

ENANTIOSELECTIVE SYNTHESIS OF PYRROLOINDOLINES AND
TRYPTOPHAN DERIVATIVES BY AN ASYMMETRIC PROTONATION
REACTION

Thesis by

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To my teachers

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ABSTRACT

Pyrroloindoline and unnatural tryptophan motifs are important targets for synthesis based on their incorporation into a diverse array of biologically active natural products. Both types of alkaloids have also found applications as chiral catalysts and tryptophan derivatives are commonly employed as biological probes. On account of their applications, these frameworks have inspired the development of numerous enantioselective, catalytic reactions. In particular, the past few years have witnessed an impressive number of novel approaches for pyrroloindoline formation.

The first project described herein involves our contribution to pyrroloindoline research. We have developed an (*R*)-BINOL•SnCl₄-catalyzed formal (3 + 2) cycloaddition reaction between 3-substituted indoles and 2-amidoacrylates that affords pyrroloindoline-2-carboxylates bearing an all-carbon quaternary center. Mechanistic studies have elucidated that the enantiodetermining step is a highly face-selective catalyst-controlled protonation reaction.

Second, application of this asymmetric protonation strategy to the synthesis of a variety of enantioenriched tryptophan derivatives is discussed. Finally, we found that these derivatives could undergo selective functionalization. More specifically, we were able to prepare novel hydroxypyrroloindolines that are currently the subject of a collaboration project with the Dougherty lab aimed at identifying novel positive allosteric modulators of ligand-gated ion channels.

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Modulator*

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LIST OF ABBREVIATIONS

5HT _{3A} R	serotonin type 3A receptor
A	alanine
AAA	Asymmetric Allylic Alkylation
Å	Ångstrom
[α] _D	specific rotation at wavelength of sodium D line
Ac	acetyl
ACAT	acyl-CoA:cholesterol acyltransferase
ACh	acetylcholine
AD	Alzheimer's Disease
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
BCRP	Breast Cancer Resistance Protein
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOX	bisoxazoline
br	broad
BTF	benzotrifluoride

Bu	butyl
<i>n</i> -Bu	butyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Bz	benzoyl
<i>c</i>	concentration for specific rotation measurements
°C	degrees Celsius
calc'd	calculated
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
cm ⁻¹	wavenumber(s)
cod	1,5-cyclooctadiene
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIC	diisopropyl carbodiimide
DM-BINAP	1,1'-binaphthalene-2,2'-diylbis[bis(3,5-dimethylphenyl)phosphine]
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide

DMSO	dimethyl sulfoxide
DNA	(deoxy)ribonucleic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E	electrophile
EC ₅₀	median effective concentration (50%)
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin <i>exempli gratia</i>)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
ETP	epidithiodiketopiperazine
FAB	fast atom bombardment
FDA	food and drug administration
FID	flame ionization detector
FT	fourier transform
g	gram(s)
GABA	γ -aminobutyric acid
GABA _A R	γ -aminobutyric acid type A receptor
gCOSY	gradient-selected correlation spectroscopy
gHMBC	gradient-selected heteronuclear multiple bond correlation
GlyR	glycine receptor
GluR _{2A}	glutamate receptor subunit 2A
h	hour(s)

HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
$h\nu$	light
Hz	hertz
IC ₅₀	median inhibition concentration (50%)
IPA	isopropanol
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
L	liter; leucine
LA	Lewis acid
LAH	lithium aluminum hydride
LBA	Lewis acid-assisted Brønsted acid
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LGIC	ligand-gated ion channel
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet; milli
m	meta
m/z	mass to charge ratio
M	metal; molar; molecular ion
Me	methyl
Mes	mesityl
mGlu ₅	metabotropic glutamate receptor
MHz	megahertz

μ	micro
μ waves	microwave irradiation
min	minute(s)
MM	multimode
mol	mole(s)
MOM	methoxymethyl
mp	melting point
mRNA	messenger ribonucleic acid
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal
NAM	negative allosteric modulator
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
nd	not determined
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
NPSP	<i>N</i> -(phenylseleno)phthalimide
nr	no reaction
Nu	nucleophile
<i>o</i>	ortho
OLED	organic light-emitting diode
<i>p</i>	para
PAM	positive allosteric modulator
Ph	phenyl

pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Phth	phthaloyl
PhMe	toluene
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl
q	quartet
ref	reference
R	generic for any atom or functional group
Red-Al	sodium bis(2-methoxyethoxy)aluminum dihydride
R_f	retention factor
rt	room temperature
s	singlet
S	serine
sat.	saturated
SFC	supercritical fluid chromatography
SiPr	<i>N,N'</i> -bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene
t	triplet
T	tyrosine
TADMAP	3-(2,2,2-triphenyl-1-acetoxyethyl)-4-(dimethylamino)pyridine
TBS	<i>tert</i> -butyldimethylsilyl

TES	triethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid; trifluoroacetyl
TfOH	triflic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight
t_R	retention time
Ts	<i>p</i> -toluenesulfonyl (tosyl)
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
UV	ultraviolet
<i>v/v</i>	volume to volume
<i>w/v</i>	weight to volume
X	anionic ligand or halide

CHAPTER 1

Recent Developments in the Catalytic, Enantioselective Construction of Pyrroloindolines Bearing All-Carbon Quaternary Stereocenters[†]

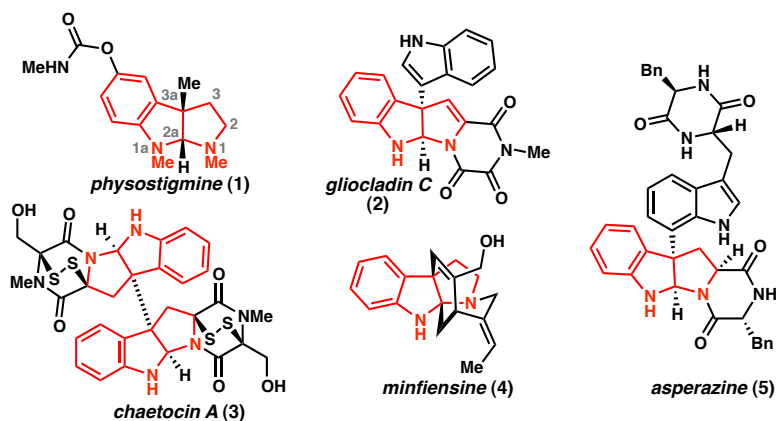
1.1 INTRODUCTION

A large family of structurally diverse natural products is characterized by the collective presence of an indoline fused at its 2 and 3 positions to a pyrrolidine, a motif commonly known as a pyrroloindoline and more precisely named hexahydropyrrolo[2,3-*b*]indole (Figure 1.1.1).¹ These alkaloids possess an array of biological properties, including cholinesterase (physostigmine (**1**)),² cancer (gliocladin C (**2**))³ and asperazine (**5**),⁴ and histone methyltransferase (chaetocin A (**3**))⁵ inhibitory activities. Furthermore, many pyrroloindoline natural products bear C3a all-carbon quaternary stereocenters and the synthetic challenge inherent in these molecules combined with promising medicinal value has inspired a myriad of methodologies targeting the enantioenriched framework.⁶

[†] This chapter was adapted from a mini-review written in collaboration with Professor Sarah Reisman.

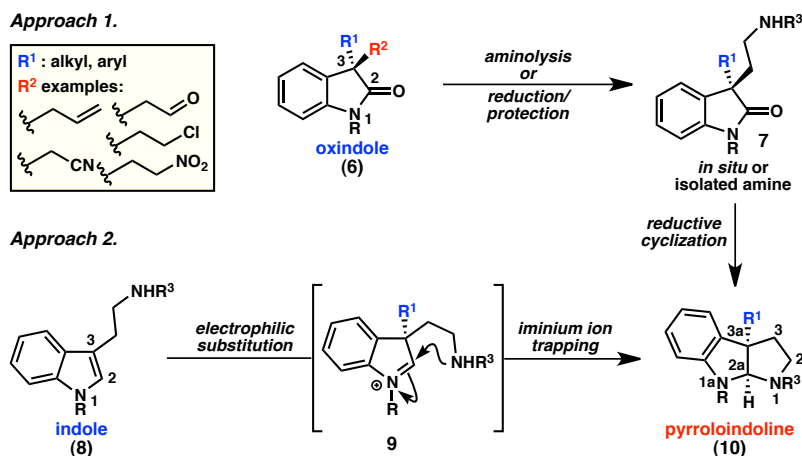
Although numerous strategies involving either chiral auxiliaries or the functionalization of L-tryptophan have been developed, this synopsis will offer an introduction to the catalytic, enantioselective approaches based on the recent growth of research within this field.

Figure 1.1.1. Representative pyrroloindoline natural products.



Catalytic, enantioselective reactions to prepare pyrroloindolines can be categorized primarily into two general approaches: (1) reactions to synthesize 3,3'-disubstituted oxindoles, which can be elaborated to the corresponding pyrroloindolines (Approach 1, Scheme 1.1.1),⁷ or (2) tandem C3-functionalization/cyclization reactions of 3-substituted indoles (Approach 2, Scheme 1.1.1). Extensive research has been conducted using both approaches, and each possesses distinct advantages. The indole functionalization approach permits direct access to pyrroloindolines, whereas the oxindoles can serve as intermediates in the synthesis of both pyrroloindoline and oxindole-based natural products.⁸

Scheme 1.1.1. General approaches for pyrroloindoline synthesis.

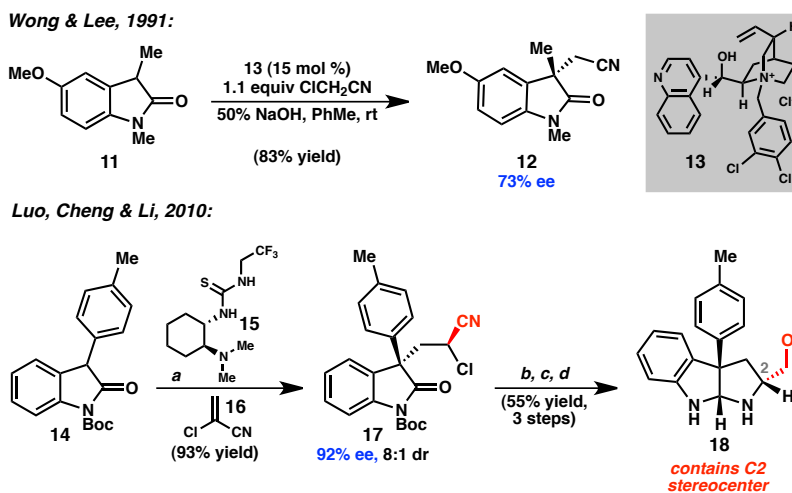


1.2 PYRROLOINDOLINE SYNTHESIS VIA 3,3'-DISUBSTITUTED OXINDOLES

3,3'-Disubstituted oxindoles are available by several methods including α -alkylation, intramolecular cyclization, and intramolecular acyl migration. The first catalytic asymmetric synthesis of a 3,3'-disubstituted oxindole was developed in 1991 at Hoechst-Roussel Pharmaceuticals Inc.⁹ Researchers Wong and Lee discovered that subjection of oxindole **11** to chloroacetonitrile in the presence of cinchoninium bromide catalyst **13** delivered enantioenriched oxindole **12** (Scheme 1.2.1). Further elaboration resulted in a formal total synthesis of the anticholinesterase natural product physostigmine (**1**, Figure 1). This approach built on the pioneering phase transfer catalysis studies of Dolling and coworkers,¹⁰ and has been succeeded by several enantioselective organocatalytic α -alkylation reactions of oxindoles.¹¹ Recently, Luo and coworkers identified a bifunctional tertiary amine thiourea (**15**) that catalyzes the conjugate addition of 3-aryl and 3-alkyloxindoles (**14**) to 2-chloroacrylonitrile (**16**).^{11c} Of the asymmetric oxindole alkylation approaches reported to date, this is the first method that directly installs an

appropriate C2-handle for advancement to diketopiperazine-based alkaloids (e.g. chaetocin A (**3**), Figure 1.1.1).

Scheme 1.2.1. Organocatalytic α -alkylation of oxindoles.

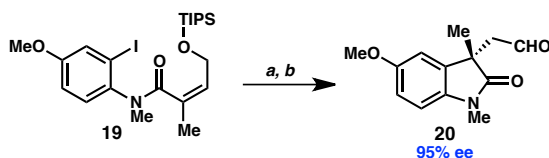


A second, foundational catalytic asymmetric method to prepare 3,3-disubstituted oxindoles was the Pd-catalyzed intramolecular Heck reaction reported by Overman and coworkers in 1993 (Scheme 1.2.2).¹² In a preliminary demonstration of the synthetic utility, physostigmine (**1**, Figure 1.1.1) was prepared from *Z*-butenanilide **19** via oxindole carboxaldehyde **20**. Recently, this reaction was applied in more elaborate contexts including the synthesis of the alkaloids minfiensine (**4**, Figure 1.1.1)¹³ and polypyrroloindoline quadrigemine C.¹⁴ These transformations are noteworthy examples of asymmetric Heck reactions that generate all-carbon quaternary centers, and have likely inspired the development of related transition metal-catalyzed cyclization reactions for the construction of pyrroloindolines.¹⁵ For example, Nakao, Hiyama, Ogoshi and coworkers reported the synthesis of (2-oxindolyl)acetonitrile derivatives by the Ni-catalyzed enantioselective intramolecular arylocyanation of alkenes (Scheme 1.2.2).^{15c,16} A

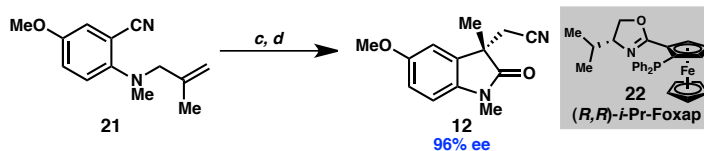
key finding in this study was that, in addition to the nickel catalyst, a Lewis acid (AlMe_2Cl) was required to achieve indoline formation. Subsequent C-H oxidation furnishes the highly enantioenriched 3,3'-dialkyl (**12**) and 3-alkyl-3'-aryloxindoles.

Scheme 1.2.2. Cyclization approaches to 3,3'-disubstituted oxindoles.

Overman and coworkers, 1993: Intramolecular Heck Reaction



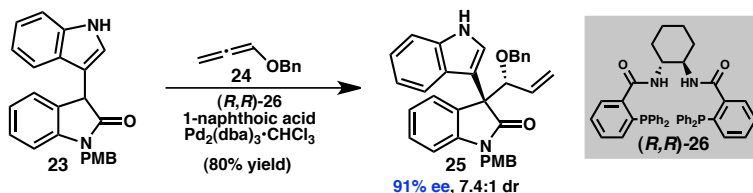
Nakao, Hiyama, Ogoshi and coworkers, 2008: Intramolecular Arylcyanation Reaction



Conditions: *a.* 10 mol % $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$, 23 mol % (*S*)-BINAP, 5.1 equiv PMP, DMA, 100 °C, 1.5 h. *b.* 3 *N* HCl, 0 to 23 °C (84 % yield, 2 steps). *c.* 10 mol % $\text{Ni}(\text{cod})_2$, 20 mol % **22**, 40 mol % AlMe_2Cl , DME, 100 °C, 10 h (88% yield); *d.* 6.0 equiv PhIO , CH_2Cl_2 , rt, 2.5 h (40% yield).

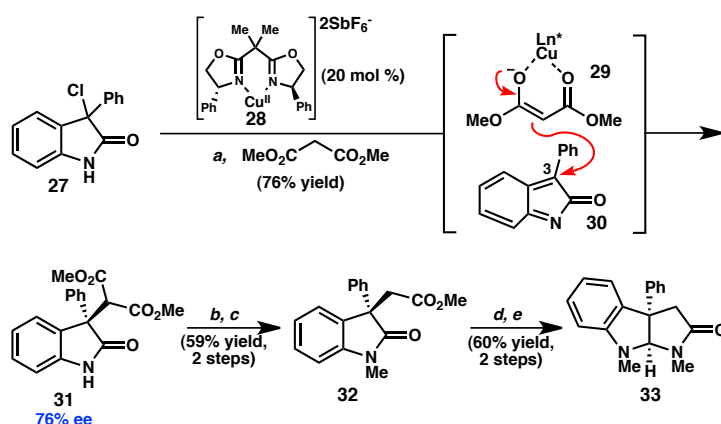
In addition to the Heck-type cyclization reactions described above, transition metal-catalyzed asymmetric allylic alkylation (AAA) reactions to prepare 3,3-disubstituted oxindoles have been developed. In 2006, Trost and coworkers reported the Mo-catalyzed AAA reaction of oxindoles using allyl carbonates as electrophiles,¹⁷ and established that these products could be easily elaborated to the corresponding pyrroloindolines. More recently, the same group developed a Pd-catalyzed AAA reaction of oxindoles using benzyloxyallene **24** as the electrophile (Scheme 1.2.3).^{18,19} The advantages of the latter reaction are that (1) it tolerates 3-indolyloxindole substrate **23**, and (2) the benzyloxy substituent in oxindole **25** provides a useful handle for the synthesis of more oxidized pyrroloindoline frameworks,²⁰ such as that found in gliocladin C and related natural products (**2**, Figure 1.1.1).

Scheme 1.2.3. Pd-catalyzed allylation of oxindoles with benzyloxyallene (**24**) (Trost and coworkers, 2011).



Conditions: 1.2 equiv **24**, 2.5 mol % $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, 7.5 mol % (R,R) -**26**, 5 mol % 1-naphthoic acid, THF, rt, 41 h.

Scheme 1.2.4. Cu-catalyzed Umpolung alkylation of 3-halo-oxindoles (Stoltz and coworkers, 2009).

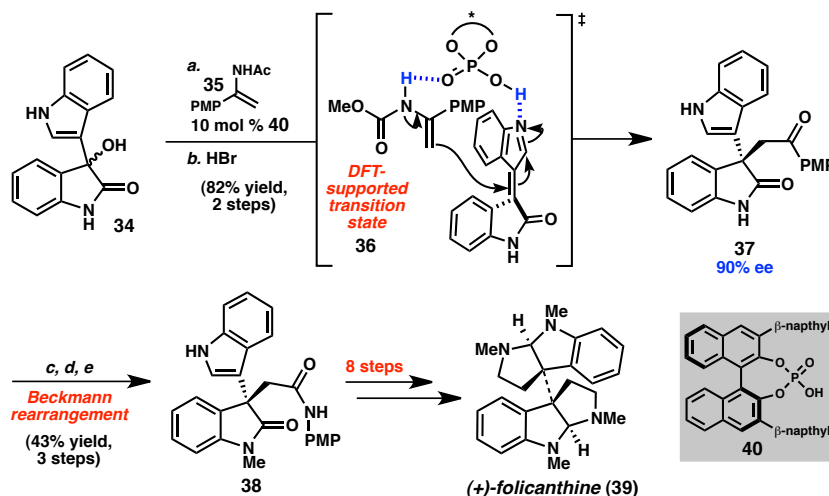


Conditions: *a*. 20 mol % (S) -PhBOX·Cu(II)· 2SbF_6^- , 3.0 equiv dimethyl malonate, 2.0 equiv Et_3N , 3 Å MS, CH_2Cl_2 , -20°C (76% yield). *b*. LiCl, H_2O , DMSO, 150°C , 12 h; *c*. *t*BuOK, MeI, THF, 0°C , 1 h; *d*. AlMe_3 , $\text{MeNH}_2 \cdot \text{HCl}$, PhMe, 50°C , 5 d; *e*. LAH, THF, 0°C , 1 h.

Most oxindole α -alkylation strategies harness the intrinsic nucleophilicity of enolate intermediates; however, two recent Umpolung approaches employ oxindoles as the electrophilic component.²¹ In a 2009 report, Stoltz and coworkers describe a Cu(II) bisoxazoline (**28**)-catalyzed stereoablative alkylation of 3-chloro-3-aryloxindoles (**27**) with dimethylmalonate, wherein coordination of the malonate to the copper catalyst presumably generates a chiral nucleophile (**29**, Scheme 1.2.4).^{21a,22} The reaction is proposed to occur by elimination of HCl from **27** to form a transient *o*-azaxylylene (**30**); subsequent attack at C3 by **29** delivers the 3,3'-disubstituted oxindole (**31**). The utility of these products in pyrroloindoline synthesis was demonstrated for oxindole **31**, which

following Krapcho dealkoxycarbonylation, *N*-methylation, aminolysis, and reductive cyclization afforded 3-phenylpyrroloindoline **33** in an operationally straightforward manner.

Scheme 1.2.5. Phosphoric acid-catalyzed Umpolung alkylation of 3-indolyloxindoles en route to (+)-folicanthine (**39**) (Gong and coworkers, 2012).



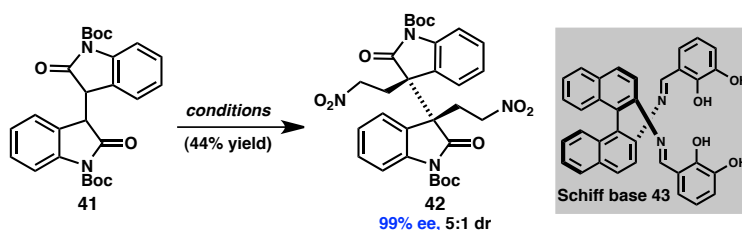
Conditions: *a.* 1.5 equiv **35**, 10 mol % **40**, Na_2SO_4 , CH_2Cl_2 , rt, 12–24 h; *b.* aqueous HBr, EtOH, rt, 8 h; *c.* $n\text{Bu}_4\text{NHSO}_4$, KOH, THF, 50 °C, 1 h; then MeI, rt, 2 h; *d.* $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, EtOH, rt, 2 d; *e.* HgCl_2 , MeCN, 80 °C, 2 h.

Gong and coworkers have discovered an alternative strategy for the in situ generation of electrophilic oxindole species that has proven instrumental for bispyrroloindoline synthesis.^{21b} This reaction involves indole-assisted dehydration, followed by chiral phosphoric acid (**40**)-catalyzed addition of enamine **35** to the transient azafulvene (**36**, Scheme 1.2.5). Mechanistic insight was provided by DFT calculations, which suggest a two-point binding model for the Brønsted acid that invokes hydrogen bonding of both the enamine and indole nitrogens. The necessary nitrogen functionality was installed by a Beckmann rearrangement to give **38**, which was elaborated in eight additional steps to (+)-folicanthine (**39**). Gong and coworkers further applied the asymmetric methodology

to 2-(alkyloxy)acetaldehydes by employing a cinchona alkaloid-derived co-catalyst and used this chemistry in a synthesis of gliocladin C (**2**, Figure 1.1.1).²³

The polypyrroloindoline alkaloids present a particular synthetic challenge due to the presence of vicinal all-carbon quaternary stereocenters and, therefore, the design of methodology tailored to these molecules is an important area of research. Shortly following Gong's report of the enamine alkylation reaction described above, Kanai, Matsunaga and coworkers also reported a concise synthesis of (+)-folicanthine (**39**) (Scheme 1.2.6).²⁴ In this case, installation of the quaternary stereocenters was accomplished by sequential Mn-catalyzed Michael additions of the readily available bisoxindole **41** to nitroethylene. Although this transformation proved more practical in terms of yield as a two-step process, it is impressive that the one-flask double Michael reaction proceeds with exceptional enantioselectivity to successfully generate both stereocenters in a single step.

Scheme 1.2.6. Mn-catalyzed double Michael reaction en route to (+)-folicanthine (**39**), (Kanai, Matsunaga and coworkers, 2012).

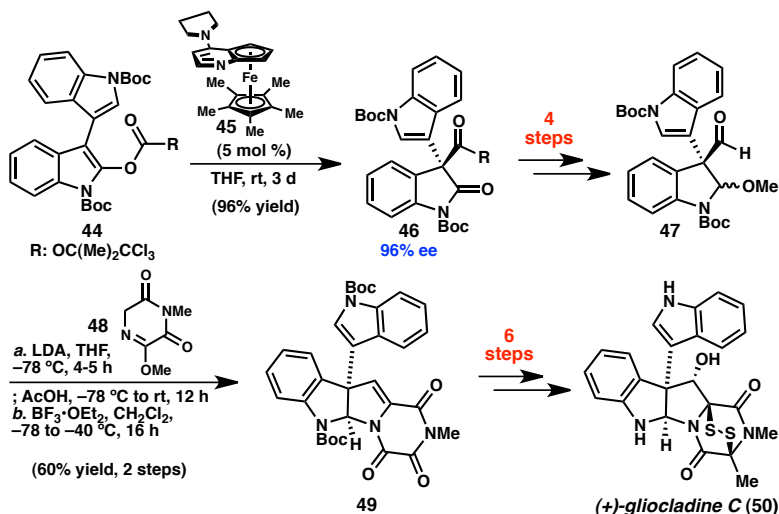


Conditions: 1.2 equiv nitroethylene, 18 mol % Mn(4-F-BzO)₂/**43** (ratio 1:1), PhMe, 5 Å MS, 50 °C, 1.5 h; then 2.0 equiv nitroethylene, 1.0 equiv 2,6-di-*tert*-butylphenol, 50 °C, 12 h.

Each of the methods discussed above depend on a reductive cyclization event as the means to access pyrroloindolines. Alternatively, the synthesis of (+)-gliocladine C (**50**) completed by Overman and coworkers required the development of a more functional

group compatible Lewis acid-promoted cyclization reaction.²⁵ These researchers further recognized the relevant utility of the planar-chiral ferrocenyl pyridine (**45**)-catalyzed intramolecular acyl O-to-C migration of indolyl carbonates initially disclosed by Fu and coworkers.²⁶ Subjection of indolyl trichloro-*tert*-butylcarbonate **44** to the reported migration conditions provided oxindole **46** in high yield and ee (Scheme 1.2.7). Intermolecular aldol reaction of further functionalized 2-methoxyindoline **47** with trioxopiperazine **48** then installed the necessary nucleophilic amide functionality and subsequent exposure to $\text{BF}_3 \cdot \text{OEt}_2$ provided didehydropyrroloindoline **49**. This cyclization product was converted to (+)-gliocladiene C (**50**) in 6 steps,²⁷ which constitutes the first total synthesis of an epidithiodiketopiperazine (ETP) natural product incorporating a β -hydroxy-substituted stereocenter.

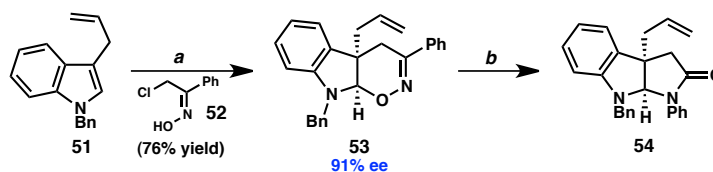
Scheme 1.2.7. First synthesis of a β -hydroxy-ETP natural product (Overman and coworkers, 2011; Fu and Hills, 2003).



As a complementary approach to asymmetric oxindole syntheses described above, Larionov and coworkers reported a strategy that invokes instead the intermediacy of an indolyl 1,2-oxazine (**53**, Scheme 1.2.8).^{28,29} Similar to the oxindole research, these studies

were driven by both the biological activity of 1,2-oxazine natural products³⁰ and the prospective conversion to pyrroloindolines. Specifically, Lewis acid-catalyzed [4+2] cycloaddition reactions of 3-alkylindoles (**51**) with nitrosoalkenes generated in situ from 2-chlorooximes (**52**) were found to afford the desired oxazines. Notably, Gilchrist and Roberts reported a related non-asymmetric NaHCO_3 -promoted reaction in 1978,³¹ but this recent addition to the literature represents the first catalytic and highly enantioselective cycloaddition of nitrosoalkenes for any dienophile.³² Beckmann rearrangement of 1,2-oxazine **53** furnished 3-allylpyrroloindoline **54**, thereby illustrating the utility of this strategy for the synthesis of both oxazines and pyrroloindolines.

Scheme 1.2.8. Nitrosoalkene [4+2]/Beckmann rearrangement approach via a 1,2-oxazine intermediate (Larionov and coworkers, 2012).



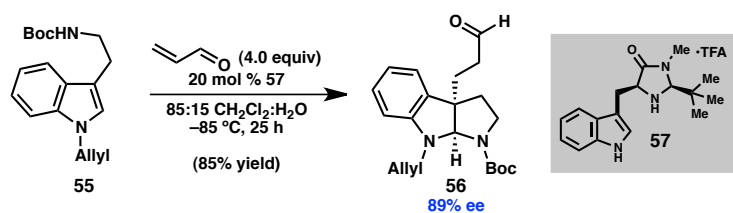
Conditions: *a*. 10 mol % CuOTf•1/2PhMe, 10 mol % (*S*)-DM-BINAP, 3.0 equiv Ag₂CO₃, 3 Å MS, CH₂Cl₂, -15 °C, 48 h; *b*. 20 mol % PBr₃, C₆H₅CF₃, 50 °C, 16 h (79% yield).

1.3 DIRECT SYNTHESIS OF PYRROLOINDOLINES FROM INDOLES AND TRYPTAMINES

Over the past decade, direct asymmetric functionalization of 3-substituted indoles has emerged as a powerful approach for the efficient preparation of pyrroloindolines. In 2004, MacMillan and coworkers reported a chiral imidazolidinone salt (**57**)-catalyzed reaction between acrolein and tryptamine derivatives (**55**) to generate enantioenriched pyrroloindolines (**56**, Scheme 1.3.1).³³ The proposed mechanism invokes condensation of **57** with acrolein to generate a chiral iminium ion,³⁴ which undergoes a cascade conjugate

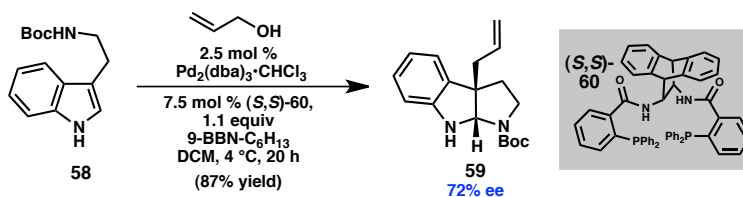
addition/cyclization reaction to deliver the pyrroloindoline framework. The appeal of this reaction is that it harnesses the intrinsic C3-nucleophilicity and provides direct access to pyrroloindolines from simple, readily available materials. The MacMillan group has utilized this organocatalytic reaction as the key step in the total syntheses of three structurally distinct pyrroloindoline alkaloids.³⁵

Scheme 1.3.1. First direct, enantioselective construction of pyrroloindolines from tryptamines (MacMillan and coworkers, 2004).



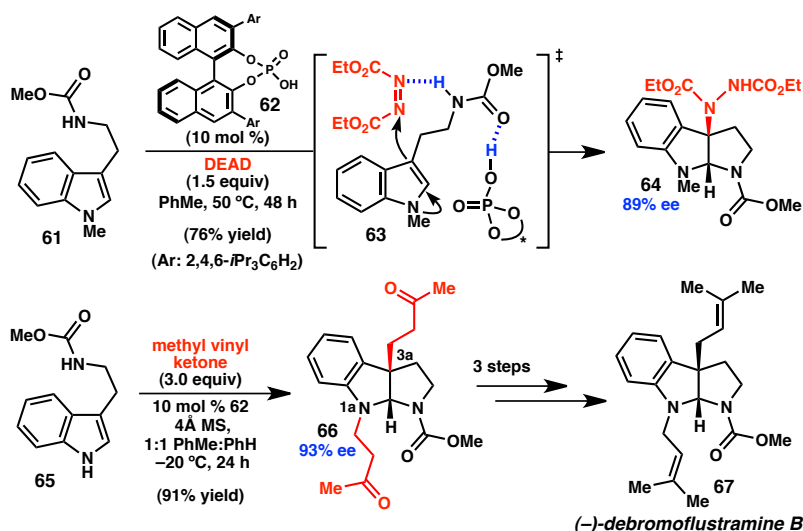
Since this initial disclosure by MacMillan and coworkers, several other methods for the direct synthesis of pyrroloindolines from tryptamine and tryptophan derivatives have been reported, and collectively these reactions provide access to a variety of enantioenriched pyrroloindoline products. In 2006, Trost and coworkers developed the first AAA reaction of allyl alcohol by including trialkylboranes as a stoichiometric promoter (Scheme 1.3.2).³⁶ Notably, the enantioselectivity of this AAA reaction is dependent on the choice of both ligand and borane, with the combination of 9-BBN-C₆H₁₃ and anthracene-derived phosphine (*S,S*)-**60** proving optimal.

Scheme 1.3.2. Pd-catalyzed tandem allylic alkylation/cyclization reaction of tryptamines (Trost and Quancard, 2006).



Antilla and coworkers recently reported chiral phosphoric acid (**62**)-catalyzed C–N and C–C bond formation/cyclization reactions of tryptamine carbamates (**61** and **65**) (Scheme 1.3.3).³⁷ Preliminary NMR investigations suggest a mechanism involving electrophile activation by a hydrogen-bonding network (**66**). Specifically, it is proposed that coordination of the tryptamine carbonyl to the catalyst enhances the carbamate acidity and results in hydrogen bonding to the electrophile (either diethylazodicarboxylate (DEAD) or methyl vinyl ketone). This methodology constitutes the first catalytic, asymmetric construction of 3-aminopyrroloindolines, a motif present in several naturally occurring alkaloids.³⁸ Furthermore, the utility of the C–C bond forming variant has been demonstrated in the concise total synthesis of (–)-debromoflustramine B (**67**). Exposure of (1*H*)-tryptamine **65** to methyl vinyl ketone resulted in substitution at both C3a and N1a to give **66**, an intermediate primed for elaboration to **67**.

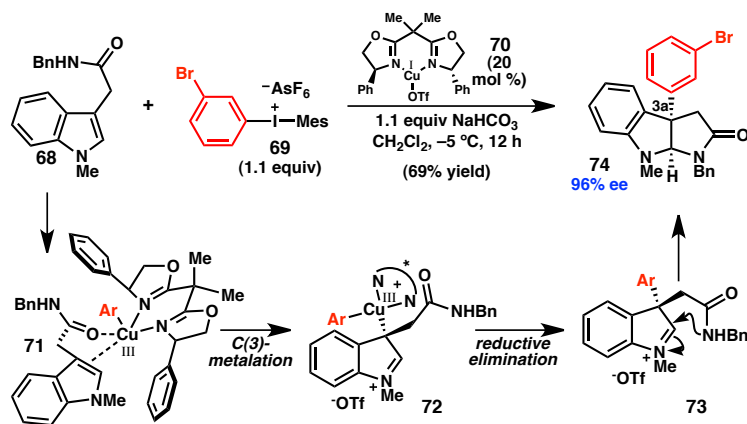
Scheme 1.3.3. Phosphoric acid (**62**)-catalyzed preparation of two pyrroloindoline motifs (Antilla and Zhang, 2012).



In a recent effort directed toward preparing 3a-arylpyrroloindolines, MacMillan and coworkers developed a Cu(I)-bisoxazoline (**70**)-catalyzed intermolecular arylation

reaction of indole acetamides using arylodonium salts (**69**, Scheme 1.3.4).^{39,40} The proposed mechanism involves electrophilic C3-metalation of the indole acetamide (**68**) by a Cu(III)-aryl complex, reductive elimination, and cyclization of the resultant 3-arylindolenine (**73**). The excellent enantioselectivity likely results from bidentate substrate coordination (**71**) involving both the carboxamide and C2-C3 π -bond of the indole. This reaction enables the direct preparation of highly enantioenriched derivatives including 3-(bromoaryl)pyrroloindolines (**74**) that contain a potential handle for advancement to the indolyl substitution patterns found in naturally occurring alkaloids such as asperazine (**5**, Figure 1.1.1).

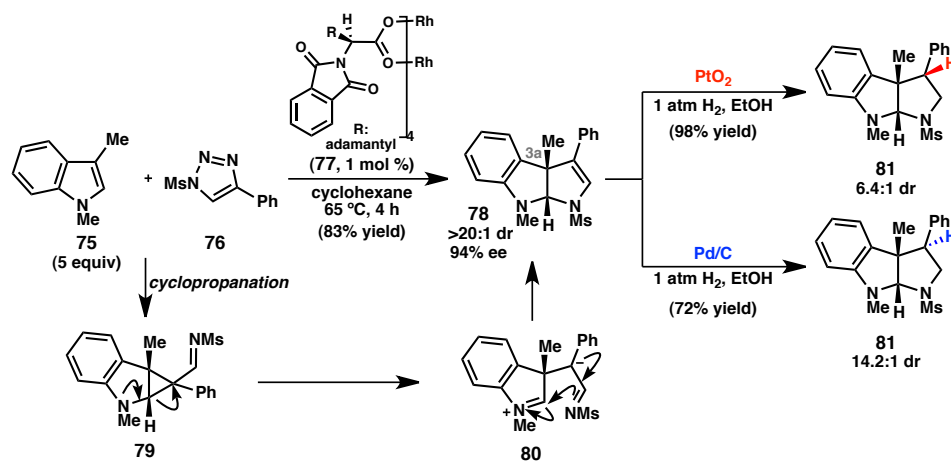
Scheme 1.3.4. Cu-catalyzed tandem arylation/cyclization reaction of indole acetamides (MacMillan and Zhu, 2012).



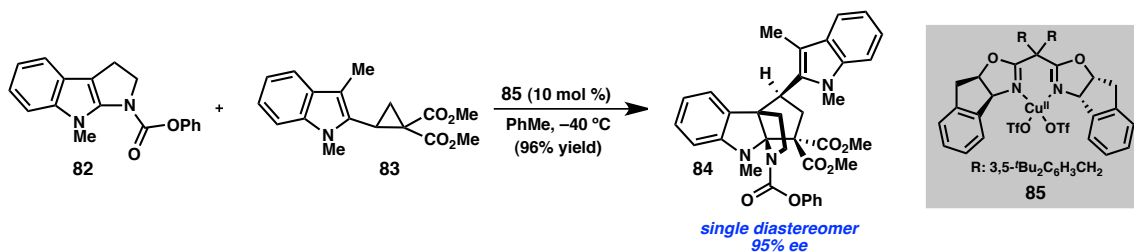
Although the majority of direct asymmetric approaches to pyrroloindolines employ tryptamine derivatives as substrates, several research groups have explored direct synthesis by formal (3 + 2) cycloaddition reactions. In 2010, we reported this approach involving the reaction of 3-substituted indoles and 2-amidoacrylates using (*R*)-BINOL·SnCl₄ as the catalyst to effect an enantiodetermining protonation (Chapter 2).⁴¹ More recently, Davies and Spangler developed a Rh₂(*S*-PTAD)₄ (**77**)-catalyzed reaction

between 3-substituted indoles (**75**) and 4-aryl-1-sulfonyl-1,2,3-triazoles (**76**) that affords didehydropyrroloindolines bearing either alkyl (**78**) or aryl substitution at C3a (Scheme 1.3.5).⁴² These products can be selectively reduced to afford either diastereomer of pyrroloindoline **81** depending on the catalyst. The formal cycloaddition to give **78** is proposed to occur by cyclopropanation of **75** with the Rh(II)-carbenoid generated in situ from **76**, followed by cyclopropane ring-opening and cyclization. An alternative formal (3 + 2) cycloaddition approach has also been disclosed by Xie, Tang, and coworkers involving the Cu(II)-bisoxazoline (**85**)-catalyzed reaction of achiral pyrroloindole **82** and donor-acceptor cyclopropane **83**, which furnishes aza-propellane **84** in excellent yield and stereoselectivity (Scheme 1.3.6).⁴³

Scheme 1.3.5. Rh-catalyzed formal (3 + 2) cycloaddition (Davies and Spangler, 2013).



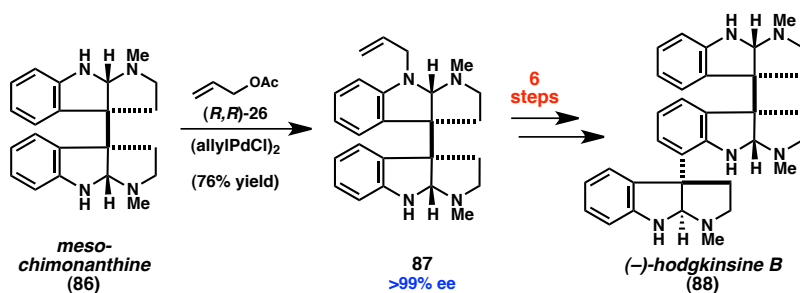
Scheme 1.3.6. Cu-catalyzed formal (3 + 2) cycloaddition (Xie, Tang, and coworkers, 2013).



1.4 SYNTHESIS OF ENANTIOENRICHED PYRROLOINDOLINES BY DESYMMETRIZATION

With the exception of the formal cycloaddition reaction, the approaches described above all rely on setting the absolute stereochemistry of the pyrroloindoline through a key, catalytic, C3-functionalization step. Alternatively, Willis and coworkers pursued a conceptually distinct strategy focused on the desymmetrization of readily accessible *meso*-chimonanthine to prepare the related trispyrroloindoline alkaloid (–)-hodgkinsine B (**88**, Scheme 1.4.1).⁴⁴ Specifically, a Pd-catalyzed *N*-allylation of the bispyrroloindoline **86** was achieved using the ligand (*R,R*)-**22**, a chiral phosphine developed by Trost and coworkers (Scheme 1.2.3).⁴⁵ This chemistry finds precedent in Taguchi and coworkers' Pd-catalyzed desymmetrization of *meso*-cyclohexane-1,2-diamides,⁴⁶ but the substrate complexity and enantioselectivity are unparalleled. In combination with the oxindole α -arylation methodology also developed by Willis and coworkers,⁴⁷ this allylic substitution-desymmetrization reaction enabled remarkably rapid access to **88**.

Scheme 1.4.1. Allylic substitution-desymmetrization reaction en route to (–)-hodgkinsine B (**88**) (Willis and coworkers, 2011).



Conditions: 1.2 equiv allyl acetate, 2.0 equiv Et₃N, 3.8 mol % (*R,R*)-**22**, (allylPdCl)₂ (2.5 mol % Pd), PhMe, 0 °C, 1.5 h.

1.5 CONCLUDING REMARKS

The complexity, biological activity, and remarkable variety exhibited by pyrroloindolines have long since established this family of natural products as an important target for total synthesis. In particular, the past two decades of research resulted in enantioselective, catalytic strategies for the synthesis of pyrroloindolines bearing C3a all-carbon quaternary stereocenters. Whereas early synthetic methods focused on the preparation of 3,3'-disubstituted oxindoles, more recent efforts have investigated the initial generation of 1,2-oxazines, desymmetrization, and direct functionalization of indoles. Despite the breadth of reported transformations, key restrictions exist regarding functional group incorporation and a highly divergent reaction remains elusive. These unmet challenges illustrate the demand for new methodologies and suggest that the pyrroloindoline scaffold will persist as an inspiration for future research in organic synthesis.

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CHAPTER 2

Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines[†]

2.1 INTRODUCTION

As discussed in Chapter 1, many approaches have recently been reported for the direct, enantioselective, catalytic construction of pyrrolindolines from indole precursors. However, when we initially began our efforts in this field only two reports of this type had been disclosed, the iminium catalysis and allylic alkylation approaches from the groups of MacMillan and Trost. This chapter describes the development of a new approach to pyrroloindolines involving an (*R*)-BINOL•SnCl₄-catalyzed formal (3 + 2) cycloaddition of 3-substituted indoles and 2-amidoacrylates. This reaction is tolerant to diverse substitution patterns and is the only direct, enantioselective approach that incorporates the necessary C2-stereocenter for advancement to diketopiperazine natural products. Mechanistic studies will be discussed that confirmed an asymmetric protonation as the enantiodetermining step and ultimately led to the development of a

[†] Part of this chapter was published as the following communication: Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. The research discussed in this chapter was completed in collaboration with Jane Ni, a graduate student in the Reisman lab.

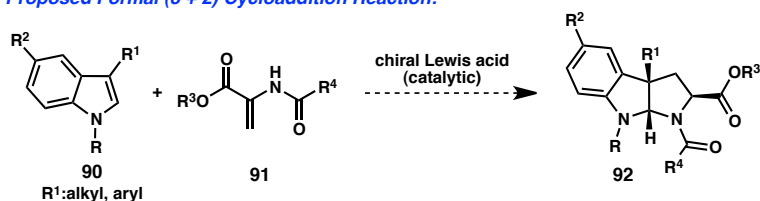
tandem conjugate addition/enantioselective protonation reaction for the synthesis of tryptophan derivatives (Chapter 3).

2.1.1 Design of the Cycloaddition Approach

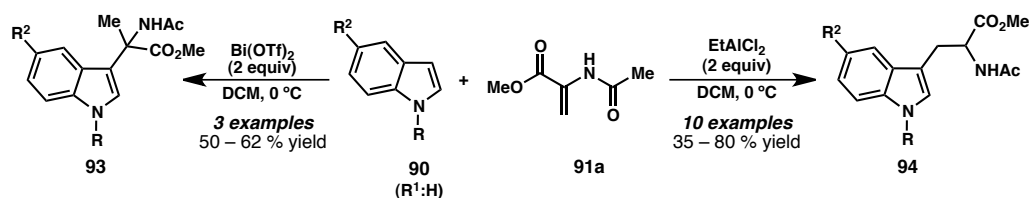
The majority of catalytic, asymmetric indole functionalization approaches to prepare pyrroloindolines, including the seminal reports of MacMillan¹ and Trost,² involve the electrophilic substitution of tryptamine substrates. In our effort to provide a complementary approach to pyrroloindolines, we became interested in the possibility of a formal (3 + 2) cycloaddition reaction between 3-substituted indoles (**90**) and 2-amidoacrylates (**91**) that constitutes a formal (3 + 2) cycloaddition (Scheme 2.1.1). Successful realization of the proposed transformation could allow rapid access to a variety of substitution patterns and the pyrroloindoline-2-carboxylate products (**92**) formed should be suitable precursors for elaboration to diketopiperazine natural products (e.g. chaetocin (**3**, Figure 1.1.1)).

Scheme 2.1.1. Our proposed reaction and precedent in tryptophan synthesis.

Proposed Formal (3 + 2) Cycloaddition Reaction:



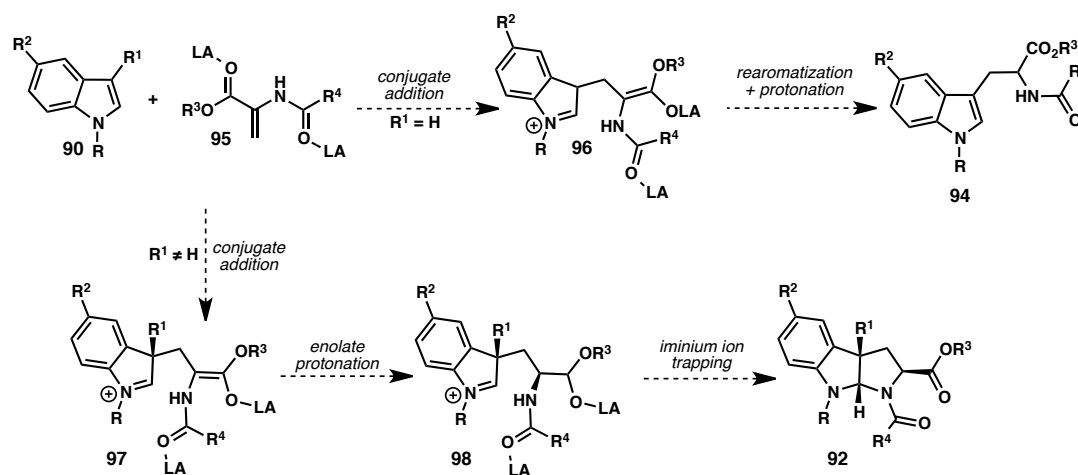
Synthesis of Tryptophan Derivatives by Piersanti and coworkers, 2008:



Although the potential for reaction between 3-substituted indoles and weak electrophiles such as amidoacrylates was unclear at the outset of this project, we were

particularly encouraged by the recent findings of Piersanti and coworkers reported in 2008.³ These authors disclosed that Lewis acids promote the condensation of C3-unsubstituted indoles (**90**, R¹:H) and methyl 2-acetamidoacrylate (**91a**) to afford Friedel–Crafts alkylation products as racemates (Scheme 2.1.1). Interestingly, the regioselectivity of addition to **91a** strongly depends on the choice of Lewis acid; whereas hard, oxaphilic Lewis acids such as EtAlCl₂ afford tryptophan derivatives (**94**), softer, more azaphilic Lewis acids such as Bi(OTf)₃ result in reaction of the acrylate via the imine tautomer to generate quaternary amides (**93**).

Scheme 2.1.2. Proposed mechanisms of **92** and **94** formation.



Mechanistically, Piersanti's reaction to prepare tryptophan **94** is proposed to occur by conjugate addition at C3 of the indole to generate transient enolate **96**, followed by rearomatization and protonation (Scheme 2.1.2). We envisioned that in the case of 3-substituted indoles, the initial conjugate addition would still occur; however, instead of rearomatization, enolate protonation and cyclization of the pendant amide nitrogen to the transiently generated iminium ion **98** could provide the desired pyrroloindoline product (**92**) in a single operation. The mechanism for the Friedel–Crafts alkylation has not been

thoroughly investigated, but notably this reaction requires two equivalents of Lewis acid. By ^1H NMR, Piersanti and coworkers found that subjection of methyl 2-acetamidoacrylate **91a** to 1 equivalent of EtAlCl_2 resulted in broadening of signals from a vinyl proton and the amide proton and methyl substituents, whereas subjection to two equivalents resulted in complete broadening of the acrylate signals. These experiments suggest that the reaction is second-order in the Lewis acid and proceeds via doubly activated enolate **95**.

The requirement of superstoichiometric Lewis acid in the Friedel–Crafts reaction suggested that the development of the formal (3 + 2) cycloaddition reaction using a catalytic Lewis acid would be challenging; however, we were encouraged by the general reactivity of amidoacrylates observed in the tryptophan synthesis as well as the potential for straightforward screening given the commercial availability of all reagents.

2.2 DEVELOPMENT OF THE FORMAL CYCLOADDITION REACTION⁴

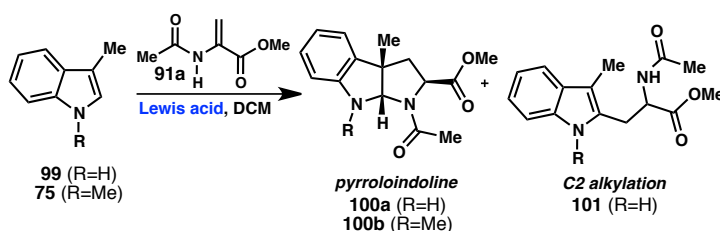
2.2.1 *Identification of an Effective Lewis Acid*

Our studies began with the reaction between 3-methylindole (**99**) and methyl 2-acetamidoacrylate (**91a**). A screen of Lewis acids revealed that use of two equivalents EtAlCl_2 delivered the desired pyrroloindoline (**100a**) as the major product in 3:1 dr favoring the *exo* diastereomer, although the C2 Friedel–Crafts alkylation product (**101**) was also observed (Table 2.2.1, entry 2). Consistent with Piersanti and coworkers' findings in the synthesis of tryptophan derivatives, no reaction occurred in the presence of stoichiometric EtAlCl_2 (entry 1); however, 1.0 equivalent of SnCl_4 was found to promote the reaction with comparable 6:1 selectivity for pyrroloindoline formation over

alkylation (entry 3). Fortunately, methylation of the indole nitrogen increased the regioselectivity for the pyrroloindoline product (entry 8). Attempted reactions with catalytic loadings identified that this reaction requires stoichiometric quantities of SnCl_4 . Interestingly, the yield of pyrroloindoline is dramatically reduced using substoichiometric quantities of SnCl_4 , with no product formed when 50 mol % is employed (entry 9).

Under our initially optimized conditions for this transformation, exposure of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) to 1.2 equivalents SnCl_4 in dichloroethane gave the desired pyrroloindoline **100b** in 64% yield as a 6:1 mixture of *exo* and *endo* diastereomers (entry 10).

Table 2.2.1. Initial Lewis acid screen.



Entry	Lewis Acid (equiv)	Substrate	Temperature (°C)	Pyrroloindoline: C-2 alkylation	dr ^a
1	EtAlCl_2 (1)	99	23	nr	--
2	EtAlCl_2 (2)	99	8	8:1	3:1
3	SnCl_4 (1)	99	23	6:1	9:1
4	MgClO_4 (1)	99	23	nr	--
5	$\text{Sc}(\text{OTf})_2$ (2)	99	23	>20:1	5:1
6	$\text{Cu}(\text{OTf})_2$ (2)	99	23	decomposition	--
7	$\text{Zn}(\text{OTf})_2$ (2)	99	23	nr	--
8	SnCl_4 (1)	75	23	>20:1 ^b	11:1
9	SnCl_4 (0.5)	75	23	nr	--
10 ^c	SnCl_4 (1.2)	75	23	>20:1 (64) ^d	6:1

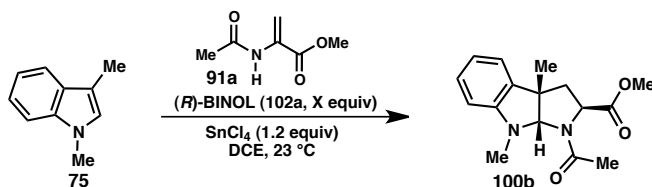
^a Determined by analysis of the crude ^1H NMR with comparison to reported spectra.⁴ ^b Complete conversion to **100b** by crude ^1H NMR. ^c Reaction run in DCE. ^d Isolated yield of **100b**. nr: no reaction.

2.2.2 Identification of Enantioselective Conditions and Optimization

In light of our preliminary results with SnCl_4 , we initiated studies targeting an asymmetric variant of the formal (3 + 2) cycloaddition reaction. A screen of a variety of

chiral ligands previously reported to be used in conjunction with SnCl_4 revealed that use of (*R*)-BINOL provides **100b** in promising enantioselectivity. Thus, treatment of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) with a 1.1:1 mixture of (*R*)-BINOL and SnCl_4 provided pyrroloindoline **100b** in 86% yield as a 4:1 mixture of diastereomers, with the *exo* diastereomer formed in 64% ee (Table 2.2.2, entry 2).

Table 2.2.2. (*R*)-BINOL loading optimization studies.



Entry	(<i>R</i>)-BINOL (equiv)	Yield (%) ^a	dr ^b	ee (%) ^{c,d}
1 ^e	0.0	64	6:1	--
2 ^f	1.1 ^g	86	4:1	64/83
3 ^h	0.3	96	5:1	62/81
4 ^h	0.2	94	5:1	63/83
5 ^h	0.1	93	5:1	61/79
6 ^h	0.05	82	5:1	51/72

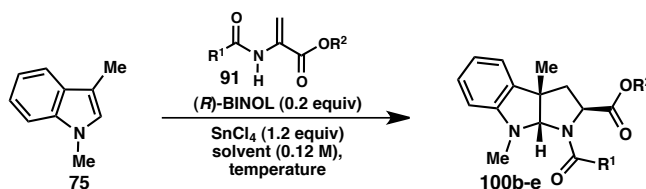
^a Isolated yield of combined diastereomers. ^b Determined by ^1H NMR analysis of crude reaction mixture. ^c Determined by chiral stationary phase SFC. ^d ee of *exo/endo* diastereomers. ^e Reaction run for 30 h. ^f Reaction run for 3.5 h. ^g 1.0 equiv of SnCl_4 was used. ^h Reaction run for 3 h.

Somewhat surprisingly, side-by-side reactions of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) combined in the presence and absence of stoichiometric BINOL, under otherwise identical conditions, revealed that BINOL accelerates the rate of the reaction and provides **100b** in improved yield.⁵ Based on these observations, it was hypothesized that similar enantioselectivities might be accessible using only catalytic quantities of (*R*)-BINOL. Gratifyingly, treatment of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) with 1.2 equivalents SnCl_4 and 20 mol % (*R*)-BINOL furnished the desired pyrroloindoline **100b** in 94% yield as a 5:1 mixture of diastereomers, favoring the *exo* diastereomer in 63% ee (Table 2.2.2, entry 4).

Remarkably, moderate levels of enantioselectivity are observed even when the reaction is conducted with 5 mol % (*R*)-BINOL (entry 6).

In our initial effort to improve the enantioselectivity, we first evaluated the effect of temperature. Unlike many transformations that proceed optimally at lower temperature, reduced ee and dr are observed for the formal (3 + 2) cycloaddition under these conditions (Table 2.2.3, entries 3–4). Alternatively, conducting the reaction above room temperature did not significantly alter the selectivity (entry 5). Notably, similar temperature effects have been reported in a few instances involving Lewis acid•BINOL complexes.⁶

Table 2.2.3. Enantioselectivity optimization studies.



Entry	R ¹ , R ²	pdt	Temperature (°C) (Time (h))	Solvent	Yield (%) ^a	dr ^b	ee (%) ^{c,d}
1	Me, Me (91a)	100b	23 (4)	DCE	94	5:1	63/83
2 ^e	Me, Me (91a)	100b	8 (24)	DCE	88 ^f	4:1	66/nd
3 ^e	Me, Me (91a)	100b	−40 (24)	DCM	69 ^f	3:1	39/nd
4 ^e	Me, Me (91a)	100b	−78 (24)	DCM	26 ^f	2:1	21/nd
5 ^e	Me, Me (91a)	100b	40 (0.5)	DCE	97 ^f	5:1	66/nd
6	CF ₃ , Me (91b)	100c	23 (4)	DCE	77	6:1	86/nd
7	Me, Bn (91c)	100d	23 (4)	DCE	81	2:1	74/82
8	CF ₃ , Bn (91d)	100e	23 (4)	DCE	81	3:1	91/90
9	CF ₃ , Bn (91d)	100e	23 (5.5)	DCM	86	4:1	94/91
10	CF ₃ , Bn (91d)	100e	23 (4)	CHCl ₃	58	3:1	88/89
11	CF ₃ , Bn (91d)	100e	23 (3.5)	CCl ₄	0	--	--

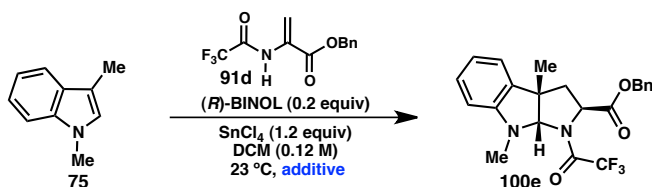
^a Isolated yield of combined diastereomers. ^b Determined by ¹H NMR analysis of crude reaction mixture. ^c Determined by chiral stationary phase SFC or HPLC. ^d ee of *exo/endo* diastereomers. ^e 1.0 equiv of SnCl₄ and 1.1 equiv (*R*)-BINOL was used. ^f Approximate conversion to **100b** based on ratio with acrylate in crude ¹H NMR. nd= not determined.

More promising effects were found by varying acrylate substitution. Utilization of methyl 2-trifluoroacetamidoacrylate (**91b**) and benzyl 2-acetamidoacrylate (**91c**) provided pyrroloindoline products **100c** and **100d** in enhanced enantioselectivities, with

the *exo* diastereomers formed in 86% and 74% ee, respectively (Table 2.2.3, entries 6-7). Fortunately, these effects were additive; reaction of benzyl 2-trifluoroacetamidoacrylate (**91d**) afforded pyrroloindoline **100e** in 81% yield as a 3:1 mixture of *exo* and *endo* diastereomers produced in 91% and 90% ee, respectively (entry 8). A solvent screen revealed that chlorinated solvents are optimal and switching from DCE to DCM afforded **100e** in 86% yield and 94% ee for the *exo* diastereomer (entry 9).

With these optimized reaction conditions in hand, we reevaluated the parameters of the formal (3 + 2) cycloaddition reaction and confirmed that a Lewis acid is required for the transformation; exposure of 1,3-dimethylindole (**75**) and **91d** to Brønsted acids, including (*R*)-BINOL, HCl, and Ph₂PO₂H (Table 2.2.4, entries 1-3) gave no reaction. Several water and acid scavenging additives were also screened but no significant change in enantioselectivity was observed in their presence (entries 4, 5 and 7).

Table 2.2.4. Additive screen.



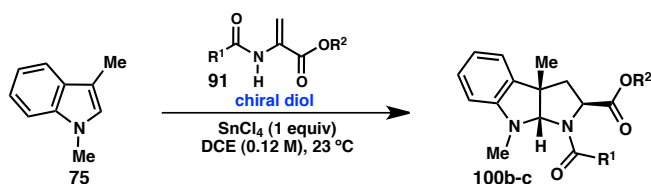
Entry	Additive (equiv)	Time (h)	Yield (%) ^a	dr ^b	ee (%) ^{c,d}
1	^e	4	0	--	--
2	HCl (1.2) ^e	7	0	--	--
3	Ph ₂ PO ₂ H (1.2) ^e	7	0	--	--
4 ^f	molecular sieves	4	70	4:1	93:89
5 ^f	MgO (1)	4.5	72	4:1	93:91
6	2,6-lutidine (1)	6	0	--	--
7	2,6-lutidine (0.2)	5	53	6:1	94:89

^a Isolated yield of combined diastereomers. ^b Determined by ¹H NMR analysis of crude reaction mixture. ^c Determined by chiral stationary phase SFC. ^d ee of *exo/endo* diastereomers. ^e Reaction run without SnCl₄. ^f Completed side-by-side with reaction under standard conditions that afforded 74% yield, 4:1 dr, 94:90% ee.

Although (*R*)-BINOL ultimately proved to afford the highest enantioselectivities, various BINOL derivatives as well as other chiral diols were also evaluated in the course

of efforts to determine optimal conditions and to investigate the mechanism of this transformation. (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102b**) promoted **100b** formation in a reduced 40% ee, suggestive of an important role for the hydroxyl protons in the enantiodetermining step (Table 2.2.5, entry 2). Furthermore, sterically hindered BINOL derivatives **102c-e** provided **100b** as a racemate, but with good diastereoselectivity (entries 3-5). 6,6'-dibromo-BINOL (**102f**), which is sterically similar to BINOL but more electron deficient, afforded pyrroloindoline **100c** in slightly reduced ee (entry 7) and non-BINOL-derived chiral diols, TADDOL (**103**) and hydrobenzoin (**104**), gave **100c** in 0 and 46% ee, respectively (entries 8 and 9).

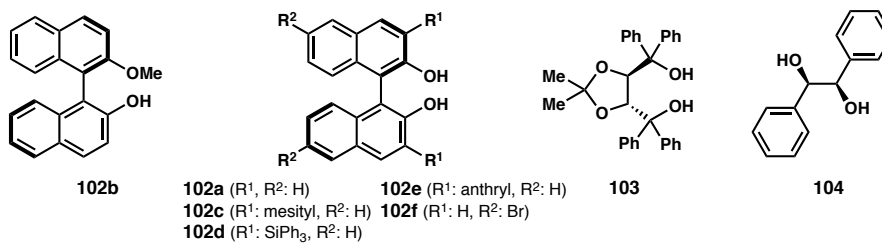
Table 2.2.5. Screen of chiral diols.



Entry	Diol (equiv)	R ¹ , R ²	Product	dr ^a	ee (%) ^{b,c}
1	102a (1.1)	Me, Me (91a)	100b	4:1	64
2	102b (1.1)	Me, Me (91a)	100b	3:1	40
3	102c (1.1)	Me, Me (91a)	100b	6:1	0
4	102d (1.1)	Me, Me (91a)	100b	>10:1	0
5	102e (1.1)	Me, Me (91a)	100b	7:1	0
6 ^d	102a (0.2)	CF ₃ , Me (91b)	100c	6:1	86
7	102f (0.2)	CF ₃ , Me (91b)	100c	8:1	81
8	13 (0.2)	CF ₃ , Me (91b)	100c	10:1	0
9	14 (0.2)	CF ₃ , Me (91b)	100c	8:1	46

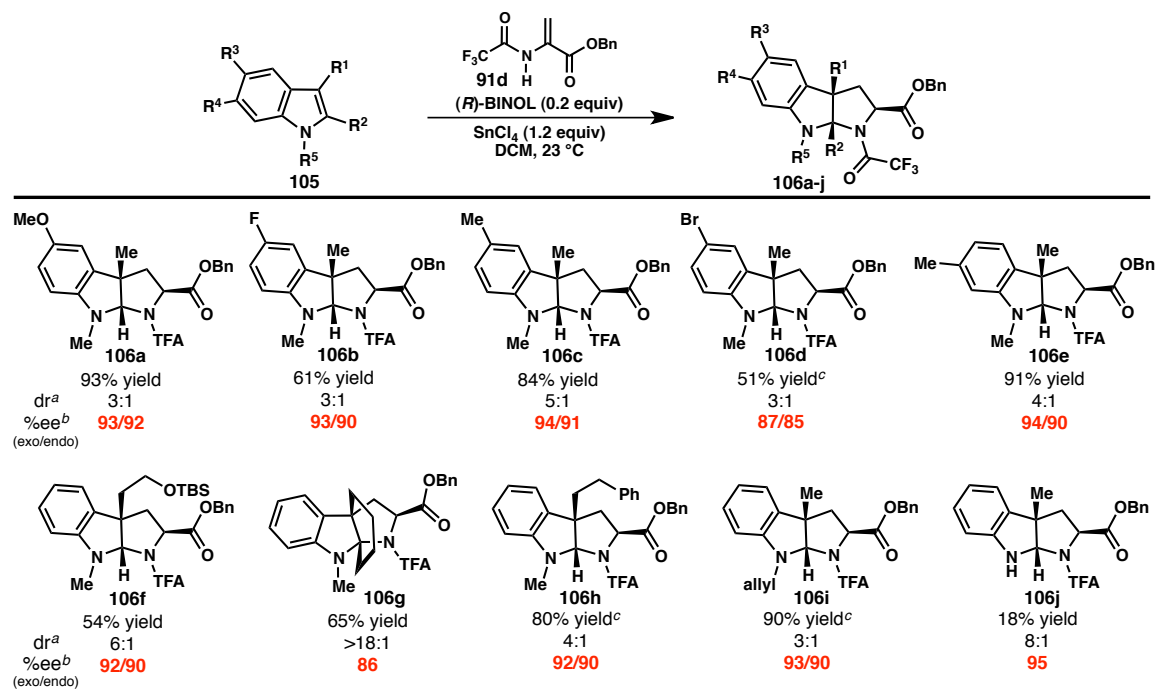
^a Determined by ¹H NMR analysis of crude reaction mixture. ^b Determined by chiral stationary phase SFC or HPLC. ^c ee of *exo* diastereomer. ^d Reaction run with 1.2 equiv SnCl₄.

Figure 2.2.1. Chiral diols.



2.2.3 Substrate Scope of Pyrroloindoline Synthesis

Scheme 2.2.1. Substrate scope.

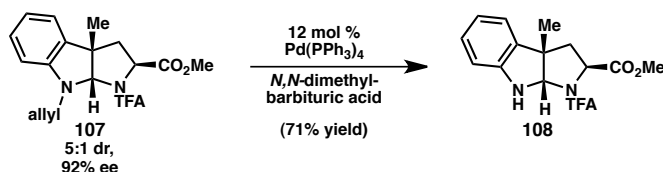


^a Determined by ^1H NMR analysis of mixture. ^b Determined by chiral SFC or HPLC analysis. ^c 1.6 equiv SnCl_4 was employed.

The enantioselective formal (3 + 2) cycloaddition with benzyl 2-trifluoroacetamidoacrylate (**91d**) is general for a range of indole substrates. Indoles substituted at C5 with either electron-donating or electron-withdrawing groups are tolerated in this reaction, although electron-poor indoles react at a slower rate (Scheme 2.2.1, **106a–e**). Indoles substituted at C3 with functionalized alkyl groups reacted in moderate to good yields with high enantioselectivity (**106f** and **106h**). Notably, the reaction of *N*-methyltetrahydrocarbazole proceeded with >18:1 diastereoselectivity, delivering the *exo* diastereomer **106g** in 86% ee. In a single step, this reaction generates the aza-propellane core of the natural products minfiensine,⁷ echitamine,⁸ and vincorine.⁹ Consistent with our preliminary findings, *N*-alkylation is important to the reactivity;

subjection of 3-methylindole to identical conditions provided pyrroloindoline **106j** in only 18% yield albeit with excellent enantioselectivity. However, *N*-allyl-3-methylindole (**105i**) was successfully employed as a substrate to afford pyrroloindoline **106i**. The combination of $\text{Pd}(\text{PPh}_3)_4$ and *N,N*-dimethylbarbituric acid have been shown to smoothly convert related methyl ester **107** to the deallylated product **108** (Scheme 2.2.2);¹⁰ this finding is particularly useful in the context of total synthesis as many pyrroloindoline natural products do not bear substitution on nitrogen.

Scheme 2.2.2. Pd-catalyzed deallylation of pyrroloindoline methyl ester **107**.

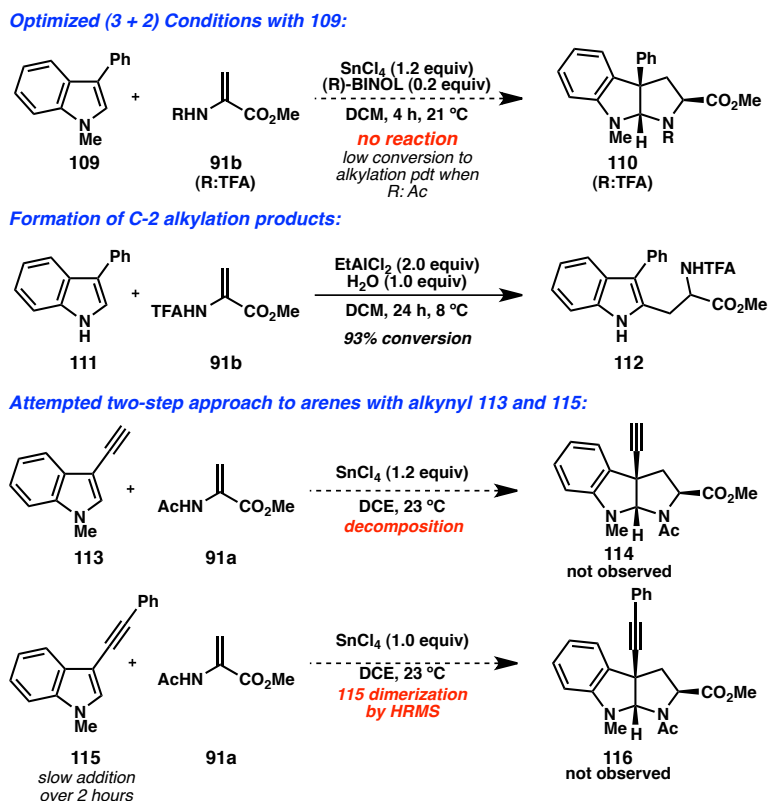


Although many substrates are well-tolerated in the formal (3 + 2) cycloaddition reaction, this transformation proved challenging for more sterically encumbered substrates. 3a-Indolylpyrroloindolines constitute a large number of pyrroloindoline natural products and thus, we were also very interested in accessing arylpyrroloindolines using the formal (3 + 2) cycloaddition methodology. However, subjection of 1-methyl-3-phenylindole (**109**) to our standard conditions with methyl 2-trifluoroacetamidoacrylate (**91b**) resulted in no reaction whereas exposure to methyl 2-acetamidoacrylate (**91a**) gave low conversion to the corresponding C2-alkylation product (Scheme 2.2.3). Clean conversion to C2-alkylation product **112** has also been observed for 3-phenylindole (**111**) in the presence of EtAlCl_2 .

Alternatively, we also envisioned a two-step approach to generate indolylpyrroloindolines through initial formation of 3a-alkynylpyrroloindolines and a

subsequent Larock annulation; however, subjection of 1-methyl-3-ethynylindole (**113**) and **91a** to SnCl_4 gave decomposition and subjection of 1-methyl-3-(phenylethynyl)indole (**115**) and **91a** to SnCl_4 resulted in dimerization of the indole, even when **115** was added slowly to the reaction mixture over 2 hours.

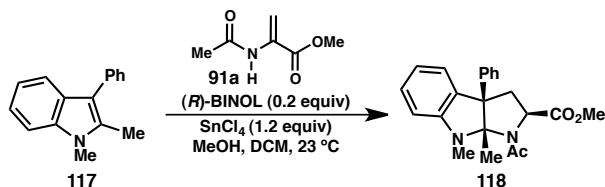
Scheme 2.2.3. Unsuccessful approaches to arylpyrroloindolines.



In a final effort to access arylpyrroloindolines, we employed 1,3-dimethyl-3-phenylindole (**117**) as the substrate to ensure complete selectivity for pyrroloindoline formation by prohibiting Friedel–Crafts alkylation. Although exposure of **117** and **91a** to standard conditions gave only trace conversion to phenylpyrroloindoline **118** (Table 2.2.6, entry 1), addition of 0.20 equiv MeOH cleanly afforded **118** in 40% yield as a single diastereomer in 91% ee (entry 4). Unfortunately, prolonged reaction times and

increased SnCl_4 loading did not substantially improve yield (entries 5 and 7) and inconsistent ees varying from 84 – 91% were obtained for the reaction (entries 4-6).

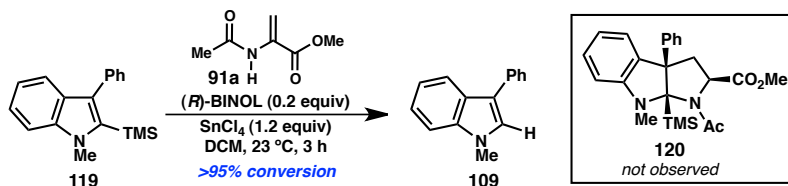
Table 2.2.6. Methanol-promoted synthesis of phenylpyrroloindoline **118**.



Entry	Scale (mmol)	MeOH (equiv)	Concentration (M)	Time (h)	117:118 ^a	Yield ^b (%)	dr ^a	ee (%) ^{c,d}
1 ^e	0.15	--	0.12	13	17:1	nd	nd	--
2 ^e	0.15	0.2 ^f	0.12	13	2:1	nd	>20:1	--
3 ^e	0.15	1.0 ^f	0.12	13	>20:1	--	--	--
4	0.20	0.20 ^g	0.11	12.5	nd	40	>20:1	91
5	0.20	0.20 ^g	0.11	64	nd	47	>20:1	88
6	0.19	0.20 ^g	0.11	12	1:2	38	>20:1	84
7 ^h	0.19	0.20 ^g	0.11	12	1:2	45	>20:1	81

^a Determined by ^1H NMR analysis of the crude reaction mixture. ^b Isolated yield. ^c Determined by chiral SFC analysis. ^d ee of *exo* diastereomer. ^e Reaction conducted with (*R/S*)-BINOL. ^f neat MeOH was added to the reaction. ^g MeOH was added from a stock solution in DCM. ^h Reaction run with 1.6 equiv SnCl_4 . nd: not determined.

Scheme 2.2.4. Subjection of 2-trimethylsilylindole **119** to cycloaddition conditions.[‡]

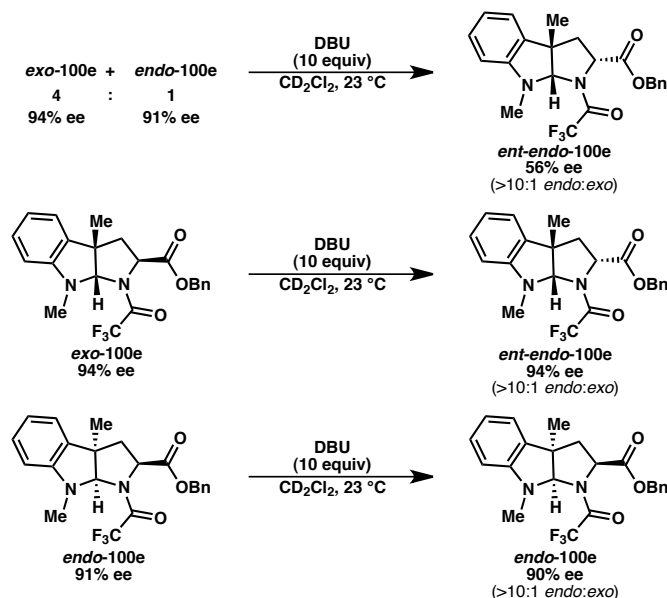


When we first discovered this transformation, no other direct enantioselective approaches to arylpyrroloindolines had been reported. Most natural products are unsubstituted at C2a and thus, we elected to pursue this transformation using 2-(trimethylsilyl)indole **119**, which could undergo desilylation in a second step following cycloaddition to generate C2-unsubstituted pyrroloindolines; however, we found that protodesilylation occurs readily in the presence of SnCl_4 to give 1-methyl-2-phenylindole

(**109**, Scheme 2.2.4).[‡] At this point, no further work is being conducted to extend this pyrroloindoline methodology to sterically encumbered substrates. However, these challenges ultimately provided inspiration for the development of a second approach to pyrroloindolines within our laboratory involving the Cu-catalyzed arylation of tryptamine¹¹ and tryptophan derivatives¹² using aryl iodonium salts.

2.3 MECHANISTIC CONSIDERATIONS

Scheme 2.3.1. Epimerization studies.

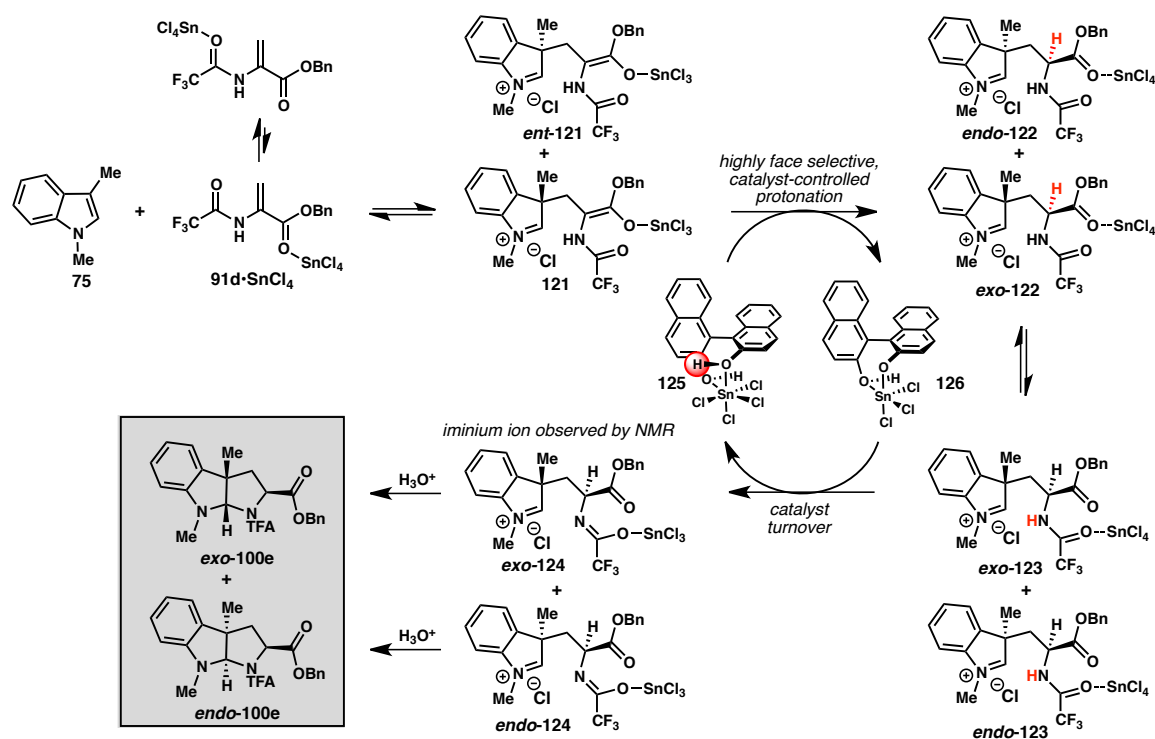


The formal (3 + 2) cycloaddition reaction favors formation of the *exo* pyrroloindoline product. Previous studies regarding pyrroloindolines have revealed that the *exo* diastereomer is the kinetic product and the *endo* diastereomer is thermodynamically favored.¹³ With the objective of accessing the *endo* diastereomer, we carried out epimerization studies on the product mixture resulting from the formal (3 + 2) cycloaddition of 1,3-dimethylindole (**75**) and benzyl 2-trifluoroacetamidoacrylate (**91d**)

[‡] This reaction was completed by Dr. Paola Romanato, a former postdoctoral scholar in the Reisman lab.

(Scheme 2.3.1). In the presence of excess DBU, the 4:1 mixture of *exo* and *endo* diastereomers (94% and 91% ee) was cleanly converted to the *endo* diastereomer. Surprisingly, the *endo* diastereomer was recovered in 56% ee, favoring the opposite enantiomer. These results indicate that the diastereomers formed in the formal (3 + 2) cycloaddition reaction are of opposite enantiomeric series. Calculations given this assumption predict an enantioselectivity of 58% ee. This result was confirmed by control experiments involving exposure of the pure *exo* diastereomer to DBU; exposure of 94% ee *exo*-**100e** to the epimerization conditions returned *ent*-*endo*-**100e** in 94% ee.

Scheme 2.3.2. Proposed mechanism for stereoselective cycloaddition reaction.



Current efforts are focused on understanding the mechanism of BINOL·SnCl₄ catalyzed pyrroloindoline formation. However, one possible scenario consistent with the experimental data is shown in Scheme 2.3.2. In this mechanism, it is proposed that SnCl₄-promoted conjugate addition of the indole to the acrylate proceeds reversibly to afford a

racemic mixture of enolates **121** and *ent*-**121**. In the second step, an irreversible, highly face-selective, catalyst controlled protonation would serve to resolve the two enantiomers into diastereomeric iminium ions *exo*-**122** and *endo*-**122**. In this mechanistic hypothesis, the diastereoselectivity depends on the relative rates of protonation of **121** and *ent*-**121**. Subsequent catalyst turnover by deprotonation of the amide followed by cyclization upon workup would deliver *exo*-**100e** and *endo*-**100e**.

It is proposed that SnCl₄•BINOL complex **125** serves as a chiral proton source to set the absolute stereochemistry of *exo*-**100e** and *endo*-**100e** by protonation of enolates **121** and *ent*-**121**. Enantioselective protonations promoted by (*R*)-BINOL•SnCl₄ complexes are well documented based on extensive studies by Yamamoto and coworkers. In these reports, it is suggested that (*R*)-BINOL•SnCl₄ serves as a chiral Lewis acid-assisted Brønsted acid (LBA) to effect protonation.¹⁴ In the Yamamoto examples, use of a less reactive stoichiometric achiral phenol is required to turnover the catalyst.^{14b} In the formation of pyrroloindolines **100e**, the active catalyst **125** might be regenerated from **126** by protonation with the amide proton of *exo*-**123** and *endo*-**123**, thereby affording **124**. These protonated iminium species are stable under the reaction conditions as identified by ¹H NMR and undergo cyclization to afford *exo*-**100e** and *endo*-**100e** during the work-up. Notably, resubjection of *exo*-**100e** to the reaction conditions cleanly regenerates iminium **124** without any erosion of ee, thus confirming the irreversibility of the protonation step.

2.4 CONCLUDING REMARKS

In summary, we have established a unique strategy for the direct preparation of enantioenriched pyrroloindolines by an (*R*)-BINOL•SnCl₄-catalyzed formal (3 + 2)

cycloaddition reaction. The transformation requires an equivalent of SnCl_4 but addition of (*R*)-BINOL creates such a large rate acceleration that the reaction can be completed with catalytic loadings of BINOL in excellent enantioselectivity. The method allows access to a variety of pyrroloindolines including new structural motifs such as aza-propellanes (**106g**). Although the reaction proceeds poorly with more sterically encumbered substrates, we have found that additional of catalytic MeOH greatly improves reactivity and enables access to phenylpyrroloindoline product **118**.

The formal (3 + 2) cycloaddition reaction has been exploited both in the development of new methodology and in total synthesis. Mechanistic studies of this reaction showed that the reaction occurs via a highly face-selective catalyst-controlled protonation and that cyclization of the resultant iminium intermediate only occurs upon work-up; these observations have respectively led to the development of a tandem conjugate addition/enantioselective protonation reaction (Chapter 3) and to the generation of indoline products by in situ iminium reduction.^{§,15} In addition, synthetic efforts using this reaction have culminated in the efficient total syntheses of two diketopiperazine-containing pyrroloindoline natural products lansai B¹⁶ and nocardioazine A.^{17,**} Further related research within the Reisman laboratory is focused on improving mechanistic understanding of the formal (3 + 2) cycloaddition reaction, application of the asymmetric protonation strategy to new methodology, and the synthesis of pyrroloindoline alkaloid natural products.

[§] This transformation was developed by Jane Ni, a graduate student in the Reisman lab.

^{**} Research directed toward these natural products has been conducted by Haoxuan Wang, a graduate student in the Reisman lab.

2.5 EXPERIMENTAL SECTION

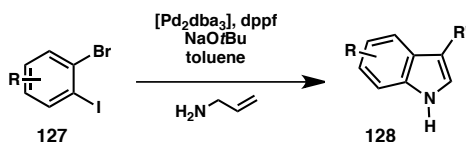
2.5.1 *Materials and Methods*

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, toluene, and hexanes were dried by passing through activated alumina columns. Dimethylformamide was dried over activated molecular sieves, dichloroethane was distilled over calcium hydride. Deuterated methylene chloride (CD_2Cl_2) for the experiments resubjecting the pyrroloindoline products to reaction conditions was dried by passing through a plug of activated alumina. All other commercially obtained reagents were used as received unless specifically indicated. EtAlCl_2 (neat) and 1 M SnCl_4 in DCM were purchased from Aldrich and (*R*)-BINOL was obtained from Alfa Aesar. (*R*)-6,6'-dibromo-BINOL (**102f**),¹⁸ (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102b**)¹⁹, TADDOL (**103**),²⁰ 3-phenylindole (**111**),²¹ and 1-methyl-3-phenylindole (**109**)²² were prepared according to literature procedures. 1-methyl-3-(phenylethynyl)indole (**115**),²³ (*R*)-3,3'-dianthryl-BINOL (**102e**),²⁴ (*R*)-3,3'-dimesityl-BINOL (**102c**)²⁵ and (*R*)-3,3'-di(triphenylsilyl)-BINOL (**102d**)²⁶ are known and were prepared by procedures adapted from the literature. 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.²⁷ using silica gel (particle size 0.032-0.063) purchased from Silicycle or pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Diastereomeric ratios were determined by integration of NMR spectra or HPLC or SFC analysis. 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 Mercury 300 (at 300 MHz and 75 MHz respectively), a Varian 400 (at 400 MHz and 100 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to internal chloroform (^1H , $\delta = 7.26$, ^{13}C , $\delta = 77.0$). 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}). Preparative HPLC was performed with either an Agilent 1100 or 1200 Series HPLC utilizing an Agilent Zorbax RX-SIL $5\mu\text{m}$ column (9.4 x 250 mm). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralcel AD or OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H and OJ-H columns (4.6 mm x 25 cm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected. HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility.

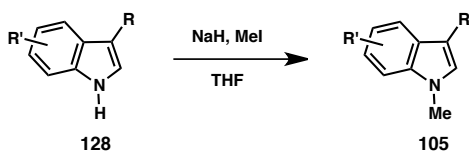
2.5.2 Substrate Synthesis

General Procedure A. Amination-Heck cascade for synthesis of indole derivatives.



Procedure was adapted from Jørgensen *et al.*²⁸ To a 50 mL Schlenk tube was added $[Pd_2dba_3]$, dppf, NaOtBu (20.8 mmol, 2.5 equiv) and toluene (10 mL). The mixture was stirred for 5 minutes, then the bromoiodide (8.3 mmol, 1.0 equiv) and allylamine (8.3 mmol, 1.0 equiv) were added. The tube was sealed, heated to 140 °C over 30 minutes and stirred at 140 °C for 21 h. The reaction was then cooled to room temperature, diluted with 40 mL hexanes, filtered through a plug of celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

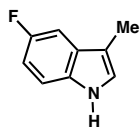
General Procedure B. N-methylation of indole derivatives.



In a flame-dried flask, the indole (1.7 mmol, 1.0 equiv) was dissolved in 11 mL THF. Sodium hydride (60% w/w, 2.5 mmol, 1.5 equiv) was added in one portion, then methyl iodide (3.4 mmol, 2.0 equiv) was added dropwise. The reaction was stirred at room temperature until consumption of starting material was observed by TLC. The reaction was diluted with ethyl acetate and the excess NaH was quenched with water. The organic layer was separated, and the aqueous layer was extracted 3× with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and

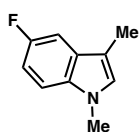
concentrated under reduced pressure. The crude residue was purified by flash chromatography.

5-Fluoro-3-methyl-1*H*-indole (**128b**).



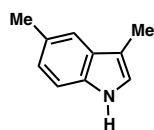
Prepared from 3.75 mmol of 2-bromo-4-fluoro-1-iodobenzene, 0.63 mol % $[\text{Pd}_2\text{dba}_3]$ and 2.5 mol % dppf using general procedure A. The product was purified by flash chromatography (10% ethyl acetate/hexanes) to yield 5-fluoro-3-methyl-1*H*-indole (**128b**, 0.22 g, 38% yield). Spectral data matches that reported in the literature.²⁸

5-Fluoro-1,3-dimethyl-1*H*-indole (**105b**).

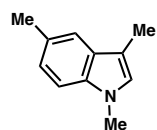


Prepared from 1.07 mmol of 5-fluoro-3-methyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (3% ethyl acetate/hexanes) to yield **105b** (0.97 g, 55% yield) as a pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.23 – 7.13 (m, 2H), 7.00 – 6.92 (m, 1H), 6.86 (s, 1H), 3.72 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.6, 132.4, 128.8, 127.2, 111.6, 109.8, 109.5, 100.8, 32.6, 9.6. IR (NaCl/thin film): 2918, 1581, 1493, 1457, 1423, 1225, 1062, 786 cm^{-1} ; HRMS (MM: ESI–APCI) calc'd for $[\text{M}+\text{H}]^+$ 164.0870, found 164.0873.

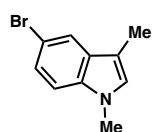
3,5-dimethyl-1*H*-indole (**128c**).



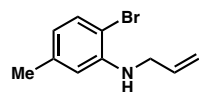
Prepared from 2.88 mmol of 2-bromo-1-iodo-4-methylbenzene,²⁹ 2.5 mol % $[\text{Pd}_2\text{dba}_3]$ and 10 mol % dppf using general procedure A. The product was purified by flash chromatography (5→13% ethyl acetate/hexanes) to yield 3,5-dimethyl-1*H*-indole (**128c**, 0.11 g, 14% yield). Spectral data matches that reported in the literature.²⁸

1,3,5-trimethyl-1*H*-indole (105c).

Prepared from 0.70 mmol of 3,5-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (2% ethyl acetate/hexanes) to yield **105c** (0.048 g, 43% yield) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.38 – 7.34 (m, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.05 (dd, J = 8.3, 1.4 Hz, 1H), 6.78 (s, 1H), 3.71 (s, 3H), 2.49 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.4, 128.8, 127.6, 126.6, 123.0, 118.6, 109.5, 108.7, 32.5, 21.5, 9.5. IR (NaCl/thin film): 2918, 1494, 1460, 1388, 1298, 1250, 1149, 1058, 885, 866, 784 cm^{-1} ; HRMS (MM: ESI–APCI) calc'd for $[\text{M}+\text{H}]^+$ 160.1121, found 160.1116.

5-Bromo-1,3-dimethyl-1*H*-indole (105d).

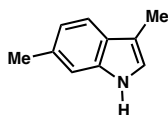
Prepared from 0.95 mmol of 5-bromo-3-methyl-1*H*-indole³⁰ using general procedure B. The product was purified by flash chromatography (5% ethyl acetate/hexanes) to yield **105d** (0.20 g, 90% yield) as a pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.70 (d, J = 1.5 Hz, 1H), 7.30 (dd, J = 8.6, 1.6 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 6.82 (s, 1H), 3.70 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.6, 130.3, 127.7, 124.1, 121.5, 111.9, 110.5, 109.7, 32.6, 9.4. IR (NaCl/thin film): 2918, 1563, 1479, 1422, 1279, 812, 785 cm^{-1} ; HRMS (APCI) calc'd for $[\text{M}+\text{H}]^+$ 224.0069, found 224.0070.

***N*-allyl-2-bromo-5-methylaniline (129).**

Procedure was adapted from Sørensen and Pombo-Villar.³¹ To a solution of 2-bromo-5-methylaniline (10.8 mmol, 1.0 equiv) in 29 mL THF at -78°C was added MeLi (2.9 M solution in dimethoxymethane, 11.8 mmol, 1.1 equiv), and stirred for 30 minutes. Allyl bromide was added dropwise, followed by

stirring at $-78\text{ }^{\circ}\text{C}$ for 10 minutes, then at room temperature for 5 hours. Then saturated NaHCO_3 (aq) solution was added, and the aqueous layer was extracted with ethyl acetate 3 $\times$. The combined organic layers were dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0 $\rightarrow$ 10% ethyl acetate/hexanes) to yield *N*-allyl-2-bromo-5-methylaniline (**129**, 1.63 g, 67% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.30 (d, $J = 8.0$ Hz, 1H), 6.46 (d, $J = 1.5$ Hz, 1H), 6.41 (ddd, $J = 8.0, 2.0, 0.6$ Hz, 1H), 5.97 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H), 5.31 (ddd, $J = 17.2, 3.3, 1.7$ Hz, 1H), 5.21 (dq, $J = 10.3, 1.5$ Hz, 1H), 4.41 (s, 1H), 3.83 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.4, 138.4, 134.7, 132.0, 118.8, 116.3, 112.4, 106.5, 46.2, 21.5. IR (NaCl/thin film): 3411, 2920, 1596, 1506, 1416, 1016, 921, 787 cm^{-1} . HRMS (MM: ESI–APCI) calc'd for $[\text{M}+\text{H}]^+$ 226.0226, found 226.0216.

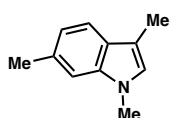
3,6-dimethyl-1*H*-indole (**128e**).



Procedure was adapted from Sørensen and Pombo-Villar.³¹ A solution of *N*-allyl-2-bromo-5-methylaniline (**129**, 1.6 mmol, 1.0 equiv), $\text{Pd}(\text{OAc})_2$ (0.16 mmol, 0.1 equiv), dppp (0.16 mmol, 0.1 equiv), Bu_4NCl (1.6 mmol, 1.0 equiv), and NaOAc (6.2 mmol, 4.0 equiv) in 24 mL DMF was heated to $120\text{ }^{\circ}\text{C}$ in a flask equipped with a reflux condenser for 16h. The reaction was cooled to room temperature, saturated NaHCO_3 (aq) solution and 100 mL water were added, and the aqueous layer was extracted with ethyl acetate 3 $\times$. The combined organic layers were dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5 $\rightarrow$ 10% ethyl acetate/hexanes) to yield 3,6-dimethyl-1*H*-indole (**128e**, 0.19 g, 85% yield) as a white powder. ^1H NMR (400 MHz, CDCl_3) δ 7.71 (br s, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.13–7.11 (m, 1H), 6.94 (dd, $J = 8.0$ Hz, 1.0 Hz, 1H), 6.87 (dd, $J =$

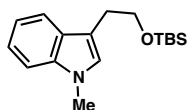
2.1 Hz, 1.1 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.7, 131.6, 126.2, 120.9, 120.8, 118.5, 111.6, 110.9, 21.7, 9.7. IR (NaCl/thin film): 3409, 2922, 1452, 1329, 1086, 908, 803, 733 cm^{-1} . HRMS (MM: ESI–APCI) calc'd for $[\text{M}+\text{H}]^+$ 146.0964, found 146.0970.

1,3,6-trimethyl-1*H*-indole (105e).



Prepared from 0.70 mmol of 3,6-dimethyl-1*H*-indole (**128e**) using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **105e** (62 mg, 56% yield) as a yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.45 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.94 (dd, J = 8.0, 0.7 Hz, 1H), 6.75 (d, J = 0.9 Hz, 1H), 3.70 (s, 3H), 2.50 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 137.4, 131.1, 126.5, 125.8, 120.2, 118.6, 109.9, 109.0, 32.4, 21.9, 9.6. IR (NaCl/thin film): 3027, 2917, 2860, 1625, 1478, 1388, 1369, 1328, 1248, 799 cm^{-1} ; HRMS (MM: ESI–APCI) calc'd for $[\text{M}+\text{H}]^+$ 160.1121, found 160.1114.

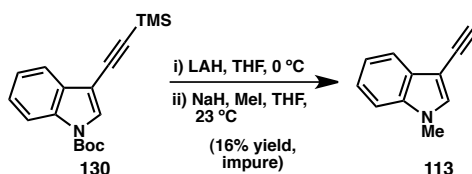
1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (105f).



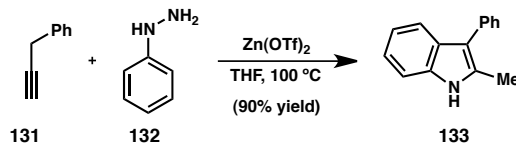
Prepared from 2.66 mmol of 3-*t*-butyldimethylsiloxyethyl-1*H*-indole³² using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **105f** (0.67 g, 87% yield) as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.63 (dt, J = 7.9, 1.0 Hz, 1H), 7.31 (dt, J = 8.2, 0.9 Hz, 1H), 7.26 – 7.23 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.13 (ddd, J = 7.9, 6.9, 1.0 Hz, 1H), 6.91 (s, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.02 (ddd, J = 7.9, 7.1, 0.8 Hz, 2H), 0.95 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.8, 128.1, 126.9, 121.4, 119.0, 118.6, 111.5, 109.1, 64.1, 32.5, 29.0, 26.0, 18.4, -5.3; IR (NaCl/thin film):

3056, 2954, 2929, 2857, 1472, 1251, 1095, 836, 737 cm^{-1} ; HRMS (ESI) calc'd for $[\text{M}+\text{H}]^+$ 290.1940, found 290.1933.

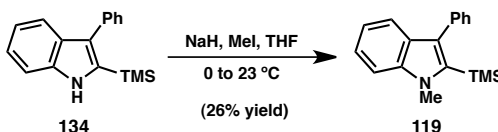
1-methyl-3-ethynylindole (**113**).



To a solution of 1-Boc-3-(trimethylsilyl)ethynylindole³³ (**130**, 290 mg, 0.930 mmol, 1.00 equiv) in 4.6 mL THF cooled to 0 °C in an ice bath was added LAH (2 M in THF, 1.1 mL, 2.2 mmol, 2.4 equiv). After 2 h stirring at 0 °C, the reaction mixture was subjected to a standard Fieser workup. The crude residue was then dried under hi-vacuum, then redissolved in 4.6 mL THF. NaH (60 wt % dispersion in oil, 56 mg, 1.4 mmol, 1.5 equiv) was then added and the reaction was then cooled to 0 °C in an ice bath, followed by addition of MeI (116 μL , 1.86 mmol, 2.00 equiv). The reaction mixture was then allowed to warm to room temperature and stirred for 3 hours, then cooled to 0 °C. MeOH was added to quench the reaction, followed by dilution with H_2O , and extraction with DCM (3 x). The combined organic layers were then dried (Na_2SO_4) and concentrated. The crude oil was subjected to silica gel column chromatography (0:100 to 5:95 EtOAc:hexanes) to yield 23.1 mg (16% yield containing impurities) of 1-methyl-3-ethynylindole (**113**) and 47.8 mg (23% yield) of a compound that is likely 1-methyl-3-((trimethylsilyl)ethynyl)indole. The ^1H NMR shifts observed for **113** vary slightly from the literature³⁴ and are thus listed herein. ^1H NMR (300 MHz, CDCl_3) δ 7.76 – 7.72 (m, 1H), 7.33 – 7.23 (m, 3H), 7.20 (ddd, J = 8.0, 6.4, 1.8 Hz, 1H), 3.75 (s, 3H), 3.21 (s, 1H).

2-methyl-3-phenylindole (133).

2-methyl-3-phenylindole (**133**) was prepared by a procedure adapted from Beller and coworkers.³⁵ A flame-dried 25 mL Schlenk tube was charged with $\text{Zn}(\text{OTf})_2$ (0.546 g, 1.50 mmol, 1.00 equiv) and flushed with argon. 4 mL THF, phenylhydrazine (**132**, 191 μL , 1.95 mmol, 1.30 equiv), and 3-phenyl-1-propyne (**131**, 187 μL , 1.50 mmol, 1.00 equiv) were added in that order and the Schlenk tube was then sealed and heated to $100\text{ }^\circ\text{C}$. After stirring at $100\text{ }^\circ\text{C}$ for 25.5 hours, the reaction mixture was allowed to cool to room temperature, and concentrated. The crude residue was purified by silica gel column chromatography to yield 282 mg (90% yield) of 2-methyl-3-phenylindole (**133**). Spectral data were in agreement with the literature.²¹

1-methyl-3-phenyl-2-(trimethylsilyl)indole (119).

A solution of 3-phenyl-2-(trimethylsilyl)indole³⁶ (**134**, 228 mg, 0.859 mmol, 1.00 equiv) in 20 mL THF was cooled to $0\text{ }^\circ\text{C}$ in an ice bath under argon, followed by addition of NaH (60 wt % dispersion in oil, 41 mg, 1.7 mmol, 2.0 equiv). After stirring 15 minutes at $0\text{ }^\circ\text{C}$, MeI (107 μL , 1.72 mmol, 2.00 equiv) was added and the reaction was allowed to warm to room temperature. After stirring 20 hours at room temperature, the reaction mixture was cooled to $0\text{ }^\circ\text{C}$ and quenched with saturated aqueous NH_4Cl then diluted with Et_2O . The organic layer was washed (saturated aqueous NaHCO_3 then brine), dried

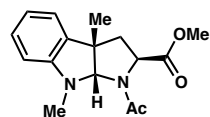
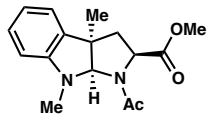
(Na₂SO₄), filtered, and concentrated. The crude residue was purified by column chromatography to yield 63 mg (26% yield) of 1-methyl-3-phenyl-2-(trimethylsilyl)indole (**119**). ¹H NMR (300 MHz, CDCl₃) δ 7.47 – 7.35 (m, 7H), 7.30 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 6.8, 1.1 Hz, 1H), 3.94 (s, 3H), 0.22 (s, 9H).

2.5.3 General Procedure C. Formal (3 + 2) Cycloaddition of Indoles and Acrylates

To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (*R*)-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of SnCl₄ (0.24 mmol, 1.20 equiv unless specifically indicated, 1 M in DCM), then stirred at room temperature. The reaction was quenched by diluting with 1 mL MeCN and 1 mL 1 M HCl, followed by addition of 5 mL H₂O. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with either saturated NaHCO_{3(aq)} or 1 M NaOH_(aq) (10 mL). The aqueous layer was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by flash chromatography.

2.5.4 Pyrroloindoline Products under General Procedure C

Pyrroloindoline 100b.

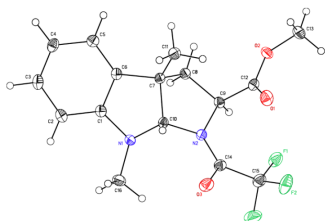
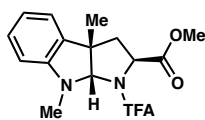
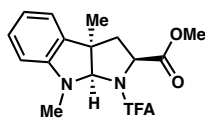
(a) *exo* diastereomer(b) *endo* diastereomer

Screen varying (*R*)-BINOL loading. All reactions were run at room temperature for 3 h in DCE with 1,3-dimethyl-1*H*-indole³⁷ (**75**, 0.2 mmol, 1 equiv), methyl 2-acetamidoacrylate³⁸ (**91a**, 0.2 mmol, 1 equiv) and SnCl₄ (1.2 equiv, 1 M in DCM) Purified by flash chromatography (0→50% ethyl acetate/hexanes). The diastereomeric ratio was determined by ¹H NMR analysis of the crude reaction mixture. The diastereomers were separated by flash chromatography (30→50% ethyl acetate/hexanes). The enantiomeric excess was determined for both diastereomers by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in hexanes, λ = 254 nm).

Exo diastereomer: pale yellow oil. t_R (major) = 9.5 min t_R (minor) = 6.2 min. ¹H NMR (400 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 7.10 – 7.01 (m, 1H), 6.95 (d, J = 7.3 Hz, 0.5H), 6.91 (d, J = 7.3 Hz, 0.5H), 6.68 (t, J = 7.4 Hz, 0.5H), 6.62 (t, J = 7.4 Hz, 0.5H), 6.43 (d, J = 7.8 Hz, 0.5H), 6.38 (d, J = 7.8 Hz, 0.5H), 5.47 (s, 0.5H), 5.04 (s, 0.5H), 4.43 (dd, J = 10.0, 1.9 Hz, 0.5H), 4.30 (dd, J = 9.7, 4.7 Hz, 0.5H), 3.73 (s, 1.5H), 3.66 (s, 1.5H), 2.98 (s, 1.5H), 2.80 (s, 1.5H), 2.44 (dd, J = 13.4, 10.0 Hz, 0.5H), 2.32 (dd, J = 13.3, 9.8 Hz, 0.5H), 2.22 (s, 0.5H), 2.18 (dd, J = 13.5, 2.0 Hz, 0.5H), 1.97 – 1.90 (m, 2H), 1.46 (s, 1.5H), 1.32 (s, 1.5H); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 172.8, 171.7, 171.5, 169.4, 149.4, 148.5, 134.2, 128.04, 128.02, 121.0, 120.8, 118.6, 117.6, 107.7, 107.1, 91.8, 90.8, 60.5, 59.6, 52.2, 51.8, 51.6, 49.2, 43.4, 41.0, 35.9, 33.8, 22.5, 22.3, 21.9; IR (NaCl/thin film): 2954, 2877,

1746, 1660, 1608, 1489, 1393, 1299, 1200, 1178, 744 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -69.7^\circ$ ($c = 0.85$, DCM); HRMS (FAB+) calc'd for $[\text{M}+\text{H}]^+$ 289.1552, found 289.1559.

Endo diastereomer: bright yellow oil. $t_{\text{R}}(\text{major}) = 4.0$ min $t_{\text{R}}(\text{minor}) = 4.7$ min. ^1H NMR (400 MHz, CDCl_3 ; compound exists as a 3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11 (t, $J = 7.6$ Hz, $1\text{H}^\S$), 7.06 (t, $J = 7.8$ Hz, 1H^*), 7.01 (d, $J = 7.1$ Hz, $1\text{H}^\S$), 6.96 (d, $J = 7.2$ Hz, 1H^*), 6.68 (t, $J = 7.4$ Hz, $1\text{H}^\S$), 6.61 (t, $J = 7.3$ Hz, 1H^*), 6.40 (d, $J = 7.8$ Hz, $1\text{H}^\S$), 6.32 (d, $J = 7.8$ Hz, 1H^*), 5.55 (s, 1H^*), 5.09 (s, $1\text{H}^\S$), 4.98 (dd, $J = 8.8, 5.8$ Hz, $1\text{H}^\S$), 4.46 (d, $J = 8.3$ Hz, 1H^*), 3.46 (s, $3\text{H}^\S$), 3.25 (s, 3H^*), 2.99 (s, 3H^*), 2.91 (s, $3\text{H}^\S$), 2.68 (d, $J = 13.6$ Hz, 1H^*), 2.44 – 2.16 (m, $1\text{H}^*, 5\text{H}^\S$), 2.05 (s, 3H^*), 1.42 (s, $3\text{H}^\S$), 1.41 (s, 3H^*); ^{13}C NMR (100 MHz, CDCl_3 ; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.4 § , 171.1*, 170.7*, 169.6 § , 150.6*, 149.0 § , 133.1 § , 132.4*, 128.7*, 128.6 § , 122.3*, 121.8 § , 118.0 § , 117.1*, 106.4 § , 105.6*, 91.1 § , 86.4*, 61.1*, 59.1 § , 52.3 § , 52.2*, 52.1 § , 50.8*, 42.6*, 41.7 § , 32.2*, 31.6 § , 24.7*, 22.8 § , 22.4*, 21.9 § ; IR (NaCl/thin film): 2953, 2869, 1740, 1656, 1610, 1493, 1407, 1302, 1236, 1204, 744 cm^{-1} ; $[\alpha]_{\text{D}}^{25} +146.5^\circ$ ($c = 0.79$, DCM) ; HRMS (FAB+) calc'd for $[\text{M}+\text{H}]^+$ 289.1552 , found 289.1549.

Pyrroloindoline 100c.(a) *exo* diastereomer(b) *endo* diastereomer

Prepared from 1,3-dimethyl-1*H*-indole **75** and methyl 2-trifluoroacetamidoacrylate³⁹ **91b** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 53.0 mg (77% yield) of **100c** in a 6:1 ratio of diastereomers (determined by ¹H NMR analysis of the purified product).

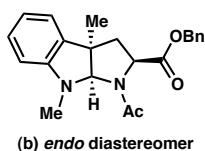
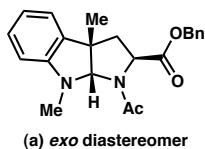
The diastereomers were separated by preparatory HPLC

(0→8% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil that crystallized upon standing in the fridge to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO₂, λ = 254 nm): *t*_R(major) = 2.8 min *t*_R(minor) = 2.4 min. ¹H NMR (400 MHz, CDCl₃; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.18 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.03 (d, *J* = 7.2 Hz, 1H*, 1H§), 6.82 (br s, *J* = 7.4 Hz, 1H§), 6.77 (t, *J* = 7.3 Hz, 1H*), 6.56 (br s, 1H§), 6.51 (d, *J* = 7.8 Hz, 1H*), 5.62 (s, 1H*), 5.34 (br s, 1H§), 4.72 (d, *J* = 9.2 Hz, 1H*), 4.44 (br s, 1H§), 3.82 (br s, 3H*), 3.77 (br s, 3H§), 3.08 (br s, 3H*), 2.87 (br s, 3H§), 2.60 (dd, *J* = 13.0, 9.9 Hz, 1H*), 2.55–2.44 (br m, 1H§), 2.37 (d, *J* = 12.7 Hz, 1H*), 2.13–2.00 (br m, 1H§), 1.51 (s, 3H§), 1.40 (s, 3H*); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.5§, 159.2* (q, *J*_{C-F} = 37.2 Hz), 149.4*, 149.2§, 134.2*§, 128.8*§, 121.5*§, 119.9§,

118.7*, 116.1* (q, $J_{\text{C-F}} = 288.4$ Hz), 109.4[§], 108.0*, 93.3*, 91.7[§], 61.3[§], 60.3*, 53.0*, 52.6[§], 49.2*[§], 44.0*, 40.6[§], 36.8*, 34.4[§], 23.5*, 22.8[§]; IR (NaCl/thin film): 2959, 1751, 1696, 1610, 1490, 1435, 1204, 1155, 988, 744 cm^{-1} ; melting point: 105.5 – 107.5 °C; $[\alpha]_{\text{D}}^{25} = -118.1^{\circ}$ ($c = 0.78$, DCM). HRMS (ESI) calc'd for $[\text{M}+\text{H}]^{+}$ 343.1270, found 343.1267.

Endo diastereomer: pale yellow oil. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.13 (t, $J = 7.7$ Hz, $1\text{H}^{\text{§}}$), 7.10 (t, $J = 7.7$ Hz, 1H^*), 7.04 (d, $J = 7.5$ Hz, $1\text{H}^{\text{§}}$), 6.98 (d, $J = 7.3$ Hz, 1H^*), 6.73 (t, $J = 7.4$ Hz, $1\text{H}^{\text{§}}$), 6.66 (t, $J = 7.4$ Hz, 1H^*), 6.43 (d, $J = 7.8$ Hz, $1\text{H}^{\text{§}}$), 6.37 (d, $J = 7.8$ Hz, 1H^*), 5.59 (s, 1H^*), 5.33 (s, $1\text{H}^{\text{§}}$), 5.07 (dd, $J = 9.4, 5.2$ Hz, $1\text{H}^{\text{§}}$), 4.74 (d, $J = 8.2$ Hz, 1H^*), 3.57 (s, $3\text{H}^{\text{§}}$), 3.16 (s, 3H^*), 3.05 (s, 3H^*), 2.80 (s, $3\text{H}^{\text{§}}$), 2.80 (d, $J = 12.7$ Hz, 1H^*), 2.42 (dd, $J = 13.3, 5.3$ Hz, $1\text{H}^{\text{§}}$), 2.37 (dd, $J = 12.9, 8.3$ Hz, 1H^*), 2.26 (dd, $J = 13.2, 9.7$ Hz, $1\text{H}^{\text{§}}$), 1.45 (s, 3H^*), 1.43 (s, $3\text{H}^{\text{§}}$); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.9*, 156.8* (q, $J_{\text{C-F}} = 36.9$ Hz), 150.4*, 148.5[§], 133.0[§], 131.8*, 129.1*, 128.7[§], 122.5*, 121.6[§], 118.6[§], 117.8*, 116.1* (q, $J_{\text{C-F}} = 288.7$ Hz), 106.9[§], 105.7*, 90.8[§], 88.5*, 60.3[§], 60.1*, 52.5*, 52.2[§], 50.4*[§], 42.9*, 41.1[§], 32.1*[§], 25.1*, 22.2[§]; IR (NaCl/thin film): 2954, 2923, 1741, 1694, 1608, 1494, 1435, 1206, 1147, 998, 860, 844, 742 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +201.5^{\circ}$ ($c = 0.11$, DCM). HRMS (ESI) calc'd for $[\text{M}+\text{H}]^{+}$ 343.1270, found 343.1278.

Pyrroloindoline 100d.

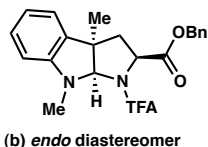
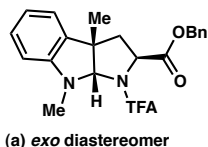
Prepared from 1,3-dimethyl-1*H*-indole **75** and benzyl 2-acetamidoacrylate⁴⁰ **91c** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The product **100d** was formed in a 2:1 ratio of diastereomers (determined by ¹H NMR analysis of the crude reaction mixture), and purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 41.3 mg

(57% yield) of the *exo* diastereomer and 17.3 mg (24% yield) of the *endo* diastereomer.

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 74% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO₂, λ = 254 nm): *t*_R(major) = 24.6 min *t*_R(minor) = 19.1 min. ¹H NMR (300 MHz, CDCl₃; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.43 – 7.29 (m, 5H*, 5H[§]), 7.19 – 7.09 (m, 1H*, 1H[§]), 7.01 (d, *J* = 7.3 Hz, 1H[§]), 6.96 (d, *J* = 7.3 Hz, 1H*), 6.76 (t, *J* = 8.4 Hz, 1H[§]), 6.70 (t, *J* = 7.4 Hz, 1H*), 6.50 (d, *J* = 8.2 Hz, 1H[§]), 6.46 (d, *J* = 8.0 Hz, 1H*), 5.54 (s, 1H*), 5.28 (d, *J* = 12.0 Hz, 1H*), 5.21 (d, *J* = 9.7 Hz, 1H[§]), 5.20 (s, 1H*, 1H[§]), 5.09 (s, 1H[§]), 4.51 (dd, *J* = 10.1, 2.1 Hz, 1H*), 4.45 (dd, *J* = 9.8, 4.8 Hz, 1H[§]), 3.06 (s, 3H*), 2.89 (s, 3H[§]), 2.53 (dd, *J* = 13.4, 10.0 Hz, 1H*), 2.42 (dd, *J* = 13.3, 9.7 Hz, 1H[§]), 2.31 (s, 3H[§]), 2.22 (dd, *J* = 13.5, 2.0 Hz, 1H*), 2.01 (dd, *J* = 13.3, 4.8 Hz, 1H[§]), 1.95 (s, 3H*), 1.49 (s, 3H[§]), 1.32 (s, 3H*); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 172.0[§], 171.6*, 170.0[§], 149.9*, 148.9[§], 135.7[§], 134.9*, 134.7*, 134.6[§], 128.8[§], 128.7*, 128.7[§], 128.5[§], 128.5*, 128.2*, 128.2[§], 121.5[§], 121.2*, 119.1[§], 118.1*, 108.1[§], 107.7*, 92.4[§], 91.4*, 67.6*, 66.9[§], 61.1*, 60.2[§], 52.3[§],

49.7*, 43.8*, 41.4[§], 36.5*, 34.3[§], 23.0[§], 22.7*, 22.7*, 22.4[§]; IR (NaCl/thin film): 3032, 2962, 2877, 1745, 1661, 1609, 1489, 1390, 1175, 1117, 744 cm⁻¹; [α]_D²⁵ = -66.9° (*c* = 0.98, DCM). HRMS (ESI) calc'd for [M+H]⁺ 365.1865, found 365.1875.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 82% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO₂, λ = 254 nm): *t*_R(major) = 11.1 min *t*_R(minor) = 12.6 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.36 – 7.28 (m, 3H*, 3H[§]), 7.23 – 7.20 (m, 2H[§]), 7.19 – 7.15 (m, 2H*), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H[§]), 7.08 (td, *J* = 7.7, 1.3 Hz, 1H*), 7.01 (dd, *J* = 7.3, 0.9 Hz, 1H[§]), 6.98 (dd, *J* = 7.3, 0.9 Hz, 1H*), 6.69 (td, *J* = 7.4, 0.9 Hz, 1H[§]), 6.64 (td, *J* = 7.4, 0.9 Hz, 1H*), 6.36 (d, *J* = 7.8 Hz, 1H[§]), 6.28 (d, *J* = 7.8 Hz, 1H*), 5.56 (s, 1H*), 5.09 (s, 1H[§]), 5.05 (dd, *J* = 9.0, 6.0 Hz, 1H[§]), 4.92 (d, *J* = 12.4 Hz, 1H[§]), 4.88 (d, *J* = 12.4 Hz, 1H*), 4.69 (d, *J* = 12.2 Hz, 1H*), 4.55 (d, *J* = 12.2 Hz, 1H*), 4.51 (dd, *J* = 8.5, 1.9 Hz, 1H*), 2.93 (s, 3H*), 2.81 (s, 3H[§]), 2.73 (dd, *J* = 12.8, 1.8 Hz, 1H*), 2.37 (dd, *J* = 13.0, 6.0 Hz, 1H[§]), 2.33 (dd, *J* = 12.8, 8.5 Hz, 1H*), 2.31 (s, 3H[§]), 2.26 (dd, *J* = 13.0, 9.0 Hz, 1H[§]), 2.05 (s, 3H*), 1.42 (s, 3H[§]), 1.41 (s, 3H*); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 170.8*, 170.5*, 169.6[§], 150.4*, 148.9[§], 135.5[§], 134.9*, 133.1[§], 132.5*, 128.8*, 128.6[§], 128.5*, 128.4[§], 128.4*, 128.2*, 128.1[§], 128.0[§], 122.4*, 121.8[§], 118.0[§], 117.2*, 106.5[§], 105.7*, 91.3[§], 86.5*, 67.3*, 66.7[§], 61.3*, 59.3[§], 52.3[§], 50.8*, 42.6*, 41.8[§], 32.3*, 31.6[§], 24.8*, 22.7[§], 22.5*, 21.9[§]; IR (NaCl/thin film): 2956, 1741, 1656, 1608, 1493, 1404, 1301, 1219, 1194, 1152, 1105, 992, 743 cm⁻¹; [α]_D²⁵ = +114.4° (*c* = 0.57, DCM). HRMS (ESI) calc'd for [M+H]⁺ 365.1865, found 365.1862.

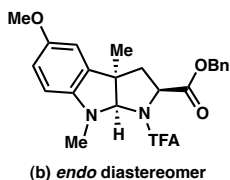
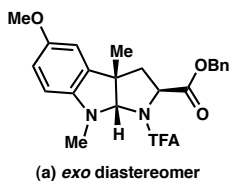
Pyrroloindoline 100e.

Prepared from 1,3-dimethyl-1*H*-indole (**75**, 0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate⁴¹ (**91d**, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→8% ethyl acetate/hexanes) to yield 54 mg (86% yield) of **100e** in a 4:1 ratio of diastereomers (determined by NMR analysis of the crude reaction mixture). The diastereomers were separated by flash chromatography (5→8% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO₂, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94%. t_R (major) = 12.5 min t_R (minor) = 10.7 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.53–7.36 (m, 5H*, 5H[§]), 7.23 (br t, J = 7.6 Hz, 1H*, 1H[§]), 7.11 (br d, J = 6.7 Hz, 1H[§]), 7.07 (br d, J = 7.2 Hz, 1H*), 6.93 – 6.86 (m, 1H[§]), 6.83 (br t, J = 7.3 Hz, 1H*), 6.64 (br d, J = 7.3 Hz, 1H[§]), 6.57 (br d, J = 7.8 Hz, 1H*), 5.69 (s, 1H*), 5.42 (s, 1H[§]), 5.36 – 5.21 (m, 2H*, 2H[§]), 4.82 (br d, J = 9.2 Hz, 1H*), 4.57 (m, 1H[§]), 3.14 (br s, 3H*), 2.94 (br s, 3H[§]), 2.60 (br dd, J = 13.3, 9.7 Hz, 1H*), 2.60 – 2.52 (m, 1H[§]), 2.41 (br d, J = 14.7 Hz, 1H*), 2.12 (br dd, J = 12.7, 6.0 Hz, 1H[§]), 1.54 (s, 3H[§]), 1.34 (s, 3H*); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 171.9*, 169.6[§], 158.9 (q, J_{C-F} = 37.0 Hz)*, 157.3 (q, J_{C-F} = 38.1 Hz)[§], 149.2*, 149.0[§], 135.1[§], 134.5*, 134.2*, 134.0[§], 128.6*, 128.6*, 128.5*, 128.4[§], 128.2[§], 128.1[§], 121.3*, 119.8[§], 188.5*, 116.0 (q, J_{C-F} =

288.6 Hz)*, 109.3[§], 107.8*, 93.1*, 91.6[§], 67.8*, 67.1[§], 61.2[§], 60.2 (q, $J_{\text{C-F}} = 2.44$ Hz)*, 52.9[§], 49.0*, 43.6*, 40.2[§], 36.5*, 34.2[§], 23.1*, 22.5[§]; IR (NaCl/thin film): 3034, 2966, 1747, 1695, 1610, 1490, 1456, 1432, 1188, 1156, 745 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -90.1^\circ$ (c = 1.11, DCM); HRMS (FAB+) calc'd for $[\text{M}+\text{H}]^+$ 419.1583, found 419.1562.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 91%. t_{R} (major) = 5.8 min t_{R} (minor) = 5.0 min. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 10.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.43 – 7.30 (m, 3H*, 3H[§]) 7.22 (dd, $J = 6.8, 2.8$ Hz, 1H[§]), 7.20–7.09 (m, 2H*, 1H[§]), 7.04 (d, $J = 7.3$ Hz, 1H[§]), 7.00 (d, $J = 7.3$ Hz, 1H*), 6.78 – 6.72 (m, 1H[§]), 6.68 (t, $J = 7.4$ Hz, 1H*), 6.36 (d, $J = 7.8$ Hz, 1H[§]), 6.27 (d, $J = 7.8$ Hz, 1H*), 5.60 (s, 1H*), 5.32 (s, 1H[§]), 5.14 (dd, $J = 9.5, 4.9$ Hz, 1H[§]), 5.04 (d, $J = 12.4$ Hz, 1H[§]), 4.94 (d, $J = 12.4$ Hz, 1H[§]), 4.79 (d, $J = 8.1$ Hz, 1H*), 4.63 (d, $J = 12.1$ Hz, 1H*), 4.36 (d, $J = 12.1$ Hz, 1H*), 2.95 (s, 3H*), 2.85 (d, $J = 12.9$ Hz, 1H*), 2.65 (s, 3H[§]), 2.46 (dd, $J = 13.3, 5.3$ Hz, 1H[§]), 2.39 (dd, $J = 13.0, 8.4$ Hz, 1H*), 2.28 (dd, $J = 13.3, 9.7$ Hz, 1H[§]), 1.46 (s, 3H*), 1.43 (s, 3H[§]); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 10.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.3[§], 169.2*, 156.9 (q, $J_{\text{C-F}} = 36.7$ Hz)[§], 150.3*, 148.5[§], 135.2[§], 134.6*, 133.1[§], , 131.8*, 129.1*, 128.7[§], 128.5[§], 128.44*, 128.40*, 128.3*, 128.2[§], 122.5*, 121.6[§], 118.6[§], 117.7*, 116.1 (q, $J=288.8$)*, 107.0[§], 105.9*, 90.9[§], 88.6*, 67.6*, 67.2[§], 60.5[§], 60.3 (q, $J_{\text{C-F}} = 3.1$ Hz)* , 52.2[§], 50.4*, 42.9*, 41.1[§], 32.0*, 29.7[§], 25.2*, 22.3[§]; IR (NaCl/thin film): 3034, 2960, 1752, 1741, 1697, 1609, 1494, 1442, 1211, 1149, 742 cm^{-1} ; $[\alpha]_{\text{D}}^{25} +187.7^\circ$ (c = 0.78, DCM) ; HRMS (FAB+) calc'd for $[\text{M}+\text{H}]^+$ 418.1504, found 418.1517.

Pyrroloindoline 106a.

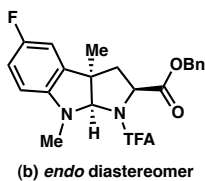
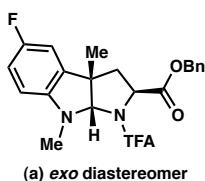
Prepared from 5-methoxy-1,3-dimethyl-1*H*-indole⁴² and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 83.1 mg (93% yield) of **106a** in a 3:1 ratio of diastereomers (determined by HPLC analysis of the purified product). The diastereomers were

separated by preparatory HPLC (0→10% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 10% IPA in hexanes, $\lambda = 254$ nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93%. t_R (major) = 11.3 min t_R (minor) = 9.9 min. ^1H NMR (400 MHz, CDCl_3 ; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.46 – 7.29 (m, 5H*, 5H§), 6.72 (d, $J = 8.4$ Hz, 1H*, 1H§), 6.63 (d, $J = 13.4$ Hz, 1H*, 1H§), 6.55 (d, $J = 8.4$ Hz, 1H§), 6.44 (d, $J = 8.5$ Hz, 1H*), 5.53 (br s, 1H*), 5.24 (br s, 2H*, 1H§), 5.19 (br s, 2H§), 4.76 (br d, $J = 9.3$ Hz, 1H*), 4.44 (t, $J = 7.8$ Hz, 1H§), 3.75 (br s, 3H*, 3H§), 3.04 (br s, 3H*), 2.86 (br s, 3H§), 2.61 – 2.48 (m, 1H*, 1H§), 2.31 (d, $J = 13.4$ Hz, 1H*), 2.09 – 1.99 (m, 1H§), 1.45 (br s, 3H§), 1.26 (br s, 3H*); ^{13}C NMR (100 MHz, CDCl_3 ; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.0* (q, $J_{\text{C-H}} = 36.8$ Hz), 154.7§, 153.6*, 143.7*§, 135.8§, 135.8*, 135.2§, 134.6*, 128.8§, 128.8*, 128.7*, 128.6§, 128.4§, 128.3*, 116.1* (q, $J_{\text{C-F}} = 288.6$ Hz), 113.4§, 113.1*, 111.5*, 109.0*, 108.8§, 94.2*, 92.4§, 68.1*, 67.3§, 61.2§, 60.4*, 55.9*, 53.6§, 49.3§, 43.8*, 39.9§, 38.1*,

36.9[§], 23.5[§], 23.4^{*}; IR (NaCl/thin film): 2963, 2833, 1748, 1694, 1497, 1432, 1156, 1030, 991, 754 cm⁻¹; [α]_D²⁵ = -78.1° (c 1.07, DCM); HRMS (ESI) calc'd for [M+H]⁺ 449.1683, found 449.1676.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 92%. t_R (major) = 6.6 min t_R (minor) = 7.4 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.37 – 7.29 (m, 3H*, 3H[§]), 7.24 – 7.21 (m, 2H[§]), 7.19 – 7.12 (m, 2H*), 6.68 (dd, J = 8.4, 2.5 Hz, 1H*, 1H[§]), 6.67 (d, J = 2.5 Hz, 1H[§]), 6.63 (d, J = 2.5 Hz, 1H*), 6.31 – 6.26 (m, 1H[§]), 6.19 (d, J = 8.4 Hz, 1H*), 5.57 (s, 1H*), 5.22 (br d, J = 1.8 Hz, 1H[§]), 5.13 (dd, J = 9.7, 5.3 Hz, 1H[§]), 5.07 (d, J = 12.3 Hz, 1H[§]), 4.97 (d, J = 12.3 Hz, 1H[§]), 4.78 (d, J = 8.4 Hz, 1H*), 4.66 (d, J = 12.1 Hz, 1H*), 4.46 (d, J = 12.1 Hz, 1H*), 3.75 (s, 3H[§]), 3.72 (s, 3H*), 2.92 (s, 3H*), 2.81 (d, J = 13.0 Hz, 1H*), 2.59 (d, J = 1.3 Hz, 3H[§]), 2.45 (dd, J = 13.3, 5.3 Hz, 1H[§]), 2.36 (dd, J = 13.0, 8.4 Hz, 1H*), 2.26 (dd, J = 13.3, 9.7 Hz, 1H[§]), 1.44 (s, 3H*), 1.40 (s, 3H[§]); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4[§], 169.1*, 156.9* (q, J_{C-F} = 36.7 Hz), 153.4[§], 152.8*, 144.7*, 142.7[§], 135.3[§], 134.7*, 134.5[§], 133.2*, 128.5*, 128.4*, 128.3*, 128.3[§], 128.1[§], 116.2* (q, J_{C-F} = 288.8 Hz), 113.5*, 112.8[§], 110.0*, 109.4[§], 107.7[§], 106.4*, 91.6[§], 89.4*, 67.7*, 67.2[§], 60.5[§], 60.2*, 56.0*, 56.9[§], 52.2[§], 50.6*, 42.8*, 40.8[§], 32.6*, 32.0[§], 25.1*, 22.2[§]; IR (NaCl/thin film): 2957, 1750, 1697, 1500, 1446, 1282, 1210, 1157, 1031, 994, 850 cm⁻¹; [α]_D²⁵ = +162.4° (c 1.41, DCM); HRMS (ESI) calc'd for [M+H]⁺ 449.1683, found 449.1682.

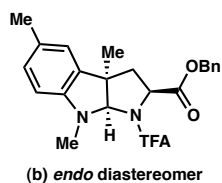
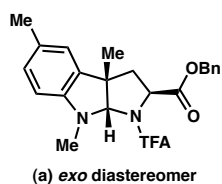
Pyrroloindoline 106b.

Prepared from 5-fluoro-1,3-dimethyl-1*H*-indole **105b** and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→12% ethyl acetate/hexanes) to yield 53.0 mg (61% yield) of **106b** in a 3:1 ratio of diastereomers (determined by ^1H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→8% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, $\lambda = 254$ nm).

Exo diastereomer: pale yellow oil. The ee was determined to be 93%. $t_{\text{R}}(\text{major}) = 14.7$ min $t_{\text{R}}(\text{minor}) = 18.0$ min. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 2.3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H^* , $5\text{H}^{\S}$), 6.85 (br t, $J = 7.8$ Hz, 1H^* , $1\text{H}^{\S}$), 6.75 (br s, $1\text{H}^{\S}$), 6.71 (br d, $J = 7.8$ Hz, 1H^*), 6.50 (br s, $1\text{H}^{\S}$), 6.39 (dd, $J = 8.4, 3.8$ Hz, 1H^*), 5.58 (br s, 1H^*), 5.34 – 5.16 (m, 2H^* , $3\text{H}^{\S}$), 4.75 (br d, $J = 9.3$ Hz, 1H^*), 4.47 (br t, $J = 6.8$ Hz, $1\text{H}^{\S}$), 3.04 (br s, 3H^*), 2.85 (br s, $3\text{H}^{\S}$), 2.55 (dd, $J = 13.2, 9.9$ Hz, 1H^*), 2.55 – 2.45 (m, $1\text{H}^{\S}$), 2.31 (br d, $J = 13.4$ Hz, 1H^*), 2.10 – 1.97 (m, $1\text{H}^{\S}$), 1.45 (br s, $3\text{H}^{\S}$), 1.24 (s, 3H^*); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 2.3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.7 § , 159.1* (q, $J_{\text{C-F}} = 37.1$ Hz), 157.0* (d, $J_{\text{C-F}} = 236.5$ Hz), 145.6*, 145.4 § , 135.7* (d, $J_{\text{C-F}} = 7.3$ Hz), 135.1 § , 134.6*, 128.9*, 128.8*, 128.7*, 128.6 § , 128.5 § , 128.4 § , 116.2* (q, $J_{\text{C-F}} = 267.0$ Hz), 114.9 § , 114.7* (d, $J_{\text{C-F}} = 23.0$ Hz), 110.5 § , 109.3* (d, $J_{\text{C-F}} = 24.3$ Hz), 108.6* (d, $J_{\text{C-F}} = 7.8$ Hz), 93.9*,

92.2[§], 68.2*, 67.5[§], 61.3[§], 60.3*, 53.2[§], 49.2*, 43.7*, 40.1[§], 37.6*, 35.6[§], 23.3*, 22.9[§]; IR (NaCl/thin film): 2966, 1748, 1698, 1495, 1434, 1350, 1270, 1157, 994, 843 cm⁻¹; [α]_D²⁵ = -81.7° (c 1.14, DCM); HRMS (ESI) calc'd for [M+H]⁺ 437.1483, found 437.1476.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R (major) = 9.1 min t_R (minor) = 10.5 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.37 – 7.30 (m, 3H*, 3H[§]), 7.24 – 7.20 (m, 2H[§]), 7.18 – 7.12 (m, 2H*), 6.83 – 6.74 (m, 1H*, 2H[§]), 6.71 (dd, J = 8.0, 2.6 Hz, 1H*), 6.23 (dd, J = 8.5, 4.0 Hz, 1H[§]), 6.14 (dd, J = 8.5, 4.0 Hz, 1H*), 5.60 (s, 1H*), 5.29 (d, J = 1.7 Hz, 1H[§]), 5.14 (dd, J = 9.6, 5.0 Hz, 1H[§]), 5.06 (d, J = 12.2 Hz, 1H[§]), 4.97 (d, J = 12.2 Hz, 1H[§]), 4.79 (d, J = 8.5 Hz, 1H*), 4.70 (d, J = 12.0 Hz, 1H*), 4.50 (d, J = 12.1 Hz, 1H*), 2.93 (s, 3H*), 2.78 (d, J = 13.1 Hz, 1H*), 2.60 (d, J = 1.3 Hz, 3H[§]), 2.45 (dd, J = 13.3, 5.0 Hz, 1H[§]), 2.37 (dd, J = 13.1, 8.5 Hz, 1H*), 2.26 (dd, J = 13.4, 9.7 Hz, 1H[§]), 1.44 (s, 3H*), 1.41 (s, 3H[§]); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.2[§], 169.0*, 156.9* (q, J_{C-F} = 36.7 Hz), 156.3* (q, J_{C-F} = 235.3 Hz), 146.5*, 144.7[§], 135.2[§], 134.5*, 133.3* (d, J_{C-F} = 7.2 Hz), 128.5*, 128.4*, 128.2[§], 116.1* (q, J_{C-F} = 288.6 Hz), 115.0* (d, J_{C-F} = 23.0 Hz), 114.5[§] (d, J_{C-F} = 23.1 Hz), 110.2* (d, J_{C-F} = 24.4 Hz), 109.6* (d, J_{C-F} = 24.6 Hz), 107.3[§] (d, J_{C-F} = 7.7 Hz), 106.0* (d, J_{C-F} = 7.9 Hz), 91.3[§], 89.1*, 67.8*, 67.3[§], 60.4[§], 60.2*, 52.2[§], 50.4*, 42.8[§], 40.9[§], 32.4*, 31.5[§], 25.1*, 22.3[§]; IR (NaCl/thin film): 2961, 1749, 1698, 1498, 1439, 1270, 1207, 1157, 995, 852, 752 cm⁻¹; [α]_D²⁵ = +156.8° (c 1.16, DCM); HRMS (ESI) calc'd for [M+H]⁺ 437.1483, found 437.1490.

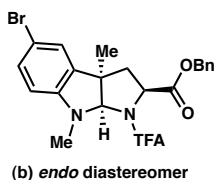
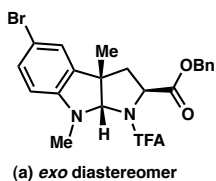
Pyrroloindoline 106c.

Prepared from 5-methyl-1,3-dimethyl-1*H*-indole (**105c**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 72.9 mg (84% yield) of **106c** in a 5:1 ratio of diastereomers (determined by ¹H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94% by chiral SFC analysis (OJ-H, 2.5 mL/min, 2% IPA in CO₂, λ = 254 nm): *t*_R(major) = 20.5 min *t*_R(minor) = 16.6 min. ¹H NMR (400 MHz, CDCl₃; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 (br s, 5H*, 5H§), 6.97 (br d, *J* = 7.7 Hz, 1H*, 1H§), 6.85 (br s, 1H§), 6.81 (br s, 1H*), 6.50 (br d, *J* = 7.6 Hz, 1H§), 6.42 (br d, *J* = 7.9 Hz, 1H*), 5.56 (br s, 1H*), 5.32 – 5.15 (br m, 2H*, 3H§), 4.76 (br d, *J* = 9.3 Hz, 1H*), 4.47 (br t, *J* = 7.5 Hz, 1H§), 3.05 (br s, 3H*), 2.87 (br s, 3H§), 2.61 – 2.46 (m, 1H*, 1H§), 2.30 (d, *J* = 21.3 Hz, 1H*), 2.27 (s, 3H*, 3H§), 2.09 – 1.98 (br m, 1H§), 1.45 (br s, 3H§), 1.26 (s, 3H§); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.1* (q, *J*_{C-F} = 36.8 Hz), 157.7§ (q, *J*_{C-F} = 37.9 Hz), 147.3*§, 135.2§, 134.6*, 134.5*, 134.4§, 129.7§, 129.2§, 129.0*, 128.8*, 128.8*, 128.7*, 128.6*, 128.4*, 128.2§, 122.3*§, 116.1* (q, *J*_{C-F} = 288.7 Hz), 110.0§, 108.2*, 93.8*, 92.1§, 68.0*, 67.3§, 61.4§, 60.4*, 53.3§, 49.2*, 43.9*, 40.2§, 37.4*, 35.6§, 23.4*, 23.2§, 20.7*§; IR (NaCl/thin film): 2965, 1748, 1697, 1499, 1456, 1433, 1348,

1194, 1153, 992, 754 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -87.1^{\circ}$ (c 0.90, DCM); HRMS (APCI) calc'd for $[\text{M}+\text{H}]^{+}$ 433.1734, found 433.1713.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 91% by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 6.5$ min $t_{\text{R}}(\text{minor}) = 7.3$ min. ^1H NMR (300 MHz, CDCl_3 ; compound exists as a 6.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 – 7.29 (m, 3H^* , $3\text{H}^{\S}$), 7.23 – 7.18 (m, $2\text{H}^{\S}$), 7.18 – 7.10 (m, 2H^*), 6.96 – 6.84 (m, 1H^* , $2\text{H}^{\S}$), 6.81 (br s, 1H^*), 6.27 (d, $J = 7.9$ Hz, $1\text{H}^{\S}$), 6.18 (d, $J = 7.9$ Hz, 1H^*), 5.57 (s, 1H^*), 5.25 (br d, $J = 1.9$ Hz, $1\text{H}^{\S}$), 5.12 (dd, $J = 9.6, 5.4$ Hz, $1\text{H}^{\S}$), 5.05 (d, $J = 12.4$ Hz, $1\text{H}^{\S}$), 4.94 (d, $J = 12.2$ Hz, $1\text{H}^{\S}$), 4.78 (d, $J = 8.4$ Hz, 1H^*), 4.63 (d, $J = 12.2$ Hz, 1H^*), 4.41 (d, $J = 12.2$ Hz, 1H^*), 2.92 (s, 3H^*), 2.82 (d, $J = 13.0$ Hz, 1H^*), 2.61 (d, $J = 1.4$ Hz, $3\text{H}^{\S}$), 2.44 (dd, $J = 13.3, 5.3$ Hz, $1\text{H}^{\S}$), 2.37 (dd, $J = 13.0, 8.4$ Hz, 1H^*), 2.26 (s, $3\text{H}^{\S}$), 2.23 (s, 3H^*), 1.44 (s, 3H^*), 1.41 (s, $3\text{H}^{\S}$); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 6.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4 § , 169.2*, 156.9* (q, $J_{\text{C-F}} = 36.6$ Hz), 148.2*, 135.3 § , 134.7*, 133.3 § , 132.0*, 129.3*, 128.9 § , 128.5 § , 128.5*, 128.4*, 128.3 § , 128.2*, 128.1 § , 126.9* § , 123.2*, 122.5 § , 116.2* (q, $J_{\text{C-F}} = 288.8$ Hz), 107.0 § , 105.9*, 91.3 § , 89.0*, 67.6*, 67.2 § , 60.5 § , 60.2*, 52.2 § , 50.4*, 42.9*, 41.1 § , 32.2*, 31.4 § , 25.2* § , 22.2 § , 20.7*; IR (NaCl/thin film): 2958, 1752, 1698, 1619, 1505, 1443, 1210, 1158, 995, 851, 752 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +176.4^{\circ}$ (c 0.97, DCM); HRMS (ESI) calc'd for $[\text{M}+\text{H}]^{+}$ 433.1734, found 433.1737.

Pyrroloindoline 106d.

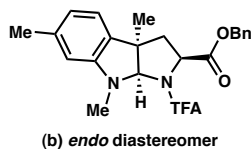
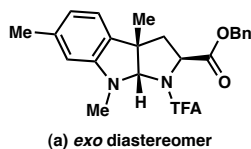
Prepared from 5-bromo-1,3-dimethyl-1*H*-indole (**105d**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C, in DCE with 1.6 equivalents SnCl_4 . The reaction was allowed to run for 57 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 50 mg (51% yield) of **106d** in a 3:1 ratio of diastereomers (determined by ^1H NMR analysis of the pure product).

The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes).

Exo diastereomer: The enantiomeric excess was determined to be 87% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, $\lambda = 254$ nm): t_{R} (major) = 14.7 min t_{R} (minor) = 12.5 min. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H*, 5H §), 7.24 (br d, $J = 8.3$ Hz, 1H*, 1H §), 7.11 (br s, 1H §), 7.05 (br s, 1H*), 6.41 (br d, $J = 7.1$ Hz, 1H §), 6.35 (br d, $J = 8.3$ Hz, 1H*), 5.60 (br s, 1H*), 5.34 (br s, 1H §), 5.28 – 5.15 (m, 2H*, 2H §), 4.74 (br d, $J = 9.0$ Hz, 1H*), 4.50 (br t, $J = 7.0$ Hz, 1H §), 3.03 (br s, 3H*), 2.83 (br s, 3H §), 2.53 (br dd, $J = 12.9, 10.2$ Hz, 1H*), 2.47 (br t, $J = 11.1$ Hz, 1H §), 2.30 (br d, $J = 13.4$ Hz, 1H*), 2.02 (br dd, $J = 12.2, 6.5$ Hz, 1H §), 1.45 (br s, 1H §), 1.23 (br s, 3H*); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.6 § , 159.18 (q, $J_{\text{C-F}} = 37.1$ Hz)*, 157.42 (d, $J_{\text{C-F}} = 39.7$ Hz) § , 148.4*, 148.0 § , 136.4*, 136.2 § , 135.0 § , 134.5*, 131.5 § , 131.4*, 128.9*, 128.8*, 128.7*, 128.4 § , 124.7*, 116.0 (q, $J_{\text{C-F}} = 288.5$ Hz)*, 111.5 § , 110.5*, 110.2 § , 109.4*, 93.1*, 91.5 § , 68.2*, 67.5 § , 61.4 § , 60.2*, 52.9 § , 49.1*, 43.7*, 40.4 § , 36.7*, 33.9 § , 23.2*, 22.3 § ; IR (NaCl/thin film):

3034, 2965, 2931, 1747, 1698, 1602, 1489, 1205, 1154, 806, 751 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -86.4^{\circ}$ (c = 0.60, DCM); HRMS (FAB+) calc'd for $[\text{M}+\text{H}]^{+}$ 498.0589, found 498.0576.

Endo diastereomer: The enantiomeric excess was determined to be 85% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 7.3$ min $t_{\text{R}}(\text{minor}) = 8.1$ min. ^1H NMR (400 MHz, CDCl_3 ; compound exists as a 12.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 – 7.30 (m, 3H*, 3H §), 7.23 – 7.13 (m, 3H*, 3H §), 7.11 (s, 1H §), 7.08 (s, 1H*), 6.19 (d, $J = 8.5$ Hz, 1H §), 6.13 (d, $J = 8.3$ Hz, 1H*), 5.59 (s, 1H*), 5.33 (s, 1H §), 5.14 (dd, $J = 10.0, 4.9$ Hz, 1H §), 5.06 (d, $J = 11.9$ Hz, 1H §), 4.93 (dd, $J = 11.9$ Hz, 1H §), 4.79 (d, $J = 8.4$ Hz, 1H*), 4.64 (d, $J = 12.0$ Hz, 1H*), 4.56 (d, $J = 12.0$, 1H*), 2.94 (s, 3H*), 2.78 (d, $J = 13.2$ Hz, 1H*), 2.61 (s, 3H §), 2.45 (dd, $J = 13.7, 3.9$ Hz, 1H §), 2.37 (dd, $J = 13.1, 8.4$ Hz, 1H*), 2.26 (dd, $J = 14.3, 9.9$ Hz, 1H §), 1.44 (s, 3H*), 1.41 (s, 3H §); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 12.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.0*, 156.9 (q, $J_{\text{C-F}} = 37.0$ Hz)*, 149.4*, 134.4*, 134.2*, 131.8*, 131.4 § , 125.5*, 124.9 § , 116.1(q, $J_{\text{C-F}} = 288.6$ Hz)*, 108.9*, 108.3 § , 107.5 § , 107.3*, 90.6 § , 88.5*, 67.9*, 67.4 § , 60.4 § , 60.2*, 50.4*, 42.8*, 41.1 § , 32.1*, 25.3*, 22.5 § ; IR (NaCl/thin film): 3034, 2962, 2930, 1749, 1698, 1602, 1493, 1442, 1261, 1211, 1151, 804, 750 cm^{-1} ; $[\alpha]_{\text{D}}^{25} + 156.3^{\circ}$ (c = 0.24, DCM) ; HRMS (FAB+) calc'd for $[\text{M}+\text{H}]^{+}$ 498.0589, found 498.0606.

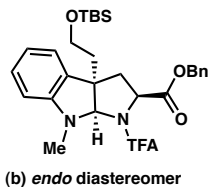
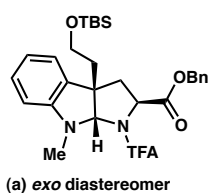
Pyrroloindoline 106e.

Prepared from 6-methyl-1,3-dimethyl-1*H*-indole (**105e**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 6 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 78.3 mg (91% yield) of **106e** in a 4:1 ratio of diastereomers (determined by ^1H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, $\lambda = 254$ nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94%. $t_{\text{R}}(\text{major}) = 14.5$ min $t_{\text{R}}(\text{minor}) = 12.9$ min. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 (br s, 5H*, 5H §), 6.93 (br d, $J = 7.1$ Hz, 1H §), 6.89 (br d, $J = 7.4$ Hz, 1H*), 6.65 (br d, $J = 6.8$ Hz, 1H §), 6.58 (br d, $J = 7.3$ Hz, 1H*), 6.42 (br s, 1H §), 6.35 (br s, 1H*), 5.60 (br s, 1H*), 5.32 (br s, 1H §), 5.29 – 5.14 (m, 2H*, 2H §), 4.76 (br d, $J = 9.2$ Hz, 1H*), 4.50 (br t, $J = 7.2$ Hz, 1H §), 3.07 (br s, 3H*), 2.88 (br s, 3H §), 2.61 – 2.42 (m, 1H*, 1H §), 2.32 (br s, $J = 5.8$ Hz, 4H*, 3H §), 2.10 – 1.98 (m, 1H §), 1.46 (s, 3H §), 1.27 (s, 3H*); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.1*, 169.9 § , 159.2* (q, $J_{\text{C-F}} = 37.0$ Hz), 157.7 § (q, $J_{\text{C-F}} = 38.4$ Hz), 149.6*, 149.5 § , 139.0 § , 138.8*, 135.2 § , 134.7*, 131.7*, 131.4 § , 128.9*, 128.8*, 128.7*, 128.6*, 128.5 § , 128.4 § , 121.3 § , 121.2*, 120.7 § , 119.3*, 116.1* (q, $J_{\text{C-F}} = 288.4$ Hz), 116.0 § (q, $J_{\text{C-F}} = 286.5$ Hz), 110.5 § , 108.9*, 93.6*,

92.0[§], 68.1*, 67.4[§], 61.5[§], 60.5*, 52.9[§], 49.0*, 43.9*, 40.4[§], 36.8*, 34.7[§], 23.5*, 23.0[§], 21.7*[§]; IR (NaCl/thin film): 2964, 1748, 1697, 1616, 1499, 1456, 1423, 1160, 1004, 752 cm⁻¹; $[\alpha]_D^{25} = -85.6^\circ$ (*c* 0.93, DCM); HRMS (EI+) calc'd for M⁺ 432.1661, found 432.1663.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R (major) = 7.8 min t_R (minor) = 8.3 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.38 – 7.29 (m, 3H*, 3H[§]), 7.21 (dd, *J* = 6.6, 2.9 Hz, 2H[§]), 7.16 – 7.10 (m, 2H*), 6.92 (d, *J* = 7.4 Hz, 1H[§]), 6.86 (d, *J* = 7.4 Hz, 1H*), 6.55 (d, *J* = 7.4 Hz, 1H[§]), 6.49 (dd, *J* = 7.4, 0.6 Hz, 1H*), 6.17 (s, 1H[§]), 6.06 (s, 1H*), 5.57 (s, 1H*), 5.28 (d, *J* = 1.9 Hz, 1H[§]), 5.12 (dd, *J* = 9.6, 5.2 Hz, 1H[§]), 5.03 (d, *J* = 12.3 Hz, 1H[§]), 4.95 (d, *J* = 12.3 Hz, 1H[§]), 4.78 (d, *J* = 8.4 Hz, 1H*), 4.67 (d, *J* = 12.1 Hz, 1H*), 4.33 (d, *J* = 12.2 Hz, 1H*), 2.91 (s, 3H*), 2.82 (d, *J* = 12.9 Hz, 1H*), 2.62 (d, *J* = 1.4 Hz, 3H[§]), 2.43 (dd, *J* = 13.3, 5.2 Hz, 1H[§]), 2.36 (dd, *J* = 12.9, 8.3 Hz, 1H*), 2.30 (s, 3H[§]), 2.28 (s, 3H*), 2.24 (dd, *J* = 13.3, 9.6 Hz, 1H[§]), 1.43 (s, 3H*), 1.40 (s, 3H[§]); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.4[§], 169.3*, 156.9* (q, *J*_{C-F} = 36.8 Hz), 150.4*, 148.7[§], 139.0*, 138.7[§], 135.2[§], 134.7*, 130.3[§], 129.0*, 128.5[§], 128.4*, 128.4*, 128.3[§], 128.2*, 122.3*, 121.3[§], 119.1[§], 118.4*, 116.2* (q, *J*_{C-F} = 288.7 Hz), 108.0[§], 106.8*, 91.1[§], 88.9*, 67.6*, 67.2[§], 60.5[§], 60.3*, 52.0[§], 50.2*, 42.9*, 41.1[§], 32.0*, 31.0[§], 25.3*[§], 22.4[§], 21.8*; IR (NaCl/thin film): 2923, 1740, 1698, 1612, 1501, 1440, 1214, 1150, 1011, 849, 746 cm⁻¹; $[\alpha]_D^{25} = +165.5^\circ$ (*c* 0.53, DCM); HRMS (ESI) calc'd for [M+H]⁺ 433.1739, found 433.1756.

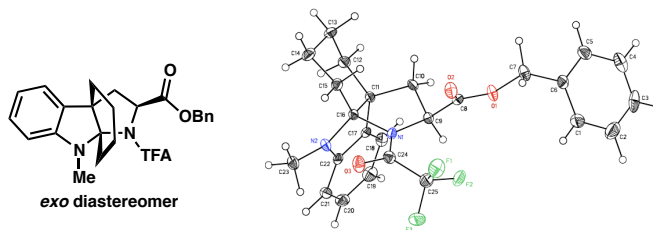
Pyrroloindoline 106f.

Prepared from 1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (**105f**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 20 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 61 mg (54% yield) of **106f** in a 6:1 ratio of diastereomers (determined by ^1H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→5% ethyl acetate/hexanes).

Exo diastereomer: The enantiomeric excess was determined to be 92% by chiral HPLC analysis (OD-H, 1 mL/min, 0.6% EtOH in hexanes, $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 10.7$ min $t_{\text{R}}(\text{minor}) = 12.1$ min. ^1H 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 7.38 (br s, 5H*, 5H §), 7.17 (t, $J = 7.6$ Hz, 1H*, 1H §), 7.00 (br d, $J = 6.7$ Hz, 1H*, 1H §), 6.87–6.78 (br m, 1H §), 6.76 (br t, $J = 6.7$ Hz, 1H*), 6.59 (br d, $J = 6.0$ Hz, 1H §), 6.51 (br d, $J = 7.4$ Hz, 1H*), 5.89 (br s, 1H*), 5.79 (br s, 1H §), 5.30 – 5.10 (m, 2H*, 2H §), 4.61 (br s, 1H*), 4.32 (br s, 1H §), 3.60 (br d, $J = 22.3$ Hz, 2H §), 3.49 (br s, 2H*), 3.10 (s, 3H*), 2.94 (br s, 3H §), 2.74 – 2.64 (m, 1H*), 2.63 – 2.52 (m, 1H §), 2.39 (br d, $J = 10.1$ Hz, 1H*), 2.18 (br t, $J = 9.9$ Hz, 1H §), 1.97 (br s, 2H §), 1.82 (br td, $J = 13.6, 7.9$ Hz, 2H*), 0.86 (br s, 9H*, 9H §), 0.02 – -0.06 (m, 6H*, 6H §); ^{13}C NMR (100 MHz, CDCl_3 ; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9 § , 159.0 (q, $J_{\text{C-F}} = 37.9$ Hz)*, 157.7 (q, $J_{\text{C-F}} = 38.1$ Hz) § , 150.5 § , 150.0*, 135.2 § , 134.7*, 131.7 § , 131.5*, 128.8* § , 128.6* § , 128.4* § , 122.4* § ,

119.9[§], 118.4*, 116.0 (q, J_{C-F} = 288.0 Hz)*, 110.0[§], 108*, 90.8*, 89.5[§], 67.9*, 67.3[§], 60.5[§], 59.6*, 56.4[§], 52.3*, 43.5*, 39.9[§], 39.1[§], 39.0*, 36.4*, 35.7[§], 25.8*, 18.1[§], -5.6*[§]; IR (NaCl/thin film): 3035, 2955, 2930, 2857, 2884, 1750, 1694, 1492, 1432, 1257, 1201, 1158, 1106, 837 cm⁻¹; $[\alpha]_D^{25}$ = -95.3° (c = 1.38, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 562.2475, found 562.2468.

Endo diastereomer: The enantiomeric excess was determined to be 90% by chiral HPLC analysis (AD-H, 1 mL/min, 0.5% EtOH in hexanes, λ = 254 nm): t_R (major) = 6.5 min t_R (minor) = 5.8 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 16.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.38 – 7.29 (m, 3H*, 3H[§]), 7.20 – 7.07 (m, 3H*, 3H[§]), 6.96 (d, J = 7.2 Hz, 1H*, 1H[§]), 6.69 (t, J = 7.5 Hz, 1H[§]), 6.65 (t, J = 7.4 Hz, 1H*), 6.27 (d, J = 8.2 Hz, 1H[§]), 6.25 (d, J = 7.9 Hz, 1H*), 5.90 (s, 1H[§]), 5.83 (s, 1H*), 5.12 (dd, J = 9.3, 3.0 Hz, 1H[§]), 4.86 (d, 12.2 Hz, 1H[§]), 4.79 (d, J = 12.2 Hz, 1H[§]), 4.77 (d, J = 8.2 Hz, 1H*), 4.60 (d, J = 12.1 Hz, 1H*), 4.33 (d, J = 12.2 Hz, 1H*), 3.65 – 3.49 (m, 2H*, 2H[§]), 2.92 (s, 3H*), 2.88 (d, J = 13.1 Hz, 1H*), 2.67 (s, 3H[§]), 2.58 (dd, J = 13.1, 3.3 Hz, 1H[§]), 2.49 (dd, J = 13.1, 8.4 Hz, 1H*), 2.28 (dd, J = 13.7, 10.1 Hz, 1H[§]), 2.07 – 1.84 (m, 2H*, 2H[§]), 0.87 (s, 9H*), 0.80 (s, 9H[§]), 0.00 (d, J = 4.0 Hz, 6H*), -0.09 (d, J = 13.9 Hz, 6H[§]); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 16.7:1 mixture of rotamers, only the major rotamer is reported) δ 169.3, 156.8 (q, J_{C-F} = 37.9 Hz), 151.2, 134.7, 129.6, 129.2, 128.43, 128.37, 128.2, 123.5, 117.5, 116.2 (q, J_{C-F} = 289.0 Hz), 107.5, 105.9, 87.1, 67.5, 59.9, 59.4, 53.0, 42.2, 40.4, 31.9, 25.9, 18.2, -5.6 (J = 6.1 Hz); IR (NaCl/thin film): 3034, 2954, 2930, 2857, 1742, 1699, 1609, 1494, 1441, 1255, 1207, 1146, 1104, 837, 745 cm⁻¹; $[\alpha]_D^{25}$ +148.5° (c = 0.33, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 562.2475, found 562.2458.

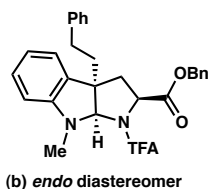
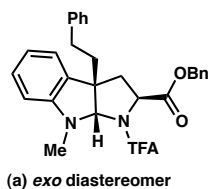
Pyrroloindoline 106g.

Prepared from 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole⁴³ and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 11 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 60 mg (65% yield) of **106g** in a >18:1 ratio of diastereomers (determined by ¹H NMR analysis of the pure product). The diastereomers were separated by prep HPLC (0→10% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The oil was crystallized from ethyl acetate/hexanes to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, $\lambda = 254$ nm): t_R (major) = 4.5 min t_R (minor) = 6.9 min. ¹H NMR (300 MHz, CDCl₃; compound exists as a >20:1 mixture of rotamers) δ 7.44 – 7.29 (m, 5H), 7.16 (t, $J = 7.2$ Hz, 1H), 7.02 (d, $J = 7.0$ Hz, 1H), 6.72 (t, $J = 7.4$ Hz, 1H), 6.51 (d, $J = 7.8$ Hz, 1H), 5.20 (dd, $J = 29.3, 12.1$ Hz, 2H), 4.43 (t, $J = 8.2$ Hz, 1H), 3.20 (d, $J = 15.5$ Hz, 1H), 3.10 (s, 3H), 2.75 (dd, $J = 13.0, 8.6$ Hz, 1H), 2.28 (dd, $J = 13.0, 9.3$ Hz, 1H), 2.02 – 1.75 (m, 2H), 1.75 – 1.55 (m, $J = 12.9$ Hz, 1H), 1.53 – 1.38 (m, 1H), 1.36 – 1.07 (m, 3H); ¹³C NMR (125 MHz, CDCl₃; compound exists as a >20:1 mixture of rotamers) δ 172.4, 157.7 (q, $J_{C-F} = 36.3$ Hz), 148.0, 134.9, 133.7, 128.7, 128.6, 128.4, 120.8, 118.0, 115.8 (q, $J_{C-F} = 289.8$ Hz), 112.3, 107.1, 95.6, 67.6, 58.4 (q, $J_{C-F} = 3.5$ Hz), 52.3, 35.2, 33.9, 30.7, 26.8, 21.5, 20.4 ; IR (NaCl/thin film): 3034, 2928, 2857, 1749,

1693, 1609, 1490, 1214, 1186, 1160, 741 cm^{-1} ; melting point: 106 – 108 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} = -92.6^{\circ}$ ($c = 1.40$, DCM); HRMS (ESI+) calc'd for $[\text{M}+\text{H}]^{+}$ 459.1890, found 459.1892.

Pyrrolidinoindoline 106h.

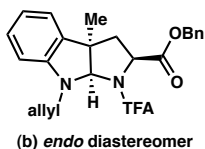
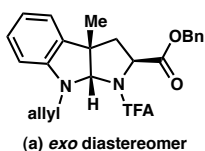


Prepared from 3-phenethyl-1-methyl-1*H*-indole⁴⁴ and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents SnCl_4 . The reaction was allowed to run for 9.5 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 81 mg (80% yield) of **106h** in a 4:1 ratio of diastereomers (determined by ^1H NMR analysis of the crude reaction mixture). The diastereomers were separated by preparatory HPLC (0→6% ethyl acetate/hexanes). The enantiomeric excess of both diastereomers was determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, $\lambda = 254$ nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 92%. $t_{\text{R}}(\text{major}) = 33.3$ min $t_{\text{R}}(\text{minor}) = 28.0$ min. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.28 (m, 5H*, 5H §), 7.28 – 7.16 (m, 4H*, 4H §), 7.12 – 7.06 (br s, 3H §), 7.02 (m, 3H*), 6.90–6.81 (br s, 1H §), 6.81 (t, $J = 6.9$ Hz, 1H*), 6.63 – 6.57 (m, $J = 9.8$ Hz, 1H §), 6.55 (br d, $J = 7.5$ Hz, 1H*), 5.70 (br s, 1H*), 5.45 (br s, 1H §), 5.25–5.15 (m, 2H*, 2H §), 4.69 (br d, $J = 7.4$ Hz, 1H*), 4.39 (br s, 1H §), 3.12 (br s, 3H*), 2.90 (br s, 3H §), 2.78 – 1.73 (m, 6H*, 6H §); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.8 § , 159.0 (q, $J_{\text{C-F}} = 36.7$ Hz)*, 157.60 (q, $J_{\text{C-F}} = 32.9$ Hz) § , 150.3* § , 141.0* § , 135.1 § , 134.5*, 132.0*, 131.6 § , 129.1 § , 128.9 § , 128.8 § ,

128.7*, 128.4*, 128.2*, 126.0*[§], 122.3[§], 121.9*, 120.1[§], 118.9*, 116.0 (q, $J_{\text{C-F}} = 288.4$ Hz)*, 109.7[§], 108.3*, 90.4*, 89.2[§], 68.1*, 67.4[§], 60.7[§], 59.5*, 57.5[§], 53.7*, 43.5*, 40.0[§], 39.0*, 38.6[§], 36.9*, 35.1[§], 31.9*[§]; IR (NaCl/thin film): 3030, 2921, 2852, 1747, 1694, 1607, 1492, 1455, 1433, 1190, 1152, 750 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -113.8^{\circ}$ (c = 1.17, DCM); HRMS (ESI) calc'd for $[\text{M}+\text{H}]^{+}$ 509.2047, found 509.2052.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. $t_{\text{R}}(\text{major}) = 11.6$ min $t_{\text{R}}(\text{minor}) = 17.5$ min. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 14.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.37 – 7.30 (m, 3H*, 3H[§]), 7.23 (d, $J = 7.6$ Hz, 2H*, 2H[§]), 7.19 – 7.12 (m, 4H*, 4H[§]), 7.07 (d, $J = 7.3$ Hz, 2H*, 2H[§]), 7.03 (d, $J = 7.2$ Hz, 1H*, 1H[§]), 6.76 (t, $J = 7.3$ Hz, 1H[§]), 6.71 (t, $J = 7.3$ Hz, 1H*), 6.33 (d, $J = 7.8$ Hz, 1H[§]), 6.28 (d, $J = 7.8$ Hz, 1H*), 5.70 (s, 1H*), 5.49 (s, 1H[§]), 5.13 (dd, $J = 9.4, 3.5$ Hz, 1H[§]), 4.91 (d, $J = 12.2$ Hz, 1H[§]), 4.83 (d, $J = 12.2$ Hz, 1H[§]), 4.80 (d, $J = 8.2$ Hz, 1H*), 4.63 (d, $J = 12.1$ Hz, 1H*), 4.37 (d, $J = 12.1$ Hz, 1H*), 2.94 (s, 3H*), 2.86 (d, $J = 12.9$ Hz, 1H*), 2.65 (s, 3H[§]), 2.59 (td, $J = 12.9, 5.3$ Hz, 1H*), 2.53 – 2.46 (m, 1H[§]), 2.45 – 2.32 (m, 2H*), 2.27 (dd, $J = 13.2, 9.6$ Hz, 1H[§]), 2.23 – 2.18 (m, 1H[§]), 2.15 – 1.89 (m, 2H*, 2H[§]); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 14.5:1 mixture of rotamers, only the major rotamer is reported) δ 169.2, 156.8 (q, $J_{\text{C-F}} = 36.9$ Hz), 151.3, 141.2, 134.7, 129.6, 129.4, 128.5, 128.43, 128.41, 128.3, 128.2, 126.0, 123.1, 117.8, 116.2 (q, $J = 288.9$ Hz), 105.9, 86.9, 67.7, 60.0 (q, $J_{\text{C-F}} = 3.2$ Hz). 54.3, 47.5, 42.2, 41.0, 31.9, 31.1; IR (NaCl/thin film): 2919, 2850, 1738, 1694, 1607, 1493, 1455, 1441, 1204, 1142, 744 cm^{-1} ; $[\alpha]_{\text{D}}^{25} +119.6^{\circ}$ (c = 0.87, DCM); HRMS (ESI) calc'd for $[\text{M}+\text{H}]^{+}$ 509.2047, found 509.2048.

Pyrroloindoline 106i.

Prepared from 1-allyl-3-methyl-1*H*-indole⁴⁵ and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents SnCl₄. The reaction was allowed to run for 15 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 79.7 mg (90% yield) of **106i** in a 3:1 ratio of diastereomers (determined by SFC analysis of the purified products, before the diastereomers were separated). The diastereomers were separated by flash chromatography (0→10% ethyl acetate/hexanes).

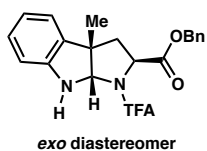
Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO₂, λ = 254 nm): t_R (major) = 5.7 min t_R (minor) = 4.3 min. ¹H NMR (400 MHz, CDCl₃; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 (br s, 5H*, 5H[§]), 7.14 (t, J = 7.7 Hz, 1H*, 1H[§]), 7.09 – 6.95 (br m, 1H[§]), 7.00 (br d, J = 7.2 Hz, 1H*), 6.90 – 6.71 (br m, 1H[§]), 6.76 (br t, J = 7.3 Hz, 1H*), 6.68 – 6.44 (br m, 1H[§]), 6.54 (br d, J = 7.9 Hz, 1H*), 5.82 (br ddd, J = 21.5, 10.5, 5.7 Hz, 1H*, 1H[§]), 5.73 (br s, 1H*), 5.52 (br s, 1H[§]), 5.34 – 5.09 (m, 4H*, 4H[§]), 4.75 (br d, J = 9.2 Hz, 1H*), 4.40 (br s, 1H[§]), 4.26 (br d, J = 13.1 Hz, 1H*), 4.04 (br dd, J = 16.3, 5.9 Hz, 1H*, 1H[§]), 3.83 (br s, 1H[§]), 2.60 (br dd, J = 13.3, 9.8 Hz, 1H*, 1H[§]), 2.36 (br d, J = 13.4 Hz, 1H*), 2.20 – 2.03 (m, 1H[§]), 1.46 (s, J = 10.6 Hz, 3H[§]), 1.27 (s, J = 8.7 Hz, 3H*); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.8[§], 158.9* (q, J_{C-F} = 37.0 Hz), 148.4*[§], 134.8*, 134.6*, 133.8*, 133.4[§], 128.8*, 128.7*, 128.7*, 121.5*, 120.3[§], 118.7*, 117.7[§],

116.7*, 116.0* (q, $J_{\text{C-F}} = 288.5$ Hz), 110.8[§], 108.4*, 91.3*, 89.7[§], 68.0*, 67.4[§], 61.1[§], 60.0*, 53.6[§], 51.8*, 50.5[§], 49.4*, 44.1*, 40.7[§], 23.5*[§]; IR (NaCl/thin film): 3035, 2968, 1748, 1694, 1609, 1488, 1424, 1339, 1257, 1148, 1026, 921, 744 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -94.3^{\circ}$ (c 1.14, DCM); HRMS (ESI) calc'd for $[\text{M}+\text{H}]^{+}$ 445.1734, found 445.1750.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 89% by chiral SFC analysis (OJ-H, 2.5 mL/min, 2% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 5.9$ min $t_{\text{R}}(\text{minor}) = 5.1$ min. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 15.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.36 – 7.30 (m, 3H*, 3H[§]), 7.19 (dd, $J = 6.5, 3.0$ Hz, 2H[§]), 7.16 – 7.11 (m, 2H*), 7.08 (td, $J = 7.7, 1.3$ Hz, 1H*, 1H[§]), 7.04 (d, $J = 7.4$ Hz, 1H[§]), 6.99 (dd, $J = 7.4, 0.9$ Hz, 1H*), 6.73 (t, $J = 7.0$ Hz, 1H[§]), 6.68 (td, $J = 7.4, 0.9$ Hz, 1H*), 6.35 (d, $J = 7.4$ Hz, 1H[§]), 6.34 (d, $J = 7.8$ Hz, 1H*), 5.77 (dddd, $J = 17.1, 10.4, 5.5, 5.1$ Hz, 1H*), 5.73 – 5.67 (m, 1H[§]), 5.58 (s, 1H*), 5.55 – 5.53 (m, 1H[§]), 5.22 (dq, $J = 17.1, 1.6$ Hz, 1H*), 5.16 (dd, $J = 9.6, 4.3$ Hz, 1H[§]), 5.14 – 5.10 (m, 2H[§]), 5.05 (dq, $J = 10.2, 1.5$ Hz, 1H*), 4.97 (d, $J = 12.3$ Hz, 1H[§]), 4.91 (d, $J = 12.3$ Hz, 1H[§]), 4.80 (d, $J = 8.5$ Hz, 1H*), 4.68 (d, $J = 12.1$ Hz, 1H*), 4.36 (d, $J = 12.1$ Hz, 1H*), 4.15 (ddt, $J = 16.7, 5.9, 1.5$ Hz, 1H*), 4.01 (ddt, $J = 16.7, 5.0, 1.6$ Hz, 1H*), 3.68 – 3.64 (m, 1H[§]), 2.88 (d, $J = 13.0$ Hz, 1H*), 2.53 (dd, $J = 13.3, 4.3$ Hz, 1H[§]), 2.40 (dd, $J = 13.0, 8.5$ Hz, 1H*), 2.26 (dd, $J = 13.3, 9.6$ Hz, 1H[§]), 1.44 (s, 1H[§]), 1.43 (s, 1H*); ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 15.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.3*, 156.9* (q, $J_{\text{C-F}} = 36.9$ Hz), 149.3*, 147.7[§], 134.7*, 134.1*, 133.2[§], 132.4[§], 132.0*, 128.9*, 128.6[§], 128.5[§], 128.5*, 128.4*, 128.3*, 128.2[§], 122.6*, 121.7[§], 118.7[§], 118.0*, 117.1[§], 116.3*, 116.2* (q, $J_{\text{C-F}} = 288.7$ Hz), 108.0[§], 106.9*, 88.1*, 67.6*, 67.3[§], 60.4[§],

60.2*, 52.7[§], 50.6*, 48.8*, 42.5*, 41.5[§], 25.8*, 23.1[§]; IR (NaCl/thin film): 2962, 1739, 1697, 1608, 1491, 1447, 1269, 1211, 1145, 851, 742 cm⁻¹; [α]_D²⁵ = +166.6° (*c* 1.52, DCM); HRMS (ESI) calc'd for [M+H]⁺ 445.1734, found 445.1740.

Pyrroloindoline **106j**.



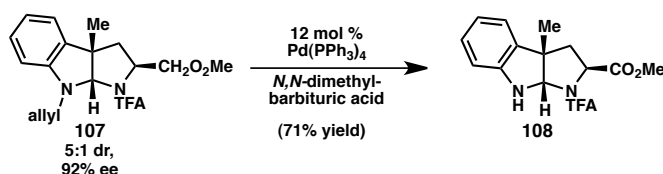
Prepared from 3-methyl-1*H*-indole (0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate (**91d**, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was

purified by flash chromatography (0→20% ethyl acetate/hexanes) to yield 10.7 mg (18% yield) of **106j** in an 8:1 ratio of diastereomers (determined by NMR analysis of the pure product). The diastereomers were separated by preparatory HPLC (5→12% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 95% by chiral SFC analysis (OJ-H, 2.5 mL/min, 7% IPA in hexanes, λ = 254 nm): t_R (major) = 9.6 min t_R (minor) = 7.4 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 7.43 – 7.31 (m, 5H), 7.12 (t, *J* = 8.1 Hz, 0.5H), 7.10 (t, *J* = 8.1 Hz, 0.5H), 7.05 (d, *J* = 4.1 Hz, 0.5H), 7.04 (d, *J* = 3.9 Hz, 0.5H), 6.82 (t, *J* = 7.5 Hz, 0.5H), 6.77 (t, *J* = 7.5 Hz, 0.5H), 6.64 (d, *J* = 7.8 Hz, 0.5H), 6.60 (d, *J* = 7.8 Hz, 0.5H), 5.63 (s, 0.5 H), 5.57 (s, 0.5H), 5.30 (s, 0.5H), 5.23 (s, 1H), 5.22 (d, *J* = 12.2 Hz, 0.5H), 5.17 (d, *J* = 12.2 Hz, 0.5H), 4.76 (s, 0.5H), 4.68 – 4.62 (m, 0.5H), 4.50 (t, *J* = 7.7 Hz, 0.5H), 2.72 (dd, *J* = 13.5, 9.2 Hz, 0.5H), 2.58 (dd, *J* = 13.1, 8.5 Hz, 0.5H), 2.33 (dd, *J* = 13.4, 3.9 Hz, 0.5H), 2.17 (dd, *J* = 13.1, 6.9 Hz, 0.5H), 1.44 (s, 1.5H), 1.31 (s, 1.5H); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 171.5, 170.2, 156.8 (q, *J*_{C-F} = 38.7 Hz), 146.8, 146.3, 135.2, 134.7, 133.2, 133.1, 128.9, 128.8, 128.7,

128.6, 128.5, 128.4, 122.3, 122.1, 120.2, 119.3, 116.1 (q, $J_{\text{C-F}} = 287.2$), 115.7 (q, $J_{\text{C-F}} = 287.2$), 109.9, 109.3, 86.5, 84.5, 68.10, 67.5, 61.3, 59.6, 54.5, 50.3, 43.7, 40.3, 24.2, 23.9; IR (NaCl/thin film): 3390, 3034, 2961, 2920, 1748, 1687, 1610, 1486, 1469, 1456, 1189, 1158, 745 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -111.8^{\circ}$ ($c = 0.22$, DCM); HRMS (EI+) calc'd for M^{+} 404.1348, found 404.1344.

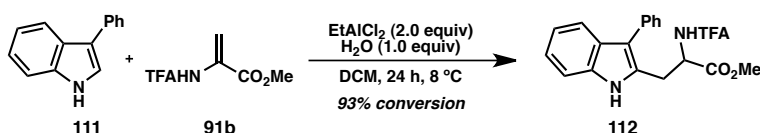
2.5.5 *Pd-catalyzed Deallylation of Pyrroloindoline Methyl Ester 107*



An oven-dried microwave vial was charged with allylpyrroloindoline **107** (55.0 mg, 0.149 mmol, 1.00 equiv), $\text{Pd}(\text{PPh}_3)_4$ (6.9 mg, 6.0 μmol , 0.040 equiv), and *N,N*-dimethylbarbituric acid (70.0 mg, 0.448 mmol, 3.01 equiv) then sealed under nitrogen. 1.1 mL DCM was added and the reaction mixture was heated to 35 $^{\circ}\text{C}$ in an oil bath. Two additional 7.0 mg portions of $\text{Pd}(\text{PPh}_3)_4$ were added after 34 hours and after 75 hours. After heating at 35 $^{\circ}\text{C}$ for 123 hours, the reaction was concentrated and the crude residue was diluted in Et_2O , washed with saturated aqueous Na_2CO_3 , dried (Na_2SO_4), filtered and concentrated. The crude residue was subjected to silica gel column chromatography (10:90 EtOAc :hexanes) to yield 34.8 mg (71% yield) of **108** as a colorless oil in an 8:1 mixture of diastereomers (determined by NMR analysis of the pure product). The product was resubjected to identical column conditions to obtain *exo*-**108** in >20:1 dr. ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 1:1 mixture of rotamers) δ 7.13 (dd, $J = 7.8, 1.2$ Hz, 0.5H), 7.10 (dd, $J = 7.9, 1.3$ Hz, 0.5H), 7.08 (ddd, $J = 1.3, 0.6, 0.6$ Hz, 0.5H), 7.07 (ddd, $J = 1.3, 0.6, 0.6$ Hz, 0.5H), 6.83 (ddd, $J = 7.5, 7.5, 1.0$ Hz, 0.5H), 6.79 (ddd, $J = 7.4,$

7.4, 1.0 Hz, 0.5H), 6.64 (ddd, $J = 7.8, 0.7, 0.7$ Hz, 0.5H), 6.61 (dt, $J = 7.8, 0.8, 0.8$ Hz, 0.5H), 5.64 (app q, $J = 1.9$ Hz, 0.5H), 5.58 (s, 0.5H), 4.62 (ap ddq, $J = 9.1, 4.4, 1.5$ Hz, 0.5H), 4.45 (dd, $J = 8.5, 7.0$ Hz, 0.5H), 3.81 (s, 1.5H), 3.77 (s, 1.5H), 2.75 (dd, $J = 13.4, 9.1$ Hz, 0.5H), 2.59 (ddd, $J = 13.2, 8.5, 0.5$ Hz, 0.5H), 2.37 (dd, $J = 13.4, 4.4$ Hz, 0.5H), 2.19 (dd, $J = 13.2, 7.0$ Hz, 0.5H), 1.49 (s, 1.5H), 1.41 (s, 1.5H).; ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 1:1 mixture of rotamers) δ 172.1, 170.9, 157.6 (q, $J_{\text{C-F}} = 37.5$ Hz), 156.7 (q, $J_{\text{C-F}} = 38.0$ Hz), 146.8, 146.4, 133.14, 133.10, 128.9, 128.7, 122.3, 122.1, 120.2, 119.3, 116.1 (q, $J_{\text{C-F}} = 287.1$ Hz), 115.7 (q, $J_{\text{C-F}} = 286.2$ Hz), 109.9, 109.4, 86.4, 84.4 (q, $J_{\text{C-F}} = 2.2$ Hz), 61.1, 59.5 (q, $J_{\text{C-F}} = 3.1$ Hz), 54.5, 53.0, 52.6, 50.3, 43.7, 40.3, 24.2, 24.0.; IR (NaCl/thin film): 3387, 2959, 1751, 1693, 1613, 1489, 1469, 1450, 1438, 1359, 1195, 1160, 1104 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -182.7^\circ$ ($c = 0.50$, DCM); HRMS (MM) calc'd for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 329.1108, found 329.1122.

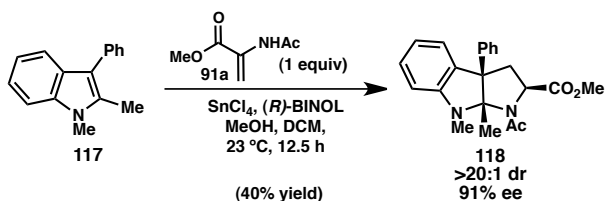
2.5.6 Preparation of Methyl 3-(3-phenyl-1H-indol-2-yl)-2-(2,2,2-trifluoroacetamido)propanoate (**112**)



A flame-dried flask was charged with 3-phenylindole (**111**, 13.6 mg, 70.0 μmol , 1.00 equiv) and trifluoromethyl 2-acetamidoacrylate (**91b**, 13.8 mg, 70.0 μmol , 1.00 equiv). 0.3 mL DCM was then added and the solution was cooled to 0 °C. EtAlCl₂ (1 M in hexanes, 0.14 mL, 2.0 mmol, 2.0 equiv) was then added dropwise, followed by 1.0 μL H₂O (63 μmol , 0.90 equiv). The reaction was then stirred in a cold room at 8 °C for 24 hours. By crude ^1H NMR, 93% conversion of **91b** was observed to cleanly afford methyl

3-(3-phenyl-1*H*-indol-2-yl)-2-(2,2,2-trifluoroacetamido)propanoate (**112**). ^1H NMR (300 MHz, CDCl_3) δ 8.42 (br s, 1H), 7.60 (dddd, $J = 7.9, 1.3, 0.7, 0.7$ Hz, 1H), 7.51 – 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 7.24 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.13 (ddd, $J = 8.1, 7.0, 1.1$ Hz, 1H), 6.82 (br d, $J = 7.5$ Hz, 1H), 4.81 (dt, $J = 7.4, 5.5$ Hz, 1H), 3.64 – 3.45 (m, 5H).; ^{13}C NMR (125 MHz, CDCl_3) δ 170.3, 157.0 (q, $J_{\text{C-F}} = 38.1$ Hz), 135.6, 134.1, 129.7, 128.8, 128.0, 127.6, 126.6, 122.7, 120.2, 119.3, 117.5, 115.3 (q, $J_{\text{C-F}} = 287.5$ Hz), 110.8, 53.1, 52.5, 28.3.; FTIR (NaCl/thin film): 3377, 3058, 2918, 2848, 1718, 1604, 1541, 1499, 1459, 1438, 1329, 1267, 1214, 1171 cm^{-1} ; HRMS (ESI) calc'd for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_3$ [M-H] 389.1119, found 389.1114.

2.5.7 Preparation of Phenylpyrroloindoline 118

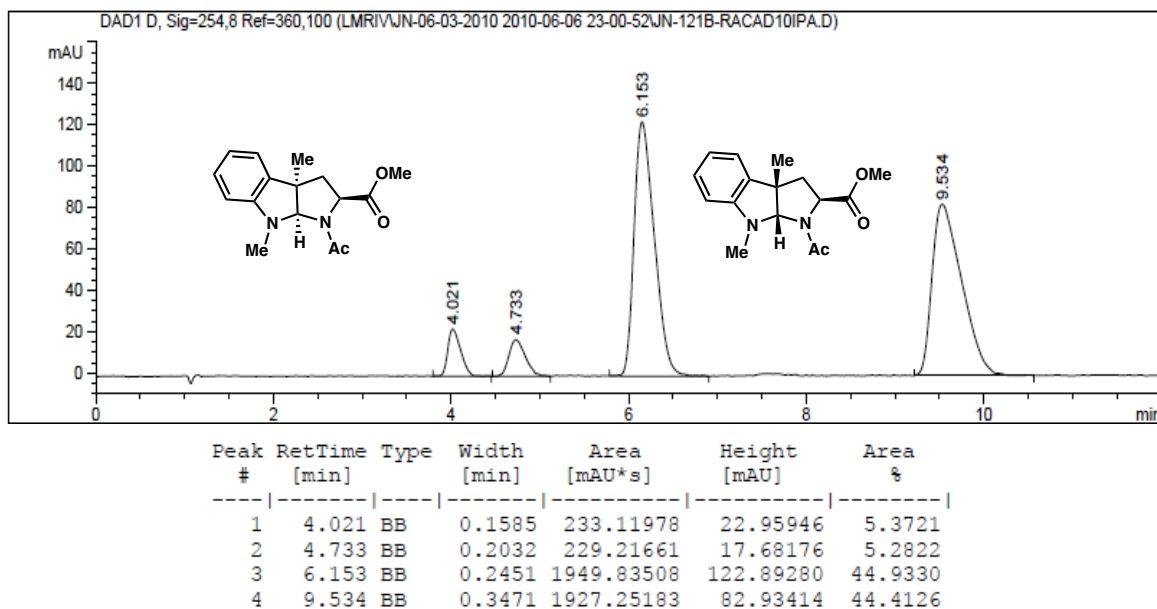


A 10 mL flame-dried flask was charged with (*R*)-BINOL (11.4 mg, 39.9 μmol , 0.20 equiv), methyl 2-acetamidoacrylate (**91a**, 28.6 mg, 0.200 mmol, 1.00 equiv), and 1,2-dimethyl-3-phenylindole⁴⁶ (**117**, 44.2 mg, 0.200 mmol, 1.00 equiv). MeOH (40 μmol , 0.20 equiv) was then added as a solution in 1.5 mL DCM (from a stock solution of 16 μL MeOH in 15 mL DCM), followed by SnCl_4 (1 M solution in DCM, 240 μL , 0.240 mmol, 1.20 equiv). After stirring in the dark 12.5 hours, the orange reaction mixture was diluted with 4 mL MeCN and 5 mL EtOAc, then washed with 10 mL of 0.1 M HCl in brine. The aqueous layer was extracted with 5 mL EtOAc and the combined organic layers were washed with 10 mL 1 M aqueous NaOH. The aqueous layer was extracted with 5 mL

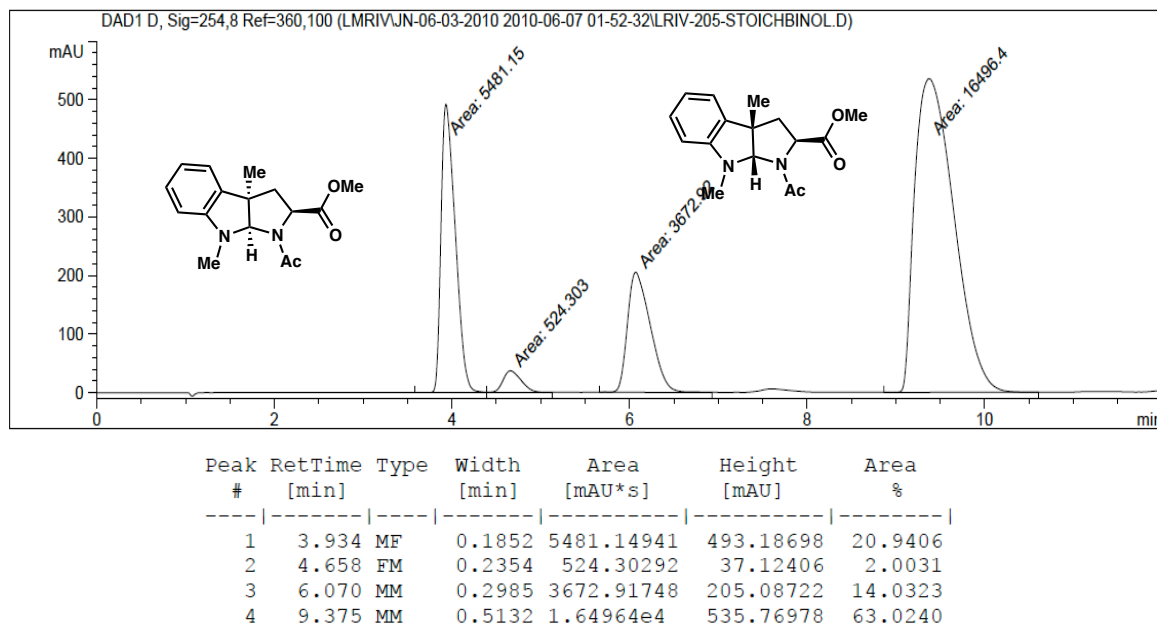
EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated.

The crude residue was purified by silica gel column chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 29 mg (40% yield) of 3a-phenylpyrroloindoline **118** as a pale yellow oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2 , $\lambda = 235$ nm): $t_R(\text{major}) = 4.4$ min, $t_R(\text{minor}) = 3.5$ min. ^1H NMR (300 MHz, CDCl_3 , compound exists as a 1.9:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.30 – 7.15 (m, 4H^* , $4\text{H}^{\S}$), 6.98 – 6.79 (m, 3H^* , $4\text{H}^{\S}$), 6.75 (d, $J = 8.1$ Hz, $1\text{H}^{\S}$), 6.68 (ddd, $J = 7.4, 7.4, 1.0$ Hz, 1H^*), 6.54 (d, $J = 7.9$ Hz, 1H^*), 4.31 – 4.16 (m, 1H^* , $1\text{H}^{\S}$), 3.82 (s, 3H^*), 3.77 (s, $3\text{H}^{\S}$), 3.09 (s, 3H^*), 3.02 (s, $3\text{H}^{\S}$), 3.01 – 2.80 (m, 2H^* , $2\text{H}^{\S}$), 2.17 (s, $3\text{H}^{\S}$), 1.76 (s, 3H^*), 1.47 (s, 3H^*), 1.35 (s, $3\text{H}^{\S}$).; ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 1.9:1 mixture of rotamers) δ 173.9, 173.7, 170.5, 170.4, 151.0, 150.2, 140.2, 139.5, 134.2, 132.8, 129.2, 129.1, 128.4, 128.3, 127.3, 127.23, 127.16, 126.9, 123.5, 122.9, 120.9, 117.8, 111.0, 106.6, 94.1, 91.0, 64.8, 61.2, 60.2, 59.3, 52.7, 52.1, 35.34, 34.28, 32.2, 31.5, 23.6, 22.7, 19.5, 17.6.; FTIR (NaCl/thin film): 3002, 2950, 1747, 1662, 1607, 1491, 1447, 1385, 1343, 1212, 1200, 1165, 1111, 1102 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -122.7^\circ$ ($c = 0.98$, CHCl_3). HRMS (ESI) calc'd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 365.1860, found 365.1867.

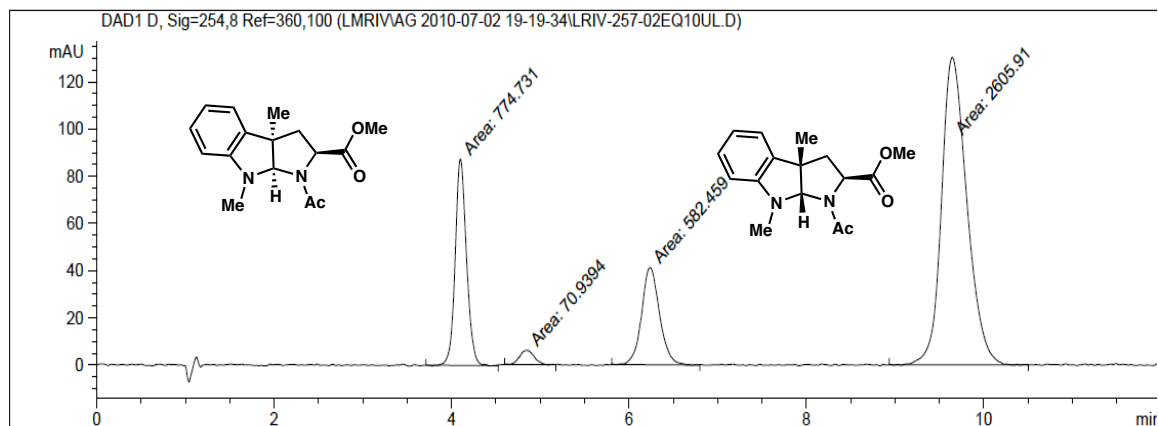
2.5.8 SFC and HPLC Traces for Racemic and Enantioenriched Products.

