ENANTIOSELECTIVE TOTAL SYNTHESIS OF DIKETOPIPERAZINE-CONTAINING NATURAL PRODUCTS: (–)-LANSAI B, (+)-NOCARDIOAZINES A AND B, AND (–)-ACETYLAPOARANOTIN

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To My Mom, Dad and Grandma
献给我的家人

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ABSTRACT

Diketopiperazine (DKP) motif is found in a wide range of biologically active natural products. This work details our efforts toward two classes of DKP-containing natural products.

Class one features the pyrroloindoline structure, derived from tryptophans. Our group developed a highly enantioselective (3 + 2) formal cycloaddition between indoles and acrylates to provide pyrroloindoline products possessing three stereocenters. Utilizing this methodology, we accomplished asymmetric total synthesis of three natural products: (–)-lansai B, (+)-nocardioazines A and B. Total synthesis of (–)-lansai B was realized in six steps, and featured an amino acid dimerization strategy. The total synthesis of (+)-nocardioazine B was also successfully completed in ten steps. Challenges were met in approaching (+)-nocardioazine A, where a seemingly easy last-step epoxidization did not prove successful. After re-examining our synthetic strategy, an early-stage epoxidation strategy was pursued, which eventually yielded a nine-step total synthesis of (+)-nocardioazine A.

Class two is the epidithiodiketopiperazine (ETP) natural products, which possesses an additional episulfide bridge in the DKP core. With the goal of accessing ETPs with different peripheral structures for structure-activity relationship studies, a highly divergent route was successfully developed, which was showcased in the formal synthesis of (–)-emethallicin E and (–)-haematocin, and the first asymmetric synthesis of (–)-acetylapoaranotin.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
AIBN	azobisisobutyronitrile
Alloc	allyloxycarbonyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
B^-	base
BARF	tetrakis(3,5-trifluoromethyl)phenylborate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphonic 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	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
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide

DCE	1,2-dichloroethane
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DKP	diketopiperazine
DMAP	4-dimethylaminopyridine
DMBA	1,3-dimethylbarbituric acid
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMDO	dimethyldioxirane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
ee	enantiomeric excess
E^+	electrophile
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
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	epidithiodiketopiperazine or epidpolythiodiketopiperazine
FAD	flavin adenine dinucleotide
g	gram(s)
G	guanine
GSH	glutathione
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
Hcy	homocysteine
HG-II	Hoveyda-Grubbs catalyst 2nd generation
HMDS	hexamethyldisilamide or hexamethyldisilazide
$h\nu$	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
LDA	lithium diisopropylamide
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)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular seives

m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
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
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
^{i}Pr	isopropyl

^{n}Pr	propyl or *norm*-propyl
psi	pounds per square inch
PyBroP	bromotripyrrolidinophosphonium hexafluorophosphate
pyr	pyridine
q	quartet
R	alkyl group
R	rectus
RCM	ring-closing metathesis
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or seconds
S	sinister
SAM	*S*-adenosyl methionine
sat.	saturated
Su	succinimide
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
temp	temperature
Teoc	trimethylsilylethoxycarbonyl
TES	triethylsilyl

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
TPP	tetraphenylporphyrin
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

Asymmetric Dearomatization via Cycloaddition Reaction[†]

1.1 INTRODUCTION

The ability to rapidly generate structural complexity remains one of the foremost challenges in synthetic organic chemistry. As such, cycloaddition reactions are highly valued for their ability to efficiently construct complex architectures in a single step. In a typical reaction, two or more unsaturated substrates are joined to form a cyclic product in which there is a net reduction of the bond multiplicity.[1] The strong enthalpic benefit of exchanging π-bonds or non-bonded electron pairs for σ-bonds is the predominant driving force for these transformations, and it typically compensates for the unfavorable entropic cost of a highly ordered transition state. Catalytic asymmetric, dearomative cycloaddition reactions are an important subclass of these transformations, as they provide rapid access to a variety of cyclic or polycyclic scaffolds in a single step and often in high

[†] Part of this chapter is submitted as a book chapter and co-written with Dr. Madeleine E. Kieffer (a graduate student in the Reisman laboratory).

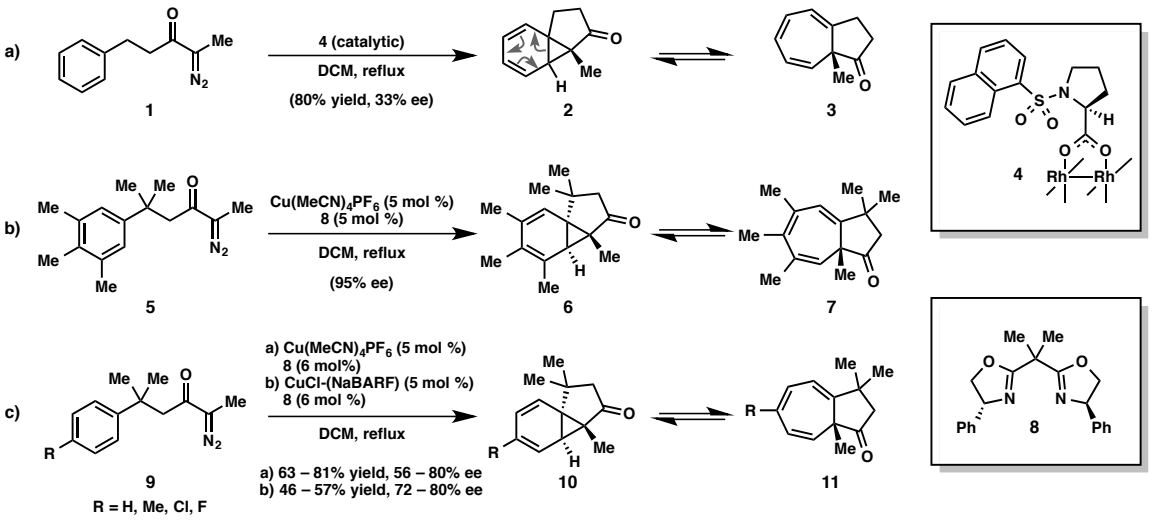
enantiomeric excess. Due in part to the potential pharmaceutical properties of heterocyclic compounds, much of the research in this field has focused on the reactions of furans, pyrroles, indoles and other heteroaromatic compounds using transition metals, Lewis acids, Brønsted acids and organo-catalysts. This chapter will cover recent advances in catalytic, asymmetric dearomatization reactions that proceed by cycloaddition.

1.2 (2 + 1) CYCLOADDITION

1.2.1 Asymmetric Büchner Reaction

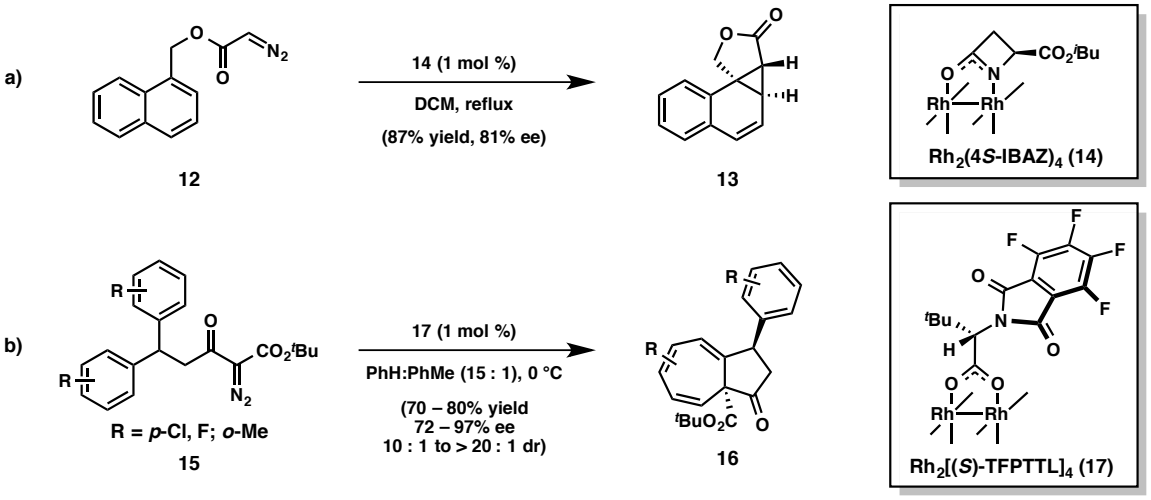
One of the most ubiquitous aromatic motifs in organic chemistry is the benzene ring. Despite its high stability, which renders it challenging to dearomatize via cycloaddition, Büchner and co-workers discovered the cyclopropanation of benzene in 1896.[2] They reported that at elevated temperatures in benzene, ethyldiazoacetate underwent thermolytic dediazotization and subsequent cyclopropanation of solvent to afford a norcaradiene product. Doering and co-workers later used nuclear magnetic resonance spectroscopy to determine that the products of the Büchner reaction were actually a mixture of cycloheptatrienes, which result from facile 6π-disrotatory ring opening of the norcaradiene followed by a series of [1,5]-hydride shift events.[3] Modern efforts to further develop this reaction and render it enantioselective have focused on transition metal-catalyzed intramolecular variants.

Scheme 1.1. *Early investigations of the asymmetric Büchner reaction*



In 1990, McKervey and co-workers reported the first catalytic, asymmetric Büchner reaction.[4] Subjection of α-diazoketone **1** to catalytic rhodium (II) carboxylate **4** provided cycloheptatriene **3** in 80% yield and 33% ee, presumably via 6π-disrotatory electrocyclic ring opening of nocaradiene product **2** (Scheme 1.1a). In a similar system, Maguire and co-workers discovered that the complex generated from $CuPF_6$ and bis(oxazoline) **8** catalyzed the cyclopropanation of α-diazoketone **5** in improved enantioselectivity (up to 95% ee, Scheme 1.1b).[5] Unfortunately, the selectivity of this transformation depends heavily on the substrate substitution pattern, and does not provide a general solution for arene cyclopropantion. In 2009, follow-up work by the same group found that addition of NaBARF further improves the ee,[6] which they suggest reveals a beneficial role of the sodium cation[7] (Scheme 1.1c). However, more detailed studies are required to elucidate the origin of this effect.

Scheme 1.2. *Asymmetric Büchner reactions in naphthyl and diaryl systems*

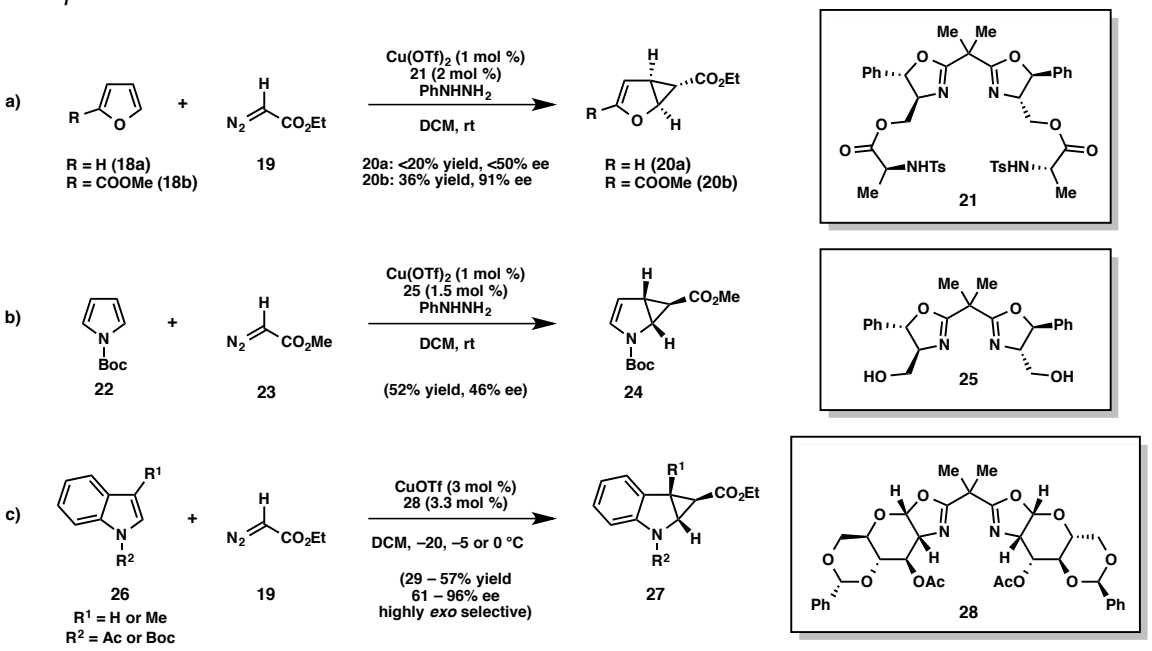


Doyle and coworkers found that $Rh_2(4S\text{-IBAZ})_4$ catalyst (**14**) could promote the intramolecular cyclopropanation of naphthyl substrate **12** in 80% yield and 81% ee (Scheme 1.2a).[8] Recently, the same group also disclosed the desymmetrization of diaryl α-diazoacetates **15** using catalytic $Rh_2[(S)\text{-TFPTTL}]_4$ (**17**, Scheme 1.2b).[9] Good to excellent enantioselectivities and high diastereoselectivity for the *trans* products were observed using *ortho*-methyl or *para*-halogenated arenes.

1.2.2 Cyclopropanation of Heterocyclic Compounds

Metal catalyzed carbenoid cyclopropanation has also been explored in heterocyclic arenes. Reiser and co-workers reported Cu/chiral bis(oxazoline)-catalyzed (2 + 1) enantioselective cycloadditions between acceptor-substituted carbenoids (diazoacetate **19** and **23**) and furans **18** or *N*-Boc-pyrrole **22** (Scheme 1.3).[10] While unsubstituted furan **18a** only provided moderate ee (<50% ee, <20% yield), good enantioselectivity (91% ee) and exclusive *exo* selectivities were observed when placing a

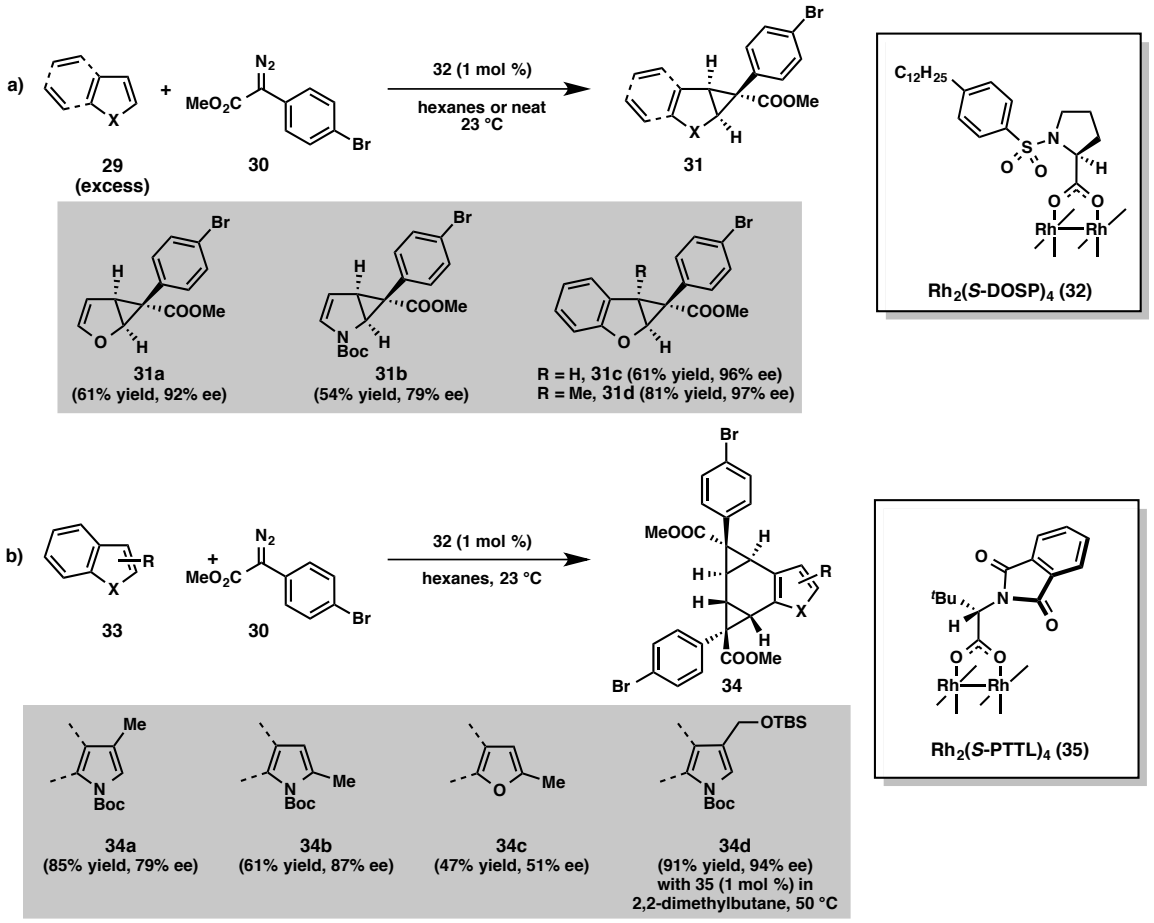
Scheme 1.3. *Copper-catalyzed asymmetric cyclopropanation of heteroarenes with acceptor-substituted carbenoids*



methyl ester at the C2 position (**18b**, Scheme 1.3a). This superior selectivity was proposed to derive from a secondary H-bonding interaction between the methyl ester and the side chain of the chiral ligand. Interestingly, the opposite facial selectivity, in moderate ee, was observed when *N*-Boc-pyrrole **22** was employed (Scheme 1.3b). Boysen and co-workers were able to further extend this cyclopropanation to *N*-acyl indole scaffolds (**26**, Scheme 1.3c).[11] Using novel carbohydrate-derived bis(oxazoline) ligand **28**, *N*-Boc-3-methylindole **26** undergoes smooth cyclopropanation to give *exo* indoline **27** in 96% ee, while moderate enantioselectivities were observed in other substrates. This methodology was successfully applied to the total synthesis of (–)-desoxyeseroline.

Cyclopropanation between donor-acceptor-substituted carbenoids and heterocycles has also been reported. Davies and co-workers extensively studied the

Scheme 1.4. *Rhodium-catalyzed asymmetric cyclopropanation of heteroarenes with donor-acceptor-substituted carbenoids*



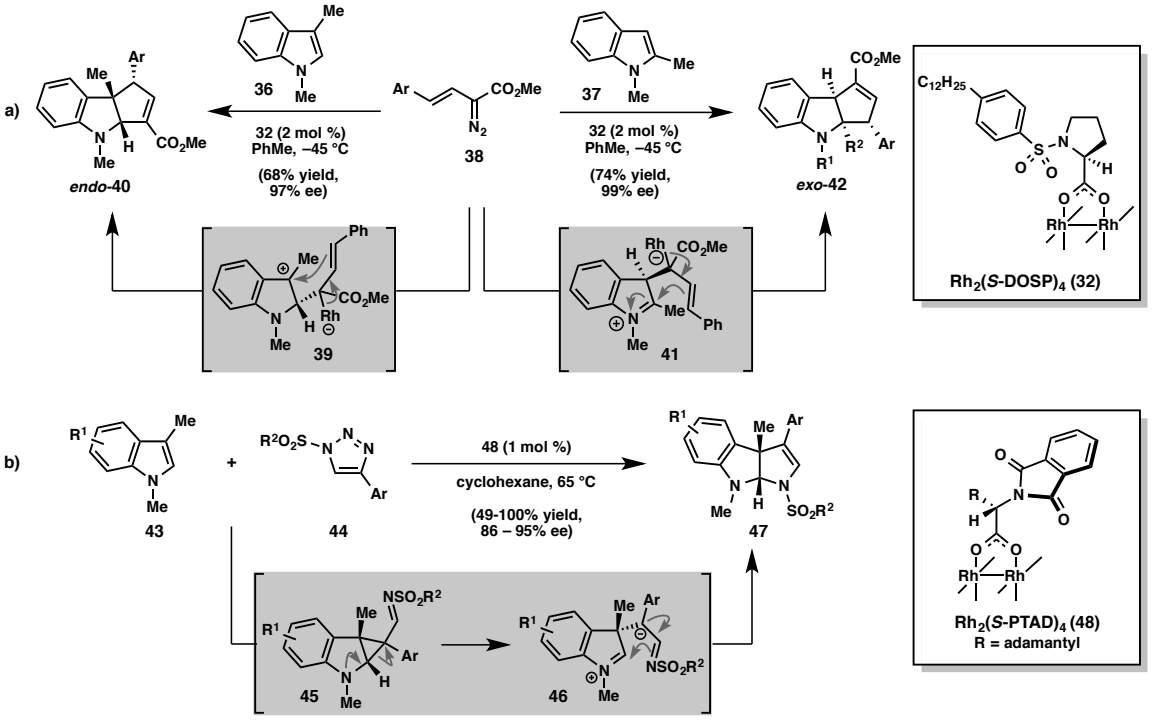
ability and propensity of diazoacetate **30** to cyclopropanate a variety of aromatic heterocycles (Scheme 1.4).[12] In contrast to the Cu-catalyzed reactions of acceptor-substituted carbenoids discussed previously, double cyclopropanation of the heteroarenes was observed with these carbenoids (Scheme 1.4b). The monocyclopropanation product could be only isolated as the major product when an excess of the heterocyclic starting material was employed (Scheme 1.4a). Rh_2(*S*-DOSP)$_4$ (**32**) was identified as the catalyst of choice to promote enantioselective cyclopropanation of furan, *N*-Boc-pyrrole, and 3-methylbenzofuran. Interestingly, double cyclopropanation on the benzenoid ring was

observed with substituted indole and 2-methylbenzofuran substrates (**34a–34d**), while unsubstituted *N*-Boc indole was less reactive and resulted in carbene dimerization.

1.3 (3 + 2) CYCLOADDITION

The unique chemistry of indoles, which possess reactivity analogous to enamines but are hydrolytically stable, has resulted in their extensive use in the development of cycloaddition and formal cycloaddition reactions. Although these types of transformations have been known for decades, it was only recently that catalytic, asymmetric variants were developed.

Scheme 1.5. *Rhodium-catalyzed enantioselective functionalization of indoles*

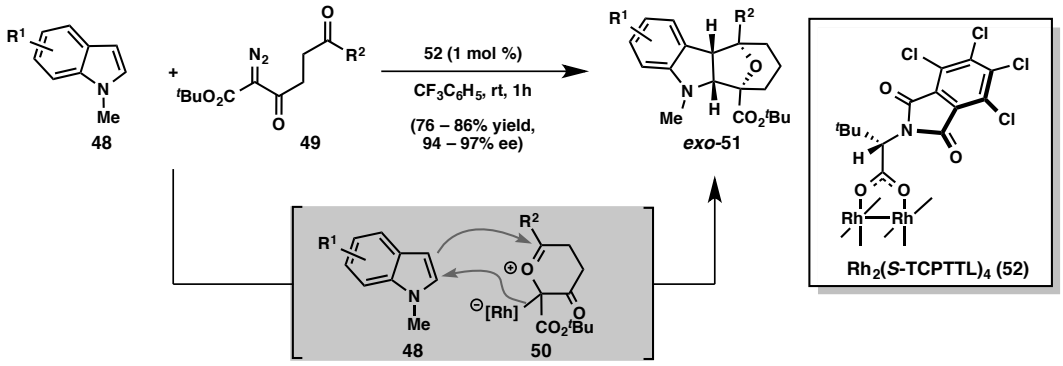


In 2009, Davies and co-workers reported that treatment of indoles with vinyl diazoacetate **38** in the presence of rhodium catalyst **32** results in formal (3 + 2)

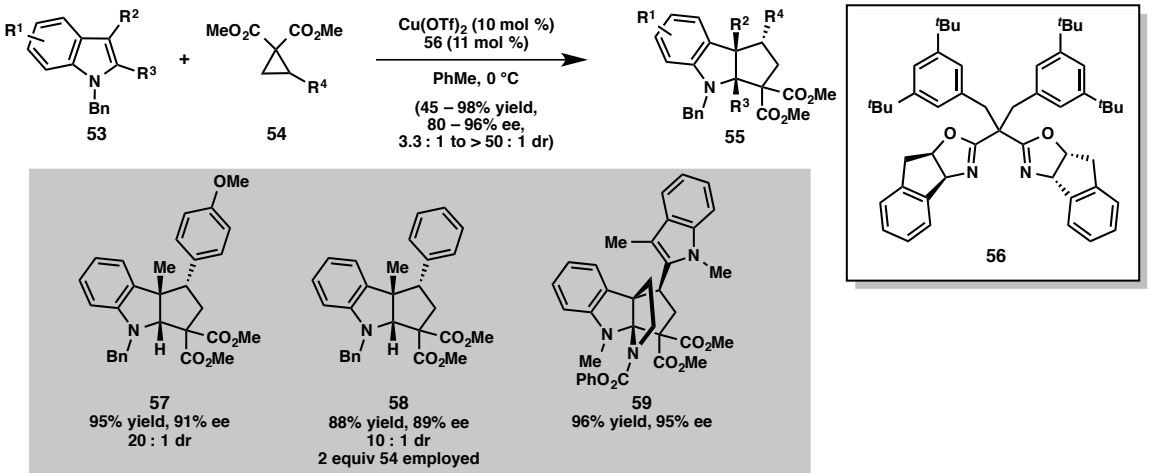
cycloaddition to provide fused tricyclic products (Scheme 1.5a).[13] Interestingly, the substitution pattern of the indole starting material greatly affects the product of this reaction. Whereas 1,3-dimethylindole (**36**) gives rise to indoline **40**, the isomeric 1,2-dimethylindole (**37**) delivers indoline **42**; both reactions occur with good to excellent diastereo- and enantioselectivity. The authors rationalize these divergent reactivities by the steric encumberance of the C2- or C3-methyl substituent, which forces the initial nucleophilic attack to occur at the unsubstituted position of the indole. The same group later disclosed that in the presence of rhodium catalyst **48**, 1-phenylsulfonyl triazoles **44** can be used to generate α-iminocarbenoids *in situ*, which react with 1,3-dimethyl indoles (**43**) to furnish pyrroloindolines (**47**) in good yields and high enantioselectivities (Scheme 1.5b).[14] In the contrast to the zwitterionic mechanism proposed in the previous reaction, the authors suggest that this reaction might proceed through initial cyclopropanation to form **45**, followed by cyclopropane opening and iminium trapping to afford the formal (3 + 2) cycloaddition product **47**.

Hashimoto and co-workers have investigated the Rh-catalyzed (3 + 2) cycloaddition reactions between *N*-methylindoles and 2-diazo-3,6-diketoesters **49** to prepare tetracyclic products (**51**), presumably via Rh-bound carbonyl ylide **50** (Scheme 1.6).[15] Polychlorinated dirhodium complex **52** was found to catalyze the formation of *exo*-tetracycle **51** in good yields and high enantioselectivities. Whereas the reaction tolerates substitution of the indole backbone, use of the analogous 2-diazo-3,5-diketoesters results in significantly lower enantioinduction. This is the only report of an asymmetric dearomatization reaction that proceeds by cycloaddition with a carbonyl ylide.

Scheme 1.6. *Rhodium-catalyzed (3 + 2) cycloaddition between indoles and diazodiketoesters*



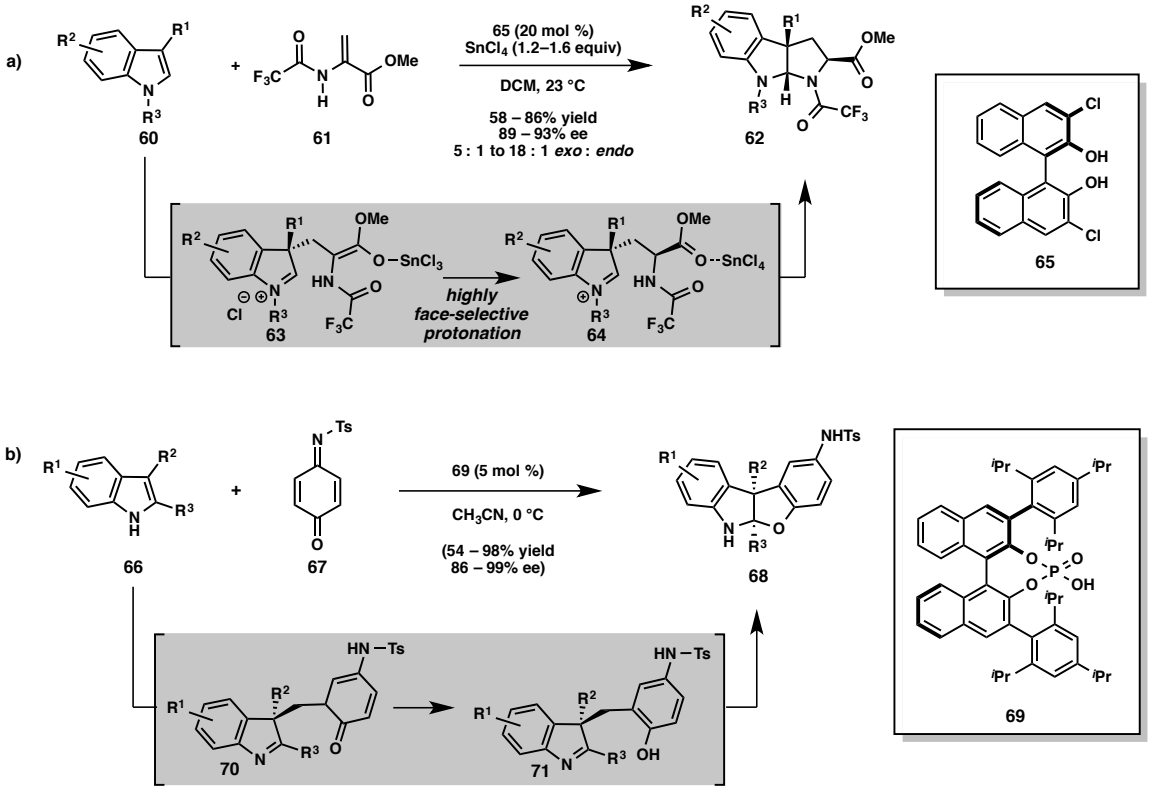
Scheme 1.7. *Asymmetric (3 + 2) cycloaddition of indoles and donor-acceptor cyclopropanes*



Donor-acceptor cyclopropanes have also been explored as dipoles in asymmetric (3 + 2) cycloaddition reactions (Scheme 1.7). Tang and co-workers found that these substrates participate in highly diastereo- and enantioseletive annulations of indoles when chiral Cu(II)-BOX complexes are used as catalysts.[16] When di-benzyl linked BOX ligand **56** is employed, a variety of substituted indoles (**53**) and aryl-substituted cyclopropanes (**54**) react to produce enantioenriched indoline products (**55**). Whereas cyclopropanes bearing electron-rich arenes react through a mechanism in which both enantiomers converge to a single diastereomer of highly enantioenriched product (e.g. **57**),

cyclopropanes bearing less electron-rich arenes undergo kinetic resolution, with only the (*R*)-configured cyclopropane proceeding to product (e.g. **58**). This methodology was successfully applied to prepare the core of the natural product borreverine (**59**).

Scheme 1.8. *Formal enantioselective (3 + 2) cycloadditions of indoles*

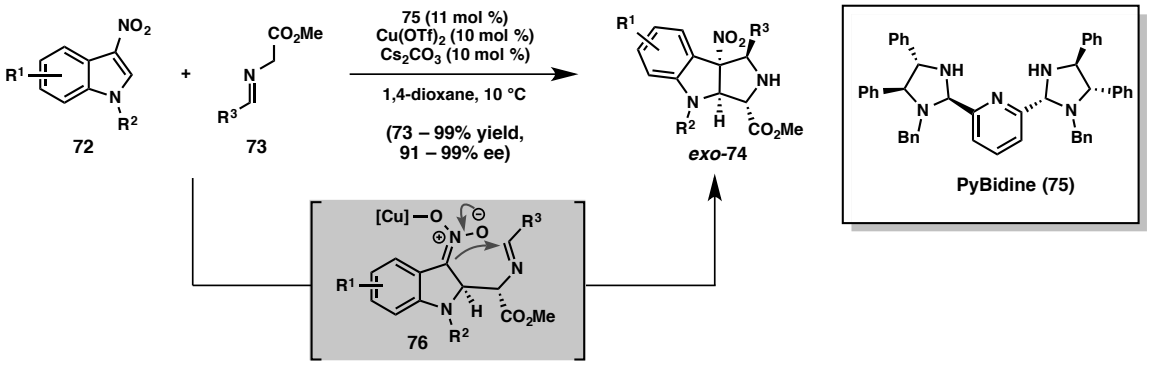


Reisman and coworkers developed a formal (3 + 2) cycloaddition between methyl 2-trifluoroacetamidoacrylate (**61**, Scheme 1.8a) and 3-substituted indoles (**60**).[17,18] Although the reaction requires stoichiometric $SnCl_4$, the chiral diol (*R*)-3,3'-dichloro-BINOL (**65**) is employed catalytically. A variety of indole substrates undergo cycloaddition with acrylate **61** to provide highly functionalized pyrroloindolines (**62**) in excellent enantioselectivities, favoring the *exo* diastereomer. Mechanistically, the reaction is proposed to proceed through cooperative Lewis acid–Brønsted acid activation. Activation of acrylate **61** by $SnCl_4$ results in nucleophilic attack of the indole to generate

a tin enolate (**63**). A catalyst-controlled protonation of the enolate by $SnCl_4$·**65** followed by cyclization affords the enantioenriched pyrroloindoline (**62**) in good yield with high diastereoselection and excellent ee.

Quinone monoimines (**67**, Scheme 1.8b) have also been found to engage in asymmetric cycloaddition reactions with indoles. Zhang and co-workers reported that chiral phosphoric acid **69** catalyzes the conjugate addition of indoles (**66**) to quinone monoimine **67**.[19] Subsequent rearomatization of enamide intermediate **70** followed by phenol cyclization furnishes benzofuroindoline products (**68**). This method tolerates a wide range of substitution on the indoles and generally proceeds with excellent enantioselectivities.

Scheme 1.9. *Formal enantioselective (3 + 2) cycloadditions between 3-nitroindoles and iminoesters*



The aforementioned (3 + 2) cycloaddition reactions generally rely on the intrinsic nucleophilicity of the C3 site of indole to initiate reactivity. Alternatively, Arai and co-workers discovered a cascade reaction between 3-nitroindoles and iminoesters that proceeds by initial Cu-catalyzed attack of an iminoenolate at C2 of the indole to generate nitronate **76** (Scheme 1.9).[20] Subsequent intramolecular nitro-Mannich addition provides indoline **74** in a highly enantio- and diastereoselective fashion. The authors suggest that

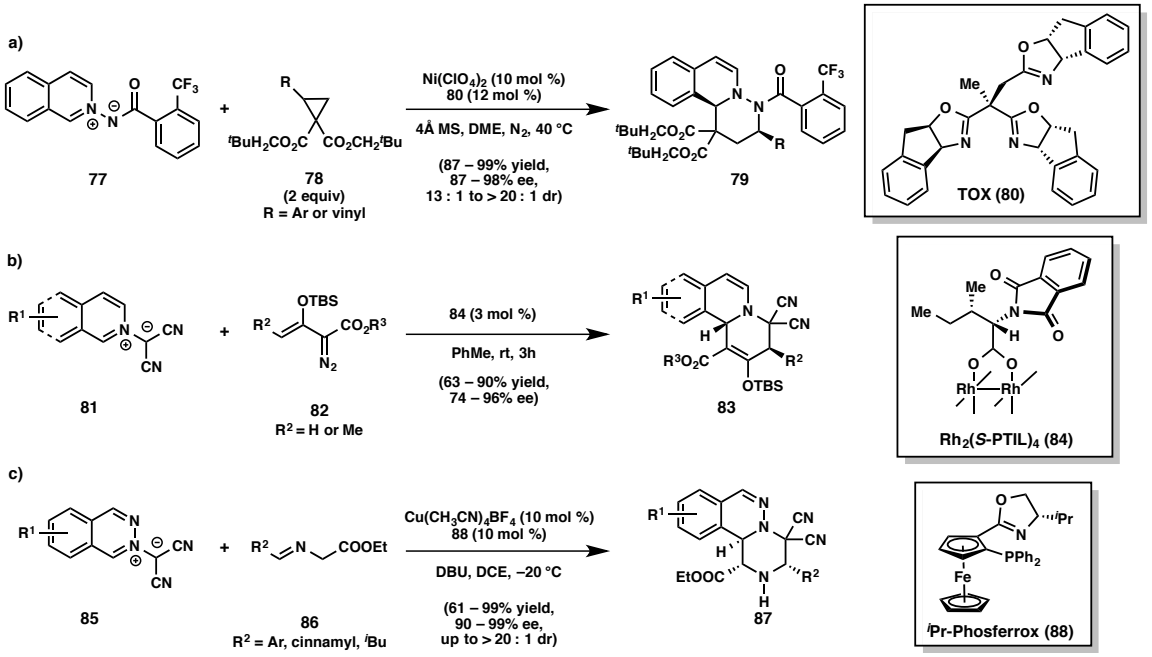
the presence of electron-withdrawing substituents at the N1 and C3 positions of indole are required to render these substrates sufficiently electrophilic at C2.

1.4 (3 + 3) CYCLOADDITION

Few examples of asymmetric dearomatization via (3 + 3) cycloaddition reactions have been reported in the literature. In 2013, Tang and co-workers reported a highly enantioselective cycloaddition between isoquinoline-derived dipole **77** and donor-acceptor cyclopropanes **78** (Scheme 1.10a).[21] Lewis acid activation of cyclopropane **78**, presumably through bidentate coordination to chiral Ni(II)-TOX catalyst (generated from **80)**, results in nucleophilic attack by azomethine imine **77**. Control experiments reveal that the reaction proceeds by a kinetic resolution of the cyclopropane, in which the *(S)*-enantiomer reacts more quickly. In order to obtain high yields of product, two equivalents of cyclopropane **78** are employed under standard conditions.

The Doyle group developed a highly enantioselective formal (3 + 3) cycloaddition between isoquinolinium or pyridinium methylides (**81**) and enol diazoacetate **82** (Scheme 1.10b).[22] Chiral dirhodium complex **84**, in conjunction with enol diazoacetate **82**, is proposed to form a chiral metallo-1,3-dipole, which can then undergo (3 + 3) cycloaddition to form a variety of quinolizidines (**82**) with good enantioinduction. Recently, the Guo group demonstrated an enantioselective (3 + 3) cycloaddition reaction between phthalazinium dicyanomethanides (**85**) and iminoesters (**86**), catalyzed by a Cu(I)/^{i}Pr-Phosferrox complex (**88**, Scheme 1.10c).[23] The authors propose that iminoester **86** is activated by the chiral Cu(I) complex to generate a metallo-1,3-dipole, which undergoes cycloaddition with phthalazinium dicyanomethanide **85**. This mild method

Scheme 1.10. *Catalytic, asymmetric (3 + 3) dearomatizing cycloaddition reactions*



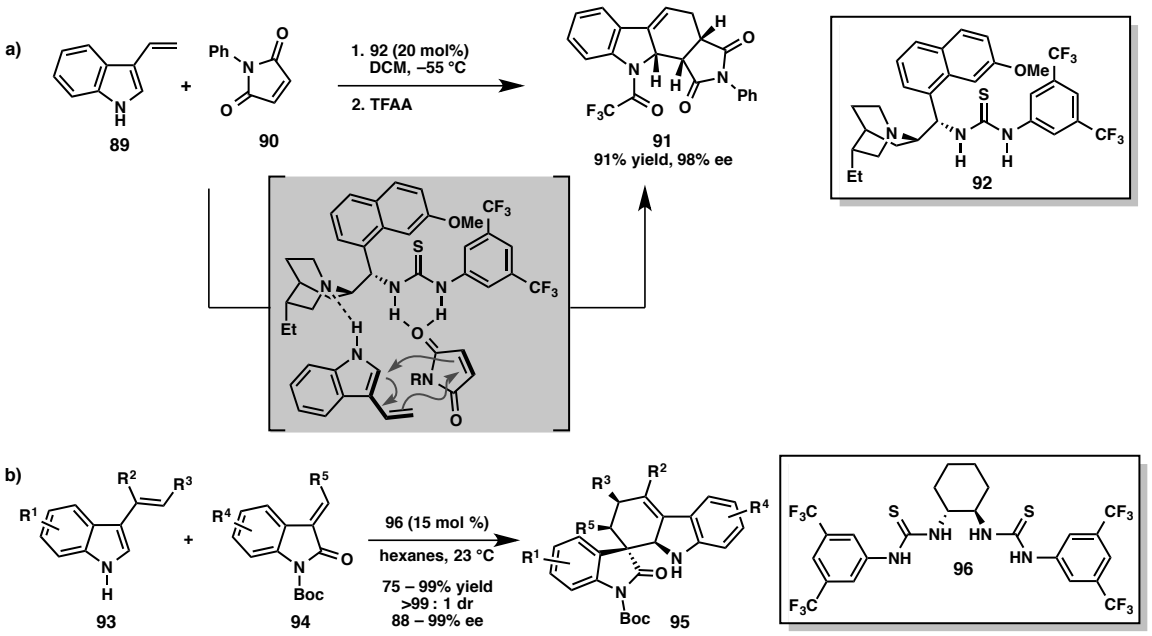
tolerates a wide range of aryl groups on the iminoester, as well as cinnamyl and isobutyl groups, and provides tricyclic compounds (**87**) in high yields with excellent diastereo- and enantioselectivities.

1.5 (4 + 2) CYCLOADDITION

Despite the large number of catalytic asymmetric Diels–Alder reactions developed to date, relatively few examples involve dearomatization. In 2008, Bernardi, Ricci, and co-workers reported the first catalytic, asymmetric Diels–Alder reaction of 3-vinyl indoles (**89**) with assorted dienophiles (e.g. **90**, Scheme 1.11a).[24] Utilizing hydrogen-bonding catalyst **92**, a variety of tetrahydrocarbazole products (**91**) could be formed in good yields and excellent enantioselectivities. The authors hypothesize that the reaction proceeds through a cooperative mechanism involving Brønsted base

activation of the 3-vinyl indole and hydrogen bond activation of the dieneophile. When a mixture of (*E*)- and (*Z*)-3-(prop-1-en-1-yl)-1*H*-indole is subjected to the reaction conditions, only the *E*-diene proceeds to product; the *Z*-diene, in which the required *S-cis* conformation is disfavored, is recovered unchanged. These findings provide empirical support for a concerted mechanism.

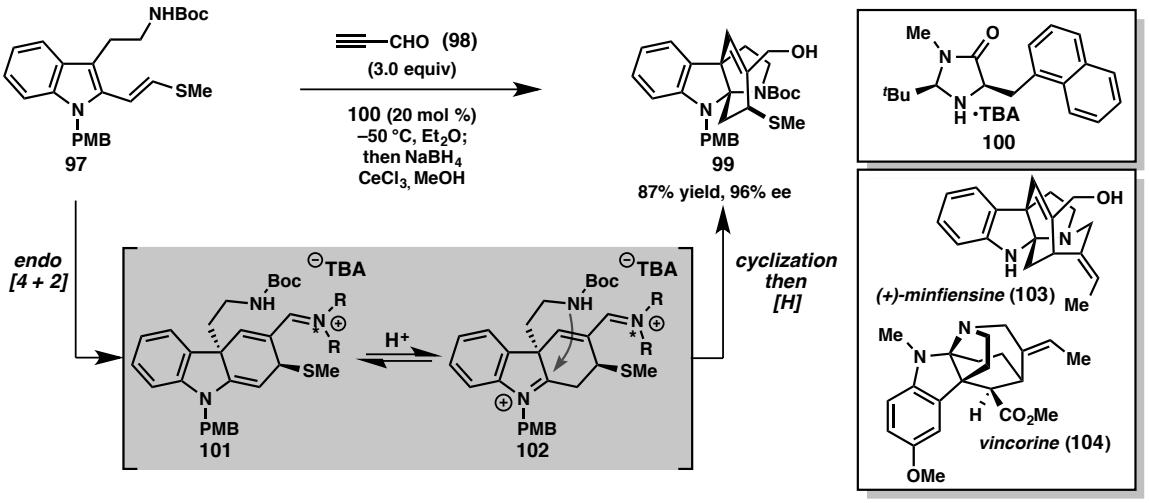
Scheme 1.11. *Organocatalytic asymmetric Diels–Alder reactions of 3-vinyl indoles*



A similar approach was successfully employed by Barbas and co-workers (Scheme 1.11b).[25] Bisthiourea **96** was found to catalyze an exceedingly mild Diels–Alder reaction between 3-vinyl indoles (**93**) and 3-methyleneindolinones (**94**) for the direct synthesis of complex carbazolespirooxindoles (**95**). The products were isolated in nearly quantitative yield and with excellent enantio- and diastereoselection.

In 2009, MacMillan and co-workers disclosed a nine-step total synthesis of (+)-minfiensine (**103**, Scheme 1.12).[26] Key to their synthesis was the development of an

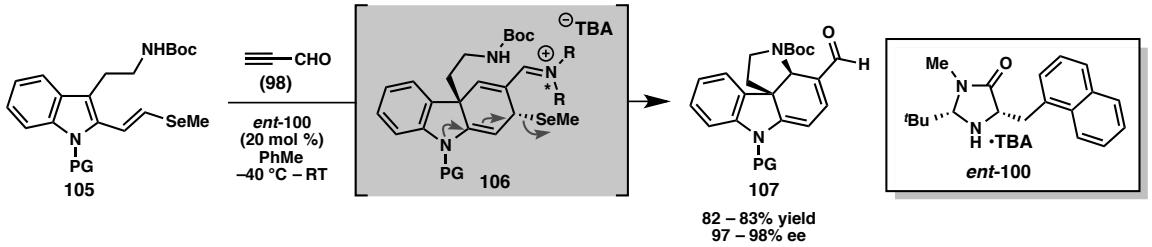
Scheme 1.12. *Organocatalytic asymmetric Diels–Alder/cyclization cascade reaction*



organocatalytic Diels-Alder/cyclization cascade reaction to construct the pyrroloindoline core of the molecule. The reaction is proposed to proceed via condensation of organocatalyst **100** with propynal (**98**) to generate an activated iminium ion, which enables an asymmetric, *endo*-selective Diels–Alder cycloaddition with diene **97** to give **101** and set the stereochemistry of the all-carbon quaternary center. Isomerization to iminium **102** followed by cyclization of the pendant amine and hydrolytic release of the catalyst provides the pyrroloindoline core. A reductive quench reduces the aldehyde to alcohol **99**, which can be further advanced to (+)-minfiensine (**103**) in only five steps. Using a similar cascade sequence, MacMillan and co-workers were also able to synthesize vincorine (**104**) in only nine steps, setting three of the four stereogenic centers in a single cascade reaction.[27]

This catalytic asymmetric dearomative cascade strategy was further applied to members of the strychnos, aspidosperma, and kopsia alkaloids.[28] In the key cascade reaction, the asymmetric (4 + 2) is followed by β-elimination of methyl selenide and

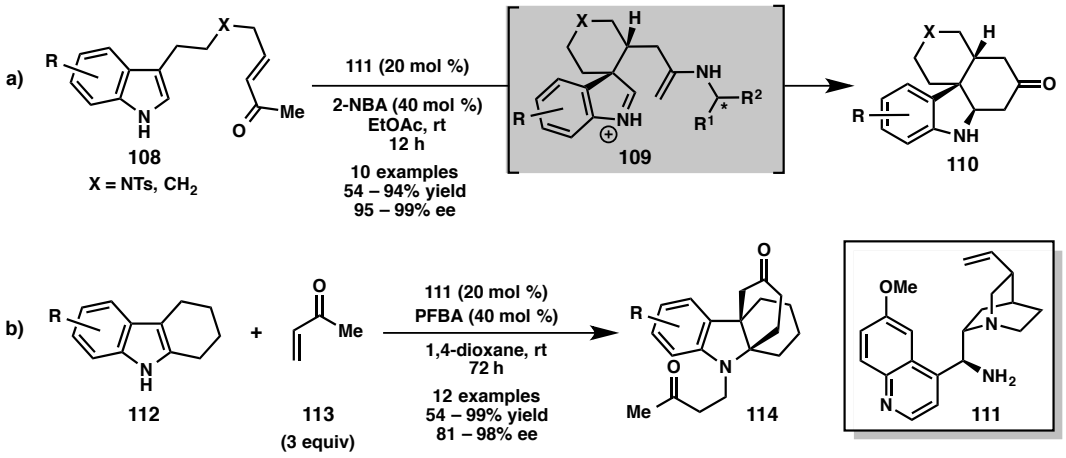
Scheme 1.13. *Organocatalytic asymmetric Diels–Alder/elimination/conjugate addition cascade reaction*



conjugate addition of the pendant amine to access tetracycle **107** (Scheme 1.13). From this common intermediate, MacMillan and co-workers successfully synthesized six structurally distinct alkaloid natural products. An analogous sequence employing an ynone instead of an ynal was used to produce (–)-minovincine.[29]

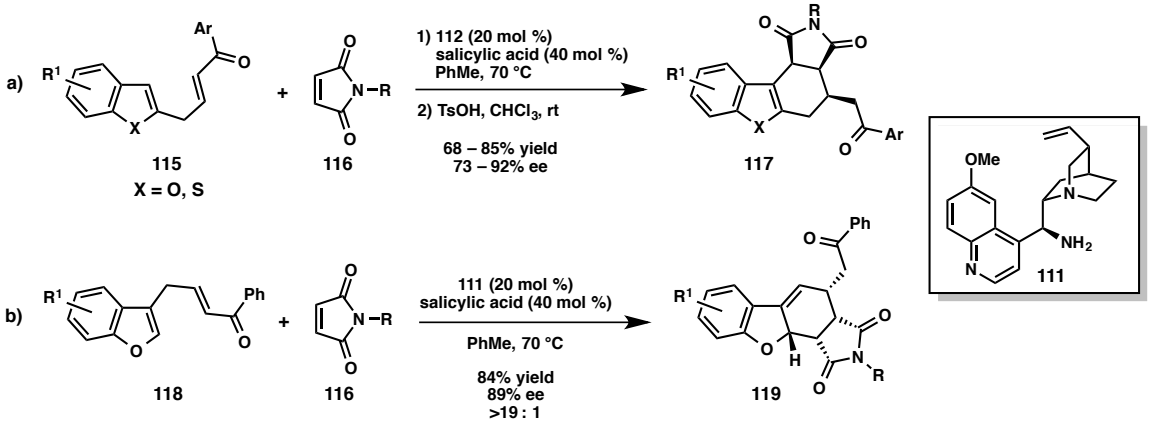
You and co-workers have developed formal (4 + 2) cycloadditions to prepare enantioenriched polycycles, which proceed by a tandem Michael addition/Mannich reaction sequence. In 2011, they reported that cinchona alkaloid **111** catalyzes the intramolecular, dearomative cycloaddition of indolyl enones (**108**) to provide tricycles (**110**) bearing three stereogenic centers (Scheme 1.14a).[30] The reaction exhibits a broad substrate scope and delivers products under mild conditions and in excellent enantioselectivities. Using similar conditions, they subsequently developed an intermolecular formal (4 + 2) cycloaddition between 2,3-disubstituted indoles (**112**) and methylvinylketone (**113**, Scheme 1.14b).[31] The tetrahydrocarbazole products **114** are produced in good yields and excellent selectivities.

Scheme 1.14. *Organocatalytic asymmetric Michael addition/Mannich cyclization cascade reactions*



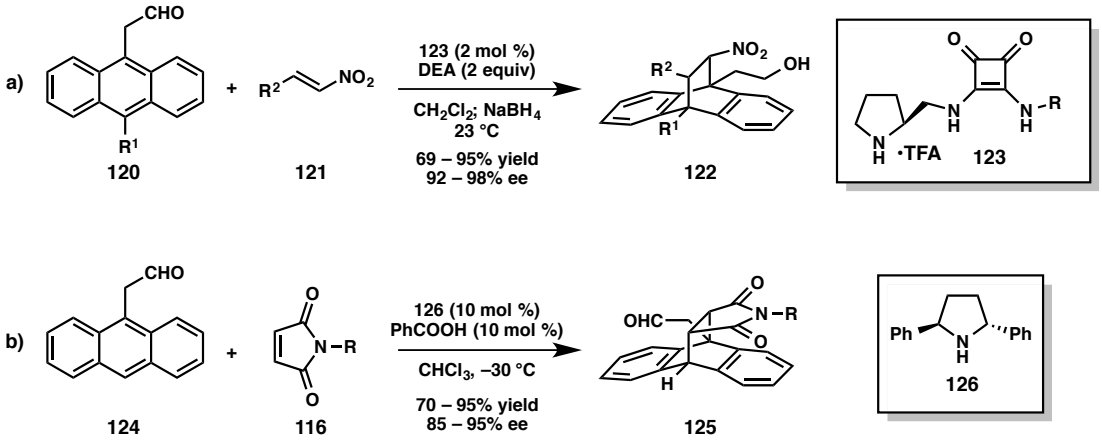
In 2014, Chen and co-workers also utilized alkaloid **111** to catalyze (4 + 2) cycloaddition reactions of heteroaryl enones (**115**, Scheme 1.15).[32] The reaction proceeds through the *in situ* generation of a trienamine species, which is proposed to result in a HOMO-activated diene. Subsequent selective (4 + 2) cycloaddition with electron deficient dienophiles delivers the observed product (**117**, **119**). C2- and C3-linked heteroaryl enones (**115** and **118**, respectively) are competent in the transformation; however, the C2-linked substrates exhibit a broader substrate scope. The polycyclic products are isolated in good yields and selectivities.

Scheme 1.15. *Organocatalytic asymmetric intermolecular Diels-Alder reactions of heteroaryl enones*



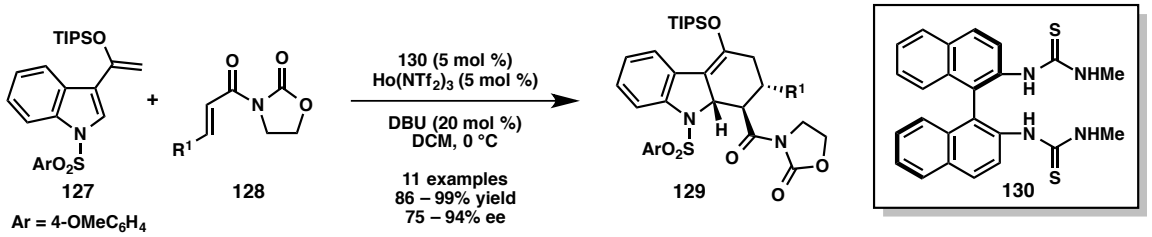
Organocatalysis has also been utilized to effect dearomative Diels–Alder reactions of anthracenylacetaldehydes (Scheme 1.16, **120** and **124**). In 2012, Jørgenson and co-workers reported the first asymmetric example of this transformation, which like the previously discussed reaction developed by Chen, utilizes a HOMO-raising strategy.[33] Good selectivity is achieved with bifunctional catalyst **123**, which is proposed to operate through a cooperative mechanism involving enamine formation with the aldehyde (**120**) and H-bond activation of the nitroalkene (**121**). A variety of (4 + 2) adducts are isolated in good yields and excellent enantioselectivities. Follow-up studies identified C2-symmetric catalyst **126**, which enabled the use of maleimides as dienophiles (**124**).[34] With this symmetric dienophile, the use of a bifunctional catalyst did not provide improved results.

Scheme 1.16. *Organocatalytic dearomative Diels-Alder reactions with anthracenylacetaldehydes*



As an alternative to organocatalysis, Nishida and co-workers disclosed the use of a novel, chiral holmium(III) complex to catalyze an enantioselective Diels–Alder reaction of 3-enoxy-indoles (**127**, Scheme 1.17).[35] Using only 5 mol % of $Ho(NTf_2)_3$·**130**, carbazole products (**129**) are isolated in excellent yields and with good enantioinduction.

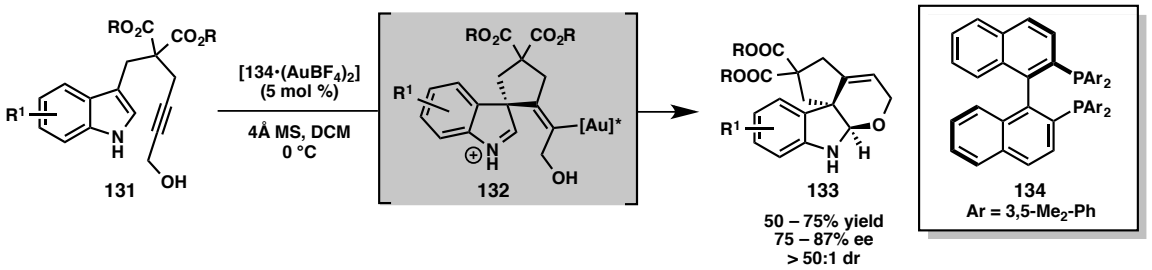
Scheme 1.17. *Holmium(III)-catalyzed enantioselective Diels-Alder reactions*



Additionally, the silylenol ether functionality was found to preclude deleterious air oxidation and 1,3-hydride shifts that can result in rearomatization of the indole ring and loss of chiral information. The silylenol ether products (**129**) could be further functionalized to afford polycycles with four contiguous stereocenters in only two steps.

Bandini and co-workers employed a chiral gold catalyst to effect the dearomatization of indoles through an intramolecular, step-wise (4 + 2) cycloaddition (Scheme 1.18).[36] Subjection of alkynyl indole precursors (**131**) to chiral dinuclear gold catalyst $(AuBF_4)_2 \cdot$**134** resulted in 5-*exo*-dig hydroindolination of the alkyne followed by iminium trapping to afford tetracyclic products (**133**) in good yields and moderate selectivities. When the corresponding tryptamine-dervied substrates were employed, 7-*endo*-dig selectivity was observed.

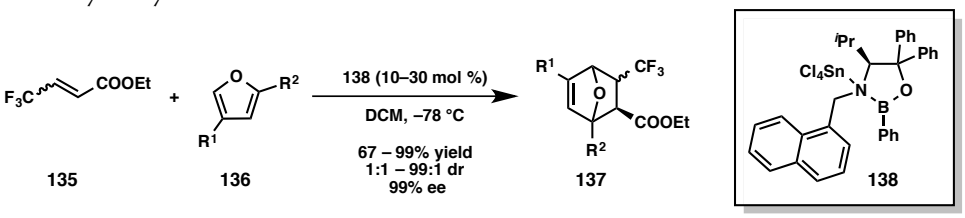
Scheme 1.18. *Gold-catalyzed intramolecular formal (4 + 2) cycloaddition reactions*



Furans have also been found to undergo catalytic asymmetric (4 + 2) cycloaddition reactions. In 2012, Shibatomi and co-workers utilized a Lewis acid-

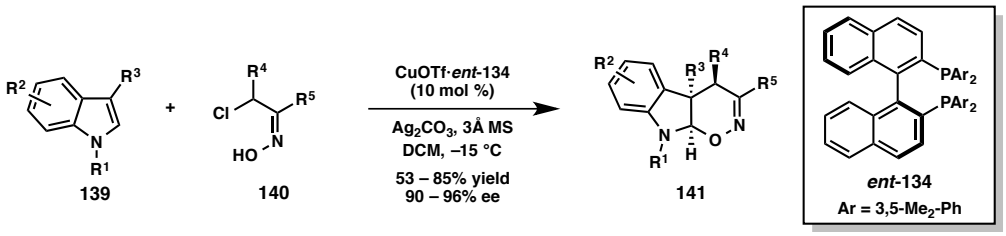
activated oxazaborolidine catalyst (**138**, Scheme 1.19) to promote an asymmetric Diels–Alder cycloaddition between furans (**136**) and β-trifluoromethylacrylates.[37] The fluorine-containing bicycles **137** were produced in good yield with moderate diastereoselection and excellent enantioselection. Substituents are tolerated at the C2- and C3-position of the furan; β-difluoromethylacrylates are also suitable dienophiles. The cycloaddition products could be further elaborated to fluorinated bioactive compounds.

Scheme 1.19. *Asymmetric Diels-Alder cycloaddition reactions of furans and β-trifluoromethylacrylates*



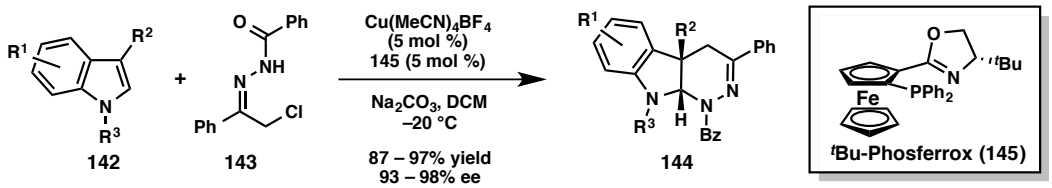
Recently, Larinov and co-workers disclosed the first example of a catalytic, enantioselective (4 + 2) annulation with highly reactive nitrosoalkenes (Scheme 1.20).[38] These alkenes were generated in-situ from 2-chlorooxime precursors (**140**), which then underwent Cu-catalyzed, asymmetric, inverse demand hetero-Diels–Alder reactions with 1,3-disubstituted indoles (**139**). The use of stoichiometric silver salts enabled catalysis through the sequestration of chloride ion. These (4 + 2) cycloadditions provide structurally unique heterocycles (**141**) in highly enantioenriched form.

Scheme 1.20. *Enantioselective (4 + 2) cycloaddition reactions of indoles and nitrosoalkenes*



A similar reaction was disclosed by Wang and co-workers in which copper catalyzes the asymmetric hetero-Diels–Alder reaction between indoles and α-halogenated hydrazones (Scheme 1.21).[39] In analogy to the generation of nitrosoalkenes from α-halooximes, it is proposed that coordination of hydrazone **143** to the chiral catalyst **145** followed by base-induced elimination of chloride generates the catalyst-bound azoalkene *in situ*, which undergoes (4 + 2) cycloaddition with a variety of indoles to furnish the 2,3-fused indoline products (**144**) in excellent yields and selectivities. The selectivities observed in this transformation are remarkable given the extremely facile un-catalyzed background reaction.

Scheme 1.21. *Enantioselective (4 + 2) cycloaddition reactions of indoles and α-halogenated hydrazones*

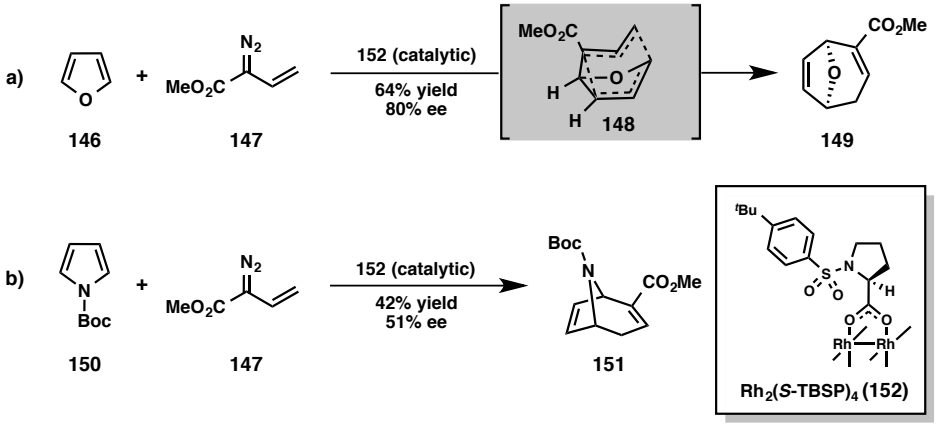


1.6 (4 + 3) CYCLOADDITION

In 1996, Davies and co-workers disclosed their efforts to develop a Rh-catalyzed asymmetric formal (4 + 3) cycloaddition between furan (**146**) and vinyldiazoester **147**.[40] They hypothesized this reaction could proceed via an initial enantioselective cyclopropanation followed by a Cope rearrangement to give bicyclic product **149** (Scheme 1.22). Using Rh_2(*S*-TBSP)$_4$ (**152**) as the catalyst, they were able to isolate the desired product in moderate yields and 80% ee. Although these conditions were limited in scope, they identified a more general solution through the use of chiral esters. Similar

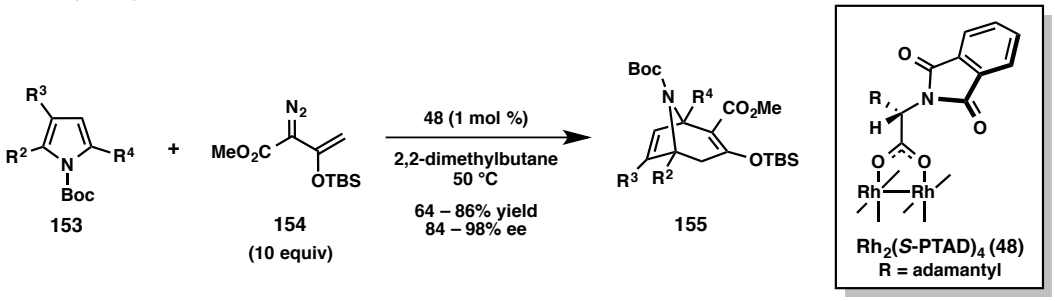
reactivity and selectivity issues were encountered when employing pyrroles, providing tropane products in low enantiomeric excess (Scheme 1.22b).[41]

Scheme 1.22. *Preliminary studies of asymmetric Rhodium-catalyzed (4 + 3) cycloaddition reactions of heteroarenes and vinyldiazoesters*



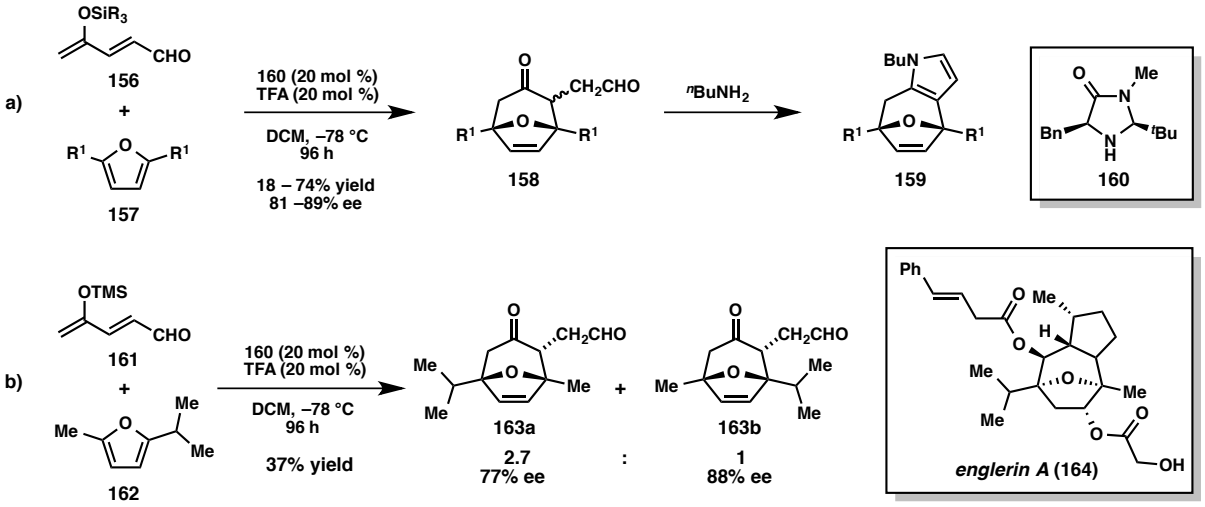
Ten years later, Davies and co-workers reported that the use of 2-(siloxy)vinyldiazoacetate **154** as a Rh-carbenoid precursor enables highly enantioselective formal (4 + 3) cycloaddition reactions of *N*-Boc-pyrroles (**153**, Scheme 1.23). The best selectivities were obtained using Rh_2(*S*-PTAD)$_4$ (**48**) as the catalyst.[42] This catalyst system was compatible with a variety of substituted *N*-Boc-pyrroles, providing functionalized tropanes (**155**) in good yields and excellent enantioselectivities.

Scheme 1.23. *Asymmetric Rh-catalyzed (4 + 3) cycloaddition reactions of pyrroles and siloxyvinyldiazoacetates*



Inspired by MacMillan's work on secondary amine-catalyzed (4 + 2) cycloadditions, Harmata and co-workers described the first organocatalytic asymmetric (4 + 3) cycloaddition (Scheme 1.24a).[43] Imidazolidinone **160** was found to catalyze the cycloaddition between disubstituted furans (e.g. **157**) and siloxydienals (e.g. **156**) to produce oxa-bicycl[3.2.1]octanones (e.g. **158**) in modest to good yields and enantioselectivities. The major side products of this reaction were alkylated furan derivatives, suggesting a step-wise cycloaddition mechanism. This methodology was subsequently employed by Lin and co-workers in their synthesis of core of englerin A (**164**).[44] Although the regioselectivity of the cycloaddition with differentially-substituted furan **162** was poor, providing a mixture of **163a** and **163b**, the desired product was produced in promising enantioselectivity (Scheme 1.24b).

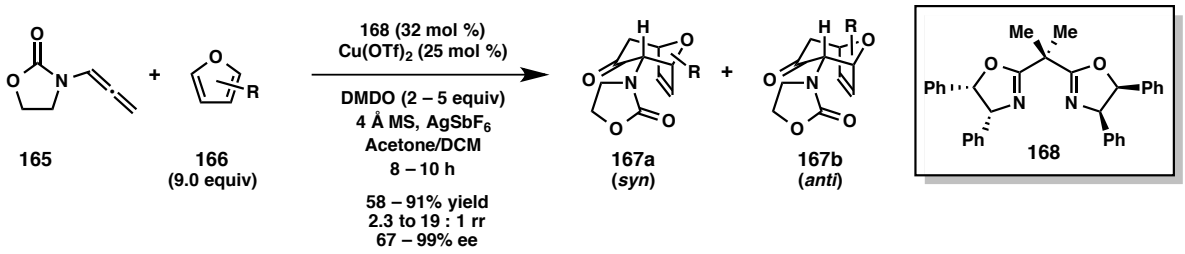
Scheme 1.24. *Organocatalytic (4 + 3) cycloaddition reactions of furans*



In 2004, a chiral Lewis acid-catalyzed (4 + 3) cycloaddition between furans and alleneamides was reported by Hsung and co-workers (Scheme 1.25).[45] The reaction occurs by *in situ* oxidative generation of a nitrogen-stabilized oxyallyl cation from

alleneamide **165**. Following (4 + 3) cycloaddition with furan **166**, the tricyclic products were isolated in moderate to good yields and enantioselectivities. The level of regioselectivity for the *syn* versus *anti* isomer of the product varied, and depended on the substitution pattern. It is proposed that enantioinduction occurs via coordination of the oxyallyl cation to $Cu(OTf)_2$·**168**, providing facial differentiation for the incoming diene. The scope of this reaction is complementary to that of Harmata (see above), as 2,5-*un*substituted furans provide the best yields and selectivities.

Scheme 1.25. *Copper-catalyzed asymmetric (4 + 3) cycloaddition reactions of furans*



1.7 CONCLUDING REMARKS

Over the past three decades, significant progress has been made in the development of new, catalytic asymmetric cyloaddition reactions of arenes. Yet, most of the progress to date has focused on the cycloadditions of heteroarenes, and indoles in particular. These systems benefit from a lower aromatic stabilization energy, relative to benzene, and thus a lower enthalpic cost to dearomatization. In essence, heteroarenes represent the "low hanging fruit." Moving forward, the discovery of novel modalities for enantioselective dearomatization reactions will be an important area of research, particularly as we seek to develop synthetically useful transformations for the dearomatization of non-hetero arenes.

Nevertheless, recently development of catalytic dearomatization transformation has introduced new and powerful synthetic tools to quickly assemble complex natural products. Chapters 2 and 3 will focus on the direct application of enantioselective formal (3 + 2) cycloaddition reaction developed in our lab (Scheme 1.8a) to access pyrroloindoline-containing diketopiperazine natural products.

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Chapter 2

Direct Application of Enantioselective (3 + 2) Formal Cycloaddition: Concise Enantioselective Total Synthesis of (–)-Lansai B[†]

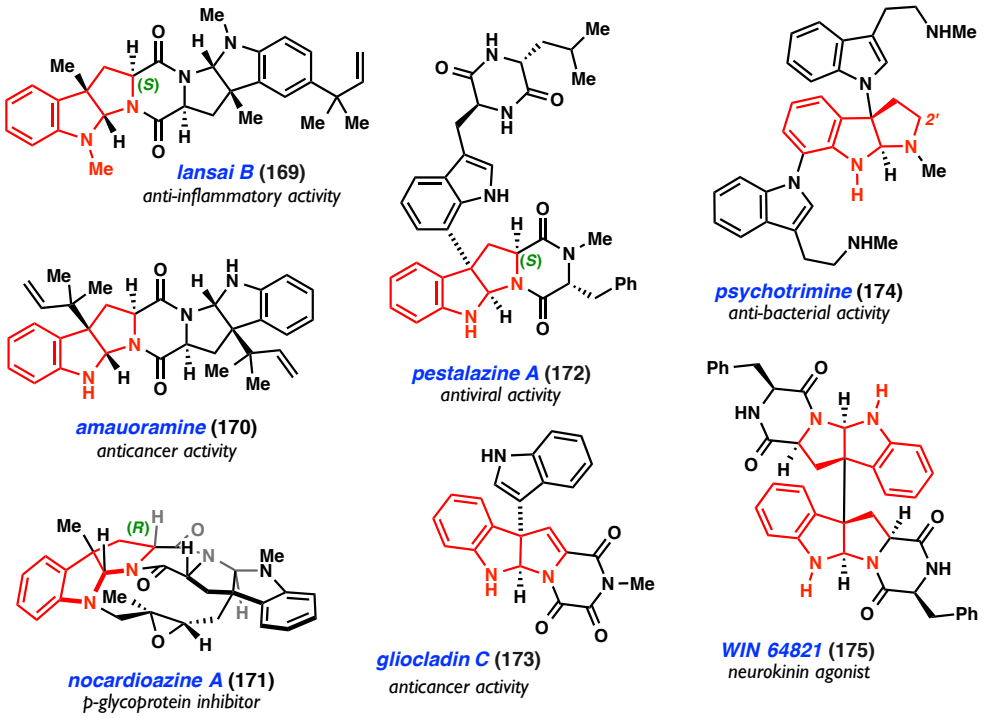
2.1 INTRODUCTION

Pyrroloindoline structure (highlighted in red, Figure 2.1) is found in a large number of natural products,[1] which possess broad spectra of pharmaceutical properties including anti-cancer[2], anti-bacterial activities[3]. Biosynthetically, pyrroloindolines are derived from tryptophan amino acid – one of the 23 proteinogenic ("protein-building") amino acids, which explains the prevalence of pyrroloindoline motif in nature.

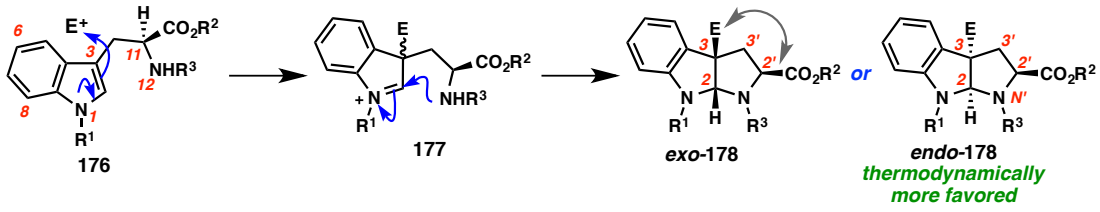
More specifically, tryptophan derivative **176** was first engaged in a nucleophilic reaction with the electrophile (E, Scheme 2.1), where the resulting iminium ion could be quenched by the subsequent cyclization of the appendant *N*-atom to provide pyrroloindolines. In this process, the C11 stereocenter could affect the facial selectivity of the nucleophilic attack and give rise to two diastereomers: *exo*-**178** and *endo*-**178**.

[†] Part of this chapter was published as the following communications: Wang, H.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2014**, *53*, 6206.

Figure 2.1. *Representative pyrroloindoline-containing natural products*



Scheme 2.1. *Biosynthetic pathway of pyrroloindoline synthesis*



In comparison, *endo* diastereomer **178**, where the C2' substituent (CO_2R^2) stands on the opposite face of the pyrrolidine ring with respect to the C3 substituent (E), is *thermodynamically more stable* due to the lesser torsional strain between C2' substituent and *N'* substituent R^3.[3,4]

Careful examination of the pyrroloindoline alkaloid family members reveals that most of them share the same C2' absolute configuration, originated from the natural abundant L-tryptophan; however, the C3 substituents can reside as either *endo* or *exo*

relative stereochemistry. For example, lansai B (**169**) contains two *exo* pyrroloindolines, while pestalazine A (**172**) possesses an *endo* pyrroloindoline. This indicates the flexibility of facial selectivity of electrophiles E approaching indoles. Intriguingly, nocardioazine A (**171**) comprises the *rare* D-tryptophans (the original isolation paper proposed the opposite absolute configuration,[5] which was corrected by this work) and the C3 stereocenters on two pyrroloindoline fragments have the opposite configurations within one molecule, which make them attractive synthetic targets.

Besides above-mentioned pyrroloindolines, there is another important subfamily of pyrroloindoline natural products lacking C2' substituent (for example, psychotrimine **174**, Figure 2.1), which have inspired numerous enantioselective methodologies to access those alkaloids[6] and will not be discussed here.

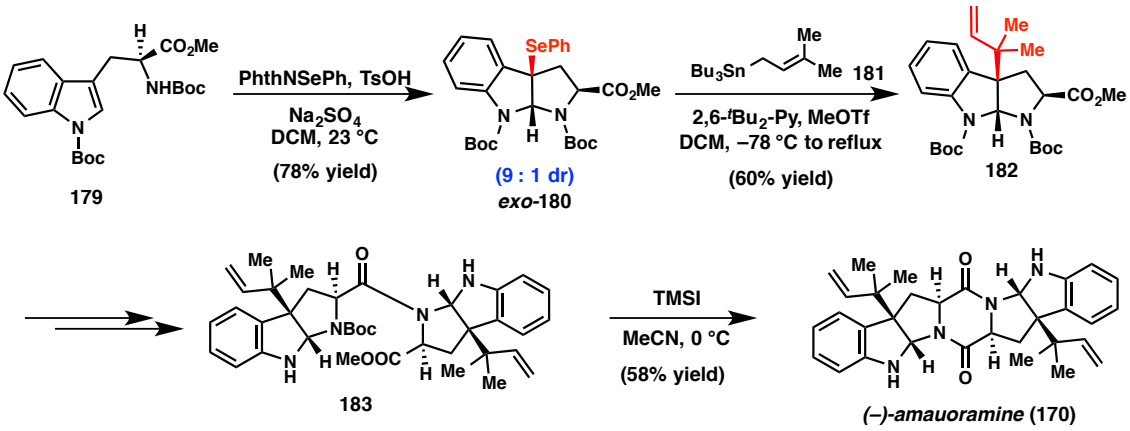
2.1.1 Cyclization of Tryptophans Accessing C3-Substituted Pyrroloindoline Alkaloids via Transient Functional Groups

Within pyrroloindoline natural products, those possessing C3 *all-carbon quaternary* centers are most prevalent and present a unique challenge for organic synthesis. Inspired by the biosynthetic pathway, many groups have been investigating substrate-controlled *diastereoselective* strategies to access related pyrroloindoline natural products. Several indirect C3-alkylation methodologies have been developed by introducing a temporary functional handle (e.g. halide atom or selenium group) for the subsequent carbon substituent installation.

In 1994, Danishefsky reported the stereospecific formation of a phenyl selenium pyrroloindoline (Scheme 2.2).[7] Starting from tryptophan derivative **179**, treatment with

N-phenylselenophthalimide in methylene chloride in the presence of catalytic *p*-toluenesulfonic acid afforded **180** in 78% yield as a 9 : 1 mixture of diastereomers favoring the kinetic *exo* product. The C3 phenylselenium functional group in **180** was then activated by MeOTf to form a transient cation, which was quenched by the following nucleophilic attack of prenyl stannane **181** to form angular reverse prenyl product **182**. Pyrroloindoline **182** was then advanced via selective deprotection and peptide coupling to provide dipeptide **183**, where the Boc group was removed and the resulting secondary amine cyclized *in situ* to form natural product (–)-amauoramine (**170**).

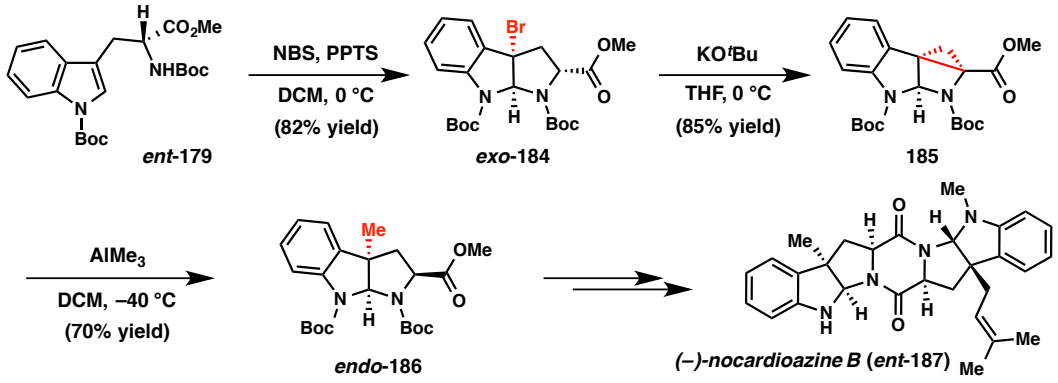
Scheme 2.2. *Total synthesis of (–)-amauoramine by Danishefsky*



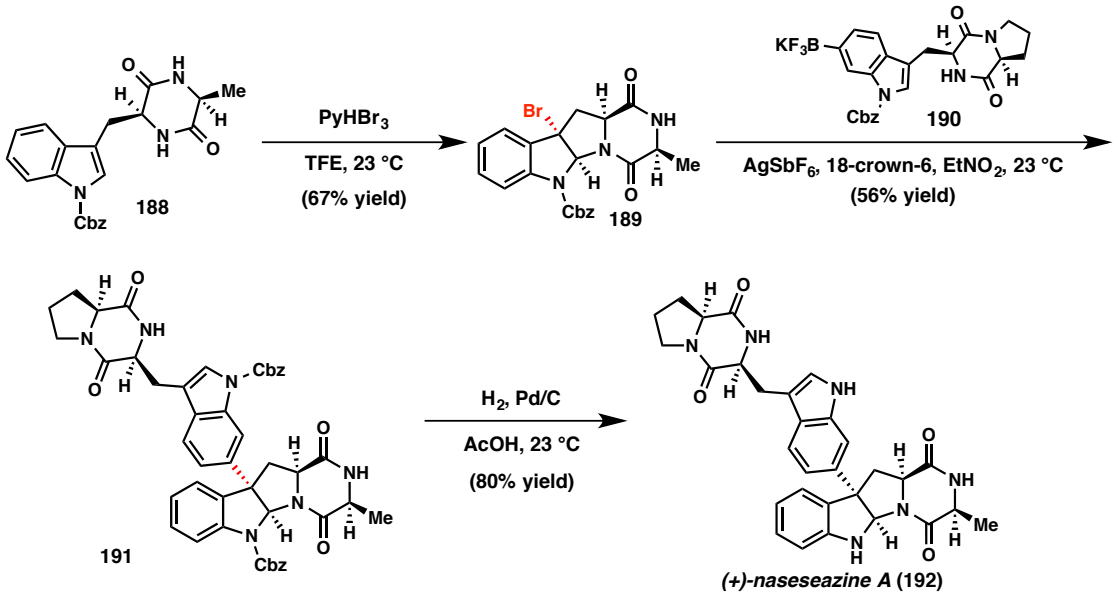
De Lera and coworkers rationalized the *exo*-selectivity observed by Danishefsky by going through an azetidine intermediate (not shown) where *exo*-selective process has a significantly lower activation energy barrier.[8] They were also able to extend this reactivity to C3-bromination using *N*-bromosuccinimide (NBS) as the electrophile. This methodology was applied in the total synthesis of (–)-nocardioazine B (*ent*-**187**) by the Ye group (Scheme 2.3).[9] The brominated *exo*-pyrroloindoline **184** was successfully prepared by treating tryptophan *ent*-**179** with NBS and pyridinium *p*-toluenesulfonate

(PPTS). Subjection of C3-Br pyrroloindoline **184** to KO^{t}Bu provided a highly strained cyclopropylazetoindoline **185**, which could undergo ring-opening by a variety of nucleophiles at the C3 position (as disclosed by Rainier and coworkers).[10] In the case of *ent*-**187** synthesis, **185** was opened by trimethylaluminum to generate C3-Me *endo*-pyrroloindoline **186**, which was advanced to *ent*-**187** in a short sequence (detailed synthetic route will be discussed in Chapter 3).

Scheme 2.3. *Total synthesis of (–)-nocardioazine B by Ye*

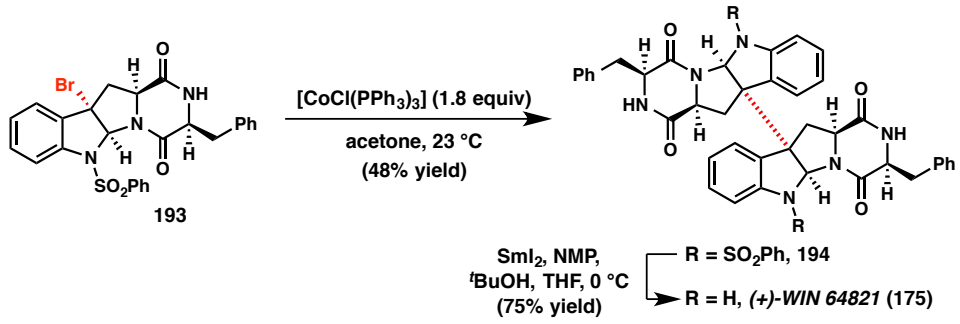


Scheme 2.4. *Total synthesis of (+)-naseseazine A by Movassaghi*



In comparison to NBS-mediated *exo*-selective bromination of tryptophans, Movassaghi and coworkers developed a method to access brominated *endo*-pyrroloindoline **189** by treating tryptophan-diketopiperazine **188** with pyridinium tribromide (Scheme 2.4).[11] Subsequent halide abstraction of **189** using silver hexafluoroantimonate ($AgSbF_6$), followed by the attack of various nucleophiles, furnished C3-substituted pyrroloindolines, where the addition of trifluoroborate **190** provided highly functionalized C3-arylated pyrroloindoline **191**. The removal of Cbz protecting groups accomplished the total synthesis of (+)-naseseazine A (**192**).

Scheme 2.5. *Total synthesis of (+)-WIN 64821 by Movassaghi*

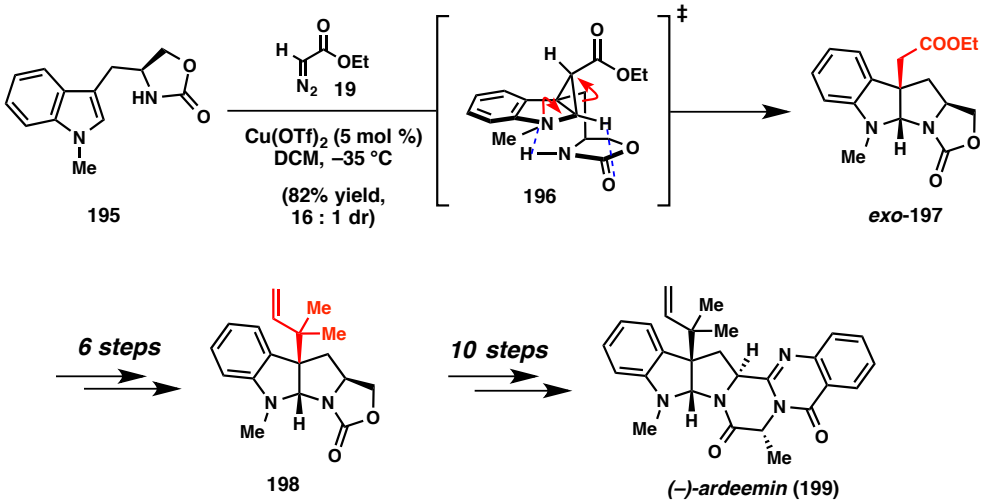


Alternatively, instead of forming a cation at the C3 position via halide abstraction, Movassaghi and coworkers were able to generate a C3 radical by treating bromo-pyrroloindoline **193** with reducing reagent tris(triphenylphosphine)cobalt chloride (Scheme 2.5).[12] The resulting radical intermediate readily dimerized to form bis(pyrroloindoline) **194**, which was converted to (+)-WIN 64821 (**175**) upon deprotection.

2.1.2 Direct Alkylation/Cyclization Strategies of Tryptophans

Even though the preinstalling of a functional handle allows the further derivatization of the C3 position of pyrroloindolines, the two-step sequence is less ideal compared to a direct incorporation of the requisite functional group at the C3 position. Qin and coworkers were able to promote a diastereoselective cyclopropanation of tryptophan derivative **195** with diazoester **19** and catalytic amount of $Cu(OTf)_2$ (Scheme 2.6).[13,14] The subsequent cyclopropane ring-opening and cyclization provided C3-substituted *exo*-pyrroloindoline **197**. However, this cyclopropanation strategy permits a narrow range of functional groups to be incorporated at C3 position, where it requires a 6-step sequence to convert **197** into the desired reverse prenylated **198** in order to prepare natural product (–)-ardeemin (**199**).

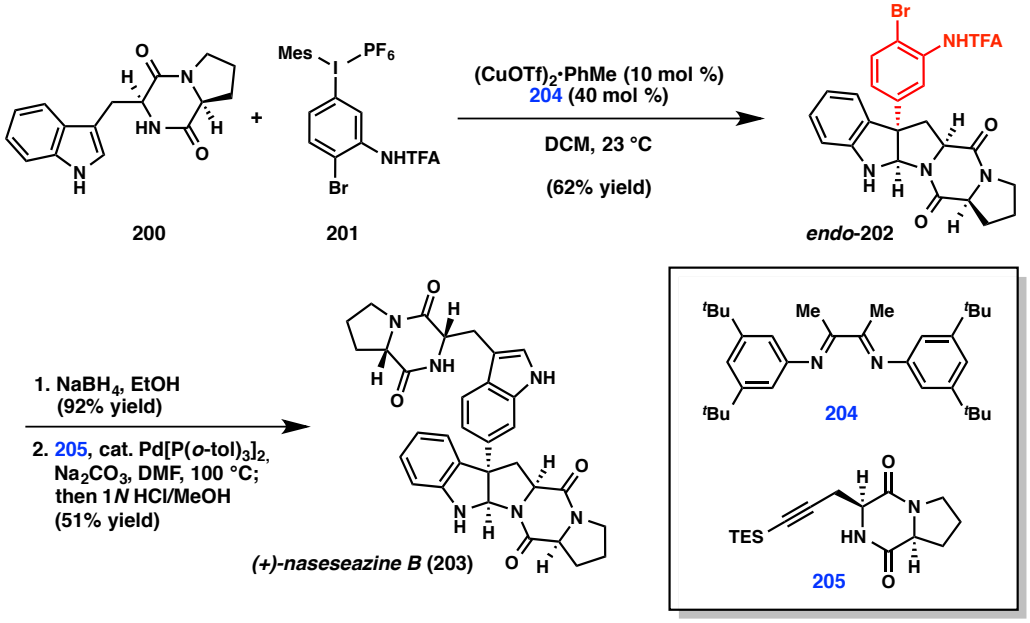
Scheme 2.6. *Total synthesis of (–)-ardeemin by Qin*



In 2013, Reisman and coworkers developed a novel diastereoselective C3-arylation methodology utilizing Cu(I)/diimine ligand **204** to catalyze aryl-group transfer from iodonium salt (e.g. **201** Scheme 2.7) onto indoles (e.g. **200**), providing a variety of

C3-arylated pyrroloindolines.[15] This methodology was applied to prepared highly functionalized pyrroloindoline **202**, which was subjected to deprotection of *N*-TFA group and the subsequent Larock indole synthesis to accomplish a concise five-step total synthesis of (+)-naseseazine B (**203**).

Scheme 2.7. *Total synthesis of (+)-naseseazine B by Reisman*

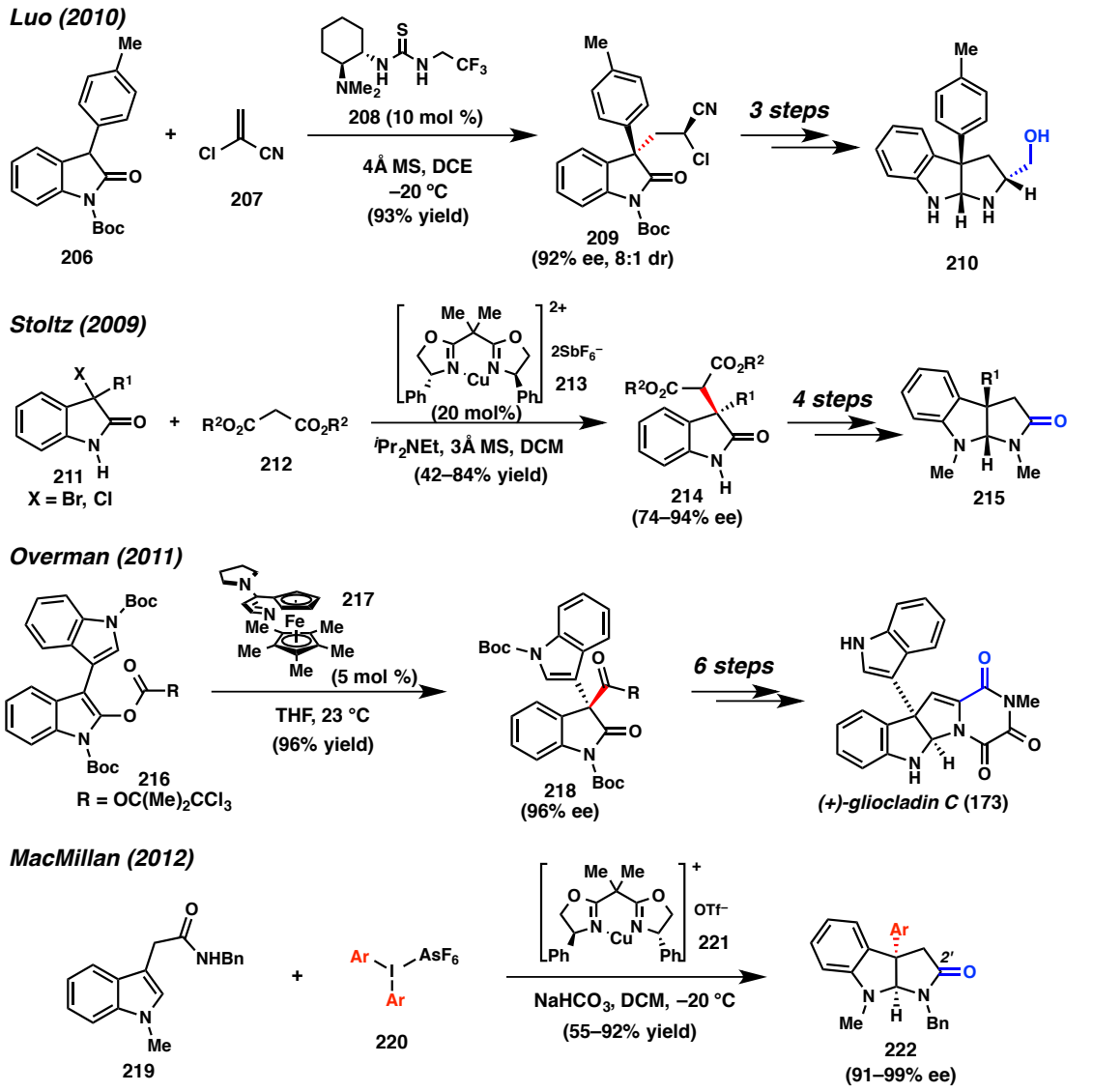


2.1.3 Enantioselective Synthesis of Pyrroloindolines

Apart from utilizing the intrinsic chiral information from tryptophan C11 stereocenter to gain access to both *exo* and *endo* products, a more challenging strategy of accessing pyrroloindoline lies in asymmetric catalysis, which could greatly broaden the substitution patterns of pyrroloindoline products suitable for total synthesis.

One indirect but practical approach involves conversion of the corresponding enantioenriched oxindole to the desired pyrroloindoline through cyclization events (Scheme 2.8).[16] Oxindoles can be functionalized at the C3 position by enantioselective

Scheme 2.8. *Selected asymmetric strategies accessing pyrroloindolines*



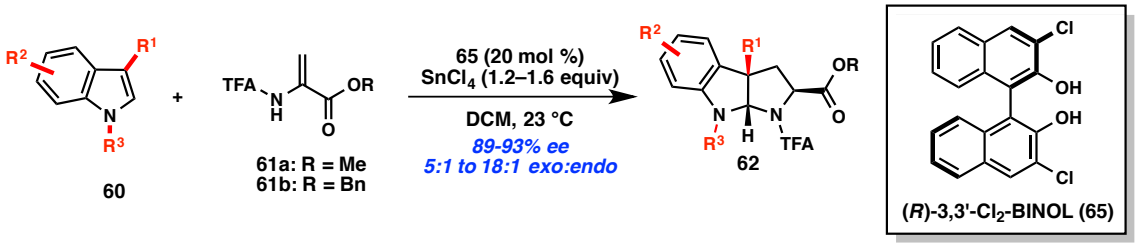
alkylations[6], which has been reported by several groups including Trost[17], Barbas[18], Stoltz[19], and Luo[20]. Most approaches utilize the intrinsic nucleophilicity of oxindoles originated from its enolate form. Luo and coworkers applied thiourea catalyst **208** to affect an asymmetric conjugate addition of 2-chloroacrylonitrile to afford product **209** in good enantioselectivities.[20] Alternatively, it is also possible to realize an umpolung strategy where the oxindoles become the electrophile. Stoltz and coworkers discovered

that oxindoles **211** could be converted to to an imine intermediate by eliminating HCl, which could be intercepted by chiral copper **213**–coordinated malonate nucleophile to generate the C3-all carbon quaternary center enantioselectively.[19]

Other ways of installing the C3 stereocenter are also investigated. In the total synthesis of (+)-gliocladin C (**173**), Overman and coworkers utilized the planar-chiral ferrocenyl pyridine **217** (initially disclosed by the Fu group)[21] to catalyze an intramolecular acyl O-to-C migration of indolyl carbonate **216** to form chiral oxindole **218**.[22] Recently, Macmillan and coworkers reported Cu/chiral Box catalyzed enantioselective direct C3-arylation of indole **219** with aryliodonium **220** to provide pyrroloindoline **222** with good selectivities.[23]

Most of the aforementioned strategies require further functional group manipulations to close the third ring in order to access the pyrroloindoline structures. In the MacMillan's strategy, extra steps are required to install necessary functional groups at the C2' position for the diketopiperazine (DKP) motif construction, which are present in various pyrroloindoline-containing DKP natural products (e.g. **171**, **172**, Figure 2.1).

Scheme 2.9. *Enantioselective pyrroloindoline synthesis by Reisman*



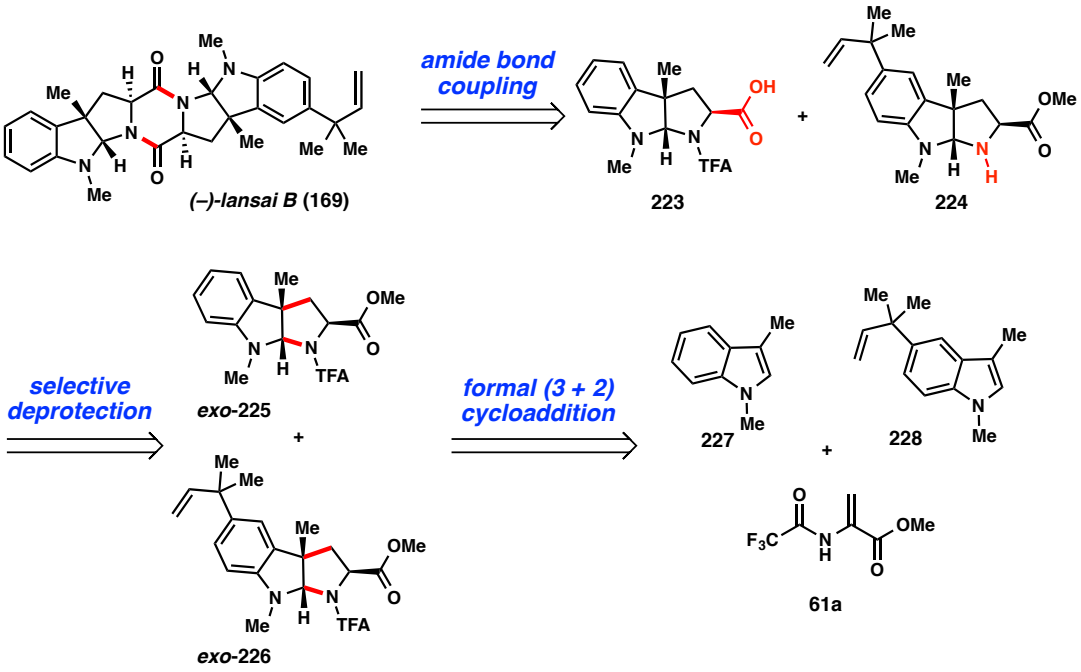
As mentioned in Chapter 1, our group developed a new method to access *exo*-pyrroloindolines directly from C3-substituted indoles and 2-amidoacrylates using $SnCl_4$ and catalytic (*R*)-3,3'-dichloro-BINOL (**65**, Scheme 2.9).[24,25] The reactions typically

proceed in good yields and high diastereo- and enantioselectivities. We anticipated that this formal (3 + 2) cycloaddition reaction could be utilized to rapidly and enantioselectively prepare natural product (–)-lansai B (**169**, Figure 2.1), which is composed of two *exo*-pyrroloindolines.

2.2 FIRST TOTAL SYNTHESIS OF (–)-LANSAI B

(–)-Lansai B (**169**) was isolated in 2008 from the endophytic microorganism *Streptomyces* sp. SUC1.[3] It has been found to exhibit anti-inflammatory activity. Retrosynthetically, it is envisioned that the diketopiperazine core could be formed from two orthogonally protected amino acids **223** and **224** via initial peptide bond formation, deprotection, then cyclization by formation of the second peptide (Scheme 2.10). These

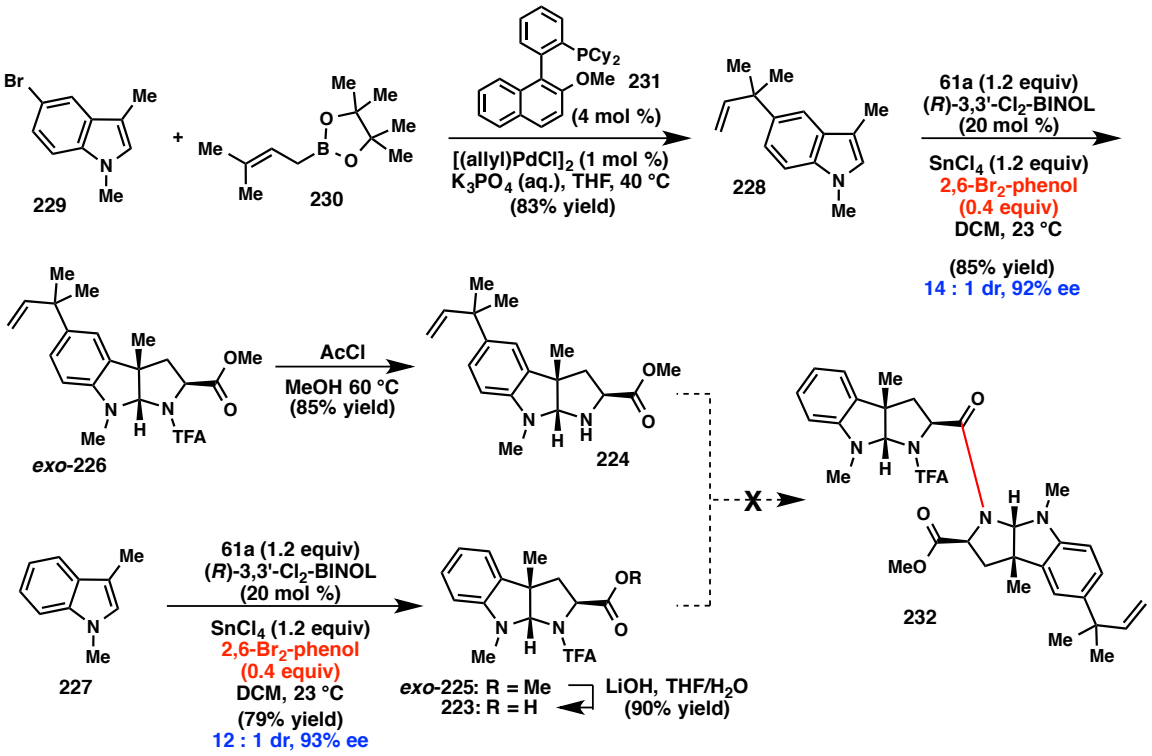
Scheme 2.10. *Retrosynthetic analysis of (–)-lansai B*



two orthogonal molecules could be accessed from selective deprotection of corresponding pyrroloindoles. The required pyrroloindolines *exo*-**225** and *exo*-**226** could in turn be synthesized by formal (3 + 2) cycloaddition reactions of the corresponding indoles **227**/**228** and acrylate **61a**.

Our efforts commenced with bromoindole **229** (Scheme 2.11), which was prepared in one step from commercially available 5-bromo-3-methyl-1*H*-indole.[24] Suzuki–Miyaura coupling of indole **229** with prenylboronate **230** furnished reverse-prenylated indole **228** in good yield using modified conditions reported by Buchwald and coworkers.[26] Subjection of indole **228** and methyl 2-trifluoroacetamidoacrylate (**61a**) to our formal (3 + 2) cycloaddition conditions on 0.2 mmol scale provided pyrroloindoline *exo*-**226** in 84% yield and 92% ee. However, lower yields of **226** were obtained when the

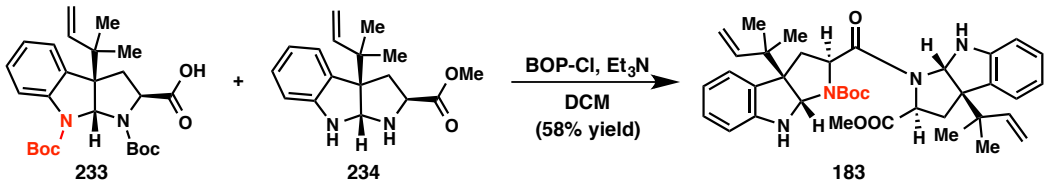
Scheme 2.11. *Attempted orthogonal peptide coupling to access (–)-lansai B*



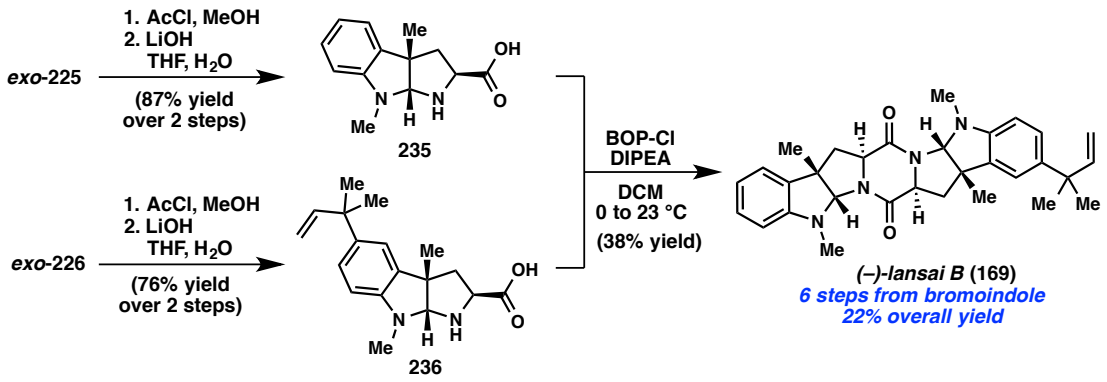
reaction was conducted on preparatively useful scales (>1.0 mmol). It was hypothesized that trace water could help to turn over the chiral catalyst on small scale; thus, a survey of several protic additives revealed that addition of 0.4 equiv 2,6-dibromophenol to the reaction mixture improves the scalability of the reaction, providing **226** in 85% yield, 14:1 dr, and 92 % ee (major diastereomer). Cleavage of the TFA group with anhydrous HCl provided amine **224**.[27] Likewise, pyrroloindoline **225** could be prepared from 1,3-dimethyl indole **227** and acrylate **61a** in 79% yield, 12:1 dr, and 93% ee (major diastereomer). Treatment with LiOH chemoselectively hydrolyzed the methyl ester to give carboxylic acid **223**.

With orthogonally protected pyrroloindolines **223** and **224** in hand, completion of the synthesis required DKP formation. Unfortunately, amide **232** was not formed under a wide variety of peptide coupling conditions (Scheme 2.11);[28] instead, decomposition of acid **223** was observed. It is important to note that Danishefsky and coworkers successfully couple two orthogonally-protected *exo*-pyrroloindolines in their synthesis of amauromine (Scheme 2.12); however, in contrast to *N*-methyl pyrroloindoline **223** in our route, the carboxylic acid partner **233**, which contained *N*-*t*-butylcarbamate protecting group, was able to be successfully coupled to amine **234** in the Danishefsky system.[29]

Scheme 2.12. *Orthogonal peptide coupling in the synthesis of amauoramine*



Scheme 2.13. *Endgame of (–)-lansai B total synthesis via amino acid dimerization*

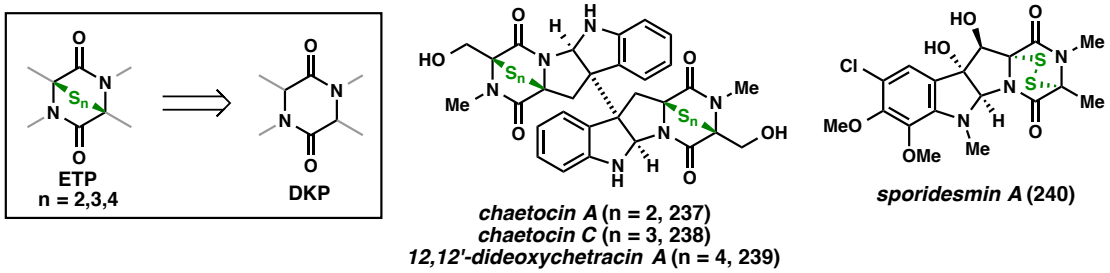


Taken together, these findings reveal that the *N*-substitution of the *exo*-pyrroloindoline significantly influences the stability of the activated ester under peptide coupling conditions. After considerable experimentation, it was determined that pyrroloindolines **225** and **226** could be converted to the corresponding amino acids **235** and **236** by TFA deprotection and saponification (Scheme 2.13). Treatment of an equimolar mixture of amino acids **235** and **236** with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) delivered (–)-lansai B (**169**) in 38% yield, matching all the spectra data of the isolation paper.[3] Each of the two homodimers was also isolated in 20% yield. Despite the modest yield on the final coupling step, the natural product is accessible in only six steps (longest linear sequence) and 20% overall yield from commercially available materials.

2.3 LANSAI B–ETP DERIVATIVES PREPARATION

The diketopiperazine (DKP) motif is the parental structure that epipolythiodiketopiperazine (ETP) molecules are built up upon,[30] which requires the incooperation of polysulfide linkage between the two carbon centers (Figure 2.2). Due to

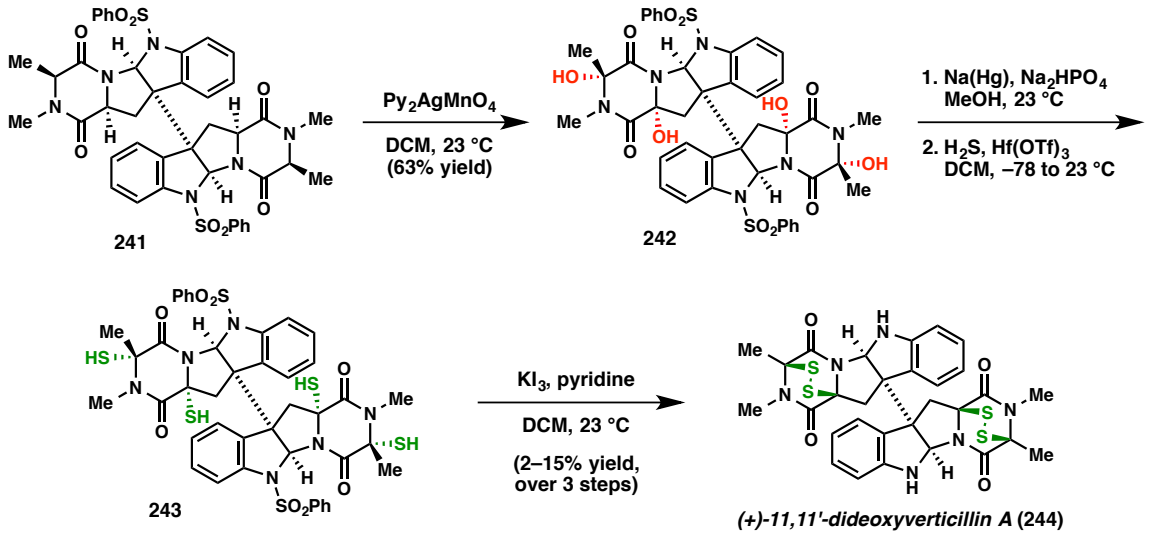
Figure 2.2. *Representative ETP natural products*



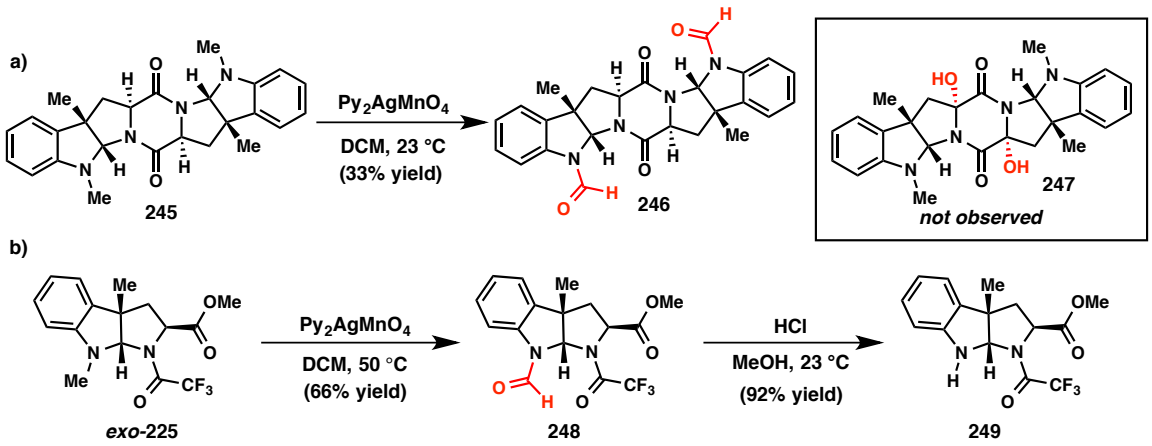
the redox activities of the sulfur-sulfur bond, ETP natural products, such as chaetocin A (**237**), present diverse therapeutic functions including virulence factors, and immunoimpressive and anti-cancer activities.[31] Synthetically, ETP natural products are often prepared from the corresponding DKP compounds.[32] Thus, access to the pyrroloindoline-containing DKP family of molecules could allow the preparation of unnatural ETP derivatives, which might possess biological importance. Having DKPs in hand including lansai B (**169**), we decided to investigate epidisulfide bridge formation to prepare related ETP compounds.

Our first attempt at thiolation utilized the conditions in Movassaghi's total synthesis of (+)-11,11'-dideoxyverticillin A (**244**, Scheme 2.14).[33] They were able to promote DKP C-H oxidations of bis(diketopiperazine) **241** using oxidant bispyridinium silver permanganate to provide tetraol **242**. Subsequent deprotection and displacement of hydroxyl groups with hydrogen sulfide afforded free thiol **243**, which could be converted to episulfide **244** upon oxidation with KI_3. Based on this methodology, DKP **245** was treated with Py_2AgMnO_4 (Scheme 2.15); however, no DKP C-H oxidation was observed (**247**), while *N*-methyl oxidation product **246** was isolated instead. The same conditions were then applied to pyrroloindoline **225**. After optimization, *N*1-oxidation was effected in 61% yield, again with no C-H oxidation observed. Subsequent formamide cleavage

Scheme 2.14. *C-H oxidation strategy for episulfide installation by Movassaghi*



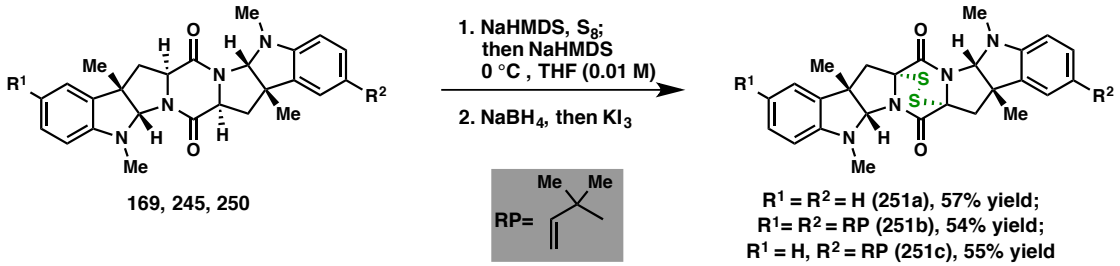
Scheme 2.15. *Attempted C-H oxidation and resulting N-demethylation sequence*



under mildly acidic conditions yielded *N*1-H product **249**, without affecting the TFA group. Similar transformation has been reported using PCC or PDC.[13,34] However, this is the first report that Py_2AgMnO_4 can promote a similar oxidation reaction and this fruitful discovery allows a mild *N*-demethylation protocol for pyrroloindolines.

Encouraged by Nicolaou's protocol for DKP sulfenylation, we returned our efforts to disulfide bridge formation.[35] In accordance with Nicolaou's procedure, a solution of DKP (**169**, **245**, **250**, Scheme 2.16) in THF was treated with sodium

Scheme 2.16. *Synthesis of lansai B-ETP derivatives*



hexamethyldisilazide (NaHMDS), and the resulting solution was added to a mixture of NaHMDS and S_8, after which additional NaHMDS was added. However, this gave low yield and messy mixture of products. After optimizing the reaction parameters, the yield was boosted up to 55% by performing at 0 °C and 0.01 M concentration. Thus, all three ETP derivatives of the lansai B analogues (**251a-c**) were synthesized.

In collaboration with City of Hope, biological evaluation of these compounds was conducted. Of the ETP derivatives screened, only homodimer ETP **251a** showed moderate activity against A2058 melanoma (3.8 μM) and DU145 prostate (4.8 μM) cell lines. Further biological examination is under way.

2.4 CONCLUDING REMARKS

In conclusion, the first asymmetric total synthesis of (–)-lansai B (**169**) has been accomplished in only six steps (longest linear sequence), featuring an enantioselective formal (3 + 2) cycloaddition to install all the requisite stereocenters. An unexpected challenge was encountered when applying the orthogonal peptide coupling strategy to access the DKP core of (–)-**169**, where the carboxylic acid coupling partner decomposes under different peptide coupling conditions. The recognition of the importance of *N*-substituent on the acid coupling partner led to the development of an amino acid

dimerization strategy to access diketopiperazines with good yields, even though it generates a statistical mixture of DKPs. This dimerization strategy might be applied to synthesis of related compounds.

During the attempts to prepare the ETP derivatives of lansai B (**169**), an unusual *N*-methyl oxidation rather than the desired C-H oxidation was observed when treating DKP with oxidant Py_2AgMnO_4. Even though it does not provide the targeted diol, this provides a mild method to demethylate *N*-Me pyrroloindolines, which is not trivial. Using Nicolaou's protocol, the successful preparation of ETP derivatives allowed the collaboration with City of Hope. Among these ETP compounds, homodimeric **251a** showed promising anti-cancer properties.

The great efficiency of the formal (3 + 2) cycloaddition methodology in achieving a concise (–)-lansai B (**169**) synthesis encouraged us to study total synthesis of structurally more complex natural products: (+)-nocardioazines A (**171**) and B (**187**), which will be discussed in Chapter 3.

2.5 EXPERIMENTAL SECTION

2.5.1 Materials and Methods

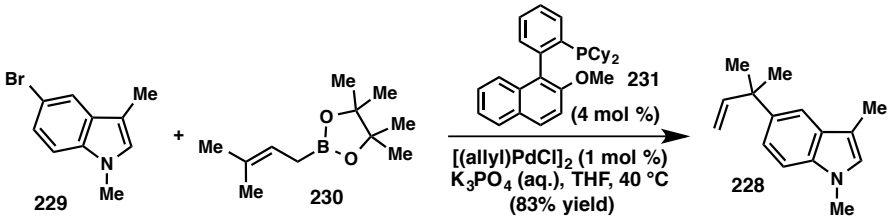
Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. 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.[36] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Bruker 400 equipped with a cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), $CHDCl_2$ (^1H, $\delta = 5.32$), CD_2HOD (^1H, $\delta = 3.31$), MeCN-*d2* (^1H, $\delta = 1.94$), or DMSO-*d5* (^1H, $\delta = 2.50$), and $CDCl_3$ (^{13}C, $\delta = 77.0$), CD_2Cl_2 (^{13}C, $\delta = 54.0$), CD_3OD (^{13}C, $\delta = 49.0$), MeCN-*d3* (^{13}C, $\delta = 118.3$), or DMSO-*d6* (^{13}C, $\delta = 40.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. 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.

2.5.2 Preparative Procedures and Spectroscopic Data

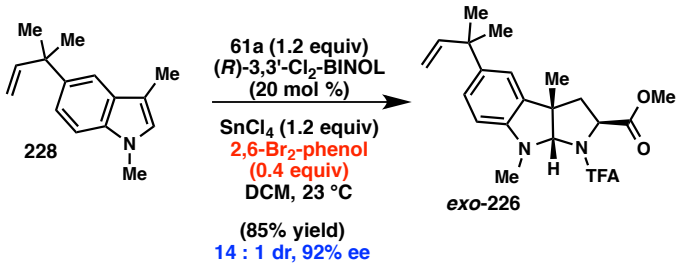
Preparation of reverse prenylated indole 228[26]



To a flame-dried 50 mL Schlenk tube was added $[(allyl)PdCl]_2$ (9 mg, 0.025 mmol, 1 mol %) and phosphine ligand **231** (42 mg, 0.098 mmol, 4 mol %). Then the tube was evacuated and charged with argon three times. Allyl boronic acid pinacol ester **230** (0.65 ml, 2.95 mmol, 1.2 equiv) and dimethyl-bromoindole[24] **229** (560 mg, 2.50 mmol, 1.0 equiv) were added using a microsyringe. THF (5 mL) and 2.5 M K_3PO_4 (5 mL) were then added to the reaction flask. The Schlenk tube was sealed and the reaction was heated to 40 °C for 24 hours. It was then cooled to room temperature and diluted with EtOAc (25 mL). The mixed layers were then washed with distilled water (25 mL). The aqueous layer was then extracted with EtOAc (3 x 25 mL). Combined organic layers were washed with brine (40 mL). It was dried over $MgSO_4$, filtered and concentrated down to give a yellow oil. The crude material was then dissolved in EtOAc (30 mL) and washed with saturated KHF_2 solution (3 x 20 mL) to get rid of the remaining boronic acid pinacol ester. It was then dried over $NaSO_4$, filtered and concentrated to give a yellow oil. Flash chromatography (5% to 9% ether in hexanes) afforded reverse prenylated indole **228** as a

light yellow oil (442 mg, 2.07 mmol, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.51 (t, J = 0.9 Hz, 1H), 7.24 (dd, J = 8.7, 1.83 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 1.0 Hz, 1H), 6.13 (dd, J = 17.5, 10.6 Hz, 1H), 5.09 (dd, J = 17.6, 1.5 Hz, 1H), 5.04 (dd, J = 10.5, 1.5 Hz, 1H), 3.71 (s, 3H), 2.32 (d, J = 1.0 Hz, 3H), 1.49 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) 149.1, 138.8, 135.4, 128.3, 126.7, 120.6, 115.5, 110.1, 109.9, 108.5, 41.1, 32.5, 28.8, 9.5; IR (NaCl/thin film): 3080, 2964, 2920, 1634, 1489, 1455, 1425, 1387, 1376, 1365, 1292, 1256, 1201, 1152, 1053, 1004, 909, 874, 788; HRMS (MM) calc'd for $C_{15}H_{20}N$ $[M+H]^+$ 214.1590, found 214.1592.

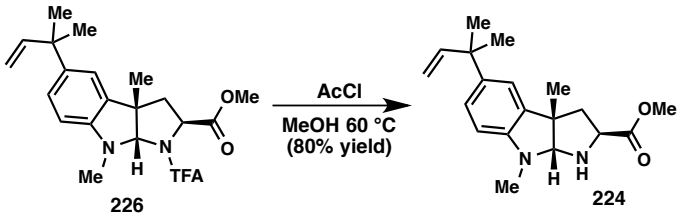
Preparation of reverse prenylated pyrroloindoline *exo*-226



To a flame-dried flask was added reverse prenylated indole **228** (350 mg, 1.64 mmol, 1.0 equiv), acrylate[37] **61a** (390 mg, 1.97 mmol, 1.2 equiv), (*R*)-3,3'-Cl_2-BINOL (117 mg, 0.33 mmol, 0.2 equiv), 2,6-dibromo-phenol (165 mg, 0.66 mmol. 0.4 equiv) and DCM (12 mL). $SnCl_4$ (1M solution in DCM, 1.97 mL, 1.97 mmol, 1.2 equiv) was added at last. The orange mixture was allowed to stir at room temperature for 24 hours. The solution was diluted with acetonitrile (10 mL) and quenched with 1M HCl (10 mL), followed by addition of distilled water (50 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 50 mL). Combined organic layers were washed with 3 M NaOH solution (3 x 75 mL). It was dried over $MgSO_4$, filtered and concentrated down to give yellow mixture of oil and solid. Flash chromatography (1% to

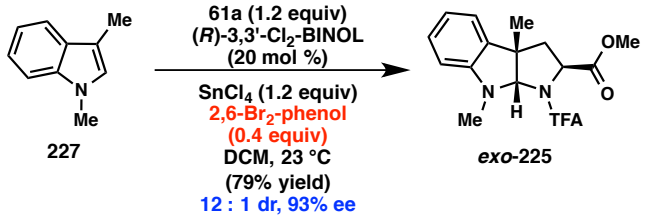
8% EtOAc in hexanes) afforded reverse prenylated pyrroloindoline **226** (14 : 1 mixture of *exo*:*endo* diastereomers by ^{1}H NMR), as a thick orange oil (568 mg, 1.34 mmol, 85% yield). The mixture of diastereomers was further purified by flash chromatography (0% to 10% EtOAc in hexanes) to give major diastereomer **226** for characterization purposes. The enantiomeric excess of *exo*-**226** was determined to be 92% by chiral SFC analysis (OD, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm): t_R(major) = 6.1 min, t_R(minor) = 5.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). $[\alpha]_D^{25}$ = –115° (*c* = 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.16 (d, *J* = 8.1 Hz, 1H*, 1H§), 7.02 (s, 1H§), 6.99 (s, 1H*), 6.52 (d, *J* = 7.7 Hz, 1H§), 6.45 (d, *J* = 8.2 Hz, 1H*), 6.00 (dd, *J* = 17.3, 10.5 Hz, 1H*, 1H§), 5.60 (s, 1H*), 5.31 (s, 1H§), 5.07 – 4.96 (m, 2H*, 2H§), 4.73 (d, *J* = 9.3 Hz, 1H*), 4.47 – 4.41 (m, 1H§), 3.82 (s, 1H*), 3.77 (s, 1H§), 3.06 (s, 1H*), 2.86 (s, 1H§), 2.60 (dd, *J* = 13.1, 9.9 Hz, 1H*), 2.52 (t, *J* = 10.7 Hz, 1H§), 2.38 (d, *J* = 12.5 Hz, 1H*), 2.14 – 1.98 (m, 1H§), 1.57 – 1.31 (m, 9H*, 9H§); ^{13}C NMR (126 MHz, $CDCl_3$) 172.6*, 170.6§, 159.1* (q, *J* = 37.0 Hz), 157.5§ (q, *J* = 39.6 Hz), 148.4*, 148.2§, 147.5*, 147.3§, 140.6§, 139.3*, 134.1*, 134.0§, 126.5§, 126.3*, 119.3*§, 116.1* (q, *J* = 288.5 Hz), 115.9§ (app d, *J* = 287.2 Hz), 110.4§, 110.2*, 109.2§, 107.6*, 93.7*, 92.1§, 61.2§, 60.3*, 53.3§, 53.0*, 52.5§, 49.3*, 44.0*, 40.7§, 40.7*, 40.4§, 37.1*, 34.9§, 28.4*§, 23.5*, 22.9§; FTIR (NaCl, thin film): 3081, 2965, 2874, 2822, 1753, 1698, 1618, 1496, 1434, 1359, 1283, 1257, 1204, 1156, 1117, 1054, 995, 912, 844, 813 cm^{-1}; HRMS (ESI) calc'd for $C_{21}H_{26}F_3N_2O_3$ $[M+H]^+$ 411.1890, found 411.1901.

Preparation of reverse prenylated pyrroloindoline amine 224



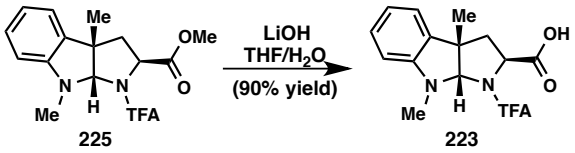
Acetyl chloride (0.40 mL, 5.69 mmol, 5.0 equiv) was added slowly to dry methanol (5 mL). The mixture was added to reverse prenylated pyrroloindoline **226** (467 mg, 1.14 mmol, 1.0 equiv, 14 : 1 mixture of *exo*:*endo* diastereomers by ^{1}H NMR) dissolved in dry methanol (7 mL). After being heated to 60 °C for three days, the reaction was quenched with saturated sodium bicarbonate (5 mL), and concentrated down to get rid of methanol. The residue was diluted with DCM (10 mL) and washed with water (10 mL). Aqueous layer was back extracted with DCM (3 x 5 mL). Combined organic layer was dried over Na_2SO_4, filtered and concentrated down to give a chartreuse oil. Flash chromatography (20% to 80% EtOAc in hexanes) afforded reverse prenylated secondary amine **224**, as a yellow oil (326 mg, 1.04 mmol, 80% yield). $[\alpha]_D^{25}$ = –58° (*c* = 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 1H), 6.02 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.02 (ddd, *J* = 19.0, 14.0, 1.4 Hz, 2H), 4.61 (s, 1H), 3.76 (dd, *J* = 9.5, 6.8 Hz, 1H), 3.73 (s, 3H), 2.82 (s, 3H), 2.67 (br s, 1H), 2.40 (dd, *J* = 12.2, 6.8 Hz, 1H), 1.93 (dd, *J* = 12.3, 9.4 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 148.7, 148.6, 137.4, 134.6, 125.5, 120.3, 109.8, 105.0, 92.2, 59.7, 52.5, 52.0, 46.0, 40.5, 31.8, 28.4, 25.6; FTIR (NaCl, thin film): 3350, 3080, 2962, 2925, 2868, 1738, 1634, 1615, 1498, 1450, 1377, 1358, 1326, 1282, 1233, 1202, 1133, 1055, 996, 911, 862, 808 cm^{-1}; HRMS (APCI) calc'd for $C_{19}H_{27}N_2O_2$ $[M+H]^+$ 315.2067, found 315.2067.

