DEVELOPMENT OF ASYMMETRIC PROTONATION REACTIONS FOR THE SYNTHESIS OF INDOLINE ALKALOIDS

Thesis by

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To my teachers

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movies. Nevertheless we seem to get along, and he has kept me balanced during these crazy years.

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ABSTRACT

Nitrogen-containing heterocycles, such as indolines and pyrroloindolines, are prevalent in a variety of diverse natural products, many of which exhibit remarkable biological activities. These frameworks have inspired innovative research aimed at discovering novel methods for their stereoselective preparation.

We have developed an enantioselective synthesis of pyrroloindolines based on a formal (3 + 2) cycloaddition of indoles and 2-amidoacrylates. This reaction is promoted by (*R*)-BINOL•$SnCl_4$; this complex is a Lewis acid-assisted Brønsted acid that effects a highly face-selective catalyst-controlled protonation of an enolate. Mechanistic studies also determined that the initial product of this reaction is an indolinium ion, which upon aqueous workup undergoes cyclization to the pyrroloindoline.

Based on this result, we investigated alternative nucleophiles to trap the indolinium ion. First, addition of sodium borohydride to the optimized reaction conditions yields indoline-containing amino acid derivatives.

Next, carbon nucleophiles were explored. Indole substrates incorporating a tethered alkene were exposed to the conditions for the formal (3 + 2) cycloaddition, resulting in a conjugate addition/asymmetric protonation/Prins cyclization cascade. In this transformation, the indolinium ion is attacked by the olefin, and the resulting carbocation is quenched by a chloride ion. Zirconium tetrachloride was found to be the optimal Lewis acid. Stoichiometric proton and chloride sources were also found to be crucial for reactivity.

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LIST OF ABBREVIATIONS

A	alanine
AAA	Asymmetric Allylic Alkylation
Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1'-Bi(2-naphthol)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
br	broad
BTF	benzotrifluoride
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
Bz	benzoyl
c	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′-diyl)bis[bis(3,5-dimethylphenyl)phosphine]
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
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 exempli gratia)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
ETP	epidithiodiketopiperazine
FAB	fast atom bombardment
FID	flame ionization detector
FT	fourier transform
g	gram(s)
gCOSY	gradient-selected correlation spectroscopy
gHMBC	gradient-selected heteronuclear multiple bond correlation
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
IPA	isopropanol
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
LA	Lewis acid

LAH	lithium aluminum hydride
LBA	Lewis acid-assisted Brønsted acid
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
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
MHz	megahertz
μ	micro
μwaves	microwave irradiation
min	minute(s)
MM	multimode
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
nr	no reaction
o	ortho
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Phth	phthaloyl
PhMe	toluene
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
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
sat.	saturated
SFC	supercritical fluid chromatography
t	triplet
TBS	*tert*-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	*p*-toluenesulfonyl (tosyl)
p-TSA	*p*-toluenesulfonic acid
UV	ultraviolet
v/*v*	volume to volume
w/*v*	weight to volume
X	anionic ligand or halide

CHAPTER 1

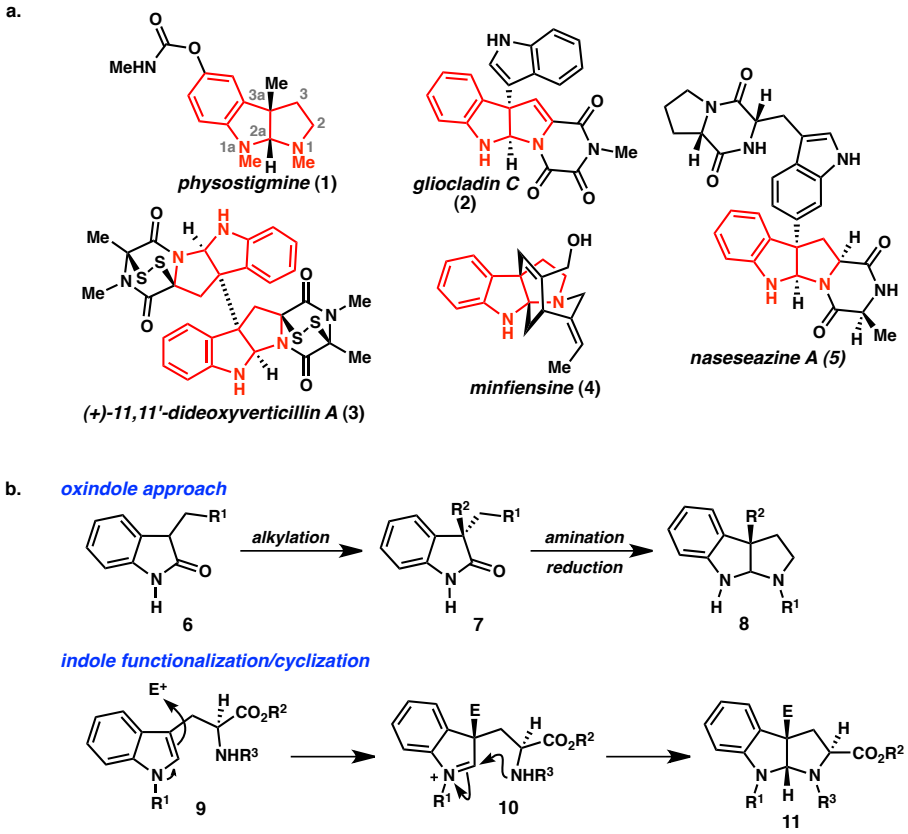
Strategies for the Total Synthesis of Pyrroloindoline Natural Products

1.1 Introduction

The pyrroloindoline motif (denoted in red, Figure 1a) constitutes the core heterocyclic motif of a structurally diverse class of natural products. These compounds have been shown to exhibit remarkable biological activities in a broad range of pharmacological screens, including anticancer,[1,2] antibacterial,[3] anti-inflammatory[4] activities, as well as the inhibition of cholinesterase.[5] The C3a all-carbon quaternary center found in many of these compounds incorporates a wide variety of substituents. The inherent challenge of preparing such structures, combined with their promising medicinal value, has led to the development of a variety of methods for their synthesis.[6-8]

This chapter will provide an overview of strategies for the preparation of the pyrroloindoline motif in the context of natural product total synthesis. These synthetic approaches can generally be divided into two categories: (1) preparation of a suitably-functonalized oxindole, which can then be elaborated to the pyrroloindoline, and (2) tandem C3 functionalization of the indole followed by cyclization to form the pyrroloindoline (Figure 1b).

Figure 1. (a) Selected pyrroloindoline natural products. (b) Strategies for pyrroloindoline formation.

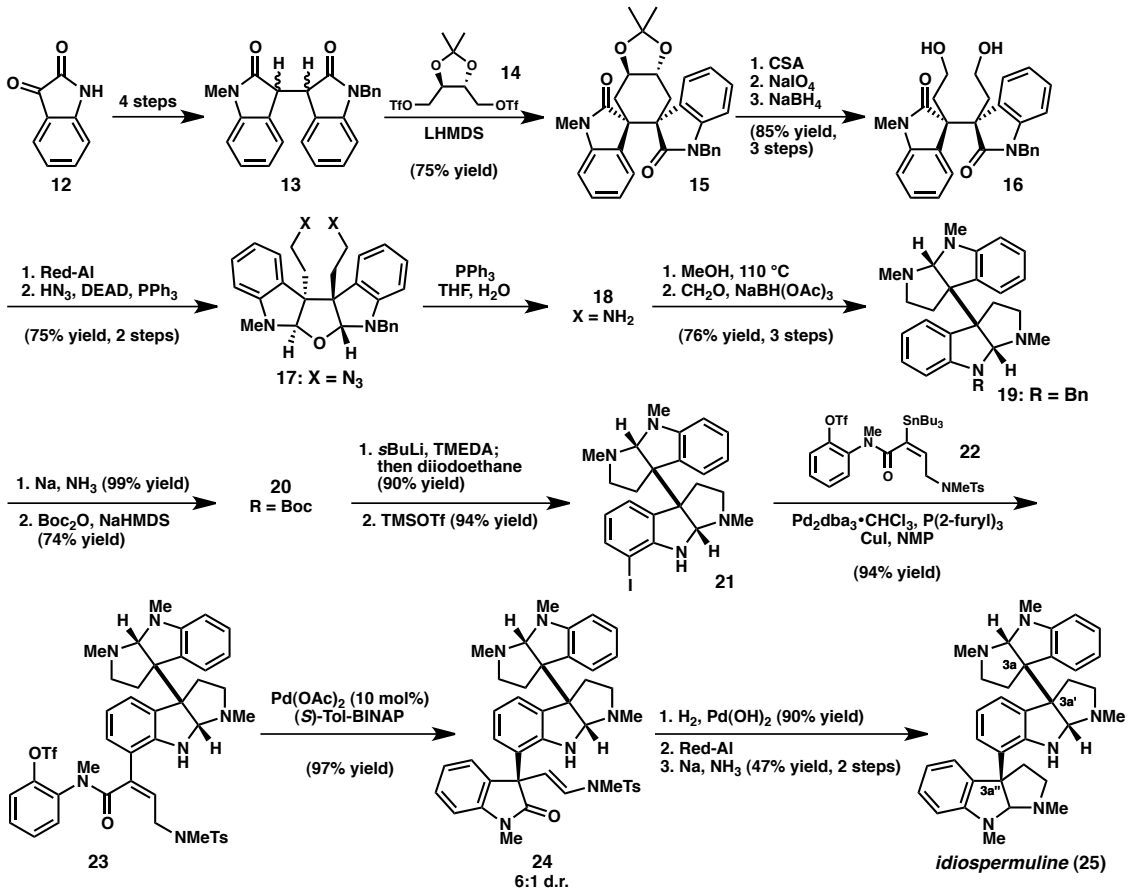


1.2 Pyrroloindoline Synthesis via Oxindoles

Various methods to prepare 3,3-disubstituted oxindoles have been developed, and these intermediates can in turn be elaborated to pyrroloindolines. Overman uses two distinct strategies to access 3,3-disubstituted oxindoles in his synthesis of idiospermuline (**25**), a natural product with three pyrroloindoine units linked together (Figure 2).[9] The two vicinal quaternary stereocenters (3a and 3a') were generated by the reaction of tartrate-derived dielectrophile **14** and the lithium dienolate of dihydroisoindigo **13**. Bisoxindole **15** was converted to bispyrroloindoline **19** via a sequence of several steps, including reduction with Red-Al to an unstable diol which was immediately converted to

diazide **17** by a Mitsunobu reaction. Reduction to diamine **18**, cyclization by heating, and reductive methylation yields bispyrroloindoline **19**.

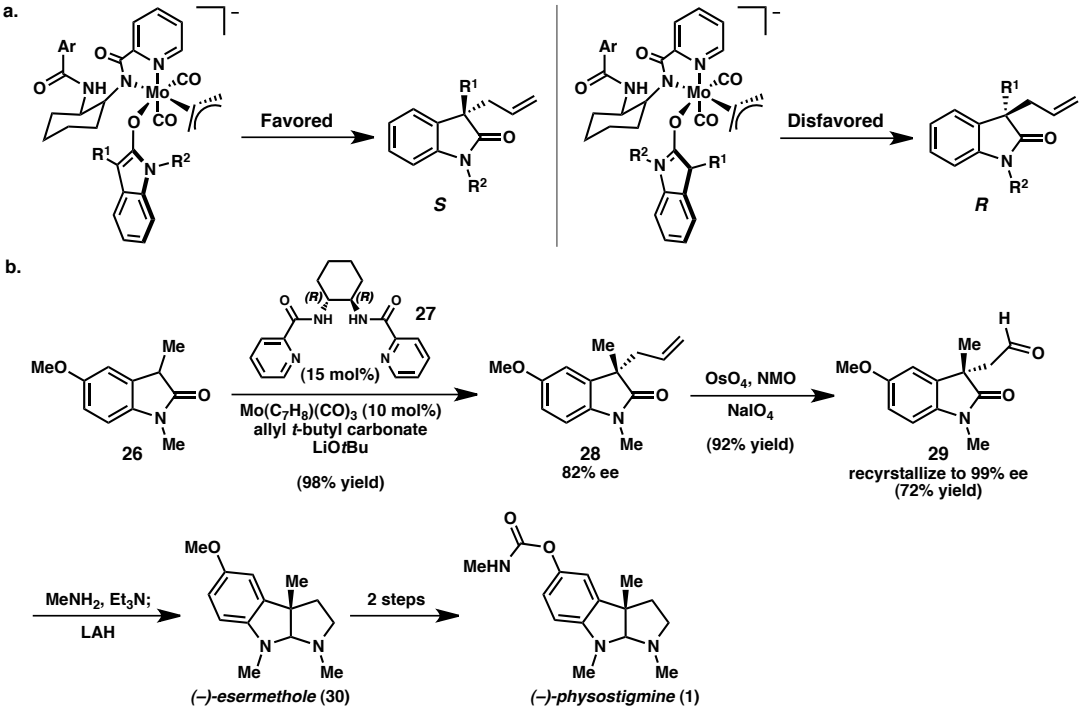
Figure 2. Total synthesis of idiospermuline by Overman and coworkers.



From there, the plan was to install the third quaternary stereocenter (3a") by a catalytic asymmetric Heck cyclization. In the event, *ortho*-lithiation of **20** and quenching with diiodoethane gave iodide **21**. The carbon framework of the third pyrroloindoline motif was then introduced by Stille cross-coupling with stannyl butenanilide **22** to furnish (*Z*)-butenanilide **23**. The best stereoselectivity for the intramolecular Heck reaction was observed with (*S*)-Tol-BINAP as the ligand and $Pd(OAc)_2$ as the precatalyst. The product

of this cyclization was formed as a 6:1 mixture of epimers, which were more readily-separated at the end of the synthesis using preparative HPLC. The total synthesis of idiospermuline was completed by hydrogenation to the saturated sulfonamide, reduction of the oxindole carbonyl with Red-Al, and treatment with excess sodium in ammonia.

Figure 3. (a) Model for enantioinduction for the Mo-catalyzed AAA. (b) Mo-catalyzed AAA applied to the formal synthesis of (–)-physostigmine by Trost.



The Trost laboratory has developed a molybdenum-catalyzed asymmetric allylic alkylation (AAA reaction) of 3-alkyloxindoles to furnish oxindoles with C3 all-carbon quaternary stereocenters.[10] The Mo-catalyzed AAA reaction involves precoordination of the nucleophile to the metal followed by reductive elimination, as opposed to the palladium-catalyzed process in which the nucleophile directly attacks the π-allyl from the

face opposite palladium (Figure 3a). The authors proposed that the intimate interaction between the nucleophiles and chiral molybdenum would make this system amenable for asymmetric catalysis. Indeed, high enantioselectivities are observed with *trans*-1,2-diaminocyclohexane-derived ligand **27**; in the proposed model for enantiodiscrimination, the favored approach minimizes steric congestion between the ligand and the enolate of the oxindole as the C-terminus of the enolate moves toward the π-allyl. In the alternative approach, the bulk of the oxindole sterically clashes with the ligand during bond formation.

The optimal conditions for the Mo-catalyzed AAA reaction were applied to a formal total synthesis of (–)-physostigmine (Figure 3b). Allylated oxindole **28** was oxidized to aldehyde **29**, which could be recrystallized twice to 99% ee. Reductive cyclization yielded (–)-esermethole (**30**), which could be transformed to (–)-physostigmine (**1**) in two steps.

1.3 Pyrroloindoline Synthesis via C3 Functionalization/Cyclization

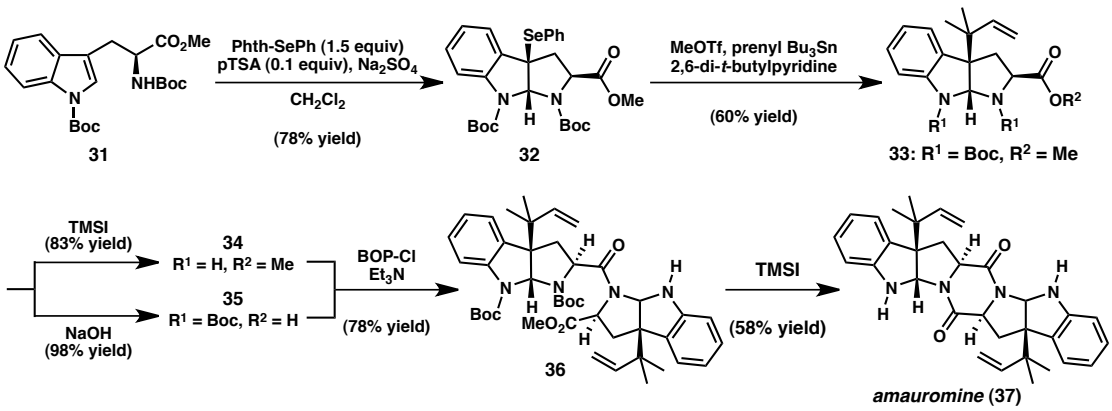
Electrophilic functionalization at the 3-position of indoles followed by cyclization is an efficient method for the preparation of pyrroloindoline natural products. While many syntheses are stereospecific and start from tryptophan, an abundant source of chiral material, the past decade has also witnessed the development of powerful catalytic, asymmetric methods for the preparation of the pyrroloindoline core.

Danishefsky and coworkers completed a total synthesis of the reverse-prenylated natural product amauromine (**37**) from a tryptophan precursor (Figure 4).[11] While they were not hopeful that a direct alkylative cyclization could introduce the dimethallyl moiety at the requisite *gem*-dimethyl carbon, they instead proposed that a heteroatom-

mediated oxidative cyclization followed by alkylation with a reverse-prenyl nucleophile would be more successful. Successful implementation of this strategy would require efficient transmission of stereochemical information from the tryptophan stereocenter to the emerging quaternary carbon.

In the forward sense, the synthesis started with bis(Boc)tryptophan methyl ester **31**, which was subjected to *N*-phenylselenophthalimide and catalytic *p*-toluenesulfonic acid to give 3-selenylated pyrroloindoline **32**. Treatment with methyl triflate and prenyl tributylstannane gave pyrroloindoline **33** bearing the reverse prenyl group at the desired position. BOP-Cl mediated coupling of differentially-protected pyrroloindolines **34** and **35** provided dipeptide **36**. Removal of the remaining Boc groups resulted in spontaneous cyclization to furnish amauromine (**37**).

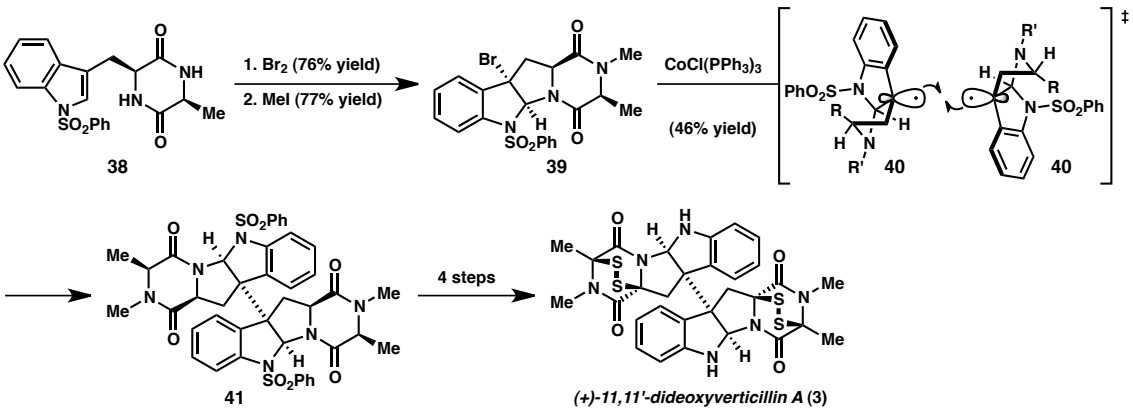
Figure 4. Total synthesis of amauromine by Danishefsky.



Movassaghi and coworkers were the first to report a total synthesis of a dimeric epidithiodiketopiperazine alkaloid (Figure 5).[12] While Overman employed a dialkylation strategy to access the C3a-C3a'-linked pyrroloindoline framework of idiospermuline

(Figure 2), Movassaghi utilized a reductive dimerization approach to access the similar bispyrroloindoline motif of (+)-11,11'-dideoxyverticillin (**3**). Diketopiperazine **38**, derived from tryptophan and alanine, was exposed to molecular bromine, leading to cyclization to the brominated pyrroloindoline (**39**). Bromide **39** served as a precursor to tertiary radical **40**; in the presence of $CoCl(PPh_3)_3$, dimerization occurs to provide bispyrroloindoline **41**. This intermediate can then be elaborated to the natural product.

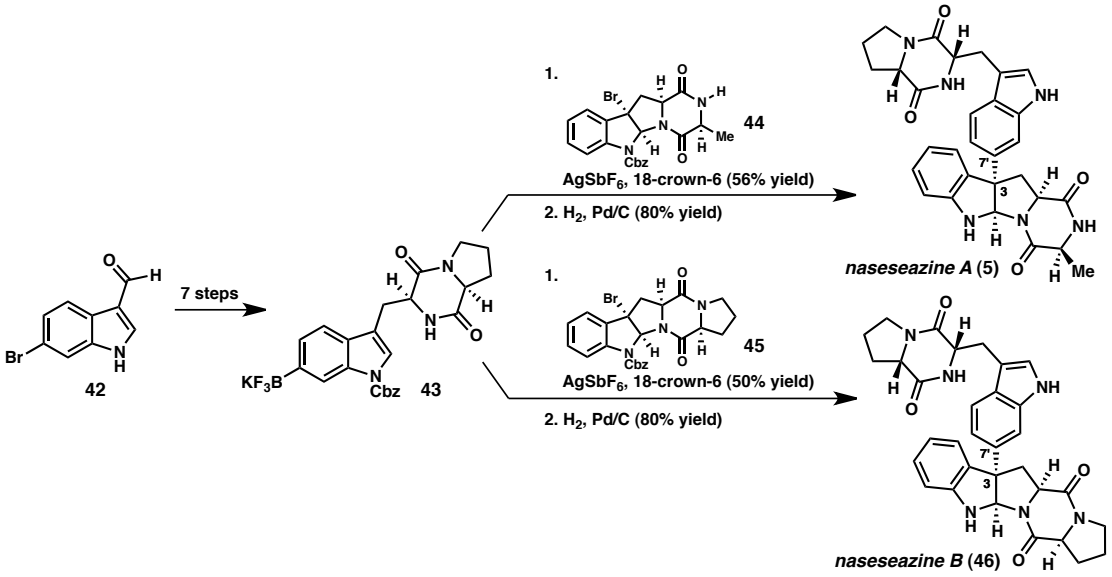
Figure 5. Total synthesis of (+)-11,11′-dideoxyverticillin A by Movassaghi.



Pyrroloindolines with aryl substituents at C3a are an especially challenging class of compounds to access. The structural complexity of these compounds have attracted the attention of many groups, and much progress has been made in recent years toward the total syntheses of these natural products. Movassaghi and coworkers effected the total syntheses of dimeric diketopiperazine alkaloids (+)-naseseazines A and B (**5** and **46**, Figure 6), in which the key C3-C7' bond was forged by a Friedel–Crafts-based method.[13] Bromide **44** and **45** (obtained by bromocyclization of a tryptophan derivative) provided

the C3-electrophiles, and trifluoroborate **43** was the nucleophilic partner; arylation was achieved with $AgSbF_6$ and 18-crown-6.

Figure 6. Friedel–Crafts-based methodology for the total syntheses of naseseazines A and B by Movassaghi.



Extremely efficient routes to naseseazines A and B (**5** and **46**) were recently developed by Maddi Kieffer and Kangway Chuang, graduate students in the Reisman lab (Figure 7).[14] Rather than functionalizing a 3-bromopyrroloindoline derivative, the direct C3 arylation/cyclization of diketopiperazines **47** and **51** were effected in the presence of a copper catalyst and a diimine ligand to furnish pyrroloindolines **49** and **52** in short order. Trifluoroacetamide cleavage followed by modified Larock indolizations completed the total syntheses.

Figure 7. Total syntheses of naseseazines A and B by Reisman employing direct formation of arylpyrroloindolines.

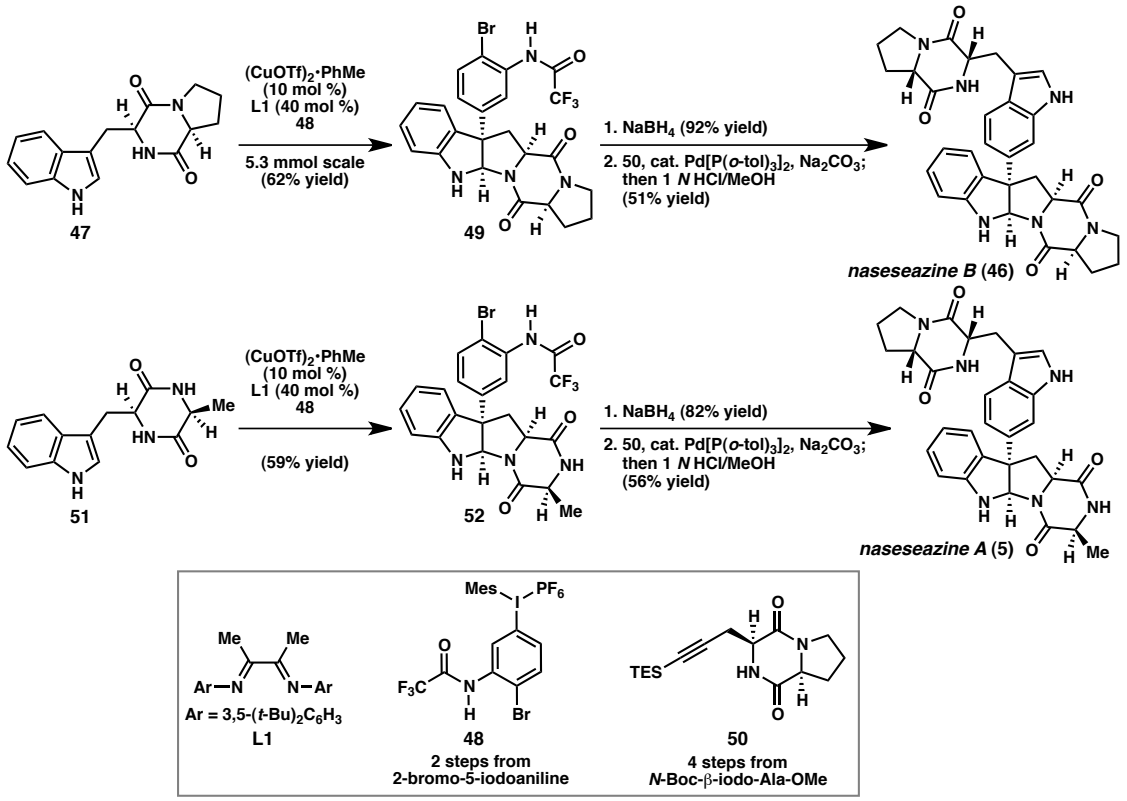
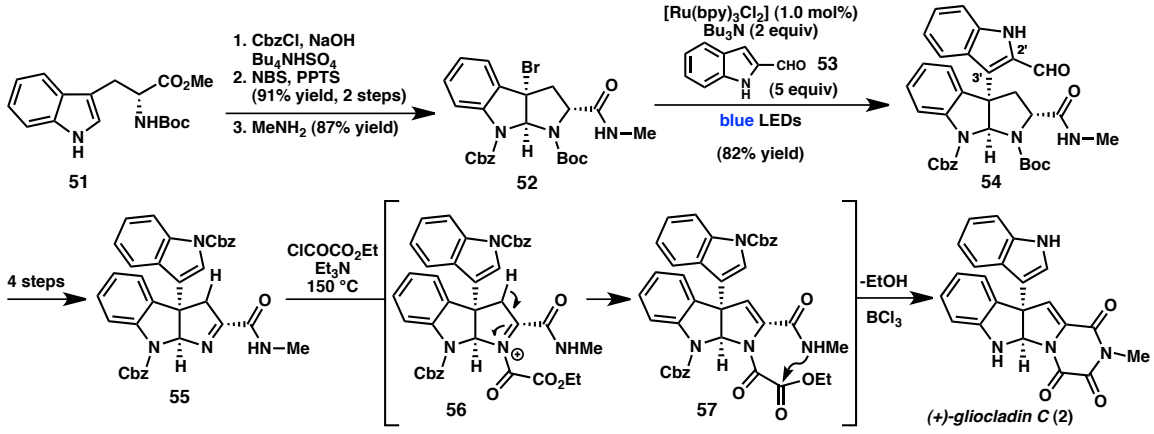
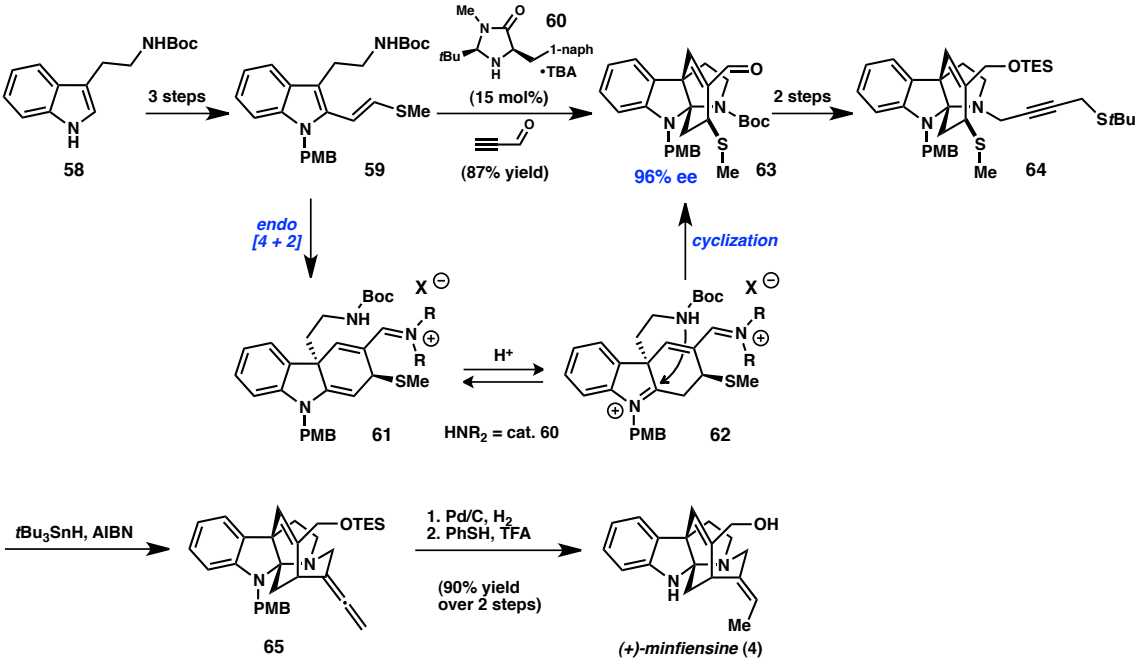


Figure 8. Total synthesis of (+)-gliocladin C by Stephenson employing visible-light phtotoredox catalysis.



The Stephenson laboratory developed a radical reaction for the coupling of pyrroloindolines and indoles mediated by visible-light photoredox catalysis (Figure 8).[15] Exposure of tryptophan-derived bromopyrroloindoline **52** to the photocatalyst tris(bipyridyl)ruthenium(II) chloride generates the dehalogenated tertiary benzylic radical, which is trapped with indole derivative **53**. The C-2' aldehyde of indole **53** is required to block coupling to the pyrroloindoline at this position.

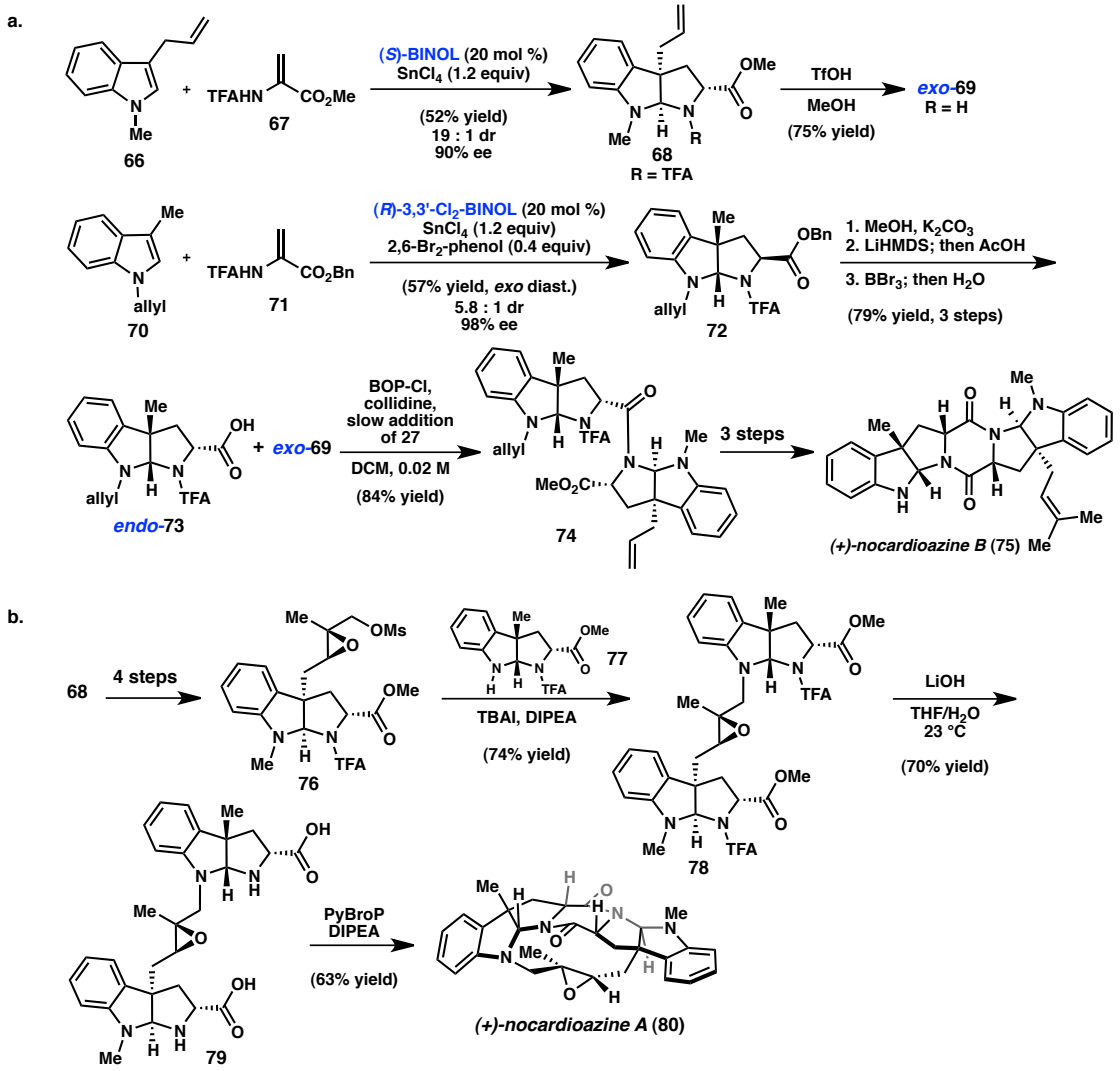
Figure 9. Enantioselective organocatalytic cyclization casacade applied to the total synthesis of minfiensine by MacMillan.



The MacMillan laboratory has completed a total synthesis of the *Strychnos* alkaloid minfiensine (**4**) utilizing an enantioselective organocatalytic Diels–Alder/amine cyclization cascade to construct the pyrroloindoline core (Figure 9). Condensation of secondary amine catalyst **60** with propynal generates an iminium ion with the acetylenic group directed away from the bulky *t*-butyl substituent of the catalyst. In this

conformation, the aryl ring shields the top face of the alkyne. An *endo*-selective Diels–Alder cycloaddition with tryptamine derivative **59** produces tricycle **61**. Enamine protonation gives rise to iminium ion **62**, which undergoes amine cyclization to deliver pyrroloindoline **63**. Elaboration to minfiensine can be achieved in five more steps.

Figure 10. Total syntheses of nocardioazines A and B by Reisman.



In Chapter 2, the development of an (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2) cycloaddition to prepare enantioenriched pyrroloindolines directly from 3-substituted indoles and 2-amidoacrylates will be described. Haoxuan Wang, a graduate student of the Reisman lab, has applied this methodology to the total syntheses of lansai B (not shown) and nocardioazines A and B (**80** and **75**, Figure 10). Structural analysis reveals that nocardioazines A and B are each composed of one *endo* and one *exo* pyrroloindoline with opposite configurations at the quaternary sterecenter. Thus, the total syntheses of these natural products are especially well-suited for asymmetric catalysis, as either enantiomer of the required pyrroloindoline building block can be accessed by selecting the appropriate enantiomer of the catalyst.

Nocardioazine B (**75**) was obtained by coupling of differentially-protected pyrroloindoline building blocks ***endo*-73** and ***exo*-69** with BOP-Cl. On the other hand, the synthesis of nocardioazine A (**80**) required early-stage epoxidation (to form **76**) followed by PyBroP-mediated intramolecular diketopiperazine formation from the free amino acid moieties of **79**.

1.4 Concluding Remarks

The pyrroloindoline family of natural products exhibit exceptional structural complexity, variety, and biological activity. This chapter outlines the strategies that have been utilized to access pyrroloindoline natural products. While early syntheses focused on the preparation of 3,3-disubstituted oxindoles, the direct functionalization of indoles has emerged as an efficient route to these targets. More recently, catalytic methods have allowed rapid access to complex, stereochemically-dense structures. In pursuing total syntheses of the compounds, limitations in the existing technology are highlighted. These

challenges will surely continue to inspire the development of novel methodologies for the preparation of the pyrroloindoline scaffold.

1.5 Notes and References

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CHAPTER 2

Enantioselective Synthesis of Pyrroloindolines by a Formal (3 + 2) Cycloaddition[†]

2.1 Introduction

Catalytic, asymmetric methods for the construction of pyrroloindolines were recently reviewed by Dr. Lindsay Repka.[1] At the outset of our efforts in this field, only two such methods existed for the direct preparation of pyrroloindolines from indole precursors: MacMillan's organocatalytic addition-cyclization of tryptamines with α,β-unsaturated aldehydes,[2] and Trost's palladium-catalyzed C3-allylation of 3-substituted indoles.[3]

This chapter describes the development of a novel approach to the enantioselective preparation of pyrroloindolines, utilizing an (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2) cycloaddition of 3-substituted indoles and 2-amidoacrylates. This reaction is tolerant to diverse substitution patterns and incorporates the necessary C2-substitution for advancement to diketopiperazine pyrroloindoline natural products. Mechanistic

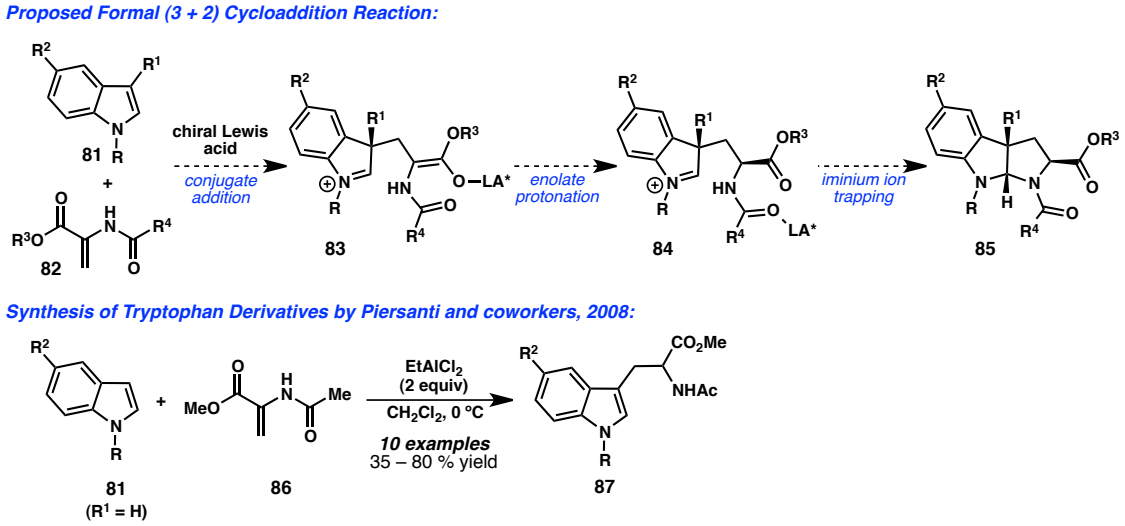
[†] Portions of this chapter have been reproduced from published studies (see references 7 and 19) and the supporting information found therein. The research presented in this chapter was completed in collaboration with Dr. Lindsay M. Repka, formerly a graduate student of the Reisman group, and Haoxuan Wang, a graduate student in the Reisman group.

studies are consistent with the proposal that this reaction proceeds *via* an asymmetric protonation as the enantiodetermining step and has consequently led to the development of related tandem conjugate addition/enantioselective protonation reaction for the synthesis of indoline-containing amino acid derivatives.

2.2 Development of a Formal (3 + 2) Cycloaddition

In our approach to the enantioselective preparation of pyrroloindolines, we aimed to develop a convergent reaction between 3-substituted indoles (**81**) and 2-amidoacrylates (**82**), in what would constitute a formal (3 + 2) cycloaddition. These readily-accessible substrates would facilitate rapid access to a variety of substituted pyrroloindoline products (**85**). We envisioned that this reaction would proceed via Lewis acid-activation of the acrylate leading to nucleophilic attack by the indole in a 1,4-fashion. The transiently generated iminion ion intermediate would then undergo cyclization by the pendant amine to generate the desired product (Figure 1).

Figure 1. Proposed pyrroloindoline synthesis and precedent by Piersanti.



However, we recognized that several challenges might be encountered in putting this proposal to practice. First, 2-amidoacrylates are relatively unreactive conjugate acceptors due to electron donation from the nitrogen lone pair. Second, controlling the absolute stereochemistry of the all-carbon quaternary center formed at C3 of the indole substrate was also anticipated to be a challenge, as it would require a remote chiral ligand to discriminate between prochiral faces of the nucleophilic indole. Finally, Lewis acid binding to the product might prevent turnover.

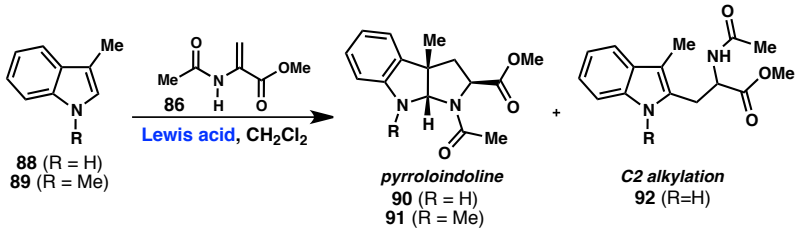
Despite these challenges, we were encouraged by results reported by Piersanti and coworkers; they found that unsubstituted indoles react with 2-amidoacrylates in the presence of two equivalents of $EtAlCl_2$ to give Friedel–Crafts alkylation products in good yield, thus confirming that 2-amidoacrylates can act as competent electrophiles (Figure 1).[4] The C3 substitution of the indole substrates for the proposed pyrroloindoline reaction would preclude formation of the Friedel–Crafts products observed by Piersanti, but reaction at C2 may lead to undesired Friedel–Crafts side products.

2.2.1 Identification of an Optimal Lewis Acid

Our studies began with the model substrates 3-methylindole (**88**) and methyl 2-acetamidoacrylate (**86**). A screen of Lewis acids revealed that use of 2.0 equivalents $EtAlCl_2$ delivered the desired pyrroloindoline (**90**) as the major product in 3:1 dr favoring the *exo* diastereomer (C3 substituent *syn* to ester, as shown), along with the C2 Friedel–Crafts alkylation product (**92**) (Table 1, entry 2). $SnCl_4$ was also found to effectively promote this reaction with 6:1 selectivity for pyrroloindoline formation over alkylation (entry 7). Fortunately, *N*-methylation of the indole improved selectivity for the pyrroloindoline product (entry 8). Attempts to lower the loading of Lewis acid were

unsuccessful: no product was observed when 50 mol % of $SnCl_4$ was employed (entry 9). Under the optimized conditions for the racemic reaction, exposure of 1,3-dimethylindole (**89**) and methyl 2-acetamidoacrylate (**86**) to 1.2 equivalents $SnCl_4$ in dichloroethane gave the desired pyrroloindoline **91** in 64% yield as a 6:1 mixture of *exo* and *endo* diastereomers (entry 10).

Table 1. Initial Lewis acid screen.



Entry	Lewis Acid (equiv)	Substrate	Temperature (°C)	Pyrroloindoline: C-2 alkylation	dr[a]
1	$EtAlCl_2$ (1)	**88**	23	nr	--
2	$EtAlCl_2$ (2)	**88**	8	8:1	3:1
3	$MgClO_4$ (1)	**88**	23	nr	--
4	$Sc(OTf)_2$ (2)	**88**	23	>20:1	5:1
5	$Cu(OTf)_2$ (2)	**88**	23	decomposition	--
6	$Zn(OTf)_2$ (2)	**88**	23	nr	--
7	$SnCl_4$ (1)	**88**	23	6:1	9:1
8	$SnCl_4$ (1)	**89**	23	>20:1[b]	11:1
9	$SnCl_4$ (0.5)	**89**	23	nr	--
10[c]	$SnCl_4$ (1.2)	**89**	23	>20:1 (64)[d]	6:1

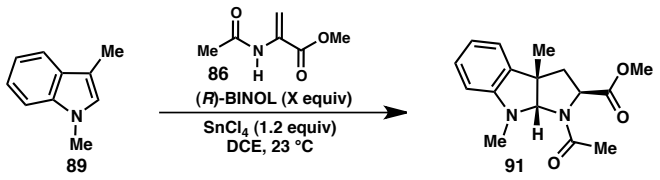
[a] Determined by analysis of the crude ^1H NMR with comparison to reported spectra. [b] Complete conversion to **91** by crude ^1H NMR. [c] Reaction run in DCE. [d] Isolated yield of **91**. nr: no reaction.

2.2.2 Optimization of the Enantioselective Reaction

Having identified a Lewis acid to effect pyrroloindoline formation in a racemic fashion, our next goal was to render this reaction enantioselective. A small screen of chiral ligands revealed that (*R*)-BINOL provided promising enantioselectivity: treatment of 1,3-dimethylindole (**89**) and methyl 2-acetamidoacrylate (**86**) with a 1.1:1 mixture of (*R*)-BINOL and $SnCl_4$ provided pyrroloindoline **91** in 86% yield as a 4:1 mixture of diastereomers, with the *exo* diastereomer formed in 64% ee (Table 2, entry 2).

Performing side-by-side reactions with and without (*R*)-BINOL revealed that the ligand accelerated the rate of reaction.[5] Thus it was hypothesized that high levels of enantioselectivity could be maintained with catalytic quantities of (*R*)-BINOL. Gratifyingly, treatment of 1,3-dimethylindole (**89**) and methyl 2-acetamidoacrylate (**86**) with 1.2 equivalents $SnCl_4$ and 20 mol % (*R*)-BINOL furnished the desired pyrroloindoline **91** in 94% yield as a 5:1 mixture of diastereomers, favoring the *exo* diastereomer in 63% ee (Table 2, entry 4). Remarkably, moderate levels of enantioselectivity are still observed when the reaction is conducted with only 5 mol % (*R*)-BINOL (entry 6).

Table 2. Optimization of (R)-BINOL loading.



Entry	(R)-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

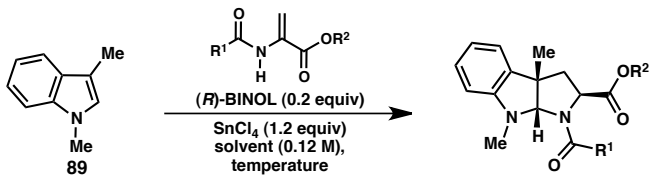
[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC. [d] ee of *exo*/*endo* diastereomers. [e] Reaction run for 30 h. [f] Reaction run for 3.5 h. [g] 1.0 equiv of $SnCl_4$ was used. [h] Reaction run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

Efforts to improve the enantioselectivity of the formal (3 + 2) cycloaddition started with an investigation of the temperature effects. It was found that ee and dr are reduced at lower temperatures (Table 3, entries 3-4). Alternatively, gentle heating of the

reaction did not significantly alter the selectivity (entry 5). Similar temperature effects in reactions promoted by Lewis acid•BINOL complexes have been reported.[6]

On the other hand, varying substitution on the acrylate was found to significantly improve selectivity in this reaction. Methyl 2-trifluoroacetamidoacrylate (**67**) provided pyrroloindoline product **94** in 86% ee (*exo* diastereomer), while benzyl 2-acetamidoacrylate (**93**) provided pyrroloindoline **95** in 74% ee (Table 3, entries 6-7). These effects were found to be additive: reaction of benzyl 2-trifluoroacetamidoacrylate (**71**) afforded pyrroloindoline **96** 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 were optimal and switching from DCE to DCM provided **96** in 86% yield and 94% ee for the *exo* diastereomer (entry 9).

Table 3. Enantioselectivity optimization studies.

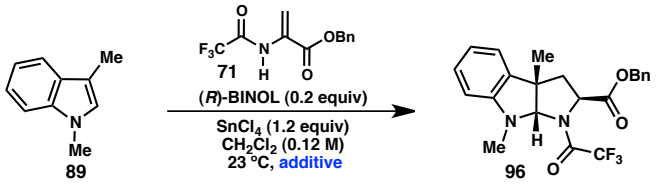


Entry	R^1, R^2	pdt	Temperature (°C) (Time (h))	Solvent	Yield (%)[a]	dr[b]	ee (%)[c,d]
1	Me, Me (**86**)	**91**	23 (4)	DCE	94	5:1	63/83
2[e]	Me, Me (**86**)	**91**	8 (24)	DCE	88[f]	4:1	66/nd
3[e]	Me, Me (**86**)	**91**	–40 (24)	CH_2Cl_2	69[f]	3:1	39/nd
4[e]	Me, Me (**86**)	**91**	–78 (24)	CH_2Cl_2	26[f]	2:1	21/nd
5[e]	Me, Me (**86**)	**91**	40 (0.5)	DCE	97[f]	5:1	66/nd
6	CF_3, Me (**67**)	**94**	23 (4)	DCE	77	6:1	86/nd
7	Me, Bn (**93**)	**95**	23 (4)	DCE	81	2:1	74/82
8	CF_3, Bn (**71**)	**96**	23 (4)	DCE	81	3:1	91/90
9	CF_3, Bn (**71**)	**96**	23 (5.5)	CH_2Cl_2	86	4:1	94/91
10	CF_3, Bn (**71**)	**96**	23 (4)	$CHCl_3$	58	3:1	88/89
11	CF_3, Bn (**71**)	**96**	23 (3.5)	CCl_4	0	--	--

[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H 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 $SnCl_4$ and 1.1 equiv (*R*)-BINOL was used. [f] Approximate conversion to **91** based on ratio with acrylate in crude ^{1}H NMR. nd= not determined.

A control reaction performed in the absence of $SnCl_4$ confirmed that the Lewis acid is essential (Table 4, entry 1). Furthermore, the Brønsted acids HCl and Ph_2PO_2H fail to promote the formal (3 + 2) cycloaddition (entries 1-3). Several water and acid scavenging additives were also screened but did not result in significant changes in enantioselectivity (entries 4, 5, and 7).

Table 4. Brønsted acid and 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_2PO_2H (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

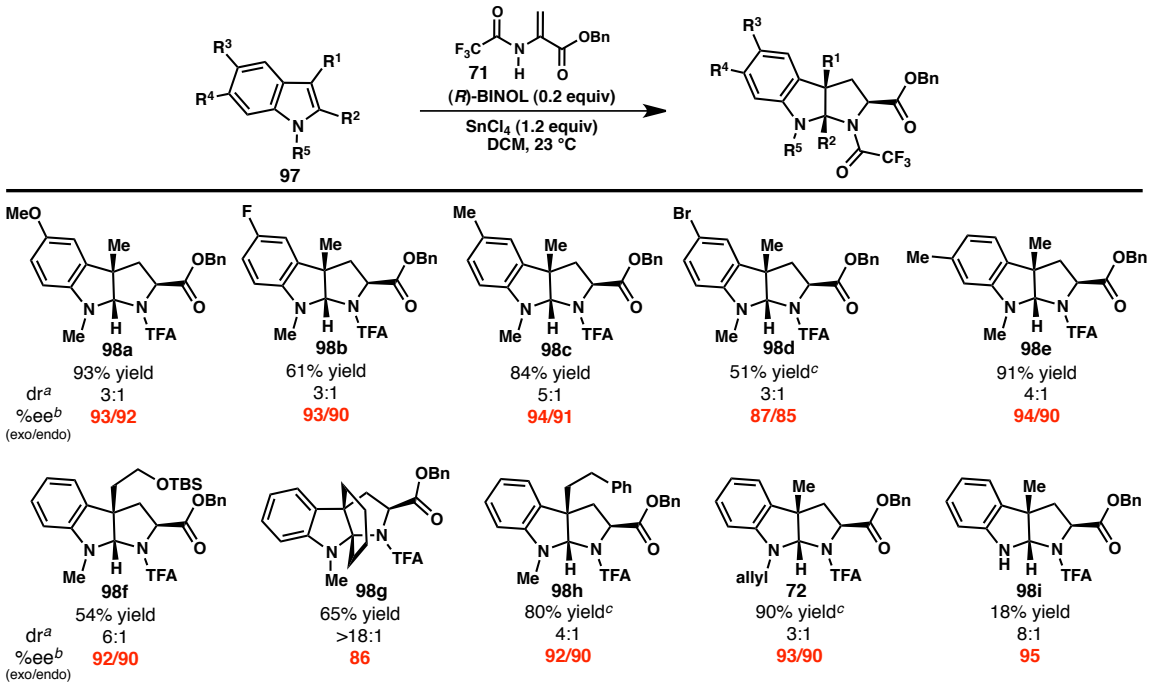
[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC. [d] ee of *exo*/*endo* diastereomers. [e] Reaction run without $SnCl_4$. [f] Completed side-by-side with reaction under standard conditions that afforded 74% yield, 4:1 dr, 94:90% ee.

2.2.3 Substrate Scope of the Enantioselective Pyrroloindoline Synthesis

With optimized conditions for the enantioselective formal (3 + 2) cycloaddition, the scope of indole substrates was investigated (Figure 2).[7,8] Indoles substituted at C5 with either electron-donating or electron-withdrawing groups are well-tolerated, although electron-poor indoles react at a slower rate, requiring 1.6 equivalents of $SnCl_4$ in some cases. Indoles with functionalized C3 substituents react in moderate to good yields with high enantioselectivity (**98f** and **98h**). Notably, the reaction of *N*-

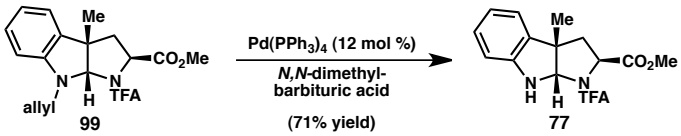
methyltetrahydrocarbazole proceeds with >18:1 diastereoselectivity, delivering the *exo* diastereomer **98g** in 86% ee. This reaction generates the aza-propellane core of the natural products minfiensine,[9] echitamine,[10] and vincorine[11] in a single step. *N*-substitution is important for reactivity: subjection of 3-methylindole to identical conditions provides pyrroloindoline **98i** in only 18% yield, albeit with excellent enantioselectivity. However, *N*-allyl-3-methylindole successfully affords pyrroloindoline **72** in good yield and enantioselectivity. Deallylation of **99** can be effected with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid to give pyrroloindoline **77** with an unprotected indoline nitrogen (Figure 3).[12]

Figure 2. Substrate scope.



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

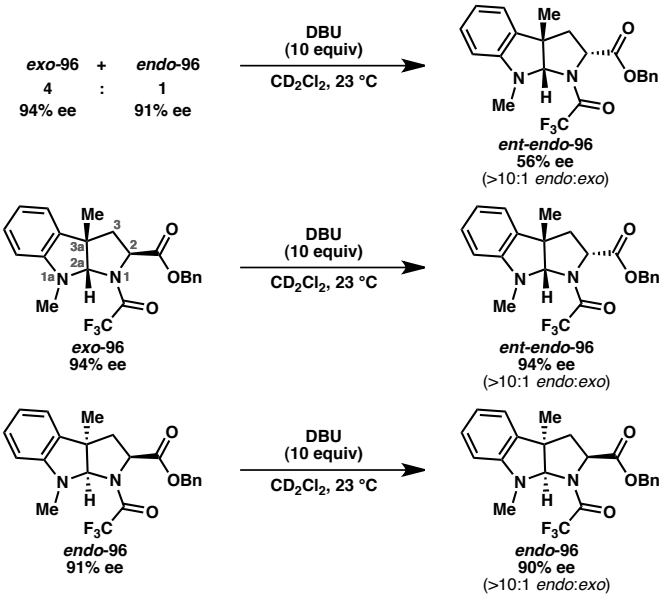
Figure 3. Pyrroloindoline deallylation.



2.2.4 Mechanistic Considerations

The *exo* diasteromer is the predominant product of the formal (3 + 2) cycloaddition reaction. Previously, it was reported that the *exo* diastereomer of related pyrroloindolines is the kinetic product, while the *endo* diastereomer is thermodynamically favored.[13]

Figure 4. Epimerization studies.

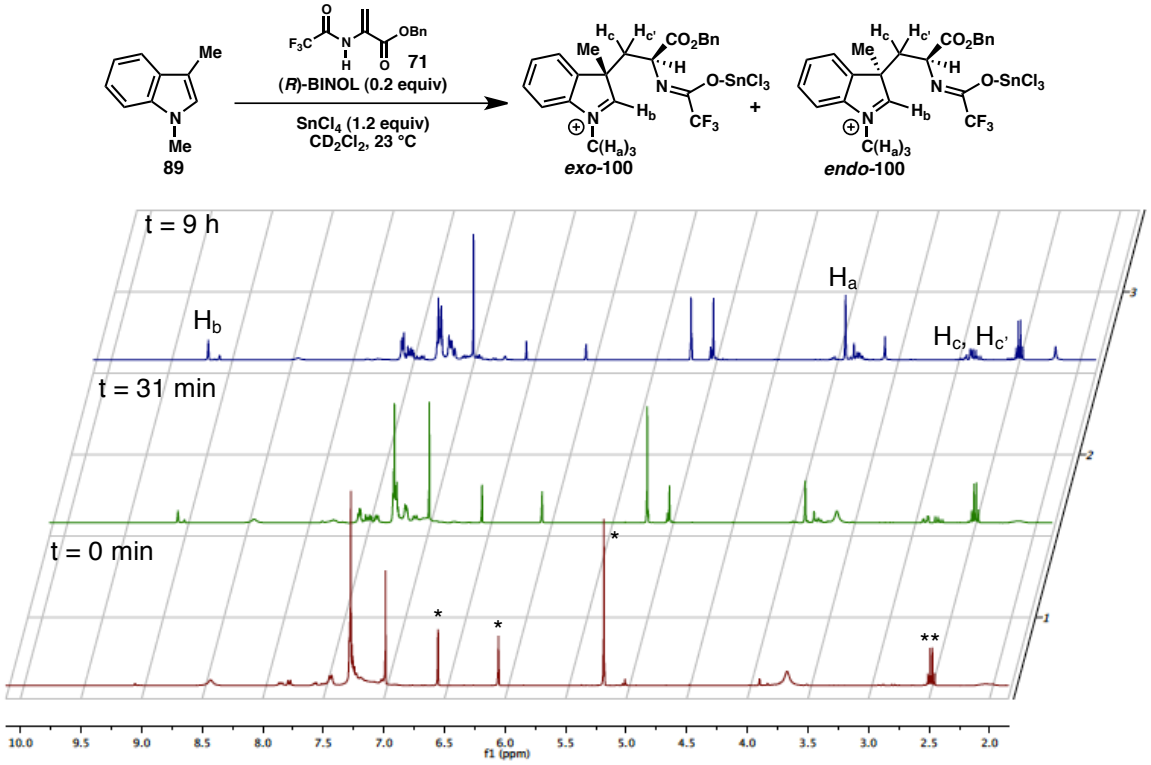


In order to determine whether this applies to the pyrroloindolines produced by the formal (3 + 2) cycloaddition, a 4:1 mixture of *exo*- and *endo*-**96** was exposed to excess DBU. Clean conversion to the *endo* diastereomer was observed, but surprisingly, the

product was isolated in 56% ee favoring the opposite enantiomer (Figure 4). Subsequently, treatment of pure *exo*-**96** with DBU provided *ent-endo*-**96** in 94% ee. Pure *endo*-**96** exposed to the epimerization conditions returned *endo*-**96** without significant erosion of ee. The studies indicate that the initially-formed diastereomers of **96** must possess the same configuration at C2, and the opposite configurations at the C2a and C3a bridgehead carbons.

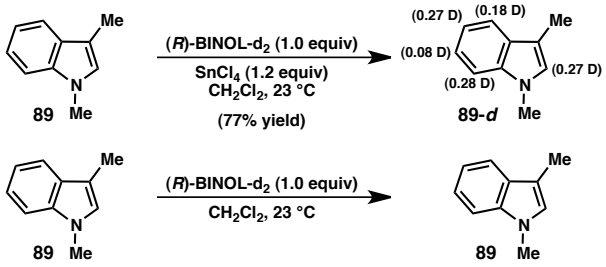
We then sought to obtain further mechanistic insight by monitoring the reaction using ^{1}H NMR spectroscopy. The formal (3 + 2) cycloaddition between 1,3-dimethylindole (**89)** and benzyl trifluoroacetamidoacrylate (**71**) is amenable to in situ NMR monitoring, since it is homogenous over the course of the reaction. Figure 5 shows a sample of ^{1}H NMR spectra taken over the first nine hours of the reaction, and reveals several interesting aspects of this transformation. Notably, upon addition of $SnCl_4$ and (*R*)-BINOL (**7**) to a mixture of **89** and **71**, the indole proton resonances broaden significantly (Figure 5, t = 0). This broadening is also observed in the absence of acrylate **71**; however, $SnCl_4$ alone does not alter the ^{1}H NMR spectrum of **89**. It is possible that this broadening is due to a rapid, dynamic, proton exchange process promoted by (*R*)-BINOL•$SnCl_4$, which is consistent with the finding that (*R*)-BINOL that is deuteurated at the hydroxyl groups undergoes rapid D-H exchange with indole **89** under the reaction conditions (Figure 6). Interestingly, the chemical shifts of the acrylate remain unchanged, indicating that there is no significant accumulation of an acrylate–$SnCl_4$ complex. Over the course of the reaction, resonances corresponding to an indole–acrylate adduct grow in; however, these peaks do not correspond to the pyrroloindoline product.

Figure 5. In situ monitoring of the formal (3 + 2) cycloaddition using ^{1}H NMR.



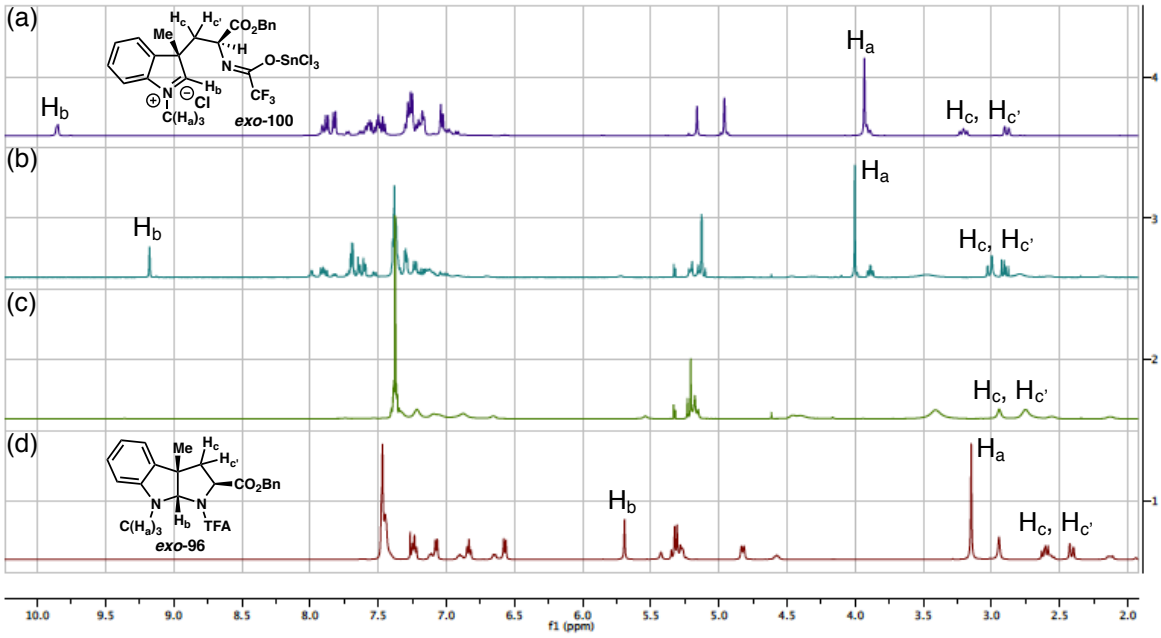
acrylate denoted by *; 1,4-diethylbenzene (internal standard) denoted by **.

*Figure 6. Deuterium-labelling studies with (*R*)-BINOL-d$_2$ and 1,3-dimethylindole.*



We hypothesized that in the presence of a strong Lewis acid, such as $SnCl_4$, coordination of the amide might favor the ring-opened iminium ions ***exo*-100/*endo*-100**. To test this hypothesis, we resubjected diastereomerically-pure ***exo*-100** to $SnCl_4$ (1.2 equiv) and varying equivalents of (*R*)-BINOL (Figure 7).

Figure 7. NMR spectra of (a) pyrroloindoine ***exo-96****, $SnCl_4$ (1.2 equiv), (R)-BINOL (1.2 equiv) (b) pyrroloindoine* ***exo-96****, $SnCl_4$ (1.2 equiv), (R)-BINOL (0.2 equiv) (c) pyrroloindoine* ***exo-96****, $SnCl_4$ (1.2 equiv) (d) pyrroloindoline* ***exo-96****.*



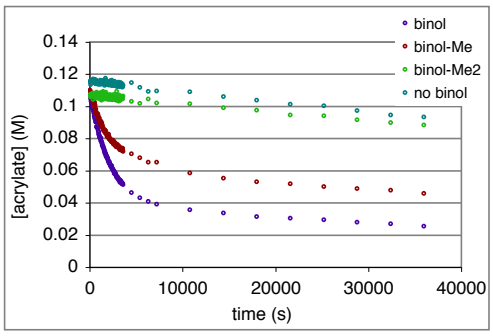
The NMR spectra of the mixtures were dependent on the quantity of (*R*)-BINOL present; in the presence of 20 mol % (*R*)-BINOL, the ^{1}H NMR spectra closely resembled that of the indole–acrylate adduct observed in the in situ ^{1}H NMR experiment. Notably, this species exhibits a resonance between 9 and 10 ppm (depending on concentration of (*R*)-BINOL, Figure 7a and b), which we assign to the indolinium proton (H_b). In addition, the *N*-methyl group (H_a) in this species is shifted downfield relative to the pyrroloindoline (4.0 ppm versus 3.1 and 2.9 ppm for the two rotamers of the *exo* diastereomer), and is consistent with literature data for other iminium ions.[14] This structural assignment is further supported by 2D ^{1}H–^{13}C NMR correlation data. In the presence of $SnCl_4$ alone, the pyrroloindoline peaks broaden, likely due to dynamic interconversion between the ring-opened and -closed forms (Figure 7c). The fact that

addition of 1.0 equivalent (*R*)-BINOL resolves this mixture into one species suggests that (*R*)-BINOL•$SnCl_4$ might preferentially stabilize the open structure. Importantly, following aqueous work up, pyrroloindoline ***exo*-96** is cleanly reisolated with no indication of epimerization or racemization.

In order to help elucidate the mode of activation by (*R*)-BINOL, reactions were carried out with mono- and bis-methylated derivatives (Figure 8). The progress of the reaction can be quantified by integrating the vinyl protons of the acrylate relative to 1,4-diethylbenzene as an internal standard. Use of (*R*)-BINOL-Me results in a moderate decrease in both rate and enantioselectivity (83% ee, exo diastereomer), whereas (*R*)-BINOL-Me_2 shows no rate enhancement over $SnCl_4$ alone. This experiment suggests that BINOL does not activate $SnCl_4$ by dative coordination alone; rather, the free hydroxyl moieties of BINOL are required.

Further kinetic analysis of (*R*)-BINOL-catalyzed reaction has been complicated by several factors, including the presence of the racemic background reaction (particularly at higher $SnCl_4$:(*R*)-BINOL ratios) and product inhibition.

Figure 8. Methylation of BINOL decreases reaction rate.



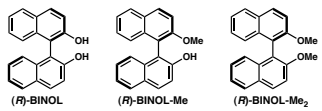
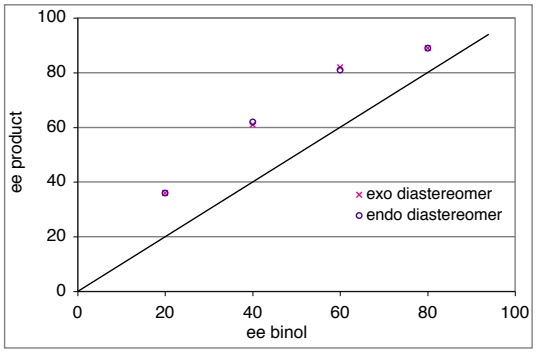
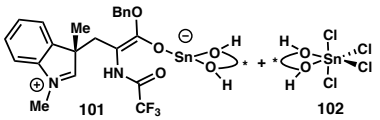


Figure 9. Non-linear effect observed with scalemic BINOL (4:1 d.r. for all reactions).





The pyrroloindoline synthesis was performed with scalemic BINOL to investigate the presence of non-linear effects.[15] Figure 9 shows that a positive non-linear relationship was indeed observed. A possible explanation for the observed non-linear effect is the interaction shown in Figure 27, where BINOL-bound tin enolate **101** is protonated by another BINOL•$SnCl_4$ species. If the heterochiral combination of (*R*)- and (*S*)-BINOL is less reactive than the homochiral combinations (i.e. a reservoir for the minor enantiomer of catalyst), then a positive non-linear effect will be observed. As the observed non-linear effect is not highly pronounced, BINOL-bound tin enolate may only be a minor species, while the majority of tin enolate species in solution are not coordinated by BINOL. This situation is likely because BINOL is present in a catalytic quantity with a large excess of $SnCl_4$.

Although further mechanistic studies are required, our observations lead us to favor a cooperative Lewis acid–Lewis acid-assisted Brønsted acid mechanism, shown in Figure 10. Activation of acrylate **71** by coordination to $SnCl_4$ results in reversible conjugate addition by the indole, generating a racemic mixture of Sn-enolates **101** and

***ent*-101**. Highly face selective protonation of **101/*ent*-101** by (*R*)-BINOL•$SnCl_4$ complex **102** resolves the two enantiomers into diastereomers in a rate- and selectivity-determining step. In this scenario, the ee of the two pyrroloindoline products would reflect the face selectivity of the protonation step, while the dr would reflect the difference in the rate of protonation of the two chiral enolates **101** and ***ent*-101**, due to "matching" and "mismatching" effects with chiral complex **102**.[16] The stoichiometric proton source required to turn over complex **103** could potentially be the N-H of trifluoroacetamide ***exo*-105/*ent-endo*-105**, which upon coordination to $SnCl_4$ would be rendered sufficiently acidic.

Figure 10. Proposed mechanism.

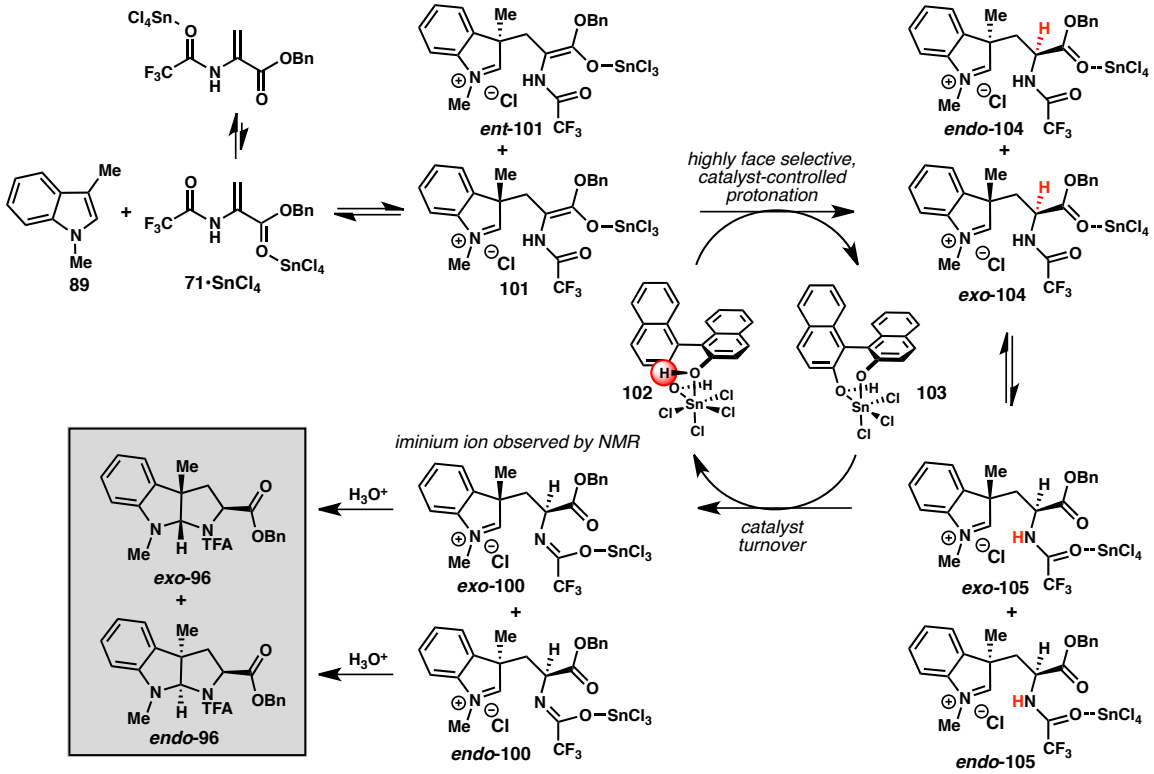
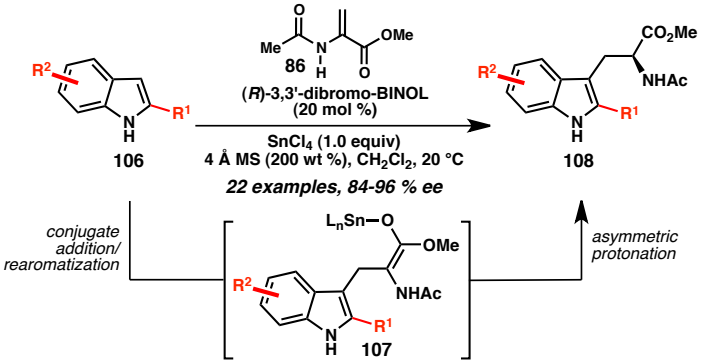


Figure 11. LBA-catalyzed conjugate addition/asymmetric protonation.



The proposed mechanism is consistent with Yamomoto's prior reports that (*R*)-BINOL•$SnCl_4$ (**102**) behaves as a "Lewis acid-assisted Brønsted acid (LBA)," which is capable of catalyzing the enantioselective protonation of silyl enolates.[17] However, the pyrroloindoline formation described above represents the first example of a tandem conjugate addition/asymmetric protonation process catalyzed by **102**. Based on this mechanistic proposal for pyrroloindoline formation, the Reisman group has identified similar conditions for the synthesis of unnatural tryptophan derivatives from 2-substituted indoles (**106**) and methyl 2-acetamidoacrylate (**86**), in which the sole stereogenic center is set during an asymmetric protonation step (Figure 11).[18‡]

2.2.5 Second Generation Reaction Conditions

The fact that diastereomers formed in the pyrroloindoline synthesis are of opposite enantiomeric series presents a practical challenge for synthetic applications. Specifically, in order to preclude racemization via epimerization during subsequent synthetic steps, it is imperative to separate the two diastereomers. Unfortunately,

‡ This work was performed by Maddi Kieffer (a graduate student) and Dr. Lindsay Repka (a former graduate student).

depending on the indole substitution pattern, separation of the diastereomers can be tedious using standard silica gel chromatography. In addition, the modest diastereoselectivity results in lower isolated yields of the pure *exo*-diastereomer. In an effort to identify conditions more amenable to application in total synthesis endeavors, we sought to re-optimize the reaction parameters for the formal (3 + 2) cycloaddition with the objective of improving the *diastereoselectivity* while maintaining synthetically useful enantioselectivity.

The first generation optimization studies determined that the enantio- and diastereoselectivity of pyrroloindoline formation are highly dependent on the substitution of the 2-amidoacrylate: the highest *enantioselectivity* was attained using benzyl 2-trifluoroacetamidoacrylate (**71**), while the highest *diastereoselectivity* was attained using methyl 2-trifluoroacetamidoacrylate (**67**) (Table 3). In the later case, the ee's of two diastereomers were only modestly reduced. Thus, we returned to the use of acrylate **67** in the cycloaddition, and sought to improve the ee and dr by optimizing the catalyst structure.

A screen of other chiral diol scaffolds showed that the (*R*)-BINOL backbone is optimal (Figure 12). A variety of (*R*)-BINOL derivatives were then investigated, revealing that several catalysts containing substitution at the 3- and 3'-positions provided an improvement in both dr and ee (Table 5). Hypothesizing that catalyst selectivity might correlate to the pK_a of the BINOL O-H protons, several 6,6'-derivatives were also prepared in order to isolate the electronic and steric effects; however, no linear correlation was observed. Ultimately, (*R*)-3,3'-Cl_2-BINOL was identified as the catalyst that provided the optimal combination of ee, dr, and overall yield.

Figure 12. Chiral diol screen.

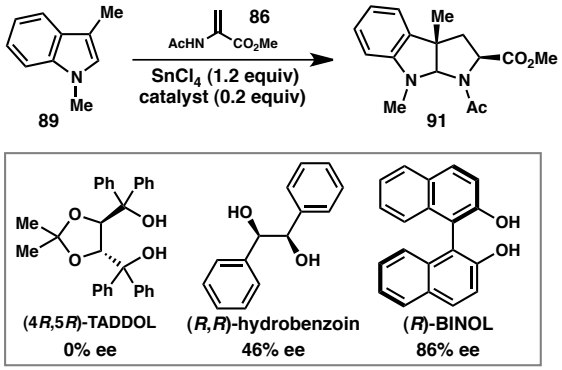
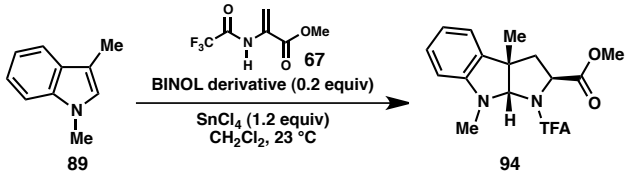


Table 5. (R)-BINOL-derivative screen.

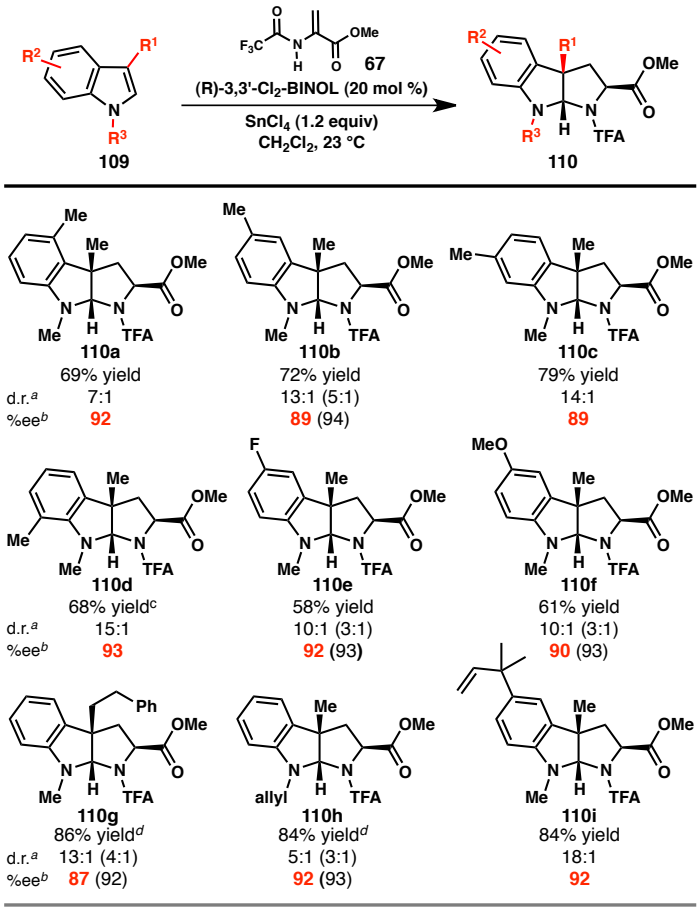


Entry	BINOL derivative	Yield (%)[a]	d.r.[b]	ee (%)[c]
1	H	88	10:1	90
2	6,6'-$(OMe)_2$	63	6:1	82
3	6,6'-Br_2	65	8:1	86
4	3,3'-Me_2	63	8:1	90
5	3,3'-Br_2	63	16:1	90
6	3,3'-Cl_2	73	14:1	91

[a] Isolated yield of *exo*:*endo* mixture. [b] Determined by ^1H NMR analysis of crude reaction mixture. [c] Determined by HPLC using chiral stationary phase.

With these newly optimized conditions in hand, a survey of indole substrates was conducted (Table 6).[19] As previously observed, indoles bearing electron-donating substrates on the aryl backbone provide the highest yields, however, both electron-rich and electron-poor substrates provided high ee's. More sterically-hindered indoles were less reactive and required 1.6 equivalents of $SnCl_4$, but nevertheless yielded the desired pyrroloindoline in good yield with high selectivity.

Table 6. Substrate scope of second generation pyrroloindoline synthesis.



[a] Determined by ^{1}H NMR analysis of crude reaction mixture. Values in parentheses are dr obtained using acrylate **71** and (*R*)-BINOL. [b] Determined by SFC using chiral stationary phase. Values in parentheses are ee obtained using acrylate **71** and (*R*)-BINOL. [c] Isolated yield of *exo*-diastereomer. [d] 1.6 equiv $SnCl_4$ was employed.

2.3 Concluding Remarks

We have developed a novel strategy for the prepararation of enantioenriched pyrroloindolines by an (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2) cycloaddition reaction. The transformation utilizes readily accessible indole and 2-amidoacrylate substrates to directly synthesize a variety of substituted pyrroloindoline products. Catalysis by (*R*)-BINOL allows excellent enantioselectivities to be achieved, even with an excess of Lewis acid.

Mechanistic studies have provided a more thorough understanding of this transformation. It is proposed that this reaction occurs via a highly face-selective catalyst-controlled protonation and that cyclization of the resultant iminium intermediate only occurs upon work-up. Thus, the diastereomeric products possess opposite configurations as the bridgehead quaternary carbon. The implications of these experiments have resulted in the reoptimization of the conditions for this reaction to provide higher levels of selectivity.

The mechanistic proposal has led to the development of other methods for indole alkaloid synthesis, including a tandem conjugate addition/enantioselective protonation reaction to generate tryptophan derivatives,[§] a conjugate addition/in situ reduction to yield indoline amino acid derivatives (Chapter 2), and a conjugate addition/asymmetric protonation/Prins cyclization reaction (Chapter 3).

In addition, this reaction has been utilized to prepare the core pyrroloindoline motifs in the enantioselective total syntheses of the natural products (–)-lansai B[20] and (+)-nocardioazine A.[21**] 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 methodologies, and the synthesis of pyrroloindoline natural products.

[§] This work was performed by Maddi Kieffer (a graduate student in the Reisman lab) and Dr. Lindsay Repka (a former graduate student in the Reisman lab).

[**] Research conducted by Haoxuan Wang, a graduate student in the Reisman lab.

2.4 Experimental Section

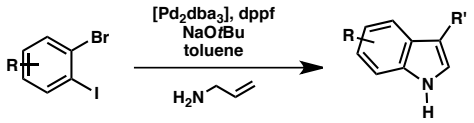
2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, toluene, and hexanes were dried by passing through activated alumina columns. Dimethylformamide was dried over activated molecular sieves, and 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'-dimethoxy-BINOL,[18] (*R*)-6,6'-dibromo-BINOL,[22] (*R*)-3,3'-dimethyl-BINOL,[23] (*R*)-3,3'-dibromo-BINOL,[24] and (*R*)-3,3'-dichloro-BINOL[25] were prepared according to literature procedures. 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. 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 (^{1}H, δ = 7.26, ^{13}C, δ = 77.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Preparative HPLC was performed with either an Agilent 1100 or 1200 Series HPLC utilizing an Agilent Zorbax RX-SIL 5μm 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.

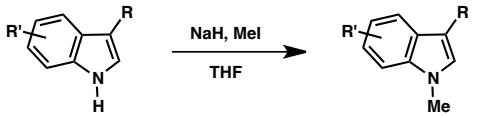
2.4.2 Substrate Synthesis

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



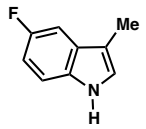
Procedure was adapted from Jørgensen *et al*.[26] To a 50 mL Schlenk tube was added [Pd_2dba_3], dppf, NaO*t*Bu (20.8 mmol, 2.5 equiv), and toluene (10 mL). The mixture was stirred for 5 minutes, then the bromoiodide (8.3 mmol, 1.0 equiv) and allylamine (8.3 mmol, 1.0 equiv) were added. The tube was 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.



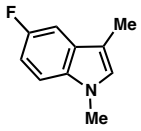
In a flame-dried flask, the indole (1.7 mmol, 1.0 equiv) was dissolved in 11 mL THF. Sodium hydride (60% w/w, 2.5 mmol, 1.5 equiv) was added in one portion, then methyl iodide (3.4 mmol, 2.0 equiv) was added dropwise. The reaction was stirred at room temperature until consumption of starting material 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.



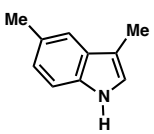
Prepared from 3.75 mmol of 2-bromo-4-fluoro-1-iodobenzene, 0.63 mol % [Pd_2dba_3] and 2.5 mol % dppf using general procedure A. The product was purified by flash chromatography (10% ethyl acetate/hexanes) to yield 5-fluoro-3-methyl-1*H*-indole (**128b**, 0.22 g, 38% yield). Spectral data matches that reported in the literature.[26]

5-Fluoro-1,3-dimethyl-1*H*-indole (97b).



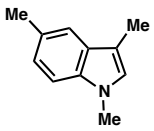
Prepared from 1.07 mmol of 5-fluoro-3-methyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (3% ethyl acetate/hexanes) to yield **97b** (0.97 g, 55% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 2H), 7.00 – 6.92 (m, 1H), 6.86 (s, 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 $[M+H]^+$ 164.0870, found 164.0873.

3,5-dimethyl-1*H*-indole.



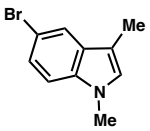
Prepared from 2.88 mmol of 2-bromo-1-iodo-4-methylbenzene,[27] 2.5 mol % [Pd_2dba_3] and 10 mol % dppf using general procedure A. The product was purified by flash chromatography (5→13% ethyl acetate/hexanes) to yield 3,5-dimethyl-1*H*-indole (0.11 g, 14% yield). Spectral data matches that reported in the literature.[26]

1,3,5-trimethyl-1*H*-indole (97c).



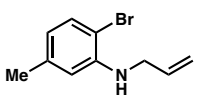
Prepared from 0.70 mmol of 3,5-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (2% ethyl acetate/hexanes) to yield **97c** (0.048 g, 43% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.05 (dd, *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 $[M+H]^+$ 160.1121, found 160.1116.

5-Bromo-1,3-dimethyl-1*H*-indole (97d).



Prepared from 0.95 mmol of 5-bromo-3-methyl-1*H*-indole[28] using general procedure B. The product was purified by flash chromatography (5% ethyl acetate/hexanes) to yield **97d** (0.20 g, 90% yield) as a pale yellow oil. ^{1}H 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 $[M+H]^+$ 224.0069, found 224.0070.

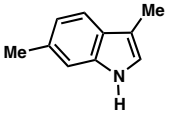
***N*-allyl-2-bromo-5-methylaniline.**



Procedure was adapted from Sørensen and Pombo-Villar.[29] 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 °C for 10 minutes, then at room temperature for 5 h. Then saturated $NaHCO_{3\,(aq)}$ solution was added, and the aqueous layer was extracted with ethyl acetate 3×. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield *N*-allyl-2-bromo-5-methylaniline (1.63 g, 67% yield) as a yellow oil. ^{1}H 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 $[M+H]^+$ 226.0226, found 226.0216.

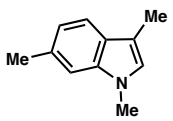
3,6-dimethyl-1*H*-indole.



Procedure was adapted from Sørensen and Pombo-Villar.[29] A solution of *N*-allyl-2-bromo-5-methylaniline (1.6 mmol, 1.0 equiv), $Pd(OAc)_2$ (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 °C in a flask equipped with a reflux condenser for 16 h. The reaction was cooled to room temperature, saturated $NaHCO_{3\,(aq)}$ solution and 100 mL water were added, then the aqueous layer was extracted with ethyl acetate 3×. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 3,6-dimethyl-1*H*-indole (0.19 g, 85% yield) as a white powder. ^{1}H 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,

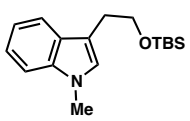
1.1 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 131.6, 126.2, 120.9, 120.8, 118.5, 111.6, 110.9, 21.7, 9.7. IR (NaCl/thin film): 3409, 2922, 1452, 1329, 1086, 908, 803, 733 cm^{-1}. HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 146.0964, found 146.0970.

1,3,6-trimethyl-1*H*-indole (97e).



Prepared from 0.70 mmol of 3,6-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **97e** (62 mg, 56% yield) as a yellow oil. ^{1}H 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 $[M+H]^+$ 160.1121, found 160.1114.

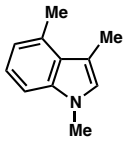
1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (97f).



Prepared from 2.66 mmol of 3-*t*-butyldimethylsiloxyethyl-1*H*-indole[30] using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **97f** (0.67 g, 87% yield) as an orange oil. ^{1}H 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 $[M+H]^+$ 290.1940, found 290.1933.

1,3,4-trimethyl-1*H*-indole



Procedure for Vilsmeier-Haack reaction followed by $LiAlH_4$ reduction was adapted from Petit et al.[31] In a flame-dried flask under nitrogen, $POCl_3$ (0.42 mL, 4.6 mmol) was added at 0 °C to 4-methyl-1*H*-indole (0.5 g, 3.8 mmol) in DMF (7.6 mL). The reaction was stirred at room temperature overnight. 2N $NaOH_{(aq)}$ was added, the solution was stirred for 2 h, and then poured into EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude aldehyde was carried forward without further purification.

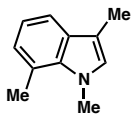
In a flame-dried flask under nitrogen, a solution of the Vilsmeier-Haack product (0.39 g, 2.5 mmol) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (0.19 g, 5 mmol) in THF (1.6 mL). The reaction was heated to reflux for 4 h, then cooled to room temperature and stirred overnight. The reaction was diluted with Et_2O and cooled to 0 °C. Water (0.19 mL) was added slowly, then 15% $NaOH_{(aq)}$ (0.19 mL), and then water (0.6 mL) were added. The mixture was warmed to room temperature and stirred for 15 minutes. Some $MgSO_4$ was added, the mixture was stirred for 15 minutes, filtered, and concentrated. The crude indole was carried forward without further purification.

In a flame-dried flask, the indole (0.3 g, 2.1 mmol) was dissolved in THF (13 mL). Sodium hydride (60% w/w, 124 mg, 3.1 mmol) was added in one portion, then methyl iodide (0.26 mL, 4.1 mmol) 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 (44% yield over three steps).

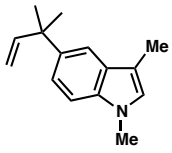
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12-7.05 (m, 2H), 6.81 (ddd, *J* = 6.6, 1.4, 0.8 Hz, 1H), 6.76 (d, *J* = 0.9 Hz, 1H), 3.69 (s, 3H), 2.72 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 131.4, 126.9, 126.7, 121.5, 120.0, 110.9, 107.0, 32.5, 20.0, 12.8; IR (NaCl/thin film): 2918, 1608, 1573, 1551, 1497, 1453, 1417, 1313, 1250, 1205, 1157, 1057, 767, 739 cm^{-1}.

1,3,7-trimethyl-1*H*-indole



Prepared according to the procedure for 1,3,4-trimethyl-1*H*-indole. Spectral data matches that reported in the literature.[32]

1,3-dimethyl-5-reverse prenyl-1*H*-indole



In glovebox, $Pd_2(dba)_3$ (51 mg, 6 mmol) and SPhos (91 mg, 22 mmol) was stirred at room temperature in THF (3 mL) for 1 h until a dark yellow homogeneous solution was formed. Then the solution was transferred into a schlenk tube. Iododimethyl indole (300 mg, 1.11 mmol), trifluorosilane[33] (256 mg in 2.1 mL THF, 1.66 mmol), TBAF (1 M solution in THF, 1.66 mL), and THF (7 mL) were added to the schlenk tube. The reaction mixture was heated to 60°C for 36 h. More TBAF (1M solution in THF, 0.55 mL) was added at 12-h intervals. The reaction was quenched with 5% EtOAc in hexanes and filtered through a silica plug. The organic solution was concentrated to give orange oil. It was then purified by flash chromatography (5% to 9% EtOAc in hexanes) to give reverse prenylated indole

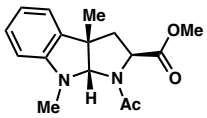
XX as a light yellow oil (177 mg, 0.84 mmol, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.51 (t, J = 0.9 Hz, 1H), 7.24 (dd, J = 8.7, 1.83 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 1.0 Hz, 1H), 6.13 (dd, J = 17.5, 10.6 Hz, 1H), 5.09 (dd, J = 17.6, 1.5 Hz, 1H), 5.04 (dd, J = 10.5, 1.5 Hz, 1H), 3.71 (s, 3H), 2.32 (d, J = 1.0 Hz, 3H), 1.49 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) 149.1, 138.8, 135.4, 128.3, 126.7, 120.6, 115.5, 110.1, 109.9, 108.5, 41.1, 32.5, 28.8, 9.5; IR (NaCl/thin film): 3080, 2964, 2920, 1634, 1489, 1455, 1425, 1387, 1376, 1365, 1292, 1256, 1201, 1152, 1053, 1004, 909, 874, 788; HRMS (MM) calc'd for $C_{15}H_{19}N$ $[M+H]^+$ 214.1590, found 214.1592.

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

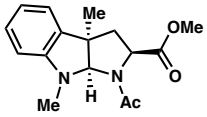
To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (*R*)-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of $SnCl_4$ (0.24 mmol, 1.20 equiv unless specifically indicated, 1 M in DCM), then stirred at room temperature. The reaction was quenched by diluting with 1 mL MeCN and 1 mL 1 M HCl, followed by addition of 5 mL H_2O. 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 (Na_2SO_4), filtered, and concentrated. The crude residue was purified by flash chromatography.

2.4.4 Pyrroloindoline Products under General Procedure C

Pyrroloindoline 91.



(a) *exo* diastereomer



(b) *endo* diastereomer

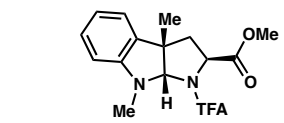
Screen varying (*R*)–BINOL loading. All reactions were run at room temperature for 3 h in DCE with 1,3-dimethyl-1*H*-indole[34] (**89**, 0.2 mmol, 1 equiv), methyl 2-acetamidoacrylate[35] (**86**, 0.2 mmol, 1 equiv) and $SnCl_4$ (1.2 equiv, 1 M in DCM). Purified by flash chromatography (0→50% ethyl acetate/hexanes). The diastereomeric ratio was determined by ^{1}H 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).

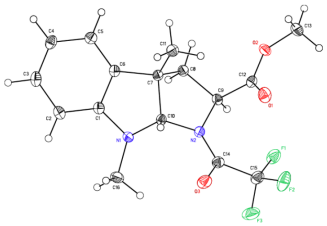
Exo diastereomer: pale yellow oil. t_R(major) = 9.5 min t_R(minor) = 6.2 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 7.10 – 7.01 (m, 1H), 6.95 (d, *J* = 7.3 Hz, 0.5H), 6.91 (d, *J* = 7.3 Hz, 0.5H), 6.68 (t, *J* = 7.4 Hz, 0.5H), 6.62 (t, *J* = 7.4 Hz, 0.5H), 6.43 (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); ^{13}C NMR (100 MHz, $CDCl_3$; 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}; $[\alpha]_D^{25}$ –69.7° (c = 0.85, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 289.1552, found 289.1559.

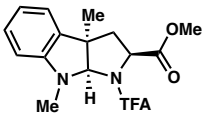
Endo diastereomer: bright yellow oil. t_R(major) = 4.0 min t_R(minor) = 4.7 min. ^1H NMR (400 MHz, $CDCl_3$; compound exists as a 3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11 (t, *J* = 7.6 Hz, 1H§), 7.06 (t, *J* = 7.8 Hz, 1H*), 7.01 (d, *J* = 7.1 Hz, 1H§), 6.96 (d, *J* = 7.2 Hz, 1H*), 6.68 (t, *J* = 7.4 Hz, 1H§), 6.61 (t, *J* = 7.3 Hz, 1H*), 6.40 (d, *J* = 7.8 Hz, 1H§), 6.32 (d, *J* = 7.8 Hz, 1H*), 5.55 (s, 1H*), 5.09 (s, 1H§), 4.98 (dd, J= 8.8, 5.8 Hz, 1H§), 4.46 (d, *J* = 8.3 Hz, 1H*), 3.46 (s, 3H§), 3.25 (s, 3H*), 2.99 (s, 3H*), 2.91 (s, 3H§), 2.68 (d, *J* = 13.6 Hz, 1H*), 2.44 – 2.16 (m, 1H*, 5H§), 2.05 (s, 3H*), 1.42 (s, 3H§), 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}; $[\alpha]_D^{25}$ +146.5° (c = 0.79, DCM) ; HRMS (FAB+) calc'd for $[M+H]^+$ 289.1552 , found 289.1549.

Pyrroloindoline 94.





(a) *exo* diastereomer



(b) *endo* diastereomer

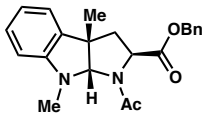
Prepared from 1,3-dimethyl-1*H*-indole **89** and methyl 2-trifluoroacetamidoacrylate[36] **67** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 53.0 mg (77% yield) of **94** in a 6:1 ratio of diastereomers (determined by ^{1}H 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 CO_2, λ = 254 nm): t_R(major) = 2.8 min t_R(minor) = 2.4 min. ^{1}H NMR (400 MHz, $CDCl_3$; 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*); ^{13}C NMR (100 MHz, $CDCl_3$; 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, $J_{C\text{-}F}$ = 37.2 Hz), 149.4*, 149.2§, 134.2*§, 128.8*§, 121.5*§, 119.9§,

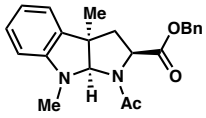
118.7*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), 109.4[§], 108.0*, 93.3*, 91.7[§], 61.3[§], 60.3*, 53.0*, 52.6[§], 49.2*[§], 44.0*, 40.6[§], 36.8*, 34.4[§], 23.5*, 22.8[§]; IR (NaCl/thin film): 2959, 1751, 1696, 1610, 1490, 1435, 1204, 1155, 988, 744 cm^{-1}; melting point: 105.5 – 107.5 °C; $[\alpha]_D^{25}$ = –118.1° (*c* = 0.78, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 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, 1H[§]), 7.10 (t, *J* = 7.7 Hz, 1H*), 7.04 (d, *J* = 7.5 Hz, 1H[§]), 6.98 (d, *J* = 7.3 Hz, 1H*), 6.73 (t, *J* = 7.4 Hz, 1H[§]), 6.66 (t, *J* = 7.4 Hz, 1H*), 6.43 (d, *J* = 7.8 Hz, 1H[§]), 6.37 (d, *J* = 7.8 Hz, 1H*), 5.59 (s, 1H*), 5.33 (s, 1H[§]), 5.07 (dd, *J* = 9.4, 5.2 Hz, 1H[§]), 4.74 (d, *J* = 8.2 Hz, 1H*), 3.57 (s, 3H[§]), 3.16 (s, 3H*), 3.05 (s, 3H*), 2.80 (s, 3H[§]), 2.80 (d, *J* = 12.7 Hz, 1H*), 2.42 (dd, *J* = 13.3, 5.3 Hz, 1H[§]), 2.37 (dd, *J* = 12.9, 8.3 Hz, 1H*), 2.26 (dd, *J* = 13.2, 9.7 Hz, 1H[§]), 1.45 (s, 3H*), 1.43 (s, 3H[§]); ^{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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ = +201.5° (*c* = 0.11, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 343.1270, found 343.1278.

Pyrroloindoline 95.



(a) *exo* diastereomer



(b) *endo* diastereomer

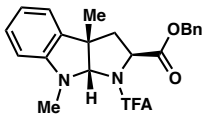
Prepared from 1,3-dimethyl-1*H*-indole **89** and benzyl 2-acetamidoacrylate[37] **93** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The product **95** was formed in a 2:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the crude reaction mixture), 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 CO_2, λ = 254 nm): t_R(major) = 24.6 min t_R(minor) = 19.1 min. ^{1}H NMR (300 MHz, $CDCl_3$; 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*); ^{13}C NMR (100 MHz, $CDCl_3$; 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§,

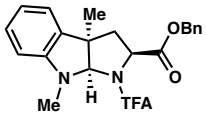
49.7*, 43.8*, 41.4§, 36.5*, 34.3§, 23.0§, 22.7*, 22.7*, 22.4§; IR (NaCl/thin film): 3032, 2962, 2877, 1745, 1661, 1609, 1489, 1390, 1175, 1117, 744 cm^{-1}; $[\alpha]_D^{25}$ = –66.9° (*c* = 0.98, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 365.1865, found 365.1875.

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 CO_2, λ = 254 nm): t_R(major) = 11.1 min t_R(minor) = 12.6 min. ^{1}H 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 7.36 – 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*); ^{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 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}; $[\alpha]_D^{25}$ = +114.4° (*c* = 0.57, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 365.1865, found 365.1862.

Pyrroloindoline 96.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

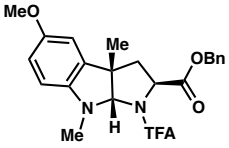
Prepared from 1,3-dimethyl-1*H*-indole (**89**, 0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate[38] (**71**, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→8% ethyl acetate/hexanes) to yield 54 mg (86% yield) of **96** 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 CO_2, 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. ^{1}H 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 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*); ^{13}C NMR (100 MHz, $CDCl_3$; 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, $J_{C\text{-}F}$ = 37.0 Hz)*, 157.3 (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ =

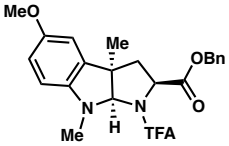
288.6 Hz)*, 109.3§, 107.8*, 93.1*, 91.6§, 67.8*, 67.1§, 61.2§, 60.2 (q, $J_{C\text{-}F}$ = 2.44 Hz)*, 52.9§, 49.0*, 43.6*, 40.2§, 36.5*, 34.2§, 23.1*, 22.5§; IR (NaCl/thin film): 3034, 2966, 1747, 1695, 1610, 1490, 1456, 1432, 1188, 1156, 745 cm^{-1}; $[\alpha]_D^{25}$ –90.1° (c = 1.11, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 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. ^{1}H 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$= 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}; $[\alpha]_D^{25}$ +187.7° (c = 0.78, DCM) ; HRMS (FAB+) calc'd for $[M+H]^+$ 418.1504, found 418.1517.

Pyrroloindoline 98a.



(a) *exo* diastereomer



(b) *endo* diastereomer

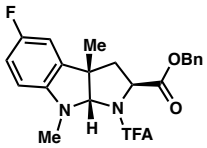
Prepared from 5-methoxy-1,3-dimethyl-1*H*-indole[39] and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 83.1 mg (93% yield) of **98a** in a 3:1 ratio 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, λ = 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. ^{1}H 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, $J_{C\text{-}H}$ = 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, $J_{C\text{-}F}$ = 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*,

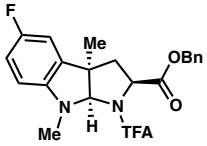
36.9[§], 23.5[§], 23.4*; IR (NaCl/thin film): 2963, 2833, 1748, 1694, 1497, 1432, 1156, 1030, 991, 754 cm^{-1}; $[\alpha]_D^{25}$ = –78.1° (*c* 1.07, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 449.1683, found 449.1676.

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. ^{1}H NMR (500 MHz, $CDCl_3$; 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[§]); ^{13}C NMR (125 MHz, $CDCl_3$; 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ = +162.4° (*c* 1.41, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 449.1683, found 449.1682.

Pyrroloindoline 98b.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

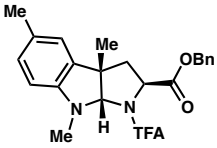
Prepared from 5-fluoro-1,3-dimethyl-1*H*-indole **97b** and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→12% ethyl acetate/hexanes) to yield 53.0 mg (61% yield) of **98b** in a 3:1 ratio of diastereomers (determined by ^{1}H 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, λ = 254 nm).

Exo diastereomer: pale yellow oil. The ee was determined to be 93%. t_R(major) = 14.7 min t_R(minor) = 18.0 min. ^{1}H 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*, 5H§), 6.85 (br t, J = 7.8 Hz, 1H*, 1H§), 6.75 (br s, 1H§), 6.71 (br d, J = 7.8 Hz, 1H*), 6.50 (br s, 1H§), 6.39 (dd, J = 8.4, 3.8 Hz, 1H*), 5.58 (br s, 1H*), 5.34 – 5.16 (m, 2H*, 3H§), 4.75 (br d, J = 9.3 Hz, 1H*), 4.47 (br t, J = 6.8 Hz, 1H§), 3.04 (br s, 3H*), 2.85 (br s, 3H§), 2.55 (dd, J = 13.2, 9.9 Hz, 1H*), 2.55 – 2.45 (m, 1H§), 2.31 (br d, J = 13.4 Hz, 1H*), 2.10 – 1.97 (m, 1H§), 1.45 (br s, 3H§), 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, $J_{C\text{-}F}$ = 37.1 Hz), 157.0* (d, $J_{C\text{-}F}$ = 236.5 Hz), 145.6*, 145.4§, 135.7* (d, $J_{C\text{-}F}$ = 7.3 Hz), 135.1§, 134.6*, 128.9*, 128.8*, 128.7*, 128.6§, 128.5§, 128.4§, 116.2* (q, $J_{C\text{-}F}$ = 267.0 Hz), 114.9§, 114.7* (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.5§, 109.3* (d, $J_{C\text{-}F}$ = 24.3 Hz), 108.6* (d, $J_{C\text{-}F}$ = 7.8 Hz), 93.9*,

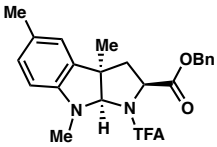
92.2[§], 68.2*, 67.5[§], 61.3[§], 60.3*, 53.2[§], 49.2*, 43.7*, 40.1[§], 37.6*, 35.6[§], 23.3*, 22.9[§]; IR (NaCl/thin film): 2966, 1748, 1698, 1495, 1434, 1350, 1270, 1157, 994, 843 cm^{-1}; $[\alpha]_D^{25}$ = –81.7° (*c* 1.14, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 437.1483, found 437.1476.

