, 6.6 Hz, 1H), 2.35 ? 2.28 (m, 1H), 2.14 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.28 (s, 9H), 0.97 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.8, 170.6, 170.6, 147.2, 136.0, 135.7, 131.7, 128.8, 128.6, 128.0, 126.5, 125.8, 119.2, 110.4, 80.9, 80.9, 80.6, 76.8, 64.7, 64.6, 53.0, 52.3, 51.4, 39.6, 39.1, 28.0, 27.5; FTIR (NaCl, thin film) 3453, 2978, 2931, 1732, 1608, 1456, 1393, 1368, 1257, 1151, 844, 738 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 573.2959, found 573.2924.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(4-methoxyphenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269k)

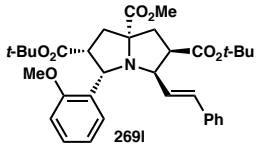


269k

According to the general procedure using 6 mol% AgOAc/QUINAP in 0.1M THF, pyrrolizidine **269k** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 86% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R

(minor) = 9.8 min, t_R (major) = 10.5 min. $[\alpha]_D^{25}$ = -201.710° (c = 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36 – 7.20 (m, 7H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 15.6 Hz, 1H), 6.04 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.75 (d, *J* = 8.3 Hz, 1H), 4.19 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.65 – 3.56 (m, 1H), 3.36 (td, *J* = 7.9, 4.0 Hz, 1H), 2.99 (dd, *J* = 13.3, 4.0 Hz, 1H), 2.38 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.13 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.28 (s, 9H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.1, 171.0, 170.9, 158.5, 136.4, 135.1, 133.2, 128.9, 128.4, 127.7, 126.5, 126.3, 113.2, 80.6, 80.1, 76.5, 65.0, 64.6, 55.3, 52.9, 52.2, 51.2, 38.9, 38.9, 28.0, 27.5; FTIR (NaCl, thin film) 2977, 1726, 1603, 1511, 1367, 1248, 1151, 1034, 845, 752 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 578.3112, found 578.3119.

(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methoxy-3-((*E*)-styryl)-5-(*o*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269l)

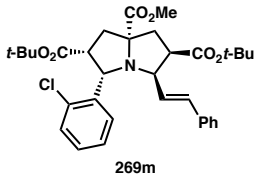


269l

According to the general procedure pyrrolizidine **269l** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 72% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 15% IPA in CO2, λ = 254 nm): t_R (major) = 4.0 min, t_R (minor) = 4.6 min. $[\alpha]_D^{25}$ = –188.252° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.89 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.30 – 7.23 (m, 3H), 7.23 – 7.12 (m, 3H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 6.02 (dd, *J* = 15.6, 10.4 Hz, 1H), 5.01 (d, *J* = 7.8 Hz, 1H), 4.14 (dd, *J* = 10.3, 7.6 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.55 (td, *J* = 7.7, 1.5 Hz, 1H), 3.01 (d, *J* = 12.8 Hz, 1H), 2.35 (dd, *J* = 9.4, 4.0 Hz, 2H), 2.10 (dd, *J* = 13.1, 7.7 Hz, 1H), 1.28 (s, 9H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.5, 171.8, 170.7, 157.0, 136.7, 134.8,

129.2, 129.0, 128.3, 127.4, 127.4, 127.0, 126.5, 120.3, 109.3, 80.6, 79.6, 76.2, 64.4, 59.6, 55.0, 52.1, 51.5, 51.3, 39.7, 39.3, 36.6, 28.0, 27.3, 24.6; FTIR (NaCl, thin film) 2977, 2949, 1723, 1600, 1489, 1458, 1437, 1391, 1367, 1294, 1242, 1152, 1106, 1031, 968, 848, 756 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 578.3112, found 578.3137.

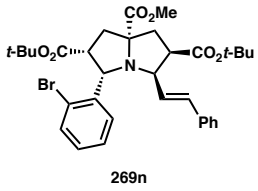
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(2-chlorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269m)



269m

According to the general procedure pyrrolizidine **269m** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 87% yield and 94% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO2, λ = 254 nm): t_R (minor) = 5.3 min, t_R (minor) = 6.2 min. $[\alpha]_D^{25}$ = -76.881° (c = 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.08 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.29 – 7.18 (m, 7H), 7.14 (td, *J* = 7.6, 1.7 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 10.4 Hz, 1H), 5.11 (d, *J* = 8.1 Hz, 1H), 4.09 (dd, *J* = 10.6, 7.8 Hz, 1H), 3.80 (s, 3H), 3.67 (td, *J* = 7.8, 1.5 Hz, 1H), 3.62 (dt, *J* = 11.8, 7.1 Hz, 1H), 3.04 (d, *J* = 13.0 Hz, 1H), 2.40 (dd, *J* = 13.0, 6.7 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.12 (dd, *J* = 13.2, 7.7 Hz, 1H), 1.29 (s, 9H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) 177.2, 171.2, 170.6, 138.4, 136.5, 135.4, 133.5, 130.5, 128.4, 128.3, 127.9, 127.6, 126.6, 126.5, 126.2, 80.7, 80.0, 76.4, 64.1, 62.3, 52.2, 51.4, 50.8, 39.7, 39.1, 28.0, 27.3; FTIR (NaCl, thin film) 3444, 2978, 1728, 1456, 1393, 1367, 1256, 1205, 1152, 1034, 969, 844, 752 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 582.2617, found 582.2617.

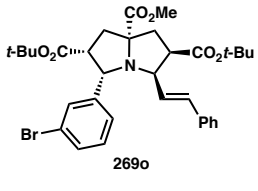
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(2-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269n)



269n

According to the general procedure pyrrolizidine **269n** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 89% yield and 93% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 3% IPA in CO2, λ = 254 nm): t_R (minor) = 4.4 min, t_R (major) = 5.0 min. $[\alpha]_D^{25}$ = -85.978° (c = 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.41 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.35 – 7.15 (m, 6H), 7.07 (td, *J* = 7.6, 1.7 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.98 (dd, *J* = 15.6, 10.4 Hz, 1H), 5.07 (d, *J* = 8.1 Hz, 1H), 4.08 (dd, *J* = 10.3, 7.5 Hz, 1H), 3.81 (s, 3H), 3.70 (td, *J* = 7.9, 1.2 Hz, 1H), 3.61 (dt, *J* = 11.7, 7.2 Hz, 1H), 3.04 (d, *J* = 13.1 Hz, 1H), 2.42 – 2.32 (m, 2H), 2.12 (dd, *J* = 13.2, 7.7 Hz, 1H), 1.29 (s, 9H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.2, 171.2, 170.6, 139.9, 136.5, 135.5, 131.7, 130.9, 128.3, 128.3, 127.6, 127.3, 126.5, 126.2, 123.9, 80.7, 80.0, 76.5, 64.7, 64.0, 52.2, 51.4, 50.7, 39.7, 39.2, 28.0, 27.3; FTIR (NaCl, thin film) 2977, 1727, 1457, 1392, 1367, 1293, 1257, 1203, 1151, 1094, 1022, 968, 843, 751 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 626.2112, found 628.2134.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(3-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269o)

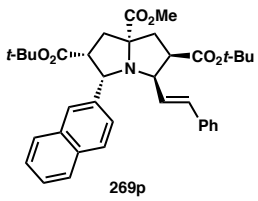


269o

According to the general procedure pyrrolizidine **269o** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 82% yield and 92% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in

CO2, λ = 254 nm): t_R (minor) = 6.9 min, t_R (major) = 8.0 min. $[\alpha]_D^{25}$ = -102.419° (c = 0.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (s, 1H), 7.38 – 7.20 (m, 6H), 7.13 (t, *J* = 7.8 Hz, 2H), 6.33 (d, *J* = 15.6 Hz, 1H), 6.01 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.77 (d, *J* = 8.3 Hz, 1H), 4.18 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.82 (s, 3H), 3.61 (ddd, *J* = 12.4, 7.4, 6.6 Hz, 1H), 3.40 (td, *J* = 7.9, 3.3 Hz, 1H), 2.99 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.40 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.31 (t, *J* = 12.8 Hz, 1H), 2.12 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.29 (s, 9H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.9, 170.7, 170.6, 143.8, 136.2, 135.5, 131.0, 129.8, 129.5, 128.5, 127.8, 126.5, 125.9, 122.1, 80.8, 80.5, 76.7, 64.7, 64.5, 53.0, 52.2, 51.2, 39.3, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 2978, 1728, 1594, 1569, 1456, 1393, 1367, 1293, 1257, 1204, 1151, 969, 845, 746 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 626.2112, found 626.2127.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(naphthalen-2-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269p)

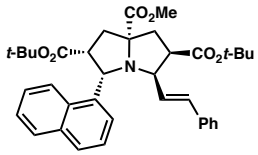


269p

According to the general procedure using 6 mol% AgOAc/QUINAP in 0.1M THF, pyrrolizidine **269p** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 93% yield and 92% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 6.0 min, t_R (minor) = 9.8 min. $[\alpha]_D^{25}$ = -387.655° (c = 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H), 7.85 – 7.77 (m, 2H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.52 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.30 – 7.19 (m, 4H), 6.29 (d, *J* = 15.6 Hz, 1H), 6.09 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.99 (d, *J* = 8.2 Hz, 1H), 4.27 (dd, *J* = 10.3, 7.6 Hz, 1H), 3.86 (s, 3H), 3.74 – 3.65 (m, 1H), 3.50 (td, *J* = 7.8, 3.4 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.3

Hz, 1H), 2.45 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.38 (t, *J* = 12.7 Hz, 1H), 2.19 (dd, *J* = 13.2, 7.7 Hz, 1H), 1.30 (s, 9H), 0.82 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.11, 170.96, 170.71, 138.60, 136.30, 135.25, 133.30, 132.77, 128.40, 127.91, 127.66, 127.39, 127.18, 126.46, 126.41, 126.25, 125.47, 125.11, 80.68, 80.12, 76.64, 65.26, 64.83, 53.11, 52.19, 51.25, 39.26, 39.05, 27.99, 27.22; FTIR (NaCl, thin film) 2977, 1727, 1457, 1391, 1368, 1256, 1199, 1151, 845, 751 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 598.3163, found 598.3155.

(2*R*,3*S*,5*R*,6*R*)-di-*tert*-butyl-3-(naphthalen-1-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6-dicarboxylate (269q)

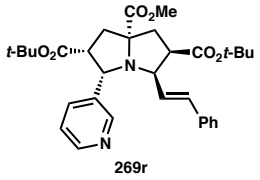


269q

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **269q** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 84% yield and 93% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (minor) = 8.4 min, t_R (major) = 9.8 min. $[\alpha]_D^{25}$ = -188.706° (c = 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (d, *J* = 7.1 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.83 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.38 (dddd, *J* = 22.6, 8.2, 6.8, 1.3 Hz, 2H), 7.20 – 7.13 (m, 3H), 7.01 –6.98 (m, 2H), 6.17 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.6, 10.3 Hz, 1H), 5.56 (d, *J* = 8.4 Hz, 1H), 4.19 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.84 (s, 3H), 3.77 (td, *J* = 8.0, 1.8 Hz, 1H), 3.70 (dt, *J* = 11.2, 7.4 Hz, 1H), 3.11 (dd, *J* = 13.0, 1.5 Hz, 1H), 2.45 (dd, *J* = 9.3, 3.3 Hz, 2H), 2.19 (dd, *J* = 13.1, 7.7 Hz, 1H), 1.28 (s, 9H), 0.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.3, 171.1, 170.9, 136.4, 136.3, 135.3, 133.4, 131.7, 128.3, 128.3, 127.5, 127.2, 126.6, 126.4, 125.9, 125.3, 124.8, 123.3, 80.7, 79.6, 76.3, 64.4, 61.5, 52.3,

52.2, 51.5, 40.0, 39.2, 28.0, 26.9; FTIR (NaCl, thin film) 2977, 1727, 1596, 1457, 1391, 1367, 1152, 968, 775, 752 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 598.3163, found 598.3156.

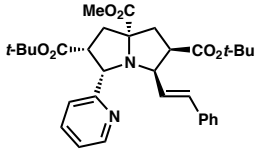
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(pyridin-3-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269r)



269r

According to the general procedure pyrrolizidine **269r** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 90% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 20% IPA in CO2, λ = 254 nm): t_R (major) = 2.7 min, t_R (minor) = 3.7 min. $[\alpha]_D^{25}$ = -218.400° (c = 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.53 (s, 1H), 8.43 (d, *J* = 4.7 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.18 (m, 6H), 6.31 (d, *J* = 15.6 Hz, 1H), 6.01 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.83 (d, *J* = 8.3 Hz, 1H), 4.15 (dd, *J* = 10.2, 7.7 Hz, 1H), 3.80 (s, 3H), 3.59 (dt, *J* = 12.1, 7.0 Hz, 1H), 3.44 (td, *J* = 8.0, 3.4 Hz, 1H), 3.01 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.40 (dd, *J* = 13.2, 6.5 Hz, 1H), 2.31 (t, *J* = 12.7 Hz, 1H), 2.15 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.27 (s, 9H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.78, 170.62, 149.35, 147.87, 136.89, 136.00, 135.63, 128.50, 127.89, 126.46, 125.69, 123.19, 80.83, 80.61, 76.63, 64.78, 62.65, 52.75, 52.28, 51.26, 39.26, 38.90, 27.98, 27.40; FTIR (NaCl, thin film) 2978, 1730, 1586, 1457, 1420, 1369, 1256, 1152, 1026, 844, 737 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 549.2954, found 549.2954.

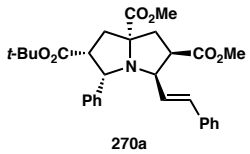
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl-7a-methyl-3-(pyridin-2-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (269s)



269s

According to the general procedure pyrrolizidine **269s** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 33% yield and 44% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 20% IPA in CO2, λ = 254 nm): t_R (major) = 2.2 min, t_R (minor) = 3.9 min. $[\alpha]_D^{25}$ = –68.157° (c = 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.1 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.67 – 7.55 (m, 2H), 7.26 – 7.19 (m, 2H), 7.08 (dd, *J* = 6.5, 5.1 Hz, 2H), 6.45 (dd, *J* = 22.7, 15.6 Hz, 1H), 6.04 (dt, *J* = 28.1, 14.0 Hz, 1H), 4.83 (d, *J* = 7.9 Hz, 1H), 4.26 (dt, *J* = 22.8, 11.4 Hz, 1H), 3.75 (d, *J* = 8.7 Hz, 2H), 3.68 – 3.59 (m, 1H), 3.51 (td, *J* = 8.0, 5.5 Hz, 1H), 3.08 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.38 – 2.35 (m, 1H), 2.34 (d, *J* = 3.1 Hz, 1H), 2.22 (dt, *J* = 15.5, 7.8 Hz, 1H), 1.31 – 1.20 (m, 8H), 1.06 (s, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.04, 170.94, 170.47, 161.47, 136.22, 135.97, 128.47, 127.85, 126.66, 125.49, 122.60, 121.63, 80.80, 80.20, 76.64, 66.44, 66.06, 52.27, 52.18, 50.80, 39.08, 38.87, 28.06, 27.54; FTIR (NaCl, thin film) 2976, 1726, 1589, 1457, 1434, 1366, 1256, 1151, 968, 847, 751 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 549.2959, found 549.2908.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2-*tert*-butyl-6,7a-dimethyl-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (270a)

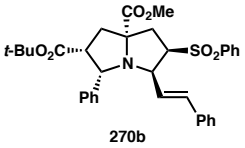


270a

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and methyl acrylate as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **270a** was obtained as a white foam after silica gel column chromatography

(5→20% ethyl acetate in hexanes) in 92% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (major) = 7.6 min, t_R (minor) = 9.4 min. $[\alpha]_D^{25}$ = -96.513° (c = 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 – 7.38 (m, 2H), 7.32 – 7.21 (m, 6H), 7.19 – 7.15 (m, 2H), 6.34 (d, *J* = 15.6 Hz, 1H), 6.03 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.83 (d, *J* = 8.4 Hz, 1H), 4.28 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.82 (s, 3H), 3.70 (ddd, *J* = 11.9, 7.7, 6.8 Hz, 1H), 3.56 (s, 3H), 3.44 (td, *J* = 7.8, 4.5 Hz, 1H), 3.03 (dd, *J* = 13.3, 4.5 Hz, 1H), 2.45 (dd, *J* = 13.2, 6.6 Hz, 1H), 2.37 (dd, *J* = 13.2, 11.9 Hz, 1H), 2.19 (dd, *J* = 13.3, 7.8 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.8, 172.4, 170.8, 140.9, 136.4, 135.3, 128.5, 127.9, 127.8, 127.8, 126.8, 126.6, 125.8, 80.3, 76.8, 65.3, 52.6, 52.3, 51.8, 50.5, 39.1, 38.7, 27.4; FTIR (NaCl, thin film) 3450, 2978, 1730, 1493, 1451, 1367, 1152, 970, 844, 747 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 506.2537, found 506.2523.

(2*R*,3*S*,5*R*,6*R*,7a*S*)-2-*tert*-butyl-7a-methyl-3-phenyl-6-(phenylsulfonyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (270b)

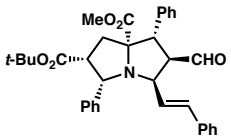


270b

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and vinyl sulphone as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **270b** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 64% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (minor) = 3.9 min, t_R (major) = 4.6 min; $[\alpha]_D^{25}$ = -10.465° (c = 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.10 (m, 11H), 6.28 (dd, *J* = 15.6, 10.6 Hz, 1H), 5.96 (d, *J* = 15.6 Hz, 1H), 4.87 (d, *J* = 8.6 Hz,

1H), 4.41 – 4.29 (m, 1H), 3.98 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.80 (s, 3H), 3.43 (ddd, *J* = 16.7, 10.2, 6.2 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.8 Hz, 1H), 2.69 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.56 (t, *J* = 12.5 Hz, 1H), 2.14 (dd, *J* = 13.3, 7.8 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.8, 170.8, 140.4, 138.9, 136.1, 135.6, 133.6, 128.8, 128.4, 128.4, 127.8, 127.8, 126.8, 126.7, 124.0, 80.3, 75.8, 68.0, 64.6, 64.0, 52.4, 52.1, 38.9, 36.9, 27.3, 27.3; FTIR (NaCl, thin film) 2979, 1726, 1446, 1367, 1305, 1248, 1148, 1085, 749, 722 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 588.2414, found 588.2407.

(2*R*,3*S*,5*R*,6*R*,7*S*,7a*S*)-2-*tert*-butyl-7a-methyl-6-formyl-3,7-diphenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (270c)

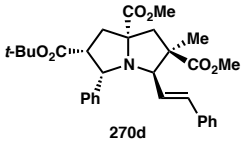


270c

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and cinnamaldehyde as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **270c** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 90% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OB-H, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (minor) = 3.7 min, t_R (major) = 4.9 min; $[\alpha]_D^{25}$ = -39.981° (c = 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.64 (d, *J* = 1.8 Hz, 1H), 7.37 – 7.11 (m, 14H), 6.44 (d, *J* = 15.5 Hz, 1H), 6.14 (dd, *J* = 15.5, 10.7 Hz, 1H), 4.87 (d, *J* = 7.9 Hz, 1H), 4.79 (dd, *J* = 10.7, 8.1 Hz, 1H), 4.55 (ddd, *J* = 12.0, 8.1, 1.7 Hz, 1H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.47 (td, *J* = 7.9, 4.5 Hz, 1H), 3.30 (s, 3H), 3.04 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.40 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.33 – 1.23 (m, 1H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.9, 174.1, 170.5, 140.4, 136.1, 136.0, 135.9, 128.5, 128.5, 128.1, 127.9, 127.6, 127.4, 126.8, 126.7, 125.8, 81.8, 80.4, 64.6, 63.1, 60.1, 54.2, 52.7, 51.4, 37.3, 27.4; FTIR (NaCl, thin

film) 2978, 1728, 1495, 1452, 1391, 1367, 1204, 1152, 1073, 747 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 552.2744, found 552.2712.

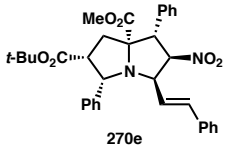
(2*R*,3*R*,5*S*,6*R*,7a*S*)-6-*tert*-butyl-2,7a-dimethyl-2-methyl-5-phenyl-3-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (270d)



270d

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and methyl methacrylate as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **270d** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 91% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OB-H, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (major) = 2.8 min, t_R (minor) = 3.3 min; $[\alpha]_D^{25}$ = -67.966° (c = 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.26 – 7.17 (m, 6H), 7.13 – 7.07 (m, 3H), 6.39 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 9.7 Hz, 1H), 5.02 (d, *J* = 9.0 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.84 (s, 3H), 3.64 (s, 3H), 3.56 (ddd, *J* = 9.0, 7.8, 6.3 Hz, 1H), 3.02 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 2.36 – 2.28 (m, 2H), 1.38 (s, 3H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.8, 176.8, 170.9, 142.1, 136.7, 134.6, 128.3, 128.2, 127.7, 127.5, 126.7, 126.4, 125.1, 80.2, 76.9, 75.0, 65.4, 56.1, 56.1, 52.3, 51.9, 50.4, 48.0, 39.0, 27.4, 23.1; FTIR (NaCl, thin film) 2950, 1727, 1493, 1433, 1450, 1367, 1253, 1152, 1121, 969, 746 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 520.2694, found 520.2644.

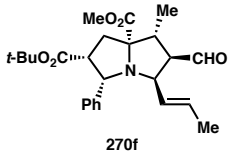
(2*R*,3*S*,5*R*,6*R*,7*R*,7a*S*)-2-*tert*-butyl-7a-methyl-6-nitro-3,7-diphenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (270e)



270e

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and crotonaldehyde as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **270e** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 89% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (minor) = 6.0 min, t_R (major) = 7.4 min; $[\alpha]_D^{25}$ = -27.059° (c = 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.15 (m, 15H), 6.48 (d, *J* = 15.5 Hz, 1H), 6.22 – 6.11 (m, 1H), 5.05 (d, *J* = 8.1 Hz, 1H), 4.94 (dd, *J* = 10.1, 8.0 Hz, 1H), 4.23 (d, *J* = 11.1 Hz, 1H), 3.59 (td, *J* = 7.9, 4.9 Hz, 1H), 3.38 (s, 3H), 3.12 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.48 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.2, 170.2, 139.9, 138.2, 135.6, 133.7, 128.8, 128.4, 128.3, 128.3, 127.9, 127.5, 127.1, 127.0, 126.8, 122.0, 92.1, 80.6, 80.5, 65.3, 64.8, 57.2, 51.6, 51.5, 37.1, 27.4; FTIR (NaCl, thin film) 2949, 1730, 1550, 1452, 1205, 1152, 1074, 911, 734 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 569.2646, found 569.2632.

(2*R*,3*S*,5*R*,6*R*,7*R*,7a*S*)-2-*tert*-butyl-7a-methyl-6-formyl-7-methyl-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (270f)

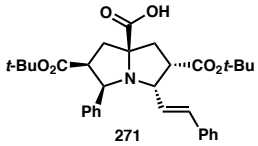


270f

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and crotonaldehyde as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **270f** was obtained as a white foam after silica gel column chromatography

(5→20% ethyl acetate in hexanes) in 59% yield (3:1mixture of diastereomers) and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 5% IPA in CO2, λ = 254 nm): t_R (major) = 5.9 min, t_R (minor) = 6.7 min; $[\alpha]_D^{25}$ = -39.981° (c = 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.56 (d, *J* = 1.6 Hz, 1H), 7.30 – 7.20 (m, 5H), 5.50 (dq, *J* = 14.8, 6.5 Hz, 1H), 5.27 (ddd, *J* = 15.0, 10.9, 1.6 Hz, 1H), 4.70 (d, *J* = 7.9 Hz, 1H), 4.36 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.78 (s, 3H), 3.48 (ddd, *J* = 11.7, 8.2, 1.5 Hz, 1H), 3.33 – 3.26 (m, 1H), 3.00 (dd, *J* = 13.6, 5.3 Hz, 1H), 2.44 (tt, *J* = 13.6, 6.8 Hz, 1H), 2.04 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.61 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.2, 175.3, 170.6, 141.0, 132.6, 128.3, 127.8, 127.8, 127.6, 127.6, 127.4, 126.7, 80.3, 80.3, 77.3, 77.0, 76.8, 64.4, 63.3, 62.3, 52.6, 51.7, 43.3, 36.8, 27.5, 17.7, 13.7; FTIR (NaCl, thin film) 2976, 2932, 1732, 1453, 1367, 1367, 974, 745 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 428.2431, found 428.2431.

(2*S*,3*R*,5*S*,6*S*,7a*S*)-2,6-bis(*tert*-butoxycarbonyl)-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-7a-carboxylic acid (271)

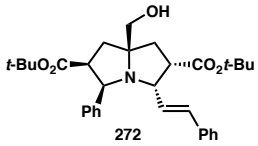


271

20 mg of pyrrolizidine ***ent*-269a** was dissolved in 0.4 ml THF. 4.4 mg of LiOH was dissolved in 0.4 ml of H_2O and then transferred to the organic solution. The reaction was allowed to stir for 14 h and then quenched with 1 ml of 10% NaH_2PO_4 and extracted with 1 ml DCM three times. The organic solution was then dried with $MgSO_4$, filtered, and concentrated. The crude mixture was then purified (5→20% ethyl acetate in hexanes) to afford 14 mg of **271** in 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR 7.32 – 7.22 (m, 6H), 7.12 (dd, *J* = 7.6, 1.7 Hz, 4H), 6.32 (d, *J* = 15.5 Hz, 1H), 5.98 (dd, *J* = 15.5, 10.5 Hz, 1H), 4.87 (d, *J* = 7.7 Hz, 1H), 4.29 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.45 (tdd, *J* = 7.6, 6.0, 3.9 Hz, 2H), 2.88 (dd, *J* =

13.9, 2.5 Hz, 1H), 2.74 (dd, *J* = 13.3, 6.5 Hz, 1H), 2.47 – 2.33 (m, 2H), 1.28 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.83, 171.33, 169.92, 138.32, 136.48, 135.82, 128.54, 128.37, 128.18, 127.54, 127.21, 126.56, 123.56, 81.67, 81.41, 78.12, 77.28, 77.02, 76.77, 66.20, 65.71, 53.40, 51.37, 38.80, 38.53, 27.99, 27.42; FTIR (NaCl, thin film) 2977, 2928,1725, 1495, 1454, 1367, 1250, 1151, 1030, 970, 845, 744 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 534.2832, found 534.285.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-di-*tert*-butyl-7a-(hydroxymethyl)-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6-dicarboxylate (272)

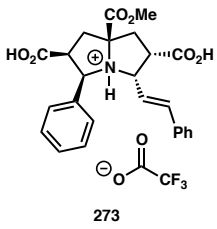


272

20 mg of pyrrolizidine ***ent*-269a** was dissolved in 0.73 ml THF and put to 0 ºC. 0.11 ml of 1 M $LiEt_3BH$ in THF was added drop-wise. The reaction was then quenched with 1 ml of saturated aqueous NH_4Cl and extracted with 1 ml DCM three times. The organic solution was then dried with $MgSO_4$, filtered, and concentrated. The crude mixture was then purified (5→20% ethyl acetate in hexanes) to afford 14 mg of **272** in 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.15 – 7.06 (m, 4H), 7.06 – 6.99 (m, 2H), 6.94 – 6.91 (m, 2H), 6.29 (d, *J* = 15.6 Hz, 1H), 5.90 (dd, *J* = 15.6, 9.8 Hz, 1H), 4.89 (d, *J* = 9.4 Hz, 1H), 4.15 – 4.05 (m, 1H), 3.48 (s, 2H), 3.47 – 3.42 (m, 1H), 3.18 (dd, *J* = 17.4, 8.7 Hz, 1H), 2.62 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.17 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.03 (dd, *J* = 13.5, 8.9 Hz, 1H), 1.95 (dd, *J* = 13.4, 8.4 Hz, 1H), 1.22 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.15, 172.26, 141.97, 136.59, 134.14, 128.32, 128.23, 127.92, 127.51, 126.87, 126.31, 126.09, 80.87, 80.41, 77.28, 77.02, 76.77, 75.48, 66.18, 65.77, 65.54, 51.63, 50.12, 38.22, 36.07, 29.72, 28.01, 27.40; FTIR (NaCl, thin film) 2975,

2928,1722, 1493, 1452, 1367, 1249, 1151, 1030, 970, 846, 743 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 520.3012, found 520.3012.

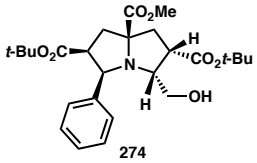
(2*S*,3*R*,5*S*,6*S*,7a*S*)-2,6-dicarboxy-7a-(methoxycarbonyl)-3-phenyl-5-((*E*)-styryl)octahydropyrrolizin-4-ium 2,2,2-trifluoroacetate (273)



273

To a stirring solution of triester ***ent*-269a** (204 mg, 0.372 mmol) in 2.6 mL of CH_2Cl_2 was added triethylsilane (0.29 mL, 1.8 mmol), followed by 1.0 mL of trifluoroacetic acid. The resulting solution was stirred for 20 h, and subsequently concentrated *in vacuo*. The crude residue was dissolved in 4 mL of Et_2O, and added dropwise to 30 mL of vigorously stirring hexanes, resulting in precipitation of a white solid (the reaction vessel was rinsed twice with 2 mL of Et_2O, and the rinsates added to the hexanes mixture). The solids were isolated by filtration to afford 180 mg (88% yield) of trifluoroacetate salt **273** as a white amorphous solid. $[\alpha]_D^{25}$ = +171.4° (c = 1.04, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.89 (s, 3H), 7.36 – 7.26 (m, 10H), 6.52 (d, *J* = 15.5 Hz, 1H), 6.23 (dd, *J* = 15.5, 10.5 Hz, 1H), 5.16 (d, *J* = 7.4 Hz, 1H), 4.68 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.84 (s, 3H), 3.67 – 3.60 (m, 1H), 2.97 (dd, *J* = 13.9, 3.4 Hz, 1H), 2.69 – 2.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.8, 173.6, 171.5, 160.7 (q, $J_{C\text{-}F}$ = 36.5 Hz), 140.9, 136.1, 134.8, 129.9, 129.7, 129.6, 129.5, 128.4, 127.9, 120.0, 117.2 (q, $J_{C\text{-}F}$ = 290.8 Hz), 81.1, 69.5, 68.8, 54.5, 52.3, 50.3, 38.8, 38.1; FTIR (NaCl, thin film) 2960, 2530, 1955, 1907, 1732, 1652, 1495, 1454, 1439, 1409, 1318, 1263, 1193, 1141, 976, 797, 750 cm^{-1}; HRMS (MM) calc'd for $[M–C_2F_3O_2]^+$ 436.1760, found 436.1779.

(3a*R*,5*R*,6*S*,7a*R*,8a*S*)-7a-(methoxycarbonyl)-1-oxo-5-phenyloctahydro-1*H*-furo[3,4-*b*]pyrrolizine-6-carboxylic acid (274)

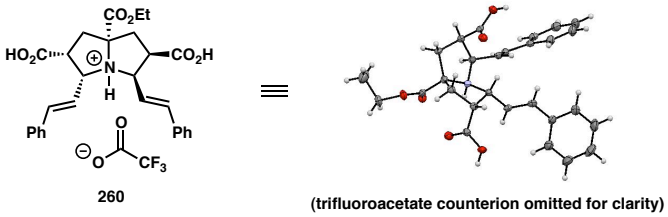


274

A solution of styrene ***ent*-269a** (150 mg, 0.274 mmol) and *p*-toluenesulfonic acid hydrate (261 mg, 1.37 mmol) in 2.8 mL of EtOAc was cooled to –78 °C with stirring. Ozone was bubbled through the solution until it became a pale blue suspension. The suspension was then sparged with oxygen (until the blue color no longer persisted), warmed to 0 °C in an ice bath, and diluted with 2.8 mL of saturated aqueous $NaHCO_3$. Sodium borohydride (104 mg, 2.75 mmol) was added portionwise, and the resulting mixture was stirred vigorously at 0 °C for 1 h. An additional portion of sodium borohydride (104 mg, 2.75 mmol) was added, and vigorous stirring continued at 0 °C for 1 h. A final portion of sodium borohydride (52 mg, 1.37 mmol) was added, and vigorous stirring continued at 0 °C for 1 h. The reaction mixture was then further diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc (5 x 5 mL) (**NOTE:** effervescence was allowed to subside prior to extraction), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was subjected to silica gel column chromatography (50:1→10:1 CH_2Cl_2–Et_2O), to afford 83 mg (64% yield) of **274** as a white foam. $[\alpha]_D^{25}$ = +346.27 (c = 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 – 7.42 (m, 2H), 7.29 – 7.24 (m, 2H), 7.21 – 7.17 (m, 1H), 4.83 (d, *J* = 8.9 Hz, 1H), 3.79 (s, 3H), 3.68 – 3.60 (m, 2H), 3.57 – 3.48 (m, 2H), 3.28 (dd, *J* = 16.7, 8.2 Hz, 1H), 2.95 (dd, *J* = 13.0, 5.8 Hz, 1H), 2.41 (dd, *J* = 13.1, 7.9 Hz, 1H), 2.32 – 2.23 (m, 2H), 2.20 (dd, *J* = 8.7, 5.0 Hz, 1H), 1.49 (s, 9H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.56, 174.21, 170.85, 141.72, 128.11, 127.91, 127.17, 81.90, 80.16, 77.26, 77.00, 76.75, 64.83,

64.01, 60.67, 52.25, 51.25, 49.13, 39.75, 37.40, 27.98, 27.38; FTIR (NaCl, thin film) 3502, 2977, 2929, 1729, 1478, 1456, 1392, 1367, 1303, 1252, 1209, 1152, 1094, 1042, 919, 845, 735 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 476.2643, found 476.2644.

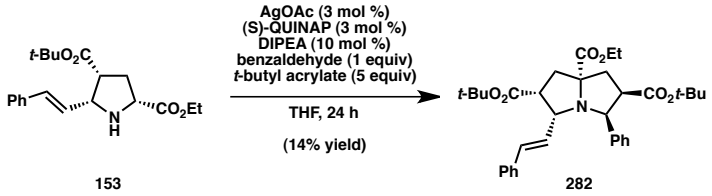
(2*R*,3*R*,5*R*,6*R*)-2,6-dicarboxy-7a-(ethoxycarbonyl)-3,5-di((*E*)-styryl)octahydropyrrolizin-4-ium 2,2,2-trifluoroacetate (260)



To a stirring solution of triester **258** (racemic, 191 mg, 0.325 mmol) in 2.3 mL of CH_2Cl_2 was added triethylsilane (0.26 mL, 1.6 mmol), followed by 0.93 mL of trifluoroacetic acid. The resulting solution was stirred for 24 h, and subsequently concentrated *in vacuo*. The crude residue was suspended in 3 mL of EtOAc, and added dropwise to 35 mL of vigorously stirring hexanes, resulting in precipitation of a white solid (the reaction vessel was rinsed twice with 2 mL of EtOAc, and the rinsates added to the hexanes mixture). The solids were isolated by filtration to afford 153 mg (80% yield) of trifluoroacetate salt **260** as a white amorphous solid. Crystals suitable for X-ray diffraction analysis (XRD) were obtained by vapor diffusion of pentane into a saturated solution of **260** in acetone. ^{1}H NMR (acetone-d_6, 500 MHz) δ 9.88 (s, 3H), 7.54 – 7.50 (m, 2H), 7.38 – 7.26 (m, 7H), 7.25 – 7.20 (m, 1H), 6.85 (d, J = 15.5 Hz, 1H), 6.74 (dd, J = 15.7, 1.1 Hz, 1H), 6.50 (dd, J = 15.5, 10.6 Hz, 1H), 6.34 (dd, J = 15.7, 7.6 Hz, 1H), 4.72 (dd, J = 10.6, 7.5 Hz, 1H), 4.63 (td, J = 7.4, 1.3 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.69 (ddd, J = 11.7, 7.6, 6.8 Hz, 1H), 3.57 (dt, J = 9.0, 7.6 Hz, 1H), 2.93 (dd, J = 13.7, 9.0 Hz, 1H), 2.65 – 2.54 (m, 1H),

2.49 (dd, *J* = 13.7, 7.7 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 173.8 (br), 171.8, 171.2, 158.5 (q, $J_{C\text{-}F}$ = 36.1 Hz), 137.5 (br), 136.4, 135.9, 132.5 (br), 128.7, 128.4, 127.9, 127.1, 126.4, 125.7 (br), 122.6 (br), 115.8 (q, $J_{C\text{-}F}$ = 291.8 Hz), 76.5, 68.0, 64.8, 61.7, 49.3, 48.5, 36.8, 35.4, 14.0; FTIR (NaCl, thin film) 3029, 2528, 1718, 1653, 1452, 1405, 1375, 1263, 1191, 1139, 971, 797, 749, 720 cm^{-1}; HRMS (MM) calc'd for $[M–C_2F_3O_2]^+$ 476.2068, found 476.2068.

(2*R*,3*S*,5*R*,6*R*,7a*S*)-2,6-di-*tert*-butyl 7a-ethyl 3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (282)

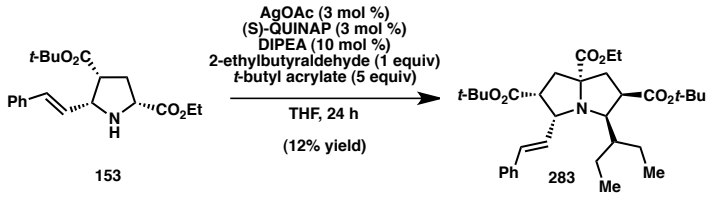


153 282

3 mol % catalyst solution in THF was pre-stirred for 30 minutes and then added to 52 mg of pyrrolidine **153**. 15 μl of benzaldehyde was added followed by 11 μl of *t*-Bu Acrylate and 3 μl of DIPEA. After 24 h the reaction mixture was concentrated and purified by silica gel column chromatography (5→20% ethyl acetate in hexanes) to afford **282** in 14% yield. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 10.6 min, t_R (minor) = 11.5 min. $[\alpha]_D^{25}$ = –66.858° (c = 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H), 7.23 – 7.13 (m, 5H), 6.33 (dd, *J* = 15.7, 0.8 Hz, 1H), 6.07 (dd, *J* = 15.7, 7.1 Hz, 1H), 4.79 (d, *J* = 9.0 Hz, 1H), 4.25 (tdd, *J* = 10.7, 7.1, 3.6 Hz, 2H), 3.84 – 3.73 (m, 1H), 3.69 (t, *J* = 7.2 Hz, 1H), 3.11 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.88 (dd, *J* = 13.4, 6.9 Hz, 1H), 2.51 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.37 (t, *J* = 13.2 Hz, 1H), 2.20 (dd, *J* = 13.4, 8.1 Hz, 1H), 1.33 (dd, *J* = 23.0, 12.8 Hz, 1H), 1.26 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.81,

170.86, 170.59, 138.21, 137.26, 130.50, 129.44, 128.97, 128.32, 128.24, 127.95, 127.00, 126.37, 80.56, 80.38, 76.04, 67.07, 63.22, 61.05, 51.89, 50.88, 39.01, 37.18, 28.07, 27.98, 27.35, 14.35; FTIR (NaCl, thin film) 2977, 2930,1728, 1599, 1494, 1477, 1458, 1367, 1247, 1152, 1096, 1029, 969, 848, 744 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3169, found 562.3148.

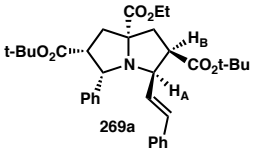
(2*R*,3*R*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(pentan-3-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (283)



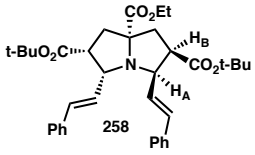
3 mol % catalyst solution in THF was pre-stirred for 30 minutes and then added to 52 mg of pyrrolidine **153**. 18 μl of 2-ethyl butyraldehyde was added followed by 11 μl of *t*-Bu Acrylate and 3 μl of DIPEA. After 24 h the reaction mixture was concentrated and purified by silica gel column chromatography (5→20% ethyl acetate in hexanes) to afford **283** in 12% yield and 96% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 5% IPA in CO2, λ = 254 nm): t_R (minor) = 3.4 min, t_R (major) = 5.3 min. $[\alpha]_D^{25}$ = –70.072° (c = 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.35 – 7.26 (m, 2H), 7.23 – 7.17 (m, 2H), 6.74 (d, *J* = 15.6 Hz, 1H), 6.16 (dd, *J* = 15.7, 6.7 Hz, 1H), 4.46 – 4.38 (m, 1H), 4.26 – 4.14 (m, 2H), 3.60 (ddd, *J* = 13.0, 8.8, 6.3 Hz, 1H), 3.35 (dd, *J* = 11.7, 6.7 Hz, 1H), 2.91 (ddd, *J* = 10.3, 6.8, 3.7 Hz, 1H), 2.74 (dd, *J* = 14.3, 10.2 Hz, 1H), 2.66 (t, *J* = 13.0 Hz, 1H), 2.09 (dd, *J* = 12.8, 6.2 Hz, 1H), 1.89 (dd, *J* = 14.3, 3.7 Hz, 1H), 1.54 (s, 9H), 1.38 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 1H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.57,

174.77, 170.79, 137.62, 131.09, 130.48, 128.37, 126.91, 126.46, 80.95, 80.55, 75.83, 69.39, 60.89, 60.41, 48.34, 47.21, 41.04, 38.19, 35.98, 28.15, 28.15, 21.78, 20.75, 14.31, 10.48, 7.55; FTIR (NaCl, thin film) 2974, 1718, 1559, 1457, 1366, 1247, 1146, 847 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 556.3638, found 556.3625.

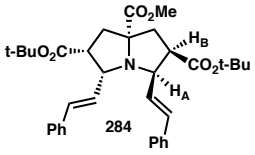
Table 4.3. *Relevant ^1H NMR data for stereochemical assignment of pyrrolizidines* ***270a-f***



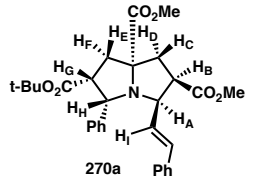
X, Y	J_{XY} (Hz)
H_A, H_B	7.5, 7.7



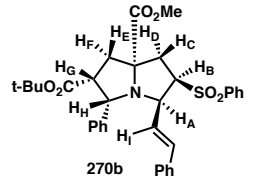
X, Y	J_{XY} (Hz)
H_A, H_B	7.6



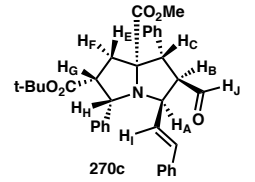
X, Y	J_{XY} (Hz)
H_A, H_B	7.5, 7.8



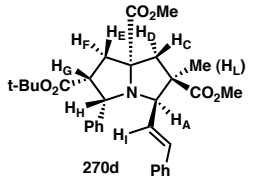
X, Y	J_{XY} (Hz)
H_A, H_B	7.8
H_B, H_C	13.2
H_B, H_D	6.6
nOe interactions	
H_A–H_B	H_B–H_D
H_C–H_E	H_I–H_H
H_E–H_G	H_I–H_C
H_G–H_H	no H_I–H_B



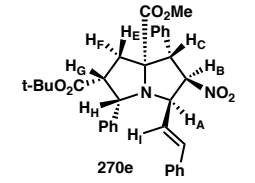
X, Y	J_{XY} (Hz)
H_A, H_B	6.6, 7.0
H_B, H_C	12.0, 12.1
H_B, H_D	6.6, 7.0
nOe interactions	
H_A–H_B	H_B–H_D
H_C–H_E	H_I–H_H
H_E–H_G	H_I–H_C
H_G–H_H	no H_I–H_B



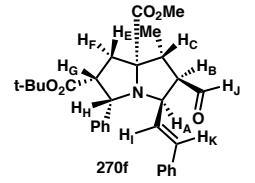
X, Y	J_{XY} (Hz)
H_A, H_B	8.1
H_B, H_C	12.0
H_B, H_J	1.8
nOe interactions	
H_A–H_B	H_I–H_H
H_C–H_E	H_I–H_C
H_E–H_G	no H_I–H_B
H_G–H_H	—



X, Y	J_{XY} (Hz)
—	—
—	—



X, Y	J_{XY} (Hz)
H_A, H_B	8.0
H_B, H_C	11.1



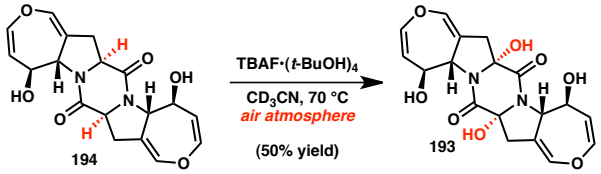
X, Y	J_{XY} (Hz)
H_A, H_B	8.2
H_B, H_C	11.8

—	—
nOe interactions	
H_A–H_L	H_G–H_H
H_D–H_L	H_I–H_H
H_E–H_C	—
H_E–H_G	—

—	—
nOe interactions	
H_A–H_B	H_I–H_H
H_C–H_E	H_I–H_C
H_E–H_G	H_H–H_C
H_G–H_H	H_H–H_E

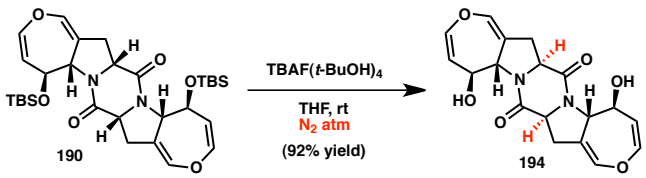
H_B, H_J	1.6
nOe interactions	
H_A–H_B	H_I–H_H
H_C–H_E	H_K–H_C
H_E–H_G	H_I–H_C
H_G–H_H	no H_I–H_B

Oxidation of diketopiperazine 194 to tetraol 193



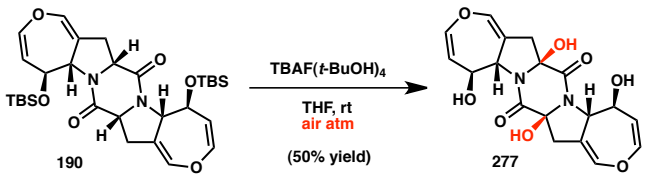
Diketopiperazine **194** (2.0 mg, 5.6 μmol) and mesitylene (~1 μL) were dissolved in CD_3CN (600 μL) and transferred to an NMR tube. An initial ^{1}H NMR spectrum was acquired in order to determine the exact ratio of starting material to internal standard. The solution was then transferred to a 1-dram vial equipped with a stir bar, and TBAF(*t*-BuOH)$_4$ (43 mg, 77 μmol) was added. The vial (open to ambient air until now) was sealed with a Teflon screw cap and was then heated to 70 °C with vigorous stirring. After 4 h, the orange-brown solution was cooled to room temperature and transferred to an NMR tube. A final ^{1}H NMR spectrum was acquired, and it was determined that tetraol **193** had been formed in 50% yield (based on the mesitylene internal standard) and was the predominant dihydrooxepine-containing species.