100b: racemic

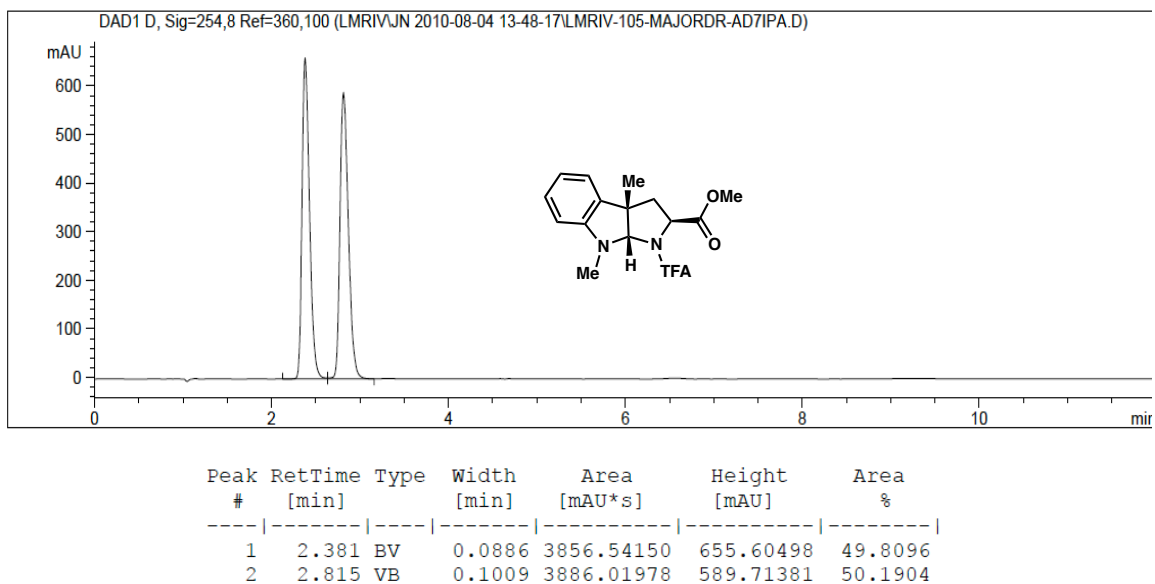
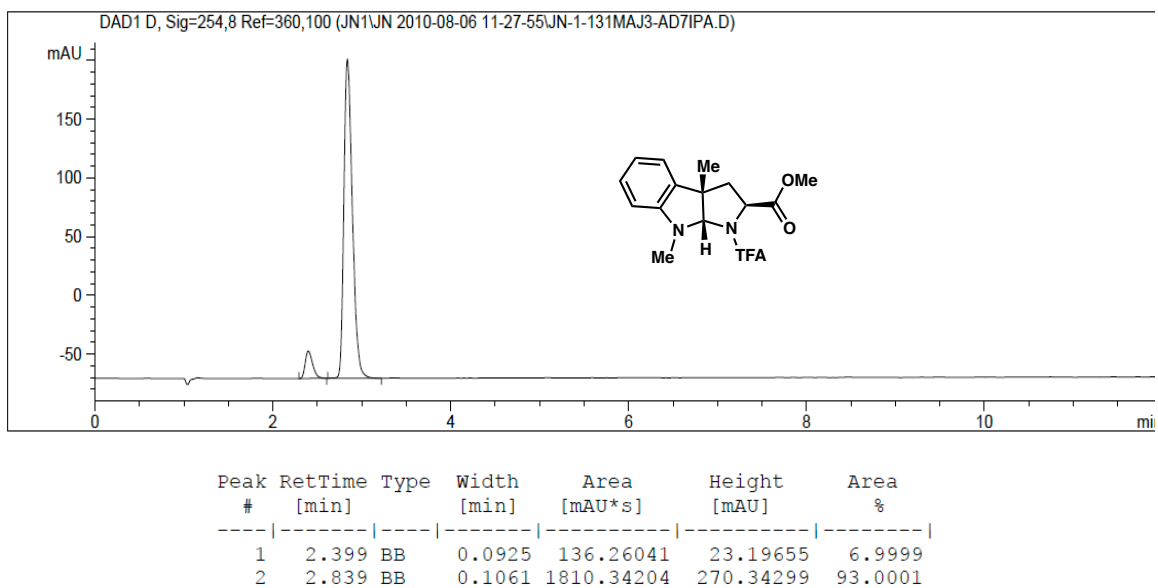
100b (Table 2.2.2, **entry 2**): enantioenriched, *exo*: 64% ee, *endo*: 83% ee (1.1 equiv BINOL)

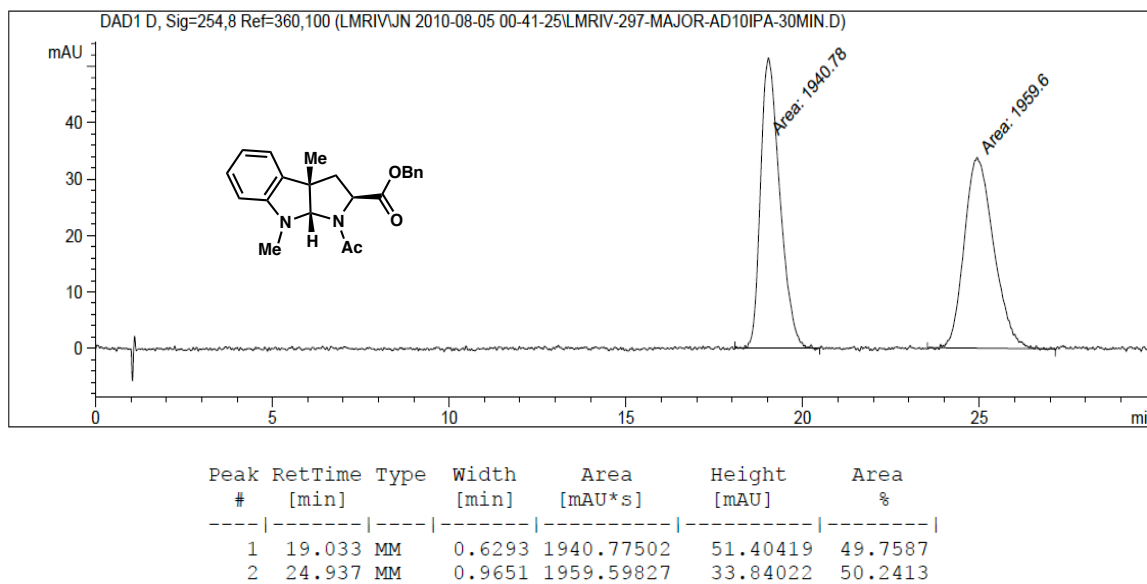
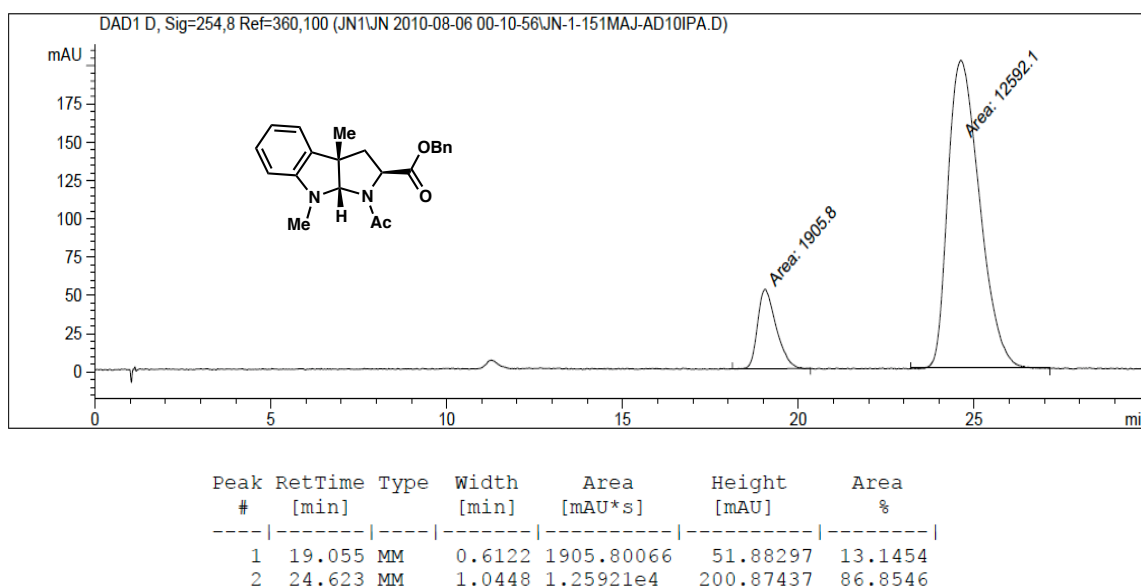


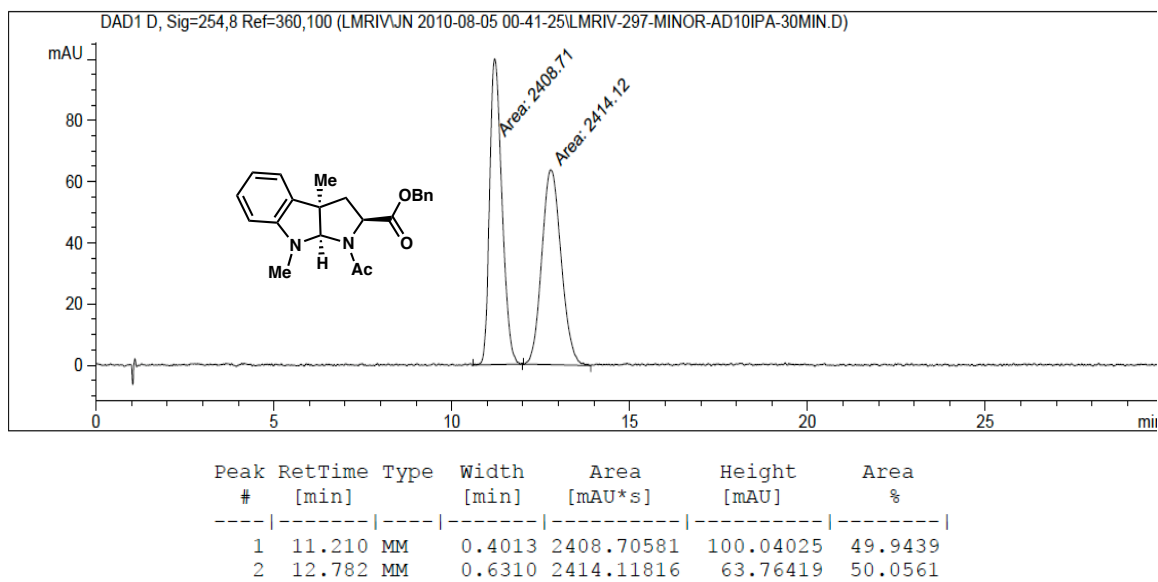
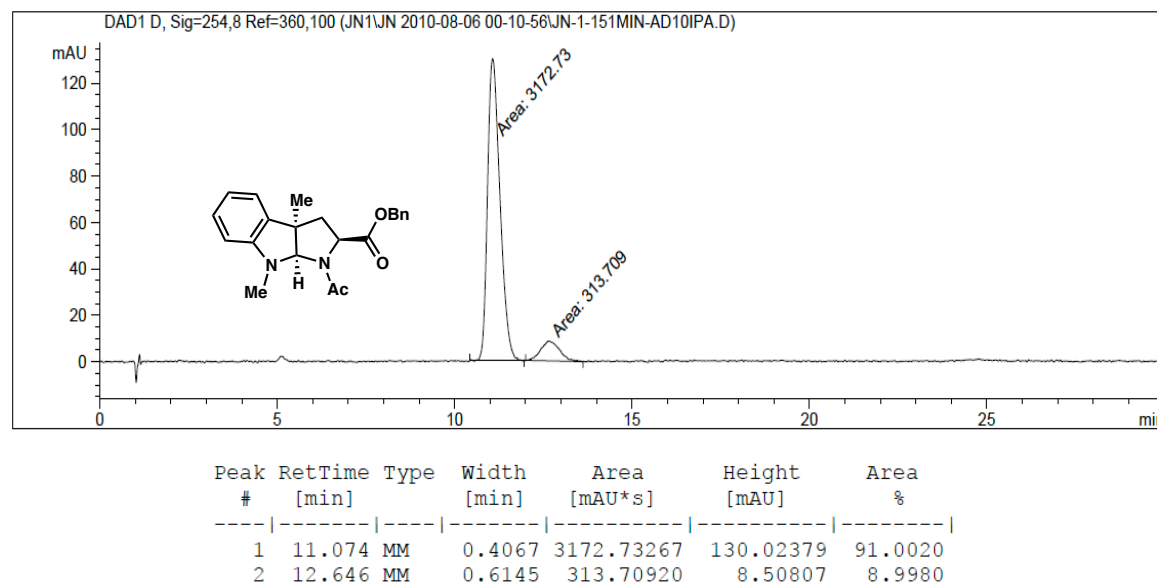
100b (Table 2.2.2, **entry 4**): enantioenriched, *exo*: 63% ee, *endo*: 83% ee (0.2 equiv BINOL)

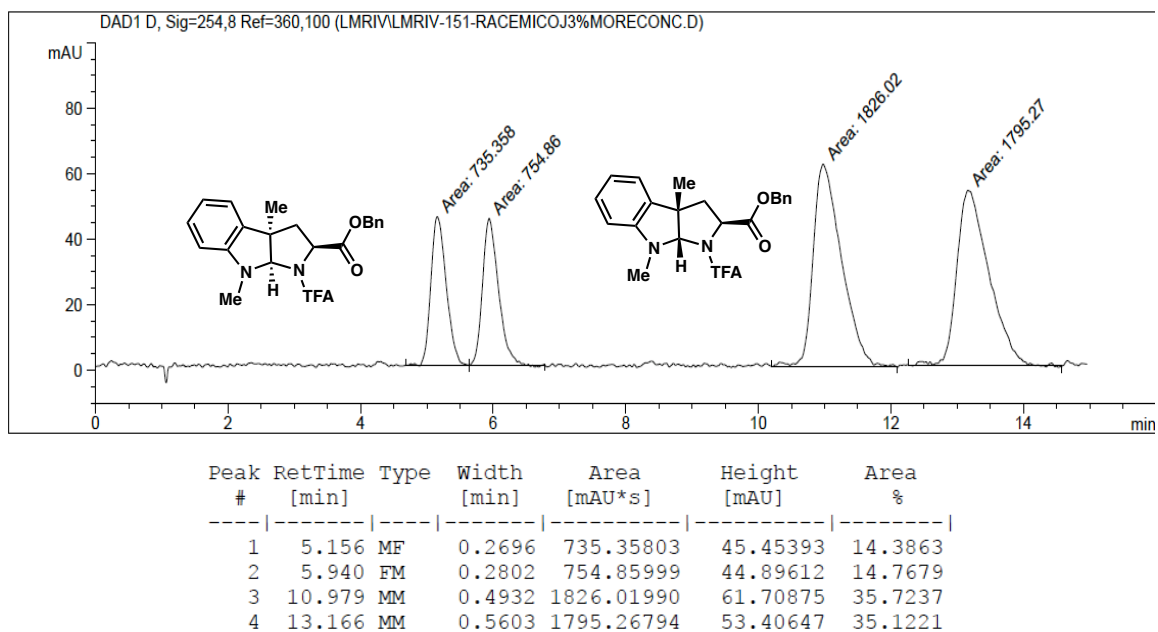
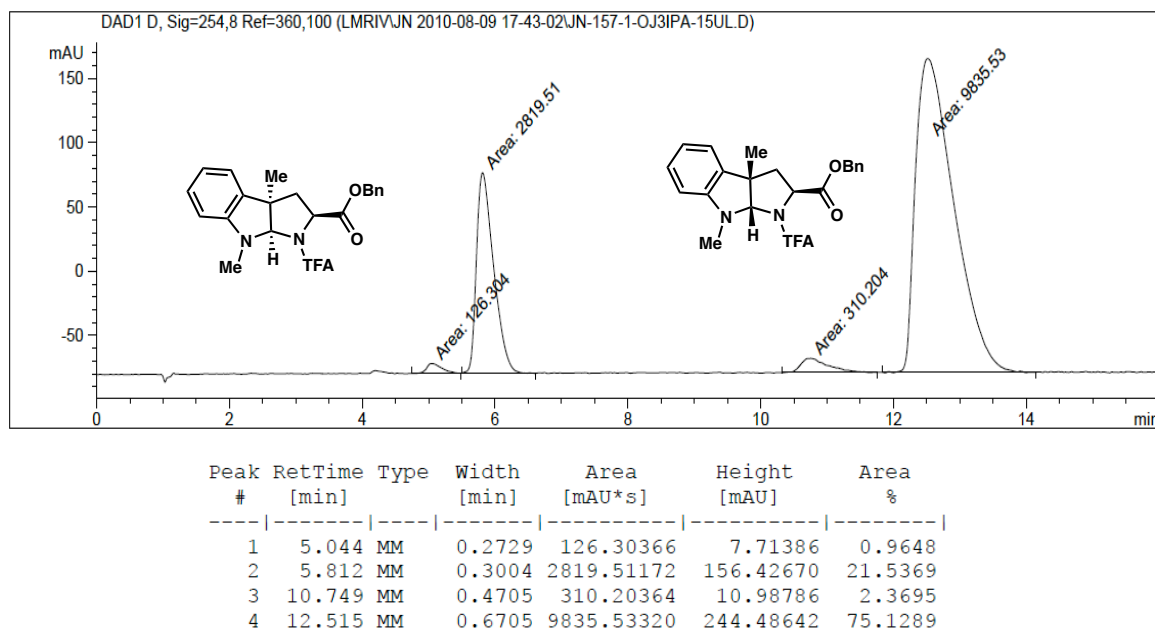


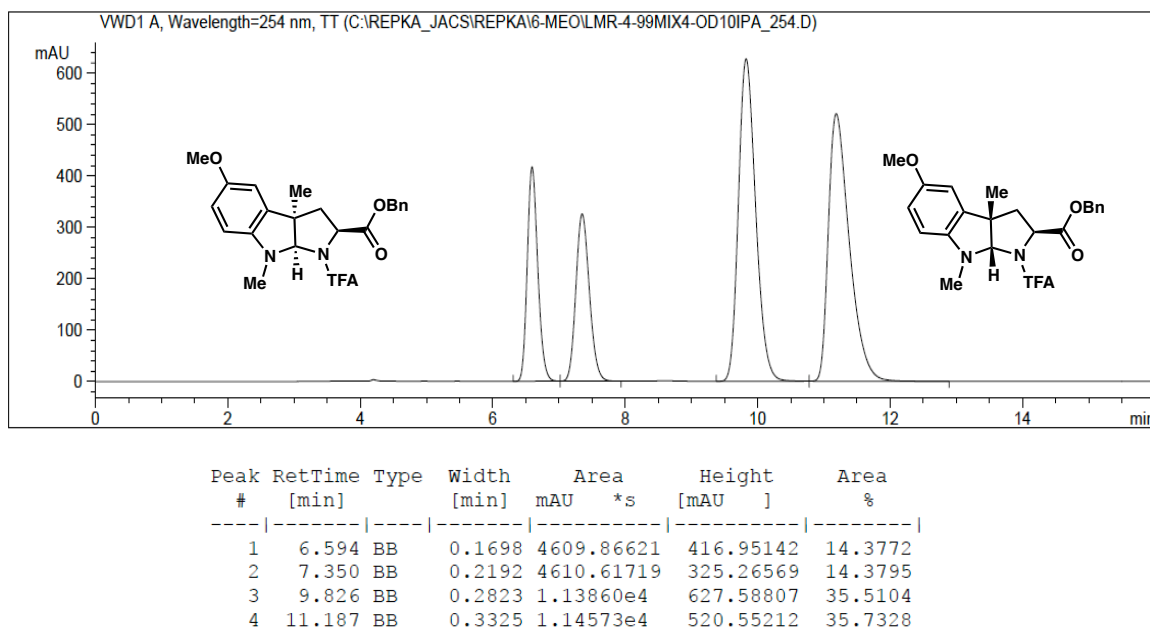
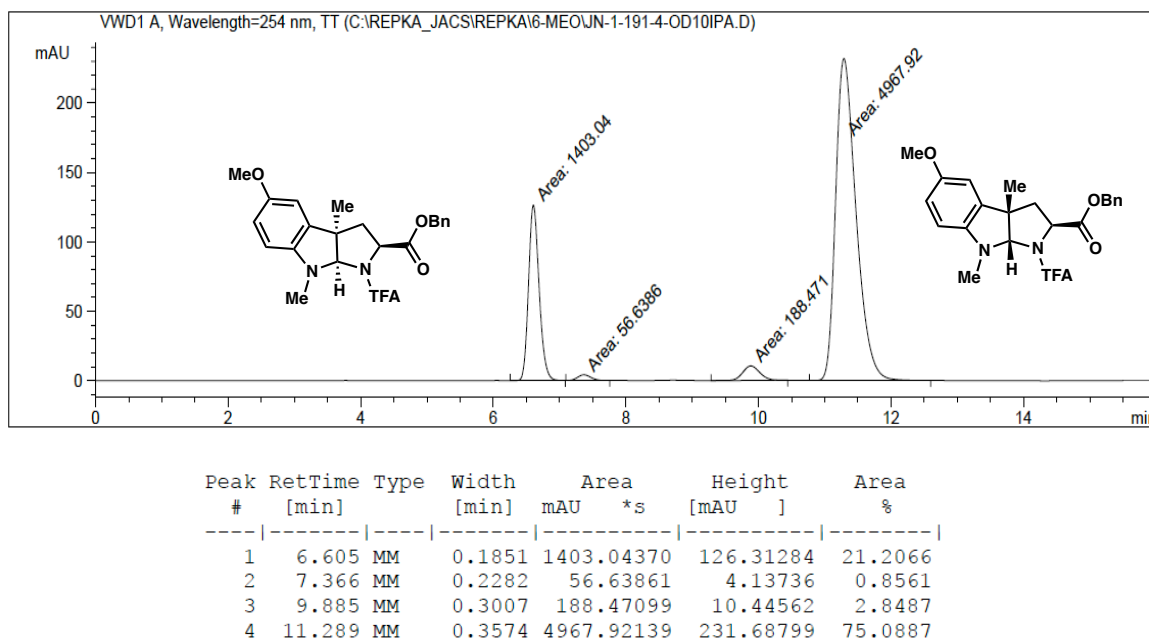
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.100	MM	0.1473	774.73053	87.65621	19.2048
2	4.852	MM	0.1955	70.93945	6.04832	1.7585
3	6.238	MM	0.2351	582.45917	41.28461	14.4386
4	9.647	MM	0.3330	2605.91260	130.42717	64.5981

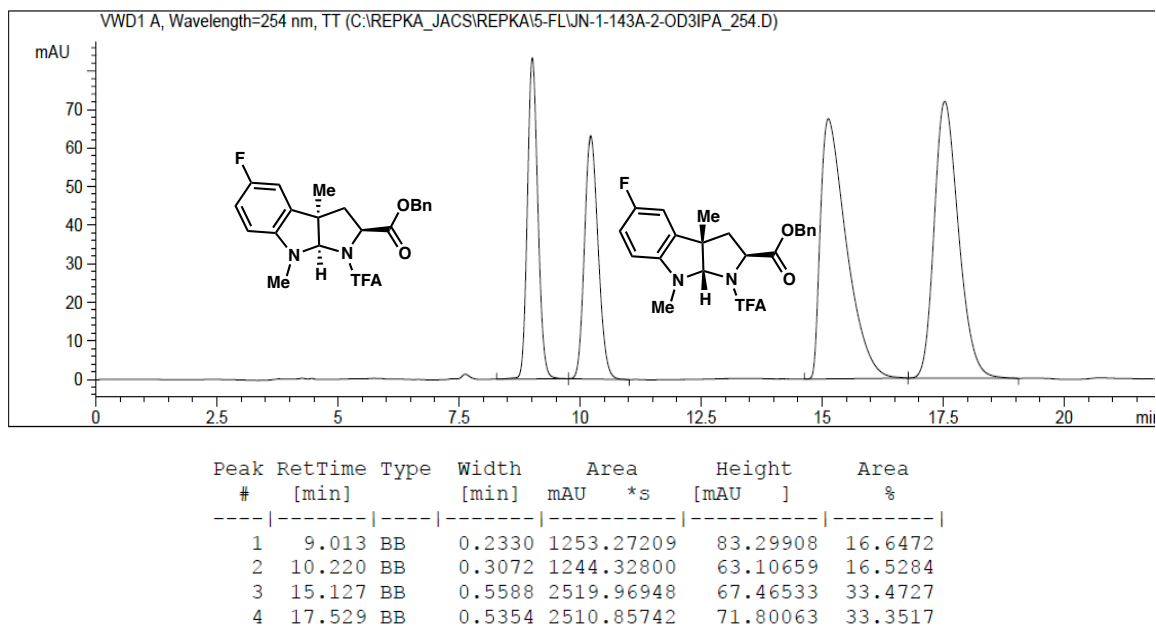
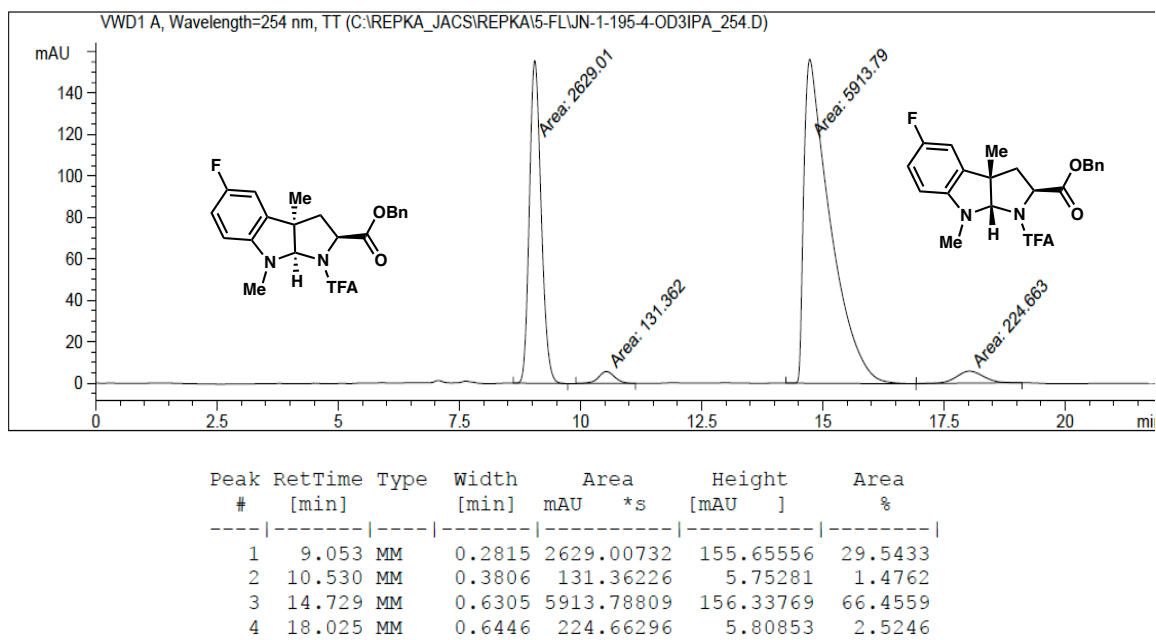
exo-100c (Table 2.2.3, **entry 6**): racemic**exo-100c** (Table 2.2.3, **entry 6**): enantioenriched, 86% ee

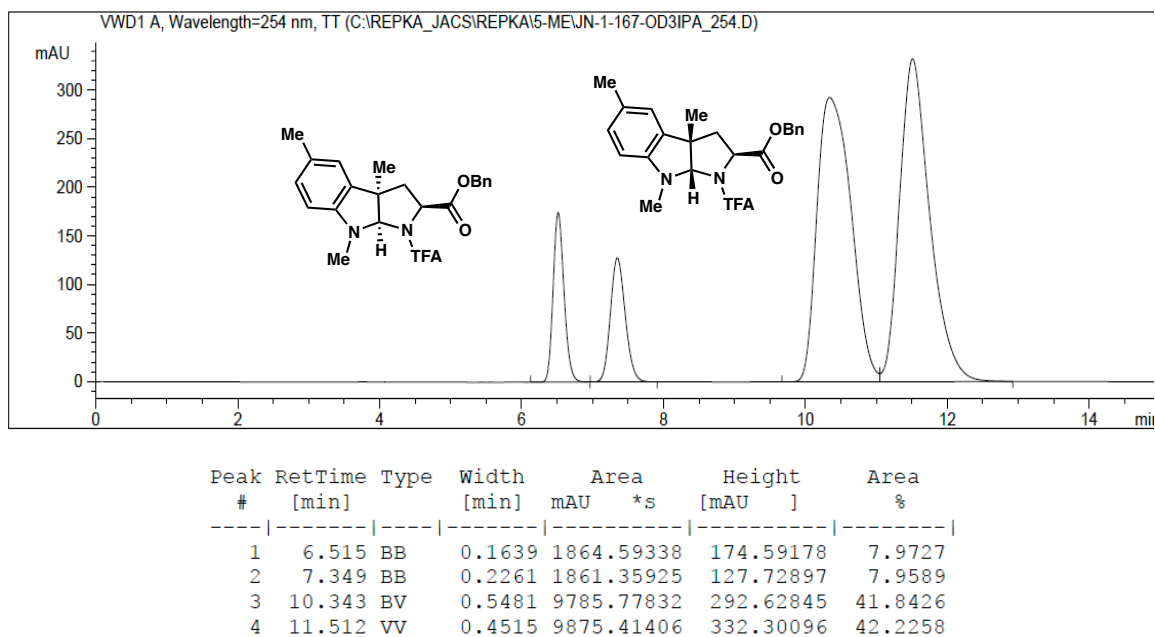
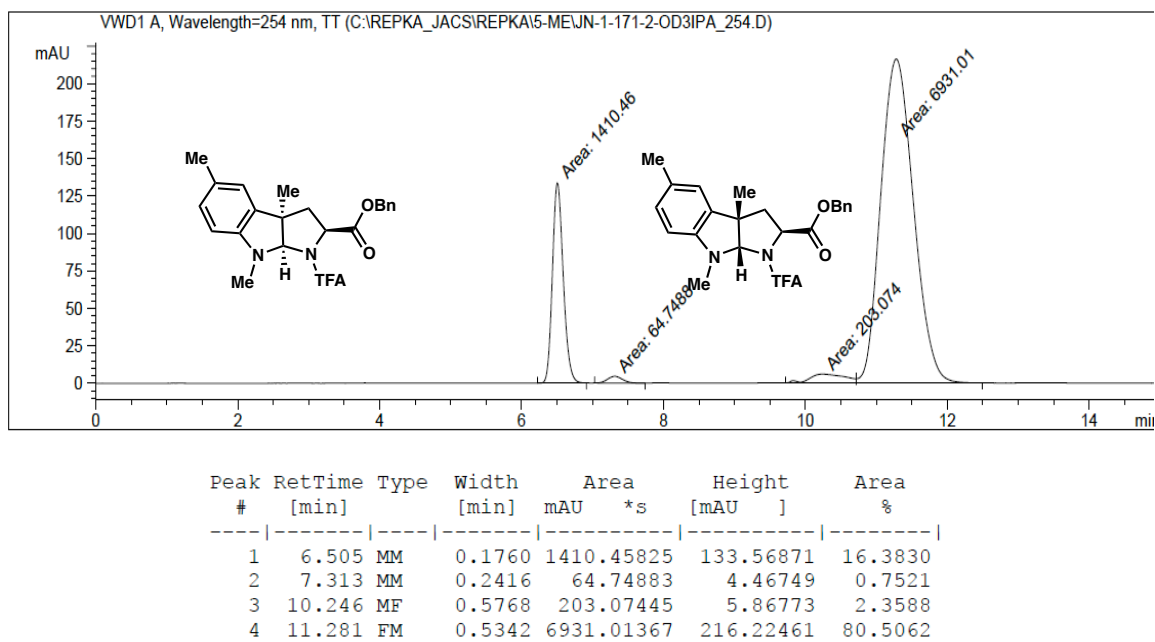
exo-100d (Table 2.2.3, **entry 7**): racemic**exo-100d** (Table 2.2.3, **entry 7**): enantioenriched, 74% ee

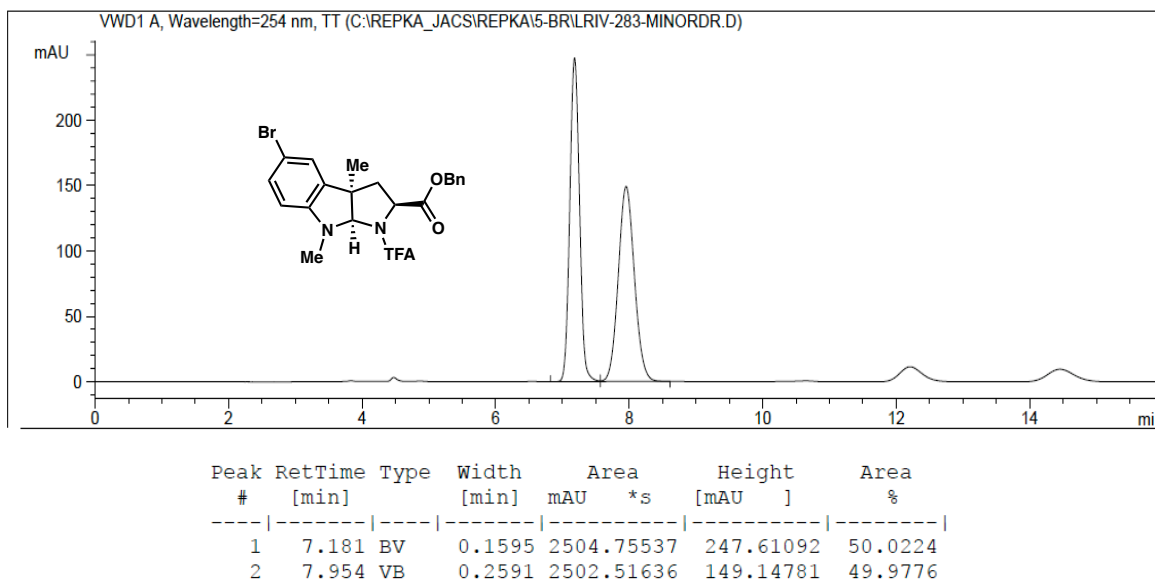
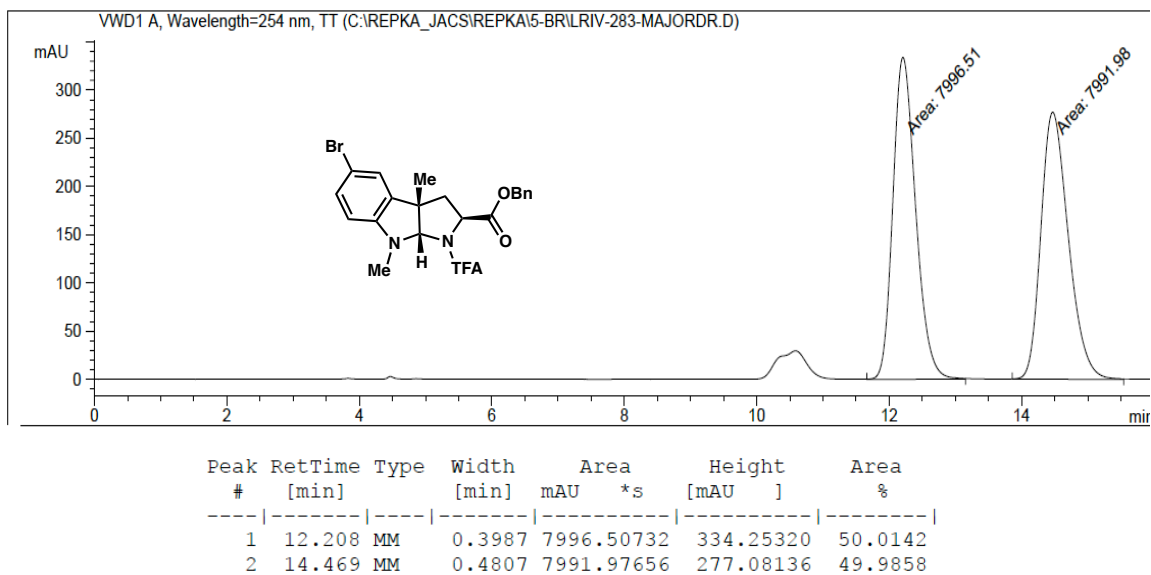
endo-100d (Table 2.2.3, **entry 7**): racemic**endo-100d** (Table 2.2.3, **entry 7**): enantioenriched, 82% ee

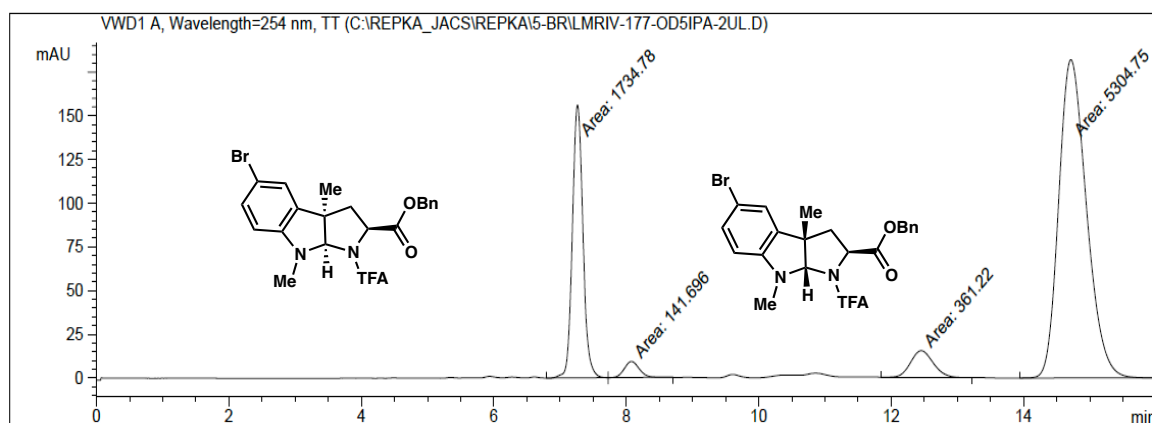
100e (Table 2.2.3, entry 9): racemic**100e** (Table 2.2.3, entry 9): enantioenriched, *exo*: 94% ee, *endo*: 91% ee

106a (Scheme 2.2.1): racemic**106a** (Scheme 2.2.1): *exo*: 93% ee, *endo*: 92% ee

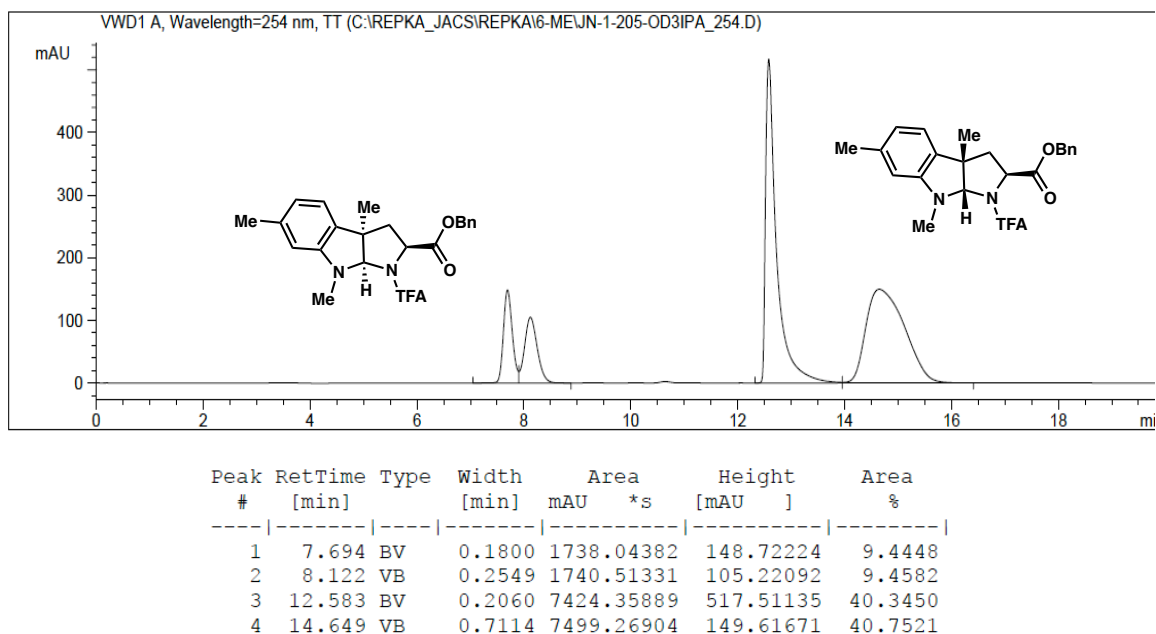
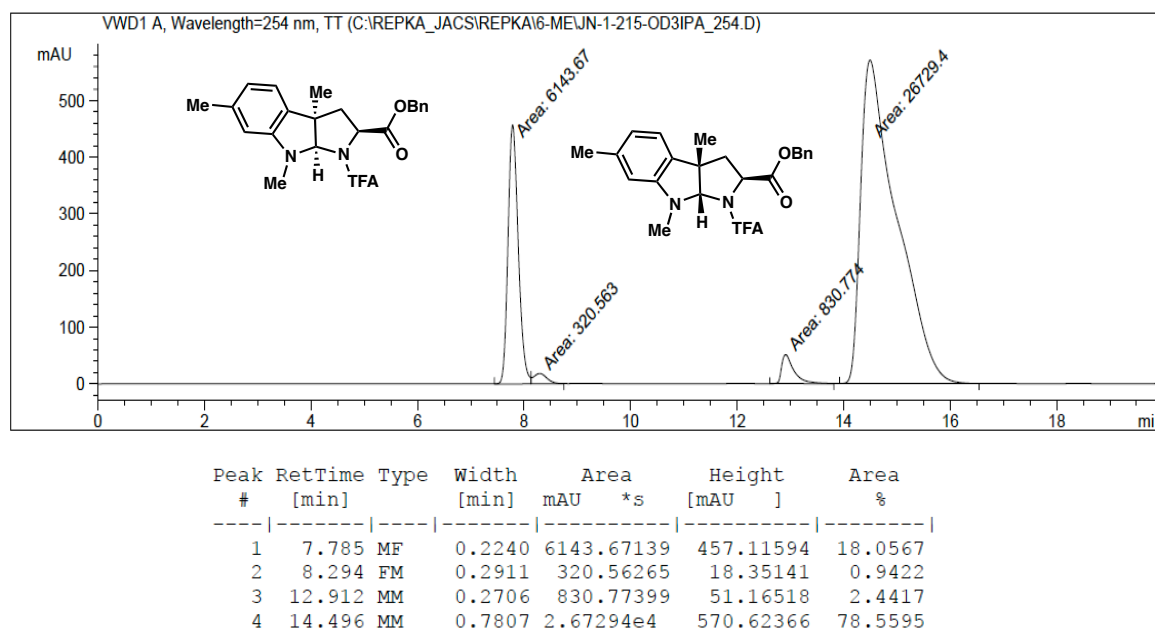
106b (Scheme 2.2.1): racemic**106b** (Scheme 2.2.1): *exo*: 93% ee *endo*: 90% ee

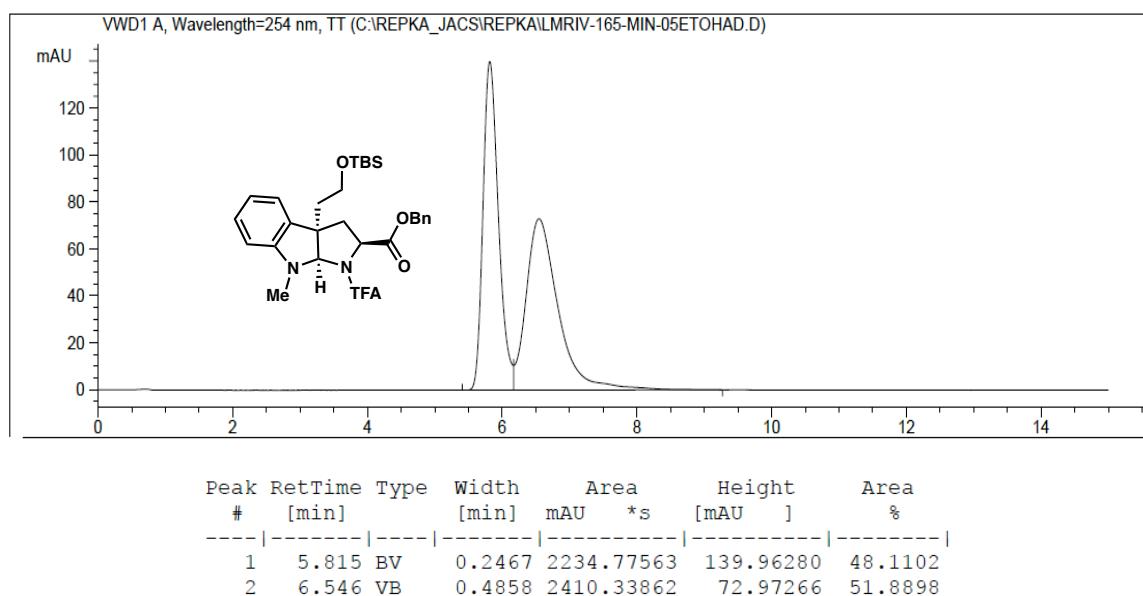
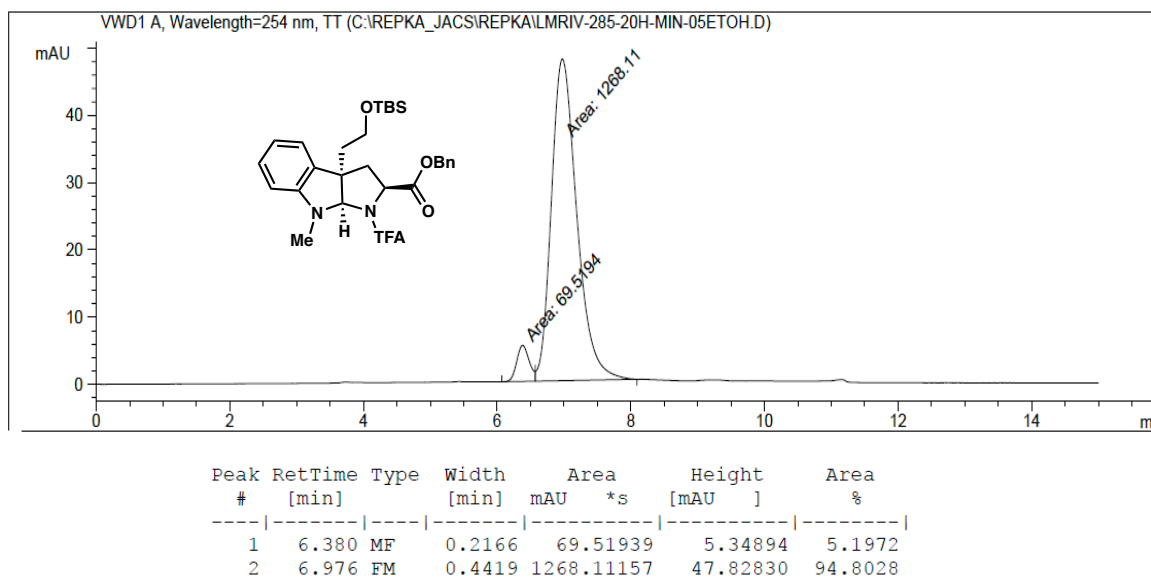
106c (Scheme 2.2.1): racemic**106c** (Scheme 2.2.1): enantioenriched, *exo*: 94% ee, *endo*: 91% ee

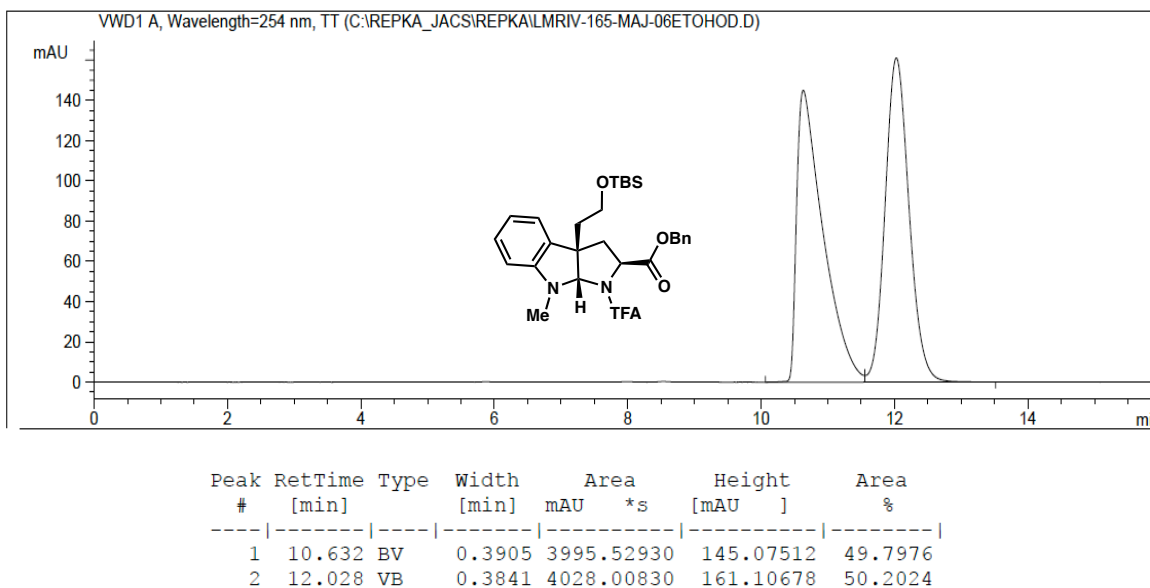
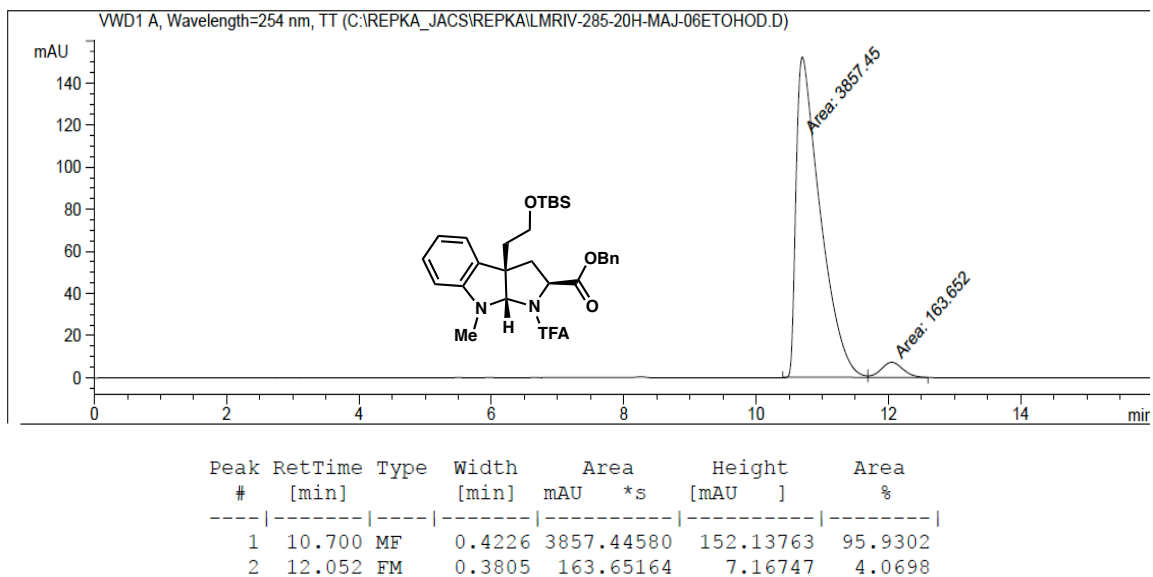
endo-106d (Scheme 2.2.1): racemic**exo-106d** (Scheme 2.2.1): racemic

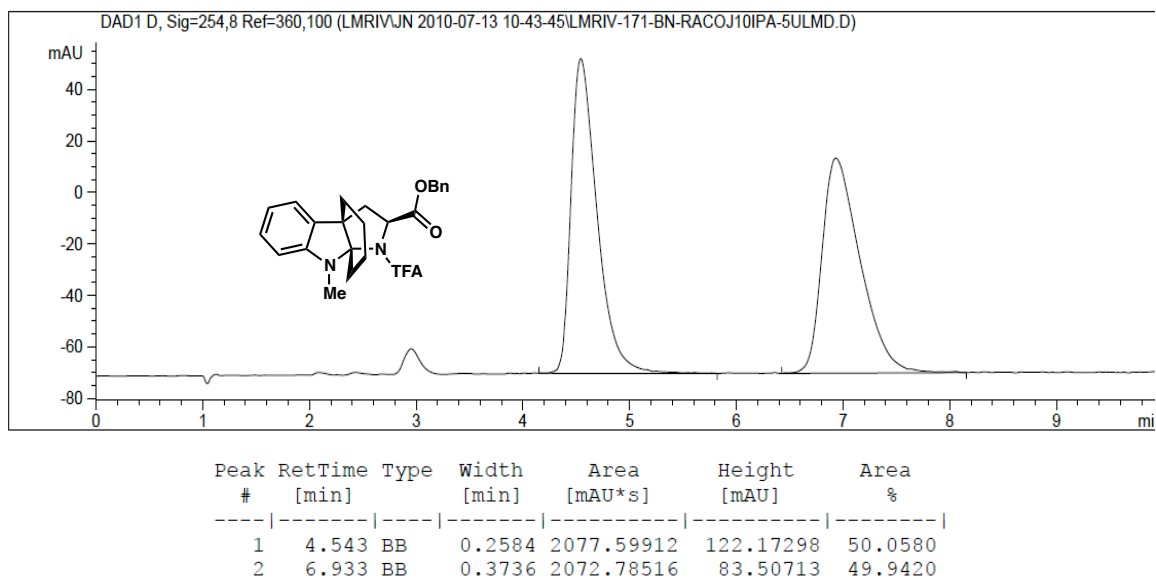
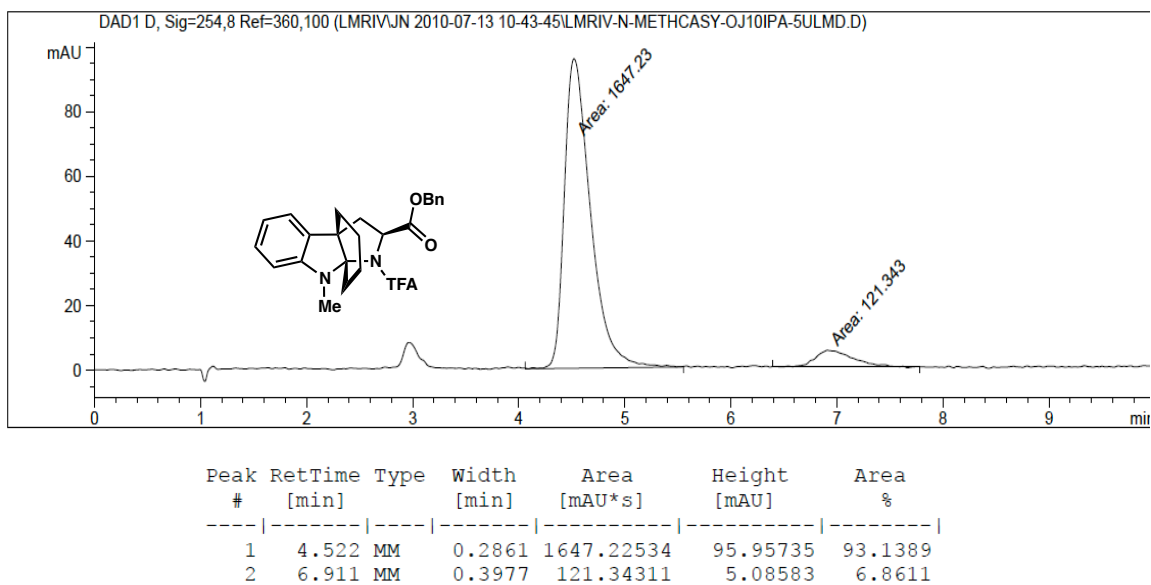
106d (Scheme 2.2.1): *exo*: 87% ee, *endo*: 85% ee

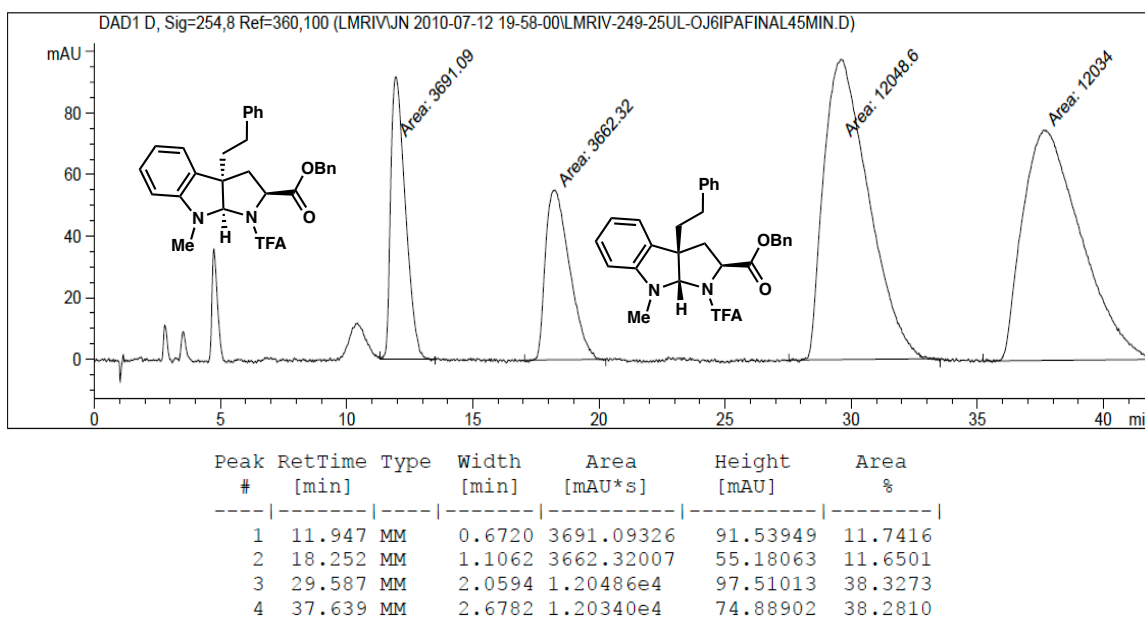
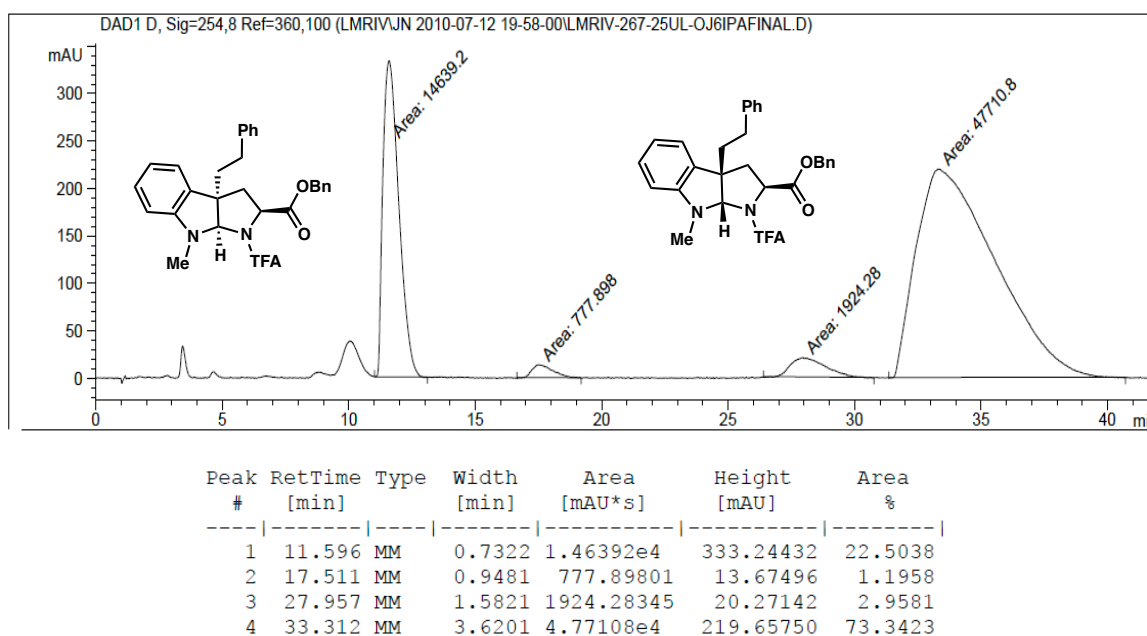
Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	7.263	MF	0.1852	1734.78003		156.08707	23.0002
2	8.076	FM	0.2580	141.69585		9.15505	1.8786
3	12.454	MM	0.3947	361.21967		15.25336	4.7892
4	14.714	MM	0.4855	5304.75488		182.11263	70.3320

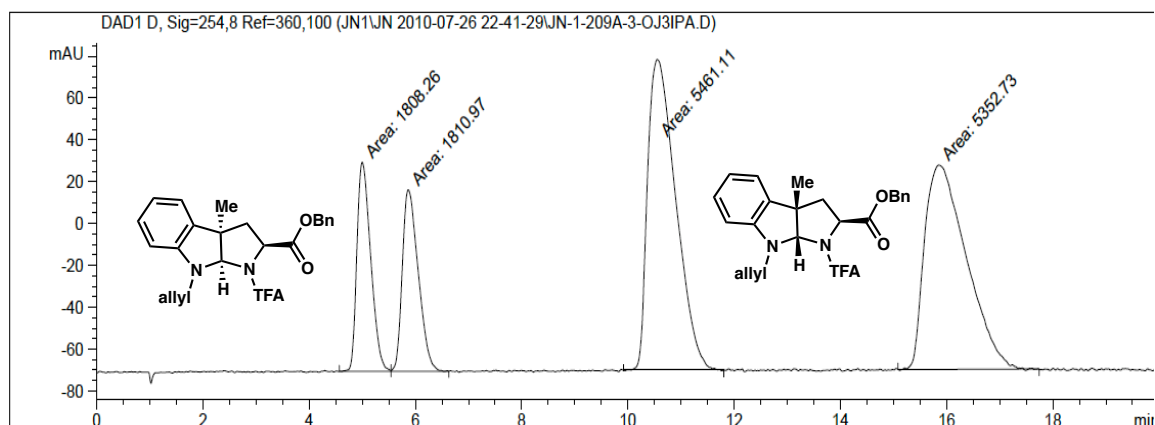
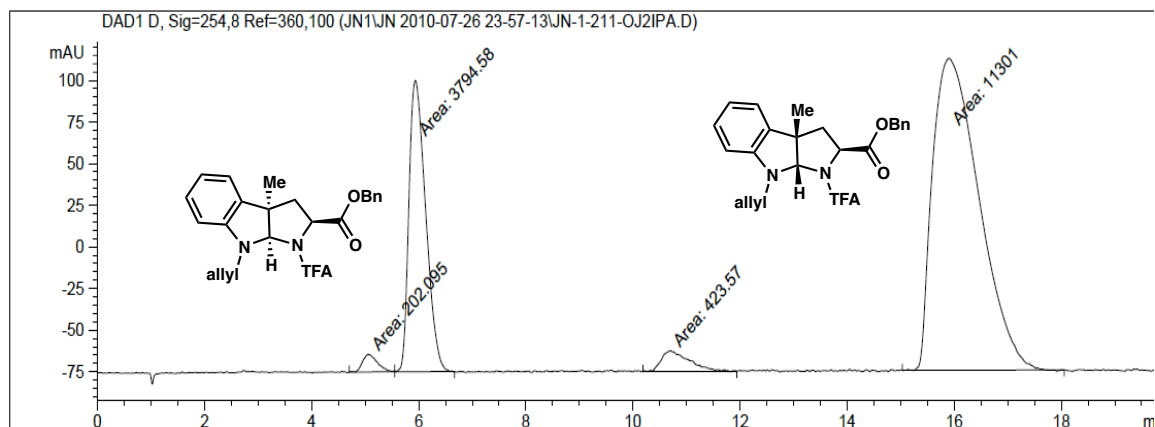
106e (Scheme 2.2.1): racemic**106e** (Scheme 2.2.1): *exo*: 94% ee, *endo*: 90% ee

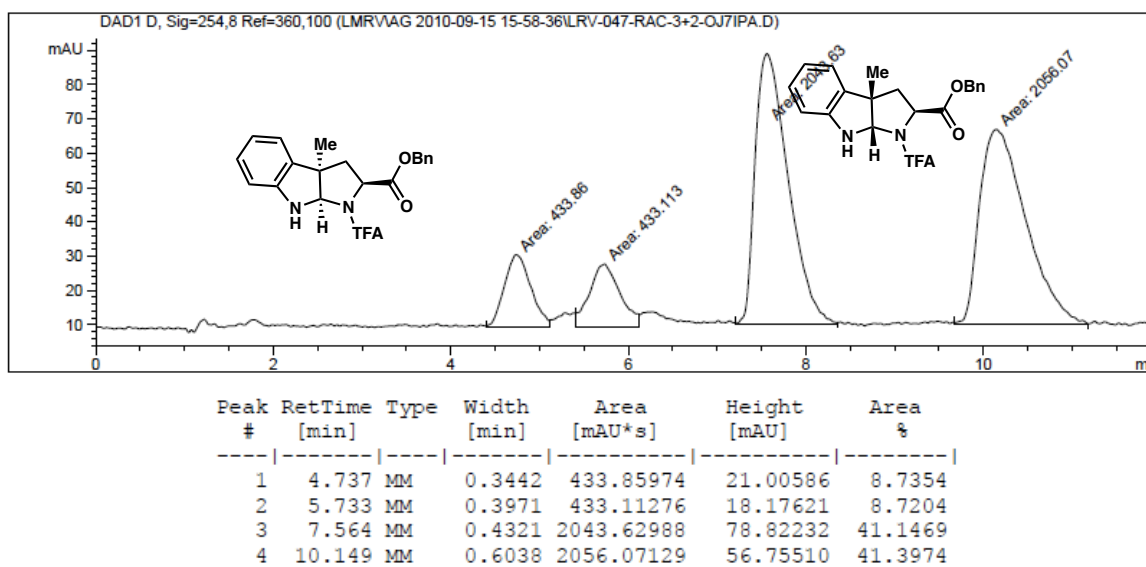
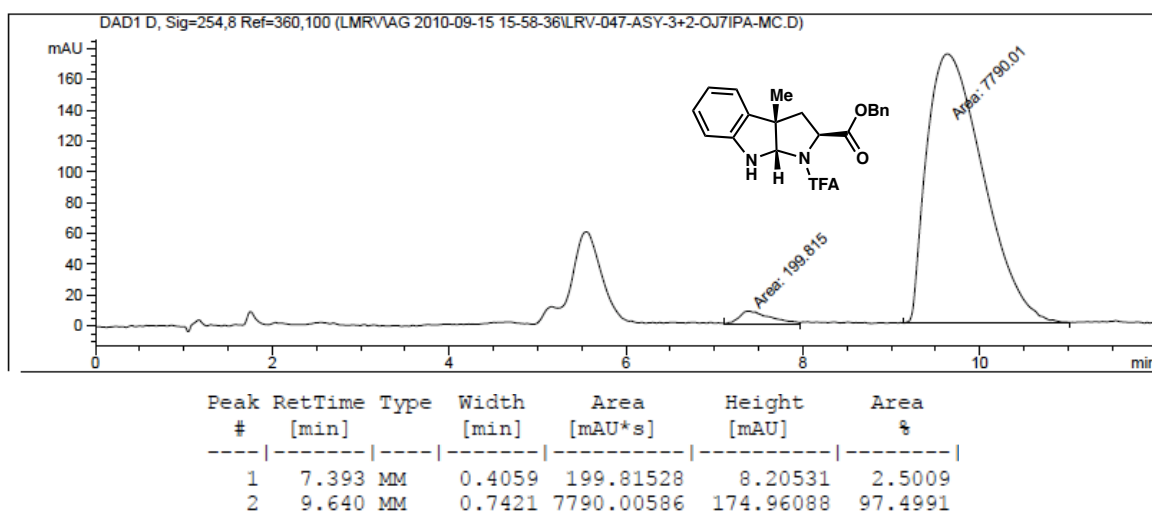
endo-106f (Scheme 2.2.1): racemic**endo-106f** (Scheme 2.2.1): 90% ee

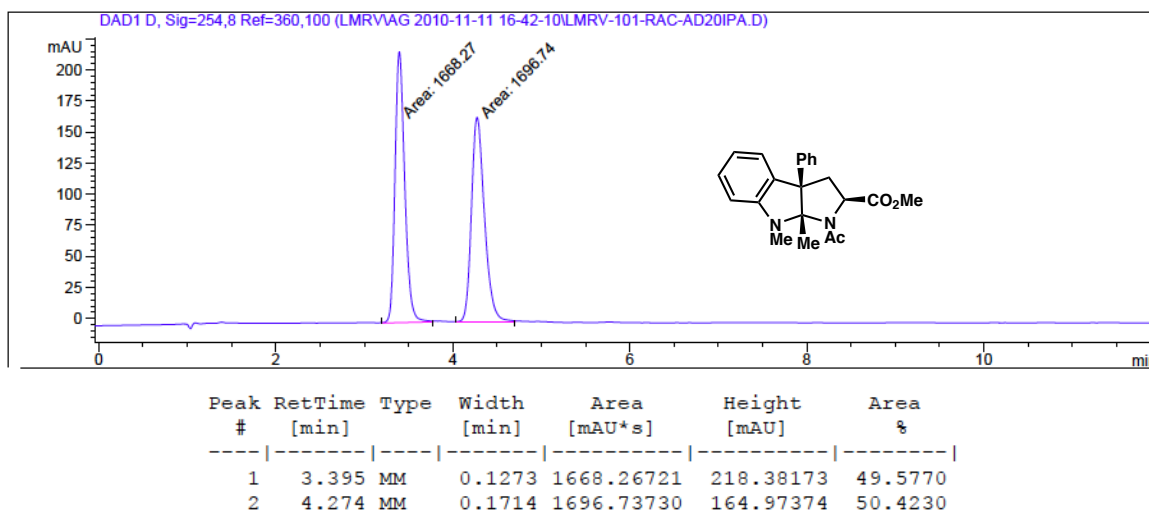
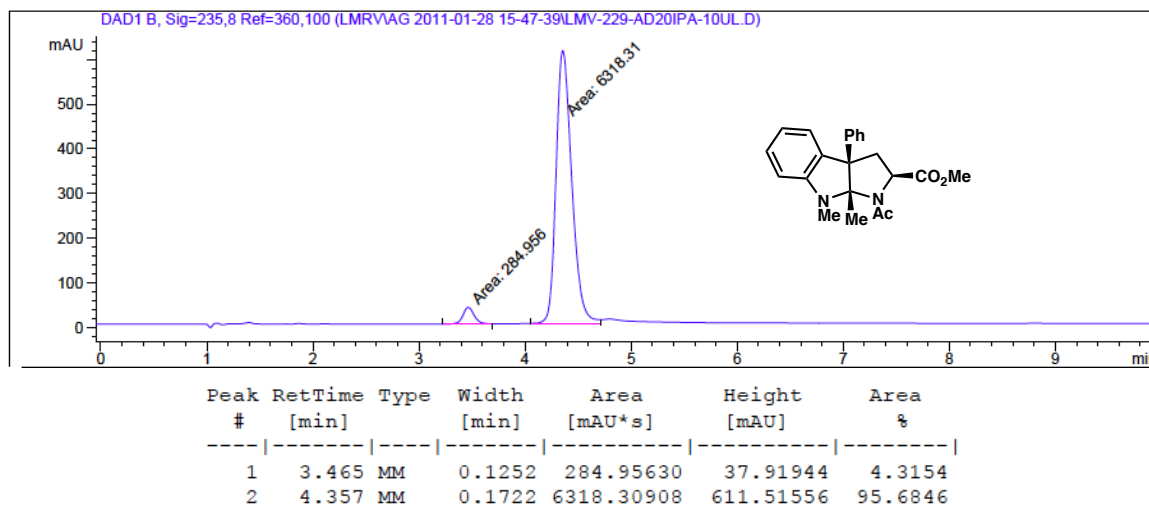
exo-106f (Scheme 2.2.1): racemic**exo-106f** (Scheme 2.2.1): 92% ee

106g (Scheme 2.2.1): racemic**106g** (Scheme 2.2.1): *exo*: 86% ee

106h (Scheme 2.2.1): racemic**106h** (Scheme 2.2.1): *exo*: 92% ee, *endo*: 90% ee

106i (Scheme 2.2.1): racemic**106i** (Scheme 2.2.1): *exo*: 93% ee, *endo*: 90% ee

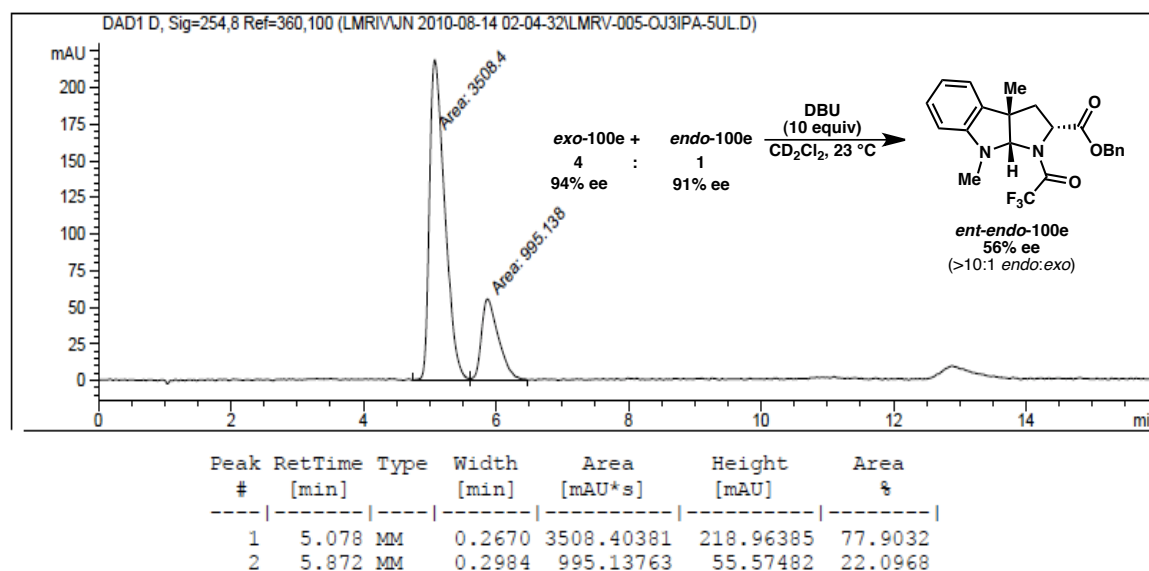
106j (Scheme 2.2.1): racemic**106j** (Scheme 2.2.1): enantioenriched, *exo*: 95% ee

3a-phenylpyrroloindoline 118: racemic**3a-phenylpyrroloindoline 118: 91% ee**

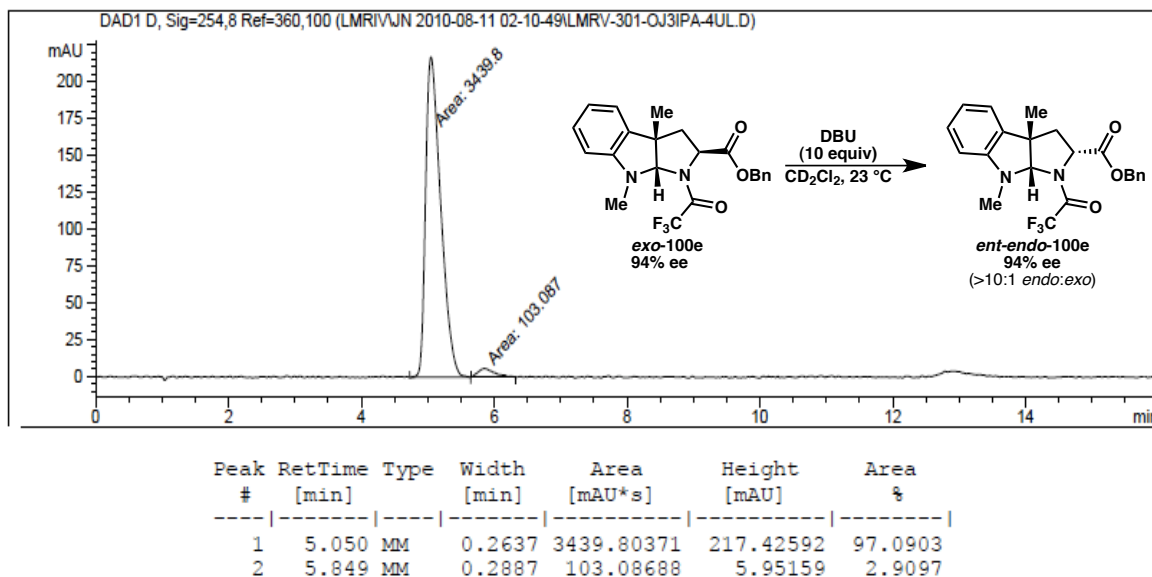
2.5.9 General Procedure D. Epimerization Studies

To an NMR tube was added a solution of pyrroloindoline **100e** (0.063 mmol, 1.00 equiv) in CD₂Cl₂ (0.46 mL), followed by DBU (0.63 mmol, 10.00 equiv). The reaction was monitored by ¹H NMR until the ratio of diastereomers reached an equilibrium. At this point the reaction was diluted with 3 mL CHCl₃ and 25 mL ethyl acetate and washed with saturated NaHCO_{3(aq)} (3 x 15 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated to give the mixture of pyrroloindoline diastereomers as a pale yellow oil with quantitative recovery of material.

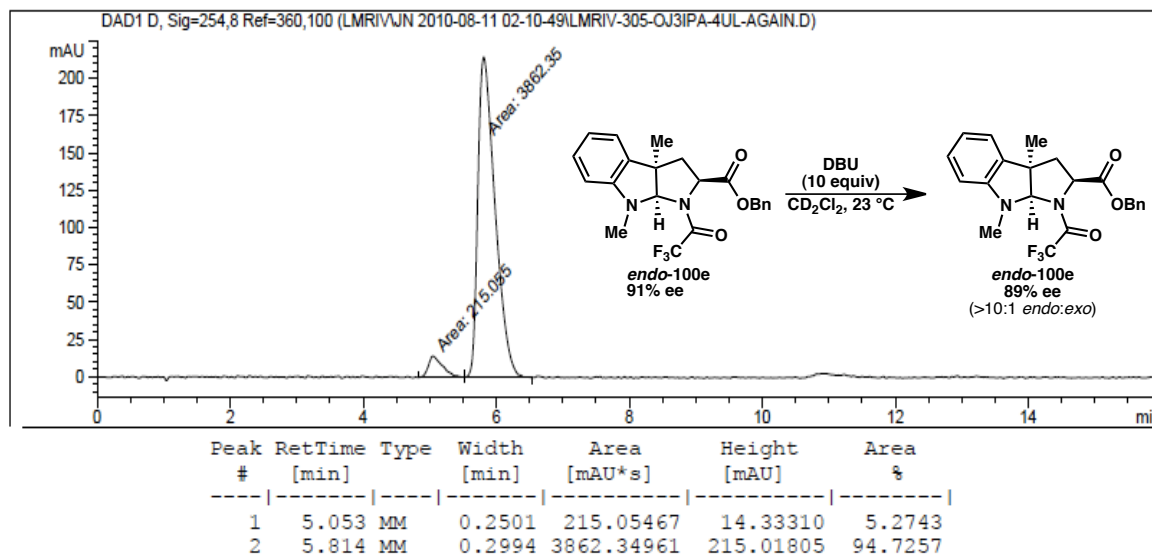
Experiment 1: Treatment of a 4:1 mixture of *exo*-**100e** (94% ee) + *endo*-**100e** (91% ee) with DBU (10 equiv) for 65 h to give >10:1 *ent-endo*-**100e** (56% ee).



Experiment 2: Treatment of diastereomerically pure **exo-100e** (94% ee) with DBU (10 equiv) for 96 h to give >10:1 **ent-endo-100e** (94% ee).



Experiment 3: Treatment of diastereomerically pure **endo-100e** (91% ee) with DBU (10 equiv) for 30 h to return **endo-100e** (89% ee).



2.5.10 **Resubjection of Pure Exo and Endo Pyrroloindolines to Reaction Conditions**

To an NMR tube was added a solution of pure pyrroloindoline *exo*-**100e** (0.073 mmol, 1.00 equiv, 94% ee) in CD₂Cl₂ (297 μL), followed by (*R*)-BINOL (from a 0.0675 M solution in CD₂Cl₂, 0.015 mmol, 0.20 equiv) and SnCl₄ (from a 0.72 M solution in CD₂Cl₂, 0.088 mmol, 1.2 equiv). After 4 h at room temperature, the solution was quenched according to general procedure C. The same experiment was performed with pure *endo*-**100e** (91% ee), except at a concentration of 0.065 M. In both cases, no epimerization or erosion of ee was observed.

2.6 NOTES AND REFERENCES

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- (46) 1,2-dimethyl-3-phenylindole (**117**) was prepared from 2-methyl-3-phenylindole (**133**) according to a literature procedure: Berti, C.; Greci, L.; Poloni, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1610.

APPENDIX 1

Spectra Relevant to Chapter 2:

Formal (3 + 2) Cycloaddition Approach

to Pyrroloindolines

JN-1-197-col

Sample Name:

JN-1-197-col

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/jni/vnmrsys/data

Sample directory:

JN-1-197-col

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdc13

Data collected on: Jul 19 2010

Temp. 25.0 C / 298.1 K

Sample #22, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.706 sec

Width 4810.0 Hz

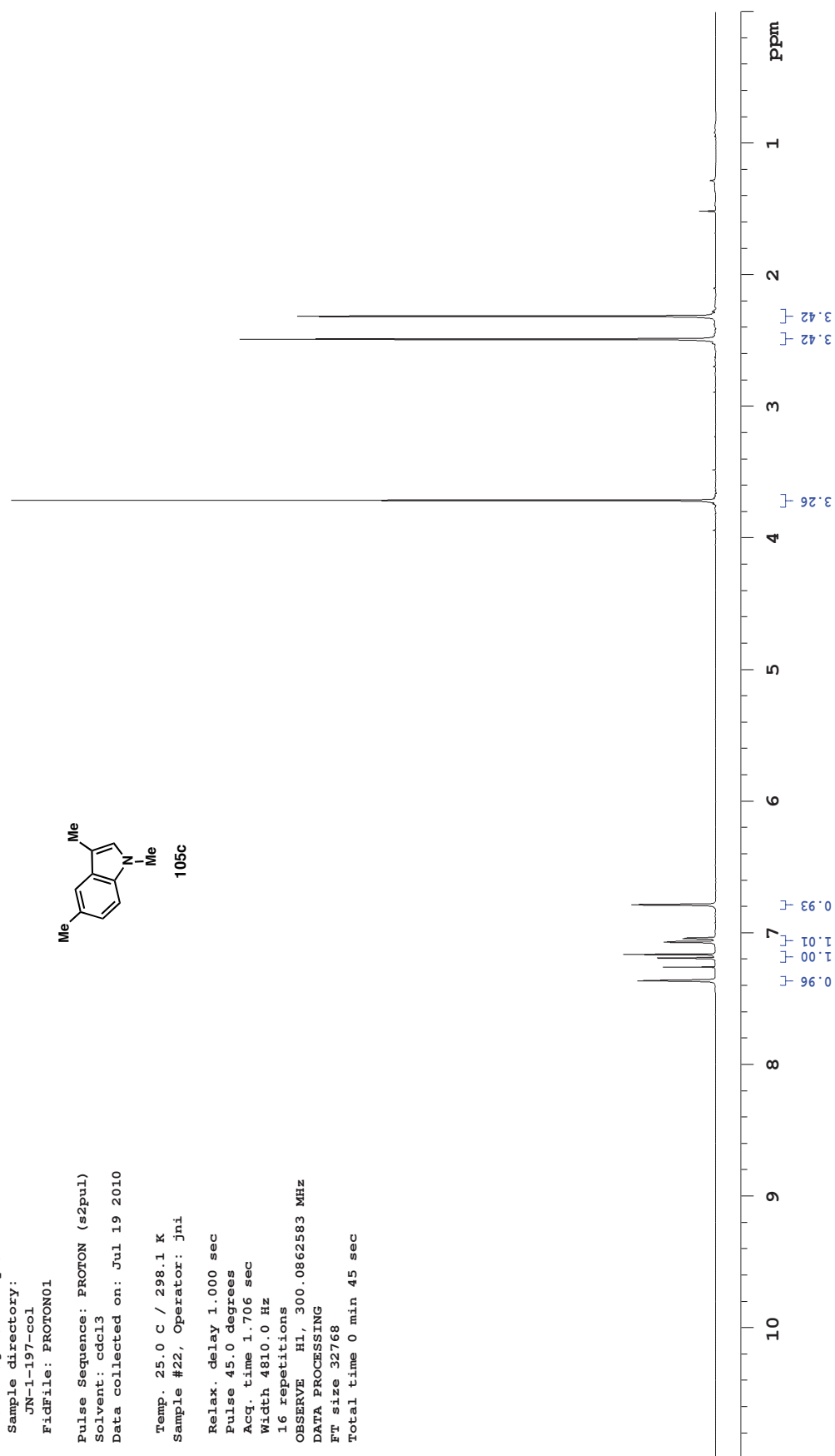
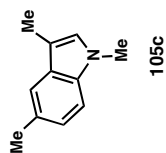
16 repetitions

OBSERVE H1, 300.0862583 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 45 sec



JN-1-197

Sample Name:

JN-1-197

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-197

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 19 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

3200 repetitions

OBSERVE C13, 125.6602406 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

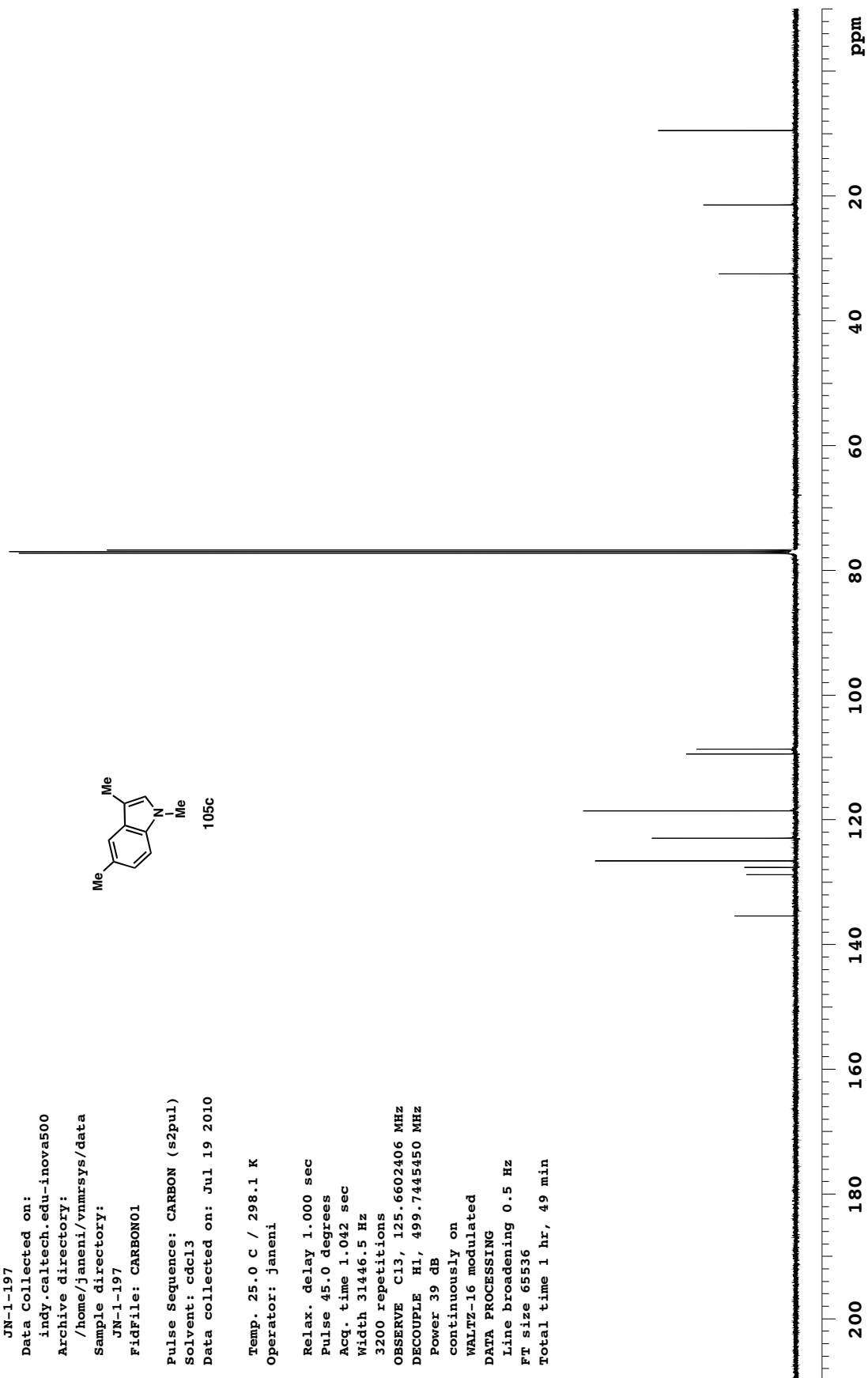
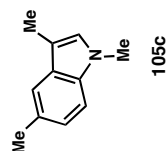
WALTZ-16 modulated

DATA PROCESSING

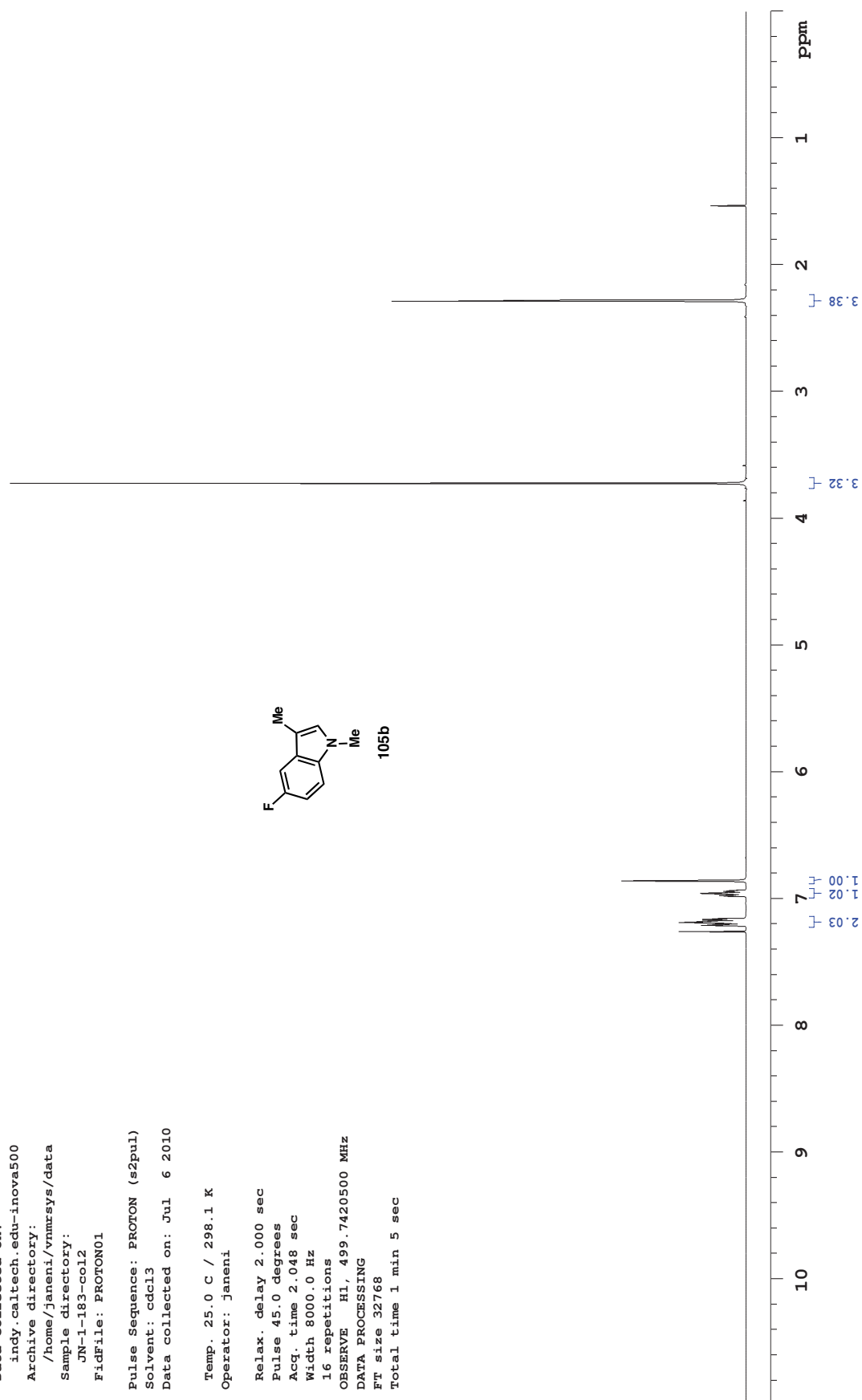
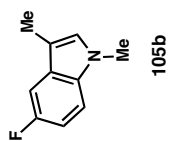
Line broadening 0.5 Hz

FT size 65536

Total time 1 hr, 49 min



Total time 1 min 5 sec



JN-1-183-col2

Sample Name:

JN-1-183-col2

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrSYS/data

Sample directory:

JN-1-183-col2

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 6 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

3200 repetitions

OBSERVE C13, 125.6602397 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

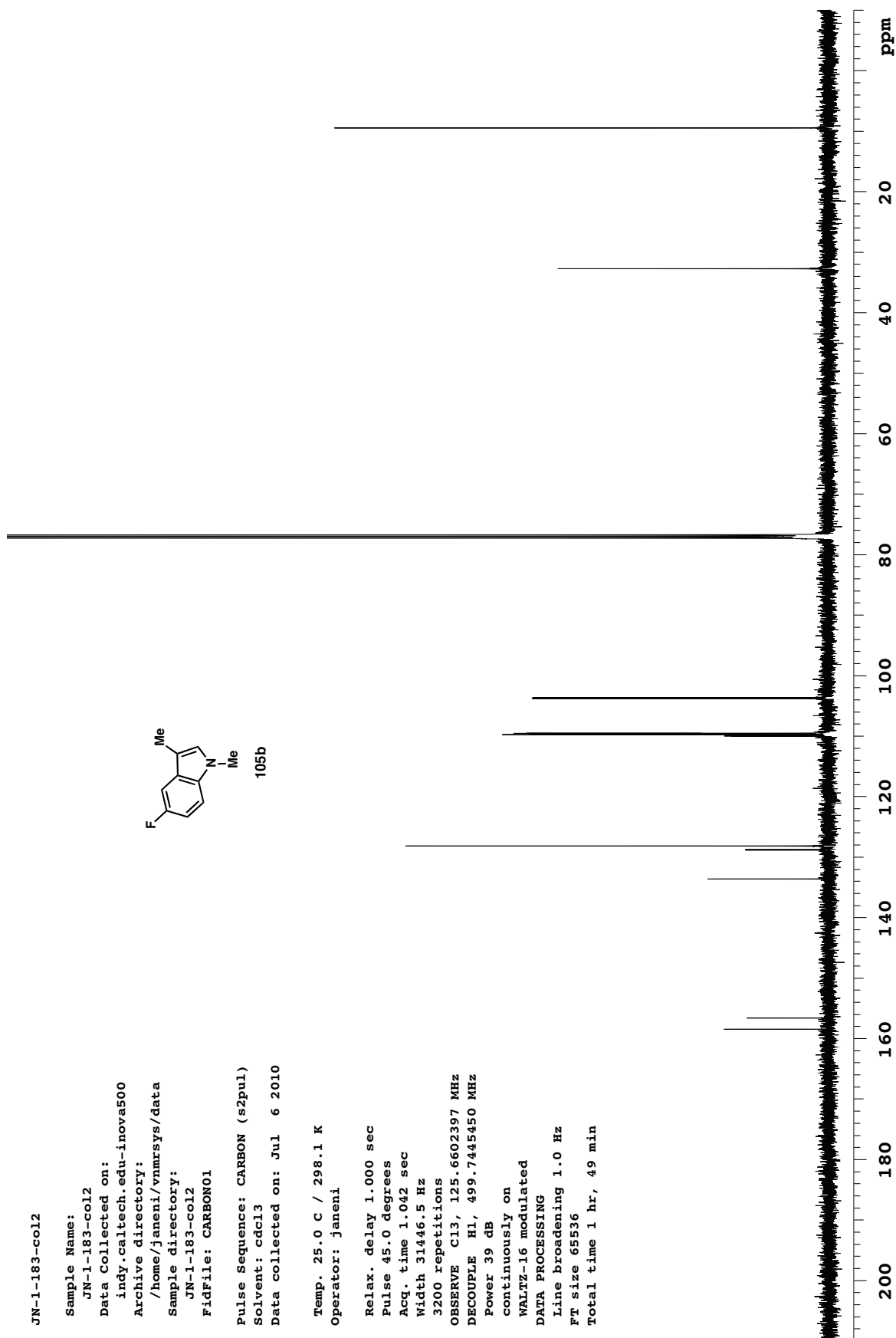
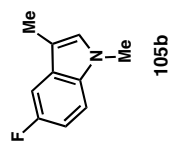
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 1 hr, 49 min



JN-1-181-col

Sample Name:

JN-1-181-col

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-181-col

File: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 27 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.048 sec

Width 8000.0 Hz

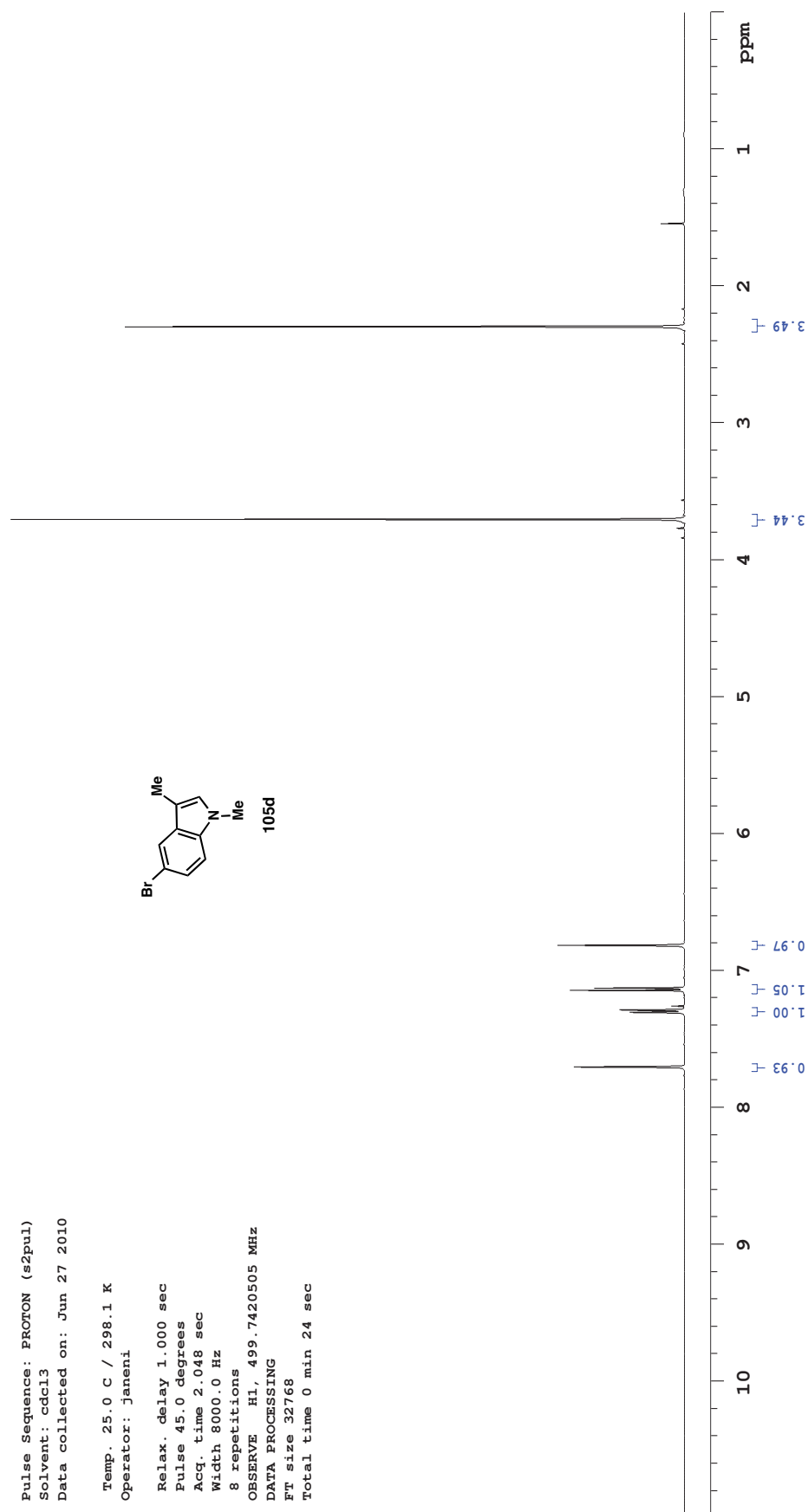
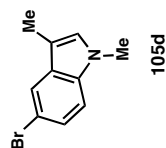
8 repetitions

OBSERVE H1, 499.7420505 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 24 sec



JN-1-181-col

Sample Name:

JN-1-181-col

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-181-col

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jun 27 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

3200 repetitions

OBSERVE C13, 125.6602458 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

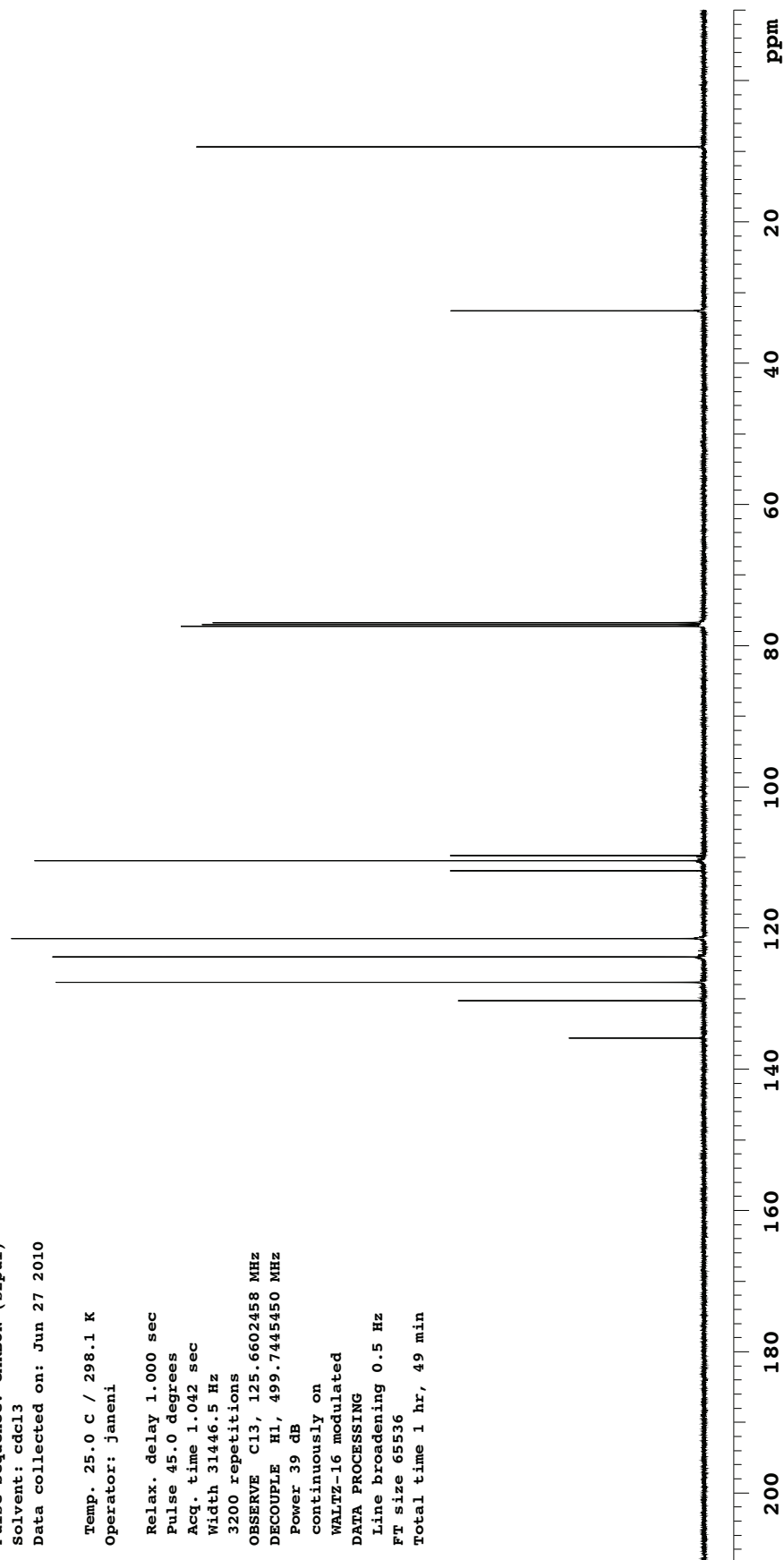
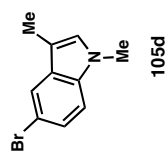
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 1 hr, 49 min



JN-1-199-col

Sample Name:

JN-1-199-col

Data Collected on:

sienna.caltech.edu-vnmrs400

Archive directory:

/home/jni/vnmrsys/data

Sample directory:

JN-1-199-col

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdc13

Data collected on: Jul 24 2010

Temp. 26.0 C / 299.1 K

Sample #11, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.556 sec

Width 6410.3 Hz

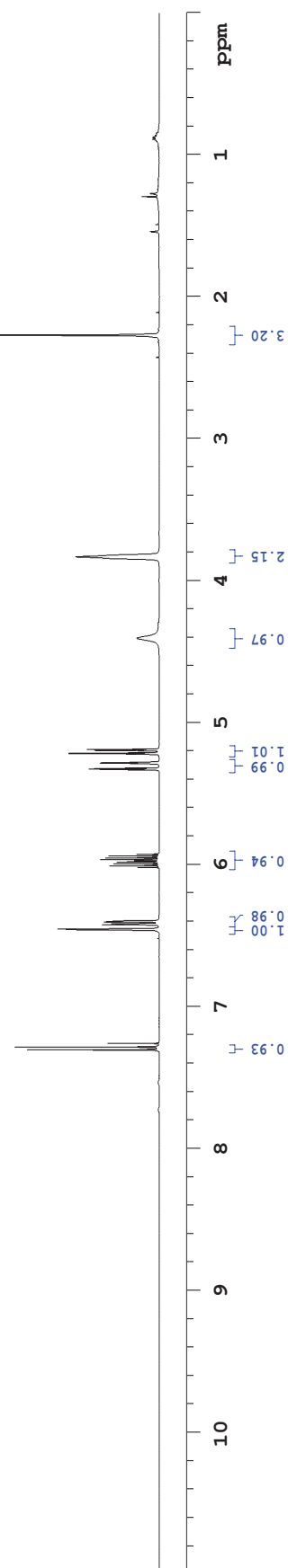
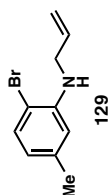
16 repetitions

OBSERVE H1, 399.7942813 MHz

DATA PROCESSING

Ft size 32768

Total time 0 min 57 sec



JN-1-199-col

Sample Name:

JN-1-199-col

Data Collected on:

siena.caltech.edu-vmrs400

Archive directory:

/home/jni/vmrsys/data

Sample directory:

JN-1-199-col

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 24 2010

Temp. 26.0 C / 299.1 K

Sample #11, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.285 sec

Width 25510.2 Hz

2000 repetitions

OBSERVE C13, 100.5283540 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

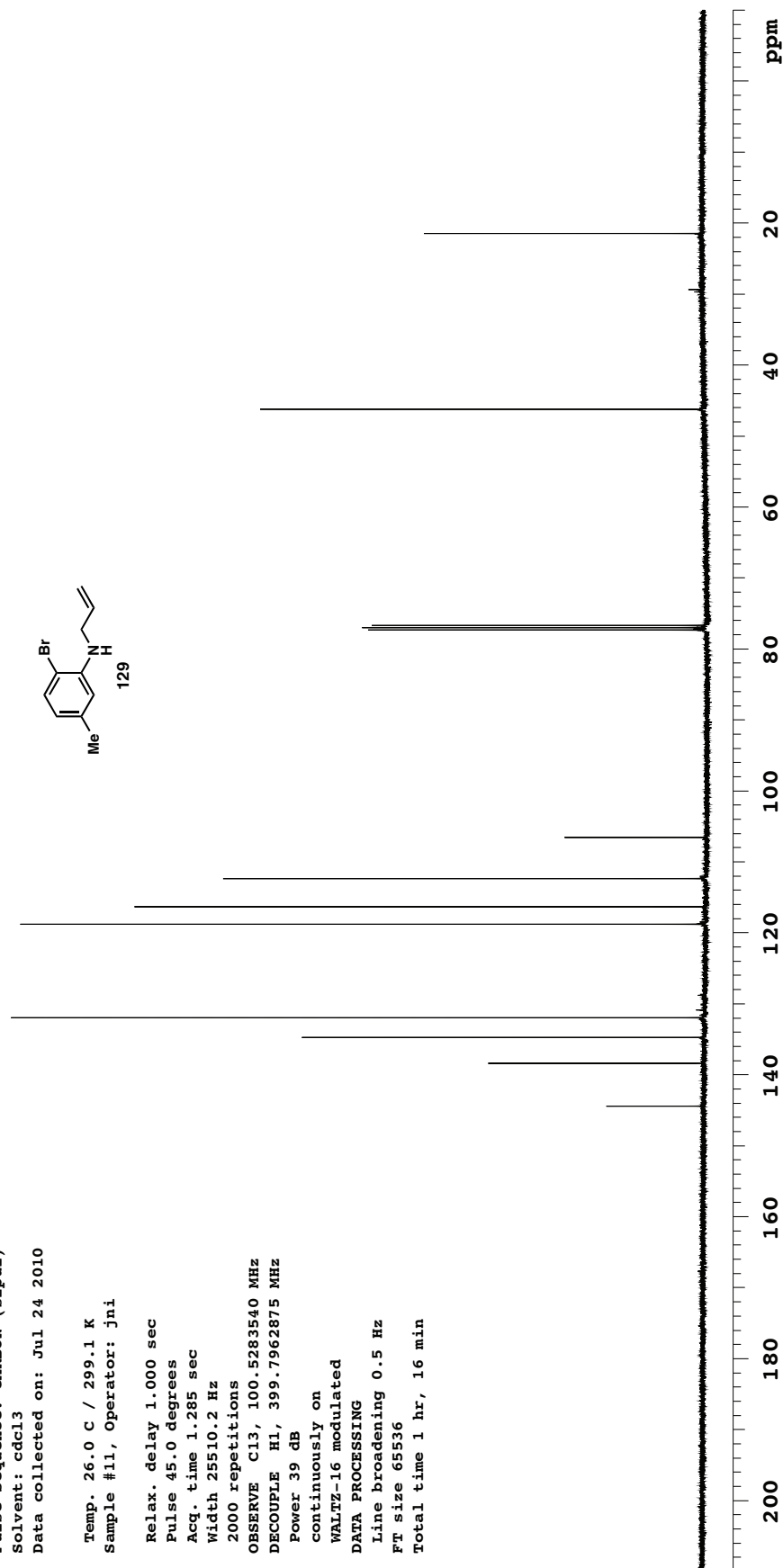
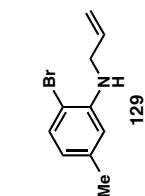
WALTZ-16 modulated

DATA PROCESSING

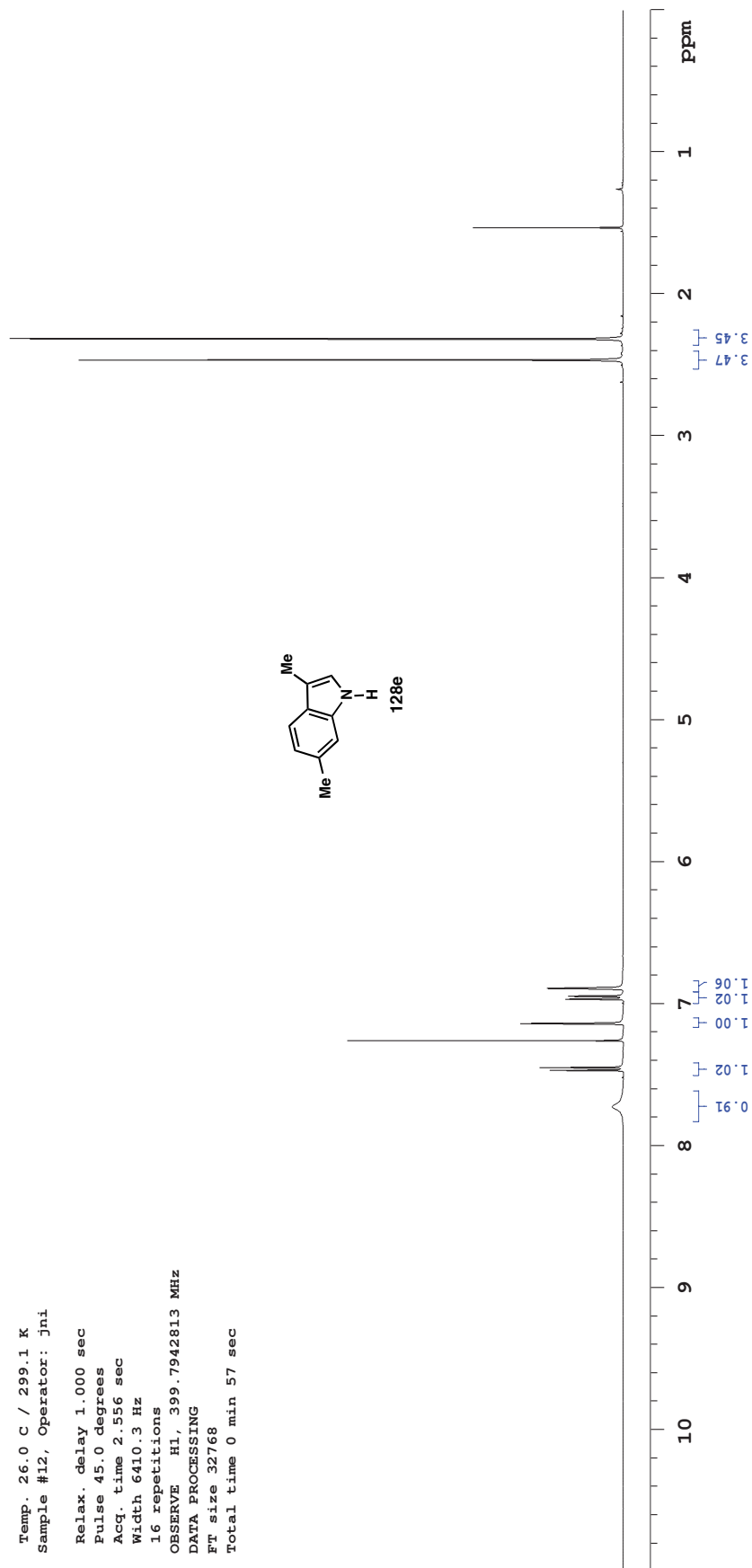
Line broadening 0.5 Hz

Ft size 65536

Total time 1 hr, 16 min



Total time 0 min 57 sec



JN-1-201-col

Sample Name:

JN-1-201-col
Data Collected on:
siena.caltech.edu-vmrs400
Archive directory:
/home/jni/vmrsys/data
Sample directory:
JN-1-201-col
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3
Data collected on: Jul 24 2010

Temp. 26.0 C / 299.1 K

Sample #12, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.285 sec

Width 25510.2 Hz

4000 repetitions

OBSERVE C13, 100.5283515 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

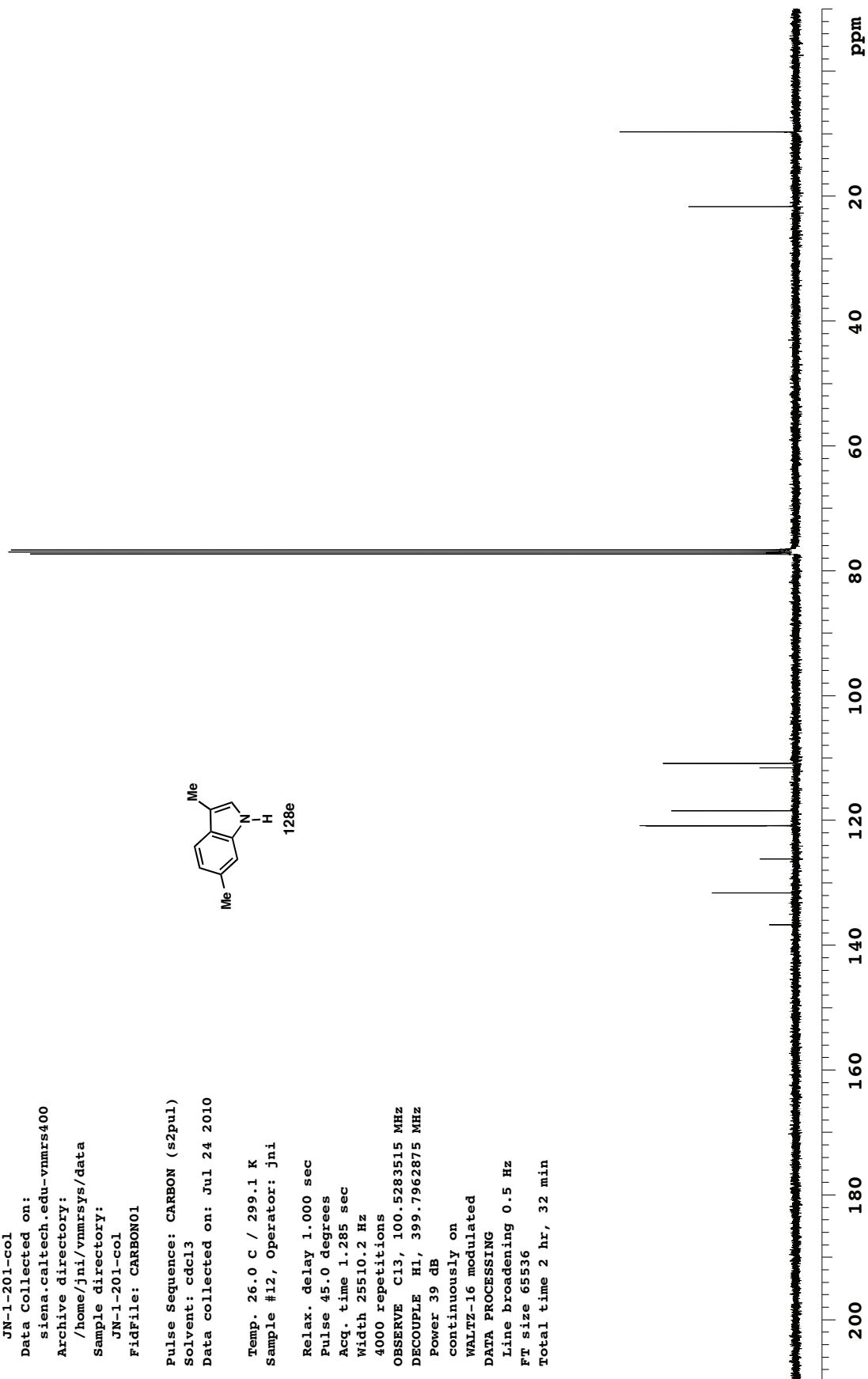
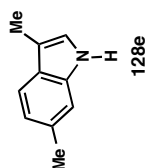
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 2 hr, 32 min



JN-1-203-col

Sample Name:

JN-1-203-col

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/jni/vnmrsys/data

Sample directory:

JN-1-203-col

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 19 2010

Temp. 25.0 C / 298.1 K

Sample #21, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.706 sec

Width 4810.0 Hz

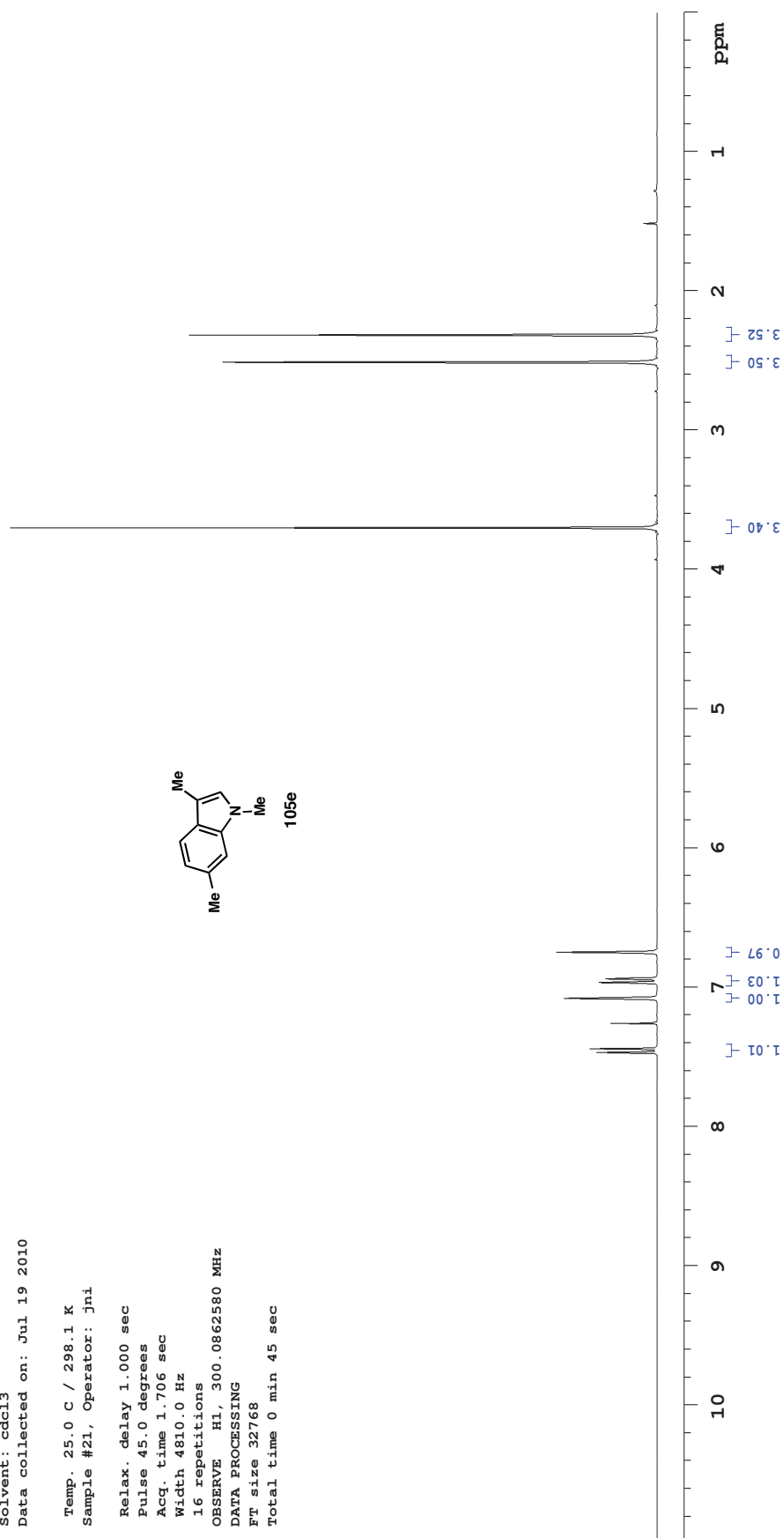
16 repetitions

OBSERVE H1, 300.0862580 MHz

DATA PROCESSING

Ft size 32768

Total time 0 min 45 sec



JN-1-203

Sample Name:

JN-1-203

Data Collected on:

siena.caltech.edu-vmrs400

Archive directory:

/home/jni/vmrsys/data

Sample directory:

JN-1-203

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 19 2010

Temp. 25.0 C / 298.1 K

Sample #3, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.285 sec

Width 25510.2 Hz

5000 repetitions

OBSERVE C13, 100.5283529 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

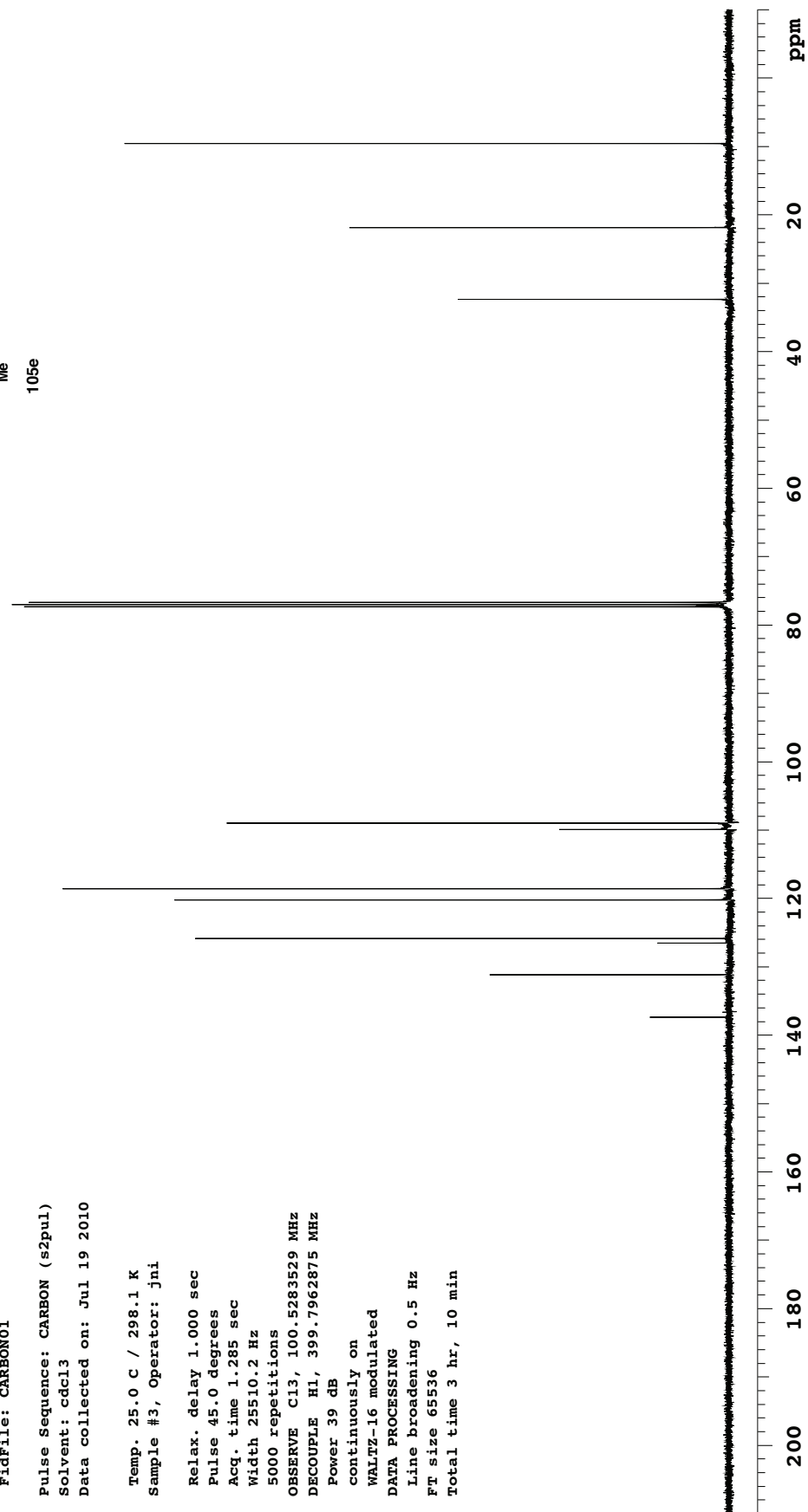
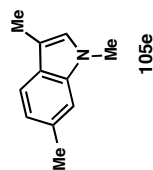
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 3 hr, 10 min



LMRIV-N-me-TBStryptophol

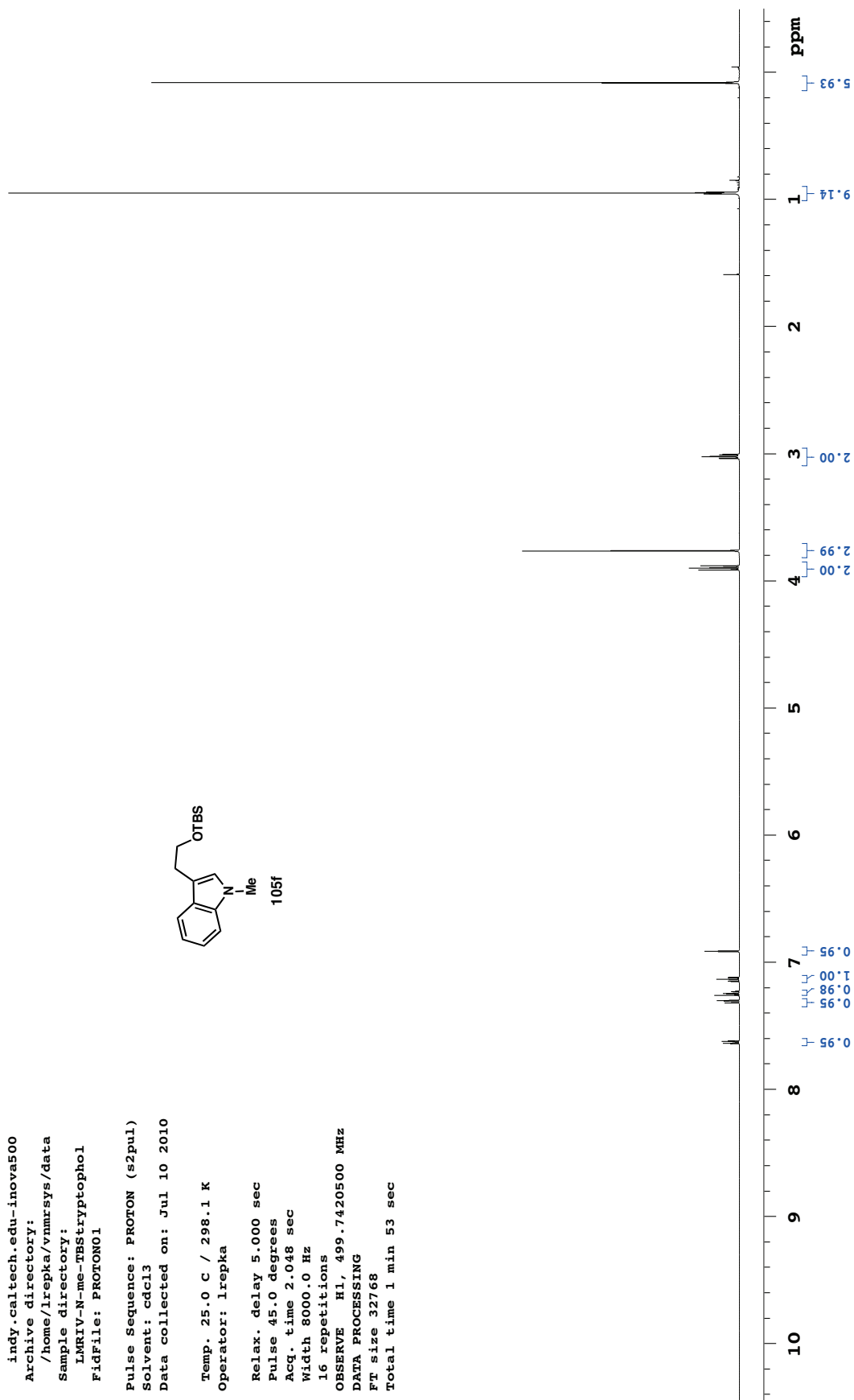
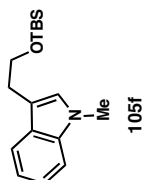
Sample Name:
 LMRIV-N-me-TBStryptophol
 Data Collected on:
 indy.caltech.edu-inoVa500
 Archive directory:
 /home/lrepka/vnmrSYS/data
 Sample directory:
 LMRIV-N-me-TBStryptophol
 FIDFile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jul 10 2010

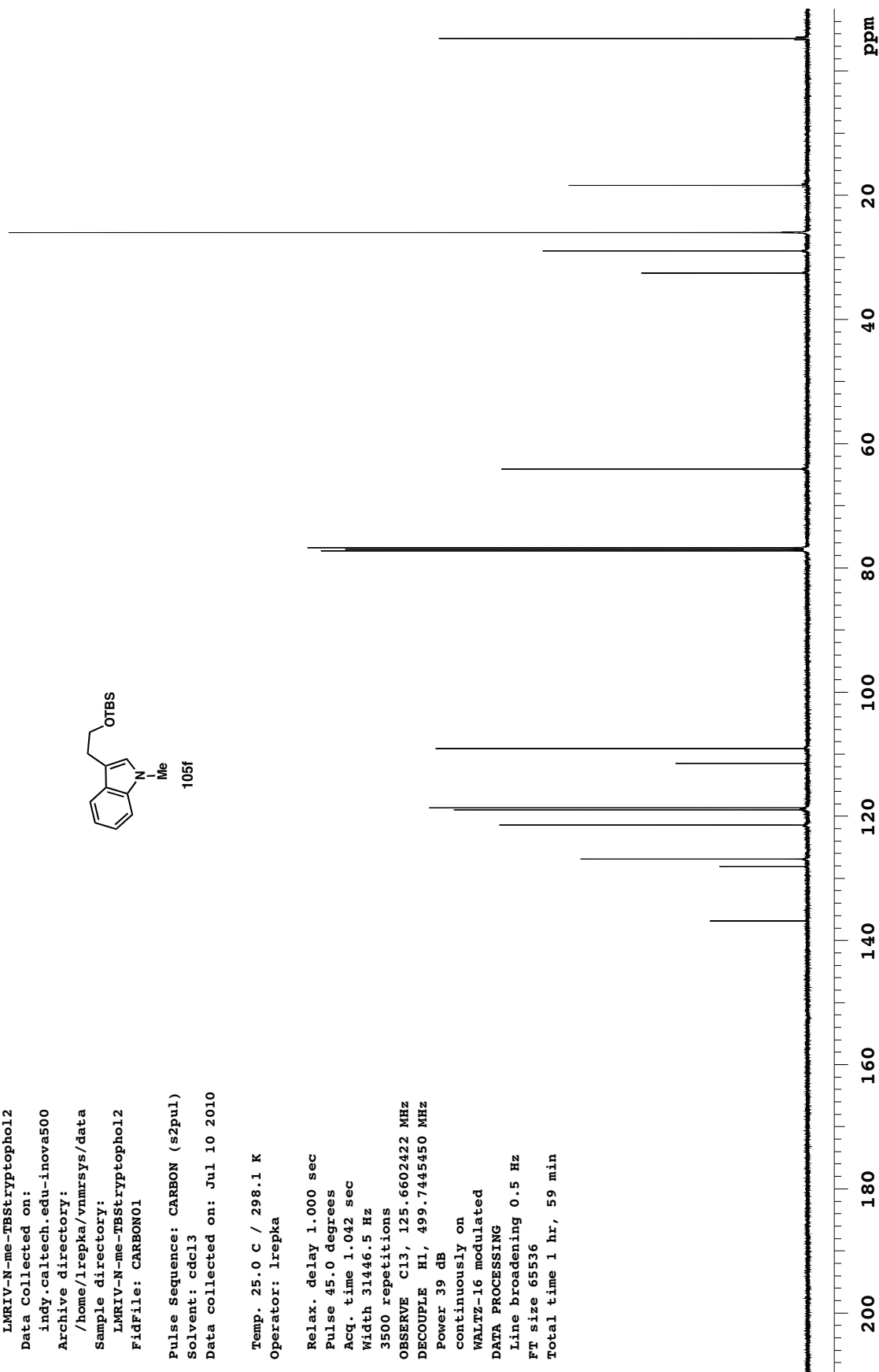
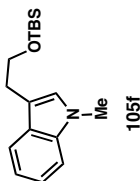
Temp. 25.0 C / 298.1 K
 Operator: lrepka

Relax. delay 5.000 sec
 Pulse 45.0 degrees
 Acq. time 2.048 sec
 Width 8000.0 Hz
 16 repetitions

OBSERVE H1, 499.7420500 MHz
 DATA PROCESSING
 FT size 32768
 Total time 1 min 53 sec



Total time 1 hr, 59 min



LMRIV-057-fxns2-11

Sample Name:

LMRIV-057-fxns2-11

Archive directory:

Sample directory:

FidFile: LMRIV-057-fxns16-20

Pulse Sequence: Proton (s2pul)

Solvent: cdcl3

Data collected on: Mar 1 2010

Operator: lrepka

VNMR-400 "erice.caltech.edu"

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.998 sec

Width 4796.2 Hz

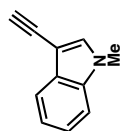
8 repetitions

OBSERVE H1, 299.8165711 MHz

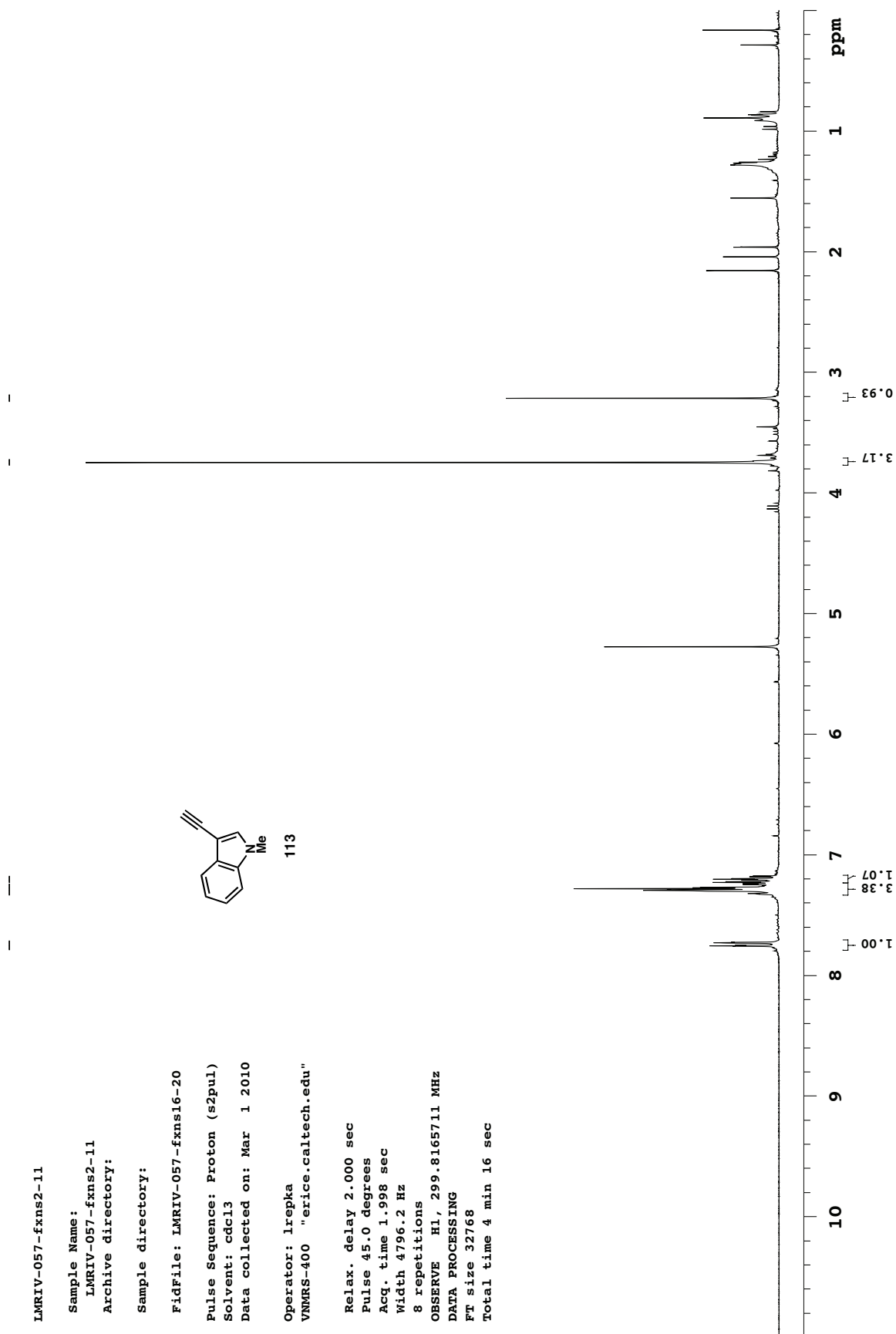
DATA PROCESSING

FT size 32768

Total time 4 min 16 sec



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PR4_F1

Sample Name:

PR4_F1

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/jchal/vnmrsys/data

Sample directory:

PR4_F1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Mar 14 2011

Sample #2, Operator: jchal

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 4798.5 Hz

16 repetitions

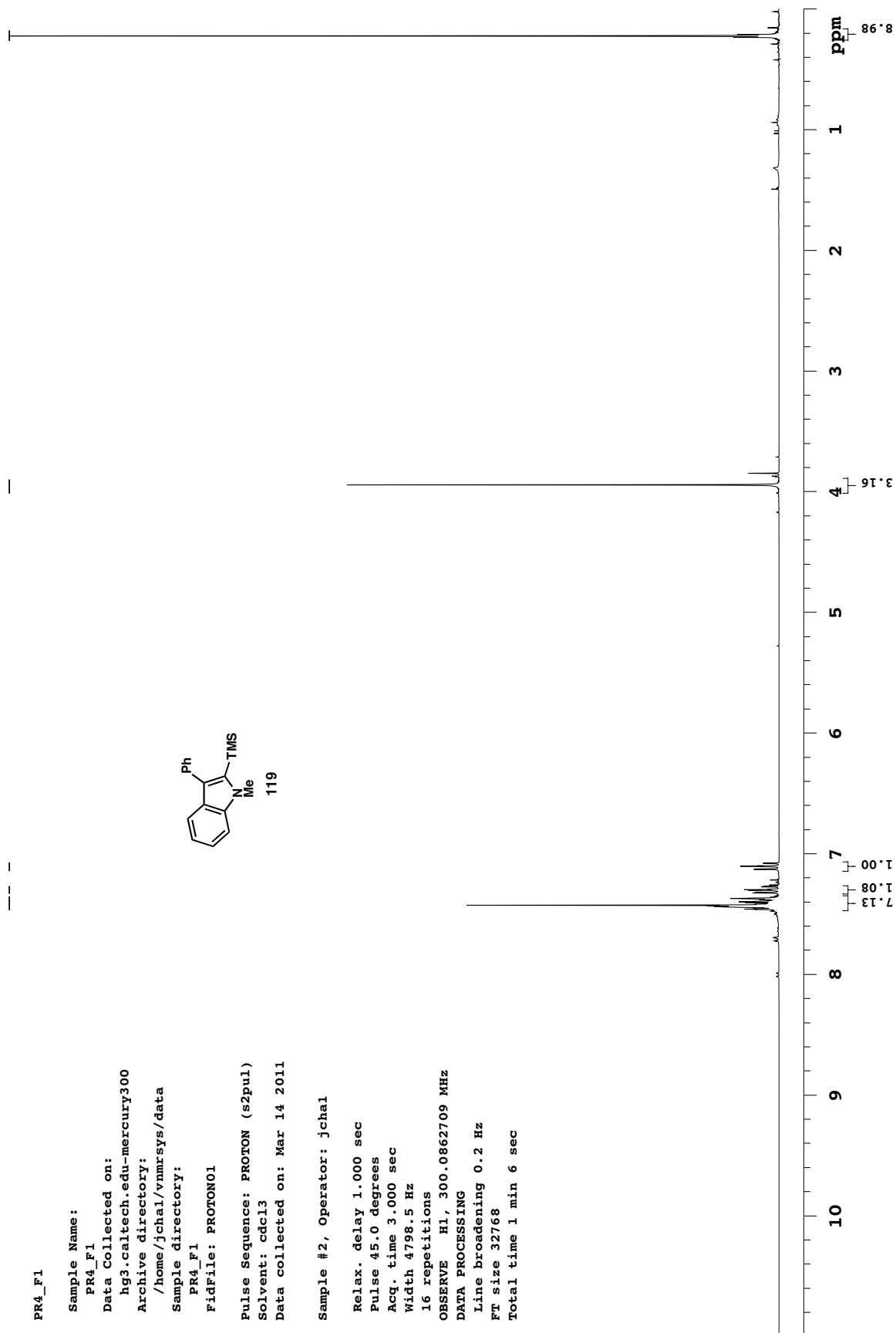
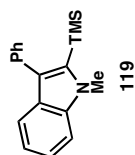
OBSERVE H1, 300.0862709 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 32768

Total time 1 min 6 sec



LMRIV-291-majordr-hsqc

Sample Name:

LMRIV-291-majordr-hsqc

Data Collected on:

siena.caltech.edu-vnmrs400

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-291-majordr-hsqc

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 1 2010

Temp. 25.0 C / 298.1 K

Sample #2, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.556 sec

Width 6410.3 Hz

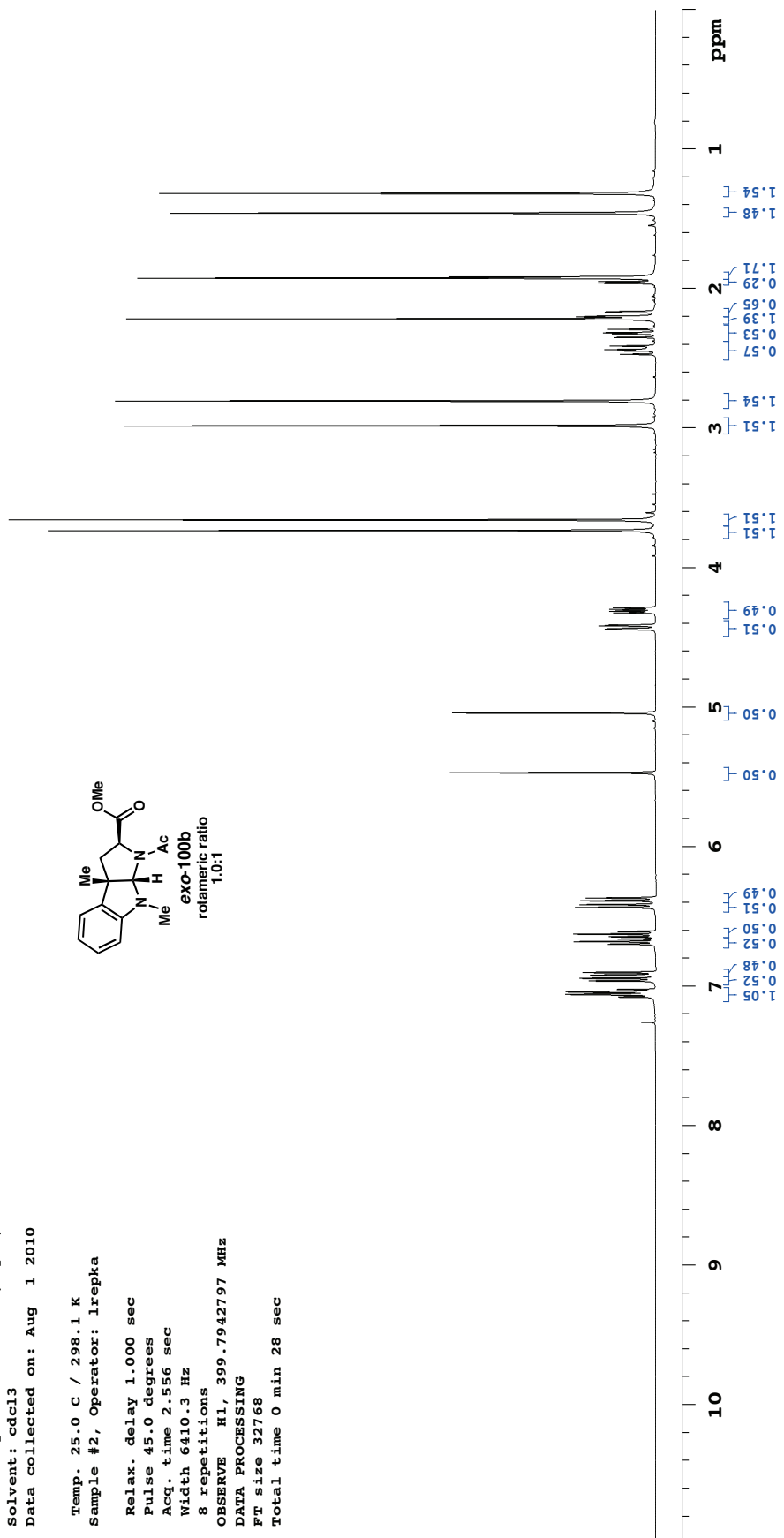
8 repetitions

OBSERVE H1, 399.7942797 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 28 sec



LMRIV-291-major-dr-conc

Sample Name:

LMRIV-291-major-dr-conc

Data Collected on:

siena.caltech.edu-vmrs400

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-291-major-dr-conc

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 31 2010

Temp. 25.0 C / 298.1 K

Sample #11, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.468 sec

Width 22321.4 Hz

3000 repetitions

OBSERVE C13, 100.5283980 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

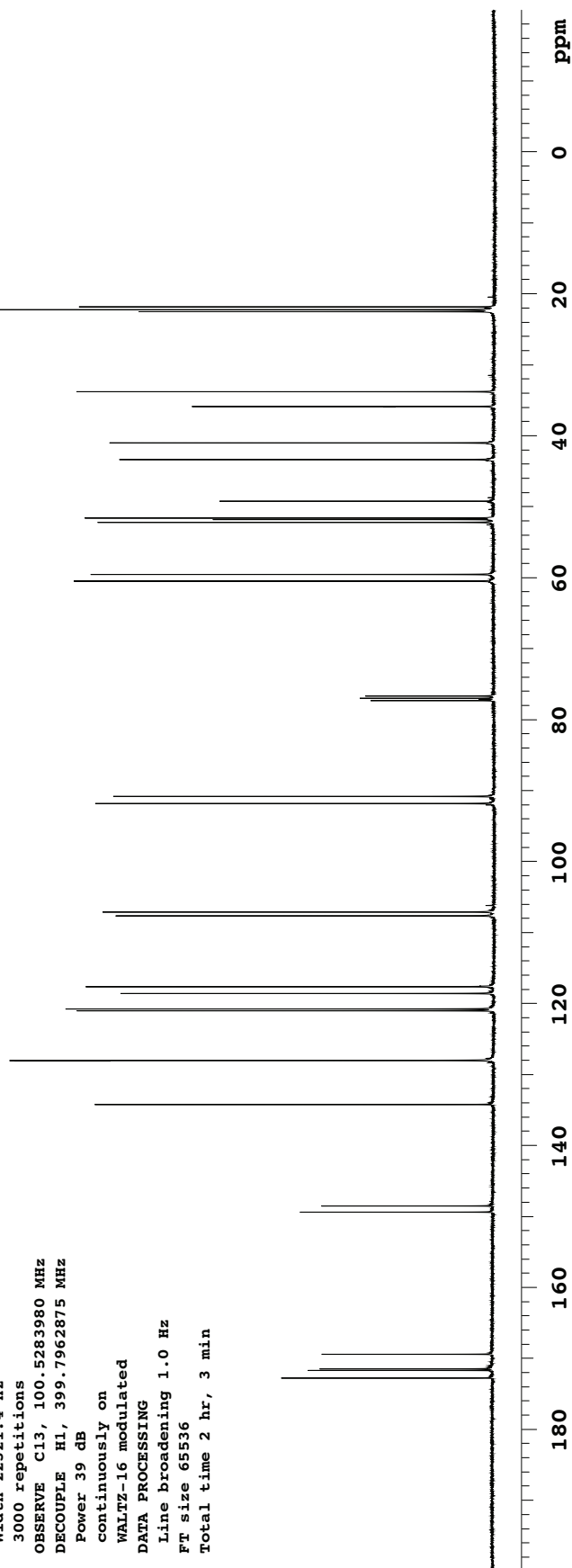
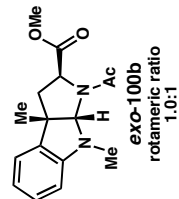
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

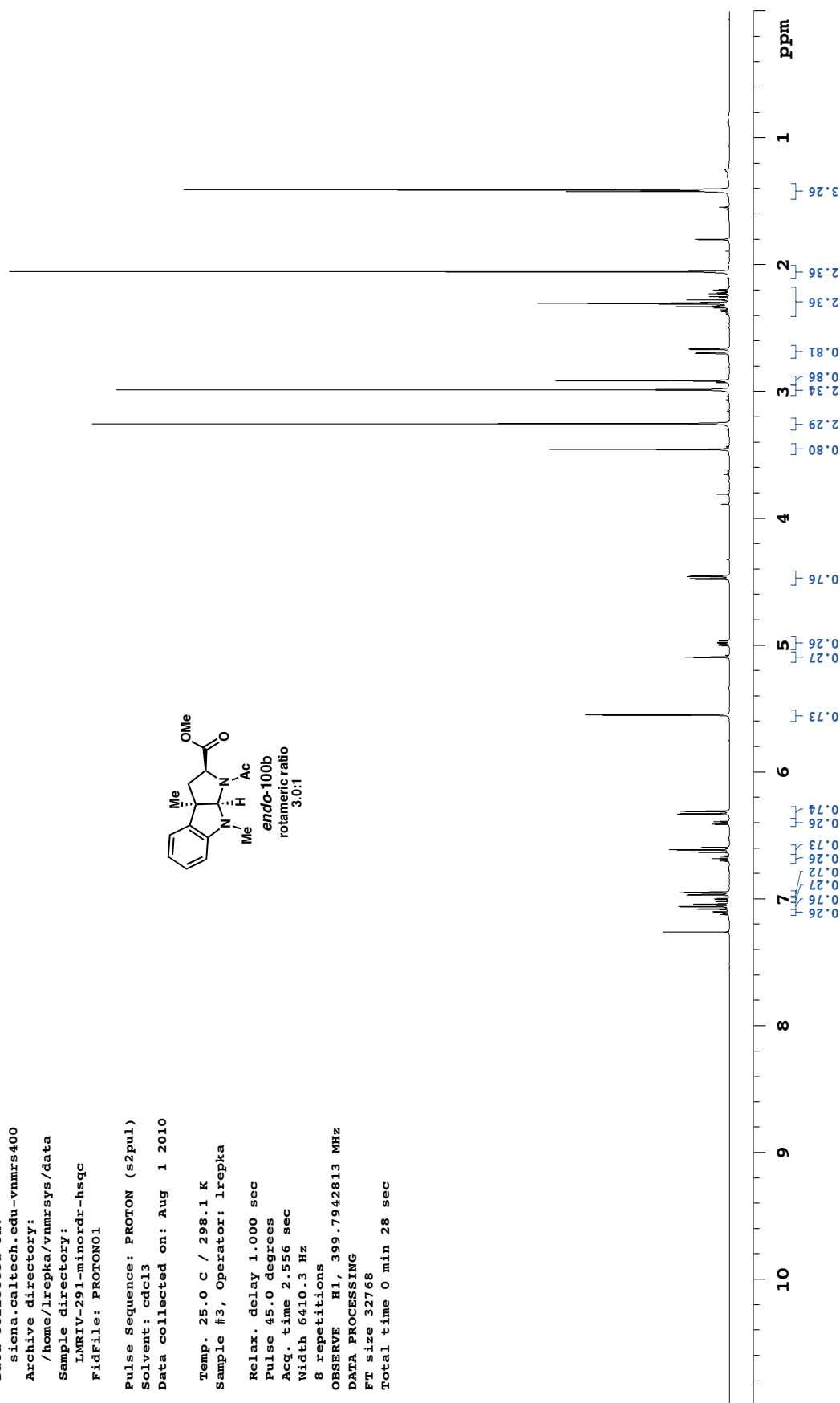
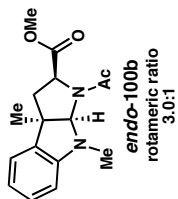
Total time 2 hr, 3 min



```

8 repetitions
OBSERVE H1, 399.7942813 MHz
DATA PROCESSING
FFT size 32768
Total time 0 min 28 sec

```



LMRIV-291-minordr

Sample Name:

LMRIV-291-minordr
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-291-minordr
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 31 2010

Temp. 25.0 C / 298.1 K
Sample #12, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.258 sec
Width 26041.7 Hz
14500 repetitions

OBSERVE C13, 100.5283574 MHz
DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

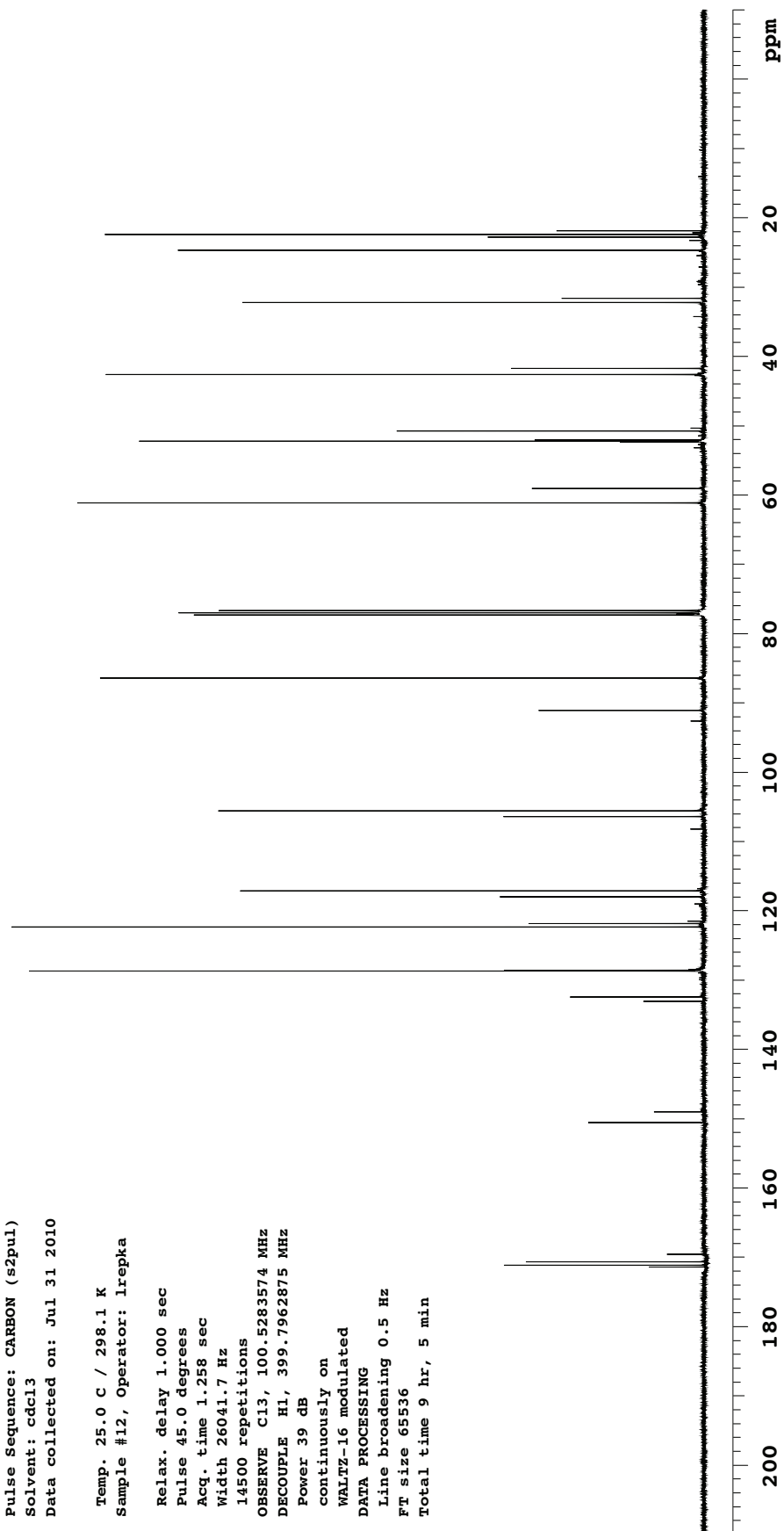
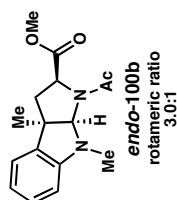
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 9 hr, 5 min



JN-1-131-majordiast

Sample Name:

JN-1-131-majordiast

Data Collected on:

sienna.caltech.edu-vmrs400

Archive directory:

/home/jni/vmrsys/data

Sample directory:

JN-1-131-majordiast

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: ccd13

Data collected on: Aug 5 2010

Temp. 25.0 C / 298.1 K

Sample #1, Operator: jni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.556 sec

Width 6410.3 Hz

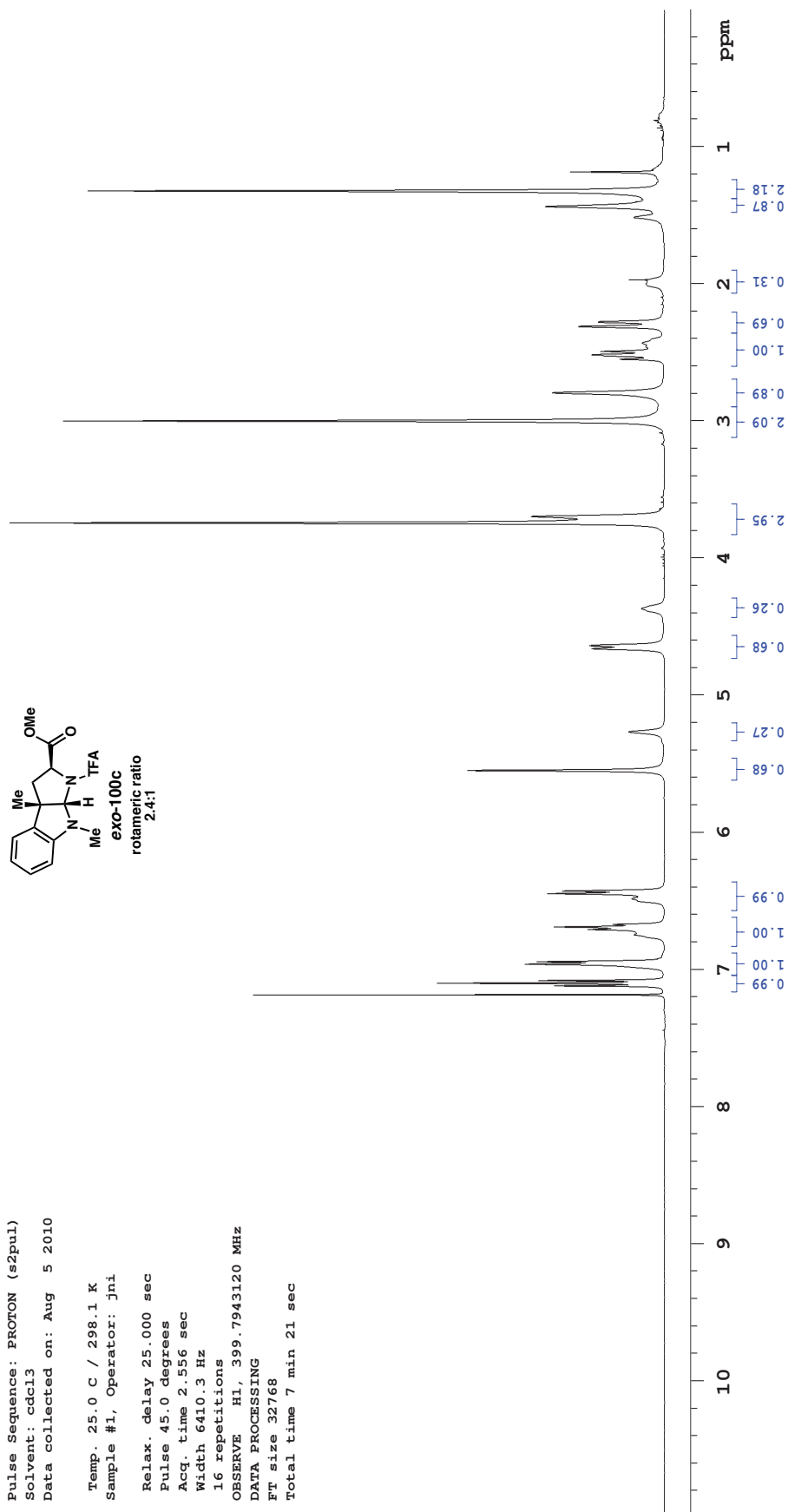
16 repetitions

OBSERVE H1, 399.7943120 MHz

DATA PROCESSING

Ft size 32768

Total time 7 min 21 sec



JN-1-131-majordiast

Sample Name:

JN-1-131-majordiast
Data Collected on:
siena.caltech.edu-vmrs400
Archive directory:
/home/jni/vmrsys/data
Sample directory:
JN-1-131-majordiast
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2010

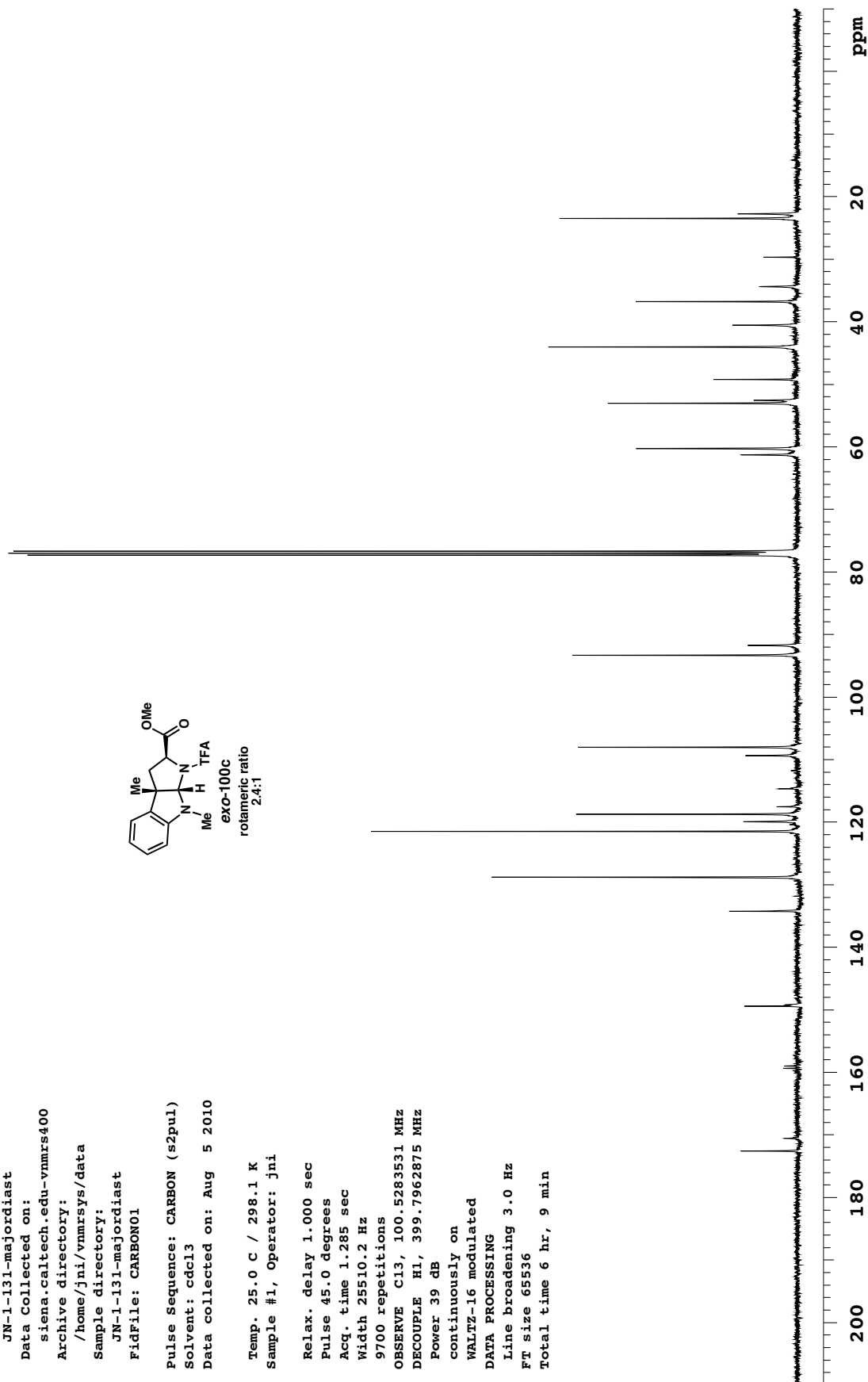
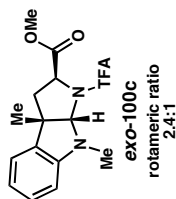
Temp. 25.0 C / 298.1 K
Sample #1, Operator: jni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
9700 repetitions

OBSERVE C13, 100.5283531 MHz
DECOUPLE H1, 399.7962875 MHz

Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 6 hr, 9 min



JN-1-131-minordiast3

Sample Name:

JN-1-131-minordiast3

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vmrsys/data

Sample directory:

JN-1-131-minordiast3

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 5 2010

Operator: Janeni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

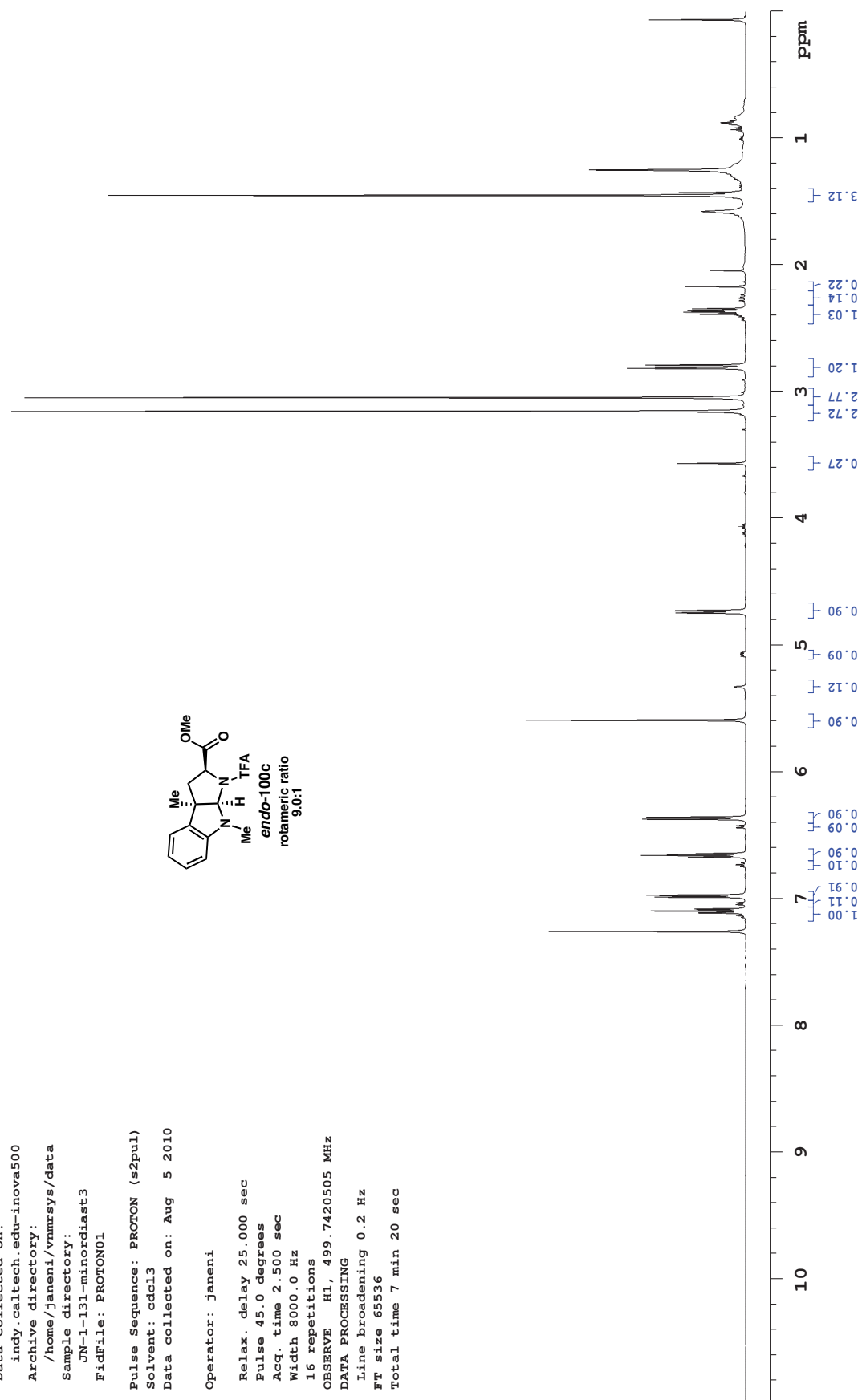
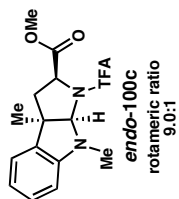
OBSERVE H1, 499.7420505 MHz

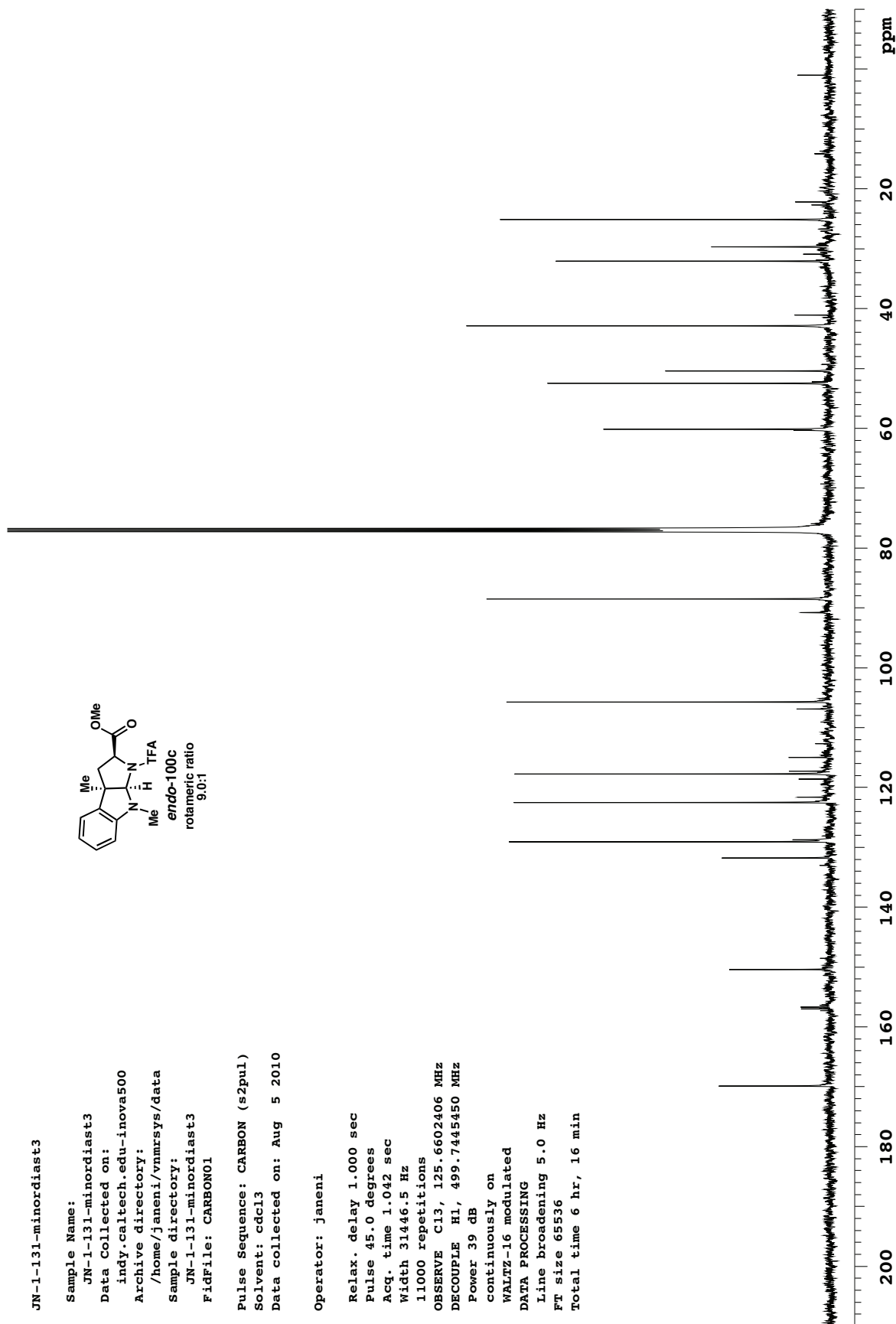
DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 7 min 20 sec





JN-1-151-major

Sample Name:

JN-1-151-major

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/jni/vnmrSYS/data

Sample directory:

JN-1-151-major

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 24 2010

Temp. 25.0 C / 298.1 K

Sample #20, Operator: jni

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.706 sec

Width 4810.0 Hz

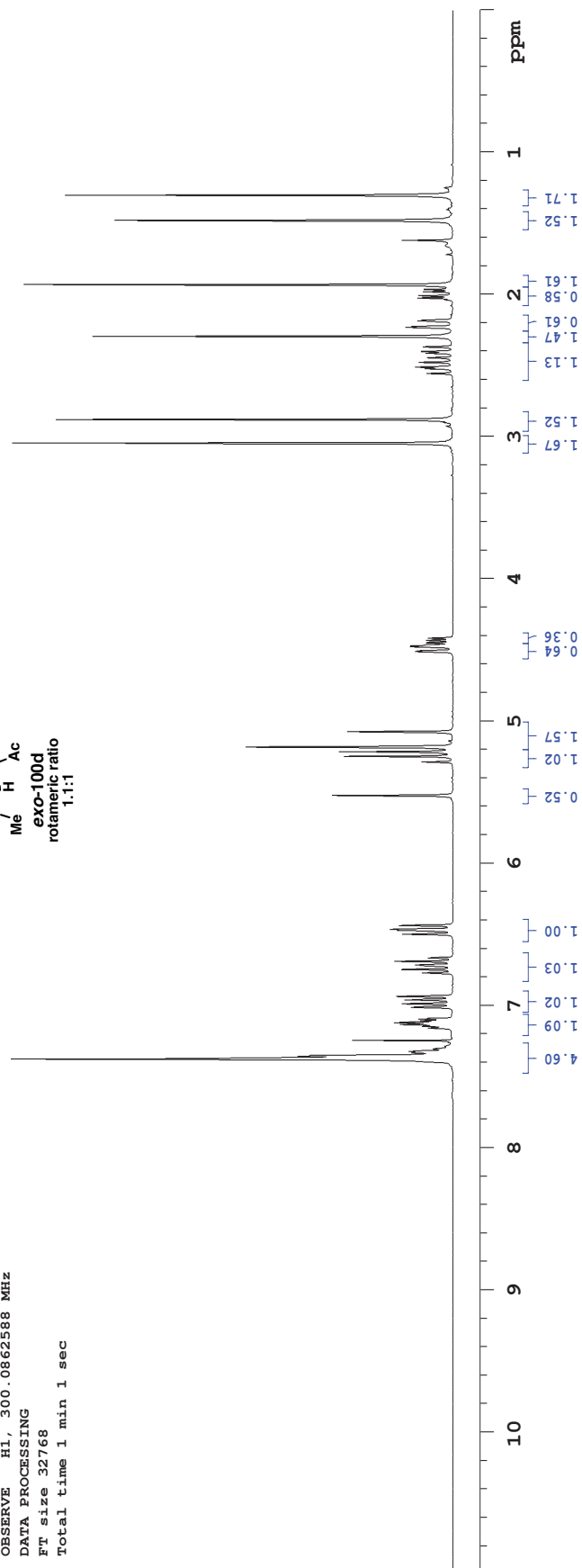
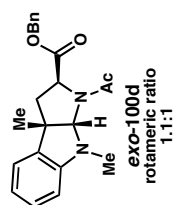
16 repetitions

OBSERVE H1, 300.0862588 MHz

DATA PROCESSING

FT size 32768

Total time 1 min 1 sec



JN-1-151

Sample Name:

JN-1-151

Data Collected on:

siena.caltech.edu-vmrs400

Archive directory:

/home/jni/vmrsys/data

Sample directory:

JN-1-151

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jun 26 2010

Sample #1, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.285 sec

Width 25510.2 Hz

8500 repetitions

OBSERVE C13, 100.5283573 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

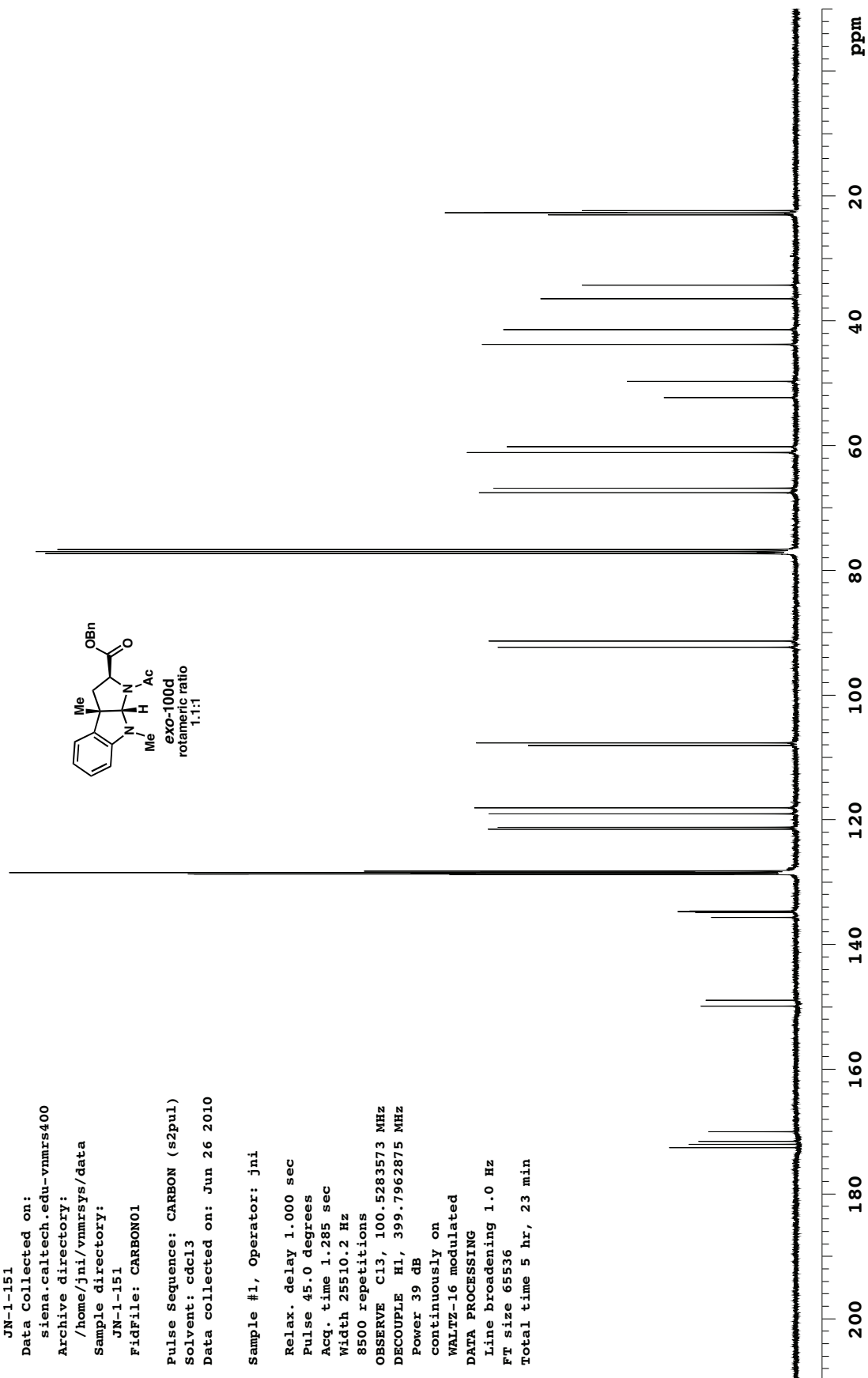
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 5 hr, 23 min



JN-1-151-minordiast3

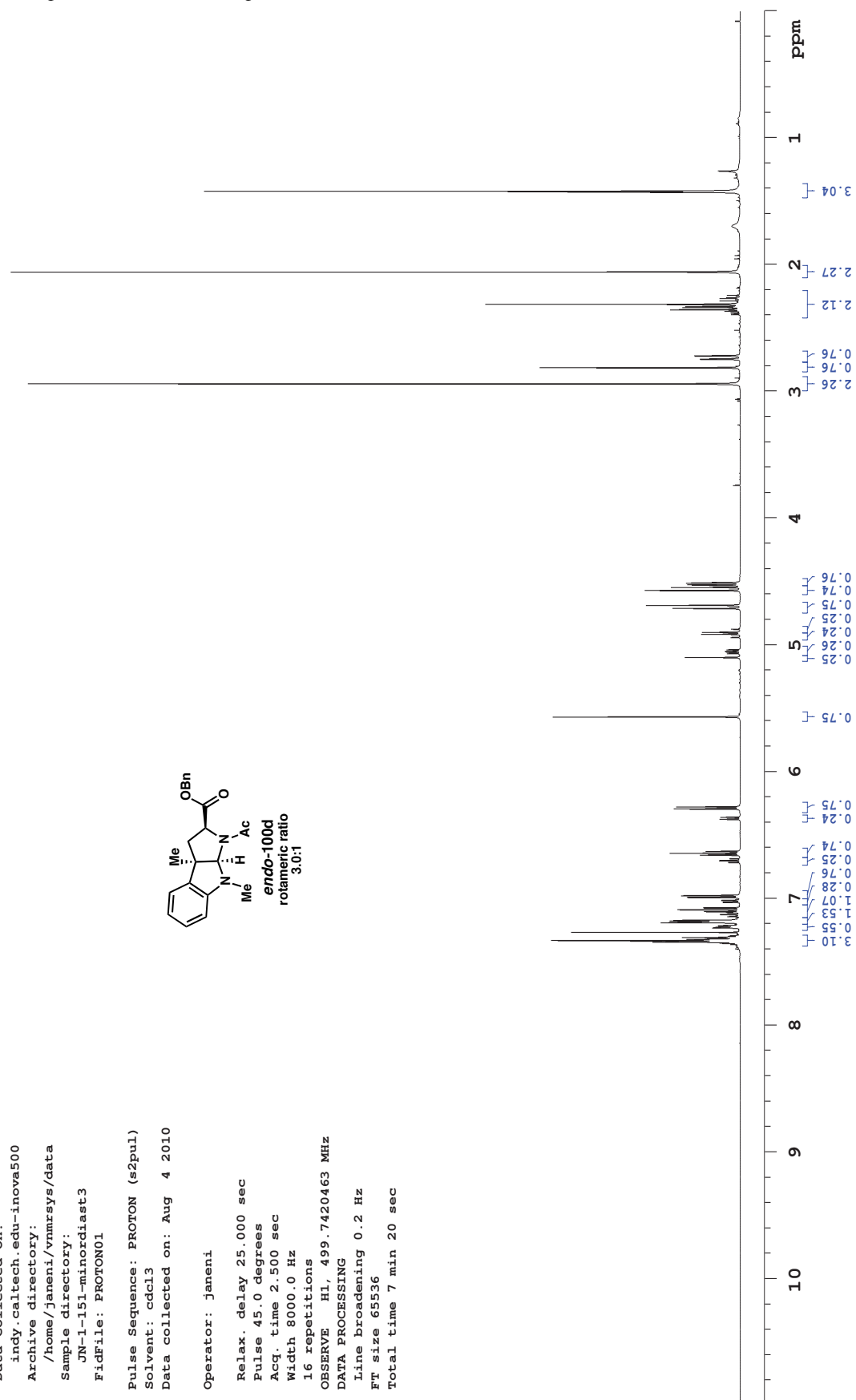
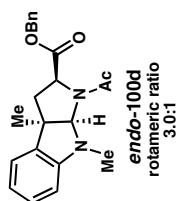
Sample Name:
 JN-1-151-minordiast3
 Data Collected on:
 indy.caltech.edu-inova500
 Archive directory:
 /home/janeni/vmrsys/data
 Sample directory:
 JN-1-151-minordiast3
 File: PROT001

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Aug 4 2010

Operator: janeni

Relax. delay 25.000 sec
 Pulse 45.0 degrees
 Acq. time 2.500 sec
 Width 8000.0 Hz
 16 repetitions

OBSERVE H1, 499.7420463 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 7 min 20 sec



JN-1-151-minordiast3

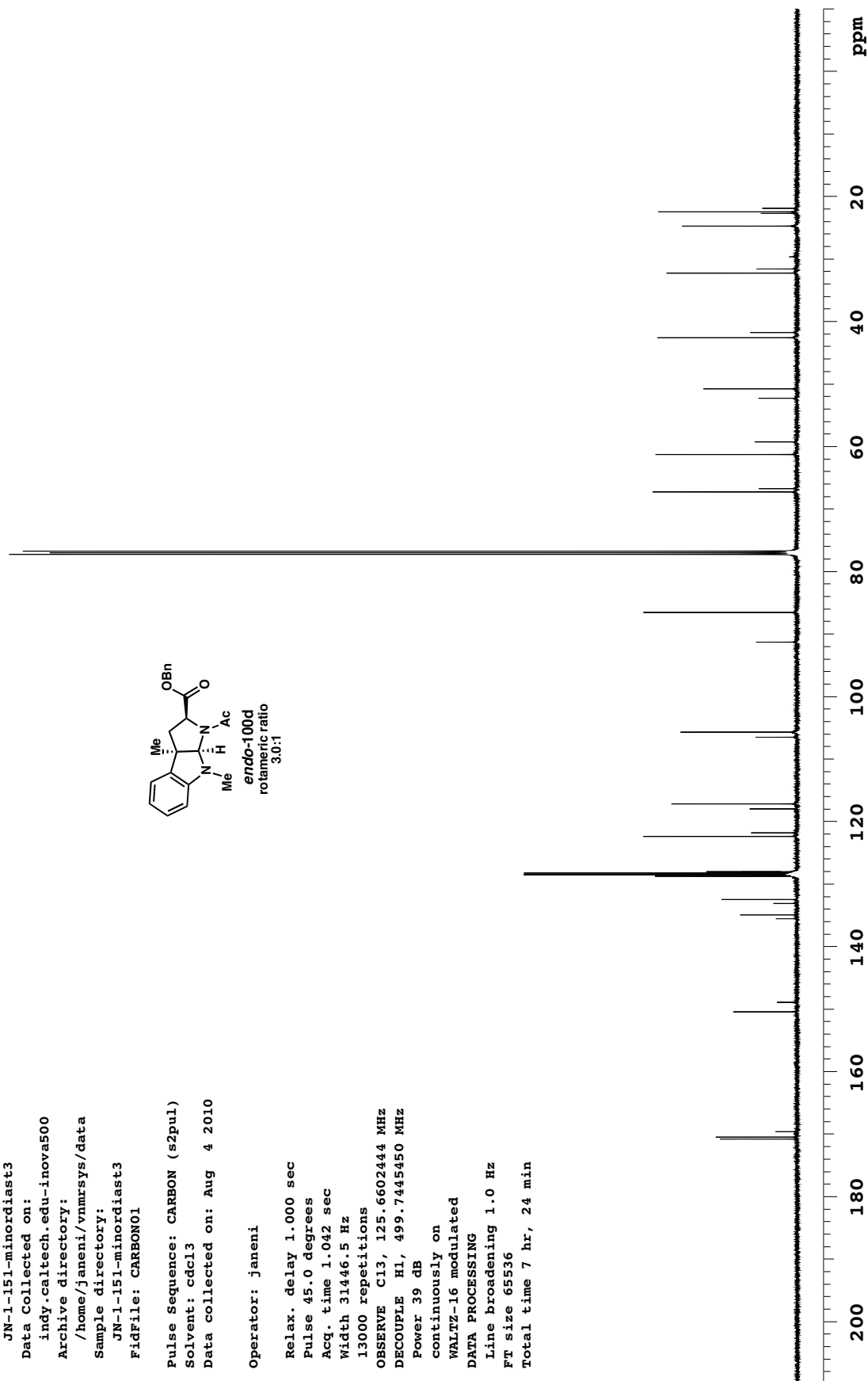
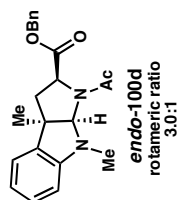
Sample Name:

JN-1-151-minordiast3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-1-151-minordiast3
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2010

Operator: janeni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13000 repetitions
OBSERVE C13, 125.6602444 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 7 hr, 24 min



LMRIV-287-majordr-rd25

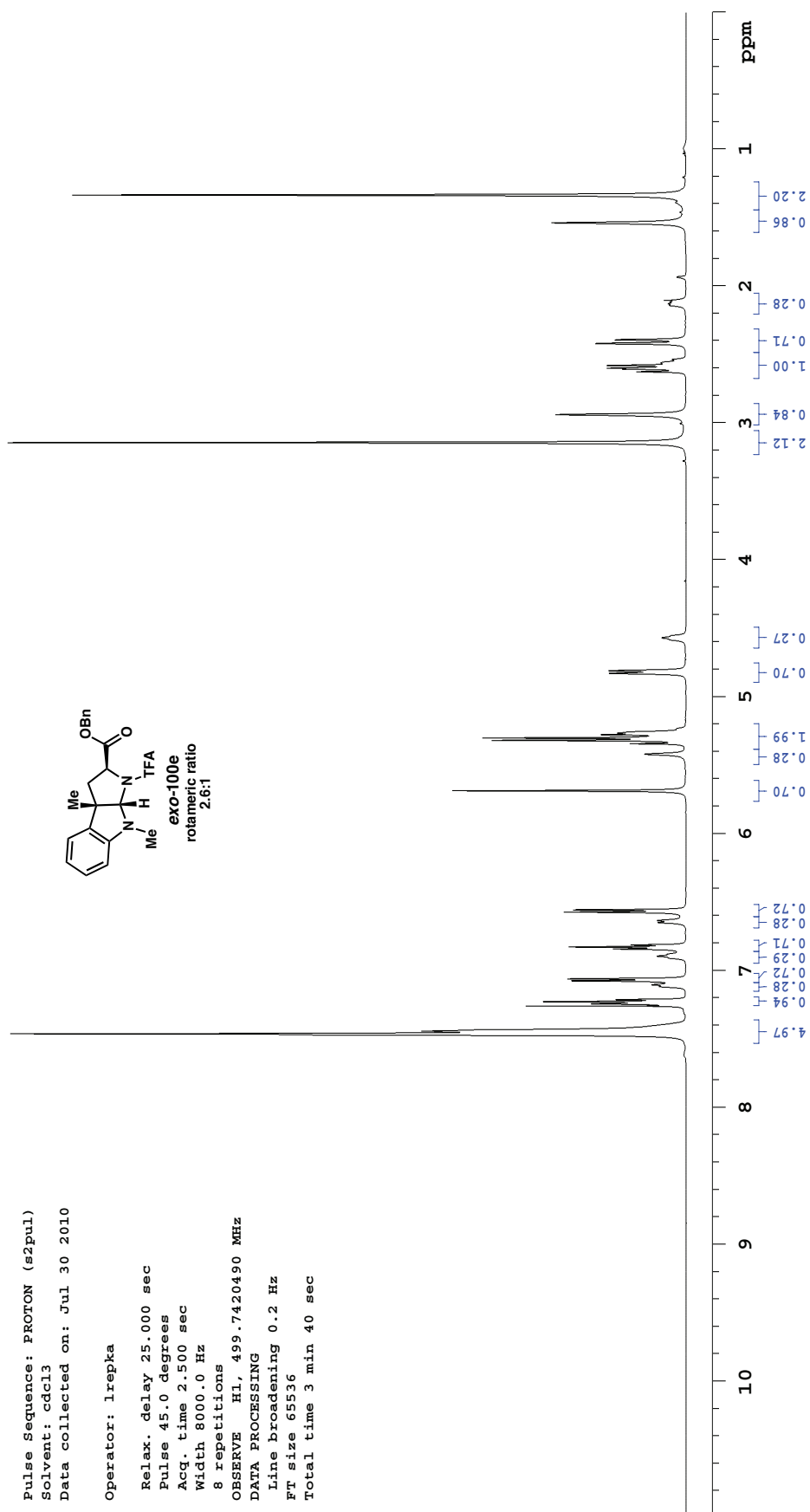
Sample Name:
 LMRIV-287-majordr-rd25
 Data Collected on:
 indy.caltech.edu-inova500
 Archive directory:
 /home/lrepka/vnmrsys/data
 Sample directory:
 LMRIV-287-majordr-rd25
 FIDFile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jul 30 2010

Operator: lrepka

Relax. delay 25.000 sec
 Pulse 45.0 degrees
 Acq. time 2.500 sec
 Width 8000.0 Hz
 8 repetitions

OBSERVE H1, 499.7420490 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 3 min 40 sec



LMRIV-scale-up-12h-major

Sample Name:

LMRIV-scale-up-12h-major

Data Collected on:

siena.caltech.edu-vmrs400

Archive directory:

/home/lrepka/vmrsys/data

Sample directory:

LMRIV-scale-up-12h-major

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 29 2010

Temp. 25.0 C / 298.1 K

Sample #1, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.285 sec

Width 25510.2 Hz

11500 repetitions

OBSERVE C13, 100.5283829 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

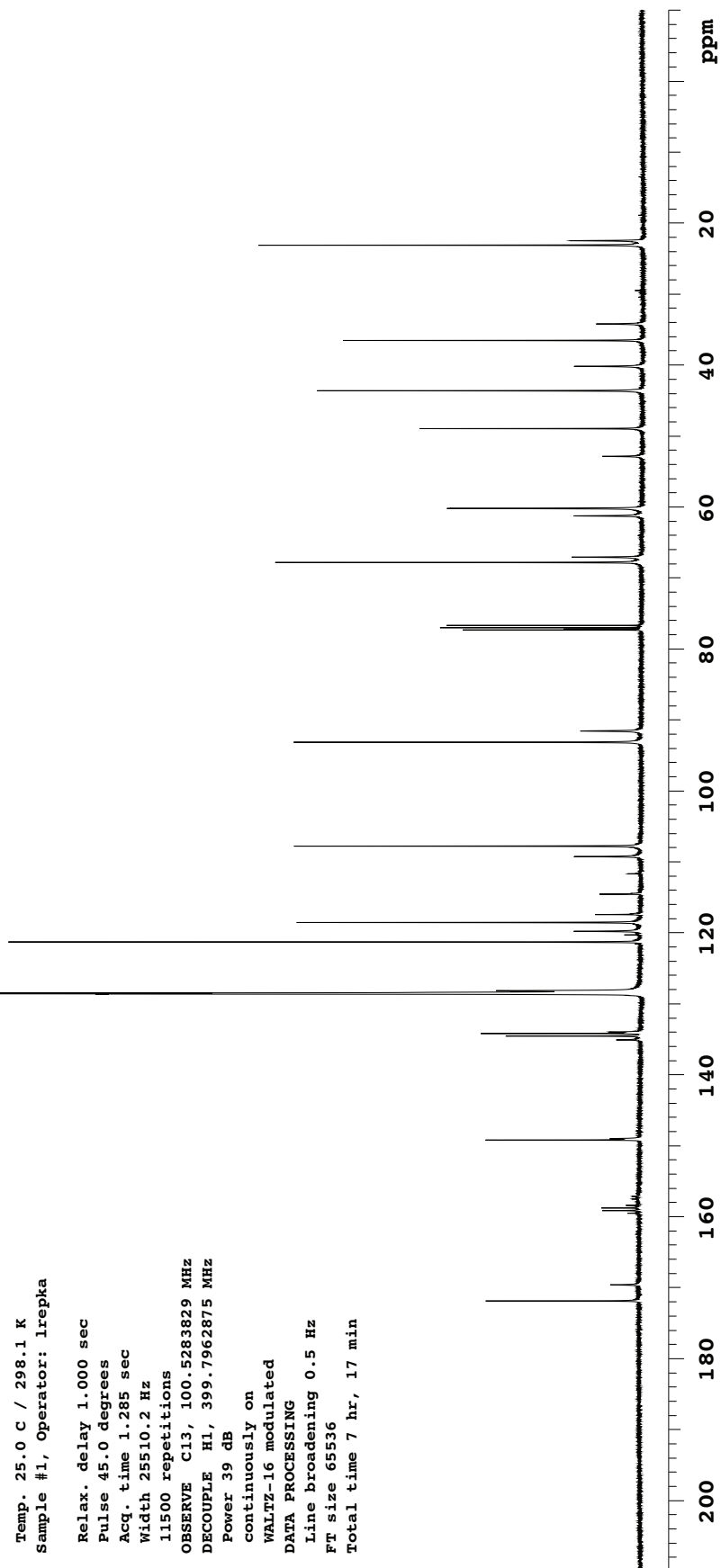
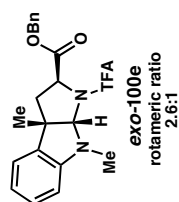
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 7 hr, 17 min



LMRIV-287-minor-8-5-10

Sample Name:

LMRIV-287-minor-8-5-10

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-287-minor-8-5-10

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 5 2010

Temp. 25.0 C / 298.1 K

Sample #46, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 1.706 sec

Width 4810.0 Hz

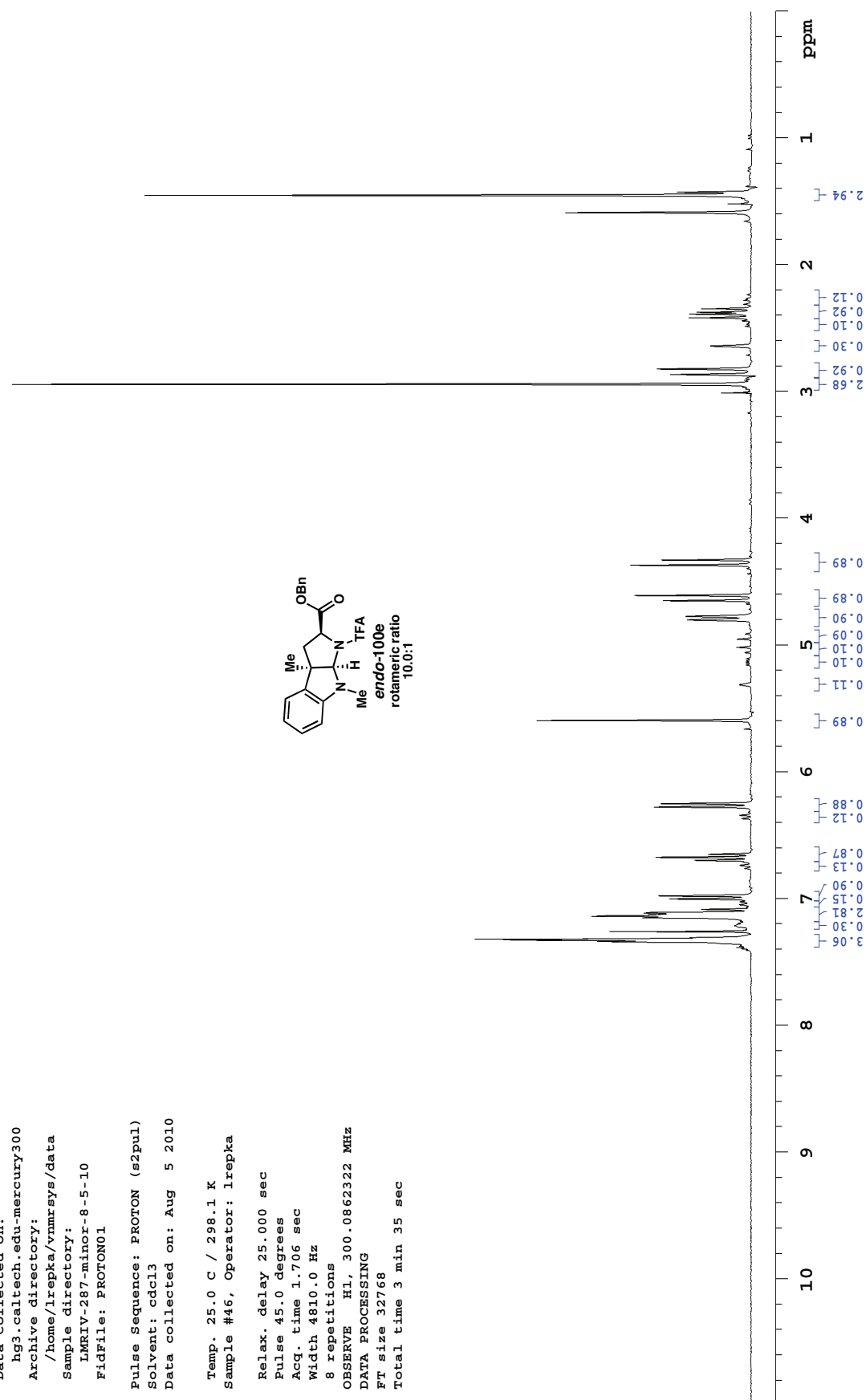
8 repetitions

OBSERVE H1, 300.0862322 MHz

DATA PROCESSING

FT size 32768

Total time 3 min 35 sec



LMRIV-scale-up-12h-minordr

Sample Name:

LMRIV-scale-up-12h-minordr

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-scale-up-12h-minordr

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 29 2010

Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

13500 repetitions

OBSERVE C13, 125.6602412 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

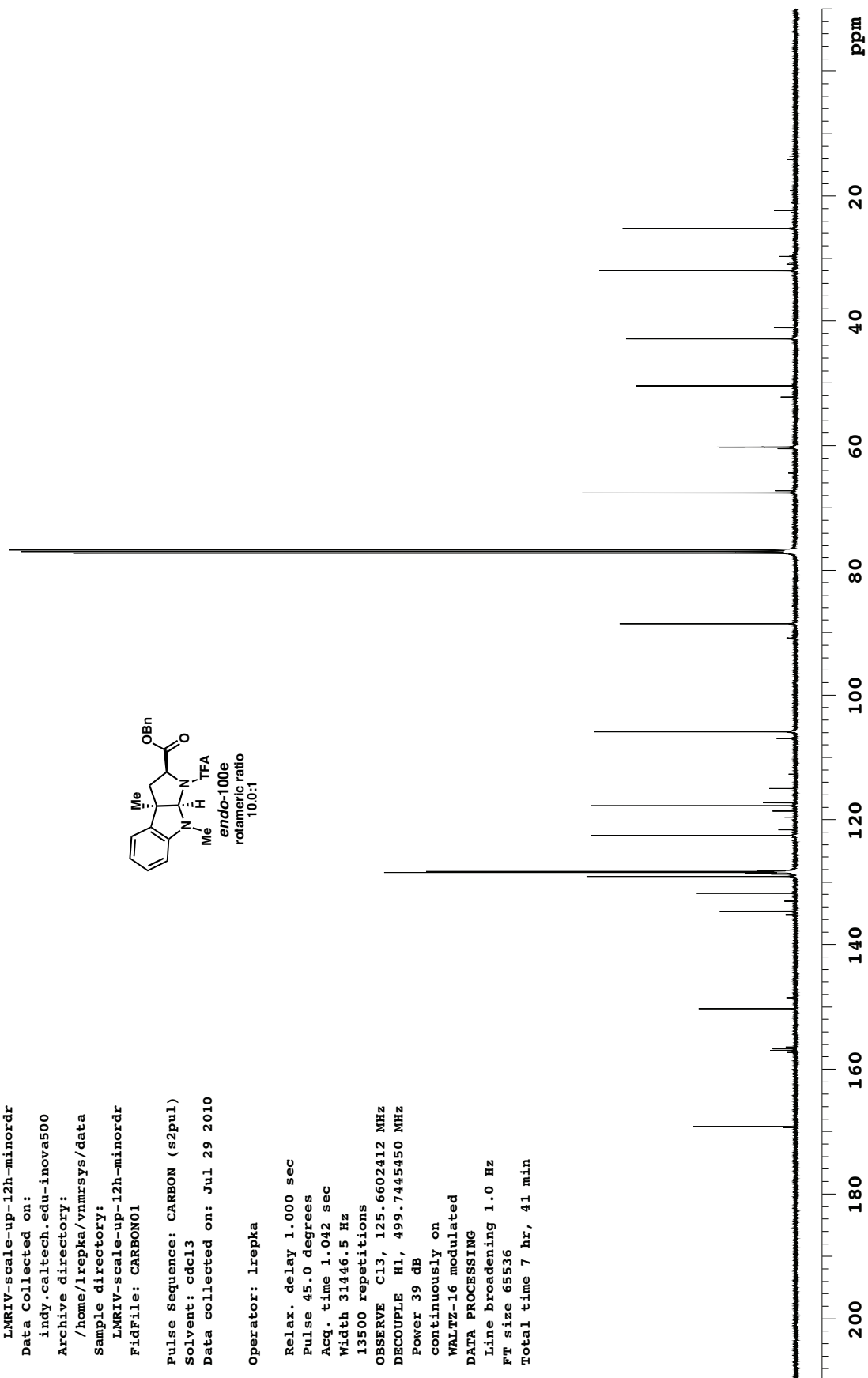
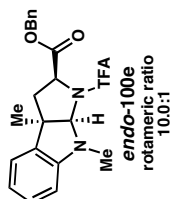
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 7 hr, 41 min



JN-1-191-majordiast

Sample Name:

JN-1-191-majordiast

Data Collected on:

sienna.caltech.edu—vnmrs400

Archive directory:

/home/jni/vnmrsys/data

Sample directory:

JN-1-191-majordiast

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdc13

Data collected on: Jul 19 2010

Temp. 25.0 C / 298.1 K

Sample #5, Operator: jni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.556 sec

Width 6410.3 Hz

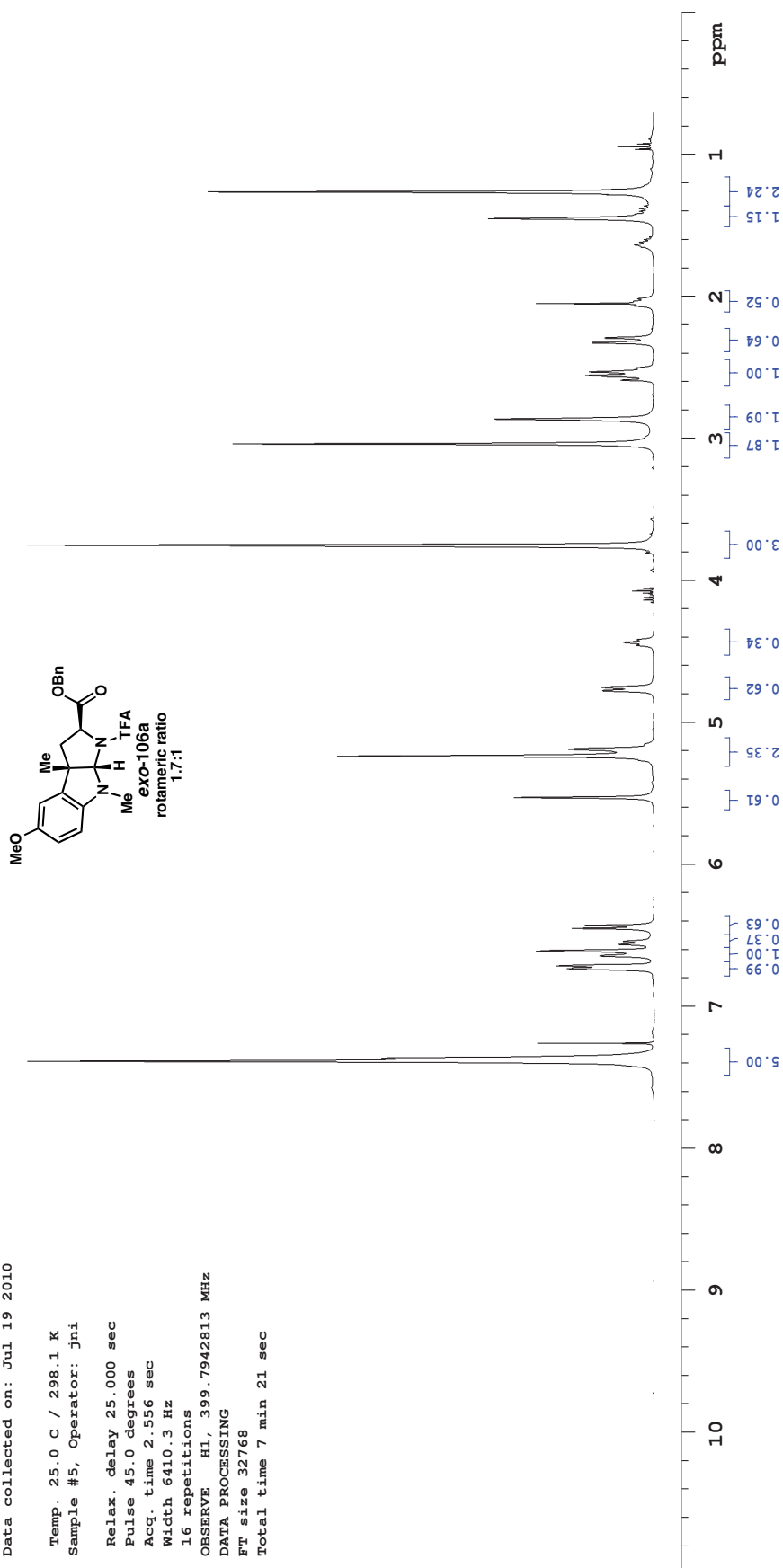
16 repetitions

OBSERVE H1, 399.7942813 MHz

DATA PROCESSING

FT size 32768

Total time 7 min 21 sec



JN-1-191-majordiast

Sample Name:

JN-1-191-majordiast
Data Collected on:
siena.caltech.edu-vmrs400
Archive directory:
/home/jni/vmrsys/data
Sample directory:
JN-1-191-majordiast
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 19 2010

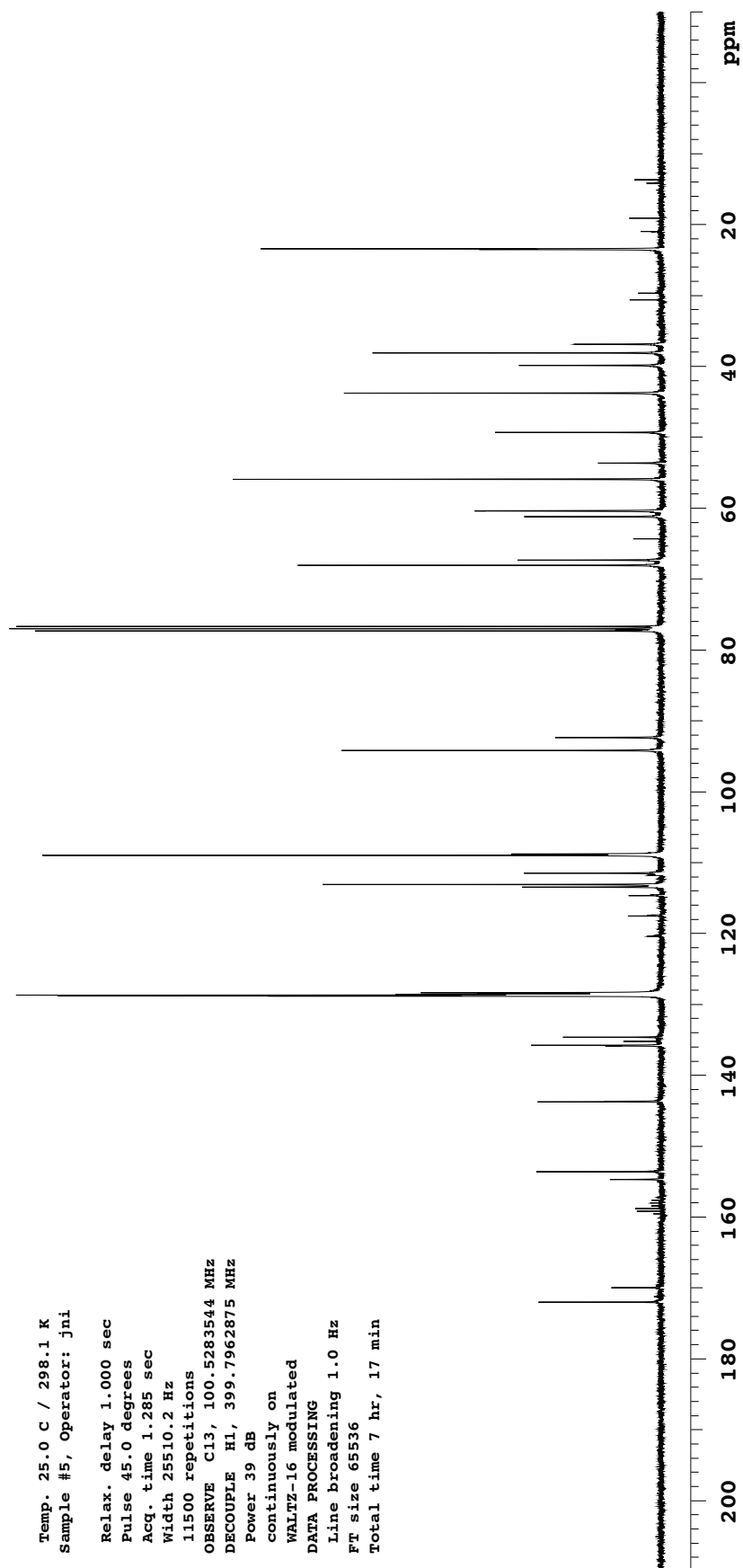
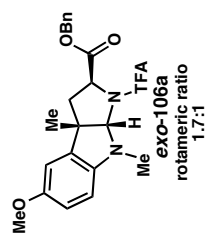
Temp. 25.0 C / 298.1 K
Sample #5, Operator: jni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
11500 repetitions

OBSERVE C13, 100.5283544 MHz
DECOUPLE H1, 399.7962875 MHz

Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 7 hr, 17 min



JN-1-191-minordiast

Sample Name:

JN-1-191-minordiast

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-191-minordiast

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 18 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

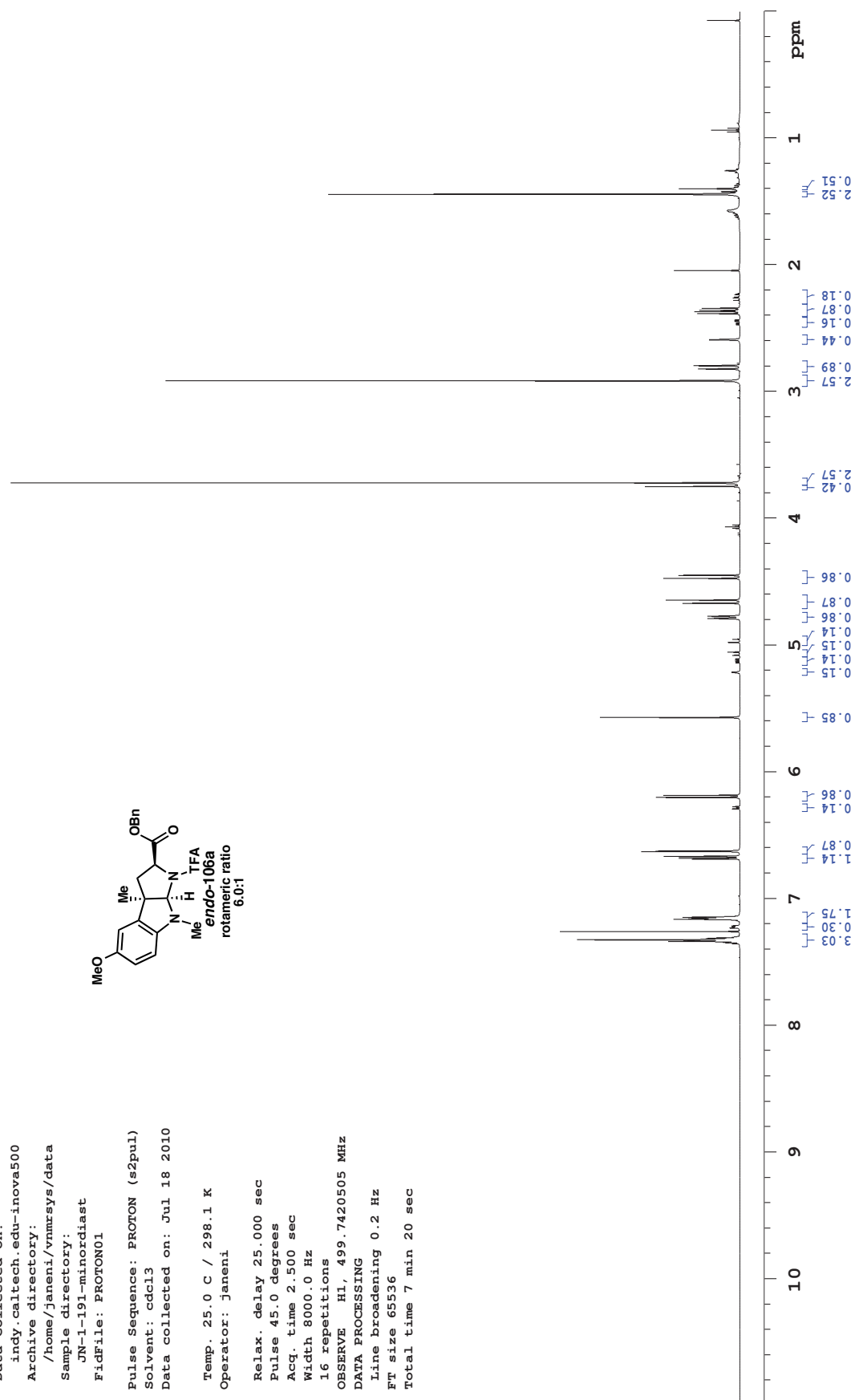
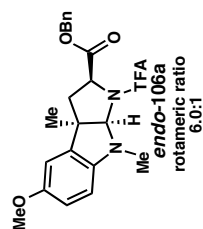
OBSERVE H1, 499.7420505 MHz

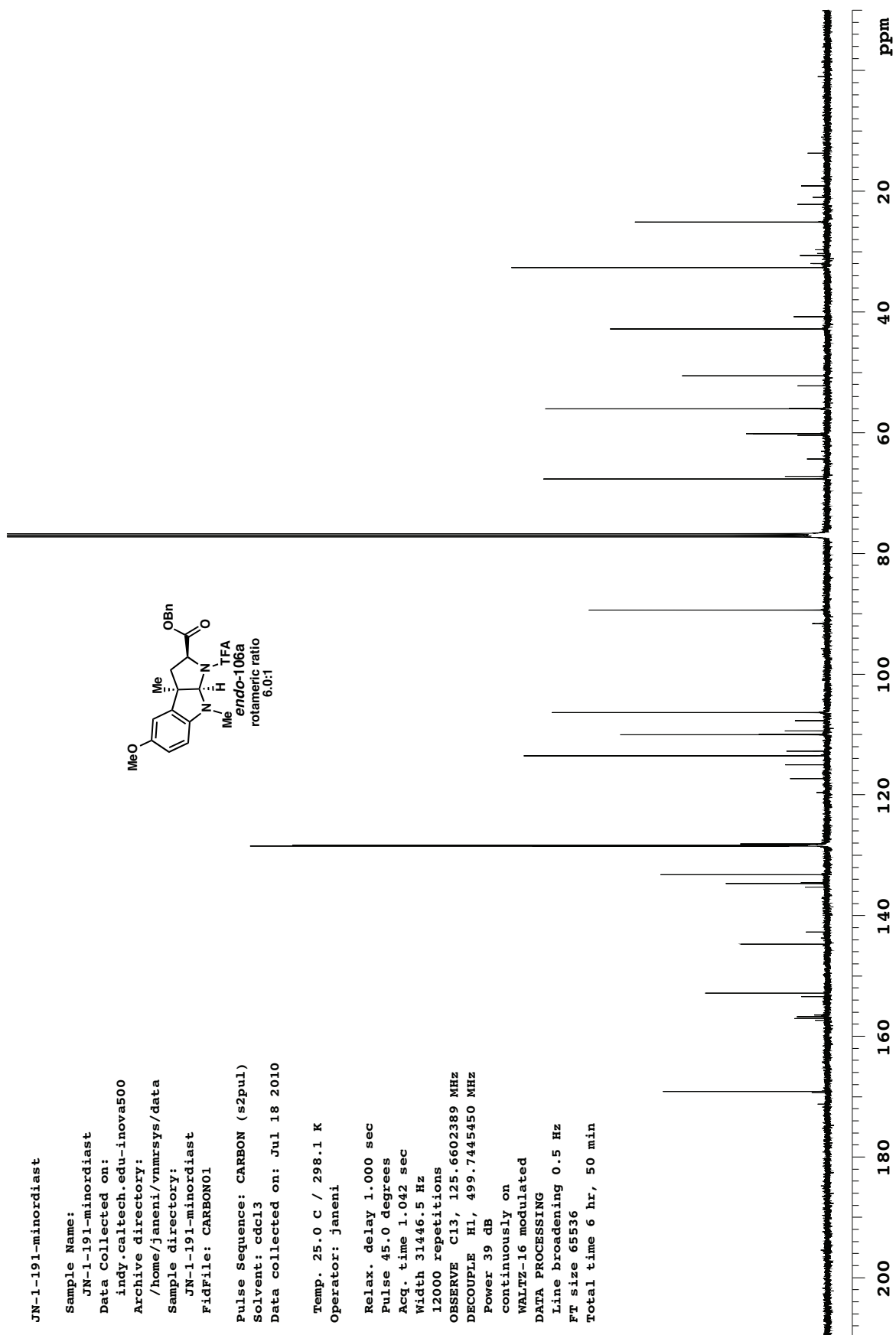
DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 7 min 20 sec





JN-1-195-majordiast4

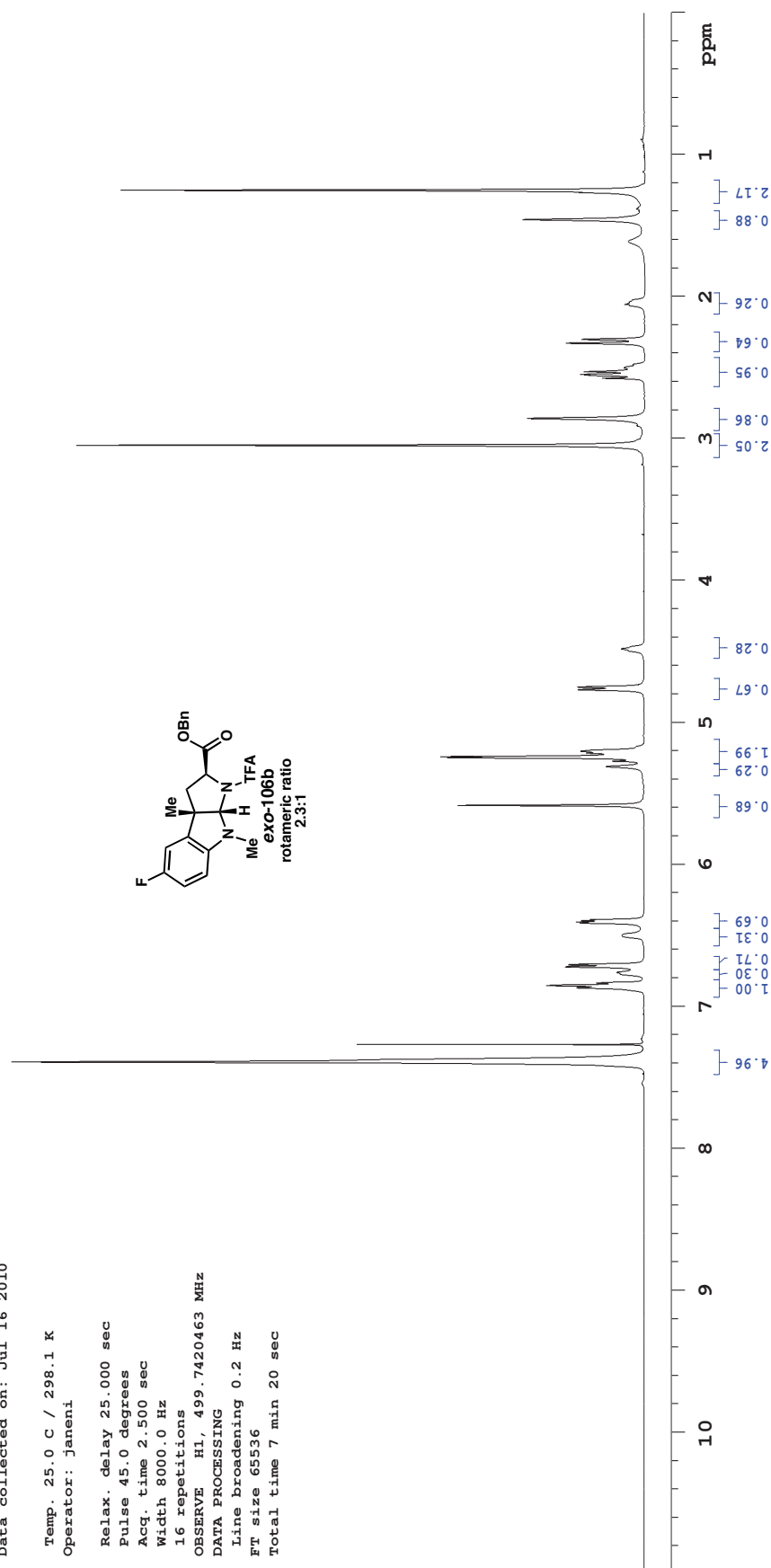
Sample Name:
JN-1-195-majordiast4
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-1-195-majordiast4
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 16 2010

Temp. 25.0 C / 298.1 K
Operator: janeni

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions

OBSERVE H1, 499.7420463 MHz
DATA PROCESSING
Line broadening 0.2 Hz
Ft size 65536
Total time 7 min 20 sec



JN-1-195-majordiast4

Sample Name:

JN-1-195-majordiast4

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-195-majordiast4

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 16 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

13000 repetitions

OBSERVE C13, 125.6602389 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

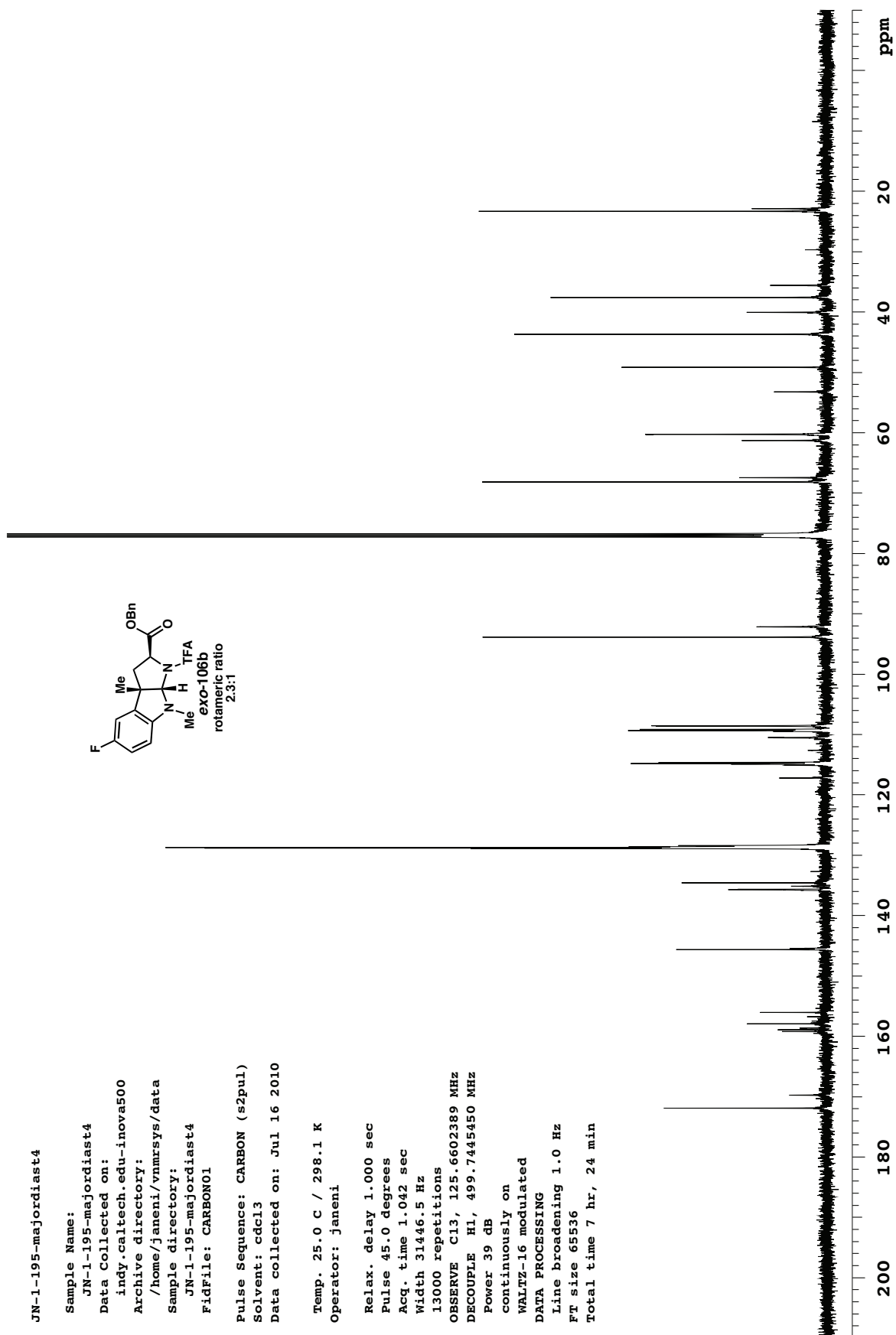
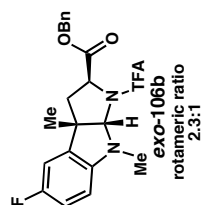
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 7 hr, 24 min



JN-1-195-minordiast

Sample Name:

JN-1-195-minordiast

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-195-minordiast

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 15 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

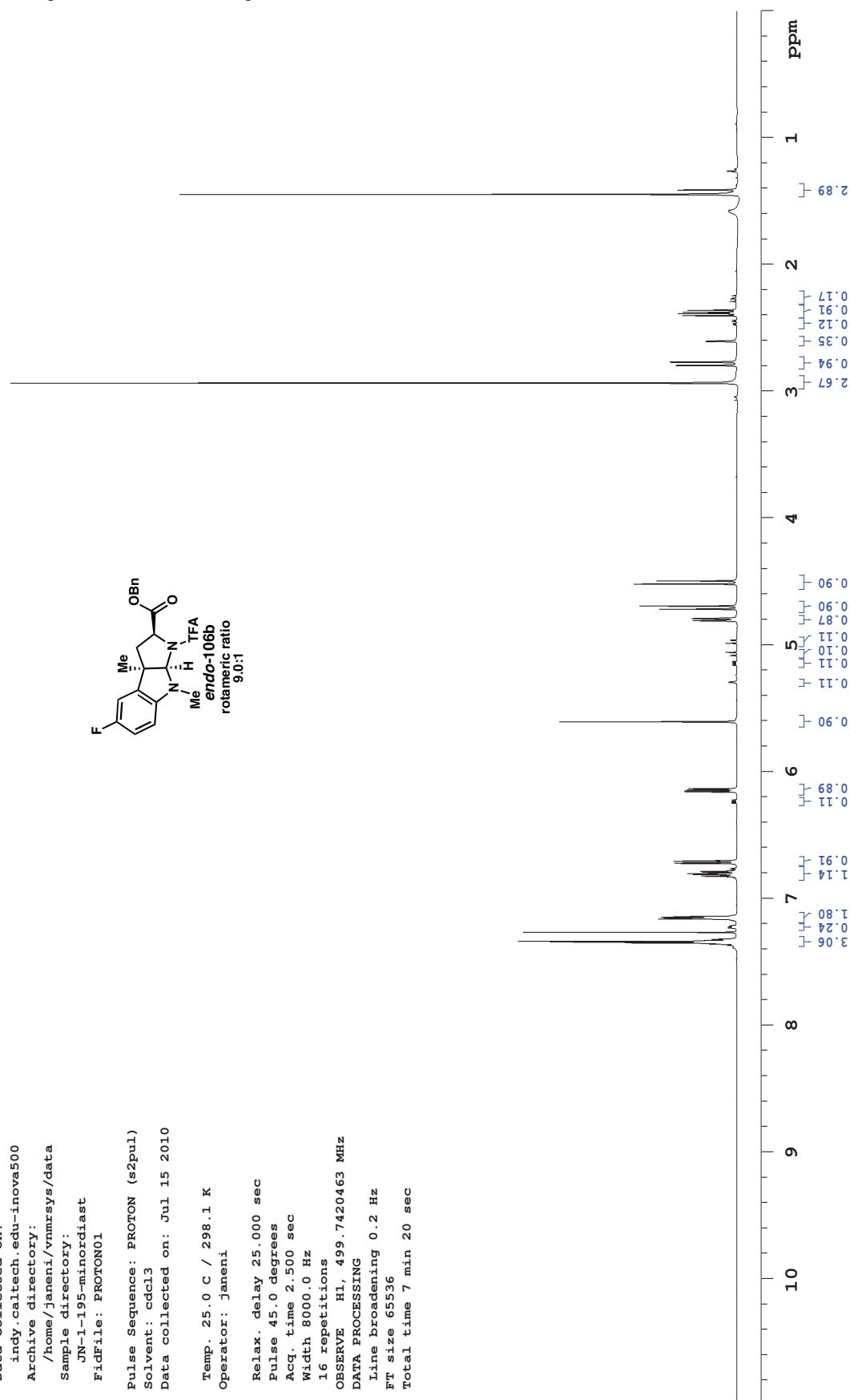
OBSERVE H1, 499.7420463 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 7 min 20 sec



JN-1-195-minordiast

Sample Name:

JN-1-195-minordiast
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-1-195-minordiast
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 15 2010

Temp. 25.0 C / 298.1 K
Operator: janeni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13000 repetitions

OBSERVE C13, 125.6602387 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB

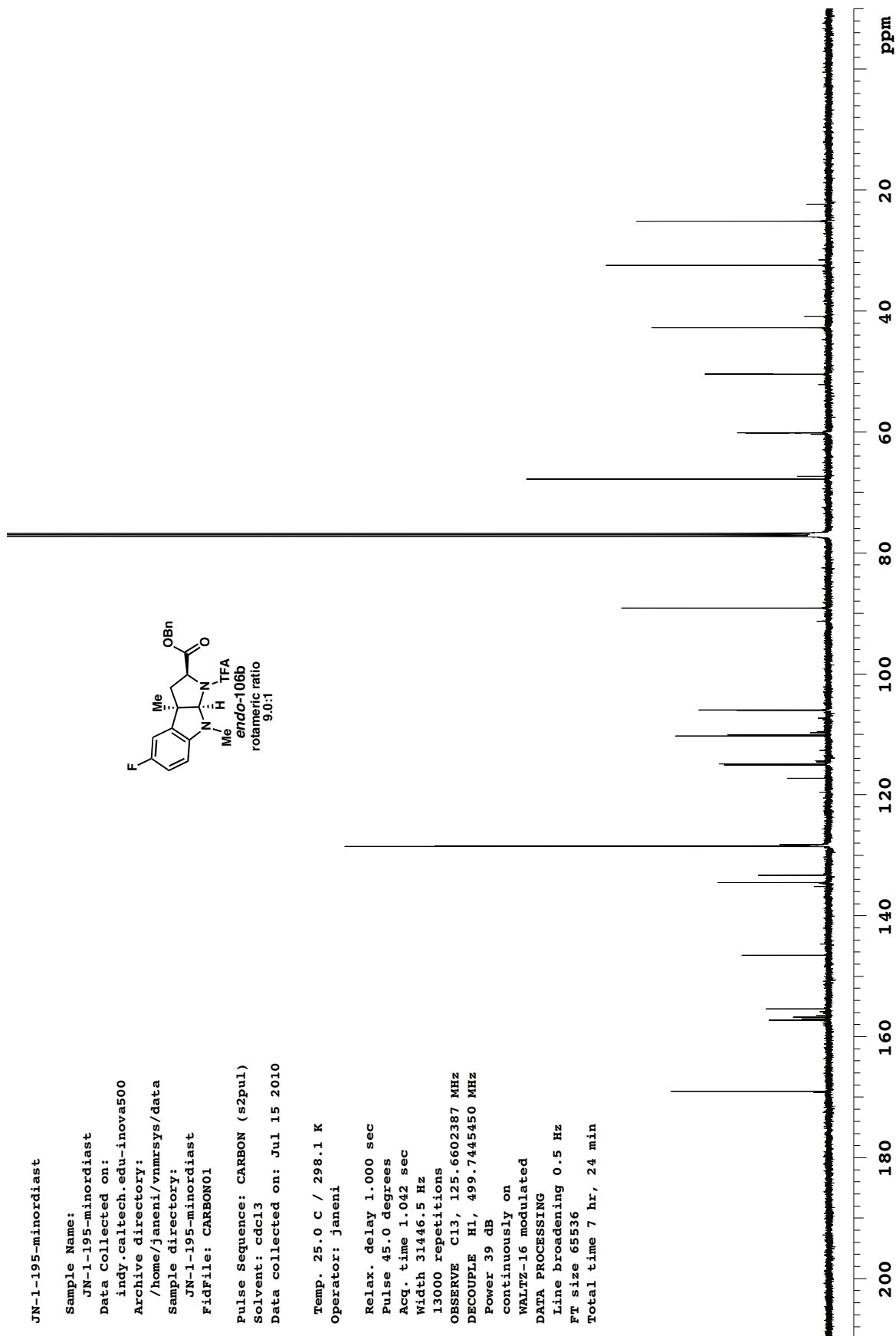
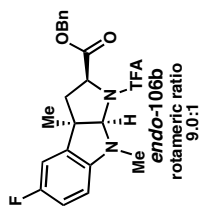
continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz
FT size 65536

Total time 7 hr, 24 min

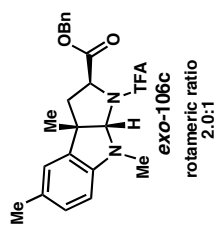


JN-1-171-majdiast

Sample Name:
JN-1-171-majdiast
Data Collected on:
sienna.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-171-majdiast
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 14 2010

Temp. 25.0 C / 298.1 K
Sample #4, Operator: jni
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7942813 MHz
DATA PROCESSING
Ft size 32768
Total time 7 min 21 sec



JN-1-171-majdiast

Sample Name:

JN-1-171-majdiast
Data Collected on:
siena.caltech.edu-vmrs400
Archive directory:
/home/jni/vmrsys/data
Sample directory:
JN-1-171-majdiast
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 14 2010

Temp. 25.0 C / 298.1 K
Sample #4, Operator: jni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
11000 repetitions

OBSERVE C13, 100.5283542 MHz
DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

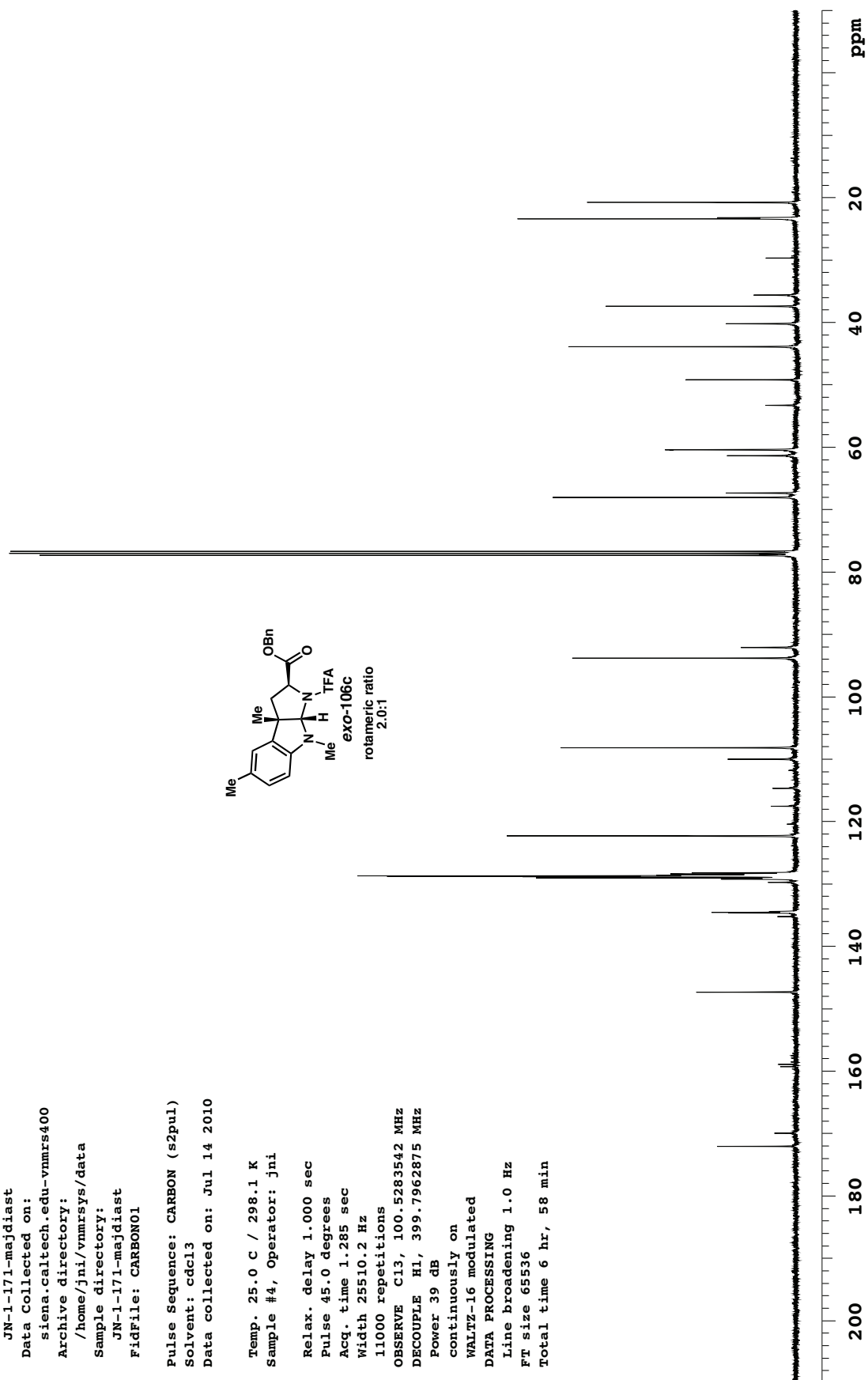
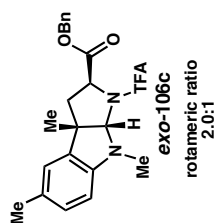
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 6 hr, 58 min



JN-1-171-mindiast2

Sample Name:

JN-1-171-mindiast2

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/jni/vnmrsys/data

Sample directory:

JN-1-171-mindiast2

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 13 2010

Temp. 25.0 C / 298.1 K

Sample #17, Operator: jni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 1.706 sec

Width 4810.0 Hz

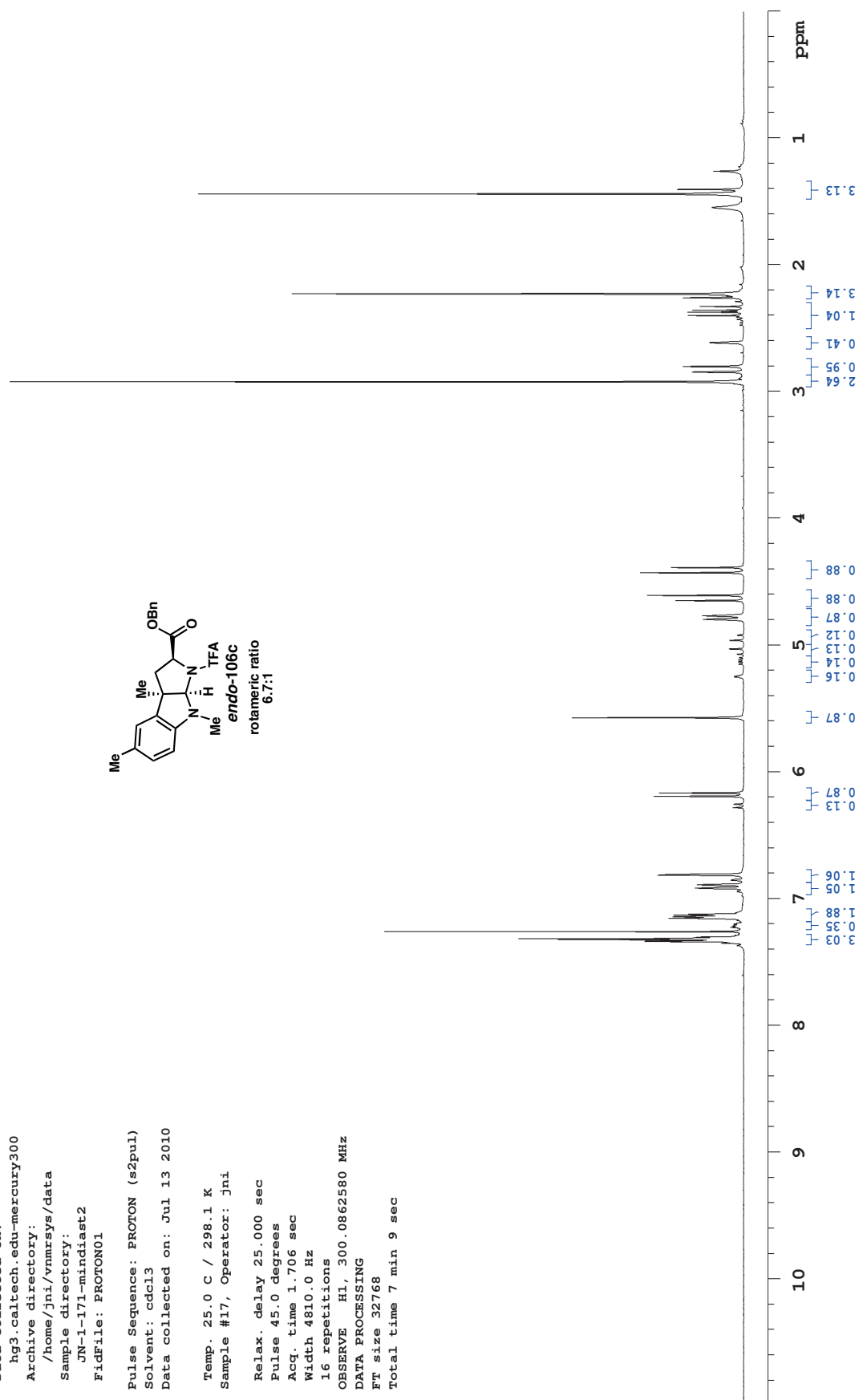
16 repetitions

OBSERVE H1, 300.0862580 MHz

DATA PROCESSING

Ft size 32768

Total time 7 min 9 sec



JN-1-171-minordiast2

Sample Name:

JN-1-171-minordiast2

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrSYS/data

Sample directory:

JN-1-171-minordiast2

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 14 2010

Temp. 25.0 C / 298.1 K

Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

13000 repetitions

OBSERVE C13, 125.6602382 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

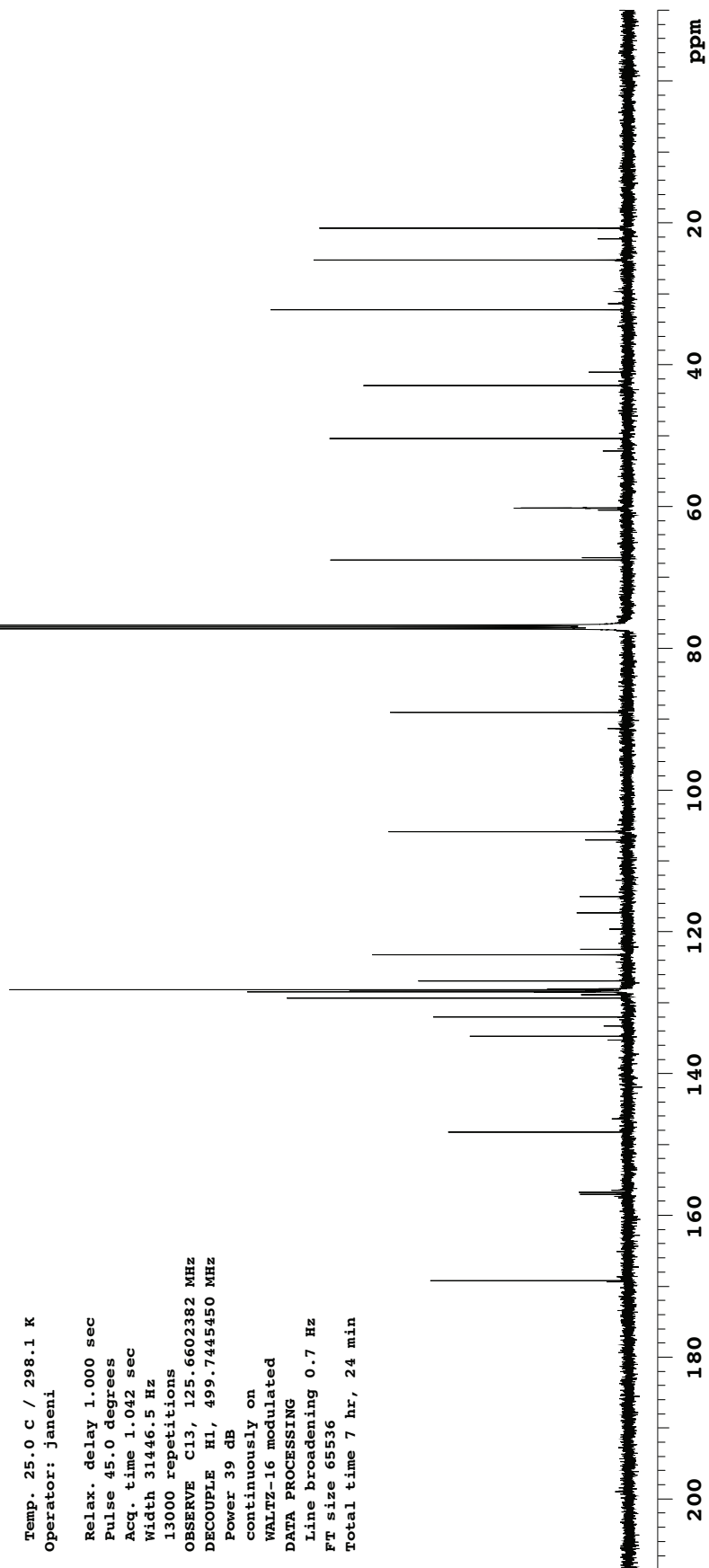
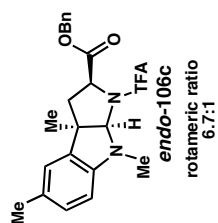
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.7 Hz

FT size 65536

Total time 7 hr, 24 min



LMRIV-177-majordr-hsqc2

Sample Name:

LMRIV-177-majordr-hsqc2

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-177-majordr-hsqc2

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 31 2010

Operator: lrepka

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

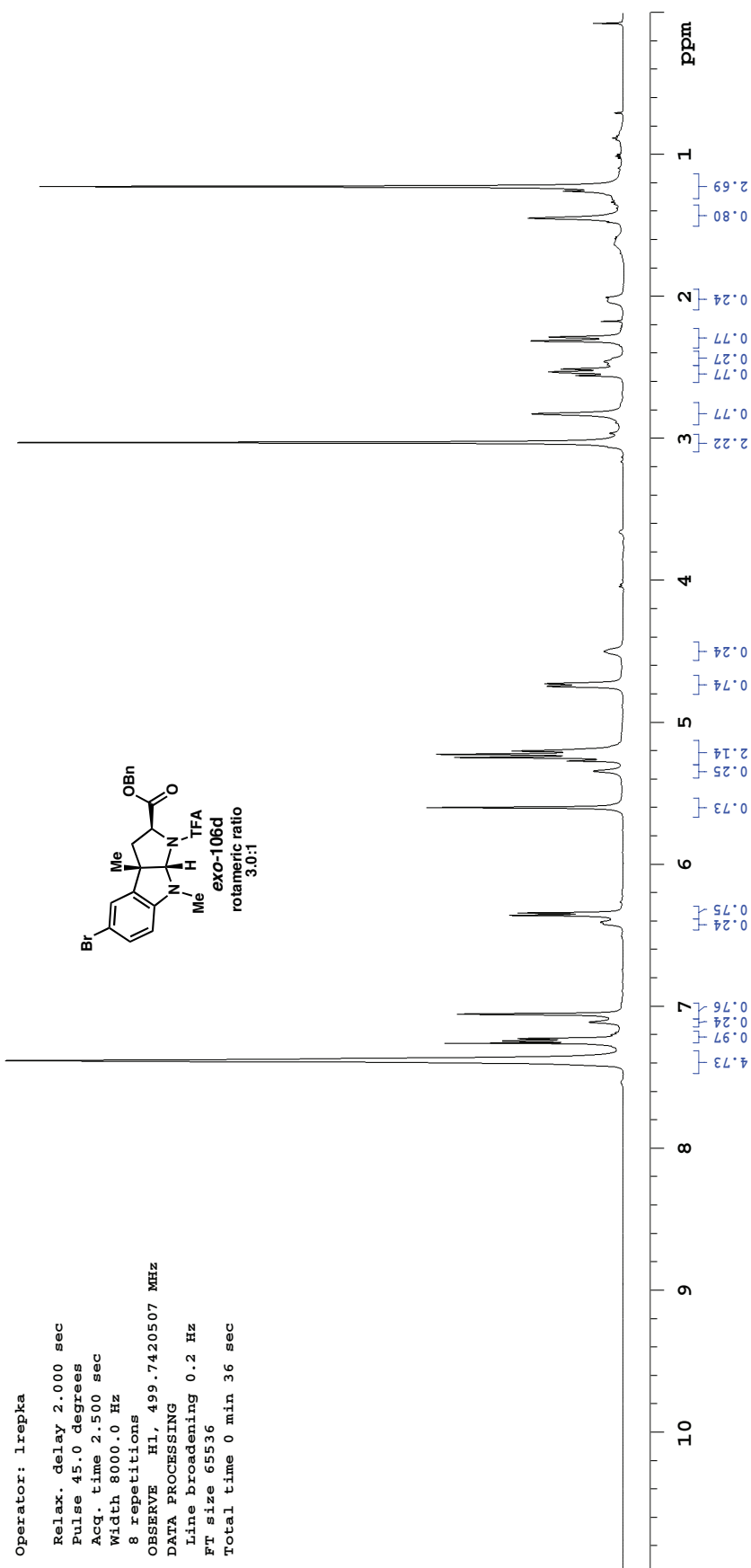
OBSERVE H1, 499.7420507 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 0 min 36 sec



LMRIV-177-major-dr-7-31-10

Sample Name:

LMRIV-177-major-dr-7-31-10

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-177-major-dr-7-31-10

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 31 2010

Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.022 sec

Width 32051.3 Hz

13250 repetitions

OBSERVE C13, 125.6602418 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

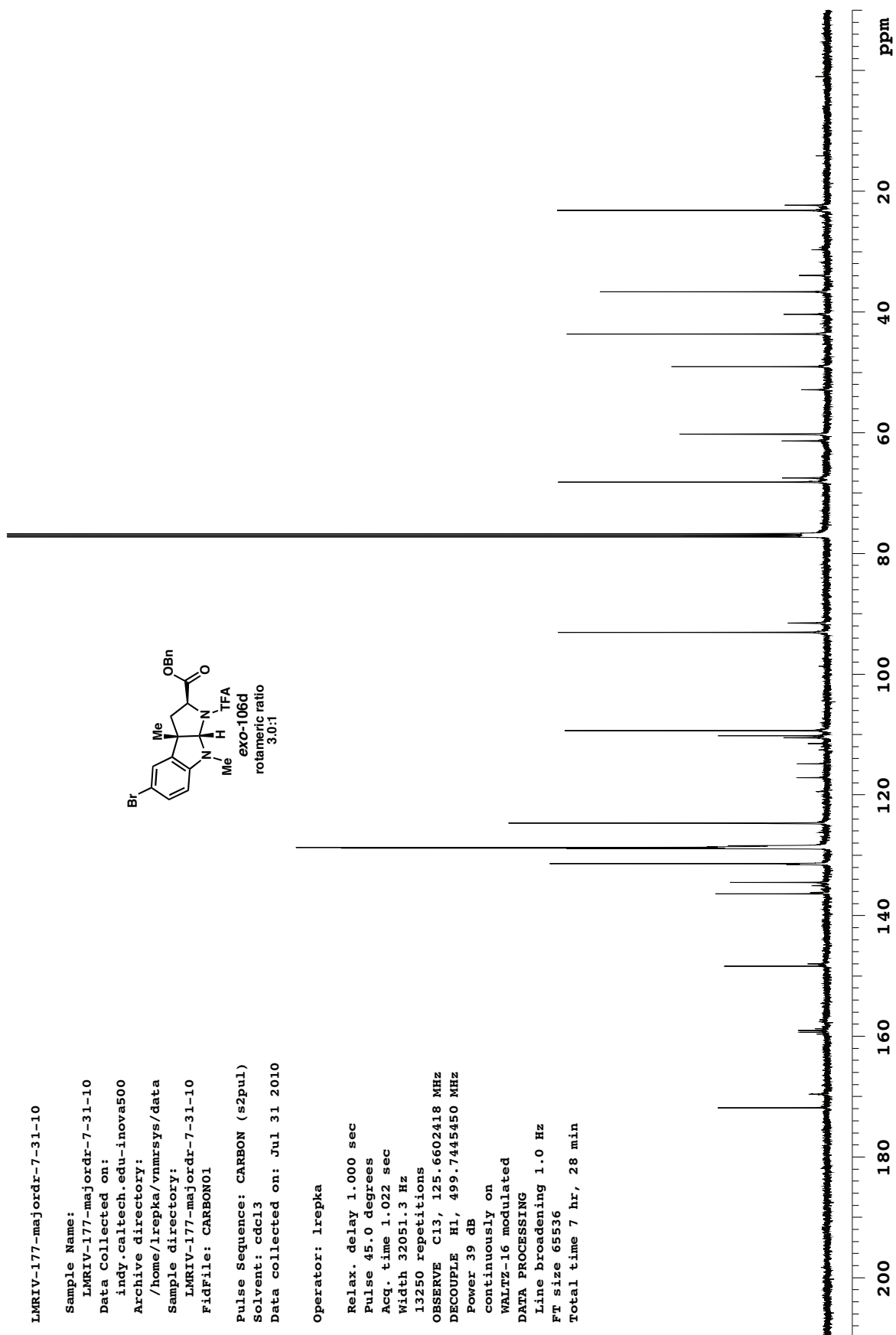
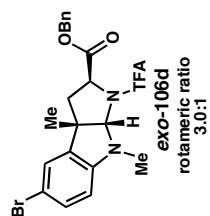
WALTZ-16 modulated

DATA PROCESSING

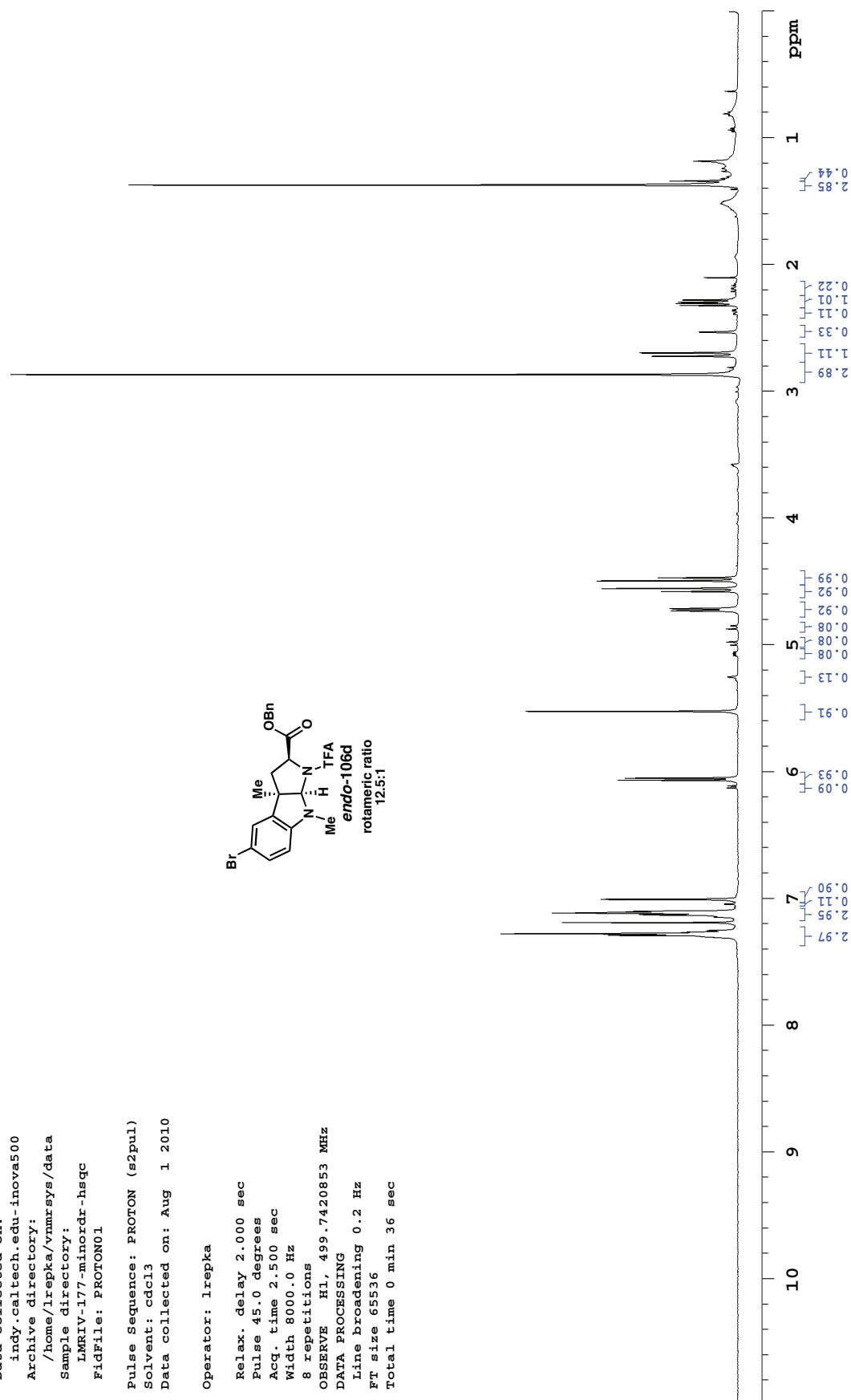
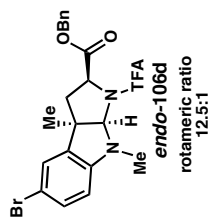
Line broadening 1.0 Hz

FT size 65536

Total time 7 hr, 28 min



Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420853 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 36 sec



LMRIV-177-minordr

Sample Name:

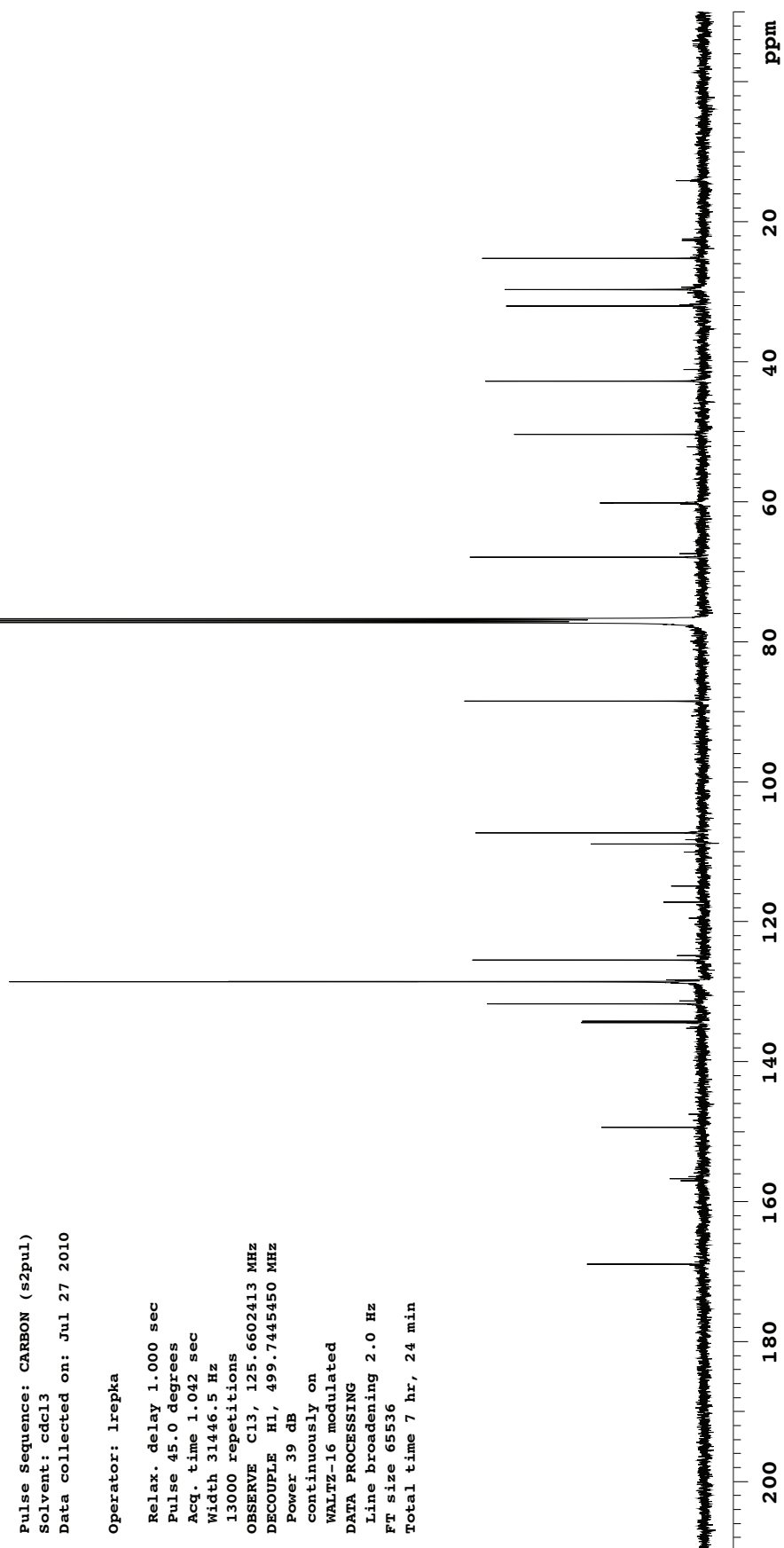
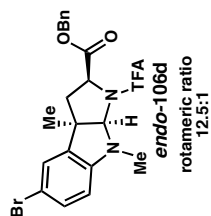
LMRIV-177-minordr
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-177-minordr
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3
Data collected on: Jul 27 2010

Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13000 repetitions
OBSERVE C13, 125.6602413 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 7 hr, 24 min



JN-1-215-majoridiast2

Sample Name:

JN-1-215-majoridiast2

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-215-majoridiast2

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 3 2010

Operator: janeni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

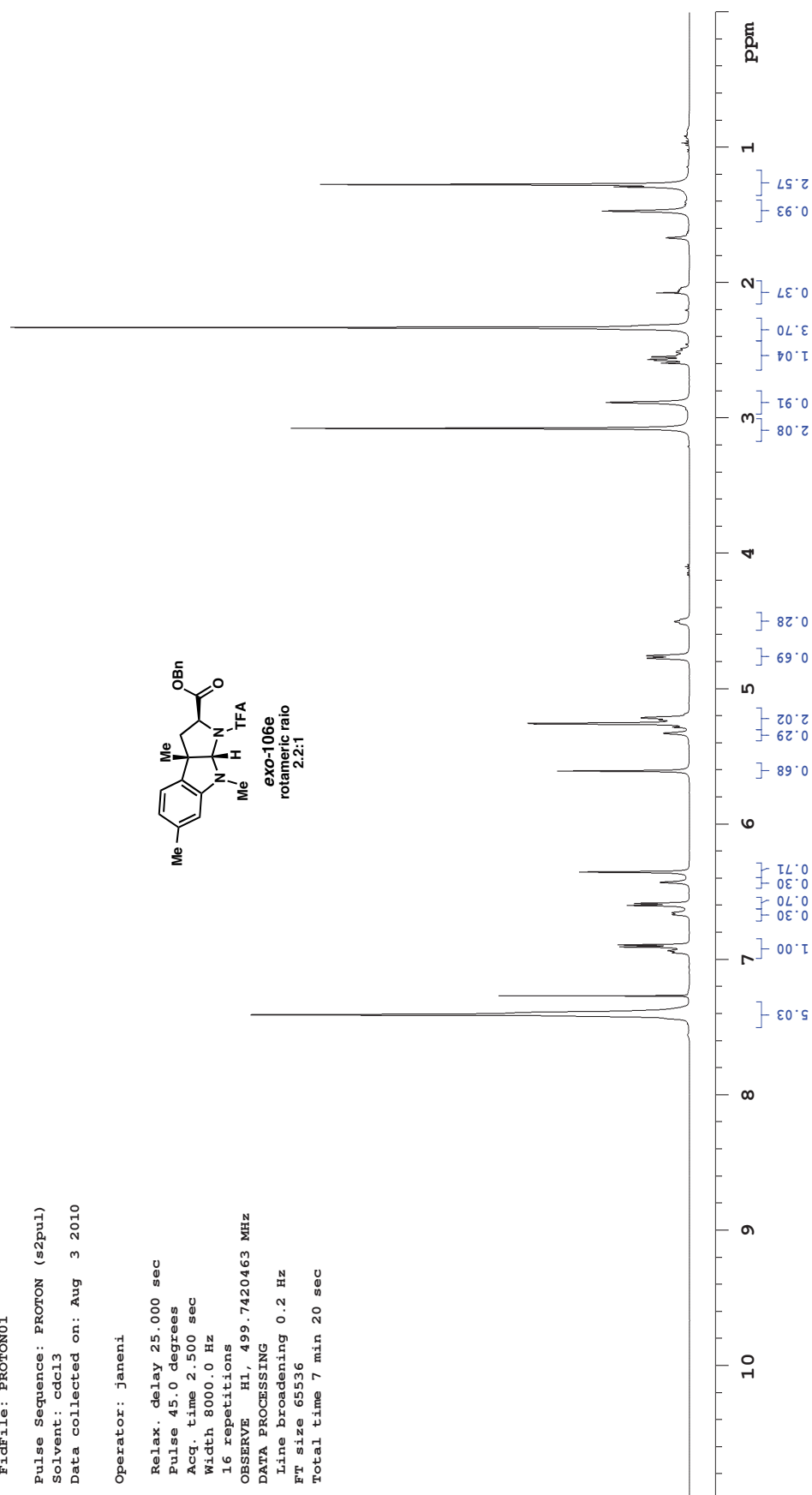
OBSERVE H1, 499.7420463 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 7 min 20 sec



JN-1-215-majordiast2

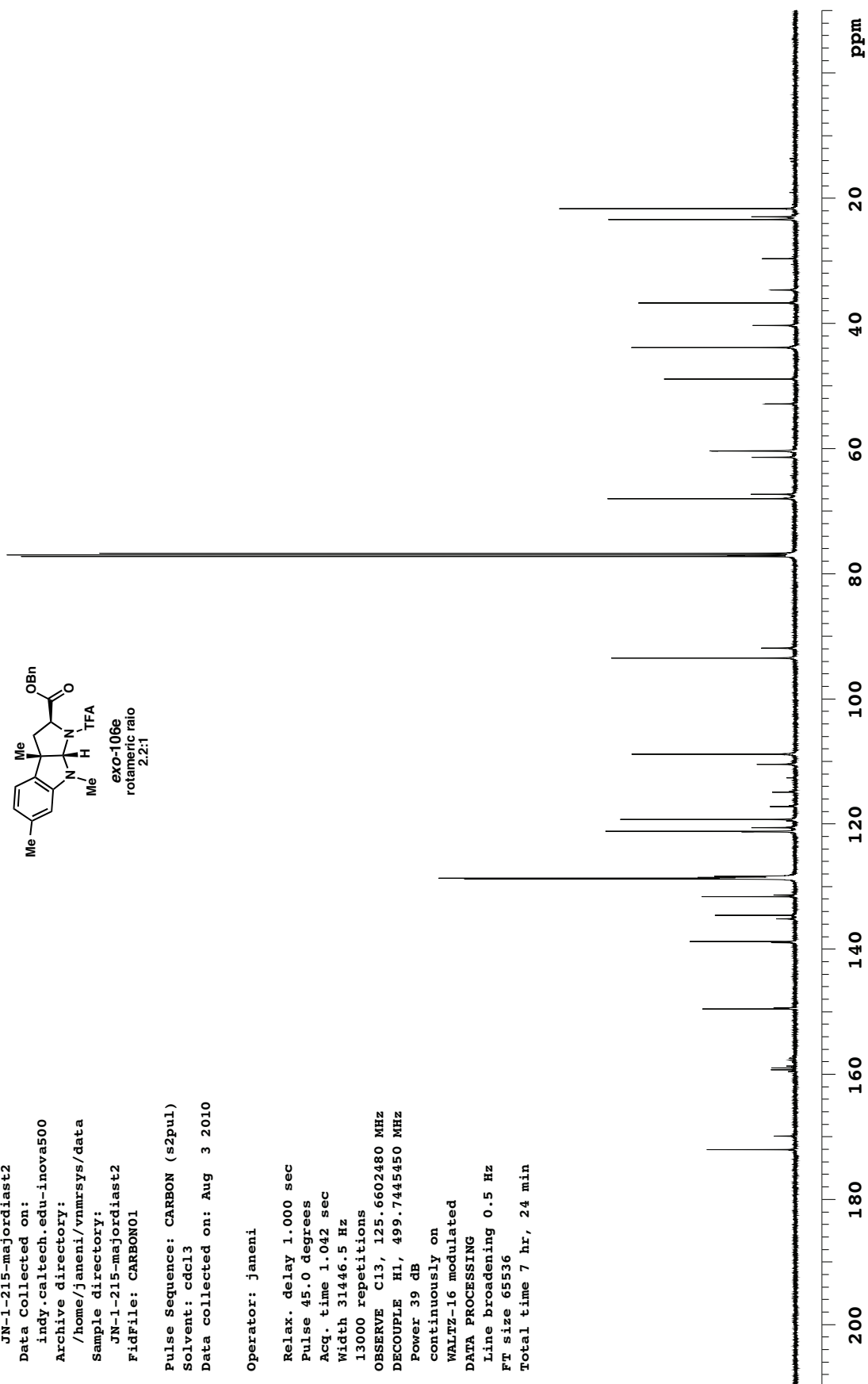
Sample Name:

JN-1-215-majordiast2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-1-215-majordiast2
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 3 2010

Operator: janeni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13000 repetitions
OBSERVE C13, 125.6602480 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 24 min



JN-1-215-minordiast2

Sample Name:

JN-1-215-minordiast2

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-215-minordiast2

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 2 2010

Operator: janeni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

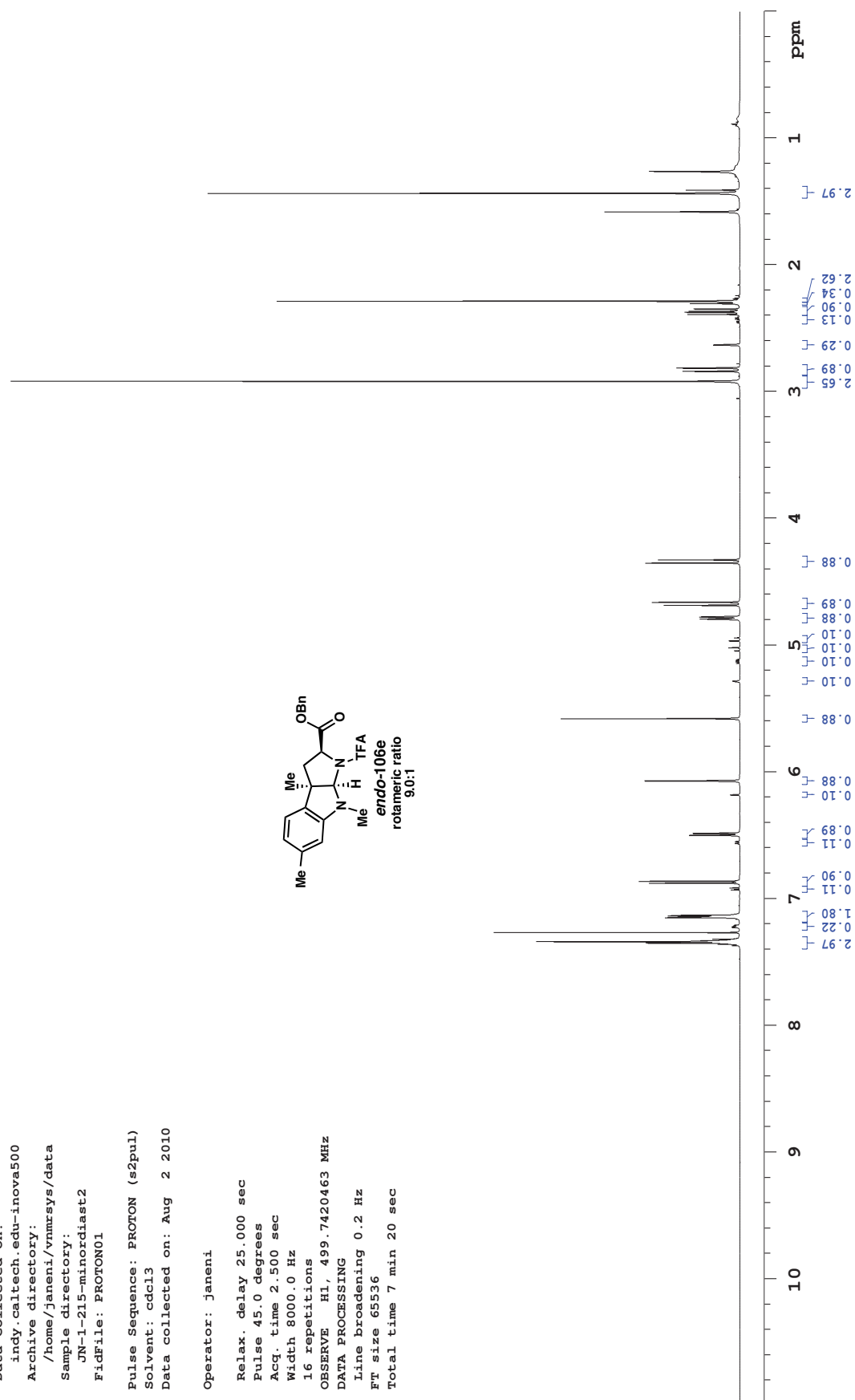
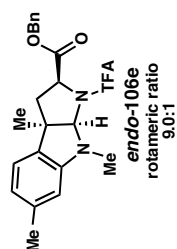
OBSERVE H1, 499.7420463 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 7 min 20 sec



JN-1-215-minordiast2

Sample Name:

JN-1-215-minordiast2

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-215-minordiast2

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Aug 2 2010

Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

12500 repetitions

OBSERVE C13, 125.6602413 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

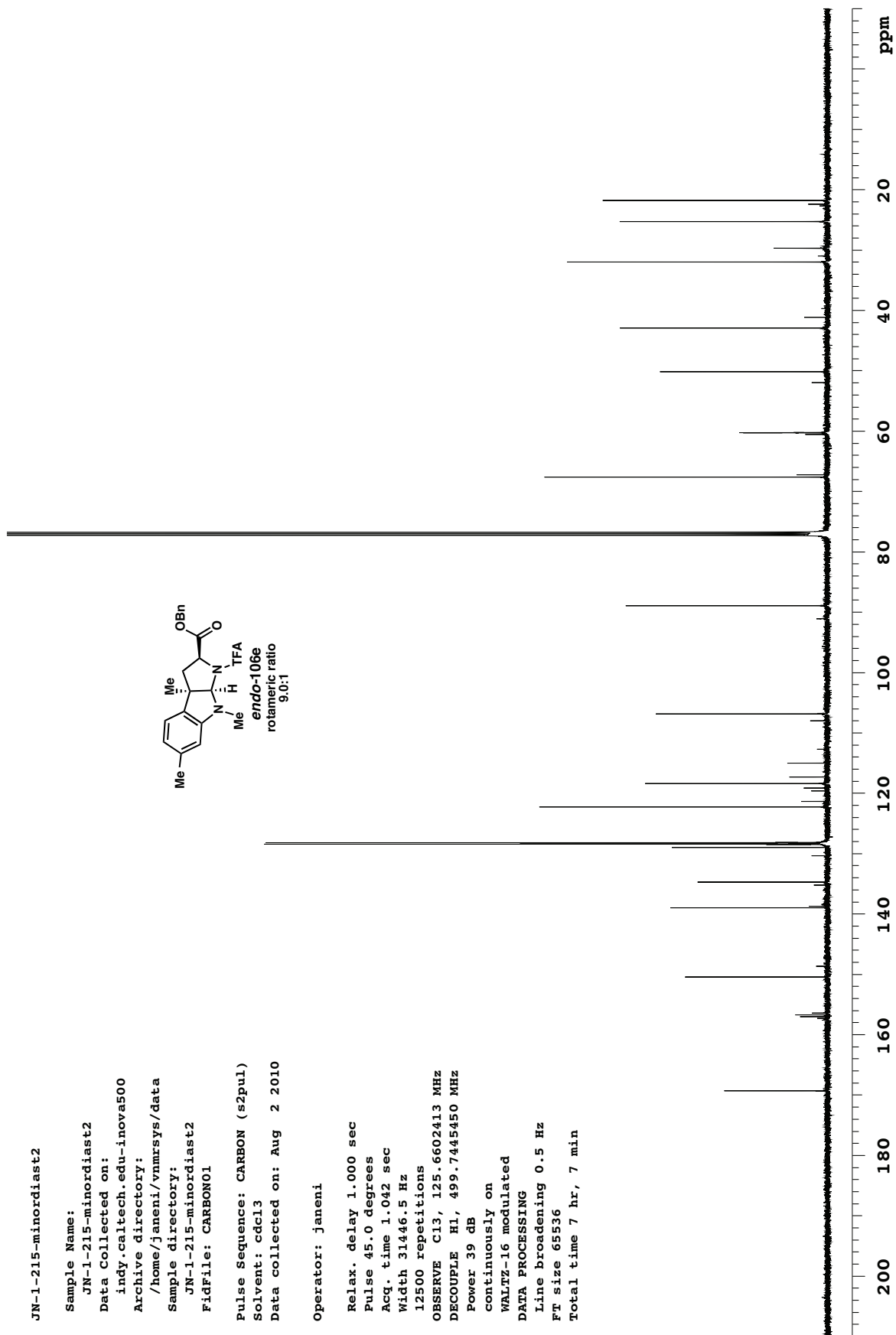
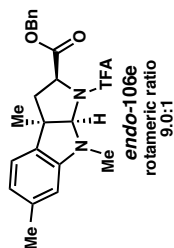
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 7 hr, 7 min



LMRIV-285-major-rd25

Sample Name:

LMRIV-285-major-rd25

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-285-major-rd25

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 30 2010

Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

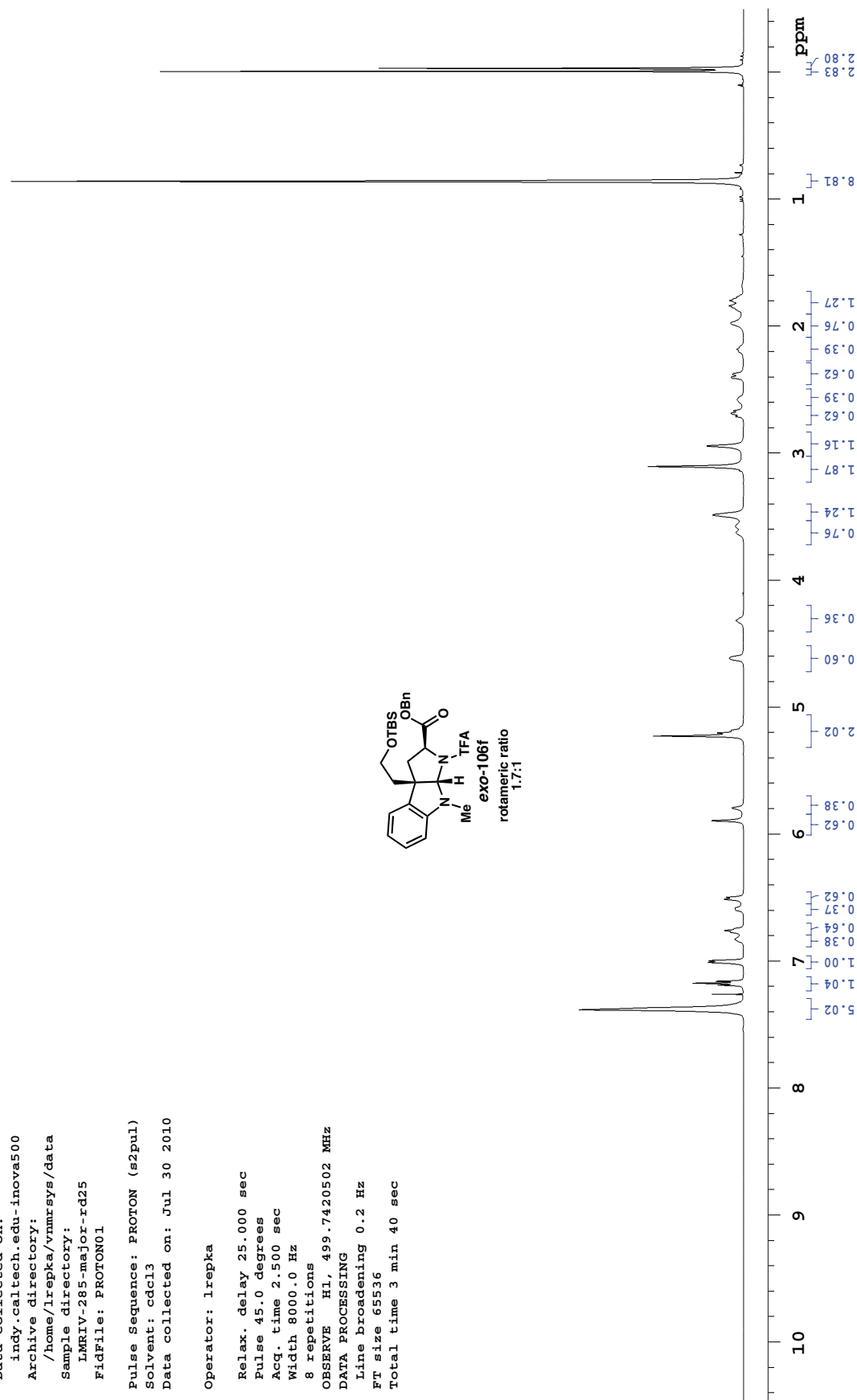
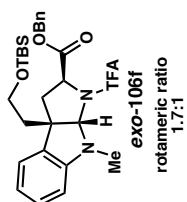
OBSERVE H1, 499.7420502 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 3 min 40 sec



LMRIV-285-major-dr-2-again

Sample Name:

LMRIV-285-major-dr-2-again

Data Collected on:

siena.caltech.edu-vnmrs400

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-285-major-dr-2-again

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 30 2010

Temp. 25.0 C / 298.1 K

Sample #2, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.258 sec

Width 26041.7 Hz

10500 repetitions

OBSERVE C13, 100.5283569 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

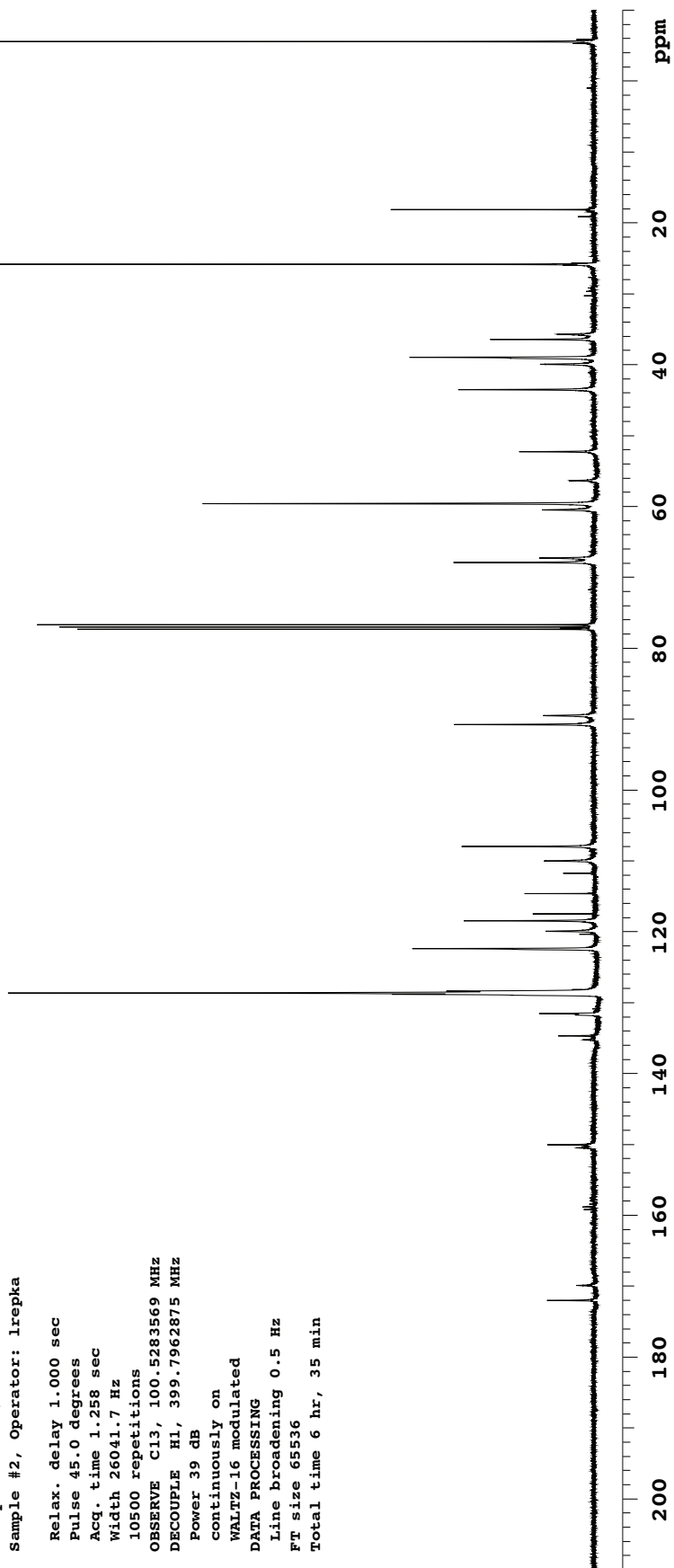
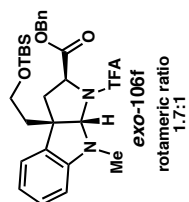
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 6 hr, 35 min



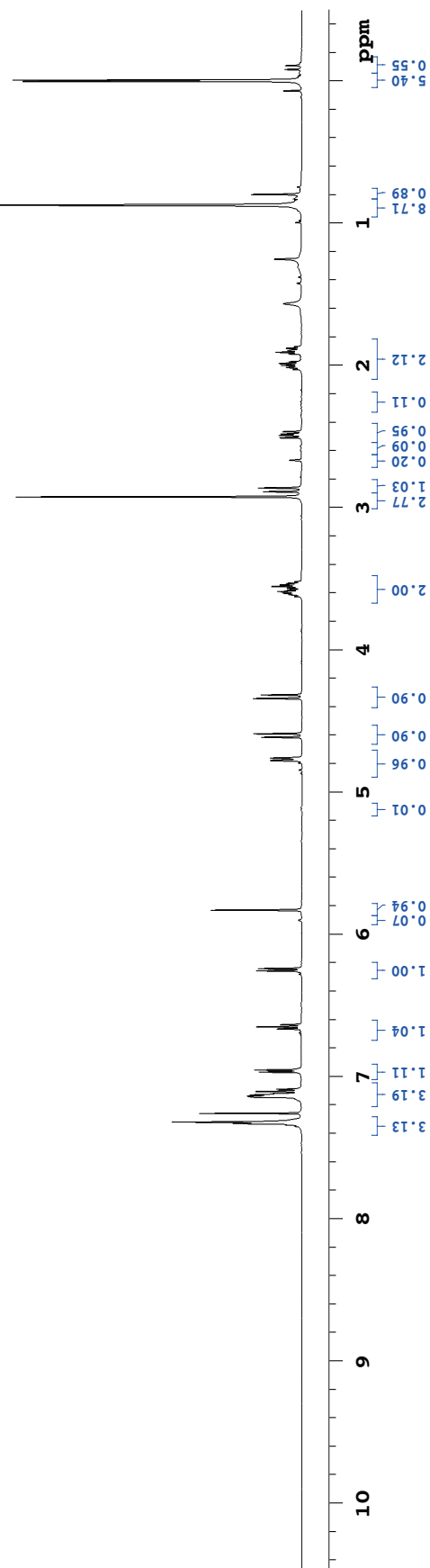
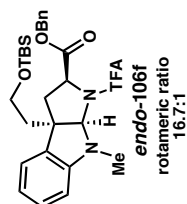
LMRIV-285-minor-rd25

Sample Name:
 LMRIV-285-minor-rd25
 Data Collected on:
 indy.caltech.edu-inova500
 Archive directory:
 /home/lrepka/vnmrsys/data
 Sample directory:
 LMRIV-285-minor-rd25
 FIDfile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jul 30 2010

Operator: lrepka

Relax. delay 25.000 sec
 Pulse 45.0 degrees
 Acq. time 2.500 sec
 Width 8000.0 Hz
 8 repetitions
 OBSERVE H1, 499.7420512 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 3 min 40 sec



LMRIV-285-minordr-2-carbon

Sample Name:

LMRIV-285-minordr-2-carbon

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-285-minordr-2-carbon

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 30 2010

Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.022 sec

Width 32051.3 Hz

13000 repetitions

OBSERVE C13, 125.6602398 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

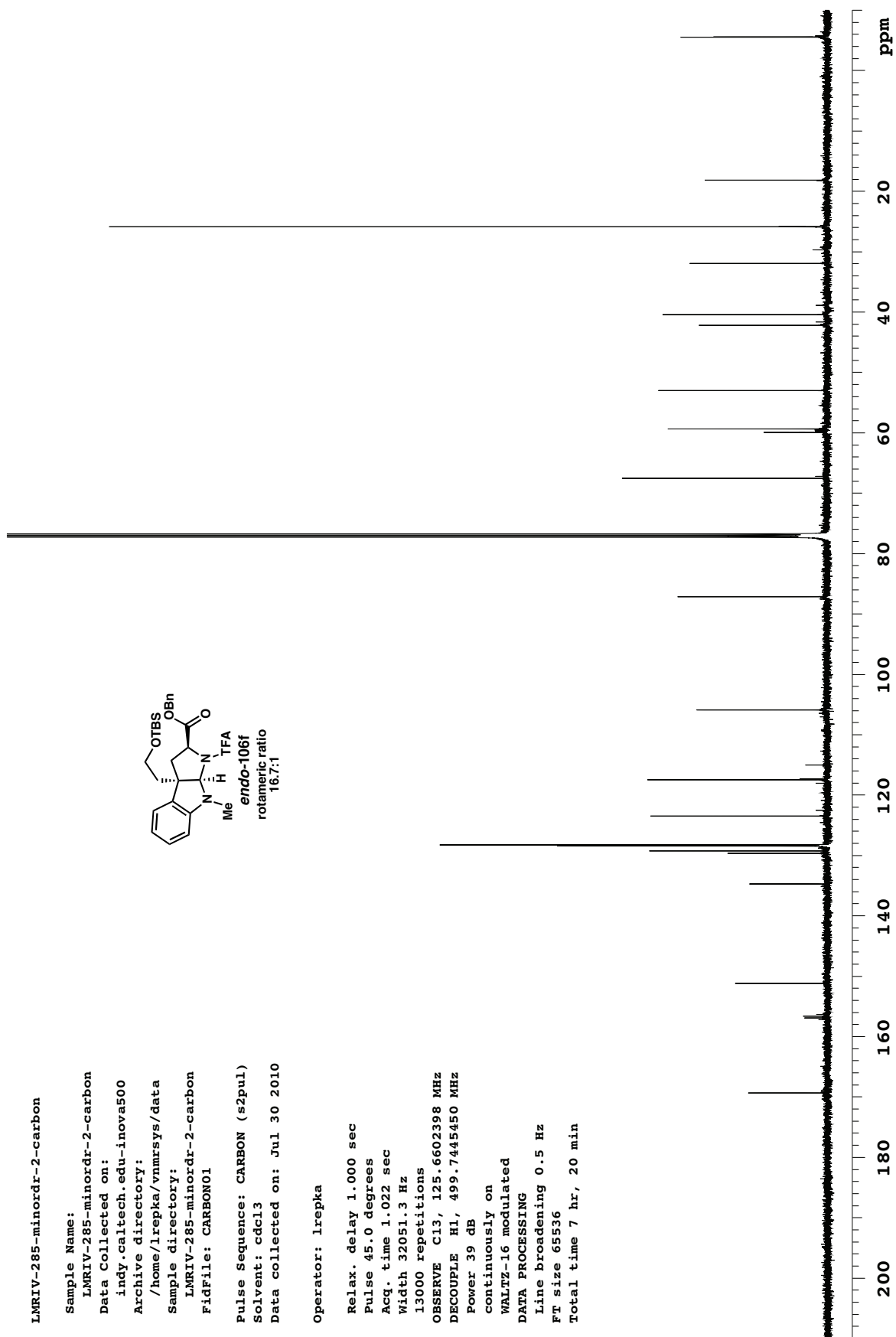
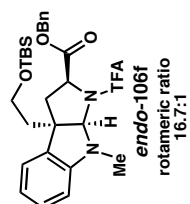
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 7 hr, 20 min



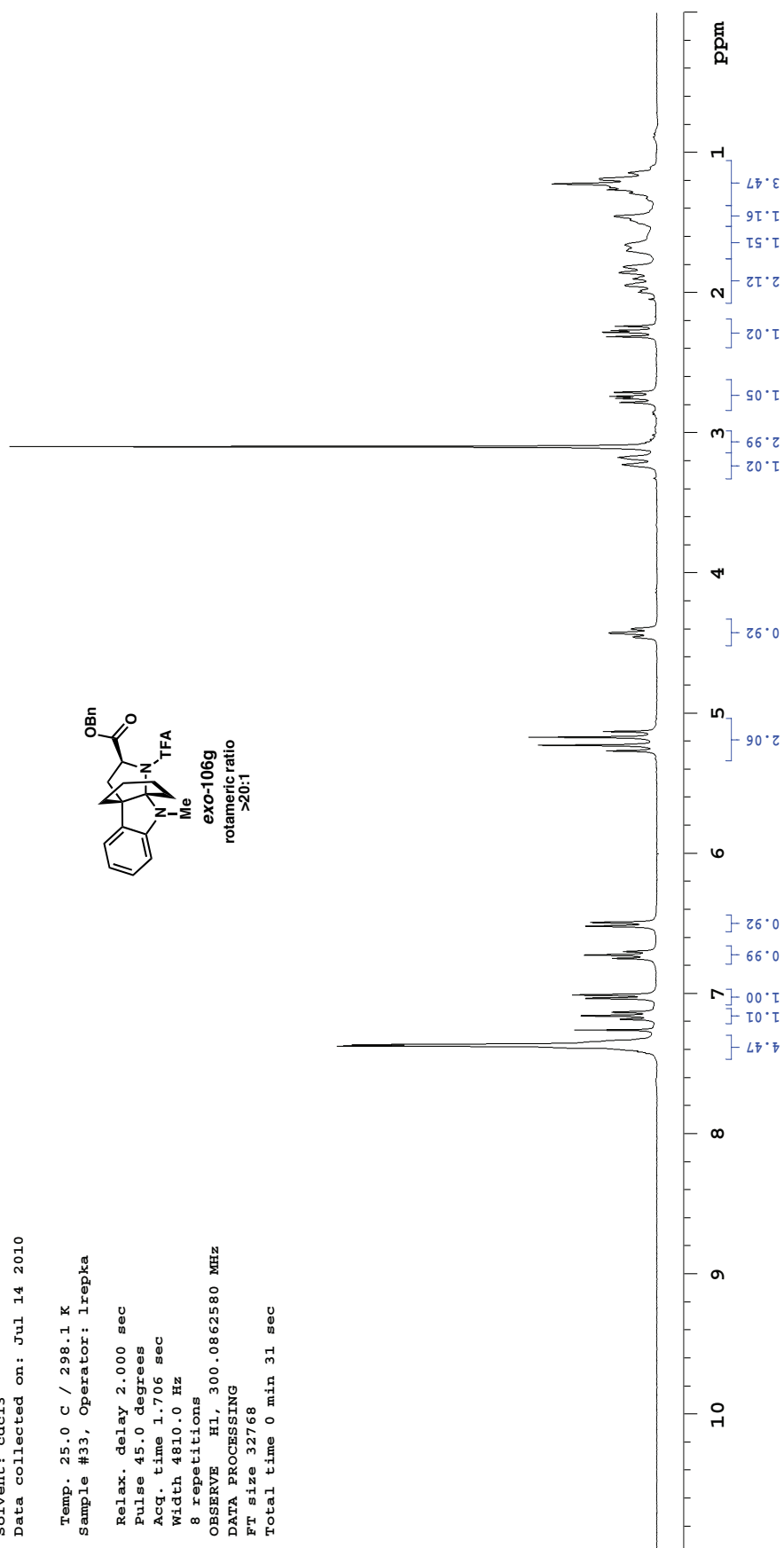
LMRIV-275-pentanewash

Sample Name:
 LMRIV-275-pentanewash
 Data Collected on:
 hg3.caltech.edu-mercury300
 Archive directory:
 /home/lrepka/vnmrsys/data
 Sample directory:
 LMRIV-275-pentanewash
 FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jul 14 2010

Temp. 25.0 C / 298.1 K
 Sample #33, Operator: lrepka

Relax. delay 2.000 sec
 Pulse 45.0 degrees
 Acq. time 1.706 sec
 Width 4810.0 Hz
 8 repetitions
 OBSERVE H1, 300.0862580 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 31 sec



LMRIV-275

Sample Name:

LMRIV-275

Data Collected on:

siena.caltech.edu-vmrs400

Archive directory:

/home/jni/vmrsys/data

Sample directory:

LMRIV-275

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 15 2010

Temp. 25.0 C / 298.1 K

Sample #8, Operator: jni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.285 sec

Width 25510.2 Hz

11500 repetitions

OBSERVE C13, 100.5283535 MHz

DECOUPLE H1, 399.7962875 MHz

Power 39 dB

continuously on

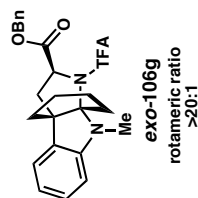
WALTZ-16 modulated

DATA PROCESSING

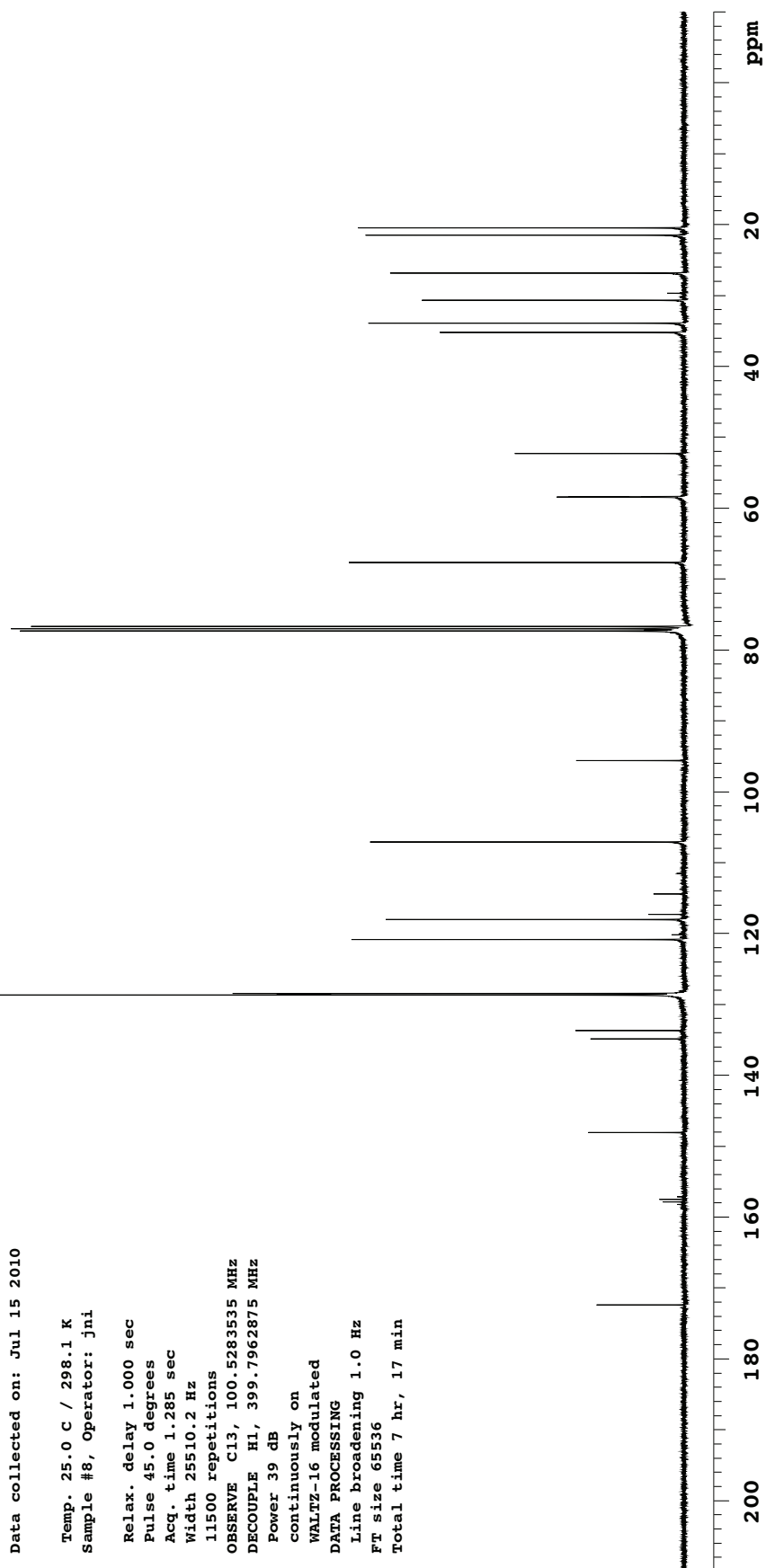
Line broadening 1.0 Hz

FT size 65536

Total time 7 hr, 17 min



exo-106g
rotameric ratio
>20:1



LMRIV-267-major diastereomer

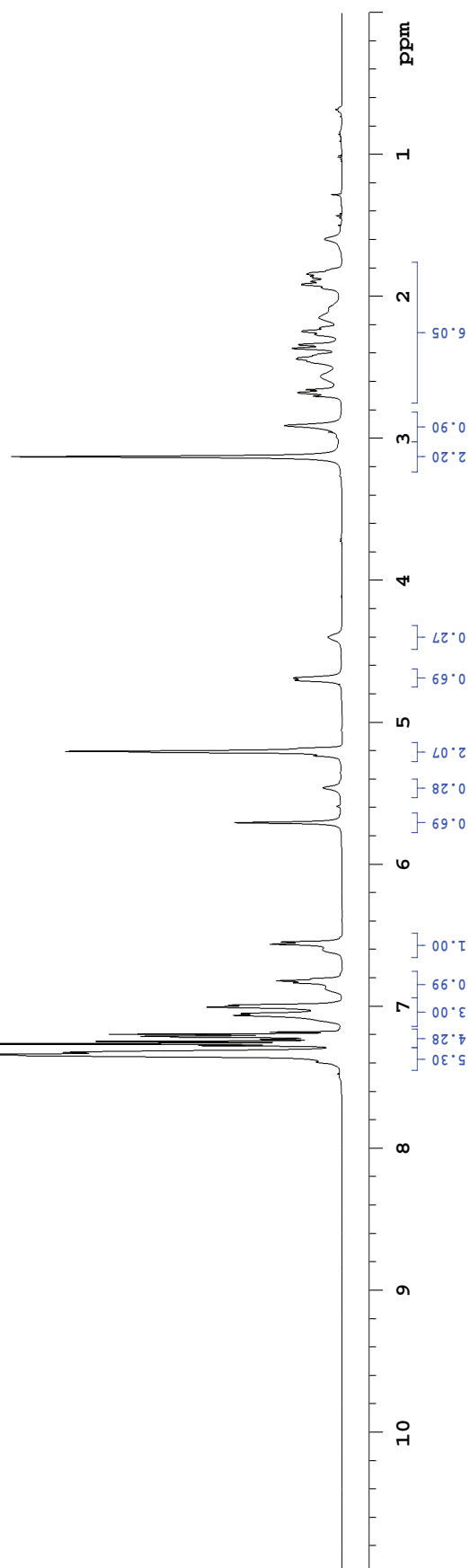
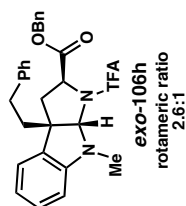
Sample Name:
 LMRIV-267-majordr
 Data Collected on:
 indy.caltech.edu-ino500
 Archive directory:
 /home/lrepka/vnmrsys/data
 Sample directory:
 LMRIV-267-majordr
 FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jul 19 2010

Temp. 25.0 C / 298.1 K
 Operator: lrepka

Relax. delay 25.000 sec
 Pulse 45.0 degrees
 Acq. time 2.500 sec
 Width 8000.0 Hz
 16 repetitions

OBSERVE H1, 499.7420463 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 7 min 20 sec



LMRIV-267-majorshigemi

Sample Name:

LMRIV-267-majorshigemi
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-267-majorshigemi
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 20 2010

Temp. 25.0 C / 298.1 K
Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
12400 repetitions

OBSERVE C13, 125.6602469 MHz
DECOUPLE H1, 499.7445450 MHz

Power 39 dB
continuously on

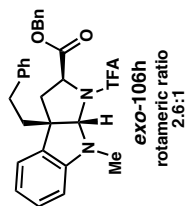
WALTZ-16 modulated

DATA PROCESSING

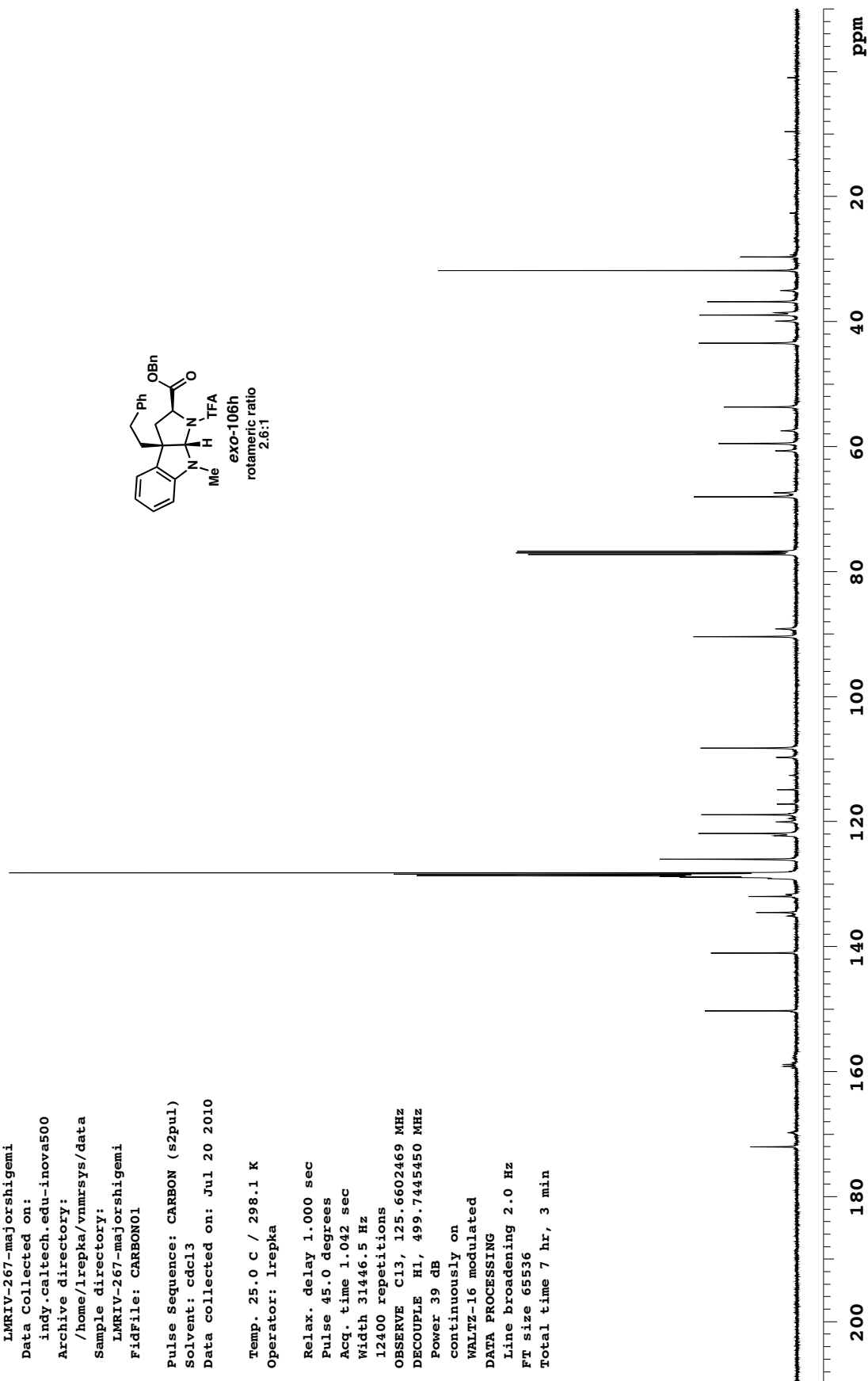
Line broadening 2.0 Hz

FT size 65536

Total time 7 hr, 3 min



exo-106h
rotameric ratio
2.6:1



LMRIV-267-minor3

Sample Name:

LMRIV-267-minor3

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRIV-267-minor3 20100717_01

FidFile: data_s2pul_001

Pulse Sequence: PROTON (s2pul)

Solvent: CDCl₃

Data collected on: Jul 17 2010

Temp. 25.0 C / 298.1 K

Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.049 sec

Width 7996.0 Hz

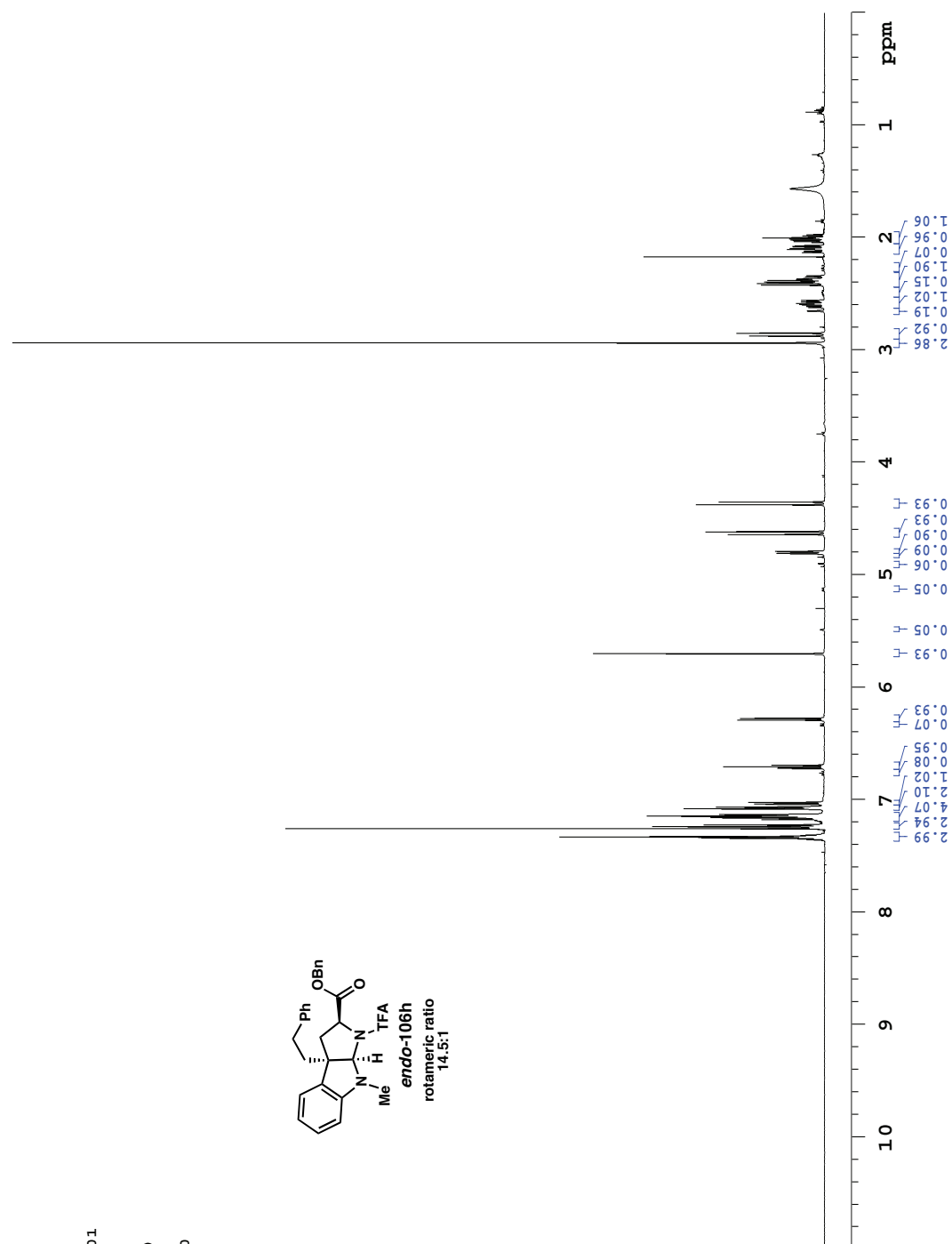
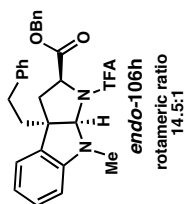
8 repetitions

OBSERVE H1, 499.7420487 MHz

DATA PROCESSING

Ft size 32768

Total time 3 min 36 sec



LMRIV-267-minor3

Sample Name:

LMRIV-267-minor3

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrSYS/data

Sample directory:

LMRIV-267-minor3_20100717_01

FidFile: data_s2pul_002

Pulse Sequence: CARBON (s2pul)

Solvent: CDCl₃

Data collected on: Jul 17 2010

Temp. 25.0 C / 298.1 K

Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.043 sec

Width 31409.5 Hz

12000 repetitions

OBSERVE C13, 125.6602386 MHz

DECOUPLE H1, 499.7445450 MHz

Power 39 dB

continuously on

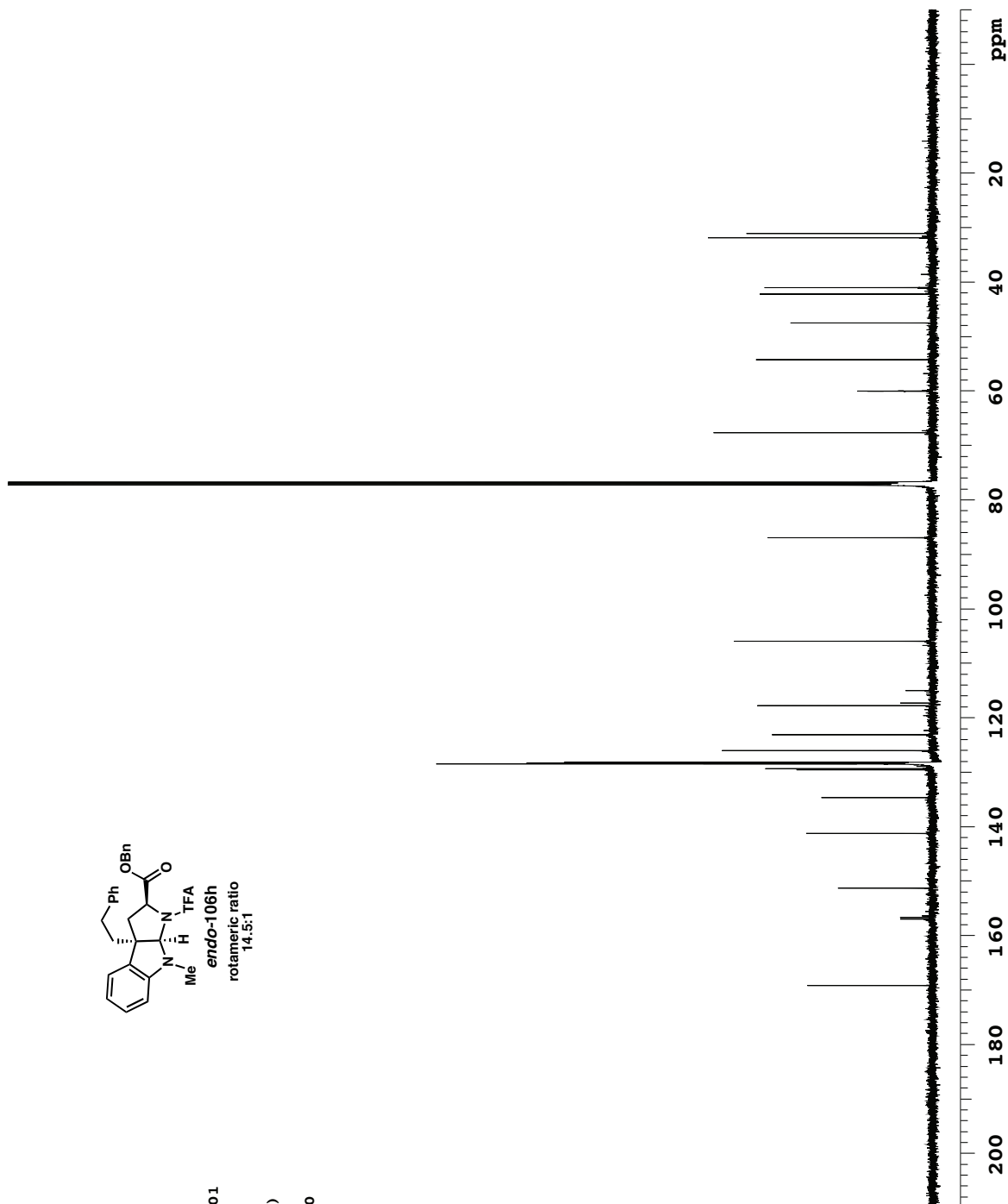
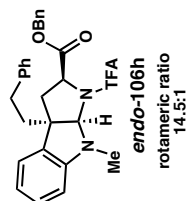
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 6 hr, 50 min



JN-1-211-majordiast

Sample Name:

JN-1-211-majordiast

Data Collected on:

sienna.caltech.edu—vnmrs400

Archive directory:

/home/jni/vnmrsys/data

Sample directory:

JN-1-211-majordiast

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdc13

Data collected on: Jul 28 2010

Temp. 25.0 C / 298.1 K

Sample #6, Operator: jni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.556 sec

Width 6410.3 Hz

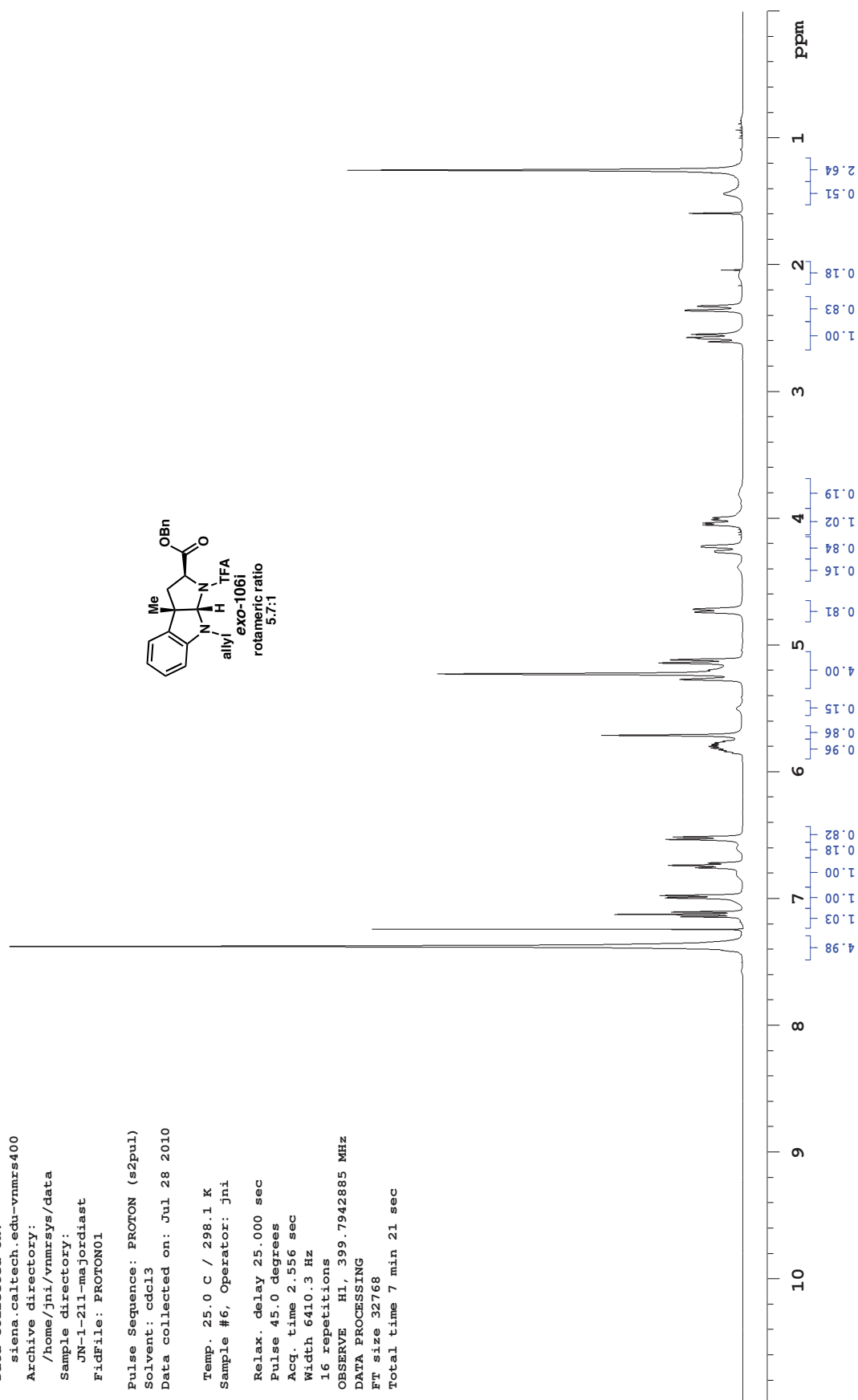
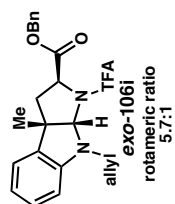
16 repetitions

OBSERVE H1, 399.7942885 MHz

DATA PROCESSING

FT size 32768

Total time 7 min 21 sec



JN-1-211-majordiast

Sample Name:

JN-1-211-majordiast
Data Collected on:
siena.caltech.edu-vmrs400
Archive directory:
/home/jni/vmrsys/data
Sample directory:
JN-1-211-majordiast
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 28 2010

Temp. 25.0 C / 298.1 K
Sample #6, Operator: jni

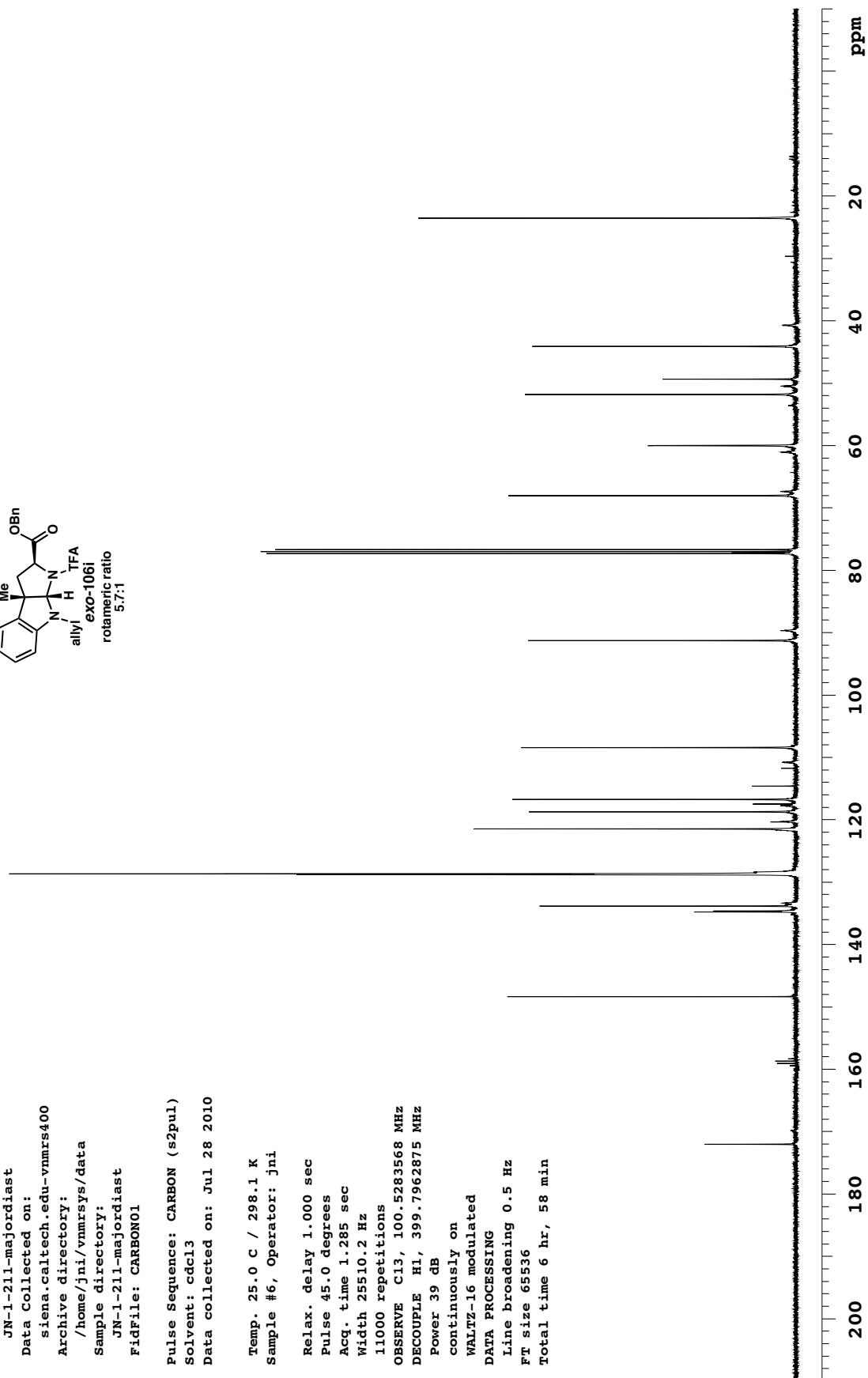
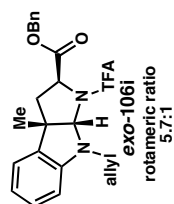
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
11000 repetitions

OBSERVE C13, 100.5283568 MHz
DECOUPLE H1, 399.7962875 MHz

Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz
FT size 65536
Total time 6 hr, 58 min



JN-1-211-minordiast

Sample Name:

JN-1-211-minordiast

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-1-211-minordiast

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 28 2010

Operator: janeni

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

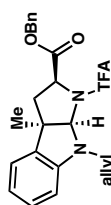
OBSERVE H1, 499.7420463 MHz

DATA PROCESSING

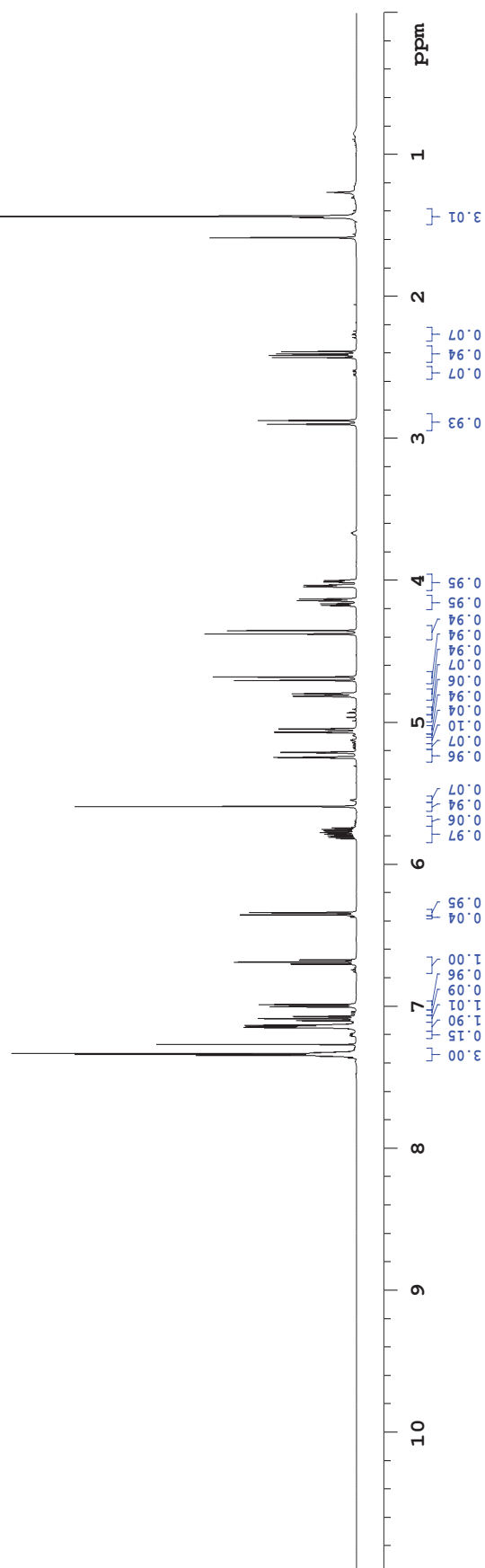
Line broadening 0.2 Hz

Ft size 65536

Total time 7 min 20 sec



endo-1061
rotameric ratio
15.7:1



JN-1-211-minordiast

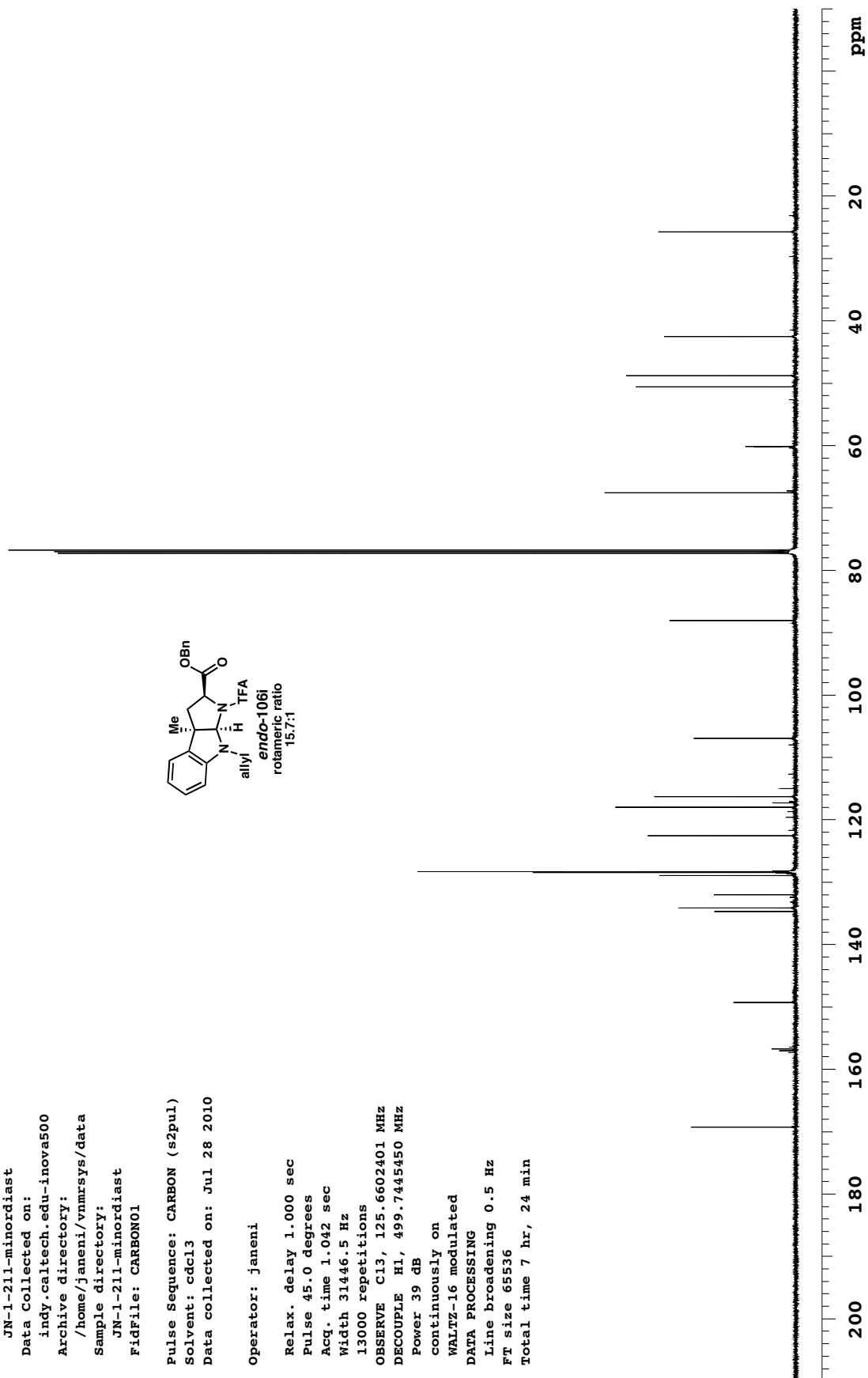
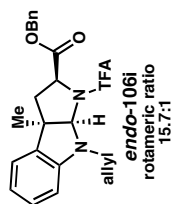
Sample Name:

JN-1-211-minordiast
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-1-211-minordiast
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 28 2010

Operator: janeni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13000 repetitions
OBSERVE C13, 125.6602401 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 24 min



LMRV-047-major01r

Sample Name:

LMRV-047-major01r
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRV-047-major01r
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Sep 16 2010

Temp. 25.0 C / 298.1 K

Sample #35, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

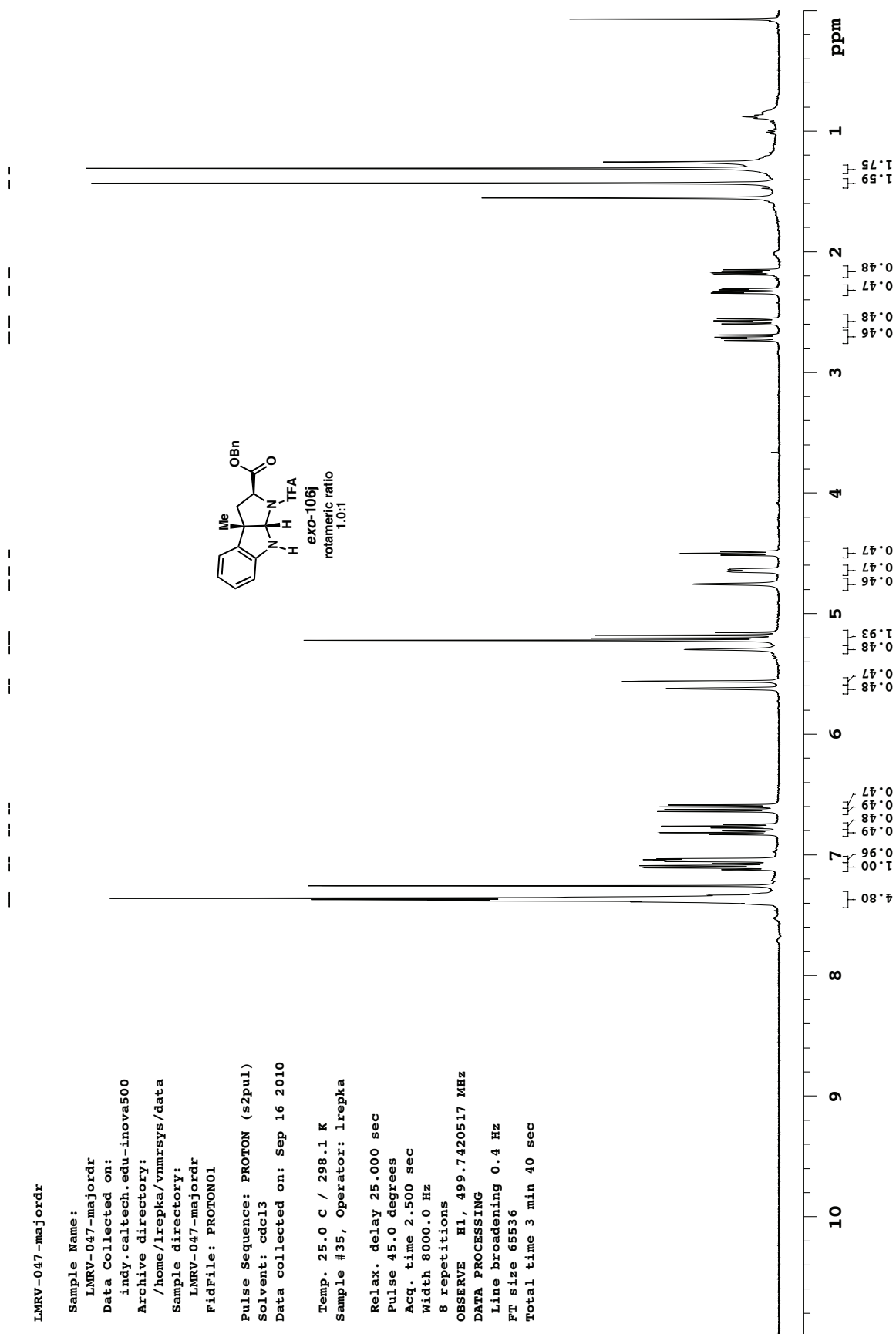
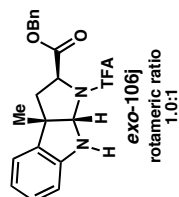
OBSERVE H1, 499.7420517 MHz

DATA PROCESSING

Line broadening 0.4 Hz

FT size 65536

Total time 3 min 40 sec



LMRV-047-majordr

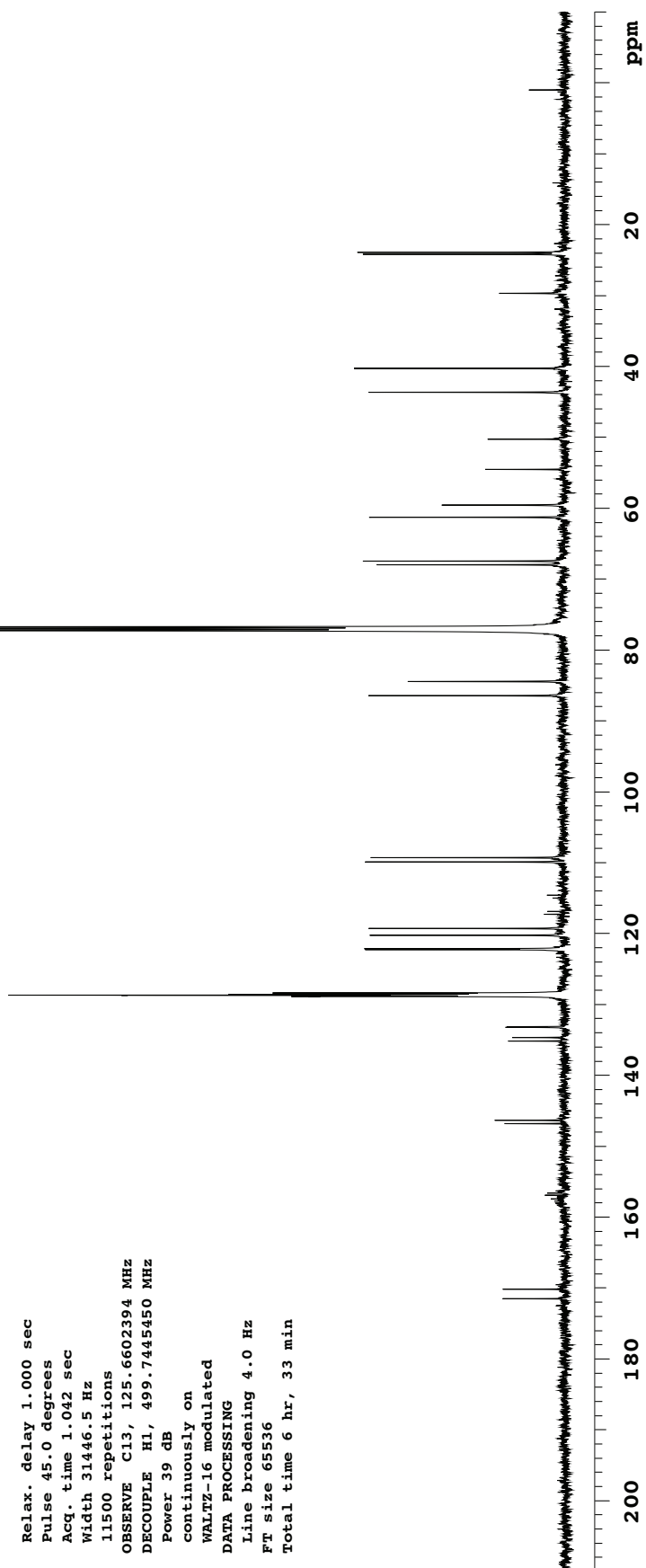
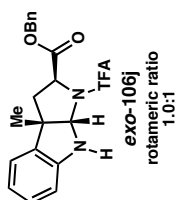
Sample Name:

LMRV-047-majordr
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrSYS/data
Sample directory:
LMRV-047-majordr
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 16 2010

Temp. 25.0 C / 298.1 K
Sample #35, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
11500 repetitions
OBSERVE C13, 125.6602394 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 65536
Total time 6 hr, 33 min



JN-3-101-carbon

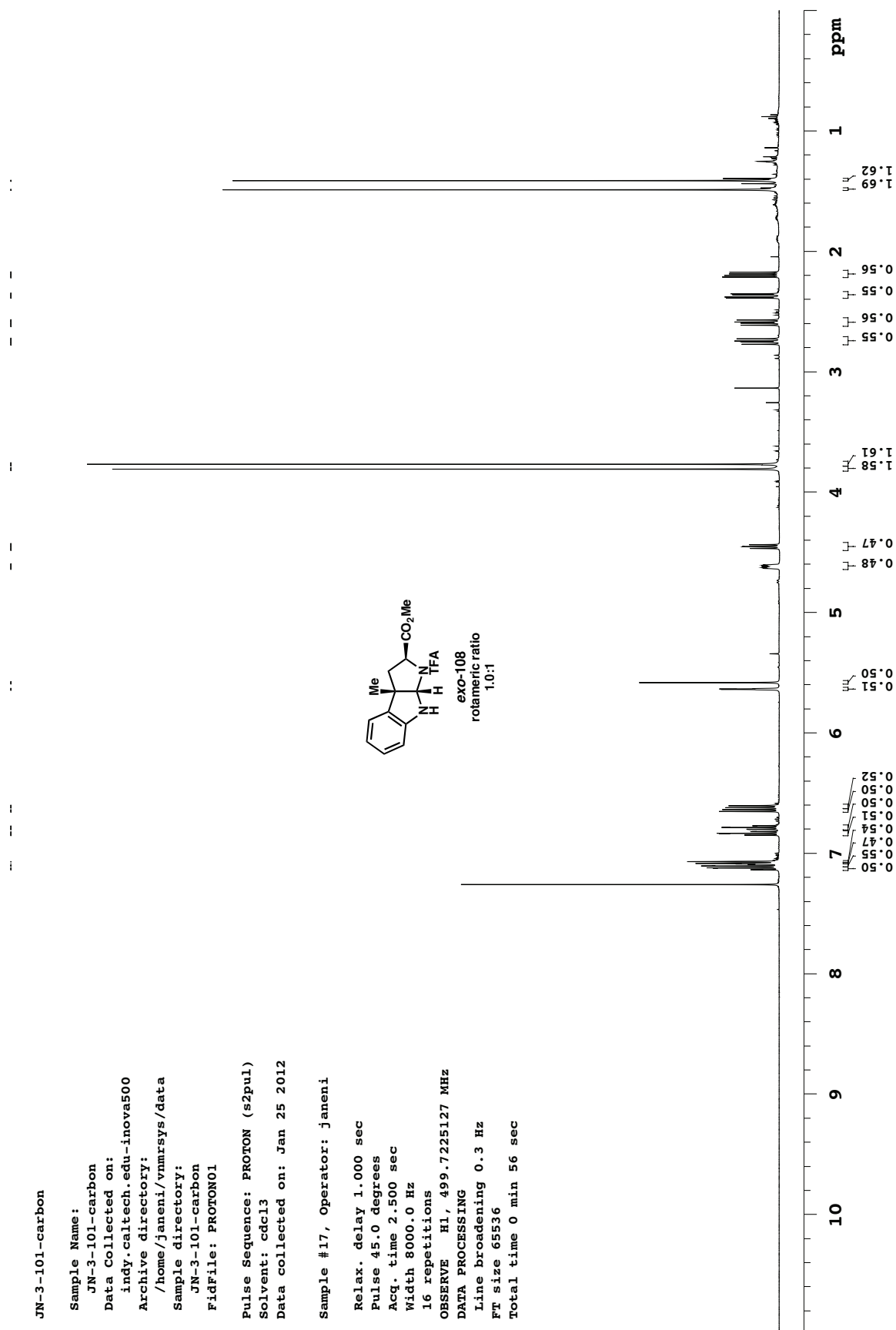
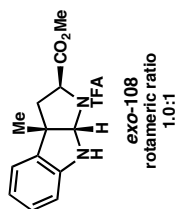
Sample Name:

JN-3-101-carbon
 Data Collected on:
 indy.caltech.edu-inova500
 Archive directory:
 /home/janeni/vnmrsys/data
 Sample directory:
 JN-3-101-carbon
 FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jan 25 2012

Sample #17, Operator: janeni

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.500 sec
 Width 8000.0 Hz
 16 repetitions
 OBSERVE H1, 499.7225127 MHz
 DATA PROCESSING
 Line broadening 0.3 Hz
 FT size 65536
 Total time 0 min 56 sec



JN-3-101-carbon

Sample Name:

JN-3-101-carbon

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/janeni/vnmrsys/data

Sample directory:

JN-3-101-carbon

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jan 25 2012

Sample #17, Operator: janeni

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

10000 repetitions

OBSERVE C13, 125.6553277 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

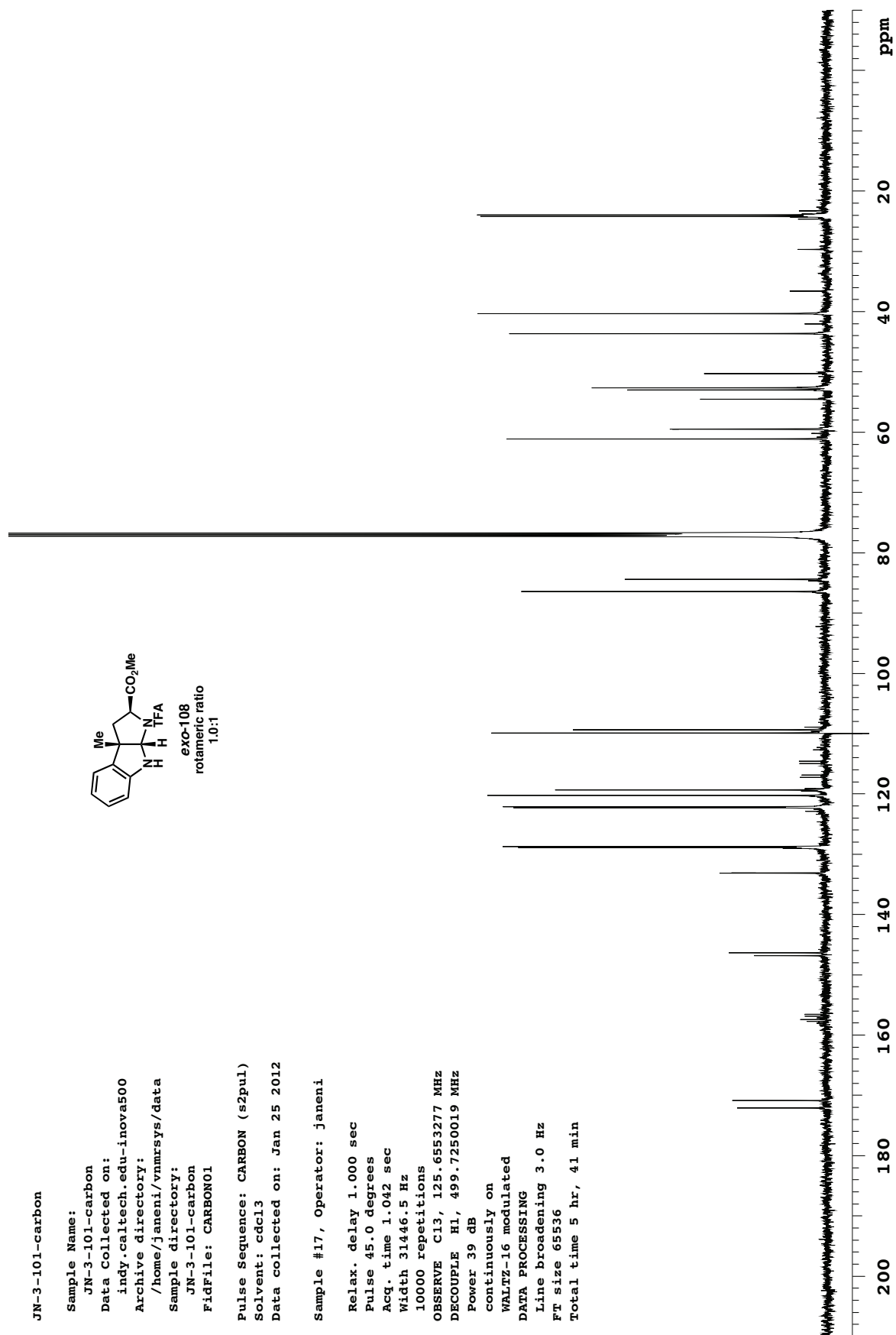
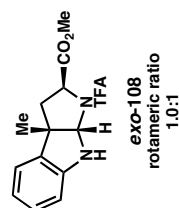
WALTZ-16 modulated

DATA PROCESSING

Line broadening 3.0 Hz

FT size 65536

Total time 5 hr, 41 min



LMRII-073-1.0workup

Sample Name:

LMRII-073-1.0workup

Archive directory:

Sample directory:

FidFile: LMRII-073-1.0workup

Pulse Sequence: Proton (s2pul)

Solvent: cdcl3

Data collected on: Sep 25 2009

Operator: lrepka

VNMRS-400 "erice.caltech.edu"

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.998 sec

Width 4796.2 Hz

2 repetitions

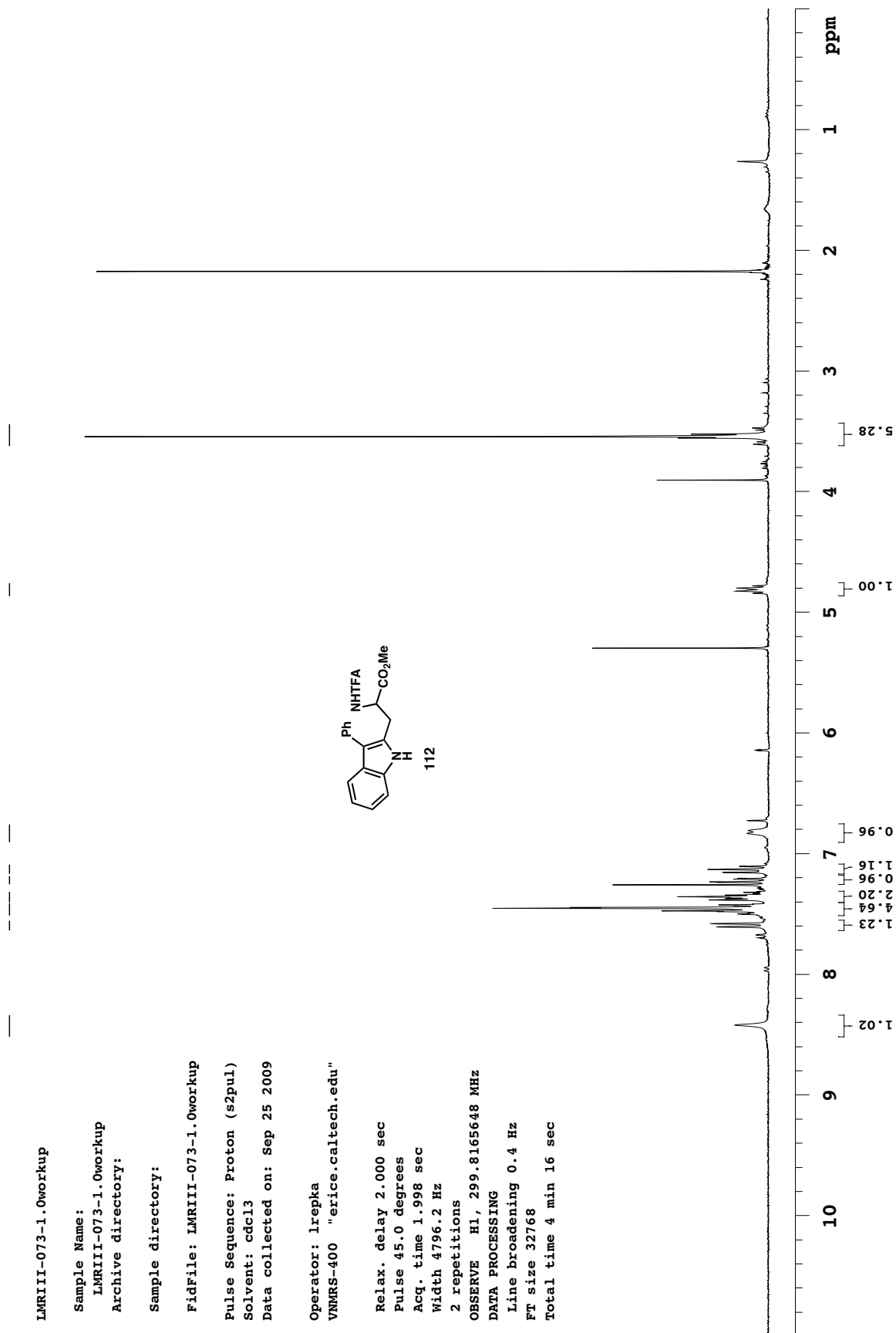
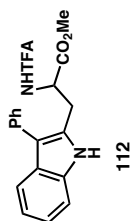
OBSERVE H1, 299.8165648 MHz

DATA PROCESSING

Line broadening 0.4 Hz

FT size 32768

Total time 4 min 16 sec



LMRIII-107

Sample Name:

LMRIII-107

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

Sample directory:

FidFile: Carbon_01

Pulse Sequence: Carbon (s2pul)

Solvent: cdcl3

Data collected on: Oct 7 2009

Sample #38, Operator: slevin

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.300 sec

Width 30165.9 Hz

800 repetitions

OBSERVE C13, 125.6635224 MHz

DECOUPLE H1, 499.7575738 MHz

Power 39 dB

continuously on

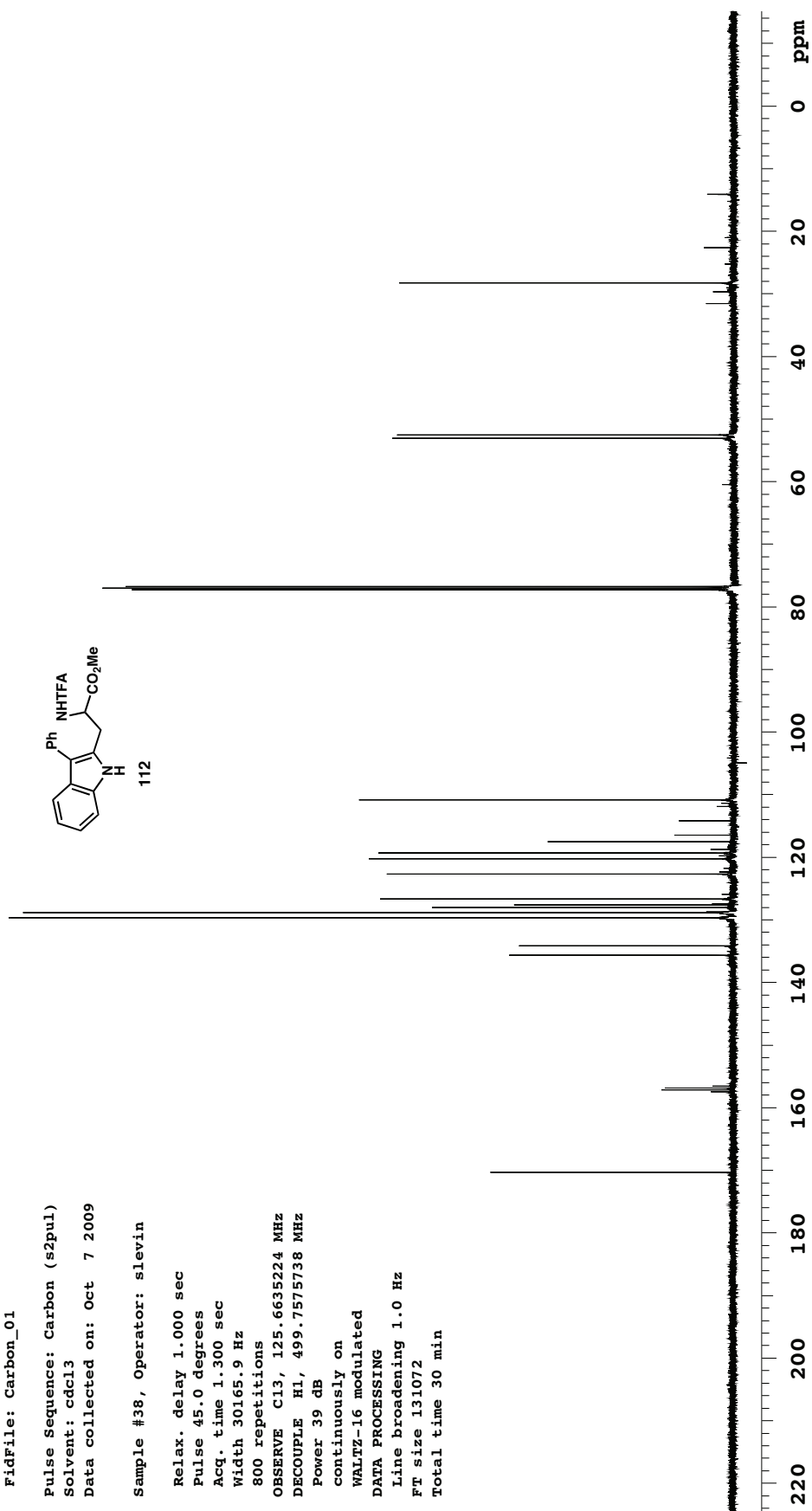
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

Ft size 131072

Total time 30 min



LMRV-229-column

Sample Name:

LMRV-229-column

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRV-229-column

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jan 28 2011

Sample #33, Operator: lrepka

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 4798.5 Hz

16 repetitions

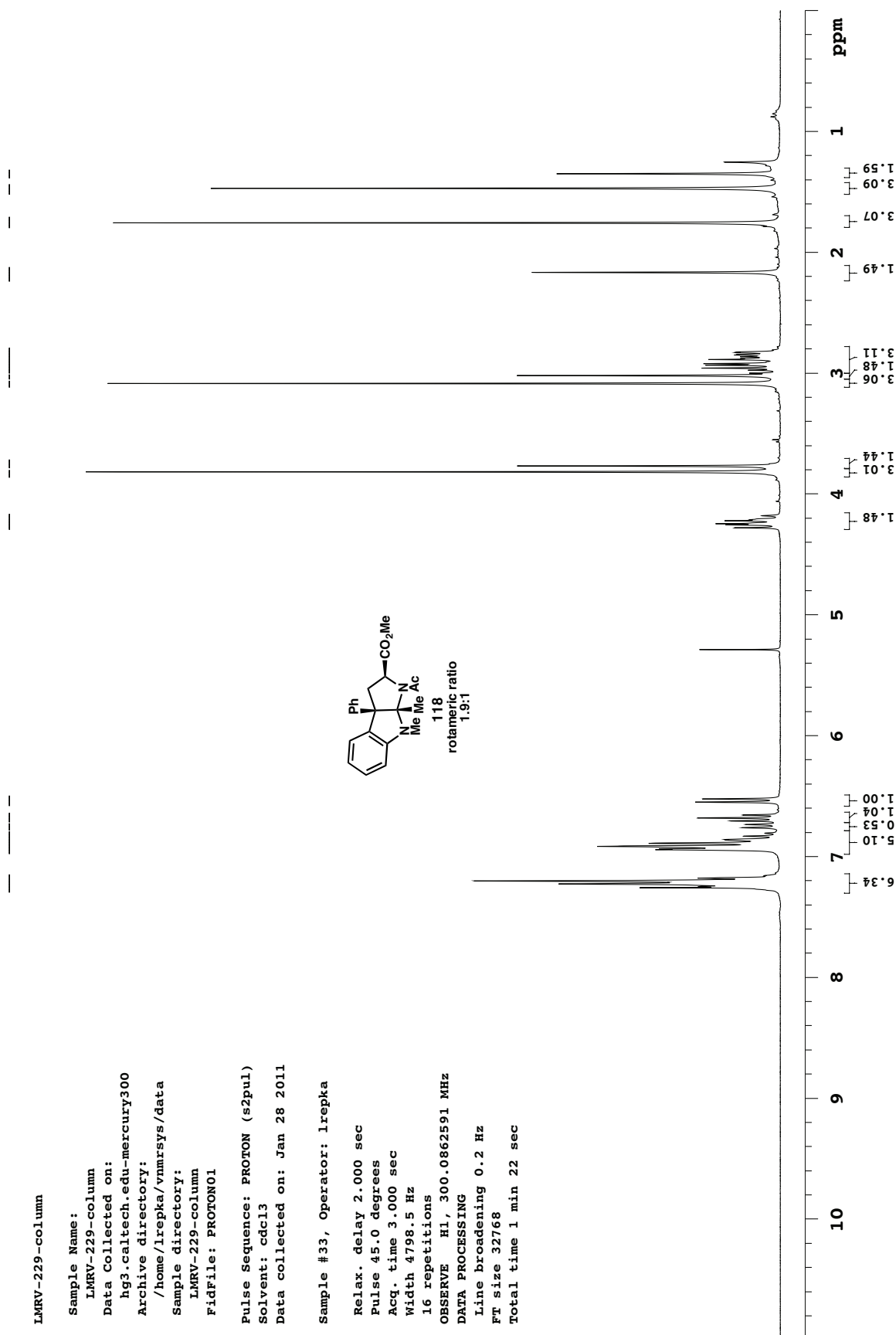
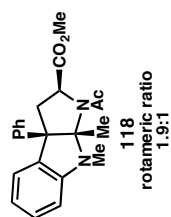
OBSERVE H1, 300.0862591 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 32768

Total time 1 min 22 sec



LMRV-233—carbon

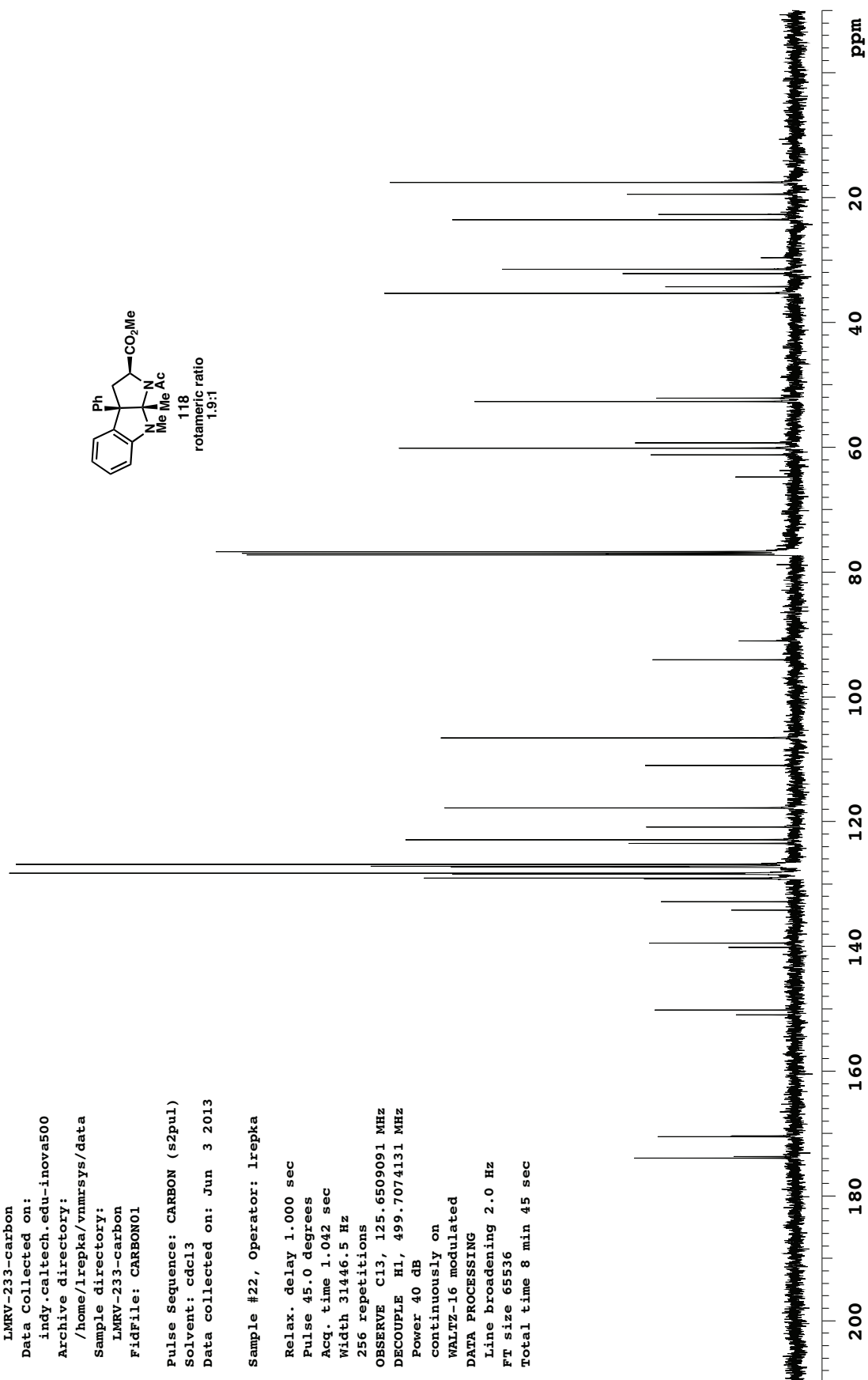
Sample Name:

LMRV-233—carbon
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRV-233—carbon
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 3 2013

Sample #22, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6509091 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 8 min 45 sec



APPENDIX 2

X-Ray Crystallography Reports Relevant to Chapter 2:

Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines[†]

[†] The work disclosed in this appendix for the x-ray crystallographic analysis of **100c** and **106g** was completed entirely by Larry Henling and Dr. Michael Day in the Caltech X-ray crystallography lab.

A2.1 CRYSTAL STRUCTURE ANALYSIS OF PYRROLLOINDOLINE 106g

Figure A2.1. Pyrroloindoline **106g** is shown with 50% probability ellipsoids. 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 787164.

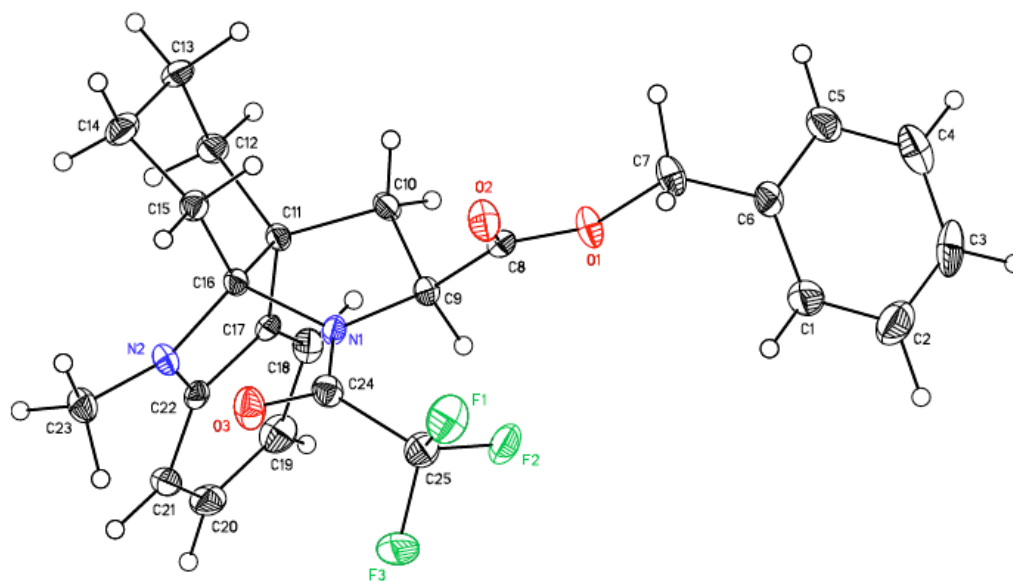


Table A2.1. Crystal data and structure refinement for pyrroloindoline **106g** (CCDC 787164).

Empirical formula	C ₂₅ H ₂₅ F ₃ N ₂ O ₃
Formula weight	458.47
Crystallization Solvent	Hexanes/ethyl acetate
Crystal Habit	Plate
Crystal size	0.23 x 0.19 x 0.02 mm ³
Crystal color	Colorless



Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoK α	
Data Collection Temperature	100(2) K	
θ range for 5569 reflections used in lattice determination	2.19 to 24.93°	
Unit cell dimensions	a = 9.8089(6) Å b = 8.4633(5) Å c = 13.9252(9) Å	$\alpha = 90^\circ$ $\beta = 108.657(3)^\circ$ $\gamma = 90^\circ$
Volume	1095.26(12) Å ³	
Z	2	
Crystal system	Monoclinic	
Space group	P 2 ₁	
Density (calculated)	1.390 Mg/m ³	
F(000)	480	
Data collection program	Bruker APEX2 v2009.7-0	
θ range for data collection	2.19 to 30.52°	
Completeness to $\theta = 30.52^\circ$	91.3 %	
Index ranges	-13 $\leq h \leq$ 13, -11 $\leq k \leq$ 11, -19 $\leq l \leq$ 19	
Data collection scan type	ω scans; 8 settings	
Data reduction program	Bruker SAINT-Plus v7.66A	
Reflections collected	20200	
Independent reflections	5883 [$R_{\text{int}} = 0.0461$]	
Absorption coefficient	0.109 mm ⁻¹	
Absorption correction	None	
Max. and min. transmission	0.9978 and 0.9755	

Table A2.1 (continued)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5883 / 1 / 398
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.140
Final R indices [$I > 2\sigma(I)$, 4601 reflections]	$R1 = 0.0393$, $wR2 = 0.0443$
R indices (all data)	$R1 = 0.0561$, $wR2 = 0.0463$
Type of weighting scheme used	Sigma
Weighting scheme used	$w = 1/\sigma^2(F_o^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Unknown
Absolute structure parameter	0.1(4)
Largest diff. peak and hole	0.245 and -0.273 e.Å ⁻³

Special Refinement Details

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

It is not possible to reliably determine the absolute configuration of this molecule due to the lack of atoms with sufficient anomalous scattering.

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

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances,

angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table A2.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for pyrroloindoline **106g** (CCDC 787164). $U(\text{eq})$ is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
F(1)	3918(1)	4664(1)	10172(1)	32(1)
F(2)	3607(1)	4695(1)	8564(1)	27(1)
F(3)	3993(1)	2504(1)	9381(1)	33(1)
O(1)	1918(1)	7940(1)	7621(1)	20(1)
O(2)	1842(1)	7188(1)	9164(1)	22(1)
O(3)	1481(1)	2670(1)	9761(1)	25(1)
N(1)	684(1)	4212(1)	8351(1)	14(1)
N(2)	-1102(1)	2048(2)	7926(1)	14(1)
C(1)	4492(2)	9288(2)	7202(1)	28(1)
C(2)	5169(2)	9805(2)	6533(2)	35(1)
C(3)	4687(2)	11150(2)	5965(2)	32(1)
C(4)	3526(2)	11960(2)	6066(1)	31(1)
C(5)	2821(2)	11417(2)	6732(1)	25(1)
C(6)	3305(2)	10072(2)	7304(1)	18(1)
C(7)	2596(2)	9456(2)	8032(1)	22(1)
C(8)	1606(2)	6946(2)	8279(1)	16(1)
C(9)	838(2)	5515(2)	7694(1)	14(1)
C(10)	-729(2)	5990(2)	7108(1)	15(1)
C(11)	-1598(2)	4502(2)	7091(1)	13(1)
C(12)	-3220(2)	4815(2)	6864(1)	18(1)
C(13)	-3617(2)	5480(2)	7758(1)	21(1)
C(14)	-3057(2)	4415(2)	8680(1)	21(1)
C(15)	-1419(2)	4324(2)	8991(1)	16(1)
C(16)	-899(2)	3723(2)	8148(1)	13(1)
C(17)	-1397(2)	3220(2)	6391(1)	13(1)
C(18)	-1534(2)	3247(2)	5377(1)	19(1)
C(19)	-1410(2)	1830(2)	4889(1)	23(1)
C(20)	-1171(2)	419(2)	5432(1)	22(1)
C(21)	-1052(2)	377(2)	6453(1)	18(1)
C(22)	-1167(2)	1787(2)	6929(1)	14(1)
C(23)	-1076(2)	774(2)	8626(1)	19(1)
C(24)	1708(2)	3572(2)	9147(1)	17(1)
C(25)	3315(2)	3892(2)	9305(1)	22(1)

Table A2.3. Bond lengths [Å] and angles [°] for pyrroloindoline **106g** (CCDC 787164).

F(1)-C(25)	1.3329(18)	C(18)-H(18)	0.935(15)
F(2)-C(25)	1.3403(19)	C(19)-C(20)	1.393(2)
F(3)-C(25)	1.3374(18)	C(19)-H(19)	0.969(15)
O(1)-C(8)	1.3487(18)	C(20)-C(21)	1.389(2)
O(1)-C(7)	1.4743(19)	C(20)-H(20)	0.965(15)
O(2)-C(8)	1.1966(17)	C(21)-C(22)	1.387(2)
O(3)-C(24)	1.2187(19)	C(21)-H(21)	0.994(15)
N(1)-C(24)	1.3487(18)	C(23)-H(23A)	1.054(15)
N(1)-C(9)	1.4715(19)	C(23)-H(23B)	0.989(15)
N(1)-C(16)	1.5426(18)	C(23)-H(23C)	1.010(14)
N(2)-C(22)	1.3868(18)	C(24)-C(25)	1.544(2)
N(2)-C(23)	1.4491(19)		
N(2)-C(16)	1.4507(18)	C(8)-O(1)-C(7)	116.90(12)
C(1)-C(2)	1.377(3)	C(24)-N(1)-C(9)	127.88(13)
C(1)-C(6)	1.387(2)	C(24)-N(1)-C(16)	118.98(12)
C(1)-H(1)	0.945(17)	C(9)-N(1)-C(16)	112.63(11)
C(2)-C(3)	1.380(3)	C(22)-N(2)-C(23)	122.70(14)
C(2)-H(2)	1.029(19)	C(22)-N(2)-C(16)	109.17(13)
C(3)-C(4)	1.374(3)	C(23)-N(2)-C(16)	127.76(14)
C(3)-H(3)	0.968(16)	C(2)-C(1)-C(6)	121.29(18)
C(4)-C(5)	1.401(2)	C(2)-C(1)-H(1)	119.9(10)
C(4)-H(4)	0.946(18)	C(6)-C(1)-H(1)	118.8(11)
C(5)-C(6)	1.383(2)	C(1)-C(2)-C(3)	119.92(19)
C(5)-H(5)	0.969(14)	C(1)-C(2)-H(2)	121.2(11)
C(6)-C(7)	1.494(2)	C(3)-C(2)-H(2)	118.8(11)
C(7)-H(7A)	1.088(16)	C(4)-C(3)-C(2)	119.75(18)
C(7)-H(7B)	0.972(14)	C(4)-C(3)-H(3)	118.6(10)
C(8)-C(9)	1.518(2)	C(2)-C(3)-H(3)	121.6(10)
C(9)-C(10)	1.545(2)	C(3)-C(4)-C(5)	120.33(18)
C(9)-H(9)	1.013(13)	C(3)-C(4)-H(4)	118.3(11)
C(10)-C(11)	1.517(2)	C(5)-C(4)-H(4)	121.3(11)
C(10)-H(10A)	1.001(13)	C(6)-C(5)-C(4)	119.98(18)
C(10)-H(10B)	0.990(14)	C(6)-C(5)-H(5)	121.8(9)
C(11)-C(17)	1.513(2)	C(4)-C(5)-H(5)	118.2(9)
C(11)-C(12)	1.543(2)	C(5)-C(6)-C(1)	118.71(17)
C(11)-C(16)	1.557(2)	C(5)-C(6)-C(7)	121.90(16)
C(12)-C(13)	1.525(2)	C(1)-C(6)-C(7)	119.38(15)
C(12)-H(12A)	0.954(15)	O(1)-C(7)-C(6)	106.95(13)
C(12)-H(12B)	1.045(15)	O(1)-C(7)-H(7A)	111.0(9)
C(13)-C(14)	1.521(2)	C(6)-C(7)-H(7A)	111.9(9)
C(13)-H(13A)	1.068(16)	O(1)-C(7)-H(7B)	105.6(9)
C(13)-H(13B)	0.952(14)	C(6)-C(7)-H(7B)	115.4(9)
C(14)-C(15)	1.526(2)	H(7A)-C(7)-H(7B)	105.8(12)
C(14)-H(14A)	0.955(14)	O(2)-C(8)-O(1)	125.53(15)
C(14)-H(14B)	0.953(14)	O(2)-C(8)-C(9)	126.07(15)
C(15)-C(16)	1.510(2)	O(1)-C(8)-C(9)	108.32(13)
C(15)-H(15A)	0.950(14)	N(1)-C(9)-C(8)	113.32(12)
C(15)-H(15B)	1.009(16)	N(1)-C(9)-C(10)	103.92(12)
C(17)-C(18)	1.375(2)	C(8)-C(9)-C(10)	108.33(12)
C(17)-C(22)	1.404(2)	N(1)-C(9)-H(9)	112.3(8)
C(18)-C(19)	1.404(2)	C(8)-C(9)-H(9)	108.3(8)

Table A2.3 (continued)

C(10)-C(9)-H(9)	110.5(7)	N(2)-C(16)-N(1)	111.25(12)
C(11)-C(10)-C(9)	104.52(12)	C(15)-C(16)-N(1)	109.73(12)
C(11)-C(10)-H(10A)	114.5(7)	N(2)-C(16)-C(11)	102.90(12)
C(9)-C(10)-H(10A)	110.4(7)	C(15)-C(16)-C(11)	115.86(13)
C(11)-C(10)-H(10B)	112.1(8)	N(1)-C(16)-C(11)	99.95(11)
C(9)-C(10)-H(10B)	109.6(7)	C(18)-C(17)-C(22)	120.54(15)
H(10A)-C(10)-H(10B)	105.7(10)	C(18)-C(17)-C(11)	131.23(15)
C(17)-C(11)-C(10)	114.67(13)	C(22)-C(17)-C(11)	107.92(14)
C(17)-C(11)-C(12)	109.24(12)	C(17)-C(18)-C(19)	119.20(16)
C(10)-C(11)-C(12)	113.47(13)	C(17)-C(18)-H(18)	121.0(10)
C(17)-C(11)-C(16)	101.33(12)	C(19)-C(18)-H(18)	119.7(9)
C(10)-C(11)-C(16)	105.18(12)	C(20)-C(19)-C(18)	119.67(16)
C(12)-C(11)-C(16)	112.29(13)	C(20)-C(19)-H(19)	122.6(10)
C(13)-C(12)-C(11)	114.34(13)	C(18)-C(19)-H(19)	117.7(10)
C(13)-C(12)-H(12A)	107.5(10)	C(21)-C(20)-C(19)	121.50(17)
C(11)-C(12)-H(12A)	107.9(9)	C(21)-C(20)-H(20)	118.3(9)
C(13)-C(12)-H(12B)	111.6(8)	C(19)-C(20)-H(20)	120.2(9)
C(11)-C(12)-H(12B)	108.0(8)	C(22)-C(21)-C(20)	118.26(16)
H(12A)-C(12)-H(12B)	107.2(11)	C(22)-C(21)-H(21)	121.5(9)
C(14)-C(13)-C(12)	110.66(15)	C(20)-C(21)-H(21)	120.2(9)
C(14)-C(13)-H(13A)	108.2(8)	N(2)-C(22)-C(21)	129.06(15)
C(12)-C(13)-H(13A)	112.9(9)	N(2)-C(22)-C(17)	110.12(14)
C(14)-C(13)-H(13B)	110.4(9)	C(21)-C(22)-C(17)	120.82(14)
C(12)-C(13)-H(13B)	110.4(9)	N(2)-C(23)-H(23A)	111.7(9)
H(13A)-C(13)-H(13B)	104.1(12)	N(2)-C(23)-H(23B)	111.3(9)
C(13)-C(14)-C(15)	109.41(14)	H(23A)-C(23)-H(23B)	108.3(11)
C(13)-C(14)-H(14A)	109.4(9)	N(2)-C(23)-H(23C)	110.2(8)
C(15)-C(14)-H(14A)	111.8(8)	H(23A)-C(23)-H(23C)	107.9(12)
C(13)-C(14)-H(14B)	110.8(9)	H(23B)-C(23)-H(23C)	107.3(12)
C(15)-C(14)-H(14B)	109.7(8)	O(3)-C(24)-N(1)	124.92(15)
H(14A)-C(14)-H(14B)	105.7(12)	O(3)-C(24)-C(25)	114.67(14)
C(16)-C(15)-C(14)	112.55(13)	N(1)-C(24)-C(25)	120.33(14)
C(16)-C(15)-H(15A)	110.5(9)	F(1)-C(25)-F(3)	107.01(13)
C(14)-C(15)-H(15A)	112.1(8)	F(1)-C(25)-F(2)	107.80(13)
C(16)-C(15)-H(15B)	108.1(9)	F(3)-C(25)-F(2)	106.44(14)
C(14)-C(15)-H(15B)	107.2(8)	F(1)-C(25)-C(24)	110.64(14)
H(15A)-C(15)-H(15B)	106.1(11)	F(3)-C(25)-C(24)	108.48(13)
N(2)-C(16)-C(15)	115.92(14)	F(2)-C(25)-C(24)	116.05(13)

Table A2.4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^4$) for pyrroloindoline **106g** (CCDC 787164). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$.

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
F(1)	210(5)	405(7)	277(6)	-65(5)	-6(4)	-86(5)
F(2)	160(5)	341(6)	323(6)	69(5)	108(4)	-5(5)
F(3)	213(6)	254(6)	502(7)	52(5)	91(5)	83(5)
O(1)	264(7)	161(6)	174(6)	-7(5)	60(5)	-94(5)
O(2)	303(7)	209(7)	174(6)	-42(5)	108(5)	-79(5)
O(3)	193(6)	262(7)	244(7)	90(6)	17(5)	-38(5)
N(1)	107(7)	148(7)	153(7)	23(6)	45(5)	-12(6)
N(2)	187(7)	114(7)	132(7)	12(6)	51(6)	-22(6)
C(1)	209(10)	220(10)	396(12)	34(10)	81(9)	15(9)
C(2)	232(11)	385(12)	455(13)	-89(11)	156(9)	-69(10)
C(3)	311(12)	403(13)	251(11)	-71(9)	108(9)	-241(10)
C(4)	362(12)	230(11)	267(11)	65(10)	12(9)	-97(10)
C(5)	209(10)	169(9)	342(11)	-11(8)	39(9)	-20(8)
C(6)	151(9)	168(9)	190(9)	-37(7)	18(7)	-58(7)
C(7)	257(10)	155(9)	236(10)	-40(8)	53(8)	-94(8)
C(8)	122(8)	159(9)	202(9)	-4(8)	64(7)	8(7)
C(9)	149(9)	130(8)	134(8)	17(7)	51(7)	-6(7)
C(10)	160(9)	100(8)	179(9)	12(7)	43(7)	-1(7)
C(11)	125(8)	108(8)	149(8)	4(7)	37(6)	-11(7)
C(12)	135(9)	164(9)	222(9)	6(8)	27(7)	9(8)
C(13)	127(9)	189(9)	315(10)	-24(9)	93(8)	20(8)
C(14)	182(10)	250(10)	242(10)	-46(9)	120(8)	-1(8)
C(15)	164(9)	166(9)	162(8)	-8(8)	68(7)	-12(7)
C(16)	104(8)	115(8)	170(8)	8(7)	31(7)	-9(7)
C(17)	83(8)	144(8)	174(8)	-2(7)	42(7)	-2(6)
C(18)	173(9)	207(10)	186(9)	24(8)	51(7)	-16(8)
C(19)	249(10)	297(11)	173(9)	-38(9)	93(8)	-11(8)
C(20)	208(9)	197(9)	256(10)	-91(9)	96(8)	-6(8)
C(21)	161(9)	136(8)	236(10)	-1(8)	58(7)	8(7)
C(22)	89(8)	146(8)	172(8)	-22(8)	37(7)	-24(7)
C(23)	235(10)	170(10)	177(9)	34(8)	81(8)	-14(8)
C(24)	173(9)	160(9)	175(9)	-21(8)	39(7)	-19(7)
C(25)	180(10)	232(10)	248(10)	11(8)	48(8)	1(8)

Table A2.5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for pyrroloindoline **106g** (CCDC 787164).

	x	y	z	U _{iso}
H(1)	4843(17)	8390(20)	7608(13)	38(6)
H(2)	6021(19)	9190(20)	6434(14)	55(7)
H(3)	5155(16)	11553(18)	5500(11)	26(5)
H(4)	3201(18)	12870(20)	5659(13)	51(6)
H(5)	2013(15)	12023(17)	6791(10)	19(5)
H(7A)	1806(16)	10280(20)	8136(12)	37(5)
H(7B)	3239(14)	9221(18)	8708(11)	20(5)
H(9)	1360(13)	5177(17)	7207(10)	10(4)
H(10A)	-798(13)	6411(15)	6422(9)	3(4)
H(10B)	-1028(13)	6869(17)	7465(10)	13(4)
H(12A)	-3714(15)	3834(17)	6680(11)	15(4)
H(12B)	-3564(14)	5555(17)	6232(11)	21(4)
H(13A)	-3204(16)	6640(20)	7967(11)	35(5)
H(13B)	-4632(15)	5603(18)	7581(11)	23(5)
H(14A)	-3490(14)	3396(17)	8527(10)	10(4)
H(14B)	-3337(14)	4805(17)	9231(11)	13(4)
H(15A)	-1022(14)	3712(18)	9588(11)	13(4)
H(15B)	-1040(15)	5431(19)	9167(11)	22(4)
H(18)	-1721(14)	4191(18)	5008(11)	19(5)
H(19)	-1521(15)	1876(19)	4172(11)	24(4)
H(20)	-1059(14)	-557(18)	5107(11)	14(4)
H(21)	-902(14)	-646(18)	6824(11)	20(4)
H(23A)	-103(16)	136(19)	8815(12)	40(5)
H(23B)	-1203(13)	1175(17)	9259(12)	11(4)
H(23C)	-1889(14)	10(18)	8313(11)	21(5)

A2.2 CRYSTAL STRUCTURE ANALYSIS OF PYRROLOINDOLINE 100c

Figure 2.2. Pyrroloindoline **100c** is shown with 50% probability ellipsoids. 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 788553.

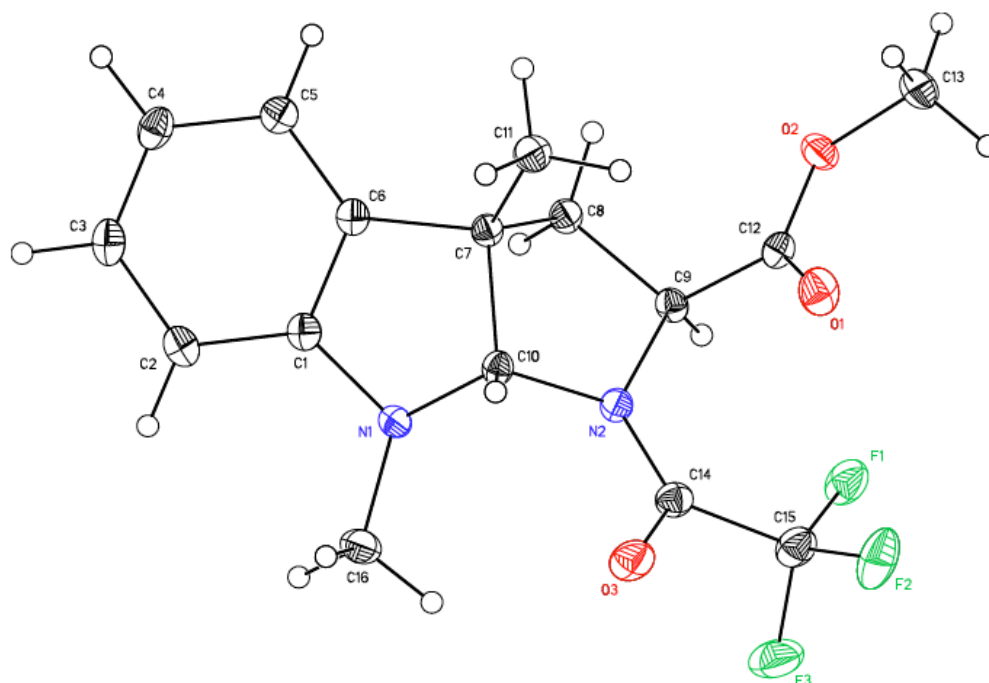


Table A2.6. Crystal data and structure refinement for pyrroloindoline **100c** (CCDC 788553).

Empirical formula	C ₁₆ H ₁₇ F ₃ N ₂ O ₃		
Formula weight	342.32		
Crystallization Solvent	Chloroform		
Crystal Habit	Block		
Crystal size	0.31 x 0.30 x 0.28 mm ³		
Crystal color	Colorless		
Data Collection			
Type of diffractometer	Bruker SMART 1000		
Wavelength	0.71073 Å MoKα		
Data Collection Temperature	100(2) K		
θ range for 9932 reflections used in lattice determination	3.07 to 36.76°		
Unit cell dimensions	a = 13.9506(5) Å b = 7.2073(2) Å c = 16.3208(5) Å	α= 90° β= 107.9900(10)° γ = 90°	
Volume	1560.77(9) Å ³		
Z	4		
Crystal system	Monoclinic		
Space group	P 2 ₁ /c		
Density (calculated)	1.457 Mg/m ³		
F(000)	712		
Data collection program	Bruker SMART v5.630		
θ range for data collection	1.53 to 37.55°		
Completeness to θ = 37.55°	88.2 %		
Index ranges	-22 ≤ h ≤ 22, -11 ≤ k ≤ 12, -26 ≤ l ≤ 26		
Data collection scan type	ω scans at 7 settings		
Data reduction program	Bruker SAINT v6.45A		
Reflections collected	35665		
Independent reflections	7261 [R _{int} = 0.0549]		
Absorption coefficient	0.125 mm ⁻¹		
Absorption correction	None		
Max. and min. transmission	0.9660 and 0.9624		

Table A2.6 (continued)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	7261 / 0 / 285
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.940
Final R indices [$I > 2\sigma(I)$, 4934 reflections]	$R1 = 0.0469$, $wR2 = 0.0737$
R indices (all data)	$R1 = 0.0757$, $wR2 = 0.0765$
Type of weighting scheme used	Sigma
Weighting scheme used	$w = 1/\sigma^2(F_o^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.427 and -0.429 e.Å ⁻³

Special Refinement Details

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

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

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

Table A2.7. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for pyrroloindoline **100c** (CCDC 788553). $U(\text{eq})$ is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
F(1)	7030(1)	5654(1)	4071(1)	26(1)
F(2)	5844(1)	4727(1)	4558(1)	34(1)
F(3)	7372(1)	4868(1)	5397(1)	32(1)
O(1)	5686(1)	3285(1)	2789(1)	23(1)
O(2)	6430(1)	4211(1)	1815(1)	19(1)
O(3)	6740(1)	1296(1)	4926(1)	23(1)
N(1)	8666(1)	-681(1)	4302(1)	15(1)
N(2)	7456(1)	1872(1)	3869(1)	14(1)
C(1)	9002(1)	-1980(1)	3811(1)	15(1)
C(2)	9801(1)	-3225(1)	4089(1)	19(1)
C(3)	10002(1)	-4371(1)	3469(1)	20(1)
C(4)	9425(1)	-4302(1)	2610(1)	18(1)
C(5)	8620(1)	-3049(1)	2340(1)	16(1)
C(6)	8421(1)	-1888(1)	2943(1)	14(1)
C(7)	7622(1)	-411(1)	2841(1)	13(1)
C(8)	7975(1)	1517(1)	2628(1)	14(1)
C(9)	7490(1)	2906(1)	3095(1)	14(1)
C(10)	7643(1)	-124(1)	3784(1)	13(1)
C(11)	6586(1)	-959(1)	2246(1)	18(1)
C(12)	6424(1)	3475(1)	2559(1)	15(1)
C(13)	5449(1)	4754(2)	1236(1)	24(1)
C(14)	6975(1)	2367(1)	4443(1)	16(1)
C(15)	6795(1)	4432(1)	4596(1)	21(1)
C(16)	8848(1)	-1024(1)	5219(1)	20(1)

Table A2.8. Bond lengths [Å] and angles [°] for pyrroloindoline **100c** (CCDC 788553).