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, $CDCl_3$; 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[§]); ^{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 169.2[§], 169.0*, 156.9* (q, $J_{C\text{-}F}$ = 36.7 Hz), 156.3* (q, $J_{C\text{-}F}$ = 235.3 Hz), 146.5*, 144.7[§], 135.2[§], 134.5*, 133.3* (d, $J_{C\text{-}F}$ = 7.2 Hz), 128.5*, 128.4*, 128.2[§], 116.1* (q, $J_{C\text{-}F}$ = 288.6 Hz), 115.0* (d, $J_{C\text{-}F}$ = 23.0 Hz), 114.5[§] (d, $J_{C\text{-}F}$ = 23.1 Hz), 110.2* (d, $J_{C\text{-}F}$ = 24.4 Hz), 109.6* (d, $J_{C\text{-}F}$ = 24.6 Hz), 107.3[§] (d, $J_{C\text{-}F}$ = 7.7 Hz), 106.0* (d, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ = +156.8° (*c* 1.16, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 437.1483, found 437.1490.

Pyrroloindoline 98c.



(a) *exo* diastereomer



(b) *endo* diastereomer

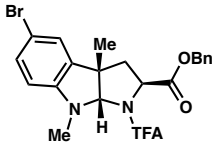
Prepared from 5-methyl-1,3-dimethyl-1*H*-indole (**97c**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 72.9 mg (84% yield) of **98c** in a 5:1 ratio of diastereomers (determined by ^{1}H 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 CO_2, λ = 254 nm): t_R(major) = 20.5 min t_R(minor) = 16.6 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 (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§); ^{13}C NMR (100 MHz, $CDCl_3$; 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, $J_{C\text{-}F}$ = 36.8 Hz), 157.7§ (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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,

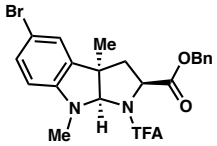
1194, 1153, 992, 754 cm^{-1}; $[\alpha]_D^{25}$ = –87.1° (*c* 0.90, DCM); HRMS (APCI) calc'd for $[M+H]^+$ 433.1734, found 433.1713.

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, λ = 254 nm): t_R(major) = 6.5 min t_R(minor) = 7.3 min. ^{1}H 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*, 3H§), 7.23 – 7.18 (m, 2H§), 7.18 – 7.10 (m, 2H*), 6.96 – 6.84 (m, 1H*, 2H§), 6.81 (br s, 1H*), 6.27 (d, *J* = 7.9 Hz, 1H§), 6.18 (d, *J* = 7.9 Hz, 1H*), 5.57 (s, 1H*), 5.25 (br d, *J* = 1.9 Hz, 1H§), 5.12 (dd, *J* = 9.6, 5.4 Hz, 1H§), 5.05 (d, *J* = 12.4 Hz, 1H§), 4.94 (d, *J* = 12.2 Hz, 1H§), 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, 3H§), 2.44 (dd, *J* = 13.3, 5.3 Hz, 1H§), 2.37 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.26 (s, 3H§), 2.23 (s, 3H*), 1.44 (s, 3H*), 1.41 (s, 3H§); ^{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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ = +176.4° (*c* 0.97, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 433.1734, found 433.1737.

Pyrroloindoline 98d.



(a) *exo* diastereomer



(b) *endo* diastereomer

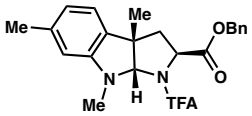
Prepared from 5-bromo-1,3-dimethyl-1*H*-indole (**97d)** and benzyl 2-trifluoroacetamidoacrylate using general procedure C, in DCE with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 57 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 50 mg (51% yield) of **98d** in a 3:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the pure product). The diastereomers were separated by prepatory 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, λ = 254 nm): t_R(major) = 14.7 min t_R(minor) = 12.5 min. ^{1}H 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, $J_{C\text{-}F}$ = 37.1 Hz)*, 157.42 (d, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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):

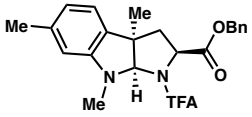
3034, 2965, 2931, 1747, 1698, 1602, 1489, 1205, 1154, 806, 751 cm^{-1}; $[\alpha]_D^{25}$ –86.4° (c = 0.60, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 498.0589, found 498.0576.

Endo diastereomer: The enantiomeric excess was determined to be 85% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, λ = 254 nm): t_R(major) = 7.3 min t_R(minor) = 8.1 min. ^{1}H 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_{C-F} = 37.0 Hz)*, 149.4*, 134.4*, 134.2*, 131.8*, 131.4§, 125.5*, 124.9§, 116.1(q, J_{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}; $[\alpha]_D^{25}$ + 156.3° (c = 0.24, DCM) ; HRMS (FAB+) calc'd for $[M+H]^+$ 498.0589, found 498.0606.

Pyrroloindoline 98e.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

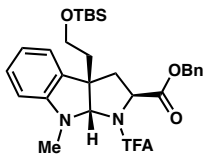
Prepared from 6-methyl-1,3-dimethyl-1*H*-indole (**97e**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 6 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 78.3 mg (91% yield) of **98e** in a 4:1 ratio of diastereomers (determined by ^{1}H 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, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94%. t_R(major) = 14.5 min t_R(minor) = 12.9 min. ^{1}H 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, $J_{C\text{-}F}$ = 37.0 Hz), 157.7§ (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 288.4 Hz), 116.0§ (q, $J_{C\text{-}F}$ = 286.5 Hz), 110.5§, 108.9*, 93.6*,

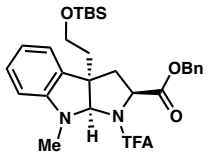
92.0[§], 68.1*, 67.4[§], 61.5[§], 60.5*, 52.9[§], 49.0*, 43.9*, 40.4[§], 36.8*, 34.7[§], 23.5*, 23.0[§], 21.7*[§]; IR (NaCl/thin film): 2964, 1748, 1697, 1616, 1499, 1456, 1423, 1160, 1004, 752 cm^{-1}; $[\alpha]_D^{25}$ = –85.6º (*c* 0.93, DCM); HRMS (EI+) calc'd for $M^{+\bullet}$ 432.1661, found 432.1663.

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. ^{1}H 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 7.38 – 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[§]); ^{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 169.4[§], 169.3*, 156.9* (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ = +165.5º (*c* 0.53, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 433.1739, found 433.1756.

Pyrroloindoline 98f.



(a) *exo* diastereomer



(b) *endo* diastereomer

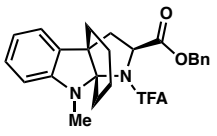
Prepared from 1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (**97f**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 20 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 61 mg (54% yield) of **98f** in a 6:1 ratio of diastereomers (determined by ^{1}H 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, λ = 254 nm): t_R(major) = 10.7 min t_R(minor) = 12.1 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (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, $J_{C\text{-}F}$ = 37.9 Hz)*, 157.7 (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 288.0 Hz)*, 110.0§, 108*, 90.8*, 89.5§, 67.9*, 67.3§,

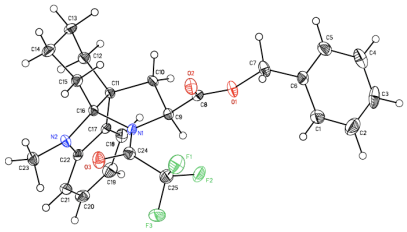
60.5[§], 59.6*, 56.4[§], 52.3*, 43.5*, 39.9[§], 39.1[§], 39.0*, 36.4*, 35.7[§], 25.8*, 18.1[§], -5.6*[§]; IR (NaCl/thin film): 3035, 2955, 2930, 2857, 2884, 1750, 1694, 1492, 1432, 1257, 1201, 1158, 1106, 837 cm^{-1}; $[\alpha]_D^{25} = -95.3°$ (c =1.38, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 562.2475, 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. ^{1}H NMR (500 MHz, $CDCl_3$; 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[§]); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 16.7:1 mixture of rotamers, only the major rotamer is reported) δ 169.3, 156.8 (q, $J_{C\text{-}F}$ = 37.9 Hz), 151.2, 134.7, 129.6, 129.2, 128.43, 128.37, 128.2, 123.5, 117.5, 116. 2 (q, $J_{C\text{-}F}$ = 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 98g.



exo diastereomer

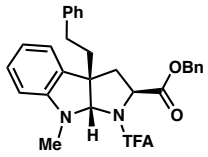


Prepared from 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole [40] and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 11 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 60 mg (65% yield) of **98g** in a >18:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the pure product). The diastereomers were separated by prep HPLC (0→10% ethyl acetate/hexanes).

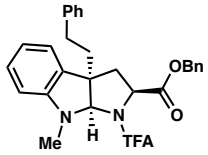
Exo diastereomer: pale yellow oil. The oil was crystallized from ethyl acetate/hexanes to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, λ = 254 nm): t_R(major) = 4.5 min t_R(minor) = 6.9 min. ^{1}H NMR (300 MHz, $CDCl_3$; 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); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a >20:1 mixture of rotamers) δ 172.4, 157.7 (q, $J_{C\text{-}F}$ = 36.3 Hz), 148.0, 134.9, 133.7, 128.7, 128.6, 128.4, 120.8, 118.0, 115.8 (q, $J_{C\text{-}F}$ = 289.8 Hz), 112.3, 107.1, 95.6, 67.6, 58.4 (q, $J_{C\text{-}F}$ = 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 °C; $[\alpha]_D^{25} = -92.6°$ (c = 1.40, DCM); HRMS (ESI+) calc'd for $[M+H]^+$ 459.1890, found 459.1892.

Pyrrolidinoindoline 98h.



(a) *exo* diastereomer



(b) *endo* diastereomer

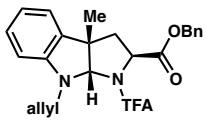
Prepared from 3-phenethyl-1-methyl-1*H*-indole [41] and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 9.5 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 81 mg (80% yield) of **98h** 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, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 92%. t_R(major) = 33.3 min t_R(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_{C-F} = 36.7 Hz)*, 157.60 (q, J_{C-}

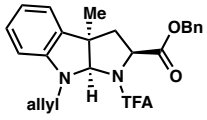
$_F$ = 32.9 Hz)[§], 150.3*[§], 141.0*[§], 135.1[§], 134.5*, 132.0*, 131.6[§], 129.1[§], 128.9[§], 128.8[§], 128.7*, 128.4*, 128.2*, 126.0*[§], 122.3[§], 121.9*, 120.1[§], 118.9*, 116.0 (q, $J_{C\text{-}F}$ = 288.4 Hz)*, 109.7[§], 108.3*, 90.4*, 89.2[§], 68.1*, 67.4[§], 60.7[§], 59.5*, 57.5[§], 53.7*, 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}; $[\alpha]_D^{25}$ –113.8° (c =1.17, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 509.2047, found 509.2052.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 11.6 min t_R(minor) = 17.5 min. ^{1}H 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ +119.6° (c = 0.87, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 509.2047, found 509.2048.

Pyrroloindoline 72.



(a) ***exo*** diastereomer



(b) ***endo*** diastereomer

Prepared from 1-allyl-3-methyl-1*H*-indole [42] and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents $SnCl_4$. 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 **72** 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).

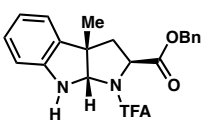
Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min t_R(minor) = 4.3 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted 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*); ^{13}C NMR (100 MHz, $CDCl_3$; 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ = –94.3º (*c* 1.14, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 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, λ = 254 nm): t_R(major) = 5.9 min t_R(minor) = 5.1 min. ^{1}H 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ = +166.6º (*c* 1.52, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 445.1734, found 445.1740.

Pyrroloindoline 98i.



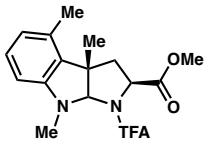
***exo* diastereomer**

Prepared from 3-methyl-1*H*-indole (0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate (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 **98i** in an 8:1 ratio of diastereomers (determined by NMR analysis of the pure product). The diastereomers were separated by prepatory 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. ^{1}H NMR (500 MHz, $CDCl_3$; 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) ; ^{13}C NMR (125 MHz, $CDCl_3$; 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, $J_{C\text{-}F}$ = 287.2), 115.7 (q, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ –111.8° (c = 0.22, DCM); HRMS (EI+) calc'd for $M^{+\bullet}$ 404.1348, found 404.1344.

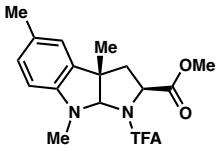
Pyrroloindoline 110a.



The d.r. was determined to be 7:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 46.4 mg (66% yield) of **110a**. The enantiomeric excess was determined to be 95% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 3.1 min t_R(minor) = 2.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.08 (t, J = 7.8 Hz, 1H*, 1H§), 6.65-6.57 (m, 1H§), 6.55 (d, J = 7.6 Hz, 1H*), 6.45-6.40 (m, 1H§), 6.38 (d, J = 7.8 Hz, 1H*), 5.49 (s, 1H*), 5.29 (s, 1H§), 4.74 (d, J = 9.3 Hz, 1H*), 4.45 (m, 1H§), 3.83 (s, 3H*), 3.78 (s, 3H§), 3.12 (s, 3H*), 2.85 (s, 3H§), 2.68 (dd, J = 13.3, 9.7 Hz, 1H*), 2.64-2.59 (m, 1H§), 2.53 (dd, J = 13.3, 1.6 Hz, 1H*), 2.33 (s, 3H§), 2.31 (s, 3H*), 2.20-2.10 (m, 1H§), 1.60 (s, 3H§), 1.47 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 3.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.7*, 170.5§, 159.0§ (q, $J_{C\text{-}F}$ = 37.2 Hz), 150.6*, 149.7§, 133.1§, 132.7*, 131.6*, 130.9§, 128.8*§, 122.6§, 121.5*, 116.1* (q, $J_{C\text{-}F}$ = 288.3 Hz), 107.3§, 106.2*,

94.0*, 92.0§, 61.3§, 60.0*, 53.1*, 52.6§, 50.0*, 42.7*, 39.4§, 37.4*, 34.6§, 24.1*, 23.3§, 18.5*§; IR (NaCl/thin film): 3047, 2957, 2930, 2880, 2825, 1752, 1701, 1596, 1477, 1434, 1385, 1356, 1338, 1293, 1263, 1254, 1216, 1204, 1155, 1097, 1064, 1020, 989, 854, 772, 744, 727 cm^{-1}; $[\alpha]_D^{25}$ = –158.8 (*c* = 1.01, $CHCl_3$). HRMS (APCI) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1426.

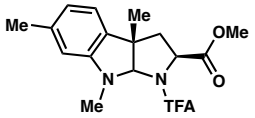
Pyrroloindoline 110b.



The d.r. was determined to be 13:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 48.2 mg (68% yield) of **110b**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 4.4 min t_R(minor) = 2.7 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.98 (d, *J* = 7.4 Hz, 1H*, 1H§), 6.87 (s, 1H§), 6.84 (s, 1H*), 6.50 (d, *J* = 7.8 Hz, 1H§), 6.43 (d, *J* = 8.0 Hz, 1H*), 5.57 (s, 1H*), 5.27 (s, 1H§), 4.73 (d, *J* = 9.3 Hz, 1H*), 4.41 (t, *J* = 7.6 Hz, 1H§), 3.82 (s, 3H*), 3.76 (s, 3H§), 3.05 (s, 3H*), 2.86 (s, 3H§), 2.59 (dd, *J* = 13.3, 9.7 Hz, 1H*), 2.55-2.48 (m, 1H§), 2.35 (dd, *J* = 13.5, 2.2 Hz, 1H*), 2.28 (br s, 3H§), 2.20-2.10 (m, 1H§), 1.49 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.7§, 159.1§ (q, $J_{C\text{-}F}$ = 37.0 Hz), 147.3*, 147.2§, 134.4*§, 129.7§, 129.2§, 129.1*, 128.2*, 122.3*§, 116.1* (q, $J_{C\text{-}F}$ = 288.2 Hz), 109.9§, 108.2*, 93.8*, 92.1§, 61.2§, 60.3*, 53.2§, 53.0*, 52.5§, 49.2*, 44.0*, 40.3§, 37.4*, 35.5§, 23.5*, 23.2§, 20.8*§; IR

(NaCl/thin film): 2958, 2924, 2873, 2822, 1750, 1699, 1618, 1500, 1435, 1384, 1356, 1339, 1288, 1257, 1201, 1152, 1117, 1094, 1057, 1035, 986, 874, 844, 807, 761, 728 cm^{-1}; $[\alpha]_D^{25}$ = –128.4 (*c* = 1.08, $CHCl_3$). HRMS (APCI) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1407.

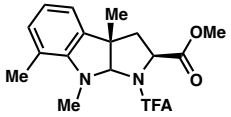
Pyrroloindoline 110c.



The d.r. was determined to be 14:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 58.8 mg (83% yield) of **110c**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 3.4 min t_R(minor) = 2.8 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.99-6.93 (m, $1H^{\S}$), 6.91 (d, *J* = 7.4 Hz, 1H*), 6.65 (d, *J* = 6.7 Hz, $1H^{\S}$), 6.58 (d, *J* = 7.3 Hz, 1H*), 6.41 (s, $1H^{\S}$), 6.34 (s, 1H*), 5.60 (s, 1H*), 5.31 (s, $1H^{\S}$), 4.72 (d, *J* = 9.0 Hz, 1H*), 4.48-4.39 (m, $1H^{\S}$), 3.82 (s, 3H*), 3.77 (s, $3H^{\S}$), 3.06 (s, 3H*), 2.86 (s, $3H^{\S}$), 2.58 (dd, *J* = 13.2, 9.2 Hz, 1H*), 2.52-2.45 (m, $1H^{\S}$), 2.39-2.33 (m, 1H*), 2.32 (br s, 3H*, $3H^{\S}$), 2.10-2.00 (m, $1H^{\S}$), 1.49 (s, $3H^{\S}$), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, $170.6^{\S}$, $159.1^{\S}$ (q, $J_{C\text{-}F}$ = 37.9 Hz), 149.6*, $149.4^{\S}$, $139.0^{\S}$, 138.9*, 131.5*, $131.4^{\S}$, $121.2^{*\S}$, $120.6^{\S}$, 119.3*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), $110.4^{\S}$, 108.9*, 93.5*, $91.9^{\S}$, $61.3^{\S}$, 60.3*, 53.0*, $52.9^{\S}$, $52.5^{\S}$, 49.0*, 44.0*, $40.5^{\S}$, 36.7*, $34.6^{\S}$, 23.6*, $23.0^{\S}$, 21.7*; IR (NaCl/thin film): 2958, 2929, 2875, 2813, 1750, 1697, 1617, 1594, 1499, 1435, 1382,

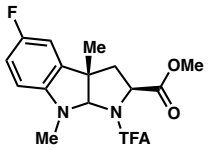
1356, 1341, 1294, 1257, 1203, 1190, 1148, 1111, 1094, 1059, 1034, 1006, 985, 877, 852, 803, 763, 729 cm^{-1}; $[\alpha]_D^{25}$ = –115.4 (*c* = 1.54, $CHCl_3$). HRMS (MM) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1434.

Pyrroloindoline 110d.



The d.r. was determined to be 15:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 48.1 mg (68% yield) of **110d** (major diastereomer only). The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 3.6 min t_R(minor) = 2.5 min. ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.05-7.00 (m, 1H*), 7.00-6.93 (m, 2H*, 1H§), 6.91 (d, *J* = 7.2 Hz, 1H§), 6.82 (t, *J* = 7.4 Hz, 1H§), 5.27 (s, 1H§), 5.14 (d, *J* = 1.6 Hz, 1H*), 4.59 (dd, *J* = 9.1, 2.3 Hz, 1H§), 4.06 (dd, *J* = 11.2, 6.6 Hz, 1H*), 3.80 (s, 3H§), 3.72 (s, 3H*), 3.26 (s, 3H§), 2.99 (s, 3H*), 2.67 (dd, *J* = 12.6, 6.6 Hz, 1H*), 2.57 (dd, *J* = 13.4, 9.2 Hz, 1H§), 2.30 (s, 3H§), 2.22 (s, 3H*), 2.13-2.03 (m, 1H*, 1H§), 1.47 (s, 3H*), 1.42 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6§, 171.1*, 158.7*, 149.9*, 148.8§, 136.6*§, 131.4§, 131.0*, 126.6*, 124.01*, 122.6§, 121.2§, 119.6*, 119.4§, 116.0* (q, $J_{C\text{-}F}$ = 285.8 Hz), 95.6§, 92.5*, 60.3*, 59.2§, 55.1*, 52.9§, 52.4*, 49.7§, 44.0§, 41.9§, 41.0*, 38.6*, 26.3*, 26.0§, 18.9§, 17.5*; IR (NaCl/thin film): 2963, 1753, 1684, 1437, 1359, 1269, 1162, 1120, 1103, 1086, 1067, 977 cm^{-1}; $[\alpha]_D^{25}$ = –27.0 (*c* = 0.91, CH_2Cl_2). HRMS (MM) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1434.

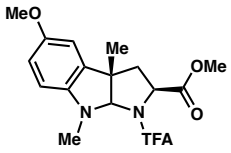
Pyrroloindoline 110e.



The d.r. was determined to be 10:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 41.4 mg (58% yield) of **110e**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 3.7 min t_R(minor) = 2.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.92-6.82 (m, 1H*, 1H§), 6.81-6.76 (m, 1H§), 6.74 (dd, J = 8.0, 2.7 Hz, 1H*), 6.50 (dd, J = 8.6, 4.1 Hz, 1H§), 6.40 (dd, J = 8.6, 4.1 Hz, 1H*), 5.60 (s, 1H*), 5.31 (s, 1H§), 4.74 (d, J = 9.3 Hz, 1H*), 4.43 (t, J = 7.8 Hz, 1H§), 3.82 (s, 3H*), 3.77 (s, 3H§), 3.04 (s, 3H*), 2.85 (s, 3H§), 2.58 (dd, J = 13.5, 9.6 Hz, 1H*), 2.53-2.45 (m, 1H§), 2.40-2.32 (m, 1H*), 2.06 (dd, J = 13.3, 6.6 Hz, 1H§), 1.49 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.4*, 170.5§, 159.0§ (q, $J_{C\text{-}F}$ = 35.8 Hz), 157.9*, 156.7§, 156.0*, 145.6*, 145.4§, 135.8§ (d, $J_{C\text{-}F}$ = 8.7 Hz), 135.6* (d, $J_{C\text{-}F}$ = 7.5 Hz), 116.0* (q, $J_{C\text{-}F}$ = 289.2 Hz), 115.1§, 114.8* (d, $J_{C\text{-}F}$ = 23.2 Hz), 110.5§ (d, $J_{C\text{-}F}$ = 7.3 Hz), 110.2§ (d, $J_{C\text{-}F}$ = 24.3 Hz), 109.4§ (d, $J_{C\text{-}F}$ = 24.1 Hz), 109.3* (d, $J_{C\text{-}F}$ = 24.4 Hz), 108.6* (d, $J_{C\text{-}F}$ = 8.1 Hz), 105.9§ (d, $J_{C\text{-}F}$ = 8.0 Hz), 93.8*, 92.1§, 61.1§, 60.2*, 53.2§, 53.1*, 52.6§, 49.2§, 43.8*, 40.1§, 37.6*, 35.5§, 23.4*, 22.9§; IR (NaCl/thin film): 2959, 2880, 2825, 1750, 1699, 1611, 1495, 1436, 1386, 1356, 1339, 1270, 1229, 1202, 1178, 1152, 1118, 1091, 1052, 1034, 986, 872, 845,

808, 756, 728 cm^{-1}; $[\alpha]_D^{25}$ = –108.5 (*c* = 1.08, $CHCl_3$). HRMS (APCI) calc'd for $C_{16}H_{16}F_4N_2O_3$ $[M+H]^+$ 361.1170, found 361.1187.

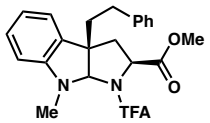
Pyrroloindoline 110f.



The d.r. was determined to be 10:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 44.8 mg (61% yield) of **110f**. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 3.8 min t_R(minor) = 2.5 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.75-6.70 (m, 1H*, 1H§), 6.67-6.65 (m, 1H§), 6.64 (d, *J* = 2.4 Hz, 1H*), 6.55 (d, *J* = 8.5 Hz, 1H§), 6.45 (d, *J* = 8.5 Hz, 1H*), 5.55 (s, 1H*), 5.24 (s, 1H§), 4.74 (d, *J* = 9.4 Hz, 1H*), 4.38 (t, *J* = 8.0 Hz, 1H§), 3.81 (s, 3H*), 3.77 (s, 3H§), 3.76 (s, 3H*, 3H§), 3.04 (s, 3H*), 2.86 (s, 3H§), 2.59 (dd, *J* = 13.5, 9.6 Hz, 1H*), 2.52 (dd, *J* = 13.0, 8.7 Hz, 1H§), 2.35 (dd, *J* = 13.5, 2.5 Hz, 1H*), 2.09-2.00 (m, 1H§), 1.48 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.5*, 170.7§, 159.0§ (q, $J_{C\text{-}F}$ = 37.1, 36.6 Hz), 154.6§, 153.6*, 143.7*, 143.6§, 135.9§, 135.7*, 116.1* (q, $J_{C\text{-}F}$ = 288.3 Hz), 113.3§, 113.0*, 111.4§, 109.02*, 108.98*, 108.8§, 94.1*, 92.3§, 61.0§, 60.3*, 56.0*, 55.9§, 53.6§, 53.1*, 52.6§, 49.3*, 43.9*, 39.9§, 38.1*, 36.8§, 23.5*§; IR (NaCl/thin film): 2958, 2833, 1750, 1691, 1598, 1497, 1434, 1384, 1356, 1341, 1281, 1259, 1231, 1203, 1154, 1093, 1062,

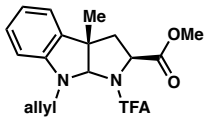
1031, 986, 870, 844, 808, 756, 728 cm^{-1}; $[\alpha]_D^{25}$ = –103.2 (*c* = 0.82, $CHCl_3$). HRMS (APCI) calc'd for $C_{17}H_{19}F_3N_2O_4$ $[M+H]^+$ 373.1370, found 373.1383.

Pyrroloindoline 110g.



The diastereomeric ratio was determined to be 13:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 74.1 mg (86% yield) of **110g**. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 8% IPA in CO_2, λ = 254 nm): t_R(major) = 5.3 min t_R(minor) = 8.1 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^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 7.32-7.15 (m, 4H*, 4H§), 7.08 (br t, *J* = 7.7 Hz, 3H*, 3H§), 6.95-6.75 (m, 1H*, 1H§), 6.65-6.50 (m, 1H*, 1H§), 5.72 (br s, 1H*), 5.46 (br s, 1H§), 4.65 (br d, *J* = 6.3 Hz, 1H*), 4.33 (br s, 1H§), 3.78 (br s, 3H*, 3H§), 3.13 (br s, 3H*), 2.90 (br s, 3H§), 2.76-1.87 (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 172.6*, 170.6§, 159.0* (q, $J_{C\text{-}F}$ = 37.5 Hz), 150.3*§, 141.1*§, 131.9*, 131.7§, 129.0*§, 128.5*§, 128.2*§, 126.1*§, 122.0*, 121.2* (q, $J_{C\text{-}F}$ = 278.2 Hz), 119.0*, 117.2§, 114.9§, 109.8§, 108.3*, 90.5*, 89.2§; IR (NaCl/thin film): 3026, 2952, 1751, 1701, 1607, 1491, 1437, 1355, 1204, 1151, 985, 749 cm^{-1}; $[\alpha]_D^{25}$ = –128.3 (*c* = 1.22, CH_2Cl_2). HRMS (MM) calc'd for $C_{23}H_{23}F_3N_2O_3$ $[M+H]^+$ 433.1734, found 433.1750.

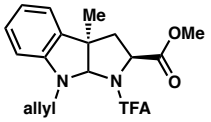
Pyrroloindoline *exo*-110h.



The diastereomeric ratio was determined to be 5:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 61.1 mg of white needles (84% yield). The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 7.8 min t_R(minor) = 3.5 min. The major and minor diastereomers were separated by reverse phase preparatory HPLC (50→95% acetonitrile/water, 0.05% trifluoroacetic acid). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 4.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.14 (td, *J* = 7.7, 1.3 Hz, 1H*, 1H§), 7.03 (br d, *J* = 7.3 Hz, 1H*, 1H§), 6.90-6.80 (br s, 1H§), 6.76 (t, *J* = 7.4 Hz, 1H*), 6.67-6.58 (br s, 1H§), 6.54 (d, *J* = 7.9 Hz, 1H*), 5.81 (dtd, *J* = 16.5, 11.6, 11.1, 6.2 Hz, 1H*, 1H§), 5.74 (s, 1H*), 5.51 (br s, 1H§), 5.27 (br d, *J* = 17.1 Hz, 1H*, 1H§), 5.14 (br d, *J* = 10.2 Hz, 1H*, 1H§), 4.72 (d, *J* = 9.1 Hz, 1H*), 4.34 (br s, 1H§), 4.25 (dd, *J* = 16.5, 3.6 Hz, 1H*), 4.04 (dd, *J* = 16.5, 6.2 Hz, 1H*), 4.00-3.94 (m, 1H§), 3.82 (s, 3H*), 3.76 (s, 3H§), 2.62 (dd, *J* = 13.3, 9.7 Hz, 1H*), 2.58-2.49 (m, 1H§), 2.40 (dd, *J* = 13.5, 2.6 Hz, 1H*), 2.11 (br s, 1H§), 1.48 (s, 3H§), 1.39 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 4.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.6§, 158.9§ (q, $J_{C\text{-}F}$ = 36.9 Hz), 148.4*, 134.7*, 133.8*, 133.3§, 128.7*, 121.7§, 121.5*, 120.3§, 118.8*, 117.8§, 116.8*, 116.0* (q, $J_{C\text{-}F}$ = 288.4 Hz), 110.8§, 108.5*, 91.3*, 89.6§, 60.9§, 59.9*, 53.0*, 52.5§, 51.8*, 50.4§, 49.4*, 44.3*, 40.8§, 23.7*, 23.4§; IR (NaCl/thin film): 3053, 2958, 2877, 1751, 1700, 1691, 1685, 1642, 1608, 1487, 1437, 1384, 1356, 1340, 1309, 1257, 1205, 1151, 1106, 1093, 1027, 991, 925, 841, 817, 792,

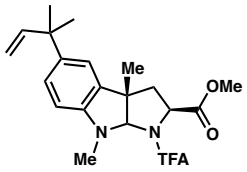
744 cm^{-1}; $[\alpha]_D^{25}$ = –146.2 (*c* = 1.60, $CHCl_3$). HRMS (APCI) calc'd for $C_{18}H_{19}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1416.

Pyrroloindoline *endo*-110h.



^1H NMR (500 MHz, $CDCl_3$; compound exists as a 15.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11-7.07 (m, 1H§), 7.06 (td, *J* = 7.6, 1.3 Hz, 1H*), 7.06-7.03 (m, 1H§), 6.98 (dd, *J* = 7.3, 0.7 Hz, 1H*), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H§), 6.66 (td, *J* = 7.4, 1.0 Hz, 1H*), 6.46-6.44 (m, 1H§), 6.44 (d, *J* = 7.9 Hz, 1H*), 5.87 (dddd, *J* = 17.1, 10.3, 5.9, 5.1 Hz, 1H*), 5.82-5.75 (m, 1H§), 5.57 (s, 1H*), 5.53 (d, *J* = 1.4 Hz, 1H§), 5.30 (dq, *J* = 17.2, 1.7 Hz, 1H*), 5.22-5.19 (m, 1H§), 5.16 (dq, *J* = 10.2, 1.5 Hz, 1H*), 5.10 (dd, *J* = 9.5, 4.5 Hz, 1H§), 4.75 (dt, *J* = 8.4, 1.3 Hz, 1H*), 4.24-4.13 (m, 2H*), 3.85 (ddd, *J* = 49.3, 17.2, 5.1 Hz, 2H§), 3.53 (s, 3H§), 3.17 (s, 3H*), 2.85 (d, *J* = 13.0 Hz, 1H*), 2.50 (dd, *J* = 13.2, 4.5 Hz, 1H§), 2.39 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.25 (dd, *J* = 13.3, 9.6 Hz, 1H§), 1.44 (s, 3H§), 1.42 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 15.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 170.0*, 156.8§ (q, $J_{C\text{-}F}$ = 36.8 Hz), 149.3*, 147.8§, 134.2*, 133.2§, 132.6§, 132.0*, 128.9*, 128.6§, 122.5*, 121.7§, 118.7§, 118.0*, 117.1§, 116.3*, 116.1* (q, $J_{C\text{-}F}$ = 288.6 Hz), 108.0§, 106.8*, 88.7§, 88.1*, 60.3§, 60.1* (q, $J_{C\text{-}F}$ = 3.1 Hz), 52.6§, 52.5§, 52.4*, 50.6*, 49.0*, 46.6§, 42.5*, 41.4§, 25.7*, 22.9§; IR (NaCl/thin film): 3055, 2954, 2869, 1760, 1742, 1699, 1607, 1490, 1447, 1436, 1338, 1317, 1274, 1254, 1208, 1183, 1144, 1105, 1093, 1032, 999, 942, 922, 887, 842, 859, 742 cm^{-1}; $[\alpha]_D^{25}$ = +188.1 (*c* = 0.275, $CHCl_3$). HRMS (APCI) calc'd for $C_{18}H_{19}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1429.

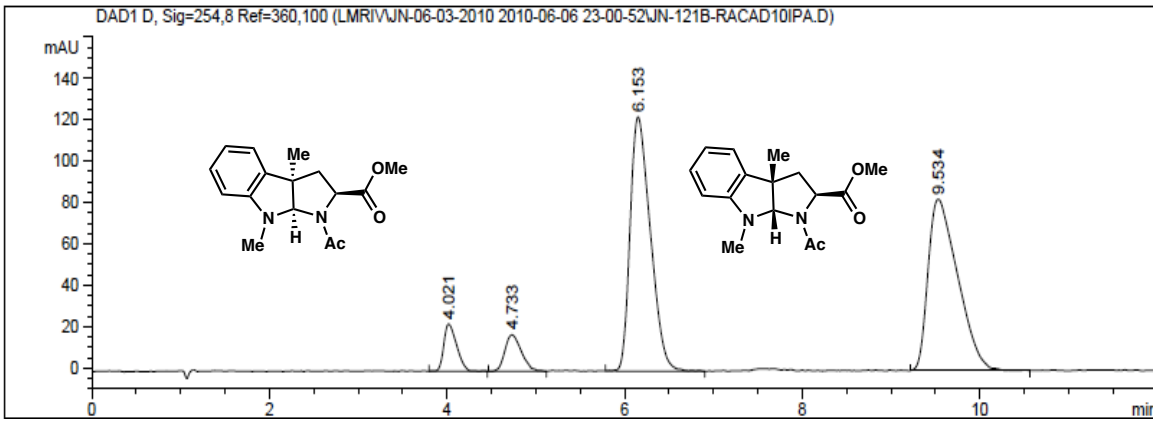
Pyrroloindoline 110i.



The diastereomeric ratio was determined to be 18:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 68.6 mg (84% yield) of **110i.** The enantiomeric excess was determined to be 92% by chiral SFC analysis (OD, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm): t_R(major) = 6.5 min t_R(minor) = 5.6 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.16 (d, *J* = 8.1 Hz, 1H*, 1H§), 7.02 (s, 1H§), 6.99 (s, 1H*), 6.52 (d, *J* = 7.7 Hz, 1H§), 6.45 (d, *J* = 8.2 Hz, 1H*), 6.00 (dd, *J* = 17.3, 10.5 Hz, 1H*, 1H§), 5.60 (s, 1H*), 5.31 (s, 1H§), 5.07 – 4.96 (m, 2H*, 2H§), 4.73 (d, *J* = 9.3 Hz, 1H*), 4.47 – 4.41 (m, 1H§), 3.82 (s, 1H*), 3.77 (s, 1H§), 3.06 (s, 1H*), 2.86 (s, 1H§), 2.60 (dd, *J* = 13.1, 9.9 Hz, 1H*), 2.52 (t, *J* = 10.7 Hz, 1H§), 2.38 (d, *J* = 12.5 Hz, 1H*), 2.14 – 1.98 (m, 1H§), 1.57 – 1.31 (m, 9H*, 9H§); ^{13}C NMR (126 MHz, $CDCl_3$) ; IR (NaCl/thin film): 3081, 2965, 2874, 2822, 1753, 1698, 1618, 1496, 1434, 1359, 1283, 1257, 1204, 1156, 1117, 1054, 995, 912, 844, 813; $[\alpha]_D^{25}$ = -115 (*c* = 0.450, $CHCl_3$). HRMS (ESI) calc'd for $C_{21}H_{25}F_3N_2O_3$ $[M+H]^+$ 411.1890, found 411.1901.

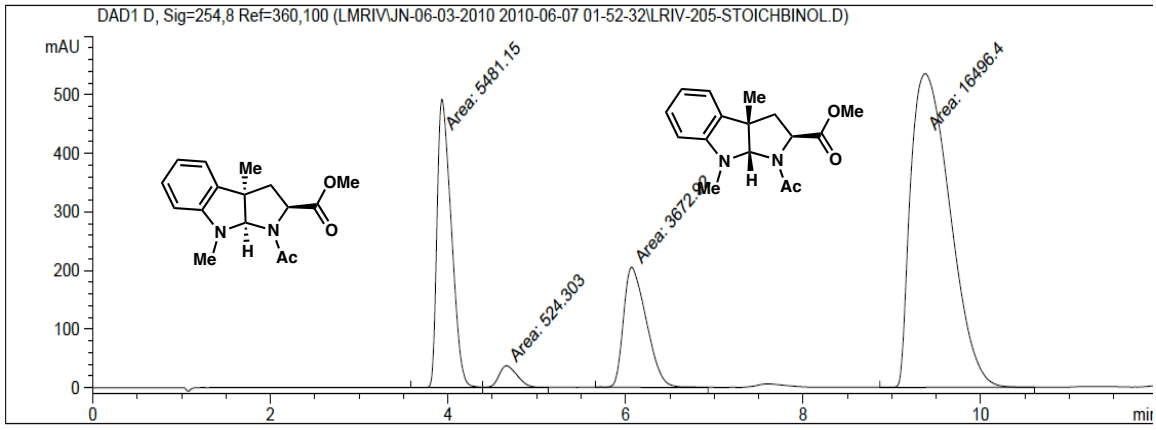
2.4.5 SFC and HPLC Traces for Racemic and Enantioenriched Products

91: racemic



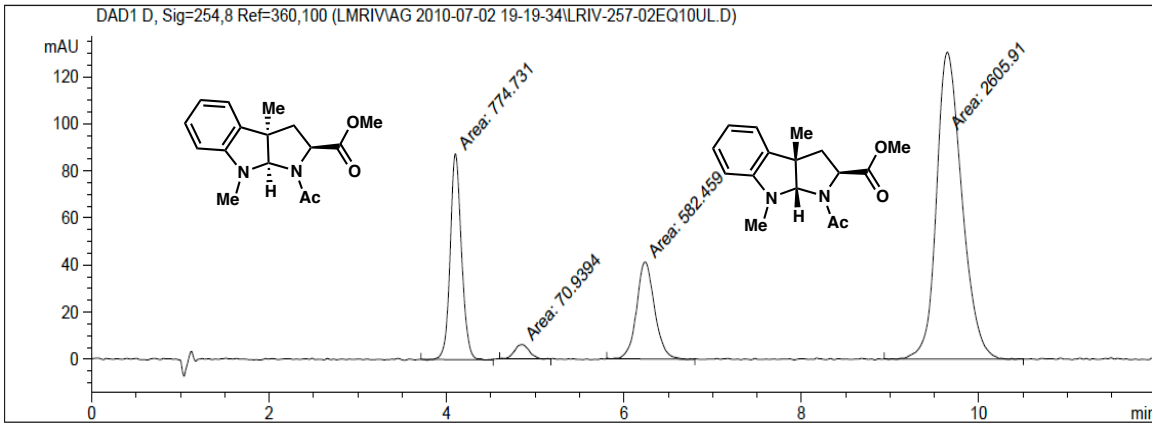
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.021	BB	0.1585	233.11978	22.95946	5.3721
2	4.733	BB	0.2032	229.21661	17.68176	5.2822
3	6.153	BB	0.2451	1949.83508	122.89280	44.9330
4	9.534	BB	0.3471	1927.25183	82.93414	44.4126

91 (**Table 3, entry 2**): enantioenriched, *exo:* 64% ee, *endo*: 83% ee (1.1 equiv BINOL)



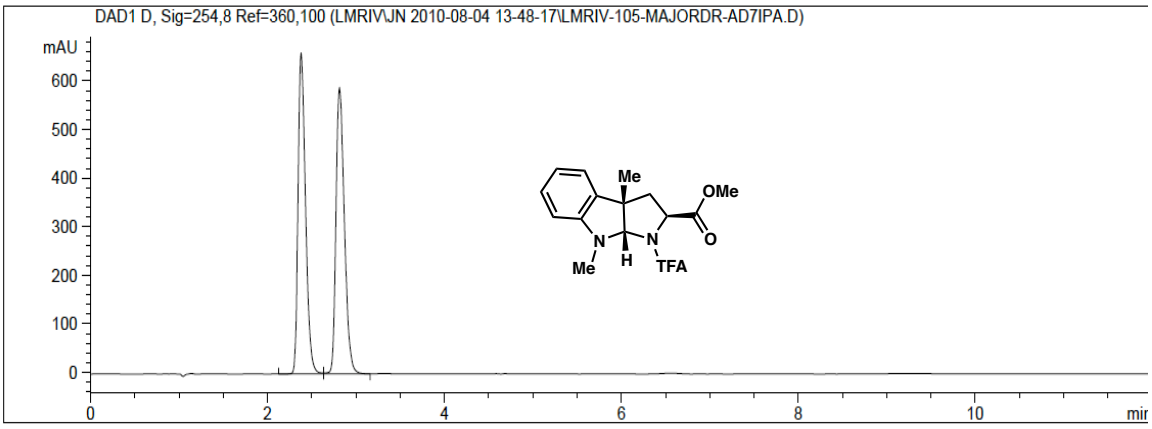
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.934	MF	0.1852	5481.14941	493.18698	20.9406
2	4.658	FM	0.2354	524.30292	37.12406	2.0031
3	6.070	MM	0.2985	3672.91748	205.08722	14.0323
4	9.375	MM	0.5132	1.64964e4	535.76978	63.0240

91 (**Table 3, entry 4**): enantioenriched, *exo:* 63% ee, *endo*: 83% ee (0.2 equiv BINOL)



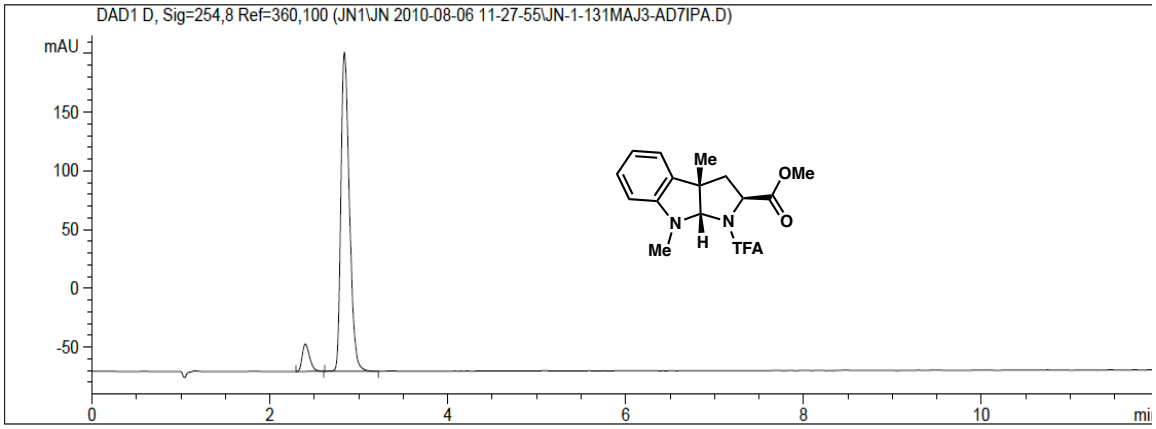
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.100	MM	0.1473	774.73053	87.65621	19.2048
2	4.852	MM	0.1955	70.93945	6.04832	1.7585
3	6.238	MM	0.2351	582.45917	41.28461	14.4386
4	9.647	MM	0.3330	2605.91260	130.42717	64.5981

***exo*-94** (**Table 3, entry 6**): racemic



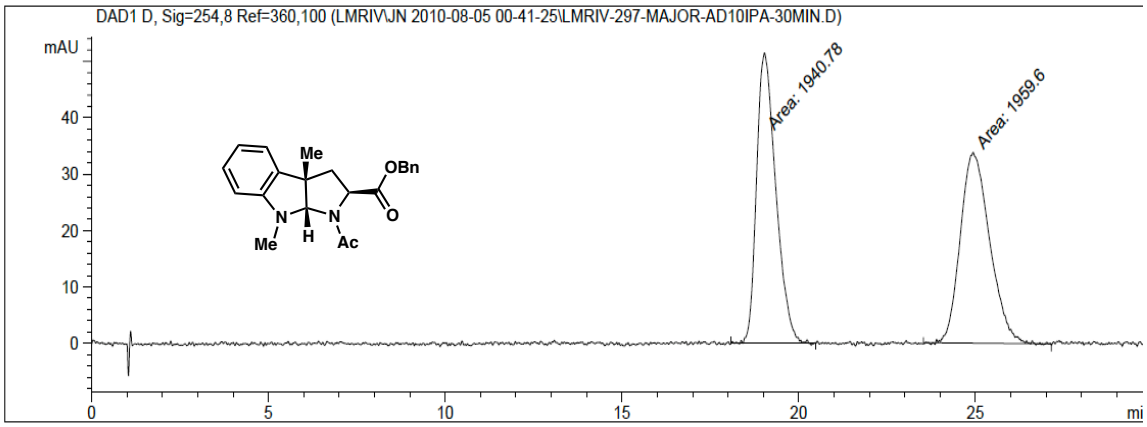
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.381	BV	0.0886	3856.54150	655.60498	49.8096
2	2.815	VB	0.1009	3886.01978	589.71381	50.1904

***exo*-94** (**Table 3, entry 6**): enantioenriched, 86% ee



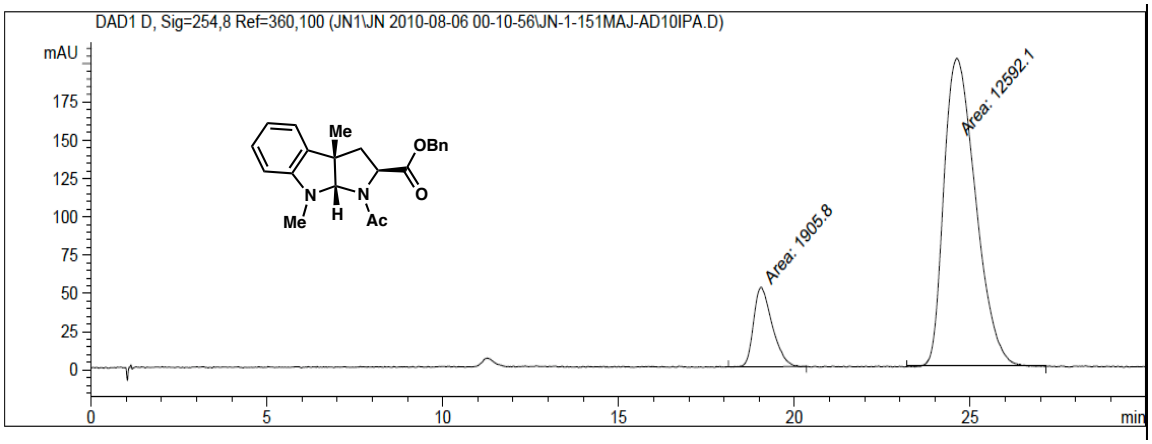
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.399	BB	0.0925	136.26041	23.19655	6.9999
2	2.839	BB	0.1061	1810.34204	270.34299	93.0001

***exo*-95** (**Table 3, entry 7**): racemic



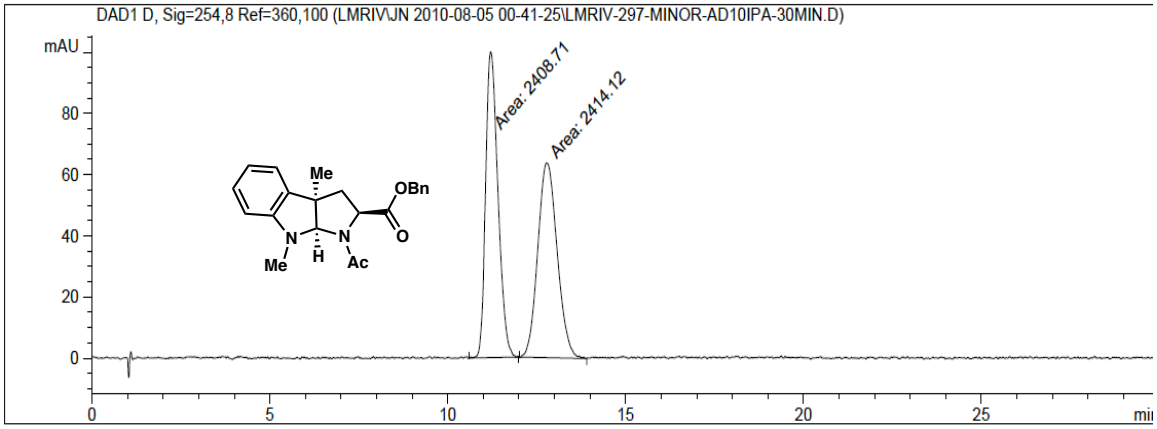
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.033	MM	0.6293	1940.77502	51.40419	49.7587
2	24.937	MM	0.9651	1959.59827	33.84022	50.2413

***exo*-95** (**Table 3, entry 7**): enantioenriched, 74% ee



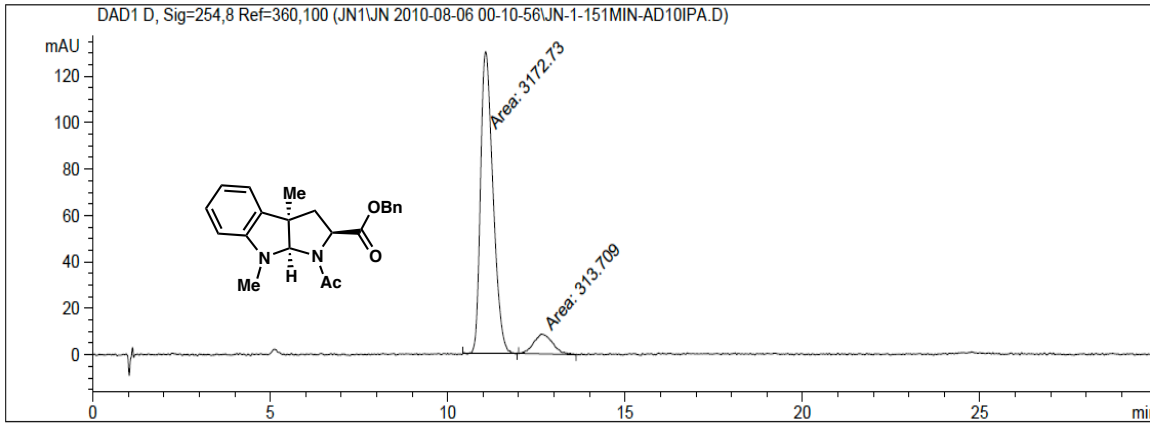
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.055	MM	0.6122	1905.80066	51.88297	13.1454
2	24.623	MM	1.0448	1.25921e4	200.87437	86.8546

***endo*-95 (Table 3, entry 7)**: racemic



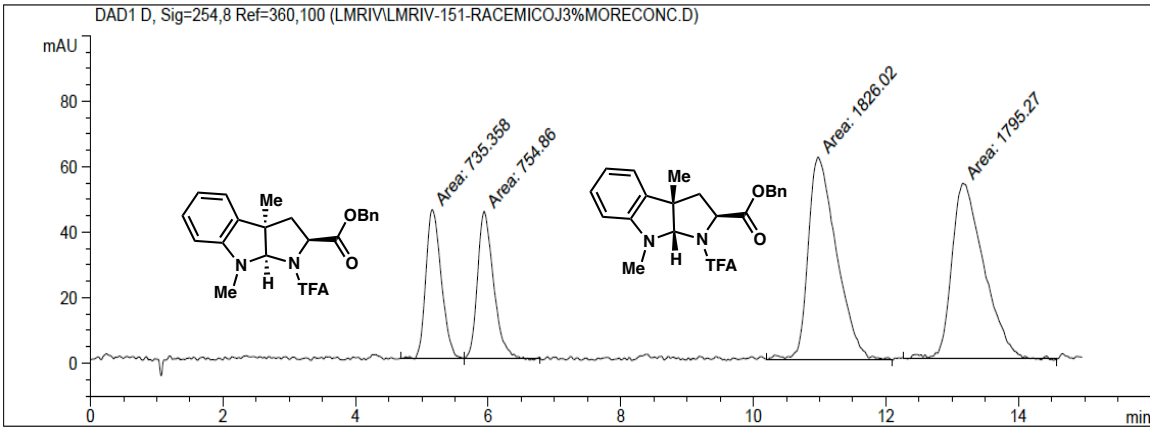
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.210	MM	0.4013	2408.70581	100.04025	49.9439
2	12.782	MM	0.6310	2414.11816	63.76419	50.0561

***endo*-95 (Table 3, entry 7)**: enantioenriched, 82% ee



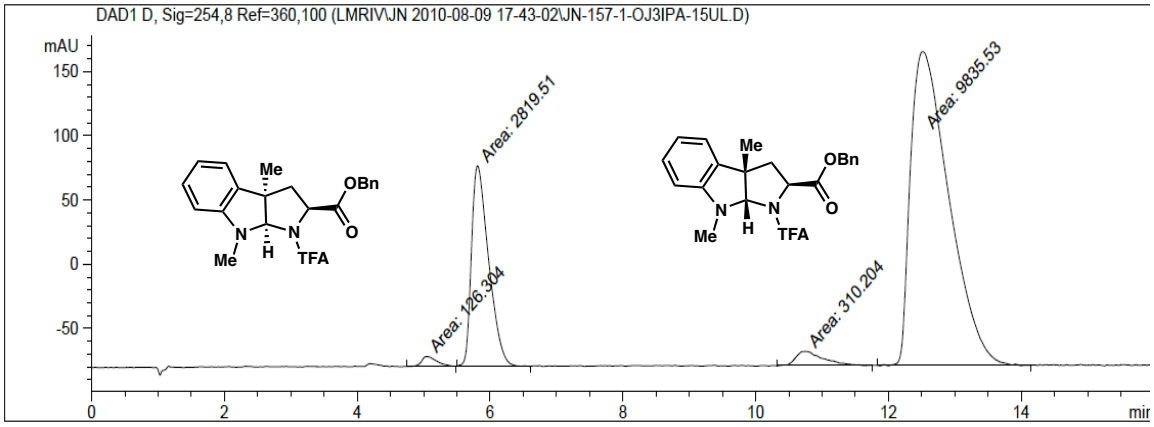
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.074	MM	0.4067	3172.73267	130.02379	91.0020
2	12.646	MM	0.6145	313.70920	8.50807	8.9980

96 (**Table 3, entry 9**): racemic



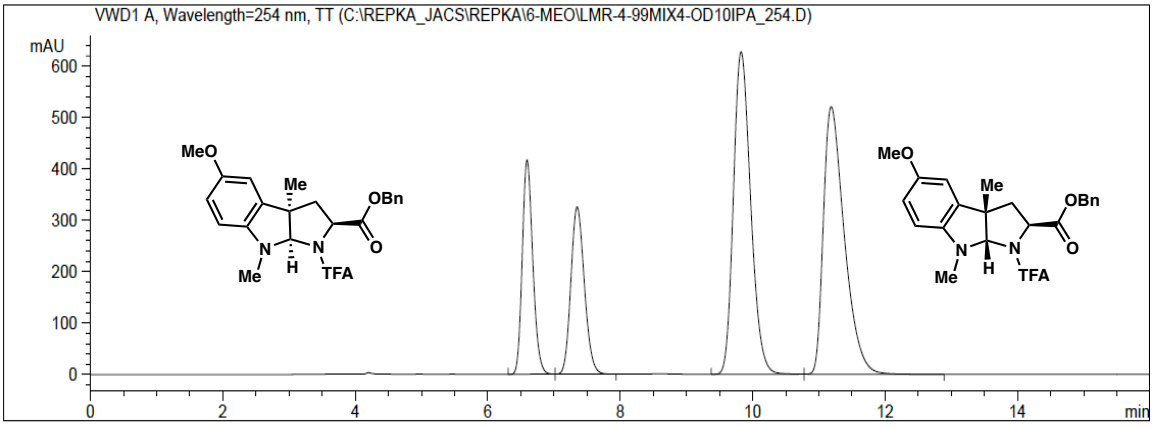
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.156	MF	0.2696	735.35803	45.45393	14.3863
2	5.940	FM	0.2802	754.85999	44.89612	14.7679
3	10.979	MM	0.4932	1826.01990	61.70875	35.7237
4	13.166	MM	0.5603	1795.26794	53.40647	35.1221

96 (**Table 3, entry 9**): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



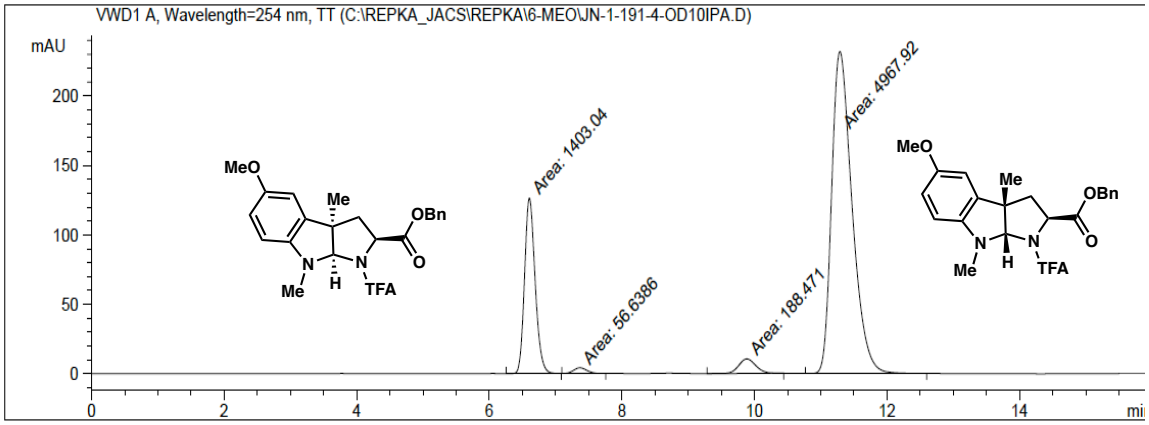
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.044	MM	0.2729	126.30366	7.71386	0.9648
2	5.812	MM	0.3004	2819.51172	156.42670	21.5369
3	10.749	MM	0.4705	310.20364	10.98786	2.3695
4	12.515	MM	0.6705	9835.53320	244.48642	75.1289

98a (Figure 2): racemic



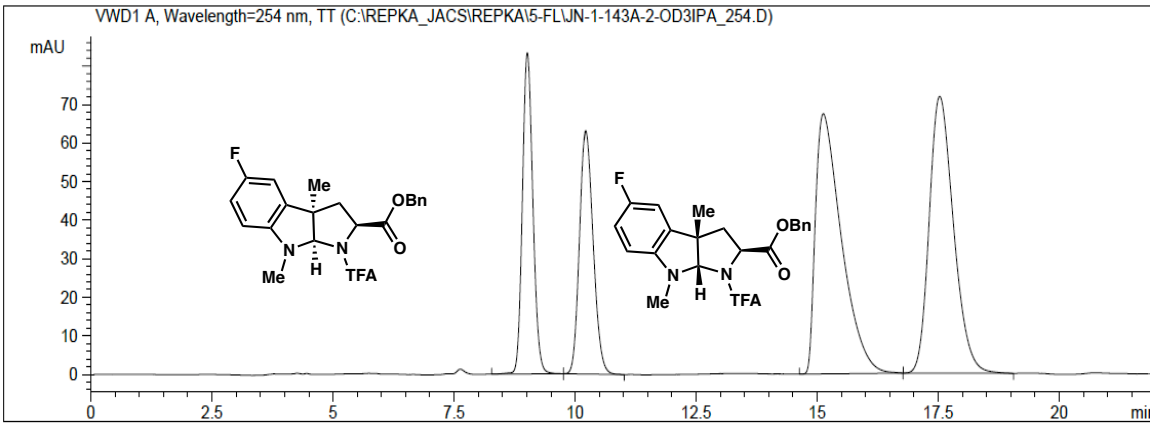
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.594	BB	0.1698	4609.86621	416.95142	14.3772
2	7.350	BB	0.2192	4610.61719	325.26569	14.3795
3	9.826	BB	0.2823	1.13860e4	627.58807	35.5104
4	11.187	BB	0.3325	1.14573e4	520.55212	35.7328

98a (Figure 2): *exo*: 93% ee, *endo*: 92% ee



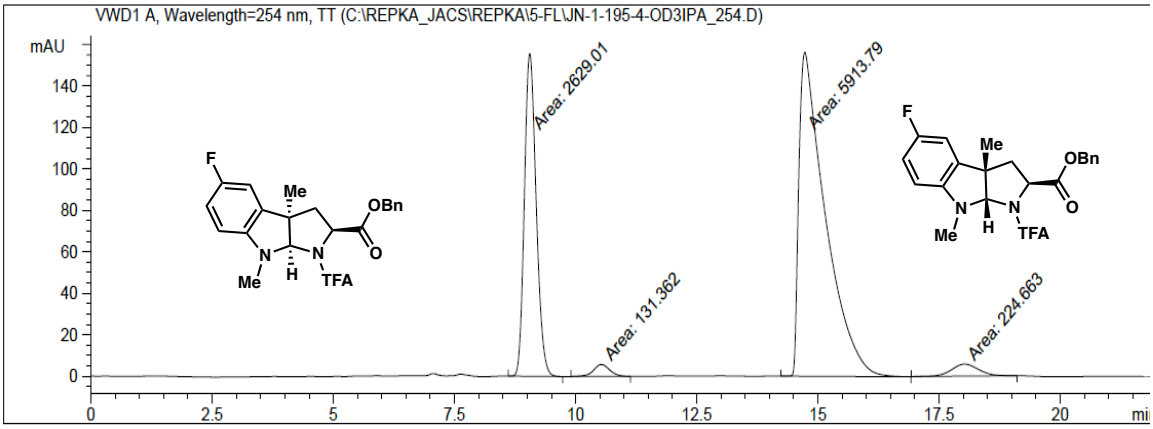
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.605	MM	0.1851	1403.04370	126.31284	21.2066
2	7.366	MM	0.2282	56.63861	4.13736	0.8561
3	9.885	MM	0.3007	188.47099	10.44562	2.8487
4	11.289	MM	0.3574	4967.92139	231.68799	75.0887

98b (Figure 2): racemic



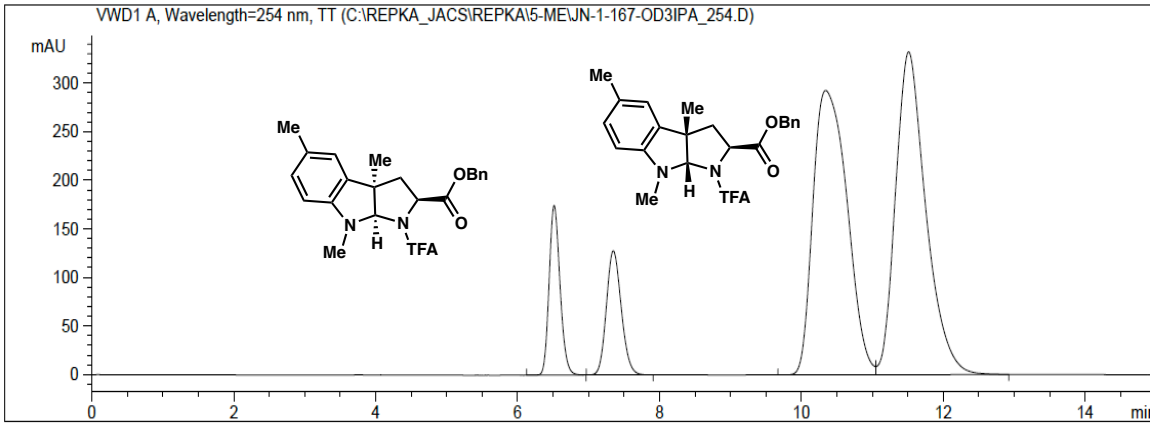
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.013	BB	0.2330	1253.27209	83.29908	16.6472
2	10.220	BB	0.3072	1244.32800	63.10659	16.5284
3	15.127	BB	0.5588	2519.96948	67.46533	33.4727
4	17.529	BB	0.5354	2510.85742	71.80063	33.3517

98b (Figure 2): *exo*: 93% ee *endo*: 90% ee



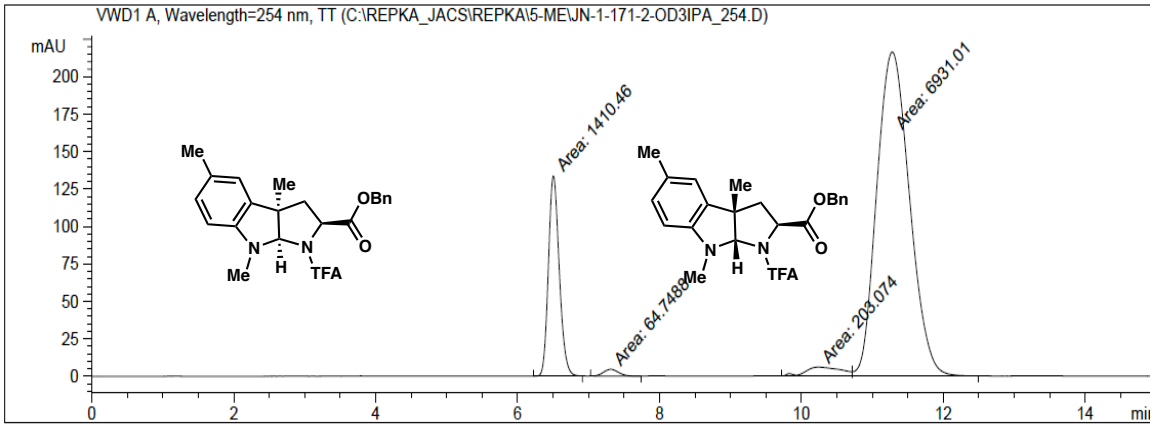
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.053	MM	0.2815	2629.00732	155.65556	29.5433
2	10.530	MM	0.3806	131.36226	5.75281	1.4762
3	14.729	MM	0.6305	5913.78809	156.33769	66.4559
4	18.025	MM	0.6446	224.66296	5.80853	2.5246

98c (Figure 2): racemic



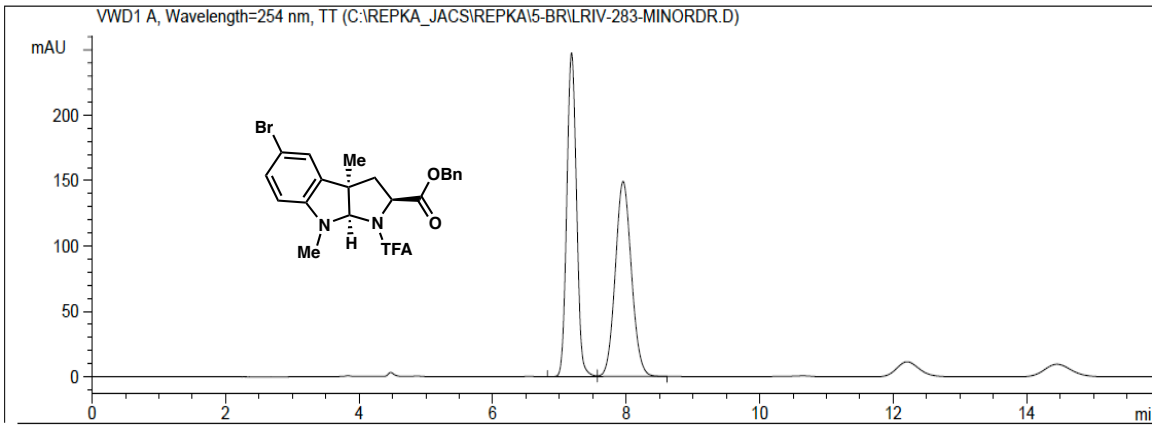
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.515	BB	0.1639	1864.59338	174.59178	7.9727
2	7.349	BB	0.2261	1861.35925	127.72897	7.9589
3	10.343	BV	0.5481	9785.77832	292.62845	41.8426
4	11.512	VV	0.4515	9875.41406	332.30096	42.2258

98c (Figure 2): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



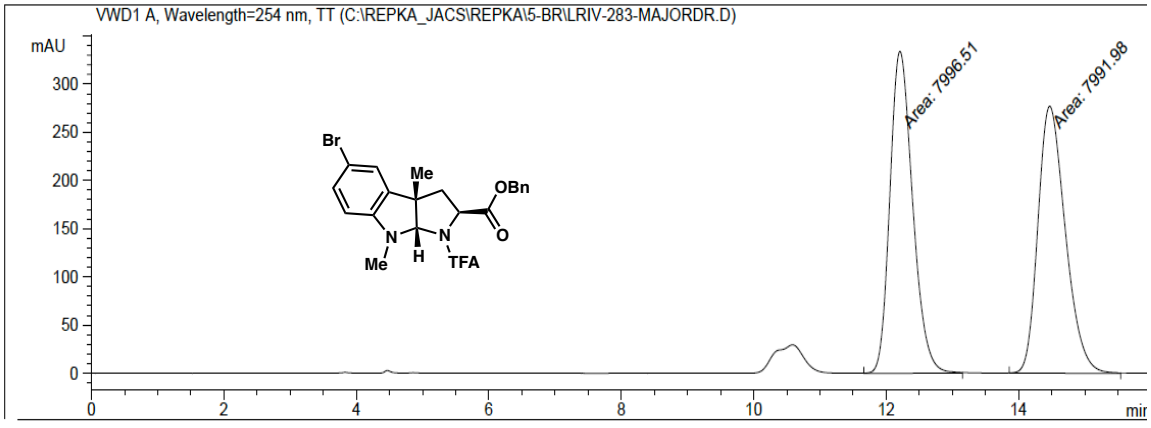
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.505	MM	0.1760	1410.45825	133.56871	16.3830
2	7.313	MM	0.2416	64.74883	4.46749	0.7521
3	10.246	MF	0.5768	203.07445	5.86773	2.3588
4	11.281	FM	0.5342	6931.01367	216.22461	80.5062

***endo*-98d** (Figure 2): racemic



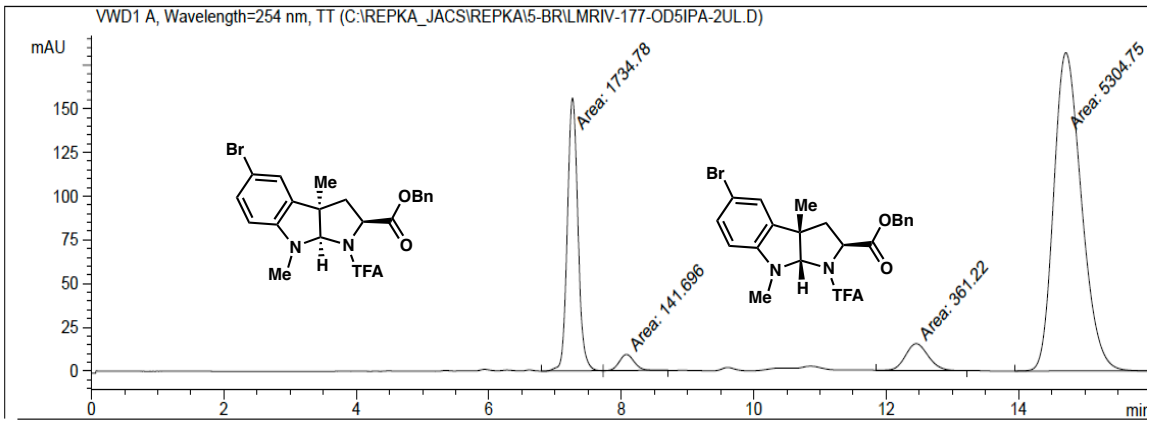
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.181	BV	0.1595	2504.75537	247.61092	50.0224
2	7.954	VB	0.2591	2502.51636	149.14781	49.9776

***exo*-98d** (Figure 2): racemic



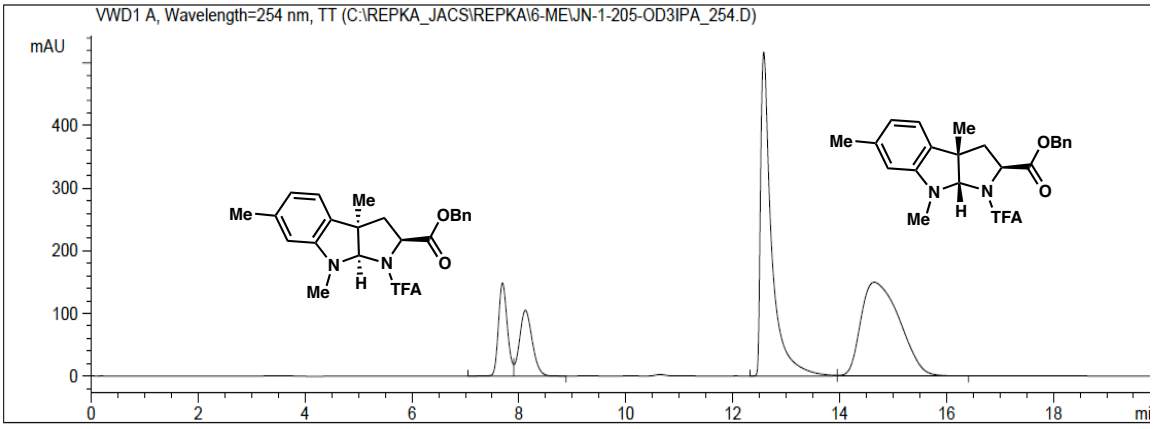
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.208	MM	0.3987	7996.50732	334.25320	50.0142
2	14.469	MM	0.4807	7991.97656	277.08136	49.9858

98d (Figure 2): *exo*: 87% ee, *endo:* 85% ee



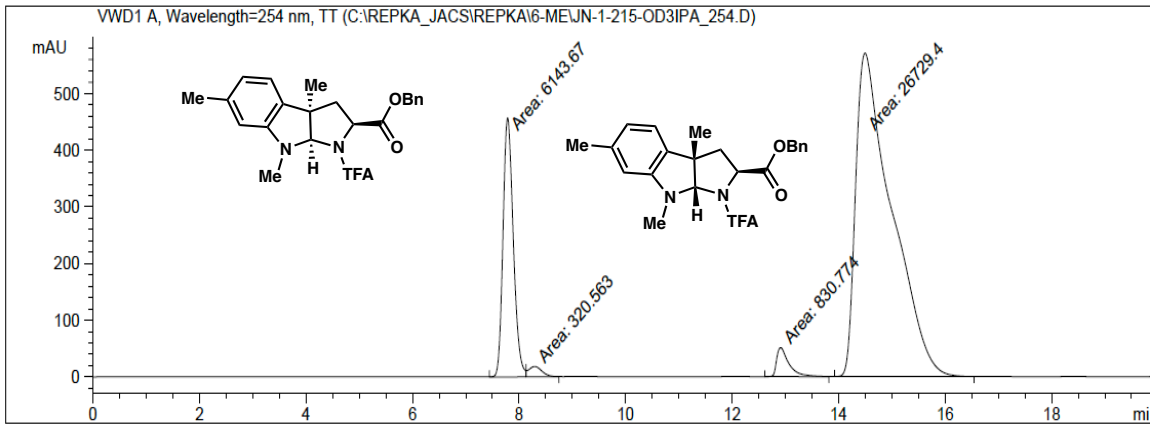
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.263	MF	0.1852	1734.78003	156.08707	23.0002
2	8.076	FM	0.2580	141.69585	9.15505	1.8786
3	12.454	MM	0.3947	361.21967	15.25336	4.7892
4	14.714	MM	0.4855	5304.75488	182.11263	70.3320

98e (Figure 2): racemic



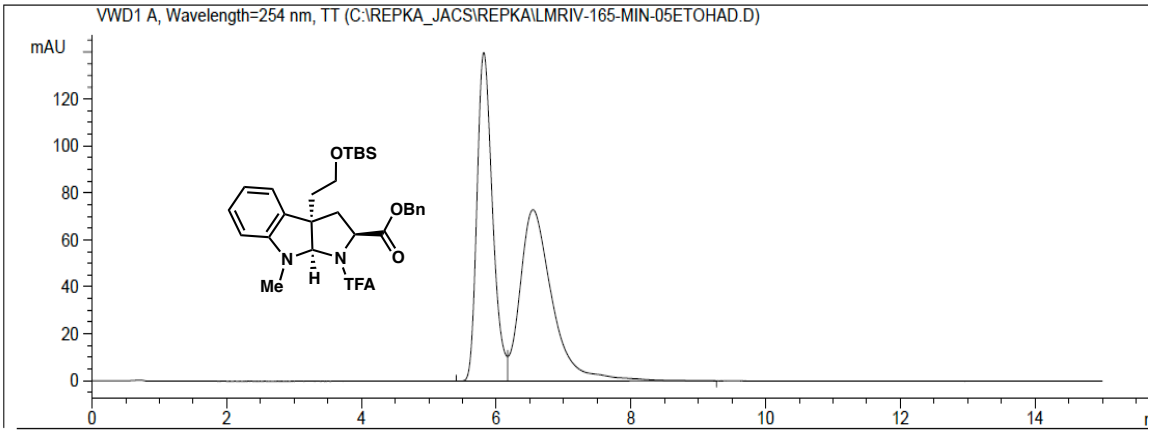
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.694	BV	0.1800	1738.04382	148.72224	9.4448
2	8.122	VB	0.2549	1740.51331	105.22092	9.4582
3	12.583	BV	0.2060	7424.35889	517.51135	40.3450
4	14.649	VB	0.7114	7499.26904	149.61671	40.7521

98e (Figure 2): *exo*: 94% ee, *endo*: 90% ee



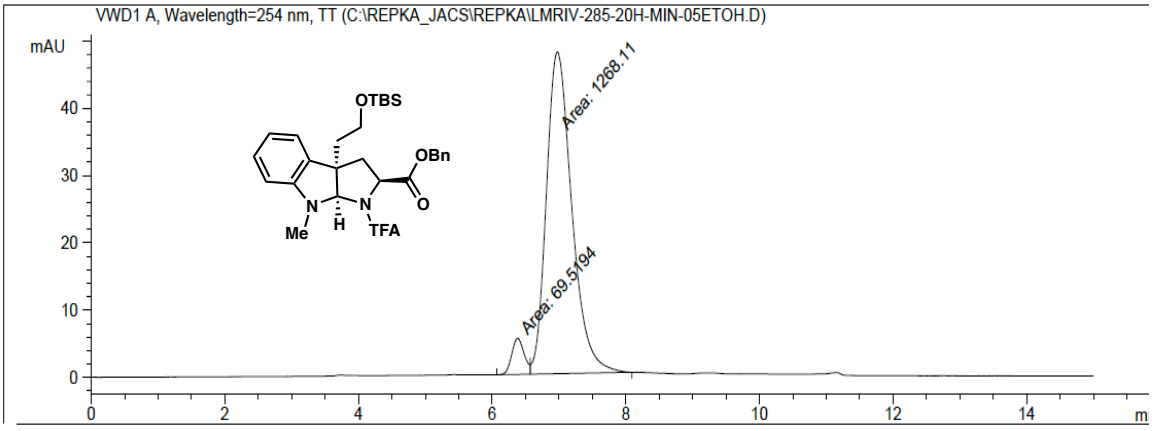
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.785	MF	0.2240	6143.67139	457.11594	18.0567
2	8.294	FM	0.2911	320.56265	18.35141	0.9422
3	12.912	MM	0.2706	830.77399	51.16518	2.4417
4	14.496	MM	0.7807	2.67294e4	570.62366	78.5595

***endo*-98f** (Figure 2): racemic



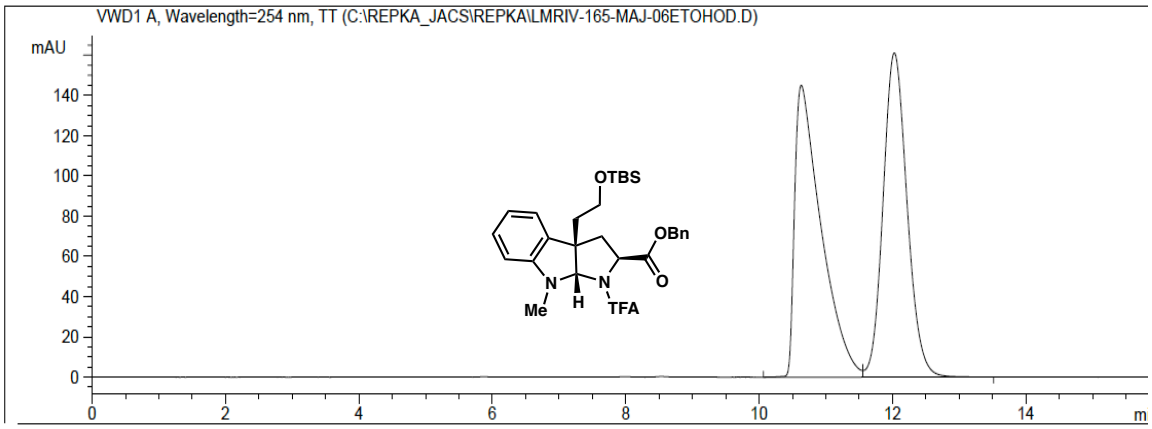
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.815	BV	0.2467	2234.77563	139.96280	48.1102
2	6.546	VB	0.4858	2410.33862	72.97266	51.8898

***endo*-98f** (Figure 2): 90% ee



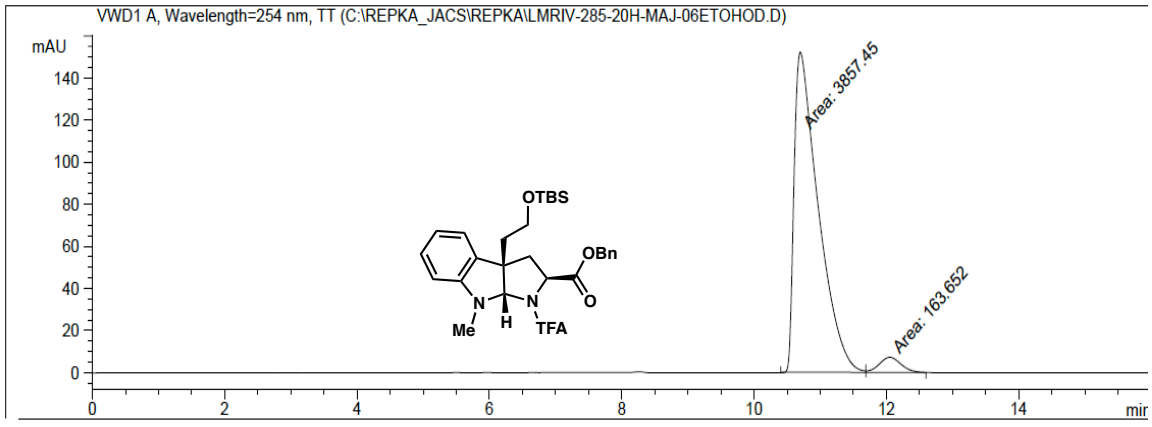
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.380	MF	0.2166	69.51939	5.34894	5.1972
2	6.976	FM	0.4419	1268.11157	47.82830	94.8028

***exo*-98f** (Figure 2): racemic



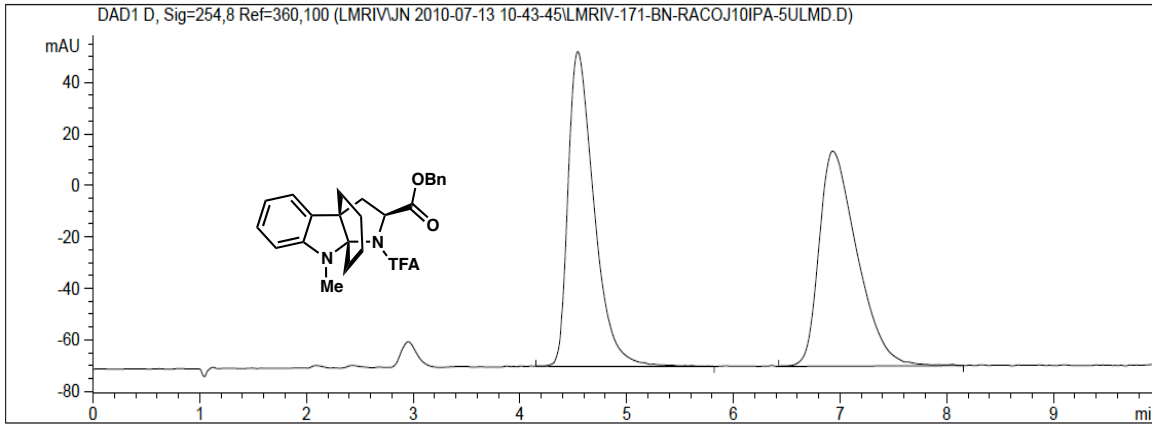
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.632	BV	0.3905	3995.52930	145.07512	49.7976
2	12.028	VB	0.3841	4028.00830	161.10678	50.2024

***exo*-98f** (Figure 2): 92% ee



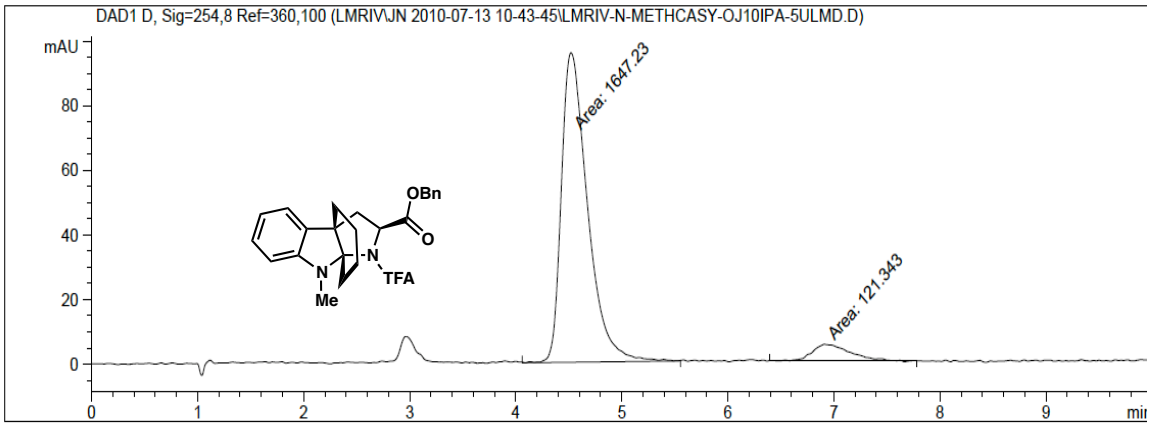
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.700	MF	0.4226	3857.44580	152.13763	95.9302
2	12.052	FM	0.3805	163.65164	7.16747	4.0698

98g (Figure 2): racemic



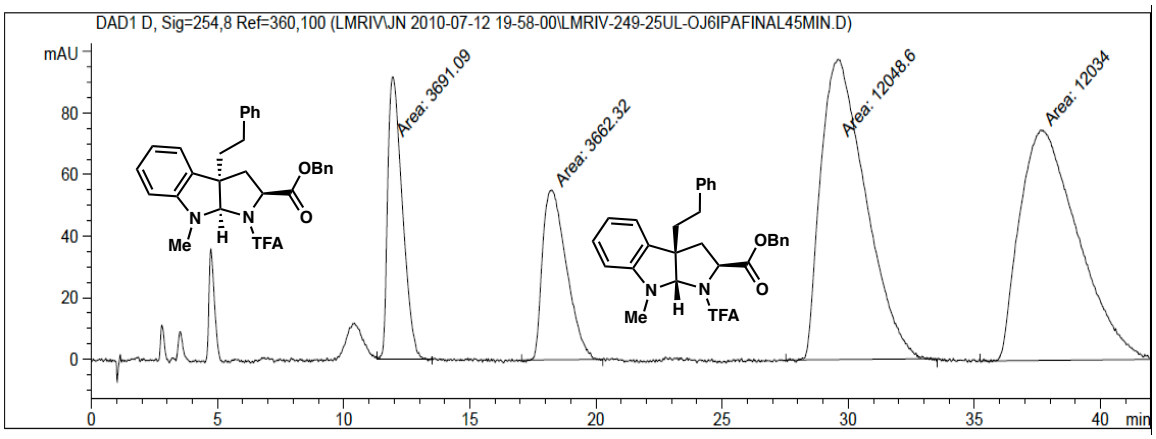
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.543	BB	0.2584	2077.59912	122.17298	50.0580
2	6.933	BB	0.3736	2072.78516	83.50713	49.9420

98g (Figure 2): *exo:* 86% ee



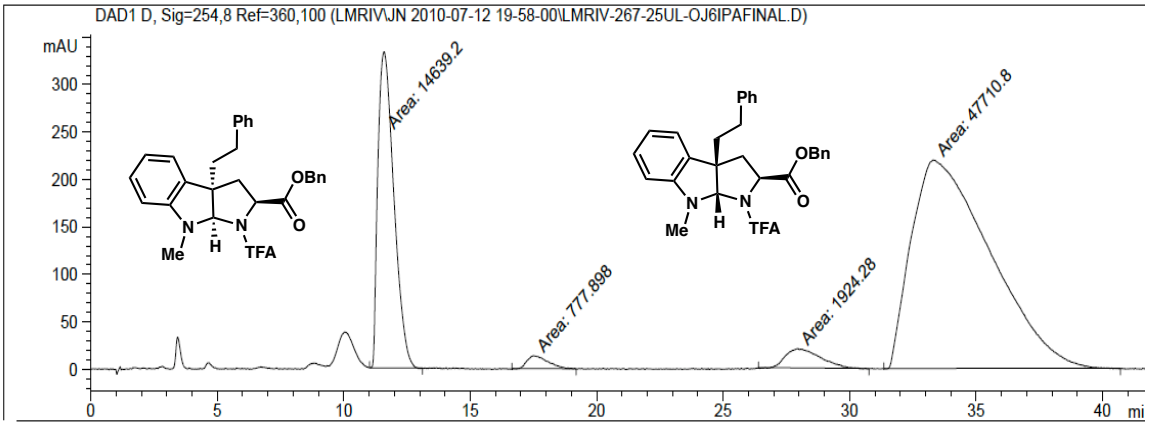
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.522	MM	0.2861	1647.22534	95.95735	93.1389
2	6.911	MM	0.3977	121.34311	5.08583	6.8611

98h (Figure 2): racemic



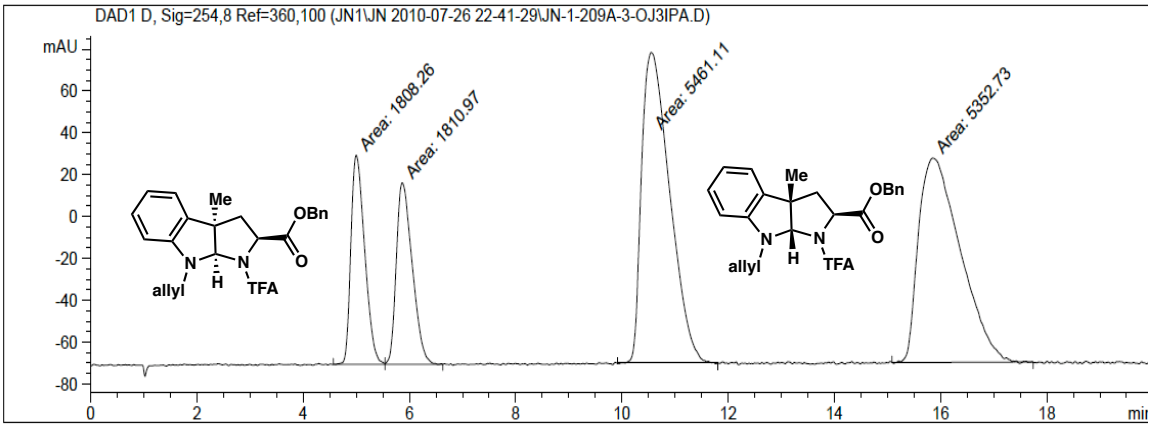
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.947	MM	0.6720	3691.09326	91.53949	11.7416
2	18.252	MM	1.1062	3662.32007	55.18063	11.6501
3	29.587	MM	2.0594	1.20486e4	97.51013	38.3273
4	37.639	MM	2.6782	1.20340e4	74.88902	38.2810

98h (Figure 2): *exo:* 92% ee, *endo*: 90% ee



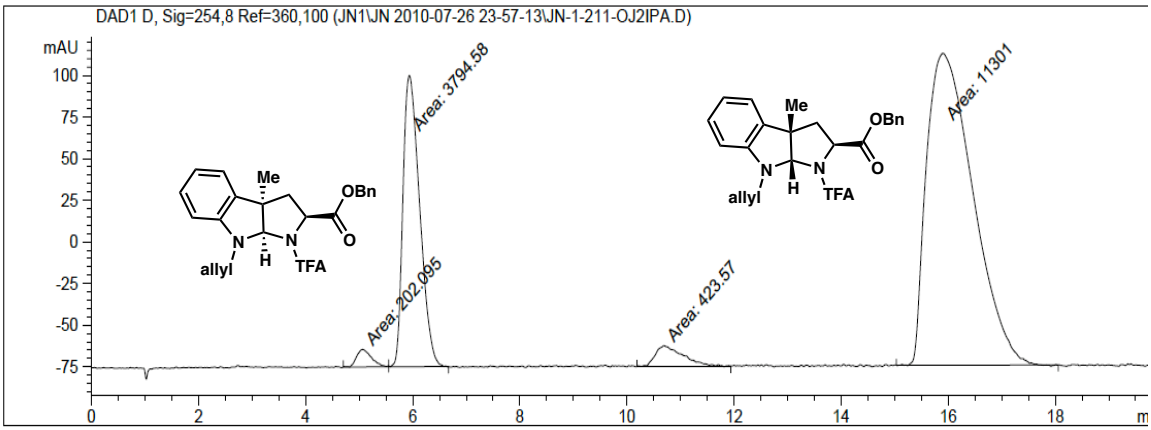
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.596	MM	0.7322	1.46392e4	333.24432	22.5038
2	17.511	MM	0.9481	777.89801	13.67496	1.1958
3	27.957	MM	1.5821	1924.28345	20.27142	2.9581
4	33.312	MM	3.6201	4.77108e4	219.65750	73.3423

72 (Figure 2): racemic



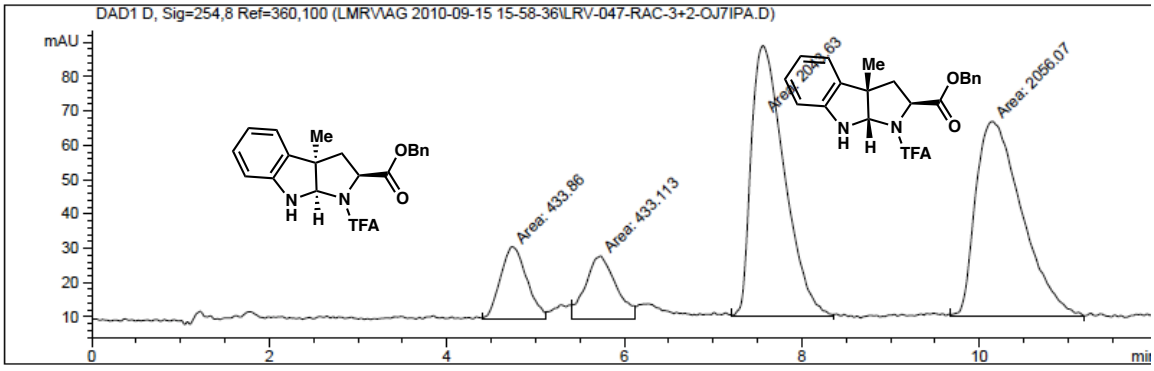
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.000	MF	0.3012	1808.26282	100.06958	12.5286
2	5.866	FM	0.3472	1810.96948	86.92387	12.5474
3	10.557	MM	0.6132	5461.11230	148.42072	37.8375
4	15.854	MM	0.9124	5352.73047	97.77415	37.0866

72 (Figure 2): *exo*: 93% ee, *endo*: 90% ee



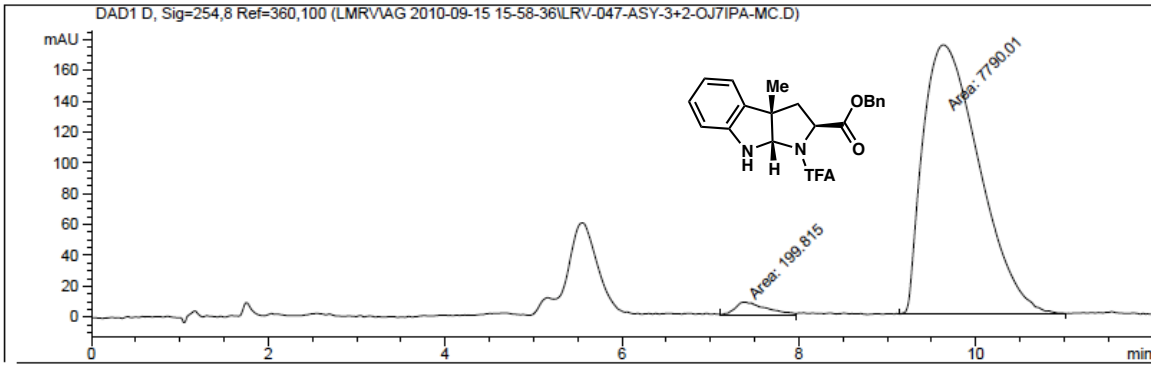
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.064	MF	0.3200	202.09525	10.52417	1.2855
2	5.937	FM	0.3612	3794.57617	175.06740	24.1367
3	10.690	MM	0.5781	423.56973	12.21119	2.6943
4	15.903	MM	1.0047	1.13010e4	187.47484	71.8835

98i (Figure 2): racemic



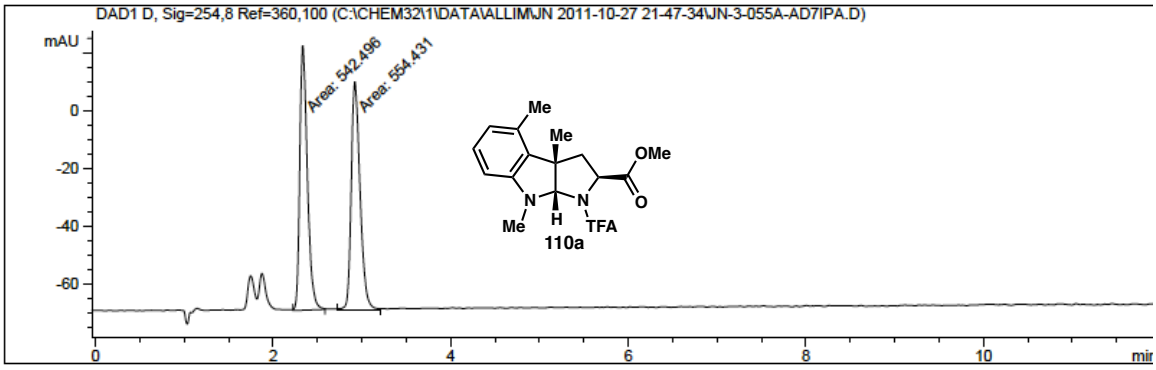
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.737	MM	0.3442	433.85974	21.00586	8.7354
2	5.733	MM	0.3971	433.11276	18.17621	8.7204
3	7.564	MM	0.4321	2043.62988	78.82232	41.1469
4	10.149	MM	0.6038	2056.07129	56.75510	41.3974

98i (Figure 2): enantioenriched, *exo*: 95% ee



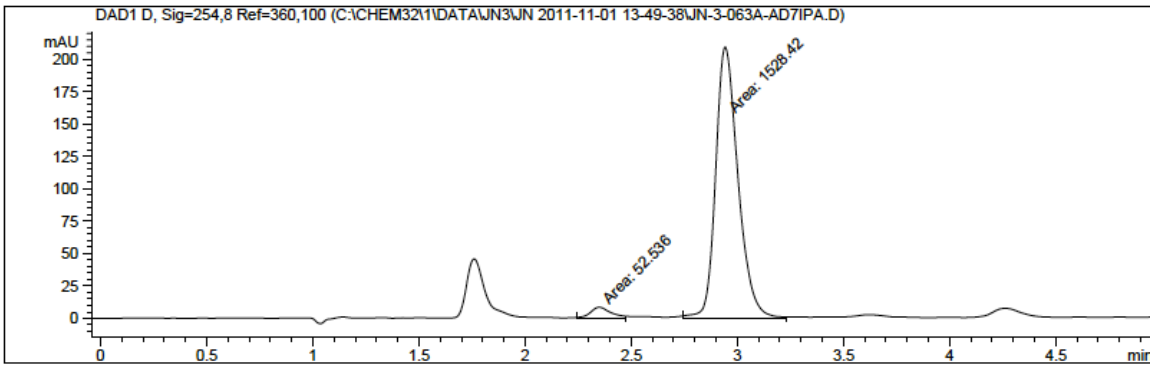
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.393	MM	0.4059	199.81528	8.20531	2.5009
2	9.640	MM	0.7421	7790.00586	174.96088	97.4991

110a (Table 6): racemic



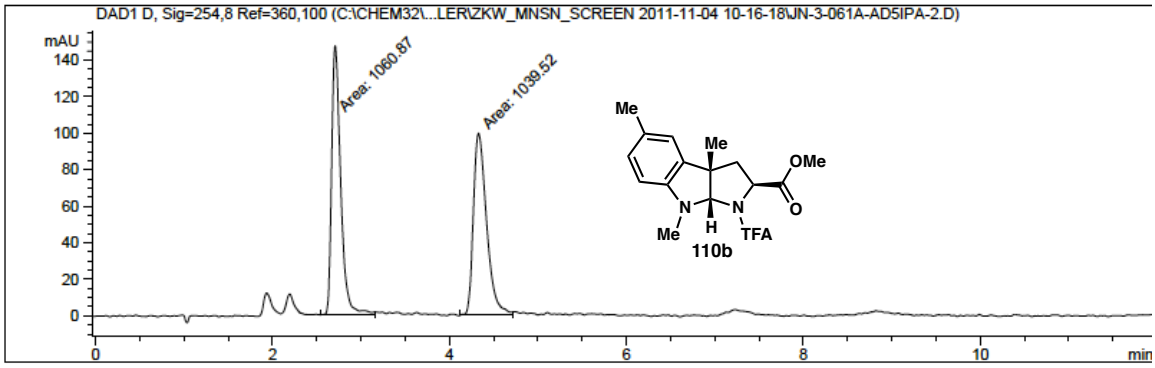
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.336	MM	0.0977	542.49573	92.54591	49.4560
2	2.923	MM	0.1161	554.43109	79.59325	50.5440

110a (Table 6): 93% ee



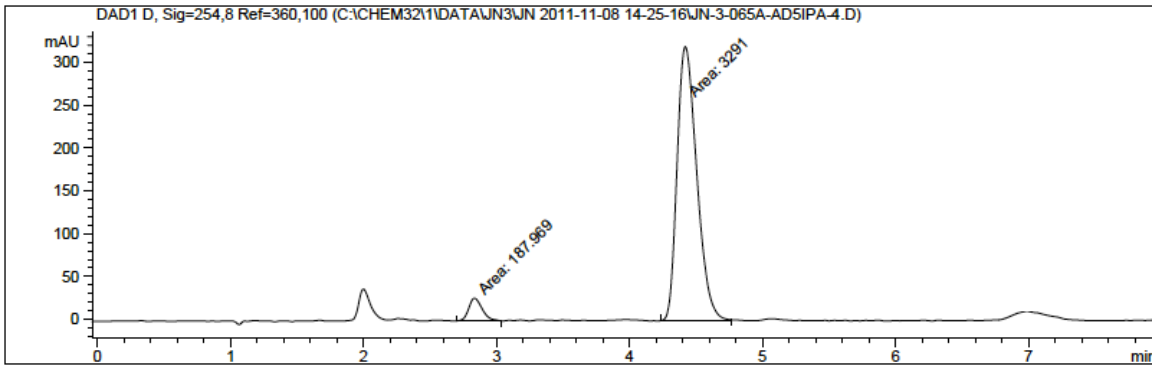
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.349	MM	0.1076	52.53596	8.13525	3.3231
2	2.943	MM	0.1211	1528.41553	210.29921	96.6769

110b (Table 6): racemic



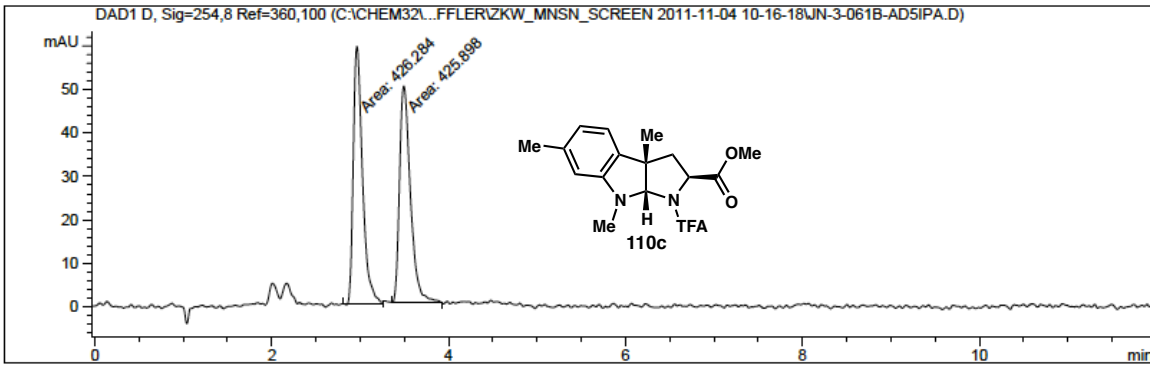
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.710	MM	0.1192	1060.87427	148.35889	50.5083
2	4.330	MM	0.1733	1039.52075	100.00130	49.4917