Preparation of dimethyl pyrroloindoline *exo*-225



To a flame-dried flask was added reverse prenylated indole **227** (300 mg, 2.07 mmol, 1.0 equiv), acrylate **61a** (489 mg, 2.48 mmol, 1.2 equiv), (*R*)-3,3'-Cl_2-BINOL (147 mg, 0.41 mmol, 0.2 equiv), 2,6-dibromo-phenol (208 mg, 0.83 mmol, 0.4 equiv) and DCM (15 mL). $SnCl_4$ (1M solution in DCM, 2.48 mL, 2.48 mmol, 1.2 equiv) was added at last. The orange mixture was allowed to stir at room temperature for 24 hours. The solution was diluted with acetonitrile (10 mL) and quenched with 1M HCl (10 mL), followed by addition of distilled water (50 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 50 mL). Combined organic layers were washed with 3 M NaOH solution (3 x 75 mL). It was dried over $MgSO_4$, filtered and concentrated down to give yellow mixture of oil and solid. Flash chromatography (1% to 8% EtOAc in hexanes) afforded dimethyl pyrroloindoline **225** (12 : 1 mixture of *exo*:*endo* diastereomers by ^{1}H NMR), as a thick orange oil (553 mg, 1.62 mmol, 79% yield). The enantiomeric excess of *exo*-**225** was determined to be 93% by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) =2.9 min, t_R(minor) = 2.4 min. Spectral data matches that reported in the literature.[2]

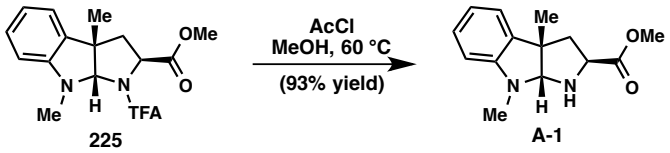
Preparation of pyrroloindoline acid 223



A solution of lithium hydroxide (14 mg, 0.58 mmol, 2.0 equiv) in distilled water (2.5 mL) was added dropwise to a solution of pyrroloindoline **225** (100 mg, 12 : 1 mixture of diastereomers, 0.29 mmol, 1.0 equiv) in THF (2.5 mL). After stirring at room temperature for 30 minutes, reaction was quenched with pH = 2.5 acidic buffer (10 mL, prepared by acidifying a 10% NaH_2PO_4 aqueous solution by $KHSO_4$ until pH reaches 2.5). It was extracted with DCM (5 x 10 mL). Combined layers were washed with brine (30 mL). The aqueous layer was back extracted with DCM (10 mL). The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated down a yellow thick oil. Flash chromatography (1% to 10% MeOH is DCM) afforded pyrroloindoline acid **223**, as a yellow solid (86 mg, 0.26 mmol, 90% yield). The minor diastereomer does not react under reaction conditions and can be isolated using flash chromatography. $[\alpha]_D^{25} = -86°$ (*c* = 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.18 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.09 (s, 1H§), 7.04 (d, *J* = 7.3 Hz, 1H*), 6.86 (s, 1H§), 6.78 (t, *J* = 7.4 Hz, 1H*), 6.60 (s, 1H§), 6.52 (d, *J* = 7.9 Hz, 1H*), 5.59 (s, 1H*), 5.31 (s, 1H§), 4.66 (s, 1H*), 4.34 (s, 1H§), 3.08 (s, 3H*), 2.91 (s, 3H§), 2.57 (s, 1H*, 1H§), 2.41 (d, *J* = 13.3 Hz, 1H*), 2.15 (s, 1H§), 1.48 (s, 3H§), 1.40 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5*, 175.8§, 159.4* (q, *J* = 37.8 Hz), 157.8§ (q, *J* = 35.6 Hz), 149.4§, 149.3*, 134.5*§, 128.9§, 128.6*, 121.7§, 121.5*, 120.4§, 118.8*, 116.2* (q, *J* = 288.5 Hz), 116.0§ (q, *J* = 286.1 Hz), 110.2§, 108.0*, 93.2*, 91.9§, 62.0§, 60.9*, 53.5§, 49.2*, 43.8*, 39.8§, 36.8*, 35.6§, 23.6*, 23.3§; FTIR (NaCl, thin film): 3215, 3053, 3027, 2966, 2933, 2876, 2824, 2519, 1689, 1609, 1489, 1450, 1432, 1344, 1300, 1256, 1202, 1157, 1107, 1094, 1063, 1021,

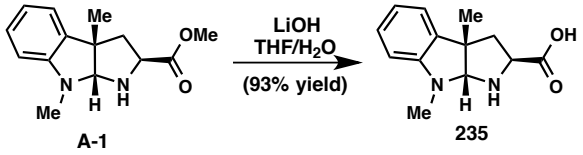
992, 949, 925, 855, 792, 754 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{16}F_3N_2O_3$ $[M+H]^+$ 329.1108, found 329.1118.

Preparation of pyrroloindoline amine A-1



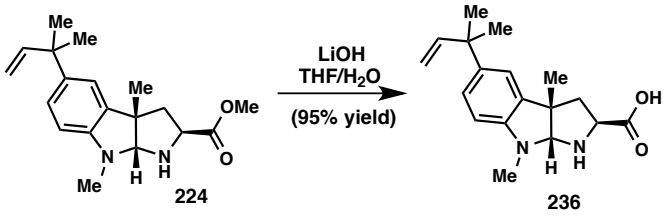
Acetyl chloride (0.35 mL, 4.88 mmol, 5.0 equiv) was added slowly to dry methanol (4 mL). The mixture was added to pyrroloindoline **225** (334 mg, 0.98 mmol, 1.0 equiv) dissolved in dry methanol (6 mL). After being heated to 60 °C for 52 hours, the reaction was quenched with saturated sodium bicarbonate (5 mL), and concentrated down to get rid of methanol. The residue was diluted with DCM (10 mL) and washed with water (10 mL). Aqueous layer was back extracted with DCM (3 x 5 mL). Combined organic layer was dried over Na_2SO_4, filtered, and concentrated down to give greenish yellow oil. Flash chromatography (20% to 80% EtOAc in hexanes) afforded secondary amine **A-1**, as a yellow oil (222 mg, 0.90 mmol, 93% yield). $[\alpha]_D^{25}$ = –34° (*c* = 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (td, *J* = 7.7, 1.2 Hz, 1H), 7.02 (dd, *J* = 6.6, 1.0 Hz, 1H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.35 (d, *J* = 7.8 Hz), 4.62 (s, 1H), 3.69 – 3.74 (m, 4H), 2.83 (s, 3H), 2.69 (br s, 1H), 2.40 (dd, *J* = 12.5, 6.6 Hz, 1H), 1.92 (dd, *J* = 12.2, 9.5 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 150.6, 134.7, 128.1, 122.3, 117.0, 105.5, 91.6, 59.8, 52.5, 52.0, 46.1, 31.5, 25.5; FTIR (NaCl, thin film): 3345, 3049, 2953, 2922, 2866, 1738, 1607, 1491, 1448, 1381, 1353, 1327, 1300, 1282, 1258, 1234, 1203, 1144, 1117, 1081, 1063, 1044, 1020, 990, 963, 909, 820, 741 cm^{-1}; HRMS (APCI) calc'd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$ 247.1441, found 247.1441.

Preparation of pyrroloindoline amino acid 235



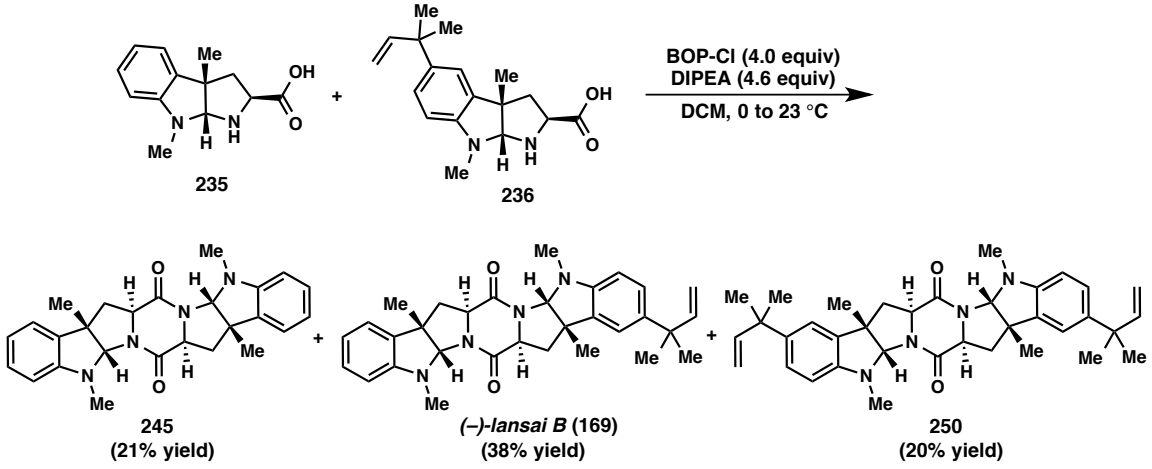
A solution of lithium hydroxide (29 mg, 1.22 mmol, 3.0 equiv) in distilled water (1.5 mL) was added dropwise to a solution of amine **A-1** (100 mg, 0.406 mmol, 1.0 equiv) in THF (1.5 mL). After stirring at room temperature for 30 minutes, reaction was quenched with 1M HCl until pH reached 6. The resulting solution was concentrated down to get rid of all solvent. The white residue was redissolved in DCM and filtered through a plug of celite to remove inorganic salt, which yielded a light yellow foam upon concentrating down. The crude product amino acid **235** was carried to the next reaction without further purification. (87.0 mg, 0.375 mmol, 93% yield). $[\alpha]_D^{25} = -91°$ (*c* = 0.94, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD) δ 7.15 – 7.10 (m, 2H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.05 (s, 1H), 3.60 (dd, *J* = 11.3, 6.5 Hz, 1H), 3.01 (s, 3H), 2.66 (dd, *J* = 13.3, 6.4 Hz, 1H), 2.22 (dd, *J* = 13.1, 11.4 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 173.3, 150.3, 134.6, 130.1, 123.6, 120.7, 108.3, 92.0, 62.0, 54.6, 49.0, 43.9, 33.6, 25.4; FTIR (NaCl, thin film): 3390, 3051, 3024, 2961, 2926, 2668, 2621, 2485, 1609, 1494, 1420, 1339, 1307, 1283, 1265, 1223, 1208, 1156, 1115, 1078, 1036, 1020, 1007, 989, 944, 923, 868, 794, 742 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1285, found 233.1291.

Preparation of reverse prenylated pyrroloindoline amino acid 236



Amino acid **236** was prepared following the same procedure as preparation of amino acid **235**. The crude product was carried to the next reaction without further purification, (64.8 mg, 0.216 mmol, 95% yield). $[\alpha]_D^{25}$ = –102° (*c* = 1.33, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.11 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.04 (d, *J* = 1.9 Hz, 1H), 6.37 (d, *J* = 8.3 Hz, 1H), 6.00 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.17 (s, 1H), 5.04 (d, *J* = 17.4 Hz, 1H), 5.00 (d, *J* = 10.6 Hz, 1H), 3.70 (dd, *J* = 12.4, 6.1 Hz, 1H), 2.99 (s, 3H), 2.56 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.30 (t, *J* = 12.6 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 173.9, 149.1, 148.3, 140.0, 133.9, 127.0, 120.8, 110.5, 106.6, 90.9, 61.4, 53.7, 43.7, 41.2, 34.1, 28.8, 25.7; FTIR (NaCl, thin film): 3400, 2963, 2928, 2873, 2804, 1602, 1502, 1439, 1387, 1377, 1358, 1333, 1289, 1253, 1226, 1211, 1175, 1127, 1098, 1066, 1036, 1007, 904, 810, 768, 753 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{25}N_2O_2$ $[M+H]^+$ 301.1911, found 301.1906.

Preparation of (–)-lansai B (169) and analogues 245, 250



Dissolved amino acid **235** (19.4 mg, 0.084 mmol, 1.0 equiv) and reverse prenylated amino acid **236** (25.1 mg, 0.084 mmol, 1.0 equiv) in dry DCM (4.1 ml). After addition of dry *N*,*N*-diisopropylethylamine (DIPEA, 67 μL, 50 mg, 0.384 mmol, 4.6 equiv), the solution was then cooled to 0 °C. Bis(2-oxo-3-oxazolidinyl) phosphonic chloride (BOP-Cl, 85 mg, 0.334 mmol, 4.0 equiv) was added in one portion. The resulting mixture was allowed to warm to room temperature and stirred for 13 hours. It was quenched with saturated sodium bicarbonate (5 mL), followed by brine (5 mL). Aqueous layer was extracted with EtOAc (3 x 5 mL). Combined organic layer was dried over Na_2SO_4, filtered, and concentrated down to give yellow mixture of oil and solid. Flash chromatography (0% to 20% EtOAc in hexanes) afforded three compounds: diketopiperazine **A-2** as white solid (7.2 mg, 0.017 mmol, 21% yield), (–)-lansai B (**169**) as white solid (15.4 mg, 0.031 mmol, 38% yield), diketopiperazine **A-3** as white solid (9.4 mg, 0.017 mmol, 20% yield).

*(–)-Lansai B (**169**)*: $[\alpha]_D^{25}$ = –505° (*c* = 0.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.05 (m, 1H), 7.07 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.04 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.01 (d, *J* = 1.9 Hz, 1H), 6.70 (td, *J* = 7.4, 0.9 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 6.28 (d, *J* = 8.1 Hz, 1H), 5.97 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.44 (s, 1H), 5.42 (s, 1H), 5.01 (dd, *J* = 14.0, 1.4 Hz, 1H), 4.99 (dd, *J* = 7.2, 1.4 Hz, 1H), 4.15 (app dddd, *J* = 13.5, 11.1, 6.1, 2.1 Hz, 2H), 2.97 (s, 3H), 2.95 (s, 3H), 2.71 (dd, *J* = 12.7, 3.0 Hz, 1H), 2.69 (dd, *J* = 12.7, 3.0 Hz, 1H), 2.18 (dd, *J* = 12.6, 6.3 Hz, 1H), 2.15 (dd, *J* = 12.7, 6.4 Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.5, 150.1, 148.6, 148.2, 138.7, 132.9, 132.8, 128.7, 126.3, 122.3, 120.2, 118.1, 110.1, 105.8, 105.4, 86.9, 86.5, 60.1, 60.1, 50.5, 50.3, 42.7, 42.7, 40.7, 33.1, 32.9, 28.5, 28.5, 25.5, 25.4; FTIR

(NaCl, thin film): 2960, 2926, 2866, 1668, 1608, 1495, 1418, 1340, 1300, 1206, 1163, 1082, 1004, 910, 810, 740 cm^{-1}; HRMS (MM) calc'd for $C_{31}H_{37}N_4O_2$ $[M+H]^+$ 497.2911, found 497.2911.

Diketopiperazine ***245***: $[\alpha]_D^{25}$ = –561° (*c* = 1.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (td, *J* = 7.6, 1.1 Hz, 1H), 7.04 (dd, *J* = 7.3, 0.7 Hz, 1H), 6.70 (td, *J* = 7.4, 0.9 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 5.44 (s, 1H), 4.15 (dd, *J* = 10.6, 5.7 Hz, 1H), 2.97 (s, 3H), 2.70 (dd, *J* = 12.7, 5.9 Hz, 1H), 2.17 (dd, *J* = 12.5, 11.5 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 150.1, 132.9, 128.7, 122.3, 118.1, 105.8, 86.5, 60.1, 50.3, 42.7, 32.9, 25.4; FTIR (NaCl, thin film): 3318, 3052, 3007, 2958, 2926, 2866, 2829, 1665, 1608, 1493, 1421, 1341, 1300, 1259, 1206, 1163, 1122, 1081, 1020, 1004, 936, 895, 818, 799, 751 cm^{-1}; HRMS (APCI) calc'd for $C_{26}H_{29}N_4O_2$ $[M+H]^+$ 429.2285, found 429.2287.

Diketopiperazine ***250***: $[\alpha]_D^{25}$ = –501° (*c* = 0.65, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.01 (d, *J* = 1.7 Hz, 1H), 6.28 (d, *J* = 8.1 Hz, 1H), 5.97 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.42 (s, 1H), 5.01 (d, *J* = 17.4 Hz, 1H), 4.99 (d, *J* = 10.4 Hz, 1H), 4.15 (dd, *J* = 10.5, 5.9 Hz, 1H), 2.96 (s, 3H), 2.70 (dd, *J* = 12.7, 5.9 Hz, 1H), 2.16 (t, *J* = 12.0 Hz, 1H), 1.46 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 148.6, 148.2, 138.6, 132.7, 126.3, 120.2, 110.1, 105.3, 86.9, 60.1, 50.4, 42.7, 40.6, 33.1, 28.50, 28.49, 25.5; FTIR (NaCl, thin film): 3080, 2962, 2923, 2867, 2824, 1666, 1612, 1500, 1414, 1341, 1317, 1289, 1208, 1161, 1081, 1004, 910, 810, 754 cm^{-1}; HRMS (MM) calc'd for $C_{36}H_{45}N_4O_2$ $[M+H]^+$ 565.3537, found 565.3549.

Table 2.1. *Comparison of ^{1}H NMR data for natural vs. synthetic (–)-lansai B (**169**)*

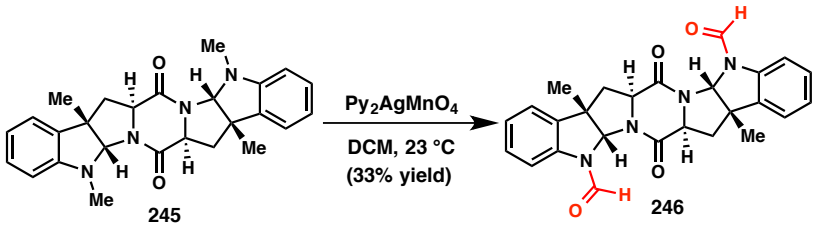
Tuntiwachwuttikul et al. Report,[3] Natural (–)-lansai B ^{1}H NMR, 300 MHz, $CDCl_3$	This Work, Synthetic (–)-lansai B ^{1}H NMR, 500 MHz, $CDCl_3$
δ 7.11 (dt, *J* = 7.8, 1.5 Hz, 1H)	δ 7.13 – 7.05 (m, 1H)
7.08 (dd, *J* = 8.1, 1.5 Hz, 1H)	7.07 (dd, *J* = 8.1, 1.8 Hz, 1H)
7.06 (dd, *J* = 7.8, 1.5 Hz, 1H)	7.04 (dd, *J* = 7.3, 1.2 Hz, 1H)
7.02 (d, *J* = 1.5 Hz, 1H)	7.01 (d, *J* = 1.9 Hz, 1H)
6.71 (dt, *J* = 7.8, 1.5 Hz, 1H)	6.70 (td, *J* = 7.4, 0.9 Hz, 1H)
6.36 (dd, *J* = 7.8, 1.5 Hz, 1H)	6.34 (d, *J* = 7.8 Hz, 1H)
6.29 (d, *J* = 8.1 Hz, 1H)	6.28 (d, *J* = 8.1 Hz, 1H)
5.99 (dd, *J* = 17.5, 10.6 Hz, 1H)	5.97 (dd, *J* = 17.4, 10.6 Hz, 1H)
5.46 (s, 1H)	5.44 (s, 1H)
5.44 (s, 1H)	5.42 (s, 1H)
5.03 (d, *J* = 10.6 Hz, 1H)	5.01 (dd, *J* = 14.0, 1.4 Hz, 1H)
5.01 (d, *J* = 17.5 Hz, 1H)	4.99 (dd, *J* = 7.2, 1.4 Hz, 1H)
4.16 (m, 1H)	4.15 (app dddd, *J* = 13.5, 11.1, 6.1, 2.1 Hz, 2H)
4.16 (m, 1H)	–
2.99 (s, 3H)	2.97 (s, 3H)
2.97 (s, 3H)	2.95 (s, 3H)
2.72 (dd, *J* = 12.3, 5.9 Hz, 1H)	2.71 (dd, *J* = 12.7, 3.0 Hz, 1H)
2.72 (dd, *J* = 12.3, 5.9 Hz, 1H)	2.69 (dd, *J* = 12.7, 3.0 Hz, 1H)
2.18 (dd, *J* = 12.3, 11.3 Hz, 1H)	2.18 (dd, *J* = 12.6, 6.3 Hz, 1H)
2.17 (dd, *J* = 12.3, 11.3 Hz, 1H)	2.15 (dd, *J* = 12.7, 6.4 Hz, 1H)
1.49 (s, 3H)	1.47 (s, 3H)
1.48 (s, 3H)	1.46 (s, 3H)
1.36 (s, 6H)	1.34 (s, 6H)

Table 2.2. *Comparison of ^{13}C NMR data for natural vs. synthetic (–)-lansai B*

Tuntiwachwuttikul et al. Report,[3] Natural (–)-lansai B ^{13}C NMR, 75 MHz, $CDCl_3$	This Work, Synthetic (–)-lansai B ^{13}C NMR, 126 MHz, $CDCl_3$	Chemical Shift Difference, Δδ
δ 165.8	δ 165.7	0.1
165.6	165.5	0.1
150.1	150.1	0.0
148.6	148.6	0.0
148.3	148.2	0.1
138.7	138.7	0.0
132.9	132.9	0.0
132.8	132.8	0.0
128.8	128.7	0.1

126.3	126.3	0.0
122.3	122.3	0.0
120.2	120.2	0.0
118.1	118.1	0.0
110.2	110.1	0.1
105.8	105.8	0.0
105.4	105.4	0.0
86.9	86.9	0.0
86.6	86.5	0.1
60.1	60.1	0.0
60.1	60.1	0.0
50.5	50.5	0.0
50.3	50.3	0.0
42.7	42.7	0.0
42.7	42.7	0.0
40.7	40.7	0.0
33.1	33.1	0.0
32.9	32.9	0.0
28.5	28.5	0.0
28.5	28.5	0.0
25.5	25.5	0.0
25.4	25.4	0.0

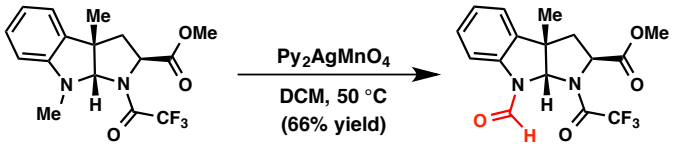
Preparation of *N*-formyl DKP 246



To a vial containing DKP **245** (5.5 mg, 0.013 mmol, 1.0 equiv) and Py_2AgMnO_4[38] (21 mg, 0.05 mmol, 4.0 equiv) was added dry DCM (0.2 mL). The resulting mixture was stirred at room temperature for 22 hours. Then a second portion of Py_2AgMnO_4 (10 mg, 0.025 mmol, 2.0 equiv) was added and the reaction was further stirred for another 18 hours. The mixture was then diluted with EtOAc (5 mL), which was sequentially washed with saturated sodium bisulfite (2 mL), saturated copper sulfate (2 mL), and saturated

ammonium chloride (2 mL). Combined organic layer was dried over Na_2SO_4, filtered, and concentrated down. Flash chromatography (20% to 100% EtOAc in hexanes) afforded *N*-formyl DKP **246** as a white solid (1.9 mg, 0.004 mmol, 33% yield). $[\alpha]_D^{25} = -378°$ (*c* = 0.105, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (s, 1H), H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.25 (td, *J* = 7.7, 1.4 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.13 (td, *J* = 7.5, 1.1 Hz, 1H), 5.80 (s, 1H), 4.13 (dd, *J* = 10.5, 5.8 Hz, 1H), 2.81 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.30 (dd, *J* = 13.0, 11.4 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 161.8, 139.8, 134.9, 129.2, 125.7, 122.6, 117.1, 80.0, 60.2, 51.0, 40.8, 24.9; FTIR (NaCl/thin film): 2963, 2924, 2868, 1678, 1599, 1552, 1485, 1464, 1446, 1413, 1378, 1344, 1292, 1232, 1206, 1157, 1102, 793, 761 cm^{-1}; HRMS (MM) calc'd for $C_{26}H_{25}N_4O_4$ $[M+H]^+$ 457.1870, found 457.1882.

Preparation of *N*-formyl pyrroloindoline 248

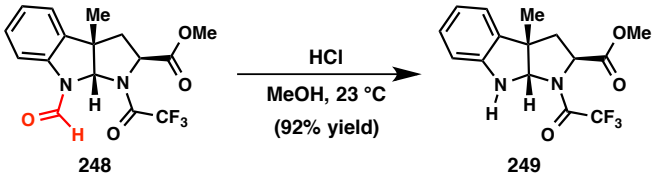


exo-225 248

To a vial containing pyrroloindoline **225** (54 mg, 0.16 mmol, 1.0 equiv) and Py_2AgMnO_4 (304 mg, 0.79 mmol, 5.0 equiv) was added dry DCM (1.6 mL). The resulting mixture was heated to 50 °C for 21 hours after being sealed. The mixture was then cooled to room temperature and diluted with EtOAc (10 mL), and sequentially washed with saturated sodium bisulfite (5 mL), saturated copper sulfate (5 mL), and saturated ammonium chloride (5 mL). Combined organic layer was dried over Na_2SO_4, filtered, and concentrated down. Flash chromatography (0% to 40% EtOAc in hexanes) afforded *N*-formyl pyrroloindoline **248** as a thick oil (37.1 mg, 0.104 mmol, 66% yield).

$[\alpha]_D^{25}$ = –159° (*c* = 1.815, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.32 (td, *J* = 7.8, 1.4 Hz, 1H), 7.23 (d, *J* = 7.1 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 5.93 (s, 1H), 4.48 (t, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.94 (dd, *J* = 13.3, 8.1 Hz, 1H), 2.31 (dd, *J* = 13.4, 8.3 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.3, 171.5, 162.1, 158.8 (q, $J_{C\text{-}F}$ = 38.2 Hz), 138.8, 135.8, 129.2, 125.7, 122.1, 118.0, 115.4 (q, $J_{C\text{-}F}$ = 287.9 Hz), 83.9, 59.9, 53.2, 50.3, 48.4, 43.9, 41.8, 24.3; FTIR (NaCl/thin film): 3014, 2961, 2931, 2874, 1752, 1691, 1603, 1484, 1467, 1452, 1437, 1409, 1389, 1381, 1357, 1331, 1312, 1288, 1277, 1253, 1212, 1166, 1106, 1067, 1021, 1007, 979, 945, 914, 878, 805, 759, 729 cm^{-1}; HRMS (MM) calc'd for $C_{16}H_{16}F_3N_2O_4$ $[M+H]^+$ 357.1057, found 357.1071.

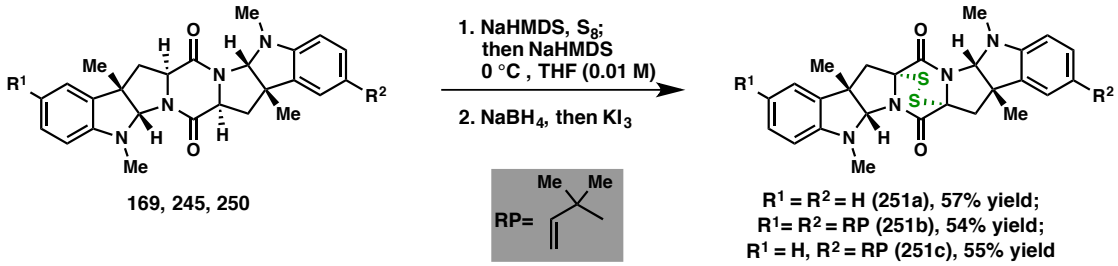
Preparation of *N*-proto-pyrroloindoline 249



248 249

To a solution of *N*-formyl-pyrroloindoline **248** (12.6 mg, 0.035 mmol, 1.0 equiv) in MeOH (0.35 mL) was added freshly prepared 1M HCl methanol solution (39 μL, 0.039 mmol, 1.1 equiv). The resulting solution was allowed to stir at room temperature for 7 hours. It was carefully quenched with saturated sodium bicarbonate (5 mL), followed by brine (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). Combined organic layer was dried over Na_2SO_4, filtered, and concentrated down. Flash chromatography (0% to 20% EtOAc in hexanes) afforded secondary amine **249**, as a colorless oil (10.6 mg, 0.032 mmol, 92% yield). Spectral data matches that reported in the literature.[39]

Preparation of lansai ETP derivatives 251a-c[35]



Typical procedure of preparation of ETP **251c**: To a suspension of sulfur (4.2 mg, 0.13 mmol) in THF (2 mL) at 0 °C under argon was added NaHMDS (0.6 M in PhMe, 330 μL, 0.20 mmol) dropwise over 2 min. This solution was stirred for an additional 1 min, and lansai B (**169**) (8.2 mg, 0.017 mmol) dissolved in THF (8.5 mL) was added dropwise at 0 °C over 2 min. The mixture was stirred for an additional 1 min, then more NaHMDS (0.6 M in PhMe, 180 μL, 0.11 mmol) was added and the resulting mixture was stirred 0.5 hours at 0 °C. The reaction mixture was quenched with saturated aq. NH_4Cl solution (5 mL). The mixture was extracted with DCM (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting brownish residue was used for the next step without further purification.

To the above crude product dissolved in a mixture of degassed THF/EtOH (1:1, 1.0 mL) at 0 °C was added $NaBH_4$ (15.6 mg, 0.41 mmol) in small portions over 1 min. The resulting mixture was stirred for 45 min while it was allowed to warmed up to 25 °C. After this time, the solution was cooled to 0 °C, and quenched by careful addition of saturated aq. NH_4Cl solution (3 mL). The resulting mixture was extracted with EtOAc (3 × 3 mL) and to the combined organic extracts was added an aq. solution of KI_3 (3 mL, 1.4 M). This mixture was stirred for 10 min and then quenched by the addition of sat. aq. $Na_2S_2O_3$ solution (3 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL),

dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (0% to 20% EtOAc in hexanes) to afford epidithiodiketopiperazine **251c** (5.0 mg, 0.009 mmol, 54% yield).

*Epidithiodiketopiperazine **251a***: $[\alpha]_D^{25} = -576°$ ($c = 0.390$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (td, $J = 7.7, 1.2$ Hz, 1H), 7.07 (dd, $J = 7.3, 0.7$ Hz, 1H), 6.76 (td, $J = 7.5, 0.7$ Hz, 1H), 6.45 (d, $J = 7.8$ Hz, 1H), 5.34 (s, 1H), 3.27 (d, $J = 14.7$ Hz, 1H), 3.07 (s, 3H), 2.59 (d, $J = 14.7$Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 149.2, 133.9, 128.9, 121.7, 118.4, 107.0, 90.7, 52.1, 44.3, 34.9, 25.1; FTIR (NaCl/thin film): 3052, 3020, 2959, 2925, 2867, 1693, 1608, 1493, 1445, 1384, 1357, 1324, 1302, 1274, 1185, 1124, 1104, 1093, 1060, 1020, 997, 941, 797, 742 cm^{-1}; HRMS (APCI) calc'd for $C_{26}H_{27}N_4O_2$ $[M+H–S_2]^+$ 491.1570, found 491.1576.

*Epidithiodiketopiperazine **251b***: $[\alpha]_D^{25} = -613°$ ($c = 0.355$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.12 (m, 2H), 7.08 (dd, $J = 7.5, 0.9$ Hz, 1H), 7.04 (d, $J = 2.0$ Hz, 1H), 6.76 (td, $J = 7.4, 0.9$ Hz, 1H), 6.46 (d, $J = 7.8$ Hz, 1H), 5.99 (dd, $J = 17.3, 10.5$ Hz, 1H), 5.35 (s, 1H), 5.32 (s, 1H), 5.02 (dd, $J = 11.0, 1.5$ Hz, 1H), 4.99 (dd, $J = 7.2, 1.4$ Hz, 1H), 3.28 (d, $J = 2.2$ Hz, 1H), 3.25 (d, $J = 2.2$ Hz, 1H), 3.09 (s, 3H), 3.04 (s, 3H), 2.59 (dd, $J = 14.5, 8.7$ Hz, 2H), 1.51 (s, 3H), 1.50 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 164.4, 149.2, 148.6, 147.4, 138.9, 133.9, 133.7, 128.9, 126.3, 121.7, 112.0, 118.4, 110.3, 107.0, 106.6, 91.2, 90.7, 76.0, 75.9, 52.3, 52.1, 44.4, 44.4, 40.7, 35.0, 34.9, 28.5, 28.5, 25.1, 24.7; FTIR (NaCl/thin film): 2961, 2925, 2868, 1693, 1608, 1494, 1358, 1317, 1302, 1186, 1120, 1053, 997, 911, 812, 753 cm^{-1}; HRMS (APCI) calc'd for $C_{31}H_{35}N_4O_2$ $[M+H–S_2]^+$ 559.2196, found 559.2183.

Epidithiodiketopiperazine ***251c***: $[\alpha]_D^{25} = -577°$ ($c = 0.210$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.1, 2.0 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 6.40 (d, J = 8.3 Hz, 1H), 5.99 (dd, J = 17.5, 10.6 Hz, 1H), 5.32 (s, 1H), 5.02 (dd, J = 11.1, 1.2 Hz, 1H), 4.99 (dd, J = 4.4, 1.2 Hz, 1H), 3.26 (d, J = 14.4 Hz, 1H), 3.05 (s, 3H), 2.59 (dd, J = 14.7 Hz, 1H), 1.50 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 148.6, 147.4, 138.9, 133.8, 126.3, 119.7, 110.3, 106.5, 91.2, 52.3, 44.4, 40.7, 35.0, 28.55, 28.50, 24.7; FTIR (NaCl/thin film): 3079, 2962, 2926, 2869, 2824, 1695, 1619, 1498, 1446, 1431, 1411, 1358, 1315, 1287, 1185, 1136, 1117, 1099, 1053, 996, 910, 809, 754 cm^{-1}; HRMS (APCI) calc'd for $C_{36}H_{43}N_4O_2$ $[M+H-S_2]^+$ 627.2822, found 627.2819.

2.6 NOTES AND REFERENCES

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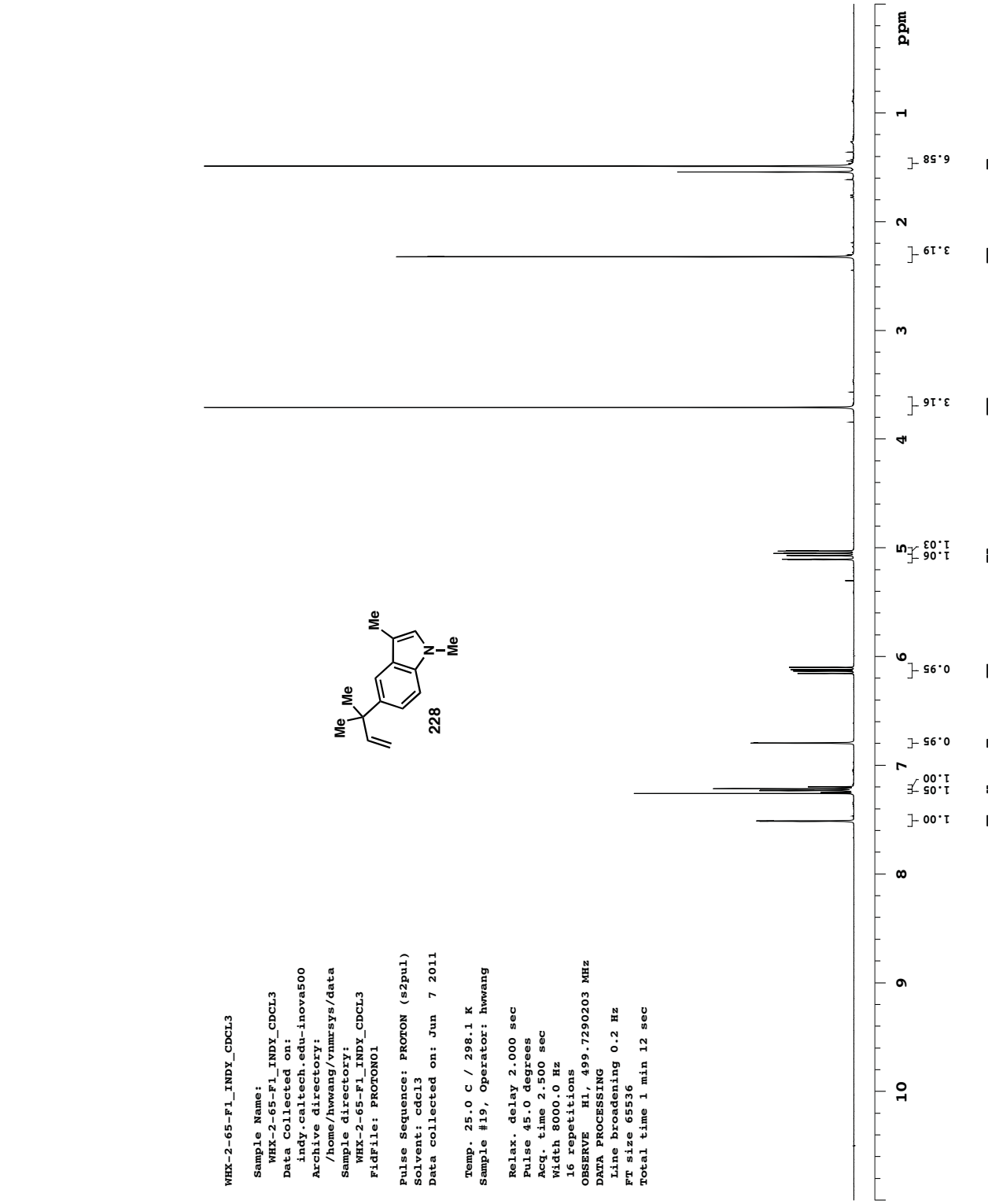
Appendix 1

Spectra Relevant to Chapter 2:
Direct Application of Enantioselective (3 + 2) Formal Cycloaddition:
Concise Enantioselective Total Synthesis of (–)-Lansai B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Sample directory:
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Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
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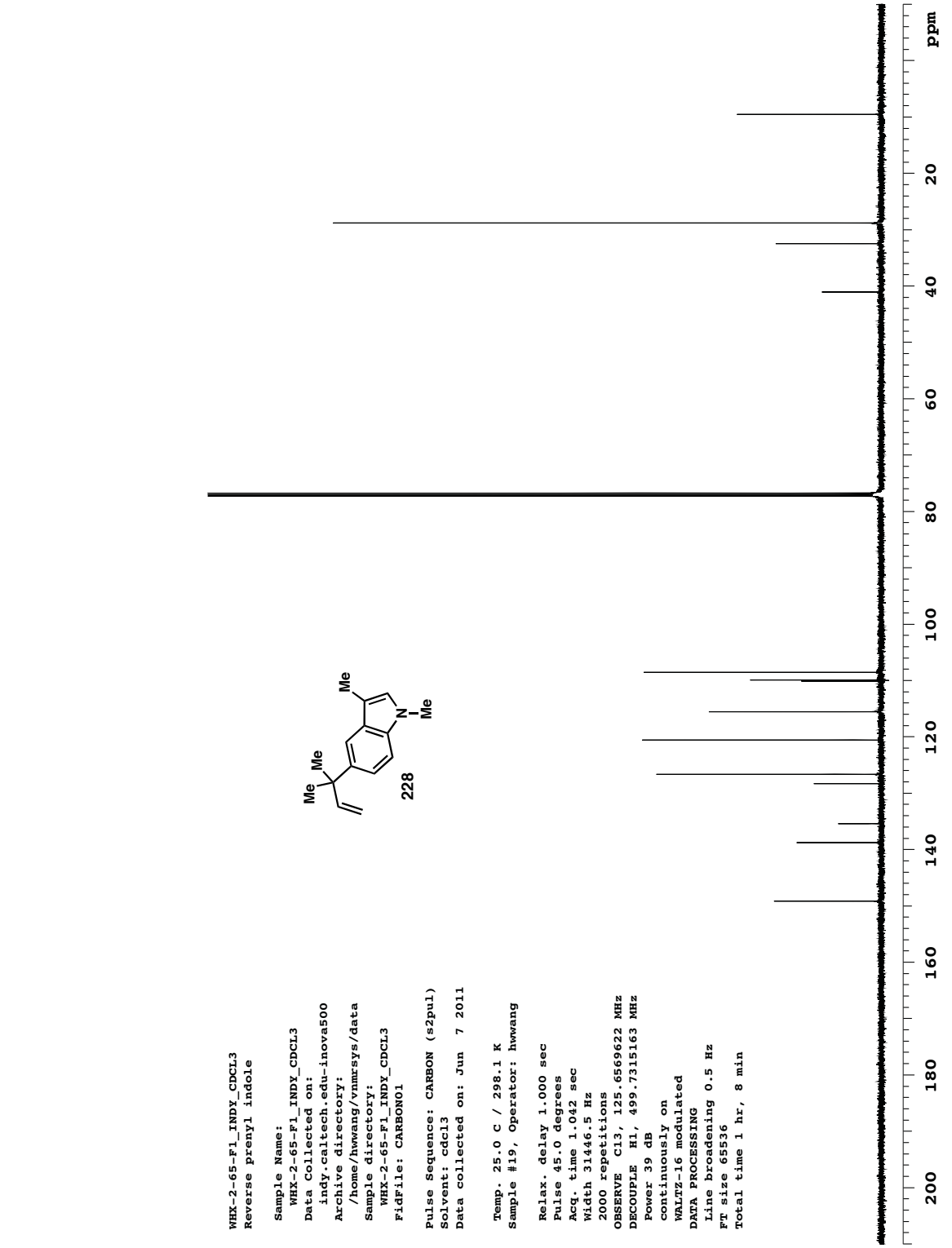
Temp. 25.0 C / 298.1 K
Sample #19, Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
Me
Me
Me
N
Me
228
ppm
10
9
8
7
6
5
4
3
2
1
1.00
1.05
1.00
0.95
0.95
1.06
1.03
3.16
3.19
6.58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Reverse prenyl indole
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Archive directory:
/home/hwang/vnmrsys/data
Sample directory:
WHX-2-65-F1_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 7 2011
Temp. 25.0 C / 298.1 K
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6569622 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
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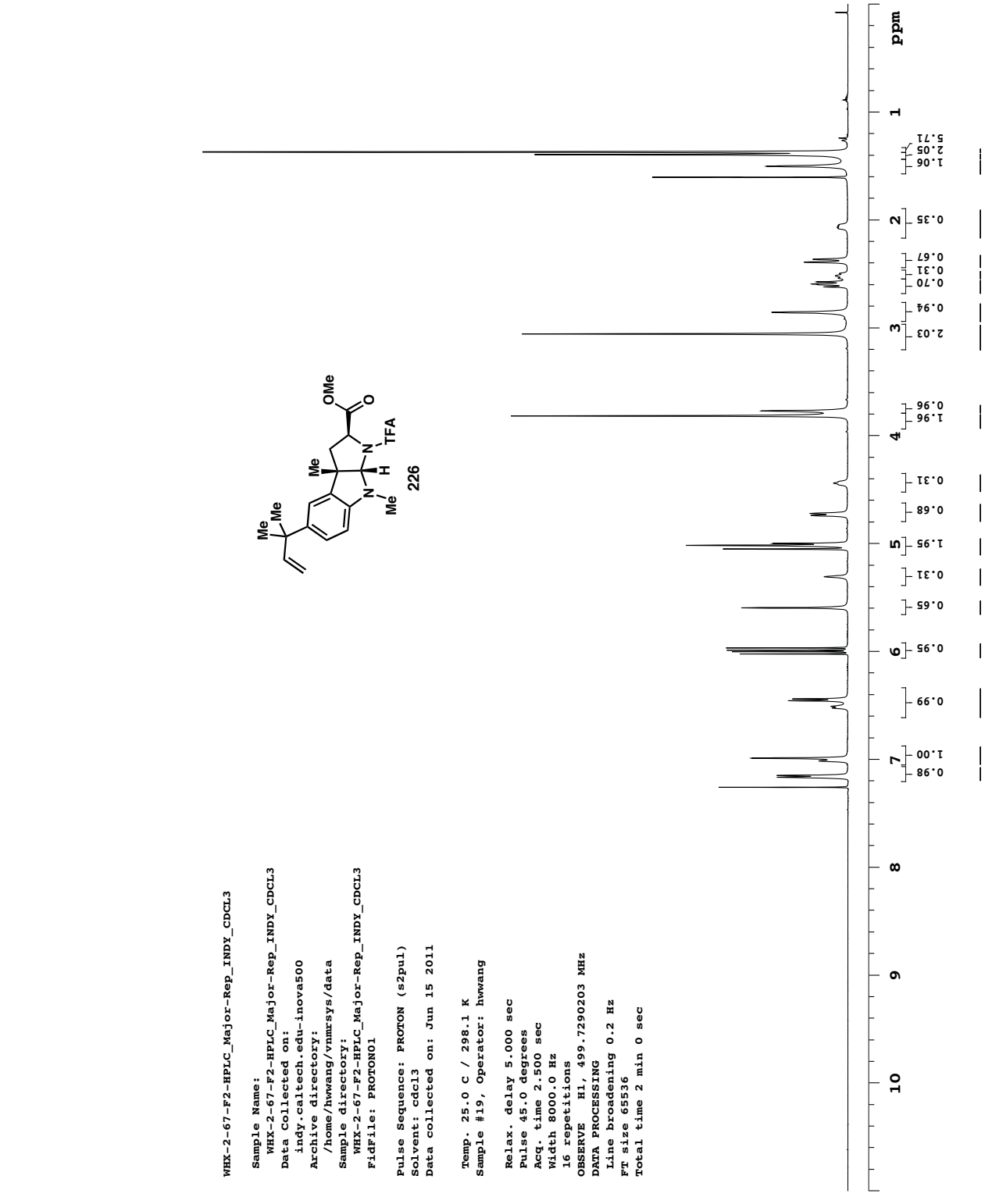
Me
Me
N
Me
228
200
180
160
140
120
100
80
60
40
20
ppm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Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
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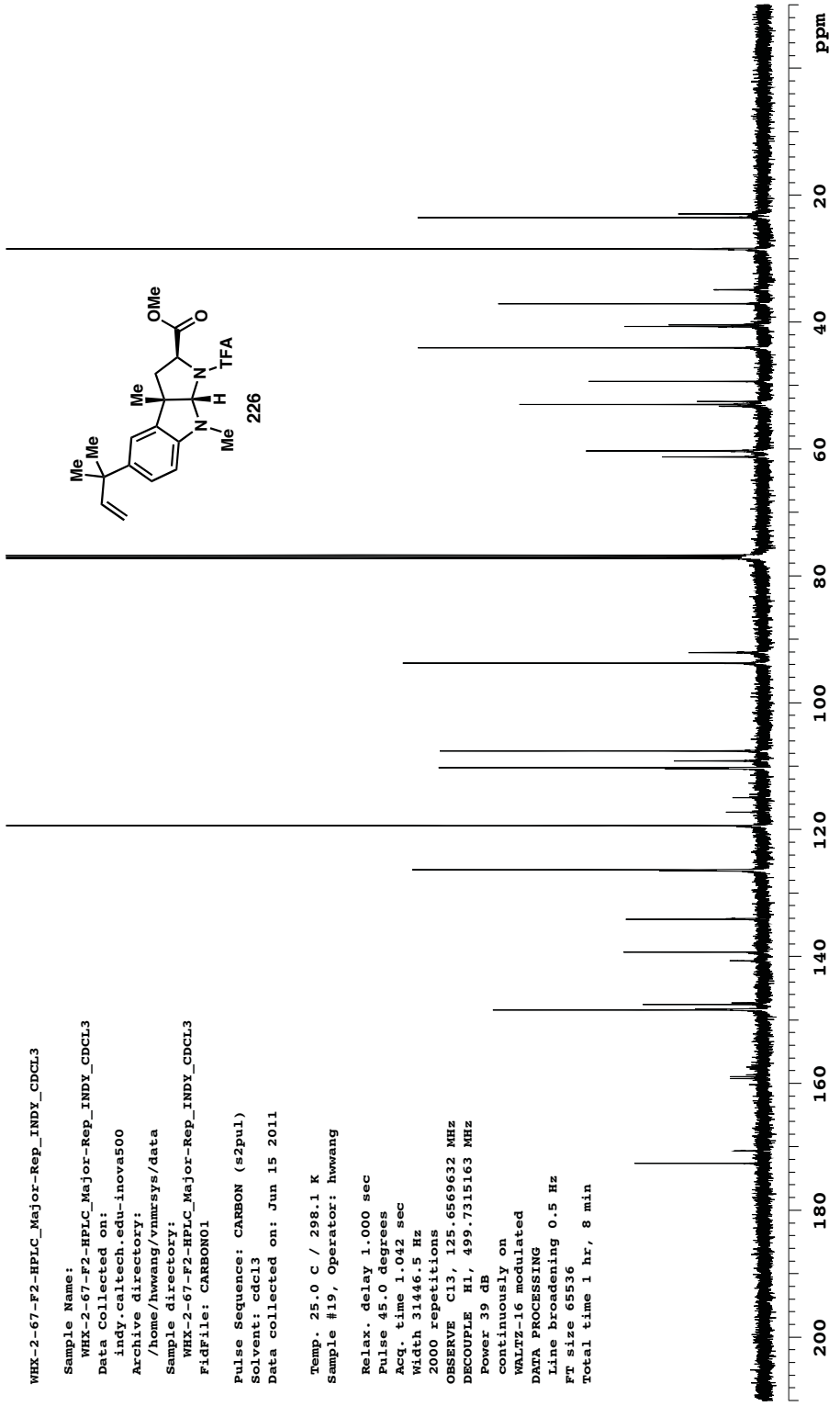
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 15 2011
Temp. 25.0 C / 298.1 K
Sample #19, Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
OMe
O
TFA
Me
Me
Me
Me
N
H
N
226
ppm
10
9
8
7
6
5
4
3
2
1
0.98
1.00
0.99
0.95
0.65
0.31
1.95
0.68
0.31
1.96
0.96
2.03
0.94
0.70
0.31
0.67
0.35
1.06
2.05
5.71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Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
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Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 15 2011
Temp. 25.0 C / 298.1 K
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Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6569632 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min
Me
Me
Me
OMe
O
N
H
TFA
N
Me
226
200
180
160
140
120
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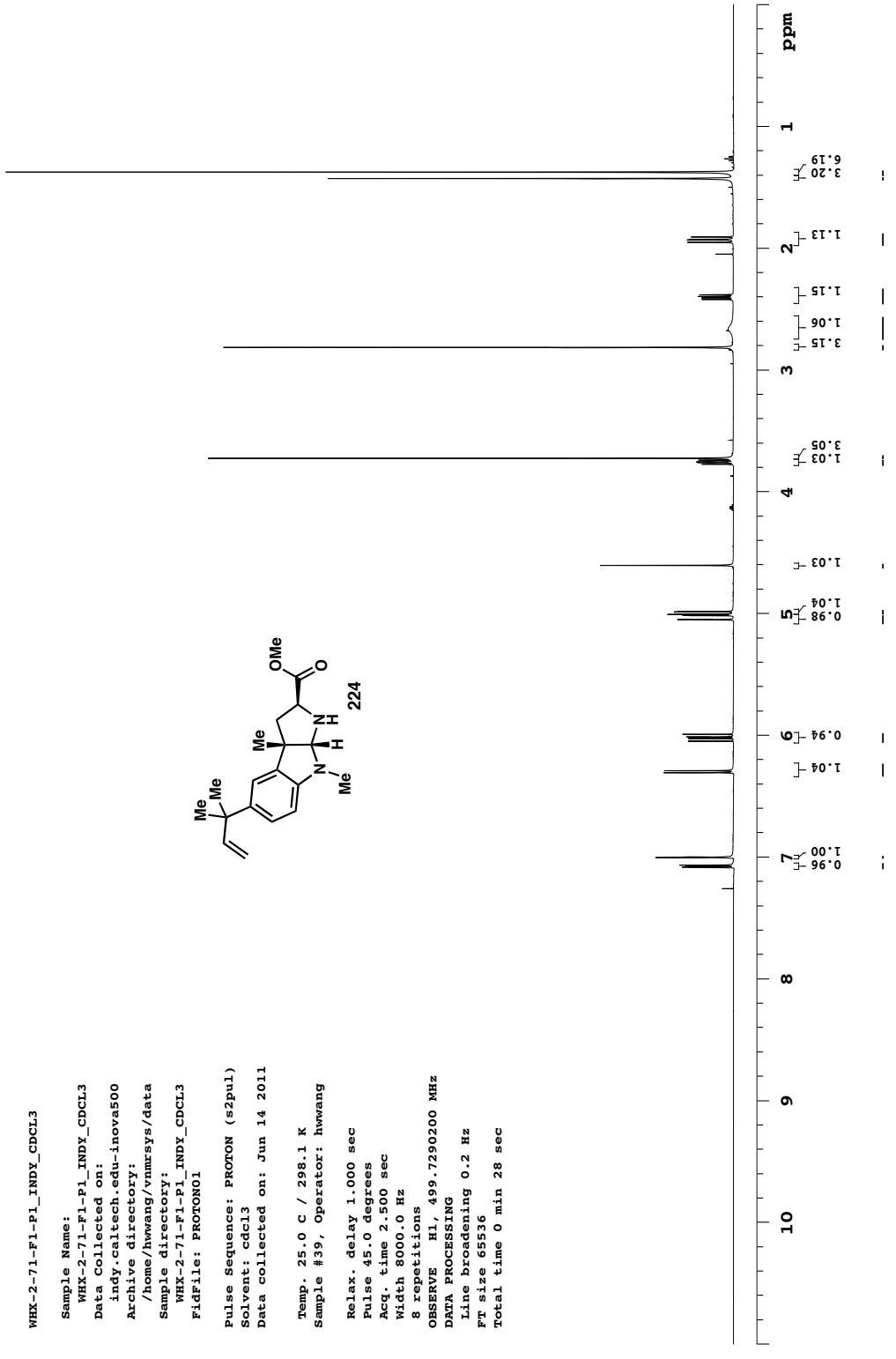
80
60
40
20
ppm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Archive directory:
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Sample directory:
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FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 14 2011
Temp. 25.0 C / 298.1 K
Sample #39, Operator: hwwang
Relax. delay 1.000 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 28 sec
OMe
O
Me
Me
Me
Me
N
H
N
H
224
ppm
10
9
8
7
6
5
4
3
2
1
0.96
1.00
1.04
0.94
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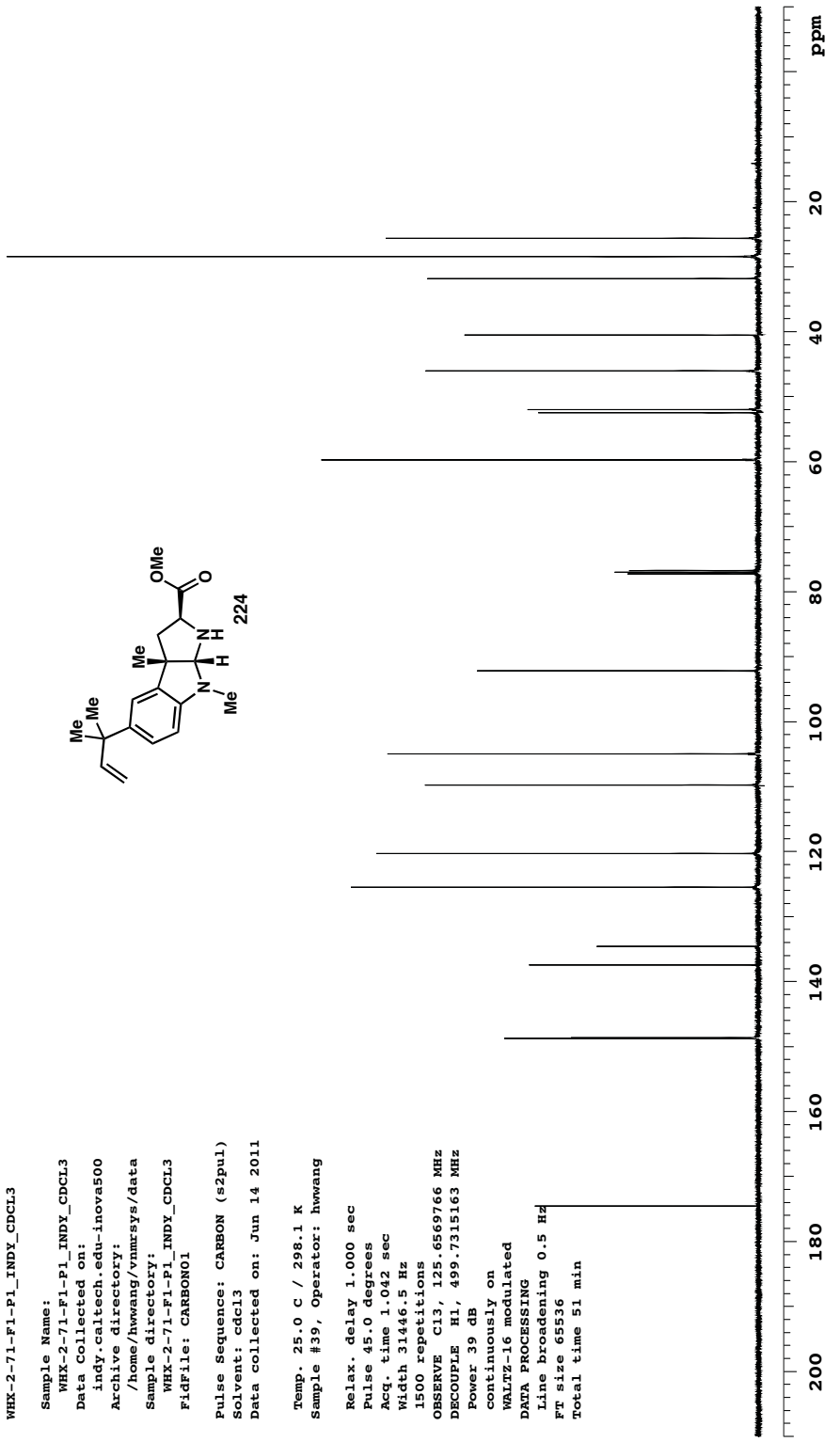
1.04
1.03
1.03
3.05
3.15
1.06
1.15
1.13
3.20
6.19


WHX-2-71-F1-P1_INDY_CDCL3
Sample Name:
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Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-71-F1-P1_INDY_CDCL3
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Solvent: cdcl3
Data collected on: Jun 14 2011
Temp. 25.0 C / 298.1 K
Sample #39, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
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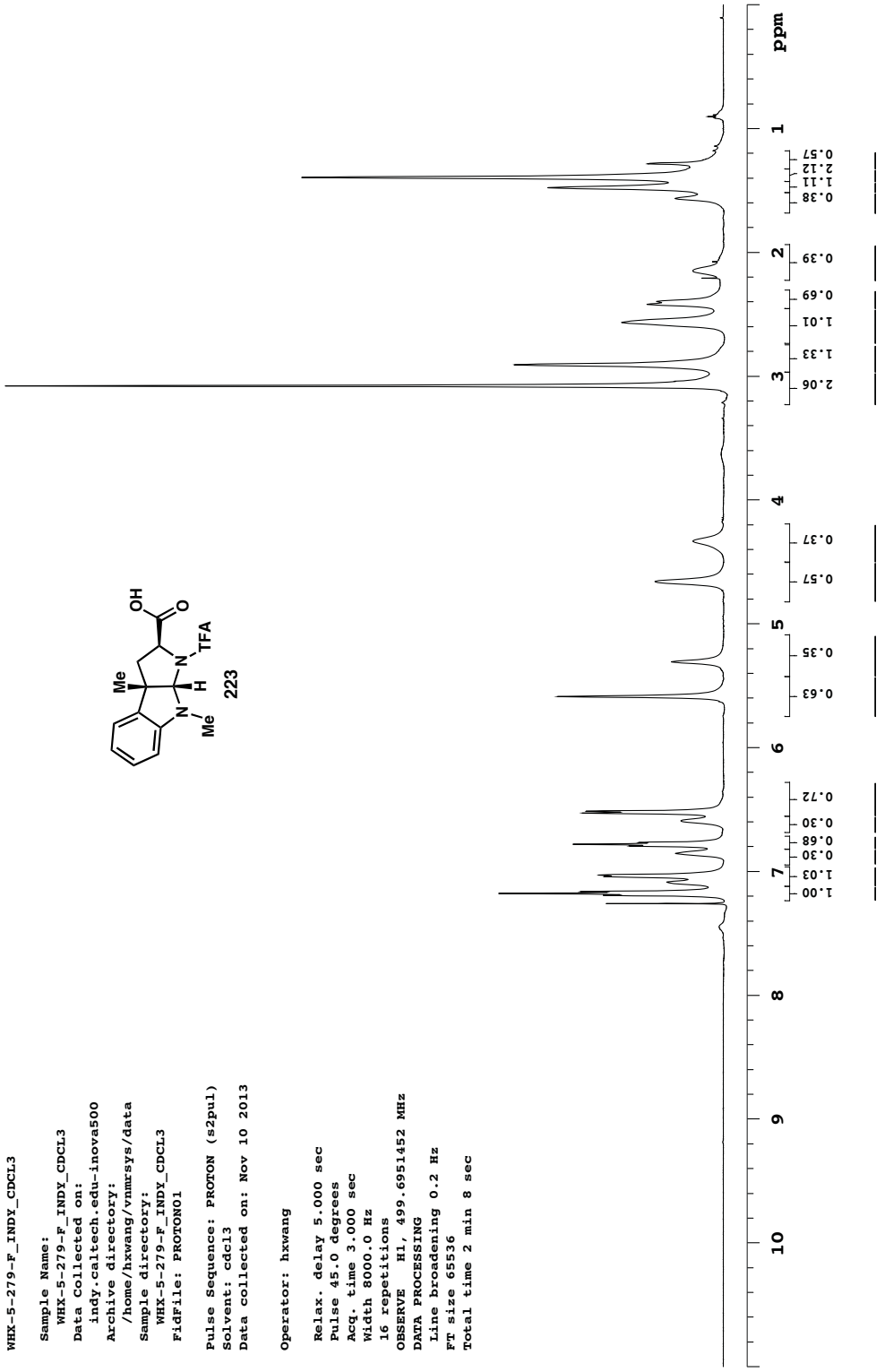
1500 repetitions
OBSERVE C13, 125.6569766 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
Me
Me
Me
OMe
O
N
H
N
H
Me
224
200
180
160
140
120
100
80
60
40
20
ppm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Archive directory:
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Sample directory:
WHX-5-279-F_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 10 2013
Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6951452 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
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O
N
TFA
Me
H
N
Me
223
ppm
1.00
1.03
0.30
0.68
0.30
0.72
0.63
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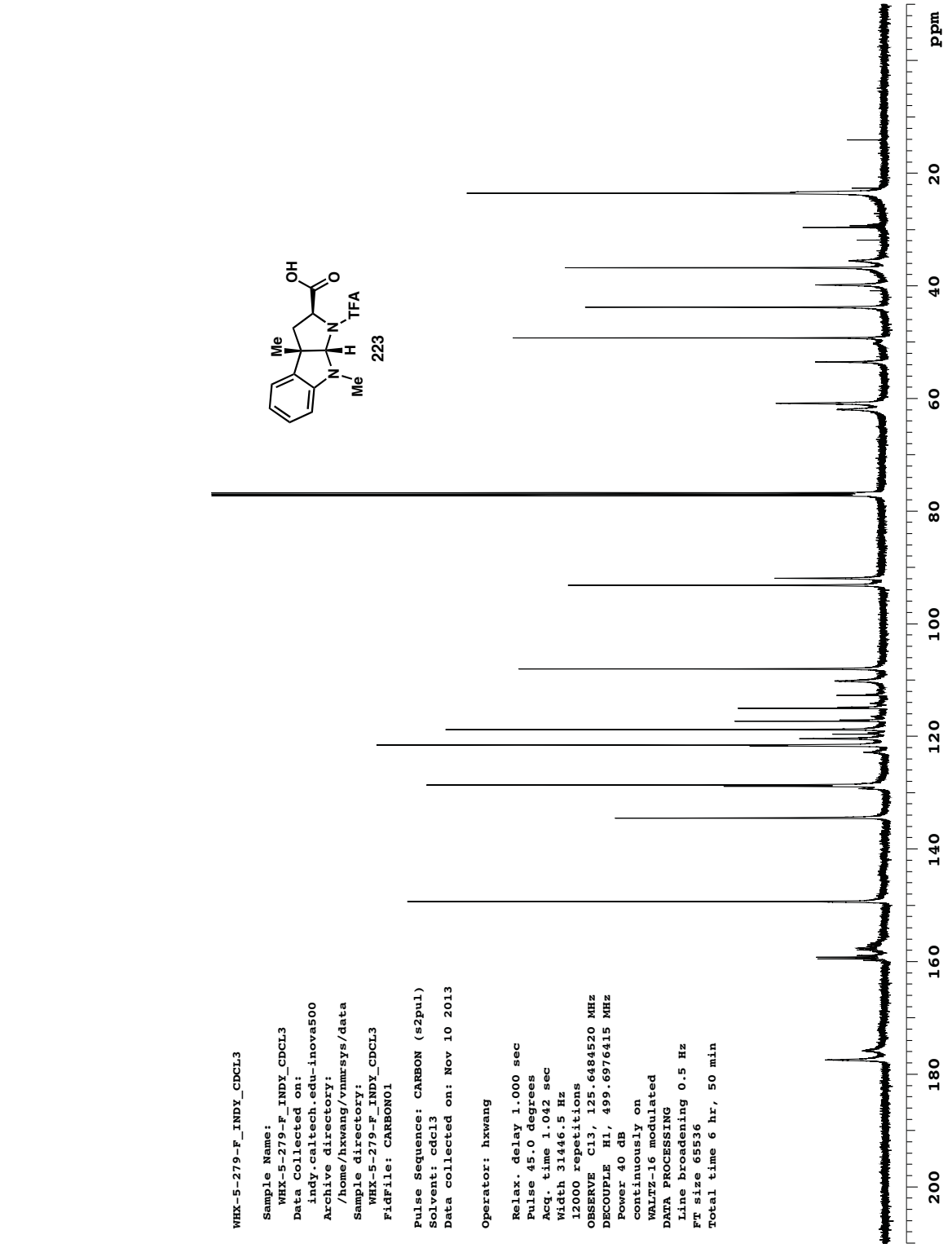
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FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 10 2013
Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
12000 repetitions
OBSERVE C13, 125.6484520 MHz
DECOUPLE H1, 499.6976415 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
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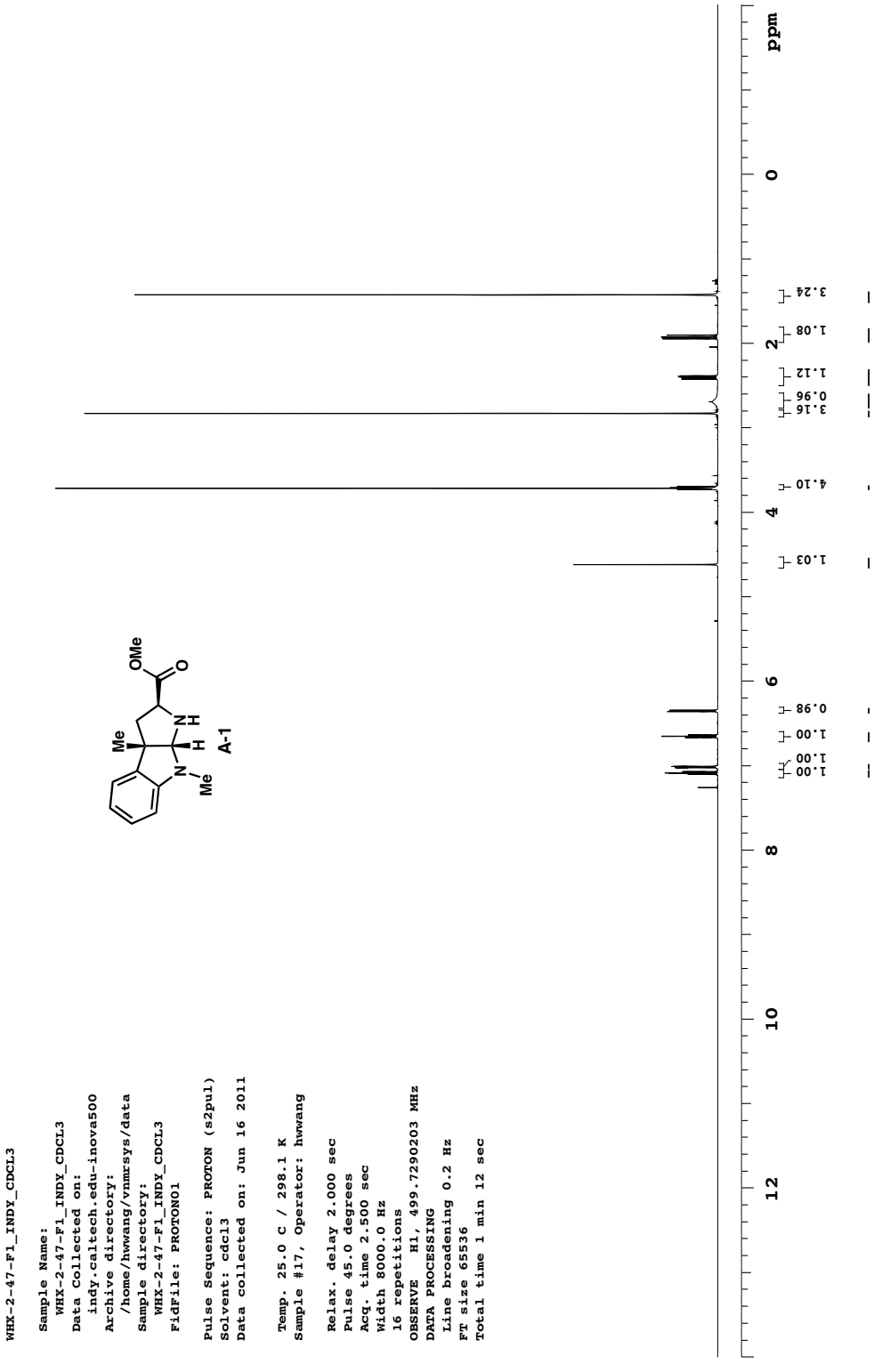
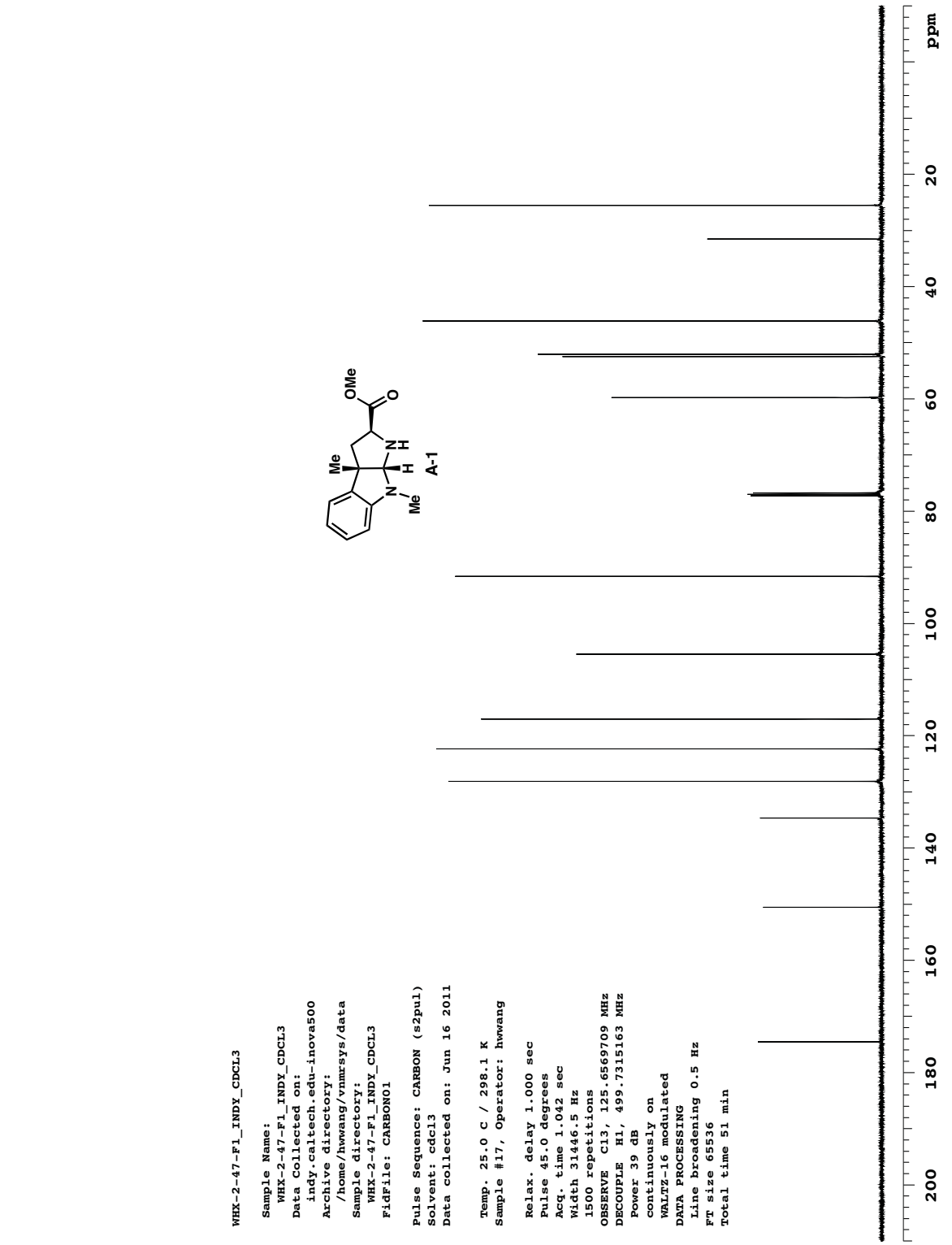
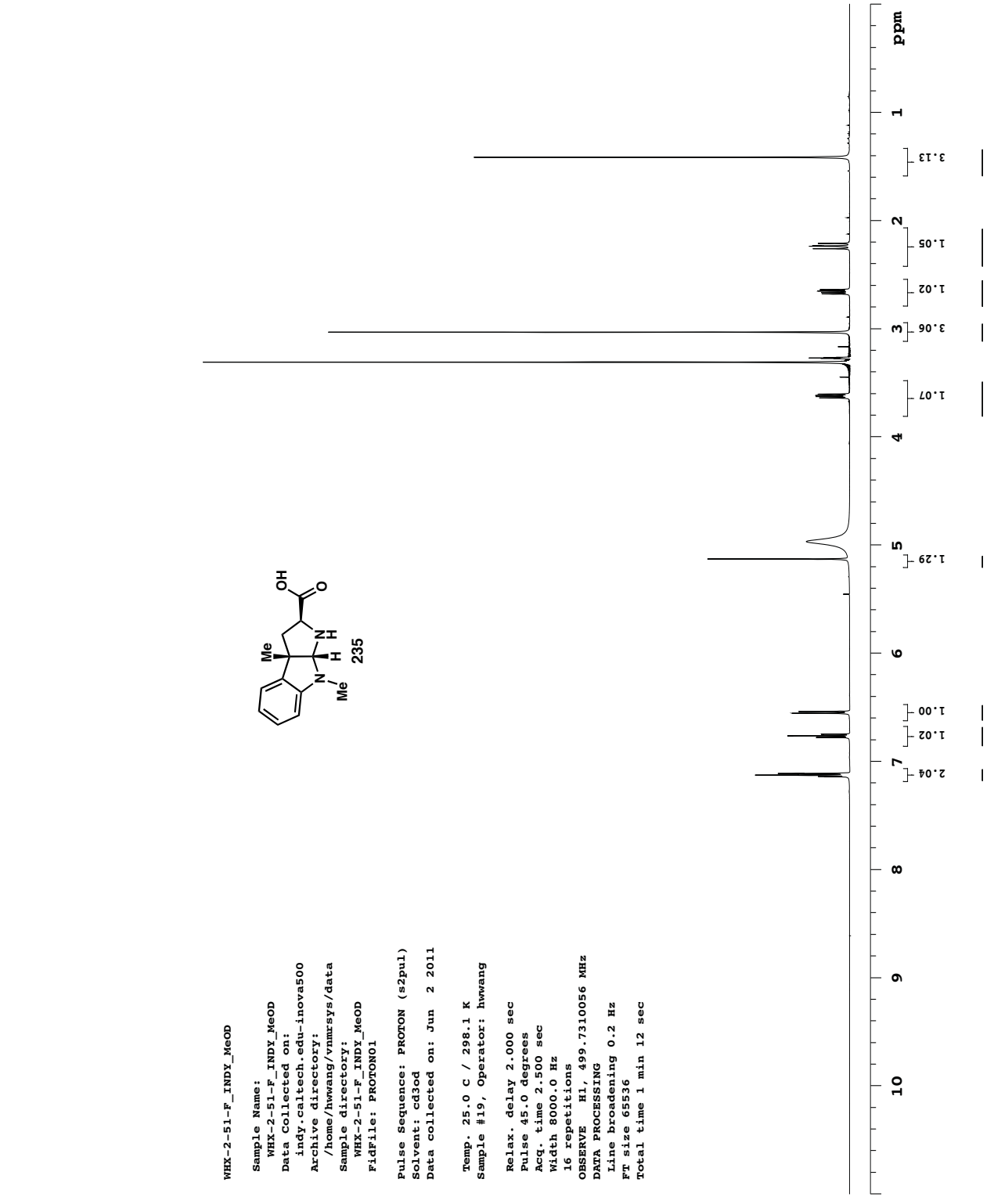
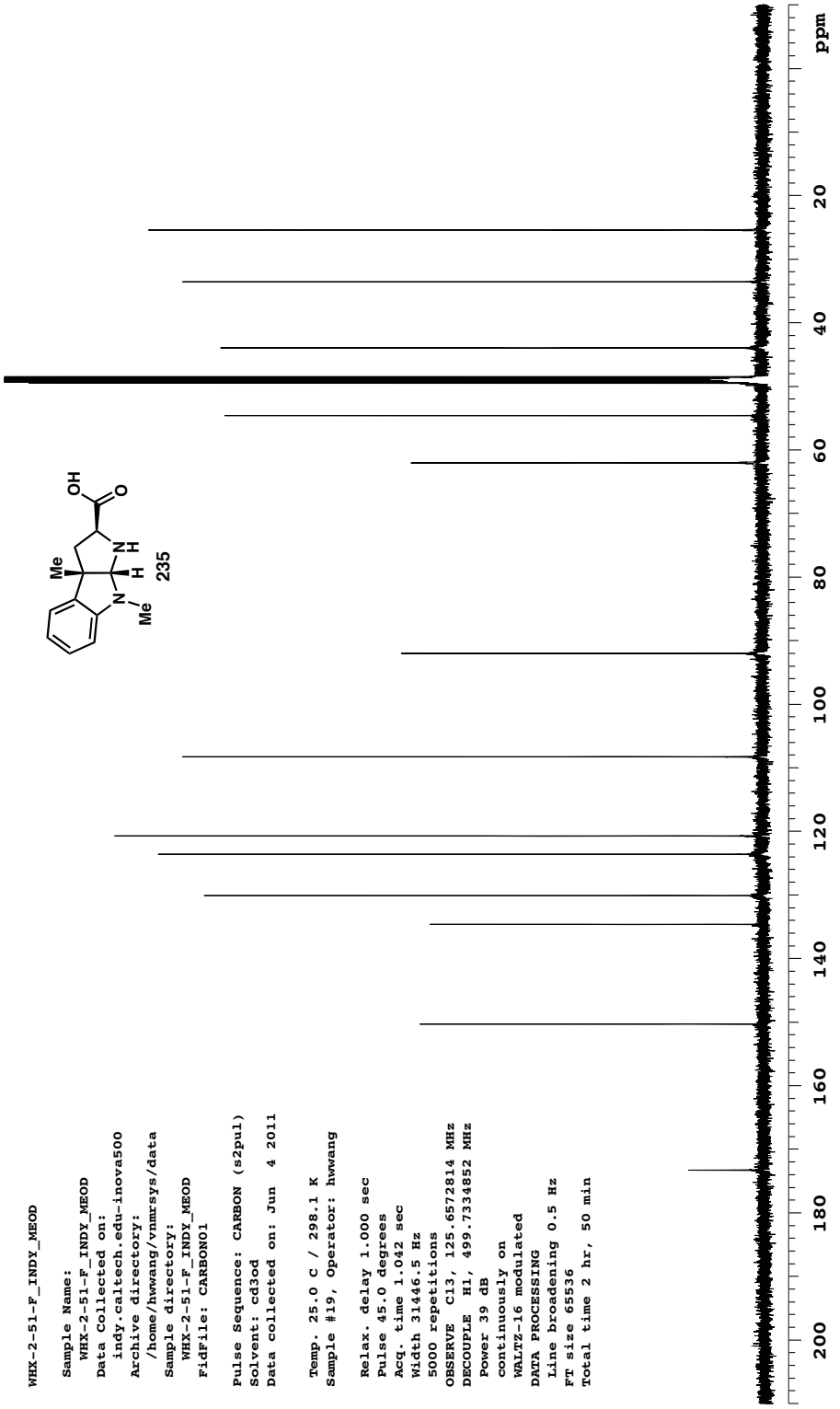
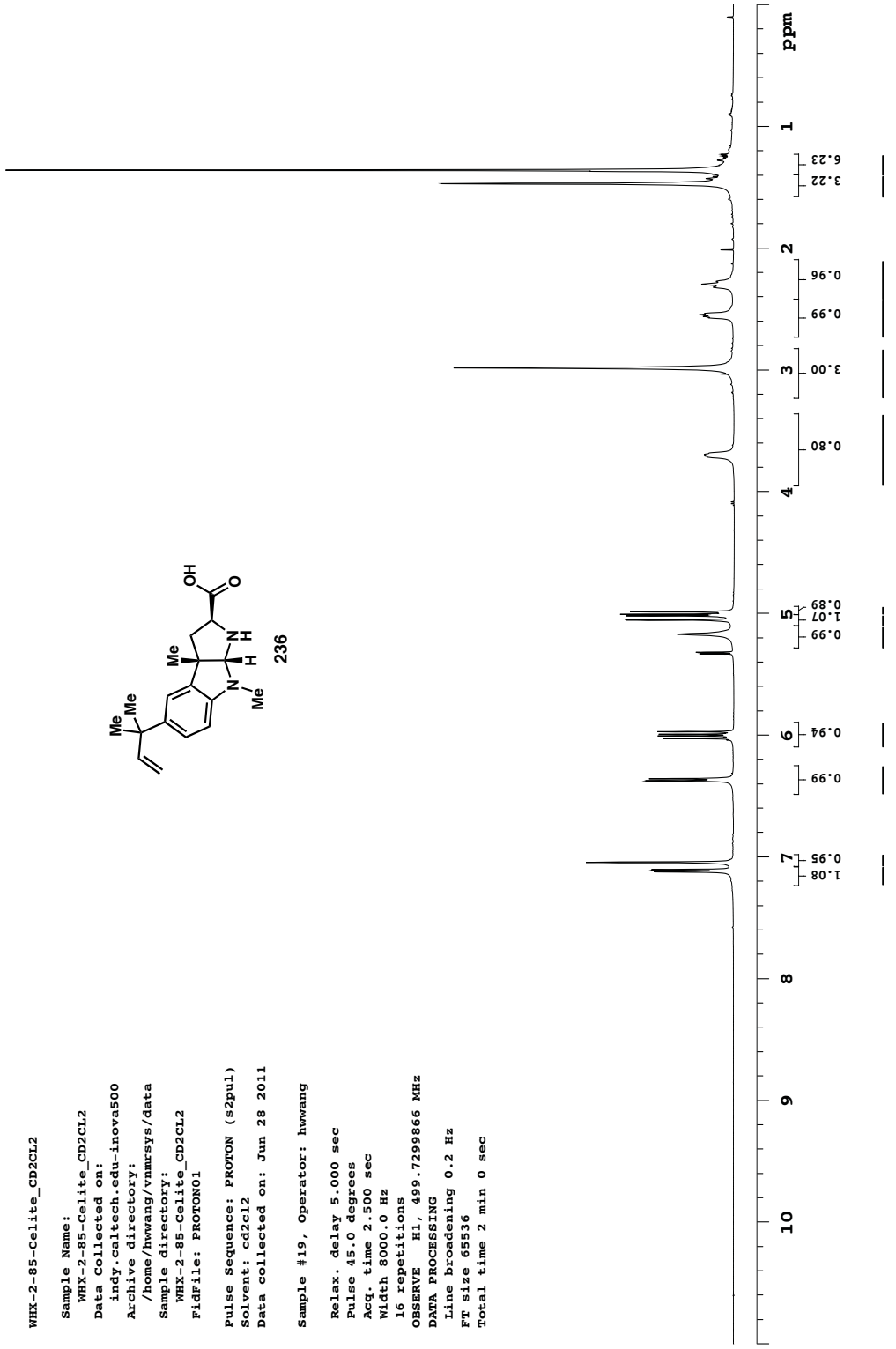
Total time 6 hr, 50 min
OH
O
Me
N
TFA
H
N
Me
223
200
180
160
140
120
100
80
60
40
20
ppm

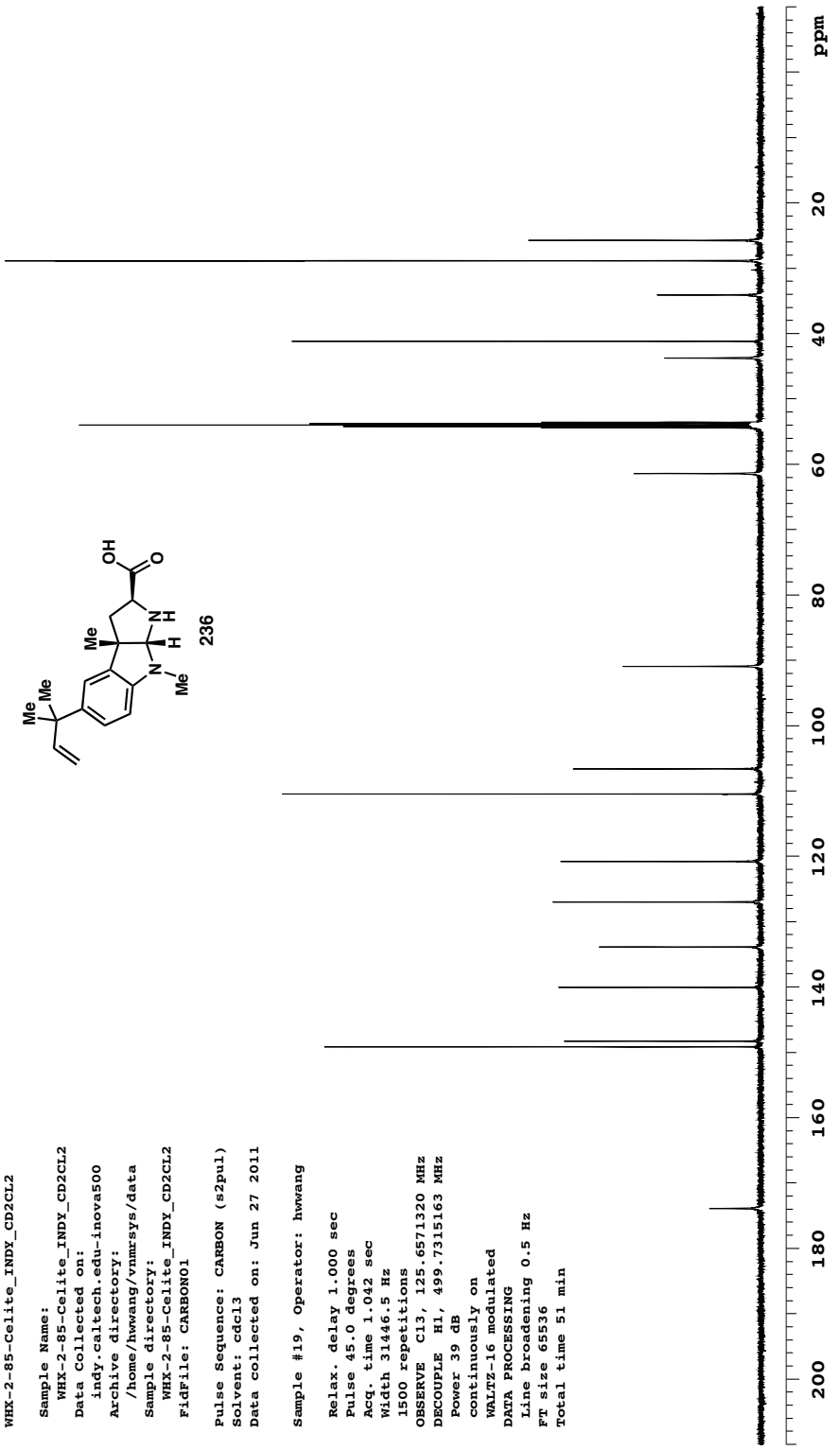

WHX-2-47-F1_INDY_CDCL3
Sample Name:
WHX-2-47-F1_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-47-F1_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 16 2011
Temp. 25.0 C / 298.1 K
Sample #17, Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
OMe
Me
N
H
N
H
Me
A-1
1.00
1.00
0.98
1.03
4.10
3.16
0.96
1.12
1.08
3.24
12
10
8
6
4
2
0
ppm

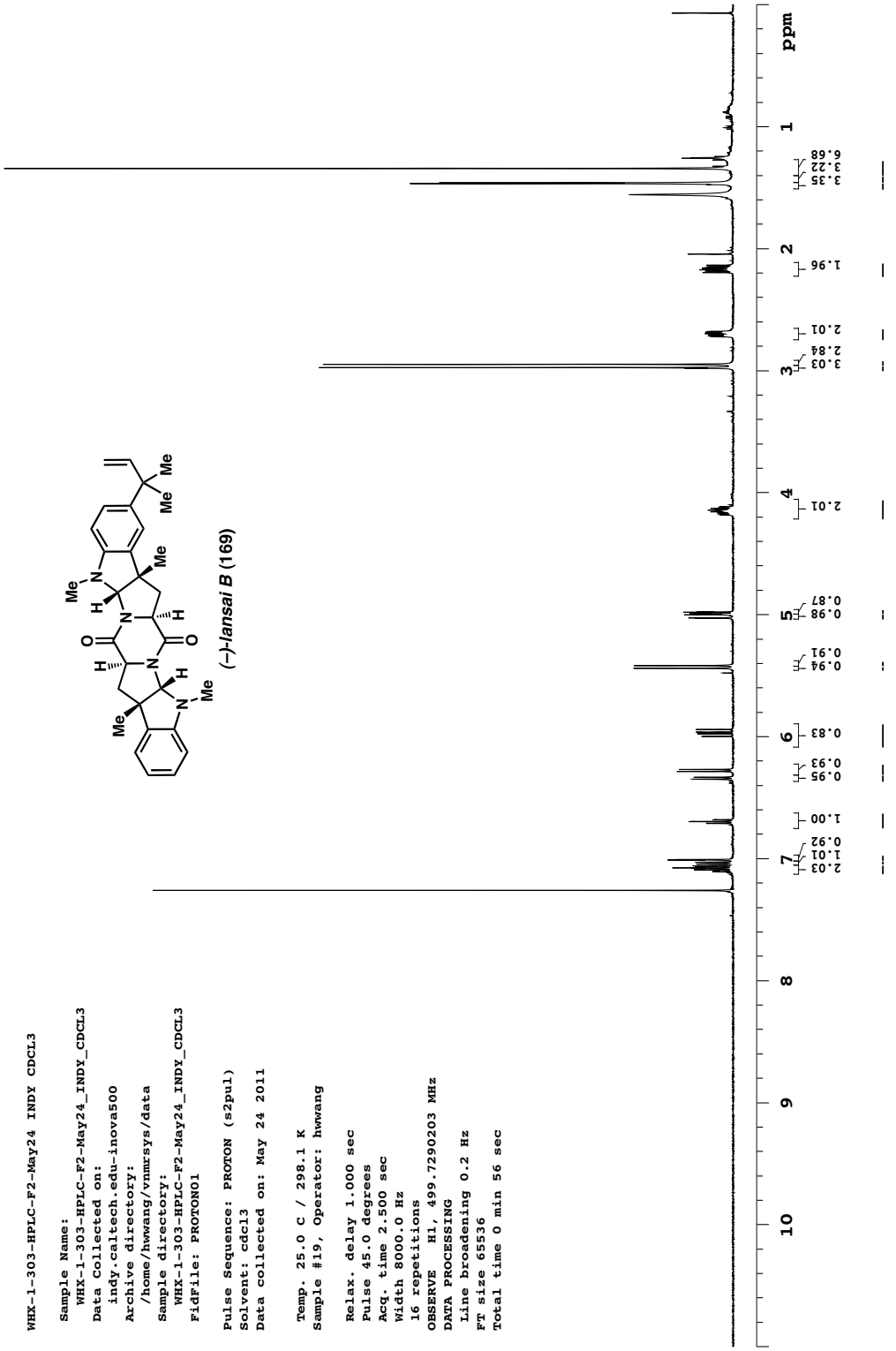

WHX-2-47-F1_INDY_CDCL3
Sample Name:
WHX-2-47-F1_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-47-F1_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 16 2011
Temp. 25.0 C / 298.1 K
Sample #17, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6569709 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
OMe
O
N
H
Me
N
H
Me
A-1
200
180
160
140
120
100
80
60
40
20
ppm

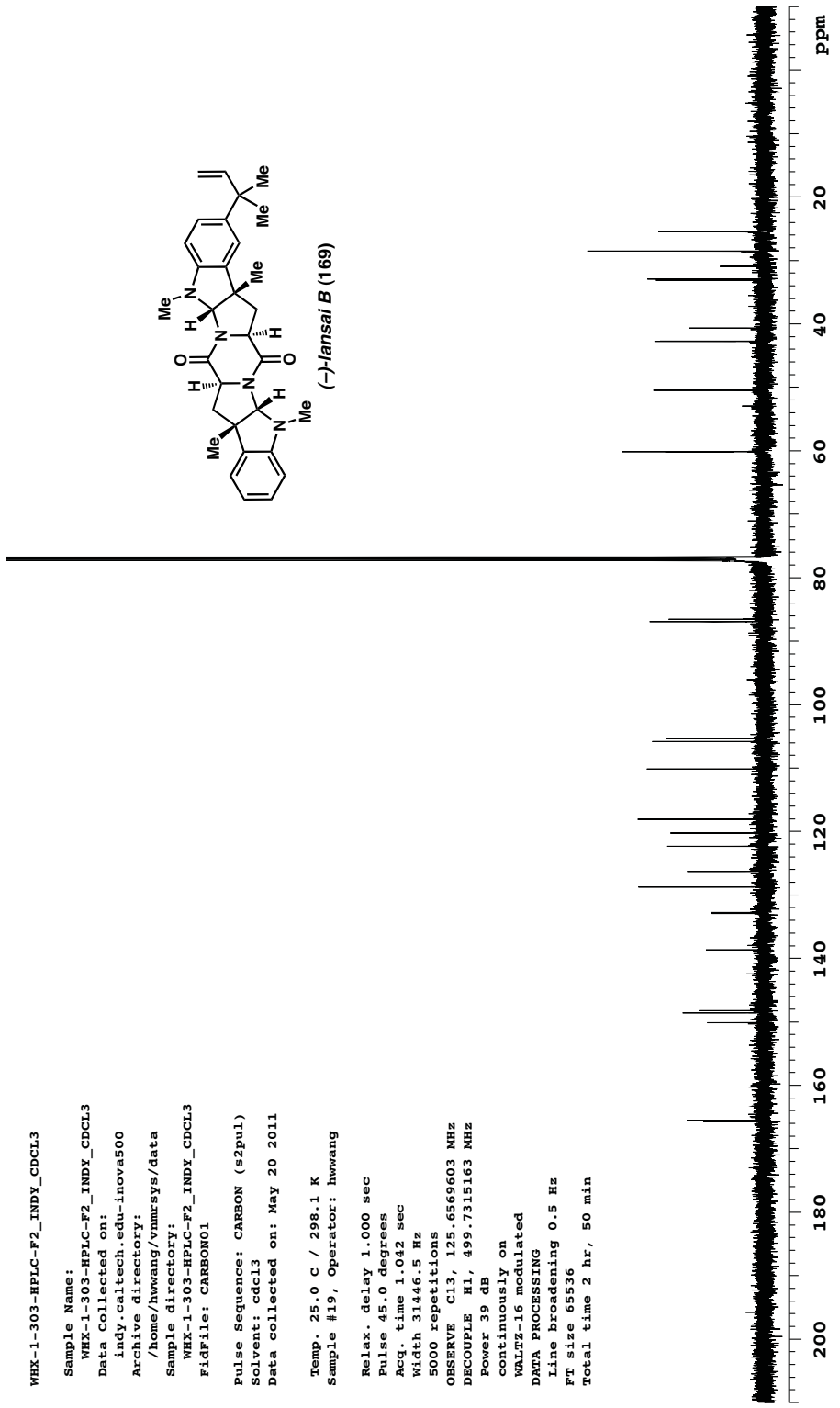

WHX-2-51-F_INDY_MeOD
Sample Name:
WHX-2-51-F_INDY_MeOD
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-51-F_INDY_MeOD
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3od
Data collected on: Jun 2 2011
Temp. 25.0 C / 298.1 K
Sample #19, Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7310056 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
OH
O
Me
N
H
N
H
N
Me
235
10
9
8
7
6
5
4
3
2
1
ppm
2.04
1.02
1.00
1.29
1.07
3.06
1.02
1.05
3.13

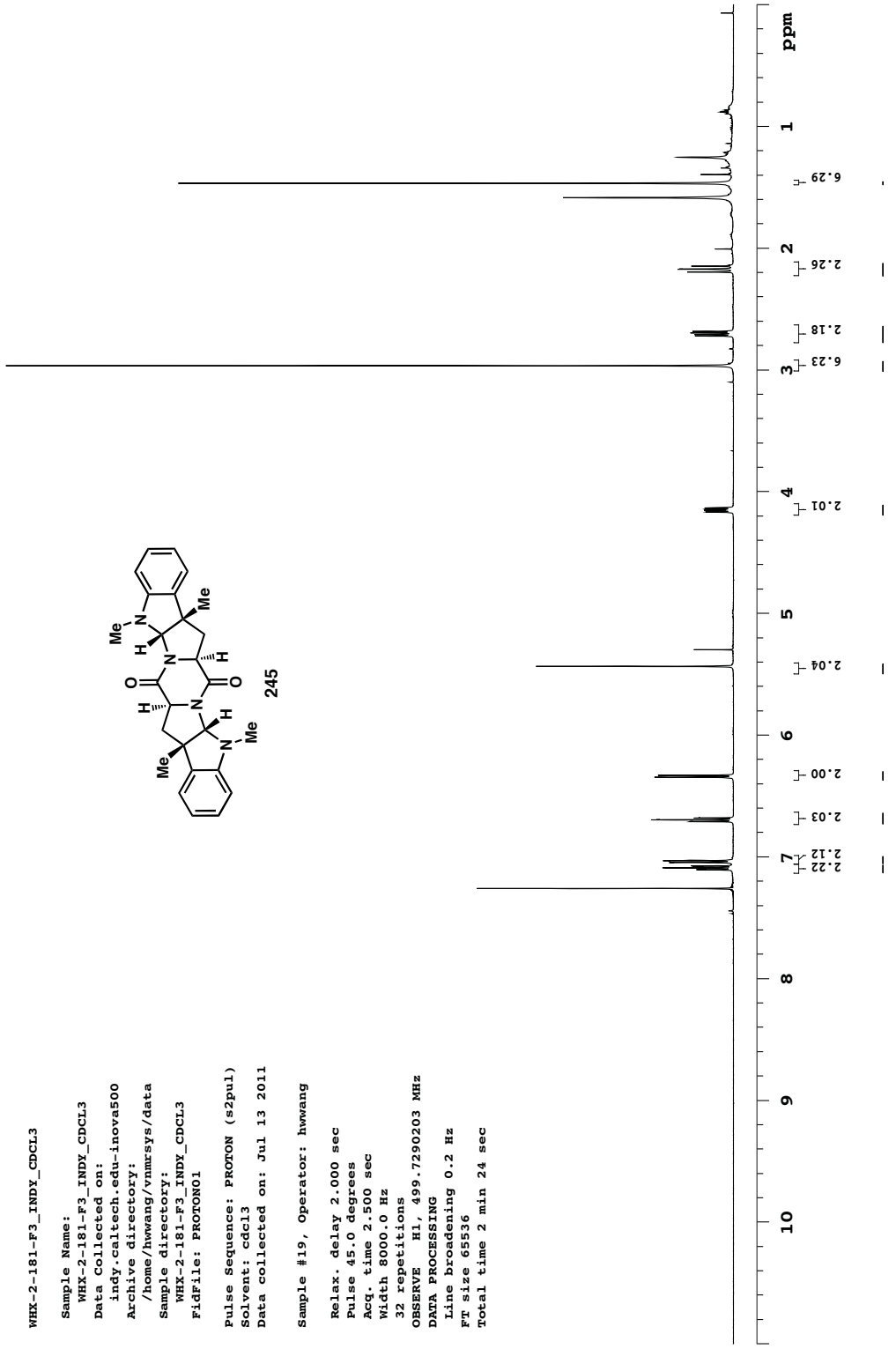

WHX-2-51-F_INDY_MEOD
Sample Name:
WHX-2-51-F_INDY_MEOD
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-51-F_INDY_MEOD
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3od
Data collected on: Jun 4 2011
Temp. 25.0 C / 298.1 K
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6572814 MHz
DECOUPLE H1, 499.7334852 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
OH
O
N
H
H
N
Me
Me
235
200
180
160
140
120
100
80
60
40
20
ppm

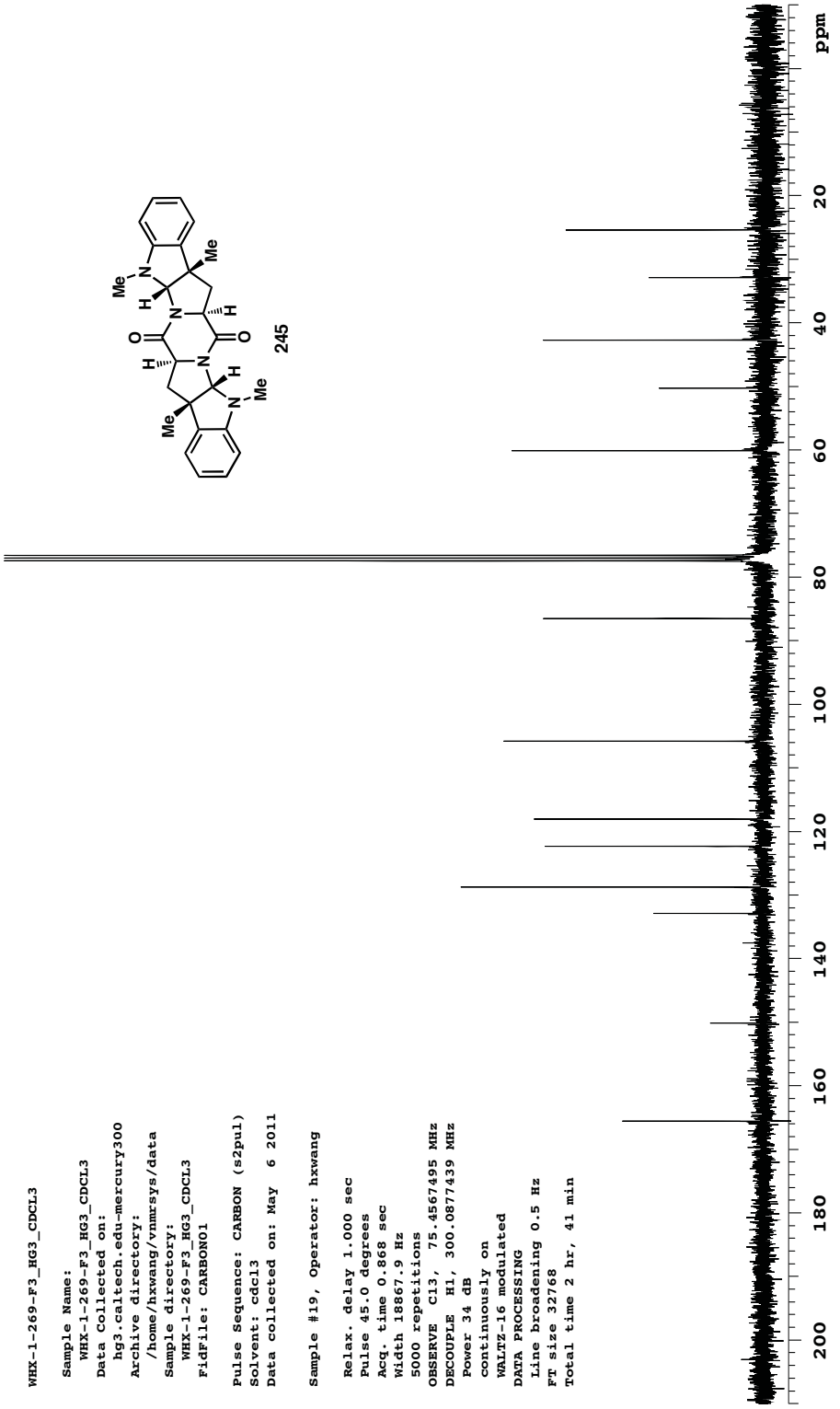

WHX-2-85-Celite_CD2CL2
Sample Name:
WHX-2-85-Celite_CD2CL2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-85-Celite_CD2CL2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd2cl2
Data collected on: Jun 28 2011
Sample #19, Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7299866 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
Me
Me
Me
Me
OH
O
N
H
N
H
236
ppm
10
9
8
7
6
5
4
3
2
1
1.08
0.95
0.99
0.94
0.99
1.07
0.89
0.80
3.00
0.99
0.96
3.22
6.23

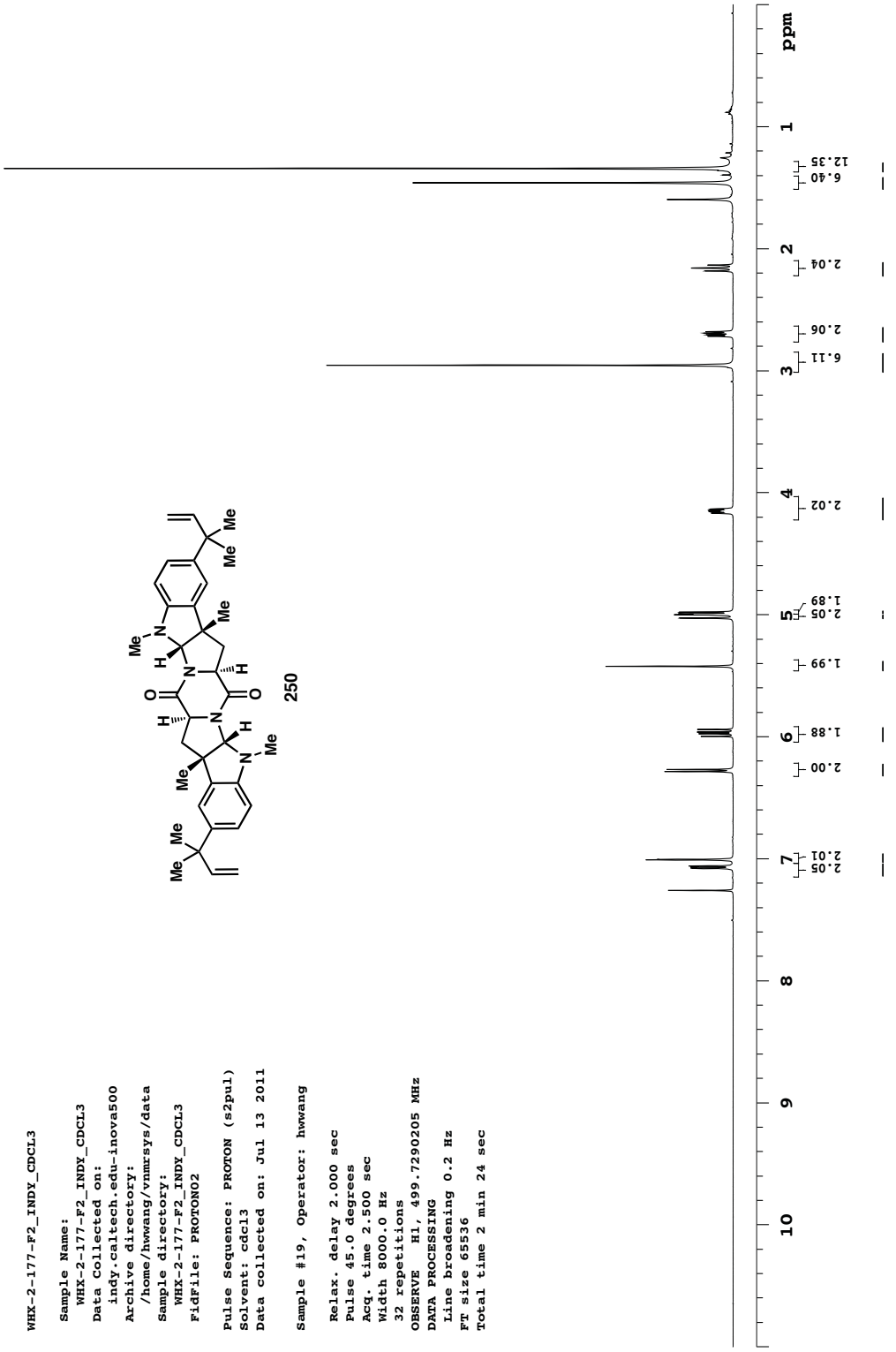

WHX-2-85-Celite_INDX_CD2CL2
Sample Name:
WHX-2-85-Celite_INDX_CD2CL2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-85-Celite_INDX_CD2CL2
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 27 2011
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6571320 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
OH
O
N
H
Me
N
H
Me
Me
Me
236
200
180
160
140
120
100
80
60
40
20
ppm

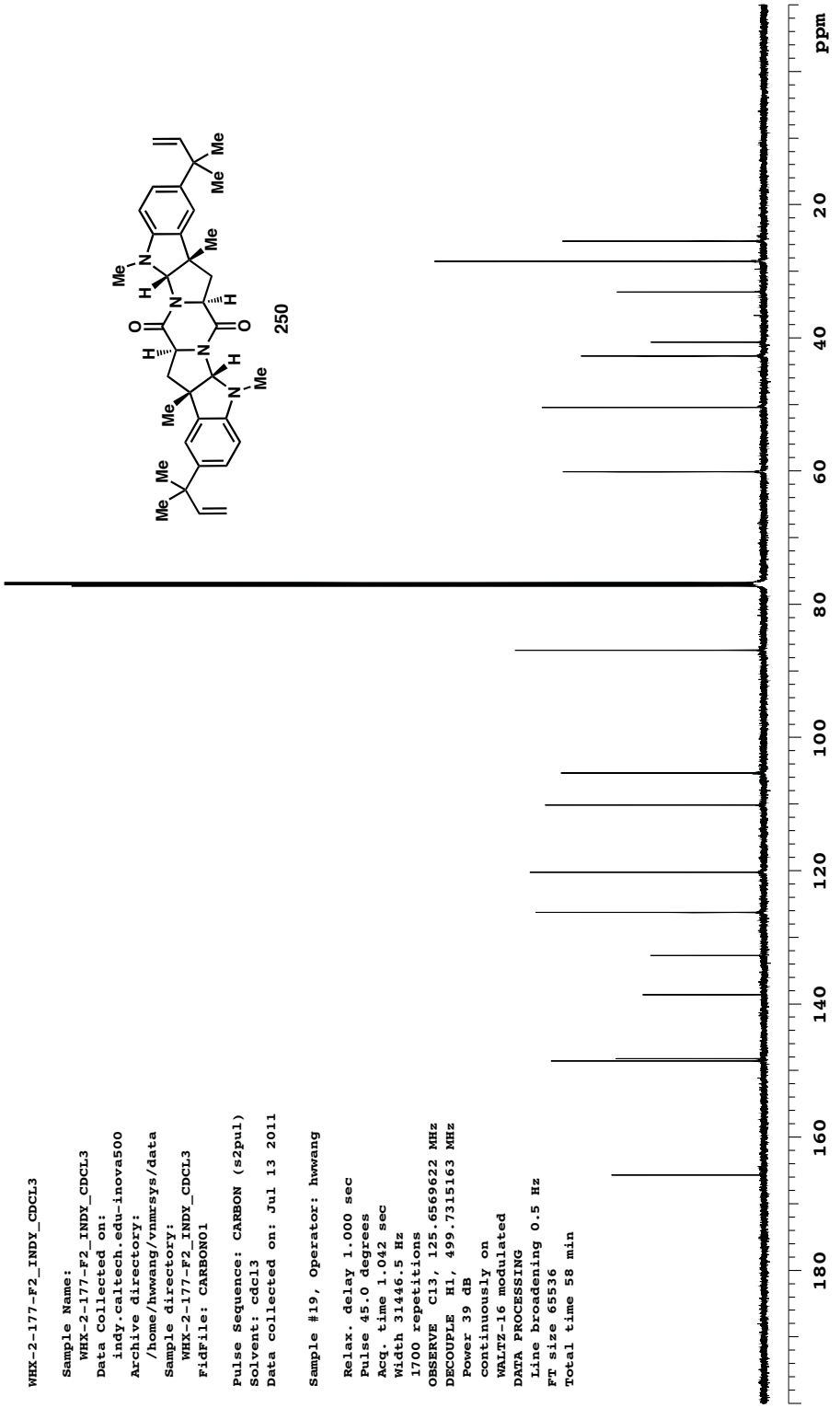

WHX-1-303-HPLC-F2-May24 INDY CDCL3
Sample Name:
WHX-1-303-HPLC-F2-May24_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-1-303-HPLC-F2-May24_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 24 2011
Temp. 25.0 C / 298.1 K
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
(–)-Iansai B (169)
ppm
10
9
8
7
6
5
4
3
2
1
2.03
1.01
0.92
1.00
0.95
0.93
0.83
0.94
0.91
0.98
0.87
2.01
3.03
2.84
2.01
1.96
3.35
3.22
6.68

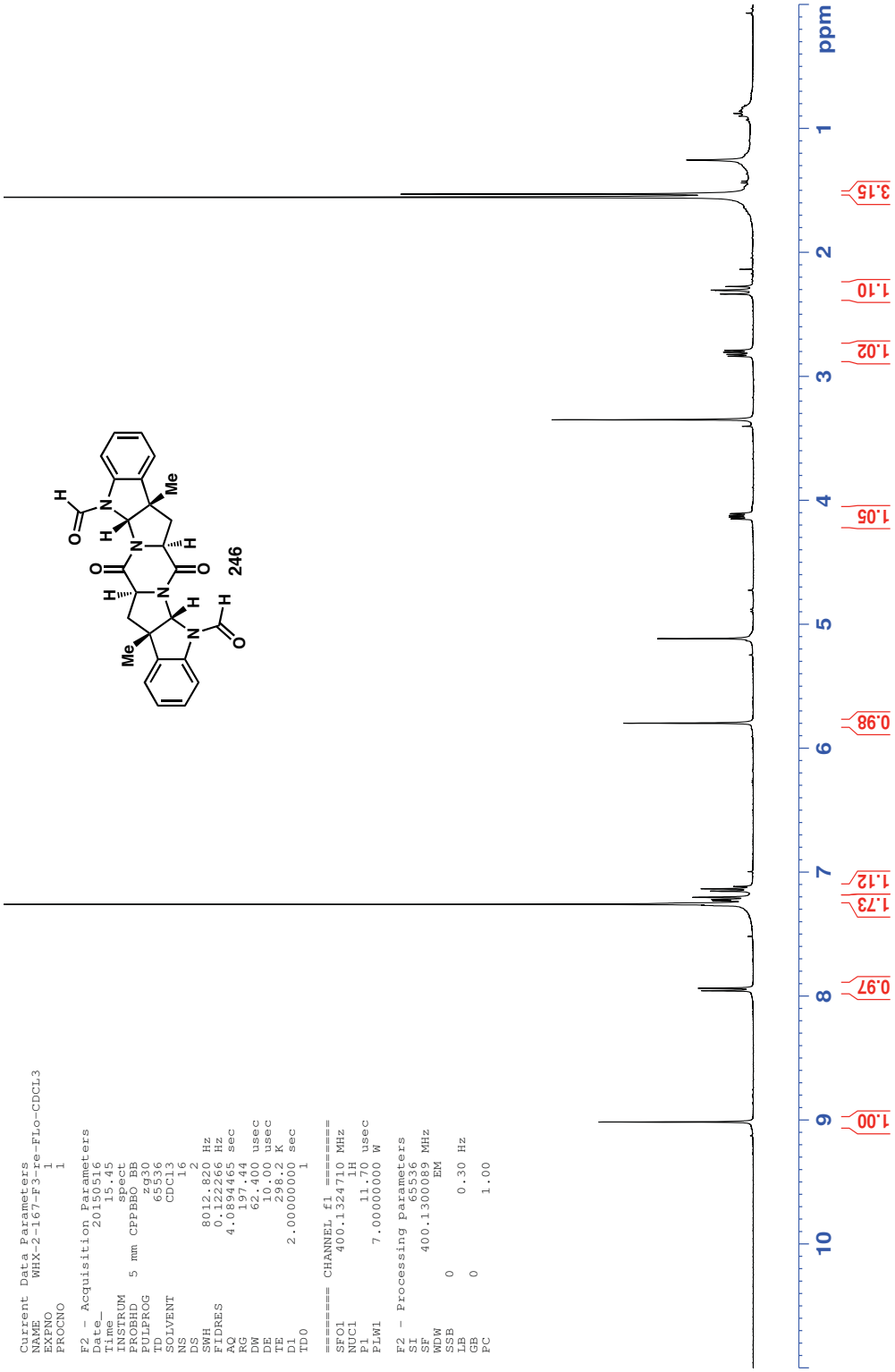

WHX-1-303-HPLC-F2_INDY_CDCL3
Sample Name:
WHX-1-303-HPLC-F2_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-1-303-HPLC-F2_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 20 2011
Temp. 25.0 C / 298.1 K
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6569603 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 2 hr, 50 min
(–)-lansai B (169)
200
180
160
140
120
100
80
60
40
20
ppm

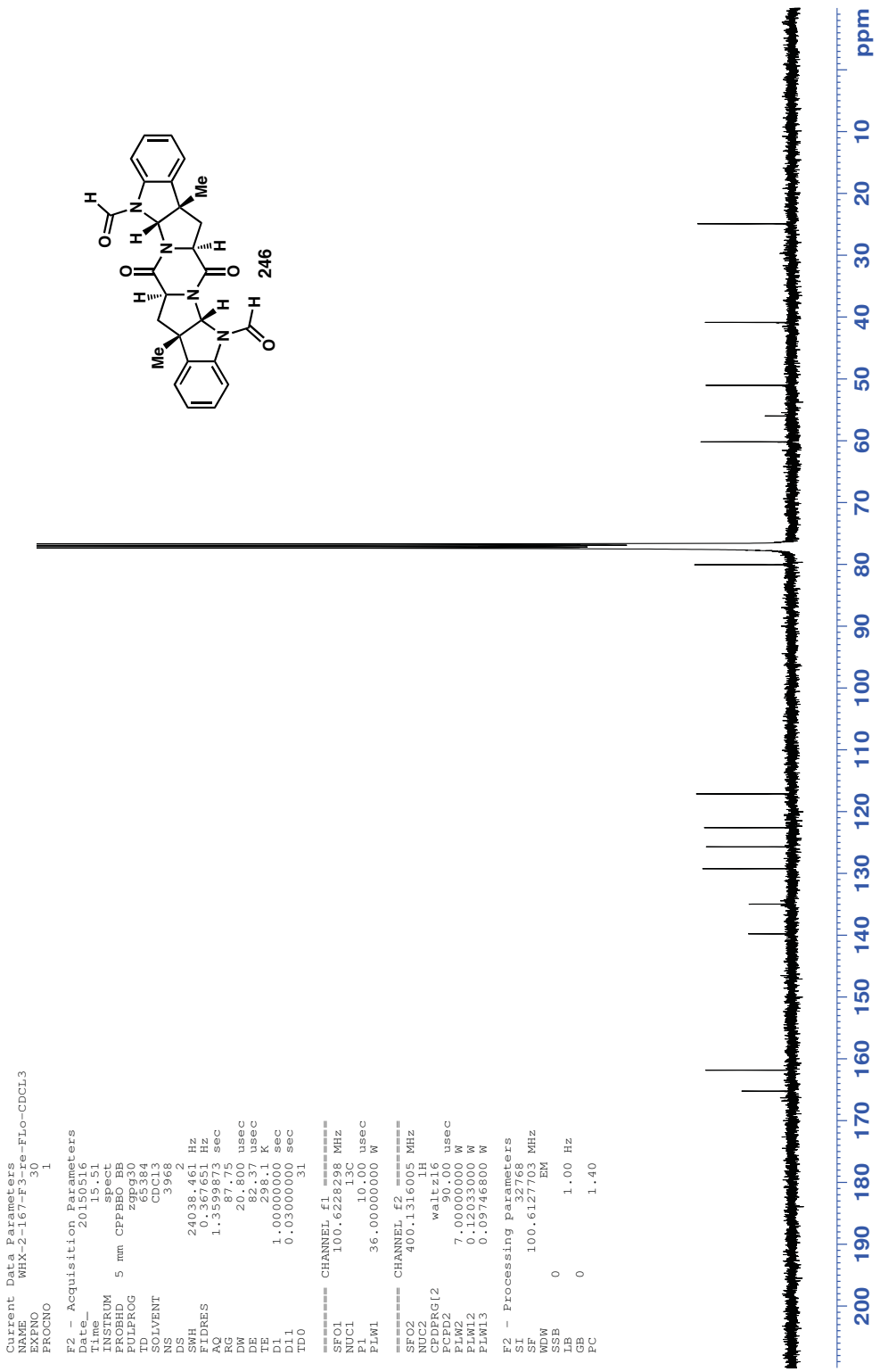

WHX-2-181-F3_INDY_CDCL3
Sample Name:
WHX-2-181-F3_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-181-F3_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 13 2011
Sample #19, Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
Me
N
H
O
N
H
O
Me
Me
N
H
N
Me
245
6.29
2.26
2.18
6.23
2.01
2.04
2.00
2.03
2.12
2.22
ppm

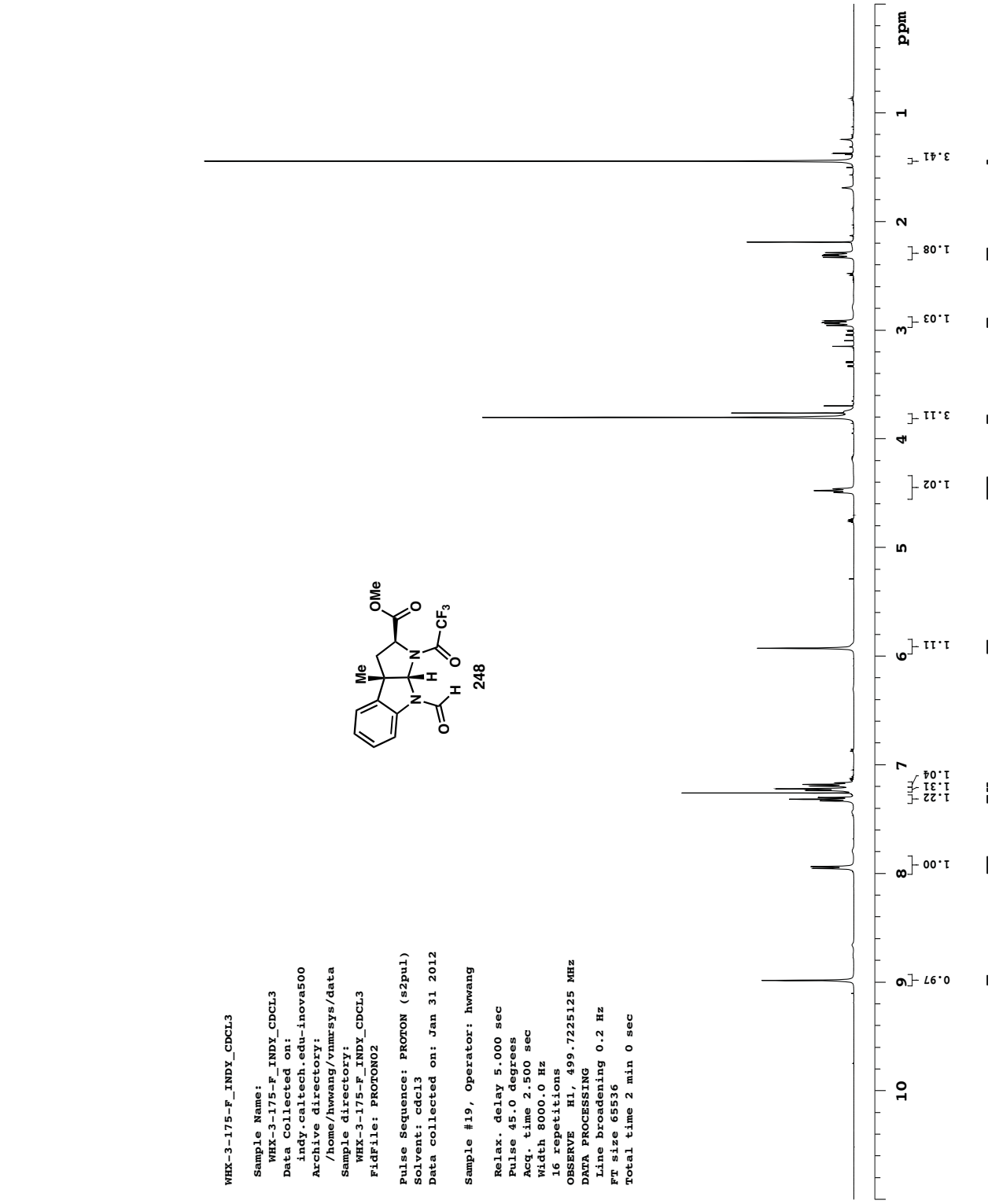

WHX-1-269-F3_HG3_CDCL3
Sample Name:
WHX-1-269-F3_HG3_CDCL3
Data Collected on:
hg3.caltech.edu-mercury300
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-1-269-F3_HG3_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 6 2011
Sample #19, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
5000 repetitions
OBSERVE C13, 75.4567495 MHz
DECOUPLE H1, 300.0877439 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 2 hr, 41 min
245
Me
Me
Me
Me
H
H
H
H
O
O
N
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

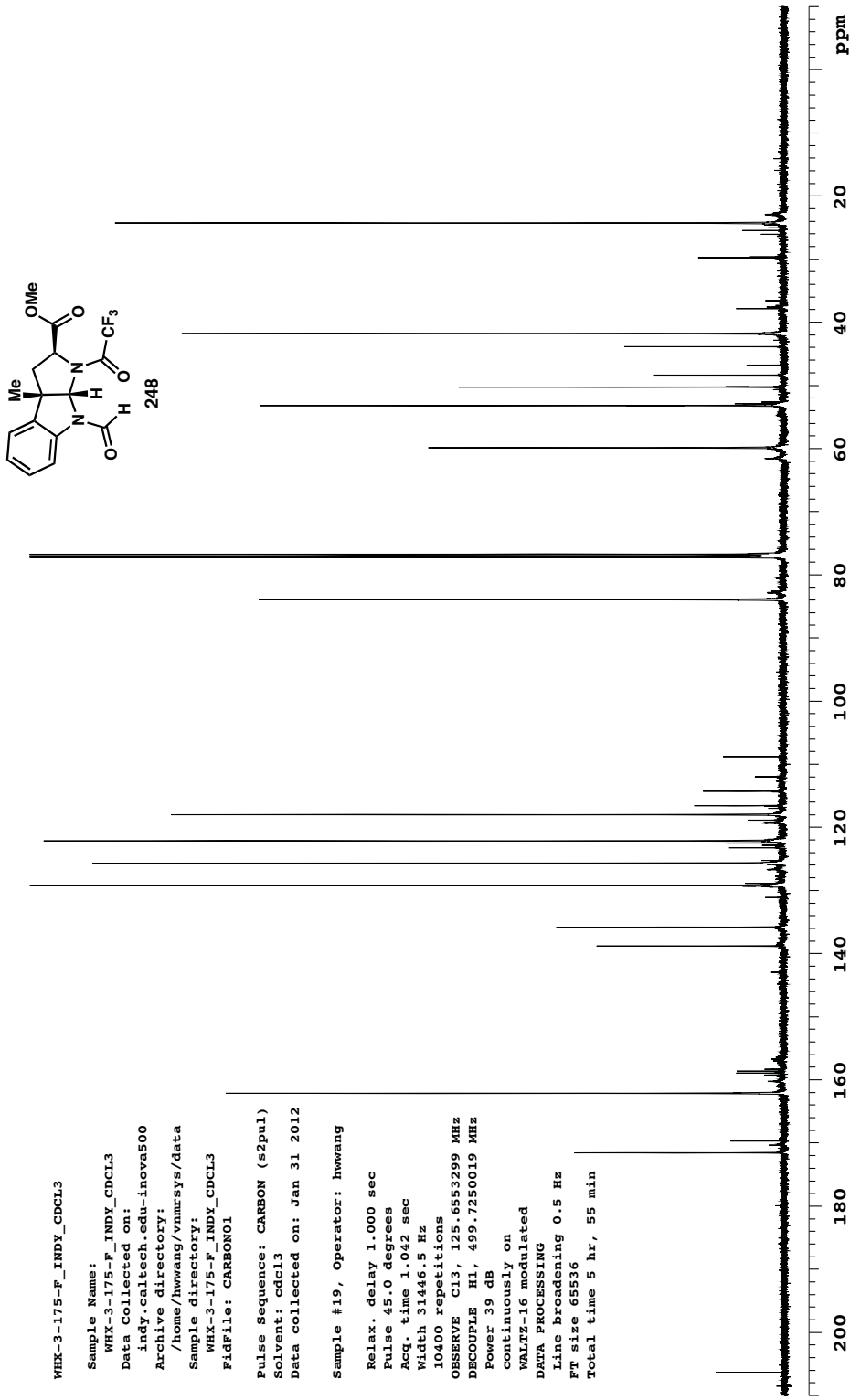

WHX-2-177-F2_INDY_CDCL3
Sample Name:
WHX-2-177-F2_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-177-F2_INDY_CDCL3
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 13 2011
Sample #19, Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290205 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
250
ppm
12.35
6.40
2.04
2.06
6.11
2.02
2.05
1.89
1.99
1.88
2.00
2.01
2.05

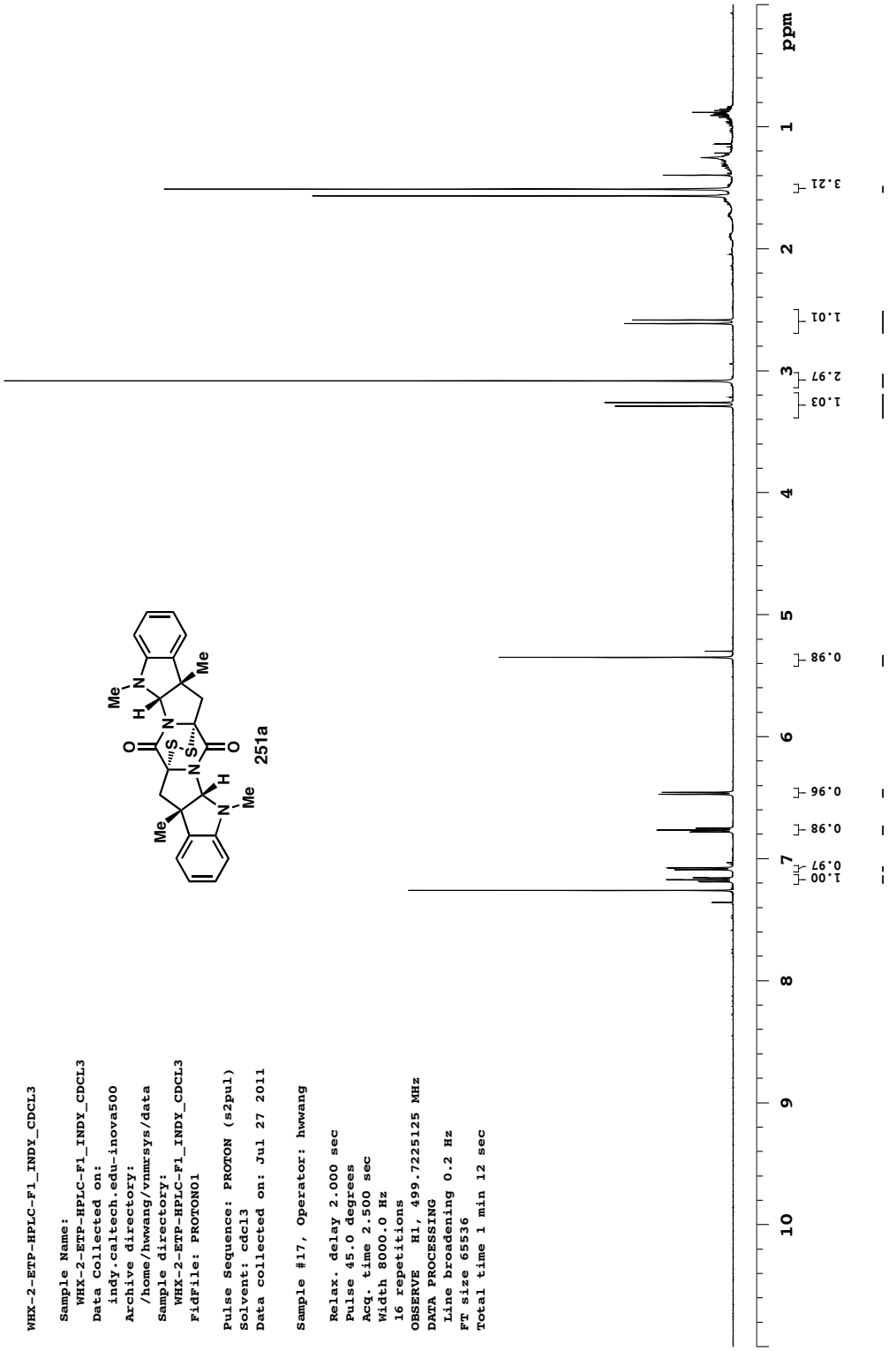

WHX-2-177-F2_INDY_CDCL3
Sample Name:
WHX-2-177-F2_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-2-177-F2_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 13 2011
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6569622 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
250
180
160
140
120
100
80
60
40
20
ppm


Current Data Parameters
NAME WHX-2-167-F3-re-FLo-CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150516
Time 15.45
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 197.44
DW 62.400 usec
DE 10.00 usec
TE 298.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300089 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
246
Me
Me
ppm
1.00
0.97
1.12
1.73
0.98
1.05
1.02
1.10
3.15


Current Data Parameters
NAME WHX-2-167-F3-re-FLo-CDCL3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150516
Time 15.51
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 3968
DS 2
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 87.75
DW 20.800 usec
DE 82.37 usec
TE 298.1 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 31
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127703 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
246
Me
Me
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


WHX-3-175-F_INDY_CDCL3
Sample Name:
WHX-3-175-F_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-3-175-F_INDY_CDCL3
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 31 2012
Sample #19, Operator: hwwang
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
OMe
Me
CF3
H
H
248
10
9
8
7
6
5
4
3
2
1
ppm
0.97
1.00
1.22
1.31
1.04
1.11
1.02
3.11
1.03
1.08
3.41


