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

Thesis by

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To my teachers
ACKNOWLEDGEMENTS

Foremost, I would like to thank Professor Sarah Reisman for accepting my request to join her lab five years ago. I couldn’t have asked for a more intelligent, supportive advisor and I have learned so much from her in all aspects of chemistry research throughout my graduate studies. It has been my privilege to watch this lab grow, literally as it has increased from five to twenty people, but also in the scientific advances that have been made and published over the past five years. It is certainly the start to a fantastic career and I look forward to seeing the research that comes out of Sarah’s group in the future.

I have also benefited greatly from the wisdom, encouragement, and enthusiasm provided by my thesis committee. In particular, I am very grateful for all of their advice during proposal defenses. Specifically, thank you to Professor Dennis Dougherty for his participation as my committee chair and also for initiating a collaboration project with our lab. I am honored to have participated in that research and I really enjoyed learning more about the research going on in his group. On the subject of collaborations, thank you to Professor John Bercaw for his assistance with my first project at Caltech on palladium catalysis. I also owe many thanks to Professor Brian Stoltz. On that note, I should also thank my chemical grandfather, Professor John Wood, as Brian and Sarah, both incredibly gifted organic chemists, completed their own graduate research under his guidance. I appreciate all of the advice Brian has given me regarding my research over the past five years and I’m also so grateful for his enthusiasm, especially when I got my first big hit on a project. I’ll always remember that.
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at Caltech. A special thanks goes to Dr. Scott Virgil, who has helped me with all of these projects. His extensive knowledge, combined with his assistance with both our glove box reactions and reaction analysis, made him invaluable. Thank you as well to Dr. Doug Behenna who devoted many hours to helping us with preparative HPLC. Finally, I’d also like to thank the students I have mentored; Kangway Chuang, who worked with me for only a month as that was more than enough guidance, and Nadine Currie, my mentee who recently graduated from Caltech.

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I have also made many friends outside of the Reisman lab while at Caltech. I have really benefited from the Stoltz group during my time here and want to especially thank all the people who moved down to the basement of Church when we got here so that we wouldn’t be on our own. In particular, I would really like to thank Alex Marziale for all of his love and support during this past year, as well as some of the closest friends I have made while at Caltech, namely Sibo Lin, Renee Thomas, and Floh Vogt. A final thanks
to those who managed the GSC soccer teams and those who took care of Norah when I left town (special thanks to Chris Gilmore for annual assistance during the holidays).

There is no way I would be at this point, writing these acknowledgements, if it weren’t for the support of my family. Thank you to Mom and Dad, my brother Mike, and Holly for everything and for the many trips you made to visit me during grad school. Thanks to my grandparents, Norah and my entire extended family as well, including the many who live in the Los Angeles area. Many thanks as well to my unofficial family who have stood by me for most of life, Sarah Goldberg, Becca Gifford, and Emmy Frank. Finally, I’d like to thank my grandfather, Dr. Benjamin Charles Repka, a fellow chemist who gave me the courage to keep charging ahead through grad school. Thank you everyone.
ABSTRACT