110b (Table 6): 89% ee



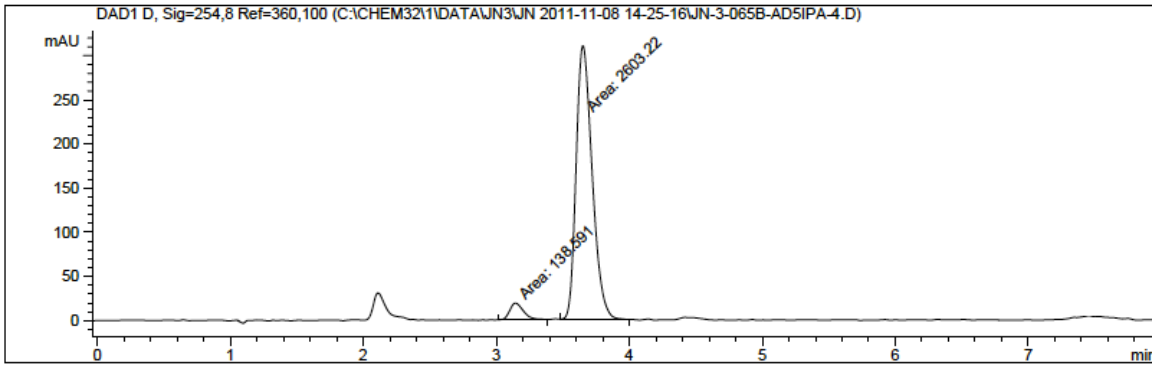
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.835	MM	0.1175	187.96922	26.66648	5.4030
2	4.420	MM	0.1709	3291.00049	320.93707	94.5970

110c (Table 6): racemic



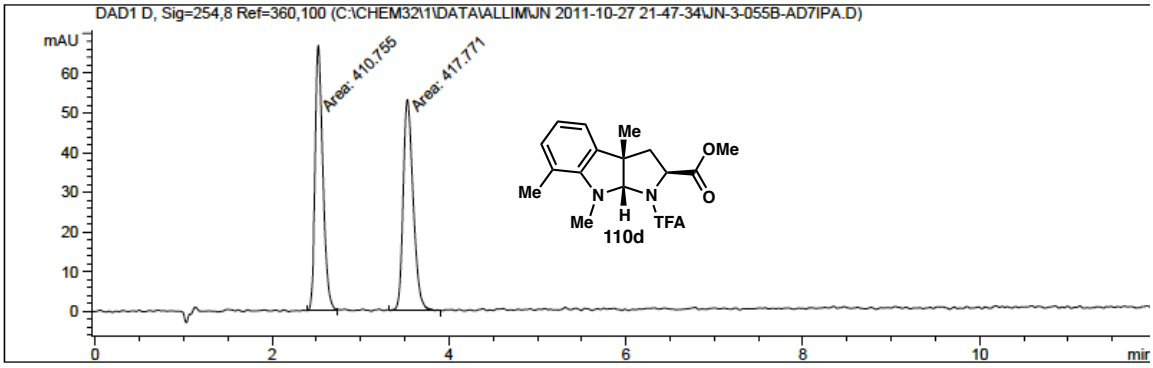
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.963	MM	0.1198	426.28387	59.32737	50.0227
2	3.494	MM	0.1424	425.89764	49.83862	49.9773

110c (Table 6): 90% ee



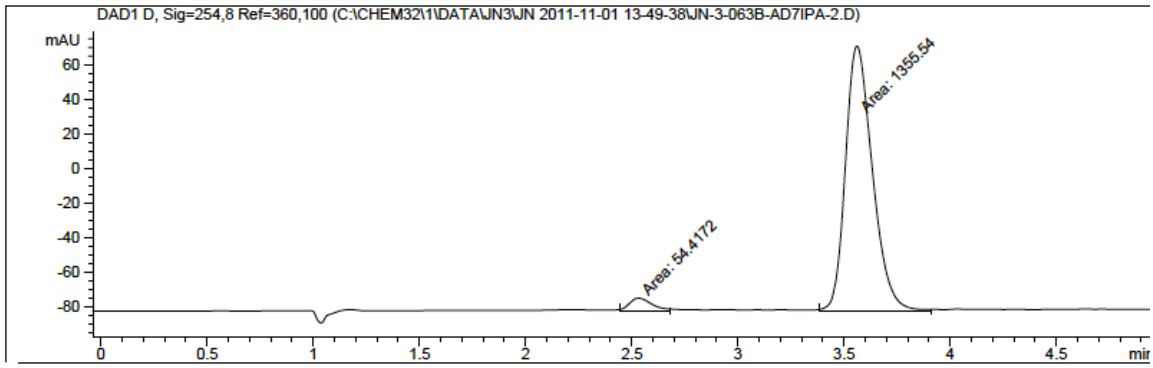
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.146	MM	0.1214	138.59100	19.02013	5.0547
2	3.652	MM	0.1394	2603.21704	311.29327	94.9453

110d (Table 6): racemic



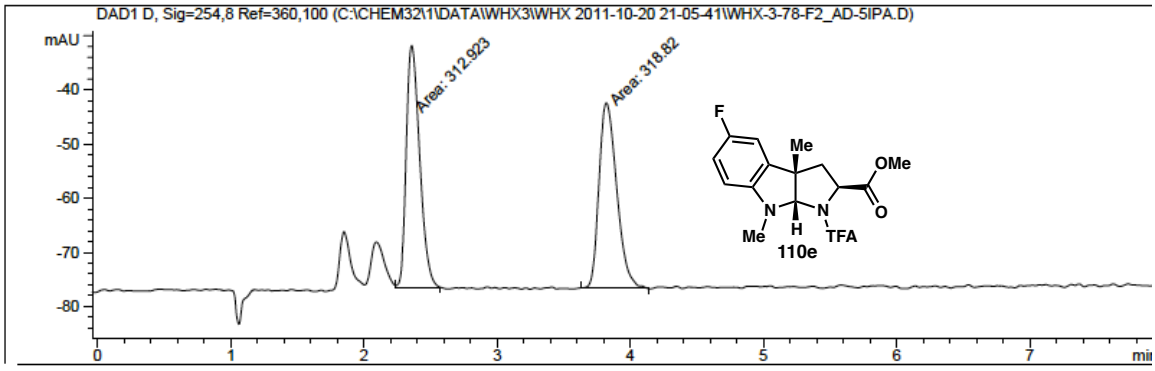
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.523	MM	0.1019	410.75467	67.19356	49.5766
2	3.531	MM	0.1306	417.77090	53.30387	50.4234

110d (Table 6): 93% ee



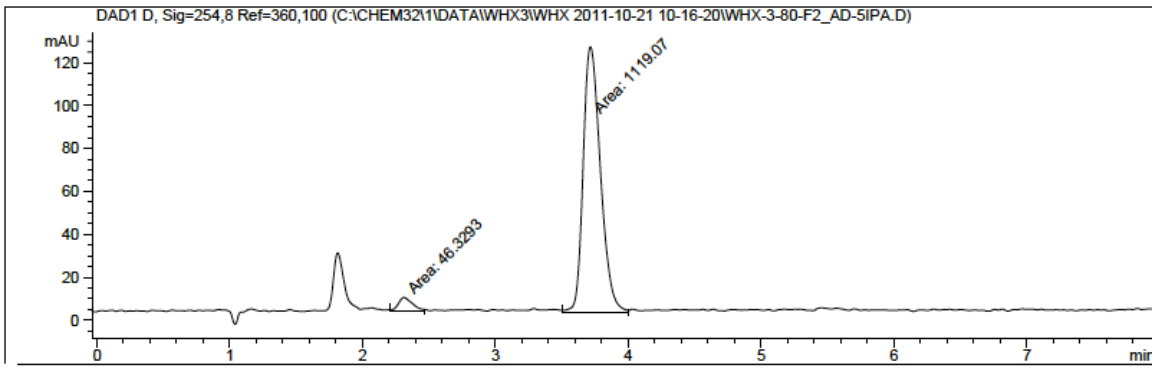
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.533	MM	0.1229	54.41724	7.38052	3.8595
2	3.562	MM	0.1470	1355.53528	153.70358	96.1405

110e (Table 6): racemic



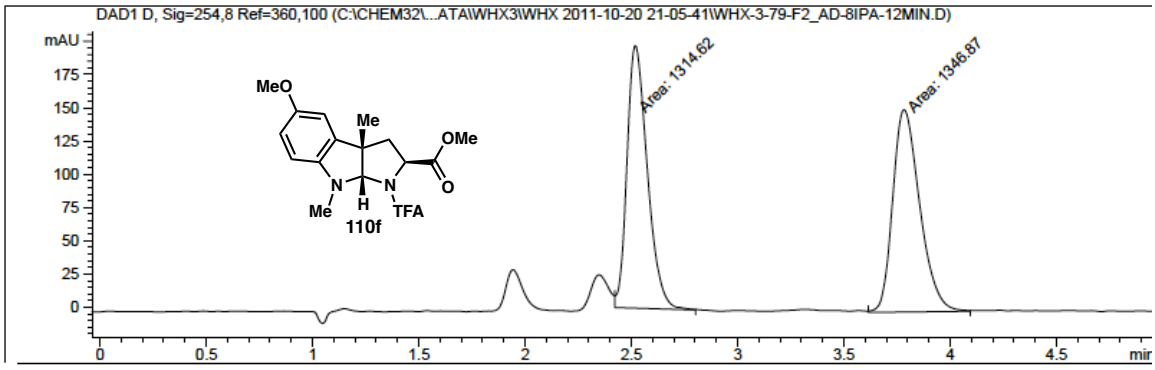
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.360	MM	0.1164	312.92303	44.79716	49.5333
2	3.821	MM	0.1548	318.81989	34.32571	50.4667

110e (Table 6): 92% ee



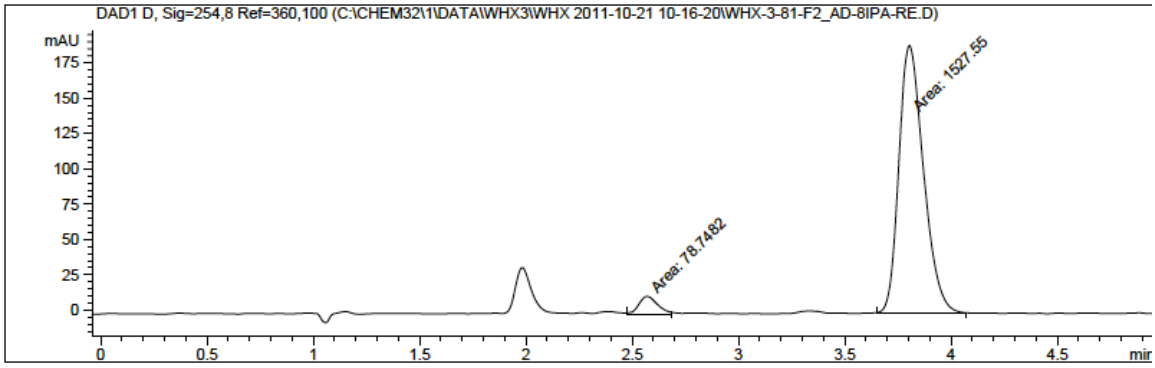
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.311	MM	0.1219	46.32927	6.33424	3.9754
2	3.714	MM	0.1503	1119.06885	124.07474	96.0246

110f (Table 6): racemic



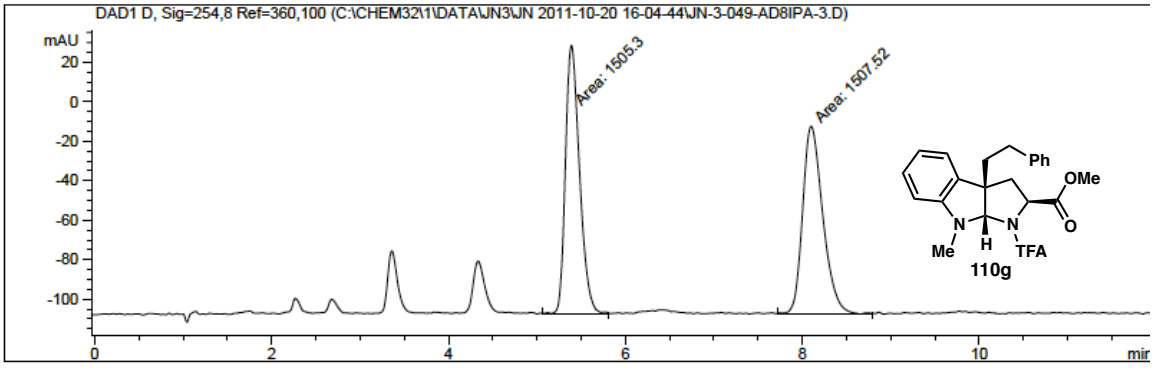
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.519	MM	0.1106	1314.62256	198.18828	49.3942
2	3.783	MM	0.1471	1346.87158	152.55568	50.6058

110f (Table 6): 90% ee



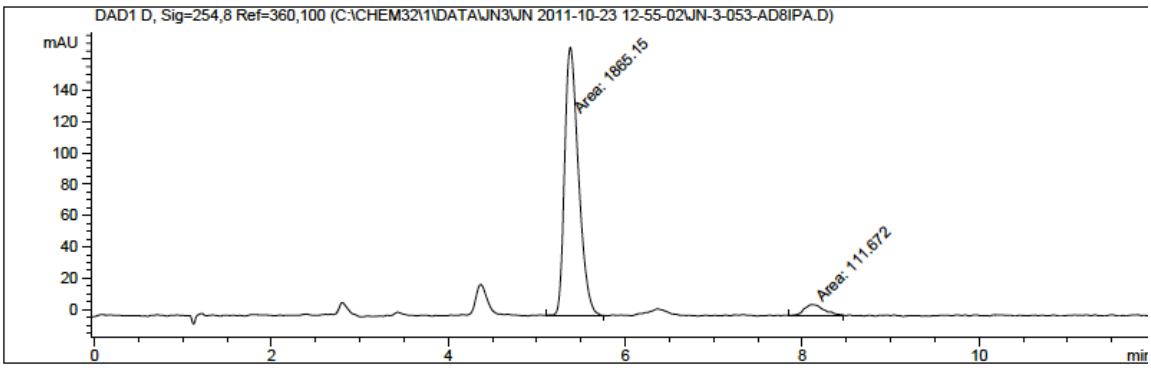
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.571	MM	0.1029	78.74822	12.75990	4.9025
2	3.805	MM	0.1340	1527.54749	190.03099	95.0975

110g (Table 6): racemic



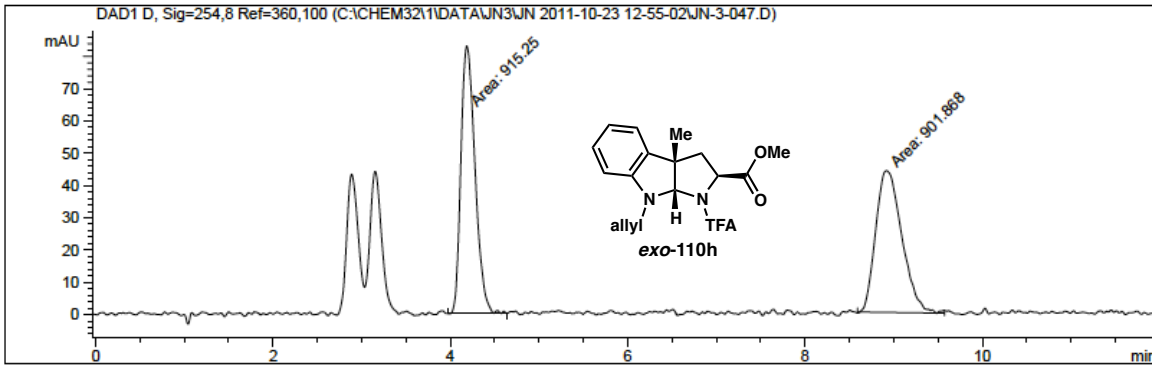
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.390	MM	0.1842	1505.30383	136.19626	49.9633
2	8.101	MM	0.2645	1507.51648	94.98624	50.0367

110g (Table 6): 89% ee



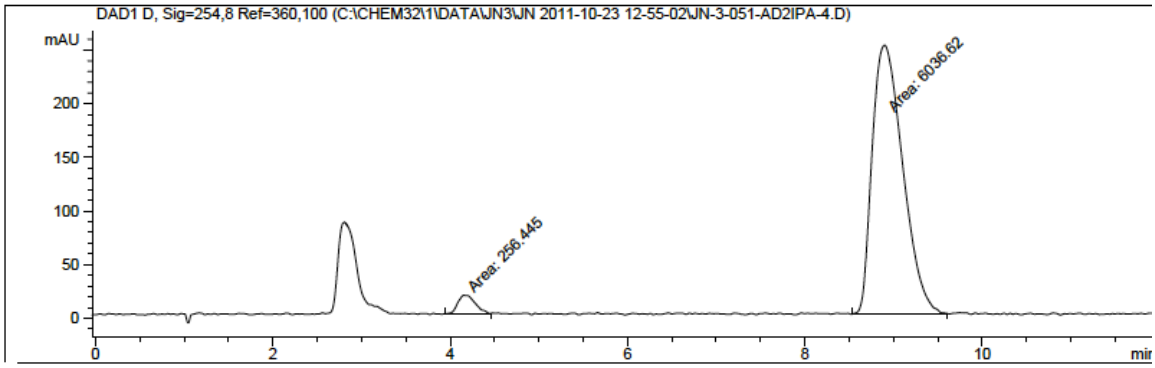
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.379	MM	0.1814	1865.15222	171.37959	94.3509
2	8.117	MM	0.2678	111.67234	6.94881	5.6491

110h (Table 6): racemic



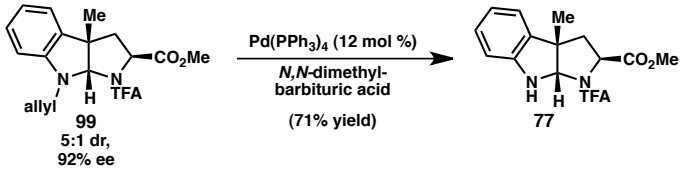
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.186	MM	0.1839	915.25043	82.94954	50.3682
2	8.920	MM	0.3422	901.86816	43.92808	49.6318

110h (Table 6): 92% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.158	MM	0.2383	256.44452	17.93594	4.0750
2	8.897	MM	0.4007	6036.61719	251.06158	95.9250

2.4.6 Pd-catalyzed Deallylation of Pyrroloindoline Methyl Ester 99



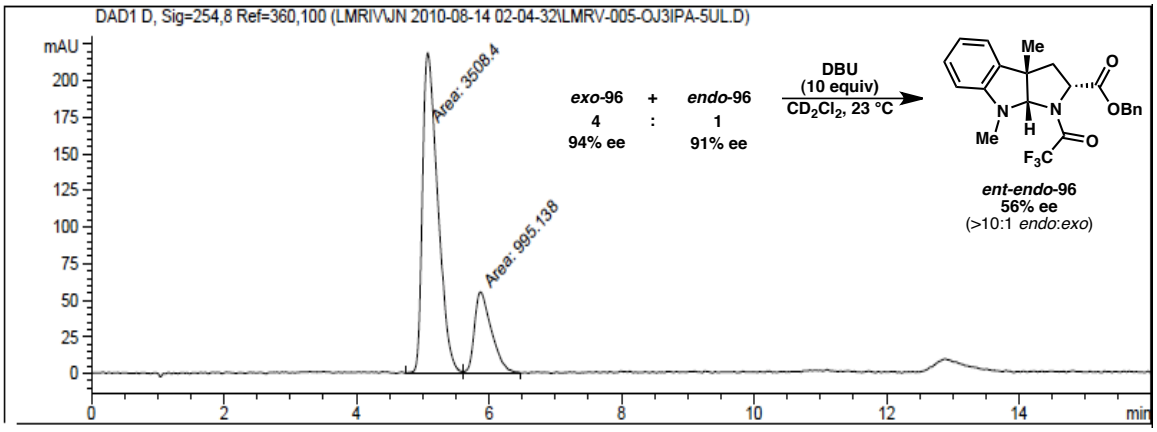
An oven-dried microwave vial was charged with allylpyrroloindoline **99** (55.0 mg, 0.149 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (6.9 mg, 6.0 μmol, 0.040 equiv), and *N,N*-dimethylbarbituric acid (70.0 mg, 0.448 mmol, 3.01 equiv) and then sealed under nitrogen. 1.1 mL DCM was added and the reaction mixture was heated to 35 ºC in an oil bath. Two additional 7.0 mg portions of $Pd(PPh_3)_4$ were added after 34 h and after 75 h. After heating at 35 ºC for 123 h, 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 **77** 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*-**77** in >20:1 dr. ^{1}H 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, $J_{C\text{-}F}$ = 37.5 Hz), 156. 7 (q, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 287.1 Hz), 115.7 (q, $J_{C\text{-}F}$ = 286.2 Hz), 109.9, 109.4, 86.4, 84.4 (q, $J_{C\text{-}F}$ = 2.2 Hz), 61.1, 59.5 (q, $J_{C\text{-}F}$ = 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}; $[\alpha]_D^{25}$ –182.7° (c = 0.50, DCM); HRMS (MM) calc'd for $C_{15}H_{16}F_3N_2O_3$ $[M+H]^+$ 329.1108, found 329.1122.

2.4.7 General Procedure D. Epimerization Studies

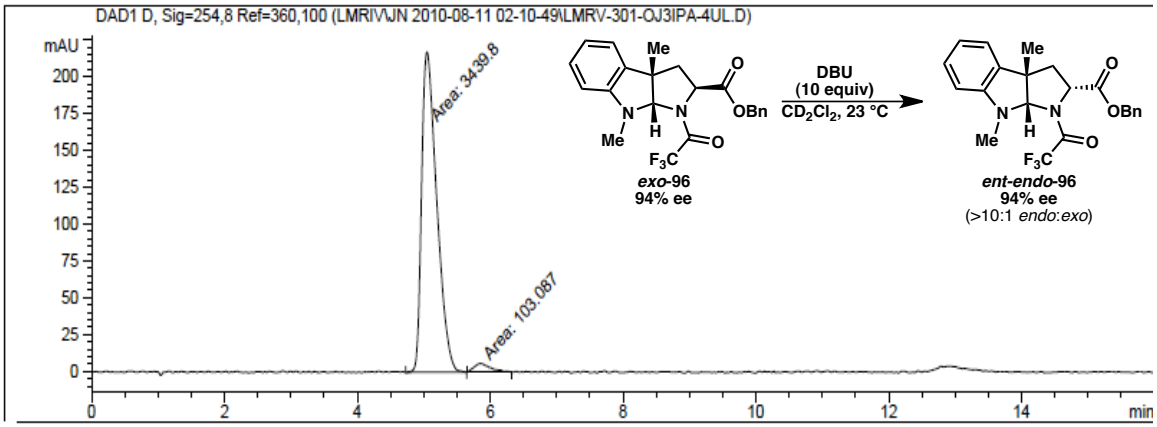
To an NMR tube was added a solution of pyrroloindoline **96** (0.063 mmol, 1.00 equiv) in CD_2Cl_2 (0.46 mL), followed by DBU (0.63 mmol, 10.00 equiv). The reaction was monitored by ^1H NMR until the ratio of diastereomers reached an equilibrium. At this point the reaction was diluted with 3 mL $CHCl_3$ and 25 mL ethyl acetate and washed with saturated $NaHCO_{3(aq)}$ (3 x 15 mL). The organic layer was dried (Na_2SO_4), 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*-96** (94% ee) **+ *endo*-96** (91% ee) with DBU (10 equiv) for 65 h to give >10:1 ***ent-endo*-96** (56% ee).



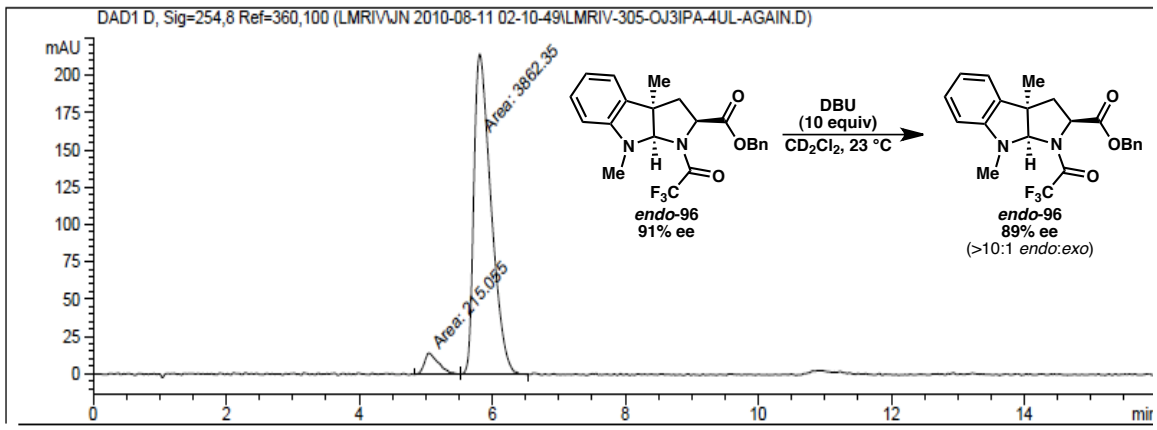
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.078	MM	0.2670	3508.40381	218.96385	77.9032
2	5.872	MM	0.2984	995.13763	55.57482	22.0968

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



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.050	MM	0.2637	3439.80371	217.42592	97.0903
2	5.849	MM	0.2887	103.08688	5.95159	2.9097

Experiment 3: Treatment of diastereomerically pure ***endo*-96** (91% ee) with DBU (10 equiv) for 30 h to return ***endo*-96** (89% ee).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.053	MM	0.2501	215.05467	14.33310	5.2743
2	5.814	MM	0.2994	3862.34961	215.01805	94.7257

2.4.8 Resubjection of Pure Exo and Endo Pyrroloindolines to Reaction Conditions

To an NMR tube was added a solution of pure pyrroloindoline *exo*-**96** (0.073 mmol, 1.00 equiv, 94% ee) in CD_2Cl_2 (297 μL), followed by (*R*)-BINOL (from a 0.0675 M solution in CD_2Cl_2, 0.015 mmol, 0.20 equiv) and $SnCl_4$ (from a 0.72 M solution in CD_2Cl_2, 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*-**96** (91% ee), except at a concentration of 0.065 M. In both cases, no epimerization or erosion of ee was observed.

2.4.9 General Procedure E. in situ Monitoring of the Formal (3 + 2) Cycloaddition by ^{1}H NMR.

In the glovebox, a 1 M solution of 1,3-dimethylindole, a 1 M solution of benzyl trifluoroacetamidoacrylate (with 0.3 equiv 1,4-diethylbenzene as an internal standard), a 0.72 M solution of $SnCl_4$, and a 0.0675 M solution of (*R*)-BINOL in CD_2Cl_2 were made. To an oven-dried NMR tube equipped with a teflon-lined cap were added 90 μL of the indole solution, μL of the acrylate + internal standard solution, 267 μL of the (*R*)-BINOL solution, and 186 μL of CD_2Cl_2. A ^{1}H NMR spectrum was taken (1 scan) to determine the initial ratio of substrates, (*R*)-BINOL, and internal standard. Immediately before beginning the collection of kinetics data, $SnCl_4$ was added via a microsyringe through the teflon cap of the NMR tube. The tube was inverted once, then quickly inserted into the instrument. The concentration of acrylate over the course of the reaction was determined by integrating its resonance at 6.3 ppm, then normalizing by the internal standard's resonance at 2.74 ppm.

2.5 Notes and References

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(3) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315.

(4) Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J. Org. Chem.* **2008**, *73*, 5654–5657.

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APPENDIX 1

Spectra Relevant to Chapter 2:

Enantioselective Synthesis of Pyrroloindolines by a Formal (3 + 2)

Cycloaddition

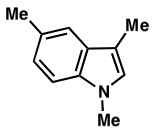
JN-1-197-col

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

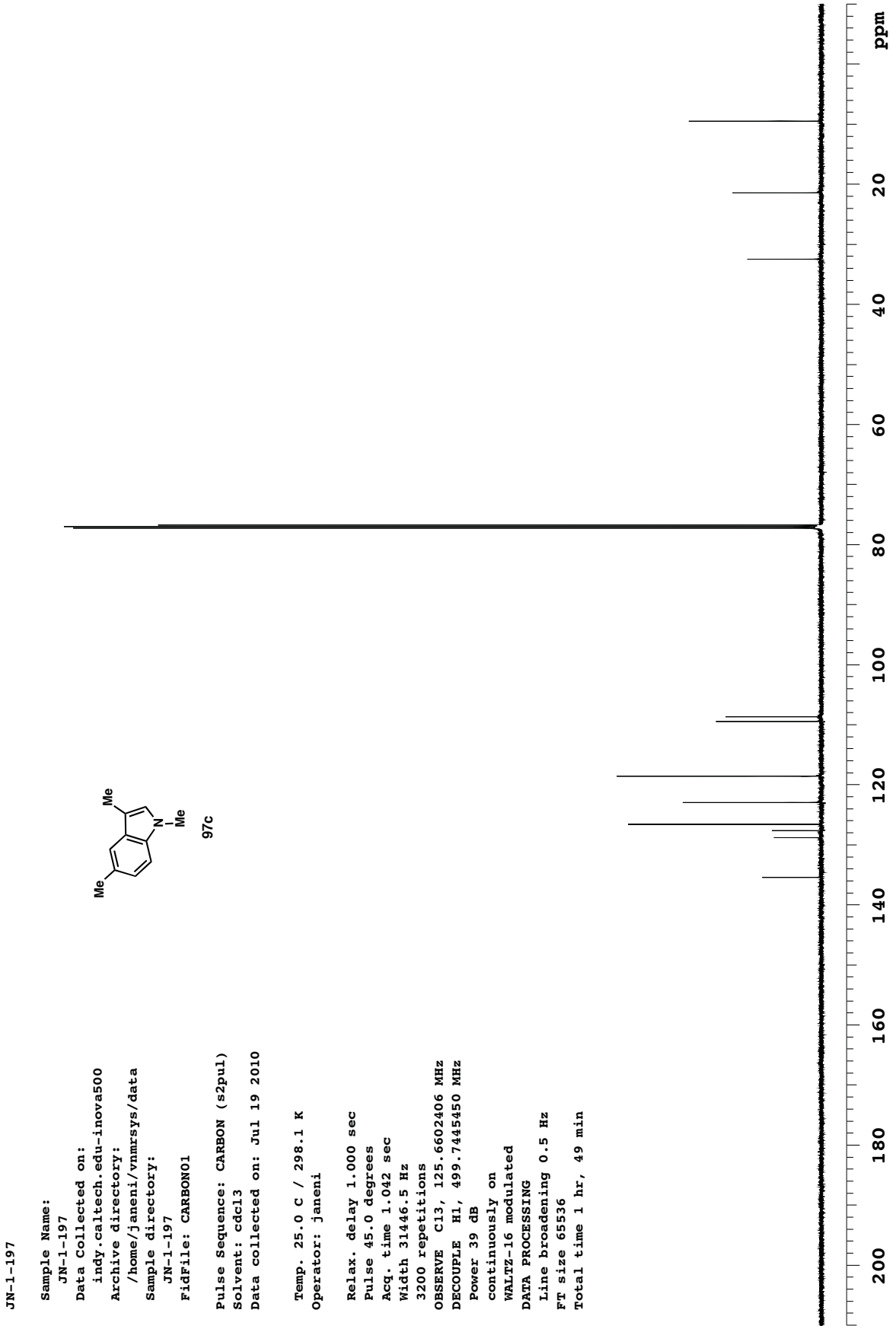
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 19 2010

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



97c


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
Me
Me
N
Me
97c
200
180
160
140
120
100
80
60
40
20
ppm

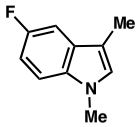
JN-1-183-col2

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: PROTON01

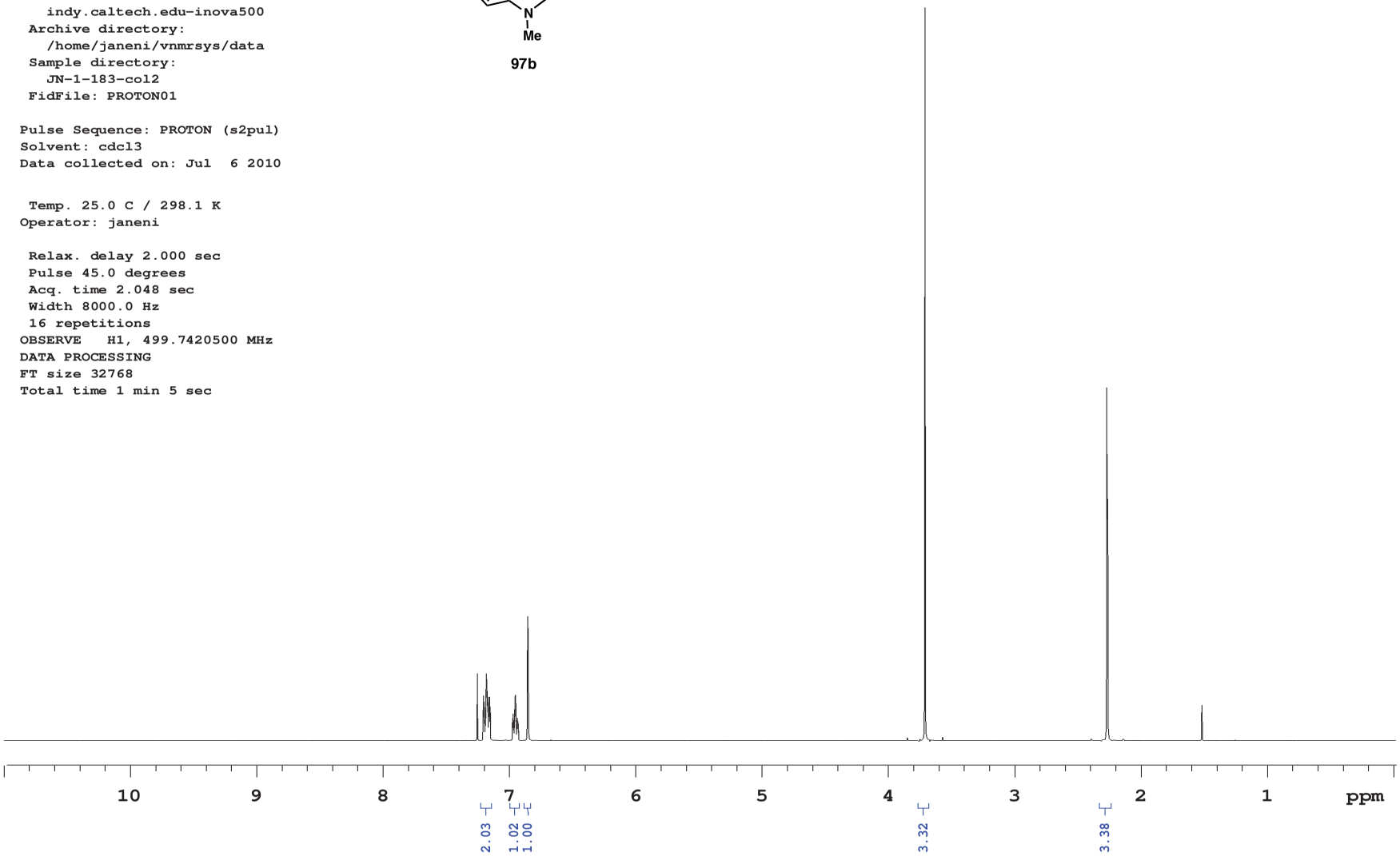
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 6 2010

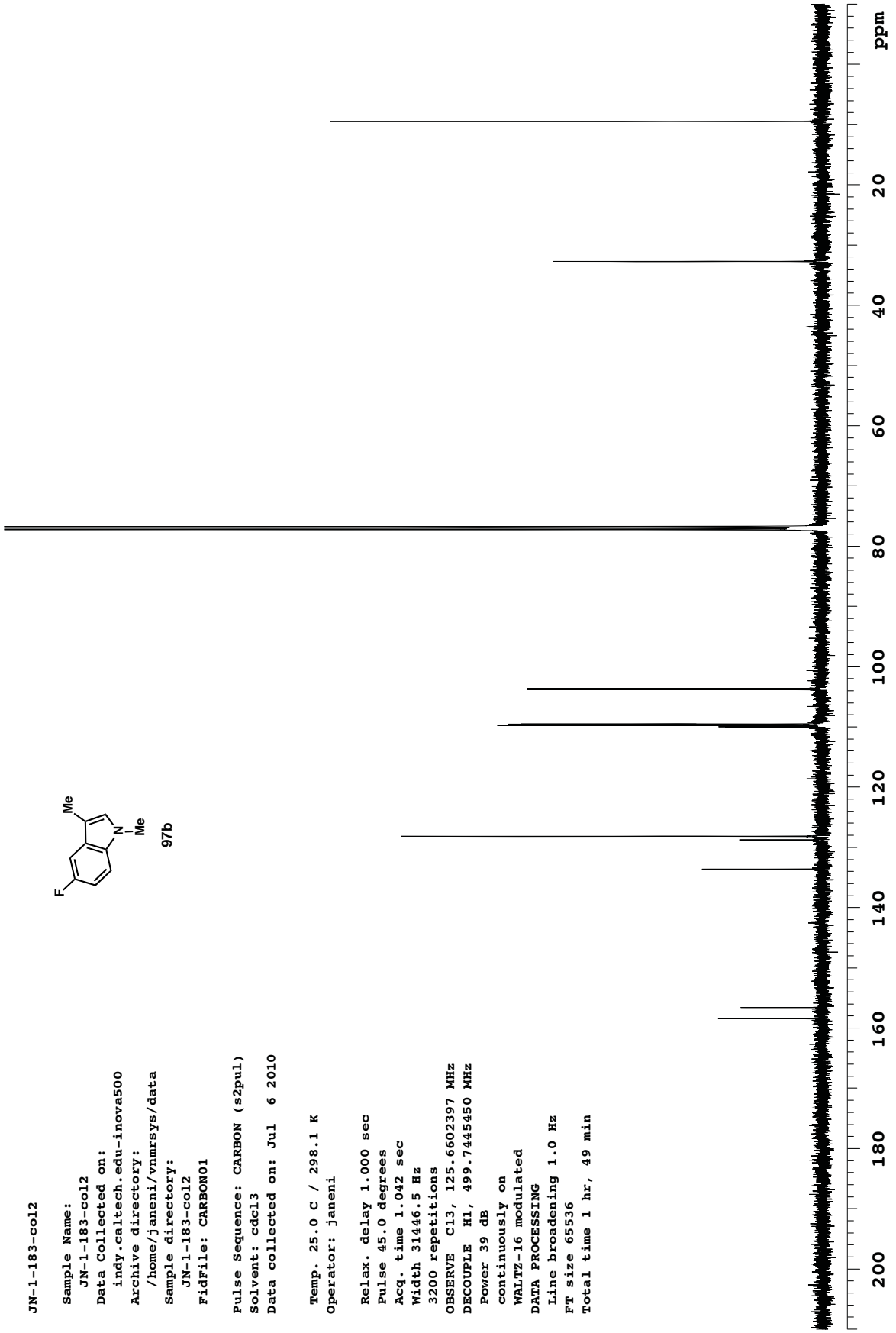
Temp. 25.0 C / 298.1 K
Operator: janeni

Relax. delay 2.000 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 5 sec



97b




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
Me
N
Me
F
97b
200
180
160
140
120
100
80
60
40
20
ppm

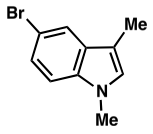
JN-1-181-col

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: PROTON01

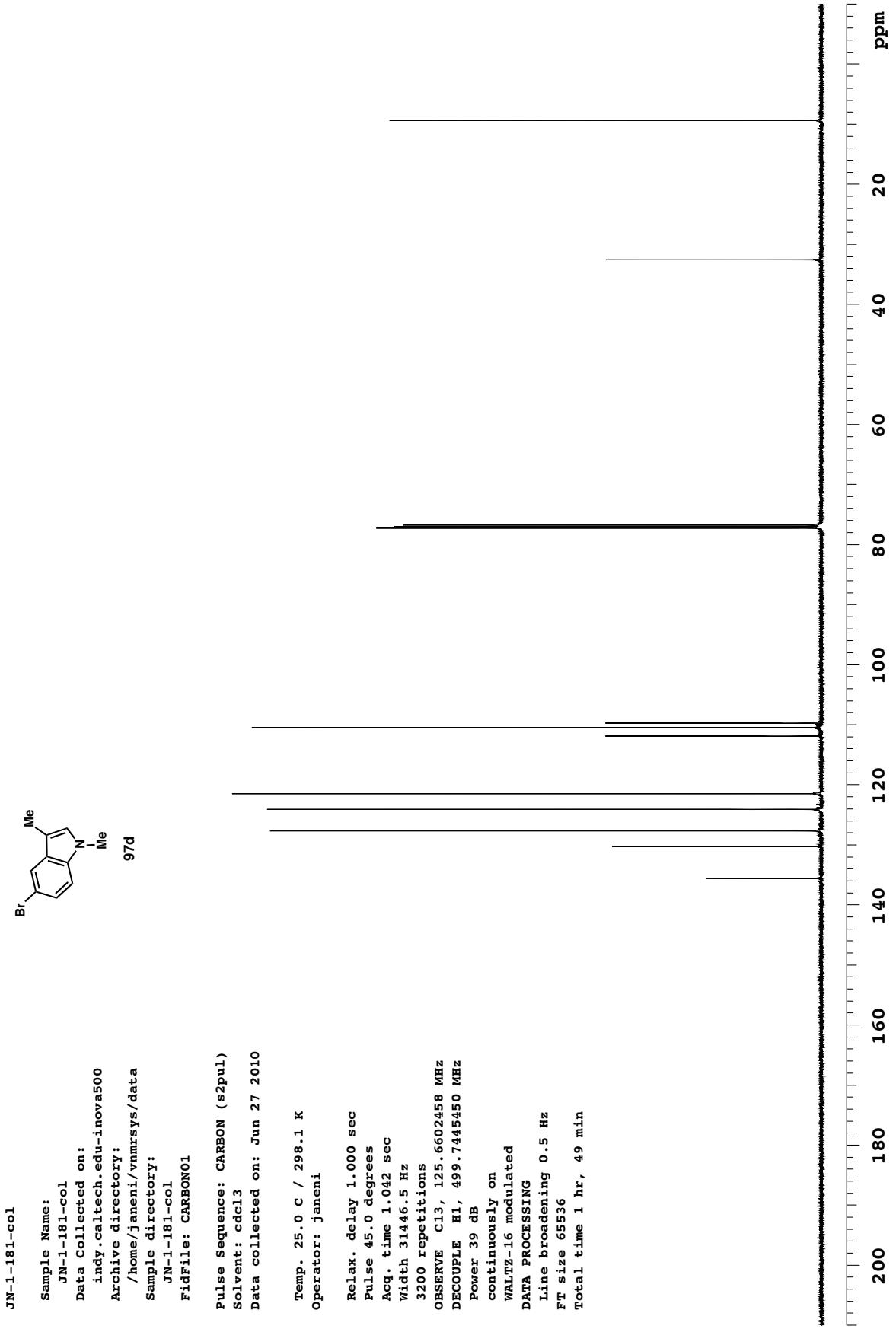
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 27 2010

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



97d


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
Me
N
Me
Br
97d
200
180
160
140
120
100
80
60
40
20
ppm

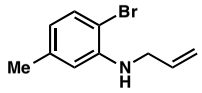
JN-1-199-col

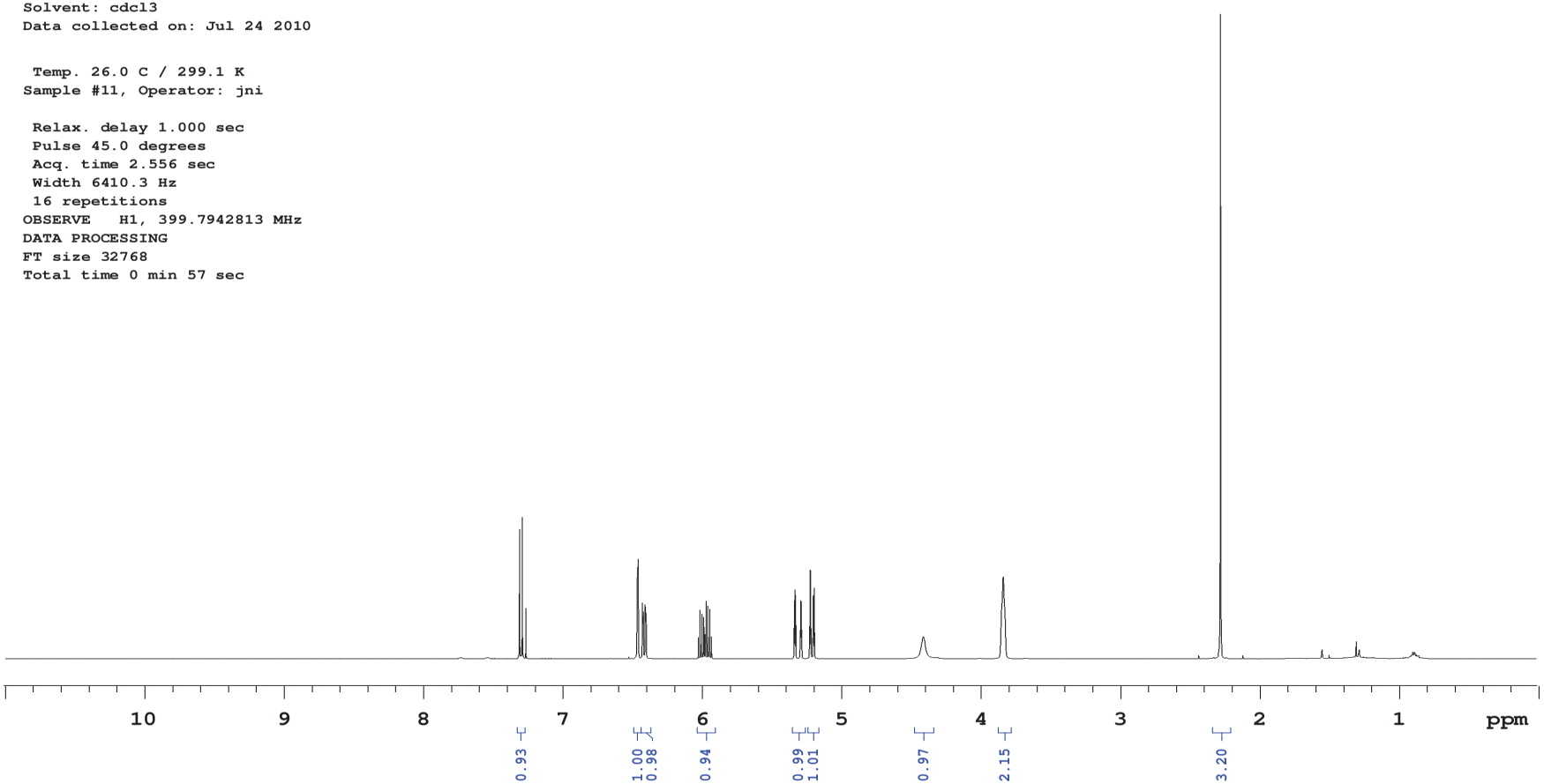
Sample Name:
JN-1-199-col
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-199-col
FidFile: PROTON01

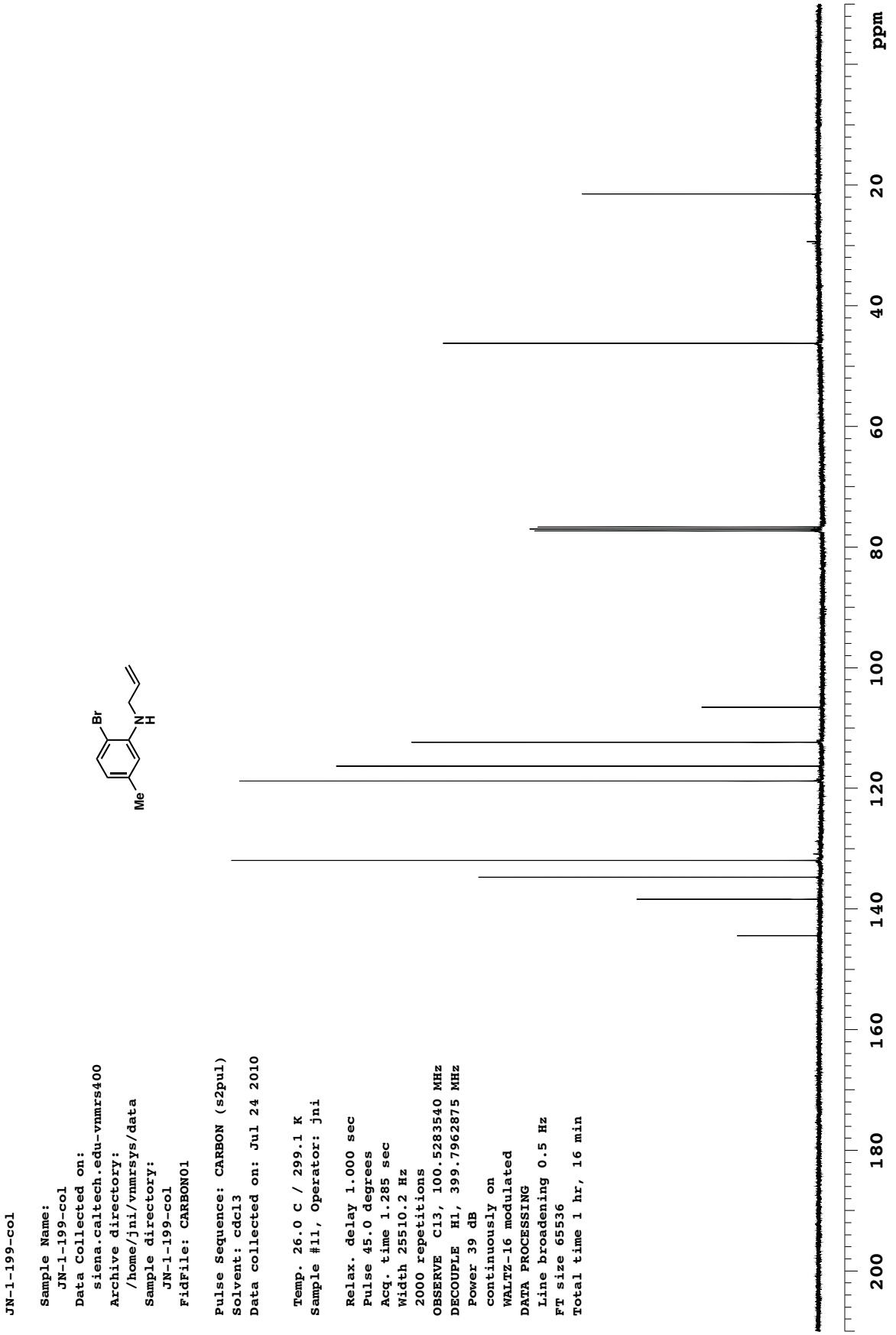
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 24 2010

Temp. 26.0 C / 299.1 K
Sample #11, Operator: jni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 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-vnmrs400
Archive directory:
/home/jni/vnmrsys/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
Br
N
H
Me
200
180
160
140
120
100
80
60
40
20
ppm

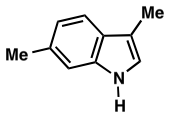
JN-1-201-col

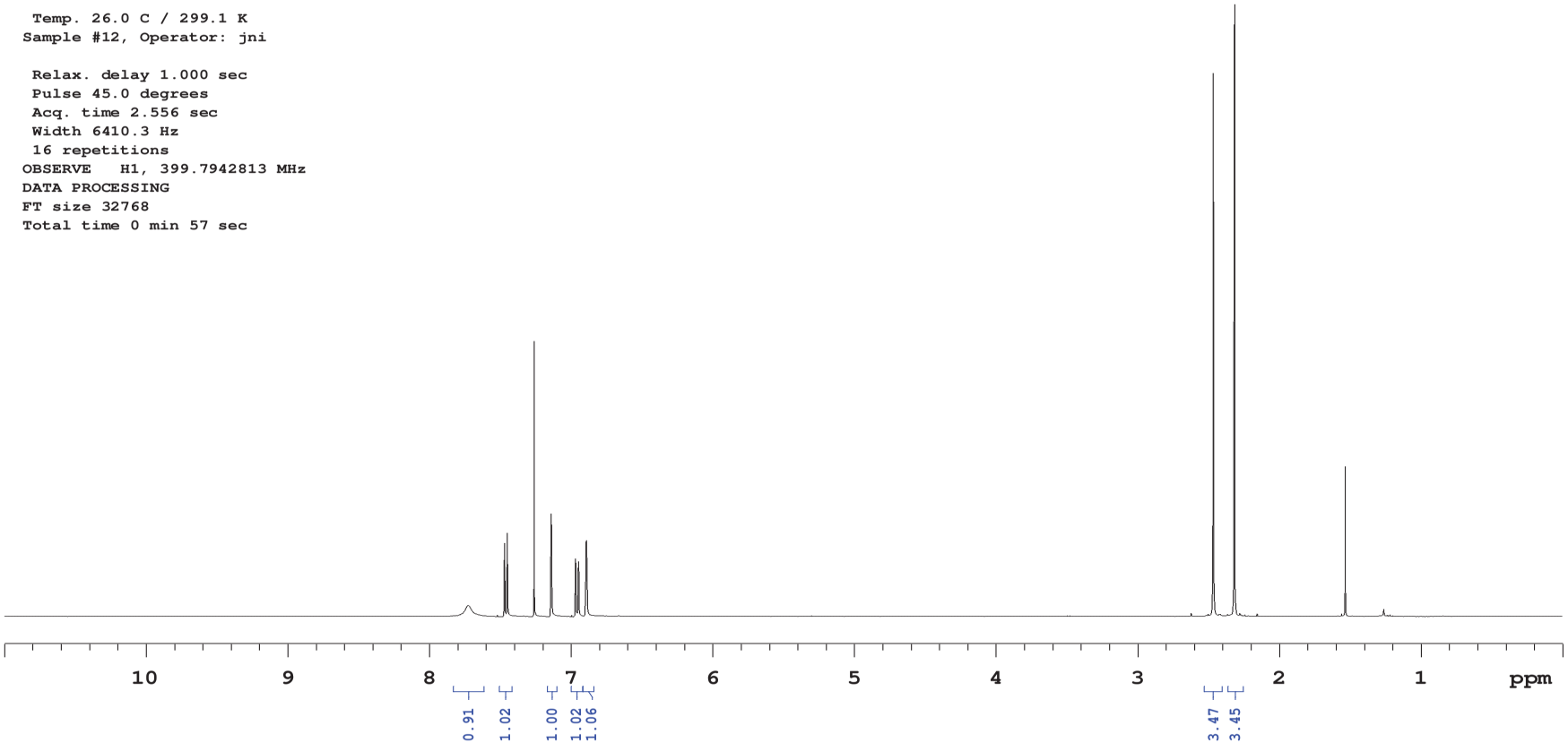
Sample Name:
JN-1-201-col
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-201-col
FidFile: PROTON01

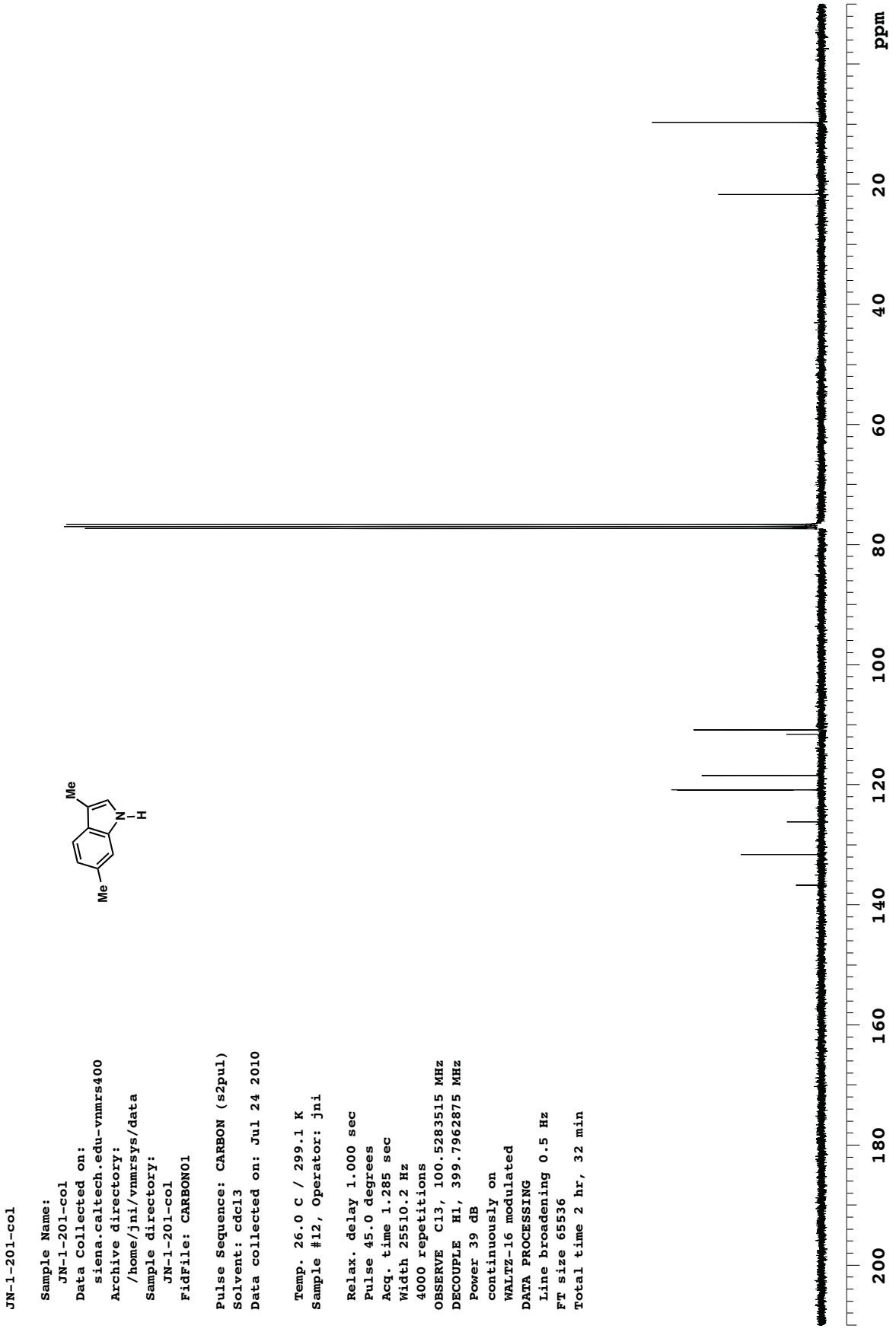
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 24 2010

Temp. 26.0 C / 299.1 K
Sample #12, Operator: jni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 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-1-201-col
Sample Name:
JN-1-201-col
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/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
Me
N
H
Me
200
180
160
140
120
100
80
60
40
20
ppm

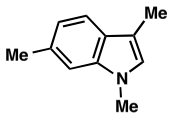
JN-1-203-col

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

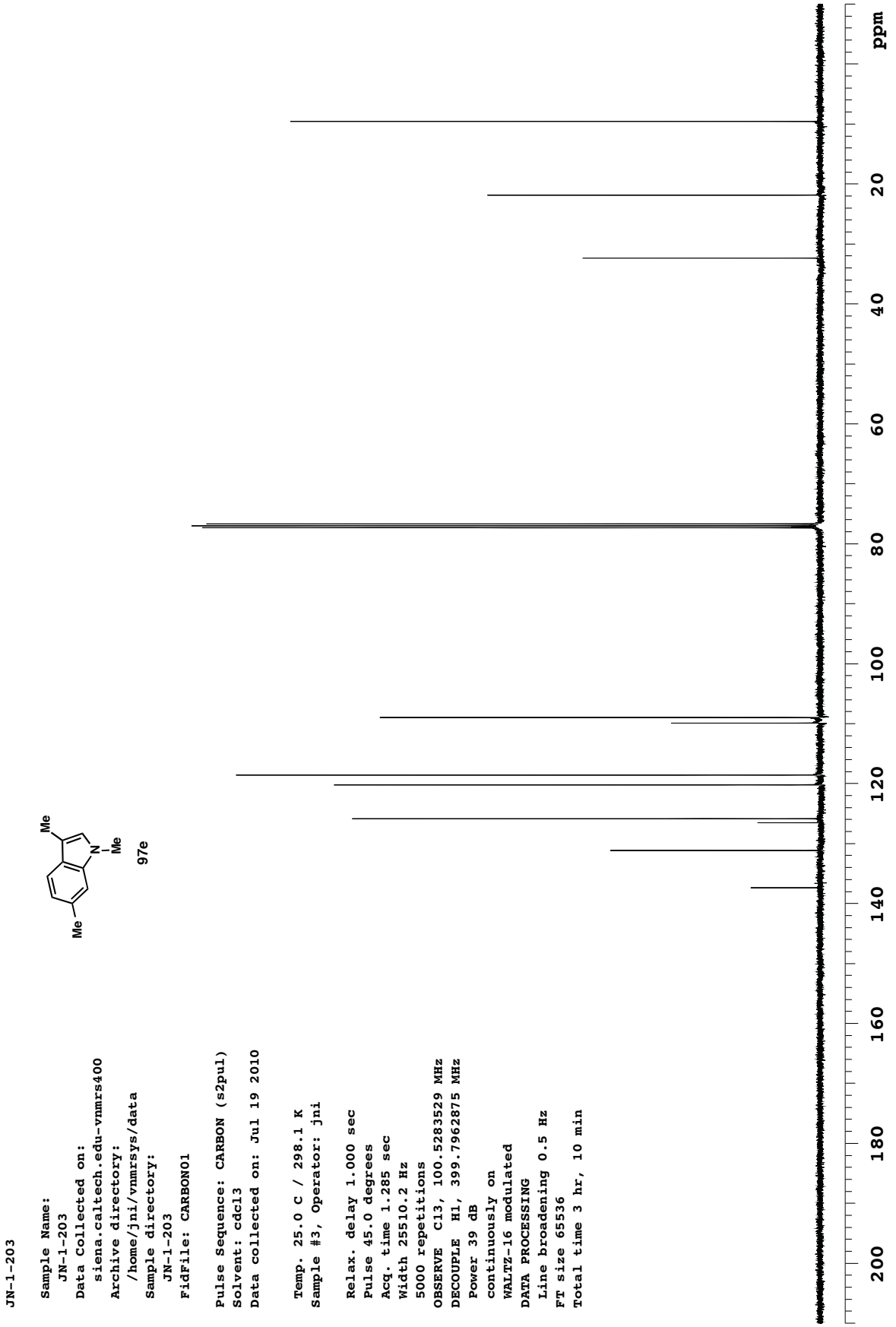
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 19 2010

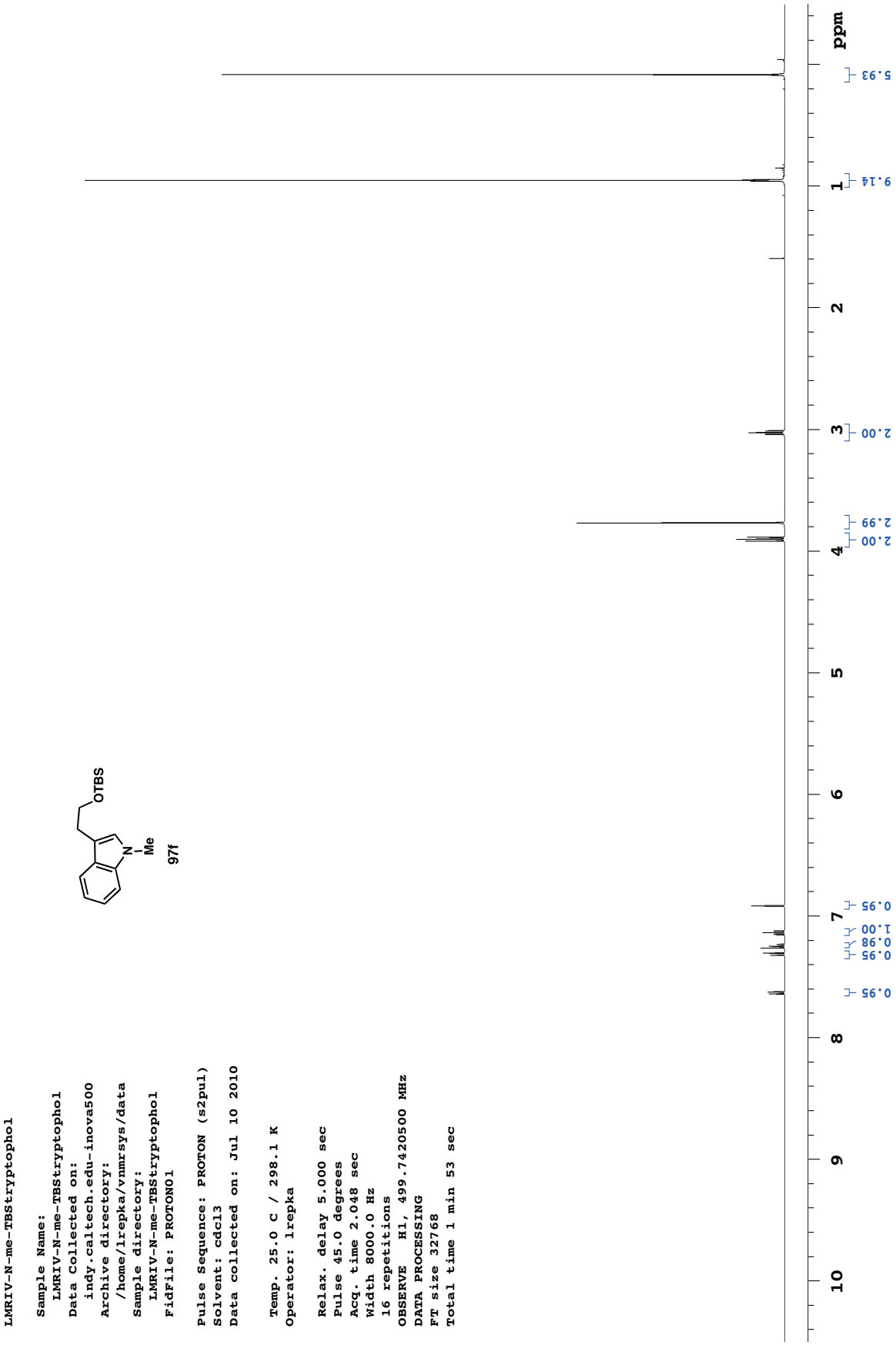
Temp. 25.0 C / 298.1 K
Sample #21, Operator: jni

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



97e


JN-1-203
Sample Name:
JN-1-203
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/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
Me
N
Me
Me
Me
97e
200
180
160
140
120
100
80
60
40
20
ppm


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
OTBS
N
Me
97f
ppm
10
9
8
7
6
5
4
3
2
1
5.93
9.14
2.00
2.99
2.00
0.95
1.00
0.98
0.95
0.95

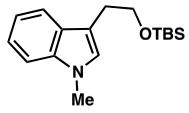
LMRIV-N-me-TBStryptophol2

Sample Name:
LMRIV-N-me-TBStryptophol2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-N-me-TBStryptophol2
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 10 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
3500 repetitions
OBSERVE C13, 125.6602422 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, 59 min



97f

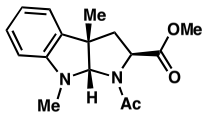
LMRIV-291-majordr-hsqc

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

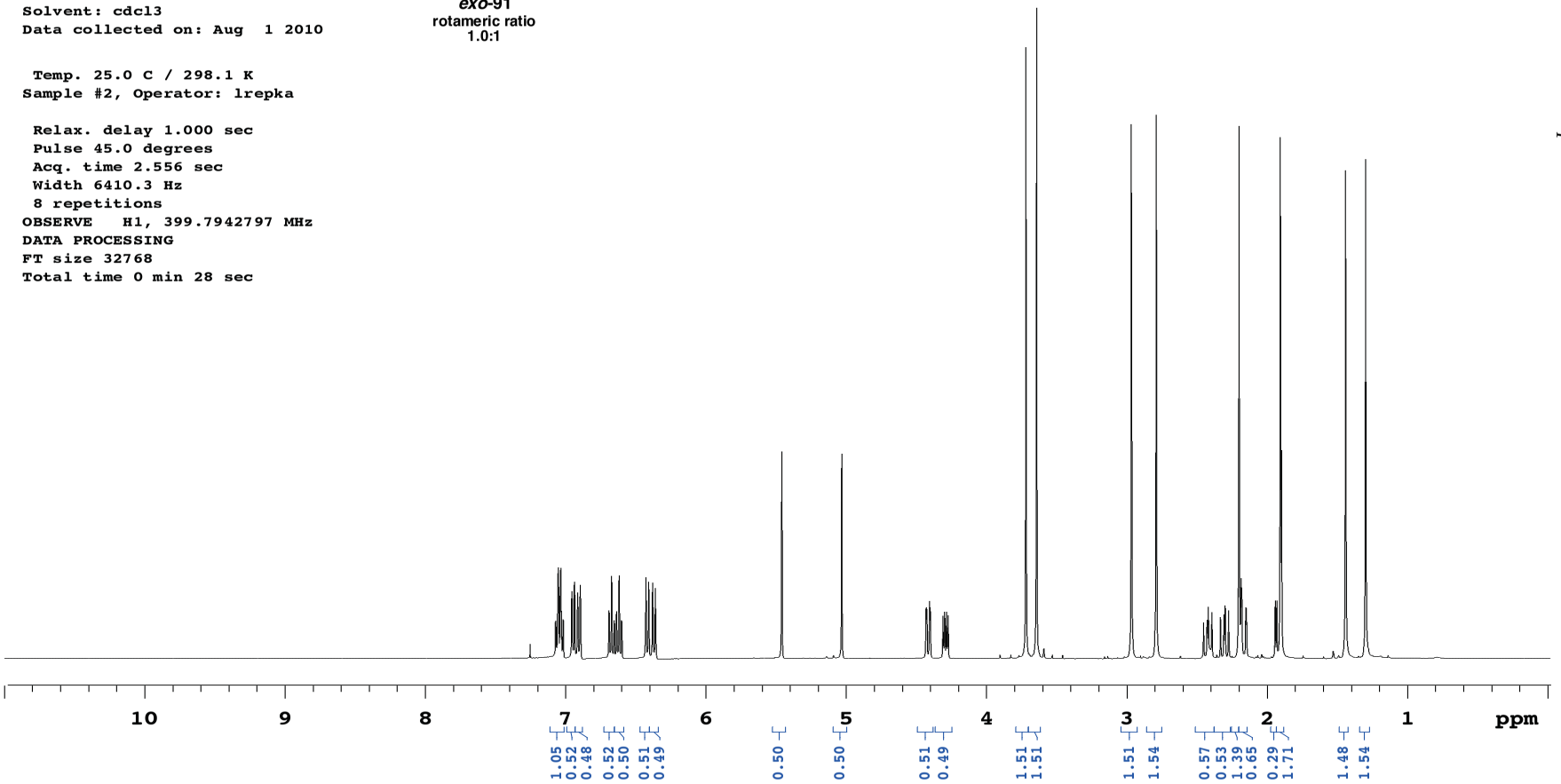
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 1 2010

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



exo-91
rotameric ratio
1.0:1



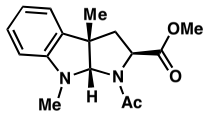
LMRIV-291-majordr-conc

Sample Name:
LMRIV-291-majordr-conc
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-291-majordr-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



exo-91
rotameric ratio
1.0:1

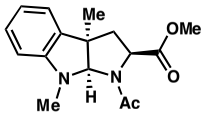
LMRIV-291-minordr-hsqc

Sample Name:
LMRIV-291-minordr-hsqc
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-291-minordr-hsqc
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 1 2010

Temp. 25.0 C / 298.1 K
Sample #3, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7942813 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec



endo-91
rotameric ratio
3.0:1

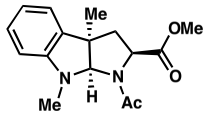
LMRIV-291-minordr

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

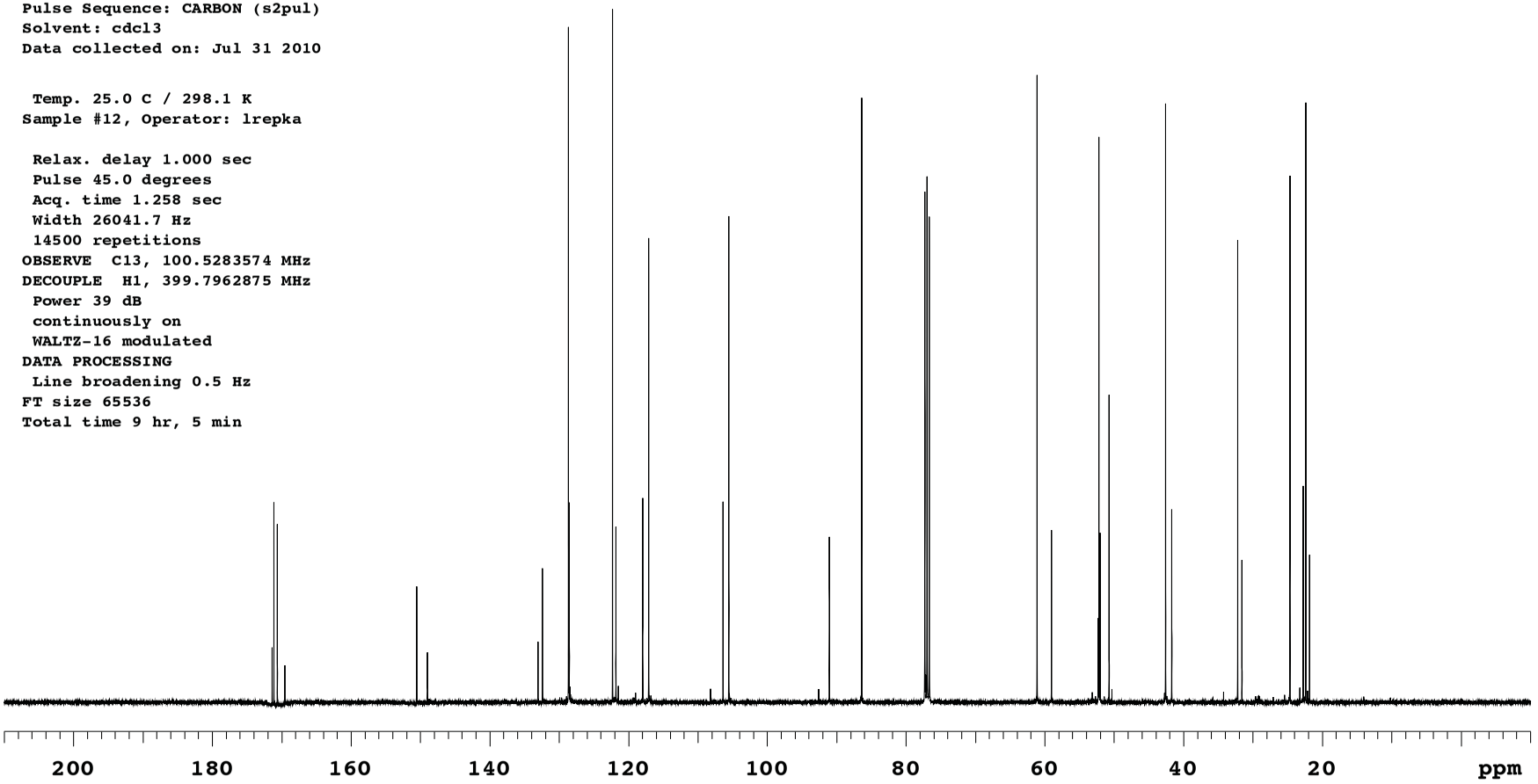
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 31 2010

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



endo-91
rotameric ratio
3.0:1



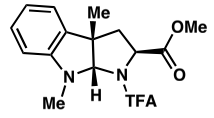
JN-1-131-majordiast

Sample Name:
JN-1-131-majordiast
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-131-majordiast
FidFile: PROTON01

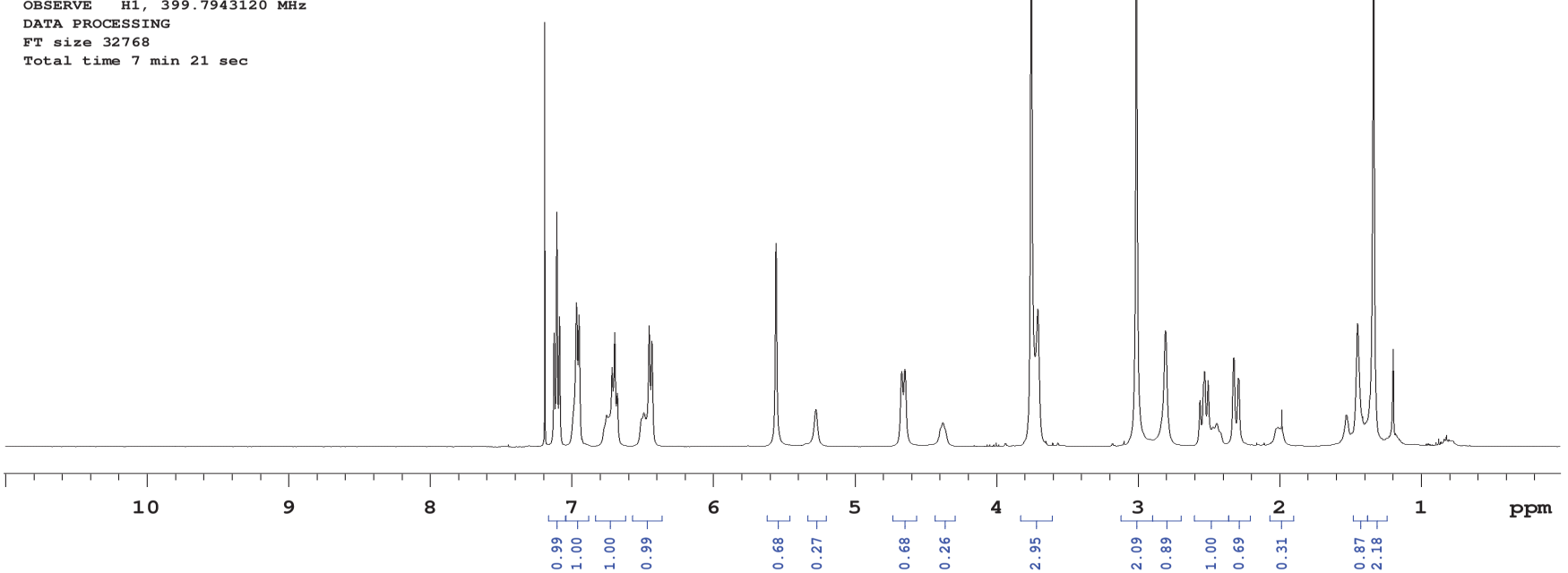
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2010

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



exo-94
rotameric ratio
2.4:1



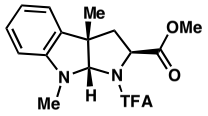
JN-1-131-majordiast

Sample Name:
JN-1-131-majordiast
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/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



exo-94
rotameric ratio
2.4:1

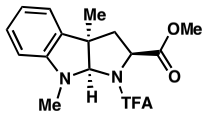
JN-1-131-minordiast3

Sample Name:
JN-1-131-minordiast3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-1-131-minordiast3
FidFile: PROTON01

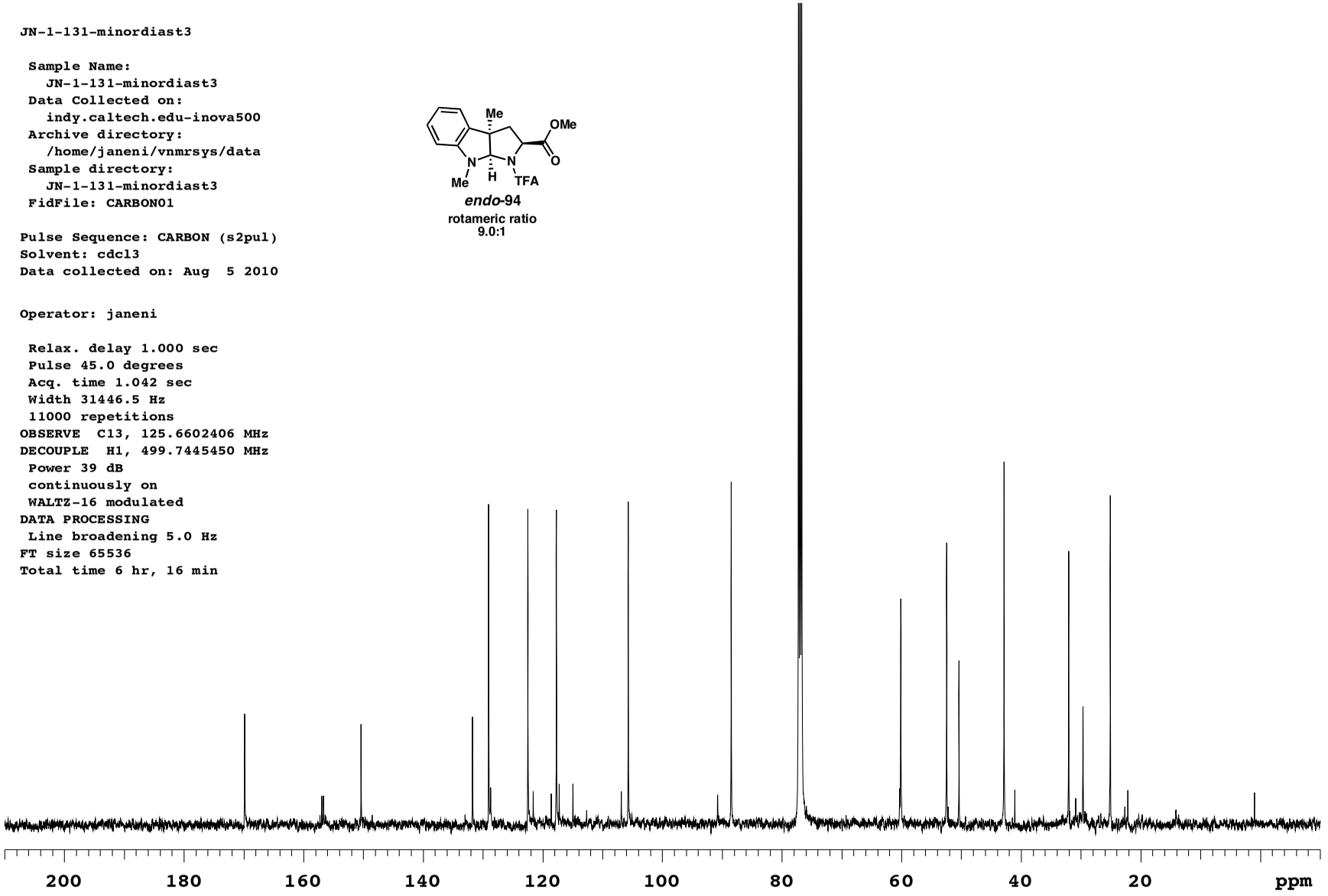
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2010

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



endo-94
rotameric ratio
9.0:1


JN-1-131-minordiast3
Sample Name:
JN-1-131-minordiast3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-1-131-minordiast3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2010
Operator: janeni
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
11000 repetitions
OBSERVE C13, 125.6602406 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 6 hr, 16 min
Me
OMe
O
N
H
N
Me
TFA
endo-94
rotameric ratio
9.0:1
200
180
160
140
120
100
80
60
40
20
ppm

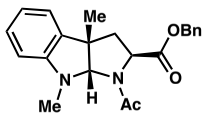
JN-1-151-major

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

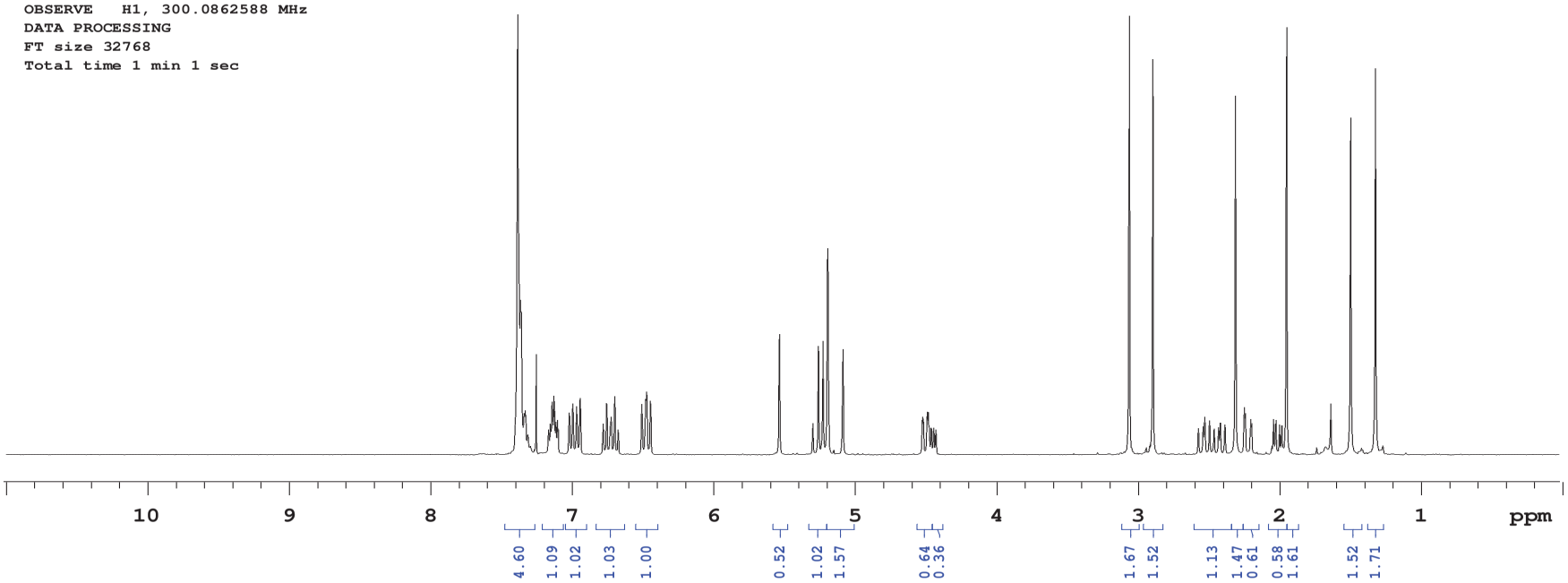
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 24 2010

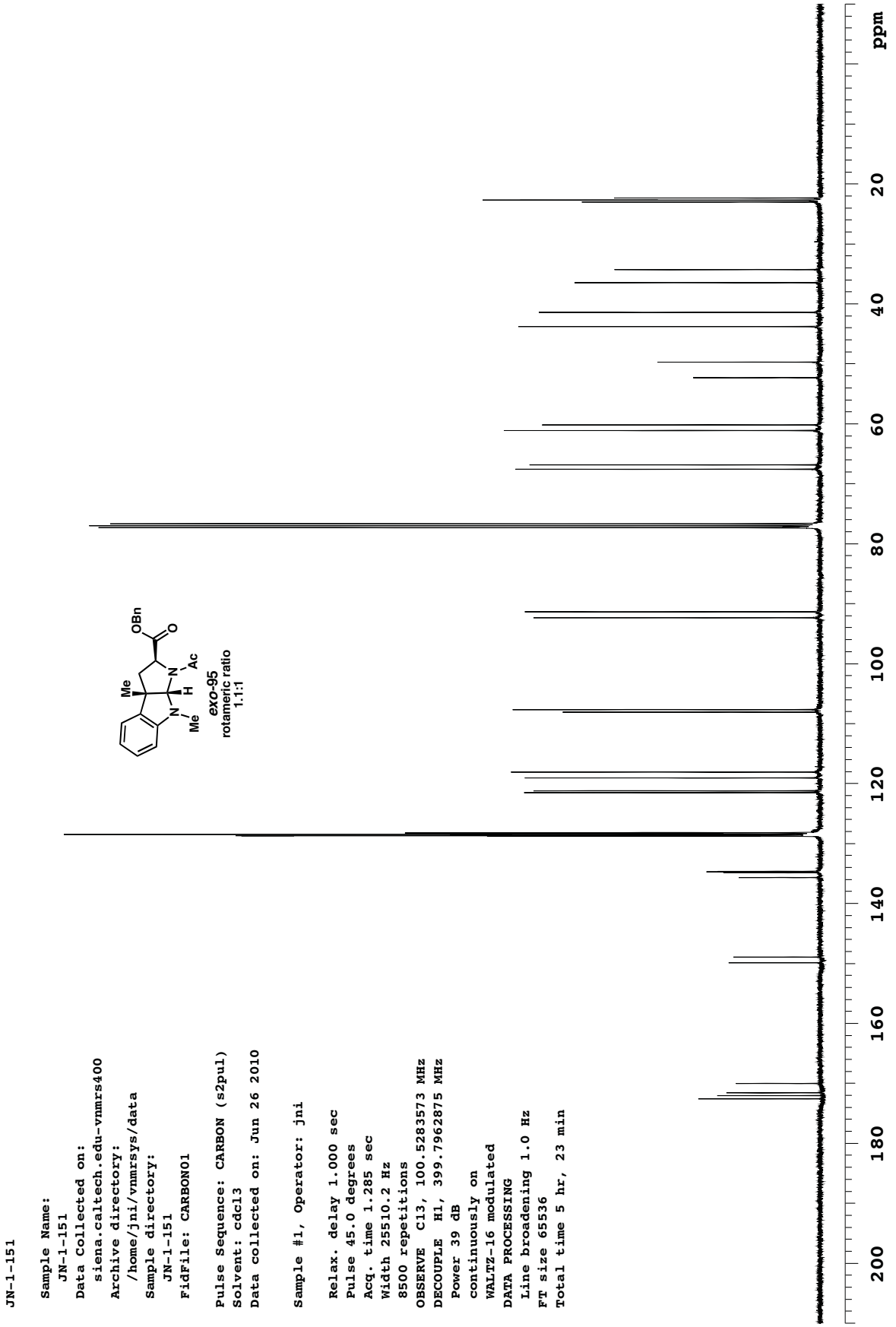
Temp. 25.0 C / 298.1 K
Sample #20, Operator: jni

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



exo-95
rotameric ratio
1.1:1




JN-1-151
Sample Name:
JN-1-151
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/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
OBn
O
N
Ac
H
N
Me
Me
exo-95
rotameric ratio
1.1:1
200
180
160
140
120
100
80
60
40
20
ppm

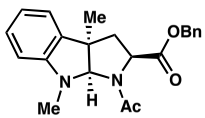
JN-1-151-minordiast3

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: PROTON01

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



***endo*-95**
rotameric ratio
3.0:1

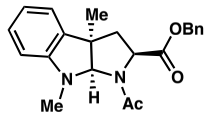
JN-1-151-minordiast3

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



endo-95
rotameric ratio
3.0:1

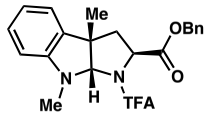
LMRIV-287-majordr-rd25

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

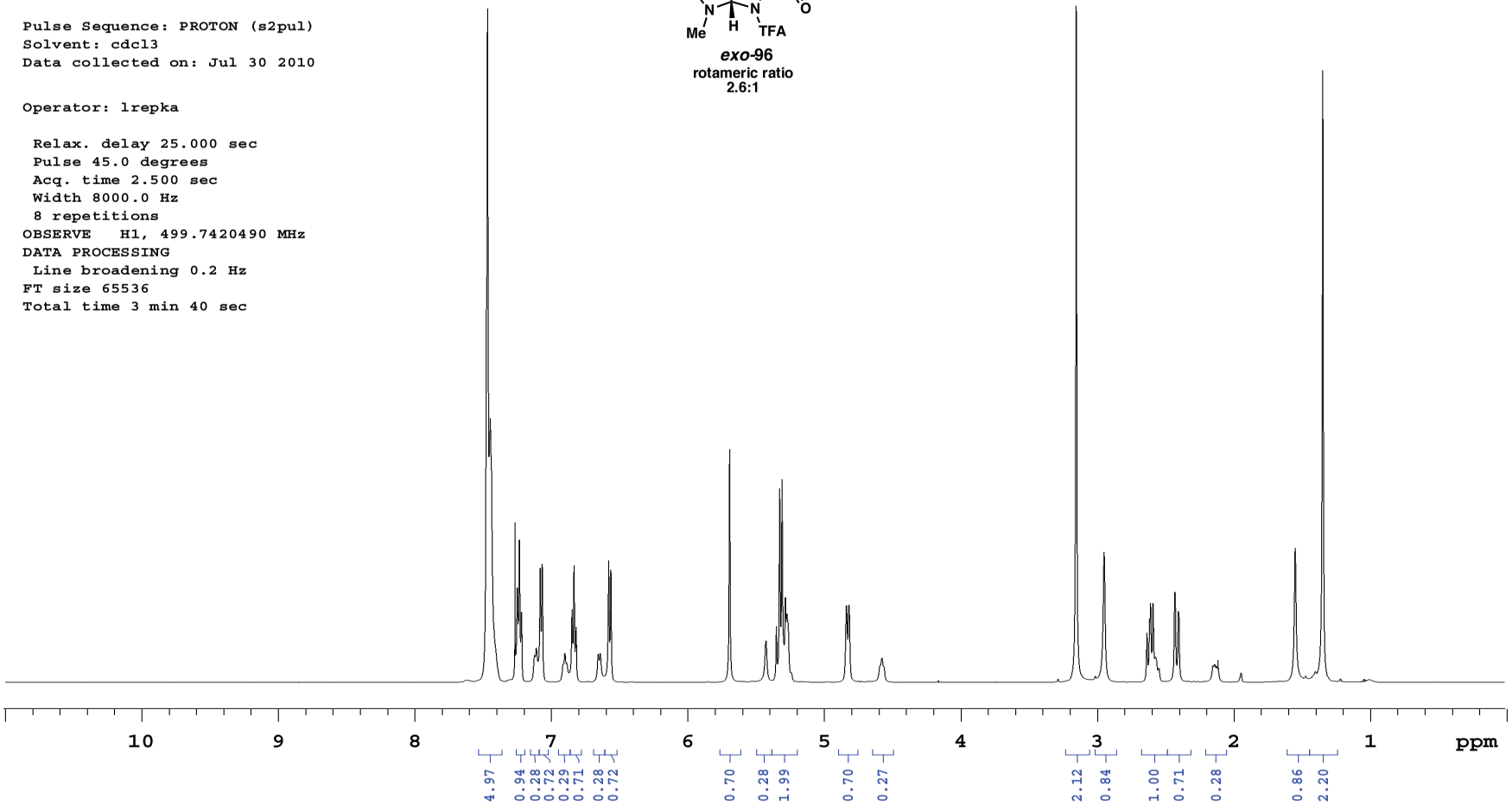
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 30 2010

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



exo-96
rotameric ratio
2.6:1



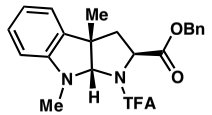
LMRIV-scale-up-12h-majordr

Sample Name:
LMRIV-scale-up-12h-majordr
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-scale-up-12h-majordr
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



exo-96
rotameric ratio
2.6:1

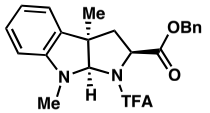
LMRIV-287-minor-8-5-10

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



endo-96
rotameric ratio
10.0:1

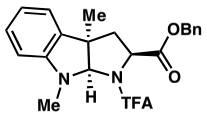
LMRIV-scale-up-12h-minordr

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



endo-96
rotameric ratio
10.0:1

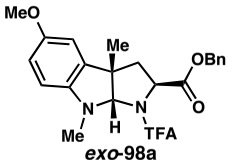
JN-1-191-majordiast

Sample Name:
JN-1-191-majordiast
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-191-majordiast
FidFile: PROTON01

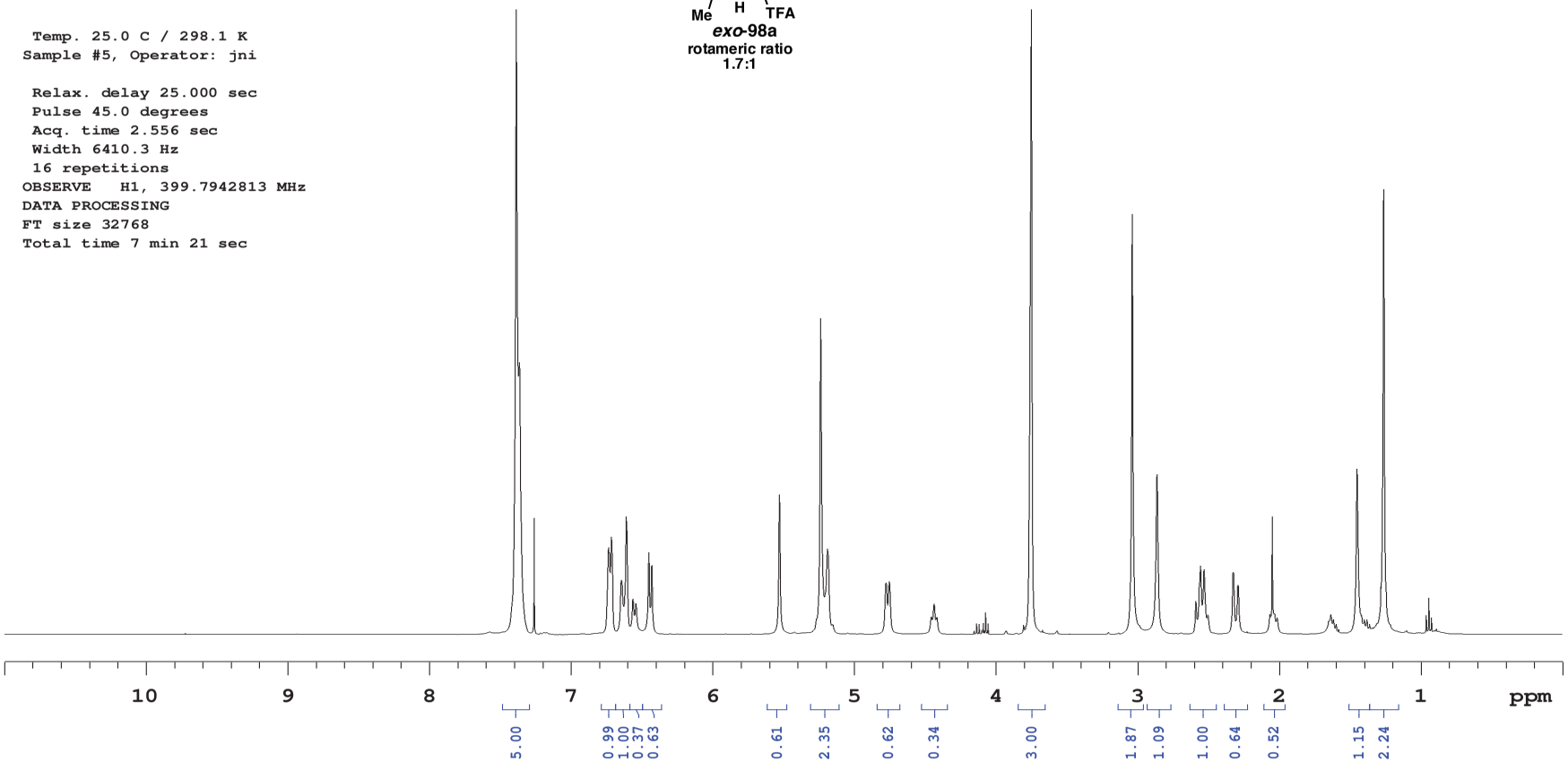
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 19 2010

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



exo-98a
rotameric ratio
1.7:1



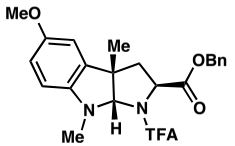
JN-1-191-majordiast

Sample Name:
JN-1-191-majordiast
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-191-majordiast
FidFile: CARBON01

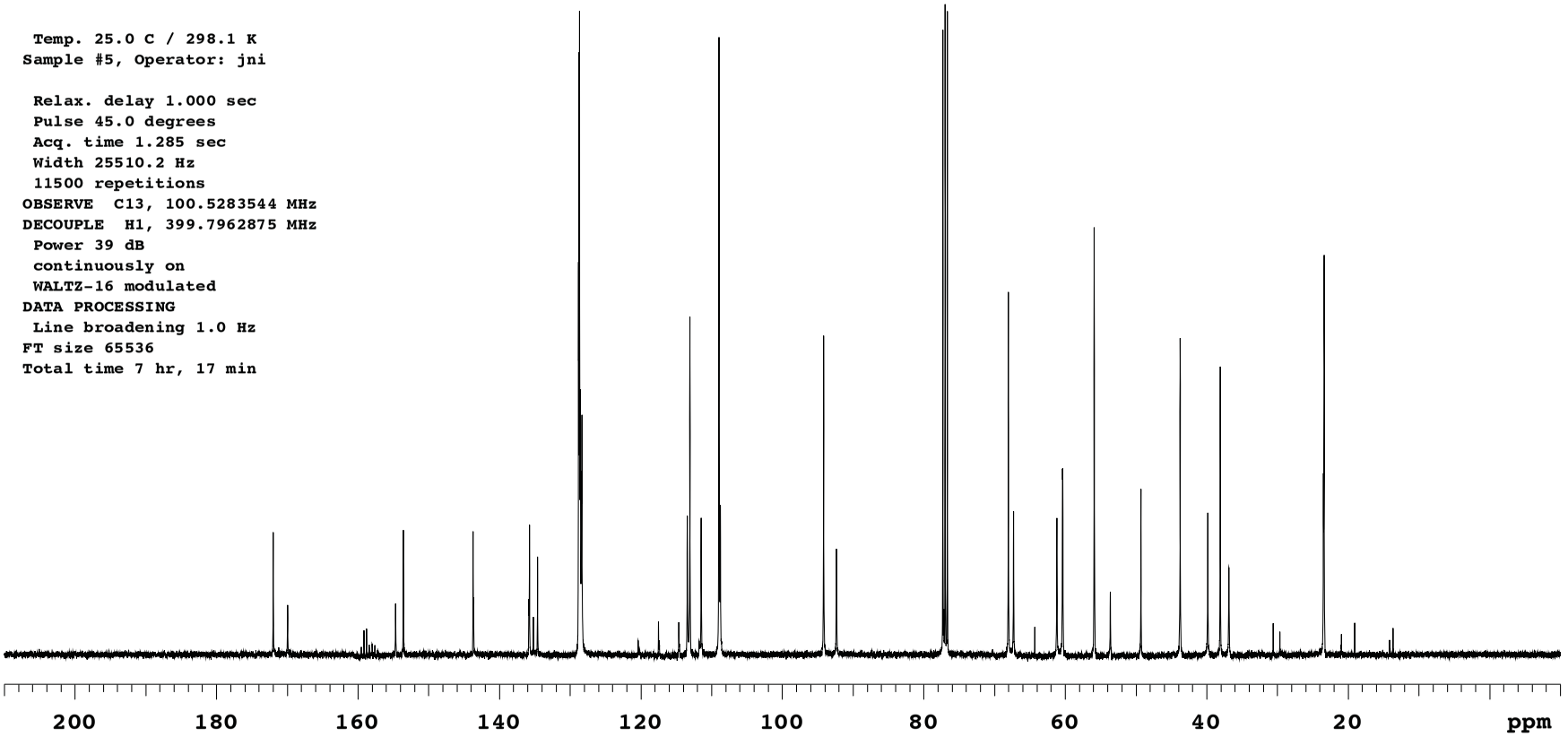
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 19 2010

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



exo-98a
rotameric ratio
1.7:1



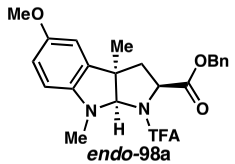
JN-1-191-minordiast

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



endo-98a
rotameric ratio
6.0:1

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: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 18 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
12000 repetitions
OBSERVE C13, 125.6602389 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 6 hr, 50 min
MeO
Me
Me
OBn
O
N
H
N
TFA
endo-98a
rotameric ratio
6.0:1
200
180
160
140
120
100
80
60
40
20
ppm

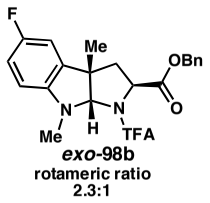
JN-1-195-majordiast4

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

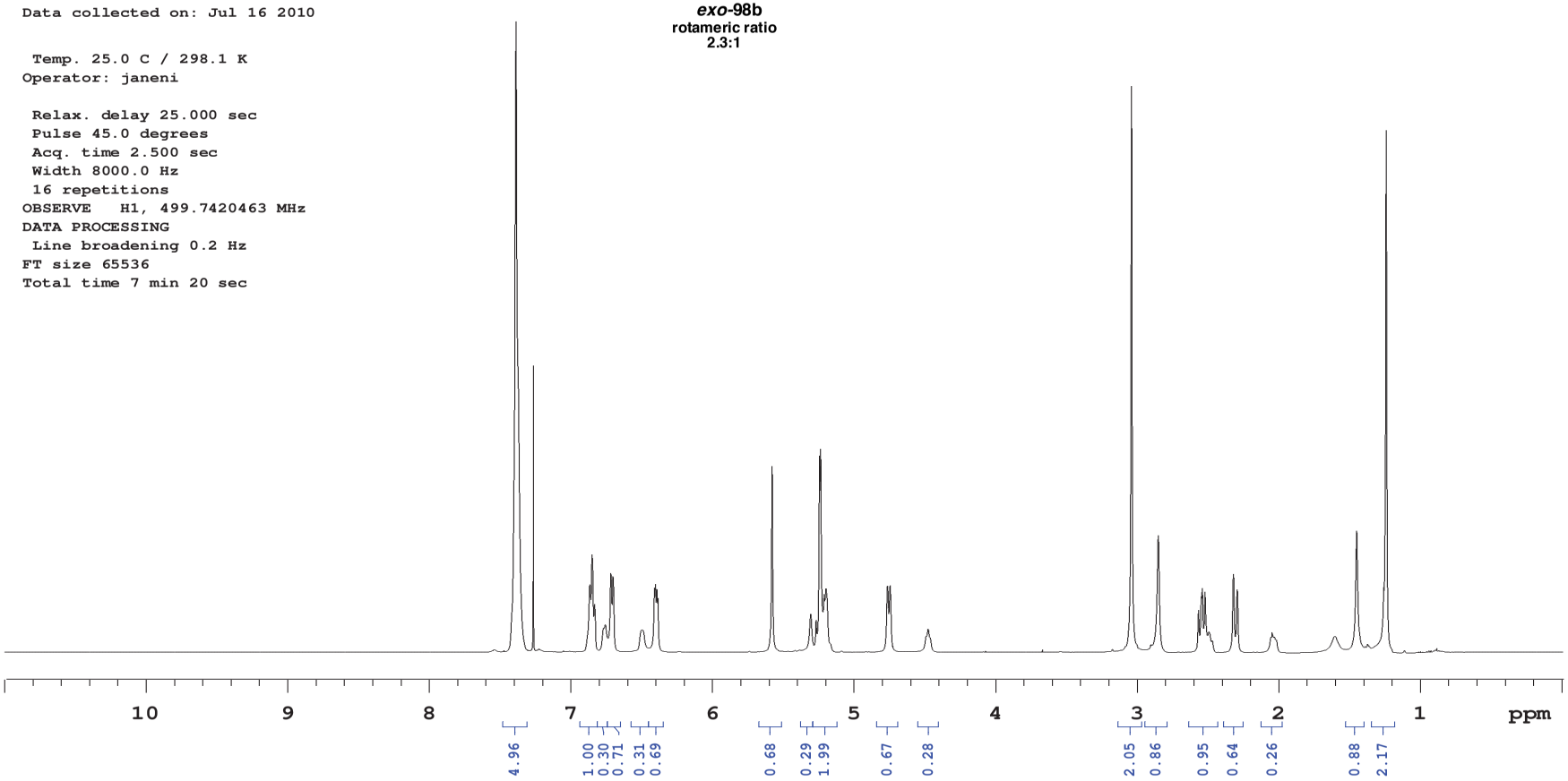
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 16 2010