WHX-3-175-F_INDY_CDCL3
Sample Name:
WHX-3-175-F_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-3-175-F_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 31 2012
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
10400 repetitions
OBSERVE C13, 125.6553299 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5 hr, 55 min
OMe
Me
CF3
248
200
180
160
140
120
100
80
60
40
20
ppm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Archive directory:
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Sample directory:
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Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
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Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
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DATA PROCESSING
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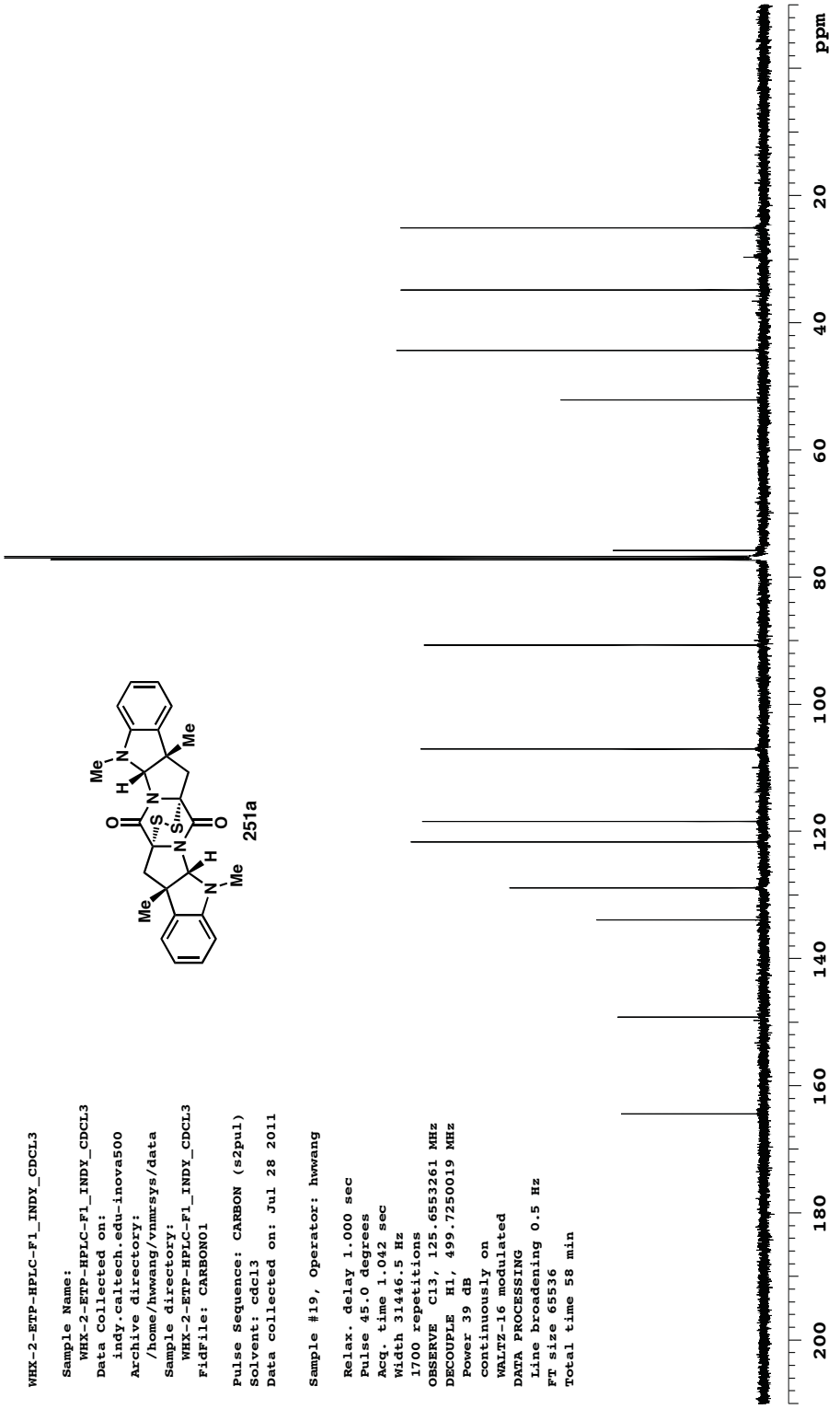
FT size 65536
Total time 1 min 12 sec
Me
N
H
N
O
S
S
N
O
H
N
Me
Me
Me
251a
ppm
10
9
8
7
6
5
4
3
2
1
1.00
0.97
0.98
0.96
0.98
1.03
2.97
1.01
3.21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Archive directory:
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Sample directory:
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Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 28 2011
Sample #19, Operator: hwwang
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Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6553261 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
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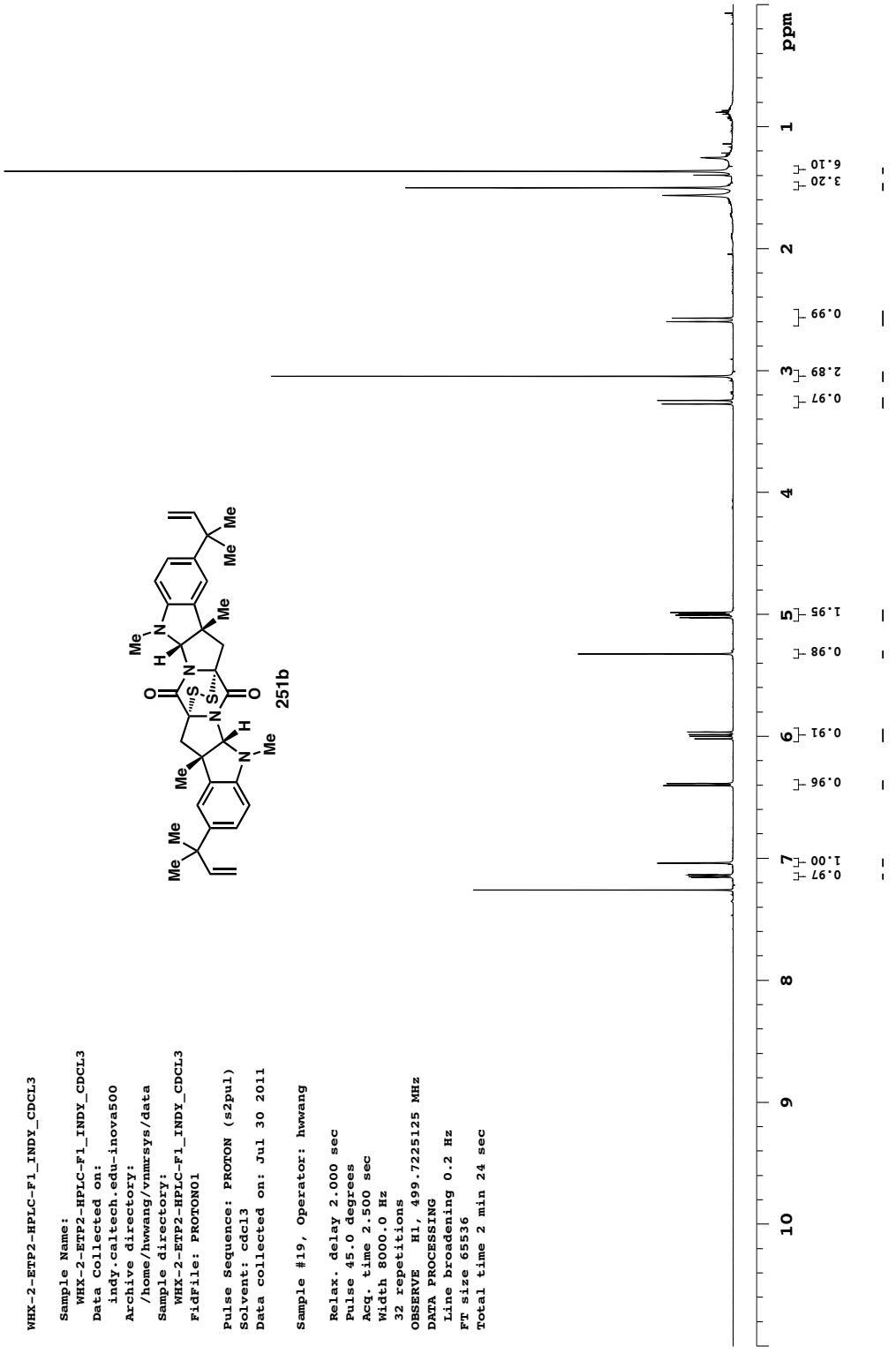
N
H
N
O
S
S
N
O
H
N
Me
Me
Me
251a
200
180
160
140
120
100
80
60
40
20
ppm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Data Collected on:
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Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
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Solvent: cdcl3
Data collected on: Jul 30 2011
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Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
251b
ppm
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9
8
7
6
5
4
3
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1
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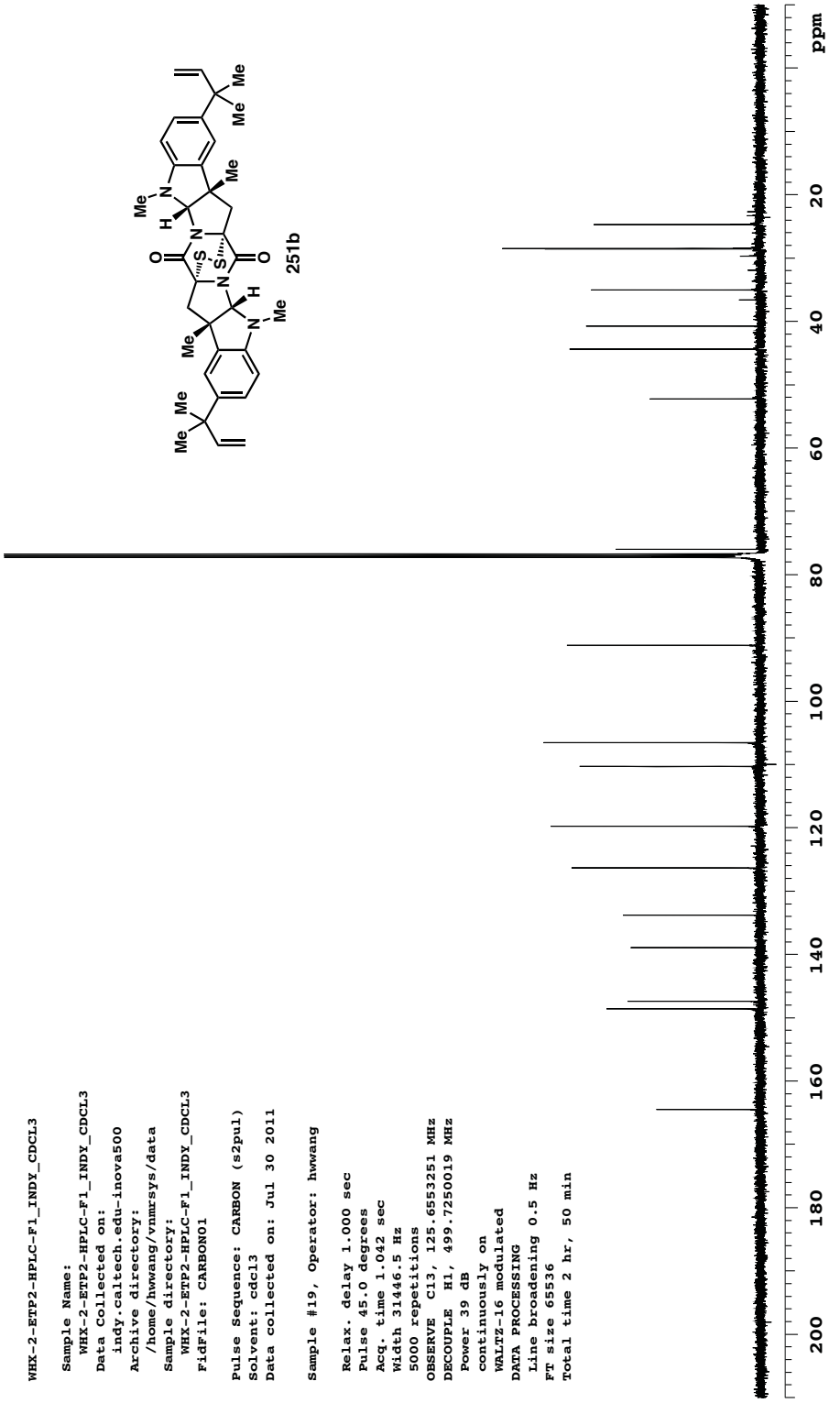
1.00
0.96
0.91
0.98
1.95
0.97
2.89
0.99
3.20
6.10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Data Collected on:
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Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
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FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 30 2011
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Pulse 45.0 degrees
Acq. time 1.042 sec
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5000 repetitions
OBSERVE C13, 125.6553251 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
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140
120
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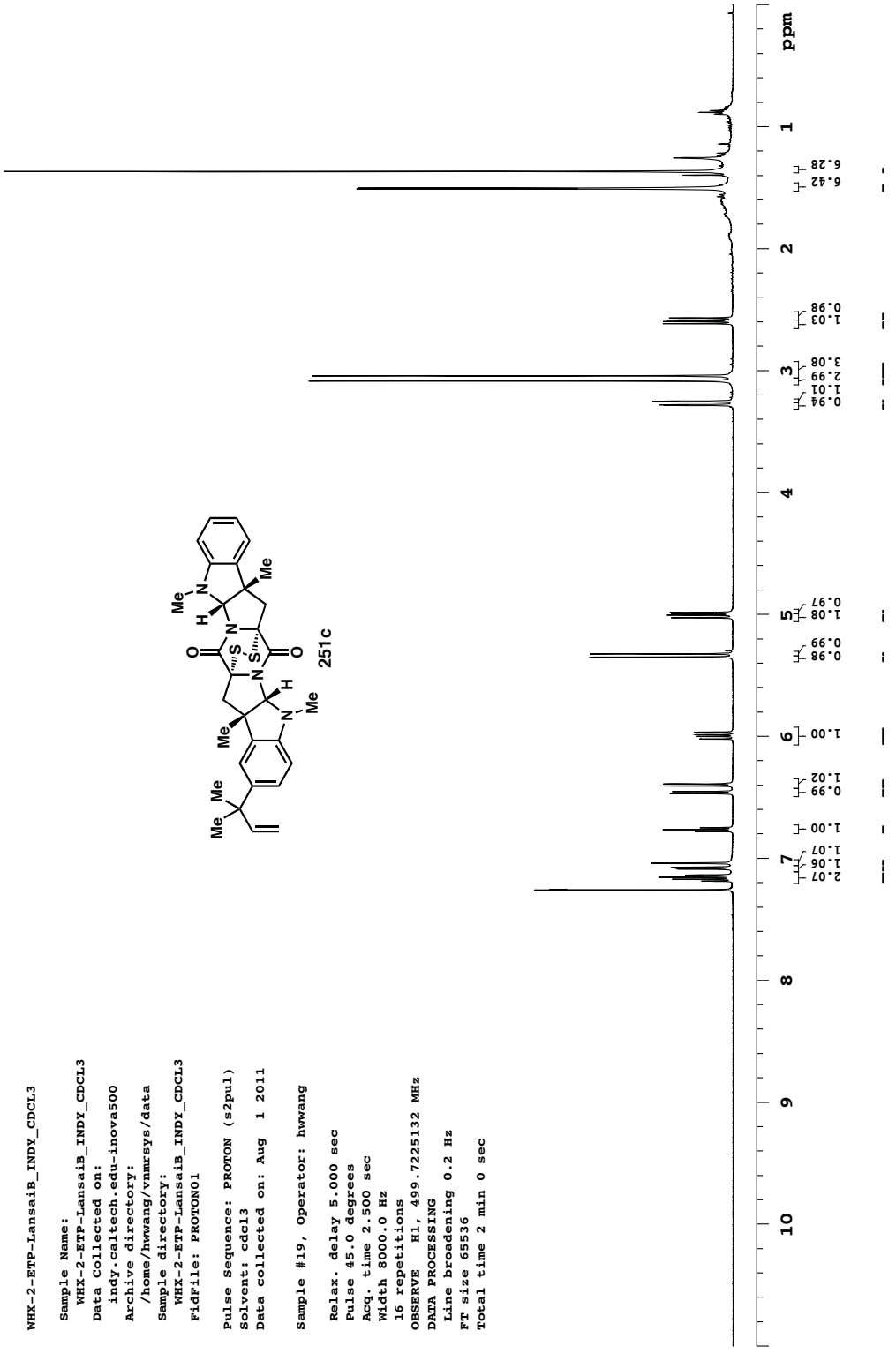
80
60
40
20
ppm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Data Collected on:
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Archive directory:
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Sample directory:
WHX-2-ETP-LansaiB_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 1 2011
Sample #19, Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225132 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
251c
ppm
10
9
8
7
6
5
4
3
2
1
2.07
1.06
1.07
1.00
0.99
1.02
1.00
0.98
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1.01
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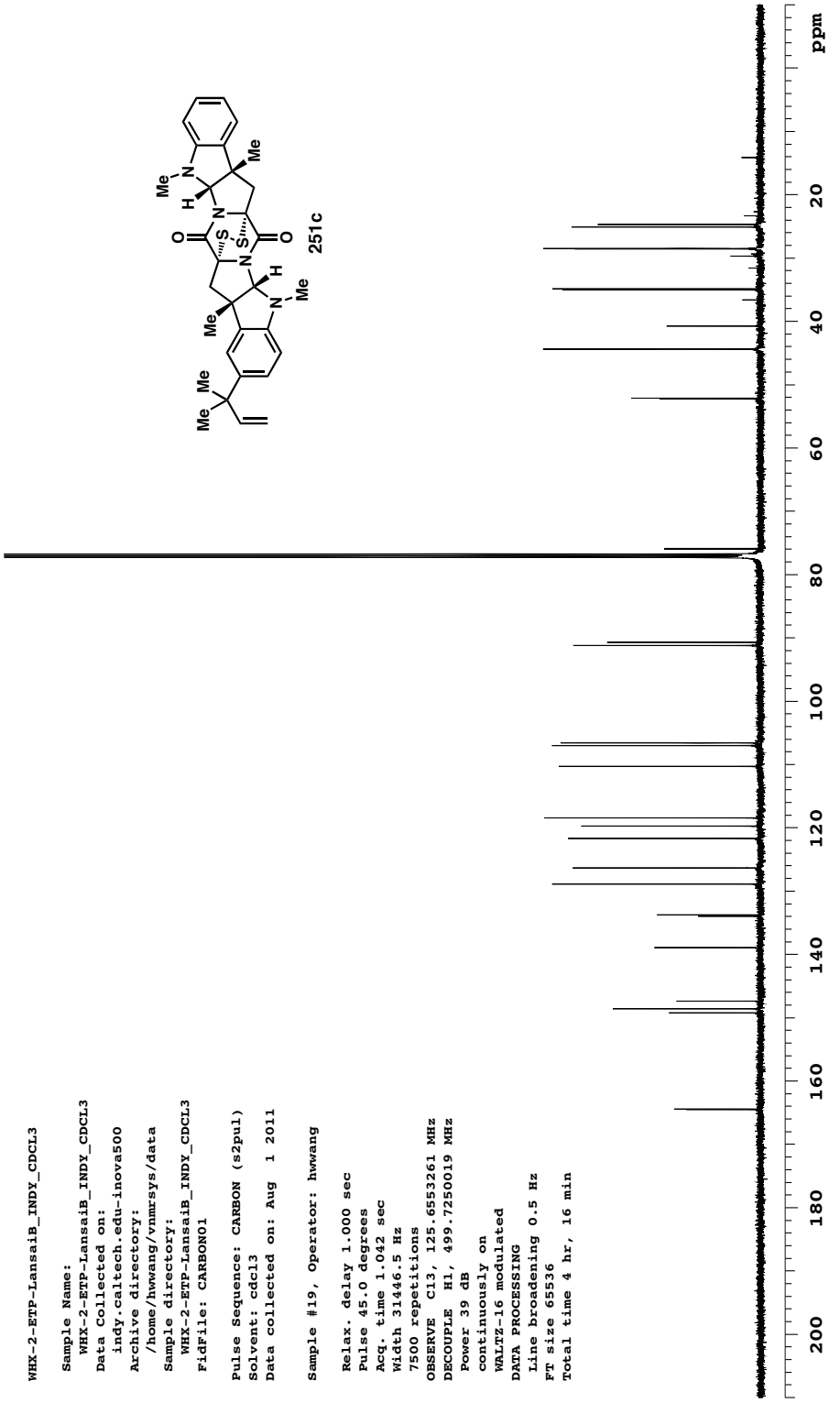
3.08
1.03
0.98
6.42
6.28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Archive directory:
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FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 1 2011
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
7500 repetitions
OBSERVE C13, 125.6553261 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 4 hr, 16 min
251c
200
180
160
140
120
100
80
60
40
20
ppm

Chapter 3

Enantioselective Total Synthesis of (+)-Nocardioazines A and B[†]

3.1 INTRODUCTION

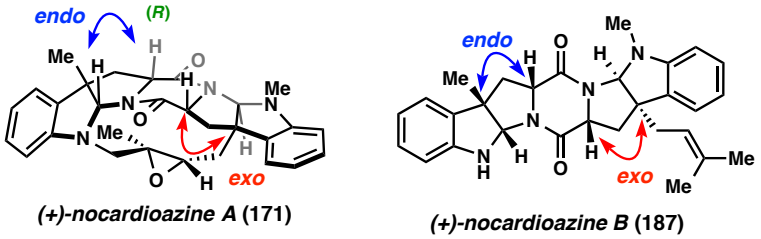
Having accomplished the first total synthesis of (–)-lansai B (**169**), which illustrated the utility of our enantioselective formal (3 + 2) cycloaddition strategy in accessing related pyrroloindolines,[1,2] we turned our attention to structurally related diketopiperazine-containing bis(pyrroloindoline) natural products (+)-nocardioazines A (**171**) and B (**187**). Both of these natural products were isolated in 2011 by Capon and coworkers as a new class of prenylated diketopiperazines from the Australian marine sediment-derived isolate, *Nocardiopsis* sp. (CMB-M0232).[3] Nocardioazine A (**171**) has been found to be a potential multidrug resistance reversal candidate due to its P-glycoprotein binding property.[3]

Although these natural products appear quite similar structurally, close analysis reveals subtle differences in the relative stereochemistry of the pyrroloindoline units.

[†] Part of this chapter was published as the following communications: Wang, H.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2014**, *53*, 6206.

Whereas lansai B (**169**) is composed of two *exo*-pyrroloindolines, **171** and **187** each possess one *endo*- and one *exo*-pyrroloindoline. Moreover, the *endo*- and *exo*-pyrroloindolines are in the opposite enantiomeric series, which is necessary to geometrically accommodate the macrocycle of **171**.

Figure 3.1. *Structures of (+)-nocardioazines A and B*



***(+)-nocardioazine A* (171)** ***(+)-nocardioazine B* (187)**

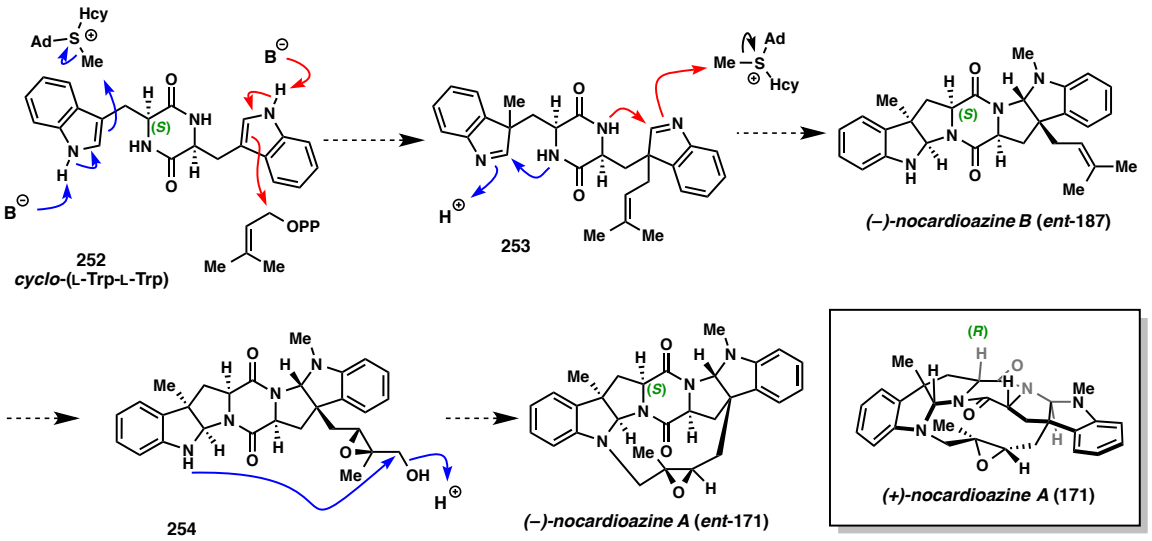
3.1.1 Proposed Biosynthesis of Nocardioazines A and B

Biosynthetically, it is proposed that both nocardioazines A and B are synthesized in bacteria from L-tryptophan cyclic dimer **252** (Scheme 3.1), which is alkylated at both C3 positions with either a methyl or a prenyl group to provide imine intermediate **253**.[3] The diketopiperazine (DKP) nitrogen atoms would then cyclize to form the pyrroloindoline core, providing nocardioazine B (*ent*-**187**). *ent*-**187** is proposed to undergo two subsequent oxidation reactions to produce hydroxyl-epoxide **254**. The elimination of water facilitated by the indoline nitrogen then forms nocardioazine A (*ent*-**171**).

It is important to note that the naturally abundant L-tryptophan series dictates the absolute stereochemistry at the DKP core to be of the (*S*)-configuration, as proposed in the isolation paper.[3] Our total synthesis work, as will be described in this chapter, and related studies by Ye and coworkers[4] have corrected the absolute stereochemistry to be of

the (*R*)-configurations, indicating that the nocardioazine family are derived from the rare D-tryptophan series. In alignment with this claim, Capon and coworkers co-isolated cyclo-(L-Trp-L-Trp) and cyclo-(L-Trp-D-Trp) along with the nocardioazines.[3] It is suggested that cyclo-(L-Trp-D-Trp) could be the biosynthetic precursor of nocardioazines A and B; however, such a hypothesis requires that the L-Trp fragment undergoes epimerization at some point during the biological pathway.

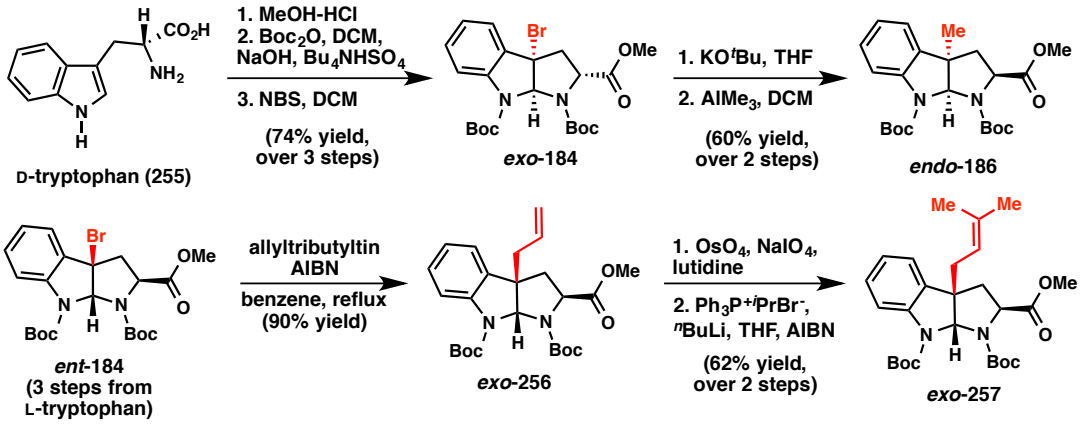
Scheme 3.1. *Proposed biosynthetic origins of nocardioazines A and B*



3.1.2 The Total Synthesis of (–)-Nocardioazine B by Ye

At the outset of our endeavor toward nocardioazines A (**171**) and B (**187**) in 2011, there were no reported total syntheses of these diketopiperazine-containing pyrroloindoline natural products. Only a year afterwards, Ye and coworkers accomplished the first total synthesis of (–)-nocardioazine B (*ent*-**187**).[4]

Scheme 3.2. *Preparation of nocardioazine B fragments from tryptophans by Ye*

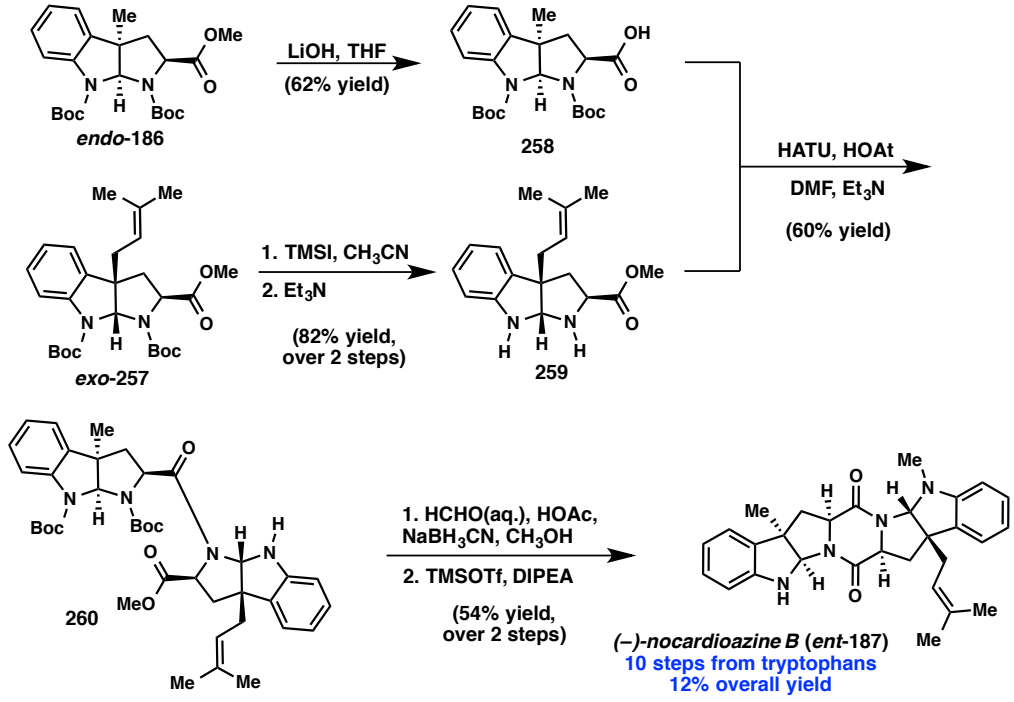


Starting from D-tryptophan (**255**), a well-established three-step procedure provided *exo*-Br-pyrroloindoline **184** in good yield (Scheme 3.2). Utilizing methodology developed by Rainier and coworkers,[5] the bromide of pyrroloindoline *exo*-**184** was converted to a methyl group via a highly strained cyclopropane intermediate (See Chapter 2, Scheme 2.3 for detailed discussion), which provided the *endo*-pyrroloindoline fragment *endo*-**186**. In order to assemble the eastern fragment of the natural product, L-tryptophan was converted to *ent*-**184** following the same procedure, and was subjected to a Keck radical alkylation, as utilized by the Danishefsky group.[6] The allyl group in **256** was subjected to a Johnson-Lemieux oxidation to form the corresponding aldehyde, which underwent a Wittig olefination reaction to provide the prenyl group of the pyrroloindoline fragment *exo*-**257**.

After preparation of both fragments, a step-wise peptide coupling strategy was pursued to form the DKP core (Scheme 3.3): *endo*-**186** was hydrolyzed to give acid **258**, and the Boc groups in *exo*-**257** were then removed to provide amine **259**. Carboxylic acid **258** and amine **259** were treated with peptide coupling reagent HATU to form dipeptide **260**, which was subsequently methylated at the aniline nitrogen under reductive

amination conditions. Upon removal of the two Boc protecting groups, the resulting secondary amine intermediate cyclized *in situ* to provide the central DKP and completed the total synthesis of (–)-nocardioazine B (*ent*-**187**). Through *de novo* exercise, Ye and coworkers were able to correct the originally proposed absolute stereochemistry of the natural product by comparison of the optical rotation signs, confirming that (+)-nocardioazine B (**187**, Figure 3.1) is the naturally occurring form. The question left unanswered was the absolute configuration of nocardioazine A (**171**), although it was presumed that it carried the same absolute configuration as **187**.

Scheme 3.3. *Endgame of (–)-nocardioazine B synthesis by Ye*



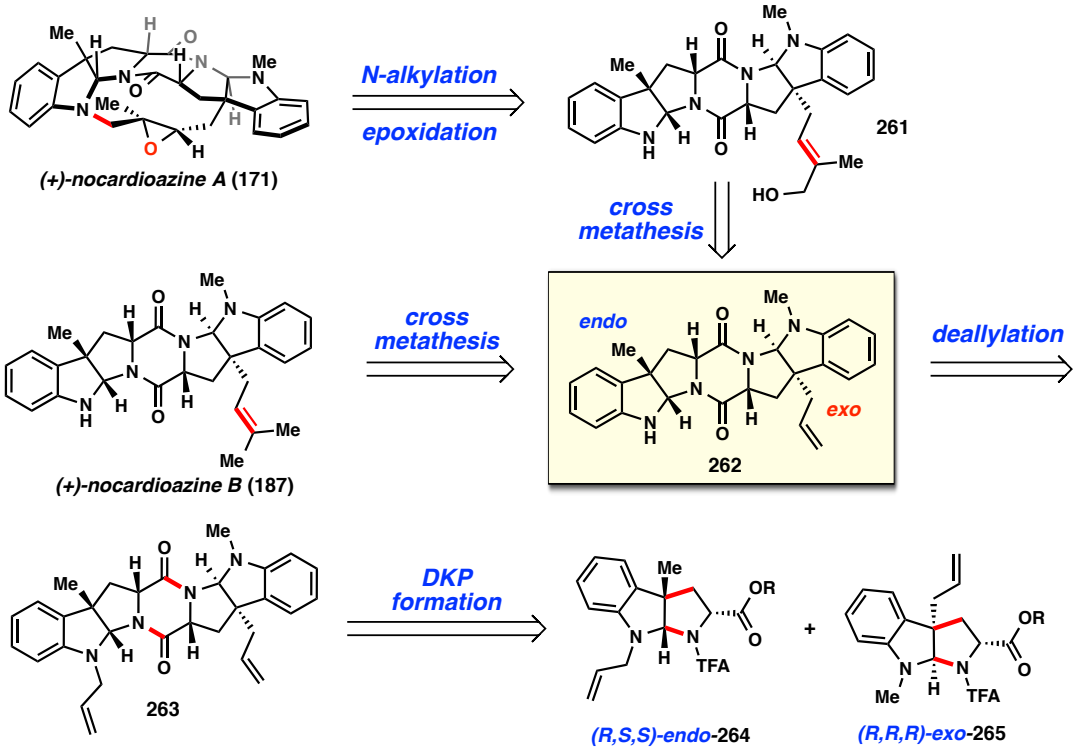
3.1.3 Retrosynthetic Analysis

The total synthesis reported by the Ye group, albeit a short synthesis, relied entirely on the chiral information obtained from D/L-tryptophan building blocks to control

the construction of subsequent stereocenters. However, we believed that a more efficient synthesis of **171** and **187** could be born by harnessing the power of asymmetric catalysis and starting from achiral starting materials.

We took particular note of the fact that the *endo*- and *exo*-pyrroloindolines are of the opposite enantiomeric series, a structural element that is necessary to geometrically accommodate the macrocycle of **171**. This interesting stereochemical relationship makes **171** and **187** appealing synthetic targets for asymmetric catalysis, where selection of the appropriate enantiomer of catalyst dictates the absolute stereochemistry of the pyrroloindoline building blocks.

Scheme 3.4. *Retrosynthetic analysis of (+)-nocardioazines A and B*



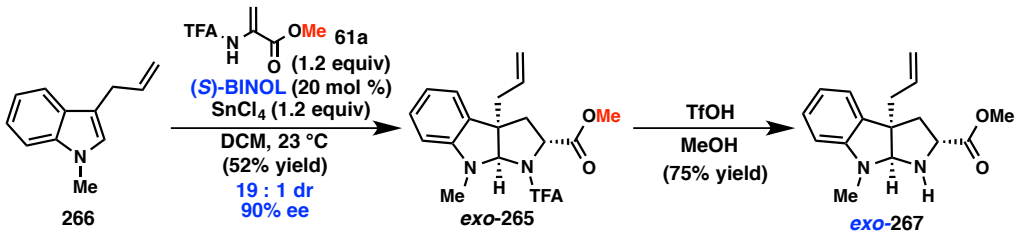
Thus, it was envisioned that both **171** and **187** could be accessed from DKP **262** (Scheme 3.4). A simple cross metathesis with isobutene would provide nocardioazine B

(**187**). On the other hand, cross metathesis with methacrolein and subsequent reduction would generate allylic alcohol **261**, which provides a suitable handle for cyclization and sets the stage for a final epoxidation event to complete the total synthesis of nocardioazine A (**171**). The divergent intermediate **262** is proposed to be accessed by coupling pyrroloindolines *endo*-**264** and *exo*-**265**. In previous studies we have demonstrated that the *exo*-diastereomer can be epimerized to the corresponding *endo*-diastereomer, thus the preparation of both *endo*-**264** and *exo*-**265** would provide a path forward.[1]

3.2 TOTAL SYNTHESIS OF (+)-NOCARDIOAZINE B

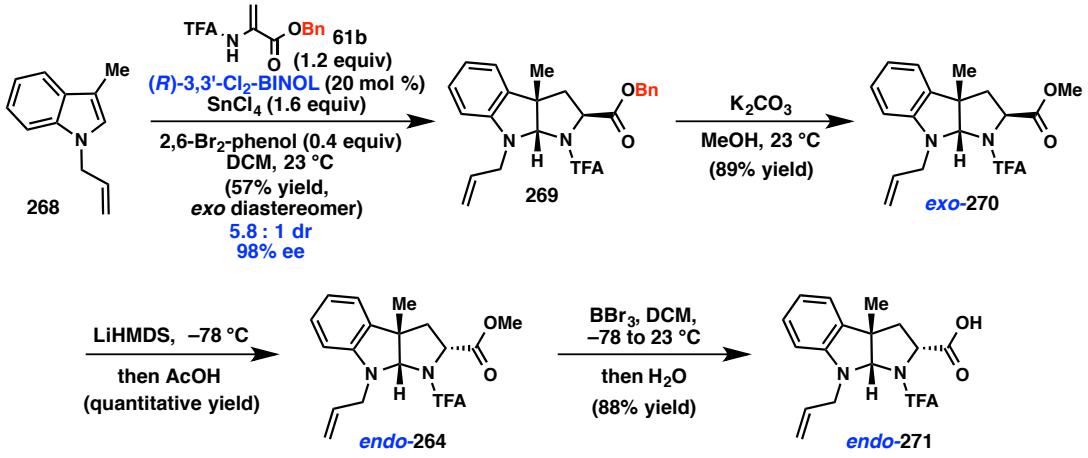
In the forward sense, treatment of a solution of *N*-methyl-3-allyl indole (**266**) and acrylate **61a** with (*S*)-BINOL (20 mol %) and $SnCl_4$ (1.2 equiv) delivered *exo*-pyrroloindoline **265** in 52% yield and 90% ee (Scheme 3.5). These conditions were highly diastereoselective for *exo*-**265** (19:1); however, the yield is modest due to allyl migration from C3 to C2 of the indole under the reaction conditions.[7] Neither addition of 2,6-dibromophenol nor use of other catalysts improved the yield of **265**. Cleavage of the TFA group using TfOH in anhydrous methanol provided, upon basic workup, *exo*-amine **267**.

Scheme 3.5. *Preparation of exo-pyrroloindoline **267** fragment*



On the other hand, treatment of *N*-allylindole **268** and benzyl trifluoroacetamidoacrylate (**61b**) with (*R*)-3,3'-dichloro-BINOL (20 mol %), $SnCl_4$ (1.6 equiv), and 2,6-dibromophenol (0.4 equiv) furnished *exo*-pyrroloindoline **269** in 57% yield and 98% ee (Scheme 3.6). It is noteworthy that additive 2,6-dibromophenol significantly improves the ee of this reaction, compared to the observed 92% ee without it.[2] The modest yield of *exo*-**269** results from the moderate diastereoselectivity (5.8:1) of the transformation. In this case, benzyl acrylate **61b** was employed instead of methyl acrylate **61a** because the dr was improved and the *exo*- and *endo*- diastereomers were more readily separated. In order to prepare the corresponding carboxylic acid **271**, benzyl ester was first converted to methyl ester **270** using K_2CO_3 in methanol. Treatment of *exo*-**270** with LiHMDS at low temperatures followed by acetic acid quench provided the thermodynamically favored *endo* diastereomer **264**, which was deprived of the methyl ester with BBr_3 to deliver *endo*-pyrroloindoline acid **271**.

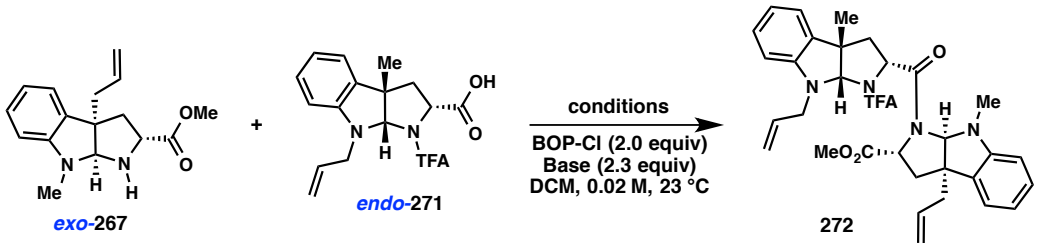
Scheme 3.6. *Preparation of endo-pyrroloindoline **271** fragment*



With access to *endo*-acid **271** and *exo*-amine **267**, we were poised to prepare key DKP **263** (Scheme 3.4). In contrast to our unsuccessful efforts to couple *exo*-

pyrroloindolines in the lansai B (**169**) synthesis (Chapter 2), mixing of *endo*-acid **271** and *exo*-amine **267** in the presence of BOP-Cl furnished the desired dipeptide **272**, albeit in low yield due to side reactions including epimerization and decomposition of **271** (entry 1, Table 3.1). After considerable optimization, we discovered that the nature of the base in the peptide coupling plays a key role in determining the reactivity. When DMAP or pyridine was used, the major product was the anhydride derived from dimerization of acid **271**. Fortunately, 2,4,6-collidine was found to be effective in favoring product formation over anhydride production to provide 45% yield of product (entry 4). The yield was further improved to 81% by slow addition of acid **271** to 2.0 equiv amine **267** (entry 6). Importantly, the unreacted amine **267** could be recovered by silica gel chromatography. When compared to the challenges encountered in the coupling of *exo*-pyrroloindolines, the ability to couple *exo*-**267** and *endo*-**271** reveals that, in addition to the identity of the *N*-substituents, the relative stereochemistry of the pyrroloindoline coupling partners is a key determinate in the ease of peptide formation.

Table 3.1. *Peptide coupling between exo-**267** and endo-**271***

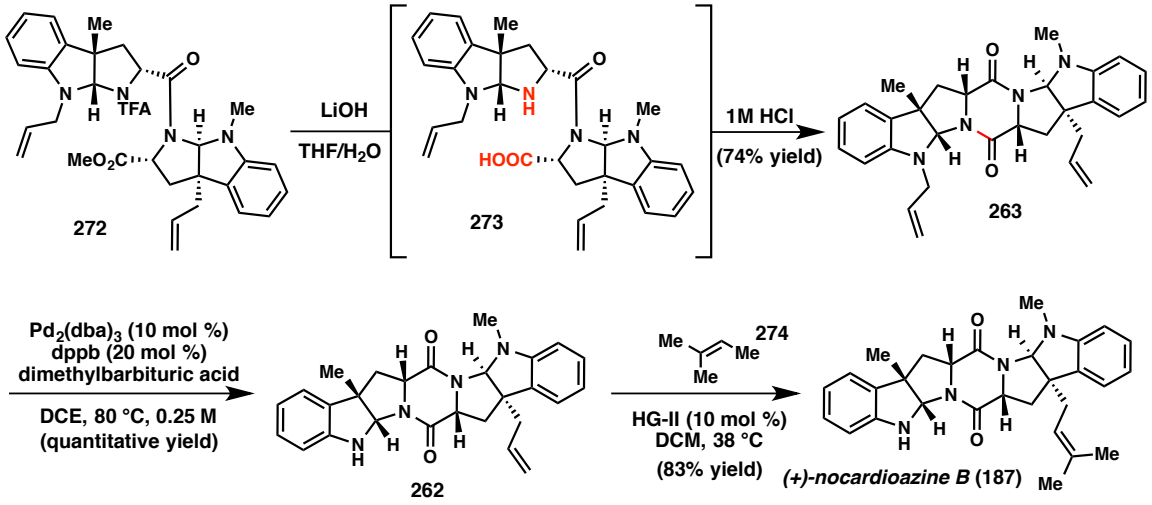


entry	*exo*-267 (equiv)	Base	Results[a]
1	1.0	DIPEA	26% yield of product + diastereomer + *N*-allyl indole
2	1.0	DMAP	anhydride
3	1.0	pyridine	anhydride
4	1.0	2,4,6-collidine	product : anhydride = 1 : 1, 45% yield
5	2.0	2,4,6-collidine	product : anhydride = 1.4 : 1, 57% yield
6[b]	2.0	2,4,6-collidine	product : anhydride = 4 : 1, 81% yield

[a] ratio determined by LCMS. [b] slow addition of *endo*-271 into reaction.

Saponification of **272** with LiOH generated amino acid **273**, which could be detected by LC-MS (Scheme 3.7). Interestingly, acidification of the reaction mixture with 1M HCl delivered DKP **263**, which represents an unusually facile DKP cyclization. Subsequent palladium-catalyzed deallylation of **263** in the presence of 1,3-dimethylbarbituric acid as the allyl scavenger gave free amine **262**.[8] Cross metathesis of **262** with 2-methyl-2-butene (**274**) provided (+)-nocardioazine B (**187**).[9] Thus, the enantioselective total synthesis of (+)-**187** was completed in nine linear steps and 21% overall yield from 3-methylindole.

Scheme 3.7. *Endgame of (+)-nocardioazine B synthesis*



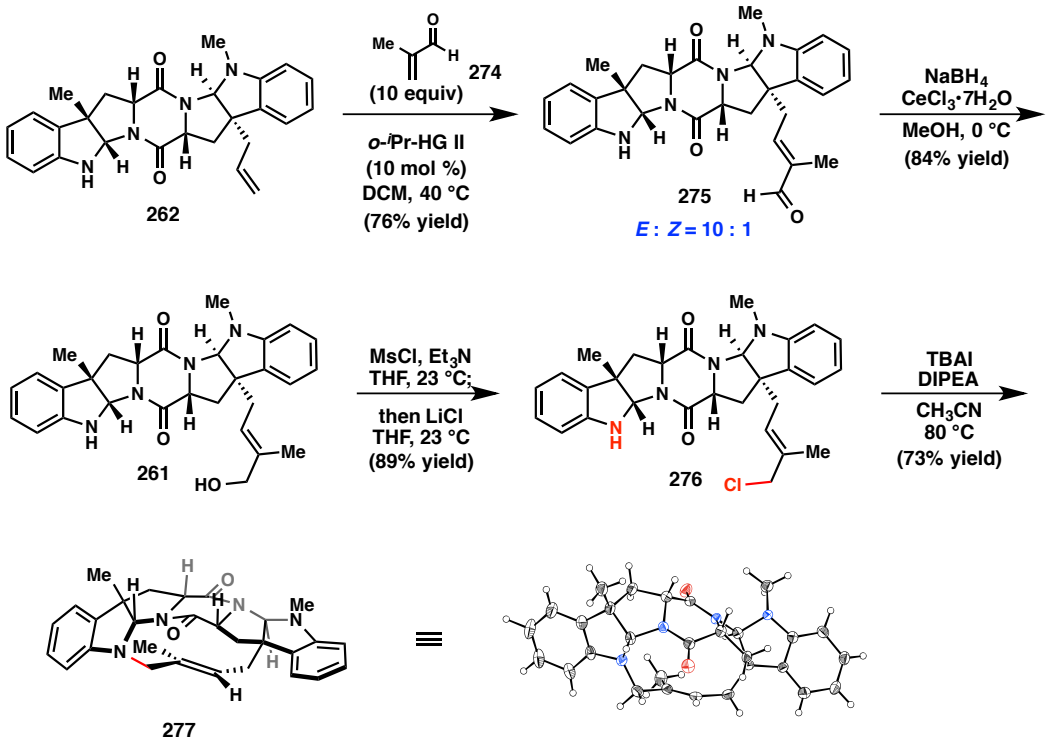
3.3 TOTAL SYNTHESIS OF (+)-NOCARDIOAZINE A

3.3.1 A Late-stage Epoxidation Strategy

At this stage, our focus shifted to advancing amine **262** to (+)-nocardioazine A (**171**). Exposure of **262** to excess methacrolein (**274**) and *ortho*-isopropyl Hoveyda-Grubbs II catalyst (10 mol %) delivered enal **275** in 76% yield as a 10 : 1 *E*/*Z* mixture

(Scheme 3.8).[10] Luche reduction followed by Finkelstein chlorination provided allyl chloride **276**. Gratifyingly, treatment of **276** with tetrabutylammonium iodide (TBAI) and base in acetonitrile at 80 °C promoted intramolecular *N*-alkylation, furnishing macrocycle **277**. Interestingly, the base was found to be important in this S_N2 process: use of a less bulky base like triethylamine provided lower yields due to competing displacement of chloride to form an ammonium salt. Interestingly, the ^{1}H NMR spectra of alkene **277** revealed two interconverting conformations, adding difficulties to the elucidation of its structure. Eventually, the structure of this unusual macrocycle **277** was confirmed by X-ray crystallography, setting the stage for the final epoxidation step.

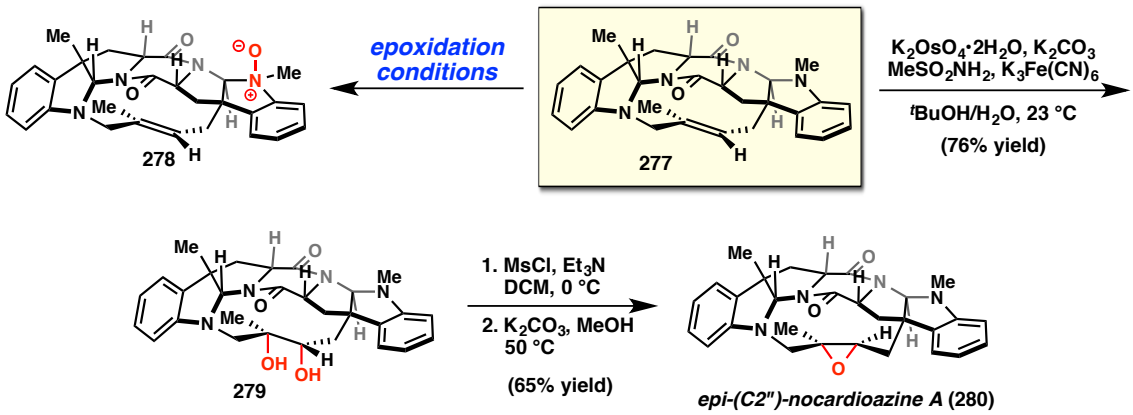
Scheme 3.8. *Preparation of macrocyclic alkene* ***277***



Unfortunately, exposure of **277** to a wide variety of epoxidation conditions, including dimethyldioxirane, *m*-chloroperoxybenzoic acid, and Jacobsen epoxidation

catalysts, failed to produce the natural product; instead, the major product was unstable *N*-oxide **278** (Scheme 3.9), which was characterized by a significant downfield shift of the *N*-methyl group in the ^{1}H NMR. Use of excess oxidant or efforts to isolate **278** and resubject it to epoxidation conditions were also unsuccessful, revealing that the trisubstituted alkenes of **277** and **278** are remarkably inert toward epoxidation. The origin of this effect is unclear; however, inspection of the crystal structure of alkene **277** suggests that it is not simply steric shielding of the double bond.

Scheme 3.9. *Attempts to install the epoxide*

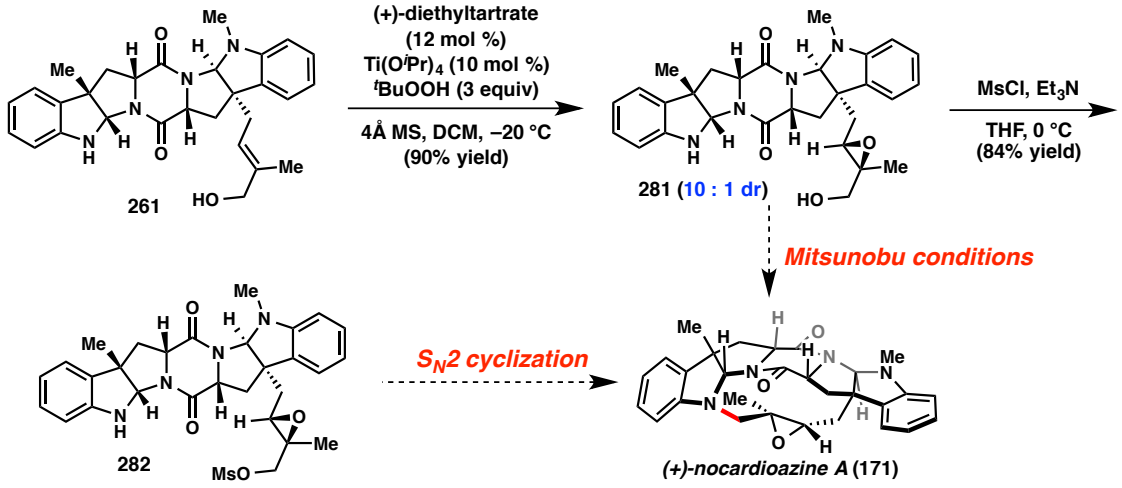


Alternatively, it was possible to diastereoselectively dihydroxylate alkene **279** using potassium osmate.[11] Selective mesylation of the secondary alcohol and exposure of the resulting mesylate to potassium carbonate in methanol closed the epoxide to form *epi*-(C2")-nocardioazine A (**280**). Unfortunately, attempts to correct the stereochemistry by double inversion strategies or oxidation/reduction sequences were unsuccessful.

Fully aware of the challenges associated with epoxidizing the macrocyclic alkene **277**, a strategy involving switching the order of epoxidation and cyclization was pursued. Epoxidation of allylic alcohol **261** proceeded smoothly under Sharpless asymmetric epoxidation conditions (Scheme 3.10).[12] However, intramolecular Mitsunobu reaction did

not occur, presumably due to the lower acidity of the aniline *N*-H in **281**. Alternatively, the primary alcohol could be converted to the mesylate (**282**). Unfortunately, either epimerization or no reaction was observed when treating **282** with a wide array of base. Other leaving groups including iodide and triflate were also explored, but no cyclization product was detected in either case. The lower reactivity toward cyclization of epoxide **282** versus alkene **277** is not entirely surprising due to the loss of reactivity gained from the allylic halide in **277**.

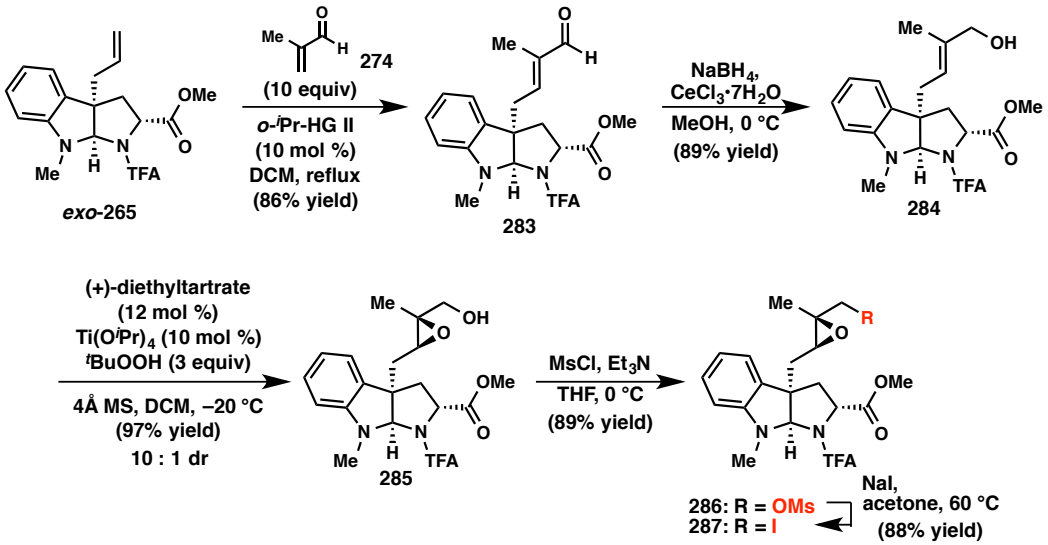
Scheme 3.10. *Attempts to promote the last-stage cyclization*



3.3.2 An Early-stage Epoxide Installation Approach

Given the challenges encountered in attempting to epoxidize late-stage intermediate **277**, a revised strategy utilizing an early-stage epoxidation and diketopiperazine-forming macrocyclization was pursued (Scheme 3.11). Thus, 3a-allyl pyrroloindoline *exo*-**265** was transformed into aldehyde **283** via cross metathesis with **274**. Luche reduction and Sharpless asymmetric epoxidation using (+)-diethyltartrate delivered epoxy alcohol **285** in 10:1 dr,[12] which was converted to mesylate **286** by

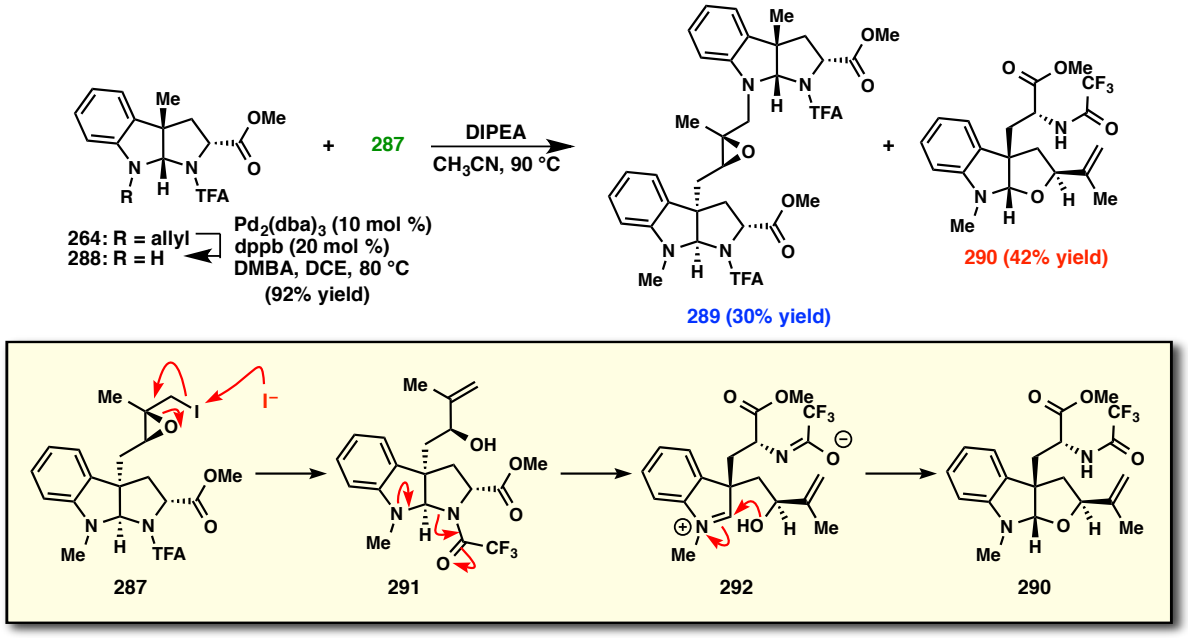
Scheme 3.11. *Early incorporation of epoxide*



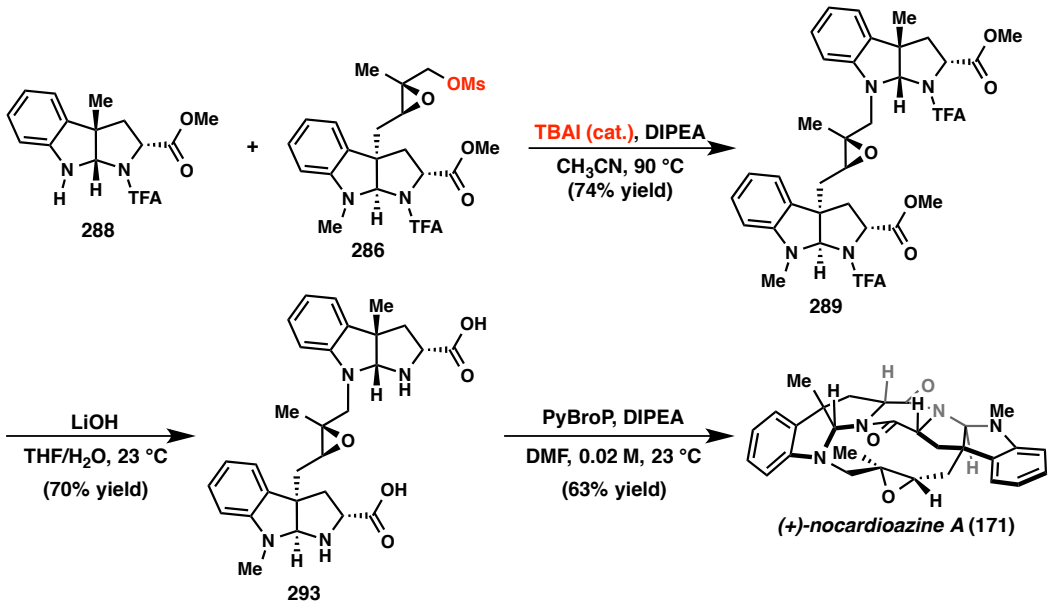
treatment with mesyl chloride. The corresponding epoxy iodide **287** could also be prepared by subjecting mesylate **286** to NaI in acetone. Concomitantly, amine **288** was prepared from *endo*-pyrroloindoline **264** by Pd-catalyzed deallylation (Scheme 3.12). Both epoxide nucleophiles **286** and **287** were exposed to amine **288** and Hünig's base in acetonitrile at high temperatures. Interestingly, mesylate **286** showed no reactivity, while iodide **287** afforded desired coupled product **289** in 30% yield. However, epoxide **289** was accompanied with the formation of side product **290** in 42% yield, which was proposed to arise from iodide-triggered epoxide opening followed by pyrroloindoline ring-opening and intramolecular trapping with the secondary alcohol.

In order to harness the reactivity of epoxide iodide and minimize the undesired rearrangement side pathway, it was proposed that the addition of a catalytic amount of an iodide source to mesylate **286** could generate epoxide iodide **287** *in situ*, thus the lower concentration of iodide would suppress the undesired side reaction pathway. Indeed, after

Scheme 3.12. *Intermolecular alkylation attempts*



Scheme 3.13. *Endgame of (+)-nocardioazine A synthesis*



considerable optimization, it was observed that treatment of amine **288** and mesylate **286** with 0.2 equivalent of TBAI and Hünig's base in acetonitrile at 90 °C delivers bis(pyrroloindoline) **289** in 74% yield (Scheme 3.13). Exposure of **289** to excess LiOH

resulted in saponification of the methyl esters and hydrolysis of the TFA groups to give bis(amino acid) **293**. We were pleased to find that subjection of **293** to bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, a peptide coupling reagent) in DMF promoted intramolecular DKP formation to afford (+)-nocardioazine A (**171**). The synthesis of (+)-**171** requires only nine steps and proceeds in 11% overall yield from 3-allylindole. Moreover, these findings establish the viability of macrocyclization by intramolecular DKP formation.

Through this process, we also established that the naturally isolated nocardioazine A (**171**) possesses the same absolute stereo configurations as nocardioazine B (**187**), suggesting that both natural products might be produced from the same biological source, namely cyclo-(L-Trp-D-Trp).

3.4 CONCLUDING REMARKS

In summary, the enantioselective total syntheses of the diketopiperazin-containing pyrroloindoline natural products (+)-nocardioazine A (**171**) and B (**187**) were accomplished. These studies demonstrate the utility of enantioselective formal (3 + 2) cycloaddition reactions to prepare highly functionalized pyrroloindolines for applications in total synthesis. In addition, subtle changes in the relative stereochemistry and nitrogen substitution patterns of pyrroloindolines were shown to significantly influence the ability to prepare bis(pyrroloindolines) by DKP formation. Further investigations of **171** as an inhibitor of P-glycoprotein are ongoing with collaboration with the Chang laboratory in UC San Diego.

3.5 EXPERIMENTAL SECTION

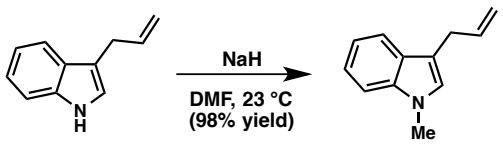
3.5.1 Materials and Methods

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.[13] 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 Bruker 400 equipped with a cryoprobe (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), $CHDCl_2$ (^{1}H, δ = 5.32), CD_2HOD (^{1}H, δ = 3.31), MeCN-*d2* (^{1}H, δ = 1.94), or DMSO-*d5* (^{1}H, δ = 2.50), and $CDCl_3$ (^{13}C, δ = 77.0), CD_2Cl_2 (^{13}C, δ = 54.0), CD_3OD (^{13}C, δ = 49.0), MeCN-*d3* (^{13}C, δ = 118.3), or DMSO-*d6* (^{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 *N*-methyl-3-allylindole 266

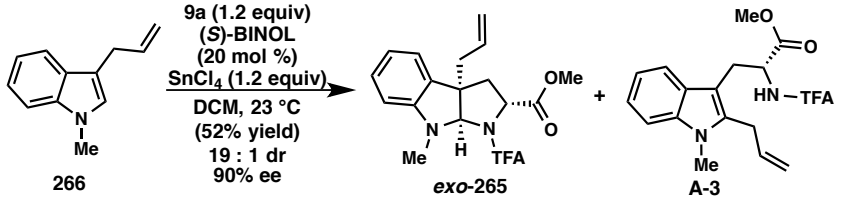


A-2 **266**

To a 500 mL flame-dried flask was added NaH (60%, 4.94 g, 123.6 mmol, 1.5 equiv) and DMF (120 mL). Commercially aviallable 3-allylindole **A-2** (12.95 g, 82.4 mmol, 1.0 equiv) was transferred to the reaction flask via DMF (40 mL). After 90 minutes, methyl iodide (7.7 mL, 123.6 mmol, 1.5 equiv) was added slowly, while the reaction flask was cooled using an ice-bath. After 1 hour, the reaction was diluted with EtOAc (100 mL) and carefully quenched with distilled water (300 mL). The mixture was separated and the aqueous layer was then extracted with EtOAc (2 x 200 mL). Combined

organic layers were washed with brine (3 x 300 mL) to get rid of DMF. It was dried over Na_2SO_4, filtered and concentrated down to a yellow oil. Flash chromatography (0% to 10% EtOAc in hexanes) afforded *N*-methyl-3-allylindole **266**, as a yellow oil (13.77 g, 80.4 mmol, 98% yield). Spectral data matches that reported in the literature.[14]

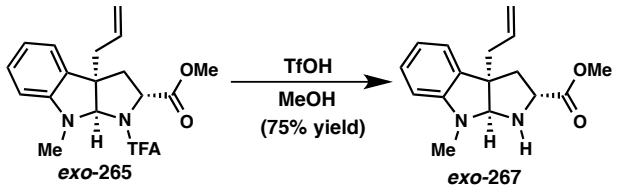
Preparation of *N*-methyl-3-allyl pyrroloindoline 265



To a flame-dried flask was added *N*-methyl-3-allylindole **266** (1.0 g, 5.80 mmol, 1.0 equiv), methyl acrylate **61a** (1.15 g, 5.80 mmol, 1.0 equiv), (*S*)-BINOL (334 mg, 1.20 mmol, 0.2 equiv), and DCM (30 mL). The reaction flask was covered with aluminum foil. $SnCl_4$ (1M solution in DCM, 9.34 mL, 9.34 mmol, 1.6 equiv) was added at last. The reaction mixture was allowed to stir at room temperature for 24 hours. The solution was diluted with acetonitrile (12 mL) and quenched with 1M HCl (12 mL), followed by addition of distilled water (60 mL). The mixture was separated and the aqueous layer was extracted with EtOAc (3 x 60 mL). Combined organic layers were washed with saturated $NaHCO_3$ solution (75 mL) and then brine (75 mL). It was dried over Na_2SO_4, filtered and concentrated down to give an orange oil. Flash chromatography (0% to 20% EtOAc in hexanes) afforded 3-allyl-pyrroloindoline **265** (19 : 1 mixture of *exo*:*endo* diastereomers by ^1H NMR), as a thick orange oil (1.10 g, 2.99 mmol, 52% yield); **A-3** was isolated as the major side product, resulting from C3 to C2 rearrangement. The mixture of diastereomers was further purified by flash chromatography (0% to 10% EtOAc in hexanes) to give major diastereomer **265** for characterization purposes. The enantiomeric

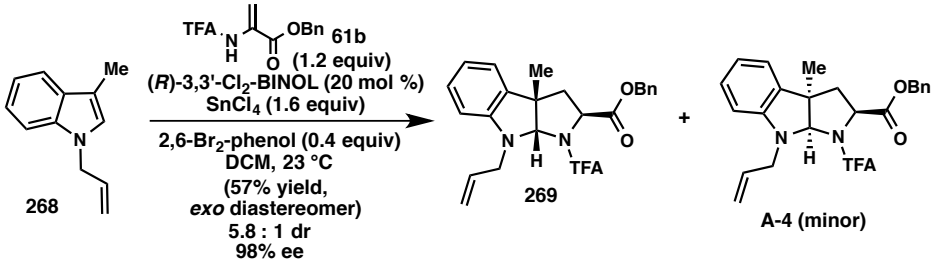
excess of *exo*-**265** was determined to be 90% by chiral SFC analysis (AD, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm): t_R(major) = 3.2 min, t_R(minor) = 6.5 min. $[\alpha]_D^{25}$ = +112° (*c* = 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.17 (t, *J* = 7.7 Hz, 1H*, 1H§), 7.05 (d, *J* = 7.3 Hz, 1H*, 1H§), 6.84 (t, *J* = 8.1 Hz, 1H§), 6.77 (t, *J* = 7.5 Hz, 1H*), 6.58 (d, *J* = 7.2 Hz, 1H§), 6.52 (d, *J* = 7.9 Hz, 1H*), 5.62 (s, 1H*), 5.60 – 5.45 (m, 1H*, 1H§), 5.44 (s, 1H§), 5.15 – 5.04 (m, 2H*, 2H§), 4.64 (d, *J* = 5.5 Hz, 1H*), 4.38 – 4.31 (m, 1H§), 3.81 (s, 3H*), 3.76 (s, 3H§), 3.10 (s, 3H*), 2.89 (s, 3H§), 2.64 (dd, *J* = 13.6, 9.3 Hz, 1H*), 2.62 – 2.57 (m, 1H§), 2.54 (dd, *J* = 14.0, 6.7 Hz, 1H*, 1H§), 2.52 – 2.47 (m, 1H§), 2.46 – 2.40 (m, 1H*), 2.32 (dd, *J* = 13.9, 8.4 Hz, 1H*), 2.19 – 2.11 (m, 1H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5*, 170.5§, 158.8* (q, *J* = 37.1 Hz), 157.5§ (q, *J* = 38.0 Hz), 150.2*§, 133.2*, 132.2§, 129.0§, 128.8*, 122.1*, 120.0§, 119.1*, 118.7§, 116.0* (q, *J* = 288.4 Hz), 115.8§ (app d, *J* = 285.2 Hz), 109.9§, 108.2*, 90.4*, 89.0§, 60.6§, 59.5*, 57.3§, 53.4*, 52.9*, 52.4§, 42.1*, 41.6*, 41.0§, 39.0§, 36.8*, 35.4§ (both ^{1}H and ^{13}C spectra were taken using the enantiomer of **23**); FTIR (NaCl, thin film): 3076, 3053, 3008, 2955, 2918, 2848, 2829, 1751, 1693, 1641, 1608, 1490, 1435, 1357, 1302, 1203, 1158, 1061, 1023, 994, 952, 925, 875, 854, 810, 795, 746 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{20}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1432.

Preparation of *exo*-pyrroloindoline amine 267



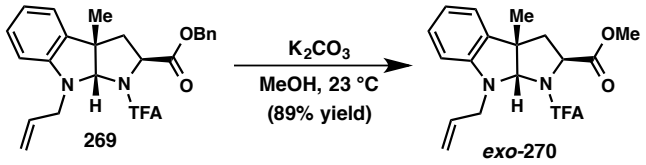
To a 200 mL flame-dried flask was added *exo*-3-allyl-pyrroloindoline **265** (6.57 g, 17.8 mmol, 1.0 equiv) and dissolved with MeOH (90 mL). Triflic acid (15.7 mL, 178.4 mmol, 10.0 equiv) was added slowly into reaction flask. The dark purple mixture was allowed to stir at room temperature for 50 hours. The solution was cautiously quenched with saturated $NaHCO_3$ solution (150 mL). The mixture was separated and the aqueous layer was extracted with DCM (3 x 150 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated down to give an orange oil. Flash chromatography (0% to 60% EtOAc in hexanes) afforded 3-allyl-pyrroloindoline amine *exo*-**267** as a thick orange oil (3.60 g, 13.2 mmol, 75% yield). $[\alpha]_D^{25}$ = +43° (*c* = 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (td, *J* = 7.6, 1.3 Hz, 1H), 6.98 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.61 (td, *J* = 7.4, 1.0 Hz, 1H), 6.31 (d, *J* = 7.8 Hz, 1H), 5.67 (dddd, *J* = 16.7, 10.1, 7.9, 6.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.68 (s, 1H), 3.64 (s, 3H), 3.62 (dd, *J* = 10.4, 6.1 Hz, 1H), 2.78 (s, 3H), 2.67 (s, 1H), 2.51 (ddt, *J* = 13.9, 6.5, 1.4 Hz, 1H), 2.41 (ddt, *J* = 13.7, 8.0, 1.1 Hz, 1H), 2.34 (dd, *J* = 12.1, 6.1 Hz, 1H), 1.95 (dd, *J* = 12.2, 10.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 150.8, 134.0, 132.2, 127.9, 122.6, 117.6, 116.4, 104.9, 88.0, 58.9, 56.0, 51.5, 44.1, 42.5, 30.9; FTIR (NaCl, thin film): 3344, 3073, 3050, 3024, 3003, 2950, 2916, 1738, 1639, 1606, 1493, 1449, 1437, 1383, 1354, 1328, 1300, 1267, 1236, 1206, 1166, 1140, 1121, 1105, 1073, 1019, 998, 973, 948, 918, 889, 817, 790, 741 cm^{-1}; HRMS (MM) calc'd for $C_{16}H_{21}N_2O_2$ $[M+H]^+$ 273.1598, found 273.1067.

Preparation of *N*-allyl pyrroloindoline 269



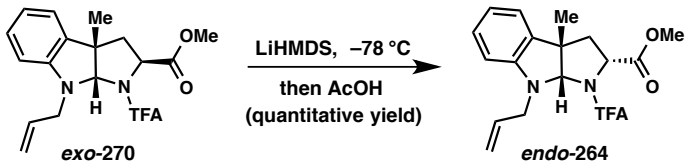
To a flame-dried flask was added *N*-allylindole **268**[15] (815 mg, 4.76 mmol, 1.0 equiv), benzyl acrylate **61b**[16] (1.56 g, 5.71 mmol, 1.2 equiv), (*R*)-3,3'-Cl_2-BINOL (338 mg, 0.95 mmol, 0.2 equiv), 2,6-dibromo-phenol (480 mg, 1.90 mmol, 0.4 equiv) and DCM (35 mL). $SnCl_4$ (1M solution in DCM, 7.62 mL, 7.62 mmol, 1.2 equiv) was added at last. The orange mixture was allowed to stir at room temperature for 42 hours. The solution was diluted with acetonitrile (12 mL) and quenched with 1M HCl (12 mL), followed by addition of distilled water (60 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 60 mL). Combined organic layers were washed with 3M NaOH solution (3 x 75 mL). It was dried over $MgSO_4$, filtered and concentrated down to give yellow mixture of oil and solid. Flash chromatography (1% to 8% EtOAc in hexanes) afforded major diastereomer *exo*-pyrroloindoline **269** as a thick orange oil (1.19 g, 2.68 mmol, 57% yield); minor diastereomer *endo*-pyrroloindoline **A-4** was also isolated as a thick orange oil (204 mg, 0.46 mmol, 10% yield). The enantiomeric excess of **269** was determined to be 98% by chiral SFC analysis (OJ, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min, t_R(minor) = 4.4 min. The enantiomeric excess of **A-4** was determined to be 93% by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min, t_R(minor) = 4.4 min. Spectral data of both diastereomers matches that reported in the literature.[2]

Preparation of *N*-allyl pyrroloindoline methyl ester 270



N-Allyl pyrroloindoline benzyl ester **269** (1.11 g, 2.51 mmol, 1.0 equiv) was dissolved in dry methanol (25 mL); then K_2CO_3 (70 mg, 0.50 mmol, 0.2 equiv) was added as one portion. After running at room temperature for 6 hours, the reaction was quenched with 1M HCl (50 mL), and extracted with EtOAc (3 x 40 mL). Combined organic layer was washed with sodium bicarbonate saturated solution (50 mL) and then dried over Na_2SO_4, filtered and concentrated down to give yellow oil. Flash chromatography (0% to 15% EtOAc in hexanes) afforded corresponding methyl ester **270**, as a white solid (818 mg, 2.22 mmol, 89% yield). Spectral data matches that reported in the literature.[3]

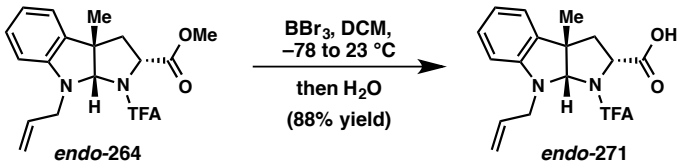
Preparation of *endo-N*-allyl pyrroloindoline 264



N-Allyl pyrroloindoline methyl ester **270** (700 mg, 1.90 mmol) was dissolved in dry THF (16 mL) and brought to –78 °C. LiHMDS solution (1M in THF, 2.85 mL, 2.85 mmol, 1.5 equiv) was added slowly to substrate in THF. After 1 hour, the reaction was quenched with acetic acid (1 mL) and warmed to room temperature. Then the reaction was quenched carefully with sodium bicarbonate saturated solution (40 mL). The aqueous layer was then extracted with EtOAc (3 x 50 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered, and concentrated

down to give a yellow oil. Flash chromatography (0% to 10% EtOAc in hexanes) afforded corresponding epimerized *endo* pyrroloindoline methyl ester **264**, as a yellow oil (700 mg, 1.90 mmol, quantitative yield). $[\alpha]_D^{25} = -200°$ (*c* = 1.62, $CHCl_3$); spectral data matches that the corresponding enantiomer reported in the literature.[3]

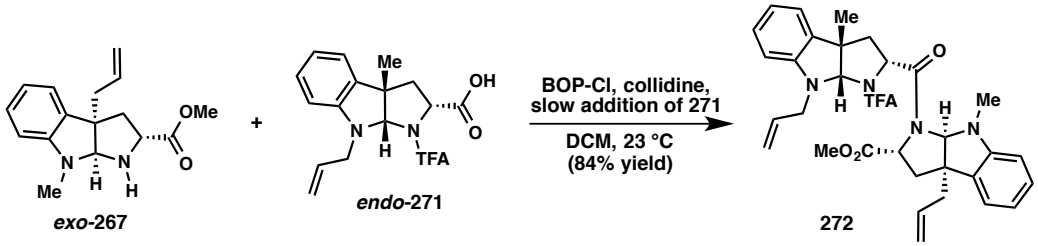
Preparation of *endo-N*-allyl pyrroloindoline carboxylic acid 271



endo-N-Allyl pyrroloindoline methyl ester **264** (1.50 g, 4.07 mmol, 1.0 equiv) was added to a flame-dried 100 mL flask and dissolved in DCM (36 mL). The flask was then cooled to –78 °C and freshly prepared BBr_3 in DCM solution (BBr_3: 1.15 mL, 12.22 mmol, 3.0 equiv; DCM: 12 mL) was added slowly into reaction flask. After 5 minutes, the reaction was allowed to warm to room temperature and stirred for 90 minutes. It was then quenched carefully with addition of distilled water (10 mL), then followed by addition of pH = 2.5 acidic buffer (40 mL, prepared by acidifying a 10% NaH_2PO_4 aqueous solution by $KHSO_4$ until pH reaches 2.5). The aqueous layer was extracted with EtOAc (4 x 40 mL). Combined organic layer was washed with brine (80 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a yellow oil. Flash chromatography (0% to 20% EtOAc in hexanes, with 1% acetic acid) afforded corresponding pyrroloindoline carboxylic acid *endo*-**271**, as a brown foam (1.26 g, 3.56 mmol, 88% yield). $[\alpha]_D^{25} = -179°$ (*c* = 1.39, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 8.0 : 1 mixture of rotamers the major rotamer is denoted by *, minor rotamer denoted by §) δ 10.90 (s, 1H*, 1H§), 7.11 (td, *J* = 7.7, 1.3 Hz, 1H§), 7.07

(dd, J = 7.4, 1.2 Hz, 1H[§]), 6.99 (td, J = 7.7, 1.3 Hz, 1H*), 6.95 (dd, J = 7.5, 1.2 Hz, 1H*), 6.75 (td, J = 7.4, 1.0 Hz, 1H[§]), 6.57 (td, J = 7.4, 0.9 Hz, 1H*), 6.50 (d, J = 7.9 Hz, 1H[§]), 6.39 (d, J = 7.9 Hz, 1H*), 5.85 (ddt, J = 17.3, 10.6, 5.4 Hz, 1H*), 5.81 – 5.72 (m, 1H[§]), 5.59 (s, 1H*), 5.55 (d, J = 1.9 Hz, 1H[§]), 5.29 (dq, J = 17.2, 1.7 Hz, 1H*), 5.22 – 5.20 (m, 1H[§]), 5.20 – 5.17 (m, 1H[§]), 5.15 (dq, J = 10.2, 1.5 Hz, 1H*), 5.06 (dd, J = 9.9, 5.4 Hz, 1H[§]), 4.73 (dt, J = 8.7, 1.5 Hz, 1H*), 4.13 (qdt, J = 16.7, 5.1, 1.7 Hz, 2H*), 3.91 – 3.69 (m, 2H[§]), 2.76 (dd, J = 13.2, 1.4 Hz, 1H*), 2.42 (dd, J = 13.1, 8.8 Hz, 1H*), 2.39 – 2.34 (m, 1H[§]), 2.29 (dd, J = 13.4, 9.9 Hz, 1H[§]), 1.45 (s, 3H[§]), 1.43 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3[§], 175.2*, 156.8 (q, $J_{C\text{-}F}$ = 37.0 Hz), 156.6 (q, $J_{C\text{-}F}$= 37.5 Hz), 149.1*, 147.3[§], 133.8*, 133.1[§], 132.4[§], 131.8*, 128.9*, 128.5[§], 122.2*, 121.4[§], 118.7[§], 118.0*, 117.1[§], 116.3*, 116.0* (q, $J_{C\text{-}F}$ = 288.5 Hz), 108.1[§], 107.1*, 88.9[§], 88.3*, 59.8[§], 59.6* (q, $J_{C\text{-}F}$ = 3.1 Hz), 52.2[§], 50.4*, 48.8*, 46.2[§], 42.3*, 41.1[§], 25.2*, 22.0[§]; FTIR (NaCl, thin film): 3079, 3057, 3026, 2963, 2928, 2870, 2647, 2560, 1729, 1696, 1608, 1491, 1448, 1352, 1314, 1253, 1210, 1184, 1145, 1106, 1093, 1083, 1027, 992, 942, 921, 888, 854, 742 cm^{-1}; HRMS (APCI) calc'd for $C_{17}H_{18}F_3N_2O_3$ $[M+H]^+$ 355.1264, found 355.1275.

Preparation of dipeptide 272

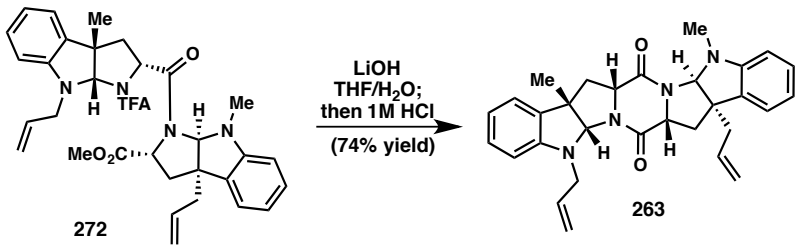


To a 250 mL flame-dried flask was added 3-allyl-amine *exo*-**267** (1.94 g, 7.11 mmol, 2.0 equiv), BOP-Cl (1.81 g, 7.11 mmol, 2.0 equiv) and dissolved with DCM (93

mL), followed by addition of 2,4,6-collidine (1.08 mL, 8.18 mmol, 2.3 equiv). Carboxylic acid *endo*-**271** (1.26 g, 3.56 mmol, 1.0 equiv) was dissolved in DCM (47 mL) and the resulting solution was added slowly into the reaction flask using a syringe pump over 12 hours. The resulting reaction solution was allowed to stir at room temperature for another 10 hours. The reaction was quenched with saturated $NaHCO_3$ solution (200 mL). The mixture was separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). Combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated down to give an orange oil. The crude material was left in the flask for 36 hours to allow the hydrolysis of anhydride formed under reaction conditions. Flash chromatography (0% to 60% EtOAc in hexanes) afforded dipeptide **272** as a pink foam (1.81 g, 2.97 mmol, 84% yield). $[\alpha]_D^{25}$ = +18° (*c* = 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, compound exists as a 1.4 : 1 : 1 mixture of rotamers) complicated spectrum, please see the attached ^{1}H NMR spectrum; ^{13}C NMR (126 MHz, DMSO-d_6, compound exists as a mixture of rotamers) δ 173.0, 171.6, 171.5, 170.8, 170.2, 168.7, 157.7 (q, $J_{C\text{-}F}$ = 36.5 Hz), 157.0 (q, $J_{C\text{-}F}$ = 36.3 Hz), 156.6 (q, $J_{C\text{-}F}$ = 36.4 Hz), 151.0, 150.6, 149.6, 149.2, 148.3, 147.2, 135.1, 134.9, 134.6, 134.5, 134.4, 134.3, 134.0, 133.9, 133.0, 132.5, 129.1, 128.7, 128.6, 128.4, 128.4, 123.1, 122.6, 122.4, 122.0, 121.3, 120.5, 119.0, 118.7, 118.6, 118.1, 118.0, 117.9, 117.9, 117.1, 117.0, 116.5, 116.3 (q, $J_{C\text{-}F}$ = 288.6 Hz), 116.3 (q, $J_{C\text{-}F}$ = 288.6 Hz), 116.3 (app d, $J_{C\text{-}F}$= 287.3 Hz), 111.5, 108.0, 107.9, 107.5, 107.5, 106.9, 91.1, 89.5, 89.3, 89.1, 87.9, 87.7, 62.2, 61.1, 60.1, 60.0, 58.8, 58.1, 55.7, 53.2, 53.1, 52.6, 52.0, 50.2, 49.9, 49.5, 49.2, 46.0, 43.4, 42.8, 42.1, 41.6, 41.5, 40.8, 38.5, 37.7, 37.6, 36.1, 32.8, 26.5, 23.4, 19.4; FTIR (NaCl, thin film): 3075, 3052, 3016, 2954, 2869, 1744, 1696, 1681, 1638, 1607, 1491, 1448, 1437, 1406, 1357, 1298, 1282, 1210,

1184, 1145, 1106, 1022, 992, 922, 847, 742 cm^{-1}; HRMS (APCI) calc'd for $C_{33}H_{36}F_3N_4O_4$ $[M+H]^+$ 609.2683, found 609.2683.

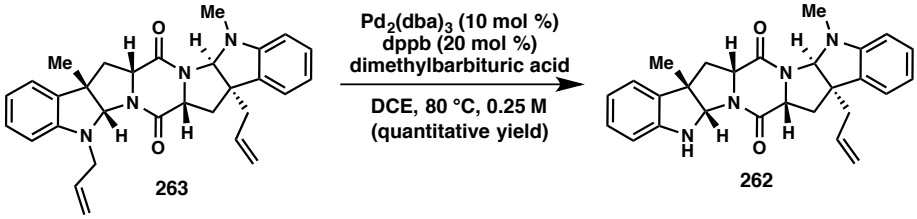
Preparation of bis(allyl)-diketopiperazine 263



To a 200 mL flask was added dipeptide **272** (1.81 g, 2.97 mmol, 1.0 equiv) and it was dissolved with THF (50 mL). LiOH (428 mg, 17.84 mmol, 6.0 equiv) was dissolved in distilled water (50 mL) and the resulting aqueous solution was added into the reaction flask. The reaction was allowed to stir at room temperature for 12 hours. 1M HCl (20 mL) was then added into the reaction, and the reaction was stirred for another 40 minutes. The mixture was extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with saturated $NaHCO_3$ (150 mL) and brine (150 mL). It was dried over Na_2SO_4, filtered and concentrated down to give a yellow oil. Flash chromatography (0% to 50% EtOAc in hexanes) afforded diketopiperazine **263** as a white solid (1.05 g, 2.18 mmol, 74% yield). $[\alpha]_D^{25}$ = +90° (*c* = 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (app tdd, *J* = 7.8, 6.6, 1.3 Hz, 2H), 7.07 (app ddd, *J* = 7.0, 5.6, 1.2 Hz, 2H), 6.75 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 (td, *J* = 7.5, 0.9 Hz, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 5.86 (dddd, *J* = 16.5, 10.4, 6.1, 4.3 Hz, 1H), 5.61 (dddd, *J* = 16.7, 10.1, 7.9, 6.4 Hz, 1H), 5.42 (s, 1H), 5.41 (s, 1H), 5.27 (dq, *J* = 17.1, 1.9 Hz, 1H), 5.13 (dq, *J* = 10.3, 1.6 Hz, 1H), 5.11 – 5.08 (m, 1H), 5.07 (q, *J* = 1.7 Hz, 1H), 4.40 (ddd, *J* = 9.9, 8.3, 1.5 Hz, 1H), 4.29 (ddt, *J* = 16.8, 4.2, 1.9 Hz, 1H), 4.16 (ddd, *J* = 10.5, 6.7, 1.4 Hz, 1H), 4.09 – 3.98 (m,

1H), 3.03 (s, 3H), 2.69 (dd, *J* = 12.9, 6.7 Hz, 1H), 2.52 (ddt, *J* = 13.8, 6.5, 1.4 Hz, 1H), 2.40 (ddt, *J* = 13.7, 8.0, 1.0 Hz, 1H), 2.36 – 2.29 (m, 3H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.3, 150.6, 148.4, 133.9, 133.8, 133.1, 131.3, 128.9, 128.5, 122.8, 121.3, 118.9, 118.3, 117.9, 116.4, 107.8, 106.1, 87.9, 84.6, 60.8, 59.7, 54.2, 51.0, 50.8, 42.7, 40.5, 40.4, 33.6, 22.1; FTIR (NaCl, thin film): 3336, 3075, 3053, 3008, 2978, 2956, 2927, 2891, 2873, 2836, 1676, 1608, 1489, 1465, 1447, 1407, 1335, 1304, 1278, 1219, 1193, 1160, 1123, 1093, 1050, 1026, 999, 978, 922, 846, 800, 746, 707 cm^{-1}; HRMS (MM) calc'd for $C_{30}H_{33}N_4O_2$ $[M+H]^+$ 481.2598, found 481.2612.

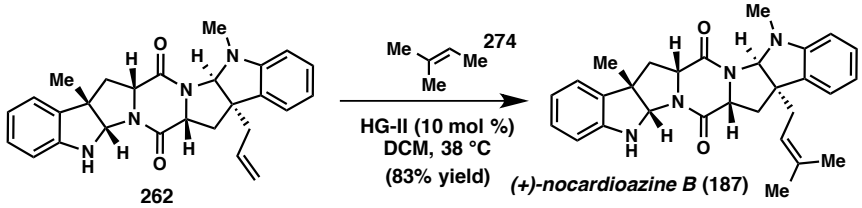
Preparation of diketopiperazine 262



To a 25 mL flame-dried screw-cap Schlenk flask was added bis(allyl)-diketopiperazine **263** (650 mg, 1.35 mmol, 1.0 equiv) and dimethylbibarturic acid (DMBA, 634 mg, 4.06 mmol, 3.0 equiv). The Schlenk flask was then evacuated and backfilled with argon three times. The solids were then dissolved in dry DCE (3.7 mL). In the meantime, in a 1-dram vial, mixed $Pd_2(dba)_3$ (62 mg, 0.068 mmol, 5 mol %) and 1,4-bis(diphenylphosphino)butane (dppb, 58 mg, 0.135 mmol, 10 mol %) in DCE (1.7 mL) and it was allowed to stir at room temperature for one hour; then the resulting solution was added into Schlenk flask. The reaction was heated to 80 °C. After 42 hours, the reaction was cooled to room temperature and quenched with saturated Na_2CO_3 aqueous solution (40 mL). The mixture was extracted with EtOAc (3 x 40 mL). Combined organic layers were washed with brine (100 mL). It was dried over Na_2SO_4,

filtered and concentrated down to give a brown oil. Flash chromatography (0% to 40% EtOAc in hexanes) afforded diketopiperazine **262**, which was contaminated with phosphine oxide formed from the dppb ligand. The mixture was then subjected to preparative reverse phase HPLC (40% to 90% CH_3CN in H_2O in 10 minutes, t_R=7.4-7.8 min), to give pure product **262** as a yellow foam (596 mg, 1.35 mmol, quantitative yield). $[\alpha]_D^{25}$ = +71° (*c* = 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12 – 7.04 (m, 3H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.72 (td, *J* = 7.4, 1.0 Hz, 1H), 6.59 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 5.56 (dddd, *J* = 16.8, 10.1, 8.0, 6.5 Hz, 1H), 5.38 (s, 1H), 5.34 (s, 1H), 5.27 (br s, 1H), 5.08 – 5.04 (m, 1H), 5.03 (dtd, *J* = 2.8, 1.8, 1.1 Hz, 1H), 4.44 (ddd, *J* = 10.1, 7.4, 1.8 Hz, 1H), 4.15 (ddd, *J* = 10.7, 6.5, 1.8 Hz, 1H), 3.01 (s, 3H), 2.65 (dd, *J* = 12.9, 6.5 Hz, 1H), 2.50 (ddt, *J* = 13.8, 6.6, 1.3 Hz, 1H), 2.46 – 2.34 (m, 3H), 2.28 (dd, *J* = 12.9, 10.7 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 165.8, 150.7, 147.0, 133.3, 133.1, 131.2, 128.8, 128.4, 122.9, 122.4, 119.2, 118.9, 117.9, 109.3, 106.1, 84.7, 83.7, 60.2, 59.2, 54.1, 51.3, 42.8, 40.7, 40.2, 33.5, 23.4; FTIR (NaCl, thin film): 3346, 3074, 3052, 3007, 2976, 2955, 2925, 2896, 2871, 2834, 1666, 1608, 1487, 1468, 1414, 1341, 1300, 1252, 1198, 1161, 1122, 1091, 1059, 1048, 1018, 1000, 978, 921, 887, 824, 746 cm^{-1}; HRMS (MM) calc'd for $C_{27}H_{29}N_4O_2$ $[M+H]^+$ 441.2285, found 441.2294.

Preparation of (+)-nocardioazine B (187)



To a 25 mL flame-dried flask was added diketopiperazine **262** (8.4 mg, 0.019 mmol, 1.0 equiv), which was then co-evaporated with benzene (2 x 1 mL), and dried under high vacuum. Hoveyda-Grubbs II catalyst (1.2 mg, 0.002 mmol, 10 mol %) was added, followed by 2-methyl-2-butene (4.5 mL). The flask was equipped with a condenser and heated to 38 °C for 10 hours. The reaction was then quenched with ethyl vinyl ether (0.1 mL) and filtered through a silica gel plug, eluting with 50% EtOAc in hexanes. The filtrate was concentrated down to give a light brown oil. Flash chromatography (5% to 50% EtOAc in hexanes) afforded (+)-nocardioazine B (**187**) as a light grey solid (7.4 mg, 0.016 mmol, 83% yield). $[\alpha]_D^{25}$ = +65° (*c* = 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 2H), 7.09 (td, J = 7.7, 1.2 Hz, 1H), 7.04 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 (td, *J* = 7.4, 1.0 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 5.35 (s, 1H), 5.31 (s, 1H), 5.21 (br s, 1H), 5.00 (tq, *J* = 4.9, 1.6 Hz, 1H), 4.44 (ddd, *J* = 9.8, 7.7, 1.8 Hz, 1H), 4.15 (ddd, *J* = 10.7, 6.5, 1.8 Hz, 1H), 3.01 (s, 3H), 2.64 (dd, *J* = 12.8, 6.5 Hz, 1H), 2.47 – 2.32 (m, 4H), 2.28 (dd, *J* = 12.8, 10.7 Hz, 1H), 1.65 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 165.9, 150.6, 147.1, 135.5, 133.4, 131.9, 128.7, 128.5, 122.8, 122.4, 119.3, 118.6, 118.0, 109.3, 106.2, 84.9, 83.7, 60.4, 59.3, 54.7, 51.3, 40.9, 39.6, 36.5, 33.6, 25.9, 23.4, 18.0; FTIR (NaCl, thin film): 3348, 3051, 2956, 2925, 2870, 2855, 1667, 1608, 1487, 1468, 1445, 1415, 1381, 1342, 1301, 1261, 1232, 1200, 1156, 1099, 1085, 1065, 1042, 1019, 1000, 976, 942, 890, 850, 822, 802, 781, 744 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_2$ $[M+H]^+$ 469.2598, found 469.2604.

Table 3.2. *Comparison of ^{1}H NMR data for natural vs. synthetic (+)-nocardioazine B (**187**)*

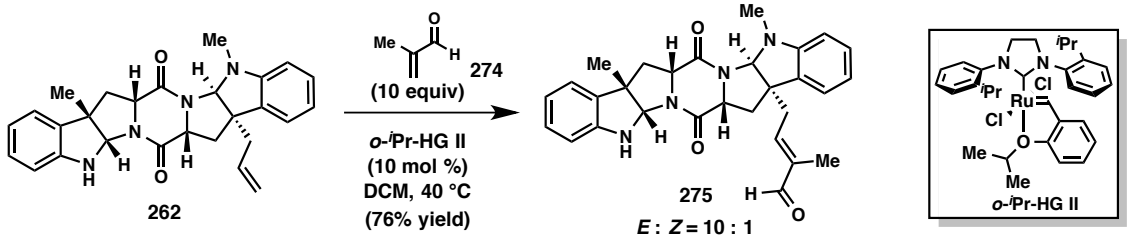
Raju et al. Report,[3] Natural (+)-nocardioazine B ^{1}H NMR, 600 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine B ^{1}H NMR, 500 MHz, $CDCl_3$
δ 7.11 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H)	δ 7.16 – 7.09 (m, 2H)
7.08 (ddd, *J* = 7.7, 7.4, 1.0 Hz, 1H)	-
7.06 (dd, *J* = 7.4, 1.0 Hz, 1H)	7.09 (td, J = 7.7, 1.2 Hz, 1H)
7.02 (dd, *J* = 7.4, 1.1 Hz, 1H)	7.04 (dd, *J* = 7.3, 1.2 Hz, 1H)
6.75 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H)	6.78 (td, *J* = 7.4, 1.0 Hz, 1H)
6.69 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H)	6.71 (td, *J* = 7.4, 1.0 Hz, 1H)
6.57 (dd, *J* = 7.7, 0.9 Hz, 1H)	6.59 (d, *J* = 7.7 Hz, 1H)
6.38 (dd, *J* = 7.7, 0.9 Hz, 1H)	6.39 (d, *J* = 7.8 Hz, 1H)
5.33 (s, 1H)	5.35 (s, 1H)
5.29 (s, 1H)	5.31 (s, 1H)
5.18 (s, 1H)	5.21 (br s, 1H)
4.98 (m, 1H)	5.00 (tq, *J* = 4.9, 1.6 Hz, 1H)
4.42 (ddd, *J* = 9.8, 7.6, 1.8 Hz, 1H)	4.44 (ddd, *J* = 9.8, 7.7, 1.8 Hz, 1H)
4.13 (ddd, *J* = 10.7, 6.5, 1.7 Hz, 1H)	4.15 (ddd, *J* = 10.7, 6.5, 1.8 Hz, 1H)
2.99 (s, 3H)	3.01 (s, 3H)
2.62 (dd, *J* = 12.9, 6.5 Hz, 1H)	2.64 (dd, *J* = 12.8, 6.5 Hz, 1H)
2.37 (m, 2H)	2.47 – 2.32 (m, 4H)
2.35 (m, 2H)	–
2.25 (dd, *J* = 12.9, 10.7 Hz, 1H)	2.28 (dd, *J* = 12.8, 10.7 Hz, 1H)
1.63 (s, 3H)	1.65 (s, 3H)
1.48 (s, 3H)	1.50 (s, 3H)
1.45 (s, 3H)	1.47 (s, 3H)

Table 3.3. *Comparison of ^{13}C NMR data for natural vs. synthetic (+)-nocardioazine B (**187**)*

Raju et al. Report,[3] Natural (+)-nocardioazine B ^{13}C NMR, 150 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine B ^{13}C NMR, 126 MHz, $CDCl_3$	Chemical Shift Difference, Δδ
δ 167.1	δ 167.3	0.2
NR	165.9	–
150.6	150.6	0.0
146.9	147.1	0.2
135.5	135.5	0.0
133.3	133.4	0.1
132.0	131.9	0.1
128.8	128.7	0.1
128.5	128.5	0.0
122.8	122.8	0.0

122.4	122.4	0.0
119.2	119.3	0.1
118.6	118.6	0.0
117.9	118.0	0.1
109.4	109.3	0.1
106.2	106.2	0.0
85.0	84.9	0.1
83.7	83.7	0.0
60.4	60.4	0.0
59.3	59.3	0.0
54.6	54.7	0.1
51.2	51.3	0.1
41.0	40.9	0.1
39.8	39.6	0.2
36.7	36.5	0.2
33.7	33.6	0.1
26.0	25.9	0.1
23.4	23.4	0.0
17.9	18.0	0.1

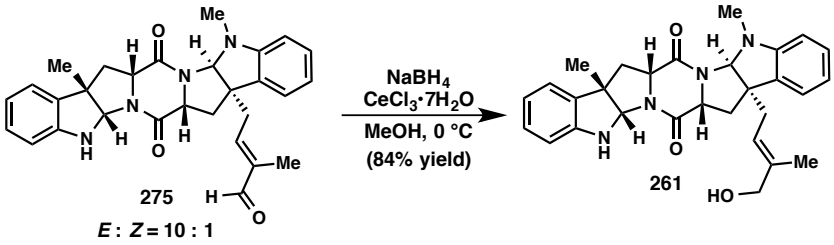
Preparation of enal 275



To a 50 mL flame-dried flask was added diketopiperazine **262** (431 mg, 0.98 mmol, 1.0 equiv) and DCM (9 mL), followed by methacrolein **274** (95%, 0.85 mL, 9.78 mmol, 10 equiv). *ortho*-^{i}Pr-Hoveyda-Grubbs II catalyst (61.3 mg, 0.10 mmol, 10 mol %) was added as a DCM solution (0.1 mL) at last. The flask was equipped with a condenser and heated to 40 °C for 18 hours. The reaction was then quenched with ethyl vinyl ether (0.5 mL) and filtered through a silica gel plug, eluting with EtOAc. The filtrate was concentrated down to give a brown oil. Flash chromatography (10% to 80% EtOAc in hexanes) afforded enal **275** as a light grey foam (*E* : *Z* = 10 : 1 mixture, 356 mg, 0.74

mmol, 76% yield). The mixture of isomers was further purified by flash chromatography (10% to 80% EtOAc in hexanes) to give (*E*)-**275** for characterization purposes. $[\alpha]_D^{25}$ = +77° (*c* = 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.17 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 – 7.02 (m, 3H), 6.82 – 6.71 (m, 2H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 6.25 (ddd, *J* = 8.7, 6.7, 1.5 Hz, 1H), 5.38 (s, 1H), 5.35 (s, 1H), 5.20 (br s, 1H), 4.47 (ddd, *J* = 9.7, 8.0, 1.8 Hz, 1H), 4.19 (ddd, *J* = 10.7, 6.5, 1.9 Hz, 1H), 3.01 (s, 3H), 2.83 – 2.71 (m, 3H), 2.41 (d, *J* = 2.4 Hz, 1H), 2.38 (s, 1H), 2.32 (dd, *J* = 12.8, 10.6 Hz, 1H), 1.66 – 1.65 (m, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.6, 166.7, 165.8, 150.4, 147.6, 146.9, 141.6, 133.2, 130.0, 129.3, 128.4, 122.5, 122.3, 119.2, 118.2, 109.3, 106.3, 84.7, 83.6, 60.2, 59.1, 53.7, 51.2, 40.7, 40.3, 37.3, 33.1, 23.2, 9.4; FTIR (NaCl, thin film): 3351, 3051, 3013, 2953, 2929, 2872, 2716, 1670, 1607, 1486, 1468, 1446, 1412, 1339, 1302, 1262, 1235, 1200, 1157, 1126, 1099, 1083, 1040, 1019, 1000, 978, 932, 883, 809, 747 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2410.

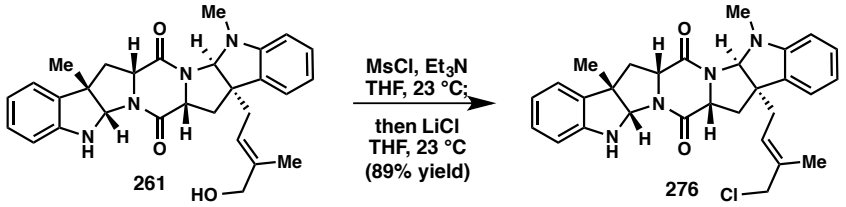
Preparation of allylic alcohol 261



To a 50 mL flask was added aldehyde **275** (*E* : *Z* = 10 : 1 mixture, 159 mg, 0.33 mmol, 1.0 equiv) and methanol (12 mL). Sonicator was used to facilitate **275** to dissolve in solution. Then, cerium chloride heptahydrate (307 mg, 0.82 mmol, 2.5 equiv) was dissolved in methanol (2 mL), while $NaBH_4$ (25 mg, 0.66 mmol, 2.0 equiv) was dissolved

in methanol (2 mL). The reaction was cooled to 0 °C. The previously prepared methanol solution of cerium chloride was added into the reaction flask, quickly followed by the addition of $NaBH_4$ methanol solution. After reacting at 0 °C for 40 minutes, the reaction was quenched with saturated ammonium chloride solution (30 mL), followed by EtOAc (30 mL). The mixture was separated and aqueous layer was extracted with EtOAc (3 x 30 mL). Combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated down to give a grey oil. Flash chromatography (20% to 90% EtOAc in hexanes) afforded allylic alcohol **261** as a white foam (133 mg, 0.27 mmol, 84% yield). $[\alpha]_D^{25}$ = +68° (*c* = 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (td, *J* = 7.7, 1.3 Hz, 1H), 7.11 – 7.06 (m, 2H), 7.05 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 (td, *J* = 7.4, 1.0 Hz, 1H), 6.59 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.36 (s, 1H), 5.35 (br s, 2H), 5.29 (ddt, *J* = 9.5, 6.7, 1.5 Hz, 1H), 4.44 (ddd, *J* = 9.9, 8.4, 1.8 Hz, 1H), 4.16 (ddd, *J* = 10.1, 7.0, 1.8 Hz, 1H), 3.90 (s, 2H), 3.00 (s, 3H), 2.61 (dd, *J* = 13.0, 7.0 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.39 – 2.30 (m, 3H), 2.15 (s, 1H), 1.56 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 165.8, 150.4, 147.0, 138.8, 133.3, 131.8, 128.8, 128.4, 122.6, 122.3, 119.3, 119.2, 118.0, 109.5, 106.2, 85.2, 83.6, 68.2, 60.3, 59.3, 54.2, 51.3, 40.8, 39.4, 35.9, 33.5, 23.2, 13.9; FTIR (NaCl, thin film): 3367, 3051, 3004, 2929, 2872, 1664, 1607, 1486, 1468, 1420, 1341, 1301, 1251, 1199, 1155, 1099, 1085, 1065, 1039, 1018, 1002, 978, 943, 892, 824, 746 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_3$ $[M+H]^+$ 485.2547, found 485.2554.

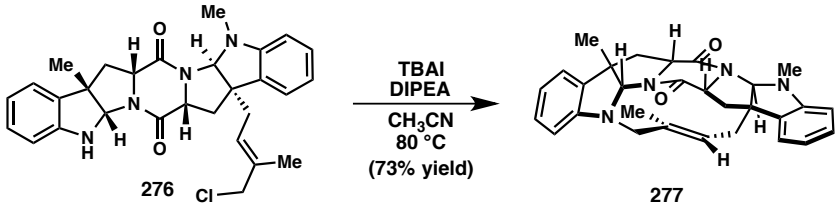
Preparation of allylic chloride 276



To a 10 mL flame-dried flask was added allylic alcohol **261** (60 mg, 0.12 mmol, 1.0 equiv) and THF (1.2 mL). The reaction was cooled to 0 °C. Mesyl chloride (MsCl, 11 μL, 0.14 mmol, 1.1 equiv) was added into the reaction solution, followed by Et_3N (35 μL, 0.25 mmol, 2.0 equiv). After 1.5 hours, the reaction was filtered through a plug of Kimwipes and washed with THF. The filtrate was concentrated down and co-evaporated with benzene. The crude material was re-dissolved in THF (1 mL), and LiOH (52.5 mg, 1.24 mmol, 10 equiv) in THF (0.2 mL) was transferred into the reaction flask. The resulting white slurry was allowed to stir at room temperature for 1.5 hours before it was quenched with saturated $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated down to give a yellow liquid. Flash chromatography (10% to 50% EtOAc in hexanes) afforded allylic chloride **276** as a light yellow foam (55 mg, 0.11 mmol, 89% yield). $[\alpha]_D^{25}$ = +68° (*c* = 1.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 7.12 – 7.06 (m, 2H), 7.05 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.72 (td, *J* = 7.4, 1.0 Hz, 1H), 6.60 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.36 (t, *J* = 6.8 Hz, 1H), 5.35 (s, 1H), 5.31 (s, 1H), 5.23 (br s, 1H), 4.45 (ddd, *J* = 9.7, 8.1, 1.8 Hz, 1H), 4.16 (ddd, *J* = 10.6, 6.5, 1.8 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.01 (s, 3H), 2.69 (dd, *J* = 12.8, 6.5 Hz, 1H), 2.45 (d, *J* = 7.5 Hz, 2H), 2.42 – 2.35 (m, 2H), 2.27 (dd, *J* = 12.8, 10.6 Hz, 1H), 1.63 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 167.1, 165.9, 150.5, 147.0, 135.3, 133.3, 130.9, 129.0, 128.5, 124.7, 122.9, 122.4, 119.3, 118.1, 109.4, 106.2, 85.0, 83.7, 60.3, 59.2, 54.2, 51.8, 51.3, 40.9, 40.0, 36.6, 33.5, 23.4, 14.5; FTIR (NaCl, thin film): 3345, 3051, 3006, 2954, 2928, 2871, 1667, 1607, 1486, 1468, 1414, 1341, 1302, 1262, 1199, 1157, 1110, 1100, 1083, 1062, 1019, 1001, 977, 932, 746 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{32}ClN_4O_2$ $[M+H]^+$ 503.2208, found 503.2221.

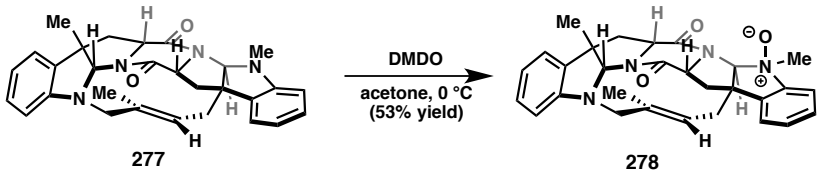
Preparation of macrocyclic alkene 277



To a 25 mL flame-dried Schlenk flask with a screw cap was added allylic chloride **276** (20 mg, 0.04 mmol, 1.0 equiv), tetra-*n*-butylammonium iodide (TBAI, 294 mg, 0.80 mmol, 20.0 equiv), and acetonitrile (4 mL). DIPEA (8.3 μL, 0.048 mmol, 1.2 equiv) was added at last from freshly prepared DIPEA stock solution. The Schlenk flask was sealed and heated to 80 °C for 24 hours. It was then cooled to room temperature and quenched with saturated $NaHCO_3$ aqueous solution (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated down to give a yellow liquid. Flash chromatography (5% to 50% EtOAc in hexanes) afforded macrocyclic alkene **277** as a white solid (13.5 mg, 0.029 mmol, 73% yield). $[\alpha]_D^{25}$ = +45° (*c* = 0.47, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN) δ 7.16 – 7.09 (m, 3H), 7.07 (td, *J* = 7.7, 1.4 Hz, 1H), 6.72 (td, *J* = 7.5, 1.0 Hz, 1H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.51 (s, 1H), 5.48 (s, 1H), 5.28 (br s, 1H), 4.57 (t, *J* = 8.8 Hz, 1H), 4.37 (d, *J* = 10.7

Hz, 1H), 4.02 (d, *J* = 16.1 Hz, 1H), 3.47 (d, *J* = 16.1 Hz, 1H), 2.89 (br s, 1H), 2.83 (s, 3H), 2.42 – 2.22 (m, 3H), 1.55 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) 149.3, 128.6, 128.6, 121.7, 121.4, 118.5, 110.0, 107.7, 91.9, 61.9, 59.2, 53.0, 34.0 (Presumably, at room temperature, the alkene in macrocyclic olefin **277** quickly underwent rotation, resulting in ^{1}H NMR signals broadening and not all carbon signals showing up); ^{1}H NMR (500 MHz, CD_3CN, 70 °C) δ 7.17 – 7.10 (m, 3H), 7.09 (td, *J* = 7.8, 1.4 Hz, 1H), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H), 6.67 (td, *J* = 7.4, 1.0 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.51 (s, 1H), 5.49 (s, 1H), 5.30 (t, *J* = 8.4 Hz, 1H), 4.58 (t, *J* = 8.7 Hz, 1H), 4.38 (dd, *J* = 11.2, 2.3 Hz, 1H), 4.03 (d, *J* = 16.3 Hz, 1H), 3.52 (d, *J* = 16.3 Hz, 1H), 2.92 (d, *J* = 13.9 Hz, 1H), 2.90 – 2.82 (m, 1H), 2.86 (s, 3H), 2.41 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.34 (d, *J* = 8.8 Hz, 1H), 2.30 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.19 (dd, *J* = 13.7, 11.3 Hz, 1H), 1.60 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, CD_3CN, 70 °C) δ 171.8, 170.5, 151.0, 149.5, 138.3, 136.1, 135.5, 129.7, 123.0, 122.9, 122.8, 122.7, 119.5, 118.7, 108.6, 108.6, 106.6, 106.5, 92.9, 92.9, 90.3, 63.2, 60.3, 60.3, 56.4, 54.3, 52.3, 41.9, 39.5, 34.7, 34.5, 34.4, 21.7, 15.2; FTIR (NaCl, thin film): 3051, 3008, 2954, 2923, 2870, 2856, 1670, 1609, 1485, 1465, 1450, 1429, 1391, 1348, 1304, 1259, 1216, 1186, 1156, 1142, 1122, 1096, 1065, 1023, 1001, 978, 921, 881, 789, 742 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_2$ $[M+H]^+$ 467.2442, found 467.2450.

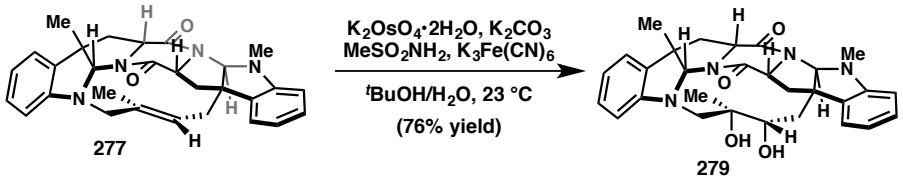
Preparation of *N*-oxide 278



277 278

To a 0.5-dram vial was transferred macrocyclic olefin **277** (2.2 mg, 0.0047 mmol, 1.0 equiv), which was dissolved in acetone (0.35 mL). The reaction was cooled to 0 °C. Freshly prepared DMDO acetone solution (0.050 M, 104 μL, 0.0052 mmol, 1.1 equiv) was added. The reaction was allowed to stir for 15 minutes before being concentrated down to give a light yellow solid. Preparative thin layer chromatography (10% MeOH in DCM) afforded *N*-oxide **278** as a white solid (1.2 mg, 0.0025 mmol, 53% yield); starting material **277** was also isolated (0.8 mg). $[\alpha]_D^{25}$ = +78° (*c* = 0.12, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.54 – 7.49 (m, 1H), 7.49 – 7.42 (m, 2H), 7.42 – 7.34 (m, 1H), 7.09 (app ddd, *J* = 7.3, 4.4, 3.0 Hz, 2H), 6.69 (t, *J* = 7.4 Hz, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 5.75 (s, 1H), 5.56 (s, 1H), 4.99 – 4.82 (m, 1H), 4.68 (t, *J* = 8.8 Hz, 1H), 4.00 (d, *J* = 16.5 Hz, 1H), 3.62 (s, 3H), 3.58 (d, *J* = 16.5 Hz, 1H), 2.89 (br s, 1H), 2.72 (t, *J* = 11.9 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.37 (t, *J* = 11.4 Hz, 1H), 2.28 (br s, 1H), 1.86 (br s, 4H), 1.52 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 70.2, 138.0, 130.5, 130.0, 129.0, 124.4, 122.1, 117.6, 99.1, 66.5, 59.6, 56.4, 52.5, 51.6, 41.1 (Presumably, at room temperature, the alkene in macrocyclic olefin **278** quickly underwent rotation, resulting in ^{1}H NMR signals broadening and not all carbon signals showing up); FTIR (NaCl, thin film): 3047, 2955, 2907, 1681, 1607, 1482, 1449, 1432, 1388, 1305, 1270, 1225, 1201, 1156, 1142, 1119, 1094, 1064, 1050, 1022, 1004, 962, 932, 917, 884, 832, 816, 805, 780, 741 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2388.

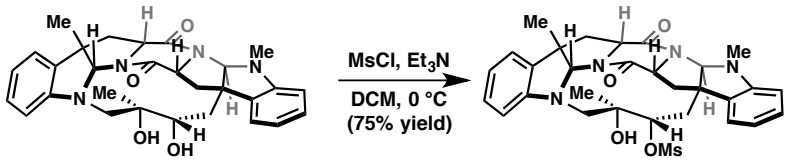
Preparation of diol 279



To a 0.5-dram vial was added $K_3Fe(CN)_6$ (10.4 mg, 0.032 mmol, 3.0 equiv), K_2CO_3 (4.5 mg, 0.033 mmol, 3.1 equiv) and $K_2OsO_4 \bullet 2H_2O$ (1.2 mg, 0.003 mmol, 30 mol %), followed by addition of distilled water (240 μL) and methanesulfonamide (3.0 mg, 0.032mmol, 3.0 equiv). 1,4-Diazabicyclooctane (DABCO, 0.6 mg, 0.005 mmol, 0.5 equiv) was added as a *t*-butanol solution (10 μL). At last, macrocyclic alkene **277** (4.8 mg, 0.010 mmol, 1.0 equiv) was added as *tert*-butanol solution (240 μL; additional heat was required to increase the solubility of **277** in *tert*-butanol; there is a small time window where **277** is completely soluble in *tert*-butanol after it cools down to room temperature, which marks the time to add it to the reaction flask). The reaction turned into a brown homogeneous solution, which was stirred for 12 hours. It was then quenched with solid Na_2SO_3, followed by addition of 2N KOH (0.5 mL). It was stirred for another two hours before it was diluted with EtOAc (2 mL). The mixture was separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). Combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (5% to 50% EtOAc in hexanes) afforded diol **279** as a white solid (3.9 mg, 0.008 mmol, 76% yield). $[\alpha]_D^{25}$ = +36° (*c* = 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (tt, *J* = 7.7, 1.5 Hz, 2H), 7.08 (ddd, *J* = 7.4, 2.4, 1.2 Hz, 2H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.82 (td, *J* = 7.4, 0.9 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.77 (s, 1H), 5.65 (s, 1H), 4.60 (dd, *J* = 10.0, 8.1 Hz, 1H), 4.47 (d, *J* = 8.7 Hz, 1H), 3.52 (d, *J* = 15.4 Hz, 1H), 3.31 (d, *J* = 15.4 Hz, 1H), 3.25 (d, *J* = 10.5 Hz, 1H), 2.96 (d, *J* = 12.6 Hz, 1H), 2.92 (s, 3H), 2.75 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.49 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.48 (s, 1H), 2.27 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.17 (dd, *J* = 15.5, 10.5 Hz, 1H), 1.99 (d, *J* = 15.6 Hz, 1H), 1.86 (s, 1H), 1.49 (s, 3H), 1.09 (s, 3H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 171.9, 170.8, 149.3, 148.8, 134.5, 133.3, 128.6, 128.3, 121.5, 119.6, 119.0, 108.7, 108.2, 91.4, 89.4, 76.7, 69.5, 62.3, 60.2, 56.3, 50.6, 50.4, 42.7, 38.6, 35.5, 34.1, 20.7, 18.3; FTIR (NaCl, thin film): 3518, 3447, 3049, 3010, 2953, 2937, 2894, 2794, 1670, 1610, 1481, 1448, 1425, 1391, 1349, 1312, 1299, 1274, 1209, 1194, 1167, 1123, 1091, 1064, 1039, 1021, 1001, 975, 940, 909, 893, 862, 832, 804, 789, 780, 752, 746, 718 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_4$ $[M+H]^+$ 501.2496, found 501.2508.

Preparation of mono-mesylate A-5

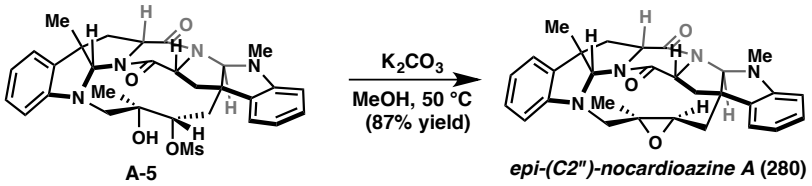


279 **A-5**

To a flame-dried 0.5-dram vial was added diol **279** (6.9 mg, 0.014 mmol, 1.0 equiv) and THF (0.2 mL). The reaction flask was cooled to 0 °C. Mesyl chloride (MsCl, 5.5 μL, 0.069 mmol, 5.0 equiv) was added into the reaction solution, followed by Et_3N (11.5 μL, 0.083 mmol, 6.0 equiv). After 40 minutes, the reaction was quenched with saturated $NaHCO_3$ (4 mL). The mixture was extracted with EtOAc (3 x 4 mL). Combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated down to give a yellow liquid. Preparative TLC chromatography (60% EtOAc in hexanes) afforded mono-mesylate **A-5** as a white solid (5.8 mg, 0.10 mmol, 75% yield). $[\alpha]_D^{25}$ = +67° (*c* = 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (td, *J* = 7.7, 1.2 Hz, 1H), 7.14 (td, *J* = 7.9, 1.3 Hz, 1H), 7.07 (ddd, *J* = 8.8, 7.4, 1.3 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.85 (td, *J* = 7.4, 1.0 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 5.83 (s, 1H), 5.62 (s, 1H), 4.61 (dd, *J* = 10.2, 8.0 Hz, 1H), 4.58 (d, *J* = 10.7 Hz, 1H), 4.46 (d, *J* = 8.5 Hz, 1H), 3.52 (d, *J* = 15.5 Hz, 1H), 3.33 (d, *J* = 15.5 Hz,

1H), 2.96 (s, 3H), 2.94 (d, *J* = 12.7 Hz, 1H), 2.83 (dd, *J* = 13.4, 10.2 Hz, 1H), 2.74 (s, 3H), 2.53 (dd, *J* = 12.7, 8.6 Hz, 1H), 2.49 (dd, *J* = 16.8, 10.8 Hz, 1H), 2.40 (s, 1H), 2.30 (dd, *J* = 13.4, 7.9 Hz, 1H), 2.13 (d, *J* = 16.8 Hz, 1H), 1.48 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.7, 149.5, 149.2, 133.3, 132.7, 128.7, 128.6, 121.5, 121.3, 120.0, 118.8, 109.8, 108.4, 90.7, 89.7, 83.5, 76.6, 62.1, 60.5, 57.9, 50.5, 50.3, 42.8, 38.9, 38.6, 34.1, 33.1, 20.6, 18.8; FTIR (NaCl, thin film): 3541, 3390, 3024, 2954, 2925, 2855, 2798, 1694, 1674, 1610, 1482, 1447, 1427, 1379, 1347, 1337, 1301, 1273, 1198, 1171, 1124, 1091, 1062, 1028, 1000, 974, 957, 944, 933, 916, 895, 851, 835, 806, 781, 752 cm^{-1}; HRMS (MM) calc'd for $C_{30}H_{35}N_4O_6S$ $[M+H]^+$ 579.2272, found 579.2278.

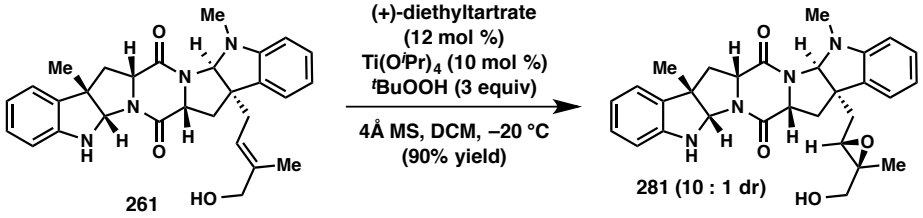
Preparation of *epi*-(C2")-nocardioazine A (280)



To a flame-dried 1-dram vial was added mono-mesylate **A-5** (4.0 mg, 0.007 mmol, 1.0 equiv) and K_2CO_3 (12.6 mg, 0.091 mmol, 13.0 equiv). Methanol (0.9 mL) was added at last. The vial was sealed using a Teflon cap and heated to 50 °C for 90 minutes. The reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ (4 mL). The mixture was extracted with EtOAc (3 x 4 mL). Combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated down to give a white liquid. Flash chromatography (10% to 50% EtOAc in hexanes) afforded *epi*-(C2")-nocardioazine A (**280**) as a white solid, which was contaminated with an unknown side product as a 10 : 1 mixture detected by ^{1}H NMR, (corrected yield: 2.9 mg, 0.0060 mmol, 87% yield). $[\alpha]_D^{25}$ = +36° (*c* = 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (td, *J* =

7.7, 1.3 Hz, 1H), 7.10 (td, *J* = 7.7, 1.2 Hz, 1H), 7.11 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 6.66 (td, *J* = 7.4, 0.9 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 5.75 (s, 1H), 5.73 (s, 1H), 4.51 (dd, *J* = 10.6, 7.6 Hz, 1H), 4.40 (d, *J* = 8.6 Hz, 1H), 3.59 (d, *J* = 15.6 Hz, 1H), 3.37 (d, *J* = 15.7 Hz, 1H), 2.95 (s, 3H), 2.91 (d, *J* = 12.6 Hz, 1H), 2.83 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.77 (dd, *J* = 13.2, 10.7 Hz, 1H), 2.66 (dd, *J* = 16.0, 3.7 Hz, 1H), 2.45 (dd, *J* = 12.7, 8.7 Hz, 1H), 2.25 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.00 (dd, *J* = 16.0, 11.6 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 171.4, 149.7, 147.1, 132.9, 132.1, 128.8, 128.3, 121.7, 121.5, 118.3, 116.9, 108.0, 105.7, 92.9, 86.8, 64.2, 62.2, 61.7, 60.0, 52.0, 50.7, 45.0, 42.1, 39.5, 33.9, 30.3, 26.1, 19.5; FTIR (NaCl, thin film): 3051, 3009, 2956, 2927, 2893, 2869, 2821, 2791, 1692, 1671, 1610, 1484, 1467, 1452, 1440, 1425, 1382, 1353, 1301, 1282, 1266, 1235, 1214, 1197, 1172, 1158, 1144, 1123, 1115, 1093, 1073, 1055, 1048, 1035, 1020, 991, 973, 958, 945, 924, 892, 881, 859, 847, 830, 801, 792, 780, 751, 742 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2387.

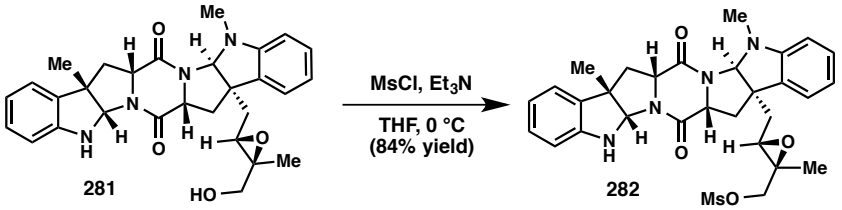
Preparation of epoxide 281



To a flame-dried 10 mL flask was added $Ti(O^iPr)_4$ (3.7 μL, 0.012 mmol, 10 mol %), activated 4Å molecular sieves and DCM (2 mL). The reaction flask was cooled to –20 °C (crushed ice mixed with NaCl at about 3 : 1 ratio). (+)-Diethyl-tartrate (2.5 μL, 0.015 mmol, 12 mol %) was added. After stirring for 5 minutes, allylic alcohol **261** (60 mg, 0.124 mmol, 1.0 equiv) was added as a DCM solution (0.5 mL). After 30 minutes,

^{t}BuOOH (5.0-6.0 M decane solution, 68 μL, 0.371 mmol, 3.0 equiv) was added. In 105 minutes, the flask was warmed to 0 °C using an ice water bath. The reaction was quenched with freshly prepared and ice-cold $FeSO_4$/citric acid solution (0.66 g $FeSO_4$, 0.22 g citric acid monohydrate, 2 mL distilled water). The mixture was extracted with Et_2O (5 x 5 mL). Combined organic layers were cooled to 0 °C and then treated with precooled 30% NaOH (w/v) in saturated NaCl solution (prepared using 10 g NaOH, 1.7 g NaCl, 30 ml distilled water). The mixture was stirred vigorously for 1 hour. Then two layers were separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated down to give a colorless oil. Flash chromatography (20% to 95% EtOAc in hexanes) afforded epoxy alcohol **281** (10 : 1 mixture of epoxide diastereomers by ^{1}H NMR), as a white foam (56.5 mg, 0.113 mmol, 90% yield). $[\alpha]_D^{25}$ = +74° (*c* = 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.6, 1.2 Hz, 1H), 7.07 (app dd, *J* = 8.0, 6.9 Hz, 3H), 6.79 – 6.74 (m, 1H), 6.72 (td, *J* = 7.5, 1.0 Hz, 1H), 6.57 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.34 (s, 1H), 5.28 (s, 1H), 4.44 (ddd, *J* = 9.9, 8.1, 1.9 Hz, 1H), 4.14 (ddd, *J* = 10.8, 6.3, 1.9 Hz, 1H), 3.41 (d, *J* = 12.2 Hz, 1H), 3.30 (d, *J* = 12.3 Hz, 1H), 3.04 (s, 3H), 2.83 – 2.71 (m, 2H), 2.42 – 2.34 (m, 2H), 2.31 (dd, *J* = 12.8, 10.9 Hz, 1H), 2.11 (dd, *J* = 14.4, 4.9 Hz, 1H), 1.87 (dd, *J* = 14.4, 7.0 Hz, 1H), 1.46 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 165.7, 150.8, 147.0, 133.3, 130.2, 129.3, 128.4, 122.8, 122.3, 119.2, 118.1, 109.4, 106.2, 84.5, 83.7, 65.3, 60.2, 59.8, 59.2, 56.6, 53.1, 51.2, 41.0, 40.9, 37.1, 33.5, 23.3, 14.3; FTIR (NaCl, thin film): 3354, 3052, 3006, 2956, 2928, 2870, 1668, 1608, 1486, 1471, 1418, 1339, 1302, 1253, 1197, 1161, 1092, 1036, 1001, 978, 894, 748 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_4$ $[M+H]^+$ 501.2496, found 501.2500.