F(1)-C(15)	1.3386(10)	C(2)-C(1)-N(1)	128.22(8)
F(2)-C(15)	1.3259(11)	C(6)-C(1)-N(1)	110.78(7)
F(3)-C(15)	1.3442(11)	C(1)-C(2)-C(3)	117.64(9)
O(1)-C(12)	1.2063(10)	C(1)-C(2)-H(2)	121.0(6)
O(2)-C(12)	1.3275(10)	C(3)-C(2)-H(2)	121.3(6)
O(2)-C(13)	1.4557(11)	C(4)-C(3)-C(2)	121.76(9)
O(3)-C(14)	1.2180(10)	C(4)-C(3)-H(3)	121.1(6)
N(1)-C(1)	1.4053(11)	C(2)-C(3)-H(3)	117.2(6)
N(1)-C(16)	1.4596(11)	C(3)-C(4)-C(5)	120.00(9)
N(1)-C(10)	1.4714(11)	C(3)-C(4)-H(4)	119.5(6)
N(2)-C(14)	1.3578(10)	C(5)-C(4)-H(4)	120.5(6)
N(2)-C(10)	1.4767(11)	C(6)-C(5)-C(4)	118.94(8)
N(2)-C(9)	1.4803(10)	C(6)-C(5)-H(5)	120.8(6)
C(1)-C(2)	1.3925(12)	C(4)-C(5)-H(5)	120.2(6)
C(1)-C(6)	1.4000(12)	C(5)-C(6)-C(1)	120.66(8)
C(2)-C(3)	1.3987(13)	C(5)-C(6)-C(7)	130.64(8)
C(2)-H(2)	0.967(11)	C(1)-C(6)-C(7)	108.71(7)
C(3)-C(4)	1.3852(14)	C(6)-C(7)-C(11)	114.12(7)
C(3)-H(3)	0.983(11)	C(6)-C(7)-C(10)	101.47(6)
C(4)-C(5)	1.4010(13)	C(11)-C(7)-C(10)	113.12(7)
C(4)-H(4)	0.987(11)	C(6)-C(7)-C(8)	112.45(7)
C(5)-C(6)	1.3827(12)	C(11)-C(7)-C(8)	113.18(7)
C(5)-H(5)	0.981(10)	C(10)-C(7)-C(8)	101.18(6)
C(6)-C(7)	1.5128(11)	C(9)-C(8)-C(7)	104.77(7)
C(7)-C(11)	1.5244(12)	C(9)-C(8)-H(8A)	107.3(5)
C(7)-C(10)	1.5431(12)	C(7)-C(8)-H(8A)	109.5(5)
C(7)-C(8)	1.5486(12)	C(9)-C(8)-H(8B)	113.3(5)
C(8)-C(9)	1.5351(12)	C(7)-C(8)-H(8B)	112.1(5)
C(8)-H(8A)	0.983(9)	H(8A)-C(8)-H(8B)	109.7(7)
C(8)-H(8B)	0.978(10)	N(2)-C(9)-C(12)	109.94(7)
C(9)-C(12)	1.5300(12)	N(2)-C(9)-C(8)	103.30(6)
C(9)-H(9)	0.988(10)	C(12)-C(9)-C(8)	113.04(7)
C(10)-H(10)	0.995(10)	N(2)-C(9)-H(9)	110.8(5)
C(11)-H(11A)	0.965(10)	C(12)-C(9)-H(9)	109.1(6)
C(11)-H(11B)	1.003(11)	C(8)-C(9)-H(9)	110.5(5)
C(11)-H(11C)	0.999(10)	N(1)-C(10)-N(2)	112.31(7)
C(13)-H(13A)	0.977(13)	N(1)-C(10)-C(7)	104.68(6)
C(13)-H(13B)	0.981(13)	N(2)-C(10)-C(7)	105.96(6)
C(13)-H(13C)	0.993(10)	N(1)-C(10)-H(10)	111.1(6)
C(14)-C(15)	1.5425(13)	N(2)-C(10)-H(10)	108.2(6)
C(16)-H(16A)	0.981(11)	C(7)-C(10)-H(10)	114.6(6)
C(16)-H(16B)	0.995(11)	C(7)-C(11)-H(11A)	110.1(6)
C(16)-H(16C)	1.032(11)	C(7)-C(11)-H(11B)	112.0(6)
		H(11A)-C(11)-H(11B)	109.4(8)
C(12)-O(2)-C(13)	115.50(7)	C(7)-C(11)-H(11C)	109.9(6)
C(1)-N(1)-C(16)	119.27(7)	H(11A)-C(11)-H(11C)	109.3(8)
C(1)-N(1)-C(10)	106.79(6)	H(11B)-C(11)-H(11C)	106.0(8)
C(16)-N(1)-C(10)	117.85(7)	O(1)-C(12)-O(2)	125.21(8)
C(14)-N(2)-C(10)	117.43(7)	O(1)-C(12)-C(9)	124.32(8)
C(14)-N(2)-C(9)	127.57(7)	O(2)-C(12)-C(9)	110.47(7)
C(10)-N(2)-C(9)	110.89(6)	O(2)-C(13)-H(13A)	110.9(7)
C(2)-C(1)-C(6)	120.99(8)	O(2)-C(13)-H(13B)	104.4(7)

H(13A)-C(13)-H(13B)	111.2(10)	F(2)-C(15)-C(14)	110.93(7)
O(2)-C(13)-H(13C)	109.8(6)	F(1)-C(15)-C(14)	116.56(7)
H(13A)-C(13)-H(13C)	108.9(9)	F(3)-C(15)-C(14)	107.73(7)
H(13B)-C(13)-H(13C)	111.6(9)	N(1)-C(16)-H(16A)	113.7(6)
O(3)-C(14)-N(2)	124.68(8)	N(1)-C(16)-H(16B)	111.6(6)
O(3)-C(14)-C(15)	114.65(8)	H(16A)-C(16)-H(16B)	106.5(9)
N(2)-C(14)-C(15)	120.31(8)	N(1)-C(16)-H(16C)	109.4(6)
F(2)-C(15)-F(1)	107.73(7)	H(16A)-C(16)-H(16C)	109.0(9)
F(2)-C(15)-F(3)	107.33(7)	H(16B)-C(16)-H(16C)	106.3(8)
F(1)-C(15)-F(3)	106.10(7)		

Table A2.9. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^4$) for pyrroloindoline **100c** (CCDC 788553). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$.

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
F(1)	397(4)	154(3)	284(3)	2(2)	184(3)	4(2)
F(2)	300(3)	299(3)	515(4)	-18(3)	244(3)	84(3)
F(3)	471(4)	268(3)	219(3)	-85(2)	112(3)	-48(3)
O(1)	161(3)	278(4)	279(4)	49(3)	99(3)	37(3)
O(2)	172(3)	254(3)	144(3)	40(3)	36(2)	56(3)
O(3)	311(4)	215(3)	224(4)	15(3)	169(3)	-8(3)
N(1)	153(4)	168(3)	124(4)	14(3)	38(3)	26(3)
N(2)	160(3)	125(3)	145(4)	17(3)	73(3)	6(3)
C(1)	144(4)	129(4)	173(4)	14(3)	58(3)	-15(3)
C(2)	166(4)	189(4)	191(5)	35(4)	37(4)	16(3)
C(3)	165(4)	164(4)	273(5)	33(4)	83(4)	31(4)
C(4)	187(4)	152(4)	244(5)	2(4)	123(4)	4(3)
C(5)	163(4)	159(4)	173(4)	12(3)	79(4)	-18(3)
C(6)	126(4)	127(4)	168(4)	18(3)	64(3)	-10(3)
C(7)	123(4)	136(4)	135(4)	9(3)	51(3)	5(3)
C(8)	135(4)	160(4)	149(4)	18(3)	62(3)	16(3)
C(9)	141(4)	135(4)	142(4)	32(3)	60(3)	2(3)
C(10)	138(4)	119(4)	153(4)	8(3)	59(3)	3(3)
C(11)	145(4)	200(5)	173(5)	-17(4)	40(3)	-2(4)
C(12)	166(4)	124(4)	174(4)	-13(3)	59(3)	5(3)
C(13)	189(5)	314(6)	181(5)	4(4)	-9(4)	86(4)
C(14)	157(4)	184(4)	157(4)	-8(3)	55(3)	-4(3)
C(15)	236(5)	199(5)	217(5)	-8(4)	119(4)	2(4)
C(16)	227(5)	211(5)	140(4)	12(4)	38(4)	0(4)

Table A2.10. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for pyrroloindoline **100c** (CCDC 788553).

	x	y	z	U _{iso}
H(2)	10204(8)	-3288(14)	4688(7)	29(3)
H(3)	10564(8)	-5250(15)	3671(7)	31(3)
H(4)	9580(8)	-5150(15)	2193(7)	25(3)
H(5)	8186(7)	-3046(13)	1739(6)	18(2)
H(8A)	8709(7)	1622(12)	2888(6)	13(2)
H(8B)	7792(7)	1733(12)	2008(6)	14(2)
H(9)	7912(7)	4029(14)	3258(6)	18(2)
H(10)	7123(7)	-838(13)	3953(6)	21(3)
H(11A)	6614(7)	-1149(14)	1668(7)	23(3)
H(11B)	6061(8)	-1(16)	2237(7)	30(3)
H(11C)	6357(7)	-2128(15)	2457(6)	25(3)
H(13A)	5013(9)	3673(18)	1051(8)	44(3)
H(13B)	5601(9)	5341(17)	748(8)	43(3)
H(13C)	5121(8)	5635(14)	1533(6)	23(3)
H(16A)	8501(8)	-2125(16)	5340(7)	36(3)
H(16B)	8625(7)	39(15)	5504(7)	25(3)
H(16C)	9612(8)	-1168(14)	5520(7)	27(3)

CHAPTER 3

Synthesis of Tryptophan Derivatives by a Tandem Friedel–Crafts Conjugate Addition/Enantioselective Protonation Reaction[†]

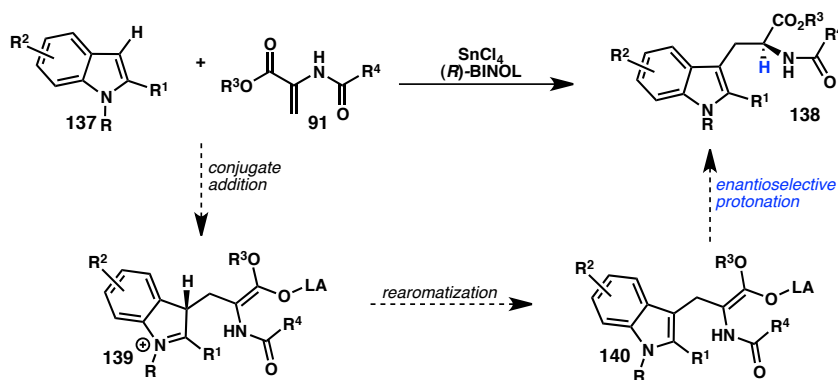
3.1 INTRODUCTION

During the development of the formal (3 + 2) cycloaddition approach to pyrroloindolines, epimerization studies were conducted on the diastereomeric products that strongly suggest that enantioinduction occurs via a highly face-selective, (*R*)-BINOL•SnCl₄ controlled protonation event (Chapter 2). We hypothesized that if catalyst-controlled protonation were operative, the related Friedel–Crafts alkylation reaction with C3-unsubstituted indoles should also proceed with high selectivity to provide enantioenriched tryptophan derivatives. Mechanistically, the proposed transformation would involve an initial conjugate addition to generate enolate **139**, which, following rearomatization and asymmetric protonation would give tryptophan derivative **138** (Scheme 3.1.1). This chapter describes the realization of our mechanistic hypothesis in the development of a tandem Friedel–Crafts conjugate addition/enantioselective

[†] Part of this chapter was published as the following article: Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131. The research discussed in this chapter was completed in collaboration with Maddi Kieffer, a graduate student in the Reisman lab.

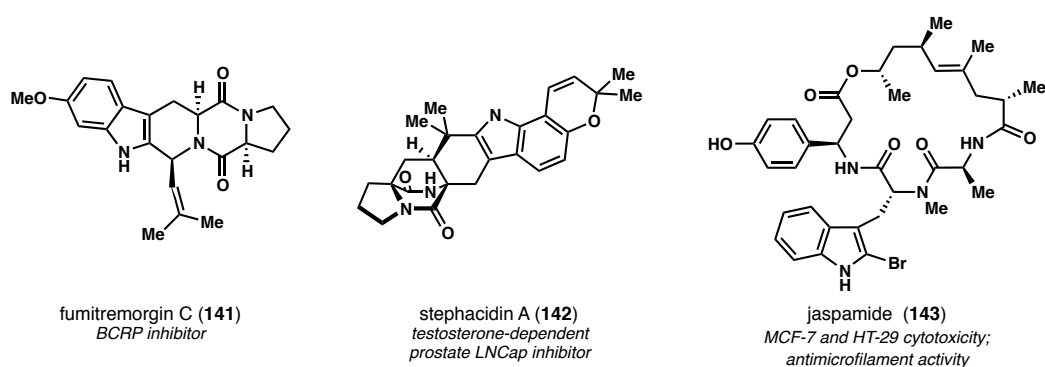
protonation reaction.

Scheme 3.1.1. Proposed mechanism of enantioselective tryptophan derivative formation.



3.1.1 Synthetic and Biological Applications of Tryptophan Derivatives

Figure 3.1.1. Tryptophan-derived biologically active natural products.

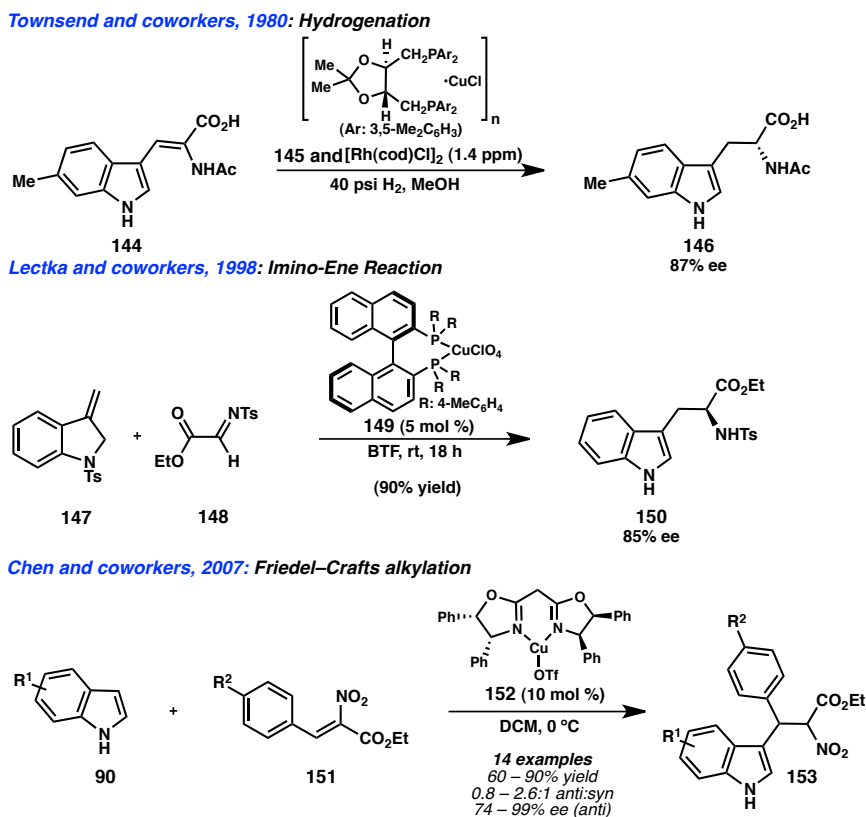


Unnatural tryptophan derivatives constitute an important target for synthetic efforts on the basis of their applications. These derivatives are incorporated into a diverse array of biologically active natural products including fumitremorgin C (**141**),¹ stephacidin A (**142**),² and the jaspamide family of cyclodepsipeptides (**143**);³ in particular, **141** has been extensively studied because of its function as an inhibitor of the breast cancer resistance protein (BCRP) (Figure 3.1.1). Furthermore, tryptophan derivatives have found applications as chiral catalysts⁴ and as biological probes. For example, these molecules have been used in protein detection and design on the basis of their fluorescent

properties,⁵ and in linear free energy relationship studies that have identified a key cation- π binding interaction for acetylcholine and the nicotinic acetylcholine receptors.⁶

3.1.2 Catalytic, Enantioselective Approaches to Tryptophan Derivatives

Scheme 3.1.2. Selected enantioselective, catalytic approaches to tryptophan derivatives.



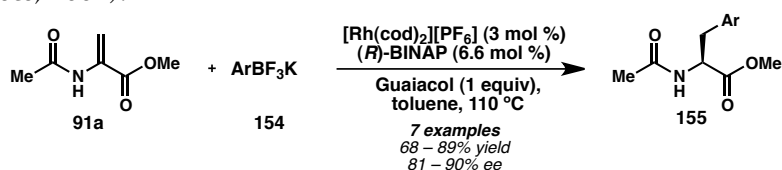
Due to the applications of tryptophan derivatives, the synthesis of these molecules has been the subject of extensive research. However, there are few convergent, enantioselective approaches to tryptophan derivatives (Scheme 3.1.2).⁷ In a seminal 1980 report, Townsend and coworkers disclosed a hydrogenation catalyst prepared from tartrate-derived ligand **145**, $[\text{Rh}(\text{cod})\text{Cl}]_2$, and H_2 that efficiently converts enamide **144** to the corresponding (*R*)-6-methyltryptophan **146** in 87% ee.^{7a} More recently, Lectka and coworkers developed the first enantioselective imino-ene reaction using an (*R*)-BINAP-

derived copper complex (**149**) that enables access to tryptophan **150** in 85% ee from 3-methylideneindole **147** and α -imino ester **148**.^{7b} When we initiated research directed toward tryptophan synthesis, one Friedel–Crafts approach had also been reported; Liu, Chen and coworkers disclosed a Cu-catalyzed enantioselective conjugate addition involving C3-unsubstituted indoles (**90**) and β -aryl-nitroacrylates (**151**) that provides β -substituted tryptophan derivatives (e.g. **153**).^{7d}

3.1.3 Tandem Conjugate Addition/Enantioselective Protonation Reactions

Throughout the past decade, many tandem conjugate addition/enantioselective protonation reactions have been developed for a variety of nucleophiles.⁸ For example, Genet and Darses reported the synthesis of phenylalanine derivatives (**155**) by a Rh-catalyzed reaction of methyl 2-acetamidoacrylate (**91a**) and potassium aryltrifluoroborates (**154**) that employs guaiacol as the stoichiometric proton source (Scheme 3.1.3).^{8h}

Scheme 3.1.3. Access to amino acids by tandem conjugate addition/enantioselective protonation (Genet and Darses, 2004).

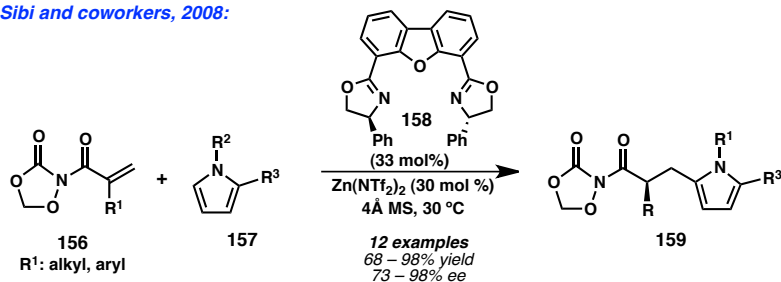


Despite considerable research, examples of tandem *Friedel–Crafts* conjugate addition/enantioselective protonation reactions are rare and were first reported in 2008. Sibi and coworkers developed an oxazolidinone-derived acrylamide (**156**) for conjugate addition of pyrroles (**157**) catalyzed by $\text{Zn}(\text{NTf}_2)_2$ and dibenzofuran-derived BOX ligand **158** (Scheme 3.1.4).^{8k} The selectivity is thought to arise by bischelation of the catalyst with

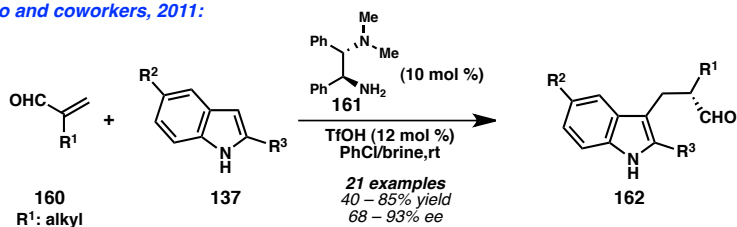
the carbonyls of **156**. The pyrrole products were prepared in excellent yield and ee; however, no examples of this reaction using indole nucleophiles have been reported. Concomitant with our work in this area, Luo and coworkers developed a related diamine **161**-catalyzed tandem conjugate addition/enantioselective protonation reaction involving C2-substituted indoles (**137**) and acrolein derivatives (**160**).⁸¹ However, to our knowledge, the research discussed in this chapter constitutes the only enantioselective protonation approach to tryptophan derivatives.⁹

Scheme 3.1.4. Tandem Friedel–Crafts conjugate addition/enantioselective protonation reactions.

Sibi and coworkers, 2008:



Luo and coworkers, 2011:



3.2 SnCl₄-PROMOTED ASYMMETRIC PROTONATION APPROACH TO TRYPTOPHAN DERIVATIVES

3.2.1 Optimization Studies

Our studies began with the investigation of 2-phenylindole (**137a**) using our previously optimized conditions for asymmetric pyrroloindoline synthesis. Surprisingly, these conditions resulted in formation of trifluoroacetamido ester **138a** in poor yield and

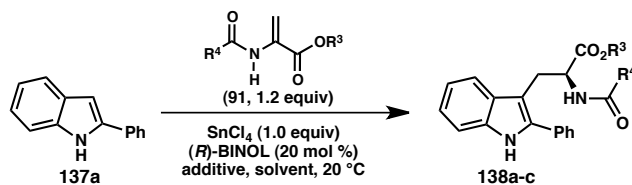
ee (Table 3.2.1, entry 1). Alternatively, treatment of **137a** and methyl 2-acetamidoacrylate (**91a**) with 1 equivalent SnCl_4 and 20 mol % (*R*)-BINOL in DCM delivers acetamido ester **138c** in 73% yield and 78% ee (entry 3).¹⁰ Importantly, we found it critical to quench these reactions with saturated aqueous NaHCO_3 ; a quench with 1 M aqueous NaOH consistently results in partial racemization and under otherwise identical conditions, **138c** was isolated in 75% ee (entry 6). We also hypothesized that adventitious HCl generated under the reaction conditions might artificially reduce the ee by serving as an achiral proton source for enolate protonation; therefore, a screen of acid and water scavenging additives was conducted. 2,6-lutidine inhibited the reaction, presumably through coordination of SnCl_4 , and no effect was observed with the inorganic bases such as K_2CO_3 (entries 7-8). However, we were pleased to find that in the presence of 4Å molecular sieves, the reaction of 2-phenylindole (**137a**) furnishes acetamido ester **138c** in an improved 86% yield and 81% ee (entry 9). As observed for pyrroloindoline formation, halogenated solvents are optimal with DCM providing the highest enantioselectivity (entries 9-11).

As observed for the formal (3 + 2) cycloaddition reaction, BINOL significantly increases the rate of the reaction, with SnCl_4 alone providing **138c** in only 13% yield (entry 4).[‡] Likewise, no reaction is observed in the absence of SnCl_4 (entry 5). Although BINOL cannot independently facilitate this transformation, it is notable that exposure to HCl results in a reaction of 2-phenylindole (**137a**) and **91a**; however, in this case **91a** preferentially reacts via the imine tautomer to give quaternary amide **165** in 38% yield (Scheme 3.2.1). By contrast, diphenylphosphate only promotes trace conversion to **165**.

[‡] For kinetics experiments involving in situ monitoring by ^1H NMR spectroscopy, see Section 3.4.10.

The reactivity promoted by HCl appears unique to **137a**; Piersanti and coworkers reported that subjection of indole and **91a** to two equivalents of HCl at 0 °C gave no reaction.^{9b} A possible explanation for this divergent reactivity is the enhanced stability of the imine intermediate resulting from conjugate addition with **137a** that derives from conjugation with the C2-phenyl substituent.

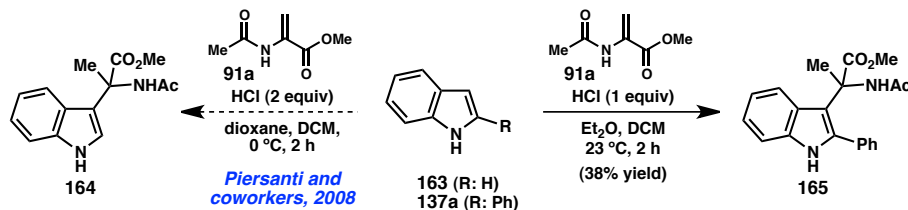
Table 3.2.1. Optimization of reaction parameters.^a



Entry	R ³ , R ⁴	pdt	Solvent	Additive	Yield (%) ^b	ee (%) ^c
1	Bn, CF ₃ (91d)	138a	DCM	--	12	35
2	Me, CF ₃ (91b)	138b	DCM	--	12	42
3	Me, Me (91a)	138c	DCM	--	73	78
4	Me, Me (91a)	138c	DCM	^d	13	--
5	Me, Me (91a)	138c	DCM	^e	0	--
6	Me, Me (91a)	138c	DCM	^f	75	75
7	Me, Me (91a)	138c	DCM	K ₂ CO ₃	73	78
8	Me, Me (91a)	138c	DCM	2,6-lutidine	0	--
9	Me, Me (91a)	138c	DCM	4Å MS	86	81
10	Me, Me (91a)	138c	DCE	4Å MS	87	79
11	Me, Me (91a)	138c	CHCl ₃	4Å MS	80	72

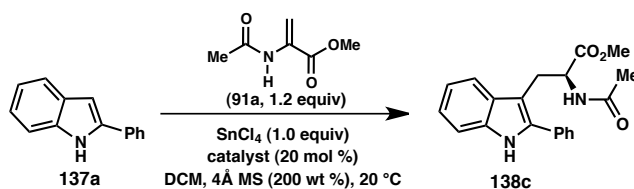
^a Reactions conducted in a glovebox on 0.2 mmol scale for 2 h. Reactions worked up using saturated aqueous NaHCO₃. ^b Isolated yield. ^c Determined by chiral stationary phase SFC. ^d Reaction run without (*R*)-BINOL. ^e Reaction run without SnCl₄. ^f Reaction worked up using 1 M aqueous NaOH.

Scheme 3.2.1. Bronsted acid-promoted reactivity of 2-phenylindole (**137a**).



The enantioselectivity of the tandem conjugate addition/enantioselective protonation reaction was further improved through catalyst optimization. Investigation of 6,6'-disubstituted BINOL derivatives did not identify more selective catalysts and indicated

that the selectivity could not be tuned solely based on electronic perturbation (Table 3.2.2, entries 8–10). Sterically hindered (*R*)-3,3'-diphenyl-BINOL (**102g**) provided acetamido ester **138c** in low yield and only 37% ee, while (*R*)-3,3'-dimethoxy-BINOL (**102l**) gave the product as a racemate possibly due to alternate binding modes for SnCl₄ that result in an unselective reaction (entries 1 and 7). We were pleased to find that 3,3'-dihalogenated derivatives of BINOL provided improved selectivity, with (*R*)-3,3'-dibromo-BINOL (**102k**) affording ester **138c** in 76% yield and 93% ee (entry 6). Notably, although our initial screening was conducted in a glovebox, this reaction can be conducted on gram scale on the benchtop without any significant effect on the yield or ee (Scheme 3.2.2).

Table 3.2.2. Catalyst optimization.^a

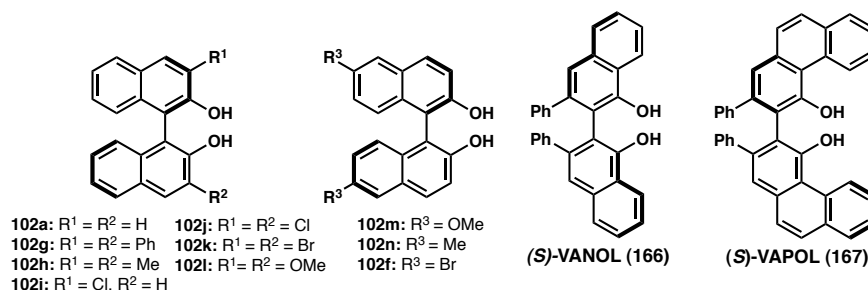
Entry	Catalyst	Loading (mol %)	Yield (%) ^b	ee (%) ^c
1	102a	20	86	81
2	102g	20	17	37
3	102h	20	83	87
4	102i	20	76	84
5	102j	20	85	90
6	102k	20	76	93
7	102l	20	7	1
8	102m	20	86	54
9	102n	20	88	78
10	102f	20	82	78
11	166	20	86	–95
12	167	20	9	–32

^a Reactions conducted in a glovebox on 0.2 mmol scale for 2 h. ^b Isolated yield. ^c Determined by chiral stationary phase SFC.

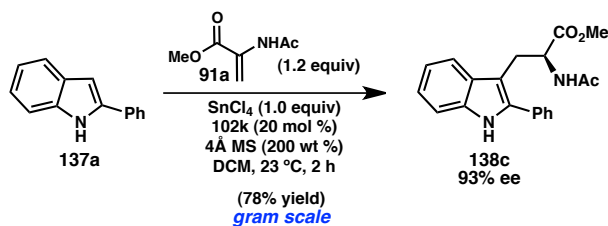
Interestingly, (*S*)-VANOL (**166**), a vaulted chiral diol developed by Wulff and coworkers,¹¹ provided the highest yield and ee we have observed to date, furnishing **138c** in 86% yield and –95% ee (Table 3.2.2, entry 11). Although 2-phenylindole (**137a**) gave

optimal results with **166**, we elected to use (*R*)-3,3'-dibromo BINOL (**102k**) in the evaluation of substrate scope. While both **102k** and **166** are commercially available, **102k** is much less expensive and readily accessible in three steps from BINOL. Furthermore, although **166** proved optimal for **137a**, this trend was not consistently observed with other indole substrates (Table 3.2.5).

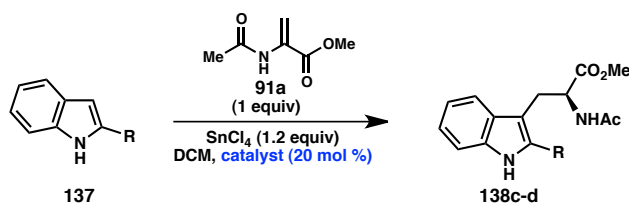
Figure 3.2.1 Catalysts.



Scheme 3.2.2. Gram-scale, benchtop synthesis of tryptophan methyl ester **138c**.



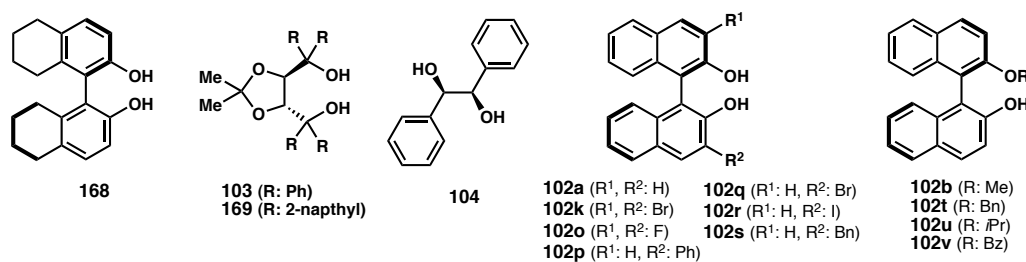
A variety of other chiral diols were also evaluated during the course of our optimization studies (Table 3.2.3). As observed for the formal (3 + 2) cycloaddition reaction, non-BINOL-derived chiral diols, including (*R*)-5,5',6,6',7,7',8,8'-octahydro-BINOL (**168**), TADDOLs **103** and **169**, and hydrobenzoin (**104**) provided tryptophan products either in low ee (entries 2,5,14) or as a racemate (entries 3-4). In addition, (*R*)-2-alkoxy-BINOL derivatives gave reduced ee, which is indicative of the key role played by the hydroxyl protons in the enantioselective protonation (entries 15-18).

Table 3.2.3. Initial catalyst optimization studies.^a

Entry	R	pdt	Catalyst	ee (%) ^b
1 ^c	Me (137b)	138d	102a	71
2 ^{c,d}	Me (137b)	138d	168	2
3 ^c	Me (137b)	138d	103	0
4 ^c	Me (137b)	138d	169	0
5 ^c	Me (137b)	138d	104	9
6 ^c	Ph (137a)	138c	102a	78
7 ^c	Ph (137a)	138c	102k	80
8 ^c	Ph (137a)	138c	102o	85
9 ^c	Ph (137a)	138c	102q	84
10 ^c	Ph (137a)	138c	102r	81
11 ^c	Ph (137a)	138c	102s	86
12 ^e	Ph (137a)	138c	102a	72
13 ^e	Ph (137a)	138c	102p	50
14 ^e	Ph (137a)	138c	168	23
15 ^e	Ph (137a)	138c	102b	20
16 ^e	Ph (137a)	138c	102t	39
17 ^e	Ph (137a)	138c	102u	7
18 ^e	Ph (137a)	138c	102v	1

^a Reactions conducted under inert atmosphere on the benchtop on 0.1 to 0.2 mmol scale. ^b Determined by chiral stationary phase SFC. ^c Reaction worked up using saturated aqueous NaHCO₃. ^d 2.0 equivs SnCl₄ was employed. ^e Reaction worked up using 1M aqueous NaOH.

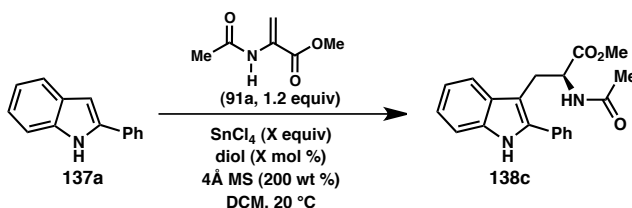
Figure 3.2.2. Catalysts for initial optimization.



With optimal conditions for tryptophan synthesis in hand, we evaluated the possibility of reducing the loading of both (*R*)-3,3'-dibromo-BINOL (**102k**) and SnCl₄ (Table 3.2.4). The loading of **102k** can be reduced as low as 10 mol % without significant erosion of ee; **138c** is obtained in reduced ee (88%) when 5 mol % **102k** is employed (entries 4-5).

However, it appears that the reaction requires a full equivalent of SnCl_4 . Unlike in the formal (3 + 2) cycloaddition and the EtAlCl_2 -promoted tryptophan synthesis by Piersanti and coworkers wherein the reactions barely proceed with substoichiometric Lewis acid loadings (Chapter 2),^{9b} we observed that the loading of SnCl_4 is directly proportional to yield; for example, use of 0.6 equiv SnCl_4 provides 66% yield of **138c**.

Table 3.2.4. Catalytic loadings of **102k** and SnCl_4 .^a



Entry	Diol	Diol (mol %)	SnCl_4 (equiv)	Yield (%) ^b	ee (%) ^c
1	102k	20	1.0	76	93
2	102k	40	1.0	76	93
3	102k	15	1.0	77	93
4	102k	10	1.0	75	92
5	102k	5	1.0	72	88
6	102a	20	1.0	86	81
7	102a	20	0.8	80	79
8	102a	20	0.6	66	77

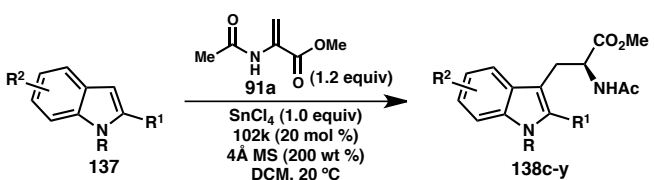
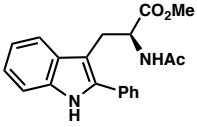
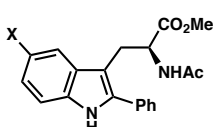
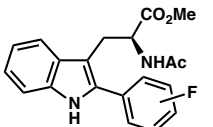
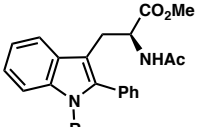
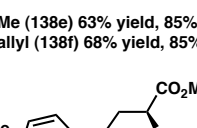
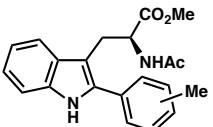
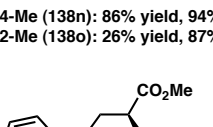
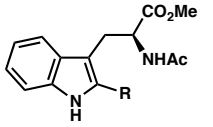
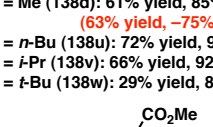
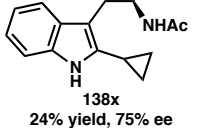
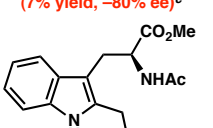
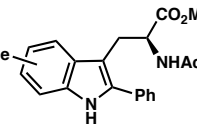
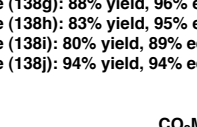
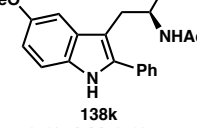
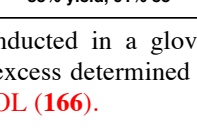
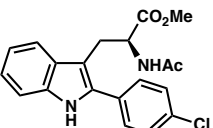
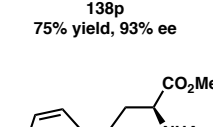
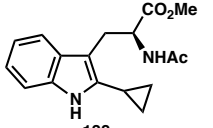
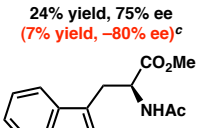
^a Reactions conducted in a glovebox on 0.2 mmol scale for 2 h. ^b Isolated yield. ^c Determined by chiral stationary phase SFC.

3.2.2 Substrate Scope of Tryptophan Synthesis

The substrate scope was explored under the optimized conditions using a 20 mol % loading of (*R*)-3,3'-dibromo-BINOL (**102k**) to ensure optimal results for all substrates (Table 3.2.5). In contrast to the trend observed in the formal (3 + 2) cycloaddition reaction (Chapter 2), *N*-alkylated indoles react in lower yield than (1*H*)-derivatives, with tryptophans **138e** and **138f** both accessed in 85% ee (entries 2-3). Electronically diverse indoles functionalized at C4, C5, C6, and C7 provided uniformly high ees; however, electron-poor indoles furnished tryptophan products in lower yields (e.g. **138l**). A variety

of alkyl and aryl substituents were tolerated at C2 of the indole although *ortho*-functionalized aryl substituents (e.g. **138t**) and very small or bulky alkyl substitution resulted in lower yields and ee (entries 18-23).

Table 3.2.5. Substrate scope.^a

		
entry	entry	entry
 1) 76% yield, 93% ee	 9) ^b Br (138l): 60% yield, 93% ee 10) ^b F (138m): 63% yield, 92% ee	 15) 4-F (138r): 78% yield, 93% ee 16) 3-F (138s): 76% yield, 92% ee 17) 2-F (138t): 35% yield, 92% ee
 2) R = Me (138e) 63% yield, 85% ee  3) R = allyl (138f) 68% yield, 85% ee	 11) 4-Me (138n): 86% yield, 94% ee  12) 2-Me (138o): 26% yield, 87% ee	 18) R = Me (138d): 61% yield, 85% ee (63% yield, –75% ee) ^c  19) R = <i>n</i> -Bu (138u): 72% yield, 91% ee  20) R = <i>i</i> -Pr (138v): 66% yield, 92% ee  21) R = <i>t</i> -Bu (138w): 29% yield, 84% ee
 4) 4-Me (138g): 88% yield, 96% ee  5) 5-Me (138h): 83% yield, 95% ee  6) 6-Me (138i): 80% yield, 89% ee  7) 7-Me (138j): 94% yield, 94% ee	 13) 75% yield, 93% ee  14) 88% yield, 92% ee	 22) 24% yield, 75% ee (7% yield, –80% ee) ^c  23) 80% yield, 90% ee

^a Reaction conducted in a glovebox for 2 h on 0.1 or 0.2 mmol scale. Isolated yields are reported. Enantiomeric excess determined by chiral SFC analysis. ^b 1.6 equivs SnCl₄ was employed. ^c Reaction run with (*S*)-VANOL (**166**).

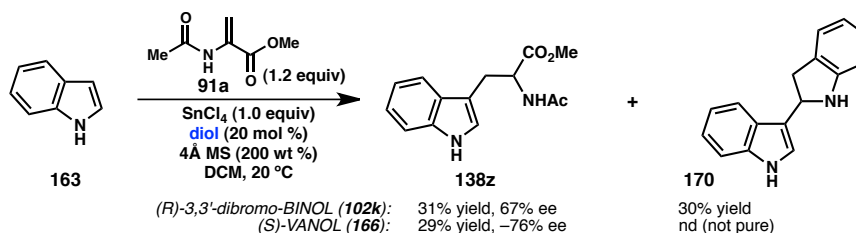
For a few cases where low yield and ee was observed, the reactions were also conducted using (*S*)-VANOL (**166**) as the catalyst (entries 18 and 22). Unfortunately, the trend observed with 2-phenylindole, wherein higher yield and ee was observed with **166**,

was found to be substrate specific. For example, reaction of 2-cyclopropylindole using **166** as the catalyst gave **138x** in 80% ee, compared to 75% with **102k**; however, the yield was reduced from 24% to 7% using **166** as the catalyst.

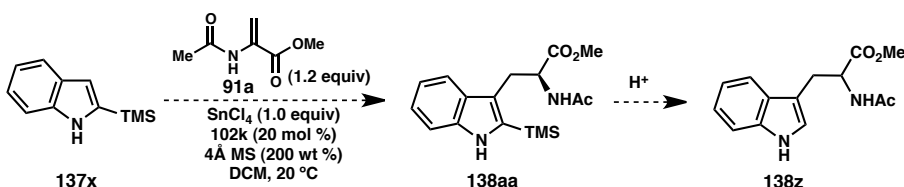
Although the tandem conjugate addition/enantioselective protonation reaction is tolerant of diverse functionalization, substitution at C2 of the indole is required to enable a highly enantioselective, efficient transformation. Exposure of indole to the standard reaction conditions results in competitive dimerization, with tryptophan **138z** formed in only 31% yield and 67% ee (Scheme 3.2.3). Unfortunately, low yields are also observed using (*S*)-VANOL (**166**) as the catalyst, although the ee is improved to –76%. As an alternative approach to C2-unsubstituted tryptophan derivatives, we have investigated the alkylation of 2-(trimethylsilyl)indole (**137x**); however, as experienced with the formal (3 + 2) cycloaddition (Scheme 2.3.1), exposure of **137x** to SnCl₄ on the benchtop resulted in rapid protodesilylation and attempts at this alkylation under strictly anhydrous conditions were unsuccessful.

Scheme 3.2.3. Efforts to access C2-unsubstituted tryptophan derivatives.^a

Direct alkylation of indole (163):



Two-step approach with 2-(trimethylsilyl)indole (137x):

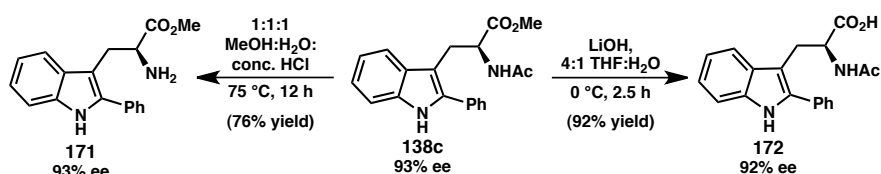


^aReactions conducted in a glovebox on 0.1 or 0.2 mmol scale. Isolated yields are reported. Enantiomeric excess was determined by chiral stationary phase SFC.

3.2.3 Derivatization of Tryptophan Products

Following the development of the tandem conjugate addition/enantioselective protonation reaction, our attention turned to investigating the functionalization of the products. Importantly, both the acetamide and ester functionalities could be selectively hydrolyzed without erosion of ee. Heating of **138c** with methanolic HCl gives primary amine **171**, whereas exposure of **138c** to LiOH cleanly affords carboxylic acid **172** (Scheme 3.2.4). For more information regarding derivatization and the development of an oxidative cyclization reaction of *N*-methyl tryptophan derivative **138e**, refer to Chapter 4.

Scheme 3.2.4. Selective hydrolysis conditions for acetamide and methyl ester of **138c**.

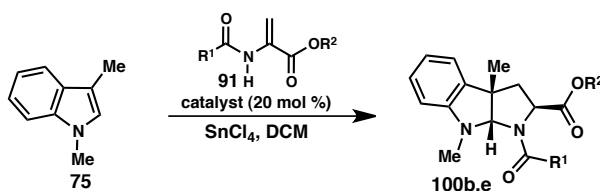


3.2.4 Comparison of New Conditions for Pyrroloindoline Formation

On the basis of mechanistic similarities, we envisioned that the optimal conditions for the tandem conjugate addition/protonation reaction might afford improved yields and selectivities for the formal (3 + 2) cycloaddition reaction. When methyl 2-acetamidoacrylate (**91a**)—the optimal partner for tryptophan synthesis—is employed, 1,3-dimethylindole (**75**) reacts in the presence of (*R*)-BINOL•SnCl₄ to give pyrroloindoline **100b** in 5:1 dr, with the major diastereomer formed in 65% ee (Table 3.2.6, entry 1). Alternatively, exposure of a mixture of **91a** and **75** to (*R*)-3,3'-dibromo-BINOL and 4Å MS furnished **100b** in an improved 8:1 dr and 87% ee for the *exo* diastereomer, albeit in lower yield (entry 2). We observed a similar trend with the benzyl 2-trifluoroacetamidoacrylate (**91d**)—the optimal partner for pyrroloindoline synthesis. The

reaction of **75** and benzyl 2-trifluoroacetamidoacrylate (**91d**) using (*R*)-3,3'-dibromo-BINOL and 4Å MS gave improved dr and the *exo* diastereomer was formed in an exceptional 98% ee, but the yield was dramatically reduced to only 39% (entry 4). Thus, an appropriate matching of acrylate and catalyst is required to obtain both high yields and selectivities.

Table 3.2.6. Comparison of conditions for pyrroloindoline formation.

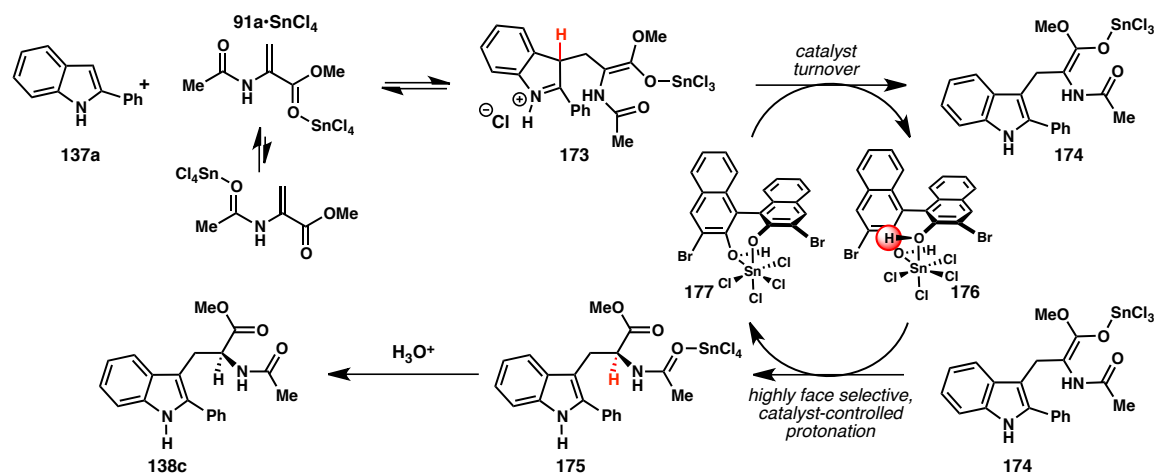


Entry	Conditions	R^1, R^2	pdt	Yield (%) ^a	dr ^b	ee (%) ^c
1 ^d	102a	Me, Me (91a)	100b	70	5:1	65/80
2 ^e	102k , 4Å MS	Me, Me (91a)	100b	58	8:1	87/85
3 ^d	102a	CF_3 , Bn (91d)	100e	86	4:1	94/91
4 ^e	102k , 4Å MS	CF_3 , Bn (91d)	100e	39	7:1	98/92

^a Isolated yield. ^b Determined by ^1H NMR analysis of mixture. ^c Determined by chiral stationary phase SFC. ^d Reaction run with 1.0 equiv acrylate, 1.2 equiv SnCl_4 . ^e Reaction run with 1.2 equiv acrylate, 1.0 equiv SnCl_4 .

These results are suggestive of subtle mechanistic differences between the tandem conjugate addition/enantioselective protonation reaction and the formal (3 + 2) cycloaddition reaction. For example, in the tryptophan synthesis it is proposed that the stoichiometric proton source required for catalyst turnover derives from C3 of the indole, which is lost during rearomatization (Scheme 3.2.5). In contrast, in the pyrroloindoline formation, the stoichiometric proton is hypothesized to derive from the Lewis acid-coordinated trifluoroacetamide group (Scheme 2.3.2). Unfortunately, deuterium labeling studies aimed at identifying the stoichiometric proton source have been inconclusive, as exposure of deuterated indoles to $\text{BINOL}\cdot\text{SnCl}_4$ results in rapid deuterium scrambling (3.4.9).

Scheme 3.2.5. Proposed catalytic cycle for tryptophan synthesis.



3.3 CONCLUDING REMARKS

In summary, the first tandem Friedel–Crafts conjugate addition/enantioselective protonation approach to tryptophan derivatives has been developed. This reaction proceeds optimally using SnCl₄•(*R*)-3,3'-dibromo BINOL as the catalyst and has allowed for the preparation of many C2-substituted tryptophan derivatives in excellent yields and ees. These derivatives have proven amenable to further functionalization, including selective hydrolysis and oxidative cyclization reactions (Chapter 4). In addition to enabling efficient access to tryptophan derivatives, the successful development of this reaction has provided further support for the mechanism of the formal (3 + 2) cycloaddition reaction. However, despite the shared enantiodetermining step for tryptophan and pyrroloindoline syntheses, the contrasting optimal conditions for each is suggestive of subtle differences in their mechanistic pathways. Further research is focused on mechanistic analysis and the application of this asymmetric protonation strategy in the design of new methodologies.

3.4 EXPERIMENTAL SECTION

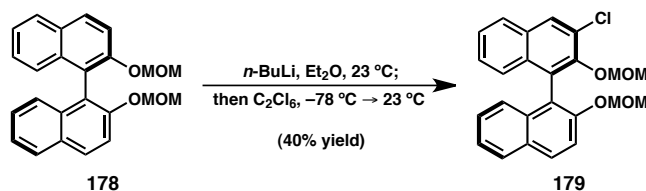
3.4.1 *Materials and Methods*

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride, deuterated methylene chloride, dioxane, ether, tetrahydrofuran, and toluene were dried by passing through activated alumina. Dichloroethane and chloroform were distilled over calcium hydride. Powdered 4Å molecular sieves were flame-dried under vacuum immediately prior to use. Potassium carbonate was dried for 12 h at 130 °C under vacuum and 2,6-lutidine was distilled over AlCl₃. All other commercially obtained reagents were used as received unless specifically indicated. (*R*)-BINOL (**102a**), 2-phenylindole (**137a**) and 2-methylindole (**137b**) were purchased from Alfa Aesar, *N*-methyl-2-phenylindole (**137c**) was obtained from Sigma-Aldrich, and 1 M SnCl₄ in DCM was purchased from Acros Organics. (*R*)-3,3'-diphenyl-BINOL (**102g**),¹² (*R*)-3,3'-dimethyl-BINOL (**102h**),¹³ (*R*)-3,3'-dichloro-BINOL (**102j**),¹⁴ (*R*)-3,3'-dibromo-BINOL (**102k**),¹⁵ (*R*)-3,3'-dimethoxy-BINOL (**102l**),¹⁵ (*R*)-6,6'-dimethyl-BINOL (**102n**),¹⁶ (*R*)-6,6'-dibromo-BINOL (**102f**),¹⁷ (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102b**),¹⁸ (*R*)-2'-isopropoxy-[1,1'-binaphthalen]-2-ol (**102u**),¹⁹ (*R*)-3,3'-difluoro-BINOL (**102o**),²⁰ (*R*)-3-phenyl-BINOL (**102p**),²¹ (*R*)-5,5',6,6',7,7',8,8'-octahydro-BINOL (**168**)²², (*R*)-2'-benzoyl-[1,1'-binaphthalen]-2-ol (**102v**),²³ (*R*)-3-bromo-BINOL (**102q**) and (*R*)-3-iodo-BINOL (**102r**),²⁴ TADDOL (**103**),²⁵ Naphthyl-TADDOL (**169**),²⁶ and 2-(trimethylsilyl)indole (**137x**),²⁷ were prepared according to literature procedures. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel column

chromatography was performed either as described by Still et al. (W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.) using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiSilica gel Rf system (Teledyne ISCO Inc.). ^1H and ^{13}C NMR were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Varian Inova 600 (at 600 MHz and 150 MHz respectively), and are reported relative to internal chloroform (^1H , $\delta = 7.26$, ^{13}C , $\delta = 77.0$) or internal acetonitrile (^1H , $\delta = 1.94$, ^{13}C , $\delta = 1.32$). 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. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, and OB-H columns (4.6 mm x 25 cm). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

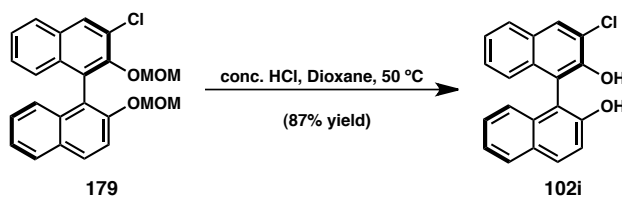
3.4.2 Catalyst and Substrate Preparation

Preparation of (*R*)-3-chloro-BINOL (**102i**)



To a flame-dried 100 mL flask containing MOM-protected (*R*)-BINOL **178**¹³ (748 mg, 2.00 mmol, 1.00 equiv) was added Et₂O (45 mL), followed by dropwise addition of *n*-BuLi as a solution in hexanes (2.5 M, 960 μL, 2.40 mmol, 1.20 equiv) at room temperature. The mixture was then stirred at room temperature for 3 h and subsequently cooled to −78 °C, followed by addition of C₂Cl₆ (569 mg, 2.40 mmol, 1.20 equiv) in one portion. The reaction mixture was allowed to warm to room temperature over 3 h, then diluted with EtOAc (15 mL) and washed with saturated aqueous NH₄Cl (50 mL). The aqueous layer was extracted with EtOAc (45 mL) and the combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude yellow oil was purified by silica gel chromatography (0:100 to 12:88 EtOAc:hexanes) to yield 328 mg (40% yield) of **179** as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.05 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 9.1 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.28 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.24 (ddd, *J* = 8.5, 6.7, 1.3 Hz, 1H), 7.18 (dddd, *J* = 8.6, 1.3, 0.7, 0.7 Hz, 1H), 7.16 (ddd, *J* = 8.5, 1.8, 0.8 Hz, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 5.04 (d, *J* = 7.0 Hz, 1H), 4.80 (d, *J* = 5.6 Hz, 1H), 4.75 (d, *J* = 5.6 Hz, 1H), 3.19 (s, 3H), 2.71 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.9, 148.9, 133.8, 132.6, 131.1, 130.0, 129.5, 128.8, 128.0, 127.9, 127.8, 127.0, 126.7, 126.4, 126.1, 125.8, 125.5, 124.2, 119.9, 116.3, 98.8, 94.9, 56.5, 55.9; IR (NaCl/thin film): 2955, 2902, 1594, 1508, 1354, 1241, 1159, 1149, 1034, 1014, 961, 922

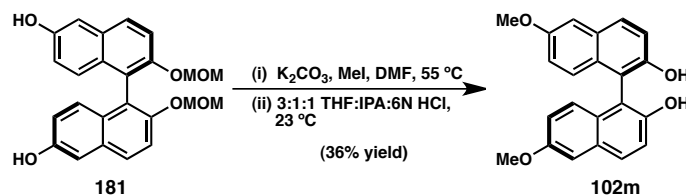
cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +69.1^\circ$ ($c = 0.90$, CHCl_3). HRMS (FAB+) calc'd for M^+ 408.1128, found 408.1128.



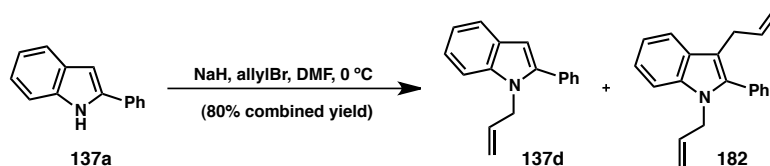
A 10 mL flask was charged with **179** (305 mg, 0.75 mmol, 1.00 equiv), dioxane (3.7 mL) and aqueous HCl (12 M, 130 μL , 1.58 mmol, 2.10 equiv), then heated to 50 $^\circ\text{C}$ for 2 h. The mixture was cooled to room temperature, then diluted with H_2O (30 mL) and extracted with EtOAc (6 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel chromatography (0:100 to 20:80 EtOAc:hexanes) to yield 210 mg (87% yield) of (*R*)-3-chloro-BINOL (**102i**) as a white foam, which was dried over P_2O_5 under vacuum. ^1H NMR (500 MHz, CDCl_3) δ 8.09 (s, 1H), 7.97 (d, $J = 8.9$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.45 – 7.35 (m, 3H), 7.34 – 7.28 (m, 2H), 7.16 (d, $J = 8.5$ Hz, 1H), 7.11 (d, $J = 8.4$ Hz, 1H), 5.60 (s, 1H), 4.94 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.1, 148.3, 133.1, 132.4, 131.3, 129.7, 129.32, 129.26, 128.4, 127.7, 127.5, 127.3, 125.1, 124.6, 124.1, 123.9, 122.4, 117.7, 113.6, 111.7; IR (NaCl/thin film): 3503, 3057, 1620, 1596, 1502, 1451, 1379, 1265, 1212, 1184, 1146, 828 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +55.4^\circ$ ($c = 1.01$, CHCl_3). HRMS (MM) calc'd for $[\text{M}-\text{H}]^-$ 319.0531, found 319.0549.

(*R*)-6,6'-dimethoxy-BINOL (**102m**) was prepared following a procedure adapted from a reported synthesis of (*R*)-3,3'-dimethoxy-BINOL (**102i**).¹⁵ To a 25 mL flask containing MOM-protected (*R*)-6,6'-dibromo-BINOL **180**¹⁷ (1.10 g, 2.07 mmol, 1.00 equiv) was added THF (6.3 mL). The flask was cooled to -78 °C, followed by dropwise addition of *n*-BuLi as a solution in hexanes (2.5 M, 2.50 mL, 6.20 mmol, 3.00 equiv). After stirring 1 hour at -78 °C, B(OMe)₃ (645 mg, 6.20 mmol, 3.00 equiv) was added and the reaction was allowed to warm to room temperature. After 14 hours, the reaction mixture was concentrated to give the crude borate intermediate, which was suspended in benzene (7.2 mL) and cooled to 0 °C, followed by dropwise addition of aqueous hydrogen peroxide (30 wt %, 0.61 mL, 5.98 mmol, 2.89 equiv). The suspension was heated to reflux for 4 hours, then cooled to room temperature, poured into ice-cold saturated aqueous NaSO₃ (20 mL), and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (30 mL), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel chromatography (0:100 to 50:50 EtOAc:hexanes) to yield 512 mg (61% yield) of **181** as a light yellow foam. ¹H NMR (500 MHz, CD₃CN) δ 7.80 (ddd, *J* = 9.1, 0.8, 0.4 Hz, 2H), 7.51 (d, *J* = 9.1 Hz, 2H), 7.20 (ddd, *J* = 2.5, 0.5, 0.5 Hz, 2H), 7.09 (br s, 2H), 6.93 (ddd, *J* = 9.1, 0.7, 0.7 Hz, 2H), 6.87 (dd, *J* = 9.1, 2.5 Hz, 2H), 5.02 (d, *J* = 6.7 Hz, 2H), 4.94 (d, *J* = 6.7 Hz, 2H), 3.11 (s, 6H) ; ¹³C NMR (125 MHz, CD₃CN) δ 154.4, 151.6, 132.1, 129.6, 128.4, 127.8, 122.1.

119.6, 118.7, 110.1, 96.0, 56.1; IR (NaCl/thin film): 3368, 2914, 1624, 1599, 1511, 1240, 1196, 1148, 1023 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +87.1^{\circ}$ ($c = 1.00$, MeCN). HRMS (MM) calc'd for $[\text{M-H}]^{-}$ 405.1344, found 405.1350.



A 15 mL flask was charged with **181** (200 mg, 0.493 mmol, 1.00 equiv) and K_2CO_3 (177 mg, 1.28 mmol, 2.60 equiv). DMF (2 mL) was added, followed by MeI (123 μL , 1.97 mmol, 4.00 equiv) dropwise. The reaction was then heated to 55 $^{\circ}\text{C}$ for 22 hours, then cooled to room temperature and quenched with saturated aqueous NH_4Cl (2 mL) and Et_3N (3 drops). The mixture was stirred at room temperature for 6 hours, then diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. THF (28 mL) and IPA (9.5 mL) were added to the crude residue, followed by dropwise addition of aqueous HCl (6.0 M, 9.4 mL). The reaction was stirred at room temperature for 3 hours, then diluted with H_2O (70 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with saturated aqueous NaHCO_3 (2 x 45 mL) and brine (45 mL), then dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 62 mg (36% yield) of (*R*)-6,6'-dimethoxy-BINOL (**102m**) as a light brown solid, which was dried over P_2O_5 under high vacuum. Spectral data are in agreement with the literature.²⁸

Preparation of 1-allyl-2-phenylindole (137d)

To a 50 mL flask was added NaH (620 mg, 15.5 mmol, 3.00 equiv) and DMF (8 mL) and the suspension was cooled to 0 °C in an ice bath. A solution of 2-phenylindole **137a** (1.00 g, 5.18 mmol, 1.00 equiv) in DMF (3 mL) was added slowly to the suspension over 15 minutes and the reaction mixture was further stirred at 0 °C for 20 minutes, followed by dropwise addition of allyl bromide (670 μ L, 7.77 mmol, 1.50 equiv). The ice bath was then removed and the mixture was stirred for 15 minutes, then quenched by addition of saturated aqueous NH_4Cl (5 mL) and Et_3N (5 drops). After 2 hours, the reaction was diluted with H_2O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (120 mL), dried (Na_2SO_4), filtered, and concentrated. The crude was then purified by reverse phase preparatory HPLC (55:45 to 95:5 MeCN: H_2O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm and 21.2 x 150 mm) to yield 687 mg (57% yield) of 1-allyl-2-phenylindole (**137d**) as a yellow solid and 331 mg (23% yield) of 1,3-diallyl-2-phenylindole (**182**) as a yellow oil.

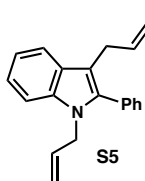
1-allyl-2-phenylindole (137d):

^1H NMR (500 MHz, CDCl_3) δ 7.65 (ddd, $J = 7.8, 1.2, 0.8$ Hz, 1H), 7.55 – 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.42 – 7.38 (m, 1H), 7.33 (br d, $J = 8.2$ Hz, 1H), 7.22 (ddd, $J = 7.0, 7.0, 1.3$ Hz, 1H), 7.15 (ddd, $J = 7.0, 7.0, 1.0$ Hz, 1H), 6.60 (br s, 1H), 6.02 (ddt, $J = 17.2, 10.5, 4.4$ Hz, 1H), 5.22 (dtd, $J = 10.5, 1.8, 1.1$

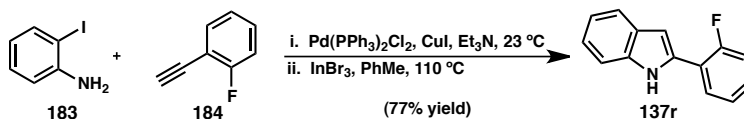
6c

Hz, 1H), 5.00 (dtd, $J = 17.1, 2.0, 1.2$ Hz, 1H), 4.74 (dt, $J = 4.2, 1.9$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.5, 137.8, 133.8, 132.7, 129.1, 128.5, 128.1, 128.0, 121.7, 120.5, 120.0, 116.5, 110.3, 102.0, 46.5; IR (NaCl/thin film): 3055, 2917, 1602, 1462, 1443, 1392, 1345, 1317, 1162 cm^{-1} ; HRMS (APCI) calc'd for $[\text{M}+\text{H}]^+ = 234.1277$, found 234.1284.

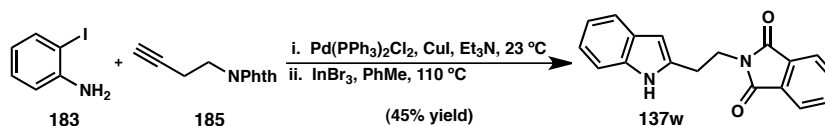
1,3-diallyl-2-phenylindole (182):



^1H NMR (500 MHz, CDCl_3) δ 7.65 (ddd, $J = 7.8, 1.2, 0.7$ Hz, 1H), 7.50 – 7.40 (m, 5H), 7.33 (ddd, $J = 8.1, 0.9, 0.9$ Hz, 1H), 7.24 (ddd, $J = 7.0, 7.0, 1.2$ Hz, 1H), 7.16 (ddd, $J = 7.0, 7.0, 1.1$ Hz, 1H), 6.05 (ddt, $J = 17.0, 10.1, 5.9$ Hz, 1H), 5.91 (ddt, $J = 17.1, 10.4, 4.7$ Hz, 1H), 5.14 (dtd, $J = 10.4, 1.8, 1.2$ Hz, 1H), 5.08 – 5.02 (m, 2H), 4.92 (dtd, $J = 17.1, 1.9, 1.3$ Hz, 1H), 4.62 (dt, $J = 4.6, 1.9$ Hz, 2H), 3.46 (dt, $J = 6.0, 1.7$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.0, 137.9, 136.7, 133.9, 131.8, 130.4, 128.3, 128.2, 128.1, 128.0, 121.7, 119.34, 119.30, 116.2, 114.6, 110.9, 110.1, 46.4, 29.2; IR (NaCl/thin film): 3056, 2915, 1637, 1463, 1443, 1408, 1360, 1340, 1191 cm^{-1} ; HRMS (MM) calc'd for $[\text{M}+\text{H}]^+ = 274.1590$, found 274.1591.

Preparation of 2-(2-fluorophenyl)indole (137r)

2-(2-fluorophenyl)indole (**137r**) was prepared by an analogous procedure to that reported by Sakai et al.²⁹ A flame-dried flask was charged with 2-iodoaniline (**183**, 200 mg, 0.90 mmol, 1.00 equiv), ethynyl-2-fluorobenzene (**184**, 133 mg, 1.10 mmol, 1.20 equiv), $\text{Pd(PPh}_3)_2\text{Cl}_2$ (13 mg, 0.02 mmol, 0.02 equiv), copper (I) iodide (2.0 mg, 0.025 mmol, 0.01 equiv) and Et_3N (4 mL). The mixture was stirred overnight at room temperature, then filtered through a plug of silica, concentrated and redissolved in PhMe (5 mL). InBr_3 (16 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was heated to $110\text{ }^\circ\text{C}$ for 5 h, then cooled to room temperature, filtered through celite, and concentrated. The crude residue was purified by silica gel chromatography (10:90 EtOAc:hexanes) to yield 148 mg (77% yield) of 2-(2-fluorophenyl)indole (**137r**) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.89 (br s, 1H), 7.80 (ddd, $J = 7.8, 7.8, 1.8$ Hz, 1H), 7.66 (dddd, $J = 2.5, 1.3, 0.8, 0.8$ Hz, 1H), 7.43 (ddd, $J = 8.1, 1.5, 0.8$ Hz, 1H), 7.32 – 7.26 (m, 1H), 7.26 – 7.16 (m, 3H), 7.14 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 6.97 (d, $J = 1.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.3 (d, $J_{\text{C-F}} = 246.4$ Hz), 134.6 (d, $J_{\text{C-F}} = 501.8$ Hz), 128.8 (d, $J_{\text{C-F}} = 8.8$ Hz), 128.1, 128.0 (d, $J_{\text{C-F}} = 4.1$ Hz), 124.8 (d, $J_{\text{C-F}} = 3.2$ Hz), 122.7, 120.6, 120.2, 119.9 (d, $J_{\text{C-F}} = 11.0$ Hz), 116.6, 116.4, 111.0, 101.6 (d, $J_{\text{C-F}} = 3.0$ Hz); IR (NaCl/thin film): 3469, 3042, 2918, 2848, 1577, 1472, 1460, 1212, 1178, 1109, 928 cm^{-1} ; HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 212.0870, found 212.0869.

Preparation of 2-(ethylphthalimide)indole (137w)

2-(ethylphthalimide)indole (**137w**) was prepared by an analogous procedure to that reported by Sakai et al.²⁹ A flame-dried flask was charged with 2-iodoaniline (**183**, 500 mg, 2.30 mmol, 1.00 equiv), 2-(but-3-yn-1-yl)isoindoline-1,3-dione (**185**, 550 mg, 2.75 mmol, 1.20 equiv), Pd(PPh₃)₂Cl₂ (32 mg, 0.05 mmol, 0.02 equiv), copper (I) iodide (4.5 mg, 0.025 mmol, 0.01 equiv) and Et₃N (8 mL). The mixture was stirred overnight at room temperature, then filtered through a plug of silica, concentrated and redissolved in PhMe (10 mL). InBr₃ (40 mg, 0.1 mmol, 0.05 equiv) was added in one portion and the mixture was heated to 110 °C for 5 h, then cooled to room temperature, filtered through celite and concentrated. The crude residue was purified by silica gel chromatography (60:40 EtOAc:hexanes) to yield 302 mg (45% yield) of 2-(ethylphthalimide)indole (**137w**) as a light yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.26 (br s, 1H), 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.06 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.33 (d, *J* = 1.2 Hz, 1H), 4.06 (t, *J* = 7.5 Hz, 2H), 3.21 (t, *J* = 7.4 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 168.3, 136.1, 134.9, 134.1, 131.9, 128.6, 123.4, 121.4, 120.0, 119.7, 110.6, 101.1, 37.1, 27.4.; IR (NaCl/thin film): 3366, 1772, 1707, 1653, 1617, 1466, 1395, 1363, 1293 cm⁻¹; HRMS (MM) calc'd for [M+H]⁺ 291.1128, found 291.1138.

3.4.3 Optimization of Reaction Parameters

3.4.3.1 General Procedure 1

An oven-dried vial was charged with 2-phenylindole (**137a**, 0.20 mmol, 1.00 equiv), the acrylate (0.24 mmol, 1.20 equiv) and an (*R*)-BINOL derivative and pumped into a glove box. The vial was charged with solvent to an indole concentration of 0.12 M, and SnCl₄ (1.00 equiv, as a 1.0 M solution in DCM) was added. The reaction was stirred at 20 °C for 2 hours, after which time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (5 mL), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

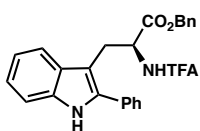
Additive screens. Reactions were performed following General Procedure 1 using 0.20 equiv (*R*)-BINOL. After the vial was pumped into the glove box, one of the following additives was added:

- flame-dried powdered 4Å molecular sieves (200 wt % relative to indole)
- K₂CO₃ (1.00 equiv)
- 2,6-lutidine (1.00 equiv)

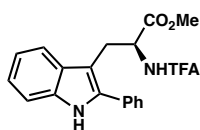
Upon addition of the additive, DCM was added to an indole concentration of 0.12 M and the reaction was further conducted as described above.

Catalyst screens. Reactions were performed following General Procedure 1 using flame-dried powdered 4Å molecular sieves (200 wt % relative to indole) as an additive and DCM as a solvent.

3.4.3.2 Characterization Data

(S)-*N*_α-Trifluoroacetyl-2-phenyltryptophan benzyl ester (**138a**)

Prepared from benzyl 2-trifluoroacetamidoacrylate³⁰ (**91d**, 65.5 mg, 0.24 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (30:70 to 70:30 DCM:hexanes) to yield 11.1 mg (12% yield) of **138a** as a yellow solid. The enantiomeric excess was determined to be 35% by chiral SFC analysis (OB-H, 2.5 mL/min, 15% IPA in CO₂, λ = 254 nm): *t*_R(major) = 11.0 min, *t*_R(minor) = 12.9 min. ¹H NMR (500 MHz, CDCl₃) δ 8.14 (br s, 1H), 7.57 (ddd, *J* = 7.9, 1.8, 0.7 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.50 – 7.45 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.29 (m, 3H), 7.24 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.11 – 7.07 (m, 2H), 6.67 (br d, *J* = 7.6 Hz, 1H), 4.95 (d, *J* = 12.2 Hz, 1H), 4.88 (dt, *J* = 7.8, 6.0 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 3.65 – 3.56 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ ¹³C NMR (125 MHz, CDCl₃) δ 170.1, 156.6 (q, *J*_{C-F} = 37.8 Hz), 136.3, 135.6, 134.6, 132.4, 129.2, 128.9, 128.5, 128.44, 128.38, 128.2, 128.1, 122.8, 120.3, 118.6, 115.3 (q, *J*_{C-F} = 287.9 Hz), 111.0, 105.6, 67.5, 53.3, 26.7; IR (NaCl/thin film): 3391, 3061, 2924, 1714, 1542, 1457, 1210, 1173 cm⁻¹; [α]_D²⁵ = +3.5° (*c* = 0.44, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 467.1577, found 467.1580.

(S)-*N*_α-Trifluoroacetyl-2-phenyltryptophan methyl ester (138b)

Prepared from methyl 2-trifluoroacetamidoacrylate³¹ (**91b**, 47.3 mg, 0.24 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (0:100 to 5:95 EtOAc:toluene, then 0:100 to 20:80 EtOAc:hexanes) to yield 9.0 mg (12% yield) of **138b** as a yellow solid. The enantiomeric excess was determined to be 42% by chiral SFC analysis (AS-H, 2.5 mL/min, 10% IPA in CO₂, λ = 254 nm): *t*_R(major) = 8.7 min, *t*_R(minor) = 7.7 min. ¹H NMR (500 MHz, CDCl₃) δ 8.17 (br s, 1H), 7.58 – 7.52 (m, 3H), 7.52 – 7.47 (m, 2H), 7.43 – 7.39 (m, 1H), 7.38 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.65 (br d, *J* = 7.3 Hz, 1H), 4.83 (dt, *J* = 7.8, 5.6 Hz, 1H), 3.66 – 3.56 (m, 2H), 3.34 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.5, 156.6 (q, *J*_{C-F} = 37.7 Hz), 136.3, 135.6, 132.5, 129.2, 129.0, 128.4, 128.2, 122.8, 120.3, 118.5, 115.3 (q, *J*_{C-F} = 287.7 Hz), 111.0, 105.5, 53.2, 52.5, 26.4; IR (NaCl/thin film): 3391, 3057, 2917, 2849, 1718, 1542, 1458, 1449, 1211, 1170 cm⁻¹; [α]_D²⁵ = +22.3° (*c* = 0.39, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 391.1264, found 391.1267.

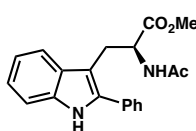
3.4.4 Optimized Conjugate Addition/Asymmetric Protonation**3.4.4.1 General Procedure 2**

An oven-dried vial was charged with the indole (1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 1.20 equiv)³² and (*R*)-3,3'-dibromo-BINOL (**102k**, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to indole). The vial was charged with DCM to an indole concentration of 0.12 M, and SnCl₄ (1.00 equiv unless specifically indicated, as a 1 M solution in DCM) was added. The reaction was stirred at 20 °C for 2 hours, after which

time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (5 mL), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

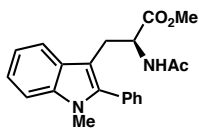
3.4.4.2 Characterization Data

(S)-N_α-Acetyl-2-phenyltryptophan methyl ester (**138c**)



Prepared from 2-phenylindole (**137a**, 19.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 25.6 mg (76% yield) of **138c** as a white foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm). $t_R(\text{major}) = 5.7$ min, $t_R(\text{minor}) = 6.9$ min. $[\alpha]_D^{25} = +37.7^\circ$ ($c = 0.94$, CHCl₃). Spectral data matches that reported in the literature.³³

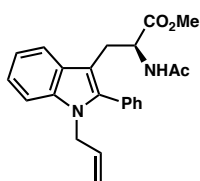
(S)-N_α-Acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**)



Prepared from 1-methyl-2-phenylindole (**137c**, 41.4 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 55:45 EtOAc:hexanes) to yield 43.4 mg (63% yield) of **138e** as a yellow solid. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO₂, λ = 254 nm): $t_R(\text{major}) = 4.6$ min, $t_R(\text{minor}) = 3.9$ min. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (ddd, $J = 7.9, 1.2, 0.7$ Hz, 1H), 7.56 – 7.49 (m, 2H), 7.48 – 7.44 (m, 1H), 7.42 – 7.38 (m, 2H), 7.34 (ddd, $J = 8.2, 0.9, 0.9$

Hz, 1H), 7.26 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.17 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 5.72 (br d, $J = 7.8$ Hz, 1H), 4.74 (dt, $J = 8.0, 5.6$ Hz, 1H), 3.57 (s, 3H), 3.39 (s, 3H), 3.41 (dd, $J = 14.7, 5.7$ Hz, 1H), 3.34 (dd, $J = 14.8, 5.6$ Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 169.5, 139.2, 136.9, 131.6, 130.7, 128.7, 128.4, 127.9, 122.0, 119.7, 118.7, 109.5, 106.7, 52.8, 52.0, 30.8, 26.6, 23.0.; IR (NaCl/thin film): 3288, 3055, 2950, 1743, 1657, 1539, 1469, 1441, 1368, 1238, 1212 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +21.3^\circ$ ($c = 0.91$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 351.1703, found 351.1708.

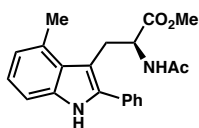
(S)- N_α -Acetyl-1-allyl-2-phenyltryptophan methyl ester (138f)



Prepared from 1-allyl-2-phenylindole (**137d**, 46.6 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 55:45 EtOAc:hexanes) to yield 51.3 mg (68% yield) of **138f** as a yellow foam. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AS-H, 2.5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm): t_{R} (major) = 2.9 min, t_{R} (minor) = 2.4 min. ^1H NMR (500 MHz, CDCl_3) δ 7.62 (ddd, $J = 7.8, 1.0, 1.0$ Hz, 1H), 7.53 – 7.47 (m, 2H), 7.47 – 7.42 (m, 1H), 7.42 – 7.37 (m, 2H), 7.30 (ddd, $J = 8.1, 0.9, 0.9$ Hz, 1H), 7.23 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.17 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 5.85 (ddt, $J = 17.1, 10.3, 4.7$ Hz, 1H), 5.76 (br d, $J = 7.9$ Hz, 1H), 5.11 (dtd, $J = 10.4, 1.7, 1.2$ Hz, 1H), 4.82 (dtd, $J = 17.1, 1.9, 1.3$ Hz, 1H), 4.76 (dt, $J = 8.0, 5.8$ Hz, 1H), 4.56 (dt, $J = 4.7, 1.8$ Hz, 2H), 3.39 (s, 3H), 3.36 (dd, $J = 14.7, 5.7$ Hz, 1H), 3.29 (dd, $J = 14.7, 5.9$ Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 169.5, 139.0, 136.3, 133.5, 131.5, 130.5, 128.7, 128.5, 128.1, 122.0, 119.8, 118.8, 116.3, 110.2, 107.2, 52.8, 52.0, 46.3, 26.8, 23.0; IR (NaCl/thin film): 3435, 3287, 3056, 2950, 2926,

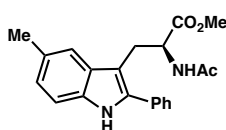
2851, 1744, 1658, 1538, 1500, 1408, 1367, 1219, 1196, 1134; $[\alpha]_D^{25} = +13.8^\circ$ ($c = 2.96$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 377.1860, found 377.1865.

(S)- N_α -Acetyl-4-methyl-2-phenyltryptophan methyl ester (138g)



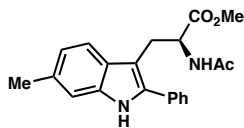
Prepared from 4-methyl-2-phenylindole³⁴ (**137e**, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 30.8 mg (88% yield) of **138g** as a white foam. The enantiomeric excess was determined to be 96% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2 , $\lambda = 254$ nm): $t_R(\text{major}) = 9.9$ min, $t_R(\text{minor}) = 8.9$ min. ^1H NMR (500 MHz, CDCl_3) δ 8.32 (br s, 1H), 7.55 – 7.45 (m, 4H), 7.44 – 7.37 (m, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 7.08 (m, 1H), 6.91 (m, 1H), 5.44 (br d, $J = 7.6$ Hz, 1H), 4.63 (td, $J = 8.2, 5.0$ Hz, 1H), 3.69 – 3.45 (m, 2H), 3.44 (s, 3H), 2.78 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.3, 169.7, 136.3, 136.1, 133.1, 130.5, 129.2, 128.9, 128.3, 126.9, 122.5, 122.3, 109.0, 107.6, 54.2, 52.1, 27.6, 22.8, 20.5; IR (NaCl/thin film): 3295, 3052, 2952, 1741, 1659, 1602, 1547, 1514, 1492, 1449, 1372, 1218; $[\alpha]_D^{25} = -29.0^\circ$ ($c = 0.63$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 351.1703, found 351.1698.

(S)- N_α -Acetyl-5-methyl-2-phenyltryptophan methyl ester (138h)

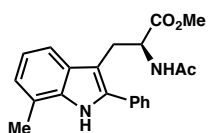


Prepared from 5-methyl-2-phenylindole²⁹ (**137f**, 42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 58.0 mg (83% yield) of **138h** as a white foam. The enantiomeric excess was determined to be 95% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm): $t_R(\text{major}) =$

4.9 min, $t_R(\text{minor}) = 6.4$ min. ^1H NMR (500 MHz, CDCl_3) δ 8.12 (br s, 1H), 7.54 (ddd, $J = 10.1, 6.1, 4.2$ Hz, 2H), 7.50 – 7.43 (m, 2H), 7.40 – 7.33 (m, 2H), 7.24 (d, $J = 8.3$ Hz, 1H), 7.06 – 7.00 (m, 1H), 5.78 (br d, $J = 8.1$ Hz, 1H), 4.83 (dt, $J = 8.1, 5.4$ Hz, 1H), 3.53 – 3.51 (m, 2H), 3.31 (s, 3H), 2.46 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1, 169.5, 136.1, 134.0, 133.3, 129.7, 129.2, 129.1, 128.2, 128.0, 124.1, 118.6, 110.6, 106.3, 52.7, 51.2, 26.5, 22.8, 21.5; IR (NaCl/thin film): 3379, 3365, 2948, 1737, 1658, 1439, 1372, 1306, 1217 cm^{-1} ; $[\alpha]_D^{25} = +33.8^\circ$ ($c = 0.26$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 351.1703, found 351.1680.

(S)-*N*_α-Acetyl-6-methyl-2-phenyltryptophan methyl ester (138i)

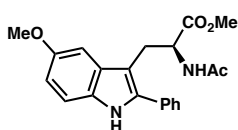
Prepared from 6-methyl-2-phenylindole³⁴ (**137g**, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 27.9 mg (80% yield) of **138i** as a colorless oil. The enantiomeric excess was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): *t*_R(major) = 9.1 min, *t*_R(minor) = 10.1 min. ¹H NMR (500 MHz, CDCl₃) δ 8.01 (br s, 1H), 7.55 (ddd, *J* = 5.8, 4.0, 2.1 Hz, 2H), 7.48 – 7.44 (m, 3H), 7.39 – 7.33 (m, 1H), 7.14 (s, 1H), 6.97 (dd, *J* = 8.3, 1.5 Hz, 1H), 5.78 (br d, *J* = 7.8 Hz, 1H), 4.83 (dt, *J* = 8.0, 5.4 Hz, 1H), 3.55 – 3.49 (m, 2H), 3.30 (s, 3H), 2.47 (s, 3H), 1.67 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 172.1, 169.6, 136.1, 135.2, 133.3, 132.4, 129.1, 128.2, 127.9, 127.3, 121.8, 118.5, 110.9, 106.5, 52.7, 52.0, 26.6, 22.9, 21.7; IR (NaCl/thin film): 3292, 3052, 2958, 2908, 1741, 1658, 1545, 1530, 1511, 1446, 1375, 1216; [α]_D²⁵ = +39.3° (*c* = 0.38, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 351.1703, found 351.1698.

(S)-*N*_α-Acetyl-7-methyl-2-phenyltryptophan methyl ester (138j)

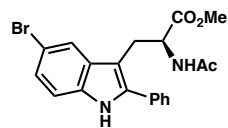
Prepared from 7-methyl-2-phenylindole³⁴ (**137h**, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 33.0 mg (94% yield) of **138j** as a white foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO₂, λ = 254 nm): *t*_R(major) = 5.6 min, *t*_R(minor) = 5.0 min. ¹H NMR (500 MHz, CDCl₃) δ 8.23 (br s, 1H), 7.61 – 7.54 (m, 2H), 7.51 – 7.45 (m, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.11 – 7.04 (m, 1H),

7.03 – 6.97 (m, 1H), 5.79 (br d, $J = 8.1$ Hz, 1H), 4.82 (dt, $J = 8.1, 5.7$ Hz, 1H), 2.55 (dd, $J = 12.5, 3.1$ Hz, 1H), 3.51 (dd, $J = 12.5, 3.1$ Hz, 1H), 3.30 (s, 3H), 2.50 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1, 169.6, 135.8, 135.3, 133.3, 129.1, 128.9, 128.4, 128.0, 123.1, 120.20, 120.18, 116.5, 107.1, 52.7, 51.9, 26.6, 22.8, 16.6; IR (NaCl/thin film): 3283, 3053, 2950, 1736, 1659, 1518, 1438, 1372, 1306, 1266, 1219, 1137, 1043; $[\alpha]_{\text{D}}^{25} = +26.5^\circ$ ($c = 0.20$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 351.1703, found 351.1708.

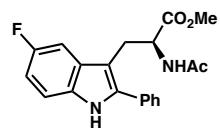
(*S*)-*N*_α-Acetyl-5-methoxy-2-phenyltryptophan methyl ester (138k**)**



Prepared from 5-methoxy-2-phenylindole³⁴ (**137i**, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 62.0 mg (85% yield) of **138k** as a colorless oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm): t_{R} (major) = 4.7 min, t_{R} (minor) = 6.5 min. ^1H NMR (500 MHz, CDCl_3) δ 8.24 (br s, 1H), 7.58 – 7.49 (m, 2H), 7.50 – 7.41 (m, 2H), 7.36 (dd, $J = 7.4, 7.4$ Hz, 1H), 7.24 (d, $J = 8.7$ Hz, 1H), 7.05 (d, $J = 2.3$ Hz, 1H), 6.90 – 6.80 (m, 1H), 5.82 (br d, $J = 7.9$ Hz, 1H), 4.82 (td, $J = 7.9, 5.4$ Hz, 1H), 3.87 (s, 3H), 3.49 (m, 2H), 3.29 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 169.6, 154.4, 136.7, 133.2, 130.8, 129.8, 129.1, 128.2, 128.0, 112.7, 111.7, 106.5, 100.5, 55.9, 52.7, 52.0, 26.6, 22.9; IR (NaCl/thin film): 3291, 3057, 2926, 1739, 1652, 1558, 1539, 1520, 1483, 1455, 1374, 1218, 1178; $[\alpha]_{\text{D}}^{25} = +32.6^\circ$ ($c = 0.93$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 367.1652, found 367.1658.

(S)-*N*_α-Acetyl-5-bromo-2-phenyltryptophan methyl ester (138l)

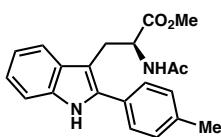
Prepared from 5-bromo-2-phenylindole³⁵ (**137j**, 54.0 mg, 0.20 mmol) with 1.6 equiv SnCl₄ following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 49.5 mg (60% yield) of **138l** as a white foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): *t*_R(major) = 5.3 min, *t*_R(minor) = 7.9 min. ¹H NMR (500 MHz, CDCl₃) δ 8.42 (br s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 7.28 – 7.24 (m, 1H), 7.22 – 7.18 (m, 1H), 5.75 (br d, *J* = 8.1 Hz, 1H), 4.82 (dt, *J* = 8.1, 5.7 Hz, 1H), 3.53 (dd, *J* = 14.9, 5.5 Hz, 1H), 3.46 (dd, *J* = 14.9, 4.8 Hz, 1H), 3.36 (s, 3H), 1.63 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.9, 169.6, 137.2, 134.2, 132.6, 131.1, 129.2, 128.3, 128.2, 125.2, 121.6, 113.1, 112.4, 106.4, 52.6, 52.1, 26.5, 22.8; IR (NaCl/thin film): 3417, 3369, 3282, 1734, 1654, 1521, 1466, 1437, 1374, 1215; [α]_D²⁵ = +47.2° (*c* = 1.04, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 415.0652, found 415.0653.

(S)-*N*_α-Acetyl-5-fluoro-2-phenyltryptophan methyl ester (138m)

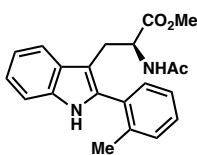
Prepared from 5-fluoro-2-phenylindole³⁴ (**137k**, 42.0 mg, 0.20 mmol) with 1.6 equiv SnCl₄ following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 44.7 mg (63% yield) of **138m** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): *t*_R(major) = 3.8 min, *t*_R(minor) = 5.2 min. ¹H NMR (500 MHz, CDCl₃) δ 8.30 (br s, 1H), 7.60 – 7.52 (m, 2H), 7.50 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 7.27 – 7.24 (m,

1H), 7.21 (dd, $J = 9.8, 2.6$ Hz, 1H), 6.94 (ddd, $J = 9.0, 9.0, 2.6$ Hz, 1H), 5.77 (br d, $J = 7.8$ Hz, 1H), 4.82 (dt, $J = 8.1, 5.4$ Hz, 1H), 3.53 (dd, $J = 14.9, 5.6$ Hz, 1H), 3.47 (dd, $J = 14.9, 5.0$ Hz, 1H), 3.35 (s, 3H), 1.64 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.7, 169.8, 168.3, 135.6, 134.2, 132.5, 131.9, 128.6, 123.5, 121.8, 119.7, 118.2, 110.8, 107.4, 52.9, 52.4, 37.0, 27.0, 25.3, 23.1; IR (NaCl/thin film): 3275, 3062, 2952, 1733, 1652, 1584, 1558, 1539, 1520, 1486, 1456, 1436, 1374, 1266, 1217, 1180; $[\alpha]_{\text{D}}^{25} = +49.9^\circ$ ($c = 1.25$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 355.1452, found 355.1455.

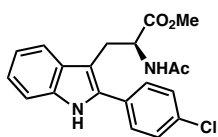
(*S*)-*N* α -Acetyl-2-(4-methylphenyl)tryptophan methyl ester (138n**)**



Prepared from 2-(4-methylphenyl)indole³⁶ (**137l**, 41.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 60.1 mg (86% yield) of **138n** as a white foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm). $t_{\text{R}}(\text{major}) = 6.6$ min, $t_{\text{R}}(\text{minor}) = 8.8$ min. ^1H NMR (500 MHz, CDCl_3) δ 8.20 (br s, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.45 (d, $J = 8.1$, 2H), 7.34 (d, $J = 8.1$, 1H), 7.28 (d, $J = 8.1$, 2H), 7.19 (ddd, $J = 7.8, 7.1, 1.2$ Hz, 1H), 7.15 – 7.09 (m, 1H), 5.77 (br d, $J = 8.1$, 1H), 4.82 (dt, $J = 7.8, 5.5$ Hz, 1H), 3.54 (dd, $J = 13.1, 4.0$ Hz, 1H), 3.50 (dd, $J = 13.1, 3.7$ Hz, 1H), 3.33 (s, 3H), 2.40 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 169.6, 138.0, 136.1, 135.6, 130.2, 129.8, 129.4, 128.1, 122.3, 119.9, 118.7, 110.9, 106.4, 52.8, 52.0, 26.6, 22.8, 21.2; IR (NaCl/thin film): 3365, 3271, 3052, 2951, 1737, 1657, 1519, 1460, 1439, 1375, 1305, 1217 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = 43.2^\circ$ ($c = 0.74$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 351.1703, found 351.1700.

(S)-*N*_α-Acetyl-2-(2-methylphenyl)tryptophan methyl ester (138o)

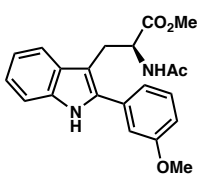
Prepared from 2-(2-methylphenyl)indole³⁷ (**137m**, 21.0 mg, 0.1 mmol) following General Procedure 2. The crude residue was purified by flash chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 9.2 mg (26% yield) of **138o**. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO₂, λ = 254 nm): *t*_R(major) = 4.3 min, *t*_R(minor) = 4.9 min. ¹H NMR (500 MHz, CDCl₃) δ 8.03 (br s, 1H), 7.62 – 7.55 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 7.22 (ddd, *J* = 8.1, 5.6, 2.1 Hz, 1H), 7.16 (ddd, *J* = 7.1, 5.6, 1.1 Hz, 1H), 5.71 (br d, *J* = 7.9 Hz, 1H), 4.82 – 4.68 (dt, *J* = 7.9, 5.4 Hz, 1H), 3.38 – 3.29 (m, 4H), 3.28 – 3.16 (m, 1H), 2.28 (s, 3H), 1.73 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 169.6, 137.3, 135.8, 135.5, 132.1, 130.9, 130.8, 128.9, 128.7, 126.0, 122.3, 119.9, 118.8, 110.8, 107.6, 52.8, 52.0, 26.6, 23.0, 20.0; IR (NaCl/thin film): 3385, 3271, 3062, 2924, 2853, 1734, 1653, 1559, 1539, 1521, 1457, 1437, 1374; [α]_D²⁵ = +21.5° (*c* = 0.29, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 351.1703, found 351.1709.

(S)-*N*_α-Acetyl-2-(4-chlorophenyl)tryptophan methyl ester (138p)

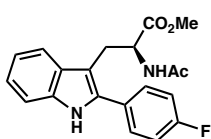
Prepared from 2-(4-chlorophenyl)indole³⁴ (**137n**, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 55.2 mg (75% yield) of **138p** as a colorless oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): *t*_R(major) = 6.1 min, *t*_R(minor) = 7.0 min. ¹H NMR (500 MHz, CDCl₃) δ 8.45 (br s, 1H), 7.56 (d, *J* = 8.1 Hz,

1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.33 (ddd, $J = 8.1, 8.1, 1.0$ Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 (ddd, $J = 8.0, 7.1, 1.1$ Hz, 1H), 5.85 (br d, $J = 8.1$ Hz, 1H), 4.83 (dt, $J = 8.1, 5.5$ Hz, 1H), 3.55 – 3.38 (m, 2H), 3.34 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1, 169.6, 135.8, 134.6, 133.9, 131.5, 129.4, 129.3, 122.7, 120.1, 118.9, 111.1, 107.1, 52.8, 52.1, 29.6, 26.7, 22.9; IR (NaCl/thin film): 3280, 3058, 2948, 1737, 1657, 1519, 1487, 1458, 1439, 1373, 1310, 1216, 1093 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +40.8^\circ$ ($c = 0.96$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 371.1157, found 371.1158.

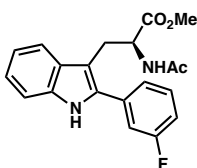
(S)- N_α -Acetyl-2-(3-methoxyphenyl)tryptophan methyl ester (138q)



Prepared from 2-(3-methoxyphenyl)indole³⁸ (**137o**, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 65.0 mg (88% yield) of **138q** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 5.9$ min, $t_{\text{R}}(\text{minor}) = 7.6$ min. ^1H NMR (500 MHz, CDCl_3) δ 8.40 (br s, 1H), 7.55 (d, $J = 8.1$ Hz, 1H), 7.40 – 7.31 (m, 2H), 7.19 (ddd, $J = 8.1, 7.1, 1.2$ Hz, 1H), 7.16 – 7.10 (m, 2H), 7.08 (dd, $J = 2.6, 1.6$ Hz, 1H), 6.91 (ddd, $J = 8.3, 2.6, 0.8$ Hz, 1H), 5.82 (br d, $J = 7.8$ Hz, 1H), 4.83 (dt, $J = 7.8, 5.5$ Hz, 1H), 3.85 (s, 3H), 3.57 – 3.49 (m, 2H), 3.35 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 169.6, 160.0, 135.8, 135.6, 134.4, 130.2, 129.3, 122.5, 120.6, 119.9, 118.8, 113.8, 113.5, 111.0, 106.7, 55.4, 52.8, 52.0, 26.6, 22.8; IR (NaCl/thin film): 3282, 3058, 2951, 1738, 1658, 1603, 1520, 1462, 1439, 1373, 1218, 1040; $[\alpha]_{\text{D}}^{25} = +40.3^\circ$ ($c = 1.16$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 367.1652, found 367.1656.

(S)-*N*_α-Acetyl-2-(4-fluorophenyl)tryptophan methyl ester (138r)

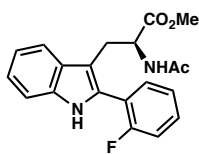
Prepared from 2-(4-fluorophenyl)indole²⁹ (**137p**, 42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc/hexanes) to yield 55.6 mg (78% yield) of **138r** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO₂, λ = 254 nm): *t*_R(major) = 6.1 min, *t*_R(minor) = 6.9 min. ¹H NMR (500 MHz, CDCl₃) δ 8.19 (d, *J* = 47.9 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.54 – 7.51 (m, 2H), 7.36 (ddd, *J* = 8.1, 8.1, 0.9 Hz, 1H), 7.23 – 7.10 (m, 4H), 5.82 (d, *J* = 8.1 Hz, 1H), 4.83 (dt, *J* = 8.1, 5.5 Hz, 1H), 3.55 – 3.40 (m, 2H), 3.34 (s, 3H), 1.71 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 169.5, 135.6, 135.0, 130.1, 130.1, 129.4, 122.7, 120.2, 118.9, 116.2, 116.1, 110.9, 106.9, 52.8, 52.0, 26.7, 22.9.; IR (NaCl/thin film): 3364, 3271, 3061, 2925, 2853, 1738, 1661, 1553, 1505, 1460, 1440, 1373, 1221, 1158; [α]_D²⁵ = +38.2° (*c* = 0.65, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 355.1452, found 355.1460.

(S)-*N*_α-Acetyl-2-(3-fluorophenyl)tryptophan methyl ester (138s)

Prepared from 2-(3-fluorophenyl)indole³⁶ (**137q**, 42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 ethyl acetate/hexanes) to yield 50.6 mg (76% yield) of **138s** as a white foam. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): *t*_R(major) = 3.8 min, *t*_R(minor) = 4.6 min. ¹H NMR (500 MHz, CDCl₃) δ 8.65 (br s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.33-7.31 (m, 2H), 7.27-7.24

(m, 1H), 7.19 (ddd, $J = 8.2, 7.0, 1.0$ Hz, 1H), 7.13 (ddd, $J = 7.9, 7.0, 1.0$ Hz, 1H), 7.07 – 7.03 (m, 1H), 5.89 (br d, $J = 8.1$ Hz, 1H), 4.84 (dt, $J = 8.1, 5.5$ Hz, 1H), 3.53 (dd, $J = 13.6, 4.7$ Hz, 1H), 3.49 (dd, $J = 13.6, 4.2$ Hz, 1H), 3.34 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1, 169.7, 162.9 (d, $J_{\text{C-F}} = 246.3$ Hz), 135.8, 135.2 (d, $J_{\text{C-F}} = 7.5$ Hz), 134.5 (d, $J_{\text{C-F}} = 2.5$ Hz), 130.6 (d, $J_{\text{C-F}} = 8.8$ Hz), 129.2, 123.9 (d, $J_{\text{C-F}} = 3.8$ Hz), 122.8, 120.0, 118.9, 115.1 (d, $J_{\text{C-F}} = 21.2$ Hz), 114.7 (d, $J_{\text{C-F}} = 21.2$ Hz), 111.1, 107.3, 52.8, 52.0, 26.7, 22.8; IR (NaCl/thin film): 3370, 3275, 3060, 2952, 1735, 1655, 1614, 1585, 1522, 1438, 1374, 1266, 1200, 1155 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +37.6^\circ$ ($c = 1.21$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 355.1452, found 355.1450.

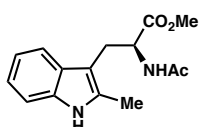
(S)- N_α -Acetyl-2-(2-fluorophenyl)tryptophan methyl ester (138t)



Prepared from 2-(2-fluorophenyl)indole (**137r**, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 12.4 mg (35% yield) of **138t**. The enantiomeric excesses was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 9.5$ min, $t_{\text{R}}(\text{minor}) = 8.4$ min. ^1H NMR (500 MHz, CDCl_3) δ 8.28 (s, 1H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.55 (ddd, $J = 7.5, 7.5, 1.8$ Hz, 1H), 7.45 – 7.35 (m, 2H), 7.29 (ddd, $J = 7.5, 7.5, 1.2$ Hz, 1H), 7.25 – 7.20 (m, 1H), 7.19 – 7.10 (m, 1H), 5.83 (br d, $J = 7.6$ Hz, 1H), 4.85 (dt, $J = 7.9, 5.5$ Hz, 1H), 3.55 – 3.39 (m, 2H), 3.36 (s, 2H), 1.73 (s, 3H).; ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 169.5, 159.8 (d, $J_{\text{C-F}} = 246.3$ Hz), 135.9, 131.4 (d, $J_{\text{C-F}} = 3.8$ Hz), 130.2 (d, $J_{\text{C-F}} = 8.8$ Hz), 129.73, 128.65, 124.8 (d, $J_{\text{C-F}} = 3.8$ Hz), 122.84, 120.6 (d, $J_{\text{C-F}} = 15.0$ Hz), 120.0, 119.0, 116.4 (d, $J_{\text{C-F}} = 21.3$ Hz), 111.0, 108.8, 52.5, 52.0, 26.8, 26.8, 22.9; IR

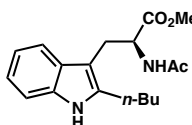
(NaCl/thin film): 3275, 3058, 2925, 2853, 1734, 1653, 1523, 1490, 1457, 1437, 1374, 1245, 1216, 1130, 1104; $[\alpha]_{\text{D}}^{25} = +39.8^\circ$ ($c = 0.41$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 355.1452, found 355.1463.

(S)- N_α -Acetyl-2-methyltryptophan methyl ester (138d)



Prepared from 2-methylindole (**137b**, 26.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (50:50 to 100:0 EtOAc:hexanes) to yield 31.0 mg (61% yield) of **138d** as a white foam. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 3.9$ min, $t_{\text{R}}(\text{minor}) = 2.7$ min. $[\alpha]_{\text{D}}^{25} = +25.9^\circ$ ($c = 0.99$, CHCl_3). Spectral data matches that reported in the literature.³³

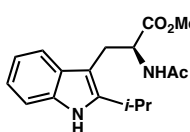
(S)- N_α -Acetyl-2-butyltryptophan methyl ester (138u)



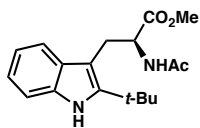
Prepared from 2-butylindole³⁹ (**137s**, 35.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 45.8 mg (72% yield) of **138u** as a colorless oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 5.1$ min, $t_{\text{R}}(\text{minor}) = 4.2$ min. ^1H NMR (500 MHz, CDCl_3) δ 8.03 (br s, 1H), 7.46 – 7.40 (m, 1H), 7.31 – 7.24 (m, 1H), 7.15 – 6.99 (m, 2H), 6.00 (br d, $J = 7.8$ Hz, 1H), 4.88 (dt, $J = 8.1$, 5.7 Hz, 1H), 3.65 (s, 3H), 3.26 (dd, $J = 5.7$, 0.9 Hz, 2H), 2.69 (td, $J = 7.8$ 2.2 Hz, 2H), 1.93 (s, 3H), 1.66 – 1.57 (m, 2H), 1.45 – 1.31 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR

(125 MHz, CDCl₃) δ 172.6, 169.6, 137.4, 135.2, 128.8, 121.3, 119.5, 117.9, 110.4, 105.26, 105.29, 53.0, 52.3, 31.8, 26.8, 25.7, 23.2, 22.6, 13.9; IR (NaCl/thin film): 3296, 3058, 2955, 2871, 1737, 1658, 1562, 1530, 1463, 1439, 1376, 1217, 1129; $[\alpha]_D^{25} = -16.3^\circ$ ($c = 0.83$, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 317.1860, found 317.1855.

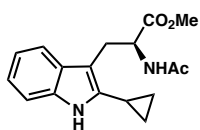
(S)-N_α-Acetyl-2-isopropyltryptophan methyl ester (138v)



Prepared from 2-isopropylindole⁴⁰ (**137t**, 32.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 39.6 mg (66% yield) of **138v** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 15% IPA in CO₂, $\lambda = 254$ nm). t_R (major) = 6.4 min, t_R (minor) = 5.6 min. ¹H NMR (500 MHz, CDCl₃) δ 8.16 (br s, 1H), 7.48 – 7.41 (m, 1H), 7.30 – 7.27 (m, 1H), 7.15 – 7.02 (m, 2H), 6.04 (br d, $J = 8.0$ Hz, 1H), 4.89 (dt, $J = 8.1$, 5.7 Hz, 1H), 3.66 (s, 3H), 3.29 (dd, $J = 12.7$, 4.0 Hz, 1H), 3.26 (dd, $J = 12.7$, 3.4 Hz, 1H), 3.18 (m, 1H), 1.93 (s, 3H), 1.31 (d, $J = 3.3$ Hz, 3H), 1.30 (d, $J = 3.3$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.6, 169.7, 142.7, 135.2, 128.7, 121.3, 119.5, 117.9, 110.6, 103.6, 53.0, 52.3, 26.7, 25.3, 23.2, 23.0; IR (NaCl/thin film): 3305, 2962, 1734, 1700, 1653, 1559, 1539, 1506, 1457, 1436, 1374, 1299, 1217 cm⁻¹; $[\alpha]_D^{25} = +22.2^\circ$ ($c = 0.35$, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 303.1703, found 303.1709.

(S)-*N*_α-Acetyl-2-(tert-butyl)tryptophan methyl ester (138w)

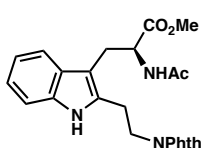
Prepared from 2-(tert-butyl)indole³³ (**137u**, 35.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 18.1 mg (29% yield) of **138w** as a yellow oil. The enantiomeric excess was determined to be 84% by chiral SFC analysis (OD-H, 2.5 mL/min, 10% IPA in CO₂, λ = 254 nm): *t*_R(major) = 12.8 min, *t*_R(minor) = 14.2 min. ¹H NMR (500 MHz, CDCl₃) δ 8.07 (br s, 1H), 7.47 (dd, *J* = 14.0, 7.1 Hz, 1H), 7.27 (dd, *J* = 5.8, 4.8 Hz, 1H), 7.15 – 7.03 (m, 2H), 6.06 (br d, *J* = 7.4 Hz, 1H), 4.84 (m, 1H), 3.54 (s, 3H), 3.38 – 3.29 (m, 2H), 1.86 (s, 3H), 1.49 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 173.2, 169.6, 143.4, 133.9, 129.8, 121.3, 119.4, 117.7, 110.4, 104.3, 53.7, 52.2, 33.2, 30.7, 28.6, 23.0; IR (NaCl/thin film): 3326, 3047, 2961, 2918, 2868, 1734, 1653, 1539, 1457, 1436, 1374, 1303, 1254, 1211, 1128; [α]_D²⁵ = +12.4° (*c* = 0.36, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 317.1860, found 317.1856.

(S)-*N*_α-Acetyl-2-cyclopropyltryptophan methyl ester (138x)

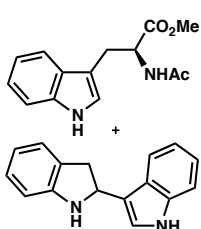
Prepared from 2-cyclopropylindole⁴¹ (**137v**, 16.0 mg, 0.10 mmol) following General Procedure 2 except that 1.0 equiv methyl 2-acetamidoacrylate (**91a**) was employed. The crude residue was purified by silica gel chromatography (50:50 EtOAc:hexanes) to yield 4.6 mg (24% yield) of **138x** as a colorless oil. The enantiomeric excess was determined to be 75% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm). *t*_R(major) = 2.6 min *t*_R(minor) = 2.3 min. ¹H NMR (500 MHz, CDCl₃) δ 7.65 (br s, 1H), 7.41 (ddt, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.24 (ddd, *J* = 7.9, 1.3, 0.8 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.1, 1.5 Hz, 1H), 7.10 – 7.03 (m,

1H), 6.03 (br d, $J = 8.0$ Hz, 1H), 4.93 (dt, $J = 8.0, 5.6$ Hz, 1H), 3.67 (s, 3H), 3.36 (d, $J = 5.6$ Hz, 2H), 2.02 (tt, $J = 8.4, 5.3$ Hz, 1H), 1.94 (s, 3H), 1.05 – 1.01 (m, 2H), 0.79 – 0.76 (m, 2H).; ^{13}C NMR (125 MHz, CDCl_3) δ 172.6, 169.6, 137.6, 134.6, 129.1, 121.5, 119.7, 117.6, 110.4, 106.9, 53.0, 52.4, 26.8, 23.3, 7.4, 7.10, 7.06.; IR (NaCl/thin film): 3297, 3058, 3006, 2952, 2926, 1736, 1654, 1523, 1468, 1439, 1375, 1339, 1309, 1217 cm^{-1} ; HRMS (ESI) calc'd for $[\text{M}+\text{H}]^+$ 301.1547, found 301.1546.

(S)- N_α -Acetyl-2-(ethylphthalimide)tryptophan methyl ester (138y**)**



Prepared from 2-(ethylphthalimide)indole (**137w**, 29.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (70:30 to 100:0 EtOAc:hexanes) to yield 34.6 mg (80% yield) of **138y** as a yellow foam. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 7.3$ min, $t_{\text{R}}(\text{minor}) = 6.3$ min. ^1H NMR (500 MHz, CDCl_3) δ 8.47 (br s, 1H), 7.83 (dd, $J = 5.4, 2.9$ Hz, 2H), 7.72 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.46 (d, $J = 8.1$ Hz, 1H), 7.31 (ddd, $J = 8.1, 8.1, 1.0$ Hz, 1H), 7.13 (ddd, $J = 8.1, 7.1, 1.2$ Hz, 1H), 7.07 (ddd, $J = 10.5, 5.8, 2.2$ Hz, 1H), 6.13 (br d, $J = 8.1$ Hz, 1H), 4.92 (dt, $J = 8.2, 6.0$ Hz, 1H), 4.05 – 3.89 (m, 2H), 3.66 (s, 3H), 3.33 – 2.98 (m, 4H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.7, 169.8, 168.3, 135.6, 134.2, 132.5, 131.9, 128.6, 123.5, 121.8, 119.7, 118.2, 110.8, 107.4, 52.9, 52.4, 37.0, 27.0, 25.3, 23.1; IR (NaCl/thin film): 3369, 3280, 3052, 2948, 1770, 1738, 1711, 1659, 1530, 1438, 1397, 1371; $[\alpha]_{\text{D}}^{25} = +14.8^\circ$ ($c = 0.96$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 355.1452, found 355.1455.

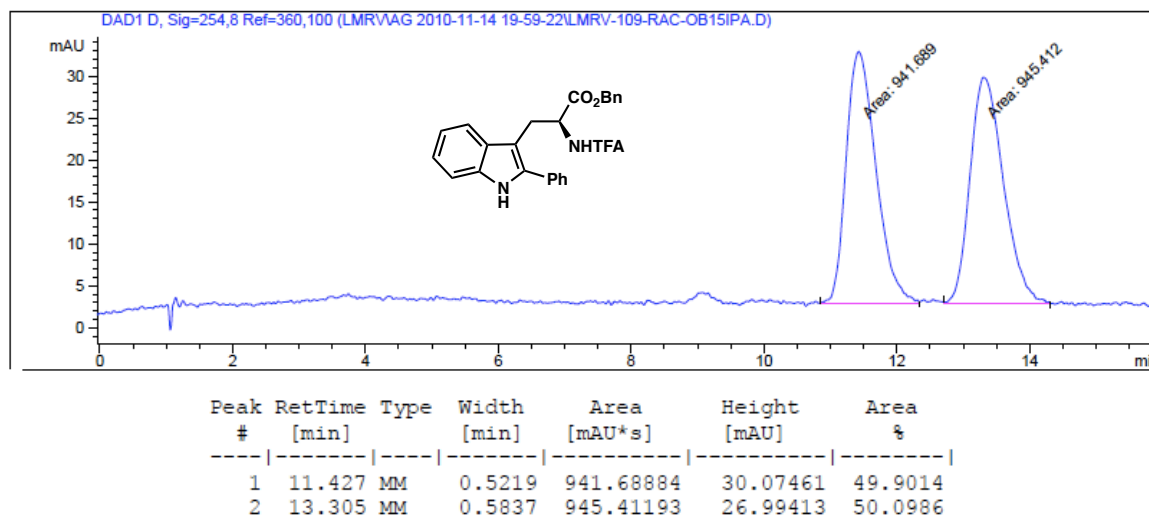
(S)-N α -Acetyltryptophan methyl ester (138z) and indole dimer (170)

Prepared from indole (**163**, 23.4 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 17.9 mg (contains 9 wt % EtOAc, 31% corrected yield) of **138z** as a light pink oil and 7.0 mg (30% yield) of **170** as a light yellow oil. The enantiomeric excess of **138z** was determined to be 67% by chiral SFC analysis (OD-H, 2.5 mL/min, 15% IPA in CO₂, $\lambda = 254$ nm): t_R (major) = 11.4 min, t_R (minor) = 10.6 min. $[\alpha]_D^{25} = +39.3^\circ$ ($c = 0.83$, CHCl₃). Spectral data for both (S)-N α -acetyltryptophan methyl ester⁴² and the indole dimer⁴³ are in agreement with the literature.

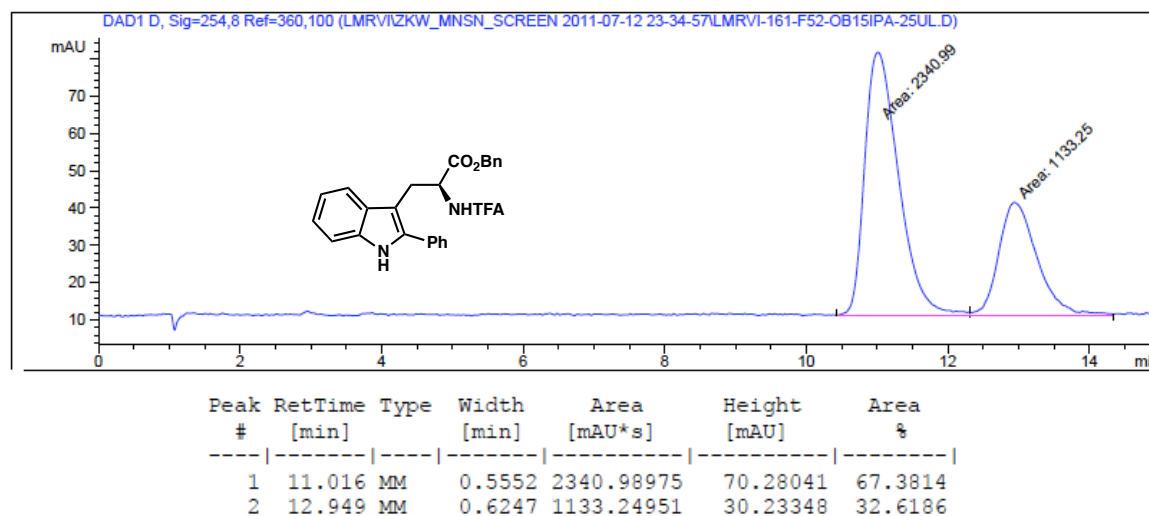
3.4.5 SFC Traces for Racemic and Enantioenriched Tryptophan Derivatives

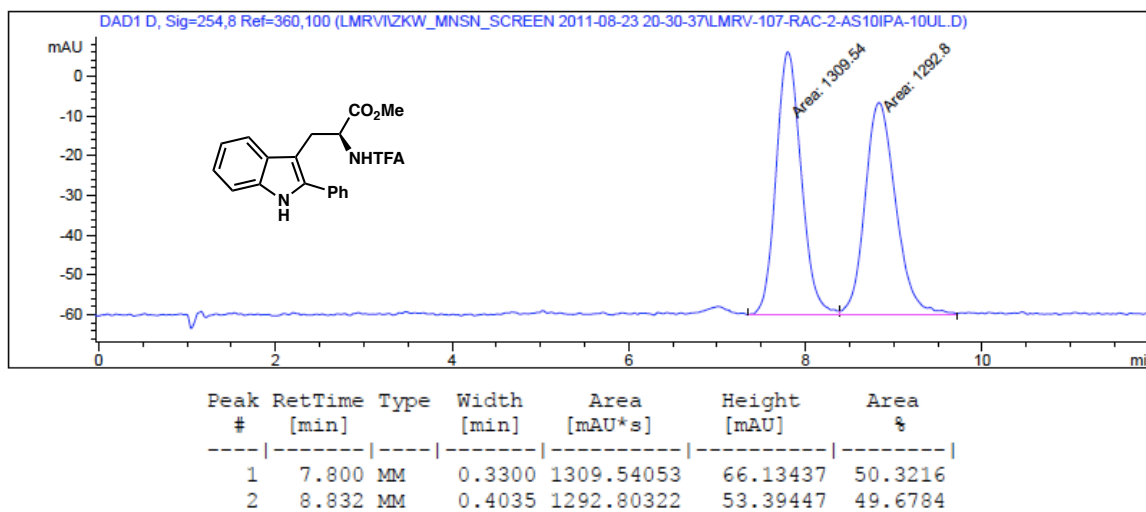
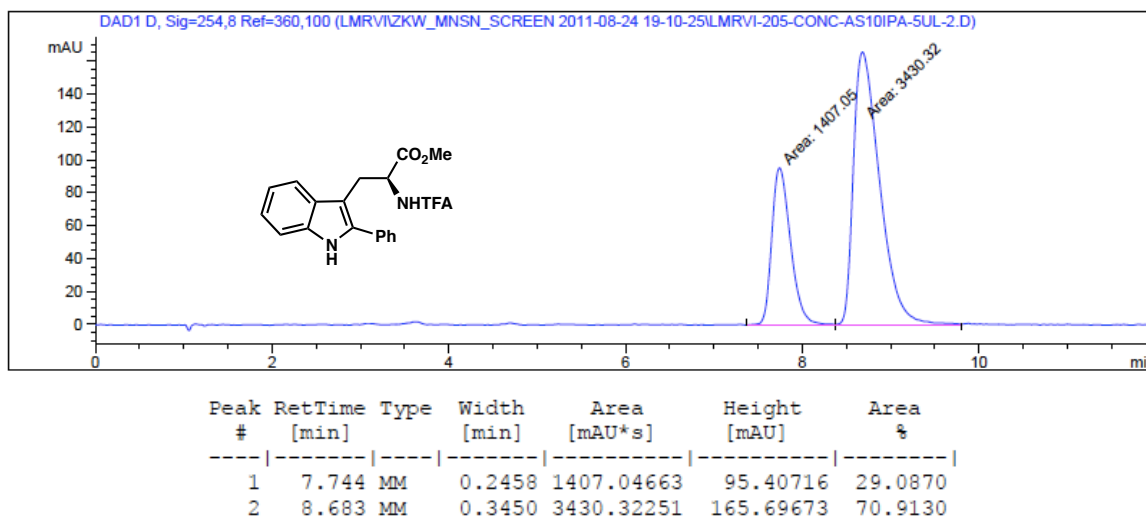
Optimization of Reaction Parameters

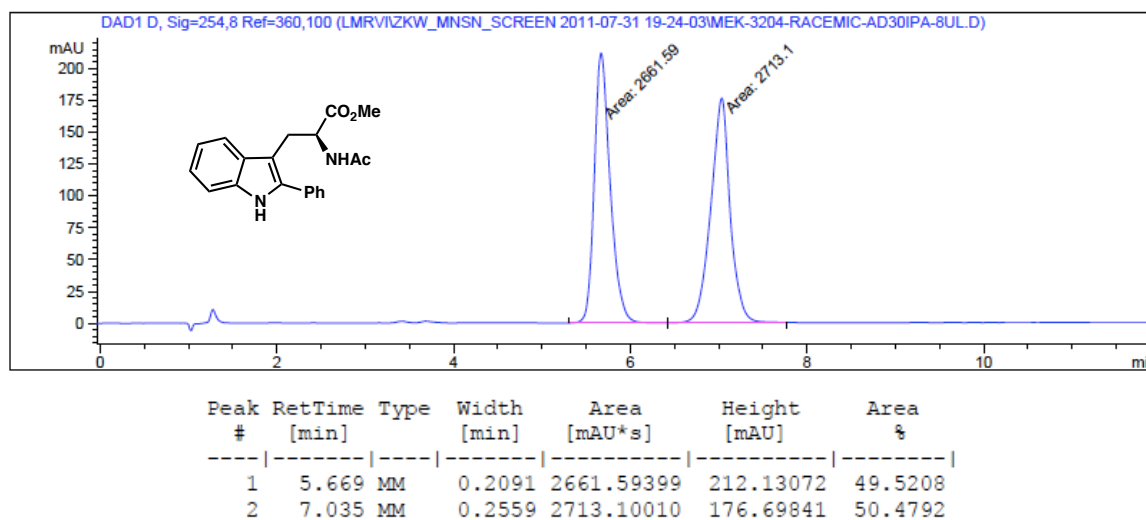
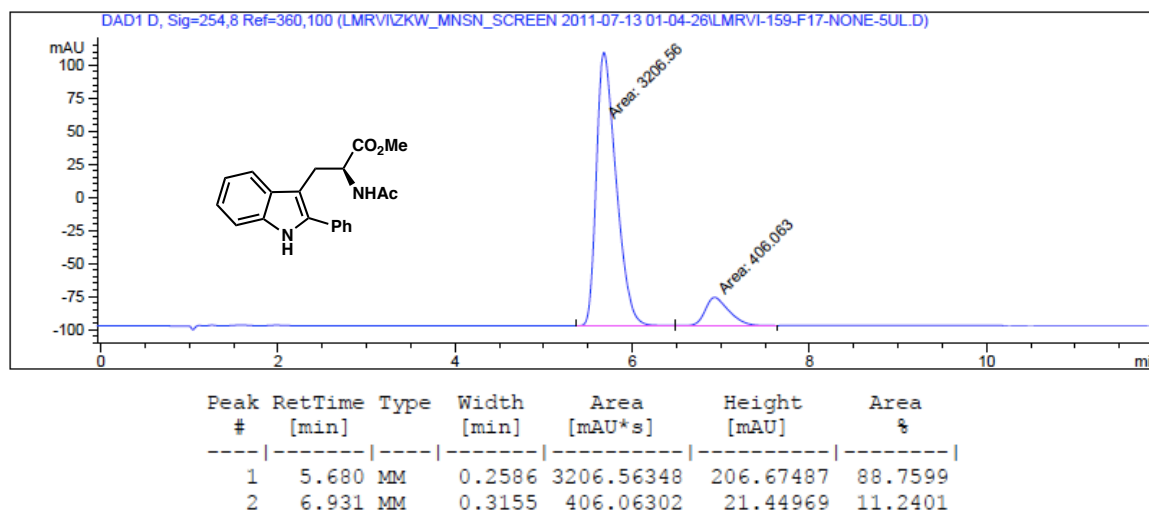
138a (Table 3.2.1, entry 1): racemic



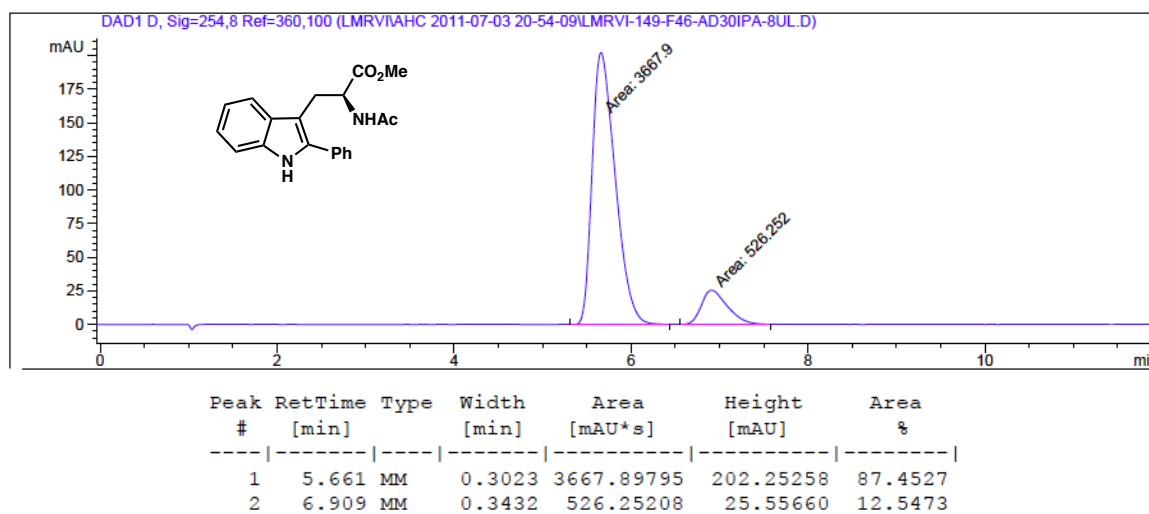
138a (Table 3.2.1, entry 1): enantioenriched, 35% ee



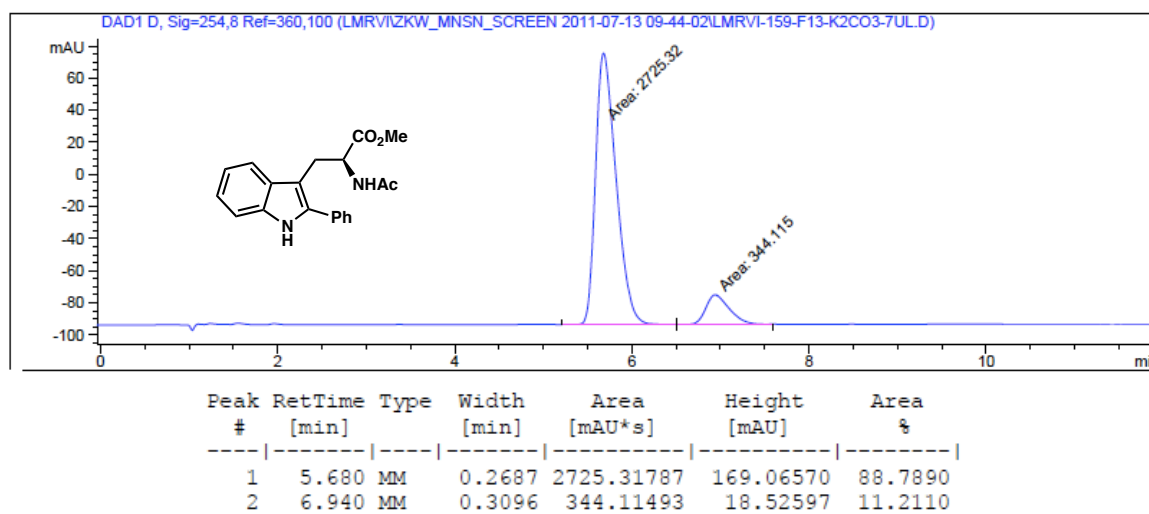
138b (Table 3.2.1, **entry 2**): racemic**138b** (Table 3.2.1, **entry 2**): enantioenriched, 42% ee

138c: racemic**138c** (Table 3.2.1, entry 3, no additive, DCM as solvent): enantioenriched, 78% ee

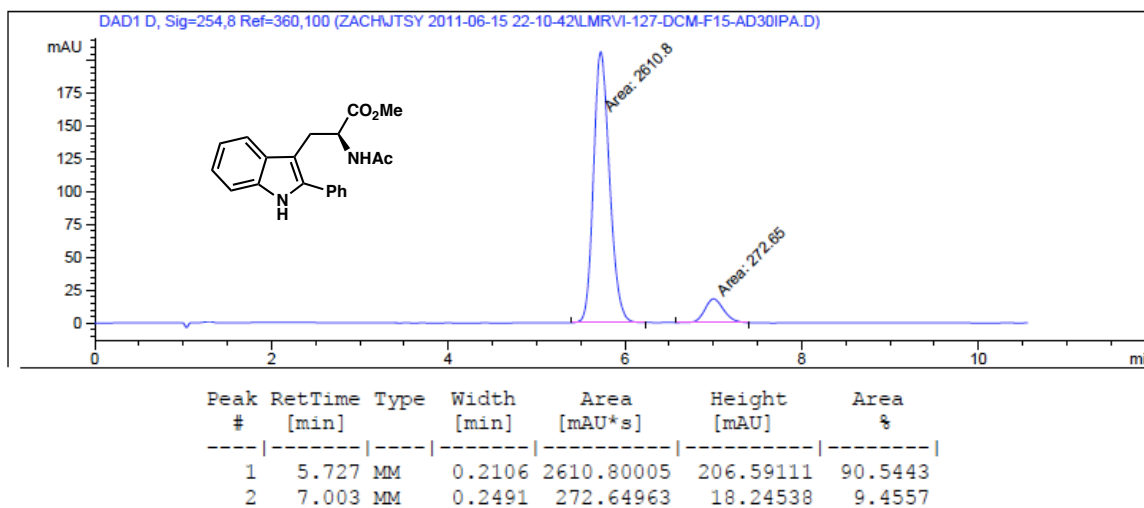
138c (Table 3.2.1, **entry 6**, no additive, 1M NaOH workup): enantioenriched, 75% ee



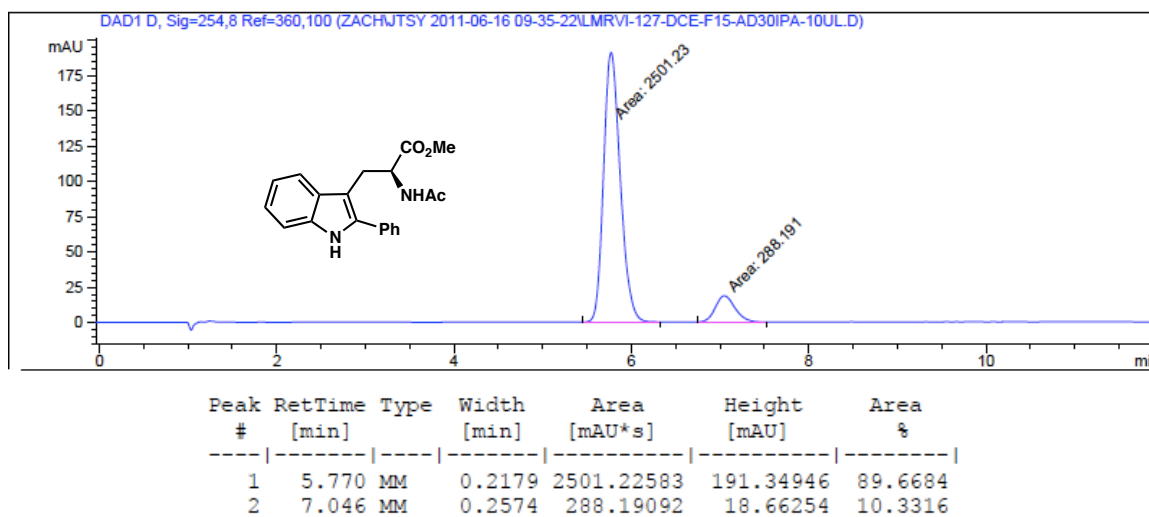
138c (Table 3.2.1, **entry 7**, with K_2CO_3 , DCM as solvent): enantioenriched, 78% ee



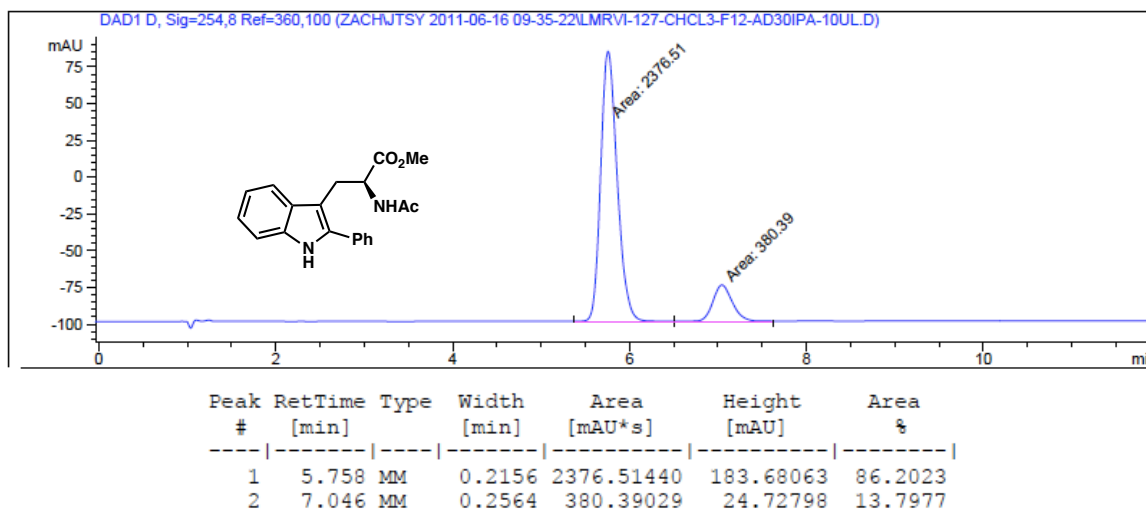
138c (Table 3.2.1, **entry 9**, with 4Å MS, DCM as solvent): enantioenriched, 81% ee



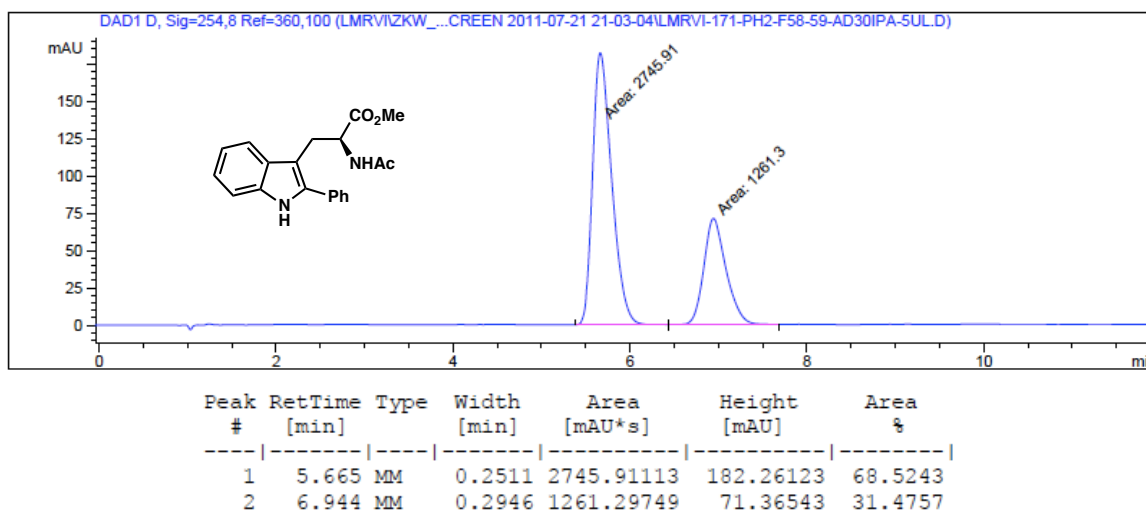
138c (Table 3.2.1, **entry 10**, with 4Å MS, DCE as solvent): enantioenriched, 79% ee



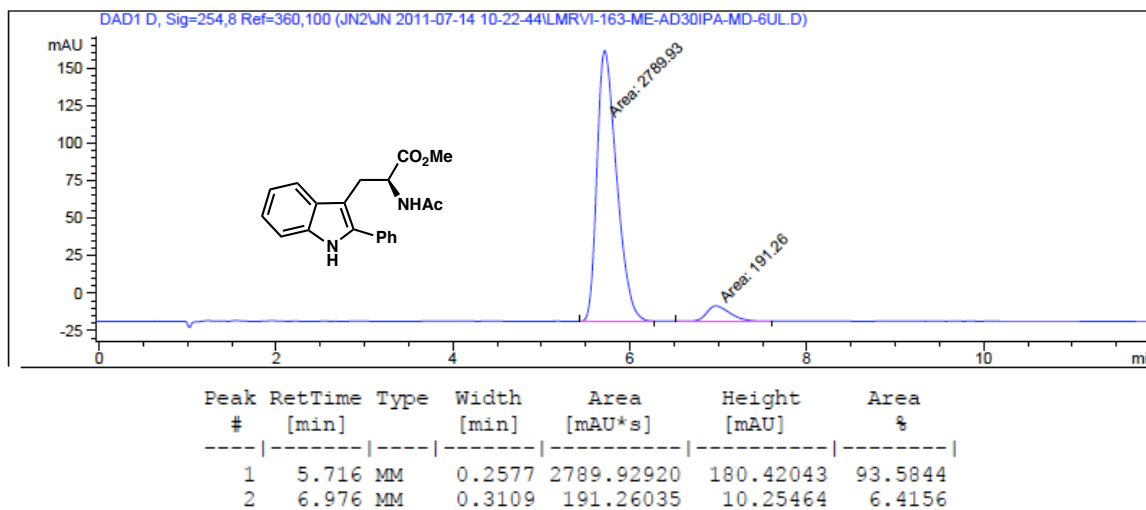
138c (Table 3.2.1, **entry 11**, with 4Å MS, CHCl₃ as solvent): enantioenriched, 72% ee



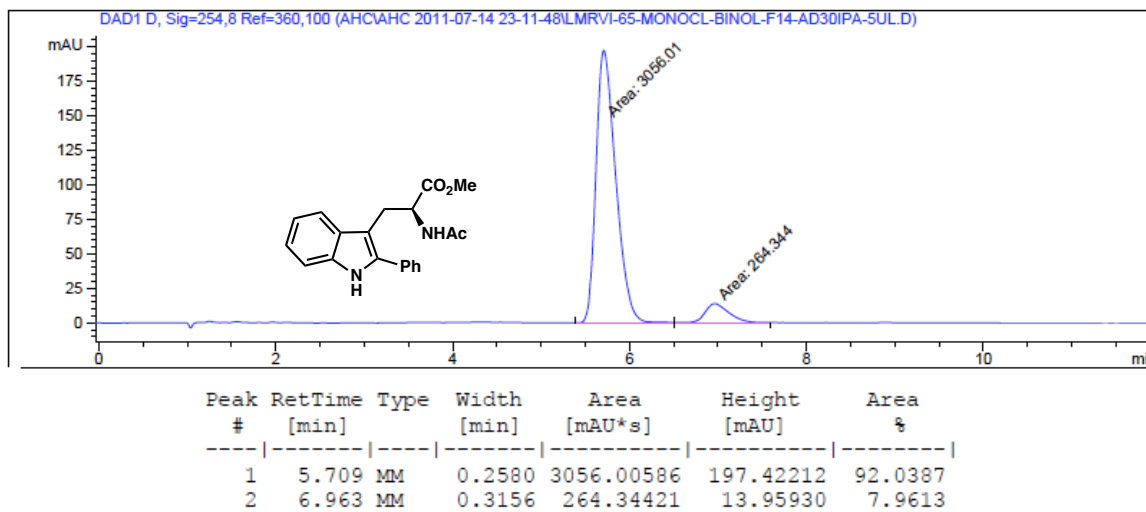
138c (Table 3.2.2, **entry 2**, (*R*)-3,3'-diphenyl-BINOL (**102g**)): enantioenriched, 37% ee



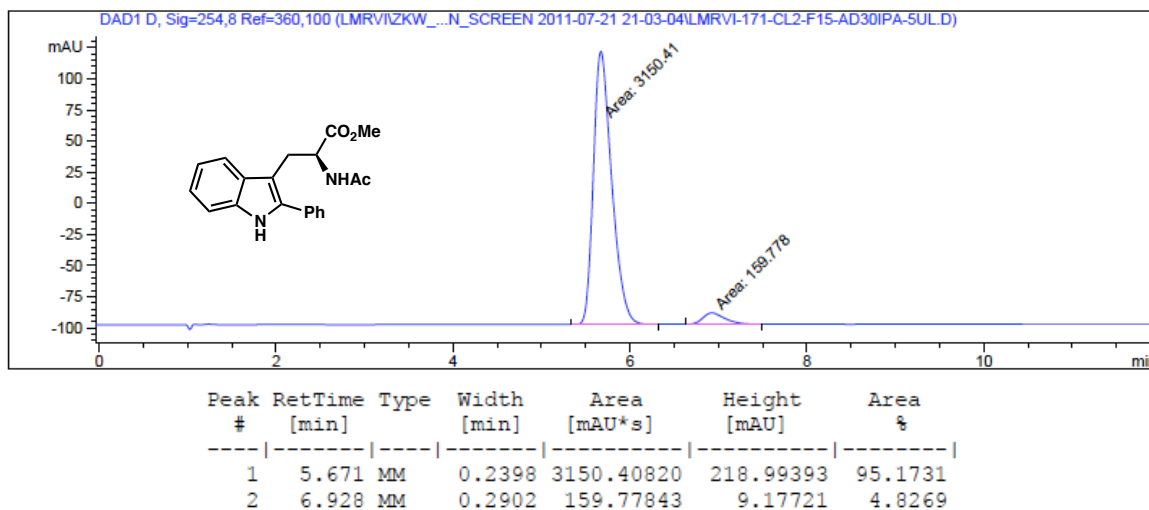
138c (Table 3.2.2, **entry 3**, (*R*)-3,3'-dimethyl-BINOL (**102h**)): enantioenriched, 87% ee



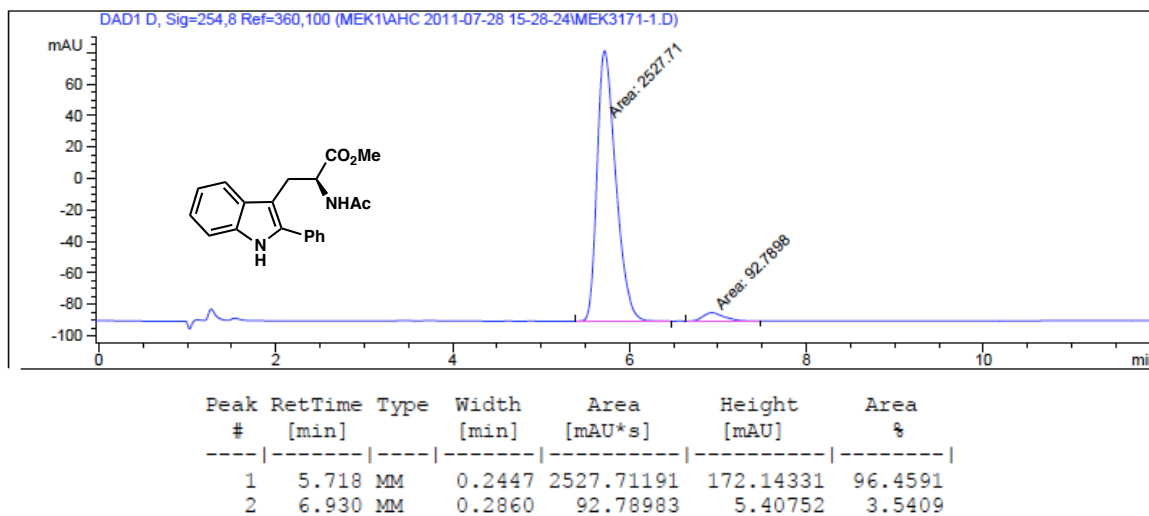
138c (Table 3.2.2, **entry 4**, (*R*)-3-chloro-BINOL (**102i**)): enantioenriched, 84% ee



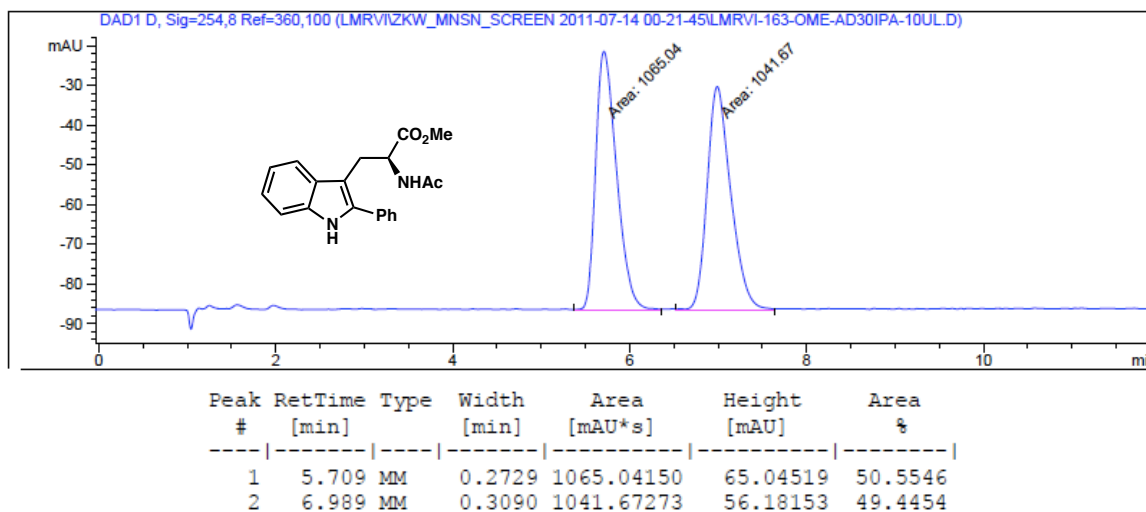
138c (Table 3.2.2, **entry 5**, (*R*)-3,3'-dichloro-BINOL (**102j**)): enantioenriched, 90% ee



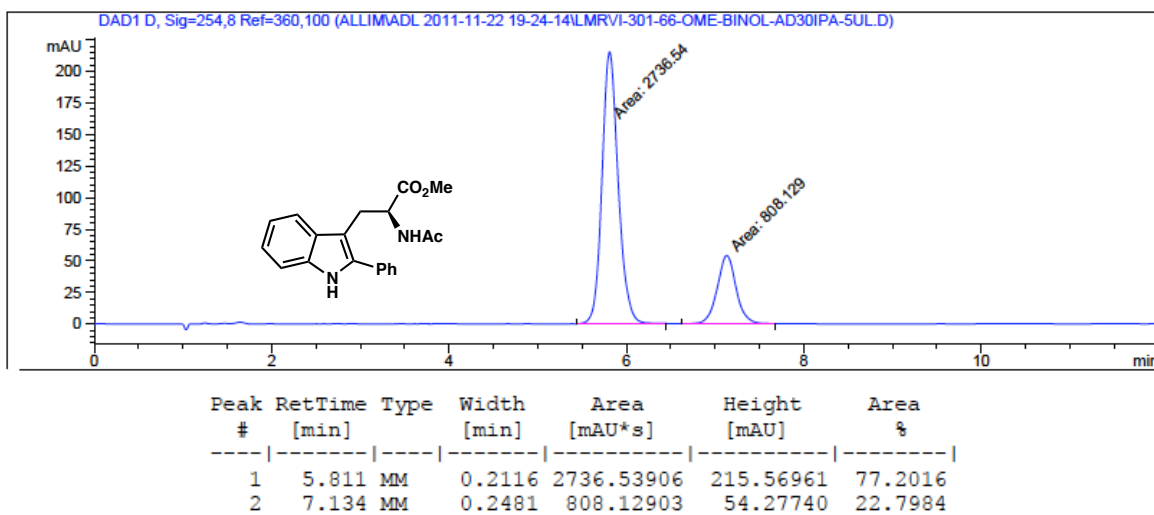
138c (Table 3.2.2, **entry 6**, (*R*)-3,3'-dibromo-BINOL (**102k**)): enantioenriched, 93% ee



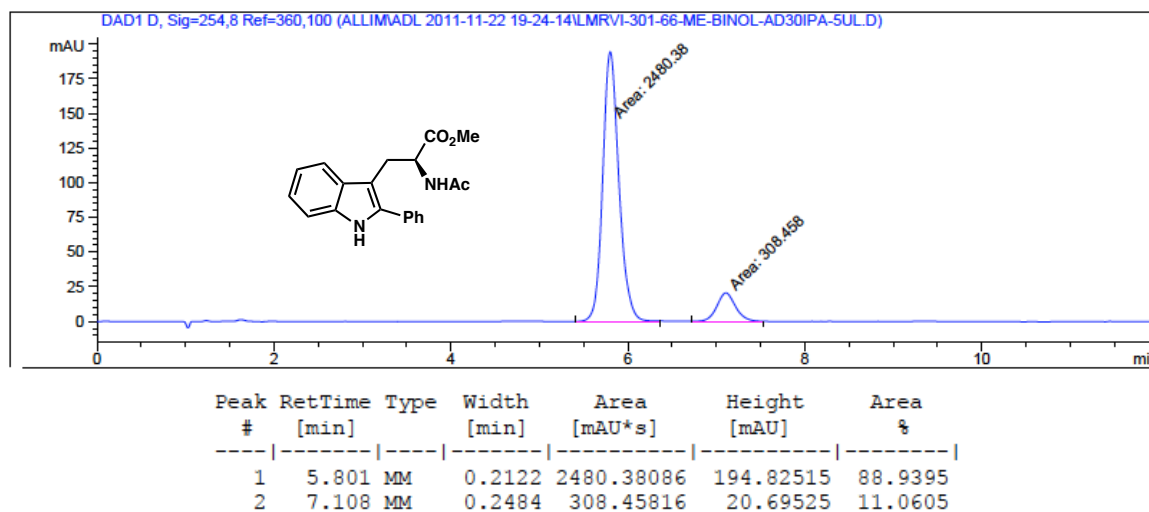
138c (Table 3.2.2, **entry 7**, (*R*)-3,3'-dimethoxy-BINOL (**102l**)): enantioenriched, 1% ee



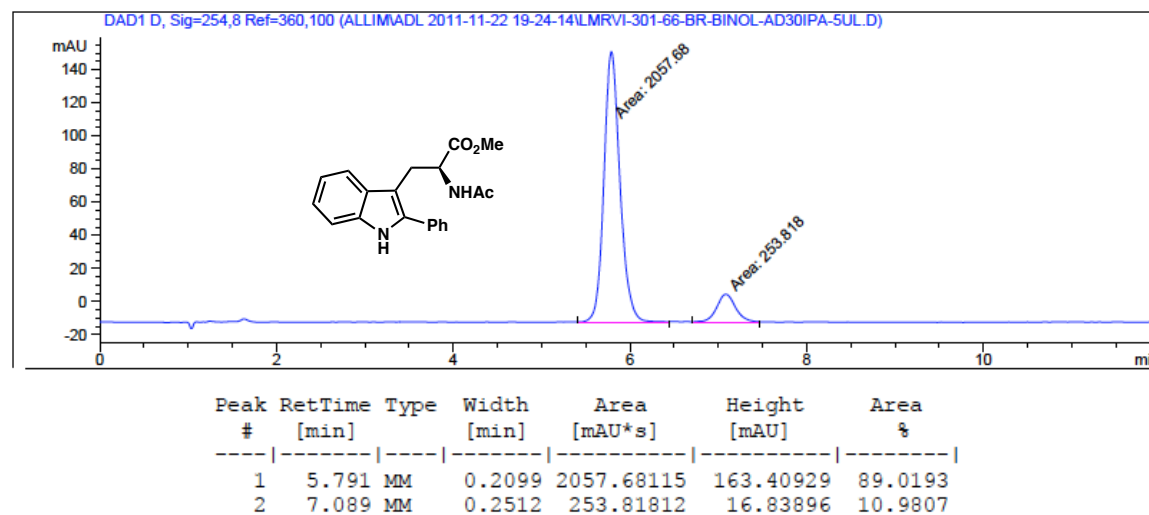
138c (Table 3.2.2, **entry 8**, (*R*)-6,6'-dimethoxy-BINOL (**102m**)): enantioenriched, 54% ee



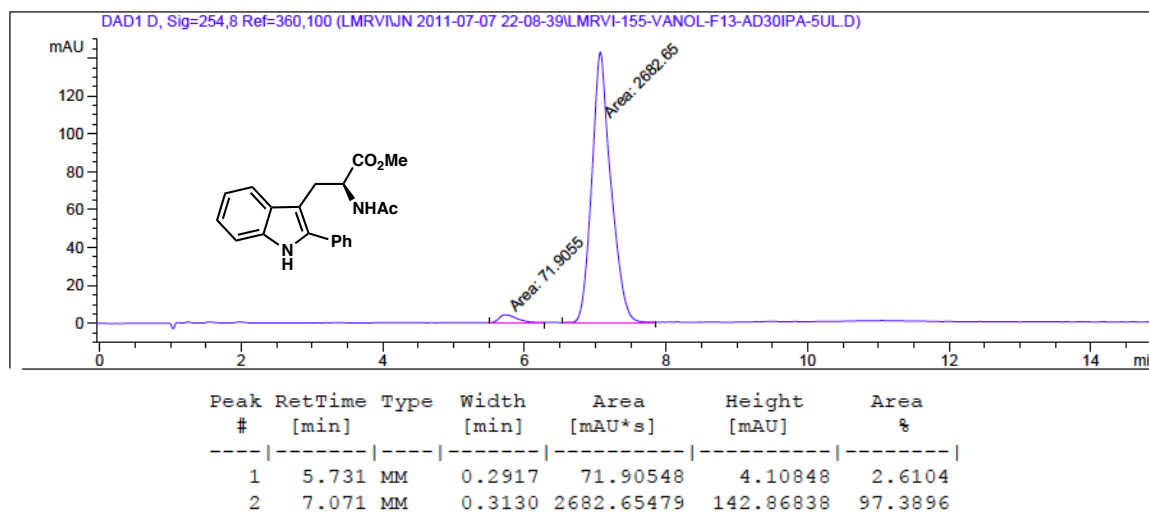
138c (Table 3.2.2, **entry 9**, (*R*)-6,6'-dimethyl-BINOL (**102n**)): enantioenriched, 78% ee



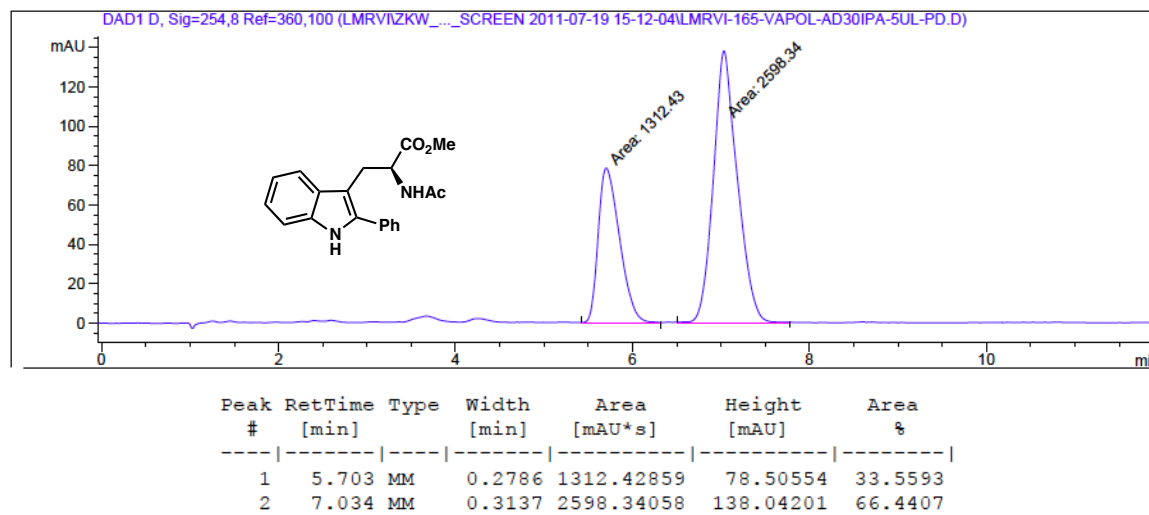
138c (Table 3.2.2, **entry 10**, (*R*)-6,6'-dibromo-BINOL (**102f**)): enantioenriched, 78% ee



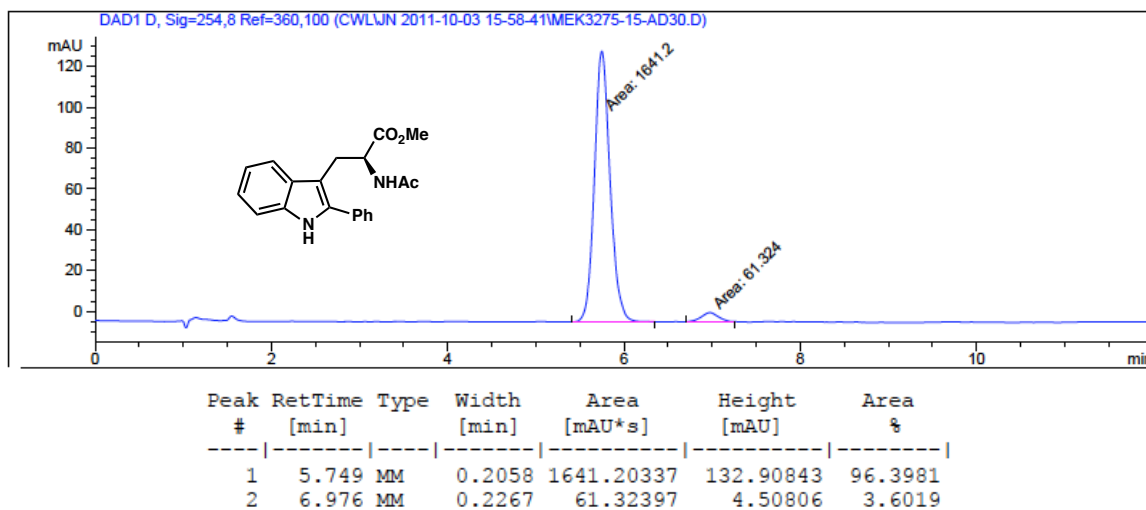
138c (Table 3.2.2, **entry 11**, (*S*)-VANOL (**166**)): enantioenriched, –95% ee



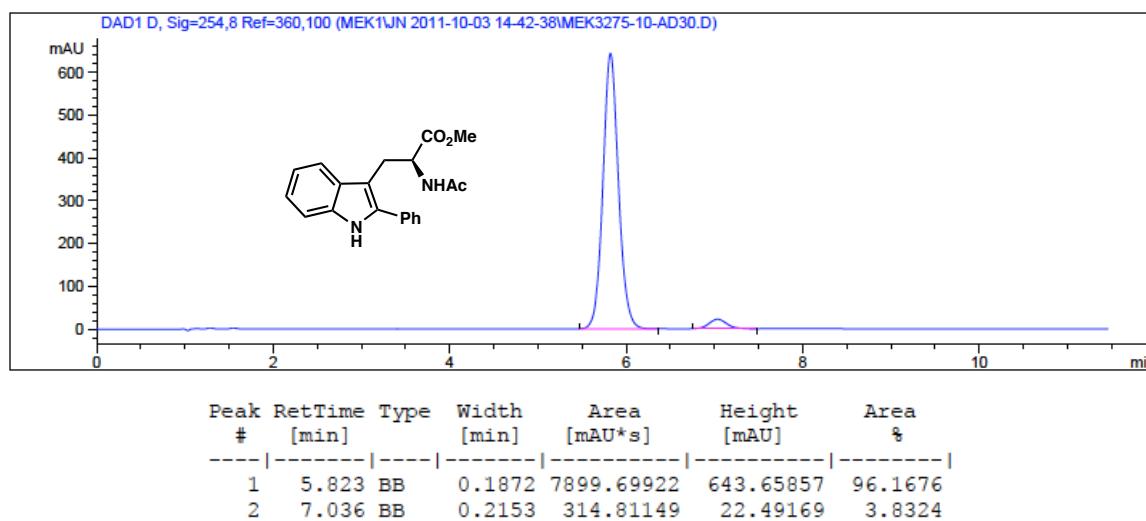
138c (Table 3.2.2, **entry 12**, (*S*)-VAPOL (**167**)): enantioenriched, –33% ee



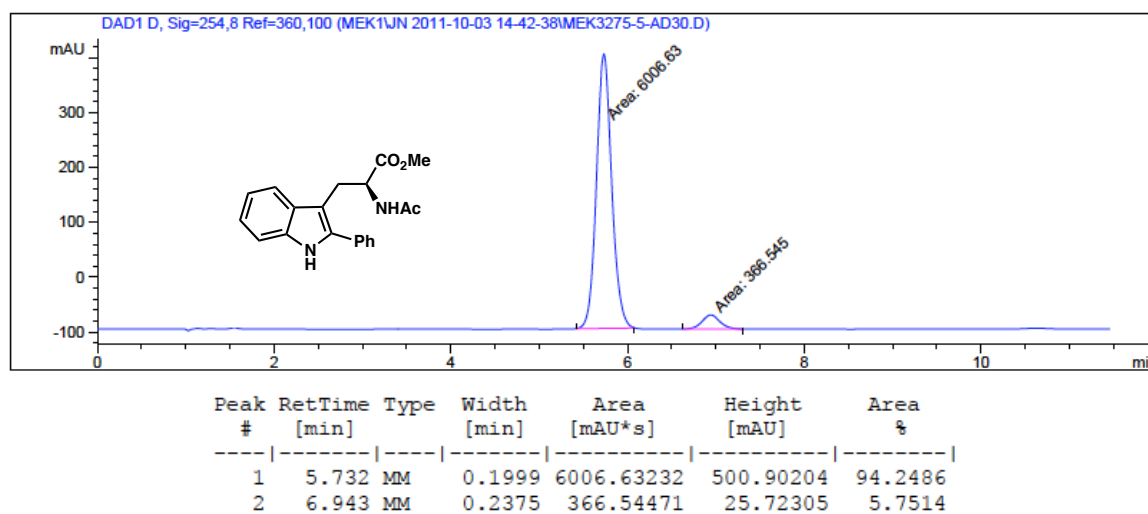
138c (Table 3.2.4, **entry 3**, 15 mol % **102k**): enantioenriched, 93% ee



138c (Table 3.2.4, **entry 4**, 10 mol % **102k**): enantioenriched, 92% ee

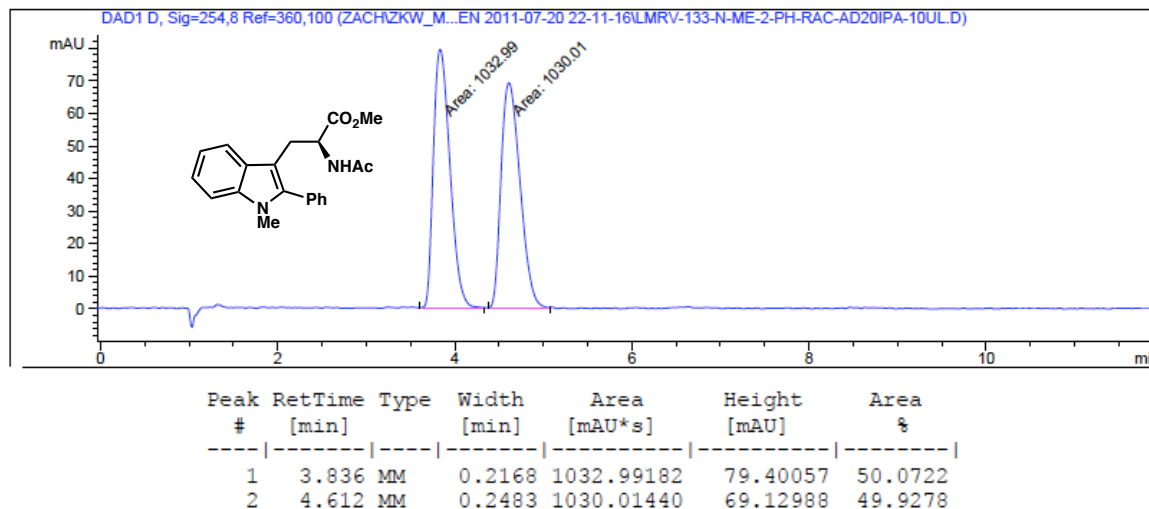


138c (Table 3.2.4, **entry 5**, 5 mol % **102k**): enantioenriched, 88% ee

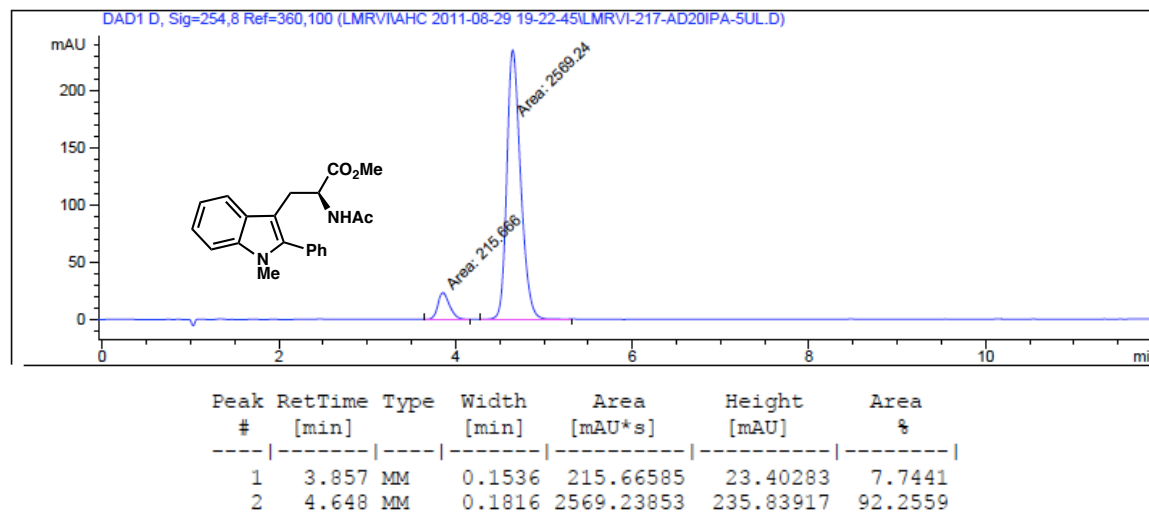


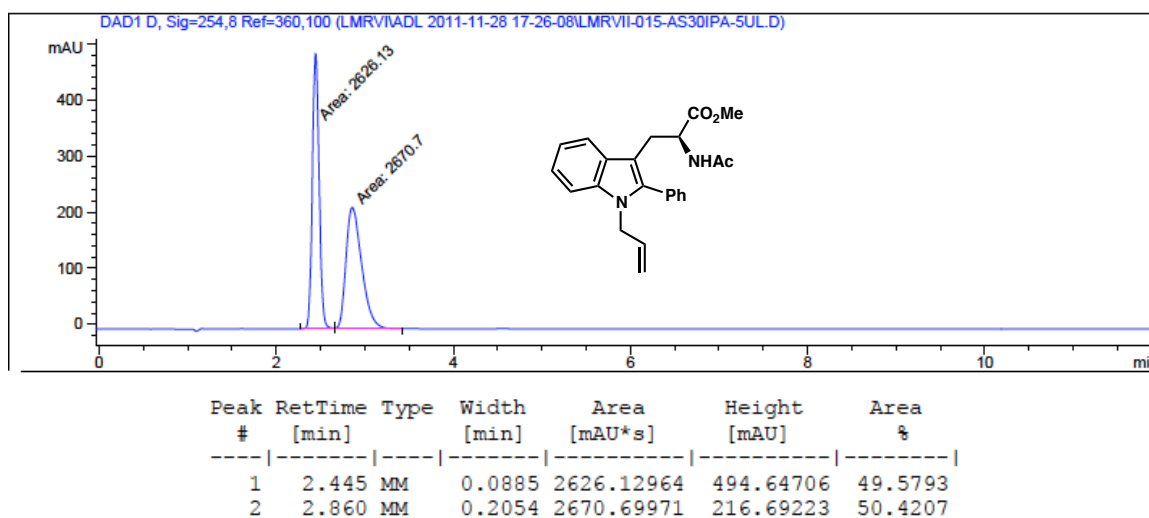
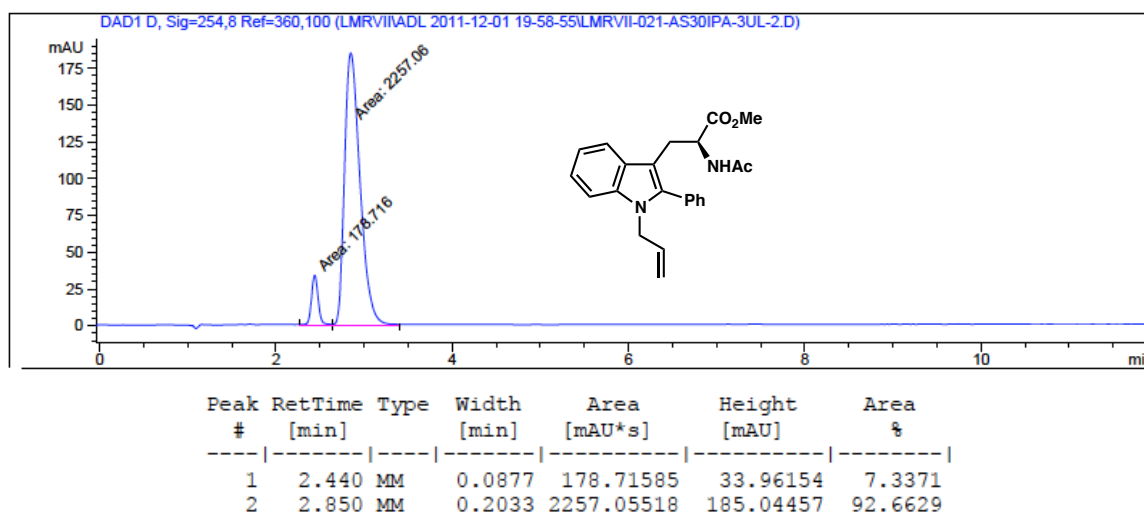
Substrate scope of the conjugate addition/asymmetric protonation

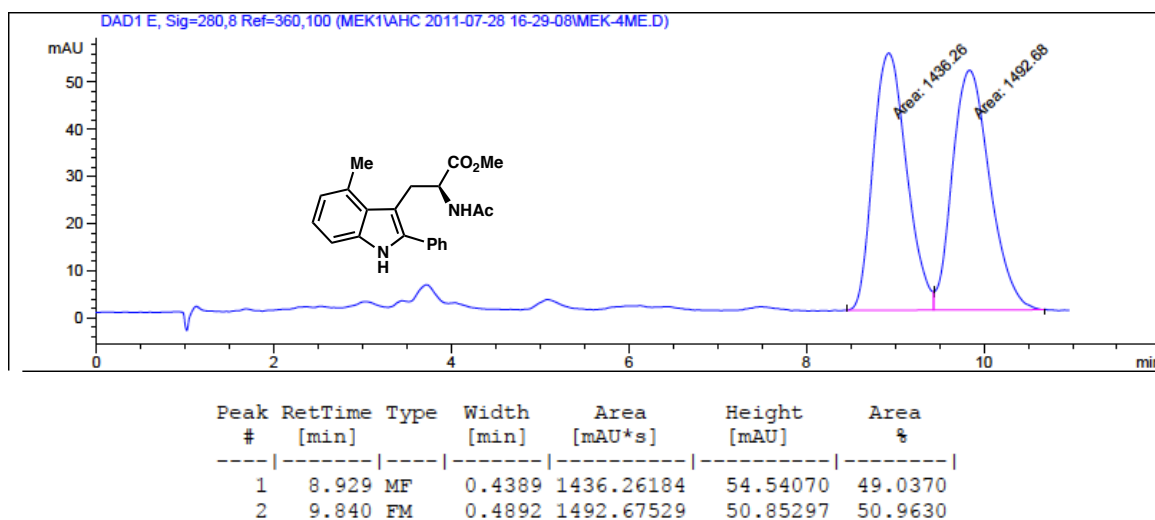
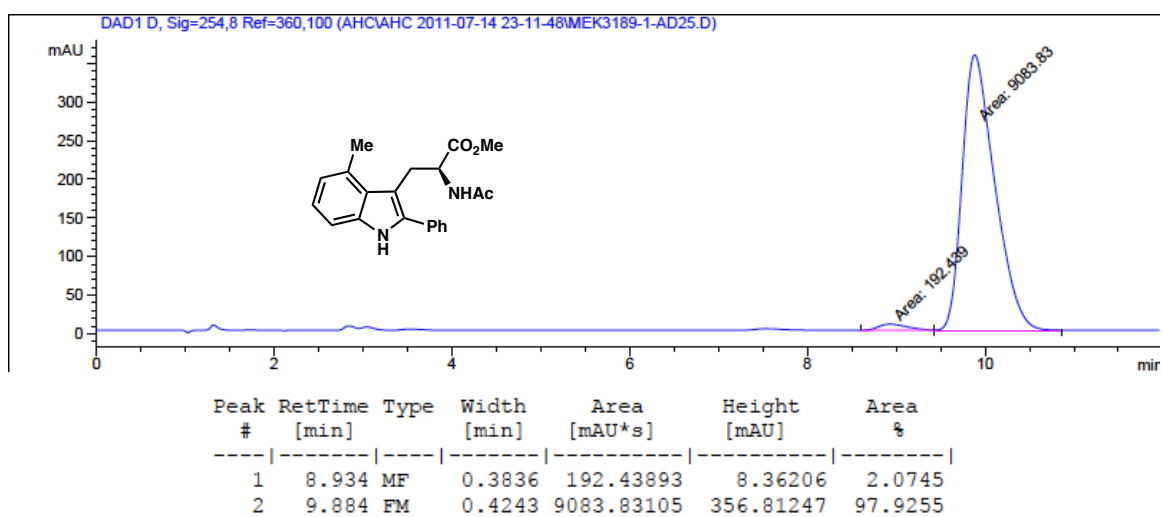
138e (Table 3.2.5, entry 2): racemic

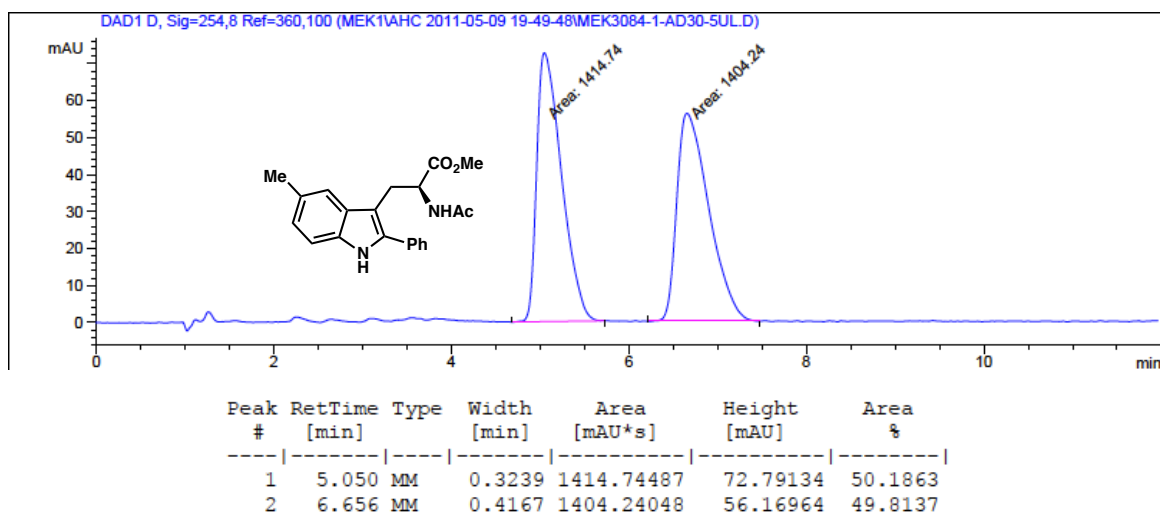
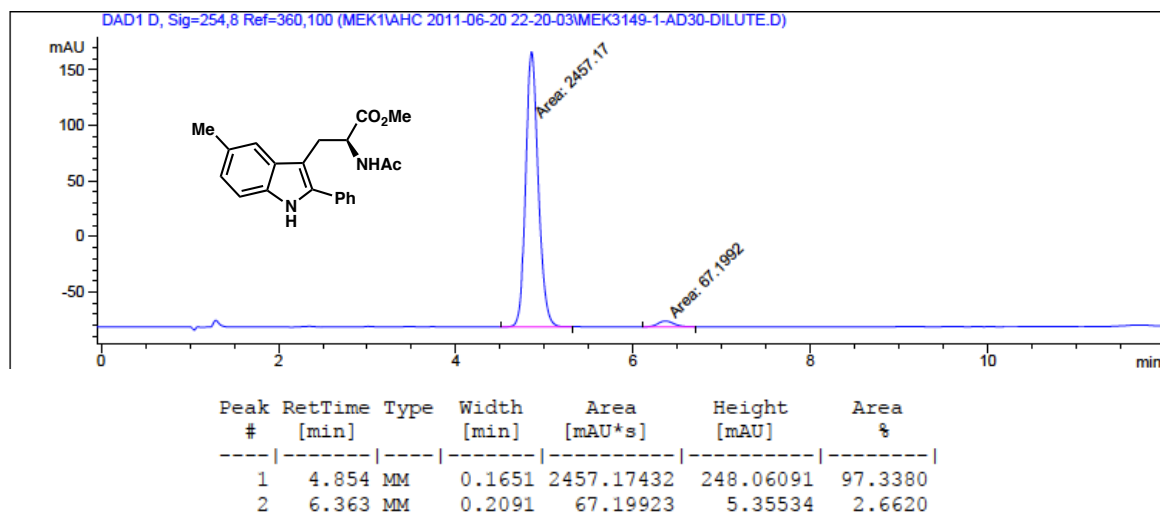


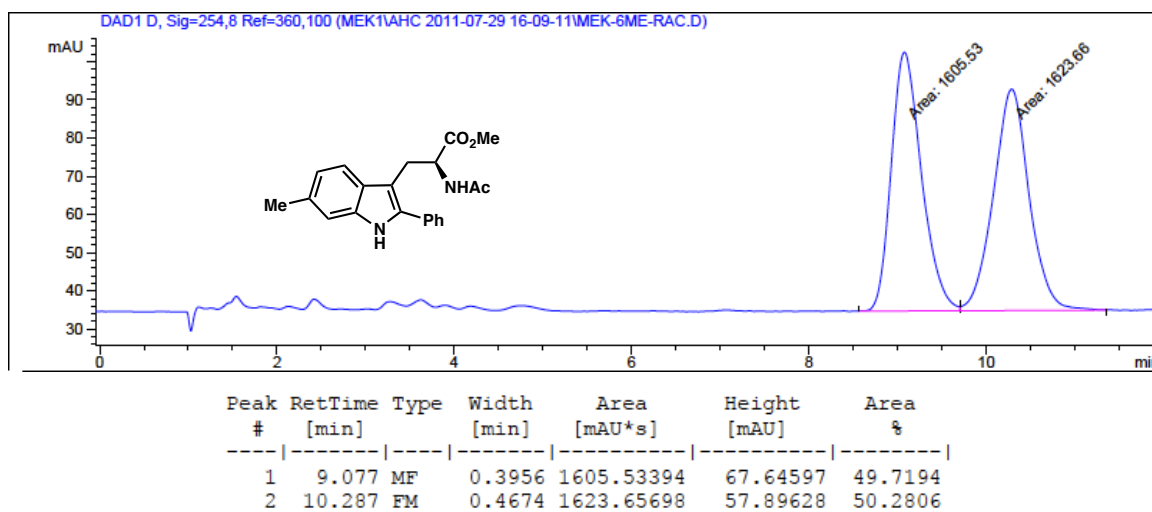
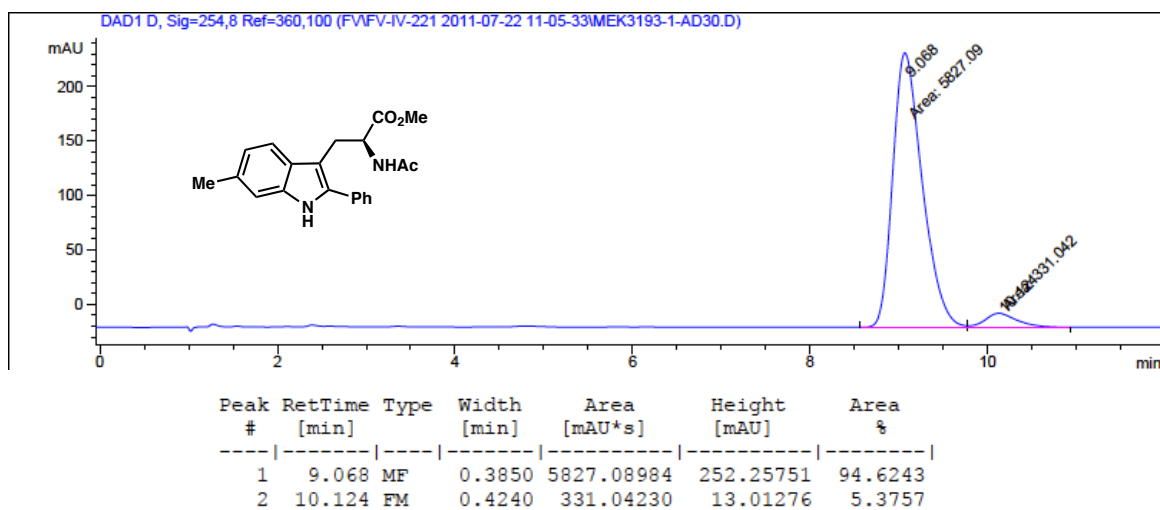
138e (Table 3.2.5, entry 2): enantioenriched, 85% ee

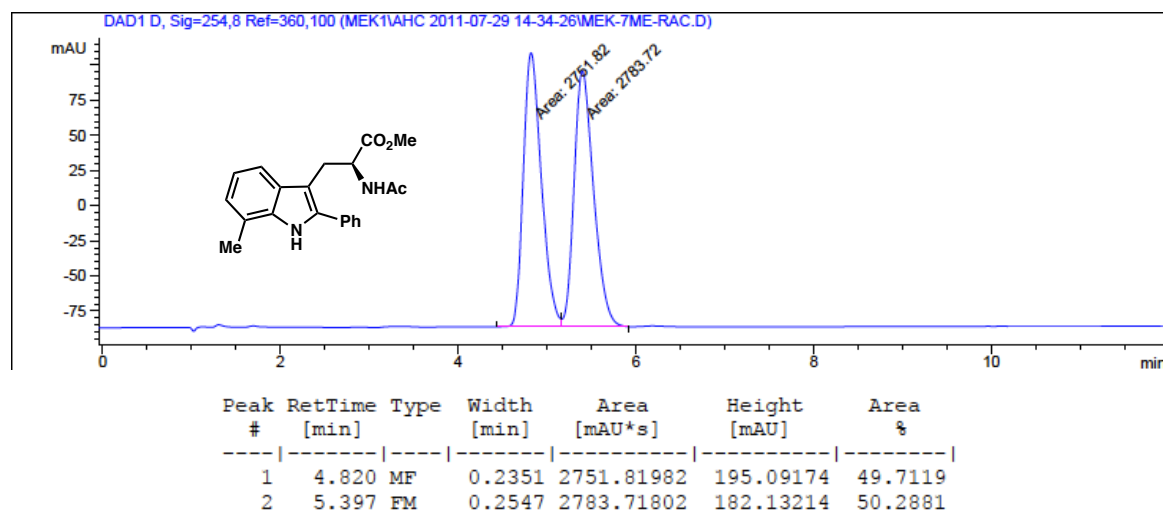
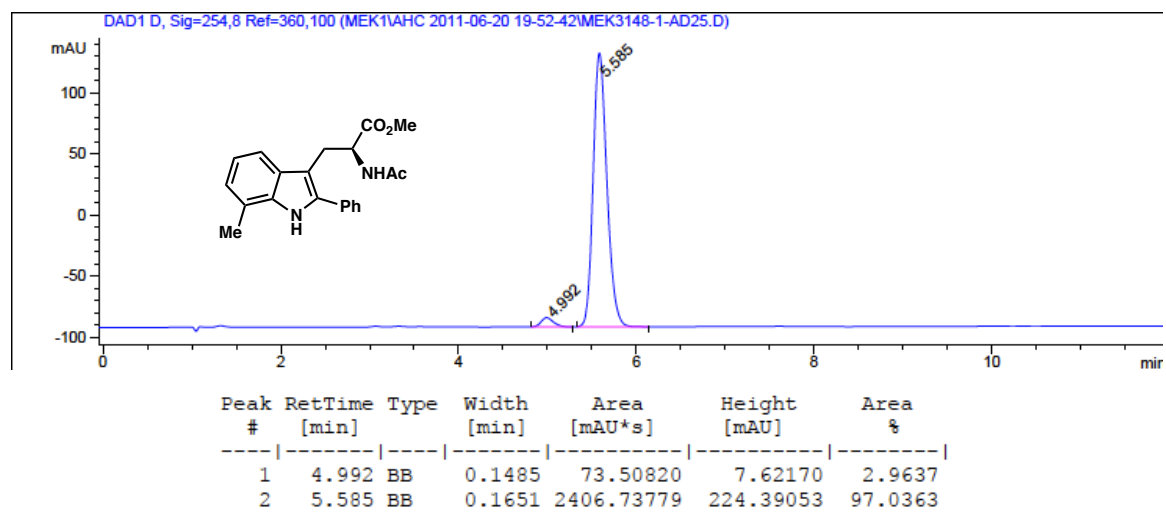


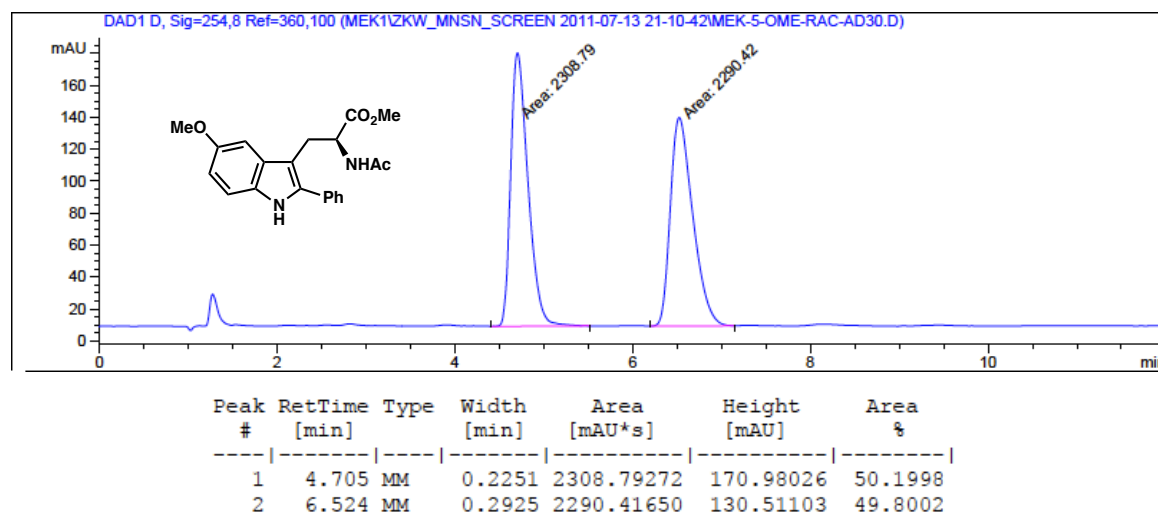
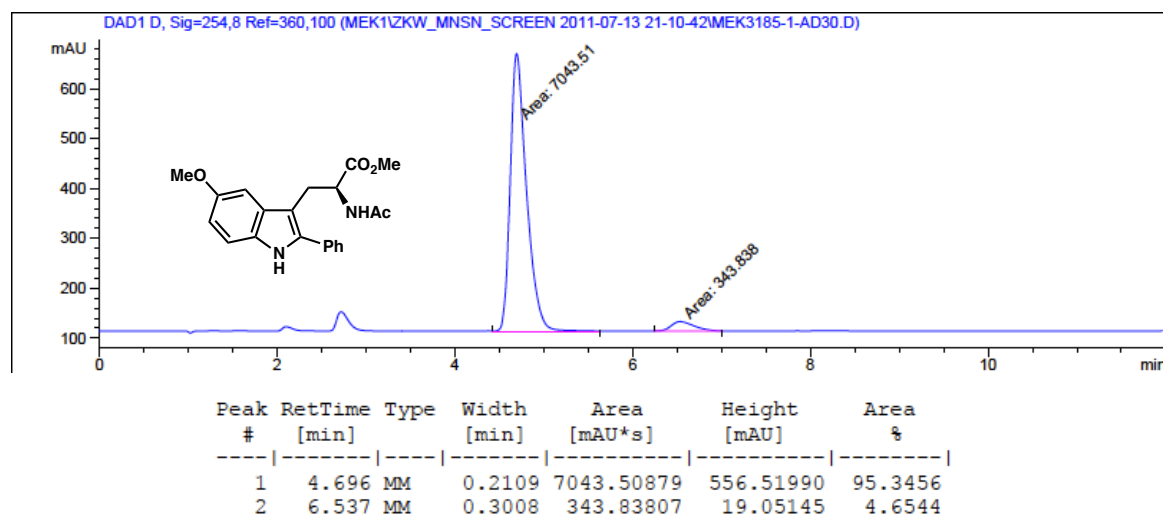
138f (Table 3.2.5, **entry 3**): racemic**138f** (Table 3.2.5, **entry 3**): enantioenriched, 85% ee

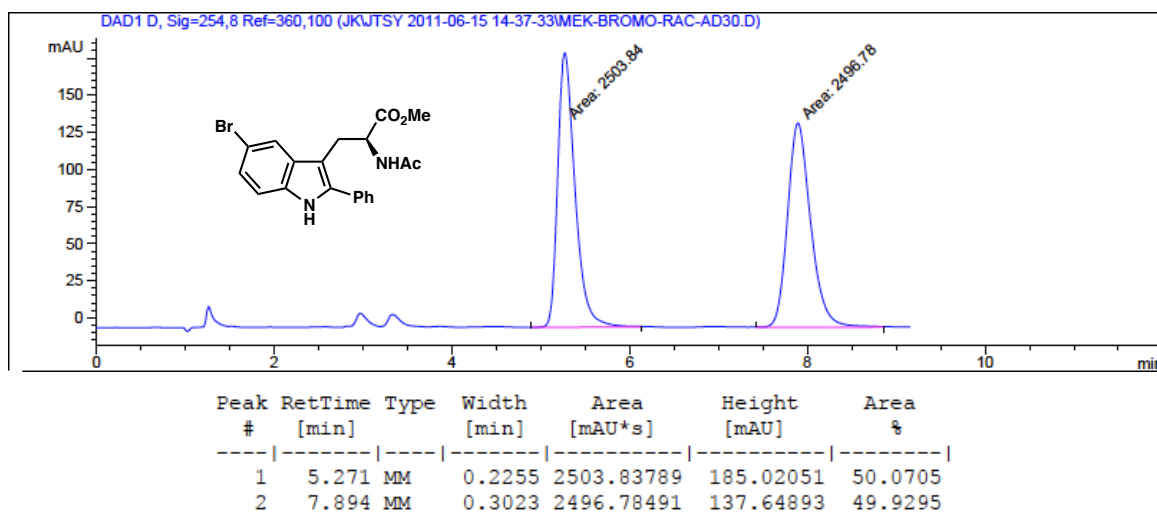
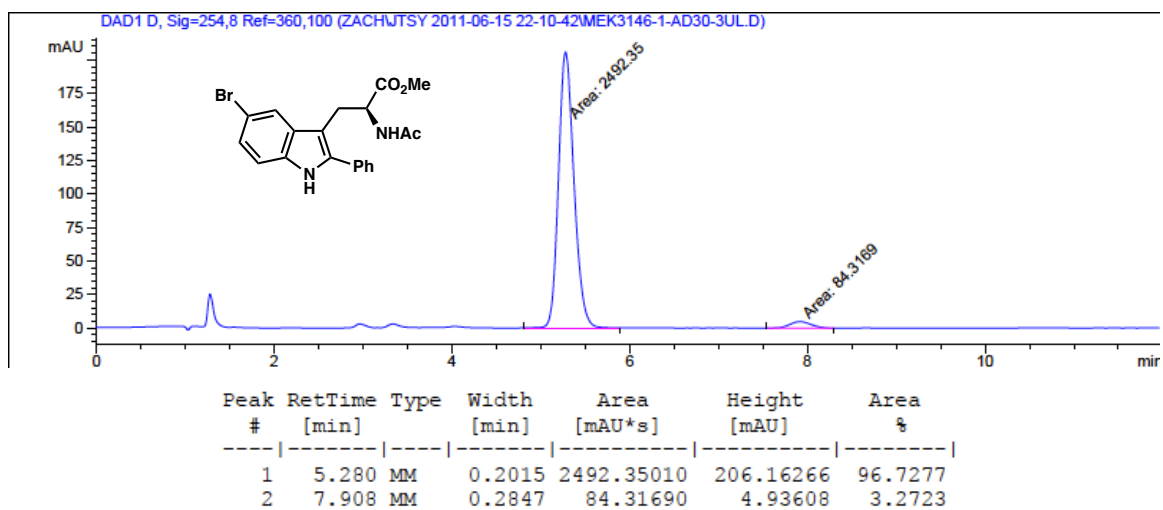
138g (Table 3.2.5, **entry 4**): racemic**138g** (Table 3.2.5, **entry 4**): enantioenriched, 96% ee

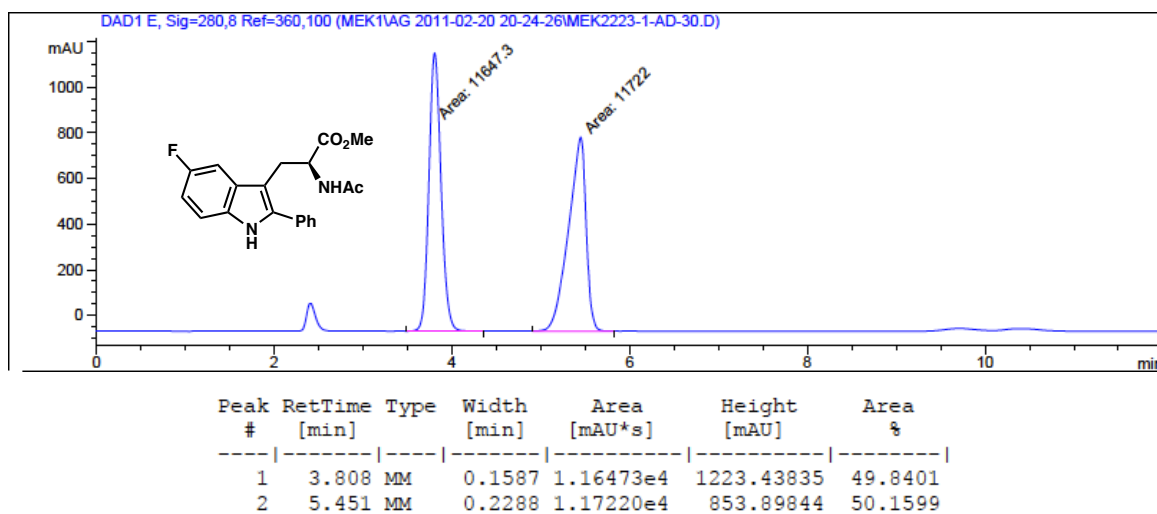
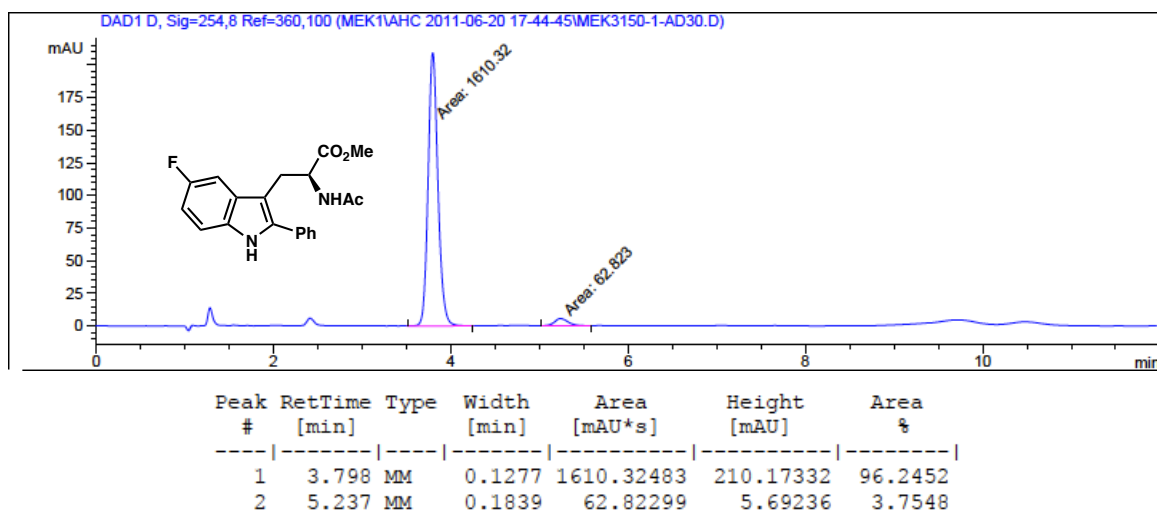
138h (Table 3.2.5, **entry 5**): racemic**138h** (Table 3.2.5, **entry 5**): enantioenriched, 95% ee

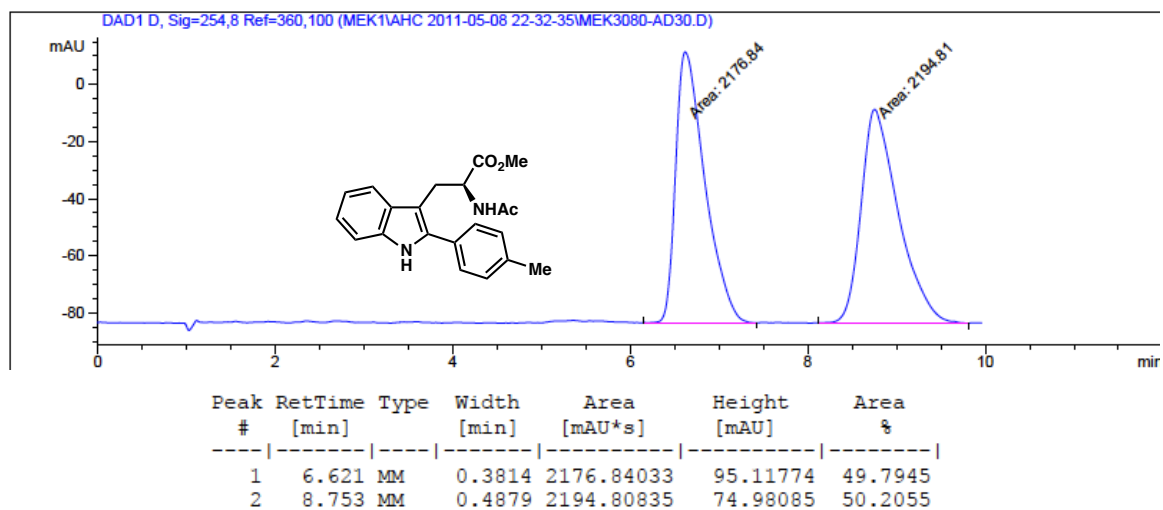
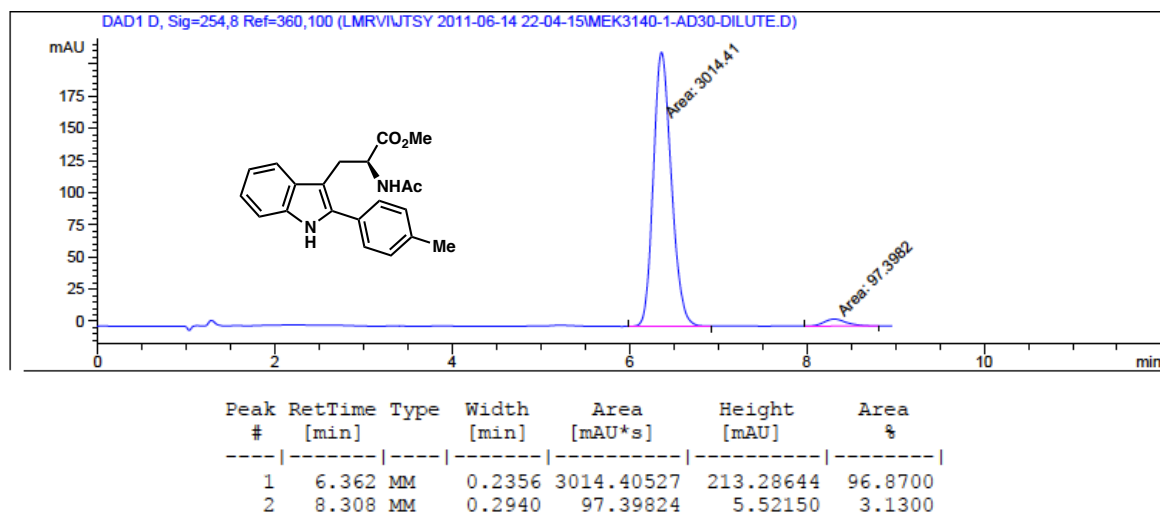
138i (Table 3.2.5, **entry 6**): racemic**138i** (Table 3.2.5, **entry 6**): enantioenriched, 89% ee