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

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

Second, application of this asymmetric protonation strategy to the synthesis of a variety of enantioenriched tryptophan derivatives is discussed. Finally, we found that these derivatives could undergo selective functionalization. More specifically, we were able to prepare novel hydroxypyrroloindolines that are currently the subject of a collaboration project with the Dougherty lab aimed at identifying novel positive allosteric modulators of ligand-gated ion channels.
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<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>$5\mathrm{HT}_{3A}$</td>
<td>serotonin type 3A receptor</td>
</tr>
<tr>
<td>A</td>
<td>alanine</td>
</tr>
<tr>
<td>AAA</td>
<td>Asymmetric Allylic Alkylation</td>
</tr>
<tr>
<td>Å</td>
<td>Ångstrom</td>
</tr>
<tr>
<td>$\left[\alpha\right]_D$</td>
<td>specific rotation at wavelength of sodium D line</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACAT</td>
<td>acyl-CoA:cholesterol acyltransferase</td>
</tr>
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<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s Disease</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
</tr>
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<td>app</td>
<td>apparent</td>
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<tr>
<td>AIBN</td>
<td>2,2’-azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
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</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BBN</td>
<td>borabicyclononane</td>
</tr>
<tr>
<td>BCRP</td>
<td>Breast Cancer Resistance Protein</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′-bis(diphenylphosphino)-1,1′-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1′-bi(2-naphthol)</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>BOX</td>
<td>bisoxazoline</td>
</tr>
<tr>
<td>br</td>
<td>broxide</td>
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<tr>
<td>BTF</td>
<td>benzotri fluoride</td>
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</table>
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
<table>
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<tr>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>(deoxy)ribonucleic acid</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1′-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>E</td>
<td>electrophile</td>
</tr>
<tr>
<td>EC₅₀</td>
<td>median effective concentration (50%)</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>e.g.</td>
<td>for example (Latin exempli gratia)</td>
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<tr>
<td>equiv</td>
<td>equivalent</td>
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<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>ETP</td>
<td>epidithiodiketopiperazine</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>FDA</td>
<td>food and drug administration</td>
</tr>
<tr>
<td>FID</td>
<td>flame ionization detector</td>
</tr>
<tr>
<td>FT</td>
<td>fourier transform</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-aminobutyric acid</td>
</tr>
<tr>
<td>GABAₐR</td>
<td>γ-aminobutyric acid type A receptor</td>
</tr>
<tr>
<td>gCOSY</td>
<td>gradient-selected correlation spectroscopy</td>
</tr>
<tr>
<td>gHMBC</td>
<td>gradient-selected heteronuclear multiple bond correlation</td>
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<tr>
<td>GlyR</td>
<td>glycine receptor</td>
</tr>
<tr>
<td>GluR₂A</td>
<td>glutamate receptor subunit 2A</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
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<td>Description</td>
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<td>--------------</td>
<td>-------------</td>
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<tr>
<td>HMDS</td>
<td>1,1,1,3,3,3-hexamethyldisilazane</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectroscopy</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>$h\nu$</td>
<td>light</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
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</table>
| IC$_{50}$    | median inhibition concentration (50%)
<p>| IPA          | isopropanol |
| IR           | infrared (spectroscopy) |
| $J$          | coupling constant |
| $\lambda$    | wavelength |
| L            | liter; leucine |
| LA           | Lewis acid |
| LAH          | lithium aluminum hydride |
| LBA          | Lewis acid-assisted Brønsted acid |
| LC-MS        | liquid chromatography-mass spectrometry |
| LDA          | lithium diisopropylamide |
| LGIC         | ligand-gated ion channel |
| LHMDS        | lithium bis(trimethylsilyl)amide |
| m            | multiplet; milli |
| $m$          | meta |
| $m/z$        | mass to charge ratio |
| M            | metal; molar; molecular ion |
| Me           | methyl |
| Mes          | mesityl |
| mGlu$_i$     | metabotropic glutamate receptor |
| MHz          | megahertz |</p>
<table>
<thead>
<tr>
<th>Symbol</th>
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<tr>
<td>µ</td>
<td>micro</td>
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<tr>
<td>µwaves</td>
<td>microwave irradiation</td>
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<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>MM</td>
<td>multimode</td>
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<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl (mesyl)</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>n</td>
<td>nano</td>
</tr>
<tr>
<td>N</td>
<td>normal</td>
</tr>
<tr>
<td>NAM</td>
<td>negative allosteric modulator</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>nd</td>
<td>not determined</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
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<td>NOESY</td>
<td>nuclear Overhauser enhancement spectroscopy</td>
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<tr>
<td>NPSP</td>
<td>N-(phenylseleno)phthalimide</td>
</tr>
<tr>
<td>nr</td>
<td>no reaction</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>OLED</td>
<td>organic light-emitting diode</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PAM</td>
<td>positive allosteric modulator</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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</table>
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
S  serine
sat.  saturated
SFC  supercritical fluid chromatography
SiPr  $N,N'$-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene
$t$  triplet
T  tyrosine
TADMAP  3-(2,2,2-triphenyl-1-acetoxyethyl)-4-(dimethylamino)pyridine
TBS  tert-butyldimethylsilyl
<table>
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<tr>
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<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl (trifyl)</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid; trifluoroacetyl</td>
</tr>
<tr>
<td>TfOH</td>
<td>triflic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TIPS</td>
<td>triisopropylsilyl</td>
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<tr>
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<td>thin-layer chromatography</td>
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<tr>
<td>TMS</td>
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<tr>
<td>TOF</td>
<td>time-of-flight</td>
</tr>
<tr>
<td>$t_r$</td>
<td>retention time</td>
</tr>
<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl (tosyl)</td>
</tr>
<tr>
<td>$p$-TSA</td>
<td>$p$-toluenesulfonic acid</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>$v/v$</td>
<td>volume to volume</td>
</tr>
<tr>
<td>$w/v$</td>
<td>weight to volume</td>
</tr>
<tr>
<td>X</td>
<td>anionic ligand or halide</td>
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CHAPTER 1

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

1.1 INTRODUCTION

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

† This chapter was adapted from a mini-review written in collaboration with Professor Sarah Reisman.
Although numerous strategies involving either chiral auxiliaries or the functionalization of L-tryptophan have been developed, this synopsis will offer an introduction to the catalytic, enantioselective approaches based on the recent growth of research within this field.

Figure 1.1.1. Representative pyrroloindoline natural products.

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

3,3’-Disubstituted oxindoles are available by several methods including α-alkylation, intramolecular cyclization, and intramolecular acyl migration. The first catalytic asymmetric synthesis of a 3,3’-disubstituted oxindole was developed in 1991 at Hoechst-Roussel Pharmaceuticals Inc. Researchers Wong and Lee discovered that subjection of oxindole 11 to chloroacetonitrile in the presence of cinchoninium bromide catalyst 13 delivered enantioenriched oxindole 12 (Scheme 1.2.1). Further elaboration resulted in a formal total synthesis of the anticholinesterase natural product physostigmine (1, Figure 1). This approach built on the pioneering phase transfer catalysis studies of Dolling and coworkers, and has been succeeded by several enantioselective organocatalytic α-alkylation reactions of oxindoles. Recently, Luo and coworkers identified a bifunctional tertiary amine thiourea (15) that catalyzes the conjugate addition of 3-aryl and 3-alkyloxindoles (14) to 2-chloroacrylonitrile (16). Of the asymmetric oxindole alkylation approaches reported to date, this is the first method that directly installs an
appropriate C2-handle for advancement to diketopiperazine-based alkaloids (e.g. chaetocin A (3), Figure 1.1.1).

Scheme 1.2.1. Organocatalytic α-alkylation of oxindoles.