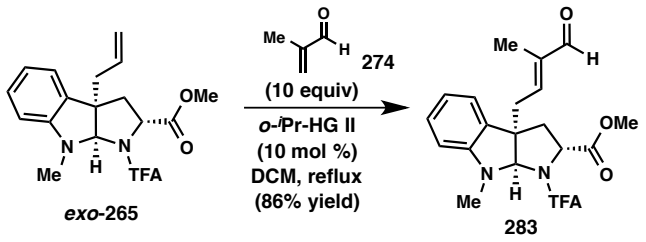
Preparation of mesylate 282



To a half-a-dram vial was added alcohol **281** (7 mg, 0.014 mmol, 1.0 equiv), which was co-evaporated with benzene (0.4 mL) and dried in vacuo. Under N_2, alcohol **281** was dissolved in THF (0.1 mL) and cooled to 0 °C, when MsCl (1.2 μL, 0.015 mmol, 1.1 equiv) and Et_3N (3.9 μL, 0.028 mmol, 2.0 equiv) were added in sequence as a freshly prepared THF stock solution. The reaction mixture was allowed to stir at 0 °C for 40 minutes before filtering through a Kimwipe plug and concentrating down to give a colorless oil. Flash chromatography (5% to 70% EtOAc in hexanes) afforded epoxy mesylate **282**, as a colorless oil (6.8 mg, 0.012 mmol, 84% yield). $[\alpha]_D^{25}$ = +74° (*c* = 0.735, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12 – 7.04 (m, 3H), 6.78 (td, *J* = 7.6, 1.1 Hz, 1H), 6.75 (td, *J* = 7.4, 0.9 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.35 (s, 1H), 4.46 (td, *J* = 8.9, 1.8 Hz, 1H), 4.16 (ddd, *J* = 10.2, 5.9, 1.5 Hz, 1H), 4.02 (d, *J* = 11.5 Hz, 1H), 3.84 (d, *J* = 11.5 Hz, 1H), 3.04 (s, 3H), 2.95 (s, 3H), 2.78 (dd, *J* = 12.7, 6.2 Hz, 1H), 2.65 (dd, *J* = 7.2, 4.7 Hz, 1H), 2.38 (d, *J* = 8.9 Hz, 2H), 2.28 (dd, *J* = 12.8, 11.0 Hz, 1H), 2.16 (dd, *J* = 14.4, 4.8 Hz, 1H), 1.86 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 165.8, 150.9, 147.0, 133.3, 129.7, 129.5, 128.5, 122.8, 122.4, 119.3, 118.2, 109.3, 106.3, 84.2, 83.7, 73.3, 59.8, 59.2, 57.6, 57.5, 53.0, 51.3, 41.3, 41.0, 37.7, 36.9, 33.4, 23.3, 14.1; FTIR (NaCl, thin film): 3364, 3011, 2958, 2932, 1668, 1608, 1486, 1471, 1445, 1418,

1354, 1300, 1253, 1197, 1175, 1092, 1018, 978, 961, 896, 817, 750, 667, 644 cm^{-1}; HRMS (MM) calc'd for $C_{30}H_{35}N_4O_6S$ $[M+H]^+$ 579.2272, found 579.2287.

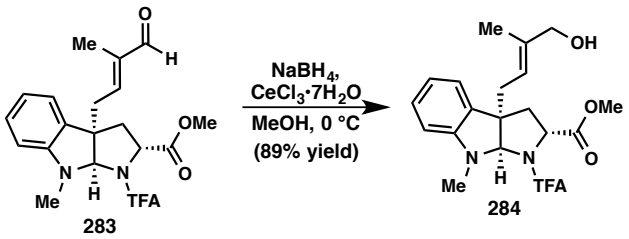
Preparation of aldehyde 283



To a 50 mL flame-dried flask was added 3-allyl pyrroloindoline **265** (1.0 g, 2.7 mmol, 1.0 equiv) and DCM (20 mL), followed by methacrolein (95%, 2.36 mL, 27.1 mmol, 10 equiv). *ortho*-^{i}Pr-Hoveyda-Grubbs II catalyst (170 mg, 0.27 mmol, 10 mol %) was added as a DCM solution (4 mL) at last. The flask was equipped with a condenser and heated to 40 °C for 3 days. The reaction was then quenched with ethyl vinyl ether (1.5 mL) and filtered through a silica gel plug, eluting with EtOAc. The filtrate was concentrated down to give a brown oil. Flash chromatography (5% to 35% EtOAc in hexanes) afforded aldehyde **283** as a light brown thick oil (951 mg, 2.32 mmol, 86% yield). $[\alpha]_D^{25}$ = +106° (*c* = 1.27, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 9.26 (s, 1H§), 9.20 (s, 1H*), 7.14 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.03 (d, *J* = 7.4 Hz, 1H*, 1H§), 6.79 (s, 1H§), 6.73 (t, *J* = 7.4 Hz, 1H*), 6.60 – 6.51 (m, 1H§), 6.48 (d, *J* = 8.0 Hz, 1H*), 6.33 – 6.17 (m, 1H§), 6.13 (t, *J* = 7.0 Hz, 1H*), 5.55 (s, 1H*), 5.38 (s, 1H§), 4.66 (d, *J* = 7.5 Hz, 1H*), 4.38 (s, 1H§), 3.77 (s, 3H*), 3.71 (s, 3H§), 3.01 (s, 3H*), 2.83 (s, 3H§), 2.74 (d, *J* = 7.7 Hz, 2H*, 2H§), 2.69 (d, *J* = 10.2 Hz, 1H*), 2.57 (s, 1H§), 2.44 (d, *J* = 13.0 Hz, 1H*), 2.18 (s, 1H§), 1.66 (s, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ

194.3*§, 172.4*, 170.2§, 158.6* (q, *J* = 37.3 Hz), 157.1§ (q, *J* = 39.4 Hz), 149.7*, 149.5§, 147.4*, 147.2§, 141.5*§, 130.9*, 130.5§, 129.3§, 129.1*, 121.7*§, 119.9§, 118.9*, 115.7* (q, *J* = 288.7 Hz), 109.5§, 108.1*, 90.1*, 88.9§, 60.5§, 59.4*, 56.8§, 53.1*, 52.9*, 52.3§, 42.4*, 39.1§, 36.2*, 35.5*, 34.6§, 34.2§, 9.2*§; FTIR (NaCl, thin film): 3421, 3052, 3026, 2955, 2827, 2717, 1751, 1688, 1609, 1490, 1437, 1358, 1302, 1204, 1155, 1061, 1021, 985, 932, 873, 850, 794, 754 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{22}F_3N_2O_4$ $[M+H]^+$ 411.1526, found 411.1531.

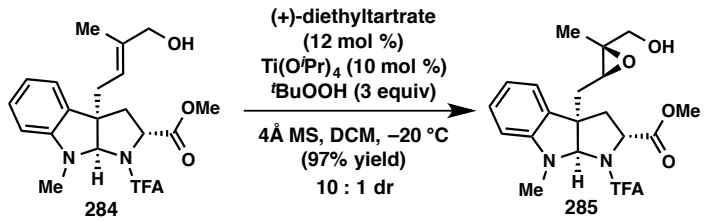
Preparation of allylic alcohol 284



To a 100 mL flask was added aldehyde **283** (636 mg, 1.55 mmol, 1.0 equiv) and methanol (31 mL). Then, cerium chloride heptahydrate (693 mg, 1.86 mmol, 1.2 equiv) was dissolved in methanol (2.5 mL), while $NaBH_4$ (59 mg, 1.55 mmol, 1.0 equiv) was mixed with methanol (1.2 mL). The reaction was cooled to 0 °C. The pre-generated methanol solution of cerium chloride was added into the reaction flask, quickly followed by the slow addition of $NaBH_4$ methanol solution. After reacting at 0 °C for 15 minutes, the reaction was quenched with saturated ammonium chloride solution (70 mL), followed by EtOAc (50 mL). The mixture was separated and aqueous layer was extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with brine (120 mL), dried over Na_2SO_4, filtered, and concentrated down to give a grey oil. Flash chromatography (5% to 60% EtOAc in hexanes) afforded allylic alcohol **284** as a light brown thick oil

(567 mg, 1.37 mmol, 89% yield). $[\alpha]_D^{25}$ = +88° (*c* = 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.6:1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.01 (d, *J* = 7.5 Hz, 1H*, 1H§), 6.80 – 6.76 (m, 1H§), 6.71 (t, *J* = 7.4 Hz, 1H*), 6.53 (d, *J* = 7.9 Hz, 1H§), 6.46 (d, *J* = 7.9 Hz, 1H*), 5.52 (s, 1H*), 5.37 (s, 1H§), 5.25 (t, *J* = 7.2 Hz, 1H§), 5.13 (t, *J* = 7.4 Hz, 1H*), 4.63 (d, *J* = 7.5 Hz, 1H*), 4.30 (t, *J* = 8.0 Hz, 1H§), 3.85 (s, 2H§), 3.83 (s, 2H*), 3.77 (s, 3H*), 3.69 (s, 3H§), 3.02 (s, 3H*), 2.85 (s, 3H§), 2.61 (dd, *J* = 13.6, 9.3 Hz, 2H*, 2H§), 2.53 – 2.44 (m, 1H*), 2.41 (d, *J* = 3.9 Hz, 2H§), 2.39 (d, *J* = 6.8 Hz, 2H*), 2.17 – 2.09 (m, 1H§), 1.55 (s, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5*, 170.6§, 158.7* (q, $J_{C\text{-}F}$ = 37.0 Hz), 157.4§ (q, $J_{C\text{-}F}$ = 38.1 Hz), 149.9§, 149.8*, 138.6*§, 132.3*, 132.1§, 128.8§, 128.6*, 121.9§, 121.8*, 119.9§, 119.1*, 118.6*§, 115.8* (q, $J_{C\text{-}F}$ = 288.5 Hz), 115.7§ (app d, $J_{C\text{-}F}$ = 286.6 Hz), 109.8§, 108.0*, 90.2*, 89.0§, 67.6*§, 60.5§, 59.4*, 57.6§, 53.5*, 52.8*, 52.3§, 41.9*, 38.4§, 36.4*, 35.3§, 34.3*, 34.1§, 13.6*§; FTIR (NaCl, thin film): 3421, 3052, 2954, 2921, 2875, 1749, 1690, 1608, 1490, 1437, 1356, 1301, 1203, 1155, 1062, 1021, 994, 931, 852, 794, 746, 727 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{24}F_3N_2O_4$ $[M+H]^+$ 413.1683, found 413.1690.

Preparation of epoxy alcohol 285

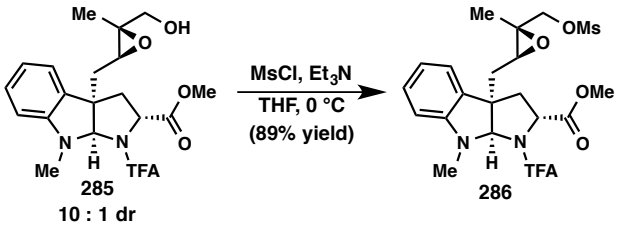


To a flame-dried 50 mL flask was added $Ti(O^iPr)_4$ (31 μL, 0.105 mmol, 10 mol %), activated 4Å molecular sieves, and DCM (18 mL). The reaction flask was cooled to –

20 °C (crushed ice mixed with NaCl at about 3 : 1 ratio). (+)-Diethyl-tartrate (21.5 μL, 0.126 mmol, 12 mol %) was added. After stirring for 5 minutes, allylic alcohol **284** (432 mg, 1.05 mmol, 1.0 equiv) was added as a DCM solution (2 mL). After 30 minutes, ^{t}BuOOH (5.0-6.0 M decane solution, 0.57 mL, 3.14 mmol, 3.0 equiv) was added. In 90 minutes, the flask was warmed to 0 °C using an ice water bath. The reaction was quenched with freshly prepared $FeSO_4$/citric acid solution (4 g $FeSO_4$, 0.66 g citric acid monohydrate, 12 mL distilled water). The mixture was extracted with Et_2O (4 x 20 mL). Combined organic layers were cooled to 0 °C and then treated with precooled 30% NaOH (w/v) in saturated NaCl solution (prepared using 30 g NaOH, 5 g NaCl, 90 ml distilled water). The mixture was stirred vigorously for 1 hour. Then two layers were separated and the aqueous layer was extracted with Et_2O (2 x 80 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated down to give a colorless oil. Flash chromatography (10% to 70% EtOAc in hexanes) afforded epoxy alcohol **285** (10 : 1 mixture of epoxide diastereomers by ^{1}H NMR), as a white foam (434 mg, 1.01 mmol, 97% yield). $[\alpha]_D^{25}$ = +104° (*c* = 0.87, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.7 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.17 (td, *J* = 7.7, 1.2 Hz, 1H*, 1H§), 7.03 (d, *J* = 7.3 Hz, 1H*, 1H§), 6.80 (d, *J* = 8.4 Hz, 1H§), 6.77 (d, *J* = 7.2 Hz, 1H*), 6.56 (d, *J* = 8.4 Hz, 1H§), 6.52 (d, *J* = 8.7 Hz, 1H*), 5.89 (s, 1H*), 5.82 (s, 1H§), 4.70 – 4.53 (m, 1H*), 4.33 (t, *J* = 8.1 Hz, 1H§), 3.77 (s, 3H*), 3.73 (s, 3H§), 3.55 – 3.43 (m, 1H*, 1H§), 3.42 – 3.26 (m, 1H*, 1H§), 3.12 (s, 3H*), 2.91 (s, 3H§), 2.85 – 2.78 (m, 1H§), 2.78 – 2.65 (m, 2H*), 2.61 – 2.50 (m, 1H§), 2.41 (dd, *J* = 13.4, 4.7 Hz, 1H§), 2.22 (d, *J* = 14.7 Hz, 1H§), 2.12 (d, *J* = 12.5 Hz, 1H*), 2.02 – 1.86 (m, 2H*), 1.78 (dd, *J* = 15.4, 8.6 Hz, 1H§), 1.23 (s, 3H§), 1.15 (s, 3H*); ^{13}C

NMR (126 MHz, $CDCl_3$) δ 172.4*, 170.6§, 158.6* (q, $J_{C\text{-}F}$ = 37.1 Hz), 157.6§ (q, $J_{C\text{-}F}$ = 37.9 Hz), 150.2*§, 131.4*, 130.7§, 129.2*§, 122.0*§, 119.9§, 188.8*, 115.9* (q, $J_{C\text{-}F}$ = 288.3 Hz), 109.5§, 108.3*, 90.1*, 88.8§, 65.0*§, 60.9§, 60.23*, 60.15*, 59.1*, 56.4*, 56.3§, 52.9*§, 52.6*§, 42.9*, 40.4§, 36.8*, 35.7*, 34.9§, 34.8§, 14.3*§; FTIR (NaCl, thin film): 3462, 3004, 2955, 1751, 1691, 1609, 1490, 1437, 1358, 1302, 1203, 1159, 1103, 1063, 1034, 985, 928, 848, 754 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{24}F_3N_2O_5$ $[M+H]^+$ 429.1632, found 429.1643.

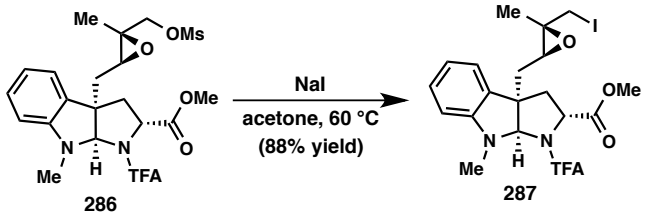
Preparation of epoxy mesylate 286



To a flame-dried 25 mL flask was added epoxy alcohol **285** (284 mg, 0.66 mmol, 1.0 equiv) and DCM (6.6 mL). The reaction flask was cooled to 0 °C. Methanesulfonyl chloride (MsCl, 57 μL, 0.73 mmol, 1.1 equiv) was added, followed by Et_3N (185 μL, 1.33 mmol, 2.0 equiv). After stirring for 1 hour, the reaction was quenched with saturated $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (4 x 15 mL). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated down to give a colorless oil. Flash chromatography (5% to 60% EtOAc in hexanes) afforded epoxy mesylate **286** as a white foam (296 mg, 0.58 mmol, 89% yield; resulting epoxy mesylate diastereomers from previous step were readily separated at this stage). $[\alpha]_D^{25}$ = +89° (*c* = 0.85, $CHCl_3$); ^1H (500 MHz, $CDCl_3$; compound exists as a 1.7 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted

by [§]) δ 7.17 (t, *J* = 7.8 Hz, 1H*, 1H[§]), 7.04 (d, *J* = 7.3 Hz, 1H*, 1H[§]), 6.87 – 6.71 (m, 1H*, 1H[§]), 6.65 – 6.47 (m, 1H*, 1H[§]), 5.87 (s, 1H*), 5.79 (s, 1H[§]), 4.60 (s, 1H*), 4.33 (s, 1H[§]), 4.08 (d, *J* = 14.0 Hz, 1H[§]), 4.04 (d, *J* = 11.1 Hz, 1H*), 3.89 (s, 1H[§]), 3.85 (d, *J* = 10.6 Hz, 1H*), 3.76 (s, 3H*), 3.73 (s, 3H[§]), 3.10 (s, 3H*), 2.94 (s, 3H*, 3H[§]), 2.88 (s, 3H[§]), 2.72 (dt, *J* = 18.8, 9.4 Hz, 1H*, 1H[§]), 2.68 – 2.60 (m, 1H*), 2.55 (dd, *J* = 13.2, 8.1 Hz, 1H[§]), 2.39 (dd, *J* = 13.4, 4.6 Hz, 1H*), 2.28 (d, *J* = 14.6 Hz, 1H[§]), 2.16 (d, *J* = 14.7 Hz, 1H*), 2.13 – 2.06 (m, 1H[§]), 1.95 (t, *J* = 11.7 Hz, 1H[§]), 1.76 (dt, *J* = 15.0, 5.7 Hz, 1H*), 1.34 (s, 3H[§]), 1.25 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4*, 170.4[§], 158.5* (q, $J_{C\text{-}F}$ = 37.3 Hz), 157.4[§] (q, $J_{C\text{-}F}$ = 36.8 Hz), 150.1*[§], 130.9*, 130.1[§], 129.3*[§], 121.9*[§], 119.7[§], 118.8*, 115.8[§] (q, $J_{C\text{-}F}$ = 288.7 Hz), 109.3[§], 108.2*, 90.0*, 88.6[§], 73.2[§], 73.1*, 60.2[§], 59.0*, 57.4*[§], 57.4*, 56.2[§], 52.9*[§], 52.4*[§], 42.9*, 40.3[§], 37.4*[§], 36.7*, 35.3*, 34.5[§], 34.1[§], 14.0*[§]; FTIR (NaCl, thin film): 3028, 2956, 1747, 1693, 1608, 1489, 1439, 1360, 1303, 1203, 1175, 1160, 1106, 1063, 1022, 982, 962, 897, 846, 817, 755 cm^{-1}; HRMS (MM) calc'd for $C_{21}H_{26}F_3N_2O_7S$ $[M+H]^+$ 507.1407, found 507.1411.

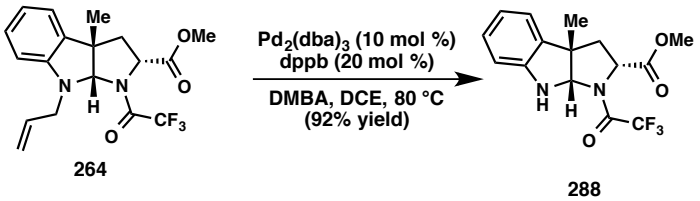
Preparation of epoxy iodide 287



To a 10 mL flame-dried flask equipped with a condenser was added epoxy mesylate **286** (146 mg, 0.288 mmol, 1.0 equiv) and sodium iodide (432 mg, 2.88 mmol, 10.0 equiv). Acetone (2.8 mL) was then added and the reaction was heated to 60 °C, resulting in a yellow clear solution gradually turning blurry. After 90 minutes, the reaction was cooled to room temperature and the mixture was quenched with saturated

NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). Combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL). It was dried over Na_2SO_4, filtered and concentrated down to give an oil. Flash chromatography (1% to 25% EtOAc in hexanes) afforded epoxy iodide **287**, as white foam (136 mg, 0.253 mmol, 88% yield). $[\alpha]_D^{25}$ = +110° (*c* = 0.545, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.7 : 1 mixture of rotamers the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.20 (t, *J* = 7.7 Hz, 1H*, 1H§), 7.06 (d, *J* = 7.2 Hz, 1H*, 1H§), 6.88 – 6.76 (m, 1H*, 1H§), 6.61 – 6.49 (m, 1H*, 1H§), 5.88 (s, 1H*), 5.78 (s, 1H§), 4.62 (s, 1H*), 4.35 (s, 1H§), 3.79 (s, 3H*), 3.76 (s, 3H§), 3.14 (s, 3H*), 3.10 – 3.03 (m, 3H§), 2.93 (d, *J* = 10.7 Hz, 2H*, 2H§), 2.79 – 2.62 (m, 1H*, 1H§), 2.62 – 2.53 (m, 1H§), 2.49 – 2.40 (m, 1H*), 2.35 – 2.21 (m, 1H§), 2.15 (d, *J* = 15.1 Hz, 1H*), 2.02 – 1.87 (m, 1H§), 1.73 (dd, *J* = 14.6, 8.1 Hz, 1H*), 1.45 (s, 3H§), 1.37 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4*, 170.5§, 158.6* (q, $J_{C\text{-}F}$ = 36.2, 35.4 Hz), 150.2*§, 131.3*, 130.5§, 129.3*§, 122.0*§, 119.9§, 118.9*, 115.9* (q, $J_{C\text{-}F}$ = 288.9 Hz), 109.5§, 108.5*, 90.1*, 88.7§, 62.5*, 60.3§, 59.2*§, 56.3§, 53.0*, 52.6§, 52.4*, 43.0*, 40.5§, 36.9*, 36.4*, 35.2§, 34.7§, 16.4*§, 13.1*§; FTIR (NaCl, thin film): 3444, 3054, 3022, 3005, 2956, 1747, 1699, 1608, 1489, 1435, 1386, 1360, 1303, 1203, 1158, 1023, 986, 929, 853, 809, 755 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{23}F_3N_2O_4I$ $[M+H]^+$ 539.0649, found 539.0633.

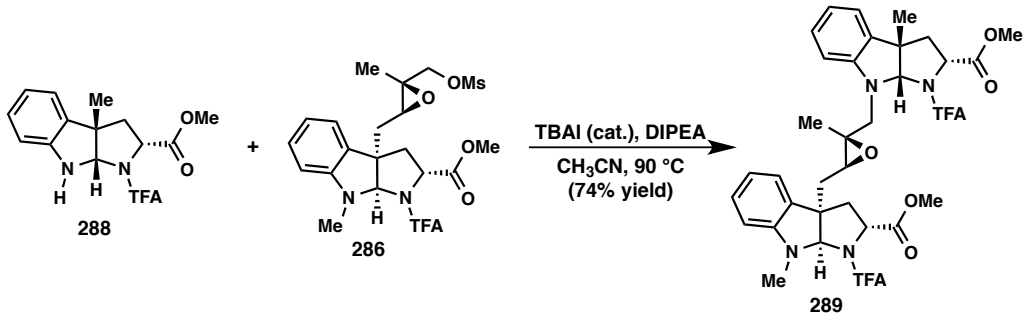
Preparation of amine 288



To a 25 mL flame-dried screw-cap Schlenk flask was added *N*-allyl pyrroloindoline **264** (500 mg, 1.36 mmol, 1.0 equiv) and dimethylbibarturic acid (636 mg, 4.07 mmol, 3.0 equiv). The Schlenk flask was then evacuated and backfilled with argon three times. The solids were then dissolved in dry DCE (3.8 mL). In the meantime, in a 1-dram vial, $Pd_2(dba)_3$ (62 mg, 0.068 mmol, 5 mol %) and 1,4-bis(diphenylphosphino)butane (dppb, 58 mg, 0.135 mmol, 10 mol %) were mixed in DCE (1.6 mL) and the mixture was allowed to stir at room temperature for 1 hour; then the resulting solution was added into Schlenk flask. The reaction was heated to 80 °C. After 4 days, the reaction was cooled to room temperature and quenched with saturated Na_2CO_3 aqueous solution (40 mL). The mixture was extracted with EtOAc (3 x 40 mL). Combined organic layers were washed with brine (100 mL). It was dried over Na_2SO_4, filtered and concentrated down to give a brown oil. Flash chromatography (1% to 20% EtOAc in hexanes) afforded amine **288**, which was contaminated with phosphine oxide formed from the dppb ligand. The mixture was then subjected to preparative reverse phase HPLC (t = 0 – 14 min, 65% to 75% CH_3CN in H_2O; t = 14 – 15 min, 75% to 95% CH_3CN in H_2O; t = 15 – 17 min, 95% to 100% CH_3CN in H_2O; t = 17 – 17.5 min, 100% to 65% CH_3CN in H_2O; t = 17.5 – 25 min, 65% CH_3CN in H_2O; t_R = 16.5 – 20.0 min), to give pure product **43** as a yellow oil (408 mg, 1.24 mmol, 92% yield). $[\alpha]_D^{25}$ = –228° (c = 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.4 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.08 – 7.01 (m, 1H*, 2H§), 7.00 (ddd, J = 7.4, 1.3, 0.6 Hz, 1H*), 6.75 (td, J = 7.4, 0.9 Hz, 1H§), 6.70 (td, J = 7.5, 0.9 Hz, 1H*), 6.61 – 6.58 (m, 1H§), 6.58 (dt, J = 7.9, 0.7 Hz, 1H*), 5.45 (tt, J = 1.9, 1.1 Hz, 1H§), 5.34 (s, 1H*), 5.21 (br s, 1H§), 4.91 (dd, J = 8.7, 2.3 Hz, 1H§), 4.74

(ddd, J = 8.9, 1.9, 1.0 Hz, 1H*), 3.24 (s, 3H[§]), 3.12 (s, 3H*), 2.86 (d, J = 13.2 Hz, 1H*), 2.70 (dd, J = 13.0, 2.3 Hz, 1H[§]), 2.50 (dd, J = 13.2, 8.5 Hz, 1H*), 2.33 (dd, J = 13.0, 8.7 Hz, 1H[§]), 1.46 (s, 3H[§]), 1.42 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0*, 169.5[§], 156.8* (q, $J_{C\text{-}F}$ = 37.3 Hz), 155.9[§] (q, $J_{C\text{-}F}$ = 37.5 Hz), 148.8*, 147.6[§], 131.3[§], 131.0*, 128.9*[§], 122.8*, 122.7[§], 119.4[§], 119.0*, 116.2[§] (q, $J_{C\text{-}F}$ = 287.4 Hz), 115.8* (q, $J_{C\text{-}F}$ = 288.0 Hz), 108.9[§], 108.8*, 84.6*, 83.2[§], 60.7[§], 60.1* (q, $J_{C\text{-}F}$ = 3.2 Hz), 54.4[§], 52.4*, 52.2[§], 50.7*, 41.9*, 40.2[§], 24.4[§], 24.2*; FTIR (NaCl, thin film): 3401, 3055, 2957, 2929, 2871, 2121, 1738, 1687, 1612, 1521, 1485, 1470, 1455, 1408, 1354, 1334, 1315, 1302, 1260, 1204, 1148, 1104, 1065, 1034, 1018, 1000, 977, 939, 904, 865, 837, 748, 718 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{16}F_3N_2O_3$ $[M+H]^+$ 329.1108, found 329.1113.

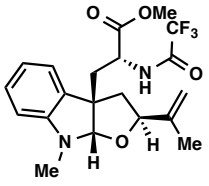
Preparation of bis(pyrroloindoline) 289



To a 0.5-dram vial was added amine **288** (76 mg, 0.23 mmol, 3.0 equiv), which was then co-evaporated with benzene (2 x 1 mL). Epoxy mesylate **286** (39 mg, 0.08 mmol, 1.0 equiv) was added as a solid, followed by tetra-*n*-butylammonium iodide (TBAI, 5.7 mg, 0.015 mmol, 0.2 equiv), and acetonitrile (90 μL). DIPEA (20 μL, 0.12 mmol, 1.5 equiv) was added at last. The vial was sealed using a Teflon cap and heated to 90 °C for 5 days. It was then cooled to room temperature and quenched with saturated $NaHCO_3$ aqueous solution (2 mL). The mixture was extracted with EtOAc (5 x 2 mL).

Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated down to give a yellow liquid. Flash chromatography (1% to 28% EtOAc in hexanes) afforded bis(pyrroloindoline) **289** as a light yellow oil (41.9 mg, 0.057 mmol, 74% yield). Starting material **288** can be recovered. $[\alpha]_D^{25} = -21°$ ($c = 0.61$, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN; *half of proton peaks* in compound exist as a 1.6 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.15 (td, J = 7.7, 1.2 Hz, 1H*, 1H§), 7.11 – 7.00 (m, 1H*, 1H§, 1H), 6.92 (dd, J = 7.3, 1.2 Hz, 1H), 6.83 (t, J = 8.1 Hz, 1H§), 6.78 (t, J = 7.3 Hz, 1H*), 6.66 (t, J = 7.4 Hz, 1H), 6.56 – 6.48 (m, 1H*, 1H§), 6.47 (d, J = 8.1 Hz, 1H), 5.90 (s, 1H*), 5.79 (s, 1H§), 5.37 (s, 1H), 4.70 (d, J = 8.2 Hz, 1H), 4.64 – 4.55 (m, 1H*), 4.29 (t, J = 8.2 Hz, 1H§), 3.75 (s, 3H*), 3.73 (s, 3H§), 3.59 – 3.35 (m, 2H*, 2H§), 3.13 (s, 3H), 3.05 (s, 3H*), 2.81 (s, 3H§), 2.78 (d, J = 13.0 Hz, 1H), 2.73 (dd, J = 13.8, 9.4 Hz, 1H§), 2.67 – 2.59 (m, 1H*), 2.42 (dd, J = 13.5, 4.4 Hz, 1H*), 2.31 (dd, J = 13.0, 8.4 Hz, 1H), 2.33 – 2.27 (m, 1H§), 2.21 (d, J = 14.3 Hz, 1H*), 2.17 – 2.10 (m, 1H§), 1.87 (dt, J = 16.5, 6.3 Hz, 1H§), 1.76 – 1.60 (m, 1H*), 1.30 (s, 3H§), 1.25 (s, 3H*, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3*, 170.6§, 169.6, 158.5* (q, $J_{C\text{-}F}$ = 37.4 Hz), 157.8§ (app d, $J_{C\text{-}F}$ = 41.7 Hz), 156.9 (q, $J_{C\text{-}F}$ = 36.8 Hz), 150.8§, 150.5*, 149.5, 131.7*, 131.4, 131.0§, 129.3§, 129.1*, 128.9*§, 122.3*§, 122.0, 120.1§, 118.8*, 118.3, 116.1 (q, $J_{C\text{-}F}$ = 288.5 Hz), 116.0* (q, $J_{C\text{-}F}$ = 288.6 Hz), 115.8§ (q, $J_{C\text{-}F}$ = 286.1 Hz), 110.0§, 108.5*, 107.3, 90.2*, 88.9, 88.8§, 60.2§, 60.0*, 60.0, 59.8§, 59.5*, 59.1*§, 57.6*, 56.8§, 52.9*, 52.8*, 52.5§, 52.4, 52.1§, 50.6, 42.9*, 42.4, 40.1§, 37.0*, 36.2*, 35.8§, 35.7§, 25.8, 15.5§, 15.4*; FTIR (NaCl, thin film): 2956, 2927, 1750, 1694, 1608, 1491, 1436, 1357, 1341, 1302, 1255, 1206, 1155, 1105, 1065, 1034, 998,

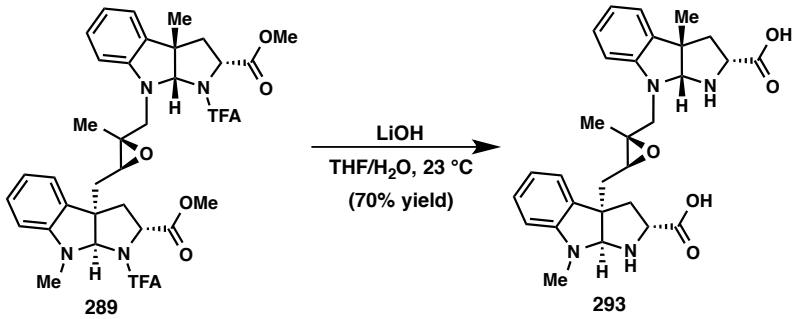
944, 861, 845, 845, 747 cm^{-1}; HRMS (MM) calc'd for $C_{35}H_{37}F_6N_4O_7$ $[M+H]^+$ 739.2561, found 739.2570.



290

When epoxy iodide **287** was used instead of epoxy mesylate, a 42% yield of rearranged product **290** was isolated. $[\alpha]_D^{25} = -122°$ (*c* = 0.475, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (td, *J* = 7.6, 1.3 Hz, 1H), 7.03 (ddd, *J* = 7.3, 1.3, 0.5 Hz, 1H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 1H), 5.23 (s, 1H), 4.94 (dt, *J* = 1.9, 1.0 Hz, 1H), 4.86 – 4.74 (m, 1H), 4.33 (td, *J* = 8.1, 4.8 Hz, 1H), 3.99 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.64 (s, 3H), 2.89 (s, 3H), 2.65 (dd, *J* = 14.7, 4.9 Hz, 1H), 2.37 – 2.19 (m, 2H), 1.91 (dd, *J* = 11.8, 11.1 Hz, 1H), 1.68 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 156.3 (q, $J_{C\text{-}F}$ = 37.6 Hz), 151.4, 143.3, 129.7, 129.4, 123.0, 118.0, 115.5 (q, $J_{C\text{-}F}$ = 287.9 Hz), 111.8, 106.2, 101.7, 80.7, 55.3, 52.9, 50.9, 46.1, 39.2, 30.4, 17.9; FTIR (NaCl, thin film): 3307, 2953, 2924, 2853, 1747, 1713, 1608, 1557, 1495, 1442, 1290, 1262, 1208, 1179, 1033, 1021, 997, 959, 900, 743 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{24}F_3N_2O_4$ $[M+H]^+$ 413.1683, found 413.1690.

Preparation of bis(amino acid) 293

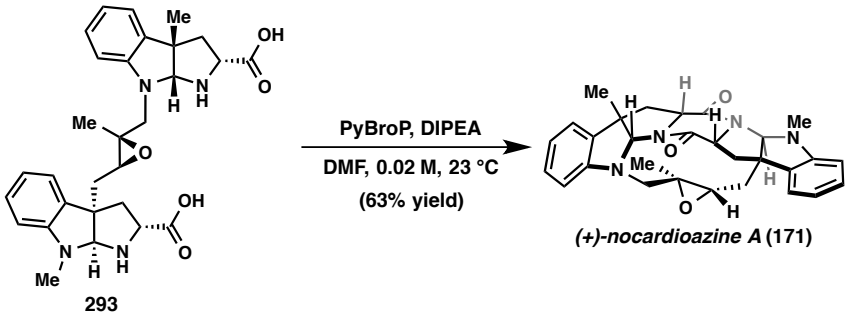


289 **293**

A solution of lithium hydroxide (7.4 mg, 0.31 mmol, 5.0 equiv) in distilled water (200 μL) was added dropwise to a solution of bis(pyrroloindoline) **289** (45.7 mg, 0.062

mmol, 1.0 equiv) in THF (350 μL) and distilled water (150 μL). After stirring at room temperature for 6 hours, the reaction was quenched with 1M HCl until pH reached 7 (210 μL). The resulting solution was concentrated down using rotavap to get rid of THF, and then put under high vacuum to give a yellow oil. It was dissolved in methanol and subjected to reverse phase preparative HPLC (10% to 60% CH_3CN in H_2O over 12 min, t_R = 6.8 – 8.0 min), giving bis(amino acid) **293** as a white solid (22.3 mg, 0.043 mmol, 70% yield). $[\alpha]_D^{25}$ = +59° (*c* = 0.59, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.20 – 7.15 (m, 2H), 7.11 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.79 (td, *J* = 7.4, 0.8 Hz, 1H), 6.77 (td, *J* = 7.5, 0.8 Hz, 1H), 6.55 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.21 (d, *J* = 7.9 Hz, 1H), 5.21 (s, 1H), 4.88 (s, 1H), 4.10 (dd, *J* = 8.6, 3.2 Hz, 1H), 3.67 (d, *J* = 16.2 Hz, 1H), 3.62 (d, *J* = 16.2 Hz, 1H), 3.51 (dd, *J* = 12.3, 5.9 Hz, 1H), 3.35 (dd, *J* = 8.2, 3.6 Hz, 1H), 2.90 (s, 3H), 2.85 (dd, *J* = 13.5, 3.2 Hz, 1H), 2.64 (t, *J* = 12.7 Hz, 1H), 2.52 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.46 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.19 (dd, *J* = 15.1, 3.7 Hz, 1H), 2.06 (dd, *J* = 15.1, 8.2 Hz, 1H), 1.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 174.3, 173.5, 151.2, 149.7, 134.3, 133.7, 130.3, 130.0, 124.1, 124.0, 121.0, 120.0, 107.8, 107.6, 93.4, 88.2, 62.2, 61.7, 61.3, 57.8, 57.7, 54.5, 54.4, 42.5, 42.4, 36.7, 33.1, 26.4, 15.6; FTIR (NaCl, thin film): 3049, 2957, 2930, 2603, 1631, 1607, 1490, 1462,1451, 1402, 1383, 1350, 1308, 1275, 1213, 1187, 1129, 1106, 1043, 1026, 921, 860, 741 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{35}N_4O_5$ $[M+H]^+$ 519.2602, found 519.2615.

Preparation of (+)-nocardioazine A (171)



To a 0.5-dram vial was added bis(amino acid) **293** (2.9 mg, 0.006 mmol, 1.0 equiv). It was co-evaporated with benzene (1 mL). DMF (280 μL) was added into the vial. At 0 °C, DIPEA (4.5 μL, 0.026 mmol, 4.6 equiv) was added, followed by bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, 10.4 mg, 0.022 mmol, 4.0 equiv). After 5 minutes, the reaction was allowed to stir at room temperature. After 24 hours, the reaction was quenched with saturated $NaHCO_3$ solution (1 mL). The aqueous layer was extracted with EtOAc (5 x 1 mL). Combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated down to give a light yellow oil. Flash chromatography (5% to 40% EtOAc in hexanes) afforded (+)-nocardioazine A (**171**) as a white solid (1.7 mg, 0.0035 mmol, 63% yield). $[\alpha]_D^{25}$ = +45° (*c* = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (td, *J* = 7.7, 1.3 Hz, 1H), 7.16 (td, *J* = 7.7, 1.3 Hz, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 2H), 6.79 (td, *J* = 7.5, 0.9 Hz, 1H), 6.74 (td, *J* = 7.4, 0.9 Hz, 1H), 6.49 (t, *J* = 7.3 Hz, 2H), 5.66 (s, 1H), 5.40 (s, 1H), 4.55 – 4.49 (m, 2H), 3.73 (d, *J* = 15.3 Hz, 1H), 3.33 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.28 (dd, *J* = 14.2, 1.8 Hz, 1H), 2.93 (s, 3H), 2.80 (dd, *J* = 15.0, 3.4 Hz, 1H), 2.76 (d, *J* = 15.4 Hz, 1H), 2.62 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.40 (dd, *J* = 14.3, 11.2 Hz, 1H), 2.31 (dd, *J* = 13.7, 8.8 Hz, 1H), 1.53 (dd, *J* = 14.9, 10.7 Hz, 1H), 1.52 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$)

δ 169.8, 169.0, 149.0, 147.2, 133.7, 133.3, 128.9, 128.7, 121.7, 121.3, 118.7, 118.0, 107.6, 105.5, 91.6, 88.2, 62.7, 61.8, 61.6, 59.3, 53.4, 51.2, 51.1, 40.2, 36.5, 35.0, 34.3, 20.1, 14.2; FTIR (NaCl, thin film): 3051, 3011, 2956, 2923, 2871, 2821, 2793, 1681, 1608, 1483, 1453, 1428, 1390, 1359, 1345, 1303, 1278, 1245, 1216, 1190, 1158, 1146, 1119, 1095, 1068, 1053, 1038, 1024, 1001, 981, 966, 920, 909, 890, 874, 841, 829, 810, 788, 750, 703 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2409.

Table 3.5. *Comparison of ^1H NMR data for natural vs. synthetic (+)-nocardioazine A (**171**)*

Raju et al. Report,[3] Natural (+)-nocardioazine A ^1H NMR, 600 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine A ^1H NMR, 500 MHz, $CDCl_3$
δ 7.16 (ddd, *J* = 7.7, 7.5, 1.2 Hz, 1H)	δ 7.18 (td, *J* = 7.7, 1.3 Hz, 1H)
7.14 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H)	7.16 (td, *J* = 7.7, 1.3 Hz, 1H)
7.09 (dd, *J* = 7.6, 1.2 Hz, 1H)	7.10 (td, *J* = 7.5, 1.0 Hz, 2H)
7.07 (dd, *J* = 7.4, 1.1 Hz, 1H)	–
6.76 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 1H)	6.79 (td, *J* = 7.5, 0.9 Hz, 1H)
6.73 (ddd, *J* = 7.7, 7.4, 0.7 Hz, 1H)	6.74 (td, *J* = 7.4, 0.9 Hz, 1H)
6.48 (dd, *J* = 7.7, 0.8 Hz, 1H)	6.49 (t, *J* = 7.3 Hz, 2H)
6.47 (dd, *J* = 7.7, 0.7 Hz, 1H)	–
5.64 (s, 1H)	5.66 (s, 1H)
5.38 (s, 1H)	5.40 (s, 1H)
4.50 (m, 1H)	4.55 – 4.49 (m, 2H)
4.49 (m, 1H)	–
3.72 (d, *J* = 15.5 Hz, 1H)	3.73 (d, *J* = 15.3 Hz, 1H)
3.30 (dd, *J* = 11.0, 3.7 Hz, 1H)	3.33 (dd, *J* = 11.0, 3.5 Hz, 1H)
3.26 (dd, *J* = 14.4, 1.6 Hz, 1H)	3.28 (dd, *J* = 14.2, 1.8 Hz, 1H)
2.91 (s, 3H)	2.93 (s, 3H)
2.79 (dd, *J* = 11.0, 3.7 Hz, 1H)	2.80 (dd, *J* = 15.0, 3.4 Hz, 1H)
2.74 (d, *J* = 15.5 Hz, 1H)	2.76 (d, *J* = 15.4 Hz, 1H)
2.60 (dd, *J* = 13.7, 9.1 Hz, 1H)	2.62 (dd, *J* = 13.7, 9.2 Hz, 1H)
2.38 (dd, *J* = 14.4, 11.0 Hz, 1H)	2.40 (dd, *J* = 14.3, 11.2 Hz, 1H)
2.30 (dd, *J* = 13.7, 8.7 Hz, 1H)	2.31 (dd, *J* = 13.7, 8.8 Hz, 1H)
1.51 (obscured, 1H)	1.53 (dd, *J* = 14.9, 10.7 Hz, 1H)
1.50 (s, 3H)	1.52 (s, 3H)
1.10 (s, 3H)	1.12 (s, 3H)

Table 3.6. *Comparison of ^{13}C NMR data for natural vs. synthetic (+)-nocardioazine A (**171**)*

Raju et al. Report,[3] Natural (+)-nocardioazine A ^{13}C NMR, 150 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine A ^{13}C NMR, 126 MHz, $CDCl_3$	Chemical Shift Difference, Δδ
δ 169.6	δ 169.8	0.2
168.8	169.0	0.2
148.8	149.0	0.2
146.9	147.2	0.3
133.6	133.7	0.1
133.0	133.3	0.3
128.8	128.9	0.1
128.4	128.7	0.3
121.5	121.7	0.2
121.1	121.3	0.2
118.4	118.7	0.3
117.8	118.0	0.2
107.4	107.6	0.2
105.4	105.5	0.1
91.5	91.6	0.1
88.0	88.2	0.2
62.4	62.7	0.3
61.7	61.8	0.1
61.4	61.6	0.2
59.2	59.3	0.1
53.3	53.4	0.1
51.0	51.2	0.2
50.9	51.1	0.2
40.1	40.2	0.1
36.4	36.5	0.1
34.9	35.0	0.1
34.2	34.3	0.1
19.9	20.1	0.2
14.1	14.2	0.1

3.6 NOTES AND REFERENCES

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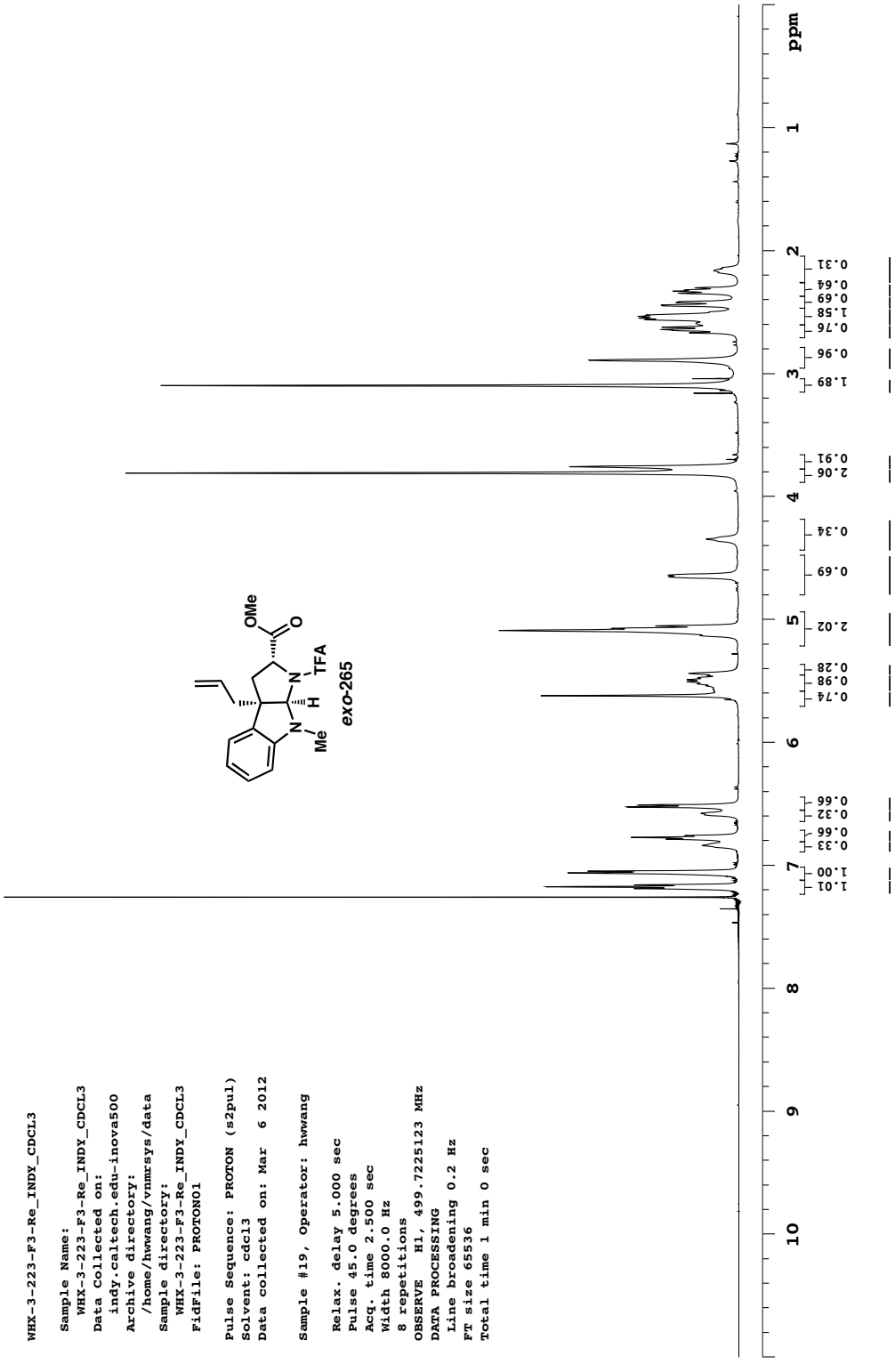
Appendix 2

Spectra Relevant to Chapter 3:
Enantioselective Total Synthesis of (+)-Nocardioazines A and B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Sample directory:
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Solvent: cdcl3
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Pulse 45.0 degrees
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Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225123 MHz
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Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
OMe
O
N
H
TFA
Me
exo-265
ppm
1.01
1.00
0.33
0.66
0.32
0.66
0.74
0.98
0.28
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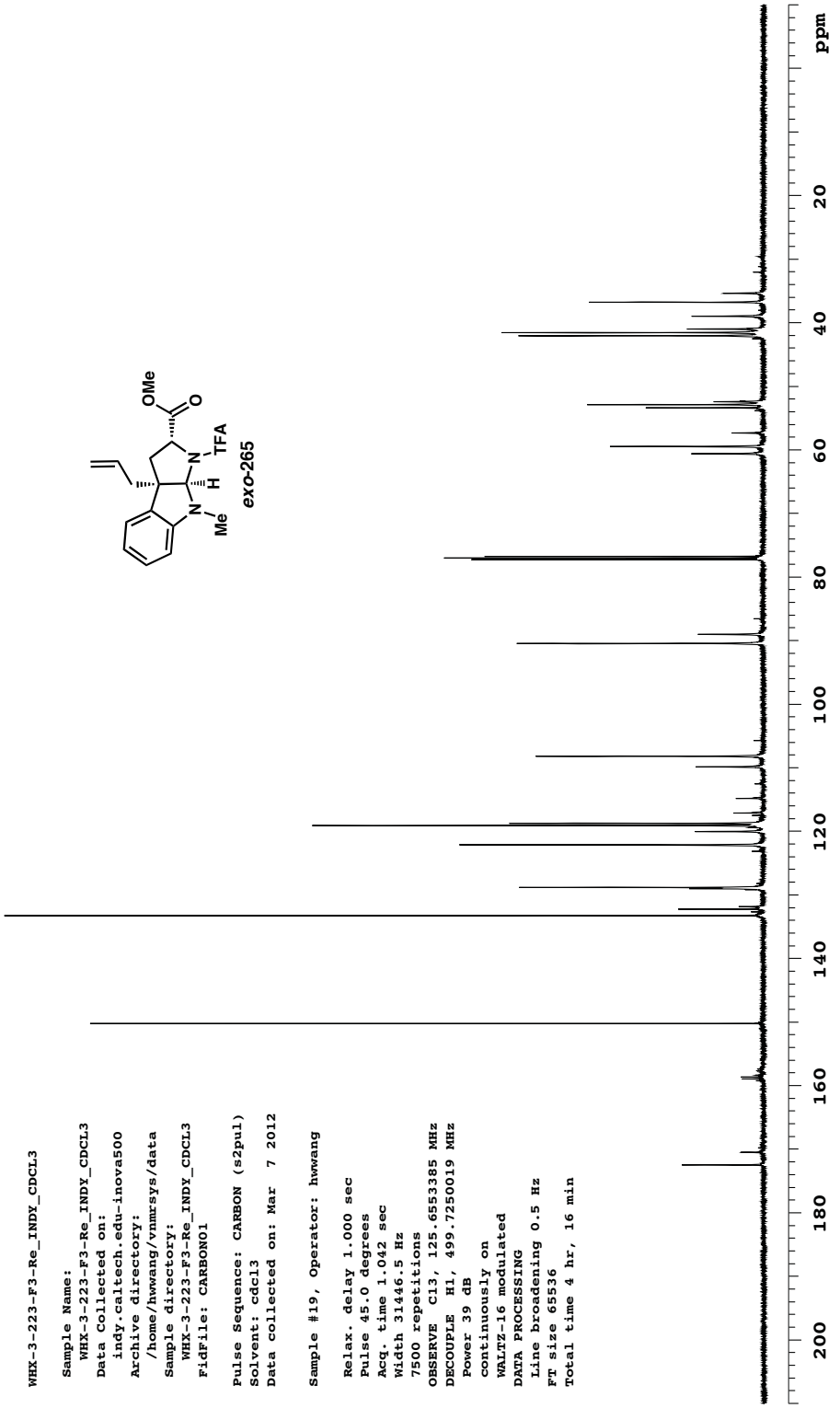
0.64
0.31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DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
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Total time 4 hr, 16 min
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O
N
H
TFA
N
Me
exo-265
200
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140
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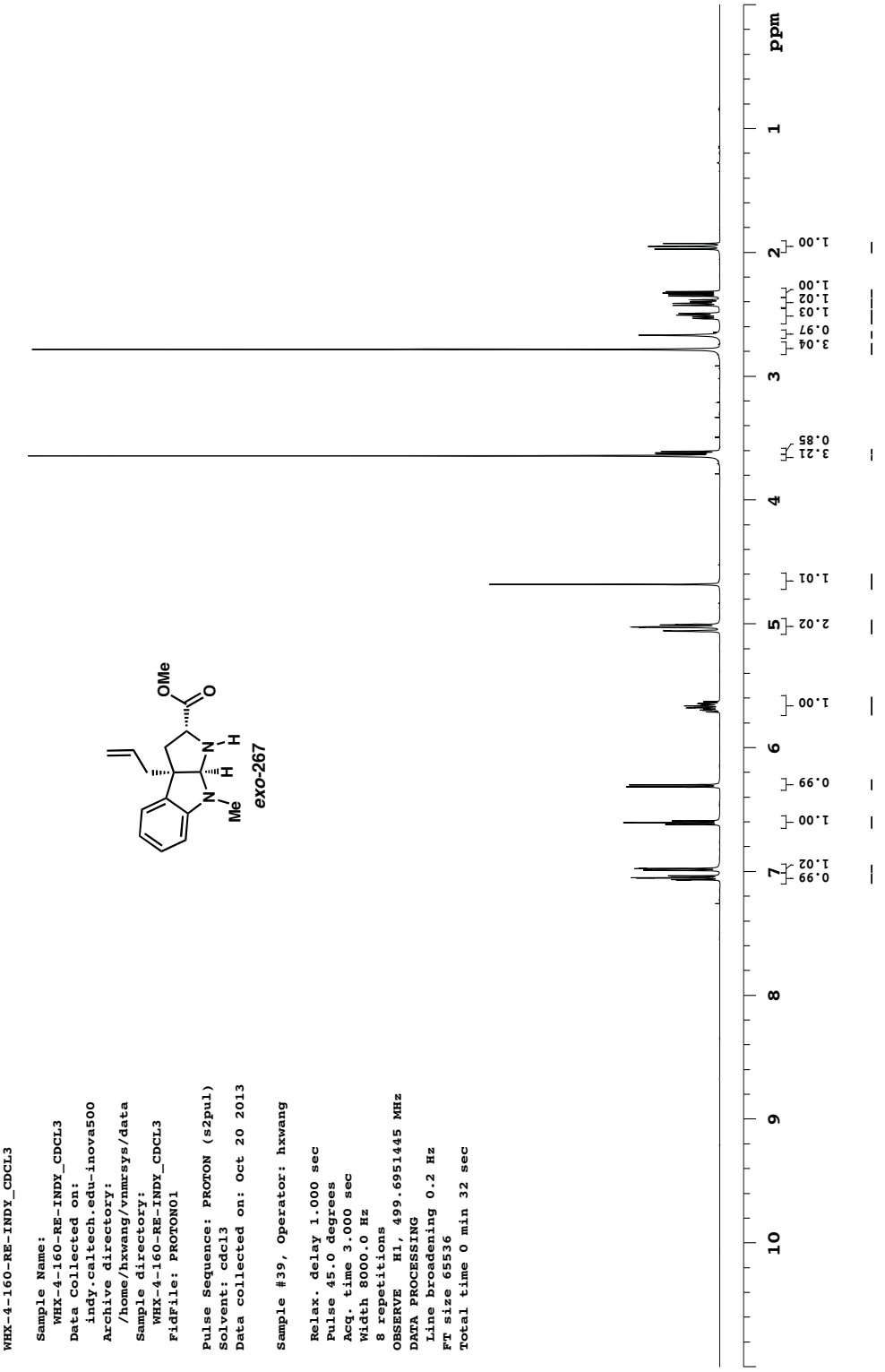
40
20
ppm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Solvent: cdcl3
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Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
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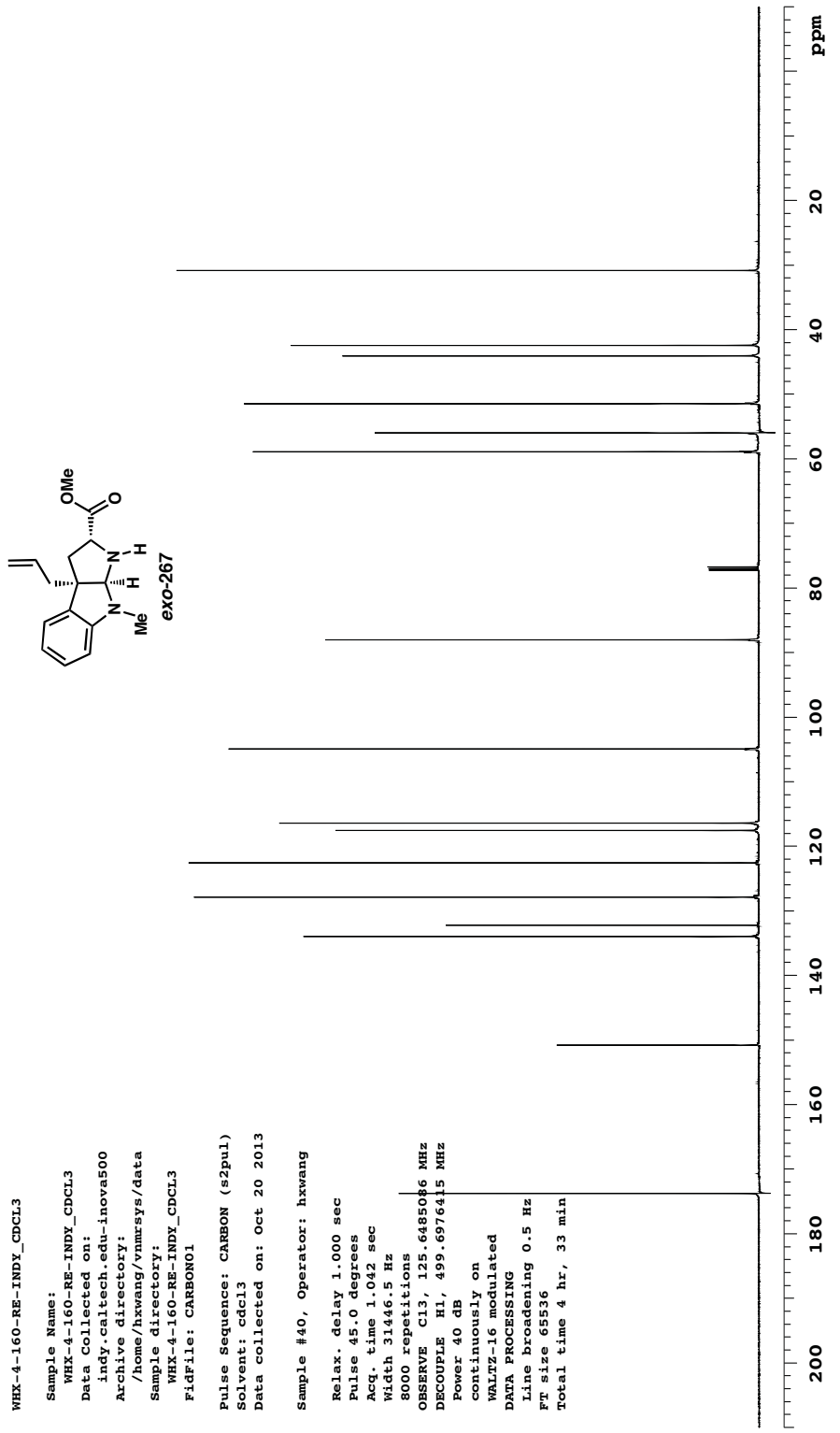
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
OMe
O
N
H
H
N
Me
exo-267
ppm
10
9
8
7
6
5
4
3
2
1
0.99
1.02
1.00
0.99
1.00
2.02
1.01
3.21
0.85
3.04
0.97
1.03
1.02
1.00
1.00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Solvent: cdcl3
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8000 repetitions
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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 4 hr, 33 min
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H
H
N
Me
exo-267
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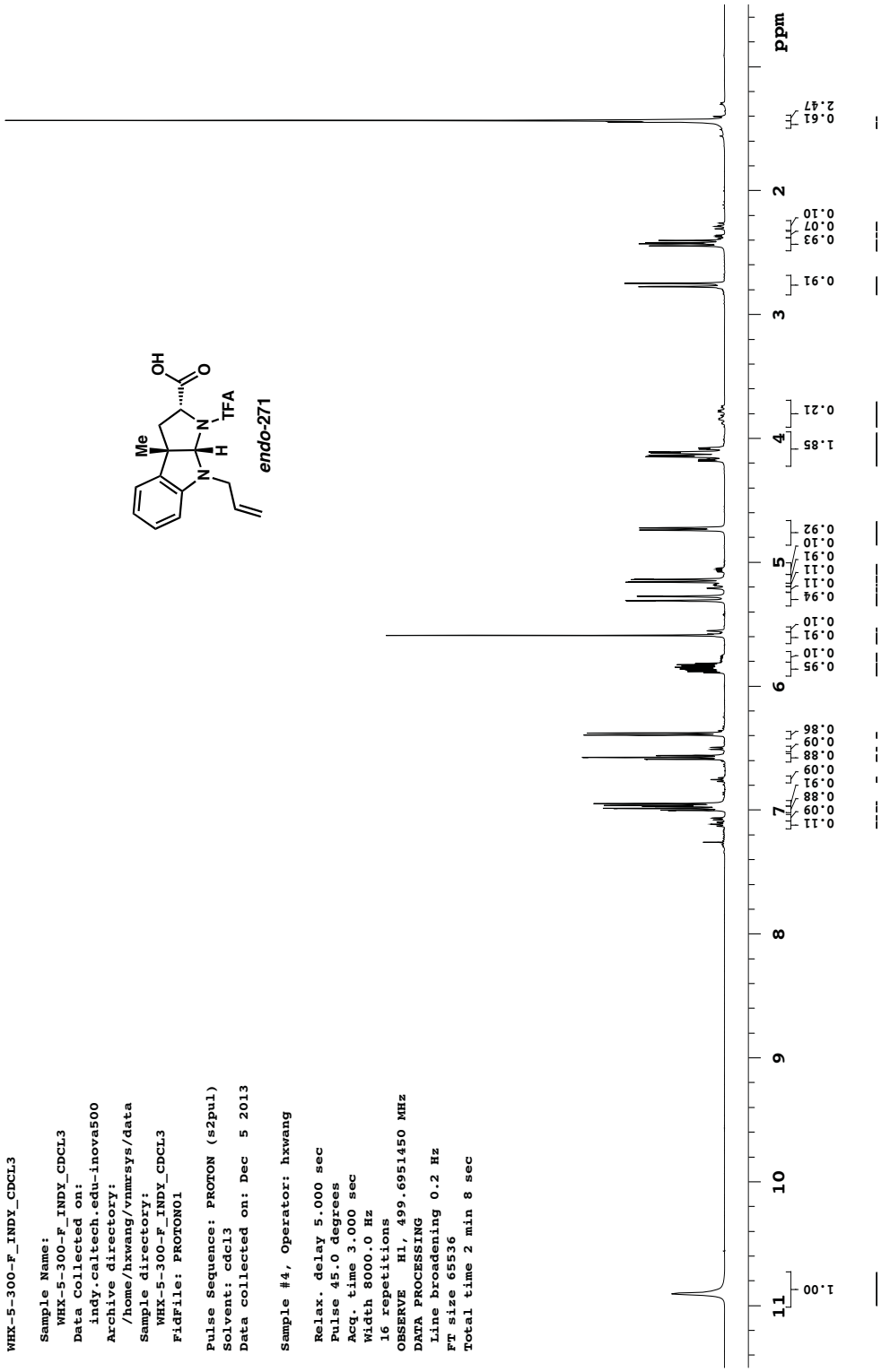
180
160
140
120
100
80
60
40
20
ppm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Data Collected on:
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Archive directory:
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FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 5 2013
Sample #4, Operator: hxwang
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Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6951450 MHz
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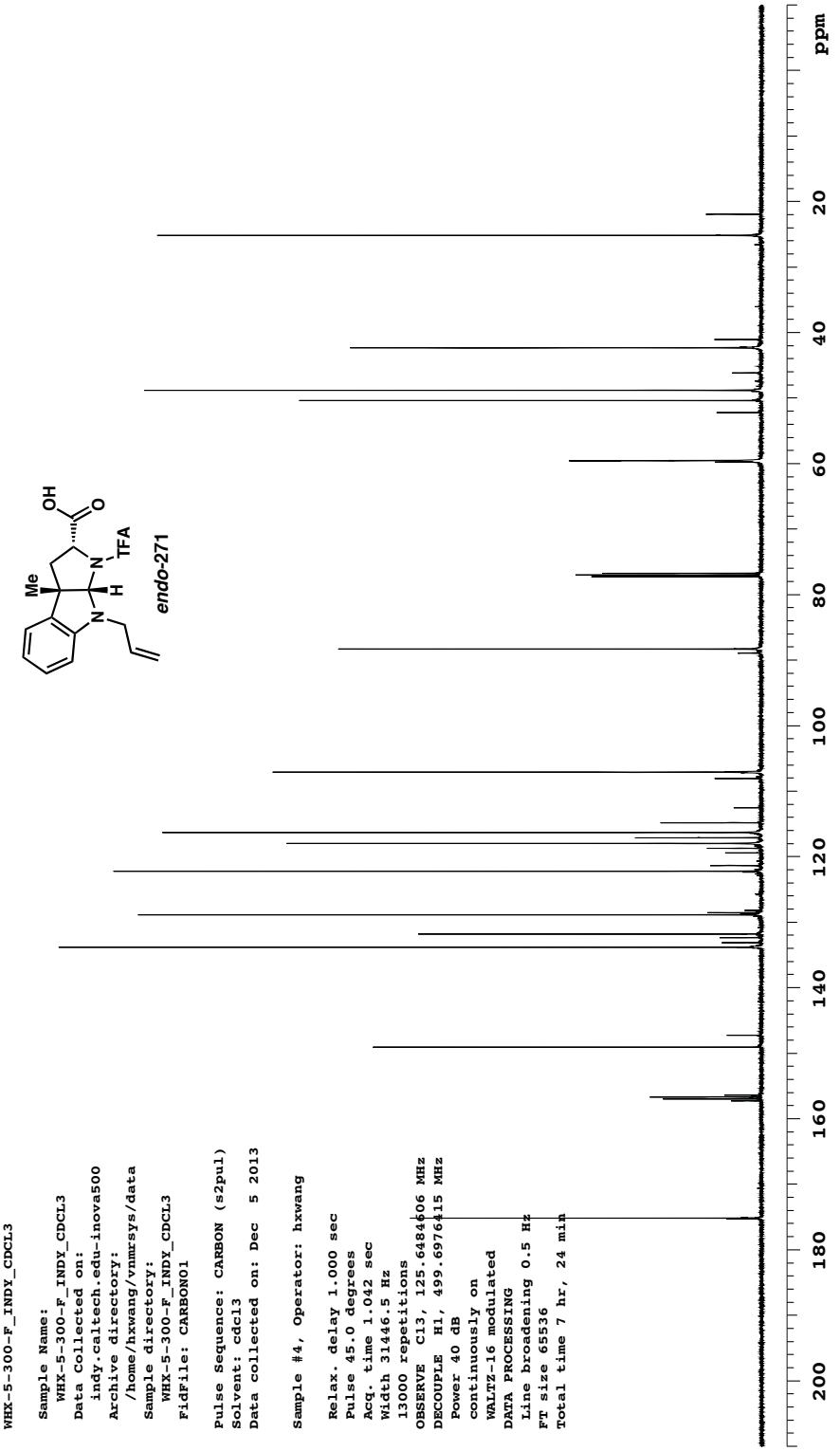
TFA
endo-271
ppm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Acq. time 1.042 sec
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OBSERVE C13, 125.6484606 MHz
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Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 24 min
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H
N
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endo-271
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180
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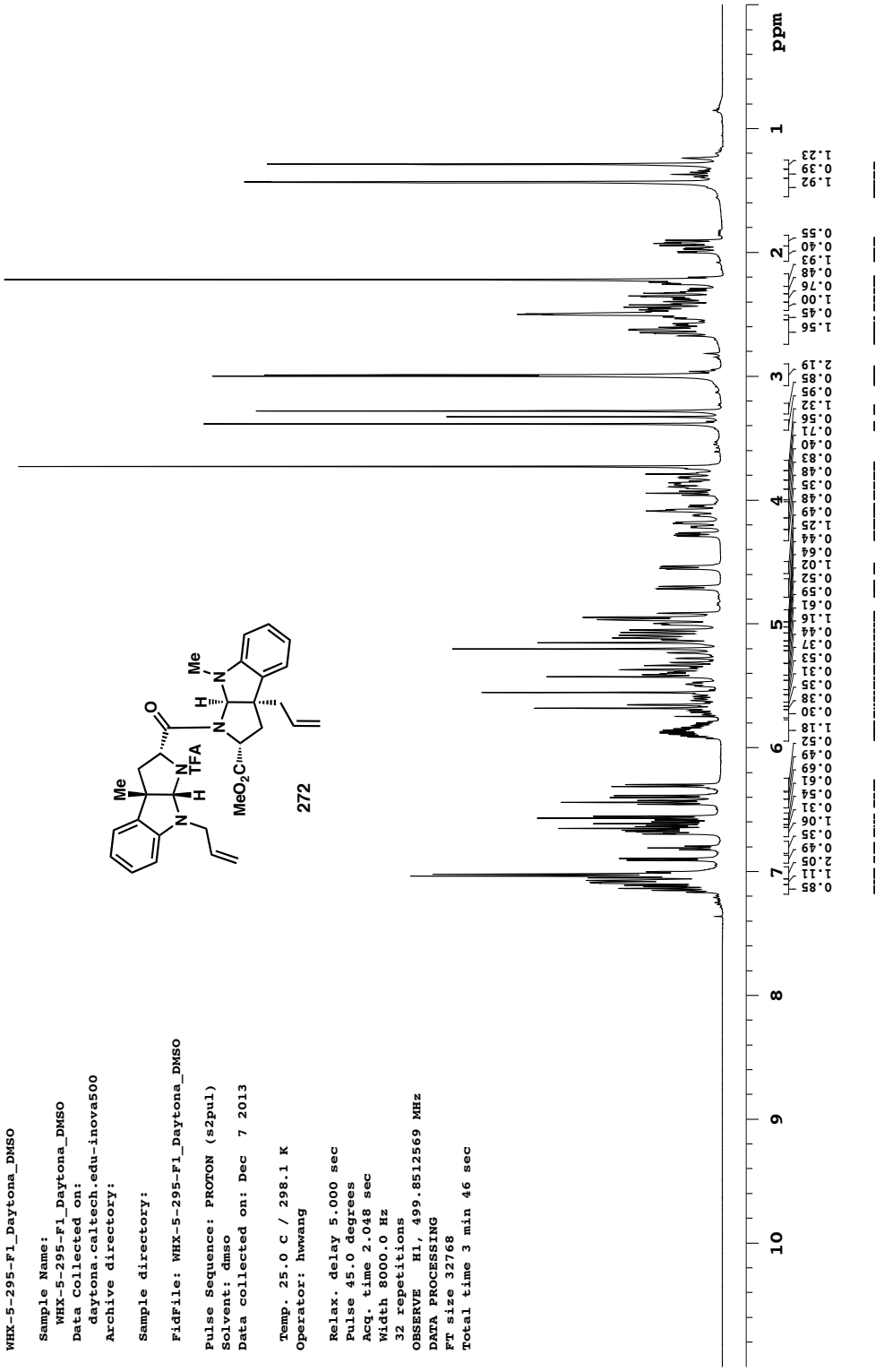
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Archive directory:
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Solvent: dmso
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Temp. 25.0 C / 298.1 K
Operator: hwwang
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Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
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Total time 3 min 46 sec
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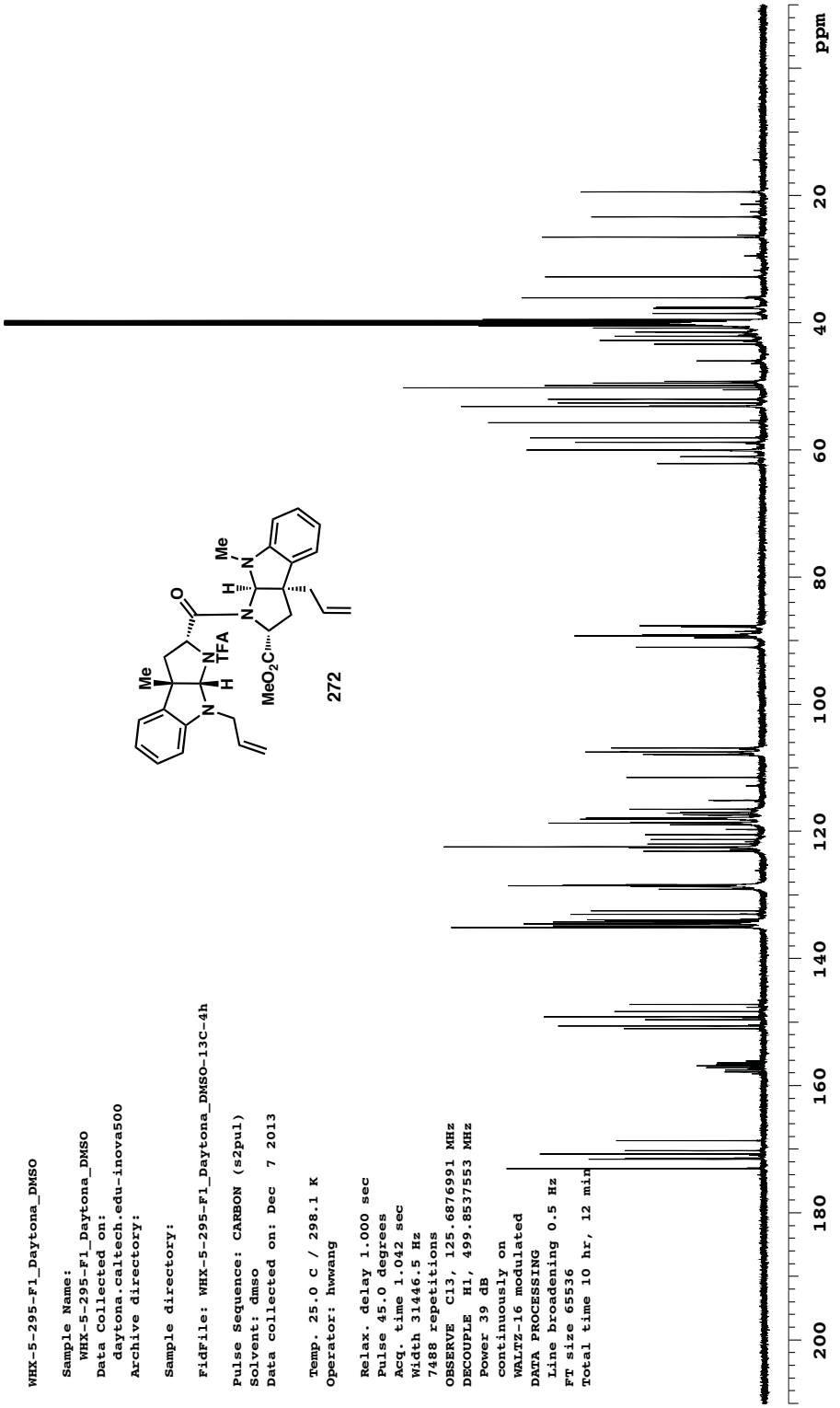
TFA
MeO2C
272
ppm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Solvent: dmso
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Operator: hwwang
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Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
7488 repetitions
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DECOUPLE H1, 499.8537553 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
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Line broadening 0.5 Hz
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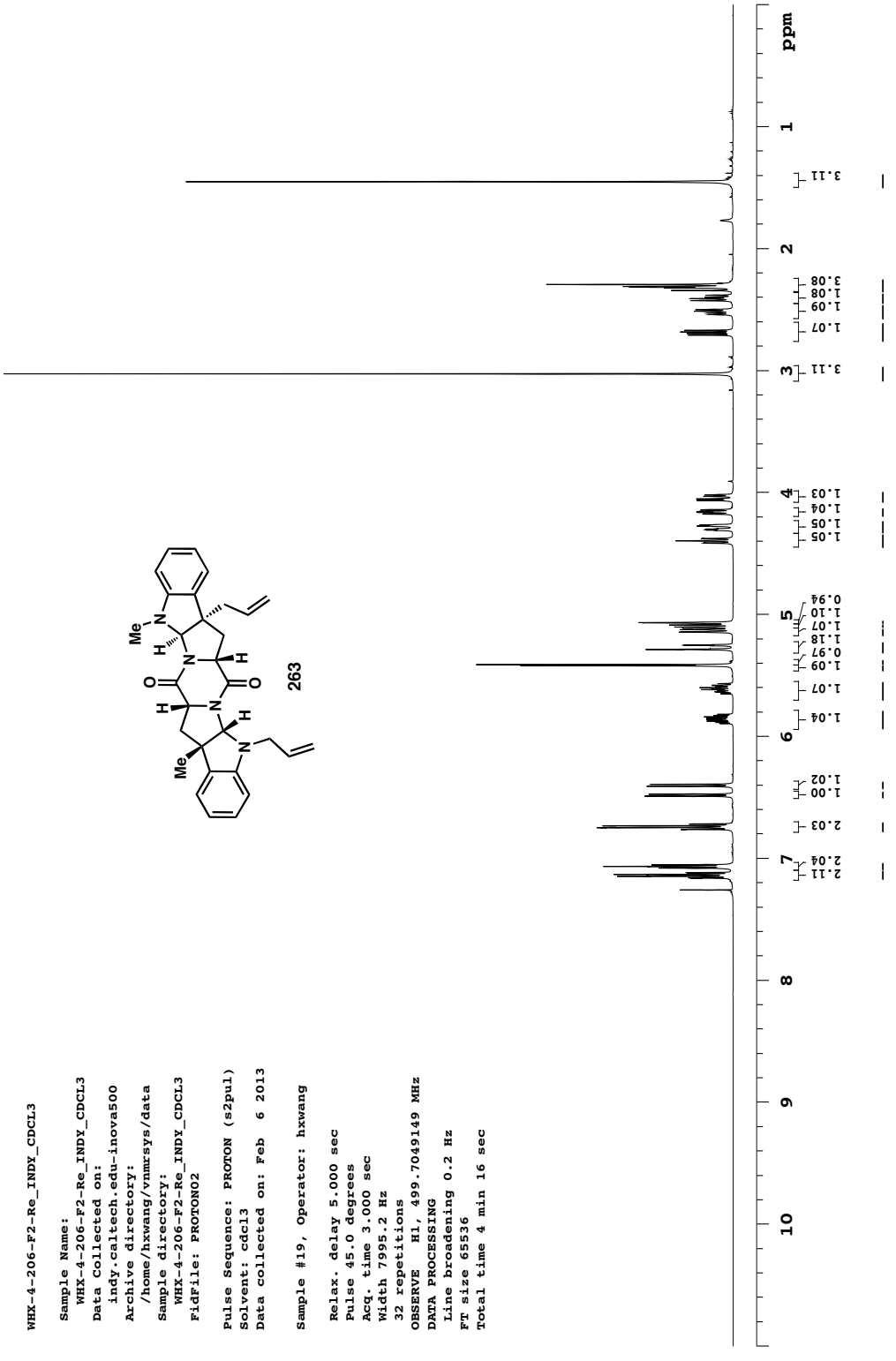
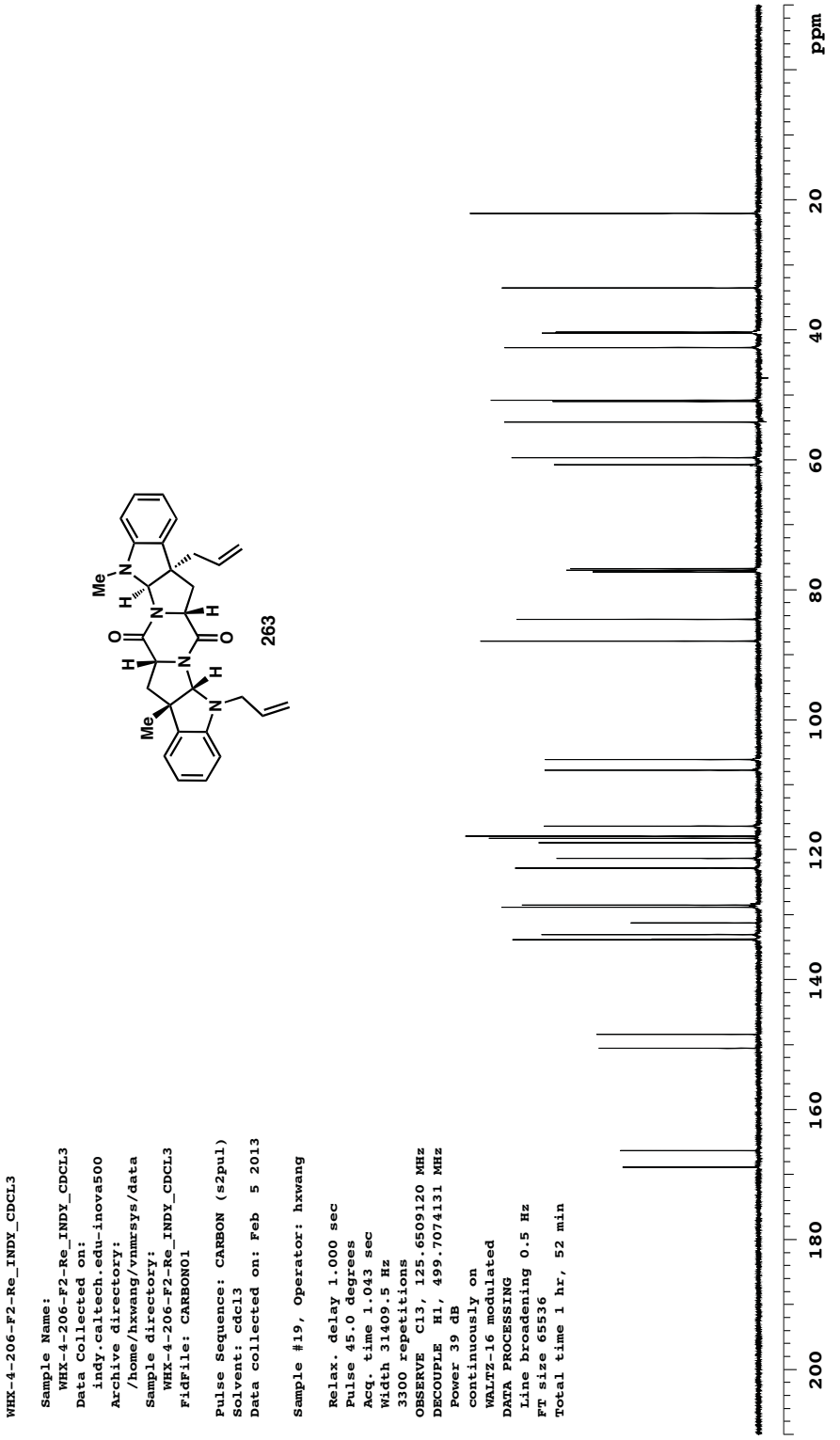
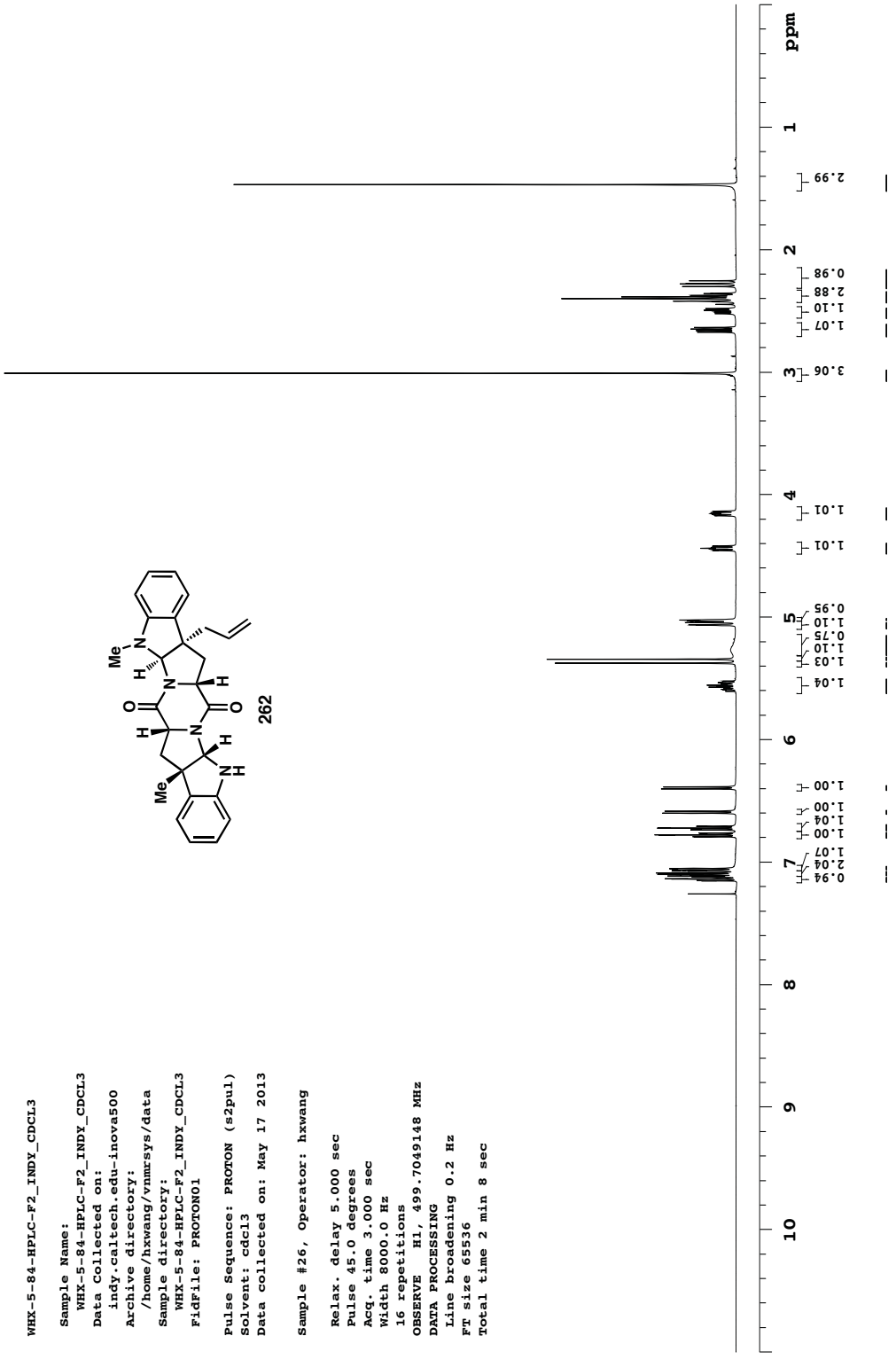
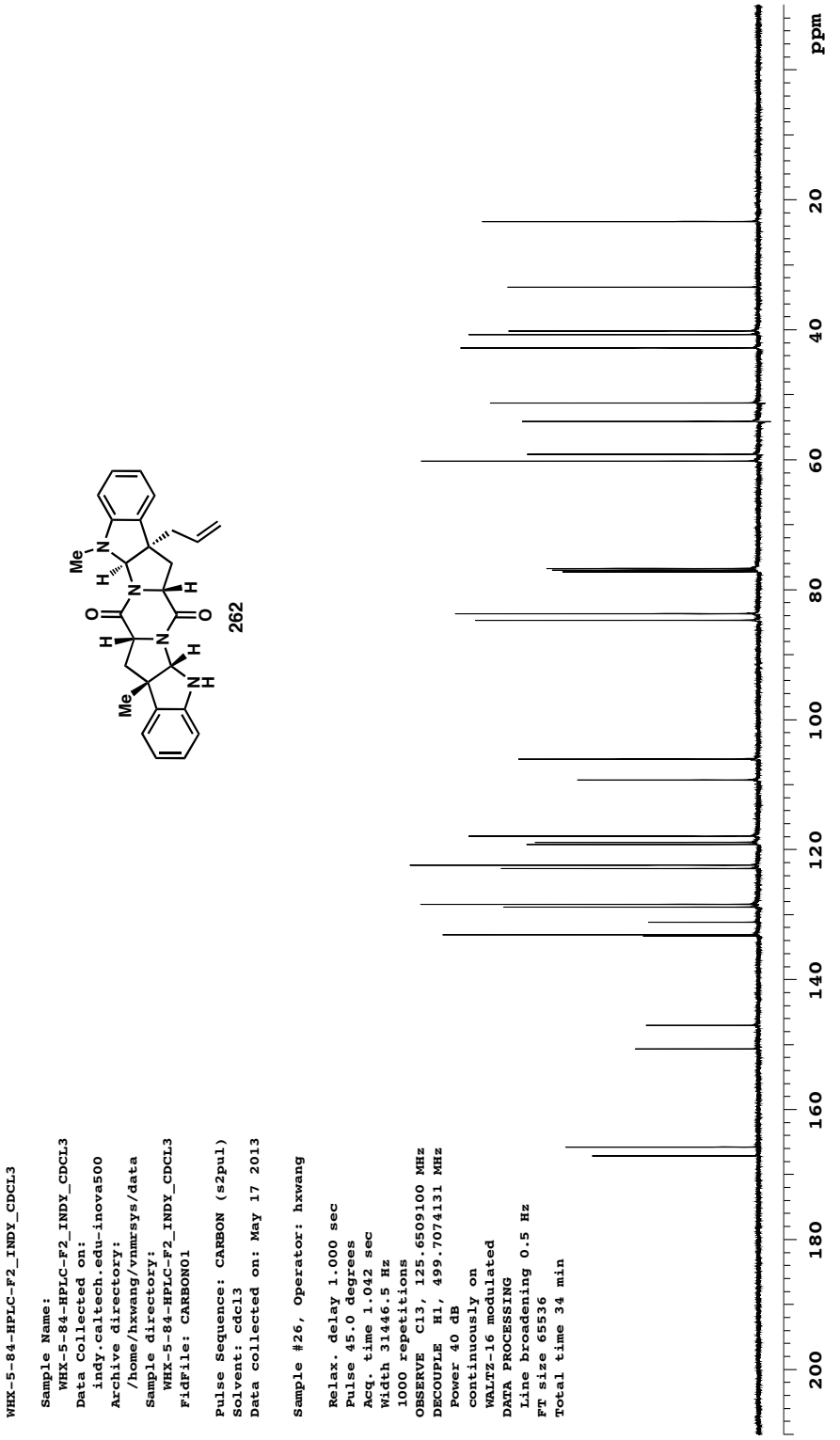
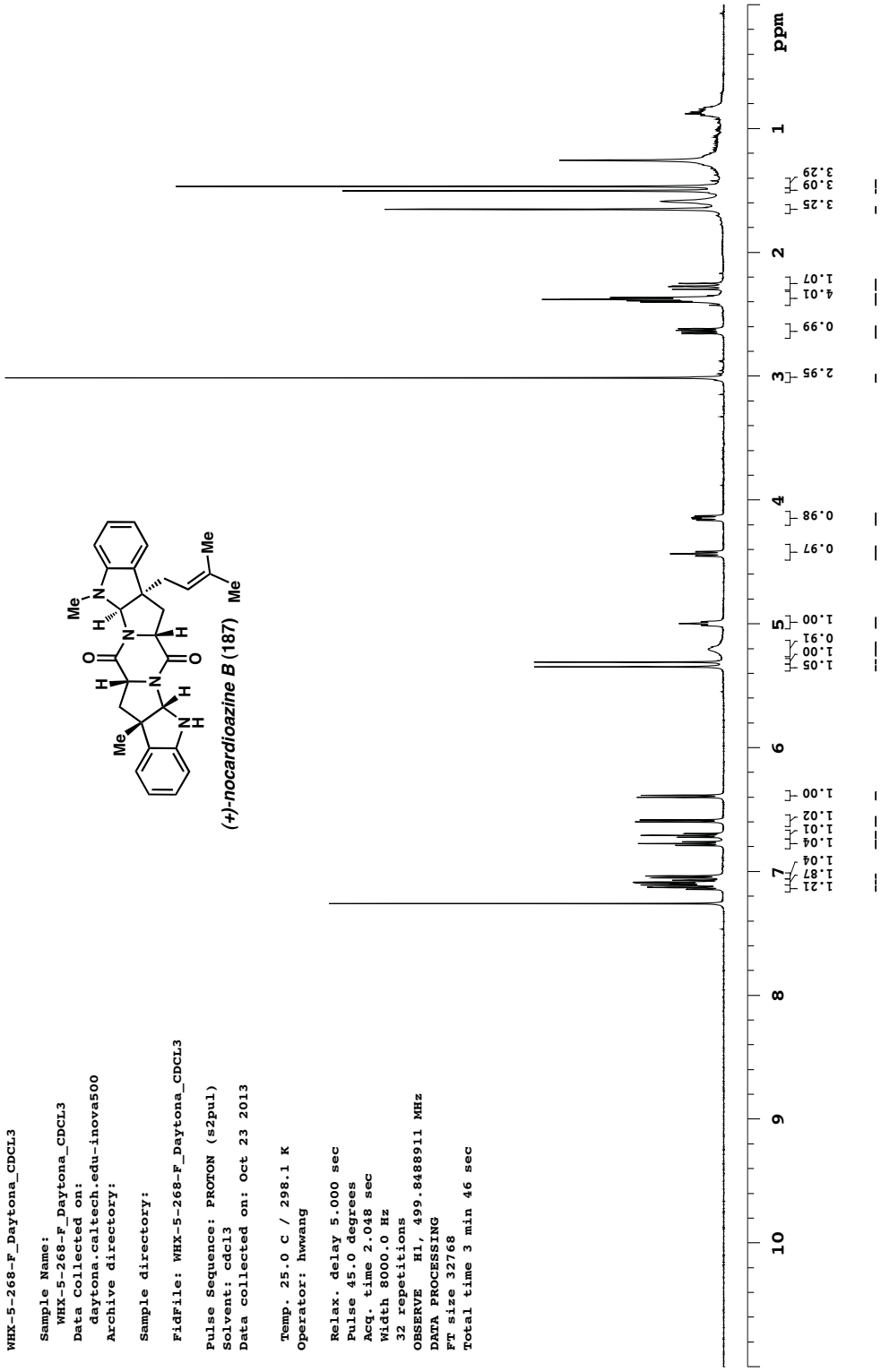
Me
TFA
MeO2C
272
200
180
160
140
120
100
80
60
40
20
ppm

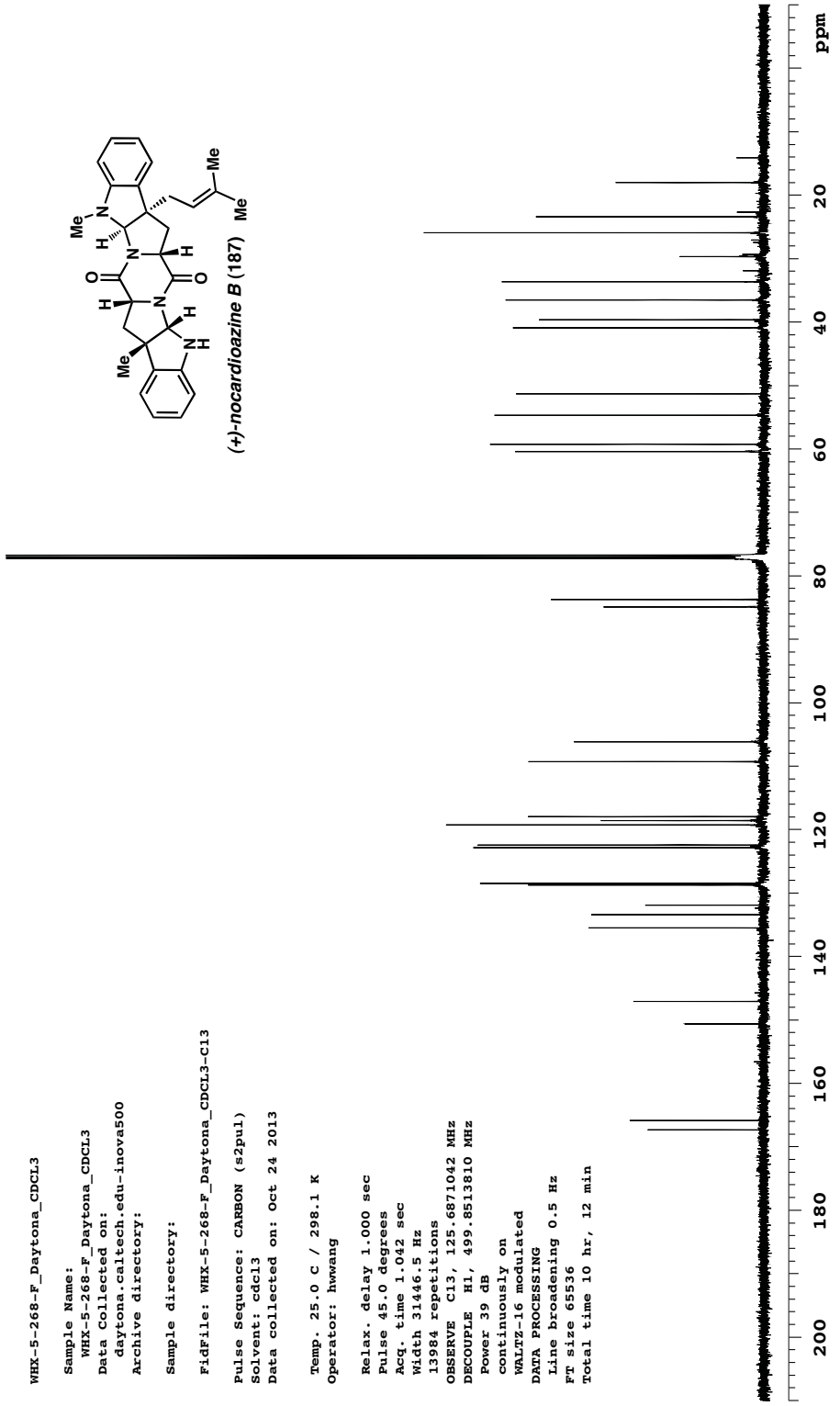

WHX-4-206-F2-Re_INDY_CDCL3
Sample Name:
WHX-4-206-F2-Re_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-4-206-F2-Re_INDY_CDCL3
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 6 2013
Sample #19, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7995.2 Hz
32 repetitions
OBSERVE H1, 499.7049149 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 16 sec
263
ppm

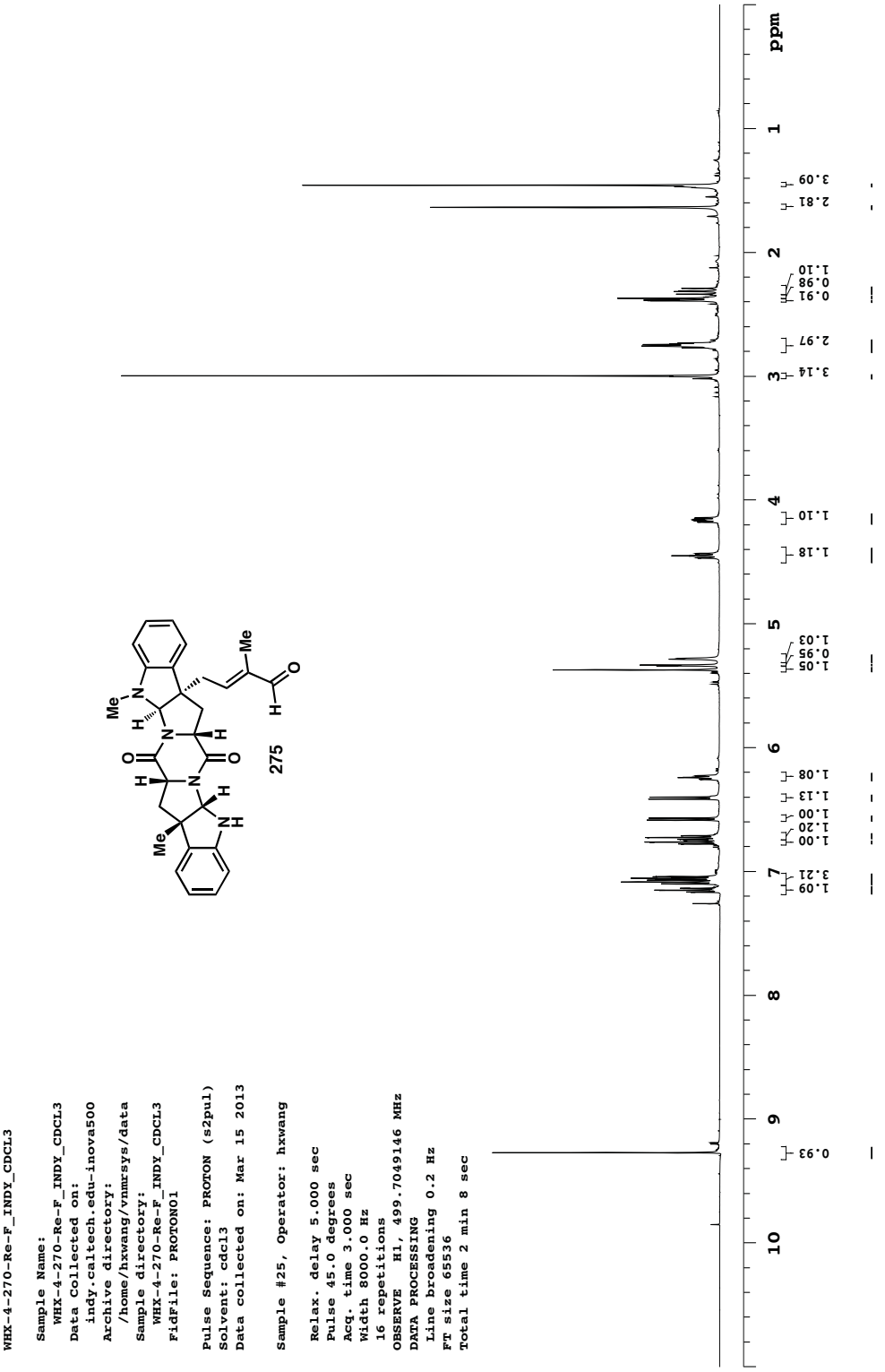

WHX-4-206-F2-Re_INDY_CDCL3
Sample Name:
WHX-4-206-F2-Re_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-4-206-F2-Re_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 5 2013
Sample #19, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
3300 repetitions
OBSERVE C13, 125.6509120 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 1 hr, 52 min
Me
N
H
N
H
O
O
H
N
H
N
Me
263
200
180
160
140
120
100
80
60
40
20
ppm

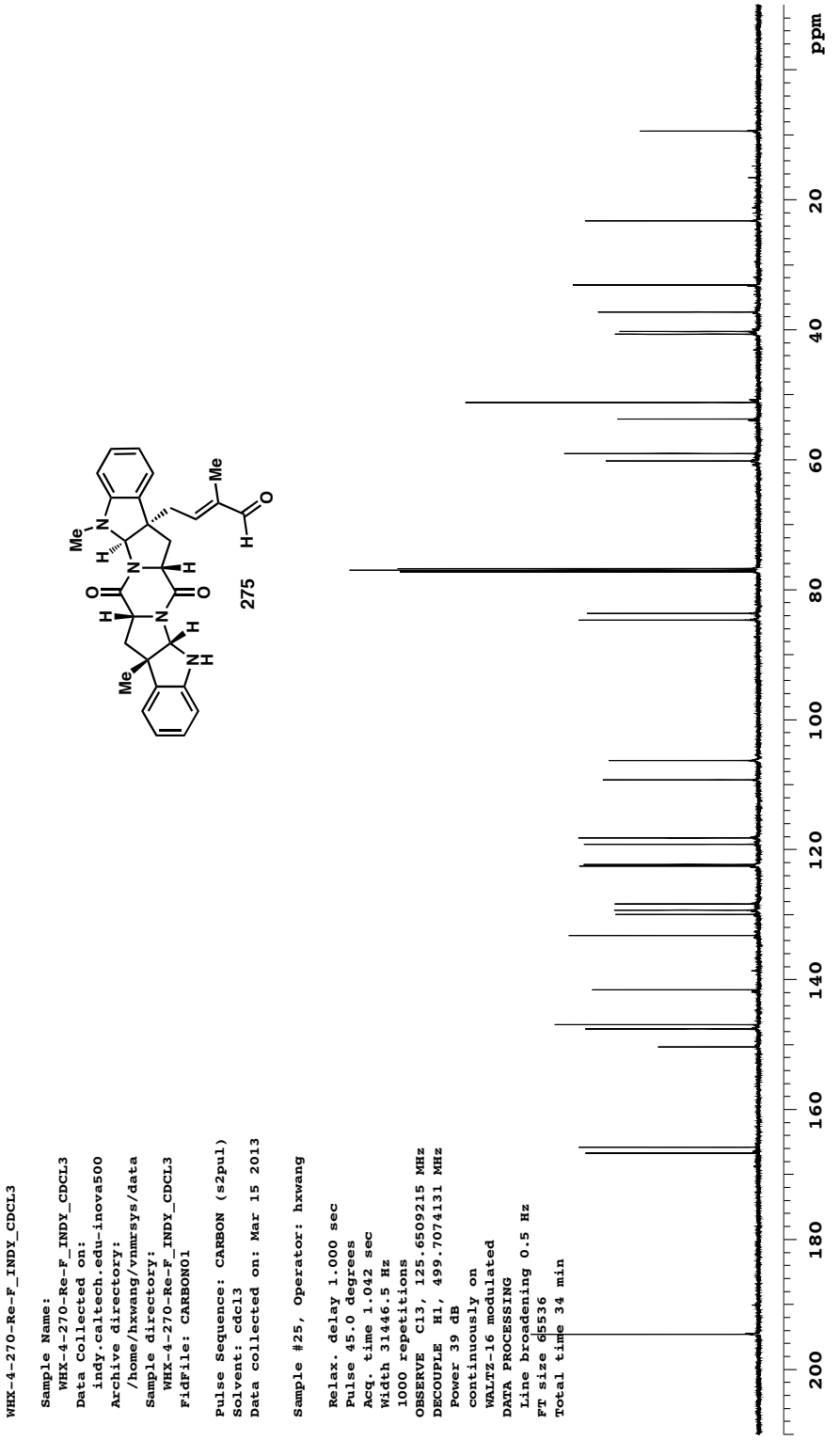

WHX-5-84-HPLC-F2_INDY_CDCL3
Sample Name:
WHX-5-84-HPLC-F2_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-84-HPLC-F2_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 17 2013
Sample #26, Operator: hxwang
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
262
ppm
10
9
8
7
6
5
4
3
2
1
0.94
2.04
1.07
1.00
1.04
1.00
1.00
1.04
1.03
1.10
0.75
1.10
0.95
1.01
1.01
3.06
1.07
1.10
2.88
0.98
2.99

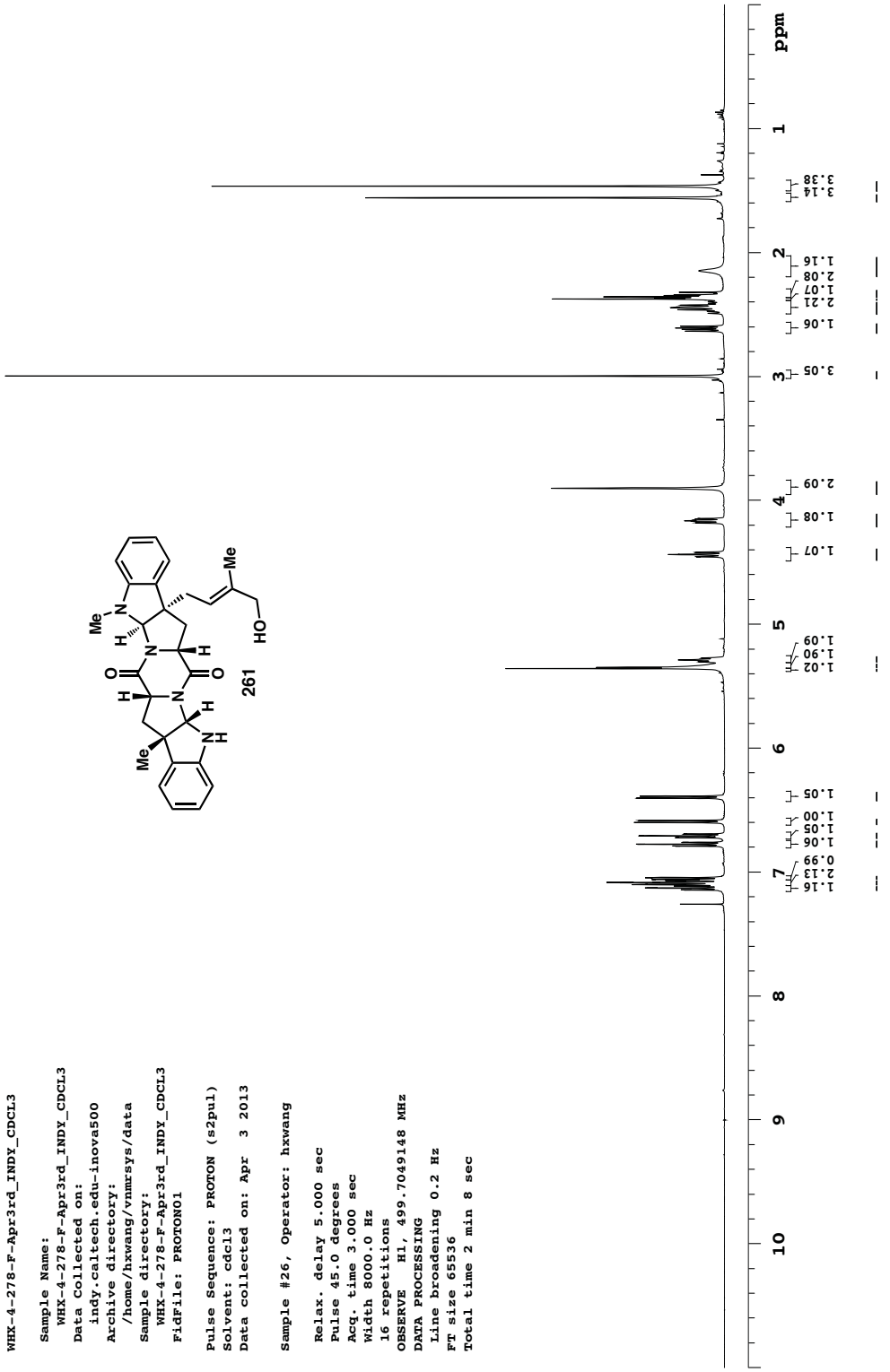

WHX-5-84-HPLC-F2_INDY_CDCL3
Sample Name:
WHX-5-84-HPLC-F2_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-84-HPLC-F2_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 17 2013
Sample #26, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6509100 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 34 min
Me
H
N
O
H
N
H
O
H
N
H
Me
262
200
180
160
140
120
100
80
60
40
20
ppm

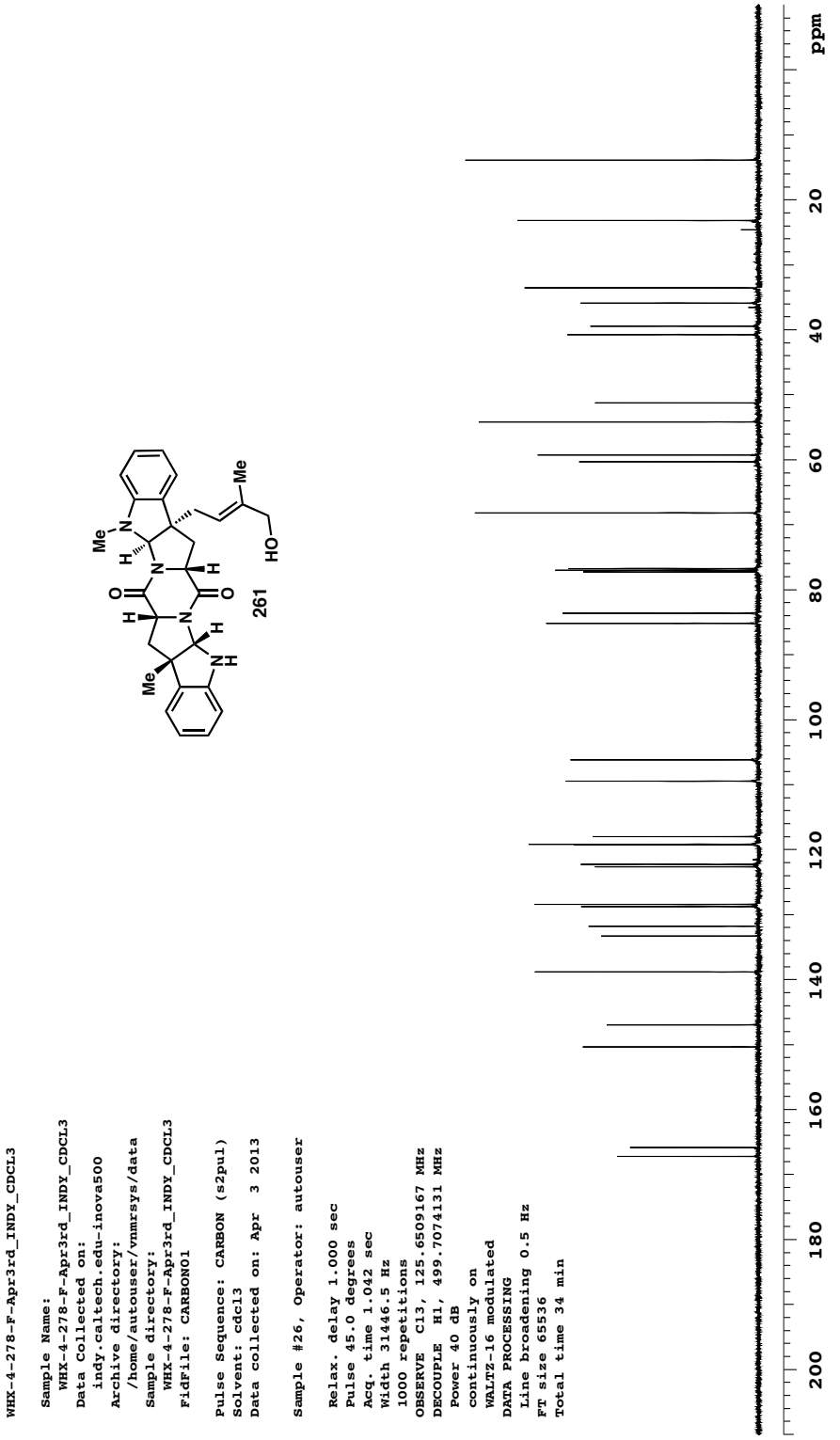

WHX-5-268-F_Daytona_CDCL3
Sample Name:
WHX-5-268-F_Daytona_CDCL3
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-268-F_Daytona_CDCL3
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 23 2013
Temp. 25.0 C / 298.1 K
Operator: hwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.8488911 MHz
DATA PROCESSING
FT size 32768
Total time 3 min 46 sec
(+)-nocardioazine B (187)
ppm
1.21
1.87
1.04
1.04
1.01
1.02
1.00
1.05
1.00
0.91
1.00
0.97
0.98
2.95
0.99
4.01
1.07
3.25
3.09
3.29

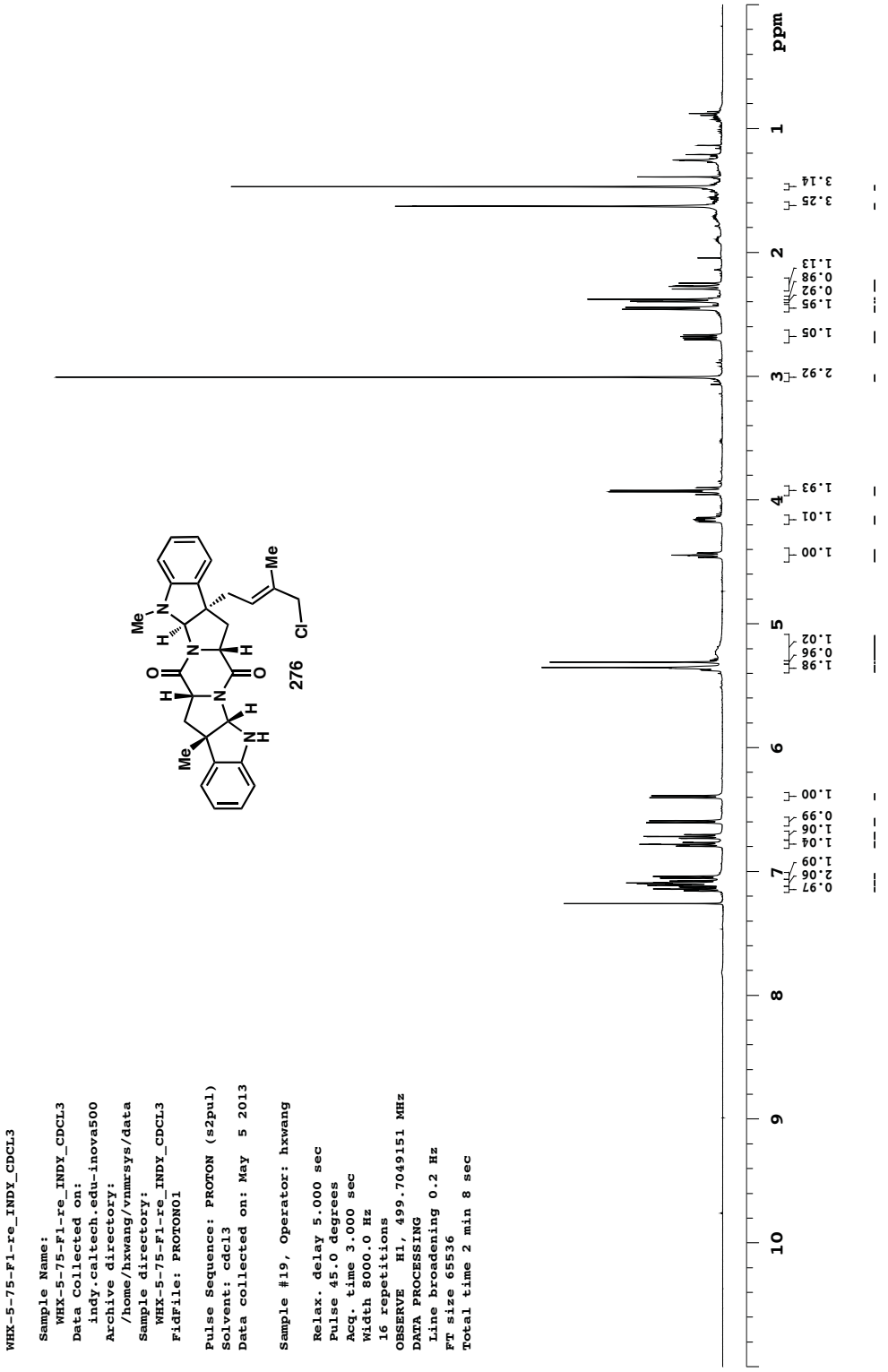

WHX-5-268-F_Daytona_CDCL3
Sample Name:
WHX-5-268-F_Daytona_CDCL3
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-268-F_Daytona_CDCL3-C13
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 24 2013
Temp. 25.0 C / 298.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13984 repetitions
OBSERVE C13, 125.6871042 MHz
DECOUPLE H1, 499.8513810 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 10 hr, 12 min
(+)-nocardioazine B (187)
200
180
160
140
120
100
80
60
40
20
ppm

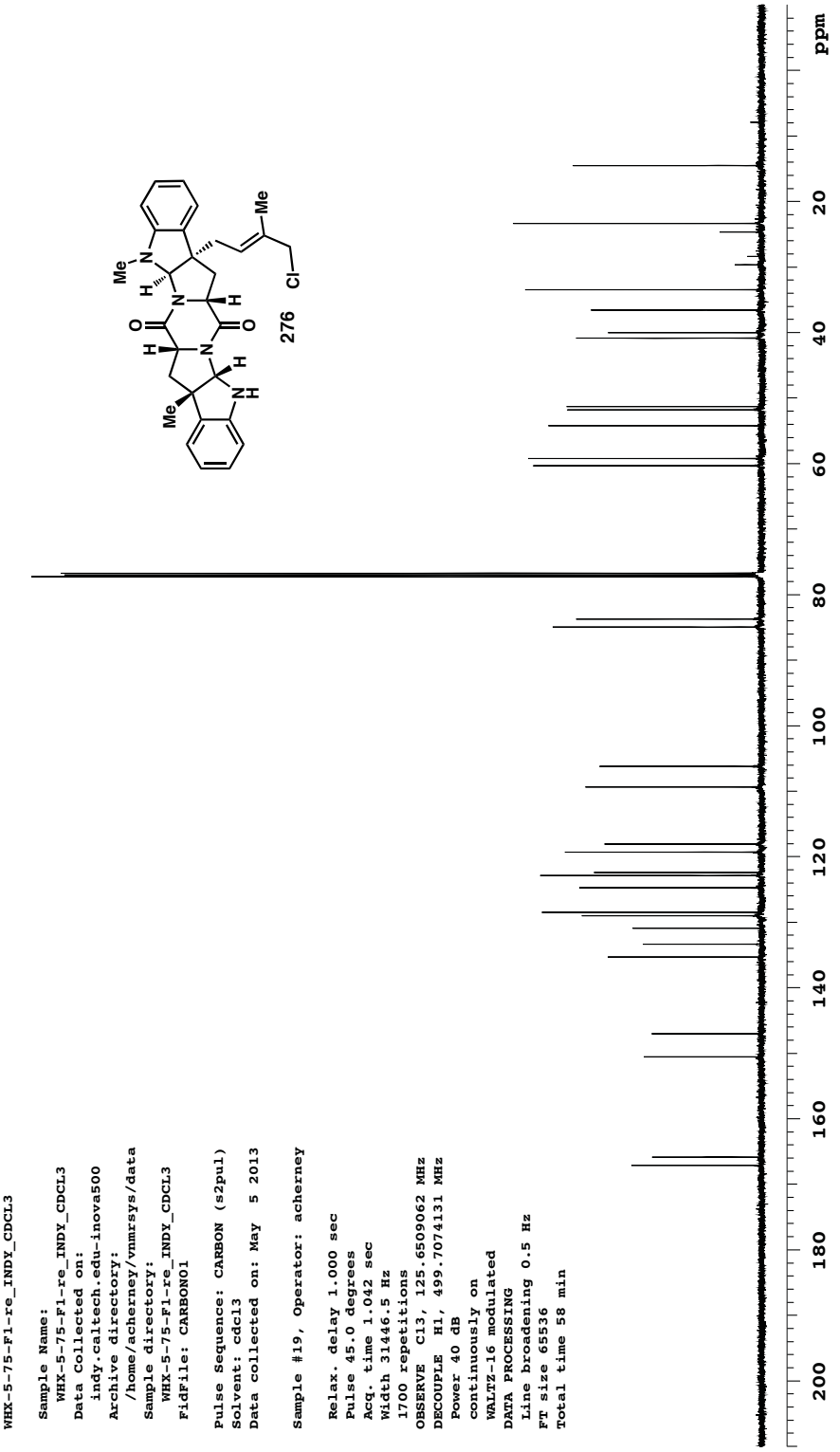

WHX-4-270-Re-F_INDY_CDCL3
Sample Name:
WHX-4-270-Re-F_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-4-270-Re-F_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 15 2013
Sample #25, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049146 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
275
ppm
0.93
1.09
3.21
1.00
1.20
1.00
1.13
1.08
1.05
0.95
1.03
1.10
1.18
3.14
2.97
0.91
0.98
1.10
2.81
3.09

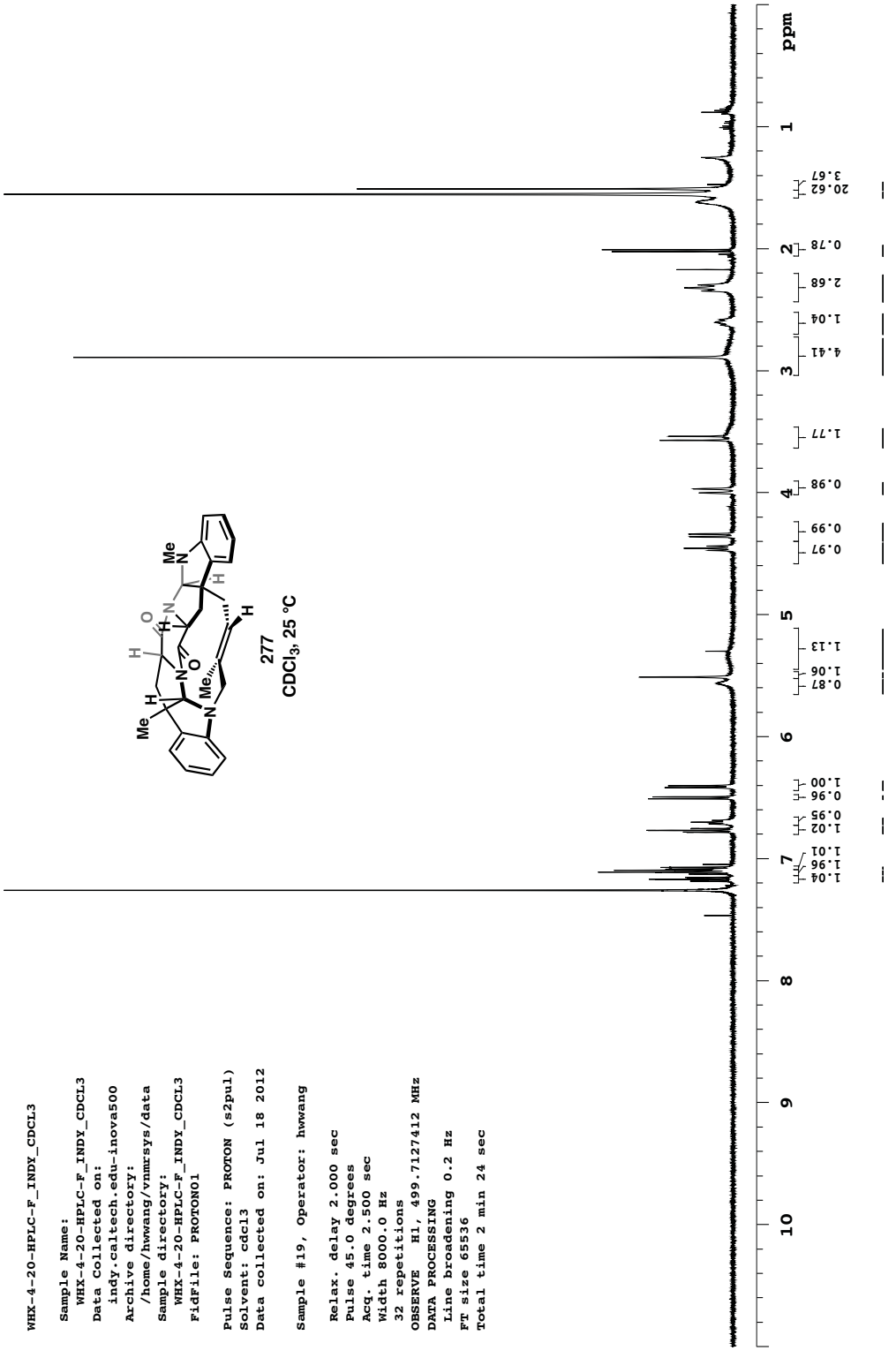

WHX-4-270-Re-F_INDY_CDCL3
Sample Name:
WHX-4-270-Re-F_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-4-270-Re-F_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 15 2013
Sample #25, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6509215 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
275
200
180
160
140
120
100
80
60
40
20
ppm

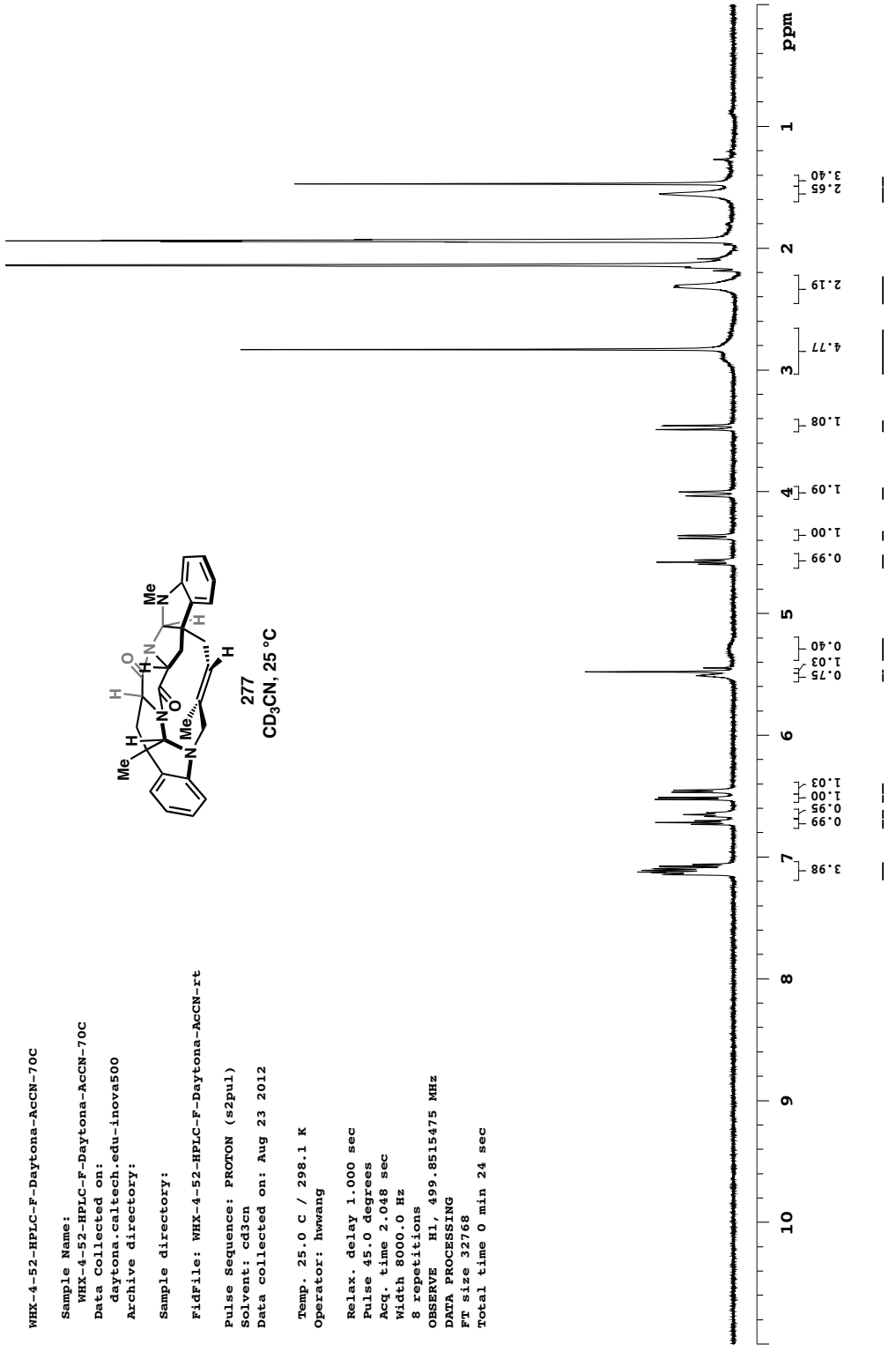

WHX-4-278-F-Apr3rd_INDY_CDCL3
Sample Name:
WHX-4-278-F-Apr3rd_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-4-278-F-Apr3rd_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2013
Sample #26, Operator: hxwang
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
261
ppm
1.16
2.13
0.99
1.06
1.05
1.00
1.05
1.02
1.90
1.09
1.07
1.08
2.09
3.05
1.06
2.21
1.07
2.08
1.16
3.14
3.38