Preparation of diol 194 from bis(*tert*-butyldimethylsilyl) ether 190



A solution of bis(*tert*-butyldimethylsilyl) ether **190** (105 mg, 0.179 mmol) in 9 mL THF and a separate solution of TBAF•(*t*-BuOH)$_4$ (1.20 g, 2.15 mmol) in 9 mL THF were each sparged with N_2 for 1 h. The solution of TBAF•(*t*-BuOH)$_4$ was then added to the solution of **190**, and the resulting mixture was stirred under N_2 for 52 h. The reaction mixture was then diluted with sat. *aq*. Na_2SO_4 and extracted with EtOAc (3x). The combined organics were then washed with sat. *aq*. Na_2SO_4 and filtered through a plug of SiO_2. The resulting aqueous wash was back-extracted with EtOAc, and the resulting organic layer again passed through the SiO_2 plug, which was finally rinsed with excess EtOAc. The resulting filtrate was then concentrated *in vacuo*, and purification via flash chromatography (gradient elution, 1→5% MeOH in 1:1 CH_2Cl_2/EtOAc) to afford diol **194** (59.2 mg, 92% yield) as an off-white amorphous solid.

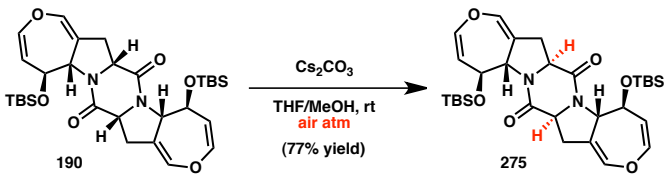
Preparation of tetraol 277 from bis(*tert*-butyldimethylsilyl) ether 190



A solution of bis(*tert*-butyldimethylsilyl) ether **190** (11 mg, 0.017 mmol) in 1.7 mL of THF under an air atmosphere was treated with TBAF•(*t*-BuOH)$_4$ (114 mg, 0.204 mmol), and the resulting solution was stirred for 46 h. The mixture was then diluted with sat. *aq*. Na_2SO_4 and extracted with EtOAc (3x). The combined organics were then washed with sat. *aq*. Na_2SO_4 and filtered through a plug of SiO_2. The resulting aqueous wash was back-extracted with EtOAc, and the resulting organic layer again passed through the SiO_2 plug, which was finally rinsed with excess EtOAc. The resulting filtrate was then concentrated *in vacuo*, and purification via flash chromatography (gradient

elution, 1:1→1:2 hexanes–EtOAc followed by 100% EtOAc) to afford tetraol **277** (3.3 mg, 50% yield) as a white amorphous solid. $[\alpha]_D^{25.0} = -188$ ° (*c* = 0.17, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3CN) δ 6.65 – 6.62 (m, 2H), 6.32 (dd, *J* = 8.4, 1.9 Hz, 2H), 5.93 (d, *J* = 1.6 Hz, 2H), 5.69 (d, *J* = 0.9 Hz, 2H), 4.79 (ddd, *J* = 8.1, 2.4, 2.4 Hz, 2H), 4.66 (dd, *J* = 8.4, 1.8 Hz, 2H), 4.29 (dddd, *J* = 7.9, 1.7, 1.7, 1.7 Hz, 2H), 3.02 – 2.94 (m, 2H), 2.84 (ddd, *J* = 16.4, 1.1, 0.6 Hz, 2H); ^{13}C NMR (126 MHz, CD_3CN) δ 170.2, 140.9, 140.1, 115.6, 109.5, 91.9, 69.1, 67.7, 38.5; IR (NaCl/thin film): 3305, 2922, 2851, 1672, 1400, 1323, 1284, 1199, 1132, 1063, 1034, 978, 917, 869, 796, 767, 735 cm^{-1}; LRMS (ESI/APCI) calc'd for $C_{18}H_{17}N_2O_8$ $[M-H]^-$ 389.1, found 389.1.

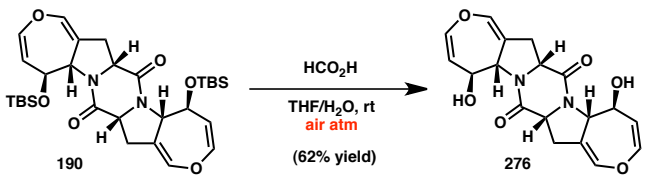
Preparation of 275 from bis(*tert*-butyldimethylsilyl) ether 190



A solution of diketopiperazine **190** (10.0 mg, 0.0170 mmol) in 2.5 mL THF/MeOH (1:1) was treated with Cs_2CO_3 (222 mg, 0.680 mmol), and the resulting mixture was stirred under an air atmosphere overnight. The mixture was then diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were then washed with sat. *aq*. NH_4Cl, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (isocratic elution, 3:1 hexanes–EtOAc) afforded diketopiperazine **275** (7.7 mg, 77% yield) as a white, amorphous solid. $[\alpha]_D^{25.0} = -323$ ° (*c* = 0.39, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (ddd, *J* = 2.5, 2.5, 1.0 Hz, 2H), 6.14 (dd, *J* = 8.2, 2.2 Hz, 2H), 5.09 (dddd, *J* = 8.0, 1.6, 1.6, 1.6 Hz, 2H), 4.75 (dd, *J* = 8.2, 1.8 Hz, 2H), 4.25 – 4.20 (m, 4H), 3.00 (dddd, *J* = 14.9, 6.4, 1.2, 1.2 Hz, 2H), 2.74 (dddd, *J* =

14.7, 11.7, 2.1, 2.1 Hz, 2H), 0.90 (s, 18H), 0.08 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 138.6, 137.0, 112.4, 110.1, 69.2, 62.8, 58.1, 35.4, 25.7, 18.0, -4.6, -4.7; IR (NaCl/thin film): 2948, 2924, 2884, 2853, 1670, 1418, 1335, 1288, 1282, 1257, 1243, 1198, 1183, 1162, 1128, 1101, 1072, 1059, 1018, 996, 939, 904, 889, 871, 834, 806, 774, 723 cm^{-1}; HRMS (ESI) calc'd for $C_{24}H_{31}N_2O_5Si$ $[M–C_6H_{15}OSi]^+$ 455.1997, found 455.2008 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion).

Preparation of diol 276 from bis(*tert*-butyldimethylsilyl) ether 190



To a solution of bis(*tert*-butyldimethylsilyl) ether **190** (8.9 mg, 0.015 mmol) in 1.05 mL THF/H_2O (6:1) was added 0.45 mL HCO_2H with stirring. After 2.5 h, the mixture was quenched with sat. *aq*. $NaHCO_3$ and extracted with EtOAc (3x). The combined organics were then washed with sat. *aq*. $NaHCO_3$ (back-extracting the aqueous with EtOAc), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (gradient elution, 1:1→2:3 hexanes–EtOAc) afforded diol **276** (3.4 mg, 62% yield). $[\alpha]_D^{25.0}$ = –264 ° (*c* = 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 2H), 6.27 (dd, *J* = 8.3, 1.9 Hz, 2H), 6.12 (d, *J* = 2.2 Hz, 2H), 4.78 (dd, *J* = 8.3, 1.8 Hz, 2H), 4.70 (ddd, *J* = 8.1, 2.2, 2.2 Hz, 2H), 4.44 (dd, *J* = 10.3, 8.0 Hz, 2H), 4.30 (dddd, *J* = 8.0, 2.0, 2.0, 2.0 Hz, 2H), 2.98 – 2.86 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 140.2, 139.1, 114.4, 108.7, 69.2, 66.9, 62.1, 29.5; IR (NaCl/thin film): 3583, 3305, 2916, 2848, 1663, 1419, 1351, 1319, 1294, 1206, 1174, 1129, 1079,

1035, 905, 884, 808, 750 cm^{-1}; HRMS (ESI) calc'd for $C_{18}H_{15}N_2O_4$ $[M–H_2O–HO]^+$ 323.1026, found 323.1050 (detected fragment has undergone loss of H_2O and $OH^–$).

4.6 NOTES AND REFERENCES

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(10) Specifically, the AgOAc/(*S*)-QUINAP conditions require a substantially shorter prestir for catalyst generation. The resulting catalyst solution is homogeneous and could be used as a stock solution, facilitating our methodological studies.

(11) We have consistently found that pyrrolizidine **258** can be isolated in higher yields than the corresponding pyrrolidine **153**. We attribute this to challenges in isolating and purifying the free N–H pyrrolidine.

(12) Although the studies reported herein utilized co-catalytic quantities of DIPEA, we have determined that cycloadditons can also be carried out in the absence of DIPEA, with equal or slightly reduced yields.

(13) The AgOAc/QUINAP-catalyzed 1,3-DCA between **141** and **152** at 23 °C furnishes pyrrolidine **153** in 77% ee.

(14) *N*-(2-Pyridylmethyl)imines have been shown to participate in Cu-catalyzed asymmetric (1,3)-DCA reactions: Padilla, S.; Tejero, R.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2012**, *12*, 5608.

(15) Ee values obtained using standard conditions: **269c** (80%), **269d** (83%), **269e** (73%), **269q** (84%), **269k** (84%), **269p** (82%).

(16) (*R*)-QUINAP was used.

(17) On 0.15 mmol scale, **269a** could be prepared in 88% yield and 90% ee using 1 mol% catalyst in conjunction with a 48 h reaction period for the first (1,3)-DCA. Use of 1 mol% catalyst under standard conditions provided **269a** in 64% yield and 86% ee.

(18) Kim, D.-W.; Jeong, H.-J.; Lim, S.-T.; Sohn, M.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 8404.

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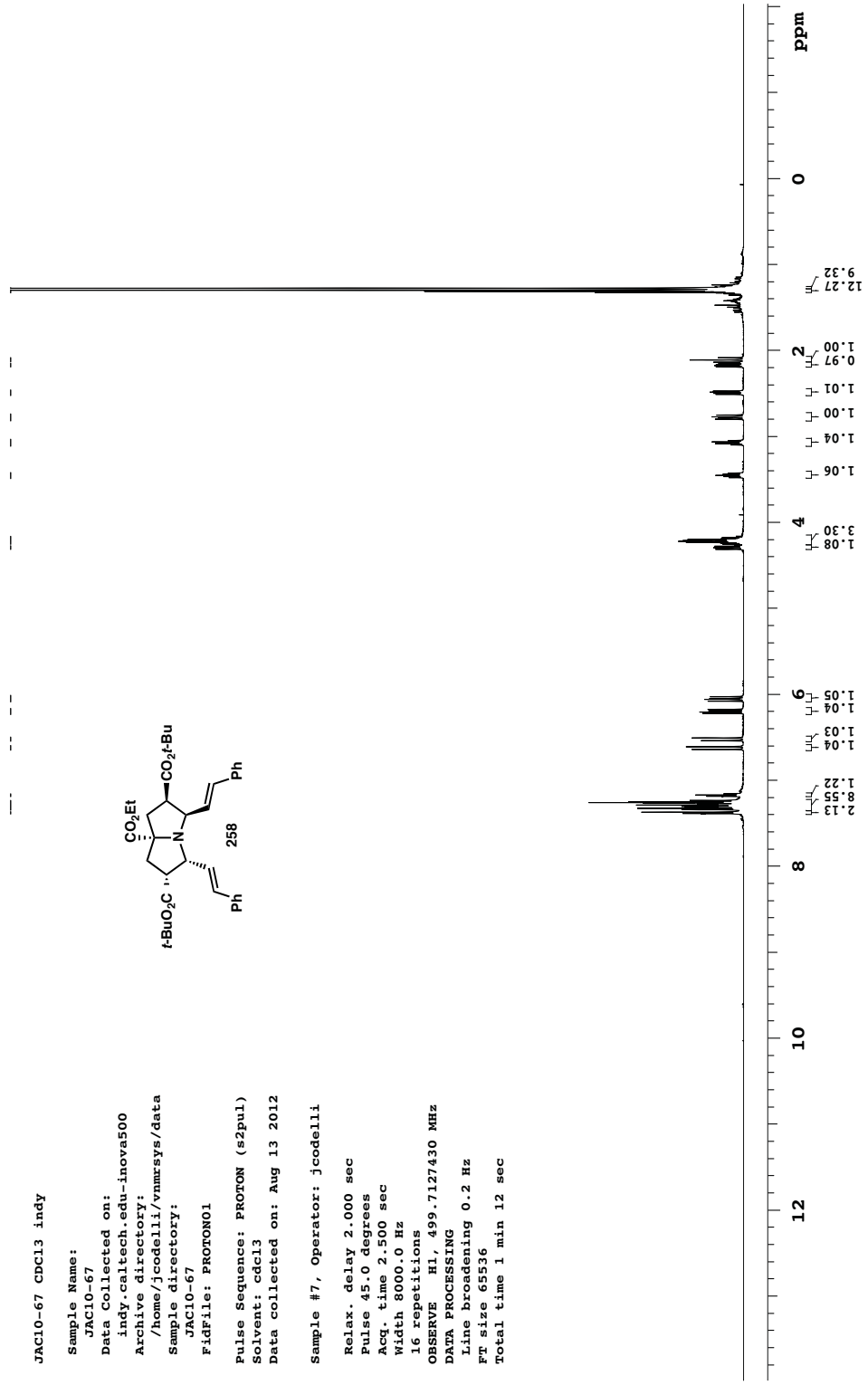
Appendix 4

Spectra Relevant to Chapter 4:
Further Investigation of Side Reactions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Pulse 45.0 degrees
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Width 8000.0 Hz
16 repetitions
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Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
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CO2t-Bu
t-BuO2C
Ph
Ph
258
ppm
12
10
8
6
4
2
0
2.13
8.55
1.22
1.04
1.03
1.04
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1.06
1.04
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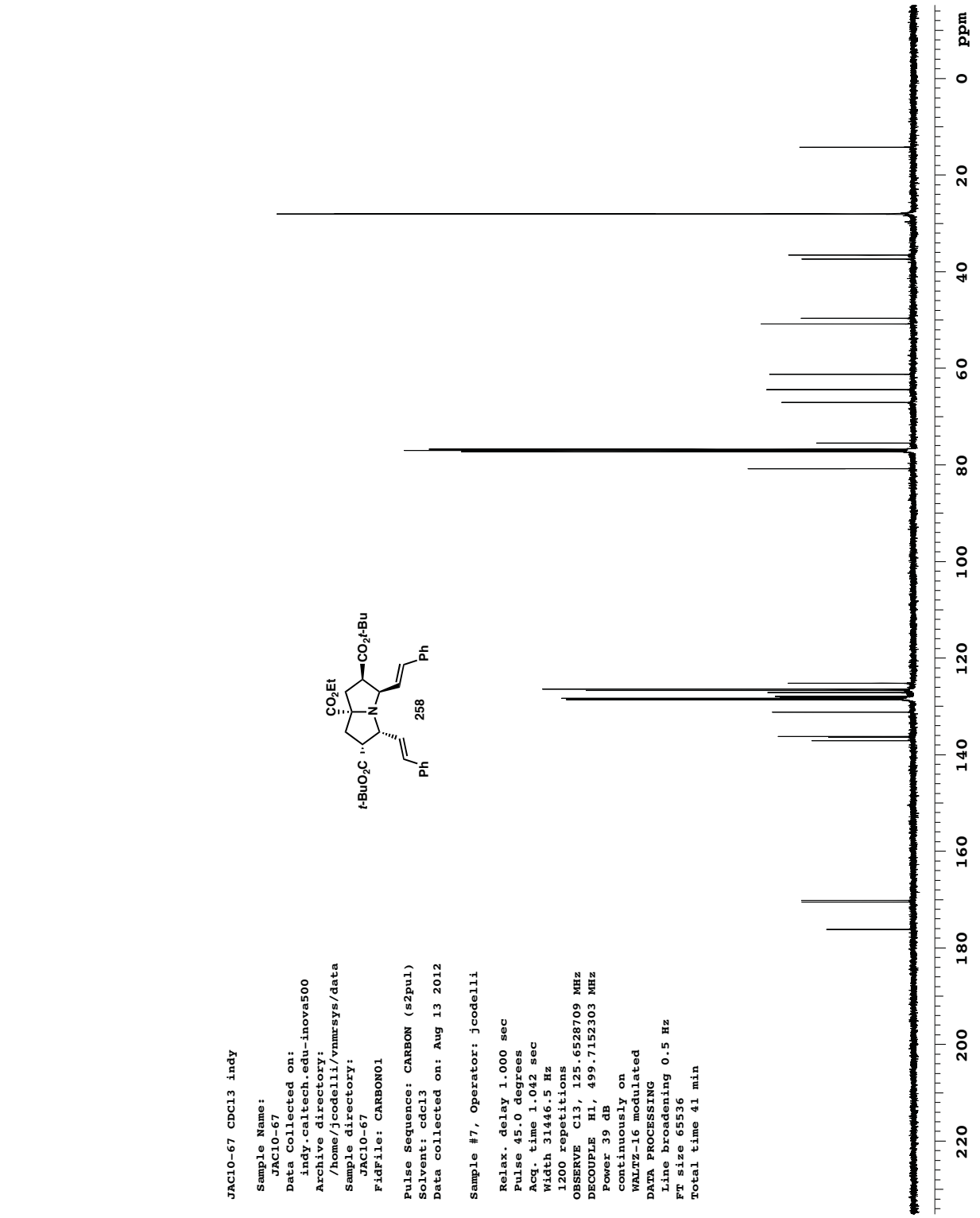
1.01
0.97
1.00
1.08
3.30
12.27
9.32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Power 39 dB
continuously on
WALTZ-16 modulated
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FT size 65536
Total time 41 min
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CO2t-Bu
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180
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140
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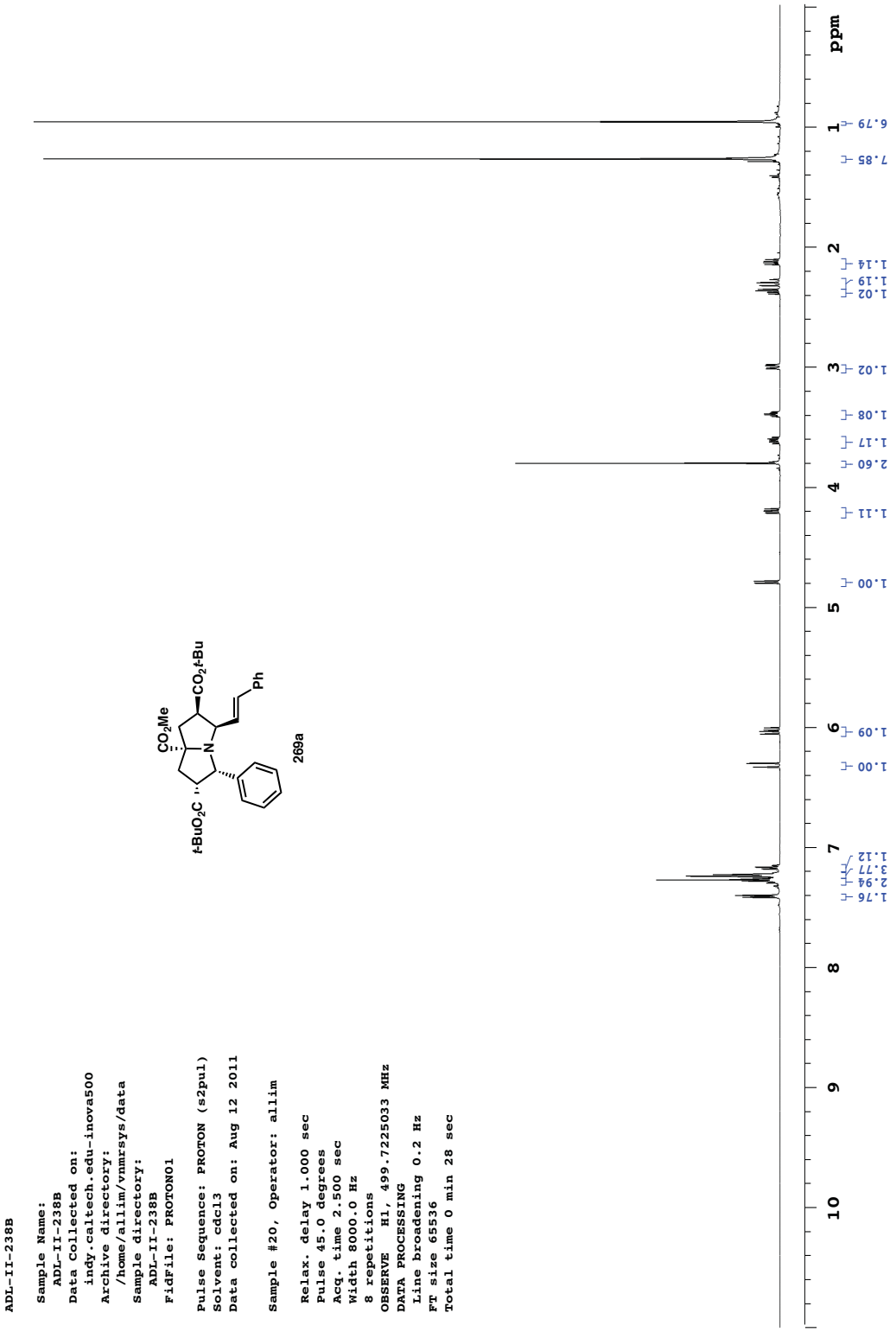
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Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
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Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
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CO2tBu
Ph
tBuO2C
269a
ppm
6.79
7.85
1.14
1.19
1.02
1.02
1.08
1.17
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1.11
1.00
1.09
1.00
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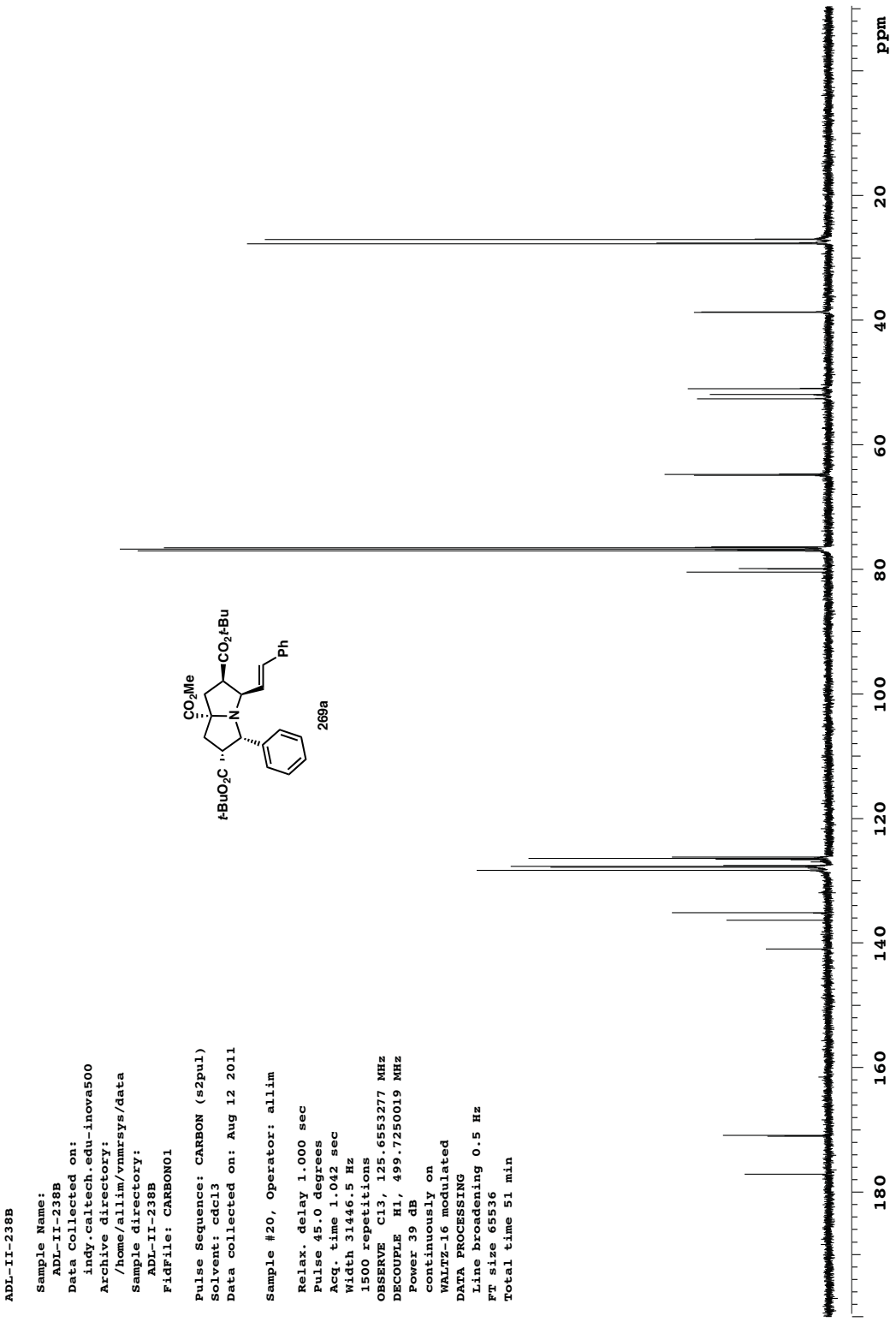
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Solvent: cdcl3
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DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
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CO2t-Bu
Ph
t-BuO2C
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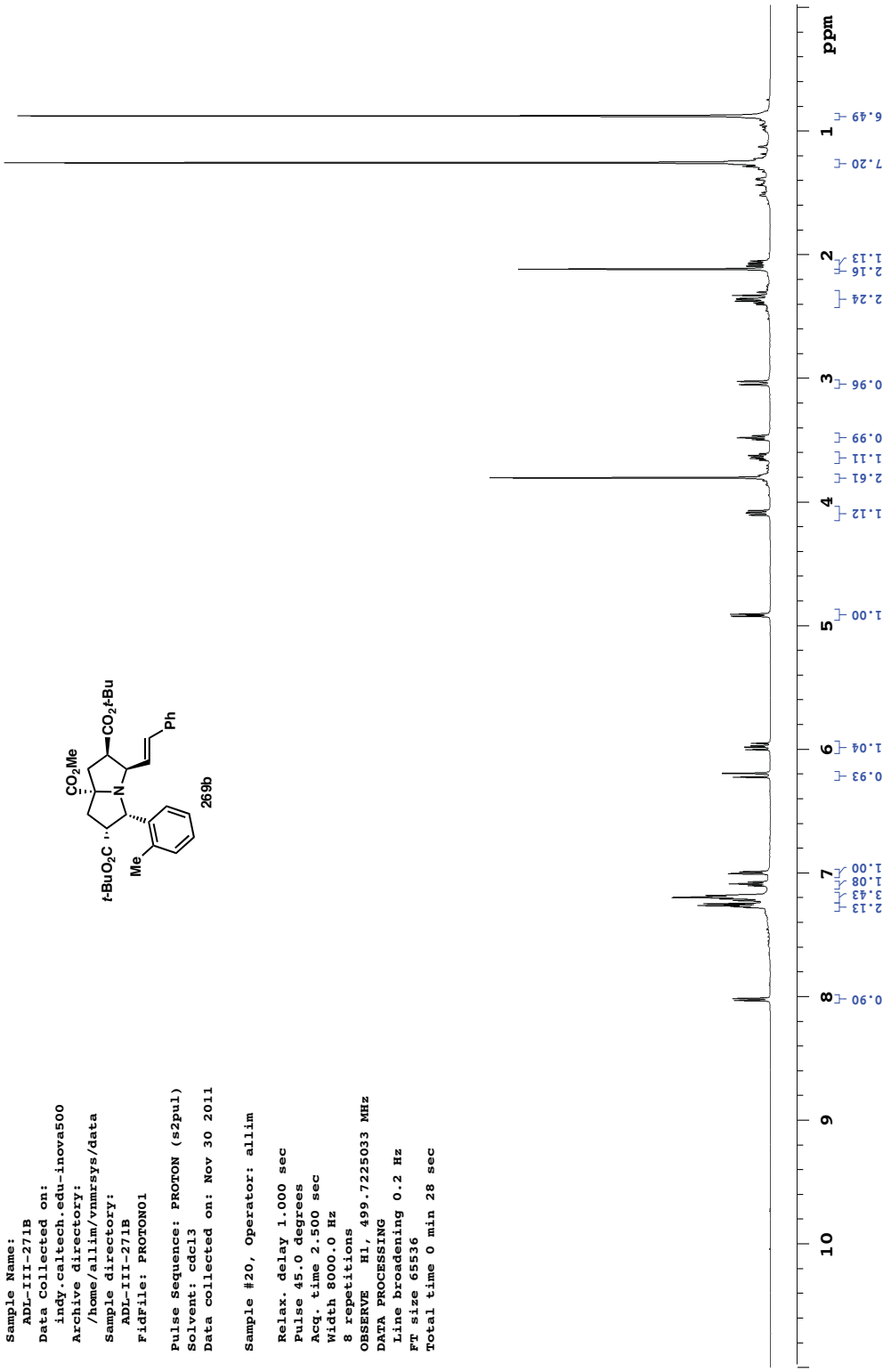
180
160
140
120
100
80
60
40
20
ppm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Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
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DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
N
Me
269b
ppm
10
9
8
7
6
5
4
3
2
1
0.90
2.13
3.43
1.08
1.00
0.93
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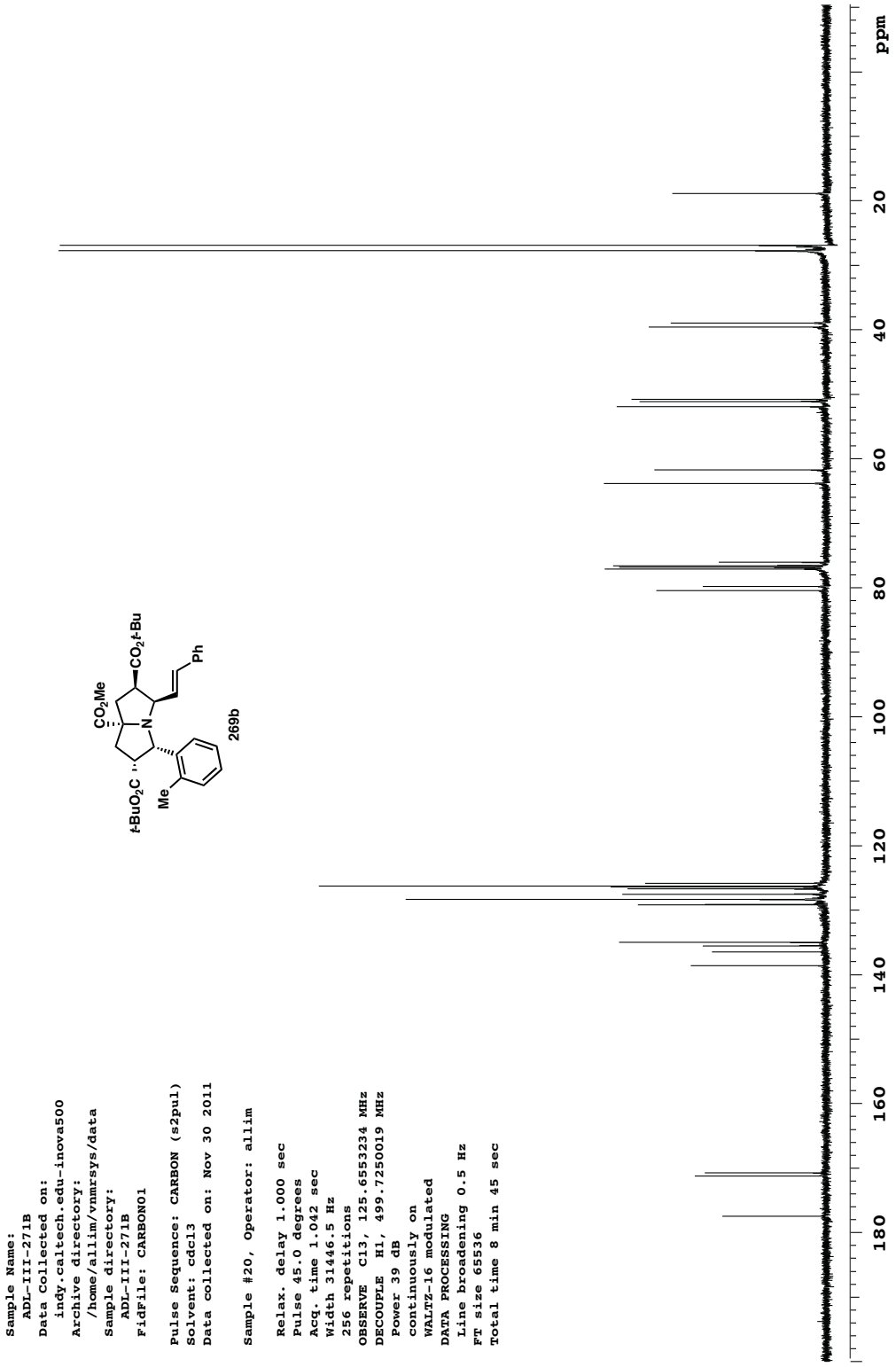
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Acq. time 1.042 sec
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256 repetitions
OBSERVE C13, 125.6553234 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 8 min 45 sec
CO2Me
CO2t-Bu
Ph
N
t-BuO2C
Me
269b
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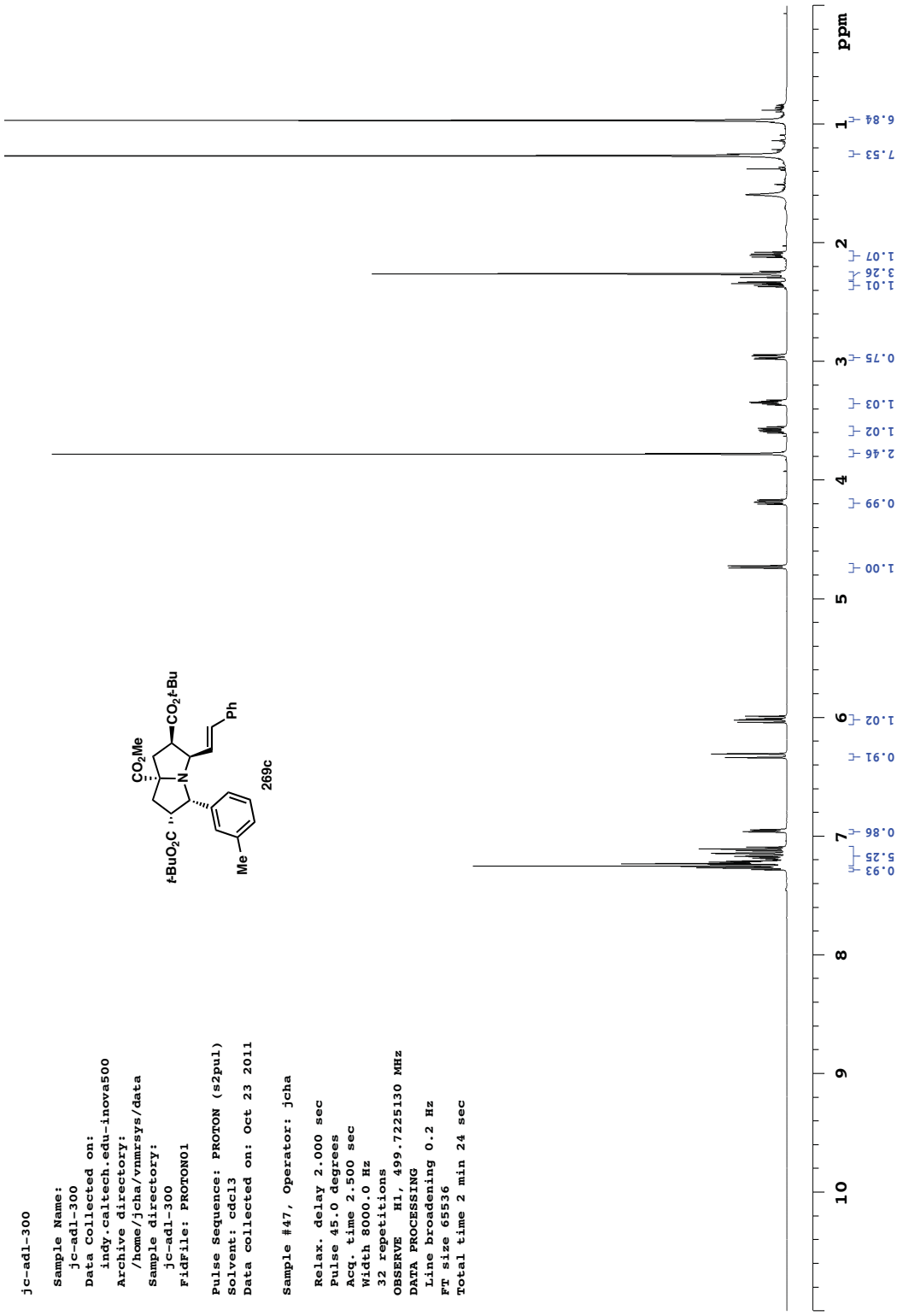
160
140
120
100
80
60
40
20
ppm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32 repetitions
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DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Me
269c
ppm
6.84
7.53
1.07
3.26
1.01
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1.03
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2.46
0.99
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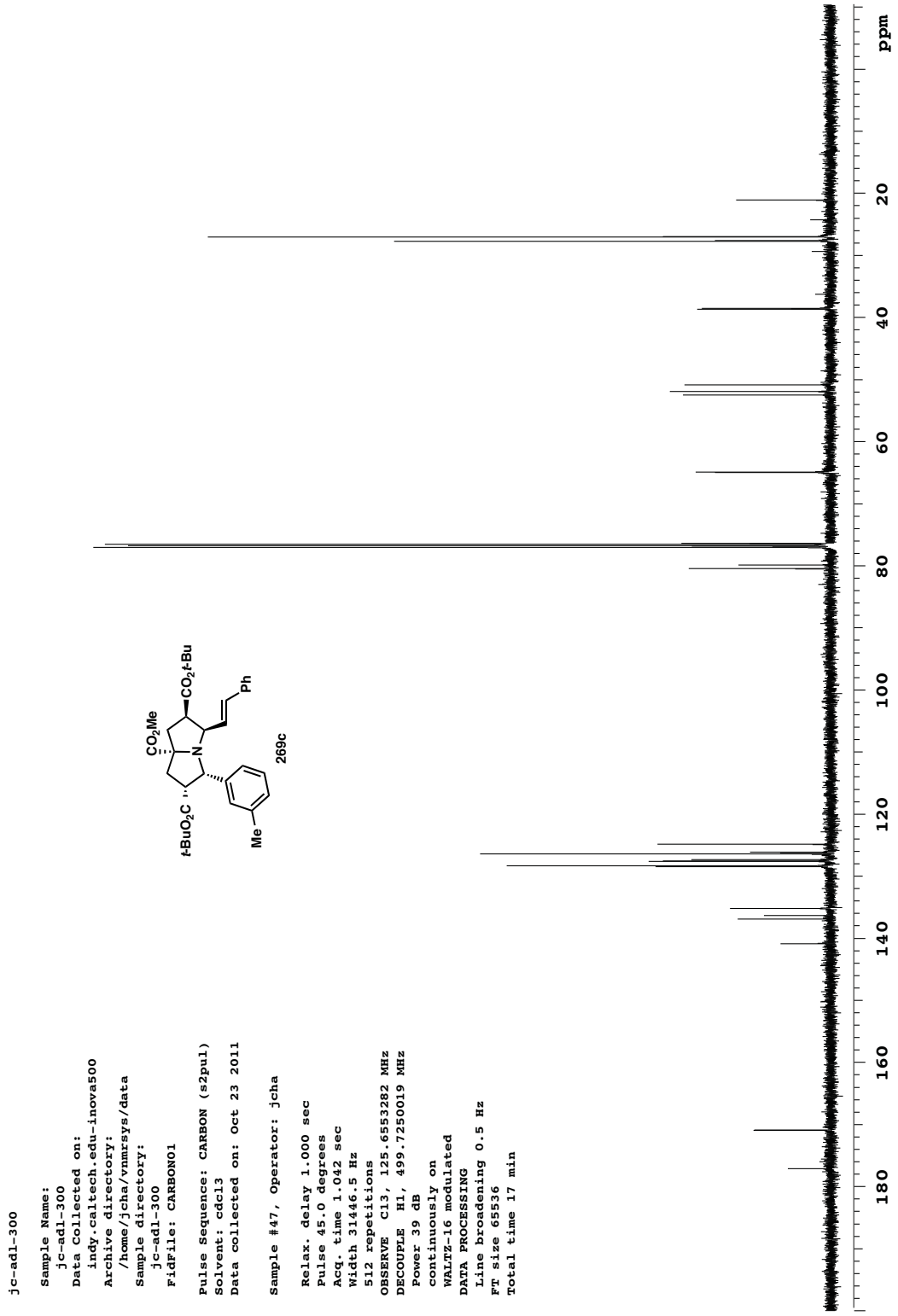
5.25
0.93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512 repetitions
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DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
CO2Me
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Ph
t-BuO2C
Me
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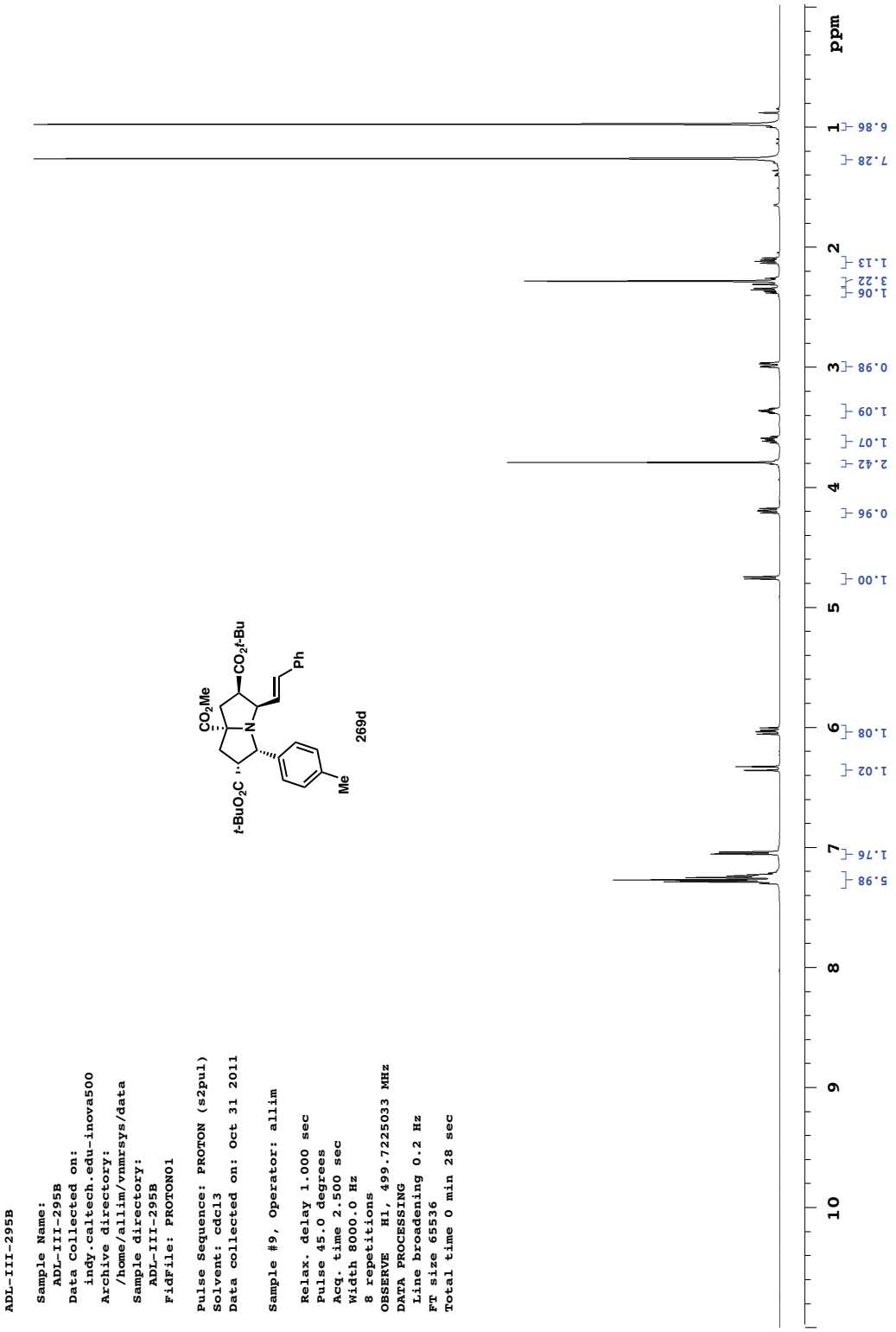
140
120
100
80
60
40
20
ppm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Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Me
269d
ppm
6.86
7.28
1.13
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1.00
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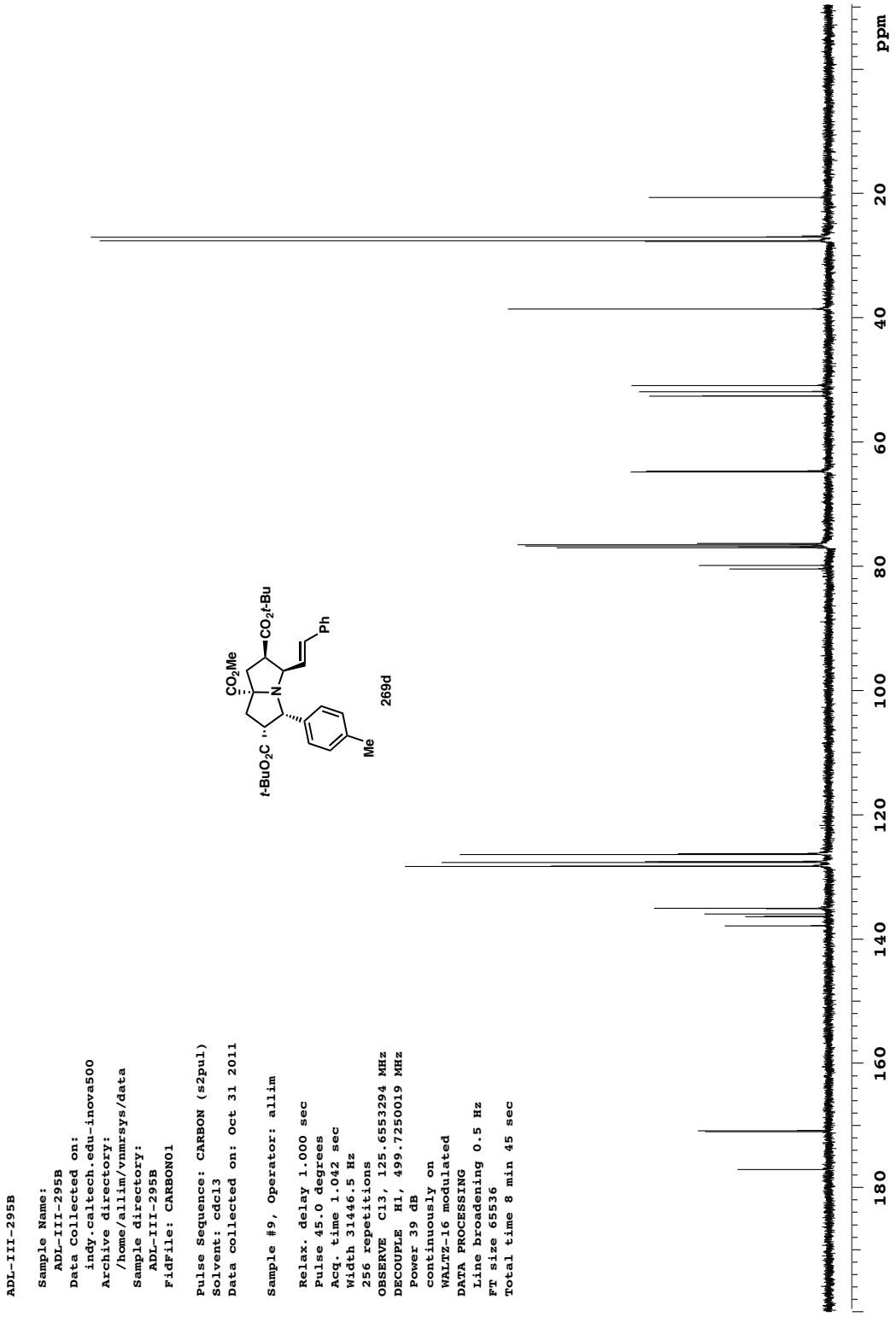
1.76
5.98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continuously on
WALTZ-16 modulated
DATA PROCESSING
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N
t-BuO2C
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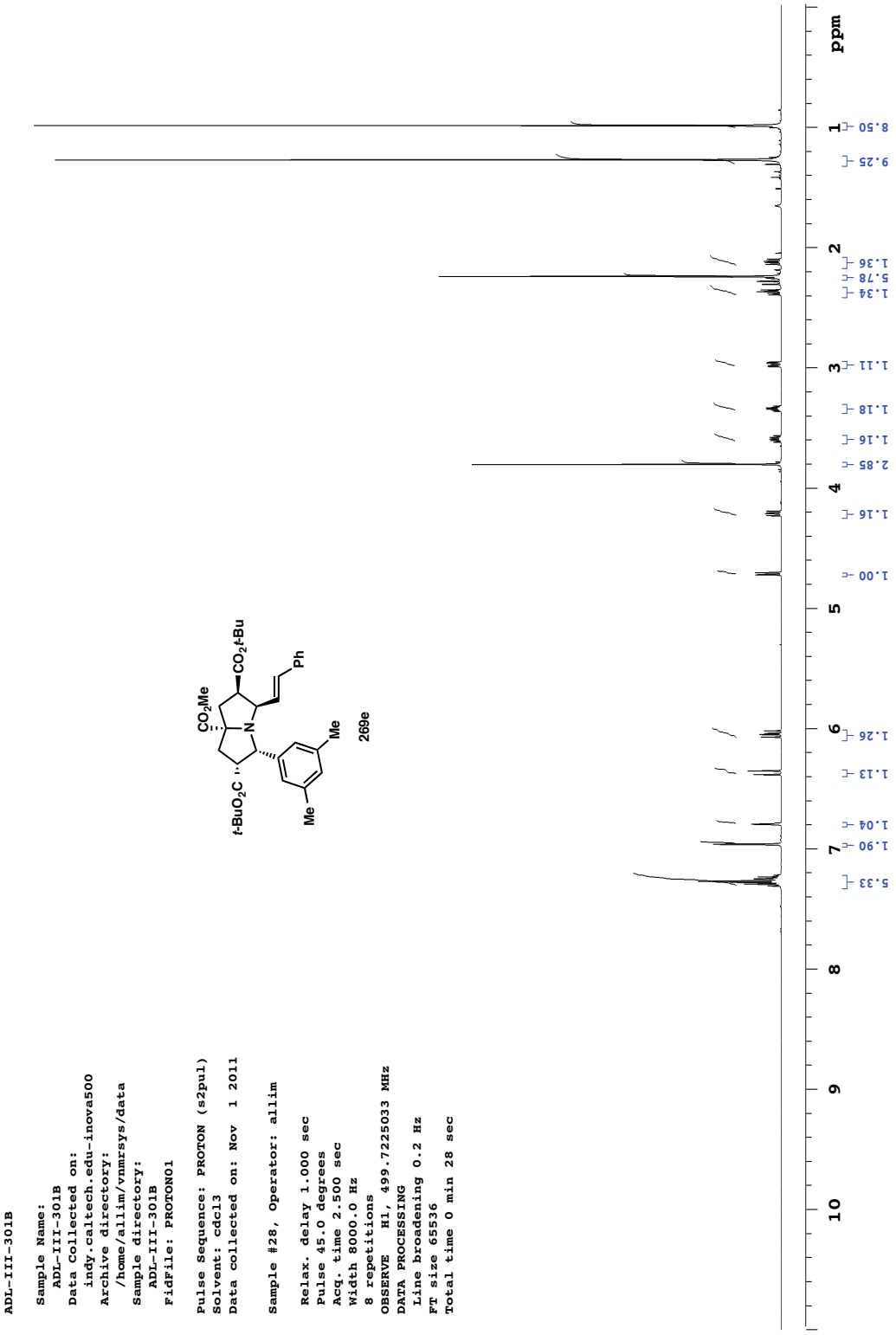
140
120
100
80
60
40
20
ppm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Solvent: cdcl3
Data collected on: Nov 1 2011
Sample #28, Operator: allim
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Pulse 45.0 degrees
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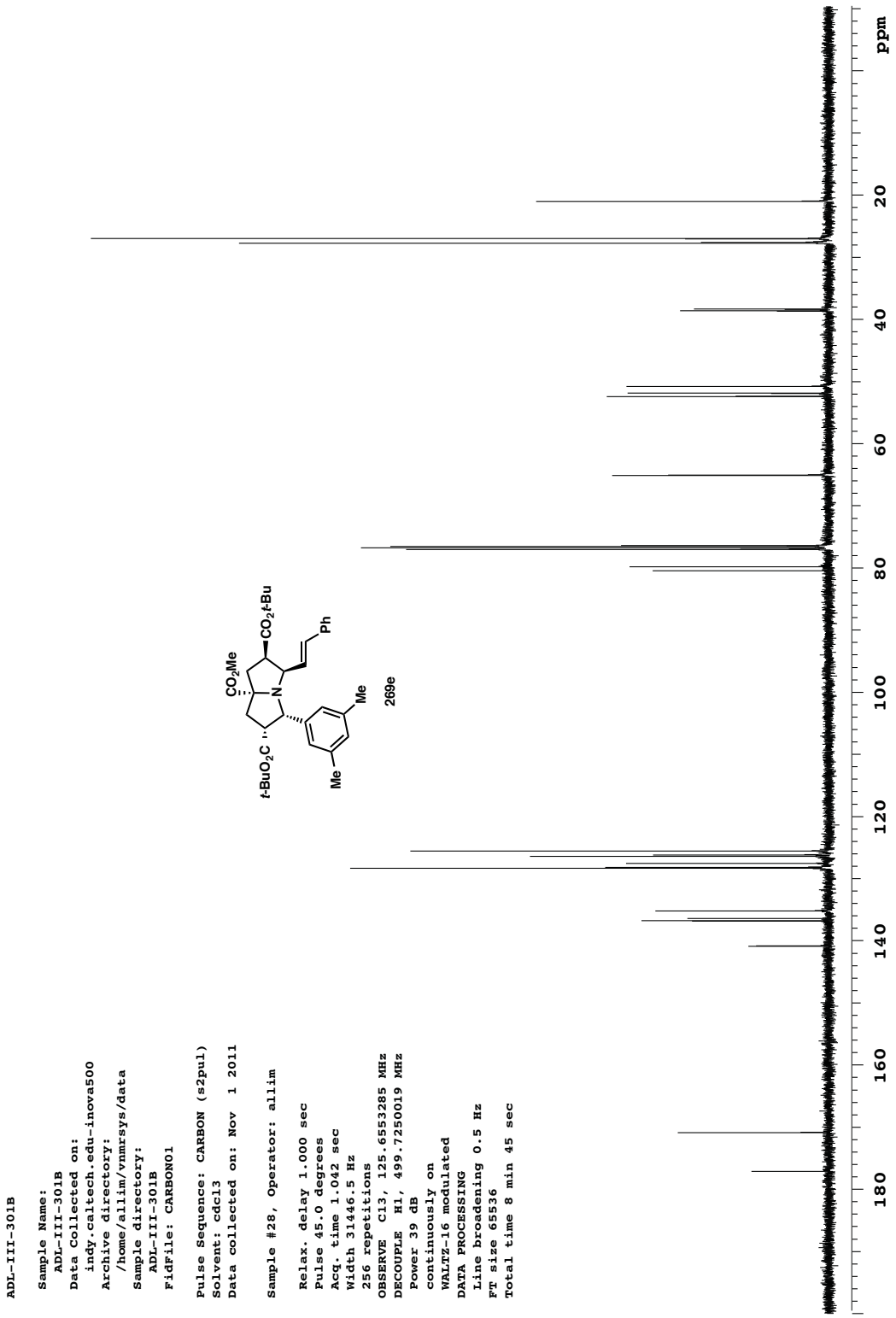
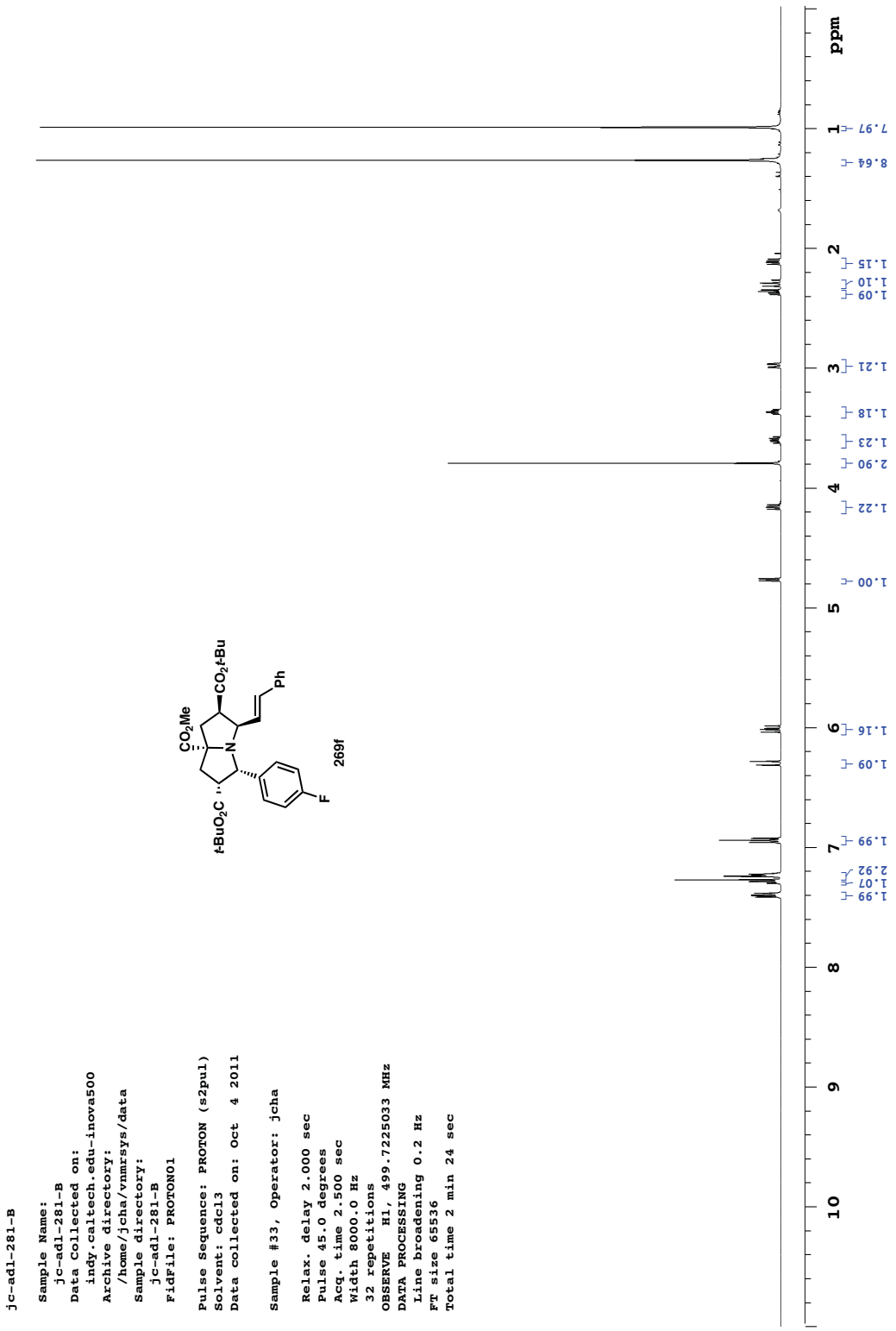
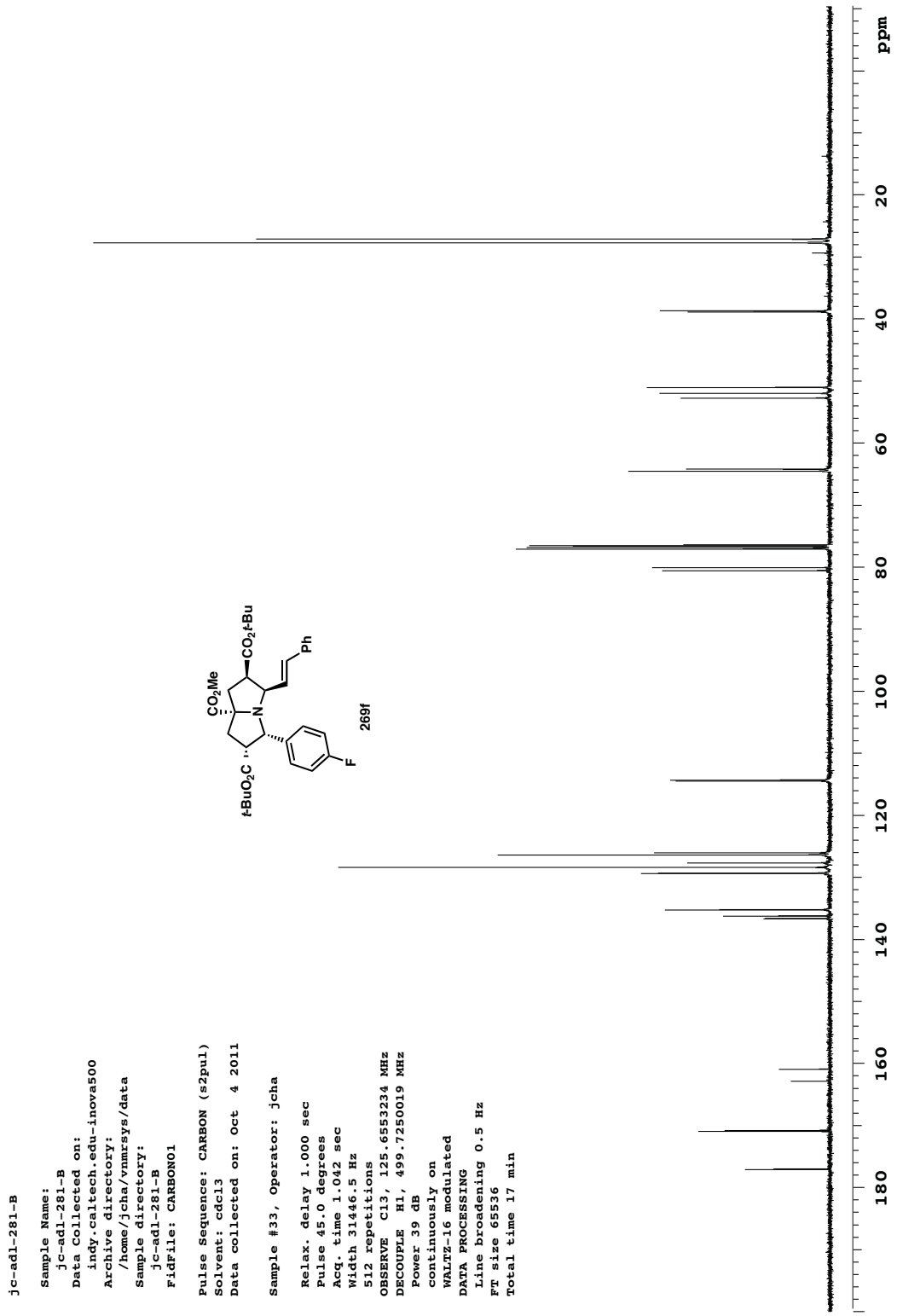
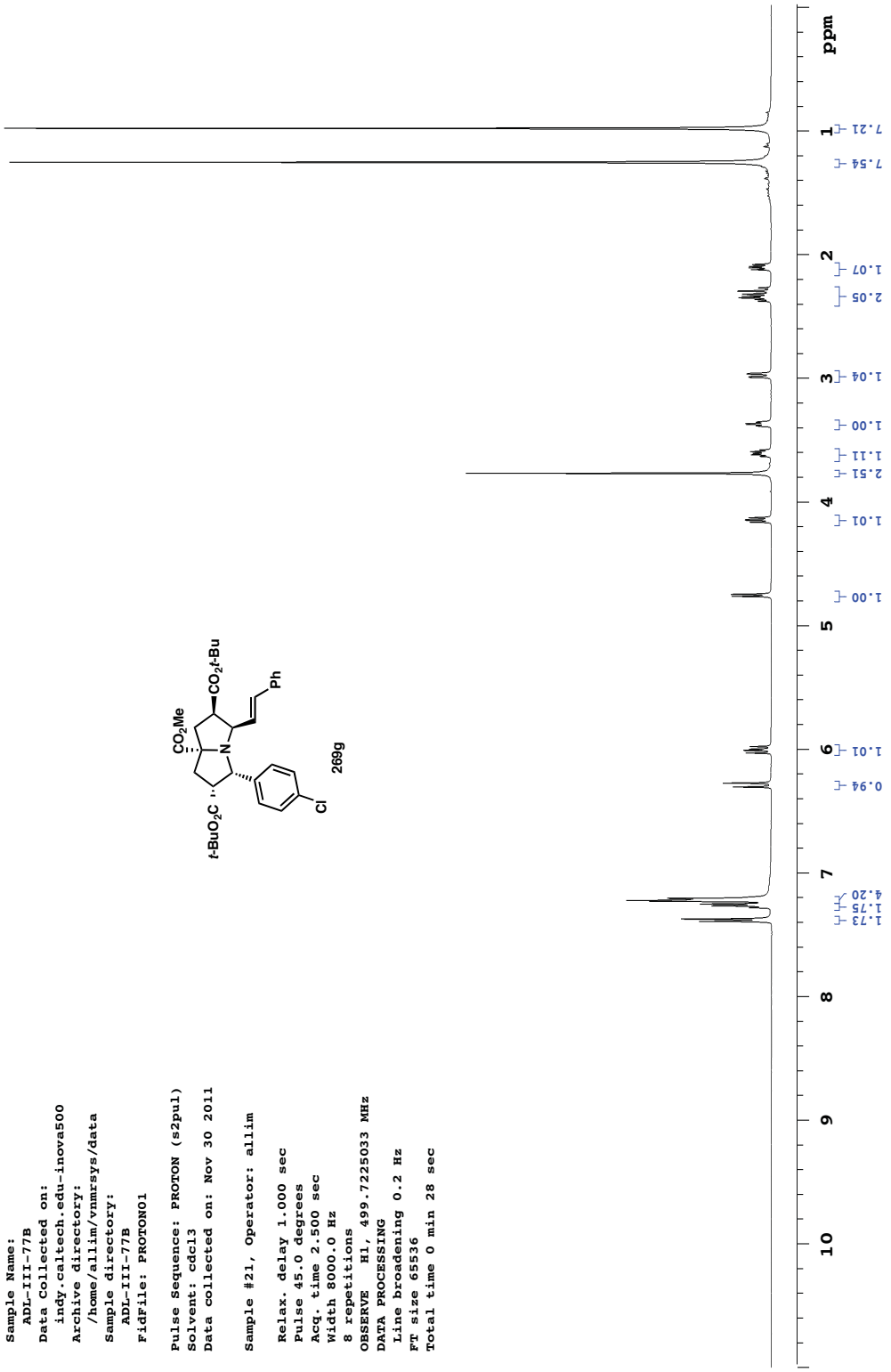
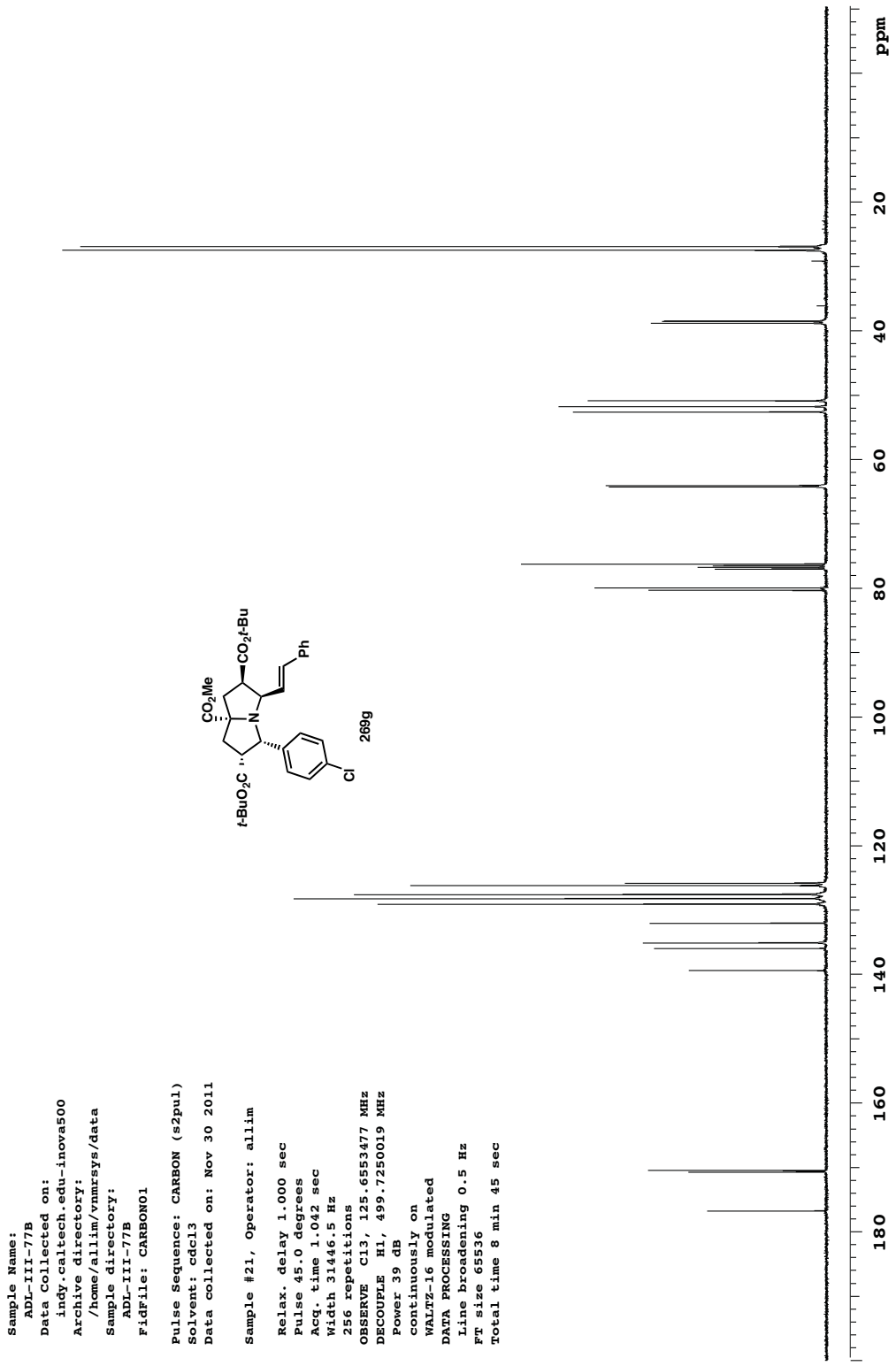
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2tBu
Ph
Me
Me
t-BuO2C
269e
ppm
8.50
9.25
1.36
5.78
1.34
1.11
1.18
1.16
2.85
1.16
1.00
1.26
1.13
1.04
1.90
5.33