A second, foundational catalytic asymmetric method to prepare 3,3-disubstituted oxindoles was the Pd-catalyzed intramolecular Heck reaction reported by Overman and coworkers in 1993 (Scheme 1.2.2). In a preliminary demonstration of the synthetic utility, physostigmine (1, Figure 1.1.1) was prepared from Z-butenanilide 19 via oxindole carboxaldehyde 20. Recently, this reaction was applied in more elaborate contexts including the synthesis of the alkaloids minfiensine (4, Figure 1.1.1) and polypyrroloindoline quadrigemine C. These transformations are noteworthy examples of asymmetric Heck reactions that generate all-carbon quaternary centers, and have likely inspired the development of related transition metal-catalyzed cyclization reactions for the construction of pyrroloindolines. For example, Nakao, Hiyama, Ogoshi and coworkers reported the synthesis of (2-oxindolyl)acetonitrile derivatives by the Ni-catalyzed enantioselective intramolecular arylcyanation of alkenes (Scheme 1.2.2).
key finding in this study was that, in addition to the nickel catalyst, a Lewis acid (AlMe₂Cl) was required to achieve indoline formation. Subsequent C-H oxidation furnishes the highly enantioenriched 3,3’-dialkyl (12) and 3-alkyl-3’-aryloxindoles.

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

Conditions: a. 10 mol % Pd₂dba₃·CHCl₃, 23 mol % (S)-BINAP, 5.1 equiv PMP, DMA, 100 °C, 1.5 h. b. 3 N HCl, 0 to 23 °C (84 % yield, 2 steps). c. 10 mol % Ni(cod), 20 mol % 22, 40 mol % AlMe₂Cl, DME, 100 °C, 10 h (88% yield); d. 6.0 equiv PhIO, CH₂Cl₂, rt, 2.5 h (40% yield).

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

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

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

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

Conditions: a. 20 mol % (S)-PhBOX-Cu(II)·2SbF$_6$, 3.0 equiv dimethyl malonate, 2.0 equiv Et$_3$N, 3 Å MS, CH$_2$Cl$_2$, −20 °C (76% yield), b. LiCl, H$_2$O, DMSO, 150 °C, 12 h; c. iBuOK, MeI, THF, 0 °C, 1 h; d. AlMe$_3$, MeNH$_2$·HCl, PhMe, 50 °C, 5 d; d. LAH, THF, 0 °C, 1 h.

Most oxindole α-alkylation strategies harness the intrinsic nucleophilicity of enolate intermediates; however, two recent Umpolung approaches employ oxindoles as the electrophilic component.$^{21}$ In a 2009 report, Stoltz and coworkers describe a Cu(II) bisoxazoline (28)-catalyzed stereoablative alkylation of 3-chloro-3-aryloxindoles (27) with dimethylmalonate, wherein coordination of the malonate to the copper catalyst presumably generates a chiral nucleophile (29, Scheme 1.2.4).$^{21a,22}$ The reaction is proposed to occur by elimination of HCl from 27 to form a transient o-azaxylylene (30); subsequent attack at C3 by 29 delivers the 3,3’-disubstituted oxindole (31). The utility of these products in pyrroloindoline synthesis was demonstrated for oxindole 31, which
following Krapcho dealkoxycarbonylation, N-methylation, aminolysis, and reductive cyclization afforded 3-phenylpyrroloindoline 33 in an operationally straightforward manner.

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

Conditions: a. 1.5 equiv 35, 10 mol % 40, Na₂SO₄, CH₂Cl₂, rt, 12-24 h; b. aqueous HBr, EtOH, rt, 8 h; c. nBu₄NHSO₄, KOH, THF, 50 °C, 1 h; then MeI, rt, 2 h; d. NH₂OH•HCl, pyridine, EtOH, rt, 2 d; e. HgCl₂, MeCN, 80 °C, 2 h.

Gong and coworkers have discovered an alternative strategy for the in situ generation of electrophilic oxindole species that has proven instrumental for bispyrroloindoline synthesis.²¹b This reaction involves indole-assisted dehydration, followed by chiral phosphoric acid (40)-catalyzed addition of enamine 35 to the transient azafulvene (36, Scheme 1.2.5). Mechanistic insight was provided by DFT calculations, which suggest a two-point binding model for the Brønsted acid that invokes hydrogen bonding of both the enamine and indole nitrogens. The necessary nitrogen functionality was installed by a Beckmann rearrangement to give 38, which was elaborated in eight additional steps to (+)-folicanthine (39). Gong and coworkers further applied the asymmetric methodology
to 2-(alkyloxy)acetaldehydes by employing a cinchona alkaloid-derived co-catalyst and used this chemistry in a synthesis of gliocladin C (2, Figure 1.1.1).\textsuperscript{23}

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

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

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

Each of the methods discussed above depend on a reductive cyclization event as the means to access pyrroloindolines. Alternatively, the synthesis of (+)-glioclidine C (50) completed by Overman and coworkers required the development of a more functional
group compatible Lewis acid-promoted cyclization reaction.\textsuperscript{25} These researchers further recognized the relevant utility of the planar-chiral ferrocenyl pyridine (45)-catalyzed intramolecular acyl O-to-C migration of indolyl carbonates initially disclosed by Fu and coworkers.\textsuperscript{26} Subjection of indolyl trichloro-\textit{tert}-butylcarbonate 44 to the reported migration conditions provided oxindole 46 in high yield and ee (Scheme 1.2.7). Intermolecular aldol reaction of further functionalized 2-methoxyindoline 47 with trioxopiperazine 48 then installed the necessary nucleophilic amide functionality and subsequent exposure to BF\textsubscript{3}•OEt\textsubscript{2} provided didehydropyrroloindoline 49. This cyclization product was converted to (+)-gliocladine C (50) in 6 steps,\textsuperscript{27} which constitutes the first total synthesis of an epidithiodiketopiperazine (ETP) natural product incorporating a β-hydroxy-substituted stereocenter.