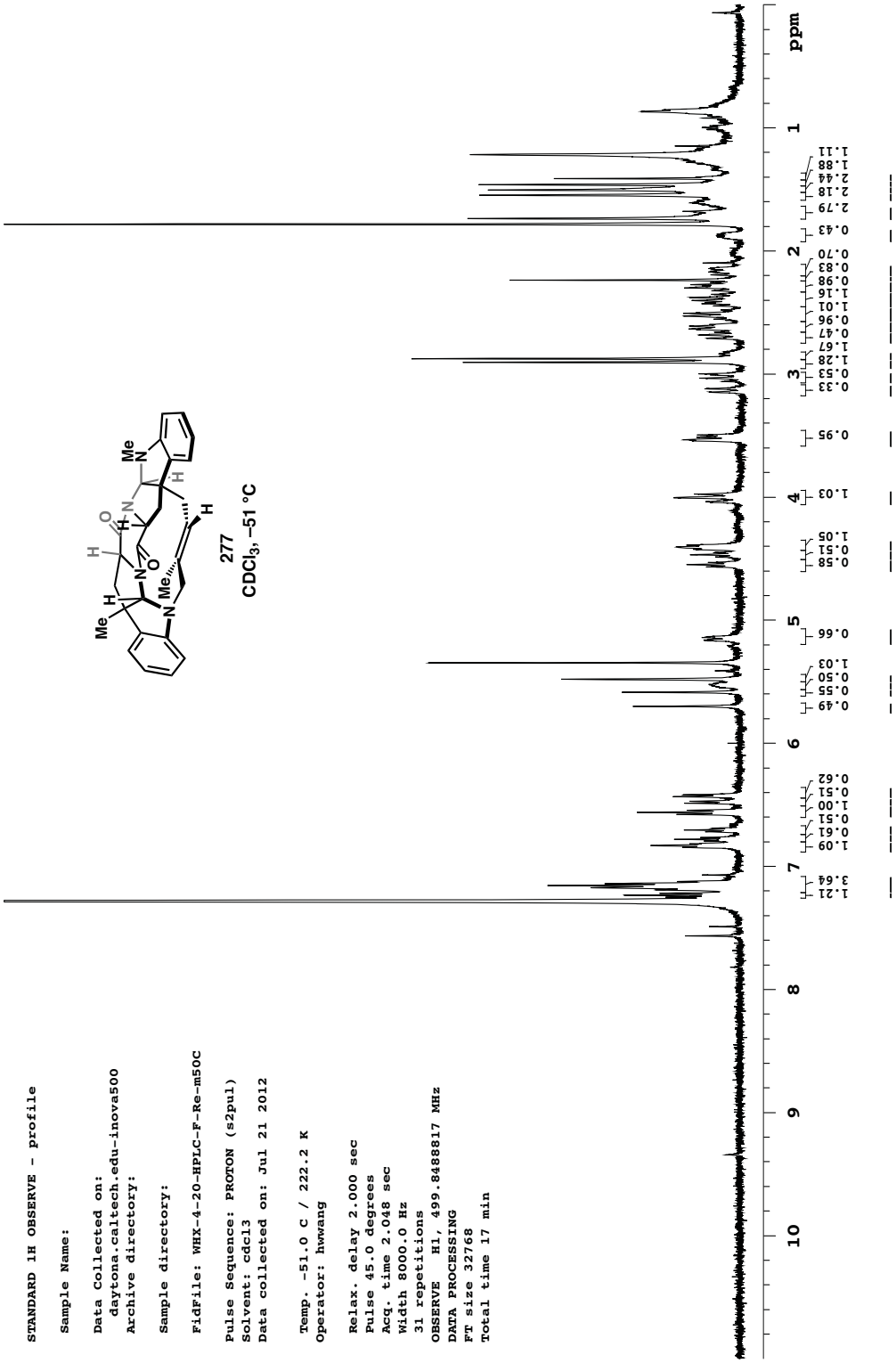

WHX-4-278-F-Apr3rd_INDY_CDCL3
Sample Name:
WHX-4-278-F-Apr3rd_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/autouser/vnmrsys/data
Sample directory:
WHX-4-278-F-Apr3rd_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2013
Sample #26, Operator: autouser
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6509167 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 34 min
Me
N
H
N
H
O
H
O
N
H
N
H
Me
Me
HO
261
200
180
160
140
120
100
80
60
40
20
ppm

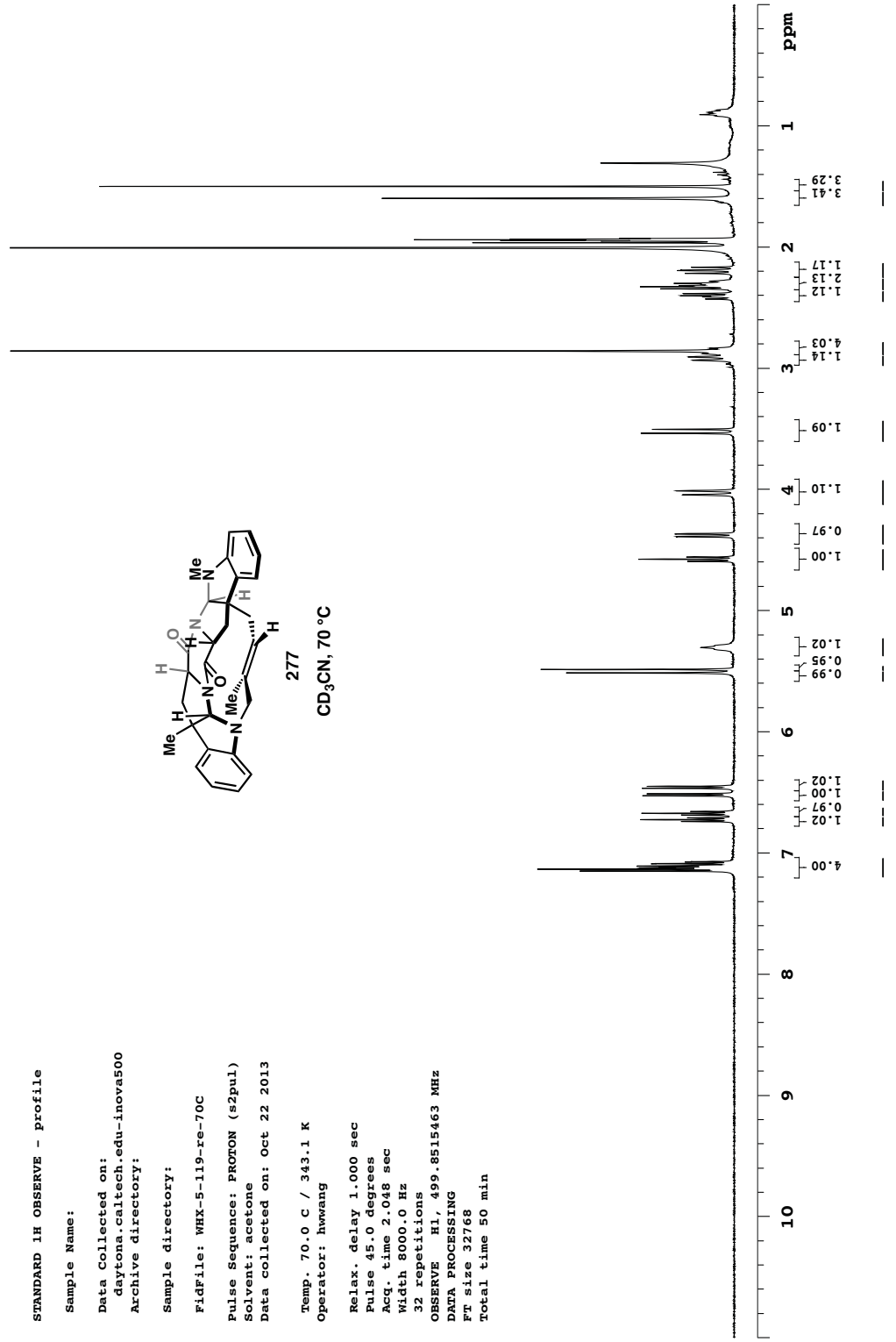

WHX-5-75-F1-re_INDY_CDCL3
Sample Name:
WHX-5-75-F1-re_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-75-F1-re_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 5 2013
Sample #19, Operator: hxwang
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
276
ppm
10
9
8
7
6
5
4
3
2
1
0.97
2.06
1.09
1.00
1.04
1.06
0.99
1.00
1.98
0.96
1.02
1.00
1.01
1.93
2.92
1.05
1.95
0.92
0.98
1.13
3.25
3.14

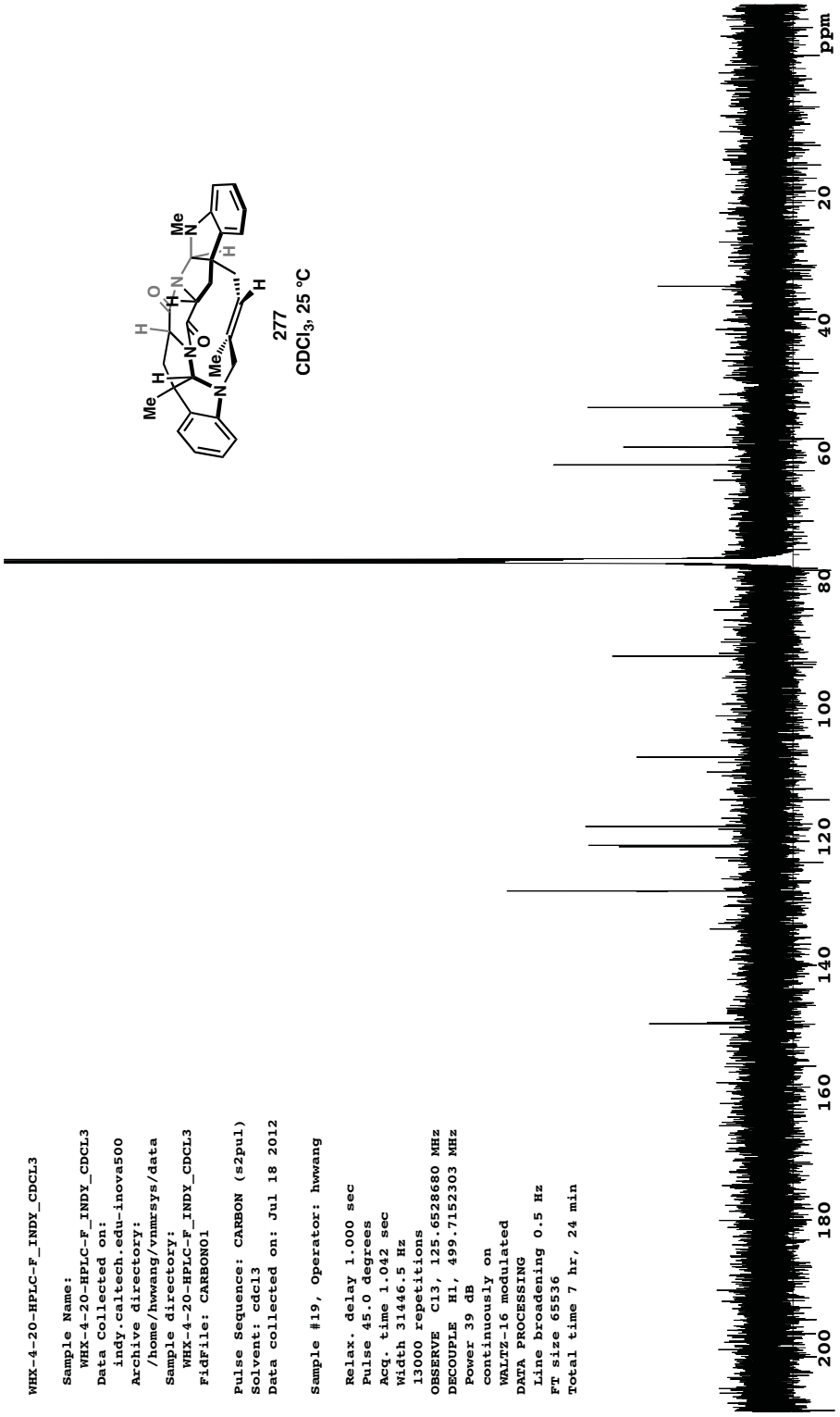

WHX-5-75-F1-re_INDY_CDCL3
Sample Name:
WHX-5-75-F1-re_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/acherney/vnmrsys/data
Sample directory:
WHX-5-75-F1-re_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 5 2013
Sample #19, Operator: acherney
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 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 58 min
276
ppm
200
180
160
140
120
100
80
60
40
20

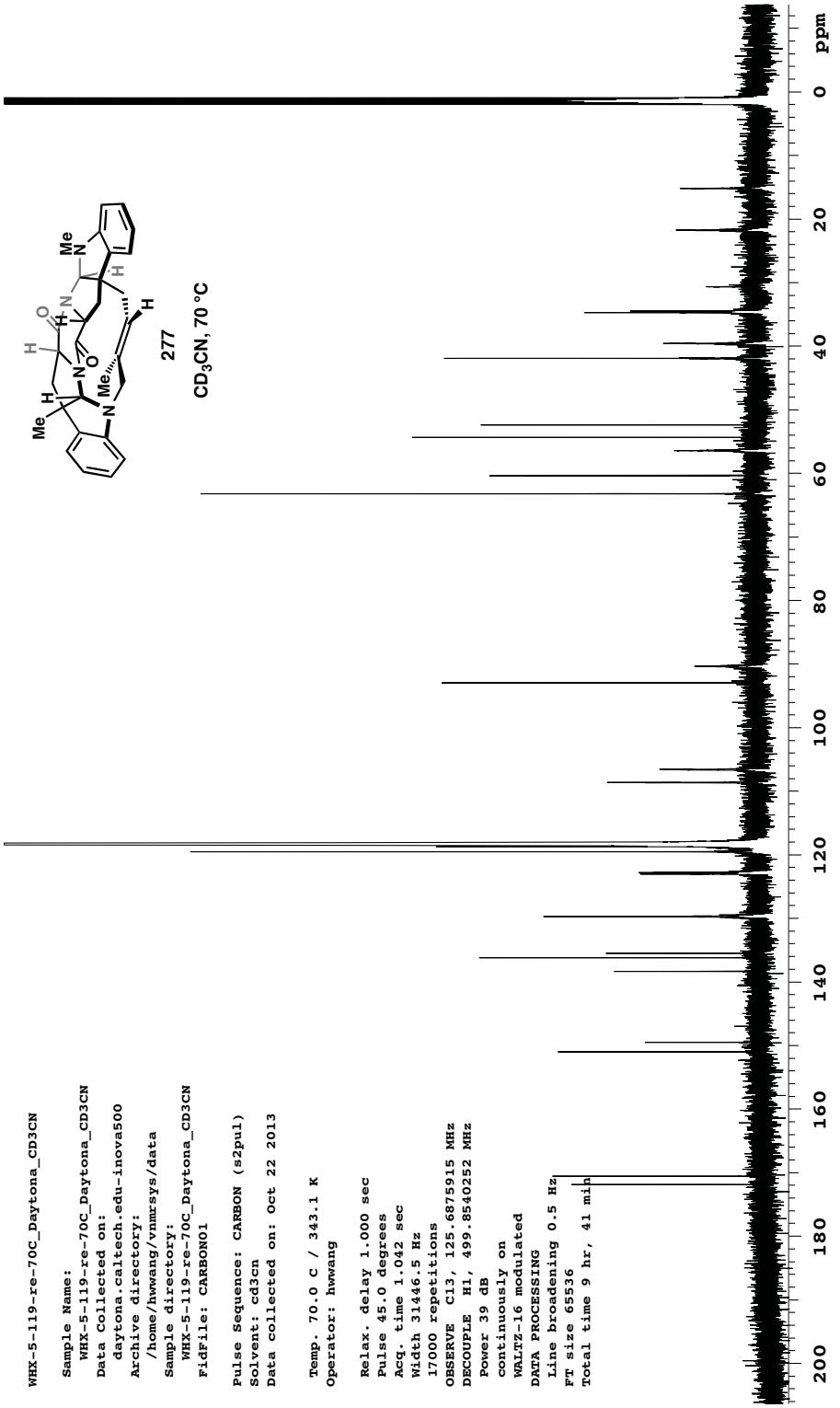

WHX-4-20-HPLC-F_INDY_CDCL3
Sample Name:
WHX-4-20-HPLC-F_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-4-20-HPLC-F_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 18 2012
Sample #19, Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
277
CDCl3, 25 °C
ppm
1.04
1.96
1.01
1.02
0.95
0.96
1.00
0.87
1.06
1.13
0.97
0.99
0.98
1.77
4.41
1.04
2.68
0.78
20.62
3.67

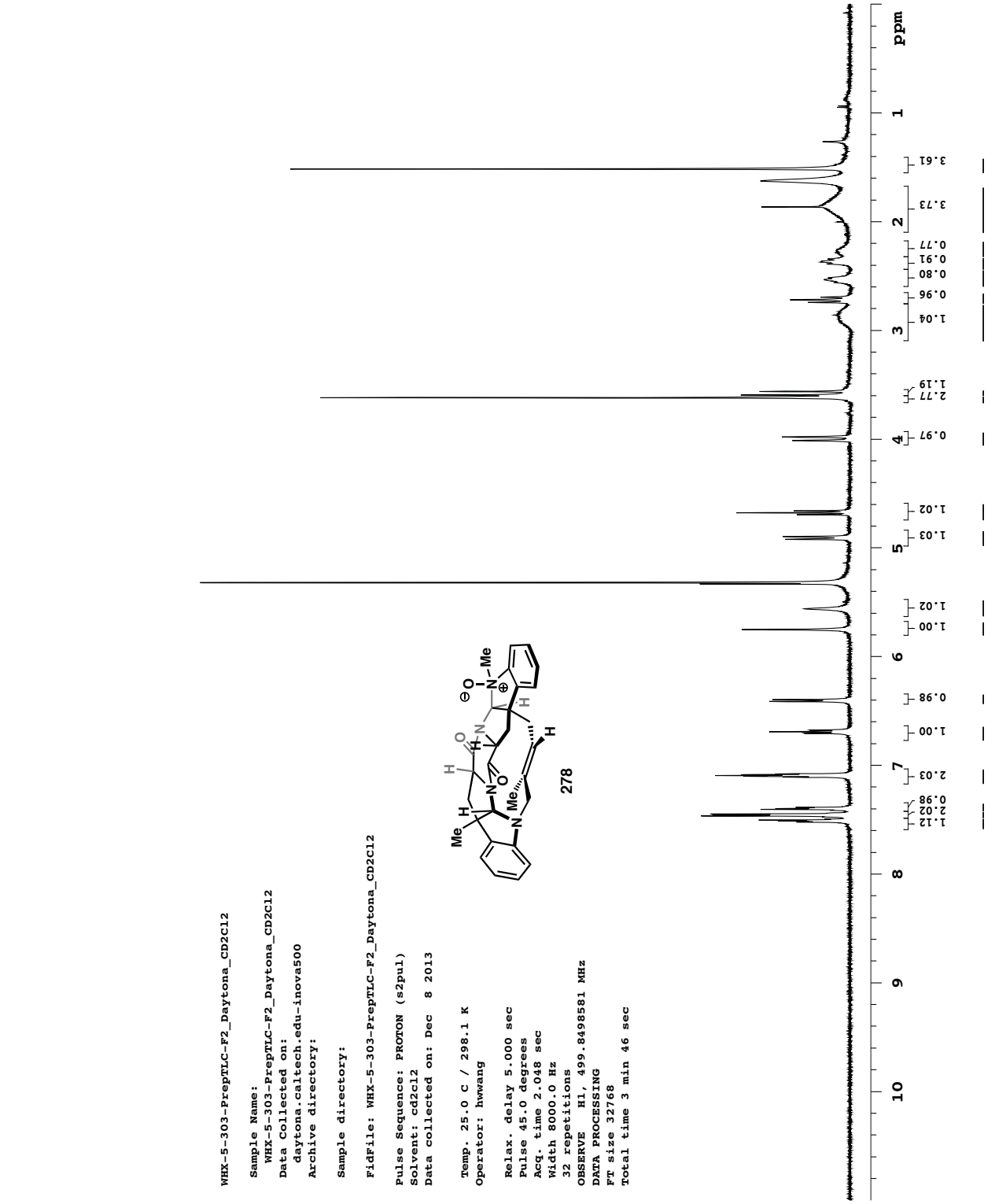

WHX-4-52-HPLC-F-Daytona-AcCN-70C
Sample Name:
WHX-4-52-HPLC-F-Daytona-AcCN-70C
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-4-52-HPLC-F-Daytona-AcCN-rt
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Aug 23 2012
Temp. 25.0 C / 298.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.8515475 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 24 sec
277
CD3CN, 25 °C
ppm
3.98
0.99
1.00
0.95
1.03
0.75
1.03
0.40
1.09
1.00
0.99
1.08
4.77
2.19
2.65
3.40

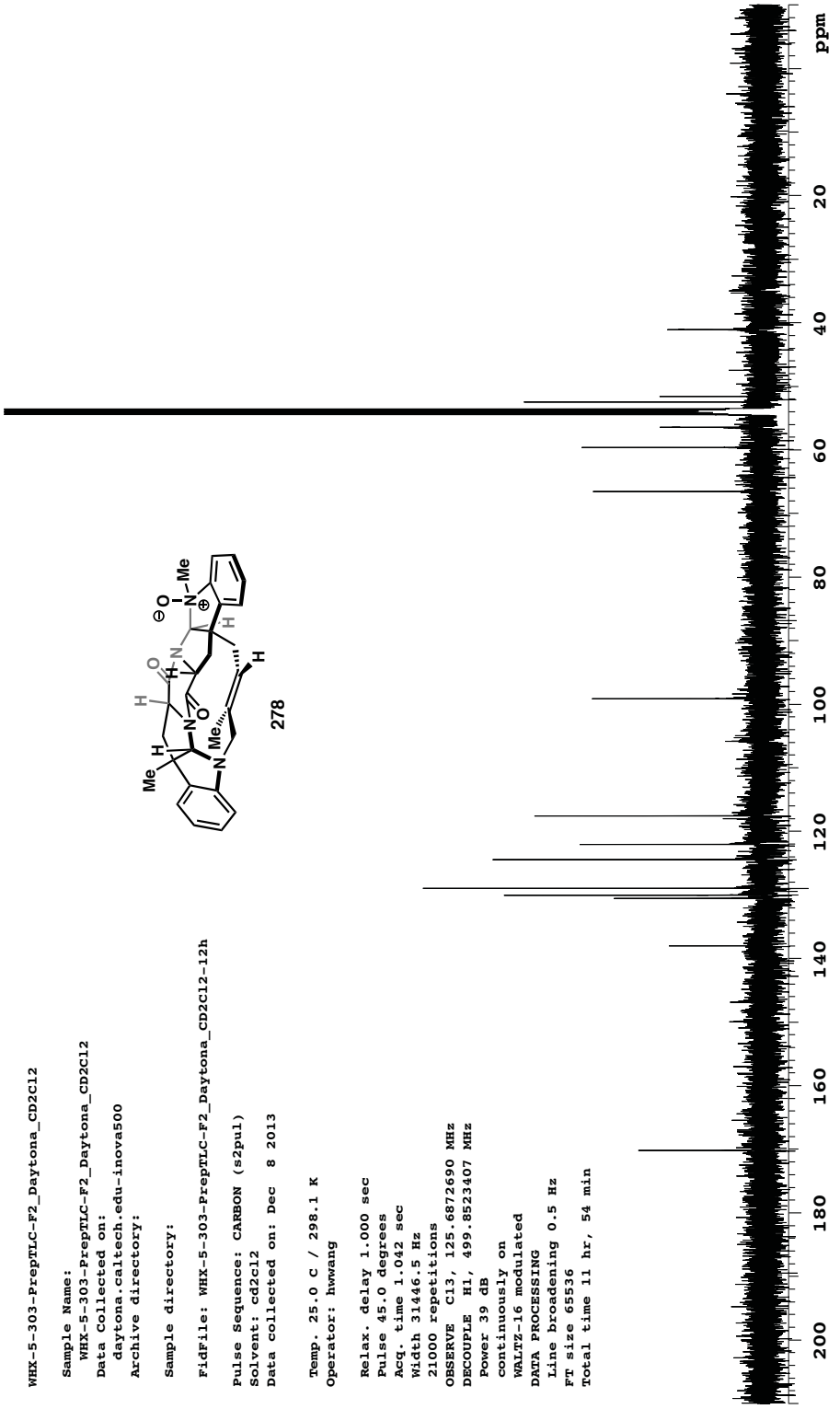

STANDARD 1H OBSERVE - profile
Sample Name:
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-4-20-HPLC-F-Re-m50C
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 21 2012
Temp. -51.0 C / 222.2 K
Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
31 repetitions
OBSERVE H1, 499.8488817 MHz
DATA PROCESSING
FT size 32768
Total time 17 min
277
CDCl3, –51 °C
ppm

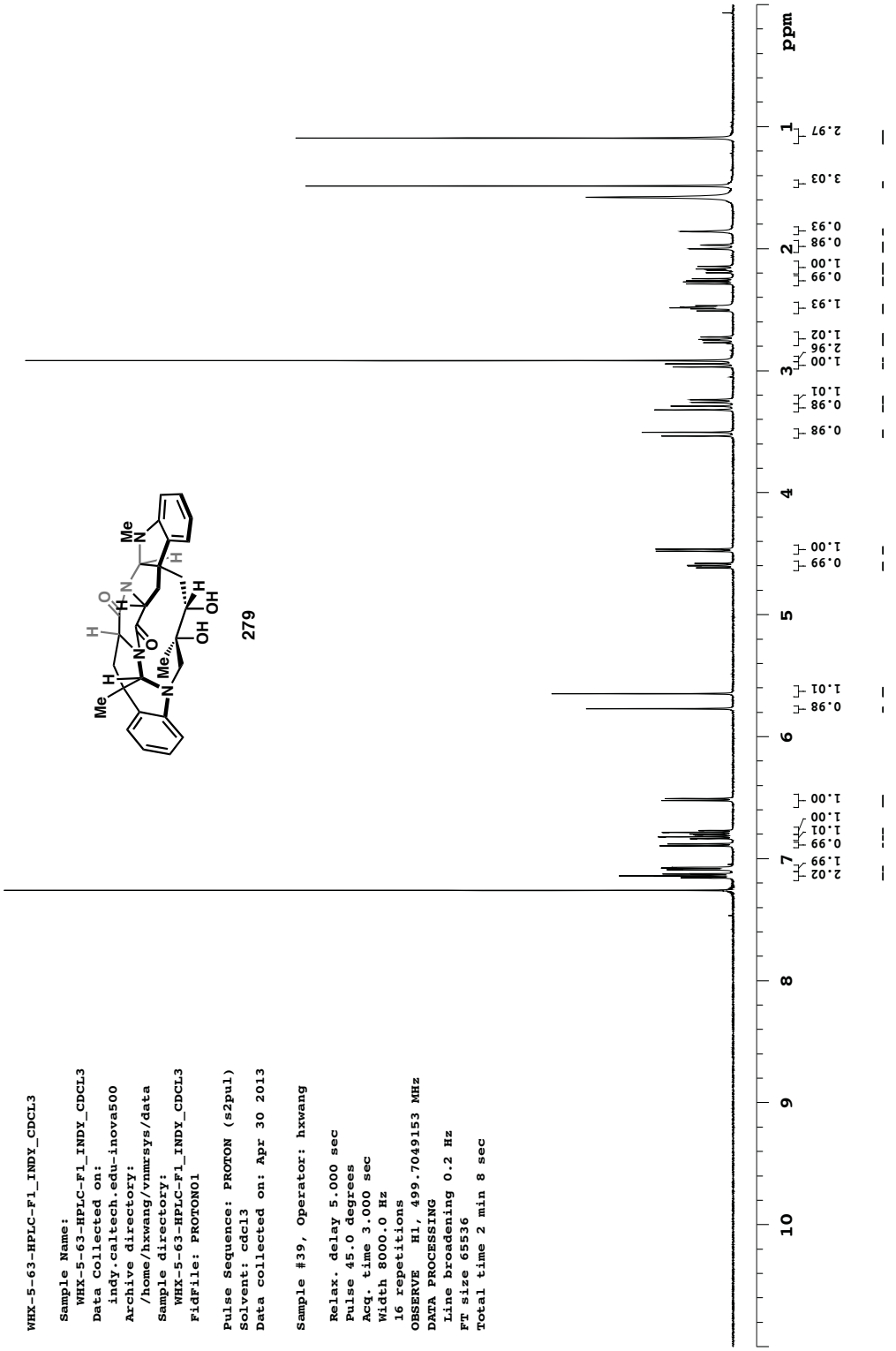

STANDARD 1H OBSERVE - profile
Sample Name:
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-119-re-70C
Pulse Sequence: PROTON (s2pul)
Solvent: acetone
Data collected on: Oct 22 2013
Temp. 70.0 C / 343.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.8515463 MHz
DATA PROCESSING
FT size 32768
Total time 50 min
277
CD3CN, 70 °C
ppm
4.00
1.02
0.97
1.00
1.02
0.99
0.95
1.02
1.00
0.97
1.00
1.09
1.14
4.03
1.12
2.13
1.17
3.41
3.29

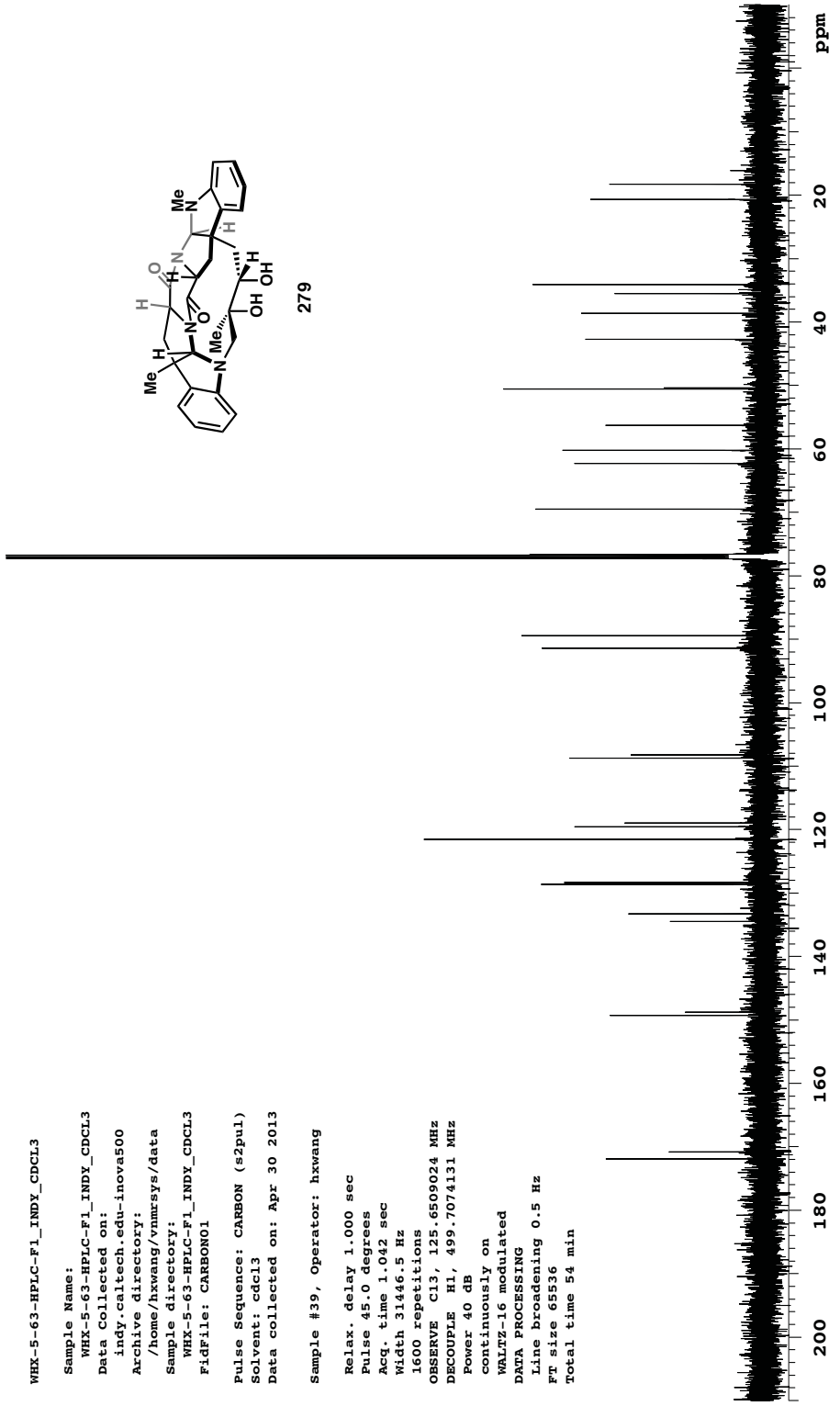

WHX-4-20-HPLC-F_INDY_CDCL3
Sample Name:
WHX-4-20-HPLC-F_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-4-20-HPLC-F_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 18 2012
Sample #19, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13000 repetitions
OBSERVE C13, 125.6528680 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 7 hr, 24 min
277
CDCl3, 25 °C
ppm
200
180
160
140
120
100
80
60
40
20

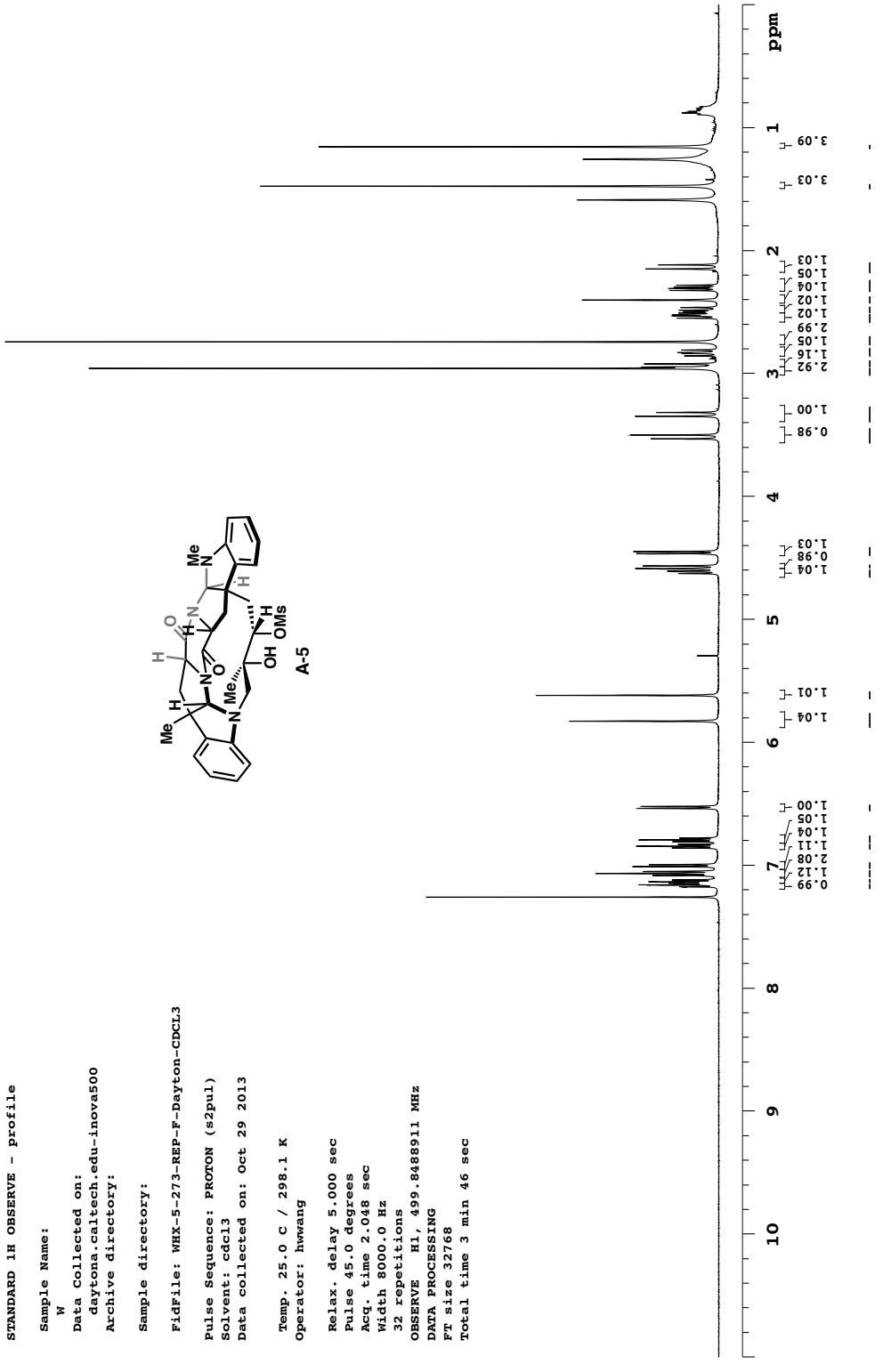

WHX-5-119-re-70C_Daytona_CD3CN
Sample Name:
WHX-5-119-re-70C_Daytona_CD3CN
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-5-119-re-70C_Daytona_CD3CN
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Oct 22 2013
Temp. 70.0 C / 343.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
17000 repetitions
OBSERVE C13, 125.6875915 MHz
DECOUPLE H1, 499.8540252 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 hr, 41 min
277
CD3CN, 70 °C
Me
N
H
O
N
H
N
O
Me
H
Me
N
H
H
200
180
160
140
120
100
80
60
40
20
0
ppm

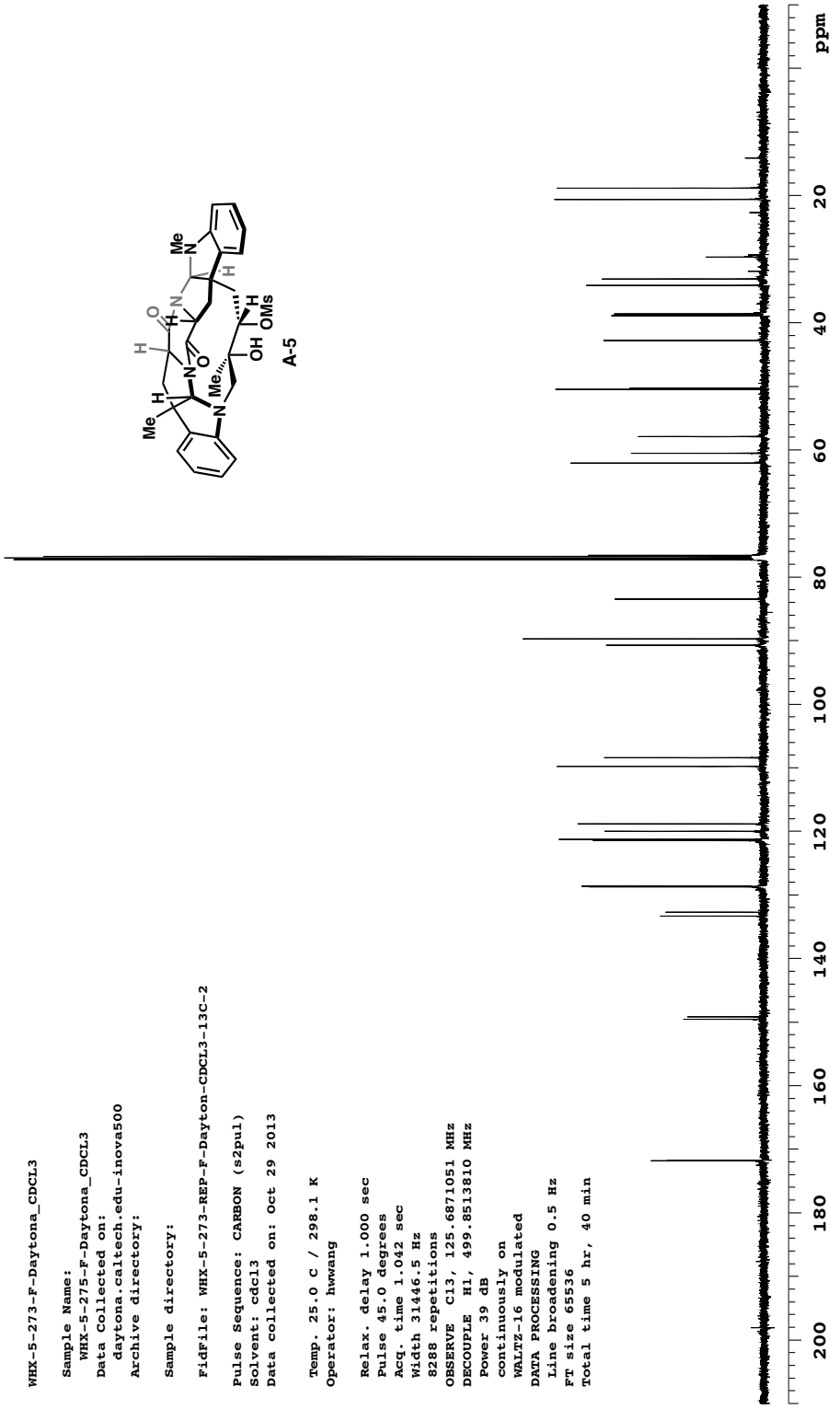

WHX-5-303-PrepTLC-F2_Daytona_CD2Cl2
Sample Name:
WHX-5-303-PrepTLC-F2_Daytona_CD2Cl2
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-303-PrepTLC-F2_Daytona_CD2Cl2
Pulse Sequence: PROTON (s2pul)
Solvent: cd2cl2
Data collected on: Dec 8 2013
Temp. 25.0 C / 298.1 K
Operator: hwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.8498581 MHz
DATA PROCESSING
FT size 32768
Total time 3 min 46 sec
278
ppm
10
9
8
7
6
5
4
3
2
1
1.12
2.02
0.98
2.03
1.00
0.98
1.00
1.02
1.03
1.02
0.97
2.77
1.19
1.04
0.96
0.80
0.91
0.77
3.73
3.61

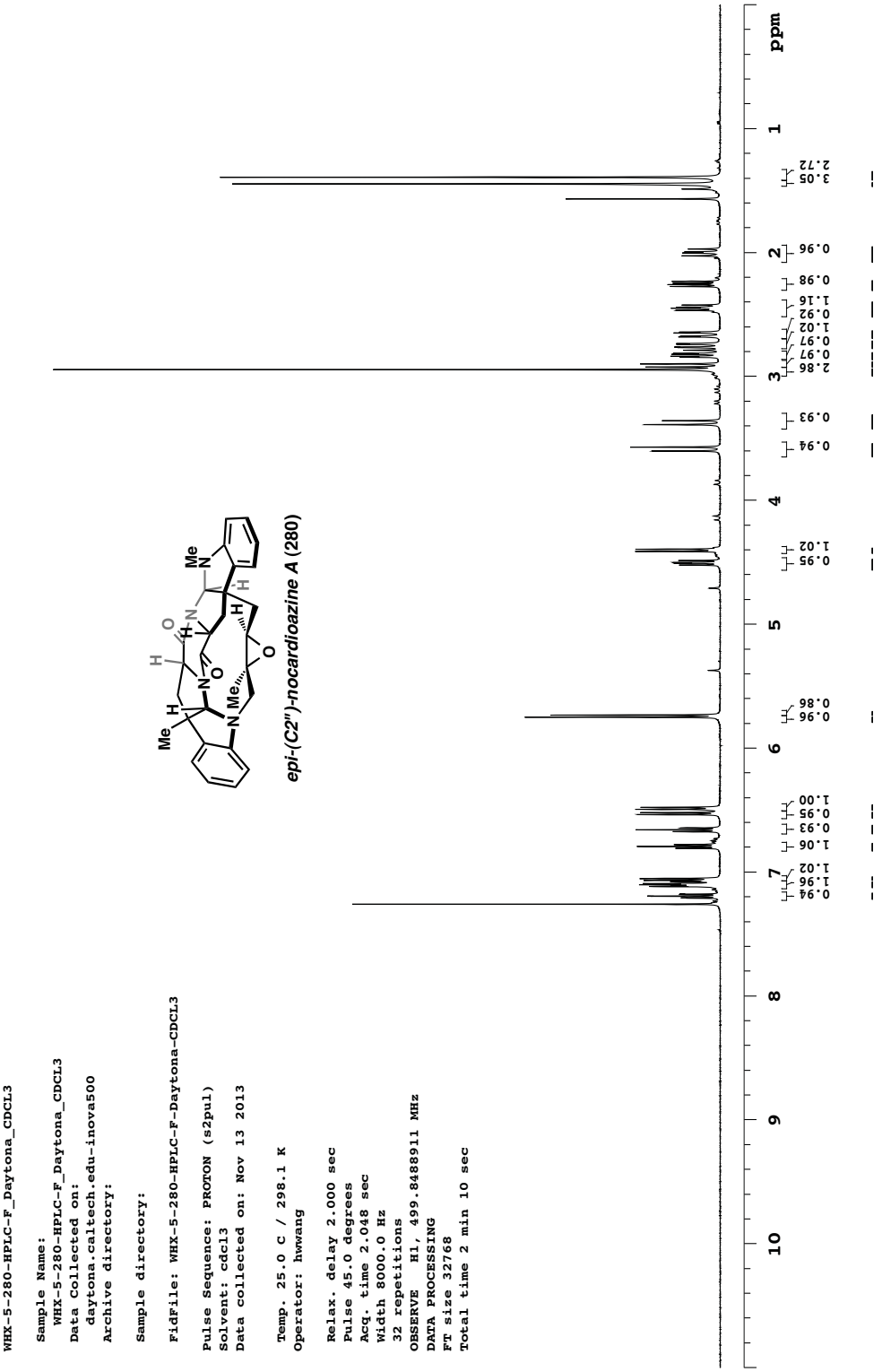

WHX-5-303-PrepTLC-F2_Daytona_CD2Cl2
Sample Name:
WHX-5-303-PrepTLC-F2_Daytona_CD2Cl2
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-303-PrepTLC-F2_Daytona_CD2Cl2-12h
Pulse Sequence: CARBON (s2pul)
Solvent: cd2cl2
Data collected on: Dec 8 2013
Temp. 25.0 C / 298.1 K
Operator: hwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
21000 repetitions
OBSERVE C13, 125.6872690 MHz
DECOUPLE H1, 499.8523407 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 11 hr, 54 min
278
200
180
160
140
120
100
80
60
40
20
ppm

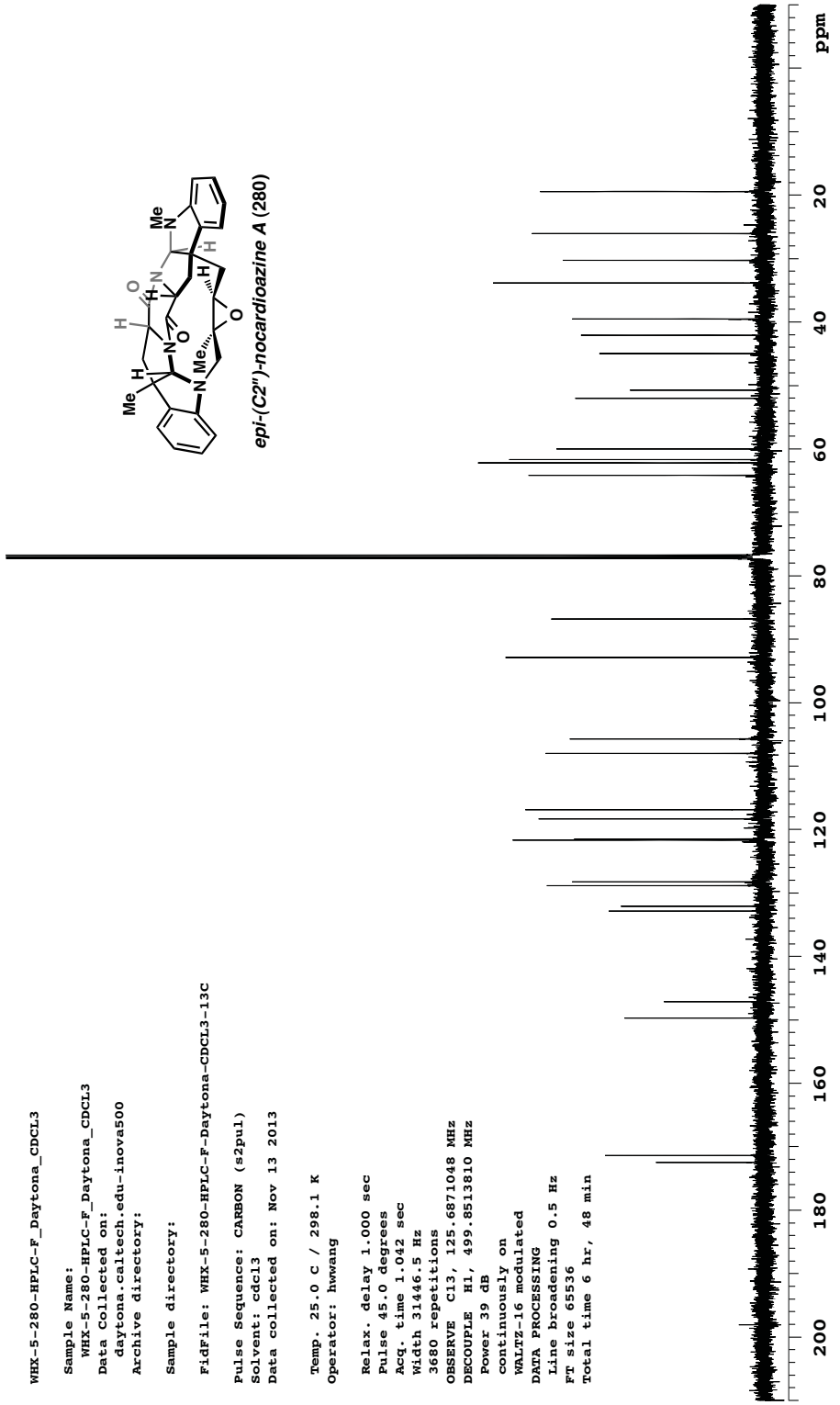

WHX-5-63-HPLC-F1_INDY_CDCL3
Sample Name:
WHX-5-63-HPLC-F1_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-63-HPLC-F1_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2013
Sample #39, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049153 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
279
ppm
10
9
8
7
6
5
4
3
2
1
2.02
1.99
0.99
1.01
1.00
1.00
0.98
1.01
0.98
1.00
0.99
1.00
1.00
2.96
1.02
1.93
0.99
1.00
0.98
0.93
3.03
2.97

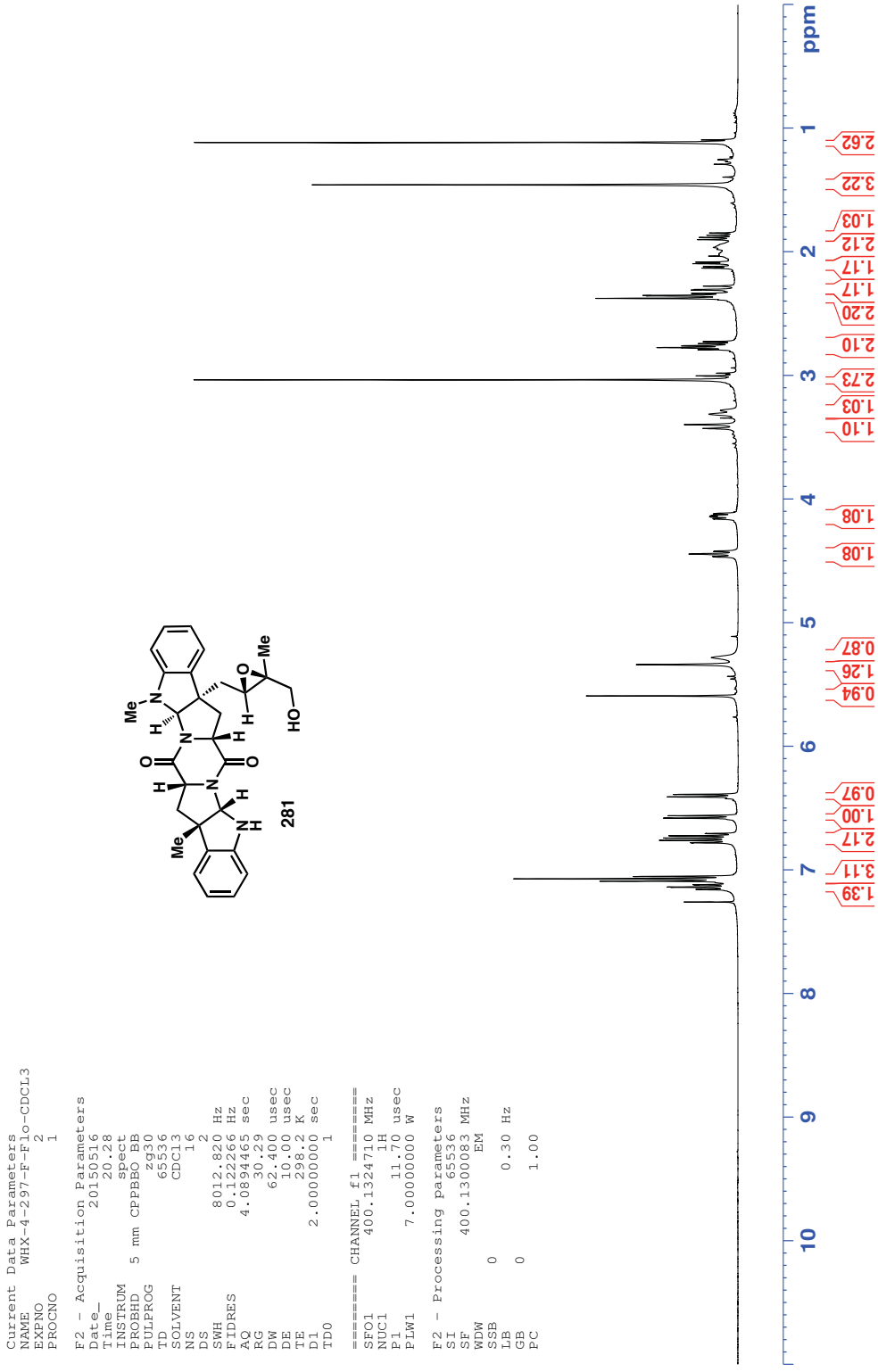

WHX-5-63-HPLC-F1_INDY_CDCL3
Sample Name:
WHX-5-63-HPLC-F1_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-63-HPLC-F1_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2013
Sample #39, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6509024 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 54 min
279
200
180
160
140
120
100
80
60
40
20
ppm

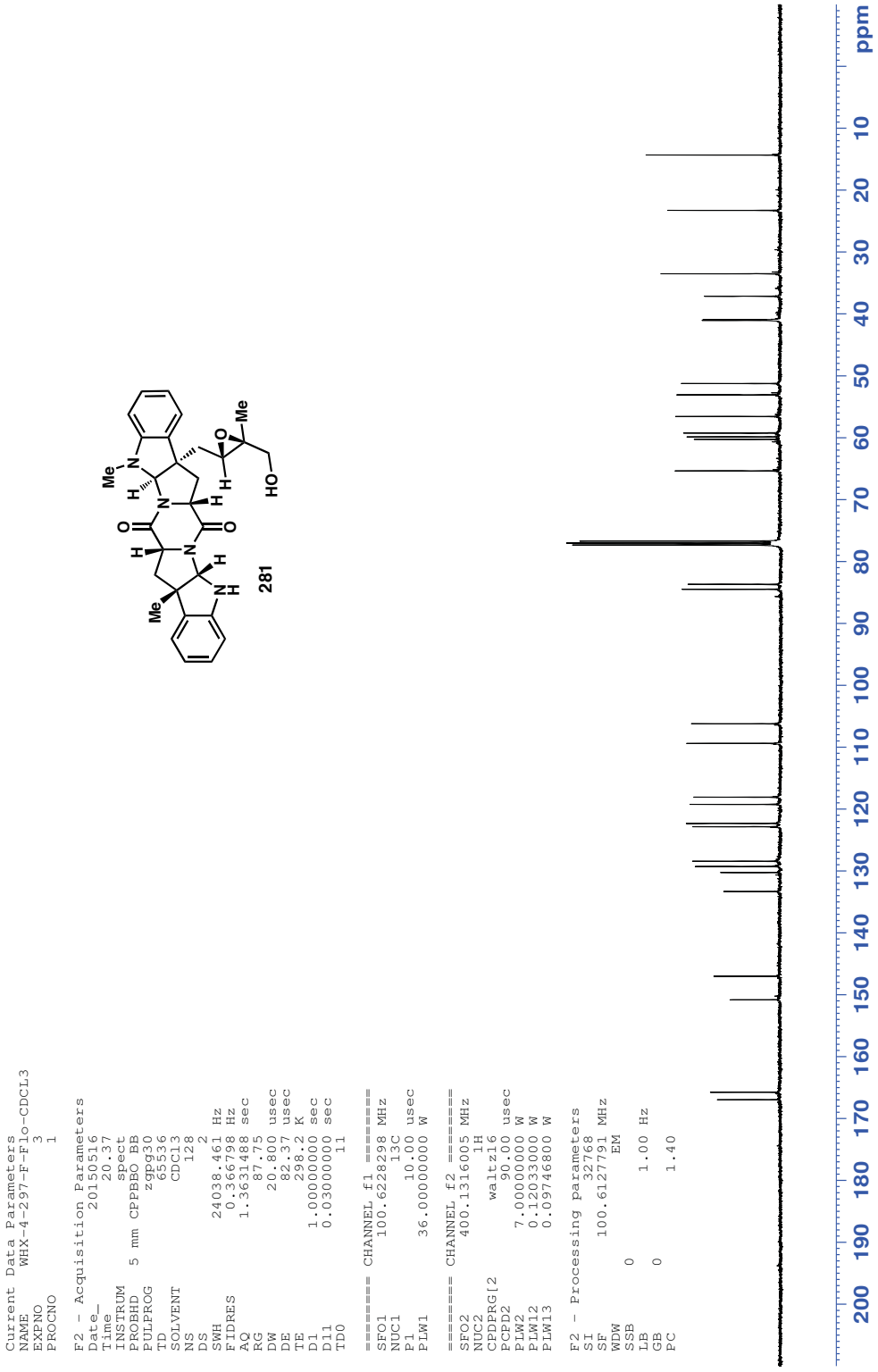

STANDARD 1H OBSERVE - profile
Sample Name:
W
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-273-REP-F-Dayton-CDCL3
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 29 2013
Temp. 25.0 C / 298.1 K
Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.8488911 MHz
DATA PROCESSING
FT size 32768
Total time 3 min 46 sec
A-5
ppm
3.09
3.03
2.92
1.16
1.05
2.99
1.02
1.02
1.04
1.05
1.03
0.98
1.00
1.04
0.98
1.03
1.01
1.04
0.99
1.12
2.08
1.11
1.04
1.05
1.00

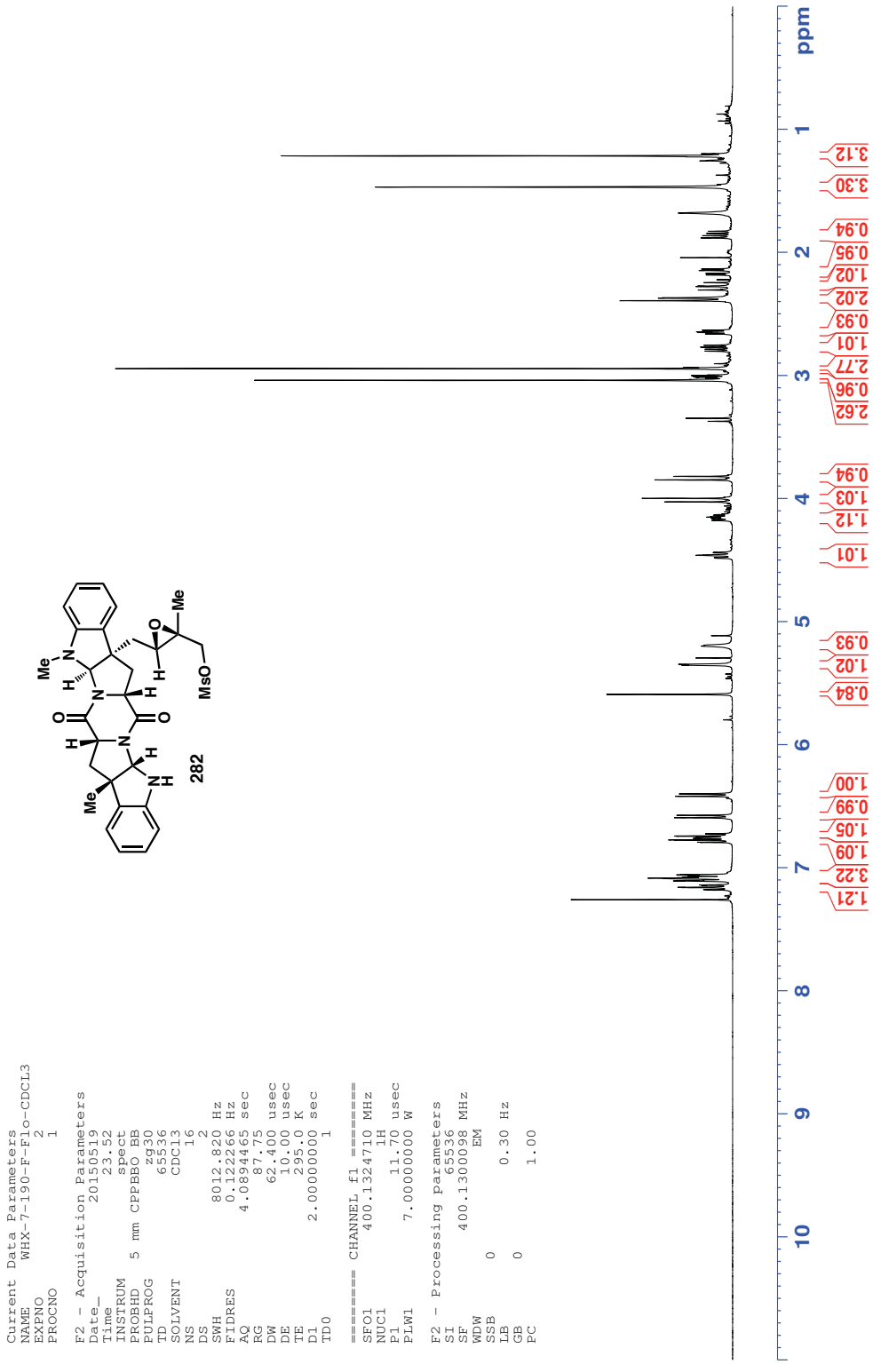

WHX-5-273-F-Daytona_CDCL3
Sample Name:
WHX-5-275-F-Daytona_CDCL3
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-273-REP-F-Dayton-CDCL3-13C-2
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 29 2013
Temp. 25.0 C / 298.1 K
Operator: hwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
8288 repetitions
OBSERVE C13, 125.6871051 MHz
DECOUPLE H1, 499.8513810 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5 hr, 40 min
A-5
200
180
160
140
120
100
80
60
40
20
ppm

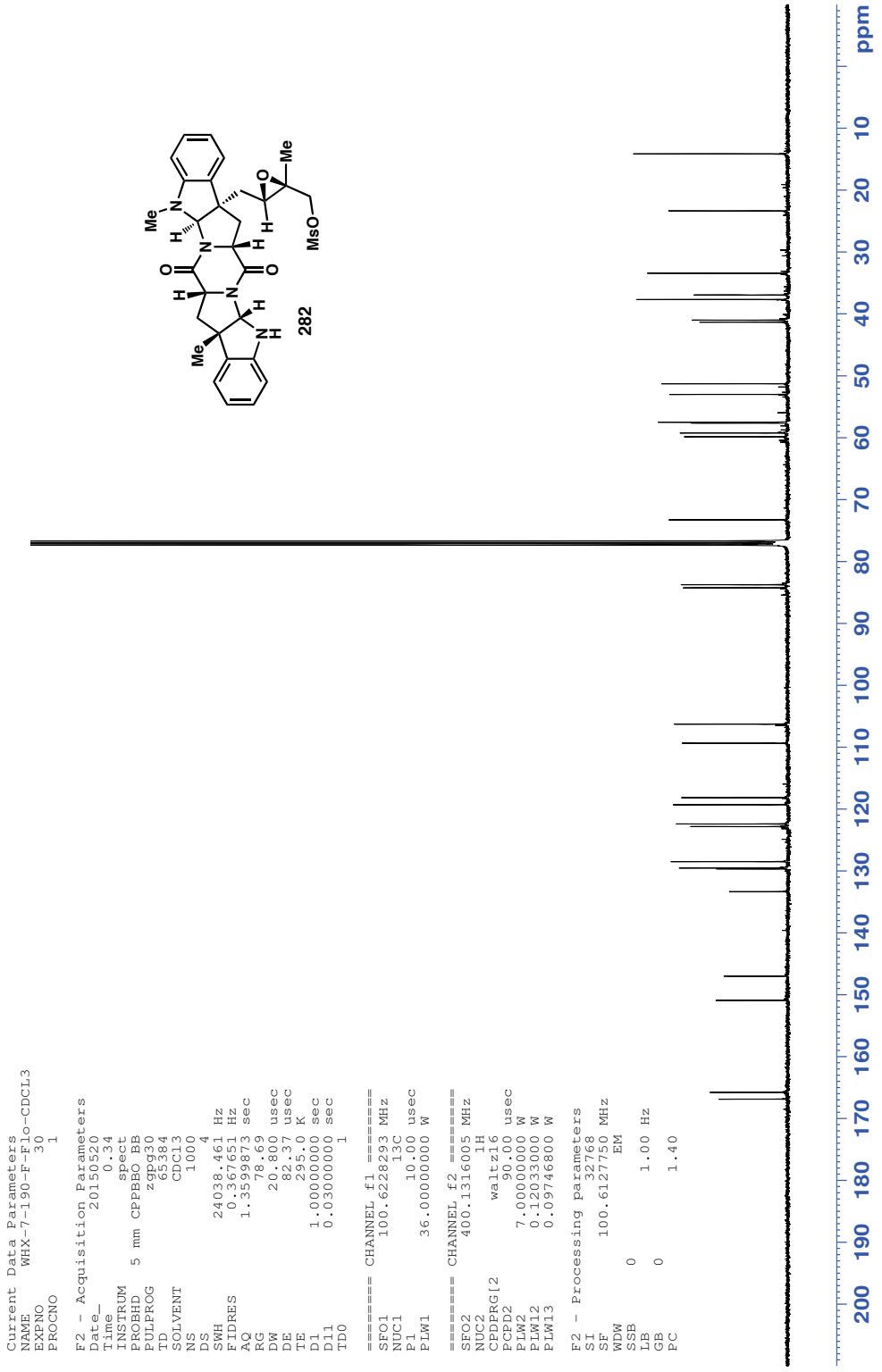

WHX-5-280-HPLC-F_Daytona_CDCL3
Sample Name:
WHX-5-280-HPLC-F_Daytona_CDCL3
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-280-HPLC-F-Daytona-CDCL3
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 13 2013
Temp. 25.0 C / 298.1 K
Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.8488911 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 10 sec
epi-(C2'')-nocardioazine A (280)
ppm
0.94
1.96
1.02
1.06
0.93
0.95
1.00
0.96
0.86
0.95
1.02
0.94
0.93
2.86
0.97
0.97
1.02
0.92
1.16
0.98
0.96
3.05
2.72

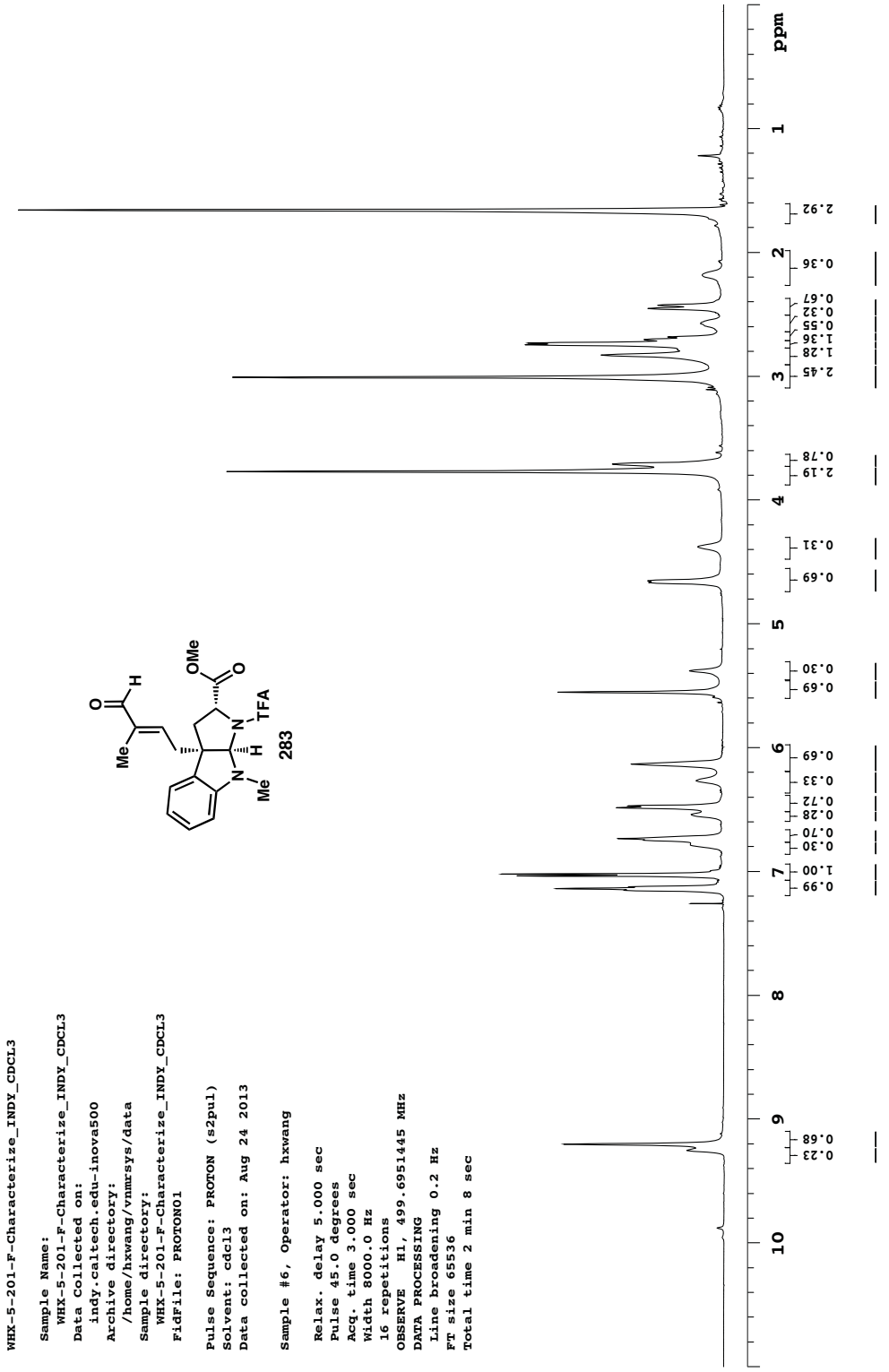

WHX-5-280-HPLC-F_Daytona_CDCL3
Sample Name:
WHX-5-280-HPLC-F_Daytona_CDCL3
Data Collected on:
daytona.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: WHX-5-280-HPLC-F-Daytona-CDCL3-13C
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 13 2013
Temp. 25.0 C / 298.1 K
Operator: hwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3680 repetitions
OBSERVE C13, 125.6871048 MHz
DECOUPLE H1, 499.8513810 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 6 hr, 48 min
epi-(C2'')-nocardioazine A (280)
ppm
200
180
160
140
120
100
80
60
40
20

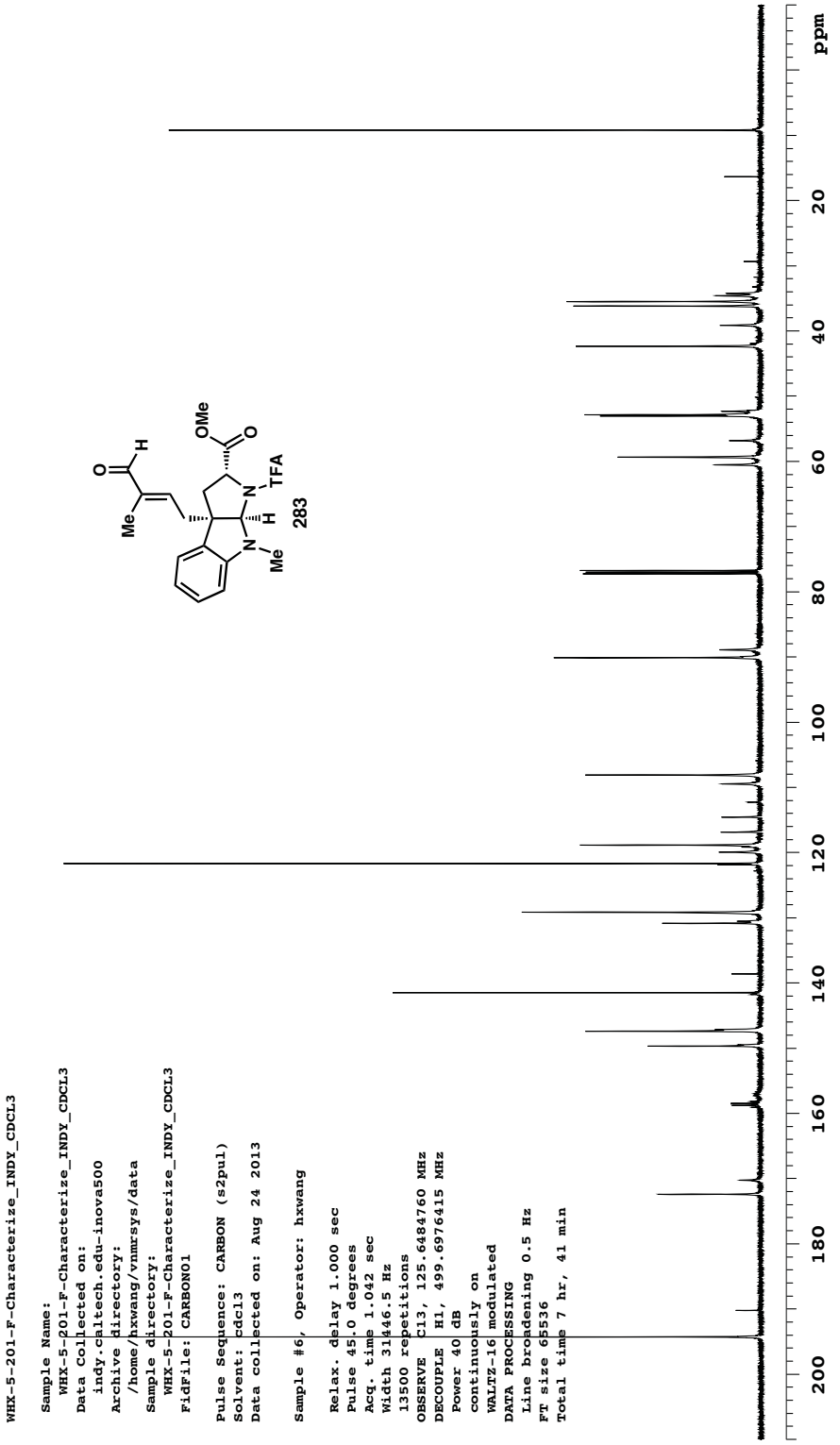

Current Data Parameters
NAME WHX-4-297-F-Flo-CDCL3
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150516
Time_ 20.28
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 30.29
DW 62.400 usec
DE 10.00 usec
TE 298.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300083 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
281
ppm
1 2 3 4 5 6 7 8 9 10
2.62
3.22
1.03
2.12
1.17
1.17
2.20
2.10
2.73
1.03
1.10
1.08
1.08
0.87
1.26
0.94
0.97
1.00
2.17
3.11
1.39

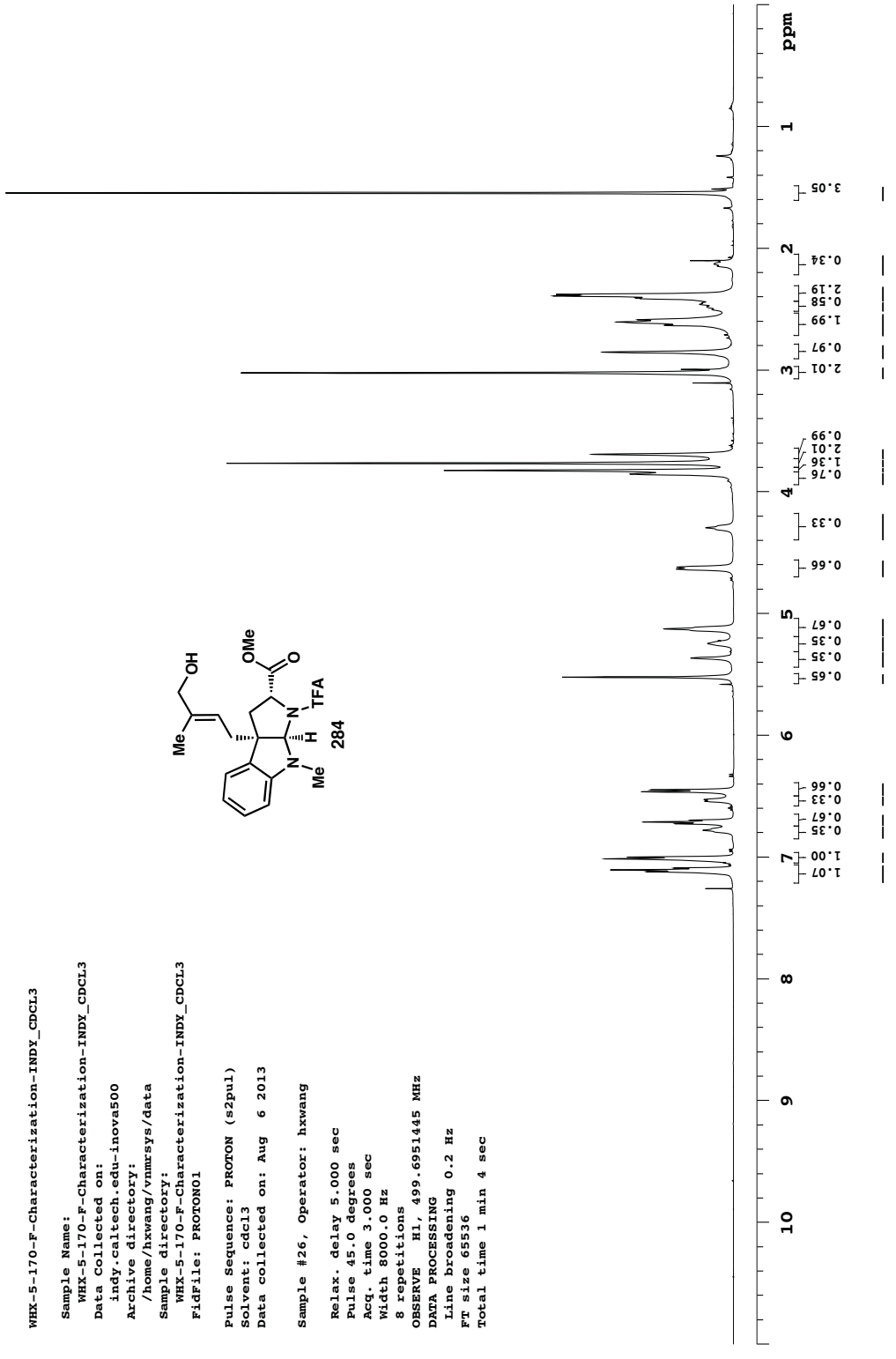

Current Data Parameters
NAME WHX-4-297-F-Flo-CDCL3
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150516
Time_ 20.37
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 128
DS 2
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 87.75
DW 20.800 usec
DE 82.37 usec
TE 298.2 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 11
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127791 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
Me
N
H
O
Me
HO
281
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

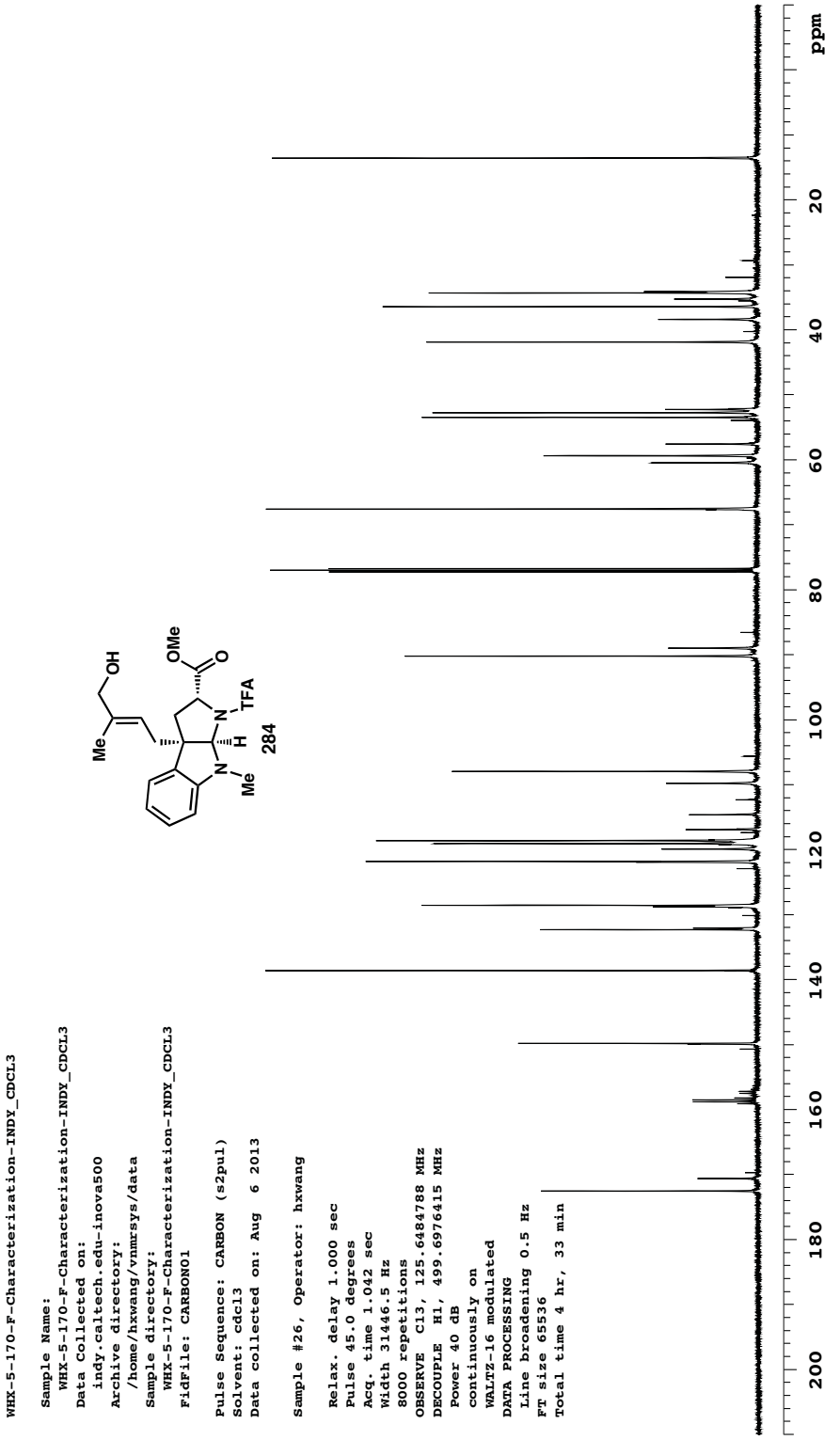

Current Data Parameters
NAME WHX-7-190-F-Flo-CDCl3
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150519
Time_ 23.52
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 87.75
DW 62.400 usec
DE 10.00 usec
TE 295.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300098 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Me
N
H
O
MsO
282
ppm
1.21
3.22
1.09
1.05
0.99
1.00
0.84
1.02
0.93
1.01
1.12
1.03
0.94
2.62
0.96
2.77
1.01
0.93
2.02
1.02
0.95
0.94
3.30
3.12

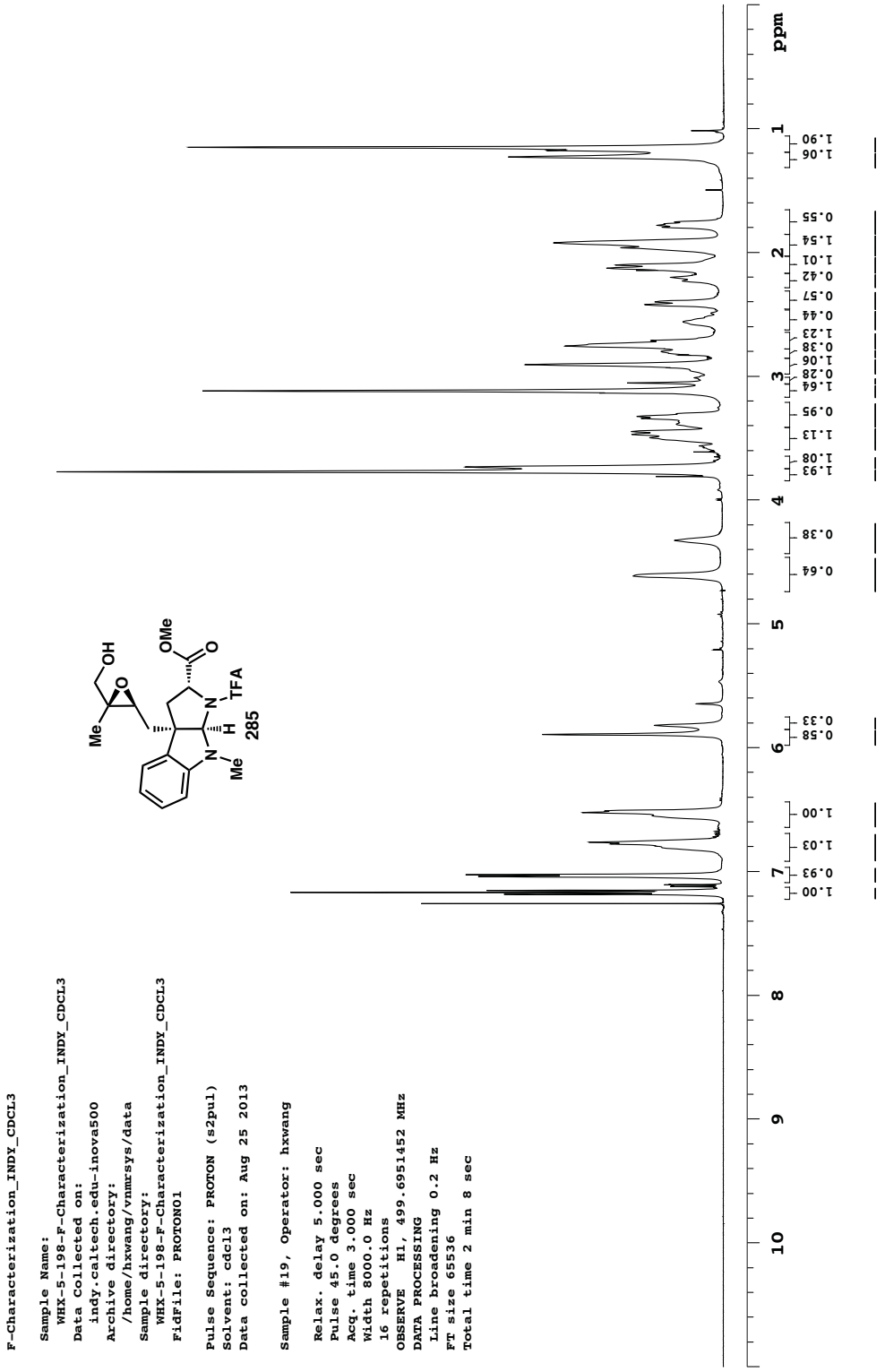

Current Data Parameters
NAME WHX-7-190-F-Flo-CDCl3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150520
Time_ 0.34
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 1000
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 78.69
DW 20.800 usec
DE 82.37 usec
TE 295.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127750 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
Me
N
H
O
Me
MsO
282
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

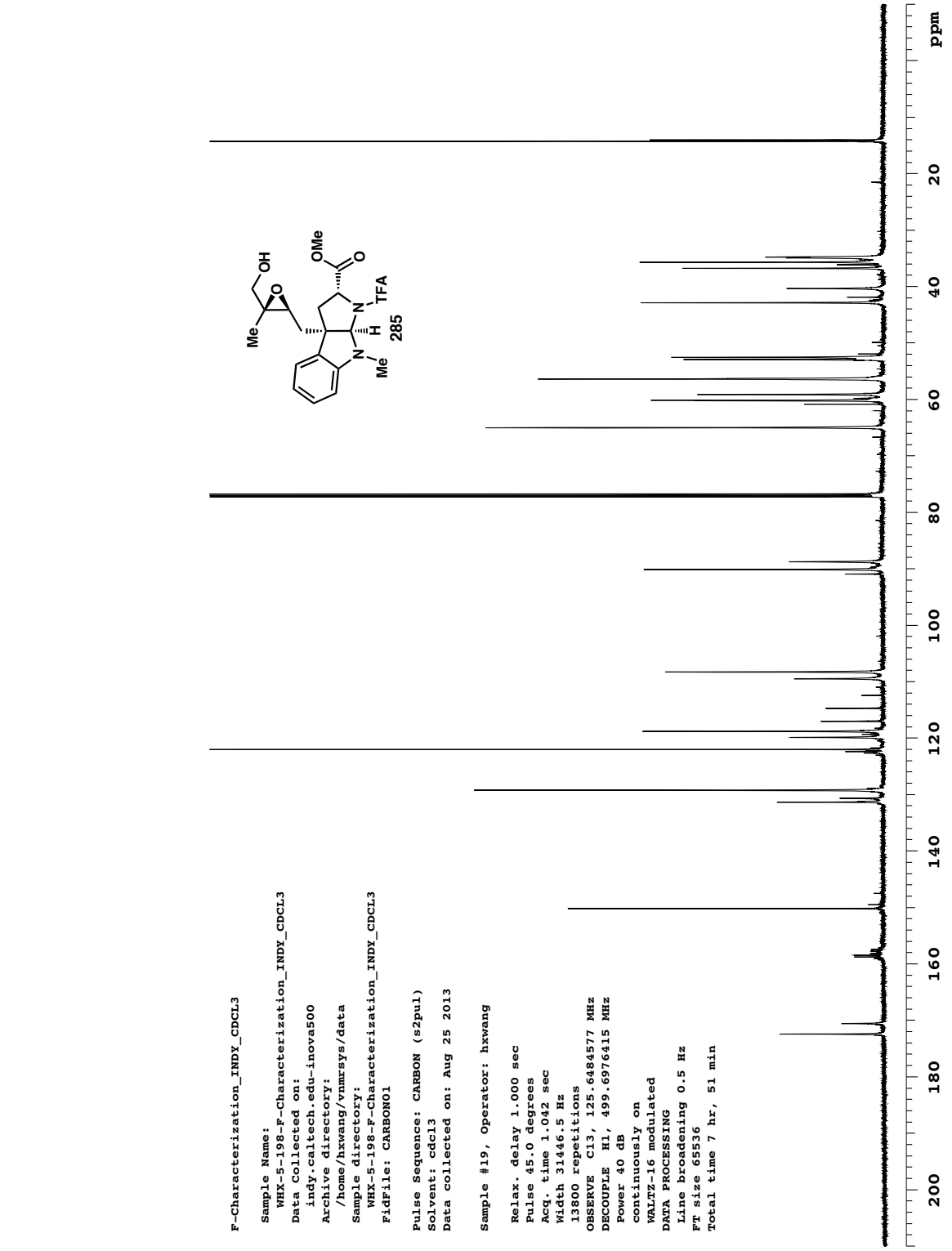

WHX-5-201-F-Characterize_INDY_CDCL3
Sample Name:
WHX-5-201-F-Characterize_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-201-F-Characterize_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 24 2013
Sample #6, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6951445 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
283
ppm

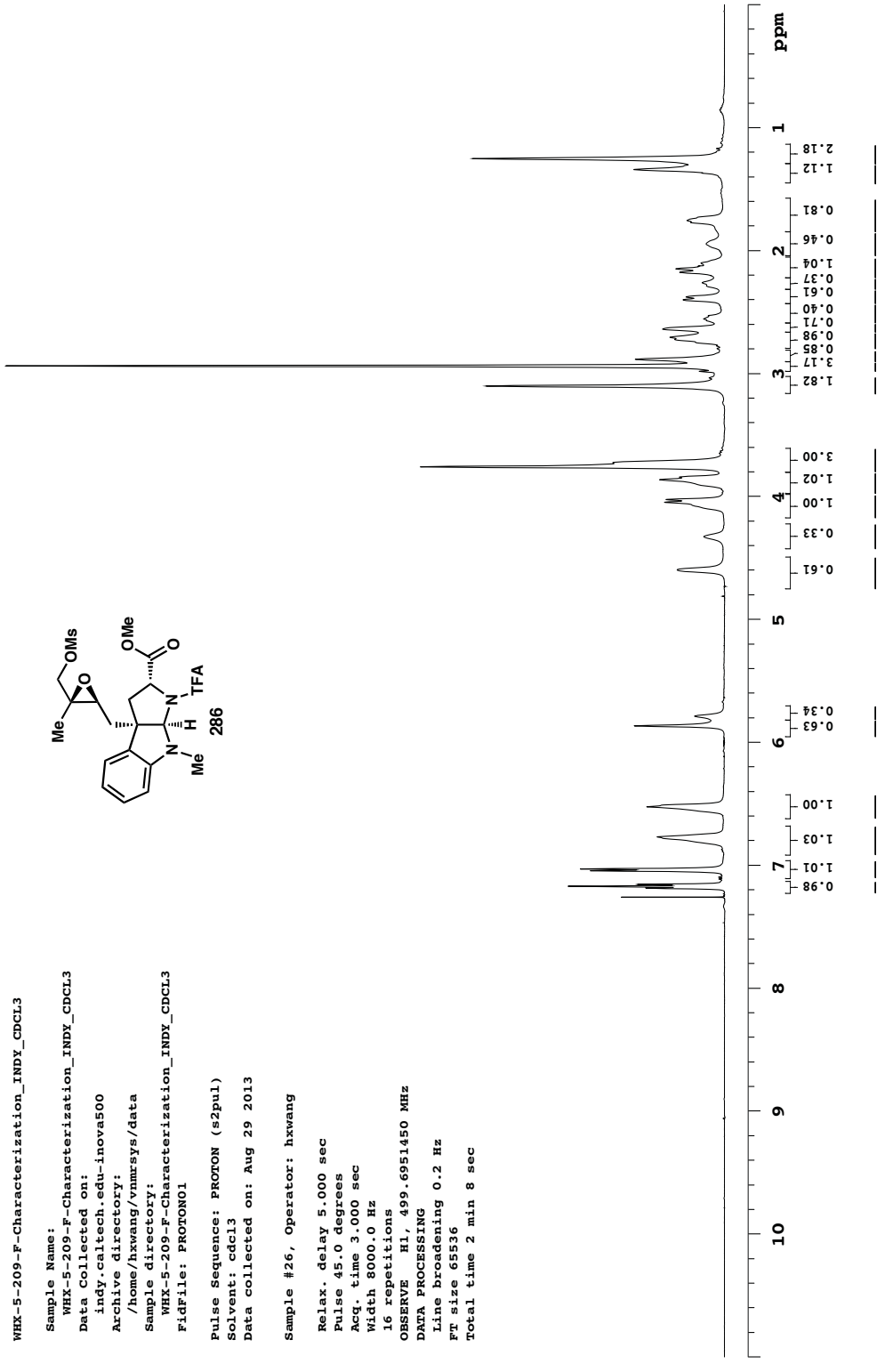

WHX-5-201-F-Characterize_INDY_CDCL3
Sample Name:
WHX-5-201-F-Characterize_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-201-F-Characterize_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 24 2013
Sample #6, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13500 repetitions
OBSERVE C13, 125.6484760 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 7 hr, 41 min
O
H
Me
OMe
O
N
H
TFA
N
Me
283
200
180
160
140
120
100
80
60
40
20
ppm

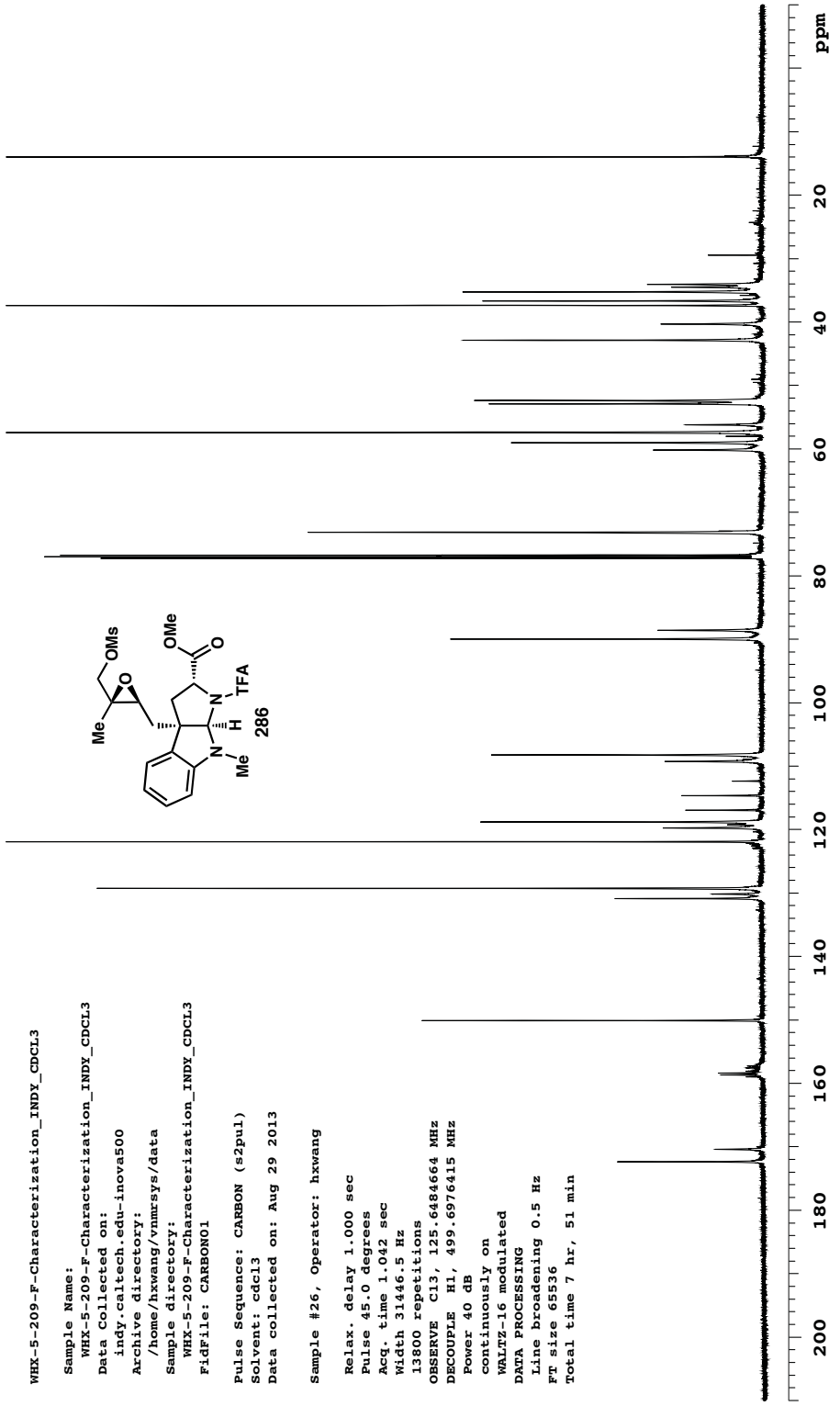

WHX-5-170-F-Characterization-INDY_CDCL3
Sample Name:
WHX-5-170-F-Characterization-INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-170-F-Characterization-INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 6 2013
Sample #26, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6951445 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 4 sec
OH
OMe
O
N
TFA
H
Me
N
Me
284
ppm
10
9
8
7
6
5
4
3
2
1
1.07
1.00
0.35
0.67
0.33
0.66
0.65
0.35
0.35
0.67
0.66
0.33
0.76
1.36
2.01
0.99
2.01
0.97
1.99
0.58
2.19
0.34
3.05

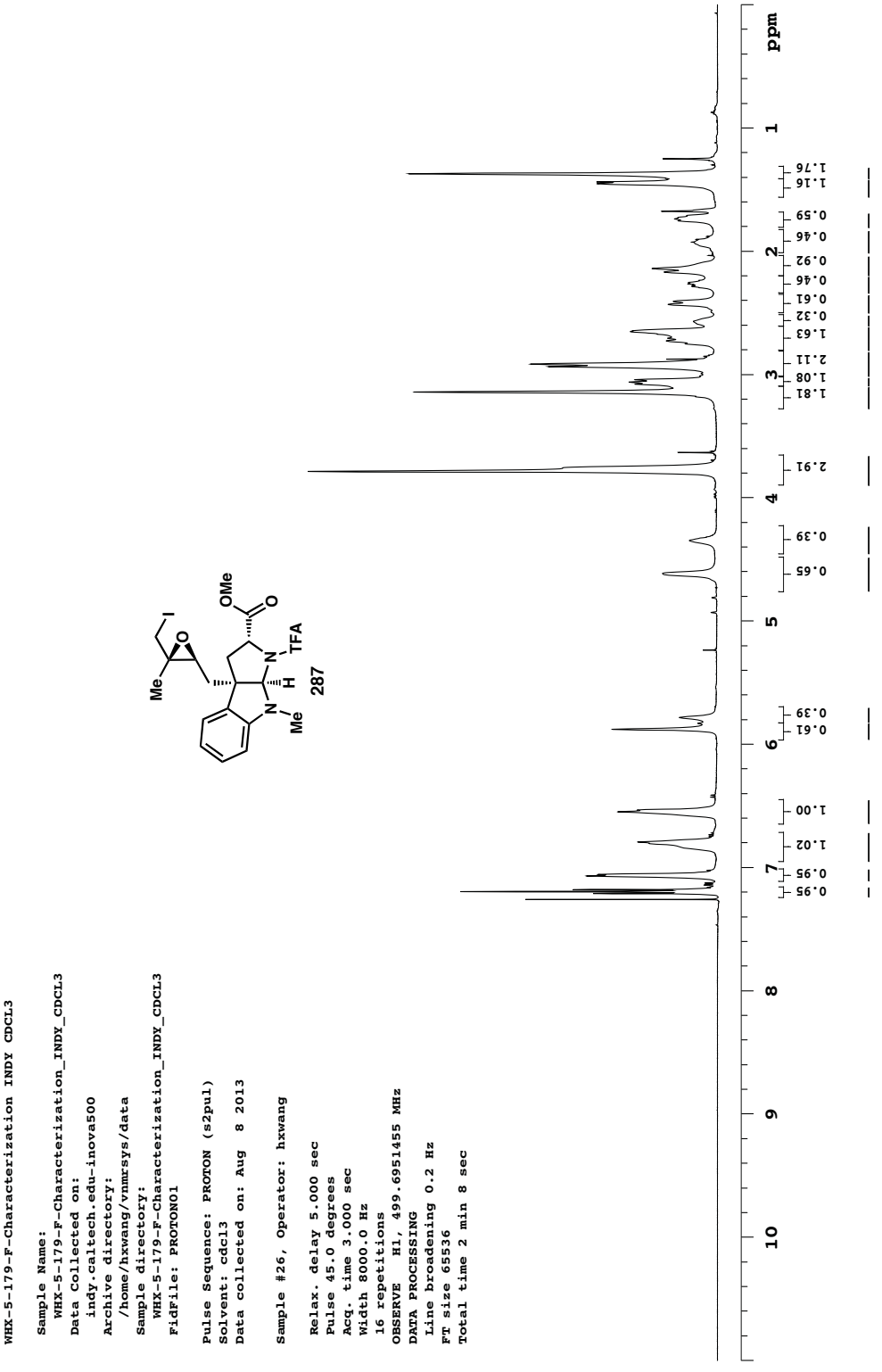

WHX-5-170-F-Characterization-INDY_CDCL3
Sample Name:
WHX-5-170-F-Characterization-INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-170-F-Characterization-INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 6 2013
Sample #26, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
8000 repetitions
OBSERVE C13, 125.6484788 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 4 hr, 33 min
OH
OMe
O
N
TFA
H
Me
N
Me
284
200
180
160
140
120
100
80
60
40
20
ppm

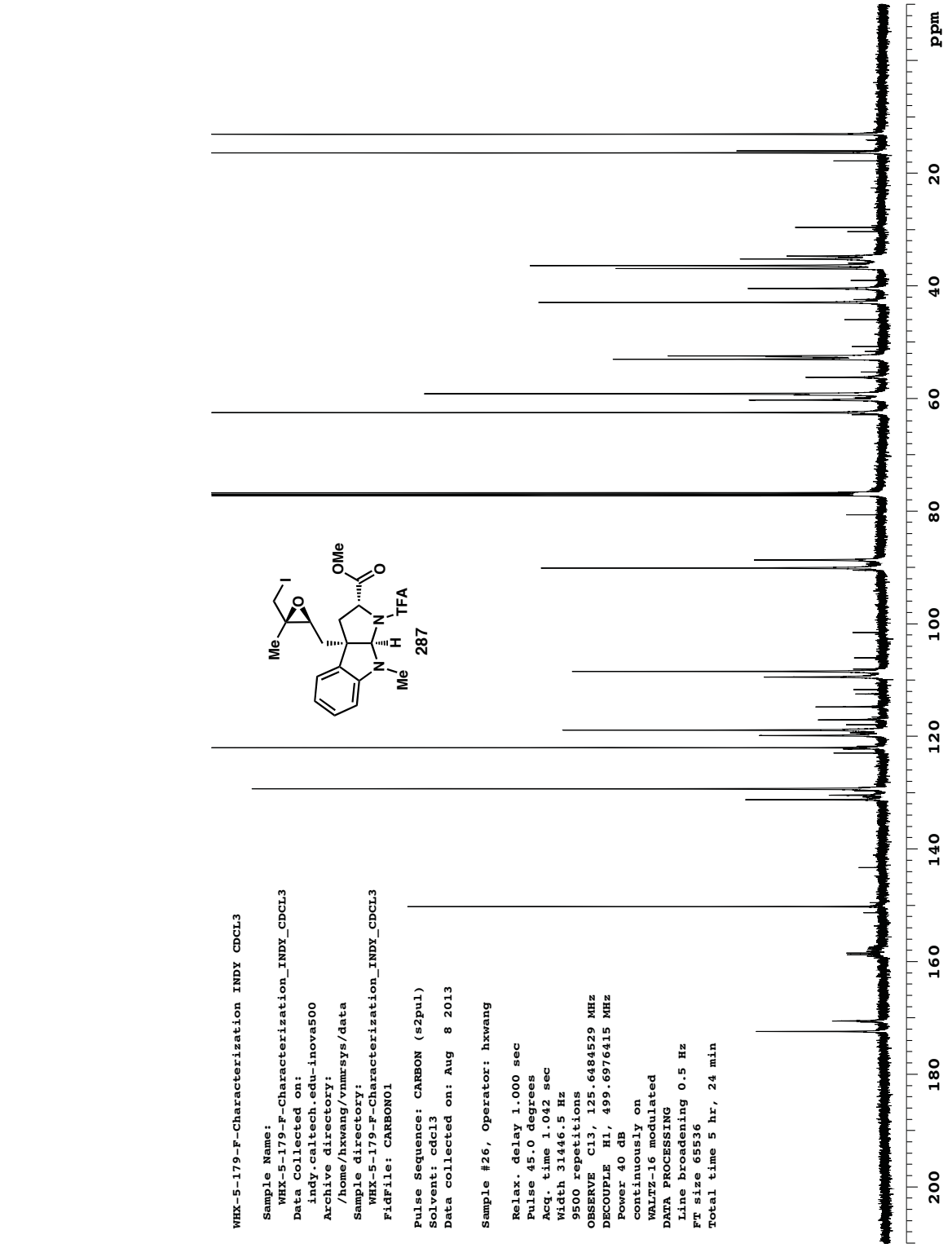

F-Characterization_INDY_CDCL3
Sample Name:
WHX-5-198-F-Characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-198-F-Characterization_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 25 2013
Sample #19, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6951452 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
OH
O
Me
OMe
O
N
H
TFA
N
Me
285
ppm
1.00
0.93
1.03
1.00
0.58
0.33
0.64
0.38
1.93
1.08
1.13
0.95
1.64
0.28
1.06
0.38
1.23
0.44
0.57
0.42
1.01
1.54
0.55
1.06
1.90

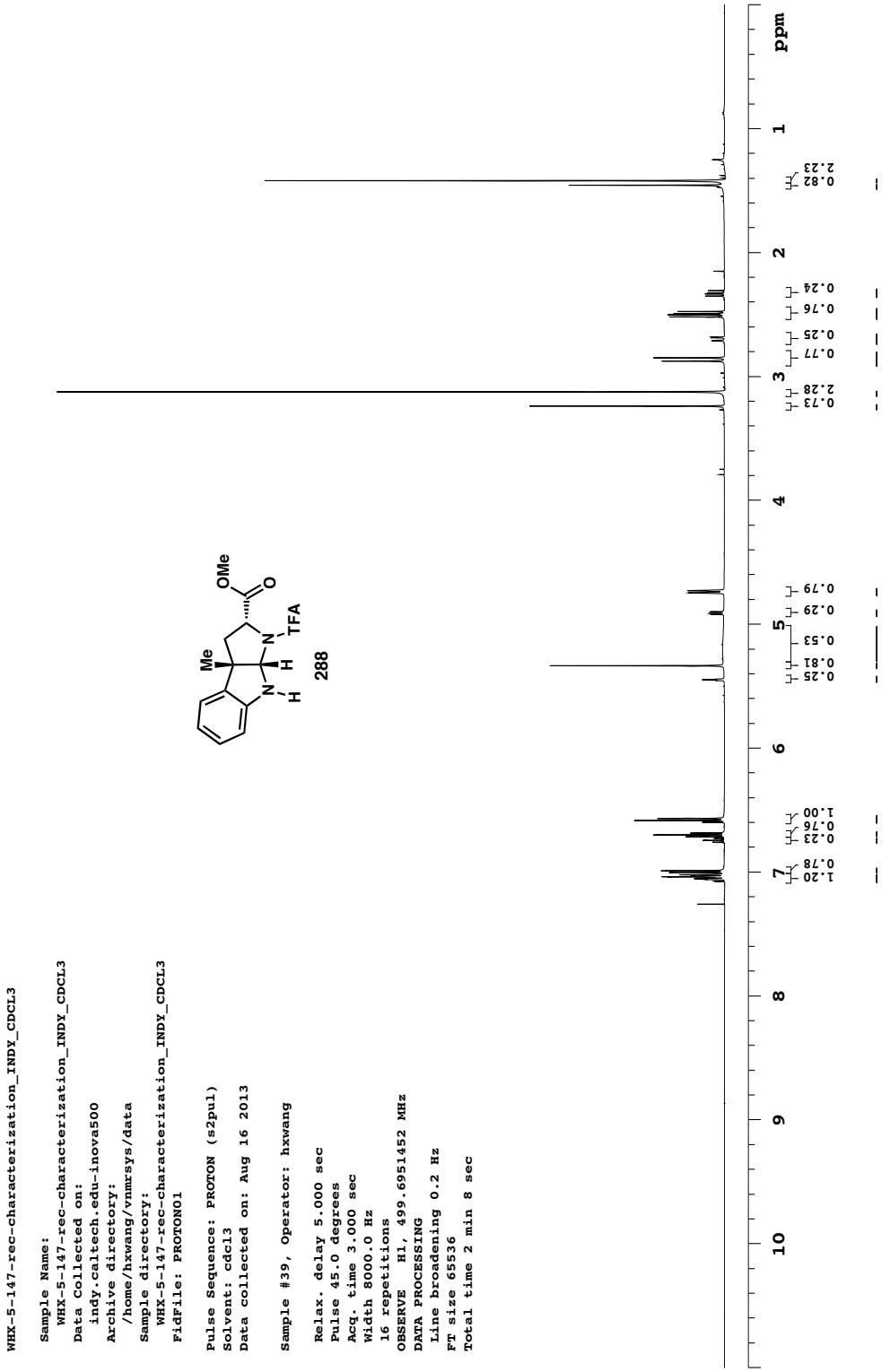

F-Characterization_INDY_CDCL3
Sample Name:
WHX-5-198-F-Characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-198-F-Characterization_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 25 2013
Sample #19, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13800 repetitions
OBSERVE C13, 125.6484577 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 7 hr, 51 min
OH
Me
O
OMe
O
N
H
TFA
N
Me
285
200
180
160
140
120
100
80
60
40
20
ppm

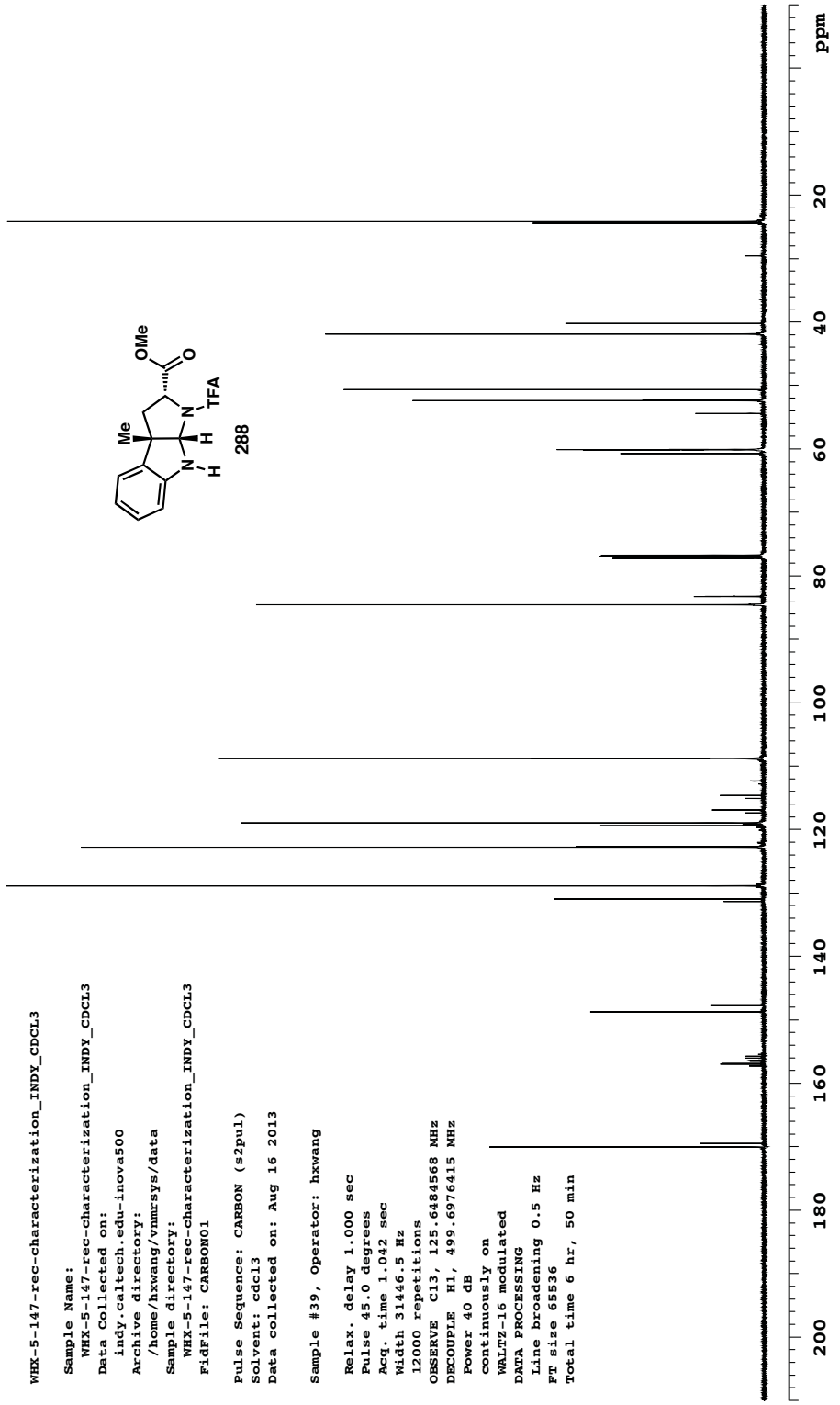

WHX-5-209-F-Characterization_INDY_CDCL3
Sample Name:
WHX-5-209-F-Characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-209-F-Characterization_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 29 2013
Sample #26, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6951450 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
OMs
O
Me
OMe
O
N
H
N
Me
TFA
286
ppm
10
9
8
7
6
5
4
3
2
1
0.98
1.01
1.03
1.00
0.63
0.34
0.61
0.33
1.00
1.02
3.00
1.82
3.17
0.85
0.98
0.71
0.40
0.61
0.37
1.04
0.46
0.81
1.12
2.18

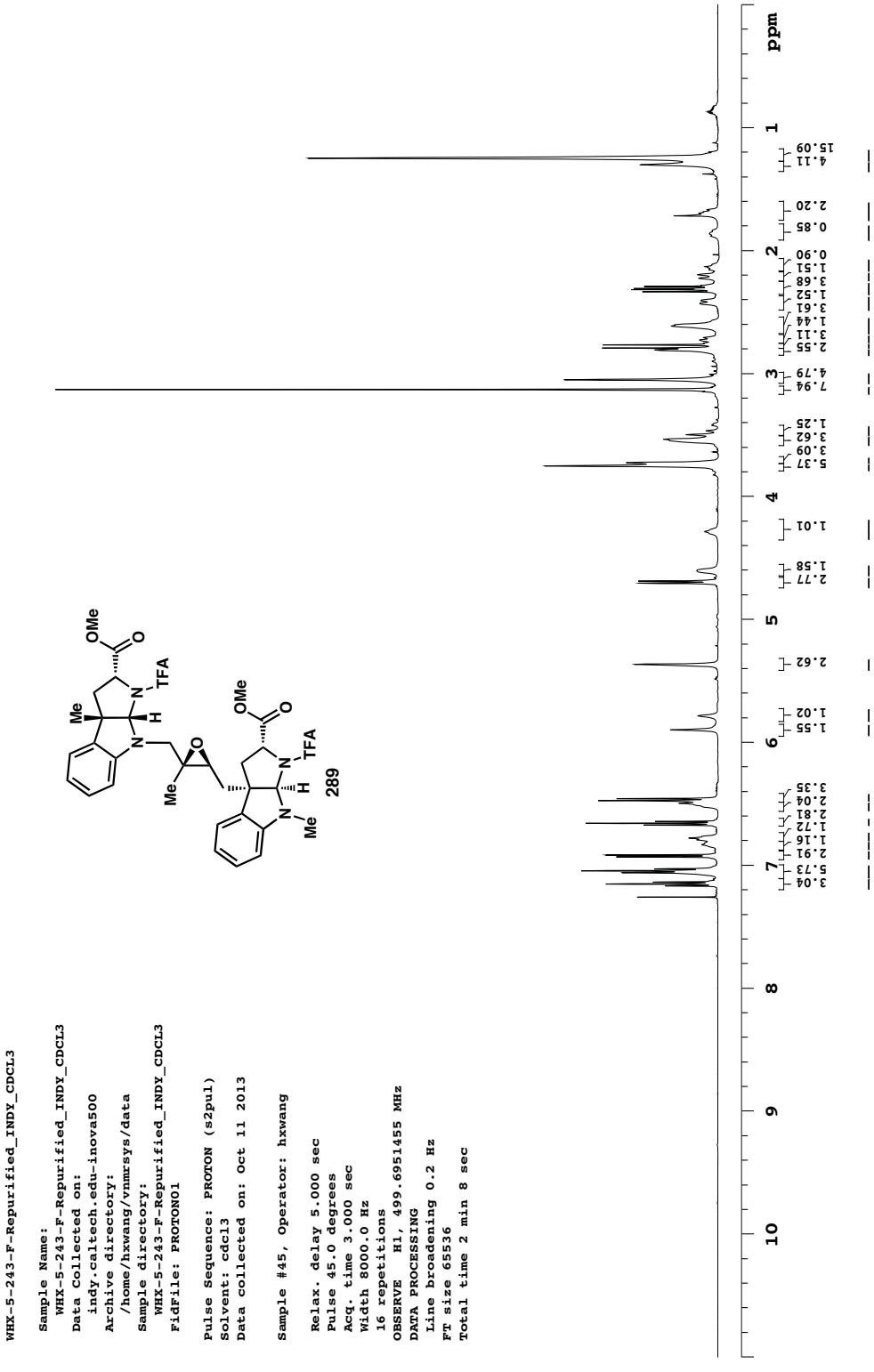

WHX-5-209-F-Characterization_INDY_CDCL3
Sample Name:
WHX-5-209-F-Characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-209-F-Characterization_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 29 2013
Sample #26, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13800 repetitions
OBSERVE C13, 125.6484664 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 7 hr, 51 min
OMs
OMe
O
Me
N
H
TFA
286
200
180
160
140
120
100
80
60
40
20
ppm

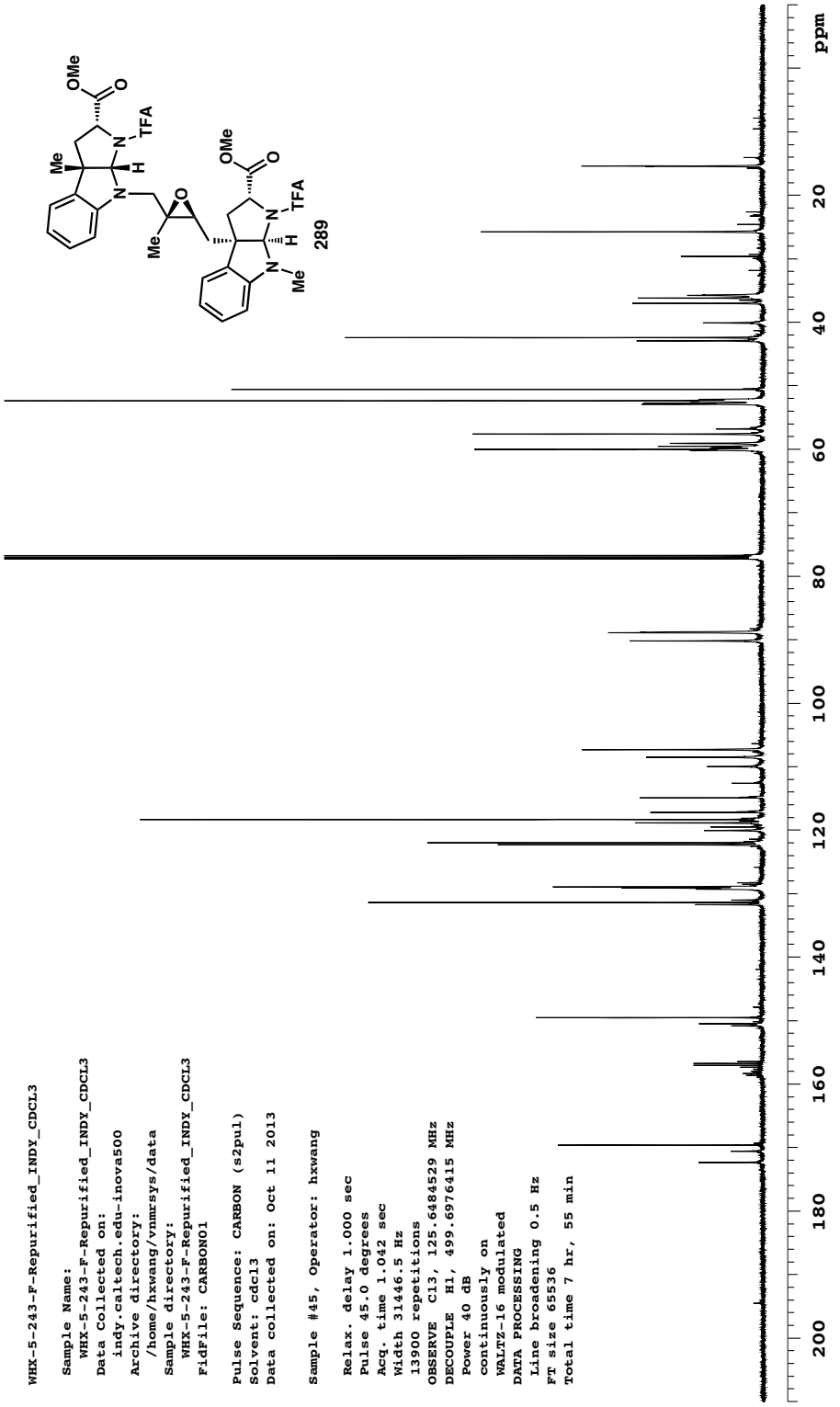

WHX-5-179-F-Characterization INDY CDCL3
Sample Name:
WHX-5-179-F-Characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-179-F-Characterization_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 8 2013
Sample #26, Operator: hxwang
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
Me
I
O
OMe
O
N
H
TFA
N
Me
287
ppm
10
9
8
7
6
5
4
3
2
1
0.95
0.95
1.02
1.00
0.61
0.39
0.65
0.39
2.91
1.81
1.08
2.11
1.63
0.32
0.61
0.46
0.92
0.46
0.59
1.16
1.76

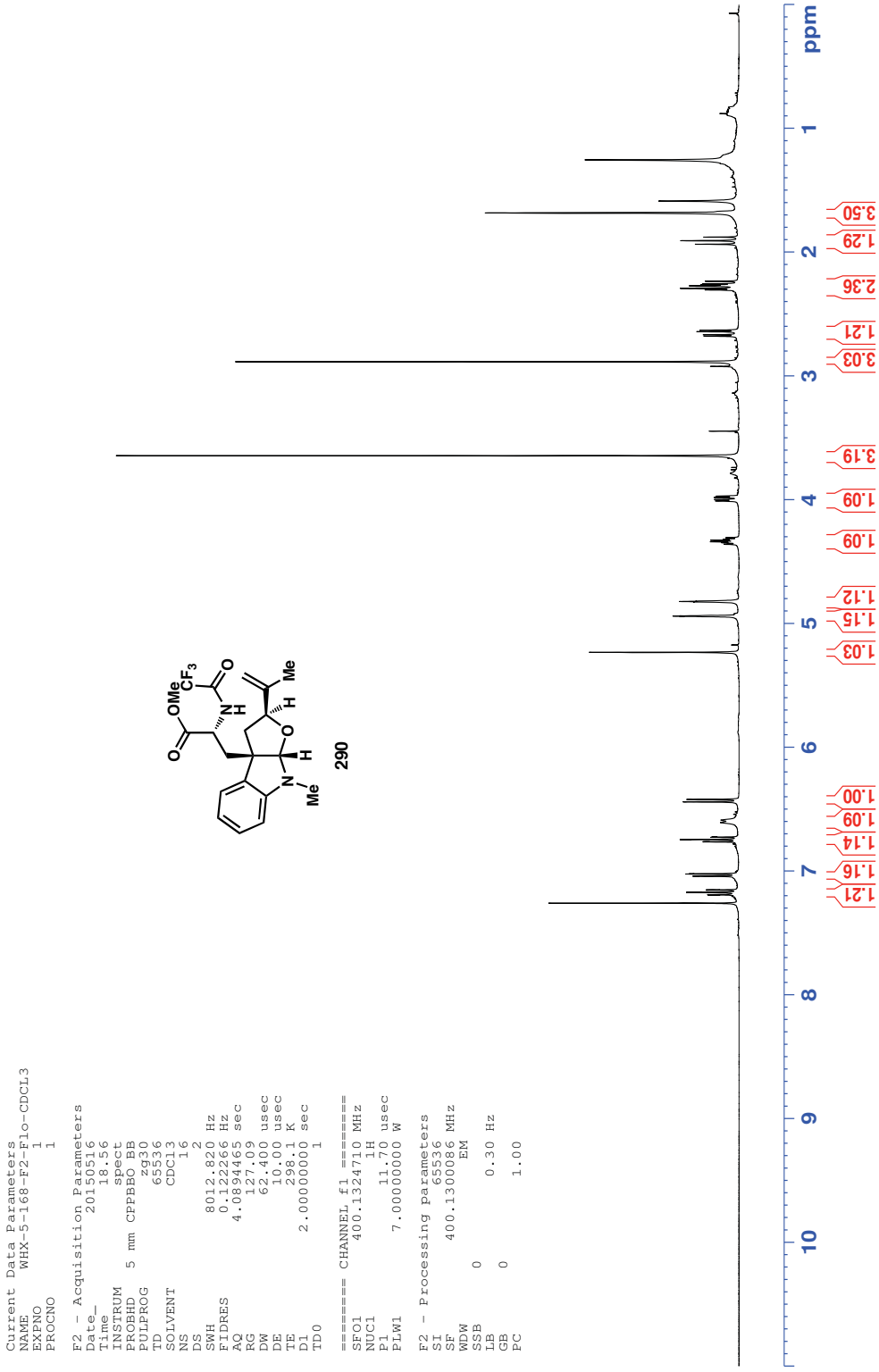

WHX-5-179-F-Characterization INDY CDCL3
Sample Name:
WHX-5-179-F-Characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-179-F-Characterization_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 8 2013
Sample #26, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
9500 repetitions
OBSERVE C13, 125.6484529 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 5 hr, 24 min
Me
I
O
OMe
O
N
H
TFA
N
Me
287
200
180
160
140
120
100
80
60
40
20
ppm

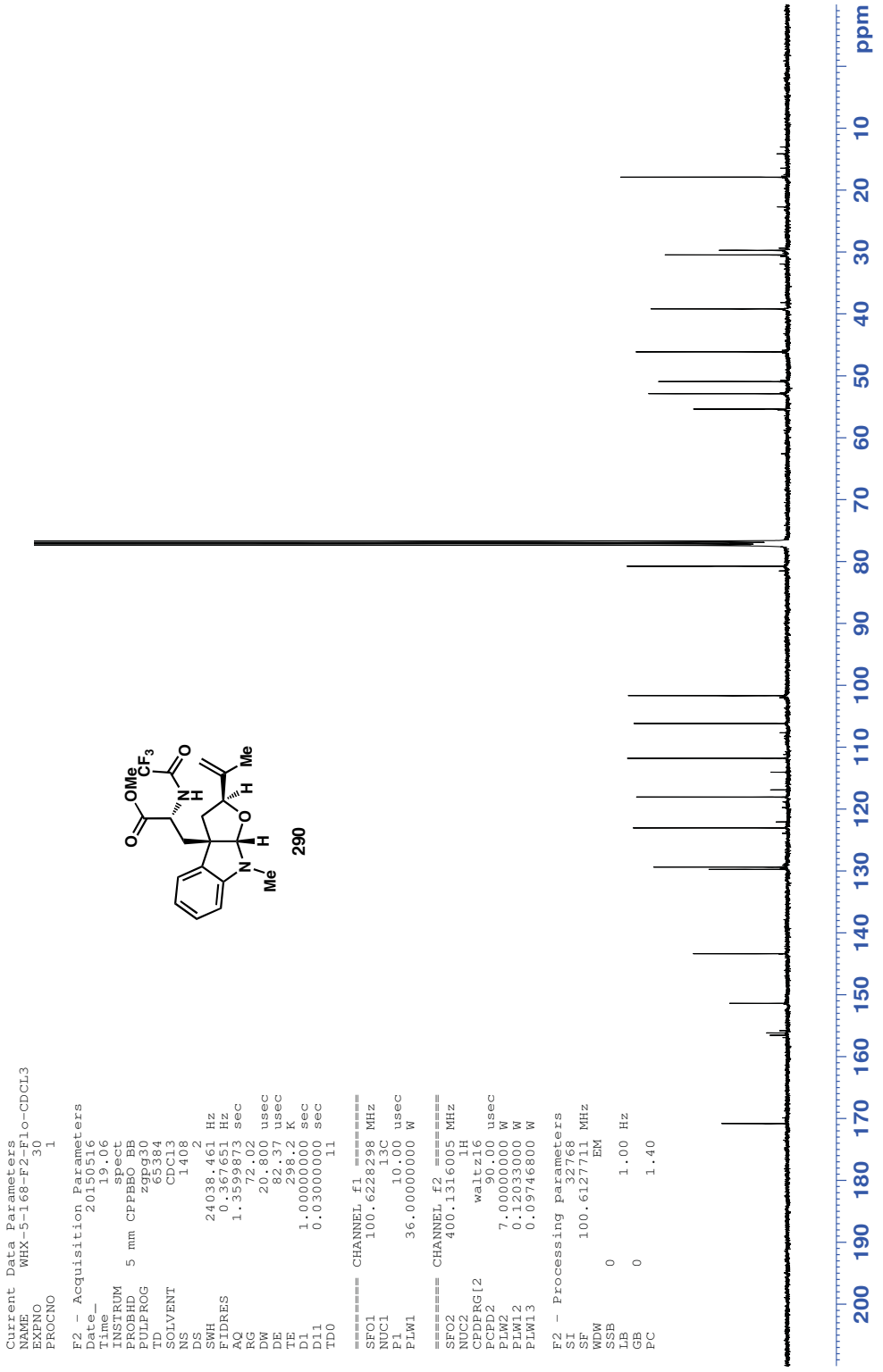

WHX-5-147-rec-characterization_INDY_CDCL3
Sample Name:
WHX-5-147-rec-characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-147-rec-characterization_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 16 2013
Sample #39, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6951452 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
OMe
O
Me
N
H
TFA
288
ppm
0.82
2.23
0.73
2.28
0.77
0.25
0.76
0.24
0.79
0.29
0.53
0.81
0.25
1.20
0.78
0.23
0.76
1.00

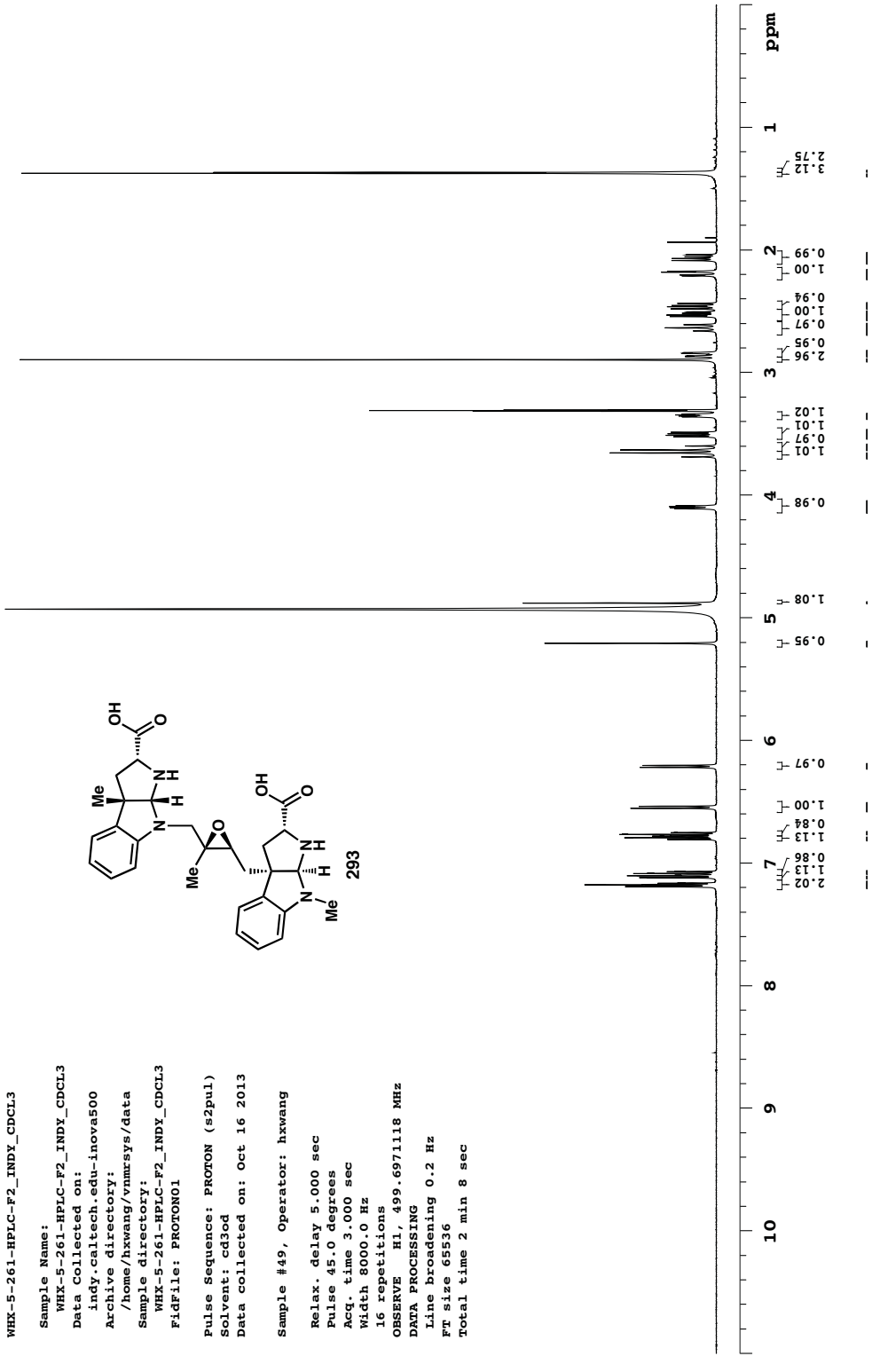

WHX-5-147-rec-characterization_INDY_CDCL3
Sample Name:
WHX-5-147-rec-characterization_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-147-rec-characterization_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 16 2013
Sample #39, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
12000 repetitions
OBSERVE C13, 125.6484568 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 6 hr, 50 min
OMe
O
Me
TFA
H
H
288
200
180
160
140
120
100
80
60
40
20
ppm

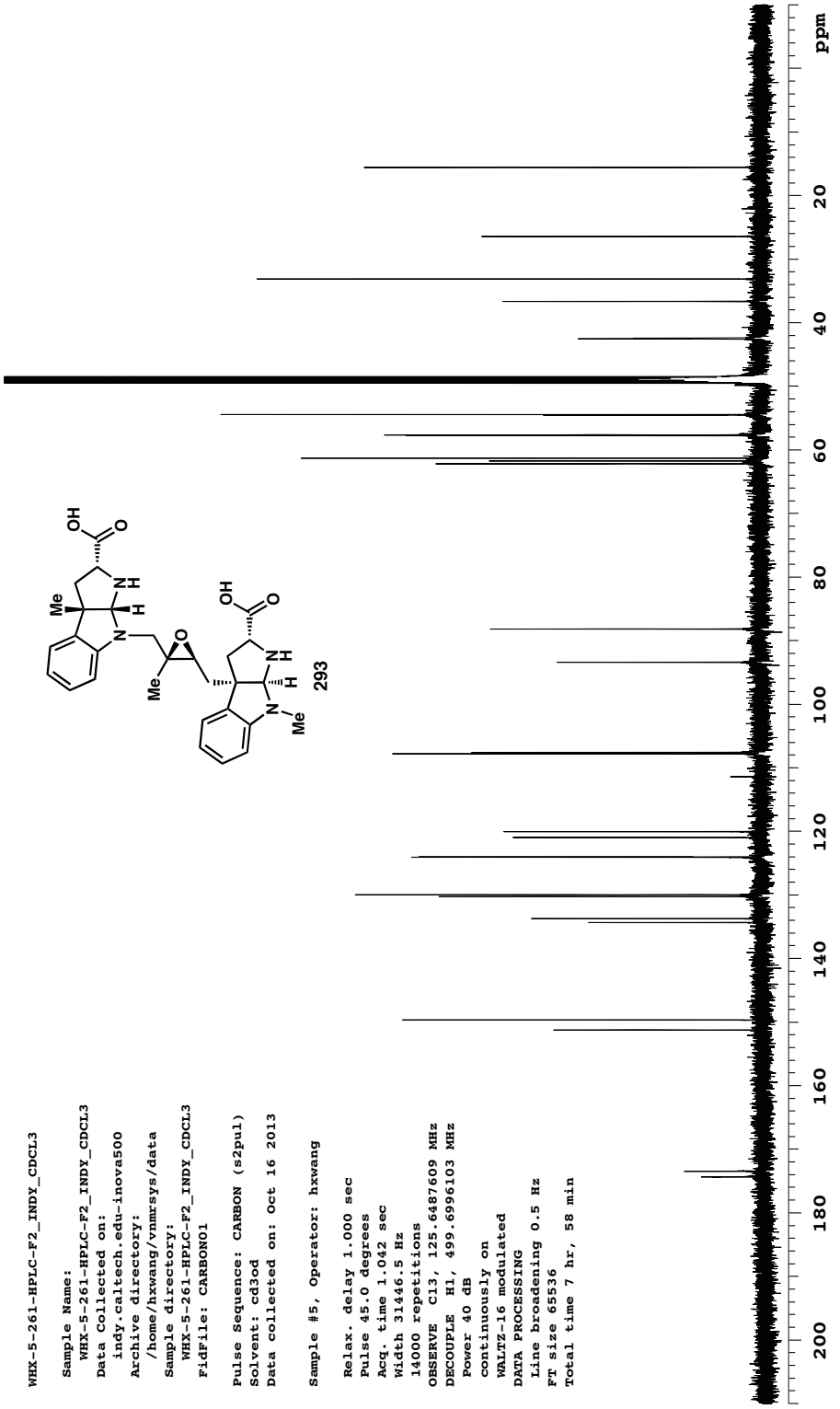

WHX-5-243-F-Repurified_INDY_CDCL3
Sample Name:
WHX-5-243-F-Repurified_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-243-F-Repurified_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2013
Sample #45, Operator: hxwang
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
OMe
Me
TFA
289
ppm
10
9
8
7
6
5
4
3
2
1
3.04
5.73
2.91
1.16
1.72
2.81
2.04
3.35
1.55
1.02
2.62
2.77
1.58
1.01
5.37
3.09
3.62
1.25
7.94
4.79
2.55
3.11
1.44
3.61
1.52
3.68
1.51
0.90
0.85
2.20
4.11
15.09

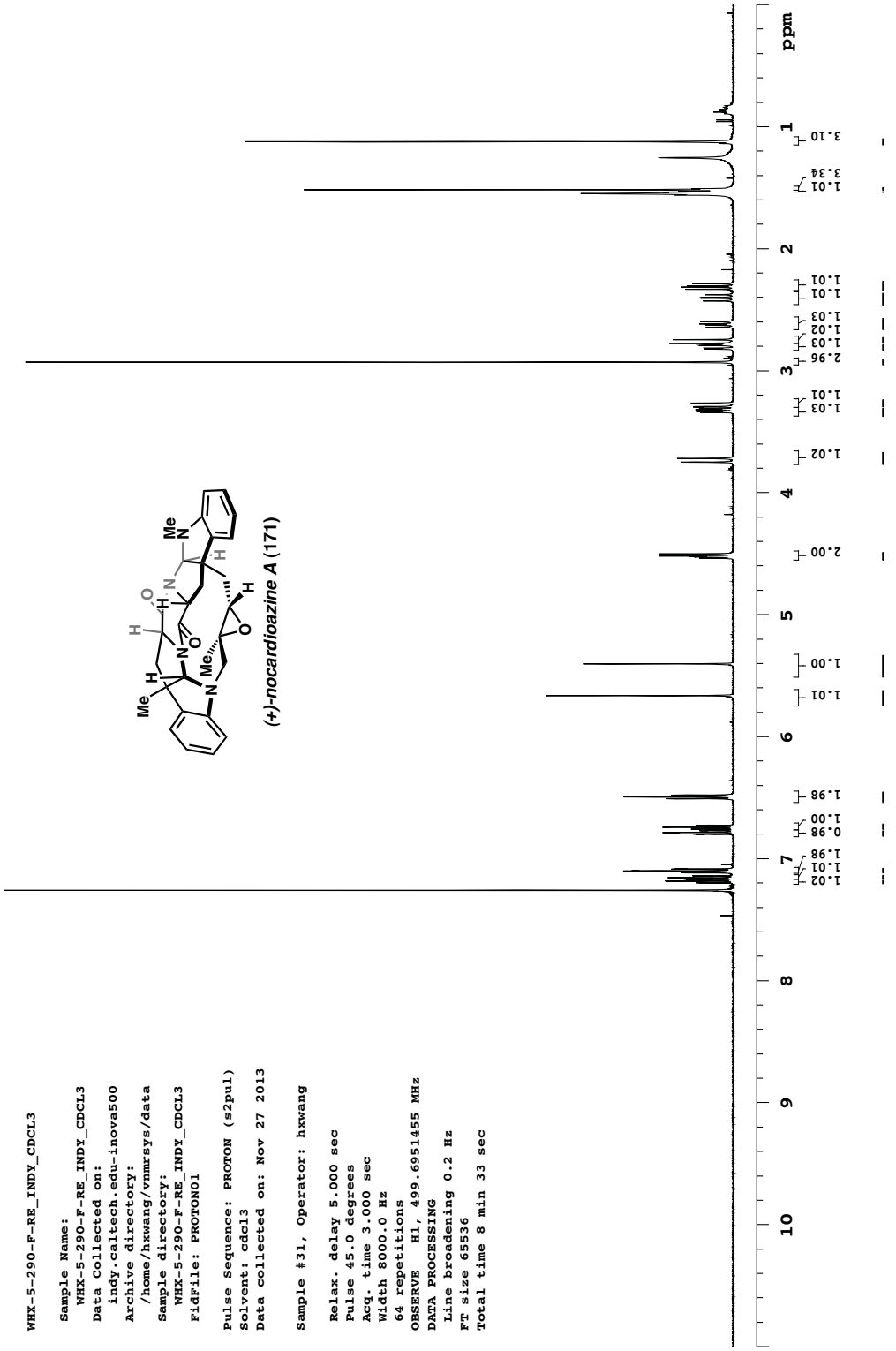

WHX-5-243-F-Repurified_INDY_CDCL3
Sample Name:
WHX-5-243-F-Repurified_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-243-F-Repurified_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2013
Sample #45, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13900 repetitions
OBSERVE C13, 125.6484529 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 7 hr, 55 min
OMe
O
Me
TFA
H
N
O
289
ppm
200
180
160
140
120
100
80
60
40
20

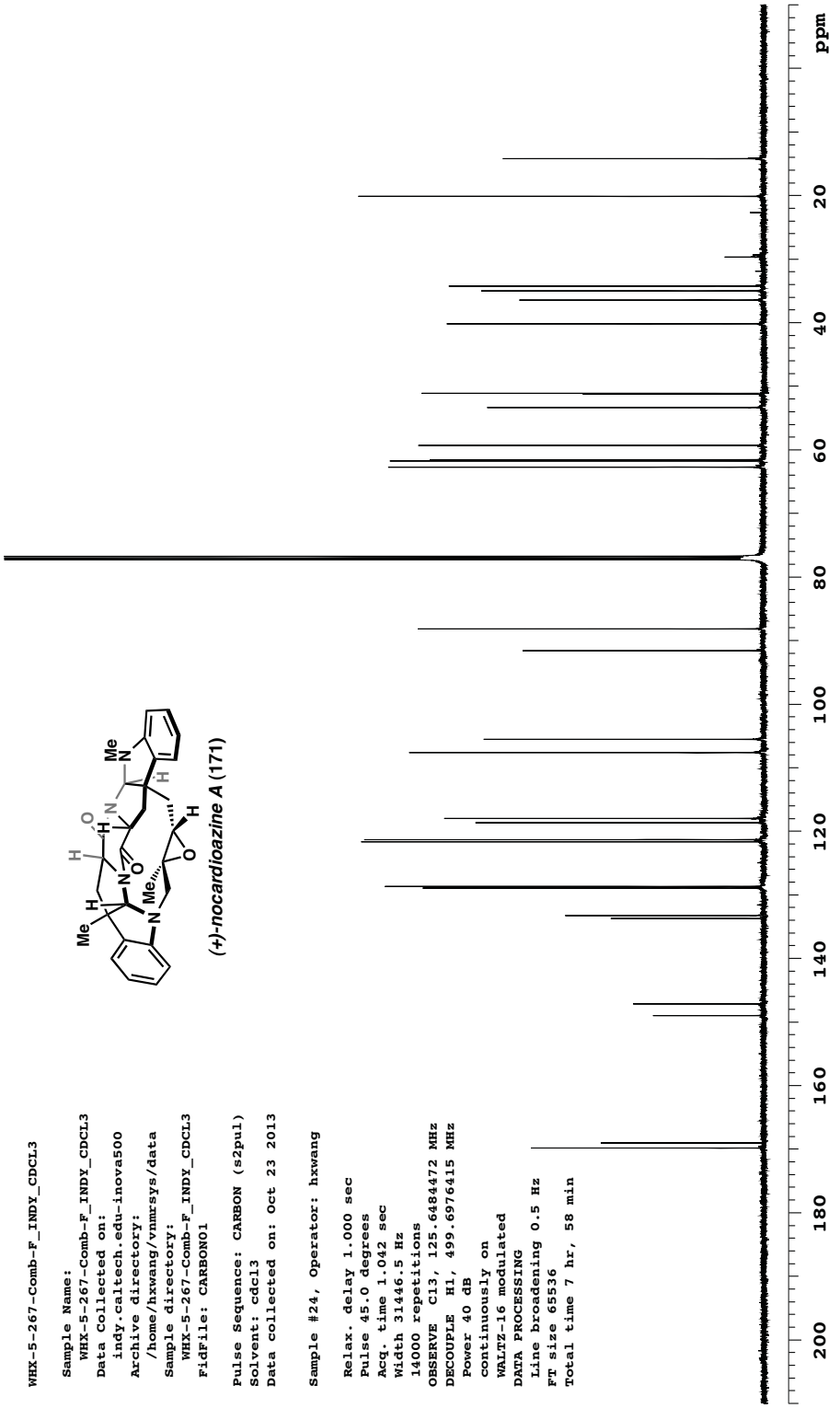

Current Data Parameters
NAME WHX-5-168-F2-Flo-CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150516
Time 18.56
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 127.09
DW 62.400 usec
DE 10.00 usec
TE 298.1 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300086 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
290
ppm
1.21
1.16
1.14
1.09
1.00
1.03
1.15
1.12
1.09
1.09
3.19
3.03
1.21
2.36
1.29
3.50


Current Data Parameters
NAME WHX-5-168-F2-Flo-CDCL3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150516
Time 19.06
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 1408
DS 2
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 72.02
DW 20.800 usec
DE 82.37 usec
TE 298.2 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 11
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127711 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OMe
CF3
O
N
H
O
H
Me
O
N
H
Me
290
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


WHX-5-261-HPLC-F2_INDY_CDCL3
Sample Name:
WHX-5-261-HPLC-F2_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-261-HPLC-F2_INDY_CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3od
Data collected on: Oct 16 2013
Sample #49, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6971118 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
293
ppm


WHX-5-261-HPLC-F2_INDY_CDCL3
Sample Name:
WHX-5-261-HPLC-F2_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-261-HPLC-F2_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3od
Data collected on: Oct 16 2013
Sample #5, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
14000 repetitions
OBSERVE C13, 125.6487609 MHz
DECOUPLE H1, 499.6996103 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 58 min
293
ppm
200
180
160
140
120
100
80
60
40
20


WHX-5-290-F-RE_INDY_CDCL3
Sample Name:
WHX-5-290-F-RE_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-290-F-RE_INDY_CDCL3
FidFile: PROTONO1
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 27 2013
Sample #31, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.6951455 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 8 min 33 sec
(+)-nocardioazine A (171)
ppm
1.02
1.01
1.00
0.98
1.00
1.98
1.02
1.01
1.00
2.00
1.02
1.03
1.01
2.96
1.03
1.02
1.03
1.01
1.01
1.01
3.34
1.01
3.10


WHX-5-267-Comb-F_INDY_CDCL3
Sample Name:
WHX-5-267-Comb-F_INDY_CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-5-267-Comb-F_INDY_CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 23 2013
Sample #24, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
14000 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 7 hr, 58 min
(+)-nocardioazine A (171)
200
180
160
140
120
100
80
60
40
20
ppm

Appendix 3

X-Ray Crystallography Reports Relevant to Chapter 3: Enantioselective Total Synthesis of (+)-Nocardioazines A and B[†]

[†] The work disclosed in this appendix for the X-ray crystallographic analysis of **277** completed entirely by Larry Henling and Dr. Michael Day in the Caltech X-ray crystallography lab.