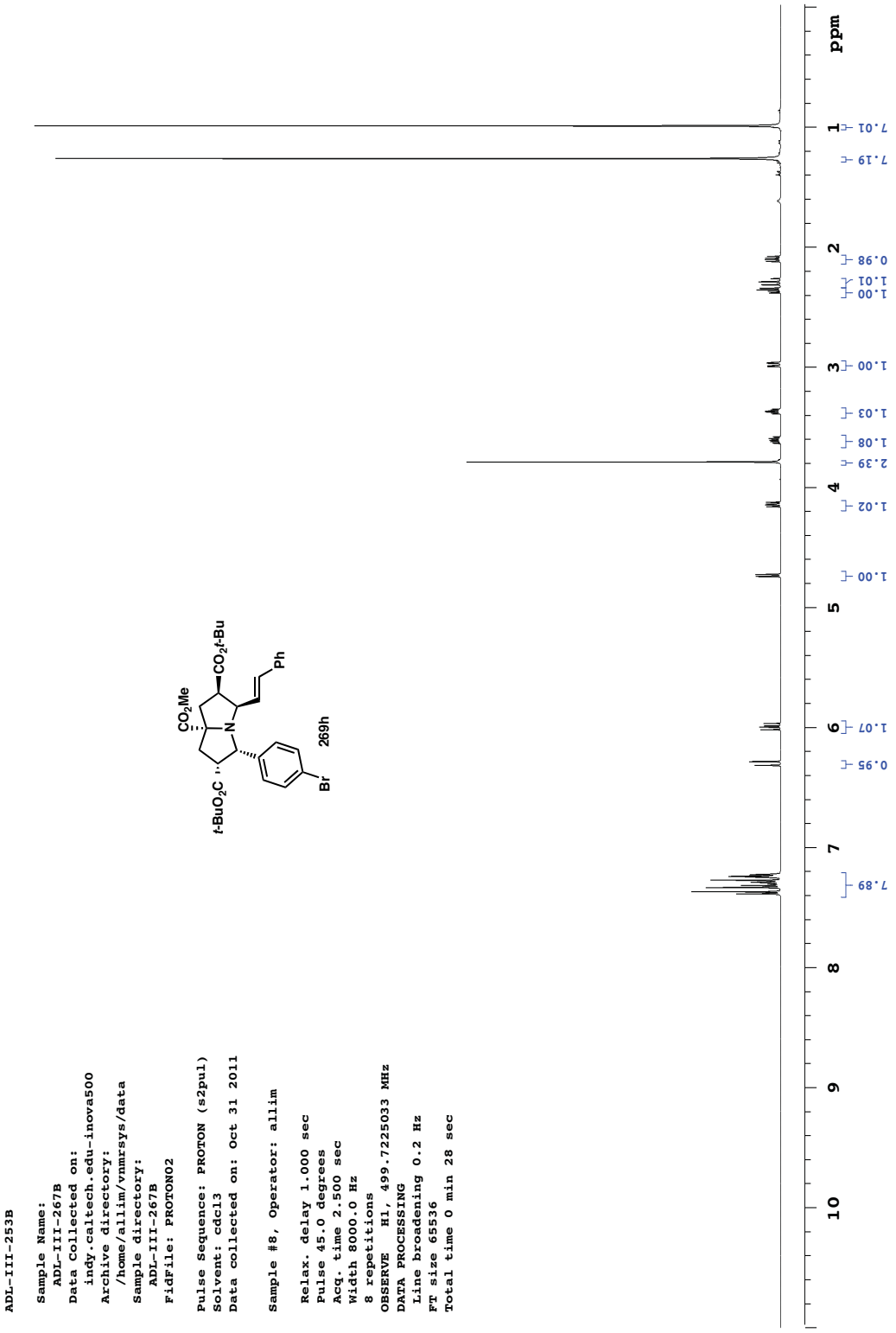

ADL-III-301B
Sample Name:
ADL-III-301B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-301B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 1 2011
Sample #28, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553285 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
N
Me
Me
269e
180
160
140
120
100
80
60
40
20
ppm

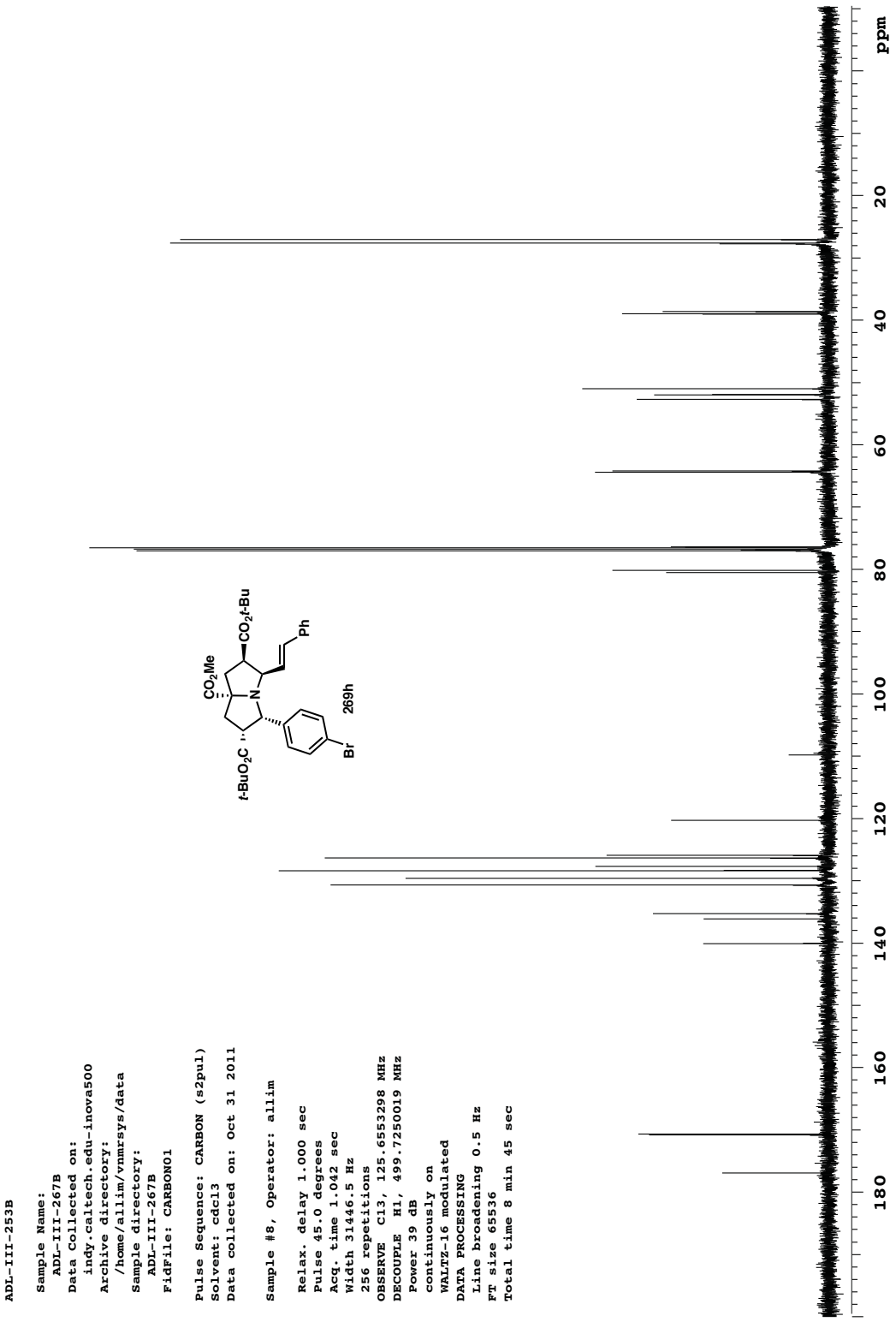

jc-adl-281-B
Sample Name:
jc-adl-281-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-adl-281-B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 4 2011
Sample #33, Operator: jcha
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
F
269f
ppm
7.97
8.64
1.15
1.10
1.09
1.21
1.18
1.23
2.90
1.22
1.00
1.16
1.09
1.99
2.92
1.07
1.99

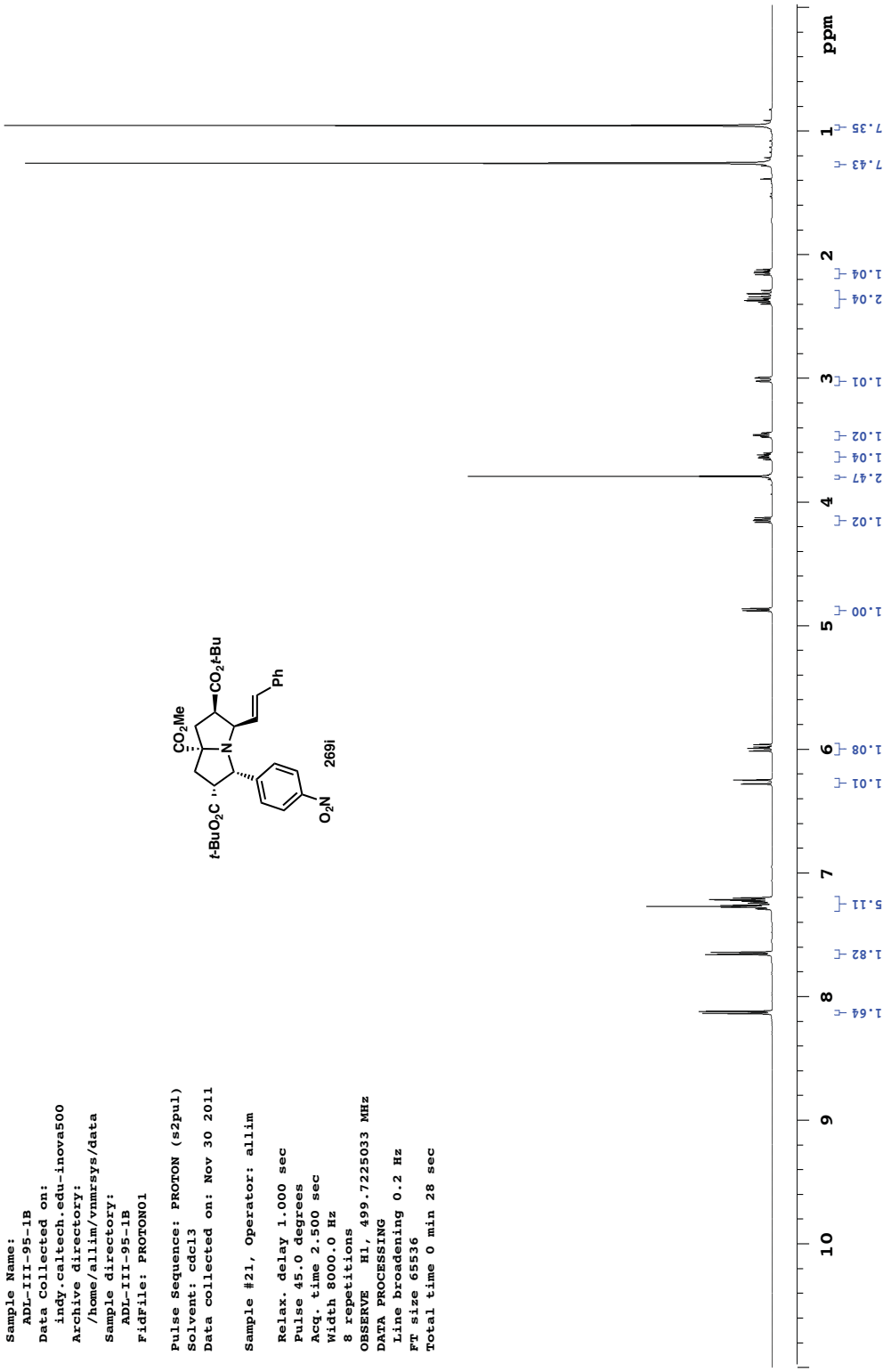

jc-adl-281-B
Sample Name:
jc-adl-281-B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcha/vnmrsys/data
Sample directory:
jc-adl-281-B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 4 2011
Sample #33, Operator: jcha
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553234 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
CO2Me
CO2tBu
Ph
N
tBuO2C
F
269f
180
160
140
120
100
80
60
40
20
ppm

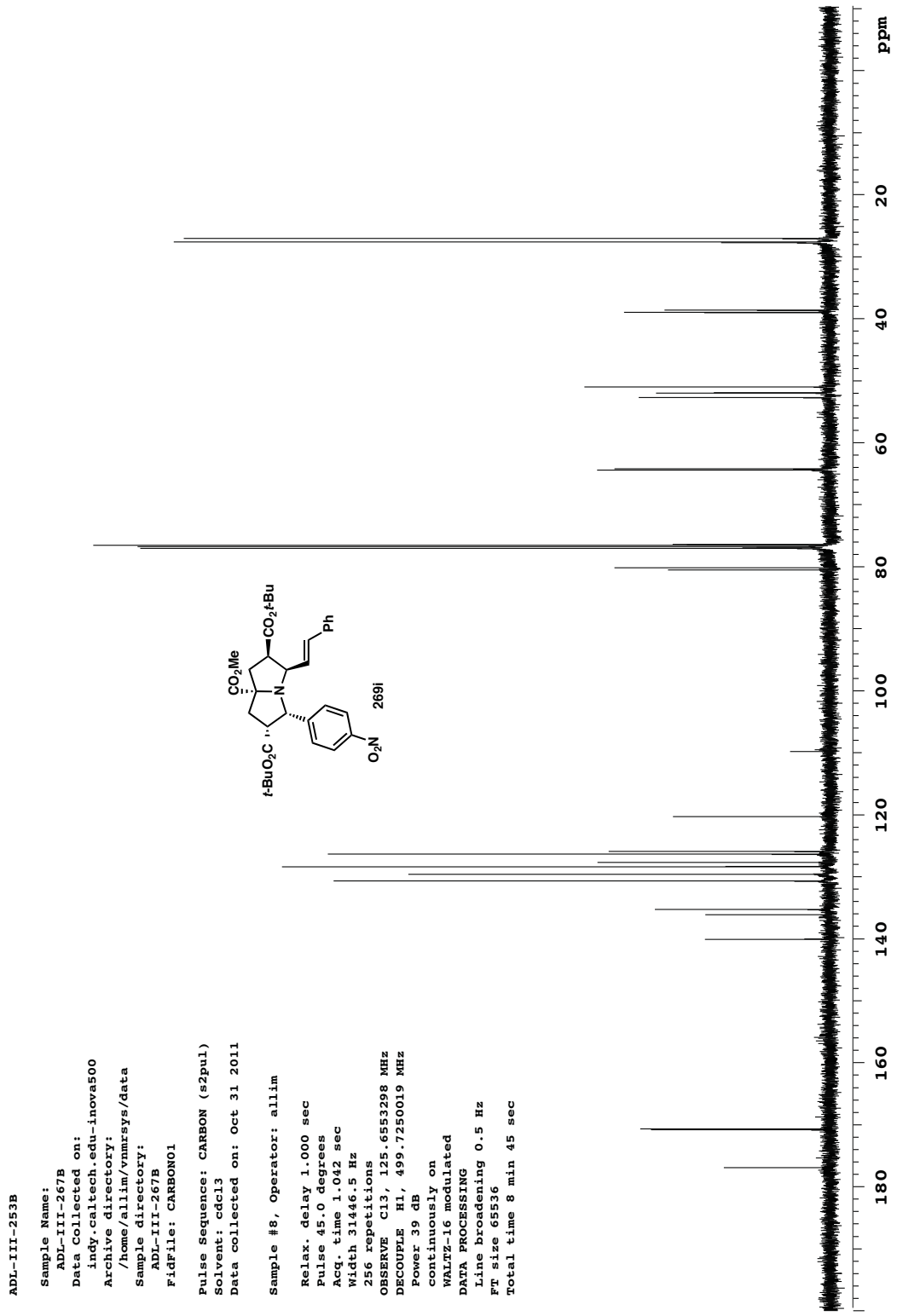

Sample Name:
ADL-III-77B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-77B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 30 2011
Sample #21, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Cl
269g
ppm
7.21
7.54
1.07
2.05
1.04
1.00
1.11
2.51
1.01
1.00
1.01
0.94
4.20
1.75
1.73

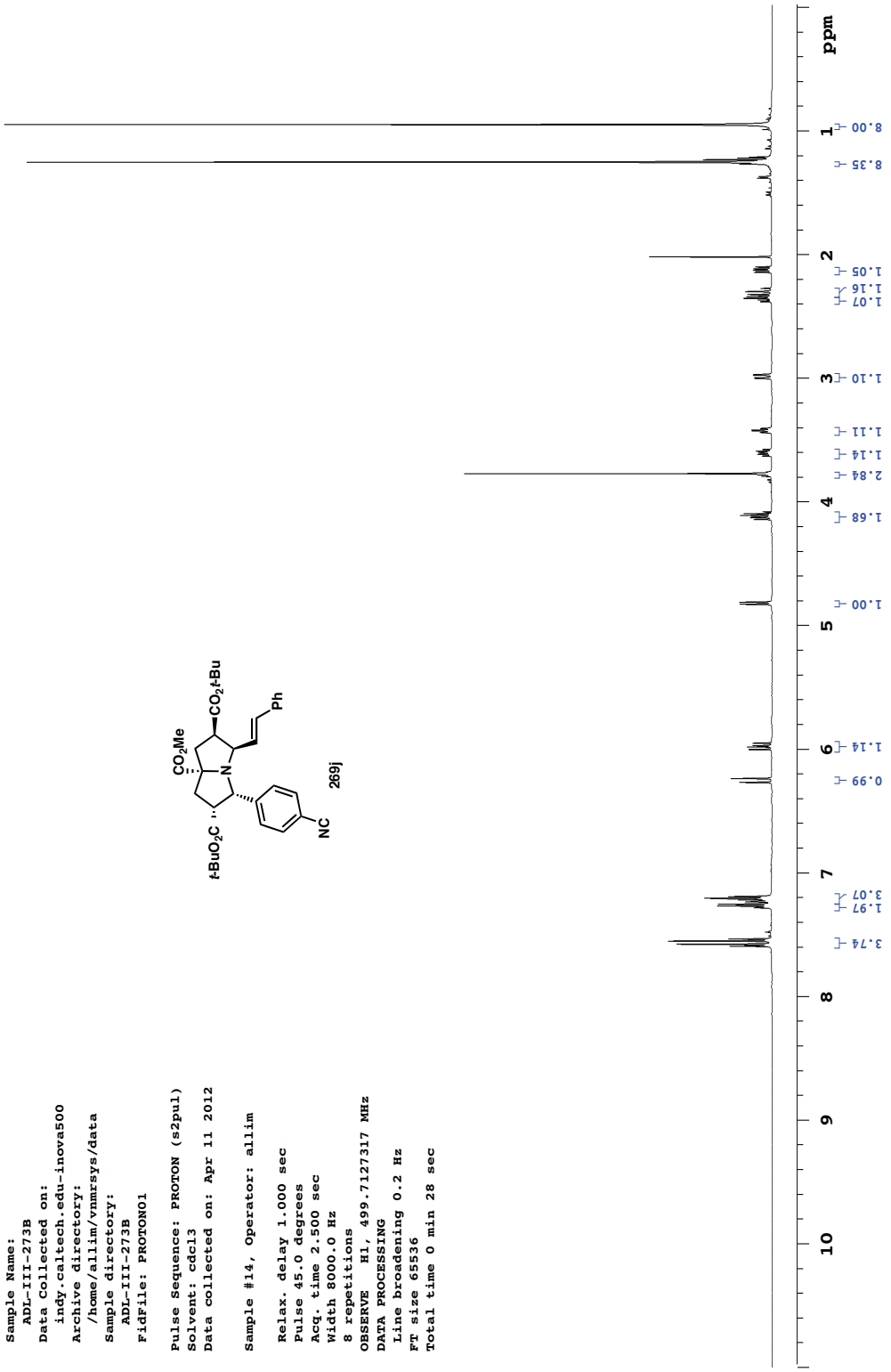

Sample Name:
ADL-III-77B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-77B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 30 2011
Sample #21, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553477 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Cl
269g
180
160
140
120
100
80
60
40
20
ppm