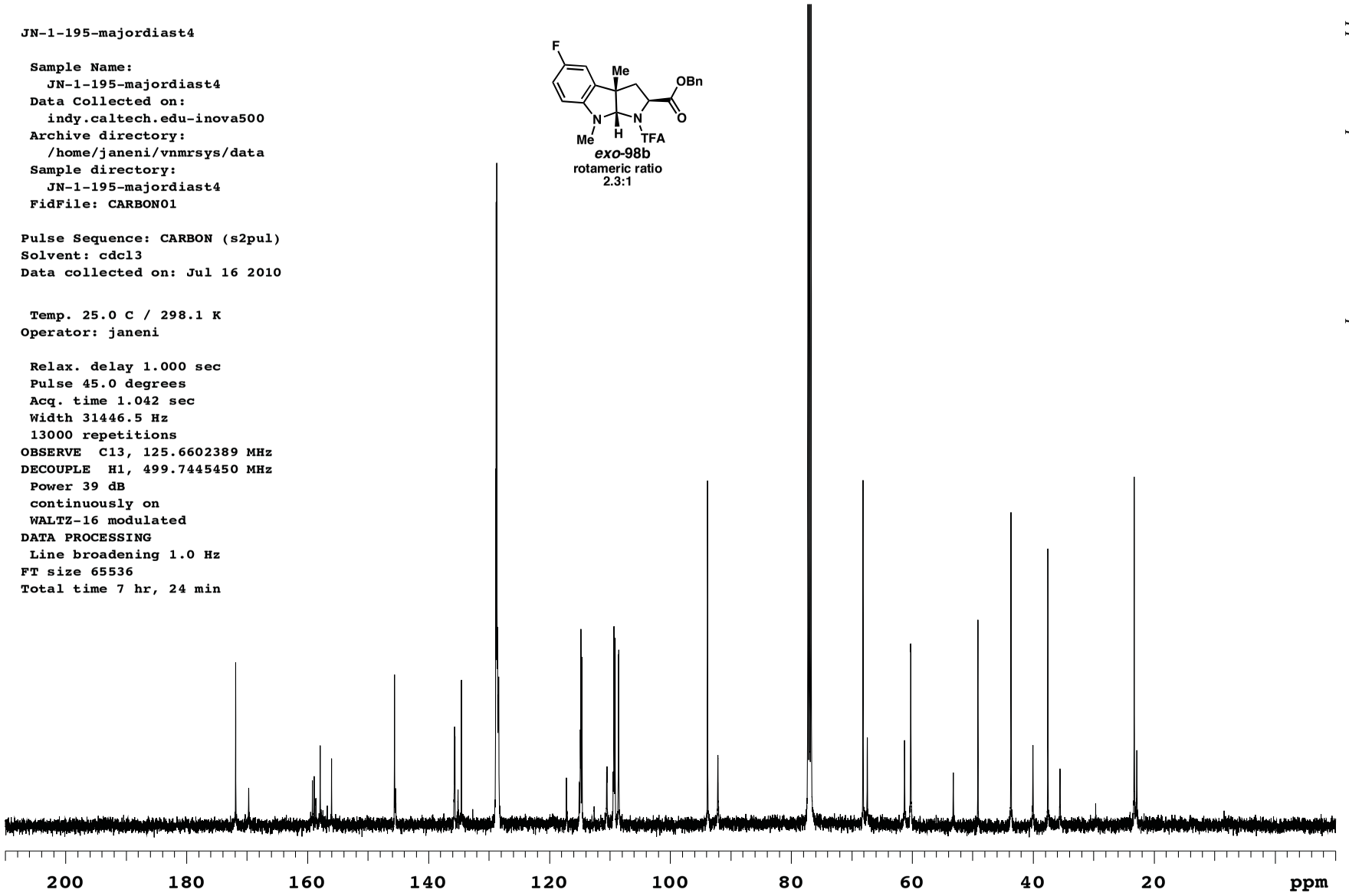
Temp. 25.0 C / 298.1 K
Operator: janeni

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



exo-98b
rotameric ratio
2.3:1




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
F
Me
OBn
N
N
O
Me
H
TFA
exo-98b
rotameric ratio
2.3:1
200
180
160
140
120
100
80
60
40
20
ppm

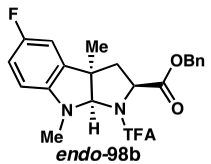
JN-1-195-minordiast

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

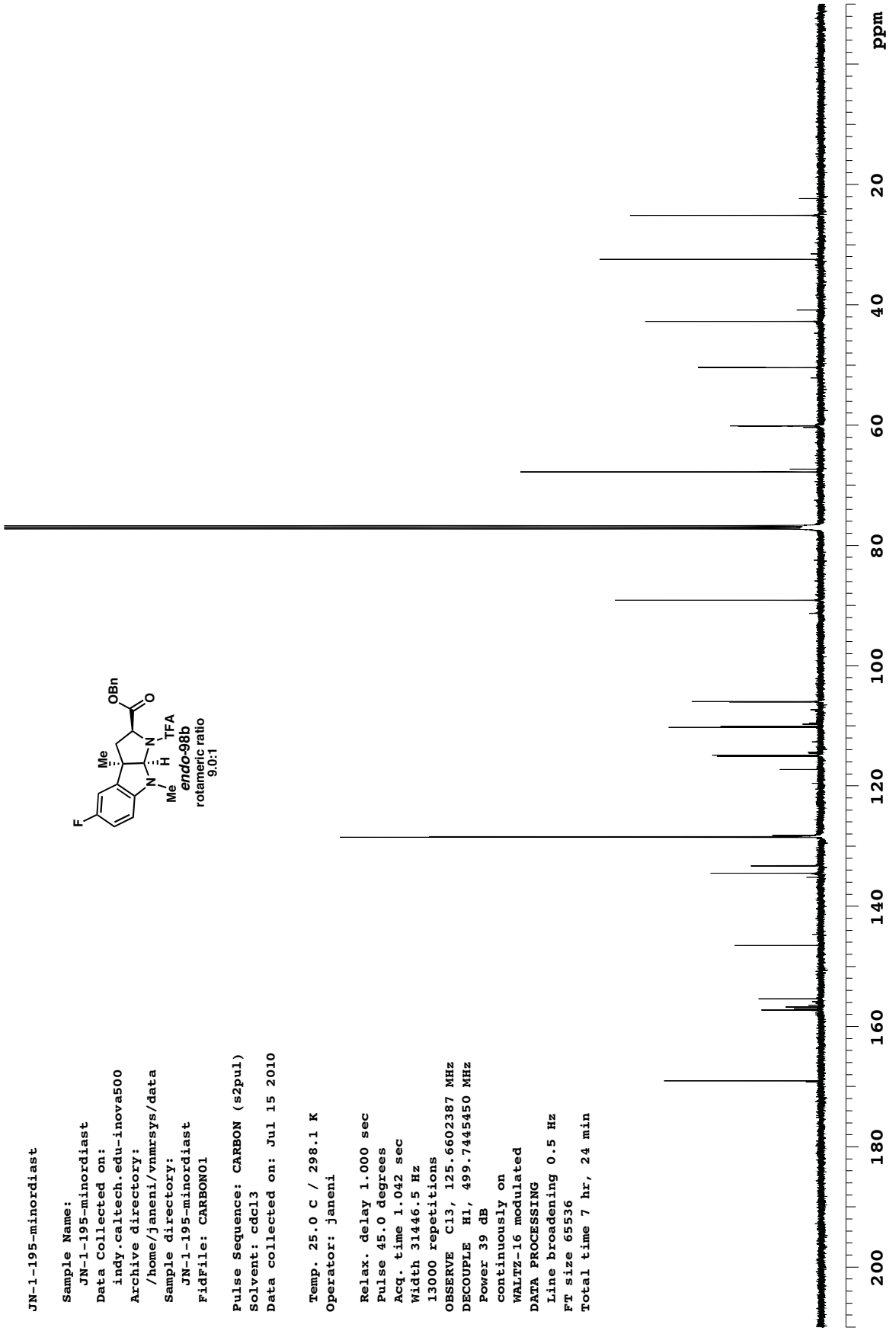
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 15 2010

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



endo-98b
rotameric ratio
9.0:1


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
OBn
O
Me
N
H
TFA
Me
F
endo-98b
rotameric ratio
9.0:1
200
180
160
140
120
100
80
60
40
20
ppm

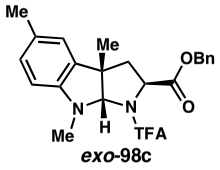
JN-1-171-majdiast

Sample Name:
JN-1-171-majdiast
Data Collected on:
siena.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

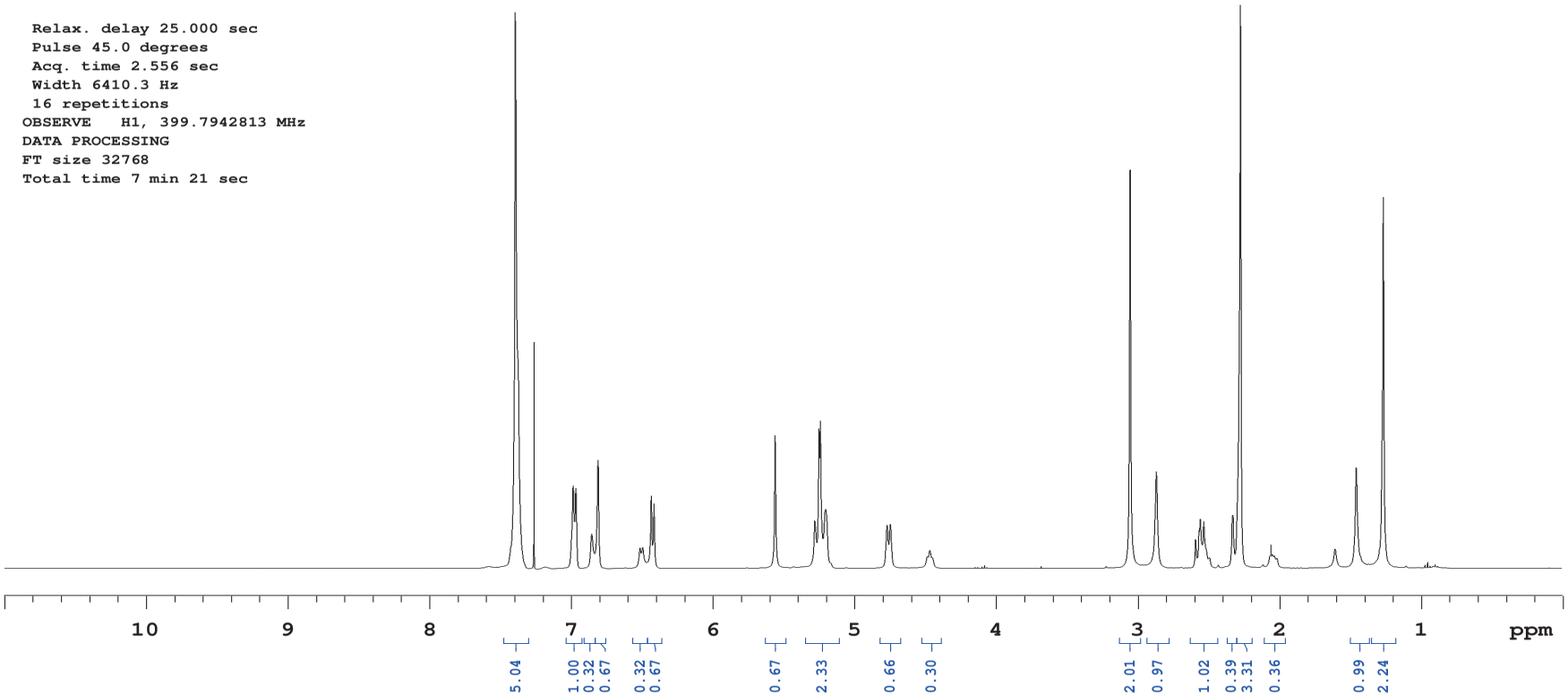
Temp. 25.0 C / 298.1 K
Sample #4, Operator: jni

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



exo-98c

rotameric ratio
2.0:1



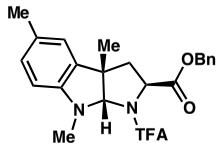
JN-1-171-majdiast

Sample Name:
JN-1-171-majdiast
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-171-majdiast
FidFile: CARBON01

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

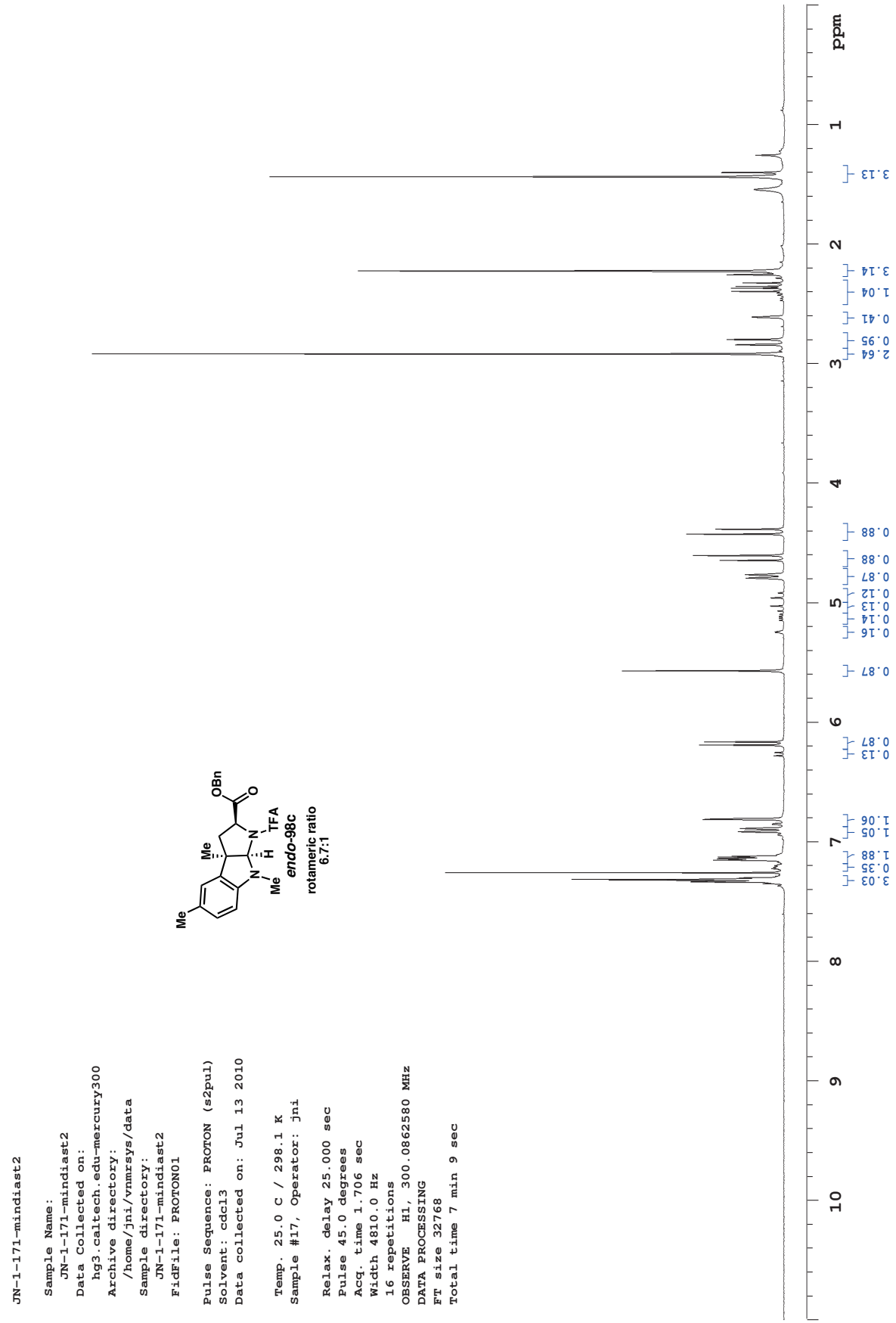
Temp. 25.0 C / 298.1 K
Sample #4, Operator: jni

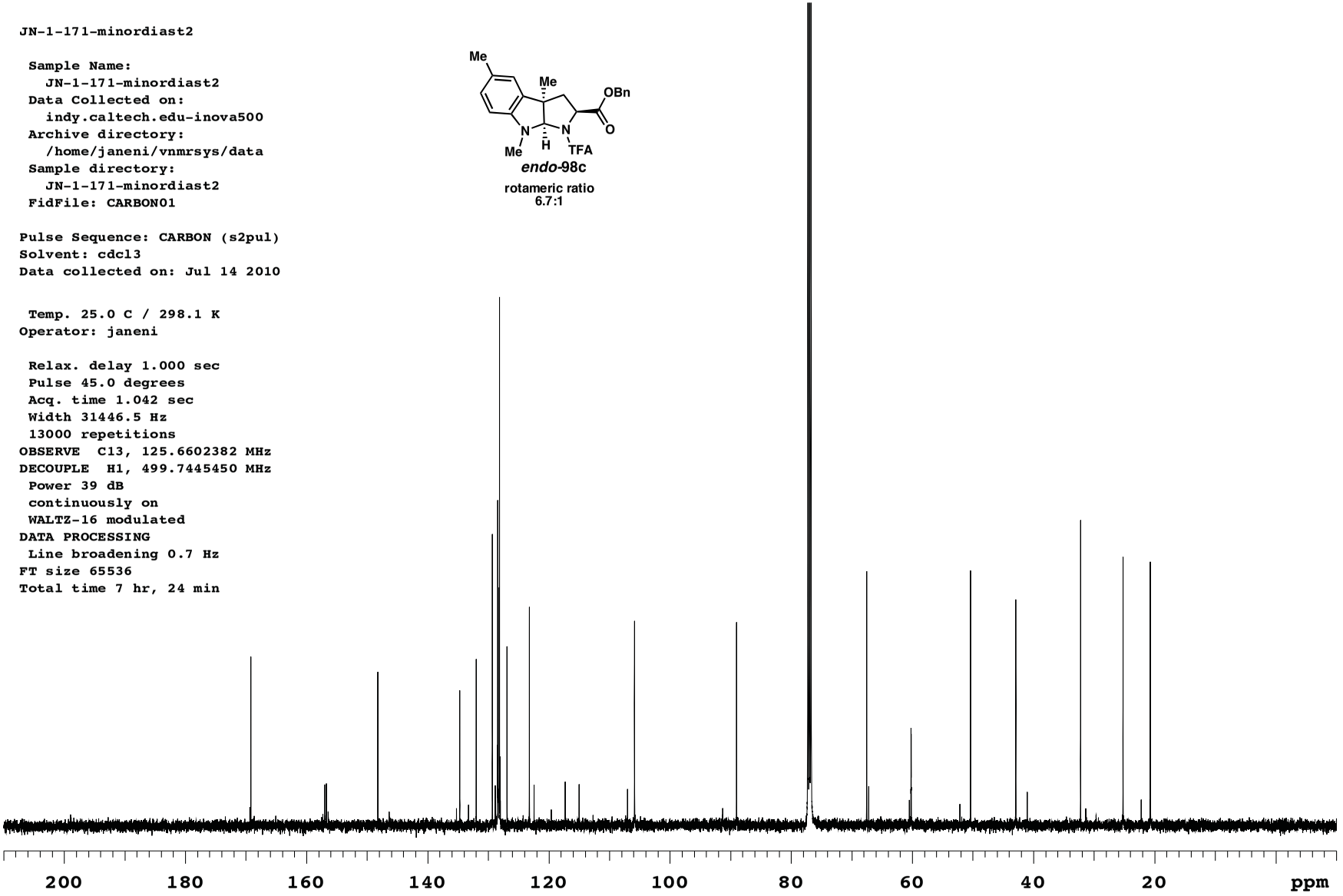
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
11000 repetitions
OBSERVE C13, 100.5283542 MHz
DECOUPLE H1, 399.7962875 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 6 hr, 58 min

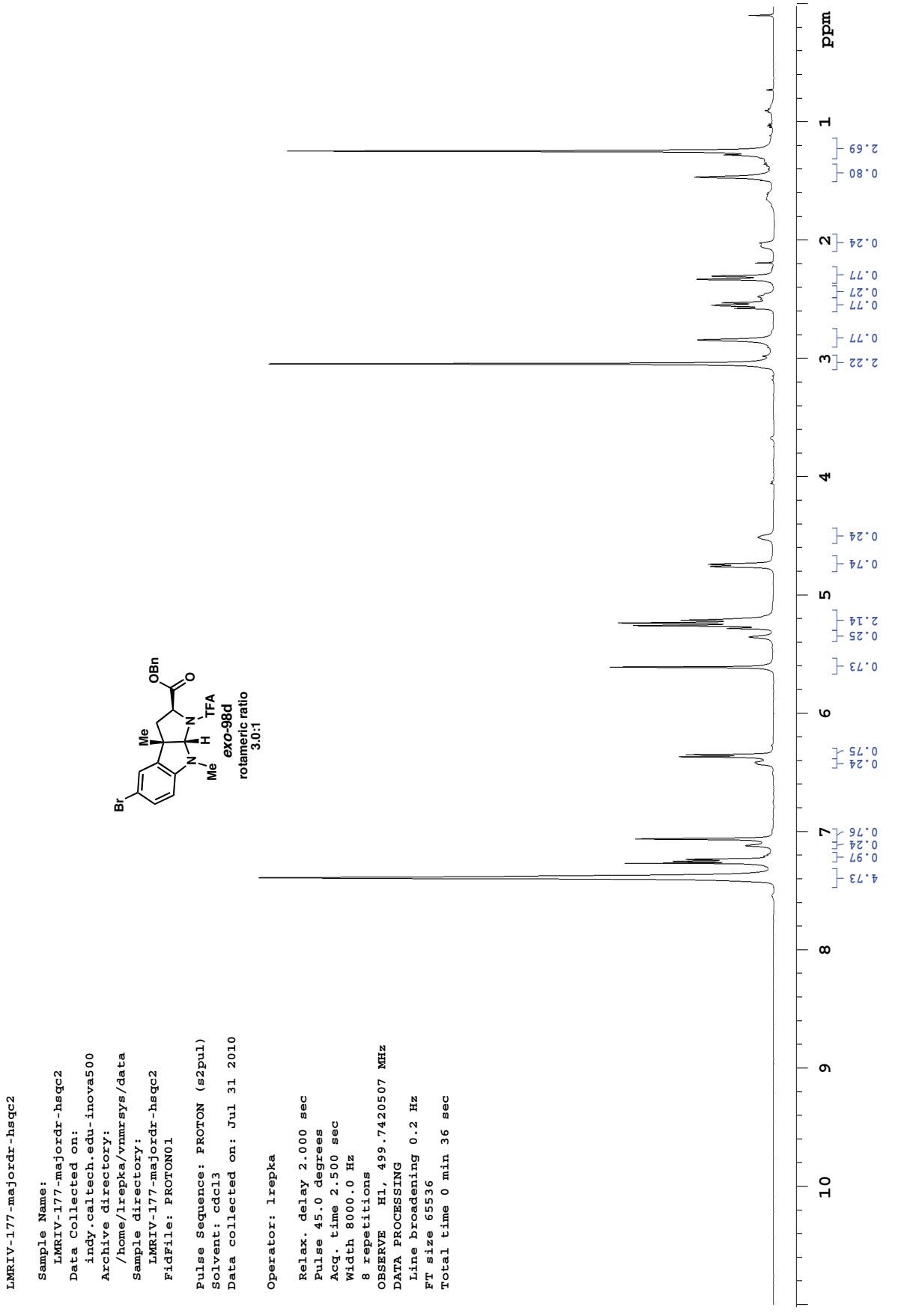


exo-98c

rotameric ratio
2.0:1


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
OBn
O
N
H
TFA
Me
Me
Me
N
endo-98c
rotameric ratio
6.7:1
ppm
10
9
8
7
6
5
4
3
2
1
3.13
3.14
1.04
0.41
0.95
2.64
0.88
0.88
0.87
0.12
0.13
0.14
0.16
0.87
0.87
0.13
1.06
1.05
1.88
0.35
3.03


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
Me
Me
OBn
N
H
N
O
Me
TFA
endo-98c
rotameric ratio
6.7:1
200
180
160
140
120
100
80
60
40
20
ppm


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
OBn
O
Me
N
H
TFA
N
Me
Br
exo-98d
rotameric ratio
3.0:1
ppm
10
9
8
7
6
5
4
3
2
1
2.69
0.80
0.24
0.77
0.27
0.77
0.77
2.22
0.24
0.74
2.14
0.25
0.73
0.75
0.24
0.76
0.24
0.97
4.73

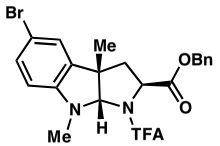
LMRIV-177-majordr-7-31-10

Sample Name:
LMRIV-177-majordr-7-31-10
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-177-majordr-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



exo-98d
rotameric ratio
3.0:1

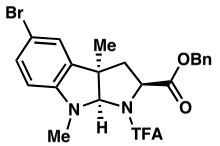
LMRIV-177-minordr-hsqc

Sample Name:
LMRIV-177-minordr-hsqc
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-177-minordr-hsqc
FidFile: PROTON01

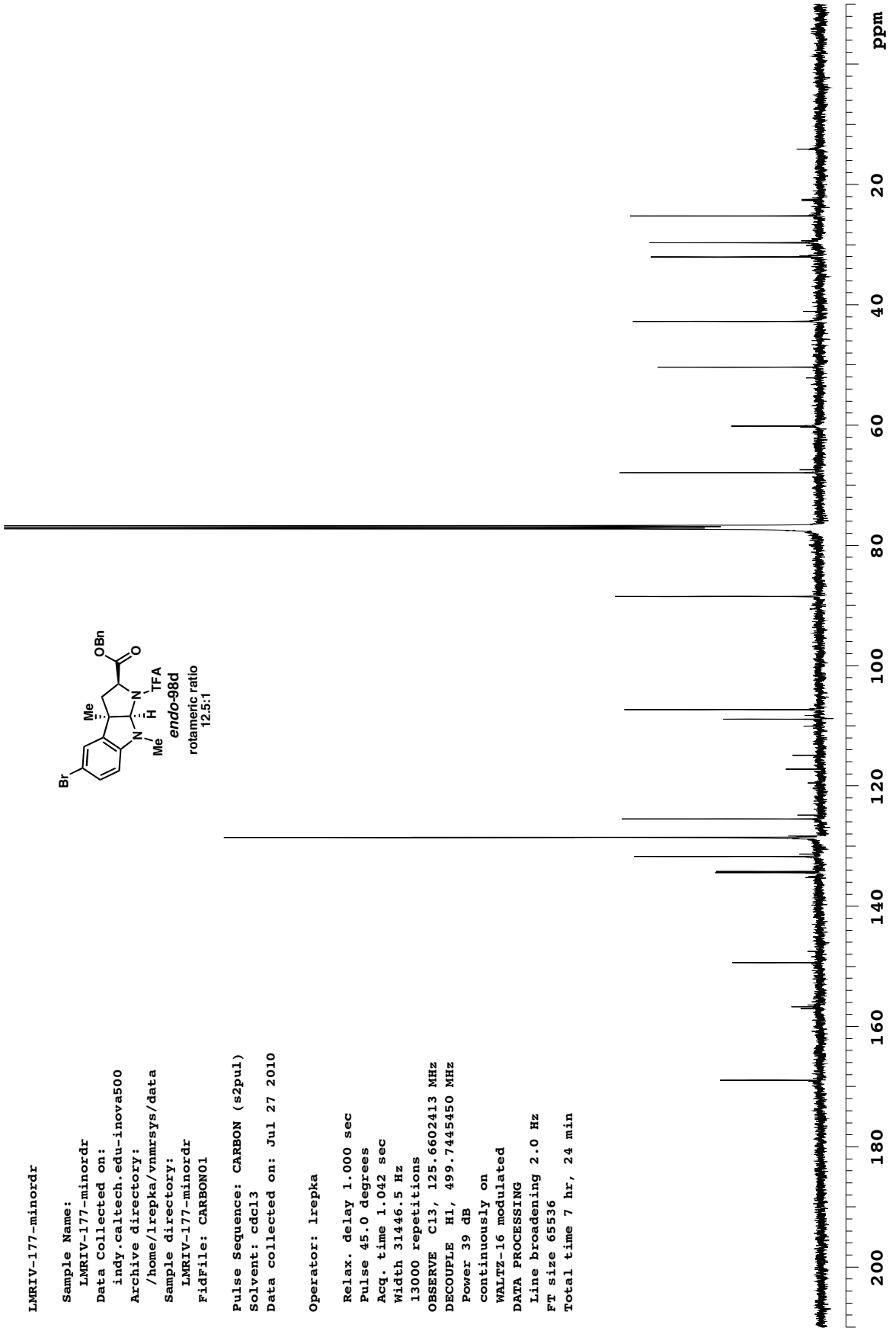
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 1 2010

Operator: lrepka

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



endo-98d
rotameric ratio
12.5:1


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
OBn
O
N
H
TFA
Me
Me
Br
endo-98d
rotameric ratio
12.5:1
200
180
160
140
120
100
80
60
40
20
ppm

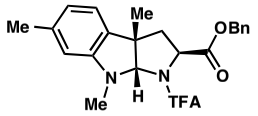
JN-1-215-majordiast2

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: PROTON01

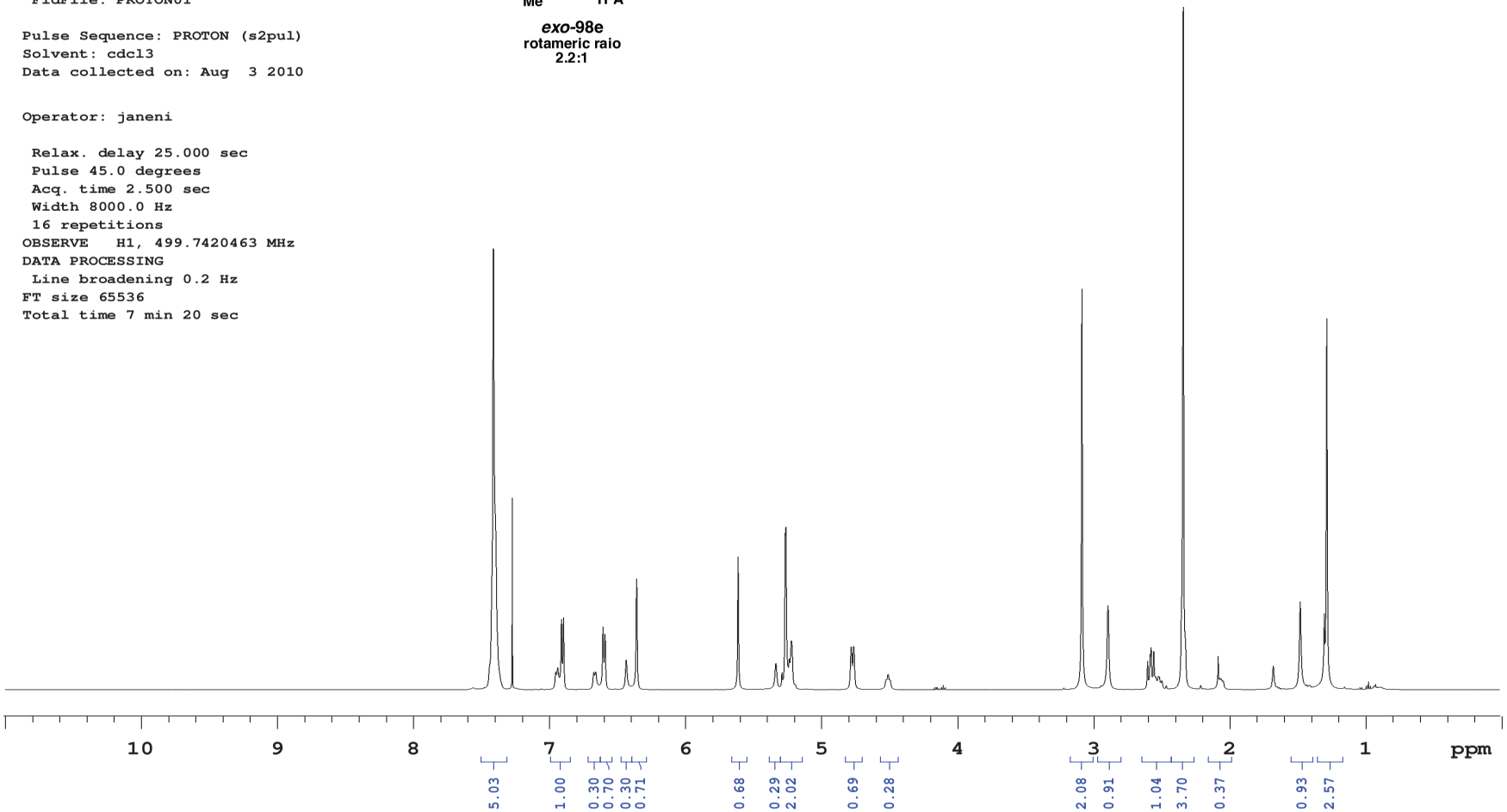
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 3 2010

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



***exo*-98e**
rotameric raio
2.2:1



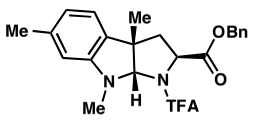
JN-1-215-majordiast2

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



exo-98e
rotameric raio
2.2:1

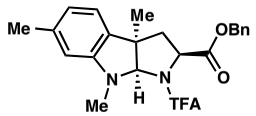
JN-1-215-minordiast2

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



endo-98e
rotameric ratio
9.0:1

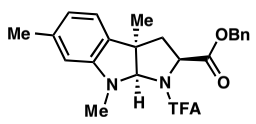
JN-1-215-minordiast2

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



endo-98e
rotameric ratio
9.0:1

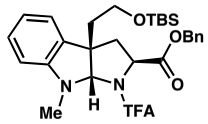
LMRIV-285-major-rd25

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



exo-98f
rotameric ratio
1.7:1

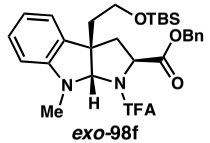
LMRIV-285-majordr-2-again

Sample Name:
LMRIV-285-majordr-2-again
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-285-majordr-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



exo-98f
rotameric ratio
1.7:1

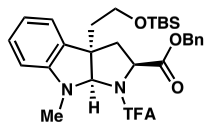
LMRIV-285-minor-rd25

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

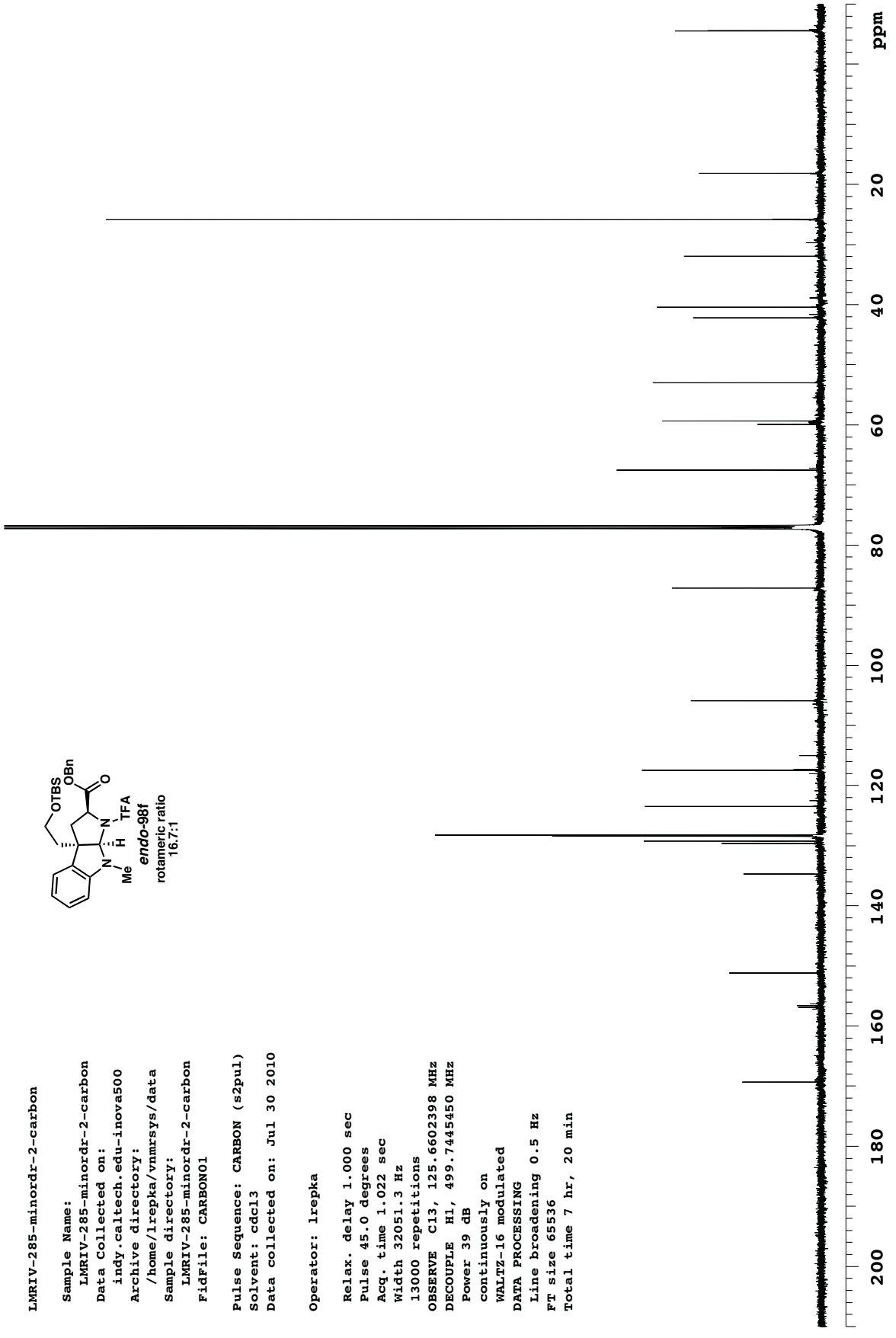
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 30 2010

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



endo-98f
rotameric ratio
16.7:1


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
OTBS
OBn
O
N
H
TFA
Me
endo-98f
rotameric ratio
16.7:1
200
180
160
140
120
100
80
60
40
20
ppm

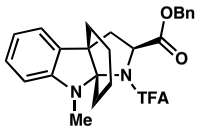
LMRIV-275-pentanewash

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

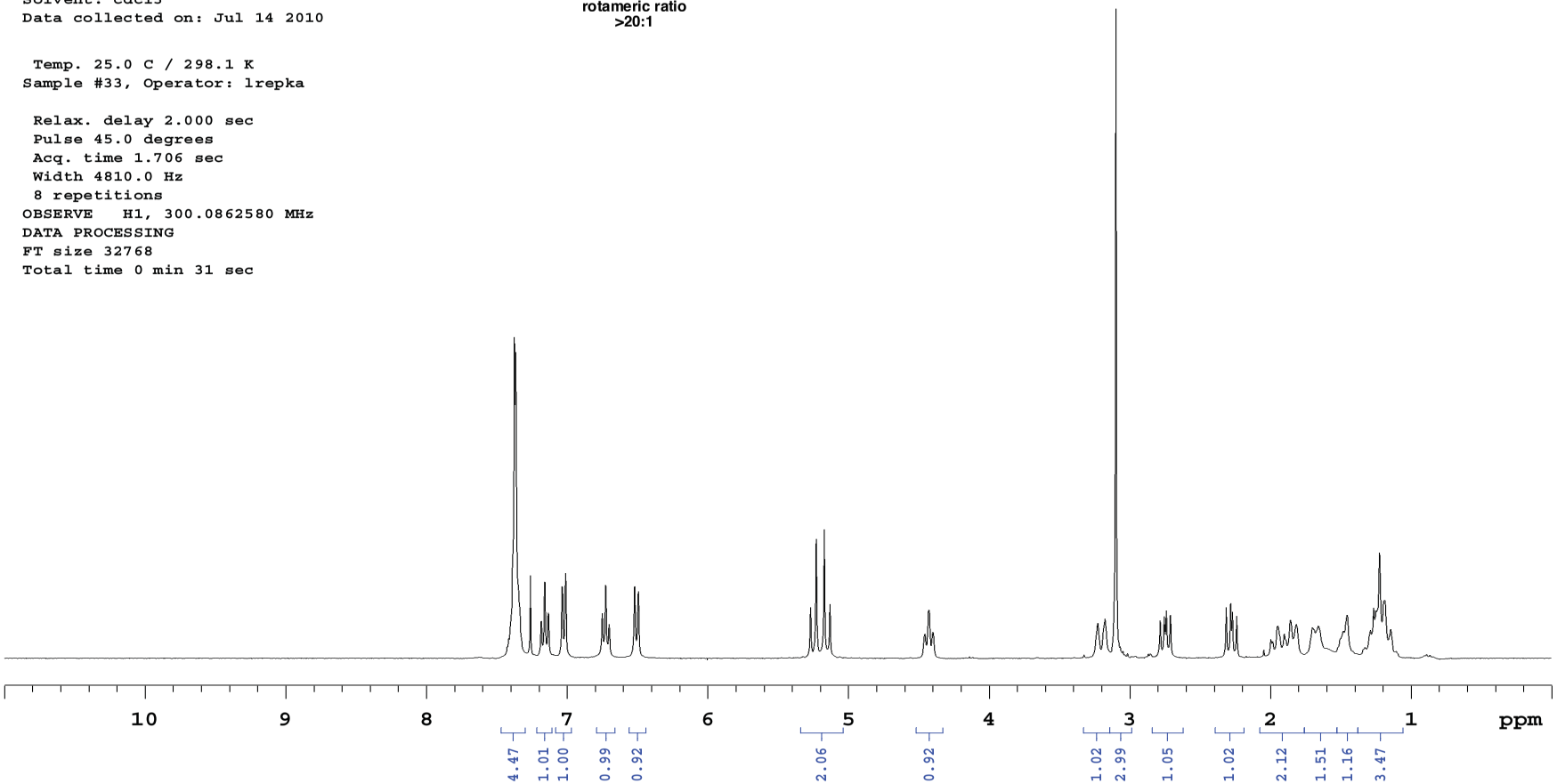
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 14 2010

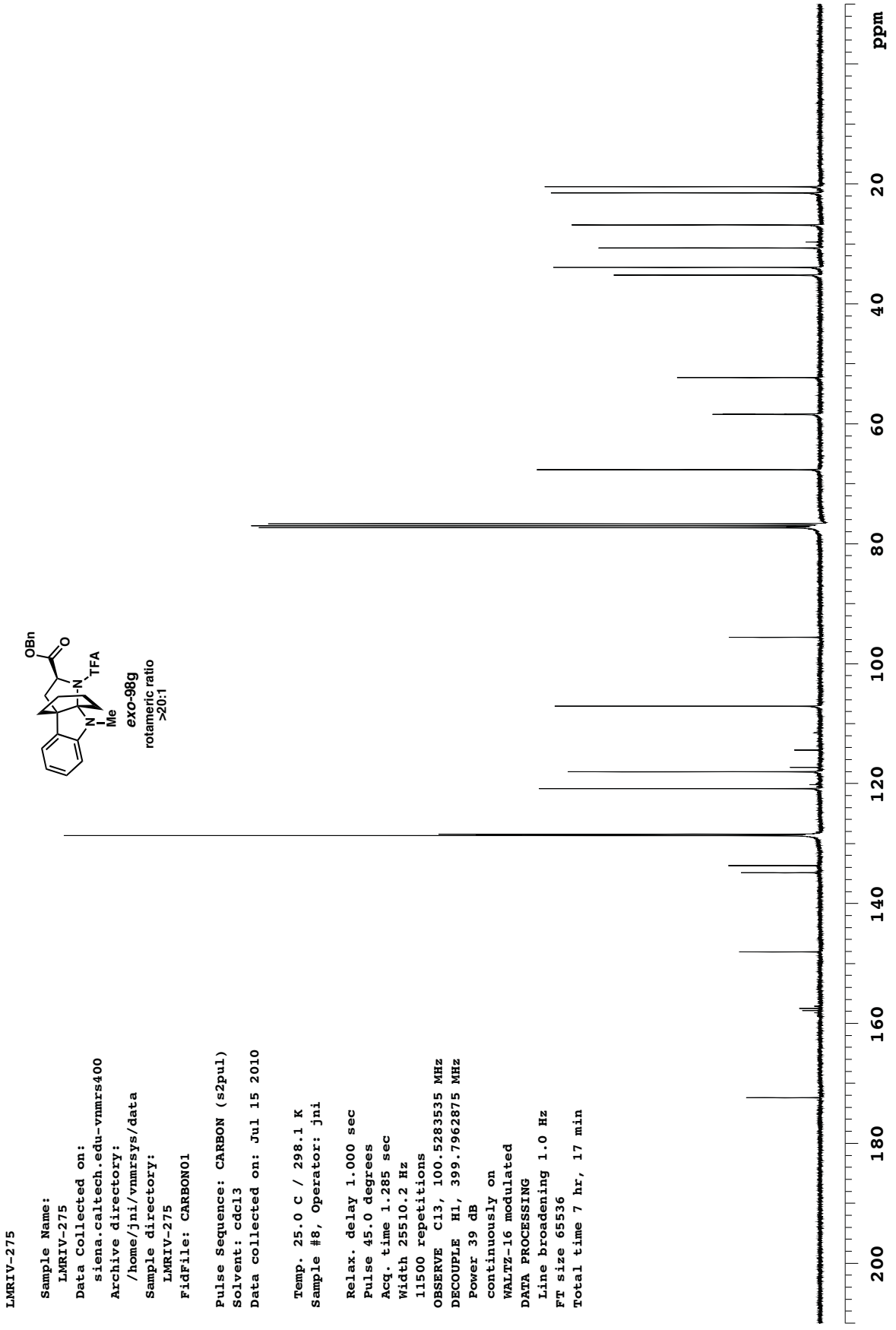
Temp. 25.0 C / 298.1 K
Sample #33, Operator: lrepka

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



exo-98g
rotameric ratio
>20:1




LMRIV-275
Sample Name:
LMRIV-275
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/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
OBn
O
N
TFA
N
Me
exo-98g
rotameric ratio
>20:1
200
180
160
140
120
100
80
60
40
20
ppm

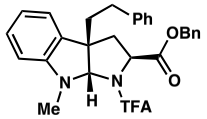
LMRIV-267-major diastereomer

Sample Name:
LMRIV-267-majordr
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRIV-267-majordr
FidFile: PROTON01

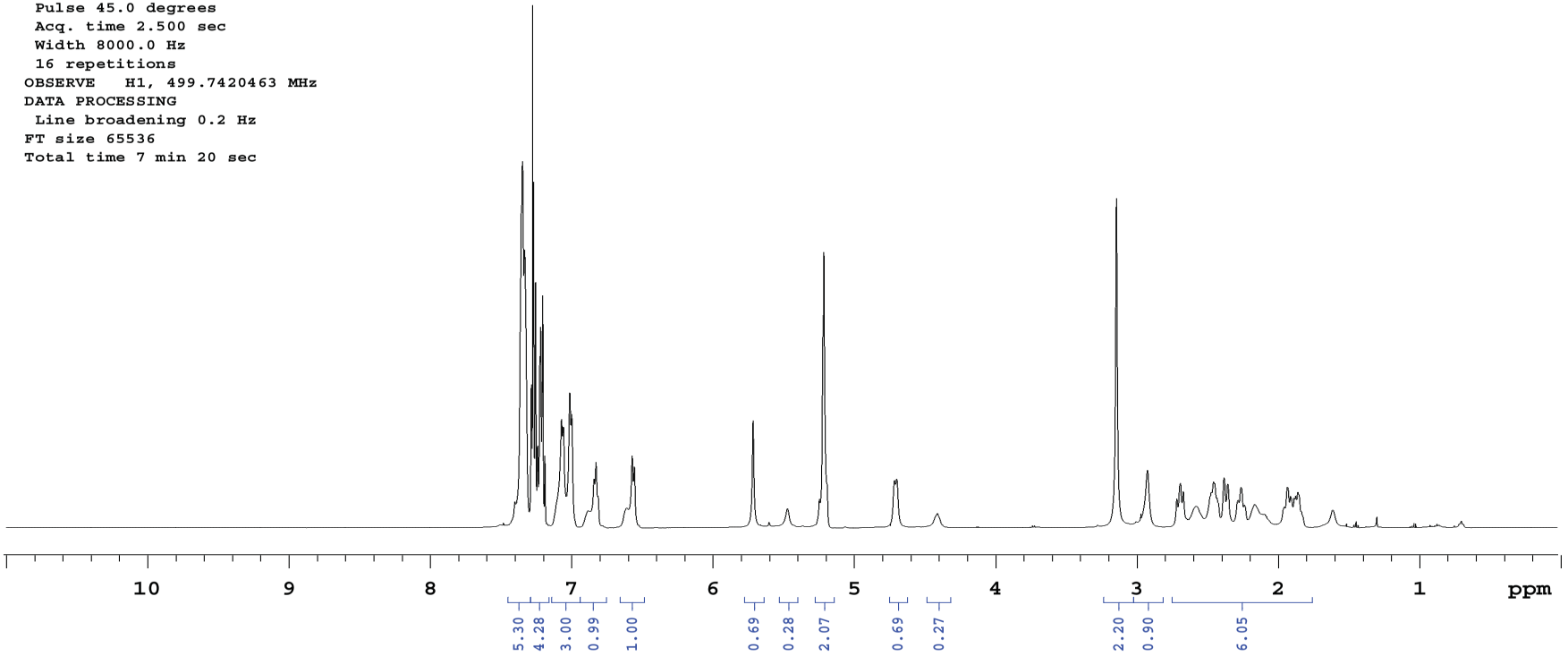
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 19 2010

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



exo-98h
rotameric ratio
2.6:1



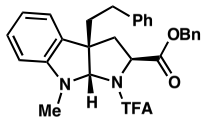
LMRIV-267-majorshigemi

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-98h
rotameric ratio
2.6:1

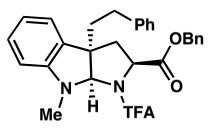
LMRIV-267-minor3

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



***endo*-98h**
rotameric ratio
14.5:1

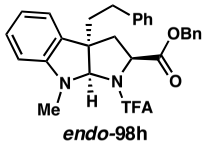
LMRIV-267-minor3

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_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



endo-98h
rotameric ratio
14.5:1

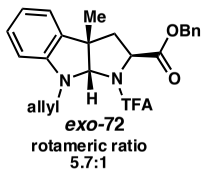
JN-1-211-majordiast

Sample Name:
JN-1-211-majordiast
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-1-211-majordiast
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
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



exo-72
rotameric ratio
5.7:1

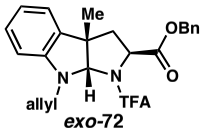
JN-1-211-majordiast

Sample Name:
JN-1-211-majordiast
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/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



exo-72
rotameric ratio
5.7:1

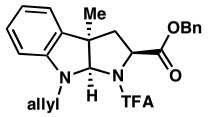
JN-1-211-minordiast

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: PROTON01

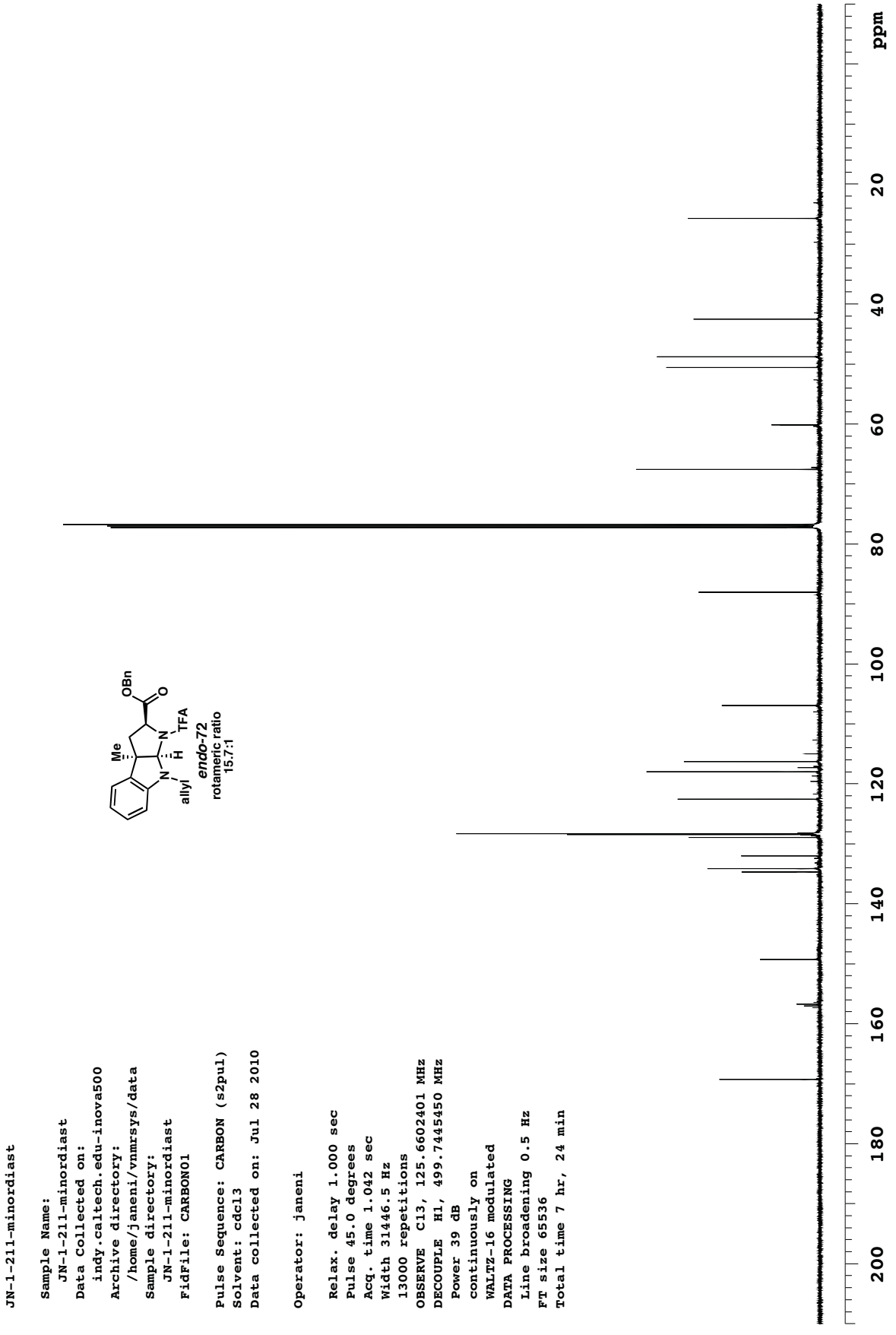
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 28 2010

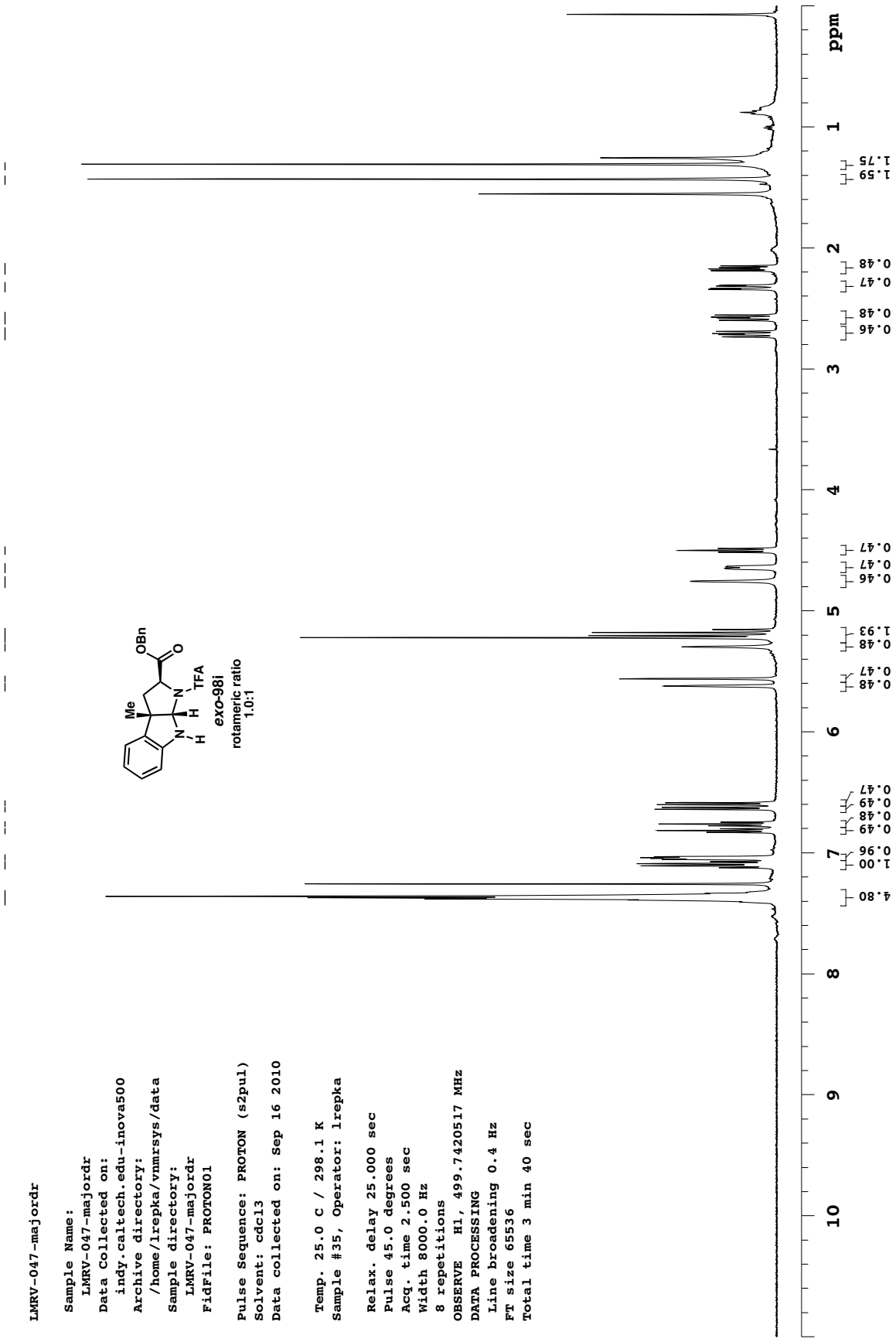
Operator: janeni

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-72
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
OBn
O
Me
N
TFA
H
allyl
endo-72
rotameric ratio
15.7:1
200
180
160
140
120
100
80
60
40
20
ppm


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: 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
OBn
O
Me
N
H
H
N
TFA
exo-98i
rotameric ratio
1.0:1
ppm
1 2 3 4 5 6 7 8 9 10
1.75
1.59
0.48
0.47
0.48
0.46
0.47
0.46
0.47
0.48
1.93
0.48
0.47
0.47
0.49
0.48
0.49
0.47
0.96
1.00
4.80

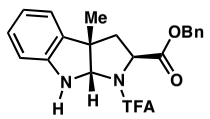
LMRV-047-majordr

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



exo-98i
rotameric ratio
1.0:1

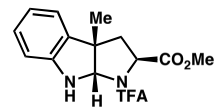
JN-3-101-carbon

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

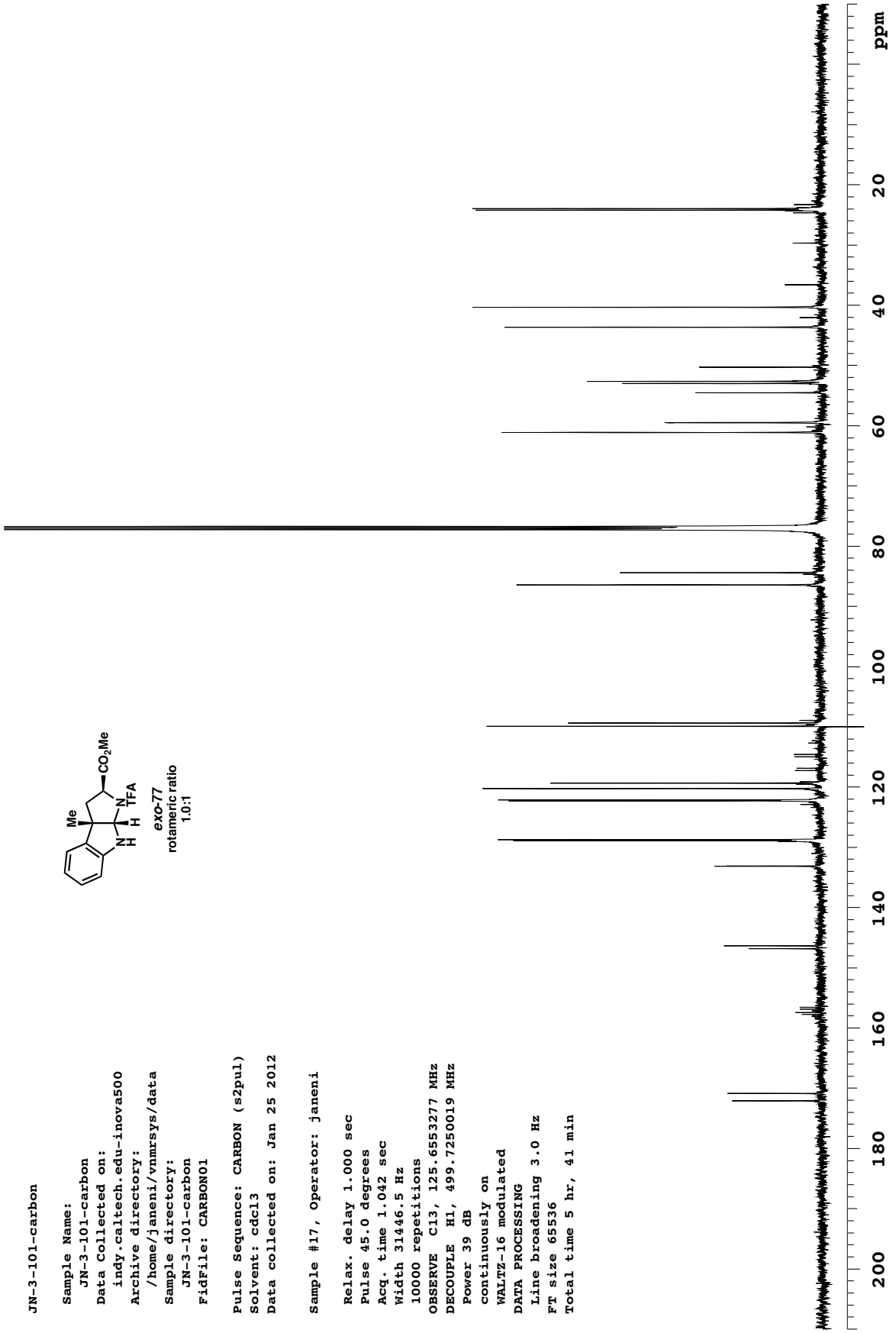
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 25 2012

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



exo-77
rotameric ratio
1.0:1

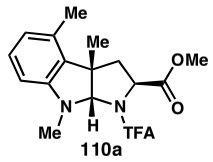

JN-3-101-carbon
Sample Name:
JN-3-101-carbon
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-3-101-carbon
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 25 2012
Sample #17, Operator: janeni
Relax. delay 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
Me
CO2Me
N
H
N
H
TFA
exo-77
rotameric ratio
1.0:1
200
180
160
140
120
100
80
60
40
20
ppm

WHX-3-99-Rep-F2-Jan_22_INDY_CDCL3

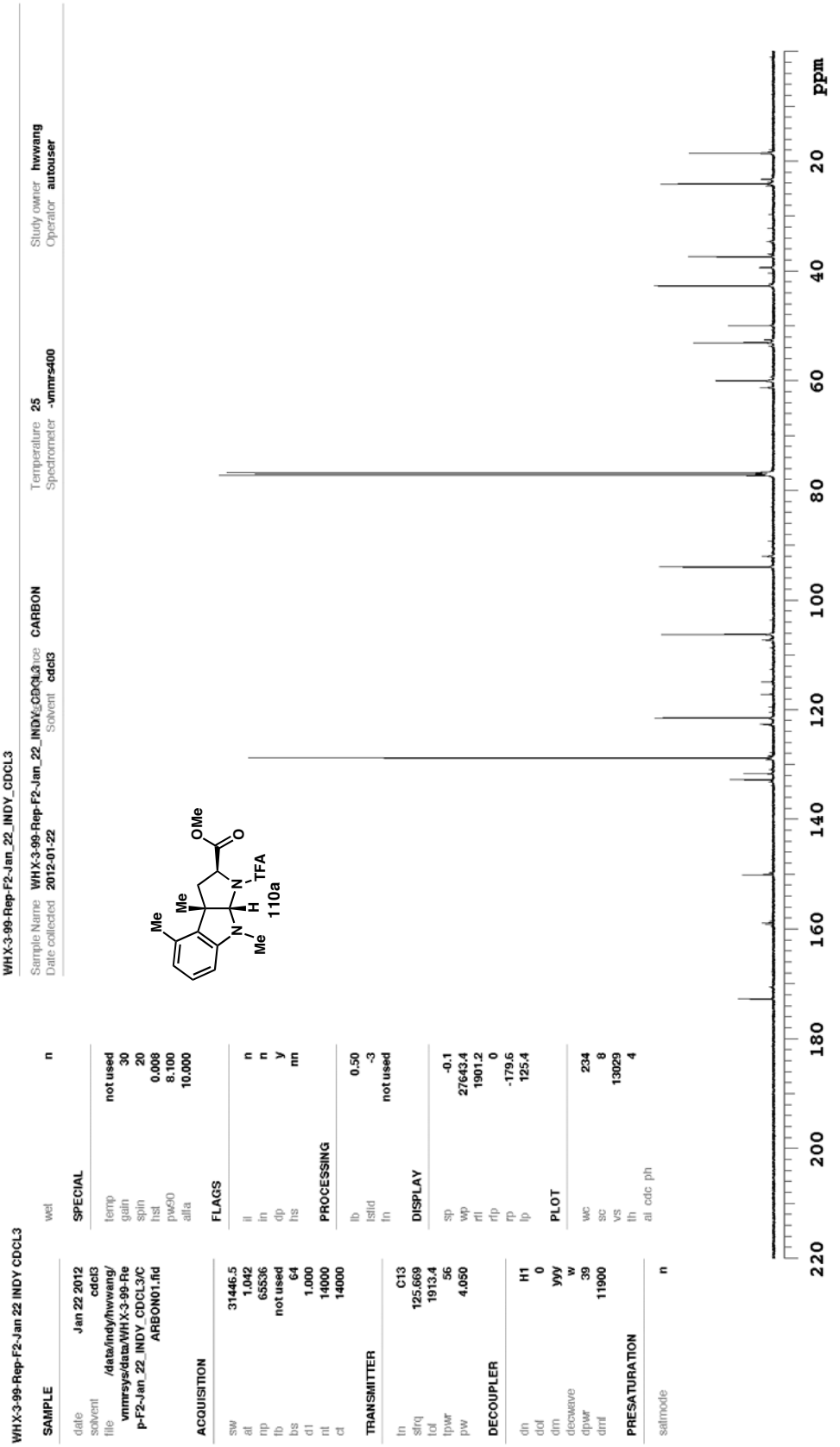
SAMPLE	
date	Jan 22 2012
solvent	cdcl3
file	/data/indy/hwwang/vnmrsys/data/WHX-3-99-Rep-F2-Jan_22_INDY_CDCL3/PROTON01.fid
ACQUISITION	
sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	5.000
nt	16
ct	16
TRANSMITTER	
tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850
DECOUPLER	
dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258
PRESATURATION	
satmode	n
wet	n
SPECIAL	
temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600
FLAGS	
il	n
in	n
dp	y
hs	nn
PROCESSING	
lb	0.20
fn	not used
DISPLAY	
sp	-250.0
wp	5496.8
rfl	1048.3
rfp	0
rp	179.6
lp	-20.2
PLOT	
wc	234
sc	8
vs	157
th	3
al ph	

WHX-3-99-Rep-F2-Jan_22_INDY_CDCL3

Sample Name WHX-3-99-Rep-F2-Jan_22_INDY_CDCL3 Experiment PROTON Temperature 25 Study owner hwwang
Date collected 2012-01-22 Solvent cdcl3 Spectrometer -vnmrs400 Operator autouser



110a


WHX-3-99-Rep-F2-Jan 22 INDY CDCL3
SAMPLE
wet n
date Jan 22 2012
solvent cdcl3
file /data/indy/hwwang/
vnmrsys/data/WHX-3-99-Re
p-F2-Jan_22_INDY_CDCL3/C
ARBON01.fid
ACQUISITION
sw 31446.5
at 1.042
np 65536
fb not used
bs 64
d1 1.000
nt 14000
ct 14000
TRANSMITTER
tn C13
sfrq 125.669
tof 1913.4
tpwr 56
pw 4.050
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 39
dmf 11900
PRESATURATION
satmode n
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
lstld -3
fn not used
DISPLAY
sp -0.1
wp 27643.4
rfl 1901.2
rfp 0
rp -179.6
lp 125.4
PLOT
wc 234
sc 8
vs 13029
th 4
al cdc ph
WHX-3-99-Rep-F2-Jan_22_INDY_CDCL3
Sample Name WHX-3-99-Rep-F2-Jan_22_INDY_CDCL3
Date collected 2012-01-22
Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner hwwang
Operator autouser
Me
Me
OMe
O
N
H
N
TFA
Me
110a
220 200 180 160 140 120 100 80 60 40 20 ppm

WHX-3-101-Rep-F2_INDY_CDCL3

SAMPLE

date	Jan 9 2012
solvent	cdcl3
file	/data/Indy/hwwang/vnmrsys/data/WHX-3-101-Rep-F2_INDY_CDCL3/PROTON02.fid

ACQUISITION

sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	5.000
nt	32
ct	32

TRANSMITTER

tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

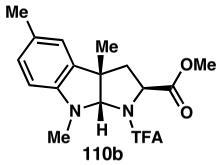
sp	-250.0
wp	5496.8
rfl	1001.7
rfp	0
rp	169.4
lp	-1.4

PLOT

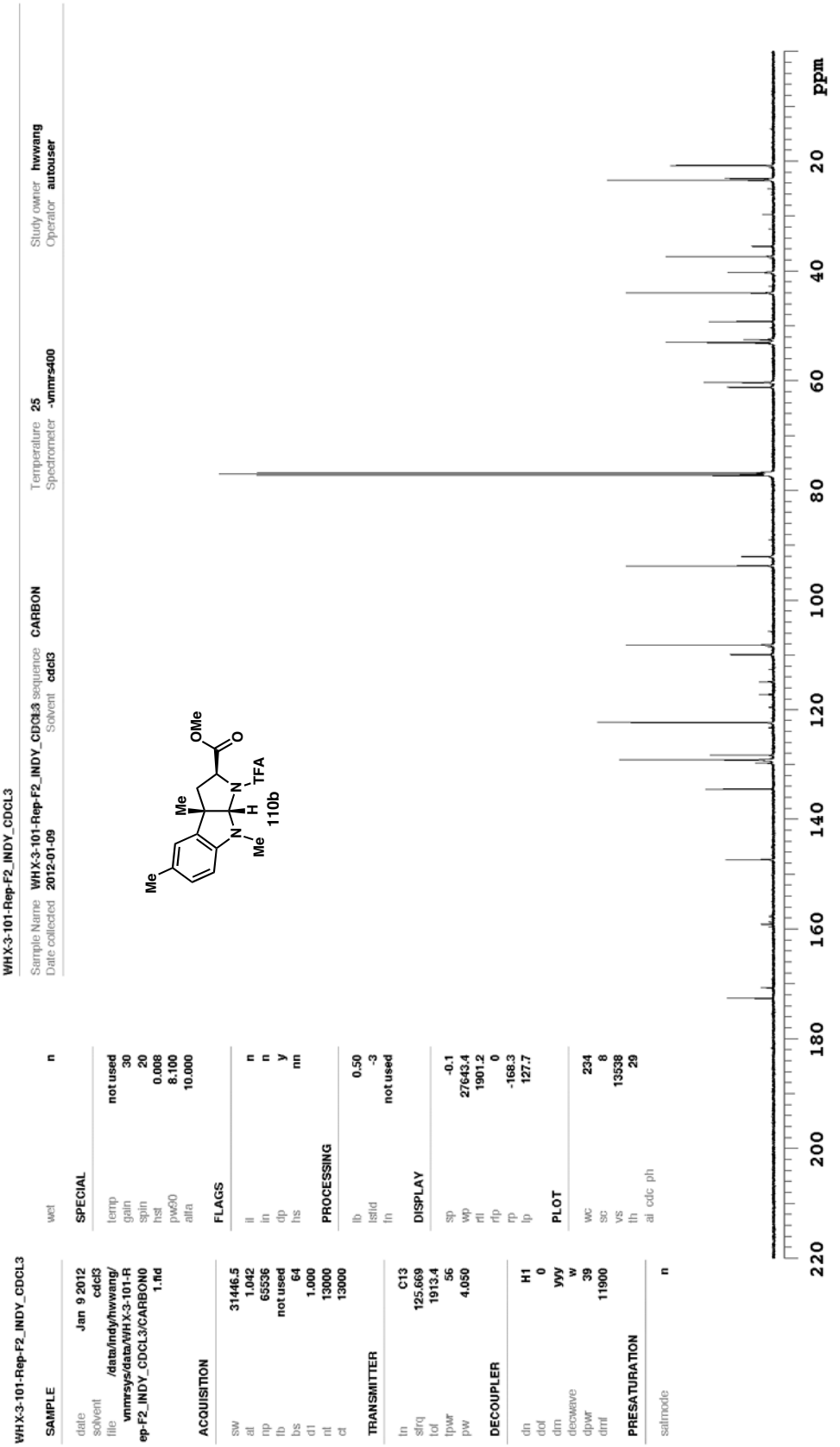
wc	234
sc	8
vs	128
th	54
ai ph	

WHX-3-101-Rep-F2_INDY_CDCL3

Sample Name WHX-3-101-Rep-F2_INDY_CDCL3 sequence PROTON Temperature 25 Study owner hwwang
Date collected 2012-01-09 Solvent cdcl3 Spectrometer -vnmrs400 Operator autouser



110b


WHX-3-101-Rep-F2_INDY_CDCL3
WHX-3-101-Rep-F2_INDY_CDCL3
Sample Name WHX-3-101-Rep-F2_INDY_CDCL3 sequence CARBON
Date collected 2012-01-09 Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner hwwang
Operator autouser
SAMPLE
date Jan 9 2012
solvent cdcl3
file /data/indy/hwwang/vnmrsys/data/WHX-3-101-Rep-F2_INDY_CDCL3/CARBON0 1.fid
ACQUISITION
sw 31446.5
at 1.042
np 65536
fb not used
bs 64
d1 1.000
nt 13000
ct 13000
TRANSMITTER
tn C13
sfrq 125.669
tof 1913.4
tpwr 56
pw 4.050
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dmf 11900
PRESATURATION
satmode n
wet n
SPECIAL
temp
gain not used
spin 30
hst 20
pw90 0.008
alfa 8.100
10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
lsfid -3
fn not used
DISPLAY
sp -0.1
wp 27643.4
rfl 1901.2
rfp 0
rp -168.3
lp 127.7
PLOT
wc 234
sc 8
vs 13538
th 29
ai cdc ph
Me
Me
OMe
O
N
H
TFA
Me
110b
220 200 180 160 140 120 100 80 60 40 20 ppm

WHX-3-102-Rep-F2_INDY_CDCL3

SAMPLE

date	Jan 10 2012
solvent	cdcl3
file	/data/indy/hwwang/vnmrsys/data/WHX-3-102-Rep-F2_INDY_CDCL3/PROTON02.fid

ACQUISITION

sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	5.000
nt	32
ct	32

TRANSMITTER

tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

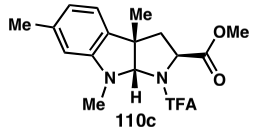
sp	-250.0
wp	5496.8
rfl	1001.7
rfp	0
rp	164.3
lp	11.7

PLOT

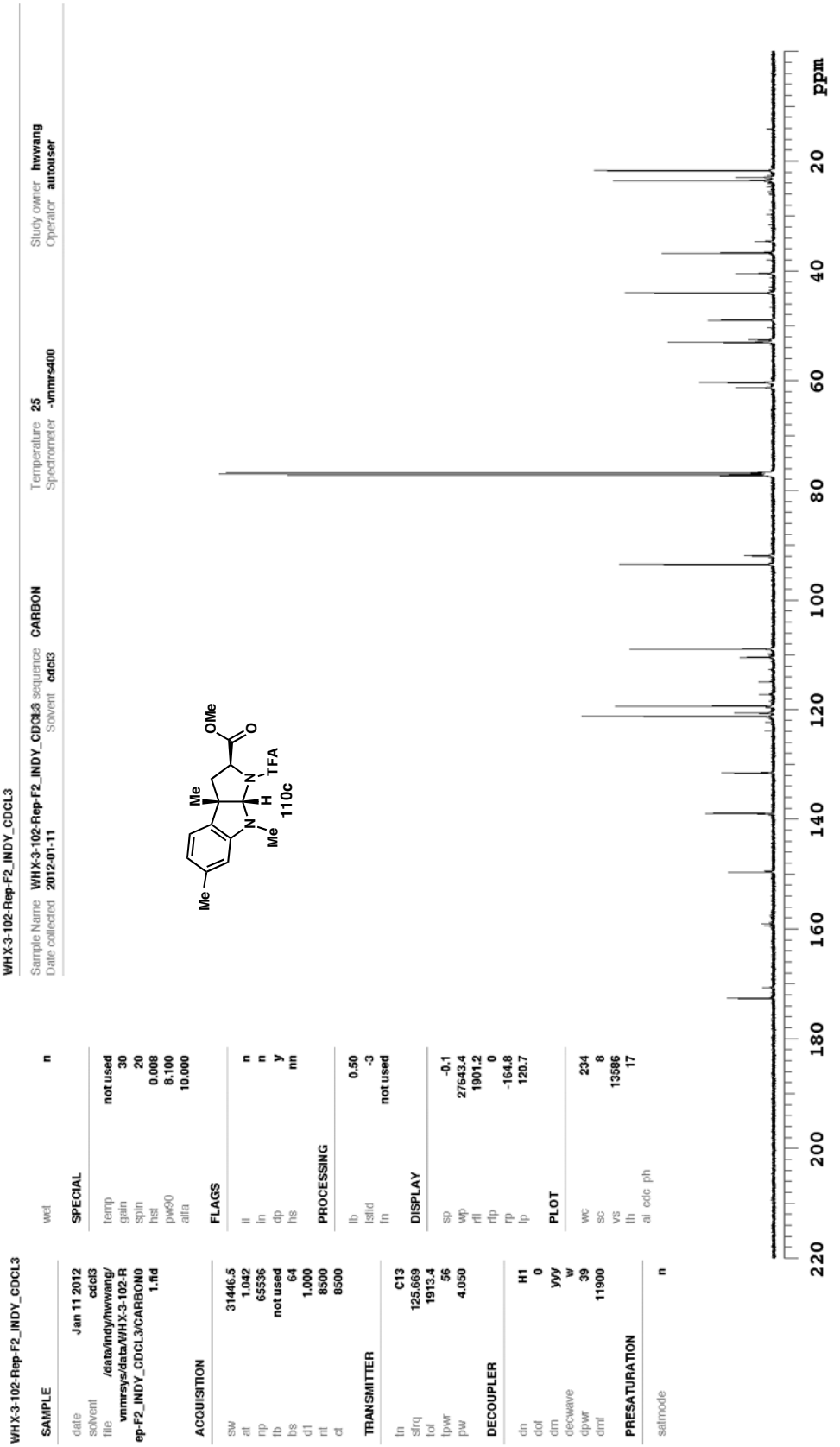
wc	234
sc	8
vs	88
th	54
ai ph	

WHX-3-102-Rep-F2_INDY_CDCL3

Sample Name WHX-3-102-Rep-F2_INDY_CDCL3 sequence PROTON Temperature 25 Study owner hwwang
Date collected 2012-01-10 Solvent cdcl3 Spectrometer -vnmrs400 Operator autouser



110c



WHX-3-102-Rep-F2_INDY_CDCL3

SAMPLE		wet	n
date	Jan 11 2012	**SPECIAL**	
solvent	cdcl3		
file	/data/indy/hwwang/	temp	not used
	vnmrsys/data/WHX-3-102-R	gain	30
	ep-F2_INDY_CDCL3/CARBON0	spin	20
	1.fid	hst	0.008
		pw90	8.100
		alfa	10.000
ACQUISITION		**FLAGS**	
sw	31446.5	il	n
at	1.042	in	n
np	65536	dp	y
tb	not used	hs	nn
bs	64		
d1	1.000	**PROCESSING**	
nt	8500		
ct	8500	lb	0.50
		lsfid	-3
TRANSMITTER		fn	not used
tn	C13		
sfrq	125.669	**DISPLAY**	
tof	1913.4		
tpwr	56	sp	-0.1
pw	4.050	wp	27643.4
		rfl	1901.2
DECOUPLER		rfp	0
dn	H1	rp	-164.8
dof	0	lp	120.7
dm	yyy	**PLOT**	
decwave	w		
dpwr	39	wc	234
dmf	11900	sc	8
		vs	13586
PRESATURATION		th	17
		al cdc ph	
satmode	n		

JN-3-063b-colmaj

SAMPLE

date	Nov 1 2011
solvent	cdcl3
file	/data/indy/janeni/ vnmrsys/data/JN-3-063b-c olmaj/PROTON01.fid

ACQUISITION

sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	5.000
nt	16
ct	16

TRANSMITTER

tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

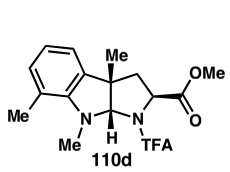
sp	-0.2
wp	5496.8
rfl	1001.7
rfp	0
rp	-177.7
lp	-24.8

PLOT

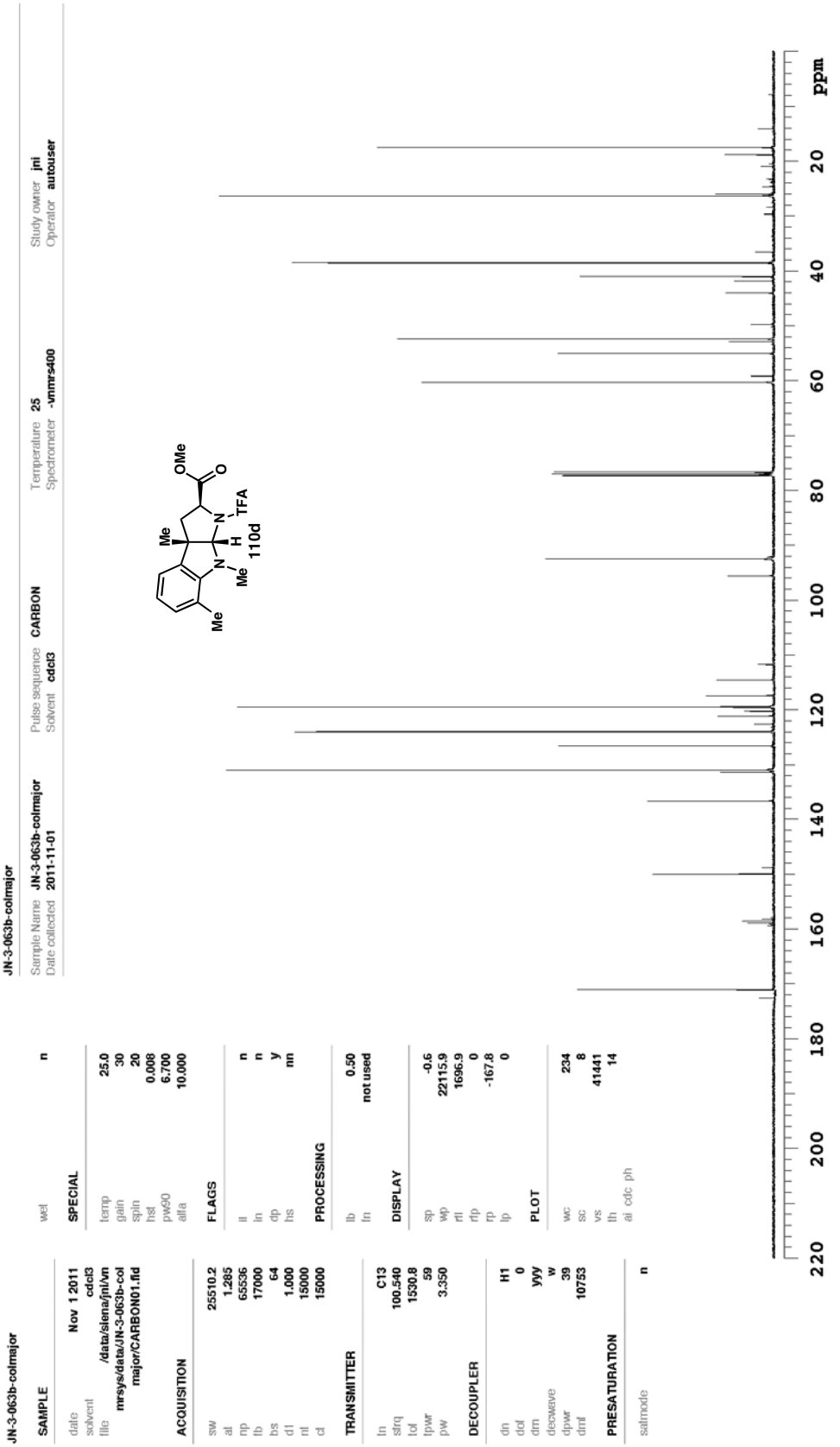
wc	234
sc	8
vs	29
th	54
ai ph	

JN-3-063b-colmaj

Sample Name JN-3-063b-colmaj | Pulse sequence PROTON | Temperature 25 | Study owner janeni
Date collected 2011-11-01 | Solvent cdcl3 | Spectrometer -vnmrs400 | Operator autouser



110d



JN-3-063b-colmajor

SAMPLE		wet	n
date	Nov 1 2011	**SPECIAL**	
solvent	cdcl3		
file	/data/siena/jni/vn mrsys/data/JN-3-063b-col major/CARBON01.fid	temp	25.0
		gain	30
		spin	20
		hst	0.008
ACQUISITION		pw90	6.700
		alfa	10.000
sw	25510.2	**FLAGS**	
at	1.285		
np	65536	il	n
fb	17000	in	n
bs	64	dp	y
d1	1.000	hs	nn
nt	15000		
ct	15000	**PROCESSING**	
TRANSMITTER		lb	0.50
		fn	not used
tn	C13		
sfrq	100.540	**DISPLAY**	
tof	1530.8		
tpwr	59	sp	-0.6
pw	3.350	wp	22115.9
DECOUPLER		rfl	1696.9
		rfp	0
dn	H1	rp	-167.8
dof	0	lp	0
dm	yyy	**PLOT**	
dmm	w		
dmf	39	wc	234
	10753	sc	8
		vs	41441
PRESATURATION		th	14
		ai	cdc ph
satmode	n		

WHX-3-80-F2-Rep-F2_INDY_CDCL3

SAMPLE

date	Oct 28 2011
solvent	cdcl3
file	/data/indy/hwwang/ vnmrsys/data/WHX-3-80-F2 -Rep-F2_INDY_CDCL3/PROTO N01.fid

ACQUISITION

sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	5.000
nt	16
ct	16

TRANSMITTER

tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

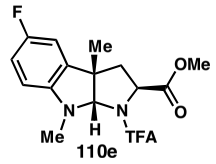
sp	-250.0
wp	5496.8
rfl	1001.7
rfp	0
rp	168.6
lp	11.3

PLOT

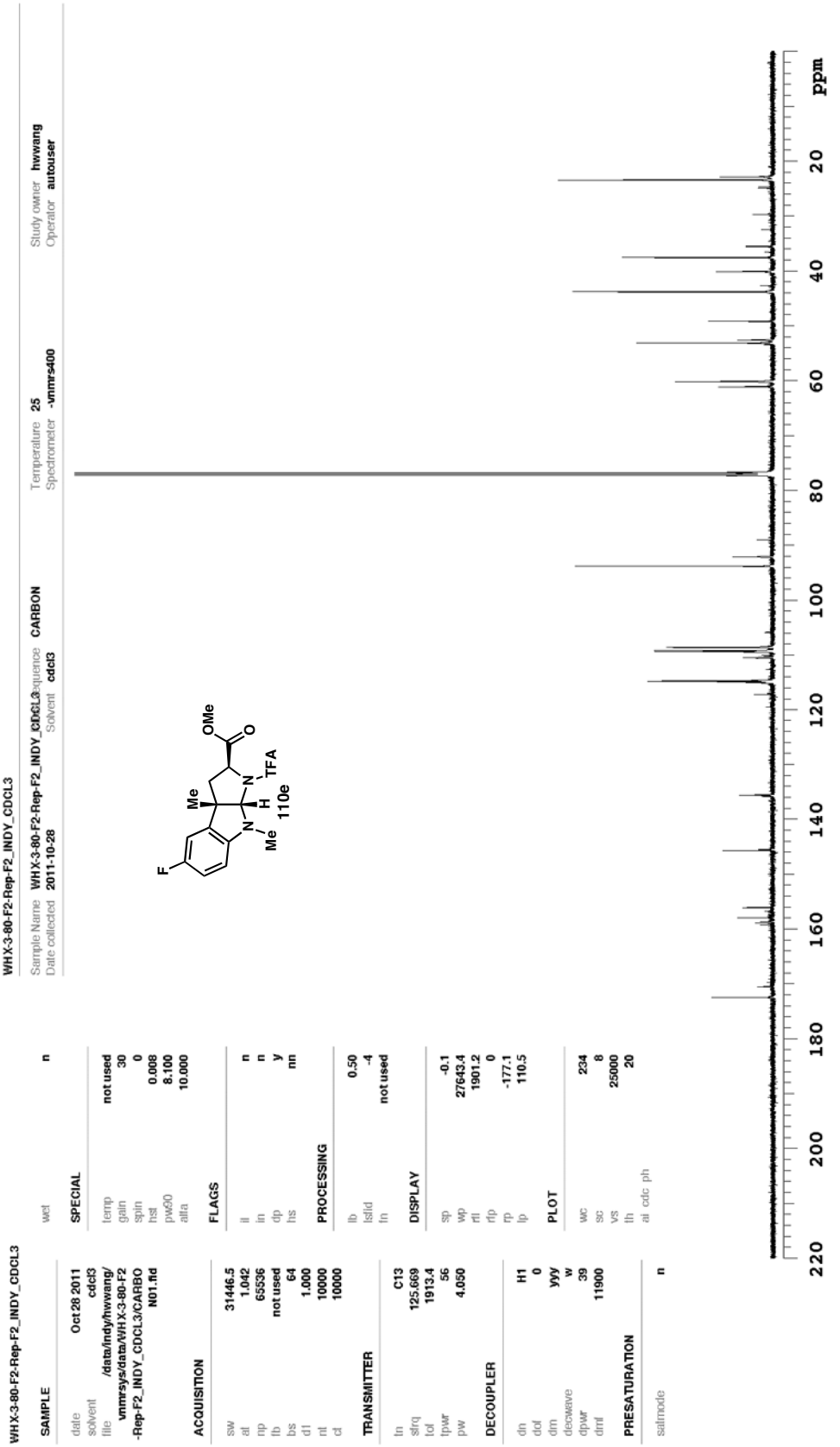
wc	234
sc	8
vs	142
th	54
ai ph	

WHX-3-80-F2-Rep-F2_INDY_CDCL3

Sample Name WHX-3-80-F2-Rep-F2_INDY_CDCL3 Sequence PROTON Temperature 25 Study owner hwwang
Date collected 2011-10-28 Solvent cdcl3 Spectrometer -vnmrs400 Operator autouser

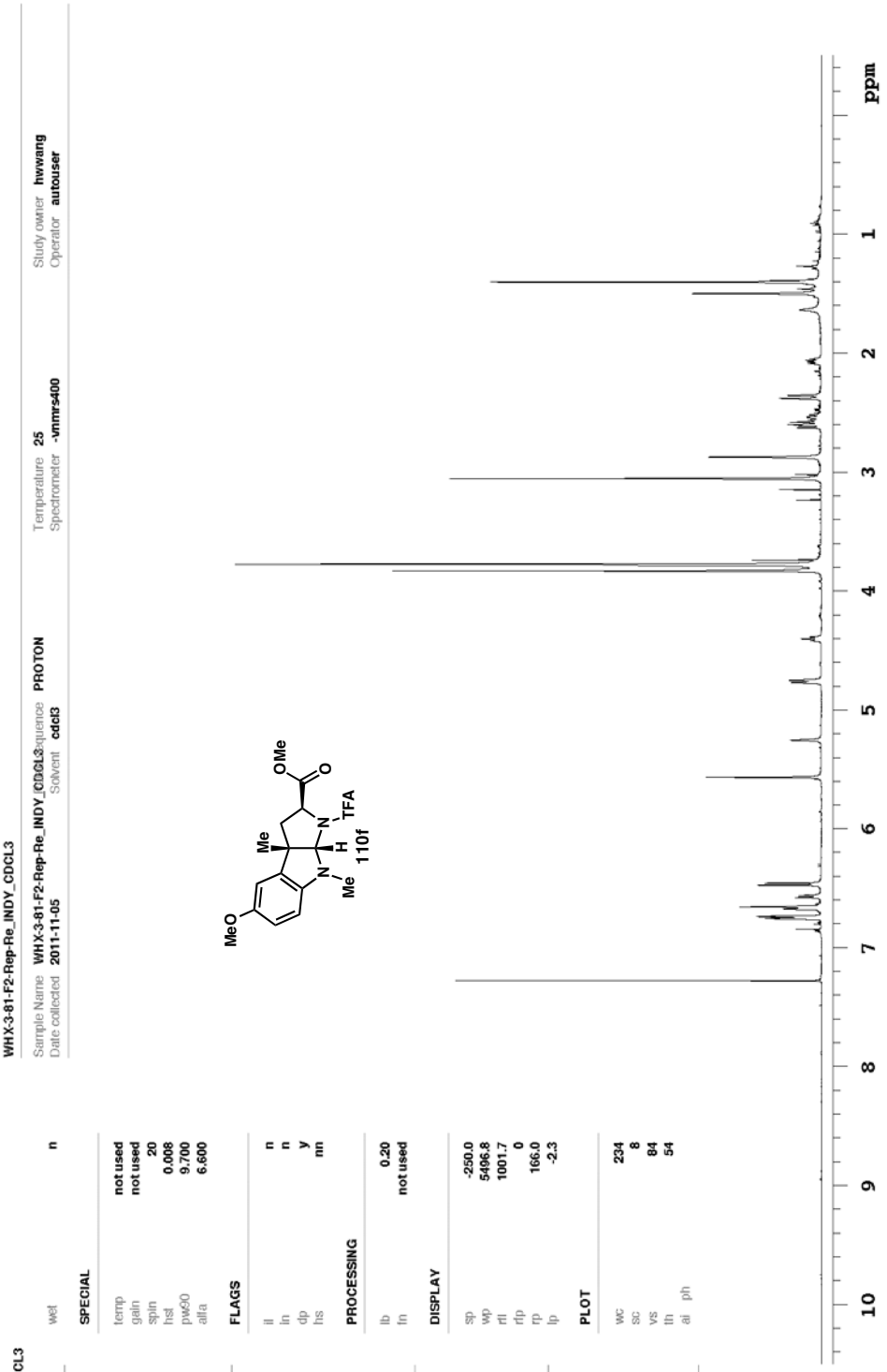


110e



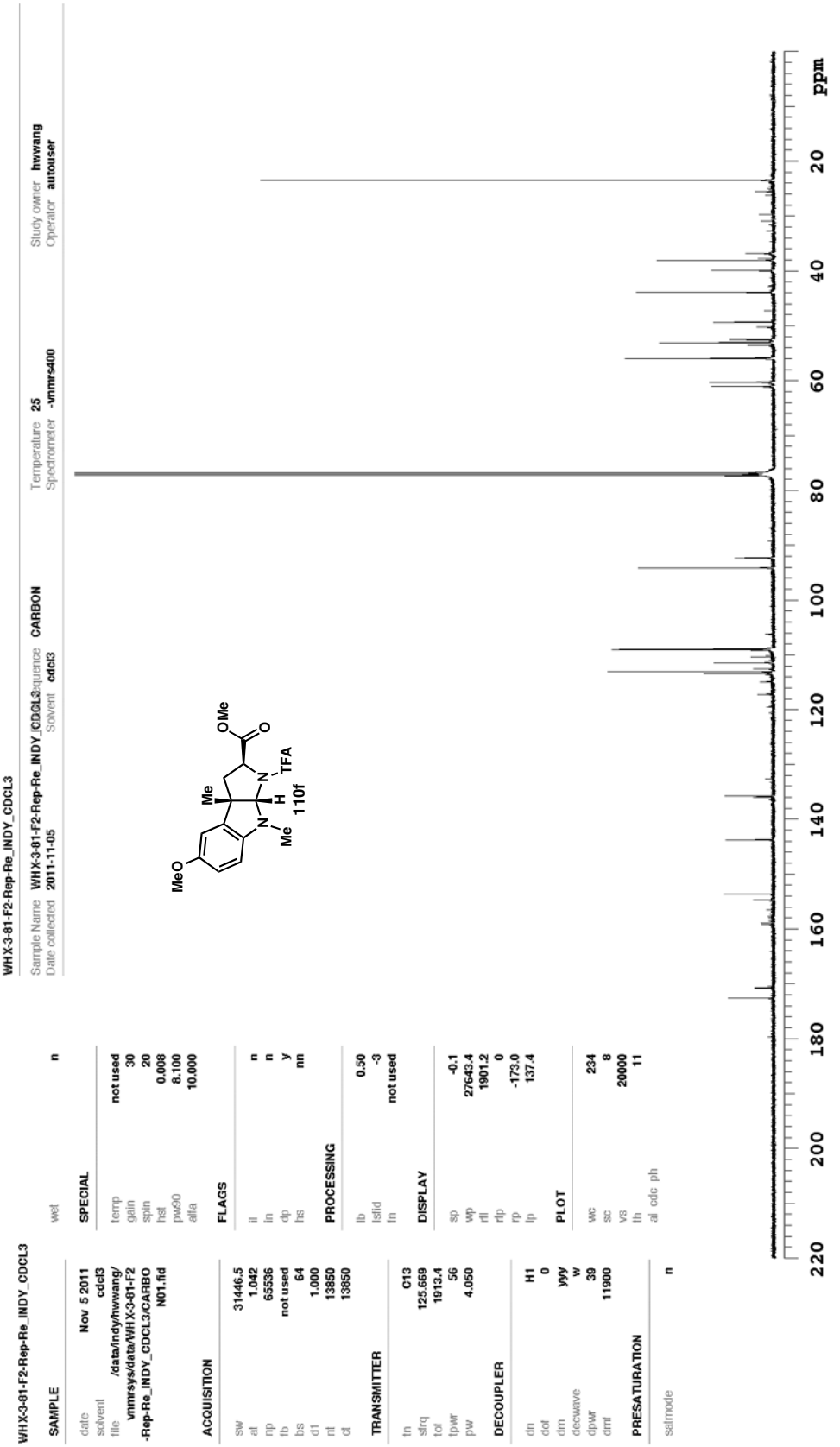
WHX-3-80-F2-Rep-F2_INDY_CDCL3

SAMPLE		wet	n		
date	Oct 20 2011	**SPECIAL**			
solvent	cdcl3				
file	/data/indy/hwwang/	temp	not used		
	vnmrsys/data/VHX-3-80-F2	gain	30		
	-Rep-F2_INDY_CDCL3/CARBO	spin	0		
	N01.fid	hst	0.008		
		pw90	8.100		
ACQUISITION		alfa	10.000		
sw	31446.5	**FLAGS**			
at	1.042	il	n		
np	65536	in	n		
fb	not used	dp	y		
bs	64	hs	nn		
d1	1.000				
nt	10000	**PROCESSING**			
ct	10000				
		lb	0.50		
TRANSMITTER		lsfid	-4		
		fn	not used		
tn	C13				
sfrq	125.669	**DISPLAY**			
tof	1913.4				
tpwr	56	sp	-0.1		
pw	4.050	wp	27643.4		
		rfl	1901.2		
DECOUPLER		rfp	0		
		rp	-177.1		
dn	H1	lp	110.5		
dof	0				
dm	yyy	**PLOT**			
decmode	w				
dpwr	39	wc	234		
dmf	11900	sc	8		
		vs	25000		
PRESATURATION		th	20		
		ai	cdc	ph	
satmode	n				



WHX-3-81-F2-Rep-Re_INDY_CDCL3

SAMPLE		wet	n
date	Nov 5 2011	SPECIAL	
solvent	cdcl3		
file	/data/indy/hwwang/	temp	not used
	vnmrsys/data/WHX-3-81-F2	gain	not used
	-Rep-Re_INDY_CDCL3/PROTO	spin	20
	N02.fid	hst	0.008
		pw90	9.700
		alfa	6.600
ACQUISITION		FLAGS	
sw	8000.0	il	n
at	2.500	in	n
np	40000	dp	y
fb	not used	hs	nn
bs	32		
d1	5.000	PROCESSING	
nt	32		
ct	32	lb	0.20
		fn	not used
TRANSMITTER			
tn	H1	DISPLAY	
sfrq	499.726	sp	-250.0
tof	499.7	wp	5496.8
tpwr	61	rfl	1001.7
pw	4.850	rfp	0
		rp	166.0
DECOUPLER		lp	-2.3
dn	C13		
dof	0	PLOT	
dm	nnn		
dmm	g	wc	234
dpwr	35	sc	8
dmf	32258	vs	84
		th	54
PRESATURATION		ai ph	
satmode	n		



WHX-3-81-F2-Rep-Re_INDY_CDCL3

SAMPLE		wet	n		
date	Nov 5 2011	**SPECIAL**			
solvent	cdcl3				
file	/data/indy/hwwang/vnmrsys/data/WHX-3-81-F2-Rep-Re_INDY_CDCL3/CARBON01.fid	temp	not used		
		gain	30		
		spin	20		
		hst	0.008		
		pw90	8.100		
		alfa	10.000		
ACQUISITION		**FLAGS**			
sw	31446.5	il	n		
at	1.042	in	n		
np	65536	dp	y		
fb	not used	hs	nn		
bs	64	**PROCESSING**			
d1	1.000				
nt	13850	lb	0.50		
ct	13850	lsfid	-3		
TRANSMITTER		lfn	not used		
tn	C13	**DISPLAY**			
sfrq	125.669				
tof	1913.4	sp	-0.1		
tpwr	56	wp	27643.4		
pw	4.050	rfl	1901.2		
DECOUPLER		rfp	0		
dn	H1	rp	-173.0		
dof	0	lp	137.4		
dm	yyy	**PLOT**			
dmm	w				
dpwr	39	wc	234		
dmf	11900	sc	8		
		vs	20000		
PRESATURATION		th	11		
satmode	n	al cdc ph			

JN-3-053-col2

SAMPLE

date	Oct 23 2011
solvent	cdcl3
file	/data/indy/janeni/ vnmrsys/data/JN-3-053-co l2/PROTON02.fid

ACQUISITION

sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	25.000
nt	16
ct	16

TRANSMITTER

tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

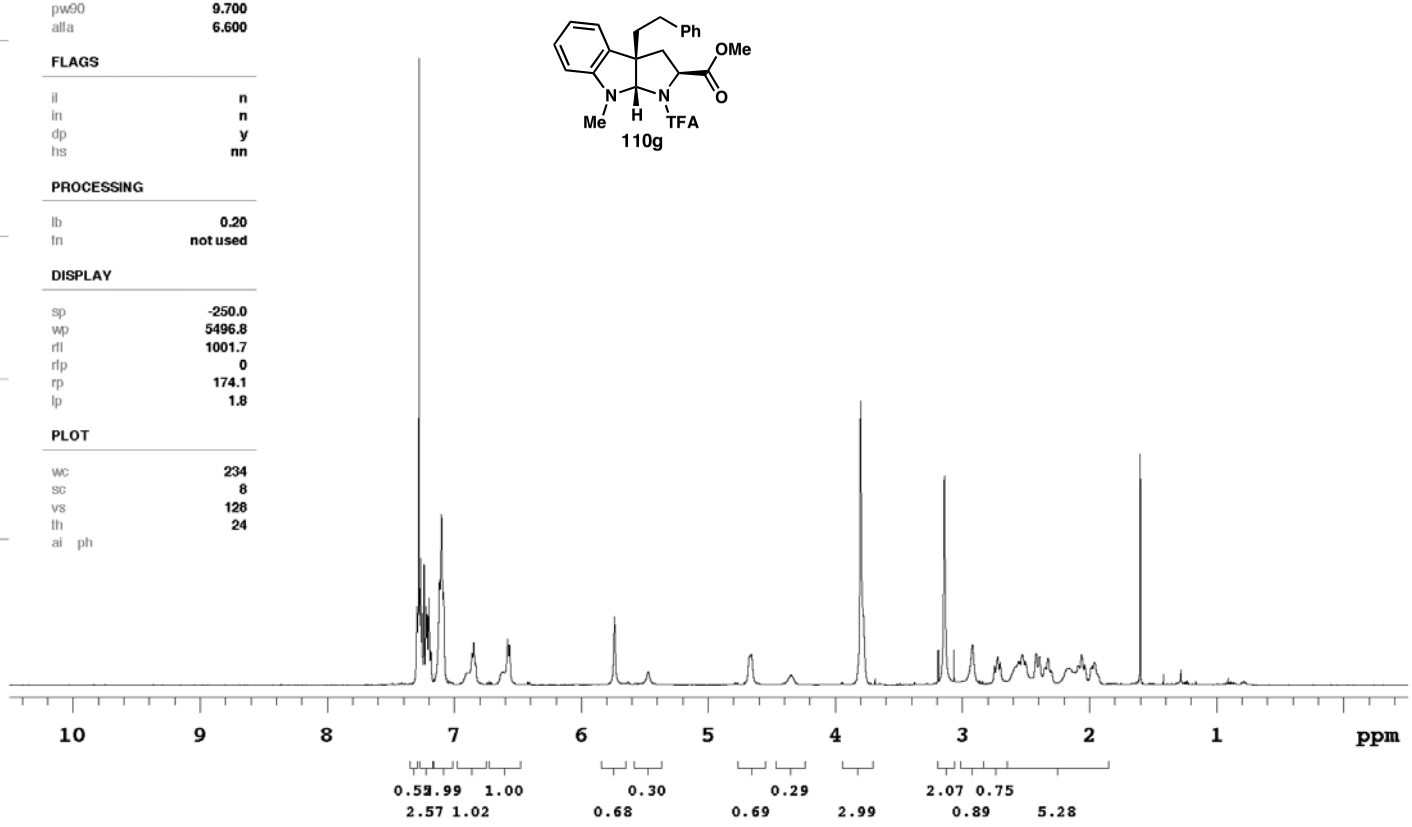
sp	-250.0
wp	5496.8
rfl	1001.7
rfp	0
rp	174.1
lp	1.8