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

As a complementary approach to asymmetric oxindole syntheses described above, Larionov and coworkers reported a strategy that invokes instead the intermediacy of an indolyl 1,2-oxazine (53, Scheme 1.2.8).\textsuperscript{28,29} Similar to the oxindole research, these studies
were driven by both the biological activity of 1,2-oxazine natural products\textsuperscript{30} and the prospective conversion to pyrroloindolines. Specifically, Lewis acid-catalyzed [4+2] cycloaddition reactions of 3-alkylindoles (51) with nitrosoalkenes generated in situ from 2-chlorooximes (52) were found to afford the desired oxazines. Notably, Gilchrist and Roberts reported a related non-asymmetric NaHCO\textsubscript{3}-promoted reaction in 1978,\textsuperscript{31} but this recent addition to the literature represents the first catalytic and highly enantioselective cycloaddition of nitrosoalkenes for any dienophile.\textsuperscript{32} Beckmann rearrangement of 1,2-oxazine 53 furnished 3-allylpyrroloindoline 54, thereby illustrating the utility of this strategy for the synthesis of both oxazines and pyrroloindolines.

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

\[
\text{Conditions: } a. \; 10 \text{ mol } \% \text{ CuOTf} \cdot 1/2\text{PhMe}, \; 10 \text{ mol } \% \; (S)-\text{DM}-\text{BINAP}, \; 3.0 \text{ equiv } \text{Ag}_2\text{CO}_3, \; 3\text{Å MS}, \; \text{CH}_2\text{Cl}_2, \; -15 ^\circ \text{C}, \; 48 \text{ h}; \; b. \; 20 \text{ mol } \% \; \text{PBr}_3, \; \text{C}_6\text{H}_5\text{CF}_3, \; 50 ^\circ \text{C}, \; 16 \text{ h (79\% yield)}.\]

1.3 \hspace{1cm} DIRECT SYNTHESIS OF PYRROLOINDOLINES FROM INDOLES AND TRYPTAMINES

Over the past decade, direct asymmetric functionalization of 3-substituted indoles has emerged as a powerful approach for the efficient preparation of pyrroloindolines. In 2004, MacMillan and coworkers reported a chiral imidazolidinone salt (57)-catalyzed reaction between acrolein and tryptamine derivatives (55) to generate enantioenriched pyrroloindolines (56, Scheme 1.3.1).\textsuperscript{33} The proposed mechanism invokes condensation of 57 with acrolein to generate a chiral iminium ion,\textsuperscript{34} which undergoes a cascade conjugate
addition/cyclization reaction to deliver the pyrroloindoline framework. The appeal of this reaction is that it harnesses the intrinsic C3-nucleophilicity and provides direct access to pyrroloindolines from simple, readily available materials. The MacMillan group has utilized this organocatalytic reaction as the key step in the total syntheses of three structurally distinct pyrroloindoline alkaloids.\textsuperscript{35}

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

Since this initial disclosure by MacMillan and coworkers, several other methods for the direct synthesis of pyrroloindolines from tryptamine and tryptophan derivatives have been reported, and collectively these reactions provide access to a variety of enantioenriched pyrroloindoline products. In 2006, Trost and coworkers developed the first AAA reaction of allyl alcohol by including trialkylboranes as a stoichiometric promoter (Scheme 1.3.2).\textsuperscript{36} Notably, the enantioselectivity of this AAA reaction is dependent on the choice of both ligand and borane, with the combination of 9-BBN-C\textsubscript{6}H\textsubscript{13} and anthracene-derived phosphine (S,S)-60 proving optimal.

Scheme 1.3.2. Pd-catalyzed tandem allylic alkylation/cyclization reaction of tryptamines (Trost and Quancard, 2006).
Antilla and coworkers recently reported chiral phosphoric acid (62)-catalyzed C–N and C–C bond formation/cyclization reactions of tryptamine carbamates (61 and 65) (Scheme 1.3.3). Preliminary NMR investigations suggest a mechanism involving electrophile activation by a hydrogen-bonding network (66). Specifically, it is proposed that coordination of the tryptamine carbonyl to the catalyst enhances the carbamate acidity and results in hydrogen bonding to the electrophile (either diethylazodicarboxylate (DEAD) or methyl vinyl ketone). This methodology constitutes the first catalytic, asymmetric construction of 3-aminopyrroloindolines, a motif present in several naturally occurring alkaloids. Furthermore, the utility of the C–C bond forming variant has been demonstrated in the concise total synthesis of (−)-debromoflustramine B (67). Exposure of (1H)-tryptamine 65 to methyl vinyl ketone resulted in substitution at both C3a and N1a to give 66, an intermediate primed for elaboration to 67.