Figure A3.1. *Macrocyclic alkene* ***277****. 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 997790.*

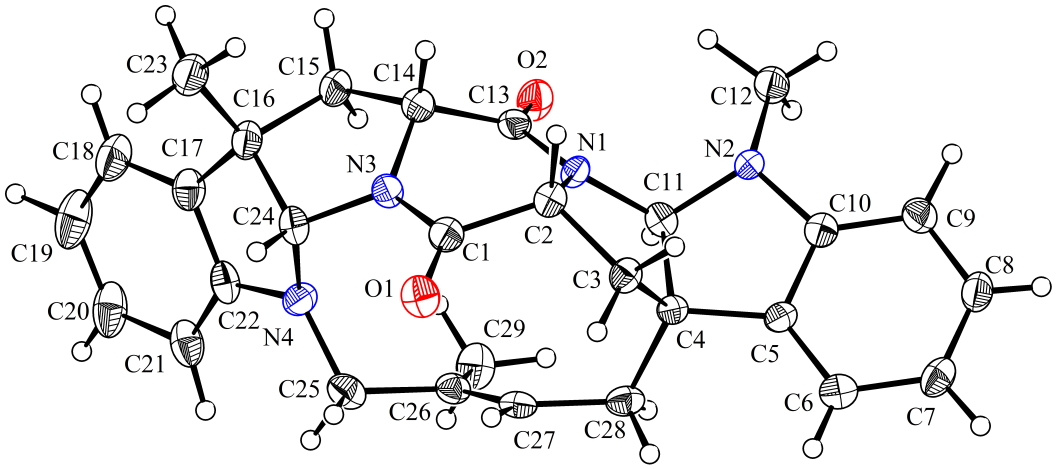


Table A3.1. *Crystal data and structure refinement for macrocyclic alkene* ***277*** *(CCDC 997790).*

Empirical formula	$C_{29}\ H_{30}\ N_4\ O_2$
Formula weight	466.57
Crystallization solvent	DCM/Pentane
Crystal shape	blade
Crystal color	colourless
Crystal size	0.03 x 0.2 x 0.36 mm

Data Collection

Preliminary photograph(s)	rotation	
Type of diffractometer	Bruker APEX-II CCD	
Wavelength	0.71073 Å MoK	
Data collection temperature	100.15 K	
Theta range for 5293 reflections used in lattice determination	2.40 to 20.69°	
Unit cell dimensions	a = 8.2481(3) Å b = 12.7097(5) Å c = 22.8106(8) Å	a= 90° b= 90° g = 90°
Volume	2391.26(15) $Å^3$	
Z	4	
Crystal system	orthorhombic	
Space group	P 21 21 21 (# 19)	
Density (calculated)	1.296 g/cm^3	
F(000)	992	
Theta range for data collection	2.4 to 29.4°	
Completeness to theta = 25.000°	99.9%	
Index ranges	-11 £ h £ 10, -16 £ k £ 16, -30 £ l £ 29	
Data collection scan type	and scans	
Reflections collected	42025	
Independent reflections	5687 [R_{int}= 0.1002]	
Reflections > 2s(I)	3486	
Average s(I)/(net I)	0.1114	
Absorption coefficient	0.08 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	1.0000 and 0.8355	

Table A3.1 (cont.)

Structure solution and Refinement

Primary solution method	dual
Secondary solution method	?
Hydrogen placement	?
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5687 / 0 / 437
Treatment of hydrogen atoms	refall
Goodness-of-fit on F^2	1.13
Final R indices [I>2s(I), 3486 reflections]	R1 = 0.0522, *w*R2 = 0.0632
R indices (all data)	R1 = 0.1217, *w*R2 = 0.0725
Type of weighting scheme used	calc
Weighting scheme used	
Max shift/error	0.000
Average shift/error	0.000
Absolute structure parameter	0.6(8)
Extinction coefficient	0.0112(8)
Largest diff. peak and hole	0.21 and -0.23 e·$Å^{-3}$

Programs Used

Cell refinement	?
Data collection	?
Data reduction	SAINT v8.27A (Bruker, 2012)
Structure solution	
Structure refinement	
Graphics	

Table A3.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for macrocyclic alkene* ***277*** *(CCDC 997790). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
O(1)	7309(2)	5733(2)	8607(1)	29(1)
O(2)	12123(2)	5018(2)	10081(1)	30(1)
N(1)	9738(3)	5862(2)	9901(1)	20(1)
N(3)	9952(3)	5296(2)	8768(1)	21(1)
N(2)	9195(3)	6507(2)	10884(1)	21(1)
N(4)	9753(3)	3417(2)	8592(1)	24(1)
C(26)	7924(3)	3412(2)	9447(1)	22(1)
C(13)	11173(4)	5437(2)	9738(1)	22(1)
C(6)	4946(4)	6119(2)	11133(1)	25(1)
C(10)	7760(3)	6589(2)	11204(1)	21(1)
C(11)	8986(3)	5648(2)	10462(1)	20(1)
C(5)	6497(3)	6100(2)	10906(1)	20(1)
C(22)	10876(4)	2697(2)	8370(1)	24(1)
C(24)	10142(3)	4459(2)	8346(1)	24(1)
C(1)	8540(4)	5774(2)	8907(1)	24(1)
C(27)	6821(3)	4127(2)	9606(1)	24(1)
C(8)	5939(4)	7100(3)	11959(2)	28(1)
C(9)	7532(4)	7080(2)	11738(1)	26(1)
C(16)	11970(3)	4392(2)	8235(1)	26(1)
C(28)	6452(4)	4540(2)	10204(1)	24(1)
C(25)	8138(4)	3156(3)	8800(1)	28(1)
C(4)	7146(3)	5638(2)	10344(1)	18(1)
C(3)	7000(4)	6423(2)	9821(1)	22(1)
C(17)	12209(4)	3228(2)	8137(1)	27(1)
C(2)	8613(3)	6375(2)	9487(1)	21(1)
C(14)	11466(3)	5529(3)	9087(1)	24(1)
C(7)	4685(4)	6635(2)	11664(1)	27(1)
C(18)	13463(4)	2675(3)	7887(1)	36(1)
C(12)	10752(4)	6581(3)	11188(2)	28(1)
C(29)	9013(4)	2825(3)	9858(2)	33(1)
C(15)	12677(4)	4735(3)	8837(2)	29(1)
C(21)	10792(4)	1611(3)	8356(1)	31(1)
C(23)	12541(5)	5104(3)	7738(2)	34(1)
C(20)	12072(5)	1067(3)	8094(1)	39(1)
C(19)	13375(5)	1583(3)	7862(2)	45(1)

Table A3.3. *Bond lengths [Å] and angles [°] for macrocyclic alkene* ***277*** *(CCDC 997790).*

O(1)-C(1)	1.227(3)
O(2)-C(13)	1.228(3)
N(1)-C(13)	1.353(3)
N(1)-C(11)	1.447(3)
N(1)-C(2)	1.477(3)
N(3)-C(24)	1.445(3)
N(3)-C(1)	1.351(3)
N(3)-C(14)	1.475(4)
N(2)-C(10)	1.395(3)
N(2)-C(11)	1.466(3)
N(2)-C(12)	1.462(4)
N(4)-C(22)	1.397(3)
N(4)-C(24)	1.473(3)
N(4)-C(25)	1.453(4)
C(26)-C(27)	1.336(4)
C(26)-C(25)	1.521(4)
C(26)-C(29)	1.498(4)
C(13)-C(14)	1.510(4)
C(6)-H(6)	0.92(2)
C(6)-C(5)	1.380(4)
C(6)-C(7)	1.396(4)
C(10)-C(5)	1.390(4)
C(10)-C(9)	1.381(4)
C(11)-H(11)	1.04(2)
C(11)-C(4)	1.541(4)
C(5)-C(4)	1.509(4)
C(22)-C(17)	1.396(4)
C(22)-C(21)	1.383(4)
C(24)-H(24)	1.03(3)
C(24)-C(16)	1.531(4)
C(1)-C(2)	1.529(4)
C(27)-H(27)	1.04(3)
C(27)-C(28)	1.493(4)
C(8)-H(8)	0.90(3)
C(8)-C(9)	1.407(4)
C(8)-C(7)	1.367(4)
C(9)-H(9)	1.01(3)
C(16)-C(17)	1.509(4)
C(16)-C(15)	1.554(4)
C(16)-C(23)	1.524(4)
C(28)-H(28A)	1.00(3)
C(28)-H(28B)	0.94(2)
C(28)-C(4)	1.541(4)
C(25)-H(25A)	1.05(3)
C(25)-H(25B)	1.02(3)
C(4)-C(3)	1.560(4)
C(3)-H(3A)	1.03(3)
C(3)-H(3B)	0.98(3)
C(3)-C(2)	1.534(4)

C(17)-C(18)	1.374(4)
C(2)-H(2)	1.10(3)
C(14)-H(14)	0.99(2)
C(14)-C(15)	1.530(4)
C(7)-H(7)	0.95(3)
C(18)-H(18)	0.94(3)
C(18)-C(19)	1.391(5)
C(12)-H(12A)	0.98(4)
C(12)-H(12B)	1.10(3)
C(12)-H(12C)	1.00(3)
C(29)-H(29A)	1.00(3)
C(29)-H(29B)	1.04(3)
C(29)-H(29C)	1.01(3)
C(15)-H(15A)	1.05(3)
C(15)-H(15B)	0.97(3)
C(21)-H(21)	0.98(3)
C(21)-C(20)	1.397(5)
C(23)-H(23A)	1.05(3)
C(23)-H(23B)	1.03(3)
C(23)-H(23C)	1.05(3)
C(20)-H(20)	0.97(3)
C(20)-C(19)	1.366(5)
C(19)-H(19)	1.10(3)

C(13)-N(1)-C(11)	122.9(2)
C(13)-N(1)-C(2)	123.4(2)
C(11)-N(1)-C(2)	112.3(2)
C(24)-N(3)-C(14)	112.6(2)
C(1)-N(3)-C(24)	125.5(2)
C(1)-N(3)-C(14)	121.6(2)
C(10)-N(2)-C(11)	107.5(2)
C(10)-N(2)-C(12)	119.6(2)
C(12)-N(2)-C(11)	117.6(3)
C(22)-N(4)-C(24)	107.9(2)
C(22)-N(4)-C(25)	125.2(2)
C(25)-N(4)-C(24)	122.0(2)
C(27)-C(26)-C(25)	119.2(3)
C(27)-C(26)-C(29)	125.2(3)
C(29)-C(26)-C(25)	115.6(3)
O(2)-C(13)-N(1)	123.8(3)
O(2)-C(13)-C(14)	123.8(3)
N(1)-C(13)-C(14)	112.3(2)
C(5)-C(6)-H(6)	121.4(15)
C(5)-C(6)-C(7)	118.5(3)
C(7)-C(6)-H(6)	120.0(15)
C(5)-C(10)-N(2)	110.2(2)
C(9)-C(10)-N(2)	127.6(3)
C(9)-C(10)-C(5)	122.1(3)
N(1)-C(11)-N(2)	113.0(2)
N(1)-C(11)-H(11)	107.5(13)
N(1)-C(11)-C(4)	105.6(2)
N(2)-C(11)-H(11)	113.3(13)
N(2)-C(11)-C(4)	103.7(2)

C(4)-C(11)-H(11)	113.4(13)
C(6)-C(5)-C(10)	120.2(3)
C(6)-C(5)-C(4)	130.8(3)
C(10)-C(5)-C(4)	108.9(2)
C(17)-C(22)-N(4)	110.0(3)
C(21)-C(22)-N(4)	129.0(3)
C(21)-C(22)-C(17)	120.9(3)
N(3)-C(24)-N(4)	112.6(2)
N(3)-C(24)-H(24)	110.4(15)
N(3)-C(24)-C(16)	105.0(2)
N(4)-C(24)-H(24)	110.2(15)
N(4)-C(24)-C(16)	103.1(2)
C(16)-C(24)-H(24)	115.3(14)
O(1)-C(1)-N(3)	124.3(3)
O(1)-C(1)-C(2)	122.5(3)
N(3)-C(1)-C(2)	113.2(2)
C(26)-C(27)-H(27)	116.2(15)
C(26)-C(27)-C(28)	128.8(3)
C(28)-C(27)-H(27)	114.9(15)
C(9)-C(8)-H(8)	118(2)
C(7)-C(8)-H(8)	120(2)
C(7)-C(8)-C(9)	121.6(3)
C(10)-C(9)-C(8)	116.7(3)
C(10)-C(9)-H(9)	124.6(15)
C(8)-C(9)-H(9)	118.7(15)
C(24)-C(16)-C(15)	102.0(2)
C(17)-C(16)-C(24)	102.0(2)
C(17)-C(16)-C(15)	110.9(3)
C(17)-C(16)-C(23)	115.6(3)
C(23)-C(16)-C(24)	113.2(3)
C(23)-C(16)-C(15)	111.9(3)
C(27)-C(28)-H(28A)	111.3(15)
C(27)-C(28)-H(28B)	107.9(14)
C(27)-C(28)-C(4)	115.5(2)
H(28A)-C(28)-H(28B)	105(2)
C(4)-C(28)-H(28A)	108.9(15)
C(4)-C(28)-H(28B)	107.4(14)
N(4)-C(25)-C(26)	112.0(2)
N(4)-C(25)-H(25A)	105.5(15)
N(4)-C(25)-H(25B)	110.0(15)
C(26)-C(25)-H(25A)	110.1(15)
C(26)-C(25)-H(25B)	113.2(15)
H(25A)-C(25)-H(25B)	106(2)
C(11)-C(4)-C(3)	101.8(2)
C(5)-C(4)-C(11)	101.3(2)
C(5)-C(4)-C(28)	113.3(2)
C(5)-C(4)-C(3)	112.0(2)
C(28)-C(4)-C(11)	114.2(2)
C(28)-C(4)-C(3)	113.1(2)
C(4)-C(3)-H(3A)	112.4(14)
C(4)-C(3)-H(3B)	109.9(16)
H(3A)-C(3)-H(3B)	105(2)
C(2)-C(3)-C(4)	106.7(2)

C(2)-C(3)-H(3A)	112.7(14)
C(2)-C(3)-H(3B)	109.9(16)
C(22)-C(17)-C(16)	108.4(2)
C(18)-C(17)-C(22)	120.2(3)
C(18)-C(17)-C(16)	131.4(3)
N(1)-C(2)-C(1)	111.0(2)
N(1)-C(2)-C(3)	104.2(2)
N(1)-C(2)-H(2)	107.6(12)
C(1)-C(2)-C(3)	114.5(2)
C(1)-C(2)-H(2)	107.6(12)
C(3)-C(2)-H(2)	111.8(12)
N(3)-C(14)-C(13)	109.5(2)
N(3)-C(14)-H(14)	109.1(13)
N(3)-C(14)-C(15)	103.7(2)
C(13)-C(14)-H(14)	108.5(13)
C(13)-C(14)-C(15)	114.9(3)
C(15)-C(14)-H(14)	110.9(13)
C(6)-C(7)-H(7)	121.6(16)
C(8)-C(7)-C(6)	120.8(3)
C(8)-C(7)-H(7)	117.6(16)
C(17)-C(18)-H(18)	119.5(17)
C(17)-C(18)-C(19)	119.2(3)
C(19)-C(18)-H(18)	121.3(17)
N(2)-C(12)-H(12A)	106(2)
N(2)-C(12)-H(12B)	109.3(16)
N(2)-C(12)-H(12C)	110.4(15)
H(12A)-C(12)-H(12B)	114(3)
H(12A)-C(12)-H(12C)	108(2)
H(12B)-C(12)-H(12C)	109(2)
C(26)-C(29)-H(29A)	112.3(18)
C(26)-C(29)-H(29B)	109.6(16)
C(26)-C(29)-H(29C)	107.2(18)
H(29A)-C(29)-H(29B)	110(3)
H(29A)-C(29)-H(29C)	113(3)
H(29B)-C(29)-H(29C)	104(2)
C(16)-C(15)-H(15A)	112.7(15)
C(16)-C(15)-H(15B)	110.2(17)
C(14)-C(15)-C(16)	105.7(2)
C(14)-C(15)-H(15A)	105.3(15)
C(14)-C(15)-H(15B)	107.0(17)
H(15A)-C(15)-H(15B)	115(2)
C(22)-C(21)-H(21)	127.2(16)
C(22)-C(21)-C(20)	117.7(3)
C(20)-C(21)-H(21)	114.9(16)
C(16)-C(23)-H(23A)	108.3(17)
C(16)-C(23)-H(23B)	109.8(17)
C(16)-C(23)-H(23C)	112.1(16)
H(23A)-C(23)-H(23B)	106(2)
H(23A)-C(23)-H(23C)	115(2)
H(23B)-C(23)-H(23C)	105(2)
C(21)-C(20)-H(20)	119.2(18)
C(19)-C(20)-C(21)	121.6(4)
C(19)-C(20)-H(20)	119.2(18)

C(18)-C(19)-H(19)	120.2(16)
C(20)-C(19)-C(18)	120.3(3)
C(20)-C(19)-H(19)	119.4(16)

Symmetry transformations used to generate equivalent atoms.

Table A3.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for for macrocyclic alkene* ***277*** *(CCDC 997790). 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)	299(12)	311(13)	263(12)	14(10)	-58(10)	52(10)
O(2)	204(11)	433(14)	277(12)	-44(11)	-10(10)	68(10)
N(1)	188(13)	226(14)	175(13)	3(11)	42(11)	-1(11)
N(3)	205(14)	224(15)	209(14)	-27(11)	-13(12)	16(12)
N(2)	171(14)	250(15)	209(13)	-43(12)	34(11)	-26(11)
N(4)	232(15)	191(14)	288(14)	-7(12)	66(11)	-5(12)
C(26)	220(16)	170(16)	266(16)	-8(14)	1(14)	-16(15)
C(13)	168(17)	233(18)	259(18)	-42(15)	2(14)	-13(14)
C(6)	229(19)	238(18)	283(19)	29(15)	-12(17)	11(15)
C(10)	249(17)	163(15)	218(16)	34(15)	12(15)	19(14)
C(11)	224(16)	187(18)	203(17)	0(15)	-36(14)	29(14)
C(5)	179(17)	186(18)	231(17)	13(13)	27(14)	-2(13)
C(22)	315(19)	251(19)	169(16)	-32(15)	-37(15)	77(16)
C(24)	285(18)	239(18)	200(17)	-45(15)	-3(15)	37(15)
C(1)	257(18)	196(18)	252(18)	13(15)	13(15)	7(15)
C(27)	185(17)	237(19)	282(19)	-3(15)	-24(15)	-66(14)
C(8)	320(20)	283(19)	236(19)	-29(16)	66(16)	16(17)
C(9)	297(19)	230(18)	254(18)	-18(15)	7(15)	-29(15)
C(16)	288(18)	266(18)	217(16)	-27(15)	52(14)	22(15)
C(28)	164(19)	239(19)	320(20)	8(16)	1(15)	-10(14)
C(25)	266(19)	230(20)	330(20)	-47(16)	-38(16)	-4(15)
C(4)	173(15)	180(16)	202(16)	3(13)	5(12)	-6(14)
C(3)	210(18)	194(18)	243(17)	0(15)	24(15)	47(15)
C(17)	331(19)	260(20)	208(17)	9(14)	9(15)	46(16)
C(2)	222(17)	203(19)	206(16)	32(14)	8(14)	36(13)
C(14)	221(17)	250(20)	253(18)	-28(16)	11(14)	-4(15)
C(7)	270(20)	252(18)	296(19)	20(16)	95(17)	53(15)
C(18)	390(20)	350(20)	330(20)	-13(18)	129(18)	69(19)
C(12)	222(19)	370(20)	246(18)	-38(19)	-22(16)	6(17)
C(29)	380(20)	290(20)	320(20)	18(19)	14(18)	99(19)
C(15)	223(19)	360(20)	278(19)	-79(17)	54(16)	11(16)
C(21)	480(20)	220(20)	229(18)	-13(16)	2(17)	52(19)
C(23)	400(30)	290(20)	320(20)	-24(17)	108(18)	-16(17)
C(20)	620(30)	260(20)	290(20)	5(17)	109(19)	140(20)
C(19)	530(30)	440(30)	380(20)	-10(20)	159(19)	230(20)

Table A3.5. *Hydrogen coordinates (x 10^3) and isotropic displacement parameters ($Å^2$x 10^3) for macrocyclic alkene* ***277*** *(CCDC 997790).*

	x	y	z	U_{iso}
H(6)	408(3)	584(2)	1093(1)	11(7)
H(11)	943(3)	493(2)	1061(1)	14(7)
H(24)	944(3)	460(2)	798(1)	31(8)
H(27)	618(3)	448(2)	927(1)	34(9)
H(8)	580(3)	733(2)	1233(1)	39(10)
H(9)	842(3)	743(2)	1197(1)	32(9)
H(28A)	681(3)	404(2)	1051(1)	25(8)
H(28B)	532(3)	458(2)	1024(1)	8(7)
H(25A)	801(3)	235(2)	873(1)	29(8)
H(25B)	729(3)	350(2)	854(1)	31(8)
H(3A)	601(3)	626(2)	956(1)	20(7)
H(3B)	682(3)	714(2)	997(1)	31(8)
H(2)	909(3)	716(2)	939(1)	20(7)
H(14)	1181(3)	626(2)	900(1)	6(7)
H(7)	364(3)	667(2)	1184(1)	22(8)
H(18)	1437(3)	304(2)	774(1)	26(9)
H(12A)	1073(4)	724(3)	1141(2)	73(13)
H(12B)	1174(4)	654(2)	1086(1)	56(10)
H(12C)	1087(3)	599(2)	1148(1)	17(7)
H(29A)	891(4)	308(3)	1027(2)	55(11)
H(29B)	1021(4)	289(2)	972(1)	48(10)
H(29C)	876(3)	205(3)	981(1)	50(10)
H(15A)	1271(3)	412(2)	914(1)	30(8)
H(15B)	1370(4)	511(2)	878(1)	37(9)
H(21)	990(3)	117(2)	849(1)	31(9)
H(23A)	1381(4)	506(2)	772(1)	39(9)
H(23B)	1227(4)	587(3)	784(1)	50(10)
H(23C)	1192(3)	495(2)	734(1)	42(9)
H(20)	1204(3)	31(2)	808(1)	40(10)
H(19)	1440(4)	112(2)	768(1)	50(10)

Table A3.6*. Hydrogen bonds for macrocyclic alkene* ***277*** *[Å and °]. (CCDC 997790).*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(12)-H(12B)...O(2)	1.10(3)	2.65(3)	3.406(4)	125(2)

Symmetry transformations used to generate equivalent atoms.

Chapter 4

Enantioselective Total Synthesis of Epidithiodiketopiperazine Natural Product (–)-Acetylapoaranotin[†]

4.1 INTRODUCTION

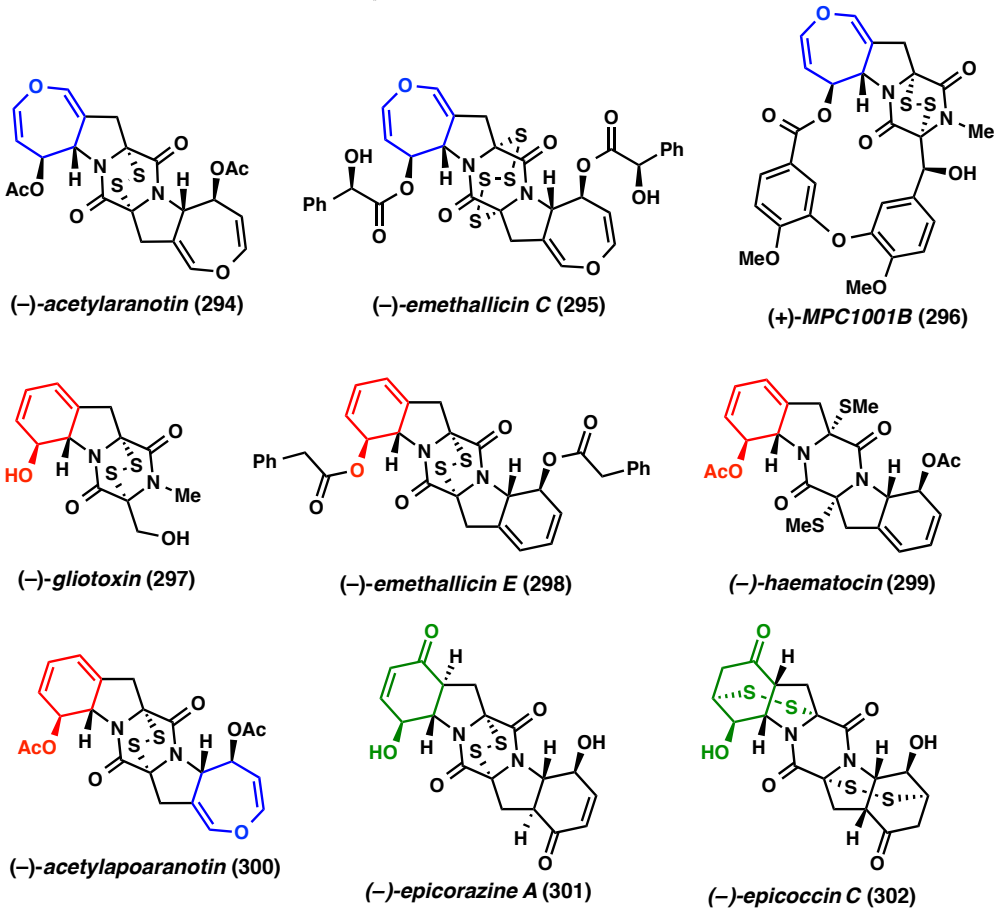
Polysulfide bridge-containing natural products, especially the epipolythiodiketopiperazine (ETP) family members, have become an important class of molecules at the interface between organic chemistry and chemical biology due to their activities in either redox-cycling to generate reactive oxygen species (ROS) or covalent modification of cysteine residues.[1] These complex molecules share a common polysulfide linkage, yet a wide range of biological activity, including antiproliferative and cytotoxic activities against various human cancer cell lines, have been identified within the ETP family members, indicating the importance of their diverse peripheral structural features (**294** to **302**, Figure 4.1).[2,3] Thus, the development of a modular synthetic strategy to

[†] The research discussed in this chapter was completed in collaboration with Clinton J. Regan (graduate student) and Dr. Paola Romanato (postdoctoral fellow) in the Reisman Laboratory.

access these related natural products could facilitate the corresponding structure-activity relationship (SAR) studies.

Among these compounds, our laboratory has accomplished the first asymmetric total synthesis of dihydrooxepine-containing natural product (–)-acetylaranotin (**294**),[4] which commenced our ongoing synthetic program to access other dihydrooxepine subfamily members such as (–)-emethallicin C (**295**) and (+)-MPC1001B (**296**). A related subfamily that has attracted our attention is the *cyclohexadienol*-containing natural products (motif highlighted in red) including C_2-symmetric (–)-emethallicin E (**298**) and (–)-haematocin (**299**), as well as the heterodimer natural product between those two subfamilies, namely (–)-acetylapoaranotin (**300**).

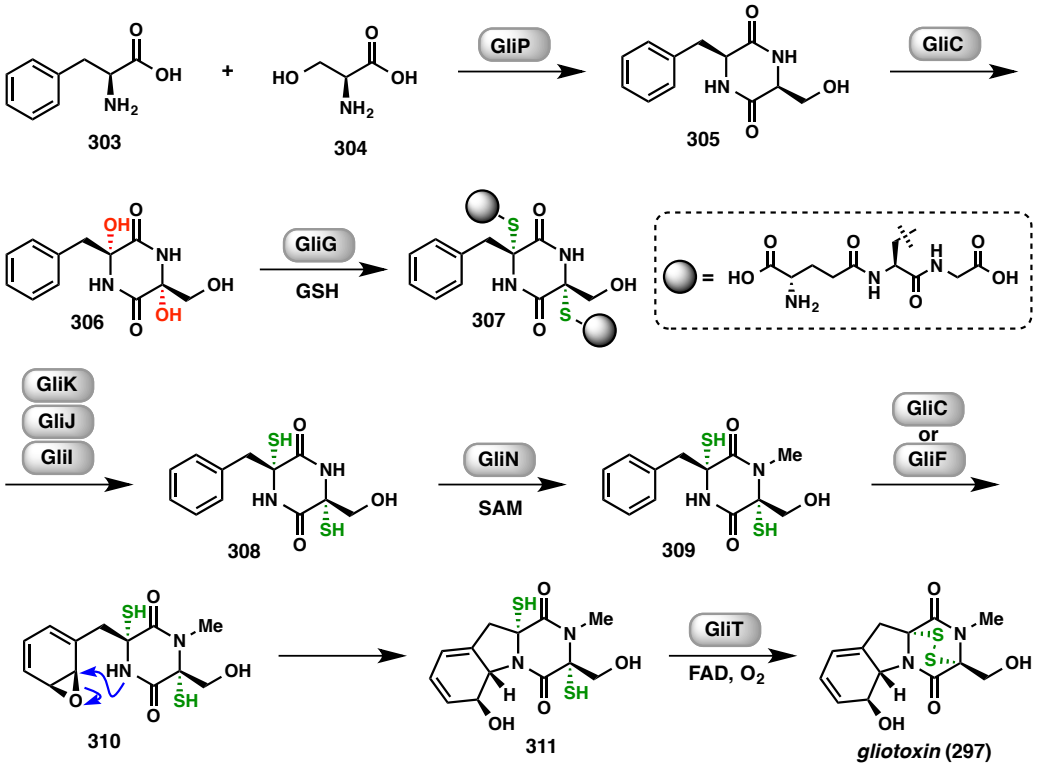
Figure 4.1. *Selected ETP natural products*



4.1.1 Biological Origins

Among the cyclohexadienol ETP subfamily, the biosynthesis of (–)-gliotoxin (**297**, Figure 4.1) has been intensely investigated.[5-8] Utilizing gene-mutagenesis and mass spectroscopy techniques, the entire biosynthetic pathway of **297** has been well mapped (Scheme 4.1).

Scheme 4.1. *A brief picture of (–)-gliotoxin biosynthesis*



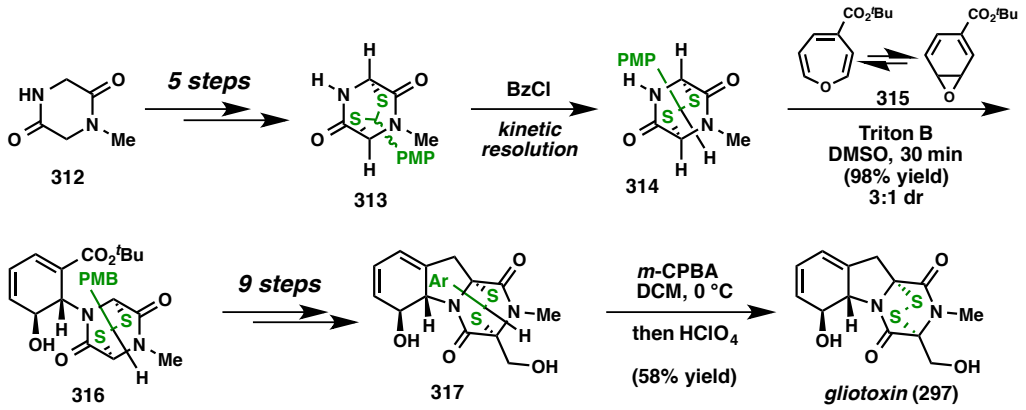
Starting with cyclization of L-phenylalanine (**303**) and L-serine (**304**) mediated by peptide synthetase GliP, the resulting DKP **305** is oxidized by a hydroxylase (GliC) to provide diol **306**. Subsequent elimination of hydroxyl groups in **306** followed by thiol addition of glutathiones (GSH) furnishes the key sulfur-transfer intermediate **307**, where the C-S bonds are cleaved by the enzyme sequence GliK/GliJ/GliI to produce free dithiol **308**. *N*-Methylation followed by a P450 enzyme (GliC or GliF)-mediated epoxidation

produces epoxide **310**, which undergoes intramolecular epoxide opening to furnish the core of gliotoxin. The final step includes oxidation of the free thiol groups to disulfide bridge via GliT enzyme and O_2. This biosynthetic pathway is likely related to other cyclohexadienol subfamily members (**297**-**300**).

4.1.2 Previous Synthetic Efforts

Due to the intriguing biological properties of these ETP natural products, a number of synthetic efforts toward them have been reported in the past few decades.[9] The simplest cyclohexadienol ETP family member, (–)-gliotoxin (**297**), was successfully synthesized by Kishi and coworkers in 1976 (Scheme 4.2).[10]

Scheme 4.2. *Total synthesis of gliotoxin by Kishi*

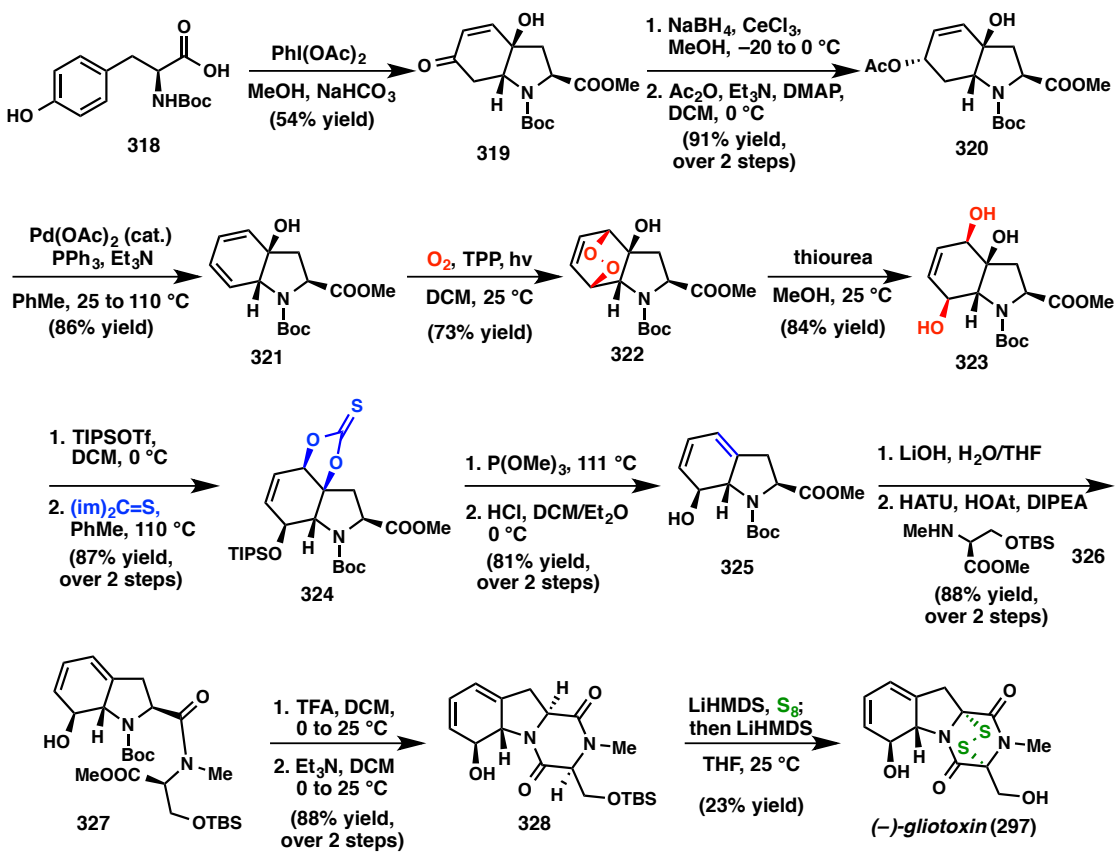


Beginning with glycine-derived diketopiperazine (DKP) **312**, dithioacetal **314** was prepared in six steps (including a kinetic resolution step). Deprotonation at the DKP nitrogen followed by nucleophilic addition to oxepine **315** provided cyclohexadienol **316** in 3 : 1 dr. Subsequent functional group manipulation in nine steps advanced **316** to diol **317**, which possesses the core of gliotoxin (**297**). Diol **317** was then subjected to

deprotection of the dithioacetal using *m*-CPBA and acidic workup to accomplish the synthesis of gliotoxin.

For a long period of time, the Kishi synthesis of gliotoxin utilizing the dithiol acetal-protecting strategy represented the state of the art for the preparation of ETP natural products. Since the early 2000s, a new wave of ETP synthesis has emerged featuring a late-stage sulfenylation strategy pioneered by Movassaghi,[11] Nicolaou,[12] and Reisman[4] groups.

Scheme 4.3. *Total synthesis of (–)-gliotoxin by Nicolaou*

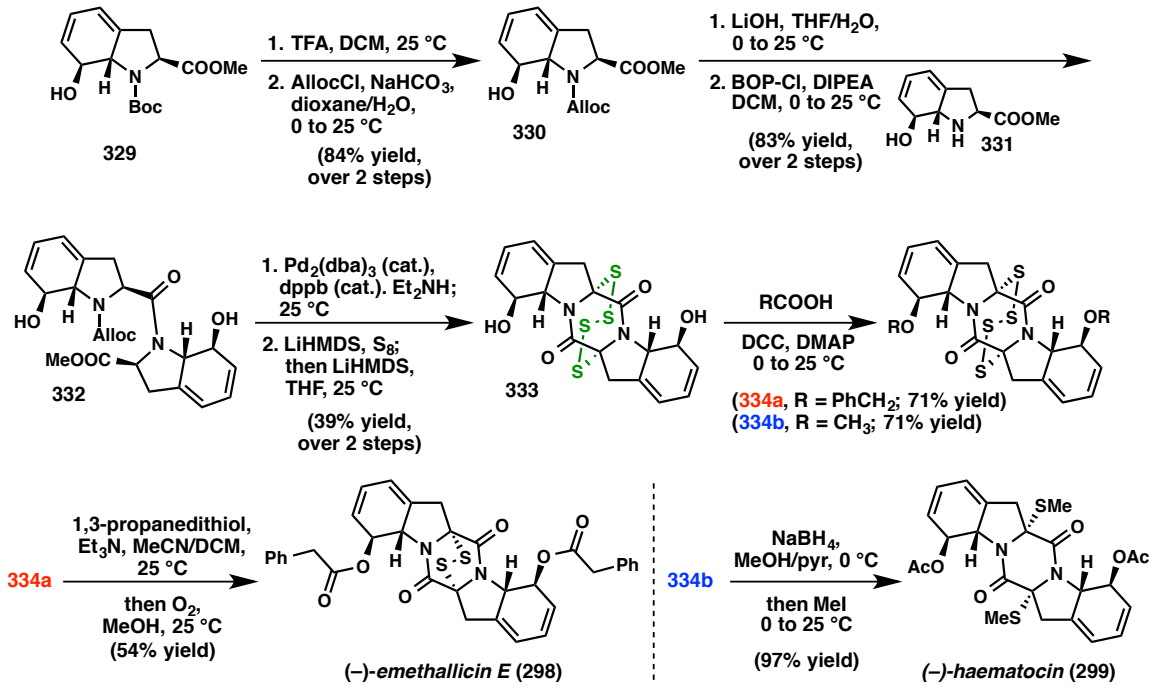


Based on the initial work by Sundberg and coworkers,[13] Nicolaou and coworkers began with enantiopure *N*-Boc-L-tyrosine **318** (Scheme 4.3), which was subjected to oxidative intramolecular dearomatization conditions followed by lactone opening with

methoxide and subsequent cyclization to yield hydroxyl enone[14] **319**.[2] Luche reduction and acetylation provided allylic acetate **320**, which was converted to diene **321** under palladium catalyzed elimination conditions. In order to install the correct oxidation states, diene **321** was subjected under photooxygenation conditions to form endoperoxide **322**, which was reduced with thiourea to afford triol **323**. Subsequent silylation, Corey-Winter olefination, and desilylation provided the cyclohexadienol core in **325**. DKP formation with L-serine derivative **326** and sulfenylation using LiHMDS and elemental sulfur accomplished the synthesis of gliotoxin (**297**), which represents a mild methodology to incorporate the sulfur bridge in DKP substrates.[15]

The cyclohexadienol intermediate **325** was used as the key intermediate to access C_2-symmetric ETP natural products (–)-emethallicin E (**298**) and (–)-haematocin (**299**),

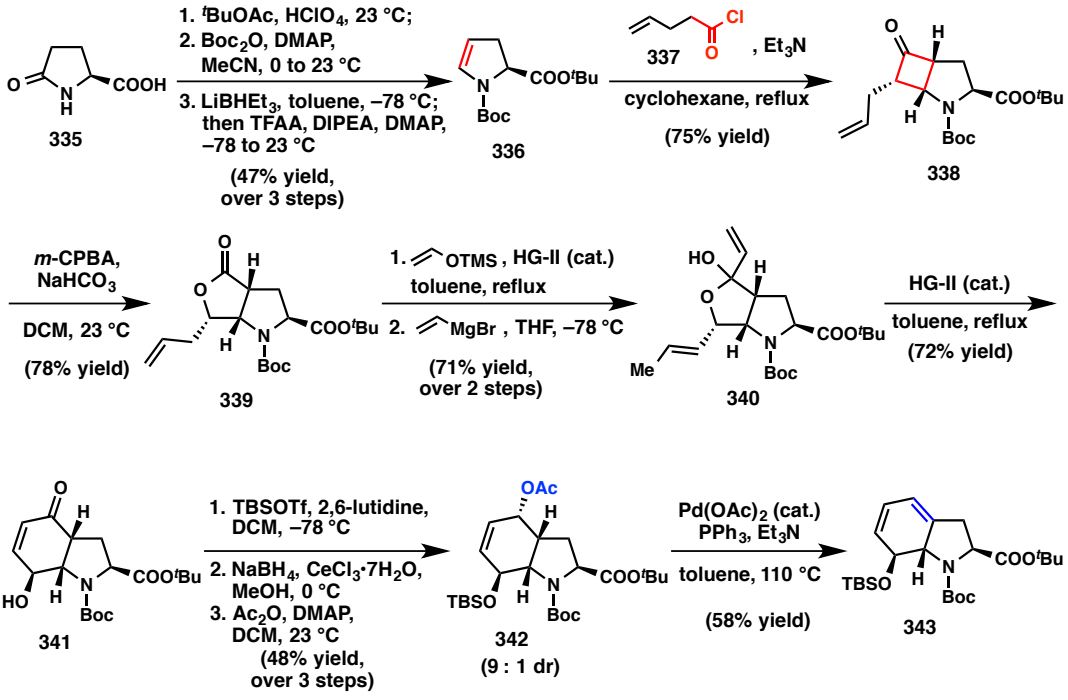
Scheme 4.4. *Total synthesis of (–)-emethallicin E and (–)-haematocin by Nicolaou*



illustrated by Nicolaou and coworkers.[2] The Boc protecting group in **329** was switched to allyl carbamate in **330** in two steps, which was hydrolyzed and coupled with secondary amine **331** to provide dipeptide **332**. Subsequent palladium-catalyzed deprotection of Alloc group triggered *in situ* DKP formation, which was followed by the sulfenylation step to form tetrasulfide **333**. Ester formation of diol **333** with phenylacetic acid or acetic acid afforded esters **334a** and **334b**, respectively. **334a** was then subjected to 1,3-propane dithiol-mediated reduction followed by aerobic oxidation to provide (–)-emethallicin E (**298**). On the other hand, **334b** was subjected to $NaBH_4$ reduction/methylation sequence to produce (–)-haematocin (**299**).

An alternative strategy to access the cyclohexadienol fragment was reported by Bräse and coworkers (Scheme 4.5).[16] L-Pyroglutamic acid (**335**) was converted to enamine **336** in a three-step sequence. The following key reaction involves a diastereoselective [2 + 2] ketene cycloaddition to provide bicyclic cyclobutanone **338**, which was subjected to the Baeyer-Villiger ring expansion to afford **339**. Ruthenium hydride catalyzed alkene isomerization and vinyl Grignard addition yielded lactol **340**, which was converted to hydroxyl enone **341** via a ring-closing metathesis. Enone **341** was then converted to allylic acetate **342** in three steps, which was subsequently treated under palladium-catalyzed elimination conditions to provide the cyclohexadienol building block **343**. However, Bräse and coworkers did not advance this key building block **343** to related cyclohexadienol ETP natural products in the report.

Scheme 4.5. *Preparation of cyclohexadienol fragment by Bräse*



4.2 SYNTHETIC EFFORTS TOWARD CYCLOHEXADIENOL ETP

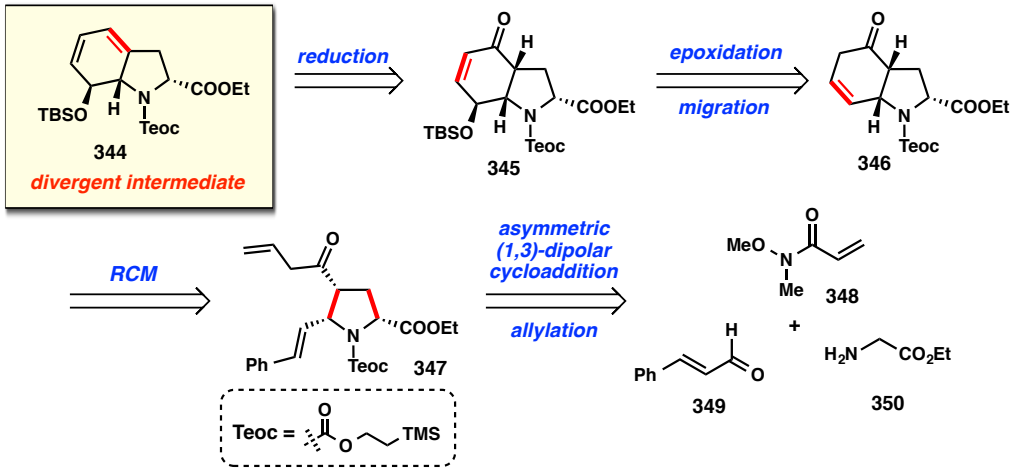
4.2.1 Retrosynthetic Analysis

Both strategies reported by Nicolaou and Bräse groups rely on starting materials from the chiral pool. As our ongoing project to access various ETP family members, especially the *cyclohexadienol* subfamily, a strategy involving a catalytic *asymmetric* stereocenters-assembling step is proposed to access the key cyclohexadienol fragment **344** (Scheme 4.6).

Retrosynthetically, this common cyclohexadienol building block **344** was envisioned to be prepared using an asymmetric (1,3)-dipolar cycloaddition to assemble the central pyrrolidine core, followed by chemo-selective allyl addition to a Weinreb amide to provide a ring-closing metathesis (RCM) substrate **347**. Subsequent

RCM/epoxidation/rearrangement would give access to enone **345**, which could then be converted to cyclohexadiene **344** through vinyl triflate formation and reduction.

Scheme 4.6. *Retrosynthesis analysis of cyclohexadienol building block **344***

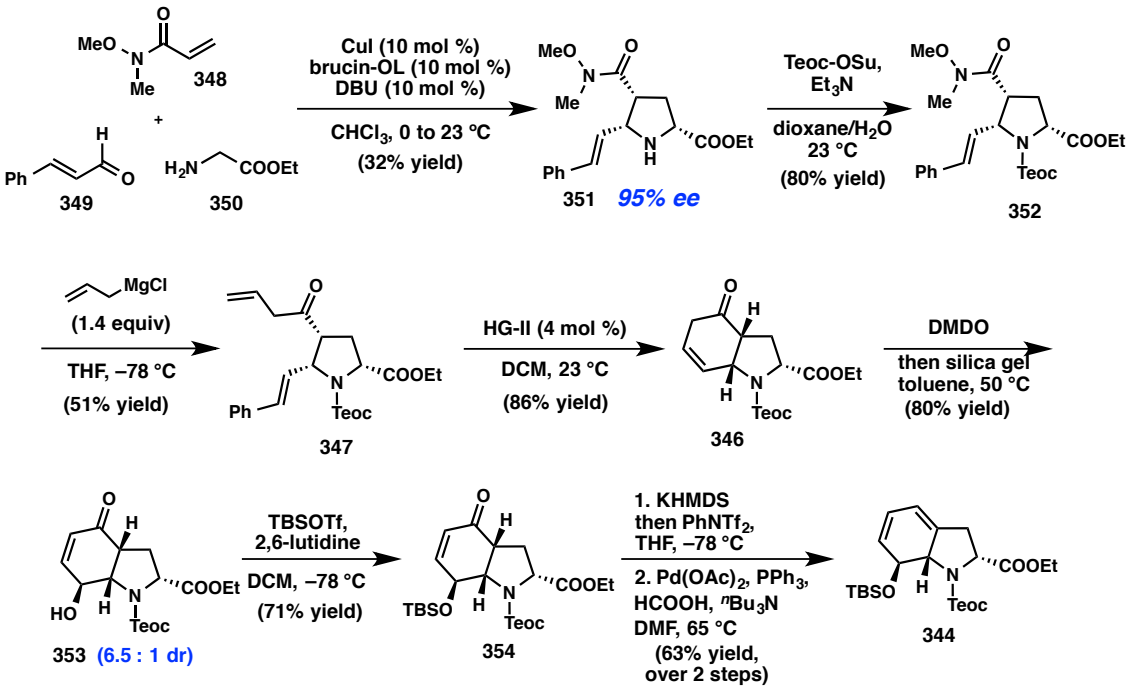


4.2.2 Preparation of Cyclohexadienol Fragment and Formal Synthesis of (–)-Emethallicin E and (–)-Haematocin

In the forward sense, copper/brucin-OL-catalyzed (1,3)-dipolar cycloaddition between Weinreb amide **348**, cinnamaldehyde **349**, and glycinate **350** provided pyrrolidine **351** in 32% yield and 95% ee (Scheme 4.7),[17] which was subsequently protected as its (trimethylsilyl)ethyl carbamate (Teoc) **352**. The following allyl Grignard addition proved to be challenging due to competitive addition to the ethyl ester. Nevertheless, with careful control of reagent stoichiometry, mono-addition product **347** could be isolated in 51% yield on a multi-gram scale.

Treatment of non-conjugated diene **347** with Hoveyda-Grubbs II catalyst yielded ring-closing product **346** in good yield. In order to install the allylic hydroxyl moiety, alkene **346** was oxidized with dimethyldioxirane (DMDO) and the resulting epoxide was

Scheme 4.7. *Asymmetric route accessing cyclohexadienol* ***344***

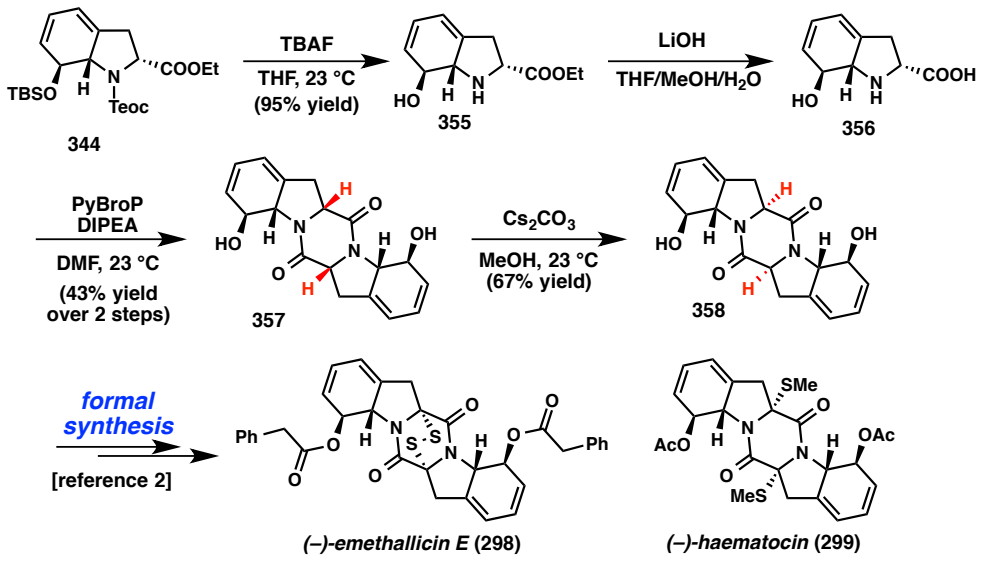


directly heated with silica gel in toluene to effect isomerization, providing the enone product as a 6.5 : 1 inseparable mixture of diastereomers. Protection of alcohol **353** as its TBS ether **354** allowed facile separation of the two diastereomers using silica gel chromatography. Subsequent formation of vinyl triflate followed by palladium-catalyzed reduction[18] provided the key divergent intermediate **344**.

In order to access C_2-symmetric emethallicin E (**298**) and haematocin (**299**), diene **344** was first globally deprotected with excess TBAF (Scheme 4.8), followed by hydrolysis, to afford amino acid **356**. Successful dimerization using peptide coupling reagent PyBroP furnished DKP **357**, which was then epimerized to form the thermodynamically more favored diastereomer **358** using cesium carbonate in MeOH. Dimeric intermediate **358** has been prepared by Nicolaou and coworkers to access both (–)-**298** and (–)-**299** in short sequences (Scheme 4.4)[2]. Thus, a formal total synthesis of

these natural products is completed. In comparison, our current synthetic route shortens their synthesis by three steps.

Scheme 4.8. *Formal synthesis of (–)-emethallicin E and (–)-haematocin*



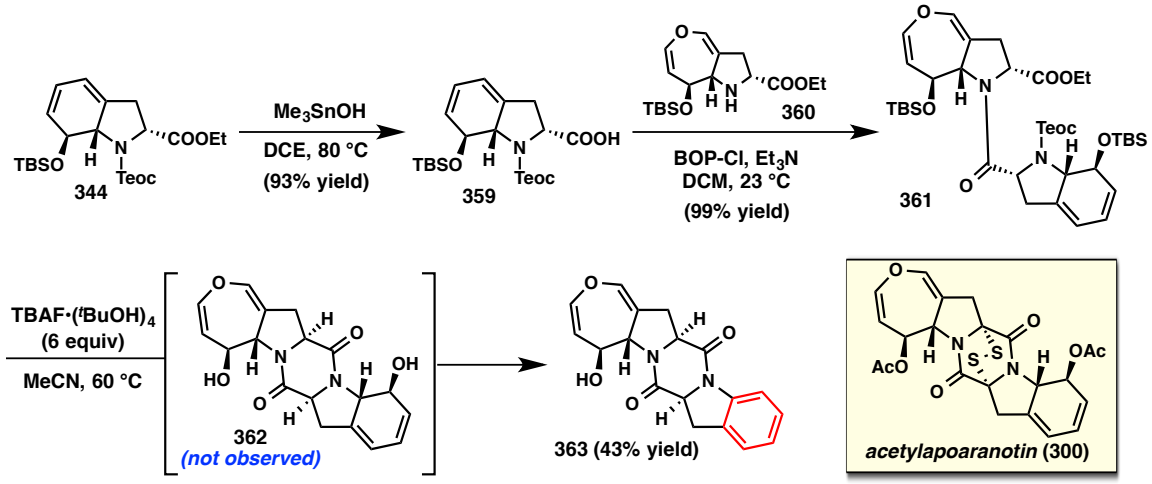
4.2.3 Attempts to Prepare (–)-Acetylapoaranotin

Having established an efficient route to prepare C_2-symmetric cyclohexadienol-containing ETP natural products, we next turned our attention to the hybrid natural product between the dihydrooxepine/cyclohexadiene subfamilies, (–)-acetylapoaranotin (**300**, Figure 4.1). It was recognized that the sequential peptide coupling strategy was preferred for the selective synthesis of heterodimeric diketopiperazines, such as **300**.

Starting from the key diene intermediate **344**, treatment with trimethyltinhydroxide afforded carboxylic acid **359**,[19] which was successfully coupled with amine **360** (prepared according to reference 4) in excellent yield. The resulting dipeptide **361** was subjected to the TBAF•(^{t}BuOH)$_4$ conditions reported in the total synthesis of acetylaranotin (**294**, Figure 4.1) by our group.[4] Unfortunately, undesired

aromatized product **363** was isolated. It is hypothesized that following the desired removal of the Teoc and TBS groups, cyclization and epimerization proceeded smoothly; however, the resulting allylic secondary alcohol on the cyclohexadienol fragment (**362**) was not stable under the reaction conditions and was further eliminated, giving rise to aromatized product **363**. Interestingly, this side product mapped well onto another ETP family member, deoxyapoaranotin, which shows direct cytotoxic effects toward HCT116 colon cancer cell lines.[20] A more expedient route toward deoxyapoaranotin could be accomplished starting from (*R*)-indoline carboxylic acid.

Scheme 4.9. *Attempts to prepare the DKP core in acetylapoaranotin*

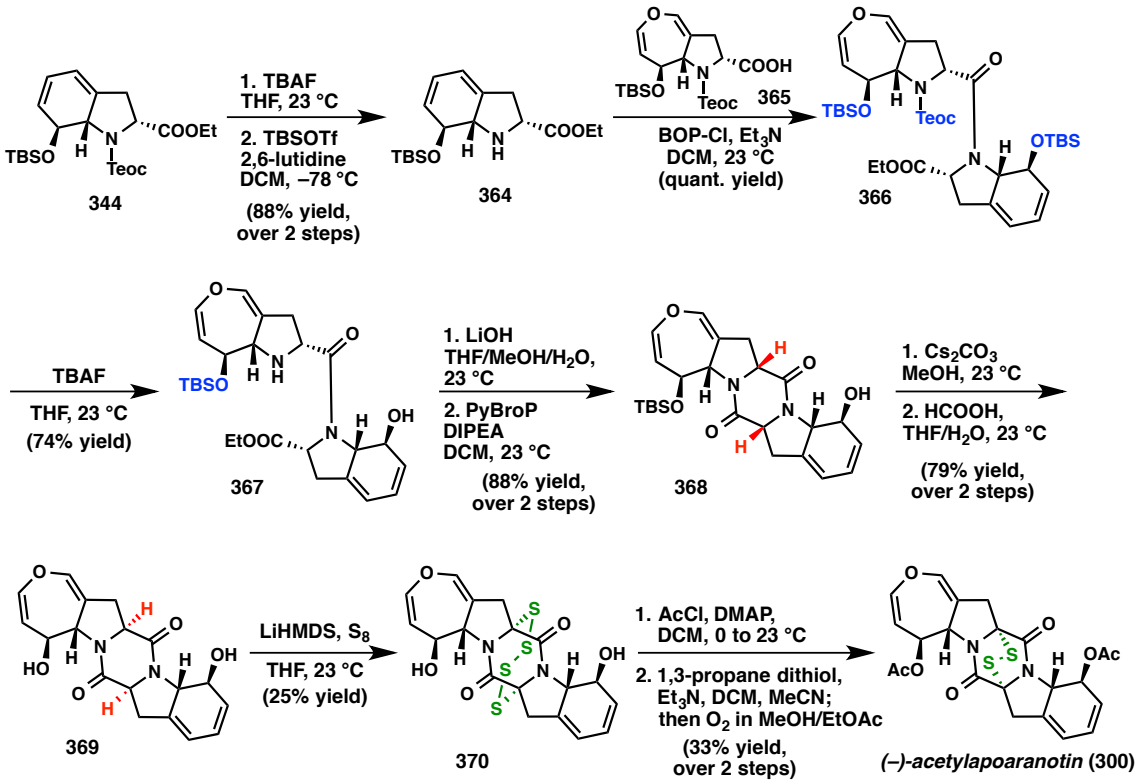


4.2.4 Total Synthesis of (–)-Acetylapoaranotin

Aware that the cyclohexadiene alcohol moiety readily undergoes both elimination and oxidation, a mild and *stepwise* DKP formation strategy was investigated.

Cyclohexadienol **344** was transformed to TBS-ether **364** by global desilylation and reprotection of the more reactive secondary alcohol group (Scheme 4.10). Secondary amine **364** was then coupled with carboxylic acid **365** (prepared according to reference 4)

Scheme 4.10. *Completion of (–)-acetylapoaranotin total synthesis*



to provide dipeptide **366**. Interestingly, it was found that the Teoc group as well as the TBS group on the cyclohexadienol fragment could be selectively removed using TBAF, while the TBS group on the dihydrooxepine fragment remained intact. The resulting ethyl ester was then hydrolyzed and subjected to peptide coupling reagent PyBroP to provide DKP **368** without any sign of aromatized product. DKP **368** was then epimerized using Cs_2CO_3 and removal of the last TBS group was effected under mildly acidic conditions. Notably, attempts to employ TBAF for desilylation gave exclusively aromatized side product. Diol **369** was subjected to LiHMDS/S_8 to afford tetrasulfide **370**, accompanied with a small amount of aromatized side product. Nevertheless, tetrasulfide **370** could be advanced to (–)-acetylapoaranotin (**300**) following the previously established two-step protocol.[4] Thus, (–)-**300** was successfully prepared for the first time in 22 steps starting

from commercially available starting materials. Ongoing efforts focus on optimization of the current synthetic route.

4.3 CONCLUDING REMARKS

In summary, we have developed an efficient asymmetric synthetic route allowing access to a series of natural products in the cyclohexadienol ETP subfamily including (–)-emethallicin E (**298**), (–)-haematocin (**299**), (–)-acetylapoaranotin (**300**). Through this endeavor, it was found that the labile nature of the allylic alcohol cyclohexadienol fragment required a mild and eventually stepwise DKP formation strategy to prepare the core of (–)-acetylapoaranotin (**300**). By employing this strategy, the first enantioselective total synthesis of (–)-**300** was accomplished in 22 steps (longest linear sequence).

Intermediates in this synthetic route could be intercepted to synthesize other related 6,5-bicyclic ETP subfamilies, for example, (–)-epicorazine A (**301**, Figure 4.1) and (–)-epiccocin C (**302**). Synthetic studies directed toward realizing this goal are ongoing in our laboratory.

4.4 EXPERIMENTAL SECTION

4.4.1 Materials and Methods

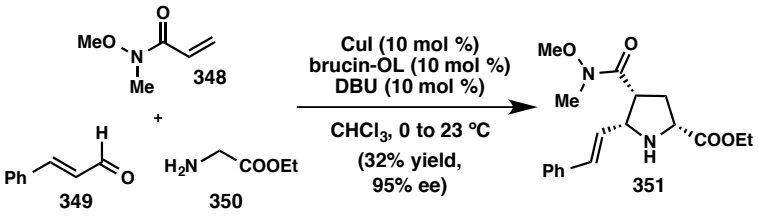
Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise 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.[21] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Bruker 400 equipped with a cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), $CHDCl_2$ (^1H, $\delta = 5.32$), CD_2HOD (^1H, $\delta = 3.31$), MeCN-*d2* (^1H, $\delta = 1.94$), or DMSO-*d5* (^1H, $\delta = 2.50$), and $CDCl_3$ (^{13}C, $\delta = 77.0$), CD_2Cl_2 (^{13}C, $\delta = 54.0$), CD_3OD (^{13}C, $\delta = 49.0$), MeCN-*d3* (^{13}C, $\delta = 118.3$), or DMSO-*d6* (^{13}C, $\delta = 40.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. 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.

4.4.2 Preparative Procedures and Spectroscopic Data

Preparation of pyrrolidine 351

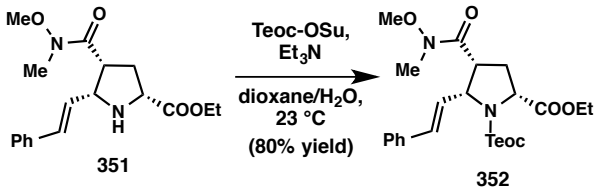


(Isolation of ethyl glycinate) The ethyl glycinate HCl salt (5.1 g, 36.5 mmol) was freebased by first being taken up in DCM (10 mL) then washed with 3.56M KOH (10 mL). The layers were separated and the aqueous phase was further extracted with DCM (2 x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated down by rotary evaporation to yield 3.14 g of glycinate ethyl ester **350** (83% recovery).

(Formation of imime) The free amine **350** (3.14 g, 30.5 mmol, 1.0 equiv) was taken up in $CHCl_3$ (61 mL) with silica gel (9.1 g, 0.3 g/mmol) and cooled to 0 °C under air. Cinnamaldehyde **349** (3.8 mL, 30.5 mmol, 1.0 equiv) was added dropwise, and the solution was kept at 0 °C for 7 hours while capped. The silica gel was filtered off and rinsed with more $CHCl_3$. The resulting imine was used immediately.

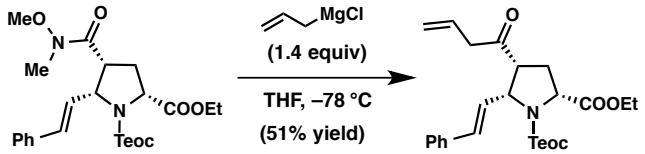
(Dipolar cycloaddition reaction) A round-bottom flask was charged with brucin-OL (1.31 g, 3.05 mmol, 10 mol %), CuI (580 mg, 3.05 mmol, 10 mol %) and $CHCl_3$ (61 mL) then cooled to 0 °C. After 5 minutes, DBU (0.46 mL, 3.05 mmol, 10 mol %) was added and the solution went from cream to deep jade-green over the next twenty minutes. Weinreb amide acrylamide **348** (3.88 g, 33.7 mmol, 1.1 equiv) was added followed by the filtered imine slowly over 10 minutes. The solution was kept at 0 °C for 5.5 hours before being warmed up to room temperature and stirred for another 23 hours. The crude reaction was concentrated down to roughly half the volume, and directly subjected to silica gel column chromatography using a gradient of 20 to 100% EtOAc in hexanes (with 1% Et_3N) to yield 3.21 g (32% yield, 9.7 mmol) of pyrrolidine **351** as a thick light brown oil. The enantiomeric excess of **351** was determined to be 95% by chiral HPLC analysis (OD, 1 mL/min, 15% IPA in hexanes, λ = 254 nm): t_R(major) = 24.2 min, t_R(minor) = 14.2 min. $[\alpha]_D^{25}$ = +152° (*c* = 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 7.21 – 7.16 (m, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.10 (dd, *J* = 15.7, 8.3 Hz, 1H), 4.22 (qd, *J* = 7.1, 3.2 Hz, 2H), 4.12 (t, *J* = 7.9 Hz, 1H), 3.86 (t, *J* = 8.4 Hz, 1H), 3.65 (s, 3H), 3.59 (q, *J* = 7.7 Hz, 1H), 3.05 (s, 3H), 2.56 (s, 1H), 2.45 – 2.28 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$) δ 173.7, 173.4, 136.6, 131.9, 128.3, 127.5, 127.4, 126.4, 63.6, 61.3, 61.0, 59.8, 45.3, 33.2, 32.2, 14.1; FTIR (NaCl/thin film) 3340, 3298, 3057, 3024, 2979, 2937, 2902, 1955, 1882, 1735, 1654, 1599, 1493, 1448, 1388, 1321, 1255, 1197, 1108, 1073, 1056, 1028, 1008, 969, 901, 861, 834, 786, 754 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{24}N_2O_4$ $[M+H]^+$ 333.1809, found 333.1817.

Preparation of Teoc-pyrrolidine 352



Pyrrolidine **351** (1.77 g, 5.31 mmol, 1.0 equiv) was suspended in H_2O (14 mL) and 1,4-dioxane (14 mL). Triethylamine (1.48 mL, 10.62 mmol, 2.0 equiv) was added followed by Teoc-OSu (2.06 g, 7.96 mmol, 1.5 equiv). The resulting solution was allowed to stir for 20 hours at room temperature. The solution was acidified with 36 mL 1M HCl then extracted with DCM (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to yield a light orange oil. Flash chromatography (50% to 60% EtOAc in hexanes) afforded Teoc-pyrrolidine **352**, as a thick yellow oil (2.03 g, 4.26 mmol, 80% yield). $[\alpha]_D^{25}$ = +101° (*c* = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 7.38 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 6.70 (dd, *J* = 15.8, 1.1 Hz, 1H), 6.05 (dd, *J* = 15.8, 7.6 Hz, 1H), 4.92 (t, *J* = 7.8 Hz, 1H), 4.30 (dd, *J* = 10.3, 7.6 Hz, 1H), 4.21 (qd, *J* = 7.1, 1.0 Hz, 2H), 4.18 – 4.12 (m, 2H), 3.75 (s, 3H), 3.61 (dt, *J* = 12.2, 7.4 Hz, 1H), 3.08 (s, 3H), 2.46 (q, *J* = 12.0 Hz, 1H), 2.33 (dt, *J* = 13.0, 7.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.97 (dd, *J* = 8.8, 7.5 Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, compound exists as a 1:1 mixture of rotamers) δ 173.8, 173.5, 171.3, 155.8, 155.0, 137.8, 132.8, 129.6, 128.6, 127.7, 127.3, 127.2, 64.3, 64.2, 62.3, 62.0, 61.8, 61.7, 61.2, 59.7, 59.4, 46.6, 45.9, 32.8, 31.6, 30.6, 18.4, 18.3, 14.6, -1.4, -1.5; FTIR (NaCl, thin film): 2953, 2900, 1747, 1700, 1668, 1404, 1345, 1282, 1250, 1186, 1112, 1038, 1012, 961, 860, 838, 756, 694 cm^{-1}; HRMS (MM) calc'd for $C_{22}H_{33}N_2O_6Si$ $[M–C_2H_4+H]^+$ 449.2102, found 449.2110 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of diene 347

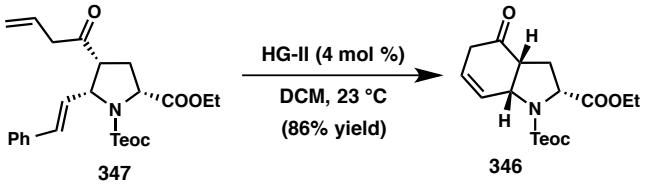


352 347

Weinreb amide **352** (2.37 g, 4.97 mmol, 1.0 equiv) was dissolved in dry THF (42 mL) under N_2 and the solution was brought to –78 °C. A solution of allyl Grignard (0.85M in THF, diluted two times with THF from commercially available reagent; 8.2 mL, 6.96 mmol, 1.4 equiv) was added slowly over the course of 4 hours using a syringe pump at –78 °C. When the addition was done, the reaction was allowed to stir for another 10 minutes before being quenched with 30 mL of AcOH/THF/H_2O (1:1:1) and warmed to room temperature. The reaction was then carefully basified with saturated $NaHCO_3$ solution until no more bubbles occurred. The aqueous layer was then extracted with EtOAc (3 x 150 mL). Combined organic layer was washed with brine (200 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a yellow oil. Flash chromatography (5% to 30% EtOAc in hexanes) afforded diene **347**, as a yellow oil (1.15 g, 2.51 mmol, 51% yield). $[\alpha]_D^{25} = –8°$ (c = 0.495, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 7.39 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 6.77 (dd, J = 15.9, 0.9 Hz, 1H), 6.01 (ddd, J = 15.7, 8.1, 0.8 Hz, 1H), 5.95 – 5.77 (m, 1H), 5.16 – 5.10 (m, 1H), 5.12 – 5.07 (m, 1H), 4.97 (t, J = 8.0 Hz, 1H), 4.30 (dd, J = 9.8, 8.0 Hz, 1H), 4.20 (qt, J = 7.2, 1.2 Hz, 2H), 4.17 – 4.10 (m, 2H), 3.55 (dt, J = 11.6, 7.5 Hz, 1H), 3.26 (dt, J = 6.9, 1.3 Hz, 2H), 2.48 – 2.23 (m, 2H), 1.27 (td, J = 7.1, 0.7 Hz, 3H), 1.06 – 0.88 (m, 2H), 0.03 (d, J = 0.8 Hz, 9H); ^{13}C NMR (101 MHz, CD_3CN, compound exists as a 1:1 mixture of rotamers) δ 205.5, 205.4, 173.6, 173.3, 155.6, 154.8, 137.5, 133.74, 133.68, 131.6, 129.7, 128.9,

128.8, 127.3, 126.6, 126.5, 119.1, 64.4, 64.3, 62.1, 62.0, 61.9, 61.7, 59.8, 59.5, 54.7, 54.1, 48.2, 30.5, 29.5, 18.4, 14.6, -1.47, -1.52; FTIR (NaCl, thin film): 3082, 3060, 3024, 2981, 2952, 2899, 1749, 1702, 1450, 1408, 1371, 1344, 1285, 1250, 1185, 1168, 1110, 1038, 962, 924, 860, 837, 751, 694 cm^{-1}; HRMS (MM) calc'd for $C_{23}H_{32}NO_5Si$ $[M–C_2H_4+H]^+$ 430.2044, found 430.2053 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

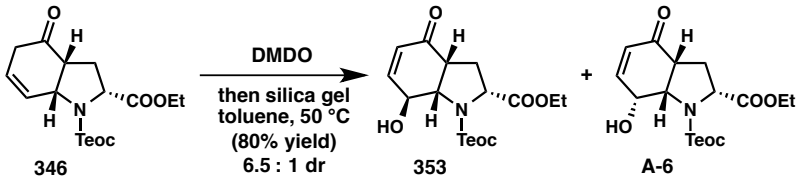
Preparation of ketone 346



To a 500 mL flame-dried flask was added diene **347** (1.15 g, 2.51 mmol, 1.0 equiv) and DCM (250 mL). Hoveyda-Grubbs II catalyst (63 mg, 0.10 mmol, 4 mol %) was added and the resulting light green solution was allowed to stir at room temperature for 4 hours. The reaction was then quenched with DMSO (380 μL, 50 equiv) and stirred for another 22 hours. It was filtered through a silica gel plug, eluting with EtOAc, and the filtrate was concentrated down to give a light brown oil. Flash chromatography (5% to 25% EtOAc in hexanes) afforded ketone **346**, as a light brown oil (761 mg, 2.15 mmol, 86% yield). $[\alpha]_D^{25} = –117°$ (c = 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 65 °C) δ 6.04 (dq, J = 10.2, 2.5 Hz, 1H), 5.80 (dtd, J = 10.2, 3.7, 1.6 Hz, 1H), 4.79 (dt, J = 7.6, 2.3 Hz, 1H), 4.32 (dd, J = 8.3, 7.1 Hz, 1H), 4.24 – 4.15 (m, 2H), 4.12 (qd, J = 7.1, 1.1 Hz, 2H), 3.05 (q, J = 8.0 Hz, 1H), 2.99 – 2.80 (m, 2H), 2.45 – 2.26 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 65 °C) δ 207.5, 173.3, 155.8, 128.1, 124.4, 64.7, 62.2, 61.2, 60.2, 51.0, 38.2, 32.8, 19.0, 14.8, -1.0; FTIR

(NaCl, thin film): 3042, 2953, 2899, 1749, 1703, 1454, 1412, 1350, 1249, 1186, 1112, 1033, 988, 964, 946, 860, 838, 769, 695 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{24}NO_5Si$ [M–C_2H_4+H]$^+$ 326.1418, found 326.1419 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of enone 353

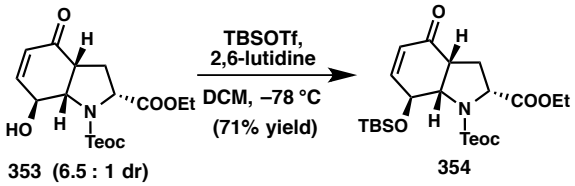


To ketone **346** (761 mg, 2.15 mmol, 1.0 equiv) in a 200 mL round-bottom flask was added freshly prepared DMDO acetone solution (0.0905 M, 48 mL, 4.30 mmol, 2.0 equiv) and the resulting solution was allowed to stir at room temperature for 90 minutes (the reaction was monitored by taking ^{1}H NMR spectra of aliquot of the reaction solution). The reaction was then concentrated down and put under high vacuum for 90 minutes to get rid of residue solvent. The crude material was then dissolved in toluene (215 mL) and mixed with silica gel (17.2 g). The resulting mixture was heated to 50 °C for 1 hour and cooled down to room temperature. It was filtered through a silica gel plug, eluting with EtOAc, and the filtrate was concentrated down to give a light brown oil. Flash chromatography (5% to 40% EtOAc in hexanes) afforded enone **353**, (6.5 : 1 mixture of diastereomers by ^{1}H NMR), as a thick colorless oil (630 mg, 1.71 mmol, 80% yield). The mixture of diastereomers was carried to the next reaction. Analytically pure products were isolated using preparative reverse phase HPLC (50% to 60% CH_3CN in H_2O over 10 minutes, t_R(**353**) = 8.0-8.7 min, t_R(**A-6**) = 9.5-10.0 min).

*Major diastereomer **353***. $[\alpha]_D^{25}$ = –23° (*c* = 1.925, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 10.4, 2.1 Hz, 1H), 6.00 (dd, *J* = 10.4, 2.5 Hz, 1H), 4.91 (s, 1H), 4.78 (dt, *J* = 7.2, 2.3 Hz, 1H), 4.38 (dd, *J* = 8.6, 7.3 Hz, 1H), 4.33 (dd, *J* = 9.8, 7.6 Hz, 1H), 4.25 – 4.12 (m, 4H), 3.04 (dt, *J* = 12.8, 8.2 Hz, 1H), 2.65 (dt, *J* = 12.7, 7.6 Hz, 1H), 1.95 (td, *J* = 12.8, 9.7 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.01 – 0.88 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 171.7, 156.8, 150.5, 126.9, 70.0, 65.2, 65.1, 61.6, 59.2, 45.6, 32.8, 17.7, 14.1, -1.6; FTIR (NaCl, thin film): 3413, 2953, 2899, 1744, 1676, 1457, 1420, 1374, 1350, 1304, 1250, 1215, 1188, 1166, 1118, 1069, 1032, 960, 861, 839, 770, 695 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{24}NO_6Si$ $[M–C_2H_4+H]^+$ 342.1367, found 342.1378 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

*Minor diastereomer **A-6***. $[\alpha]_D^{25}$ = –58° (*c* = 0.405, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 7.08 (dd, *J* = 10.0, 5.9 Hz, 1H), 6.10 (d, *J* = 10.0 Hz, 1H), 4.70 – 4.56 (m, 1H), 4.39 (dd, *J* = 9.5, 7.9 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.27 – 4.15 (m, 5H), 3.08 (dt, *J* = 12.0, 8.3 Hz, 1H), 2.62 (dt, *J* = 12.2, 8.2 Hz, 1H), 2.13 (app q, *J* = 11.6 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.10 – 0.90 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, compound exists as a mixture of rotamers) δ 198.7, 175.2, 155.7, 148.0, 147.2, 132.3, 131.9, 64.9, 63.2, 62.7, 61.6, 60.8, 60.4, 47.1, 46.7, 34.5, 33.9, 18.3, 14.4, -1.5; FTIR (NaCl, thin film): 3445, 2953, 2900, 1698, 1404, 1377, 1348, 1303, 1251, 1203, 1177, 1114, 1065, 1030, 999, 975, 942, 899, 853, 838, 769, 696 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{24}NO_6Si$ $[M–C_2H_4+H]^+$ 342.1367, found 342.1376 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

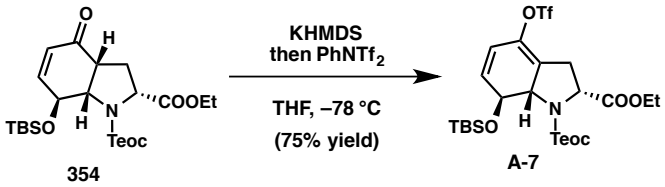
Preparation of TBS ether 354



To enone **353** (462 mg, 1.25 mmol, 1.0 equiv; as a 6.5 : 1 mixture of diastereomers) in a flame-dried 50 mL round-bottom flask was added dry DCM (12 mL), which was brought to –78 °C. 2,6-Lutidine (0.72 mL, 6.25 mmol, 5.0 equiv) was added, followed by slow addition of TBSOTf (0.57 mL, 2.50 mmol, 2.0 equiv). The resulting clear solution was allow to stir at –78 °C for 90 minutes. It was quenched with pH7 buffer (15 mL) and warmed to room temperature. The mixture was then separated and the aqueous layer was then extracted with EtOAc (3 x 20 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered and concentrated down to give a colorless oil (extra time under high vacuum could remove the residue 2,6-lutidine and help the subsequent purification step). Flash chromatography (1% to 18% EtOAc in hexanes) afforded TBS ether **354** as a single diastereomer, as a colorless oil (425 mg, 0.825 mmol, 71% yield). $[\alpha]_D^{25}$ = +49° (*c* = 0.650, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 6.79 (dd, *J* = 10.3, 2.8 Hz, 1H), 6.13 – 5.74 (m, 1H), 4.86 (br s, 1H), 4.43 – 4.37 (m, 2H), 4.22 (app q, *J* = 8.8 Hz, 1H), 4.18 – 4.04 (m, 3H), 2.96 (dt, *J* = 10.1, 7.5 Hz, 1H), 2.52 (dt, *J* = 12.9, 8.2 Hz, 1H), 2.11 (q, *J* = 10.5 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 8.5 Hz, 2H), 0.95 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 197.7, 173.6, 156.8, 151.9, 129.0, 69.4, 66.3, 64.8, 62.3, 61.3, 48.1, 33.4, 26.6, 19.0, 18.9, 14.9, -1.1, -4.0, -4.2; FTIR (NaCl, thin film): 2953, 2929, 2896, 2856, 1748, 1701, 1682, 1462, 1405, 1375, 1340, 1319, 1289, 1250, 1211, 1187, 1155, 1099, 1058, 985, 956, 939, 862, 829, 779 cm^{-1}; HRMS (MM) calc'd

for $C_{21}H_{38}NO_6Si_2$ $[M–C_2H_4+H]^+$ 456.2232, found 456.2231 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

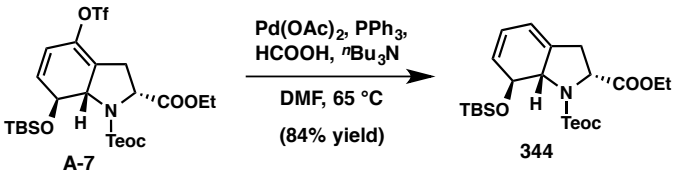
Preparation of vinyl triflate A-7



A flame-dried 50 mL round-bottom flask was charged with TBS ether **354** (200 mg, 0.41 mmol, 1.0 equiv), which was dissolved in dry THF (7.4 mL) and cooled to –78 °C. A solution of KHMDS (0.5M in toluene, 0.9 mL, 0.45 mmol, 1.1 equiv) was added slowly. The reaction solution turned dark red upon addition and was stirred for 5 minutes before the addition of a THF solution of $PhNTf_2$ (162 mg, 0.45 mmol, 1.1 equiv; prepared by dissolving 180 mg in 1 mL THF and used 0.9 mL). It was reacted for another 2 hours before quenching with 1% NaOH solution (10 mL) and warmed to room temperature. The mixture was then separated and the organic layer was washed with 1% NaOH solution (10 mL). The aqueous layer was then extracted with ether (3 x 20 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered and concentrated down to give a light yellow oil. Flash chromatography (1% to 8% EtOAc in hexanes) afforded vinyl triflate **A-7**, as a colorless oil (191 mg, 0.31 mmol, 75% yield; **A-7** was labile and it is recommended to carry to the next reaction as soon as possible). $[\alpha]_D^{25}$ = +14° (*c* = 0.69, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 5.96 (d, *J* = 10.2 Hz, 1H), 5.87 (dd, *J* = 10.2, 2.3 Hz, 1H), 5.06 – 4.90 (m, 3H), 4.28 (ddd, *J* = 10.9, 9.3, 7.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.09 (ddd, *J* = 10.8, 9.2, 7.1 Hz, 1H), 3.00 – 2.76 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.03 (ddd, *J* = 9.3, 7.0, 1.8 Hz, 2H), 0.93 (s,

9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 172.8, 157.1, 140.7, 138.6, 132.1, 124.6, 121.7, 121.5, 115.1, 75.6, 67.8, 65.2, 64.6, 62.7, 31.9, 26.7, 19.1, 18.8, 14.8, -1.1, -4.0, -4.4 (one of the quartet of -CF_3 carbons is masked under the solvent peak and the rest of the three peaks are underlined); FTIR (NaCl, thin film): 3426, 2954, 2930, 2898, 2857, 1750, 1722, 1709, 1423, 1403, 1361, 1334, 1295, 1251, 1213, 1142, 1104, 1037, 973, 943, 894, 839, 779, 769, 693, 619 cm^{-1}; HRMS (MM) calc'd for $C_{22}H_{37}F_3NO_8SSi_2$ $[M–C_2H_4+H]^+$ 588.1725, found 588.1744 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

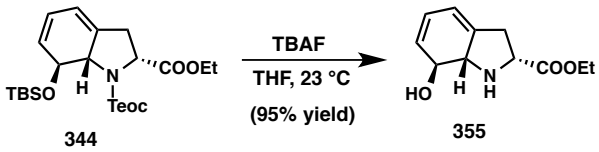
Preparation of diene 344



To a flame-dried 50 mL round-bottom flask was added vinyl triflate **A-7** (260 mg, 0.42 mmol, 1.0 equiv), $Pd(OAc)_2$ (19 mg, 0.084 mmol, 20 mol %), and PPh_3 (44 mg, 0.169 mmol, 40 mol %). The system was purged with N_2 and charged with dry DMF (8 mL), ^{n}Bu$_3$N (0.50 mL, 2.11 mmol, 5.0 equiv), and HCOOH (48 μL, 1.27 mmol, 3.0 equiv). The resulting yellow clear solution was then heated to 65 °C for 15 minutes, at which point the reaction turned black. It was then diluted with EtOAc (25 mL) and washed with 1M HCl (25 mL), H_2O (25 mL) and brine (25 mL). The aqueous layers were each extracted with ether (20 mL). Combined organic layer was then dried over Na_2SO_4, filtered and concentrated down to give a brown oil. Flash chromatography (1% to 10% EtOAc in hexanes) afforded diene **344**, as a light yellow oil (165 mg, 0.35 mmol, 84% yield). $[\alpha]_D^{25}$ = +55° (*c* = 1.43, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 5.88 –

5.81 (m, 1H), 5.81 – 5.73 (m, 1H), 5.65 (d, *J* = 9.6 Hz, 1H), 4.87 – 4.76 (m, 2H), 4.74 – 4.64 (m, 1H), 4.33 – 4.23 (m, 1H), 4.17 (qd, *J* = 7.1, 1.0 Hz, 2H), 4.07 (ddd, *J* = 10.8, 9.0, 7.3 Hz, 1H), 2.93 – 2.80 (m, 1H), 2.63 (d, *J* = 15.9 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.02 (ddd, *J* = 8.8, 7.1, 1.1 Hz, 2H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 173.5, 157.6, 142.0, 135.3, 125.6, 119.1, 76.7, 66.7, 64.7, 64.3, 62.3, 35.1, 26.8, 19.2, 18.9, 15.0, -1.0, -3.8, -4.3; FTIR (NaCl, thin film): 3049, 2954, 2928, 2897, 2855, 1750, 1722, 1699, 1472, 1398, 1361, 1329, 1290, 1250, 1204, 1180, 1105, 1031, 958, 839, 776, 701, 670 cm^{-1}; HRMS (MM) calc'd for $C_{21}H_{38}NO_5Si_2$ $[M–C_2H_4+H]^+$ 440.2283, found 440.2298 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

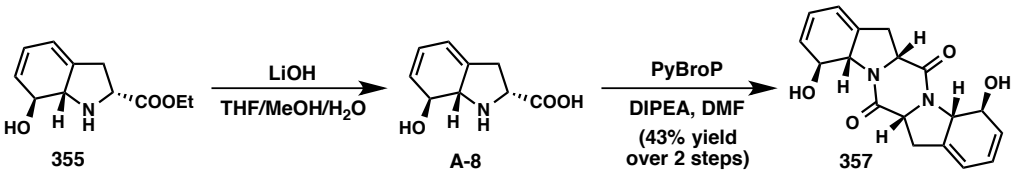
Preparation of dienol 355



Diene **344** (28.6 mg, 0.061 mmol, 1.0 equiv) was dissolved in dry THF (1.1 mL) in a 1-dram vial. TBAF (1M in THF, 0.18 mL, 0.18 mmol, 3 equiv) was added and the resulting light brown solution was allowed to stir at room temperature for 2 hours and 20 minutes before being quenched with saturated Na_2SO_4 solution (2 mL). The mixture was then further diluted with brine (1 mL) and extracted with EtOAc (12 x 5 mL). Each of the EtOAc extractions was filtered through a short silica gel plug. Combined organic layer was concentrated down to give a light brown oil. Flash chromatography (60% to 100% EtOAc in hexanes) afforded dienol **355**, as a light brown oil (12.9 mg, 0.06 mmol, 95% calculated yield, accompanied by 5% aromatized side product). $[\alpha]_D^{25}$ = +190° (*c* = 0.60, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 9.7, 4.8, 2.8 Hz, 1H), 5.71 (dt, *J* =

4.9, 2.5 Hz, 1H), 5.65 (d, *J* = 9.8 Hz, 1H), 4.58 (d, *J* = 15.1 Hz, 1H), 4.21 (qd, *J* = 7.1, 2.5 Hz, 2H), 3.86 (t, *J* = 8.0 Hz, 1H), 3.82 (dd, *J* = 14.2, 2.8 Hz, 1H), 3.04 (br s, 2H), 2.90 (dd, *J* = 17.7, 8.3 Hz, 1H), 2.66 (dd, *J* = 17.6, 7.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 141.1, 130.3, 124.7, 115.9, 74.8, 66.4, 61.2, 59.3, 33.9, 14.2; FTIR (NaCl, thin film): 3337, 3043, 2980, 2928, 2853, 1738, 1553, 1446, 1377, 1329, 1200, 1082, 1061, 1033, 862, 750, 711 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.1125, found 210.1125.

Preparation of *syn*-diol 357

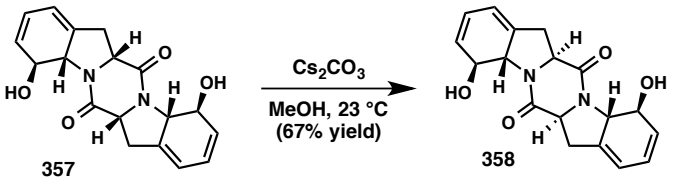


In a half-a-dram vial, dienol **355** (1.2 mg, 0.006 mmol, 1.0 equiv) was dissolved in THF (50 μL) and MeOH (50 μL). A solution of LiOH (1.4 mg, 0.060 mmol, 10 equiv) in water (50 μL) was added into the vial and the reaction was allowed to stir at room temperature for 10 minutes. It was then quenched with 1M HCl (57 μL) and all the solvents were removed under vacuum to provide a brown oil/solid crude material. It was subjected to the next reaction *directly*. Due to the high polarity of amino acid **A-8**, analytical pure sample could be obtained by preparative reverse phase HPLC (0% to 5% CH_3CN in H_2O over 10 minutes, t_R = 3.0-7.0 min). $[\alpha]_D^{25}$ = +254° (*c* = 0.33, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.91 (ddd, *J* = 9.7, 4.9, 2.7 Hz, 1H), 5.84 (dt, *J* = 5.0, 2.6 Hz, 1H), 5.68 (dd, *J* = 9.7, 1.8 Hz, 1H), 4.81 (d, *J* = 14.9 Hz, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 4.03 (dd, *J* = 9.1, 7.4 Hz, 1H), 3.05 (dd, *J* = 17.9, 9.0 Hz, 1H), 2.81 (dd, *J* = 17.7, 7.3 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 174.7, 138.1, 131.3, 125.7, 118.7, 72.3,

67.8, 62.9, 33.8; FTIR (NaCl, thin film): 3380, 3044, 2916, 2849, 1624, 1417, 1380, 1314, 1253, 1145, 1068, 987, 875, 833, 794, 762, 712, 624 cm^{-1}; HRMS (MM) calc'd for $C_9H_{12}NO_3$ $[M+H]^+$ 182.0812, found 182.0815.

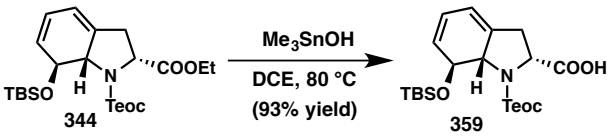
The crude material was first dissolved in small amount of MeOH (ca. 0.1 mL) and co-evaporated with benzene to further get rid of water. It was then dissolved in DMF (0.3 mL). Under N_2, DIPEA (6 μL, 0.034 mmol, 6 equiv), and PyBroP (10.7 mg, 0.023 mmol, 4 equiv) were added in sequence. The resulting light brown solution was allowed to stir at room temperature for 22 hours. It was then quenched with saturated $NaHCO_3$ (1 mL). The mixture was separated and the aqueous layer was then extracted with DCM (5 x 1 mL). Combined organic layer was washed with brine (5 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a light brown oil. Preparative TLC (80% EtOAc in hexanes) afforded *syn*-diol **357**, as a white solid (0.4 mg, 0.0012 mmol, 43% yield over 2 steps). $[\alpha]_D^{25}$ = +230° (*c* = 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 1.3 Hz, 1H), 5.93 (ddd, *J* = 9.5, 5.0, 2.8 Hz, 1H), 5.89 – 5.82 (m, 1H), 5.75 (ddt, *J* = 9.6, 2.0, 1.0 Hz, 1H), 4.75 – 4.65 (m, 1H), 4.48 (dd, *J* = 13.2, 3.0 Hz, 1H), 4.41 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.34 – 3.18 (m, 1H), 3.16 – 2.93 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 133.4, 129.5, 123.6, 118.7, 71.8, 68.9, 60.5, 29.3; FTIR (NaCl, thin film): 3281, 2922, 2853, 1651, 1423, 1381, 1351, 1336, 1295, 1273, 1255, 1230, 1192, 1147, 1083, 1061, 721, 671 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1339, found 327.1342.

Preparation of *anti*-diol 358



A 1-dram vial was charged with *syn*-diol **357** (1.2 mg, 0.0037 mmol, 1.0 equiv) and Cs_2CO_3 (48 mg, 0.147 mmol, 40 equiv). In the meantime, dry MeOH (0.75 mL) was fully degassed by bubbling N_2 through and was added to the vial under N_2. The resulting mixture gradually turned into a clear yellow solution and was stirred for 30 minutes. It was then quenched with saturated $NaHCO_3$ (3 mL) and the mixture was extracted with EtOAc (5 x 3 mL). Combined organic layer was washed with brine (15 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (20% to 100% EtOAc in hexanes) afforded *anti*-diol **358**, as a white solid (0.8 mg, 0.0024 mmol, 67% yield). $[\alpha]_D^{25} = -159°$ (c = 0.075, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.96 – 5.86 (m, 2H), 5.76 (dt, J = 9.5, 1.4 Hz, 1H), 4.78 – 4.63 (m, 3H), 2.99 (dd, J = 15.5, 7.2 Hz, 1H), 2.88 (t, J = 13.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 132.7, 130.0, 123.0, 119.0, 73.6, 68.1, 62.5, 32.2; FTIR (NaCl, thin film): 3305, 3039, 2924, 2853, 2713, 1626, 1553, 1447, 1381, 1354, 1330, 1290, 1265, 1237, 1201, 1139, 1087, 1057, 767, 710 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1339, found 327.1336.

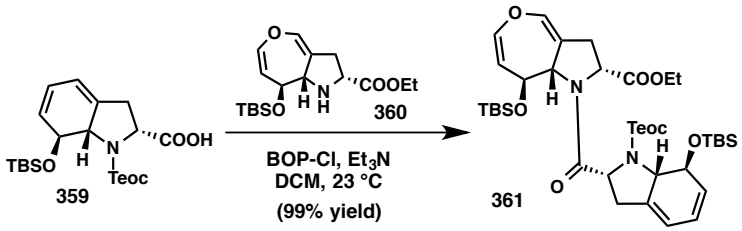
Preparation of carboxylic acid 359



Diene **344** (9.1 mg, 0.019 mmol, 1.0 equiv) was transferred to a 0.5-dram vial, to which was added Me_3SnOH (35.2 mg, 0.195 mmol, 10 equiv) and dry DCE (0.4 mL).

The vial was then sealed with a Teflon cap and heated to 80 °C for 22 hours. It was then cooled to room temperature and quenched with pH2.5 buffer (0.5 mL). The mixture was separated and the aqueous layer was then extracted with EtOAc (5 x 1 mL). Combined organic layer was washed with brine (5 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a light brown oil. Flash chromatography (1% to 6% MeOH in DCM) afforded carboxylic acid **359**, as a light brown oil (7.9 mg, 0.018 mmol, 93% yield). $[\alpha]_D^{25}$ = +44° (*c* = 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.77 (m, 2H), 5.69 (d, *J* = 9.5 Hz, 1H), 4.93 – 4.79 (m, 1H), 4.72 (d, *J* = 14.4 Hz, 1H), 4.58 (d, *J* = 14.4 Hz, 1H), 4.38 (d, *J* = 10.3 Hz, 1H), 4.09 (q, *J* = 9.5 Hz, 1H), 2.99 – 2.77 (m, 2H), 1.07 (dd, *J* = 9.6, 7.9 Hz, 2H), 0.90 (s, 9H), 0.04 (s, 3H), 0.04 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$, 45 °C) δ 175.1, 157.6, 139.4, 134.6, 124.3, 118.7, 75.4, 65.0, 64.6, 62.8, 32.8, 26.0, 18.2, 18.0, -1.5, -4.6, -5.1; FTIR (NaCl, thin film): 3121, 3051, 2954, 2928, 2897, 2856, 1747, 1699, 1471, 1418, 1360, 1335, 1250, 1178, 1107, 1042, 1020, 970, 957, 862, 838, 776, 700, 667, 627 cm^{-1}; HRMS (MM) calc'd for $C_{19}H_{34}NO_5Si_2$ [M–C_2H_4+H]$^+$ 412.1970, found 412.1977 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

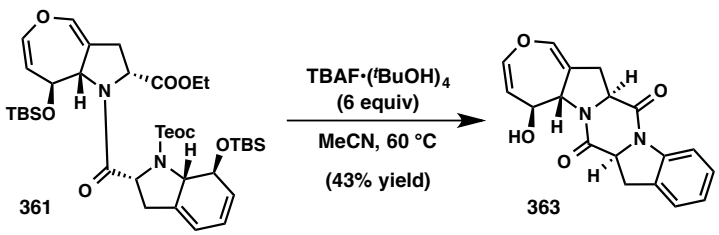
Preparation of dipeptide 361



To a 1-dram vial was transferred carboxylic acid **359** (7.9 mg, 0.018 mmol, 1.0 equiv) and amine **360** (6.7 mg, 0.020 mmol, 1.1 equiv), using DCM, and the mixture of starting materials was co-evaporated with benzene (1 mL). It was then dissolved in dry

DCM (0.35 mL), followed by the addition of Et_3N (25 μL, 0.18 mmol, 10 equiv) and BOP-Cl (22.9 mg, 0.09 mmol, 5 equiv). The mixture was allowed to stir at room temperature for 25 hours and quenched with saturated $NaHCO_3$ (1 mL). Then the mixture was extracted with EtOAc (5 x 1 mL). Combined organic layer was washed with brine (5 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a mixture of white solid and light brown oil. Flash chromatography (2% to 8% EtOAc in hexanes) afforded dipeptide **361**, as a colorless oil (13.4 mg, 0.018 mmol, 99% yield). $[\alpha]_D^{25}$ = +38° (*c* = 0.865, $CHCl_3$); ^{1}H NMR δ (400 MHz, CD_3CN) 6.48 (td, *J* = 2.5, 1.2 Hz, 1H), 6.23 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.87 – 5.80 (m, 1H), 5.72 (qd, *J* = 2.2, 1.3 Hz, 1H), 5.67 (br s, 1H), 5.57 (d, *J* = 9.6 Hz, 1H), 5.47 (dd, *J* = 5.7, 3.0 Hz, 1H), 4.83 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.79 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.75 – 4.72 (m, 2H), 4.46 (dt, *J* = 7.9, 2.1 Hz, 1H), 4.28 – 4.18 (m, 1H), 4.13 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.98 (dt, *J* = 16.4, 8.5 Hz, 1H), 2.87 (dddd, *J* = 15.8, 10.1, 2.6, 1.6 Hz, 1H), 2.68 (dq, *J* = 15.8, 1.6 Hz, 1H), 2.65 – 2.60 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.03 – 0.98 (m, 2H), 0.93 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.06 (s, 3H), 0.02 (s, 9H), -0.08 (s, 3H), -0.10 (s, 3H); ^{13}C NMR δ (101 MHz, CD_3CN, 50 °C) 173.5, 173.3, 158.1, 145.7, 139.8, 137.3, 134.5, 126.2, 117.4, 116.9, 112.0, 75.8, 72.4, 67.7, 65.1, 64.2, 62.4, 61.7, 58.8, 35.4, 33.2, 26.8, 26.6, 19.1, 19.1, 19.0, 14.8, -1.2, -2.8, -4.1, -4.6, -5.1; FTIR (NaCl, thin film): 3049, 3014, 2954, 2929, 2895, 2856, 1747, 1717, 1694, 1652, 1472, 1463, 1428, 1393, 1348, 1329, 1315, 1250, 1213, 1179, 1139, 1094, 1039, 974, 949, 860, 837, 780, 756, 701, 667, 632 cm^{-1}; HRMS (MM) calc'd for $C_{38}H_{64}N_2O_8Si_3Na$ $[M+Na]^+$ 783.3863, found 783.3866.

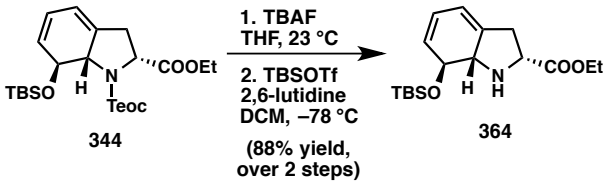
Preparation of DKP 363 (undesired reaction pathway)



A 5 mL Schlenk tube was added TBAF•(^{t}BuOH)$_4$ (4.8 mg, 0.009 mmol, 6 equiv), followed by addition of dipeptide **361** (1.1 mg, 0.0014 mmol, 1.0 equiv) as a CH_3CN solution (0.16 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 1 h and 30 min, the reaction mixture was cooled to room temperature, was diluted with saturated Na_2SO_4 solution, and extracted with EtOAc (5 x 0.5 mL). 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 preparative TLC (50% EtOAc in hexanes) afforded alcohol **363**, as a white solid (0.2 mg, 0.0006 mmol, 43% yield). $[\alpha]_D^{25}$ = –331° (*c* = 0.355, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.13 (td, *J* = 7.5, 1.1 Hz, 1H), 6.53 (q, *J* = 2.0 Hz, 1H), 6.20 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.41 (d, *J* = 4.5 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.92 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.87 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.50 (td, *J* = 9.0, 1.7 Hz, 1H), 4.40 (ddt, *J* = 8.2, 4.3, 2.1 Hz, 1H), 3.61 (ddt, *J* = 16.6, 10.0, 1.2 Hz, 1H), 3.41 (dd, *J* = 16.5, 10.1 Hz, 1H), 3.06 (dt, *J* =

9.0, 1.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 163.6, 140.4, 138.5, 137.7, 129.7, 128.0, 125.4, 125.0, 116.2, 110.4, 110.3, 71.5, 64.4, 61.0, 58.8, 33.2, 30.7; FTIR (NaCl, thin film): 3338, 3013, 2928, 2859, 1668, 1602, 1486, 1464, 1418, 1328, 1287, 1248, 1192, 1129, 1077, 1047, 978, 916, 860, 821, 755, 665, 625 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{15}N_2O_3$ $[M–OH]^+$ 307.1077, found 307.1081 (detected fragment has undergone loss of hydroxyl anion).

Preparation of amine 364

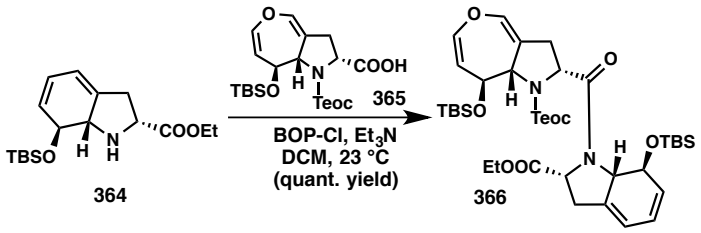


A 1-dram vial of diene **344** (24.7 mg, 0.053 mmol, 1.0 equiv) was dissolved in dry THF (0.85 mL), followed by addition of a THF solution of TBAF (1M in THF, 160 μL, 0.16 mmol, 3 equiv). The reaction solution was allowed to stir at room temperature for 2 hours and quenched with saturated Na_2SO_4 solution (5 mL). The solution was extracted using EtOAc (20 x 4 mL) and each EtOAc extraction was filtered through a short silica gel plug. Combined organic layer was concentrated down to give a brown oil, which was subjected to the next reaction immediately.

The crude material was dissolved in DCM (0.5 mL) and the solution was brought down to –78 °C. 2,6-Lutidine (31 μL, 0.265 mmol, 5 equiv) was added, followed by TBSOTf (24 μL, 0.106 mmol, 2 equiv). After stirring for 50 minutes, a second portion of TBSOTf (12 μL, 0.053 mmol, 1 equiv) was added, which was allowed to react for another 40 minutes. It was quenched with saturated NH_4Cl solution (2 mL) and extracted with EtOAc (3 x 3 mL). Combined organic layer was washed with saturated $NaHCO_3$

solution (10 mL) and brine (10 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a colorless oil. Flash chromatography (1% to 16% EtOAc in hexanes) afforded amine **364**, as a colorless oil (14.9 mg, 0.046 mmol, 88% yield). $[\alpha]_D^{25}$ = +181° (*c* = 0.745, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 9.6, 4.8, 2.1 Hz, 1H), 5.66 (dt, *J* = 5.0, 2.5 Hz, 1H), 5.55 (d, *J* = 9.6 Hz, 1H), 4.61 (d, *J* = 14.0 Hz, 1H), 4.20 (qd, *J* = 7.2, 1.8 Hz, 2H), 3.90 – 3.63 (m, 2H), 2.85 (dd, *J* = 17.7, 8.2 Hz, 1H), 2.68 (dd, *J* = 17.5, 6.8 Hz, 1H), 1.28 (td, *J* = 7.2, 1.9 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 141.4, 131.4, 124.3, 115.4, 76.2, 65.9, 60.9, 59.2, 33.4, 25.9, 18.1, 14.2, -4.38, -4.40; FTIR (NaCl, thin film): 3366, 3045, 2955, 2929, 2896, 2856, 1739, 1472, 1464, 1384, 1330, 1253, 1198, 1156, 1097, 1035, 1006, 983, 921, 892, 859, 837, 777, 705 cm^{-1}; HRMS (MM) calc'd for $C_{17}H_{30}NO_3Si$ $[M+H]^+$ 324.1989, found 324.1980.

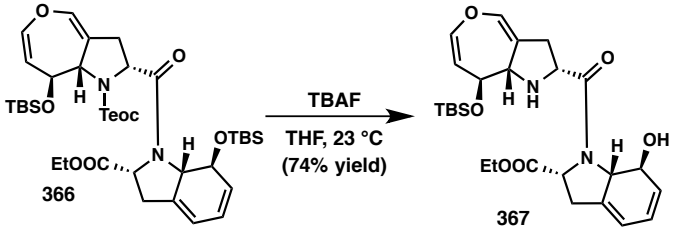
Preparation of bisTBS-dipeptide 366



To a 1-dram vial was transferred amine **364** (14.5 mg, 0.045 mmol, 1.0 equiv) and carboxylic acid **365** (21.5 mg, 0.047 mmol, 1.05 equiv), using DCM, and the mixture of starting materials was co-evaporated with benzene (1 mL). It was then dissolved in dry DCM (0.9 mL), followed by the addition of Et_3N (63 μL, 0.45 mmol, 10 equiv) and BOP-Cl (57 mg, 0.224 mmol, 5 equiv). The mixture was allowed to stir at room temperature for 25 hours and quenched with saturated $NaHCO_3$ (2 mL). The mixture was extracted with EtOAc (5 x 2 mL). Combined organic layer was washed with brine (10

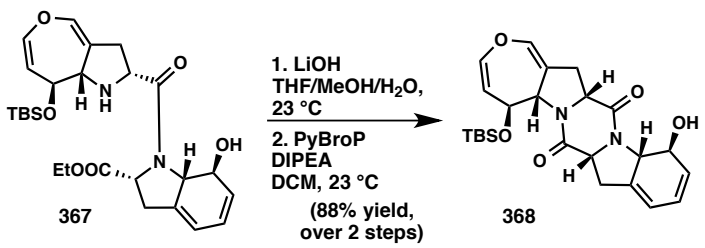
mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a mixture of white solid and light brown oil. Flash chromatography (1% to 8% EtOAc in hexanes) afforded dipeptide **366**, as a colorless oil (35 mg, 0.046 mmol, quantitative yield). $[\alpha]_D^{25}$ = +42° (*c* = 0.865, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 6.50 – 6.39 (m, 1H), 6.21 (dt, *J* = 8.2, 1.1 Hz, 1H), 5.91 (ddd, *J* = 9.6, 4.5, 1.8 Hz, 1H), 5.88 – 5.81 (m, 2H), 5.78 (d, *J* = 9.7 Hz, 1H), 5.55 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.16 (t, *J* = 5.2 Hz, 1H), 4.90 (d, *J* = 14.6 Hz, 1H), 4.68 (d, *J* = 8.3 Hz, 1H), 4.50 (s, 2H), 4.29 – 4.13 (m, 3H), 4.05 (q, *J* = 10.5, 9.7 Hz, 1H), 2.86 (ddd, *J* = 15.0, 8.6, 2.6 Hz, 2H), 2.79 – 2.74 (m, 2H), 2.61 (d, *J* = 14.9 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.07 – 1.01 (m, 1H), 0.97 (s, 9H), 0.87 (s, 9H), 0.12 (s, 6H), 0.04 (s, 3H), 0.04 (s, 9H), -0.09 (s, 3H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 174.8, 172.9, 142.8, 139.5, 135.7, 135.5, 126.3, 119.5, 111.9, 76.4, 72.0, 65.9, 65.5, 65.1, 62.9, 62.6, 56.9, 35.8, 34.3, 27.2, 26.9, 26.6, 19.3, 19.2, 18.9, 14.9, -1.1, -2.7, -3.8, -4.3, -4.4; FTIR (NaCl, thin film): 3052, 2954, 2928, 2897, 2856, 1745, 1715, 1686, 1655, 1473, 1463, 1431, 1359, 1331, 1304, 1290, 1251, 1208, 1188, 1176, 1143, 1102, 1063, 1029, 929, 837, 779, 701, 666 cm^{-1}; HRMS (MM) calc'd for $C_{26}H_{33}N_2O_6Si$ [M–$C_6H_{16}OSi$–$C_6H_{15}OSi$]$^+$ 497.2101, found 497.2110 (detected fragment has undergone elimination of *tert*-butyldimethylsilanol, as well as loss of *tert*-butyldimethylsilanolate anion).

Preparation of dipeptide 367



A 2-dram vial of bisTBS dieptide **366** (11.3 mg, 0.015 mmol, 1.0 equiv) was dissolved in dry THF (1.4 mL), followed by addition of a THF solution of TBAF (1M in THF, 90 μL, 0.09 mmol, 6 equiv). The reaction solution was allowed to stir at room temperature for 2 hours and quenched with saturated Na_2SO_4 solution (3 mL). The solution was extracted with EtOAc (4 x 3 mL) and each EtOAc extraction was filtered through a short silica gel plug. Combined organic layer was washed with brine (15 mL) and concentrated down to give a brown oil. Flash chromatography (10% to 60% EtOAc in hexanes) afforded dipeptide **367**, as a colorless oil (5.5 mg, 0.011 mmol, 74% yield). $[\alpha]_D^{25}$ = +37° (*c* = 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 – 6.28 (m, 2H), 6.09 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.84 – 5.75 (m, 2H), 5.75 – 5.67 (m, 1H), 4.96 (d, *J* = 8.6 Hz, 1H), 4.84 (dq, *J* = 13.0, 1.6 Hz, 1H), 4.80 – 4.72 (m, 1H), 4.66 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.41 (dt, *J* = 7.3, 2.1 Hz, 1H), 4.31 – 4.13 (m, 2H), 3.94 (dd, *J* = 8.1, 5.3 Hz, 1H), 3.85 – 3.80 (m, 1H), 2.99 (ddt, *J* = 14.9, 8.1, 1.8 Hz, 1H), 2.88 (dddd, *J* = 13.6, 9.2, 3.0, 1.7 Hz, 1H), 2.84 – 2.70 (m, 1H), 2.48 (ddt, *J* = 14.9, 5.5, 1.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 170.6, 138.4, 135.0, 132.8, 130.9, 122.1, 118.8, 115.4, 110.9, 73.8, 71.4, 68.4, 65.3, 62.2, 61.0, 58.7, 34.64, 34.57, 25.9, 18.0, 14.1, -4.48, -4.52; FTIR (NaCl, thin film): 3345, 2955, 2927, 2885, 2855, 1740, 1685, 1639, 1437, 1370, 1327, 1297, 1253, 1206, 1181, 1087, 1065, 1025, 878, 838, 778 cm^{-1}; HRMS (MM) calc'd for $C_{26}H_{39}N_2O_6Si$ $[M+H]^+$ 503.2572, found 503.2585.

Preparation of TBS-DKP 368

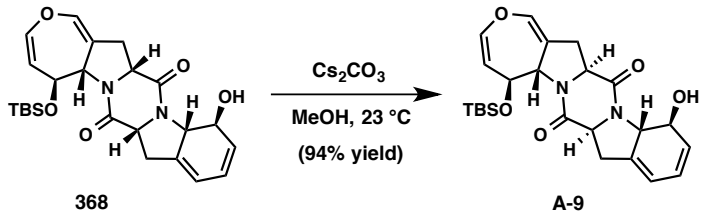


In a 1-dram vial, bisTBS-dipeptide **367** (5.5 mg, 0.011 mmol, 1.0 equiv) was dissolved in THF (180 μL) and MeOH (180 μL). A solution of LiOH (1.3 mg, 0.055 mmol, 5 equiv) in water (180 μL) was added into the vial and the reaction was allowed to stir at room temperature for 30 minutes. It was then quenched with pH7 buffer (3 mL)/brine (0.2 mL) and extracted with EtOAc (10 x 2 mL). The combined organic layer was concentrated under vacuum to provide a light yellow oil crude material. It was subjected to the next reaction directly.

The crude material was first dissolved in small amount of DCM (ca. 0.1 mL) and co-evaporated with benzene (1 mL). It was then dissolved in DCM (2.2 mL). Under N_2, DIPEA (5.7 μL, 0.033 mmol, 3 equiv) and PyBroP (10.2 mg, 0.022 mmol, 2 equiv) were added in sequence. The resulting light yellow solution was allowed to stir at room temperature for 18 hours. It was then quenched with saturated $NaHCO_3$ (4 mL). The mixture was separated and the aqueous layer was then extracted with EtOAc (5 x 4 mL). Combined organic layer was washed with brine (25 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a light yellow solid. Flash chromatography (10% to 90% EtOAc in hexanes) afforded TBS-DKP **368**, as a white solid (4.4 mg, 0.010 mmol, 88% yield over 2 steps). $[\alpha]_D^{25}$ = +38° (*c* = 0.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.48 (s, 1H), 6.22 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.91 (ddd, *J* = 9.8, 5.0, 2.8 Hz, 1H), 5.83 (dq, *J* = 5.3, 2.8 Hz, 1H), 5.74 (d, *J* = 9.7 Hz, 1H), 4.81 – 4.63 (m, 3H),

4.47 (dd, *J* = 13.3, 3.0 Hz, 1H), 4.39 (dd, *J* = 11.8, 8.3 Hz, 1H), 4.35 (dd, *J* = 11.7, 7.1 Hz, 1H), 4.02 (dt, *J* = 8.2, 1.7 Hz, 1H), 3.30 – 3.19 (m, 1H), 3.08 (dd, *J* = 19.1, 11.0 Hz, 1H), 2.90 (ddt, *J* = 16.0, 7.5, 0.9 Hz, 1H), 2.81 (ddt, *J* = 16.0, 11.0, 2.5 Hz, 1H), 0.88 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 169.0, 140.9, 138.0, 133.9, 129.2, 123.5, 118.2, 117.8, 109.4, 71.6, 71.3, 68.7, 64.2, 61.9, 61.5, 29.8, 27.9, 25.9, 18.4, -4.5, -4.9; FTIR (NaCl, thin film): 3260, 2949, 2926, 2892, 2855, 1693, 1646, 1471, 1460, 1428, 1388, 1355, 1329, 1289, 1249, 1232, 1155, 1133, 1101, 1066, 981, 940, 898, 837, 775, 721, 670, 630 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{17}N_2O_4$ [M–$C_6H_{15}OSi$]$^+$ 325.1183, found 325.1191 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion).