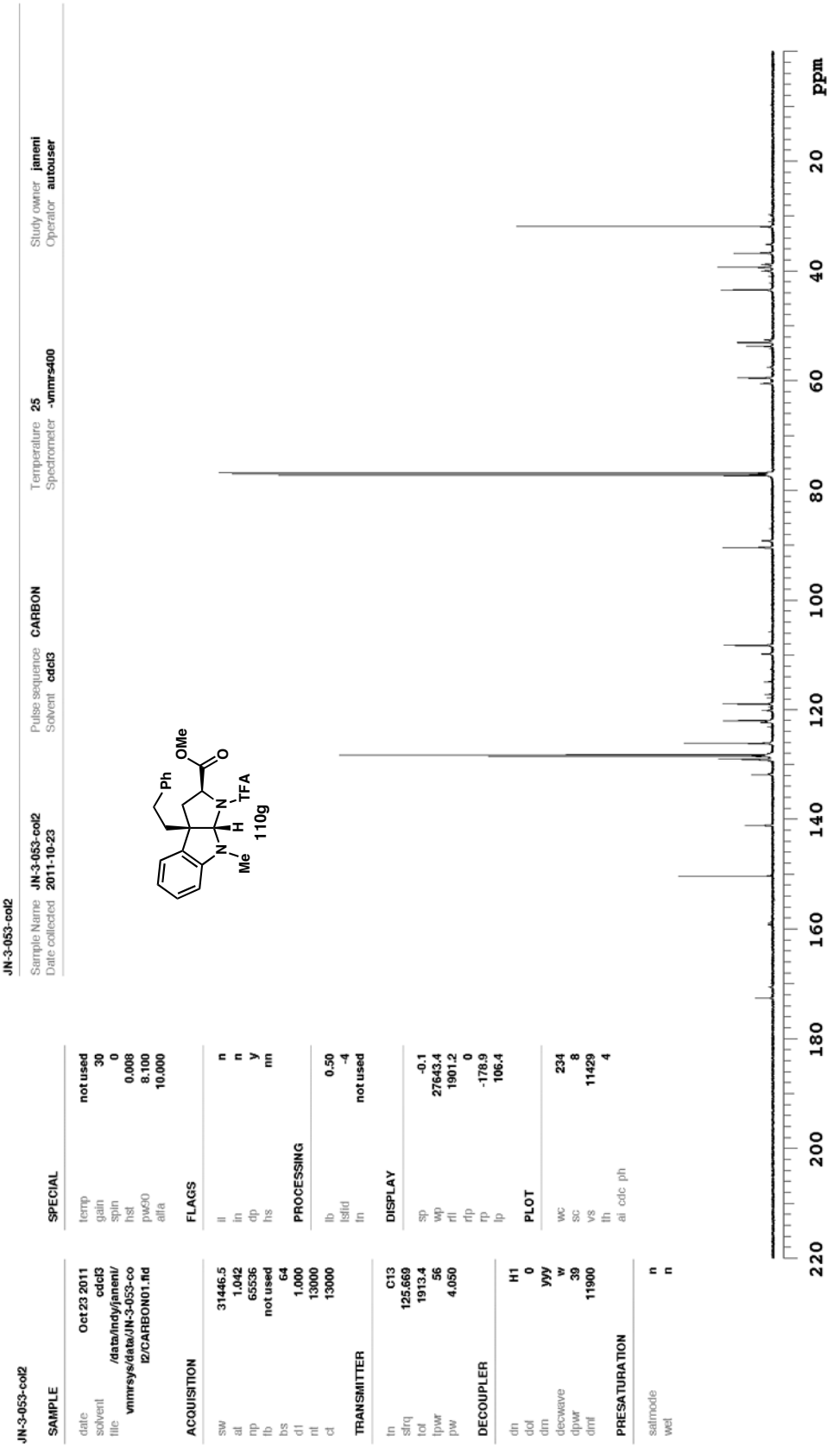
PLOT

wc	234
sc	8
vs	128
th	24
ai ph	

JN-3-053-col2

Sample Name JN-3-053-col2	Pulse sequence PROTON	Temperature 25	Study owner janeni
Date collected 2011-10-23	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser




JN-3-053-col2
Sample Name JN-3-053-col2
Date collected 2011-10-23
Pulse sequence CARBON
Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner janeni
Operator autouser
Ph
OMe
O
N
H
TFA
Me
110g
220 200 180 160 140 120 100 80 60 40 20 ppm
JN-3-053-col2
SAMPLE
SPECIAL
date Oct 23 2011
solvent cdcl3
file /data/lndy/janeni/vnmrsys/data/JN-3-053-co2/CARBON01.fid
temp not used
gain 30
spin 0
hst 0.008
pw90 8.100
alfa 10.000
ACQUISITION
FLAGS
sw 31446.5
at 1.042
np 65536
fb not used
bs 64
d1 1.000
nt 13000
ct 13000
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
lsfid -4
fn not used
TRANSMITTER
tn C13
sfrq 125.669
tof 1913.4
tpwr 56
pw 4.050
DISPLAY
sp -0.1
wp 27643.4
rfl 1901.2
rfp 0
rp -178.9
lp 106.4
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
decwave 39
dpwr 11900
dmf
PLOT
wc 234
sc 8
vs 11429
th 4
al cdc ph
PRESATURATION
satmode n
wet n

WHX-3-84-HPLC-F2_INDY_CDCL3

SAMPLE

date	Jan 28 2012
solvent	cdcl3
file	/data/indy/hwwang/vnmrsys/data/WHX-3-84-HPLC-F2_INDY_CDCL3/PROTON02.fid

ACQUISITION

sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	5.000
nt	16
ct	16

TRANSMITTER

tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

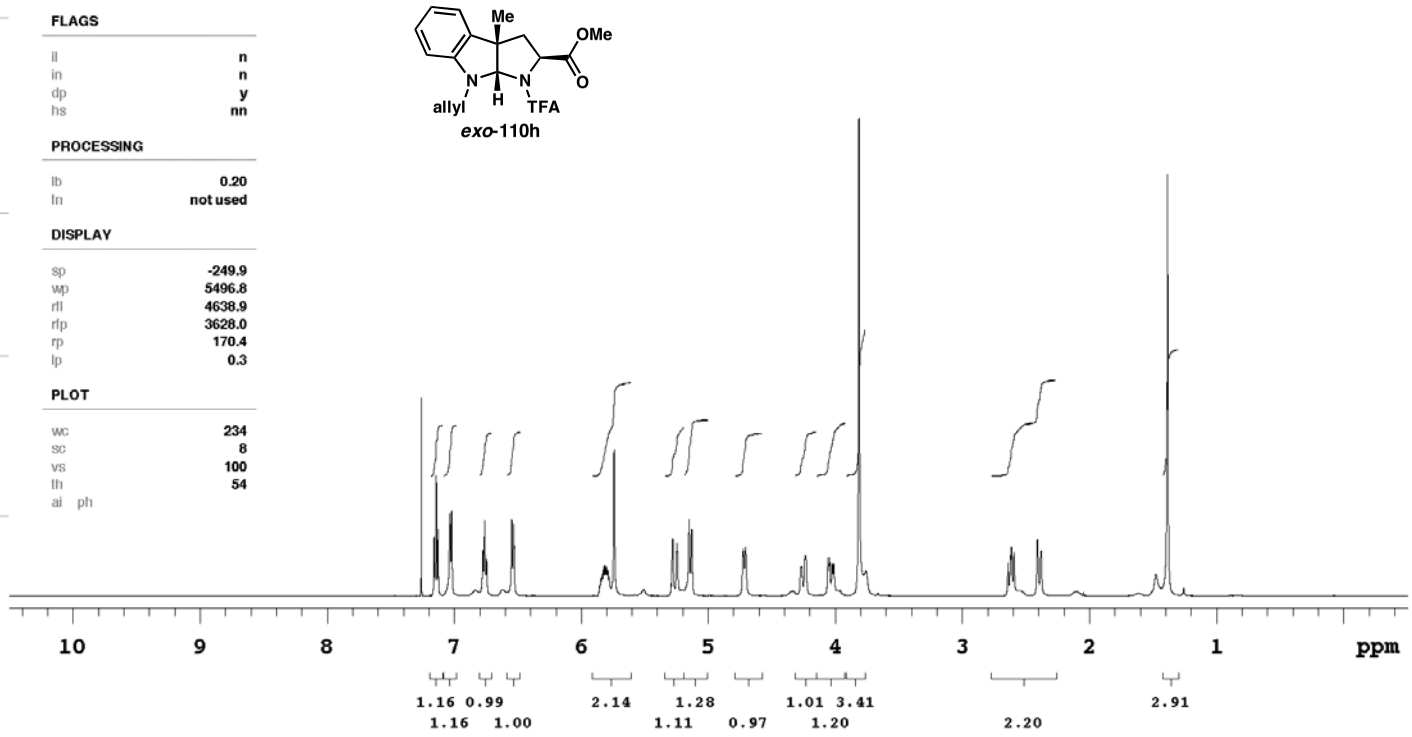
sp	-249.9
wp	5496.8
rfl	4638.9
rfp	3628.0
rp	170.4
lp	0.3

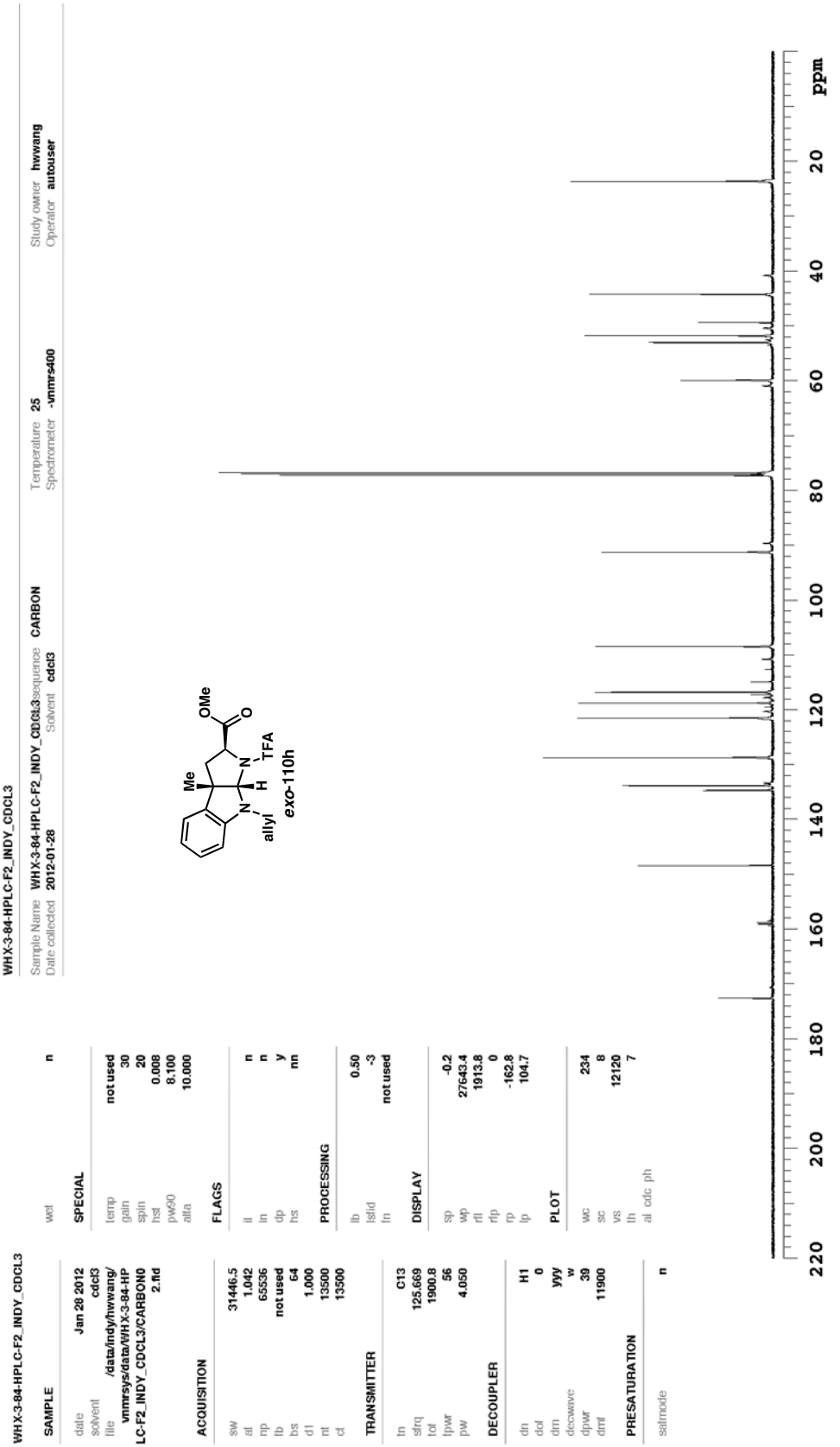
PLOT

wc	234
sc	8
vs	100
th	54
ai ph	

WHX-3-84-HPLC-F2_INDY_CDCL3

Sample Name WHX-3-84-HPLC-F2_INDY_CDCL3 | Sequence PROTON | Temperature 25 | Study owner hwwang
Date collected 2012-01-28 | Solvent cdcl3 | Spectrometer -vnmrs400 | Operator autouser





WHX-3-84-HPLC-F2_INDY_CDCL3

SAMPLE		wet	n
date	Jan 28 2012	**SPECIAL**	
solvent	cdcl3		
file	/data/indy/hwwang/	temp	not used
	vnmrsys/data/WHX-3-84-HP	gain	30
	LC-F2_INDY_CDCL3/CARBON0	spin	20
	2.fid	hst	0.008
		pw90	8.100
		alfa	10.000
ACQUISITION		**FLAGS**	
sw	31446.5	il	n
at	1.042	in	n
np	65536	dp	y
fb	not used	hs	nn
bs	64		
d1	1.000	**PROCESSING**	
nt	13500	lb	0.50
ct	13500	lsfid	-3
TRANSMITTER		ln	not used
tn	C13	**DISPLAY**	
sfrq	125.669	sp	-0.2
tof	1900.8	wp	27643.4
tpwr	56	rfl	1913.8
pw	4.050	rfp	0
DECOUPLER		rp	-162.8
dn	H1	lp	104.7
dof	0		
dm	yyy	**PLOT**	
decwave	w	wc	234
dpwr	39	sc	8
dmf	11900	vs	12120
		th	7
PRESATURATION		al odc ph	
satmode	n		

WHX-3-84-HPLC-F1_INDY_CDCL3

SAMPLE

date	Jan 25 2012
solvent	cdcl3
file	/data/indy/hwwang/vnmrsys/data/WHX-3-84-HPLC-F1_INDY_CDCL3/PROTON01.fid

ACQUISITION

sw	8000.0
at	2.500
np	40000
fb	not used
bs	32
d1	5.000
nt	32
ct	32

TRANSMITTER

tn	H1
sfrq	499.726
tof	499.7
tpwr	61
pw	4.850

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	g
dpwr	35
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	not used
spin	20
hst	0.008
pw90	9.700
alfa	6.600

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

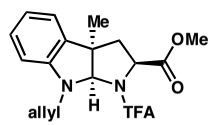
sp	-250.0
wp	5496.8
rfl	1001.7
rfp	0
rp	164.5
lp	8.3

PLOT

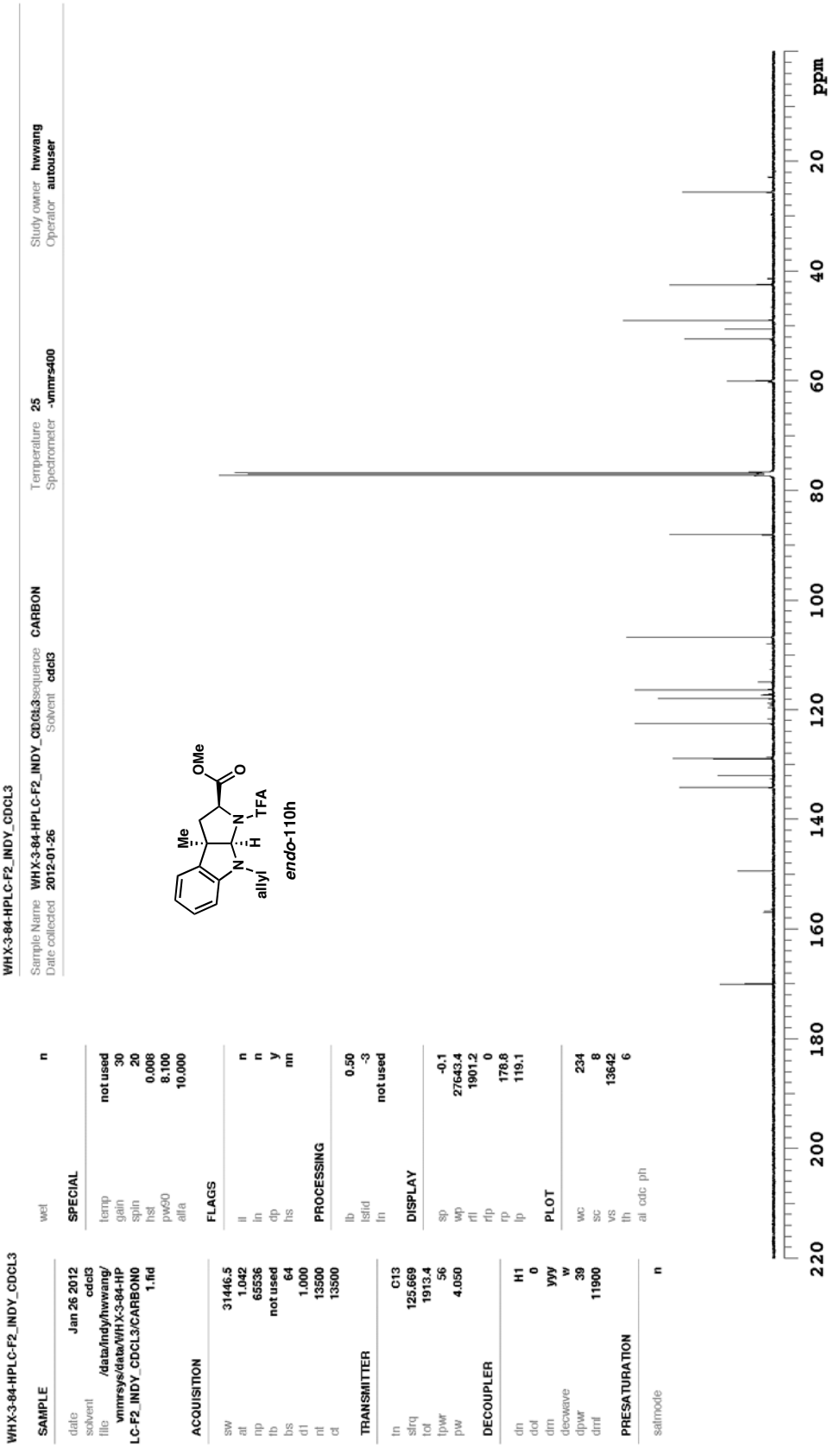
wc	234
sc	8
vs	49
th	54
ai ph	

WHX-3-84-HPLC-F1_INDY_CDCL3

Sample Name WHX-3-84-HPLC-F1_INDY_CDCL3 Sequence PROTON Temperature 25 Study owner hwwang
Date collected 2012-01-25 Solvent cdcl3 Spectrometer -vnmrs400 Operator autouser



endo-110h



WHX-3-84-HPLC-F2_INDY_CDCL3

SAMPLE	
date	Jan 26 2012
solvent	cdcl3
file	/data/Indy/hwwang/vnmrsys/data/WHX-3-84-HP LC-F2_INDY_CDCL3/CARBON0 1.fid
ACQUISITION	
sw	31446.5
at	1.042
np	65536
fb	not used
bs	64
d1	1.000
nt	13500
ct	13500
TRANSMITTER	
tn	C13
sfrq	125.669
tof	1913.4
tpwr	56
pw	4.050
DECOUPLER	
dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	11900
PRESATURATION	
satmode	n

wet	n
SPECIAL	
temp	not used
gain	30
spin	20
hst	0.008
pw90	8.100
alfa	10.000
FLAGS	
il	n
in	n
dp	y
hs	nn
PROCESSING	
lb	0.50
lsfid	-3
fn	not used
DISPLAY	
sp	-0.1
wp	27643.4
rfl	1901.2
rfp	0
rp	178.8
lp	119.1
PLOT	
wc	234
sc	8
vs	13642
th	6
ai cdc ph	

APPENDIX 2

X-Ray Crystallography Reports Relevant to Chapter 2:

Enantioselective Synthesis of Pyrroloindolines by a Formal (3 + 2)

Cycloaddition[†]

[†] 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 PYROLLOINDOLINE 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.*

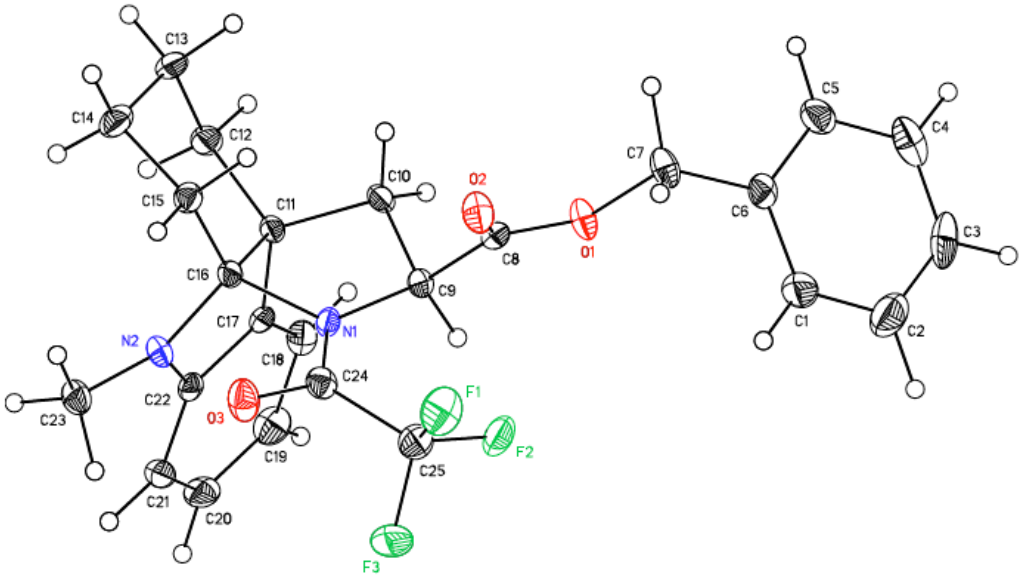


Table A2.1. Crystal data and structure refinement for pyrroloindoline ***106g*** *(CCDC 787164).*

Empirical formula	$C_{25}H_{25}F_3N_2O_3$
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 MoKα	
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	α= 90° β= 108.657(3)° γ = 90°
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 θ = 30.52°	91.3 %	
Index ranges	$-13 \le h \le 13, -11 \le k \le 11, -19 \le l \le 19$	
Data collection scan type	ω scans; 8 settings	
Data reduction program	Bruker SAINT-Plus v7.66A	
Reflections collected	20200	
Independent reflections	5883 [R_{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>2σ(I), 4601 reflections]	R1 = 0.0393, *w*R2 = 0.0443
R indices (all data)	R1 = 0.0561, *w*R2 = 0.0463
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Unknown
Absolute structure parameter	0.1(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 (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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

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

Table A2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for pyrroloindoline ***106g*** *(CCDC 787164). U(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 ($Å^2$x 10^4) for pyrroloindoline ***106g*** *(CCDC 787164). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
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 (x 10^4) and isotropic displacement parameters ($Å^2$x 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.*

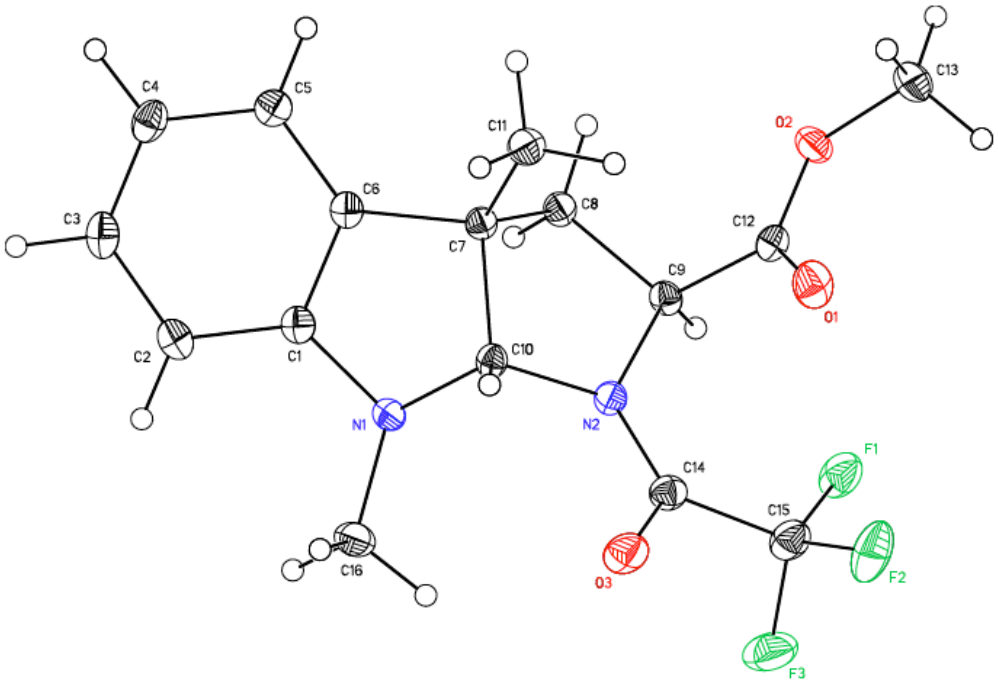


*Table A2.6. Crystal data and structure refinement for pyrroloindoline **100c** (CCDC 788553).*

Empirical formula	$C_{16}H_{17}F_3N_2O_3$
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	$-22 \le h \le 22, -11 \le k \le 12, -26 \le l \le 26$	
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>2σ(I), 4934 reflections]	R1 = 0.0469, *w*R2 = 0.0737
R indices (all data)	R1 = 0.0757, *w*R2 = 0.0765
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.427 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 (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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

Table A2.7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for pyrroloindoline ***100c*** *(CCDC 788553). U(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 ($Å^2x\ 10^4$) for pyrroloindoline ***100c*** *(CCDC 788553). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
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 (x 10^4) and isotropic displacement parameters (Å^{2}x 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

Conjugate Addition/in situ Reduction for the Synthesis of Indolines[*]

3.1 Introduction

In addition to the pyrroloindolines discussed in Chapters 1 and 2, there are a great number of structurally distinct natural products that incorporate an indoline moiety. These compounds feature diverse substitution about the heterocyclic core, and several exhibit promising biological activities (see Figure 1 for representative examples).[1] Many groups have developed methods for the stereoselective preparation of non-pyrroloindoline indolines, including transformations starting from tryptophan, as well as catalytic asymmetric reactions using organo- or transition metal catalysts.

Mechanistic studies on the formal (3 + 2) cycloaddition to prepare enantioenriched pyrroloindolines (described in Chapter 2) revealed that the initial product of this reaction is an indolinium ion (**119)**, and that cyclization to form the pyrroloindoline (**121**) does not occur until aqueous work-up. Thus, we proposed that these intermediates could be trapped with an external hydride source (Figure 2). This chapter describes the development of this approach for the preparation of indoline-

[*] Portions of this chapter have been reproduced from a published study (see reference 13) and the supporting information found therein. The research presented in this chapter was completed in collaboration with Haoxuan Wang, a graduate student in the Reisman group.

containing amino acid derivatives bearing an all-carbon quaternary stereocenter at the C3 position (**120**).

Figure 1. Selected indoline natural products.

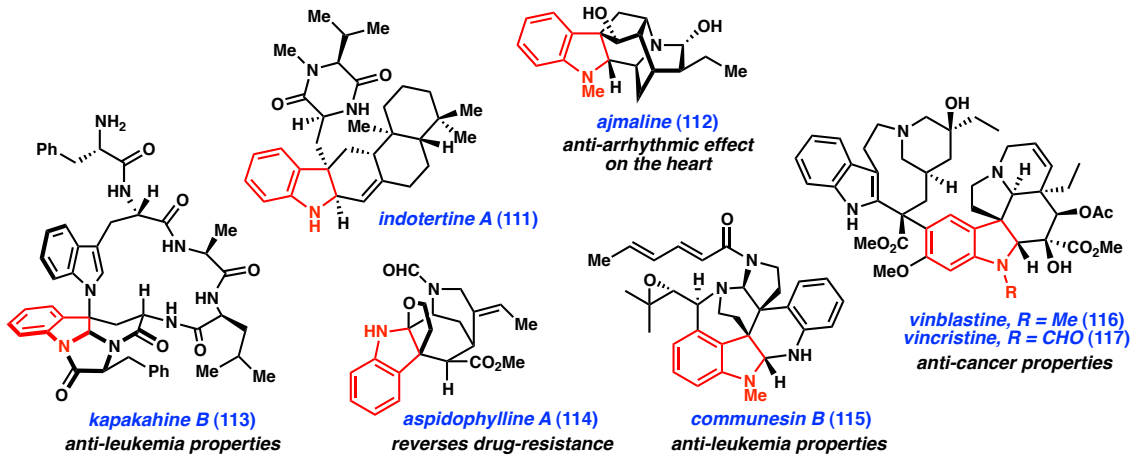
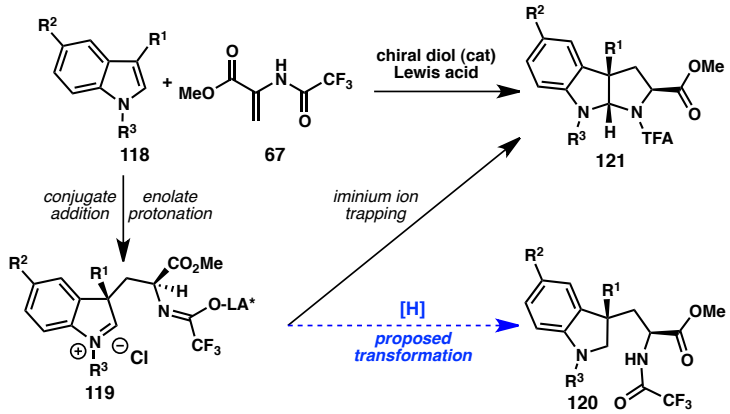


Figure 2. Proposed in situ reduction of an iminium ion intermediate to generate indolines.

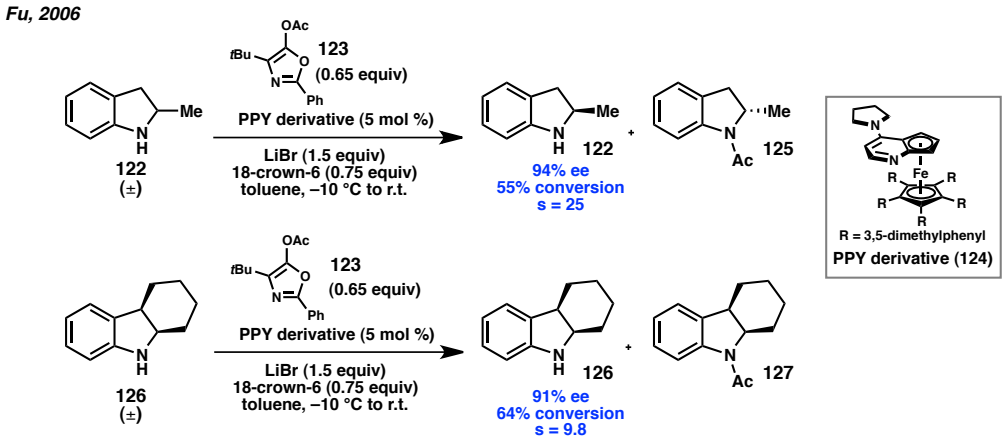


3.1.1 Methods for the Enantioselective Preparation of Indolines

Several methods to access enantioenriched indolines have been developed. One such approach is to effect a kinetic resolution of racemic indolines. Fu and coworkers

achieved this goal using a planar-chiral PPY derivative (**124**) as the catalyst (Figure 3).[2] High selectivity factors were achieved by employing a catalyst possessing a highly sterically-demanding C_5Ar_5 group.

Figure 3. Kinetic resolution of indolines



Besides resolutions, there are also several catalytic, asymmetric methods to prepare indolines; these can be divided into two classes: (a) those that start from a related nitrogen-containing heterocycle, such as indoles or oxindoles, and (b) those that directly form the indoline framework. In the first class, a common approach to prepare indolines from indoles or oxindoles is *via* asymmetric reduction. For example, Zhang and coworkers achieved the asymmetric hydrogenation of unprotected indoles (e.g., **128**) with a palladium catalyst and chiral phosphine ligand (Figure 4).[3] Protonation of the indole by a Brønsted acid forms an indolinium ion (**130**), which is more readily reduced. A dynamic kinetic resolution occurs to afford 2,3-disubstituted indolines (**131**) with high enantiomeric excess. An organocatalyzed version of this reaction was developed by Chen and coworkers (Figure 4).[4] In this transformation, in situ-generated HCl effects C3

protonation to give the indolinium followed by chiral Lewis base mediated enantioselective hydrosilylation.

Figure 4. Enantioselective indoline synthesis by hydrogenation of indoles.

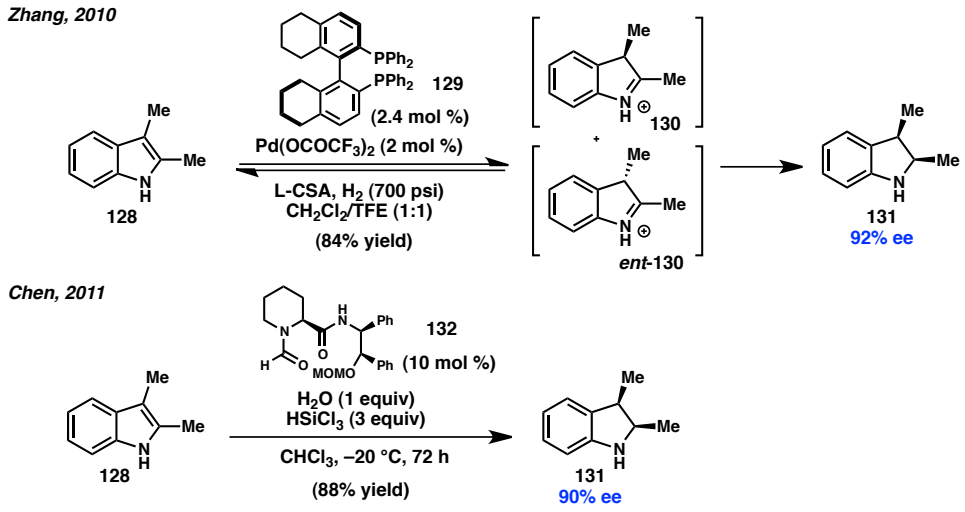
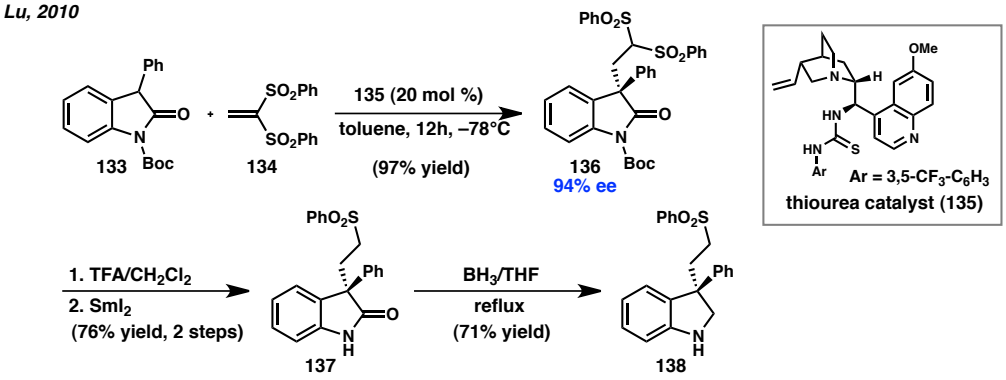


Figure 5. Enantioselective indoline synthesis by reduction of oxindoles.

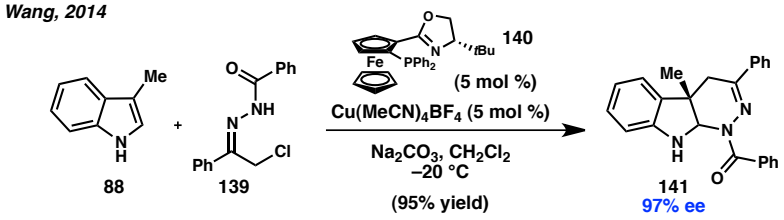


The Lu laboratory reported the enantioselective preparation of indolines with an all-carbon quaternary center by reduction of the corresponding oxindole (Figure 5).[5] Thiourea-catalyzed asymmetric conjugate of oxindole **133** to vinyl sulfone **134** generates

the C3 stereocenter. While direct reduction of oxindole **136** led to the formation of retro-Michael side products, one aryl sulfone group can be selectively removed with SmI_2 to allow subsequent reduction with BH_3 to afford the corresponding indoline (**138**).

In contrast to methods to access indolines by the reduction of indoles, Wang and coworkers developed an asymmetric inverse-electron-demand aza-Diels–Alder reaction of indoles and azoalkenes.[6] This reaction is catalyzed by a Cu^I/*t*Bu-Phosferrox complex to give [2,3]-fused indoline tetrahydropyridazine heterocycles (Figure 6). The azoalkenes are formed in situ from α-halogeno hydrazones in the presence of a base; coordination to a copper complex enhances its reactivity compared to the uncatalyzed background reaction.

Figure 6. Indoline synthesis via Diels–Alder cycloaddition.

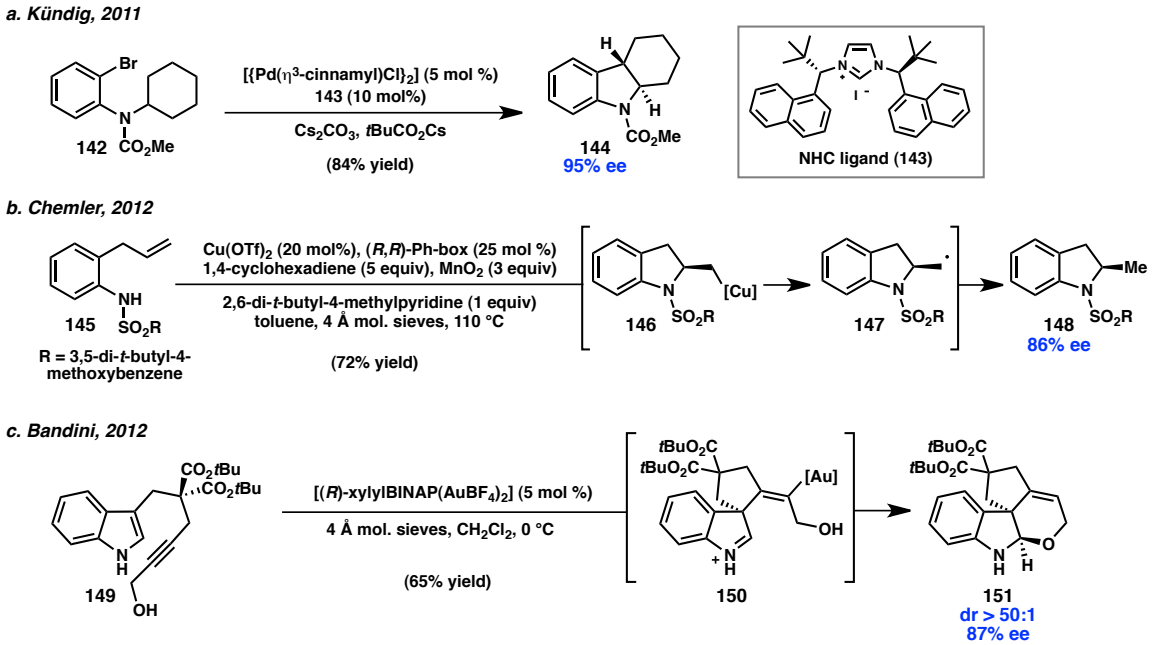


The second class of methods to access indolines involves direct preparation of the heterocyclic framework. Of these methods, several transition metal-catalyzed cyclization reactions have been developed. Kündig and coworkers prepared enantioenriched, *trans*-fused indolines by palladium-catalyzed activation of enantiotopic methylene C–H bonds (Figure 7).[7] This reaction utilizes NHC ligands derived from chiral *o*-substituted α-alkylphenethyl amines.

The Chemler laboratory disclosed an enantioselective, intramolecular copper-catalyzed alkene hydroamination to afford indolines (Figure 7).[8] This reaction is thought to occur *via* initial *cis* aminocupration, resulting in an unstable organocopper(II) intermediate (**146**) that undergoes homolysis to generate a primary organic radical (**147**) and copper(I). Hydrogen atom abstraction from 1,4-cyclohexadiene provides the net hydroamination product.

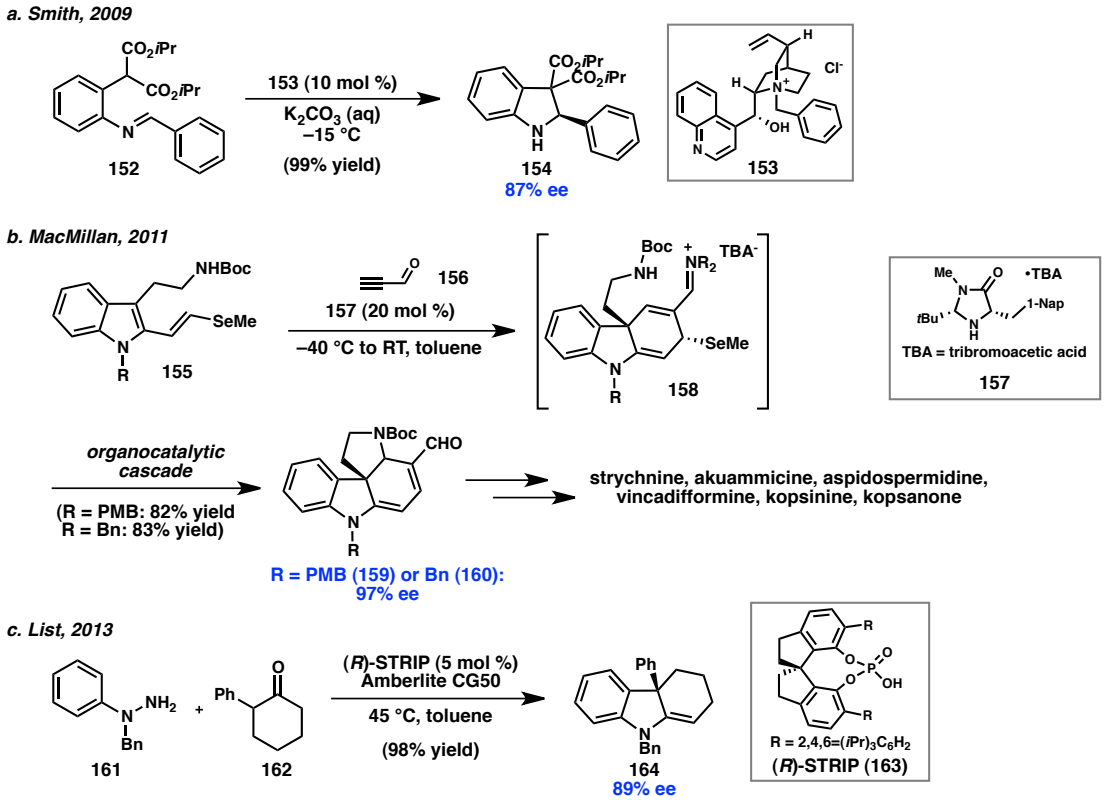
Bandini and coworkers reported a gold-catalyzed cascade reaction of functionalized propargylic alcohols (e.g. **149**) yielding indoline products (Figure 7).[9] The authors propose that this reaction involves hydroindolination of the triple bond and subsequent iminium trapping. 5-*exo-dig* cyclization was observed exclusively when a carbon-based tether between the indole and alkyne was utilized.

Figure 7. Enantioselective indoline synthesis by transition metal catalyzed (a) C–H activation, (b) hydroamination, and (c) alkyne cyclization.



In contrast to these transition-metal-catalyzed transformations, several organocatalytic methods for the direct prepartion of indolines have been reported. The Smith laboratory employed a chiral phase transfer catalyst to promote a cyclization reaction to prepare indolines (Figure 8).[10] The authors propose two possible mechanisms for this reaction: an intramolecular Mannich reaction, or an electrocyclization. These possibilities could not be distinguished by the stereochemical outcome of the reaction, because the substrates reported did not include the appropriate substituents to probe the stereospecificity that is diagnostic of pericyclic processes.

Figure 8. Organocatalytic indoline syntheses: (a) electrocyclization, (b) cascade for total syntheses of indoline natural products, and (c) Fischer indolization.



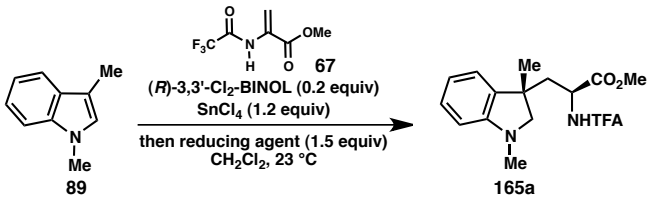
On the other hand, the MacMillan laboratory utilized an organocatalyst to promote a [4+2] cycloaddition: exposure of tryptamine derivative **155** to an imidazolidinone catalyst (**157**) results in a Diels–Alder reaction with propynal (Figure 8).[11] Incorporation of an organoselenide facilitates further cascade reactions to afford indolines **159** and **160** in excellent yield and enantioselectivity. This functionalized intermediate was further elaborated to complete highly efficient total syntheses of six structurally diverse natural products.

Another organocatalytic approach was developed by List and coworkers, in which a chiral phosphoric acid catalyzed an asymmetric Fischer indolization (Figure 8).[12] Upon condensation of α-substituted cyclic ketone **162** with phenylhydrazine (**161**), the Brønsted acid promotes the [3,3]-sigmatropic rearrangement, leading to enantioenriched fused indolines.

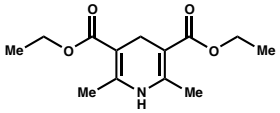
3.2 Development of the Indoline Synthesis

To assess the feasibility of our proposed indoline synthesis, indole **89** and acrylate **67** were exposed to the optimized conditions for the formal (3 + 2) cycloaddition (Chapter 2), along with a reductant (Table 1). Whereas weaker reductants such as triethylsilane and sodium triacetoxy borohydride proved ineffective, we were pleased to find that use of Hantzsch ester **166** did provide the indoline product, albeit in low yield (entry 3). Alternatively, use of sodium borohydride furnished **165a** in good yield, 15:1 dr, 92% ee (entry 5). The more soluble reducing agent lithium borohydride provided a lower yield of the desired product along with a greater amount of byproducts. The limited solubility of $NaBH_4$ and $LiBH_4$ in methylene chloride likely contributes to the compatibility of all the reagents, allowing the reaction to be carried out in one pot.

Table 1. Screen of reducing agents.



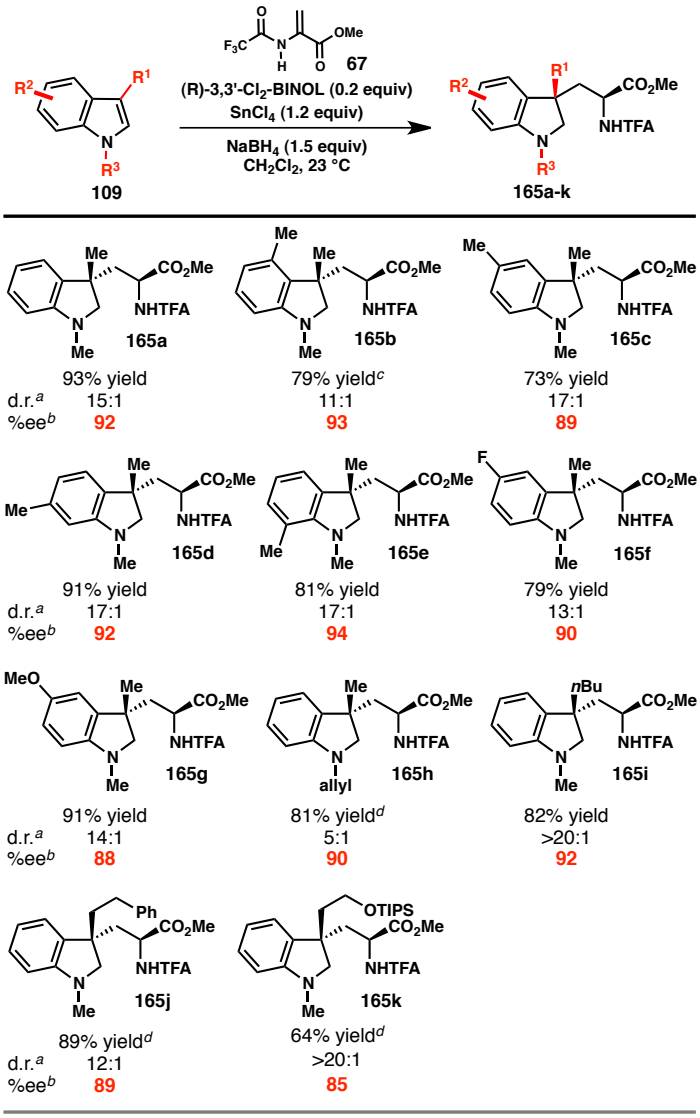
Entry	Reducing Agent	Yield (%)
1	Et_3SiH	0
2	$NaBH(OAc)_3$	0
3	Hantzsch ester **25**	3
4	$LiBH_4$	85
5	$NaBH_4$	93



3.2.1 Substrate Scope of Indoline Synthesis

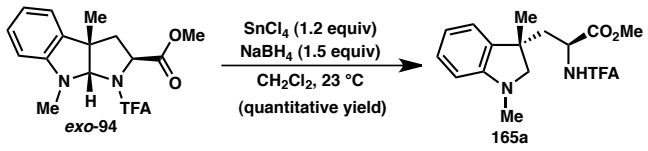
Having identified the optimal reducing agent, a survey of indole substrates was conducted (Figure 9).[13] Indoles with either electron-donating or –withdrawing substituents are good substrates for the reaction. At the 3-position, *n*-butyl and phenylethyl groups are tolerated, but reactivity decreases with increasing steric bulk and 1.6 equivalents of $SnCl_4$ are required to achieve good reactivity with the phenylethyl substrate. Whereas the cleavage of the protecting group was observed when TBS-protected tryptophol was employed, use of the TIPS-protected tryptophol furnished **165k** in good yield. The indole nitrogen can also be protected with an allyl group, which would be useful when an *N*-Me functionality is not desired in the product.

Figure 9. In situ reduction for the synthesis of indolines.



[a] Determined by ^{1}H NMR of crude reaction mixture. [b] Determined by SFC using chiral stationary phase. [c] Isolated yield of *exo*-diastereomer. [d] 1.6 equiv. $SnCl_4$ was employed.

Figure 10. Re-exposure of pyrroloindoline ***exo-94*** *to $SnCl_4$ and $NaBH_4$.*



The reduced products **165** are formed with the same diastereomeric and enantiomeric ratios as the corresponding pyrroloindolines, suggesting that iminium reduction does not affect the selectivities of the other steps. When a methylene chloride solution of pyrroloindoline ***exo*-94** and $SnCl_4$ was re-exposed to $NaBH_4$, the pyrroloindoline was reduced to indoline **165a** in quantitative yield (Figure 10). This is consistent with amide cyclization being reversible in the presence of the Lewis acid.

3.3 Concluding Remarks

Mechanistic insight into the (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2) cycloaddition (Chapter 1) has led to the development of a method for the preparation of enantioenriched indoline-containing amino acid derivatives with all-carbon quaternary centers at C3. It was determined that the intially-formed product of the formal (3 + 2) cycloaddition is an iminium ion, and that cyclization by the pendant amide to provide the pyrroloindoline does not occur until aqeous work-up. Thus, we proposed that the addition of external nucleophiles will allow access to a variety of indoline structures. This chapter explores the use of reducing agents to effect the in situ reduction of this iminium intermediate. Of the reagents screened, sodium borohydride was found to be optimal. This one-pot procedure tolerates a variety of substitution on the backbone or at C3 of the indole substrate.

3.4 Experimental Section

3.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and toluene were dried by passing through activated alumina columns. Deuterated methylene chloride (CD_2Cl_2) was dried by passing through a plug of activated alumina in a glovebox. Dimethylformamide (DMF) was dried over activated molecular sieves, and dichloroethane (DCE) was distilled over calcium hydride. All other commercially obtained reagents were used as received unless specifically indicated. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using 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. ^{1}H 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 (^{1}H, δ = 7.26, ^{13}C, δ = 77.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a

Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Preparatory HPLC was performed with either an Agilent 1100 or 1200 Series HPLC utilizing an Agilent Zorbax RX-SIL 5μm 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, 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.

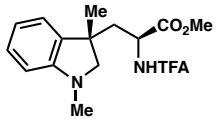
3.4.2 General Procedure: Formal (3 + 2) Cycloaddition/in situ Reduction.

To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (*R*)-3,3'-dichloro-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with CH_2Cl_2 (1.5 mL), followed by addition of $SnCl_4$ (0.24 mmol, 1.20 equiv unless specifically indicated, 1 M in CH_2Cl_2). $NaBH_4$ (0.30 mmol, 1.50 equiv) was then added, and the reaction was stirred at room temperature for 24 h (unless specifically indicated). The reaction was quenched by diluting with 1 mL MeCN and 1 mL 1 M HCl, followed by addition of 5 mL H_2O. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL). The combined organic

layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography.

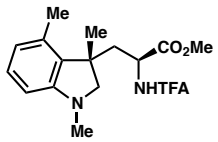
3.4.3 Indoline Products

Indoline 165a.



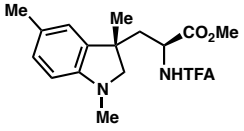
Prepared from 1,3-dimethyl-1*H*-indole [14] and methyl 2-trifluoroacetamidoacrylate using the general procedure. The diastereomeric ratio was determined to be 15:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 64.1 mg (93% yield) of **165a**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 9.9 min t_R(minor) = 5.9 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (br d, J = 5.9 Hz, 1H), 7.14 (td, J = 7.7, 1.2 Hz, 1H), 6.99 (dd, J = 7.3, 0.8 Hz, 1H), 6.76 (td, J = 7.4, 0.8 Hz, 1H), 6.54 (d, J = 7.9 Hz, 1H), 4.27 (br td, J = 7.7, 4.7 Hz, 1H), 3.65 (s, 3H), 3.31 (d, J = 9.1 Hz, 1H), 2.98 (d, J = 9.1 Hz, 1H), 2.74 (s, 3H), 2.21 (dd, J = 14.7, 4.7 Hz, 1H), 2.15 (dd, J = 14.7, 8.2 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.6 (q, $J_{C\text{-}F}$ = 37.5 Hz), 152.1, 153.3, 128.5, 122.4, 119.0, 115.6 (q, $J_{C\text{-}F}$ = 287.9 Hz), 108.4, 68.3, 52.7, 51.2, 42.8, 42.1, 35.8, 26.1; IR (NaCl/thin film): 3319, 2956, 2858, 2811, 1751, 1718, 1607, 1559, 1491, 1452, 1209, 1179, 744 cm^{-1}; $[\alpha]_D^{25}$ = +79.6 (c = 1.32, CH_2Cl_2). HRMS (MM) calc'd for $[M+H]^+$ 345.1421, found 345.1423.

Indoline 165b.



Prepared from 1,3,4-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The diastereomeric ratio was determined to be 11:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 56.8 mg (79% yield, yellow oil) of **165b** as a single diastereomer. The enantiomeric excess of the major diastereomer was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 3.9 min t_R(minor) = 3.5 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (br d, J = 4.9 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 6.42 (d, J = 7.9 Hz), 4.10 (ddd, J = 9.0, 6.5, 4.2 Hz, 1H), 3.65 (s, 3H), 3.32 (d, J = 9.3 Hz, 1H), 2.95 (d, J = 9.2 Hz, 1H), 2.71 (s, 3H), 2.45 (dd, J = 15.0, 4.0 Hz, 1H), 2.30 (s, 3H), 2.13 (dd, J = 14.8, 8.9 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.7 (q, $J_{C\text{-}F}$ = 37.5 Hz), 152.8, 134.5, 131.5, 128.8, 122.4, 115.6 (q, $J_{C\text{-}F}$ = 287.9 Hz), 106.7, 68.6, 52.7, 51.7, 43.7, 40.9, 35.9, 26.6, 18.7; IR (NaCl/thin film): 3315, 2956, 2812, 1750, 1710, 1593, 1559, 1484, 1457, 1209, 1179, 774 cm^{-1}; $[\alpha]_D^{25}$ = +66.0 (c = 1.04, CH_2Cl_2). HRMS (MM) calc'd for $[M+H]^+$ 359.1577, found 359.1591.

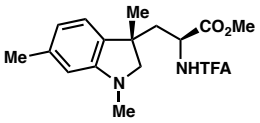
Indoline 165c.



Prepared from 1,3,5-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The diastereomeric ratio was determined to be 17:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (10→25% ethyl acetate/hexanes) to yield 52.6 mg (73% yield) of **165c**,

a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 4.8 min t_R(minor) = 3.4 min. The major diastereomer was separated by flash chromatography (7% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (br d, *J* = 4.8 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.81 (s, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 4.16 (q, *J* = 6.5 Hz, 1H), 3.67 (s, 3H), 3.27 (d, *J* = 9.1 Hz, 1H), 2.91 (d, *J* = 9.1 Hz, 1H), 2.70 (s, 3H), 2.25 (s, 3H), 2.17 (d, *J* = 6.5 Hz, 2H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.7 (q, $J_{C\text{-}F}$ = 37.5 Hz), 150.0, 135.5, 128.9, 128.8, 123.3, 115.6 (q, $J_{C\text{-}F}$ = 287.9 Hz), 108.7, 69.0, 52.7, 51.5, 42.7, 42.1, 36.4, 26.07, 20.7; IR (NaCl/thin film): 3326, 2955, 2922, 2863, 2806, 1752, 1719, 1555, 1499, 1452, 1209, 1163, 806 cm^{-1}; $[\alpha]_D^{25}$ = -+42.3 (*c* = 0.87, CH_2Cl_2). HRMS (MM) calc'd for $[M+H]^+$ 359.1577, found 359.1565.

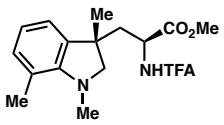
Indoline 165d.



Prepared from 1,3,6-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The diastereomeric ratio was determined to be 17:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→30% ethyl acetate/hexanes) to yield 65.0 mg (91% yield) of **165d**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 11.1 min t_R(minor) = 5.0 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 5.7 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 7.5 Hz, 1H), 6.37 (s, 1H), 4.22 (td, *J* = 7.5, 4.9 Hz), 3.66 (s, 3H), 3.29 (d, *J* = 9.1 Hz, 1H), 2.96 (d, *J* = 9.1 Hz, 1H), 2.72 (s, 3H), 2.30 (s, 3H), 2.20-2.11

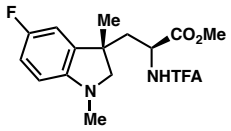
(m, 2H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.6 (q, $J_{C\text{-}F}$ = 37.5 Hz), 152.3, 138.6, 132.5, 122.2, 119.8, 115.6 (q, $J_{C\text{-}F}$ = 287.8 Hz), 109.3, 68.6, 52.7, 51.4, 42.5, 42.2, 35.8, 26.2, 21.6; IR (NaCl/thin film): 3321, 2956, 2923, 2870, 2804, 1750, 1716, 1615, 1557, 1497, 1455, 1208, 1179, 802 cm^{-1}; $[\alpha]_D^{25}$ = +76.0 (*c* = 1.56, CH_2Cl_2). HRMS (MM) calc'd for $[M+H]^+$ 359.1577, found 359.1577.

Indoline 165e.



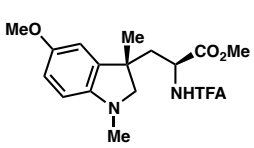
Prepared from 1,3,7-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The diastereomeric ratio was determined to be 17:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→30% ethyl acetate/hexanes) to yield 58 mg (81% yield) of **165e**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 4.3 min t_R(minor) = 3.3 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 4.7 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 4.14-4.08 (m, 1H), 3.66 (s, 3H), 3.29 (d, *J* = 9.6 Hz, 1H), 2.97 (d, *J* = 9.6 Hz, 1H), 2.93 (s, 3H), 2.37 (s, 3H), 2.17-2.06 (m, 2H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.7 (q, $J_{C\text{-}F}$ = 37.5 Hz), 149.9, 136.1, 131.8, 121.2, 120.4, 120.3, 115.6 (q, $J_{C\text{-}F}$ = 287.8 Hz), 69.7, 52.7, 51.3, 42.8, 42.3, 39.5, 26.6, 19.5; IR (NaCl/thin film): 3322, 2959, 2924, 1750, 1713, 1557, 1480, 1456, 1412, 1208, 1180, 1071, 750 cm^{-1}; $[\alpha]_D^{25}$ = +84.9 (*c* = 1.20, CH_2Cl_2). HRMS (APCI) calc'd for $[M+H]^+$ 359.1577, found 359.1595.

Indoline 165f.



Prepared from 5-fluoro-1,3-dimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The diastereomeric ratio was determined to be 13:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (10→30% ethyl acetate/hexanes) to yield 57.0 mg (79% yield) of **165f**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 3.9 min t_R(minor) = 2.9 min. The major diastereomer was separated by preparatory TLC (40% CH_2Cl_2/hexanes then 50% CH_2Cl_2/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (br d, J_{C-H} = 5.8 Hz, 1H), 6.83 (td, J_{C-H} = 8.8, 2.6 Hz, 1H), 6.72 (dd, J_{C-H} = 8.2, 2.6 Hz, 1H), 6.44 (dd, J_{C-H} = 8.5, 4.1 Hz, 1H), 4.25 (td, J_{C-H} = 7.7, 4.8 Hz, 1H), 3.68 (s, 3H), 3.31 (d, J_{C-H} = 9.2 Hz, 1H), 2.97 (d, J_{C-H} = 9.2 Hz, 1H), 2.70 (s, 3H), 2.21 (dd, J_{C-H} = 14.7, 4.8 Hz, 1H), 2.12 (dd, J_{C-H} = 14.7, 8.1 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 157.2 (d, J_{C-F} = 237.2 Hz), 156.6 (q, J_{C-F} = 37.8 Hz), 148.4, 137.1 (d, J_{C-F} = 7.1 Hz), 116.7, 114.5 (d, J_{C-F} = 23.3 Hz), 110.1 (d, J_{C-F} = 24.0 Hz), 108.8 (d, J_{C-F} = 8.1 Hz), 68.6, 52.8, 51.1, 42.8, 42.0, 36.4, 26.1; IR (NaCl/thin film): 3319, 2958, 2866, 2811, 1745, 1711, 1552, 1494, 1468, 1267, 1210, 1179, 808 cm^{-1}; $[\alpha]_D^{25}$ = +63.7 (*c* = 0.62, CH_2Cl_2). HRMS (ESI) calc'd for $[M+H]^+$ 363.1326, found 363.1334.

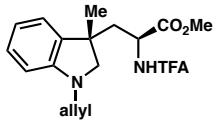
Indoline 165g.



Prepared from 5-methoxy-1,3-dimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The reaction was allowed to run for 18.5 h. The diastereomeric ratio was determined to be

14:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (10→30% ethyl acetate/hexanes) to yield 68.5 mg (91% yield) of **XX**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 88% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 7.1 min t_R(minor) = 3.6 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (br d, $J_{C\text{-}H}$ = 5.0 Hz, 1H), 6.70 (dd, $J_{C\text{-}H}$ = 8.4, 1.9 Hz, 1H), 6.62 (d, $J_{C\text{-}H}$ = 1.8 Hz, 1H), 6.50 (d, $J_{C\text{-}H}$ = 8.3 Hz, 1H), 4.01 (dd, $J_{C\text{-}H}$ = 13.1, 6.3 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.28 (d, $J_{C\text{-}H}$ = 8.6 Hz, 1H), 2.89 (d, $J_{C\text{-}H}$ = 9.1 Hz, 1H), 2.68 (s, 3H), 2.23-2.08 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.8 (q, $J_{C\text{-}F}$ = 37.5 Hz), 154.1, 146.1, 137.0, 115.6 (q, $J_{C\text{-}F}$ = 287.8 Hz), 113.1, 110.8, 109.6, 69.0, 55.8, 52.7, 51.5, 43.0, 42.0, 36.9, 26.2; IR (NaCl/thin film): 3319, 2955, 2804, 1751, 1718, 1555, 1496, 1468, 1214, 1179, 1031 cm^{-1}; $[\alpha]_D^{25}$ = +26.3 (*c* = 1.24, CH_2Cl_2). HRMS (APCI) calc'd for $[M+H]^+$ 375.1526, found 375.1542.

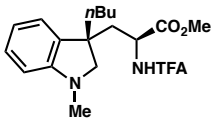
Indoline 165h.



Prepared from 1-allyl-3-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure, except the formal (3 + 2) cycloaddition was allowed to run for 24 h before adding $NaBH_4$. After adding $NaBH_4$, the reaction was allowed to run for another 24 h. The diastereomeric ratio was determined to be 5:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 60.0 mg (81% yield) of **XX**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 7.2 min t_R(minor) = 6.2 min. Isolated as a 5:1

mixture of diastereomers; the major diastereomer is denoted by *, minor diastereomer denoted by §. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (br d, *J* = 8.5 Hz, 1H§), 7.16-7.05 (m, 2H*, 1H§), 6.98 (ddd, *J* = 7.4, 1.2, 0.5 Hz, 1H*, 1H§), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H§), 6.72 (td, *J* = 7.4, 1.0 Hz, 1H*), 6.64 (d, *J* = 7.9 Hz, 1H§), 6.56 (d, *J* = 7.9 Hz, 1H*), 5.93-5.83 (m, 1H*, 1H§), 5.32-5.20 (m, 1H*, 1H§), 4.81-4.75 (m, 1H§), 4.40 (td, *J* = 7.6, 5.0, 1H*), 3.79 (ddt, *J* = 15.0, 5.9, 1.4 Hz, 1H*, 1H§), 3.73-3.70 (m, 1H§), 3.65-3.59 (m, 1H*), 3.63 (s, 3H*), 3.42 (s, 3H§), 3.31 (d, *J* = 9.3 Hz, 1H*), 3.28 (d, *J* = 9.6 Hz, 1H§), 3.07 (d, *J* = 9.6 Hz, 1H§), 3.05 (d, *J* = 9.3 Hz, 1H*), 2.35 (ddd, *J* = 14.8, 5.9, 0.6 Hz, 1H§), 2.23 (dd, *J* = 14.6, 4.9 Hz, 1H*), 2.18 (dd, *J* = 14.9, 4.6 Hz, 1H§), 2.13 (dd, *J* = 14.7, 7.8 Hz, 1H*), 1.41 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2*, 170.1§, 156.6* (q, $J_{C\text{-}F}$ = 37.6 Hz), 150.8*, 135.4*, 133.3*, 132.4§, 128.6§, 128.4*, 123.3§, 122.5*, 119.4§, 118.9§, 118.7*, 118.1*, 115.5* (q, $J_{C\text{-}F}$ = 287.9 Hz), 109.9§, 108.4*, 65.2§, 65.1*, 52.7*, 52.5§, 52.1§, 51.8*, 50.9*, 50.5§, 42.7§, 42.6*, 42.5§, 42.1*, 27.8§, 26.1*; IR (NaCl/thin film): 3316, 2957, 2923, 1750, 1718, 1605, 1554, 1487, 1460, 1437, 1209, 1165, 744 cm^{-1}; $[\alpha]_D^{25}$ = +33.412 (*c* = 1.62, CH_2Cl_2). HRMS (MM) calc'd for $[M+H]^+$ 371.1577, found 371.1582.

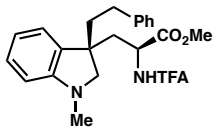
Indoline 165i.



Prepared from 3-butyl-1-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The diastereomeric ratio was determined to be >20:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 63.4 mg (82% yield) of **XX**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 92% by chiral SFC analysis (AD-

H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 7.2 min t_R(minor) = 5.3 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (br d, $J_{C\text{-}H}$ = 5.5 Hz, 1H), 7.13 (td, $J_{C\text{-}H}$ = 7.7, 1.2 Hz, 1H), 6.96 (dd, $J_{C\text{-}H}$ = 7.3, 0.7 Hz, 1H), 6.75 (t, $J_{C\text{-}H}$ = 7.3 Hz, 1H), 6.53 (d, $J_{C\text{-}H}$ = 7.8 Hz, 1H), 4.22-4.15 (m, 1H), 3.64 (s, 3H), 3.24 (d, $J_{C\text{-}H}$ = 9.3 Hz, 1H), 3.08 (d, $J_{C\text{-}H}$ = 9.3 Hz, 1H), 2.74 (s, 3H), 2.23 (dd, $J_{C\text{-}H}$ = 14.7, 8.4 Hz, 1H), 2.17 (dd, $J_{C\text{-}H}$ = 14.7, 4.7 Hz, 1H), 1.86-1.77 (m, 1H), 1.69-1.57 (m, 1H), 1.40-1.24 (m, 3H), 1.19-1.08 (m, 1H), 0.89 (t, $J_{C\text{-}H}$ = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 156.6 (q, $J_{C\text{-}F}$ = 37.5 Hz), 152.3, 134.3, 128.6, 123.0, 119.0, 115.5 (q, $J_{C\text{-}F}$ = 287.8 Hz), 108.4, 66.4, 52.7, 51.2, 46.2, 40.6, 39.3, 35.9, 26.5, 23.2, 14.0; IR (NaCl/thin film): 3319, 2956, 2932, 2860, 2809, 1751, 1718, 1606, 1559, 1491, 1465, 1207, 1178, 743 cm^{-1}; $[\alpha]_D^{25}$ = +62.0 (*c* = 1.15, CH_2Cl_2). HRMS (ESI) calc'd for $[M+H]^+$ 387.1890, found 387.1902.

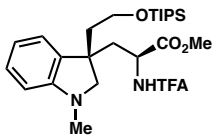
Indoline 165j.



Prepared from 1-methyl-3-phenethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure, except the formal (3 + 2) cycloaddition was allowed to run for 24 h before adding $NaBH_4$. After adding $NaBH_4$, the reaction was allowed to run for another 24 h. The diastereomeric ratio was determined to be 12:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 77.6 mg (89% yield) of **XX**. The enantiomeric excess of the major diastereomer was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 9.5 min t_R(minor) = 8.1 min. The major diastereomer was separated by flash chromatography (10% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.30-7.22 (m, 3H), 7.21-7.11 (m, 4H), 6.99 (dd, $J_{C\text{-}H}$ = 7.4, 1.0 Hz, 1H), 6.75 (td, $J_{C\text{-}H}$ = 7.4, 0.7 Hz, 1H), 6.55 (d, $J_{C\text{-}H}$ = 7.9 Hz, 1H), 4.27 (dt, $J_{C\text{-}H}$ = 12.6, 6.4 Hz, 1H), 3.63 (s, 3H), 3.30 (d, $J_{C\text{-}H}$ = 9.3 Hz, 1H), 3.17 (d, $J_{C\text{-}H}$ = 9.3 Hz, 1H), 2.76 (s, 3H), 2.68 (td, $J_{C\text{-}H}$ = 13.0, 5.0 Hz, 1H), 2.47 (td, $J_{C\text{-}H}$ = 12.9, 4.7 Hz, 1H), 2.34-2.22 (m, 2H), 2.13 (ddd, $J_{C\text{-}H}$ = 13.7, 12.3, 5.1 Hz, 1H), 1.97 (ddd, $J_{C\text{-}H}$ = 13.8, 12.6, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.6 (q, $J_{C\text{-}F}$ = 37.5 Hz), 152.4, 141.7, 133.5, 128.7, 128.5, 128.2, 126.0, 122.9, 119.0, 115.5 (q, $J_{C\text{-}F}$ = 287.8 Hz), 108.4, 66.0, 52.7, 51.1, 46.3, 41.5, 40.7, 35.8, 30.8; IR (NaCl/thin film): 3317, 2951, 2858, 2812, 1749, 1716, 1606, 1555, 1494, 1453, 1208, 1178, 745 cm^{-1}; $[\alpha]_D^{26}$ = +23.1 (*c* = 0.87, CH_2Cl_2). HRMS (MM) calc'd for $[M+H]^+$ 435.1890, found 435.1882.

Indoline 165k.

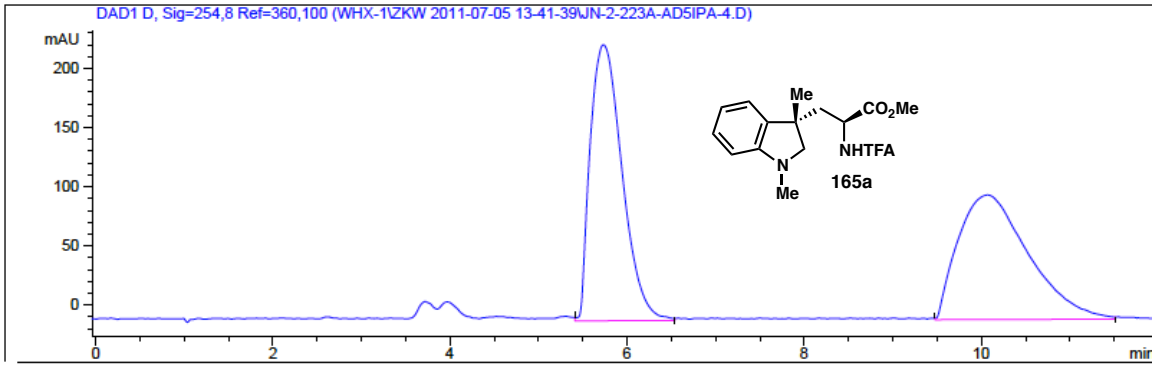


Prepared from 1-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure, except the formal (3 + 2) cycloaddition was allowed to run for 20.5 h before adding $NaBH_4$. After adding $NaBH_4$, the reaction was allowed to run for another 24 h. The diastereomeric ratio was determined to be >20:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→30% ethyl acetate/hexanes) to yield 68.3 mg (64% yield) of **XX**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 8.7 min t_R(minor) = 7.5 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (br s, 1H), 7.15 (t, $J_{C\text{-}H}$ = 7.6 Hz, 1H), 7.00 (d, $J_{C\text{-}H}$ = 7.2 Hz, 1H), 6.75 (t, $J_{C\text{-}H}$ = 7.1 Hz, 1H), 6.54 (d, $J_{C\text{-}H}$ = 7.3 Hz, 1H), 4.22-4.15 (m, 1H), 3.81 (dd, $J_{C\text{-}H}$ = 6.96, 5.35 Hz, 2H), 3.64 (s, 3H), 3.34-3.26 (m, 1H), 3.26-3.18 (m, 1H), 2.74

(s, 3H), 2.46-2.36 (m, 1H), 2.24 (dd, $J_{C\text{-}H}$ = 14.7, 3.7 Hz, 1H), 2.11-1.94 (m, 2H), 1.08-1.03 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.7 (q, $J_{C\text{-}F}$ = 37.6 Hz), 152.1, 134.3, 128.7, 123.0, 118.9, 115.6 (q, $J_{C\text{-}F}$ = 287.8 Hz), 108.5, 67.6, 60.0, 52.6, 51.2, 45.3, 41.2, 39.5, 18.0, 18.0, 11.9; IR (NaCl/thin film): 3323, 2943, 2866, 1719, 1606, 1552, 1491, 1463, 1207, 1175, 1104, 882, 742 cm^{-1}; $[\alpha]_D^{25}$ = +27.4 (*c* = 0.85, CH_2Cl_2). HRMS (APCI) calc'd for $[M+H]^+$ 531.2860, found 531.2883.

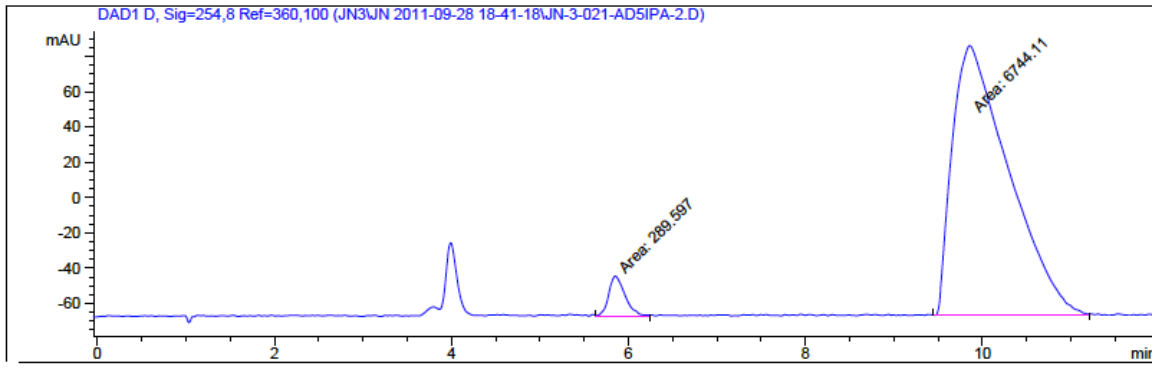
3.4.4 SFC Traces for Racemic and Enantioenriched Products

165a (Figure 9): racemic



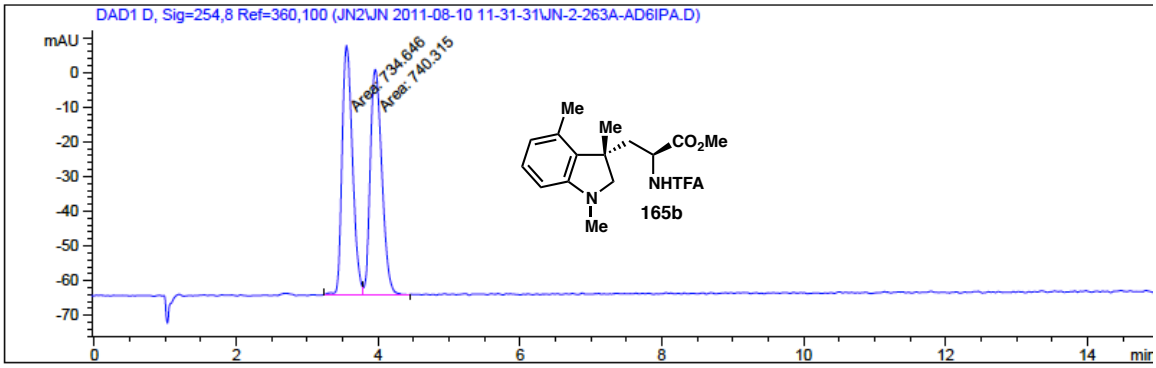
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.733	VV	0.4124	5847.14258	233.31508	50.2291
2	10.073	VV	0.7324	5793.80518	105.22972	49.7709

165a (Figure 9): 92% ee



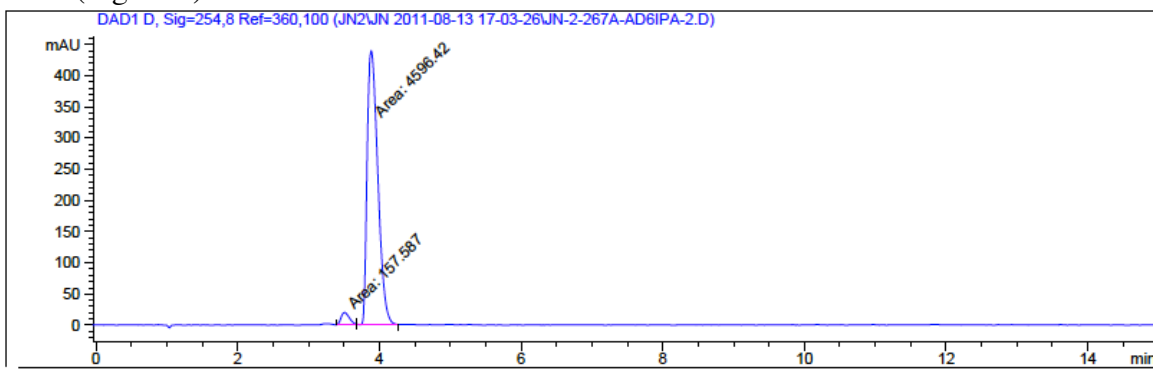
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.852	MM	0.2132	289.59744	22.63515	4.1173
2	9.857	MM	0.7372	6744.11035	152.46228	95.8827

165b (Figure 9): racemic



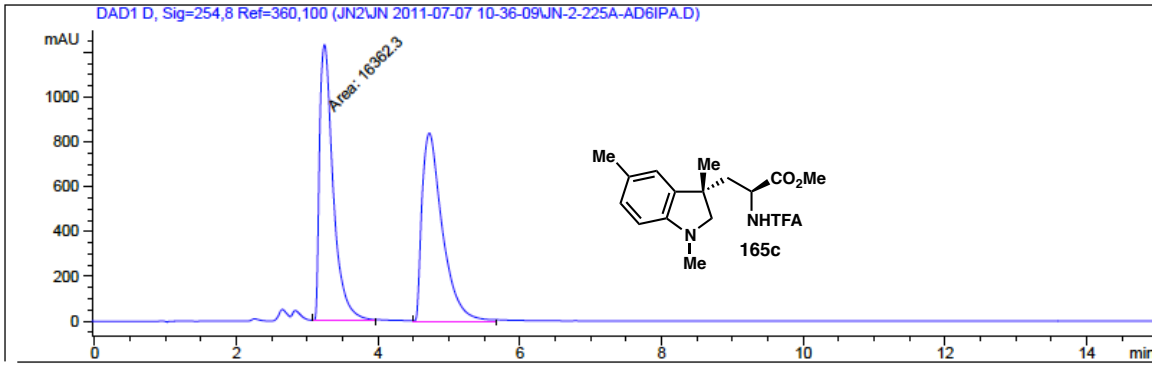
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.555	MM	0.1704	734.64594	71.86649	49.8078
2	3.960	MM	0.1899	740.31531	64.97649	50.1922

165b (Figure 9): 93% ee



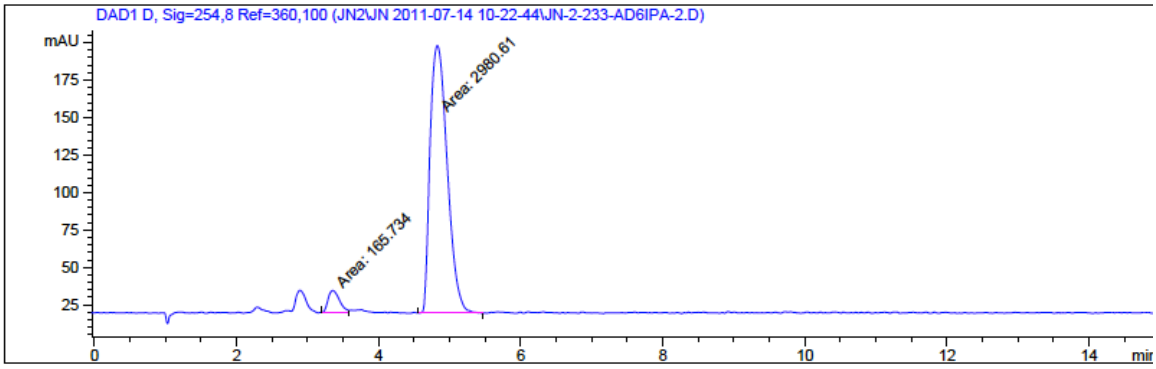
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.510	MM	0.1343	157.58659	19.55832	3.3148
2	3.886	MM	0.1745	4596.41699	439.04443	96.6852

165c (Figure 9): racemic



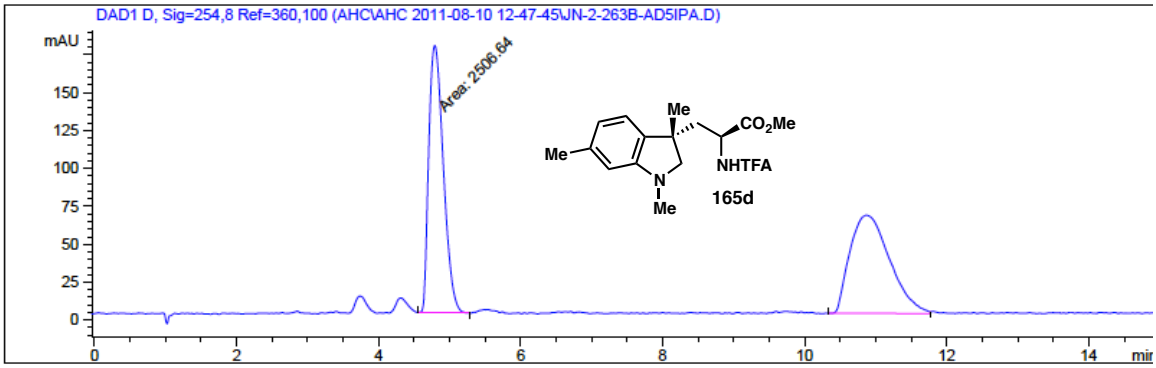
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.242	MM	0.2216	1.63623e4	1230.56165	49.1373
2	4.723	VV	0.3066	1.69368e4	842.43842	50.8627

165c (Figure 9): 89% ee



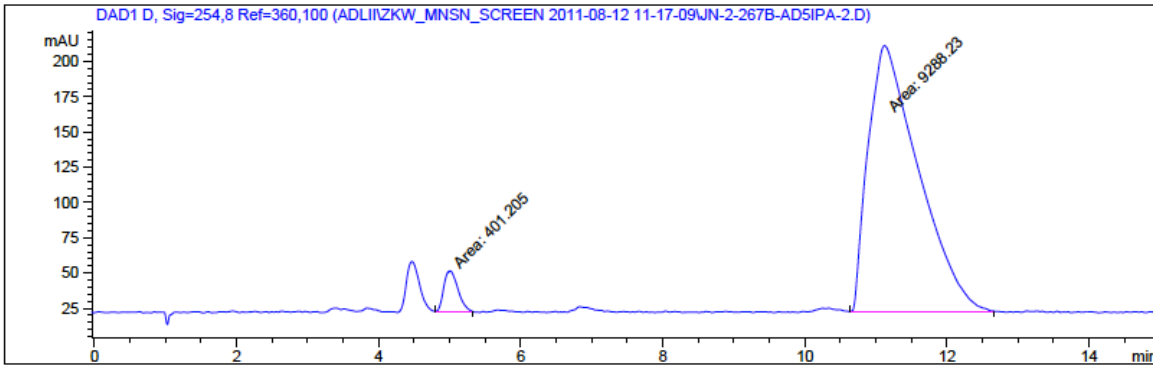
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.356	MM	0.1880	165.73442	14.69443	5.2675
2	4.826	MM	0.2787	2980.60571	178.23856	94.7325

165d (Figure 9): racemic



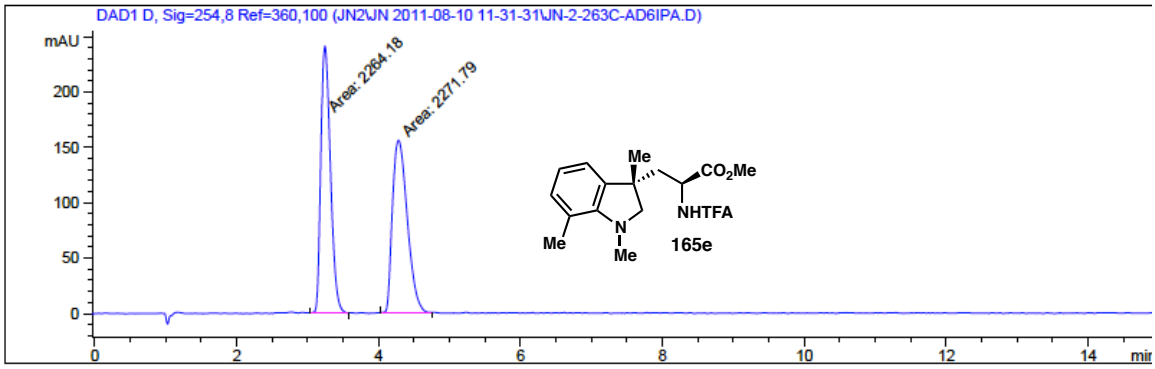
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.791	MM	0.2372	2506.63574	176.10995	49.9313
2	10.862	BV	0.5828	2513.53687	64.75647	50.0687

165c (Figure 9): 92% ee



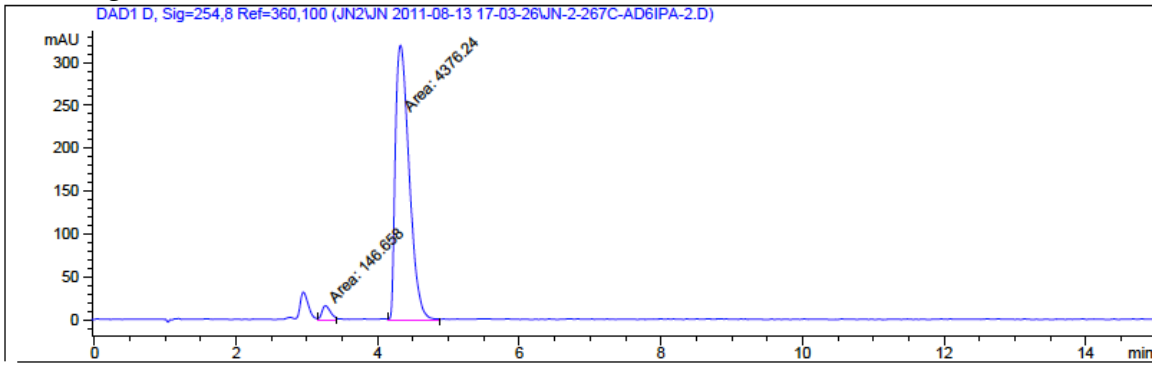
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.005	MM	0.2320	401.20471	28.82077	4.1406
2	11.122	MM	0.8212	9288.23340	188.50002	95.8594

165e (Figure 9): racemic



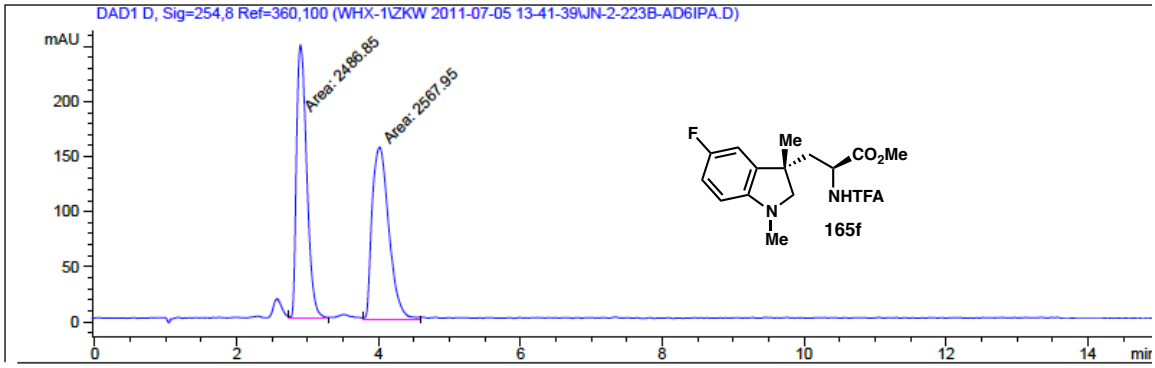
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.241	MM	0.1566	2264.17603	241.04764	49.9161
2	4.280	MM	0.2428	2271.78613	155.94717	50.0839

165e (Figure 9): 94% ee



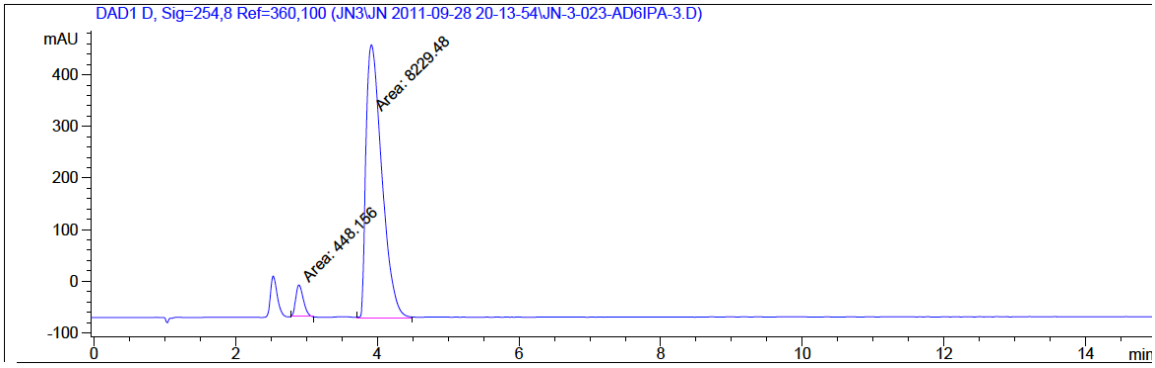
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.261	MM	0.1428	146.65776	17.12008	3.2426
2	4.322	MM	0.2272	4376.23779	321.00308	96.7574

165f (Figure 9): racemic



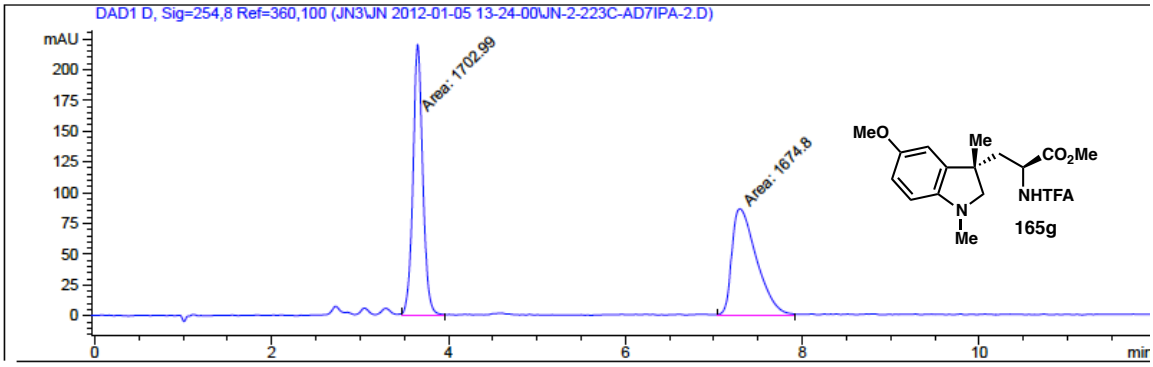
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.900	MM	0.1670	2486.84692	248.18283	49.1978
2	4.015	MM	0.2735	2567.94849	156.45912	50.8022

165f (Figure 9): 90% ee



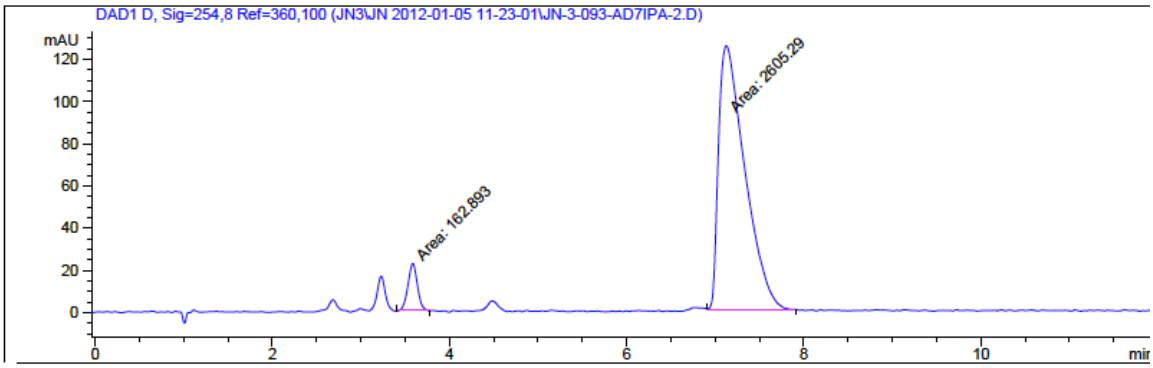
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.894	MM	0.1228	448.15573	60.80370	5.1645
2	3.917	MM	0.2592	8229.47559	529.13312	94.8355

165g (Figure 9): racemic



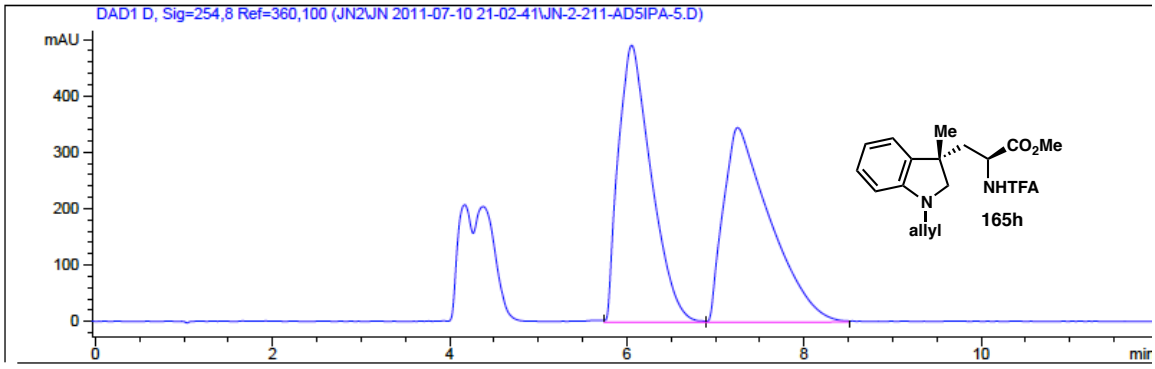
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.651	MM	0.1289	1702.99353	220.23915	50.4173
2	7.294	MM	0.3230	1674.80334	86.42379	49.5827

165g (Figure 9): 88% ee



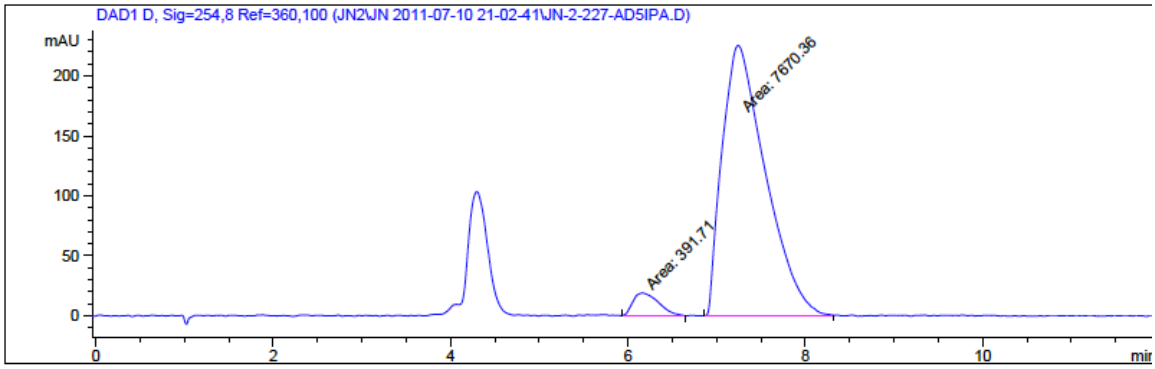
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.585	MM	0.1218	162.89281	22.29179	5.8845
2	7.127	MM	0.3462	2605.29150	125.42136	94.1155

165h (Figure 9): racemic



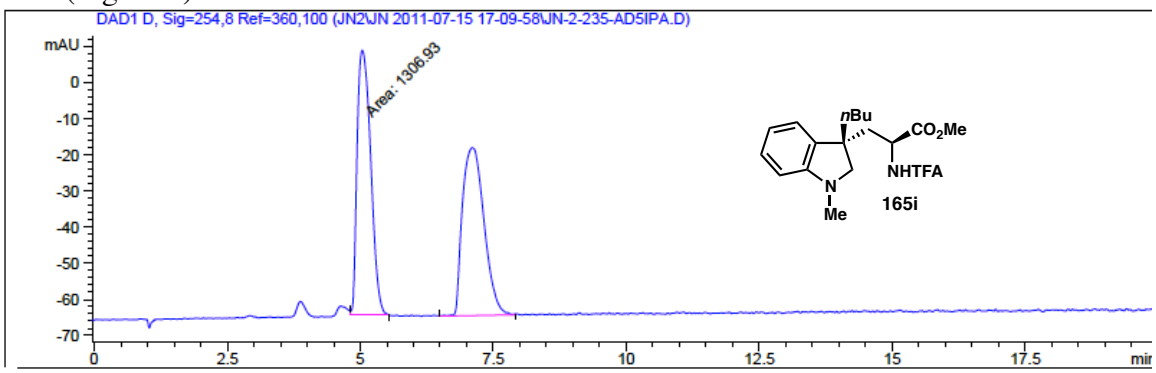
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.054	VV	0.3527	1.26647e4	491.32587	49.9094
2	7.251	VV	0.4860	1.27107e4	344.87524	50.0906

165h (Figure 9): 90% ee



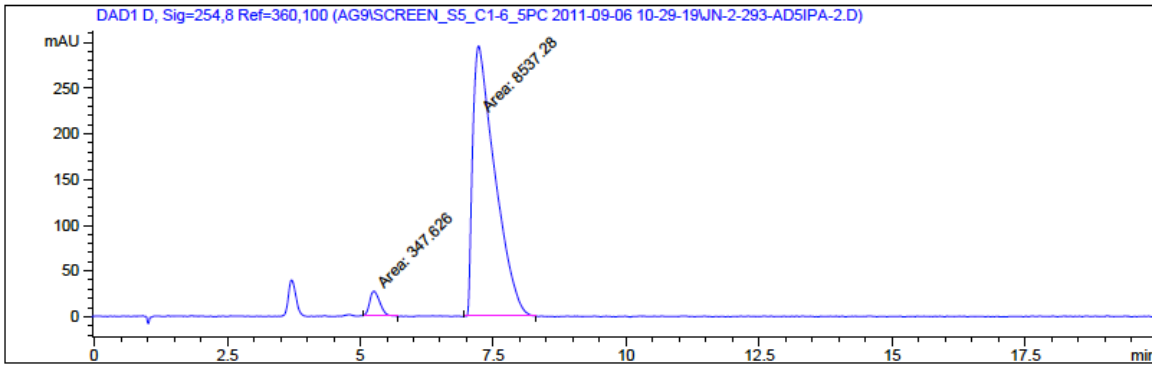
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.163	MM	0.3375	391.71039	19.34439	4.8587
2	7.244	MM	0.5670	7670.36182	225.47943	95.1413

165i (Figure 9): racemic



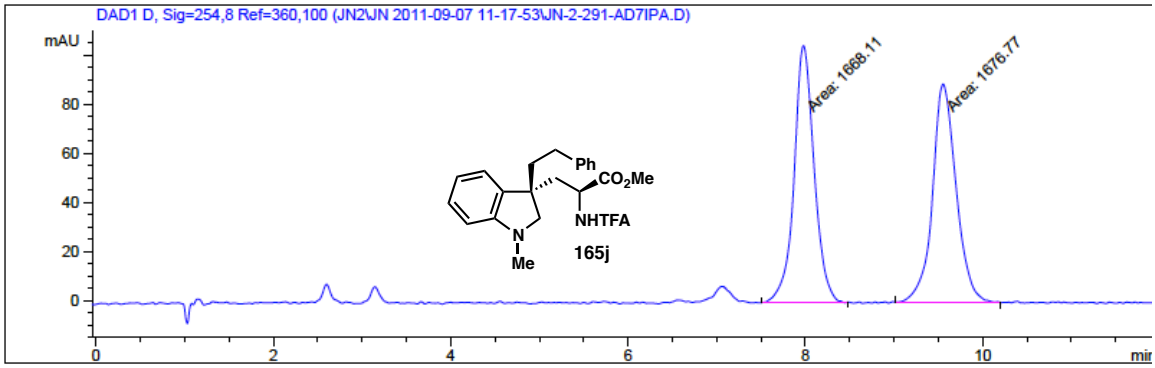
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.038	MM	0.2964	1306.92871	73.49715	49.8219
2	7.100	BB	0.4502	1316.27185	46.51159	50.1781

165i (Figure 9): 92% ee



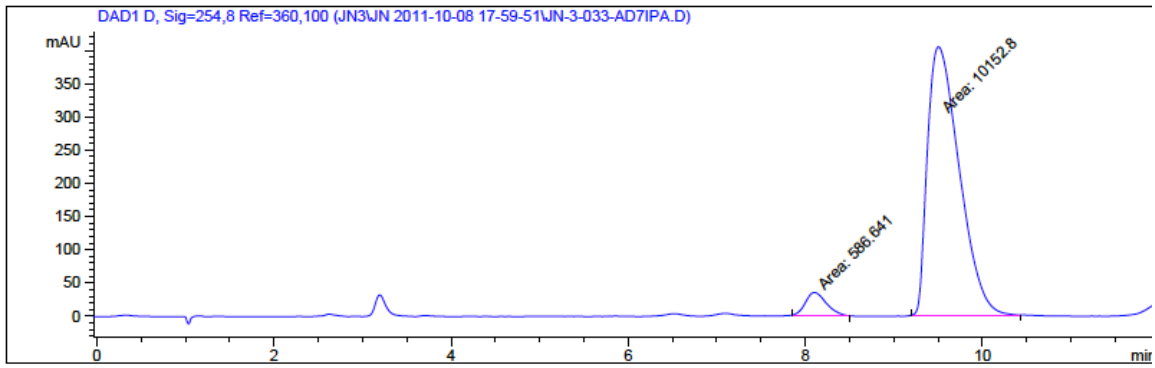
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.257	MM	0.2145	347.62573	27.00829	3.9125
2	7.226	MM	0.4818	8537.27539	295.33777	96.0875

165j (Figure 9): racemic



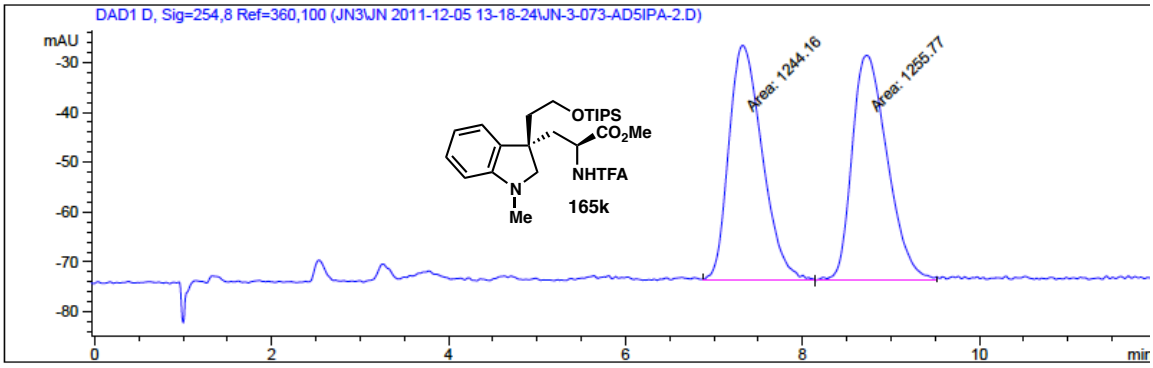
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.978	MM	0.2644	1668.11194	105.15713	49.8706
2	9.552	MM	0.3123	1676.76514	89.49041	50.1294