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

In a recent effort directed toward preparing 3a-arylpyrroloindolines, MacMillan and coworkers developed a Cu(I)-bisoxazoline (70)-catalyzed intermolecular arylation
reaction of indole acetamides using aryliodonium salts (69, Scheme 1.3.4). The proposed mechanism involves electrophilic C3-metalation of the indole acetamide (68) by a Cu(III)-aryl complex, reductive elimination, and cyclization of the resultant 3-arylindolenine (73). The excellent enantioselectivity likely results from bidentate substrate coordination (71) involving both the carboxamide and C2-C3 π-bond of the indole. This reaction enables the direct preparation of highly enantioenriched derivatives including 3-(bromoaryl)pyrroloindolines (74) that contain a potential handle for advancement to the indolyl substitution patterns found in naturally occurring alkaloids such as asperazine (5, Figure 1.1.1).

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

Although the majority of direct asymmetric approaches to pyrroloindolines employ tryptamine derivatives as substrates, several research groups have explored direct synthesis by formal (3 + 2) cycloaddition reactions. In 2010, we reported this approach involving the reaction of 3-substituted indoles and 2-amidoacrylates using \((R)\)-BINOL·SnCl\(_4\) as the catalyst to effect an enantiodetermining protonation (Chapter 2). More recently, Davies and Spangler developed a \(\text{Rh}_2(S\text{-PTAD})_4\) (77)-catalyzed reaction
between 3-substituted indoles (75) and 4-aryl-1-sulfonyl-1,2,3-triazoles (76) that affords didehydropyrroloindolines bearing either alkyl (78) or aryl substitution at C3a (Scheme 1.3.5). These products can be selectively reduced to afford either diastereomer of pyrroloindoline 81 depending on the catalyst. The formal cycloaddition to give 78 is proposed to occur by cyclopropanation of 75 with the Rh(II)-carbenoid generated in situ from 76, followed by cyclopropane ring-opening and cyclization. An alternative formal (3 + 2) cycloaddition approach has also been disclosed by Xie, Tang, and coworkers involving the Cu(II)-bisoxazoline (85)-catalyzed reaction of achiral pyrroloindole 82 and donor-acceptor cyclopropane 83, which furnishes aza-propellane 84 in excellent yield and stereoselectivity (Scheme 1.3.6).

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

Scheme 1.3.6. Cu-catalyzed formal (3 + 2) cycloaddition (Xie, Tang, and coworkers, 2013).
1.4 SYNTHESIS OF ENANTIOENRICHED PYRROLOINDOLINES BY DESYMMETRIZATION

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

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

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

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


(20) For the successful application of this strategy in the first total synthesis of gliocladin C (2, Figure 1.1.1), see: Overman, L. E.; Shin, Y. Org. Lett. 2007, 9, 339.


(22) For the initially reported non-asymmetric, DBU-promoted reaction, see: Krishnan, S.; Stoltz, B. M. Tetrahedron Lett. 2007, 48, 7571.


(29) For other indirect approaches to pyrroloindolines that require multiple transformations subsequent to the enantiodetermining step, see: (a) Lim, H. J.; RajanBabu, T. V. Org. Lett. 2011, 13, 6596. (b) Özüduru, G.; Schubach, T.; Boysen, M. M. K. Org. Lett. 2012, 14, 4990.


(32) In the only other enantioselective example, a 1,2-oxazine derivative was furnished in 42% ee using isovaleraldehyde as the dienophile and stoichiometric (S)-1-(2-pyrrolidinylmethyl)pyrrolidine as the chiral promoter: Wabnitz, T. C.; Saaby, S.; Jørgensen, K. A. Org. Biomol. Chem. 2004, 2, 828.


(37) (a) Zhang, Z.; Antilla, J. C. Angew. Chem. Int. Ed. 2012, 51, 11778. Shortly preceding this report, You and coworkers disclosed a similar enantioselective


(42) (a) Spangler, J. E.; Davies, H. M. L. J. Am. Chem. Soc. 2013, 135, 6802. Shortly preceding this report, Davies and coworkers disclosed a formal (3 + 2) cycloaddition between 4-aryl-1-sulfonyl-1,2,3-triazoles and furans: (b) Parr, B. T.; Green, S. A.; Davies, H. M. L. 2013, 135, 4716. For research by the Davies group involving Rh-catalyzed formal (3 + 2) cycloaddition reactions between indoles and α-diazoacetates, see: (c) Lian, Y.; Davies, H. M. L. J. Am. Chem. Soc. 2010, 132, 440.


CHAPTER 2

Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines†

2.1 INTRODUCTION

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

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

### 2.1.1 Design of the Cycloaddition Approach

The majority of catalytic, asymmetric indole functionalization approaches to prepare pyrroloindolines, including the seminal reports of MacMillan\(^1\) and Trost,\(^2\) involve the electrophilic substitution of tryptamine substrates. In our effort to provide a complementary approach to pyrroloindolines, we became interested in the possibility of a formal (3 + 2) cycloaddition reaction between 3-substituted indoles (90) and 2-amidoacrylates (91) that constitutes a formal (3 + 2) cycloaddition (Scheme 2.1.1). Successful realization of the proposed transformation could allow rapid access to a variety of substitution patterns and the pyrroloindoline-2-carboxylate products (92) formed should be suitable precursors for elaboration to diketopiperazine natural products (e.g. chaetocin (3, Figure 1.1.1)).