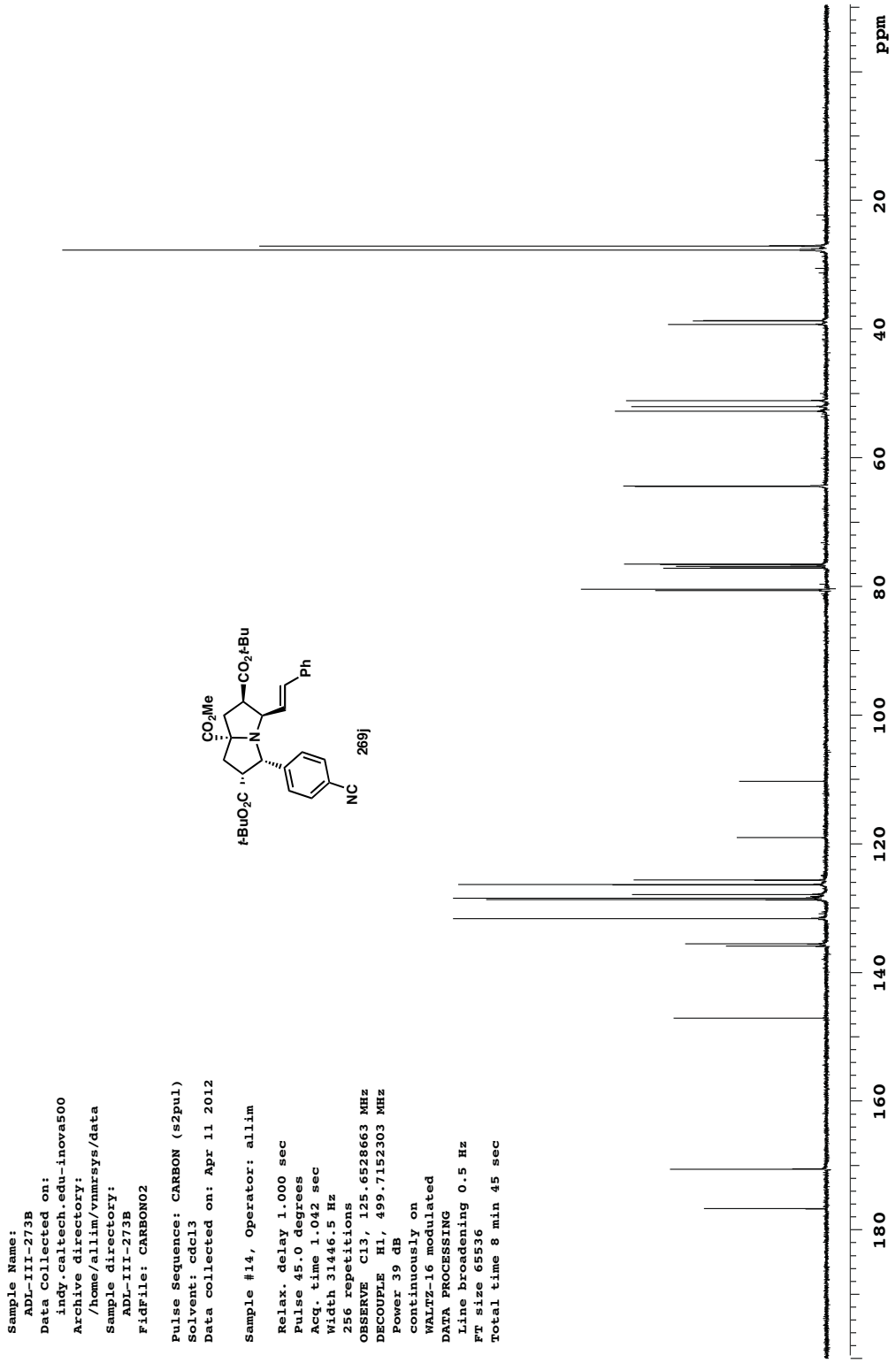

ADL-III-253B
Sample Name:
ADL-III-267B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-267B
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 31 2011
Sample #8, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Br
269h
ppm
7.01
7.19
0.98
1.01
1.00
1.00
1.03
1.08
2.39
1.02
1.00
1.07
0.95
7.89

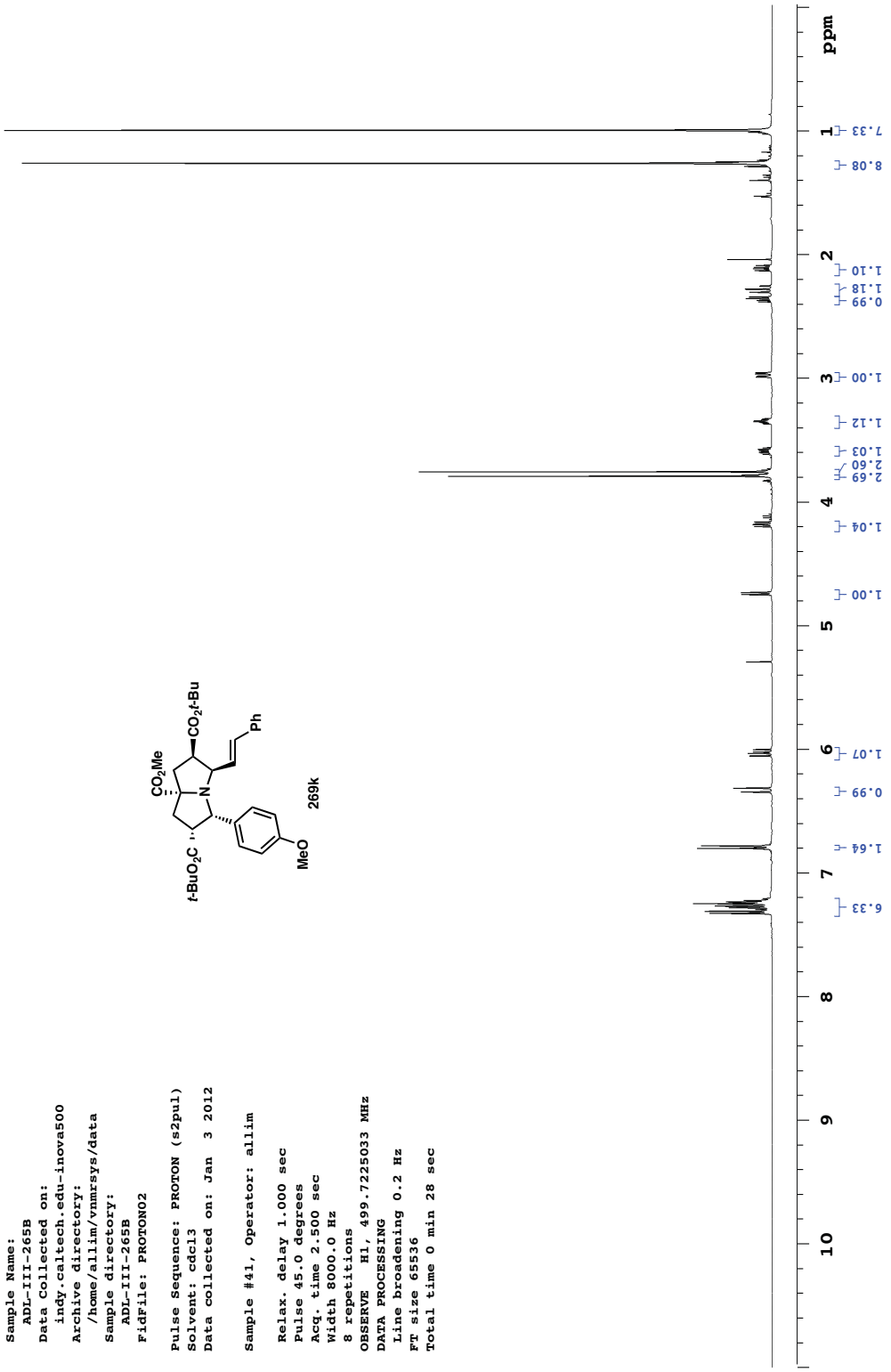

ADL-III-253B
Sample Name:
ADL-III-267B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-267B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 31 2011
Sample #8, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553298 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Br
269h
180
160
140
120
100
80
60
40
20
ppm

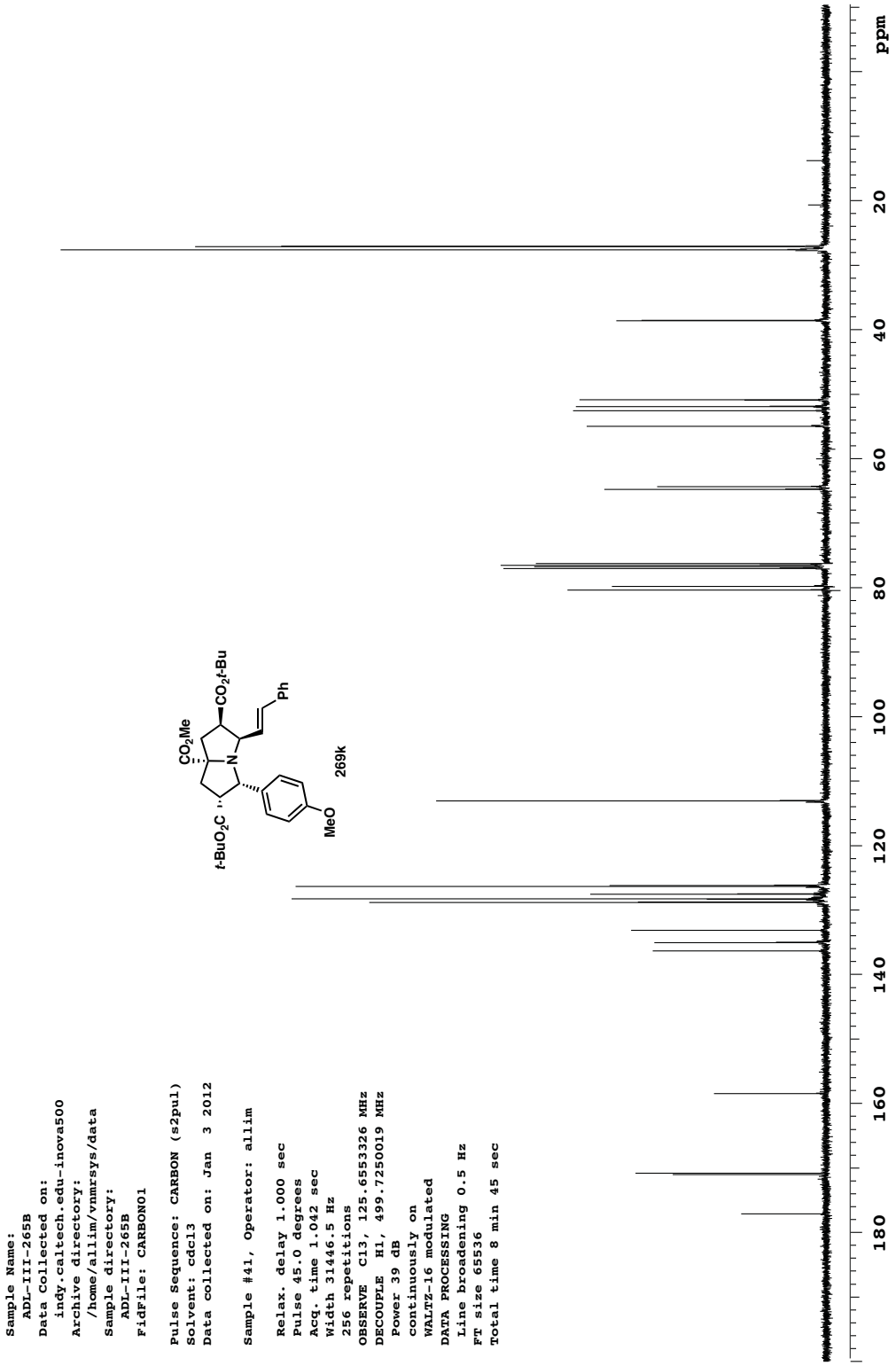

Sample Name:
ADL-III-95-1B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-95-1B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 30 2011
Sample #21, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2tBu
Ph
t-BuO2C
O2N
269i
ppm
7.35
7.43
1.04
2.04
1.01
1.02
1.04
2.47
1.02
1.00
1.08
1.01
5.11
1.82
1.64

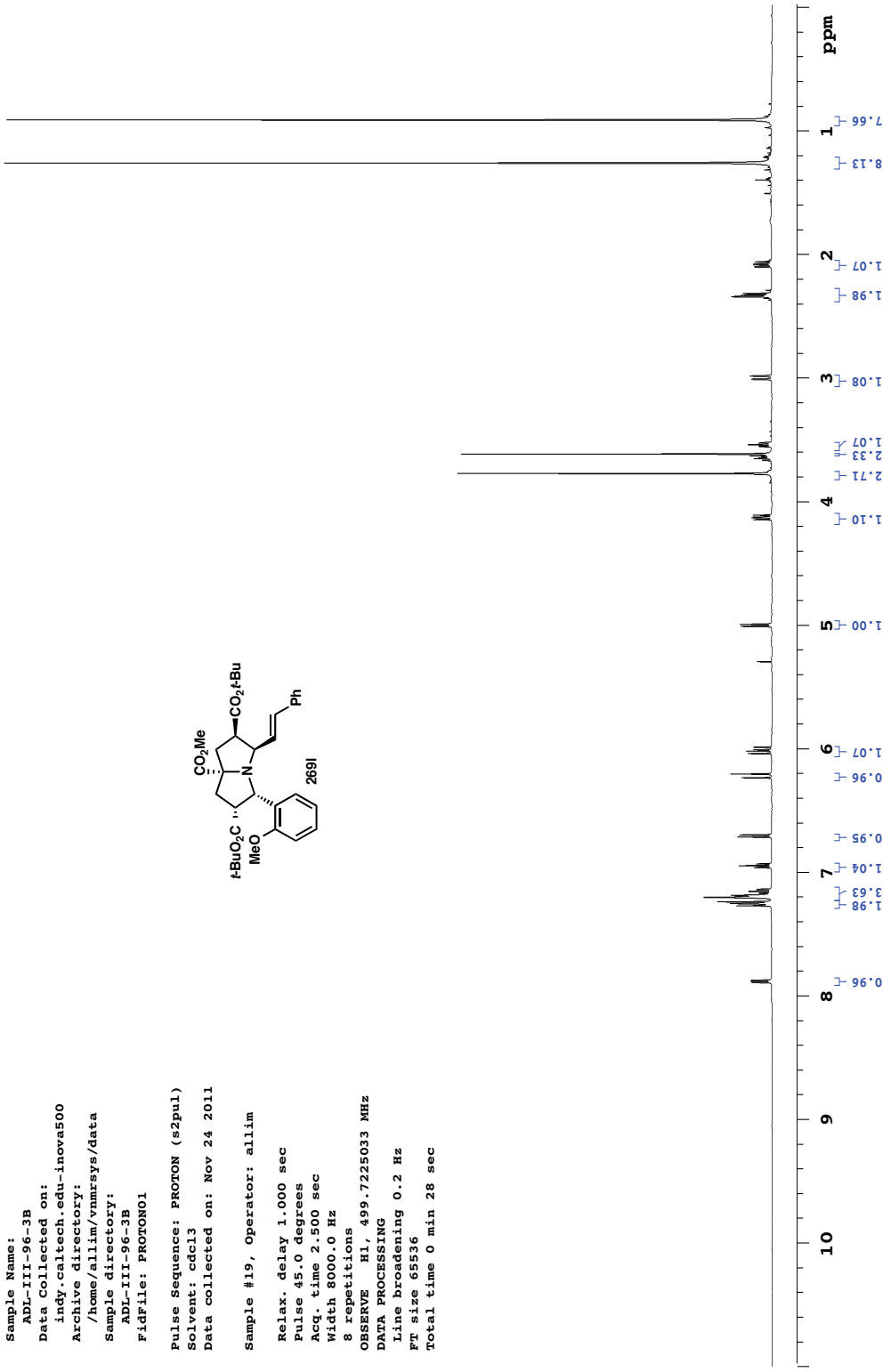

ADL-III-253B
Sample Name:
ADL-III-267B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-267B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 31 2011
Sample #8, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553298 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
O2N
269i
180
160
140
120
100
80
60
40
20
ppm

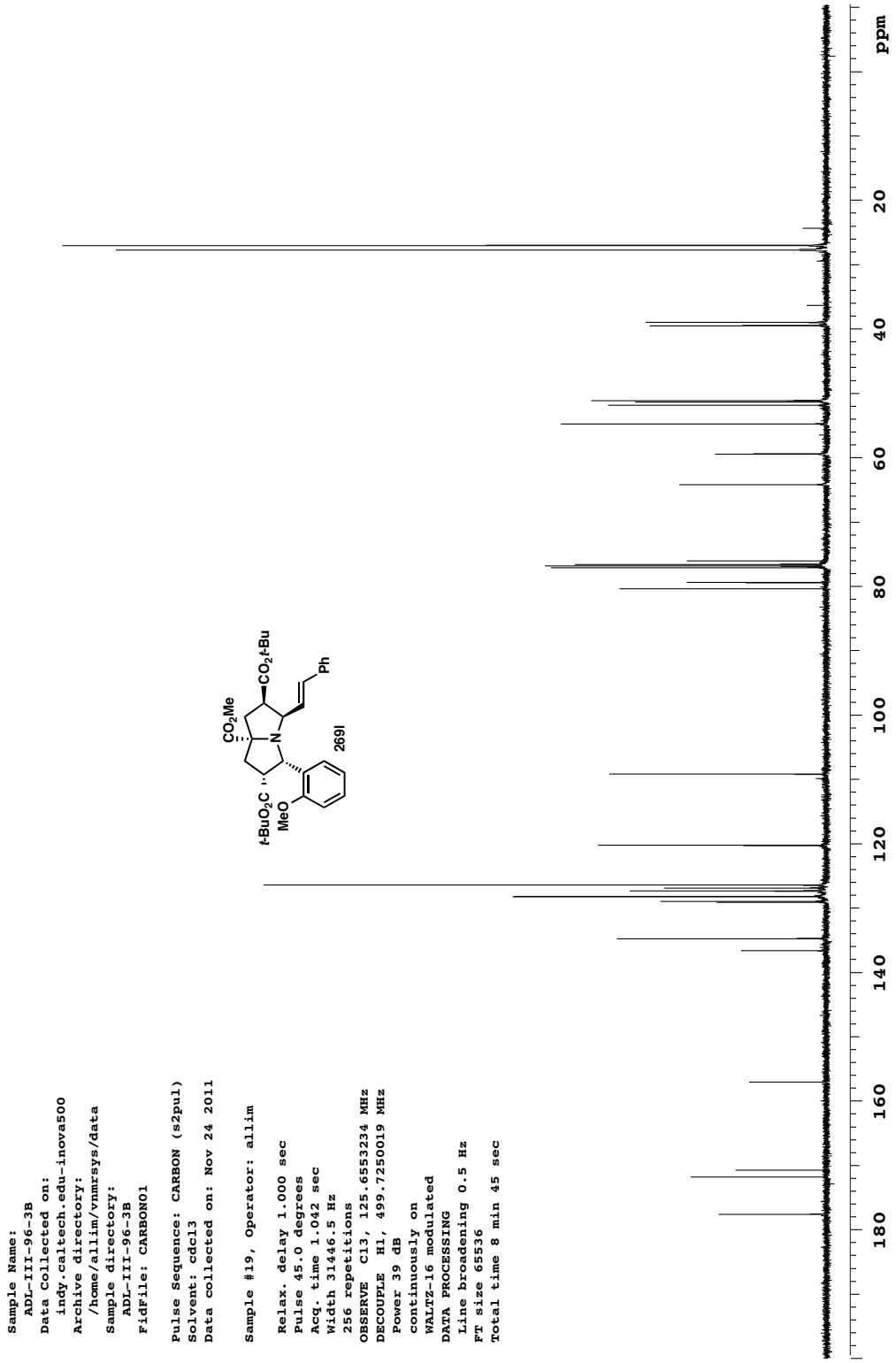

Sample Name:
ADL-III-273B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-273B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 11 2012
Sample #14, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127317 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2tBu
Ph
tBuO2C
NC
269j
ppm
8.00
8.35
1.05
1.16
1.07
1.10
1.11
1.14
2.84
1.68
1.00
1.14
0.99
3.07
1.97
3.74

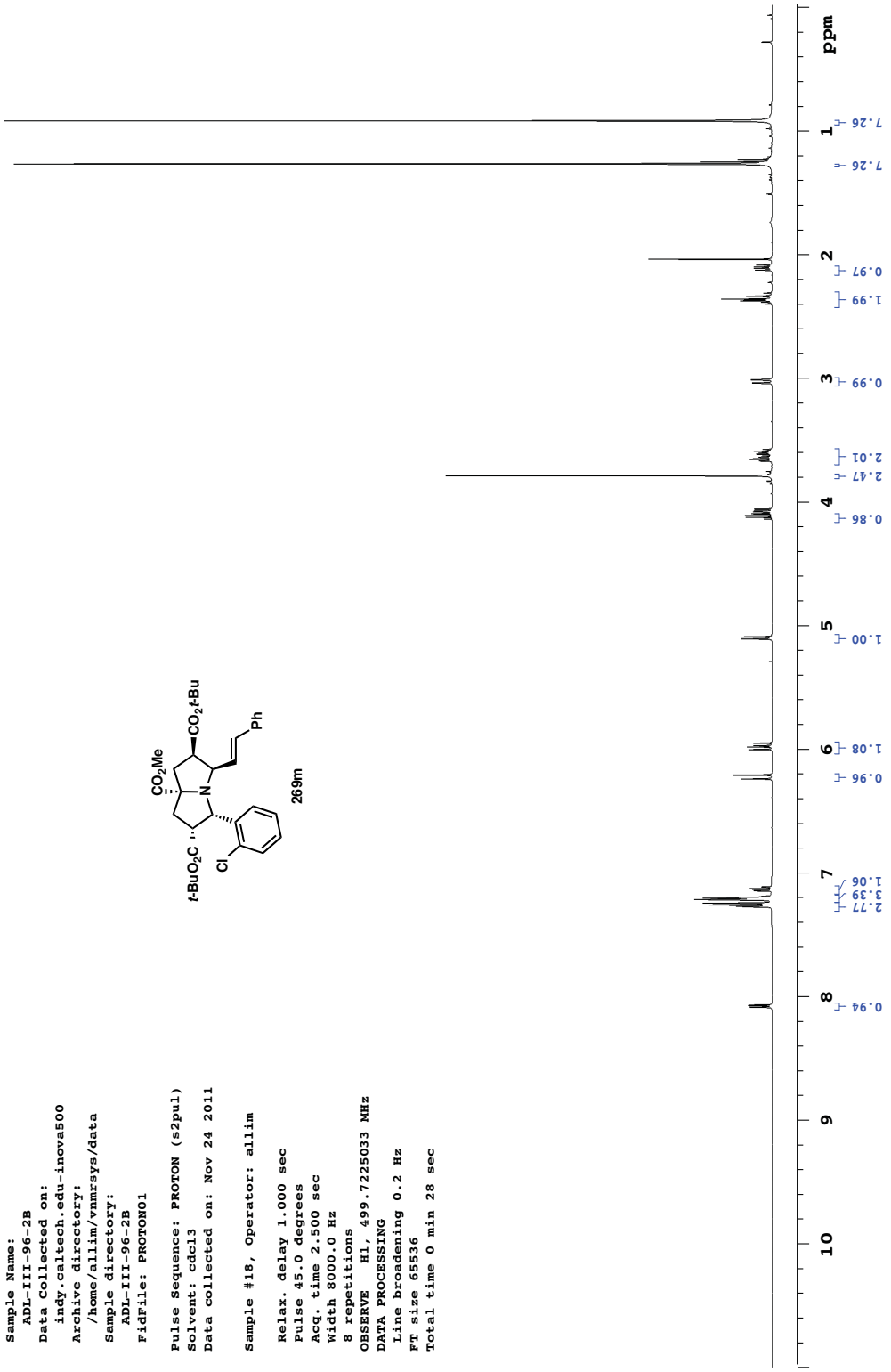

Sample Name:
ADL-III-273B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-273B
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 11 2012
Sample #14, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6528663 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
N
NC
269j
180
160
140
120
100
80
60
40
20
ppm

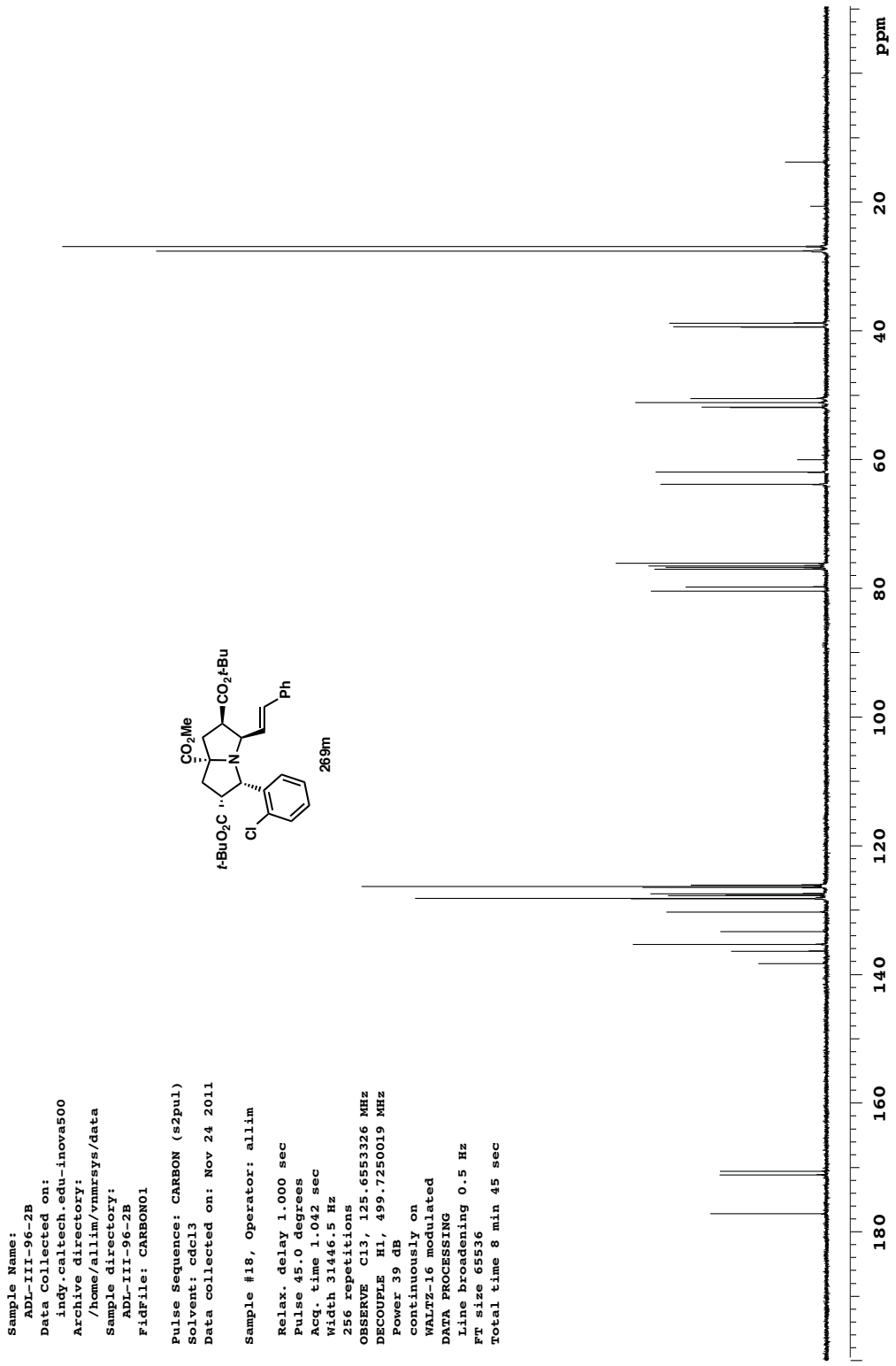

Sample Name:
ADL-III-265B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-265B
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 3 2012
Sample #41, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
MeO
269k
ppm
7.33
8.08
1.10
1.18
0.99
1.00
1.12
1.03
2.69
2.60
1.04
1.00
1.07
0.99
1.64
6.33

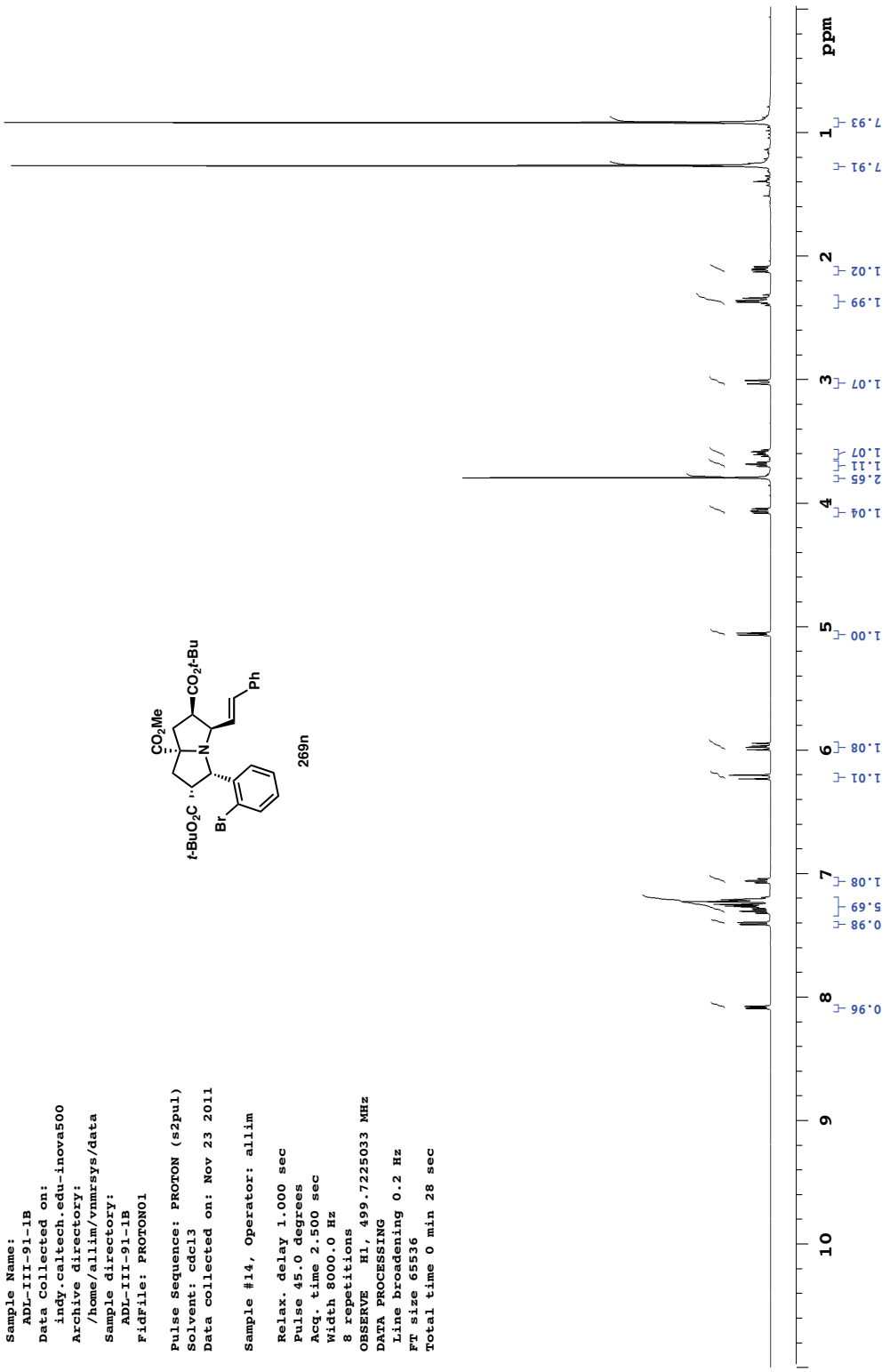

Sample Name:
ADL-III-265B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-265B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 3 2012
Sample #41, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553326 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
N
MeO
269k
180
160
140
120
100
80
60
40
20
ppm

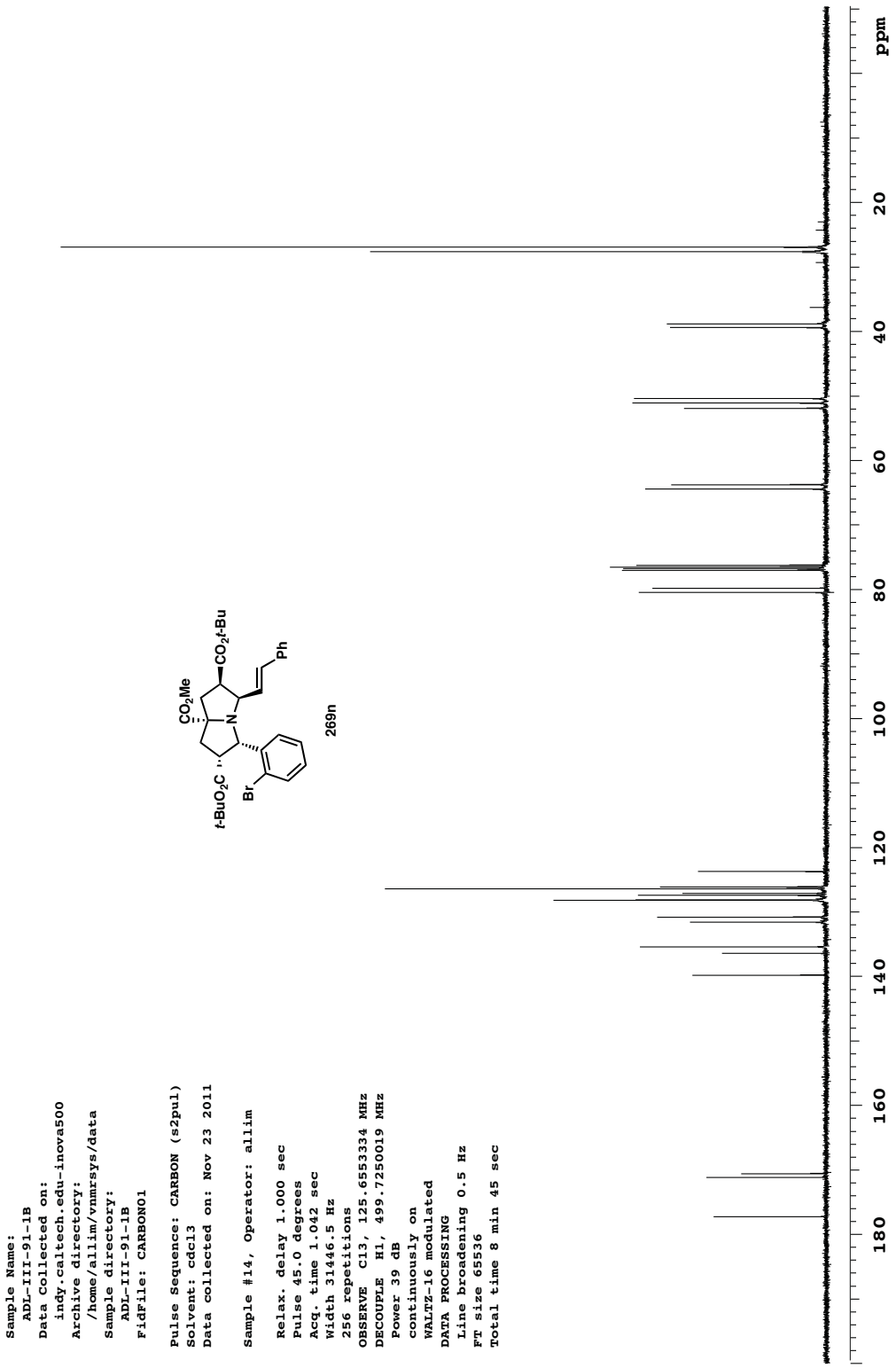

Sample Name:
ADL-III-96-3B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-96-3B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 24 2011
Sample #19, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
MeO
269I
ppm
7.66
8.13
1.07
1.98
1.08
1.07
2.33
2.71
1.10
1.00
1.07
0.96
0.95
1.04
3.63
1.98
0.96

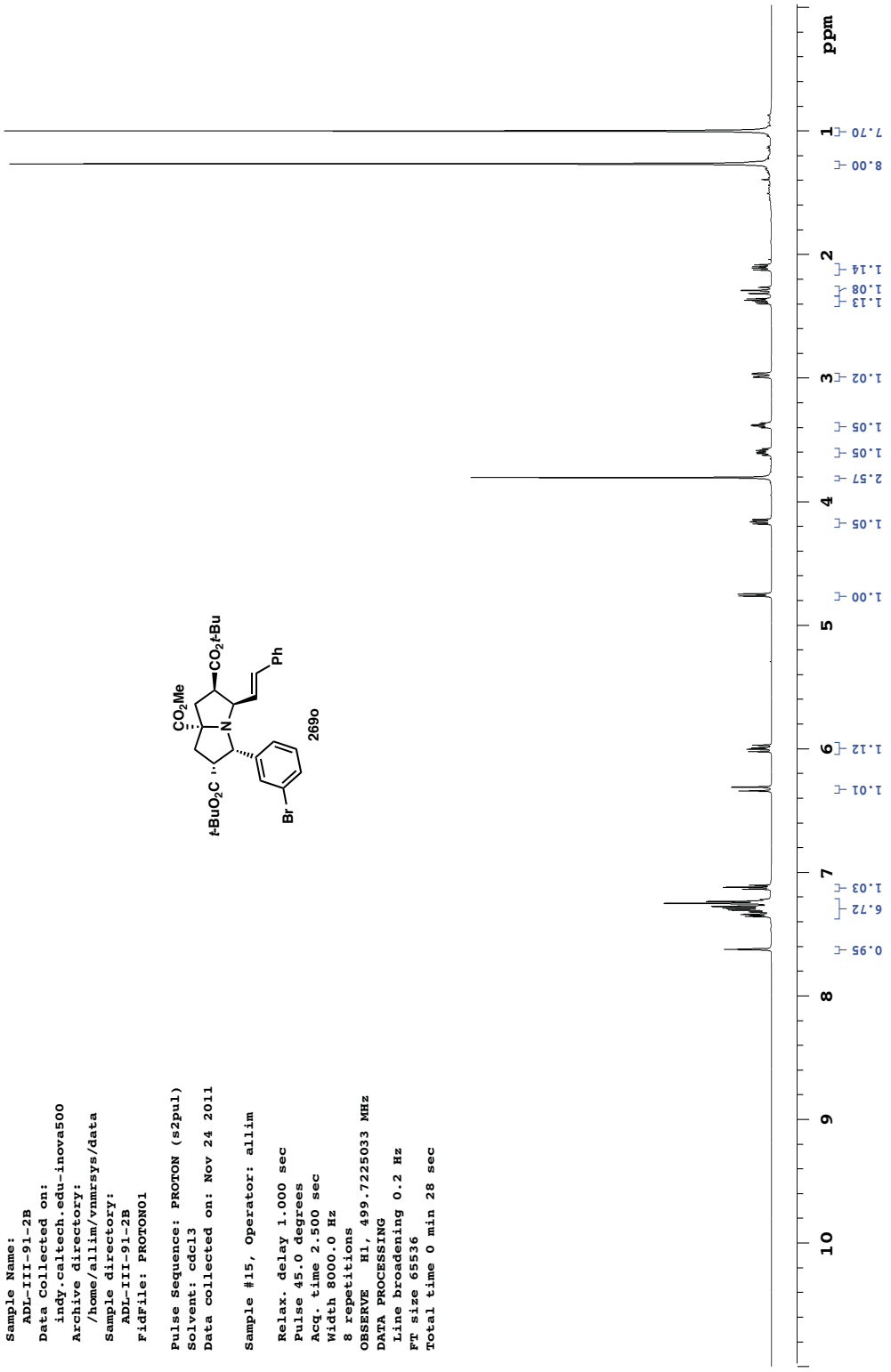

Sample Name:
ADL-III-96-3B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-96-3B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 24 2011
Sample #19, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553234 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
N
t-BuO2C
MeO
269I
180
160
140
120
100
80
60
40
20
ppm

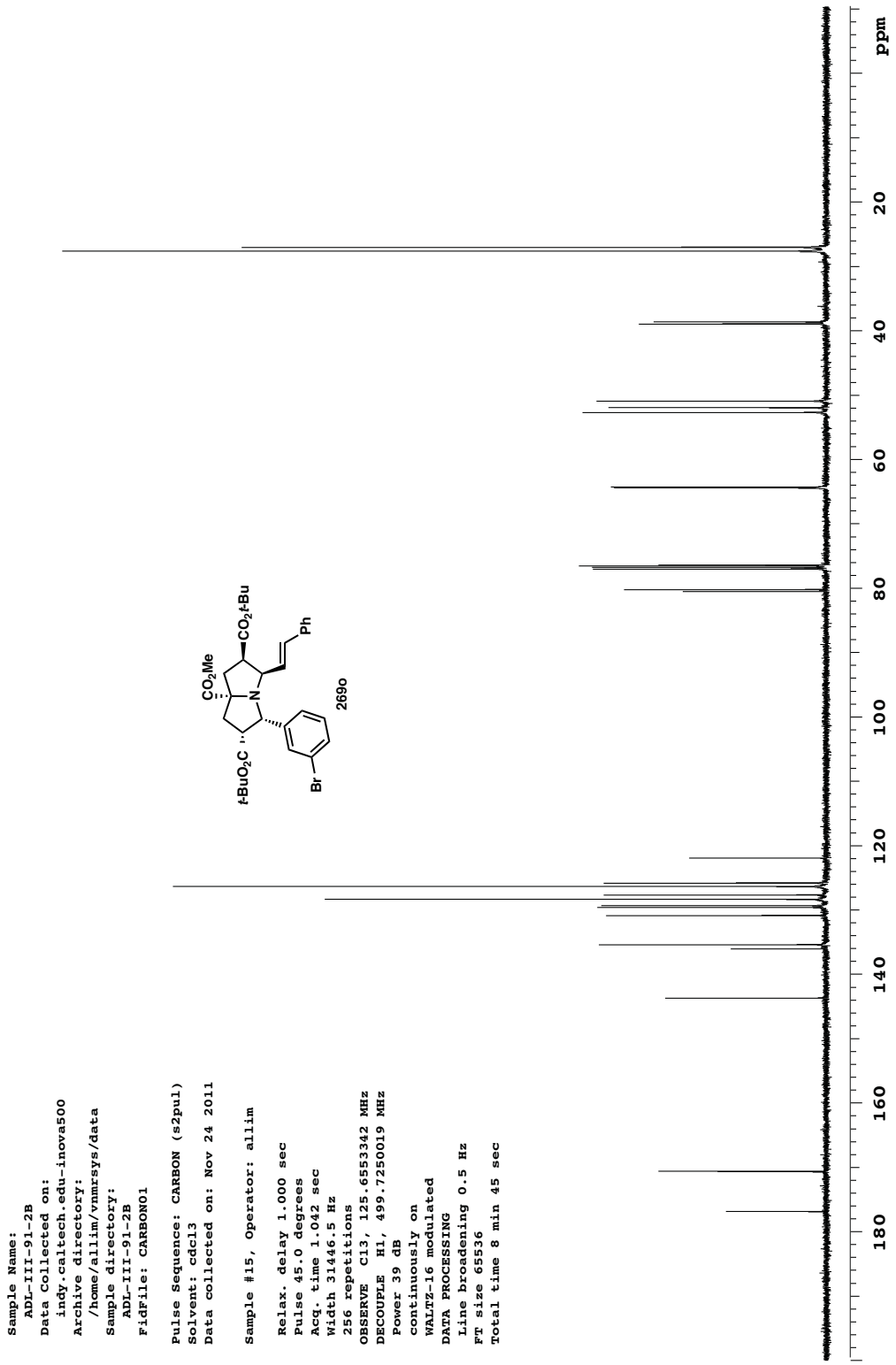

Sample Name:
ADL-III-96-2B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-96-2B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 24 2011
Sample #18, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Cl
N
269m
ppm
7.26
7.26
0.97
1.99
0.99
2.01
2.47
0.86
1.00
1.08
0.96
1.06
3.39
2.77
0.94