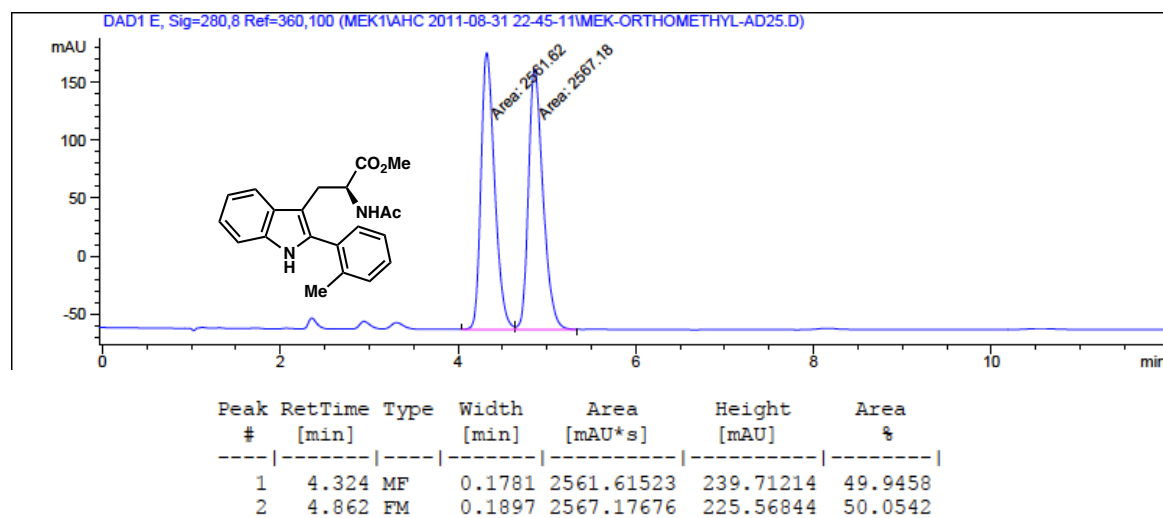
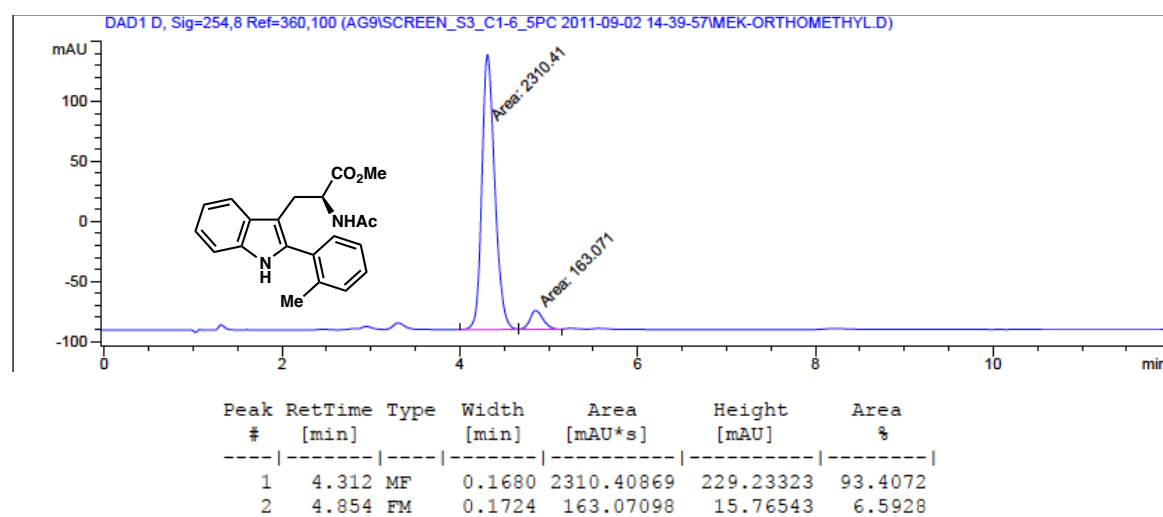
138j (Table 3.2.5, **entry 7**): racemic**138j** (Table 3.2.5, **entry 7**): enantioenriched, 94% ee

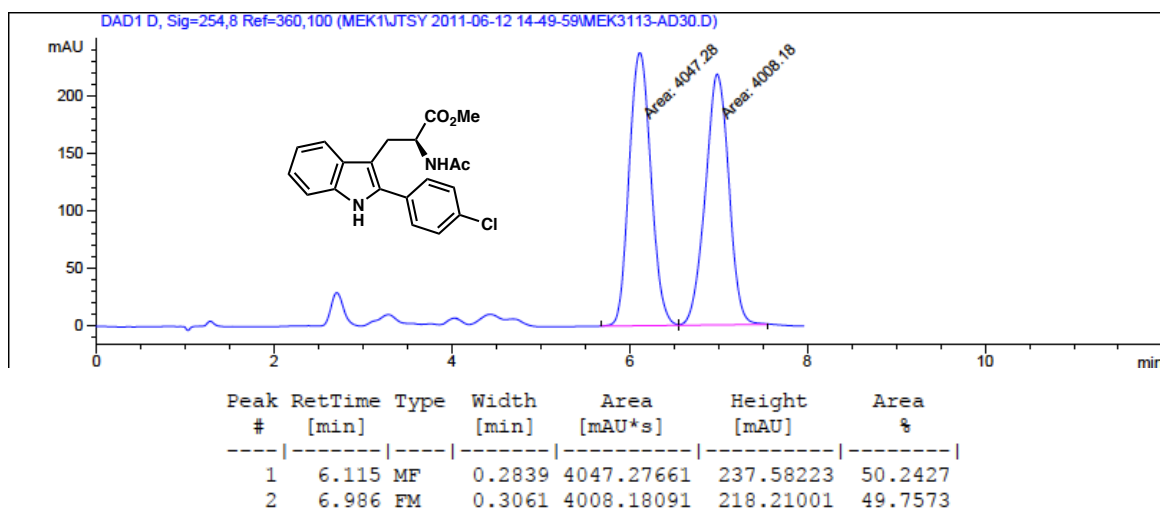
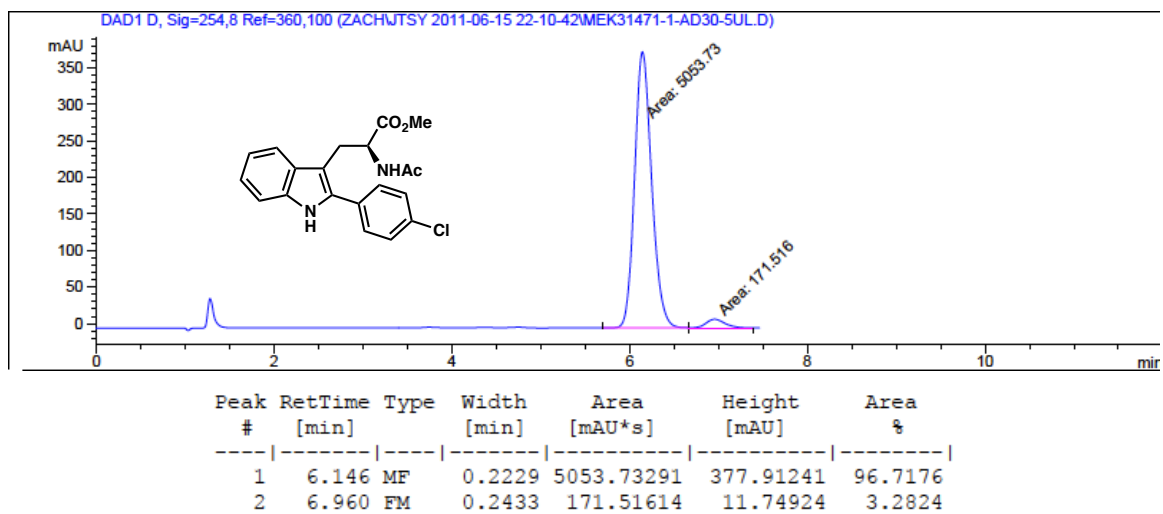
138k (Table 3.2.5, **entry 8**): racemic**138k** (Table 3.2.5, **entry 8**): enantioenriched, 91% ee

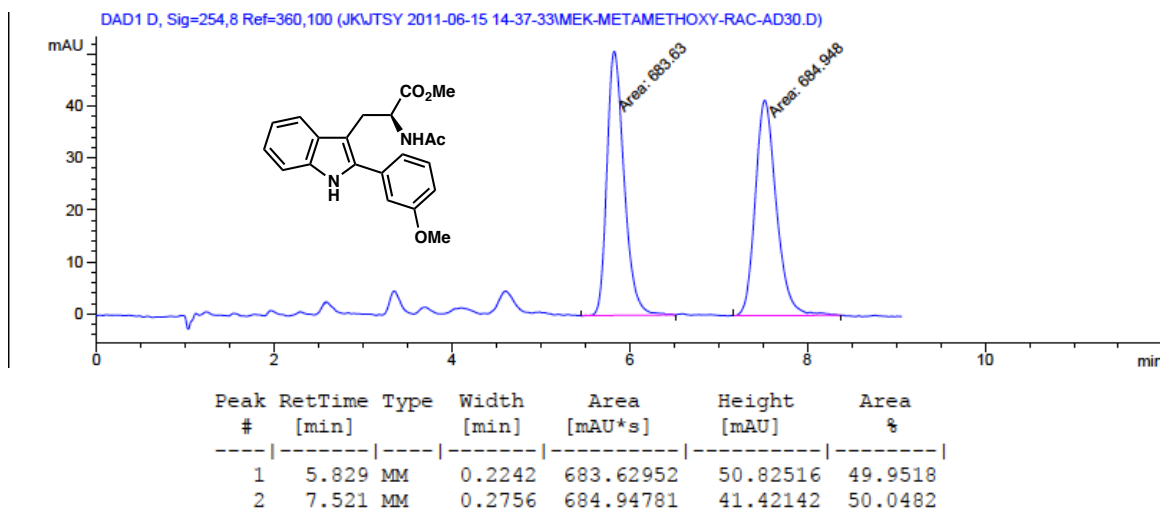
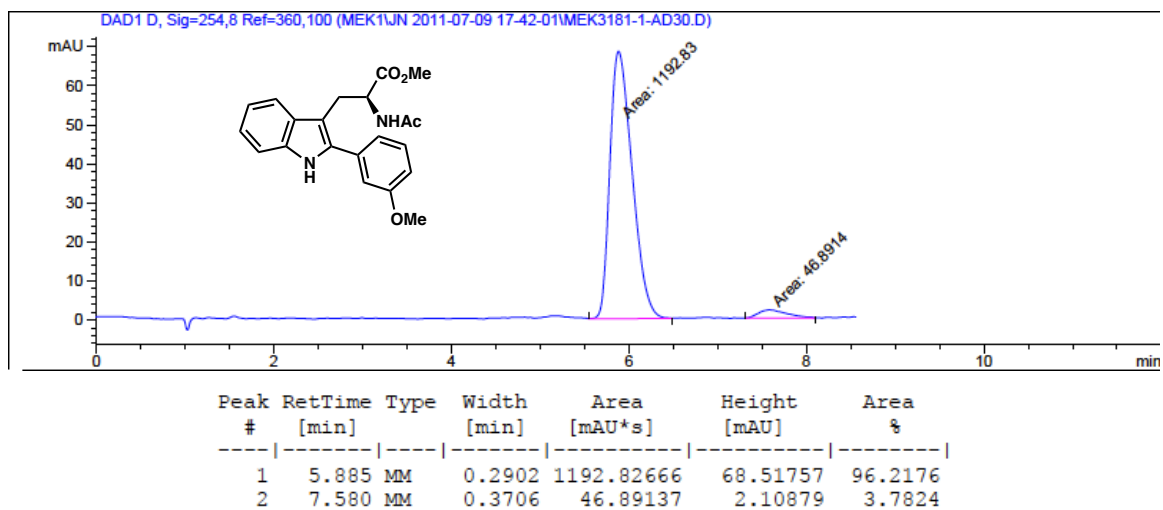
138l (Table 3.2.5, **entry 9**): racemic**138l** (Table 3.2.5, **entry 9**): enantioenriched, 93% ee

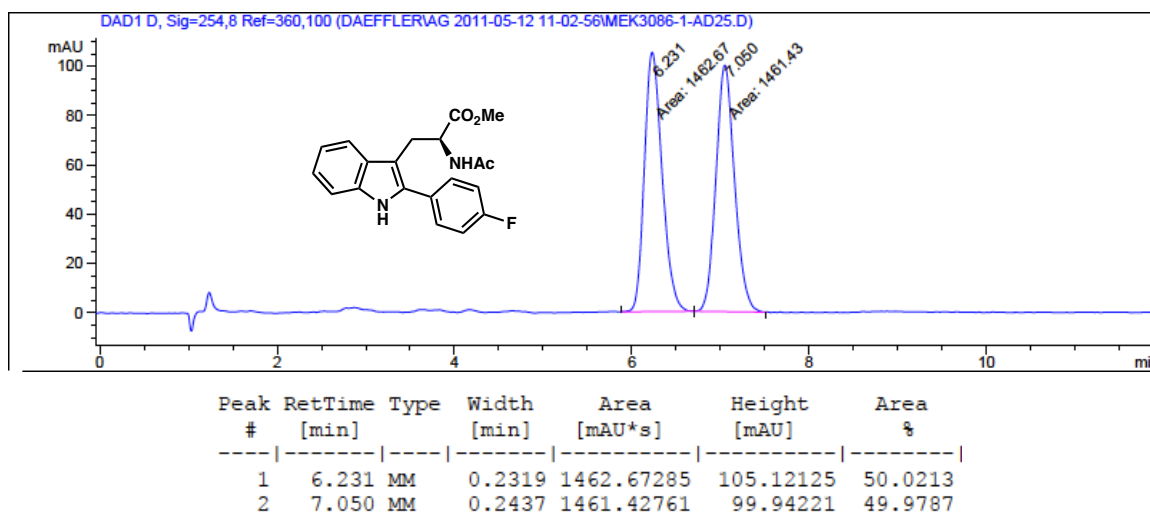
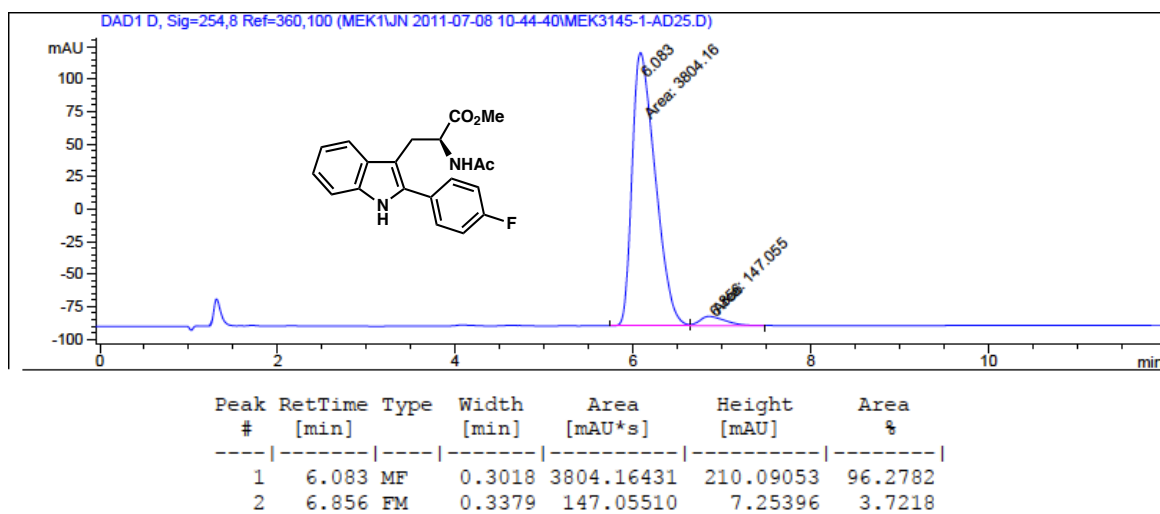
138m (Table 3.2.5, **entry 10**): racemic**138m** (Table 3.2.5, **entry 10**): enantioenriched, 92% ee

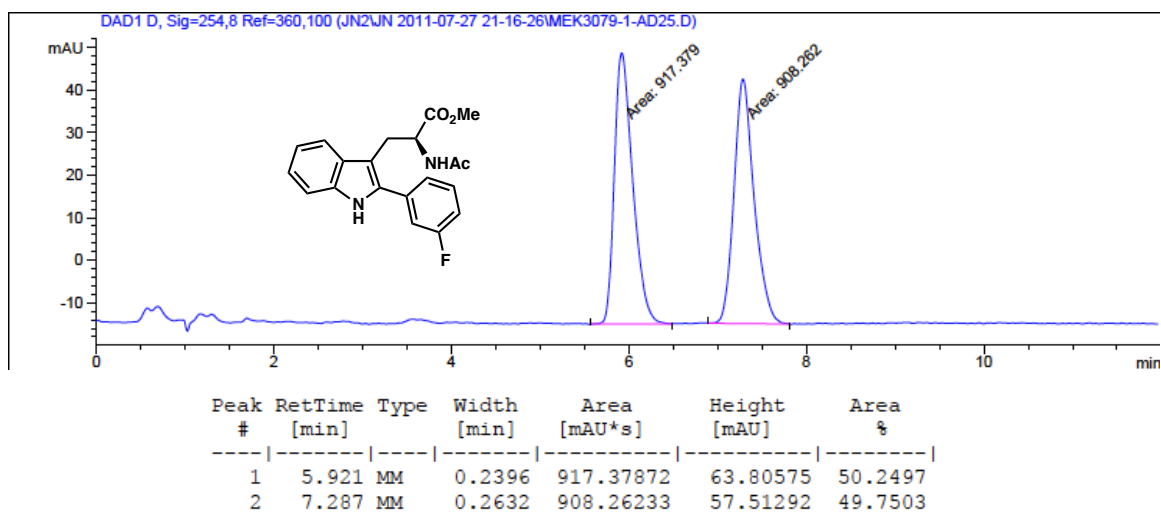
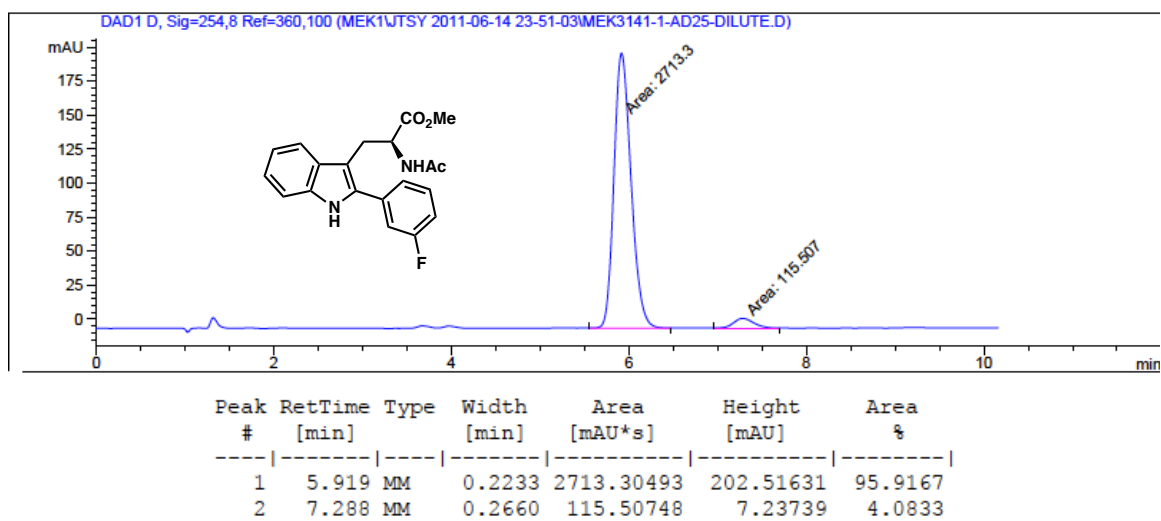
138n (Table 3.2.5, entry 11): racemic**138n** (Table 3.2.5, entry 11): enantioenriched, 94% ee

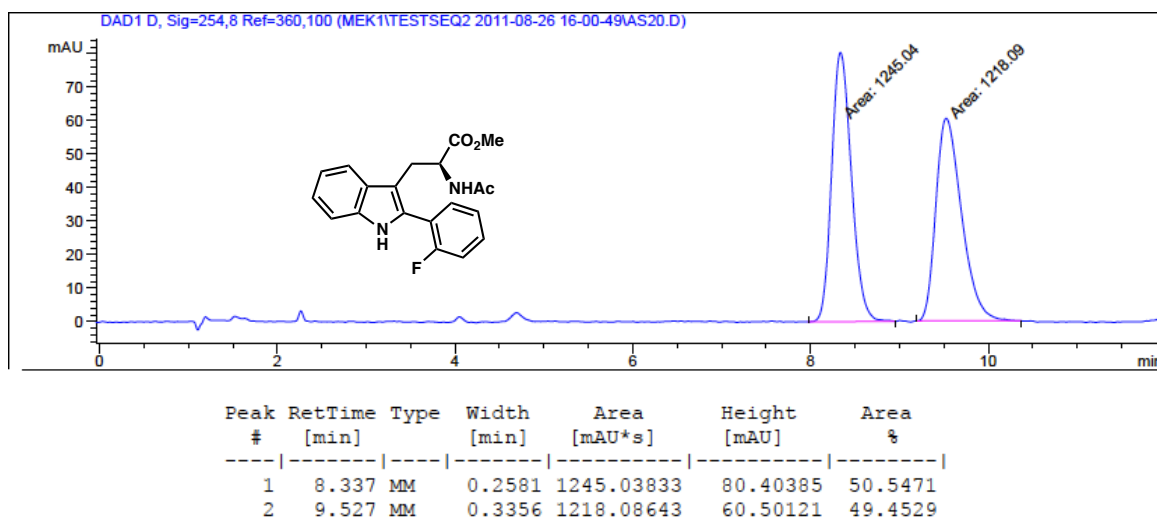
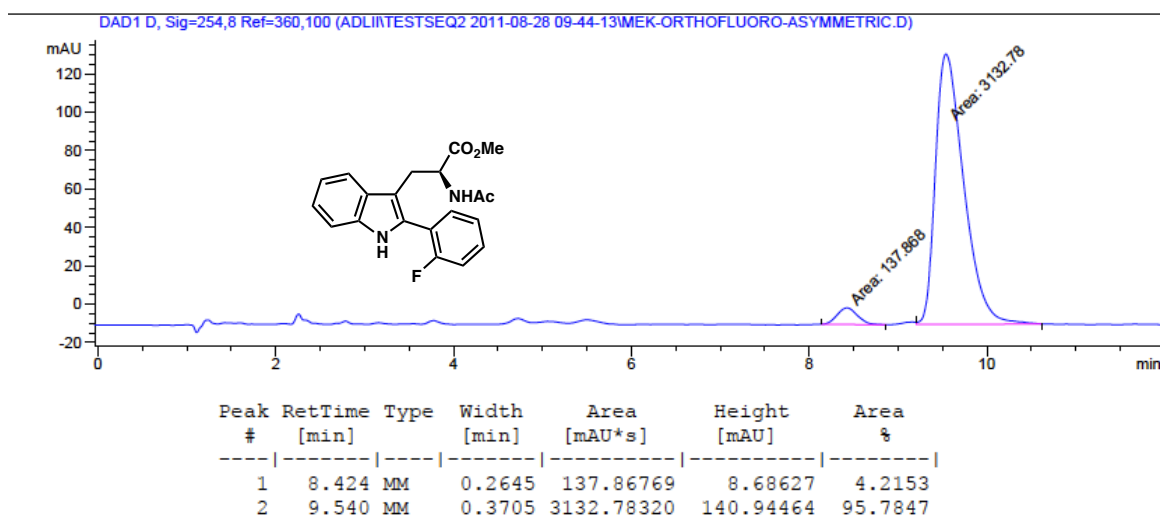
138o (Table 3.2.5, entry 12): racemic**138o** (Table 3.2.5, entry 12): enantioenriched, 87% ee

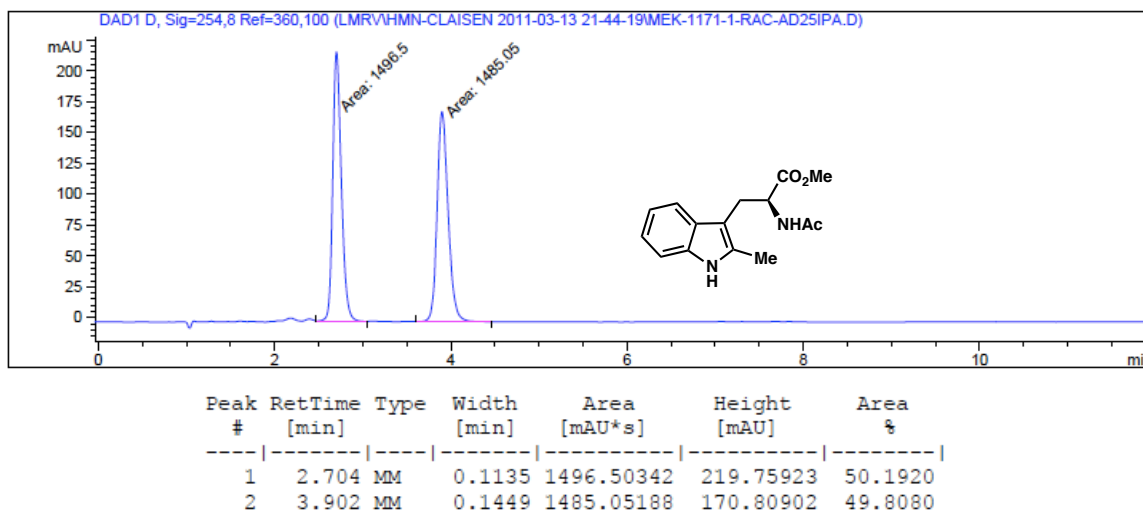
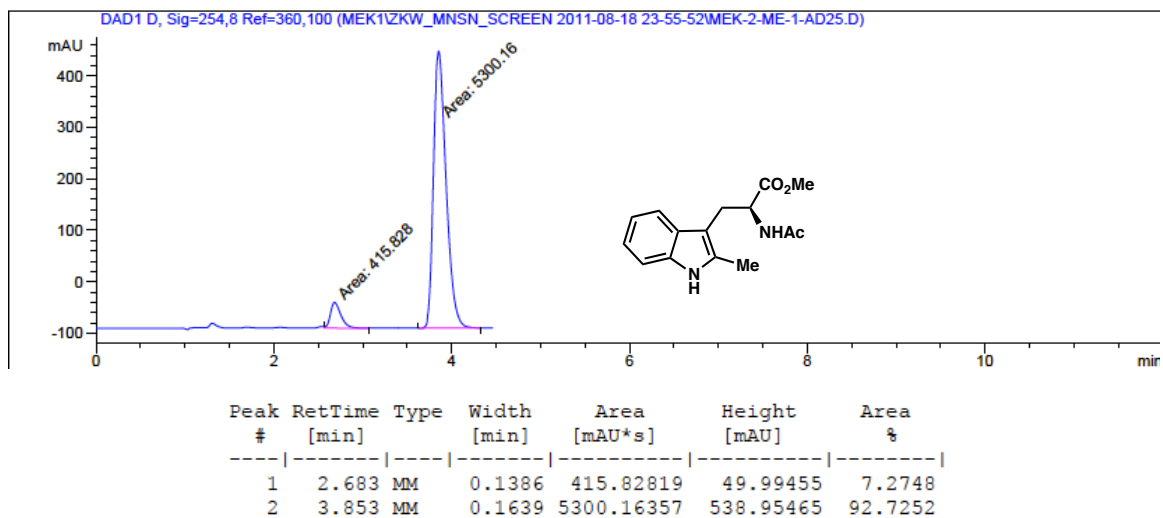
138p (Table 3.2.5, **entry 13**): racemic**138p** (Table 3.2.5, **entry 13**): enantioenriched, 93% ee

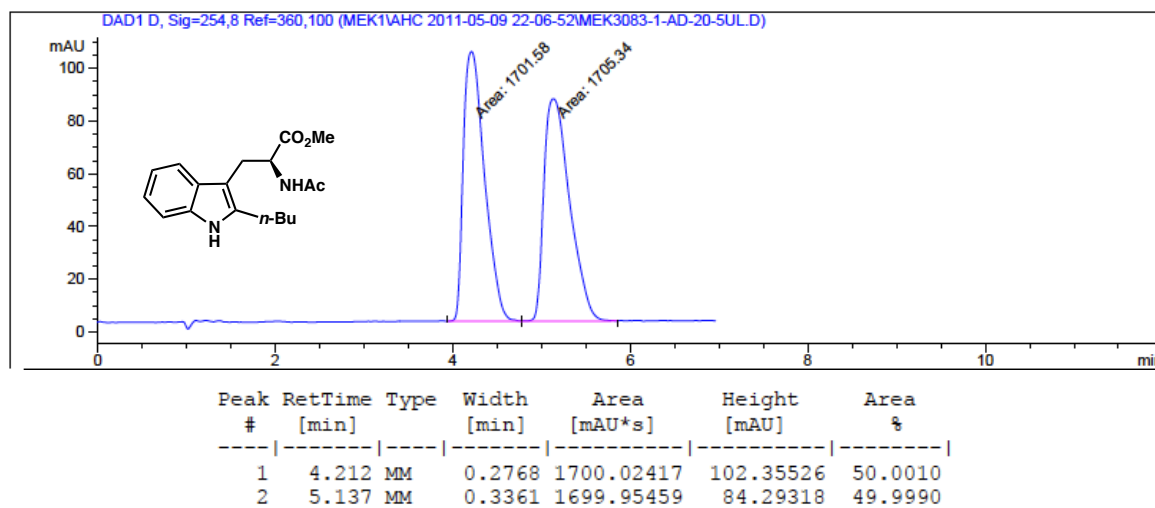
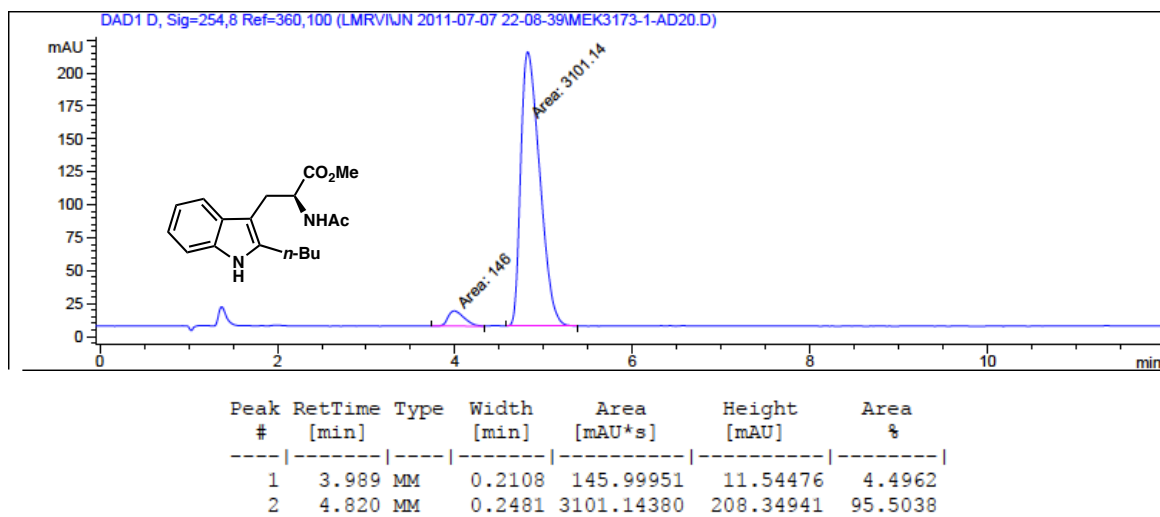
138q (Table 3.2.5, **entry 14**): racemic**138q** (Table 3.2.5, **entry 14**): enantioenriched, 92% ee

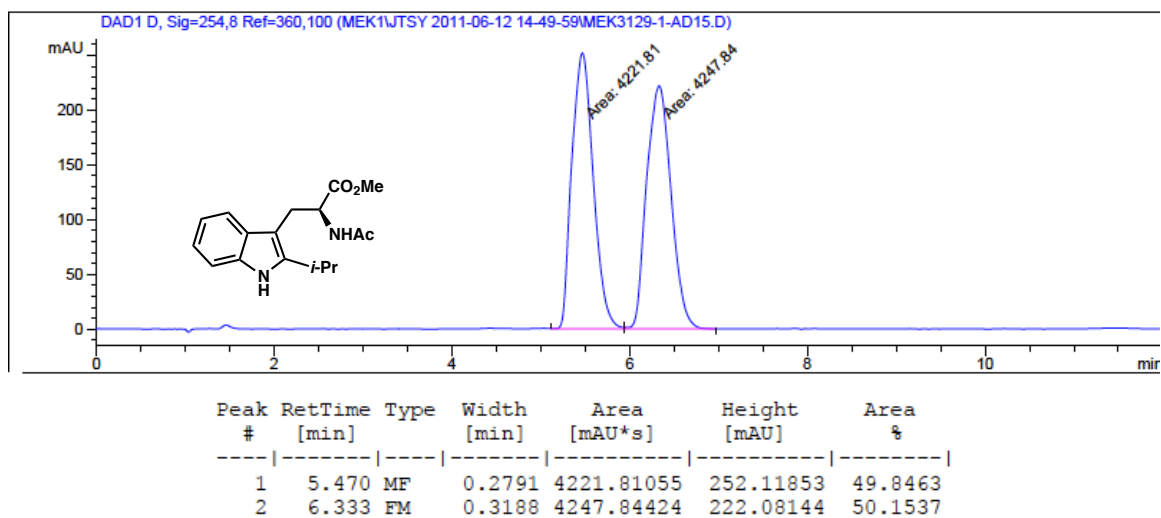
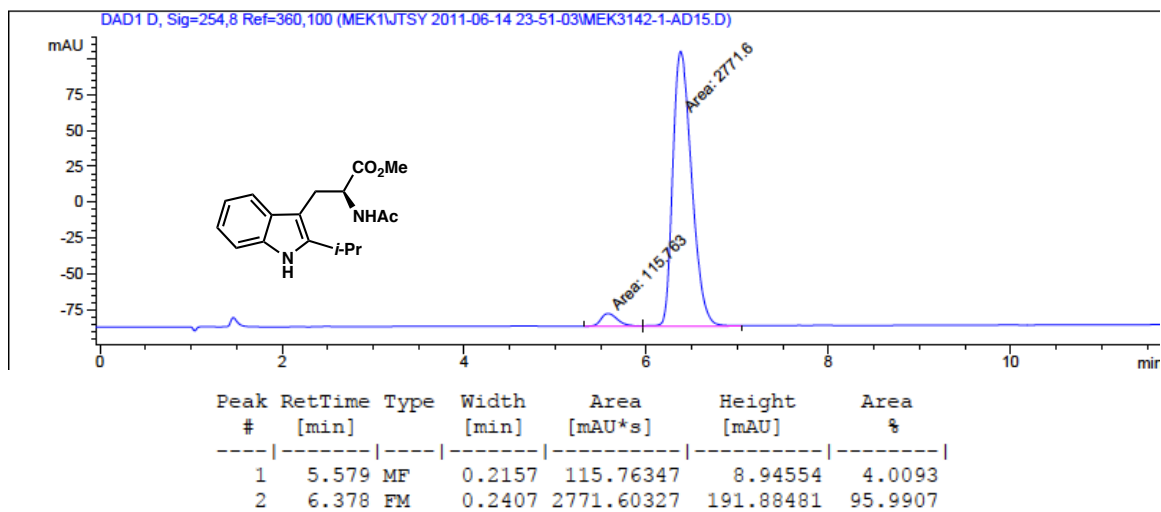
138r (Table 3.2.5, entry 15): racemic**138r** (Table 3.2.5, entry 15): enantioenriched, 93% ee

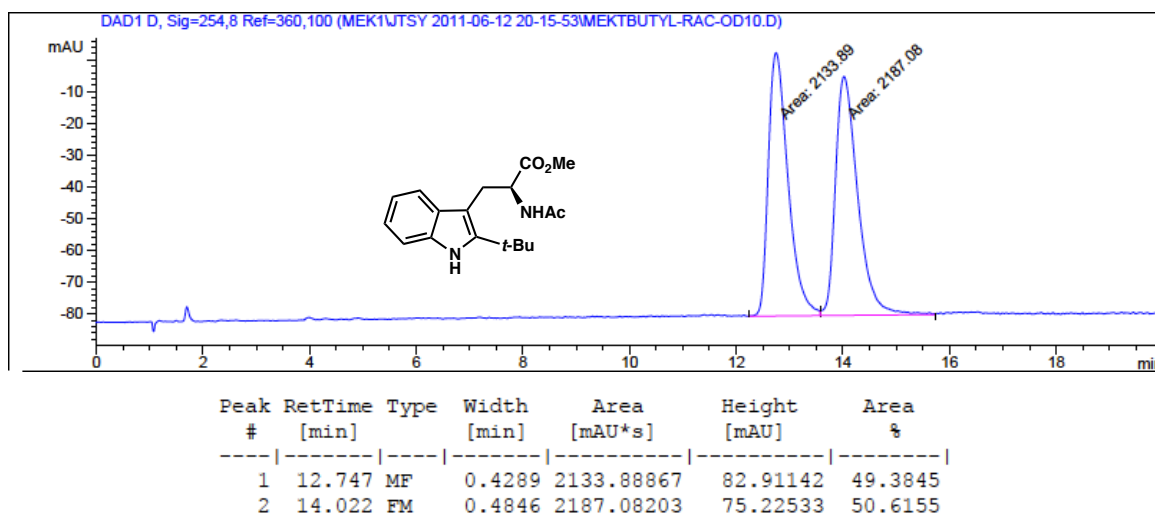
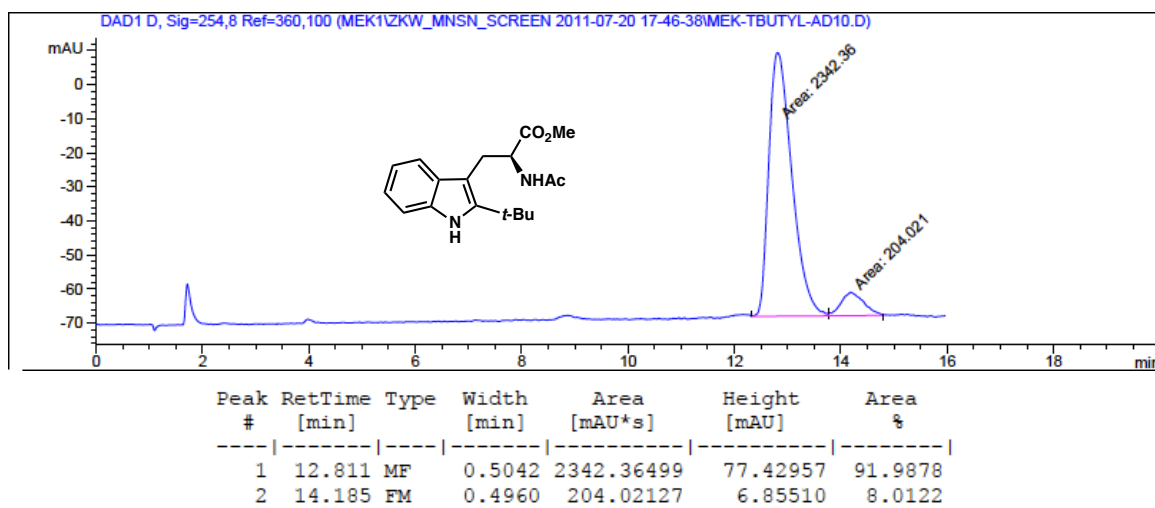
138s (Table 3.2.5, entry 16): racemic**138s** (Table 3.2.5, entry 16): enantioenriched, 92% ee

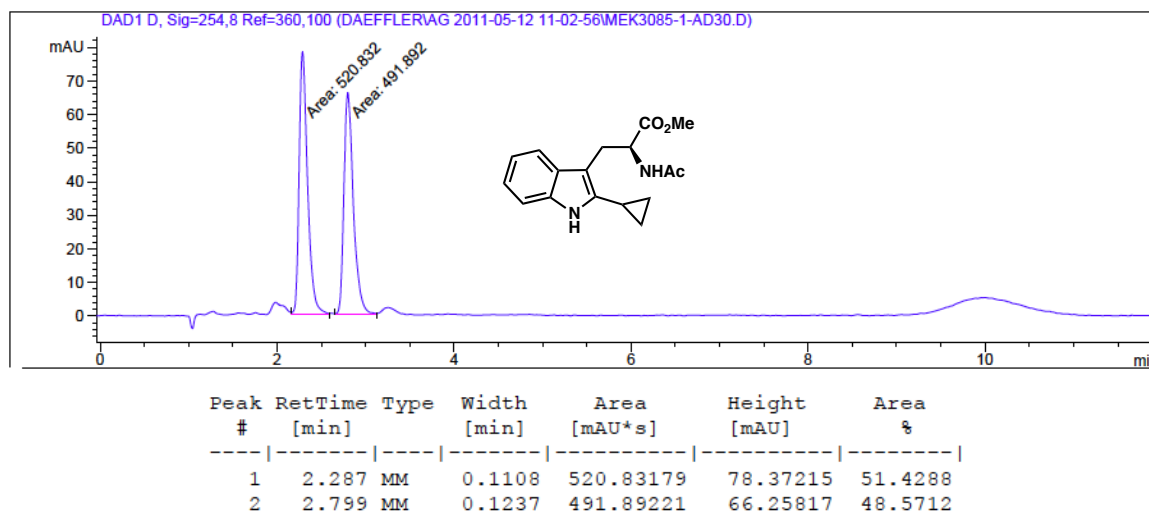
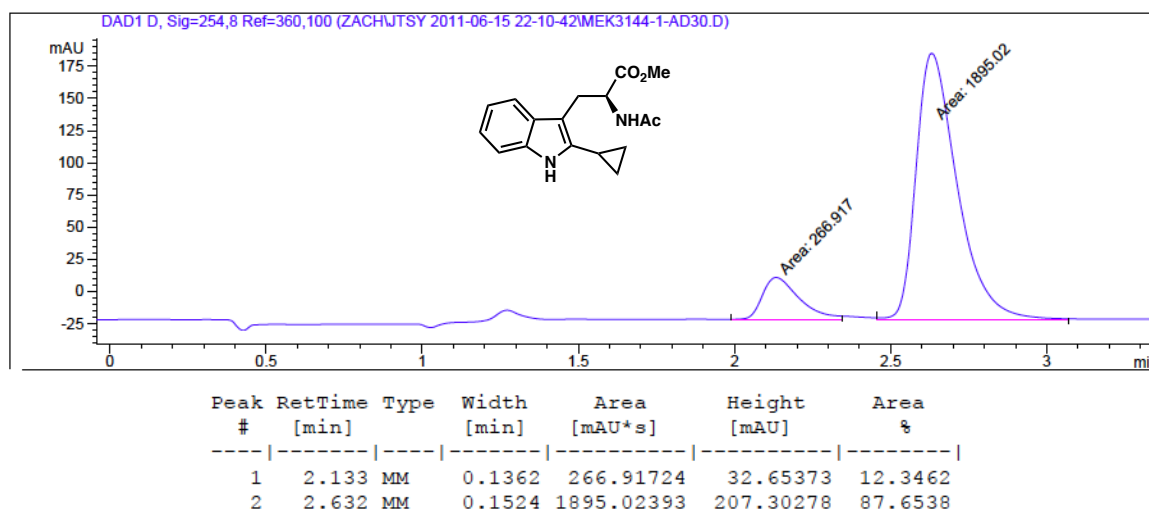
138t (Table 3.2.5, **entry 17**): racemic**138t** (Table 3.2.5, **entry 17**): enantioenriched, 92% ee

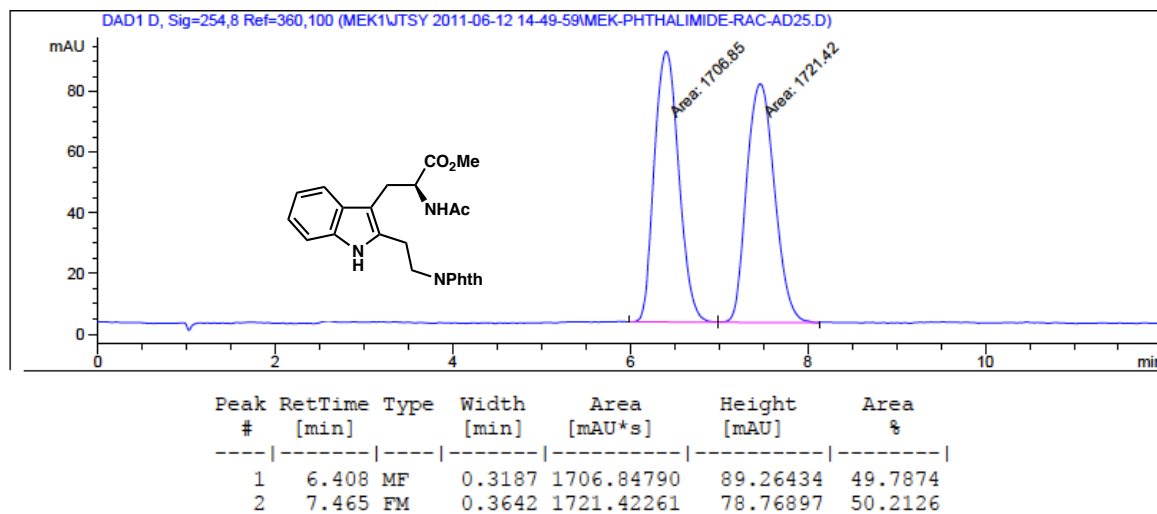
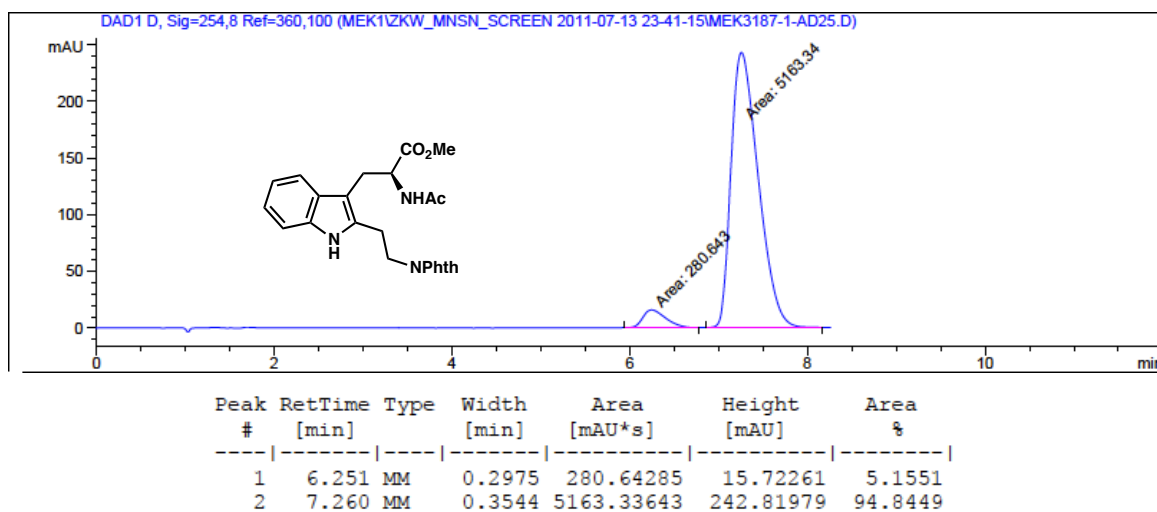
138d (Table 3.2.5, entry 18): racemic**138d** (Table 3.2.5, entry 18): enantioenriched, 85% ee

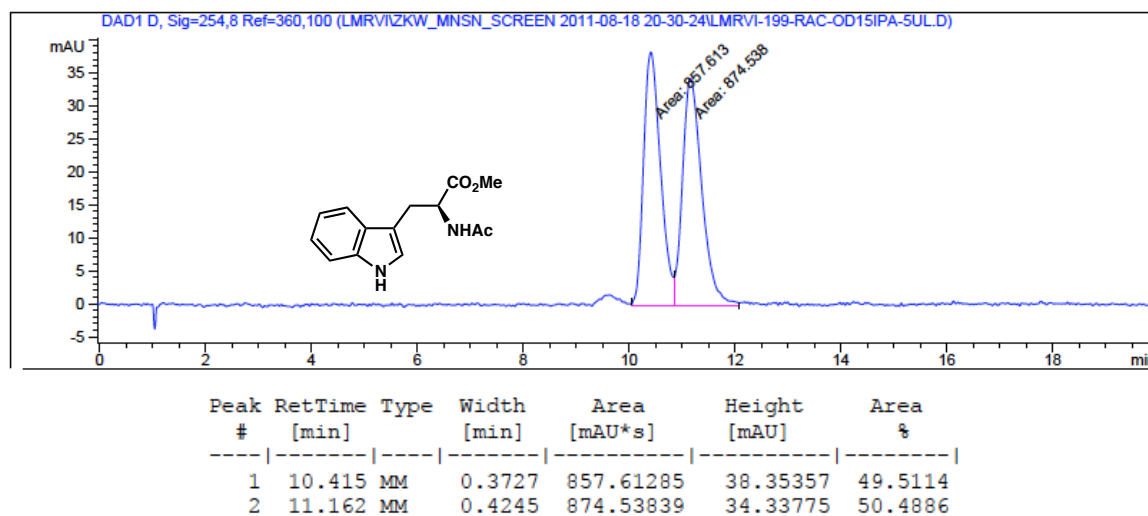
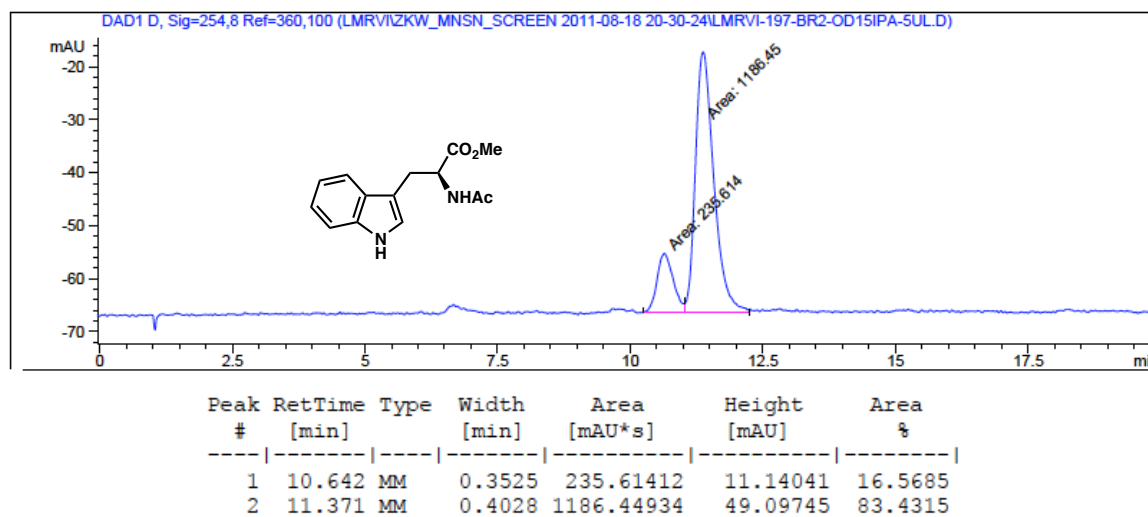
138u (Table 3.2.5, entry 19): racemic**138u** (Table 3.2.5, entry 19): enantioenriched, 91% ee

138v (Table 3.2.5, **entry 20**): racemic**138v** (Table 3.2.5, **entry 20**): enantioenriched, 92% ee

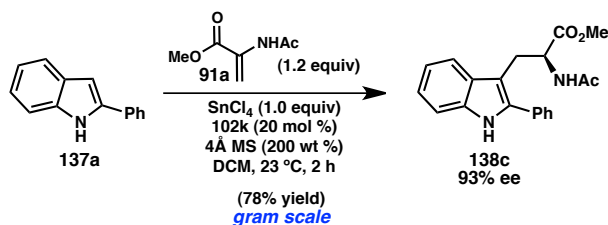
138w (Table 3.2.5, **entry 21**): racemic**138w** (Table 3.2.5, **entry 21**): enantioenriched, 84% ee

138x (Table 3.2.5, **entry 22**): racemic**138x** (Table 3.2.5, **entry 22**): enantioenriched, 75% ee

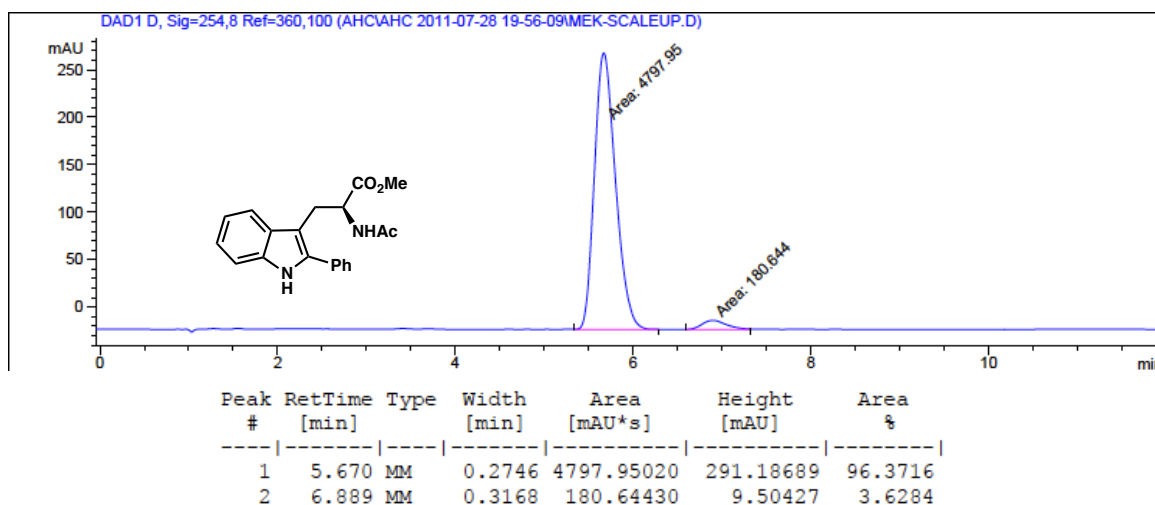
138y (Table 3.2.5, **entry 23**): racemic**138y** (Table 3.2.5, **entry 23**): enantioenriched, 90% ee

138z (Scheme 3.2.3): racemic**138z** (Scheme 3.2.3): enantioenriched, 67% ee

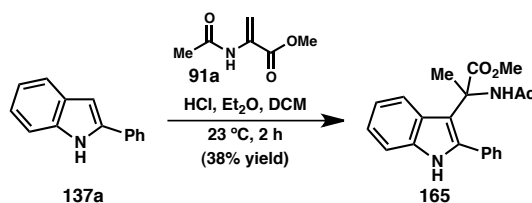
3.4.6 Scale-up Procedure



To a flame-dried flask under nitrogen containing freshly activated powdered 4Å molecular sieves (200 wt %) was added 2-phenylindole (**137a**, 1.00 g, 5.20 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 890 mg, 6.20 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (**102k**, 457 mg, 1.00 mmol, 0.20 equiv). The flask was charged with DCM (40 mL) and SnCl_4 (1 M in DCM, 5.20 mL, 5.20 mmol, 1.00 equiv) was added. The reaction was stirred at room temperature for 2 hours, then quenched by addition of 1 M HCl (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NaHCO_3 (50 mL), dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 1.33 g (77% yield) of **138c** as a pale yellow foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 5.7$ min, $t_{\text{R}}(\text{minor}) = 6.9$ min.



3.4.7 Preparation of Methyl 2-acetamido-2-(2-phenyl-1H-indol-3-yl)propanoate (**165**)

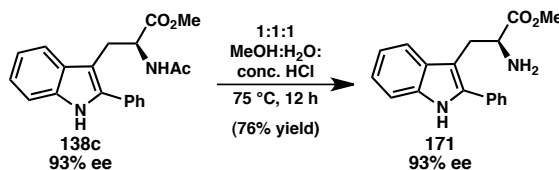


To a flame-dried flask charged with 2-phenylindole (**137a**, 38.6 mg, 0.200 mmol, 1.00 equiv) and methyl 2-acetamidoacrylate (**91a**, 34.3 mg, 0.240 mmol, 1.20 equiv) was added 1.5 mL DCM, followed by HCl dropwise (2 M in Et₂O, 100 μ L, 0.200 mmol, 1.00 equiv). After stirring in the dark 2 hours at room temperature, the dark yellow reaction solution was diluted with 10 mL EtOAc and quenched with 10 mL saturated aqueous NaHCO₃. The aqueous layer was extracted with 10 mL EtOAc and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (gradient, 0:100 to 100:0 EtOAc:hexanes) to yield 25.8 mg (38% yield) of methyl 2-acetamido-2-(2-phenyl-1H-indol-3-yl)propanoate (**165**) as a pale yellow foam. ¹H NMR (500 MHz, CDCl₃) δ 8.37 (br s, 1H), 7.79 (d, *J* = 8.0 Hz,

1H), 7.56 – 7.48 (m, 2H), 7.45 – 7.37 (m, 3H), 7.30 (ddd, $J = 8.1, 0.9, 0.9$ Hz, 1H), 7.20 (ddd, $J = 8.1, 7.1, 1.2$ Hz, 1H), 7.15 (ddd, $J = 8.2, 7.1, 1.2$ Hz, 1H), 6.70 (br s, 1H), 3.48 (s, 3H), 1.96 (s, 3H), 1.70 (s, 3H).; ^{13}C NMR (125 MHz, CDCl_3) δ 173.5, 168.8, 135.5, 135.4, 133.5, 130.6, 128.7, 128.0, 126.1, 122.2, 120.5, 120.1, 111.4, 111.1, 59.8, 52.7, 24.4, 23.3.; FTIR (NaCl/thin film): 3271, 3054, 2948, 1734, 1663, 1507, 1489, 1458, 1445, 1432, 1370, 1295, 1253, 1126 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 337.1547, found 337.1545.

3.4.8 Functionalization of Tryptophan 138c

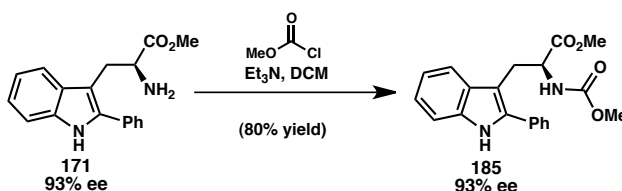
3.4.8.1 Acetamide Hydrolysis⁴⁴



A vial was charged with (S)-Nα-acetyl-2-phenyltryptophan methyl ester (**138c**, 30.0 mg, 0.09 mmol), MeOH (1 mL), H₂O (1 mL) and aqueous HCl (12 M, 1 mL). The reaction was heated to 75 °C for 12 hours, then concentrated, redissolved in DCM (10 mL) and washed with saturated aqueous NaHCO_3 (3 X 5 mL). The aqueous layers were combined and extracted with DCM (4 X 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel chromatography (99:1 DCM:MeOH) to yield 20.0 mg (76% yield) of **171** as a light yellow oil. The enantiomeric excess was determined by chiral SFC analysis of the corresponding methylcarbamate **185** (see below). ^1H NMR (500 MHz,

CDCl₃) δ 8.18 (br s, 1H), 7.67 (dd, J = 7.6, 0.7 Hz, 1H), 7.62 – 7.60 (m, 2H), 7.50 – 7.43 (m, 2H), 7.41 – 7.34 (m, 2H), 7.22 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.15 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 3.89 (dd, J = 8.4, 5.0 Hz, 1H), 3.56 (s, 3H), 3.47 – 3.38 (m, 1H), 3.27 – 3.14 (m, 1H), 1.69 (br s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 175.5, 136.1, 135.8, 132.9, 129.1, 129.0, 128.3, 128.0, 122.5, 119.9, 119.2, 110.9, 108.2, 55.2, 51.9, 30.2; IR (NaCl/thin film): 3367, 3062, 2948, 1732, 1603, 1489, 1457, 1207; $[\alpha]_D^{25}$ = -12.4° (c = 0.85, CHCl₃). HRMS (MM) calc'd for [M+H]⁺ 295.1441, found 295.1446.

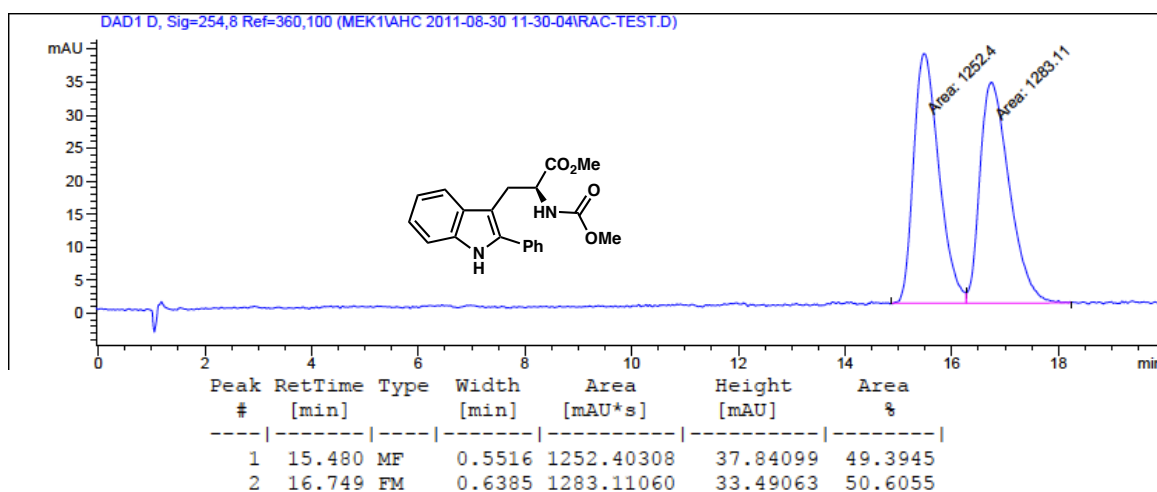
Methylcarbamate Protection



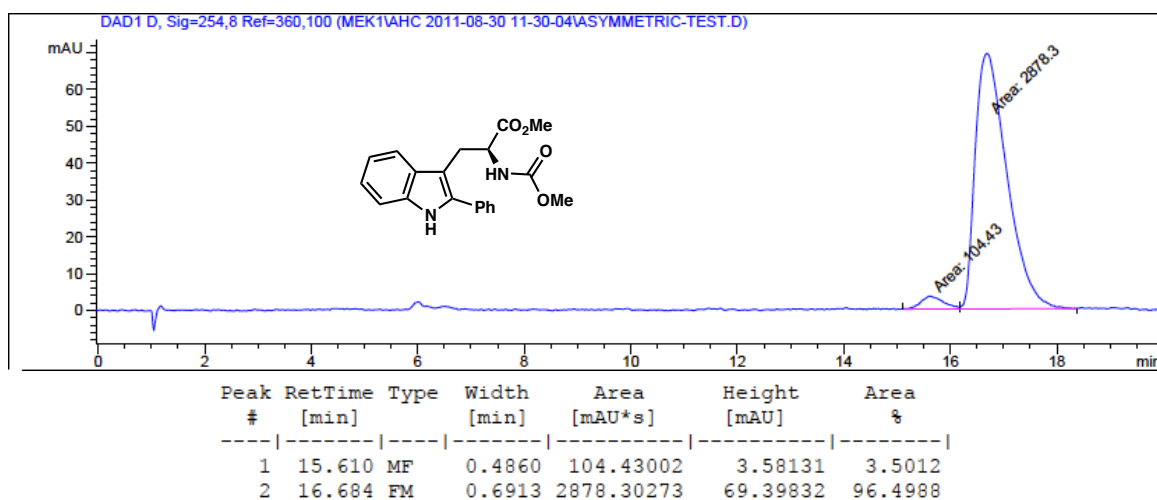
A flame-dried flask was charged with free amine **171** (19.5 mg, 0.70 mmol, 1.00 equiv), Et₃N (19 μ L, 0.13 mmol, 2.0 equiv) and DCM (5 mL). Methylchloroformate (6.0 μ L, 0.73 mmol, 1.10 equiv) was added and the solution was stirred at room temperature for 3 hours, then quenched with saturated aqueous NH₄Cl (5 mL) and extracted with EtOAc (2 X 5 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by silica gel chromatography (25:75 EtOAc:hexanes) to yield 18.5 mg (80% yield) of methylcarbamate **185** as a colorless oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OD-H, 2.5 mL/min, 15% IPA in CO₂, λ = 254 nm): t_R (major) = 16.7 min, t_R (minor) = 15.6 min. ¹H NMR (500 MHz, CDCl₃) δ 8.11 (br s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.48 – 7.45 (m, 2H), 7.40 – 7.35 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 (m, 1H), 5.06 (br d, J

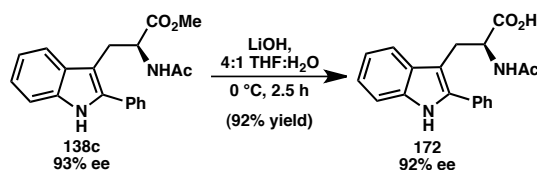
= 7.7 Hz, 1H), 4.63 – 4.59 (m, 1H), 3.54 (s, 3H), 3.50 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.3, 156.1, 136.2, 135.7, 132.9, 129.2, 129.0, 128.3, 128.0, 122.5, 120.0, 118.9, 110.9, 106.7, 54.5, 52.12, 52.07, 27.1; IR (NaCl/thin film) 3338, 2953, 2923, 2852, 1718, 1701, 1507, 1457, 1363, 1213, 1072 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +22.6^\circ$ ($c = 0.10$, CHCl_3). HRMS (MM) calc'd for $[\text{M}+\text{H}]^+$ 353.1496, found 353.1497.

Methylcarbamate (185): racemic

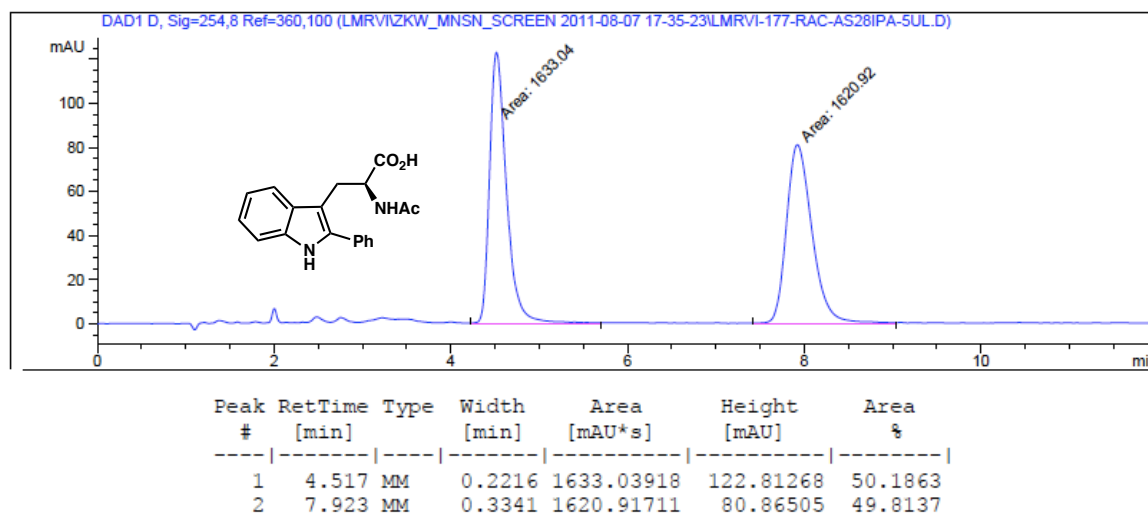
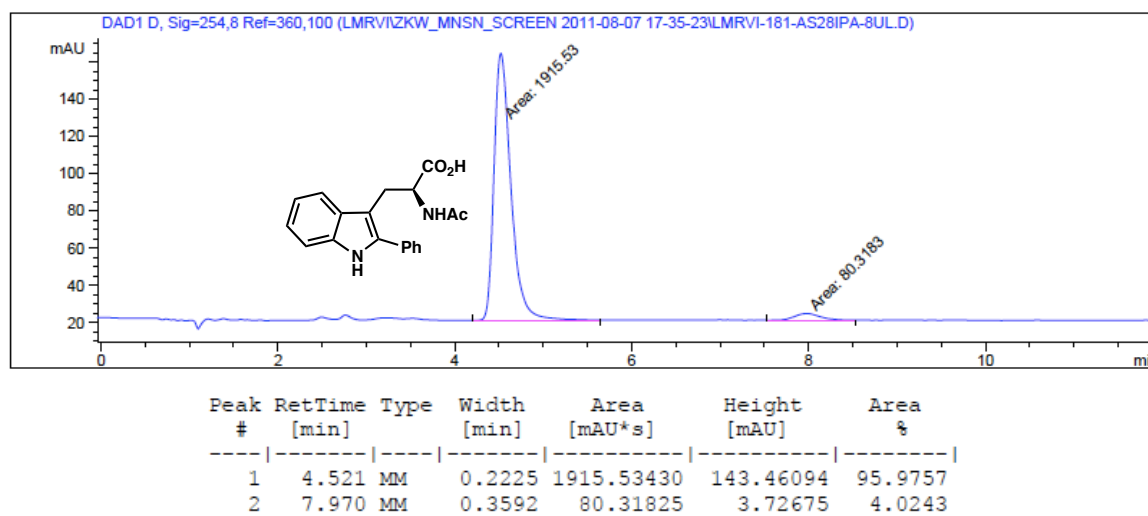


Methylcarbamate (185): enantioenriched, 93% ee



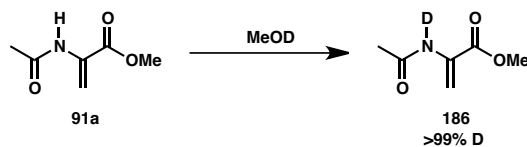
3.4.8.2 Methyl Ester Hydrolysis⁴⁵

A 10 mL flask was charged with (S)-N α -acetyl-2-phenyltryptophan methyl ester **138c** (67.2 mg, 0.20 mmol, 1.00 equiv) and THF (0.9 mL) then cooled to 0 °C, followed by dropwise addition of aqueous LiOH (1.75 M, 230 μ L, 0.40 mmol, 2.00 equiv). The reaction was vigorously stirred at 0 °C for 2 hours, then diluted with H₂O (15 mL) and extracted with EtOAc (2 x 10 mL). The aqueous layer was acidified to pH = 1.5 and extracted with EtOAc (5 x 15 mL). The combined organic layers from the acidic aqueous extraction were dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel chromatography (0:99:1 to 15:84:1 MeOH:DCM:AcOH) to yield 59.2 mg (92% yield) of carboxylic acid **172** as a pale yellow foam. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AS-H, 2.5 mL/min, 28% IPA in CO₂, λ = 254 nm): t_R (major) = 4.5 min, t_R (minor) = 8.0 min. ¹H NMR (500 MHz, CDCl₃) δ 8.21 (br s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.47 (dd, J = 7.6, 7.6 Hz, 2H), 7.40 (m, 1H), 7.37 (ddd, J = 8.0, 0.8, 0.8 Hz, 1H), 7.21 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 7.14 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 5.72 (br d, J = 7.4 Hz, 1H), 4.73 (td, J = 7.1, 5.4 Hz, 1H), 3.56 (dd, J = 14.9, 5.2 Hz, 1H), 3.49 (dd, J = 15.0, 6.9 Hz, 1H), 1.62 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.7, 170.9, 136.2, 135.7, 132.9, 129.13, 129.05, 128.3, 128.2, 122.6, 120.1, 118.8, 111.0, 106.8, 53.1, 26.2, 22.6; IR (NaCl/thin film): 3391, 3306, 3055, 3011, 2921, 2850, 1717, 1615, 1527, 1457, 1448, 1215 cm⁻¹; [α]_D²⁵ = +9.2° (c = 1.05, MeCN). HRMS (MM) calc'd for [M+H]⁺ 323.1390, found 323.1390.

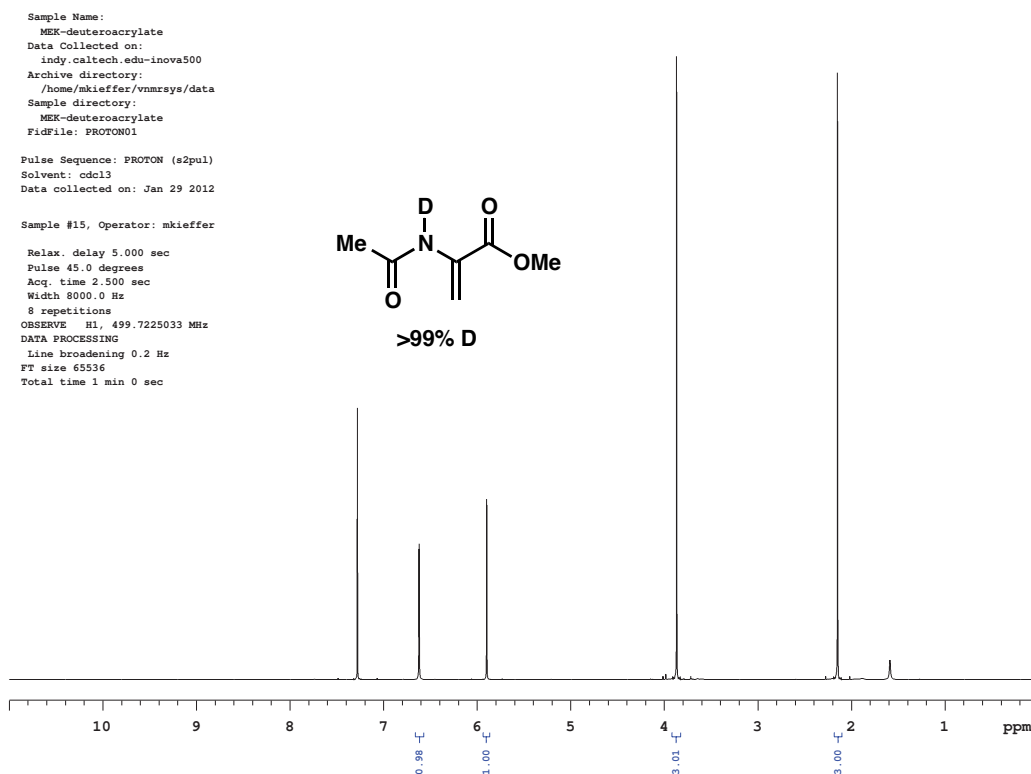
172: racemic**172: enantioenriched, 92% ee**

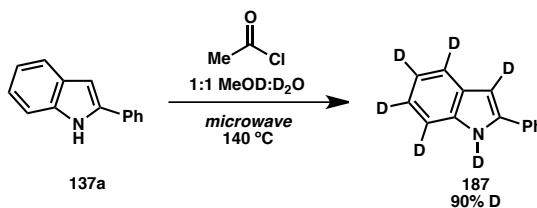
3.4.9 Deuterium Labeling Studies

Preparation of *N*-deuteroacrylate (**186**).

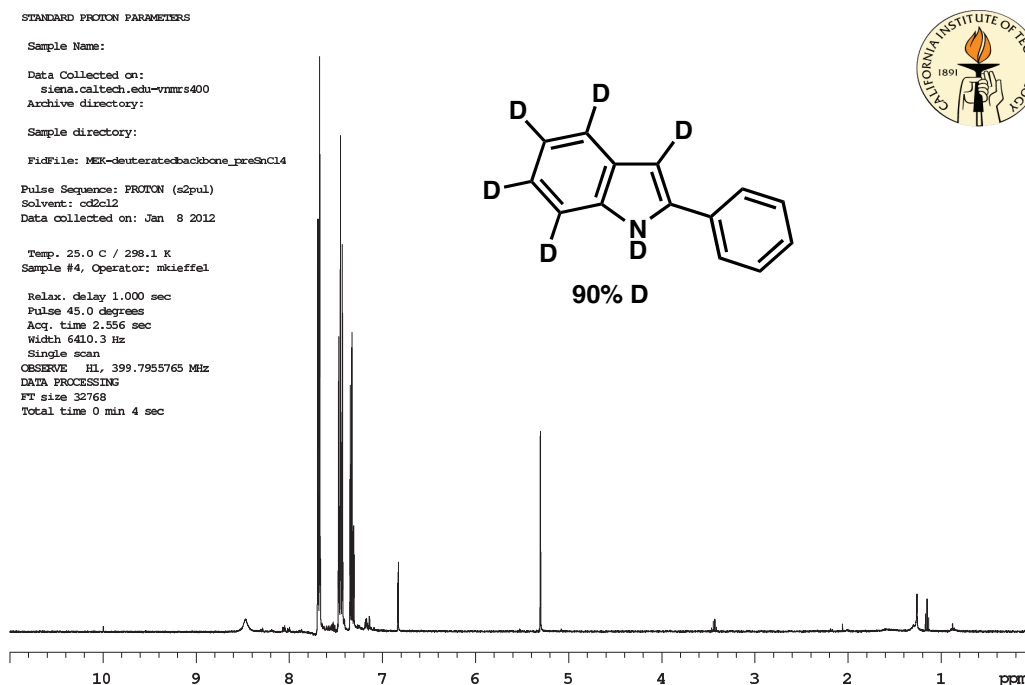


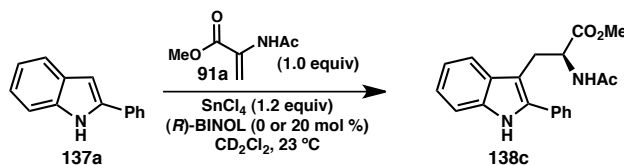
Acrylate **91a** was dissolved in MeOD (1 mL) under nitrogen. After stirring for 1 minute, the solution was concentrated under high vacuum. This procedure was repeated three times to give >99% deuterium incorporation.



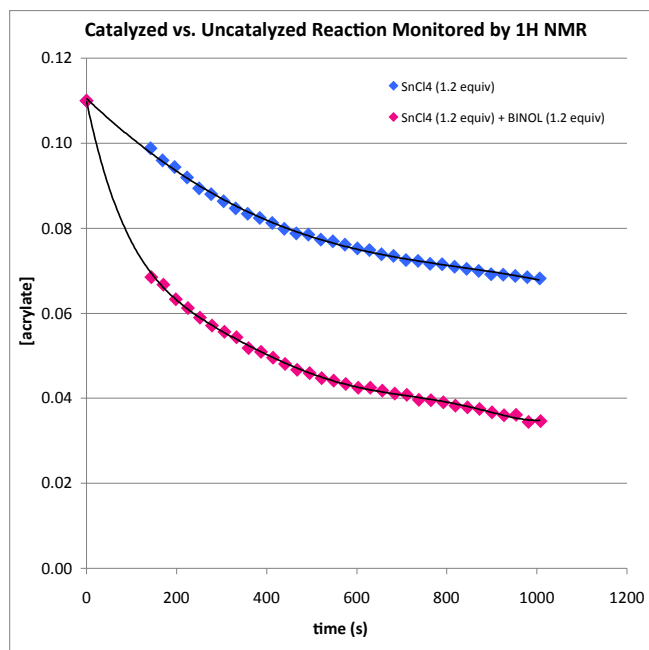
Preparation of per-deutero-2-phenylindole (187).

To MeOD (1 mL) in a microwave vial was added acetyl chloride (100 μ L), followed by 2-phenylindole (6a, 50 mg) and D₂O (1 mL). The vial was sealed and heated in a microwave to 140 °C for 1 hour. Upon cooling, the heterogenous solution was diluted with DCM. The phases were separated and the aqueous was extracted with DCM (2 x 5 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated to give per-deutero-2-phenylindole (**187**) with 90% deuterium incorporation.



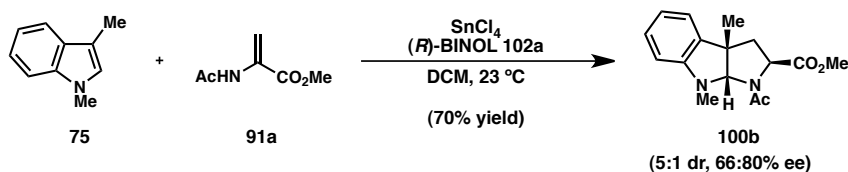
3.4.10 ^1H NMR Kinetics Experiment for SnCl_4 and (*R*)-BINOL (102a)• SnCl_4 ***Promoted Reaction of 137a and 91a.***

An oven-dried vial was charged with 2-phenylindole (**137a**, 19.0 mg, 0.10 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 14.0 mg, 0.10 mmol, 1.00 equiv), (*R*)-BINOL if necessary (6.0 mg, 0.02 mmol, 0.20 equiv) and 1,4-diethylbenzene (4.7 μL , 0.03 mmol, 0.30 equiv) as the internal standard. The vial was pumped into a glove box and charged with CD_2Cl_2 (0.75 mL, to an indole concentration of 0.12 M), then transferred to a screw-cap NMR tube. A ^1H NMR spectrum (1 scan) was taken to determine the initial ratio of acrylate and 1,4-diethylbenzene. SnCl_4 (1 M in CD_2Cl_2 , 120 μL , 0.12 mmol, 1.20 equiv) was then added through the septum of the screw-cap and the NMR tube was inverted once and quickly inserted into the spectrometer. The concentration of acrylate was monitored by ^1H NMR over 9 hours and was determined by integration of its resonance at 3.83 ppm relative to 1,4-diethylbenzene's resonance at 2.74 ppm.

Kinetics Plot

3.4.11 Comparison of Conditions for Pyrroloindoline Formation.

Table 3.2.6, entry 1:



To a flame-dried 10 mL flask was added 1,3-dimethylindole (**75**, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate **91a** (28.6 mg, 0.20 mmol, 1.00 equiv), and (*R*)-BINOL (**102a**, 11.4 mg, 0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of SnCl_4 (1 M in DCM, 240 μL , 0.24 mmol, 1.20 equiv) and the reaction mixture was stirred at room temperature for 4 hours, then quenched by diluting with MeCN (1 mL) and 1 M HCl (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO_3 (15 mL). The aqueous layer was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product **100b** was formed in a 5:1 ratio of diastereomers favoring the *exo* diastereomer (determined by ^1H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 40.1 mg (70% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the *exo* diastereomer was determined to be 66% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 9.0$ min, $t_{\text{R}}(\text{minor}) = 5.8$ min. The enantiomeric excess of the *endo* diastereomer was determined to be 80% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 3.8$ min, $t_{\text{R}}(\text{minor}) = 4.5$ min. Spectral data are in agreement with the literature.⁴⁶

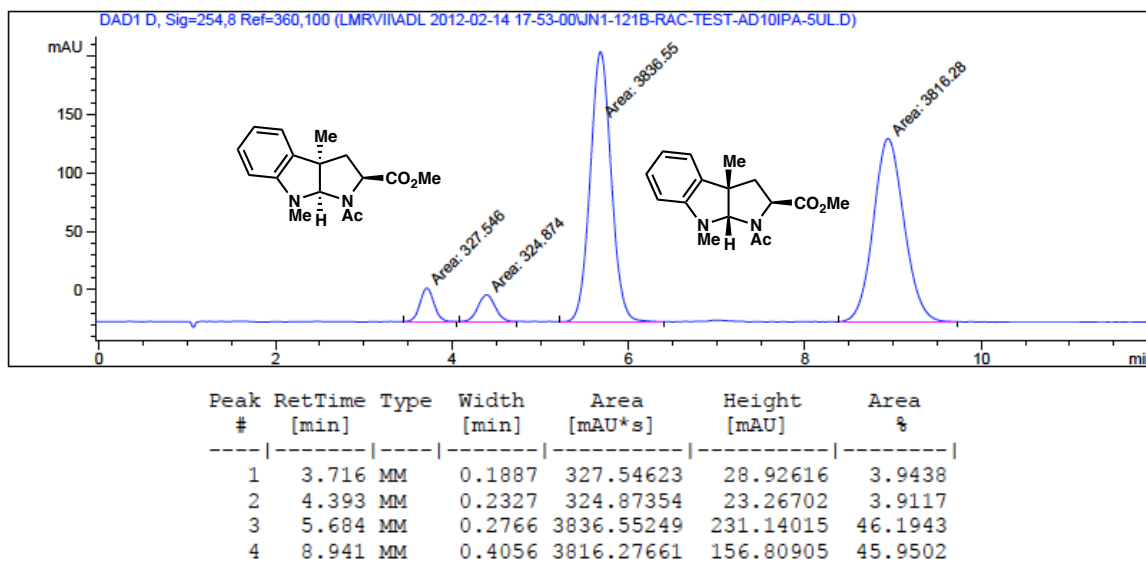
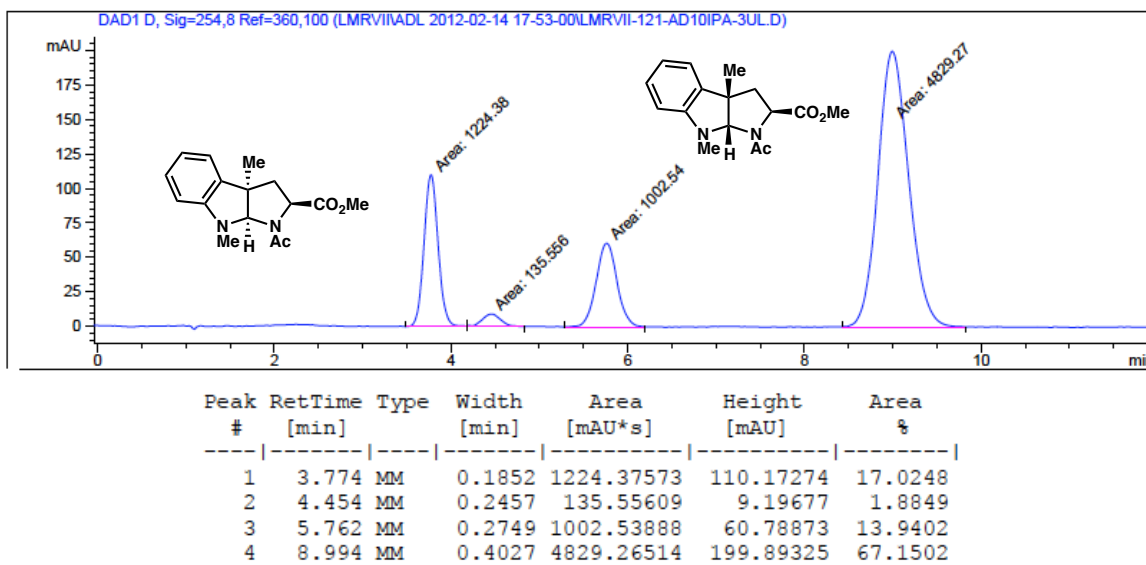
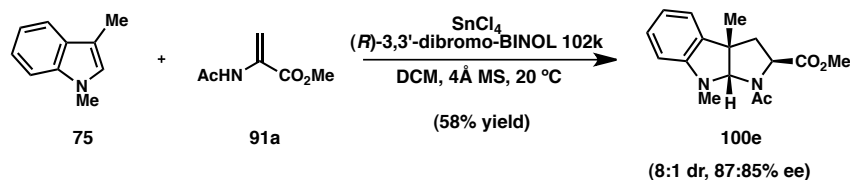
100b (Table 3.2.6, entries 1-2): racemic**100b** (Table 3.2.6, entry 1): enantioenriched, *exo*: 65% ee, *endo*: 80% ee

Table 3.2.6, entry 2:



An oven-dried vial was charged with 1,3-dimethylindole (**75**, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate **91a** (34.3 mg, 0.24 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (**102k**, 17.8 mg, 0.04 mmol, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4 Å molecular sieves (200 wt % relative to **75**). The vial was charged with DCM (1.5 mL) and SnCl_4 (1 M in DCM, 200 μL , 0.20 mmol, 1.00 equiv) was added. The reaction was stirred at 20 °C for 4 hours, after which time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO_3 (15 mL). The aqueous was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product **100b** was formed in a 8:1 ratio of diastereomers favoring the *exo* diastereomer (determined by ^1H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 33.5 mg (58% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the *exo* diastereomer was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2 , $\lambda = 254$ nm): $t_{\text{R}}(\text{major}) = 8.9$ min, $t_{\text{R}}(\text{minor}) = 5.7$ min. The enantiomeric excess of the *endo* diastereomer was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2 , $\lambda = 254$ nm):

$t_R(\text{major}) = 3.7 \text{ min}$, $t_R(\text{minor}) = 4.4 \text{ min}$. Spectral data are in agreement with the literature.⁴⁶

100b (Table 3.2.6, **entry 2**): enantioenriched, *exo*: 87% ee, *endo*: 85% ee

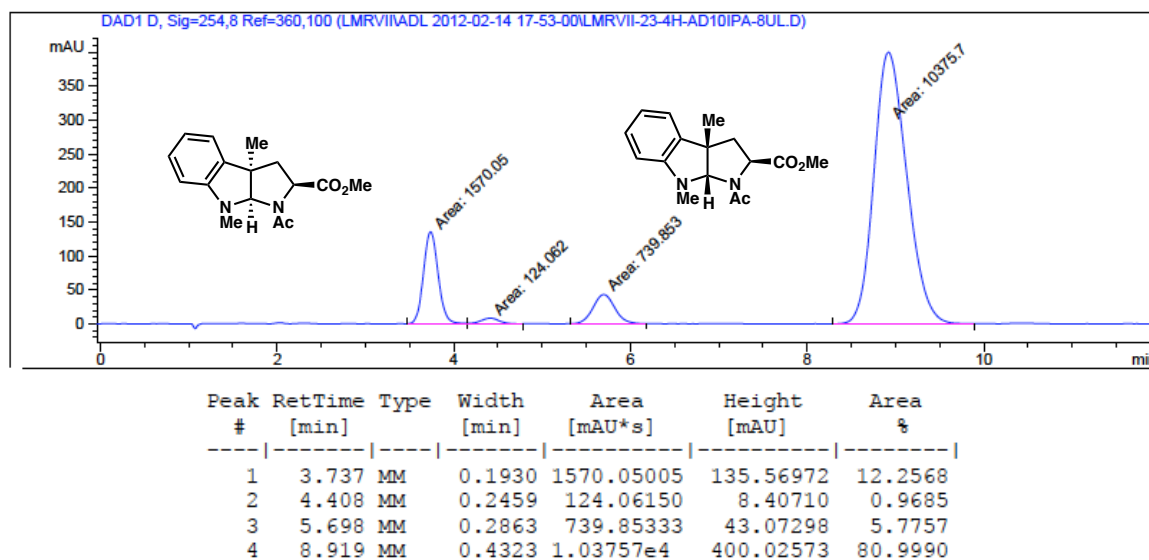
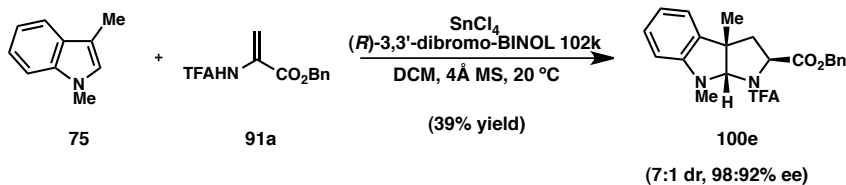


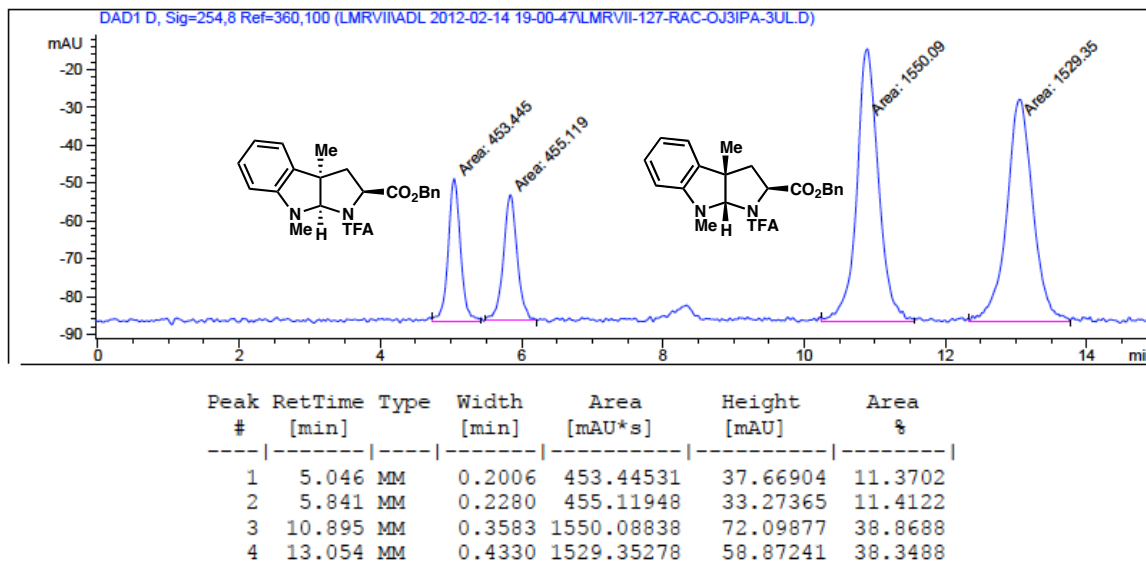
Table 3.2.6, entry 4:[§]

An oven-dried vial was charged with 1,3-dimethylindole (**75**, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate **91d** (65.5 mg, 0.24 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (**102k**, 17.8 mg, 0.04 mmol, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to **75**). The vial was charged with DCM (1.5 mL) and SnCl₄ (1 M in DCM, 200 μL, 0.20 mmol, 1.00 equiv) was added. The reaction was stirred at 20 °C for 4 hours, after which time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (15 mL). The aqueous was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The product **100e** was formed in a 7:1 ratio of diastereomers favoring the *exo* diastereomer (determined by ¹H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 32.7 mg (39% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the *exo* diastereomer was determined to be 98% by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO₂, λ = 254 nm): *t*_R(major) = 12.5 min, *t*_R(minor) = 10.9 min. The enantiomeric excess of the *endo* diastereomer was determined to be 92% by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO₂, λ = 254 nm):

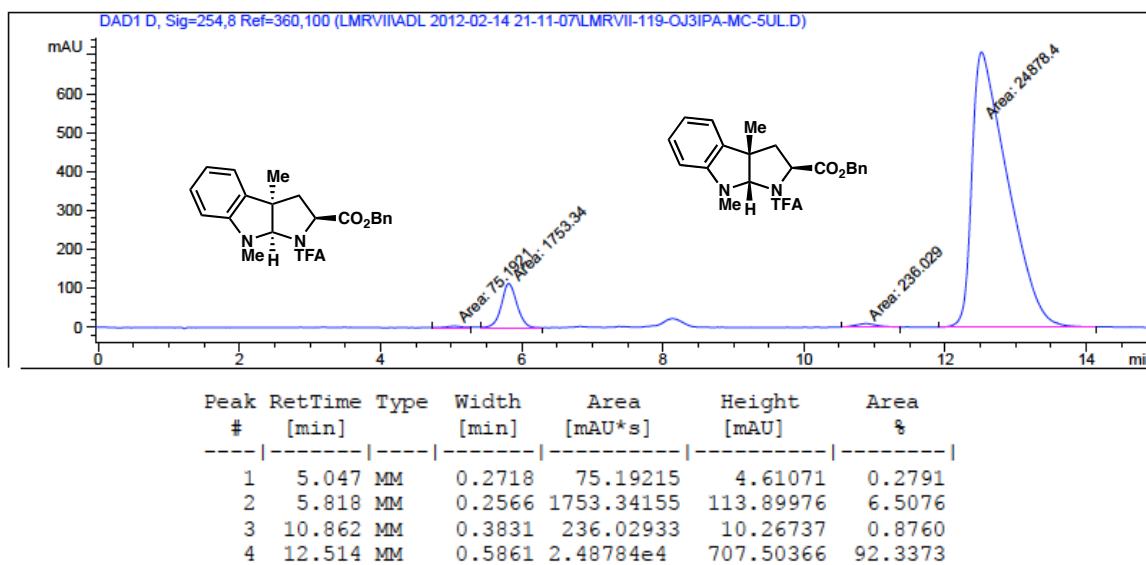
[§] For information on Table 3.2.6, entry 3, see ref. 45.

$t_R(\text{major}) = 5.8 \text{ min}$, $t_R(\text{minor}) = 5.0 \text{ min}$. Spectral data are in agreement with the literature.⁴⁶

100e (Table 3.2.6, entry 4): racemic



100e (Table 3.2.6, entry 4): enantioenriched, *exo*: 98% ee, *endo*: 92% ee



3.5 NOTES AND REFERENCES

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APPENDIX 3

Spectra Relevant to Chapter 3:

Synthesis of Tryptophan Derivatives by a Tandem Friedel–Crafts

Conjugate Addition/Enantioselective Protonation Reaction

LMRVI-067-3-Cl-2, 2'-MOM-R-BINOL

Sample Name: IMRVI-067-3-Cl-2_2-MOM-R-BINOL
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepks/vnmrsys/data
Sample directory: IMRVI-067-3-Cl-2_2-MOM-R-BINOL
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2011

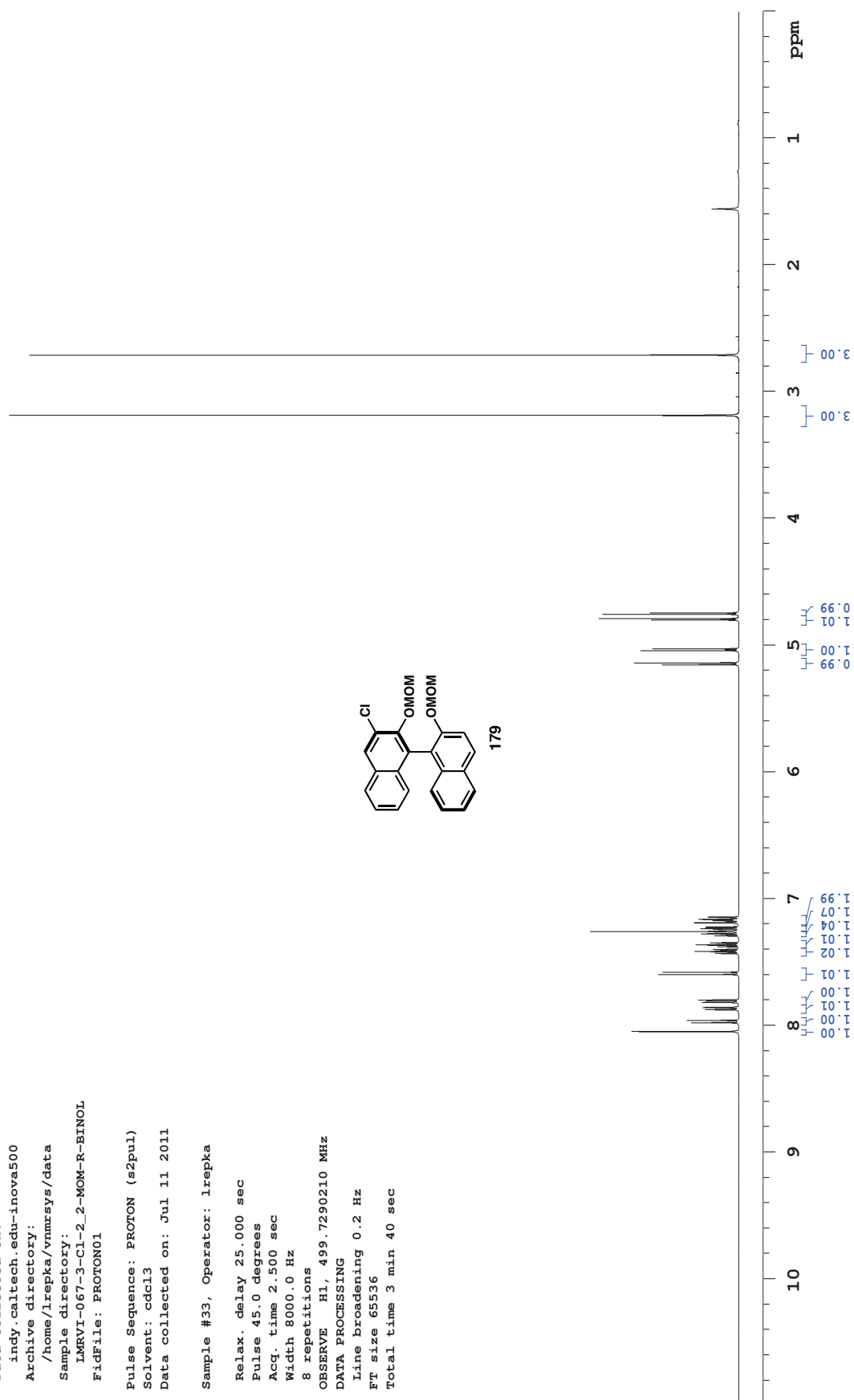
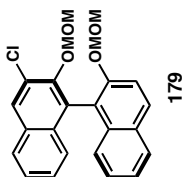
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Sample #33, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions

OBSERVE H1, 499.7290210 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 40 sec

```



LMRVI-067-3-Cl-2,2'-MOM-R-BINOL

Sample Name:

LMRVI-067-3-Cl-2,2'-MOM-R-BINOL

Data Collected on:

indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-067-3-Cl-2,2'-MOM-R-BINOL

File: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 11 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1590 repetitions

OBSERVE C13, 125.6569667 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

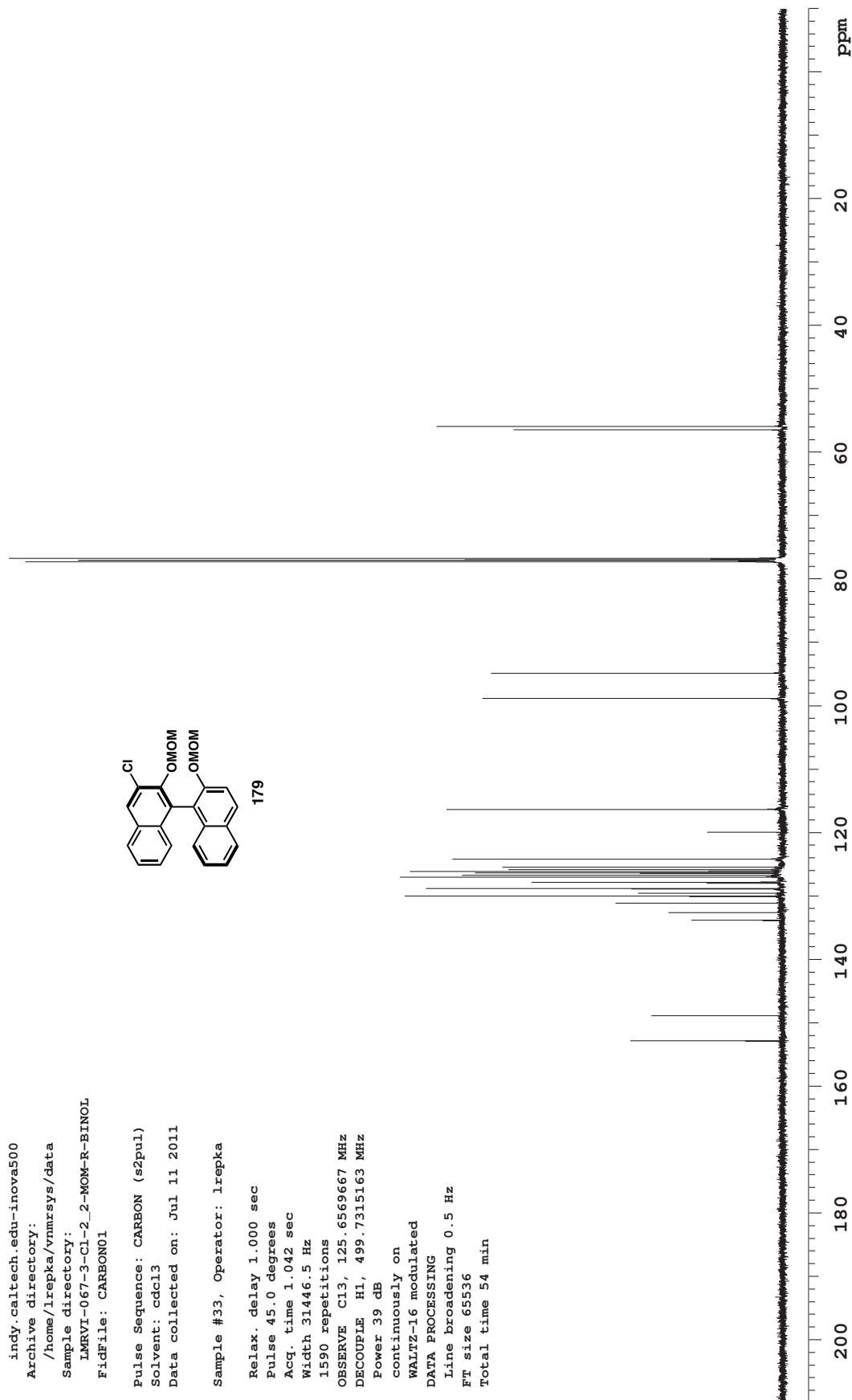
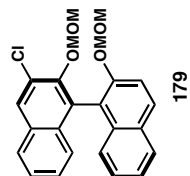
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 54 min



LMRVI-093-3-Cl-R-BINOL

Sample Name:

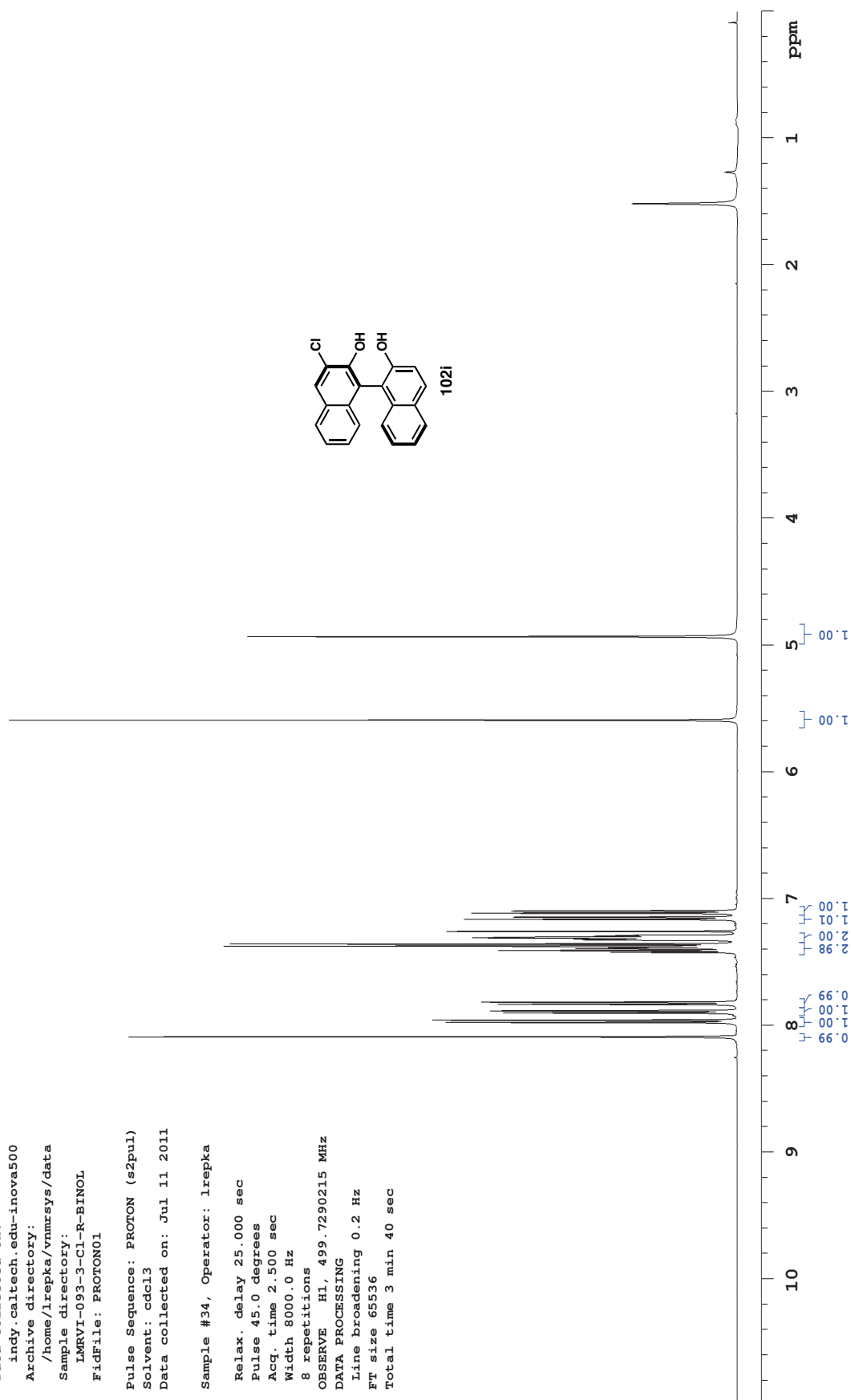
LMRVI-093-3-Cl-R-BINOL
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVI-093-3-Cl-R-BINOL
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2011

Sample #34, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions

OBSERVE H1, 499.7290215 MHz
DATA PROCESSING
Line broadening 0.2 Hz
Ft size 65536
Total time 3 min 40 sec



LMRVI-093-3-Cl-R-BINOL

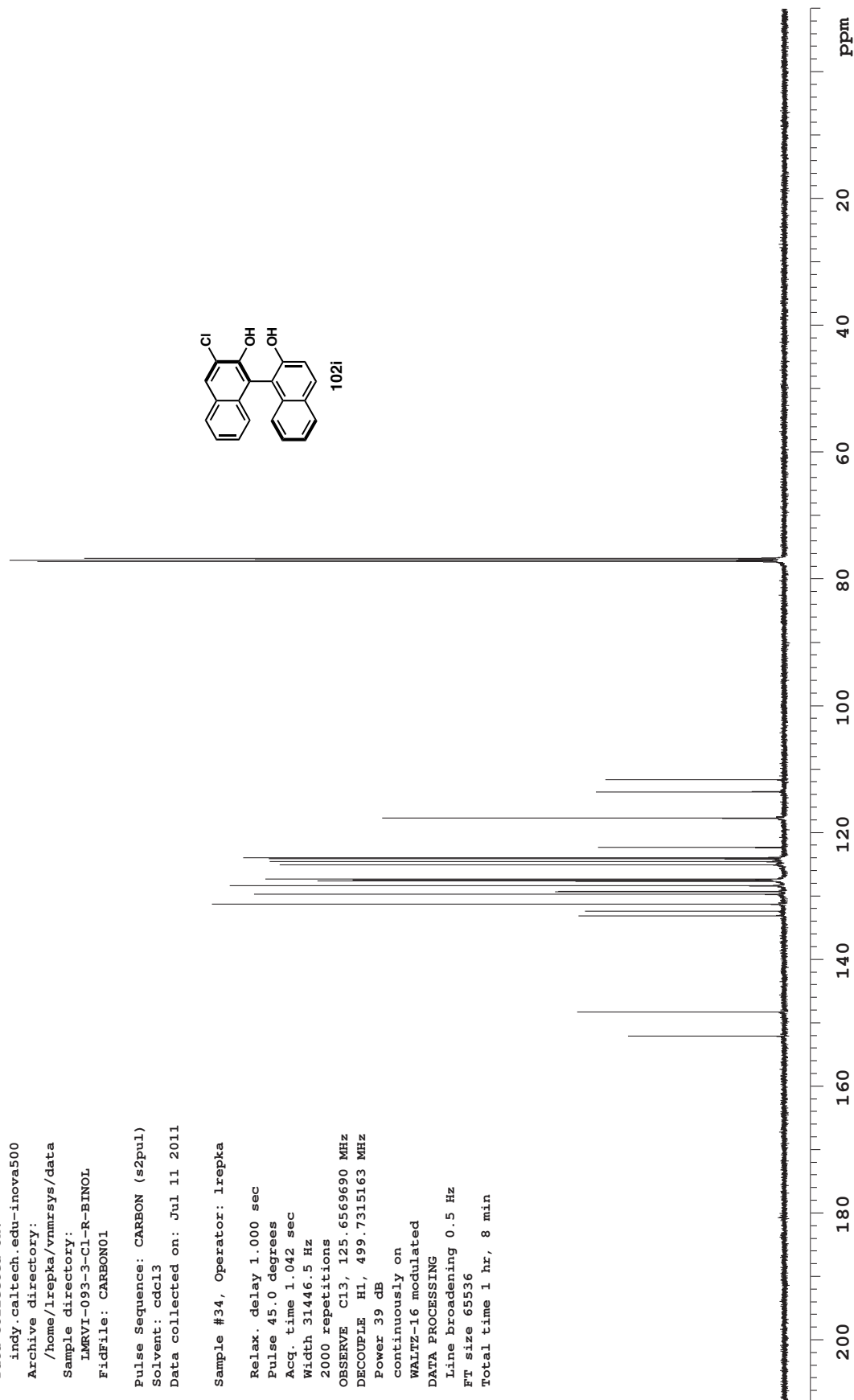
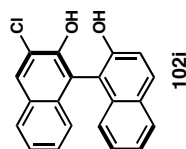
Sample Name:

LMRVI-093-3-Cl-R-BINOL
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVI-093-3-Cl-R-BINOL
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2011

Sample #34, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6569690 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min



LMRVI-279-6,6'-hydroxy-MOM BINOL

Sample Name:
LMRVI-279

Data Collected on:
indy.caltech.edu-inova500

Archive directory:
/home/lrepka/vnmrsys/data

Sample directory:
LMRVI-279

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cd3cn

Data collected on: Dec 20 2011

Sample #42, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

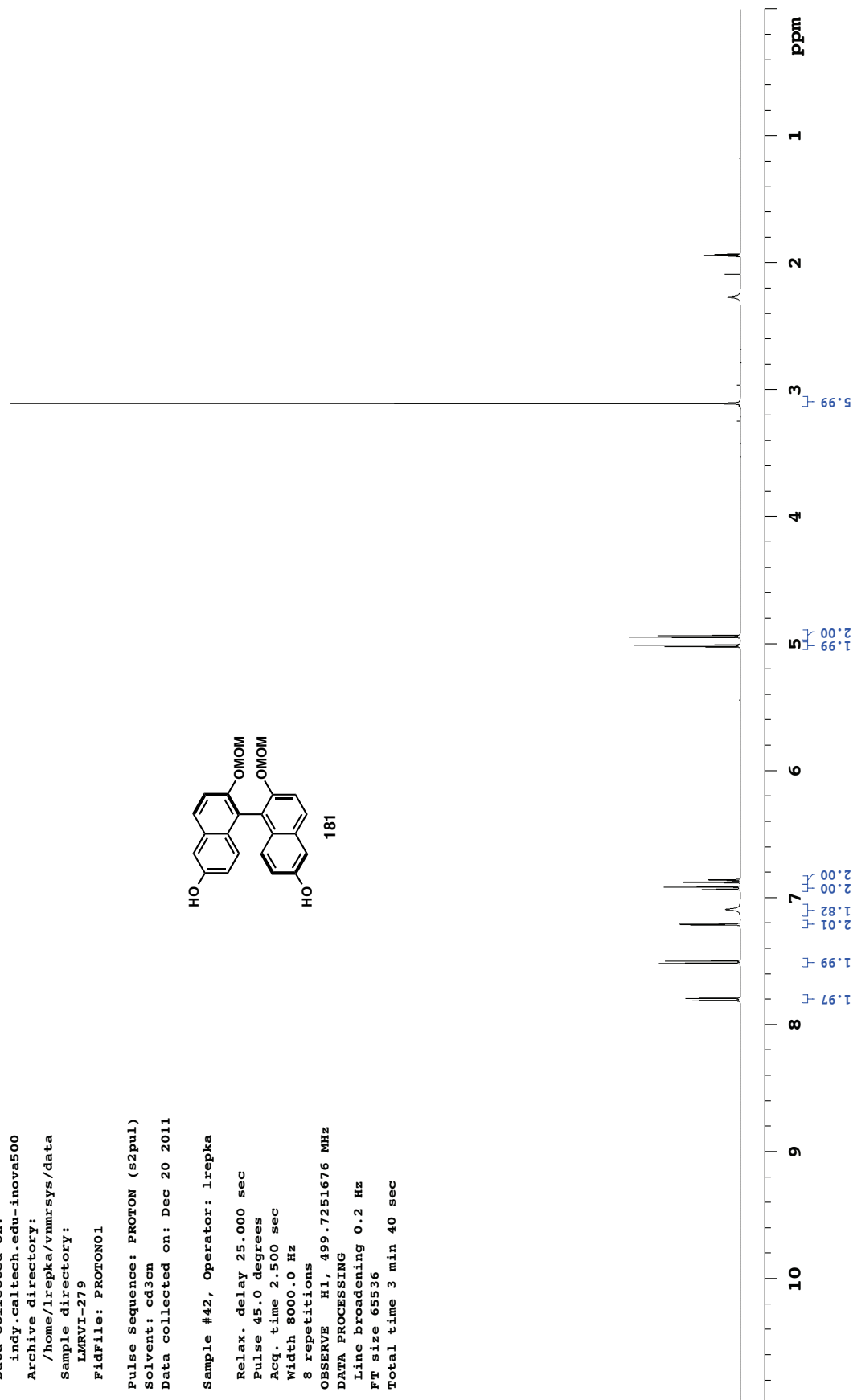
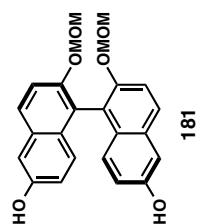
OBSERVE H1, 499.7251676 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 3 min 40 sec



LMRVI-279-6,6'-hydroxy-MOM BINOL

Sample Name:

LMRVI-279

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-279

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cd3cn

Data collected on: Dec 20 2011

Sample #42, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1500 repetitions

OBSERVE C13, 125.6558710 MHz

DECOUPLE H1, 499.7276454 MHz

Power 39 dB

continuously on

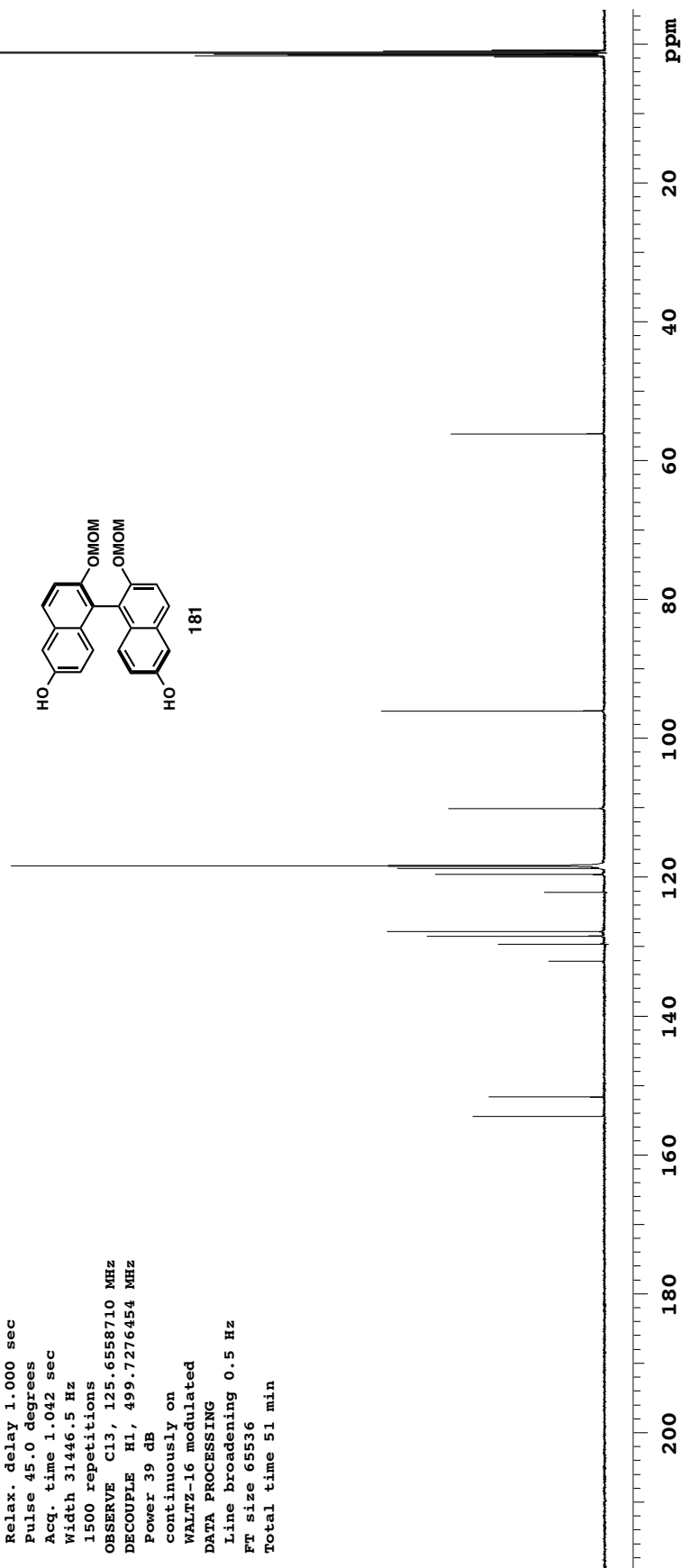
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 51 min



LMRVI-273-2-1-allyl-2-phenylindole

Sample Name:

LMRVI-273-2-1-allyl-2-phenylindole

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-273-2-1-allyl-2-phenylindole

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Dec 4 2011

Sample #33, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

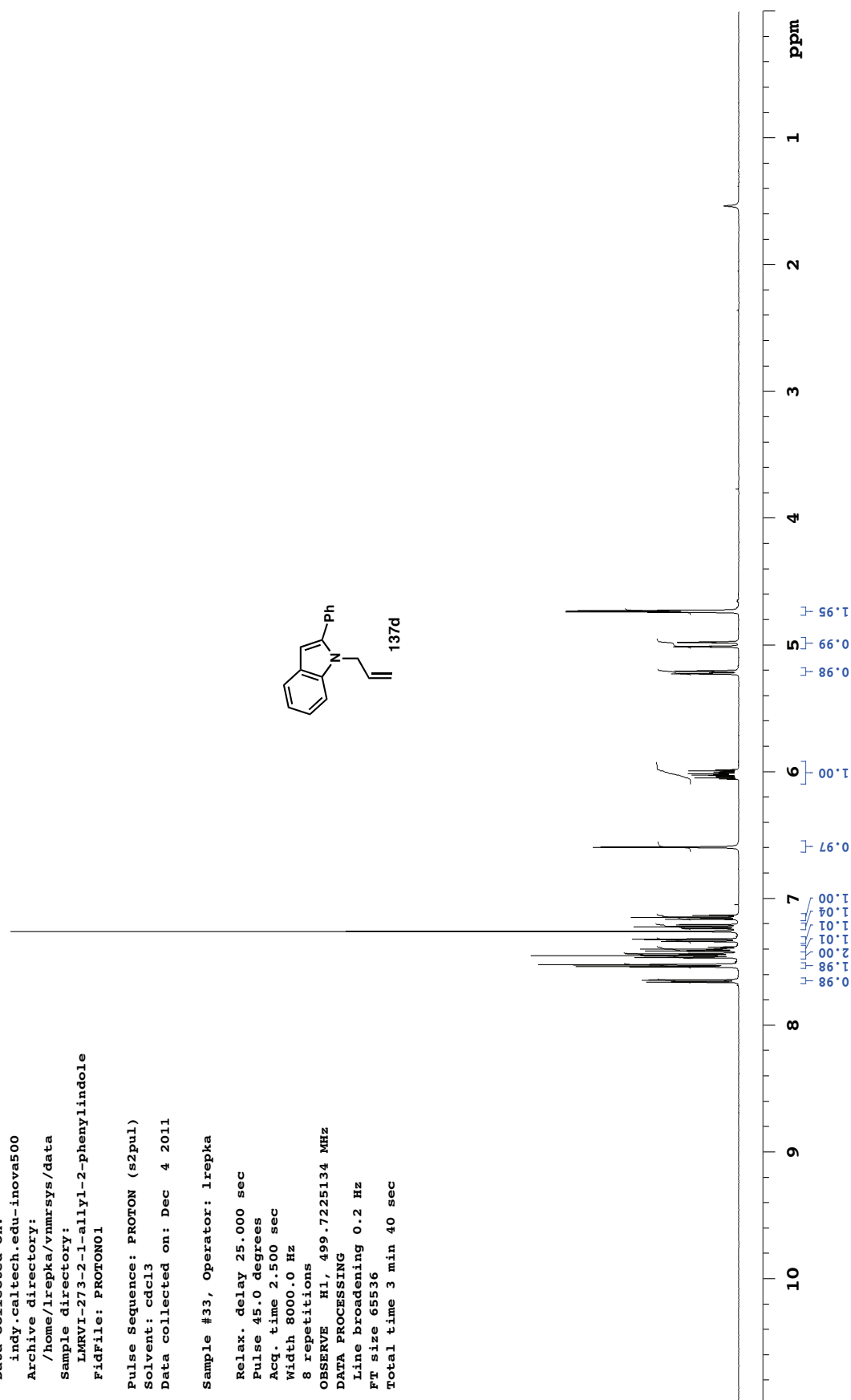
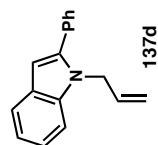
OBSERVE H1, 499.7225134 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 3 min 40 sec



LMRVI-273-1-allyl-2-phenylindole

Sample Name:

LMRVI-273-1-allyl-2-phenylindole

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-273-1-allyl-2-phenylindole

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Dec 4 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1500 repetitions

OBSERVE C13, 125.6553343 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

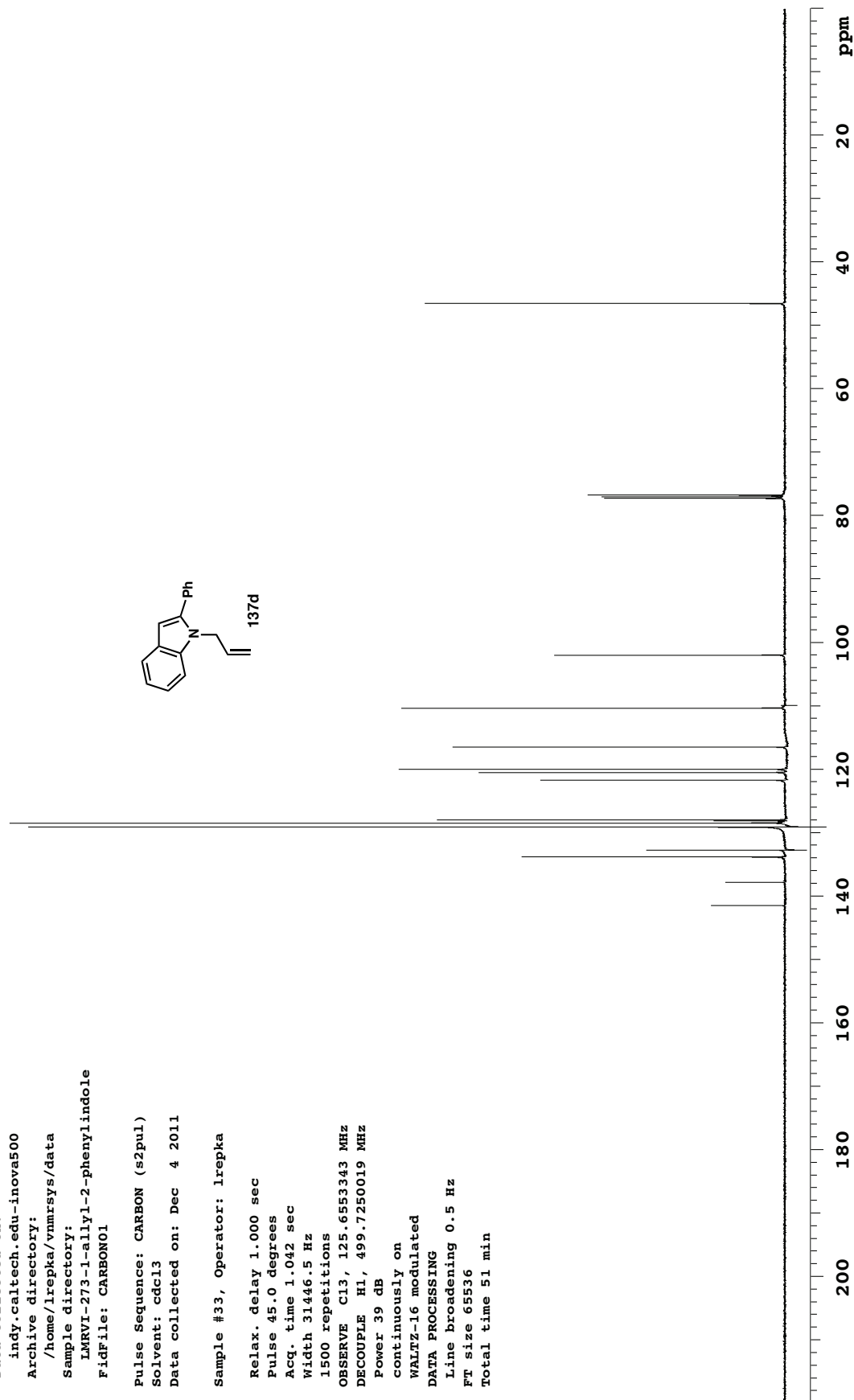
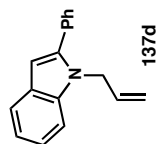
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 51 min



LMRVI-273-1,3-diallyl-2-phenylindole

Sample Name:

LMRVI-273-1,3-diallyl-2-phenylindole

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrSYS/data

Sample directory:

LMRVI-273-1,3-diallyl-2-phenylindole

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Dec 11 2011

Sample #27, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

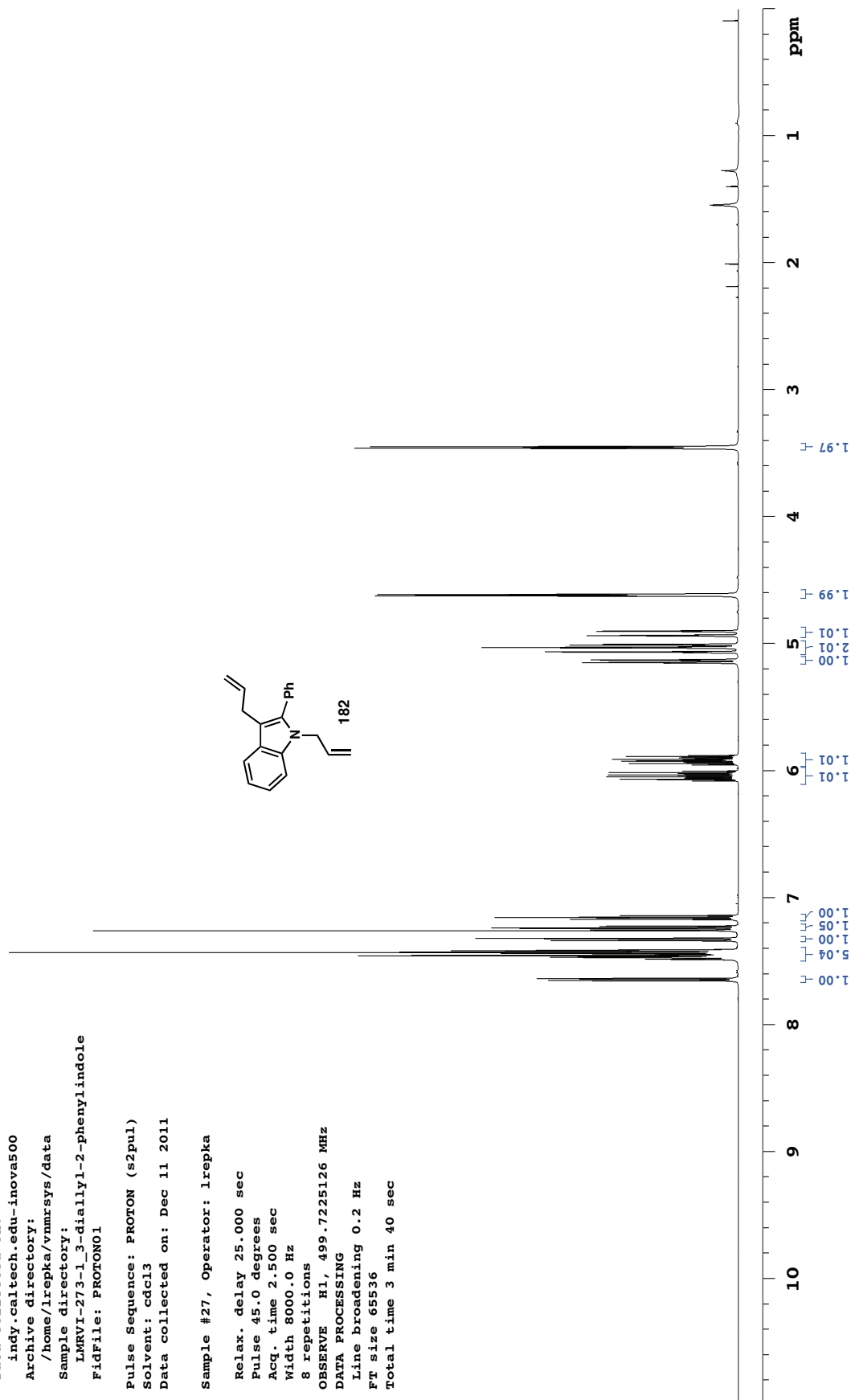
OBSERVE H1, 499.7225126 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 3 min 40 sec



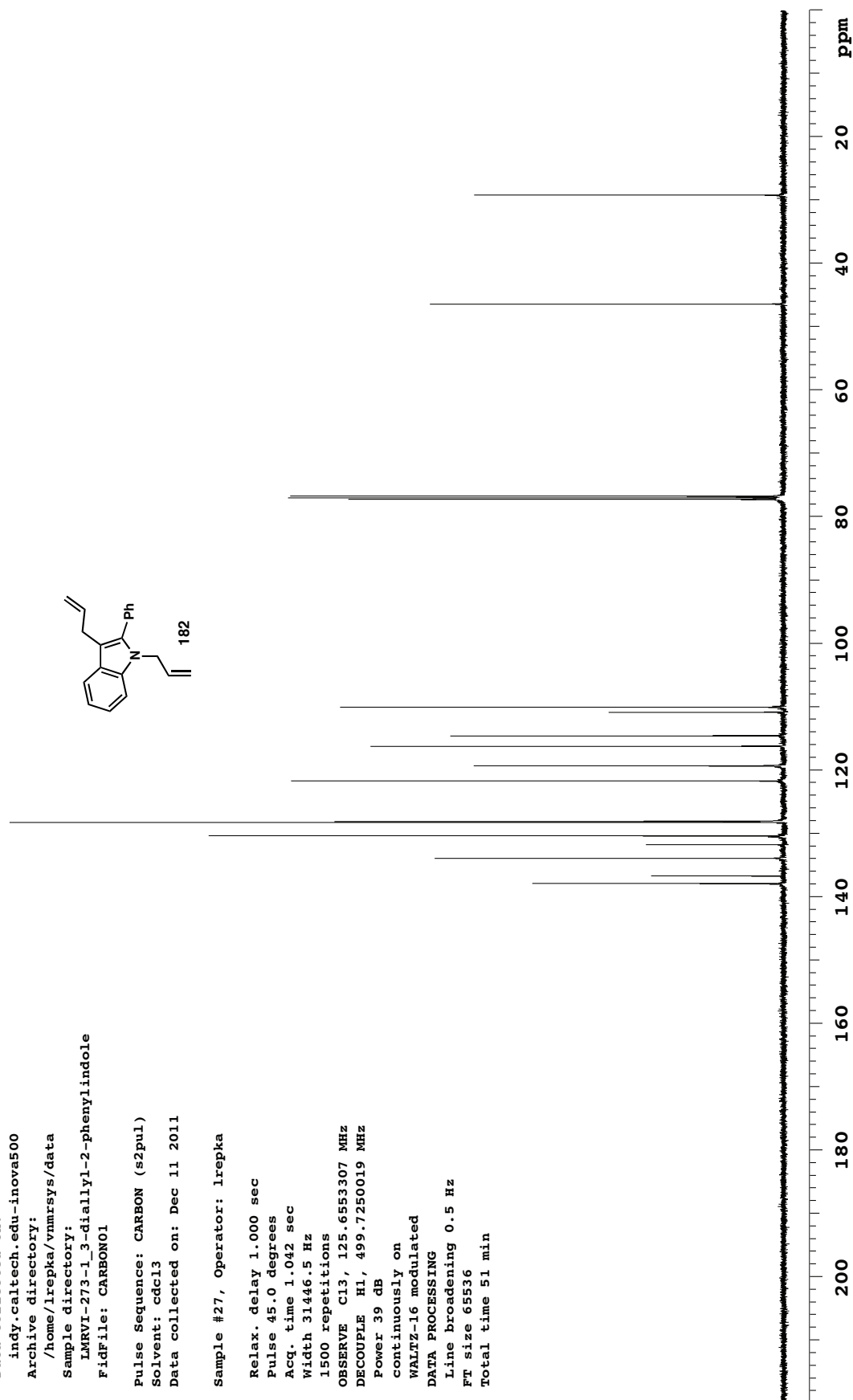
LMRVI-273-1,3-diallyl-2-phenylindole

Sample Name:
LMRVI-273-1,3-diallyl-2-phenylindole
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrSYS/data
Sample directory:
LMRVI-273-1,3-diallyl-2-phenylindole
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 11 2011

Sample #27, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553307 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min



LMRVI-219

Sample Name:

LMRVI-219

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-219

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Sep 2 2011

Sample #33, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

6 repetitions

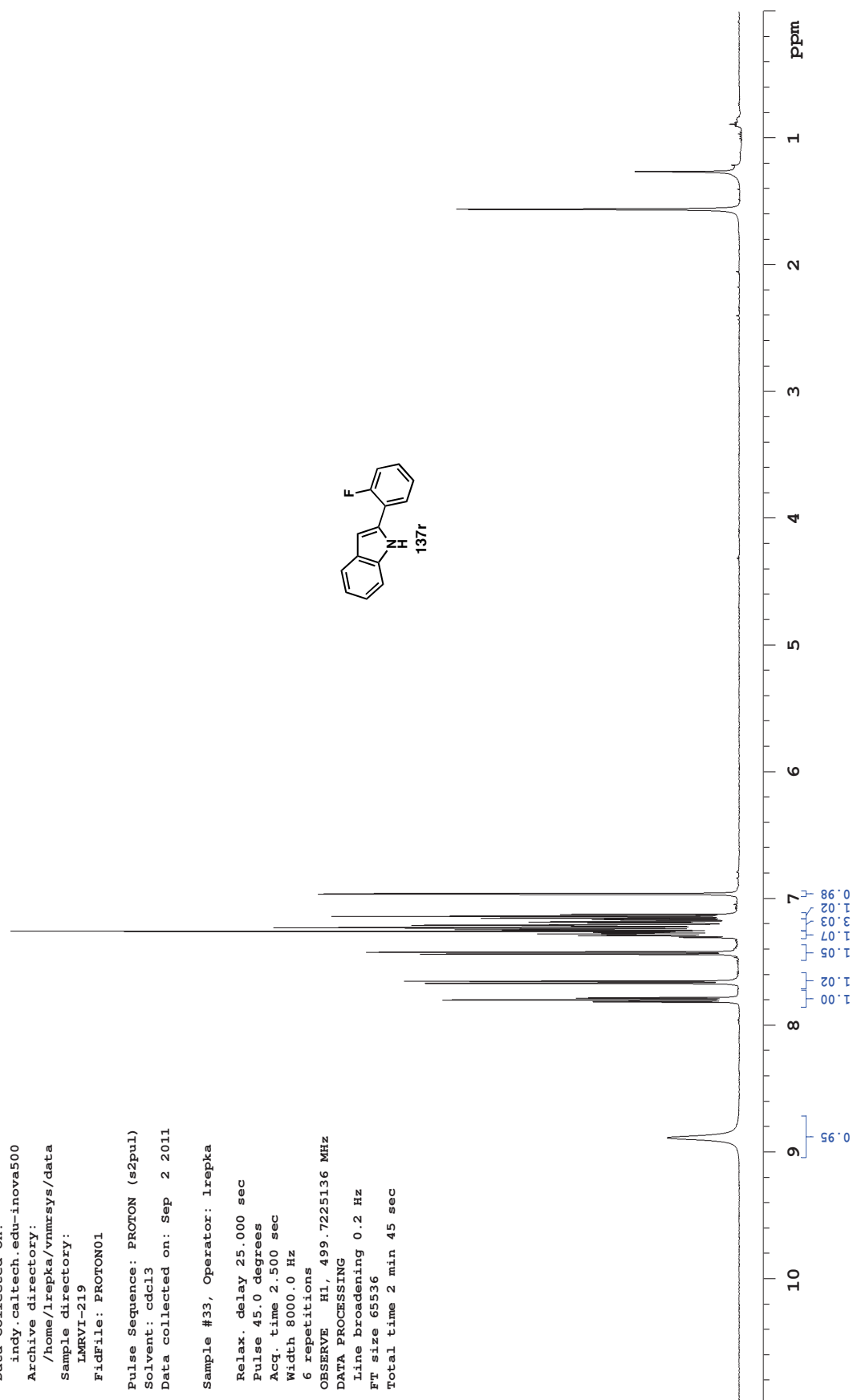
OBSERVE H1, 499.7225136 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 45 sec



LMRVI-219

Sample Name:

LMRVI-219

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-219

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Sep 2 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1600 repetitions

OBSERVE C13, 125.6553281 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

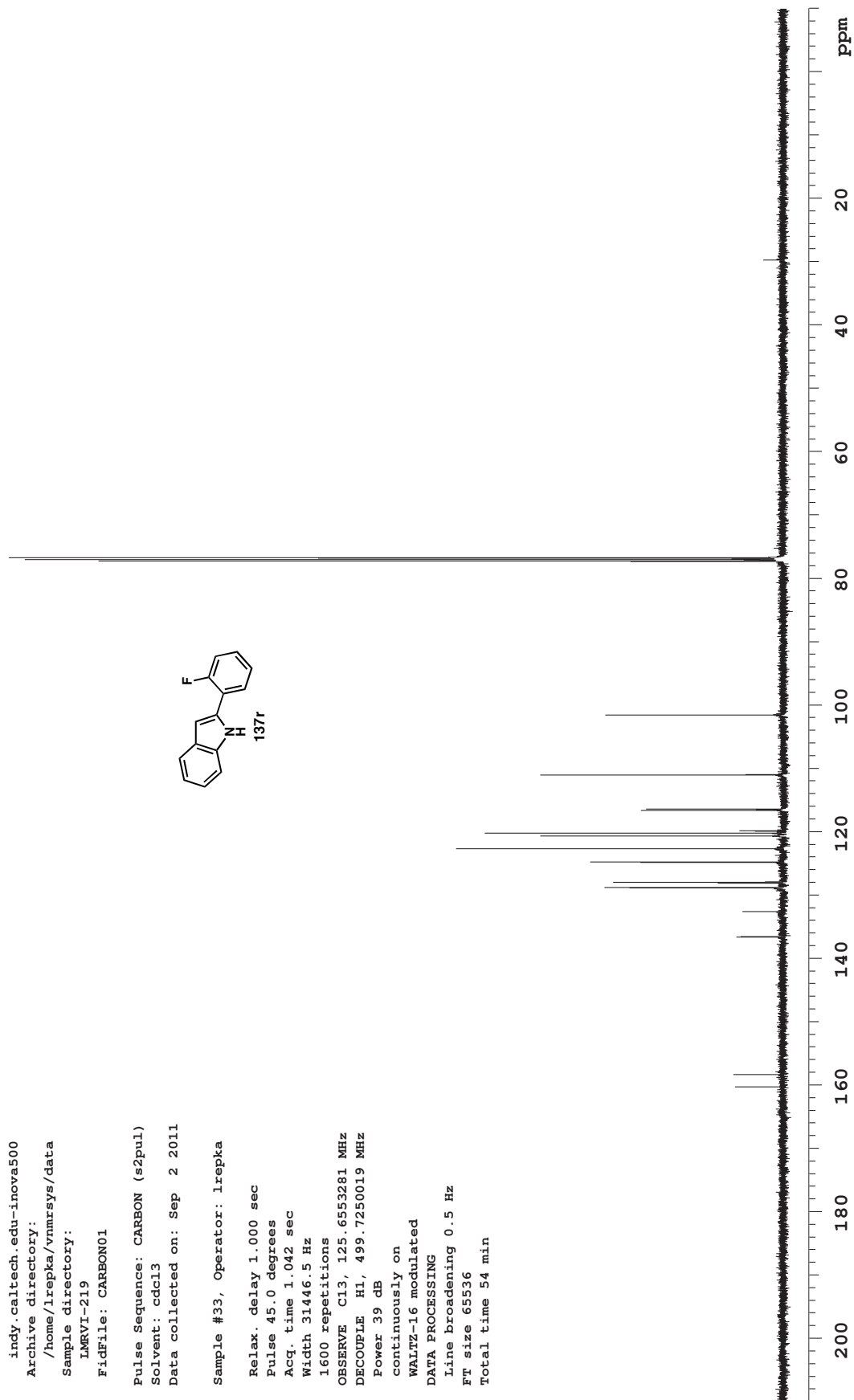
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 54 min



MEK-phthalimide-indole-final

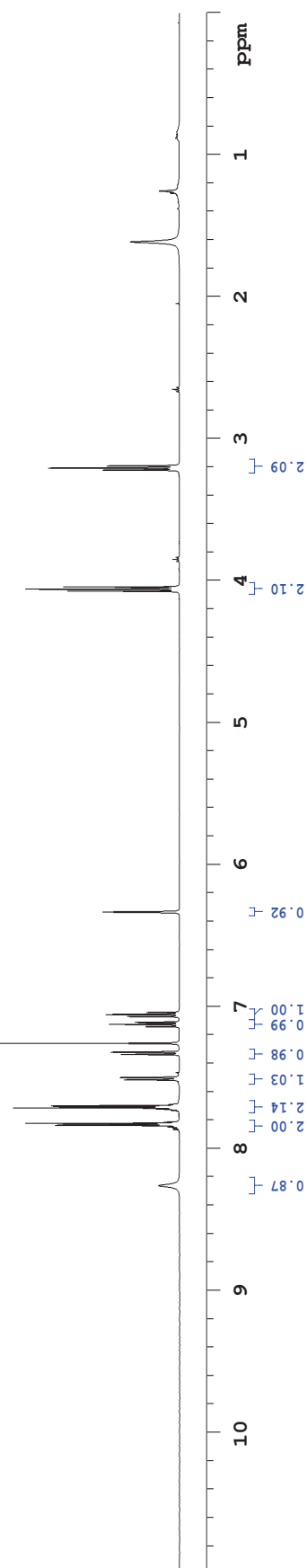
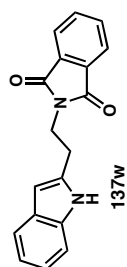
Sample Name:
MEK-phthalimide-indole-final
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkieffer/vnmrsys/data
Sample directory:
MEK-phthalimide-indole-final
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 2 2011

Sample #10, Operator: mkieffer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions

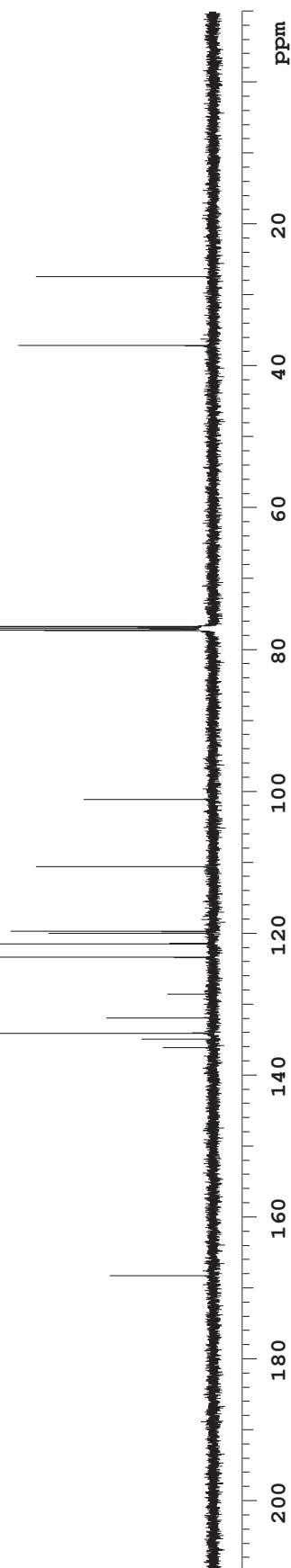
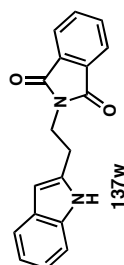
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec



MEK-phthalimide-indole-final

Sample Name:
MEK-phthalimide-indole-final
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkieffer/vnmrsys/data
Sample directory:
MEK-phthalimide-indole-final
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 2 2011

Sample #10, Operator: mkieffer
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553271 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min



LMRVI-161

Sample Name:

LMRVI-161

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-161

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 27 2011

Sample #33, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

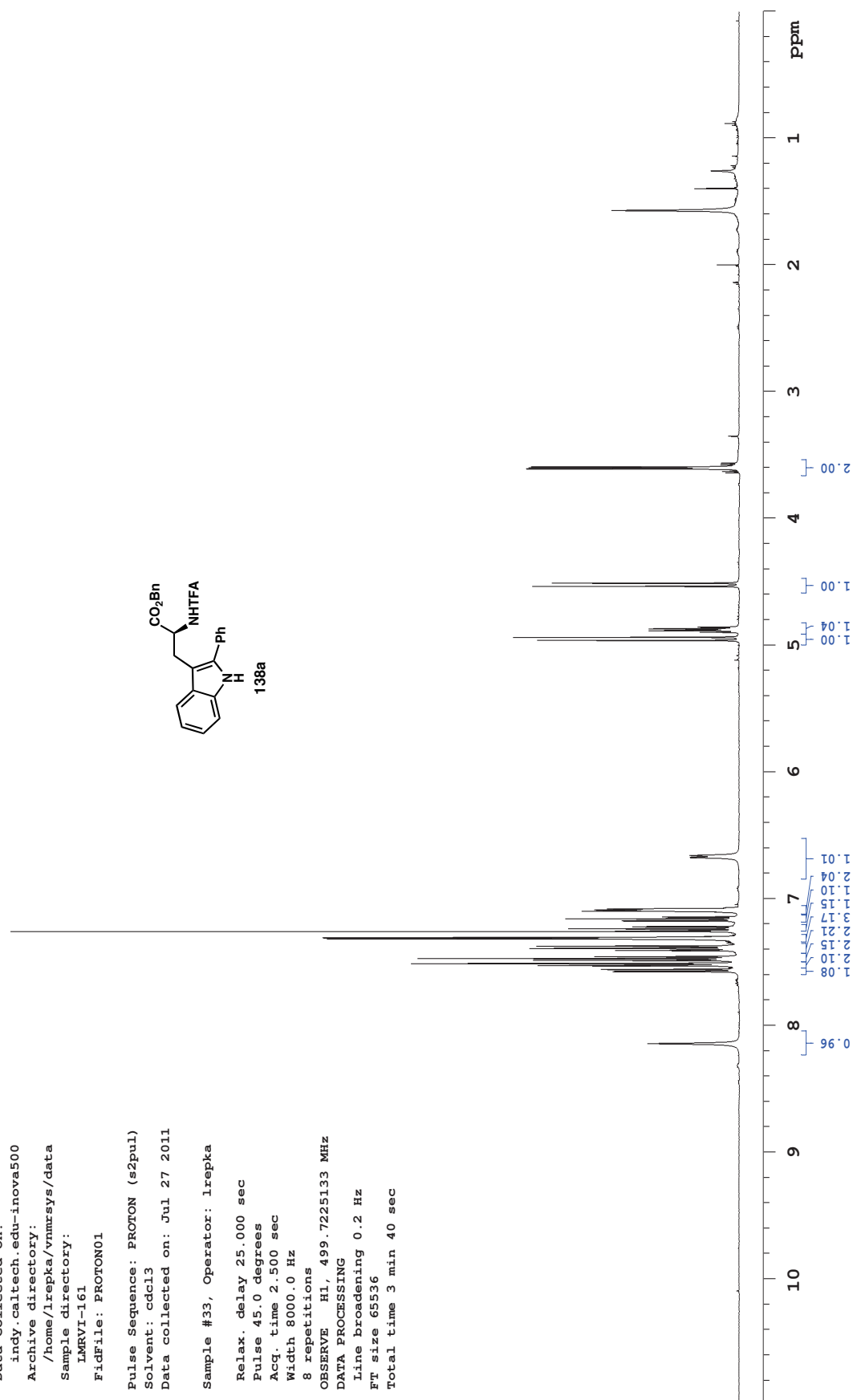
OBSERVE H1, 499.7225133 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 3 min 40 sec



LMRVI-161

Sample Name:

LMRVI-161

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-161

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: Jul 27 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

10000 repetitions

OBSERVE C13, 125.6553284 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

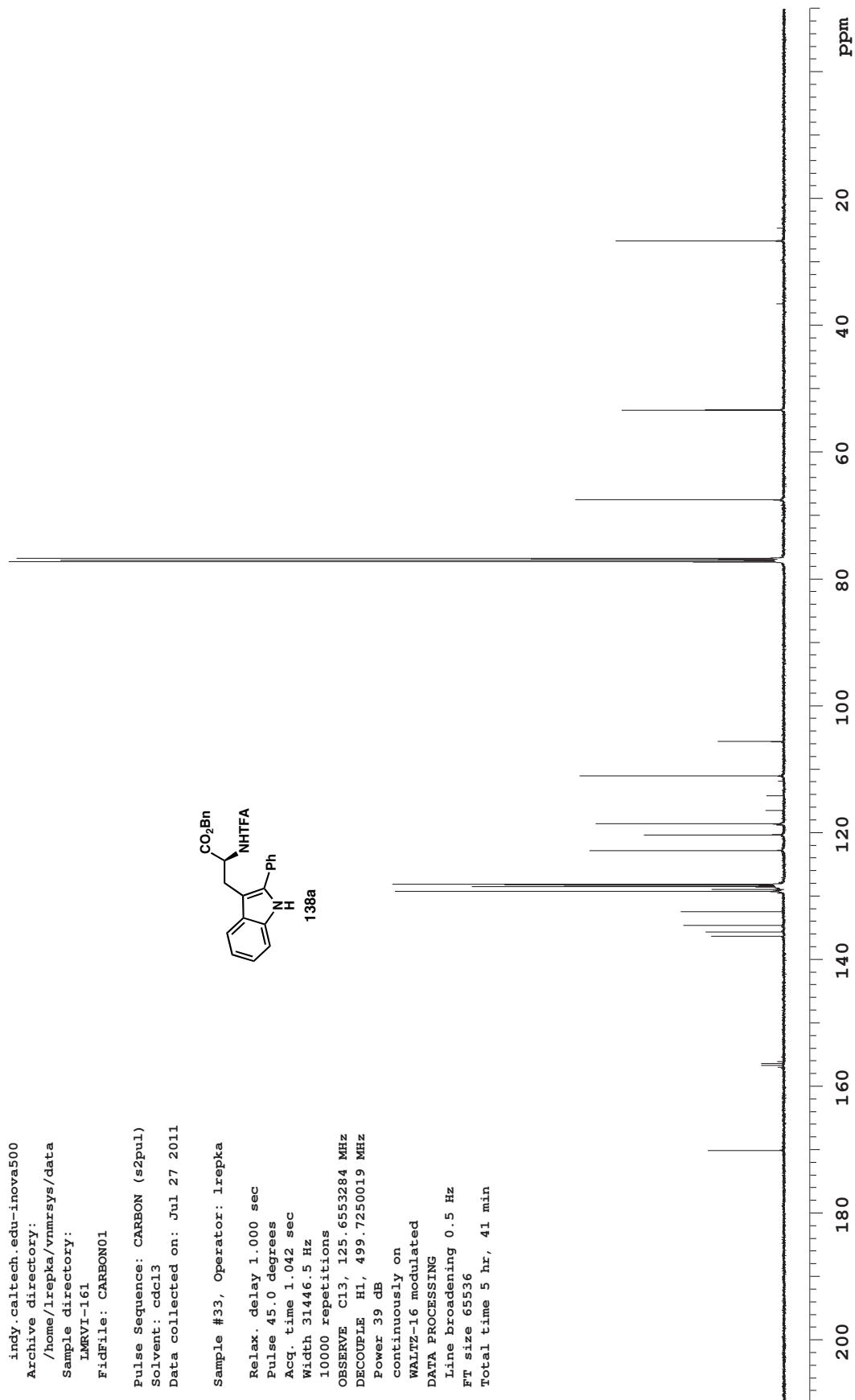
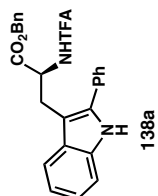
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 5 hr, 41 min



LMRVI-205-1

Sample Name:

LMRVI-205-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-205-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 23 2011

Sample #33, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

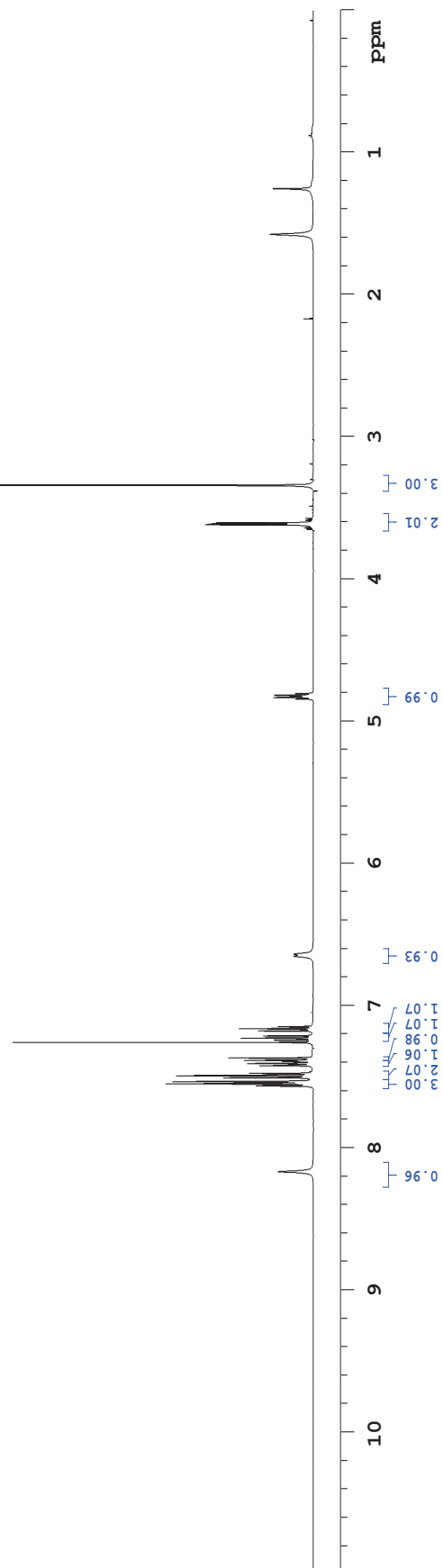
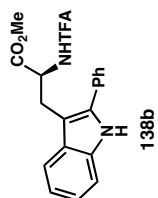
OBSERVE H1, 499.7225131 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 3 min 40 sec



LMRVI-205-1

Sample Name:

LMRVI-205-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-205-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Aug 23 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

10000 repetitions

OBSERVE C13, 125.6553292 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

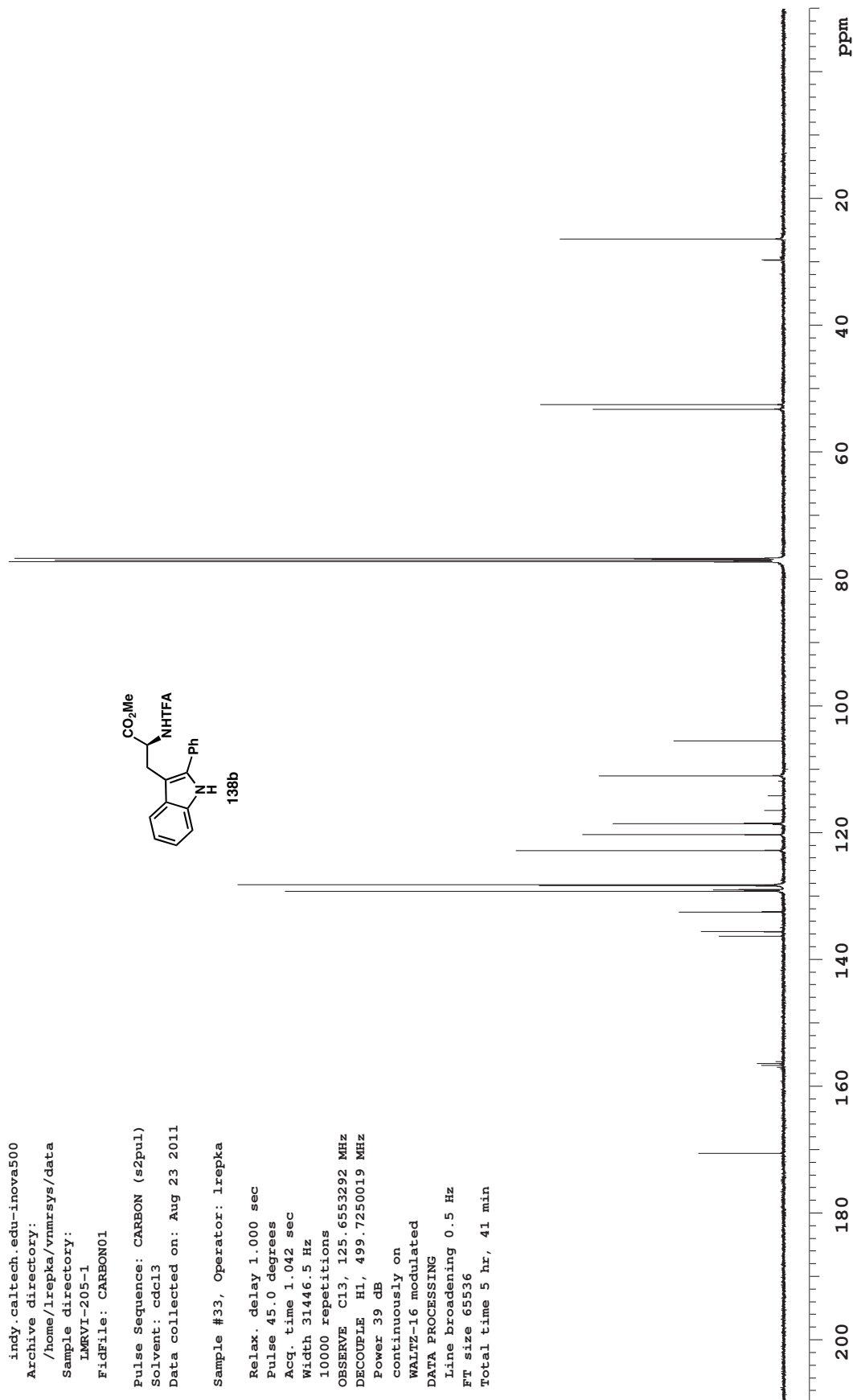
WALTZ-16 modulated

DATA PROCESSING

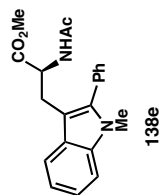
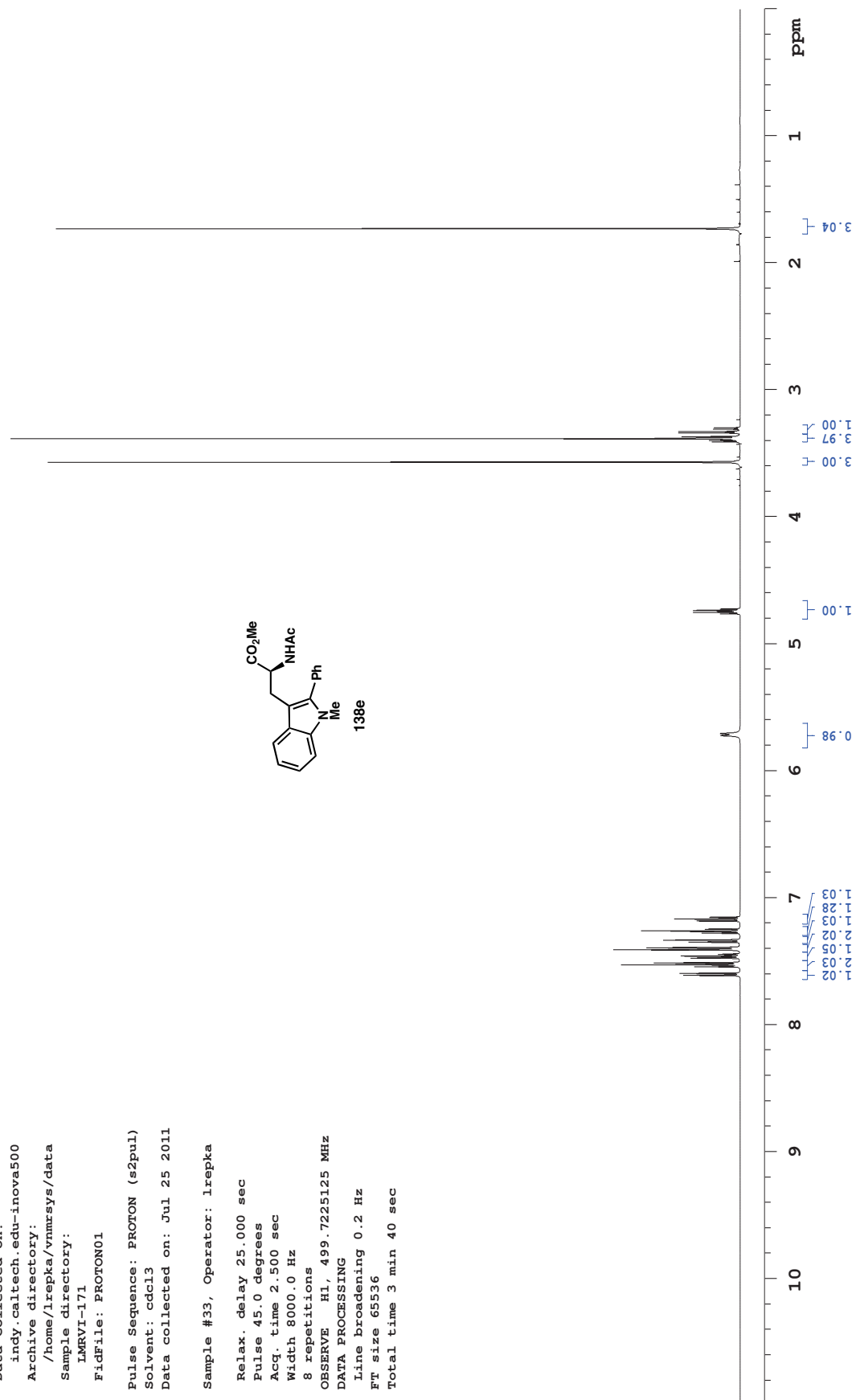
Line broadening 0.5 Hz

FT size 65536

Total time 5 hr, 41 min



Total time 3 min 40 sec



LMRVI-171

Sample Name:

LMRVI-171

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-171

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 25 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1500 repetitions

OBSERVE C13, 125.6553354 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

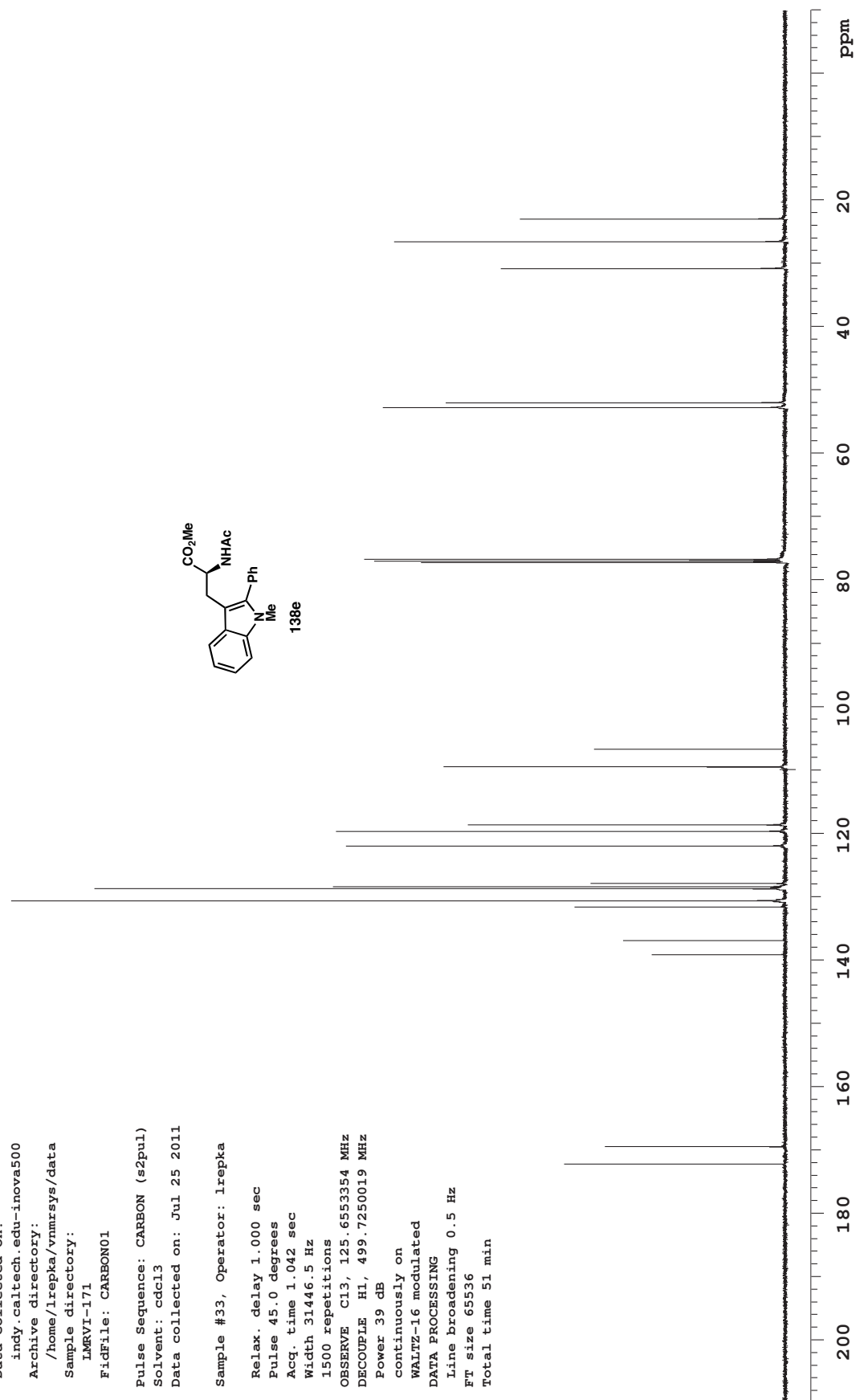
WALTZ-16 modulated

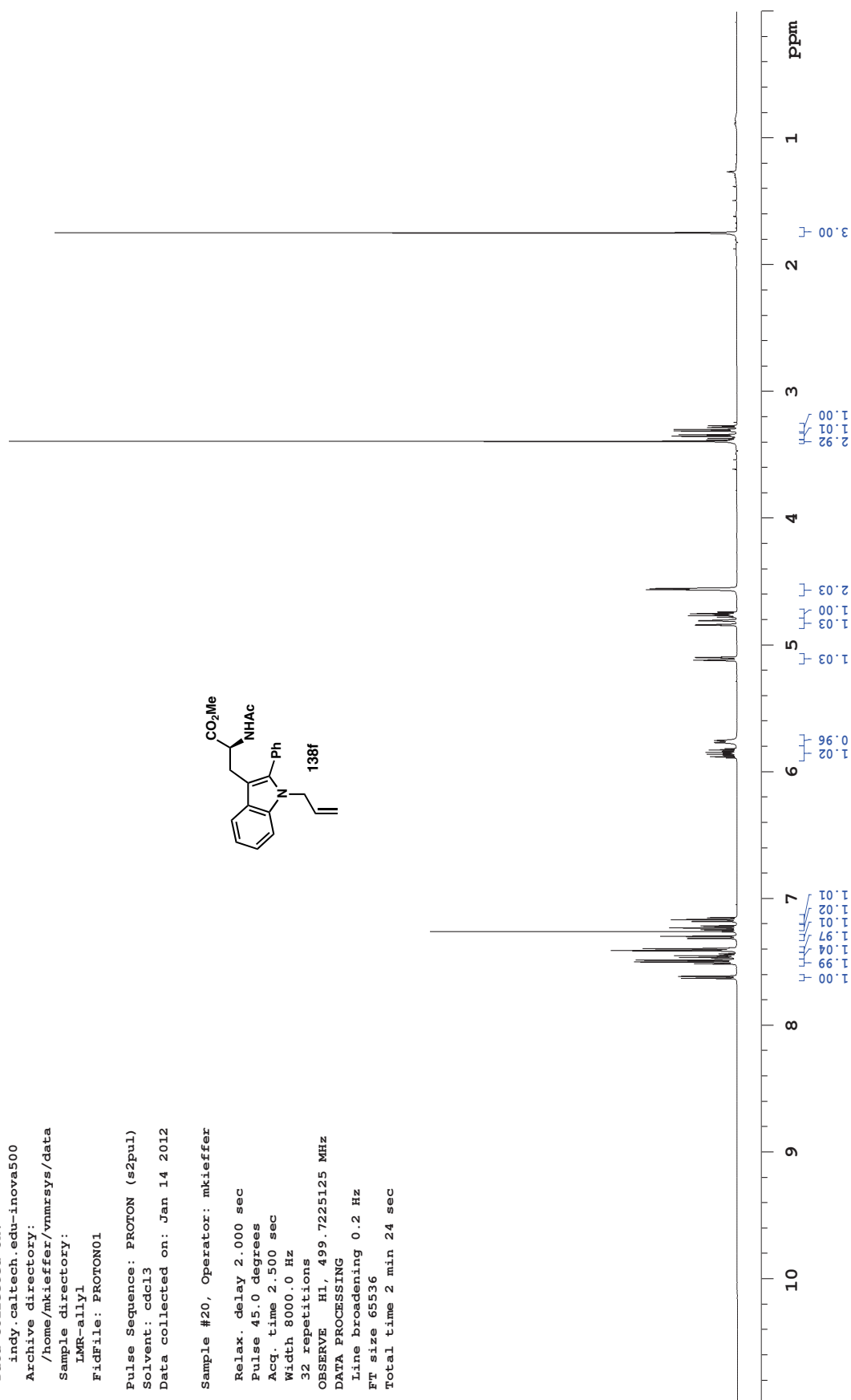
DATA PROCESSING

Line broadening 0.5 Hz

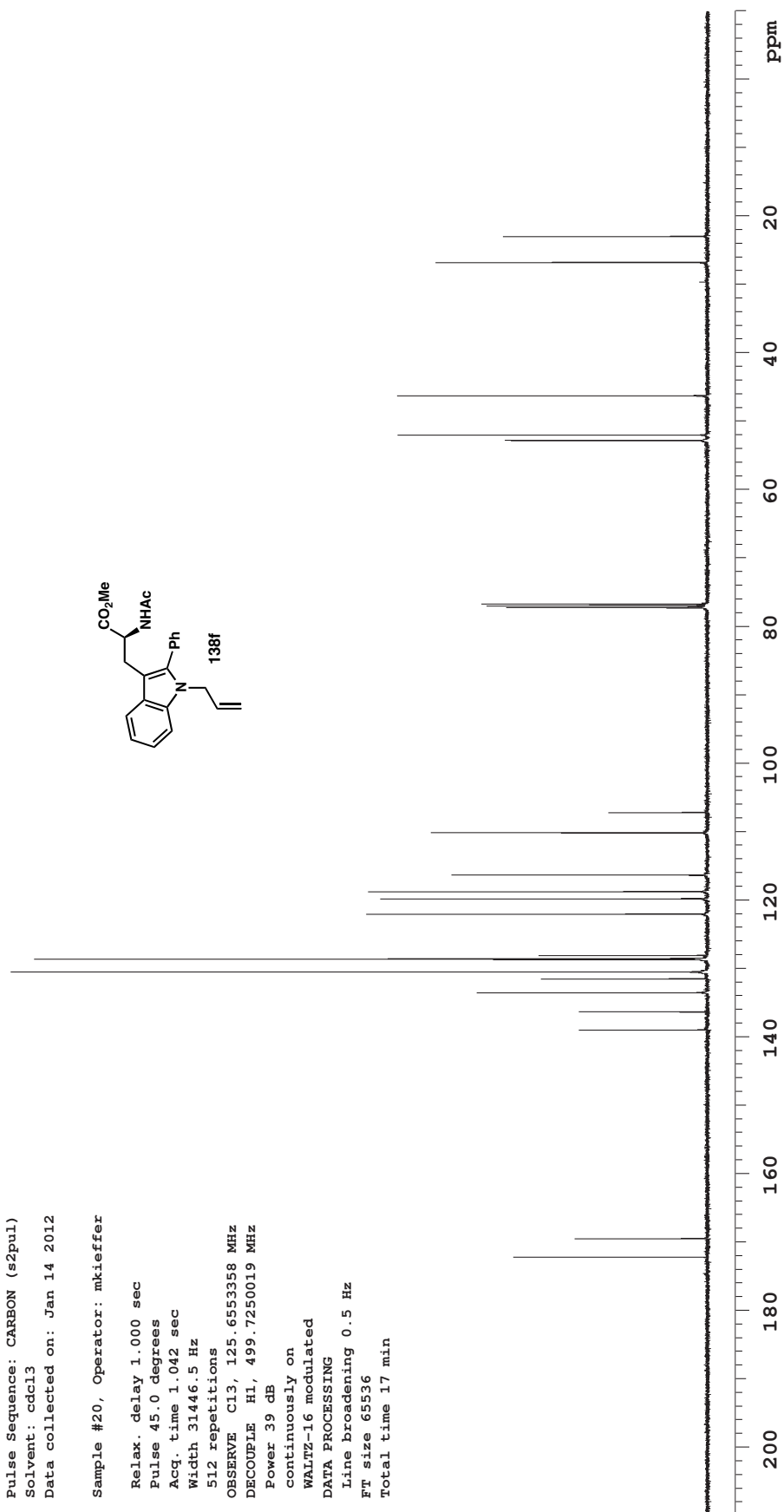
FT size 65536

Total time 51 min



CC(=O)N[C@@H](Cc1c2ccccc2c3c1n(c4ccccc43)CC=C)c5ccccc5

Sample Name:
LMR-allyl
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkieffer/vnmrsys/data
Sample directory:
LMR-allyl
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: Jan 14 2012
Sample #20, Operator: mkieffer
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553358 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min



MEK3186-1

Sample Name:

MEK3186-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3186-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 15 2011

Sample #15, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

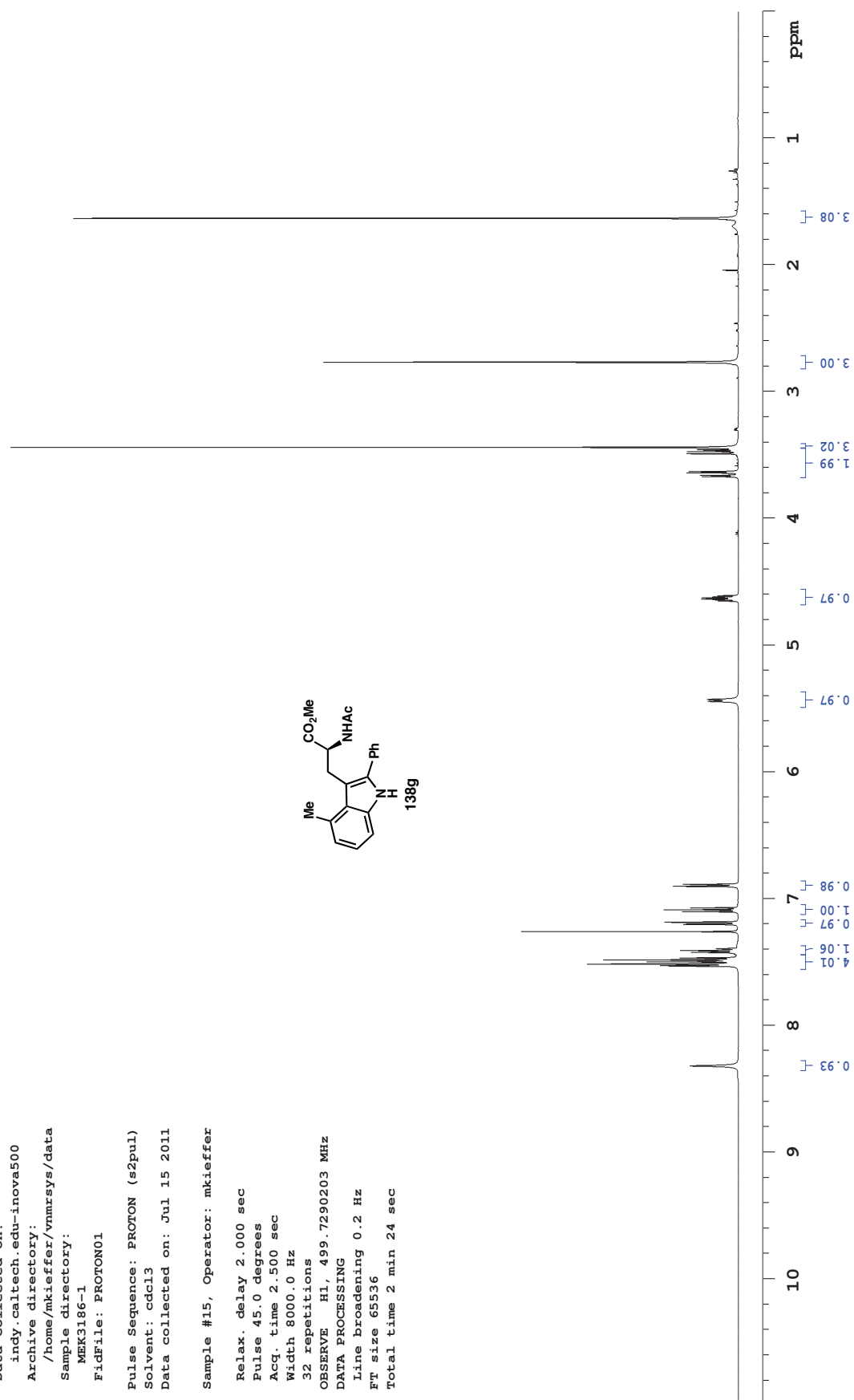
OBSERVE H1, 499.7290203 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 24 sec



MEK3186-1

Sample Name:

MEK3186-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3186-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 15 2011

Sample #15, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6553310 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

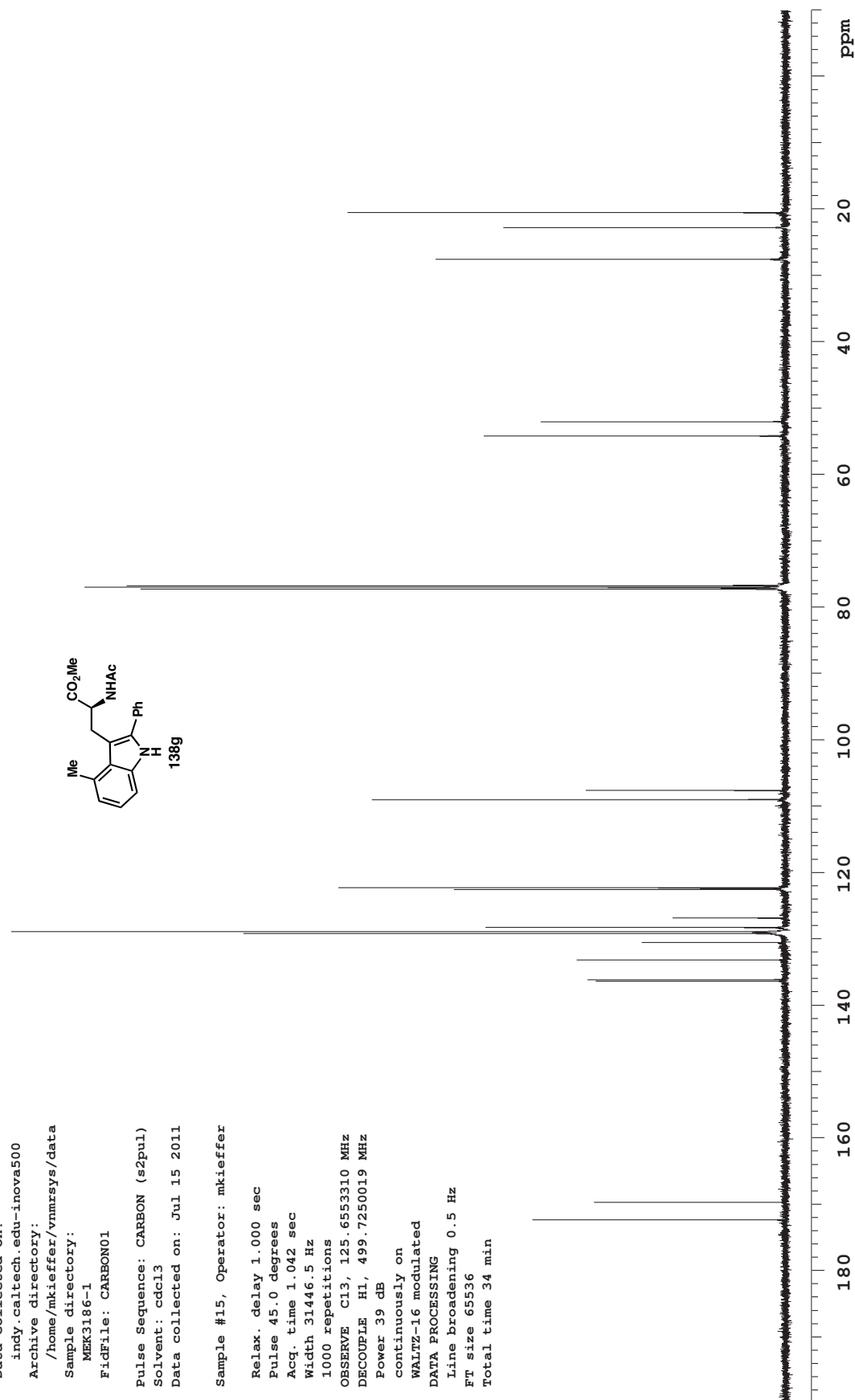
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 34 min



MEK3084-1

Sample Name:

MEK3084-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3084-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: May 9 2011

Temp. 25.0 C / 298.1 K

Sample #39, Operator: mkieffer

Relax. delay 5.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

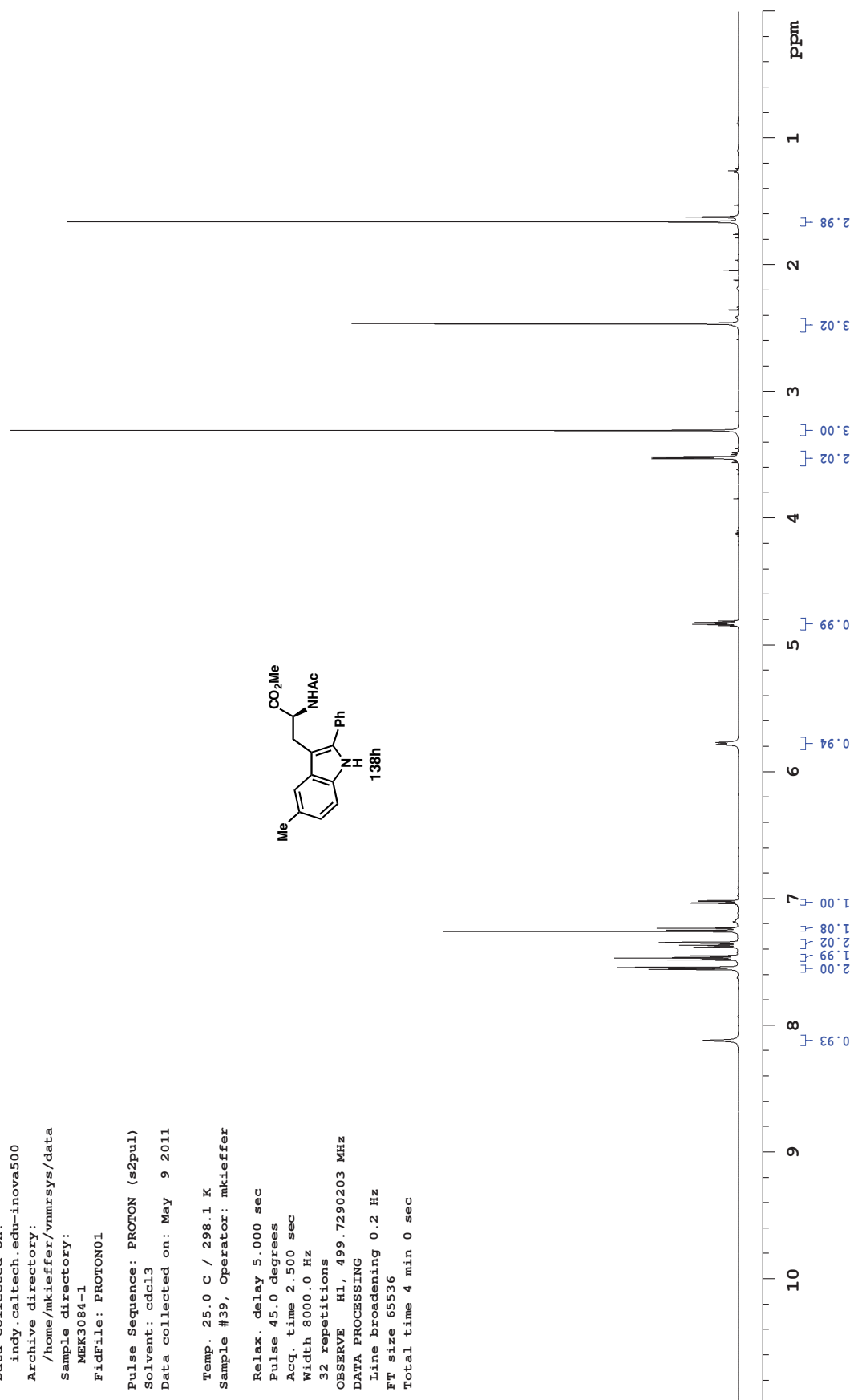
OBSERVE H1, 499.7290203 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 4 min 0 sec



MEK3084-1

Sample Name:

MEK3084-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3084-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: May 9 2011

Temp. 25.0 C / 298.1 K

Sample #39, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

512 repetitions

OBSERVE C13, 125.6569642 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

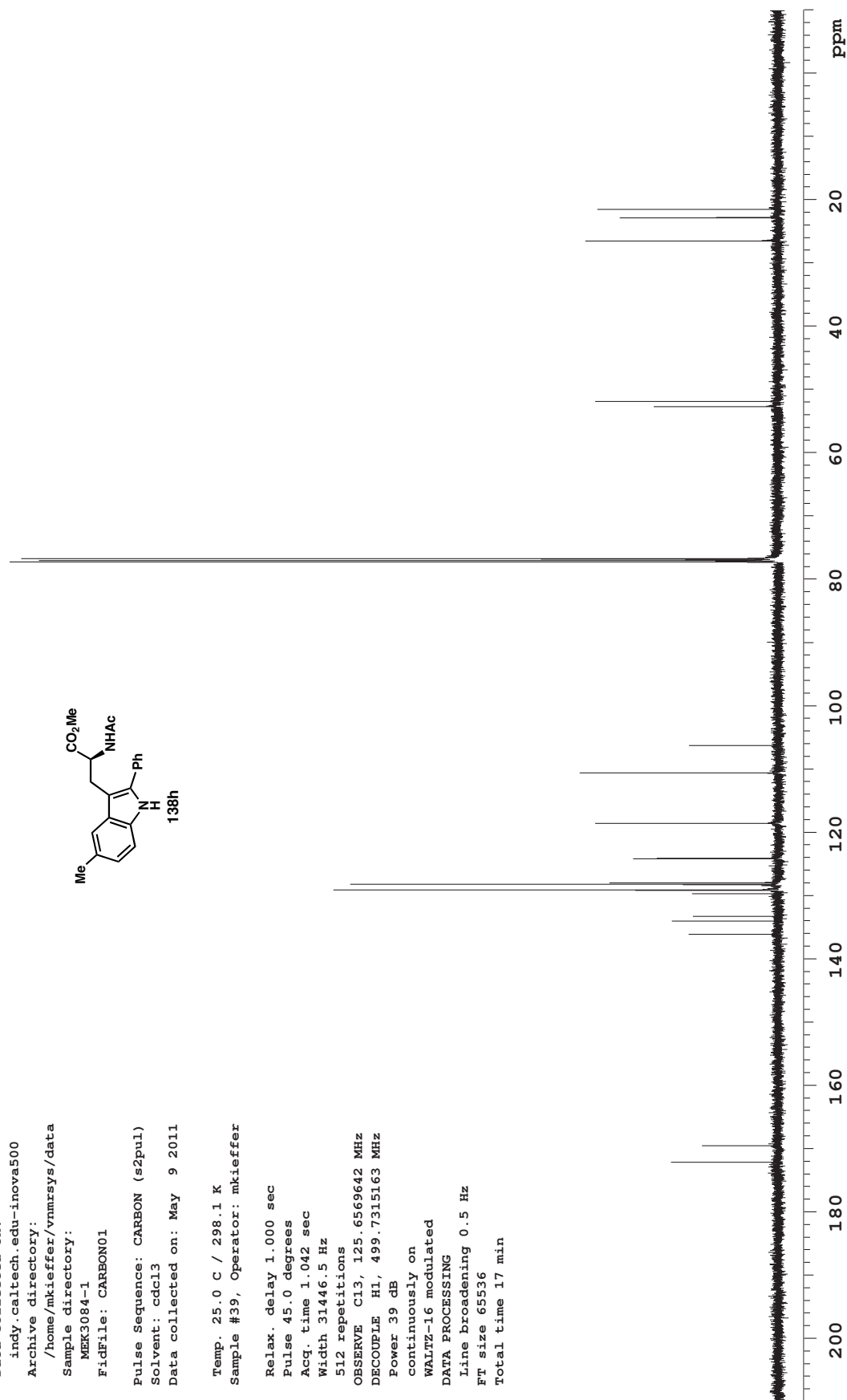
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 17 min



MEK3193-1

Sample Name:

MEK3193-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3193-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 21 2011

Sample #33, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

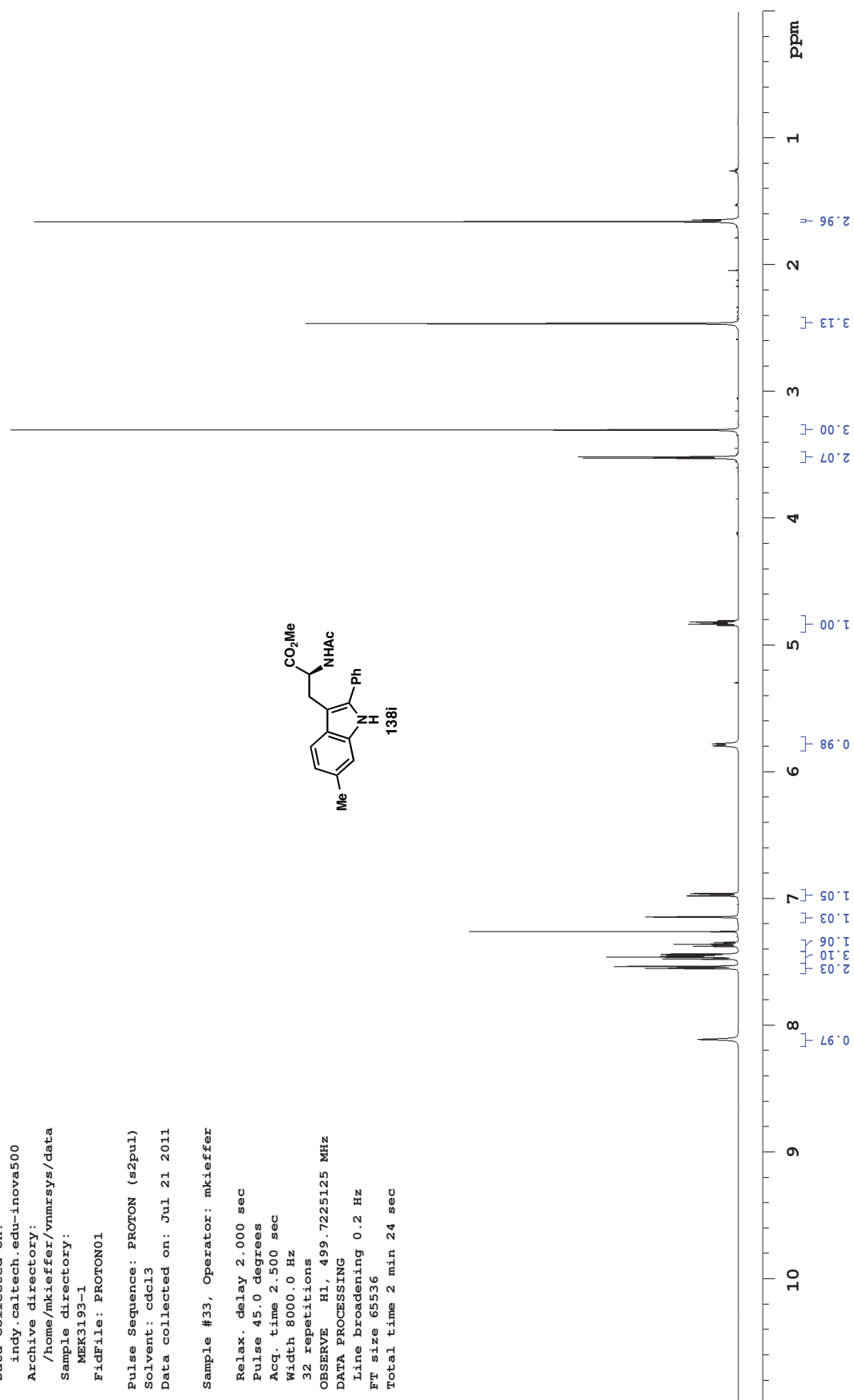
OBSERVE H1, 499.7225125 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 24 sec



MEK3193-1

Sample Name:

MEK3193-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3193-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 21 2011

Sample #33, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6553291 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

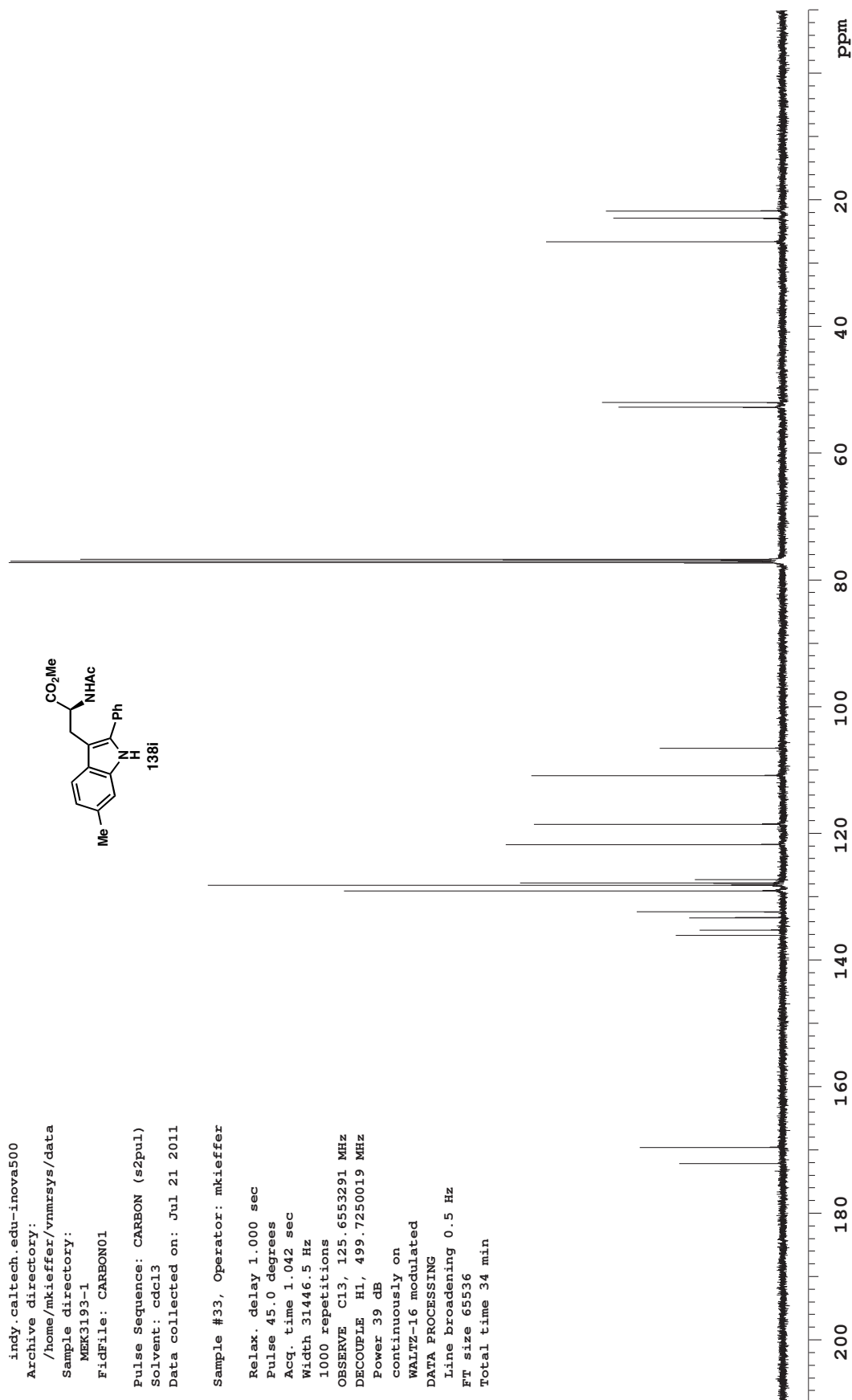
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 34 min



MEK3148-1

Sample Name:

MEK3148-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3148-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 20 2011

Temp. 25.0 C / 298.1 K

Sample #14, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

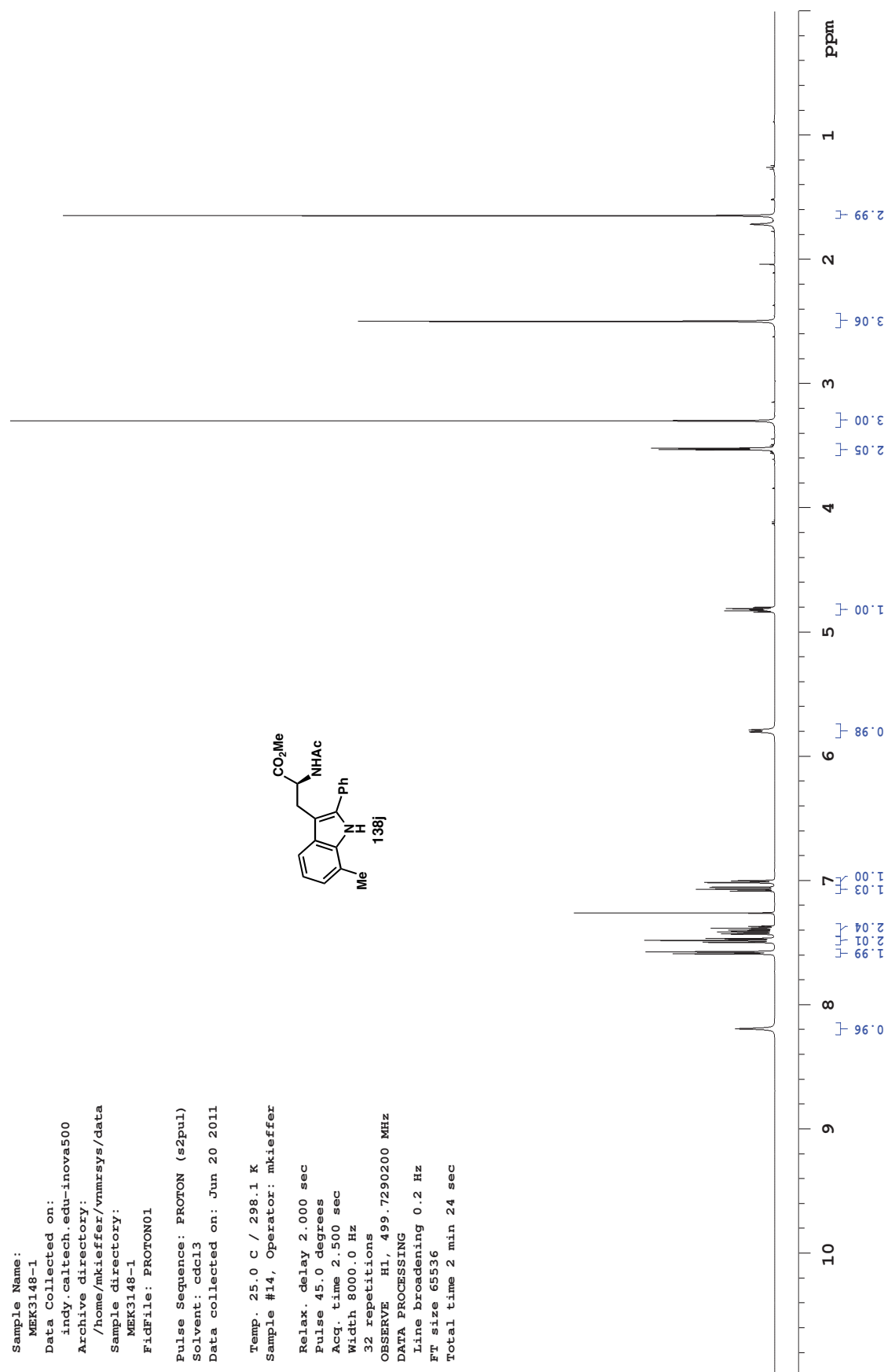
OBSERVE H1, 499.7290200 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 2 min 24 sec



MEK3130-1

Sample Name:

MEK3130-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3130-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: Jun 7 2011

Temp. 25.0 C / 298.1 K

Sample #15, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

512 repetitions

OBSERVE C13, 125.6569681 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

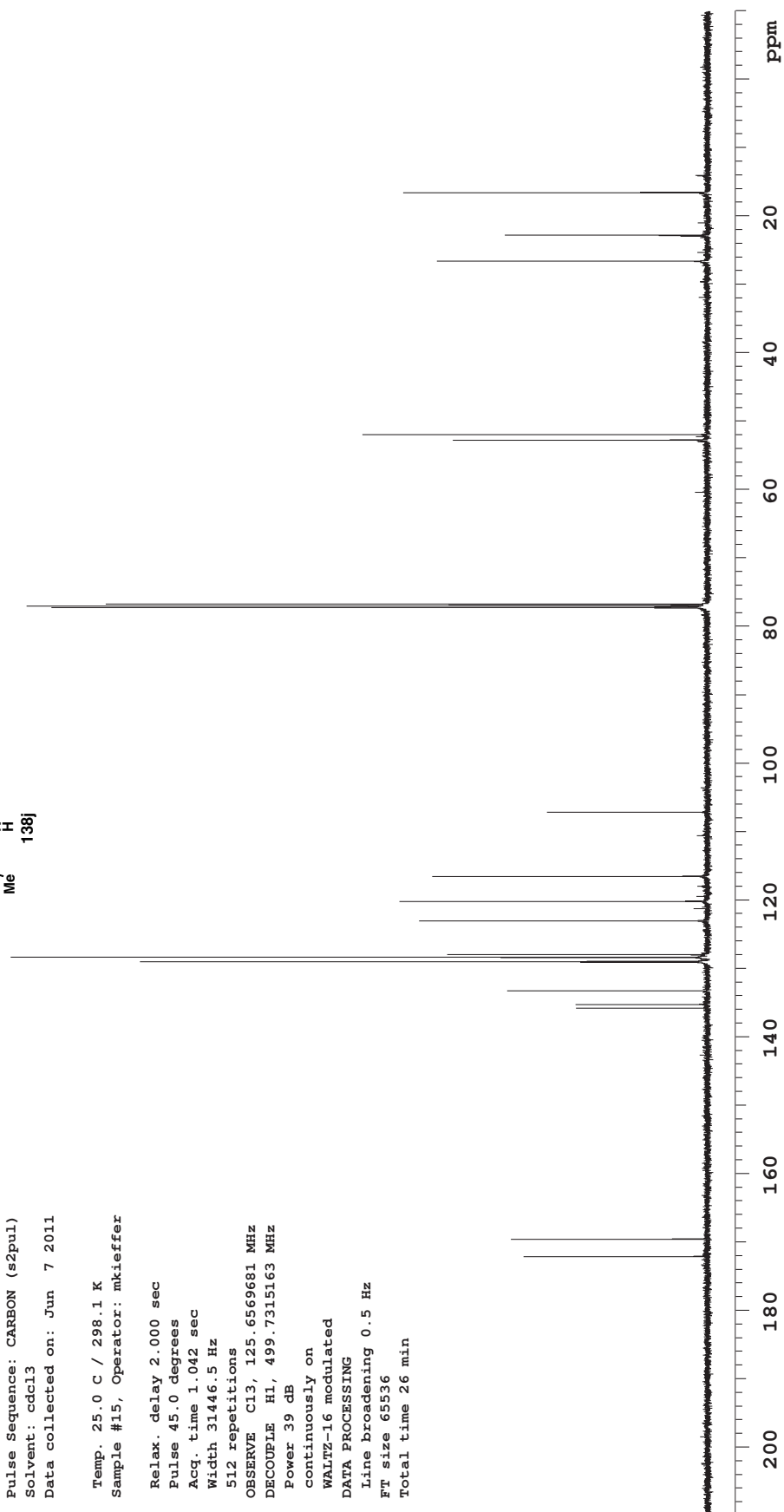
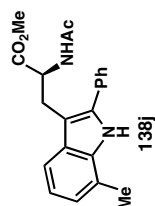
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 26 min



MEK3185-1

Sample Name:

MEK3185-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3185-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jul 15 2011

Sample #14, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

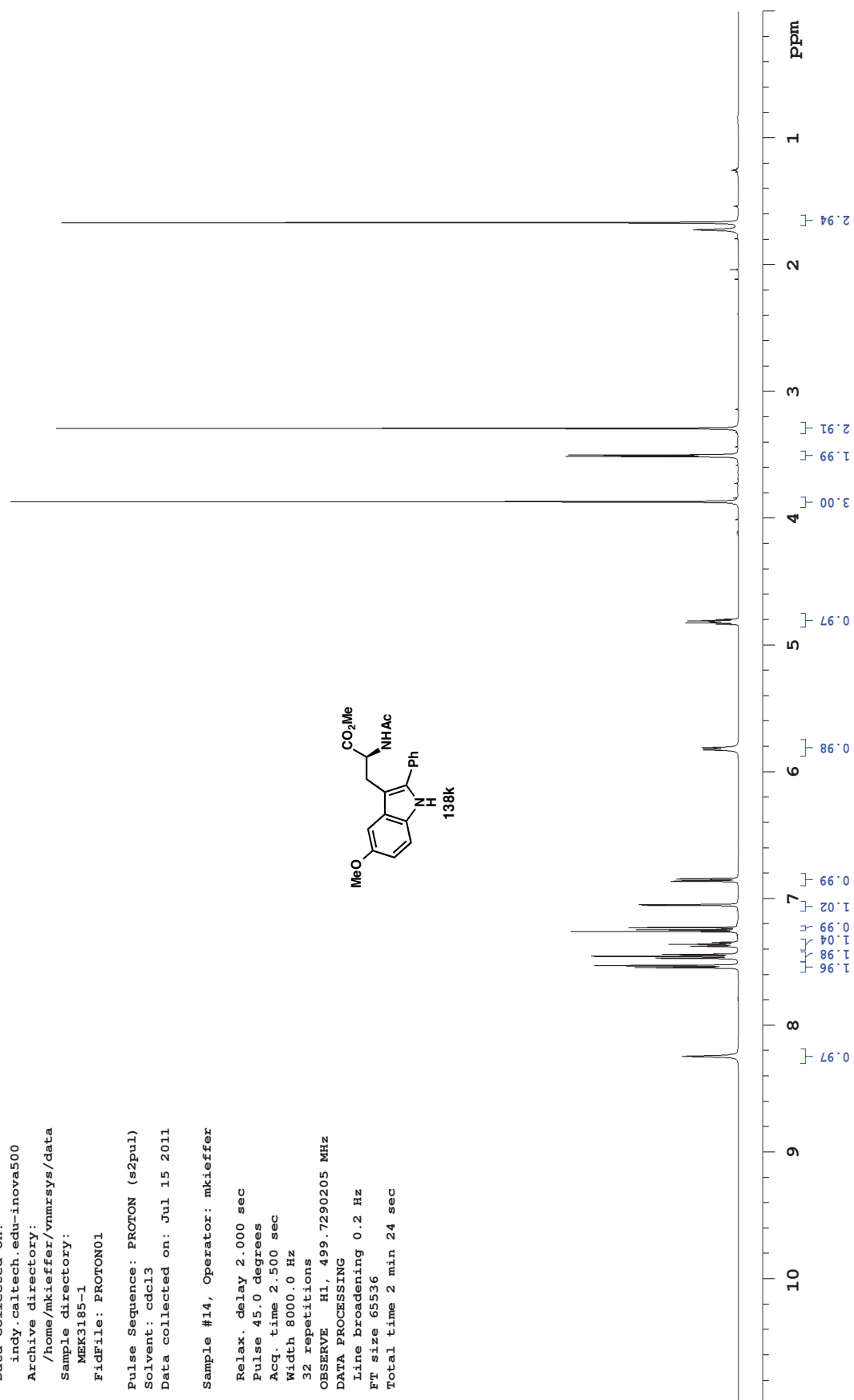
OBSERVE H1, 499.7290205 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 24 sec



MEK3185-1

Sample Name:

MEK3185-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3185-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 15 2011

Sample #14, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6553300 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

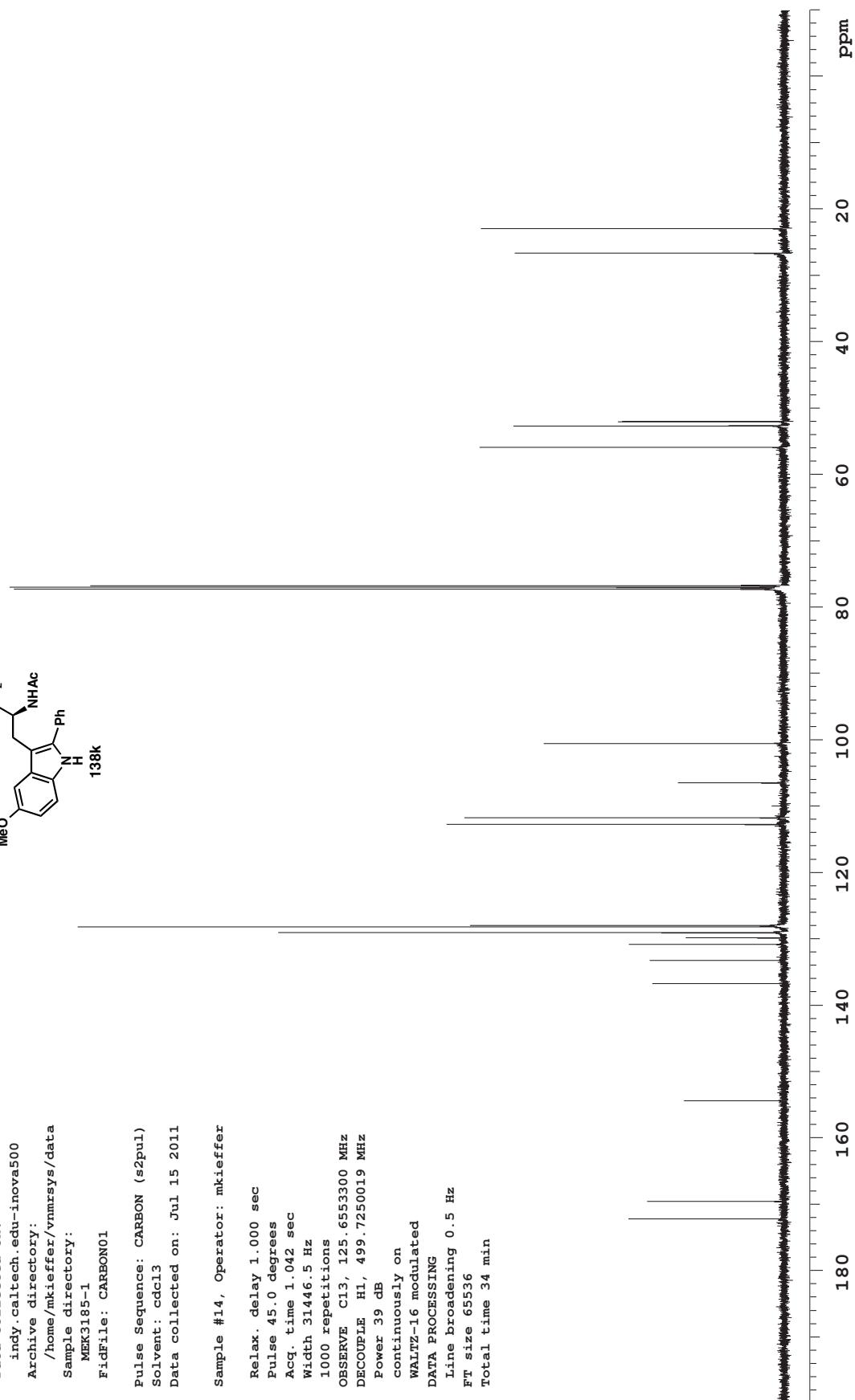
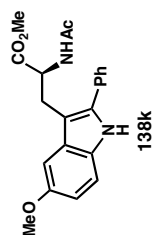
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 34 min



MEK-5-Br

Sample Name:

MEK-5-Br

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK-5-Br

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 25 2011

Sample #15, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

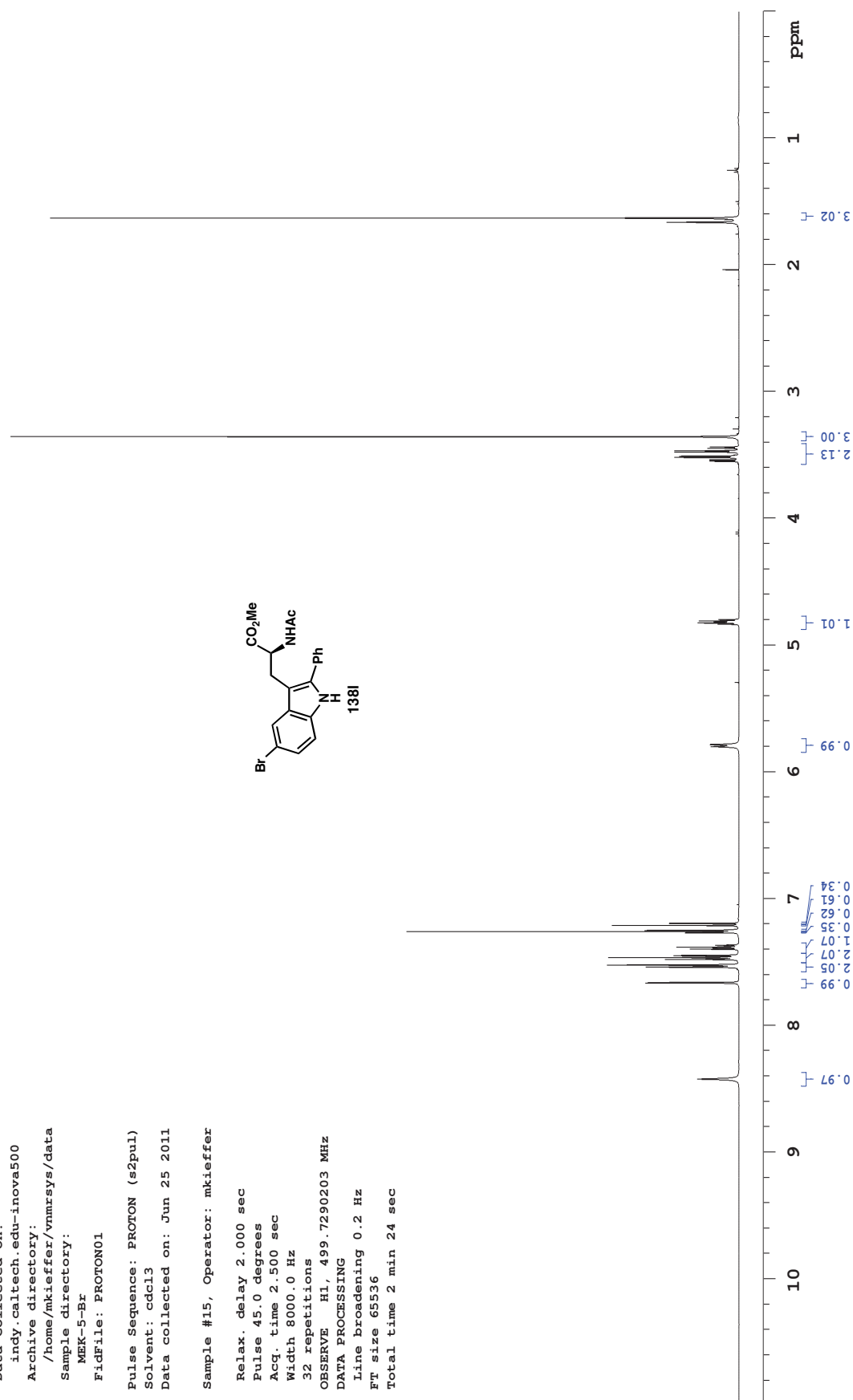
OBSERVE H1, 499.7290203 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 24 sec



MEK-5-Br

Sample Name:

MEK-5-Br

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK-5-Br

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jun 25 2011

Sample #15, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6666408 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

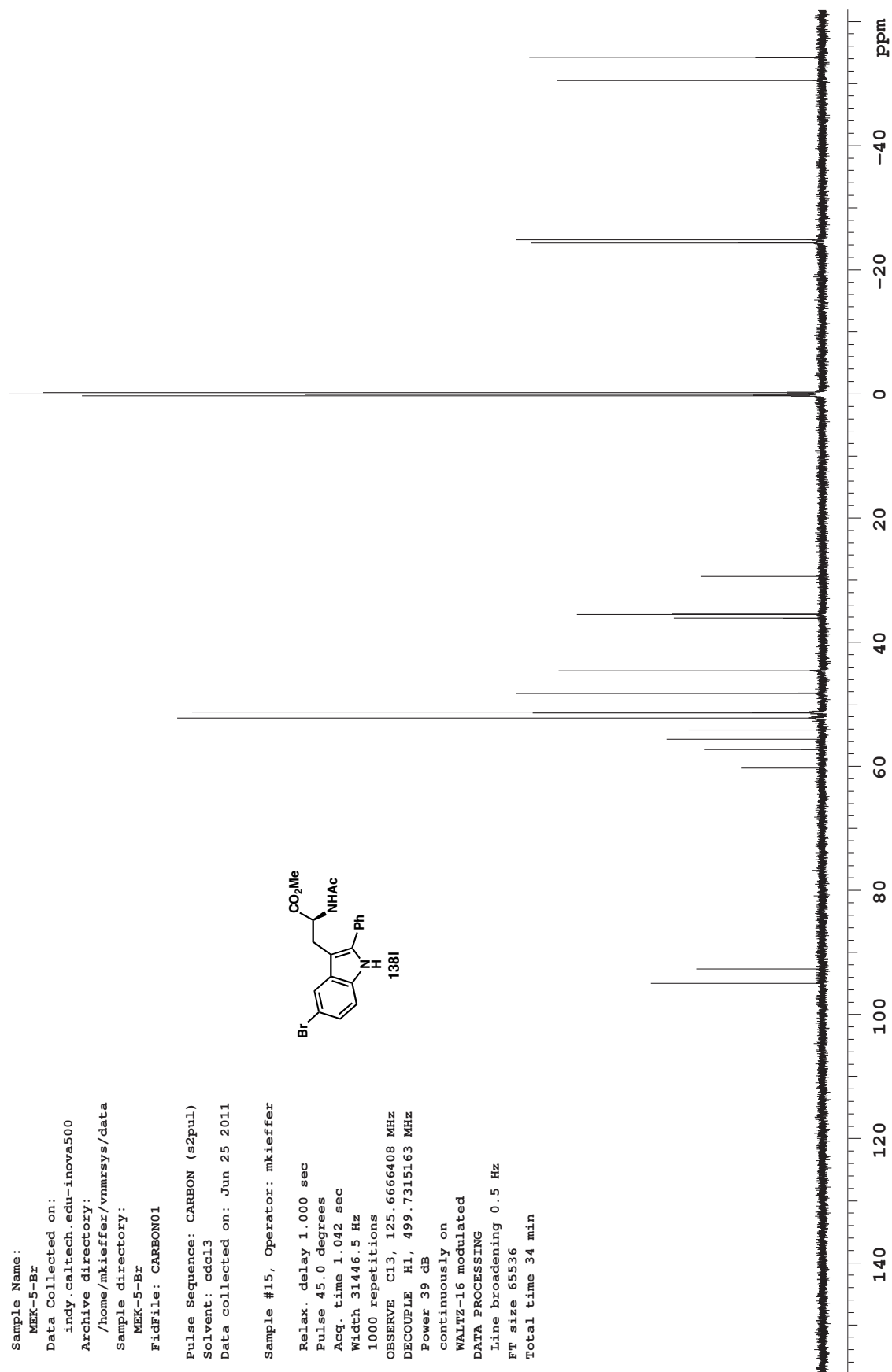
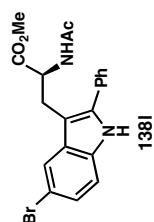
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 34 min



MEK3150-1

Sample Name:

MEK3150-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3150-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 20 2011

Temp. 25.0 C / 298.1 K

Sample #15, Operator: mkieffer

Relax. delay 5.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

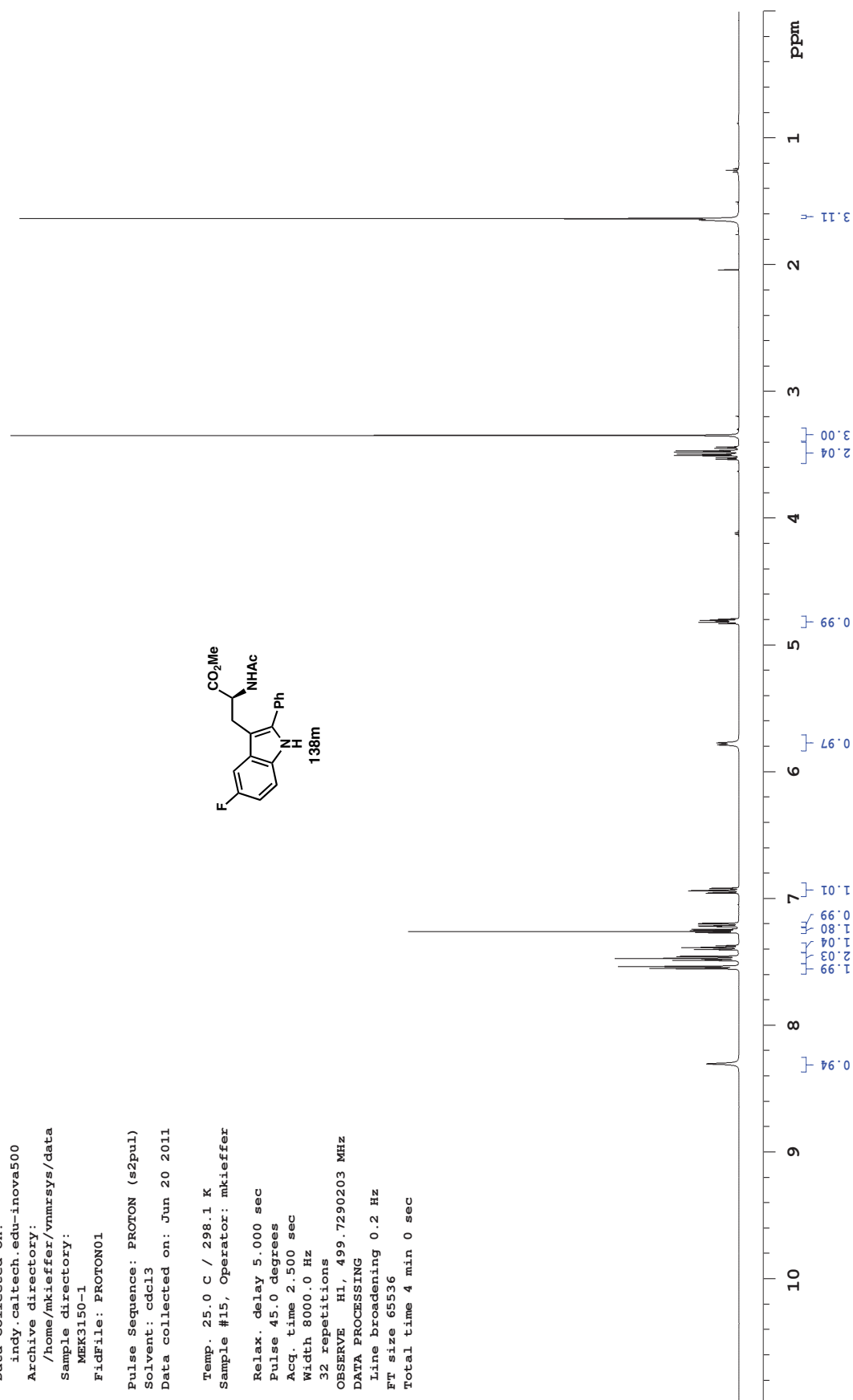
OBSERVE H1, 499.7290203 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 4 min 0 sec



MEK3150-1

Sample Name:

MEK3150-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3150-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jun 20 2011

Temp. 25.0 C / 298.1 K

Sample #15, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6569633 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

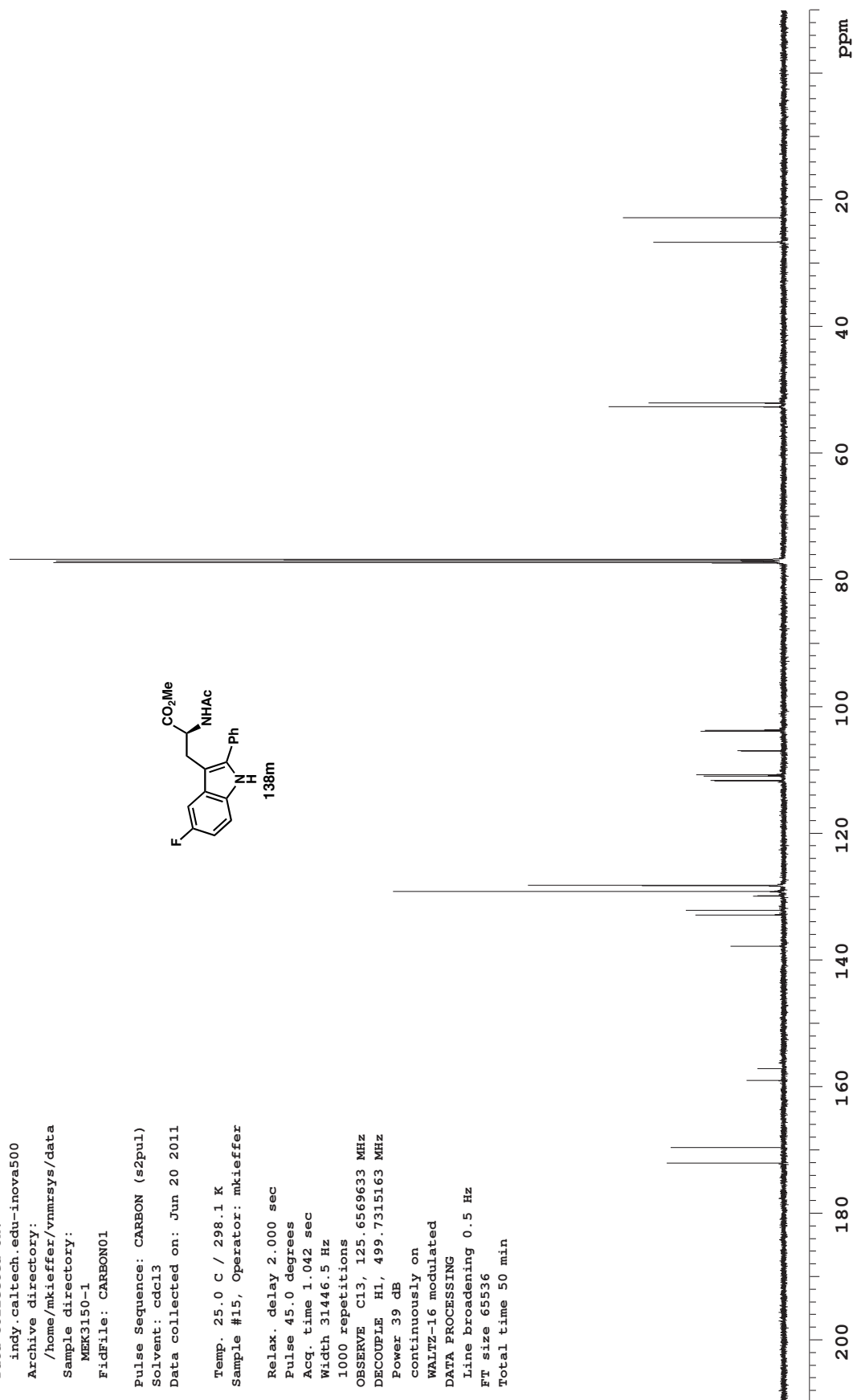
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 50 min



MEK3080-1

Sample Name:

MEK3080-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3080-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: May 8 2011

Temp. 25.0 C / 298.1 K

Sample #42, Operator: mkieffer

Relax. delay 5.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

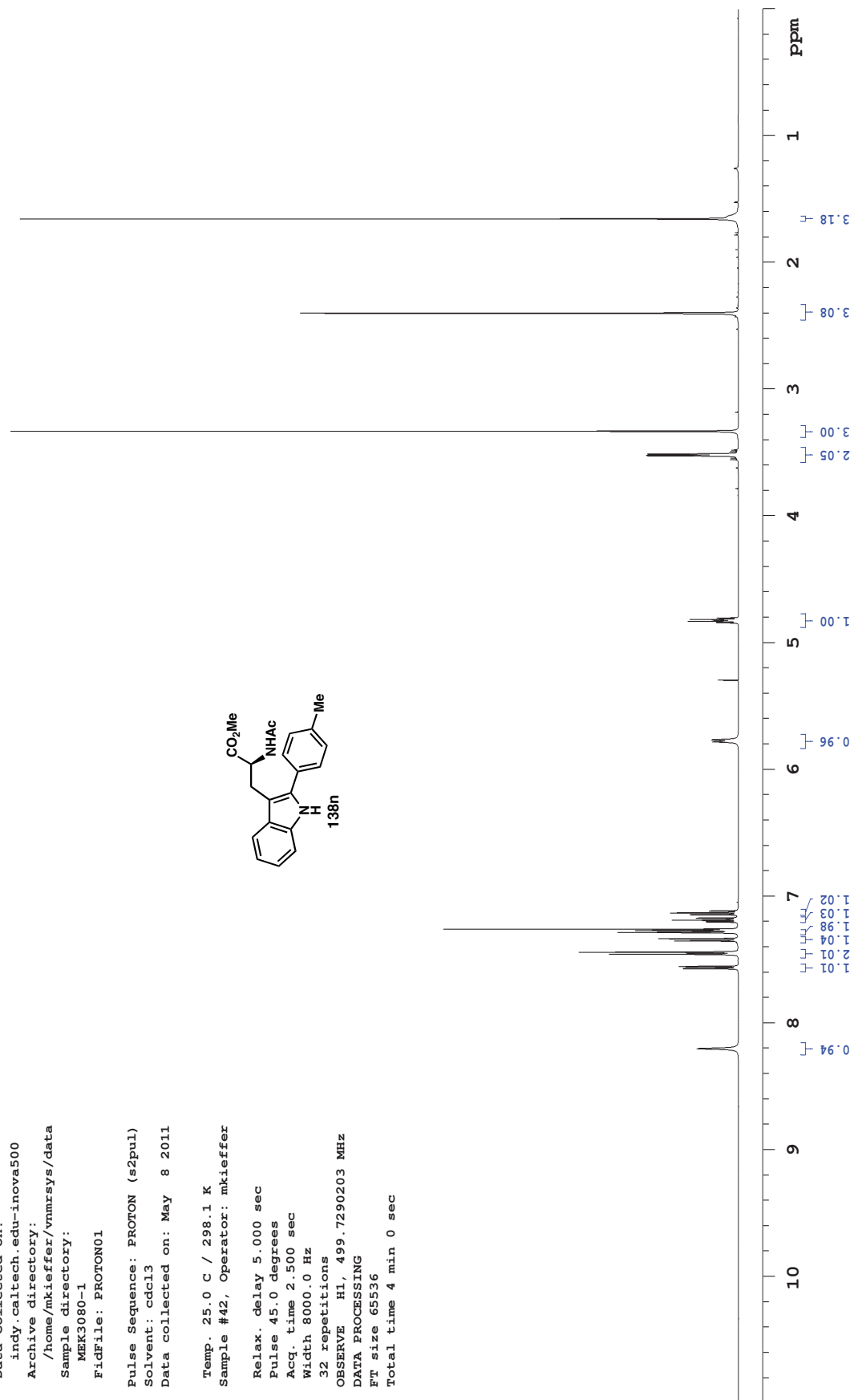
32 repetitions

OBSERVE H1, 499.7290203 MHz

DATA PROCESSING

FT size 65536

Total time 4 min 0 sec



MEK3080-1

Sample Name:

MEK3080-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmr/vars/data

Sample directory:

MEK3080-1

FidFile: current

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: May 8 2011

Temp. 25.0 C / 298.1 K

Sample #42, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

384 repetitions

OBSERVE C13, 125.6569642 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

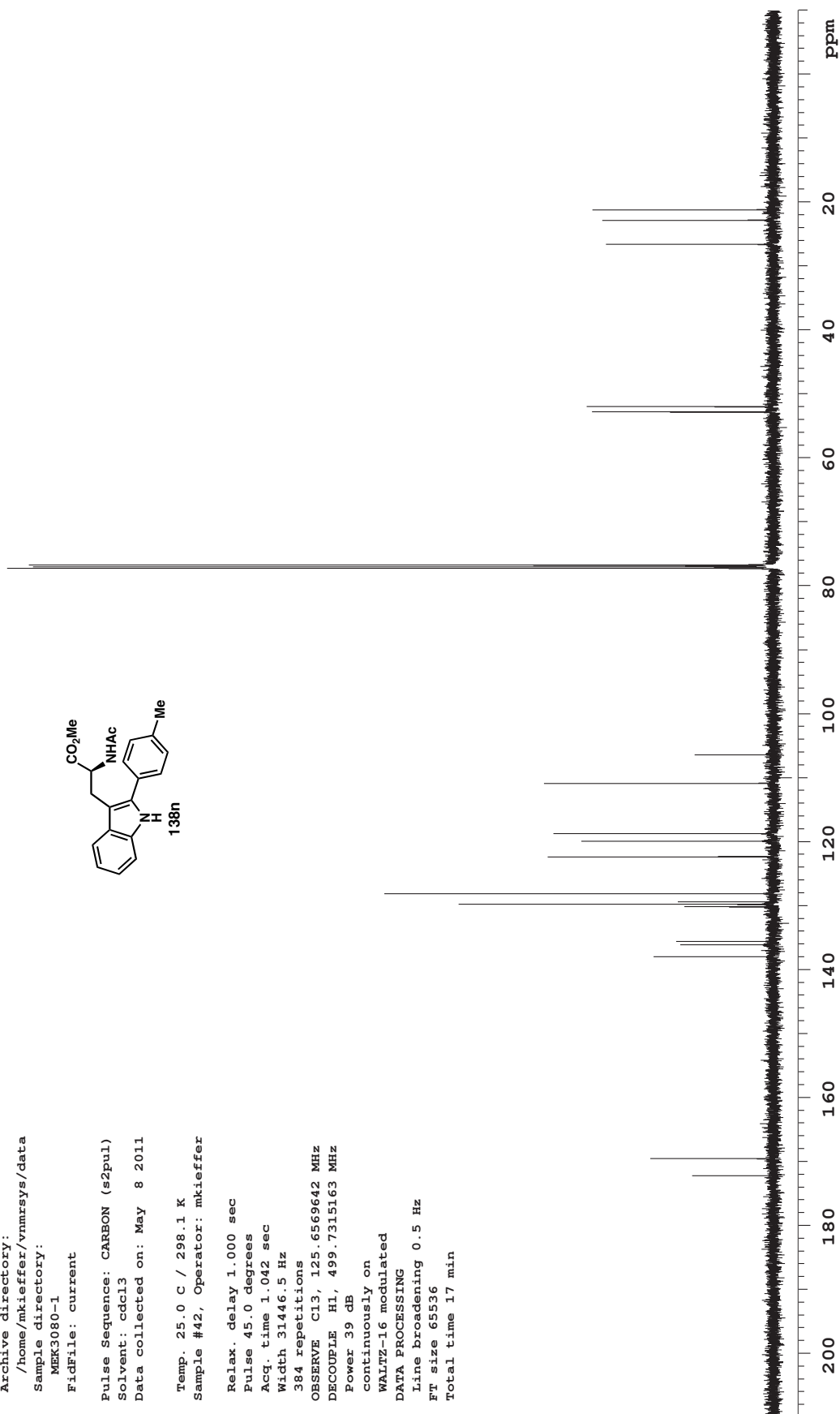
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 17 min



MEK3238-1

Sample Name:

MEK3238-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3238-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 31 2011

Sample #20, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

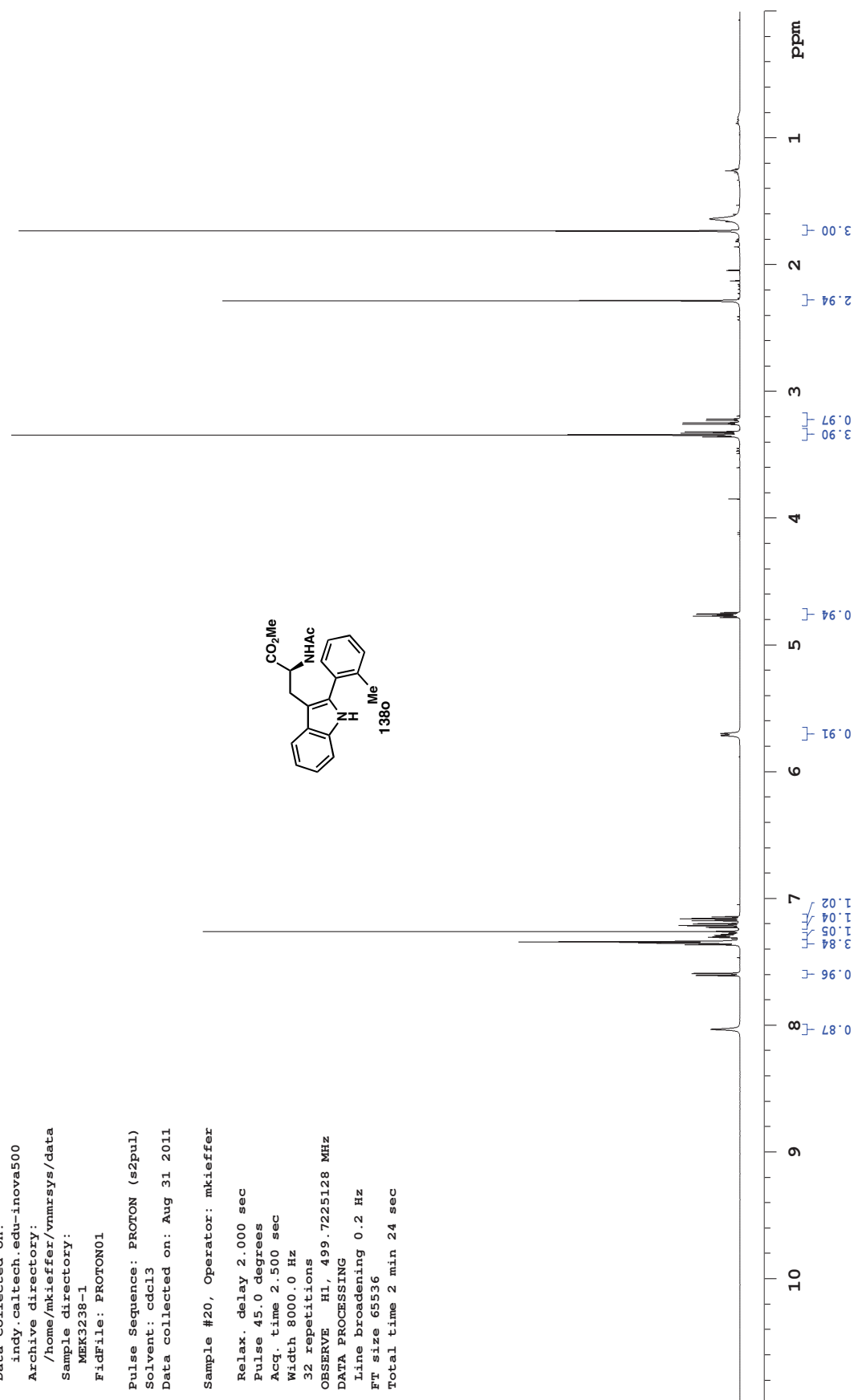
OBSERVE H1, 499.7225128 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 24 sec



MEK3238-1

Sample Name:

MEK3238-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3238-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Aug 31 2011

Sample #20, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6553271 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

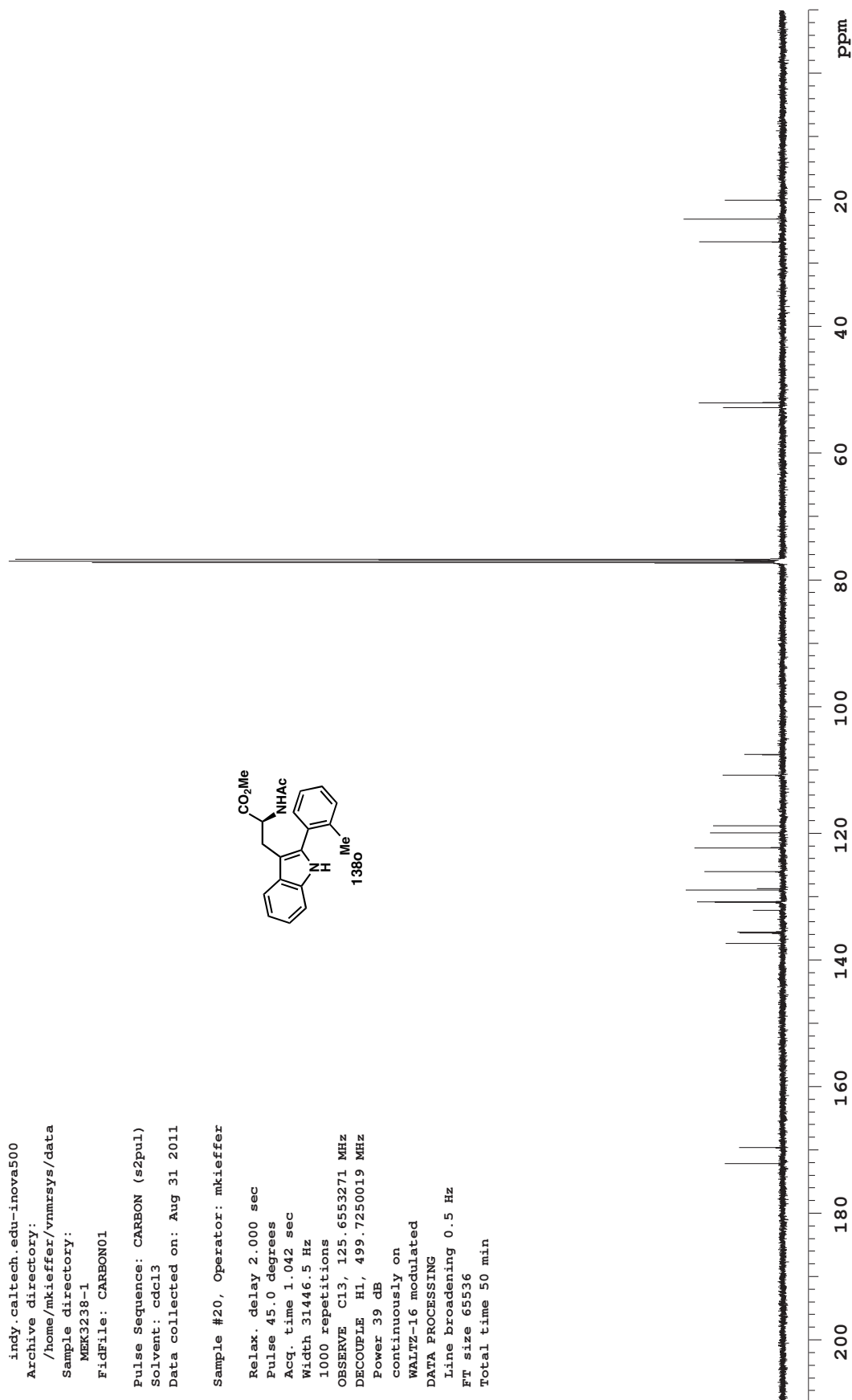
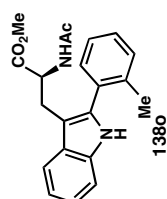
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 50 min



MEK3113-1

Sample Name:

MEK3113-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3113-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: May 24 2011

Temp. 25.0 C / 298.1 K

Sample #35, Operator: mkieffer

Relax. delay 5.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

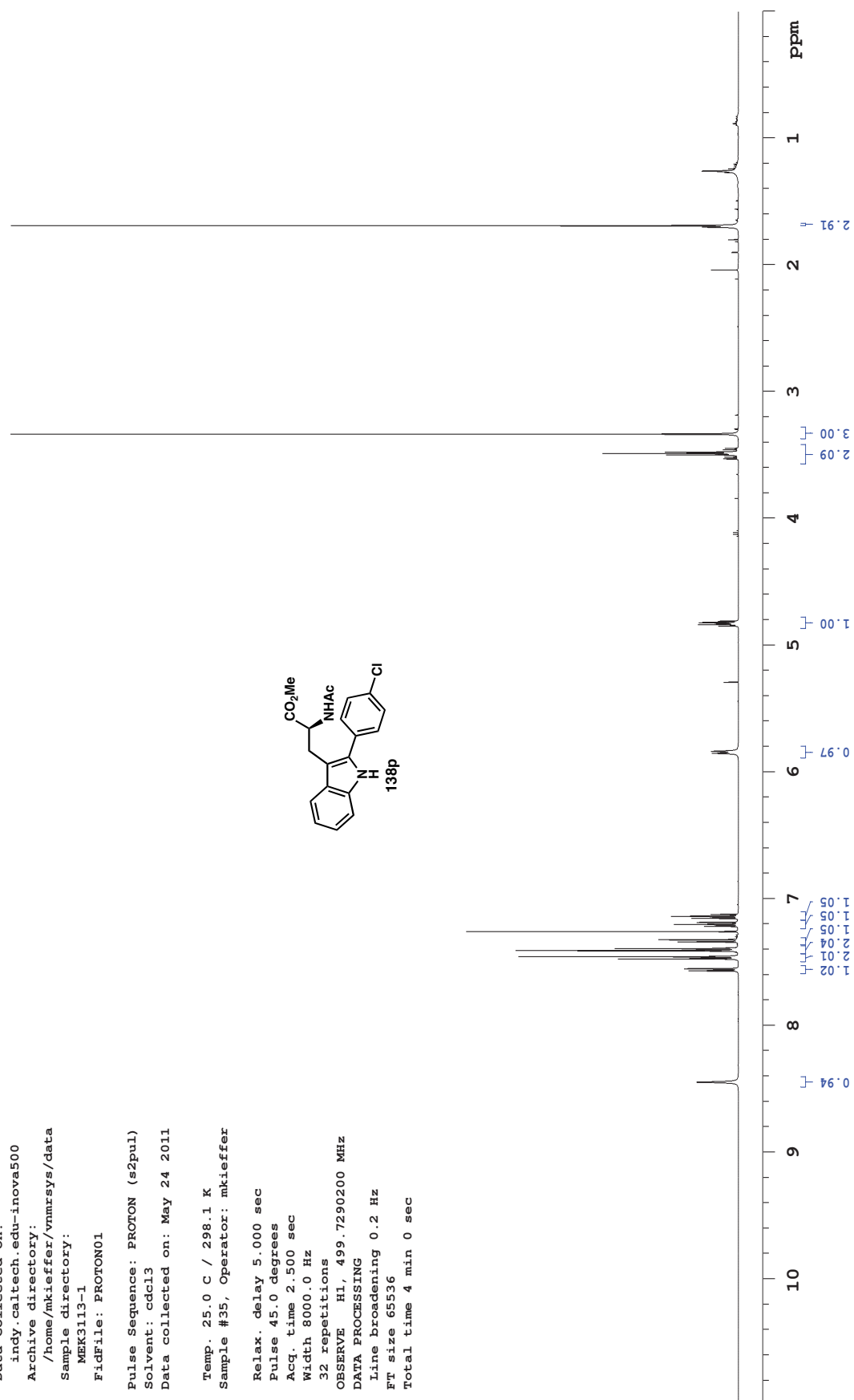
OBSERVE H1, 499.7290200 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 4 min 0 sec



MEK3113-1

Sample Name:

MEK3113-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3113-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: May 24 2011

Temp. 25.0 C / 298.1 K

Sample #35, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

2000 repetitions

OBSERVE C13, 125.6569662 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

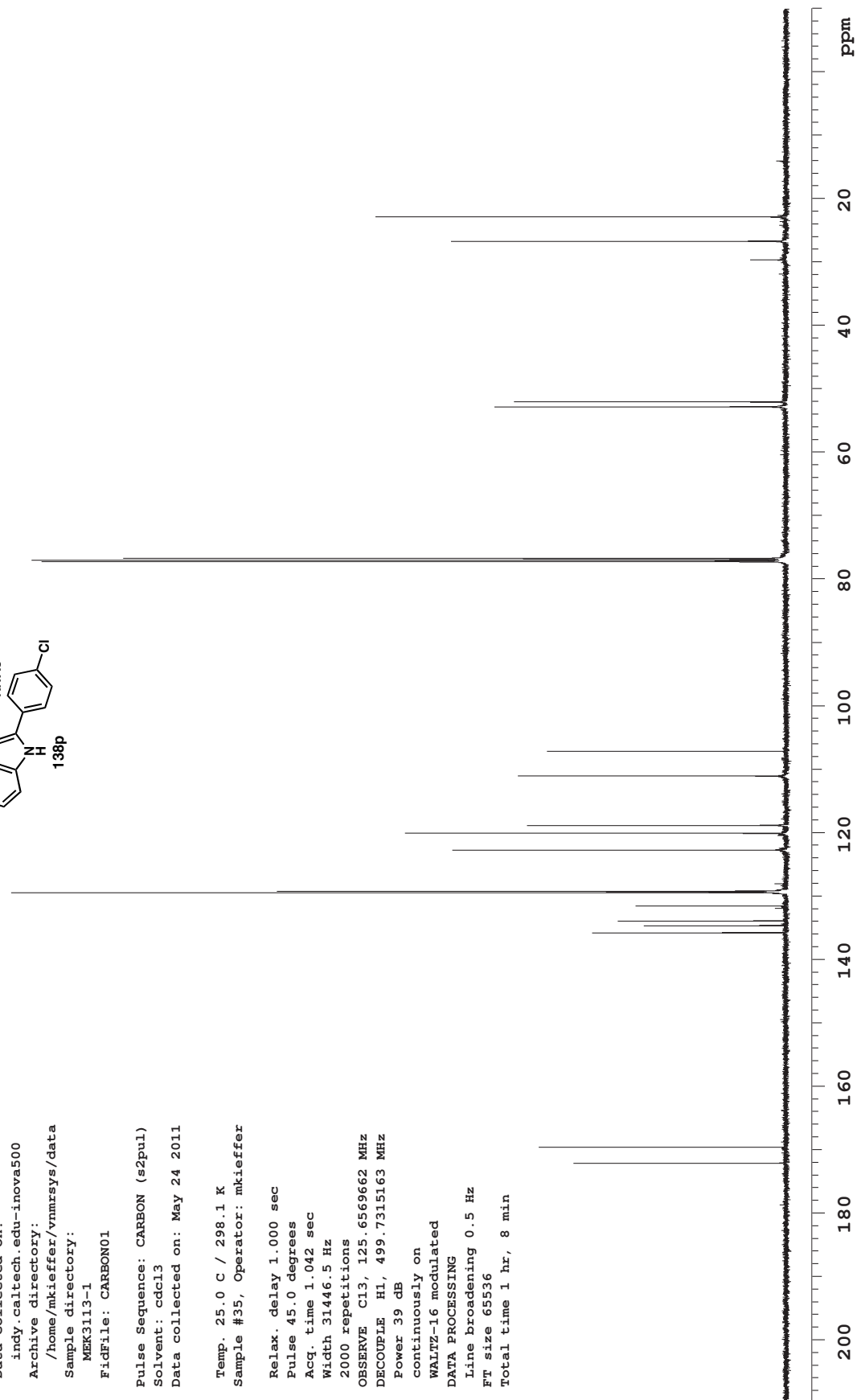
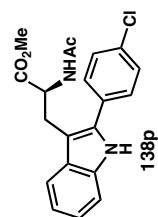
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 1 hr, 8 min



MEK-para-F

Sample Name:

MEK-para-F

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK-para-F

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 25 2011

Sample #14, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

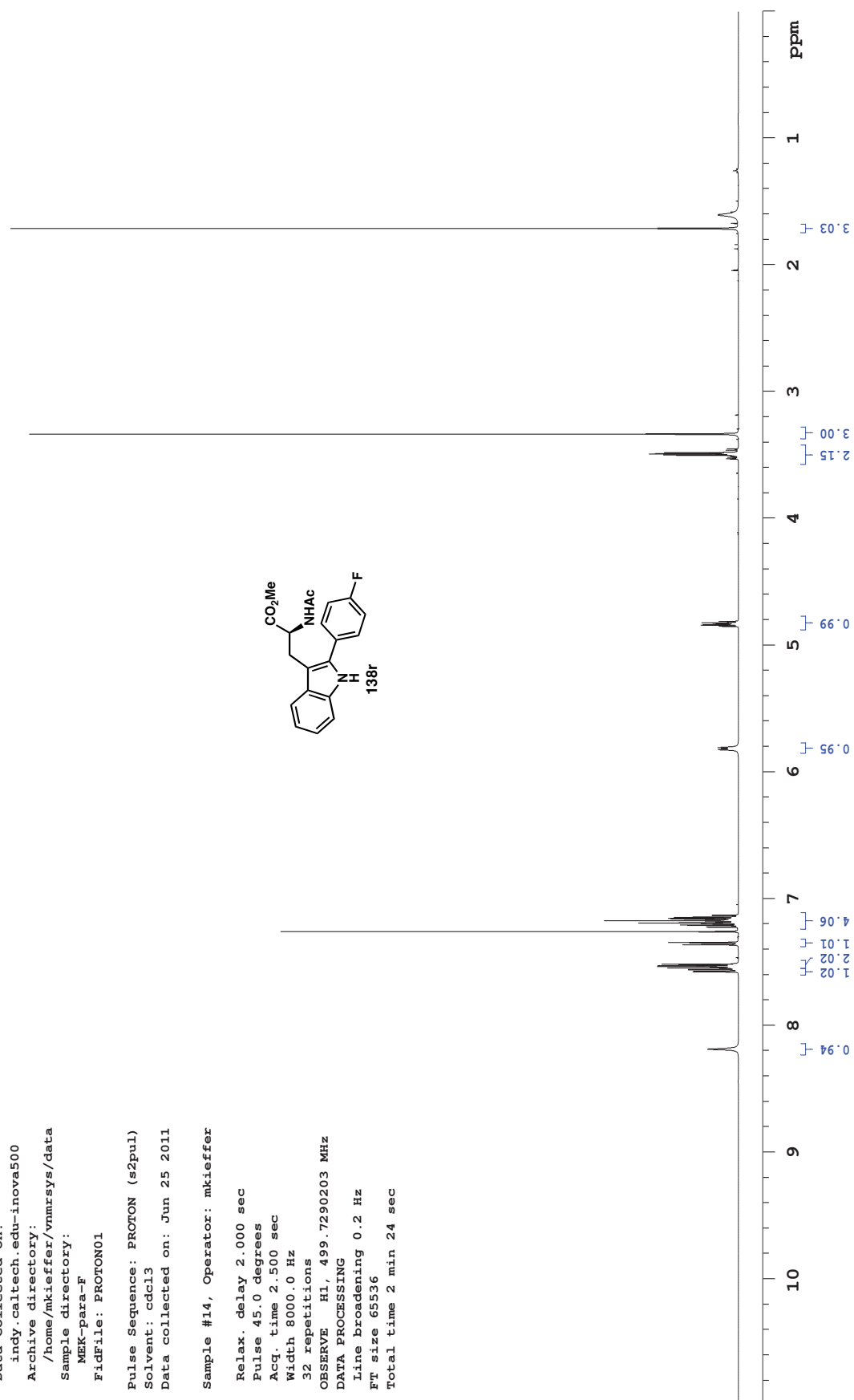
OBSERVE H1, 499.7290203 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 24 sec



MEK3086-1

Sample Name:

MEK3086-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkierfer/vnmrsys/data

Sample directory:

MEK3086-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: May 10 2011

Temp. 25.0 C / 298.1 K

Sample #39, Operator: mkierfer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

512 repetitions

OBSERVE C13, 125.6569623 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

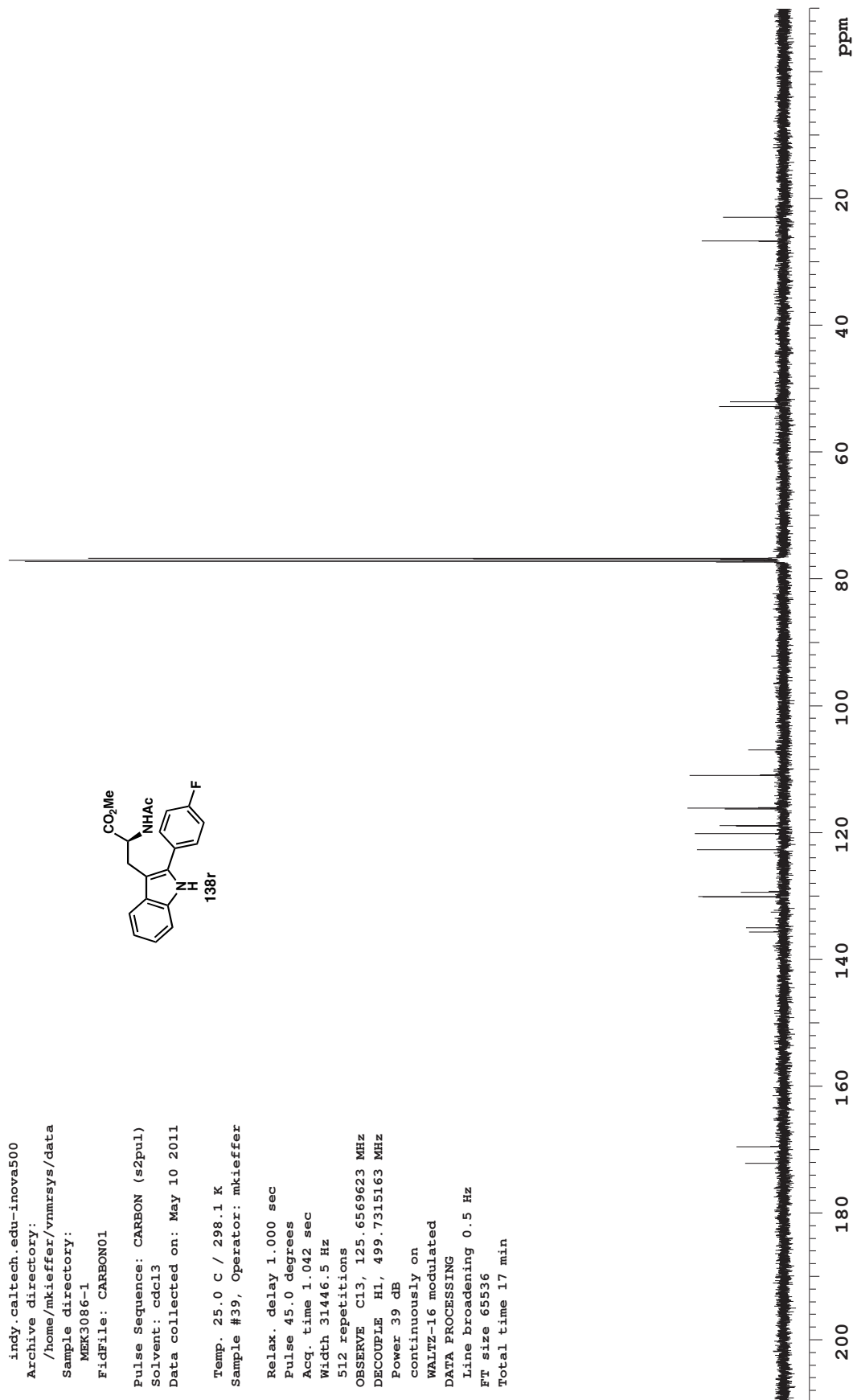
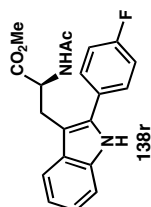
WALTZ-16 modulated

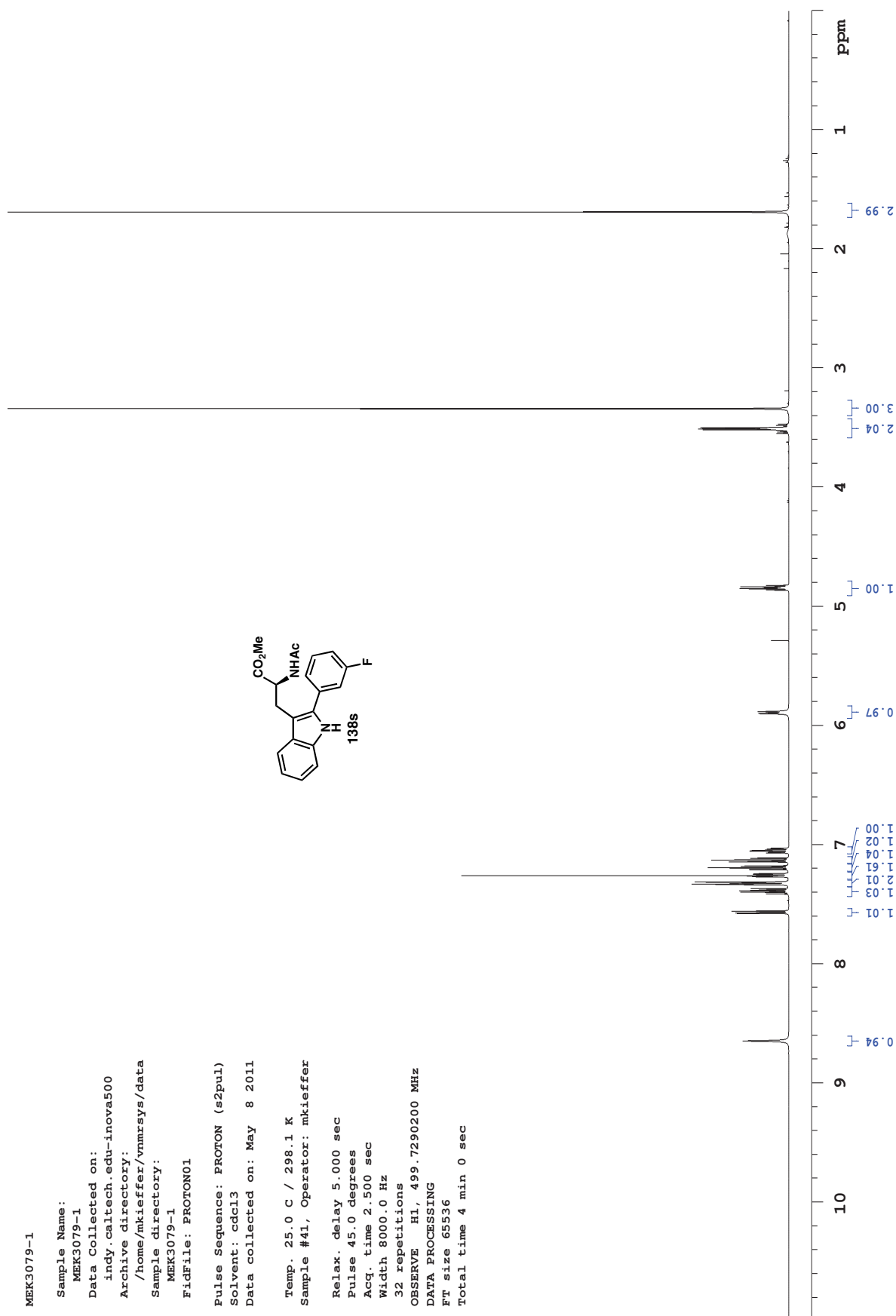
DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 17 min





MEK3079-1

Sample Name:

MEK3079-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmr500/data

Sample directory:

MEK3079-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: May 8 2011

Temp. 25.0 C / 298.1 K

Sample #41, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

256 repetitions

OBSERVE C13, 125.6569690 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

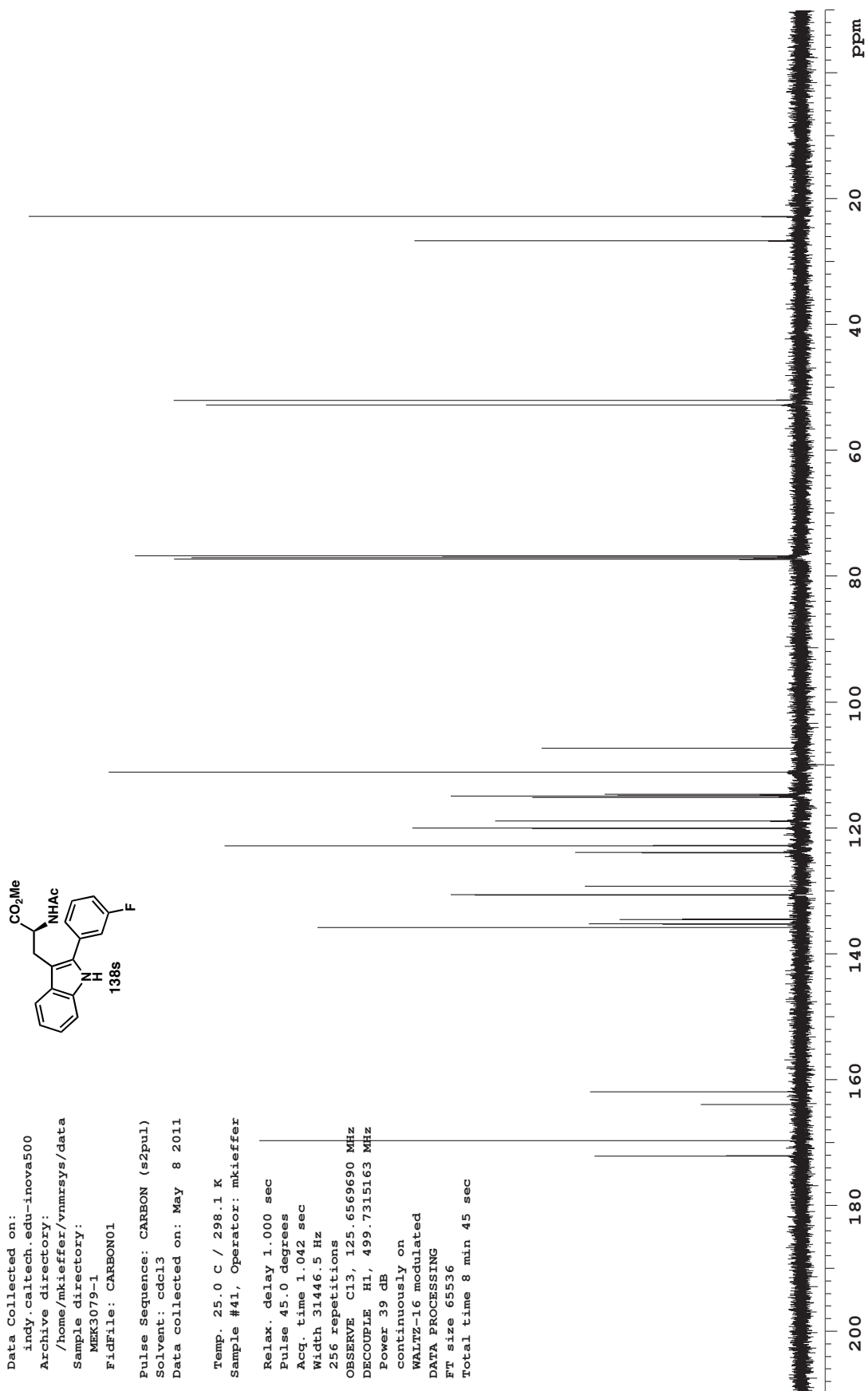
continuously on

WALTZ-16 modulated

DATA PROCESSING

FT size 65536

Total time 8 min 45 sec

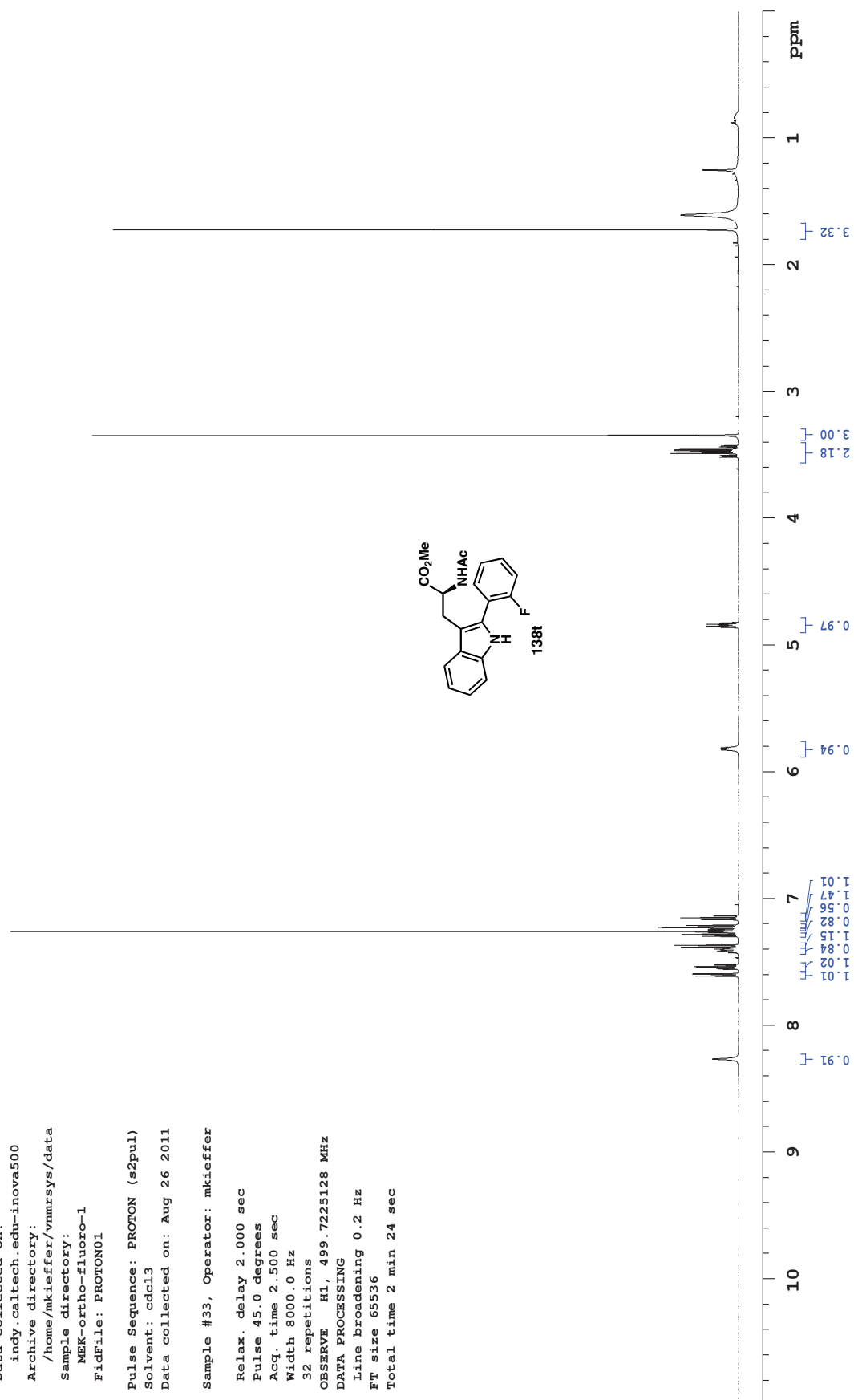


MEK-ortho-fluoro-1

Sample Name:
 MEK-ortho-fluoro-1
 Data Collected on:
 indy.caltech.edu-inova500
 Archive directory:
 /home/mkieffer/vnmrSYS/data
 Sample directory:
 MEK-ortho-fluoro-1
 FIDFile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Aug 26 2011

Sample #33, Operator: mkieffer
 Relax. delay 2.000 sec
 Pulse 45.0 degrees
 Acq. time 2.500 sec
 Width 8000.0 Hz
 32 repetitions
 OBSERVE H1, 499.7225128 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 2 min 24 sec



MEK3219-2

Sample Name:

MEK3219-2

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3219-2

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Aug 17 2011

Sample #7, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6553271 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

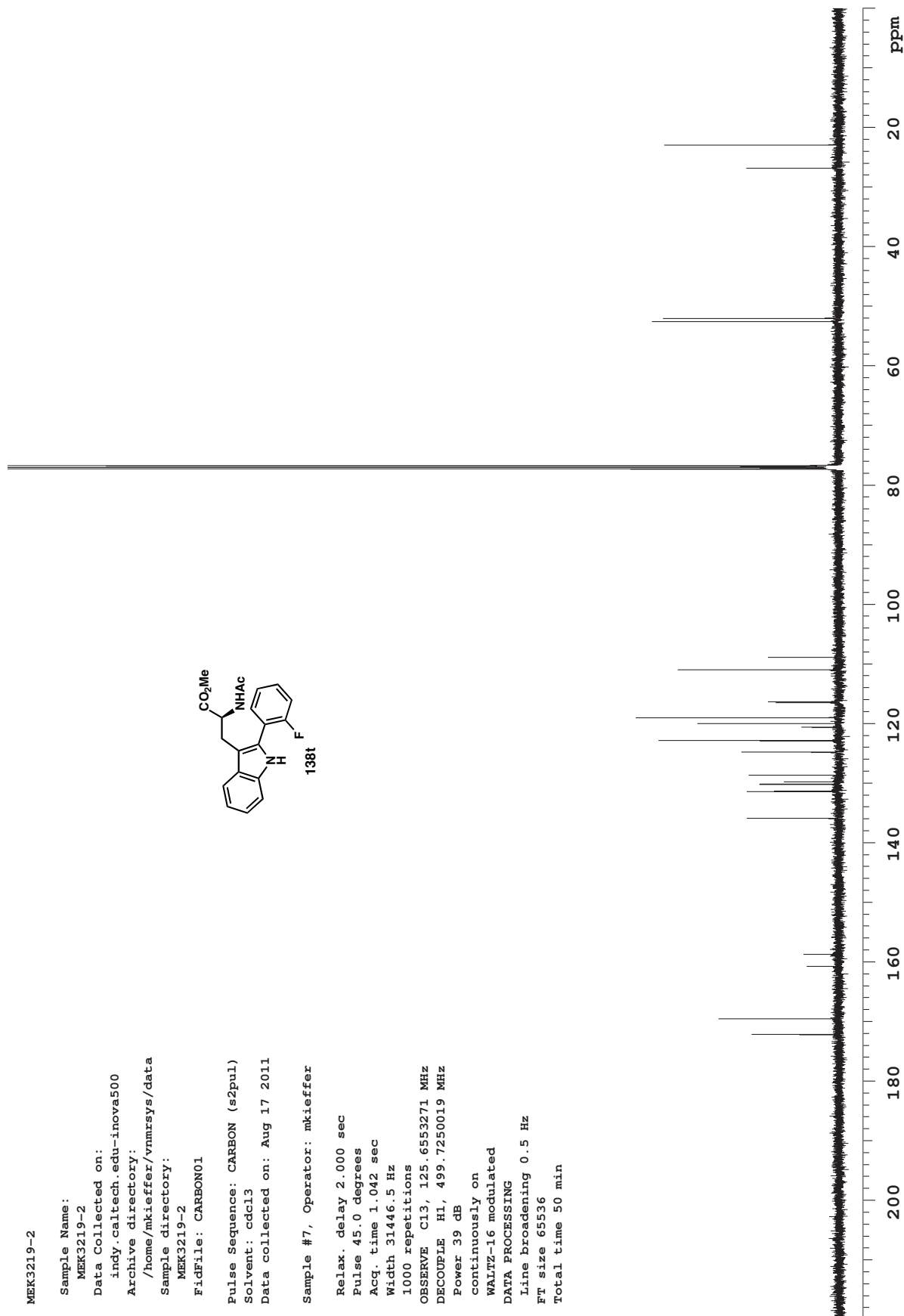
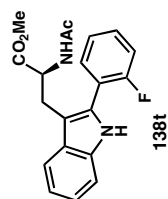
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 50 min



MEK-n-OMe

Sample Name:

MEK-n-OMe

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK-n-OMe

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 25 2011

Sample #16, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

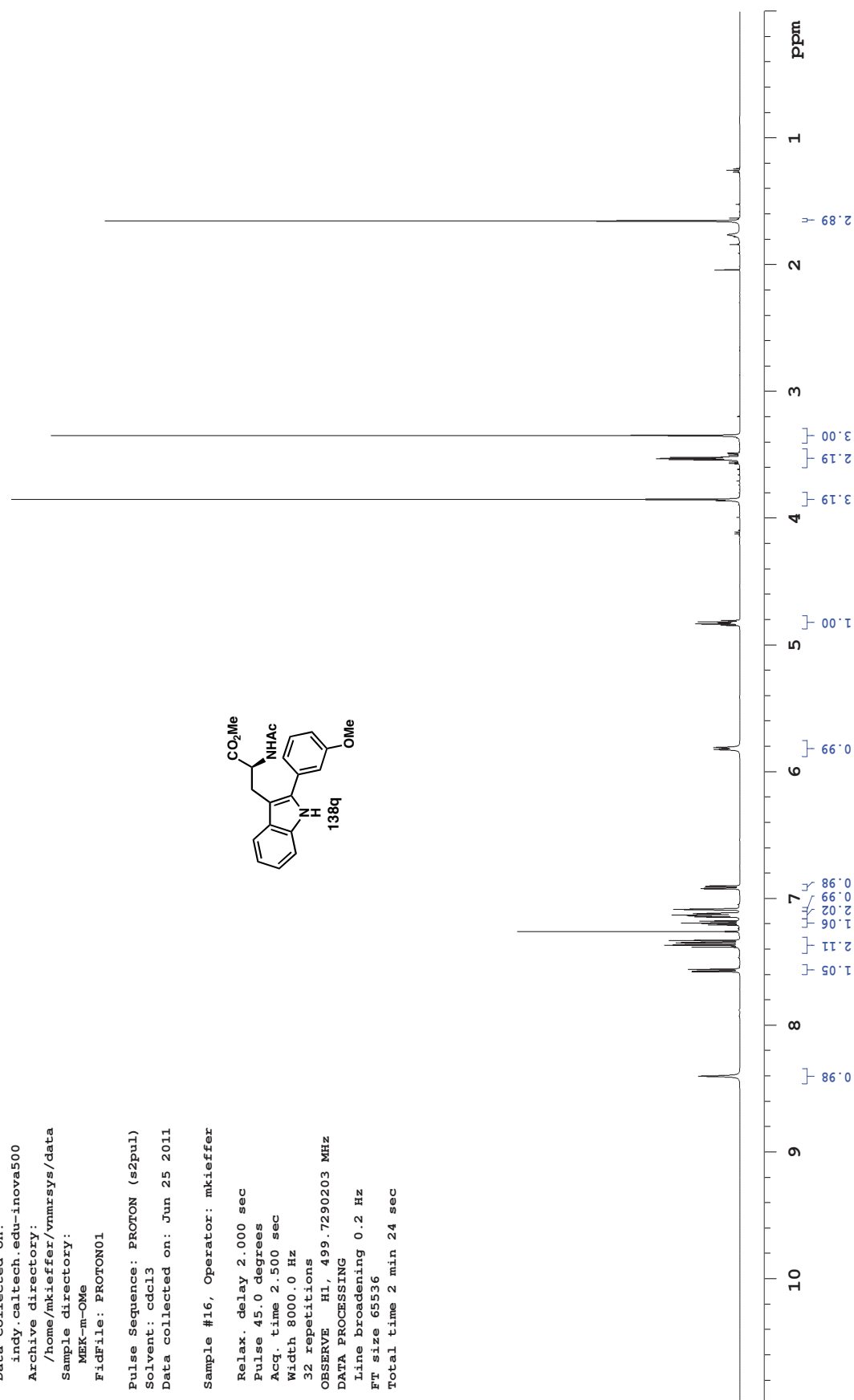
OBSERVE H1, 499.7290203 MHz

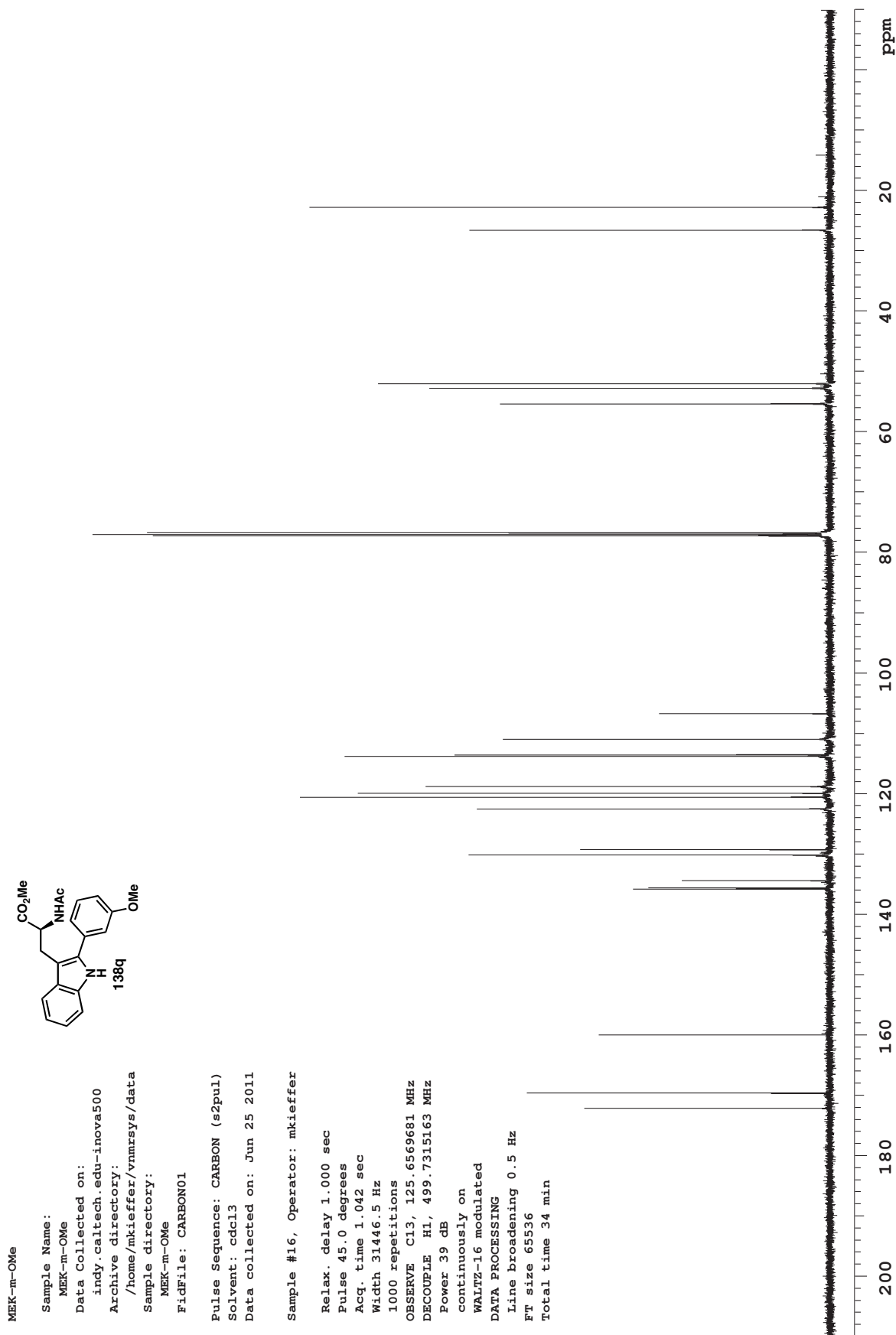
DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 2 min 24 sec





MEK3083-1

Sample Name:

MEK3083-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3083-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: May 9 2011

Temp. 25.0 C / 298.1 K

Sample #38, Operator: mkieffer

Relax. delay 5.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

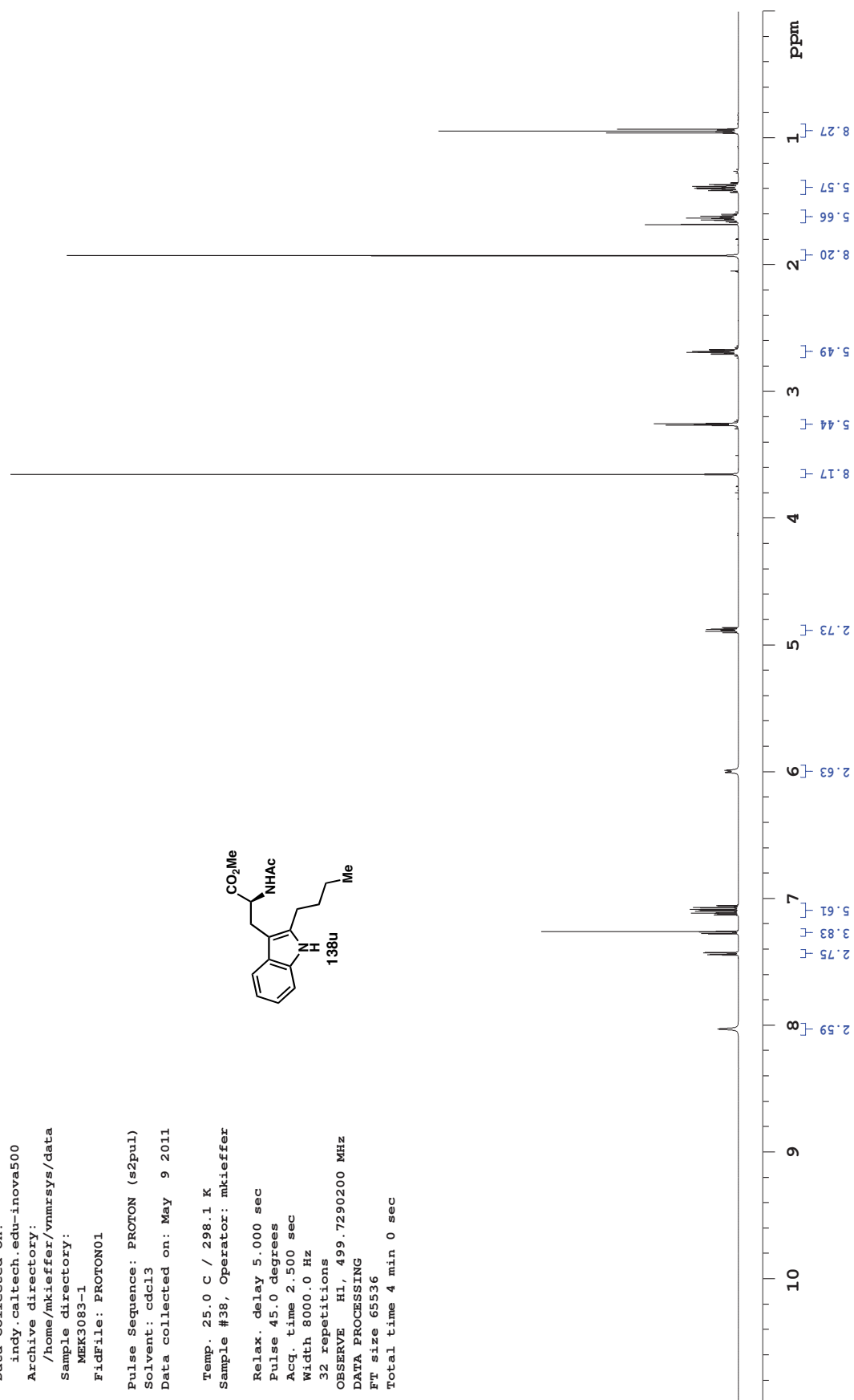
32 repetitions

OBSERVE H1, 499.7290200 MHz

DATA PROCESSING

FT size 65536

Total time 4 min 0 sec



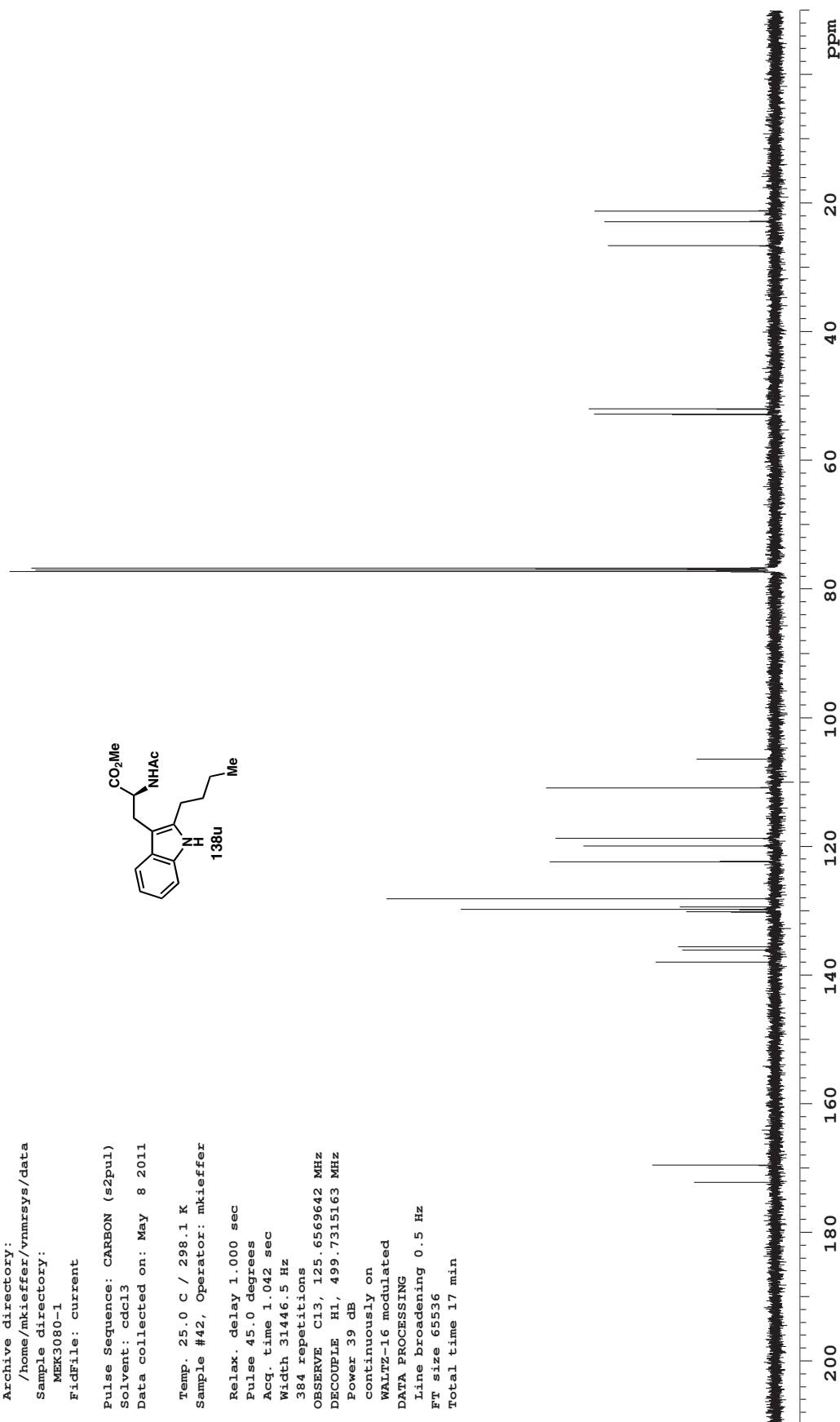
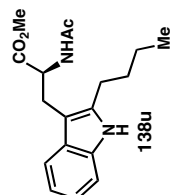
MEK3080-1

Sample Name:
MEK3080-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkieffer/vnmr/vars/data
Sample directory:
MEK3080-1
FidFile: current

Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: May 8 2011

Temp. 25.0 C / 298.1 K
Sample #42, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
384 repetitions
OBSERVE C13, 125.6569642 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min



MEK3129-1

Sample Name:

MEK3129-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3129-1

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 7 2011

Temp. 25.0 C / 298.1 K

Sample #14, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

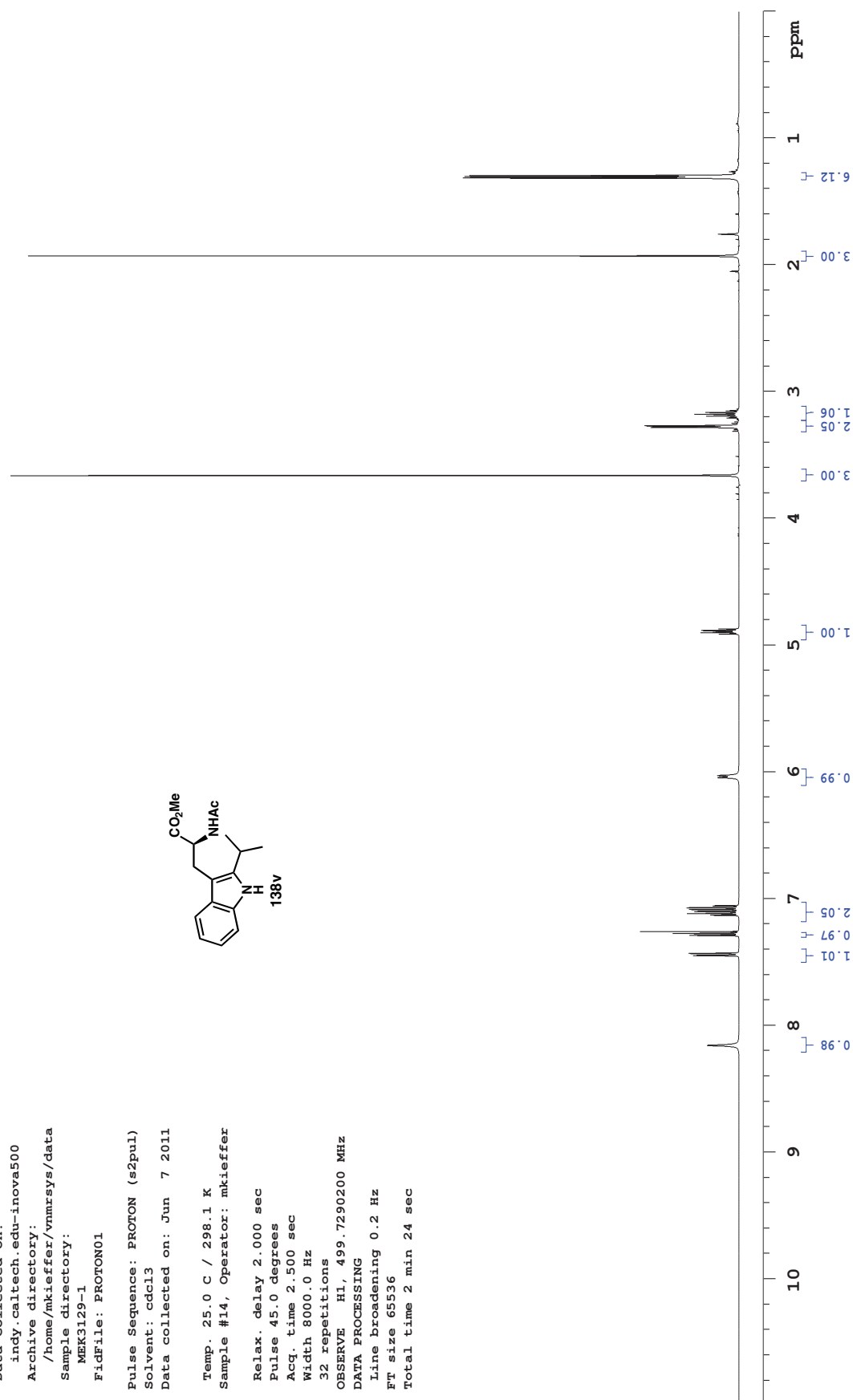
OBSERVE H1, 499.7290200 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 2 min 24 sec



MEK3129-1

Sample Name:

MEK3129-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3129-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jun 7 2011

Temp. 25.0 C / 298.1 K

Sample #14, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

512 repetitions

OBSERVE C13, 125.6569671 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

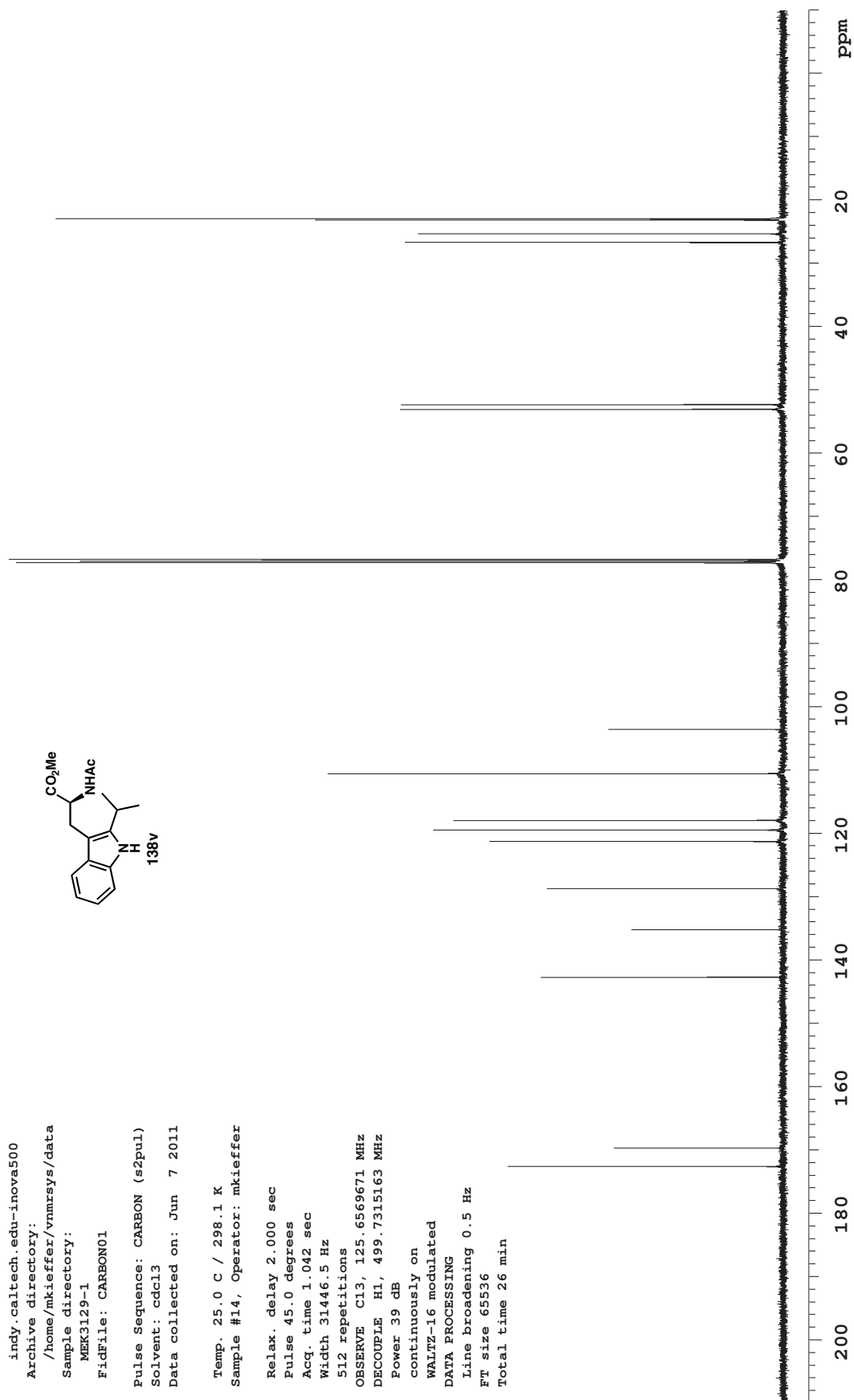
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 26 min



MEK-t-butyl-rac

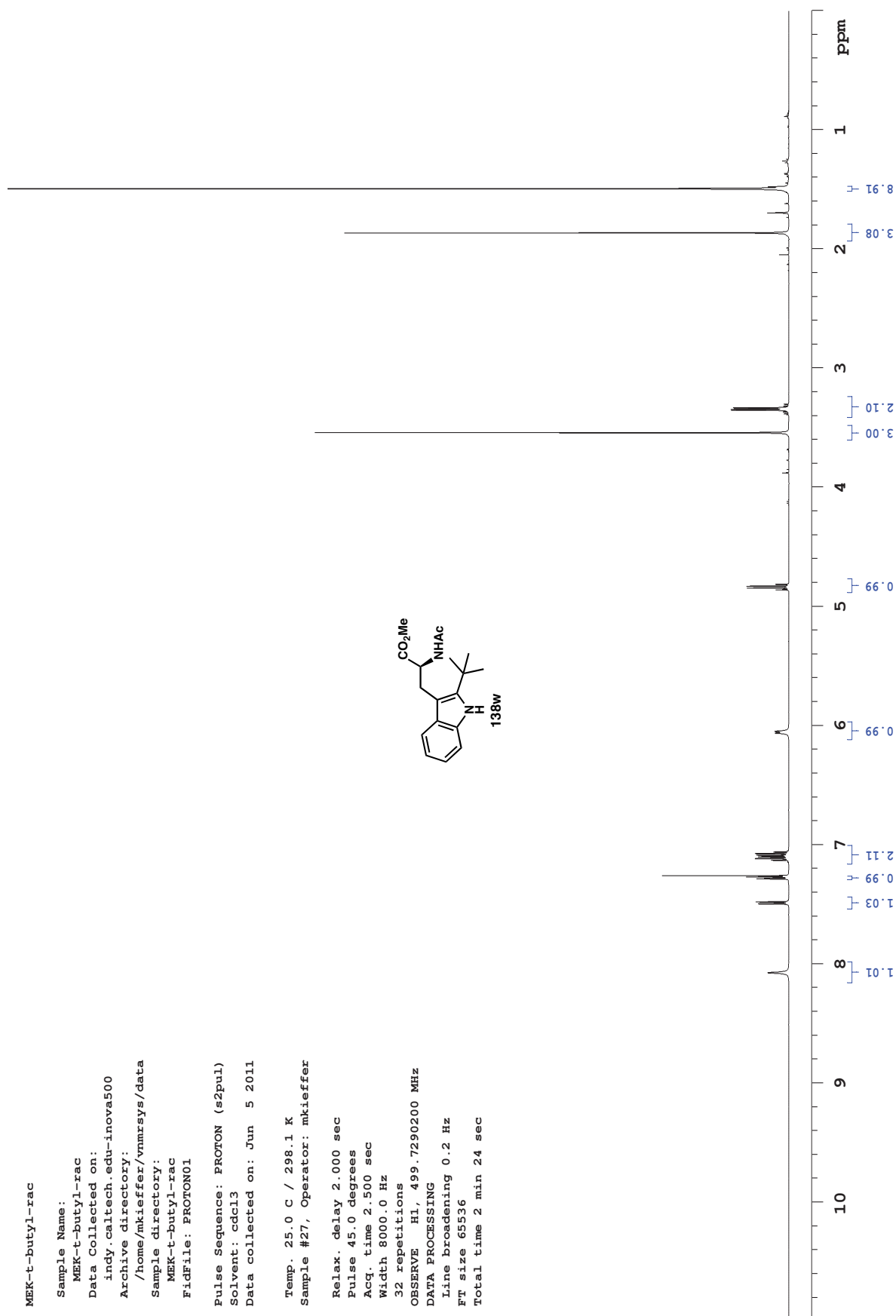
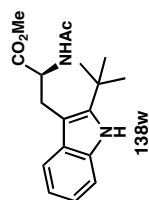
Sample Name:
MEK-t-butyl-rac
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkieffer/vnmrsys/data
Sample directory:
MEK-t-butyl-rac
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2011

Temp. 25.0 C / 298.1 K
Sample #27, Operator: mkieffer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions

OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
Ft size 65536
Total time 2 min 24 sec



MEK-t-butyl-rac

Sample Name:

MEK-t-butyl-rac

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK-t-butyl-rac

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jun 5 2011

Temp. 25.0 C / 298.1 K

Sample #27, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6569662 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

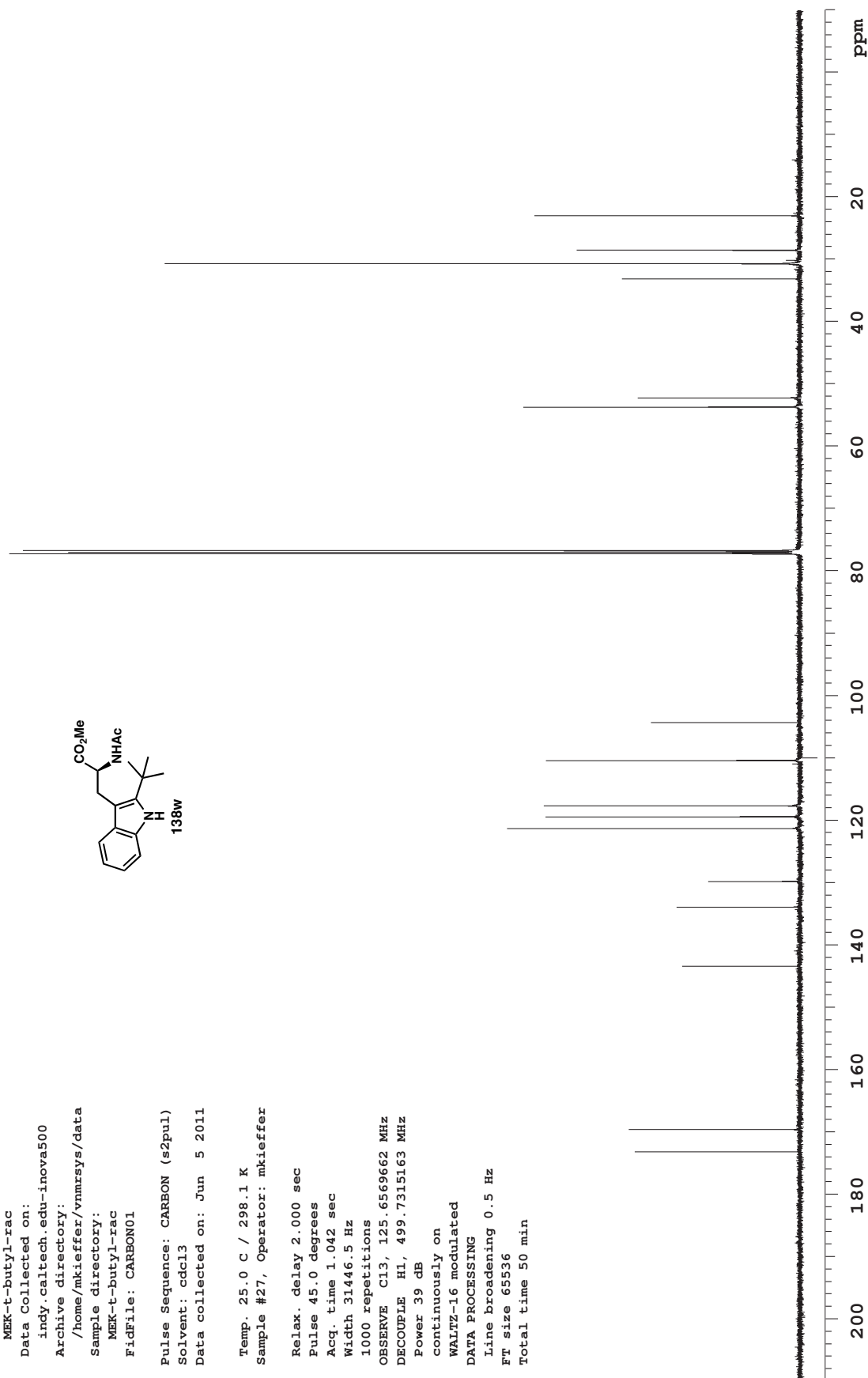
WALTZ-16 modulated

DATA PROCESSING

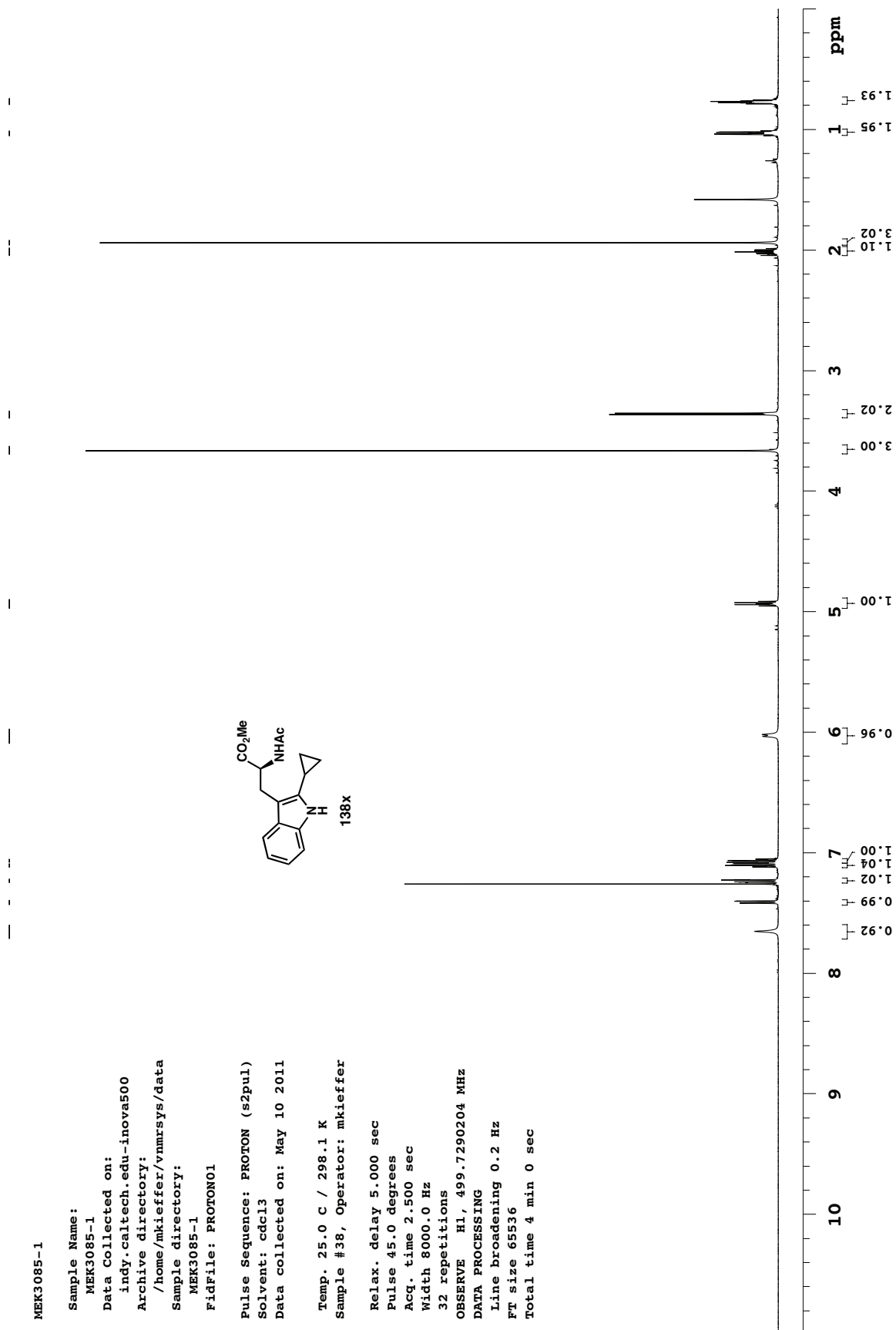
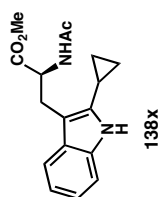
Line broadening 0.5 Hz

Ft size 65536

Total time 50 min



Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.729020
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 0 sec



MEK3085-1

Sample Name:

MEK3085-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrsys/data

Sample directory:

MEK3085-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: May 11 2011

Temp. 25.0 C / 298.1 K

Sample #38, Operator: mkieffer

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

5000 repetitions

OBSERVE C13, 125.6569616 MHz

DECOUPLE H1, 499.7315163 MHz

Power 39 dB

continuously on

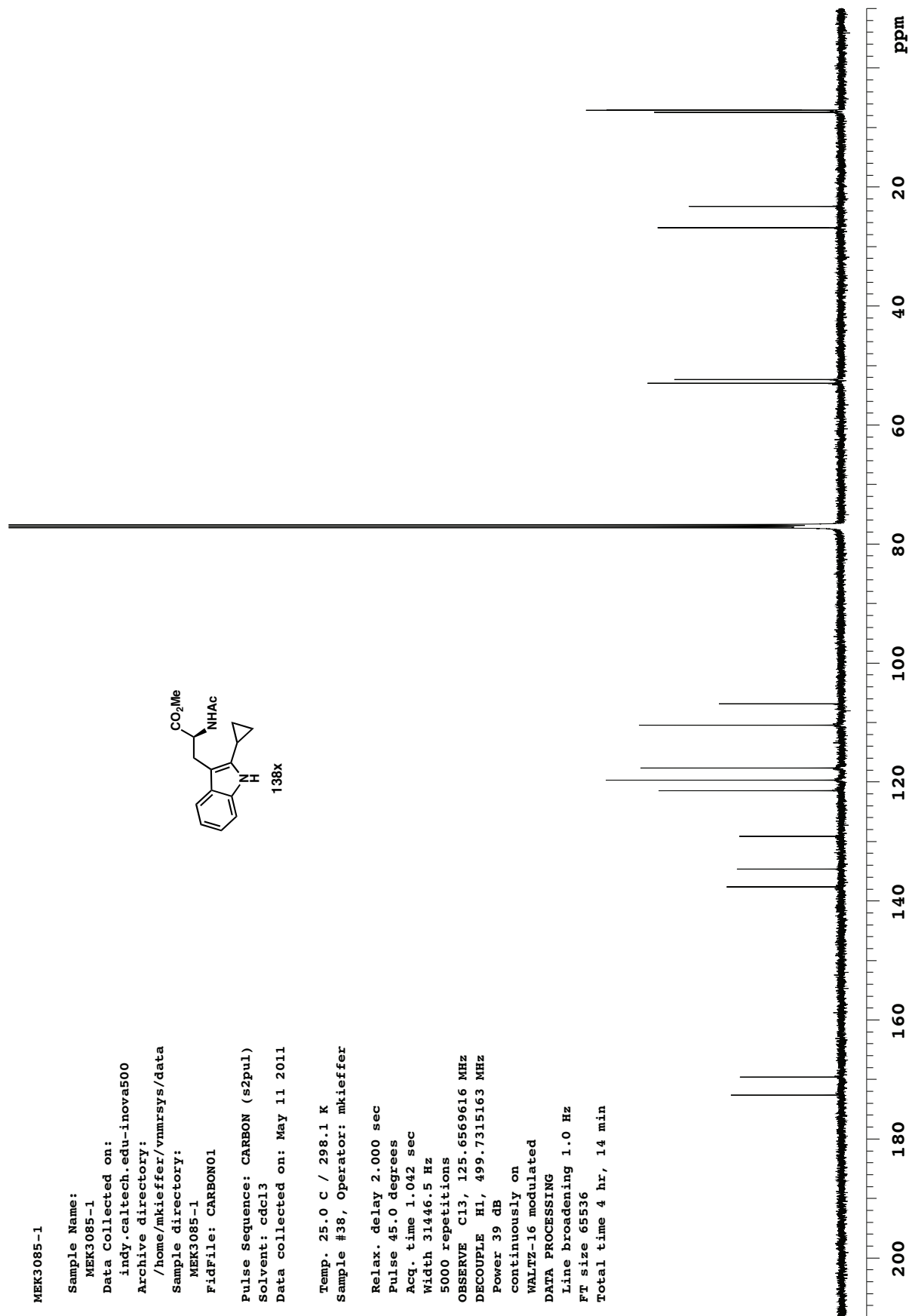
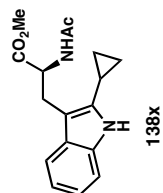
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 4 hr, 14 min



MEK-phthalimide

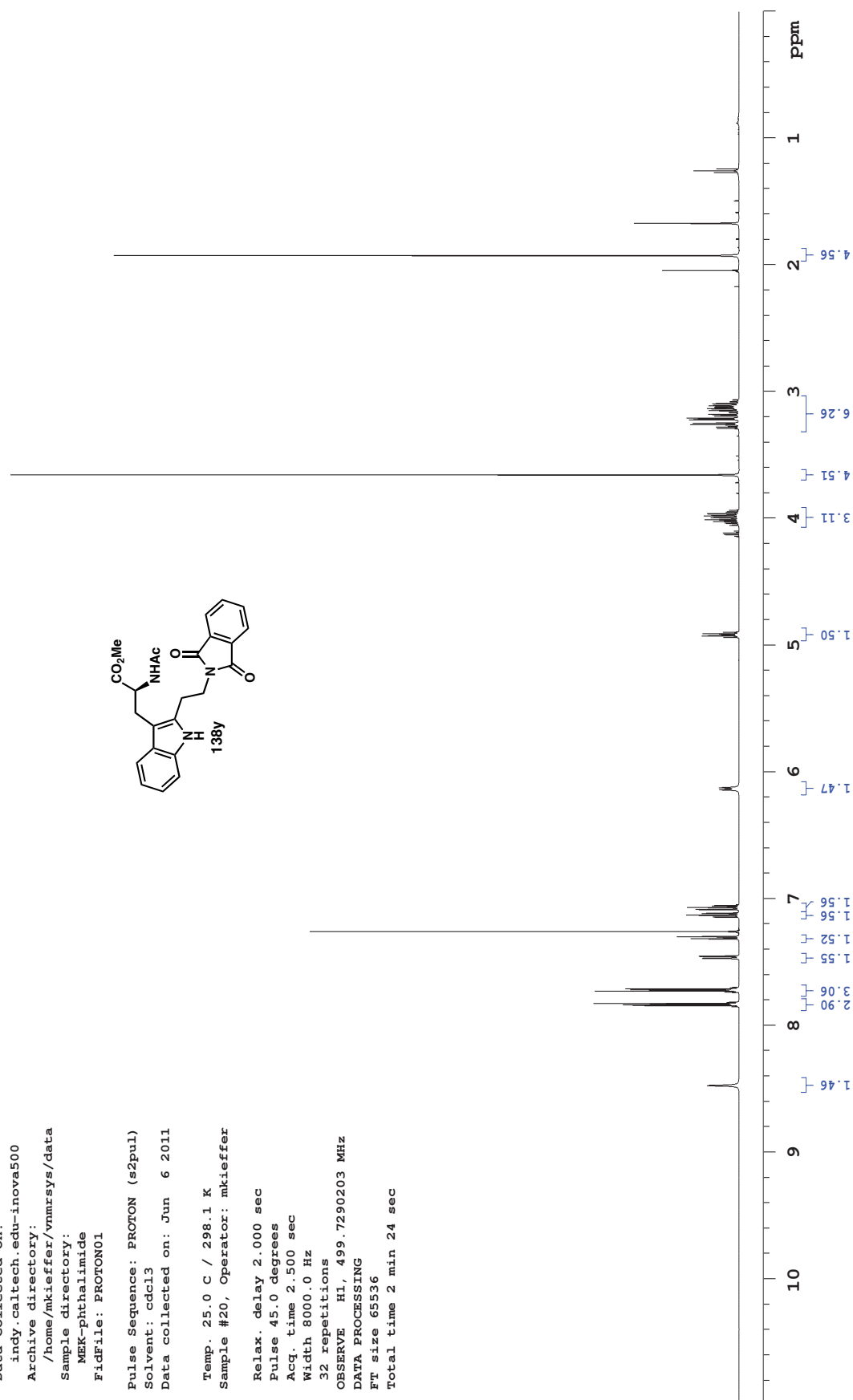
Sample Name:
MEK-phthalimide
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkieffer/vnmrSYS/data
Sample directory:
MEK-phthalimide
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 6 2011

Temp. 25.0 C / 298.1 K
Sample #20, Operator: mkieffer

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
Ft size 65536
Total time 2 min 24 sec



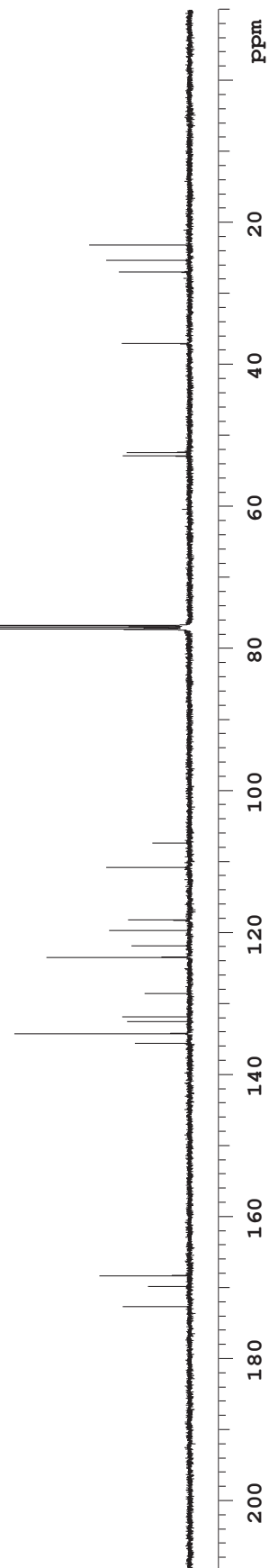
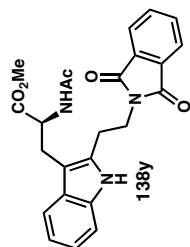
MEK-phthalimide

Sample Name:
MEK-phthalimide
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkierfer/vnmrsys/data
Sample directory:
MEK-phthalimide
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 6 2011

Temp. 25.0 C / 298.1 K
Sample #20, Operator: mkierfer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569633 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
Ft size 65536
Total time 50 min



LMRVI-209

Sample Name:

LMRVI-209

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-209

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 25 2011

Sample #27, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

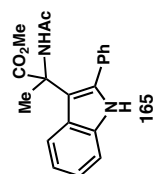
OBSERVE H1, 499.7225141 MHz

DATA PROCESSING

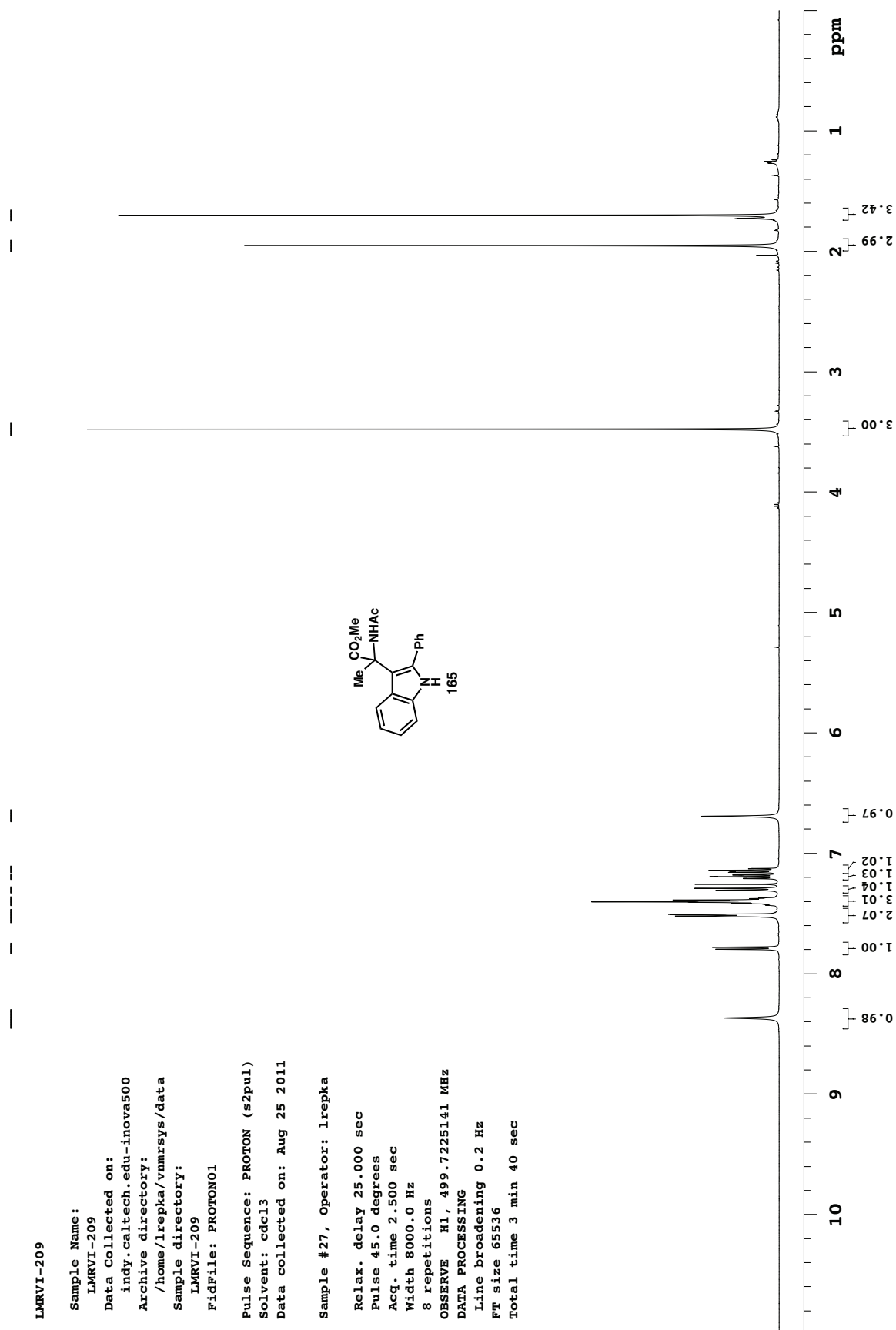
Line broadening 0.2 Hz

FT size 65536

Total time 3 min 40 sec



165



LMRVI-209

Sample Name:

LMRVI-209

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-209

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Aug 25 2011

Sample #27, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1500 repetitions

OBSERVE C13, 125.6553311 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

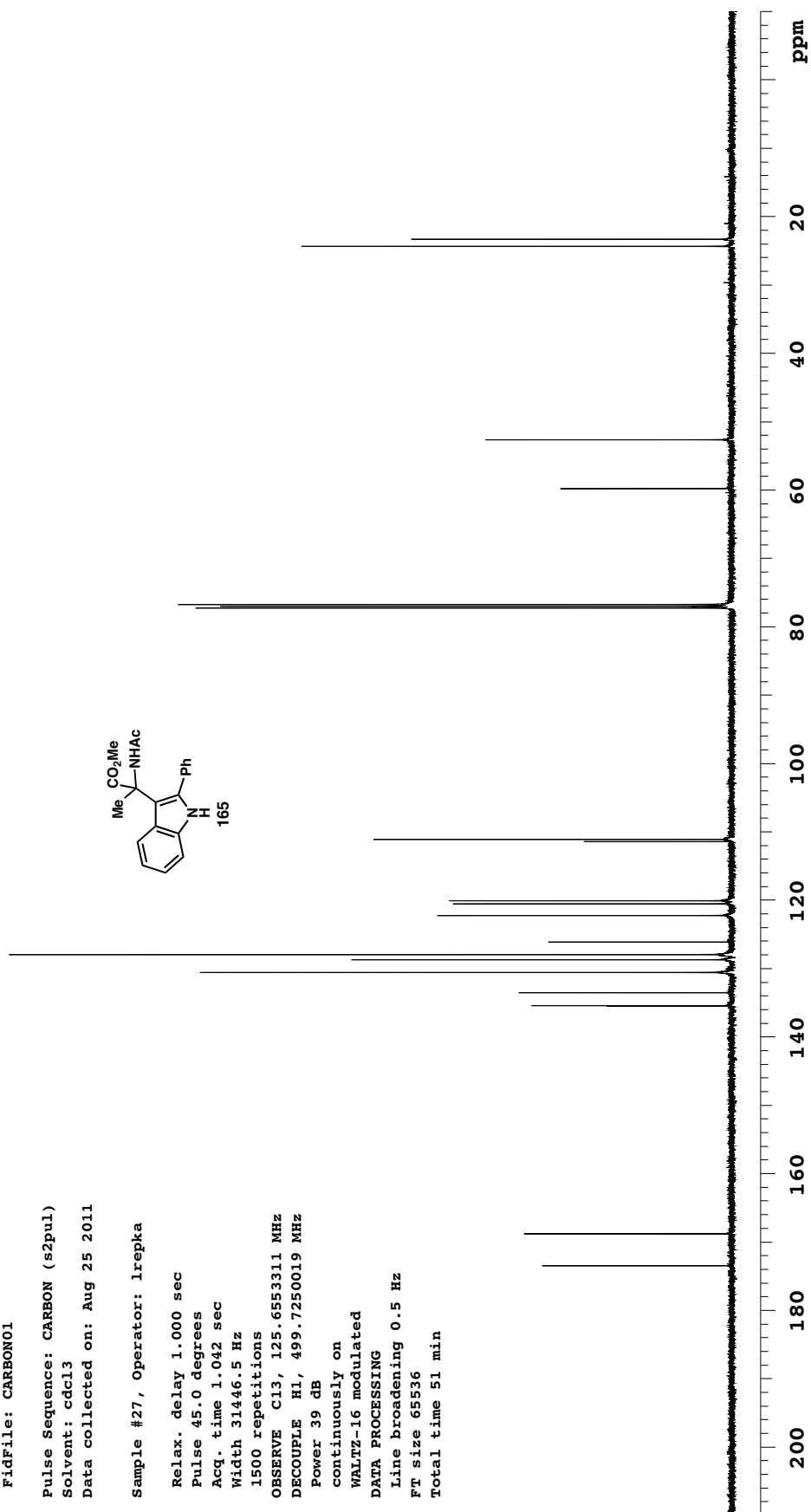
WALTZ-16 modulated

DATA PROCESSING

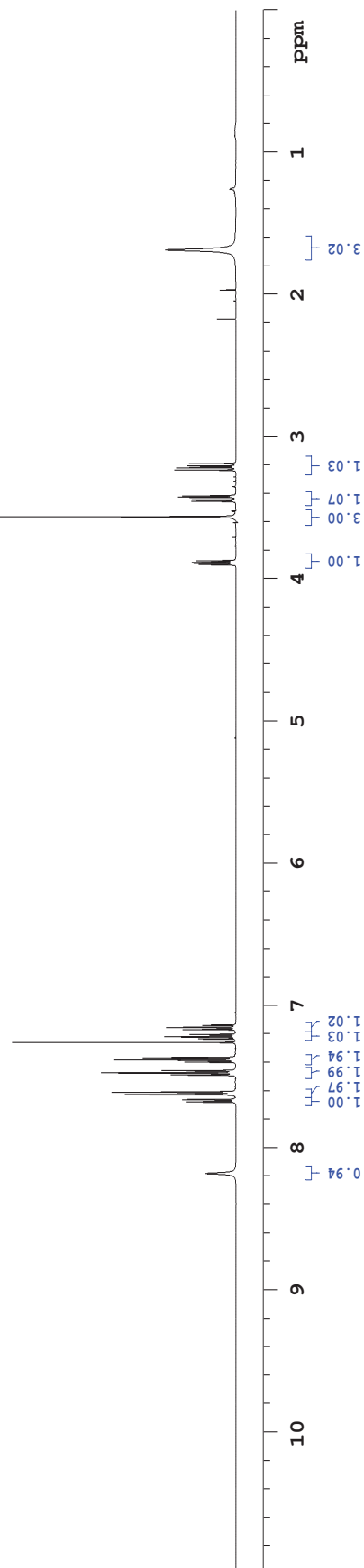
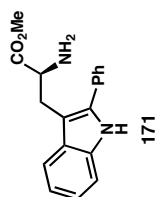
Line broadening 0.5 Hz

Ft size 65536

Total time 51 min



Total time 2 min 24 sec



MEK3206-1

Sample Name:

MEK3206-1

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/mkieffer/vnmrSYS/data

Sample directory:

MEK3206-1

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Aug 4 2011

Sample #14, Operator: mkieffer

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6553281 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

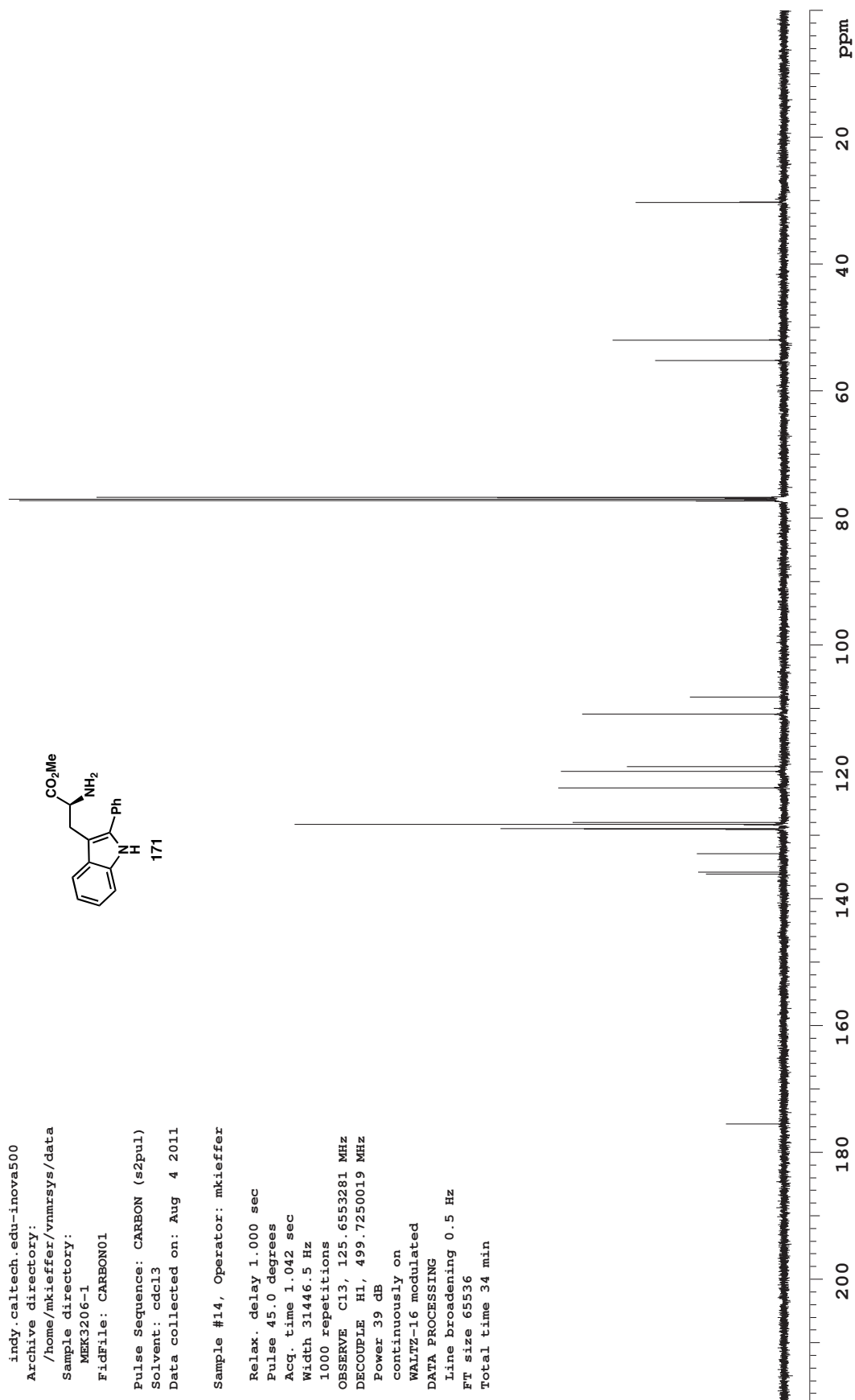
WALTZ-16 modulated

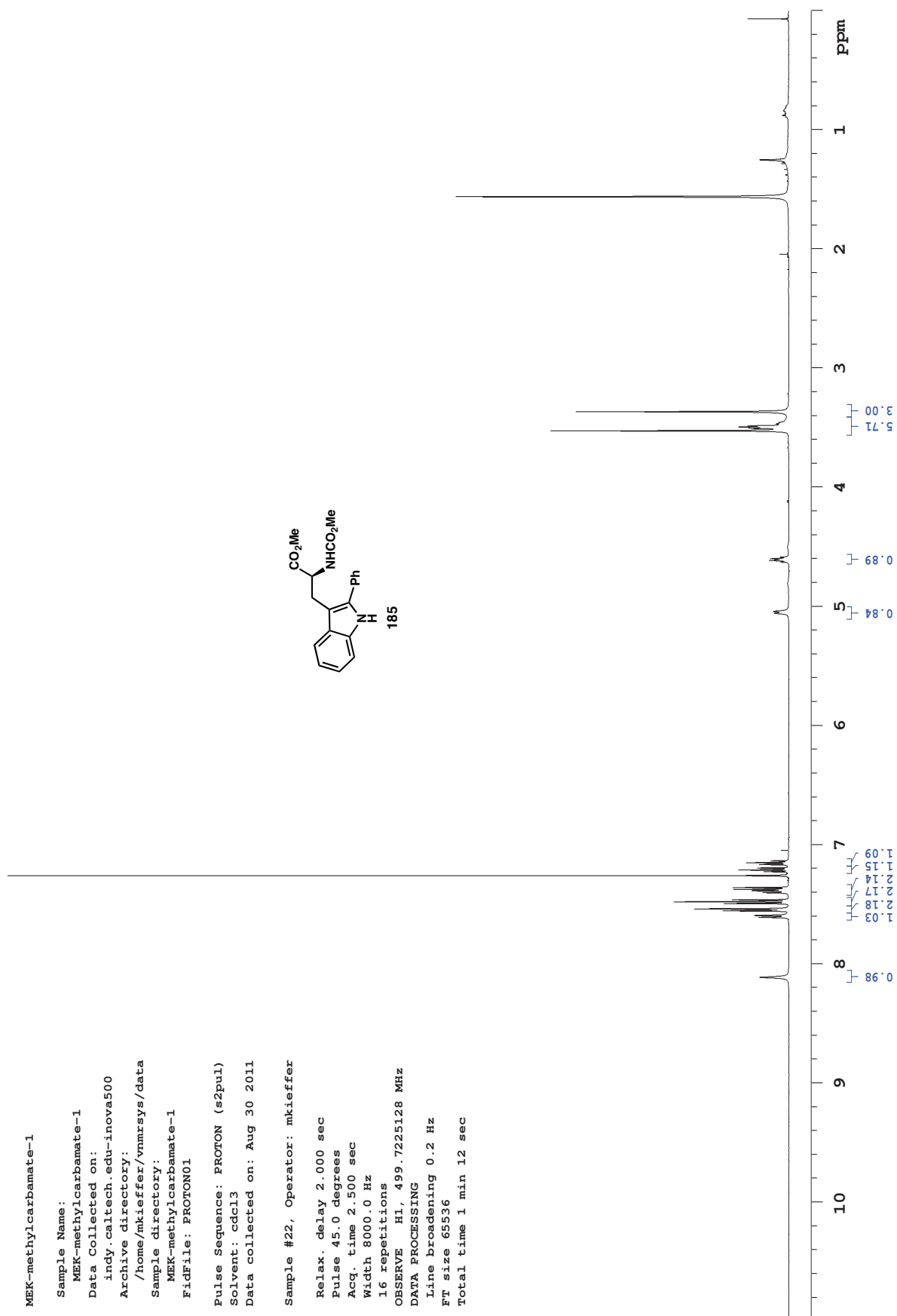
DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 34 min





MEK3233-X

Sample Name:
MEK3233-X

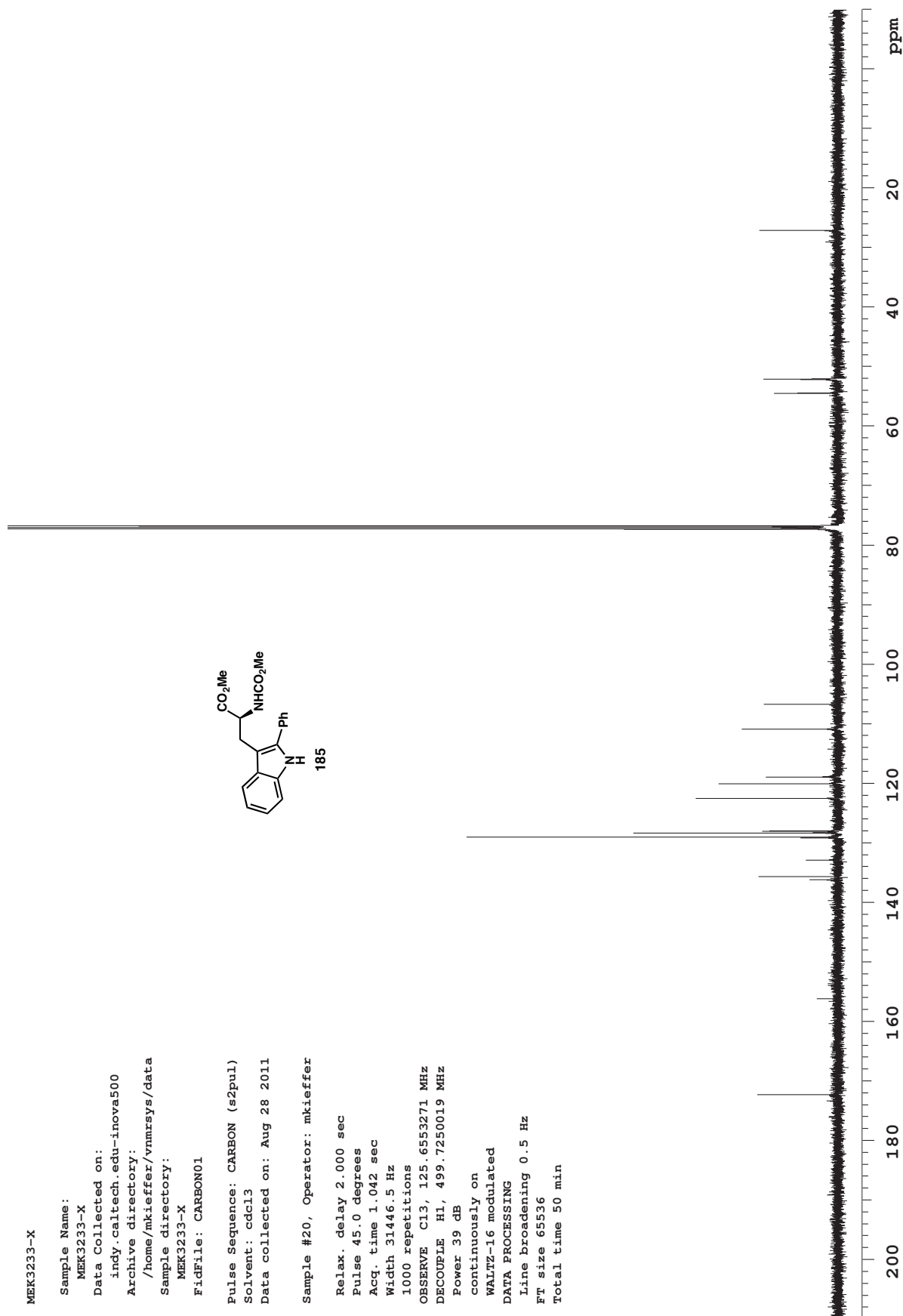
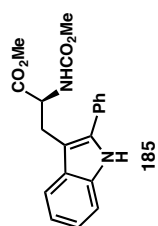
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/mkieffer/vnmrSYS/data

Sample directory:
MEK3233-X
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 28 2011

Sample #20, Operator: mkieffer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553271 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 50 min



LMRVI-181

Sample Name:

LMRVI-181

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-181

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Aug 7 2011

Sample #40, Operator: lrepka

Relax. delay 25.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

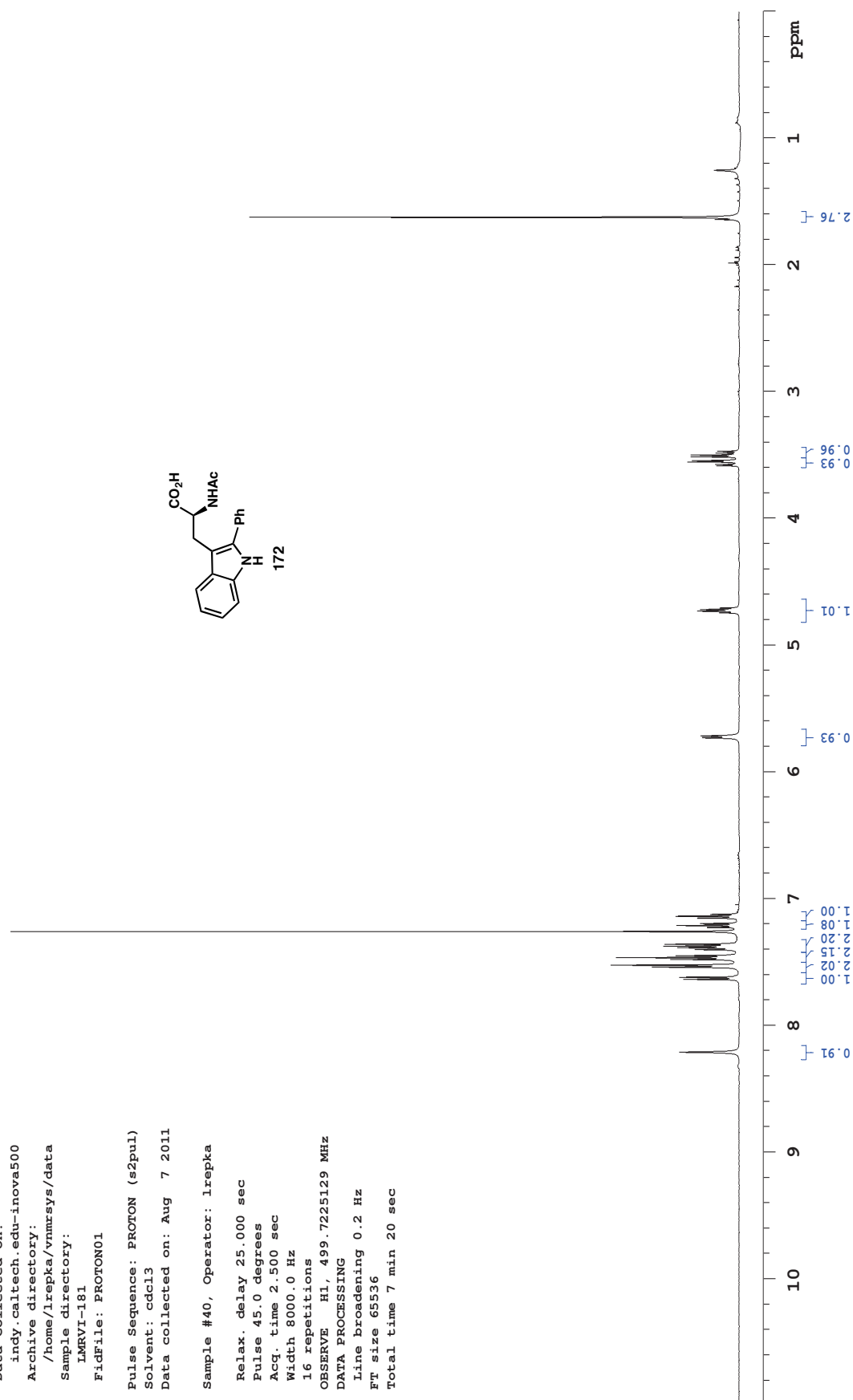
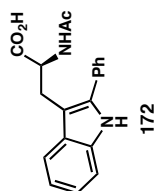
OBSERVE H1, 499.7225129 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 7 min 20 sec



LMRVI-179

Sample Name:

LMRVI-179

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-179

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: Aug 2 2011

Sample #20, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1500 repetitions

OBSERVE C13, 125.6553305 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

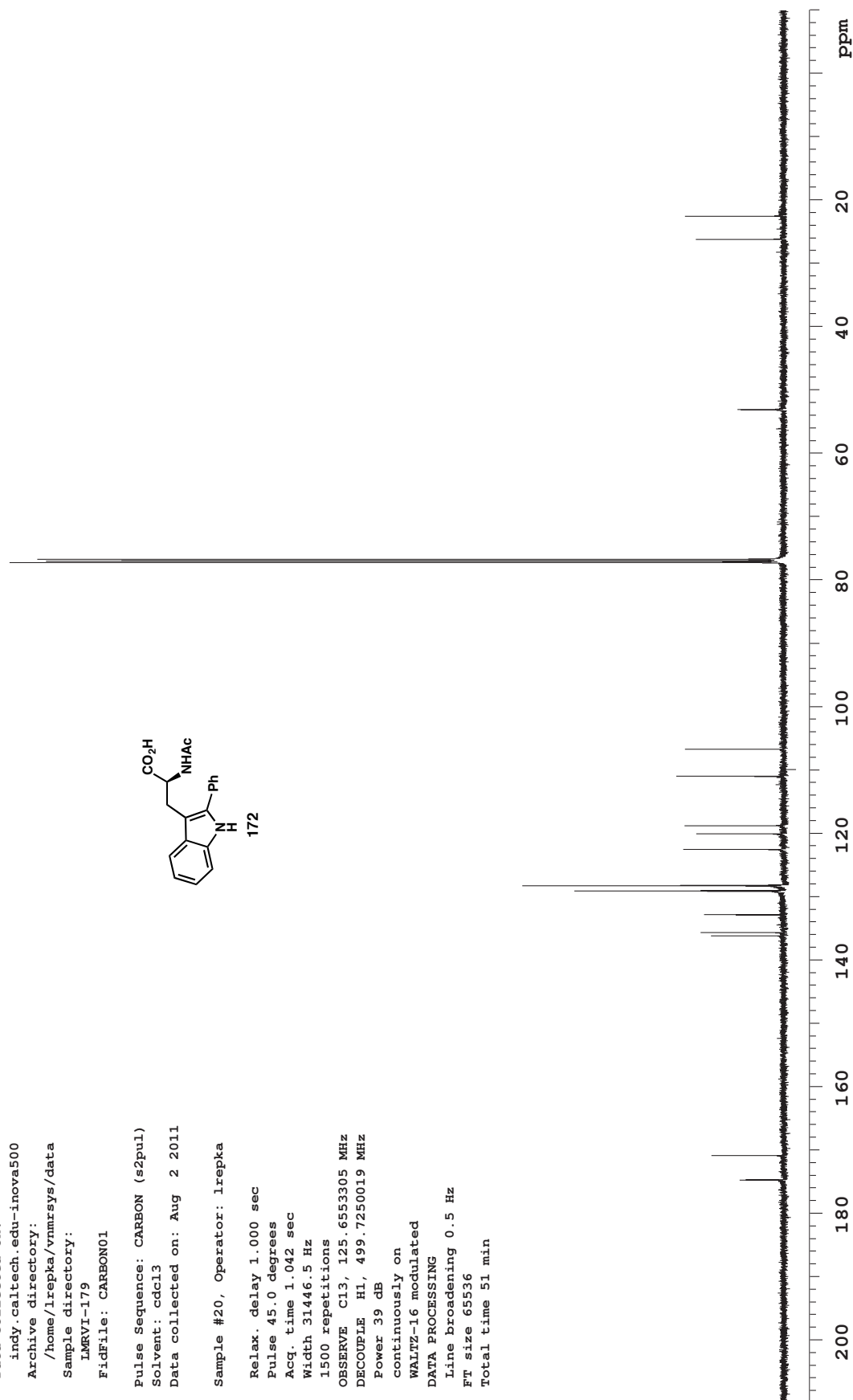
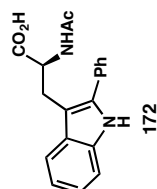
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 51 min



CHAPTER 4

Access to 2a-Phenylpyrroloindolines by an Oxidative Cyclization: Identification of a GABA_A Receptor Positive Allosteric Modulator[†]

4.1 INTRODUCTION

The pyrroloindoline family of natural products possesses a wide array of important activities and as such, there is interest in the identification of novel pyrroloindoline frameworks and biological studies thereof. In particular, we became interested in the formation of 2a-phenylpyrroloindolines from 2-phenyltryptophan derivatives, compounds generated using our tandem conjugate addition/enantioselective protonation methodology (Chapter 3). This chapter describes the development of an oxidative cyclization approach to these structures as well as an ensuing collaboration to evaluate their activity versus critical receptors in the brain. The first molecule tested, a 3a-hydroxypyrroloindoline-2-

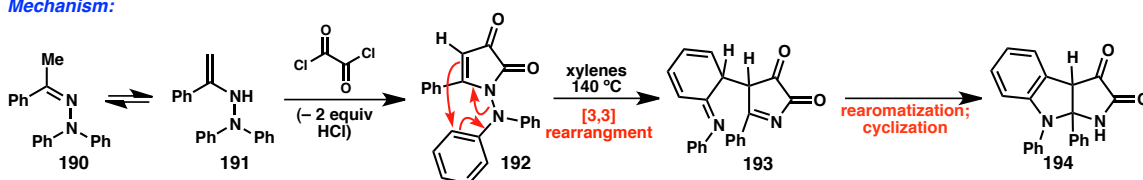
[†] The research discussed in this chapter was completed as a joint project between the Reisman and Dougherty laboratories. The experiments were designed in collaboration with Professor Sarah Reisman, Professor Dennis Dougherty, Alex Maolanon, a visiting student in the Reisman group from the Technical University of Denmark, and Christopher Marotta and Kristina Daeffler, two graduate students in the Dougherty group. Synthetic research on the second generation molecules was primarily conducted by Alex Maolanon and the electrophysiology experiments were performed by Christopher Marotta and Kristina Daeffler. Professor Henry Lester and Dr. Scott Virgil are gratefully acknowledged for helpful discussions.

carboxylic acid, was shown to be a channel inhibitor but further studies identified a compound lacking the carboxylic acid functionality that selectively activates the GABA_A receptor as a positive allosteric modulator (PAM).

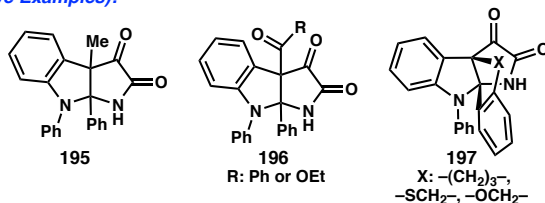
4.1.1 Prior Efforts Toward 2a-Phenylpyrroloindolines

Scheme 4.1.1. Access to 2a-phenylpyrroloindolines by a Fischer indolization rearrangement approach (Kollenz and coworkers, 1971–1994).

Mechanism:



Substrate Scope (Representative Examples):



To date, there are very few reported syntheses of 2a-phenylpyrroloindolines. In the initial work completed by Kollenz and coworkers, 2a-phenylpyrroloindolines such as **194** as well as molecules bearing an azapropellane core (**197**) were prepared via a Fischer indolization rearrangement approach (Scheme 4.1.1).¹ Specifically, condensation of *N,N*-diphenylhydrazone **190** with oxalyl chloride with concomitant loss of 2 equivalents HCl affords pyrroledione **192**, which upon heating rearranges to **194**.^{1c} Based on isotopic labeling studies,² this rearrangement is proposed to occur according to the standard mechanism for Fischer indole synthesis by a [3,3] rearrangement, rearomatization by proton transfer, and intramolecular 1,2-addition into the imine to give **194**. These pyrroloindolines were shown to be versatile intermediates capable of many

transformations including 1) selective reduction to afford α -hydroxyketone **199** or the ring-opened form **201** depending on the C3a-substitution pattern,^{1c} 2) ring-opening at high temperature to give indole **198**,^{1c} and 3) oxidative cleavage of the dione with NaOH and H₂O₂ to yield 1,2-diphenylindole (**200**, Scheme 4.1.2).^{1c} Notably, formation of azapropellane **197** has been confirmed by X-ray crystallography (Figure 4.1.1).^{1c}

Scheme 4.1.2. Derivatization of pyrroloindoline diones (Kollenz and coworkers).

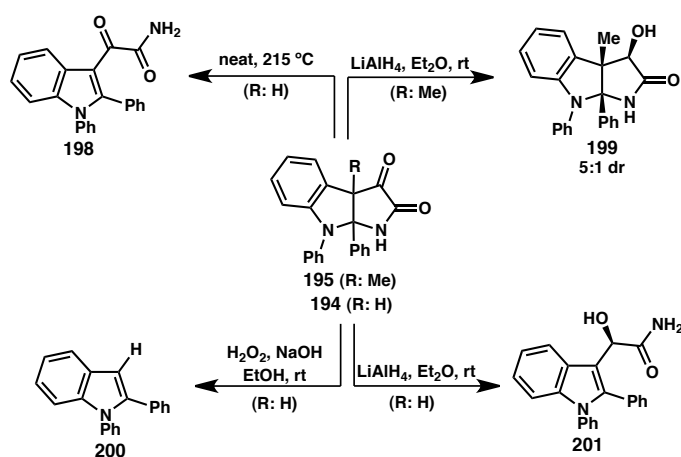
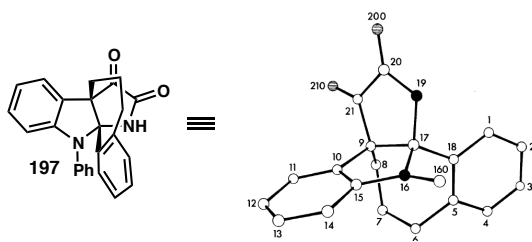


Figure 4.1.1. Confirmation of azapropellane **197** structure by X-ray analysis (Kollenz and coworkers).

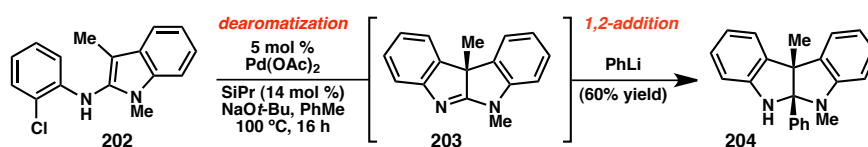


Within the past few years, two other synthetic approaches to 2a-arylpyrroloindolines have been reported. Bedford and coworkers developed a one-flask two-step protocol for generating benzene-fused pyrroloindolines including **204** by a Pd-catalyzed intramolecular dearomatization, followed by organolithium 1,2-addition into the resultant imine **203** (Scheme 4.1.3).³ In 2012, subsequent to our report of an oxidative cyclization

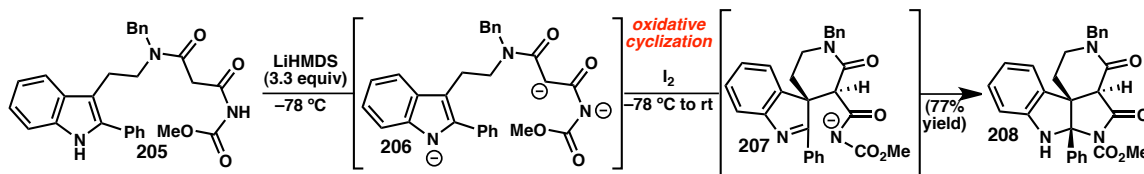
approach to 2a-phenylpyrroloindolines (Section 4.2.2), Ma, Xie, and coworkers reported access to tetracyclic pyrroloindolines including 2a-phenyl derivative **208**. This transformation occurs by deprotonation of indole malonic diamides (**205**) with LHMDS, oxidative cyclization to generate transient spirocycle **207**, and intramolecular cyclization onto the imine to give **208**.⁴

Scheme 4.1.3. Other approaches to 2a-phenylpyrroloindolines.

Bedford and coworkers, 2011:

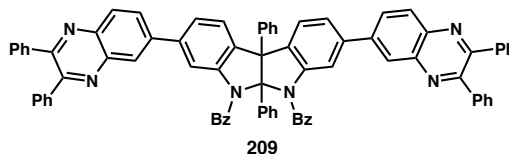


Xie, Ma and coworkers, 2012:



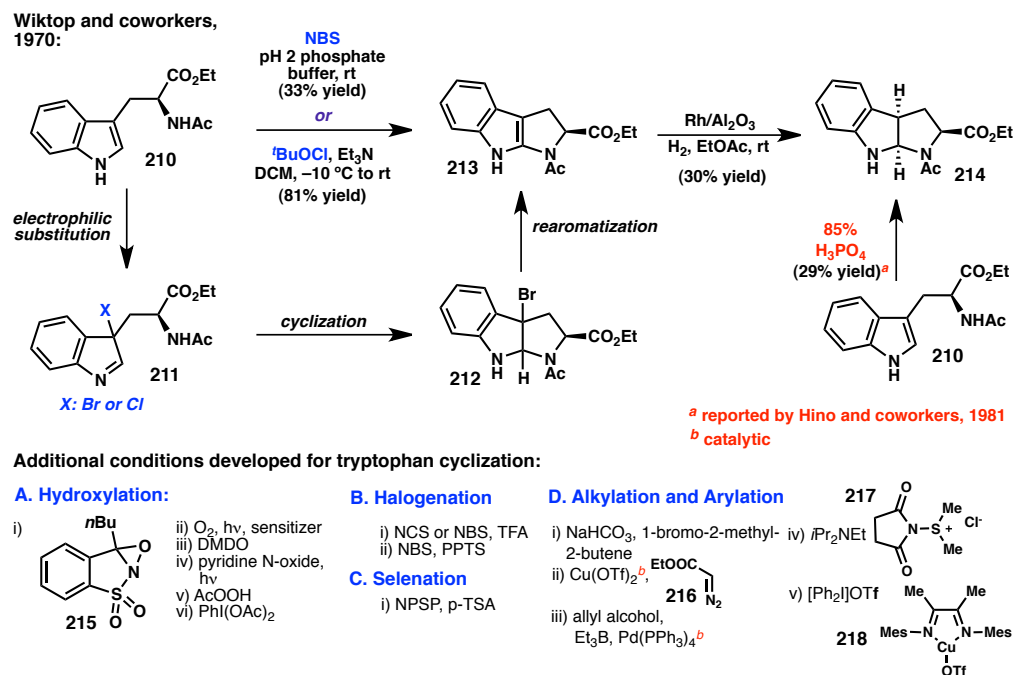
Although several synthetic efforts have been completed toward 2a-phenylpyrroloindolines, no biological assays of these compounds have yet been reported. To my knowledge, the only relevant study reported is one patent from the BASF that documents the potential application for heterocycles such as benzene-fused pyrroloindoline **209** as organic light-emitting diodes (OLEDs) (Figure 4.1.2).⁵

Figure 4.1.2. Pyrroloindoline **209** patented by the BASF for applications as an OLED.



4.1.2 Oxidative Cyclization Approaches to Pyrroloindolines

Scheme 4.1.4. Wiktop and coworkers' initial disclosure of the oxidative cyclization reaction and additional conditions.



Although many enantioselective, catalytic methodologies have recently been developed (Chapter 1), the cyclization of tryptophan derivatives remains one of the most common approaches for the synthesis of enantioenriched pyrroloindolines. In 1970, Wiktop and coworkers reported that exposure of tryptophan methyl ester **210** to either *N*-bromosuccinimide (NBS) in a pH 9.2 buffer or *tert*-butyl hypochlorite and Et₃N affords 2,3-dehydropyrroloindoline **213** (Scheme 4.1.4).⁶ Mechanistically, this reaction is proposed to occur by initial electrophilic substitution at C3 to afford indolenine intermediate **211**, followed by cyclization to give 3a-bromopyrroloindoline **212** and rearomatization with loss of HCl. Subsequent hydrogenation of **213** permitted access to pyrroloindoline **214**.

Ten years after the initial disclosure by Wiktop and coworkers, Hino and coworkers

showed that pyrroloindoline **214** could also be accessed directly from tryptophan **210** by exposure to acids such as H_3PO_4 or TFA.⁷ A myriad of other conditions for cyclization have also been reported involving C3 halogenation,⁸ selenation,⁹ hydroxylation,¹⁰ alkylation,¹¹ and arylation.¹² In the subsequent section, the details of some reports that directly pertain to our work will be discussed within the context of the development of the oxidative cyclization reaction of 2-phenyltryptophans.

4.2 THE OXIDATIVE CYCLIZATION REACTION OF 2-PHENYLTRYPTOPHANS

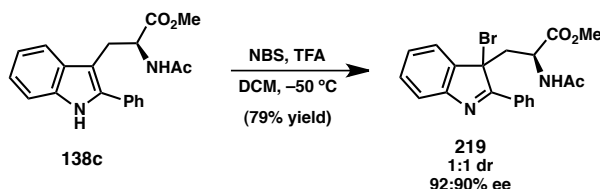
4.2.1 *Challenges and Initial Results with (1H)-2-Phenyltryptophans*

In our pursuit of a cyclization reaction for 2-phenyltryptophans, we were faced with several unique challenges. Despite the innumerable examples of these reactions, very few substrates are functionalized at C2 and we expected that steric hindrance introduced by the phenyl substituent would disfavor cyclization. However, we were encouraged by the broad range of known conditions and anticipated that a suitable choice of both substrate and electrophile could promote the desired transformation, thus enabling access to a new class of pyrroloindolines.

We began by investigating the cyclization reaction of (1H)-2-phenyltryptophan **138c** generated in the tandem conjugate addition/enantioselective protonation reaction (Chapter 3). However, subjection of **138c** to NBS and TFA at $-50\text{ }^\circ\text{C}$ failed to promote pyrroloindoline formation and instead afforded bromoindolenine **219** as a 1:1 mixture of diastereomers in excellent yield (Scheme 4.2.1). Other examples of stable 2-

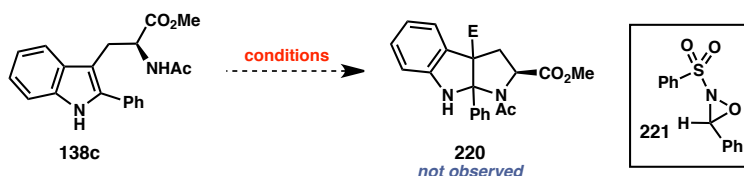
arylindolenines have been reported¹³ and the stability of **219** likely results from conjugation of the imine with the C2-phenyl substituent.

Scheme 4.2.1. Conversion of **138c** to stable bromindolenine **219**.



A variety of other oxidants were evaluated but stable indolenine formation was also observed with 1,3-dibromo-5,5-dimethylhydantoin/TFA (entry 6, Table 4.2.1), NCS/TFA (entry 7), and 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (entry 9). Subjection to acid resulted in either no reaction (entry 1) or saponification (entry 2) and other conditions including NBS/PPTS, Br₂, and PhI(TFA)₂ were also unfruitful with no pyrroloindoline product ever observed (entries 4, 5, and 8).

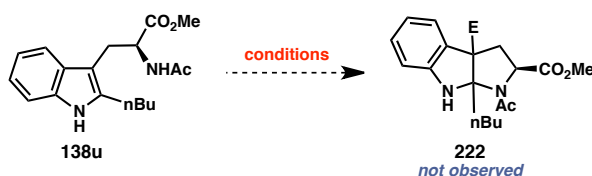
Table 4.2.1. Other derivatization studies on *N*-acetyltryptophan methyl ester **138c**.



Entry	Conditions	Temperature/Time	Result
1	neat 85% H ₃ PO ₄	50 °C, 1 h	no reaction
2	neat 85% H ₃ PO ₄	85 °C, ~ 12 h	~75% saponification by HRMS
3	neat TFA	23 °C, 1.5 h or 50 °C, 1 h	no reaction
4	NBS, PPTS, DCM	23 °C, 6 h	unidentified bromination product
5	Br ₂ , benzene	23 °C, 15 min	mixture of products
6	1,3-dibromo-5,5-dimethylhydantoin, TFA, DCM	−50 to 10 °C, 3 h	quantitative conversion to 219 (1.1:1 dr)
7	NCS, TFA, DCM	−50 °C, 1.5 h	quantitative to chloroindolenine (1.7:1 dr)
8	PhI(TFA) ₂ , 2:1 MeCN:H ₂ O	0 °C, 35 min	mixture of products
9	221 , DCM	23 °C, 24 h	47% yield of hydroxyindolenine (1:1 dr)

The conditions that facilitated bromoindolenine (**219**) formation were reevaluated for 2-butyltryptophan **138u**, for which the corresponding indolenine is anticipated to be less stable and susceptible to cyclization. In the presence of NBS and TFA, **138u** was converted to a compound containing diastereotopic methylenes (by crude ^1H NMR) but this compound was unstable to silica gel chromatography (Table 4.2.2, entry 3). Furthermore, no pyrroloindoline was formed under these conditions as indicated by the lack of characteristic upfield aromatic shifts in the ^1H NMR.

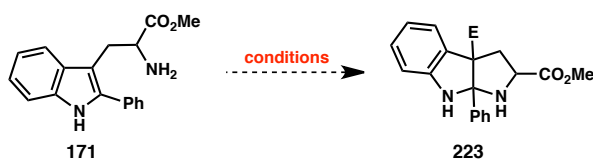
Table 4.2.2. Evaluation of 2-butyltryptophan **138u** for oxidative cyclization.



Entry	Conditions	Temperature/Time	Result
1	1 equiv 221 , DCM	23 °C, 4 h	very messy reaction
2	1.5 equiv NPSP, 1 equiv PPTS, DCM	23 °C, 13 h	minimal reaction
3 ^a	1 equiv NBS, 1 equiv TFA, DCM	−50 °C, 3.5 h	possibly indolenine by crude NMR, not isolable

^aReaction conducted with racemic **138u**. E: electrophile.

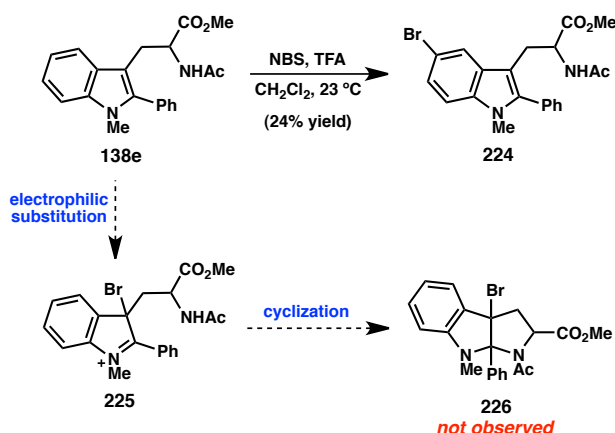
The observed high stability of bromoindolenine **219** toward cyclization also led us to evaluate more nucleophilic primary amine **171** (Table 4.2.3). Importantly, diastereotopic methylenes and upfield aromatic shifts characteristic of ring formation were observed by crude ^1H NMR following exposure to NBS (entry 3). Of all the (1*H*)-tryptophan derivatives screened, pyrroloindoline formation is only anticipated to have occurred with **171** but unfortunately these products were unstable and thus not amenable to purification on silica gel.

Table 4.2.3. Evaluation of primary amine **171** for oxidative cyclization.

Entry	Conditions	Temperature/Time	Result
1 ^a	1.50 equiv NPSP, 1 equiv PPTS, DCM	23 °C, 28.5 h	mixture of products (diastereotopic CH ₂ in crude ¹ H NMR)
2	221 , DCM	23 °C, 29.5 h	very messy reaction
3	1 equiv NBS, 9:1 DCM:TFA	–50 °C, 4 h	mixture of products (diastereotopic CH ₂ in crude ¹ H NMR, aromatic peaks upfield-not isolable)

E: electrophile.

4.2.2 NCS-Promoted Cyclization En Route to 3a-Hydroxypyrroloindolines

Scheme 4.2.2. Conversion of **138e** to 5-bromotryptophan **224**.

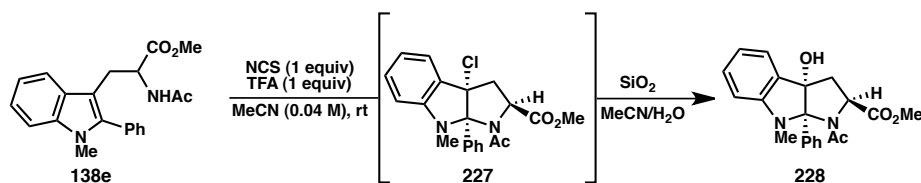
Of the conditions screened with (1*H*)-tryptophan derivatives, the results with *N*-acetyl-2-phenyltryptophan **138c** were particularly encouraging in that quantitative formation of stable haloindolenines was observed upon exposure to both NBS and NCS. These results suggested that 1-methyl-2-phenyltryptophan **138e** might prove a suitable substrate for pyrroloindoline (**226**) formation. Electrophilic substitution at C3 of **138e** would generate a positively charged indolenine (**35**) that is more reactive towards cyclization (Scheme 4.2.2). Unfortunately, subjection of **138e** to NBS and TFA at low

temperature resulted in very minimal reaction. Exposure to the same conditions at room temperature also failed to provide any pyrroloindoline (**226**); instead, bromination at C5 was observed to give **224** in 24% yield.

Alternatively, we were pleased to find that subjection of **138e** to NCS, TFA, and MeCN at room temperature provided 3-chloropyrroloindoline **227**, as confirmed by HRMS. This pyrroloindoline is unstable and, by in situ monitoring with ^1H NMR spectroscopy, was shown to decompose to a mixture of products including the starting tryptophan **138e**. However, direct subjection of chloropyrroloindoline **227** to a mixture of MeCN, H_2O , and silica gel delivered more stable 3a-hydroxypyrroloindoline **228**. A similar two-step process has been disclosed by Somei and coworkers, in which they generated 3a-hydroxypyrroloindolines from simple tryptamine derivatives by treating the intermediate 3a-halopyrroloindolines with AgCN in a mixture of MeCN and H_2O .^{8c}

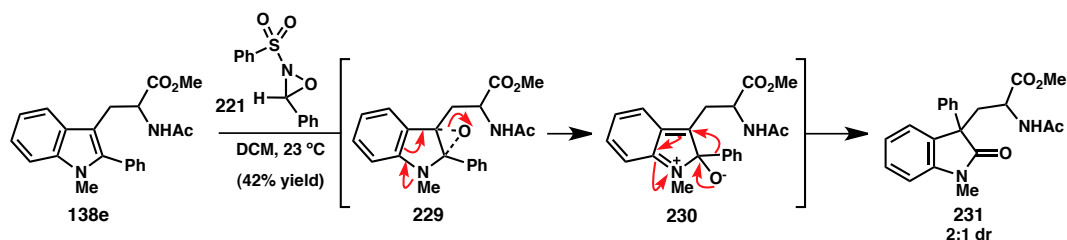
Based on the observed instability of **227**, the rate of the oxidative cyclization and the degree of decomposition was monitored over time. Exposure of **138e** to 1 equiv NCS and 1 equiv TFA for 30 minutes resulted in a 3.5:1 mixture of **138e** and **228** with very little byproduct formation. Pyrroloindoline **228** was produced as a 3:1 mixture of diastereomers favoring the *endo* diastereomer (Table 4.2.4, entry 1). In the absence of TFA, the same conditions resulted in extensive decomposition (entry 2).

Furthermore, monitoring of the reaction at longer time points determined that *exo*-**227** (not shown) is more prone to decomposition, as the dr is artificially enhanced to 20:1 over time (entries 3-7). Three hours was identified as the optimal reaction time, with 3a-hydroxypyrroloindoline **228** isolated in 52% yield as a 6:1 mixture of diastereomers favoring the *endo* diastereomer (entry 5).

Table 4.2.4. Optimization of the NCS-promoted cyclization for **138e**.^a

Entry	Time (h)	138e:228 ratio ^b	dr of 228 ^b
1	0.5	2.7:1	3:1
2 ^c	0.5	1:3.5	1:1
3	1	1:1.0	3:1
4	3	1:4.7	5:1
5 ^d	3	1:4.3	6:1 (52%) ^e
6	5	1:5.4	16:1
7	7	1:2.9	>18:1
8	9	1:3.5	>20:1
9	13	1:2.4	>10:1
10	39	7.4:1	nd

^a All reactions were run on 0.15 mmol scale. ^b Determined based on ¹H NMR analysis of the crude mixture. ^c Reaction run in the absence of 1 equiv TFA. ^d Reaction run with 85% enantioenriched (*S*)-**138e**. ^e Isolated yield of diastereomeric mixture. nd: not determined.

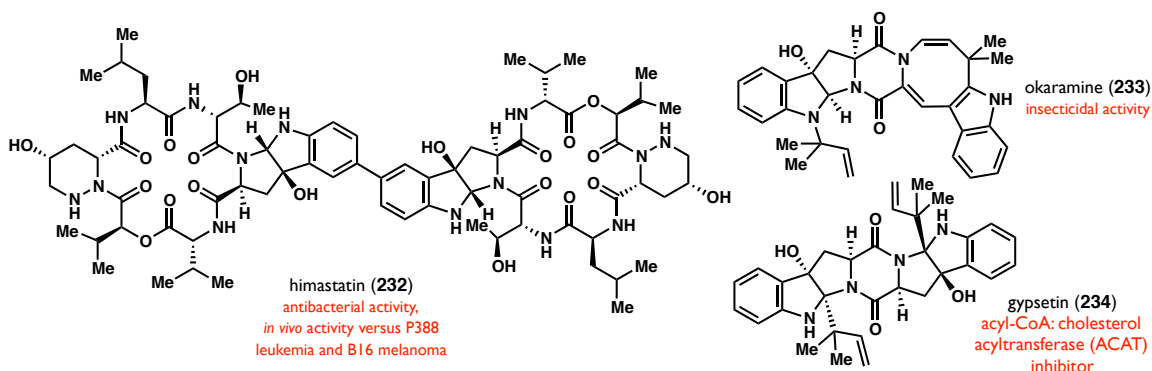
Scheme 4.2.3. Attempted direct hydroxylation of 1-methyltryptophan **138e**.

Although in situ conversion of **227** to **228** could potentially enable a more efficient process, we found that use of SiO₂ or both SiO₂ and water as additives failed to directly provide **228**. In search of a more streamlined approach to 3a-hydroxypyrroloindolines, we also attempted direct hydroxylation using 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (**221**) as the oxidant (Scheme 4.2.3). Interestingly, no **228** was observed under these conditions but oxindole **231** was isolated in 42% yield as a 2:1 mixture of diastereomers. Mechanistically, this reaction is expected to occur by epoxidation, followed by ring-opening at C3 and phenyl migration.¹⁴

4.3 FIRST GENERATION ELECTROPHYSIOLOGY EXPERIMENTS: INVESTIGATIONS OF A PYRROLOINDOLINE-2-CARBOXYLIC ACID

4.3.1 Introduction

Figure 4.3.1. Representative examples of biologically active 3-hydroxypyrroloindolines.

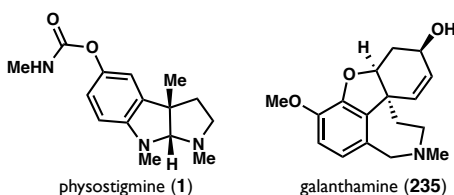


As with other pyrroloindoline natural products, the subclass of 3a-hydroxypyrroloindolines has received extensive interest due to both their structural complexity and their diverse biological activities. For example, the cyclodepsipeptide dimeric alkaloid himastatin (**232**) features inhibitory activity versus gram-positive bacteria as well as activity *in vivo* versus P388 leukemia and B16 melanoma cell lines (Figure 4.3.1).¹⁵ In addition, two structurally distinct alkaloids, okaramine A (**233**) and gypsetin (**234**), possess insecticidal¹⁶ and acyl CoA: cholesterol acyltransferase (ACAT) inhibitory activity,¹⁷ respectively.

The Dougherty laboratory at Caltech is interested in identifying binding motifs of novel positive allosteric modulators (PAMs) for ligand-gated ion channels (LGICs). A collaboration was initiated between our two research groups to investigate molecules related to 3a-hydroxy-2a-phenylpyrroloindoline **228** based on the structural similarities

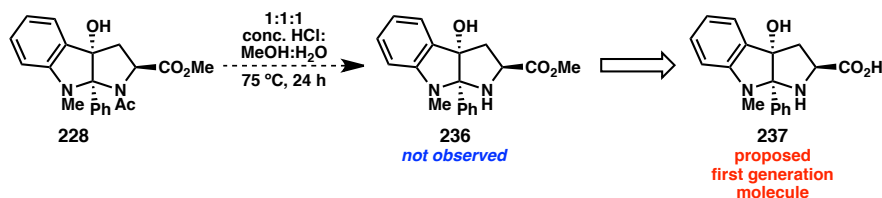
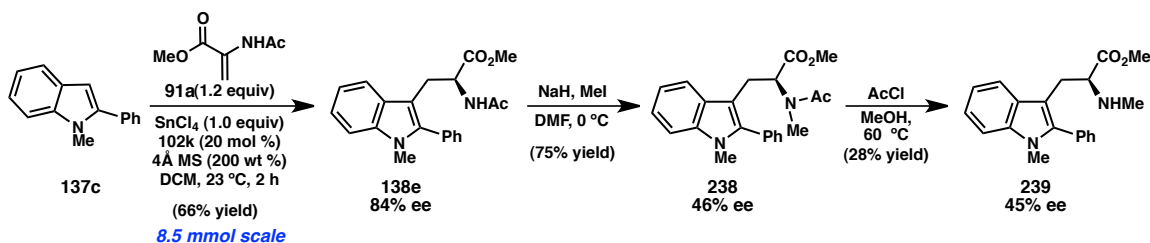
between **228** and known PAMs of the nicotinic acetylcholine receptors (nAChRs), physostigmine (**1**) and galanthamine (**235**) (Figure 4.3.2). Drugs that target ion channels have been developed for the treatment of many neurological disorders and degenerative disease.¹⁸ Specifically, the design of allosteric modulators, which bind at a site removed from that of the natural agonist, has received extensive attention given their potential for enhanced stability toward desensitization and improved receptor selectivity relative to more traditional agonist and antagonist drugs that bind in the orthosteric site.¹⁹ Notably, the activity of **1** and **235** as PAMs is likely connected to their role in the amelioration of Alzheimer's disease (AD) symptoms (**235** is an FDA-approved drug for the treatment of AD).²⁰

Figure 4.3.2. Positive allosteric modulators of nicotinic acetylcholine receptors.



4.3.2 Preparation of First Generation Target Carboxylic Acid **237**

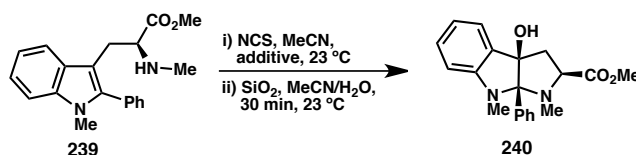
Although the oxidative cyclization that provided pyrroloindoline methyl ester **228** inspired the decision to further pursue this class of molecules, a more water-soluble derivative lacking the acetamide and methyl ester functionalities was required to begin biological studies. However, **228** could not be converted to the desired carboxylic acid **237** as attempted deprotection under conditions developed for tryptophan derivatization (Chapter 3) resulted in decomposition of the pyrroloindoline (Scheme 4.3.1).

Scheme 4.3.1. Attempted direct acetamide hydrolysis of pyrroloindoline **228**.Scheme 4.3.2. Access to cyclization substrate **239**.

Alternatively, the necessary carboxylic acid (**237**) could be prepared in short order starting with the tandem conjugate addition/enantioselective protonation reaction of 1-methyl-2-phenylindole (**137c**), which could be completed on 8.5 mmol scale on the benchtop without any significant erosion of yield or ee (Scheme 4.3.2). Subsequent methylation under standard conditions afforded tertiary amide **238** in 75% yield, albeit in a substantially reduced ee of 46%. This issue of racemization, which was persistent for various runs and different substrates, is surprising given that NaH is commonly employed for the alkylation of α -amido esters.²¹ Attempted subsequent acetamide hydrolysis under aqueous acid conditions resulted in competitive overhydrolysis; however, we found that excess AcCl and MeOH provides clean conversion to **239** as monitored over time by LCMS, albeit at a very slow rate. After 75.5 hours at 60 °C, secondary amine **239** was isolated in 28% yield and 38% of the starting material (**238**) was recovered, both in 45% ee.

The oxidative cyclization reaction of secondary amine **239** was substantially slower than that of the acetamide **138e** with better results observed in the absence of TFA (Table 4.3.1, entries 1 and 3); this reactivity might be attributed to initial *N*-chlorination of the amine followed by intramolecular delivery of the chlorine to C3, a hypothesis driven by a related report of Lindel and coworkers.²²

Table 4.3.1. Optimization of cyclization for secondary amine **239**.^a



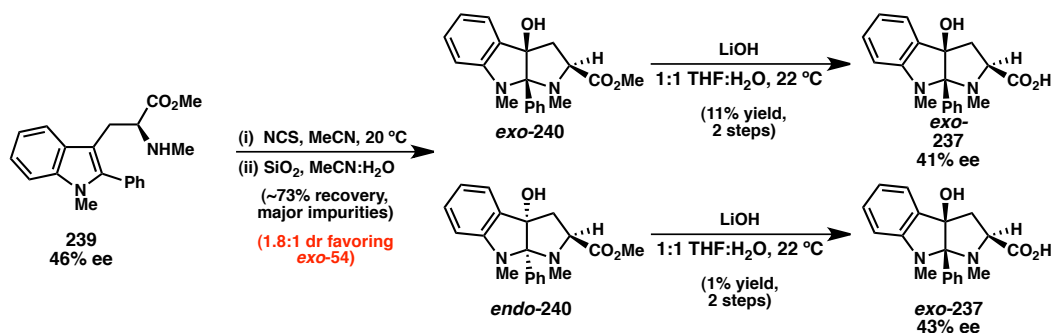
Entry	Additive	Time (h)	Conversion ^b	Yield ^b	dr ^b
1	TFA	3	41	14	1.3:1
2	TFA	13.5	66	31	1.9:1
3	-----	3	81	42	1.2:1

^a Reactions run on 14 – 20 μmol with 85% enantioenriched **239** prepared by a benzylation, reductive methylation, debenylation sequence. 1 equiv NCS and 1 equiv of additive was used. ^b Determined by crude ¹H NMR using benzyl ether as an internal standard.

Under optimal conditions using NCS, pyrroloindoline **240** was prepared in 1.8:1 dr, favoring the *exo* diastereomer (Scheme 4.3.3). Following preparative HPLC, the two diastereomers could be isolated separately albeit in less than 90% purity each. Exposure of *exo*-**240** to LiOH provided 11% isolated yield of the desired saponified product, *exo*-**237**. This reaction was only neutralized and concentrated prior to reverse phase preparative HPLC and thus the reasons for poor recovery remain unclear. Following exposure of *endo*-**240** to LiOH, formation of the desired *endo* carboxylic acid was observed by ¹H NMR analysis of the crude reaction mixture. Unfortunately, this compound was unstable to the purification conditions, yielding *exo*-**237** in 1% yield, favoring the same enantiomer as in the saponification of *exo*-**240**. These results, in addition to further studies on *endo*-**237** (Scheme 4.4.5), determined that this compound is

both highly unstable and capable of isomerization to *exo*-**237** via ring opening of the pyrroloindoline at C2a.

Scheme 4.3.3. Access to *exo*-**237** for electrophysiology experiments.



4.3.3 Electrophysiology Experiments on Carboxylic Acid **237**

Initial experiments on carboxylic acid **237** were conducted by evaluating its effect on receptor response for a variety of LGICs individually expressed in *Xenopus* oocytes (Table 4.3.2). This work was completed using an OpusXpress-6000A system and more detailed information on the experimental setup can be found in Section 4.7.2. Hydroxypyrroloindoline **237** was found to either not affect or inhibit each receptor when added at a 20 μ M concentration in combination with an EC₅₀ dose of the appropriate agonist (median effective concentration). The IC₅₀ value of **237** (median inhibition concentration with co-application of an EC₅₀ dose of agonist) was also determined for two receptors; for the α 7-T6'S nAChR, the IC₅₀ value was 5 $\pm$ 1 μ M (n=7) with a hill coefficient of 0.8 and for the (α ₄-L9'A)₃(β ₂)₂ nAChR, the IC₅₀ value was 8 $\pm$ 1 μ M (n=7) with a hill coefficient of 1.2.

There are three limiting mechanisms by which carboxylic acid **237** could inhibit the action of a ligand-gated ion channel in the presence of an agonist (such as the

experiments described above). The most interesting possibility is that **237** serves as a negative allosteric modulator (NAM), binding at a site removed from that of the agonist. NAMs can be very useful molecules for drug development; in particular, NAMs of the metabotropic glutamate receptor mGlu₅ have recently been designed for the treatment of levodopa-induced dyskinesia associated with Parkinson's disease, migraines, and Fragile X Syndrome.²³ However, it is also possible that carboxylic acid **237** serves as an antagonist, binding at the orthosteric site, or that it functions as a channel blocker and is simply adequately sized to fit in the channel after opening by the agonist and prevent the flow of ions.²⁴

Table 4.3.2. Electrophysiology data on carboxylic acid **237** (41% enantioenriched).^a

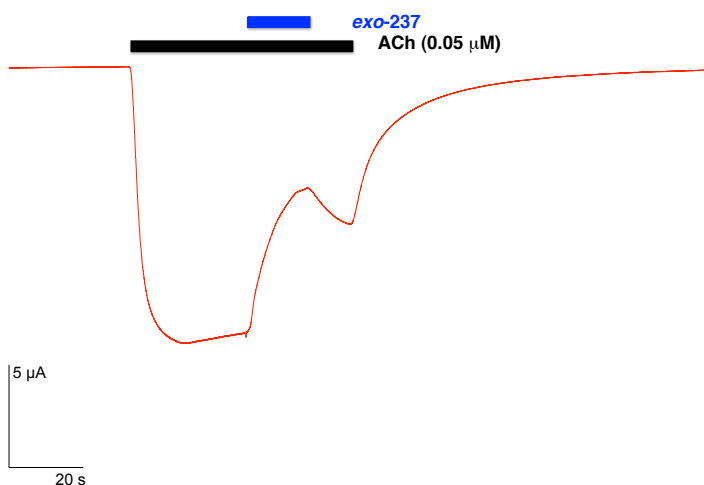
Entry	Receptor	% Current reduction
1	(α 1) ₂ (β 1-L9'S) δ γ mouse muscle nAChR	21 $\pm$ 1 ^b
2	α 7 nAChR	40 $\pm$ 9
3	α 7-T6'S nAChR	67 $\pm$ 3
4	(α 4) ₂ (β 2) ₃ nAChR	20 $\pm$ 1
5	(α 4-L9'A) ₂ (β 2) ₃ nAChR	25 $\pm$ 1
6	(α 4-L9'A) ₃ (β 2) ₂ nAChR	44 $\pm$ 1
7	α 4 β 4 nAChR	28 $\pm$ 1
8	(α 1) ₂ (β 2) γ 2 GABA _A R	27 $\pm$ 4
9	GluR _{2A}	6 $\pm$ 1
10	GlyR	6 $\pm$ 2
11	5HT _{3A} R	3 $\pm$ 2

^a Current was recorded using an OpusXpress-6000A with a two-electrode voltage clamp method. Data was acquired with a co-application of 20 μ M concentration of **237** and an EC₅₀ dose of agonist, both in ND96 buffers (see 4.7.2 for agonist EC₅₀ values). ^b Standard error of the mean (n=3 or 4).

Given that pyrroloindoline **237** did exhibit some receptor selectivity, with no significant inhibition of the GlyR, GluR_{2A}, and 5HT_{3A} receptors observed, it was deemed necessary to perform a series of follow-up experiments to ascertain additional mechanistic information. The molecule also appeared to have a slow rate of dissociation

as the current recovery after ceasing treatment with **237** was incomplete in the time course of the experiment, as shown for $(\alpha 4\text{-L9'A})_3(\beta 2)_2$ nAChR in Figure 4.3.3.

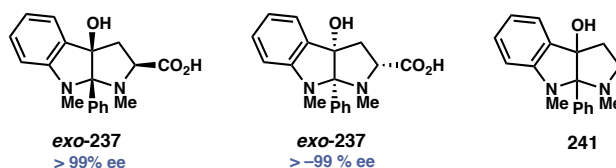
Figure 4.3.3. Electrophysiology data on *exo*-**237** (41% enantioenriched) with $(\alpha 4\text{-L9'A})_3(\beta 2)_2$ nAChR.



We decided to target several structurally related derivatives of *exo*-**237** for further experiments. These targets included both enantiomers of *exo*-**237**, and decarboxylated compound **241** (Figure 4.3.4). Dependence of current inhibition on the absolute configuration of *exo*-**237** might suggest that the compound bound in a distinct allosteric site, providing evidence against the channel blocker mechanism. Unlike **237**, which is zwitterionic, **241** should be positively charged under the conditions of electrophysiology experiments. In this case, voltage jump experiments could determine if binding occurs within the membrane of the receptor. Upon switching the cell membrane potential, positively charged molecules bound within the membrane should be expelled, allowing current to flow as expected for an isolated application of agonist. A direct correlation between the field gradient and current response would show that **241** bound within the

cell membrane, whereas voltage independence would indicate binding in the extracellular domain.

Figure 4.3.4. New targets for electrophysiology experiments.

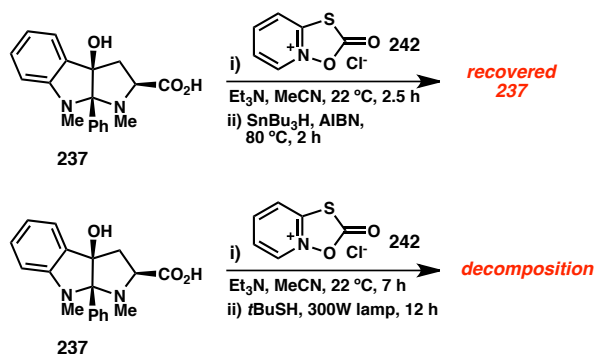


4.4 SYNTHESIS OF SECOND GENERATION TARGETS FOR ELECTROPHYSIOLOGY EXPERIMENTS

4.4.1 Synthesis of Pyrroloindolines from Tryptamine Derivatives

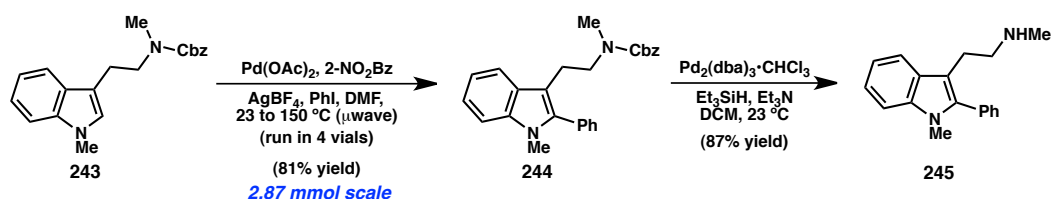
Although it would have been convenient to directly access **241** by the decarboxylation of *exo*-**237**, our initial attempts at promoting this transformation proved unfruitful (Scheme 4.4.1). The Barton ester appears to form, as the mass corresponding to decarboxylation is observed when the reaction progress is monitored by LCMS; however, subsequent exposure to radical conditions results in either decomposition or recovery of **237**.²⁵

Scheme 4.4.1. Attempted decarboxylation of **237**.



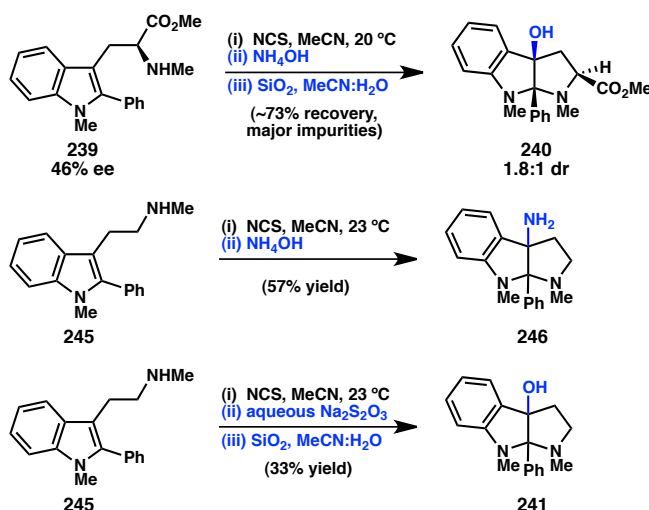
In light of these results, we decided to prepare **241** using an oxidative cyclization of the corresponding 2-phenyltryptamine **245**. Our synthesis began with the selective C2-arylation of readily available *N*-Cbz-*N*,1-dimethyltryptamine (**243**) (Scheme 4.4.2). We were pleased to find that conditions developed for C2-arylation of tryptophan derivatives by Albericio, Lavilla, and Ruiz-Rodríguez²⁶ enabled successful arylation of **243**. In the presence of iodobenzene, AgBF₄, 2-nitrobenzoic acid, and Pd(OAc)₂ with microwave heating for 4 minutes, **243** was converted to 2-phenyltryptamine **244**, which was isolated in 81% yield following purification by column chromatography. 2-phenyltryptamine **244** was cleanly deprotected using catalytic Pd₂(dba)₃ and Et₃SiH to afford secondary amine **245**.

Scheme 4.4.2. Synthesis of oxidative cyclization substrate **245**.

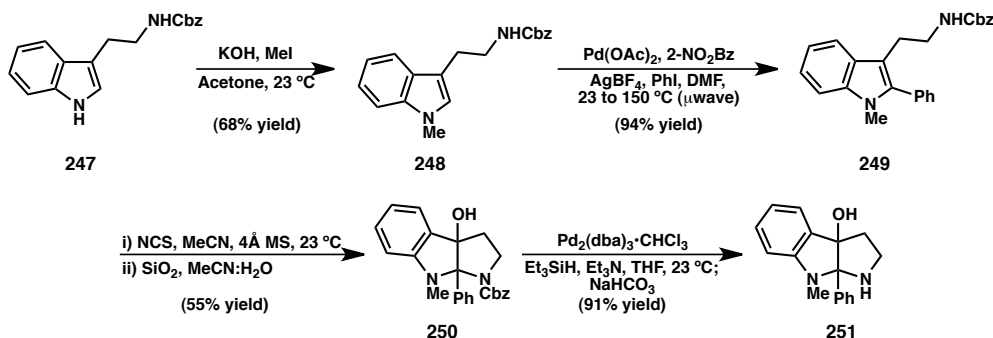


Although the oxidative cyclization reaction of **245** is particularly sensitive, pyrroloindoline formation was consistently observed with dropwise addition of NCS (purified by recrystallization) as a solution to a mixture of the substrate and 4Å molecular sieves in MeCN. In contrast to the oxidative cyclization of tryptophan **239** to 3a-hydroxypyrroloindoline **240**, use of an aqueous ammonia quench to work up the reaction of tryptamine **245** afforded stable 3a-aminopyrroloindoline **246** in 57% yield (Scheme 4.4.3). Alternatively, quenching the cyclization of tryptamine **245** with aqueous sodium thiosulfate, followed by treatment with silica gel, gave 3a-hydroxypyrroloindoline **241** in 33% yield.

Scheme 4.4.3 Divergent effects of quench for tryptophan and tryptamine cyclization substrates.



We also pursued the synthesis of monomethylated 3a-hydroxypyrroloindoline **251** (Scheme 4.4.4). Microwave-assisted arylation of known Cbz-protected tryptamine **248** provided 2-phenyltryptamine **249** in excellent yield. Oxidative cyclization under the reoptimized conditions with 4Å molecular sieves and recrystallized NCS afforded 1-Cbz-pyrroloindoline **250**. Subsequent subjection to catalytic $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and Et_3SiH generated the corresponding silyl carbamate, which upon cleavage by stirring with saturated aqueous NaHCO_3 provided target pyrroloindoline **251** in 48% yield from **248**.

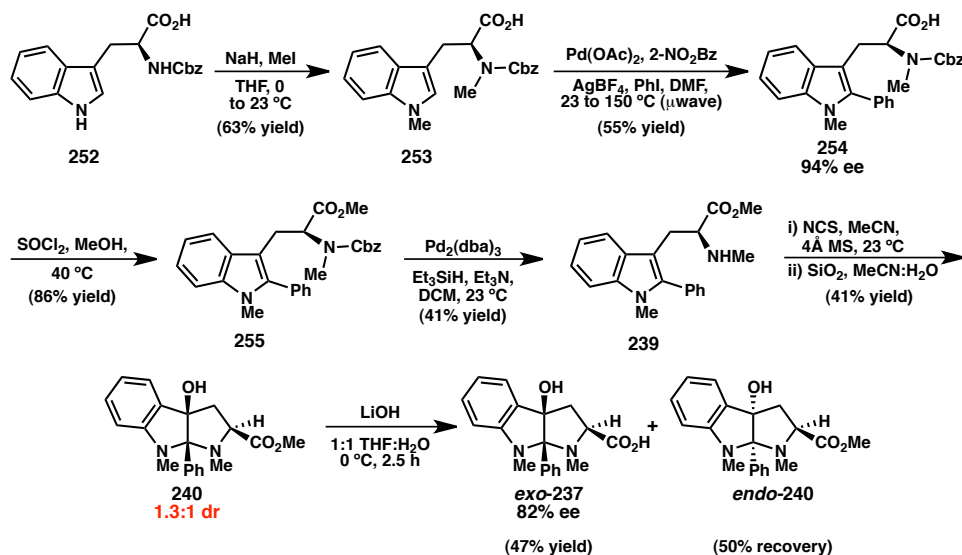
Scheme 4.4.4. Synthesis of (1H)-1a-methylpyrroloindoline **251**.

4.4.2 Second Generation Synthesis of Exo-Carboxylic Acid **237**

Several challenges were encountered in the first generation synthesis of *exo*-**237**, including racemization under methylation conditions, sluggish hydrolysis of the acetamide, and poor recovery post-saponification. As the acetamide functionality is required to obtain high ee in the enantioselective Friedel–Crafts reaction, we elected to begin the second generation synthesis of **237** with commercially available (*S*)-tryptophan.

Following Cbz protection, *N*-methylation of tryptophan **252** proceeded with minimal racemization to give **254** following C2 arylation (Scheme 4.4.5). Acid **254** was converted to the corresponding methyl ester (**255**) using thionyl chloride and MeOH. Subsequent Cbz deprotection provided secondary amine **239** in 41% yield and exposure of **239** to the optimized cyclization conditions using recrystallized NCS and 4Å molecular sieves cleanly afforded pyrroloindoline **240** as a 1.3:1 mixture of diastereomers, favoring the *exo* compound.

The mixture of diastereomers was directly subjected to saponification conditions, a step that proved very challenging in the first-generation synthesis. As before, it was determined that the *exo* diastereomer cleanly converts to *exo*-**237**, whereas the *endo* diastereomer decomposes under the reaction conditions (Scheme 4.3.3). Optimal results were obtained by conducting the reaction at 0 °C and quenching following consumption of *exo*-**240**, which permitted isolation of *exo*-**237** in 47% yield with 50% recovery of *endo*-**240**. Surprisingly, *exo*-**237** was isolated in only 82% ee (compared to 94% ee of intermediate **254**), which suggests that partial racemization may have occurred during the saponification step.

Scheme 4.4.5. Second generation access to 82% enantioenriched carboxylic acid **237**.

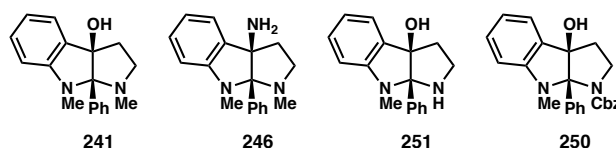
4.5 ELECTROPHYSIOLOGY EXPERIMENTS OF CYCLIC TRYPTAMINES

In an analogous fashion to the work on *exo*-**237** (Section 4.3.3), the four pyrroloindoline products derived from tryptamine were subjected to electrophysiology experiments. As observed for *exo*-**237**, the derivatives showed minimal activity with respect to the GluR_{2A}, GlyR, and 5HT_{3A} receptors (Table 4.5.1, entries 6-8). However, each molecule promoted current reduction when applied to nAChRs (entries 1-3). This structural promiscuity likely suggests that these pyrroloindolines function as channel blockers, rather than as NAMs or antagonists. However, we were pleased to find that although **241** blocks all nAChRs, it potentiates the effect of the GABA_A receptor agonist, GABA, with an increase in current of 52% at a 40 μM dose of **241** in combination with an EC₅₀ dose of GABA (11 μM , entry 4) relative to an EC₅₀ dose of GABA alone. Interestingly, **241** is also capable of activating the receptor on its own, generating about 10% of the current produced by an EC₅₀ dose of GABA (Figure 4.5.1). Experiments

conducted at varying concentrations of **241** identified a dose dependence on the receptor response (data not shown).

The activity of **241** as a PAM appears to be highly substrate specific, as demonstrated by the remarkable differences in activity produced by minor changes in structure. Pyrroloindoline **246**, which only differs in that it bears an amine functionality at C3a, produces minimal activation of the GABA_A receptor, and **251**, which lacks only the N1-methyl substituent compared to **241**, has an inhibitory effect on the receptor (Table 4.5.1, entry 4).

Table 4.5.1. Electrophysiology data on cyclic tryptamine derivatives.^a



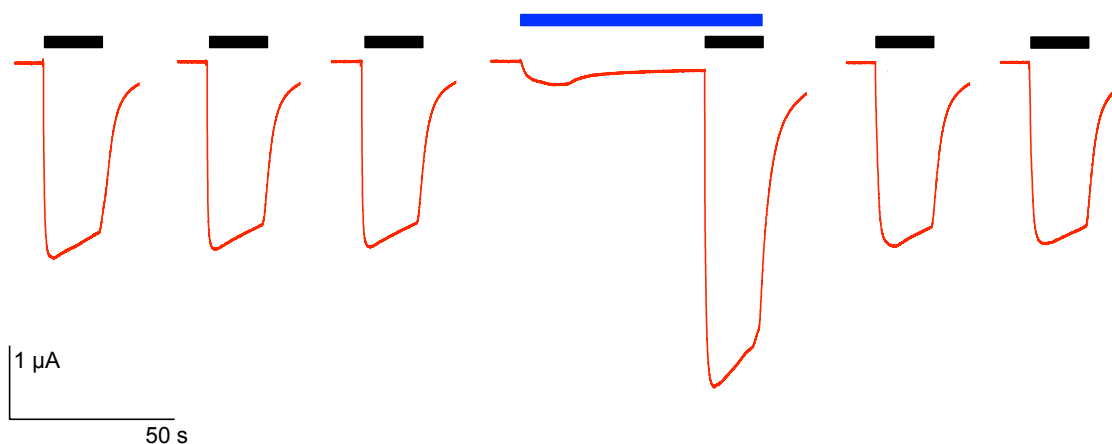
Entry	Receptor	241 ^b	246	251	250
1	(α 1) ₂ (β 1-L9'S) δ γ mouse muscle nAChR	− 53 ± 3	− 81 ± 6	− 7 ± 3	− 29 ± 3
2	α 7-T6'S nAChR	− 92 ± 4	− 96 ± 3	− 57 ± 10	− 68 ± 7
3	(α 4-L9'A) ₂ (β 2) ₃ nAChR	− 29 ± 6	− 44 ± 2	− 11 ± 2	− 47 ± 4
4	(α 1) ₂ (β 2) ₂ γ 2 GABA _A R	+ 52 ± 10	+ 10 ± 5	− 27 ± 21	− 27 ± 11
5	(α 1) ₂ (β 2) ₂ GABA _A R	+ 16 ± 2	nd	nd	nd
6	GluR _{2a}	− 9 ± 6	− 12 ± 5	− 11 ± 5	0 ± 2
7	GlyR	+ 3 ± 7	− 16 ± 6	+ 18 ± 10	− 9 ± 9
8	5HT _{3A} R	− 3 ± 5	− 11 ± 8	+ 3 ± 12	− 23 ± 4

^a % effect on current and standard error of means (n=3 or 4) shown. Current was recorded using an OpusXpress-6000A with a two-electrode voltage clamp method. Data was acquired with a co-application of 20 μ M concentration of the relevant pyrroloindoline and an EC₅₀ dose of agonist, both in ND96 buffers (see 4.7.2 for agonist EC₅₀ values). ^b Run with a 40 μ M concentration of **241**. nd: not determined.

Substrates that activate the GABA_A receptor are important starting points for drug development for the treatment of neurological disorders. In particular, benzodiazepines are a class of molecules that act as PAMs of the GABA_A receptor by binding at the interface of the α and γ subunits.²⁷ Many of these molecules are FDA-approved drugs including clonazepam (Klonopin), a treatment for epilepsy, diazepam (Valium), a

treatment for anxiety, and flurazepam (Dalmane), a treatment for insomnia. Interestingly, upon testing **241** versus a GABA_A receptor lacking the γ subunit, potentiation of the GABA-induced current was reduced three-fold and **241** did not activate the receptor in the absence of GABA (Table 4.5.1, entry 5); this result suggests that **241** might target the same location as benzodiazepine but further analysis of other GABA_A receptor analogues is required to determine the binding site.

Figure 4.5.1. Current trace for screen with **241** versus GABA_A receptor.*



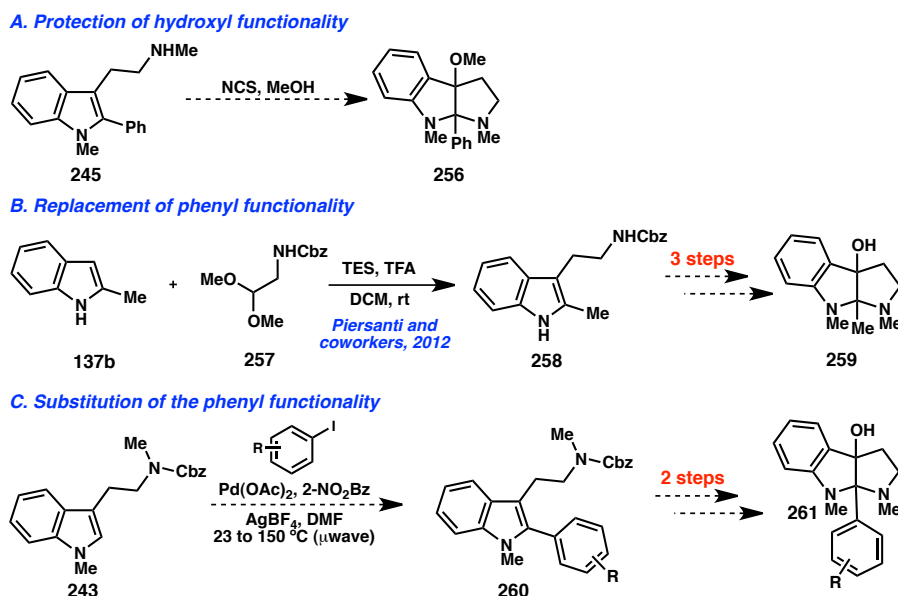
*Black corresponds to application of the agonist, blue corresponds to application of **241**. Gaps in the trace indicate a 300 second wash.

4.6 CONCLUSIONS AND FUTURE DIRECTIONS