165j (Figure 9): 89% ee



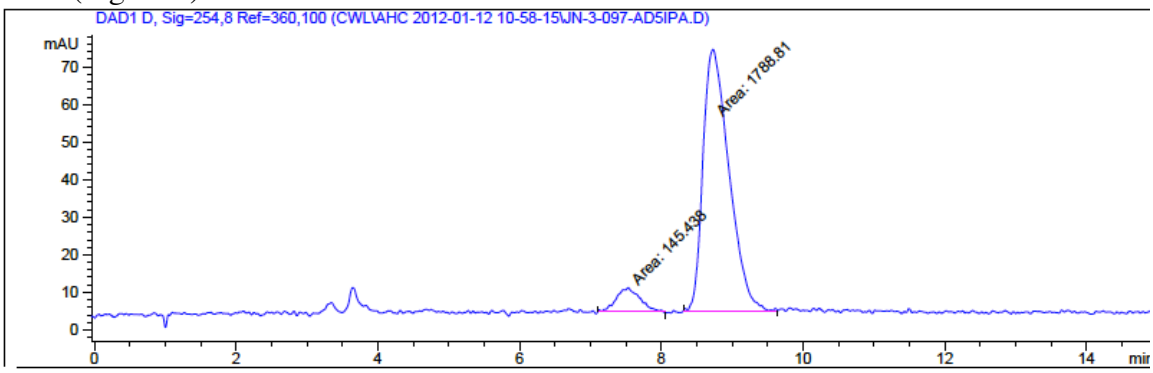
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.105	MM	0.2771	586.64099	35.28017	5.4625
2	9.505	MM	0.4177	1.01528e4	405.11353	94.5375

165k (Figure 9): racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.326	MM	0.4403	1244.16138	47.09854	49.7677
2	8.731	MM	0.4640	1255.77466	45.10927	50.2323

165k (Figure 9): 85% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.535	MM	0.3798	145.43784	6.38237	7.5191
2	8.729	MM	0.4271	1788.81250	69.80029	92.4809

3.5 Notes and References

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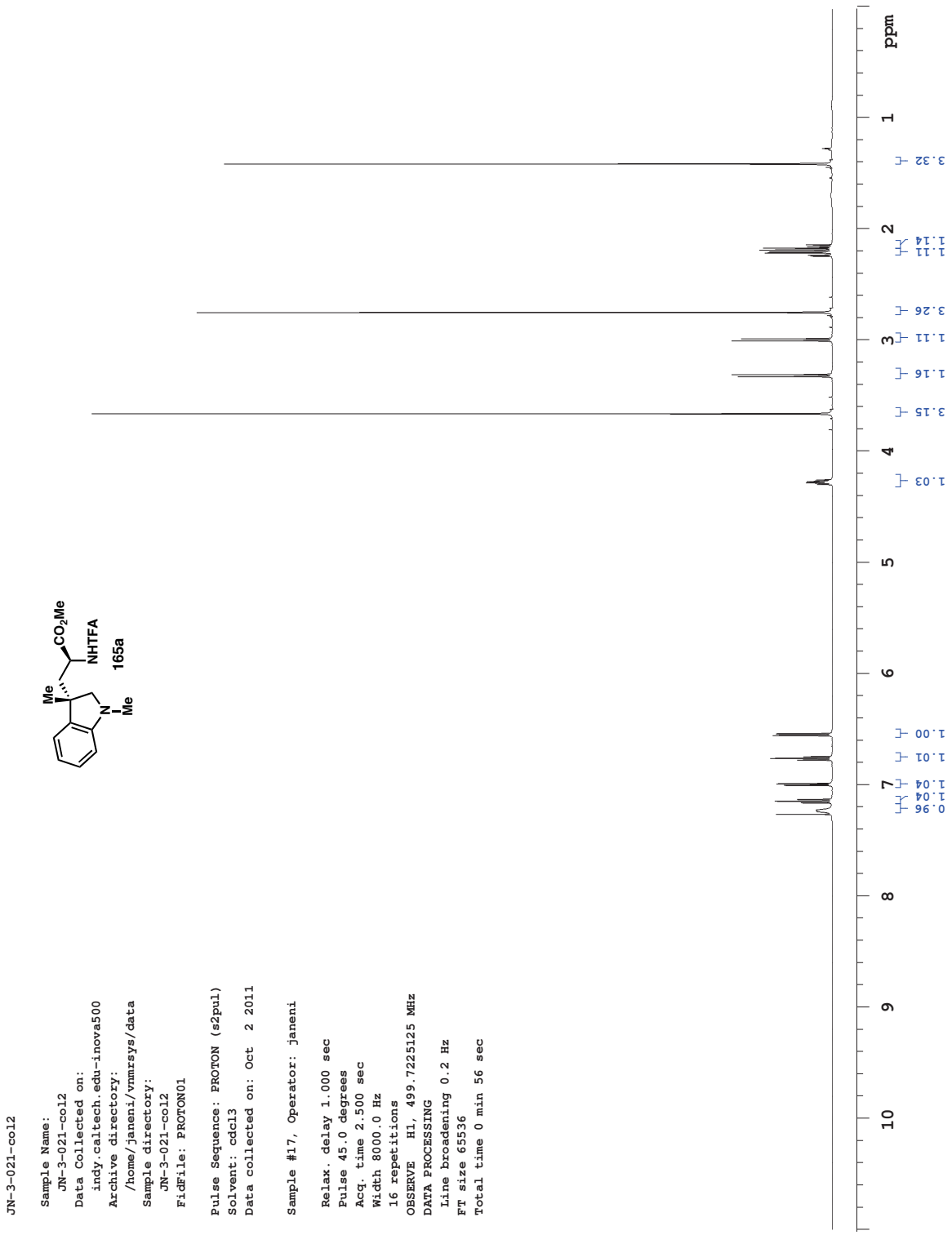
APPENDIX 3

Spectra Relevant to Chapter 3:

Conjugate Addition/in situ Reduction for the Synthesis of Indolines


JN-3-021-co12
Sample Name:
JN-3-021-co12
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-3-021-co12
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 2 2011
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, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
CO2Me
NHTFA
165a
Me
N
Me
ppm
1
2
3
4
5
6
7
8
9
10
3.32
1.14
1.11
3.26
1.11
1.16
3.15
1.03
1.00
1.01
1.04
1.04
0.96

JN-3-021-col2-carbon

SAMPLE

date	Oct 2 2011
solvent	cdcl3
file	/data/indy/janeni/vnmrsys/data/JN-3-021-col2-carbon/CARBON01.fid

ACQUISITION

sw	31446.5
at	1.042
np	65536
fb	not used
bs	64
d1	1.000
nt	6500
ct	6500

TRANSMITTER

tn	C13
sfrq	125.669
tof	1913.4
tpwr	56
pw	4.050

DECOUPLER

dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	11900

PRESATURATION

satmode	n
wet	n

SPECIAL

temp	not used
gain	30
spin	0
hst	0.006
pw90	8.100
alfa	10.000

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.50
lsfid	-4
fn	not used

DISPLAY

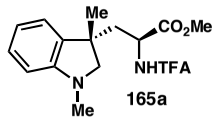
sp	-0.1
wp	27643.4
rfl	1901.2
rfp	0
rp	177.9
lp	121.9

PLOT

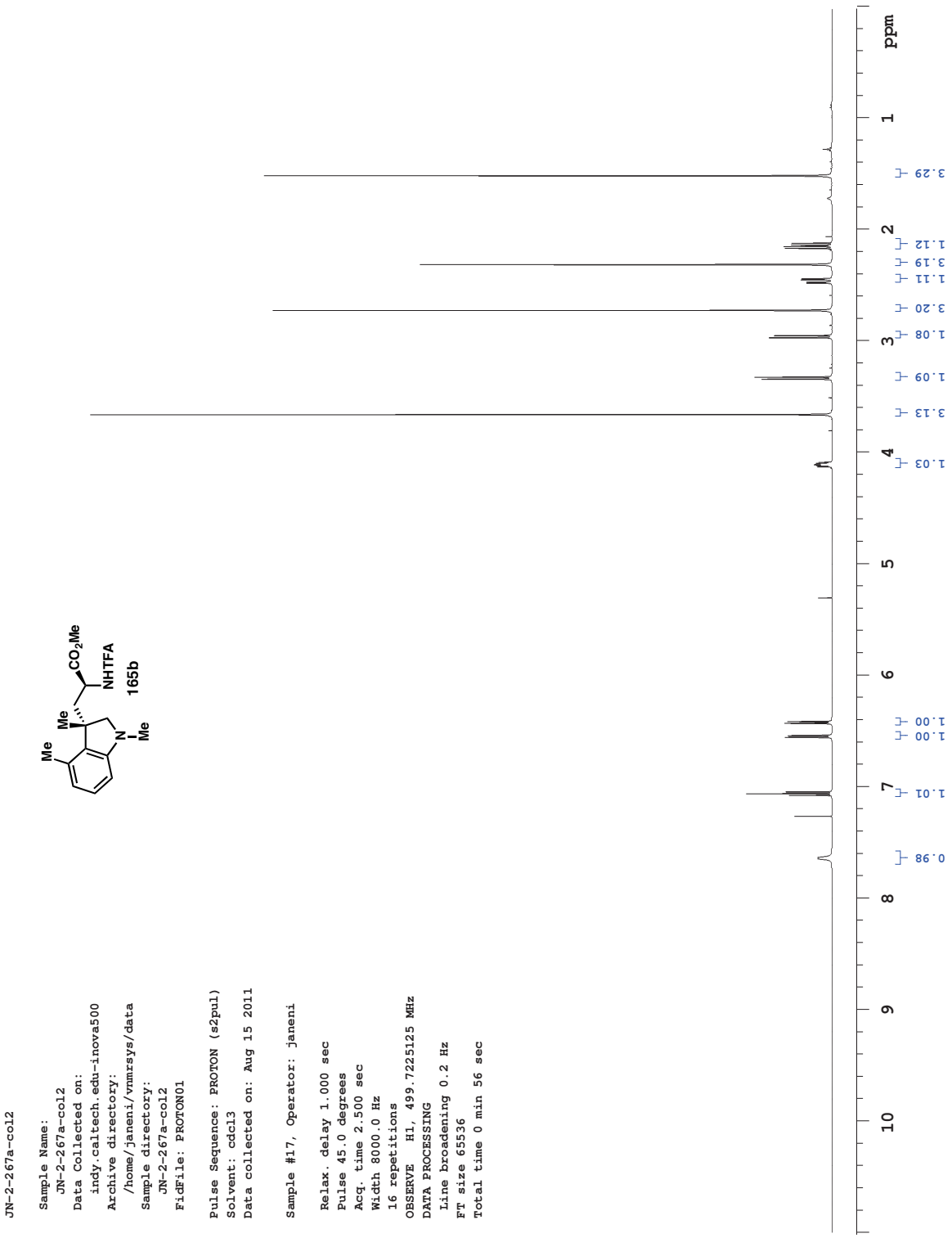
wc	234
sc	8
vs	10933
th	2
ai cdc ph	

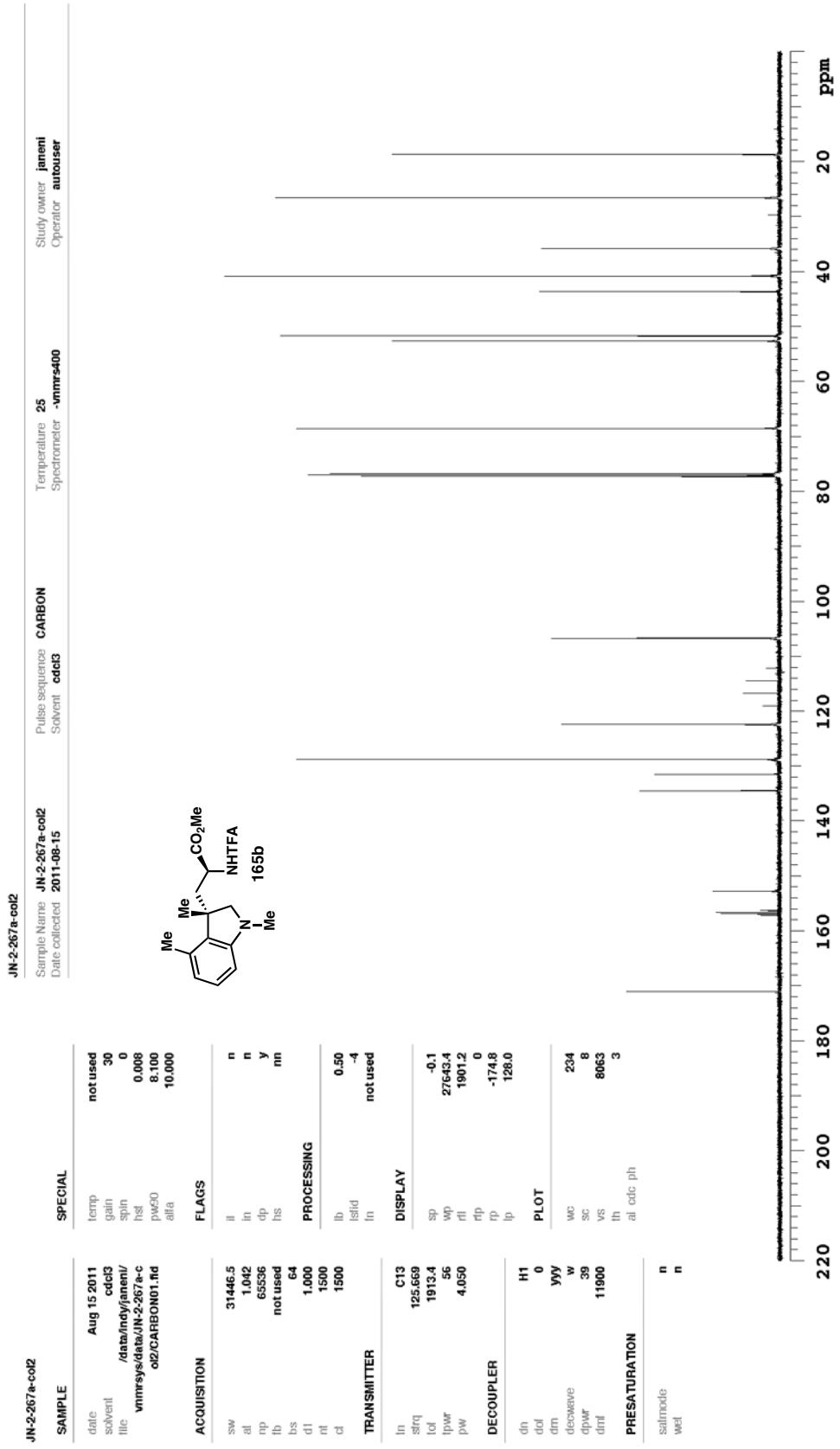
JN-3-021-col2-carbon

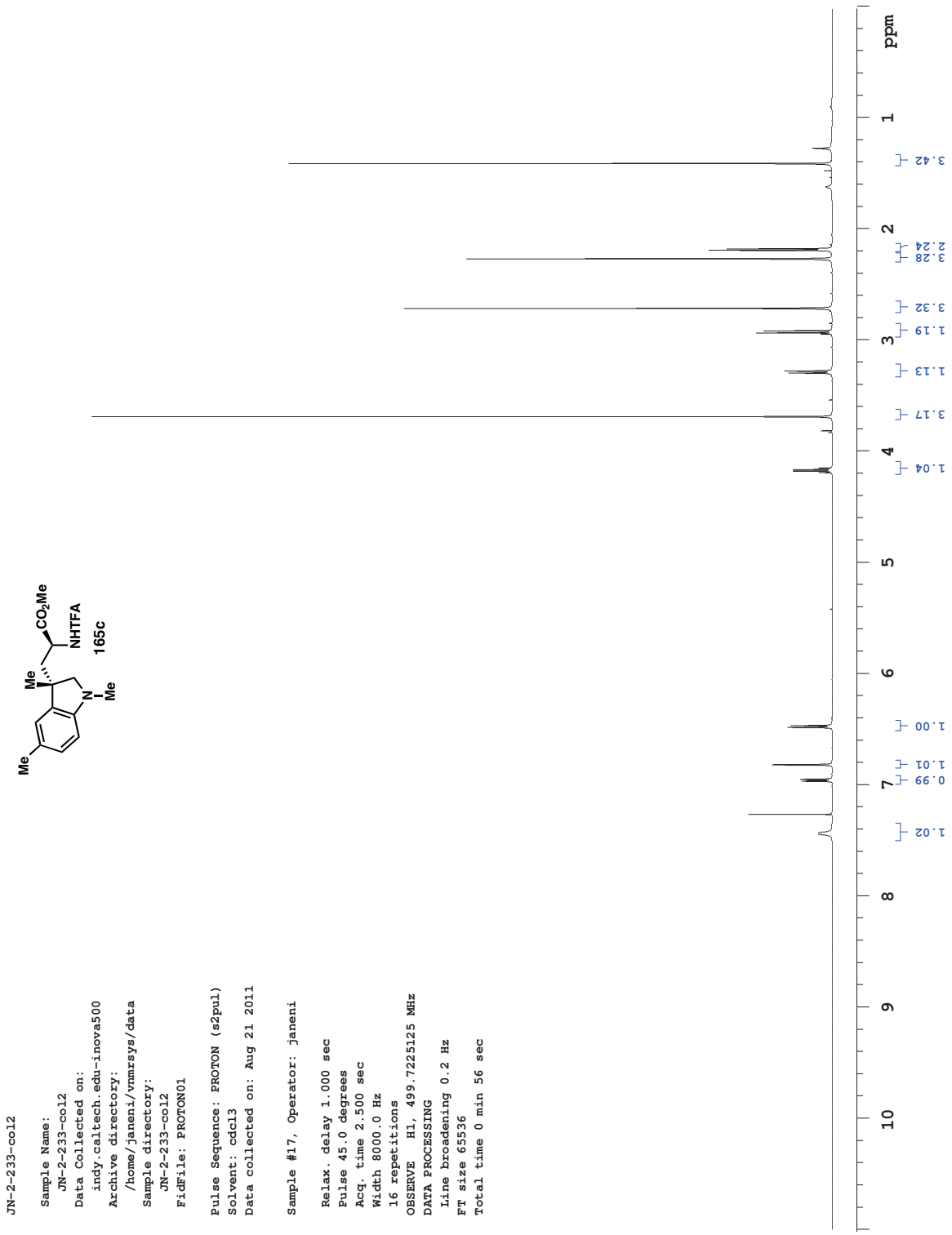
Sample Name	JN-3-021-col2-carbon	Pulse sequence	CARBON	Temperature	25	Study owner	janeni
Date collected	2011-10-02	Solvent	cdcl3	Spectrometer	-vnmrs400	Operator	autouser



165a


JN-2-267a-col2
Sample Name:
JN-2-267a-col2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-2-267a-col2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 15 2011
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, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
Me
Me
CO2Me
NHTFA
N
Me
165b
ppm
1
2
3
4
5
6
7
8
9
10
3.29
1.12
3.19
1.11
3.20
1.08
1.09
3.13
1.03
1.00
1.00
1.01
0.98


JN-2-267a-col2
Sample Name JN-2-267a-col2
Date collected 2011-08-15
Pulse sequence CARBON
Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner janeni
Operator autouser
JN-2-267a-col2
SAMPLE
date Aug 15 2011
solvent cdcl3
file /data/indy/janeni/vnmrsys/data/JN-2-267a-col2/CARBON01.fid
ACQUISITION
sw 31446.5
at 1.042
np 65536
fb not used
bs 64
d1 1.000
nt 1500
ct 1500
TRANSMITTER
tn C13
sfrq 125.669
tof 1913.4
tpwr 56
pw 4.050
DECOUPLER
dn H1
dof 0
dm yyy
decmeve w
dpwr 39
dmf 11900
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 30
spin 0
hst 0.008
pw90 8.100
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
lsfid -4
ln not used
DISPLAY
sp -0.1
wp 27643.4
rfl 1901.2
rfp 0
rp -174.8
lp 128.0
PLOT
wc 234
sc 8
vs 8063
th 3
al cdc ph
Me
Me
CO2Me
NHTFA
N
Me
165b
220
200
180
160
140
120
100
80
60
40
20
ppm


JN-2-233-co12
Sample Name:
JN-2-233-co12
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-2-233-co12
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 21 2011
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, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
Me
CO2Me
NHTFA
165c
N
Me
Me
ppm
1
2
3
4
5
6
7
8
9
10
3.42
3.28
2.24
3.32
1.19
1.13
3.17
1.04
1.00
1.01
0.99
1.02

JN-2-233-col2-carbon

SAMPLE	
date	Aug 22 2011
solvent	cdcl3
file	/data/indy/janeni/vnmrsys/data/JN-2-233-col2-carbon/CARBON01.fid

ACQUISITION	
sw	31446.5
at	1.042
np	65536
fb	not used
bs	64
d1	1.000
nt	4800
ct	4800

TRANSMITTER	
tn	C13
sfrq	125.669
tof	1913.4
tpwr	56
pw	4.050

DECOUPLER	
dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	11900

PRESATURATION	
satmode	n
wet	n

SPECIAL	
temp	not used
gain	30
spin	0
hst	0.008
pw90	8.100
alfa	10.000

FLAGS	
il	n
in	n
dp	y
hs	nn

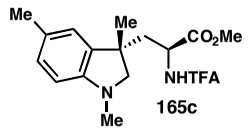
PROCESSING	
lb	0.50
lsfid	-4
fn	not used

DISPLAY	
sp	-0.1
wp	27643.4
rfl	1901.2
rfp	0
rp	165.7
lp	145.3

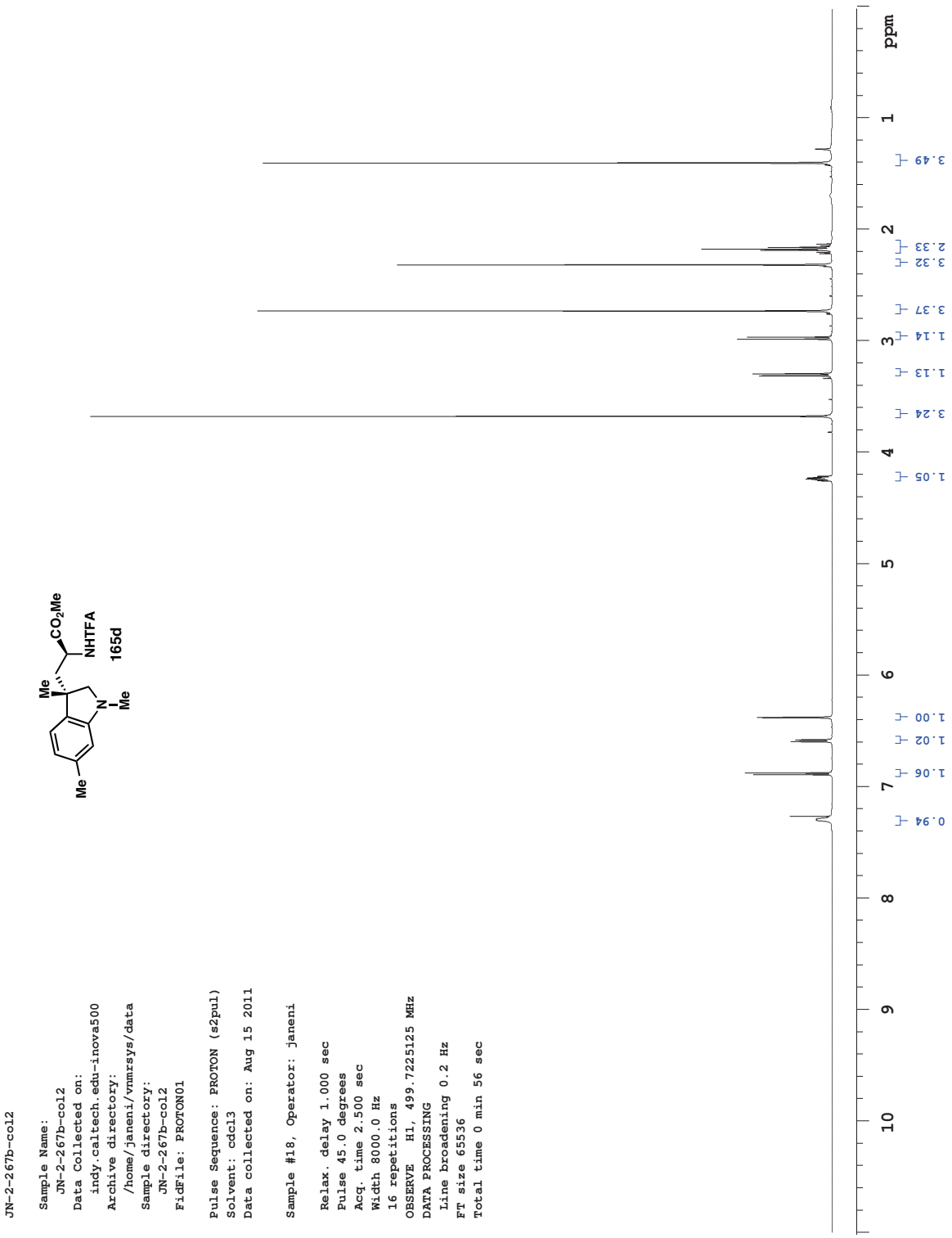
PLOT	
wc	234
sc	8
vs	10487
th	5
al cdc ph	

JN-2-233-col2-carbon

Sample Name JN-2-233-col2-carbon	Pulse sequence CARBON	Temperature 25	Study owner janeni
Date collected 2011-08-22	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser



165c


JN-2-267b-col2
Sample Name:
JN-2-267b-col2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-2-267b-col2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 15 2011
Sample #18, Operator: janeni
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
CO2Me
NHTFA
165d
Me
N
Me
Me
ppm
3.49
2.33
3.32
3.37
1.14
1.13
3.24
1.05
1.00
1.02
1.06
0.94

JN-2-267b-col2

SAMPLE

date	Aug 15 2011
solvent	cdcl3
file	/data/indy/janeni/vnmrsys/data/JN-2-267b-col2/CARBON01.fid

ACQUISITION

sw	31446.5
at	1.042
np	65536
fb	not used
bs	64
d1	1.000
nt	1500
ct	1500

TRANSMITTER

tn	C13
sfrq	125.669
tof	1913.4
tpwr	56
pw	4.050

DECOUPLER

dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	11900

PRESATURATION

satmode	n
wet	n

SPECIAL

temp	not used
gain	30
spin	0
hst	0.008
pw90	8.100
alfa	10.000

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.50
lstid	-4
fn	not used

DISPLAY

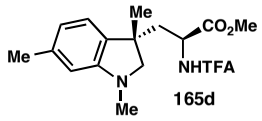
sp	-0.1
wp	27643.4
rfl	1901.2
rfp	0
rp	178.1
lp	110.2

PLOT

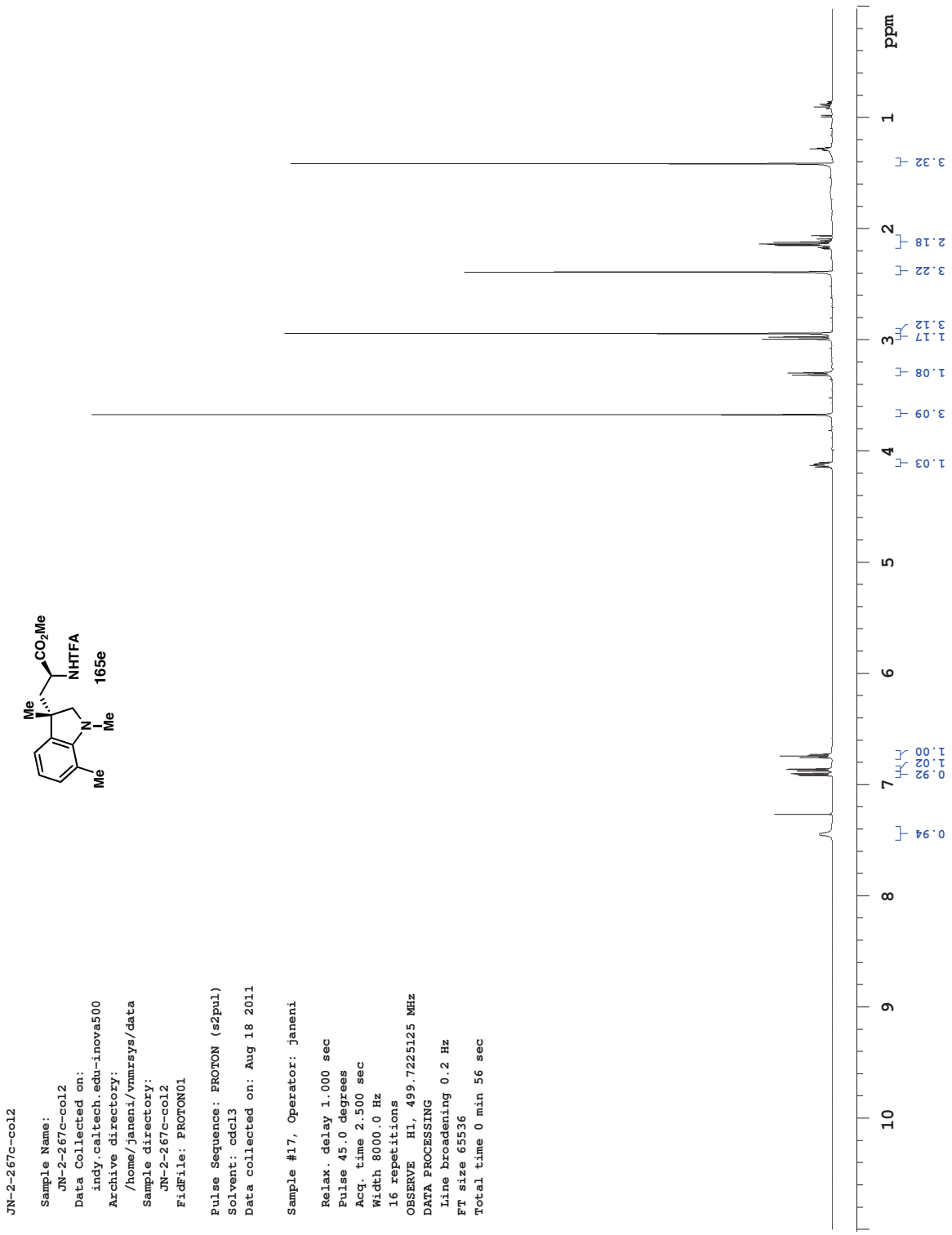
wc	234
sc	8
vs	11019
th	4
ai cdc ph	

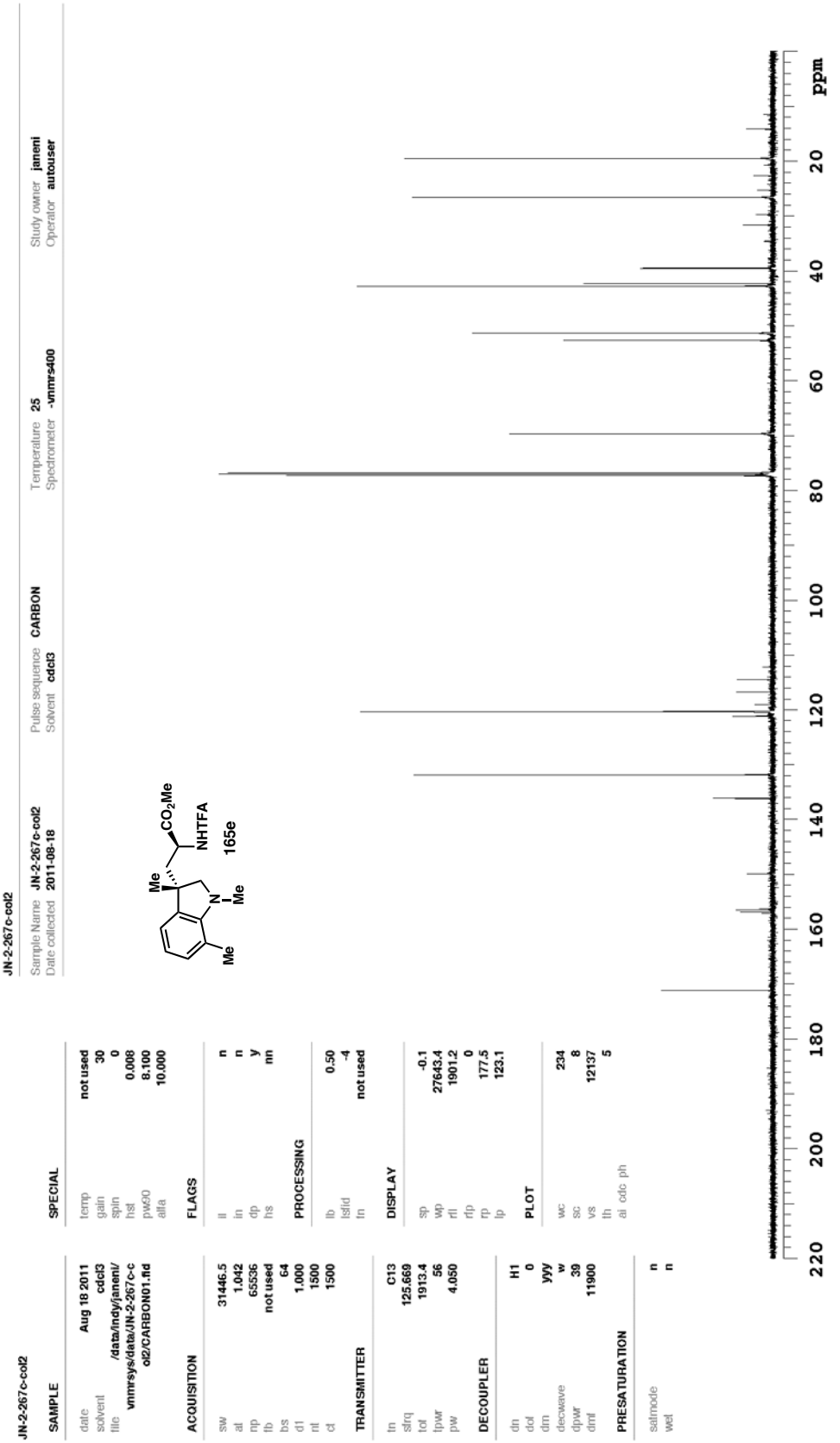
JN-2-267b-col2

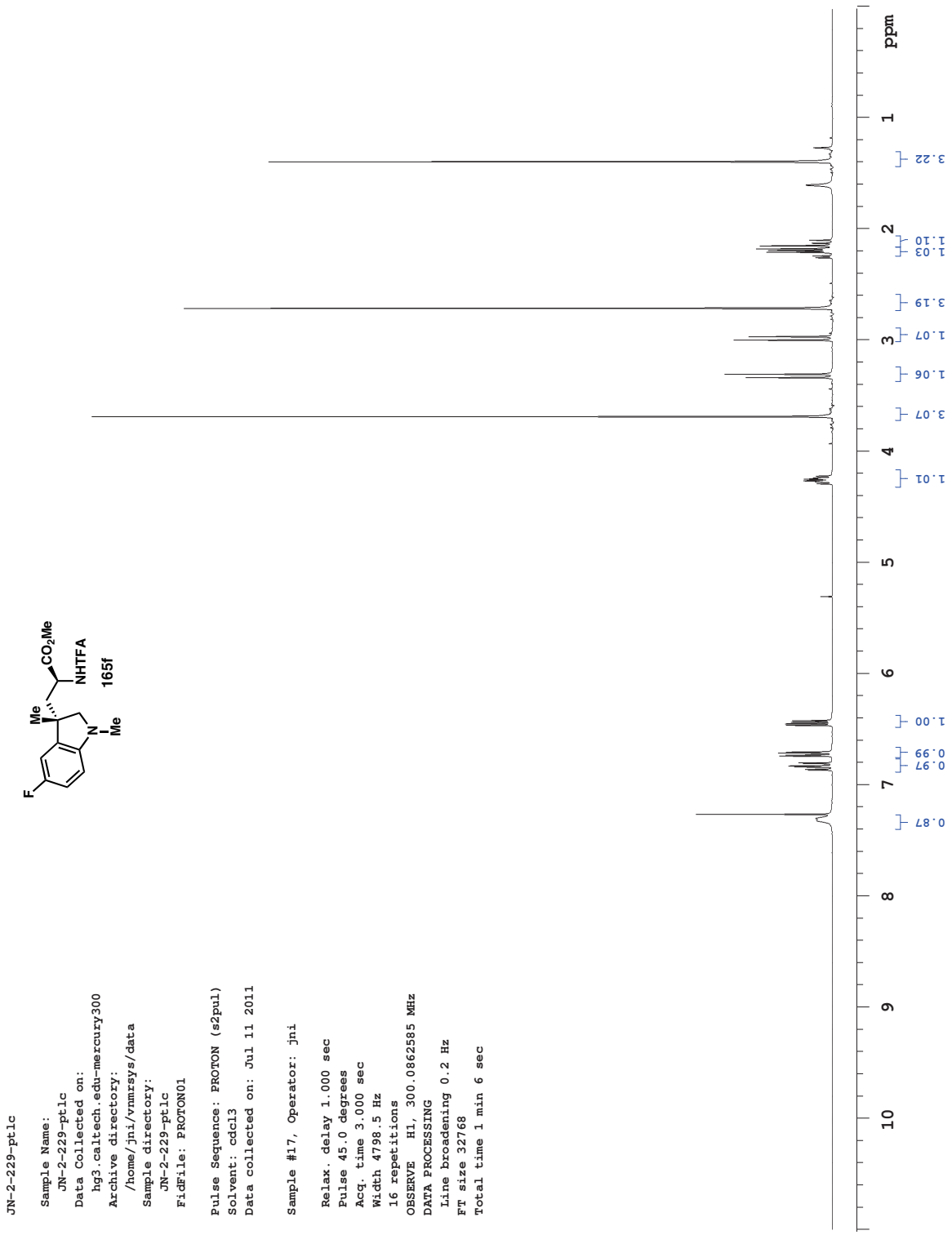
Sample Name JN-2-267b-col2	Pulse sequence CARBON	Temperature 25	Study owner janeni
Date collected 2011-08-15	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser

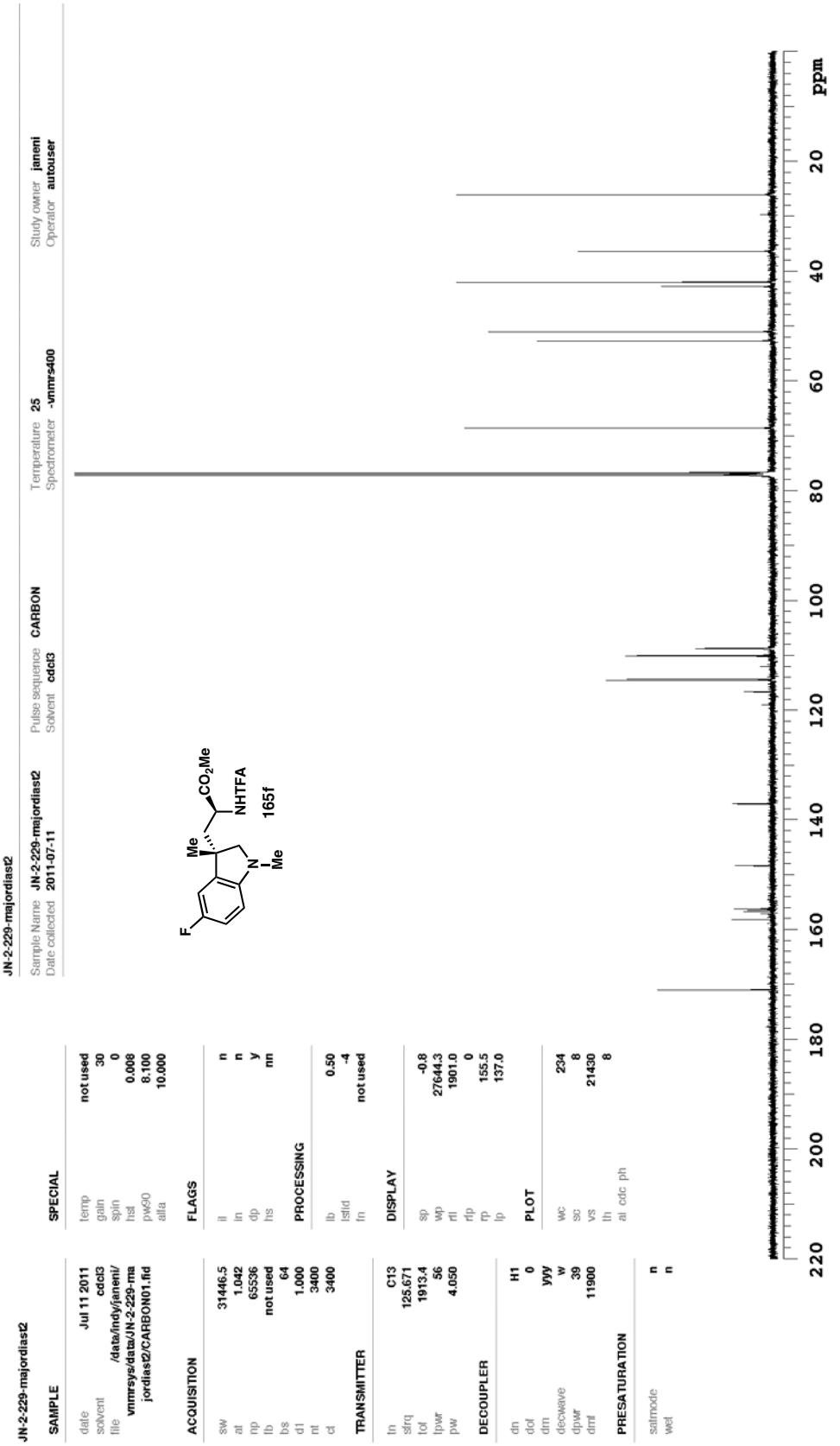


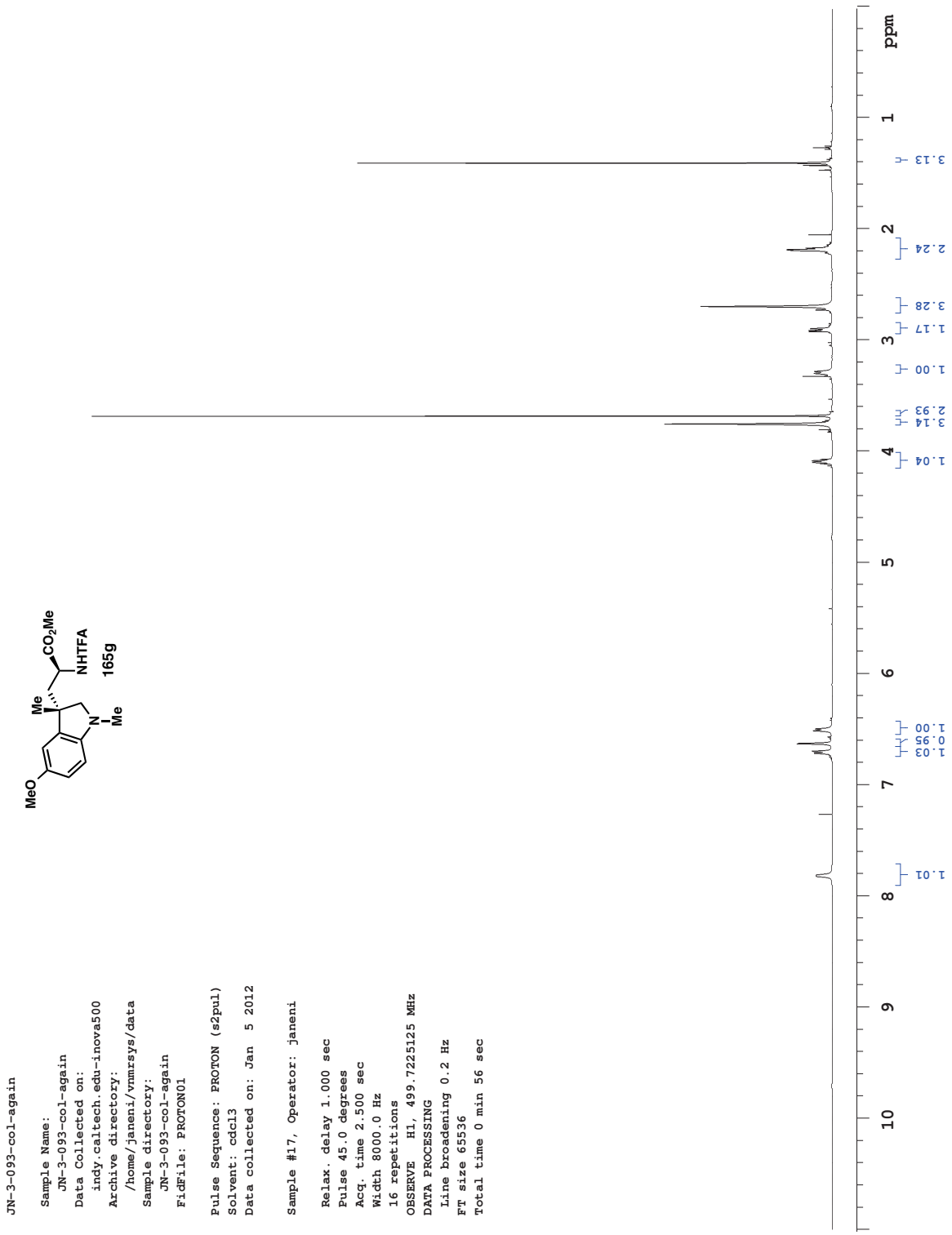
165d


JN-2-267c-col2
Sample Name:
JN-2-267c-col2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-2-267c-col2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 18 2011
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, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
CO2Me
NHTFA
165e
Me
N
Me
Me
ppm
10
9
8
7
6
5
4
3
2
1
0.94
0.92
1.02
1.00
1.03
3.09
1.08
1.17
3.12
3.22
2.18
3.32


JN-2-267c-col2
Sample Name JN-2-267c-col2
Date collected 2011-08-18
Pulse sequence CARBON
Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner janeni
Operator autouser
CO2Me
NHTFA
165e
Me
N
Me
Me
SAMPLE
SPECIAL
ACQUISITION
FLAGS
PROCESSING
TRANSMITTER
DISPLAY
DECOUPLER
PLOT
PRESATURATION
ppm


JN-2-229-ptlc
Sample Name:
JN-2-229-ptlc
Data Collected on:
hg3.caltech.edu-marcury300
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-2-229-ptlc
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2011
Sample #17, Operator: jni
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
16 repetitions
OBSERVE H1, 300.0862585 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 min 6 sec
Me
CO2Me
NHTFA
165f
N
Me
F
ppm
1
2
3
4
5
6
7
8
9
10
3.22
1.03
1.10
3.19
1.07
1.06
3.07
1.01
1.00
0.99
0.97
0.87


JN-2-229-majordiast2
Sample Name JN-2-229-majordiast2
Date collected 2011-07-11
Pulse sequence CARBON
Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner janeni
Operator autouser
Me
CO2Me
NHTFA
F
N
Me
165f
JN-2-229-majordiast2
SAMPLE
date Jul 11 2011
solvent cdcl3
file /data/lndy/janeni/
vnmrsys/data/JN-2-229-ma
jordiast2/CARBON01.fid
ACQUISITION
sw 31446.5
at 1.042
np 65536
fb not used
bs 64
d1 1.000
nt 3400
ct 3400
TRANSMITTER
tn C13
sfrq 125.671
tof 1913.4
tpwr 56
pw 4.050
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 39
dmf 11900
PRESATURATION
satmode n
wet n
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
lstld -4
fn not used
DISPLAY
sp -0.8
wp 27644.3
rfl 1901.0
rfp 0
rp 155.5
lp 137.0
PLOT
wc 234
sc 8
vs 21430
th 8
al cdc ph
220
200
180
160
140
120
100
80
60
40
20
ppm


JN-3-093-col-again
Sample Name:
JN-3-093-col-again
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-3-093-col-again
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 5 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, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
MeO
Me
CO2Me
NHTFA
N
Me
165g
ppm
1.01
1.03
0.95
1.00
1.04
3.14
2.93
1.00
1.17
3.28
2.24
3.13

JN-3-093-col-again

SAMPLE	
date	Jan 5 2012
solvent	cdcl3
file	/data/indy/janeni/ vnmrsys/data/JN-3-093-co l-again/CARBON01.fid

ACQUISITION	
sw	31446.5
at	1.042
np	65536
fb	not used
bs	64
d1	1.000
nt	7000
ct	7000

TRANSMITTER	
tn	C13
sfrq	125.669
tof	1913.4
tpwr	56
pw	4.050

DECOUPLER	
dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	11900

PRESATURATION	
satmode	n
wet	n

SPECIAL	
temp	not used
gain	30
spin	20
hst	0.008
pw90	8.100
alfa	10.000

FLAGS	
il	n
in	n
dp	y
hs	nn

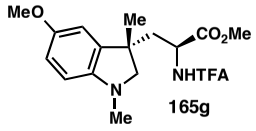
PROCESSING	
lb	0.50
lslid	-3
fn	not used

DISPLAY	
sp	-0.1
wp	27643.4
rfl	1901.2
rfp	0
rp	-162.4
lp	123.9

PLOT	
wc	234
sc	8
vs	10819
th	6
ai cdc ph	

JN-3-093-col-again

Sample Name JN-3-093-col-again	Pulse sequence CARBON	Temperature 25	Study owner janeni
Date collected 2012-01-05	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser



165g

JN-3-031-char

SAMPLE

date	Jan 30 2012
solvent	cdcl3
file	/data/siena/jni/vnmrsys/data/JN-3-031-char/PROTON01.fid

ACQUISITION

sw	6410.3
at	2.556
np	32768
fb	4000
bs	32
d1	1.000
nt	16
ct	16

TRANSMITTER

tn	H1
sfrq	399.797
tof	399.8
tpwr	63
pw	3.281

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	W40_OneNMR
dpwr	34
dmf	29412

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	25.0
gain	30
spin	20
hst	0.008
pw90	6.562
alfa	10.000

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

ln	not used

DISPLAY

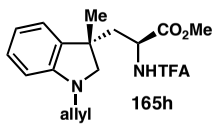
sp	-199.9
wp	4397.7
rfl	829.5
rfp	0
rp	85.6
lp	0

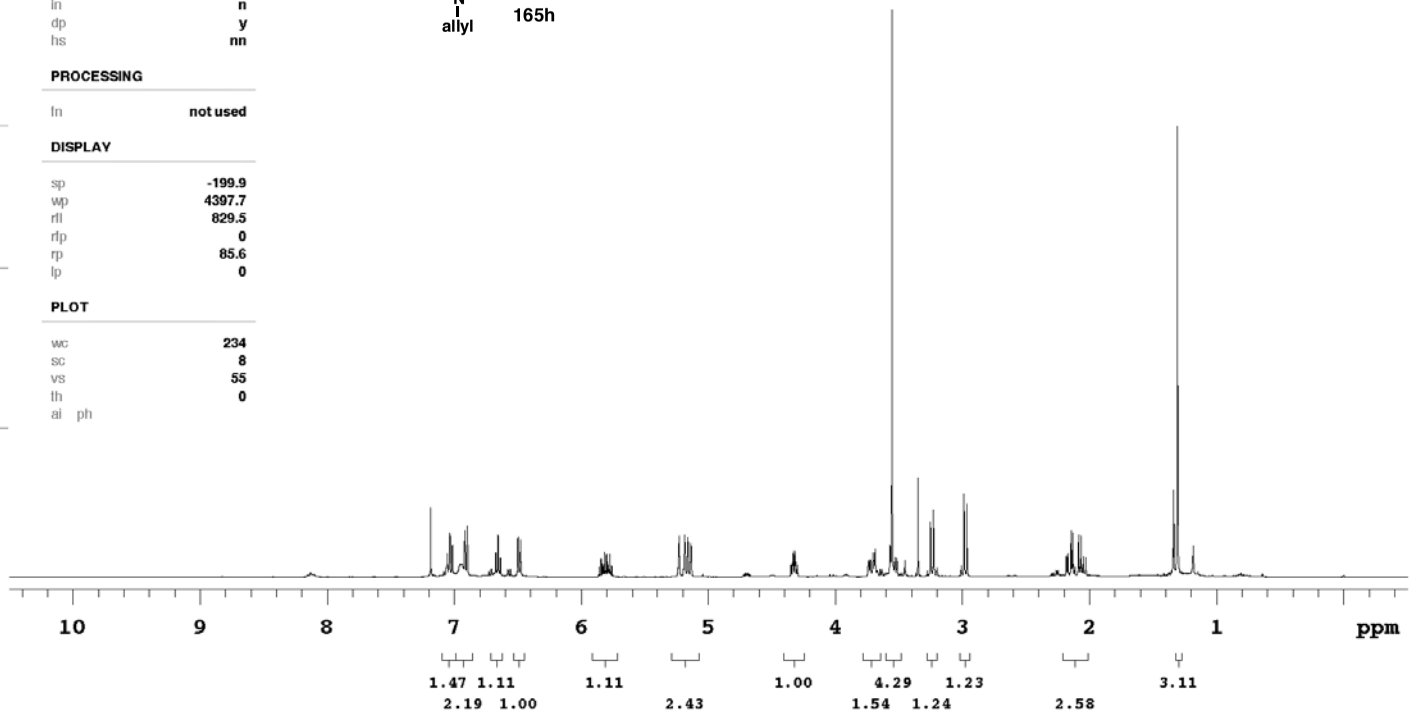
PLOT

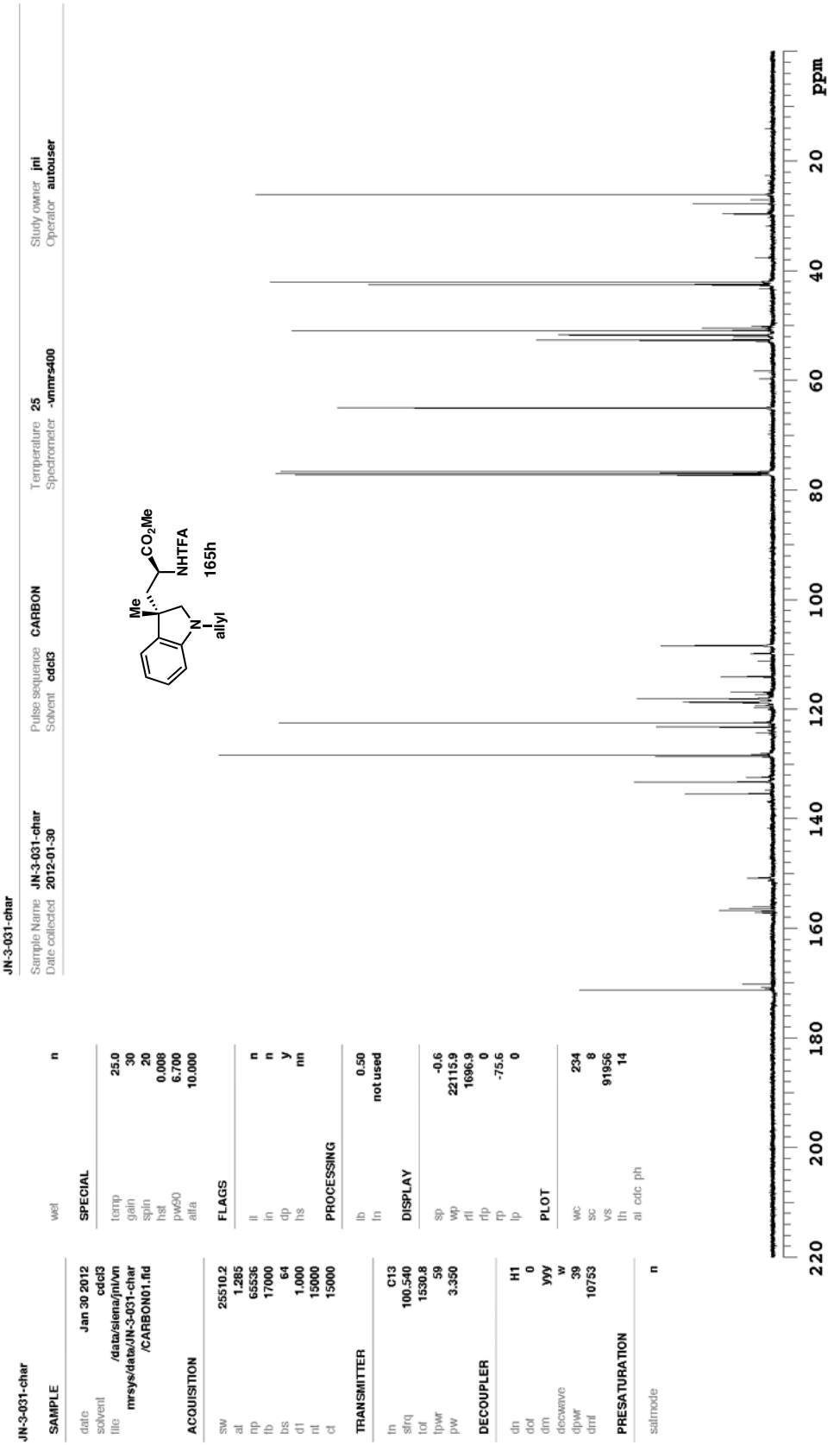
wc	234
sc	8
vs	55
th	0
ai ph	

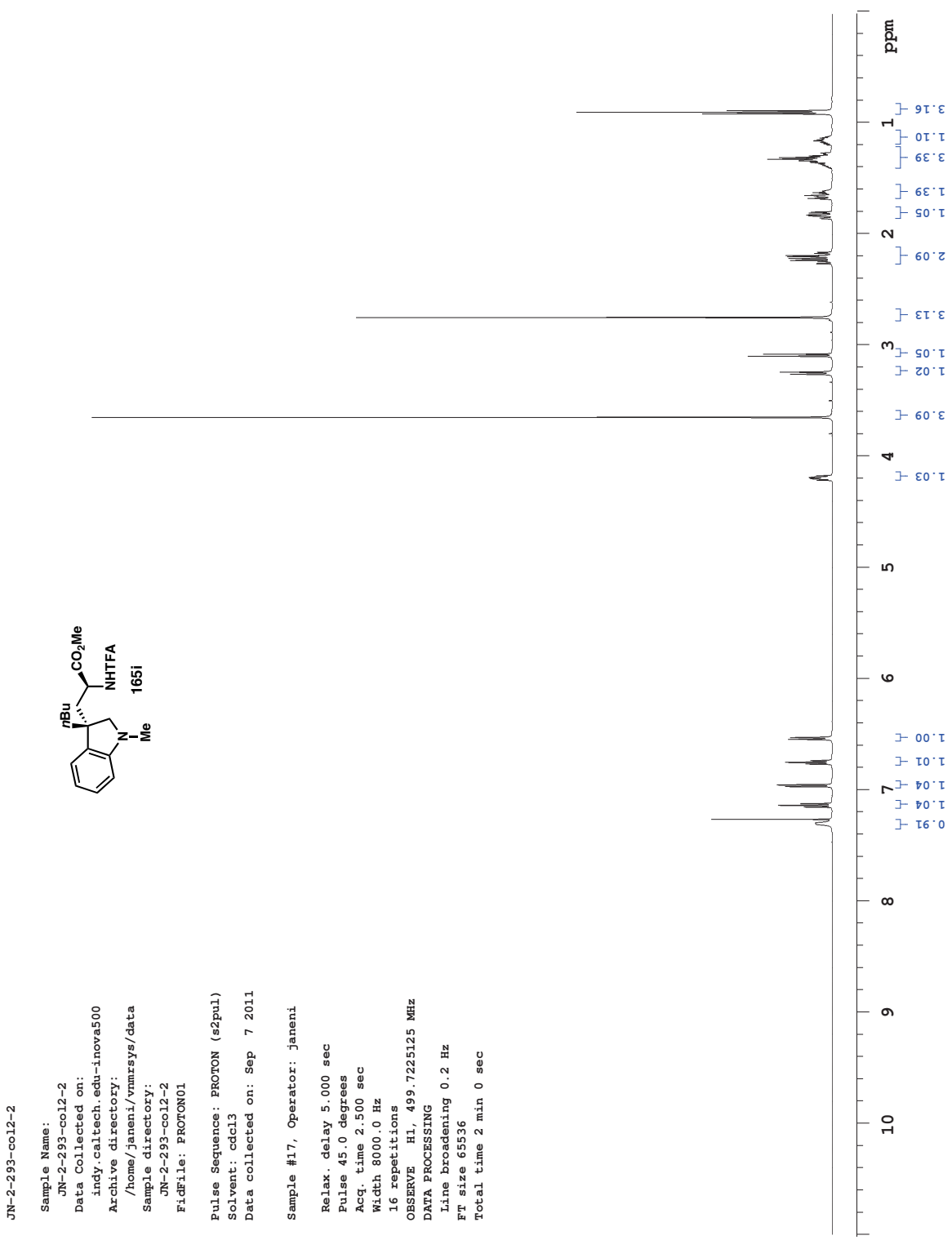
JN-3-031-char

Sample Name JN-3-031-char	Pulse sequence PROTON	Temperature 25	Study owner jni
Date collected 2012-01-30	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser






JN-3-031-char
Sample Name JN-3-031-char
Date collected 2012-01-30
Pulse sequence CARBON
Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner jnl
Operator autouser
Me
CO2Me
NHTFA
N
allyl
165h
JN-3-031-char
wet n
SAMPLE
date Jan 30 2012
solvent cdcl3
file /data/siena/jnl/vn
mrsys/data/JN-3-031-char
/CARBON01.fid
ACQUISITION
sw 25510.2
at 1.285
np 65536
fb 17000
bs 64
d1 1.000
nt 15000
ct 15000
TRANSMITTER
tn C13
sfrq 100.540
tof 1530.8
tpwr 59
pw 3.350
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 39
dmf 10753
PRESATURATION
satmode n
SPECIAL
temp 25.0
gain 30
spin 20
hst 0.008
pw90 6.700
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -0.6
wp 22115.9
rfl 1696.9
rfp 0
rp -75.6
lp 0
PLOT
wc 234
sc 8
vs 91956
th 14
ai cdc ph
220
200
180
160
140
120
100
80
60
40
20
ppm


JN-2-293-co12-2
Sample Name:
JN-2-293-co12-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-2-293-co12-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 7 2011
Sample #17, Operator: janeni
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
nBu
CO2Me
NHTFA
N
Me
165i
ppm
0.91
1.04
1.04
1.01
1.00
1.03
3.09
1.02
1.05
3.13
2.09
1.05
1.39
3.39
1.10
3.16

JN-2-293-col2-2

SAMPLE

date	Sep 7 2011
solvent	cdcl3
file	/data/indy/janeni/vnmrsys/data/JN-2-293-col2-2/CARBON01.fid

ACQUISITION

sw	31446.5
at	1.042
np	65536
fb	not used
bs	64
d1	1.000
nt	6500
ct	6500

TRANSMITTER

tn	C13
sfrq	125.669
tof	1913.4
tpwr	56
pw	4.050

DECOUPLER

dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	11900

PRESATURATION

satmode	n
wet	n

SPECIAL

temp	not used
gain	30
spin	0
hst	0.008
pw90	8.100
alfa	10.000

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.50
lstid	-4
fn	not used

DISPLAY

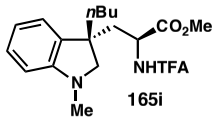
sp	-0.1
wp	27643.4
rfl	1901.2
rfp	0
rp	162.6
lp	126.1

PLOT

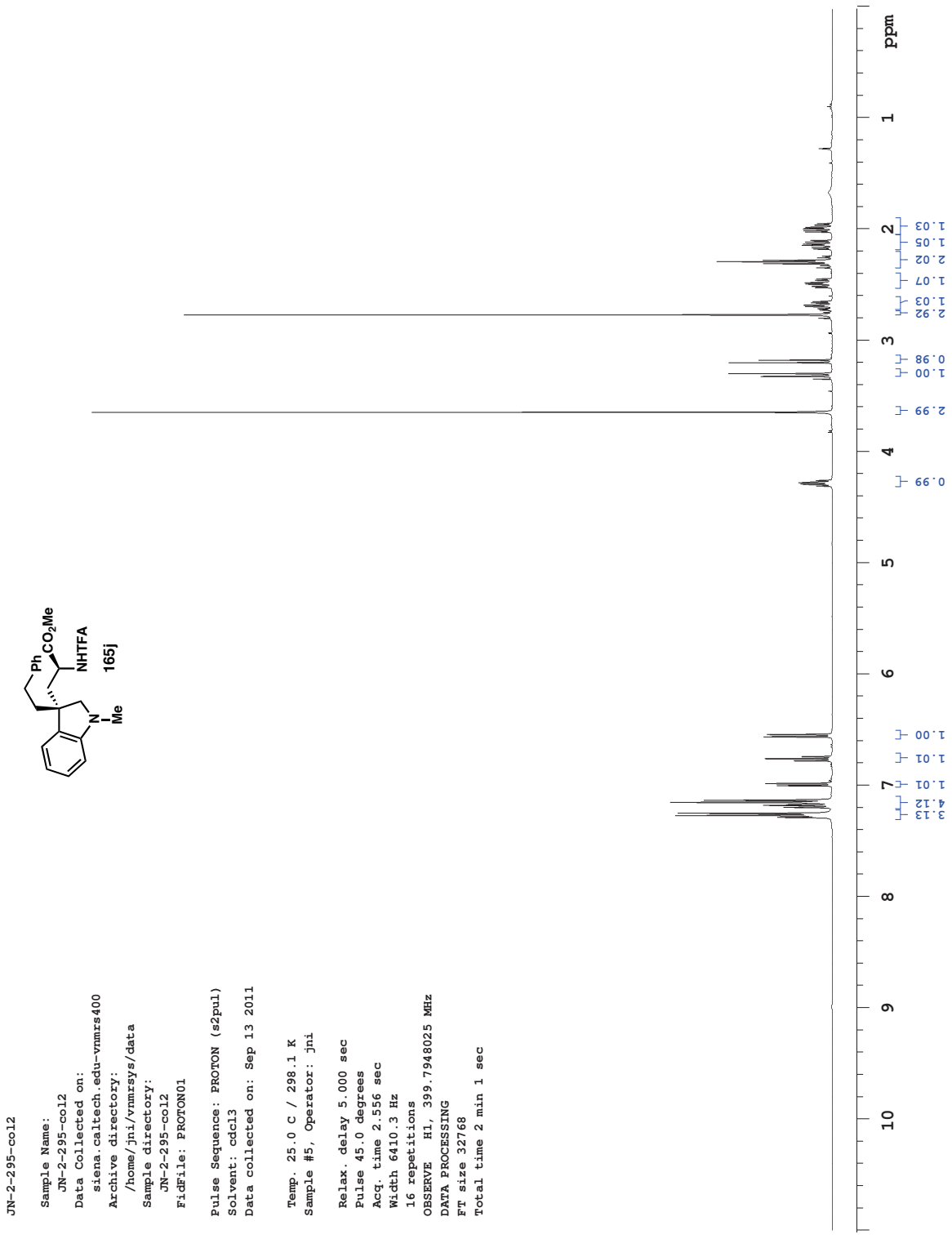
wc	234
sc	8
vs	9701
th	3
ai cdc ph	

JN-2-293-col2-2

Sample Name **JN-2-293-col2-2** | Pulse sequence **CARBON** | Temperature **25** | Study owner **janeni**
Date collected **2011-09-07** | Solvent **cdcl3** | Spectrometer **-vnmrs400** | Operator **autouser**



165i


JN-2-295-co12
Sample Name:
JN-2-295-co12
Data Collected on:
siena.caltech.edu-vnmrs400
Archive directory:
/home/jni/vnmrsys/data
Sample directory:
JN-2-295-co12
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 13 2011
Temp. 25.0 C / 298.1 K
Sample #5, Operator: jni
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7948025 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 1 sec
Ph
CO2Me
NHTFA
N
Me
165j
ppm
1
2
3
4
5
6
7
8
9
10
1.00
1.01
1.01
4.12
3.13
1.00
0.98
2.99
0.99
2.92
1.03
1.07
2.02
1.05
1.03

JN-2-295-col2

SAMPLE

date	Sep 13 2011
solvent	cdcl3
file	/siena/jni/vnmrsys /data/JN-2-295-col2/CARB ON01.fid

ACQUISITION

sw	25510.2
at	1.285
np	65536
fb	17000
bs	64
d1	1.000
nt	4500
ct	4500

TRANSMITTER

tn	C13
sfrq	100.540
tof	1530.8
tpwr	59
pw	3.350

DECOUPLER

dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	10753

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	25.0
gain	30
spin	20
hst	0.008
pw90	6.700
alfa	10.000

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.50
fn	not used

DISPLAY

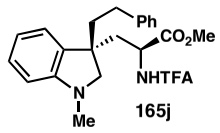
sp	-0.6
wp	22115.9
rfl	1696.9
rfp	0
rp	-109.4
lp	0

PLOT

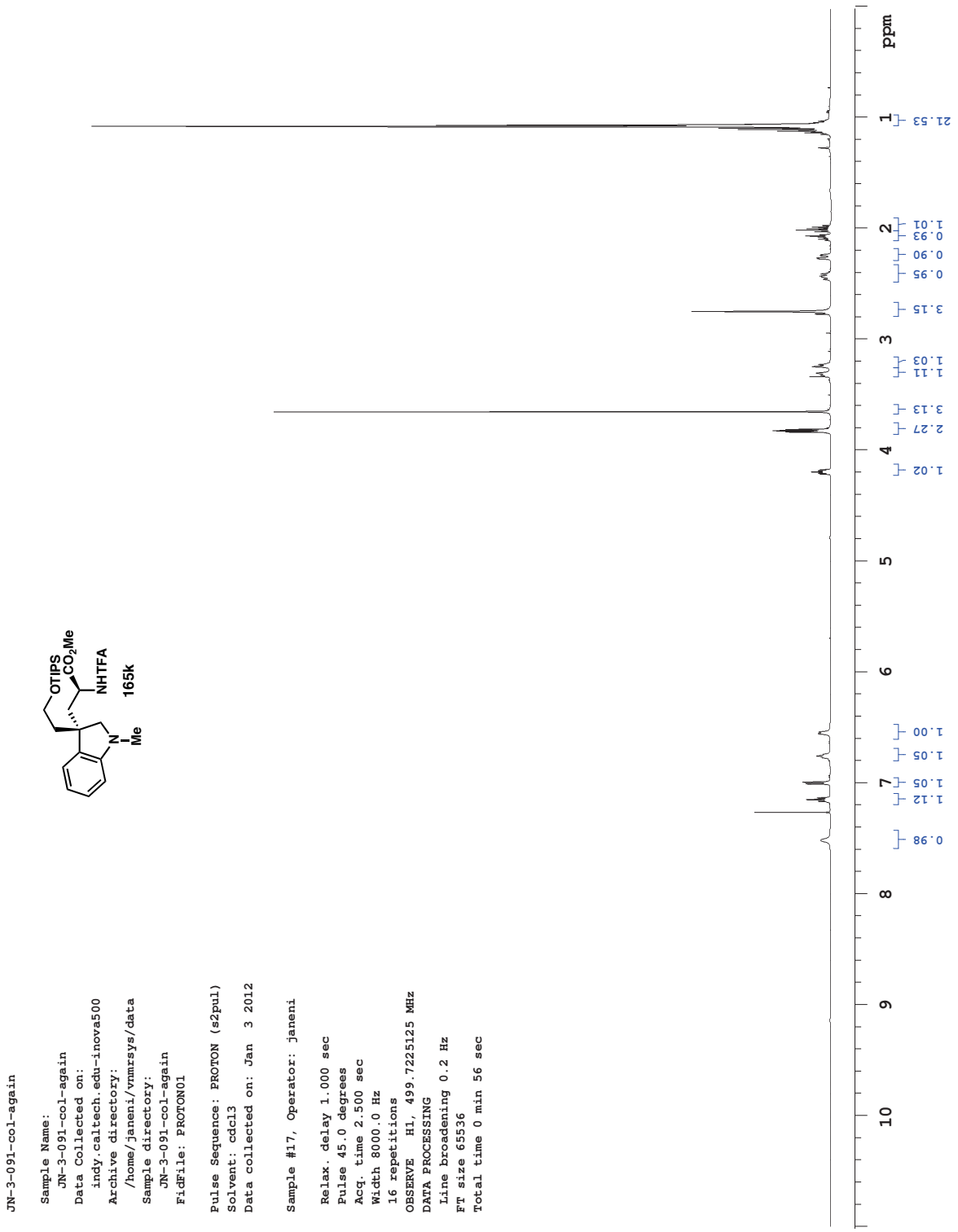
wc	234
sc	8
vs	20790
th	5
ai cdc ph	

JN-2-295-col2

Sample Name JN-2-295-col2	Pulse sequence CARBON	Temperature 25	Study owner jni
Date collected 2011-09-13	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser



165j


JN-3-091-col-again
Sample Name:
JN-3-091-col-again
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/janeni/vnmrsys/data
Sample directory:
JN-3-091-col-again
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 3 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, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
OTIPS
CO2Me
NHTFA
N
Me
165k
ppm
21.53
1.01
0.93
0.90
0.95
3.15
1.03
1.11
3.13
2.27
1.02
1.00
1.05
1.05
1.12
0.98

JN-3-091-col-again

SAMPLE	
date	Jan 3 2012
solvent	cdcl3
file	/data/indy/janeni/ vnmrsys/data/JN-3-091-co l-again/CARBON01.fid

ACQUISITION	
sw	31446.5
at	1.042
np	65536
fb	not used
bs	64
d1	1.000
nt	10000
ct	10000

TRANSMITTER	
tn	C13
sfrq	125.669
tof	1913.4
tpwr	56
pw	4.050

DECOUPLER	
dn	H1
dof	0
dm	yyy
decwave	w
dpwr	39
dmf	11900

PRESATURATION	
satmode	n
wet	n

SPECIAL	
temp	not used
gain	30
spin	20
hst	0.008
pw90	8.100
alfa	10.000

FLAGS	
il	n
in	n
dp	y
hs	nn

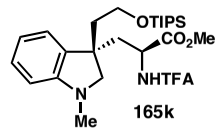
PROCESSING	
lb	0.50
lslid	-3
fn	not used

DISPLAY	
sp	-0.1
wp	27643.4
rfl	1901.2
rfp	0
rp	-167.9
lp	114.8

PLOT	
wc	234
sc	8
vs	4542
th	2
al cdc ph	

JN-3-091-col-again

Sample Name JN-3-091-col-again	Pulse sequence CARBON	Temperature 25	Study owner janeni
Date collected 2012-01-03	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser



165k

CHAPTER 4

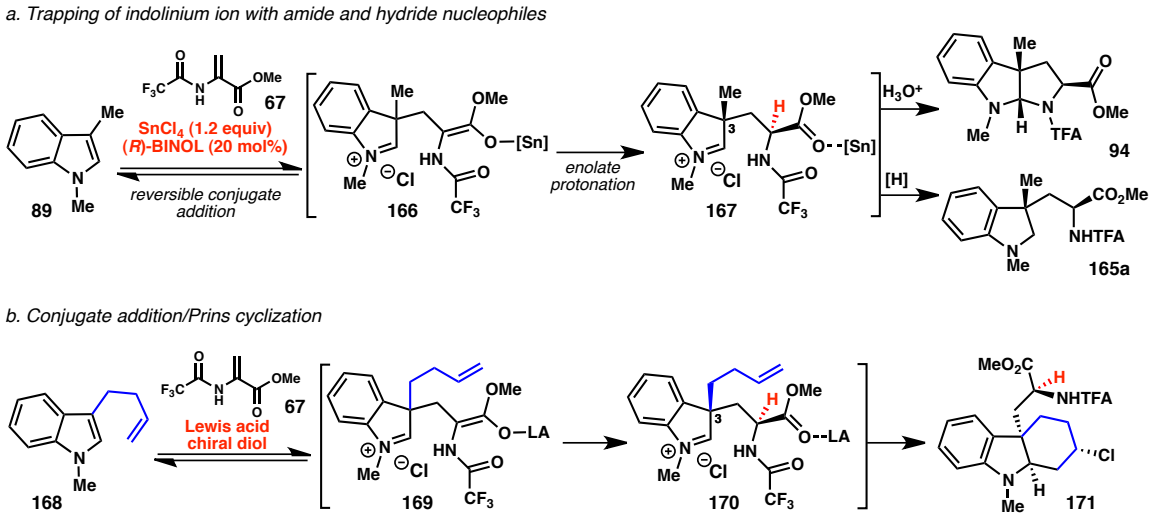
Development of a Tandem Conjugate Addition/Prins Cyclization

4.1 Introduction

Mechanistic studies of the formal (3 + 2) cycloaddition between 3-substituted indoles and 2-amidoacrylates revealed that the initial product is an iminium ion, and cyclization by the pendant amide to afford the pyrroloindoline occurs upon aqueous work-up (Chapter 2). As a result, we hypothesized that novel indoline structures could be accessed by intercepting the iminium ion with alternate nucleophiles. Chapter 3 described the use of reducing agents for this purpose; this chapter will discuss our investigation of carbon nucleophiles (Figure 1a).

Our initial goal was the development of an intramolecular cascade reaction. We envisioned that upon Lewis acid promoted conjugate addition of the indole to the acrylate, a tethered alkene would add into the iminium intermediate. The resulting carbocation would then be quenched by a nucleophile such as chloride. Overall, such a reaction would constitute a tandem conjugate addition/asymmetric protonation/Prins cyclization (Figure 1b).

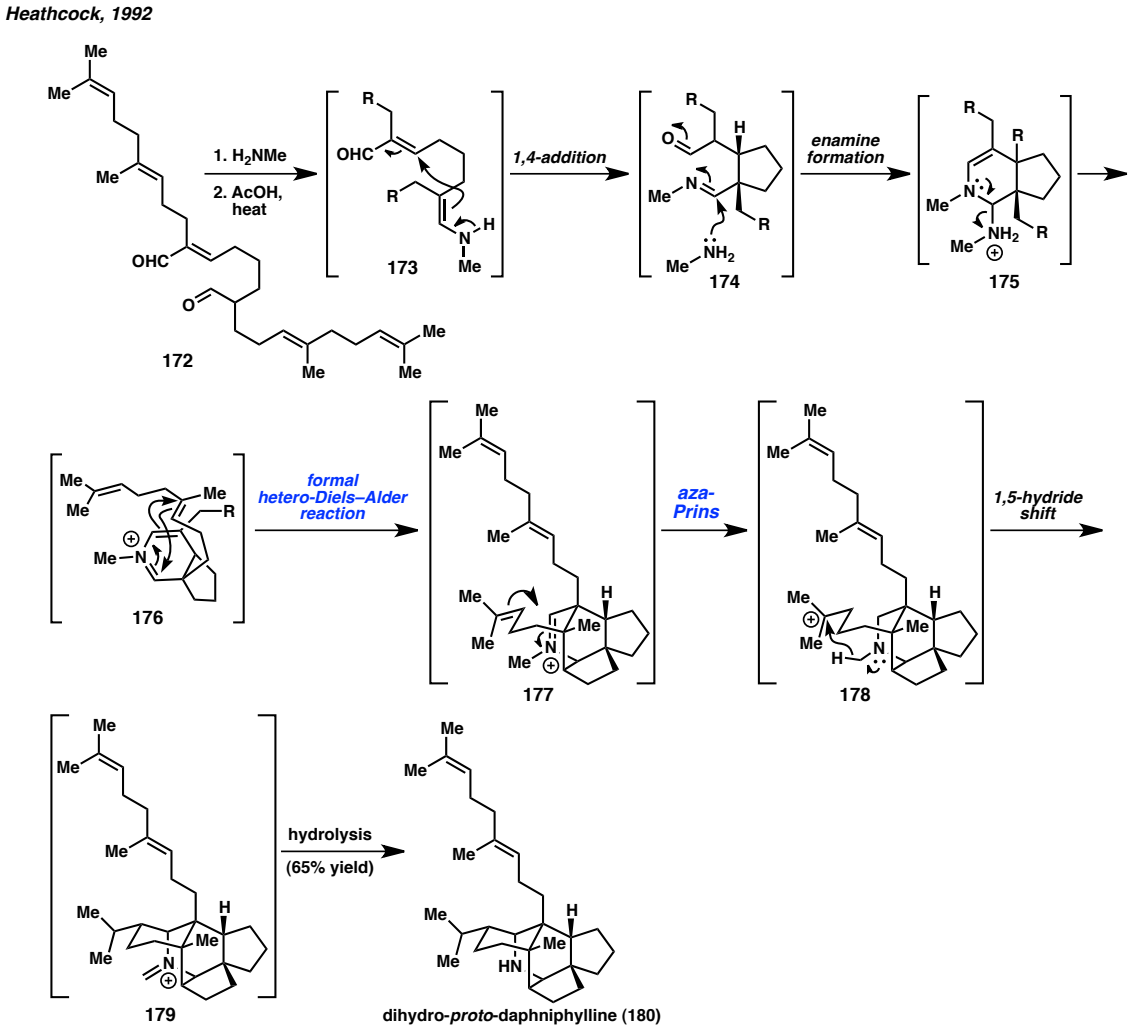
Figure 1. a) Previously developed pyrroloindoline and indoline syntheses. b) Proposed conjugate addition/Prins cyclization.



4.1.1 Cascade Reactions Incorporating Prins Cyclizations

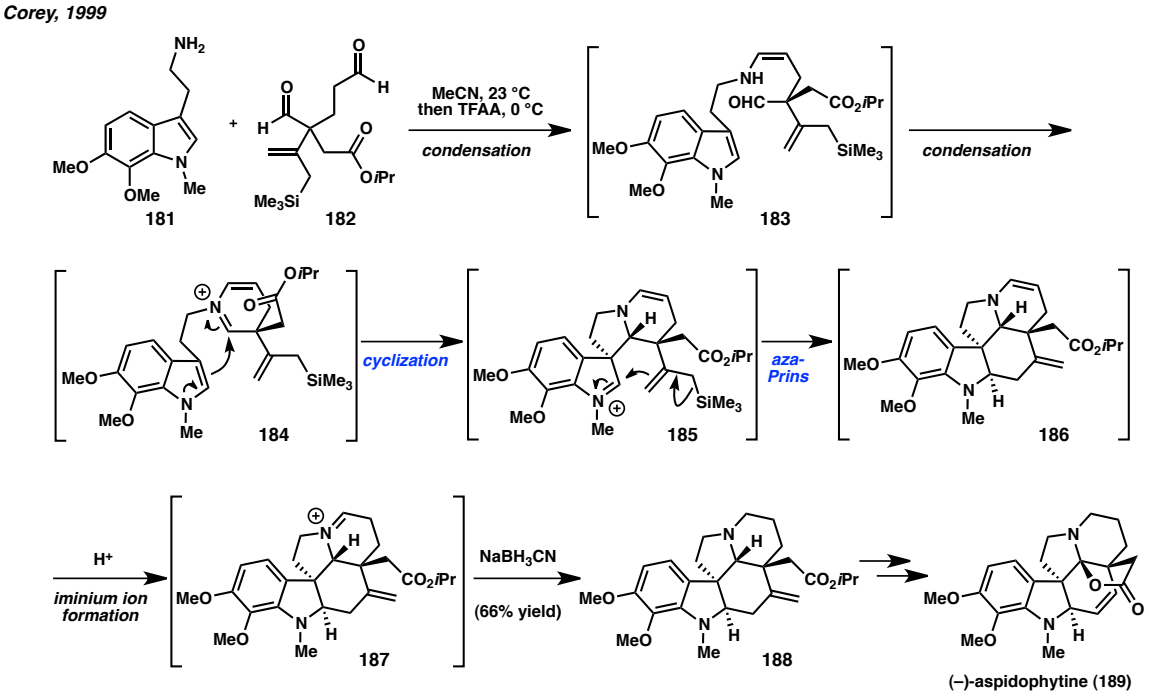
Cascade reactions have long attracted the attention of organic chemists with their ability to rapidly build up molecular complexity. Several groups have reported examples of cascades either initiated by or terminated with a Prins cyclization. Heathcock and coworkers' one-step synthesis of dihydro-*proto*-daphniphylline involves an incredible cascade of iminium ion intermediates, including a formal hetero-Diels–Alder reaction (which likely proceeds in a stepwise manner), followed by an aza-Prins cyclization to generate carbocation **178** (Figure 2).[1]

Figure 2. Iminium cascade with a Prins cyclization by Heathcock.



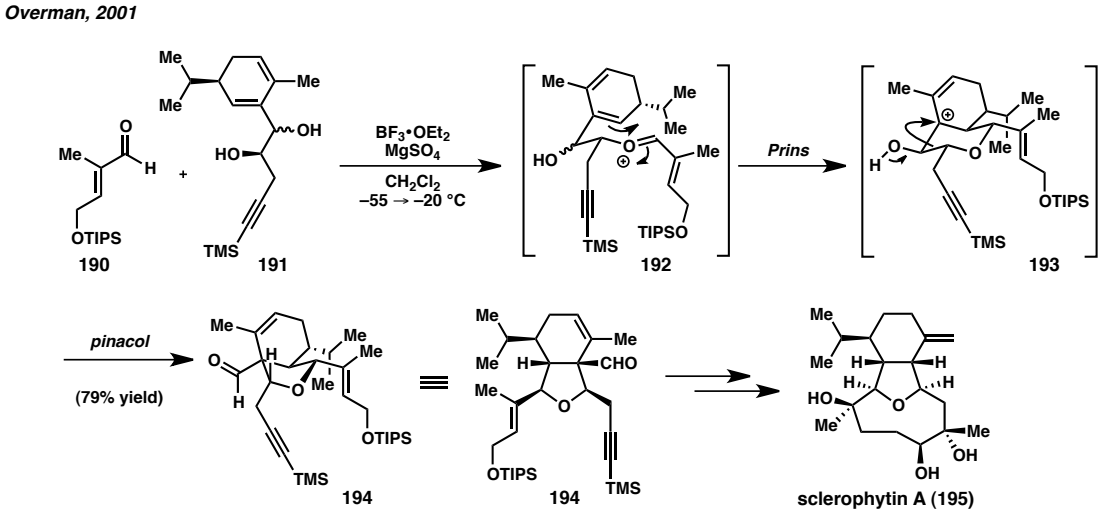
Another cascade of iminium ions was utilized by Corey and coworkers to enable an efficient synthesis of aspidophytine (Figure 3).[2] Cyclization of iminium ion **184** forms the C3 quaternary stereocenter and generates indolinium ion **185**. The stereoselectivity observed in this reaction may result from an interaction between the iminium ion carbon and the ester carbonyl oxygen of **184**, leading to preferential attack by the indole from the opposite face. The stereochemistry of spirocyclic intermediate **185** determines the facial selectivity of allylsilane attack in the subsequent aza-Prins cyclization.

Figure 3. Cascade with Prins cyclization in synthesis of (–)-aspidophytine.



The pinacol-terminated Prins cyclization was developed by the Overman group and has facilitated the total syntheses of several natural products. One such application is found in their synthesis of sclerophytin A, part of the cladiellin family of diterpene metabolites (Figure 4).[3] Lewis acid catalyzed condensation of diol **191** with aldehyde **190** forms oxocarbenium **192**. While either hydroxyl group can participate in this step, the condensation is reversible and only product **192** can carry on in the subsequent Prins cyclization. The bulky isopropyl substituent controls the stereoselectivity of this Prins cyclization, which generates allylic carbocation **193**. The cascade is terminated by a pinacol rearrangement to afford bicycle **194**.

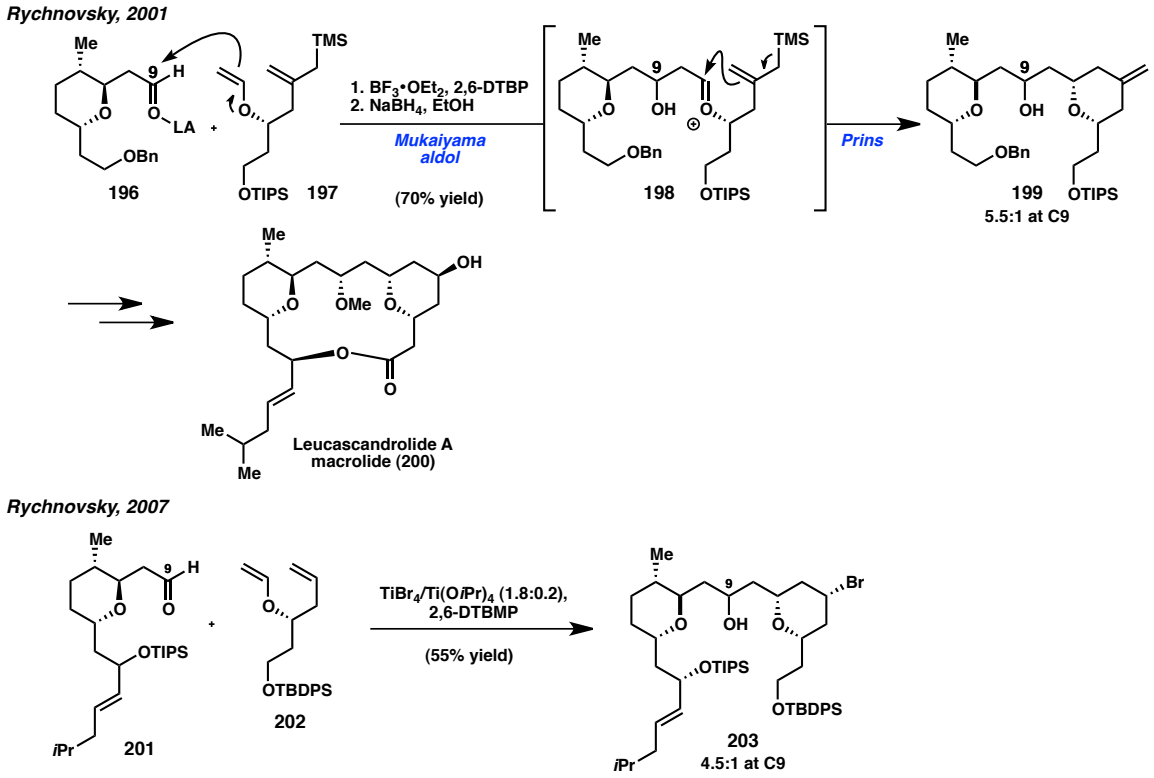
Figure 4. Prins-pinacol in synthesis of sclerophytin A.



Rychnovsky and coworkers developed a Mukaiyama aldol-Prins cyclization cascade, and demonstrated the utility of this transformation in a formal synthesis of leucascandrolide A (Figure 5).[4] Chiral aldehyde **196** and enol ether **197** underwent aldol-Prins coupling in the presence of 2.5 equivalents of BF_3•OEt_2 and 1.5 equivalents of 2,6-di-*tert*-butylpyridine to produce most of the leucascandrolide A skeleton in a single step.

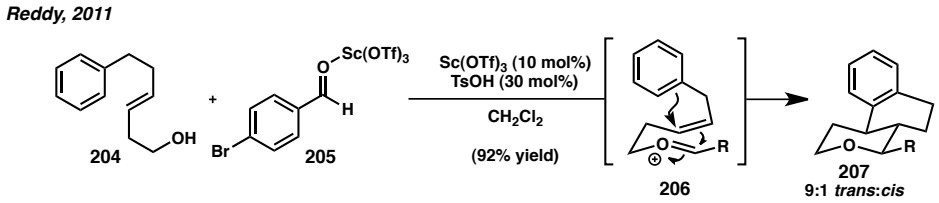
In 2007, the Rychnovsky laboratory reported a streamlined synthesis of leucascandrolide A using an improved variant of the Mukaiyama aldol-Prins coupling.[5] The second generation methodology utilizes more accessible cyclization precursors (**201** and **202**) rather than an enol ether allylsilane, and yields a more highly functionalized product (**203**) with three new stereocenters (Figure 5).

Figure 5. Mukaiyama aldol-Prins in formal synthesis of leucascandrolide A.



Reddy and coworkers developed a Prins/Friedel–Crafts cyclization to access fused tricyclic systems (Figure 6).[6] The stereochemistry of the product is determined by the olefin geometry in the starting material. However, a small amount of the minor, *cis* diastereomer is formed through a stepwise mechanism in the case shown in Figure 6.

Figure 6. Prins-Friedel–Crafts by Reddy.

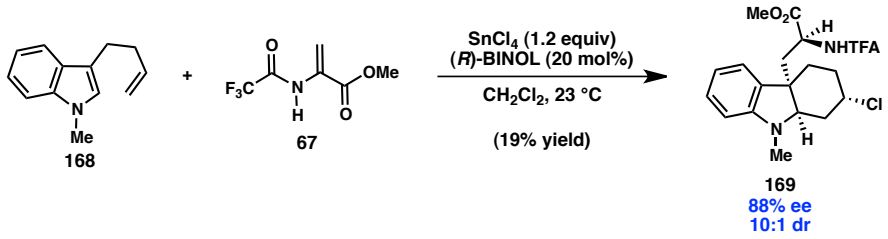


4.2 Development of a Conjugate Addition/Prins Cyclization

Although many examples exist in the literature of cascade reactions involving Prins cyclizations, a Prins cyclization triggered by a conjugate addition/asymmetric enolate protonation was not known at the outset of this project.

Preliminary studies showed that exposure of 3-homoallyl indole **168** and acrylate **67** to $SnCl_4$ and (*R*)-BINOL yields indoline **169** with a highly promising 88% ee, but low yield due to the formation of side products (Figure 7). A chloride ion from the Lewis acid serves to quench the carbocationic intermediate. While the reaction conditions are similar to the formal (3 + 2) cycloaddition, pyrroloindoline formation is precluded by addition of the tethered alkene to the indolinium ion during the course of the reaction.

Figure 7. Preliminary result for conjugate addition/Prins cyclization.



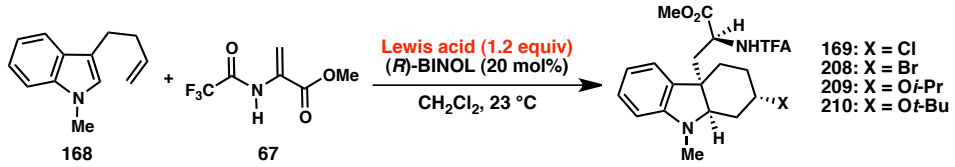
4.2.1 Catalyst Optimization

In order to improve the yield of this reaction, a screen of Lewis acids was conducted (Table 1). While tin tetracholoride provided us with our initial hit (entry 1), tin tetrabromide failed to give any of the desired Prins product (entry 2). Titanium tetrachloride provided the desired product in 27% yield and 6:1 dr, but as a racemic mixture (entry 3). Titanium isopropoxide, which would afford the product of isopropoxide-trapping of the intermediate carbocation, failed to promote this reaction

(entry 4). On the other hand, zirconium tetrachloride provided the product in 30% yield, 9:1 dr, and 40% ee (entry 5). Zirconium tert-butoxide was not an effective Lewis acid for this reaction (entry 6), while antimony pentachloride proved to be too reactive, and only indole decomposition was observed, even at –78 °C (entry 7).

While the enantioselectivity observed with zirconium tetrachloride was lower than with tin tetrachloride, the reaction was qualitatively much cleaner, with fewer side products. Thus, subsequent optimization was performed with zirconium tetrachloride.

Table 1. Lewis acid screen.

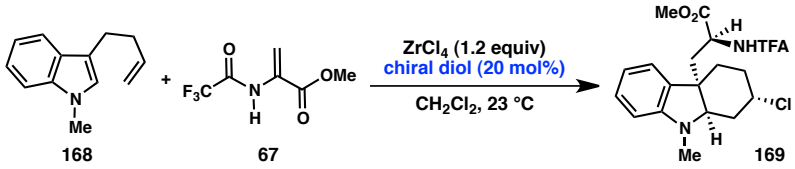


Entry	Lewis acid	Product	Yield (%)	ee (%)[a]
1	$SnCl_4$	169	19	88
2	$SnBr_4$	208	0	--
3	$TiCl_4$	169	27	0
4	$Ti(O^iPr)_4$	209	0	--
5	$ZrCl_4$	169	30	40
6	$Zr(O^tBu)_4$	210	0	--
7	$SbCl_5$	169	0	--

Next, a ligand screen was performed (Table 2). While electronic perturbation of the BINOL backbone with bromine substituents at the 6 and 6' positions failed to improve yield and ee, bromine substituents at the 3 and 3' positions, which would have both an electronic and steric influence, resulted in greatly improved ee. (*S*)-VANOL gave a similarly high levels of enantioinduction, but its high cost and difficulty in preparation make it less desirable than 3,3'-Br_2-BINOL. (*S*)-VAPOL did not yield any product, presumably due to steric hindrance, while no enantioselectivity was observed with

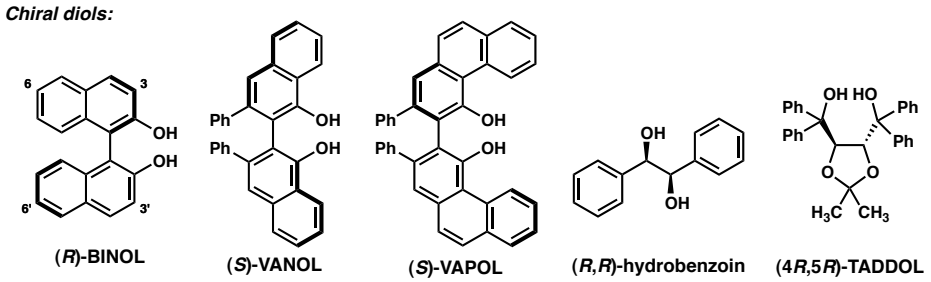
hydrobenzoin. TADDOL appeared initially promising, providing indoline **169** in 37% yield and 66% ee, but subsequent screening revealed decomposition under the reaction conditions. Thus (*R*)-3,3'-Br_2-BINOL was determined to be the optimal ligand for this transformation.

Table 2. Ligand screen.



168 67 169

Entry	Chiral Diol	Yield (%)	ee (%)[a]
1	(*R*)-BINOL	30	40
2	(*R*)-6,6'-Br_2-BINOL	38	30
3	(*R*)-3,3'-Br_2-BINOL	40	76
4	(*S*)-VANOL	33	74
5	(*S*)-VAPOL	0	--
6	(*R*,*R*)-hydrobenzoin	35	0
7	(4*R*,5*R*)-TADDOL	37	66

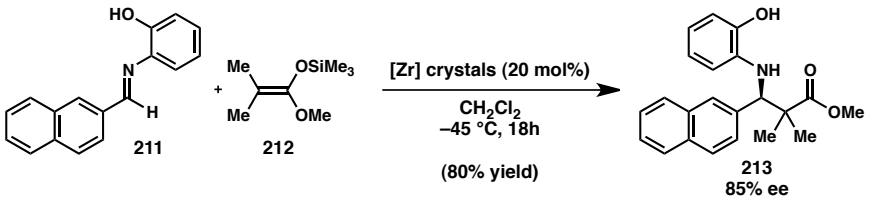


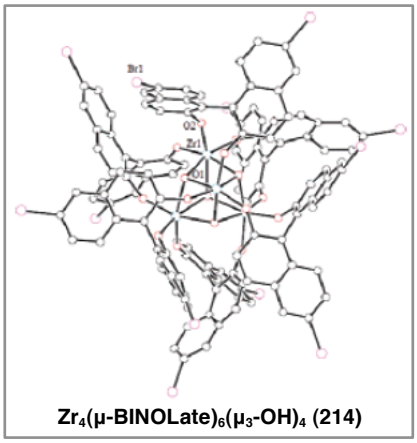
4.2.2 Reactions Promoted by Zirconium•BINOL Complexes

Chiral complexes of BINOL and zirconium have been used as Lewis acids to promote a variety of asymmetric reactions. These catalysts are generally prepared in situ from a zirconium alkoxide, resulting in a BINOLate complex. In contrast, the active catalyst in our conjugate addition/Prins cyclization contains a protonated BINOL ligand, allowing it to effect an asymmetric enolate protonation.

Chiral zirconium Lewis acids are most commonly used to activate carbonyls or imines in Strecker,[7] Mannich,[8] aldol,[9] aldehyde allylation,[10] and cycloaddition reactions.[11] The Kobayashi laboratory has developed an isolable zirconium catalyst for asymmetric Mannich reactions.[8e] Addition of hexanes to a dichloromethane solution of a zirconium alkoxide, (*R*)-6,6'-dibromo-BINOL, and *N*-methylimidazole (NMI) causes precipitation of a white powder that is a stable (over at least 6 months) but highly active catalyst (Figure 8).

Figure 8. Asymmetric Mannich reaction promoted by isolable Zr catalyst.





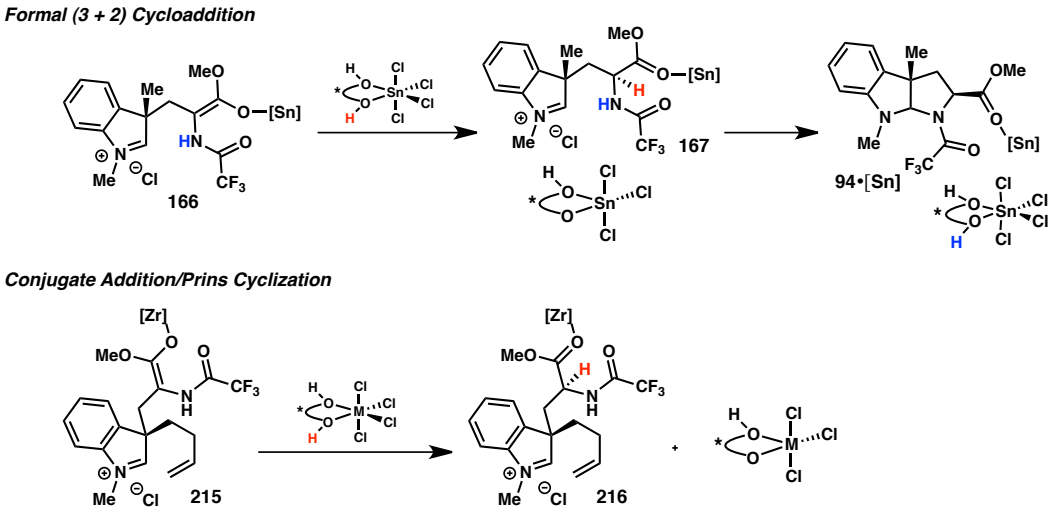
Recrystallization with *N*-benzylimidazole instead of NMI yielded single crystals suitable for X-ray crystallographic analysis. The X-ray structure showed a Zr_4(μ-BINOLate)$_6$(μ_3-OH)$_4$ complex (**214**), with four hexa-coordinated zirconium atoms and

six BINOL ligands. This represents the first X-ray crystallographic structure of a chiral zirconium-BINOL complex that is catalytically competent in Mannich-type reactions. To the best of our knowledge, there are no examples of zirconium complexes acting as chiral protonation catalysts prior to the development of our conjugate addition-Prins cyclization.

4.2.3 Investigation of Additives

Unfortunately, our initial efforts to improve the yield of the conjugate addition/asymmetric protonation/Prins cyclization by modifying the catalyst structure proved unfruitful. At this point, it was observed that the yield was correlated to catalyst loading, suggesting poor turnover of the deprotonated BINOLate.

Figure 9. Stoichiometric proton source.



One potential problem was the lack of a stoichiometric proton source to turn over the deprotonated BINOLate. In our previously studied pyrroloindoline formation, the

stoichiometric proton is likely provided by the pendant amide (Figure 9). While the full mechanistic picture of the formal (3 + 2) cycloaddition is likely more complicated than direct proton transfer from the amide to the BINOLate (as cyclization and thus amide deprotonation does not occur until work-up), we nonetheless hypothesized that a stoichiometric proton source might improve the yield of the Prins cyclization.

With this hypothesis in mind, the Prins reaction was performed with 1.6 equivalents of (*R*)-BINOL and 1.6 equivalents of $ZrCl_4$. Unfortunately, the product was isolated in only 36% yield (Figure 10). Tentatively, this result can be explained by the fact that the (*R*)-BINOL•$ZrCl_4$ complex (Figure 10, inset) is too sterically hindered to effectively activate the acrylate substrate. It may be crucial to have free $ZrCl_4$ in solution to coordinate to the acrylate, in addition to (*R*)-BINOL•$ZrCl_4$, which effects enolate protonation. Therefore, our next strategy to improve the yield of this transformation was to incorporate an external achiral, stoichiometric proton source to regenerate the BINOL catalyst.

Figure 10. Stoichiometric ligand.

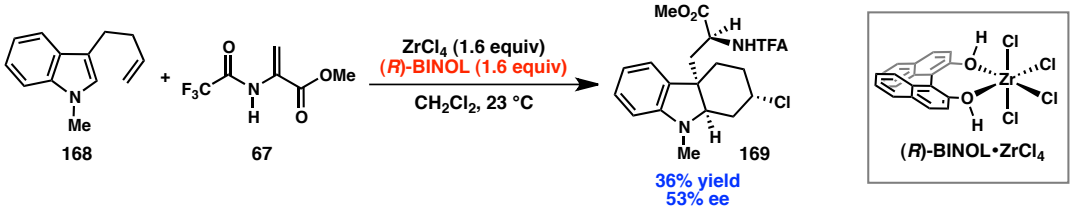
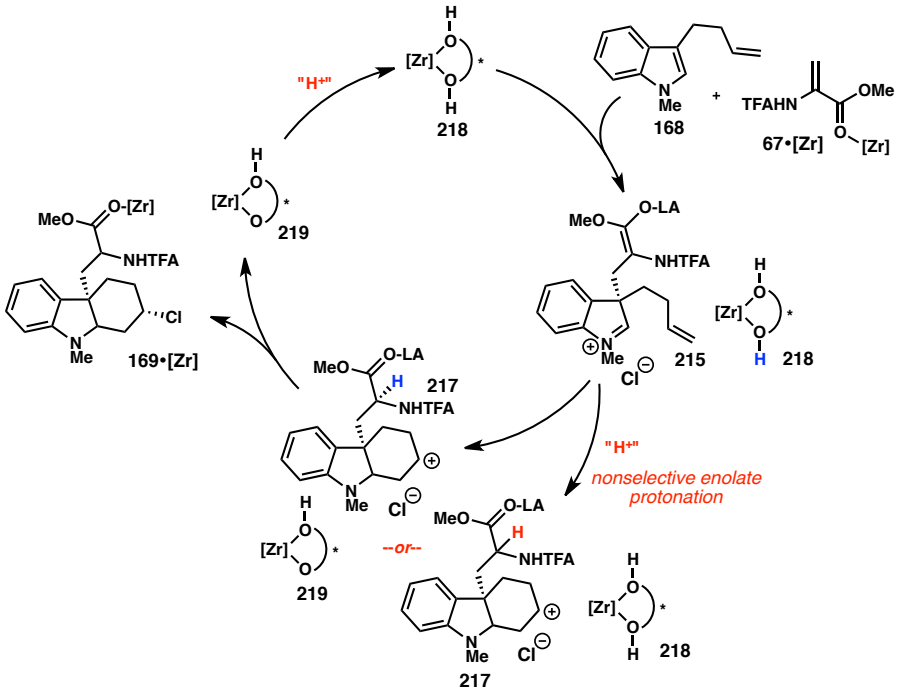


Figure 11 shows the desired reprotonation of the BINOLate by an external proton source (complex **219** → **218**). The rate of this reaction must be high enough to generate an adequate concentration of the active catalyst for protonation of the enolate. However,

this reagent may also participate in the nonselective direct protonation of enolate **215**, which would lower the ee of the product.