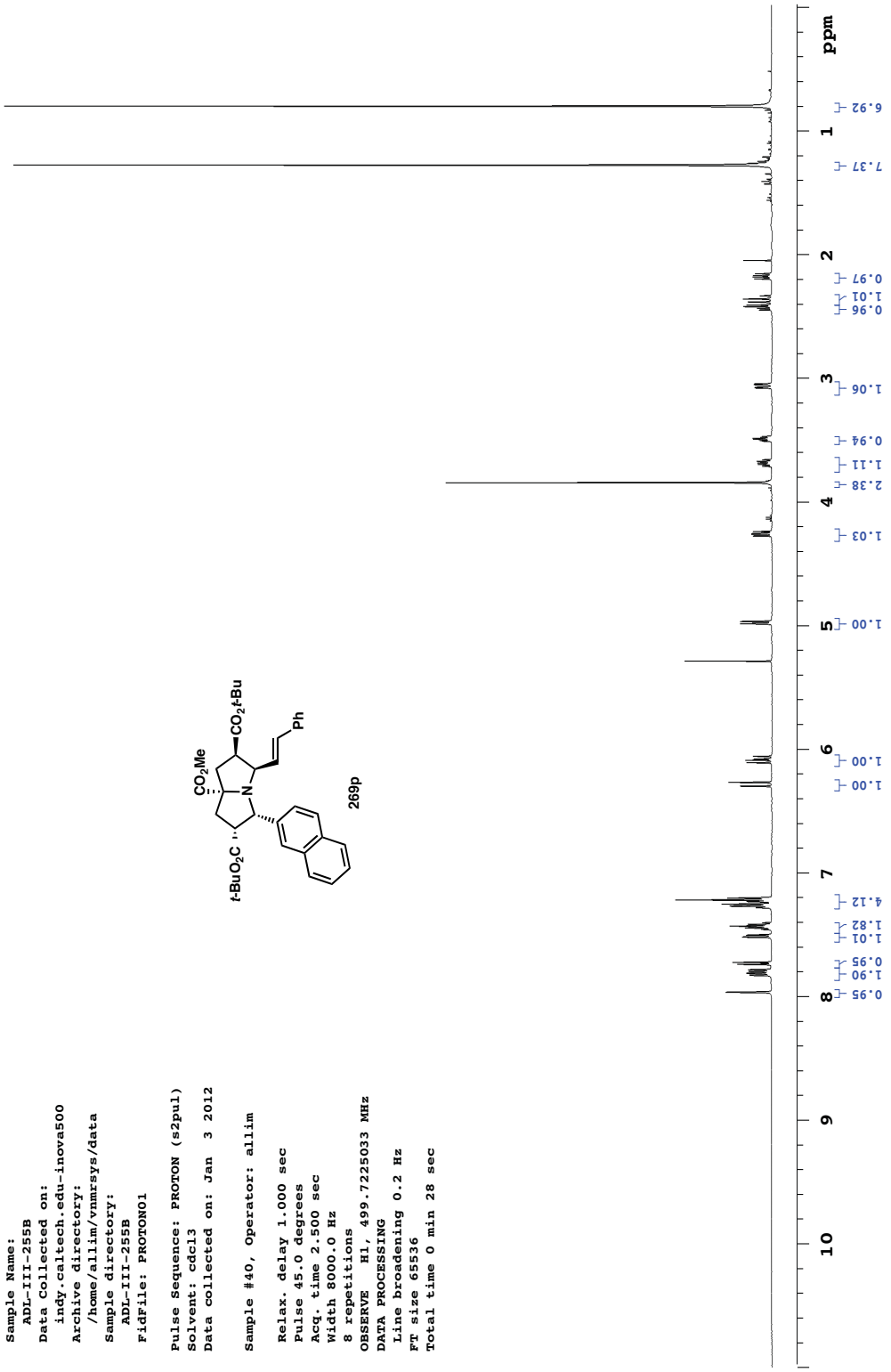

Sample Name:
ADL-III-96-2B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-96-2B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 24 2011
Sample #18, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553326 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Cl
269m
180
160
140
120
100
80
60
40
20
ppm

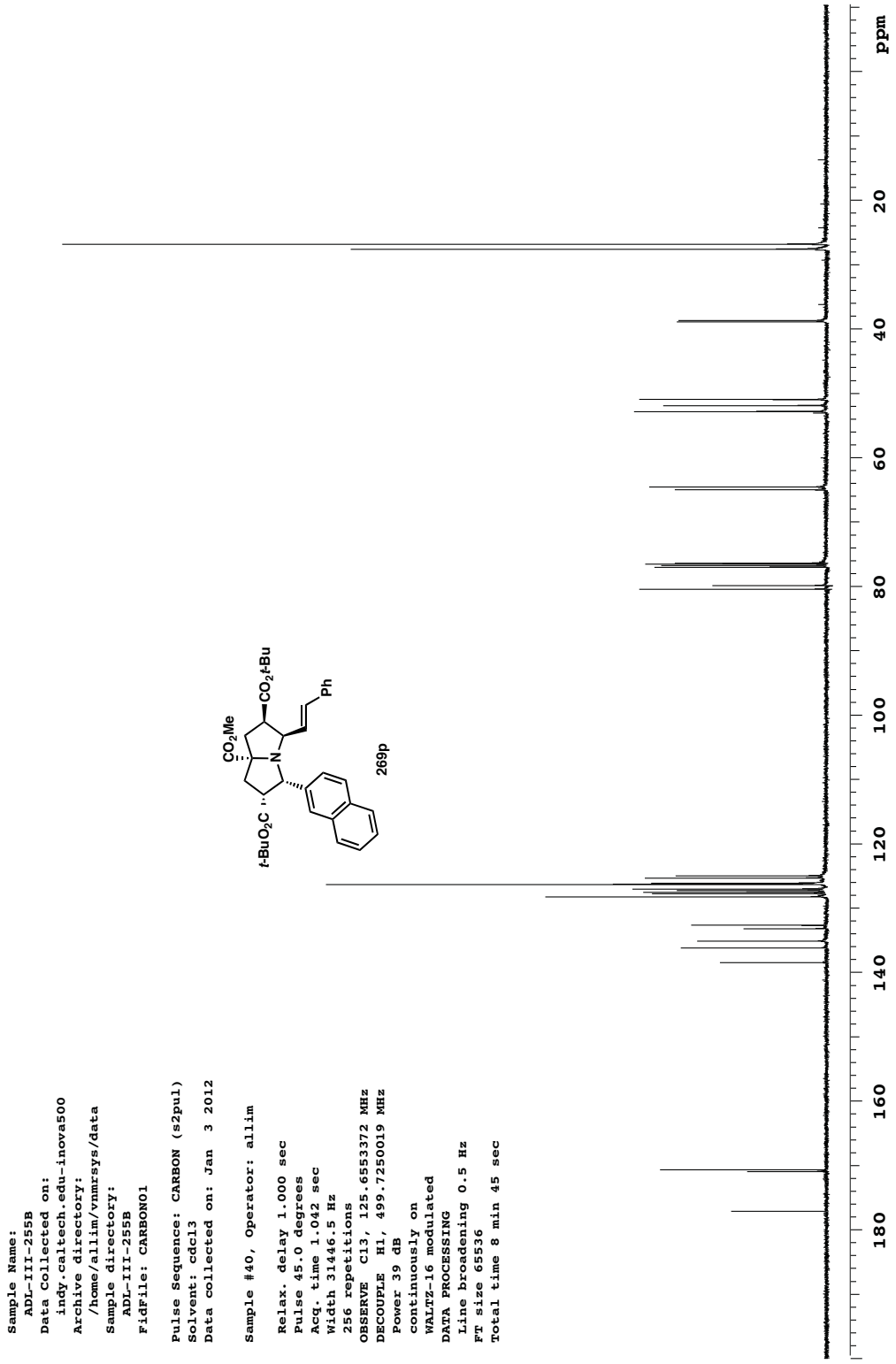

Sample Name:
ADL-III-91-1B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-91-1B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 23 2011
Sample #14, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Br
269n
ppm
7.93
7.91
1.02
1.99
1.07
1.07
1.11
2.65
1.04
1.00
1.08
1.01
1.08
5.69
0.98
0.96

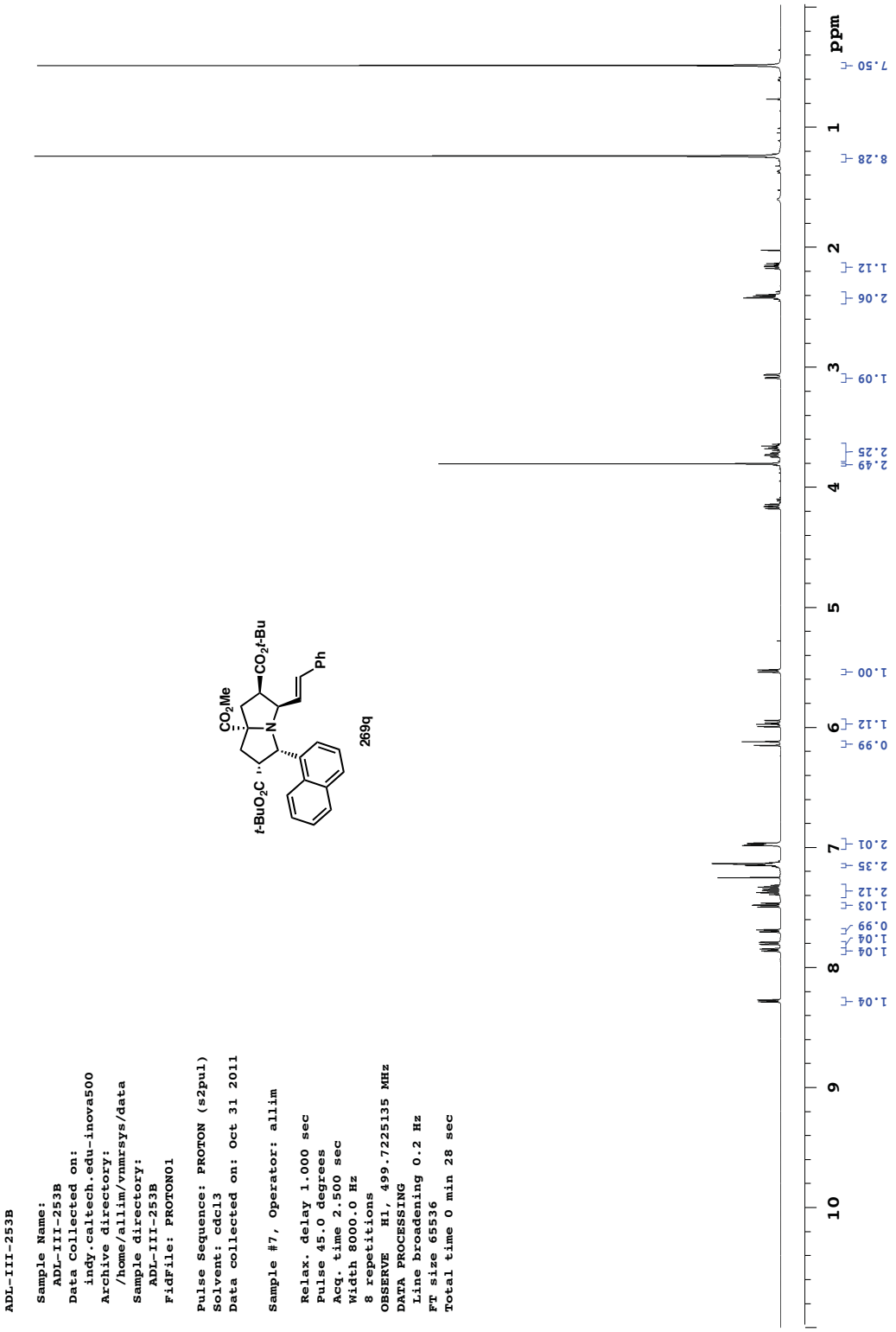

Sample Name:
ADL-III-91-1B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-91-1B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 23 2011
Sample #14, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553334 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
Br
269n
180
160
140
120
100
80
60
40
20
ppm

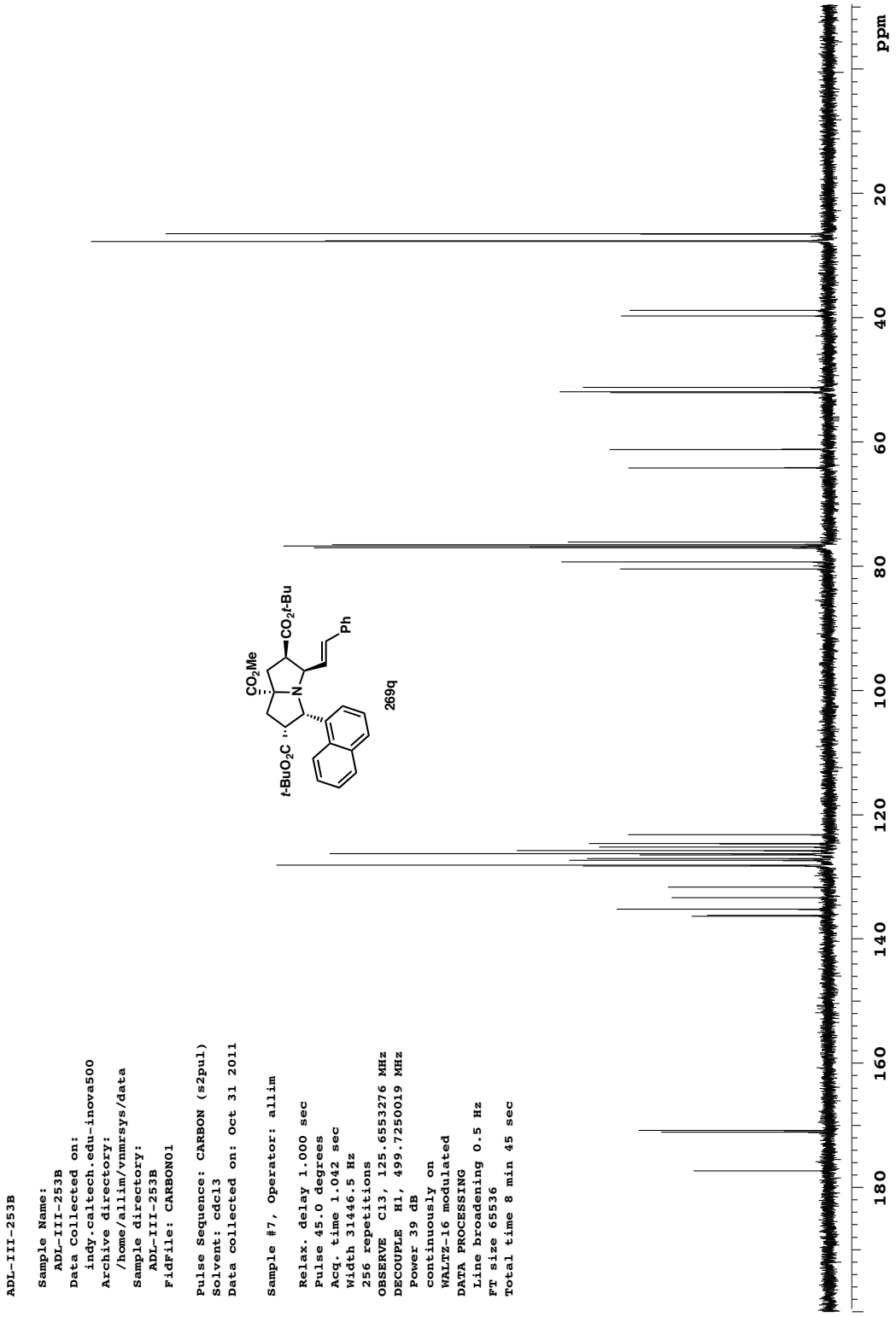

Sample Name:
ADL-III-91-2B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-91-2B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 24 2011
Sample #15, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
tBuO2C
Br
269o
ppm
7.70
8.00
1.14
1.08
1.13
1.02
1.05
1.05
2.57
1.05
1.00
1.12
1.01
1.03
6.72
0.95

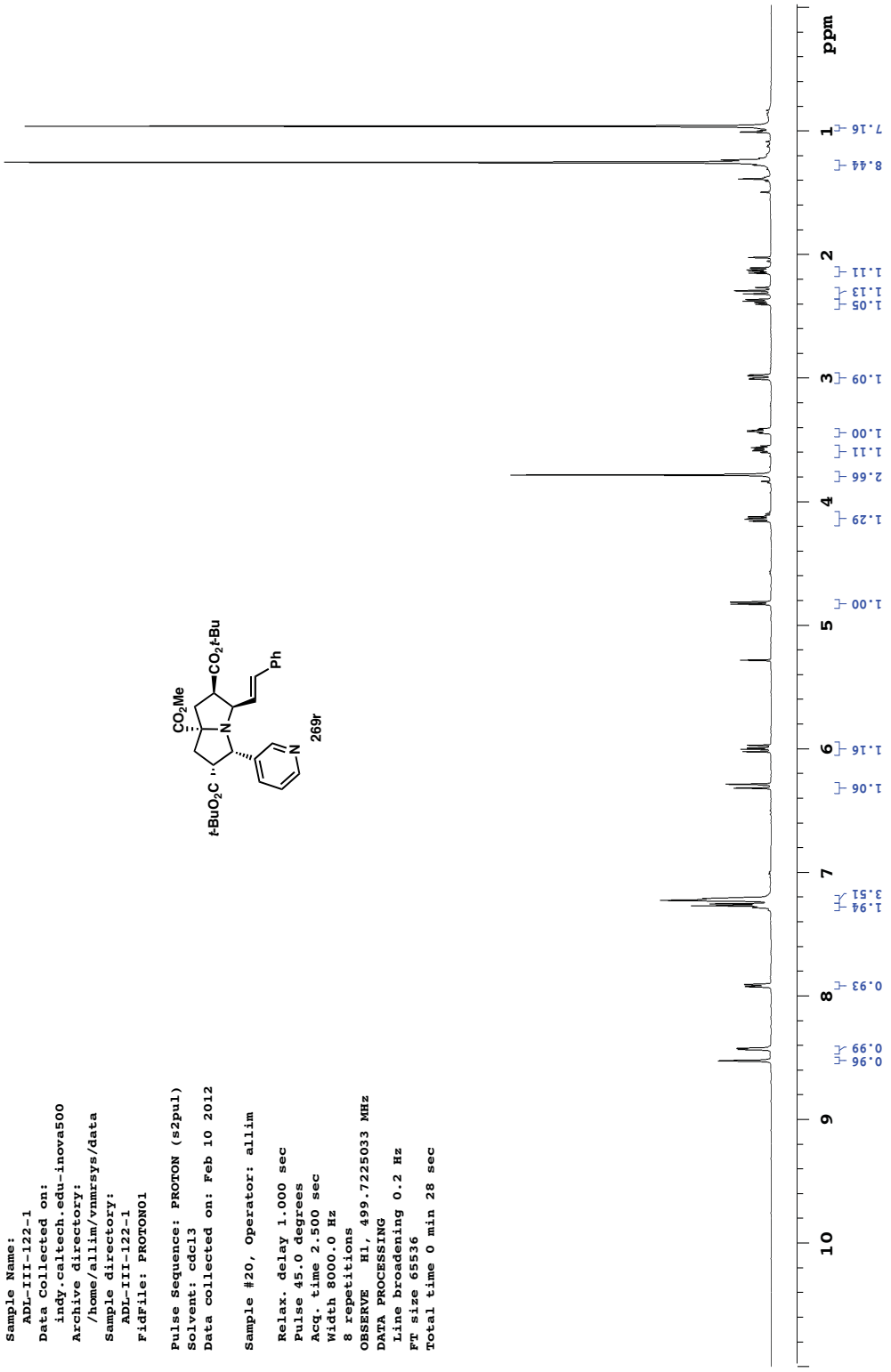

Sample Name:
ADL-III-91-2B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-91-2B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 24 2011
Sample #15, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553342 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 8 min 45 sec
CO2Me
CO2tBu
Ph
tBuO2C
N
Br
269o
180
160
140
120
100
80
60
40
20
ppm

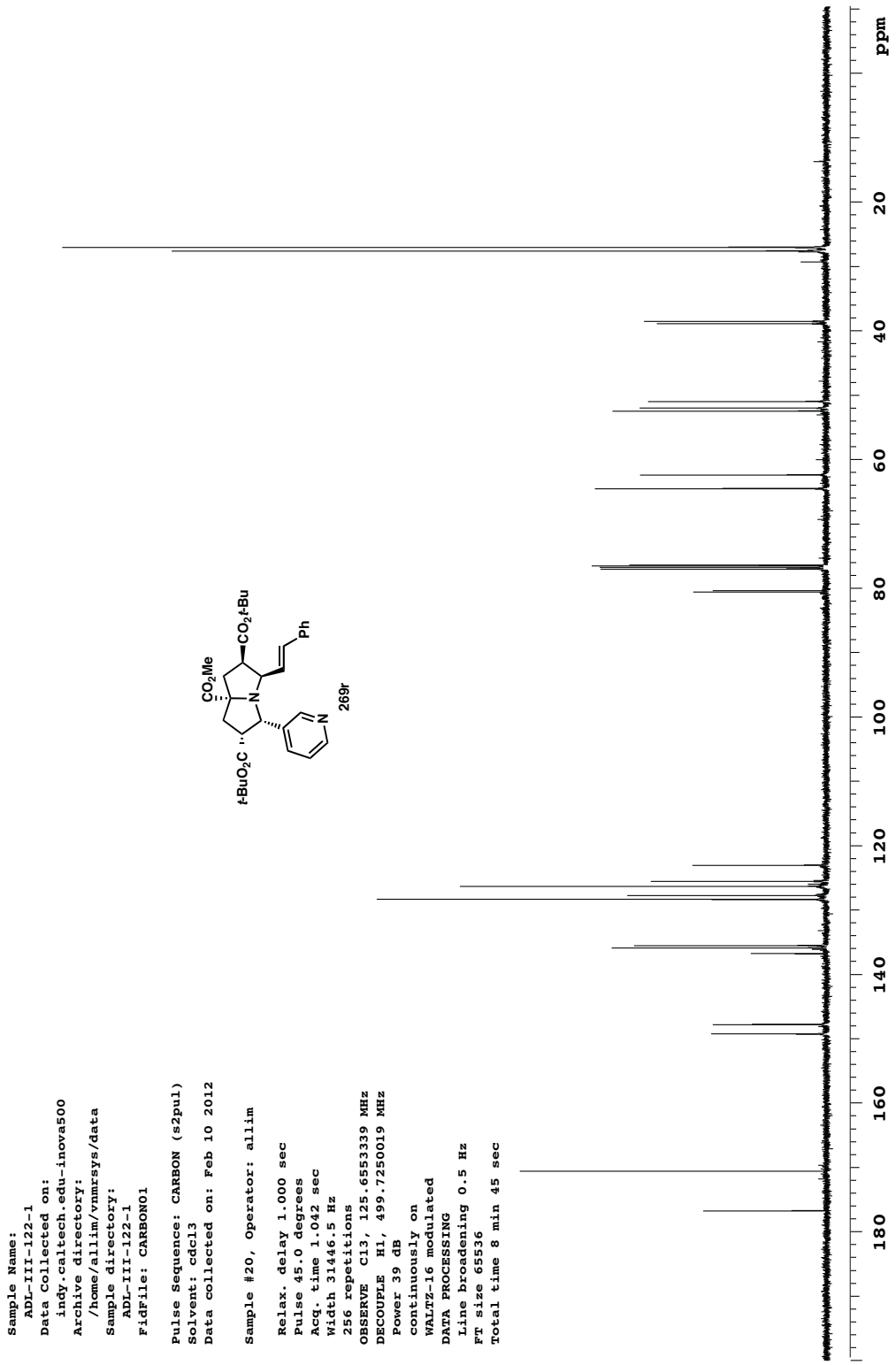

Sample Name:
ADL-III-255B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-255B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 3 2012
Sample #40, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2tBu
Ph
t-BuO2C
269p
ppm
6.92
7.37
0.97
1.01
0.96
1.06
0.94
1.11
2.38
1.03
1.00
1.00
1.00
4.12
1.01
1.82
0.95
1.90
0.95

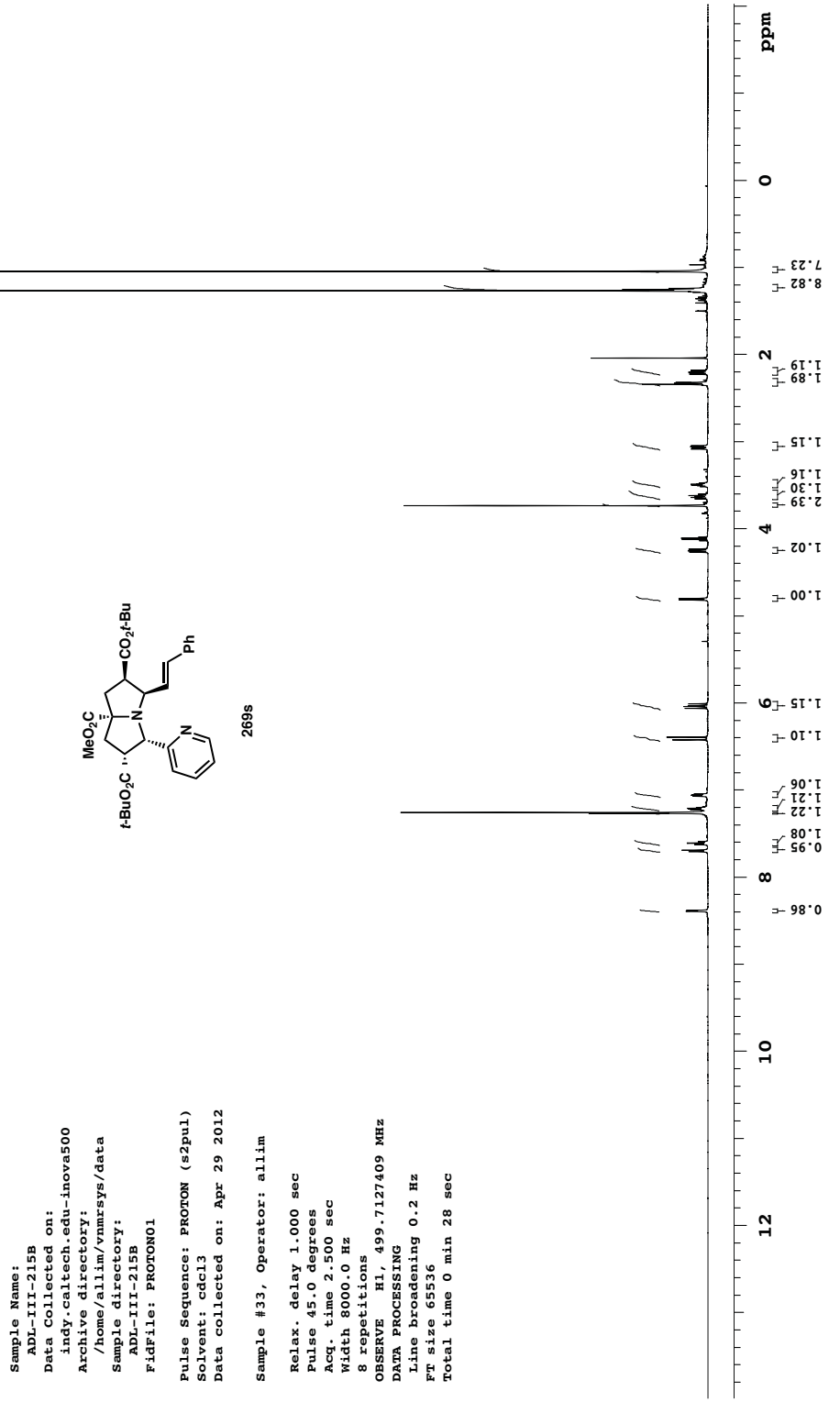

Sample Name:
ADL-III-255B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-255B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 3 2012
Sample #40, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553372 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
N
t-BuO2C
269p
180
160
140
120
100
80
60
40
20
ppm

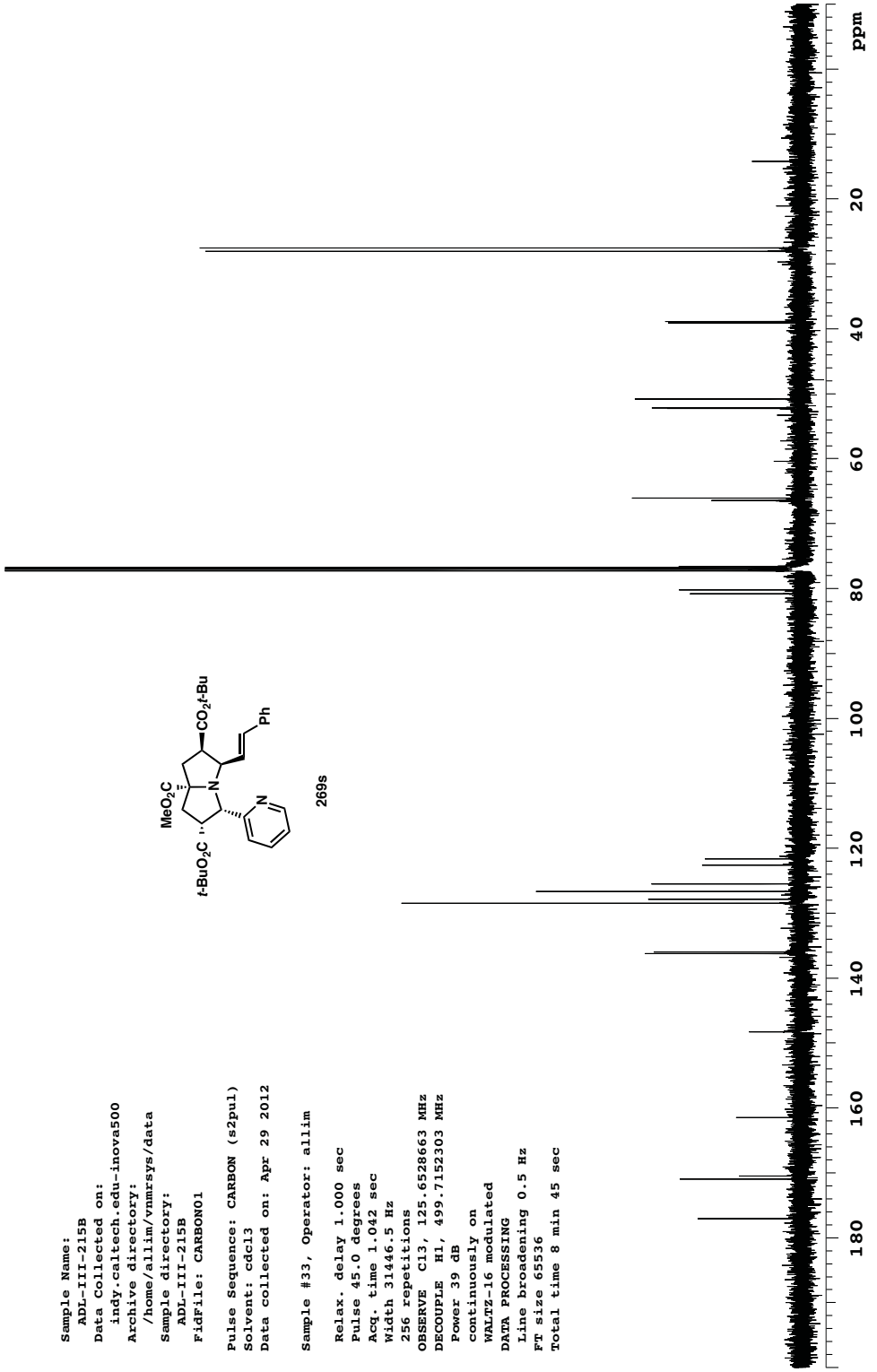

ADL-III-253B
Sample Name:
ADL-III-253B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-253B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 31 2011
Sample #7, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225135 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
269q
ppm
7.50
8.28
1.12
2.06
1.09
2.49
2.25
1.00
1.12
0.99
2.01
2.35
2.12
1.03
0.99
1.04
1.04
1.04

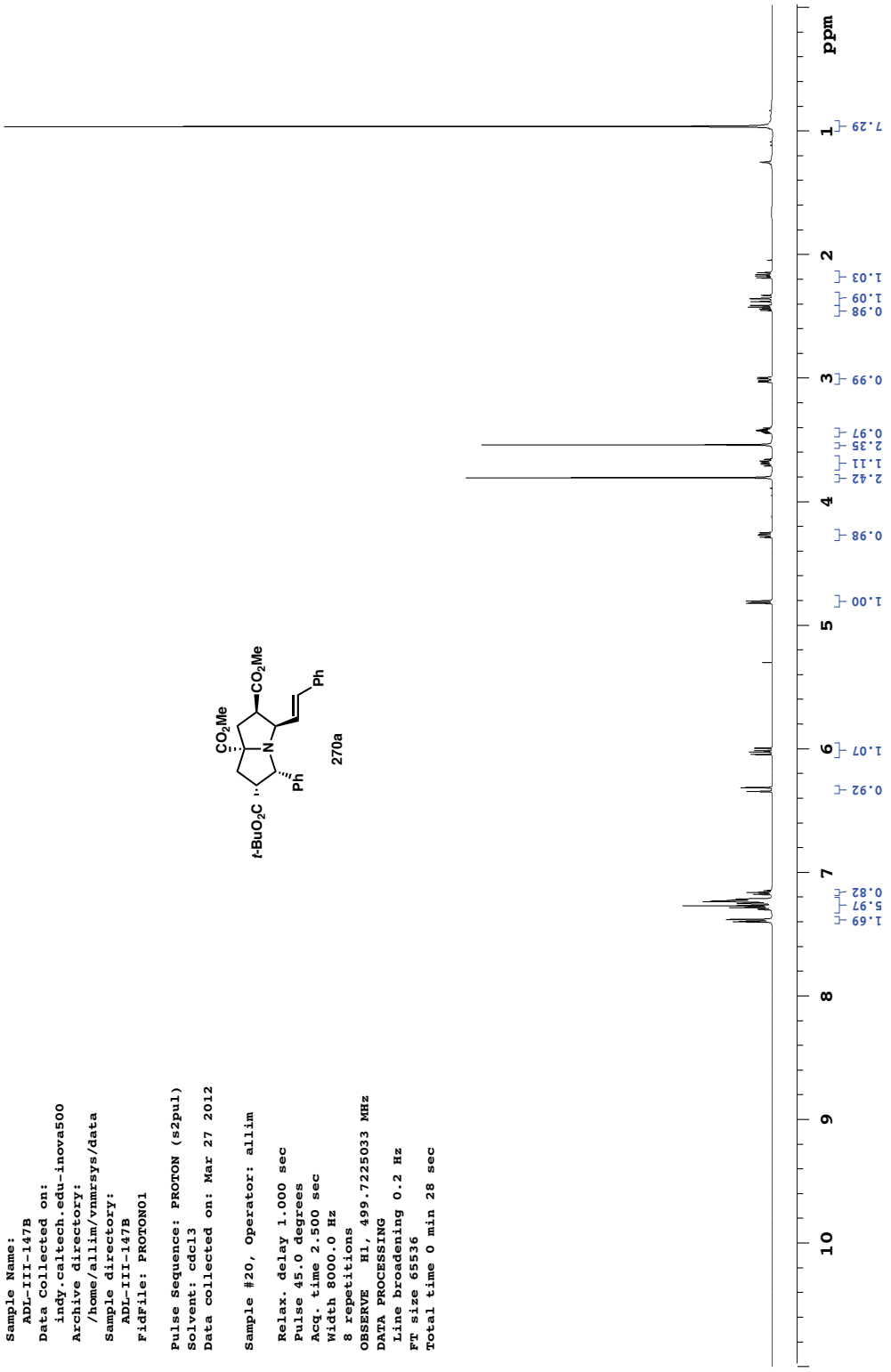

ADL-III-253B
Sample Name:
ADL-III-253B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-253B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 31 2011
Sample #7, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553276 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
N
269q
180
160
140
120
100
80
60
40
20
ppm

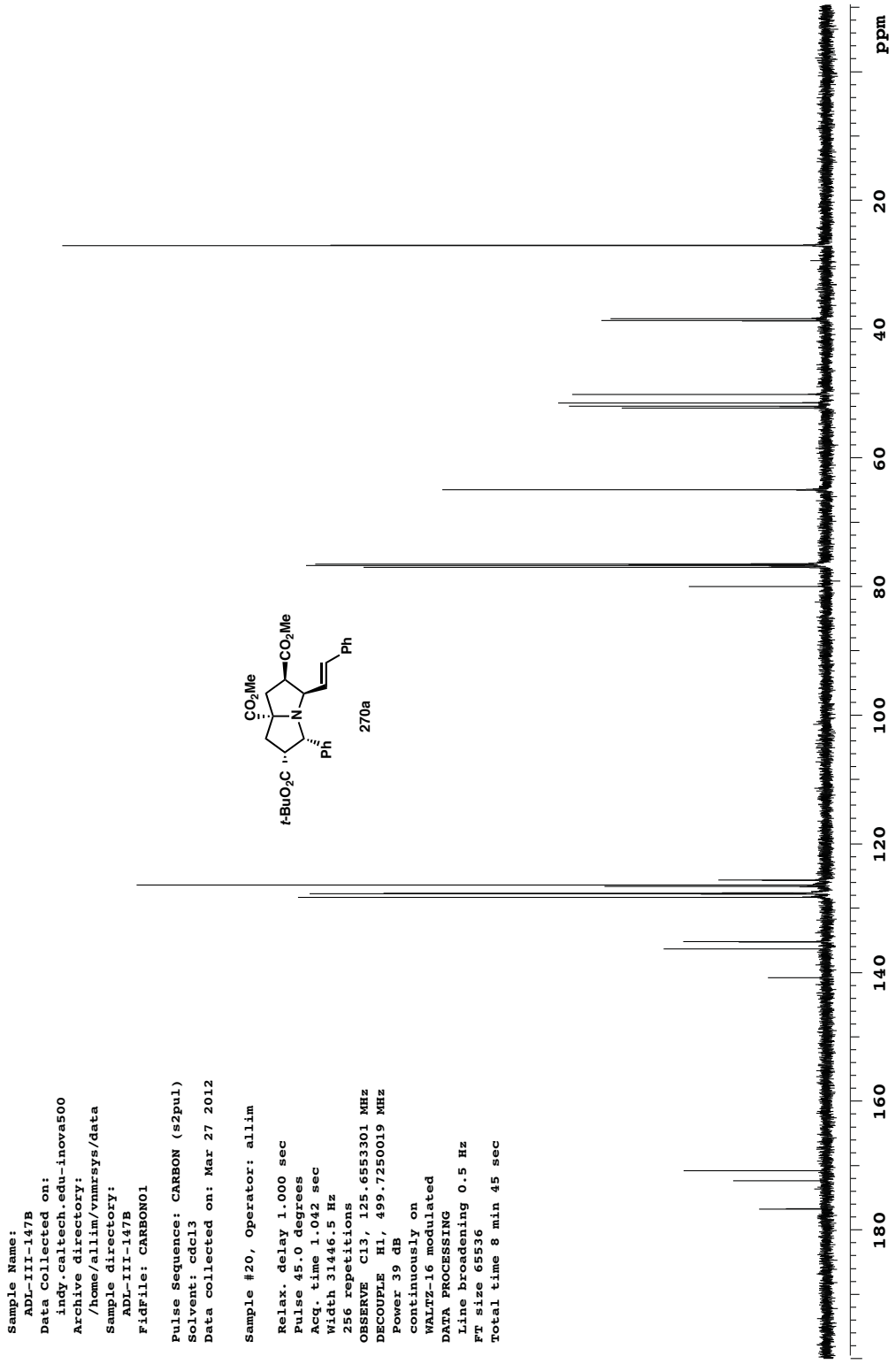

Sample Name:
ADL-III-122-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-122-1
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 10 2012
Sample #20, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
269r
ppm
7.16
8.44
1.11
1.13
1.05
1.09
1.00
1.11
2.66
1.29
1.00
1.16
1.06
3.51
1.94
0.93
0.99
0.96

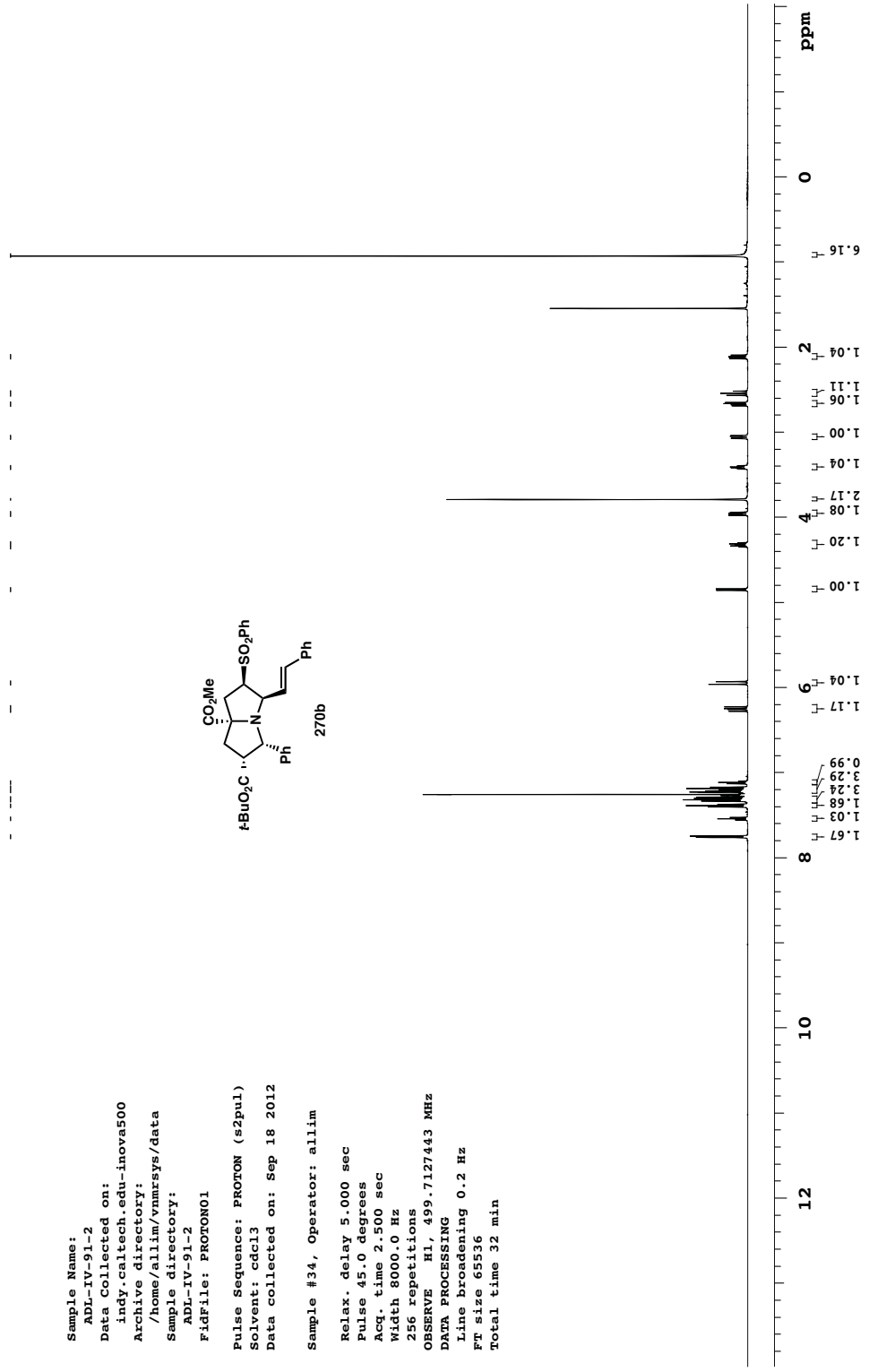

Sample Name:
ADL-III-122-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-122-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 10 2012
Sample #20, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553339 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 8 min 45 sec
CO2Me
CO2t-Bu
Ph
t-BuO2C
N
N
269r
180
160
140
120
100
80
60
40
20
ppm

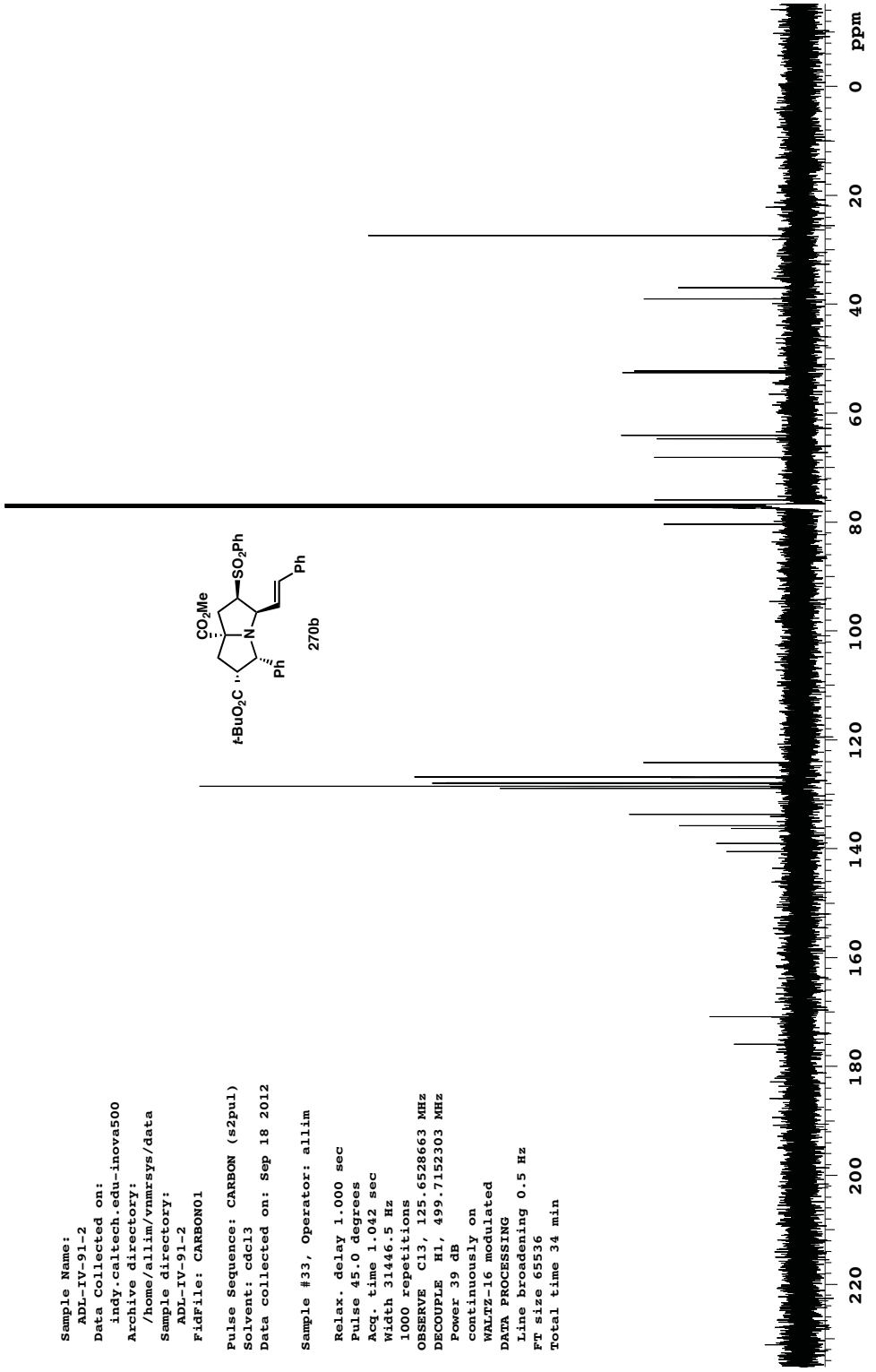

Sample Name:
ADL-III-215B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-215B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 2012
Sample #33, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127409 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
MeO2C
CO2t-Bu
t-BuO2C
Ph
N
N
269s
ppm
12
10
8
6
4
2
0
0.86
0.95
1.08
1.21
1.22
1.06
1.10
1.15
1.00
1.02
2.39
1.30
1.16
1.15
1.89
1.19
8.82
7.23