\[ \text{Proposed Formal (3 + 2) Cycloaddition Reaction:} \]

\[ \begin{align*}
\text{90} & \quad \text{91} \\
R^1 & \quad R^2 & \quad \text{chiral Lewis acid} \\
\text{alkyl, aryl} & \quad \text{catalytic} & \\
\text{N} & \quad \text{N} & \\
\text{R}^1 \text{R}^2 & \quad \text{R}^3 \text{R}^4 & \\
\text{O} & \quad \text{O} & \\
\text{R}^3 & \quad \text{R}^4 & \\
\text{H} & \quad \text{Me} & \\
\text{R}^2 & \quad \text{Me} & \\
\text{CO}_2 & \quad \text{NHAc} & \\
\text{R}^1 & \quad \text{R}^2 & \\
\text{R}^1 & \quad \text{R}^2 & \\
\text{Me} & \quad \text{Me} & \\
\text{CO}_2 & \quad \text{NHAc} & \\
\text{R} & \quad \text{R} & \\
\end{align*} \]

\[ \text{Synthesis of Tryptophan Derivatives by Piersanti and coworkers, 2008:} \]

\[ \begin{align*}
\text{93} & \quad \text{90} & \quad \text{91a} & \quad \text{94} \\
\text{NHAc} & \quad \text{Bi(OTf)}_2 & \quad \text{MeO} & \quad \text{CO}_2 & \\
\text{DCM, 0 °C} & \quad \text{2 equiv} & \quad \text{Me} & \quad \text{Me} & \\
\text{3 examples} & \quad \text{90 \footnote{(R^1\footnote{H})}} & \quad \text{10 examples} & \quad \text{90 \footnote{(R^1\footnote{H})}} & \\
\text{50 – 82 \% yield} & \quad \text{91a} & \quad \text{35 – 80 \% yield} & \\
\end{align*} \]

Although the potential for reaction between 3-substituted indoles and weak electrophiles such as amidoacrylates was unclear at the outset of this project, we were
particularly encouraged by the recent findings of Piersanti and coworkers reported in
2008. These authors disclosed that Lewis acids promote the condensation of C3-
unsubstituted indoles (90, R1:H) and methyl 2-acetamidoacrylate (91a) to afford Friedel–
Crafts alkylation products as racemates (Scheme 2.1.1). Interestingly, the regioselectivity
of addition to 91a strongly depends on the choice of Lewis acid; whereas hard, oxaphilic
Lewis acids such as EtAlCl2 afford tryptophan derivatives (94), softer, more azaphilic
Lewis acids such as Bi(OTf)3 result in reaction of the acrylate via the imine tautomer to
generate quaternary amides (93).

Scheme 2.1.2. Proposed mechanisms of 92 and 94 formation.

Mechanistically, Piersanti’s reaction to prepare tryptophan 94 is proposed to occur by
conjugate addition at C3 of the indole to generate transient enolate 96, followed by
rearomatization and protonation (Scheme 2.1.2). We envisioned that in the case of 3-
substituted indoles, the initial conjugate addition would still occur; however, instead of
rearomatization, enolate protonation and cyclization of the pendant amide nitrogen to the
transiently generated iminium ion 98 could provide the desired pyrroloindoline product
(92) in a single operation. The mechanism for the Friedel–Crafts alkylation has not been
Chapter 2–Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines

thoroughly investigated, but notably this reaction requires two equivalents of Lewis acid. By $^1$H NMR, Piersanti and coworkers found that subjection of methyl 2-acetamidoacrylate 91a to 1 equivalent of EtAlCl$_2$ resulted in broadening of signals from a vinyl proton and the amide proton and methyl substituents, whereas subjection to two equivalents resulted in complete broadening of the acrylate signals. These experiments suggest that the reaction is second-order in the Lewis acid and proceeds via doubly activated enolate 95.

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

2.2 DEVELOPMENT OF THE FORMAL CYCLOADDITION REACTION

2.2.1 Identification of an Effective Lewis Acid

Our studies began with the reaction between 3-methylindole (99) and methyl 2-acetamidoacrylate (91a). A screen of Lewis acids revealed that use of two equivalents EtAlCl$_2$ delivered the desired pyrroloindoline (100a) as the major product in 3:1 dr favoring the exo diastereomer, although the C2 Friedel–Crafts alkylation product (101) was also observed (Table 2.2.1, entry 2). Consistent with Piersanti and coworkers’ findings in the synthesis of tryptophan derivatives, no reaction occurred in the presence of stoichiometric EtAlCl$_2$ (entry 1); however, 1.0 equivalent of SnCl$_4$ was found to promote the reaction with comparable 6:1 selectivity for pyrroloindoline formation over
alkylation (entry 3). Fortunately, methylation of the indole nitrogen increased the regioselectivity for the pyrroloindoline product (entry 8). Attempted reactions with catalytic loadings identified that this reaction requires stoichiometric quantities of SnCl₄. Interestingly, the yield of pyrroloindoline is dramatically reduced using substoichiometric quantities of SnCl₄, with no product formed when 50 mol % is employed (entry 9).

Under our initially optimized conditions for this transformation, exposure of 1,3-dimethylindole (75) and methyl 2-acetamidoacrylate (91a) to 1.2 equivalents SnCl₄ in dichloroethane gave the desired pyrroloindoline 100b in 64% yield as a 6:1 mixture of exo and endo diastereomers (entry 10).