The key finding that pyrroloindoline **241** is a PAM encourages future research on 3a-hydroxy-2a-phenylpyrroloindolines. As a measure of relative therapeutic potential, the activity of **241** could be compared to marketed GABA_A receptor PAMs. Furthermore, the extensively studied pyrroloindoline natural product physostigmine (**1**) has been shown to act as a PAM of the nAChR. To our knowledge, there is no direct evidence that it acts similarly in conjunction with the GABA_A receptor and electrophysiology experiments on **1** would improve understanding of the structural requirements for potentiating GABA. Notably, this research would also help to explain conflicting data within the literature.

Lambadjieva and Georgiev reported that when the convulsant picrotoxin is injected into mice in combination with **1**, the seizure threshold is increased thus suggesting a possible role for **1** as a PAM.²⁸ However, **1** has also been shown to increase the concentration of the GABA_A PAM propofol²⁹ necessary for anaesthesia *in vivo*.³⁰

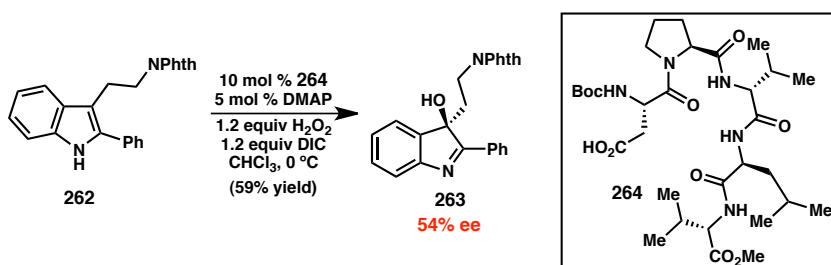
Scheme 4.6.1 Potential targets for SAR studies.



Further mechanistic insight could be gained through structural variation (Scheme 4.6.1). For example, experiments with 3a-methoxypyrroloindoline **256** would delineate the importance of the hydroxyl substituent. We expect **256** to be readily available as, in one report analogous to our own work, Somei and coworkers showed that the combination of NCS and MeOH promotes cyclization of a C2-unsubstituted tryptamine derivative to directly afford the corresponding methoxypyrroloindoline.^{8c} Other potential substrates include 2a-methylpyrroloindoline **259**, which should be accessible from known *N*-Cbz-2-methyltryptamine (**258**),³¹ and pyrroloindolines bearing functionalized aryl substituents at C2a (**261**) that could be incorporated in the arylation reaction.

Finally, **241** was originally tested as a racemate but it is possible that only one enantiomer activates the receptor; in other words, **241** might be twice as potent as is apparent based on the original data. Enantiomerically enriched **241** should be accessible by separation of the racemate on a chiral column or by an enantioselective oxidative cyclization of tryptamine **245**. For example, Miller, Movassaghi and coworkers have shown that peptide **264** can catalyze conversion of (1*H*)-2-phenyl-*N*-phthaloyltryptamine **262** to 3-hydroxyindolenine **263** in moderate ee (Scheme 4.6.2);¹³ application of this method to our system is expected to form enantioenriched **241** in one pot.

Scheme 4.6.2. Enantioselective hydroxylation of 2-phenyltryptamines (Movassaghi, Miller, and coworkers, 2011).



Although our efforts toward 3a-hydroxy-2a-phenylpyrroloindolines began in an effort to broaden the scope of our tandem conjugate addition/enantioselective protonation reaction methodology, through the collaboration of our lab with Professor Dennis Dougherty, Kristina Daeffler, and Christopher Marotta this project has evolved into a search for novel drugs for the treatment of neurological disorders and neurodegenerative diseases. We are excited to continue this collaboration and to further investigate the importance of and mechanism of **241** in its role as a positive allosteric modulator. Future work regarding **241** and possible identification of more effective derivatives of **241** could

ultimately lead to the development of a useful alternative scaffold to known drugs that target the GABA_A receptor.³²

4.7 EXPERIMENTAL SECTION

4.7.1 *Materials and Methods for Synthetic Procedures*

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, acetonitrile, dimethylformamide, and toluene were dried by passing through activated alumina columns. Methanol was distilled over calcium hydride. 4Å molecular sieves and powdered 4Å molecular sieves were flame-dried under vacuum immediately prior to use. All other commercially obtained reagents were used as received unless specifically indicated. Pd₂(dba)₃•CHCl₃ was purchased from Strem and stored in a glovebox, acetyl chloride, *N*-(benzyloxycarbonyloxy)succinimide (**266**), and 1-methyl-2-phenylindole (**137c**) were obtained from Sigma-Aldrich, and 1 M SnCl₄ in DCM was purchased from Acros Organics. (*R*)-3,3'-dibromo-BINOL (**102k**),³³ and *N*-Cbz-tryptamine (**247**)³⁴ were prepared according to literature procedures. Reactions were monitored either by using an Agilent 1290 Series LCMS with an Eclipse Plus C18 column (RRHD 1.8 μm, 2.1 x 50 mm, 11,072 plates) or by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, ninhydrin, *p*-anisaldehyde, or KMnO₄ staining. Flash column chromatography was performed either as described by Still et al.³⁵ using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged Luknova 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. Microwave experiments were performed using a Biotage Initiator[®] microwave reactor. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 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 CHCl₃ (¹H, δ = 7.26, ¹³C, δ = 77.0), MeCN (¹H, δ = 1.94, ¹³C, δ = 118.26), or DMSO (¹H, δ = 2.50). 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. 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) or mixed (MM) ionization mode. Analytic chiral SFC data was acquired with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing Chiralcel AD-H, OD-H, AS-H, OJ-H, and OB-H columns (4.6 mm x 25 cm) with visualization at either 254 nm or 235 nm. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5 μ m column (9.4 x 250 or 30 x 250 mm) or an Agilent Zorbax RX-SIL 5 μ m column (9.4 x 250 mm).

4.7.2 *Materials and Methods for Electrophysiology Experiments*

Acetylcholine chloride, glutamate, γ -aminobutyric acid (GABA), glycine, and 5-hydroxytryptamine were purchased from Sigma-Aldrich and used as received. mRNA was prepared as previously described using the Quikchange protocol for any necessary site-directed mutagenesis, and standard DNA linearization techniques, followed by *in*

vitro transcription using a T7 mMessage mMachine kit obtained from Ambion. The receptors were expressed in *Xenopus laevis* oocytes by injection of the mRNA of each of the desired subunits and incubation at 18 °C for 24 – 48 h in Ca^{2+} -containing ND96 buffer (1.8 mM CaCl_2 , 96 mM NaCl, 2 mM KCl, 1 mM MgCl_2 , 5 mM HEPES, pH 7.5). For $\alpha 7$ nAChRs, an equal amount of hRic3 was also injected into the oocytes to promote expression.³⁶

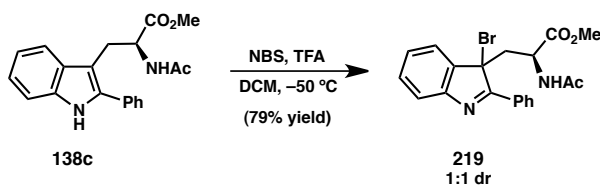
Electrophysiology experiments on the oocytes were conducted using an OpusXpress-6000A system (Axon Instruments). A two-electrode voltage clamp method was used with a holding potential of –60 mV. Prior to data collection, the health of the oocytes was evaluated by measuring the potential across the cell membrane as well as the leak current. Agonists for each receptor were employed at their EC_{50} concentrations using ND96 buffer for GABA_A R and $\alpha 7$ nAChRs and Ca^{2+} -free ND96 buffers for all other receptors. EC_{50} concentrations were calculated by applying the Hill equation to the data from measurement of the current produced at various concentrations of the agonists. The agonist concentrations used in the electrophysiology experiments on all pyrroloindolines tested are as follows: 1.2 μM acetylcholine for mouse muscle-type $(\alpha 1)_2(\beta 1\text{-L9'S})\delta\gamma$ nAChR, 1 μM acetylcholine (ACh) for $(\alpha 4)_2(\beta 2)_3$ nAChR, 0.5 μM ACh for $(\alpha 4\text{-L9'A})_2(\beta 2)_3$ nAChR, 0.05 μM ACh for $(\alpha 4\text{-L9'A})_3(\beta 2)_2$ nAChR, 100 μM ACh for $\alpha 7$ nAChR, 100 μM ACh for $\alpha 7\text{-T6'S}$ nAChR, 13 μM ACh for $\alpha 4\beta 4$ nAChR, 3 μM 5-hydroxytryptamine for 5HT_{3A} R, 14 μM glutamate for GluR_{2A} , 110 μM glycine for GlyR, 11 μM GABA for $(\alpha 1)_2(\beta 2)2\gamma 2\text{GABAAR}$, and 3 μM GABA for $(\alpha 1)_2(\beta 2)_2$ GABA_A R.

All experiments were conducted starting with three consecutive applications of agonist to the cells containing the oocytes. Those cells were then washed with either

ND96 or Ca^{2+} -free ND96 buffers depending on the receptor and the appropriate pyrroloindoline was then applied at either a 20 or 40 μM concentration as a 1 mL solution in Ca^{2+} -free ND96 buffer, followed by co-application of the agonist and 20 or 40 μM of the pyrroloindoline. Subsequent to this application, a second buffer wash was completed and the experiment was concluded with two doses of EC_{50} agonist. For experiments conducted with 20 or 40 μM concentrations of pyrroloindoline, the reported values are the average of the data acquired for 3 – 4 oocytes, with other oocytes receiving no compound used as controls. The starting potential resulting from the EC_{50} dose of agonist alone was calculated based on the average of the second and third application. A slightly different protocol was followed for IC_{50} determinations. In this case, the reported values are based on the average of data acquired for 7 oocytes and the starting potential is based on the value from a single application of agonist. IC_{50} data was acquired at eleven concentrations of **237** (0.1, 0.25, 0.5, 1., 2.5, 5, 10, 25, 50, and 100 μM).

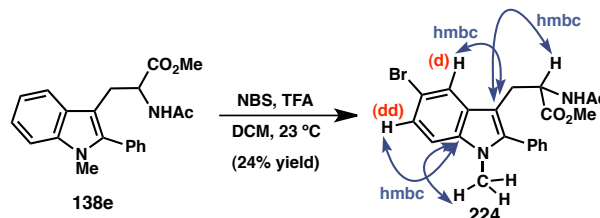
4.7.3 Synthetic Procedures

Preparation of bromoindolenine **219**.

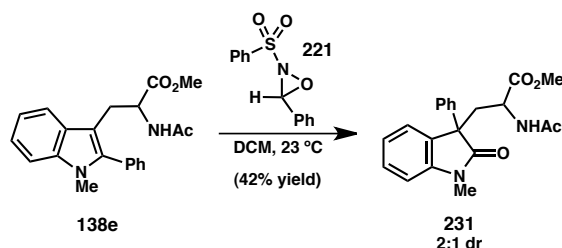


A solution of (*S*)- N_{α} -acetyl-2-phenyltryptophan methyl ester **138c** (101 mg, 0.30 mmol, 1.00 equiv) in 8.4 mL DCM was cooled to $-50\text{ }^{\circ}\text{C}$ in an MeCN/dry ice bath. NBS (53.4 mg, 0.30 mmol, 1.00 equiv) was then added, followed by 900 μL TFA. The reaction was stirred in the dark at $-50\text{ }^{\circ}\text{C}$ for 3 hours, then poured onto ice, quenched with

1.5 mL aqueous ammonia and extracted with DCM (3 x 25 mL). The combined organics were washed (40 mL H₂O, then 40 mL brine), dried (Na₂SO₄), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (30:70 to 70:30 EtOAc:hexanes) to yield 98 mg (79% yield) of bromoindolenine **219** as a bright yellow foam consisting of a 1:1 mixture of diastereomers. The enantiomeric excesses of the two diastereomers were determined to be 92% and 90% by chiral SFC analysis (AS-H, 2.5 mL/min, 20% IPA in CO₂, λ = 254 nm): t_R (major) = 3.8, t_R (minor) = 4.1 min; t_R (major) = 4.6, t_R (minor) = 6.0 min. Spectral data and optical rotation are reported for the mixture of indolenine diastereomers. ¹H NMR (500 MHz, CDCl₃) δ 8.42 – 8.32 (m, 4H), 7.70 – 7.64 (m, 2H), 7.57 – 7.49 (m, 8H), 7.47 – 7.40 (m, 2H), 7.39 – 7.30 (m, 2H), 5.37 (d, J = 7.4 Hz, 1H), 5.05 (d, J = 8.5 Hz, 1H), 4.33 (dt, J = 7.5, 5.5 Hz, 1H), 3.95 (td, J = 8.9, 4.0 Hz, 1H), 3.56 (dd, J = 14.8, 5.2 Hz, 1H), 3.47 – 3.41 (m, 4H), 3.38 – 3.32 (m, 4H), 3.23 (dd, J = 14.6, 9.3 Hz, 1H), 1.45 (s, 3H), 1.27 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 175.6, 174.8, 170.7, 170.0, 169.4, 169.2, 151.82, 151.76, 139.8, 139.6, 131.6, 131.4, 131.3, 130.5, 130.4, 128.81, 128.80, 128.7, 127.2, 126.6, 123.2, 122.5, 121.9, 121.7, 59.16, 59.14, 52.5, 52.3, 50.3, 49.8, 41.6, 41.4, 22.3, 22.0; FTIR (NaCl/thin film): 3271, 2951, 2924, 1747, 1661, 1525, 1444, 1372, 1264, 1216 cm⁻¹; [α]_D²⁵ = +17.1° (c = 0.50, CHCl₃). HRMS (MM) calc'd for C₂₀H₂₀BrN₂O₃ [M+H]⁺ 415.0652, found 415.0652.

Preparation of (*R/S*)-5-bromotryptophan methyl ester **224.**

A flame-dried flask was charged with (*R/S*)-*N*_α-acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**, 28.0 mg, 80 μmol, 1.00 equiv), 2.2 mL DCM, NBS (14.2 mg, 80 μmol, 1.00 equiv) and 240 μL TFA in that order. The yellow reaction solution was stirred at room temperature for 4.5 hours, then poured onto ice, quenched with 1.0 mL aqueous ammonia and extracted with DCM (3 x 10 mL). The combined organics were washed (15 mL H₂O, then 15 mL brine), dried (Na₂SO₄), filtered, and concentrated. The crude oil was subjected to silica gel column chromatography (50:50 to 60:40 EtOAc:hexanes), then to normal phase preparative HPLC (30:70 to 95:5 EtOAc:hexanes) using an Agilent 1200 Series HPLC with an Agilent Zorbax RX-Sil 5 μM column (9.4 x 250 mm) to yield 8.2 mg (24% yield) of (*R/S*)-5-bromotryptophan methyl ester **224** as a light yellow oil (structure assigned by 2D NMR analysis). ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, *J* = 1.8 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.49 – 7.44 (m, 1H), 7.41 – 7.36 (m, 2H), 7.32 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 5.67 (br d, *J* = 8.1 Hz, 1H), 4.74 (ddd, *J* = 8.1, 5.3, 5.3 Hz, 1H), 3.54 (s, 3H), 3.43 (s, 3H), 3.34 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.27 (dd, *J* = 14.8, 5.3 Hz, 1H), 1.73 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 169.5, 140.4, 135.6, 131.2, 130.6, 129.6, 128.9, 128.7, 124.8, 121.4, 112.9, 111.1, 106.5, 52.6, 52.2, 31.0, 26.6, 23.0.; FTIR (NaCl/thin film): 3291, 2950, 2925, 1743, 1653, 1540, 1469, 1437, 1369, 1239, 1211 cm⁻¹; HRMS (MM) calc'd for C₂₁H₂₂BrN₂O₃ [M+H]⁺ 429.0808 found 429.0797.

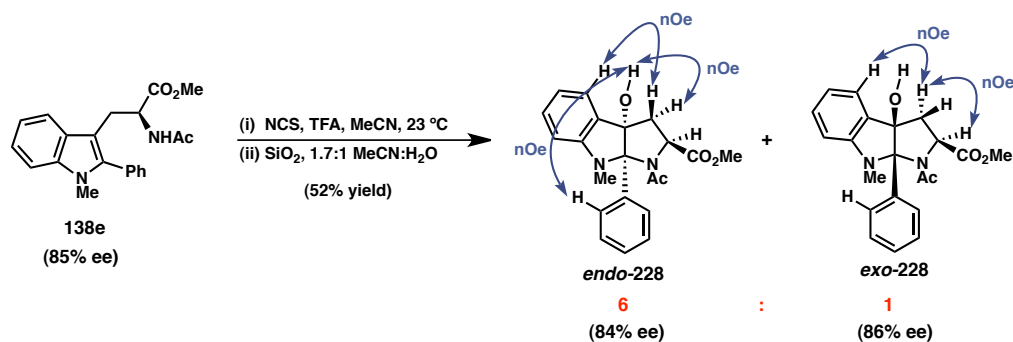
Preparation of 3-phenyloxindole 231.

A flame-dried flask was charged with (*R/S*)-*N*_α-acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**, 28.0 mg, 80 μmol, 1.00 equiv), 1.0 mL DCM, and 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (**221**, 20.9 mg, 80 μmol, 1.00 equiv) in that order. The bright yellow reaction solution was stirred at room temperature for 5 hours, then concentrated. The crude oil was subjected to silica gel column chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 6.0 mg of the major diastereomer of 3-phenyloxindole **231**. The impure mixture of product diastereomers obtained was subjected to reverse phase preparative HPLC (45:55 to 70:30 MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm) to yield 3.1 mg of the major diastereomer of 3-phenyloxindole **231** (total: 9.1 mg, 31% yield) and 3.2 mg (11% yield) of the minor diastereomer.

Major diastereomer: yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.43–7.38 (m, 3H), 7.34 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 7.31–7.27 (m, 2H), 7.26–7.21 (m, 1H), 7.16 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.90 (br d, *J* = 7.8 Hz, 1H), 5.81 (br d, *J* = 8.4 Hz, 1H), 4.66 (ddd, *J* = 8.6, 8.6, 4.7 Hz, 1H), 3.60 (s, 3H), 3.23 (s, 3H), 2.91 (dd, *J* = 14.5, 4.7 Hz, 1H), 2.61 (dd, *J* = 14.5, 8.9 Hz, 1H), 1.58 (s, 3H).; ¹³C NMR (125 MHz, CDCl₃) δ 177.6, 172.1, 169.3, 143.7, 139.5, 130.8, 128.7, 127.6, 126.6, 125.2, 122.7, 108.8, 54.7, 52.4, 49.9, 38.9, 26.6,

22.6.; FTIR (NaCl/thin film): 3308, 3057, 2952, 2931, 1746, 1709, 1659, 1611, 1494, 1471, 1373 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 367.1652, found 367.1642. *Minor diastereomer*: yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.39 (ddd, $J = 7.7, 7.7, 1.3$ Hz, 1H), 7.37-7.26 (m, 5H), 7.26-7.22 (m, 1H), 7.21 (ddd, $J = 7.5, 7.5, 1.0$ Hz, 1H), 6.92 (ddd, $J = 7.9, 1.1, 0.6$ Hz, 1H), 5.77 (br d, $J = 8.8$ Hz, 1H), 4.26 (ddd, $J = 11.0, 8.8, 3.1$ Hz, 1H), 3.64 (s, 3H), 3.17 (s, 3H), 2.87 (dd, $J = 14.4, 11.1$ Hz, 1H), 2.75 (dd, $J = 14.3, 3.1$ Hz, 1H), 1.88 (s, 3H).; ^{13}C NMR (125 MHz, CDCl_3) δ 178.4, 172.2, 169.4, 143.9, 139.8, 129.4, 129.2, 128.7, 127.7, 126.6, 125.0, 123.2, 109.0, 54.7, 52.5, 49.7, 39.0, 26.5, 22.9.; FTIR (NaCl/thin film): 3326, 3057, 2954, 2929, 1744, 1710, 1683, 1611, 1495, 1472, 1373 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 367.1652, found 367.1638.

Preparation of 3a-hydroxypyrroloindoline 228.

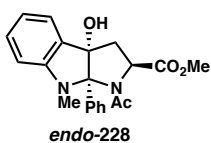


A 15 mL flask containing (S)-N $_{\alpha}$ -acetyl-1-methyl-2-phenyltryptophan methyl ester **138e** (52.5 mg, 0.150 mmol, 1.00 equiv) was flushed with argon and then charged with 3.3 mL MeCN. 1.3 M TFA in MeCN (125 μL , 0.150 mmol, 1.00 equiv) was added, followed by 0.2 M NCS in MeCN (0.75 mL, 0.150 mmol, 1.00 equiv). The flask was then sealed under argon and the solution was stirred in the dark at room temperature. After 3 hours, the reaction was quenched with 1.5 mL aqueous ammonia, poured onto

ice, and extracted with DCM (3 x 15 mL). The combined organics were washed (20 mL H₂O, then 20 mL brine), dried (Na₂SO₄), filtered, and concentrated to give the crude chloropyrroloindoline (detected by HRMS (MM) calc'd for [M+H]⁺ 385.1313, found 385.1320). The crude residue was redissolved in 2 mL MeCN then 1.2 mL H₂O and 2.5 mL SiO₂ were added. The mixture was vigorously stirred open to air at room temperature for 30 minutes, then filtered through a 1.5 mL silica plug with 50 mL EtOAc, dried (Na₂SO₄), filtered and concentrated. The crude oil contained a mixture of 3a-hydroxypyrroloindolines, formed in 6:1 dr and favoring the *endo* diastereomer (determined by ¹H NMR analysis). The crude was subjected to silica gel column chromatography (0:100 to 10:90 EtOAc:CHCl₃) to yield 30.8 mg (product contained 18 wt % CHCl₃, 46% corrected yield) of the *endo* diastereomer as a yellow oil. The *exo* diastereomer, obtained post chromatography in a mixture with (*S*)-*N*α-acetyl-1-methyl-2-phenyltryptophan methyl ester **138e**, was subjected to reverse phase preparative HPLC (30:70 to 90:10 MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm) to yield 3.5 mg (6% yield) of the *exo* diastereomer as a yellow oil.

Endo diastereomer:

The enantiomeric excess was determined to be 84% by chiral SFC analysis (AD-H, 2.5

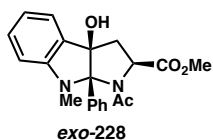


mL/min, 25% IPA in CO₂, λ = 254 nm): *t*_R(major) = 7.4, *t*_R(minor) = 4.7 min. The relative stereochemistry was assigned by 2D NMR analysis. ¹H NMR (500 MHz, CD₃CN; compound exists as a 15:1 mixture of rotamers, the major rotamer is reported) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.26 (m, 3H), 7.20 (ddd, *J* = 7.9, 7.5, 1.3 Hz, 1H), 7.12 (ddd, *J* = 7.2, 1.3, 0.5 Hz, 1H), 6.66 (ddd, *J* = 7.3, 7.3, 1.0 Hz,

1H), 6.51 (d, $J = 7.9$ Hz, 1H), 4.79 (d, $J = 8.8$ Hz, 1H), 3.19 (s, 3H), 2.97 (s, 3H), 2.90 (br s, 1H), 2.82 (d, $J = 12.7$ Hz, 1H), 2.59 (ddd, $J = 12.7, 8.8, 1.1$ Hz, 1H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN ; compound exists as a 15:1 mixture of rotamers, the major rotamer is reported) δ 172.0, 171.3, 153.1, 138.0, 131.6, 128.9, 128.6, 128.3, 125.2, 118.0, 107.1, 95.3, 88.3, 61.3, 52.7, 39.0, 32.7, 23.6; FTIR (NaCl/thin film): 3292, 3010, 2948, 1735, 1653, 1648, 1610, 1491, 1448, 1388, 1313, 1220 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +264.0^\circ$ ($c = 1.35$, CHCl_3). HRMS (MM) calc'd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 367.1652, found 367.1650.

Exo diastereomer:

The enantiomeric excess was determined to be 86% by chiral SFC analysis (OD-H, 2.5



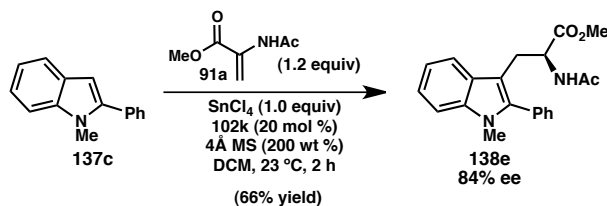
mL/min, 20% IPA in CO_2 , $\lambda = 254$ nm): t_{R} (major) = 6.2, t_{R} (minor) =

4.0 min. The relative stereochemistry was assigned by 2D NMR

analysis. ^1H NMR (500 MHz, CD_3CN ; compound exists as a 1.5:1 mixture of rotamers, the major rotamer is denoted by *, the minor rotamer by §) δ 7.60 – 7.22 (m, 6H^* , $7\text{H}^{\S}$), 7.17 (ddd, $J = 7.3, 0.6, 0.6$ Hz, 1H^*), 6.79 (dd, $J = 7.6, 7.6$ Hz, $1\text{H}^{\S}$), 6.70 (dd, $J = 7.5, 7.5$ Hz, 1H^*), 6.65 (d, $J = 7.9$ Hz, $1\text{H}^{\S}$), 6.54 (d, $J = 7.9$ Hz, 1H^*), 4.49 (dd, $J = 8.0, 6.7$ Hz, 1H^*), 4.07 (dd, $J = 10.0, 6.9$ Hz, $1\text{H}^{\S}$), 3.81 (s, 3H^*), 3.71 (s, $3\text{H}^{\S}$), 3.34 (s, $1\text{H}^{\S}$), 3.01 (s, 1H^*), 2.965 (s, 3H^*), 2.960 (s, $3\text{H}^{\S}$), 2.71 (dd, $J = 13.0, 8.1$ Hz, 1H^*), 2.68 (dd, $J = 12.6, 7.0$ Hz, $1\text{H}^{\S}$), 2.34 (dd, $J = 12.9, 6.7$ Hz, 1H^*), 2.07 (dd, $J = 12.7, 10.0$ Hz, $1\text{H}^{\S}$), 1.89 (s, 3H^*), 1.80 (s, $3\text{H}^{\S}$); ^{13}C NMR (125 MHz, CD_3CN) δ 174.1, 173.6, 172.3, 171.8, 151.2, 151.1, 136.3, 136.2, 131.6, 131.3, 130.3, 129.60, 129.57, 129.4, 128.7, 128.6, 124.4, 123.9, 119.3, 118.2, 108.0, 106.4, 98.8, 96.1, 90.1, 88.5, 61.2, 60.3, 53.3, 52.6, 40.9, 37.2, 33.4, 32.4, 24.6, 23.8; FTIR (NaCl/thin film): 3305, 2924, 1747, 1646, 1610,

1491, 1447, 1381, 1311, 1207 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -138.2^{\circ}$ ($c = 0.33$, CHCl_3). HRMS (MM) calc'd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 367.1652, found 367.1655.

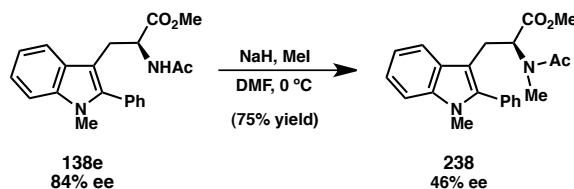
Scale-Up Procedure for (*S*)- N_{α} -acetyl-1-methyl-2-phenyltryptophan methyl ester (138e**).**



To a 250 mL flame-dried flask under nitrogen containing freshly activated powdered 4Å molecular sieves (3.50 g, 200 wt % relative to **137c**) was added 1-methyl-2-phenylindole (**137c**, 1.75 g, 8.45 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 1.45 g, 10.1 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (**102k**, 750 mg, 1.69 mmol, 0.20 equiv). The flask was charged with 65 mL DCM and SnCl_4 (1 M in DCM, 8.45 mL, 8.45 mmol, 1.00 equiv) was added. The orange reaction mixture was stirred at room temperature for 2 hours, then diluted with 15 mL MeCN, filtered, and quenched by addition of 50 mL 1 M HCl. The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with a mixture of 100 mL saturated aqueous NaHCO_3 and 300 mL brine. The aqueous layer was extracted with EtOAc (4 x 100 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 65:35 EtOAc:hexanes) to yield 1.94 g (66% yield) of (*S*)- N_{α} -acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**) as a white foam. The enantiomeric excess was determined to be 84% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2 , $\lambda =$

254 nm): $t_R(\text{major}) = 4.7$ min, $t_R(\text{minor}) = 3.9$ min. Spectral data are in agreement with prior characterization.

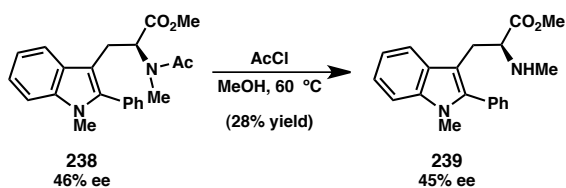
Preparation of (*S*)- N_α -acetyl- N_α ,1-dimethyl-2-phenyltryptophan methyl ester (238**).**



A solution of (*S*)- N_α -acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**, 1.93 g, 5.50 mmol, 1.00 equiv) in 11 mL DMF was cooled to 0 °C in an ice bath. NaH (60% dispersion in oil, 385 mg, 9.64 mmol, 1.75 equiv) was then added, followed by MeI (0.75 mL, 12.1 mmol, 2.20 equiv). The yellow reaction mixture was stirred at 0 °C for 1.5 hours, then quenched with 5 mL aqueous ammonia and 5 drops Et₃N. The mixture was allowed to warm to room temperature and stirred for 12 hours, then diluted with 40 mL H₂O and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (50 mL H₂O, then 2 x 50 mL brine), dried (Na₂SO₄), filtered, and concentrated. The crude oil was subjected to silica gel column chromatography (0:100 to 80:0 EtOAc:hexanes) to yield 1.51 g (75% yield) of (*S*)- N_α -acetyl- N_α ,1-dimethyl-2-phenyltryptophan methyl ester **238** as a light yellow solid. The enantiomeric excess was determined to be 46% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO₂, $\lambda = 254$ nm): $t_R(\text{major}) = 11.0$ min, $t_R(\text{minor}) = 12.5$ min. ¹H NMR (300 MHz, CDCl₃, compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by [§]) δ 7.66 (d, $J = 8.0$ Hz, 1H*), 7.62 (d, $J = 7.7$ Hz, 1H[§]), 7.55-7.10 (m, 8H*, 8H[§]), 4.86 (dd, $J = 10.0$, 4.7 Hz, 1H*), 4.62 (dd, $J = 10.2$, 4.3 Hz, 1H[§]), 3.69 (s, 3H[§]), 3.64 (s, 3H*), 3.57 (s, 3H[§]), 3.56 (s, 3H*), 3.51 (dd, $J = 11.4$, 4.6 Hz, 1H[§]), 3.46 (dd, $J = 11.5$, 4.4 Hz, 1H*), 3.28 (dd,

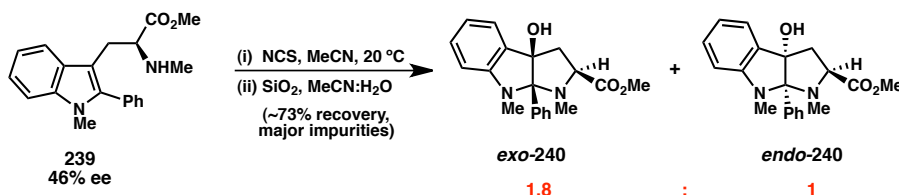
$J = 14.8, 10.1$ Hz, $1H^*$), 3.16 (dd, $J = 15.0, 10.1$ Hz, $1H^s$), 2.51 (s, $3H^*$), 2.27 (s, $3H^s$), 1.80 (s, $3H^*$), 1.44 (s, $3H^s$).; ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.2:1 mixture of rotamers) δ 171.5, 171.0, 170.9, 170.7, 139.7, 138.7, 137.10, 137.05, 131.8, 131.2, 130.6, 130.5, 128.7, 128.6, 128.4, 128.2, 127.6, 126.9, 122.1, 121.8, 119.8, 119.5, 118.7, 117.9, 109.8, 109.4, 108.6, 107.1, 60.9, 59.0, 52.4, 52.0, 34.5, 30.80, 30.77, 28.5, 24.3, 23.7, 21.7, 20.9.; FTIR (NaCl/thin film): 3052, 2949, 2242, 1740, 1735, 1653, 1648, 1469, 1442, 1432, 1400, 1364, 1329, 1268, 1214 cm^{-1} ; $[\alpha]_D^{25} = -62.0^\circ$ ($c = 0.40$, $CHCl_3$). HRMS (MM) calc'd for $C_{22}H_{25}N_2O_3$ $[M+H]^+$ 365.1860, found 365.1869.

Preparation of (*S*)- N_α ,1-dimethyl-2-phenyltryptophan methyl ester (239**).**



A flame-dried 100 mL flask charged with 20 mL MeOH was cooled to 0 °C in an ice bath. AcCl (6.5 mL, 78.5 mmol, 32.0 equiv) was added dropwise and the reaction was allowed to warm to room temperature. (*S*)- N_α -Acetyl- N_α ,1-dimethyl-2-phenyltryptophan methyl ester (**238**, 1.04 g, 2.86 mmol, 1.00 equiv) was added neat and the yellow reaction solution was then heated at 60 °C. After stirring at 60 °C for 75.5 hours, the reaction was concentrated, dissolved in 50 mL DCM, and washed with saturated aqueous $NaHCO_3$ (3 x 20 mL). The combined aqueous layers were extracted with DCM (4 x 15 mL) and the combined organic layers were then dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (0:100 to 100:0 EtOAc:DCM) to yield 259 mg (28% yield) of (*S*)- N_α ,1-dimethyl-2-phenyltryptophan methyl ester (**239**) as a yellow oil and 587 mg (contains 33 wt % DCM, 38% corrected yield) of **238** as a

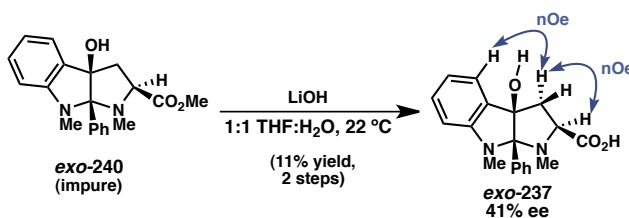
Preparation of 3a-hydroxypyrroloindoline methyl ester 240.



(*S*)-*N*_α,1-Dimethyl-2-phenyltryptophan methyl ester (**239**, 220 mg, 0.684 mmol, 1.00 equiv) was dried by azeotrope with benzene in a 50 mL flask. The flask was flushed with argon then charged with 15.5 mL MeCN. 0.2 M NCS in MeCN (3.4 mL, 0.684 mmol, 1.00 equiv) was added and the reaction was stirred in the dark at room temperature. After 4 hours, the light orange reaction solution was quenched with 7 mL aqueous ammonia, poured onto ice, and extracted with 50 mL DCM. 10 mL brine was added to the aqueous layer, which was then extracted with DCM (3 x 35 mL). The combined organic layers

were washed (50 mL H₂O, then 50 mL brine), dried (Na₂SO₄), filtered, and concentrated. The residue was redissolved in 9.3 mL MeCN then 5.6 mL H₂O and 11.7 mL SiO₂ were added. The mixture was vigorously stirred open to air at room temperature for 30 minutes, then filtered through a 12 mL silica plug with 200 mL EtOAc, dried (Na₂SO₄), filtered and concentrated. The crude residue contained a mixture of 3a-hydroxypyrroloindolines, formed in 1.8:1 dr and favoring the *exo* diastereomer (determined by ¹H NMR analysis). The crude was subjected to reverse phase preparatory HPLC (0.05:30:70 to 0.05:95:5 TFA:MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm) to yield 61.6 mg (26% recovery, <90% clean) of *endo*-**240** as a yellow-brown oil and 106 mg (46% recovery, <90% clean) of *exo*-**240** as a yellow-brown oil.

Preparation of *exo*-hydroxypyrroloindoline carboxylic acid **237**.

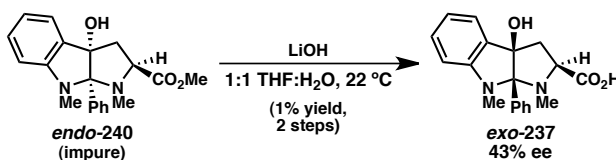


A scintillation vial was charged with the *exo*-3a-hydroxypyrroloindoline methyl ester (**240**, 106 mg, 1.00 equiv), LiOH (189 mg, 7.87 mmol, >25.0 equiv), 2 mL THF, and 2 mL H₂O. The vial was then sealed and the reaction mixture was stirred at 22 °C for 17.5 hours, then acidified to pH 7 with 1 M HCl and concentrated. The crude residue was purified by reverse phase preparatory HPLC (0.1:25:75 to 0.01:95:5 AcOH:MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (30 x 250 mm) to yield 23.5 mg (11% yield, ~95% clean) of *exo*-**237** as a yellow solid. The enantiomeric excess of *exo*-**237** was determined to be 41% by chiral SFC analysis (OJ-H,

2.5 mL/min, 20% IPA in CO₂, λ = 254 nm): t_R (major) = 2.5 min, t_R (minor) = 3.3 min.

The relative stereochemistry was assigned by 2D NMR analysis. ¹H NMR (600 MHz, DMSO-*d*₆) δ 7.6 – 7.1 (m, 7H), 6.63 (dd, J = 7.3, 7.3 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 2.99 (dd, J = 11.3, 5.0 Hz, 1H), 2.67 (s, 3H), 2.36 (dd, J = 11.7, 5.0 Hz, 1H), 2.25 (s, 3H), 2.09 (dd, J = 11.4, 11.4 Hz, 1H).; ¹³C NMR (125 MHz, CD₃CN) δ 175.9, 175.5, 152.9, 138.7, 131.2, 130.9, 130.0, 129.0, 128.7, 124.7, 117.7, 105.4, 99.0, 89.1, 65.2, 44.8, 35.6, 34.2.; FTIR (NaCl/thin film): 3404, 3050, 2917, 2849, 1718, 1609, 1491, 1448, 1370, 1311, 1200, 1098 cm⁻¹; $[\alpha]_D^{25}$ = –38.8° (c = 0.62, MeCN). HRMS (MM) calc'd for C₁₉H₂₁N₂O₃ [M+H]⁺ 325.1547, found 325.1539.

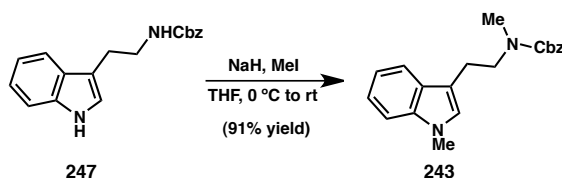
Subjection of *endo*-hydroxypyrroloindoline methyl ester **240 to saponification conditions.**



A scintillation vial was charged with the *endo*-3a-hydroxypyrroloindoline methyl ester (**240**, 61.6 mg, 1.00 equiv), LiOH (109 mg, 4.56 mmol, >25.0 equiv), 1.2 mL THF, and 1.2 mL H₂O. The vial was then sealed and the reaction mixture was stirred at 22 °C for 17.5 hours, then acidified to pH 7 with 1 M HCl and concentrated. By crude NMR, a pyrroloindoline was observed, shifts of which did not correspond to *exo*-**237**. The crude residue was subjected to reverse phase preparative HPLC (0.1:25:75 to 0.01:95:5 AcOH:MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μ M column (30 x 250 mm), followed by trituration with MeCN to yield 2.3 mg (1% yield) of *exo*-**237** as a light yellow solid. The enantiomeric excess of **237** was determined to be

43% by chiral SFC analysis (OJ-H, 2.5 mL/min, 20% IPA in CO₂, λ = 235 nm): t_R (major) = 2.6 min, t_R (minor) = 3.3 min. ¹H NMR spectral data was in agreement with prior characterization.

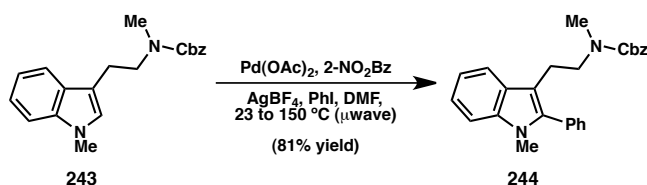
Preparation of *N*-Cbz-*N*,1-dimethyltryptamine (243).



A solution of *N*-Cbz-tryptamine (**247**) (2.43 g, 8.26 mmol, 1.00 equiv) and 90 mL THF in a flame-dried 250 mL flask was cooled to 0 °C in an ice bath. NaH (60% dispersion in oil, 1.40 g, 35.1 mmol, 4.25 equiv) was then added, followed by MeI (2.5 mL, 40 mmol, 4.8 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours, then quenched with 40 mL saturated aqueous NH₄Cl and 3 drops Et₃N. After 16.5 hours of vigorous stirring, the mixture was diluted with 20 mL H₂O. The aqueous layer was extracted with 30 mL EtOAc and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude residue was subjected to silica gel column chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 2.43 g (91% yield) of *N*-Cbz-*N*,1-dimethyltryptamine (**243**) as a yellow oil. ¹H NMR (500 MHz, CDCl₃, compound exists as a 1.4:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by [§]) δ 7.65 (d, J = 7.9 Hz, 1H[§]), 7.45 (d, J = 7.9 Hz, 1H*), 7.42–7.26 (m, 6H*, 6H[§]), 7.25–7.18 (m, 1H*, 1H[§]), 7.11 (dd, J = 7.4, 7.4 Hz, 1H[§]), 7.02 (dd, J = 7.4, 7.4 Hz, 1H*), 6.89 (s, 1H[§]), 6.79 (s, 1H*), 5.17 (s, 2H[§]), 5.10 (s, 2H*), 3.73 (s, 3H[§]), 3.71 (s, 3H*), 3.59 (t, J = 7.9 Hz, 2H[§]), 3.54 (t, J = 7.7 Hz, 2H*), 3.01 (t, J = 7.9 Hz, 2H[§]), 2.96 (t, J = 7.8 Hz, 2H*), 2.95 (s, 3H*), 2.92 (s, 3H[§]); ¹³C NMR (125

MHz, CDCl₃; compound exists as a 1.4:1 mixture of rotamers) δ 156.3, 156.2, 136.9, 136.8, 128.4, 128.0, 127.90, 127.86, 127.8, 127.7, 126.7, 121.5, 118.83, 118.78, 118.7, 111.5, 111.4, 109.2, 67.1, 66.9, 50.2, 49.8, 35.0, 34.5, 24.1, 23.4.; FTIR (NaCl/thin film): 3056, 3030, 1703, 1699, 1484, 1475, 1403, 1211, 1192, 1134 cm⁻¹; HRMS (MM) calc'd for C₂₀H₂₃N₂O₂ [M+H]⁺323.1754, found 323.1758.

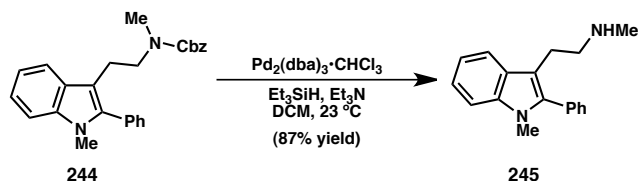
Preparation of *N*-Cbz-*N*,1-dimethyl-2-phenyltryptamine (244).



N-Cbz-*N*,1-dimethyl-2-phenyltryptamine (**244**) was prepared according to a procedure adapted from Lavilla and coworkers.²⁶ Four oven-dried microwave vials were each charged with *N*-Cbz-*N*,1-dimethyltryptamine (**243**, 231 mg, 0.717 mmol, 1.00 equiv), 2-NO₂Bz (288 mg, 1.13 mmol, 1.57 equiv), Pd(OAc)₂ (6.25 μg, 37.4 μmol, 0.052 equiv), AgBF₄ (228 mg, 1.17 mmol, 1.63 equiv, weighed into small vials in a glovebox then removed from the glovebox and transferred quickly to the microwave vials), PhI (0.33 mL, 3.0 mmol, 4.1 equiv), and 4.5 mL DMF. The microwave vials were sealed under argon and the orange reaction mixtures were stirred at room temperature for 30 minutes, then heated in the microwave for 4 min at 150 °C. The four reaction mixtures were then combined and filtered through celite with 60 mL EtOAc, washed (3 x 40 mL saturated aqueous NH₄Cl, 3 x 40 mL saturated aqueous NaHCO₃, 3 x 40 mL brine), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (8:92 EtOAc:hexanes) to yield 921 mg (81% yield) of *N*-Cbz-*N*,1-dimethyl-2-phenyltryptamine (**244**) as a yellow solid. ¹H NMR (500 MHz, CDCl₃,

compound exists as a 1.7:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.74 (d, $J = 7.9$ Hz, $1H^{\S}$), 7.53-7.22 (m, $13H^*$, $12H^{\S}$), 7.17 (dd, $J = 7.5$, 7.5 Hz, $1H^{\S}$), 7.06 (dd, $J = 7.6$, 7.6 Hz, $1H^*$), 5.09 (s, $2H^{\S}$), 4.98 (s, $2H^*$), 3.59 (s, $3H^{\S}$), 3.57 (s, $3H^*$), 3.50 (t, $J = 8.2$ Hz, $2H^{\S}$), 3.45 (t, $J = 7.8$ Hz, $2H^*$), 2.97 (t, $J = 7.5$ Hz, $2H^{\S}$), 2.91 (t, $J = 7.8$ Hz, $2H^*$), 2.78 (s, $3H^*$), 2.76 (s, $3H^{\S}$).; ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers) δ 156.1, 156.0, 138.6, 138.4, 137.1, 136.8, 131.8, 131.7, 130.4, 128.4, 128.14, 128.10, 128.0, 127.84, 127.81, 127.7, 127.5, 121.8, 119.42, 119.37, 119.0, 118.6, 109.7, 109.6, 109.4, 109.3, 67.0, 66.8, 50.5, 49.7, 34.8, 34.6, 30.81, 30.76, 23.5, 23.0; FTIR (NaCl/thin film): 3055, 3030, 2939, 1703, 1699, 1695, 1471, 1403, 1362, 1197, 1138 cm^{-1} ; HRMS (MM) calc'd for $C_{26}H_{27}N_2O_2$ $[M+H]^+$ 399.2067, found 399.2087.

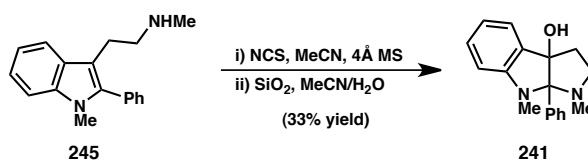
Preparation of *N*,1-dimethyl-2-phenyltryptamine (**245**).



N,1-dimethyl-2-phenyltryptamine (**245**) was prepared by a Cbz deprotection procedure adapted from Baran and coworkers.³⁷ A solution of *N*-Cbz-*N*,1-dimethyl-2-phenyltryptamine (**244**, 574 mg, 1.44 mmol, 1.00 equiv) in 15 mL DCM was prepared in a flame-dried flask under argon. Et_3SiH (9.2 mL, 57.7 mmol, 40.1 equiv) and Et_3N (0.4 mL, 2.87 mmol, 2.00 equiv) were then added, followed by $Pd_2(dba)_3 \cdot CHCl_3$ (298 mg, 0.288 mmol, 0.20 equiv). The dark red reaction solution was stirred for 15.5 hours and the resultant dark brown mixture was filtered through celite with 50 mL EtOAc, washed (2 x 40 mL saturated aqueous $NaHCO_3$, 2 x 40 mL brine), dried (Na_2SO_4), filtered, and

concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 8:92 MeOH:DCM) to yield 332 mg (87% yield) of *N*,1-dimethyl-2-phenyltryptamine (**245**) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.68 (d, $J = 7.8$ Hz, 1H), 7.53–7.38 (m, 5H), 7.35 (ddd, $J = 8.2, 0.8, 0.8$ Hz, 1H), 7.26 (ddd, $J = 8.1, 6.9, 1.0$ Hz, 1H), 7.16 (ddd, $J = 8.1, 7.0, 1.0$ Hz, 1H), 3.59 (s, 3H), 2.92 (t, $J = 7.2$ Hz, 2H), 2.82 (t, $J = 7.1$ Hz, 2H), 2.34 (s, 3H), 1.37 (s, 1H).; ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 137.0, 131.1, 130.3, 128.8, 128.5, 127.0, 122.0, 119.8, 118.7, 109.46, 107.0, 49.3, 32.4, 30.8, 21.3.; FTIR (NaCl/thin film): 3051, 2934, 2840, 2789, 1468, 1442, 1430, 1364, 1333, 1236, 1131, 1013 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{18}\text{H}_{21}\text{N}_2$ $[\text{M}+\text{H}]^+$ 265.1699, found 265.1707.

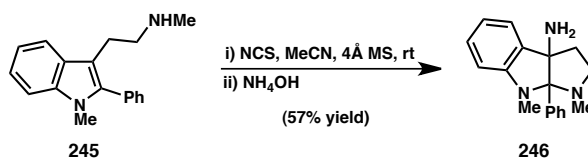
Preparation of 3a-hydroxy-1,1a-dimethyl-2a-phenylpyrroloindoline (241).



A 15 mL flame-dried flask containing *N*,1-dimethyl-2-phenyltryptamine (**245**, 59.5 mg, 0.225 mmol, 1.00 equiv) was charged with flame-dried 4 Å molecular sieves and 1.3 mL MeCN. NCS (recrystallized from toluene, 30.2 mg, 0.225 mmol, 1.00 equiv) was then added as a solution in 2 mL MeCN dropwise and the reaction was stirred in the dark at room temperature for 4 hours, followed by addition of more NCS (15.4 mg, 0.115 mmol, 0.51 equiv) as a solution in 1 mL MeCN. After 1.5 hours, the dark green reaction solution was quenched with 5 mL aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 wt %) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 30 mL brine, dried (Na_2SO_4), filtered, and concentrated. The crude oil was combined with 5 mL MeCN, 5 mL H_2O and 5 mL SiO_2 , then vigorously stirred open to air at room temperature for 30 minutes, filtered

with rinsing by EtOAc, dried (Na_2SO_4), filtered and concentrated. The crude was subjected to silica gel column chromatography (0:100 to 1:99 MeOH:DCM) and then to reverse phase preparative HPLC (0.01:18:82 to 0.01:80:20 TFA:MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm). The combined product-containing eluent was diluted with 20 mL saturated aqueous NaHCO_3 and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to yield 21.0 mg (33% yield) of 3a-hydroxy-1,1a-dimethyl-2a-phenylpyrroloindoline (**241**) as a yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.75 – 6.90 (m, 6H), 7.32 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 6.71 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 3.07 – 3.01 (m, 1H), 2.77 (s, 3H), 2.62 – 2.55 (m, 1H), 2.49 (s, 3H), 2.29 – 2.23 (m, 2H), 1.44 (br s, 1H).; ^{13}C NMR (125 MHz, CDCl_3) δ 152.5, 137.1, 130.7, 129.9, 128.7, 128.0, 123.9, 116.9, 104.0, 98.3, 90.6, 51.4, 40.5, 36.6, 34.4.; FTIR (NaCl/thin film): 3540, 3435, 3051, 2931, 2791, 1608, 1492, 1473, 1445, 1370, 1308, 1106, 1028 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 281.1648, found 281.1655.

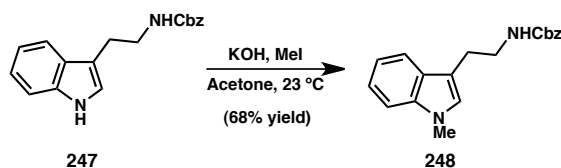
Preparation of 3a-amino-1,1a-dimethyl-2a-phenylpyrroloindoline (246).



A 15 mL oven-dried flask containing *N*,1-dimethyl-2-phenyltryptamine (**245**, 39.6 mg, 0.15 mmol, 1.00 equiv) was charged with flame-dried 4 Å molecular sieves and 0.9 mL MeCN. NCS (recrystallized from toluene, 20.1 mg, 0.15 mmol, 1.00 equiv) was then added as a solution in 1.75 mL MeCN dropwise. After stirring in the dark at room

temperature for 3 hours, the off-white reaction solution was quenched with 2.8 mL aqueous ammonia and stirred vigorously open to air for 20 minutes. The mixture was then diluted with 10 mL H₂O and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 15 mL brine, dried (Na₂SO₄), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (0:100 to 2:98 MeOH:DCM) to yield 24.0 mg (57% yield) of 3a-amino-1,1a-dimethyl-2a-phenylpyrroloindoline (**246**) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.73 (br s, 1H), 7.54 – 7.27 (m, 3H), 7.24 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.19 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H), 6.83 (br s, 1H), 6.68 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 2.96 (dd, *J* = 9.1, 7.0 Hz, 1H), 2.79 (s, 3H), 2.58 (ddd, *J* = 12.0, 9.1, 5.1 Hz, 1H), 2.47 (s, 3H), 2.20 (dd, *J* = 12.2, 5.1 Hz, 1H), 1.95 (ddd, *J* = 12.1, 12.1, 7.1 Hz, 1H), 1.12 (br s, 2H).; ¹³C NMR (125 MHz, CDCl₃) δ 152.5, 138.6, 132.0, 129.1, 128.9, 128.5, 127.8, 127.7, 123.9, 116.6, 103.6, 99.0, 74.8, 51.2, 42.0, 36.8, 34.6.; FTIR (NaCl/thin film): 3051, 2930, 2861, 2791, 2254, 1606, 1495, 1473, 1445, 1372, 1308, 1035 cm⁻¹; HRMS (MM) calc'd for C₁₈H₂₂N₃ [M+H]⁺ 280.1808, found 280.1818.

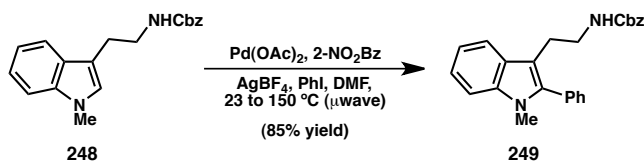
Preparation of *N*-Cbz-1-methyl-2-phenyltryptamine (**248**).



N-Cbz-1-methyltryptamine (**248**) was prepared according to a procedure adapted from Qing and coworkers.³⁸ A solution of *N*-Cbz-tryptamine (**247**, 212 mg, 0.721 mmol, 1.00 equiv) in 3 mL wet acetone was charged with KOH (202 mg, 3.60, 4.99 equiv). After 10 min, MeI (49 μL, 0.787 mmol, 1.09 equiv) was added and the orange reaction

solution was stirred 1 hour at room temperature, followed by addition of more KOH (202 mg, 3.60 mmol, 4.99 equiv) and more MeI (49 μ L, 0.787 mmol, 1.09 equiv). After stirring 3.5 hours at room temperature, the reaction was diluted with toluene, filtered, and concentrated. The crude was purified by silica gel column chromatography (5:95 to 20:80 EtOAc:hexanes) to yield 151 mg (68% yield) of *N*-Cbz-1-methyltryptamine (**248**). Spectral data are in agreement with the literature.³⁹

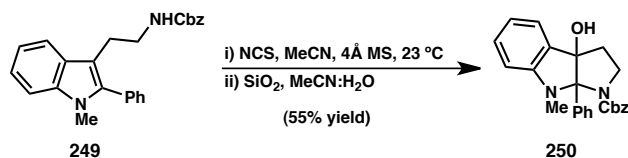
Preparation of *N*-Cbz-1-methyl-2-phenyltryptamine (249**).**



N-Cbz-1-methyl-2-phenyltryptamine (**249**) was prepared according to a procedure adapted from Lavilla and coworkers.²⁶ An oven-dried microwave vial was charged with *N*-Cbz-1-methyltryptamine (**248**, 134 mg, 0.435 mmol, 1.00 equiv), 2- NO_2Bz (147 mg, 0.653 mmol, 1.50 equiv), $\text{Pd}(\text{OAc})_2$ (3.3 μ g, 20 μ mol, 0.046 equiv), AgBF_4 (131 mg, 0.672 mmol, 1.54 equiv, weighed into a small vial in a glovebox then removed from the glovebox and transferred quickly to the microwave vial), PhI (0.19 mL, 1.70 mmol, 3.91 equiv), and 4.3 mL DMF. The microwave vial was sealed under argon and the orange solution was stirred at room temperature for 30 minutes, then heated in the microwave for 4 min at 150 $^\circ\text{C}$. The resultant brown reaction mixture was filtered through celite with EtOAc, washed (2 x 10 mL saturated aqueous NH_4Cl , 2 x 10 mL saturated aqueous NaHCO_3 , 2 x 10 mL brine), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (6:94 to 12:88 EtOAc:hexanes) to yield 142 mg (85% yield) of *N*-Cbz-1-methyl-2-phenyltryptamine (**249**) as an orange oil.

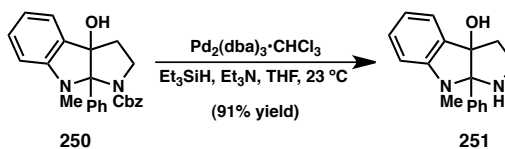
^1H NMR (500 MHz, CDCl_3 , compound exists as a 5.6:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.67 (d, $J = 7.9$ Hz, 1H^*), 7.54 (br s, $1\text{H}^{\S}$), 7.50 – 7.41 (m, 3H^* , $3\text{H}^{\S}$), 7.40 – 7.26 (m, 9H^* , $9\text{H}^{\S}$), 7.17 (dd, $J = 7.4$ Hz, 1H^*), 7.12 (br s, $1\text{H}^{\S}$), 5.04 (s, 2H^* , $2\text{H}^{\S}$), 4.73 (t, $J = 6.8$ Hz, 1H^*), 4.51 (br s, $1\text{H}^{\S}$), 3.58 (s, 3H^* , $3\text{H}^{\S}$), 3.44 (td, $J = 6.7$, 6.7 Hz, 2H^*), 3.38 (br s, $1\text{H}^{\S}$), 2.94 (t, $J = 6.9$ Hz, 2H^*), 2.90 (br s, $1\text{H}^{\S}$).; ^{13}C NMR (125 MHz, CDCl_3 ; compound exists as a 5.6:1 mixture of rotamers, only the major rotamer is reported) δ 156.2, 138.8, 137.1, 131.7, 130.6, 128.5, 128.4, 128.2, 128.0, 121.9, 119.5, 118.9, 109.6, 109.4, 66.4, 41.7, 30.8, 25.1.; FTIR (NaCl/thin film): 3413, 3339, 3055, 3030, 2940, 1718, 1701, 1511, 1368, 1361, 1334, 1233, 1132 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 385.1911, found 385.1924.

Preparation of 1-Cbz-3a-hydroxy-1a-methyl-2a-phenylpyrroloindoline (250).

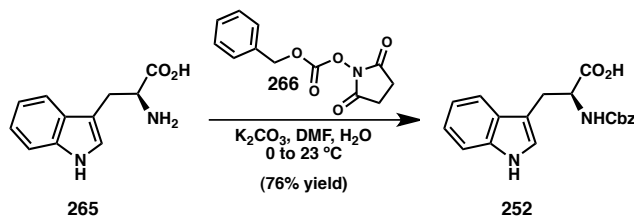


A 5 mL oven-dried flask containing *N*-Cbz-1-methyl-2-phenyltryptamine (**249**, 24.0 mg, 62.5 μmol , 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 0.5 mL MeCN. NCS (recrystallized from toluene, 8.4 mg, 0.225 mmol, 1.00 equiv) was then added as a solution in 1.25 mL MeCN dropwise. After stirring in the dark at room temperature for 6 hours, the light yellow reaction solution was quenched with 5 mL aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 wt %) and extracted with EtOAc (4 x 5 mL). The combined organic layers were washed with 15 mL brine, dried (Na_2SO_4), filtered, and concentrated. The crude residue was combined with 1.5 mL MeCN, 1.5 mL H_2O and 1.5 mL SiO_2 , then

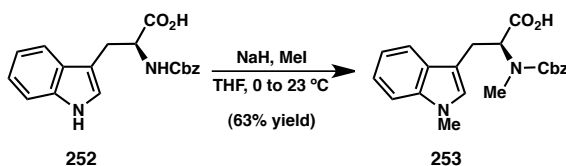
vigorously stirred open to air at room temperature for 30 minutes, filtered through a ~1.5 mL silica plug with EtOAc, and concentrated. The crude oil was purified by reverse phase preparative HPLC (60:40 to 90:10 MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μ M column (9.4 x 250 mm) to yield 13.7 mg (55% yield) of 3a-hydroxy-1-Cbz-1a-methyl-2a-phenylpyrroloindoline (**250**) as a light yellow-green oil. ¹H NMR (500 MHz, CDCl₃, compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by [§]; due to overlap in the NMR, the rotamer shifts were confirmed by HSQC 2D NMR) δ 7.48 – 7.09 (m, 11H*, 11H[§]), 6.83 – 6.75 (m, 2H*), 6.75 – 6.68 (m, 2H[§]), 6.58 (d, *J* = 7.8 Hz, 1H*), 6.50 (d, *J* = 7.9 Hz, 1H[§]), 5.12 (d, *J* = 12.4 Hz, 1H*), 5.07 – 5.01 (m, 1H*, 1H[§]), 4.85 (d, *J* = 12.3 Hz, 1H[§]), 4.05 (dd, *J* = 9.7 Hz, 1H[§]), 3.98 (dd, *J* = 9.5 Hz, 1H*), 3.30 (ddd, *J* = 11.1, 11.1, 6.2 Hz, 1H*), 3.21 (ddd, *J* = 11.5, 11.5, 5.9 Hz, 1H[§]), 3.04 (s, 3H*), 2.75 (s, 3H[§]), 2.50 – 2.39 (m, 1H*, 1H[§]), 2.31 – 2.19 (m, 1H*, 1H[§]), 1.50 (br s, 1H*, 1H[§]).; ¹³C NMR (125 MHz, CDCl₃, compound exists as a 1.1:1 mixture of rotamers) δ 155.0, 154.5, 151.1, 151.0, 136.7, 135.6, 130.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 127.3, 123.62, 123.59, 118.1, 117.8, 106.53, 106.45, 89.6, 88.6, 67.0, 66.7, 46.3, 46.2, 34.1, 33.6, 31.9, 31.3.; FTIR (NaCl/thin film): 3049, 3056, 3032, 2945, 2891, 1695, 1684, 1675, 1609, 1491, 1401, 1348, 1186, 1117, 1004 cm⁻¹; HRMS (MM) calc'd for C₂₅H₂₅N₂O₃ [M+H]⁺401.1860, found 401.1877.

Preparation of 3a-hydroxy-1a-methyl-2a-phenylpyrroloindoline (251).

A solution of 3a-hydroxy-1-Cbz-1a-methyl-2a-phenylpyrroloindoline (**250**, 10.1 mg, 25.2 μmol , 1.00 equiv) in 1.0 mL THF was prepared in a flame-dried flask. Et_3SiH (0.16 mL, 1.0 mmol, 40 equiv) and Et_3N (7.0 μL , 50 μmol , 2.0 equiv) were then added, followed by $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (5.0 mg, 4.8 μmol , 0.19 equiv). The dark red reaction solution was stirred for 18.5 hours at room temperature, then filtered through celite with THF, combined with an equal volume of saturated aqueous NaHCO_3 , and stirred at room temperature for 5 hours. The aqueous layer was then extracted with EtOAc (3 x 15 mL) and combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 2:98 $\text{MeOH}:\text{DCM}$) to yield 6.1 mg (91% yield) of 3a-hydroxy-1a-methyl-2a-phenylpyrroloindoline (**251**) as a yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 7.50 – 7.27 (m, 5H), 7.25 (ddd, $J = 7.2, 1.4, 0.5$ Hz, 1H), 7.20 (ddd, $J = 7.7, 7.7, 1.3$ Hz, 1H), 6.68 (ddd, $J = 7.4, 7.4, 1.0$ Hz, 1H), 6.42 (d, $J = 7.9$ Hz, 1H), 3.25 (ddd, $J = 9.4, 5.1, 3.8$ Hz, 1H), 2.94 – 2.83 (m, 1H), 2.63 (s, 3H), 2.32 – 2.25 (m, 2H), 1.03 – 0.89 (br m, 1H), 0.65 – 0.51 (br m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.2, 138.2, 130.7, 130.1, 128.6, 128.2, 127.4, 123.9, 117.1, 104.3, 95.2, 89.6, 43.3, 41.9, 28.5; FTIR (NaCl/thin film): 3340, 3051, 2931, 2874, 1609, 1495, 1446, 1375, 1307, 1121, 1062 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 267.1492, found 267.1502.

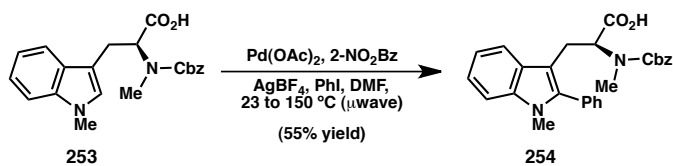
Preparation of (*S*)-*N*_α-Cbz-tryptophan (252**).**

(*S*)-*N*_α-Cbz-tryptophan (**252**) was prepared by a procedure adapted from Lapatsanis and coworkers.⁴⁰ A solution of (*S*)-tryptophan (**265**, 1.00 g, 4.90 mmol, 1.11 equiv) and K₂CO₃ (1.35 g, 9.77 mmol, 2.22 equiv) in 25 mL H₂O was cooled to 0 °C in an ice bath. *N*-(Benzyloxycarbonyloxy)succinimide (**266**, 1.10 g, 4.41 mmol, 1.00 equiv) was then added as a solution in 25 mL wet DMF and the reaction was allowed to warm to room temperature. After stirring 20 minutes, the mixture was diluted with 300 mL H₂O and washed with 20 mL Et₂O and EtOAc (2 x 35 mL). The aqueous layer was then cooled to 0 °C, acidified with 10 mL concentrated HCl, and extracted with EtOAc (5 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried (Na₂SO₄), filtered, and concentrated. DMF was still present and hence the residue was redissolved in 50 mL EtOAc, washed with brine (3 x 100 mL), dried (Na₂SO₄), filtered, and concentrated to give 1.136 g (76% yield) of (*S*)-*N*_α-Cbz-tryptophan (**252**) as a white solid. ¹H NMR spectral data were in agreement with the literature.⁴¹

Preparation of (*S*)-*N*_α-Cbz-*N*_{α,1}-dimethyltryptophan (253**).**

A solution of (*S*)-*N*_α-Cbz-tryptophan (**252**, 875 mg, 2.59 mmol, 1.00 equiv) in 5 mL THF was cooled to 0 °C in an ice bath. NaH (60% dispersion in oil, 516 mg, 12.9 mmol,

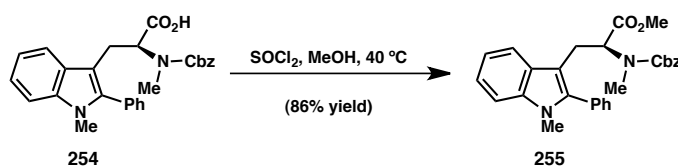
4.98 equiv) was then added, followed by MeI (0.96 mL, 15.4 mmol, 5.96 equiv). The yellow reaction mixture was allowed to warm to room temperature and stirred for 29 hours, then diluted with 10 mL H₂O and acidified with 1 mL concentrated HCl. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (3 x 30 mL), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (5:95 to 50:50 EtOAc:hexanes with 2–4% AcOH) to yield 600 mg (63% yield) of (*S*)-*N*_α-Cbz-*N*_α,1-dimethyltryptophan (**253**) as a yellow-brown foam. ¹H NMR (500 MHz, CDCl₃, compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 10.54 (br s, 1H*, 1H§), 7.60 (d, *J* = 7.9 Hz, 1H*), 7.55 (d, *J* = 7.9 Hz, 1H§), 7.38 – 7.21 (m, 6H*, 6H§), 7.16 – 7.07 (m, 2H*, 2H§), 6.85 (s, 1H*), 6.76 (s, 1H§), 5.17 (s, 2H*), 5.09 – 4.99 (m, 1H*, 3H§), 3.684 (s, 3H*), 3.677 (s, 3H§), 3.50 (d, *J* = 5.0 Hz, 1H§), 3.47 (d, *J* = 4.9 Hz, 1H*), 3.32 (dd, *J* = 15.5, 10.6 Hz, 1H*), 3.18 (dd, *J* = 15.3, 10.5 Hz, 1H§), 2.92 (s, 3H§), 2.83 (s, 3H*); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 176.5§, 176.4*, 157.0*, 156.3§, 136.93§, 136.88*, 136.6*, 136.2§, 128.5*, 128.4§, 128.01*, 127.96§, 127.9§, 127.7*, 127.3§, 127.1*, 121.8§, 121.7*, 119.1§, 119.0*, 118.5*, 118.4§, 109.5§, 109.4*, 109.32§, 109.27*, 67.6§, 67.5*, 59.9*, 59.4§, 32.67*, 32.66§, 32.0*, 31.7§, 25.0§, 24.4*.; FTIR (NaCl/thin film): 3034, 2939, 1741, 1701, 1664, 1475, 1455, 1403, 1326, 1214, 1141 cm⁻¹; [α]_D²⁵ = -40.6° (*c* = 0.68, CHCl₃). HRMS (MM) calc'd for C₂₁H₂₃N₂O₄ [M+H]⁺ 367.1652, found 367.1667.

Preparation of (*S*)-*N*_α-Cbz-*N*_α,1-dimethyl-2-phenyltryptophan (254**).**

(*S*)-*N*_α-Cbz-*N*_α,1-dimethyl-2-phenyltryptophan (**254**) was prepared according to a procedure adapted from Lavilla and coworkers.²⁶ Two oven-dried microwave vials were each charged with 2-NO₂Bz (255 mg, 1.13 mmol, 1.50 equiv), Pd(OAc)₂ (6.25 μg, 37.4 μmol, 0.050 equiv), AgBF₄ (240 mg, 1.23 mmol, 1.63 equiv, weighed into small vials in a glovebox then removed from the glovebox and transferred quickly to the microwave vials), and PhI (0.34 mL, 3.04 mmol, 4.03 equiv). A solution of (*S*)-*N*_α-Cbz-*N*_α,1-dimethyltryptophan (**253**, 276 mg, 0.754 mmol, 1.00 equiv) in 4 mL DMF was then added to each vial. The microwave vials were sealed under argon and the reaction mixtures were stirred at room temperature for 30 minutes, then heated in the microwave for 4 min at 150 °C. The two reaction mixtures were then combined and filtered through celite with 15 mL EtOAc, washed (2 x 20 mL saturated aqueous NH₄Cl, 2 x 20 mL brine), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (4:5:91 to 4:19:77 AcOH:EtOAc:hexanes) followed by washing with saturated aqueous NaHCO₃ to yield 366 mg (55% yield) of (*S*)-*N*_α-Cbz-*N*_α,1-dimethyl-2-phenyltryptophan (**254**) as a light yellow foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO₂, λ = 254 nm): *t*_R(major) = 4.6 min *t*_R(minor) = 7.2 min. ¹H NMR (300 MHz, CDCl₃, compound exists as a 2.6:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.55 (d, *J* = 7.9 Hz, 1H*), 7.46 (d, *J* = 7.9 Hz, 1H§),

7.32 – 6.85 (m, 13H^{*}, 12H[§]), 6.57 (d, $J = 7.4$ Hz, 1H[§]), 4.87 (br d, $J = 11.6$ Hz, 1H[§]), 4.78 (d, $J = 12.6$ Hz, 1H^{*}), 4.64 (d, $J = 12.6$ Hz, 1H^{*}), 4.51 (d, $J = 12.6$ Hz, 1H[§]), 4.35 (d, $J = 12.5$ Hz, 1H[§]), 4.04 (br d, $J = 10.3$ Hz, 1H^{*}), 3.53 – 3.25 (m, 5H^{*}, 4H[§]), 3.03 – 2.88 (m, 1H[§]), 2.28 (s, 3H^{*}), 2.11 (s, 3H[§]).; ¹³C NMR (125 MHz, CDCl₃; compound exists as a 2.6:1 mixture of rotamers) δ 176.5, 176.3, 156.3, 155.6, 139.4, 139.0, 137.1, 136.5, 136.1, 131.6, 131.4, 130.6, 130.5, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 127.4, 127.1, 121.9, 121.8, 119.6, 118.6, 118.4, 109.6, 109.4, 108.2, 107.8, 67.18, 67.15, 61.1, 59.7, 33.0, 32.2, 30.8, 30.7, 24.4, 23.9.; FTIR (NaCl/thin film): 3056, 3031, 2936, 1699, 1695, 1683, 1605, 1469, 1401, 1363, 1328, 1137 cm⁻¹; $[\alpha]_D^{25} = -133.3^\circ$ ($c = 0.84$, CHCl₃). HRMS (MM) calc'd for C₂₇H₂₇N₂O₄ [M+H]⁺ 443.1965, found 443.1984.

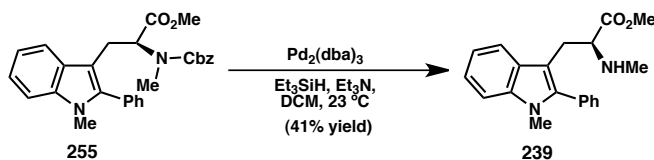
Preparation of (S)-N_α-Cbz-N_α,1-dimethyl-2-phenyltryptophan methyl ester (255**).**



A solution of (S)-N_α-Cbz-N_α,1-dimethyl-2-phenyltryptophan (**254**, 104 mg, 0.235 mmol, 1.00 equiv) in 3 mL wet MeOH was charged with SOCl₂ (34 μ L, 0.47 mmol, 2.0 equiv), then heated to 40 °C. After stirring at 40 °C for 5 hours, the reaction was diluted with 10 mL H₂O and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The crude residue was purified by silica gel column chromatography (15:85 EtOAc:hexanes) to yield 92.6 mg (86% yield) of N_α-Cbz-N_α,1-dimethyl-2-phenyltryptophan methyl ester (**255**) as a yellow oil. ¹H NMR (500 MHz, CDCl₃, compound exists as a 1.5:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by [§]) δ 7.67 (d, $J = 7.9$ Hz, 1H[§]), 7.59 (d, $J =$

7.9 Hz, 1H*), 7.49 – 7.19 (m, 11H[§], 11H*), 7.17 – 7.10 (m, 1H[§], 1H*), 6.97 – 6.90 (m, 1H[§], 1H*), 5.02 (d, *J* = 12.5 Hz, 1H[§]), 4.89 (d, *J* = 12.6 Hz, 1H[§]), 4.82 – 4.71 (m, 2H*, 1H[§]), 4.62 (d, *J* = 12.3 Hz, 1H*), 3.65 (s, 3H[§]), 3.55 (s, 3H*), 3.531 (s, 3H[§]), 3.527 (s, 3H*), 3.51 – 3.45 (m, 1H*, 1H[§]), 3.27 (dd, *J* = 14.9, 10.3 Hz, 1H[§]), 3.21 (dd, *J* = 14.9, 10.8 Hz, 1H*), 2.49 (s, 3H[§]), 2.40 (s, 3H*); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 1.5:1 mixture of rotamers) δ 171.6, 171.4, 156.0, 155.5, 139.4, 139.0, 137.0, 136.7, 136.2, 131.6, 131.5, 130.6, 130.5, 128.5, 128.4, 128.3, 128.17, 128.15, 128.1, 127.71, 127.68, 127.6, 127.54, 127.46, 127.2, 121.8, 121.7, 119.49, 119.47, 118.6, 118.4, 109.5, 109.3, 108.3, 108.0, 66.92, 66.86, 60.5, 59.9, 52.03, 51.98, 32.4, 32.3, 30.70, 30.67, 24.5, 24.1.; FTIR (NaCl/thin film): 3033, 2946, 1743, 1740, 1734, 1704, 1700, 1696, 1468, 1399, 1363, 1314, 1270, 1214, 1139 cm⁻¹; [α]_D²⁵ = -82.8° (*c* = 0.22, CHCl₃). HRMS (MM) calc'd for C₂₈H₂₉N₂O₄ [M+H]⁺ 457.2122, found 457.2128.

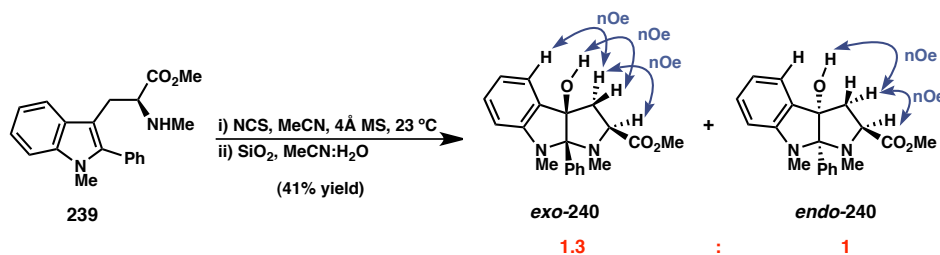
Preparation of (*S*)-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (239**).**



A solution of (*S*)-*N*_α-Cbz-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (**255**, 91.0 mg, 0.199 mmol, 1.00 equiv) in 2 mL DCM was prepared in a flame-dried flask under nitrogen. Et₃SiH (1.3 mL, 8.1 mmol, 41 equiv) and Et₃N (55 μL, 0.40 mmol, 2.0 equiv) were then added, followed by Pd₂(dba)₃ (41.0 mg, 44.8 μmol, 0.225 equiv). The dark red reaction solution was stirred for 20 hours and the resultant dark brown mixture was filtered through celite with 15 mL EtOAc, washed (saturated aqueous NaHCO₃ (2 x 15 mL), brine (2 x 15 mL)), dried (Na₂SO₄), filtered, and concentrated. The crude residue

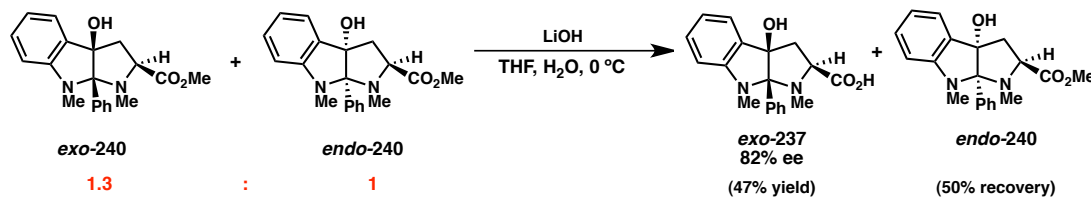
was purified by silica gel column chromatography (5:95 to 15:85 EtOAc:hexanes, then 4:14:82 NH₄OH:EtOAc:hexanes, then 4:5:91 NH₄OH:MeOH:DCM) to yield 26.4 mg (41% yield) of (*S*)-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (**239**) as a colorless oil. $[\alpha]_D^{25} = +16.1^\circ$ ($c = 0.19$, CHCl₃). ¹H NMR spectral data was in agreement with prior characterization.

Preparation of 3a-hydroxypyrroloindoline methyl ester **240**.



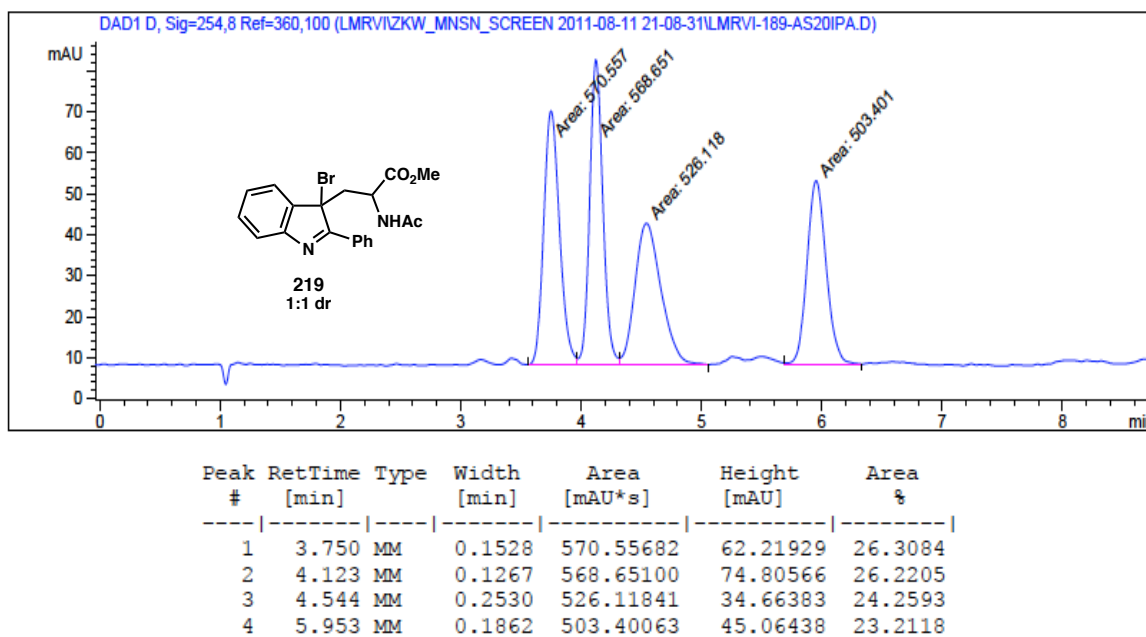
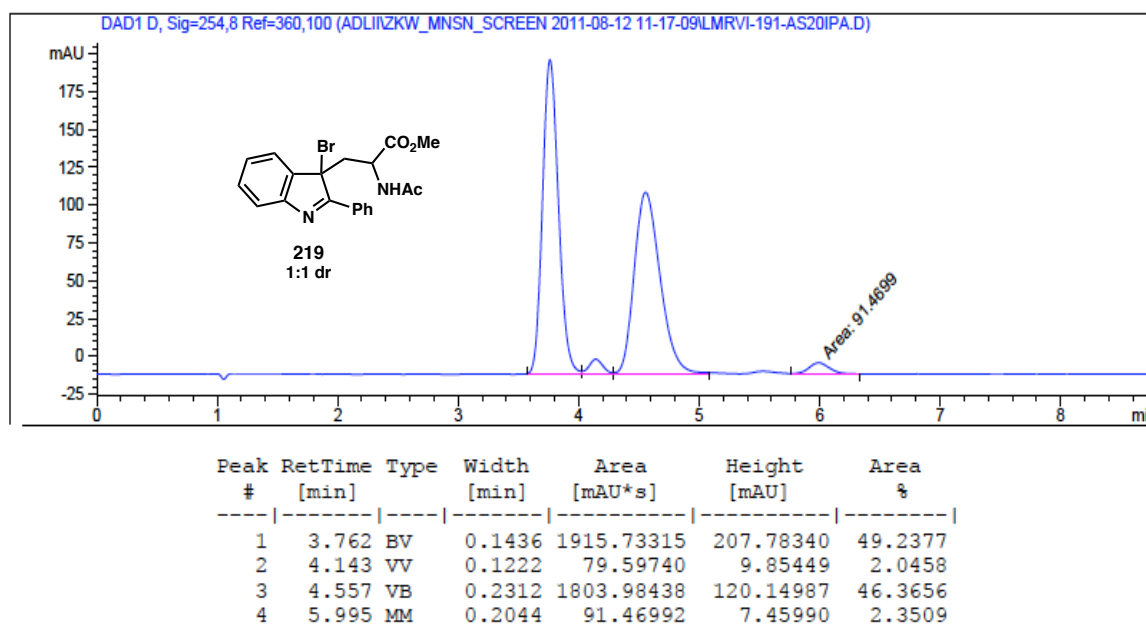
A flame-dried flask containing (*S*)-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (**239**, 24.1 mg, 0.748 mmol, 1.00 equiv) was charged with flame-dried 4 Å molecular sieves and 1 mL MeCN. NCS (recrystallized from toluene, 10.0 mg, 0.746 mmol, 1.00 equiv) was then added as a solution in 1 mL MeCN dropwise. After stirring in the dark at room temperature for 5.5 hours, more NCS (5.0 mg, 0.37 mmol, 0.50 equiv) was added as a solution in 0.5 mL MeCN. After stirring an additional 40 minutes, the reaction was quenched with 1 mL aqueous Na₂S₂O₃ (10 wt %) and the organic layer was washed with brine (2 x 3 mL), dried (Na₂SO₄), filtered, and concentrated. The residue was combined with 2 mL MeCN, 2 mL H₂O and 2 mL SiO₂, then stirred open to air at room temperature for 30 minutes. The mixture was then filtered with 20 mL EtOAc and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic layers were concentrated and purified by silica gel column chromatography (10:90 to 15:85 EtOAc:hexanes) to yield 10.3 mg (41% yield) of 3a-hydroxypyrroloindoline methyl ester **240** as a yellow oil

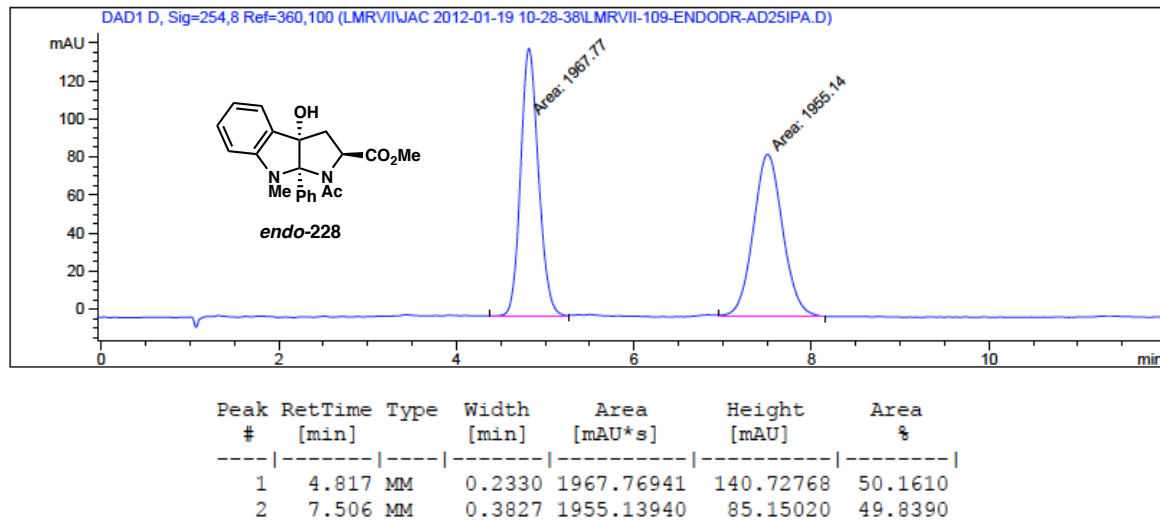
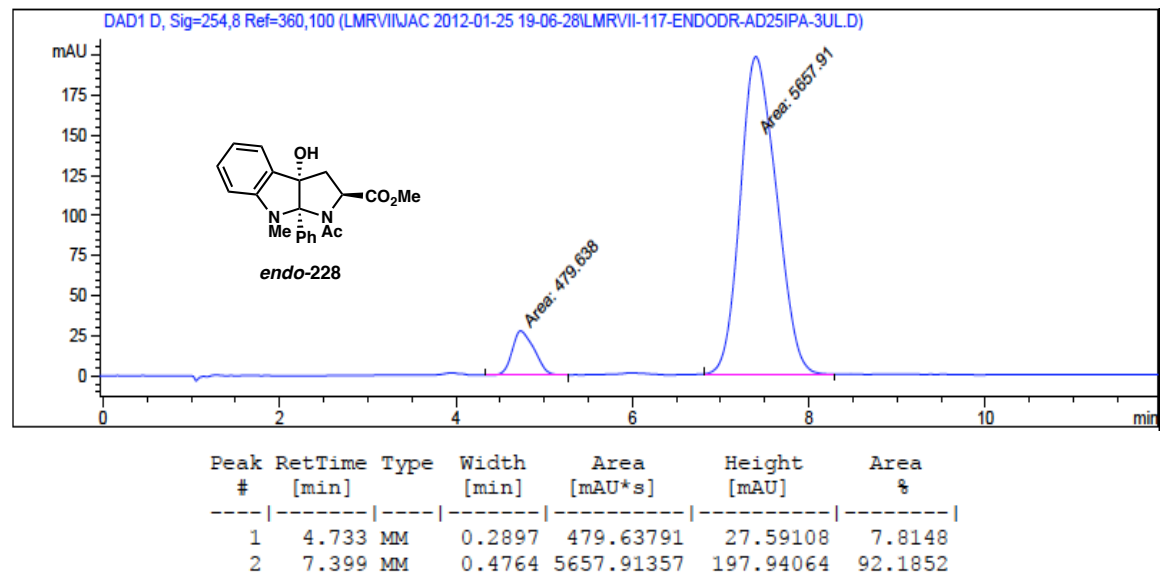
(note: by then exchanging the column solvent for 2:98 MeOH:DCM, 6.0 mg (25%) of the starting material, (*S*)-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (**239**), could be recovered). 3a-hydroxypyrroloindoline methyl ester **240** was isolated as a 1.3:1 mixture of diastereomers favoring the *exo* diastereomer as determined by ¹H NMR. Optical rotation, HRMS, and spectral data are reported for the mixture of diastereomers. The relative stereochemistry and respective ¹H and ¹³C NMR data for each diastereomer was determined by 2D NMR analysis and by comparison to the ¹H NMR spectrum of re-isolated *endo* diastereomer in the subsequent saponification step generating *exo*-3a-hydroxypyrroloindoline carboxylic acid **237** (*vide infra*). ¹H NMR (500 MHz, CDCl₃) δ 7.47 – 7.28 (m, 4H^{exo}, 4H^{endo}), 7.26 – 7.08 (m, 3H^{exo}, 3H^{endo}), 6.73 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H^{exo}), 6.64 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H^{endo}), 6.46 (dd, *J* = 8.3, 0.8 Hz, 1H^{exo}), 6.43 (d, *J* = 7.9 Hz, 1H^{endo}), 3.97 (d, *J* = 8.3 Hz, 1H^{endo}), 3.76 (s, 3H^{exo}), 3.42 (dd, *J* = 11.2, 5.4 Hz, 1H^{exo}), 3.24 (s, 3H^{endo}), 2.91 (s, 3H^{endo}), 2.80 (s, 3H^{exo}), 2.79 (s, 3H^{endo}), 2.73 (dd, *J* = 12.4, 1.0 Hz, 1H^{endo}), 2.59 (dd, *J* = 11.9, 5.4 Hz, 1H^{exo}), 2.53 (dd, *J* = 12.3, 8.5 Hz, 1H^{endo}), 2.41 (s, 3H^{exo}), 2.31 (dd, *J* = 11.6, 11.6 Hz, 1H^{exo}), 1.43 (s, 1H^{exo}), 1.31 (s, 1H^{endo}).; ¹³C NMR (125 MHz, CDCl₃) δ 173.9^{endo}, 173.3^{exo}, 151.7^{exo}, 151.5^{endo}, 137.6^{endo}, 136.9^{exo}, 130.6^{endo}, 130.3^{exo}, 129.5^{exo}, 128.8^{endo,exo}, 128.5^{endo}, 128.4^{exo}, 128.2^{endo}, 124.3^{endo}, 124.0^{exo}, 117.2^{exo}, 116.6^{endo}, 104.9^{endo}, 104.6^{exo}, 98.2^{exo}, 95.9^{endo}, 88.9^{endo}, 88.0^{exo}, 64.2^{endo}, 63.4^{exo}, 52.0^{exo}, 51.2^{endo}, 43.7^{exo}, 41.3^{endo}, 34.9^{exo}, 34.8^{endo}, 33.9^{exo}, 31.6^{endo}.; FTIR (NaCl/thin film): 3467, 2920, 2850, 1750, 1734, 1609, 1494, 1447, 1375, 1311, 1202, 1101 cm⁻¹; [α]_D²⁵ = +33.2° (*c* = 0.55, CHCl₃). HRMS (MM) calc'd for C₂₀H₂₃N₂O₃ [M+H]⁺ 339.1703, found 339.1715.

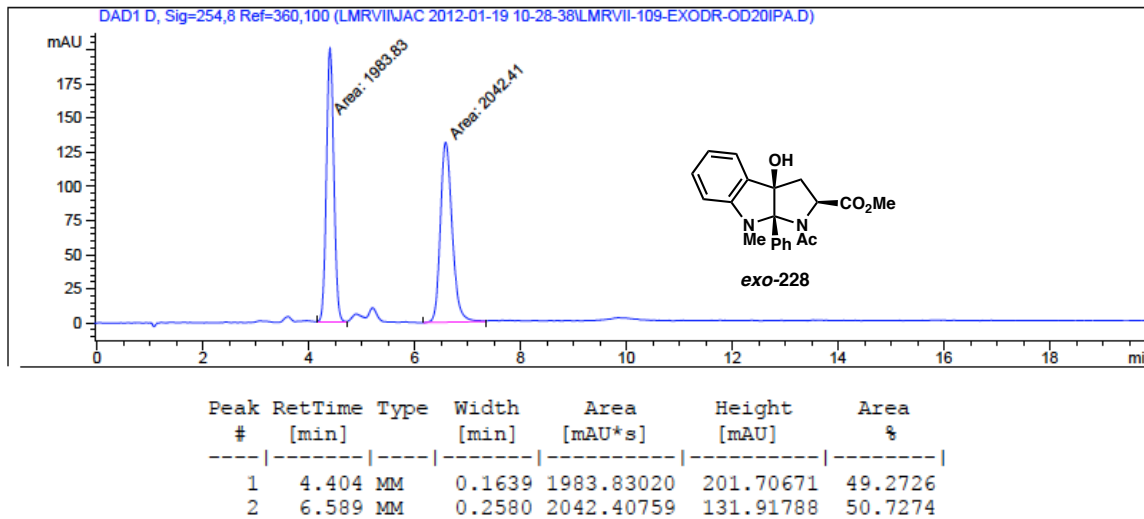
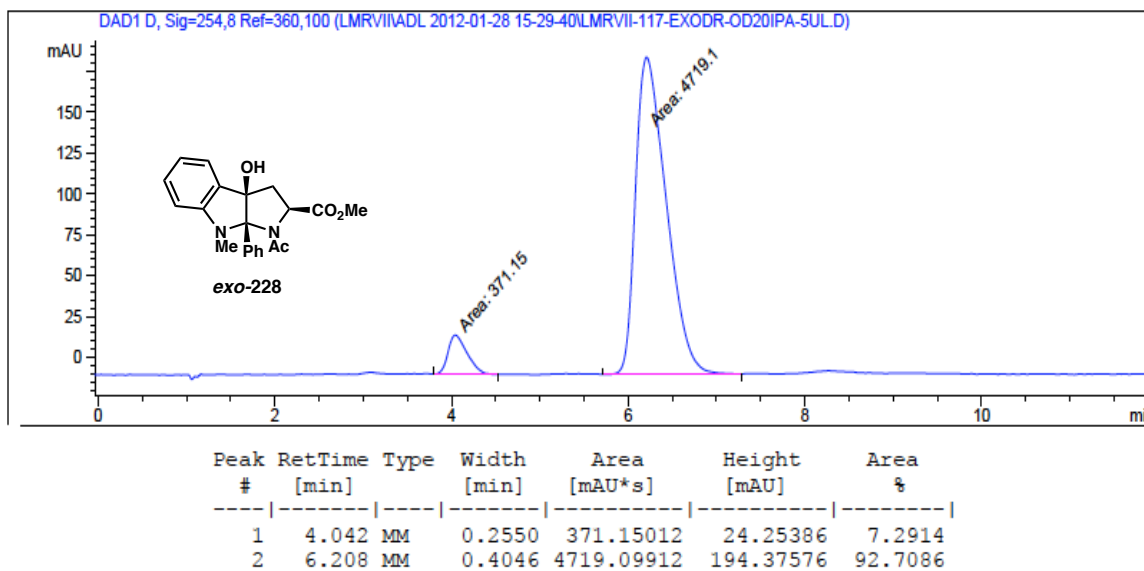
Preparation of *exo*-hydroxypyrroloindoline carboxylic acid **237.**

A solution of the 1.3:1 mixture of hydroxypyrroloindoline methyl ester **240** diastereomers (5.5 mg, 16 μ mol, 1.0 equiv) in 0.5 mL THF was cooled to 0 °C in an ice bath. LiOH (3.9 mg, 0.16 mmol, 10 equiv) was then added as a solution in 0.5 mL nanopure H₂O. After stirring 2.5 hours at 0 °C, the reaction was quenched with 3 drops 3 M HCl, diluted with 3 mL H₂O, and extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with 10 mL brine, dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (10:90 EtOAc:hexanes then 2:98 to 10:90 MeOH:DCM) to yield 1.4 mg (47% yield based on *exo*-**240**) of *exo*-hydroxypyrroloindoline carboxylic acid **237** as a yellow oil and 1.2 mg (50% recovery) of *endo*-hydroxypyrroloindoline methyl ester **240**. The enantiomeric excess of *exo*-**237** was determined to be 82% by chiral SFC analysis (OJ-H, 2.5 mL/min, 20% IPA in CO₂, λ = 254 nm): t_R (major) = 2.4 min t_R (minor) = 3.3 min. $[\alpha]_D^{25}$ (*exo*-**237**) = -99.0° (c = 0.14, MeCN). ¹H NMR spectral data for *exo*-**237** was in agreement with prior characterization and ¹H NMR data was further acquired in CDCl₃. ¹H NMR (500 MHz, CDCl₃) δ 7.66 – 7.26 (m, 7H), 6.77 (ddd, J = 7.4, 7.4, 0.9 Hz, 1H), 6.50 (ddd, J = 7.6, 0.8, 0.8 Hz, 1H), 3.44 (dd, J = 10.9, 6.0 Hz, 1H), 2.80 (s, 3H), 2.70 (dd, J = 12.4, 6.0 Hz, 1H), 2.48 (s, 3H), 2.34 (dd, J = 12.4, 10.9 Hz, 1H), 1.51 (br s, 1H).

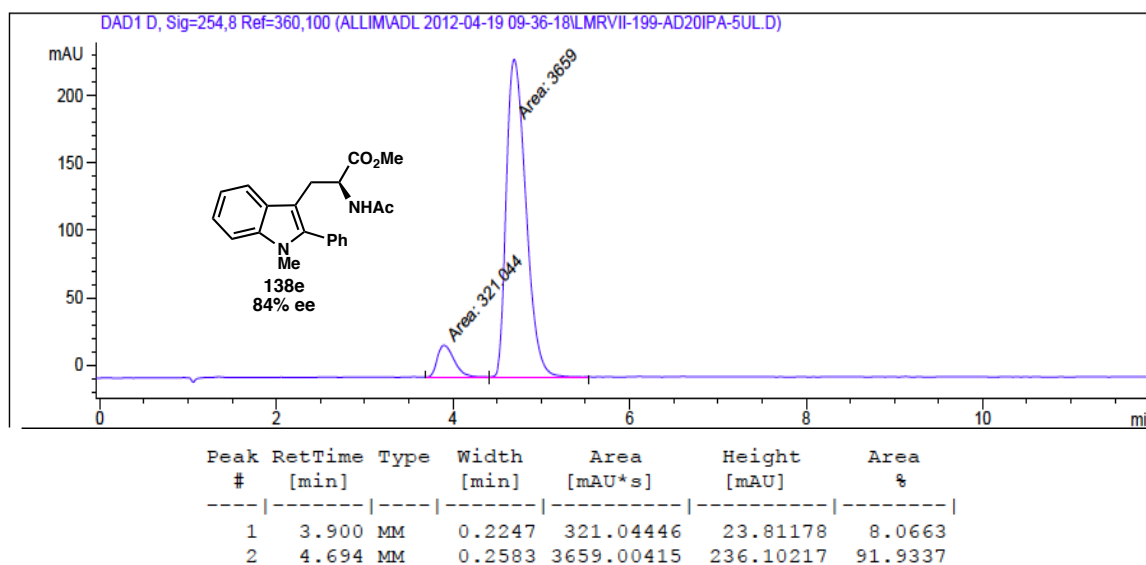
4.7.4 SFC Traces

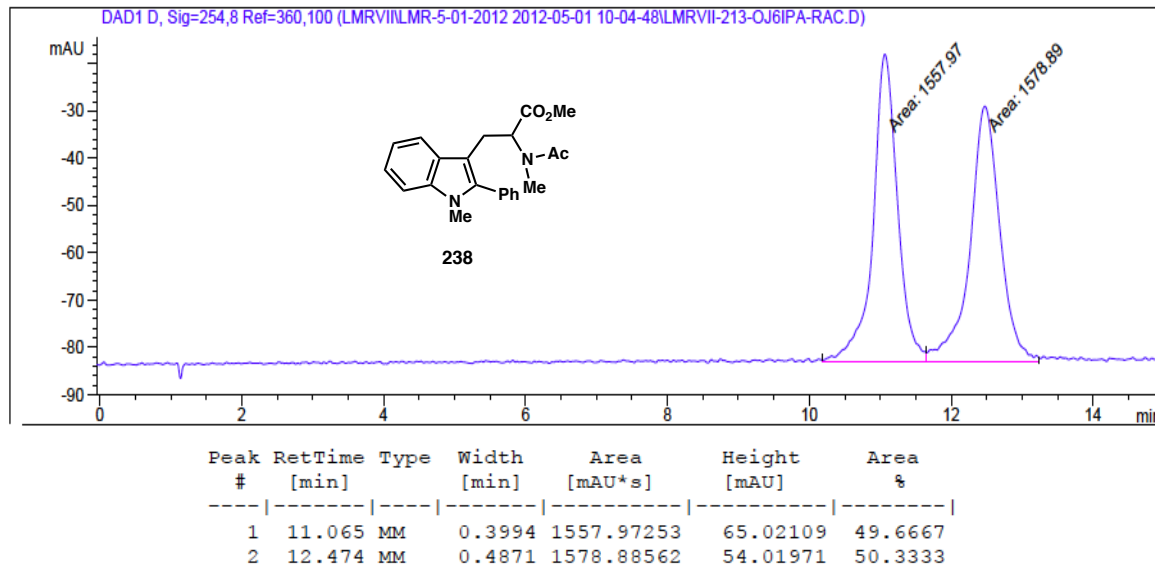
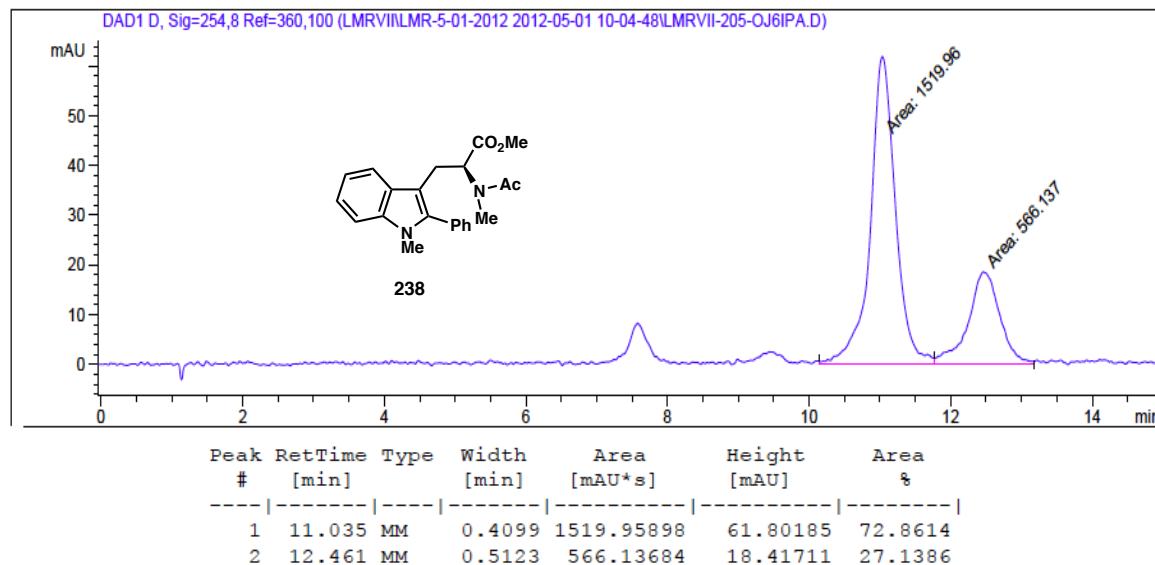
Bromoindolenine 219: 1:1 mixture of diastereomers, racemic**Bromoindolenine 219:** 1:1 mixture of diastereomers, enantioenriched, 92:90% ee

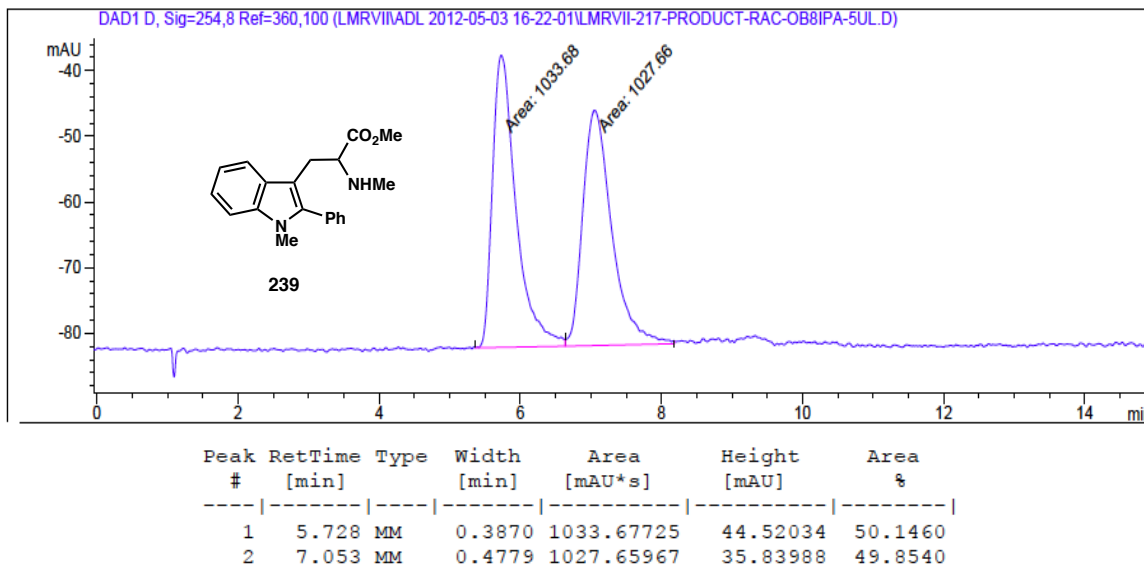
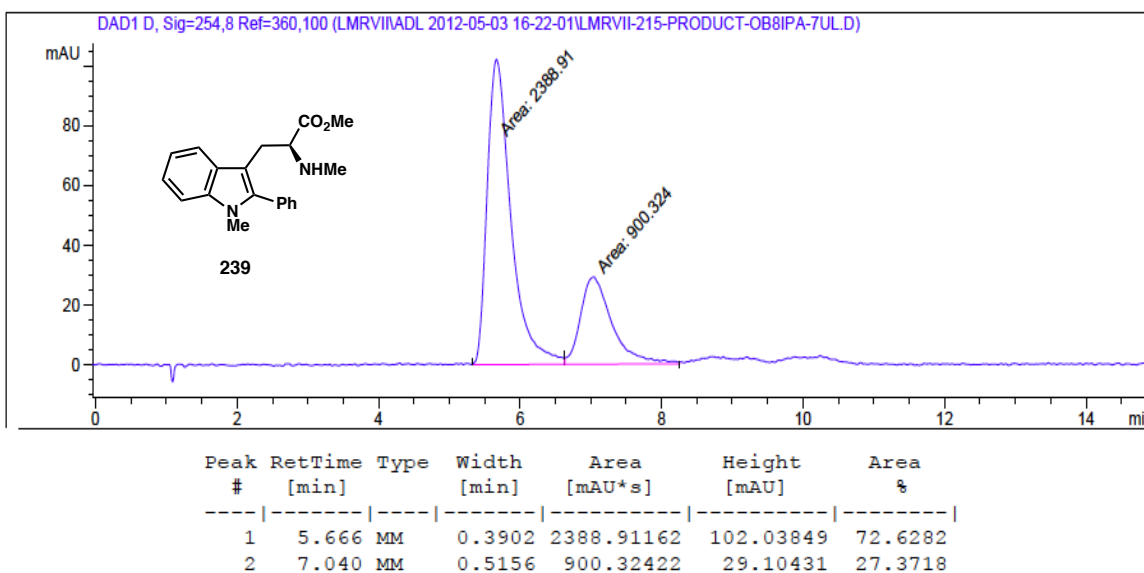
Endo-228: racemic**Endo-228:** enantioenriched, 84% ee

Exo-228: racemic**Exo-228:** enantioenriched, 85% ee

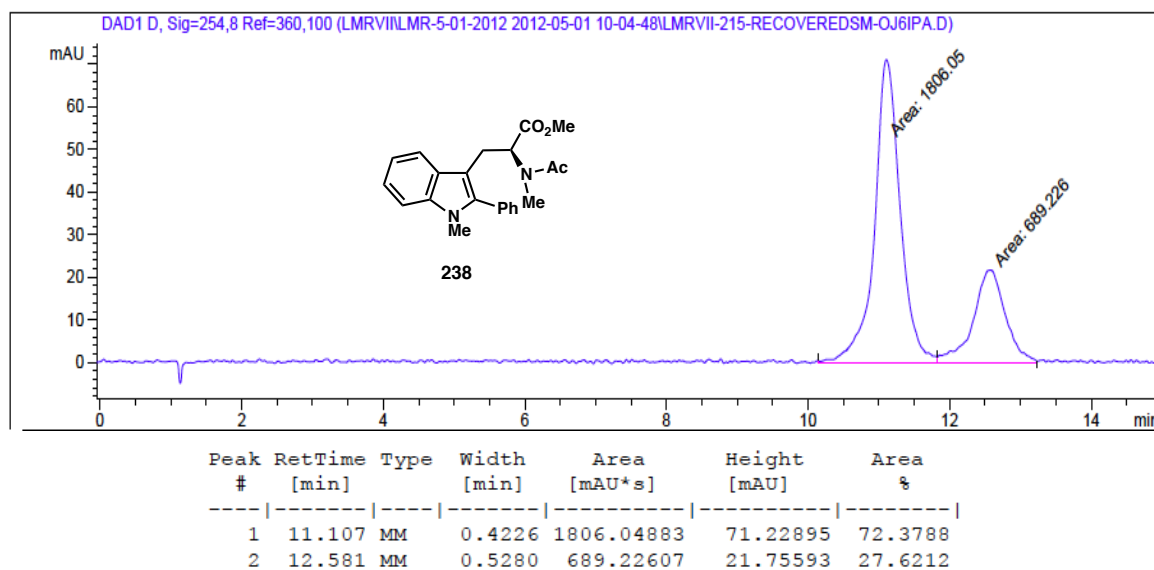
(S)-N_α-acetyl-1-methyl-2-phenyltryptophan methyl ester **138e** (scale-up procedure):
84% ee

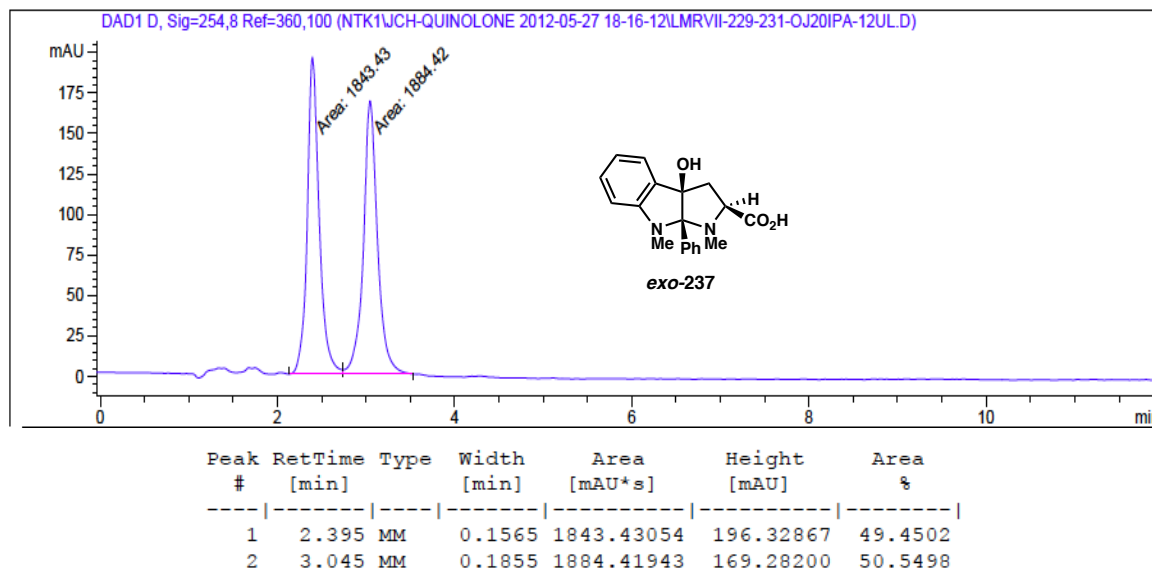
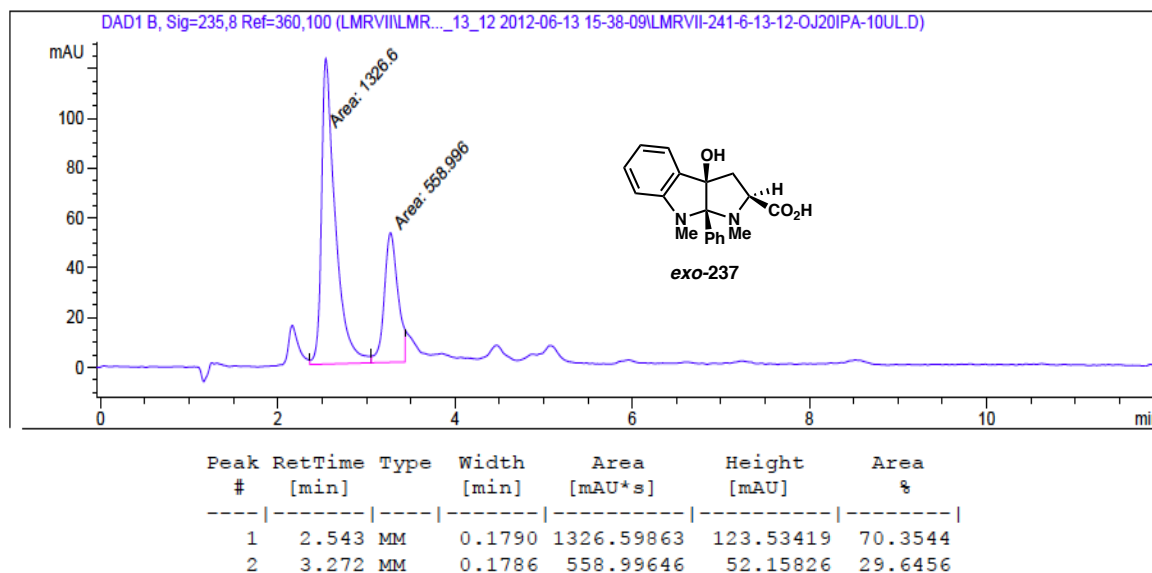


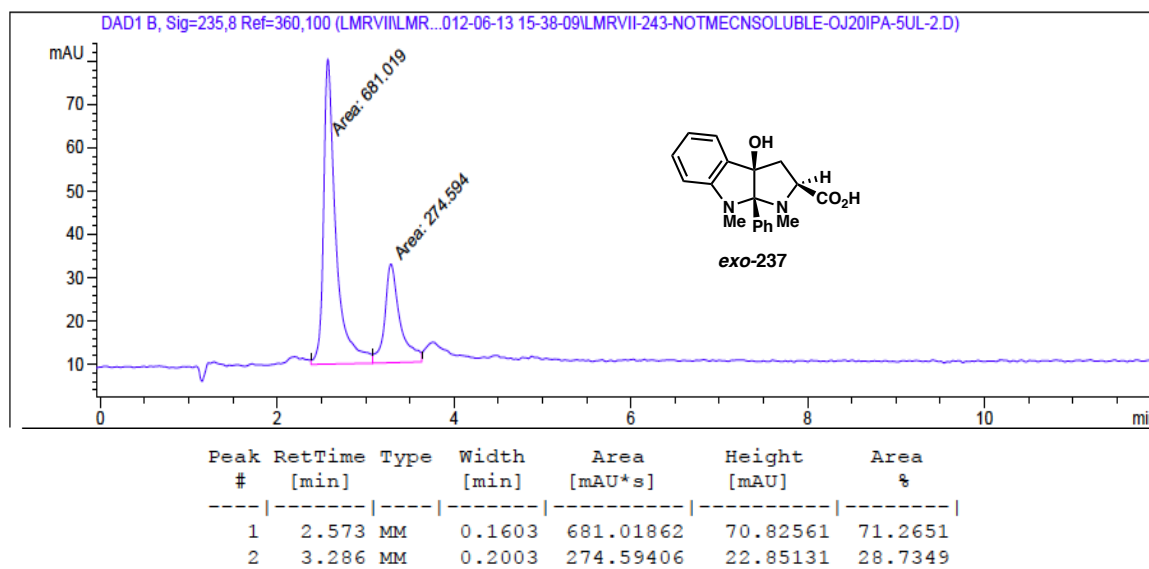
(R/S)-*N*_α-Acetyl-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (238): racemic**(S)-*N*_α-Acetyl-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (238): 46% ee**

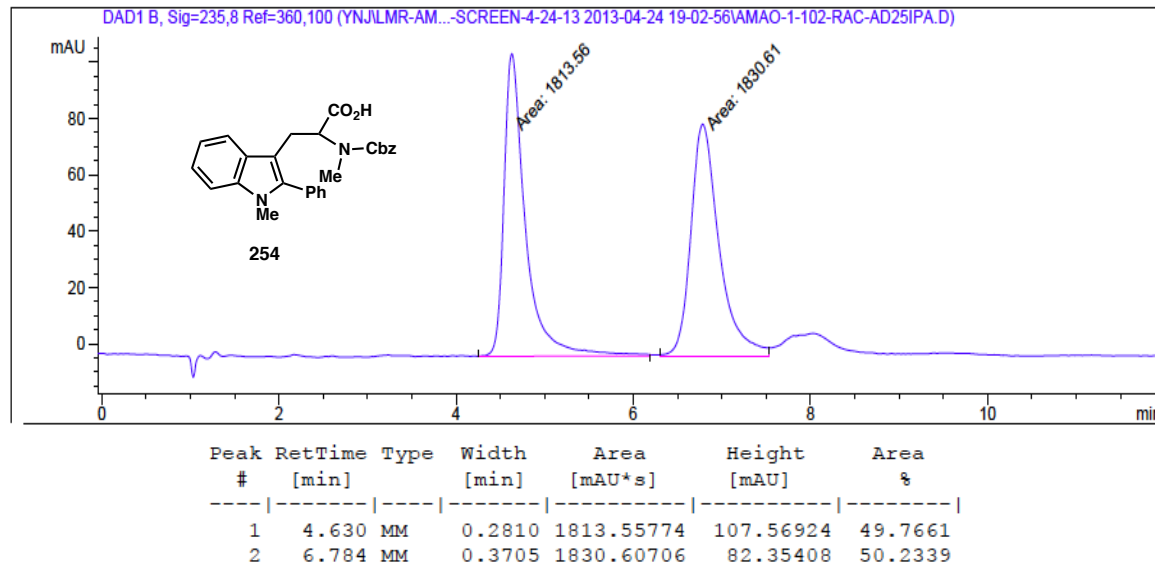
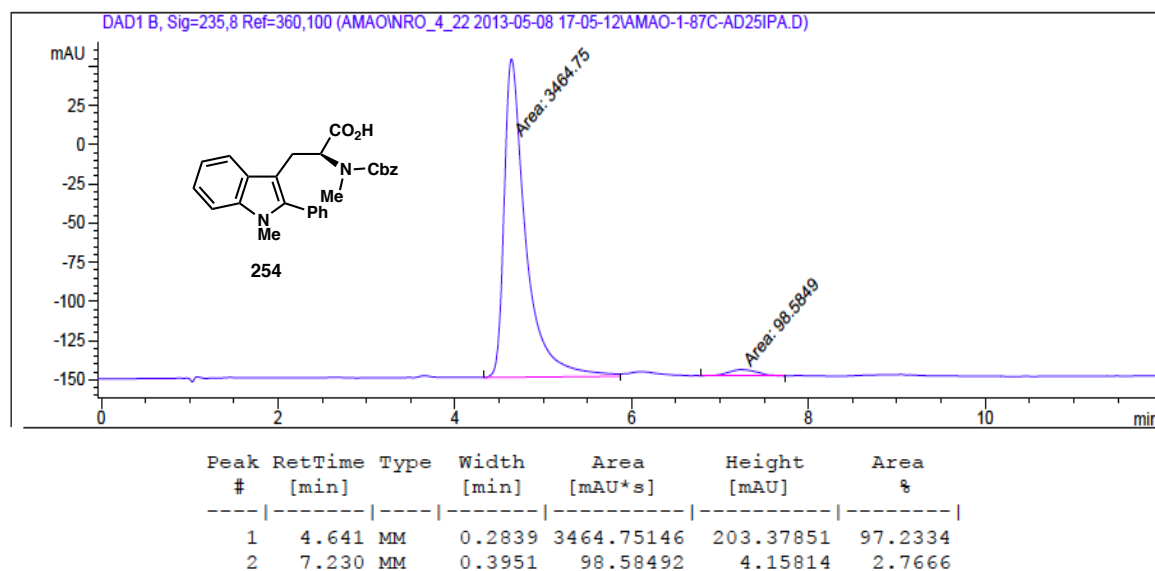
(R/S)- *N*_α,1-Dimethyl-2-phenyltryptophan methyl ester (239): racemic**(S)-*N*_α,1-Dimethyl-2-phenyltryptophan methyl ester (239): 45% ee**

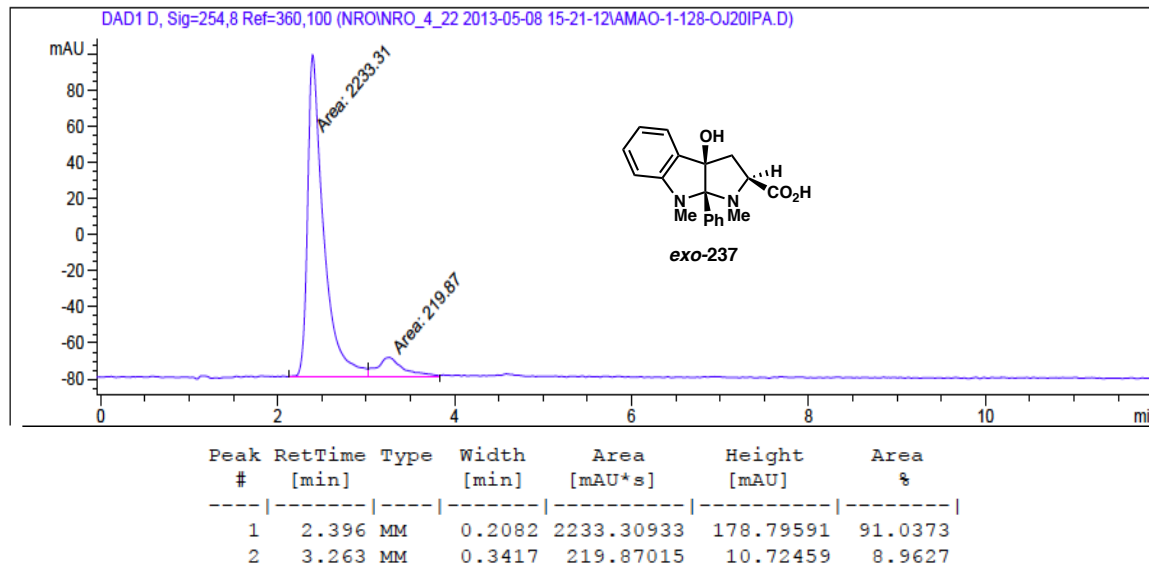
(S)-N_α-Acetyl-N_α,1-dimethyl-2-phenyltryptophan methyl ester (238, recovered starting material): 45% ee



Exo-hydroxypyrroloindoline carboxylic acid 237: racemic**Exo-hydroxypyrroloindoline carboxylic acid 237: 41% ee (first generation synthesis)**

Exo-hydroxypyrroloindoline carboxylic acid 237: 43% ee (from *endo*-240)

(*R/S*)-*N* $_{\alpha}$ -Cbz-*N* $_{\alpha}$,1-dimethyl-2-phenyltryptophan (254): racemic**(*S*)-*N* $_{\alpha}$ -Cbz-*N* $_{\alpha}$,1-dimethyl-2-phenyltryptophan (254): 94% ee**

Exo-hydroxypyrroloindoline carboxylic acid 237: 82% ee (2nd generation synthesis)

4.8 NOTES AND REFERENCES

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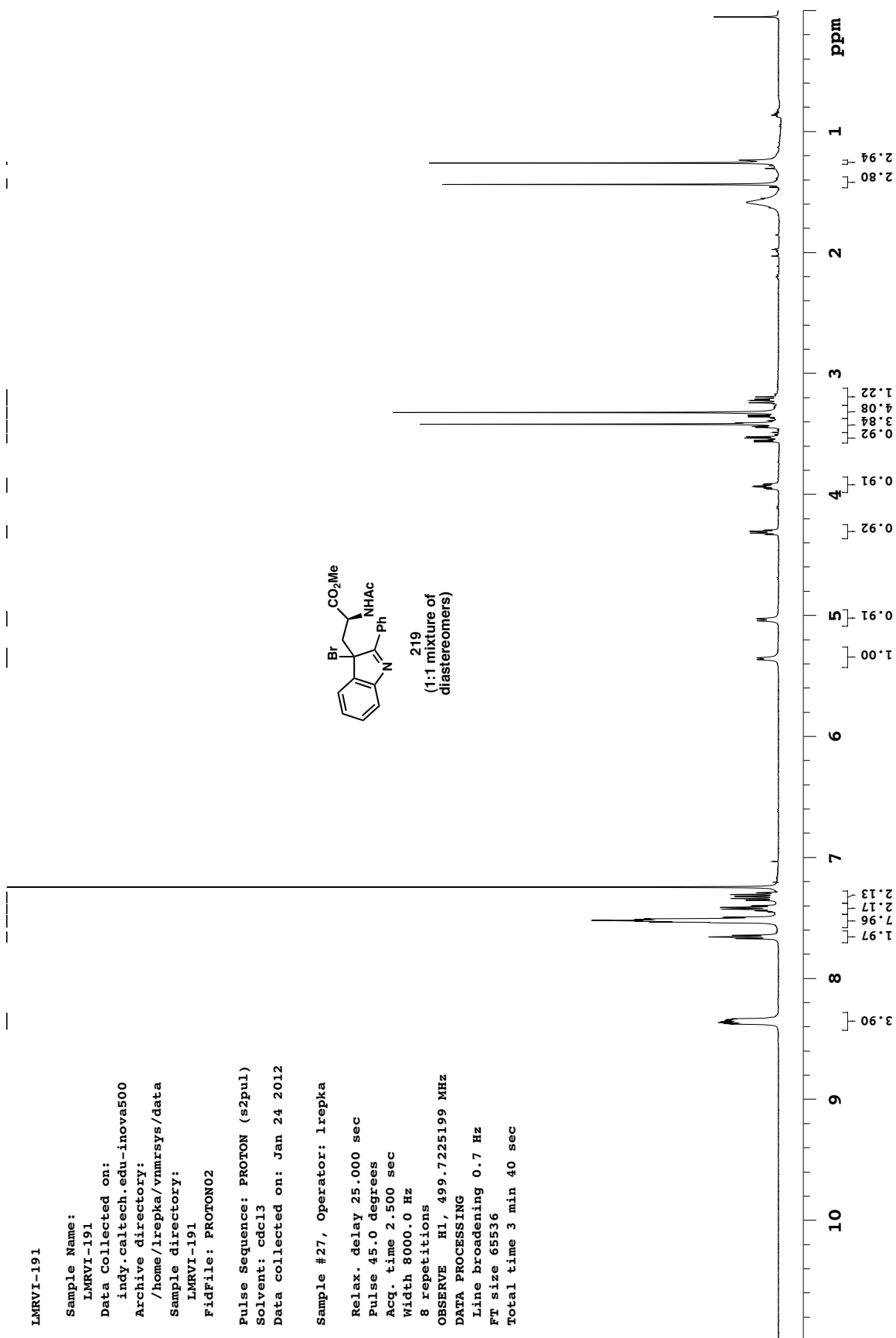
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- (41) Kleijn, L. H. J.; Müskens, F. M.; Oppedijk, S. F.; de Bruin, G.; Martin, N. I. *Tetrahedron Lett.* **2012**, *53*, 6430.

APPENDIX 4

Spectra Relevant to Chapter 4:

*Access to 2a-Phenylpyrroloindolines
by an Oxidative Cyclization Reaction*



LMRVI-191

Sample Name:

LMRVI-191

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVI-191

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Aug 11 2011

Sample #23, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1500 repetitions

OBSERVE C13, 125.6553310 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

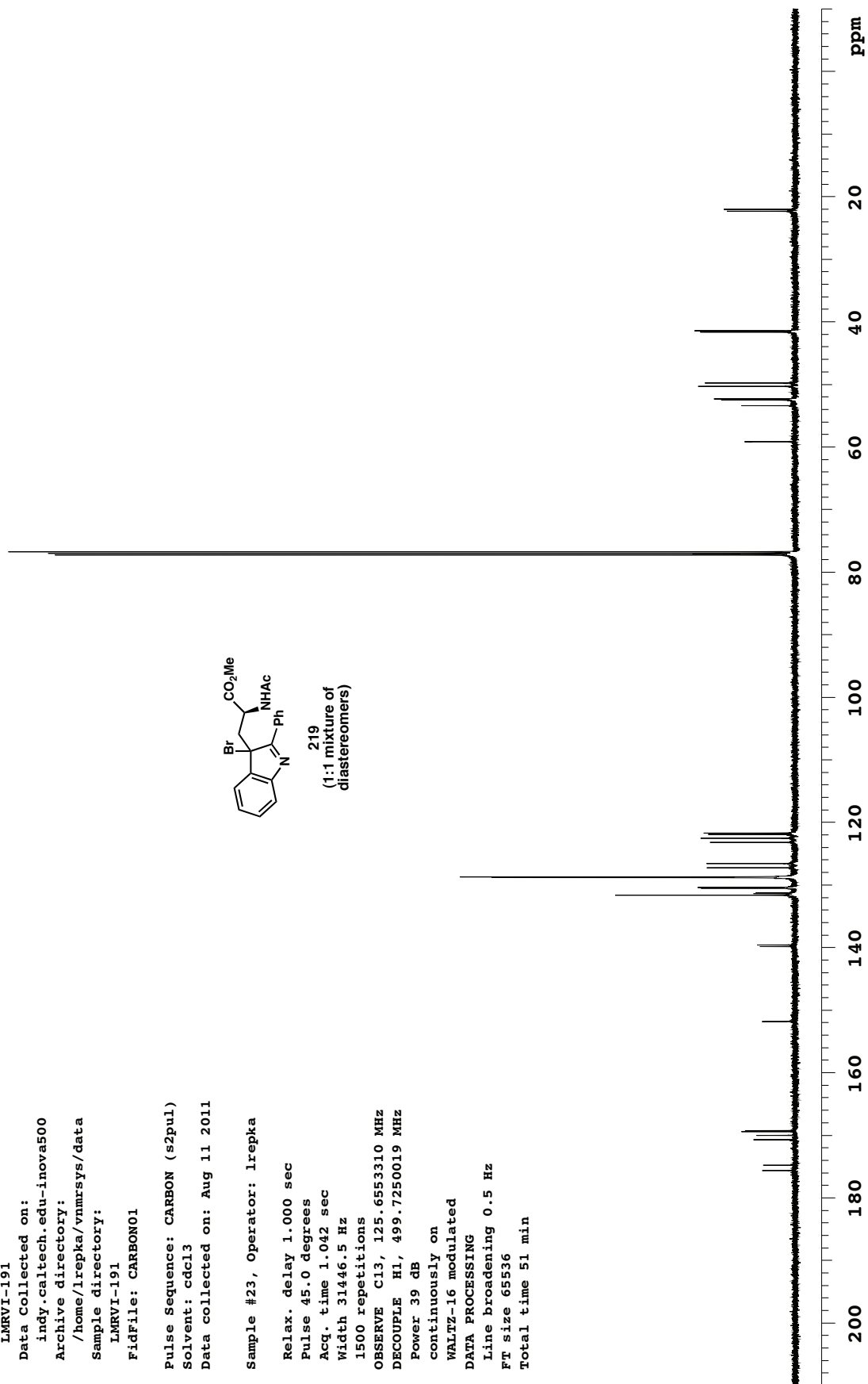
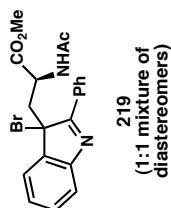
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 51 min



LMRVII-31

Sample Name:

LMRVII-31

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVII-31

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Feb 19 2012

Sample #27, Operator: lrepka

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

8 repetitions

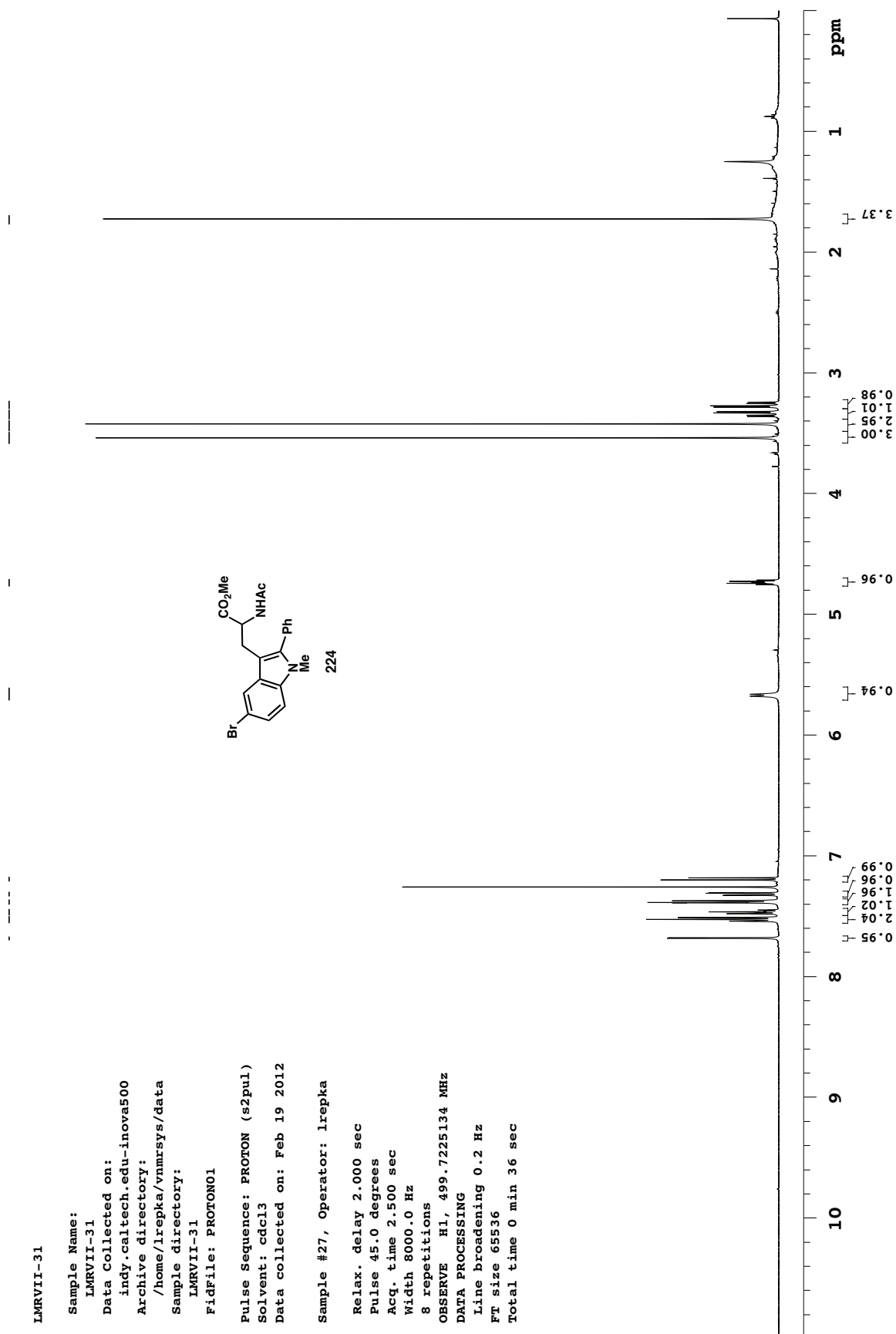
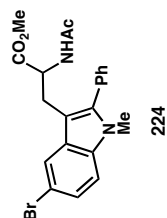
OBSERVE H1, 499.7225134 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 0 min 36 sec



LMRVII-31

Sample Name:

LMRVII-31
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-31
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

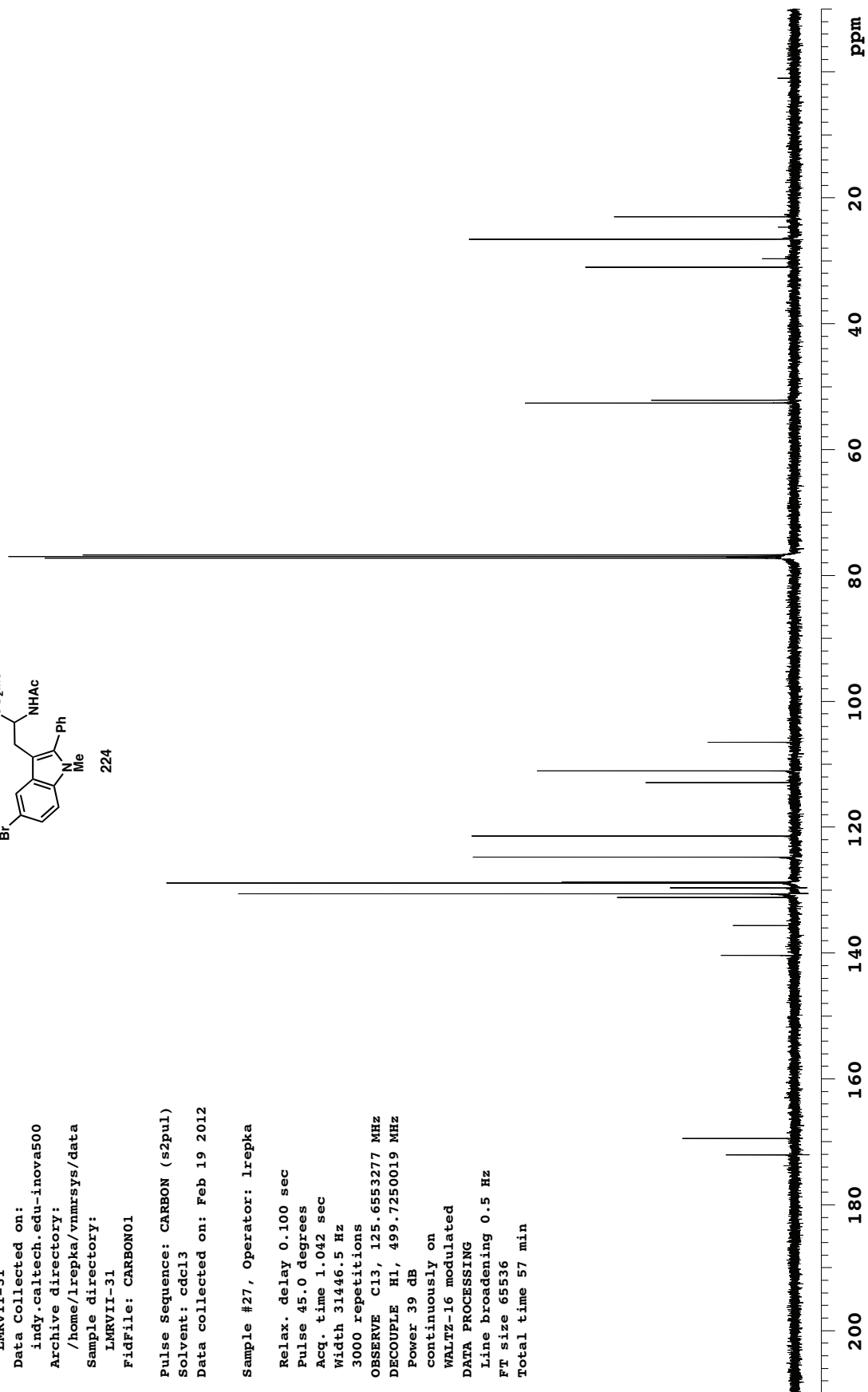
Solvent: cdcl3
Data collected on: Feb 19 2012

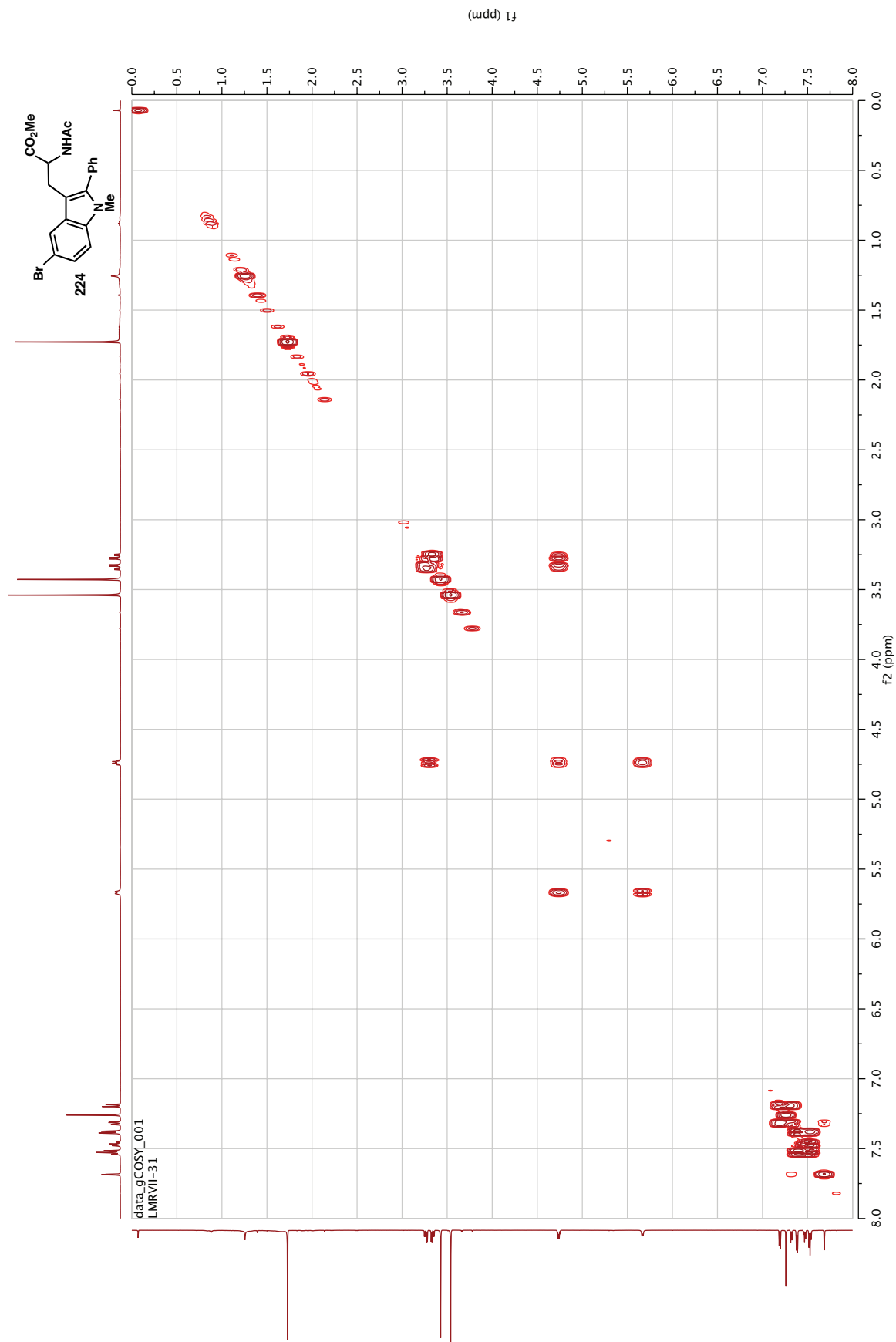
Sample #27, Operator: lrepka

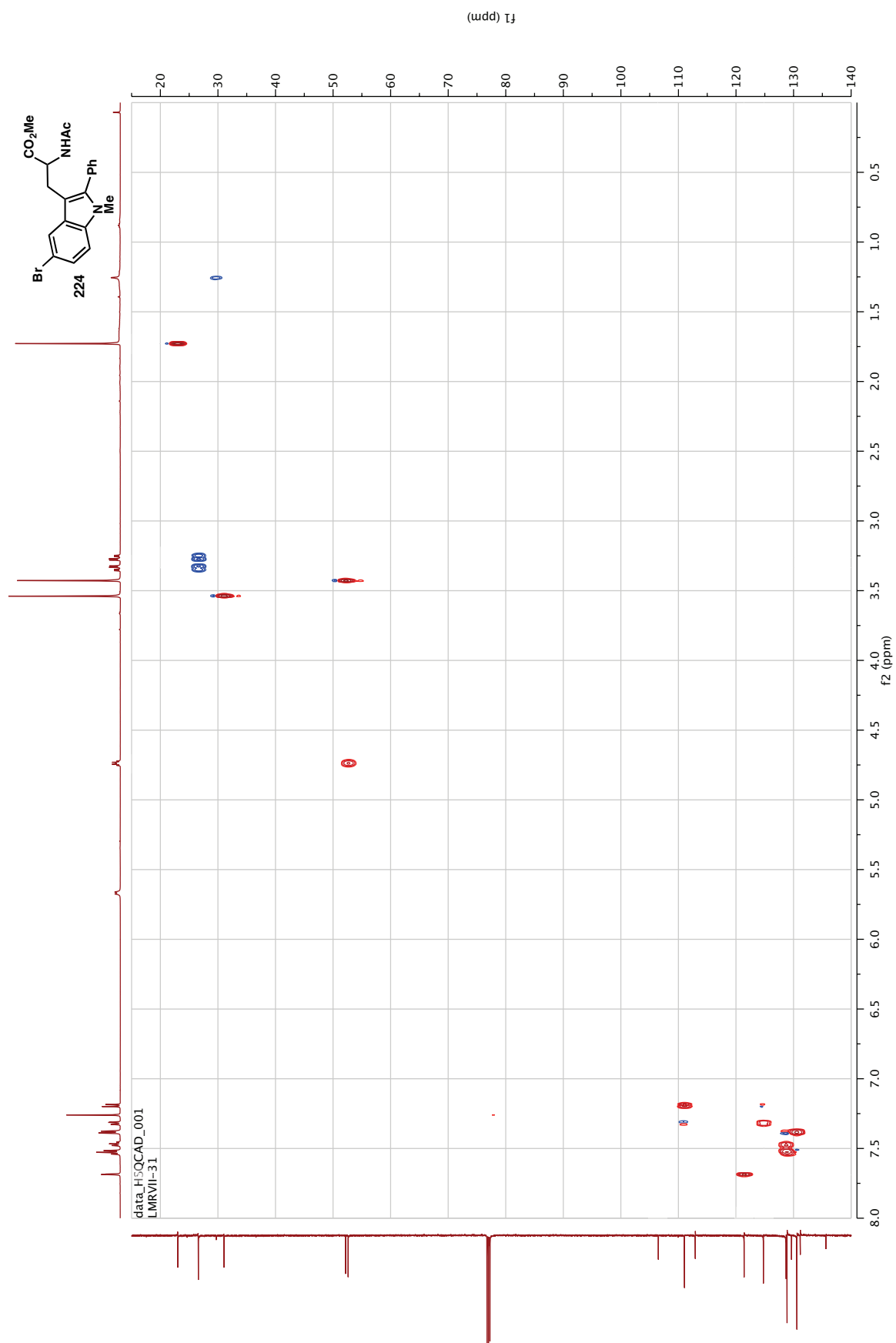
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3000 repetitions
OBSERVE C13, 125.6553277 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 57 min

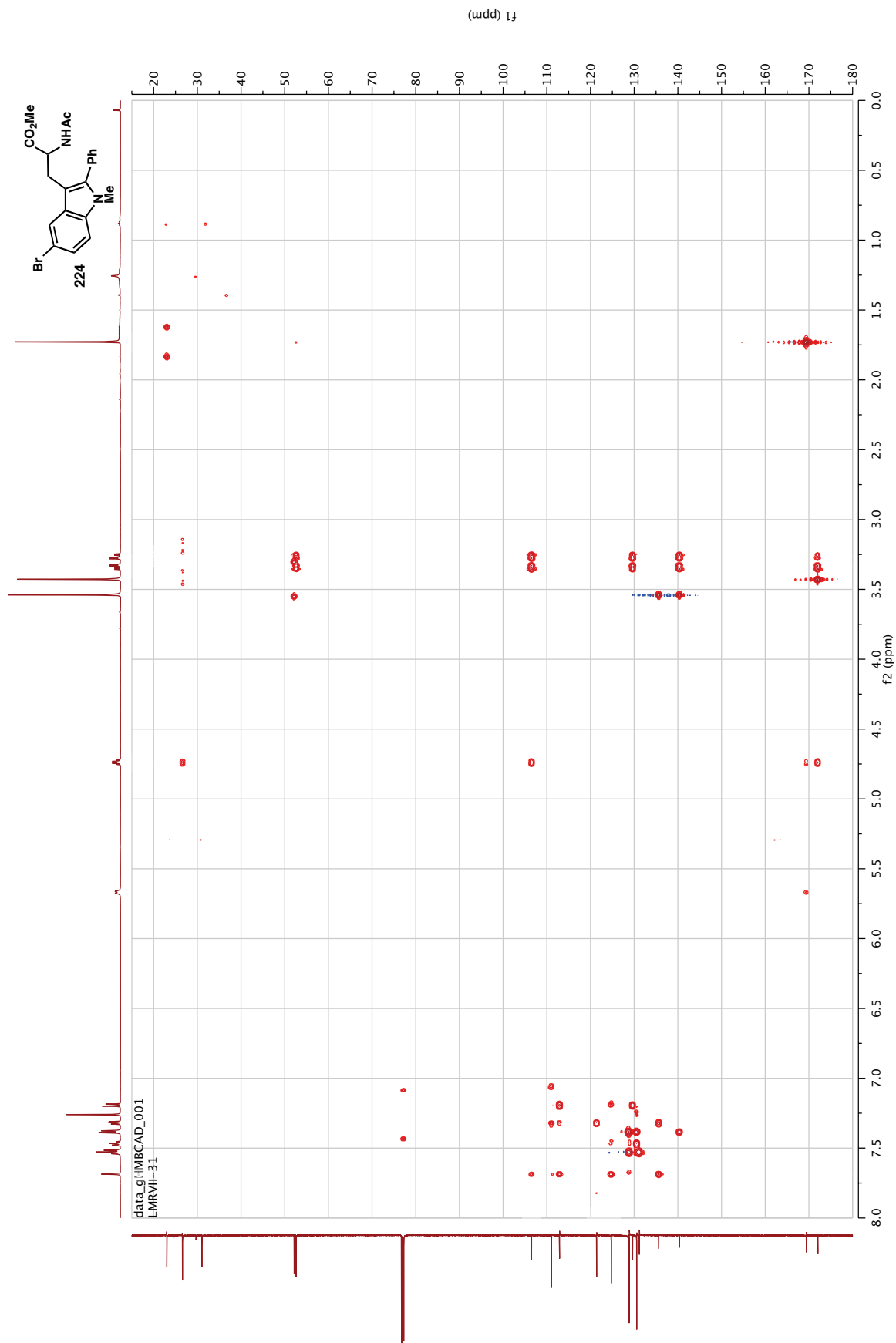


224





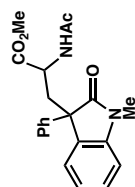




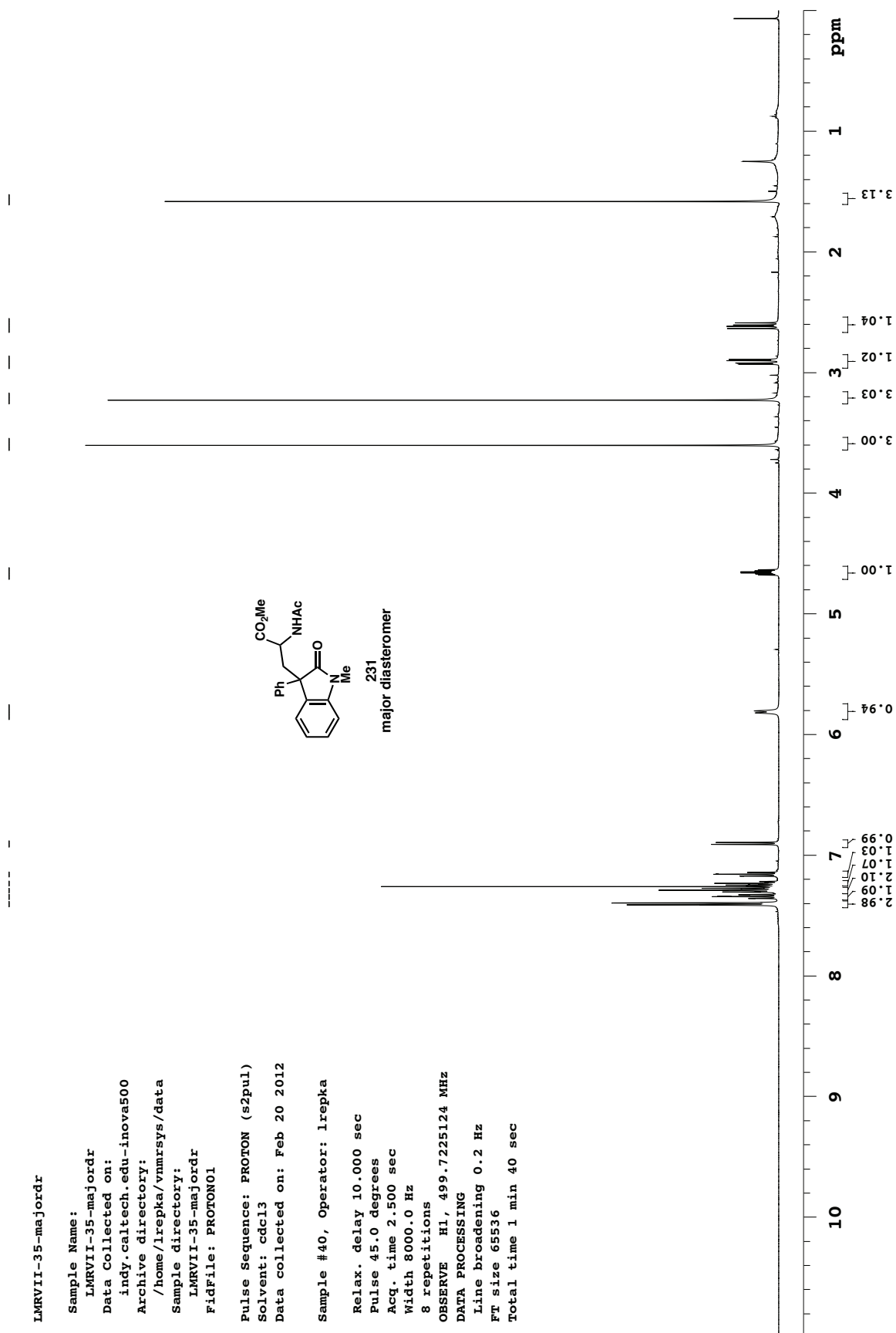
```

Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225124
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 40 sec

```



231
major diastomer



LMRVII-35-majordr

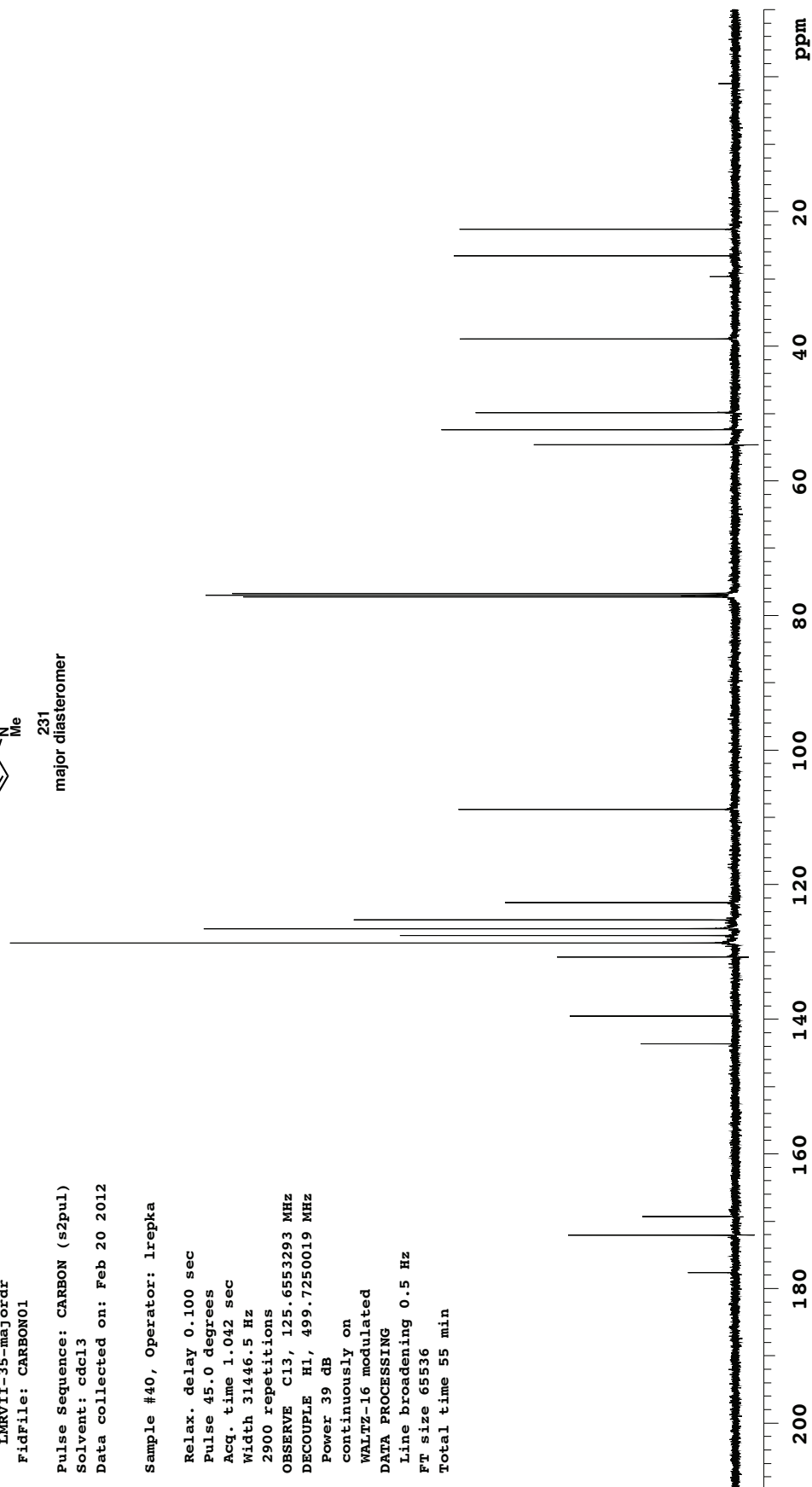
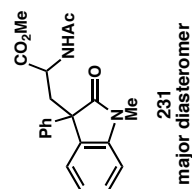
Sample Name:

LMRVII-35-majordr
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-35-majordr
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 20 2012

Sample #40, Operator: lrepka

Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2900 repetitions
OBSERVE C13, 125.6553293 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 55 min



LMRVII-35-minordr

Sample Name:

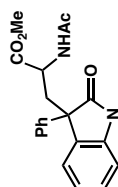
LMRVII-35-minordr
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-35-minordr
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 21 2012

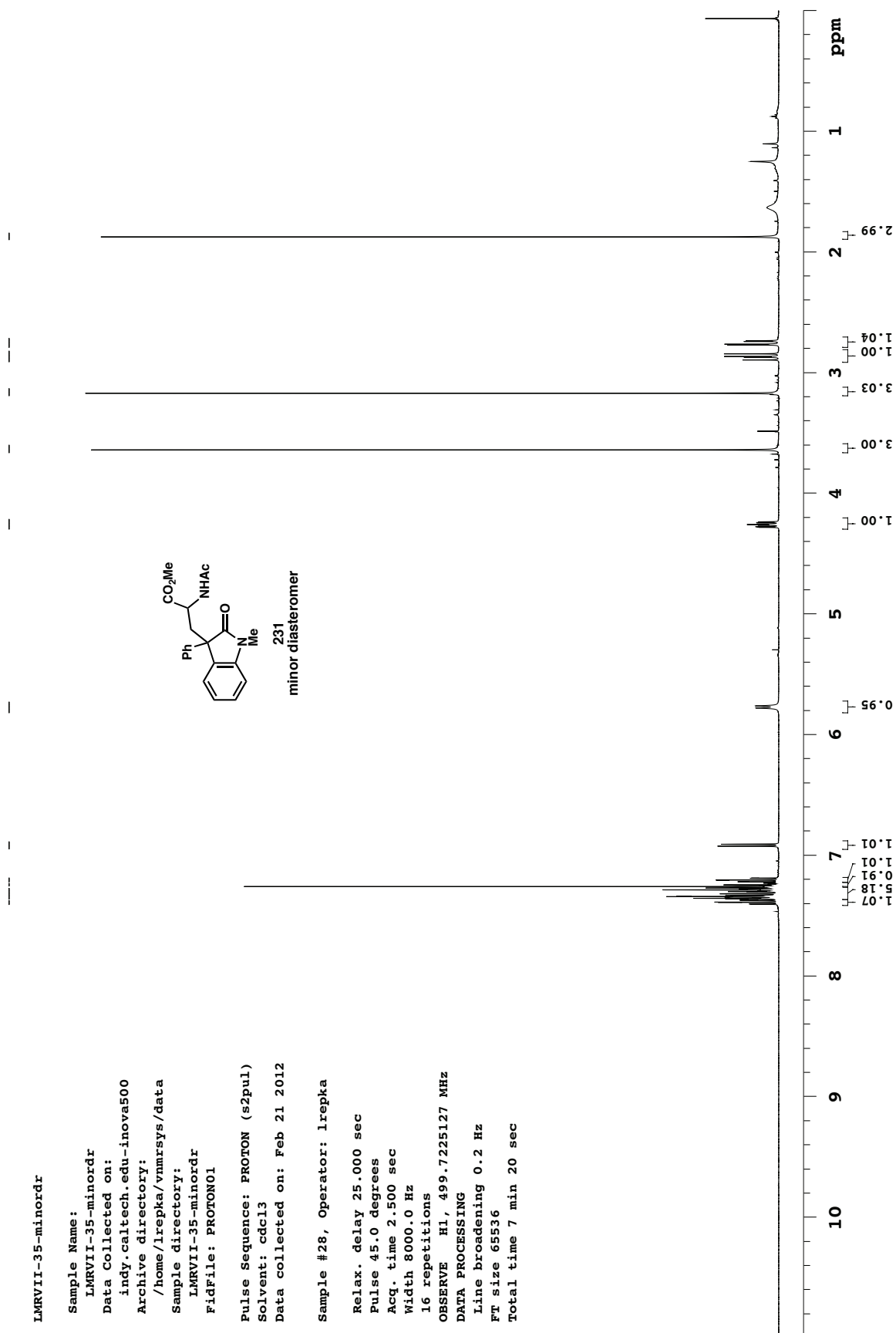
Sample #28, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz

16 repetitions
OBSERVE H1, 499.7225127 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 7 min 20 sec



231
minor diastereomer



LMRVII-35-minordr

Sample Name:

LMRVII-35-minordr

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVII-35-minordr

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Feb 21 2012

Sample #28, Operator: lrepka

Relax. delay 0.100 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

24000 repetitions

OBSERVE C13, 125.6553287 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

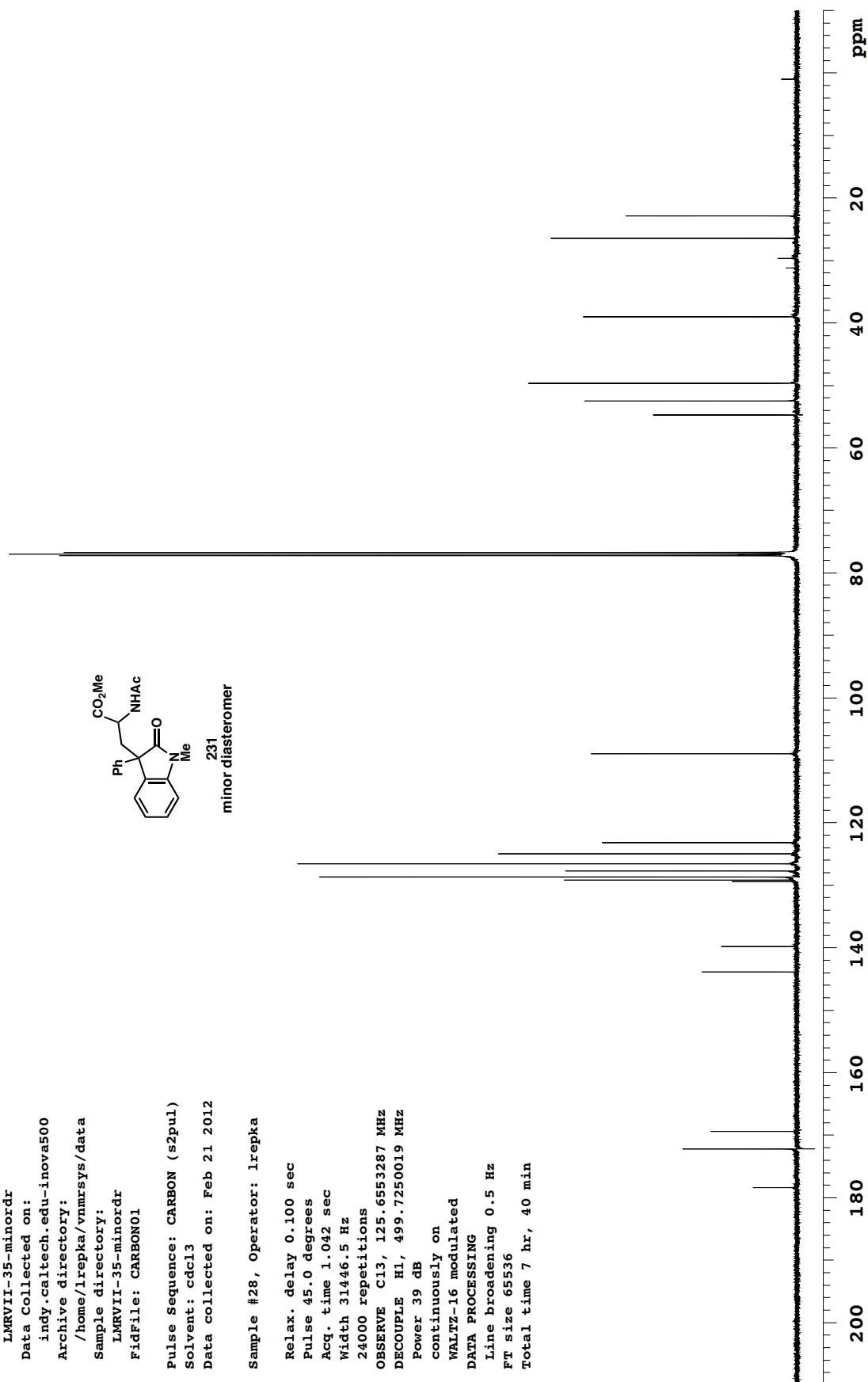
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 7 hr, 40 min



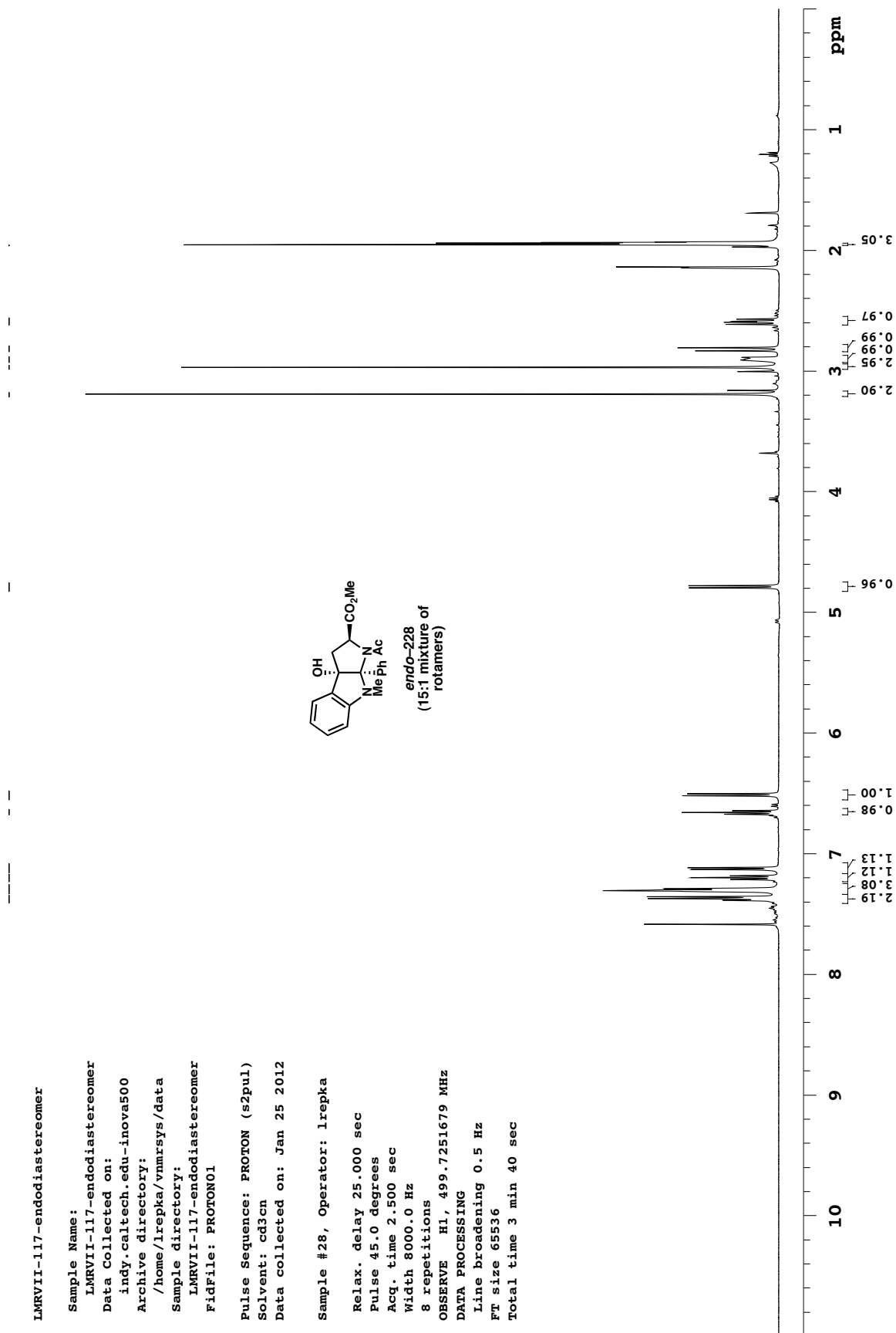
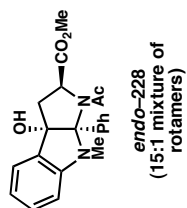
LMRVII-117-endodiastereomer

Sample Name:
LMRVII-117-endodiastereomer
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-117-endodiastereomer
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jan 25 2012

Sample #28, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7251679 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 min 40 sec



LMRVII-117-endodiastereomer

Sample Name:

LMRVII-117-endodiastereomer

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrSYS/data

Sample directory:

LMRVII-117-endodiastereomer

FidFile: CARBON02

Pulse Sequence: CARBON (s2pul)

Solvent: cd3cn

Data collected on: Jan 25 2012

Sample #20, Operator: lrepka

Relax. delay 0.100 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1900 repetitions

OBSERVE C13, 125.6558756 MHz

DECOUPLE H1, 499.7276454 MHz

Power 39 dB

continuously on

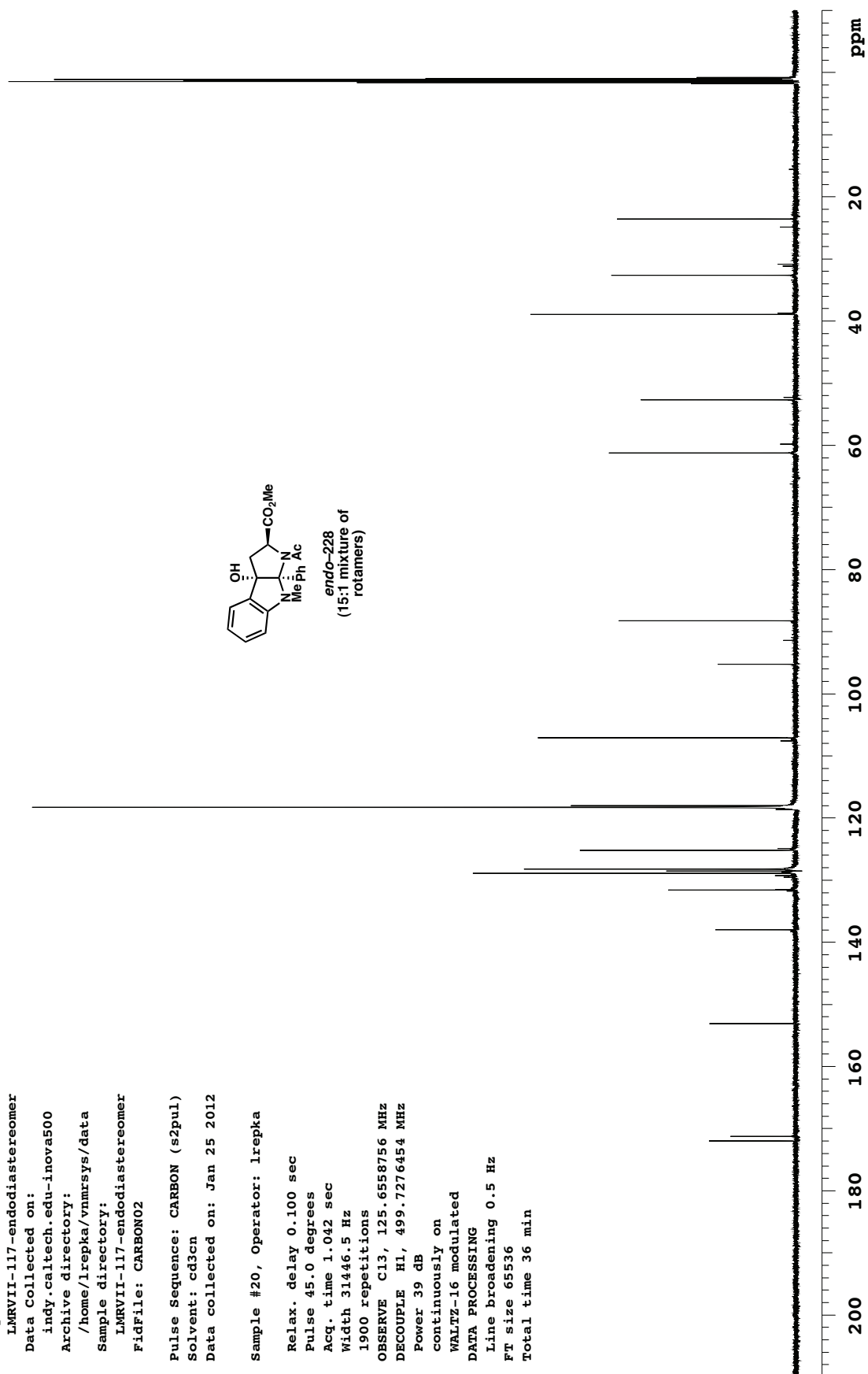
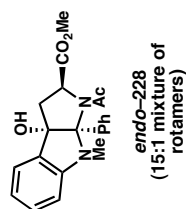
WALTZ-16 modulated

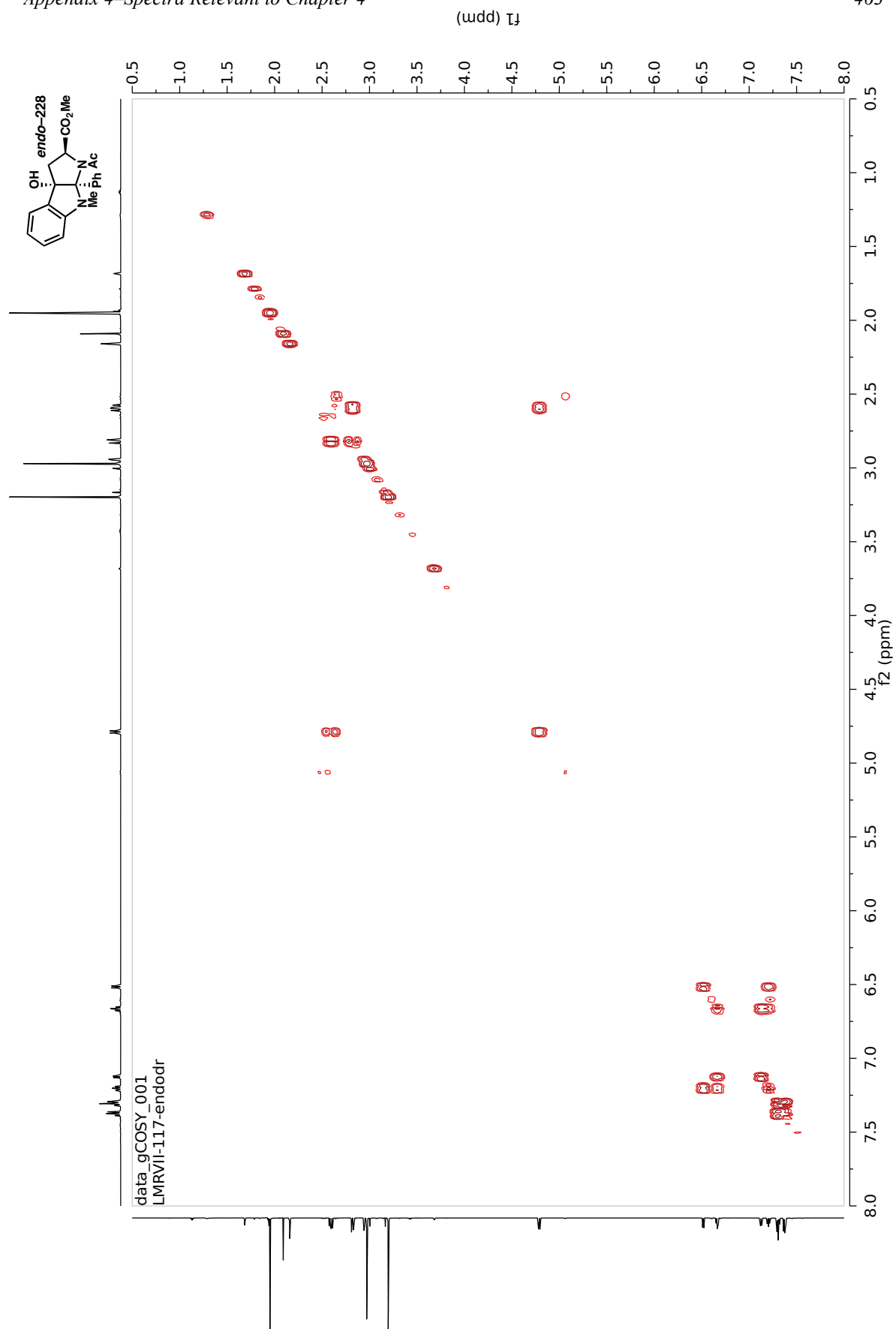
DATA PROCESSING

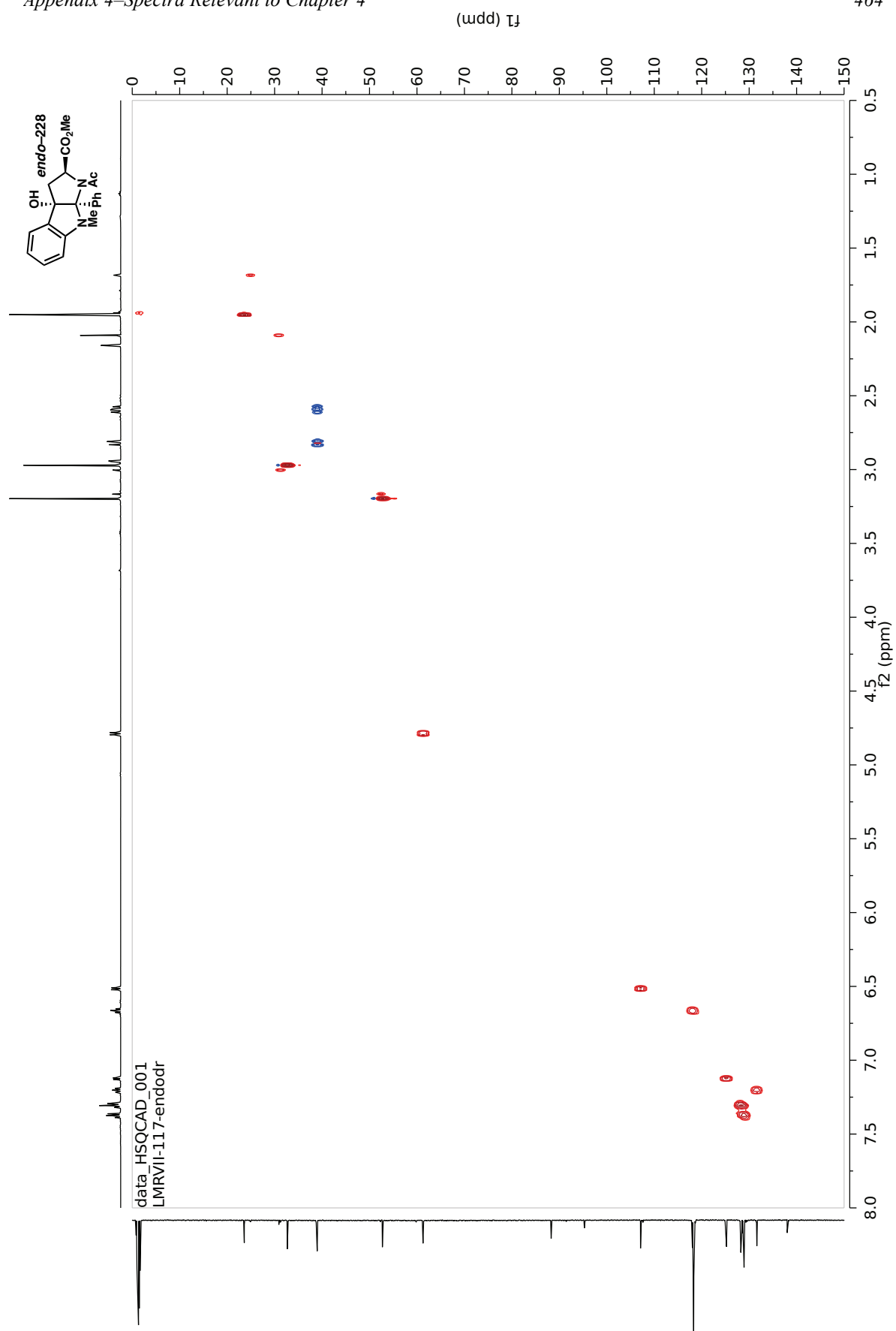
Line broadening 0.5 Hz

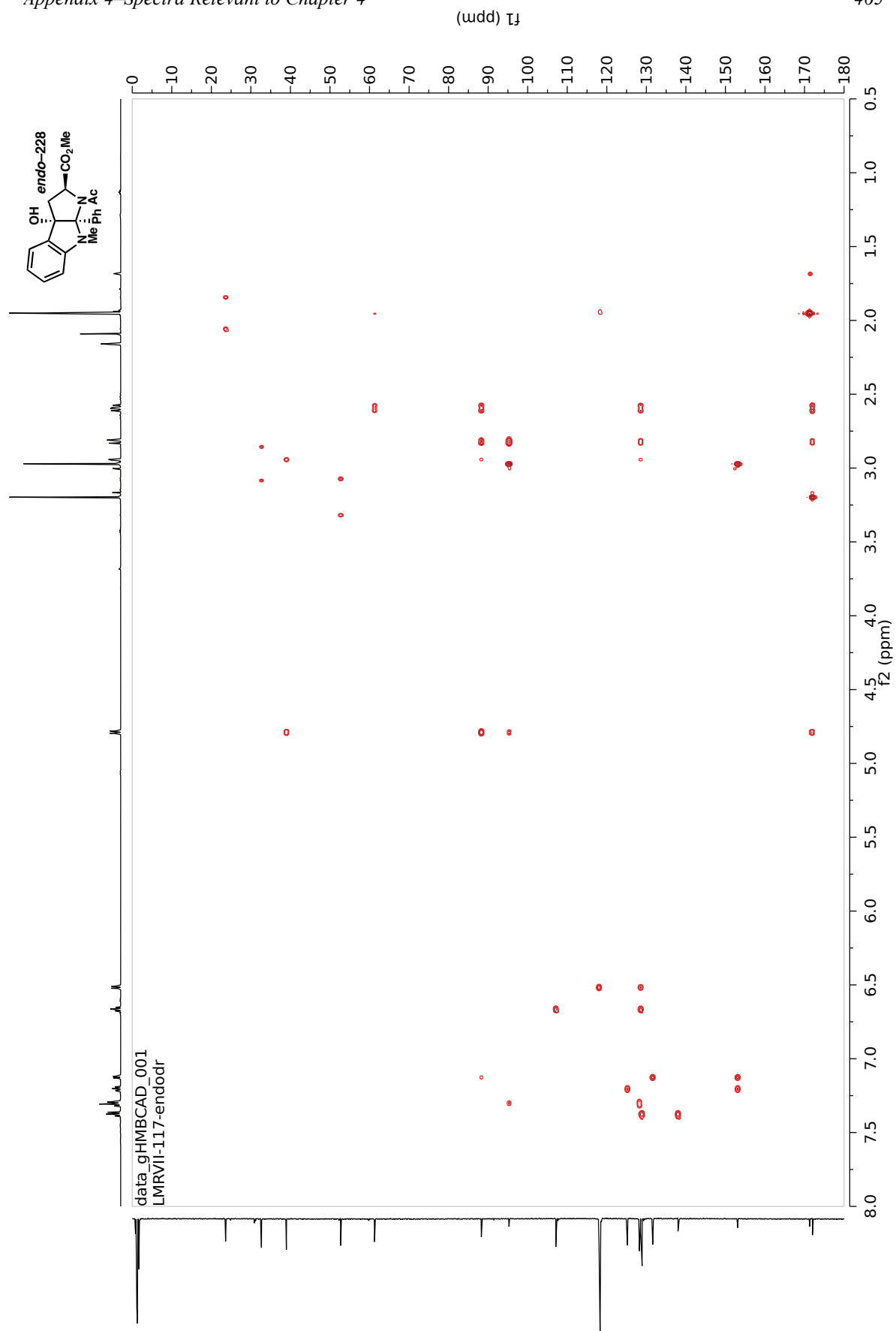
FT size 65536

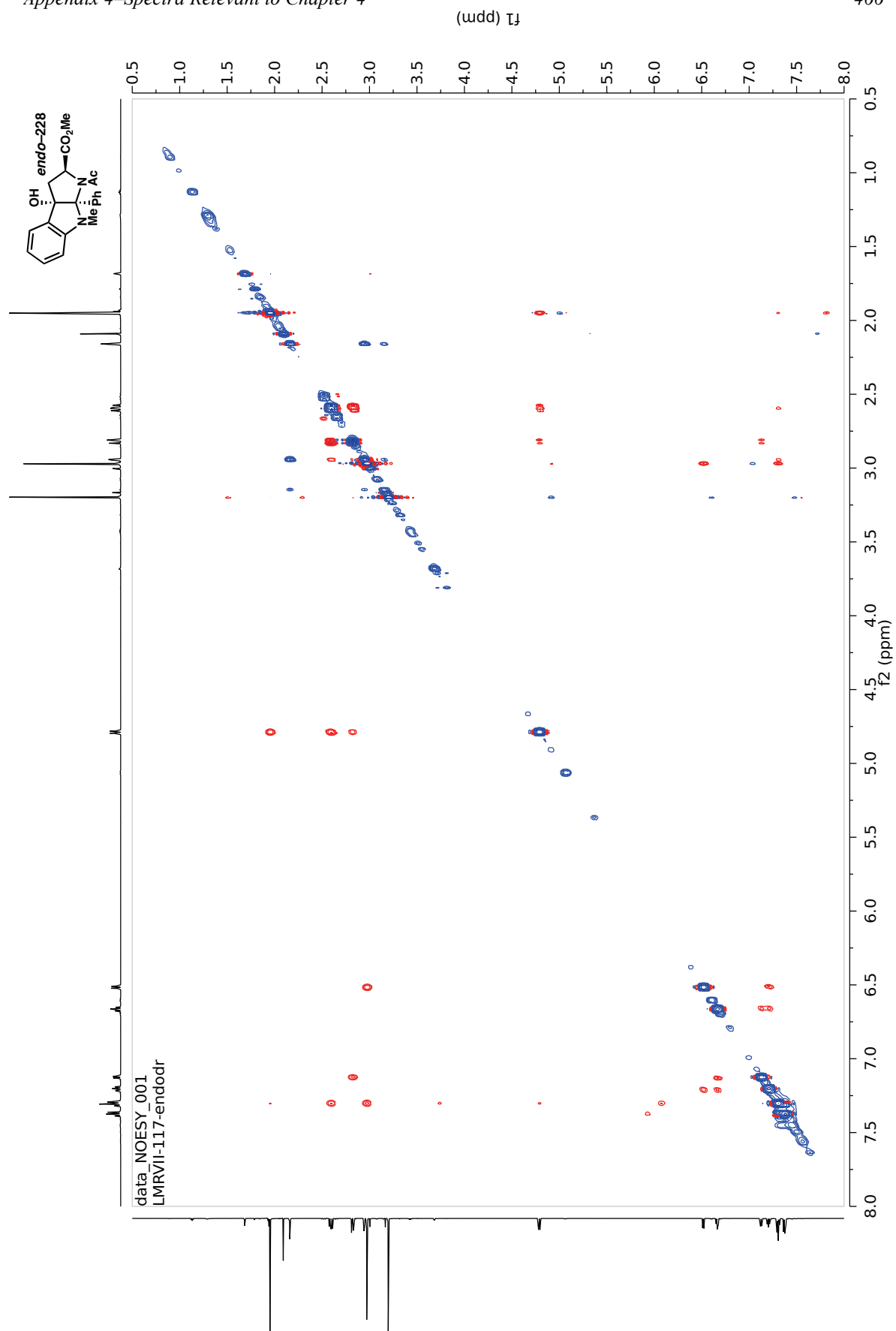
Total time 36 min



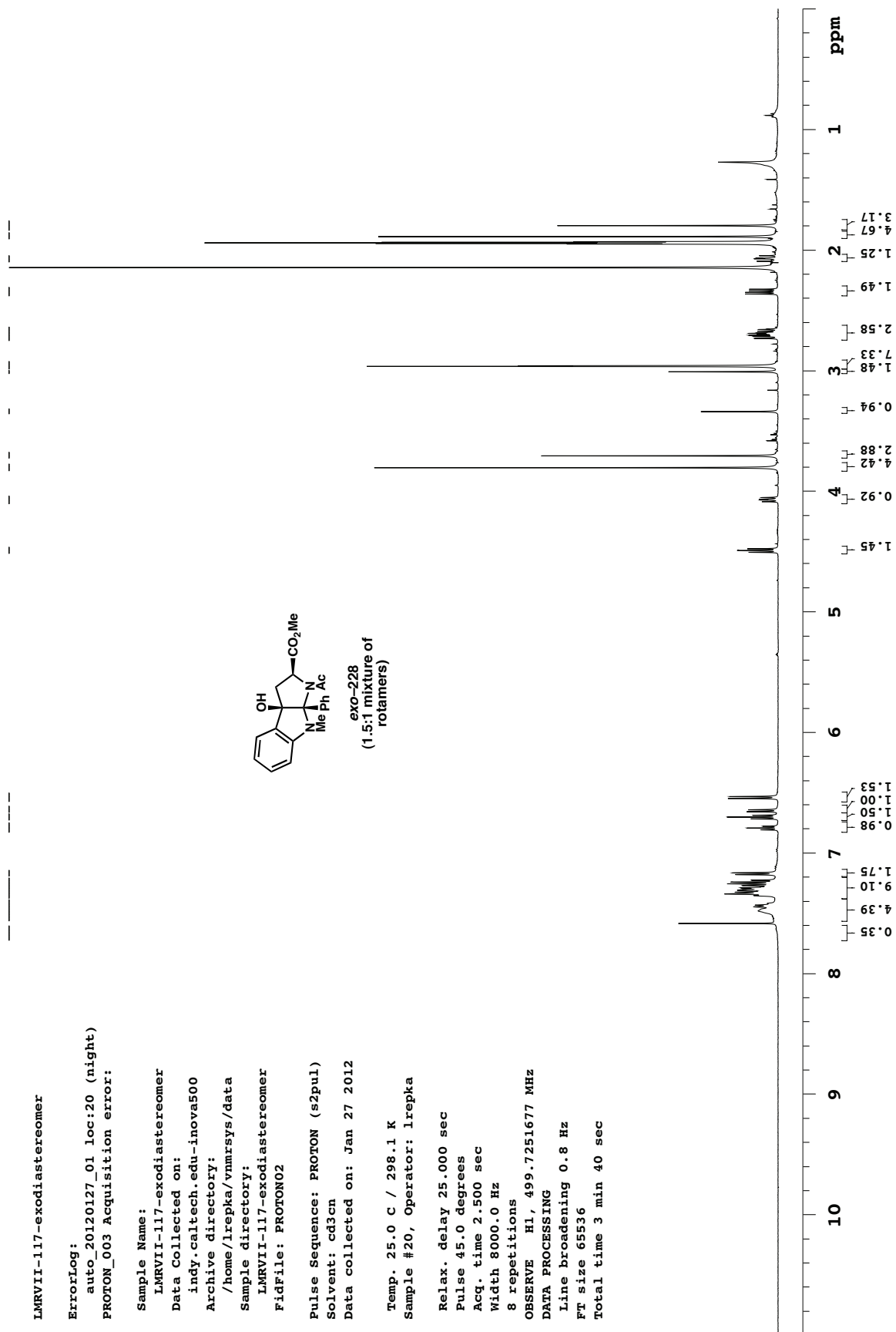








OBSERVE H1, 499.7251677 MHz
 DATA PROCESSING
 Line broadening 0.8 Hz
 FT size 65536
 Total time 3 min 40 sec



LMRVII-117-exodiastereomer

ErrorLog:

auto_20120127_01_loc:20 (night)
 PROTON_003 Acquisition error:
 CARBON_001 Acquisition error:

Sample Name:

LMRVII-117-exodiastereomer
 Data Collected on:
 indy.caltech.edu-inova500
 Archive directory:
 /home/lrepka/vnmrsys/data
 Sample directory:
 LMRVII-117-exodiastereomer
 FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
 Solvent: cd3cn
 Data collected on: Jan 27 2012

Temp. 25.0 C / 298.1 K
 Sample #20, Operator: lrepka

Relax. delay 0.100 sec
 Pulse 45.0 degrees
 Acq. time 1.042 sec
 Width 31446.5 Hz
 24300 repetitions

OBSERVE C13, 125.6558731 MHz
 DECOUPLE H1, 499.7276454 MHz

Power 39 dB
 continuously on

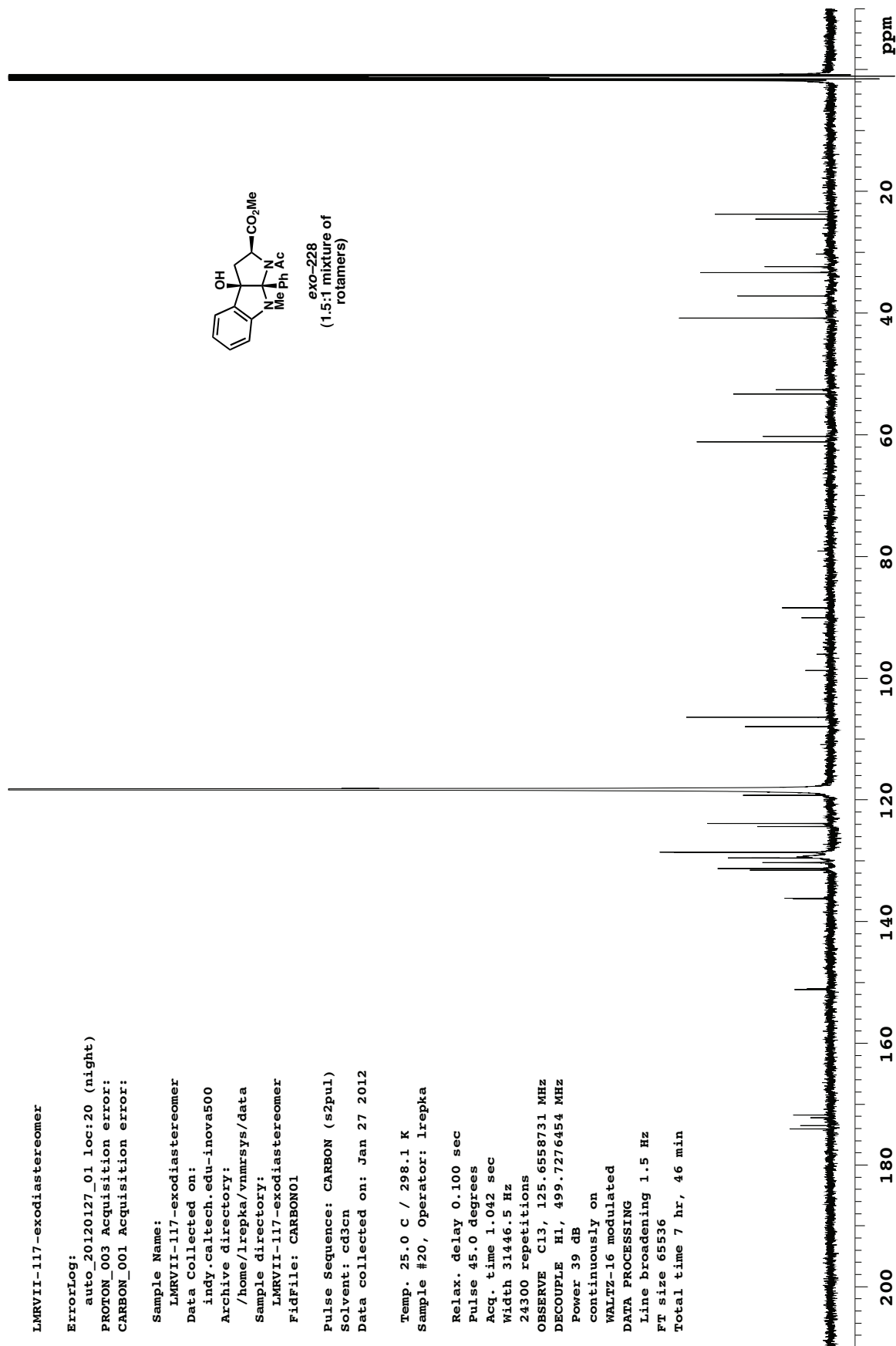
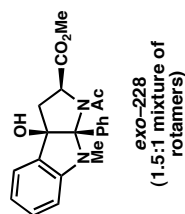
WALTZ-16 modulated

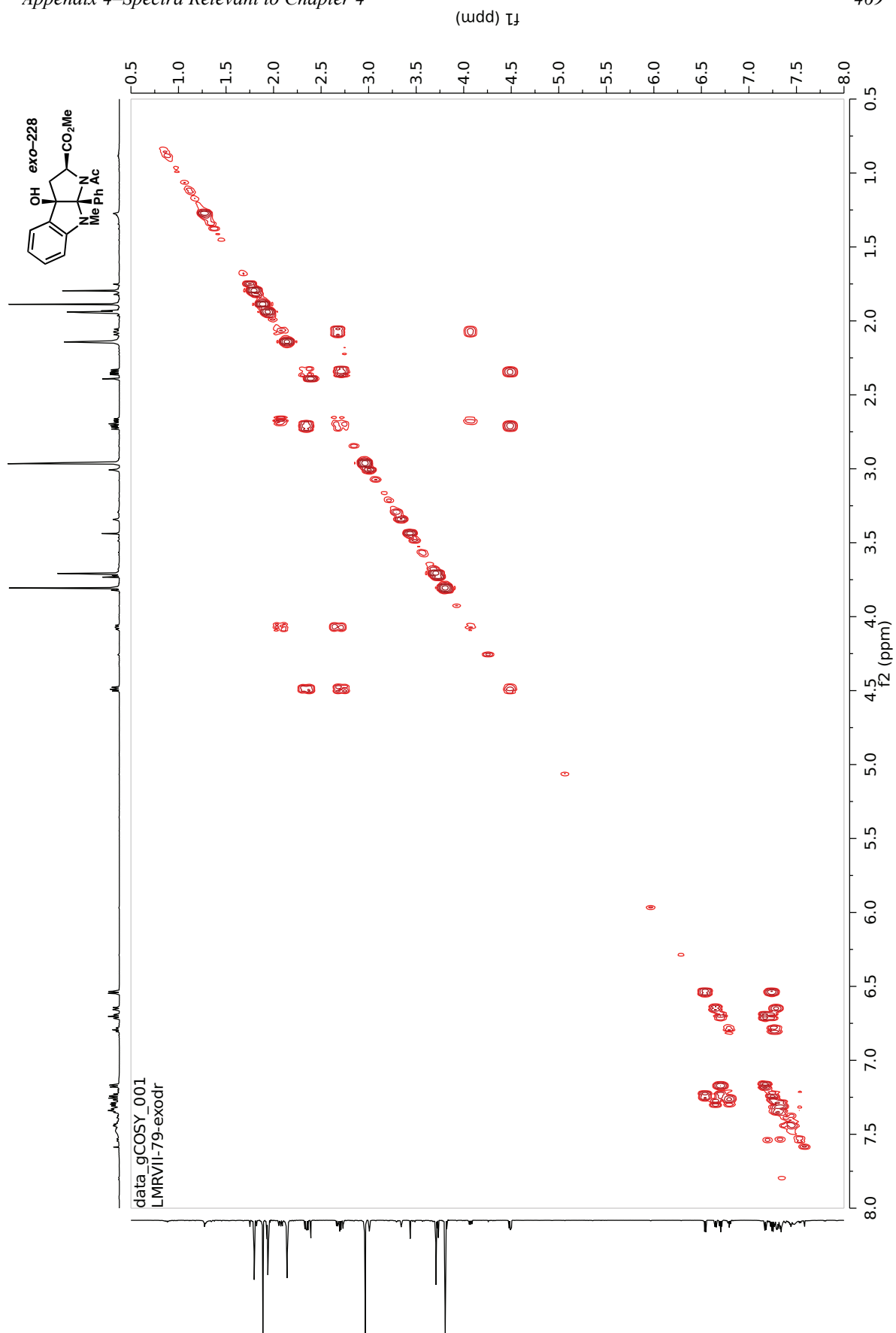
DATA PROCESSING

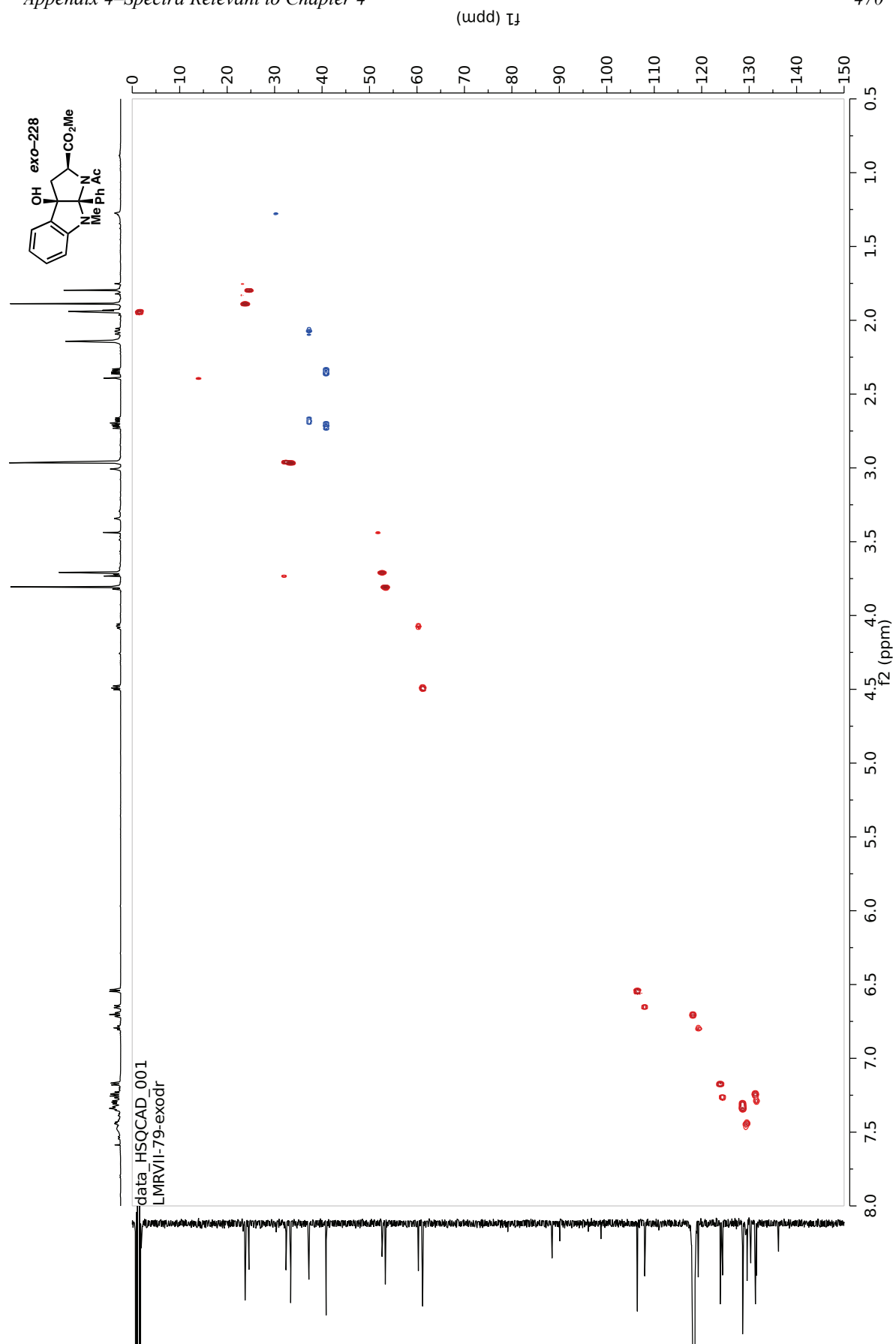
Line broadening 1.5 Hz

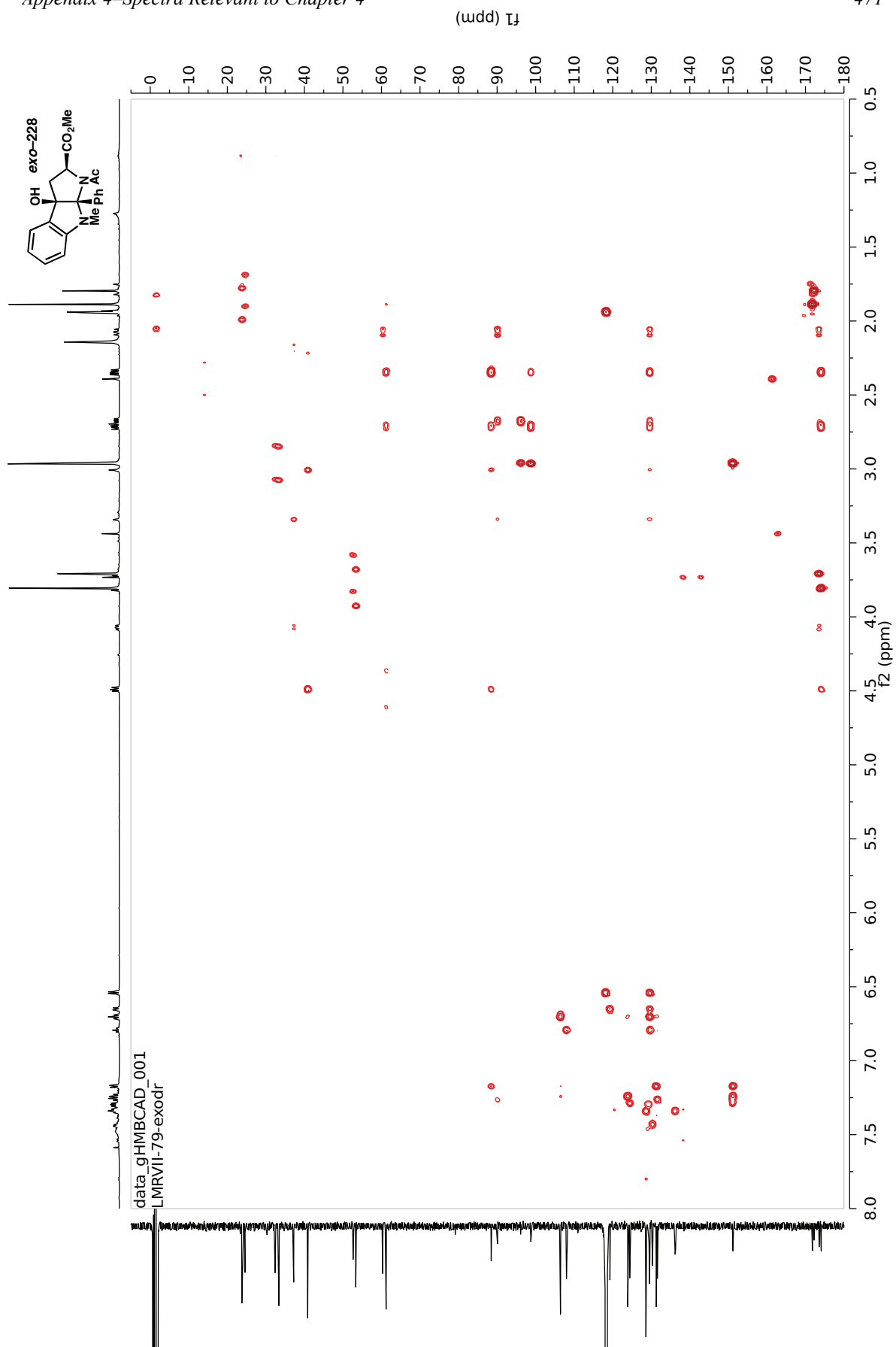
FT size 65536

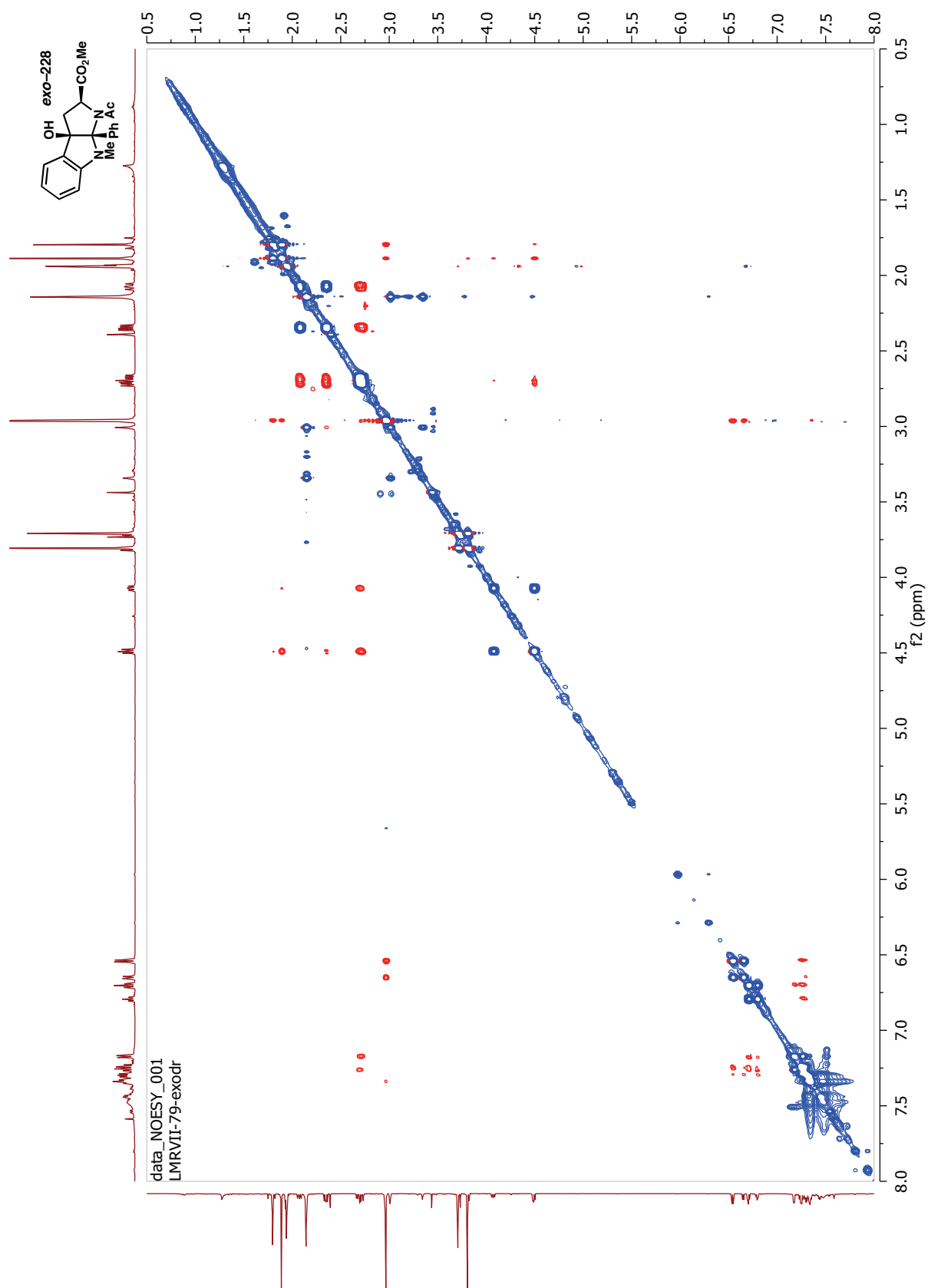
Total time 7 hr, 46 min











LMRVII-205-f25-33

Sample Name:

LMRVII-205-f25-33

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/lrepka/vnmrSYS/data

Sample directory:

LMRVII-205-f25-33

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Apr 22 2012

Sample #40, Operator: lrepka

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 4798.5 Hz

16 repetitions

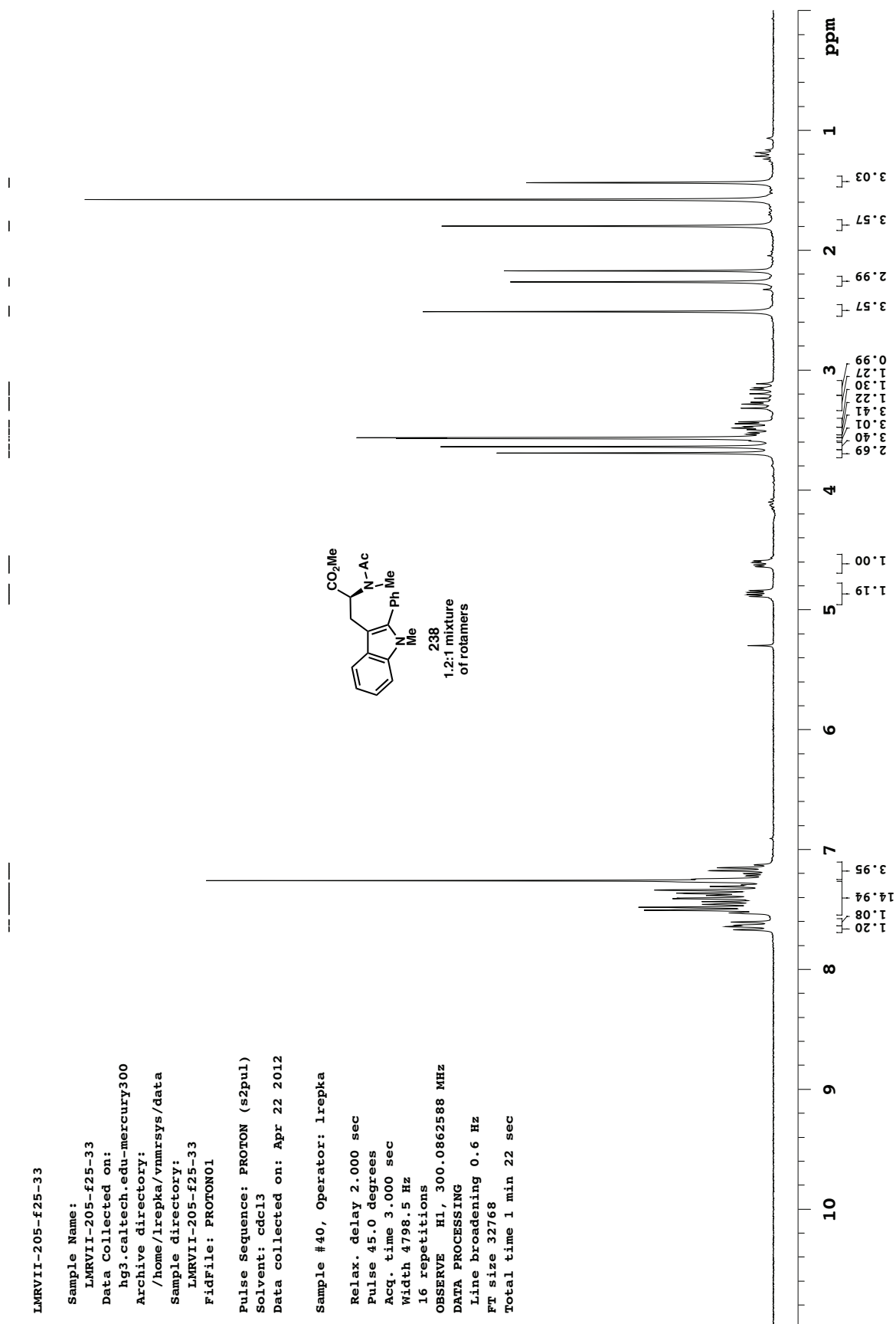
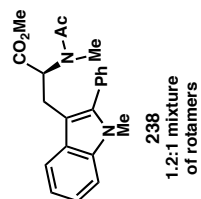
OBSERVE H1, 300.0862588 MHz

DATA PROCESSING

Line broadening 0.6 Hz

FT size 32768

Total time 1 min 22 sec



LMRVII-219-f17-23

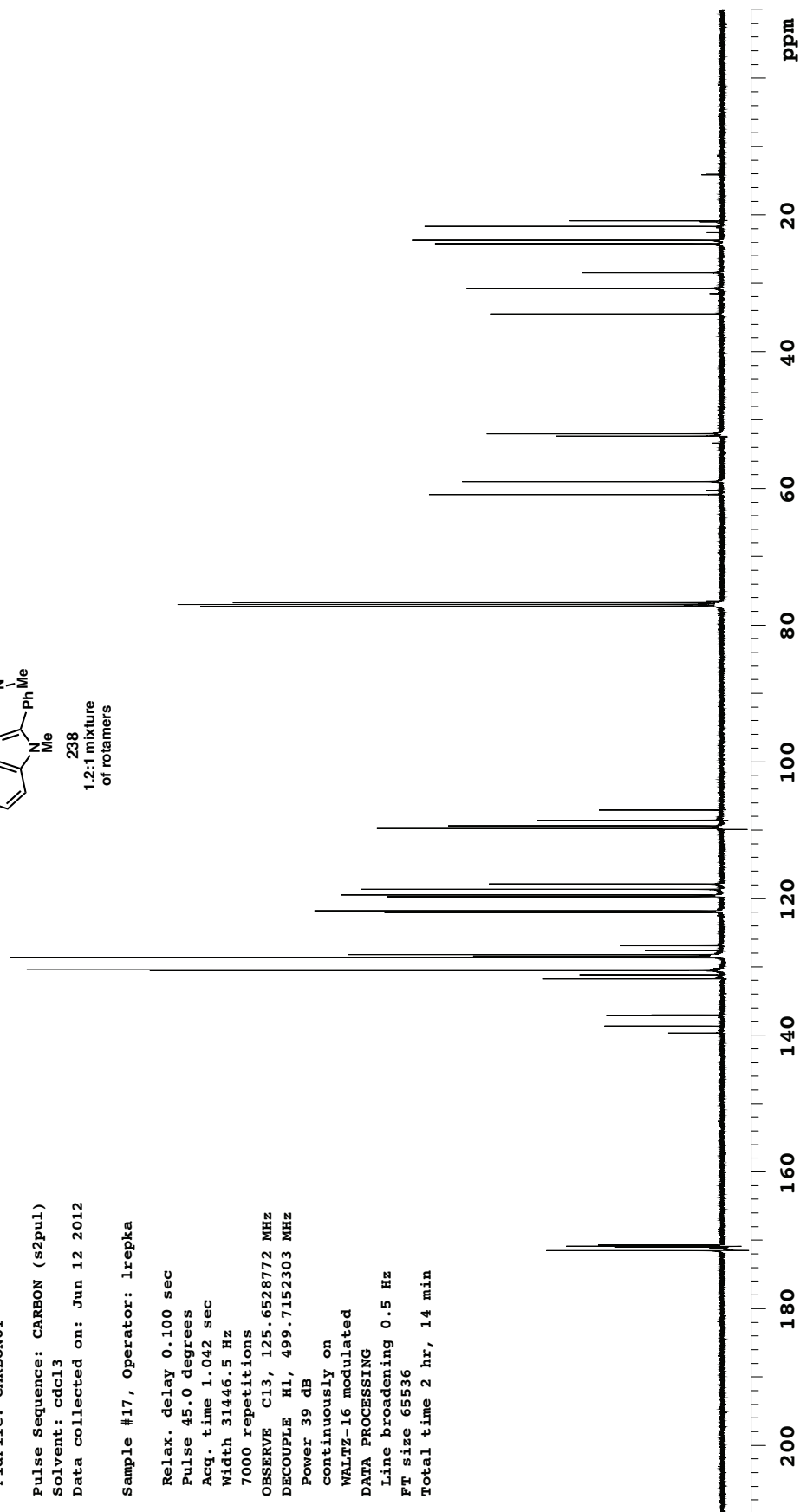
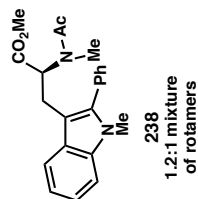
Sample Name:

LMRVII-219-f17-23
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrSYS/data
Sample directory:
LMRVII-219-f17-23
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 12 2012

Sample #17, Operator: lrepka

Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
7000 repetitions
OBSERVE C13, 125.6528772 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 2 hr, 14 min



LMRVII-215-pdt-1f56-2f31

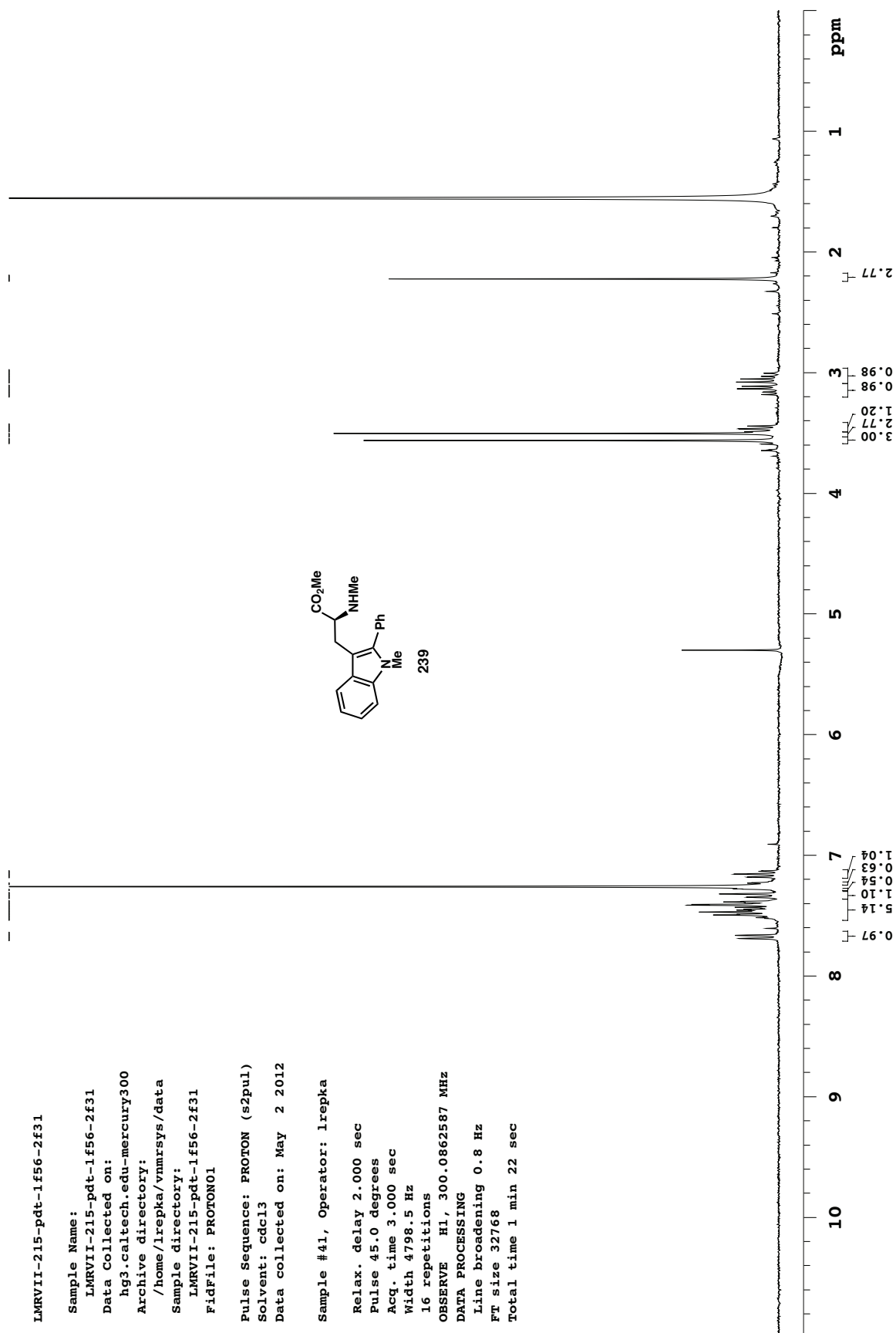
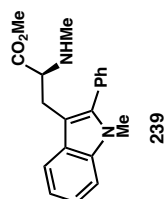
Sample Name:

LMRVII-215-pdt-1f56-2f31
Data Collected on:
hg3.caltech.edu-mercury300
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-215-pdt-1f56-2f31
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 2 2012

Sample #41, Operator: lrepka

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
16 repetitions
OBSERVE H1, 300.0862587 MHz
DATA PROCESSING
Line broadening 0.8 Hz
FT size 32768
Total time 1 min 22 sec



LMRVII-219-f25-42

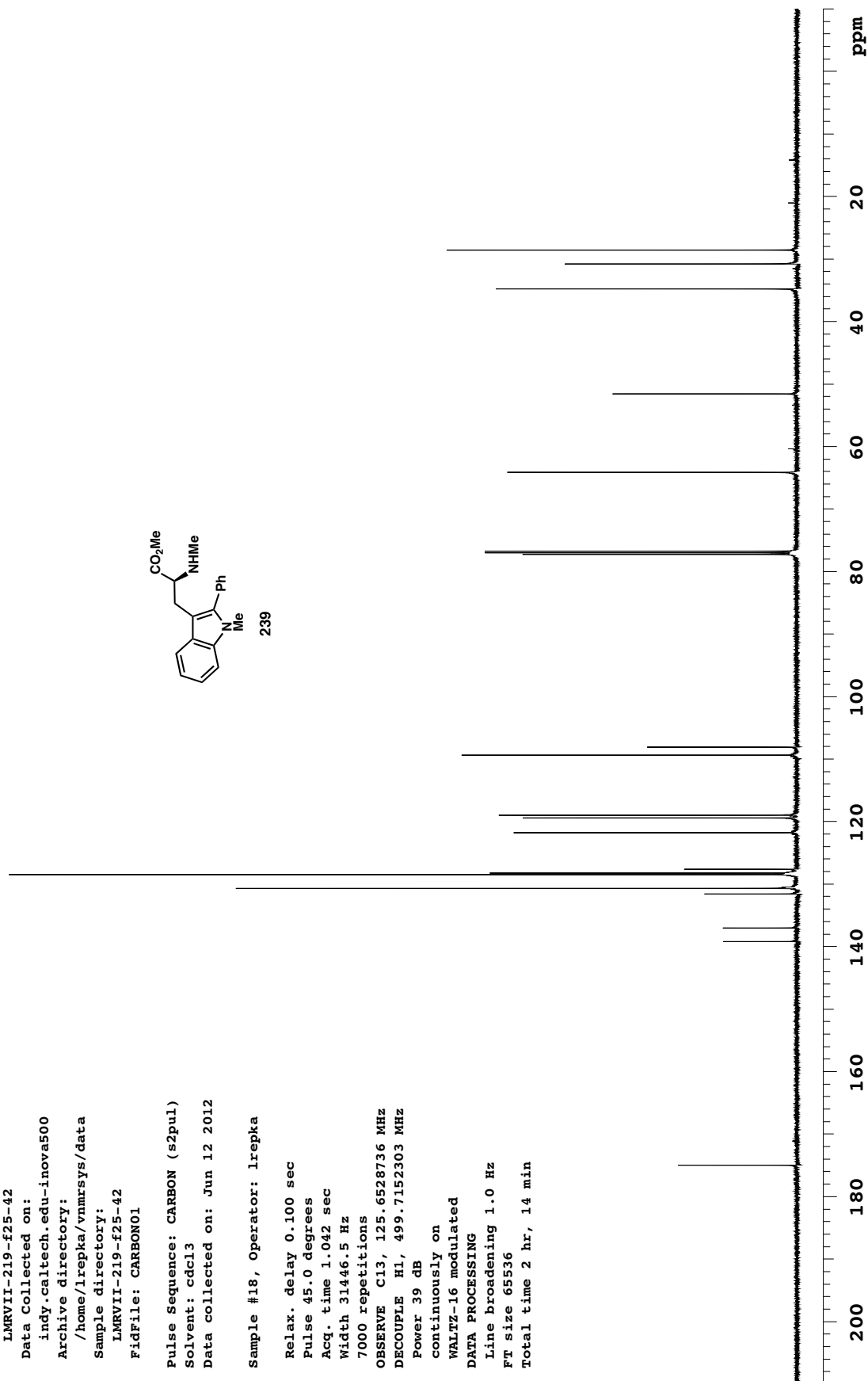
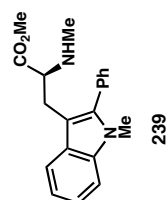
Sample Name:

LMRVII-219-f25-42
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-219-f25-42
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 12 2012

Sample #18, Operator: lrepka

Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
7000 repetitions
OBSERVE C13, 125.6528736 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 14 min



LMRVII-225-phplc-f1

Sample Name:
LMRVII-225-phplc-f1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-225-phplc-f1
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 11 2012

Sample #37, Operator: lrepka

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz

16 repetitions

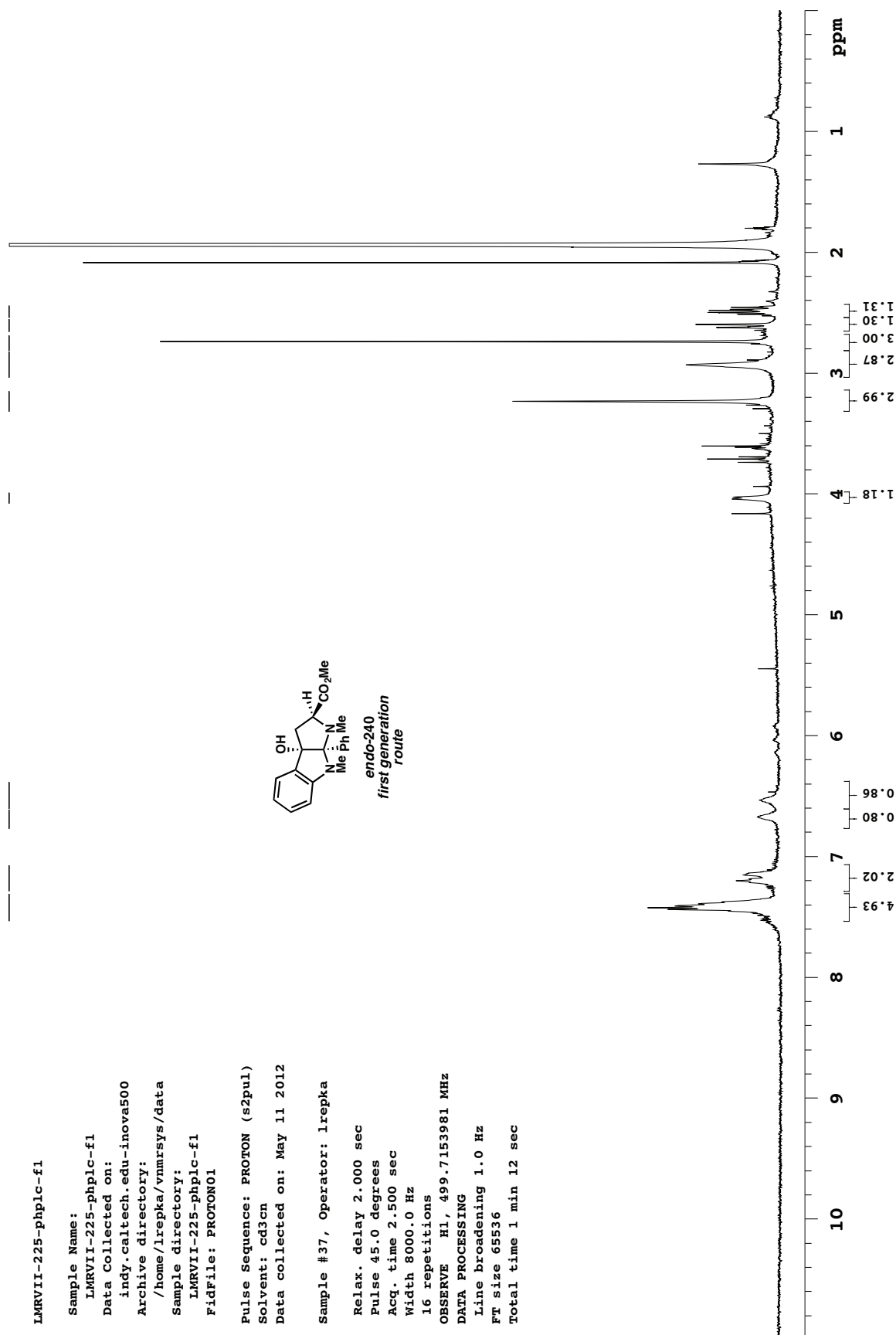
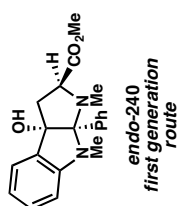
OBSERVE H1, 499.7153981 MHz

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 1 min 12 sec



LMRVII-225-phplc-f2

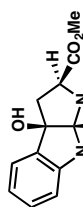
Sample Name:
LMRVII-225-phplc-f2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-225-phplc-f2
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: May 11 2012

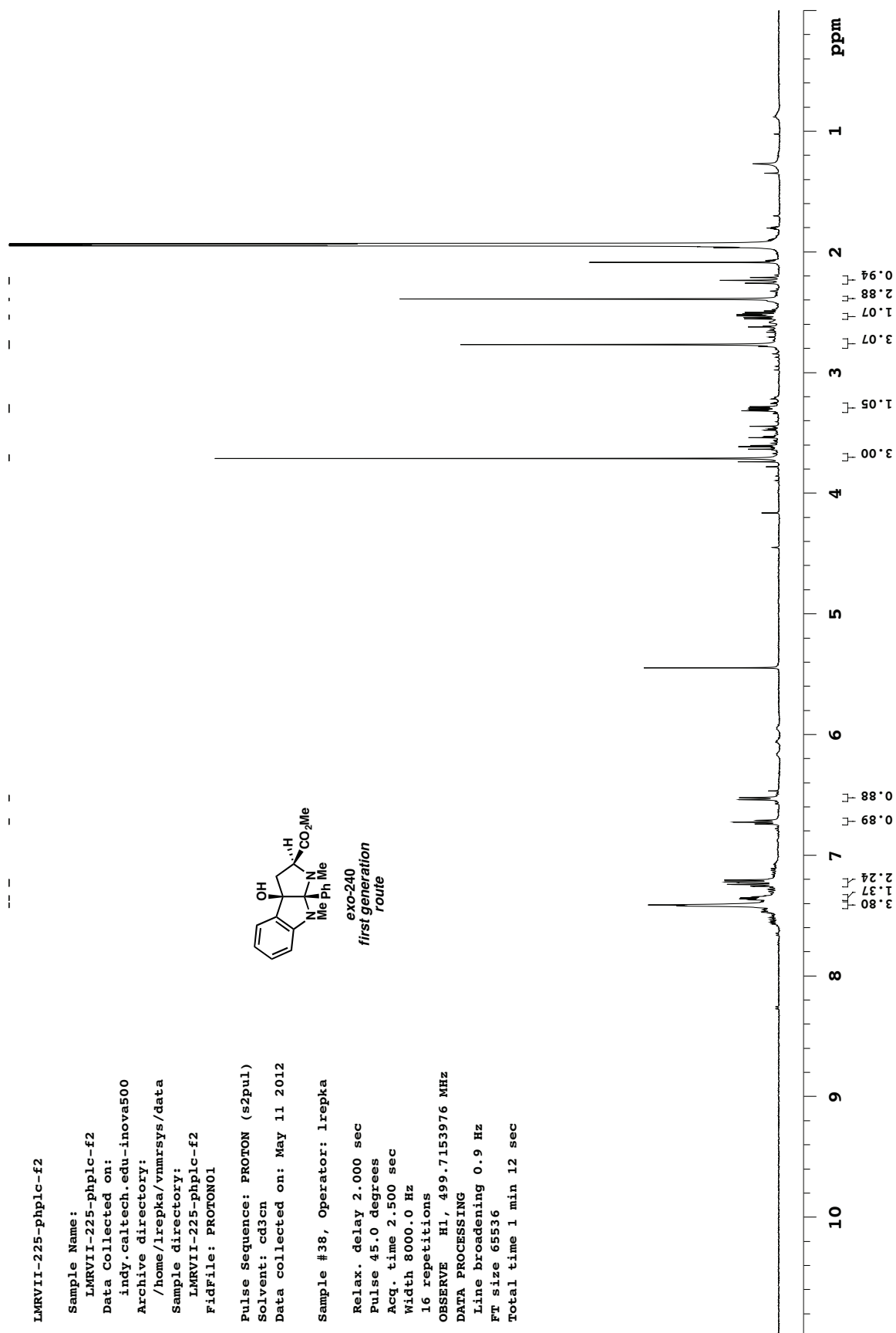
Sample #38, Operator: lrepka

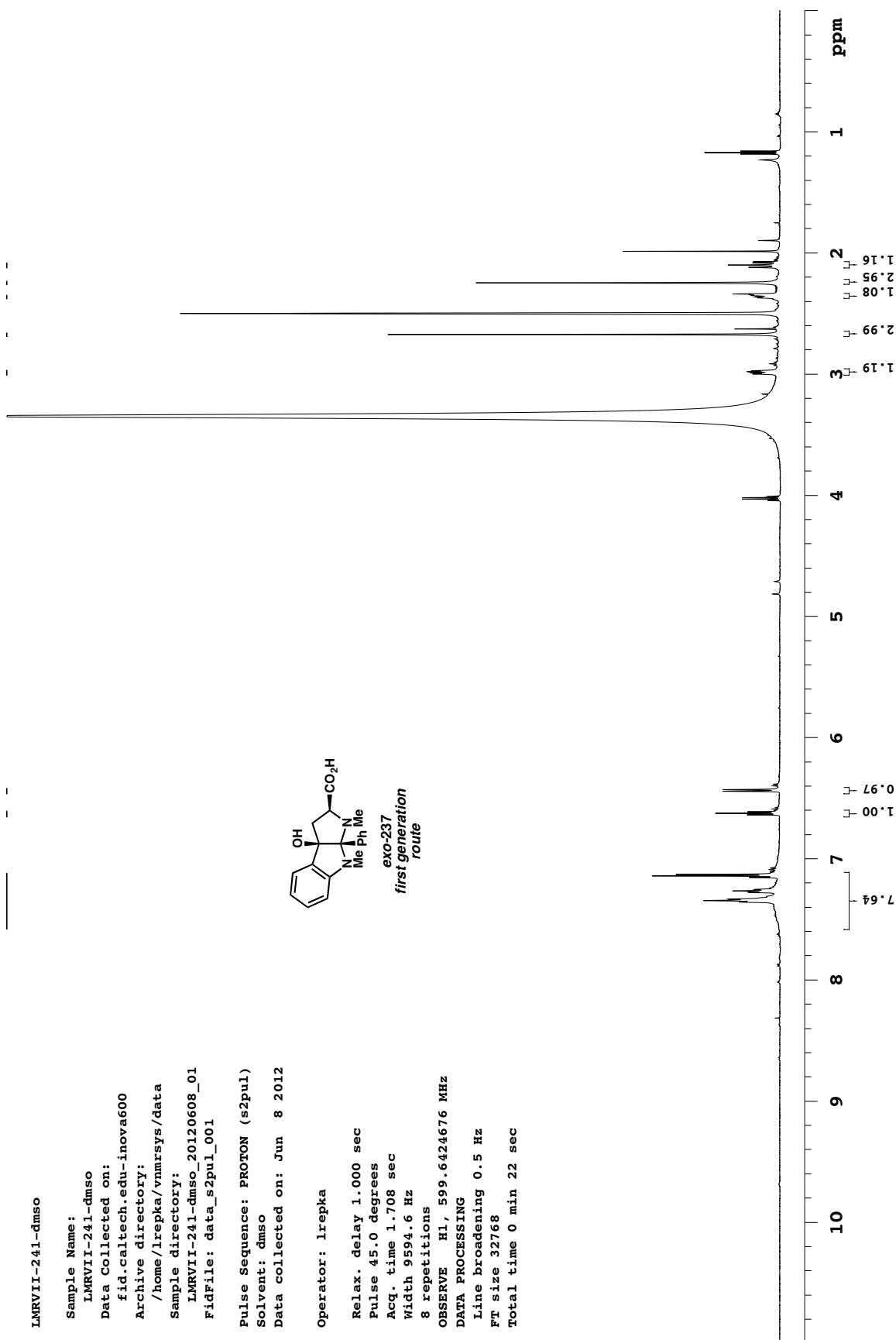
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz

16 repetitions
OBSERVE H1, 499.7153976 MHz
DATA PROCESSING
Line broadening 0.9 Hz
FT size 65536
Total time 1 min 12 sec



exo-240
first generation
route





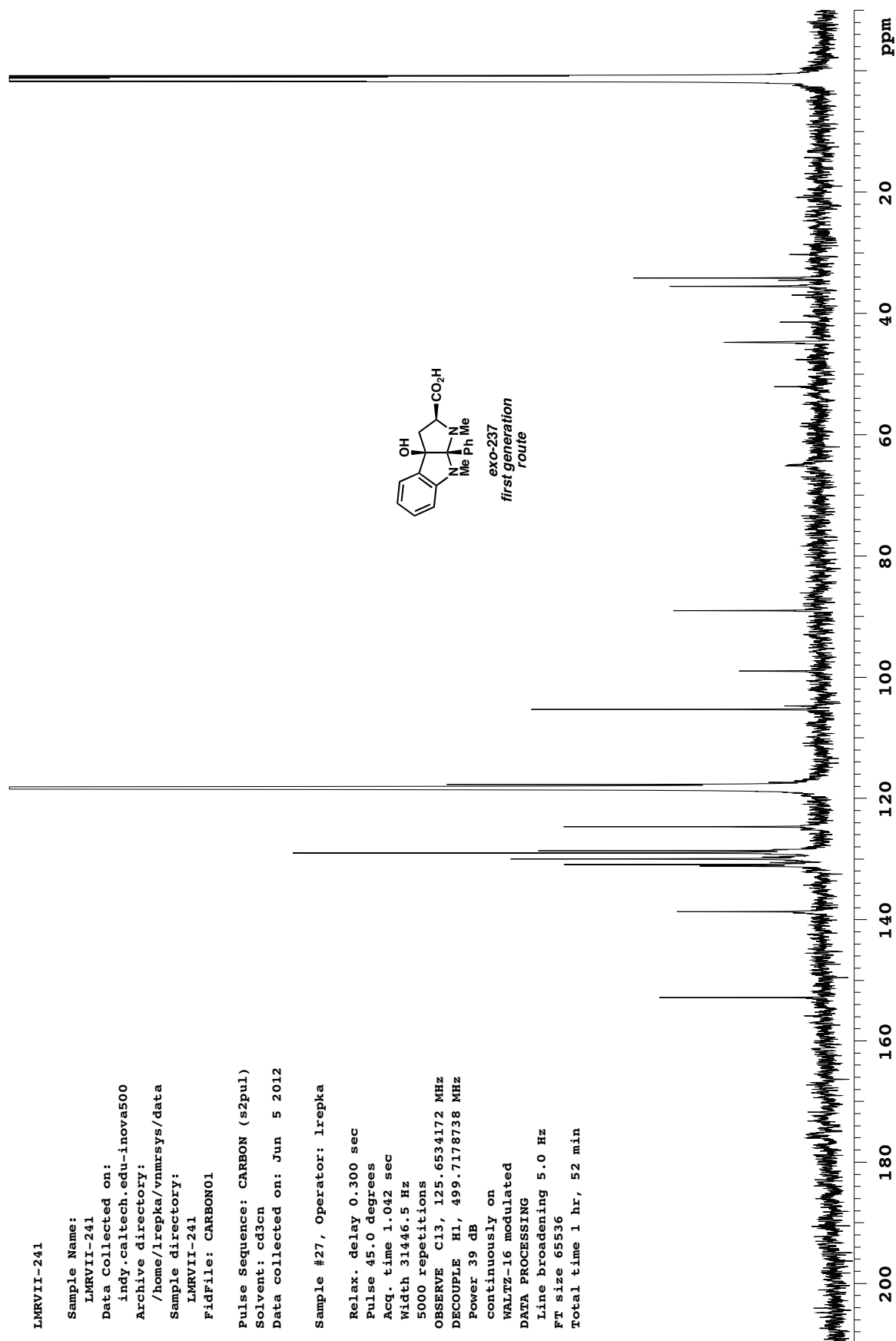
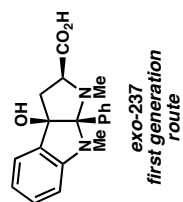
LMRVII-241

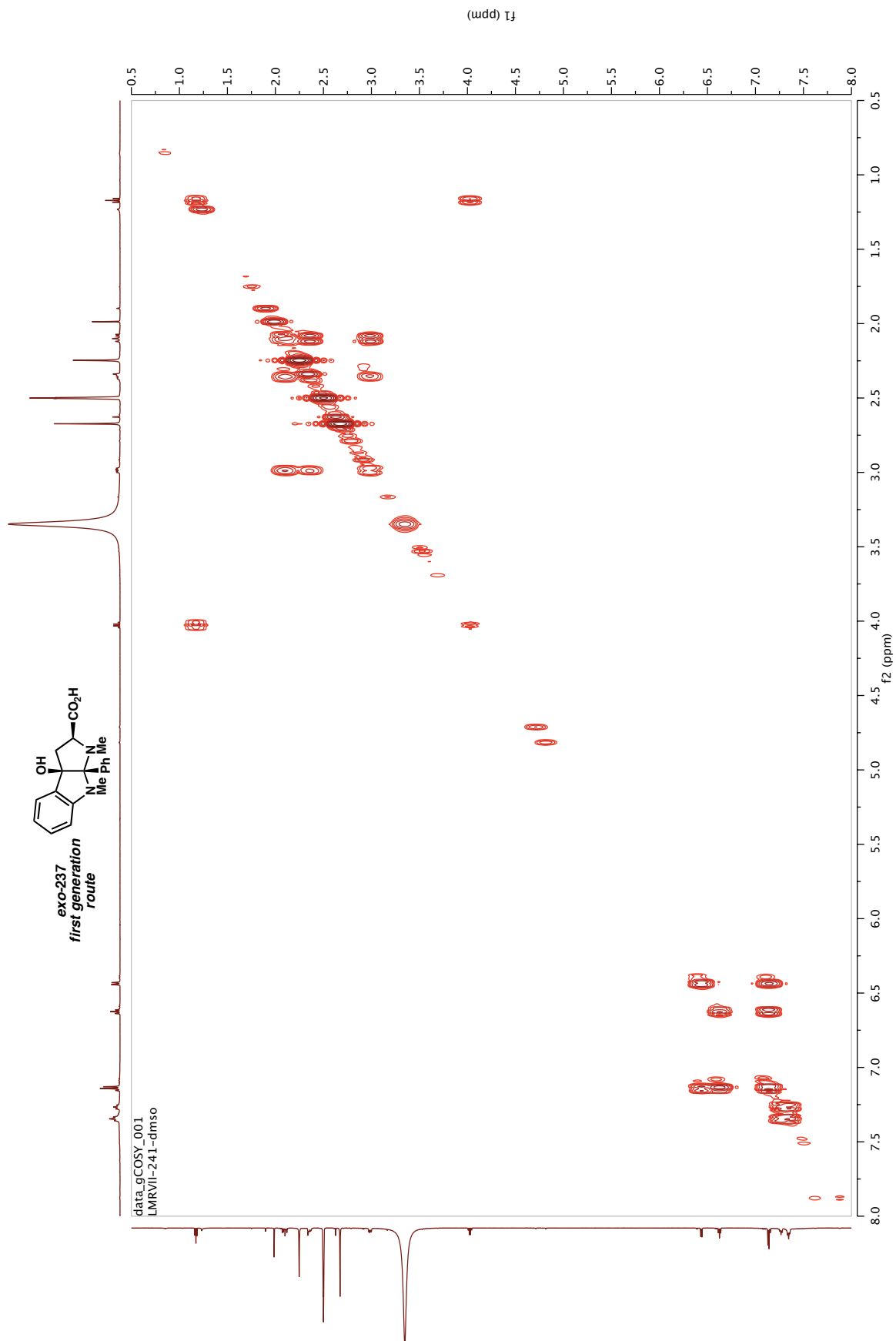
Sample Name:
LMRVII-241
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-241
FidFile: CARBON01

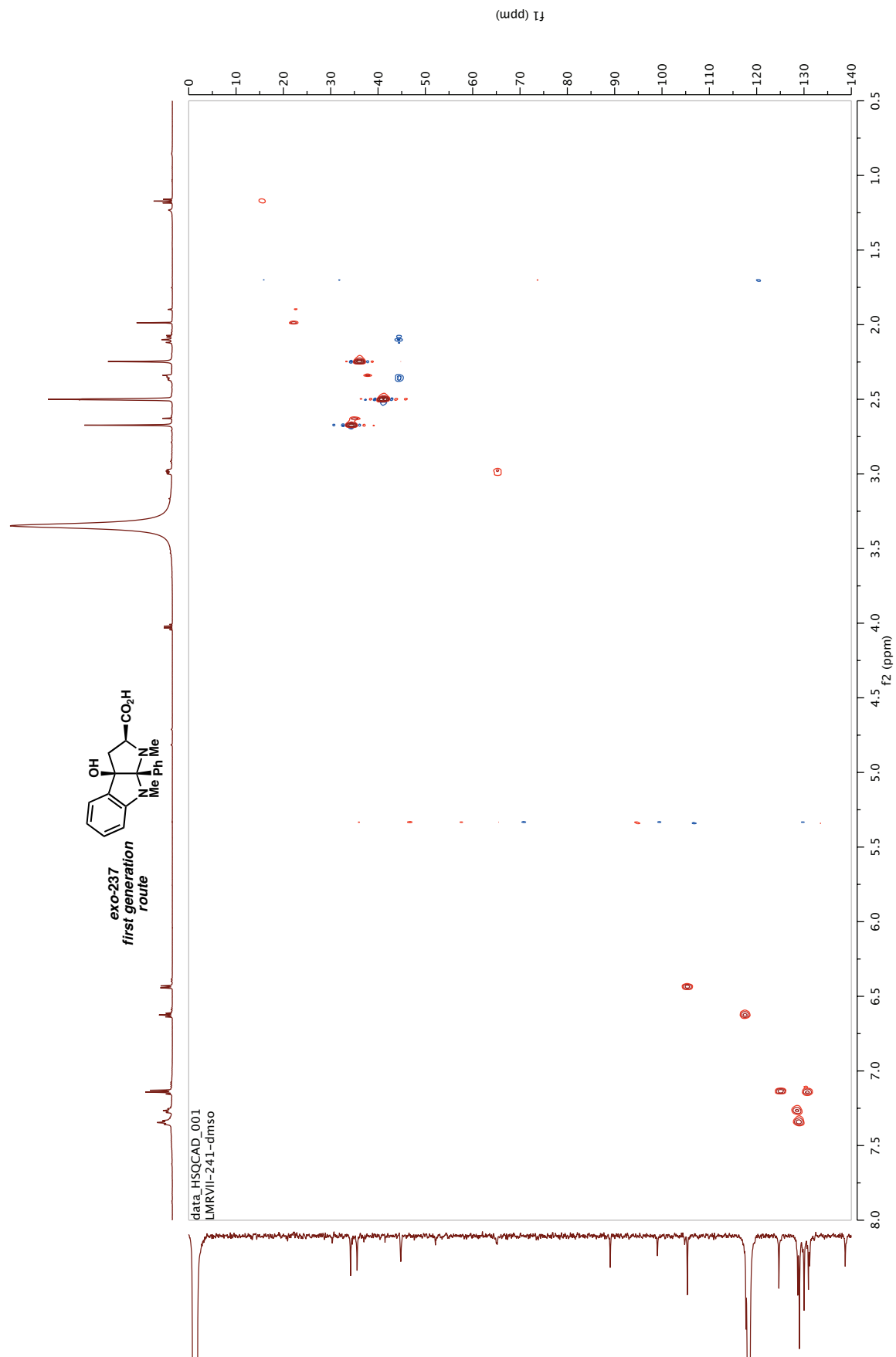
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jun 5 2012

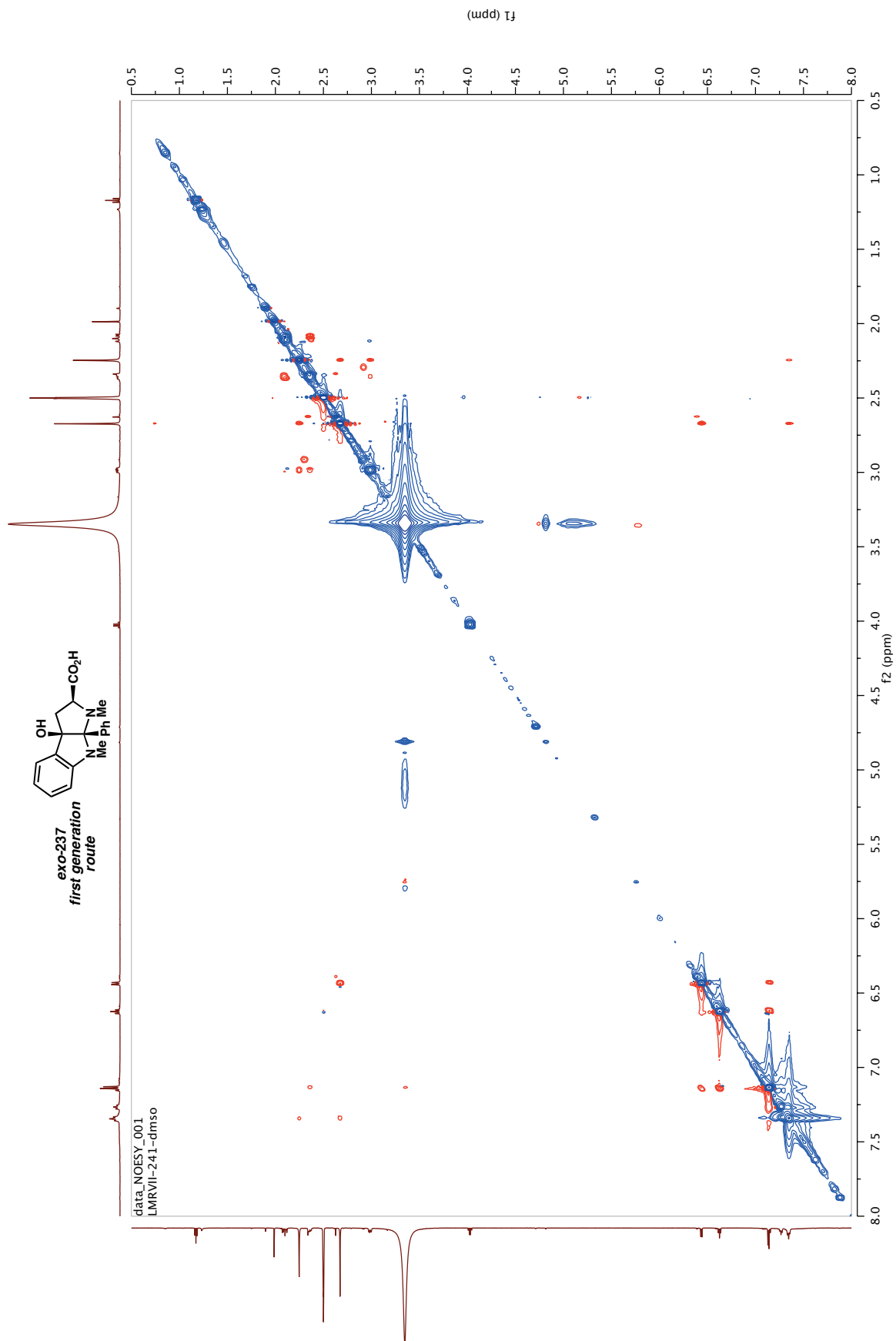
Sample #27, Operator: lrepka

Relax. delay 0.300 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6534172 MHz
DECOUPLE H1, 499.7178738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 1 hr, 52 min







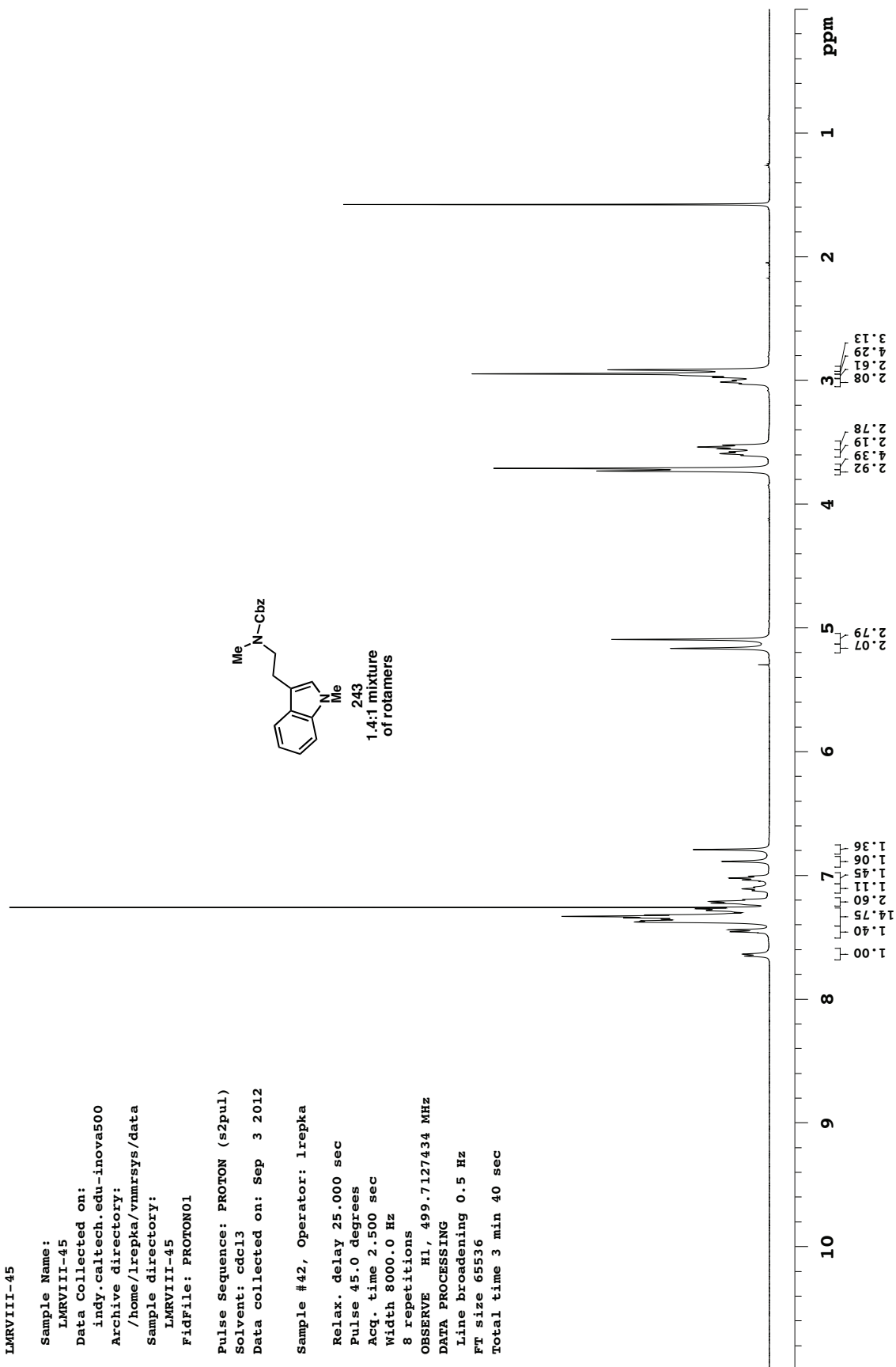
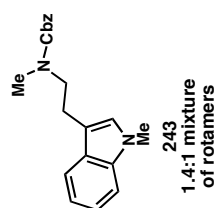


LMRVIII-45

Sample Name:
LMRVIII-45
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVIII-45
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 3 2012

Sample #42, Operator: lrepka
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127434 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 min 40 sec



LMRVIII-45-carbon

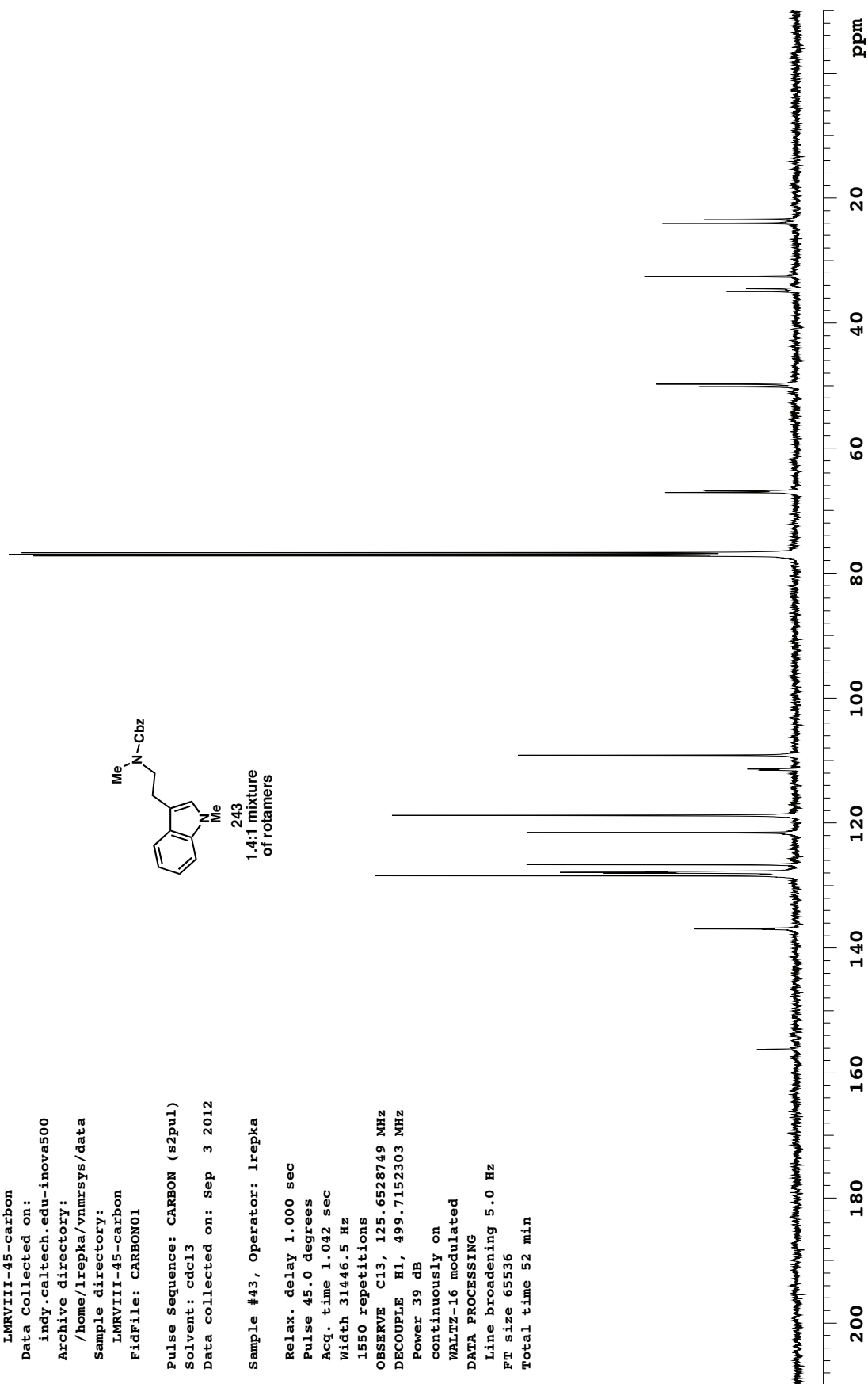
Sample Name:

LMRVIII-45-carbon
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVIII-45-carbon
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 3 2012

Sample #43, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1550 repetitions
OBSERVE C13, 125.6528749 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 52 min



AMAO-1-75

Sample Name:

AMAO-1-75

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsvs/data

Sample directory:

AMAO-1-75

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Mar 12 2013

Sample #10, Operator: amao

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 3.273 sec

Width 5006.3 Hz

16 repetitions

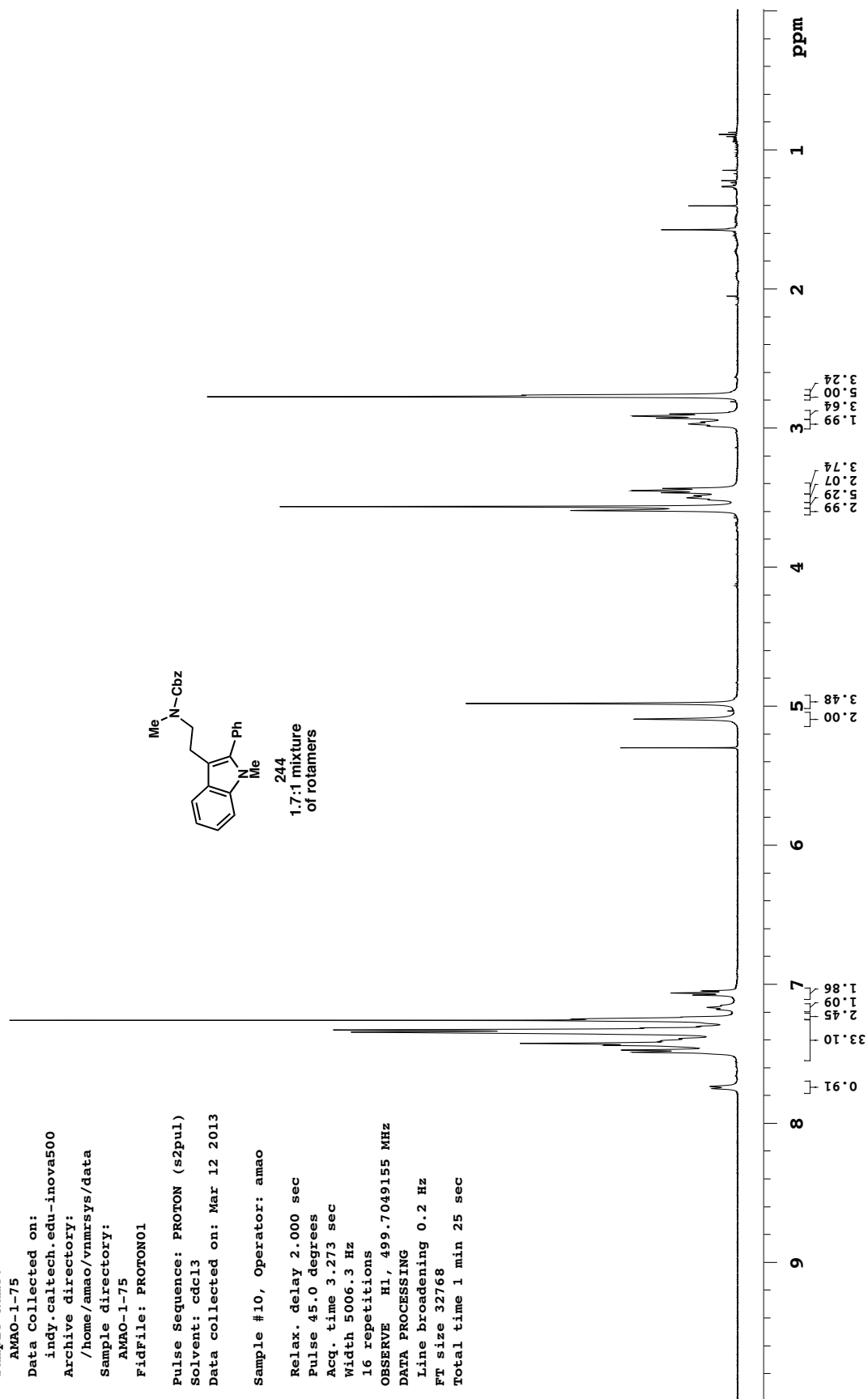
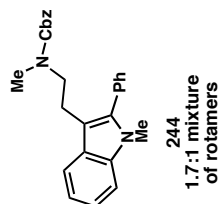
OBSERVE H1, 499.7049155 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 32768

Total time 1 min 25 sec



AMAO-1-51

Sample Name:

AMAO-1-51

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-51

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Feb 12 2013

Sample #8, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6509065 MHz

DECOUPLE H1, 499.7074131 MHz

Power 39 dB

continuously on

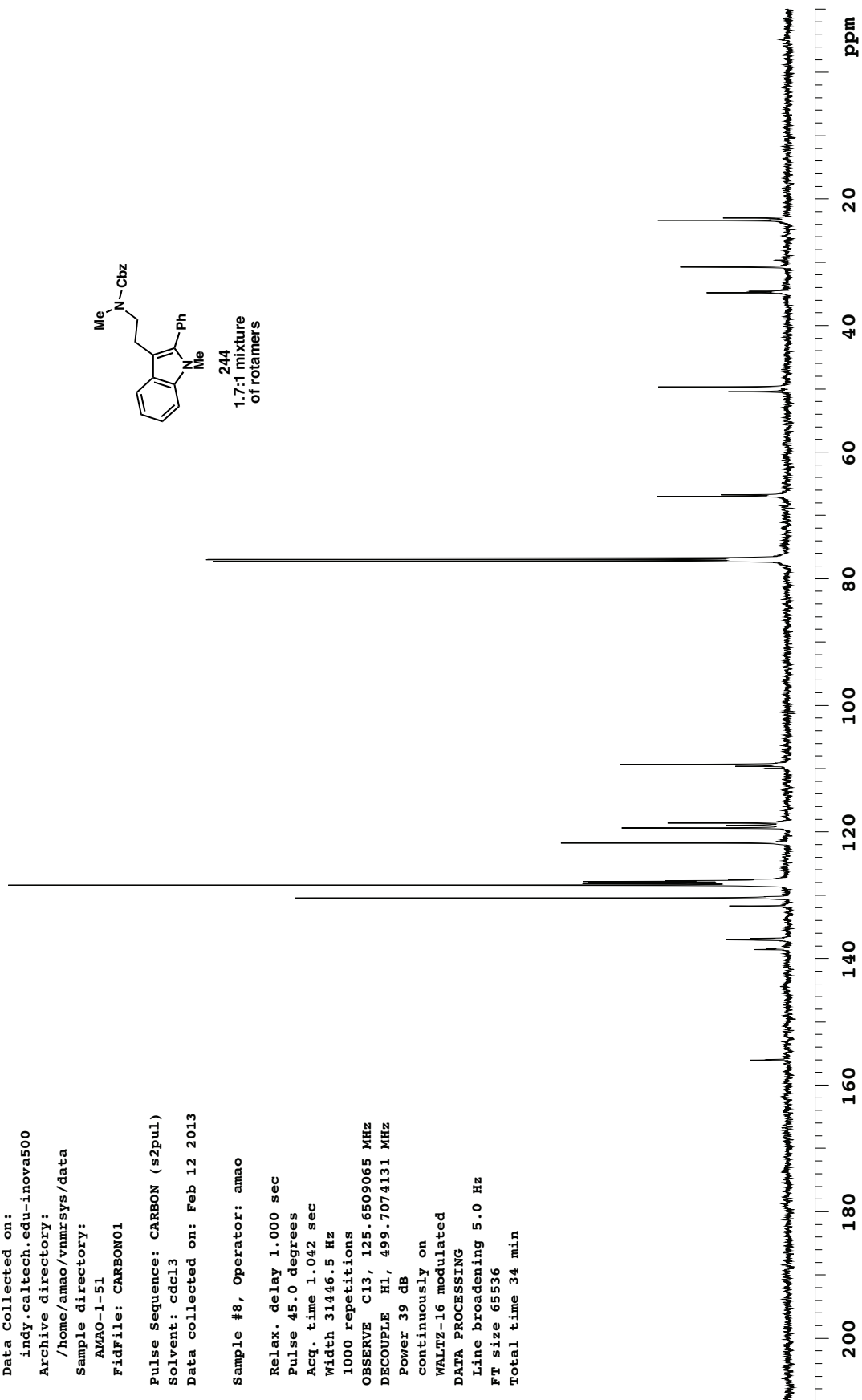
WALTZ-16 modulated

DATA PROCESSING

Line broadening 5.0 Hz

FT size 65536

Total time 34 min



AMAO-1-82

Sample Name:

AMAO-1-82

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrSYS/data

Sample directory:

AMAO-1-82

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Mar 15 2013

Sample #15, Operator: amao

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 3.273 sec

Width 5006.3 Hz

16 repetitions

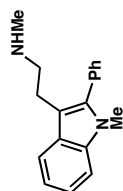
OBSERVE H1, 499.7049157 MHz

DATA PROCESSING

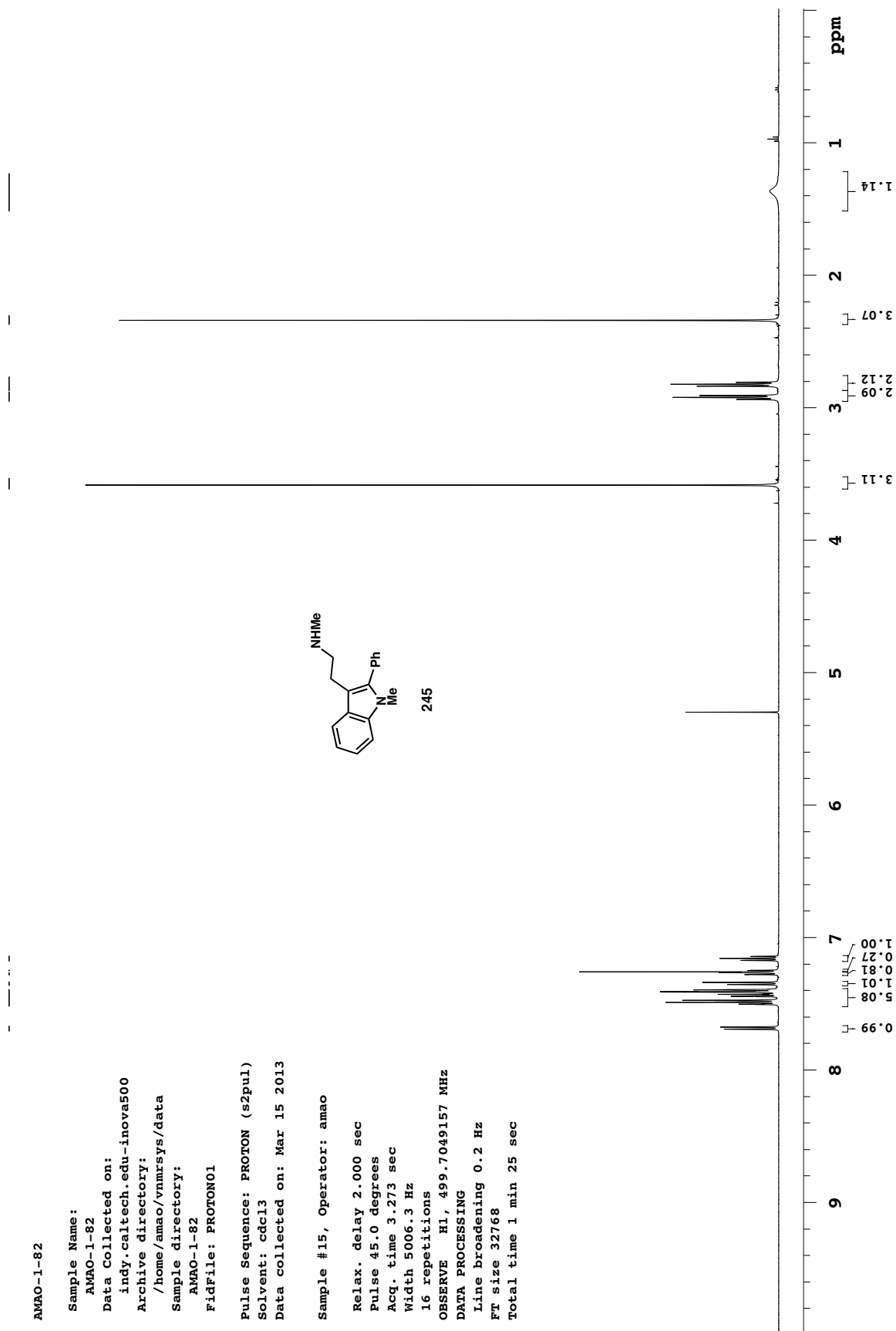
Line broadening 0.2 Hz

FT size 32768

Total time 1 min 25 sec



245



AMAO-1-15-F69-75B

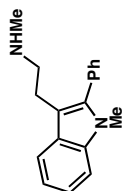
Sample Name:

AMAO-1-15-F69-75B
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/amao/vnmrsys/data
Sample directory:
AMAO-1-15-F69-75B
FidFile: CARBON01

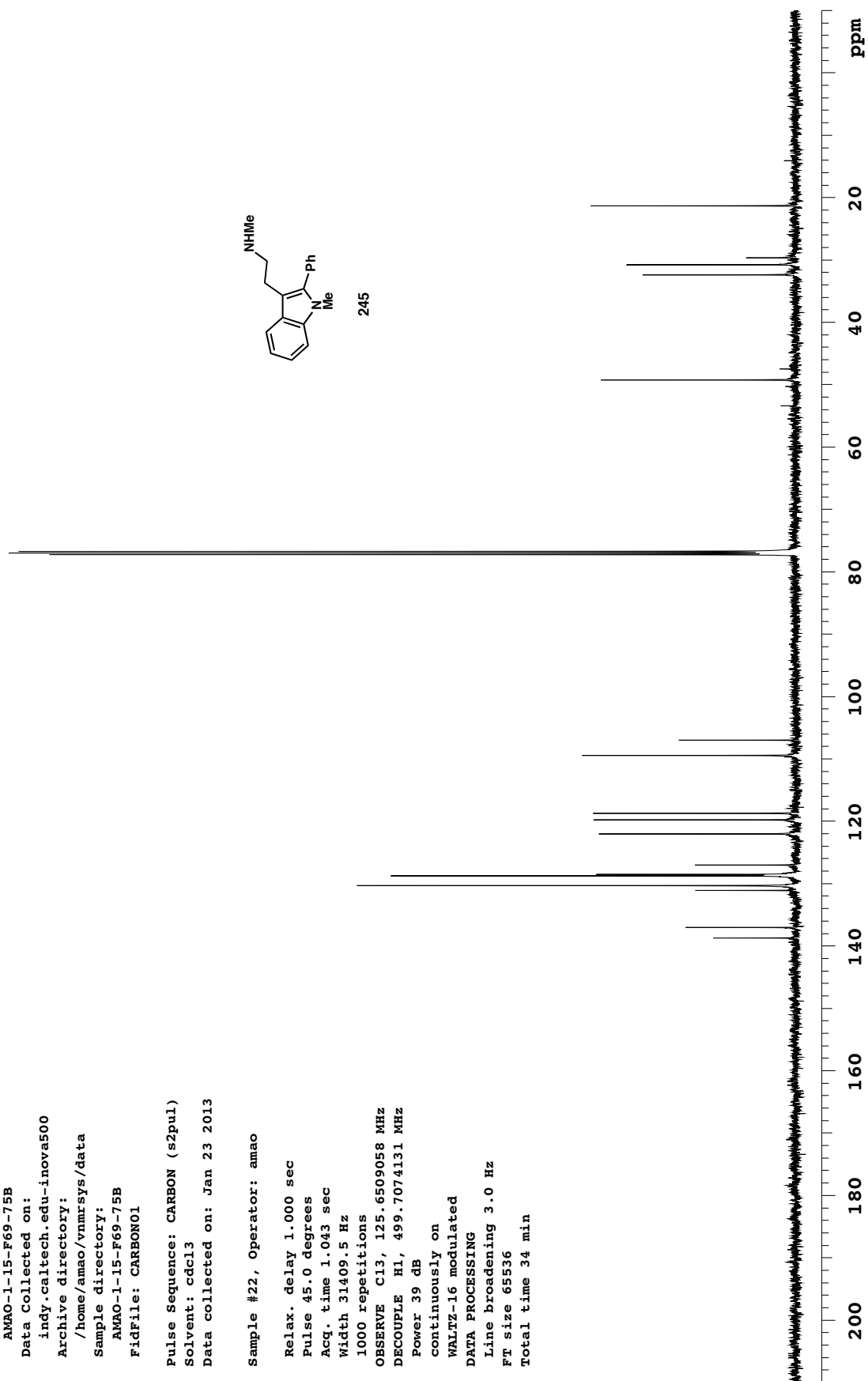
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 23 2013

Sample #22, Operator: amao

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
1000 repetitions
OBSERVE C13, 125.6509058 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 34 min



245

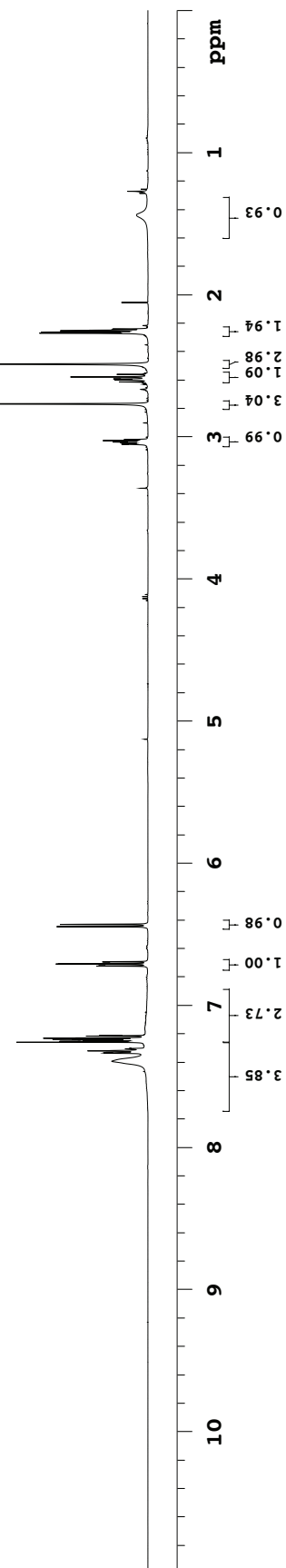
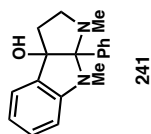


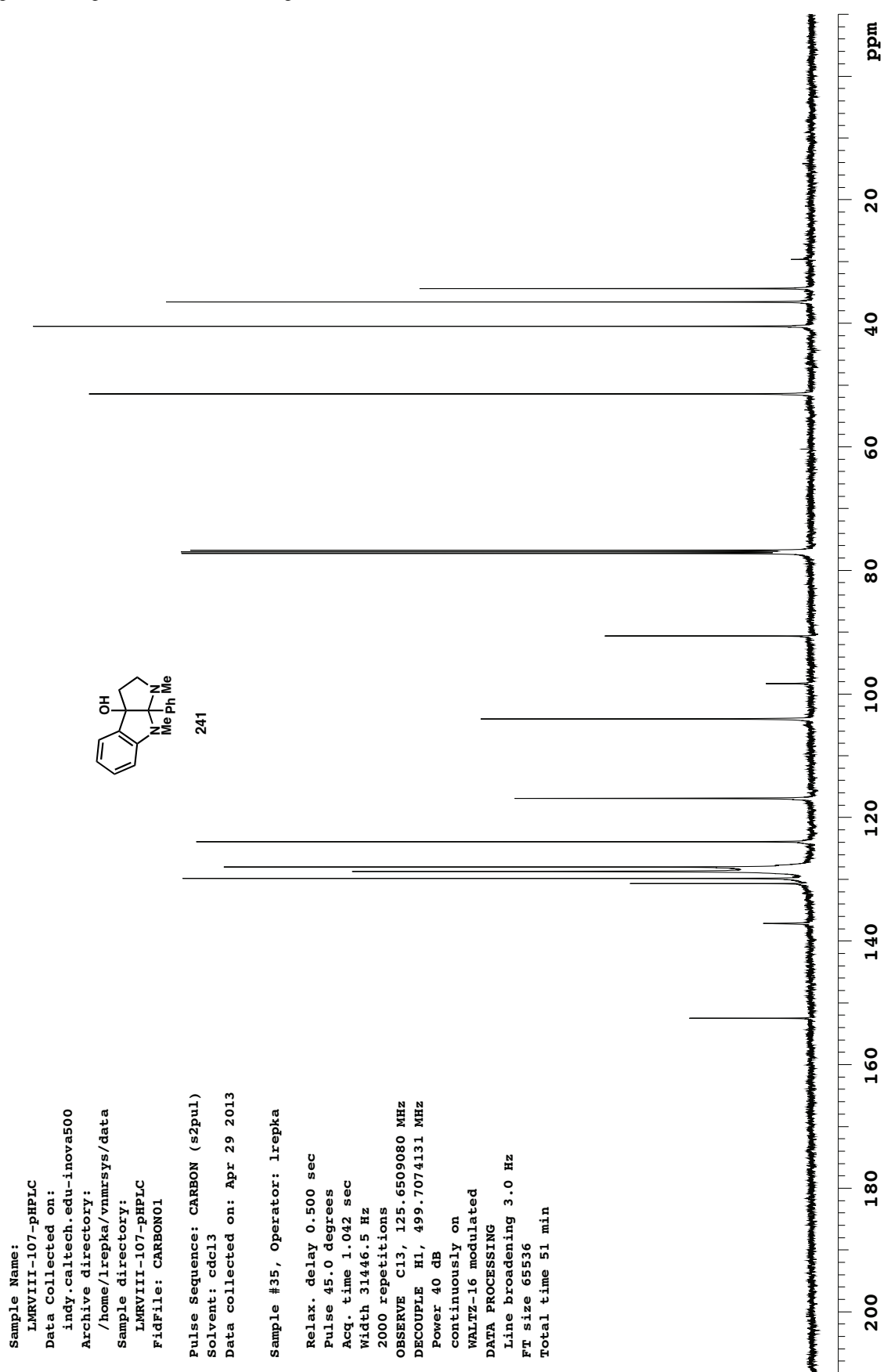
Sample Name:
LMRVIII-107-pHPLC
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVIII-107-pHPLC
FidFile: PROTON02

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 2013

Sample #35, Operator: lrepka

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049150 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec





LMRVIII-109-proton

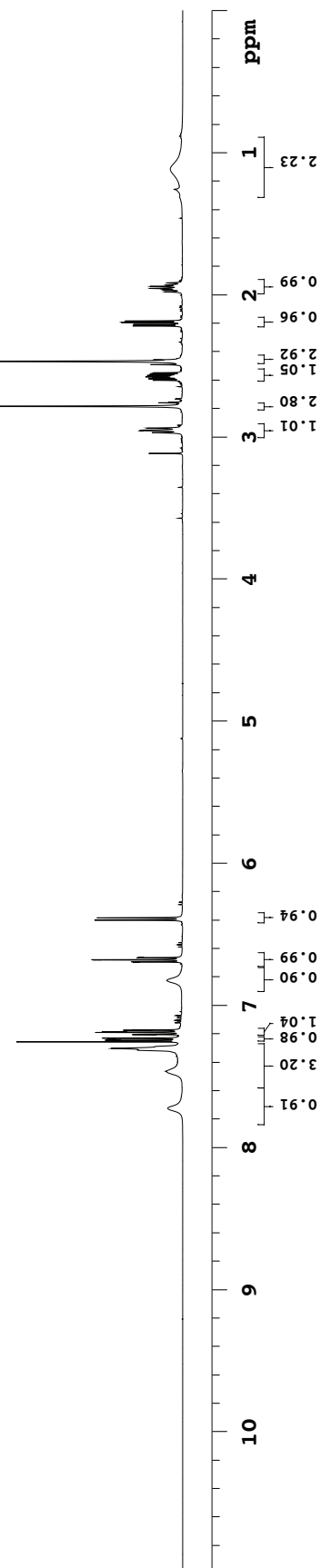
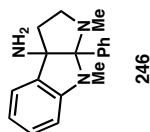
Sample Name:

LMRVIII-109-proton
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVIII-109-proton
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 26 2013

Sample #18, Operator: lrepka

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049166 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec



LMRVIII-109-carbon

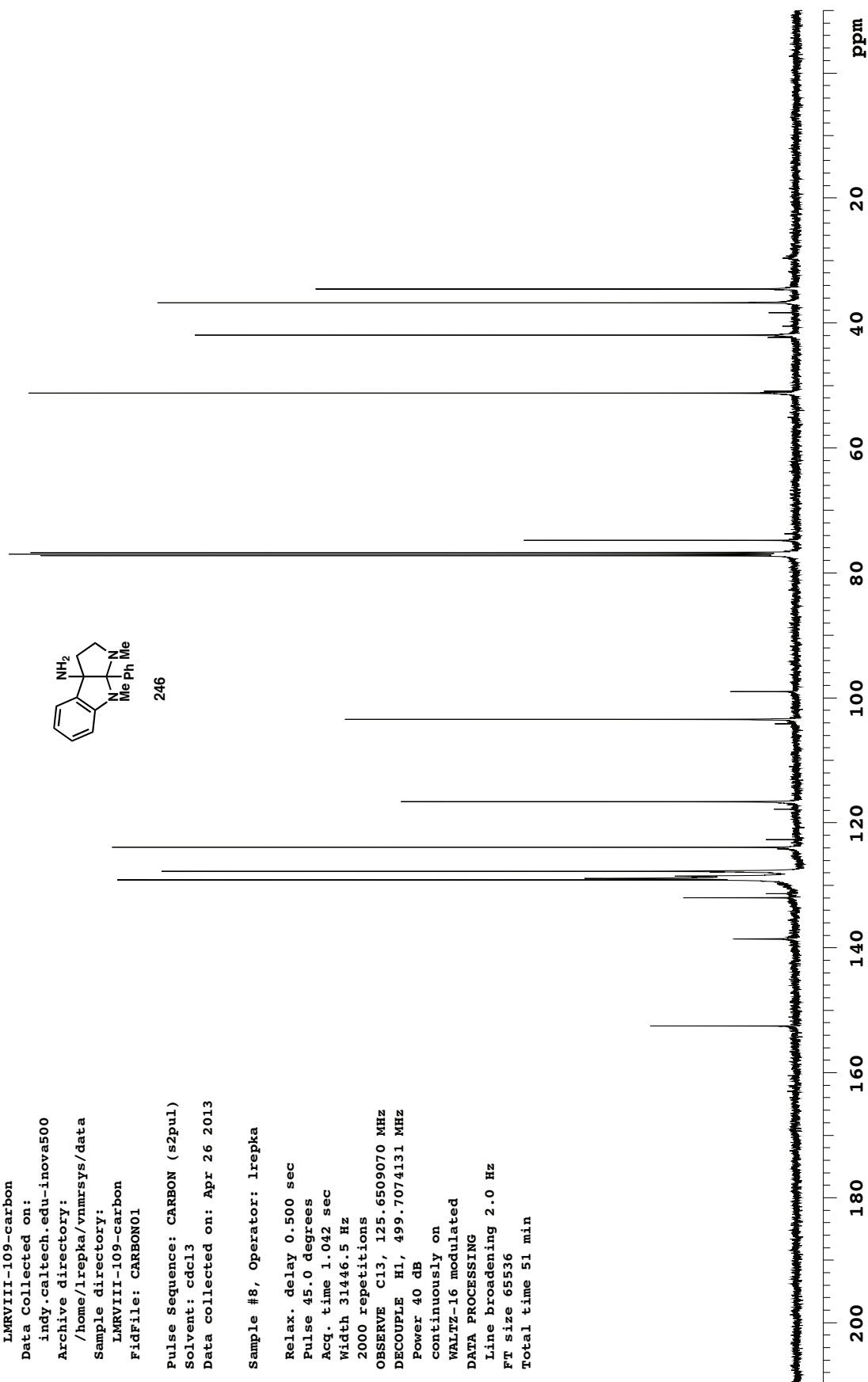
Sample Name:

LMRVIII-109-carbon
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVIII-109-carbon
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 26 2013

Sample #8, Operator: lrepka

Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6509070 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
Ft size 65536
Total time 51 min



AMAO-1-62

Sample Name:

AMAO-1-62

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsvs/data

Sample directory:

AMAO-1-62

FidFile: PROTON03

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Feb 26 2013

Sample #28, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 8000.0 Hz

8 repetitions

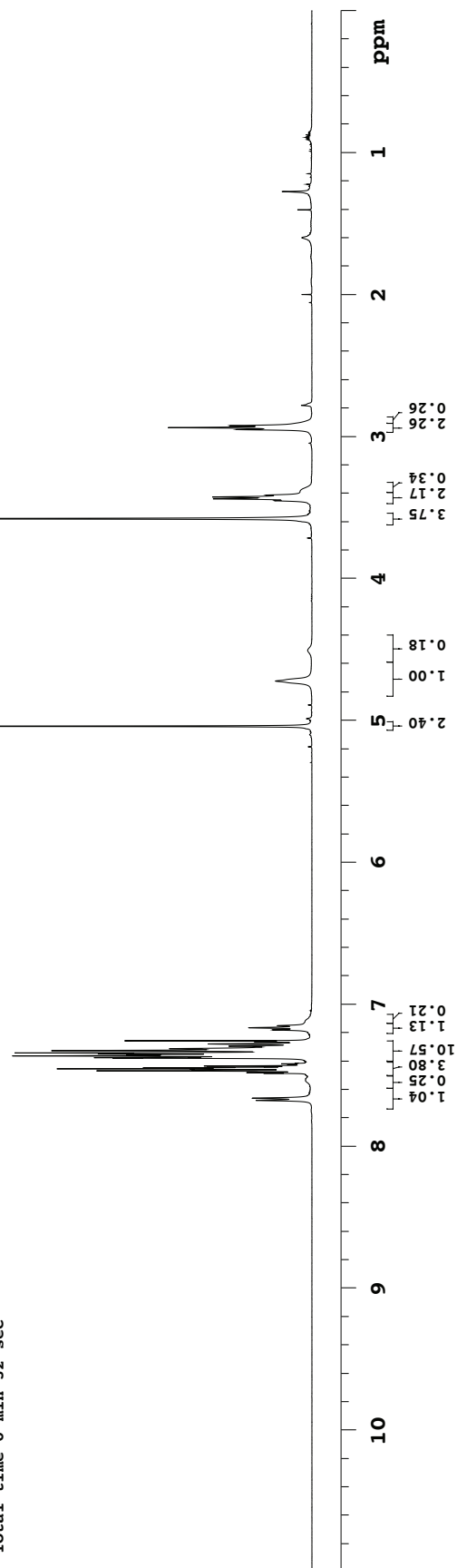
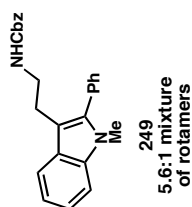
OBSERVE H1, 499.7049160 MHz

DATA PROCESSING

Line broadening 0.4 Hz

FT size 65536

Total time 0 min 32 sec



AMAO-1-62

Sample Name:

AMAO-1-62

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-62

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Feb 26 2013

Sample #28, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6509073 MHz

DECOUPLE H1, 499.7074131 MHz

Power 39 dB

continuously on

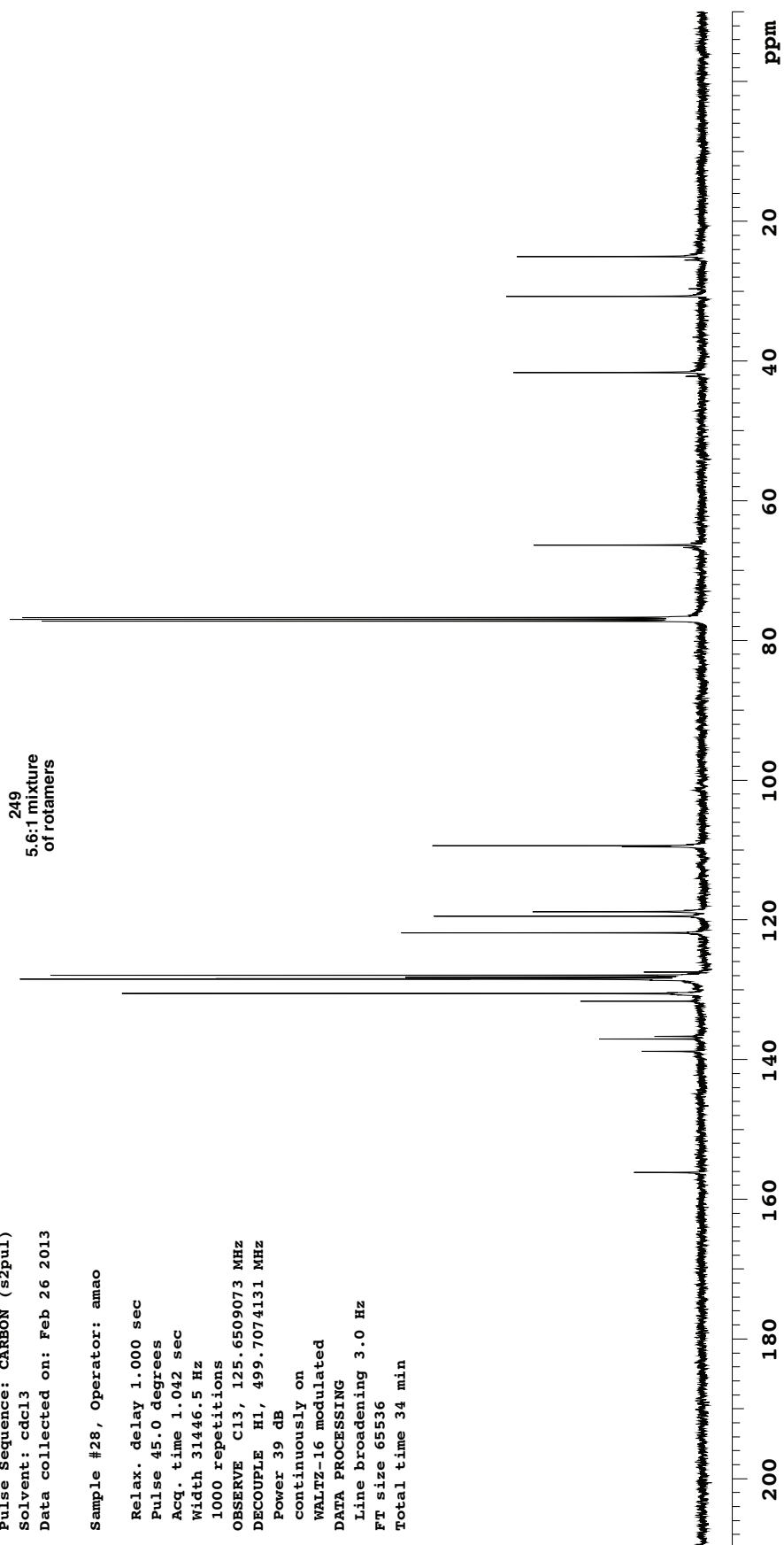
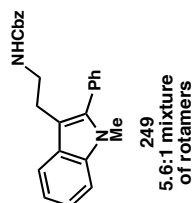
WALTZ-16 modulated

DATA PROCESSING

Line broadening 3.0 Hz

FT size 65536

Total time 34 min



LMRVIII-111-PHPLC

Sample Name:

LMRVIII-111-PHPLC

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrsys/data

Sample directory:

LMRVIII-111-PHPLC

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Apr 30 2013

Sample #34, Operator: lrepka

Relax. delay 5.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 8000.0 Hz

16 repetitions

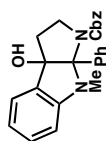
OBSERVE H1, 499.7049152 MHz

DATA PROCESSING

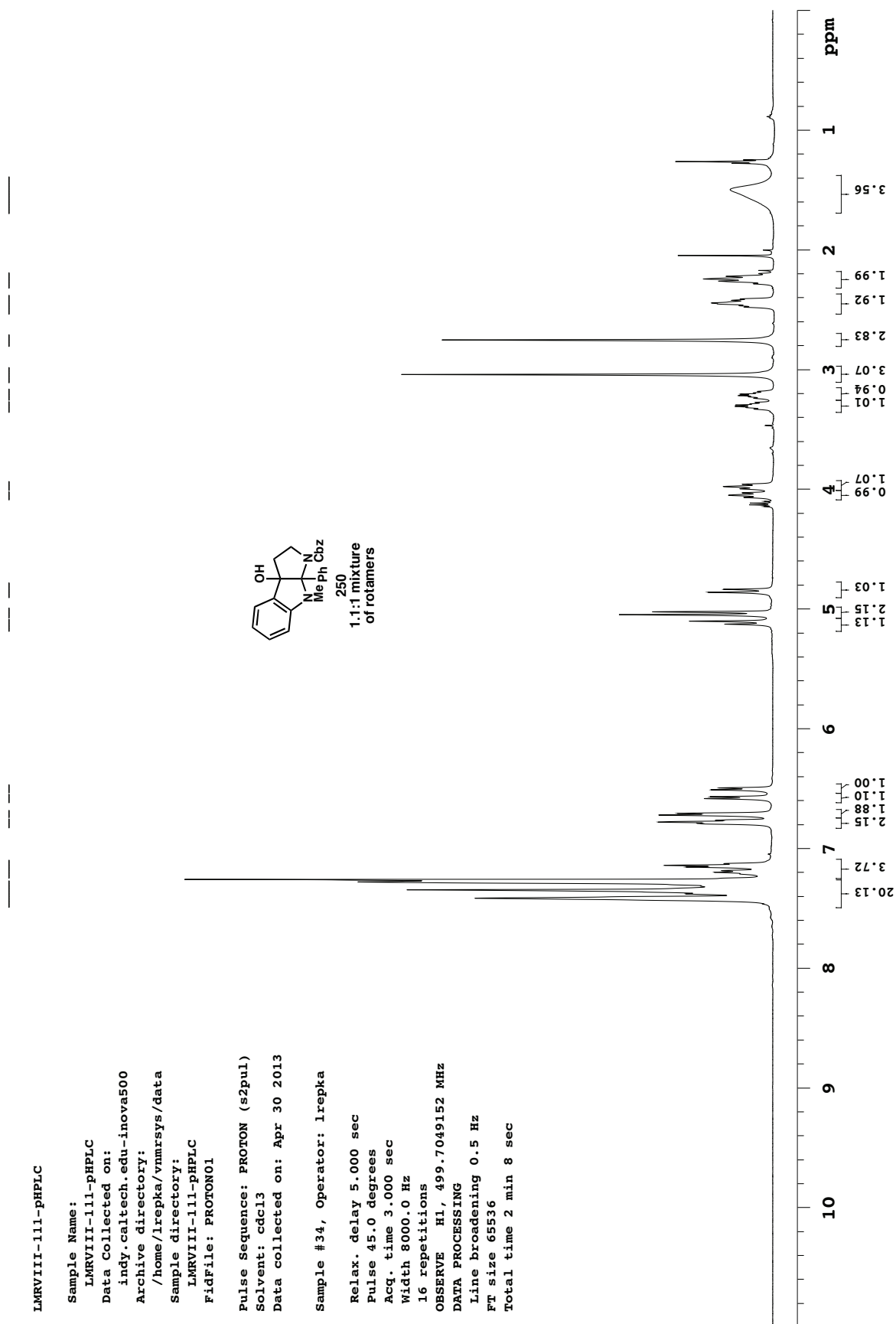
Line broadening 0.5 Hz

FT size 65536

Total time 2 min 8 sec



250
1:1:1 mixture
of rotamers



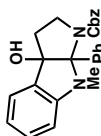
LMRVIII-111-PHPLC

Sample Name:
LMRVIII-111-PHPLC
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVIII-111-PHPLC
FidFile: CARBON01

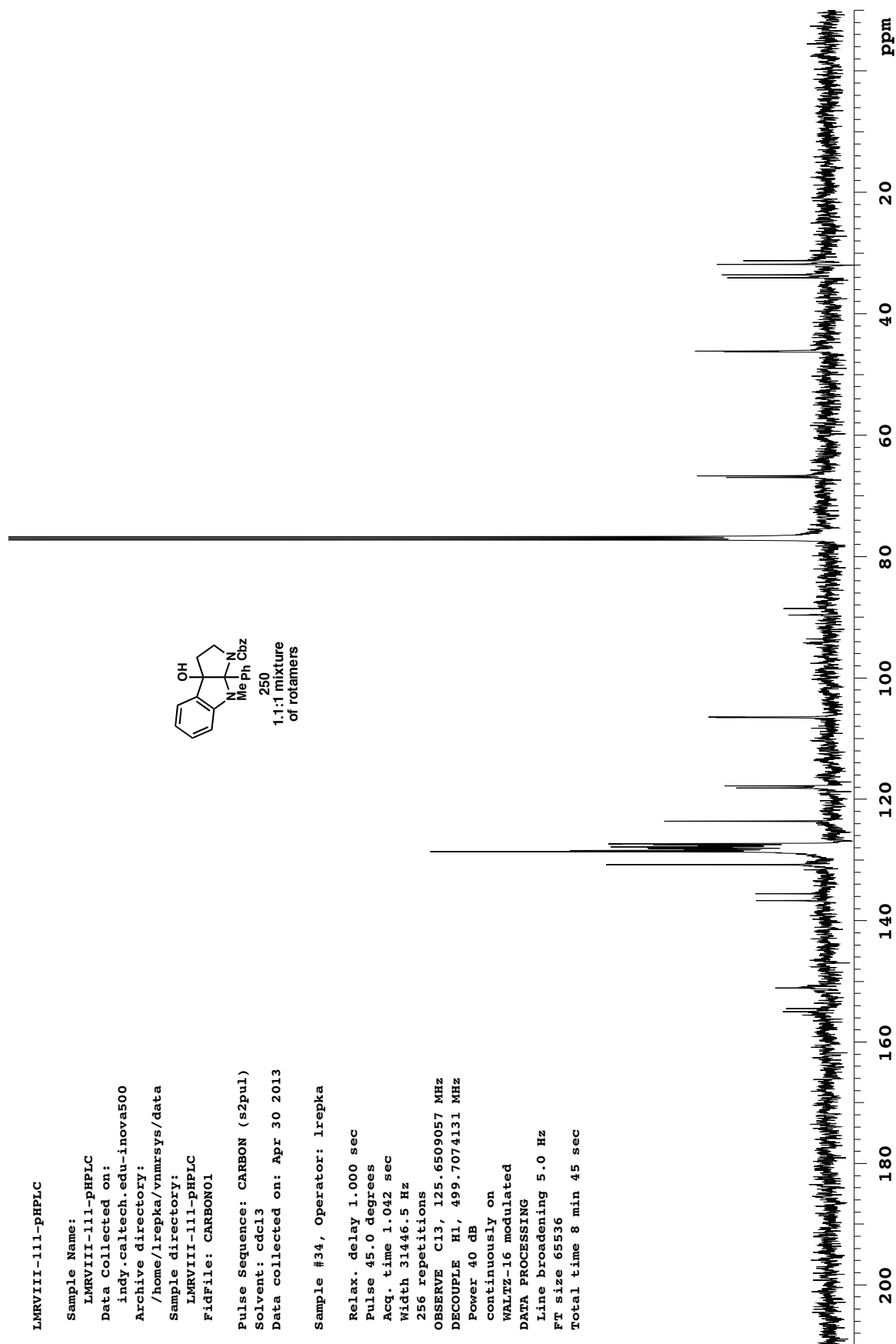
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2013

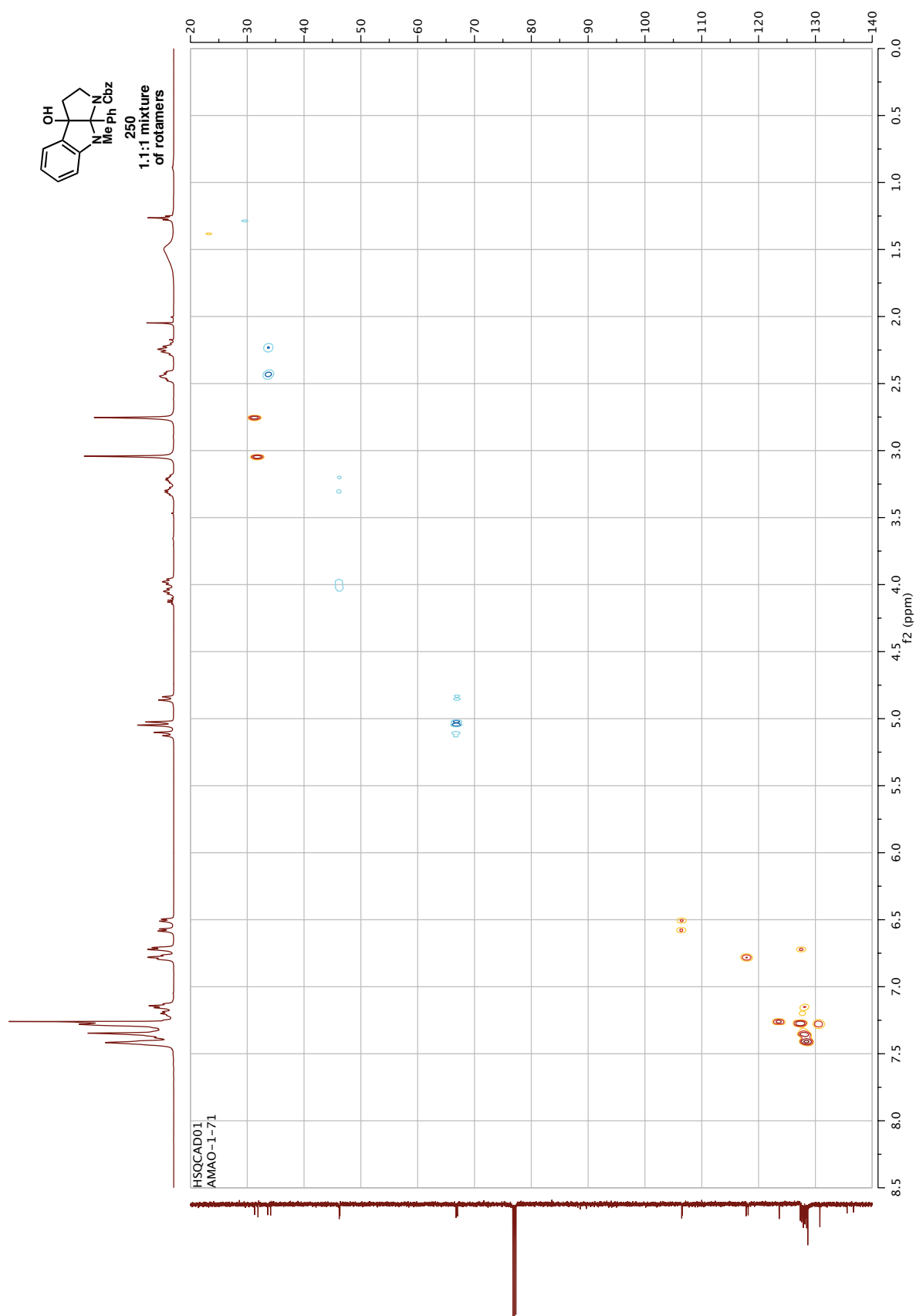
Sample #34, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6509057 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 8 min 45 sec



250
1:1:1 mixture
of rotamers





AMAO-1-98-F12-F14

Sample Name:

AMAO-1-98-F12-F14

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-98-F12-F14

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Apr 2 2013

Temp. 25.0 C / 298.1 K

Sample #14, Operator: amao

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.728 sec

Width 3003.0 Hz

16 repetitions

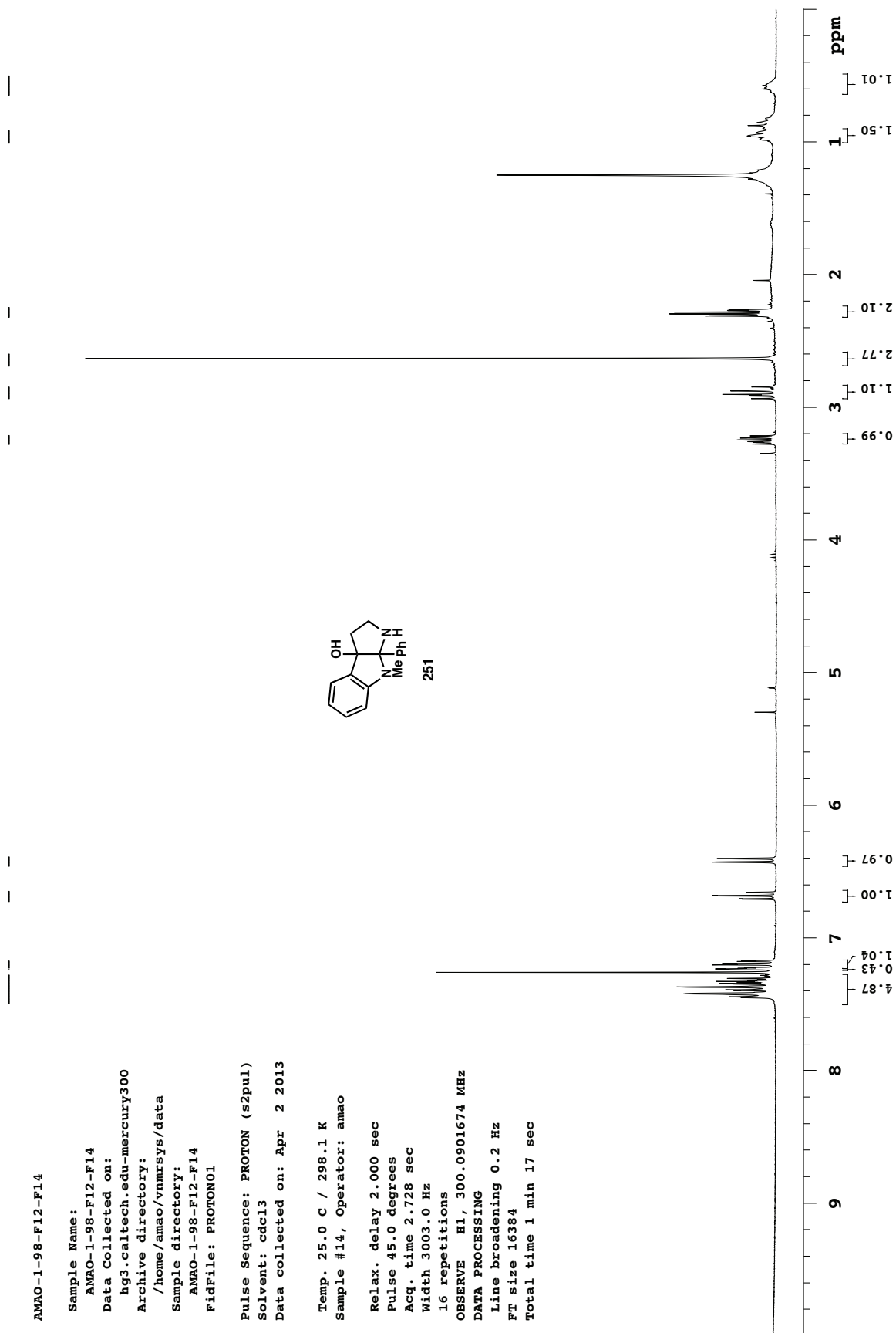
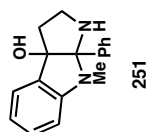
OBSERVE H1, 300.0901674 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 16384

Total time 1 min 17 sec



LMRVIII-113

Sample Name:

LMRVIII-113

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/lrepka/vnmrSYS/data

Sample directory:

LMRVIII-113

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: May 1 2013

Sample #34, Operator: lrepka

Relax. delay 0.200 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

3600 repetitions

OBSERVE C13, 125.6509034 MHz

DECOUPLE H1, 499.7074131 MHz

Power 40 dB

continuously on

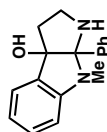
WALTZ-16 modulated

DATA PROCESSING

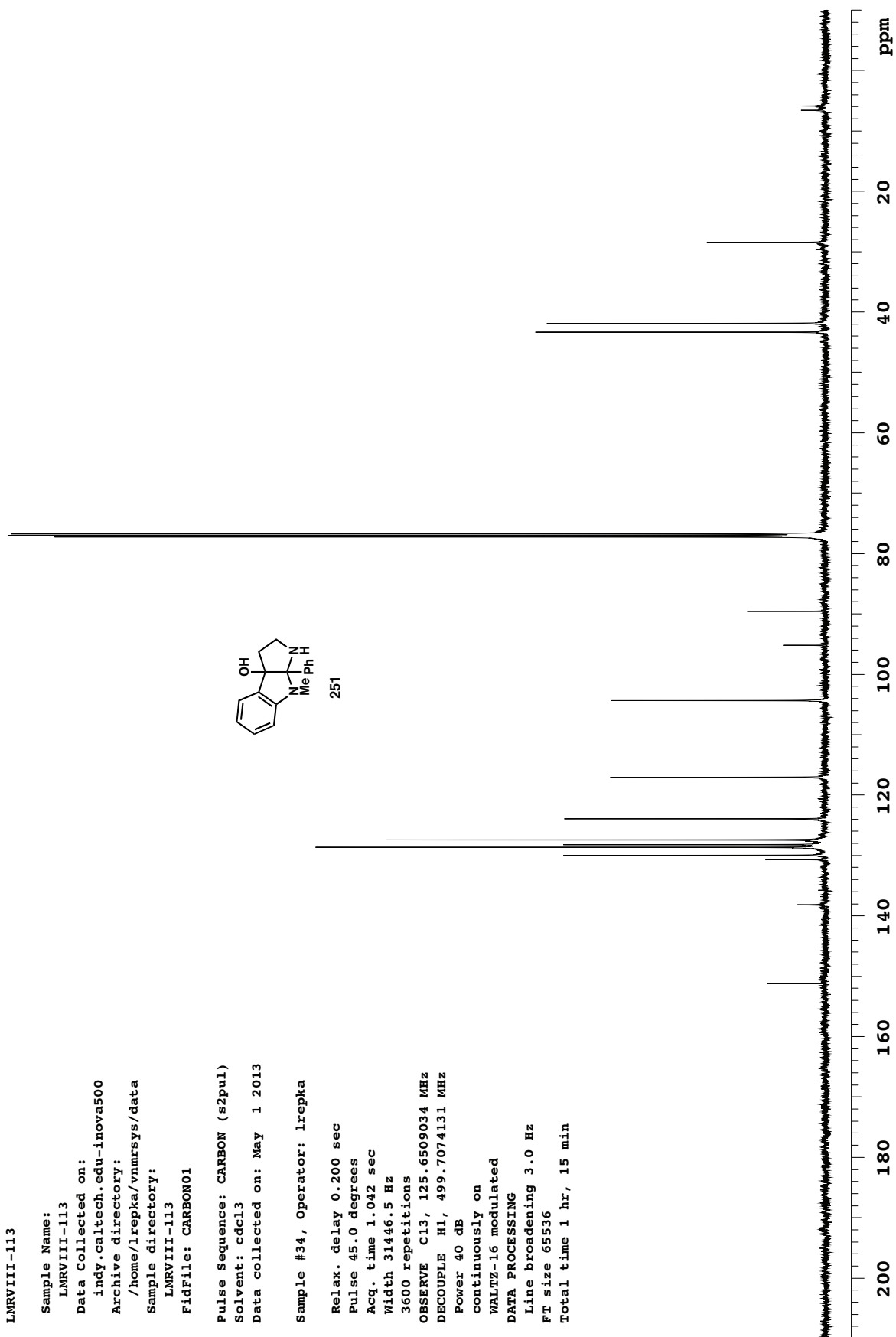
Line broadening 3.0 Hz

FT size 65536

Total time 1 hr, 15 min



251



AMAO-1-21-D

Sample Name:

AMAO-1-21-D

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-21-D

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jan 31 2013

Sample #21, Operator: amao

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 7995.2 Hz

16 repetitions

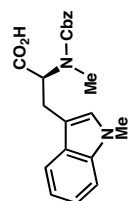
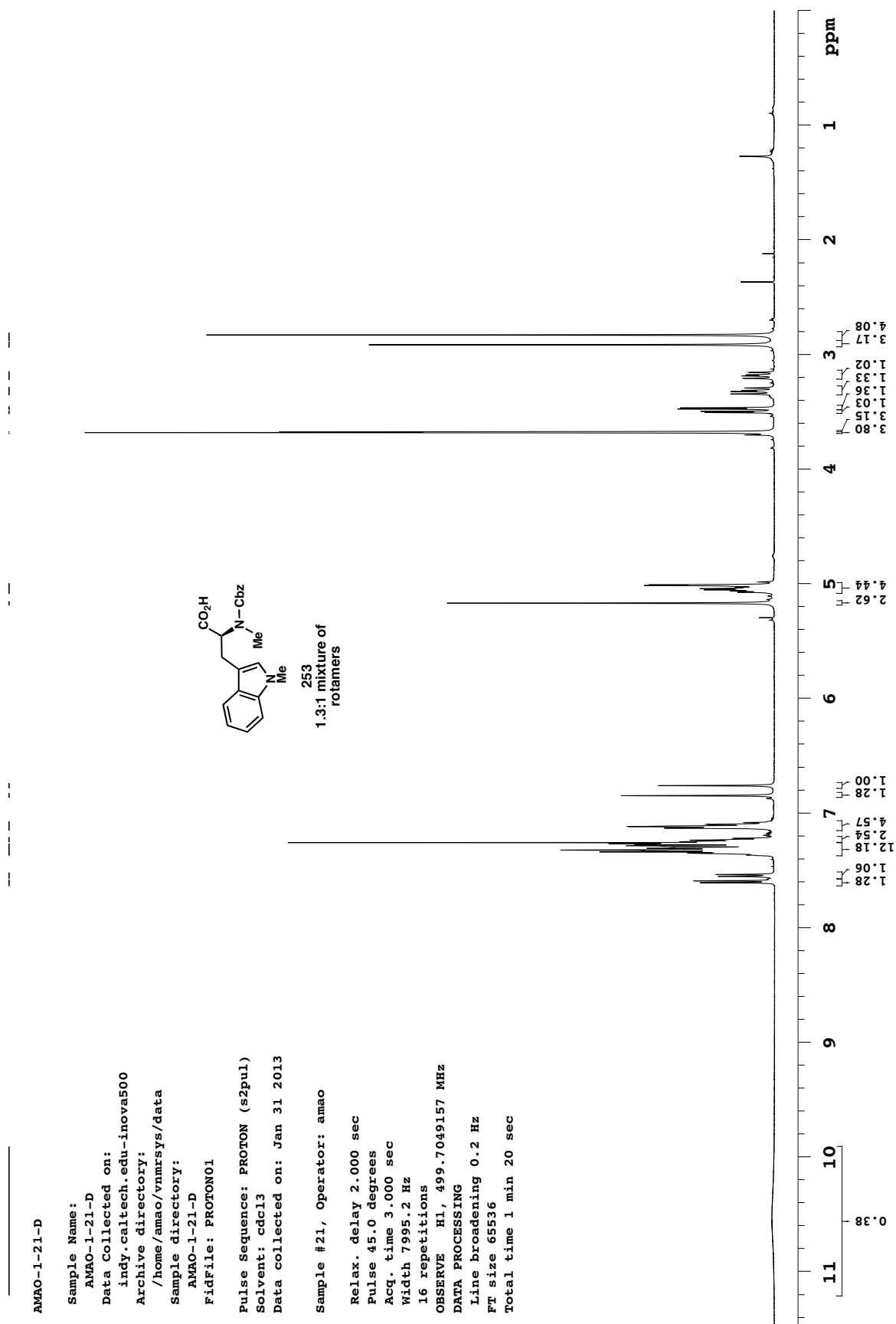
OBSERVE H1, 499.7049157 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 1 min 20 sec

253
1.3:1 mixture of
rotamers

AMAO-1-21E

Sample Name:

AMAO-1-21E

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-21E

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Feb 4 2013

Sample #5, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.043 sec

Width 31409.5 Hz

1000 repetitions

OBSERVE C13, 125.6509118 MHz

DECOUPLE H1, 499.7074131 MHz

Power 39 dB

continuously on

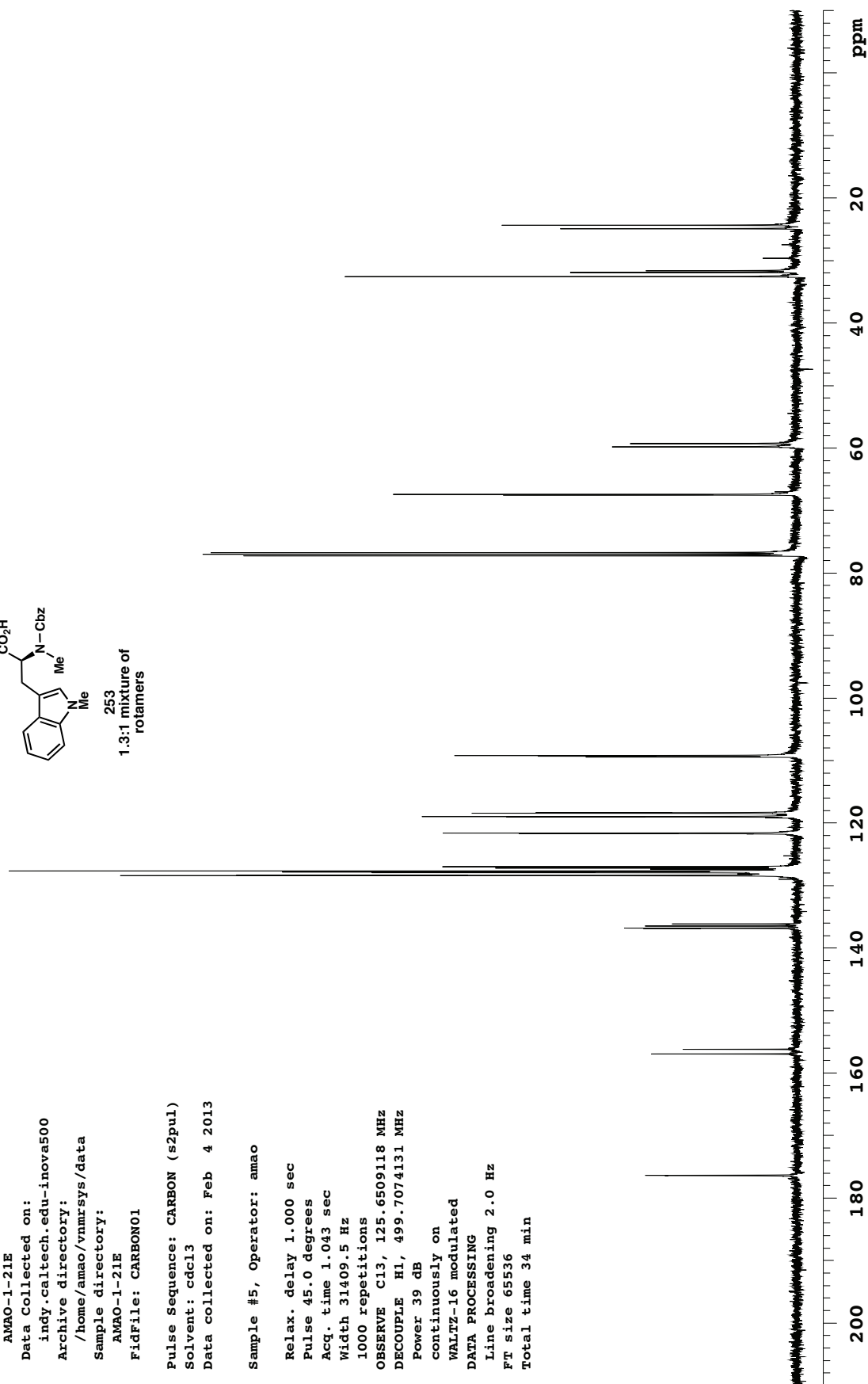
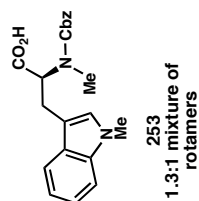
WALTZ-16 modulated

DATA PROCESSING

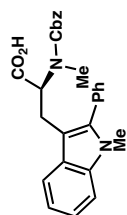
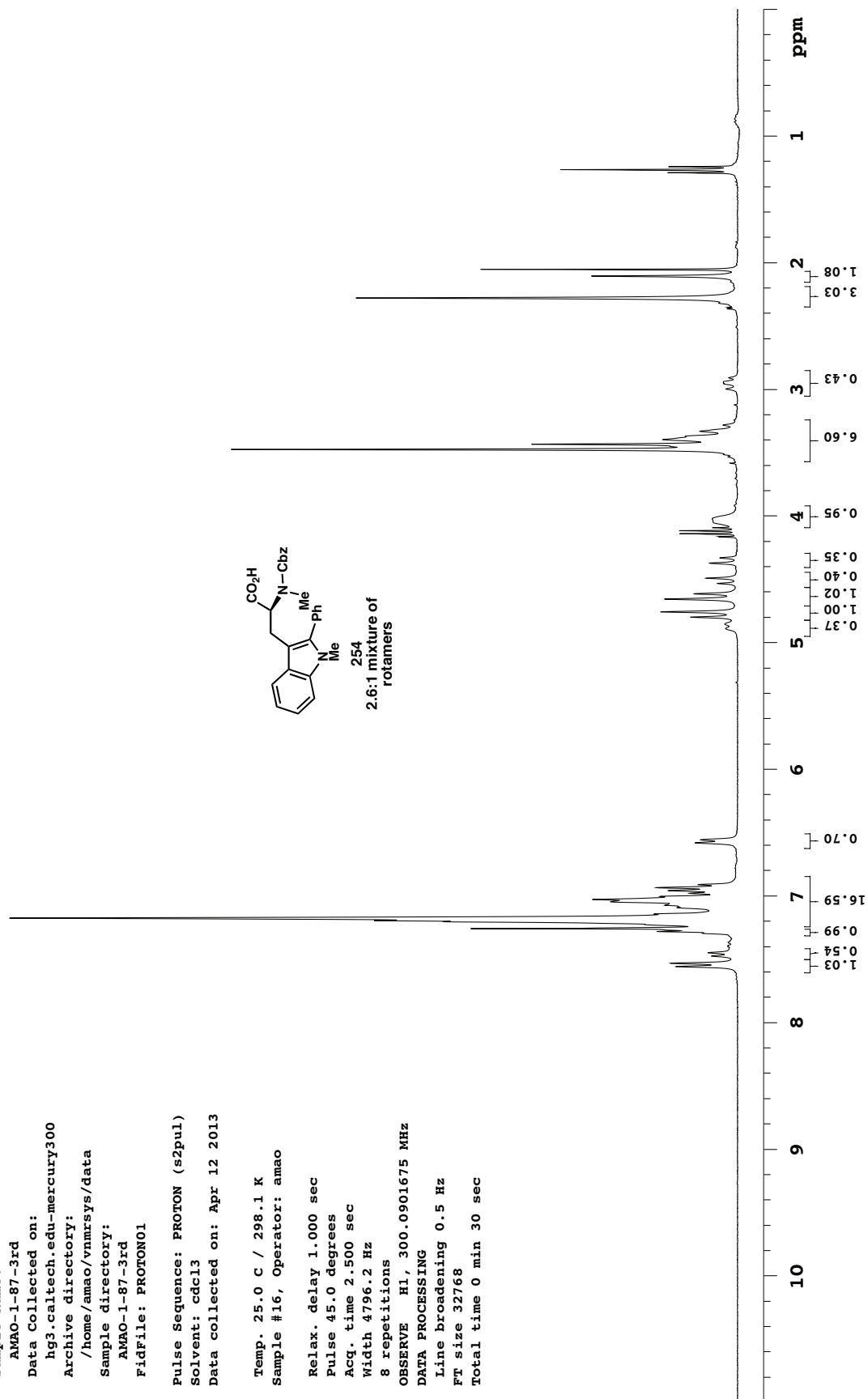
Line broadening 2.0 Hz

FT size 65536

Total time 34 min



Total time 0 min 30 sec

254
2.6:1 mixture of
rotamers

AMAO-1-41-42B

Sample Name:

AMAO-1-41-42B

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-41-42B

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Feb 10 2013

Sample #14, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.043 sec

Width 31409.5 Hz

1000 repetitions

OBSERVE C13, 125.6509097 MHz

DECOUPLE H1, 499.7074131 MHz

Power 39 dB

continuously on

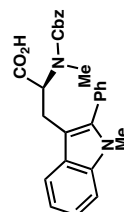
WALTZ-16 modulated

DATA PROCESSING

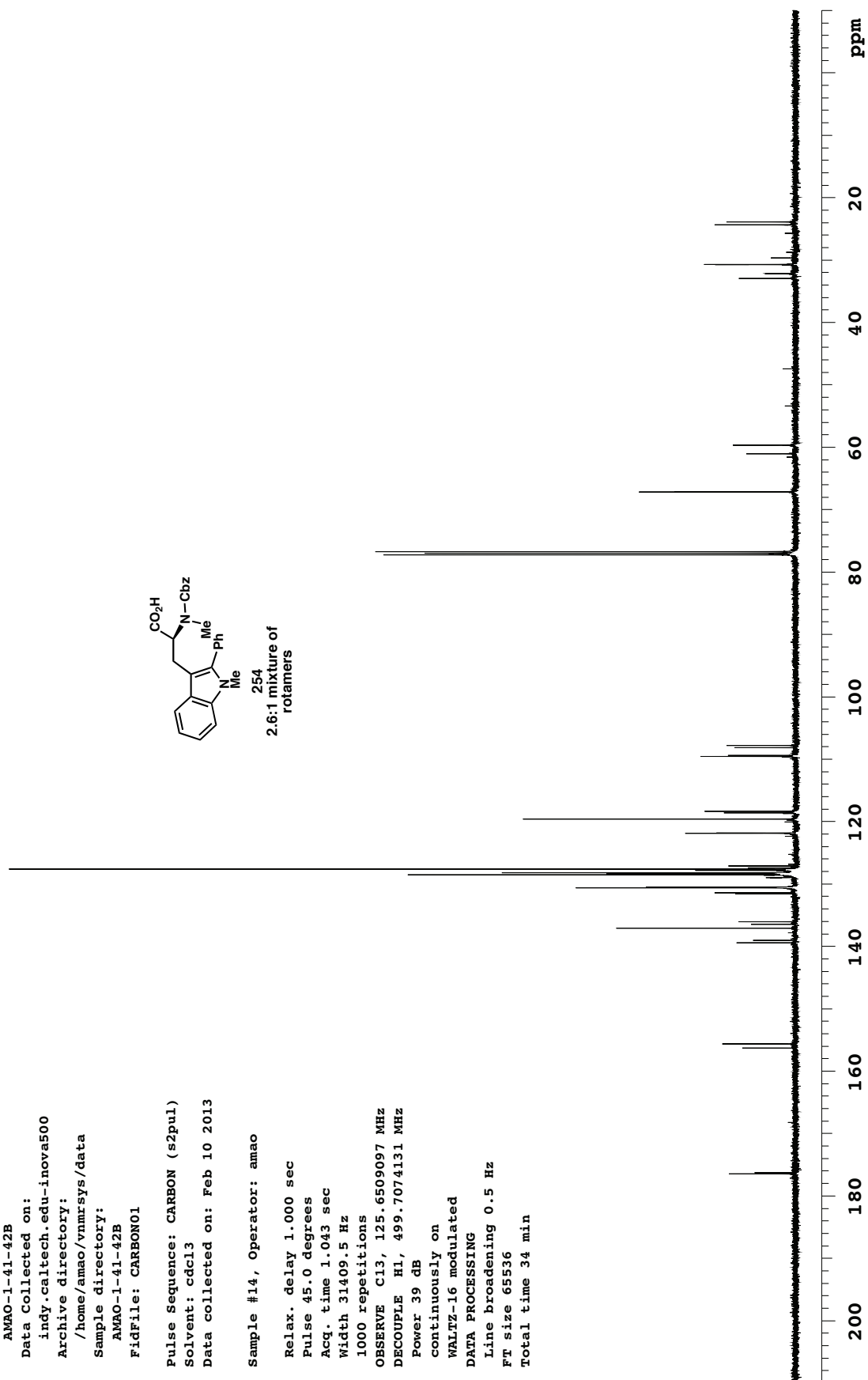
Line broadening 0.5 Hz

FT size 65536

Total time 34 min



254
2.6:1 mixture of
rotamers



AMAO-1-74

Sample Name:

AMAO-1-74

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrSYS/data

Sample directory:

AMAO-1-74

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Mar 7 2013

Sample #30, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 8000.0 Hz

8 repetitions

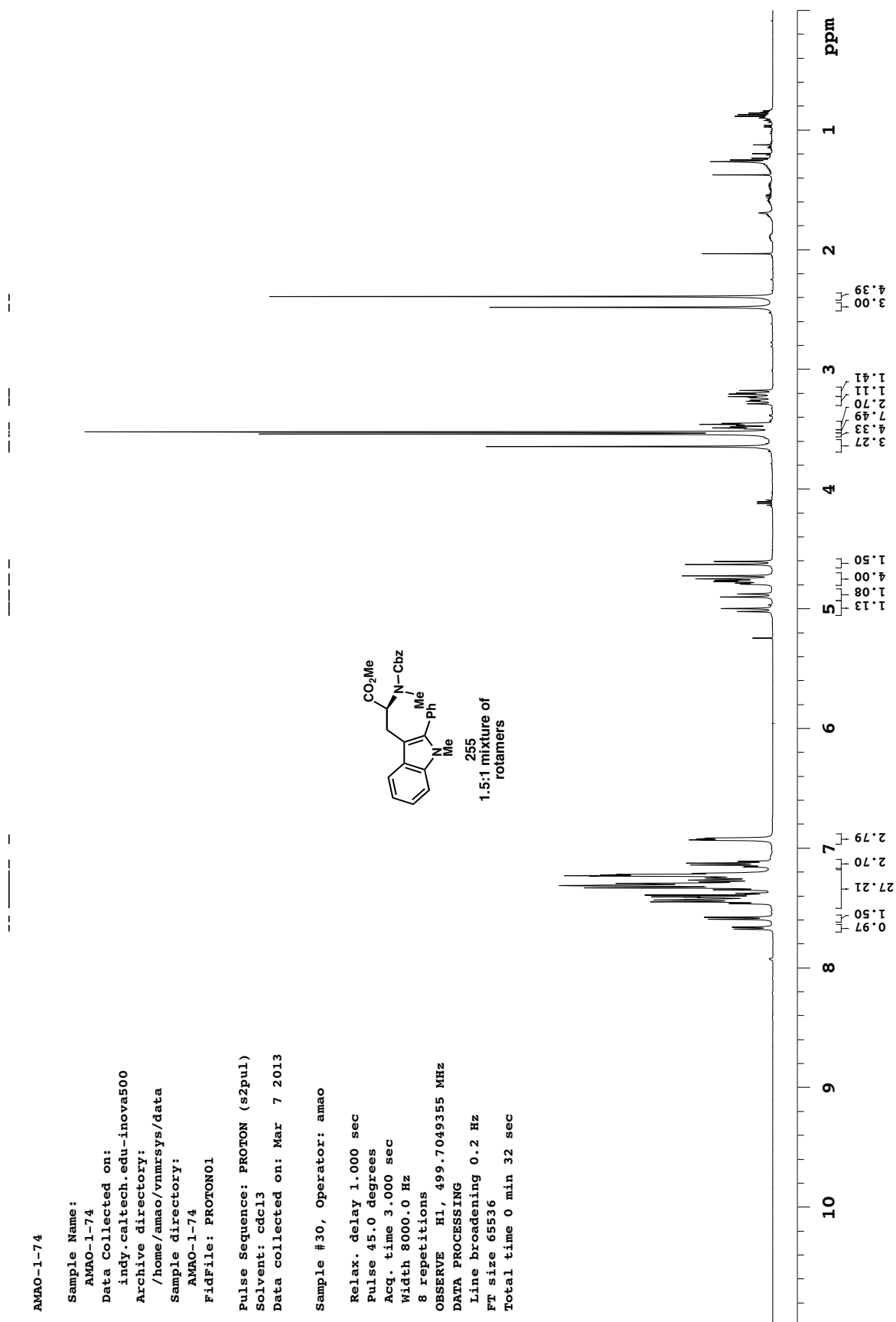
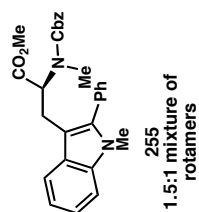
OBSERVE H1, 499.7049355 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 0 min 32 sec



AMAO-1-74

Sample Name:

AMAO-1-74

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-74

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Mar 8 2013

Sample #30, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6509173 MHz

DECOUPLE H1, 499.7074131 MHz

Power 39 dB

continuously on

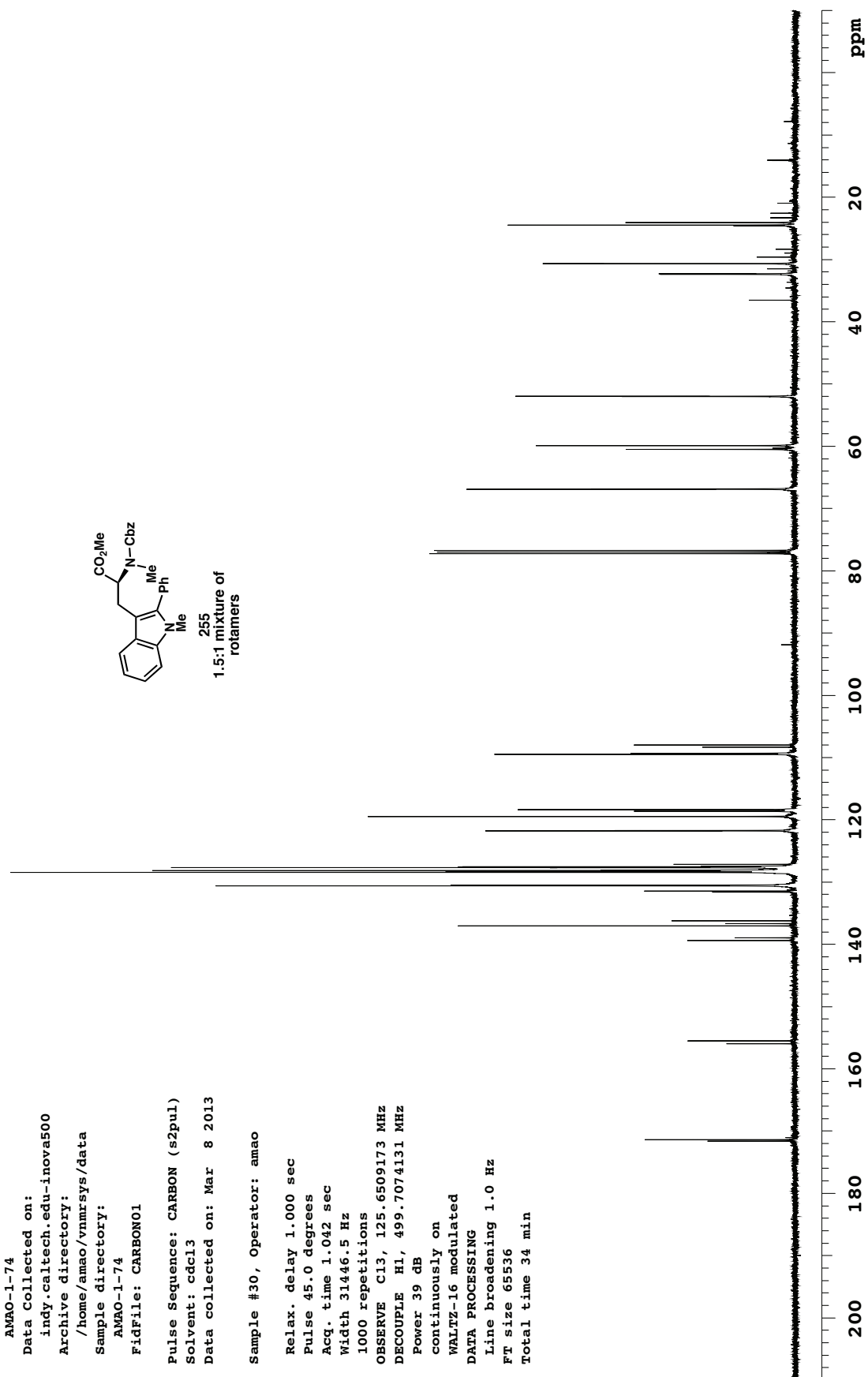
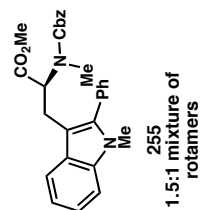
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 34 min



AMAO-1-103

Sample Name:

AMAO-1-103

Data Collected on:

indy.caltech.edu-inova500

Archive directory:

/home/amao/vnmrsys/data

Sample directory:

AMAO-1-103

FidFile: PROTON02

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: May 1 2013

Sample #1, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 3.000 sec

Width 8000.0 Hz

8 repetitions

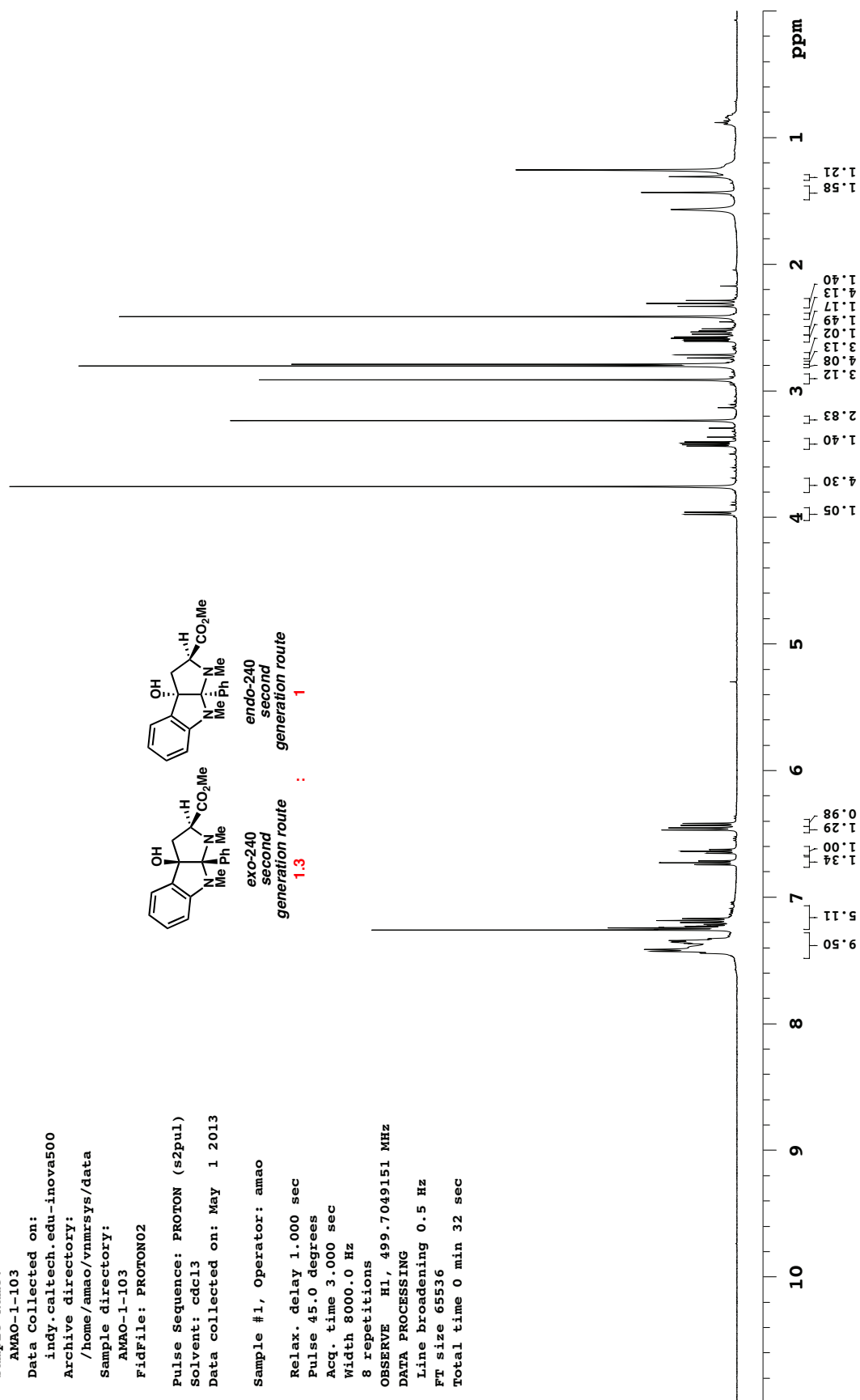
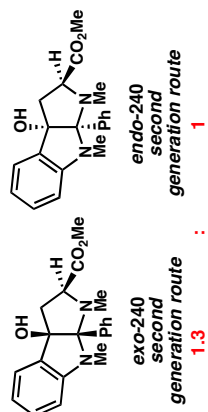
OBSERVE H1, 499.7049151 MHz

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 0 min 32 sec

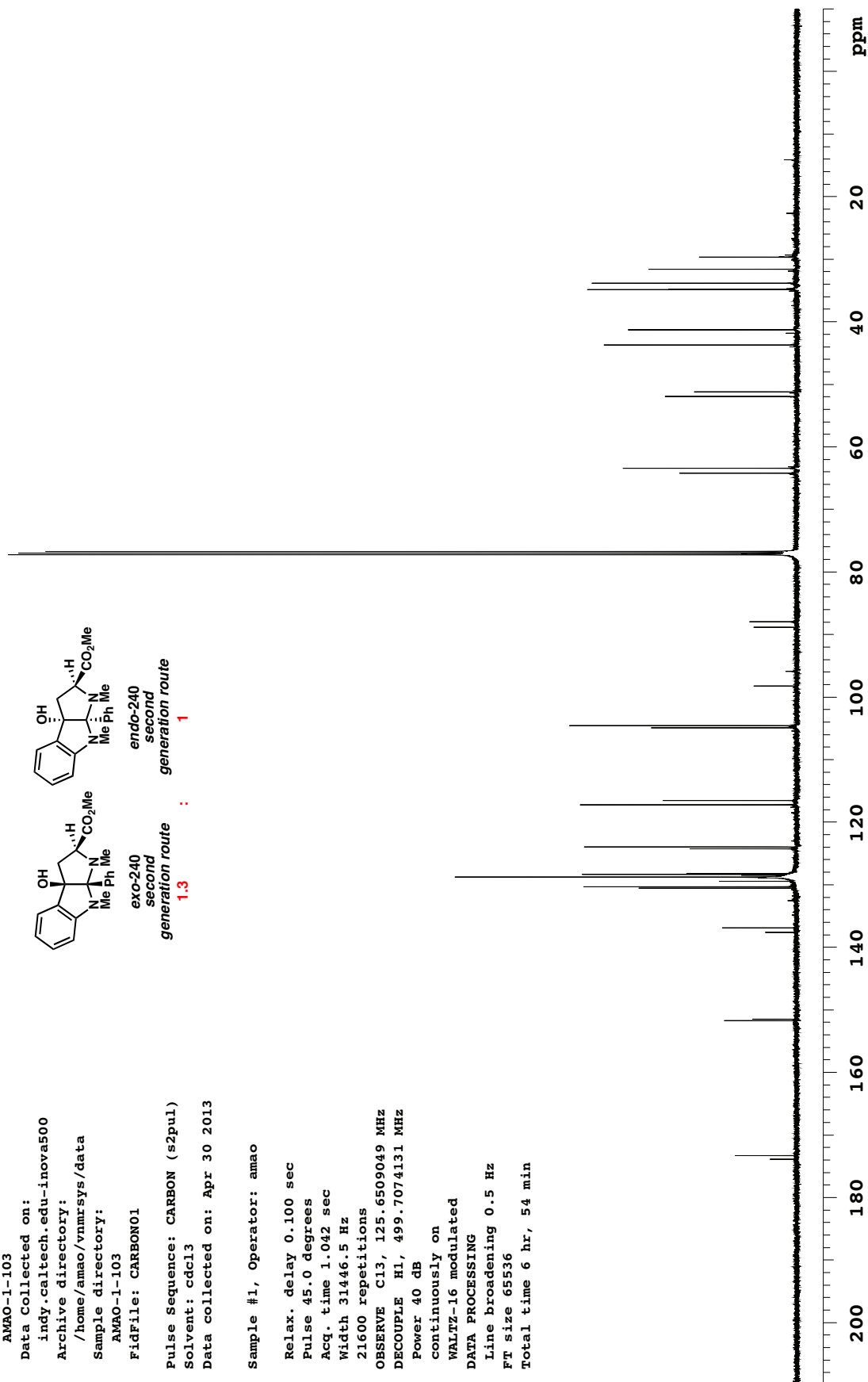


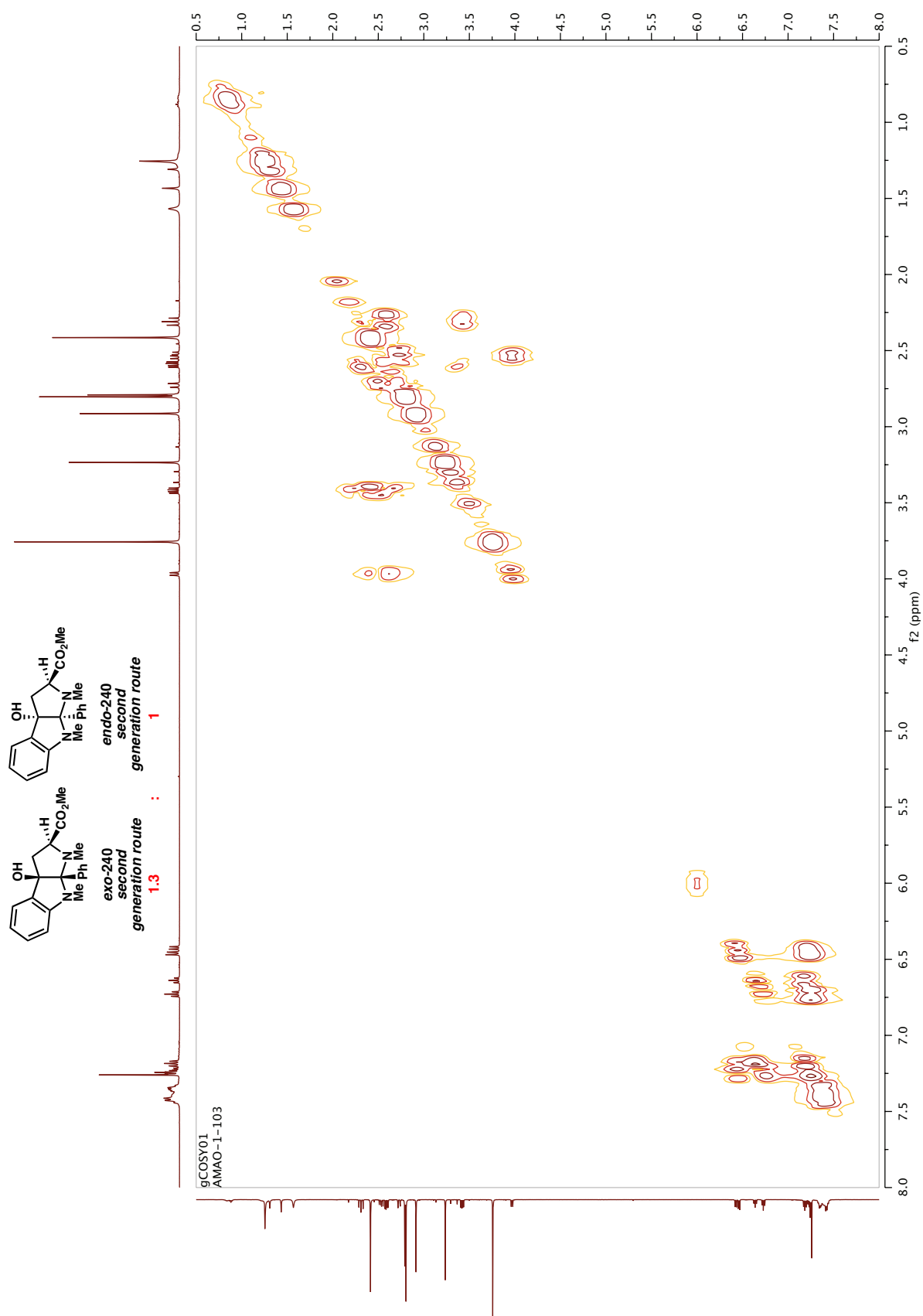
AMAO-1-103

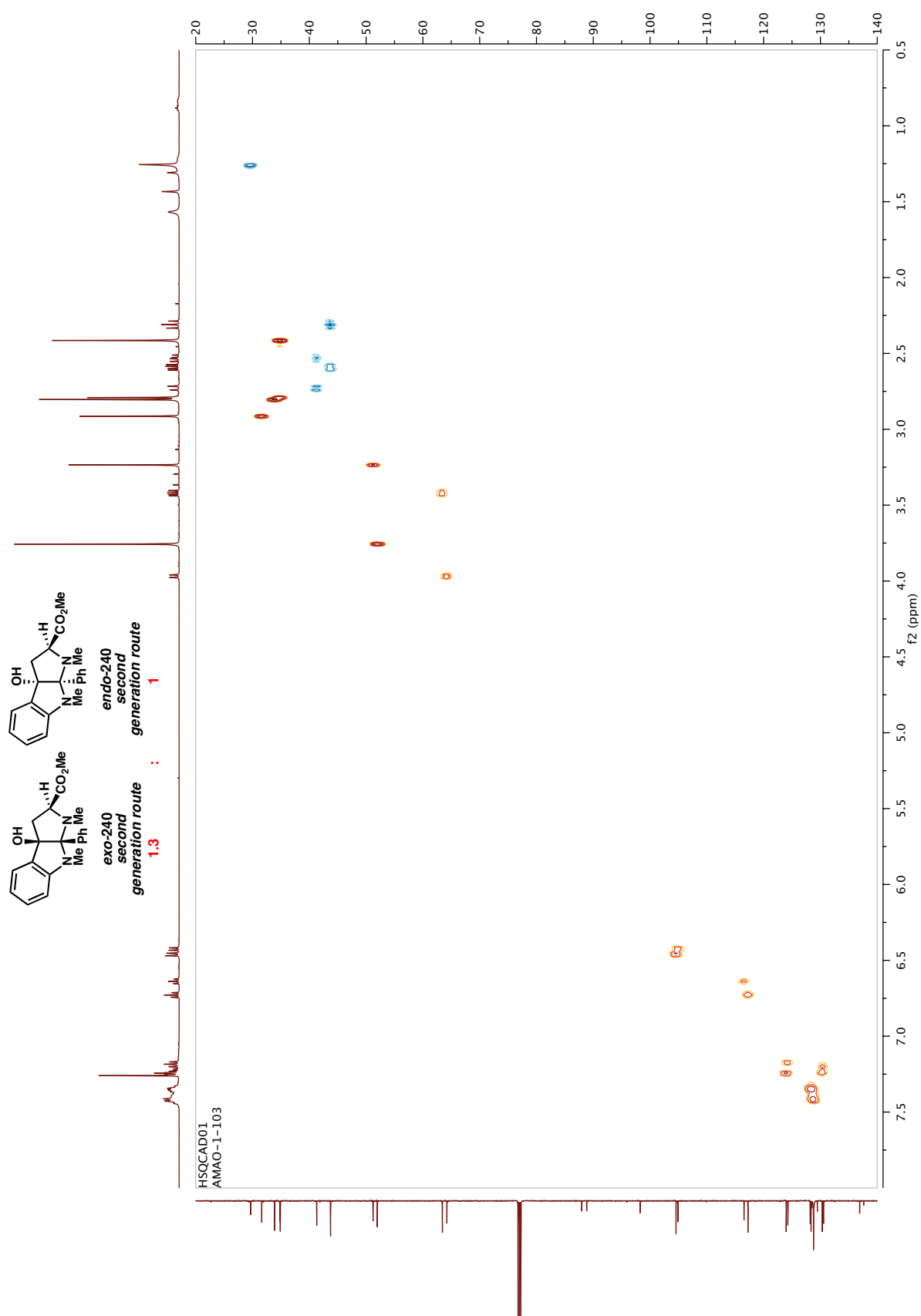
Sample Name:
AMAO-1-103
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/amao/vnmrsys/data
Sample directory:
AMAO-1-103
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2013

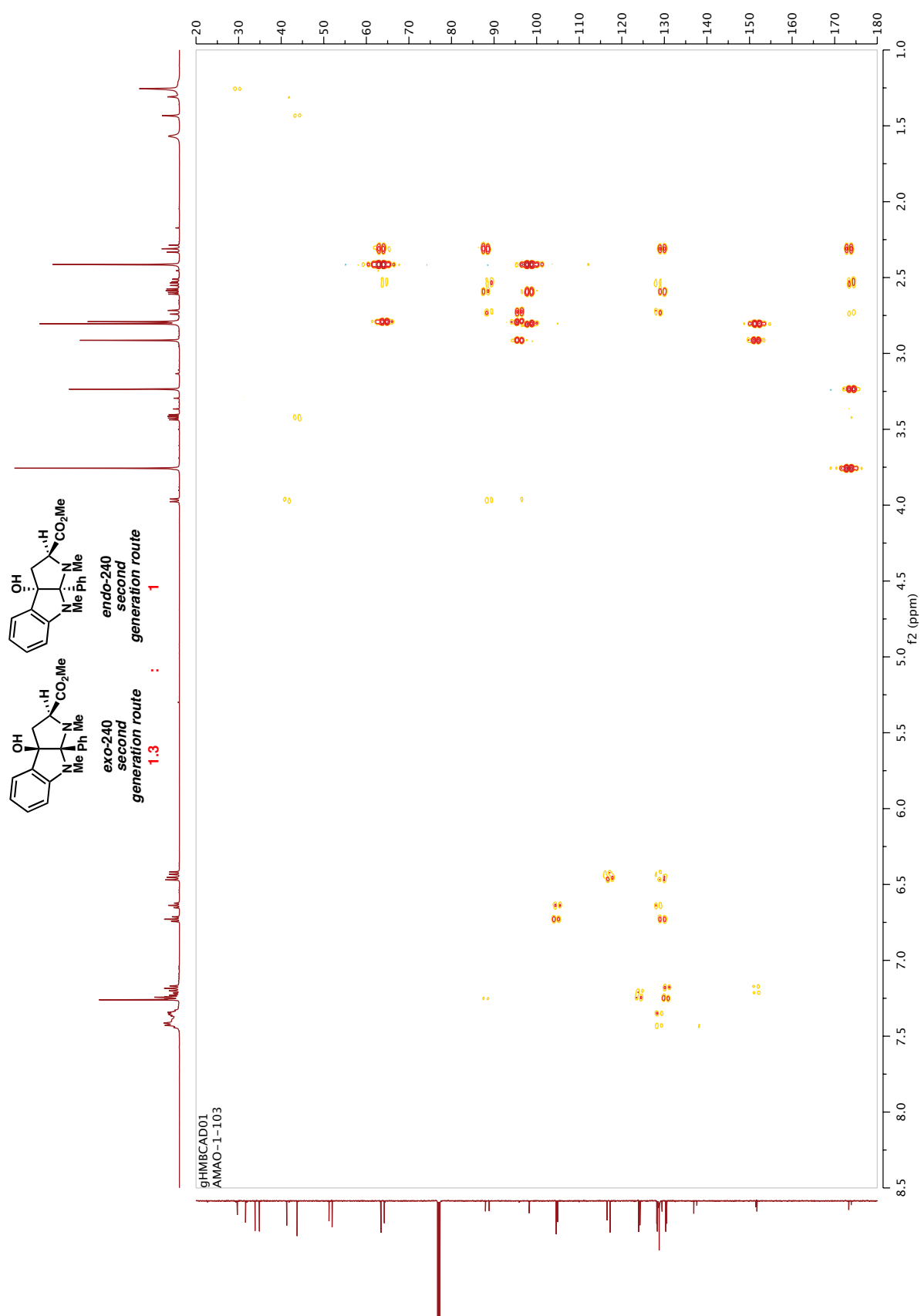
Sample #1, Operator: amao

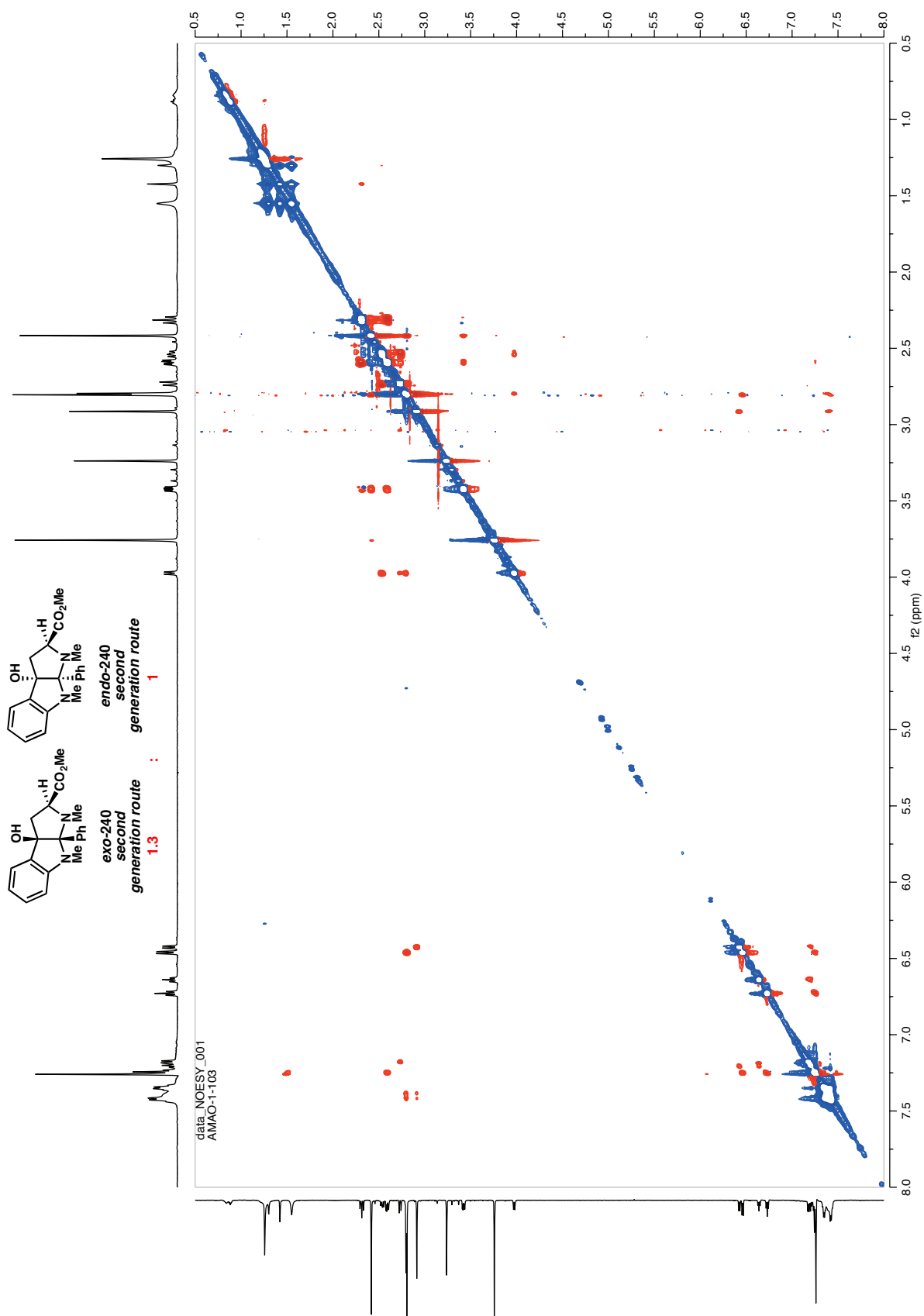
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
21600 repetitions
OBSERVE C13, 125.6509049 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 6 hr, 54 min

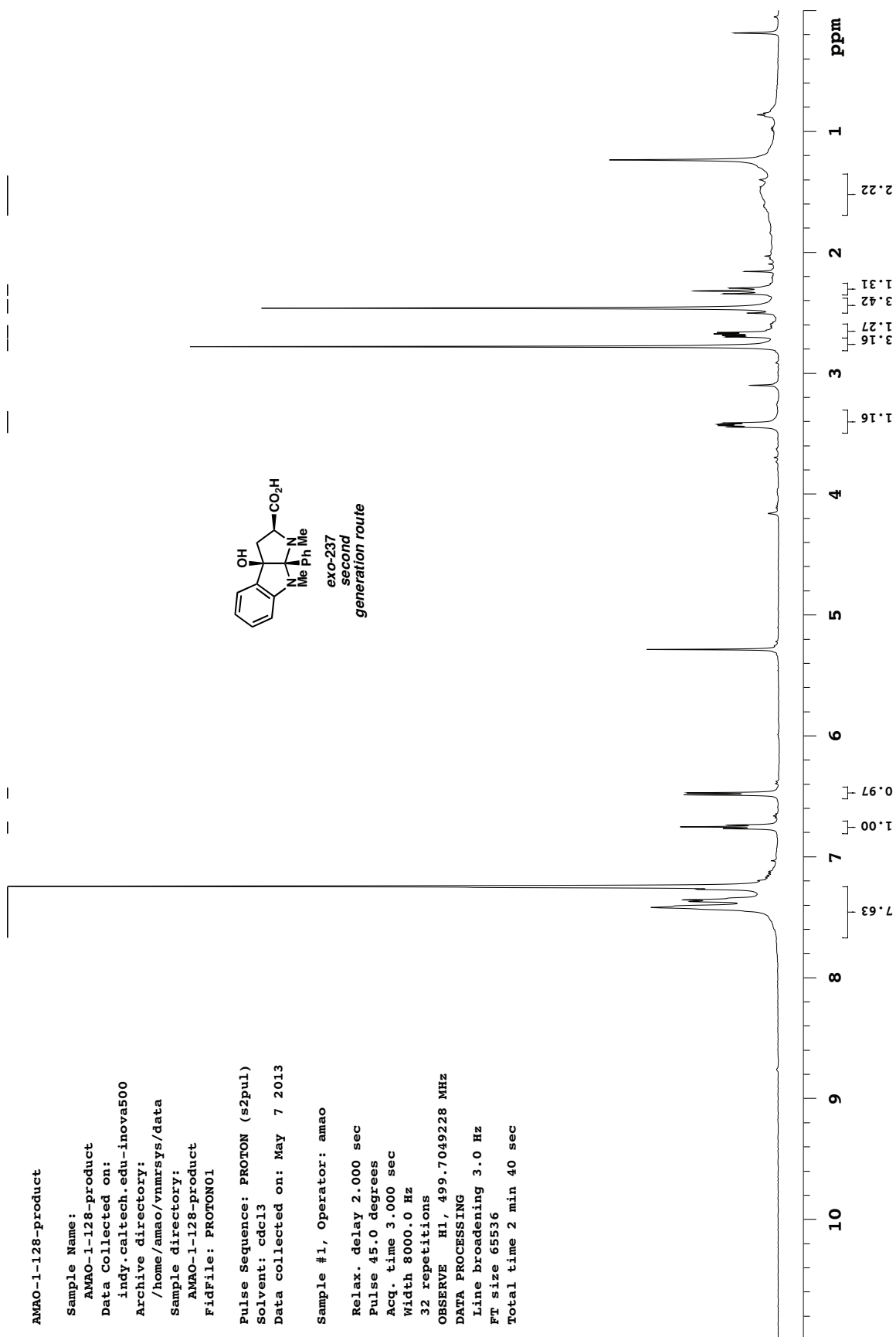












AMAO-1-128-F11-F14

Sample Name:

AMAO-1-128-F11-F14

Data Collected on:

hg3.caltech.edu-mercury300

Archive directory:

/home/amao/vnmrsvs/data

Sample directory:

AMAO-1-128-F11-F14

FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: May 7 2013

Temp. 25.0 C / 298.1 K

Sample #2, Operator: amao

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 2.500 sec

Width 4796.2 Hz

32 repetitions

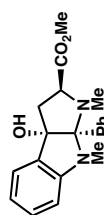
OBSERVE H1, 300.0901672 MHz

DATA PROCESSING

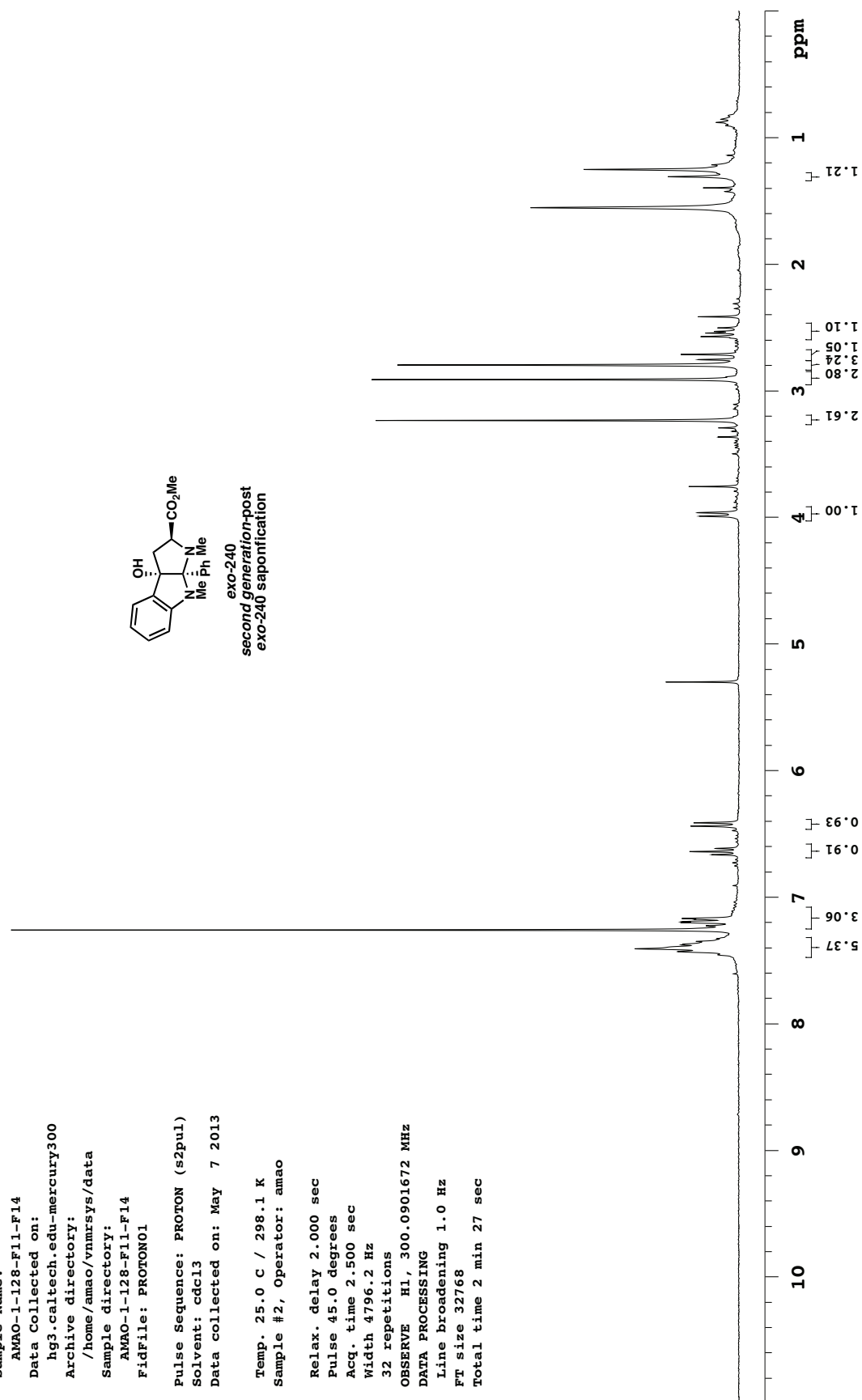
Line broadening 1.0 Hz

FT size 32768

Total time 2 min 27 sec



exo-240
second generation-post
exo-240 saponification



ABOUT THE AUTHOR

Lindsay Michelle Repka was born on May 24th, 1986 in Baltimore, Maryland to Mary Anne Facciolo and Michael X. Repka. She attended the Friends School of Baltimore from the age of six up through the end of high school. Lindsay grew up playing tennis and music, most passionately pursuing the violin and thus participating in many high school musicals. Both of her parents practice medicine and her older brother, Michael C. Repka, received his MD from their alma mater, Jefferson Medical College, this past May.

Lindsay's decision to pursue chemistry as a career resulted from an exceptional introduction at Friends in a course taught by Kenneth Drews. After graduating from high school in 2004, she moved to New York City to attend Barnard College as a chemistry major. In the fall of her second year, she took a course taught by Professor Christian Rojas, a talented teacher who aptly demonstrated both the power and elegance of organic chemistry. During the summer of 2007, Lindsay completed research in materials chemistry with Professor John Tovar at Johns Hopkins University and then pursued her senior thesis studies on amidoglycosylation reactions under the direction of Christian Rojas.

In 2008, two months after graduating from Barnard, Lindsay moved to Pasadena to join the group of Professor Sarah Reisman at the California Institute of Technology. She earned her Ph.D. in July 2013 for investigations in enantioselective synthesis of pyrroloindolines and tryptophan derivatives. In the fall of 2013, Lindsay began postdoctoral studies in the group of Professor Wilfred van der Donk at the University of Illinois at Urbana–Champaign.