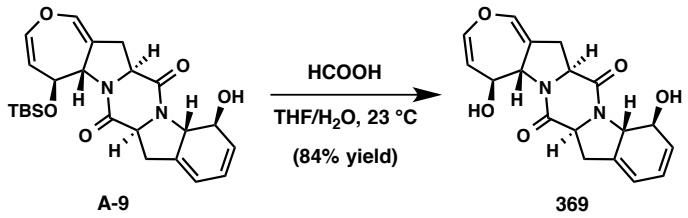
Preparation of *anti*-DKP A-9



A flame-dried 15 mL round-bottom flask was charged with TBS-DKP **368** (5.8 mg, 0.013 mmol, 1.0 equiv) and Cs_2CO_3 (166 mg, 0.508 mmol, 40 equiv). In the meantime, dry MeOH (2.6 mL) was fully degassed by bubbling N_2 through and was added to the flask under N_2. The resulting mixture gradually turned into a clear yellow solution and was stirred for 50 minutes. It was then quenched with saturated $NaHCO_3$ (20 mL) and the mixture was extracted with EtOAc (5 x 10 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (10% to 50% EtOAc in hexanes) afforded *anti*-DKP **A-9**, as a white solid (5.4 mg, 0.012 mmol, 94% yield). $[\alpha]_D^{25}$ = –305°

(c = 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (td, J = 2.5, 1.0 Hz, 1H), 6.15 (dd, J = 8.2, 2.2 Hz, 1H), 6.00 (s, 1H), 5.93 – 5.83 (m, 2H), 5.81 – 5.71 (m, 1H), 5.06 (dd, J = 7.8, 2.1 Hz, 1H), 4.91 – 4.64 (m, 3H), 4.52 (ddd, J = 11.1, 6.9, 2.0 Hz, 1H), 4.35 (ddd, J = 11.1, 7.0, 1.9 Hz, 1H), 4.22 (dt, J = 7.9, 2.0 Hz, 1H), 3.05 – 2.78 (m, 4H), 0.90 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 163.3, 138.7, 137.3, 133.3, 130.1, 123.0, 118.8, 112.1, 110.1, 73.5, 69.8, 68.3, 62.7, 62.7, 57.8, 34.6, 32.9, 25.7, 18.0, -4.6, -4.8; FTIR (NaCl, thin film): 3304, 2947, 2928, 2884, 2855, 1671, 1634, 1423, 1342, 1290, 1248, 1230, 1197, 1128, 1103, 1051, 1033, 1003, 904, 883, 870, 838, 809, 777, 750, 717 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{17}N_2O_4$ $[M–C_6H_{15}OSi]^+$ 325.1183, found 325.1194 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion).

Preparation of diol 369

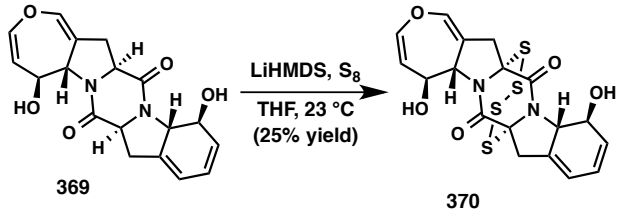


A-9 369

A 15 mL round-bottom flask was charged with *anti*-DKP **A-9** (5.4 mg, 0.012 mmol, 1.0 equiv). It was then dissolved in a mixed solvent including THF (1.44 mL), H_2O (0.24 mL), and HCOOH (0.72 mL). The resulting light yellow clear solution was allowed to stir at room temperature for 8 hours before being carefully quenched with saturated $NaHCO_3$ (15 mL); and the mixture was extracted with EtOAc (5 x 10 mL). Combined organic layer was washed with brine (30 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (10% to 95% EtOAc in hexanes) afforded diol **369**, as a white solid (3.4 mg, 0.010 mmol, 84%

yield). $[\alpha]_D^{25}$ = –456° (*c* = 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (td, *J* = 2.5, 1.1 Hz, 1H), 6.19 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.93 (s, 1H), 5.92 – 5.84 (m, 2H), 5.79 – 5.72 (m, 1H), 5.20 (d, *J* = 4.6 Hz, 1H), 4.90 (dd, *J* = 7.9, 2.1 Hz, 1H), 4.87 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.81 – 4.73 (m, 1H), 4.73 – 4.63 (m, 2H), 4.45 (ddd, *J* = 10.2, 7.5, 2.2 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.05 – 2.96 (m, 2H), 2.92 (ddt, *J* = 15.2, 10.7, 2.2 Hz, 1H), 2.81 (dddt, *J* = 17.8, 12.1, 2.5, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.7, 138.4, 137.8, 132.6, 130.2, 123.0, 119.1, 110.4, 109.6, 73.5, 71.3, 68.2, 64.2, 62.3, 58.0, 33.5, 32.6; FTIR (NaCl, thin film): 3253, 3048, 2923, 2851, 2787, 1667, 1622, 1441, 1386, 1350, 1284, 1267, 1250, 1236, 1206, 1187, 1132, 1084, 1047, 1002, 852, 823, 750, 736, 708, 629 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{17}N_2O_4$ $[M–OH]^+$ 325.1183, found 325.1194 (detected fragment has undergone loss of hydroxyl anion).

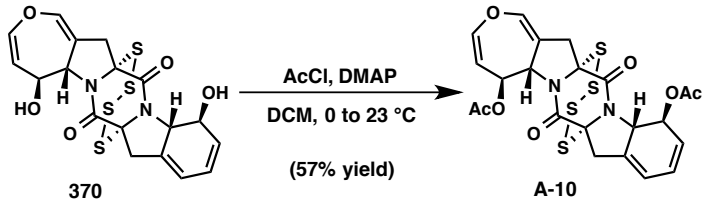
Preparation of tetrasulfide 370



To a suspension of S_8 (9 mg, 0.035 mmol, 5 equiv) in THF (3 mL) at 0 °C under argon was added LiHMDS (1 M in THF, 420 μL, 0.42 mol, 60 equiv) dropwise over 2 min. This solution was stirred for an additional 1 min, and DKP **369** (2.4 mg, 0.007 mmol, 1.0 equiv) dissolved in THF (1 mL) was added dropwise at room temperature over 2 min and rinsed with 0.3 mL THF. The reaction mixture was allowed to stir for 50 minutes and quenched with saturated $NaHCO_3$ (5 mL), and then the mixture was extracted with EtOAc (4 x 5 mL). Combined organic layer was washed with brine (20 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a yellow

solid. Preparative TLC (60% EtOAc in hexanes) afforded tetrasulfide **370**, as a yellow solid (0.8 mg, 0.0017 mmol, 25% yield). $[\alpha]_D^{25}$ = –375° (*c* = 0.045, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (t, *J* = 2.3 Hz, 1H), 6.21 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.98 – 5.91 (m, 1H), 5.92 – 5.86 (m, 1H), 5.79 (d, *J* = 9.8 Hz, 1H), 5.33 (s, 1H), 5.08 – 4.98 (m, 2H), 4.93 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.78 (d, *J* = 13.3 Hz, 1H), 4.60 (d, *J* = 4.5 Hz, 1H), 4.46 (td, *J* = 4.9, 2.3 Hz, 1H), 3.30 – 3.19 (m, 2H), 3.03 (dd, *J* = 16.1, 3.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.4, 138.9, 138.0, 131.0, 129.5, 122.9, 121.2, 110.4, 106.4, 78.1, 74.5, 72.7, 71.5, 70.1, 65.3, 41.5, 40.4; FTIR (NaCl, thin film): 3407, 2924, 2852, 1644, 1379, 1289, 1262, 1234, 1188, 1132, 1082, 1053, 971, 902, 861, 819, 744, 722, 622 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{16}N_2O_5S_4Cl$ $[M+Cl]^-$ 502.9636, found 502.9633.

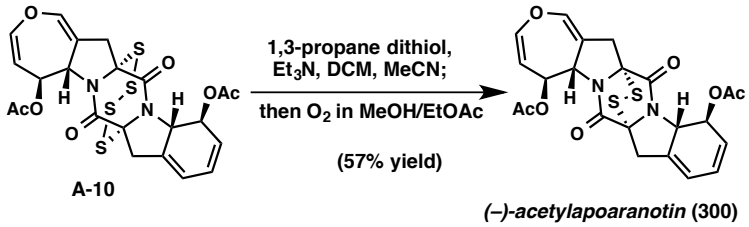
Preparation of diacetate A-10



To a stirred solution of diol **370** (0.9 mg, 1.9 μmol, 1.0 equiv) and DMAP (5.9 mg, 48 μmol, 25 equiv) in DCM (0.2 mL) at 0 °C was added acetyl chloride (2.0 μL, 29 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 saturated $NaHCO_3$ (0.5 mL) 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 preparative TLC (60% EtOAc in hexanes) to afford diacetate **A-10**, as a yellow solid (0.6

mg, 1.1 μmol, 57% yield). $[\alpha]_D^{25} = -327°$ (c = 0.03, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (t, J = 2.5 Hz, 1H), 6.26 (dd, J = 8.2, 2.3 Hz, 1H), 6.00 – 5.91 (m, 2H), 5.83 (d, J = 14.2 Hz, 1H), 5.68 – 5.59 (m, 1H), 5.37 (d, J = 14.4 Hz, 1H), 5.29 (d, J = 8.2 Hz, 1H), 5.22 (dt, J = 8.4, 2.1 Hz, 1H), 4.70 (dd, J = 8.2, 1.9 Hz, 1H), 3.31 – 3.21 (m, 2H), 3.04 (dd, J = 16.5, 6.4 Hz, 2H), 2.19 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 170.4, 166.6, 165.8, 139.6, 138.6, 131.9, 128.8, 124.9, 120.9, 108.1, 106.0, 79.4, 75.4, 74.2, 71.1, 64.2, 60.7, 41.8, 41.2, 21.5, 21.4; FTIR (NaCl, thin film): 2923, 2854, 1734, 1685, 1369, 1293, 1236, 1187, 1135, 1046, 753, 710 cm^{-1}; HRMS (LC-MM) calc'd for $C_{20}H_{17}N_2O_5S_4$ $[M–C_2H_3O_2]^+$ 493.0026, found 493.0015 (detected fragment has undergone loss of acetate anion).

Preparation of (–)-acetylapoaranotin (300)



A solution of tetrasulfide **A-10** (0.6 mg, 1.1 μmol) in DCM (0.12 mL) was diluted with MeCN (3.6 mL), then treated with a solution of Et_3N in MeCN (0.05 μL, 0.36 μmol in 10 μL of MeCN), followed by 1,3-propanedithiol (11 μL, 0.11 mmol). The resulting mixture was allowed to stand for 20 min, and was then washed with hexanes (5 x 4 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 DCM/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 50 to 100% EtOAc in hexanes. Collected the fractions and concentrated *in vacuo*. The resulting material was taken up in EtOAc (12 mL) and MeOH (12 mL). The resulting solution was sparged with O_2 for 1 hour and allowed to stir for another 4 hours. The solution was then concentrated *in vacuo*, and purified by preparative TLC (60% EtOAc in hexanes) to provide (–)-acetylapoaranotin (**300**) as a yellow solid (0.3 mg, 0.6 μmol, 57% yield). $[\alpha]_D^{25} = -281°$ (c = 0.015, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, J = 2.4 Hz, 1H), 6.30 (dd, J = 8.3, 2.1 Hz, 1H), 6.04 (d, J = 12.7 Hz, 1H), 6.00-5.95 (m, 2H), 5.69 (d, J = 8.6 Hz, 1H), 5.55 (d, J = 8.2 Hz, 1H), 5.14-5.06 (m, 1H), 5.00 (d, J = 13.1 Hz, 1H), 4.60 (dd, J = 8.2, 1.7 Hz, 1H), 4.01 (d, J = 18.3 Hz, 1H), 3.80 (d, J = 18.1 Hz, 1H), 2.99 (d, J = 18.2 Hz, 1H), 2.87 (d, J = 17.9 Hz, 1H), 2.14 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.9, 163.1, 162.2, 141.1, 139.2, 132.2, 127.8, 124.5, 119.9, 113.4, 105.3, 100.0, 78.2, 75.9, 73.9, 69.8, 64.5, 62.8, 36.1, 34.5, 21.3, 20.9; FTIR (NaCl, thin film): 2919, 2850, 1737, 1706, 1552, 1435, 1367, 1302, 1279, 1233, 1143, 1041, 962, 752, 720, 655 cm^{-1}; HRMS (ESI) calc'd for $C_{22}H_{20}N_2O_7S_2Na$ $[M+Na]^+$ 511.0610, found 511.0621.

Table 4.1. *Comparison of ^1H NMR data for natural vs. synthetic (–)-acetylapoaranotin (**300**)*

Yang et al. Report,[20] Natural (–)-acetylapoaranotin ^1H NMR, 500 MHz, $CDCl_3$	This Work, Synthetic (–)-acetylapoaranotin ^1H NMR, 400 MHz, $CDCl_3$
δ 6.61 (br ddd, *J* = 2.5, 2.0, 2.0 Hz, 1H)	δ 6.60 (d, *J* = 2.4 Hz, 1H)
6.31 (dd, *J* = 8.5, 2.0 Hz, 1H)	6.30 (dd, *J* = 8.3, 2.1 Hz, 1H)
6.05 (br dm, *J* = 13.2 Hz, 1H)	6.04 (d, *J* = 12.7 Hz, 1H)
5.99 (m, 1H)	6.00-5.95 (m, 2H)
5.96 (m, 1H)	
5.70 (ddd, *J* =8.5, 2.0, 2.0 Hz, 1H)	5.69 (d, *J* = 8.6 Hz, 1H)
5.56 (br dm, *J* = 13.2 Hz, 1H)	5.55 (d, *J* = 8.2 Hz, 1H)
5.10 (br dddd, *J* = 8.5, 2.0, 2.0, 1.5, 1H)	5.14-5.06 (m, 1H)
5.00 (br dm, *J* = 13.2 Hz, 1H)	5.00 (d, *J* = 13.1 Hz, 1H)
4.61 (dd, *J* = 8.5, 2.0 Hz, 1H)	4.60 (dd, *J* = 8.2, 1.7 Hz, 1H)
4.02 (br ddd, *J* = 18.0, 2.5, 1.5 Hz, 1H)	4.01 (d, *J* = 18.3 Hz, 1H)
3.81 (dm, *J* = 18.5 Hz, 1H)	3.80 (d, *J* = 18.1 Hz, 1H)
2.99 (ddd, *J* = 18.0, 2.0, 2.0 Hz, 1H)	2.99 (d, *J* = 18.2 Hz, 1H)
2.88(br dd, *J* = 18.5, 1.5)	2.87 (d, *J* = 17.9 Hz, 1H)
2.15 (s, 3H)	2.14 (s, 3H)
2.03 (s, 3H)	2.03 (s, 3H)

Table 4.2. *Comparison of ^{13}C NMR data for natural vs. synthetic (–)-acetylapoaranotin (**300**)*

Yang et al. Report,[20] Natural (–)-acetylapoaranotin ^{13}C NMR, 126 MHz, $CDCl_3$	This Work, Synthetic (–)-acetylapoaranotin ^{13}C NMR, 101 MHz, $CDCl_3$	Chemical Shift Difference, $\Delta\delta$
δ 170.5	δ 170.5	0.0
170.0	169.9	0.1
163.1	163.1	0.0
162.2	162.2	0.0
141.2	141.1	0.1
139.2	139.2	0.0
132.2	132.2	0.0
127.8	127.8	0.0
124.5	124.5	0.0
119.9	119.9	0.0
113.4	113.4	0.0
105.3	105.3	0.0
78.2	78.2	0.0
75.9	75.9	0.0
73.9	73.9	0.0
69.8	69.8	0.0
64.5	64.5	0.0
62.9	62.8	0.1
36.1	36.1	0.0
34.5	34.5	0.0
21.3	21.3	0.0
21.0	20.9	0.1

4.5 NOTES AND REFERENCES

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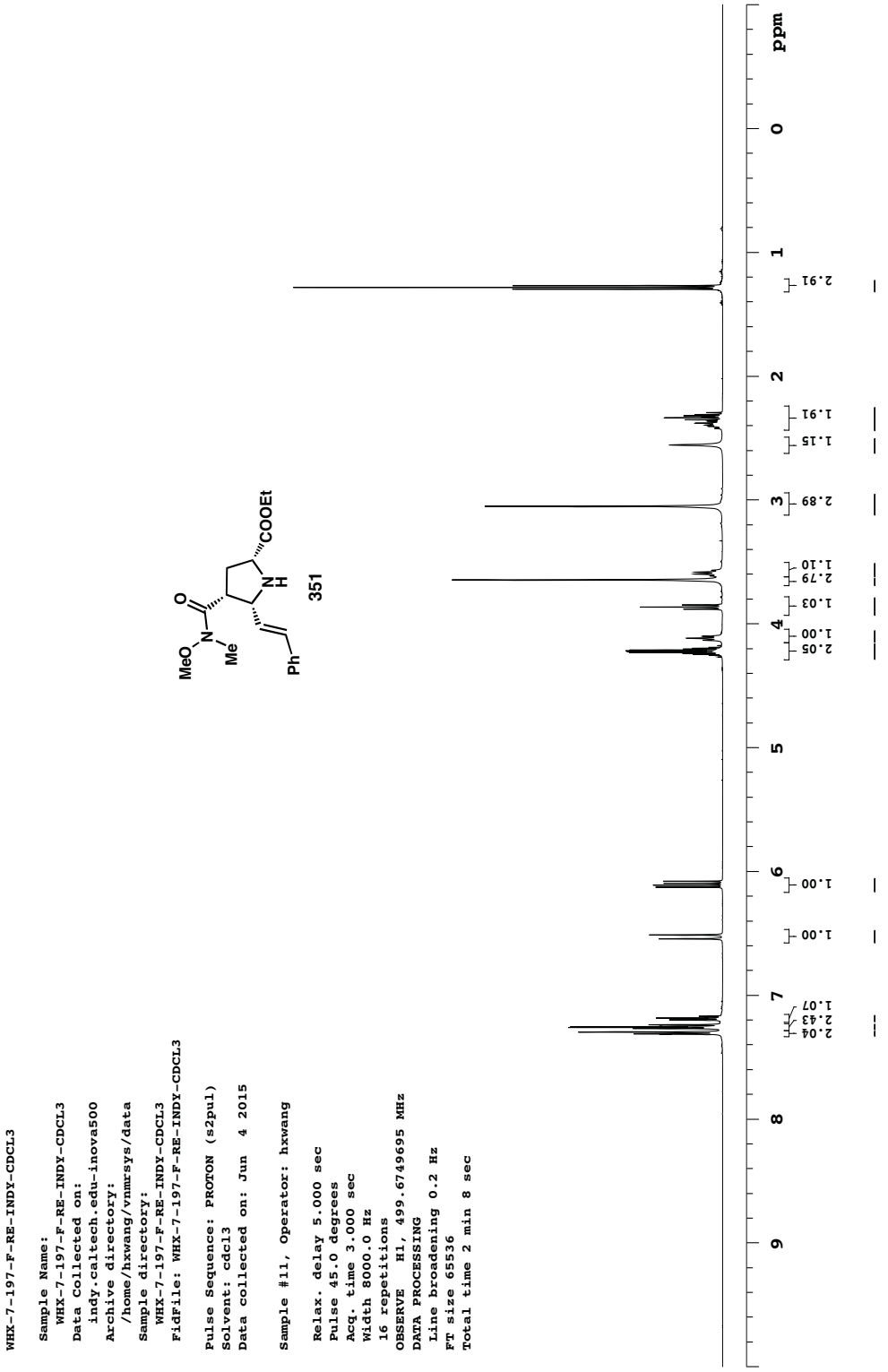
Appendix 4

Spectra Relevant to Chapter 4:
Enantioselective Total Synthesis of Epidithiodiketopiperazine Natural Product (–)-Acetylapoaranotin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Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-197-F-RE-INDY-CDCL3
FidFile: WHX-7-197-F-RE-INDY-CDCL3
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 4 2015
Sample #11, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6749695 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
MeO
N
O
Me
COOEt
N
H
Ph
351
ppm
2.91
1.91
1.15
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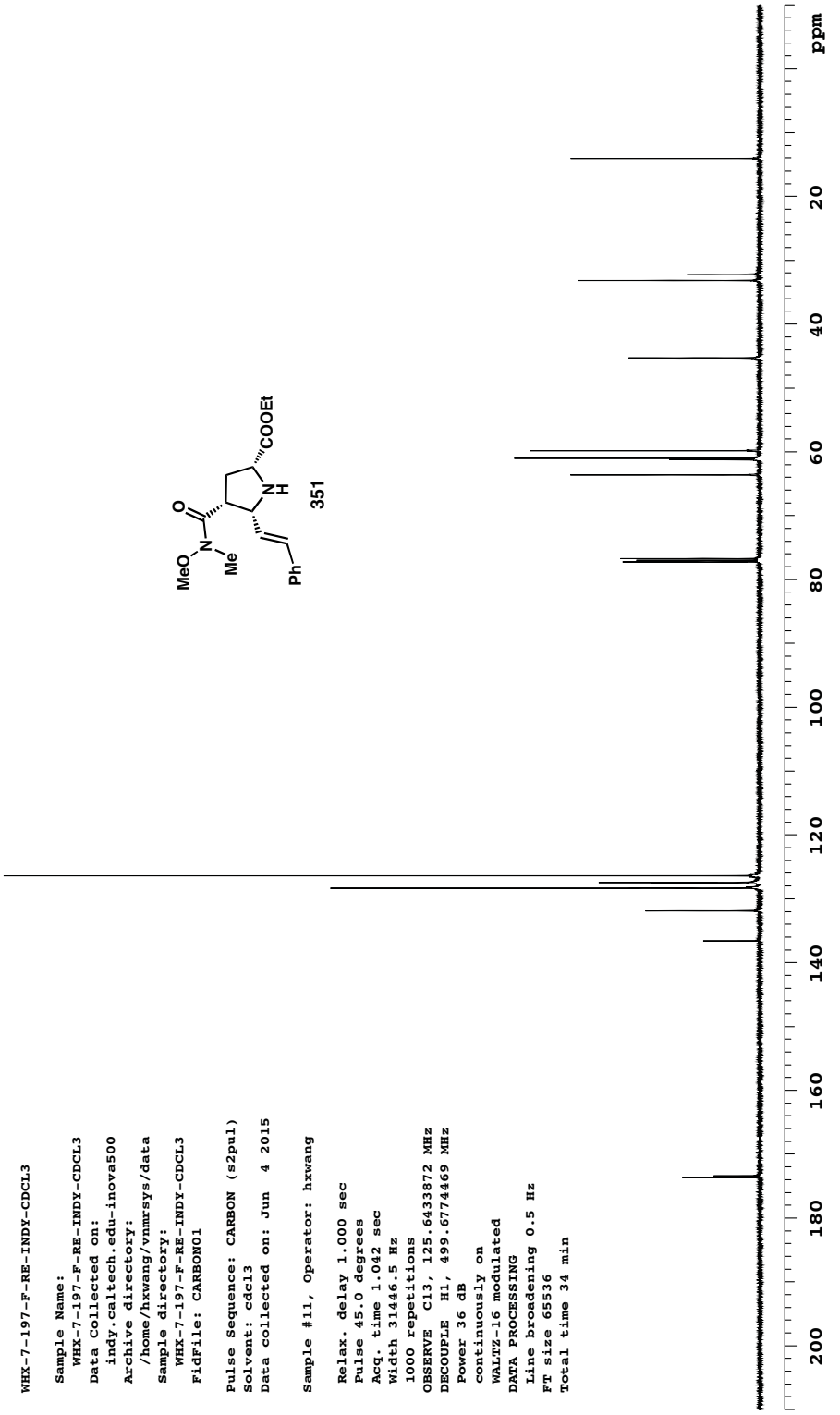
1.00
1.00
1.00
2.04
2.43
1.07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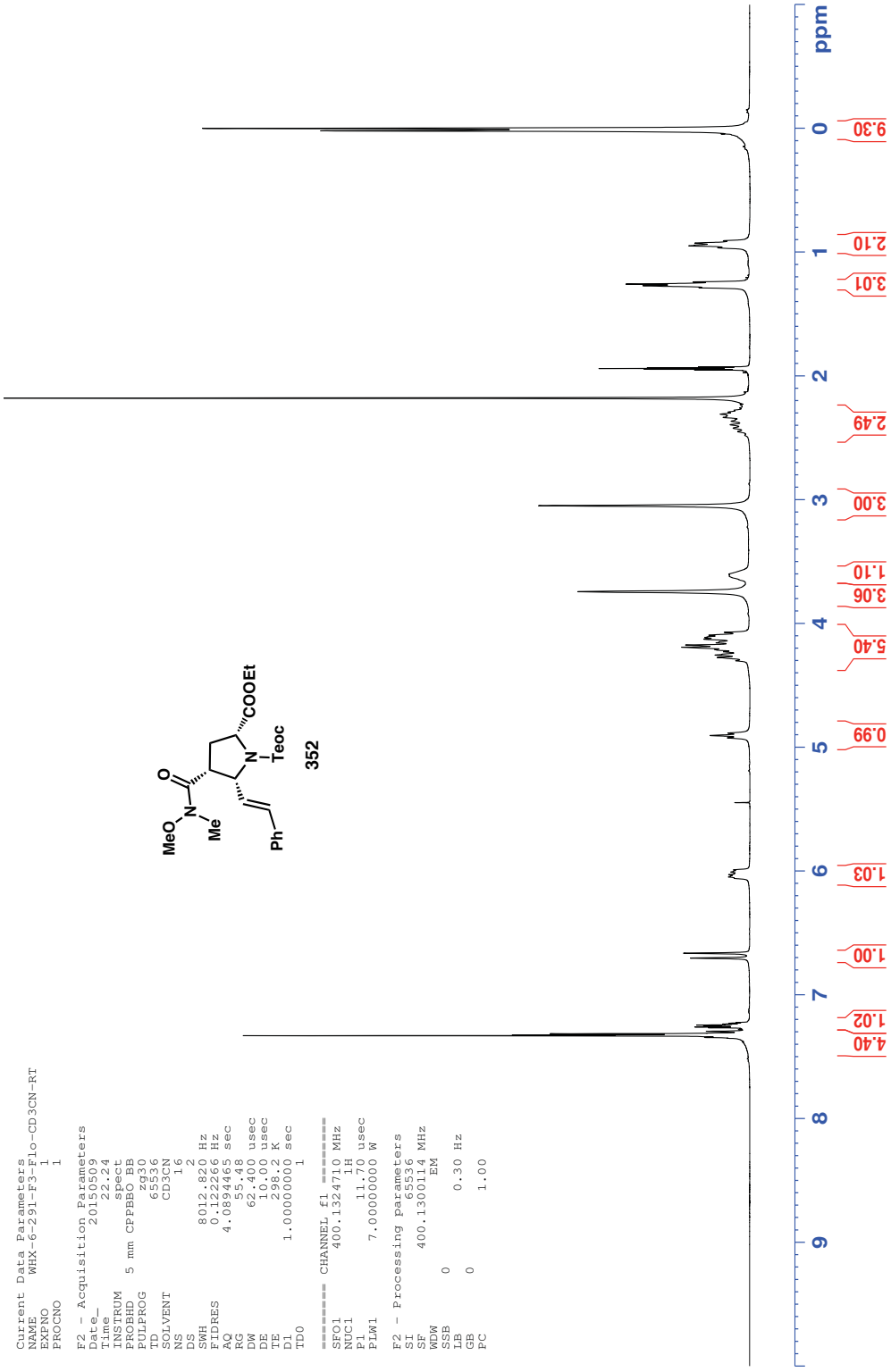
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-197-F-RE-INDY-CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 4 2015
Sample #11, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6433872 MHz
DECOUPLE H1, 499.6774469 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
MeO
N
Me
O
N
H
COOEt
Ph
351
200
180
160
140
120
100
80
60
40
20
ppm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Time 22.24
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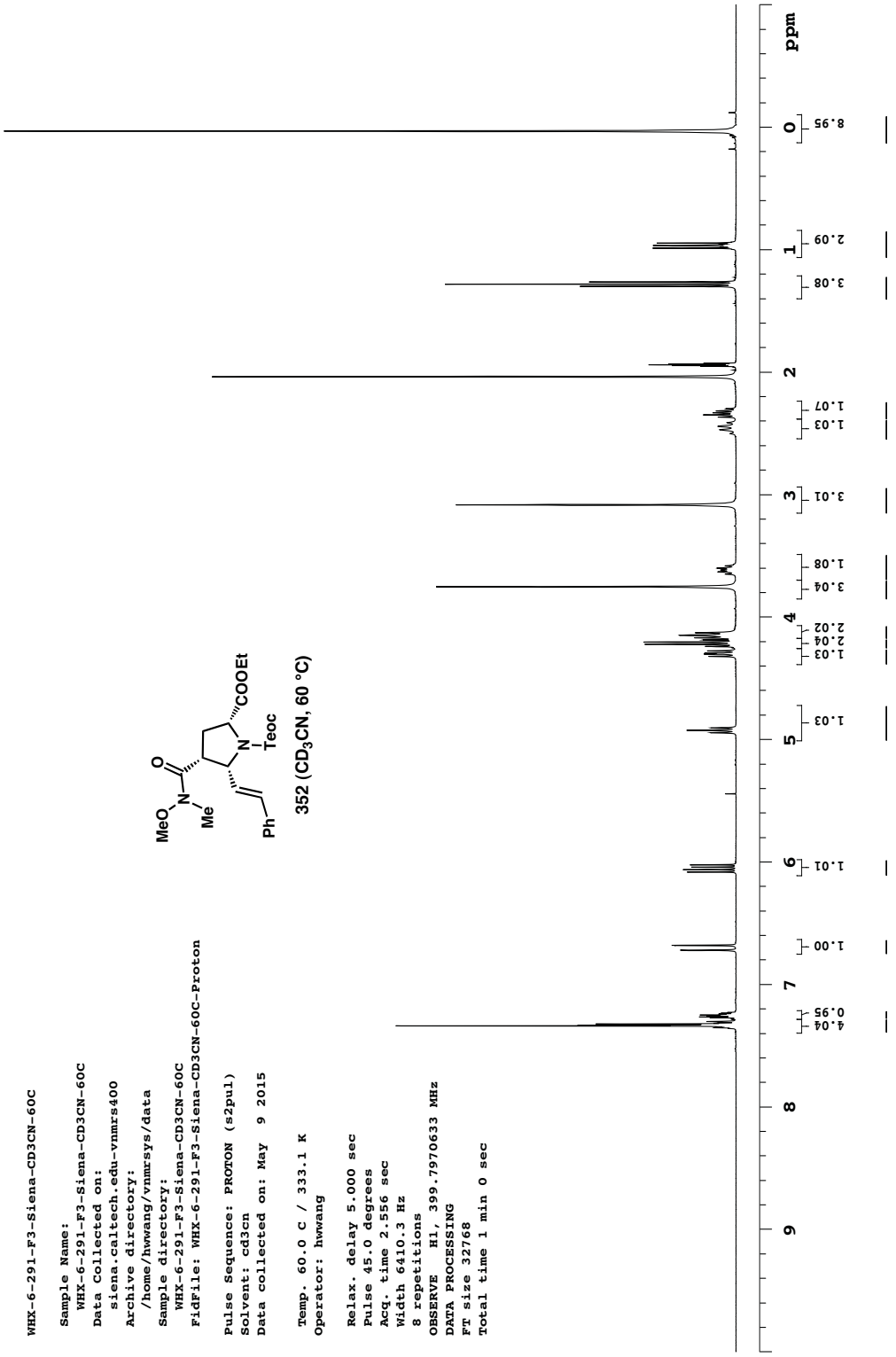
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CD3CN
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 55.48
DW 62.400 usec
DE 10.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300114 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
MeO
N
O
Me
Ph
N
Teoc
COOEt
352
ppm
9.30
2.10
3.01
2.49
3.00
1.10
3.06
5.40
0.99
1.03
1.00
1.02
4.40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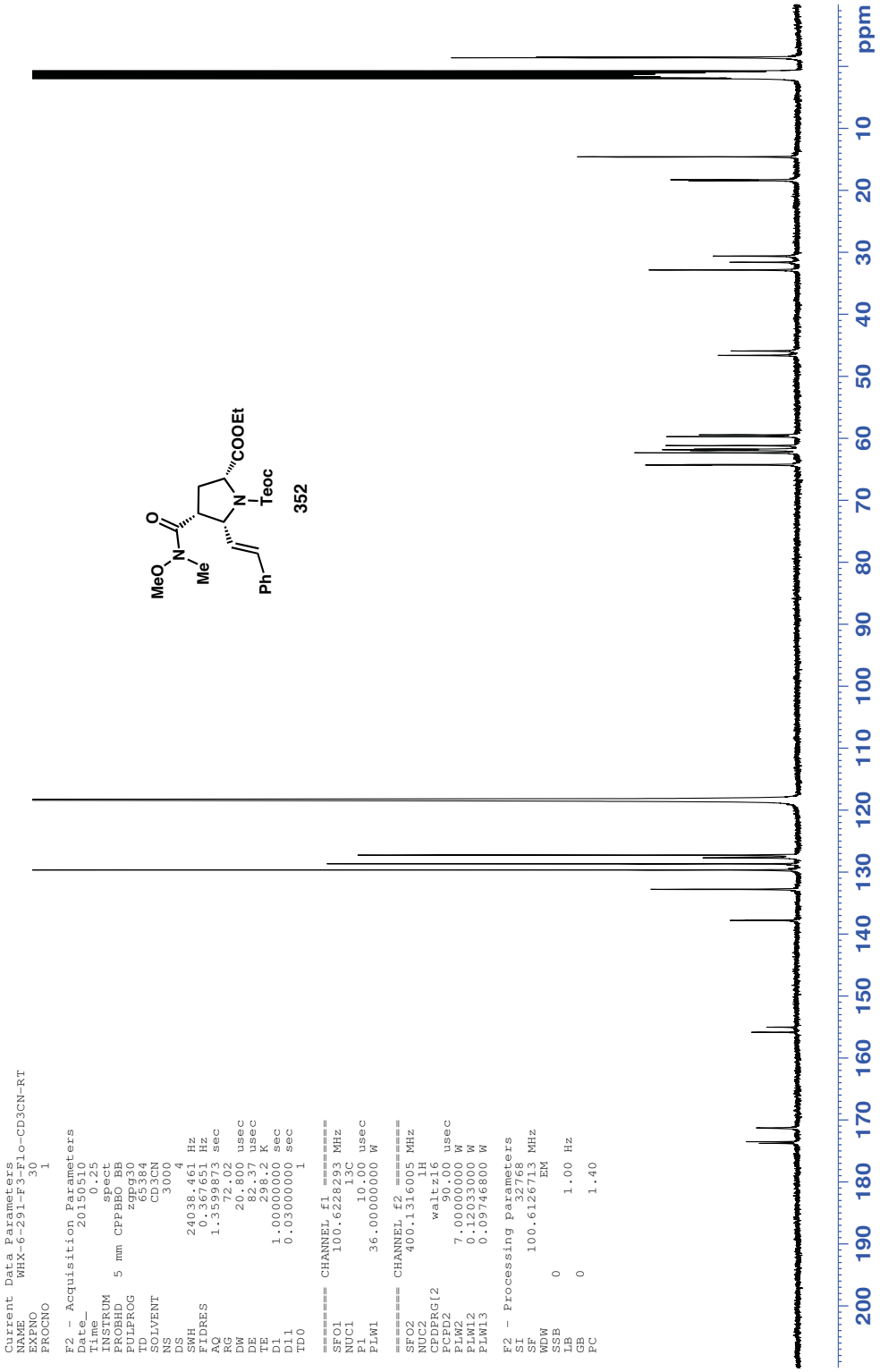
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-6-291-F3-Siena-CD3CN-60C
FidFile: WHX-6-291-F3-Siena-CD3CN-60C-Proton
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 9 2015
Temp. 60.0 C / 333.1 K
Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970633 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 0 sec
MeO
N
O
Me
COOEt
N
Teoc
Ph
352 (CD3CN, 60 °C)
ppm
9
8
7
6
5
4
3
2
1
0
4.04
0.95
1.00
1.01
1.03
1.03
2.04
2.02
3.04
1.08
3.01
1.03
1.07
3.08
2.09
8.95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PROCNO 1
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Date_ 20150510
Time 0.25
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PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CD3CN
NS 3000
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.35999873 sec
RG 72.02
DW 20.800 usec
DE 82.37 usec
TE 298.2 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6126713 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
MeO
N
Me
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Ph
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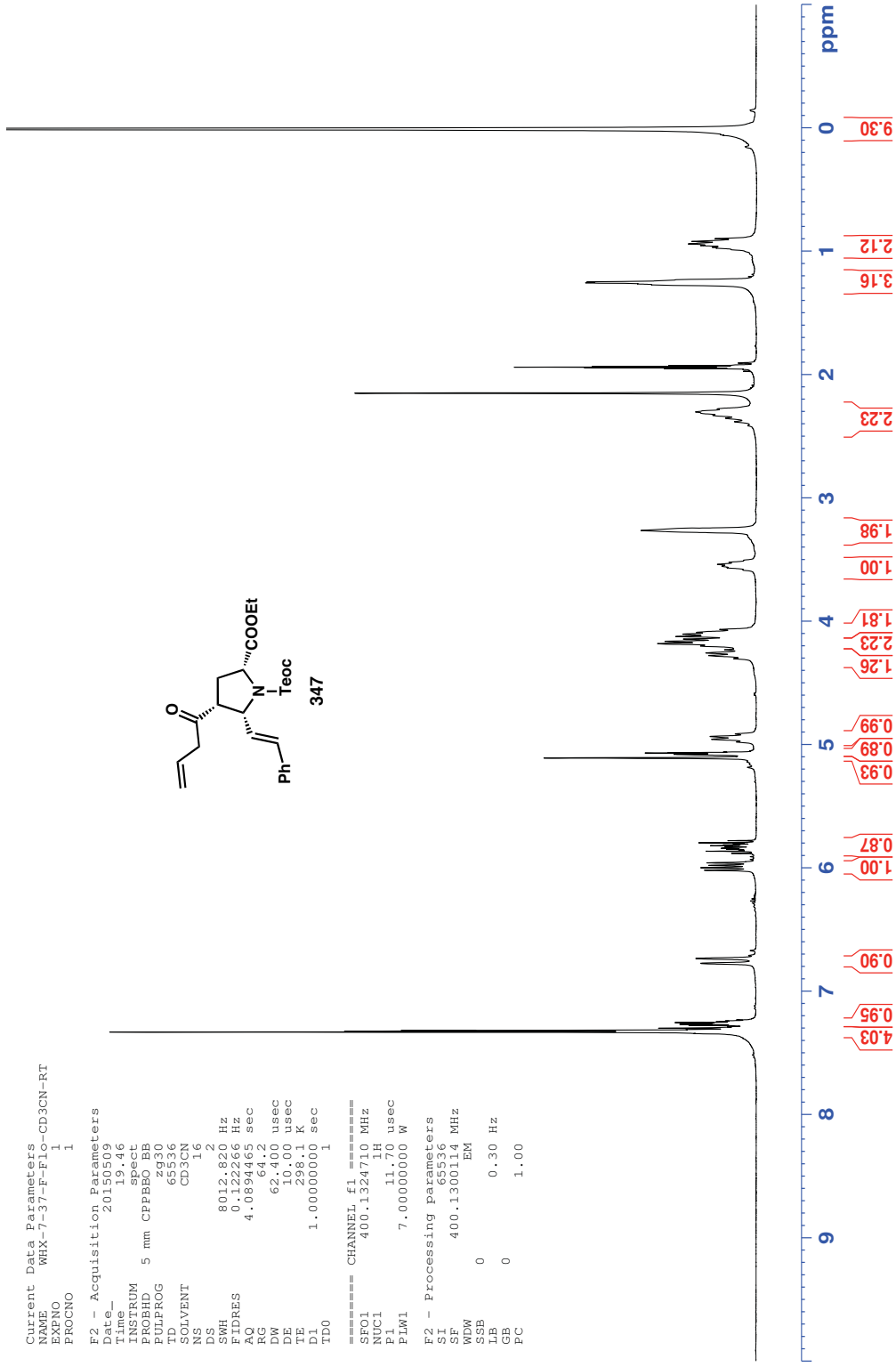
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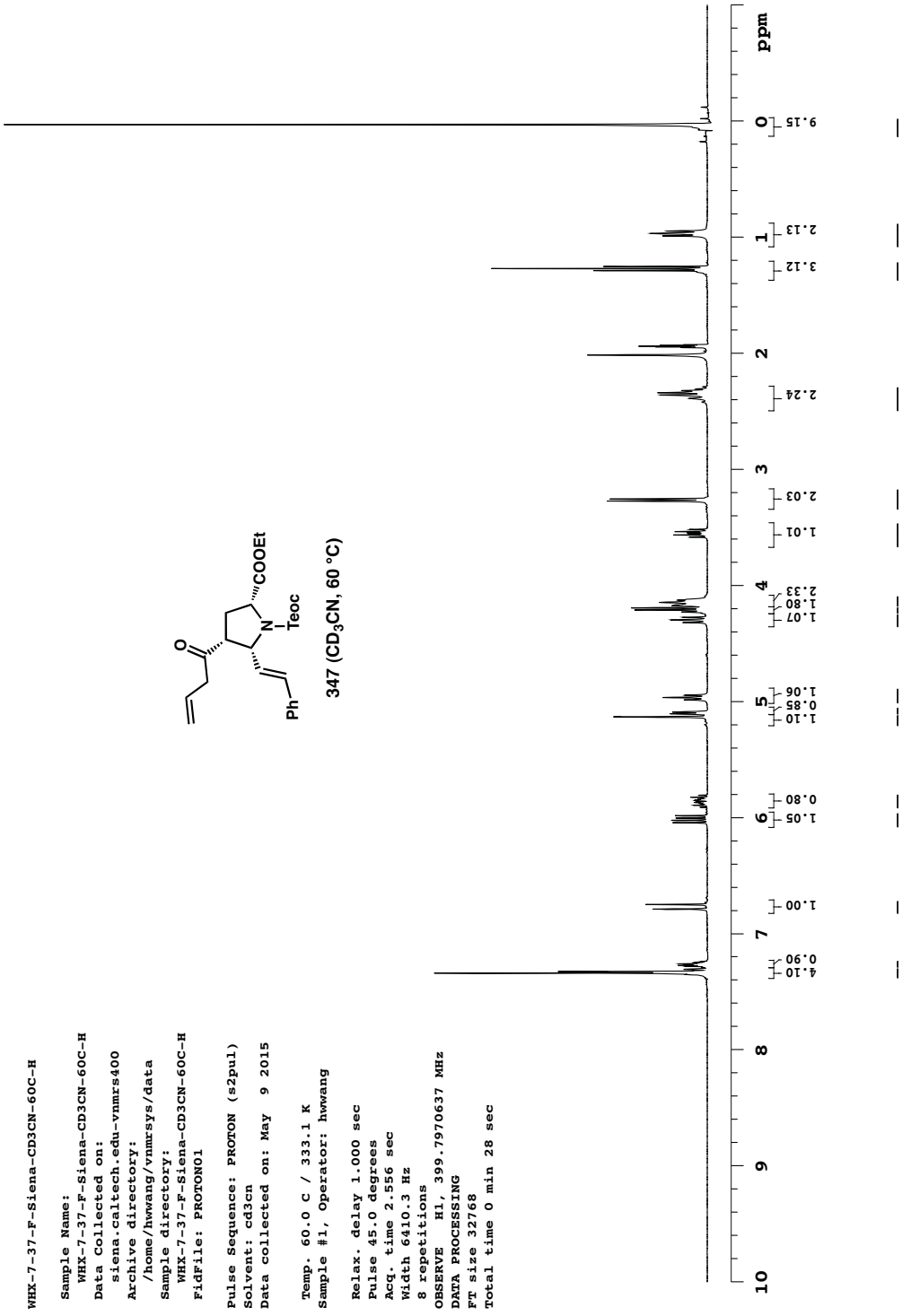
Time 19.46
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CD3CN
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 64.2
DW 62.400 usec
DE 10.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300114 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
COOEt
Teoc
Ph
347
ppm
9.30
2.12
3.16
2.23
1.98
1.00
1.81
2.23
1.26
0.99
0.89
0.93
0.87
1.00
0.90
0.95
4.03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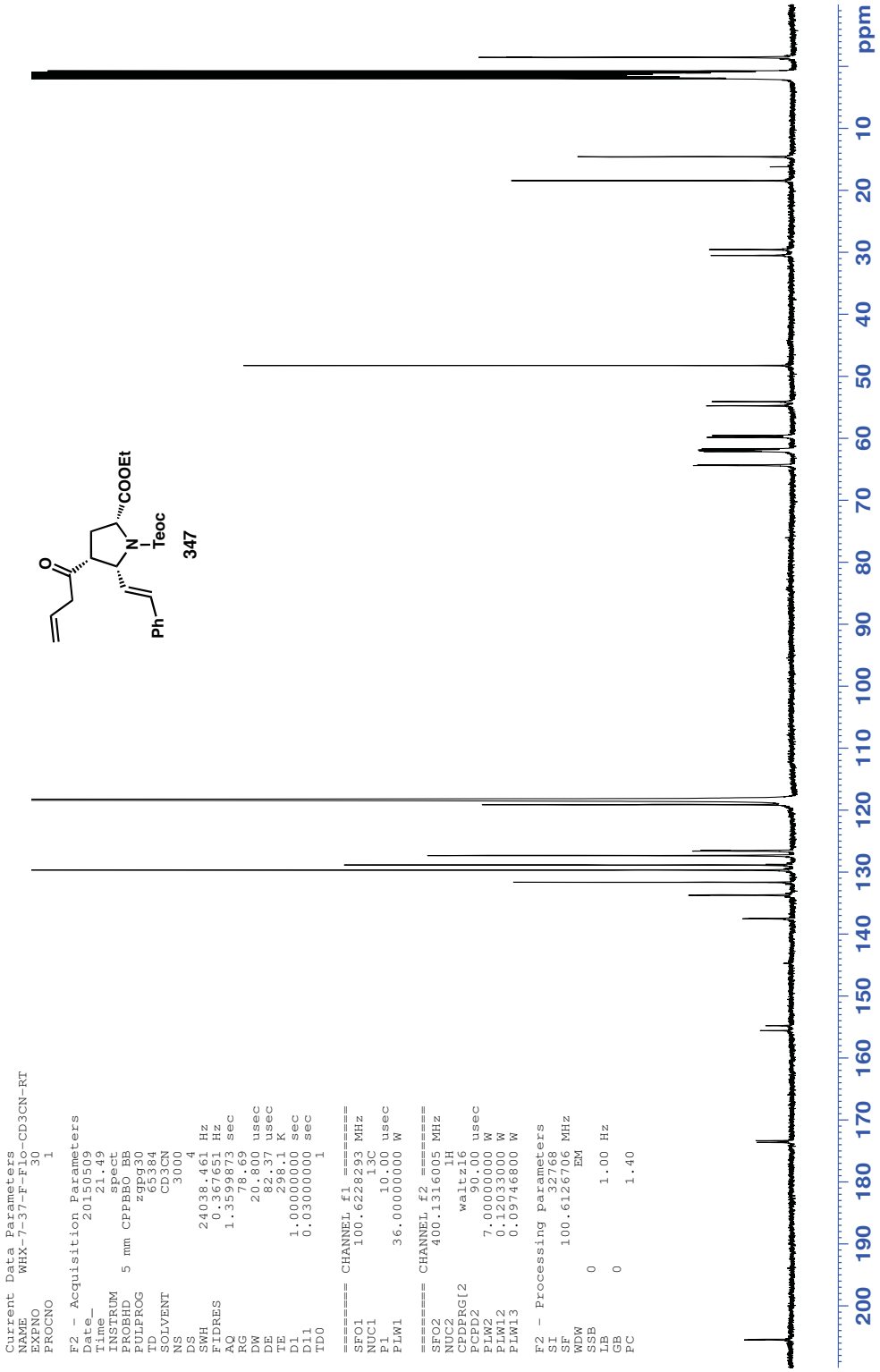
Sample Name:
WHX-7-37-F-Siena-CD3CN-60C-H
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-37-F-Siena-CD3CN-60C-H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 9 2015
Temp. 60.0 C / 333.1 K
Sample #1, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970637 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
O
COOEt
N
Teoc
Ph
347 (CD3CN, 60 °C)
ppm
9.15
2.13
3.12
2.24
2.03
1.01
2.33
1.80
1.07
1.06
0.85
1.10
0.80
1.05
1.00
0.90
4.10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EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
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Time 21.49
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PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CD3CN
NS 3000
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 78.69
DW 20.800 usec
DE 82.37 usec
TE 298.1 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6126706 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
O
COOEt
N
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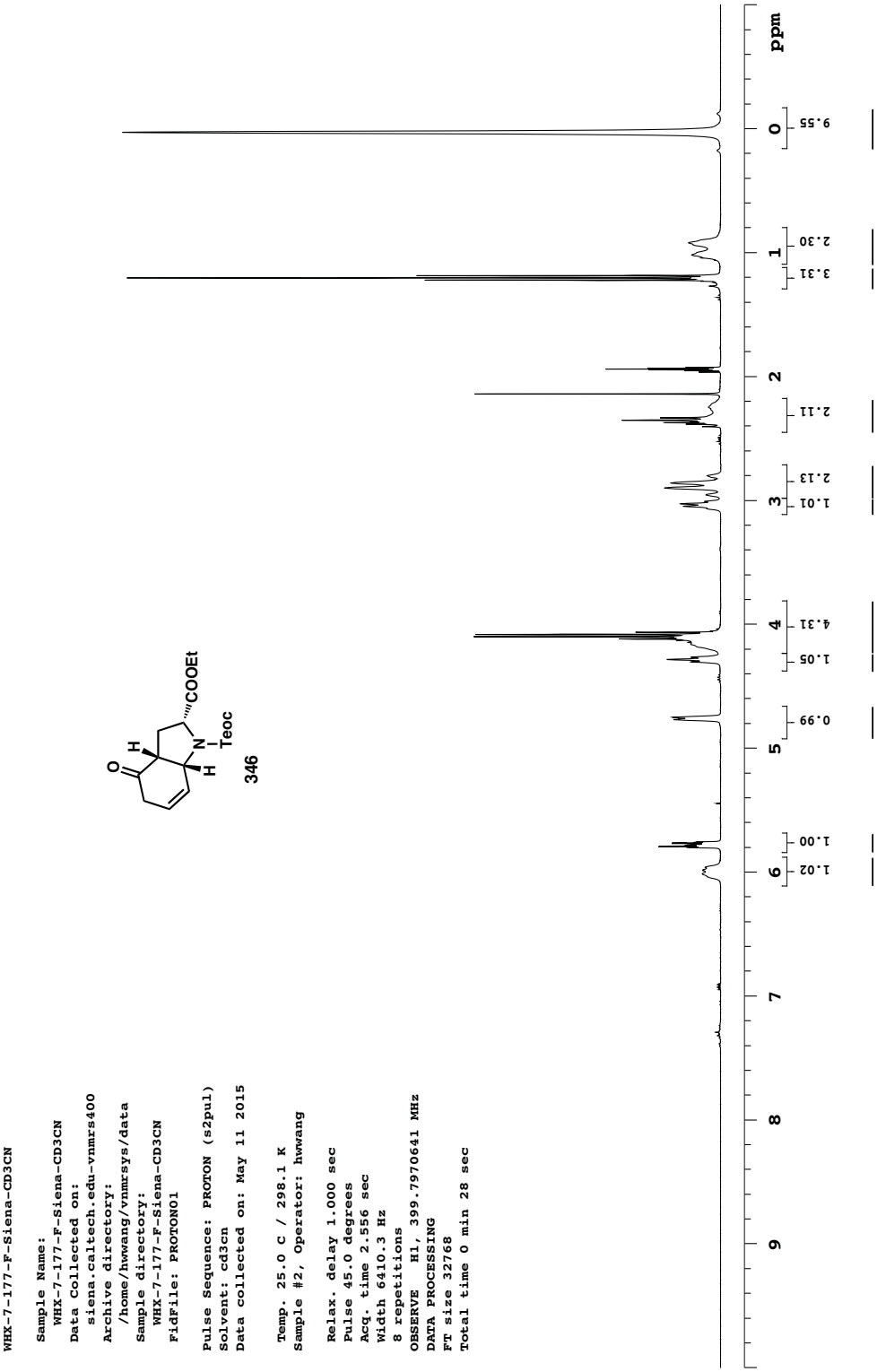
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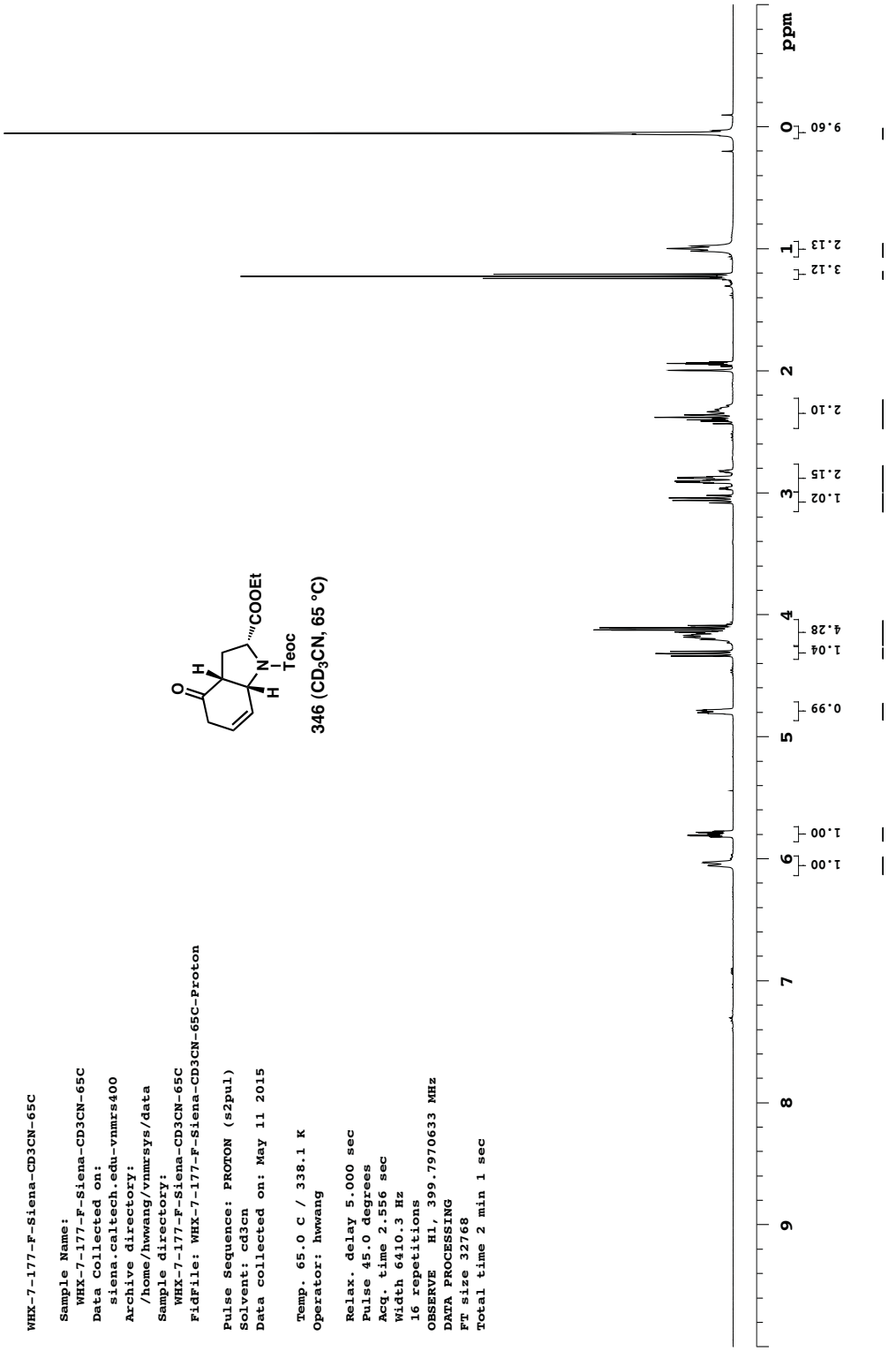
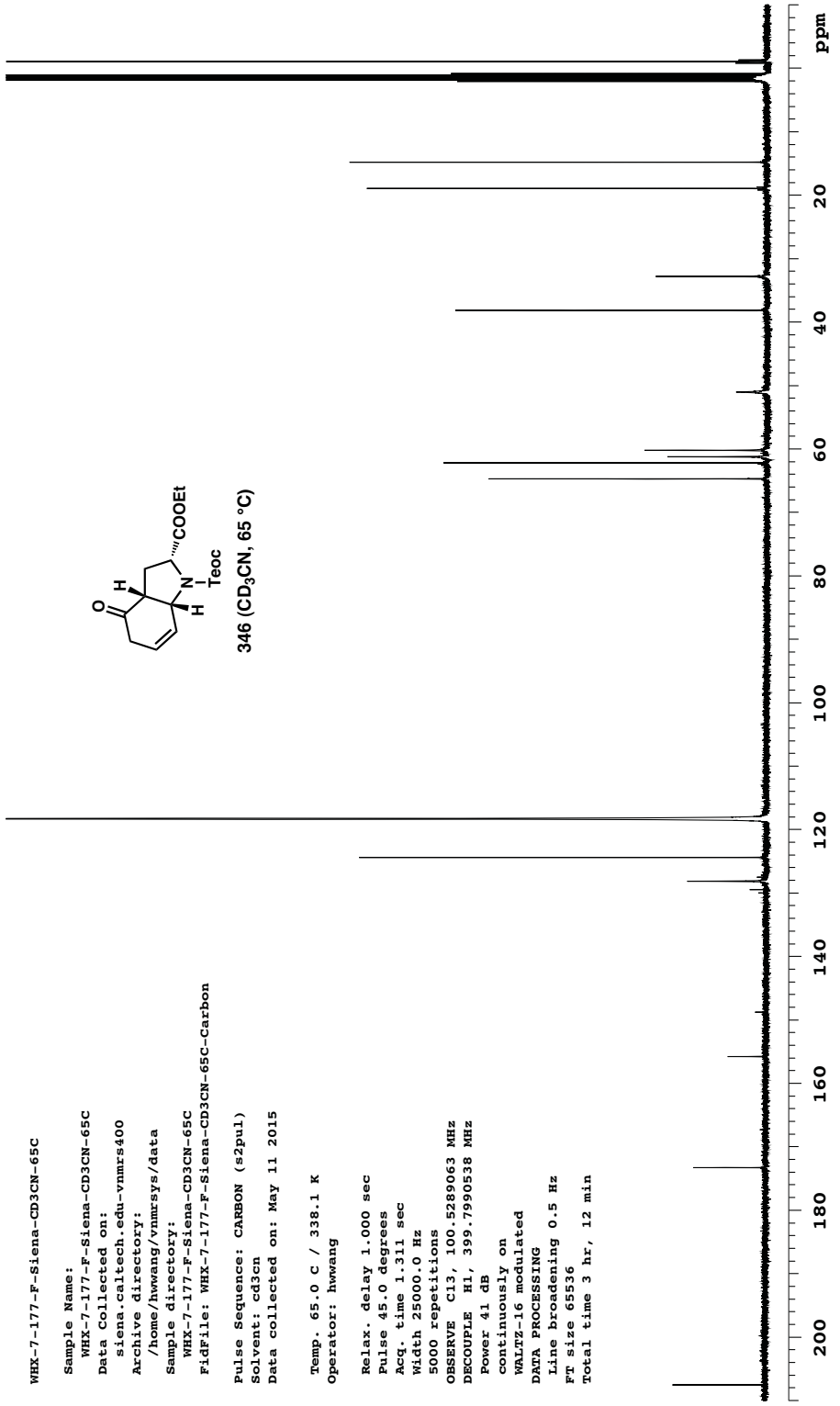
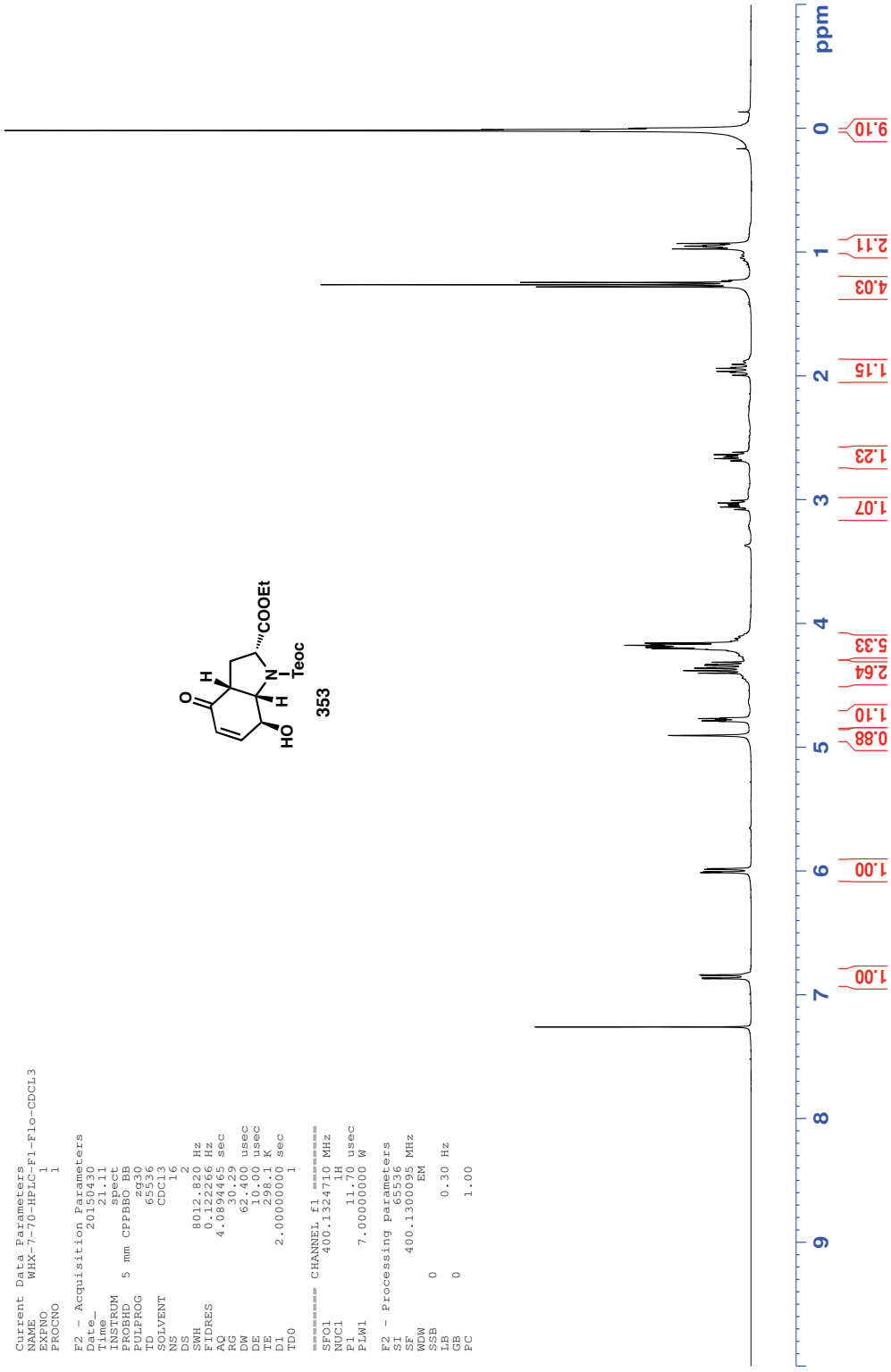
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-177-F-Siena-CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 11 2015
Temp. 25.0 C / 298.1 K
Sample #2, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970641 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
COOEt
Teoc
346
9.55
2.30
3.31
2.11
1.01
2.13
1.05
4.31
0.99
1.00
1.02
ppm


WHX-7-177-F-Siena-CD3CN-65C
Sample Name:
WHX-7-177-F-Siena-CD3CN-65C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-177-F-Siena-CD3CN-65C
FidFile: WHX-7-177-F-Siena-CD3CN-65C-Proton
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 11 2015
Temp. 65.0 C / 338.1 K
Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970633 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
COOEt
Teoc
346 (CD3CN, 65 °C)
ppm
9.60
2.13
3.12
2.10
1.02
2.15
1.04
4.28
0.99
1.00
1.00


WHX-7-177-F-Siena-CD3CN-65C
Sample Name:
WHX-7-177-F-Siena-CD3CN-65C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-177-F-Siena-CD3CN-65C
FidFile: WHX-7-177-F-Siena-CD3CN-65C-Carbon
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: May 11 2015
Temp. 65.0 C / 338.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
5000 repetitions
OBSERVE C13, 100.5289063 MHz
DECOUPLE H1, 399.7990538 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 12 min
COOEt
Teoc
346 (CD3CN, 65 °C)
ppm
200
180
160
140
120
100
80
60
40
20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PROCNO 1
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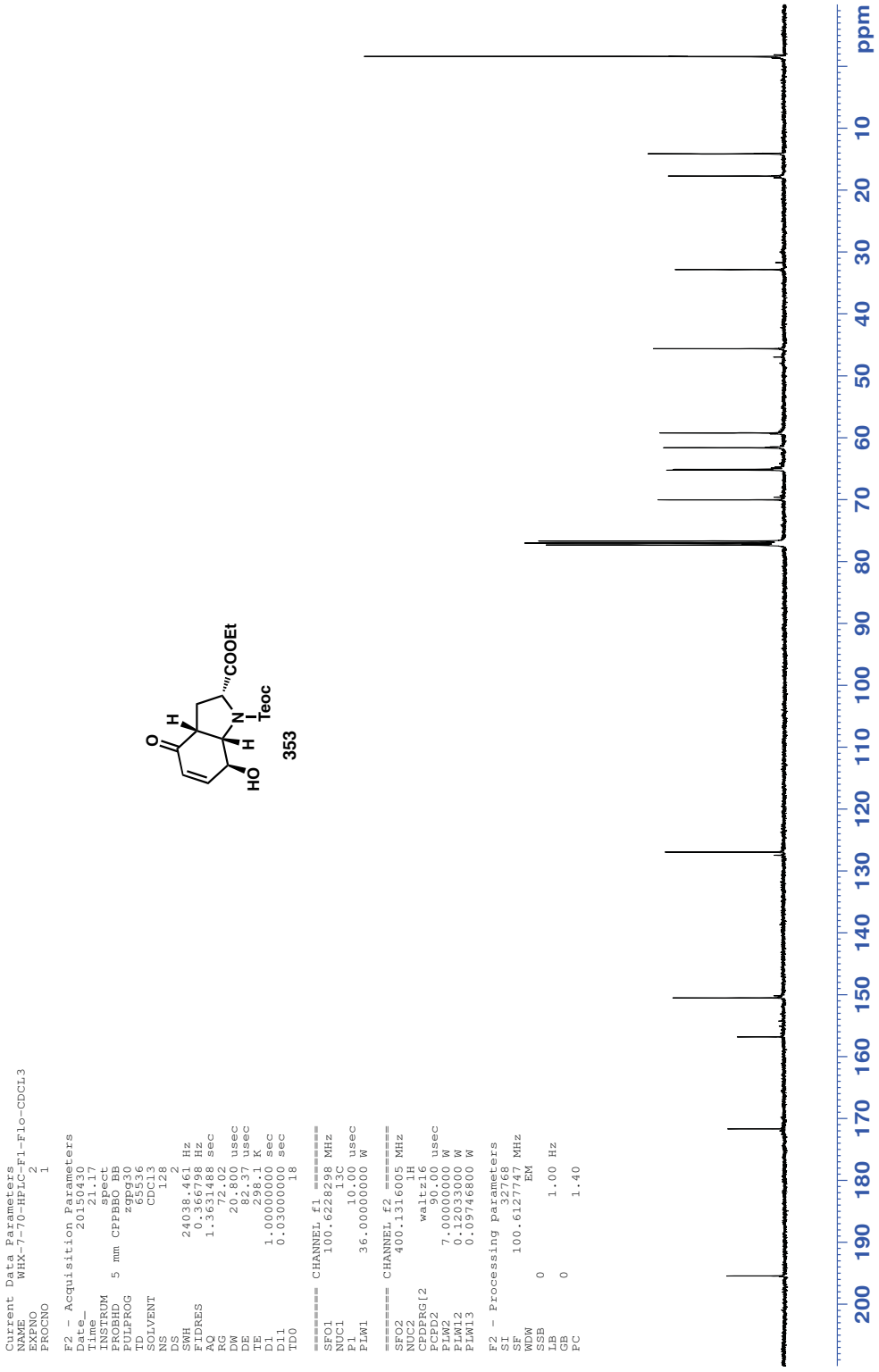
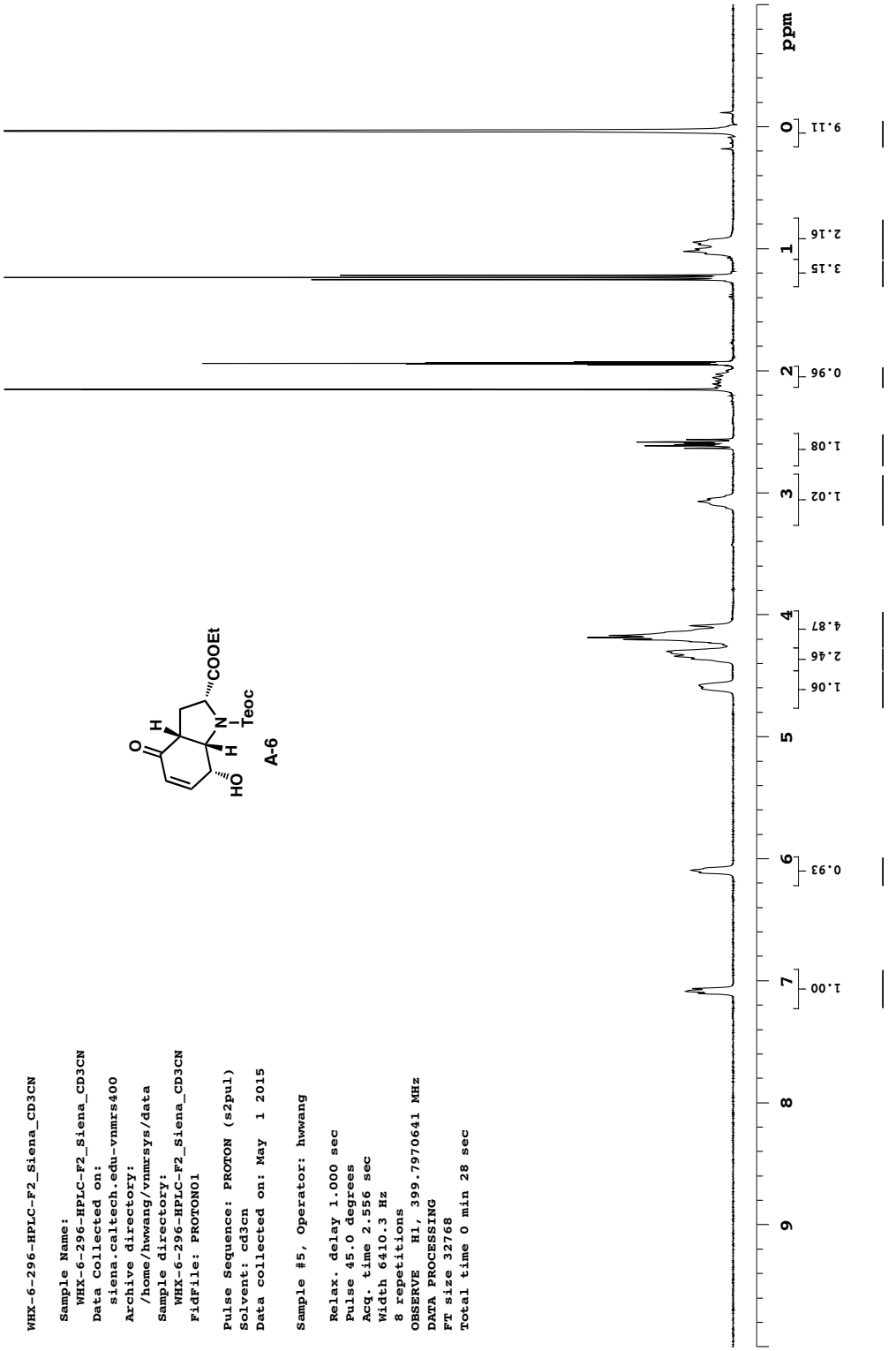
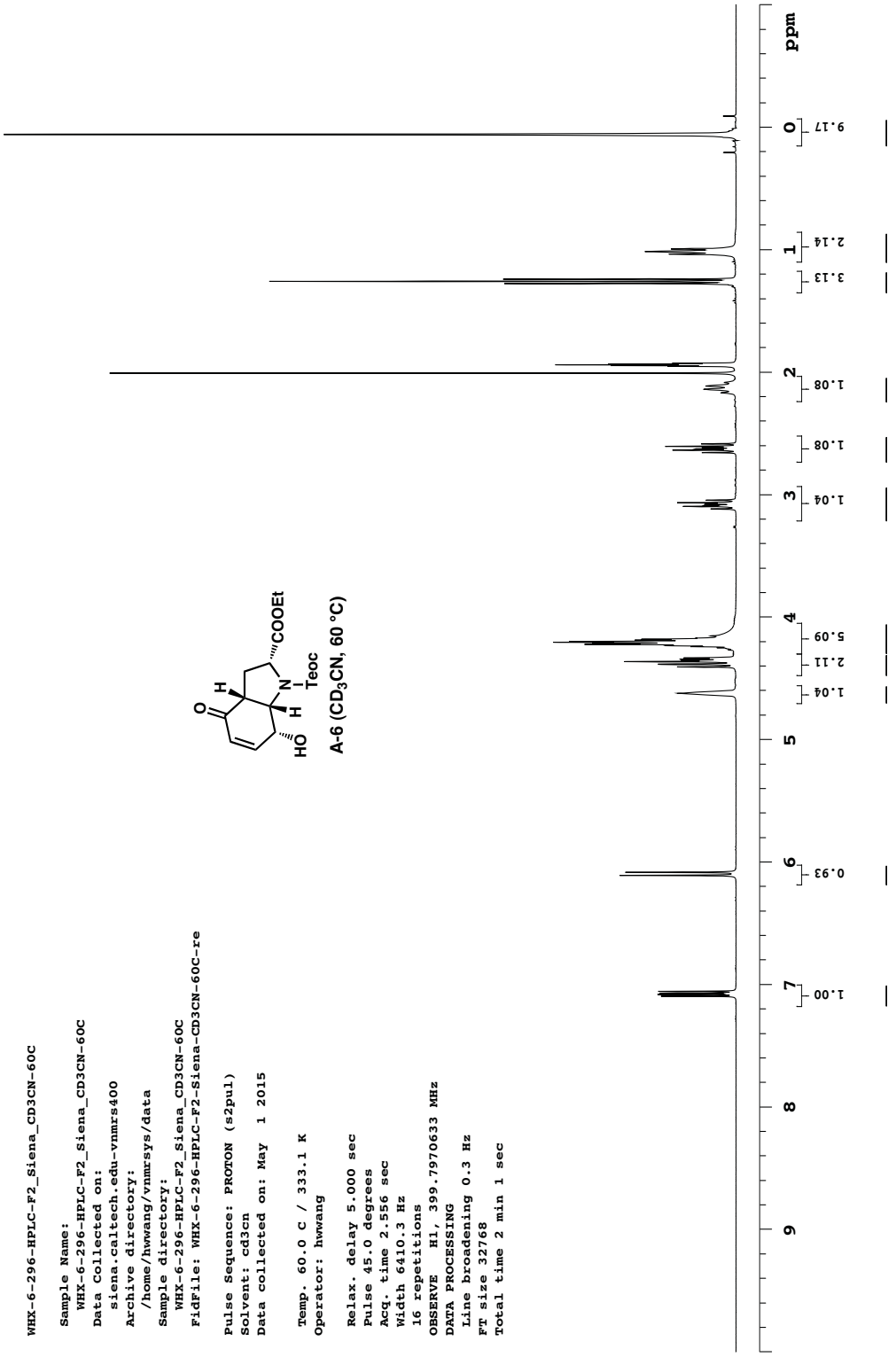
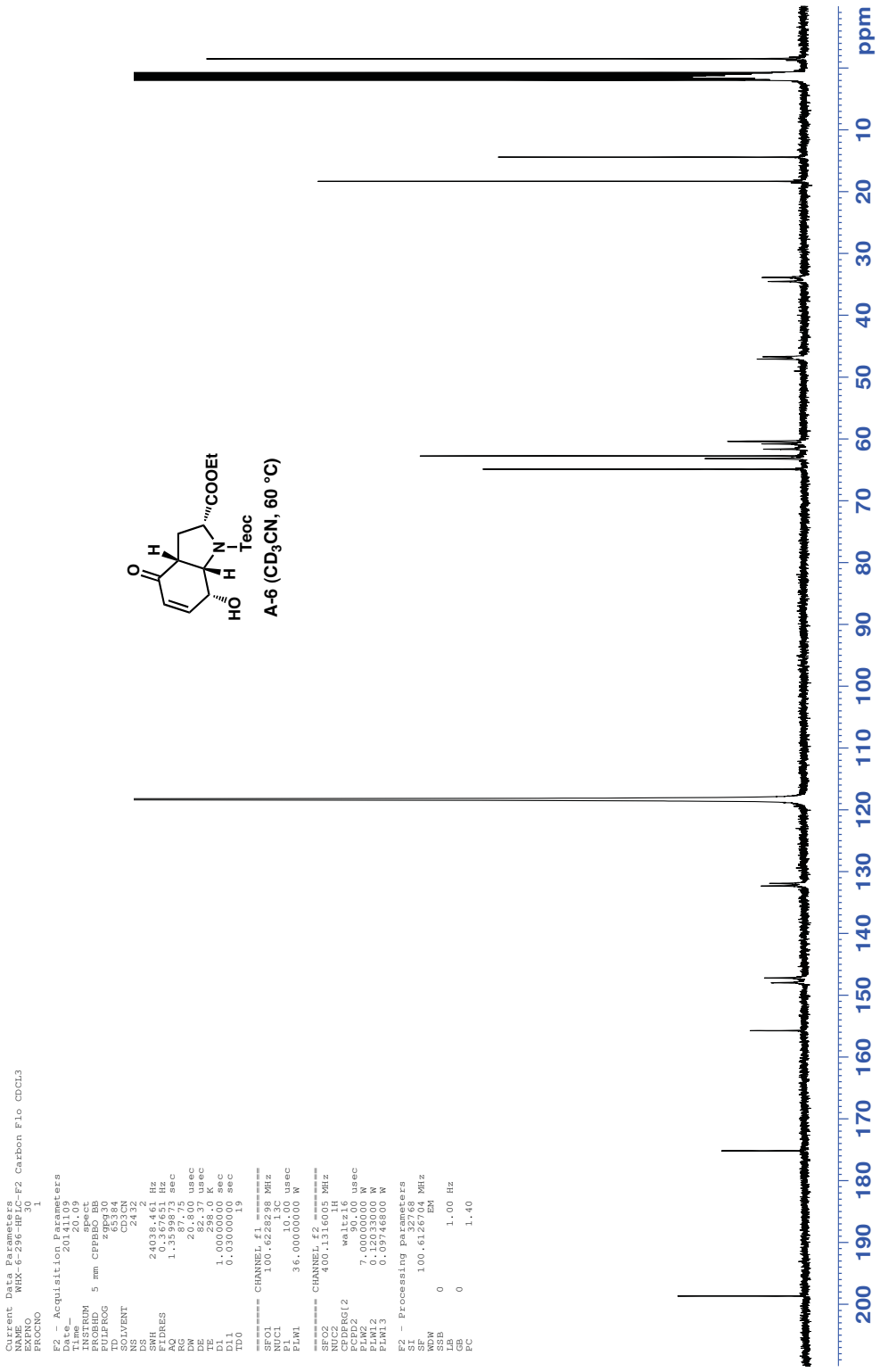
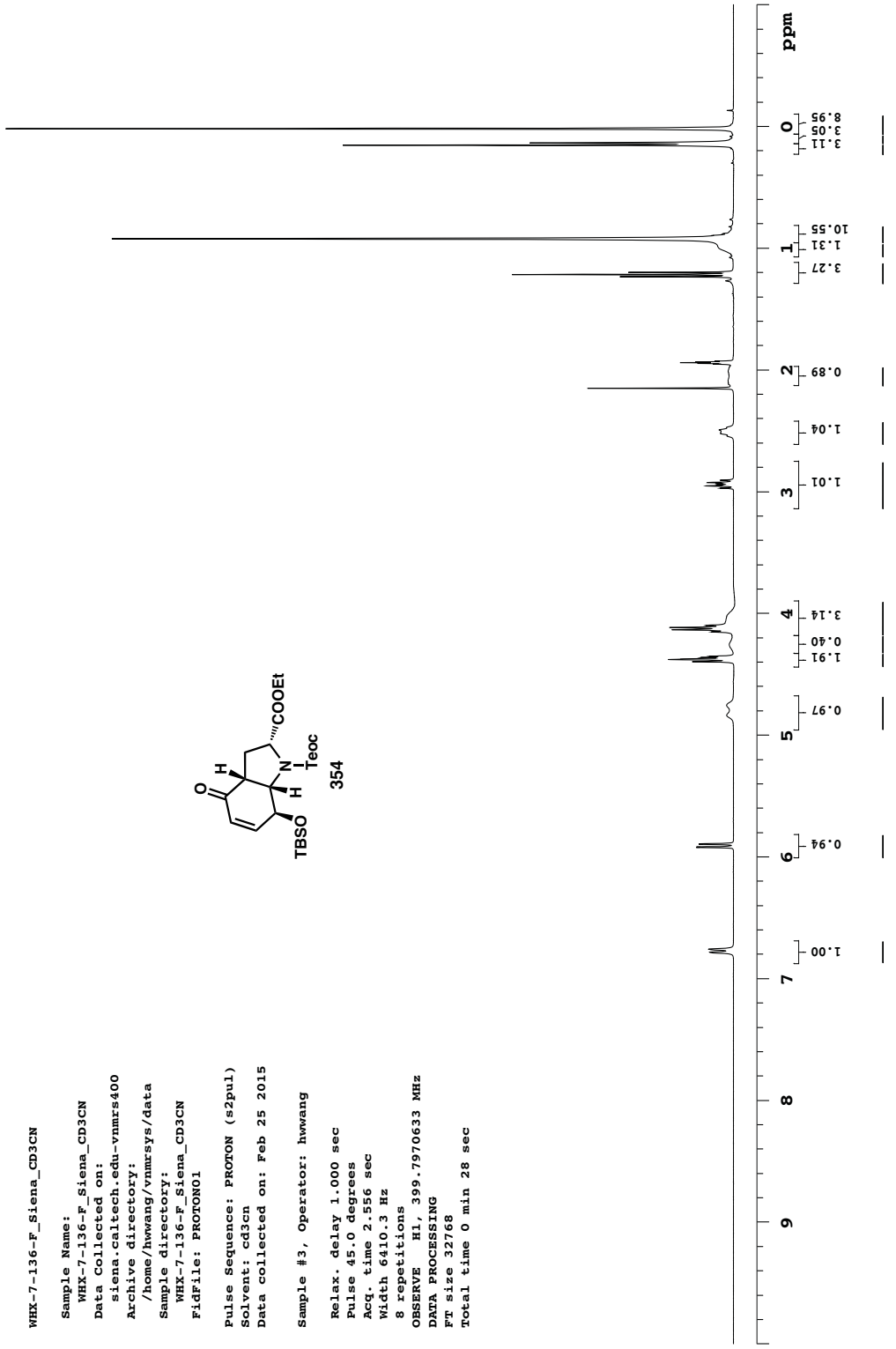
Time 21.11
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 30.29
DW 62.400 usec
DE 10.00 usec
TE 298.1 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300095 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
COOEt
Teoc
HO
353
ppm
9.10
2.11
4.03
1.15
1.23
1.07
5.33
2.64
1.10
0.88
1.00
1.00

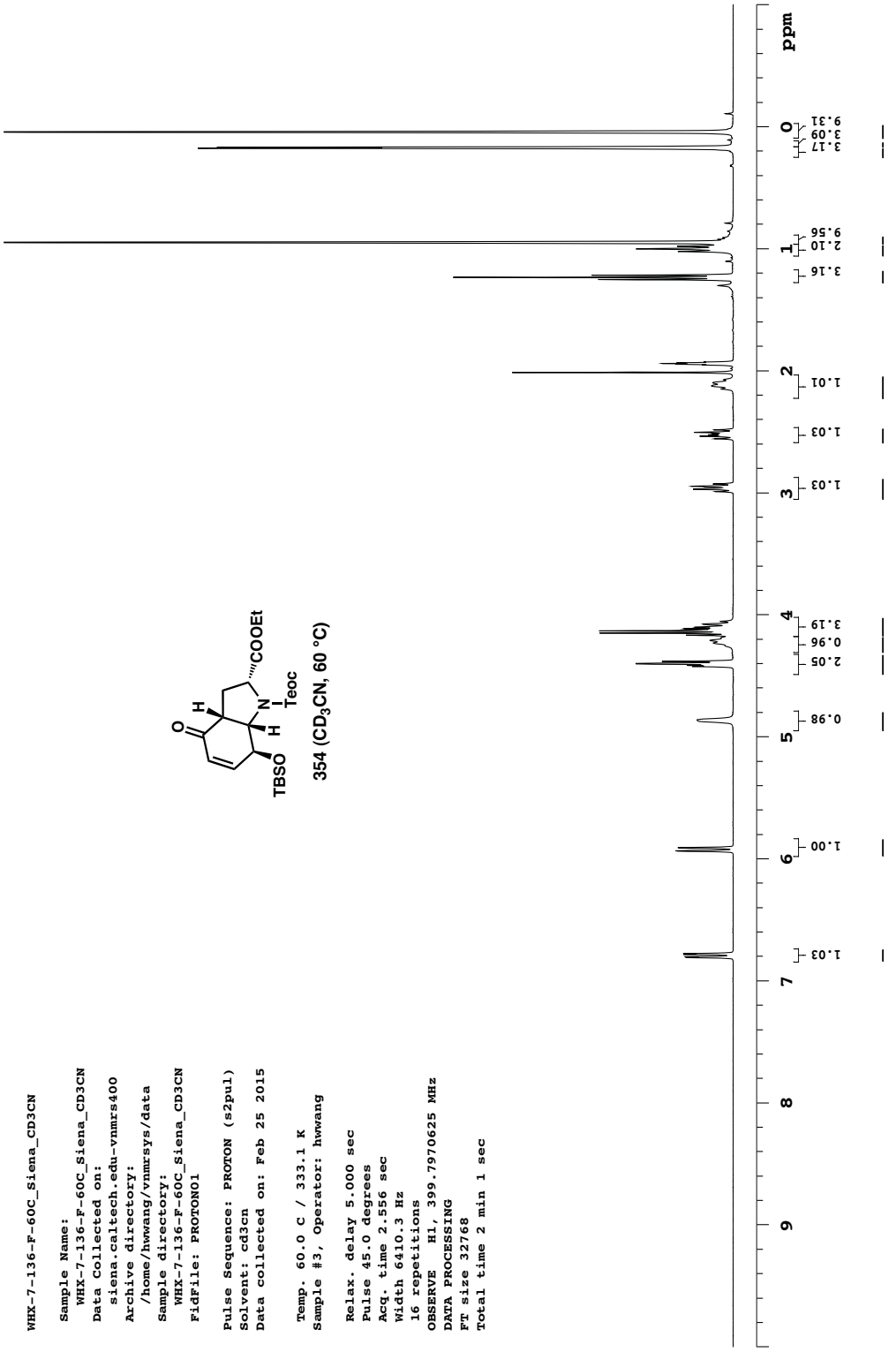

Current Data Parameters
NAME WHX-7-70-HPLC-F1-Flo-CDCL3
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150430
Time 21.17
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 128
DS 2
SWH 24038.461 Hz
FIDRES 0.366791 Hz
AQ 1.3631488 sec
RG 72.02
DW 20.800 usec
DE 82.37 usec
TE 298.1 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 18
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127747 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
O
H
HO
H
N
Teoc
COOEt
353
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

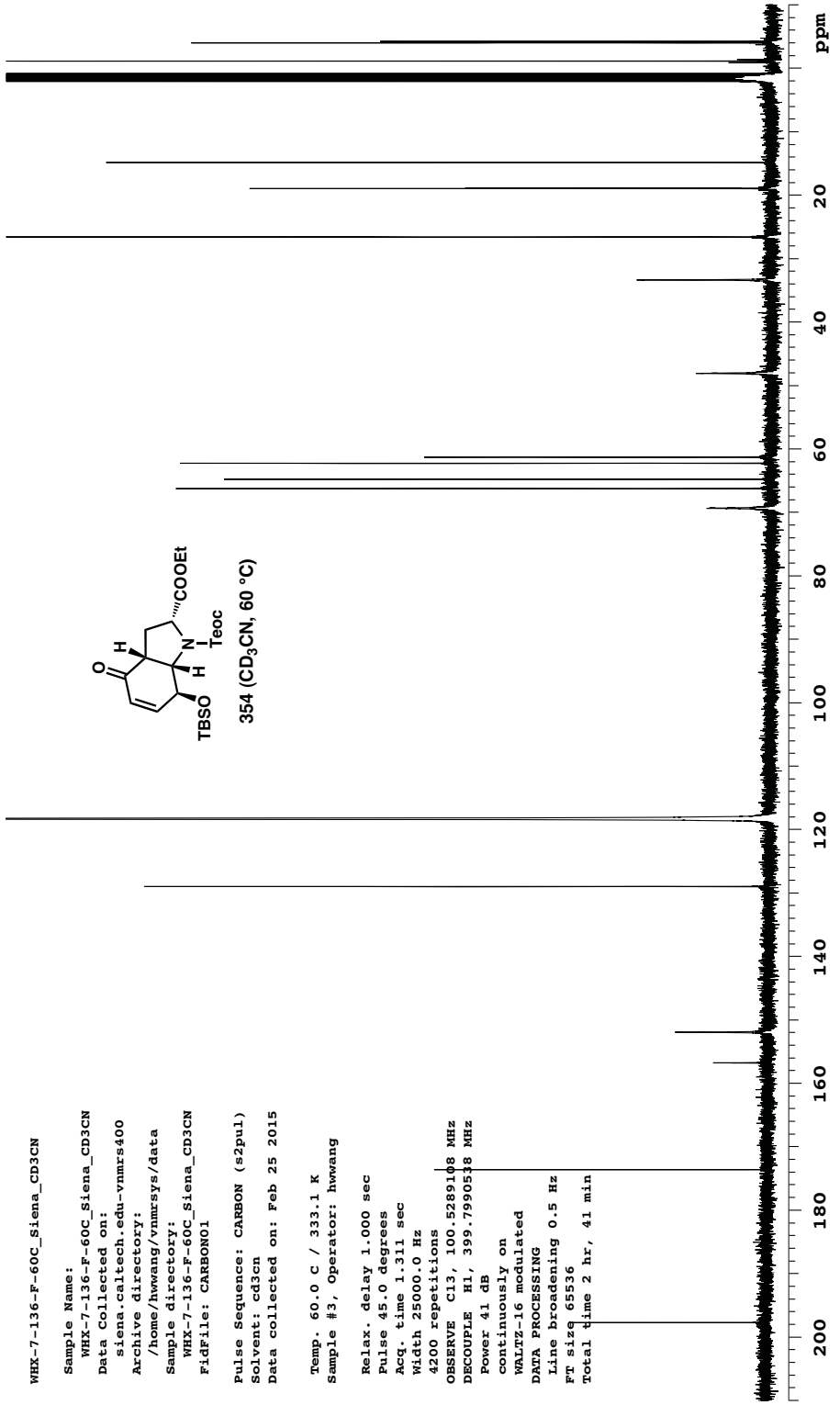

WHX-6-296-HPLC-F2_Siena_CD3CN
Sample Name:
WHX-6-296-HPLC-F2_Siena_CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-6-296-HPLC-F2_Siena_CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 1 2015
Sample #5, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970641 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
COOEt
N
Teoc
H
H
O
HO
A-6
ppm
9.11
2.16
3.15
0.96
1.08
1.02
4.87
2.46
1.06
0.93
1.00

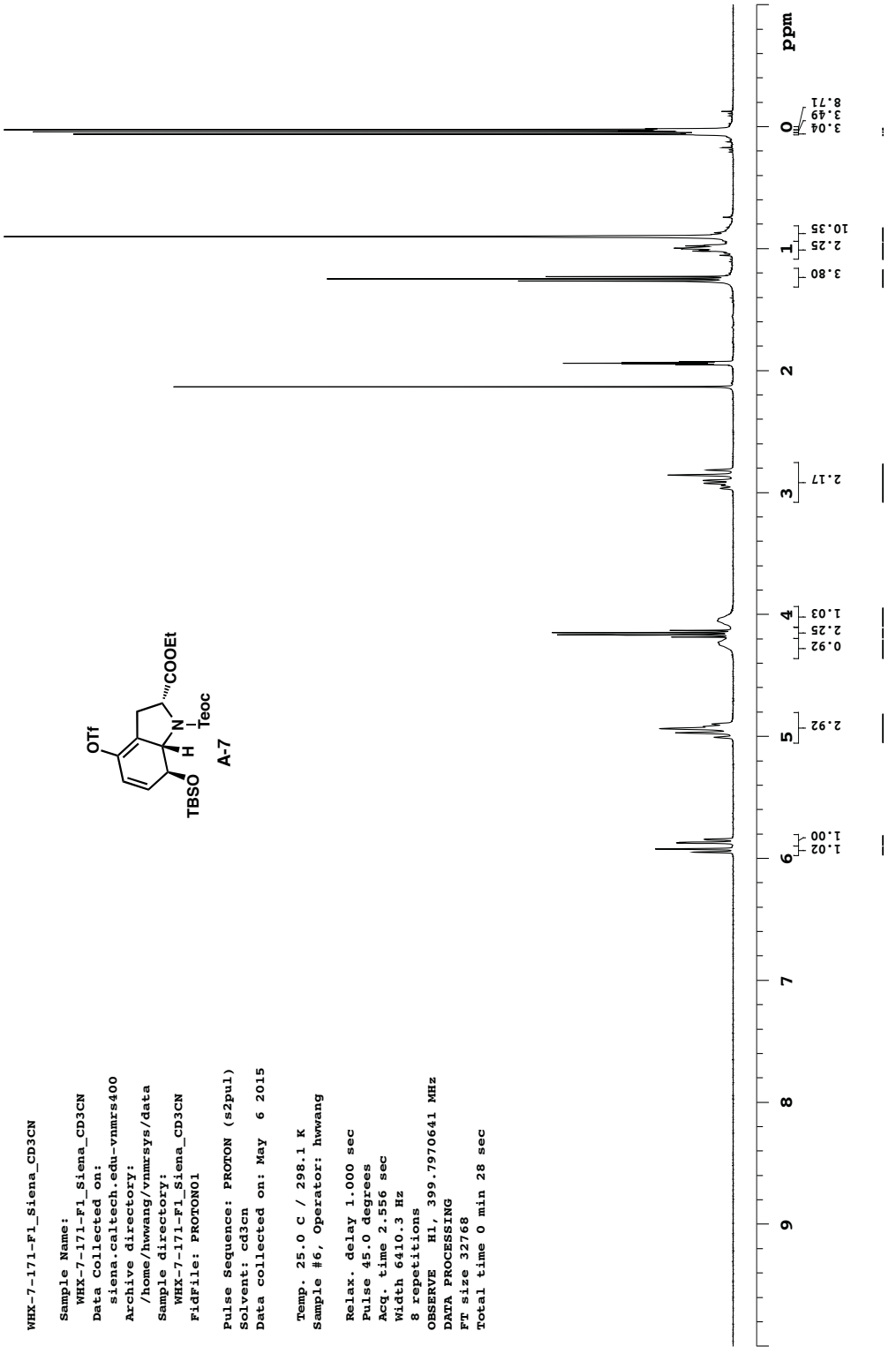

WHX-6-296-HPLC-F2_Siena_CD3CN-60C
Sample Name:
WHX-6-296-HPLC-F2_Siena_CD3CN-60C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-6-296-HPLC-F2_Siena_CD3CN-60C
FidFile: WHX-6-296-HPLC-F2-Siena-CD3CN-60C-re
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 1 2015
Temp. 60.0 C / 333.1 K
Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970633 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 2 min 1 sec
COOEt
Teoc
A-6 (CD3CN, 60 °C)
ppm
9.17
2.14
3.13
1.08
1.08
1.04
5.09
2.11
1.04
0.93
1.00

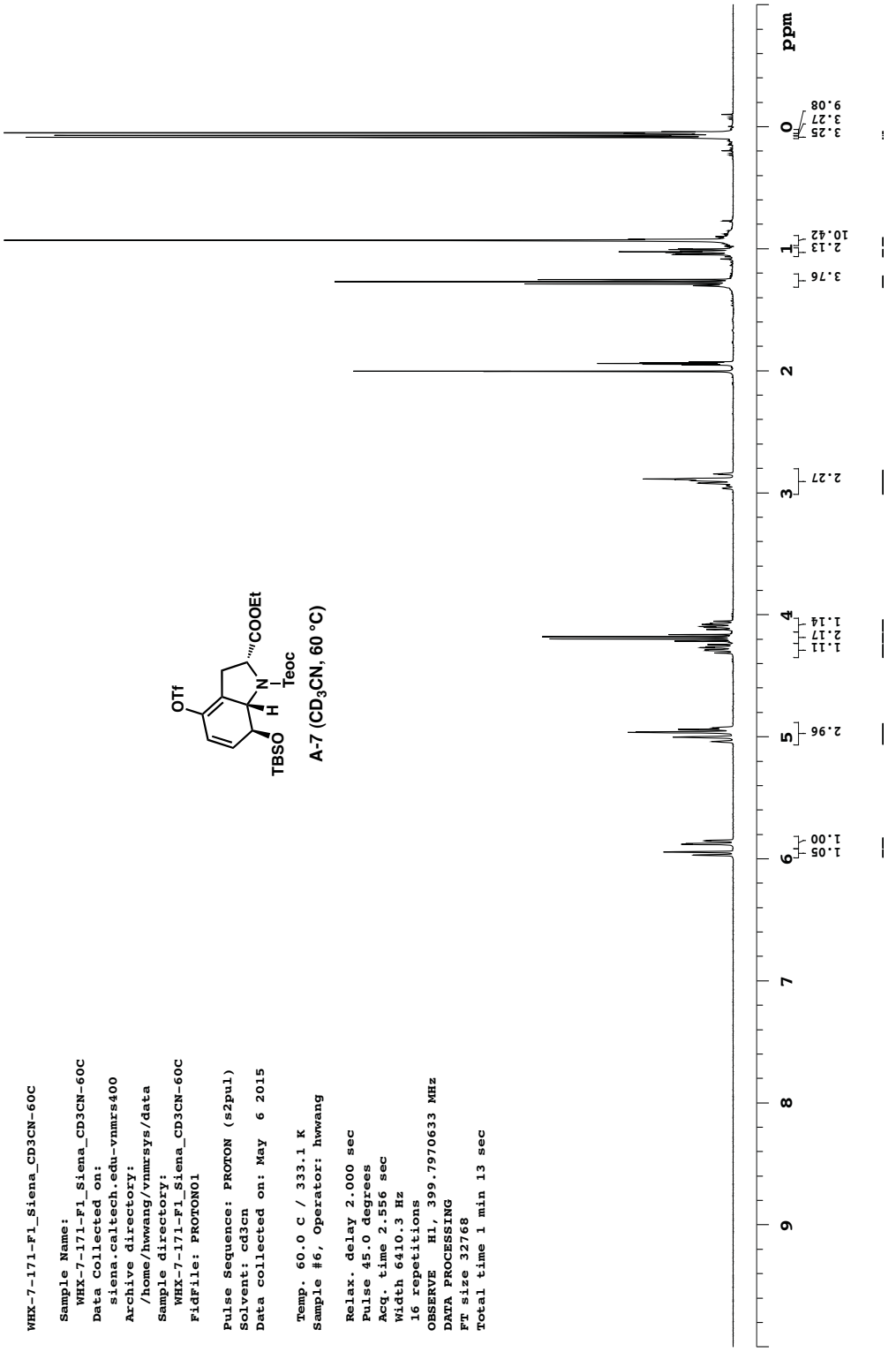

Current Data Parameters
NAME WHX-6-296-HPLC-F2 Carbon Flo CDCL3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141109
Time 20.08
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65536
SOLVENT CD3CN
NS 2432
DS 2
SWH 24038.461 Hz
FIDRES 0.367451 Hz
AQ 1.3599873 sec
RG 87.75
DW 20.800 usec
DE 22.37 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 19
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6126704 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
A-6 (CD3CN, 60 °C)
COOEt
Teoc
N
H
HO
O
H
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

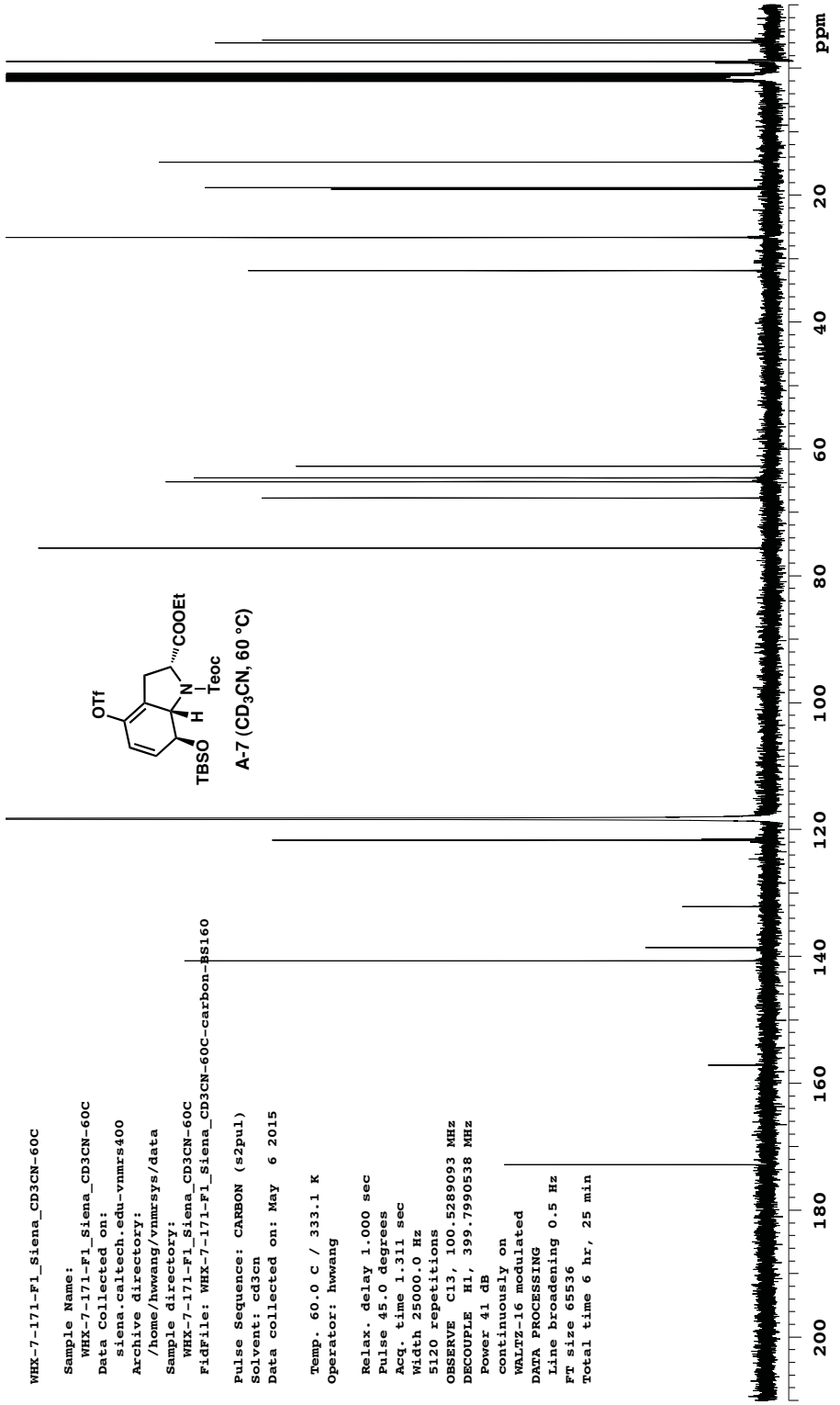

WHX-7-136-F_Siena_CD3CN
Sample Name:
WHX-7-136-F_Siena_CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-136-F_Siena_CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Feb 25 2015
Sample #3, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970633 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
TBSO
H
O
H
N
Teoc
COOEt
354
ppm
9
8
7
6
5
4
3
2
1
0
1.00
0.94
0.97
1.91
0.40
3.14
1.01
1.04
0.89
3.27
1.31
10.55
3.11
3.05
8.95

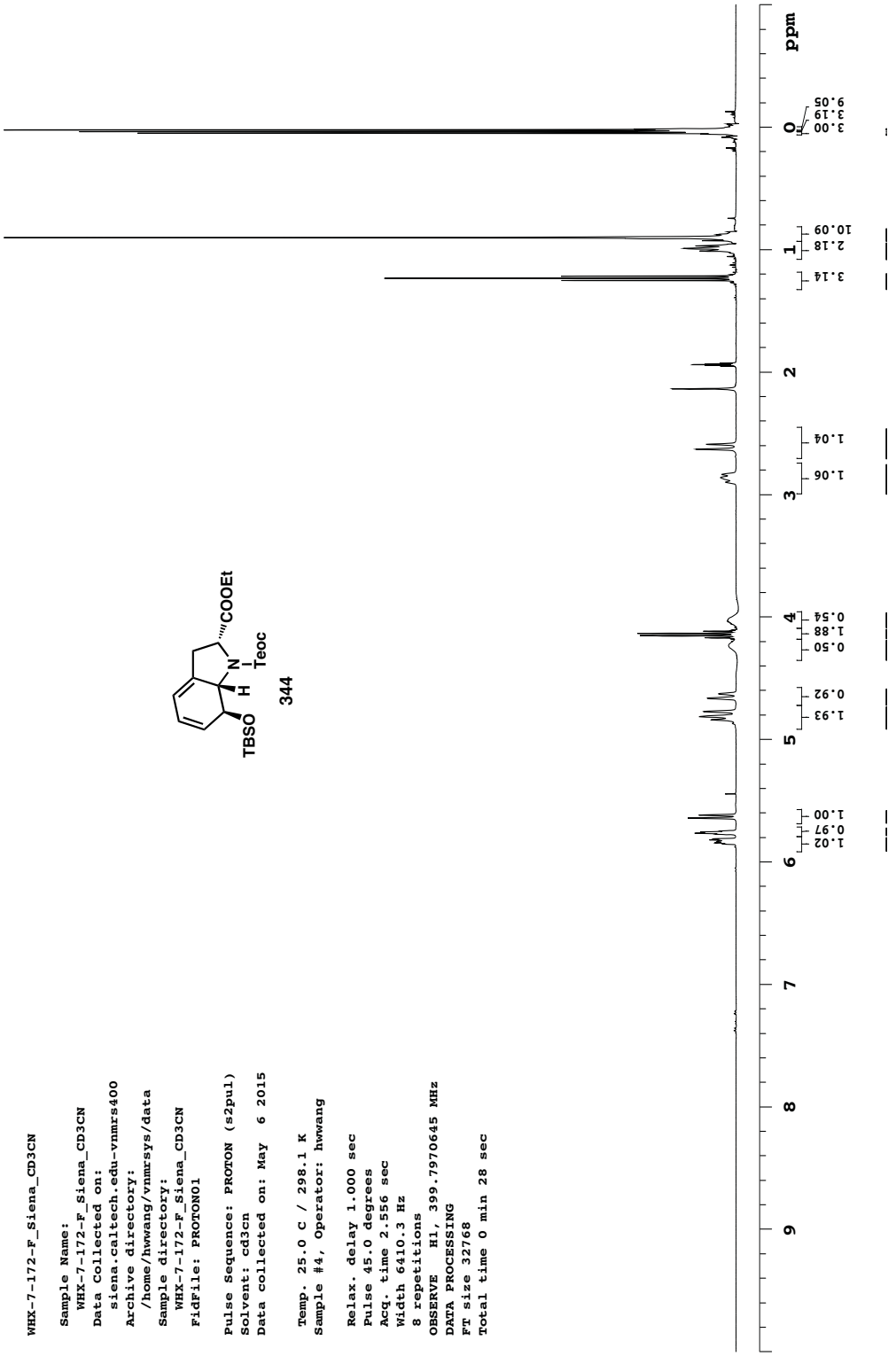

WHX-7-136-F-60C_Siena_CD3CN
Sample Name:
WHX-7-136-F-60C_Siena_CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-136-F-60C_Siena_CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Feb 25 2015
Temp. 60.0 C / 333.1 K
Sample #3, Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970625 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
TBSO
H
O
H
N
Teoc
COOEt
354 (CD3CN, 60 °C)
ppm
9.31
3.09
3.17
9.56
2.10
3.16
1.01
1.03
1.03
3.19
0.96
2.05
0.98
1.00
1.03

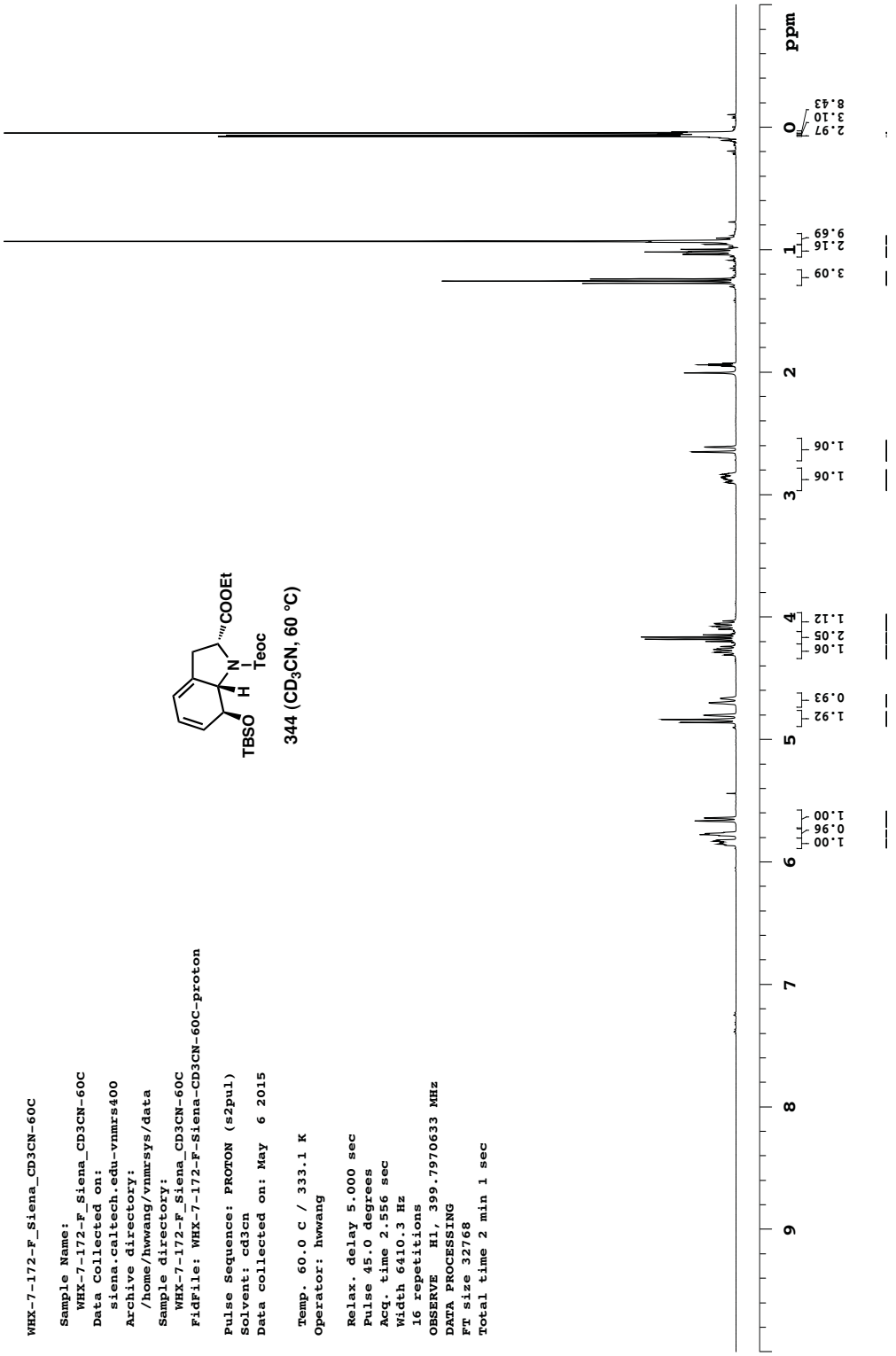

WHX-7-136-F-60C_Siena_CD3CN
Sample Name:
WHX-7-136-F-60C_Siena_CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-136-F-60C_Siena_CD3CN
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Feb 25 2015
Temp. 60.0 C / 333.1 K
Sample #3, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
4200 repetitions
OBSERVE C13, 100.5289108 MHz
DECOUPLE H1, 399.7990538 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 41 min
TBSO
H
O
H
N
Teoc
COOEt
354 (CD3CN, 60 °C)
200
180
160
140
120
100
80
60
40
20
ppm

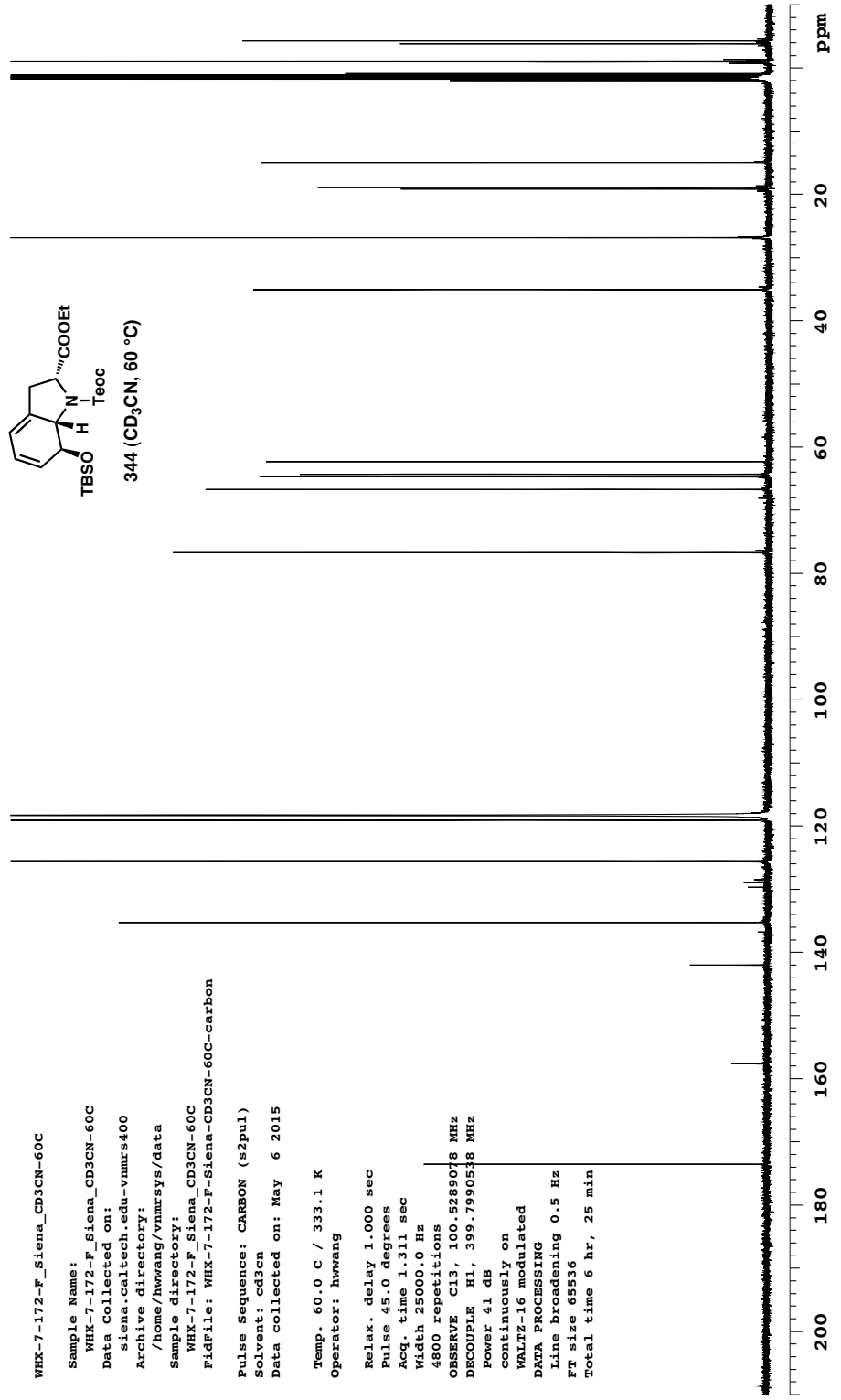

WHX-7-171-F1_Siena_CD3CN
Sample Name:
WHX-7-171-F1_Siena_CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-171-F1_Siena_CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2015
Temp. 25.0 C / 298.1 K
Sample #6, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970641 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
OTf
TBSO
H
N
Teoc
COOEt
A-7
ppm
9
8
7
6
5
4
3
2
1
0
1.02
1.00
2.92
0.92
2.25
1.03
2.17
3.80
2.25
10.35
3.04
3.49
8.71

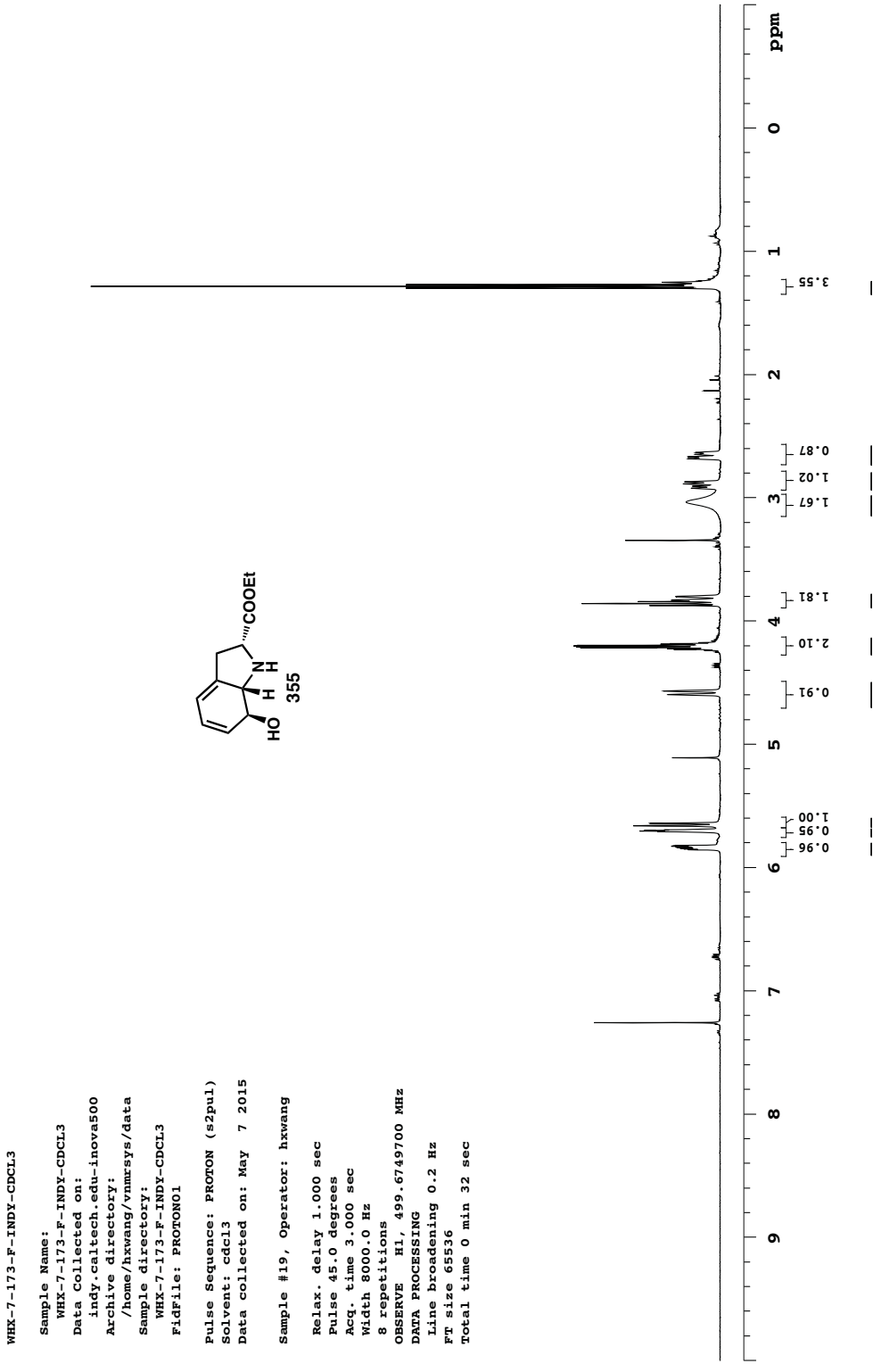

WHX-7-171-F1_Siena_CD3CN-60C
Sample Name:
WHX-7-171-F1_Siena_CD3CN-60C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-171-F1_Siena_CD3CN-60C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2015
Temp. 60.0 C / 333.1 K
Sample #6, Operator: hwwang
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970633 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 13 sec
OTf
COOEt
N
Teoc
H
TBSO
A-7 (CD3CN, 60 °C)
ppm
1.00
1.05
2.96
1.14
2.17
1.11
2.27
3.76
10.42
2.13
9.08
3.27
3.25

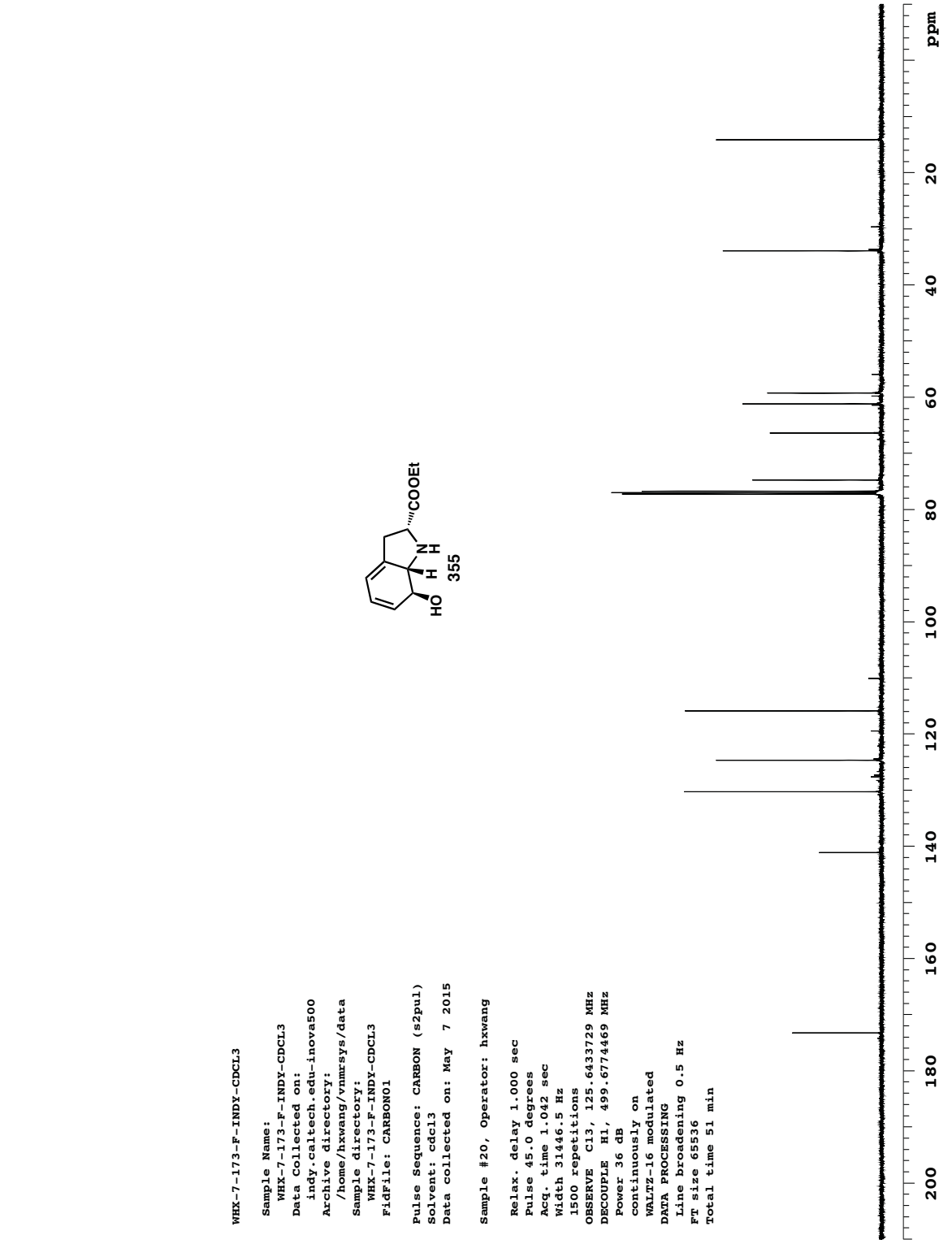

WHX-7-171-F1_Siena_CD3CN-60C
Sample Name:
WHX-7-171-F1_Siena_CD3CN-60C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-171-F1_Siena_CD3CN-60C
FidFile: WHX-7-171-F1_Siena_CD3CN-60C-carbon-BS160
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2015
Temp. 60.0 C / 333.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
5120 repetitions
OBSERVE C13, 100.5289093 MHz
DECOUPLE H1, 399.7990538 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 6 hr, 25 min
OTf
TBSO
H
N
Teoc
COOEt
A-7 (CD3CN, 60 °C)
200
180
160
140
120
100
80
60
40
20
ppm

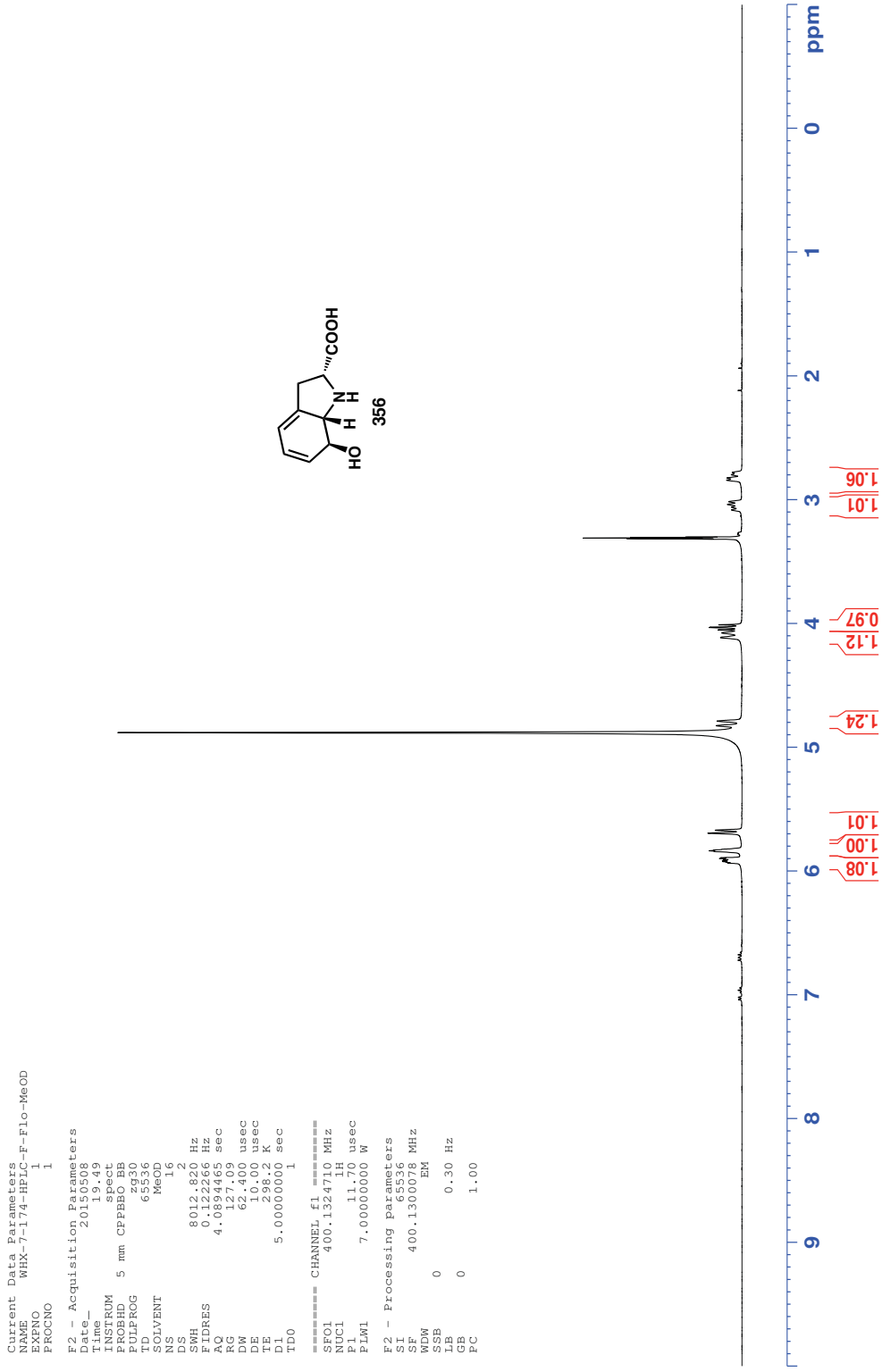

WHX-7-172-F_Siena_CD3CN
Sample Name:
WHX-7-172-F_Siena_CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-172-F_Siena_CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2015
Temp. 25.0 C / 298.1 K
Sample #4, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970645 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
TBSO
H
N
Teoc
COOEt
344
ppm
3.00
3.19
9.05
10.09
2.18
3.14
1.06
1.04
0.50
1.88
0.54
1.93
0.92
1.02
0.97
1.00

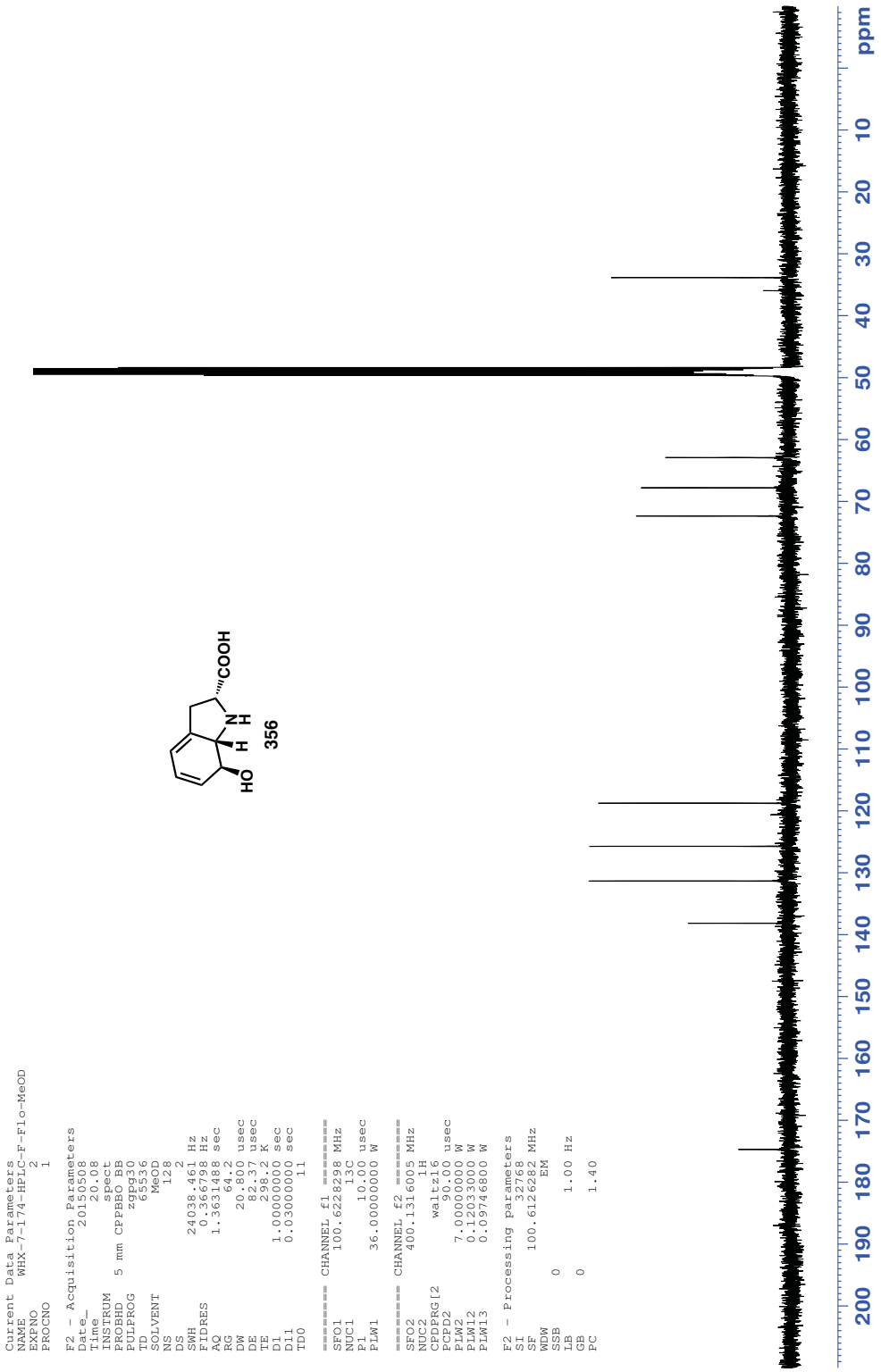

WHX-7-172-F_Siena_CD3CN-60C
Sample Name:
WHX-7-172-F_Siena_CD3CN-60C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-172-F_Siena_CD3CN-60C
FidFile: WHX-7-172-F-Siena-CD3CN-60C-proton
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2015
Temp. 60.0 C / 333.1 K
Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970633 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
TBSO
H
N
Teoc
""COOEt
344 (CD3CN, 60 °C)
ppm
2.97
3.10
8.43
3.09
2.16
9.69
1.06
1.06
1.06
2.05
1.12
1.92
0.93
1.00
0.96
1.00