Table 2.2.1. Initial Lewis acid screen.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid (equiv)</th>
<th>Substrate</th>
<th>Temperature (°C)</th>
<th>Pyrroloindoline: C-2 alkylation</th>
<th>dr¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtAlCl₂ (1)</td>
<td>99</td>
<td>23</td>
<td>nr</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>EtAlCl₂ (2)</td>
<td>99</td>
<td>8</td>
<td>8:1</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>SnCl₄ (1)</td>
<td>99</td>
<td>23</td>
<td>6:1</td>
<td>9:1</td>
</tr>
<tr>
<td>4</td>
<td>MgClO₄ (1)</td>
<td>99</td>
<td>23</td>
<td>nr</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)₂ (2)</td>
<td>99</td>
<td>23</td>
<td>&gt;20:1</td>
<td>5:1</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)₂ (2)</td>
<td>99</td>
<td>23</td>
<td>decomposition</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>Zn(OTf)₂ (2)</td>
<td>99</td>
<td>23</td>
<td>nr</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>SnCl₄ (1)</td>
<td>75</td>
<td>23</td>
<td>&gt;20:1</td>
<td>11:1</td>
</tr>
<tr>
<td>9</td>
<td>SnCl₄ (0.5)</td>
<td>75</td>
<td>23</td>
<td>nr</td>
<td>--</td>
</tr>
<tr>
<td>10</td>
<td>SnCl₄ (1.2)</td>
<td>75</td>
<td>23</td>
<td>&gt;20:1 (64)¹</td>
<td>6:1</td>
</tr>
</tbody>
</table>

* Determined by analysis of the crude ¹H NMR with comparison to reported spectra. ¹ Complete conversion to 100b by crude ¹H NMR. ² Reaction run in DCE. ³ Isolated yield of 100b. nr: no reaction.

**2.2.2 Identification of Enantioselective Conditions and Optimization**

In light of our preliminary results with SnCl₄, we initiated studies targeting an asymmetric variant of the formal (3 + 2) cycloaddition reaction. A screen of a variety of
chiral ligands previously reported to be used in conjunction with SnCl$_4$ revealed that use of (R)-BINOL provides 100b in promising enantioselectivity. Thus, treatment of 1,3-dimethylindole (75) and methyl 2-acetamidoacrylate (91a) with a 1.1:1 mixture of (R)-BINOL and SnCl$_4$ provided pyrroloindoline 100b in 86% yield as a 4:1 mixture of diastereomers, with the exo diastereomer formed in 64% ee (Table 2.2.2, entry 2).

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

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

$^a$ 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.

Somewhat surprisingly, side-by-side reactions of 1,3-dimethylindole (75) and methyl 2-acetamidoacrylate (91a) combined in the presence and absence of stoichiometric BINOL, under otherwise identical conditions, revealed that BINOL accelerates the rate of the reaction and provides 100b in improved yield.$^5$ Based on these observations, it was hypothesized that similar enantioselectivities might be accessible using only catalytic quantities of (R)-BINOL. Gratifyingly, treatment of 1,3-dimethylindole (75) and methyl 2-acetamidoacrylate (91a) with 1.2 equivalents SnCl$_4$ and 20 mol % (R)-BINOL furnished the desired pyrroloindoline 100b in 94% yield as a 5:1 mixture of diastereomers, favoring the exo diastereomer in 63% ee (Table 2.2.2, entry 4).
Remarkably, moderate levels of enantioselectivity are observed even when the reaction is conducted with 5 mol % (R)-BINOL (entry 6).

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

\textit{Table 2.2.3. Enantioselectivity optimization studies.}

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

\textsuperscript{a}Isolated yield of combined diastereomers. \textsuperscript{b}Determined by \textit{1}H NMR analysis of crude reaction mixture. \textsuperscript{c}Determined by chiral stationary phase SFC or HPLC. \textsuperscript{d}ee of \textit{exo}/\textit{endo} diastereomers. \textsuperscript{e}1.0 equiv of SnCl\textsubscript{4} and 1.1 equiv (R)-BINOL was used. \textsuperscript{f}Approximate conversion to 100b based on ratio with acrylate in crude \textit{1}H NMR. nd= not determined.

More promising effects were found by varying acrylate substitution. Utilization of methyl 2-trifluoroacetamidoacrylate (91b) and benzyl 2-acetamidoacrylate (91c) provided pyrroloindoline products 100c and 100d in enhanced enantioselectivities, with
Chapter 2–Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines

the *exo* diastereomers formed in 86% and 74% ee, respectively (Table 2.2.3, entries 6-7).

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

With these optimized reaction conditions in hand, we reevaluated the parameters of the formal (3 + 2) cycloaddition reaction and confirmed that a Lewis acid is required for the transformation; exposure of 1,3-dimethylindole (75) and 91d to Brønsted acids, including (*R*)-BINOL, HCl, and Ph$_2$PO$_2$H (Table 2.2.4, entries 1-3) gave no reaction. Several water and acid scavenging additives were also screened but no significant change in enantioselectivity was observed in their presence (entries 4, 5 and 7).