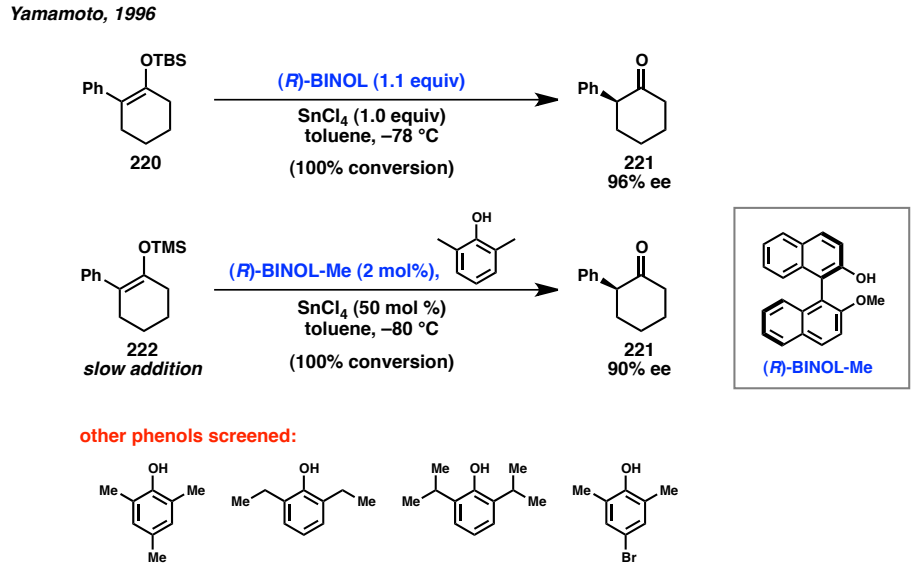
Figure 11. Incorporation of stoichiometric, achiral proton source.



Several strategies have been employed to turn over a chiral acid catalyst with a stoichiometric achiral proton source. Yamamoto and coworkers effected the enantioselective protonation of silyl enol ethers with the Lewis acid-assisted Brønsted acid (*R*)-BINOL-Me•$SnCl_4$ (Figure 12). The catalytic variant of this reaction utilizes 2,6-dimethylphenol as the stoichiometric proton source.[12] In this case, the silyl enol ether (**222**) was added slowly to the reaction in order to minimize its concentration in solution and ensure that it reacts with the catalyst rather than the phenol•$SnCl_4$ complex. The

achiral proton source was also carefully optimized after screening of several substituted phenols.

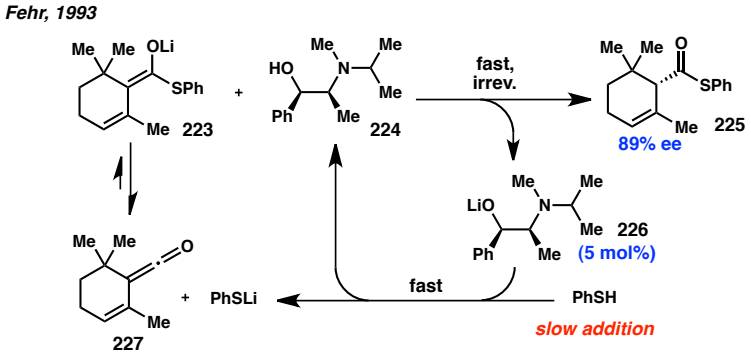
Figure 12. Catalytic enantioselective protonation of silyl enol ethers.



An early example of a catalytic enantioselective protonation of enolates was reported by Fehr and coworkers (Figure 13).[13] In this transformation, the aromatic thiol serves as both nucleophile and stoichiometric proton source in the presence of a catalytic amount of lithiated *N*-isopropylephedrine (**226**). The thiol is added slowly to the reaction to avoid accumulation. It is then deprotonated by the ephedrine-derived base to generate thiophenoxide and the chiral proton source *N*-isopropylephedrine (**224**). Addition of the thiophenoxide to ketene **227** forms enolate **223**, which is rapidly and irreversibly protonated by *N*-isopropylephedrine (**224**) to give thioester **225** and regenerate the lithium base **226**. Thus, high enantioselectivity is achieved in this reaction by slowly

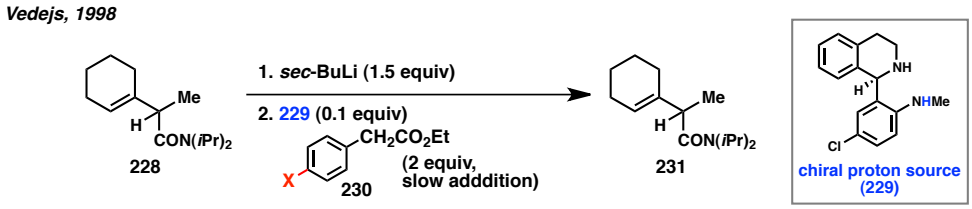
generating the enolate substrate in situ. The concentration of the stoichiometric proton source is also minimized by slow addition.

Figure 13. Catalytic enantioselective protonation of enolates.



Vedejs and Kruger undertook a systematic optimization of the pK_a of the stoichiometric proton source in a catalytic, enantioselective protonation reaction (Table 3).[14] The enantioselective protonation of the amide enolate derived from **228** was effected by chiral acid **229**. Their investigation utilized a series of substituted ethyl phenylacetate derivatives (**230**) with pK_a values spanning 22-28 (DMSO). The enantioselectivities were found to increase with the electron-donating ability of the substituent X. As the acidity of the achiral proton source increases, nonselective protonation becomes competitive, leading to lower ee's. While this reaction was performed in THF as the solvent, the literature pK_a values were determined in DMSO, so further comparisons between the pK_a values of the substrate and achiral acid should be regarded with caution.

Table 3. pK_a of achiral acid vs. enantioselectivity.

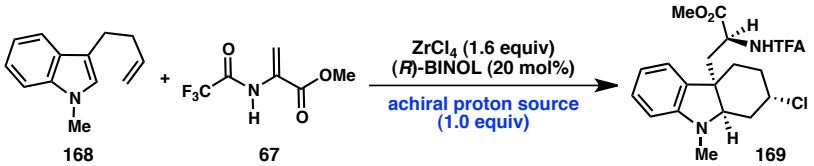


Entry	X	σ_p	ee (%)
1	Cl	0.23	40
2	H	0.00	77
3	CH_3	-0.17	85
4	CH_3O	-0.27	87
5	$(CH_3)_2n$	-0.83	92

Based on these precedents, the use of additives in the conjugate addition/Prins cyclization was investigated. Initially, various substituted phenols were added as stoichiometric proton sources. The phenol would need to be carefully optimized to minimize the rate of nonselective protonation of the enolate. While 2,6-dimethylphenol provided a boost in yield, the ee was also lower (Table 4, entry 2), indicating that nonselective enolate protonation by the achiral phenol is occurring. On the other hand, use of the more hindered 2,6-*t*-Bu_2-phenol failed to improve the yield (entry 3), i.e., the rate of proton transfer from the phenol to the BINOLate is too low.

In an attempt to reduce nonselective enolate protonation by 2,6-dimethylphenol, the indole substrate was added slowly over the course of the reaction to reduce the concentration of enolate (entry 4). Unfortunately, this only served to reduce the rate of reaction; the product was isolated in only 34% yield. As an alternative strategy to reduce the rate of nonselective protonation, various phenols were then added slowly over the course of reaction. Use of 2,6-dimethylphenol did not aid in catalyst turnover (entry 5). The less sterically hindered unsubstituted phenol and more acidic 4-bromophenol also failed to improve the yield of **169** (entries 6, 7).

Table 4. Screen of achiral proton sources.

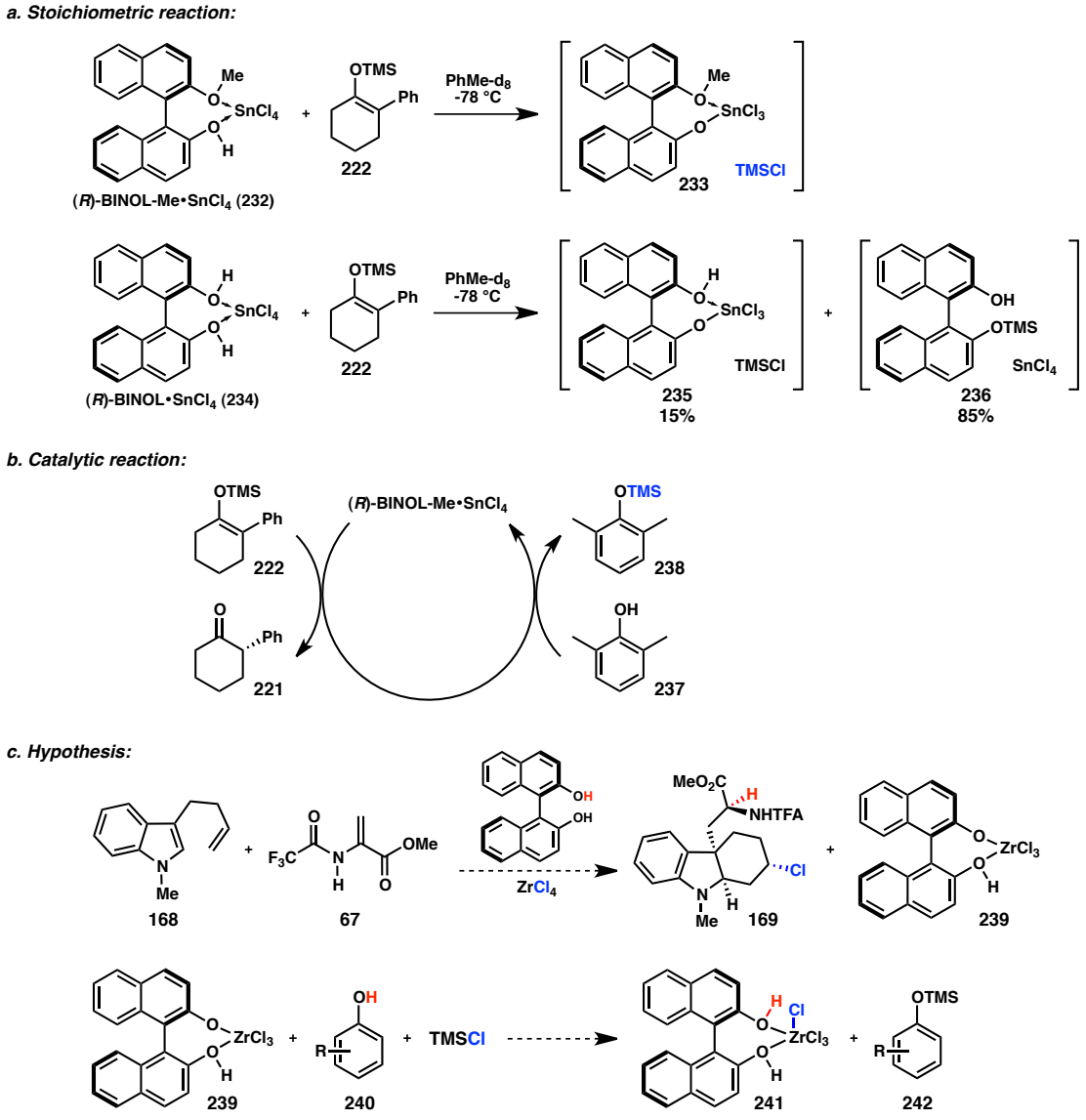


Entry	Achiral H^+ Source	Yield (%)	ee (%)
1	--	30	40
2	2,6-dimethylphenol	66	19
3	2,6-di-*t*-butylphenol	34	45
4[a]	2,6-dimethylphenol	23	26
5[b]	2,6-dimethylphenol	27	37
6[b]	phenol	33	35
7[b]	4-bromophenol	35	24

[a] slow addition of indole. [b] slow addition of achiral proton source.

NMR studies of Yamamoto's asymmetric protonation of silyl enol ethers promoted by *stoichiometric* (*R*)-BINOL-Me•$SnCl_4$ revealed formation of a tin-aryloxide species (**233**) and TMSCl (Figure 14a).[12] On the other hand, reaction with the unmethylated (*R*)-BINOL resulted in formation of the inactive silylated diol **236**. The former complex was found to be a more effective catalyst. They proposed that in the catalytic reaction employing 2,6-dimethylphenol as the stoichiometric proton source, the tin complex receives a proton and chloride from the phenol and TMSCl, respectively, and TMS-2,6-dimethylphenol is formed as a byproduct (Figure 14b). It was hypothesized in our Prins cyclization, a Lewis acid complex such as **239** is formed after donation of a proton to the enolate and a chloride to quench the carbocation. Proton transfer from a phenol to complex **239** may be unfavorable, but further addition of a chloride source such as TMSCl may aid in regenerating the active BINOL•$ZrCl_4$ complex (**241**, Figure 14c).

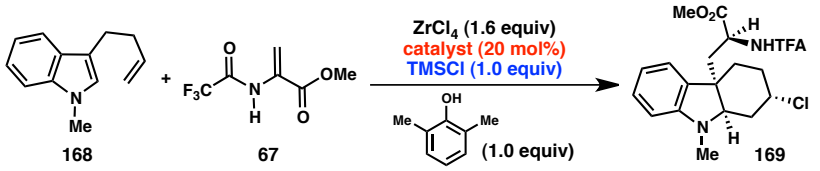
Figure 14. (a) Yamamoto's NMR studies of LBA-promoted enantioselective silyl enol ether protonation. (b) Yamamoto's catalytic enantioselective silyl enol ether protonation. (c) Hypothesis for promoting catalyst turnover in the conjugate addition/Prins cyclization.



With this hypothesis in mind, the Prins reaction was performed in the presence of 1.0 equivalent of TMSCl and 1.0 equivalent of 2,6-dimethylphenol. Gratifyingly, the product **169** was isolated in 71% yield (Table 5, entry 1). Methylation of the catalyst resulted in a slight improvement in yield and ee (entry 2). Functionalization of the diol

with a benzoyl group, which is capable of coordinating to the Lewis acid, was highly detrimental to enantioselectivity (entry 4). Catalysts substituted with bromines at the 3 and 3' positions were also screened. Surprisingly, the relationship between ee and the alkyl group (entries 5-7) was inconsistent with the analogous trend for backbone-unsubstituted catalysts (entries 1-3).

Table 5. Screen of alkylated BINOL derivatives incorporating TMSCl.



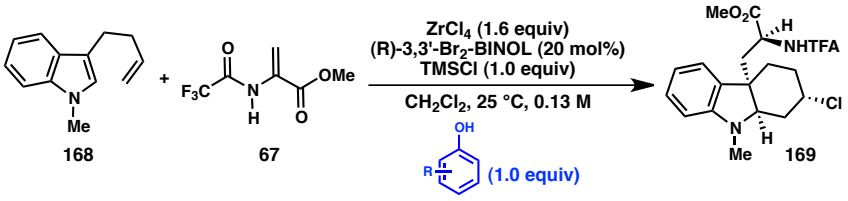
168 67 169

Entry	Catalyst	Yield (%)	ee (%)
1	(*R*)-BINOL	71	28
2	(*R*)-BINOL-Me	81	46
3	(*R*)-BINOL-Bn	90	31
4	(*R*)-BINOL-Bz	84	2
5	(*R*)-3,3'-Br_2-BINOL	72	50
6	(*R*)-3,3'-Br_2-BINOL-Me	70	12
7	(*R*)-3,3'-Br_2-BINOL-Bn	80	60

Since (*R*)-3,3'-Br_2-BINOL-Bn did not provide a significant increase in enantioselectivity compared to (*R*)-3,3'-Br_2-BINOL, most of the subsequent screening was performed with the unalkylated catalyst due to ease of preparation.

To investigate the possibility of cooperative effects between the chiral diol and the achiral, stoichiometric proton donor, a variety of phenol derivatives were screened. The rate of nonselective enolate protonation was expected to be related to the electronic and steric profile of the achiral proton source (Table 6). 3,5-Dimethoxyphenol was found to give unexpectedly high ee, albeit in only 40% yield (entry 7), while 2,6-dimethoxyphenol was less successful (entry 6).

Table 6. Screen of phenol derivatives.



Entry	Phenol Substitution	Yield (%)	ee (%)
1	2-Me	72	21
2	2,6-Me_2	72	50
3	2-OMe	52	7
4	3-OMe	47	21
5	4-OMe	66	20
6	2,6-$(OMe)_2$	36	16
7	3,5-$(OMe)_2$	40	86
8	2-F	63	52
9	2-Cl	78	80
10[a]	2-Cl	72	17
11[b]	2-Cl	71	65
12	2-Br	79	66
13	3-Cl	76	50
14	4-Cl	67	26
15	2,6-F_2	70	67
16	2,4-Cl_2	80	63
17	2,6-Cl_2	71	87
18[c]	2,6-Cl_2	66	86
19[d]	2,6-Cl_2	74	83
20[e]	2,6-Cl_2	68	87
21[f]	2,6-Cl_2	67	87
22[g]	2,6-Cl_2	77	87
23	2,6-Cl_2-4-Me	84	87
24	2,4,6-Cl_3	77	86
25	2,6-Br_2	56	86

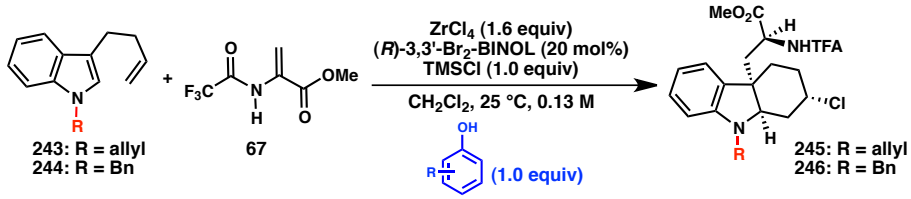
[a] (*R*)-3,3'-Br_2-BINOL-Me was used as the catalyst. [b] (*R*)-3,3'-Br_2-BINOL-Bn was used as the catalyst. [c] TESCl (1.0 equiv) instead of TMSCl. [d] [indole] = 0.2 M. [e] [indole] = 0.1 M. [f] Reaction run at 40 °C. [g] Reaction run in DCE.

Keeping in mind that the methoxy group is electron-withdrawing in the *meta* position (as reflected by its Hammett substituent constant σ_m), halogenated phenols were screened next. Of the *ortho*-monosubstituted phenols, 2-chlorophenol gave the best results. Interestingly, the alkylated catalysts (*R*)-3,3'-Br_2-BINOL-Me (entry 10) and (*R*)-3,3'-Br_2-BINOL-Bn (entry 11) in conjunction with 2-chlorophenol resulted in lower ee, in contrast to the trend observed with 2,6-dimethylphenol. Finally, *ortho*-dichlorinated

phenols were found to provide both good yields and ee's (entries 16-24); the optimal phenol also incorporates a slightly electron-donating *para*-methyl group (entry 23).

Indole substrates protected with either allyl or benzyl groups were then investigated (Table 7). Unfortunately, the optimal stoichiometric proton source (2,6-dichloro-4-methylphenol) for the reaction with *N*-methylindoles was not optimal for these alternative substrates, reflecting the delicate balance of reaction rates required to achieve good yield and enantioselectivity in this transformation. For both *N*-allyl- and *N*-benzylindoles, 2-6-dibromophenol was chosen as the optimal proton source because it is commercially available and also provides good yields and ee's.

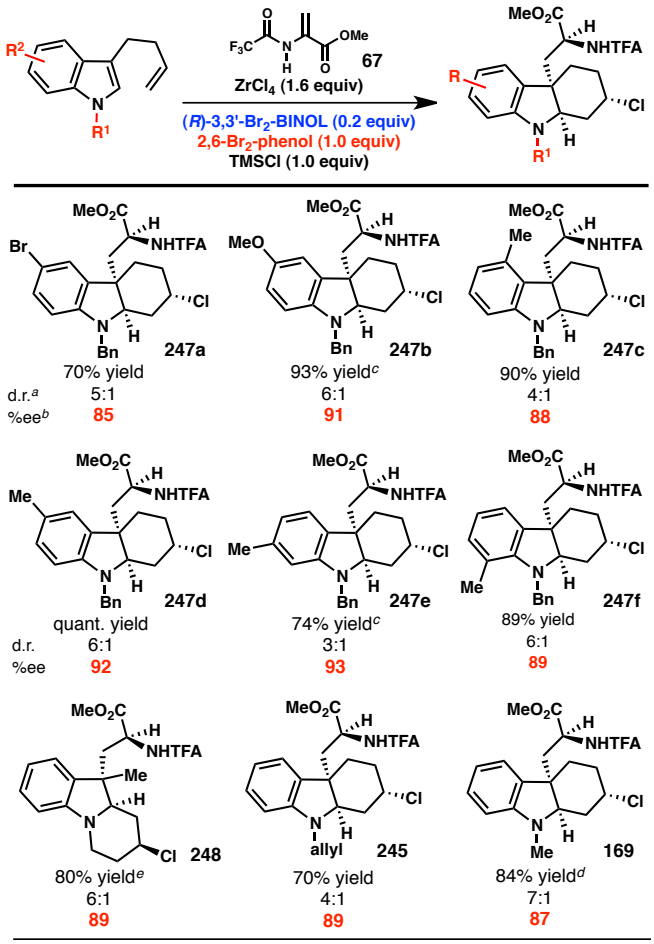
Table 7. Screen of indole protecting groups.



Entry	Protecting Group	Phenol Substitution	Yield (%)	ee (%)
1	allyl	2,6-Cl_2	70	87
2	allyl	2,6-Cl_2-4-Me	75	86
3	allyl	2,4,6-Cl_3	79	83
4	allyl	2,6-Br_2	70	90
5	allyl	2,6-Br_2-4-Me	71	87
6	allyl	2,4,6-Br_3	52	84
7	Bn	2,6-Cl_2-4-Me	74	85
8	Bn	2,6-Br_2	82	91
9	Bn	2,6-Br_2-4-Me	67	91
10	Bn	2,6-Br_2-4-OMe	77	84
11	Bn	2,6-Br_2-4-*t*Bu	78	90
12	Bn	2,4,6-Br_3	76	86

4.2.4 Substrate Scope of the Conjugate Addition/Prins Cyclization

Table 8. Substrate scope.



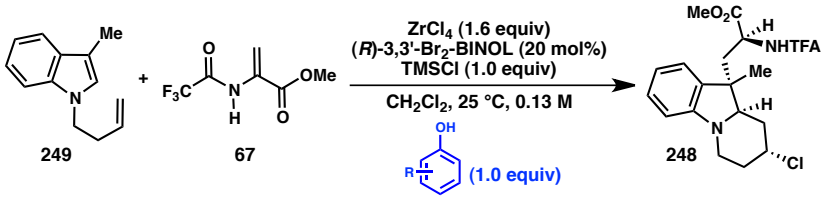
[a] Determined by ^{1}H NMR of crude reaction mixture. [b] Determined by SFC using chiral stationary phase. [c] 1.1 equiv. $ZrCl_4$ was employed. [d] 2,6-dichloro-4-methylphenol was employed. [e] 2,6-dibromo-4-*t*-butylphenol was employed.

Having identified optimal reaction parameters, a screen of indole substrates was conducted. For the 5-bromoindole substrate, the *N*-Me protecting group (to yield **247**) gave improved enantioselectivity over *N*-Bn. The benzyl group was utilized for the other substrates with indole backbone substitution. Surprisingly, both 5-methoxy- and 6-methyl-substituted substrates, when exposed to the standard reaction conditions, yielded a significant quantity of the corresponding pyrroloindoline. It is possible that the electron-

donating property of the methoxy substituent decreases the electrophilicity of the indolinium ion, thus disfavoring addition by the tethered alkene. Upon work-up, the unreacted indolinium ion is attacked by the pendant amide to give the pyrroloindoline. It is unclear why Prins cyclization is disfavored in the case of the 6-methyl-substituted substrate. Fortunately, yields of both Prins products (**246b** and **246e**) were improved by reducing the amount of $ZrCl_4$ to 1.1 equivalents.

We were pleased to find that *N*-homoallylindole smoothly underwent conjugate addition and Prins cyclization. However, under the standard reaction conditions, the product (**248**) was isolated in only 86% ee (Table 9). A screen of substituted phenols revealed 2,6-dibromo-4-*t*butylphenol to be optimal, giving the product in 89% ee and 80% yield (entry 6).

Table 9. Screen of phenol additives to N*-tethered substrate.*



Entry	Phenol Substitution	Yield (%)[a]	ee (%)
1	2,6-Cl_2	82	86
2	2,4,6-Cl_3	(62)	85
3	2,6-Cl_2-4-Me	(76)	84
4	2,6-Br_2	80	86
5	2,4,6-Br_3	84	87
6	2,6-Br_2-4-*t*Bu	80	89

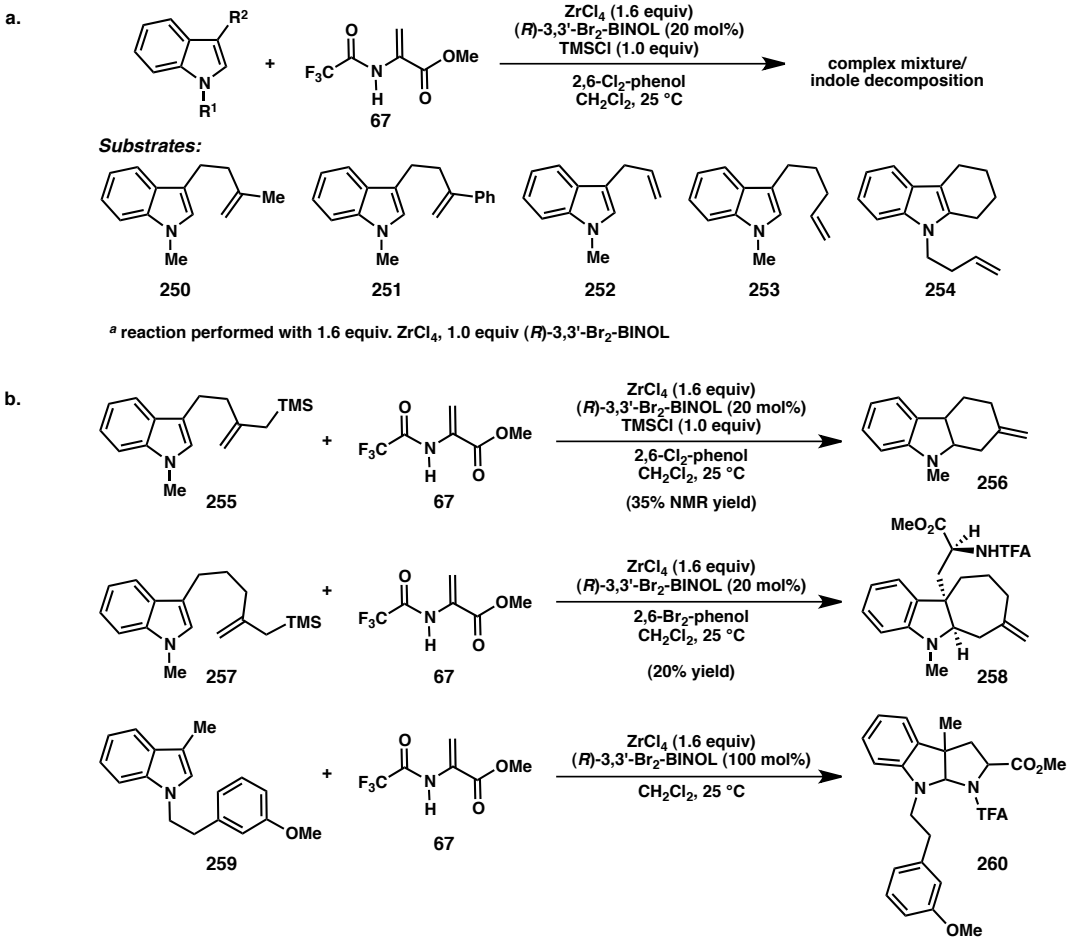
[a] Yields in parentheses are determined by integration of crude ^{1}H NMR with respect to (R)-3,3'-Br_2-BINOL. Other yields are isolated.

4.2.5 Unsuccessful Substrates

Several substrates with alternative tether structures were synthesized. When exposed to the conditions for the conjugate addition/Prins cyclization, many formed

complex mixtures of products (Figure 15a). However, some substrates underwent competing reaction mechanisms. For example, the allylsilane moiety of indole **255** facilitates cyclization such that it occurs at a faster rate than conjugate addition, and the observed product results from protonation of the indole followed by cyclization. On the other hand, a small amount of the desired product was formed from allylsilane substrate **257**, likely because cyclization to form the seven-membered ring is slower than the six-membered ring analogue (**258** vs. **256**). Friedel–Crafts substrate **259** failed to undergo cyclization by the aryl ring, forming the pyrroloindoline instead.

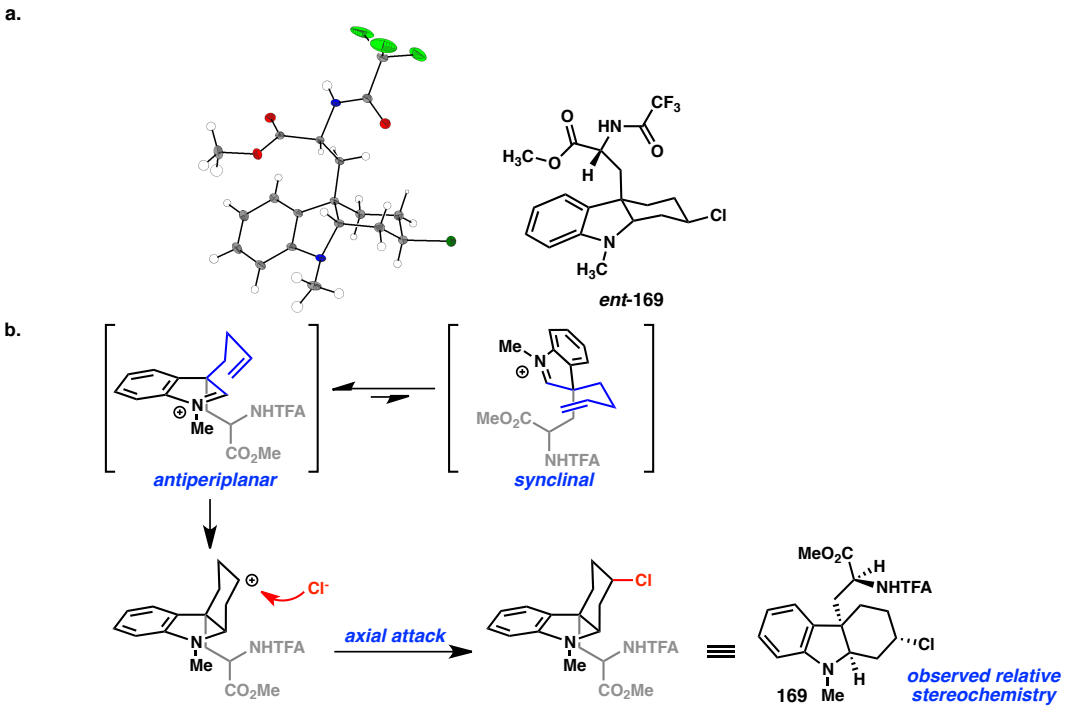
Figure 15. Unsuccesful alternative substrates.



4.2.6 Mechanistic Considerations

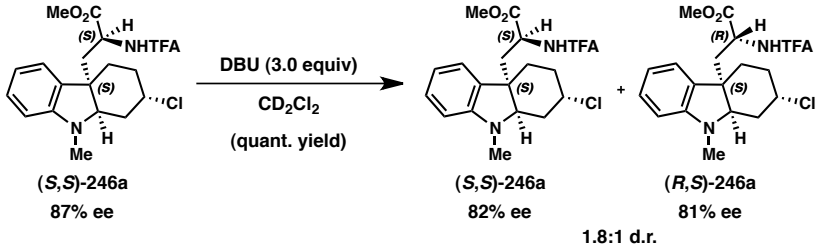
The relative stereochemistry of the major diastereomer of conjugate addition/Prins cyclization product **169** was determined by single crystal X-ray crystallography (Figure 16, crystal structure shows enantiomer). Aza-Prins cyclizations which form six-membered rings favor transition states with an antiperiplanar alignment of the iminium ion and alkene, rather than a synclinal arrangement, because overlap between the alkenyl π-system and the developing lone pair on nitrogen is maximized.[15] In this case, the observed chloride stereochemistry results from axial attack, which is generally disfavored in intermolecular cases. Alternatively, chloride delivery may occur in an intramolecular fashion from a zirconium species coordinated to the ester or amide carbonyl, or the carbocation intermediate can chair flip prior to chloride attack.

Figure 16. Relative stereochemistry of conjugate addition/Prins products.



The major product of the conjugate addition/Prins cyclization is the (*S*,*S*) diastereomer (absolute stereochemistry determined by analogy to the pyrroloindoline synthesis). Epimerization of diastereomerically pure Prins product (*S*,*S*)-**246a** returns a mixture of (*S*,*S*)-**246a** and (*R*,*S*)-**246a**, where (*R*,*S*)-**246a** is the enantiomer of the minor diastereomer formed in the Prins reaction (Figure 17). Thus, the originally-formed diastereomers (*S*,*S*)-**246a** and (*S*,*R*)-**246a** have opposite configurations at the quaternary center, which is consistent with the (*R*)-3,3'-dibromo-BINOL•$ZrCl_4$ complex acting as an asymmetric protonation catalyst in an analogous fashion to the (*R*)-BINOL•$SnCl_4$ complex. Furthermore, the configuration of the chloride is linked to the stereochemistry of the C3 quaternary center.

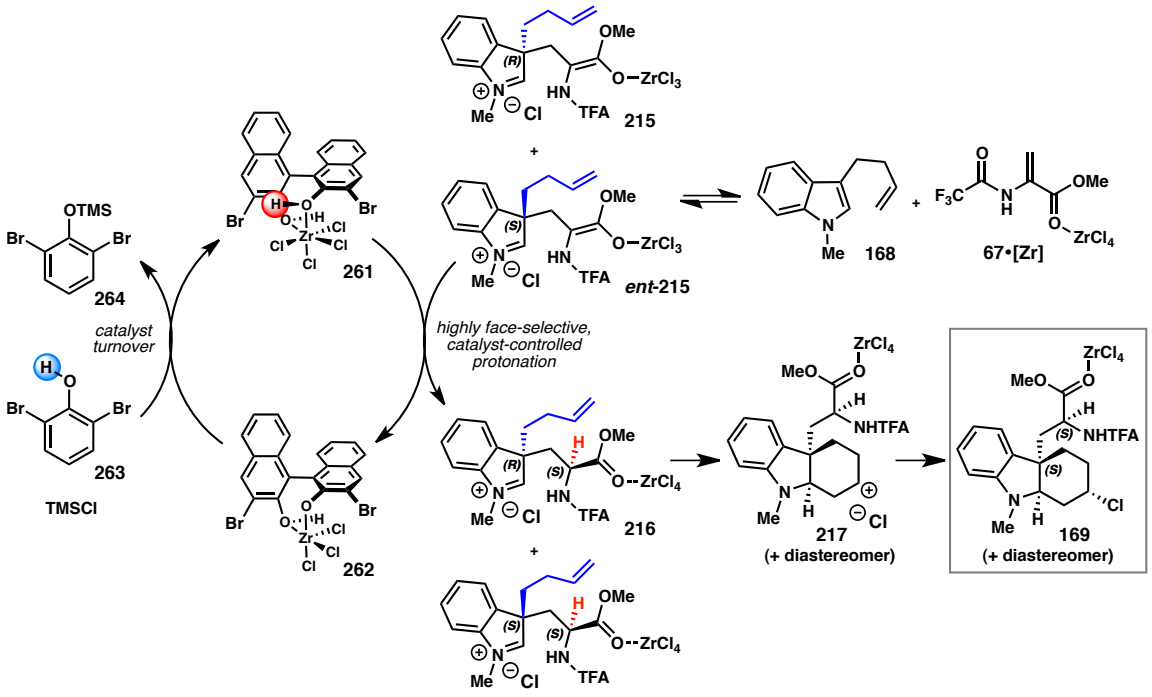
Figure 17. Epimerization study.



A possible mechanism of the conjugate addition/Prins cyclization is proposed in Figure 18. Activation of the acrylate (**67**) by a zirconium Lewis acid facilitates conjugate addition by the indole (**168**) to afford enantiomeric enolate intermediates (**215** and ***ent*-215**). Next, catalyst-controlled, face-selective enolate protonation occurs to yield iminium ions **216**. These first steps are analogous to the formal (3 + 2) cycloaddition to prepare pyrroloindolines. However, in the Prins reaction, the presence of a tethered alkene leads to intramolecular cyclization (to give **217**) followed by chloride quenching of the

resulting carbocation (to yield **169**). The (*R*)-3,3'-Br_2-BINOLate•$ZrCl_4$ complex (**262**) receives a chloride from TMSCl and a proton from the achiral phenol (**263**) to regenerate the active protonation catalyst (**261**).

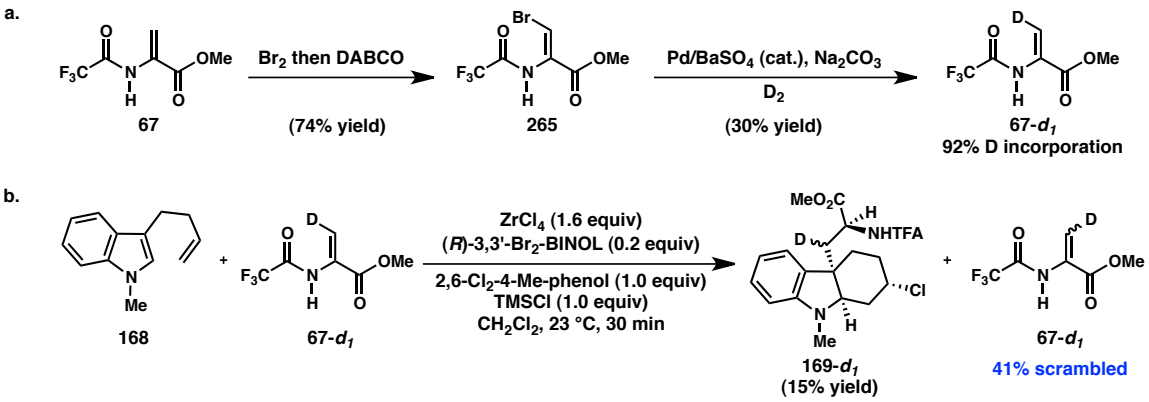
Figure 18. Proposed mechanism of the conjugate addition/Prins cyclization.



In this proposed mechanism, the initial conjugate addition step may be catalyzed by $ZrCl_4$ rather than (*R*)-3,3'-Br_2-BINOL•$ZrCl_4$, and thus is not stereoselective. However, the reversability of conjugate addition, coupled with the difference in protonation rates arising from matching/mismatching of the enantiomeric enolates with the chiral catalyst, leads to the observed diastereoselectivity. To probe the reversability of the conjugate addition step, a stereodefined deuterated acrylate (**67-*d*$_1$**) was synthesized (Figure 19a). Stereochemical information about the acrylate alkene is lost upon conjugate addition; if

this step is reversible, then the deuterium label should undergo scrambling. However, if conjugate addition is not reversible, no scrambling would be expected. When this acrylate was subjected to the Prins reaction conditions (run to low conversion), significant scrambling of the deuterium label was observed in the reisolated acrylate (Figure 19b, 41% had opposite alkene stereochemistry compared to starting acrylate). A control reaction performed in the absence of the indole substrate showed no deuterium scrambling. This result is consistent with a reversible conjugate addition step.

Figure 19. Stereochemical probe of reversability of conjugate addition.

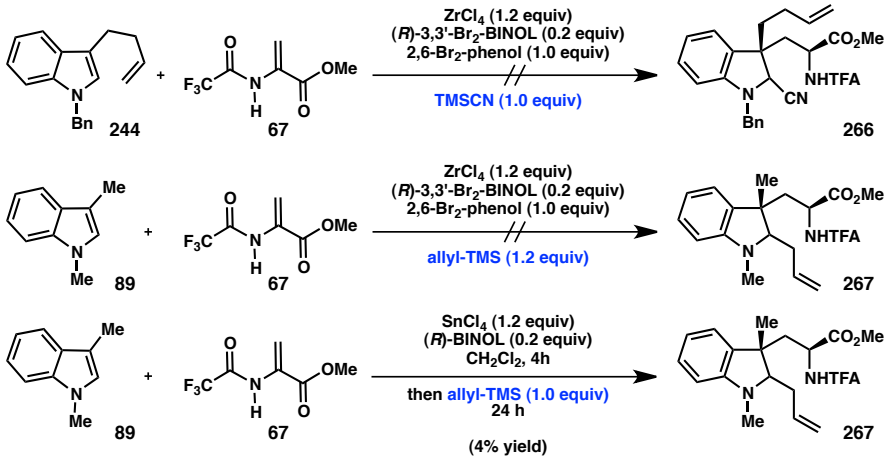


4.2.7 Extension to Intermolecular Nucleophiles

Preliminary investigations into extending this methodology to intermolecular carbon nucleophiles have been performed (Figure 20). When 3-homoallyl indole **244** was exposed to the conjugate addition/Prins cyclization conditions with TMSCN as an external nucleophile, the intermolecular trapping product was not formed. Instead, the major product observed was the Prins cyclization product. However, using $SnCl_4$ as the

Lewis acid and allyltrimethylsilane as the nucleophile gave a small amount of the C2-allylated product (**267**). Development of this methodology will likely require further screening of Lewis acids.

Figure 20. Preliminary investigation of intermolecular nucleophiles.



4.3 Concluding Remarks

We have developed a novel conjugate addition/Prins cyclization for the synthesis of enantioenriched fused indolines. This reaction is based on the observation that the formal (3 + 2) cycloaddition to prepare pyrroloindolines from 3-substituted indoles and 2-amidoacrylates forms an iminium ion as the initial product, and cyclization to the pyrroloindoline does not occur until aqueous work-up. Attempts to trap this iminium ion with alternative nucleophiles led us to design an indole substrate with a tethered alkene. This alkene undergoes an intramolecular Prins cyclization, while a chloride ion from the Lewis acid traps the resulting carbocation.

A screen of Lewis acids revealed $ZrCl_4$ to be optimal, while (*R*)-3,3'-dibromo-BINOL gave the best combination of yield and enantioselectivity. The (*R*)-3,3'-Br_2-BINOL•$ZrCl_4$ complex acts as an asymmetric protonation catalyst in an analogous fashion to the (*R*)-BINOL•$SnCl_4$ catalyst utilized in the pyrroloindoline synthesis. Additives were found to be necessary to achieve catalyst turnover in this transformation. After the (*R*)-3,3'-Br_2-BINOL•$ZrCl_4$ complex effects enolate protonation and donates a chloride ion, it receives a proton from an achiral phenol and a chloride from TMSCl.

A stereodefined, deuterium-labelled acrylate substrate was designed as a probe for the reversability of the conjugate addition step. Results from this experiment are consistent with conjugate addition being reversible.

4.4 Experimental Section

4.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, toluene, and hexanes were dried by passing through activated alumina columns. Dimethylformamide was dried over activated molecular sieves, and 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. 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. 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, δ = 7.26, ^{13}C, δ = 77.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration).

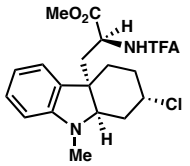
Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Preparative HPLC was performed with either an Agilent 1100 or 1200 Series HPLC utilizing an Agilent Zorbax RX-SIL 5μm 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.

4.4.2 General Procedure A. Conjugate Addition/Asymmetric Protonation/Prins Cyclization Cascade

To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.24 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (0.04 mmol, 0.20 equiv), and phenol (0.20 mmol, 1.00 equiv). The flask was charged with DCM (1.5 mL), followed by addition of TMSCl (0.2 mmol, 1.00 equiv), $ZrCl_4$ (0.32 mmol, 1.60 equiv unless specifically indicated), then stirred at room temperature for 24 h. The reaction was quenched by diluting with 1 mL MeCN and 1 mL 1 M HCl, followed by addition of 5 mL H_2O. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with either saturated $NaHCO_{3(aq)}$ (10 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 crude residue was purified by flash chromatography.

4.4.3 Indoline Products from Conjugate Addition/Asymmetric Protonation/Prins Cyclization Cascade

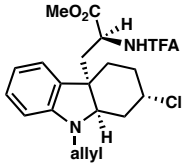
Indoline 169.



Prepared from 1-methyl-3-homoallyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **169** in 84% yield. The diastereomeric ratio was determined to be 7:1 by ^1H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 87% by chiral SFC

analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 4.9 min; t_R(minor) = 6.0 min. The major diastereomer was separated by flash chromatography (10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.7, 1.3 Hz, 1H), 6.95 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.75 (td, *J* = 7.4, 0.9 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 4.55 (td, *J* = 7.6, 5.8 Hz, 1H), 4.28 – 4.21 (m, 1H), 3.50 (s, 3H), 3.45 (t, *J* = 5.1 Hz, 1H), 2.72 (s, 3H), 2.41 (dd, *J* = 14.9, 7.4 Hz, 1H), 2.24 (dd, *J* = 14.9, 5.7 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.91 – 1.76 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 156.5 (q, $J_{C\text{-}F}$ = 37.7 Hz), 150.9, 133.0, 128.5, 121.7, 118.8, 115.5 (q, $J_{C\text{-}F}$ = 287.6 Hz), 108.8, 68.7, 55.8, 52.6, 50.2, 44.5, 37.8, 32.9, 32.8, 32.0, 31.0; IR (NaCl/thin film) 3312, 2954, 2864, 1711, 1607, 1482, 1209, 1178 cm^{-1}; $[\alpha]_D^{25}$ = +55.6 (*c* = 2.06, CH_2Cl_2). HRMS (MM) calc'd for $C_{19}H_{22}ClF_3N_2O_3$ $[M+H]^+$ 419.1344, found 419.1358.

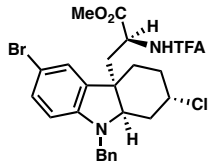
Indoline 245.



Prepared from 1-allyl-3-homoallyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **245** in 70% yield. The diastereomeric ratio was determined to be 4:1 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 89% by chiral SFC analysis (OD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 7.3 min; t_R(minor) = 4.9 min. The major diastereomer was separated by recrystallization (10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (td, *J* = 7.7, 1.3 Hz, 1H), 6.94 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.73 (td, *J* = 7.4, 0.9 Hz, 1H), 6.60 (d, *J* = 7.7 Hz, 1H), 6.57 (d,

J = 7.8 Hz, 1H), 5.87 (dddd, *J* = 17.2, 10.2, 7.0, 4.8 Hz, 1H), 5.31 (ddd, *J* = 17.2, 3.1, 1.6 Hz, 1H), 5.25 (ddd, *J* = 10.2, 2.8, 1.4 Hz, 1H), 4.62 (dd, *J* = 13.8, 7.5 Hz, 1H), 4.23 (qd, *J* = 7.6, 3.7 Hz, 1H), 3.91 (ddt, *J* = 15.9, 4.8, 1.6 Hz, 1H), 3.68 (t, *J* = 4.9 Hz, 1H), 3.64 – 3.56 (m, 1H), 3.47 (s, *J* = 2.1 Hz, 3H), 2.41 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.27 (dd, *J* = 14.8, 6.0 Hz, 1H), 2.11 (dt, *J* = 13.5, 4.1 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.93 – 1.73 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 156.4 (q, $J_{C\text{-}F}$ = 37.8 Hz), 149.6, 133.2, 133.0, 128.4, 121.8, 118.6, 117.9, 115.4 (q, $J_{C\text{-}F}$ = 288.0 Hz), 109.0, 65.8, 55.7, 52.6, 50.1, 48.2, 44.4, 37.33, 32.9, 32.2, 31.0; IR (NaCl/thin film) 3310, 2951, 1711, 1606, 1553, 1479, 1462, 1441, 1209, 1174 cm^{-1}; $[\alpha]_D^{25}$ = 78.1 (*c* = 1.39, CH_2Cl_2). HRMS (MM) calc'd for $C_{21}H_{23}ClF_3N_2O_3$ $[M+H]^+$ 445.1500, found 445.1496.

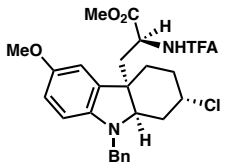
Indoline 247a.



Prepared from 1-benzyl-3-homoallyl-5-bromo-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **247a** in 70% yield. The diastereomeric ratio was determined to be 5:1 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 85% by chiral SFC analysis (OD-H, 2.5 mL/min, 10% EtOH in CO_2, λ = 254 nm): t_R(major) = 9.5 min; t_R(minor) = 7.7 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 7.15 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.62 (dd, *J* = 14.6, 6.6 Hz, 1H), 4.38 (d, *J* = 15.6 Hz, 1H), 4.22 – 4.09 (m, 2H), 3.66 (t, *J* = 4.8 Hz, 1H), 3.49 (s, 3H), 2.38 (dd, *J* = 14.9, 6.8 Hz, 1H), 2.28 (dd, *J* =

14.9, 6.2 Hz, 1H), 2.01 – 1.75 (m, 5H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 171.2, 156.5 (q, $J_{C\text{-}F}$ = 38.1 Hz), 149.3, 137.3, 135.5, 131.0, 128.8 (×2), 127.5, 127.4 (×2), 125.0, 115.4 (q, $J_{C\text{-}F}$ = 287.9 Hz), 110.4, 110.2, 66.6, 60.4, 55.3, 52.8, 50.2, 49.9, 44.7, 37.1, 33.0, 32.1, 30.9. IR (NaCl/thin film) 3308, 2951, 2864, 1713, 1475, 1210, 1175 cm^{-1}; $[\alpha]_D^{25}$ = +41.4 (*c* = 0.90, CH_2Cl_2).

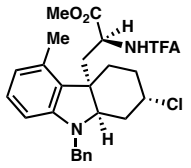
Indoline 247b.



Prepared from 1-benzyl-3-homoallyl-5-methoxy-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A (but with 1.1 equiv $ZrCl_4$) to yield **246b** in 93% yield. The diastereomeric ratio was determined to be 6:1 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 12% IPA in CO_2, λ = 254 nm): t_R(major) = 4.5 min; t_R(minor) = 4.1 min. The major diastereomer was separated by flash chromatography (15→20% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 6.63 – 6.57 (m, 2H), 6.53 (d, *J* = 7.7 Hz, 1H), 6.39 (d, *J* = 8.0 Hz, 1H), 4.60 (dd, *J* = 13.8, 6.8 Hz, 1H), 4.34 (d, *J* = 15.4 Hz, 1H), 4.23 (dd, *J* = 9.8, 6.4 Hz, 1H), 4.07 (d, *J* = 15.4 Hz, 1H), 3.72 (s, 3H), 3.55 (t, *J* = 4.6 Hz, 1H), 3.47 (s, 3H), 2.44 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.28 (dd, *J* = 14.9, 5.8 Hz, 1H), 2.16 – 2.09 (m, 1H), 1.99 – 1.72 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 156.4 (q, $J_{C\text{-}F}$ = 37.7 Hz), 153.4, 144.2, 138.0, 134.7, 128.6 (×2), 127.5 (×2), 127.3, 115.4 (q, $J_{C\text{-}F}$ =

288.0), 112.7, 109.8, 109.2, 67.0, 55.8, 52.7, 51.2, 50.1, 44.7, 36.9, 33.0, 32.3, 31.1, 29.7; IR (NaCl/thin film) 3315, 2925, 1716, 1555, 1490, 1215, 1176 cm^{-1}; $[\alpha]_D^{25}$ = +40.4 (*c* = 0.96, CH_2Cl_2). HRMS (MM) calc'd for $C_{26}H_{28}ClF_3N_2O_4$ $[M+H]^+$ 525.1762, found 525.1749.

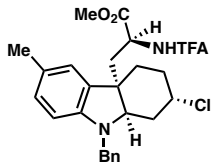
Indoline 247c.



Prepared from 1-benzyl-3-homoallyl-4-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **246c** in 90% yield. The diastereomeric ratio was determined to be 4:1 by ^1H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 90% by chiral SFC analysis (OD-H, 2.5 mL/min, 10% EtOH in CO_2, λ = 254 nm): t_R(major) = 7.5 min; t_R(minor) = 6.7 min. The major diastereomer was separated by flash chromatography (5→10% ethyl acetate/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.96 (t, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 7.9 Hz, 1H), 4.64 (q, *J* = 7.0 Hz, 1H), 4.40 (d, *J* = 15.8 Hz, 1H), 4.21 – 4.12 (m, 2H), 3.60 (t, *J* = 4.3 Hz, 1H), 3.38 (s, 3H), 2.51 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.40 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.29 (s, 3H), 2.21 (dt, *J* = 14.6, 4.3 Hz, 1H), 2.03 – 1.88 (m, 4H), 1.88 – 1.75 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 156.5 (q, $J_{C\text{-}F}$ = 37.8 Hz), 150.9, 138.0, 133.9, 129.7, 128.7 (×2), 128.3, 127.4 (×2), 127.3, 122.2, 115.4 (q, $J_{C\text{-}F}$ = 287.9 Hz), 107.0, 65.8, 55.5, 52.6, 50.6, 50.4, 46.2, 36.6, 33.1, 31.3, 31.1, 19.1; IR

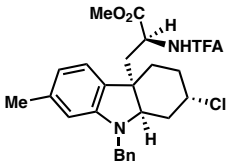
(NaCl/thin film) 3311, 2953, 1711, 1589, 1452, 1212, 1177 cm^{-1}; $[\alpha]_D^{25}$ = 79.4 (*c* = 0.81, CH_2Cl_2).

Indoline 247d.



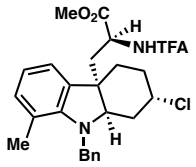
Prepared from 1-benzyl-3-homoallyl-5-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **246d** in quantitative yield. The diastereomeric ratio was determined to be 6:1 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 90% by chiral SFC analysis (OJ-H, 2.5 mL/min, 8% EtOH in CO_2, λ = 254 nm): t_R(major) = 7.0 min; t_R(minor) = 5.1 min. The major diastereomer was separated by flash chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ .39 – 7.27 (m, 5H), 6.87 (ddd, *J* = 7.9, 1.7, 0.7 Hz, 1H), 6.78 (d, *J* = 1.7 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 4.62 (td, *J* = 7.6, 5.5 Hz, 1H), 4.37 (d, *J* = 15.4 Hz, 1H), 4.24 (dt, *J* = 11.3, 3.7 Hz, 1H), 4.10 (d, *J* = 15.4 Hz, 1H), 3.56 (t, *J* = 5.2 Hz, 1H), 3.49 (s, *J* = 2.3 Hz, 3H), 2.44 (dd, *J* = 14.8, 7.5 Hz, 1H), 2.30 – 2.21 (m, 4H), 2.09 – 1.78 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 156.4 (q, $J_{C\text{-}F}$ = 37.8 Hz), 147.9, 138.0, 133.0, 128.7, 128.6 (×2), 128.0, 127.5 (×2), 127.3, 122.8, 116.6 (q, $J_{C\text{-}F}$ = 287.8 Hz), 109.0, 66.9, 56.1, 52.6, 50.4, 50.1, 44.6, 37.3, 32.8, 31.1, 30.8, 20.7; IR (NaCl/thin film) 3314, 2951, 2868, 1715, 1552, 1490, 1440, 1210, 1177 cm^{-1}; $[\alpha]_D^{25}$ = +55.3 (*c* = 0.85, CH_2Cl_2). HRMS (MM) calc'd for $C_{26}H_{28}ClF_3N_2O_3$ $[M+H]^+$ 509.1813, found 509.1831.

Indoline 247e.



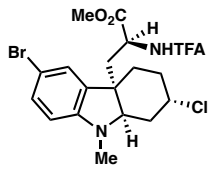
Prepared from 1-benzyl-3-homoallyl-6-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A (but with 1.1 equiv $ZrCl_4$) to yield **246e** in 74% yield. The diastereomeric ratio was determined to be 3:1 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 2.6 min; t_R(minor) = 2.1 min. The major diastereomer was separated by flash chromatography (5→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.84 (d, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 1H), 6.49 (d, *J* = 7.7 Hz, 1H), 6.33 (s, 1H), 4.60 (td, *J* = 7.7, 5.4 Hz, 1H), 4.38 (d, *J* = 15.6 Hz, 1H), 4.21 (dq, *J* = 11.0, 3.7 Hz, 1H), 4.13 (d, *J* = 15.6 Hz, 1H), 3.58 (t, *J* = 5.3 Hz, 1H), 3.49 (s, *J* = 2.4 Hz, 3H), 2.39 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.27 – 2.21 (m, 4H), 2.06 – 1.77 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 156.5 (q, $J_{C\text{-}F}$ = 37.8 Hz), 150.3, 138.6, 138.0, 129.9, 128.7 (×2), 127.4 (×2), 127.3, 121.8, 119.2, 115.4 (q, $J_{C\text{-}F}$ = 287.8 Hz), 109.8, 66.7, 56.0, 52.7, 50.1, 50.0, 44.37, 37.6, 33.0, 31.0, 30.8, 21.7; IR (NaCl/thin film) 3312, 2950, 1712, 1612, 1551, 1493, 1452, 1210, 1176 cm^{-1}; $[\alpha]_D^{25}$ = +65.8 (*c* = 0.89, CH_2Cl_2). HRMS (MM) calc'd for $C_{26}H_{28}ClF_3N_2O_3$ $[M+H]^+$ 509.1813, found 509.1823.

Indoline 247f.



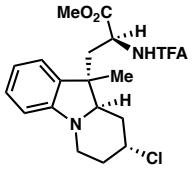
Prepared from 1-benzyl-3-homoallyl-7-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **246f** in 89% yield. The diastereomeric ratio was determined to be 6:1 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 2.7 min; t_R(minor) = 2.2 min. The major diastereomer was separated by flash chromatography (5→10% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.3 Hz, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 4.71 (d, *J* = 16.5 Hz, 1H), 4.62 – 4.49 (m, 2H), 4.19 (td, *J* = 7.9, 3.8 Hz, 1H), 3.51 (s, 3H), 3.45 (t, *J* = 4.9 Hz, 1H), 2.35 (s, 3H), 2.24 (d, *J* = 6.3 Hz, 2H), 2.04 (dt, *J* = 15.0, 4.4 Hz, 1H), 1.96 – 1.69 (m, 5H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 156.4 (q, $J_{C\text{-}F}$ = 37.7 Hz), 148.0, 139.3, 133.7, 132.3, 128.7 (×2), 127.3, 127.2 (×2), 120.4, 120.0, 119.3, 115.4 (q, $J_{C\text{-}F}$ = 287.8 Hz), 66.4, 55.9, 52.7, 52.3, 50.0, 44.6, 37.9, 33.9, 32.0, 30.8, 19.6; IR (NaCl/thin film) 3314, 2952, 1715, 1558, 1452, 1208, 1176 cm^{-1}; $[\alpha]_D^{25}$ = +57.2 (*c* = 0.94, CH_2Cl_2). HRMS (MM) calc'd for $C_{26}H_{28}ClF_3N_2O_3$ $[M–H]^-$ 507.1668, found 507.1681.

5-Bromo-N-methyl Indoline.



Prepared from 1-methyl-3-homoallyl-5-bromo-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **247** in 77% yield. The diastereomeric ratio was determined to be 5:1 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined to be 88% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% MeOH in CO_2, λ = 254 nm): t_R(major) = 1.9 min; t_R(minor) = 5.3 min. The major diastereomer was separated by flash chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.41 (d, *J* = 8.3 Hz, 1H), 4.56 (dd, *J* = 14.4, 6.7 Hz, 1H), 4.25 – 4.17 (m, 1H), 3.54 (s, *J* = 2.4 Hz, 3H), 3.47 (t, *J* = 4.9 Hz, 1H), 2.70 (s, 3H), 2.36 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.23 (ddd, *J* = 15.0, 5.9, 2.7 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.03 – 1.96 (m, 1H), 1.93 – 1.74 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 156.5 (q, $J_{C\text{-}F}$ = 37.9 Hz), 150.1, 135.6, 131.1, 124.9, 115.5 (q, $J_{C\text{-}F}$ = 287.5 Hz), 110.4, 110.1, 68.7, 55.2, 52.7, 50.1, 44.7, 37.7, 32.9, 32.8, 32.4, 31.0.; IR (NaCl/thin film) 3309, 2953, 2863, 1709, 1555, 1478, 1210, 1178 cm^{-1}; $[\alpha]_D^{25}$ = +23.7 (*c* = 0.88, CH_2Cl_2). HRMS (MM) calc'd for $C_{19}H_{21}BrClF_3N_2O_3$ $[M+H]^+$ 497.0449, found 497.0452.

Indoline 248.

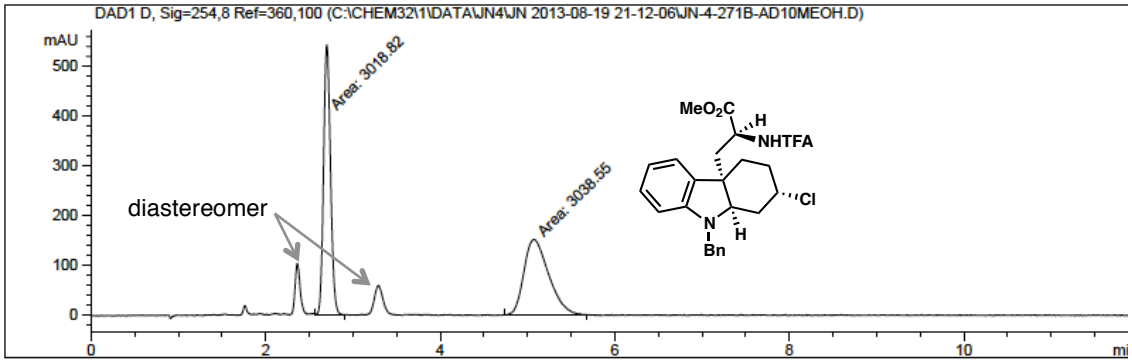


Prepared from 1-homoallyl-3-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using General Procedure A to yield **248** in 80% yield. The diastereomeric ratio was determined to be 6:1 by ^{1}H NMR analysis of the crude reaction mixture. The

enantiomeric excess of the major diastereomer was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 2.7 min; t_R(minor) = 8.7 min. The major diastereomer was separated by flash chromatography (12→15% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (td, *J* = 7.7, 1.2 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.74 (td, *J* = 7.4, 0.9 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 4.58 (td, *J* = 7.8, 4.6 Hz, 1H), 3.98 (tt, *J* = 11.8, 4.0 Hz, 1H), 3.72 (ddd, *J* = 13.3, 4.7, 2.1 Hz, 1H), 3.59 (s, *J* = 3.5 Hz, 3H), 3.16 (dd, *J* = 11.8, 2.7 Hz, 1H), 2.82 (tt, *J* = 18.4, 9.2 Hz, 1H), 2.30 (dd, *J* = 14.9, 4.7 Hz, 1H), 2.21 – 2.07 (m, 3H), 1.89 – 1.77 (m, 1H), 1.72 (q, *J* = 11.9 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 156.6 (q, $J_{C\text{-}F}$ = 37.7 Hz), 148.8, 134.4, 128.5, 122.7, 118.8, 115.5 (q, $J_{C\text{-}F}$ = 287.7 Hz), 107.3, 70.1, 57.1, 52.7, 50.3, 45.7, 43.9, 40.4, 35.9, 34.6, 21.0; IR (NaCl/thin film) 3314, 2958, 1711, 1606, 1482, 1454, 1211, 1173 cm^{-1}. HRMS (MM) calc'd for $C_{19}H_{22}ClF_3N_2O_3$ $[M+H]^+$ 419.1344, found 419.1342.

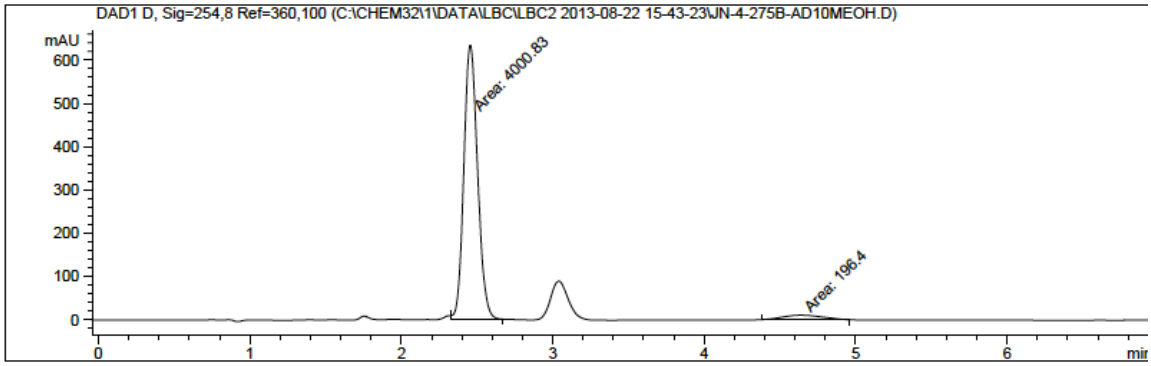
4.4.4 SFC Traces for Racemic and Enantioenriched Products

246 (Table 7, Entry 8): racemic



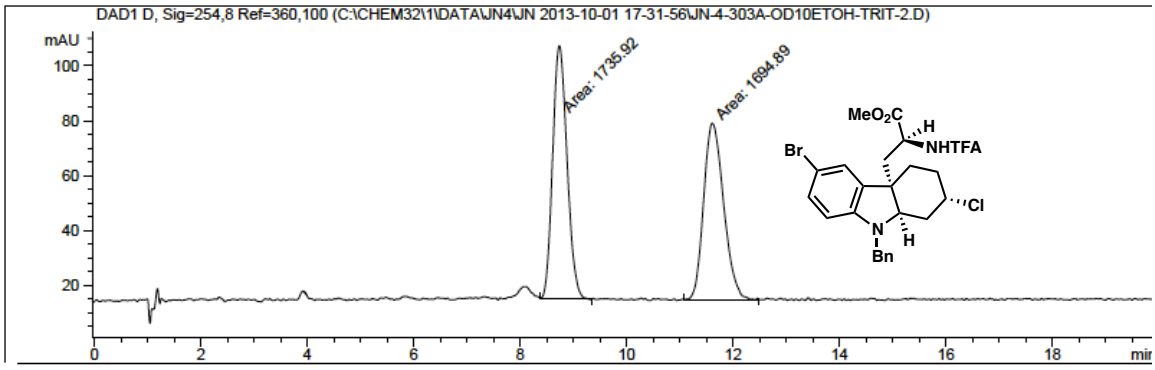
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.700	MM	0.0924	3018.81982	544.27289	49.8371
2	5.075	MM	0.3323	3038.55054	152.40765	50.1629

246 (Table 7, Entry 8): 91% ee



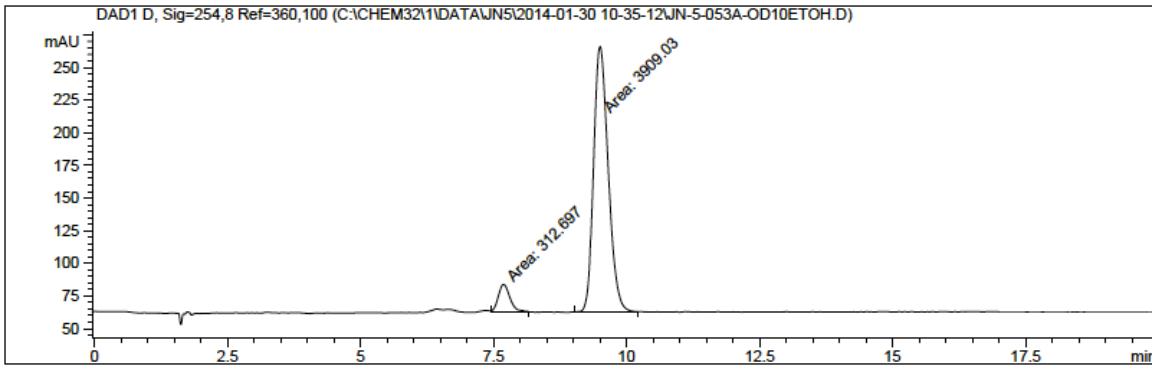
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.455	MM	0.1049	4000.83252	635.53796	95.3207
2	4.638	MM	0.3095	196.40041	10.57566	4.6793

247a (Table 8): racemic



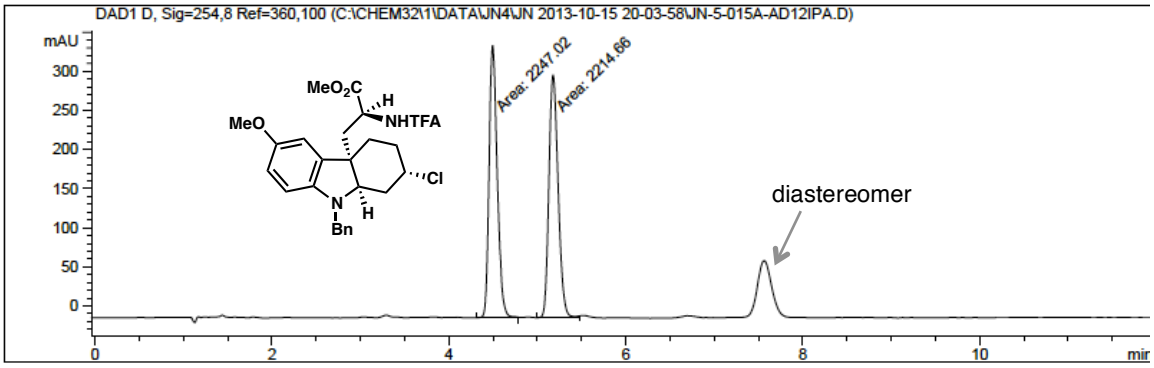
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.739	MM	0.3135	1735.92102	92.27703	50.5979
2	11.611	MM	0.4383	1694.89441	64.44508	49.4021

247a (Table 8, major diastereomer only): 85% ee



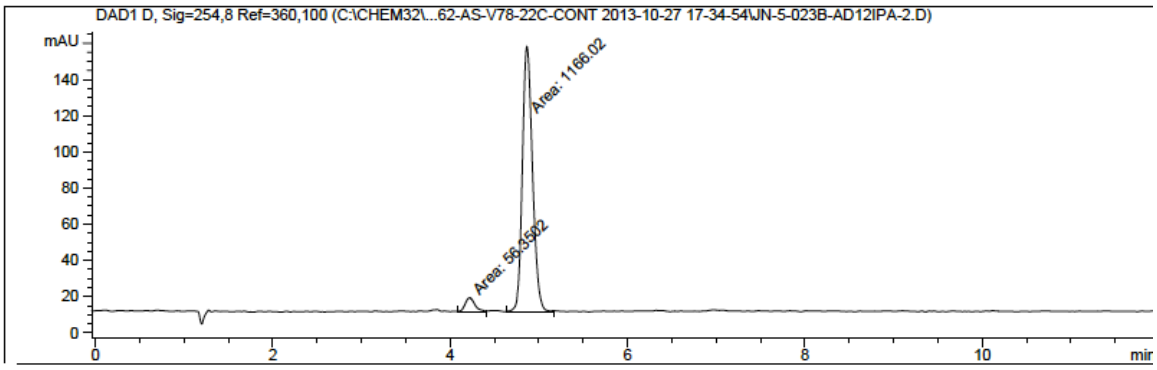
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.690	MM	0.2497	312.69736	20.87528	7.4069
2	9.505	MM	0.3200	3909.02954	203.61522	92.5931

247b (Table 8): racemic



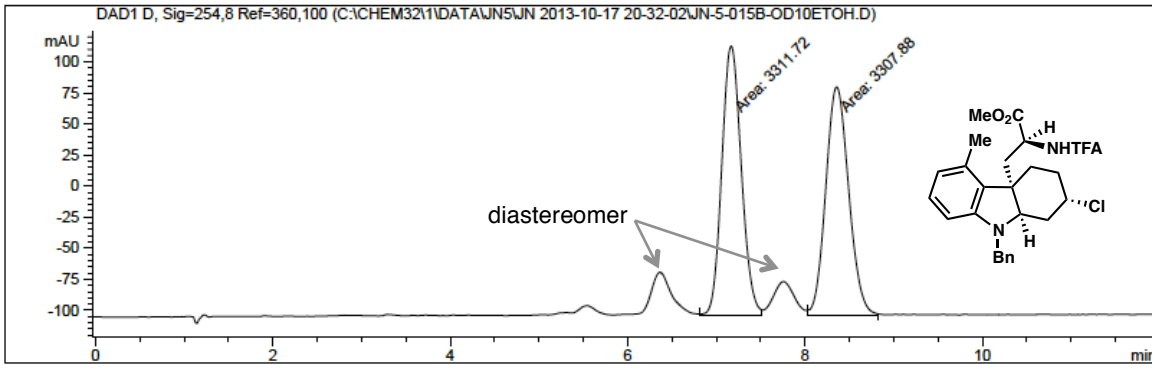
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.496	MM	0.1072	2247.02026	349.30011	50.3626
2	5.178	MM	0.1193	2214.66113	309.27405	49.6374

247b (Table 8): 91% ee



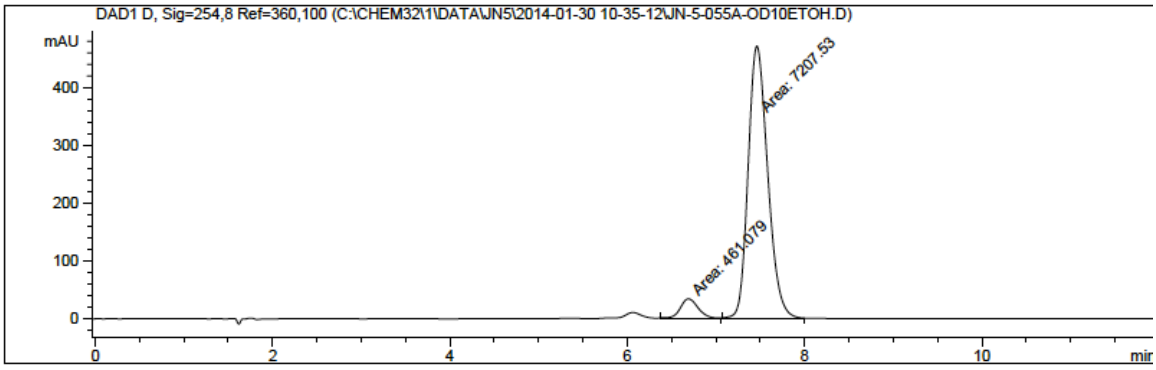
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.219	MM	0.1233	56.35015	7.61557	4.6099
2	4.866	MM	0.1325	1166.02209	146.64792	95.3901

247c (Table 8): racemic



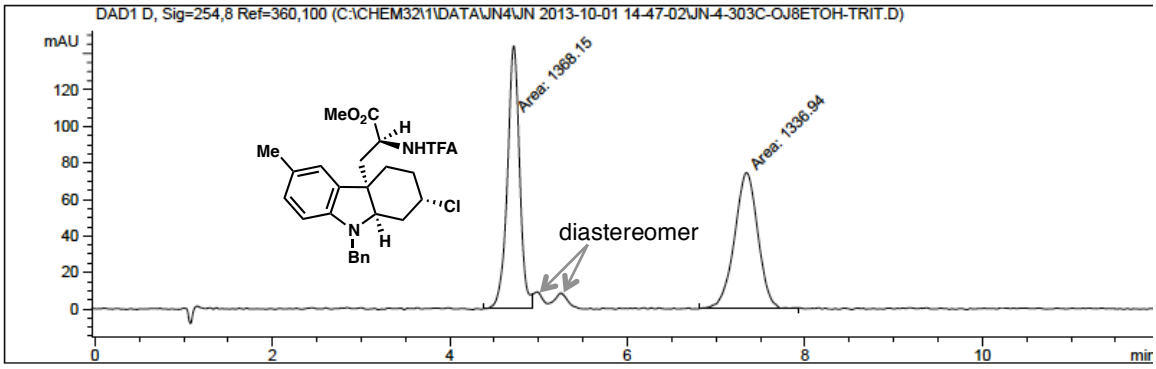
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.167	MM	0.2547	3311.72388	216.69806	50.0291
2	8.356	MM	0.3001	3307.87622	183.70784	49.9709

247c (Table 8, major diastereomer only): 88% ee



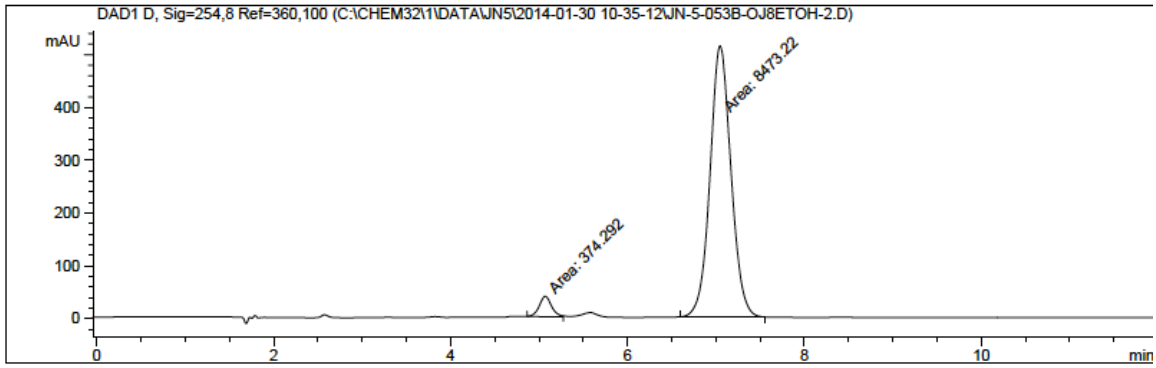
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.689	MM	0.2305	461.07950	33.33388	6.0126
2	7.461	MM	0.2553	7207.52832	470.58481	93.9874

247d (Table 8): racemic



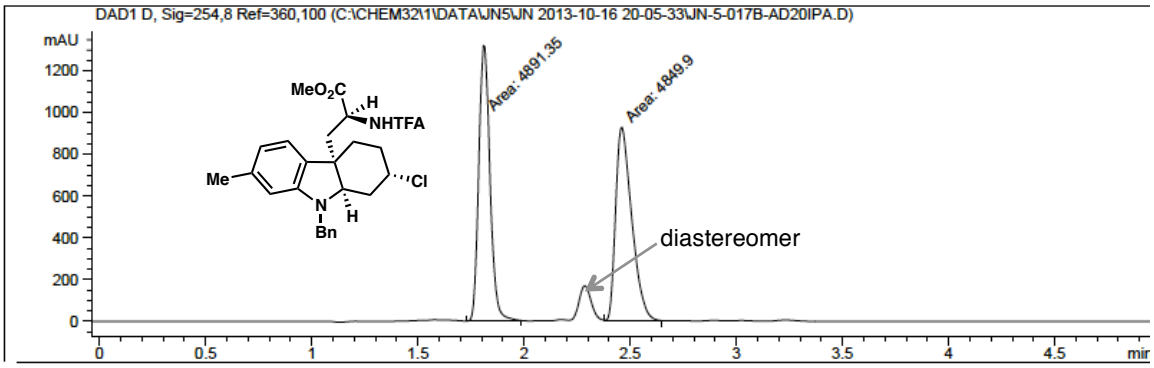
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.720	MM	0.1588	1368.15161	143.62547	50.5769
2	7.343	MM	0.3010	1336.93970	74.03839	49.4231

247d (Table 8): 92% ee



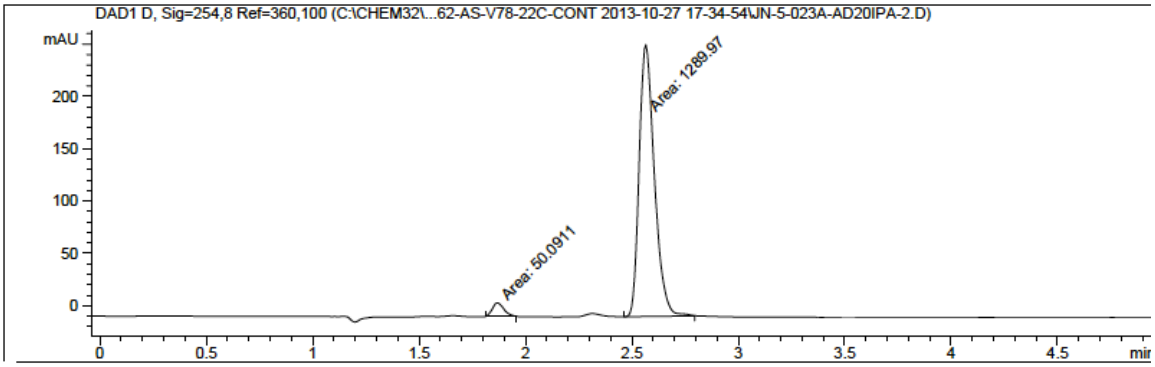
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.071	MM	0.1609	374.29236	38.77222	4.2305
2	7.047	MM	0.2750	8473.22168	513.56281	95.7695

247e (Table 8): racemic



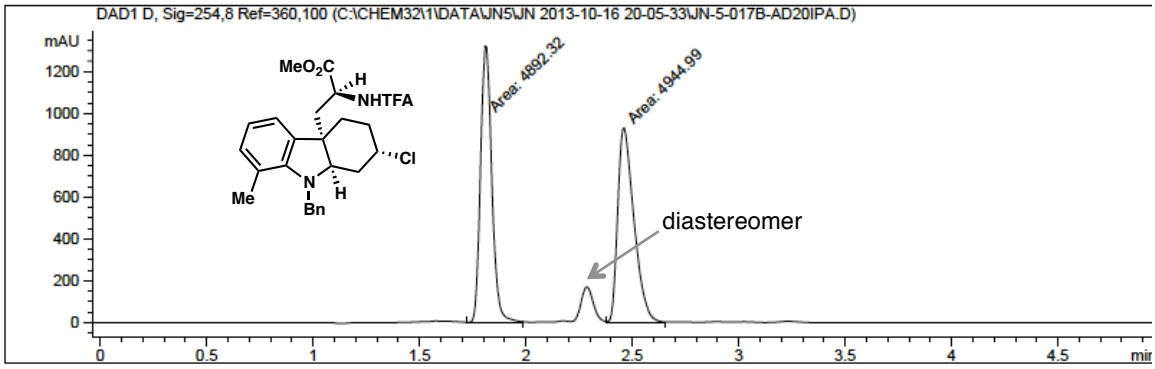
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.812	MM	0.0605	4891.34961	1347.66492	50.2127
2	2.461	MM	0.0868	4849.90088	931.37439	49.7873

247e (Table 8): 93% ee



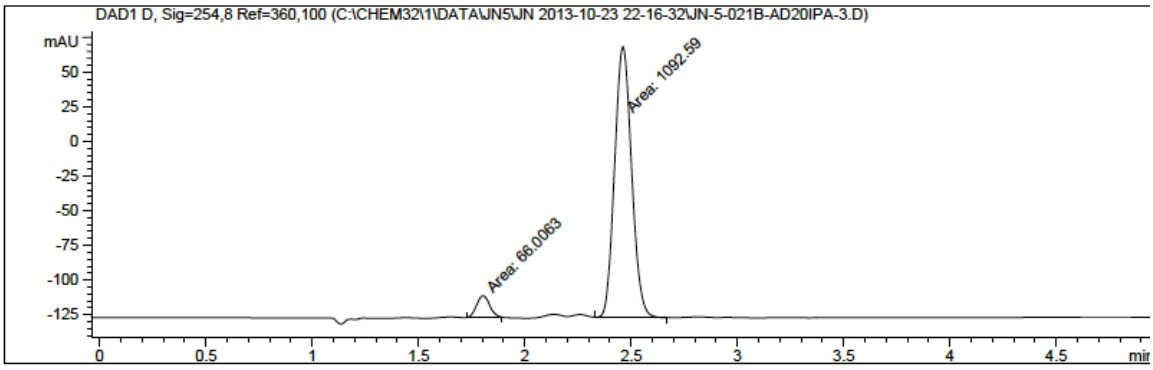
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.869	MM	0.0635	50.09111	13.15408	3.7380
2	2.565	MM	0.0826	1289.97192	260.39725	96.2620

247f (Table 8): racemic



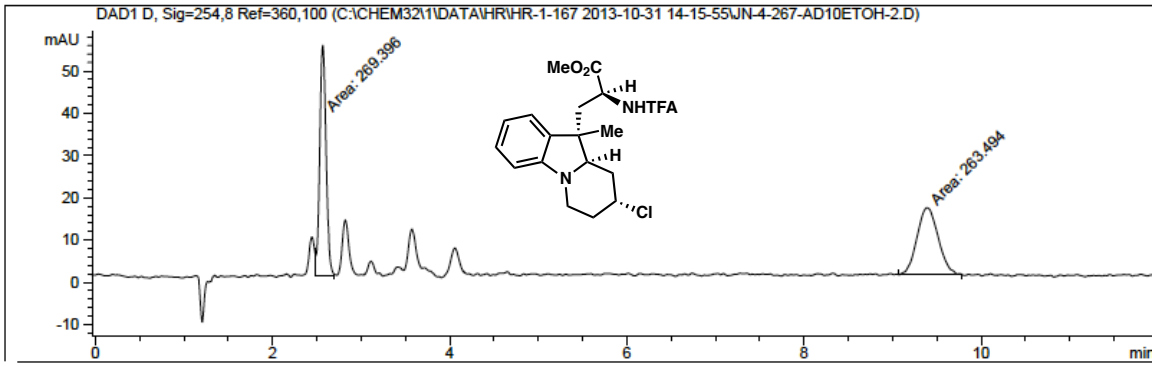
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.812	MM	0.0610	4892.31689	1336.32910	49.7323
2	2.460	MM	0.0883	4944.98926	933.73901	50.2677

247f (Table 8): 89% ee



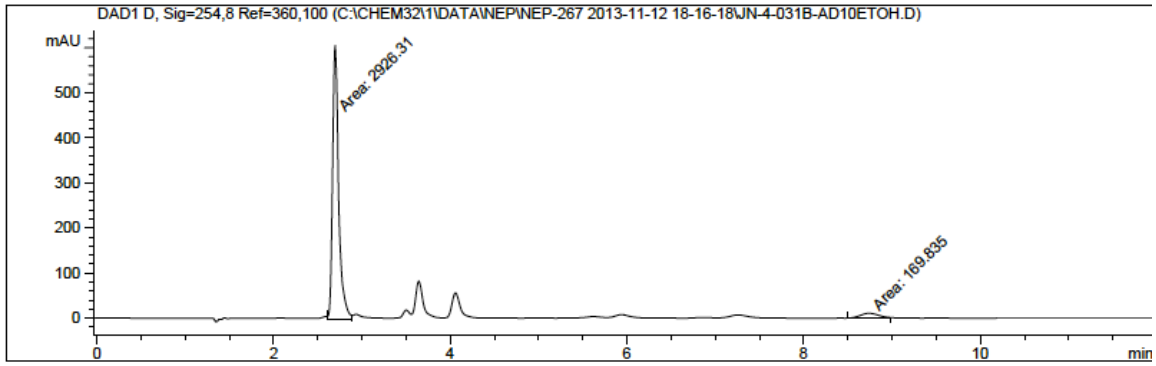
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.804	MM	0.0707	66.00635	15.56793	5.6971
2	2.462	MM	0.0929	1092.58643	196.06543	94.3029

248 (Table 8): racemic



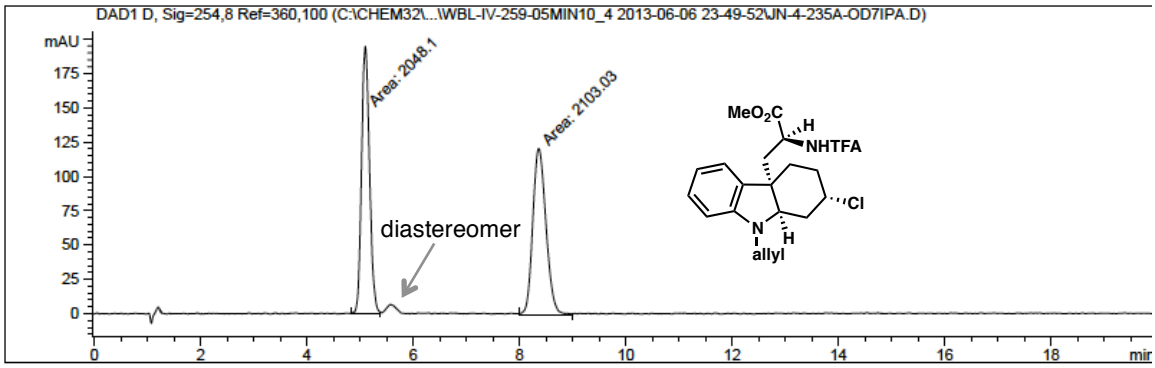
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.566	MM	0.0822	269.39600	54.61353	50.5538
2	9.388	MM	0.2768	263.49390	15.86486	49.4462

248 (Table 8): 89% ee



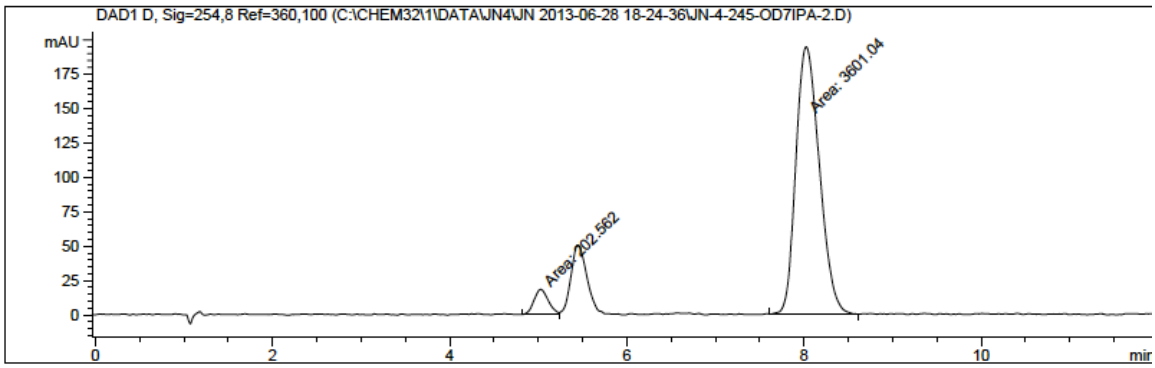
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.698	MM	0.0800	2926.30688	609.68549	94.5146
2	8.746	MM	0.2511	169.83505	11.27103	5.4854

245 (Table 8): racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.099	MM	0.1751	2048.10229	194.90222	49.3384
2	8.364	MM	0.2889	2103.03052	121.33443	50.6616

245 (Table 8): 89% ee



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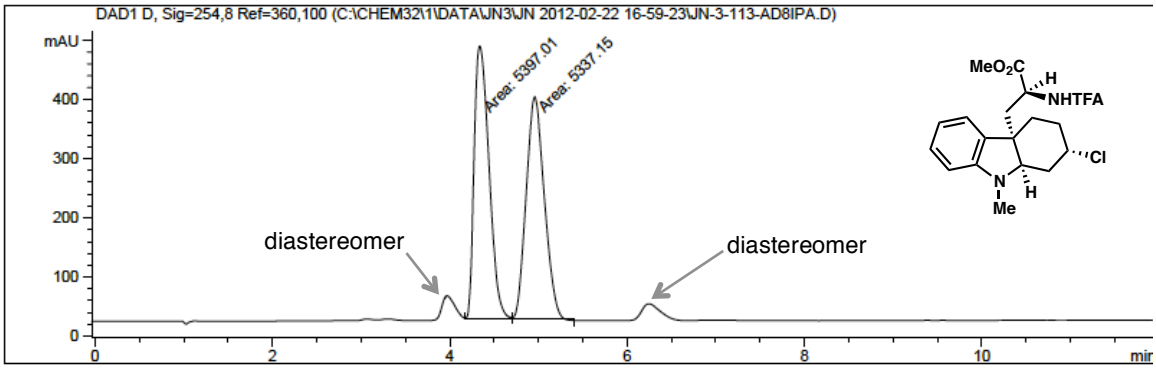
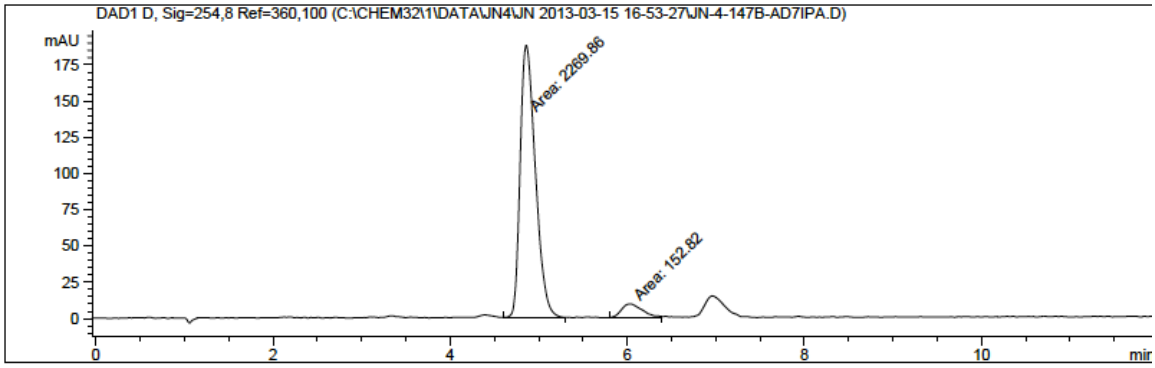
1	5.028	MM	0.1861	202.56195	18.14186	5.3255
2	8.024	MM	0.3085	3601.03638	194.54140	94.6745

169 (Table 8): racemic



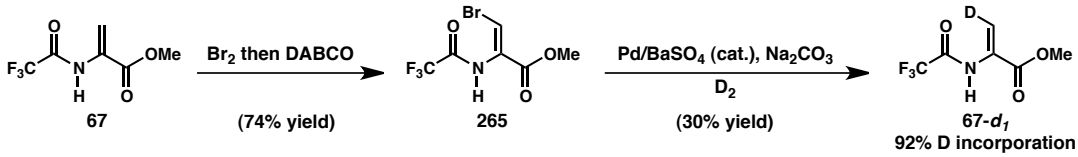
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.338	MM	0.1948	5397.01465	461.86542	50.2788
2	4.959	MM	0.2366	5337.15186	375.89224	49.7212

169 (Table 8): 87% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.860	MM	0.2008	2269.86377	188.42389	93.6921
2	6.036	MM	0.2709	152.81998	9.40274	6.3079

4.4.5 Synthesis of deuterated acrylate 67-$\mathbf{d_1}$



Acrylate **67** (10 mmol, 1.97g, 1.0 equiv) was dissolved in 50 mL CH_2Cl_2 and cooled to –78 °C. Molecular bromine (10 mmol, 0.51 mL, 1.0 equiv) was added dropwise, and the reaction was stirred for 10 minutes before moving to an ice bath, where it was stirred for 40 minutes. DABCO (10 mmol, 1.1 g, 1.0 equiv) was added as a solution in 15 mL CH_2Cl_2. The reaction was stirred for 1.5 h, then filtered through celite, and concentrated. The crude mixture was purified by flash chromatography (30% Et_2O/pentane) to yield 2.03 g (74% yield) of bromoacrylate **285**.

285: ^{1}H NMR (300 MHz, acetone) δ 7.89 (s, 1H), 3.80 (s, 3H)

Bromoacrylate **285** (3 mmol, 830 mg) was dissolved in 6 mL ethyl acetate (not dried), and $Pd/BaSO_4$ (reduced, 29 mg) was added. The reaction was sparged with D_2, then sealed and stirred until the reaction no longer progressed by TLC (approximately four days). The reaction was filtered through celite, concentrated, and purified by flash chromatography (20% Et_2O/pentane) to yield 180.5 mg (30% yield) of deuterium labelled acrylate **67-*d*$_1$**.

67-*d*$_1$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 6.13 (d, J = 1.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 155.1 (q, $J_{C\text{-}F}$ = 38.2 Hz), 129.4, 115.2 (q, $J_{C\text{-}F}$ = 288.3 Hz), 112.1 (t, $J_{C\text{-}D}$ = 26 Hz), 53.47; HRMS (MM) calc'd for $C_6H_5DF_3N_2O_3$ $[M–H]^-$ 197.0290, found 197.0295.