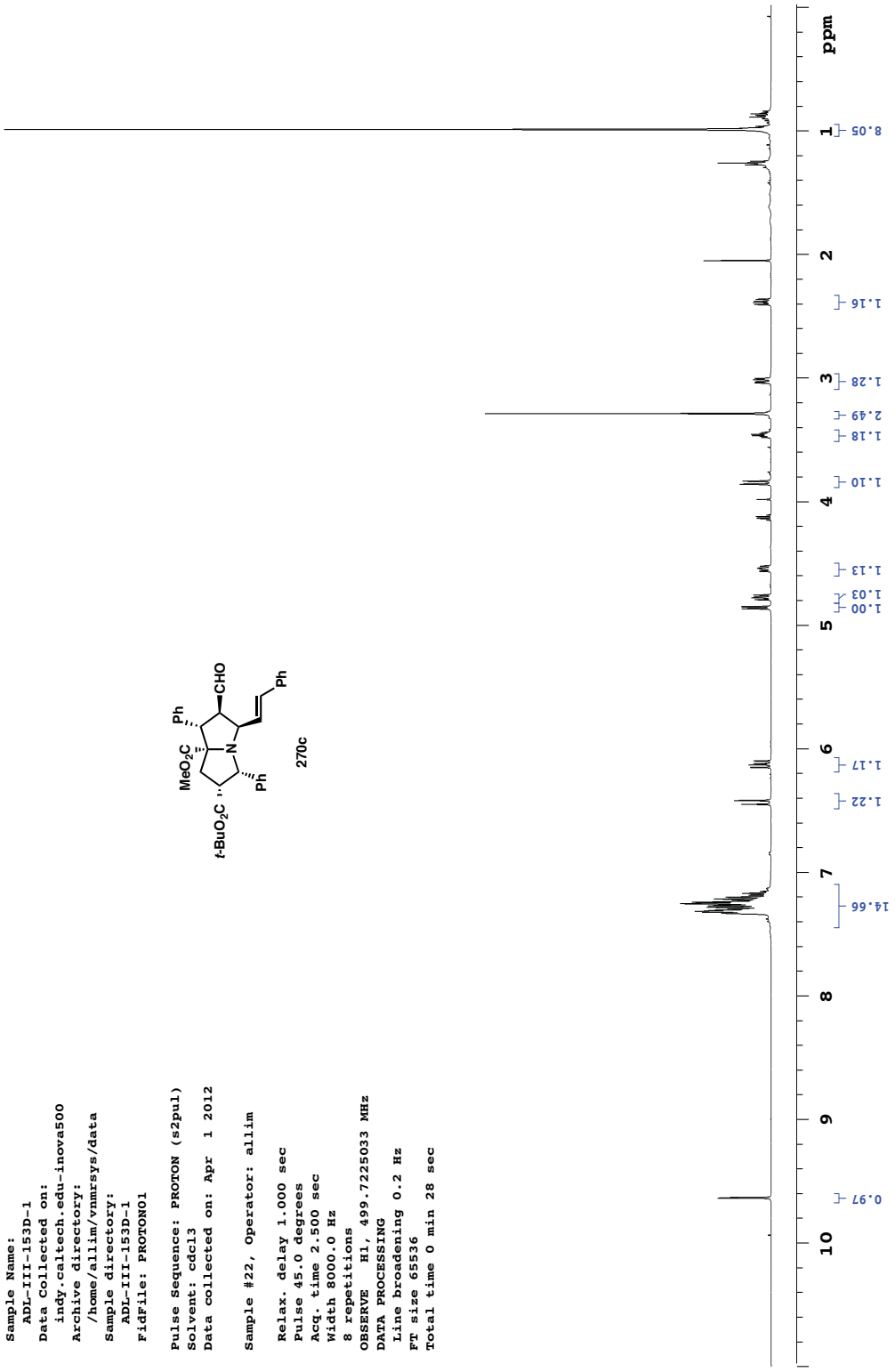

Sample Name:
ADL-III-215B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-215B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 2012
Sample #33, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6528663 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 8 min 45 sec
MeO2C
t-BuO2C
CO2t-Bu
Ph
N
N
269s
180
160
140
120
100
80
60
40
20
ppm

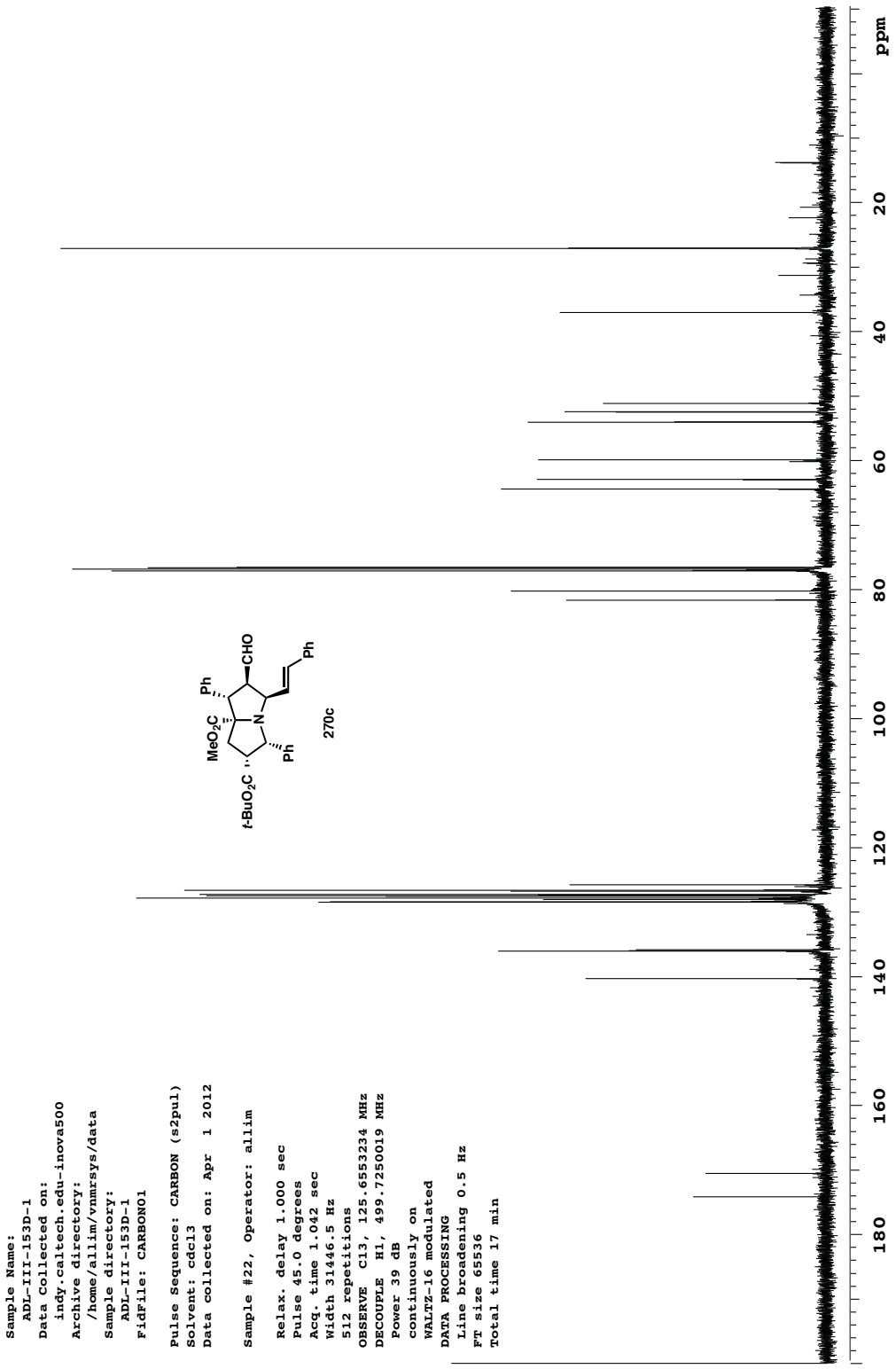

Sample Name:
ADL-III-147B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-147B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 27 2012
Sample #20, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Me
CO2Me
Ph
Ph
t-BuO2C
270a
ppm
7.29
1.03
1.09
0.98
0.99
0.97
2.35
1.11
2.42
0.98
1.00
1.07
0.92
0.82
5.97
1.69

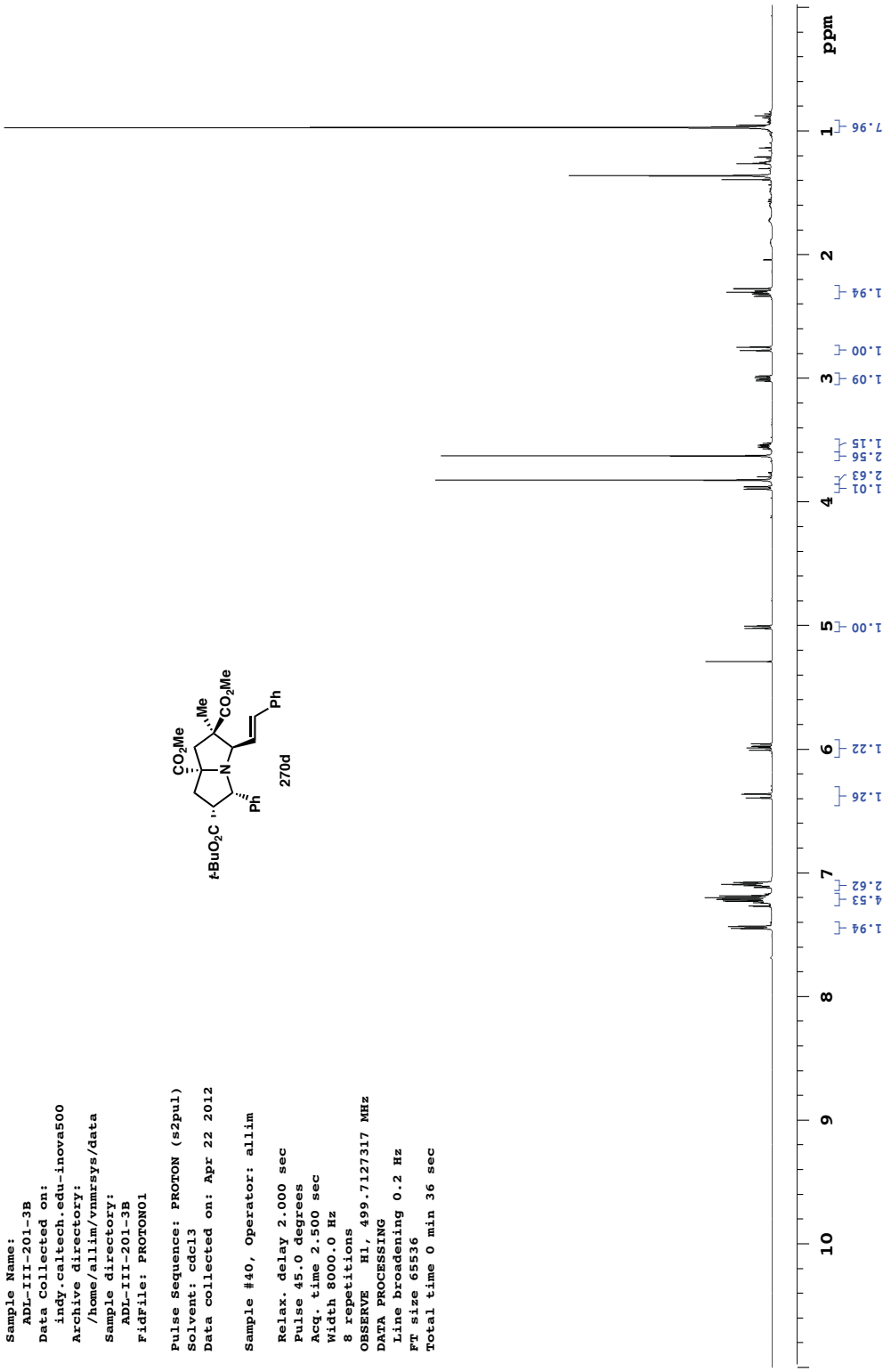

Sample Name:
ADL-III-147B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-147B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 27 2012
Sample #20, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6553301 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 8 min 45 sec
CO2Me
CO2Me
Ph
N
Ph
t-BuO2C
270a
180
160
140
120
100
80
60
40
20
ppm

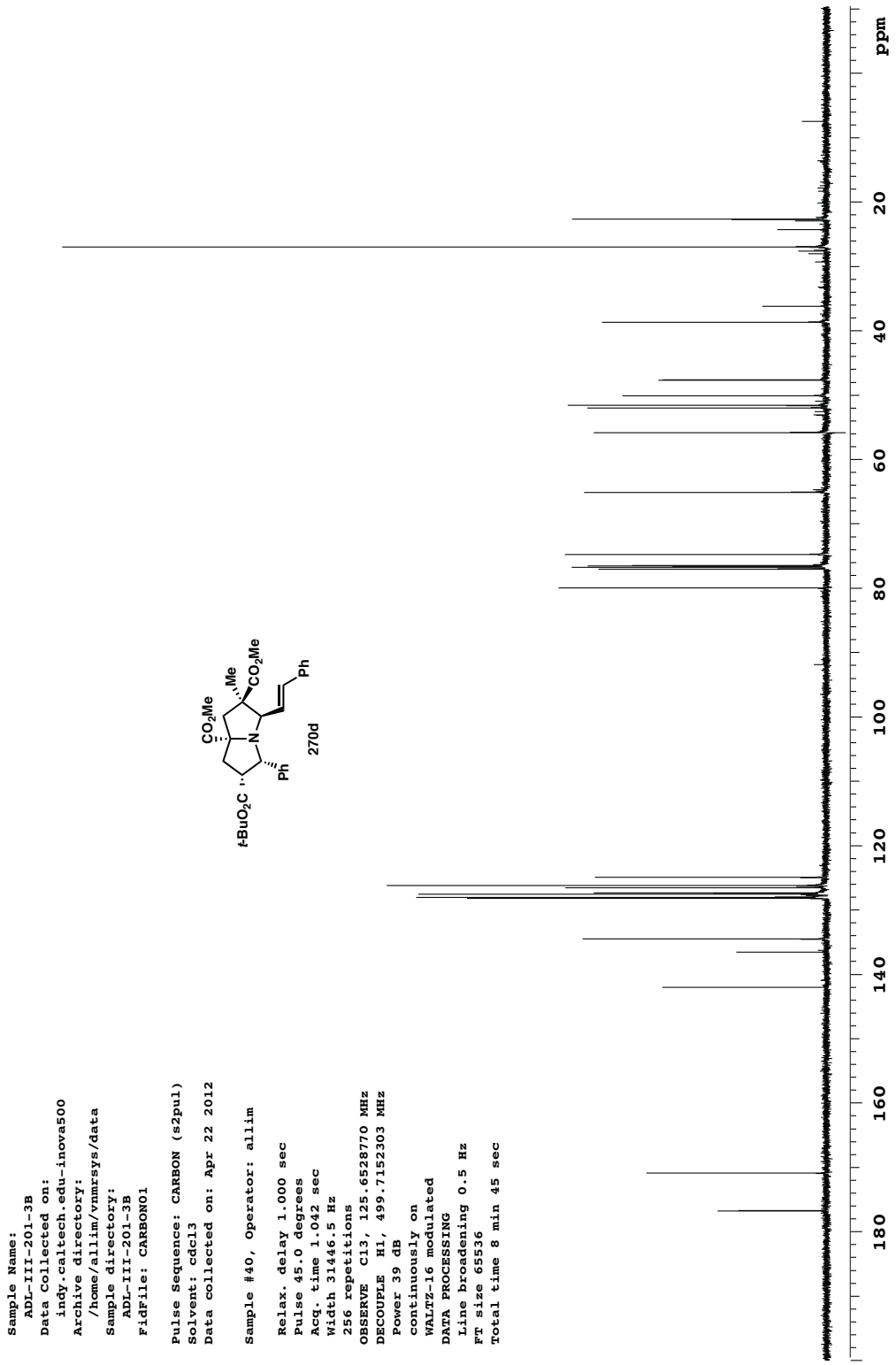

Sample Name:
ADL-IV-91-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-91-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 18 2012
Sample #34, Operator: allim
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
256 repetitions
OBSERVE H1, 499.7127443 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 32 min
CO2Me
SO2Ph
Ph
tBuO2C
Ph
270b
ppm
12
10
8
6
4
2
0
1.67
1.03
1.68
3.24
3.29
0.99
1.17
1.04
1.00
1.20
1.08
2.17
1.04
1.00
1.06
1.11
1.04
6.16

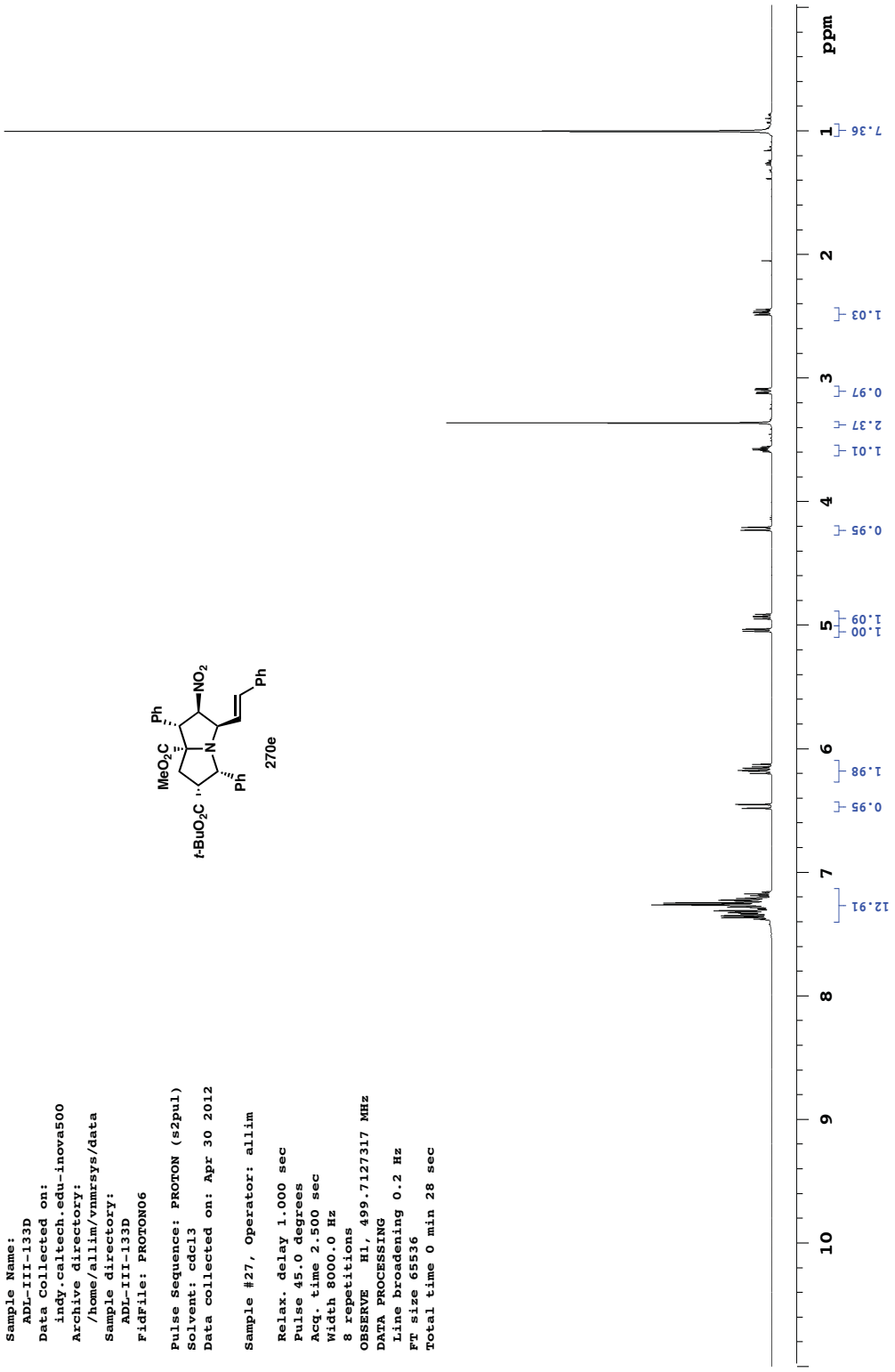

Sample Name:
ADL-IV-91-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-91-2
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 18 2012
Sample #33, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6528663 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 34 min
CO2Me
SO2Ph
Ph
N
Ph
t-BuO2C
270b
220
200
180
160
140
120
100
80
60
40
20
0
ppm

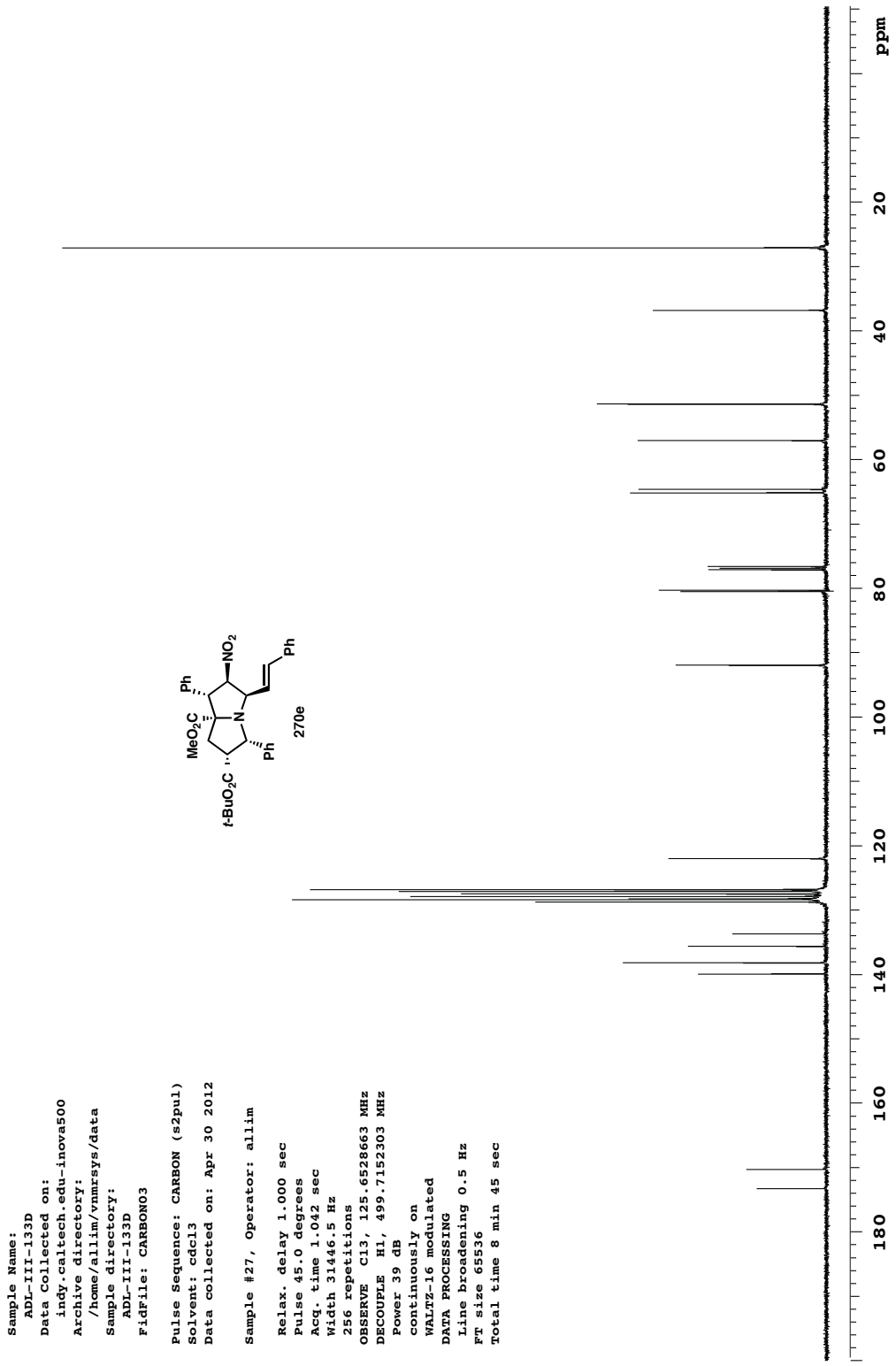

Sample Name:
ADL-III-153D-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-153D-1
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 1 2012
Sample #22, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225033 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
MeO2C
Ph
CHO
Ph
N
Ph
t-BuO2C
270c
ppm
10
9
8
7
6
5
4
3
2
1
0.97
14.66
1.22
1.17
1.00
1.03
1.13
1.10
1.18
2.49
1.28
1.16
8.05

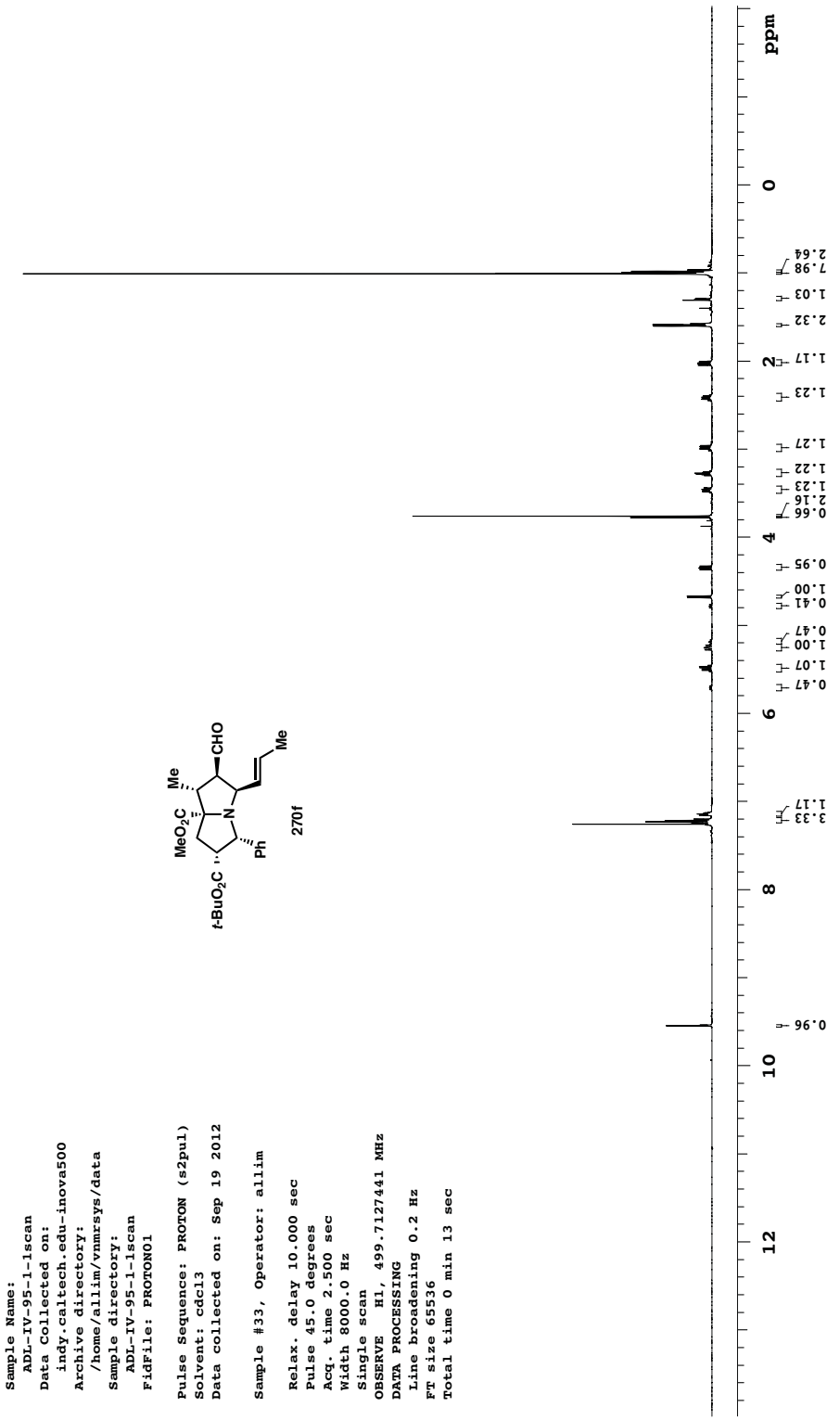

Sample Name:
ADL-III-153D-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-153D-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 1 2012
Sample #22, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553234 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
MeO2C
Ph
CHO
Ph
N
Ph
t-BuO2C
270c
180
160
140
120
100
80
60
40
20
ppm

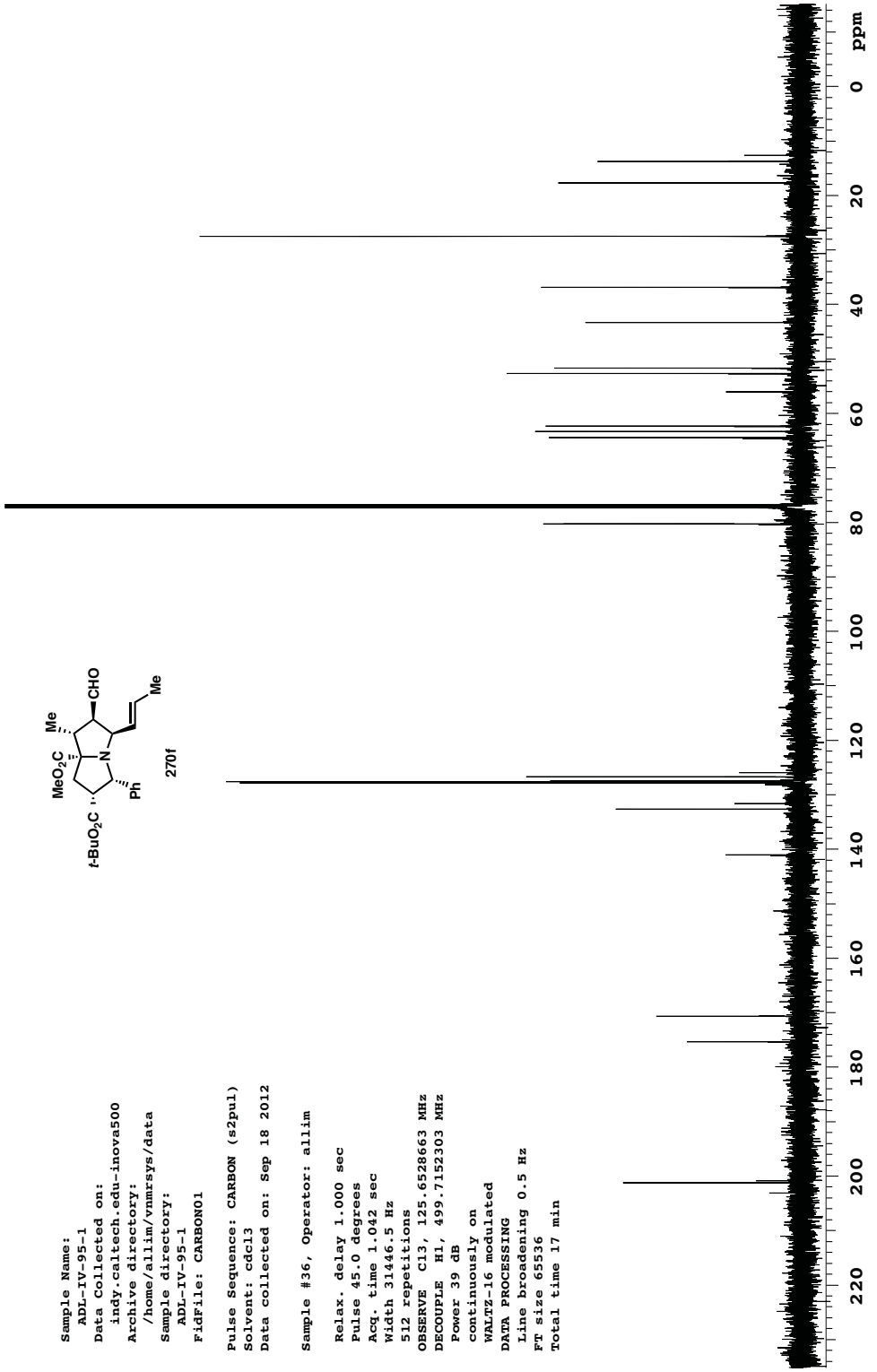

Sample Name:
ADL-III-201-3B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-201-3B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 22 2012
Sample #40, Operator: allim
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127317 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 36 sec
CO2Me
Me
CO2Me
Ph
CO2Me
Ph
t-BuO2C
270d
ppm
10
9
8
7
6
5
4
3
2
1
1.94
4.53
2.62
1.94
1.22
1.26
1.00
1.01
2.63
2.56
1.15
1.09
1.00
1.94
7.96

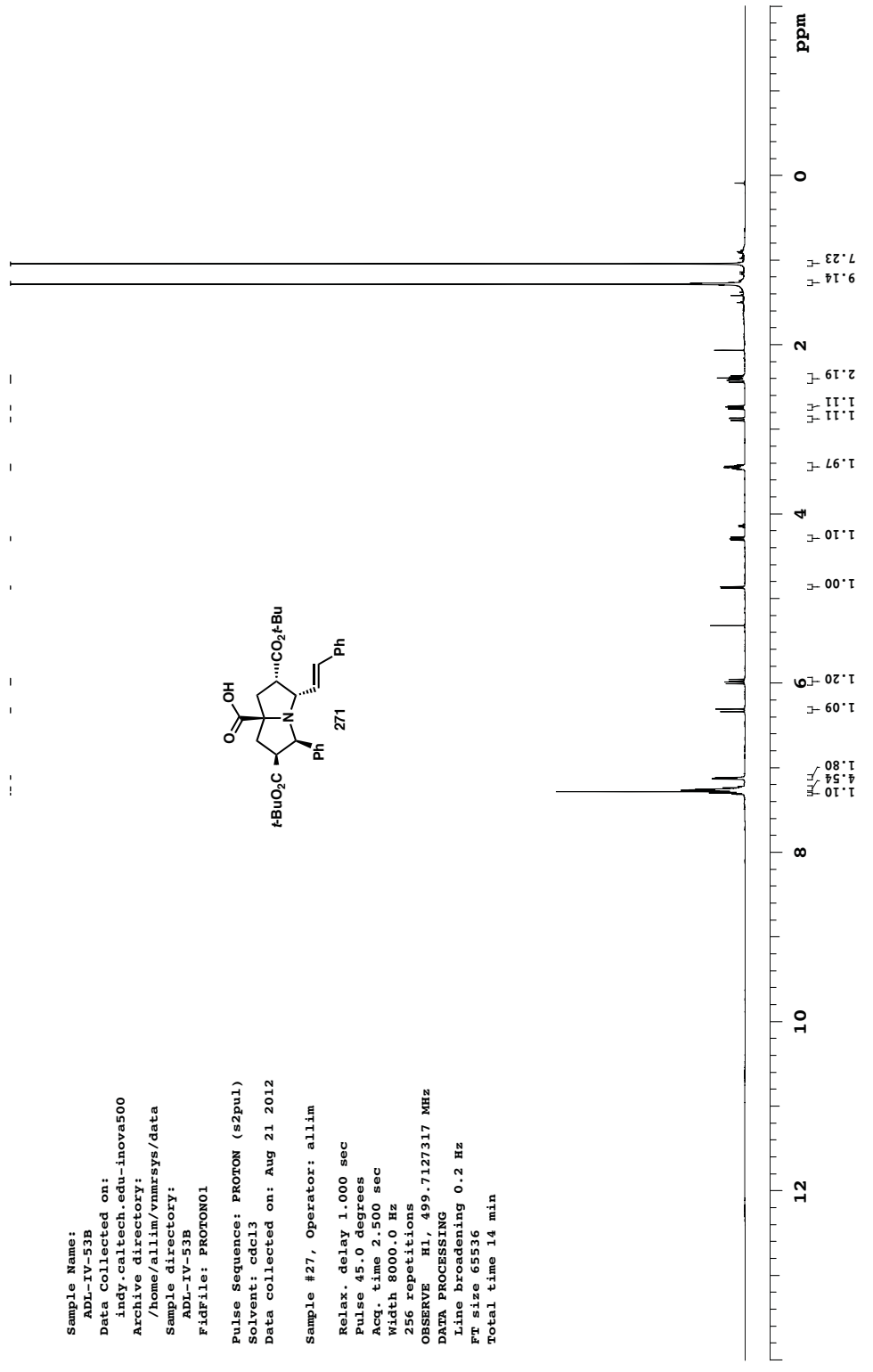

Sample Name:
ADL-III-201-3B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-201-3B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 22 2012
Sample #40, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6528770 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 8 min 45 sec
CO2Me
Me
CO2Me
Ph
N
Ph
tBuO2C
270d
180
160
140
120
100
80
60
40
20
ppm

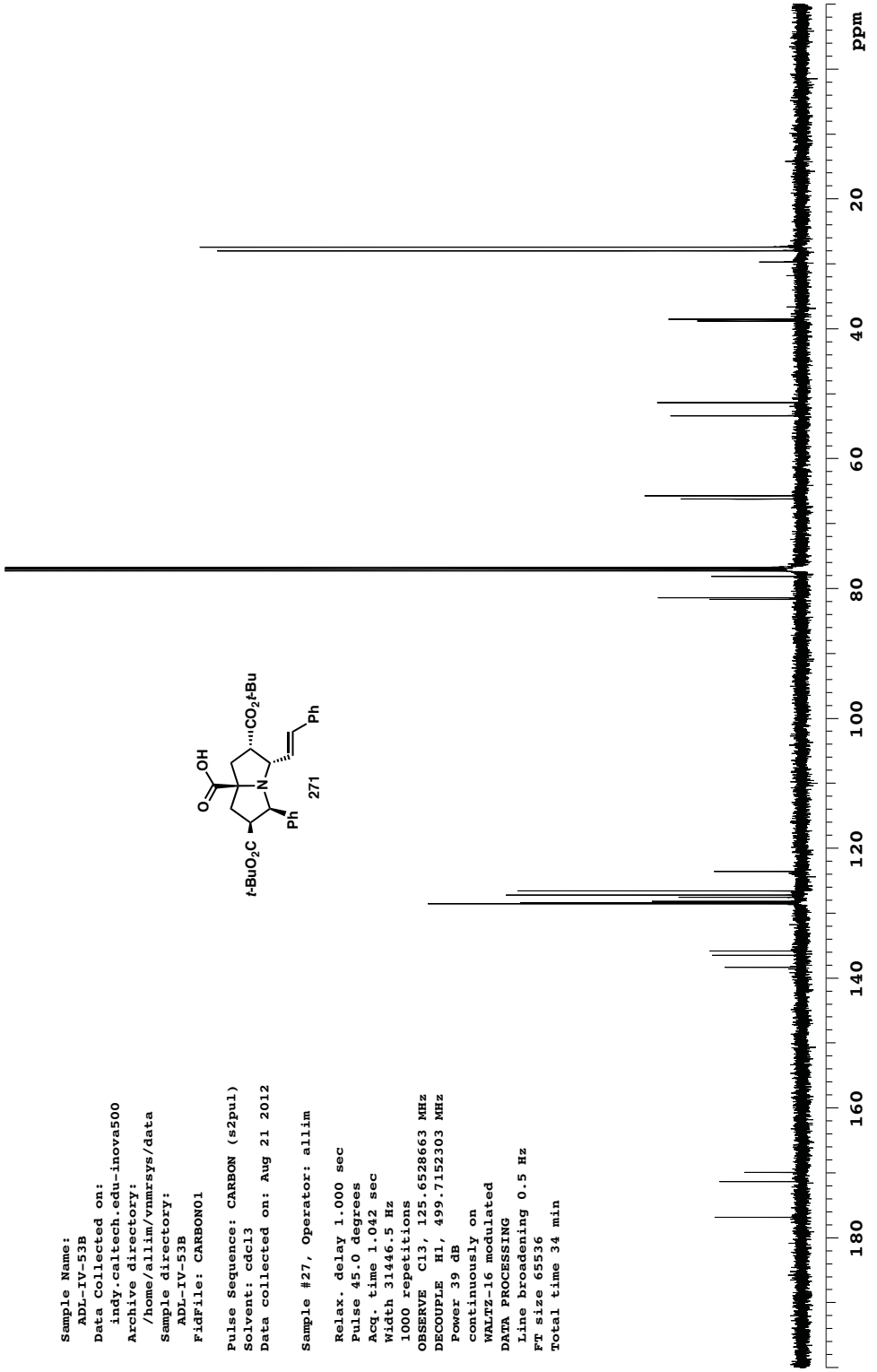

Sample Name:
ADL-III-133D
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-133D
FidFile: PROTON06
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2012
Sample #27, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127317 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
Ph
NO2
Ph
MeO2C
N
Ph
t-BuO2C
270e
ppm
1
2
3
4
5
6
7
8
9
10
7.36
1.03
0.97
2.37
1.01
0.95
1.09
1.00
1.98
0.95
12.91

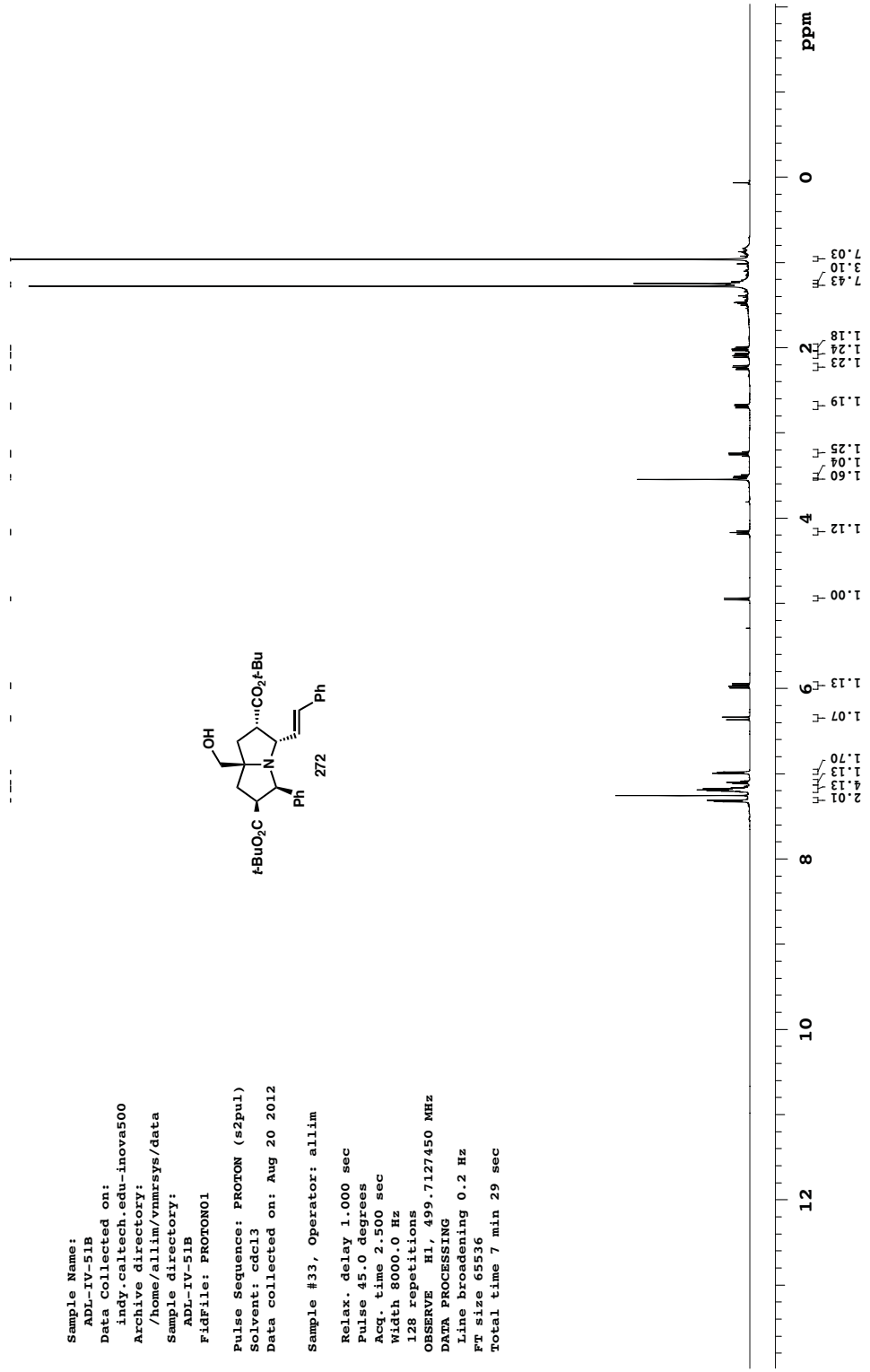

Sample Name:
ADL-III-133D
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-133D
FidFile: CARBON03
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2012
Sample #27, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6528663 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 8 min 45 sec
MeO2C
Ph
NO2
Ph
t-BuO2C
Ph
270e
180
160
140
120
100
80
60
40
20
ppm