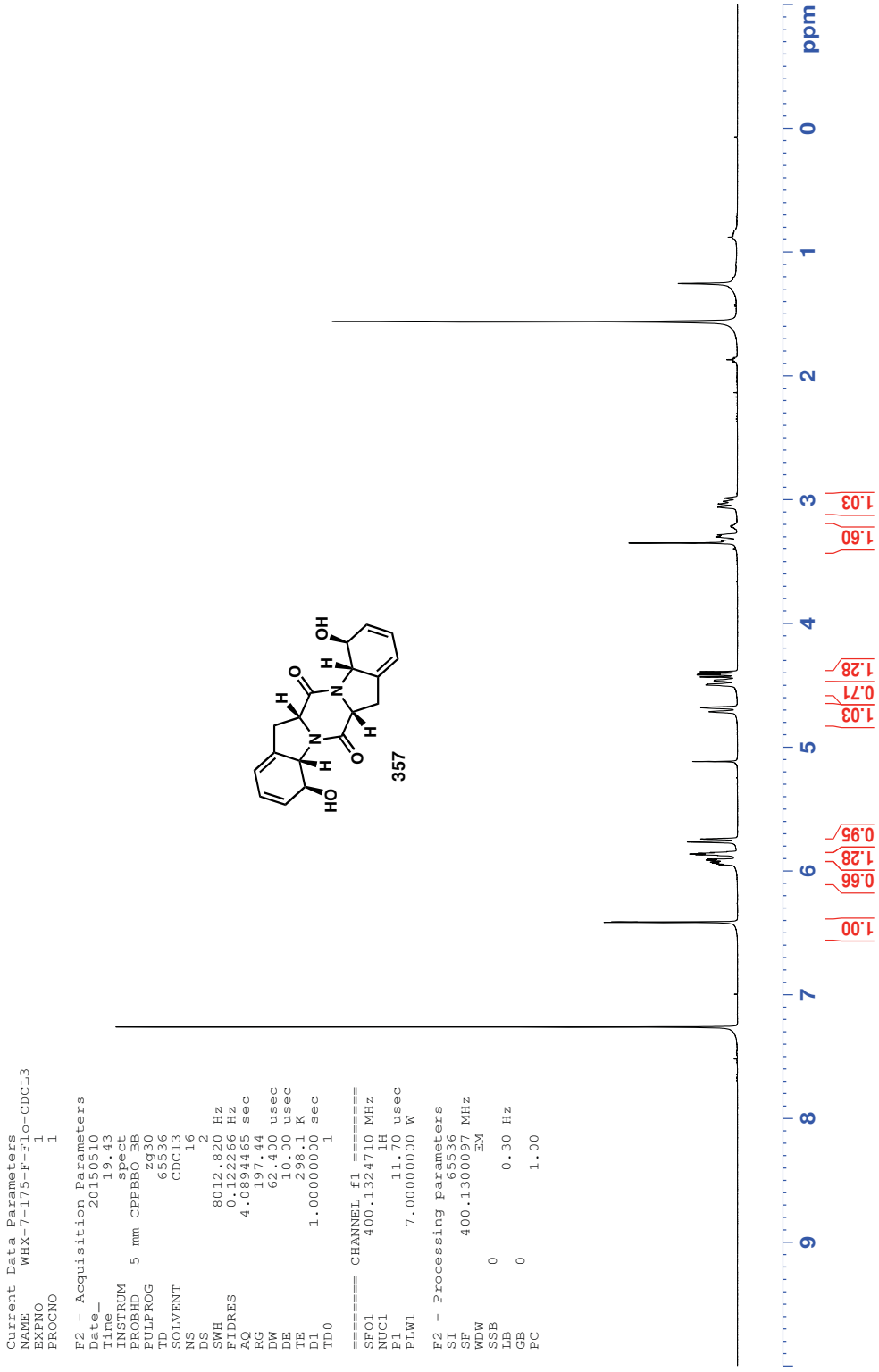

WHX-7-172-F_Siena_CD3CN-60C
Sample Name:
WHX-7-172-F_Siena_CD3CN-60C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-172-F_Siena_CD3CN-60C
FidFile: WHX-7-172-F-Siena-CD3CN-60C-carbon
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: May 6 2015
Temp. 60.0 C / 333.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
4800 repetitions
OBSERVE C13, 100.5289078 MHz
DECOUPLE H1, 399.7990538 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 6 hr, 25 min
TBSO
H
N
Teoc
COOEt
344 (CD3CN, 60 °C)
200
180
160
140
120
100
80
60
40
20
ppm

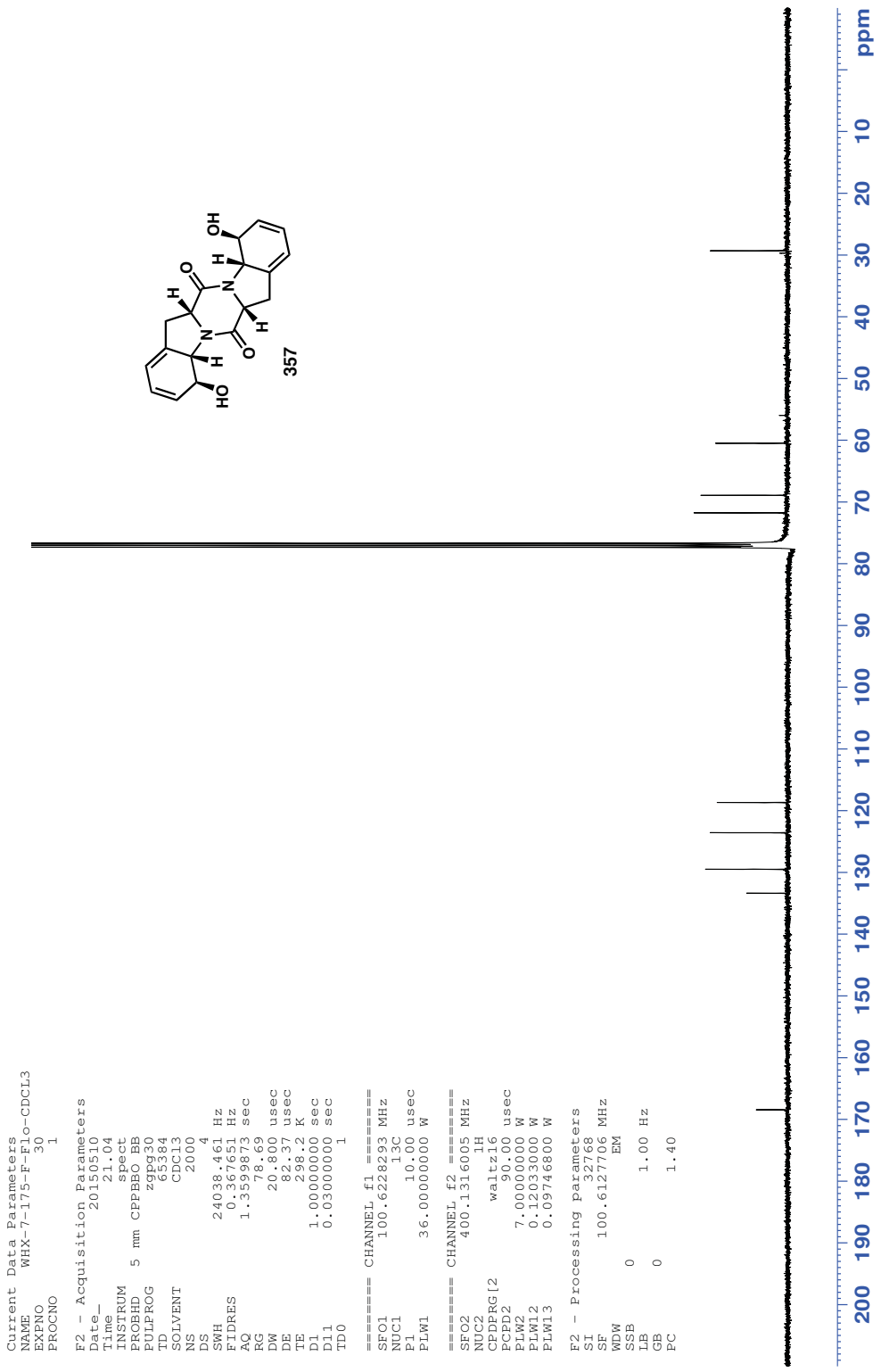

WHX-7-173-F-INDY-CDCL3
Sample Name:
WHX-7-173-F-INDY-CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-173-F-INDY-CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 7 2015
Sample #19, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6749700 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
COOEt
HO
H
N
H
355
ppm
0.96
0.95
1.00
2.10
0.91
1.81
1.67
1.02
0.87
3.55

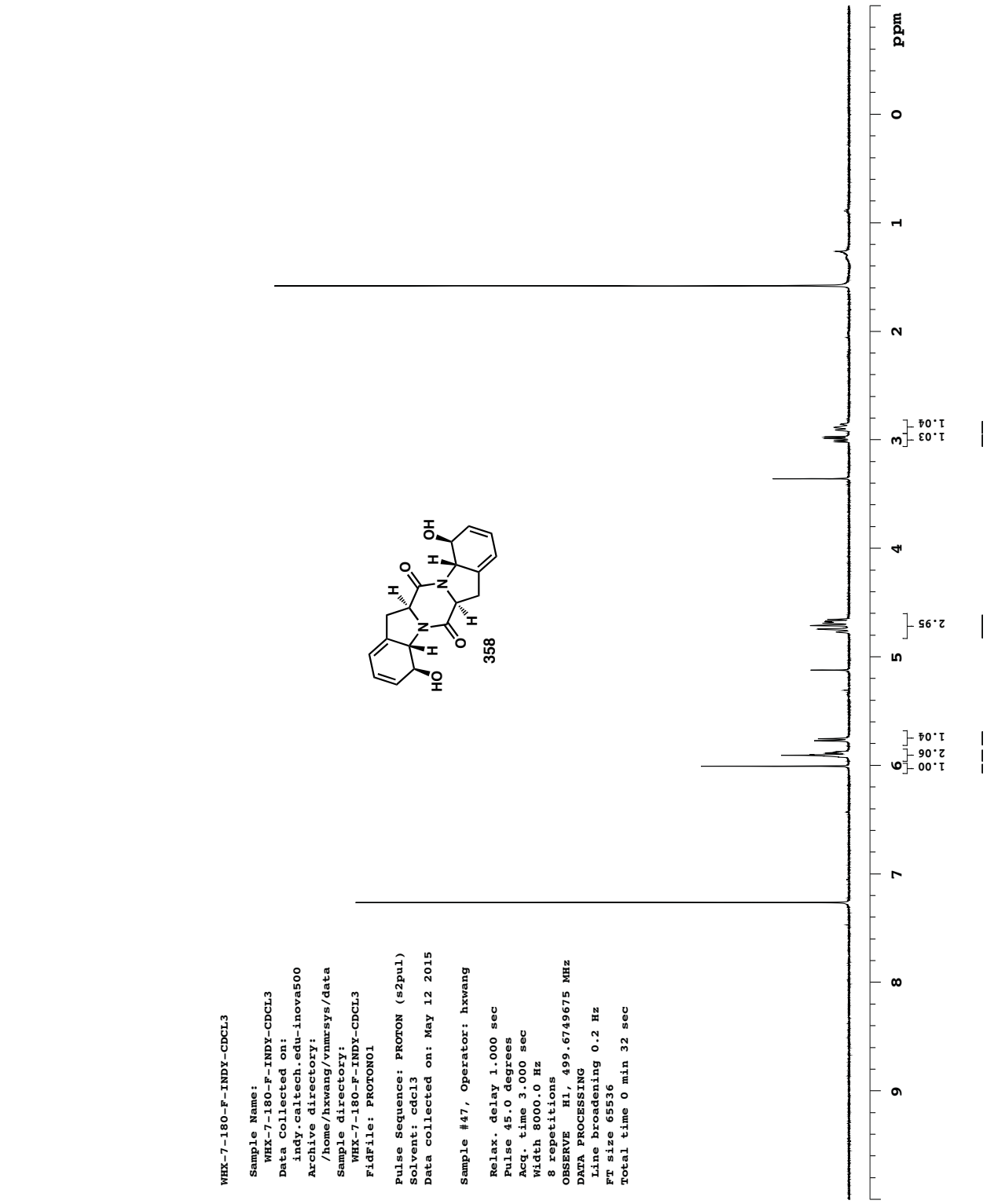

WHX-7-173-F-INDY-CDCL3
Sample Name:
WHX-7-173-F-INDY-CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-173-F-INDY-CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 7 2015
Sample #20, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6433729 MHz
DECOUPLE H1, 499.6774469 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
COOEt
N
H
HO
H
355
200
180
160
140
120
100
80
60
40
20
ppm

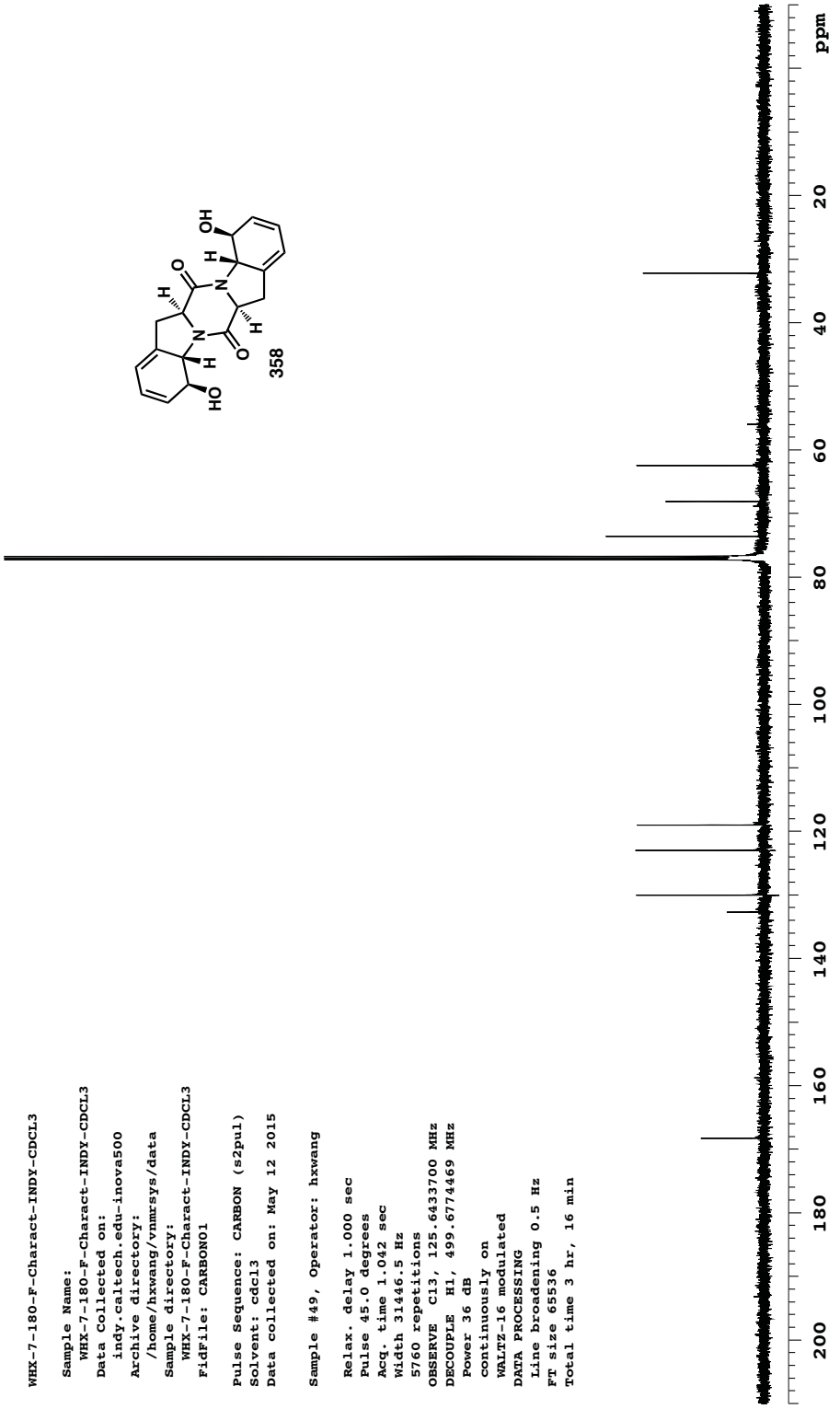

Current Data Parameters
NAME WHX-7-174-HPLC-F-Flo-MeOD
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150508
Time 19.49
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 127.09
DW 62.400 usec
DE 10.00 usec
TE 298.2 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300078 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
COOH
N
H
H
HO
356
1.08
1.00
1.01
1.24
1.12
0.97
1.01
1.06
9
8
7
6
5
4
3
2
1
0
ppm

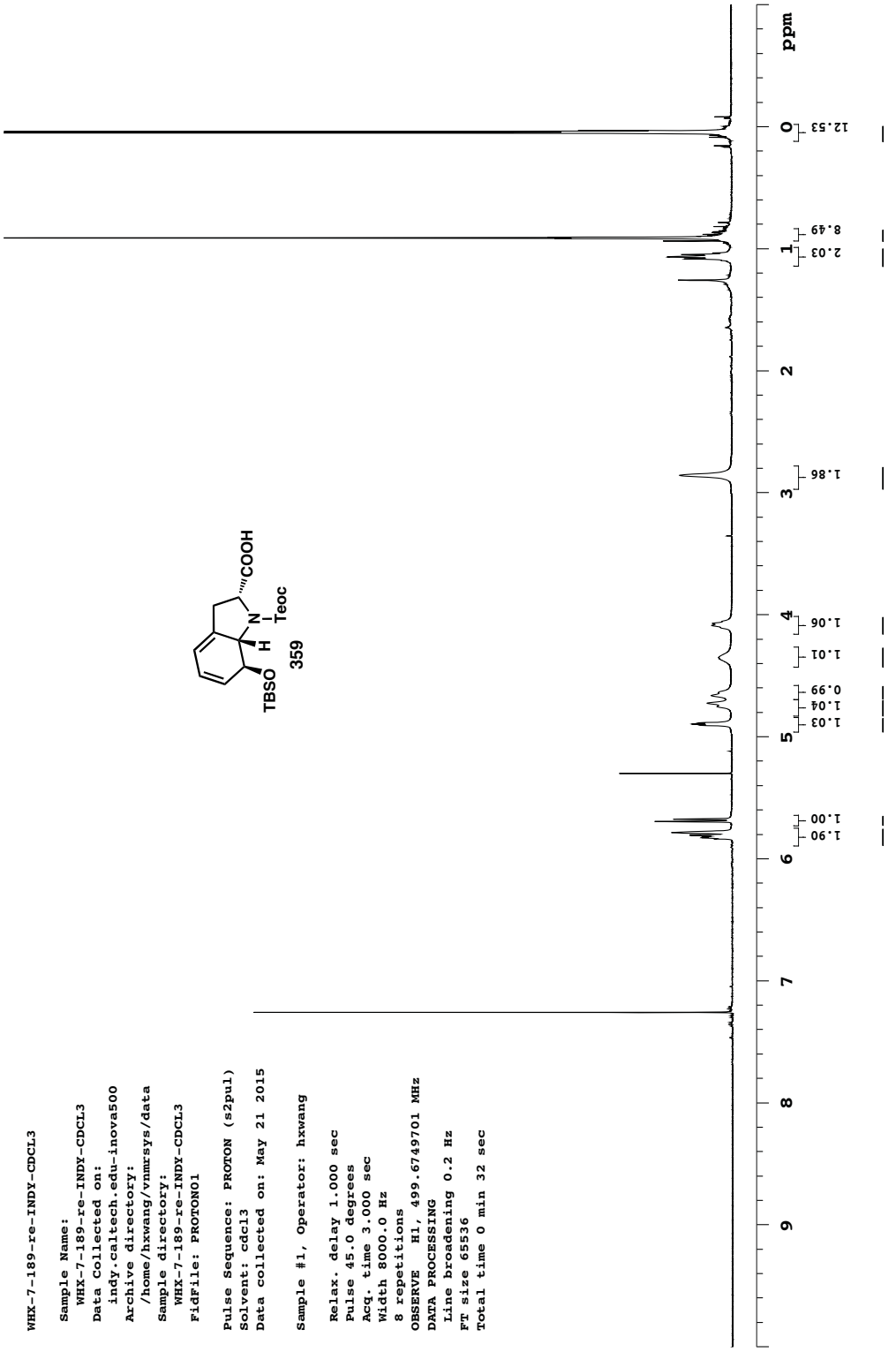

Current Data Parameters
NAME WHX-7-174-HPLC-F-Flo-MeOD
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150508
Time 20.08
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 128
DS 2
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 64.2
DW 20.800 usec
DE 82.37 usec
TE 298.2 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 11
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6126282 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
COOH
H
N
H
HO
356
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

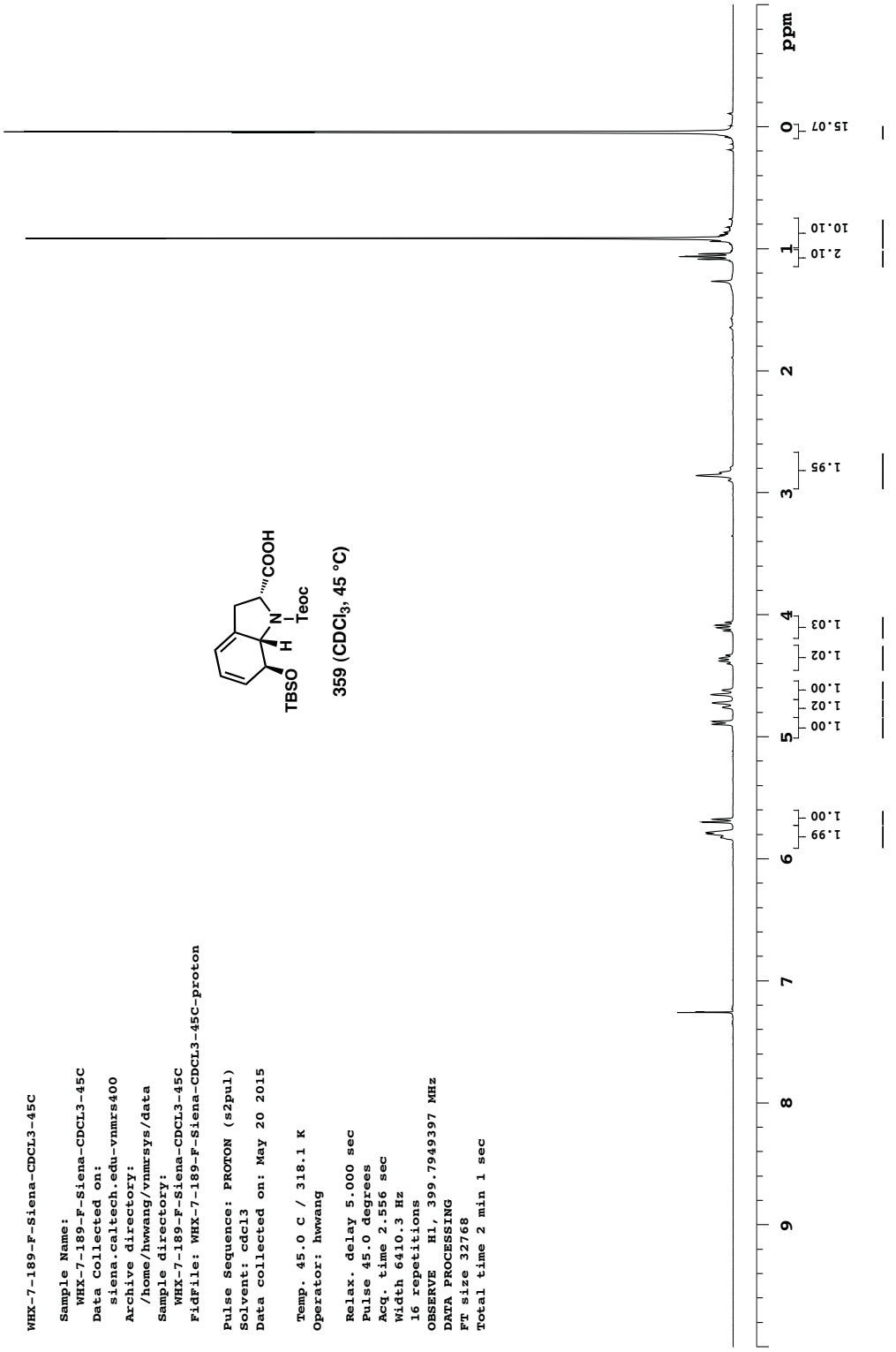

Current Data Parameters
NAME WHX-7-175-F-Flo-CDCl3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150510
Time_ 19.43
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 197.44
DW 62.400 usec
DE 10.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300097 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
H
O
N
H
H
N
O
H
HO
357
1.00
0.66
1.28
0.95
1.03
0.71
1.28
1.60
1.03
9
8
7
6
5
4
3
2
1
0
ppm

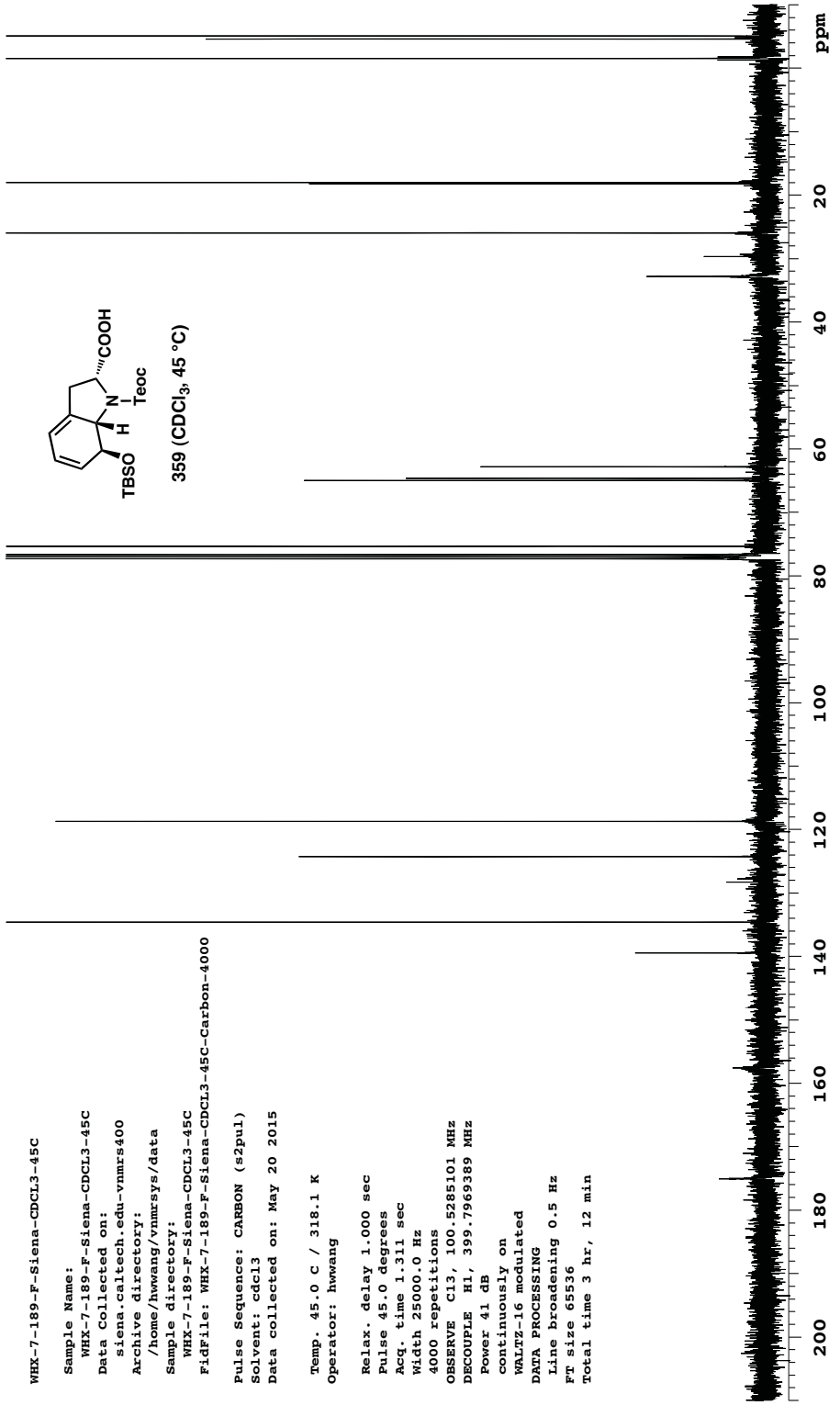

Current Data Parameters
NAME WHX-7-175-F-Flo-CDCl3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150510
Time_ 21.04
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 2000
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 78.69
DW 20.800 usec
DE 82.37 usec
TE 298.2 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.05746800 W
F2 - Processing parameters
SI 32768
SF 100.6127706 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OH
H
O
N
H
H
N
O
H
HO
357
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

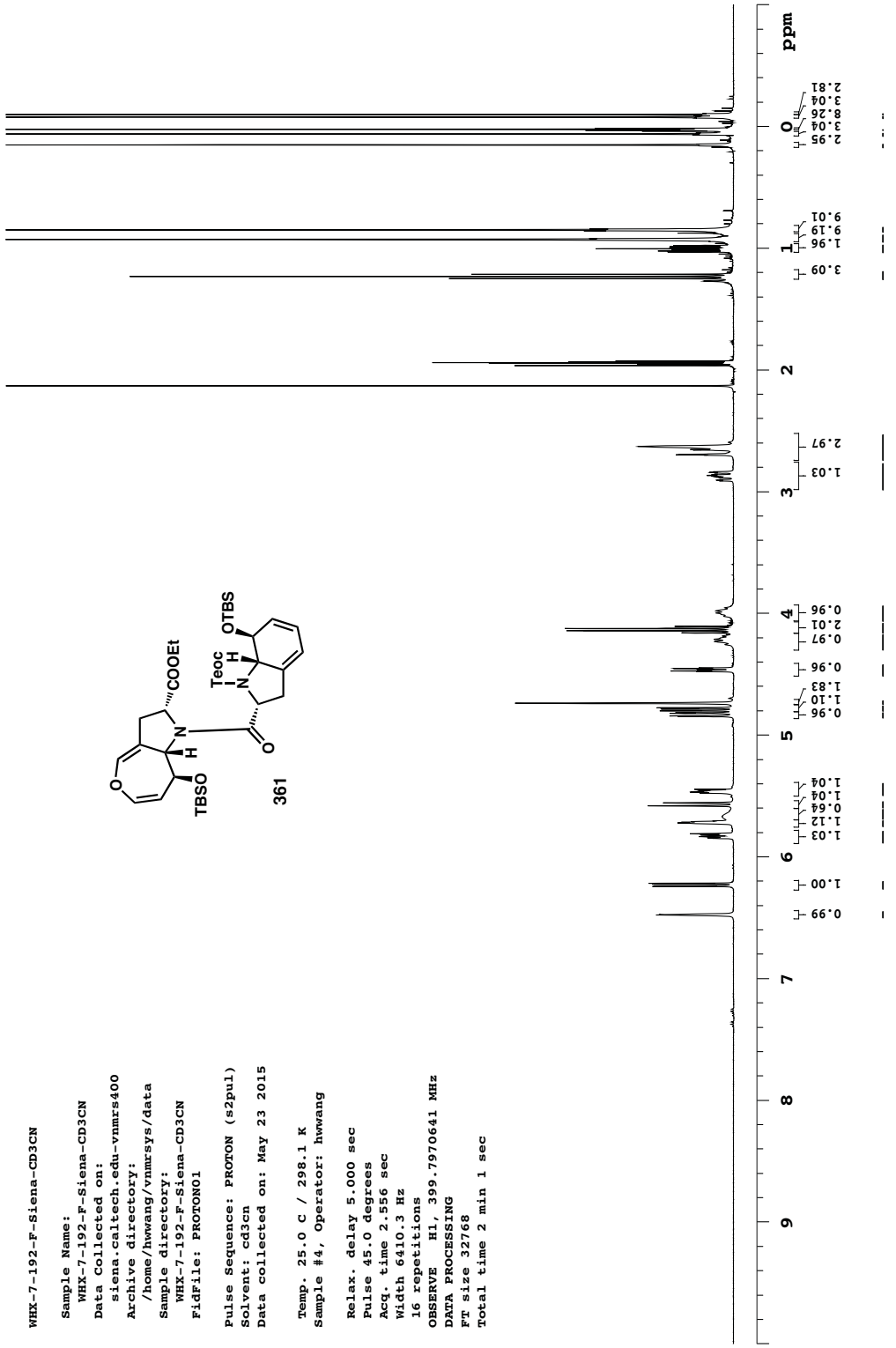

WHX-7-180-F-INDY-CDCL3
Sample Name:
WHX-7-180-F-INDY-CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-180-F-INDY-CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 12 2015
Sample #47, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6749675 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
OH
H
O
N
H
H
N
O
H
HO
358
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.06
1.04
2.95
1.03
1.04

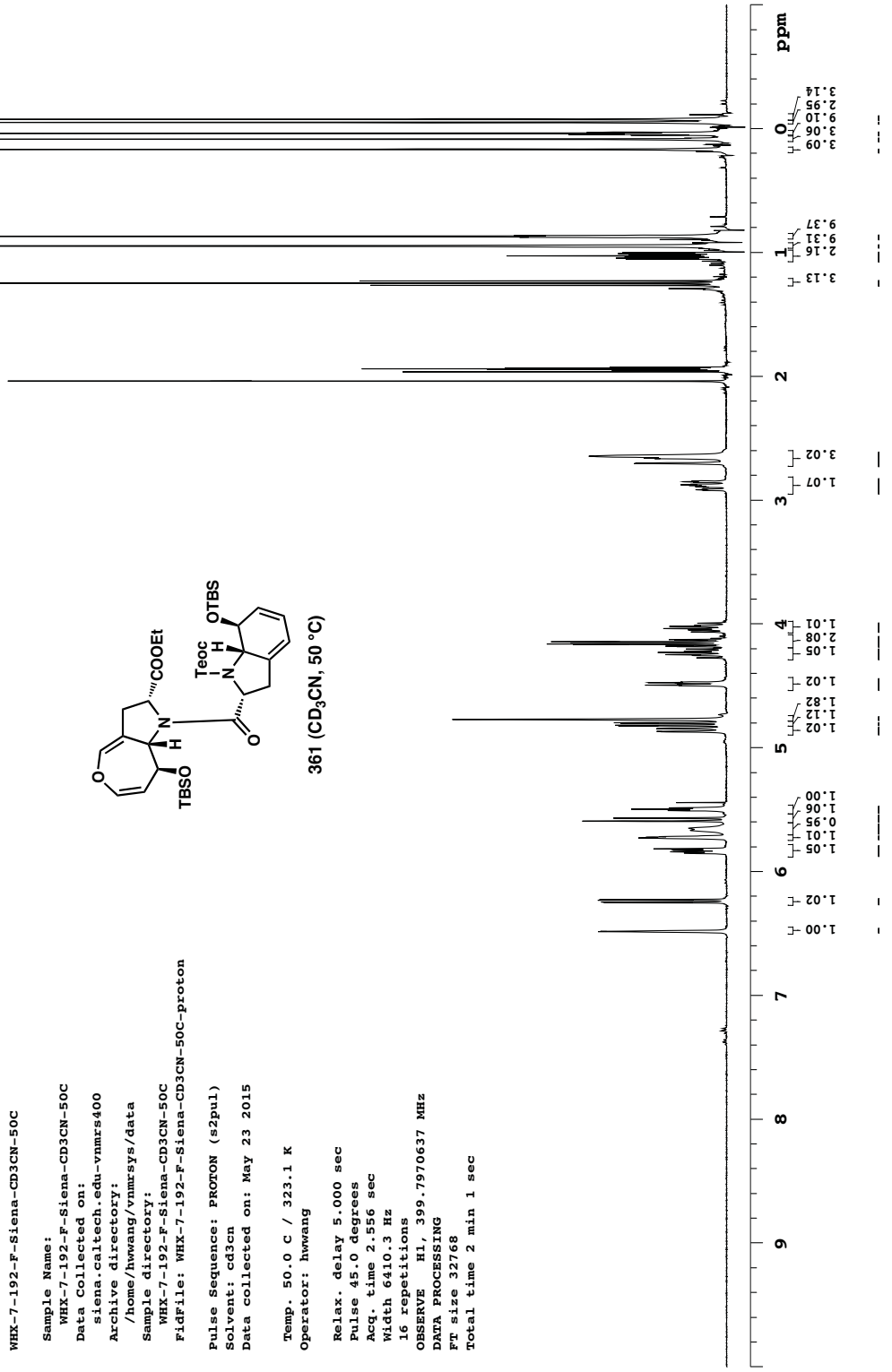

WHX-7-180-F-Charact-INDY-CDCL3
Sample Name:
WHX-7-180-F-Charact-INDY-CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-180-F-Charact-INDY-CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 12 2015
Sample #49, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5760 repetitions
OBSERVE C13, 125.6433700 MHz
DECOUPLE H1, 499.6774469 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 16 min
OH
H
O
N
H
N
H
O
H
HO
358
200
180
160
140
120
100
80
60
40
20
ppm

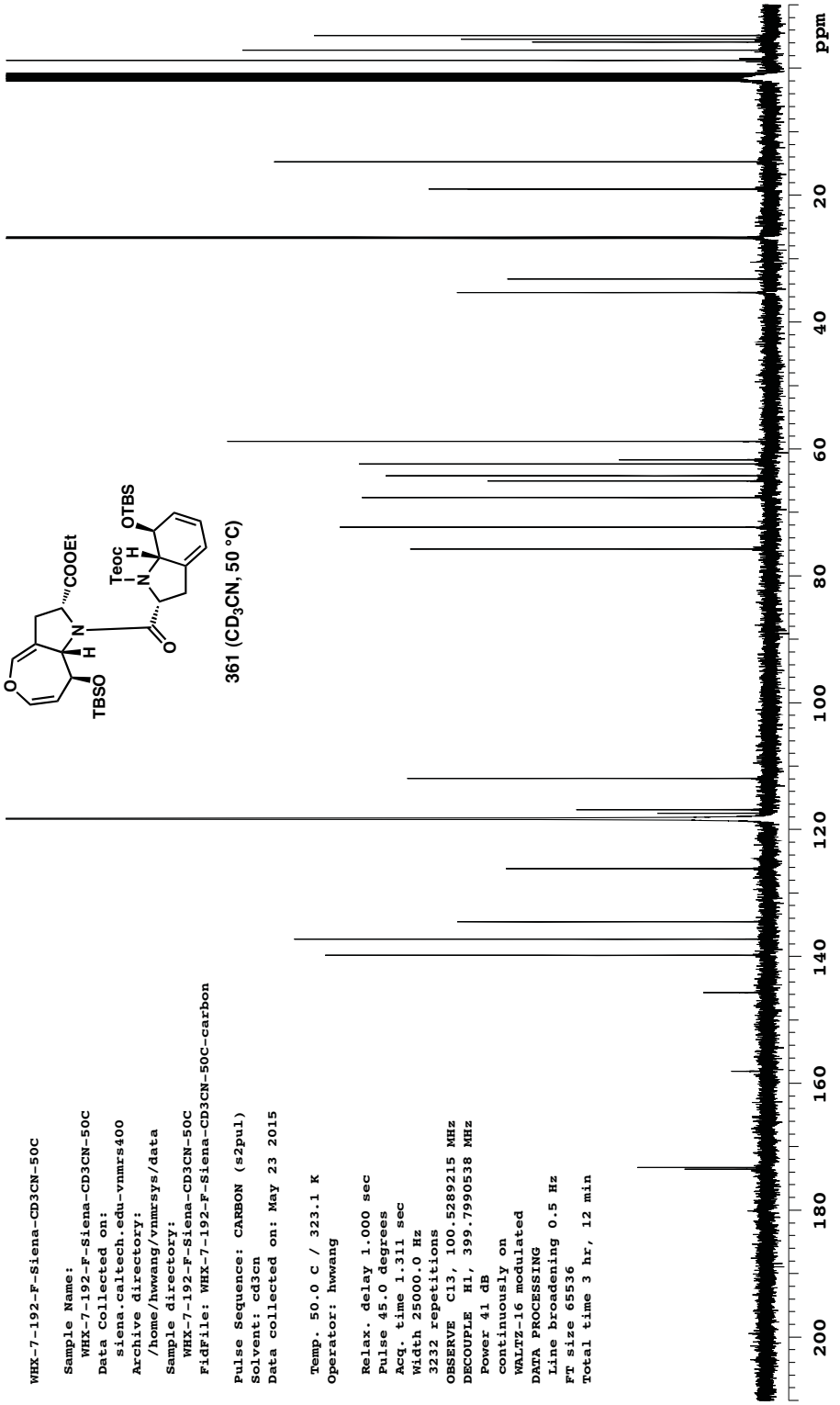

WHX-7-189-re-INDY-CDCL3
Sample Name:
WHX-7-189-re-INDY-CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-189-re-INDY-CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 21 2015
Sample #1, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.6749701 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec
COOH
N
Teoc
H
TBSO
359
ppm
12.53
8.49
2.03
1.86
1.06
1.01
1.03
1.04
0.99
1.90
1.00

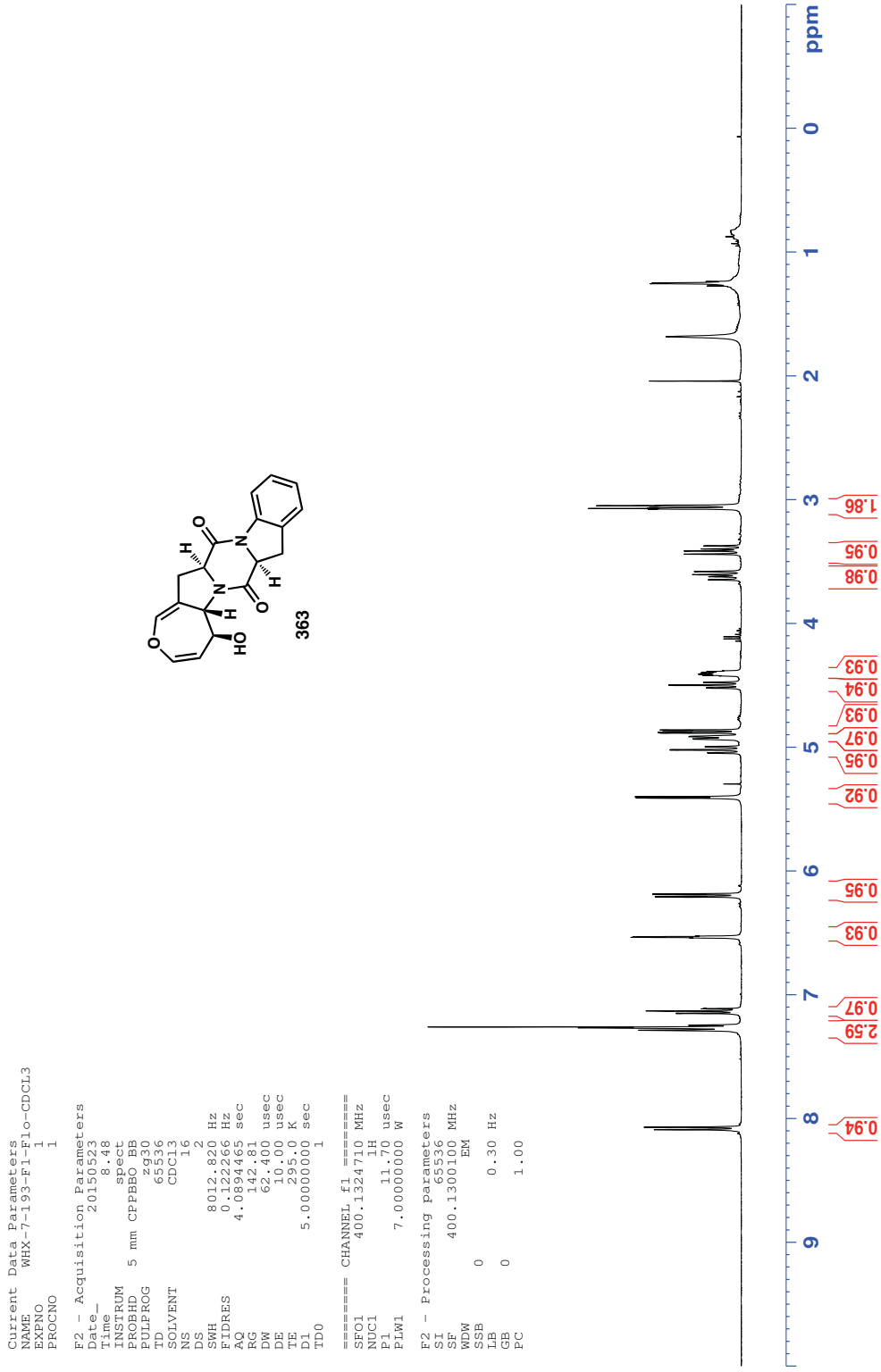

WHX-7-189-F-Siena-CDCL3-45C
Sample Name:
WHX-7-189-F-Siena-CDCL3-45C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-189-F-Siena-CDCL3-45C
FidFile: WHX-7-189-F-Siena-CDCL3-45C-proton
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 20 2015
Temp. 45.0 C / 318.1 K
Operator: hwwang
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
COOH
N
Teoc
H
TBSO
359 (CDCl3, 45 °C)
ppm
15.07
10.10
2.10
1.95
1.03
1.02
1.00
1.02
1.00
1.00
1.99
1.00

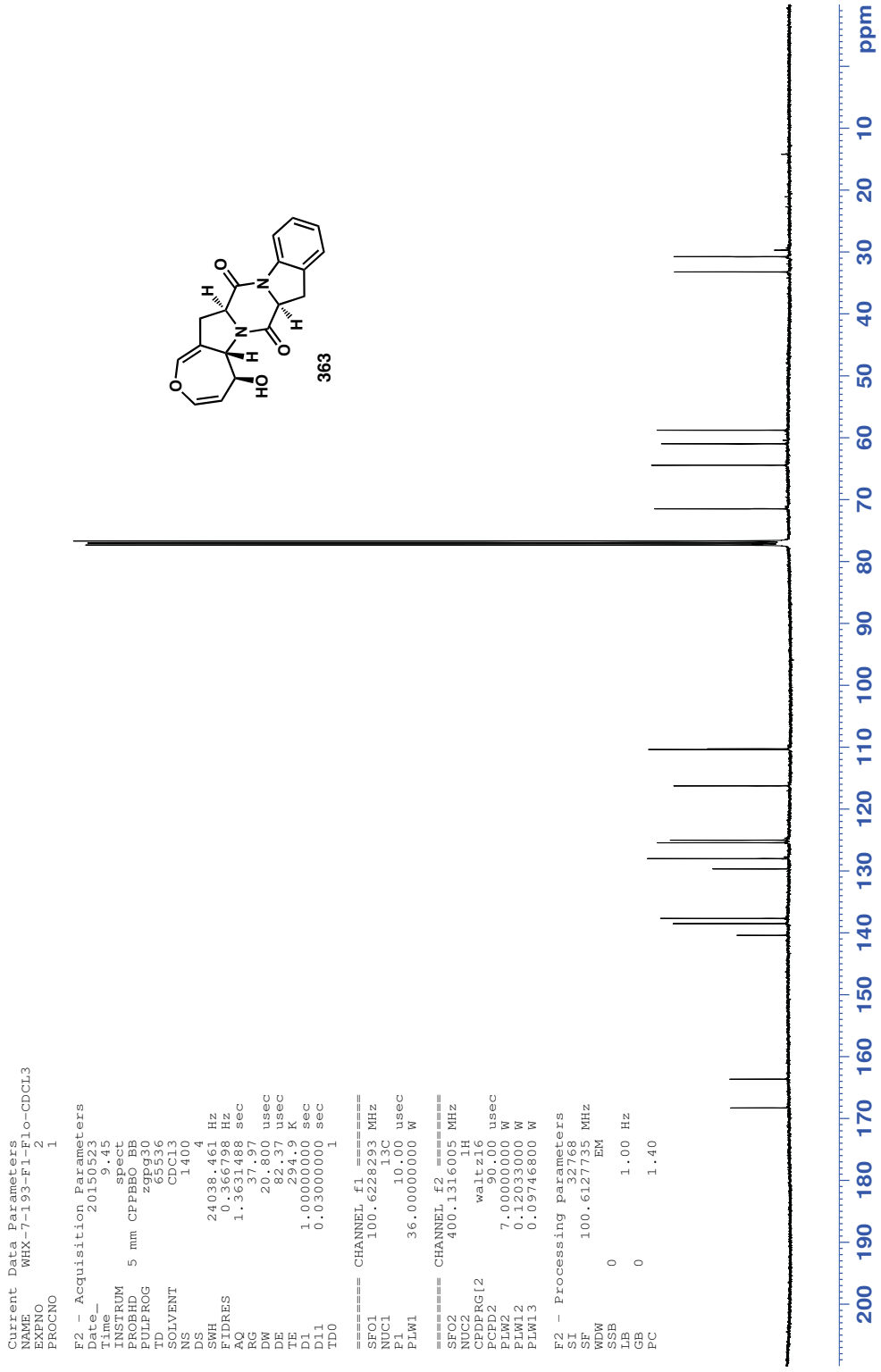

WHX-7-189-F-Siena-CDCL3-45C
Sample Name:
WHX-7-189-F-Siena-CDCL3-45C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-189-F-Siena-CDCL3-45C
FidFile: WHX-7-189-F-Siena-CDCL3-45C-Carbon-4000
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 20 2015
Temp. 45.0 C / 318.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
4000 repetitions
OBSERVE C13, 100.5285101 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 3 hr, 12 min
359 (CDCl3, 45 °C)
TBSO
H
N
Teoc
COOH
200
180
160
140
120
100
80
60
40
20
ppm

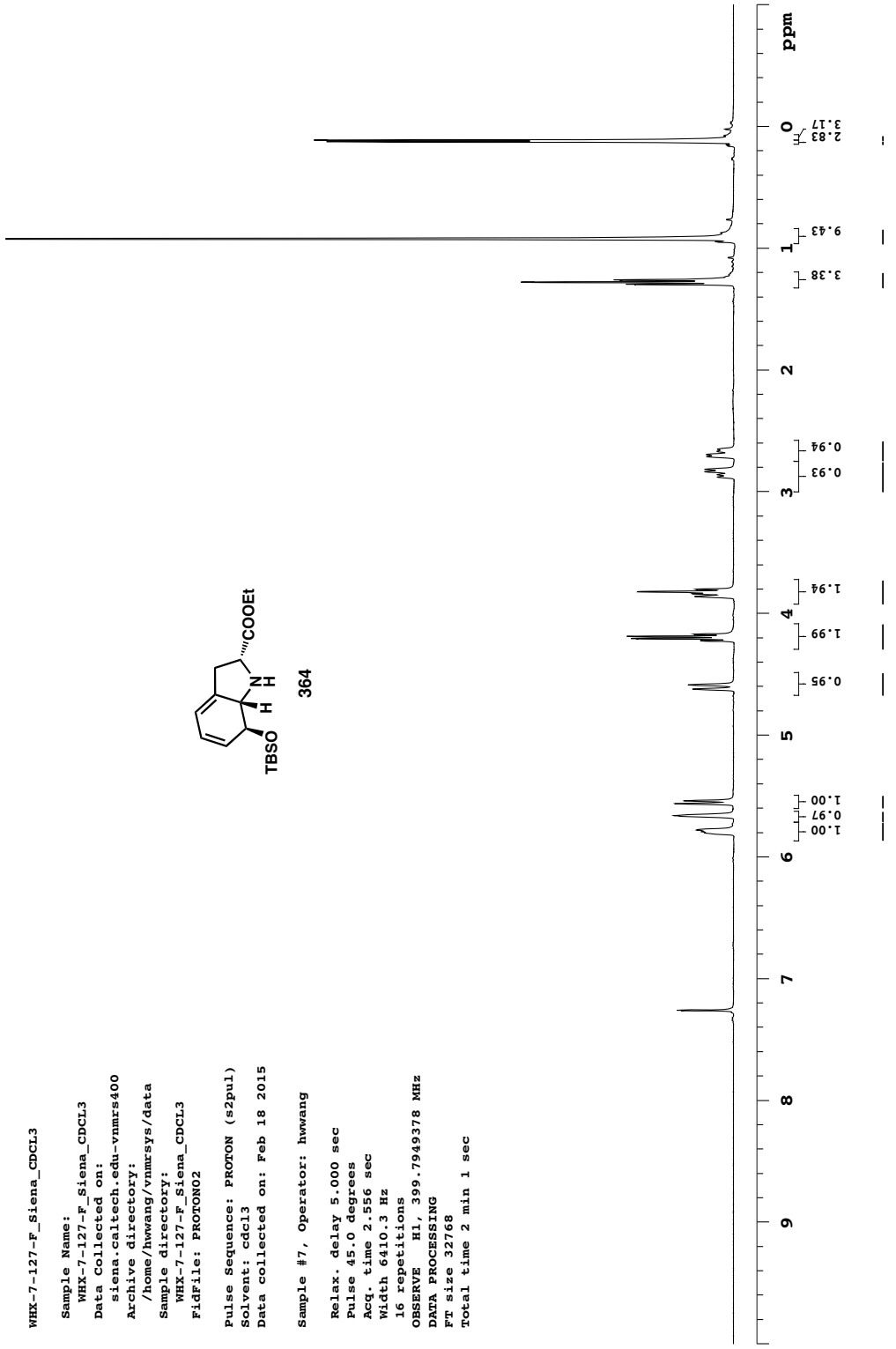

WHX-7-192-F-Siena-CD3CN
Sample Name:
WHX-7-192-F-Siena-CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-192-F-Siena-CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 23 2015
Temp. 25.0 C / 298.1 K
Sample #4, Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970641 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
COOEt
Teoc
OTBS
TBSO
361
ppm

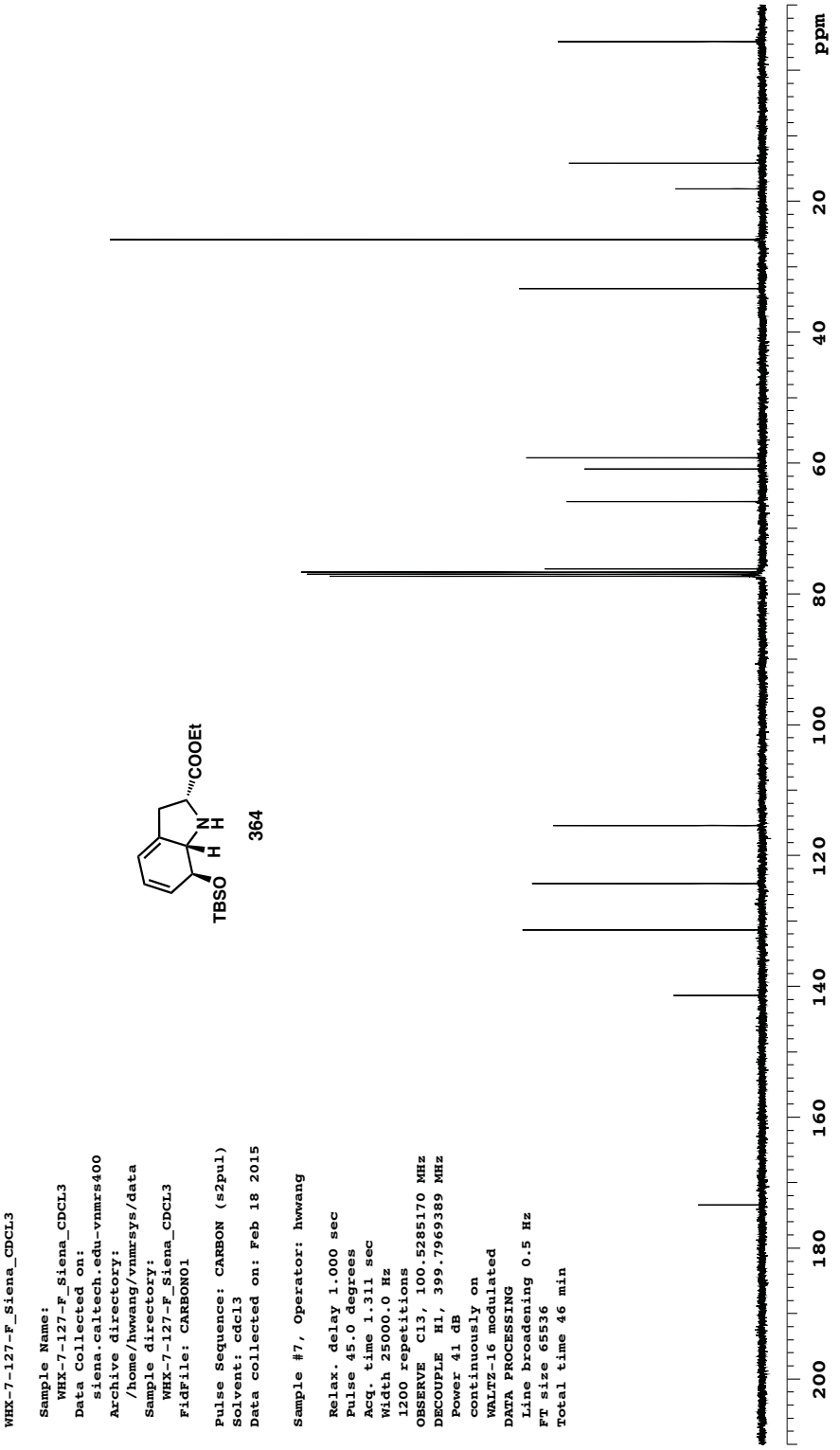

WHX-7-192-F-Siena-CD3CN-50C
Sample Name:
WHX-7-192-F-Siena-CD3CN-50C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-192-F-Siena-CD3CN-50C
FidFile: WHX-7-192-F-Siena-CD3CN-50C-proton
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 23 2015
Temp. 50.0 C / 323.1 K
Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970637 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
COOEt
TBSO
Teoc
OTBS
361 (CD3CN, 50 °C)
ppm
1.00
1.02
1.05
1.01
0.95
1.06
1.00
1.02
1.12
1.82
1.02
1.05
2.08
1.01
1.02
1.07
3.02
3.13
2.16
9.31
9.37
3.09
3.06
9.10
2.95
3.14

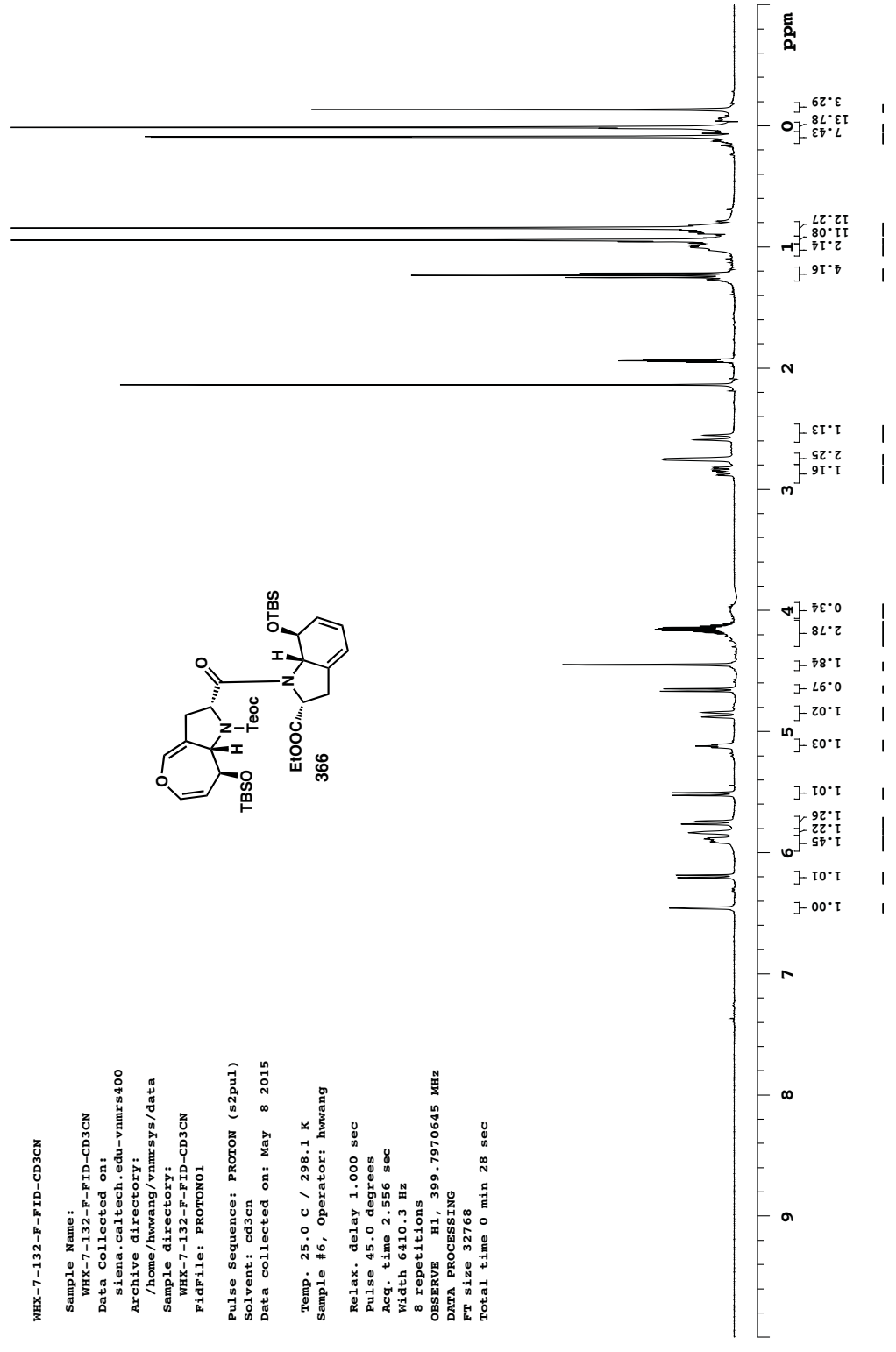

WHX-7-192-F-Siena-CD3CN-50C
Sample Name:
WHX-7-192-F-Siena-CD3CN-50C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-192-F-Siena-CD3CN-50C
FidFile: WHX-7-192-F-Siena-CD3CN-50C-carbon
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: May 23 2015
Temp. 50.0 C / 323.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
3232 repetitions
OBSERVE C13, 100.5289215 MHz
DECOUPLE H1, 399.7990538 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 12 min
COOEt
Teoc
OTBS
TBSO
361 (CD3CN, 50 °C)
200
180
160
140
120
100
80
60
40
20
ppm

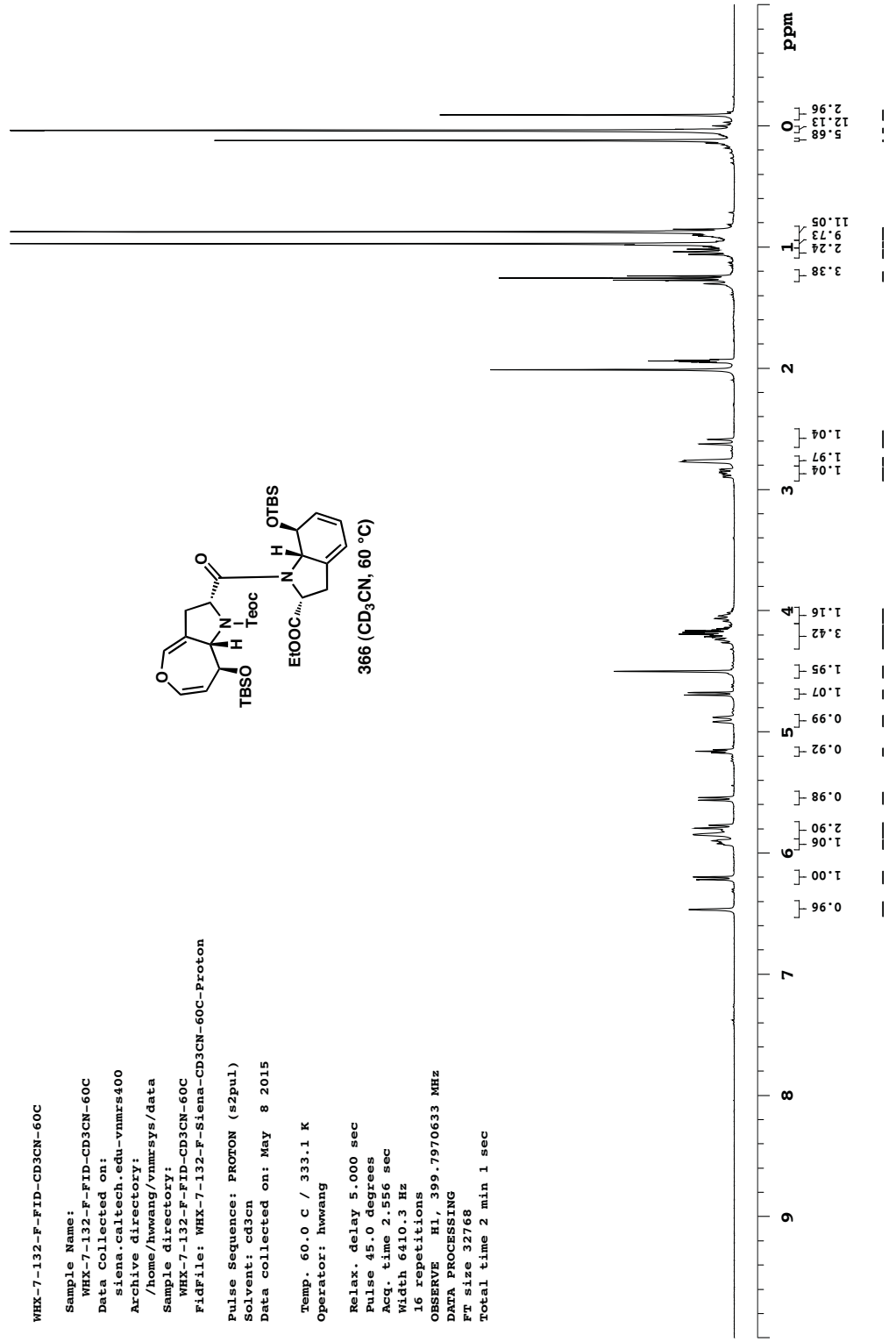

Current Data Parameters
NAME WHX-7-193-F1-Flo-CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150523
Time 8.48
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 142.81
DW 62.400 usec
DE 10.00 usec
TE 295.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300100 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
363
ppm
0 1 2 3 4 5 6 7 8 9
1.86
0.98
0.95
0.93
0.94
0.93
0.97
0.95
0.92
0.95
0.93
2.59
0.97
0.94

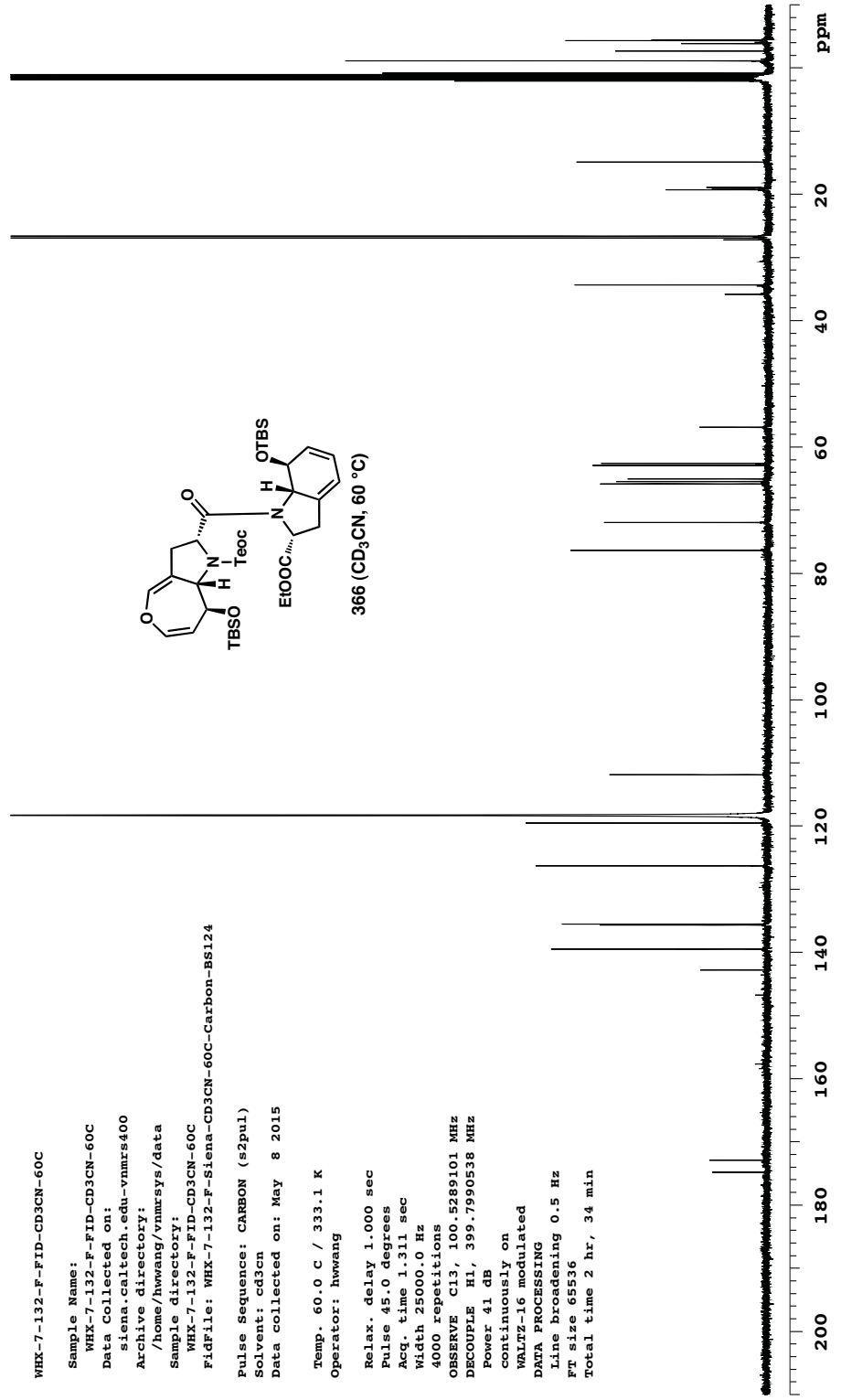

Current Data Parameters
NAME WHX-7-193-F1-Flo-CDCL3
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150523
Time 9.45
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1400
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 37.97
DW 20.800 usec
DE 82.37 usec
TE 294.9 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127735 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
363
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

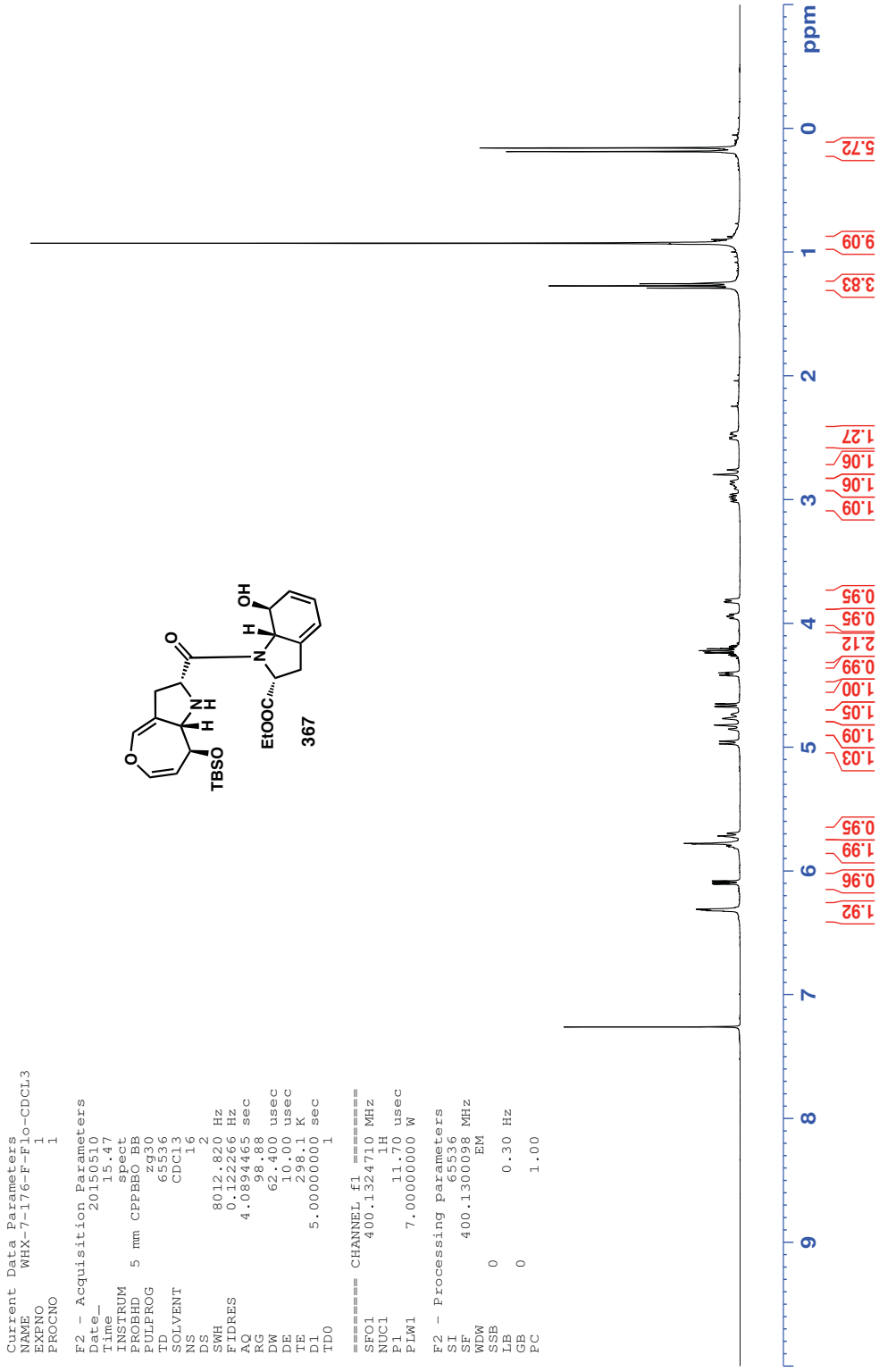

WHX-7-127-F_Siena_CDCl3
Sample Name:
WHX-7-127-F_Siena_CDCl3
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-127-F_Siena_CDCl3
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 18 2015
Sample #7, Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7949378 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
COOEt
TBSO
H
N
H
364
ppm
2.83
3.17
9.43
3.38
0.94
0.93
1.94
1.99
0.95
1.00
0.97
1.00

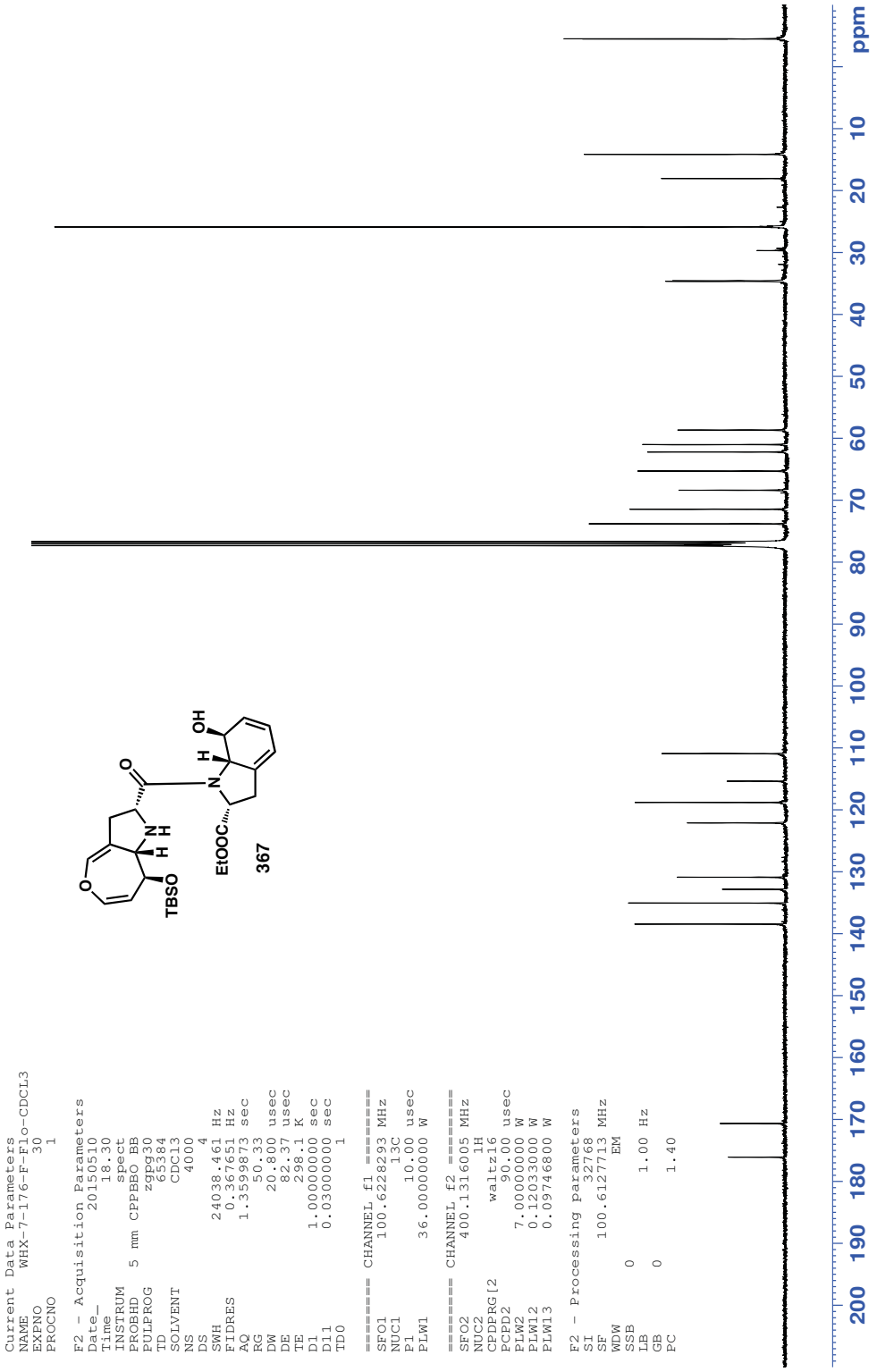

WHX-7-127-F_Siena_CDCl3
Sample Name:
WHX-7-127-F_Siena_CDCl3
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-127-F_Siena_CDCl3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 18 2015
Sample #7, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
1200 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 46 min
COOEt
N
H
H
TBSO
364
200
180
160
140
120
100
80
60
40
20
ppm

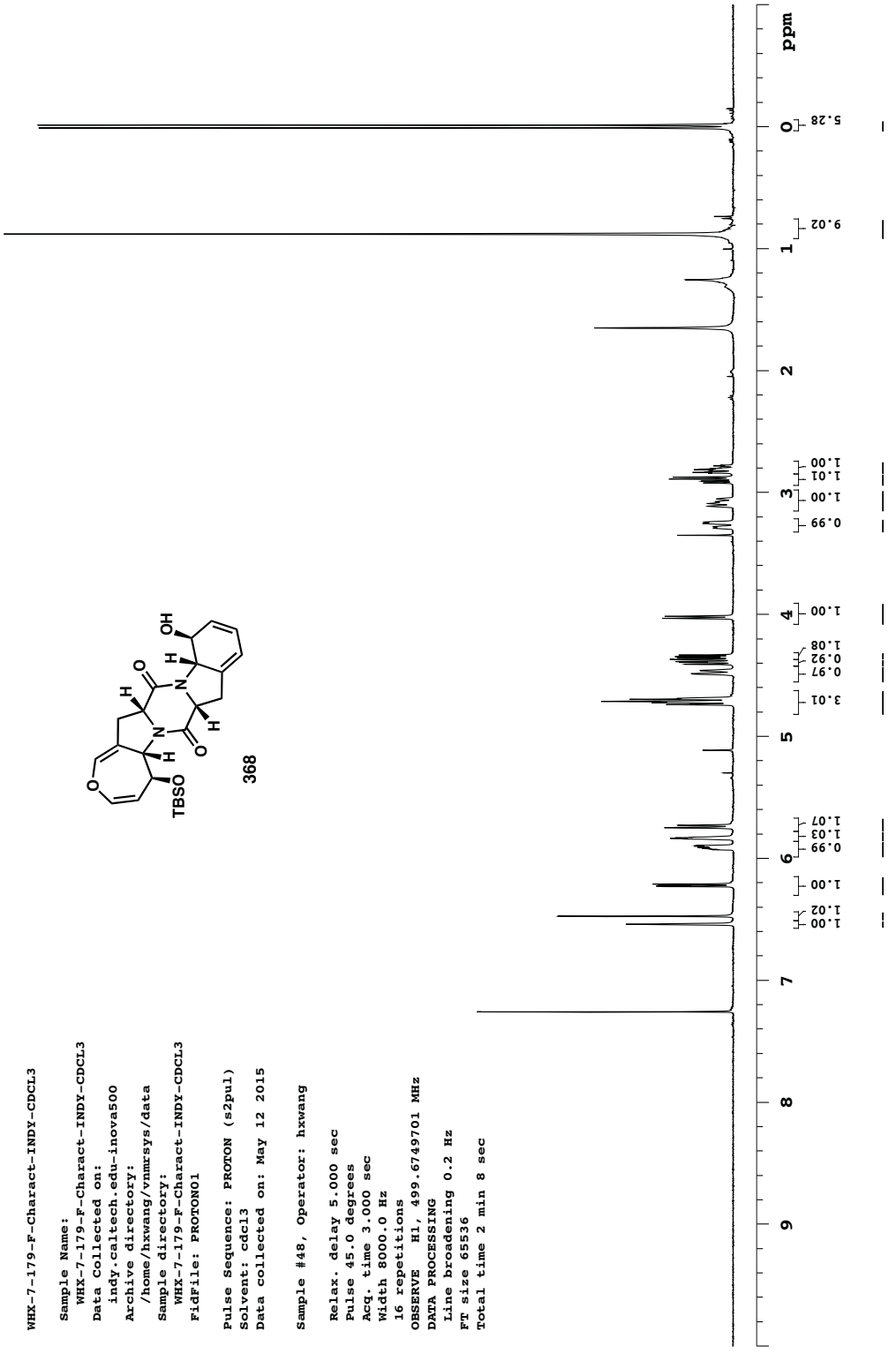

WHX-7-132-F-FID-CD3CN
Sample Name:
WHX-7-132-F-FID-CD3CN
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-132-F-FID-CD3CN
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 8 2015
Temp. 25.0 C / 298.1 K
Sample #6, Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7970645 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
TBSO
Teoc
EtOOC
OTBS
366
ppm
1.00
1.01
1.45
1.22
1.26
1.01
1.03
1.02
0.97
1.84
2.78
0.34
1.13
2.25
1.16
4.16
2.14
11.08
12.27
7.43
13.78
3.29

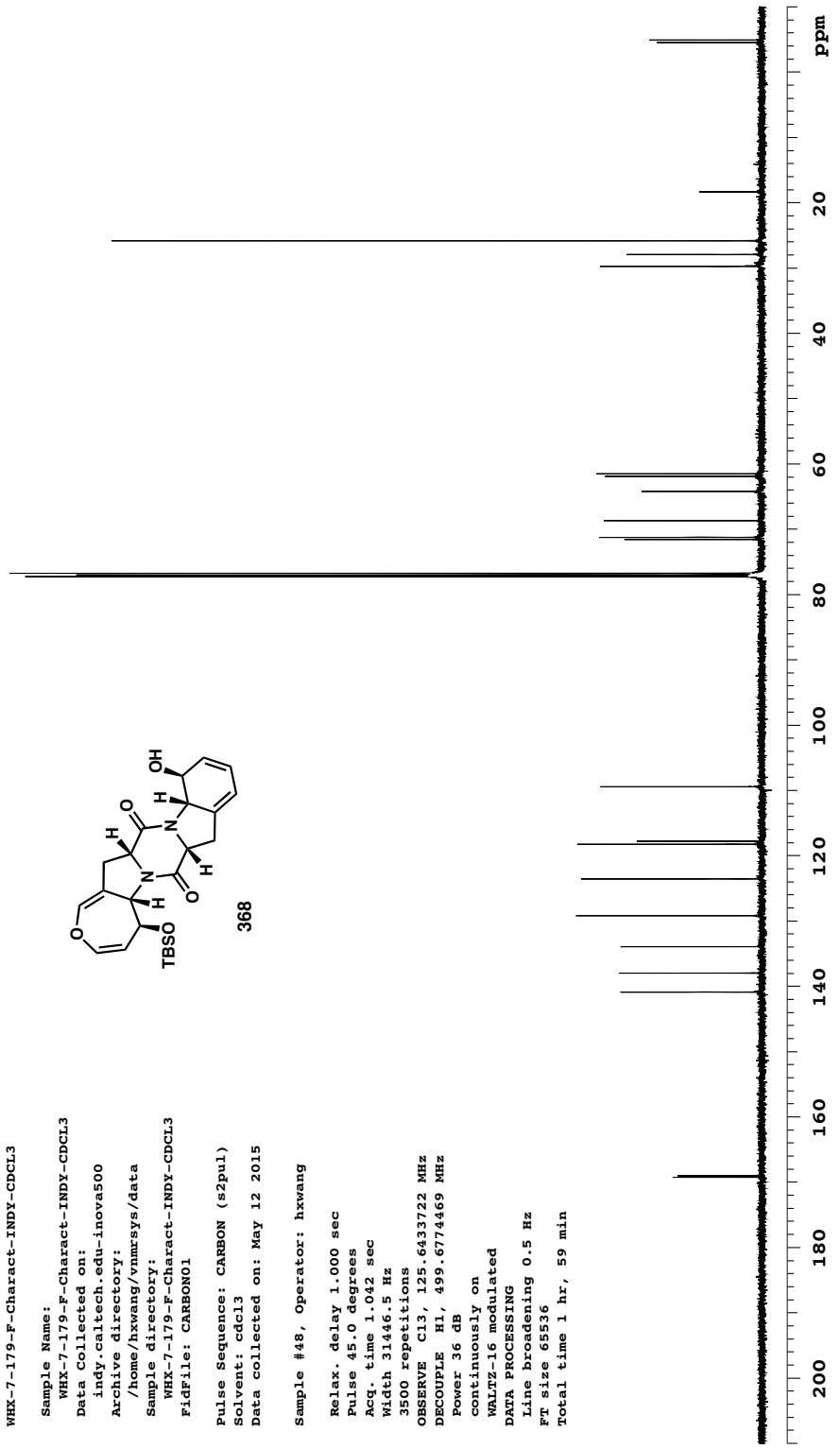

WHX-7-132-F-FID-CD3CN-60C
Sample Name:
WHX-7-132-F-FID-CD3CN-60C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-132-F-FID-CD3CN-60C
FidFile: WHX-7-132-F-Siena-CD3CN-60C-Proton
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 8 2015
Temp. 60.0 C / 333.1 K
Operator: hwwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7970633 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
TBSO
Teoc
EtOOC
OTBS
366 (CD3CN, 60 °C)
ppm
0.96
1.00
1.06
2.90
0.98
0.92
0.99
1.07
1.95
3.42
1.16
1.04
1.97
1.04
3.38
2.24
9.73
11.05
5.68
12.13
2.96

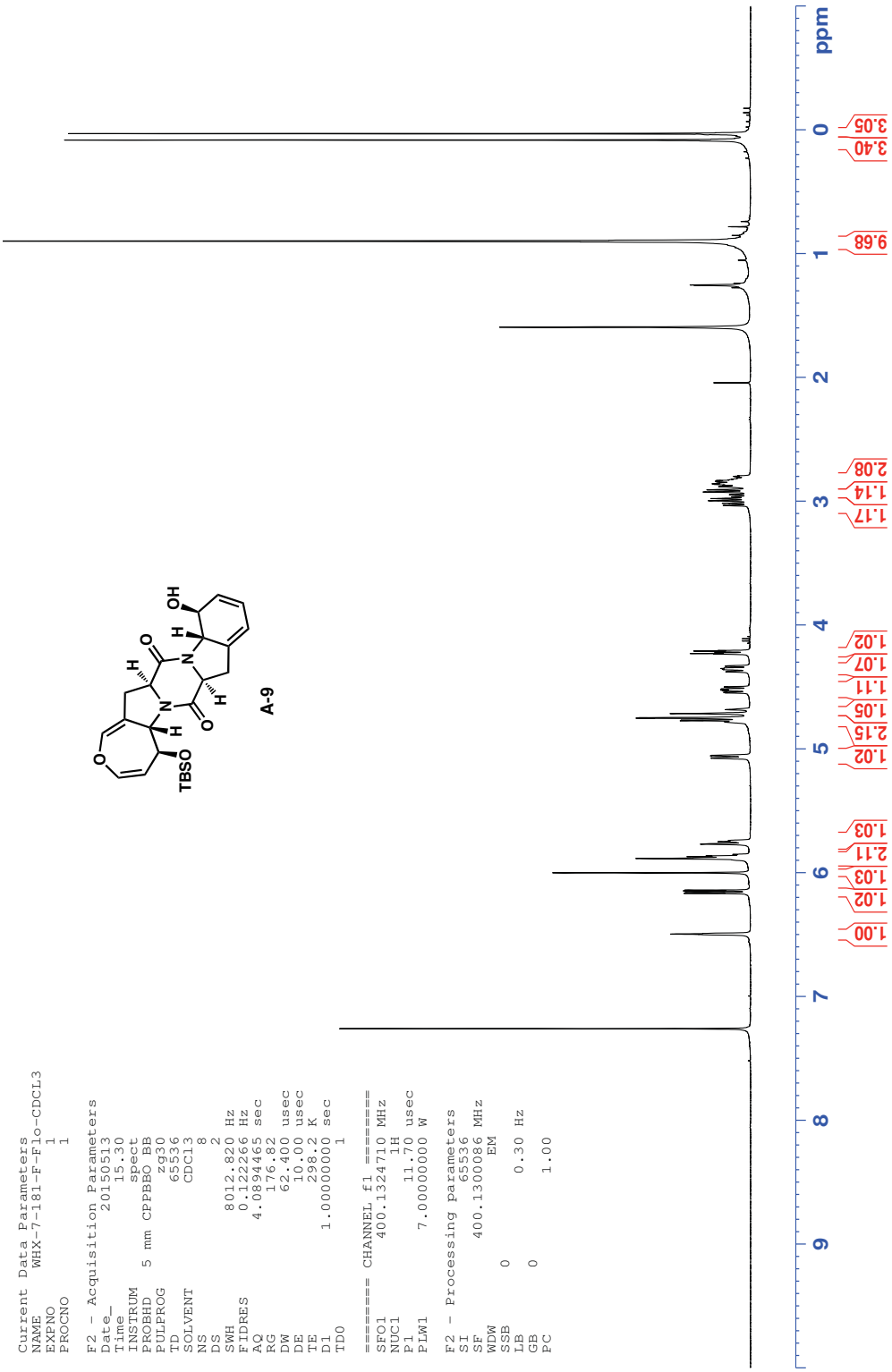

WHX-7-132-F-FID-CD3CN-60C
Sample Name:
WHX-7-132-F-FID-CD3CN-60C
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/hwwang/vnmrsys/data
Sample directory:
WHX-7-132-F-FID-CD3CN-60C
FidFile: WHX-7-132-F-Siena-CD3CN-60C-Carbon-BS124
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: May 8 2015
Temp. 60.0 C / 333.1 K
Operator: hwwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
4000 repetitions
OBSERVE C13, 100.5289101 MHz
DECOUPLE H1, 399.7990538 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 34 min
366 (CD3CN, 60 °C)
ppm
200
180
160
140
120
100
80
60
40
20

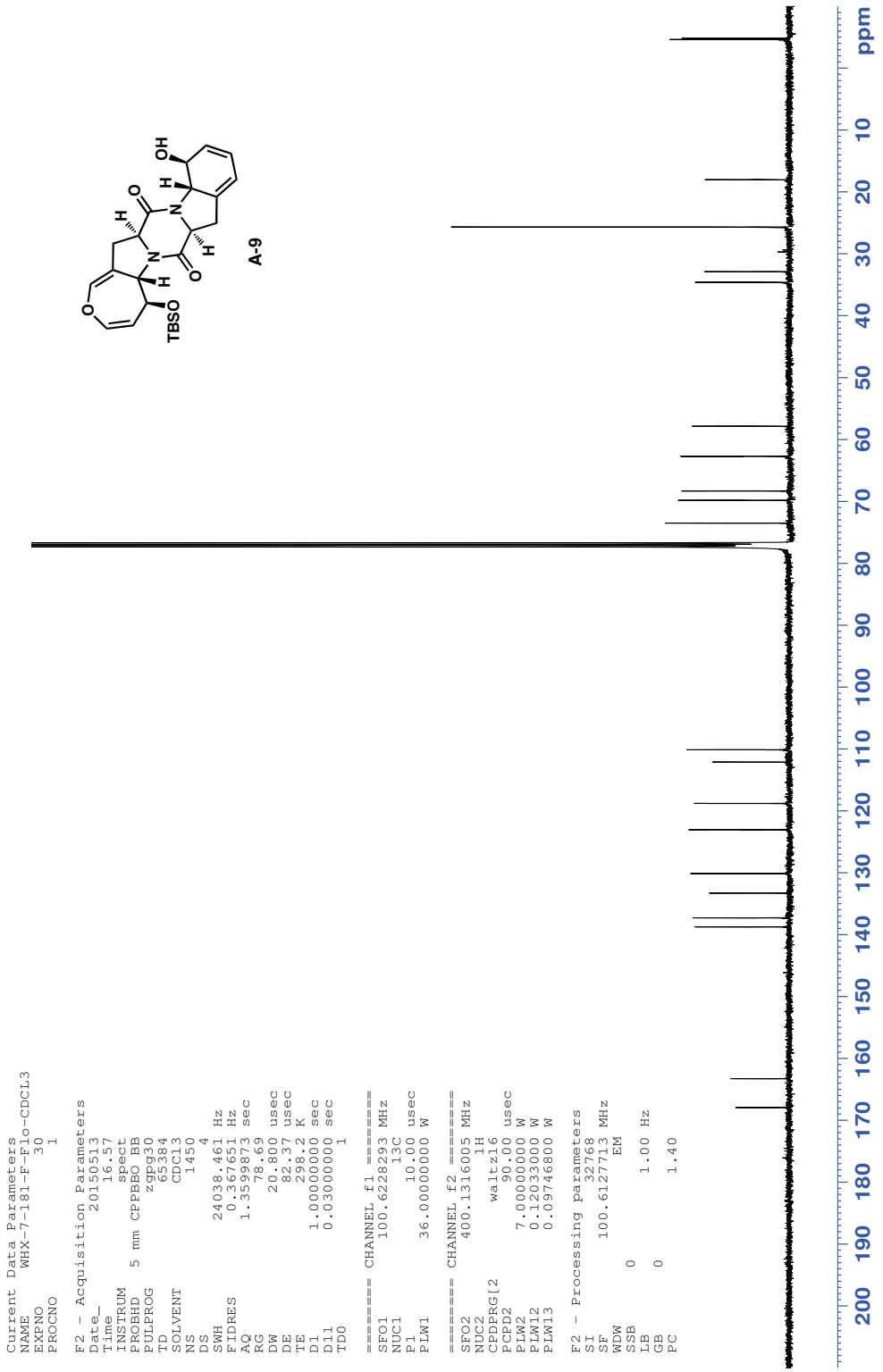

Current Data Parameters
NAME WHX-7-176-F-Flo-CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150510
Time_ 15.47
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 98.88
DW 62.400 usec
DE 10.00 usec
TE 298.1 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300098 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
TBSO
EtOOC
367
ppm
5.72
9.09
3.83
1.27
1.06
1.06
1.09
0.95
0.95
2.12
0.99
1.00
1.05
1.09
1.03
0.95
1.99
0.96
1.92

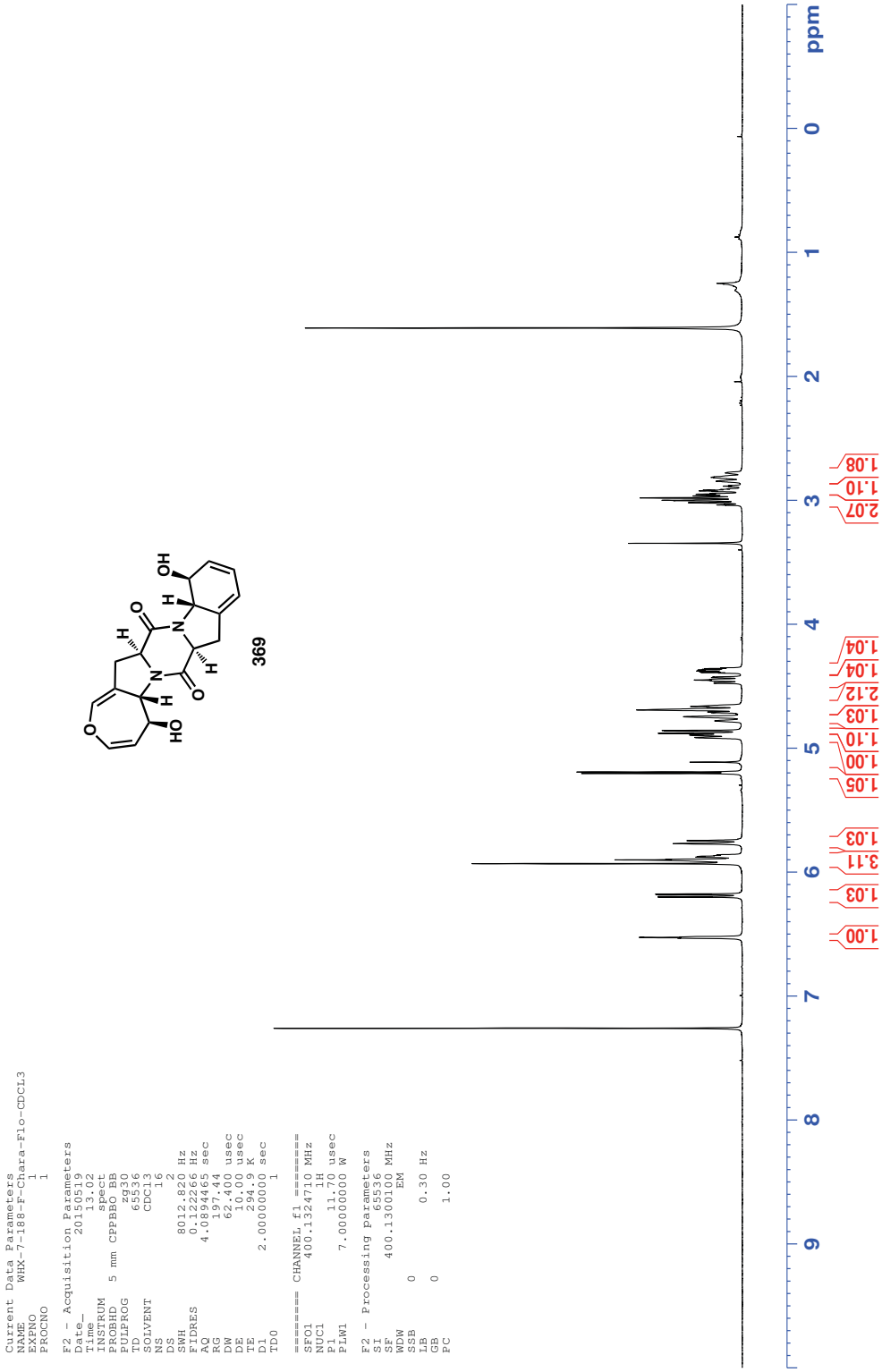

Current Data Parameters
NAME WHX-7-176-F-Flo-CDCl3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150510
Time_ 18.30
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 4000
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 50.33
DW 20.800 usec
DE 82.37 usec
TE 298.1 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127713 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
TBSO
EtOOC
OH
367
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

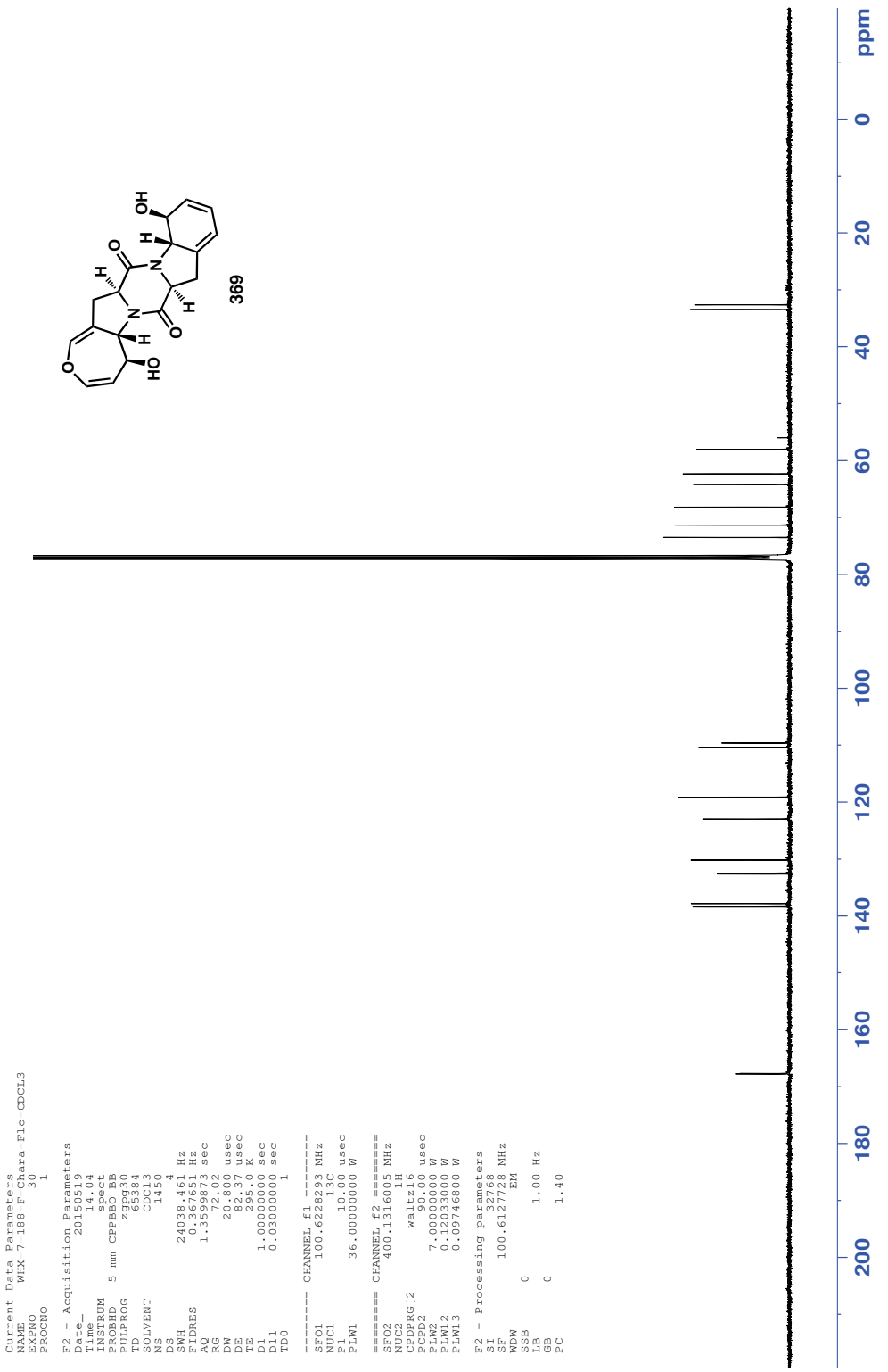

WHX-7-179-F-Charact-INDY-CDCL3
Sample Name:
WHX-7-179-F-Charact-INDY-CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-179-F-Charact-INDY-CDCL3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 12 2015
Sample #48, Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.6749701 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
TBSO
OH
368
ppm
5.28
9.02
0.99
1.00
1.01
1.00
1.00
3.01
0.97
0.92
1.08
1.00
0.99
1.03
1.07
1.00
1.02

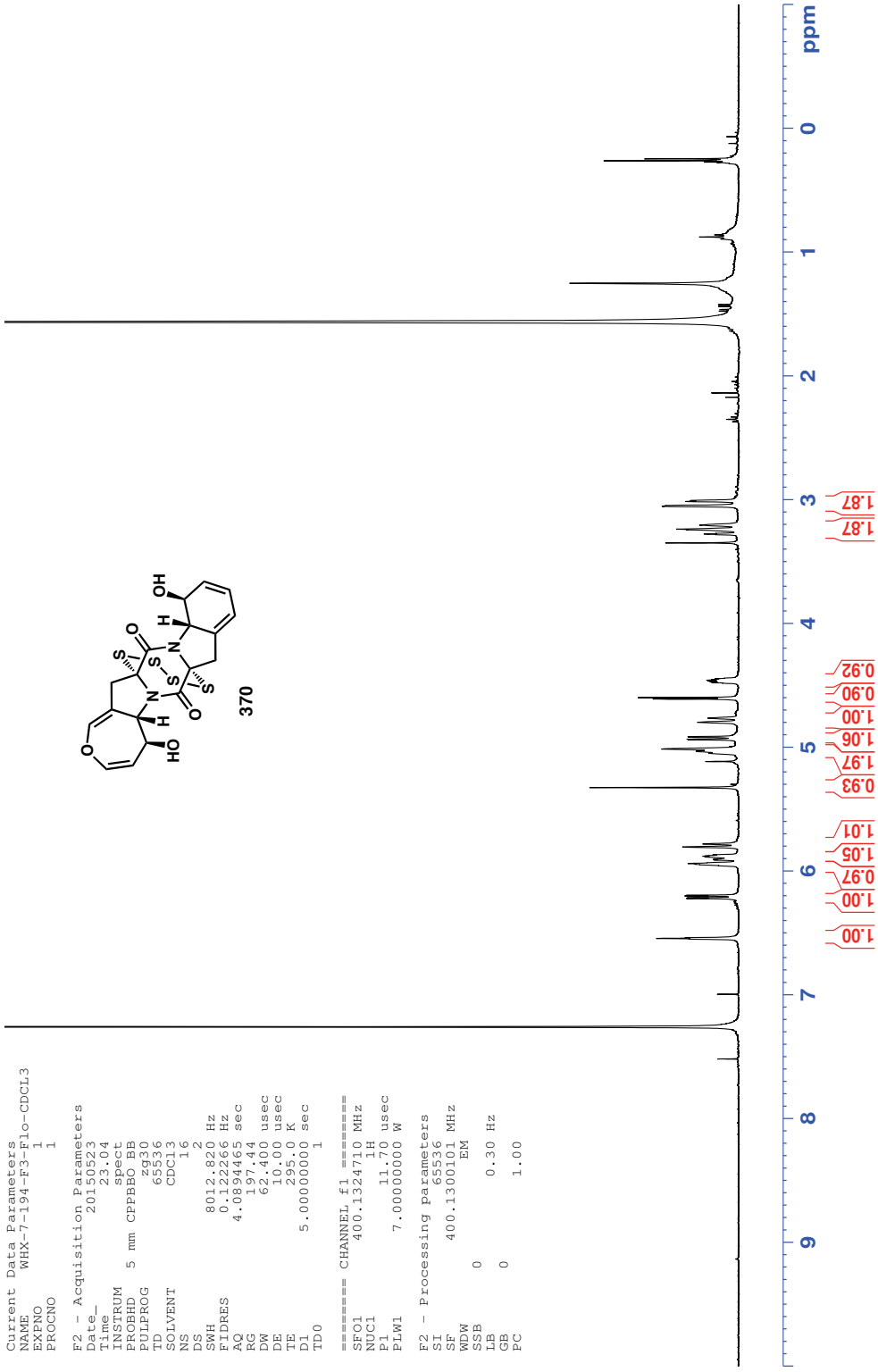

WHX-7-179-F-Charact-INDY-CDCL3
Sample Name:
WHX-7-179-F-Charact-INDY-CDCL3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/hxwang/vnmrsys/data
Sample directory:
WHX-7-179-F-Charact-INDY-CDCL3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 12 2015
Sample #48, Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3500 repetitions
OBSERVE C13, 125.6433722 MHz
DECOUPLE H1, 499.6774469 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 59 min
OH
H
O
N
H
O
N
H
O
H
TBSO
368
200
180
160
140
120
100
80
60
40
20
ppm

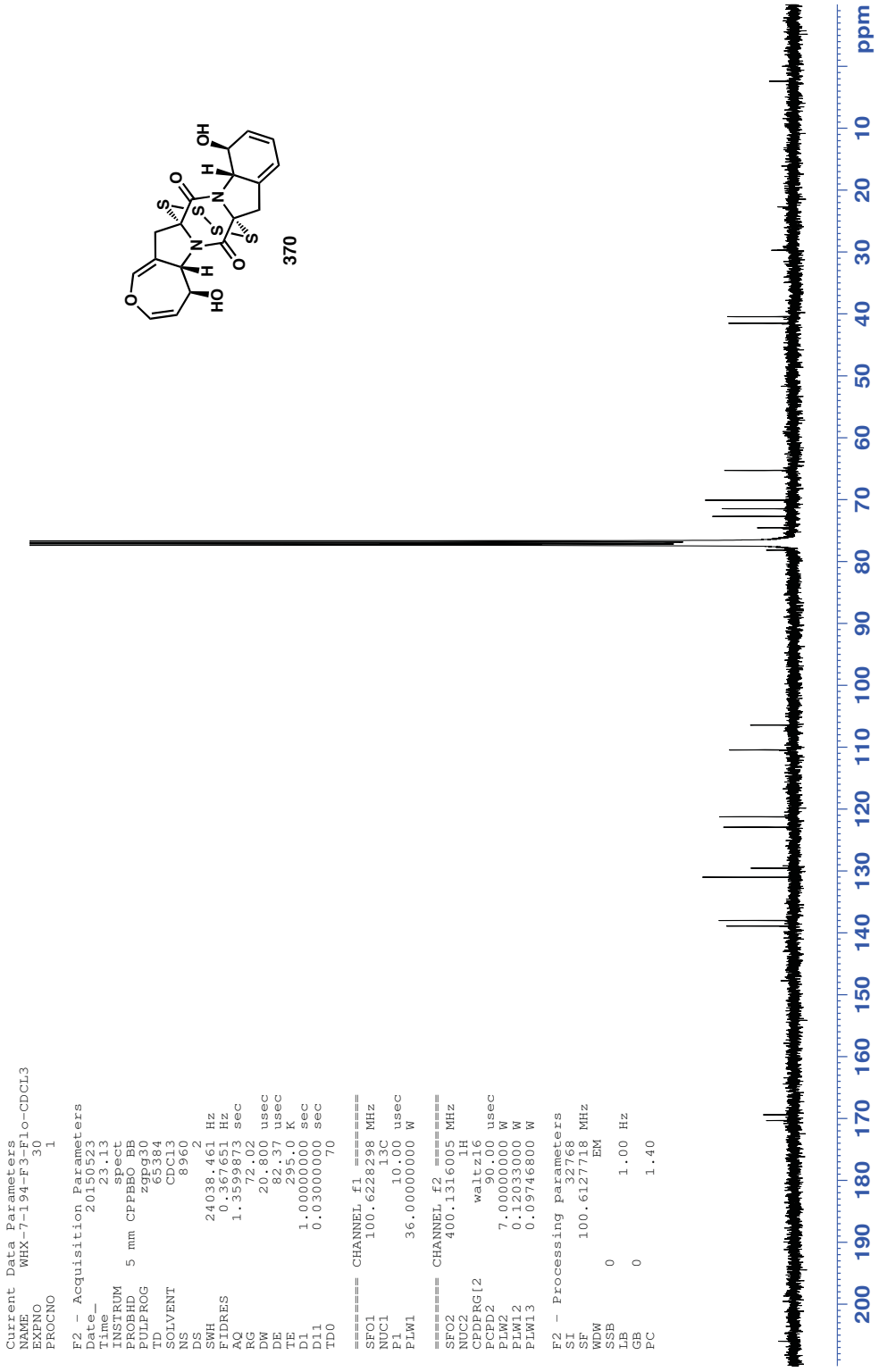

Current Data Parameters
NAME WHX-7-181-F-Flo-CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150513
Time_ 15.30
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 176.82
DW 62.400 usec
DE 10.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300086 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
A-9
TBSO
OH
ppm
1.00
1.02
1.03
2.11
1.03
1.02
1.02
2.15
1.05
1.11
1.07
1.02
1.17
1.14
2.08
9.68
3.40
3.05

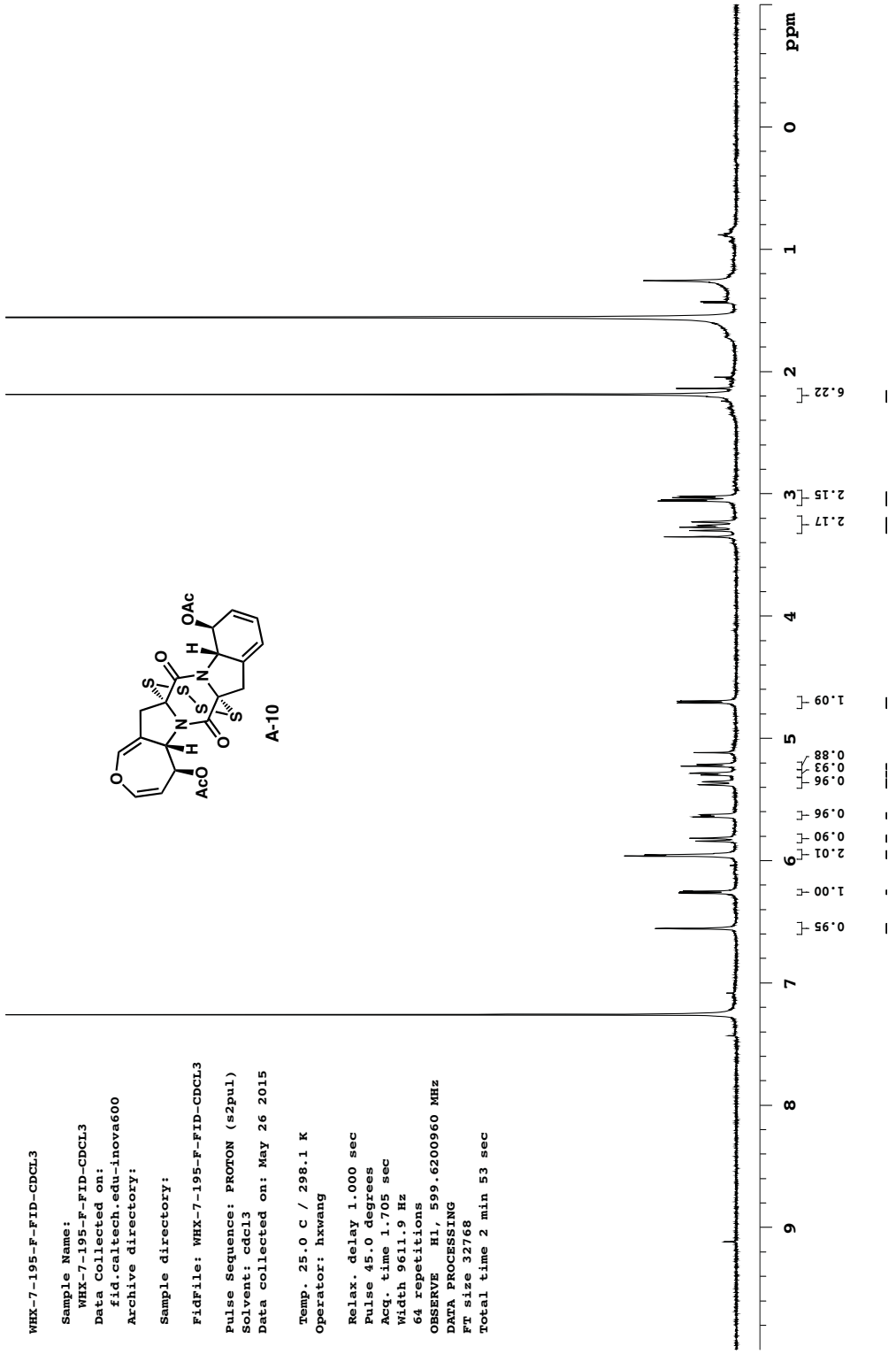

Current Data Parameters
NAME WHX-7-181-F-Flo-CDCL3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150513
Time_ 16.57
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 1450
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 78.69
DW 20.800 usec
DE 82.37 usec
TE 298.2 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127713 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
TBSO
OH
A-9
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

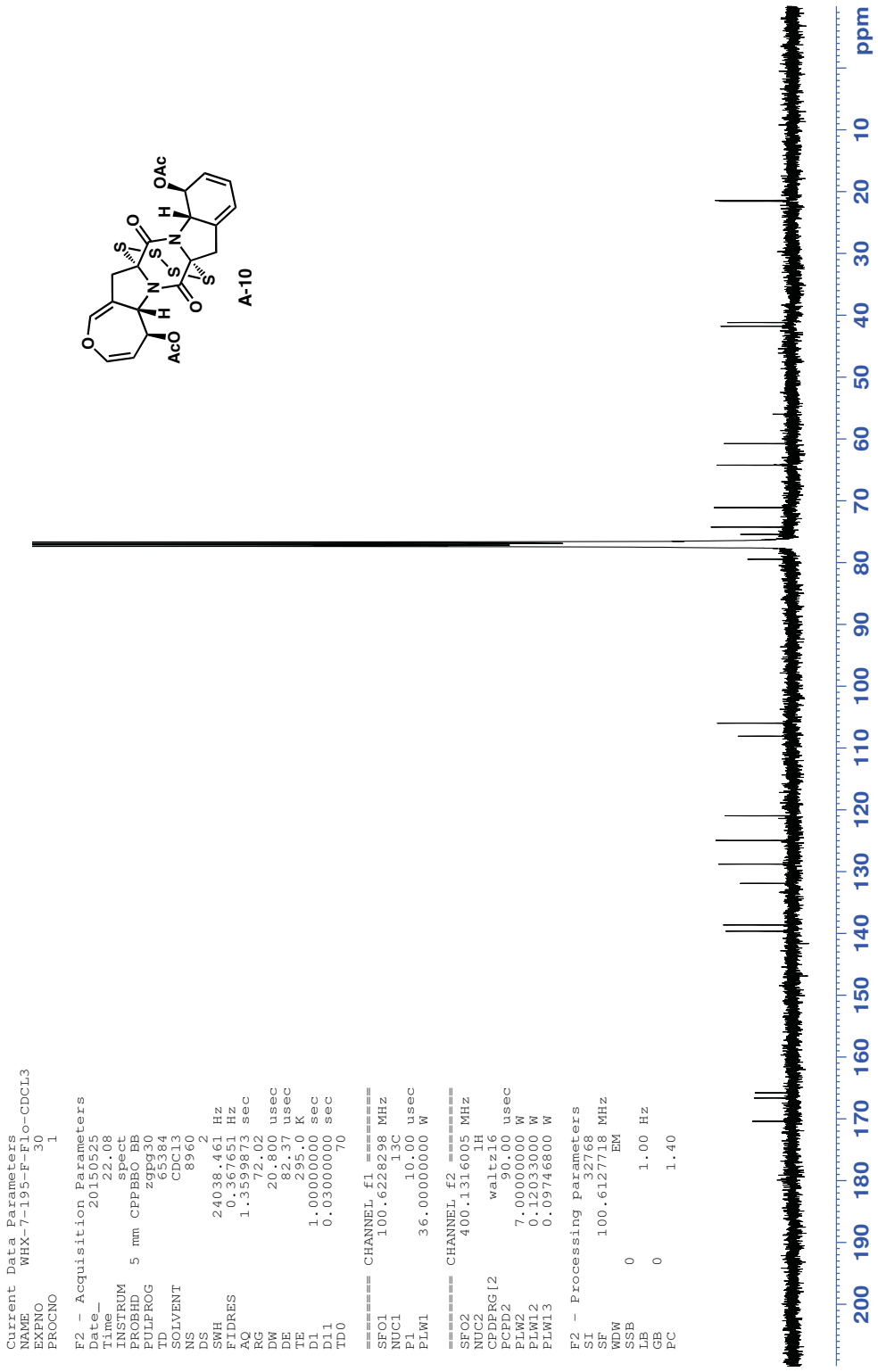

Current Data Parameters
NAME WHX-7-188-F-Chara-Flo-CDCL3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150519
Time 13.02
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 197.44
DW 62.400 usec
DE 10.00 usec
TE 294.5 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300010 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
369
OH
H
O
N
H
O
N
H
H
O
OH
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
3.11
1.03
1.05
1.00
1.10
1.03
2.12
1.04
1.04
2.07
1.10
1.08

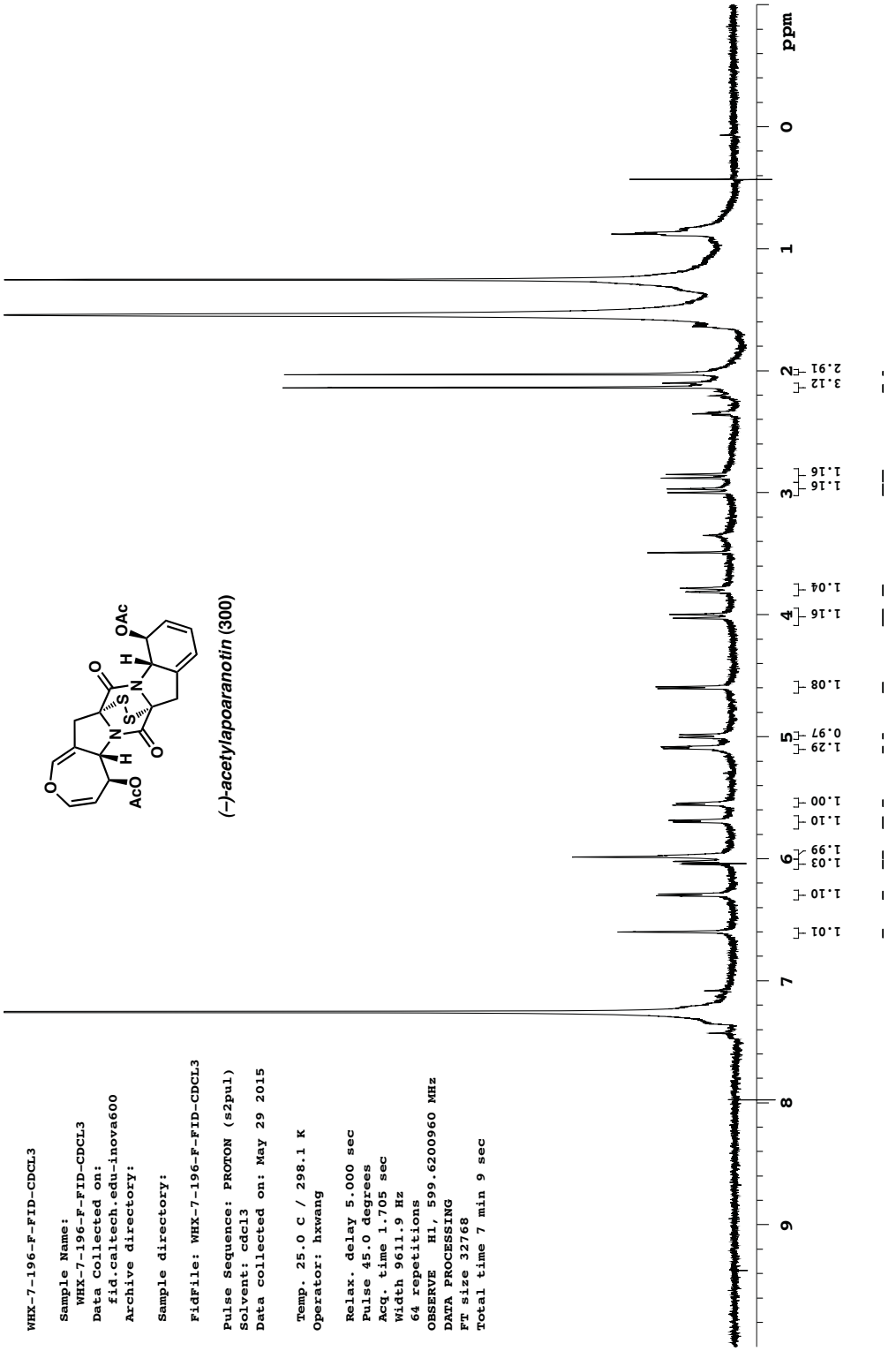

Current Data Parameters
NAME WHX-7-188-F-Chara-Flo-CDCL3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150519
Time 14.04
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 1450
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 72.02
DW 20.800 usec
DE 22.37 usec
TE 295.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127728 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
369
200
180
160
140
120
100
80
60
40
20
0
ppm

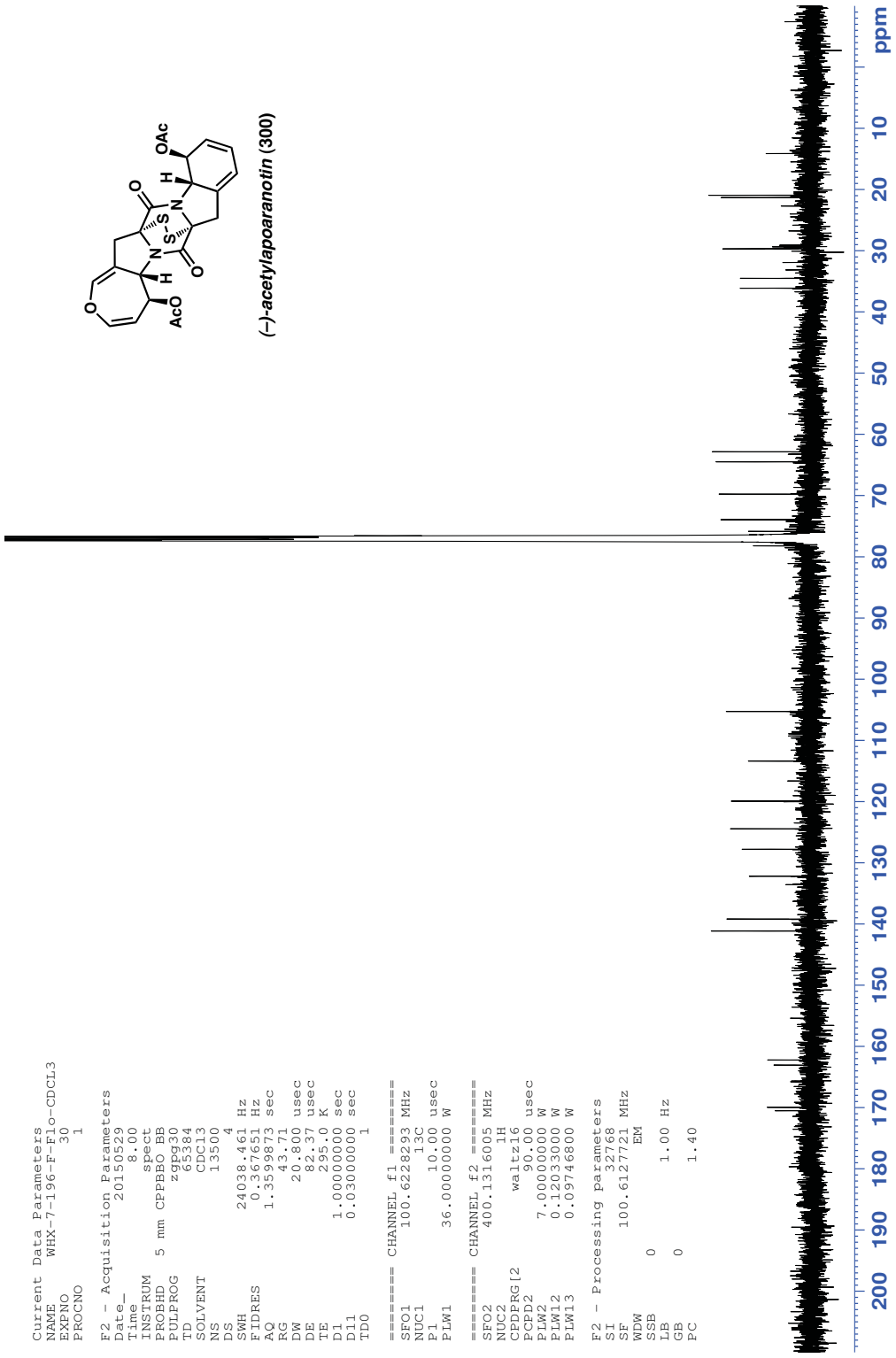

Current Data Parameters
NAME WHX-7-194-F3-Flo-CDCl3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150523
Time 23.04
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 197.44
DW 62.400 usec
DE 10.00 usec
TE 295.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.70 usec
PLW1 7.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300101 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
370
ppm
1.87
1.87
0.92
0.90
1.00
1.06
1.97
0.93
1.01
1.05
0.97
1.00
1.00


Current Data Parameters
NAME WHX-7-194-F3-flo-CDCL3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150523
Time 23.13
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 8960
DS 2
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 72.02
DW 20.800 usec
DE 82.37 usec
TE 295.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 70
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127718 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
370
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


WHX-7-195-F-FID-CDCL3
Sample Name:
WHX-7-195-F-FID-CDCL3
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
Sample directory:
FidFile: WHX-7-195-F-FID-CDCL3
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 26 2015
Temp. 25.0 C / 298.1 K
Operator: hxwang
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.705 sec
Width 9611.9 Hz
64 repetitions
OBSERVE H1, 599.6200960 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 53 sec
OAc
AcO
A-10
6.22
2.15
2.17
1.09
0.96
0.93
0.88
0.96
0.90
2.01
1.00
0.95
ppm


Current Data Parameters
NAME WHX-7-195-F-Flo-CDCl3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150525
Time_ 22.08
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 8960
DS 2
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 72.02
DW 20.800 usec
DE 82.37 usec
TE 295.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 70
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127718 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
A-10
OAc
AcO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


WHX-7-196-F-FID-CDCL3
Sample Name:
WHX-7-196-F-FID-CDCL3
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
Sample directory:
FidFile: WHX-7-196-F-FID-CDCL3
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 29 2015
Temp. 25.0 C / 298.1 K
Operator: hxwang
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 1.705 sec
Width 9611.9 Hz
64 repetitions
OBSERVE H1, 599.6200960 MHz
DATA PROCESSING
FT size 32768
Total time 7 min 9 sec
OAc
AcO
(–)-acetylapoaranotin (300)
ppm
1.01
1.10
1.03
1.99
1.10
1.00
1.29
0.97
1.08
1.16
1.04
1.16
1.16
3.12
2.91


Current Data Parameters
NAME WHX-7-196-P-Flo-CDCL3
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150529
Time_ 8.00
INSTRUM spect
PROBHD 5 mm CPPBBO BB
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 13500
DS 4
SWH 24038.461 Hz
FIDRES 0.367651 Hz
AQ 1.3599873 sec
RG 43.71
DW 20.800 usec
DE 82.37 usec
TE 295.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228293 MHz
NUC1 13C
P1 10.00 usec
PLW1 36.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 7.00000000 W
PLW12 0.12033000 W
PLW13 0.09746800 W
F2 - Processing parameters
SI 32768
SF 100.6127721 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OAc
AcO
(–)-acetylapoaranotin (300)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

ABOUT THE AUTHOR

Haoxuan Wang was born on November 27th, 1988, the year of the dragon, to Jian Wang and Nili Li in Huangshaping, a small town located in southern China, where his family still lives.

His interest in chemistry was first embarked upon when he decided to study science subjects in high school in China, which seemed to be the easiest course for him compared to math and physics. After high school, he got admitted to Fudan University as a chemistry major. Though he enjoyed learning chemistry, his first option when applying for undergraduate school was actually to become a doctor, something upon which his family insisted.

He got introduced to research in the laboratory of Professor Zhengwen Fu, where he studied the electrochemical properties of thin-film electrode materials. He later had the chance to join the laboratory of Professor Neil K. Garg for the summer of 2009, where he learned a lot about organic chemistry research by carrying through first nine steps of the synthetic route toward the natural product (–)-*N*-methylwelwitindolinone C isothiocyanate. It is this experience that got him captivated with organic chemistry, and he decided to pursue graduate school to learn more about this area.

After his experience at Fudan University, he moved across the Pacific and started his PhD studies under the guidance of Professor Sarah E. Reisman at the California Institute of Technology. He has been studying the total synthesis of several diketopiperazine-containing natural products. In the summer of 2015, he chooses to "abandon" the wonderful weather in California and move eastward to the Buchwald laboratory at the Massachusetts Institute of Technology as a postdoctoral fellow.