4.5 Notes and References

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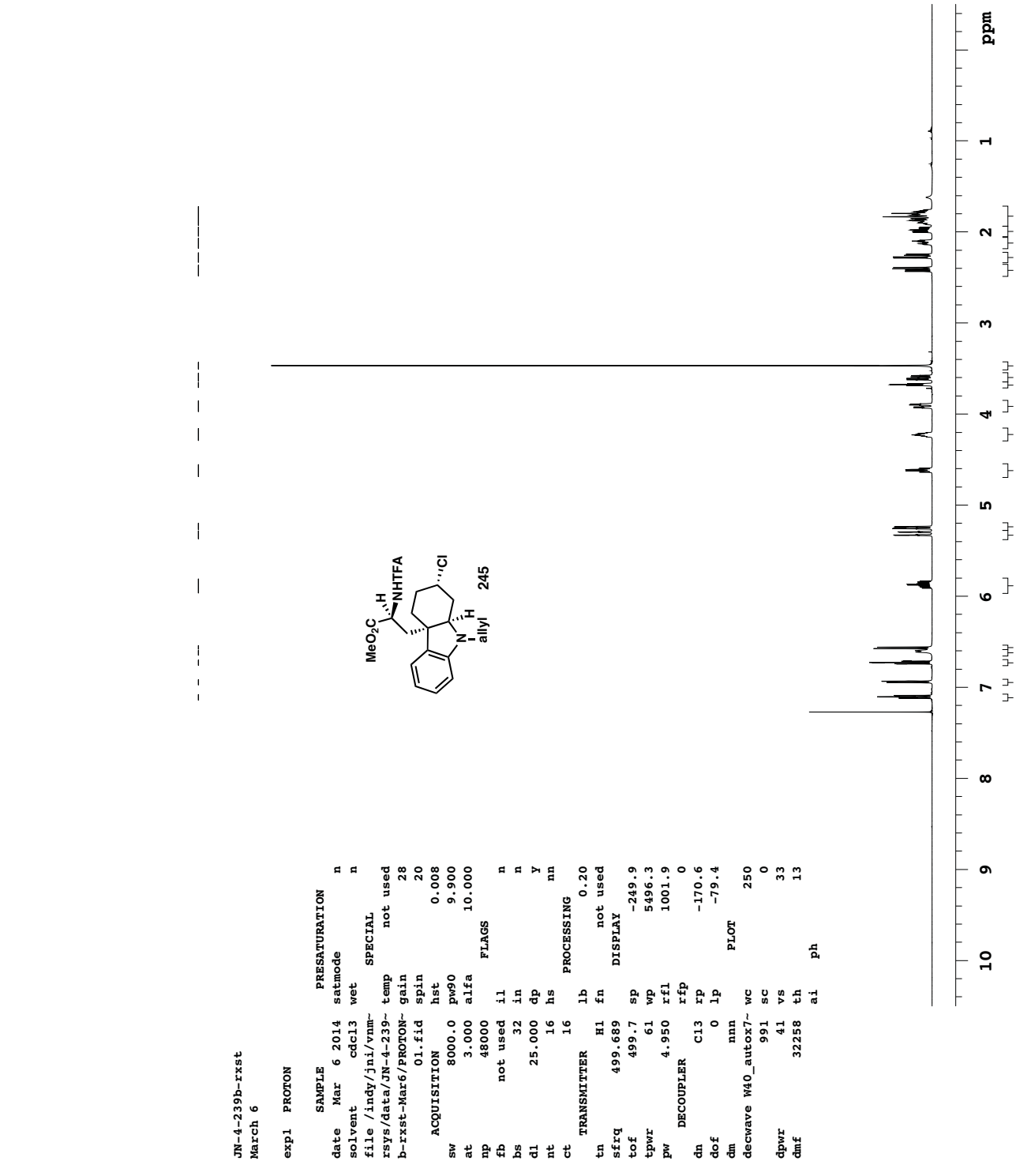
APPENDIX 4

Spectra Relevant to Chapter 4:

Development of a Tandem Conjugate Addition/Prins Cyclization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H
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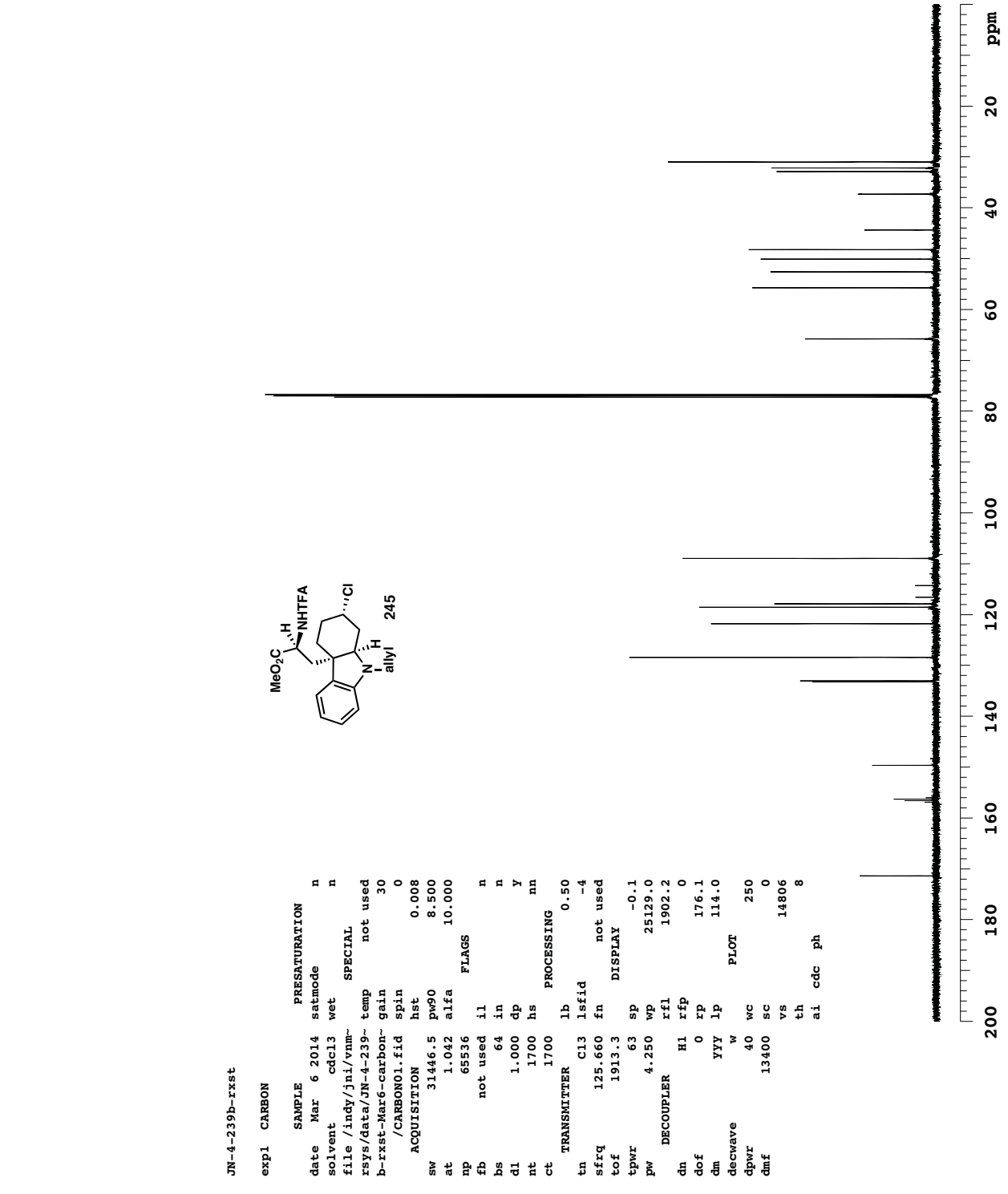
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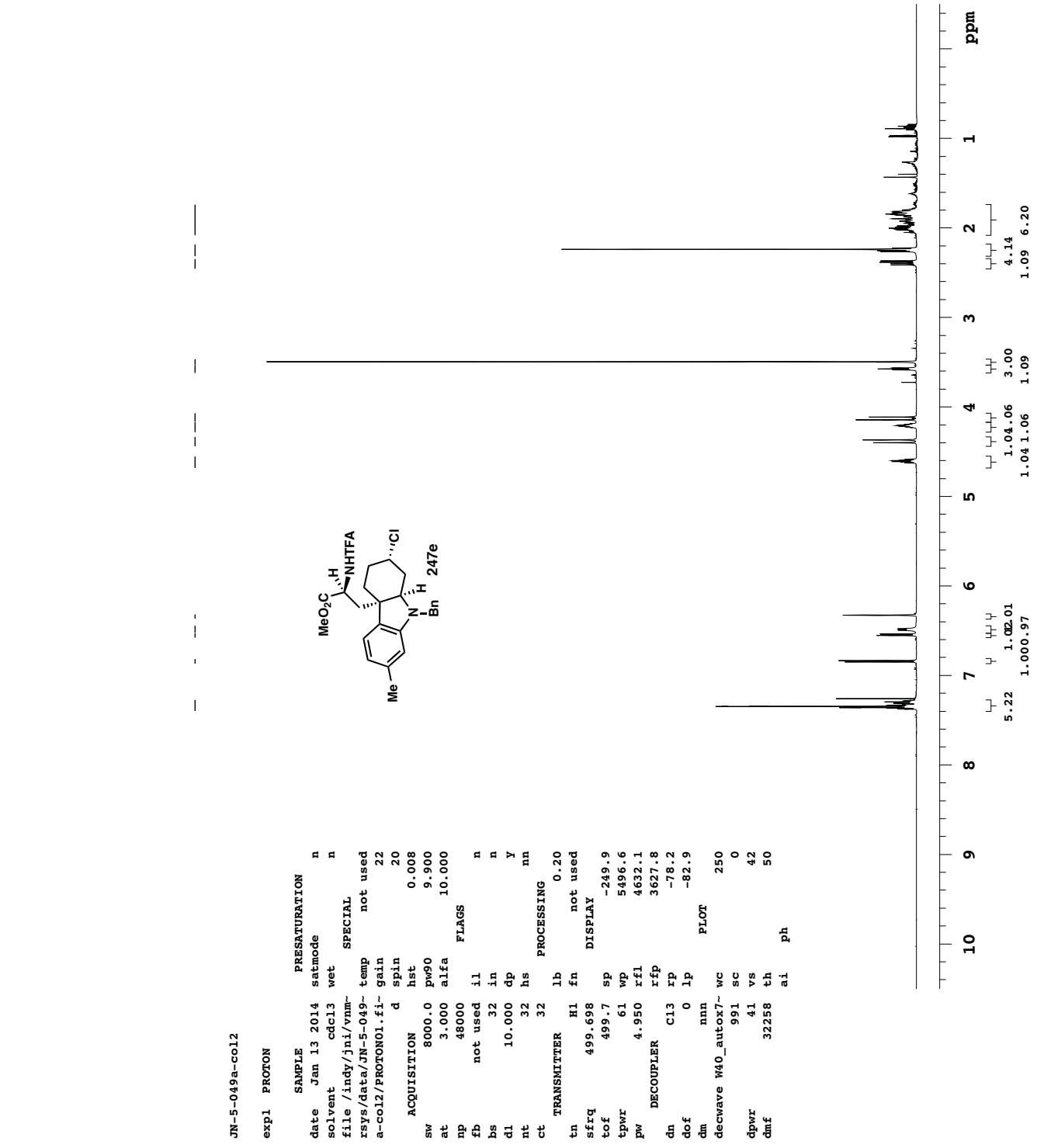
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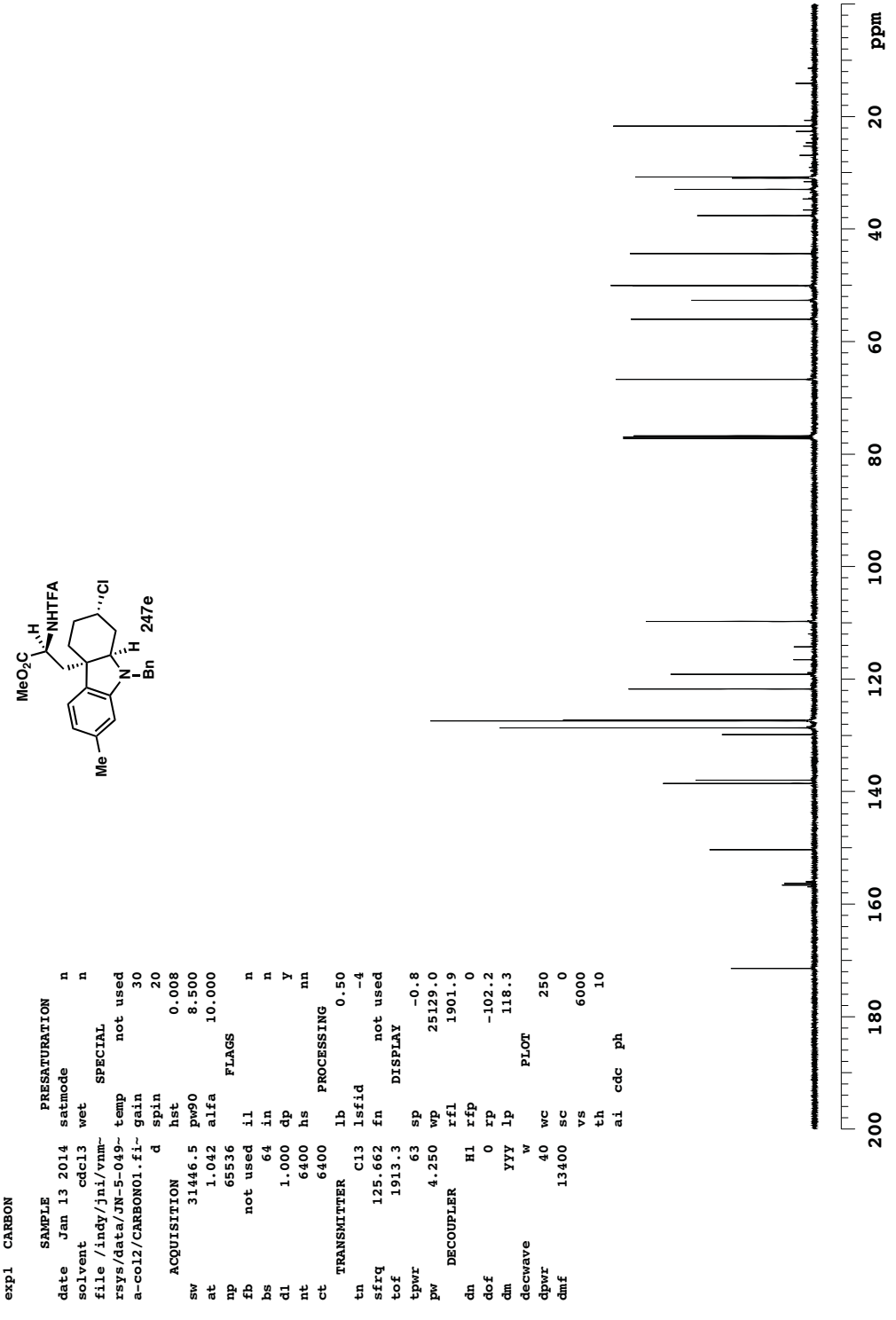
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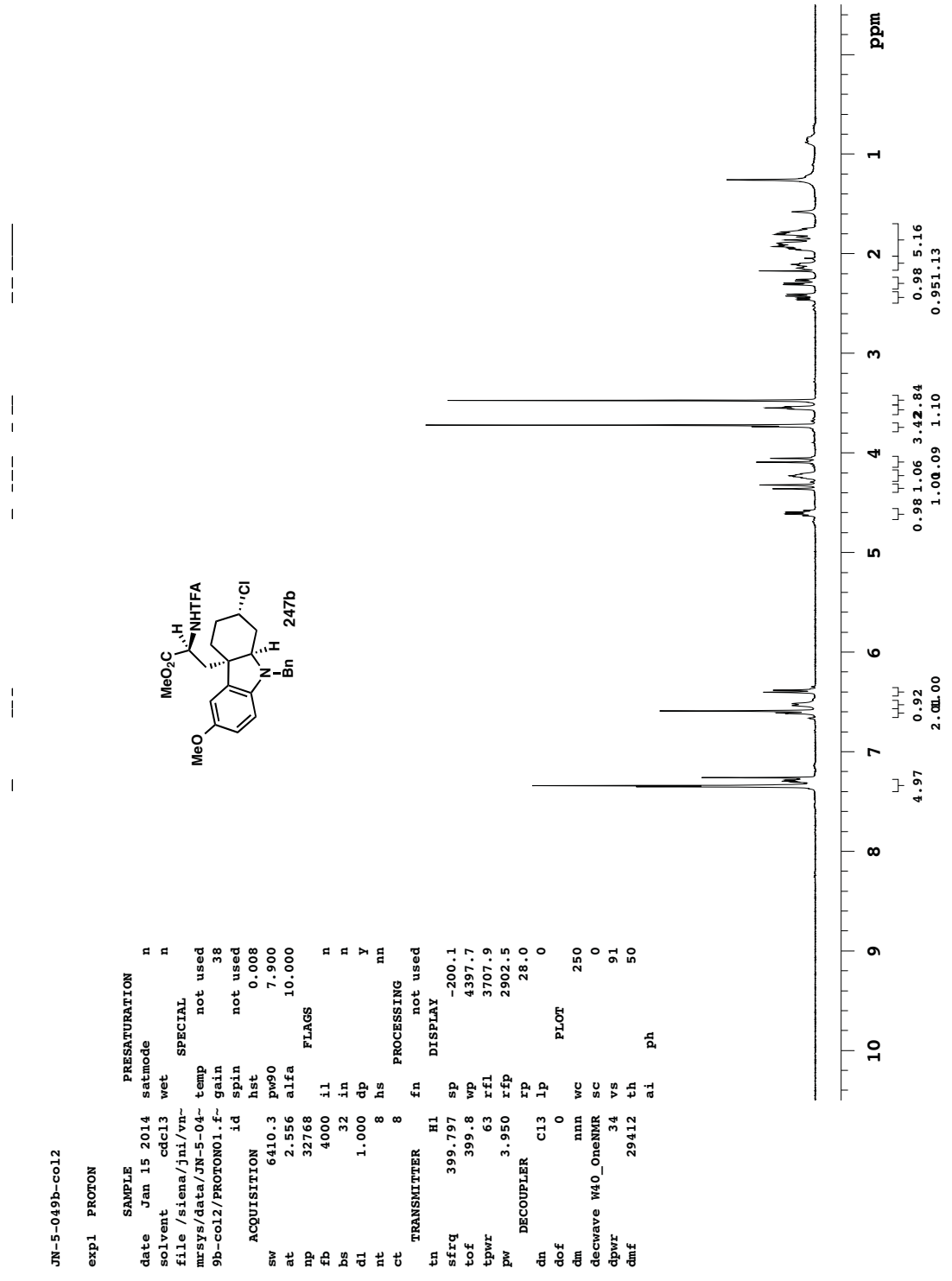
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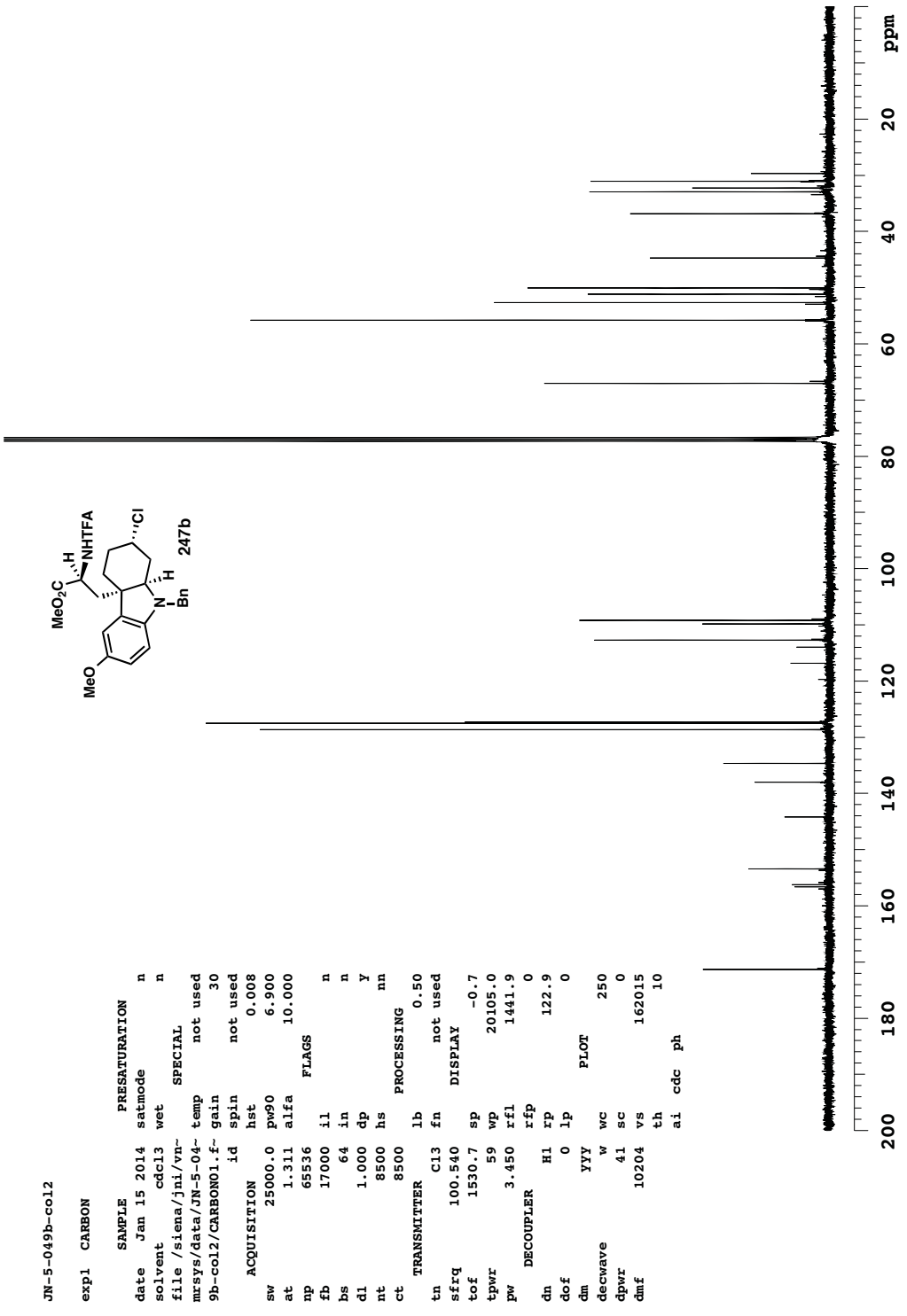
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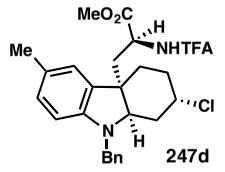
140
120
100
80
60
40
20
ppm

JN-5-053b-col2

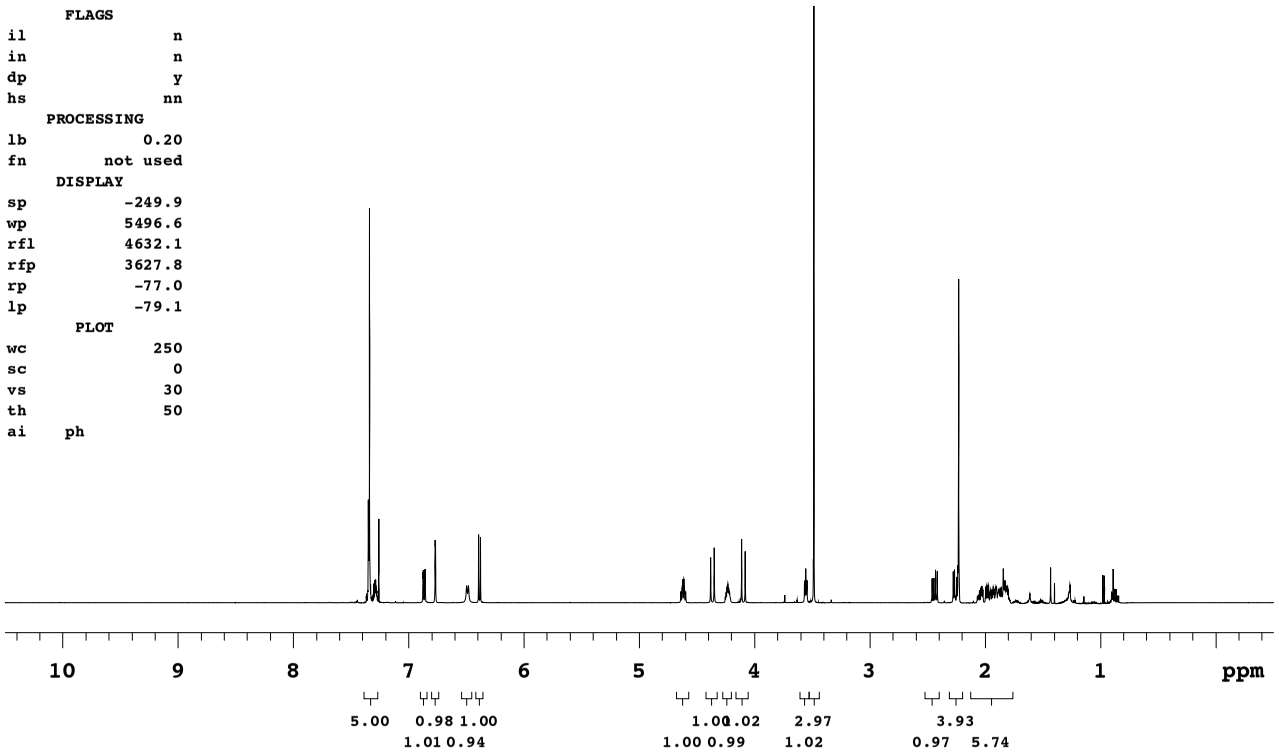
exp1 PROTON

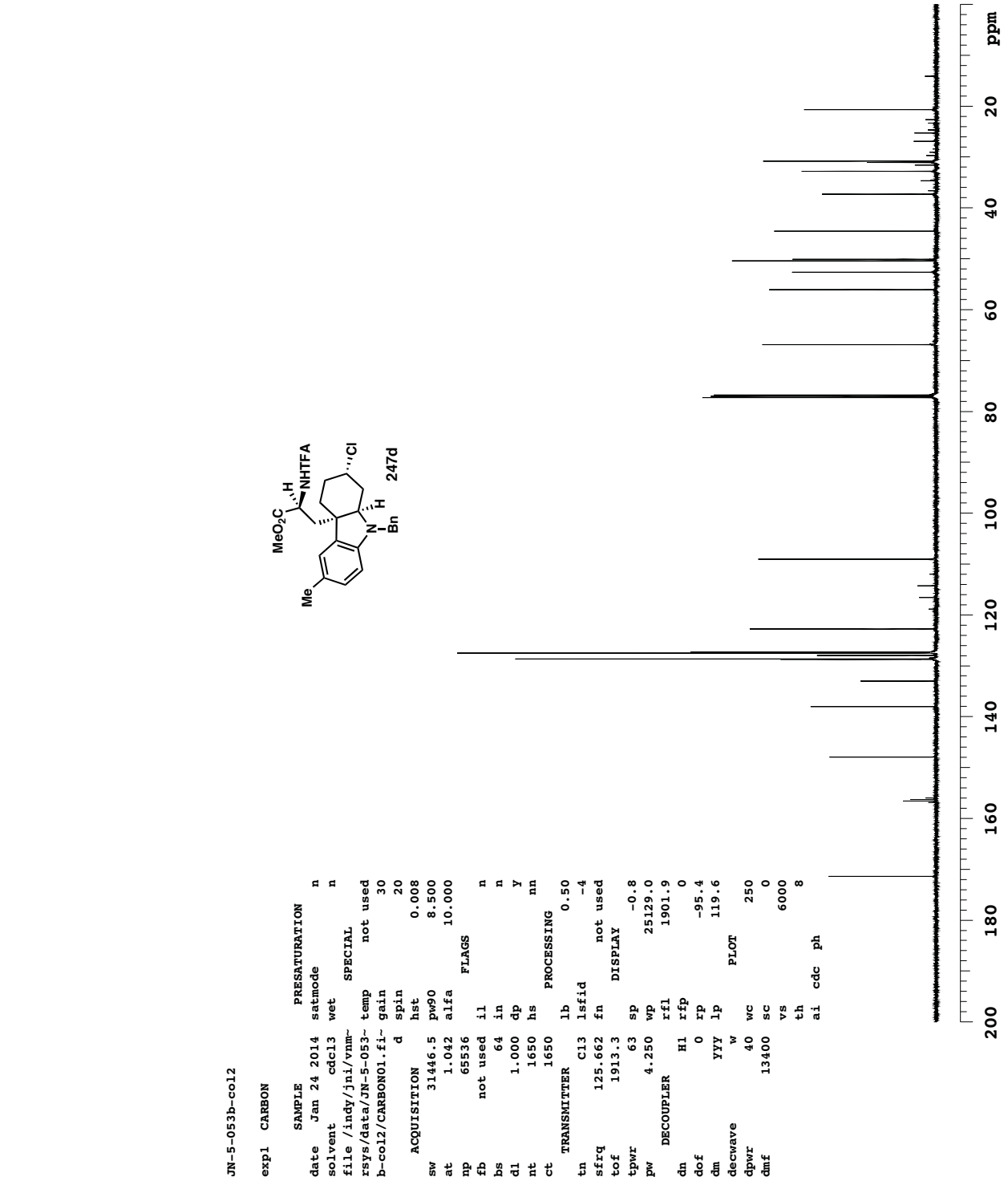
SAMPLE	
date	Jan 24 2014
solvent	cdcl3
file	/indy/jni/vnm~
	rsys/data/JN-5-053~
	b-col2/PROTON01.fi~
	d
ACQUISITION	
sw	8000.0
at	3.000
np	48000
fb	not used
bs	32
d1	25.000
nt	4
ct	4
TRANSMITTER	
tn	H1
sfrq	499.698
tof	499.7
tpwr	61
pw	4.950
DECOUPLER	
dn	C13
dof	0
dm	nnn
decwave	W40_autox7~
	991
dpwr	41
dmf	32258

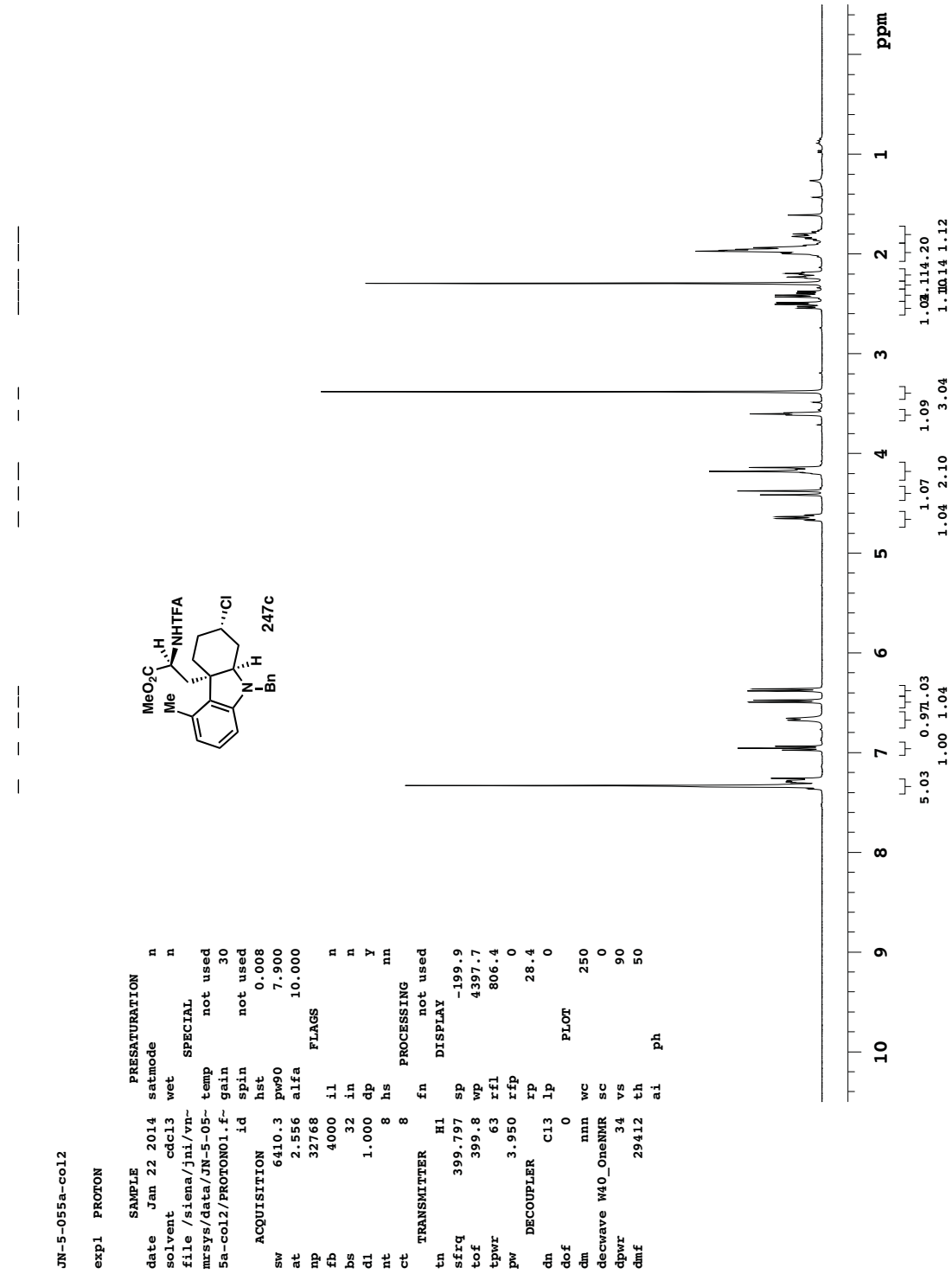
PRESATURATION	
satmode	n
wet	n
SPECIAL	
temp	not used
gain	22
spin	20
hst	0.008
pw90	9.900
alfa	10.000
FLAGS	
il	n
in	n
dp	y
hs	nn
PROCESSING	
lb	0.20
fn	not used
DISPLAY	
sp	-249.9
wp	5496.6
rfl	4632.1
rfp	3627.8
rp	-77.0
lp	-79.1
PLOT	
wc	250
sc	0
vs	30
th	50
ai	ph

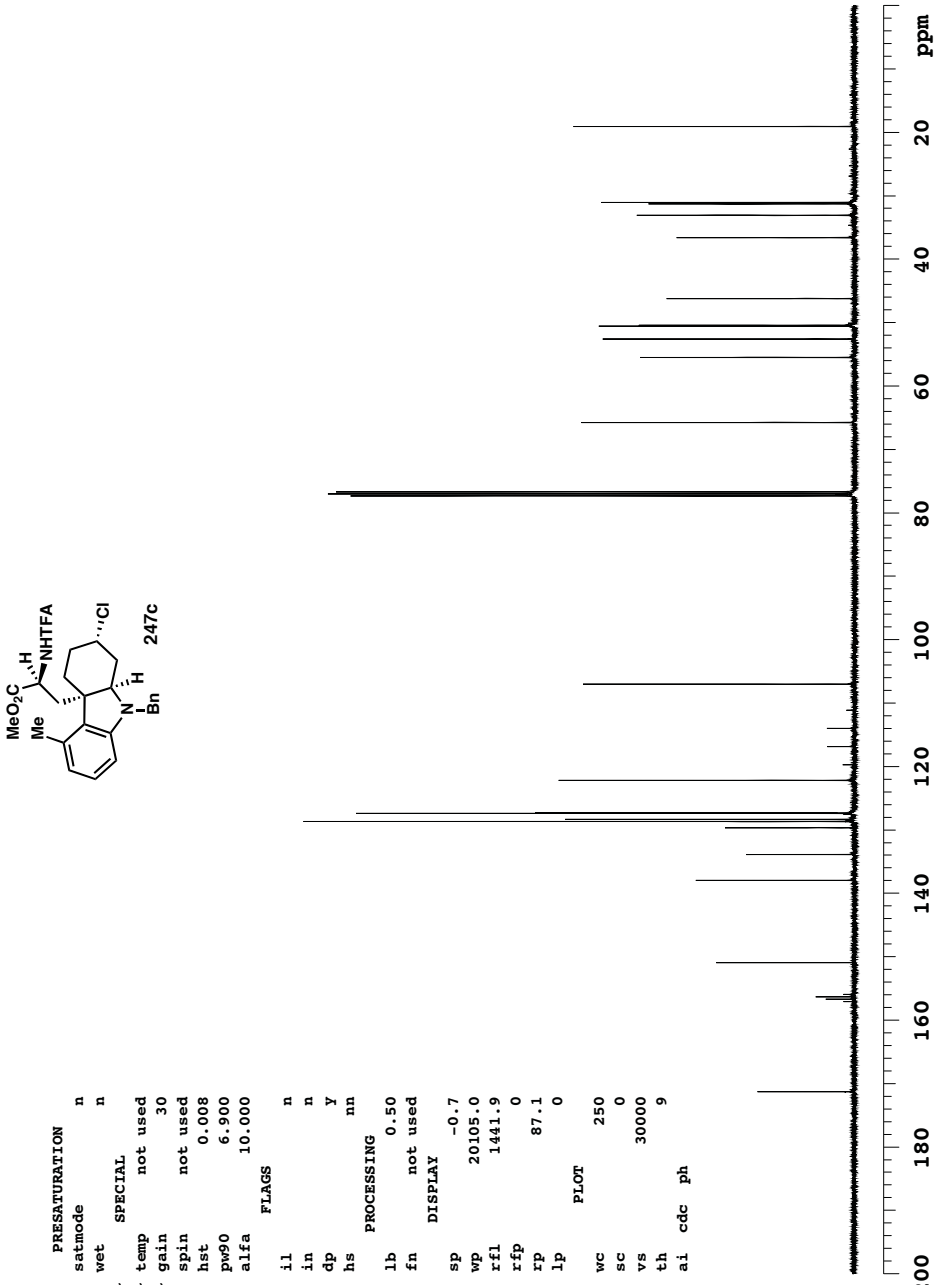


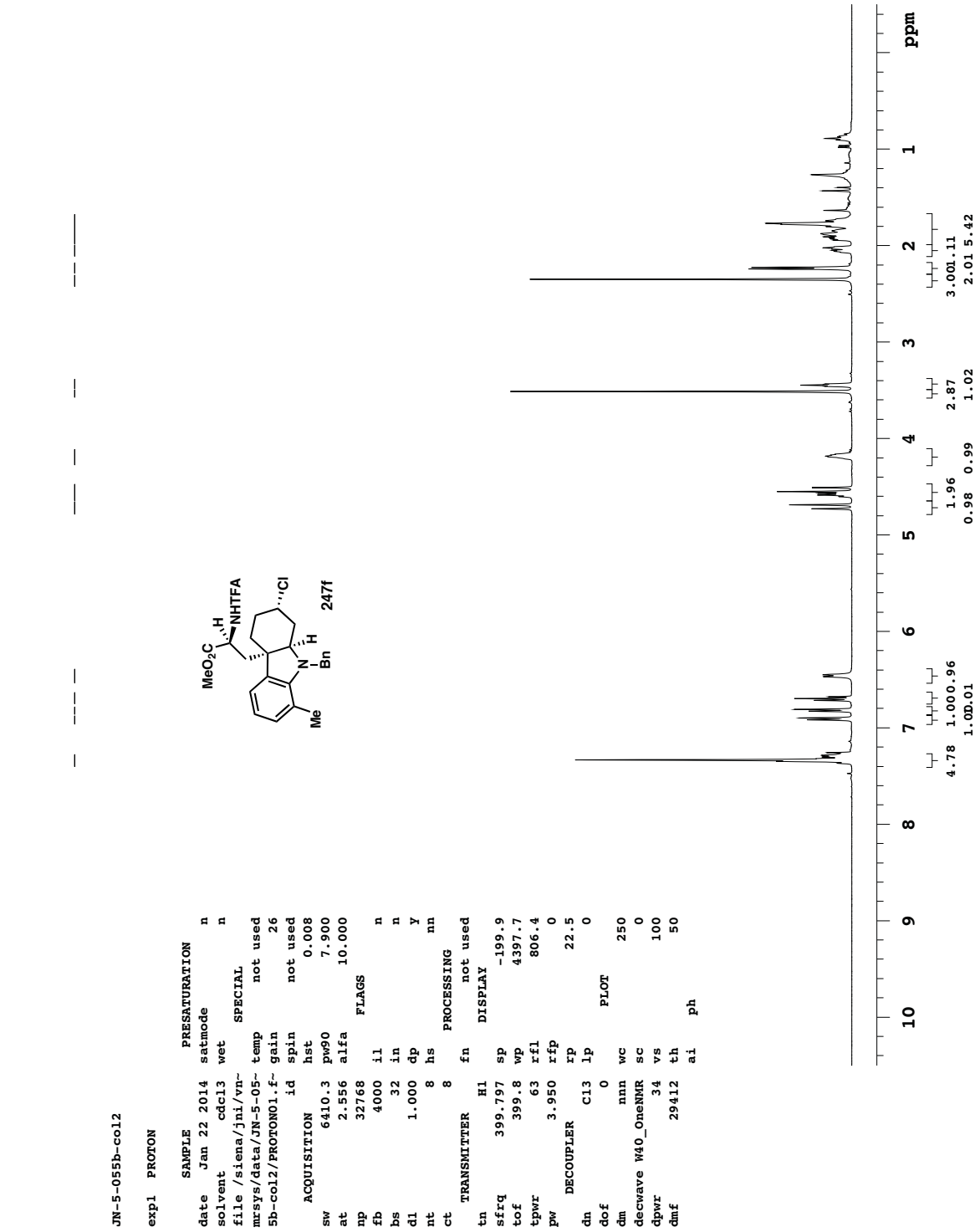
247d

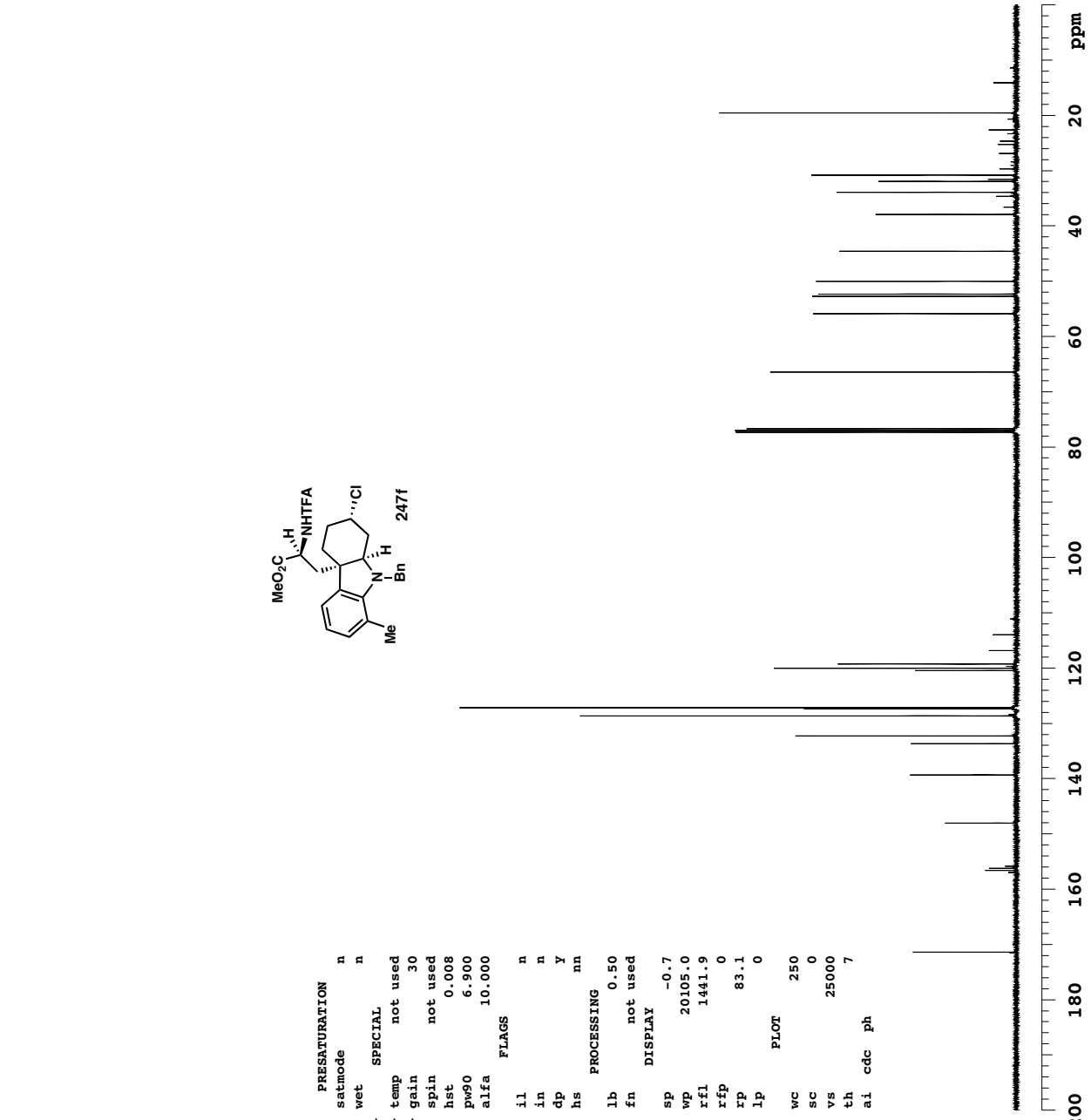



JN-5-053b-col2
exp1 CARBON
SAMPLE PRESATURATION
date Jan 24 2014 satmode n
solvent cdcl3 wet n
file /indy/jni/vnm~ SPECIAL
rsys/data/JN-5-053~ temp not used
b-col2/CARBON01.fi~ gain 30
d spin 20
ACQUISITION hst 0.008
sw 31446.5 pw90 8.500
at 1.042 alfa 10.000
np 65536 FLAGS
fb not used il n
bs 64 in n
d1 1.000 dp y
nt 1650 hs nn
ct 1650 PROCESSING
TRANSMITTER lb 0.50
tn C13 lsfid -4
sfrq 125.662 fn not used
tof 1913.3 DISPLAY
tpwr 63 sp -0.8
pw 4.250 wp 25129.0
DECOUPLER rfl 1901.9
dn H1 rfp 0
dof 0 rp -95.4
dm yyy lp 119.6
decwave w PLOT
dpwr 40 wc 250
dmf 13400 sc 0
vs 6000
th 8
ai cdc ph
MeO2C
NHTFA
Cl
N
H
Bn
247d
Me
200
180
160
140
120
100
80
60
40
20
ppm


JN-5-055a-col2
expl PROTON
SAMPLE
date Jan 22 2014
solvent cdcl3
file /siena/jni/vn~
mrsys/data/JN-5-05~
5a-col2/PROTON01.f~
ACQUISITION
sw 6410.3
at 2.556
np 32768
fb 4000
bs 32
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.797
tof 399.8
tpwr 63
pw 3.950
DECOUPLER
dn C13
dof 0
dm nnn
decwave W40_OneNMR
dpwr 34
dmf 29412
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 30
spin not used
hst 0.008
pw90 7.900
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -199.9
wp 4397.7
rfl 806.4
rfp 0
rp 28.4
lp 0
PLOT
wc 250
sc 0
vs 90
th 50
ai ph
MeO2C
Me
NHTFA
Cl
N
H
Bn
247c
10
9
8
7
6
5
4
3
2
1
ppm
5.03
0.97
1.03
1.00
1.04
1.07
2.10
1.09
3.04
1.04
1.14
20
1.00
1.14
1.12


JN-5-055a-col2
exp1 CARBON
SAMPLE PRESATURATION
date Jan 22 2014 satmode n
solvent cdcl3 wet n
file /siena/jni/vn~ SPECIAL
mrsys/data/JN-5-05~ temp not used
5a-col2/CARBON01.f~ gain 30
id spin not used
ACQUISITION hst 0.008
sw 25000.0 pw90 6.900
at 1.311 alfa 10.000
np 65536 FLAGS
fb 17000 il n
bs 64 in n
d1 1.000 dp y
nt 5000 hs nn
ct 5000 PROCESSING
TRANSMITTER lb 0.50
tn C13 fn not used
sfrq 100.540 DISPLAY
tof 1530.7 sp -0.7
tpwr 59 wp 20105.0
pw 3.450 rfl 1441.9
DECOUPLER rfp 0
dn H1 rp 87.1
dof 0 lp 0
dm yyy PLOT
decwave w wc 250
dpwr 41 sc 0
dmf 10204 vs 30000
th 9
ai cdc ph
MeO2C
NHTFA
Me
Cl
N
H
Bn
247c
200
180
160
140
120
100
80
60
40
20
ppm


JN-5-055b-col2
expl PROTON
SAMPLE
date Jan 22 2014
solvent cdcl3
file /siena/jni/vn~
mrsys/data/JN-5-05~
5b-col2/PROTON01.f~
ACQUISITION
sw 6410.3
at 2.556
np 32768
fb 4000
bs 32
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.797
tof 399.8
tpwr 63
pw 3.950
DECOUPLER
dn C13
dof 0
dm nnn
decwave W40_OneNMR
dpwr 34
dmf 29412
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 26
spin not used
hst 0.008
pw90 7.900
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -199.9
wp 4397.7
rfl 806.4
rfp 0
rp 22.5
lp 0
PLOT
wc 250
sc 0
vs 100
th 50
ai ph
MeO2C
NHTFA
Me
N
Bn
Cl
247f
4.78 1.000.96
1.00.01
1.96 2.87
0.98 0.99 1.02
3.001.11
2.01 5.42
10 9 8 7 6 5 4 3 2 1 ppm


JN-5-055b-col2
exp1 CARBON
SAMPLE
date Jan 22 2014
solvent cdcl3
file /siena/jni/vn~
mrsys/data/JN-5-05~
5b-col2/CARBON01.f~
ACQUISITION
sw 25000.0
at 1.311
np 65536
fb 17000
bs 64
d1 1.000
nt 6000
ct 6000
TRANSMITTER
tn C13
sfrq 100.540
tof 1530.7
tpwr 59
pw 3.450
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 41
dmf 10204
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 30
spin not used
hst 0.008
pw90 6.900
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -0.7
wp 20105.0
rfl 1441.9
rfp 0
rp 83.1
lp 0
PLOT
wc 250
sc 0
vs 25000
th 7
ai cdc ph
MeO2C
NHTFA
Cl
H
N
Bn
Me
247f
200
180
160
140
120
100
80
60
40
20
ppm

JN-5-053a-col2

SAMPLE

date	Jan 30 2014
solvent	cdcl3
file	/indy/jni/vnmrsys/data/JN-5-053a-col2/PROTON01.fid

ACQUISITION

sw	8000.0
at	3.000
np	48000
fb	not used
bs	32
d1	25.000
nt	4
ct	4

TRANSMITTER

tn	H1
sfrq	499.698
tof	499.7
tpwr	61
pw	4.950

DECOUPLER

dn	C13
dof	0
dm	nnn
decwave	W40_autox7991
dpwr	41
dmf	32258

PRESATURATION

satmode	n

wet	n

SPECIAL

temp	not used
gain	24
spin	20
hst	0.008
pw90	9.900
alfa	10.000

FLAGS

il	n
in	n
dp	y
hs	nn

PROCESSING

lb	0.20
fn	not used

DISPLAY

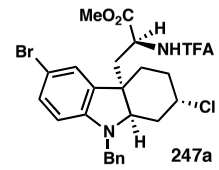
sp	-249.9
wp	5496.6
rfl	4632.1
rfp	3627.8
rp	-69.4
lp	-77.6

PLOT

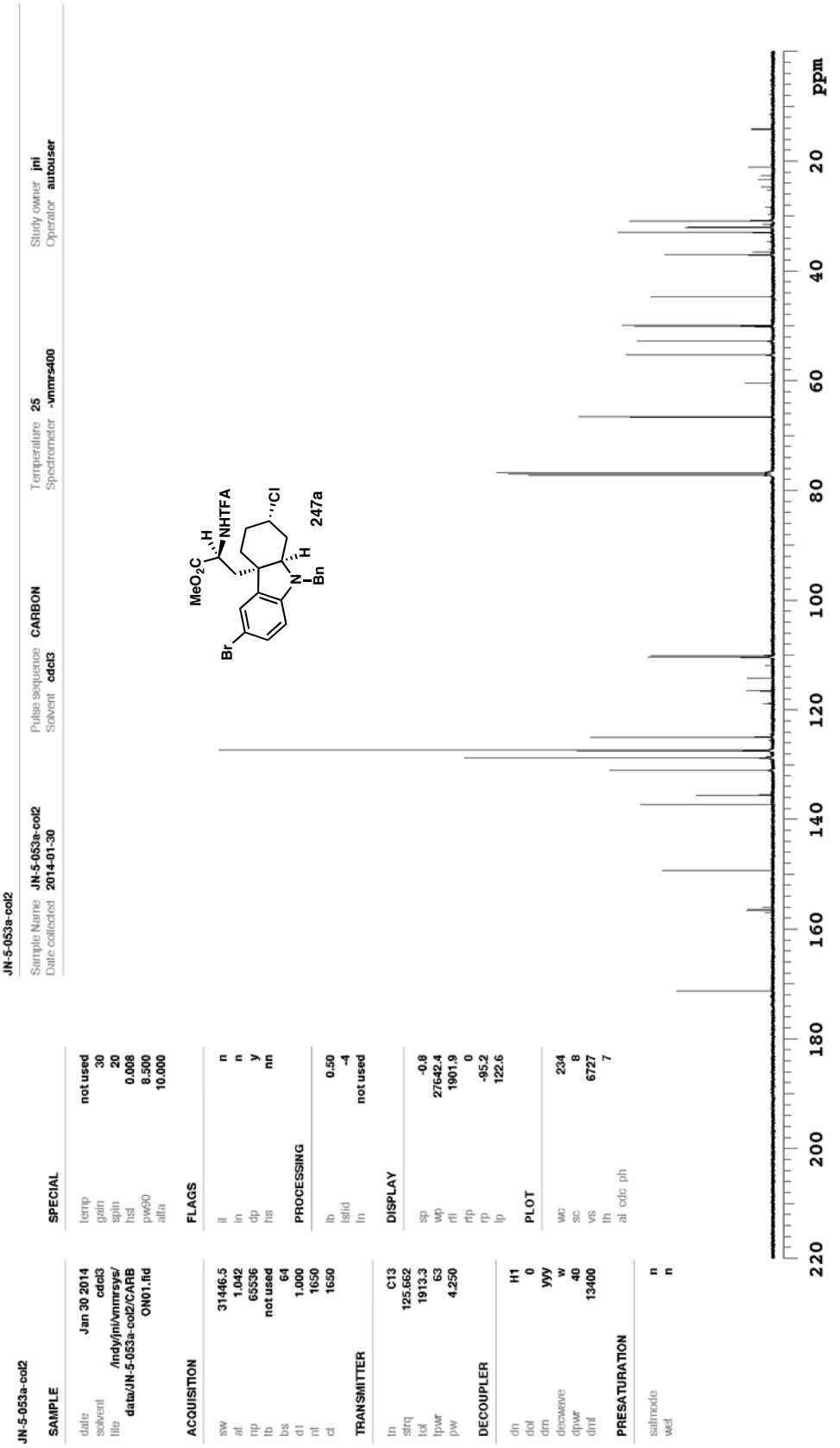
wc	234
sc	8
vs	33
th	25
ai ph	

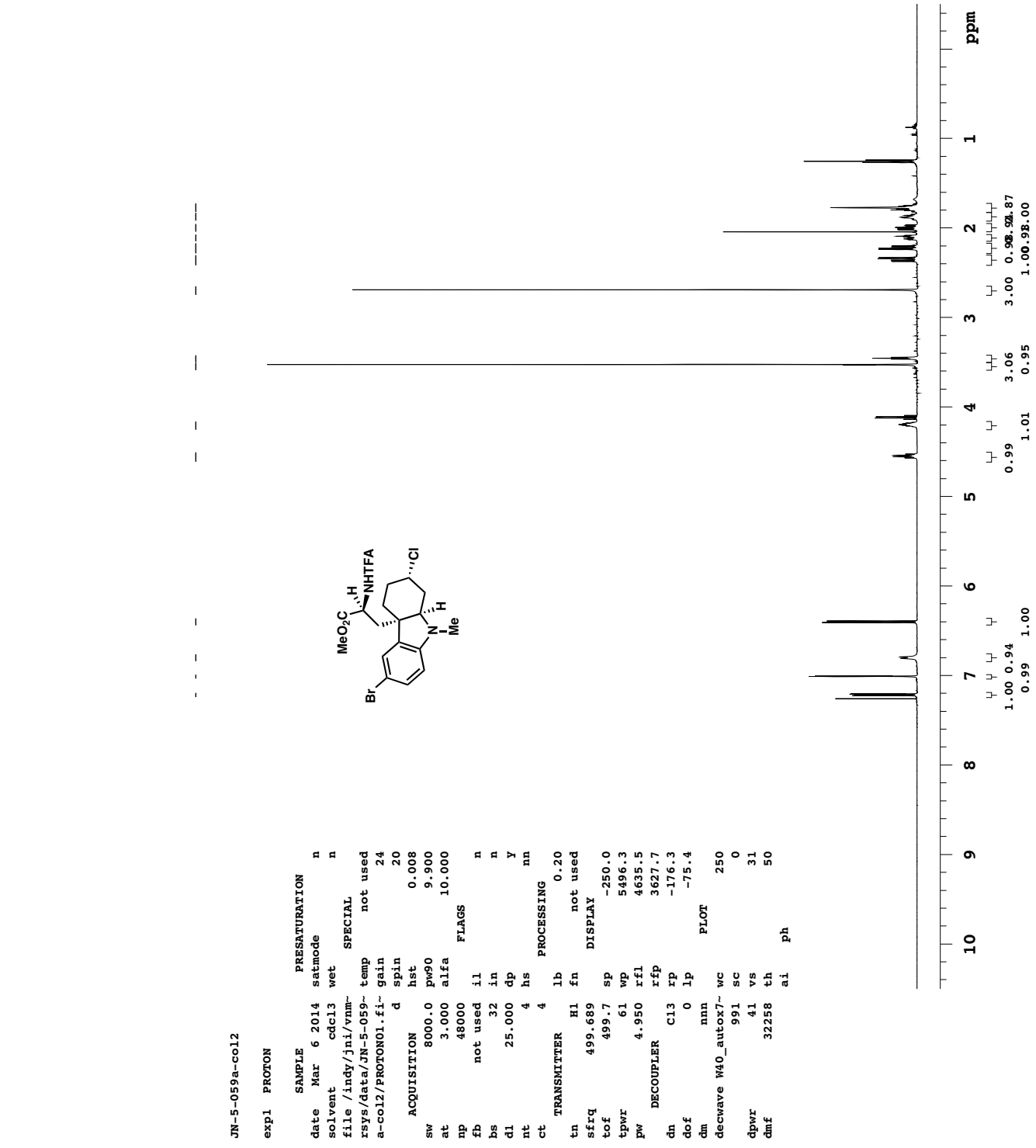
JN-5-053a-col2

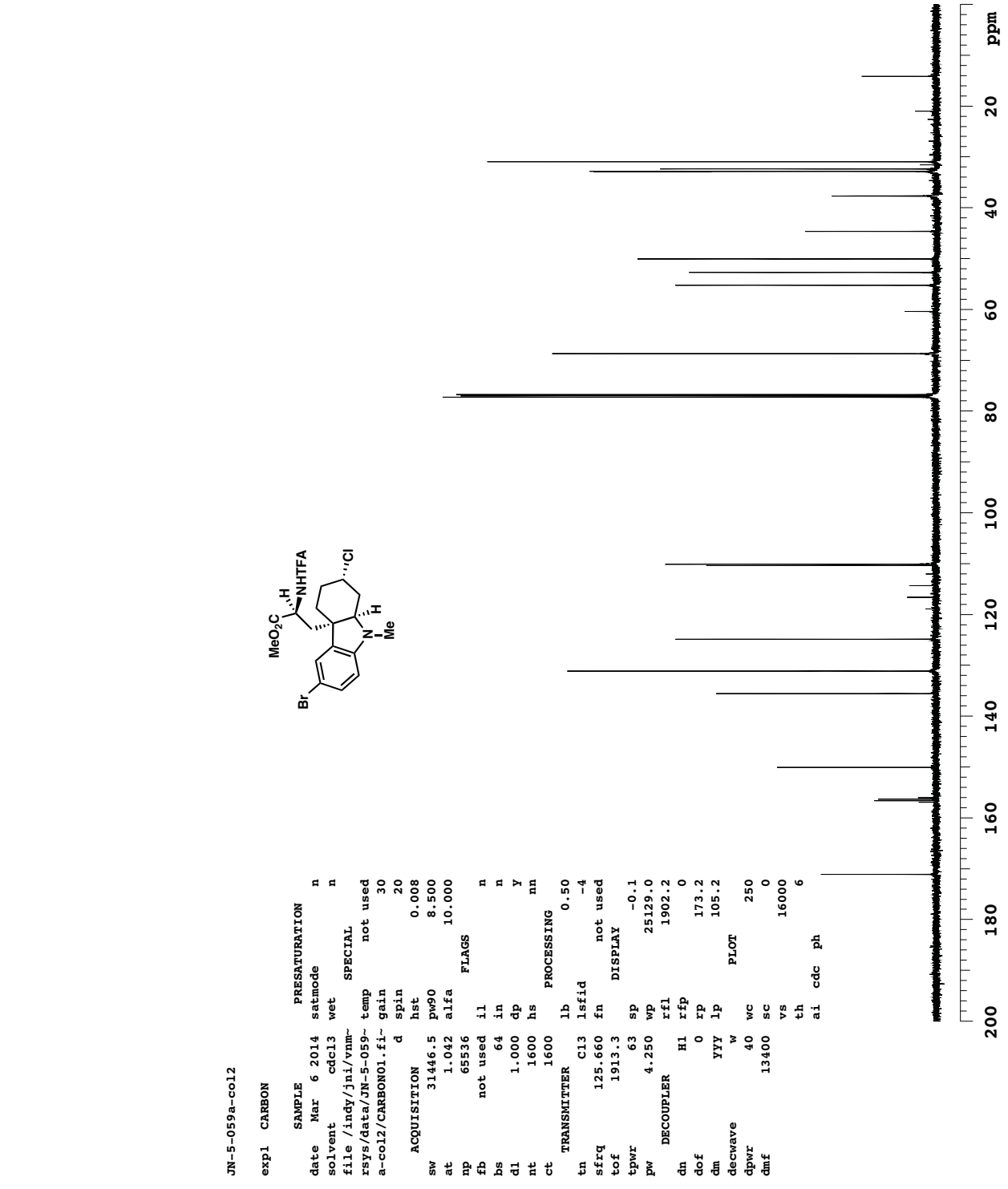
Sample Name JN-5-053a-col2	Pulse sequence PROTON	Temperature 25	Study owner jni
Date collected 2014-01-30	Solvent cdcl3	Spectrometer -vnmrs400	Operator autouser

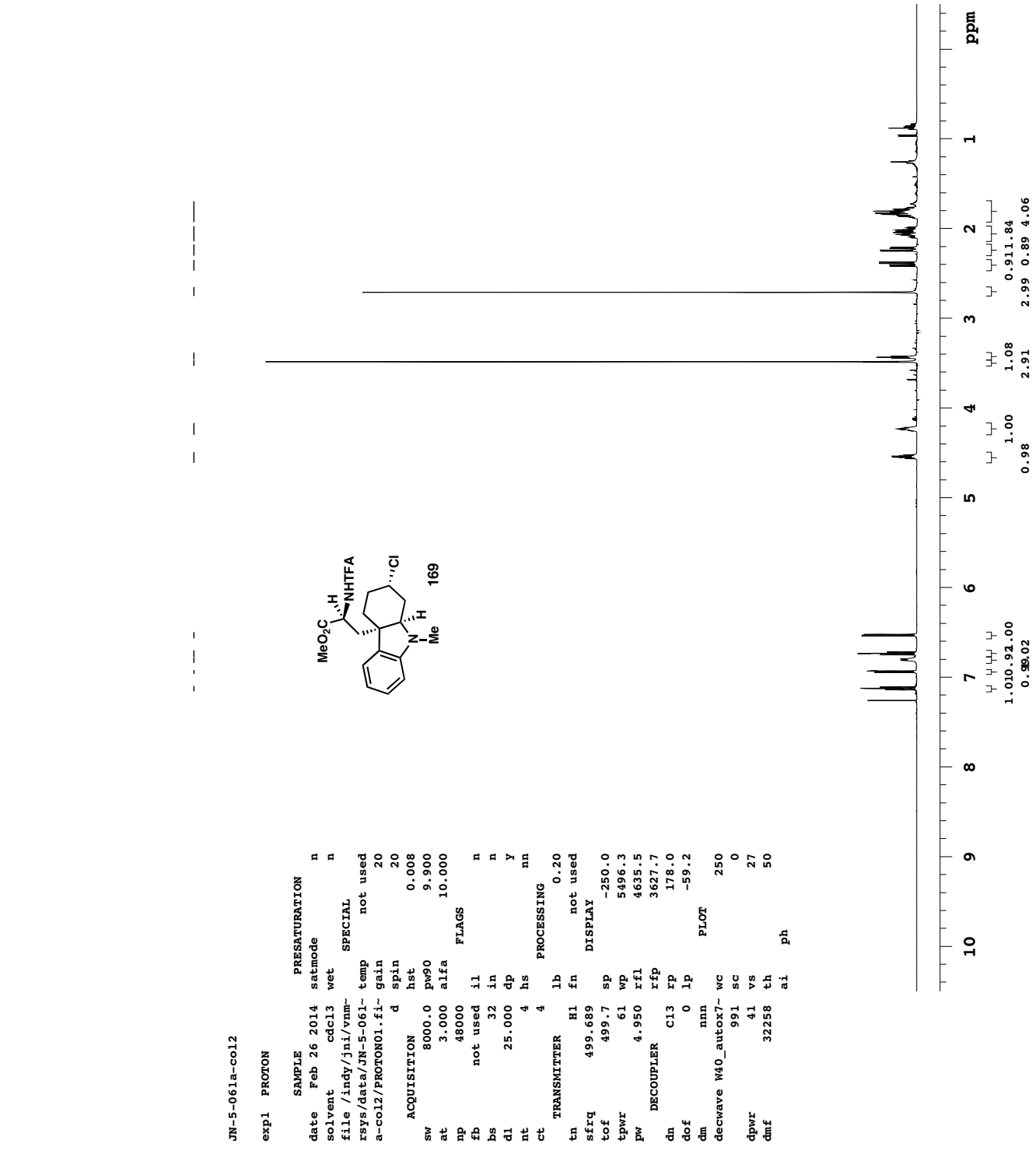


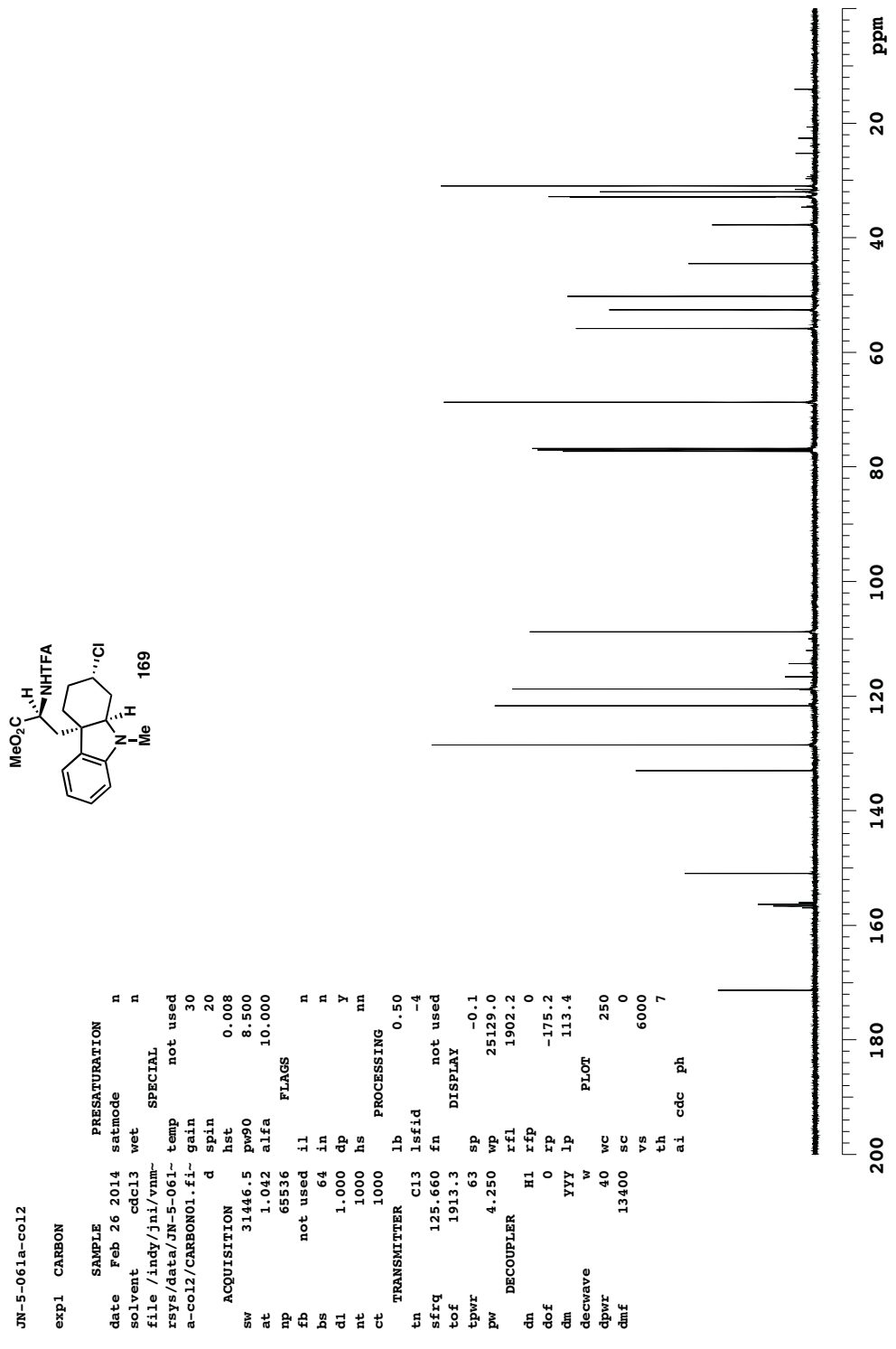
247a

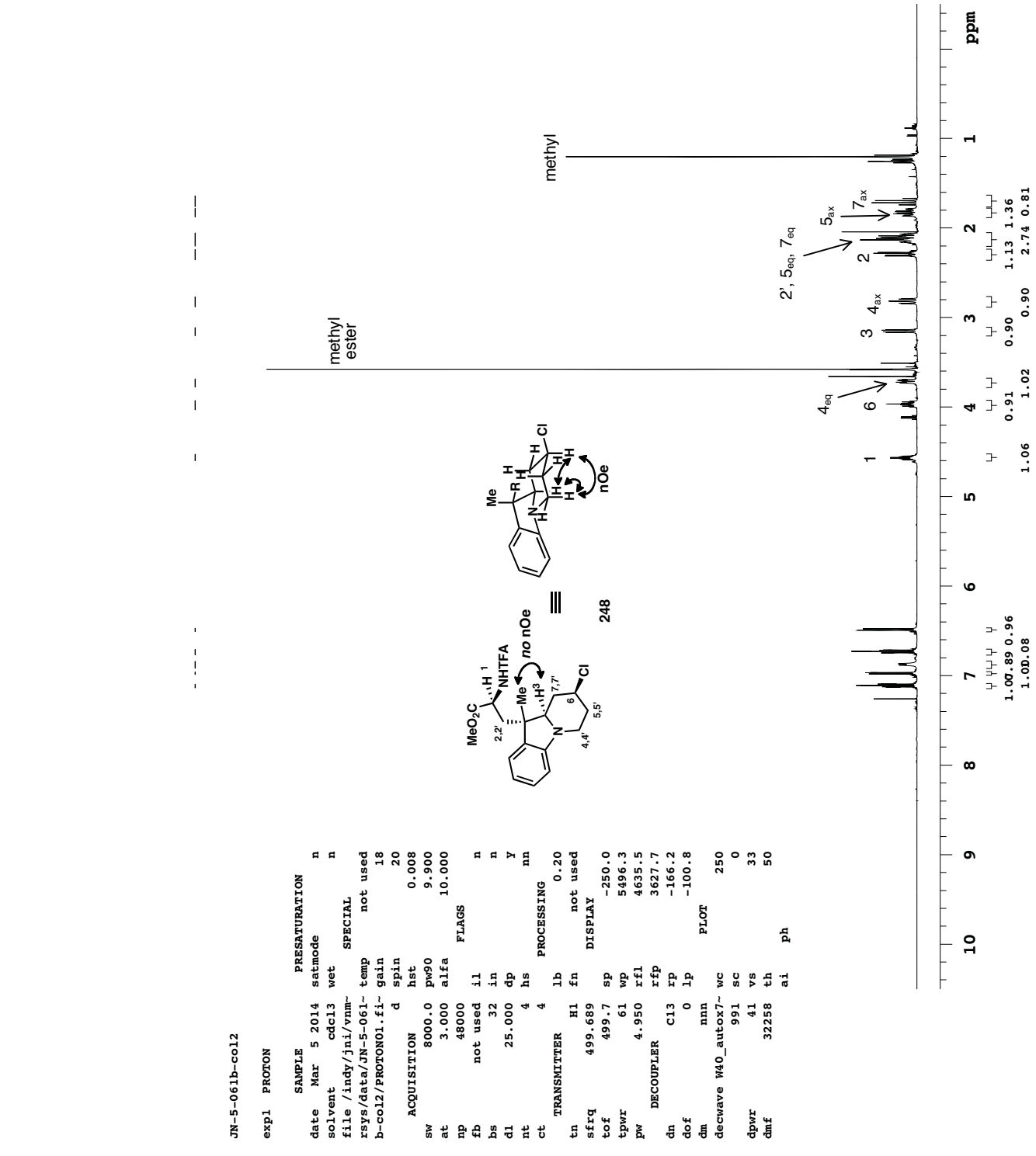

JN-5-053a-col2
Sample Name JN-5-053a-col2
Date collected 2014-01-30
Pulse sequence CARBON
Solvent cdcl3
Temperature 25
Spectrometer -vnmrs400
Study owner jni
Operator autouser
MeO2C
H
NHTFA
Cl
H
N
Bn
Br
247a
SAMPLE
SPECIAL
ACQUISITION
FLAGS
PROCESSING
TRANSMITTER
DISPLAY
DECOUPLER
PLOT
PRESATURATION
220
200
180
160
140
120
100
80
60
40
20
ppm

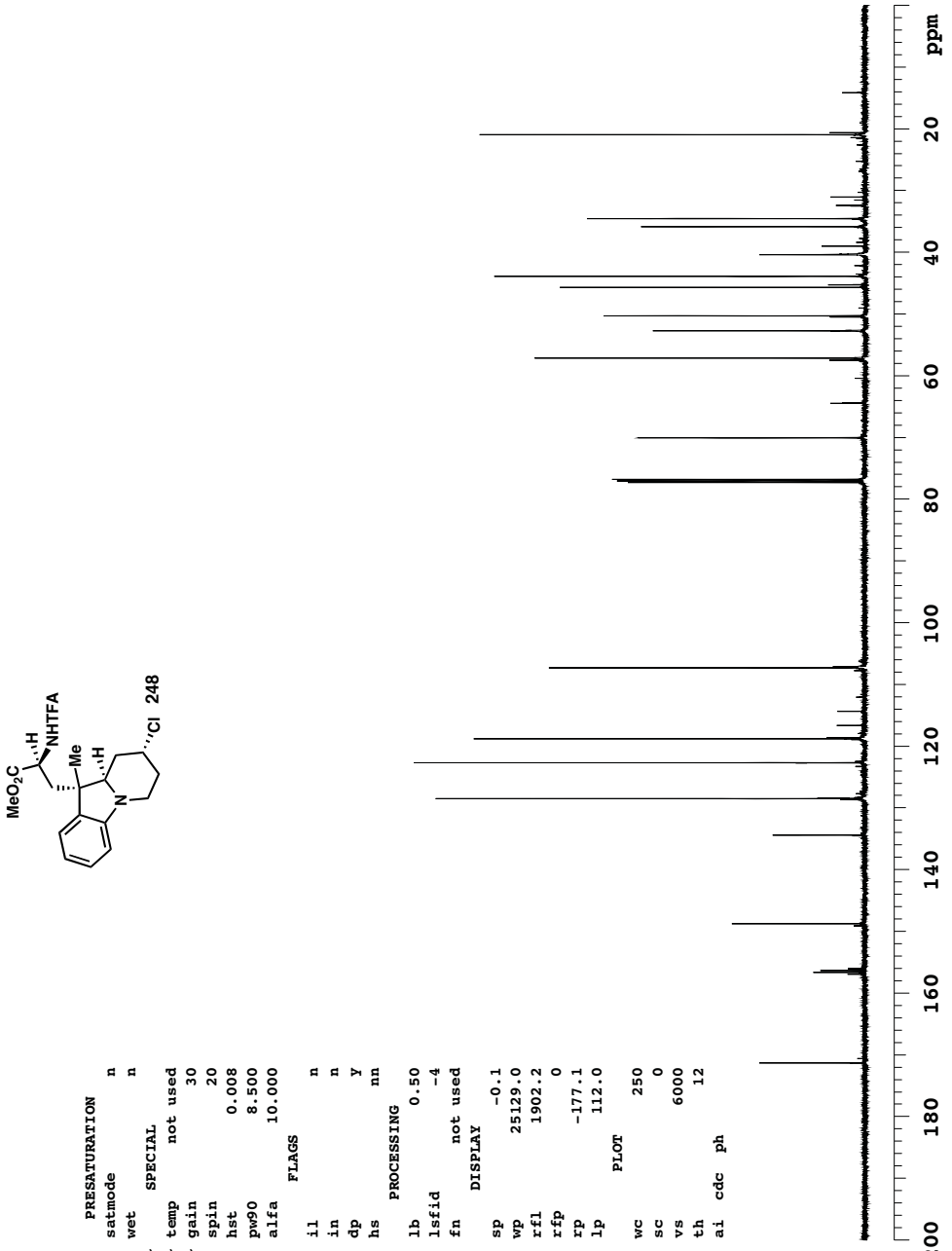

JN-5-059a-col2
expl PROTON
SAMPLE
date Mar 6 2014
solvent cdcl3
file /indy/jni/vnm~
rsys/data/JN-5-059~
a-col2/PROTON01.fi~
ACQUISITION
sw 8000.0
at 3.000
np 48000
fb not used
bs 32
d1 25.000
nt 4
ct 4
TRANSMITTER
tn H1
sfrq 499.689
tof 499.7
tpwr 61
pw 4.950
DECOUPLER
dn C13
dof 0
dm nnn
decwave W40_autox7~
991
dpwr 41
dmf 32258
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 24
d
spin 20
hst 0.008
pw90 9.900
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -250.0
wp 5496.3
rfl 4635.5
rfp 3627.7
rp -176.3
lp -75.4
PLOT
wc 250
sc 0
vs 31
th 50
ai ph
MeO2C
NHTFA
H
N
Me
Cl
Br
10 9 8 7 6 5 4 3 2 1 ppm
1.00 0.94
0.99 1.00
0.99
1.01
3.06
0.95
3.00 0.90 2.92 2.87
1.00 0.98 3.00


JN-5-059a-col2
expl CARBON
SAMPLE PRESATURATION
date Mar 6 2014 satmode n
solvent cdcl3 wet n
file /indy/jni/vnm~ SPECIAL
rsys/data/JN-5-059~ temp not used
a-col2/CARBON01.fi~ gain 30
d spin 20
ACQUISITION hst 0.008
sw 31446.5 pw90 8.500
at 1.042 alfa 10.000
np 65536 FLAGS
fb not used il n
bs 64 in n
d1 1.000 dp y
nt 1600 hs nn
ct 1600 PROCESSING
TRANSMITTER lb 0.50
tn C13 lsfid -4
sfrq 125.660 fn not used
tof 1913.3 DISPLAY
tpwr 63 sp -0.1
pw 4.250 wp 25129.0
DECOUPLER rfl 1902.2
dn H1 rfp 0
dof 0 rp 173.2
dm yyy lp 105.2
decwave w PLOT
dpwr 40 wc 250
dmf 13400 sc 0
vs 16000
th 6
ai cdc ph
MeO2C
NHTFA
Cl
Br
N
H
Me
200
180
160
140
120
100
80
60
40
20
ppm


JN-5-061a-col2
exp1 PROTON
SAMPLE
date Feb 26 2014
solvent cdcl3
file /indy/jni/vnm~
rsys/data/JN-5-061~
a-col2/PROTON01.fi~
ACQUISITION
sw 8000.0
at 3.000
np 48000
fb not used
bs 32
d1 25.000
nt 4
ct 4
TRANSMITTER
tn H1
sfrq 499.689
tof 499.7
tpwr 61
pw 4.950
DECOUPLER
dn C13
dof 0
dm nnn
decwave W40_autox7~
991
dpwr 41
dmf 32258
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 20
d
spin 20
hst 0.008
pw90 9.900
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -250.0
wp 5496.3
rfl 4635.5
rfp 3627.7
rp 178.0
lp -59.2
PLOT
wc 250
sc 0
vs 27
th 50
ai ph
MeO2C
NHTFA
Cl
N
H
Me
169
10 9 8 7 6 5 4 3 2 1 ppm
1.00 1.08 0.91 1.84
0.98 2.91 2.99 0.89 4.06
1.01 0.92 1.00
0.99 1.02


JN-5-061a-col2
exp1 CARBON
SAMPLE
date Feb 26 2014
solvent cdcl3
file /indy/jni/vnm~
rsys/data/JN-5-061~
a-col2/CARBON01.fi~
ACQUISITION
sw 31446.5
at 1.042
np 65536
fb not used
bs 64
d1 1.000
nt 1000
ct 1000
TRANSMITTER
tn C13
sfrq 125.660
tof 1913.3
tpwr 63
pw 4.250
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 40
dmf 13400
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 30
spin 20
hst 0.008
pw90 8.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
lsfid -4
fn not used
DISPLAY
sp -0.1
wp 25129.0
rfl 1902.2
rfp 0
rp -175.2
lp 113.4
PLOT
wc 250
sc 0
vs 6000
th 7
ai cdc ph
MeO2C
NHTFA
Cl
N
H
Me
169
200
180
160
140
120
100
80
60
40
20
ppm


JN-5-061b-col2
expl PROTON
SAMPLE
date Mar 5 2014
solvent cdcl3
file /indy/jni/vnm~
rsys/data/JN-5-061~
b-col2/PROTON01.fi~
ACQUISITION
sw 8000.0
at 3.000
np 48000
fb not used
bs 32
d1 25.000
nt 4
ct 4
TRANSMITTER
tn H1
sfrq 499.689
tof 499.7
tpwr 61
pw 4.950
DECOUPLER
dn C13
dof 0
dm nnn
decwave W40_autox7~
dpwr 41
dmf 32258
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 18
spin 20
hst 0.008
pw90 9.900
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.20
fn not used
DISPLAY
sp -250.0
wp 5496.3
rfl 4635.5
rfp 3627.7
rp -166.2
lp -100.8
PLOT
wc 250
sc 0
vs 33
th 50
ai ph
MeO2C
NHTFA
Me
no nOe
Cl
248
nOe
methyl ester
methyl
4eq
6
1
3
4ax
2
2', 5eq, 7eq
5ax
7ax
10
9
8
7
6
5
4
3
2
1
ppm
1.00 0.89 0.96
1.00 0.08
1.06
1.02
0.91
0.90
0.90
1.13 1.36
2.74 0.81


JN-5-061b-col2
exp1 CARBON
SAMPLE
date Mar 5 2014
solvent cdcl3
file /indy/jni/vnm~
rsys/data/JN-5-061~
b-col2/CARBON01.fi~
ACQUISITION
sw 31446.5
at 1.042
np 65536
fb not used
bs 64
d1 1.000
nt 1000
ct 1000
TRANSMITTER
tn C13
sfrq 125.660
tof 1913.3
tpwr 63
pw 4.250
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 40
dmf 13400
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain 30
d
spin 20
hst 0.008
pw90 8.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
lsfid -4
fn not used
DISPLAY
sp -0.1
wp 25129.0
rfl 1902.2
rfp 0
rp -177.1
lp 112.0
PLOT
wc 250
sc 0
vs 6000
th 12
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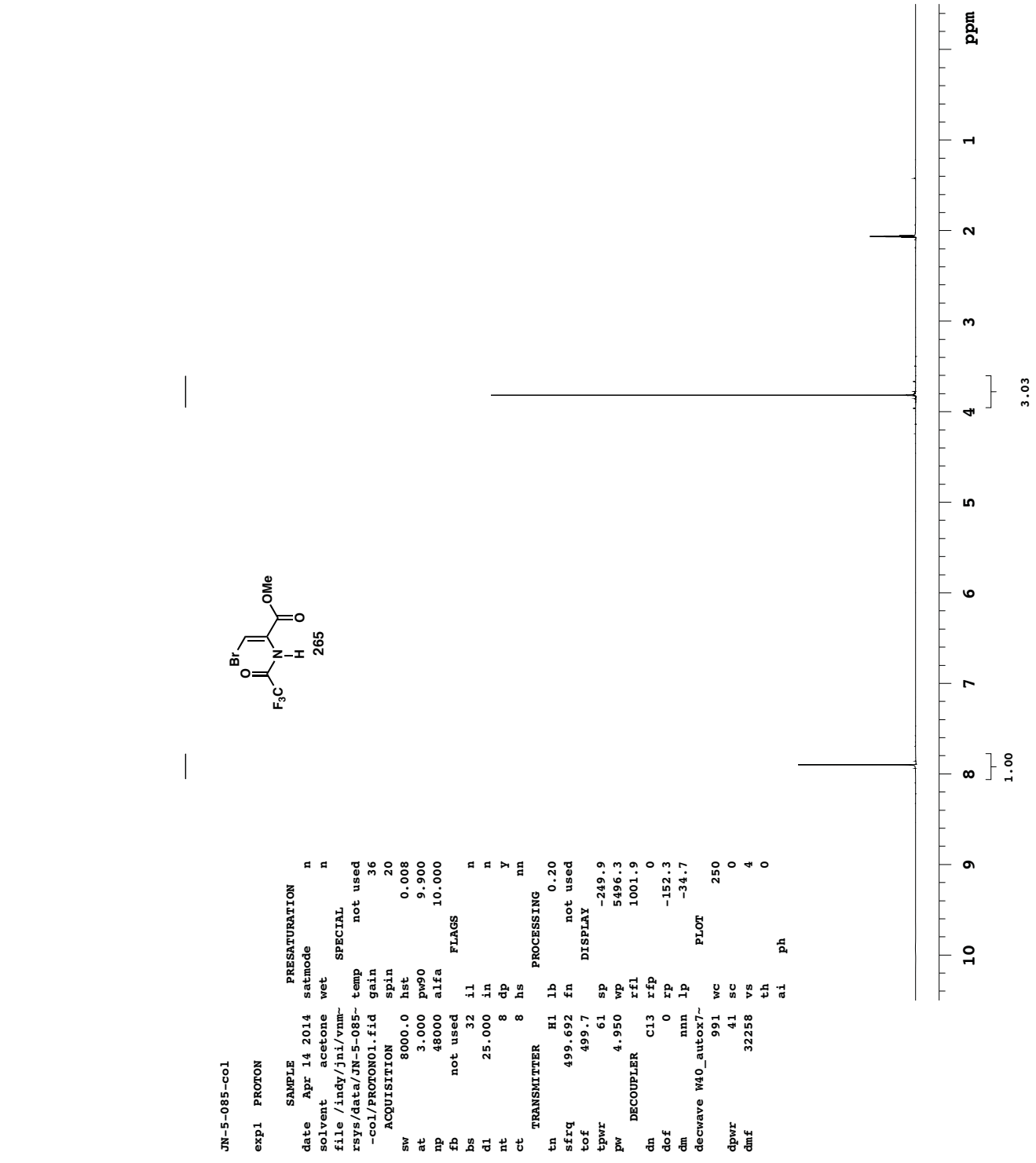
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th 0
ai ph
Br
O
N
H
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OMe
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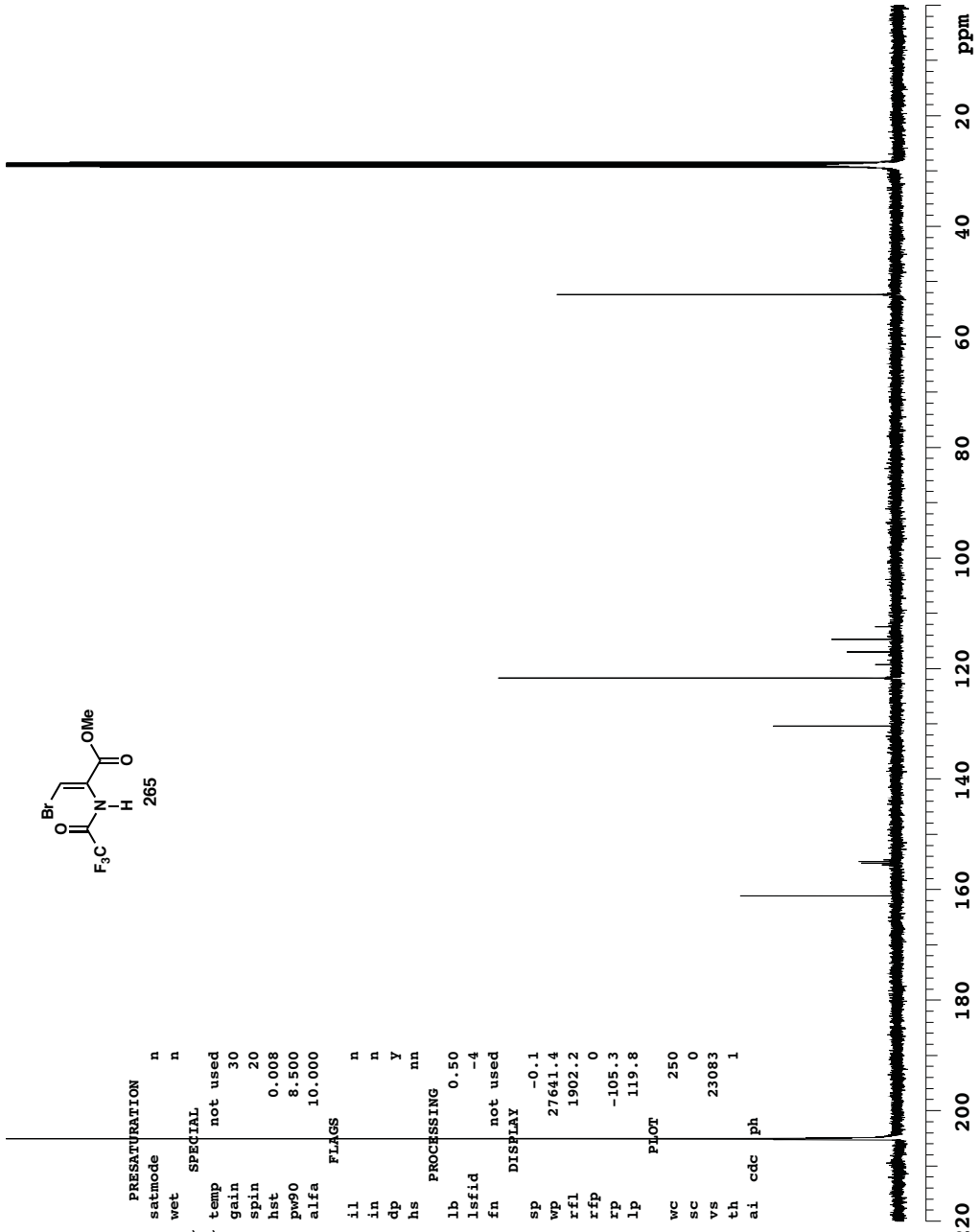
3.03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H
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OMe
O
F3C
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40
20
ppm

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Aug 5, 2014
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92% D incorporation

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rfp 0
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lp 137.8
PLOT
wc 234
sc 8
vs 30000
th 5
ai cdc ph
D
O
F3C
N
H
O
OMe
O
67-d1
92% D incorporation
200
180
160
140
120
100
80
60
40
20
ppm

APPENDIX 5

X-Ray Crystallography Reports Relevant to Chapter 4:

Development of a Tandem Conjugate Addition/Prins Cyclization[†]

[†] The work disclosed in this appendix for the x-ray crystallographic analysis of **169** was completed entirely by Larry Henling in the Caltech X-ray crystallography lab.

CRYSTAL STRUCTURE ANALYSIS OF INDOLINE 169

*Figure A5.1. Indoline ent-**169** 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 1024262.*

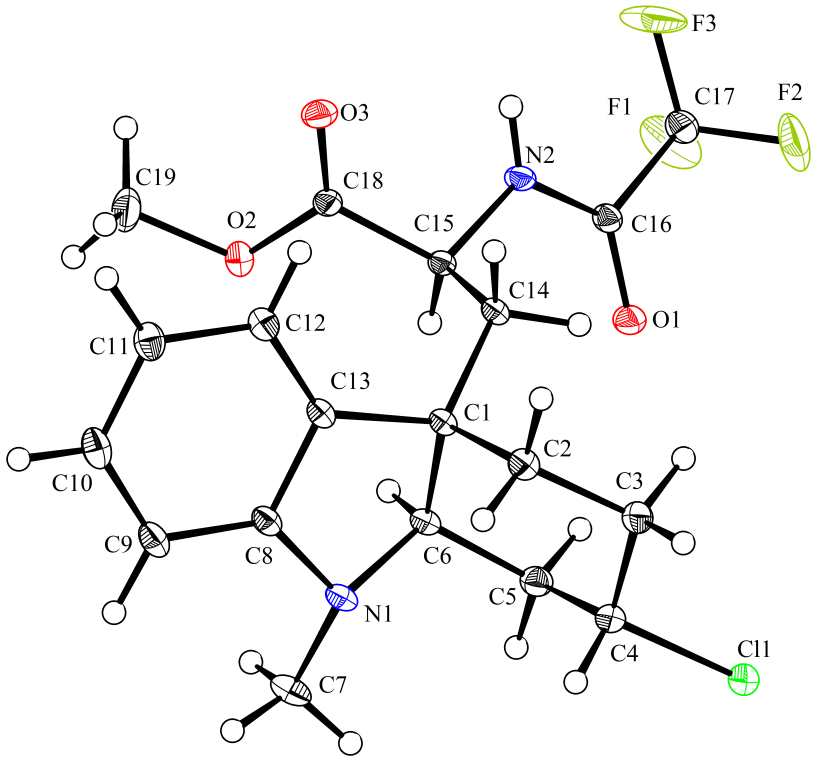

*Table A5.1. Crystal data and structure refinement indoline **169**.*

Empirical formula	$C_{19}H_{22}ClF_3N_2O_3$
Formula weight	418.84
Crystallization solvent	Hexanes/ethanol
Crystal size	0.41 x 0.36 x 0.16 mm^3

Data Collection

Wavelength	0.71073 Å	
Data Collection Temperature	100 K	
Unit cell dimensions	a = 25.1712(14) Å b = 6.5924(4) Å c = 22.8692(13) Å	α= 90° β= 91.144(3)° γ = 90°
Volume	3794.1(4) $Å^3$	
Z	8	
Crystal system	Monoclinic	
Space group	C 1 2/c 1	
Density (calculated)	1.466 Mg/m^3	
F(000)	1744	
θ range for data collection	2.383 to 46.276°	
Completeness to θ = 25.000°	99.9 %	
Index ranges	$-49 \le h \le 51, -13 \le k \le 11, -45 \le l \le 46$	
Reflections collected	124617	
Independent reflections	16624 [R_{int}= 0.0540]	
Absorption coefficient	0.253 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9131	

Table A5.1 (continued)

Structure solution and Refinement

Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	16624 / 10 / 368
Goodness-of-fit on F^2	1.025
Final R indices [I>2σ(I), 4601 reflections]	R1 = 0.0424, *w*R2 = 0.1076
R indices (all data)	R1 = 0.0654, *w*R2 = 0.1204
Extinction coefficient	n/a
Largest diff. peak and hole	0.898 and -0.650 e.$Å^{-3}$

*Table A5.2. Atomic coordinates (x 10^5) and equivalent isotropic displacement parameters ($Å^2$x 10^4) for indoline **169**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
Cl(1)	81494(2)	86530(3)	41318(2)	191(1)
F(1)	55909(4)	121930(11)	55313(3)	350(2)
F(2)	61581(3)	105543(17)	60353(3)	375(2)
F(3)	53671(4)	93585(14)	59017(4)	492(3)
F(1B)	60520(40)	114280(160)	59070(50)	390(20)
F(2B)	57010(30)	85750(110)	60750(30)	272(14)
F(3B)	53660(40)	113060(150)	56070(40)	353(18)
F(1A)	58200(30)	121770(120)	56890(40)	283(15)
F(2A)	60010(30)	95880(120)	60850(30)	251(14)
F(3A)	52150(30)	102150(120)	56800(30)	251(14)
O(1)	63065(2)	101787(7)	48267(2)	152(1)
O(2)	51942(2)	62921(8)	35600(2)	161(1)
O(3)	51164(2)	43717(8)	43673(2)	171(1)
N(1)	68410(2)	55635(8)	28749(2)	126(1)
N(2)	56778(2)	77005(8)	48939(2)	126(1)
C(1)	66036(2)	48427(8)	38471(2)	103(1)
C(2)	71284(2)	37744(9)	40410(2)	130(1)
C(3)	75492(2)	52373(10)	42907(2)	149(1)
C(4)	76701(2)	68459(10)	38361(2)	144(1)
C(5)	71755(2)	80169(9)	36510(2)	141(1)
C(6)	67331(2)	66243(8)	34310(2)	112(1)
C(7)	68878(3)	68370(11)	23594(3)	189(1)
C(8)	64758(2)	39553(9)	28541(2)	121(1)
C(9)	62818(2)	28861(10)	23700(2)	154(1)
C(10)	59133(3)	13364(10)	24637(3)	170(1)
C(11)	57431(3)	8583(9)	30217(3)	160(1)
C(12)	59472(2)	19294(9)	35063(2)	133(1)
C(13)	63085(2)	34720(8)	34201(2)	112(1)
C(14)	63080(2)	54493(8)	44004(2)	112(1)
C(15)	58192(2)	68288(8)	43281(2)	107(1)
C(16)	59462(2)	93368(8)	50808(2)	122(1)
C(17)	57594(2)	103040(10)	56528(3)	164(1)
C(18)	53377(2)	56824(9)	40940(2)	118(1)
C(19)	47517(3)	52059(13)	32938(3)	226(1)

*Table A5.3. Bond lengths [Å] and angles [°] for indoline **169**.*

Cl(1)-C(4)	1.8164(6)	F(3B)-C(17)	1.194(9)
F(1)-C(17)	1.3428(9)	F(1A)-C(17)	1.247(8)
F(2)-C(17)	1.3284(9)	F(2A)-C(17)	1.243(7)
F(3)-C(17)	1.3077(9)	F(3A)-C(17)	1.376(7)
F(1B)-C(17)	1.188(10)	O(1)-C(16)	1.2204(7)
F(2B)-C(17)	1.502(7)	O(2)-C(18)	1.3288(7)

O(2)-C(19)	1.4481(8)	C(13)-C(1)-C(6)	99.37(4)
O(3)-C(18)	1.2088(7)	C(13)-C(1)-C(14)	116.60(4)
N(1)-C(6)	1.4812(7)	C(14)-C(1)-C(2)	107.84(4)
N(1)-C(7)	1.4540(8)	C(14)-C(1)-C(6)	114.85(4)
N(1)-C(8)	1.4034(8)	C(1)-C(2)-H(2A)	109.7(7)
N(2)-H(2)	0.846(13)	C(1)-C(2)-H(2B)	108.2(8)
N(2)-C(15)	1.4662(7)	H(2A)-C(2)-H(2B)	106.2(10)
N(2)-C(16)	1.3383(7)	C(3)-C(2)-C(1)	113.45(5)
C(1)-C(2)	1.5538(7)	C(3)-C(2)-H(2A)	109.5(7)
C(1)-C(6)	1.5503(7)	C(3)-C(2)-H(2B)	109.5(7)
C(1)-C(13)	1.5142(7)	C(2)-C(3)-H(3A)	110.1(7)
C(1)-C(14)	1.5337(7)	C(2)-C(3)-H(3B)	109.6(8)
C(2)-H(2A)	0.992(12)	H(3A)-C(3)-H(3B)	107.4(10)
C(2)-H(2B)	0.949(12)	C(4)-C(3)-C(2)	109.28(5)
C(2)-C(3)	1.5342(8)	C(4)-C(3)-H(3A)	109.8(7)
C(3)-H(3A)	0.993(11)	C(4)-C(3)-H(3B)	110.7(7)
C(3)-H(3B)	0.965(12)	Cl(1)-C(4)-H(4)	104.0(7)
C(3)-C(4)	1.5201(9)	C(3)-C(4)-Cl(1)	110.09(4)
C(4)-H(4)	0.974(12)	C(3)-C(4)-H(4)	110.7(7)
C(4)-C(5)	1.5180(8)	C(5)-C(4)-Cl(1)	107.77(4)
C(5)-H(5A)	1.001(13)	C(5)-C(4)-C(3)	111.79(5)
C(5)-H(5B)	0.948(12)	C(5)-C(4)-H(4)	112.2(7)
C(5)-C(6)	1.5211(8)	C(4)-C(5)-H(5A)	112.6(7)
C(6)-H(6)	0.987(12)	C(4)-C(5)-H(5B)	108.5(7)
C(7)-H(7A)	0.973(13)	C(4)-C(5)-C(6)	112.10(5)
C(7)-H(7B)	0.961(14)	H(5A)-C(5)-H(5B)	105.6(10)
C(7)-H(7C)	0.970(14)	C(6)-C(5)-H(5A)	108.9(7)
C(8)-C(9)	1.3927(8)	C(6)-C(5)-H(5B)	108.8(7)
C(8)-C(13)	1.4059(7)	N(1)-C(6)-C(1)	102.34(4)
C(9)-H(9)	0.974(12)	N(1)-C(6)-C(5)	115.05(4)
C(9)-C(10)	1.3993(10)	N(1)-C(6)-H(6)	108.5(7)
C(10)-H(10)	0.950(13)	C(1)-C(6)-H(6)	109.3(7)
C(10)-C(11)	1.3904(9)	C(5)-C(6)-C(1)	114.56(4)
C(11)-H(11)	0.976(13)	C(5)-C(6)-H(6)	106.8(7)
C(11)-C(12)	1.4029(8)	N(1)-C(7)-H(7A)	109.9(8)
C(12)-H(12)	0.937(13)	N(1)-C(7)-H(7B)	109.6(9)
C(12)-C(13)	1.3809(8)	N(1)-C(7)-H(7C)	112.7(8)
C(14)-H(14A)	1.004(12)	H(7A)-C(7)-H(7B)	110.3(11)
C(14)-H(14B)	0.967(12)	H(7A)-C(7)-H(7C)	105.6(12)
C(14)-C(15)	1.5364(7)	H(7B)-C(7)-H(7C)	108.6(12)
C(15)-H(15)	0.951(11)	N(1)-C(8)-C(13)	110.37(5)
C(15)-C(18)	1.5169(7)	C(9)-C(8)-N(1)	128.93(5)
C(16)-C(17)	1.5373(8)	C(9)-C(8)-C(13)	120.70(5)
C(19)-H(19A)	0.986(14)	C(8)-C(9)-H(9)	121.6(7)
C(19)-H(19B)	0.966(13)	C(8)-C(9)-C(10)	118.08(5)
C(19)-H(19C)	0.986(16)	C(10)-C(9)-H(9)	120.2(7)
		C(9)-C(10)-H(10)	118.8(8)
C(18)-O(2)-C(19)	115.43(5)	C(11)-C(10)-C(9)	121.56(5)
C(7)-N(1)-C(6)	116.28(5)	C(11)-C(10)-H(10)	119.6(8)
C(8)-N(1)-C(6)	104.75(4)	C(10)-C(11)-H(11)	119.9(8)
C(8)-N(1)-C(7)	118.19(5)	C(10)-C(11)-C(12)	119.76(6)
C(15)-N(2)-H(2)	119.5(9)	C(12)-C(11)-H(11)	120.3(8)
C(16)-N(2)-H(2)	122.5(9)	C(11)-C(12)-H(12)	119.8(8)
C(16)-N(2)-C(15)	117.90(4)	C(13)-C(12)-C(11)	119.32(5)
C(6)-C(1)-C(2)	109.31(4)	C(13)-C(12)-H(12)	120.9(8)
C(13)-C(1)-C(2)	108.48(4)	C(8)-C(13)-C(1)	107.83(5)

C(12)-C(13)-C(1)	131.56(5)	F(1B)-C(17)-F(2B)	103.1(6)
C(12)-C(13)-C(8)	120.57(5)	F(1B)-C(17)-F(3B)	101.8(7)
C(1)-C(14)-H(14A)	109.5(7)	F(1B)-C(17)-C(16)	118.5(5)
C(1)-C(14)-H(14B)	108.7(7)	F(2B)-C(17)-C(16)	105.5(3)
C(1)-C(14)-C(15)	117.79(4)	F(3B)-C(17)-F(2B)	112.6(6)
H(14A)-C(14)-H(14B)	106.0(10)	F(3B)-C(17)-C(16)	114.9(4)
C(15)-C(14)-H(14A)	105.3(7)	F(1A)-C(17)-F(3A)	99.2(5)
C(15)-C(14)-H(14B)	108.9(7)	F(1A)-C(17)-C(16)	115.4(4)
N(2)-C(15)-C(14)	110.18(4)	F(2A)-C(17)-F(1A)	105.4(5)
N(2)-C(15)-H(15)	107.2(7)	F(2A)-C(17)-F(3A)	114.8(5)
N(2)-C(15)-C(18)	107.49(4)	F(2A)-C(17)-C(16)	111.5(3)
C(14)-C(15)-H(15)	111.2(7)	F(3A)-C(17)-C(16)	110.1(3)
C(18)-C(15)-C(14)	112.07(4)	O(2)-C(18)-C(15)	111.98(5)
C(18)-C(15)-H(15)	108.5(7)	O(3)-C(18)-O(2)	124.88(5)
O(1)-C(16)-N(2)	126.14(5)	O(3)-C(18)-C(15)	123.14(5)
O(1)-C(16)-C(17)	117.34(5)	O(2)-C(19)-H(19A)	104.3(8)
N(2)-C(16)-C(17)	116.43(5)	O(2)-C(19)-H(19B)	110.6(8)
F(1)-C(17)-C(16)	108.01(5)	O(2)-C(19)-H(19C)	108.7(9)
F(2)-C(17)-F(1)	104.62(8)	H(19A)-C(19)-H(19B)	114.9(11)
F(2)-C(17)-C(16)	111.85(5)	H(19A)-C(19)-H(19C)	106.3(12)
F(3)-C(17)-F(1)	107.10(8)	H(19B)-C(19)-H(19C)	111.7(12)
F(3)-C(17)-F(2)	109.85(8)		
F(3)-C(17)-C(16)	114.78(5)		

Table A5.4. Anisotropic displacement parameters ($Å^2$x 10^4) for indoline ***169****. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	179(1)	262(1)	132(1)	-11(1)	6(1)	-79(1)
F(1)	537(5)	242(3)	276(3)	-11(2)	110(3)	213(3)
F(2)	280(3)	650(6)	191(2)	-216(3)	-83(2)	147(4)
F(3)	676(6)	429(5)	387(4)	-276(4)	424(4)	-380(5)
O(1)	169(2)	154(2)	135(2)	-3(1)	24(1)	-44(1)
O(2)	162(2)	191(2)	129(2)	-11(1)	-24(1)	-23(1)
O(3)	168(2)	183(2)	164(2)	-10(1)	45(1)	-61(1)
N(1)	144(2)	147(2)	88(1)	7(1)	29(1)	13(1)
N(2)	134(2)	135(2)	110(2)	-32(1)	45(1)	-28(1)
C(1)	118(2)	108(2)	83(2)	0(1)	10(1)	10(1)
C(2)	134(2)	130(2)	127(2)	6(2)	2(1)	23(2)
C(3)	131(2)	187(2)	130(2)	11(2)	-6(1)	4(2)
C(4)	129(2)	187(2)	118(2)	-11(2)	16(1)	-22(2)
C(5)	155(2)	138(2)	130(2)	4(2)	18(2)	-13(2)
C(6)	124(2)	120(2)	93(2)	9(1)	20(1)	14(1)
C(7)	248(3)	207(3)	114(2)	33(2)	54(2)	9(2)
C(8)	137(2)	136(2)	91(2)	-6(1)	11(1)	28(1)
C(9)	183(2)	180(2)	98(2)	-22(2)	-4(2)	36(2)
C(10)	213(2)	161(2)	134(2)	-36(2)	-37(2)	27(2)
C(11)	197(2)	127(2)	153(2)	-15(2)	-25(2)	-1(2)
C(12)	168(2)	111(2)	119(2)	-1(1)	-2(1)	4(2)
C(13)	135(2)	114(2)	89(2)	-4(1)	4(1)	16(1)
C(14)	126(2)	128(2)	82(2)	-4(1)	14(1)	2(1)

C(15)	110(2)	117(2)	93(2)	-14(1)	22(1)	-12(1)
C(16)	139(2)	120(2)	108(2)	-20(1)	17(1)	-7(1)
C(17)	178(2)	175(2)	140(2)	-50(2)	28(2)	-6(2)
C(18)	110(2)	132(2)	113(2)	-26(1)	22(1)	-10(1)
C(19)	190(2)	282(3)	204(3)	-63(2)	-58(2)	-28(2)

*Table A5.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for indoline **169**.*

	x	y	z	U_{eq}
H(2)	5444(5)	7130(20)	5096(6)	24(3)
H(2A)	7051(4)	2713(18)	4335(5)	16(2)
H(2B)	7266(5)	3087(19)	3713(5)	20(3)
H(3A)	7418(5)	5894(18)	4651(5)	16(2)
H(3B)	7866(5)	4491(19)	4398(5)	20(3)
H(4)	7849(5)	6249(18)	3504(5)	21(3)
H(5A)	7248(5)	9060(20)	3344(6)	23(3)
H(5B)	7053(5)	8753(18)	3978(5)	18(3)
H(6)	6413(5)	7476(19)	3374(5)	19(3)
H(7A)	6928(5)	5990(20)	2014(6)	26(3)
H(7B)	7188(5)	7730(20)	2408(6)	34(3)
H(7C)	6573(5)	7650(20)	2283(6)	31(3)
H(9)	6384(5)	3238(19)	1974(5)	21(3)
H(10)	5770(5)	620(20)	2135(6)	24(3)
H(11)	5478(5)	-200(20)	3074(6)	25(3)
H(12)	5834(5)	1603(19)	3883(6)	21(3)
H(14A)	6556(5)	6198(18)	4673(5)	18(3)
H(14B)	6206(4)	4232(18)	4605(5)	16(2)
H(15)	5888(4)	7929(17)	4072(5)	14(2)
H(19A)	4679(5)	5930(20)	2924(6)	29(3)
H(19B)	4457(5)	5150(20)	3557(6)	29(3)
H(19C)	4873(6)	3840(20)	3184(7)	41(4)

*Table A5.6. Torsion angles [°] for indoline **169**.*

Cl(1)-C(4)-C(5)-C(6)	-176.40(4)
O(1)-C(16)-C(17)-F(1)	59.58(8)
O(1)-C(16)-C(17)-F(2)	-55.02(9)
O(1)-C(16)-C(17)-F(3)	178.96(8)
O(1)-C(16)-C(17)-F(1B)	-20.8(6)
O(1)-C(16)-C(17)-F(2B)	-135.5(3)
O(1)-C(16)-C(17)-F(3B)	99.8(5)
O(1)-C(16)-C(17)-F(1A)	28.3(5)
O(1)-C(16)-C(17)-F(2A)	-91.8(4)
O(1)-C(16)-C(17)-F(3A)	139.5(4)
N(1)-C(8)-C(9)-C(10)	-179.58(6)
N(1)-C(8)-C(13)-C(1)	-1.89(6)
N(1)-C(8)-C(13)-C(12)	179.97(5)

N(2)-C(15)-C(18)-O(2)	125.52(5)
N(2)-C(15)-C(18)-O(3)	-54.58(7)
N(2)-C(16)-C(17)-F(1)	-117.14(7)
N(2)-C(16)-C(17)-F(2)	128.26(8)
N(2)-C(16)-C(17)-F(3)	2.24(10)
N(2)-C(16)-C(17)-F(1B)	162.5(6)
N(2)-C(16)-C(17)-F(2B)	47.7(3)
N(2)-C(16)-C(17)-F(3B)	-77.0(5)
N(2)-C(16)-C(17)-F(1A)	-148.4(5)
N(2)-C(16)-C(17)-F(2A)	91.4(4)
N(2)-C(16)-C(17)-F(3A)	-37.2(4)
C(1)-C(2)-C(3)-C(4)	-57.74(6)
C(1)-C(14)-C(15)-N(2)	-164.41(4)
C(1)-C(14)-C(15)-C(18)	75.96(6)
C(2)-C(1)-C(6)-N(1)	76.90(5)
C(2)-C(1)-C(6)-C(5)	-48.30(6)
C(2)-C(1)-C(13)-C(8)	-89.99(5)
C(2)-C(1)-C(13)-C(12)	87.87(7)
C(2)-C(1)-C(14)-C(15)	170.56(4)
C(2)-C(3)-C(4)-Cl(1)	177.86(4)
C(2)-C(3)-C(4)-C(5)	58.11(6)
C(3)-C(4)-C(5)-C(6)	-55.30(6)
C(4)-C(5)-C(6)-N(1)	-67.33(6)
C(4)-C(5)-C(6)-C(1)	50.89(6)
C(6)-N(1)-C(8)-C(9)	157.32(6)
C(6)-N(1)-C(8)-C(13)	-22.82(6)
C(6)-C(1)-C(2)-C(3)	52.13(6)
C(6)-C(1)-C(13)-C(8)	24.13(5)
C(6)-C(1)-C(13)-C(12)	-158.01(6)
C(6)-C(1)-C(14)-C(15)	48.42(6)
C(7)-N(1)-C(6)-C(1)	169.74(5)
C(7)-N(1)-C(6)-C(5)	-65.38(6)
C(7)-N(1)-C(8)-C(9)	25.98(9)
C(7)-N(1)-C(8)-C(13)	-154.15(5)
C(8)-N(1)-C(6)-C(1)	37.30(5)
C(8)-N(1)-C(6)-C(5)	162.18(5)
C(8)-C(9)-C(10)-C(11)	-0.14(9)
C(9)-C(8)-C(13)-C(1)	177.99(5)
C(9)-C(8)-C(13)-C(12)	-0.15(8)
C(9)-C(10)-C(11)-C(12)	-0.71(9)
C(10)-C(11)-C(12)-C(13)	1.12(9)
C(11)-C(12)-C(13)-C(1)	-178.34(5)
C(11)-C(12)-C(13)-C(8)	-0.70(8)
C(13)-C(1)-C(2)-C(3)	159.53(4)
C(13)-C(1)-C(6)-N(1)	-36.57(5)
C(13)-C(1)-C(6)-C(5)	-161.77(4)
C(13)-C(1)-C(14)-C(15)	-67.20(6)
C(13)-C(8)-C(9)-C(10)	0.57(8)
C(14)-C(1)-C(2)-C(3)	-73.35(6)
C(14)-C(1)-C(6)-N(1)	-161.77(4)
C(14)-C(1)-C(6)-C(5)	73.03(6)
C(14)-C(1)-C(13)-C(8)	148.10(5)
C(14)-C(1)-C(13)-C(12)	-34.04(8)
C(14)-C(15)-C(18)-O(2)	-113.28(5)
C(14)-C(15)-C(18)-O(3)	66.62(7)
C(15)-N(2)-C(16)-O(1)	-0.85(9)

C(15)-N(2)-C(16)-C(17)	175.55(5)
C(16)-N(2)-C(15)-C(14)	81.91(6)
C(16)-N(2)-C(15)-C(18)	-155.71(5)
C(19)-O(2)-C(18)-O(3)	-2.63(9)
C(19)-O(2)-C(18)-C(15)	177.28(5)

*Table A5.7. Hydrogen bonds for indoline **169** [Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(3)#1	0.846(13)	2.131(13)	2.9754(6)	177.2(13)

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

ABOUT THE AUTHOR

Jane Ni was born on December 17th, 1987 in Shanghai, China to Kang Mei Wang and Wei Hua Ni. She moved to Montreal, Canada at age 3, and then to Toronto during the third grade, where her parents currently reside. She has loved swimming from a very young age, and continues to do so today. During high school, she also enjoyed sailing, especially in the beautiful lakes of Northern Ontario, and learning karate.

At the University of Toronto, she had the good fortune of having amazing chemistry professors, including Profs. Ronald Kluger and Robert Batey, and learned that chemistry actually is not a collection of foreign-looking symbols. During her second year, she had the opportunity to conduct research in the laboratory of Prof. Andrew Woolley. Later, after a developing an interest in organic chemistry, she decided to conduct research in the lab of Prof. Vy Dong, where she investigated transition metal-catalyzed C–H activation reactions. It was this experience that inspired Jane to apply to graduate school.

Upon obtaining her undergraduate degree in 2009, she decided to venture to sunnier climates to conduct doctoral research in the lab of Professor Sarah E. Reisman at the California Institute of Technology. Her graduate work focused on the development of asymmetric protonation methods for the synthesis of indoline alkaloids. In October 2014, Jane will commence a postdoctoral fellowship with Prof. Martin F. Semmelhack in the Chemistry Department at Princeton University.