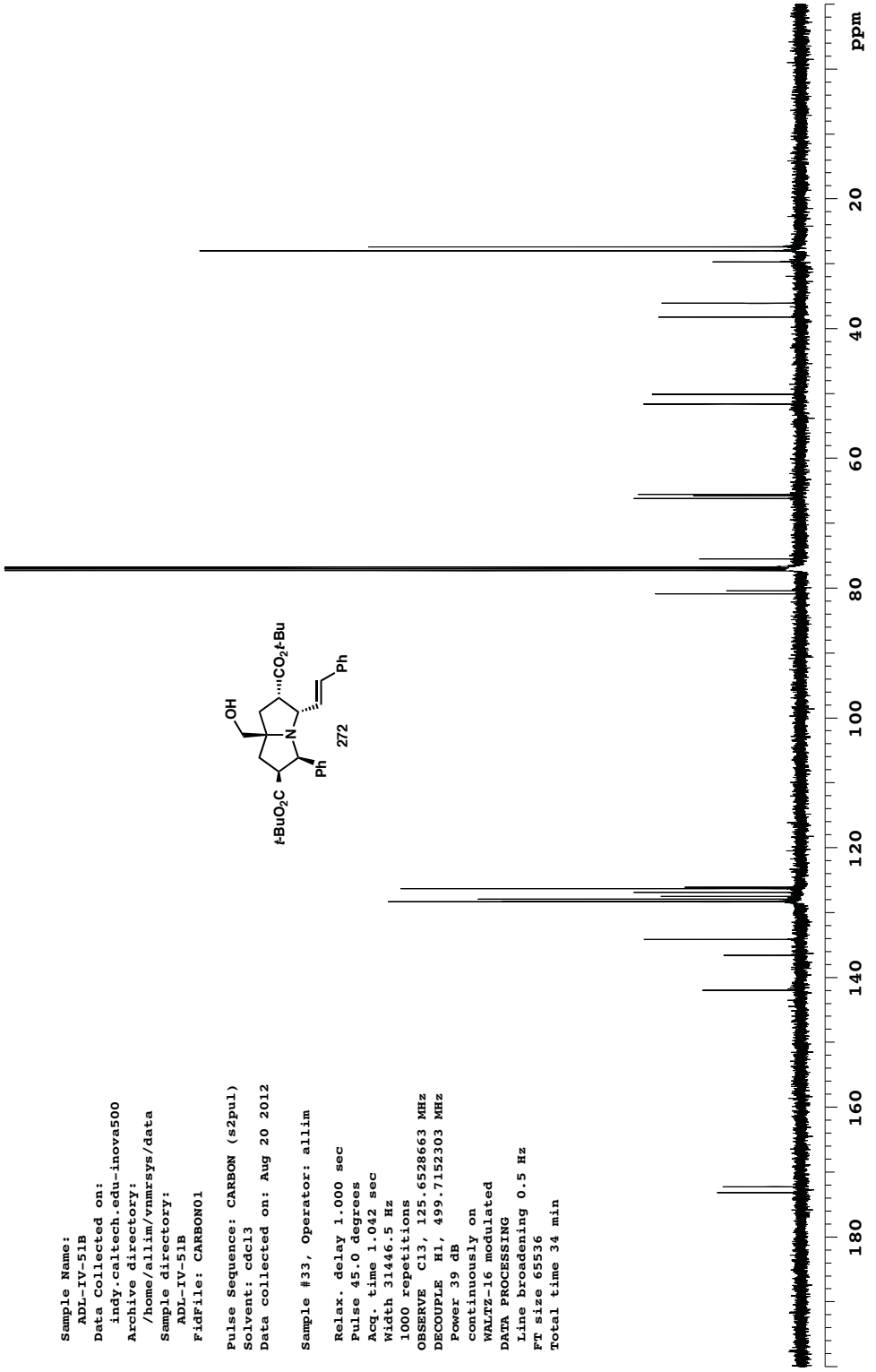

Sample Name:
ADL-IV-95-1-1scan
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-95-1-1scan
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 19 2012
Sample #33, Operator: allim
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
Single scan
OBSERVE H1, 499.7127441 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 13 sec
Me
MeO2C
CHO
Me
N
Ph
t-BuO2C
270f
ppm
12
10
8
6
4
2
0
0.96
3.33
1.17
0.47
1.07
1.00
0.47
0.41
1.00
0.95
0.66
2.16
1.23
1.22
1.27
1.23
1.17
2.32
1.03
7.98
2.64

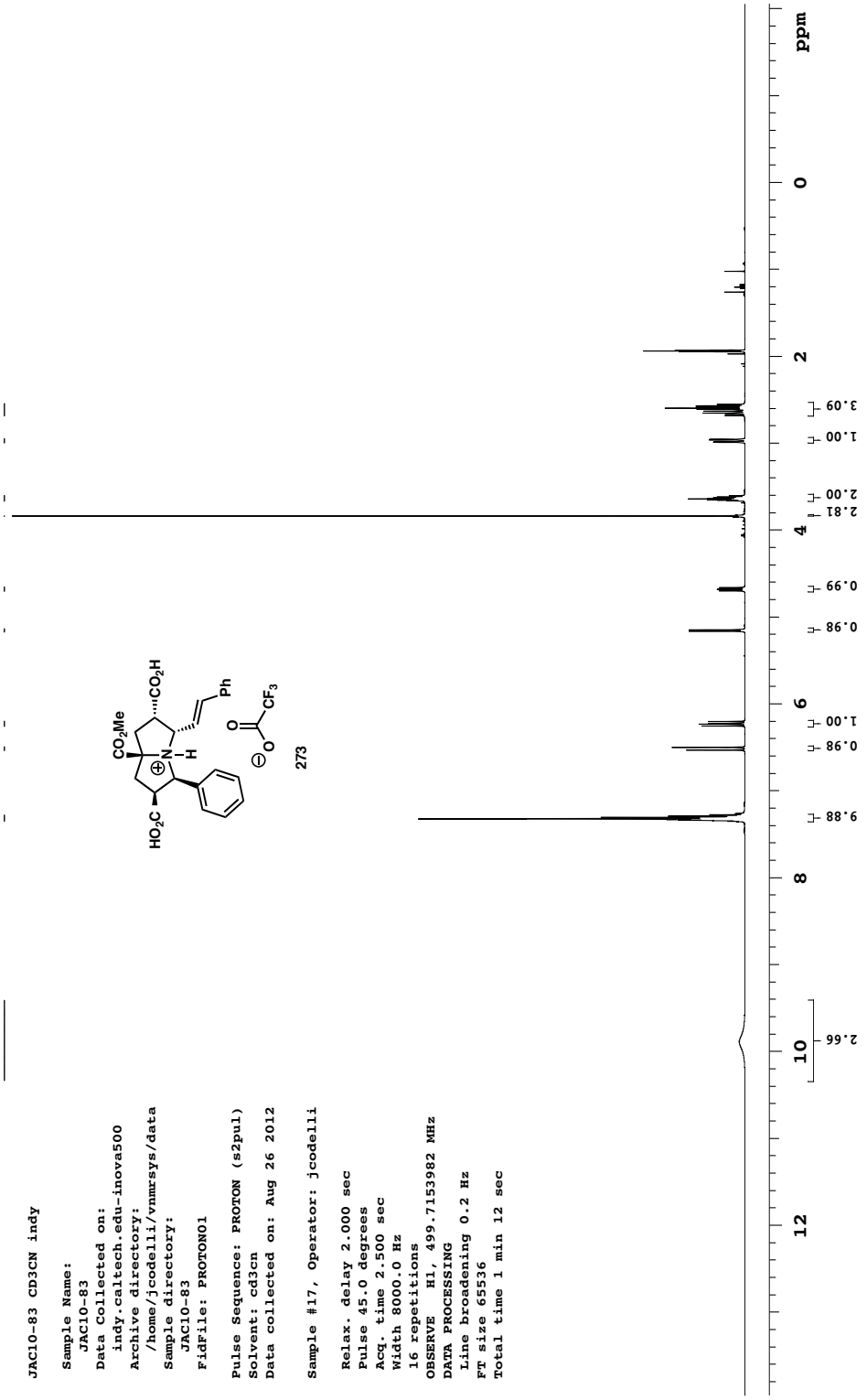

Sample Name:
ADL-IV-95-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-95-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 18 2012
Sample #36, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528663 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
Me
CHO
Me
MeO2C
N
Ph
t-BuO2C
270f
220
200
180
160
140
120
100
80
60
40
20
0
ppm

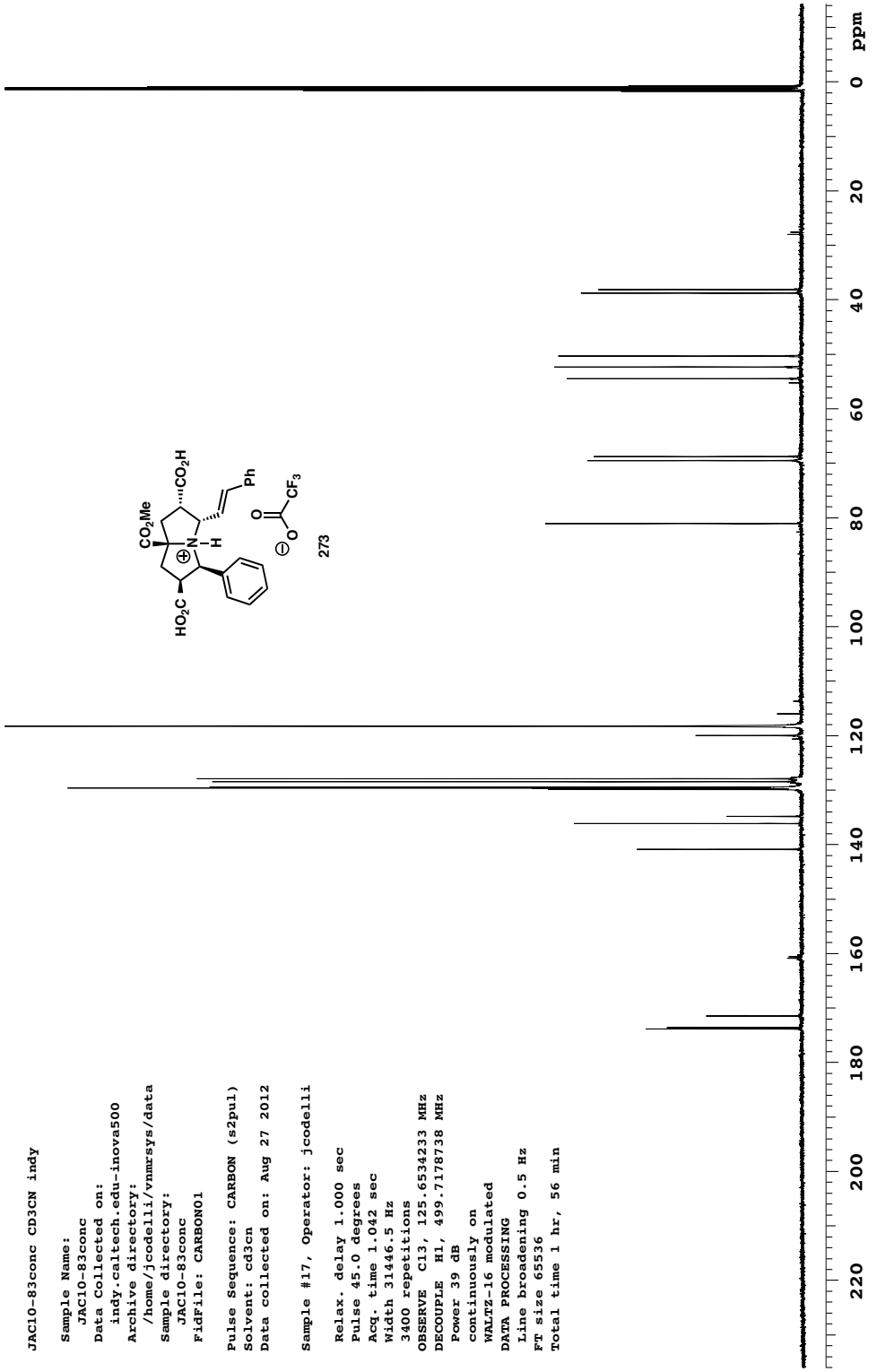

Sample Name:
ADL-IV-53B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-53B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 21 2012
Sample #27, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
256 repetitions
OBSERVE H1, 499.7127317 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 14 min
OH
O
t-BuO2C
CO2t-Bu
Ph
Ph
271
ppm
12
10
8
6
4
2
0
1.10
4.54
1.80
1.09
1.20
1.00
1.10
1.97
1.11
1.11
2.19
9.14
7.23

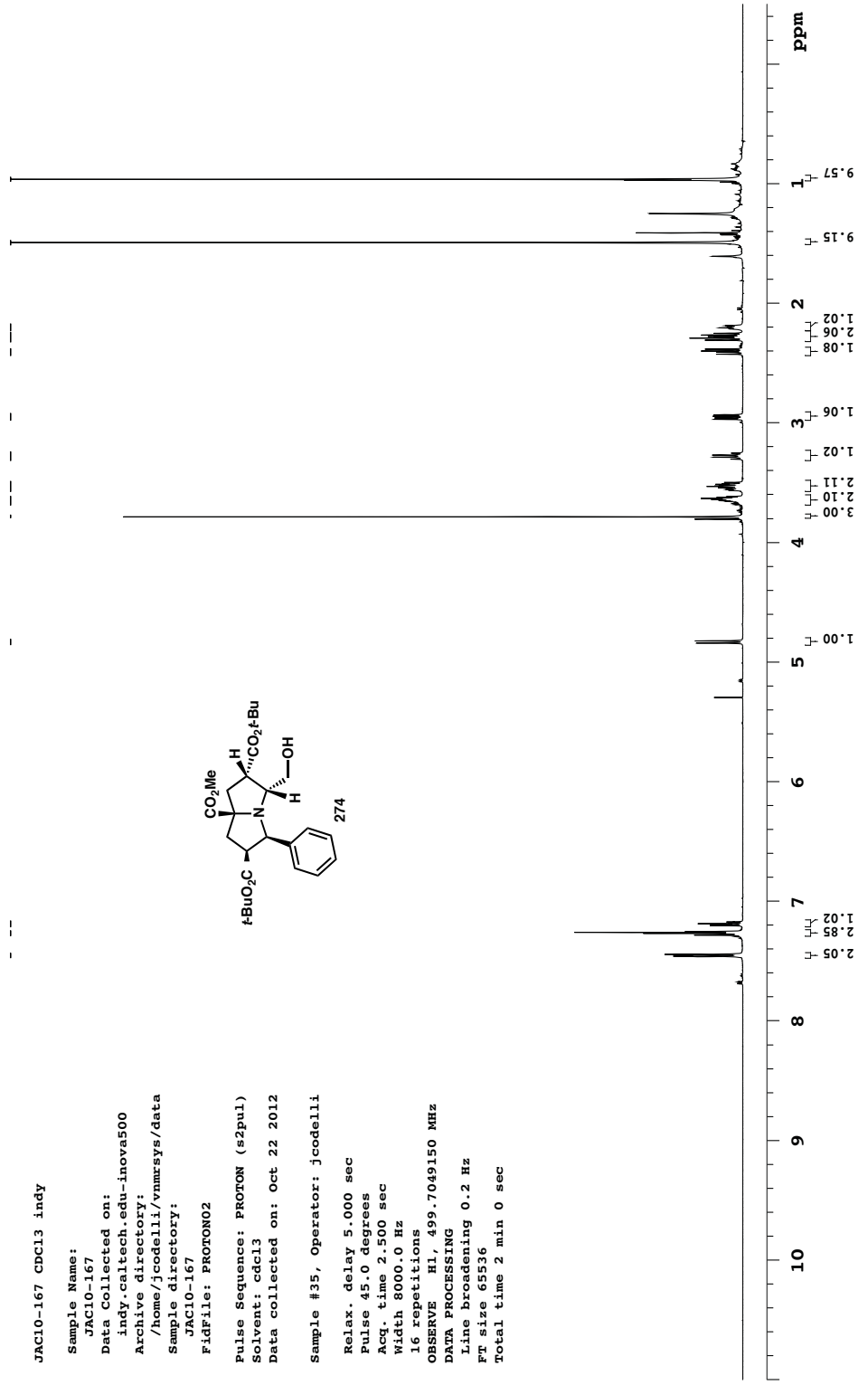

Sample Name:
ADL-IV-53B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-53B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 21 2012
Sample #27, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6528663 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 34 min
OH
O
CO2tBu
Ph
N
Ph
t-BuO2C
271
180
160
140
120
100
80
60
40
20
ppm

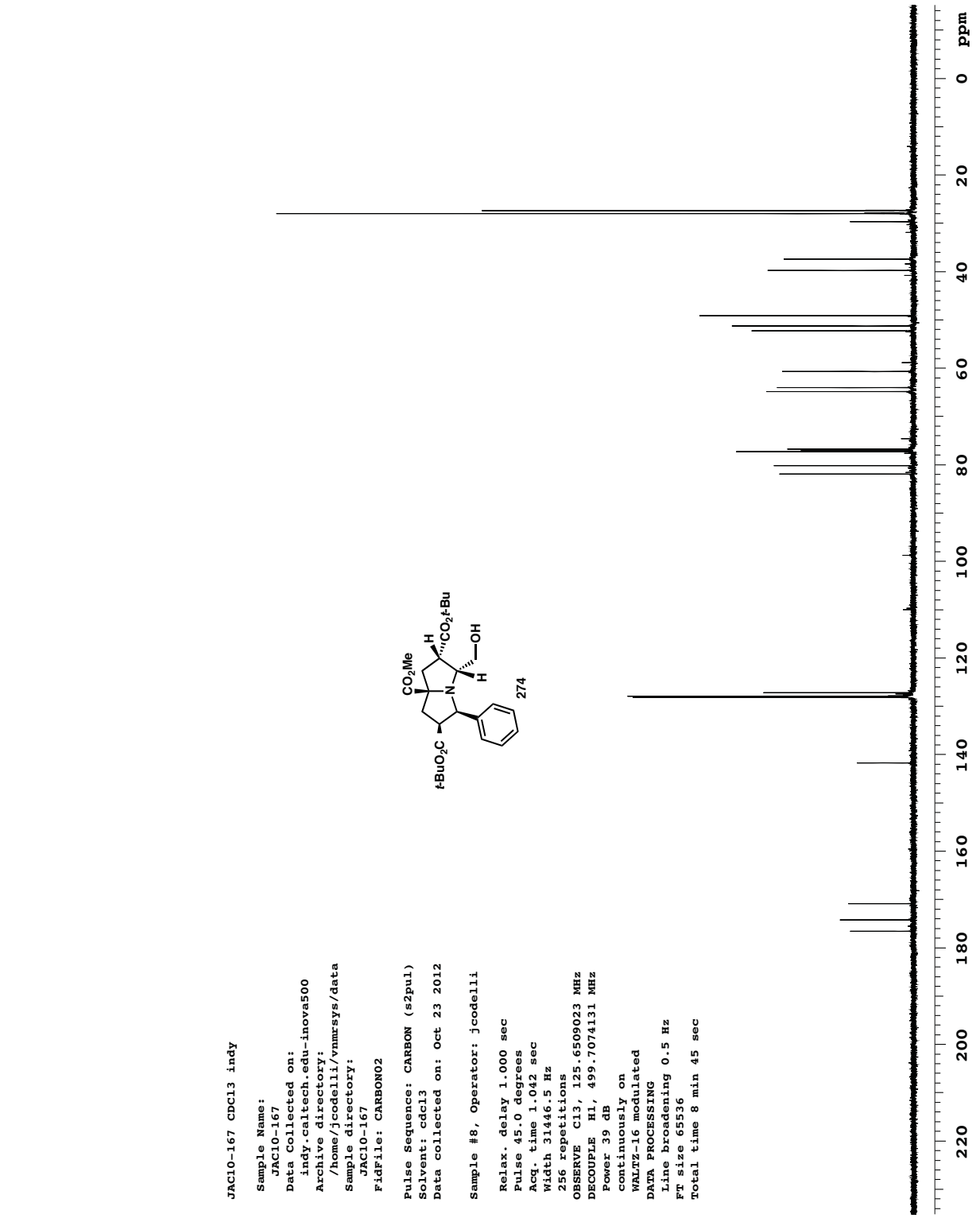

Sample Name:
ADL-IV-51B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-51B
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 20 2012
Sample #33, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7127450 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 7 min 29 sec
OH
CO2tBu
Ph
N
Ph
tBuO2C
272
ppm
12
10
8
6
4
2
0
2.01
4.13
1.13
1.70
1.07
1.13
1.00
1.12
1.60
1.04
1.25
1.19
1.23
1.24
1.18
7.43
3.10
7.03

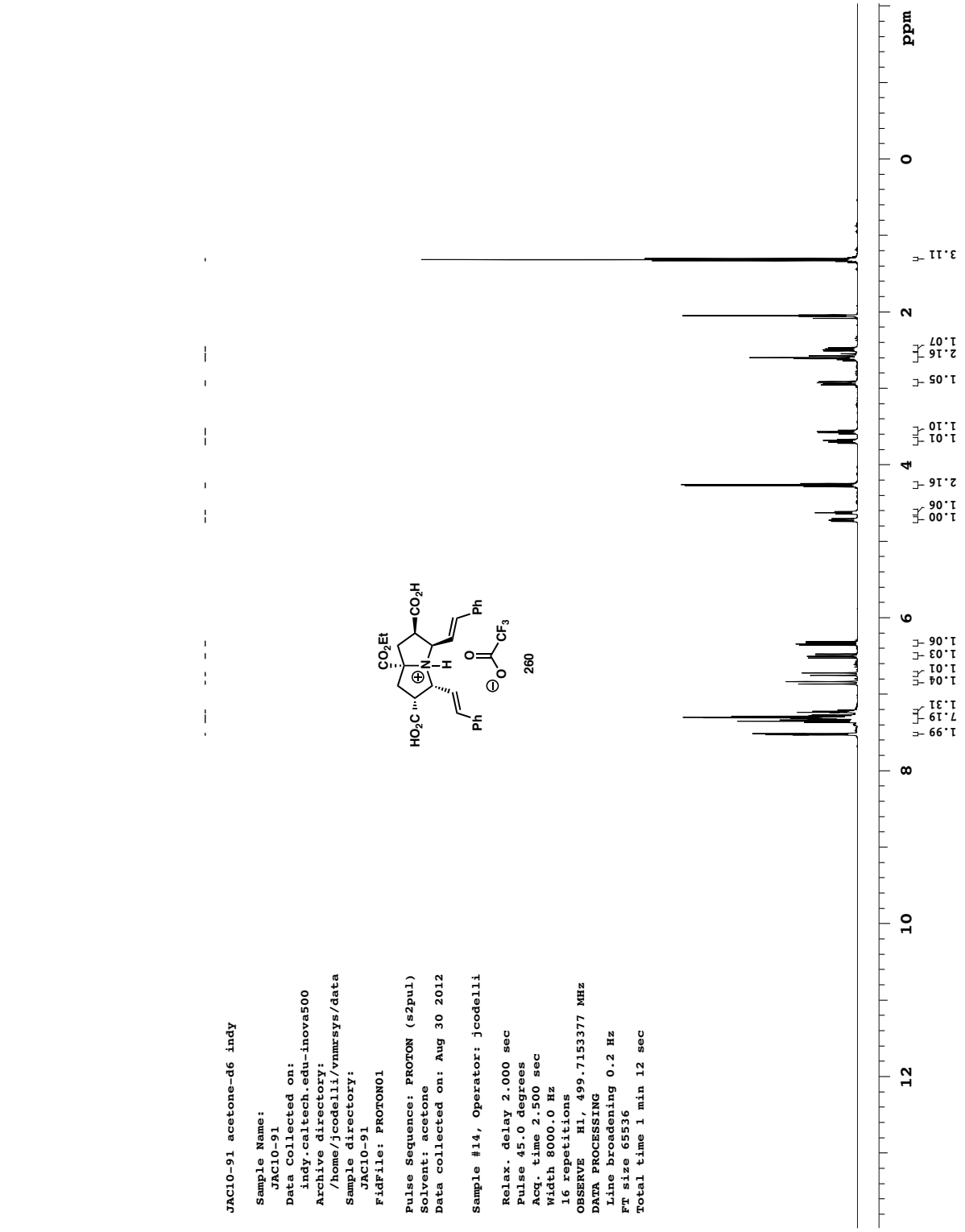

Sample Name:
ADL-IV-51B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-IV-51B
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 20 2012
Sample #33, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6528663 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 34 min
OH
CO2tBu
Ph
N
Ph
tBuO2C
272
180
160
140
120
100
80
60
40
20
ppm

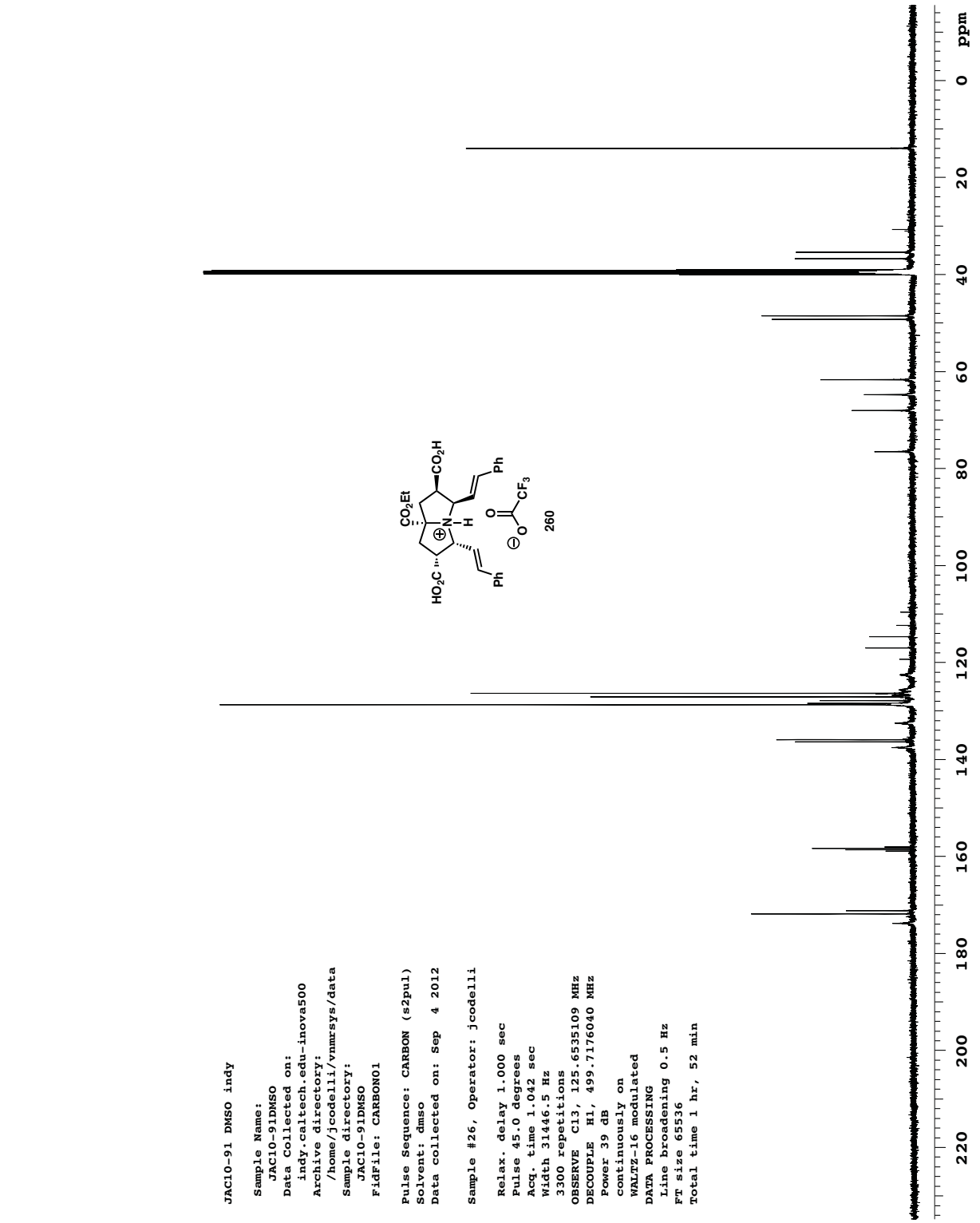

JAC10-83 CD3CN indy
Sample Name:
JAC10-83
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC10-83
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Aug 26 2012
Sample #17, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7153982 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
CO2Me
CO2H
HO2C
Ph
CF3
273
ppm
12
10
8
6
4
2
0
9.88
0.98
1.00
0.86
0.99
2.81
2.00
1.00
3.09
2.66

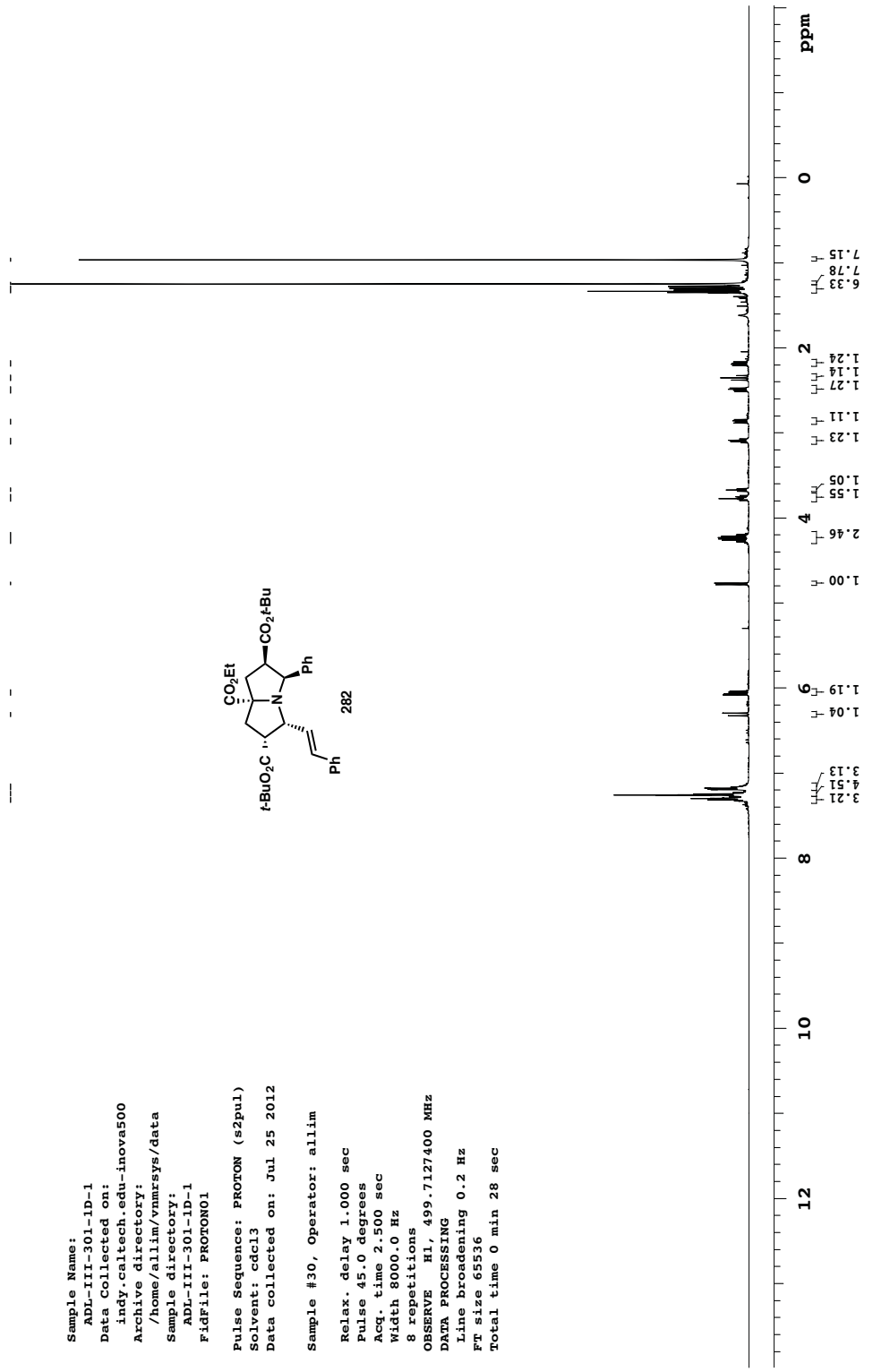

JAC10-83conc CD3CN indy
Sample Name:
JAC10-83conc
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC10-83conc
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Aug 27 2012
Sample #17, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3400 repetitions
OBSERVE C13, 125.6534233 MHz
DECOUPLE H1, 499.7178738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 56 min
CO2Me
CO2H
Ph
CF3
HO2C
273
220
200
180
160
140
120
100
80
60
40
20
0
ppm

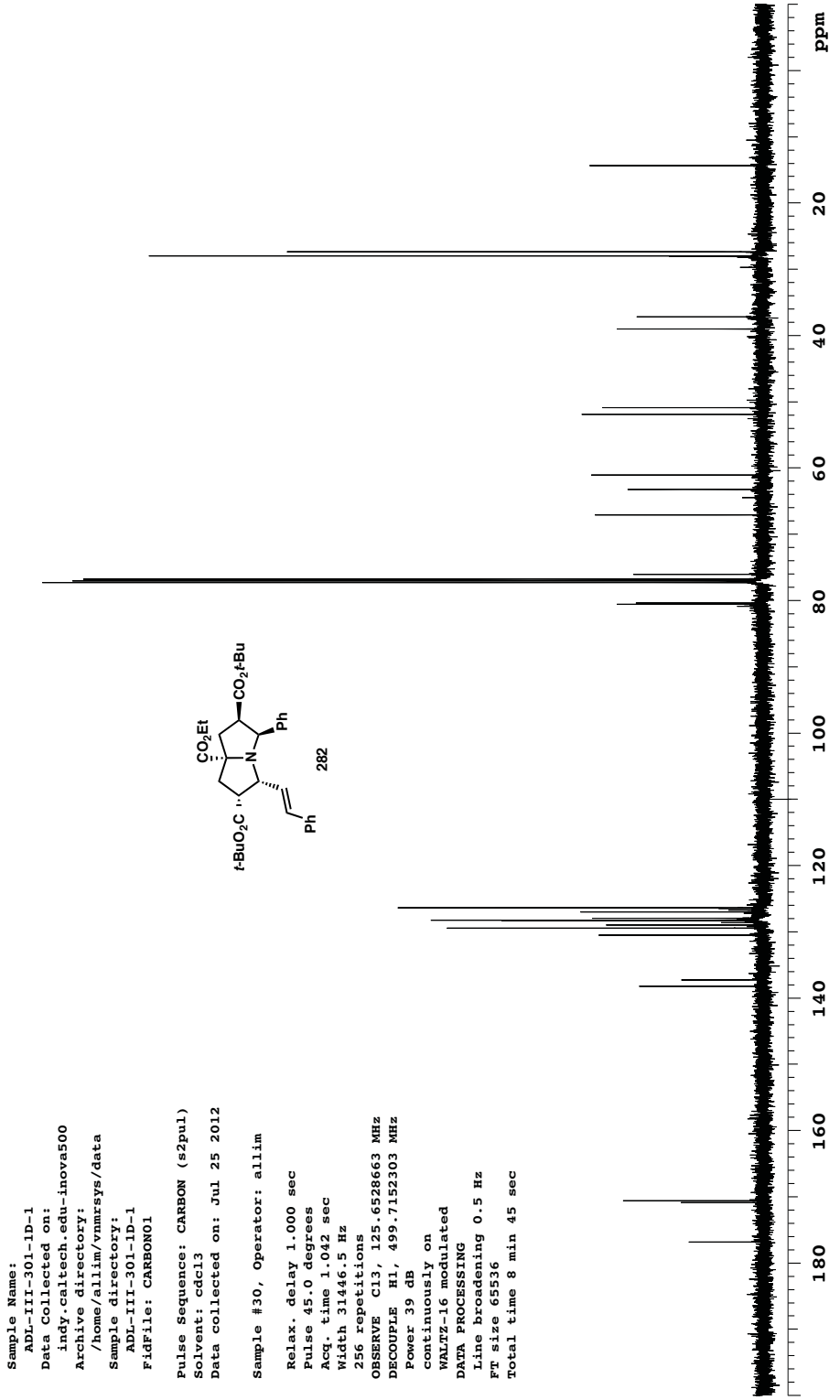

JAC10-167 CDCl3 indy
Sample Name:
JAC10-167
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC10-167
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 22 2012
Sample #35, Operator: jcodelli
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049150 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
CO2Me
H
CO2t-Bu
OH
H
t-BuO2C
274
ppm
9.57
9.15
2.05
2.85
1.02
1.00
3.00
2.10
2.11
1.02
1.06
1.08
2.06
1.02

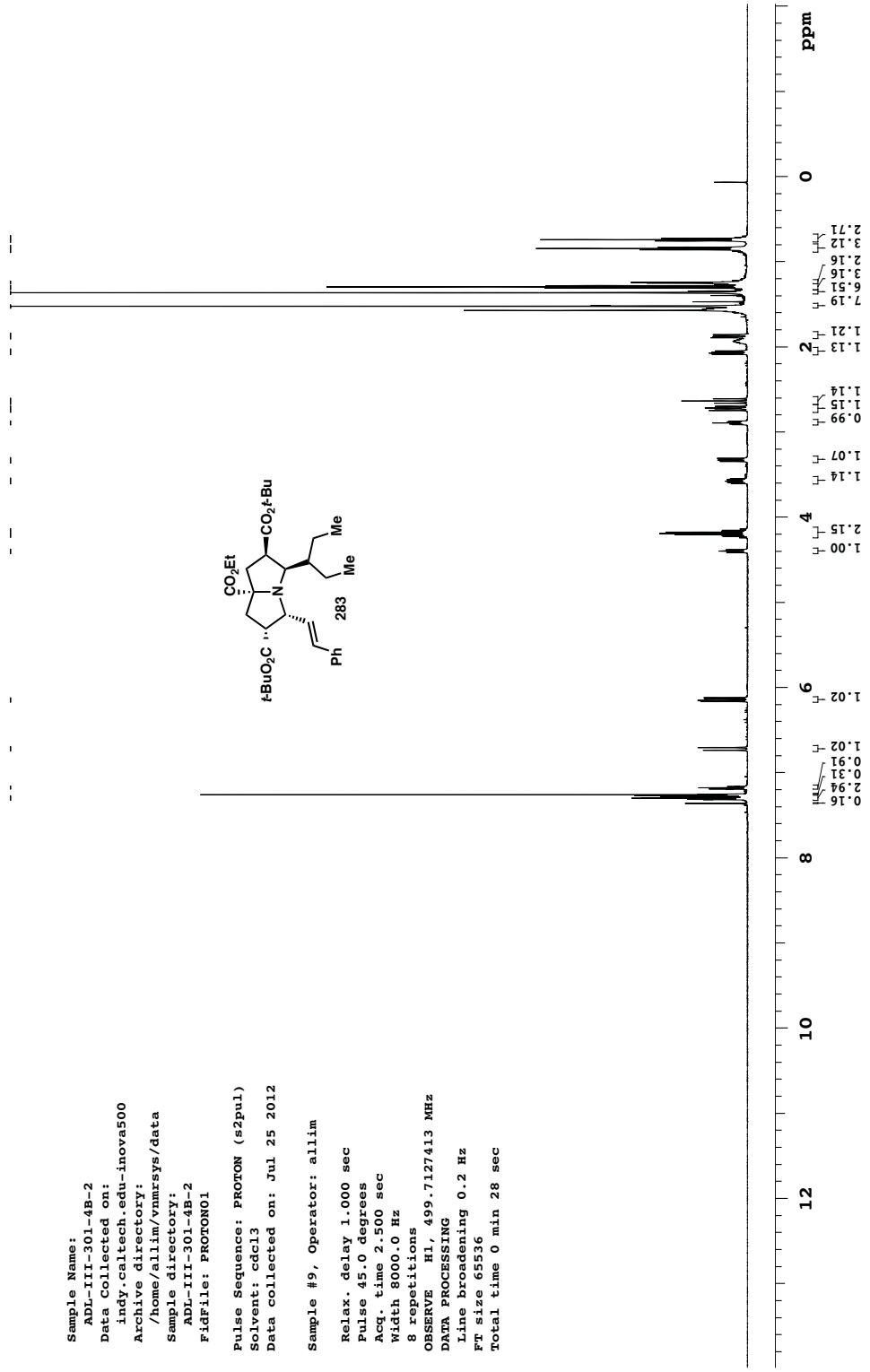

JAC10-167 CDCl3 indy
Sample Name:
JAC10-167
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC10-167
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 23 2012
Sample #8, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6509023 MHz
DECOUPLE H1, 499.7074131 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
CO2Me
H
CO2t-Bu
H
OH
N
t-BuO2C
274
220
200
180
160
140
120
100
80
60
40
20
0
ppm

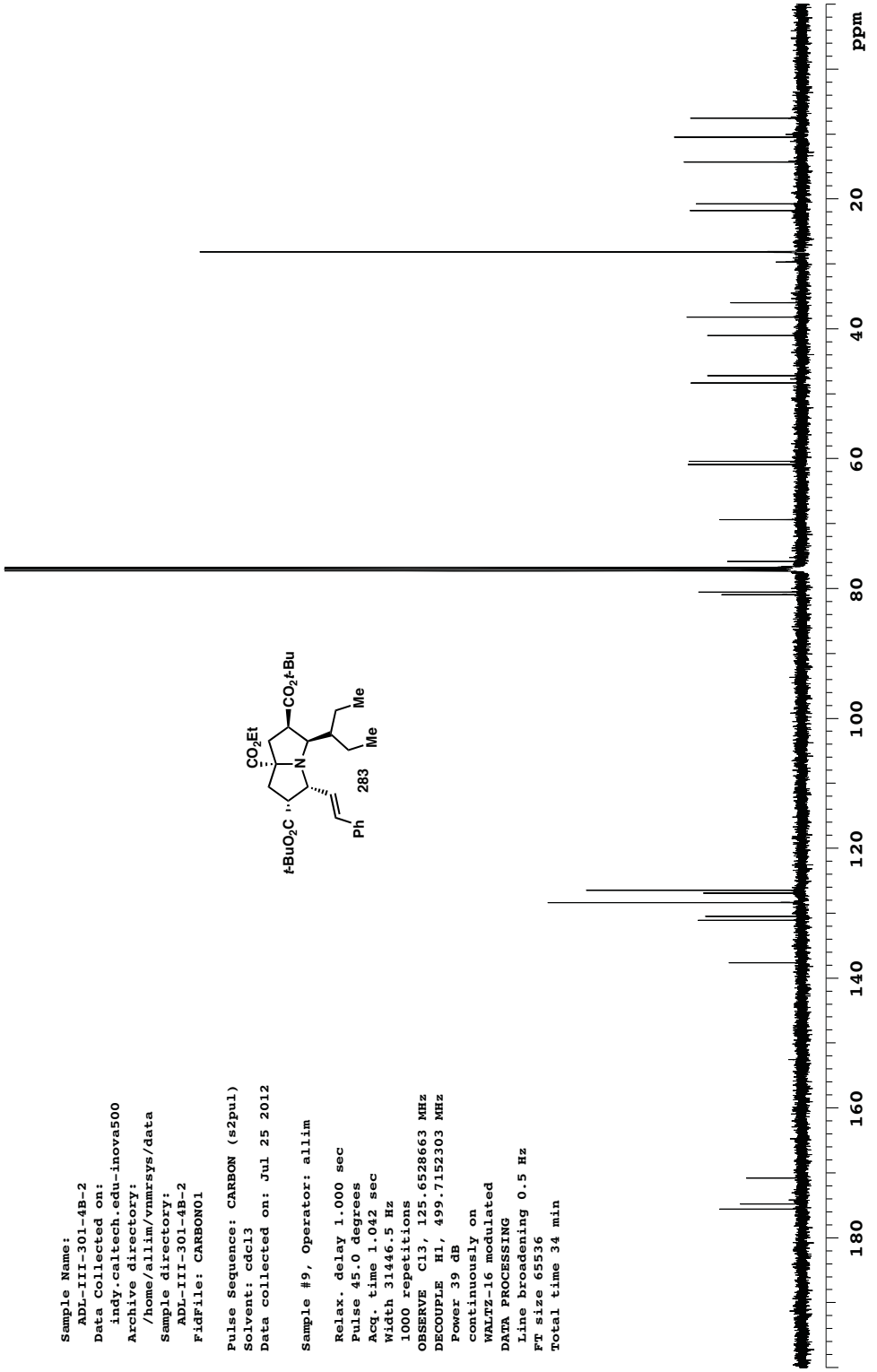

JAC10-91 acetone-d6 indy
Sample Name:
JAC10-91
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC10-91
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: acetone
Data collected on: Aug 30 2012
Sample #14, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7153377 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
CO2Et
CO2H
Ph
HO2C
Ph
O
CF3
260
ppm
12
10
8
6
4
2
0
1.99
7.19
7.31
1.04
1.01
1.03
1.06
1.00
1.06
2.16
1.01
1.10
1.05
2.16
1.07
3.11


JAC10-91 DMSO indy
Sample Name:
JAC10-91DMSO
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC10-91DMSO
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Sep 4 2012
Sample #26, Operator: jcodelli
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3300 repetitions
OBSERVE C13, 125.6535109 MHz
DECOUPLE H1, 499.7176040 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 52 min
CO2Et
CO2H
HO2C
Ph
Ph
CF3
260
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Sample Name:
ADL-III-301-1D-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-301-1D-1
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 25 2012
Sample #30, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127400 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Et
CO2t-Bu
Ph
t-BuO2C
Ph
282
ppm
12
10
8
6
4
2
0
3.21
4.51
3.13
1.04
1.19
1.00
2.46
1.55
1.05
1.23
1.11
1.27
1.14
1.24
6.33
7.78
7.15


Sample Name:
ADL-III-301-1D-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-301-1D-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 25 2012
Sample #30, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6528663 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 8 min 45 sec
CO2Et
CO2t-Bu
Ph
N
t-BuO2C
Ph
282
180
160
140
120
100
80
60
40
20
ppm


Sample Name:
ADL-III-301-4B-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-301-4B-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 25 2012
Sample #9, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127413 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
CO2Et
CO2t-Bu
t-BuO2C
Me
Me
Ph
283
ppm
0.16
2.94
0.31
0.91
1.02
1.02
2.15
1.00
1.14
1.07
0.99
1.15
1.14
1.13
1.21
7.19
6.51
3.16
2.16
3.12
2.71


Sample Name:
ADL-III-301-4B-2
Data Collected on:
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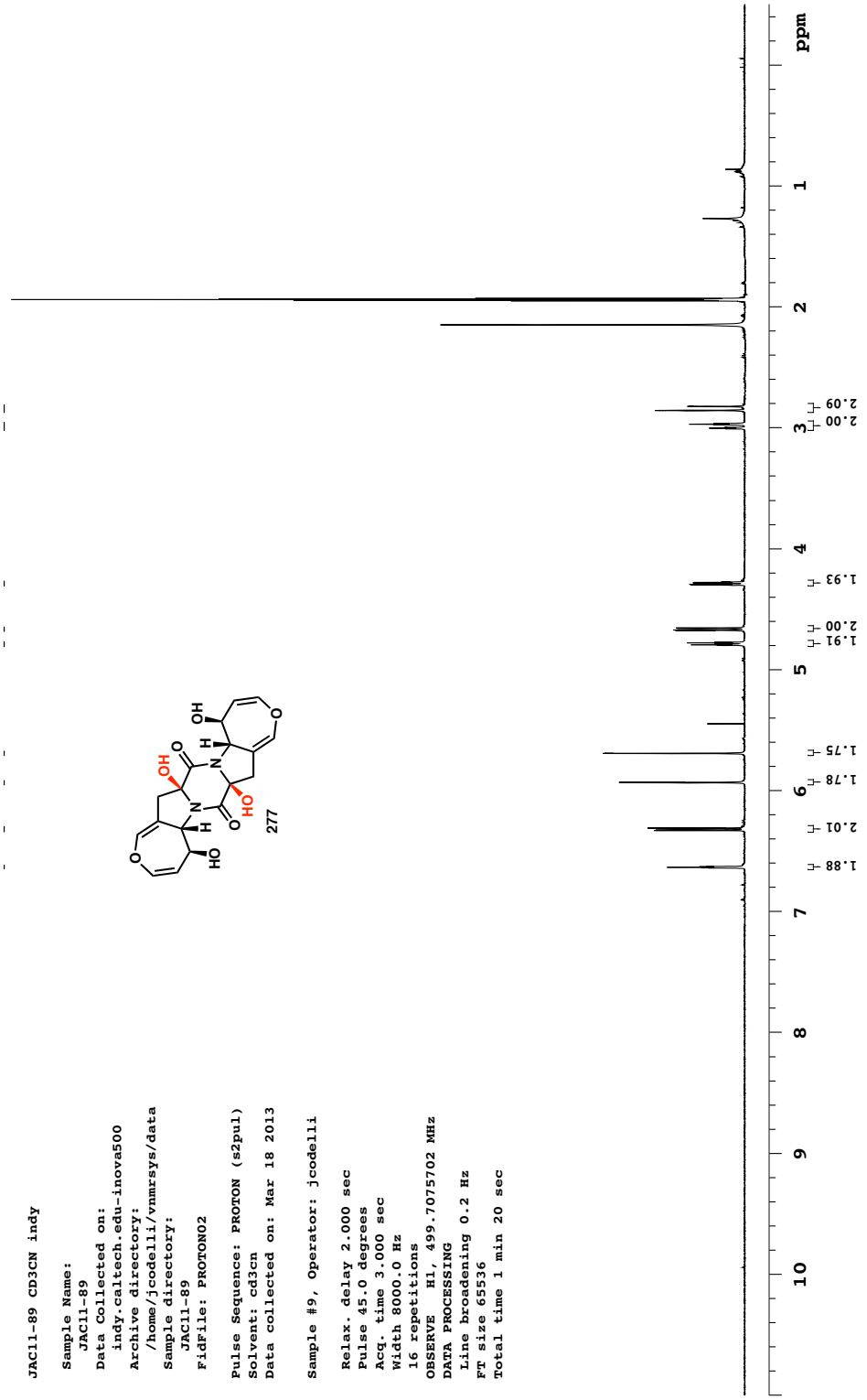
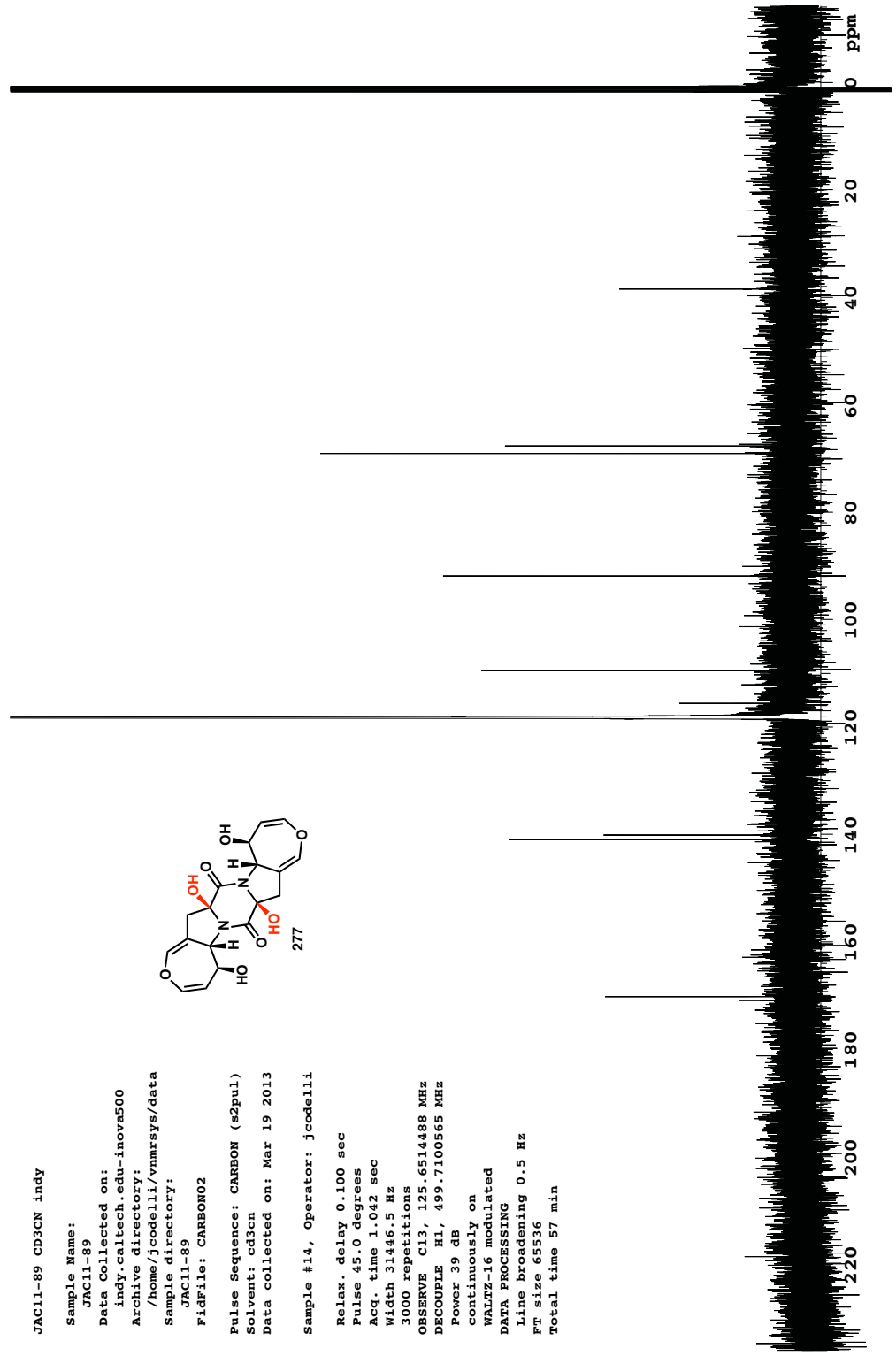
Archive directory:
/home/allim/vnmrsys/data
Sample directory:
ADL-III-301-4B-2
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 25 2012
Sample #9, Operator: allim
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6528663 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 34 min
CO2Et
CO2t-Bu
t-BuO2C
N
Me
Me
Ph
283
180
160
140
120
100
80
60
40
20
ppm


JAC11-89 CD3CN indy
Sample Name:
JAC11-89
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-89
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Mar 18 2013
Sample #9, Operator: jcodelli
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7075702 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 20 sec
277
ppm
1.88
2.01
1.78
1.75
2.00
1.91
1.93
2.00
2.09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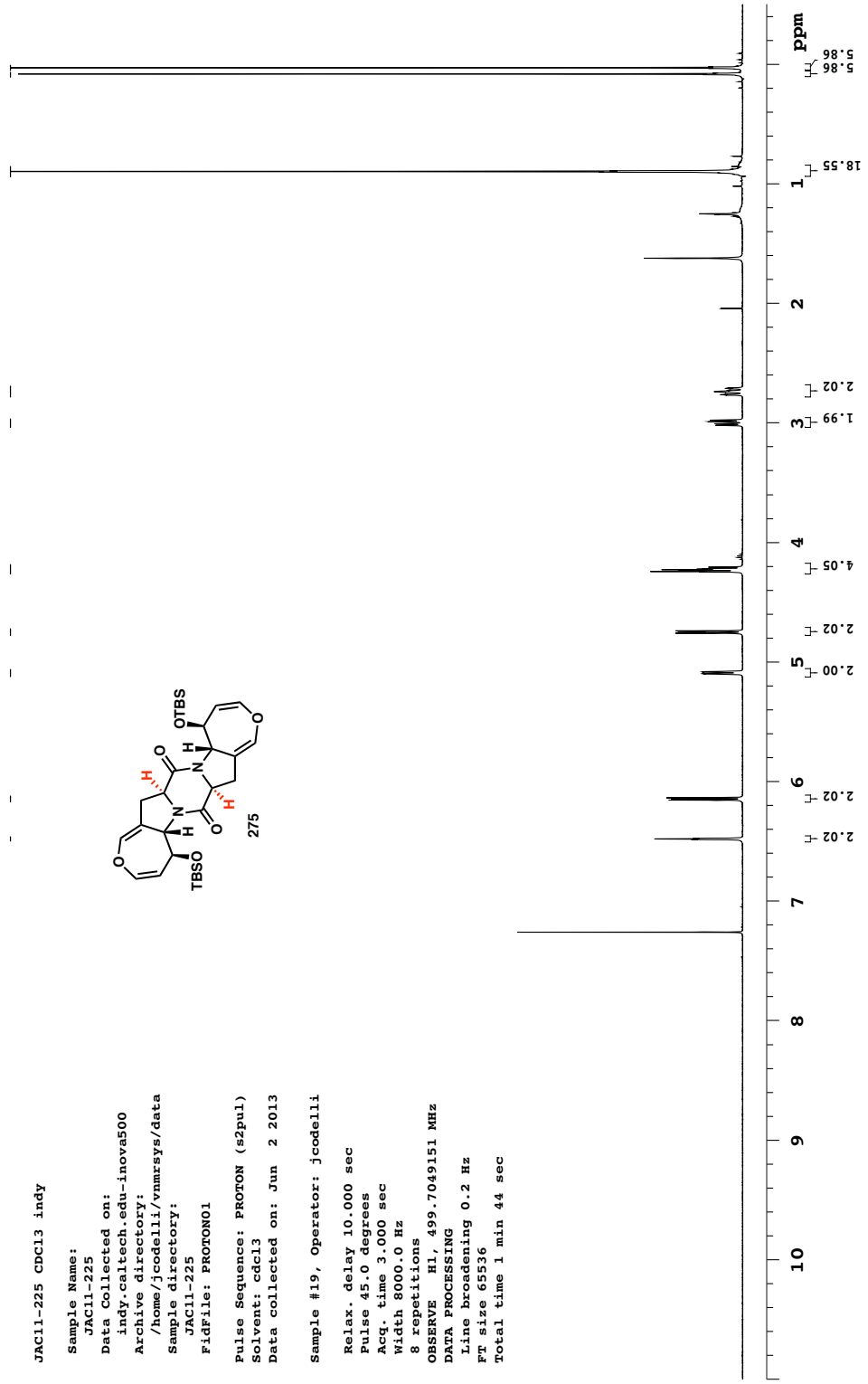
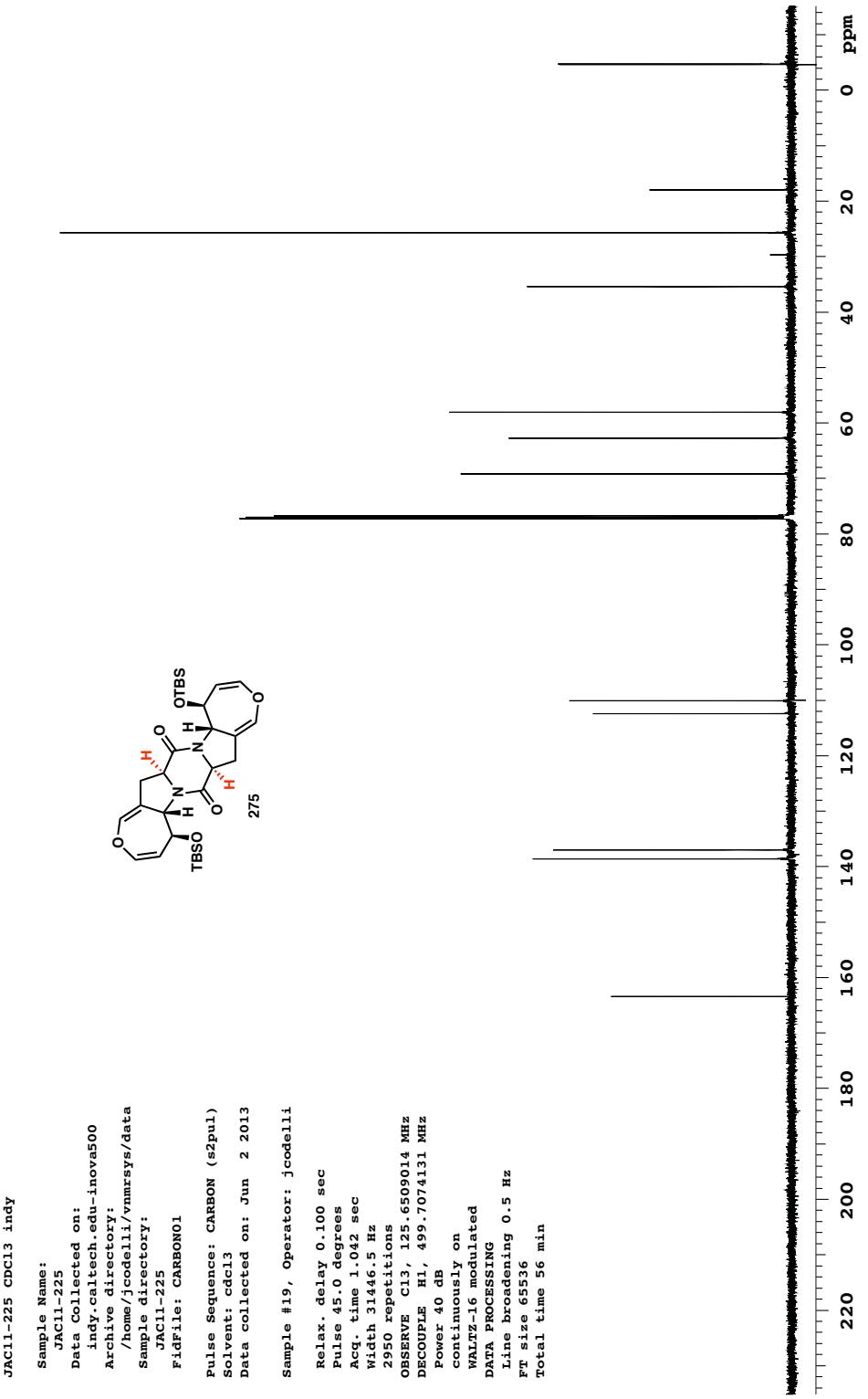
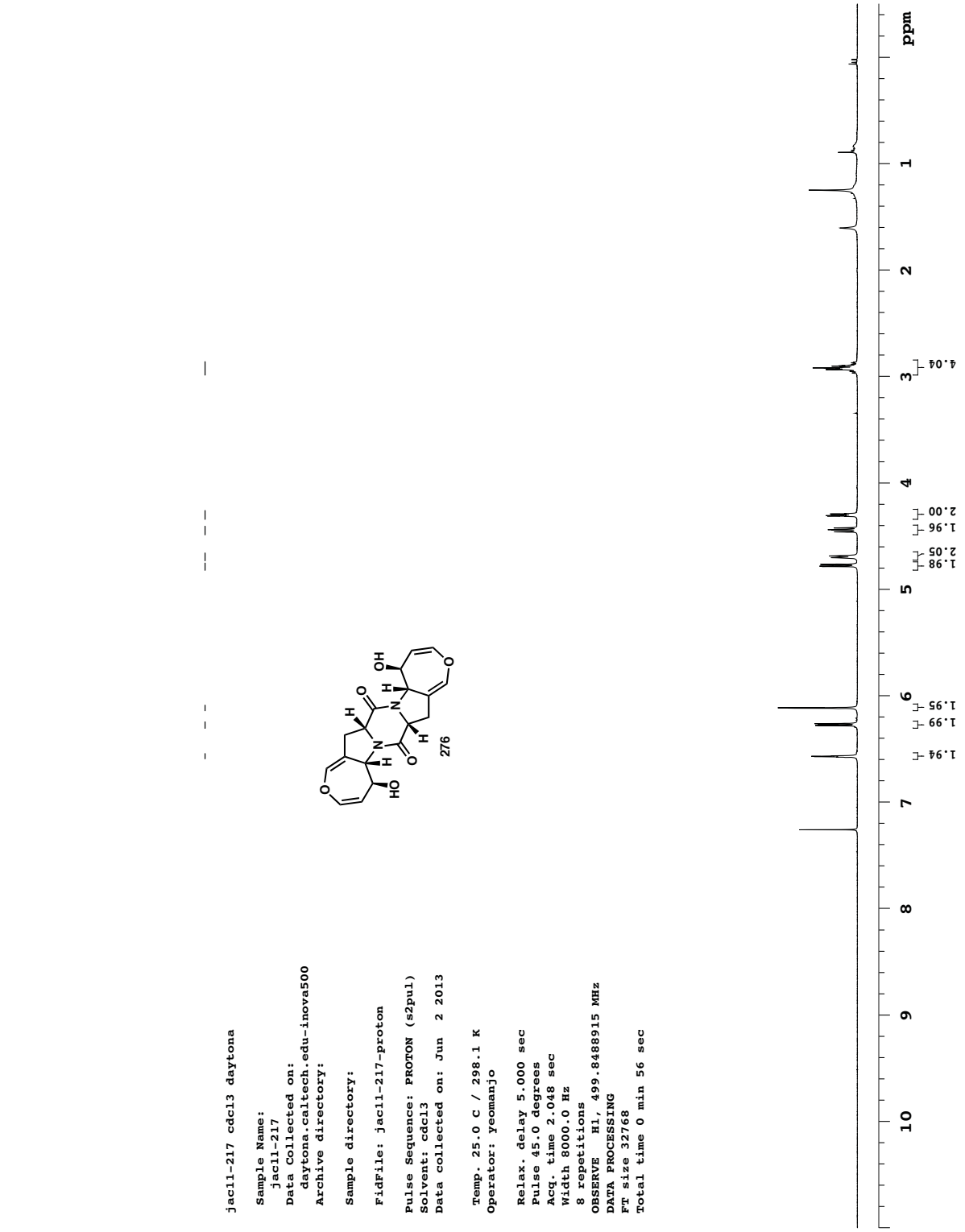
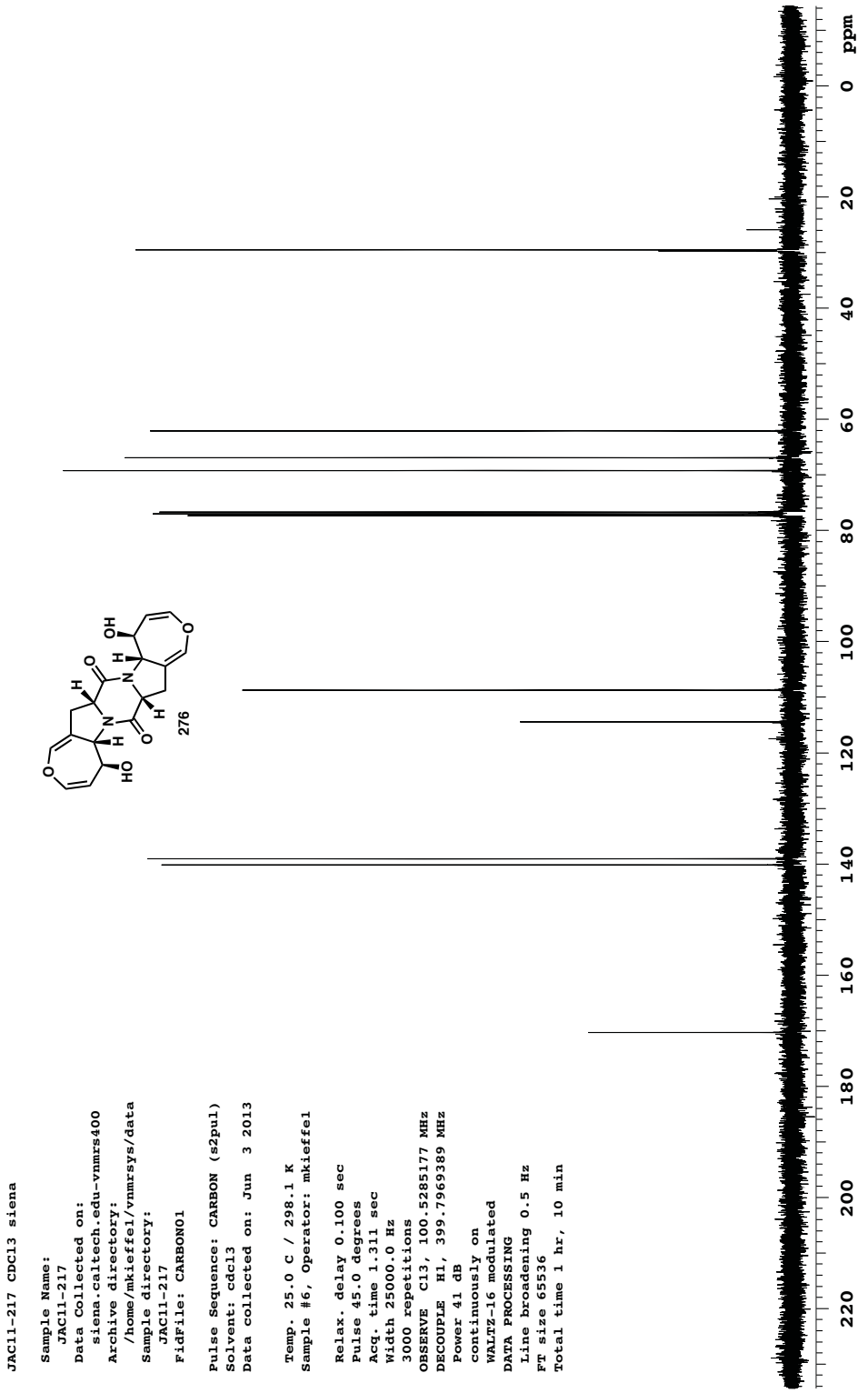
Sample Name:
JAC11-89
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-89
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Mar 19 2013
Sample #14, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3000 repetitions
OBSERVE C13, 125.6514488 MHz
DECOUPLE H1, 499.7100565 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 57 min
277
ppm
220
200
180
160
140
120
100
80
60
40
20
0


JAC11-225 CDCl3 indy
Sample Name:
JAC11-225
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-225
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 2 2013
Sample #19, Operator: jcodelli
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
OTBS
TBSO
275
ppm
5.86
5.86
18.55
2.02
1.99
2.02
4.05
2.02
2.00
2.02
2.02


JAC11-225 CDCl3 indy
Sample Name:
JAC11-225
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/jcodelli/vnmrsys/data
Sample directory:
JAC11-225
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 2 2013
Sample #19, Operator: jcodelli
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2950 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 56 min
OTBS
TBSO
275
220
200
180
160
140
120
100
80
60
40
20
0
ppm


jac11-217 cdcl3 daytona
Sample Name:
jac11-217
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: jac11-217-proton
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 2 2013
Temp. 25.0 C / 298.1 K
Operator: yeomanjo
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.8488915 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 56 sec
276
4.04
2.00
1.96
2.05
1.98
1.95
1.99
1.94
ppm


JAC11-217 CDCl3 siena
Sample Name:
JAC11-217
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/mkieffel/vnmrsys/data
Sample directory:
JAC11-217
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 3 2013
Temp. 25.0 C / 298.1 K
Sample #6, Operator: mkieffel
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
3000 repetitions
OBSERVE C13, 100.5285177 MHz
DECOUPLE H1, 399.7969389 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 10 min
276
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix 5

X-Ray Crystallography Reports Relevant to Chapter 4: Further Investigation of Side Reactions[†]

[†] The work disclosed in this appendix for the X-ray crystallographic analysis of **260** was completed entirely by Larry Henling and Dr. Michael Day in the Caltech X-ray crystallography lab.

A5.1. CRYSTAL STRUCTURE ANALYSIS OF PYRROLIZIDINE 260

Figure A5.1. *Pyrrolizidine* ***260*** *(trifluoroactetate counterion omitted). 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 831402.*

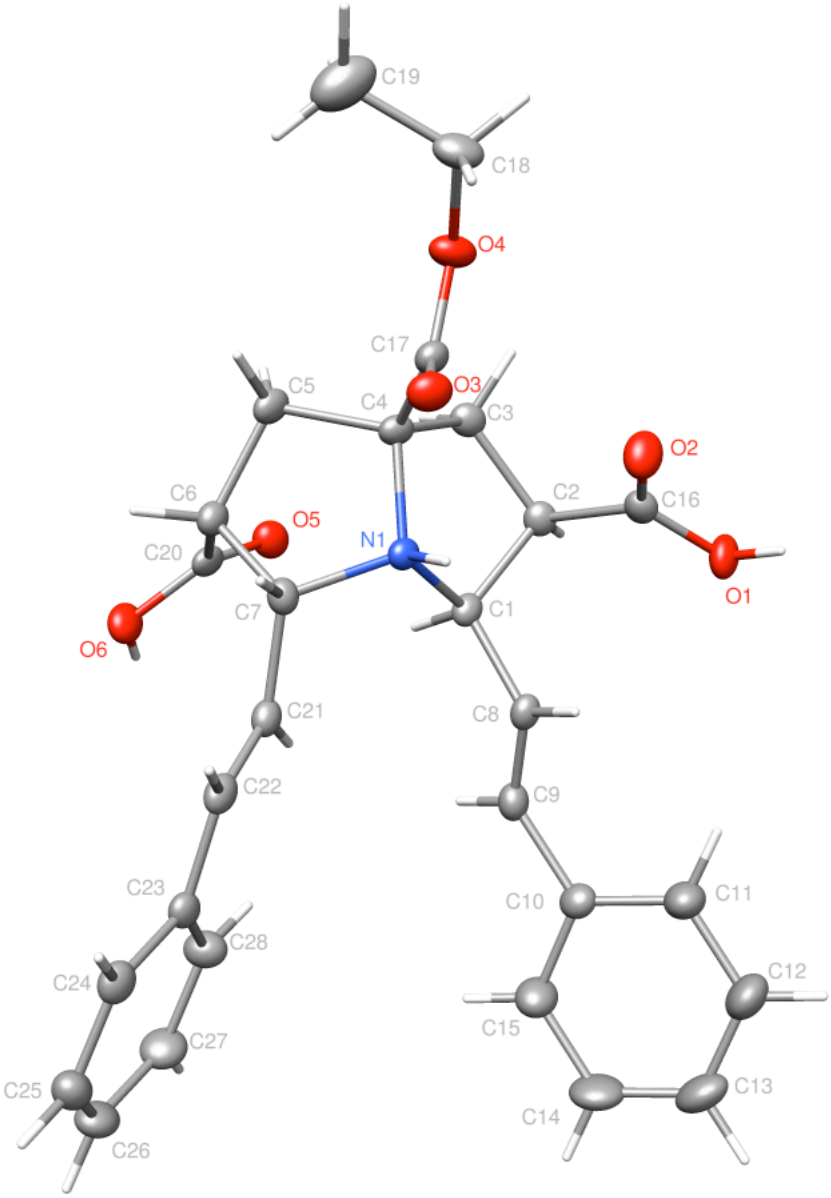


Table A5.1. *Crystal data and structure refinement for pyrrolizidine* ***260*** *(CCDC 831402).*

Empirical formula	$[C_{28}H_{30}NO_6]^+ [C_2F_3O_2]^-$
Formula weight	589.55
Crystallization Solvent	Acetone/pentanes
Crystal Habit	Plate
Crystal size	0.36 x 0.33 x 0.11 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 9978 reflections used in lattice determination	2.39 to 27.12°	
Unit cell dimensions	a = 16.1696(19) Å b = 9.6337(11) Å c = 18.988(2) Å	α= 90° β= 106.742(2)° γ = 90°
Volume	2832.4(6) $Å^3$	
Z	4	
Crystal system	Monoclinic	
Space group	P $2_1/n$	
Density (calculated)	1.383 Mg/m^3	
F(000)	1232	
θ range for data collection	1.96 to 27.61°	
Completeness to θ = 27.61°	99.5 %	
Index ranges	$-20 \le h \le 20$, $-12 \le k \le 12$, $-24 \le l \le 24$	
Data collection scan type	ω scans; 6 settings	
Reflections collected	42760	
Independent reflections	6554 [R_{int}= 0.0503]	
Absorption coefficient	0.113 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.6474	

Table A5.1 (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	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	6554 / 0 / 410
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.325
Final R indices [I>2σ(I), 4759 reflections]	R1 = 0.0492, *w*R2 = 0.0710
R indices (all data)	R1 = 0.0733, *w*R2 = 0.0735
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.013
Average shift/error	0.001
Largest diff. peak and hole	0.281 and -0.312 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 A5.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for pyrrolizidine* ***260*** *(CCDC 831402). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}	Occ
N(1)	548(1)	1210(1)	1090(1)	16(1)	1
O(1)	-1579(1)	3781(1)	489(1)	25(1)	1
O(2)	-759(1)	2797(1)	-147(1)	28(1)	1
O(3)	670(1)	806(1)	-294(1)	23(1)	1
O(4)	1170(1)	2975(1)	-361(1)	25(1)	1
O(5)	1918(1)	2777(1)	2575(1)	25(1)	1
O(6)	2539(1)	788(1)	3074(1)	26(1)	1
C(1)	36(1)	2023(2)	1518(1)	17(1)	1
C(2)	-108(1)	3419(2)	1109(1)	18(1)	1
C(3)	755(1)	3679(2)	952(1)	20(1)	1
C(4)	1065(1)	2252(2)	780(1)	18(1)	1
C(5)	2030(1)	1918(2)	1165(1)	21(1)	1
C(6)	2048(1)	890(2)	1782(1)	20(1)	1
C(7)	1179(1)	104(2)	1512(1)	19(1)	1
C(8)	-768(1)	1304(2)	1551(1)	18(1)	1
C(9)	-963(1)	1085(2)	2172(1)	22(1)	1
C(10)	-1790(1)	540(2)	2231(1)	24(1)	1
C(11)	-2548(1)	711(2)	1668(1)	36(1)	1
C(12)	-3319(1)	204(2)	1732(1)	44(1)	1
C(13)	-3350(1)	-471(2)	2361(1)	42(1)	1
C(14)	-2610(1)	-639(2)	2924(1)	44(1)	1
C(15)	-1831(1)	-126(2)	2865(1)	35(1)	1
C(16)	-848(1)	3306(2)	410(1)	20(1)	1
C(17)	911(1)	1927(2)	-29(1)	20(1)	1
C(18)	1308(1)	2725(2)	-1082(1)	28(1)	1
C(19)	2251(1)	2581(2)	-975(1)	50(1)	1
C(20)	2157(1)	1604(2)	2514(1)	21(1)	1
C(21)	906(1)	-619(2)	2099(1)	19(1)	1
C(22)	837(1)	-1988(2)	2127(1)	20(1)	1
C(23)	717(1)	-2773(2)	2753(1)	19(1)	1
C(24)	790(1)	-4211(2)	2759(1)	23(1)	1
C(25)	753(1)	-4984(2)	3366(1)	29(1)	1
C(26)	644(1)	-4326(2)	3973(1)	32(1)	1
C(27)	553(1)	-2897(2)	3971(1)	32(1)	1
C(28)	588(1)	-2134(2)	3370(1)	27(1)	1
C(31)	1037(1)	1596(3)	4807(1)	40(1)	1
C(32)	1369(1)	1469(2)	4134(1)	23(1)	1
F(1)	1353(4)	2727(5)	5180(2)	88(2)	0.751(12)
F(2)	205(3)	1790(11)	4627(3)	115(2)	0.751(12)
F(3)	1266(4)	589(4)	5255(3)	93(2)	0.751(12)
F(1B)	967(17)	2814(10)	5038(10)	101(6)	0.249(12)
F(2B)	292(10)	975(19)	4709(9)	91(6)	0.249(12)
F(3B)	1501(11)	980(30)	5382(9)	158(9)	0.249(12)
O(7)	2184(1)	1448(1)	4281(1)	30(1)	1

O(8)	829(1)	1394(1)	3536(1)	27(1)	1

Table A5.3. *Bond lengths [Å] and angles [°] for pyrrolizidine* ***260*** *(CCDC 831402).*

N(1)-C(4)	1.5278(18)	C(7)-N(1)-C(1)	117.25(11)
N(1)-C(7)	1.5317(17)	C(17)-O(4)-C(18)	118.26(12)
N(1)-C(1)	1.5326(17)	C(8)-C(1)-N(1)	113.34(12)
O(1)-C(16)	1.3149(17)	C(8)-C(1)-C(2)	114.91(12)
O(2)-C(16)	1.2127(18)	N(1)-C(1)-C(2)	101.87(11)
O(3)-C(17)	1.2078(17)	C(16)-C(2)-C(3)	112.08(13)
O(4)-C(17)	1.3201(17)	C(16)-C(2)-C(1)	110.27(12)
O(4)-C(18)	1.4692(17)	C(3)-C(2)-C(1)	103.20(12)
O(5)-C(20)	1.2102(18)	C(2)-C(3)-C(4)	105.50(12)
O(6)-C(20)	1.3228(17)	C(17)-C(4)-N(1)	107.80(12)
C(1)-C(8)	1.4903(19)	C(17)-C(4)-C(3)	115.61(13)
C(1)-C(2)	1.537(2)	N(1)-C(4)-C(3)	105.10(11)
C(2)-C(16)	1.513(2)	C(17)-C(4)-C(5)	106.40(12)
C(2)-C(3)	1.5296(19)	N(1)-C(4)-C(5)	105.64(11)
C(3)-C(4)	1.530(2)	C(3)-C(4)-C(5)	115.61(12)
C(4)-C(17)	1.518(2)	C(6)-C(5)-C(4)	106.80(12)
C(4)-C(5)	1.554(2)	C(20)-C(6)-C(5)	112.38(13)
C(5)-C(6)	1.529(2)	C(20)-C(6)-C(7)	112.28(12)
C(6)-C(20)	1.516(2)	C(5)-C(6)-C(7)	104.38(12)
C(6)-C(7)	1.548(2)	C(21)-C(7)-N(1)	114.94(12)
C(7)-C(21)	1.484(2)	C(21)-C(7)-C(6)	114.82(12)
C(8)-C(9)	1.323(2)	N(1)-C(7)-C(6)	103.75(11)
C(9)-C(10)	1.471(2)	C(9)-C(8)-C(1)	123.07(14)
C(10)-C(15)	1.382(2)	C(8)-C(9)-C(10)	125.41(15)
C(10)-C(11)	1.385(2)	C(15)-C(10)-C(11)	118.25(15)
C(11)-C(12)	1.377(2)	C(15)-C(10)-C(9)	120.36(15)
C(12)-C(13)	1.373(2)	C(11)-C(10)-C(9)	121.36(15)
C(13)-C(14)	1.366(2)	C(12)-C(11)-C(10)	120.75(17)
C(14)-C(15)	1.387(2)	C(13)-C(12)-C(11)	120.44(18)
C(18)-C(19)	1.487(2)	C(14)-C(13)-C(12)	119.58(17)
C(21)-C(22)	1.326(2)	C(13)-C(14)-C(15)	120.34(18)
C(22)-C(23)	1.468(2)	C(10)-C(15)-C(14)	120.62(17)
C(23)-C(24)	1.390(2)	O(2)-C(16)-O(1)	125.22(15)
C(23)-C(28)	1.392(2)	O(2)-C(16)-C(2)	122.11(14)
C(24)-C(25)	1.387(2)	O(1)-C(16)-C(2)	112.65(14)
C(25)-C(26)	1.371(2)	O(3)-C(17)-O(4)	126.43(15)
C(26)-C(27)	1.384(2)	O(3)-C(17)-C(4)	123.05(14)
C(27)-C(28)	1.371(2)	O(4)-C(17)-C(4)	110.09(13)
C(31)-F(1B)	1.269(11)	O(4)-C(18)-C(19)	108.20(14)
C(31)-F(3)	1.272(4)	O(5)-C(20)-O(6)	124.48(15)
C(31)-F(3B)	1.280(13)	O(5)-C(20)-C(6)	123.76(14)
C(31)-F(2)	1.303(4)	O(6)-C(20)-C(6)	111.76(14)
C(31)-F(2B)	1.311(10)	C(22)-C(21)-C(7)	122.94(15)
C(31)-F(1)	1.319(4)	C(21)-C(22)-C(23)	125.23(15)
C(31)-C(32)	1.527(2)	C(24)-C(23)-C(28)	117.80(15)
C(32)-O(8)	1.2193(17)	C(24)-C(23)-C(22)	119.29(15)
C(32)-O(7)	1.2666(18)	C(28)-C(23)-C(22)	122.78(15)
		C(25)-C(24)-C(23)	121.22(16)
C(4)-N(1)-C(7)	107.65(11)	C(26)-C(25)-C(24)	119.78(17)
C(4)-N(1)-C(1)	107.88(11)	C(25)-C(26)-C(27)	119.74(17)

C(28)-C(27)-C(26)	120.42(17)	F(3B)-C(31)-F(1)	83.5(13)
C(27)-C(28)-C(23)	121.00(17)	F(2)-C(31)-F(1)	103.5(4)
F(1B)-C(31)-F(3)	120.8(7)	F(2B)-C(31)-F(1)	130.6(7)
F(1B)-C(31)-F(3B)	103.1(10)	F(1B)-C(31)-C(32)	116.8(5)
F(3)-C(31)-F(3B)	24.3(14)	F(3)-C(31)-C(32)	113.2(3)
F(1B)-C(31)-F(2)	76.7(9)	F(3B)-C(31)-C(32)	114.6(6)
F(3)-C(31)-F(2)	111.4(4)	F(2)-C(31)-C(32)	112.1(3)
F(3B)-C(31)-F(2)	126.7(6)	F(2B)-C(31)-C(32)	112.1(7)
F(1B)-C(31)-F(2B)	107.5(9)	F(1)-C(31)-C(32)	109.9(2)
F(3)-C(31)-F(2B)	79.9(9)	O(8)-C(32)-O(7)	128.74(16)
F(3B)-C(31)-F(2B)	101.4(10)	O(8)-C(32)-C(31)	117.03(15)
F(2)-C(31)-F(2B)	35.9(7)	O(7)-C(32)-C(31)	114.23(15)
F(1B)-C(31)-F(1)	27.2(11)		
F(3)-C(31)-F(1)	106.2(3)		

Table A5.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for pyrrolizidine* ***260*** *(CCDC 831402). 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}
N(1)	139(7)	204(8)	146(7)	2(6)	30(5)	-10(6)
O(1)	174(6)	362(7)	190(6)	-20(6)	-1(5)	51(6)
O(2)	246(6)	397(8)	197(7)	-54(6)	45(5)	41(6)
O(3)	244(6)	239(7)	217(6)	-34(5)	81(5)	-48(5)
O(4)	306(7)	284(7)	190(6)	22(5)	99(5)	-62(5)
O(5)	236(6)	257(7)	229(7)	-9(5)	40(5)	-12(5)
O(6)	233(6)	350(7)	187(6)	16(6)	37(5)	45(5)
C(1)	148(8)	228(9)	144(9)	-14(7)	43(7)	10(7)
C(2)	185(8)	172(9)	184(9)	-26(7)	40(7)	-7(7)
C(3)	211(9)	199(9)	183(9)	-10(7)	45(7)	-25(7)
C(4)	160(8)	221(9)	171(9)	5(7)	48(7)	-42(7)
C(5)	142(8)	303(10)	190(9)	-6(8)	36(7)	-30(7)
C(6)	150(8)	266(10)	193(9)	22(7)	44(7)	16(7)
C(7)	174(8)	200(9)	186(9)	9(7)	42(7)	33(7)
C(8)	136(8)	187(9)	202(9)	-15(7)	26(7)	2(7)
C(9)	177(9)	235(10)	226(10)	17(8)	34(7)	31(7)
C(10)	210(9)	230(10)	291(10)	25(8)	114(8)	27(8)
C(11)	255(10)	446(13)	398(12)	148(10)	121(9)	1(9)
C(12)	215(10)	558(14)	557(14)	139(11)	102(10)	-18(10)
C(13)	294(11)	388(12)	648(15)	47(11)	256(11)	-49(10)
C(14)	458(13)	496(14)	461(13)	138(11)	288(11)	-27(11)
C(15)	302(10)	456(12)	321(11)	95(9)	125(9)	16(9)
C(16)	195(9)	182(9)	222(10)	37(8)	48(7)	-3(7)
C(17)	145(8)	252(10)	204(9)	34(8)	57(7)	-4(7)
C(18)	375(11)	319(11)	179(10)	26(8)	133(8)	-9(9)
C(19)	403(12)	682(16)	480(14)	-132(11)	243(11)	-74(11)
C(20)	112(8)	296(10)	213(9)	40(8)	27(7)	-35(8)
C(21)	145(8)	231(10)	176(9)	-5(7)	33(7)	28(7)
C(22)	147(8)	268(10)	181(9)	-22(8)	29(7)	11(7)
C(23)	131(8)	206(9)	225(10)	17(8)	17(7)	-10(7)
C(24)	174(9)	247(10)	261(10)	-22(8)	37(7)	-10(7)
C(25)	238(10)	240(10)	392(12)	83(9)	79(9)	2(8)
C(26)	310(10)	355(12)	337(11)	128(9)	138(9)	6(9)
C(27)	353(11)	366(12)	303(11)	18(9)	184(9)	16(9)
C(28)	309(10)	236(10)	308(11)	16(8)	143(8)	1(8)
C(31)	250(11)	614(17)	306(13)	-81(12)	47(9)	18(11)
C(32)	237(10)	207(9)	220(10)	-7(8)	40(8)	-13(8)
F(1)	950(30)	1110(30)	551(17)	-580(20)	176(17)	22(18)
F(2)	289(18)	2770(70)	387(15)	-300(30)	109(13)	250(30)
F(3)	1370(50)	920(30)	700(30)	484(17)	620(30)	210(20)
F(1B)	2050(170)	330(50)	1220(100)	370(60)	1380(110)	390(70)
F(2B)	590(90)	1560(110)	740(80)	-540(80)	470(80)	-890(90)
F(3B)	540(60)	4000(300)	320(50)	820(100)	330(50)	1040(100)
O(7)	178(6)	507(8)	195(6)	-11(6)	15(5)	-11(6)

O(8)	228(6)	307(7)	224(7)	-24(5)	2(5)	-14(5)

Table A5.5. *Hydrogen bonds for pyrrolizidine* ***260*** *(CCDC 831402) [Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(3)#1	0.93	2.02	2.8670(16)	149.8
O(1)-H(1A)...O(7)#2	0.84	1.74	2.5814(14)	176.1
O(6)-H(6)...O(7)	0.84	1.77	2.5979(15)	168.4

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y,-z
#2 x-1/2,-y+1/2,z-1/2

ABOUT THE AUTHOR

Julian Andrew Codelli was born on January 8th, 1986 in Atlanta, Georgia to Chris H. and Carol W. Codelli. He grew up in Livermore, California, and attended Livermore High School, where he played football and basketball. Though he had always enjoyed learning about science, he recalls becoming particularly interested in biology as a junior in high school, shortly following his diagnosis with Type 1 Diabetes.

Though Julian began his undergraduate studies at the University of California, Berkeley with the intention of majoring in molecular and cell biology, he quickly discovered a love for organic chemistry, and ultimately chose to pursue a degree in chemical biology. After a brief summer research experience with Dr. Monique Cosman at the Lawrence Livermore National Lab, where he studied the stereochemistry of DNA-arene oxide adducts as it relates to the fidelity of nucleotide excision repair, he joined Prof. Carolyn Bertozzi's laboratory. Julian's work in the Bertozzi lab focused on the design and preparation of synthetically tractable difluorocyclooctyne reagents for use in copper-free azide-alkyne cycloaddition reactions.

Following completion of his undergraduate studies, Julian made the short journey to Pasadena, CA, where in July of 2008 he began his doctoral research under the guidance of Prof. Sarah E. Reisman at the California Institute of Technology. His work has focused on the development of a synthetic strategy toward dihydrooxepine-containing epipolythiodiketopiperazine natural products, such as acetylaranotin, SCH64877, and MPC1001B. On May 18th, 2013, he married his high school sweetheart, Megan, and in September 2013, they will move to Seattle, Washington, where Julian will join the medicinal chemistry department at Gilead Sciences.