**Table 2.2.4. Additive screen.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv)</th>
<th>Time (h)</th>
<th>Yield (%)$^a$</th>
<th>dr$^b$</th>
<th>ee (%)$^{c,d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>HCl (1.2)$^e$</td>
<td>4</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Ph$_2$PO$_2$H (1.2)$^f$</td>
<td>7</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4$^g$</td>
<td>molecular sieves</td>
<td>4</td>
<td>70</td>
<td>4:1</td>
<td>93:89</td>
</tr>
<tr>
<td>5$^g$</td>
<td>MgO (1)</td>
<td>4.5</td>
<td>72</td>
<td>4:1</td>
<td>93:91</td>
</tr>
<tr>
<td>6</td>
<td>2,6-lutidine (1)</td>
<td>5</td>
<td>6</td>
<td>53</td>
<td>6:1</td>
</tr>
<tr>
<td>7</td>
<td>2,6-lutidine (0.2)</td>
<td>5</td>
<td>53</td>
<td>6:1</td>
<td>94:89</td>
</tr>
</tbody>
</table>

$^a$ 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.

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

Table 2.2.5. Screen of chiral diols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diol (equiv)</th>
<th>R¹, R²</th>
<th>Product</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>102a (1.1)</td>
<td>Me, Me (91a)</td>
<td>100b</td>
<td>4:1</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>102b (1.1)</td>
<td>Me, Me (91a)</td>
<td>100b</td>
<td>3:1</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>102c (1.1)</td>
<td>Me, Me (91a)</td>
<td>100b</td>
<td>6:1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>102d (1.1)</td>
<td>Me, Me (91a)</td>
<td>100b</td>
<td>&gt;10:1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>102e (1.1)</td>
<td>Me, Me (91a)</td>
<td>100b</td>
<td>7:1</td>
<td>0</td>
</tr>
<tr>
<td>6⁴</td>
<td>102a (0.2)</td>
<td>CF₃, Me (91b)</td>
<td>100c</td>
<td>6:1</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>102f (0.2)</td>
<td>CF₃, Me (91b)</td>
<td>100c</td>
<td>8:1</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>13 (0.2)</td>
<td>CF₃, Me (91b)</td>
<td>100c</td>
<td>10:1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>14 (0.2)</td>
<td>CF₃, Me (91b)</td>
<td>100c</td>
<td>8:1</td>
<td>46</td>
</tr>
</tbody>
</table>

⁴ Determined by ¹H NMR analysis of crude reaction mixture. ⁵ Determined by chiral stationary phase SFC or HPLC. ⁶ ee of exo diastereomer. ⁷ Reaction run with 1.2 equiv SnCl₄.

Figure 2.2.1. Chiral diols.
### 2.2.3 Substrate Scope of Pyrroloindoline Synthesis

Scheme 2.2.1. Substrate scope.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>Diastereoselectivity</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>106a</td>
<td>93%</td>
<td>3:1</td>
<td>93/92</td>
</tr>
<tr>
<td>106b</td>
<td>61%</td>
<td>3:1</td>
<td>93/90</td>
</tr>
<tr>
<td>106c</td>
<td>84%</td>
<td>5:1</td>
<td>94/91</td>
</tr>
<tr>
<td>106d</td>
<td>51%</td>
<td>3:1</td>
<td>87/85</td>
</tr>
<tr>
<td>106e</td>
<td>91%</td>
<td>4:1</td>
<td>94/90</td>
</tr>
<tr>
<td>106f</td>
<td>54%</td>
<td>6:1</td>
<td>92/90</td>
</tr>
<tr>
<td>106g</td>
<td>65%</td>
<td>&gt;18:1</td>
<td>86</td>
</tr>
<tr>
<td>106h</td>
<td>80%</td>
<td>4:1</td>
<td>92/90</td>
</tr>
<tr>
<td>106i</td>
<td>90%</td>
<td>3:1</td>
<td>93/90</td>
</tr>
<tr>
<td>106j</td>
<td>18%</td>
<td>8:1</td>
<td>95</td>
</tr>
</tbody>
</table>

* Determined by $^1$H NMR analysis of mixture. \(^{b}\) Determined by chiral SFC or HPLC analysis. \(^{c}\) 1.6 equiv SnCl$_4$ was employed.

The enantioselective formal (3 + 2) cycloaddition with benzyl 2-trifluoroacetamidoacrylate (91d) is general for a range of indole substrates. Indoles substituted at C5 with either electron-donating or electron-withdrawing groups are tolerated in this reaction, although electron-poor indoles react at a slower rate (Scheme 2.2.1, 106a-e). Indoles substituted at C3 with functionalized alkyl groups reacted in moderate to good yields with high enantioselectivity (106f and 106h). Notably, the reaction of N-methyltetrahydrocarbazole proceeded with >18:1 diastereoselectivity, delivering the exo diastereomer 106g in 86% ee. In a single step, this reaction generates the aza-propellane core of the natural products minfiensine,\(^7\) echitamine,\(^8\) and vincorine.\(^9\) Consistent with our preliminary findings, N-alkylation is important to the reactivity;
subjection of 3-methylindole to identical conditions provided pyrroloindoline 106j in only 18% yield albeit with excellent enantioselectivity. However, N-allyl-3-methylindole (105i) was successfully employed as a substrate to afford pyrroloindoline 106i. The combination of Pd(PPh$_3$)$_4$ and N,N-dimethylbarbituric acid have been shown to smoothly convert related methyl ester 107 to the deallylated product 108 (Scheme 2.2.2); this finding is particularly useful in the context of total synthesis as many pyrroloindoline natural products do not bear substitution on nitrogen.

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

Although many substrates are well-tolerated in the formal (3 + 2) cycloaddition reaction, this transformation proved challenging for more sterically encumbered substrates. 3a-Indolylpyrroloindolines constitute a large number of pyrroloindoline natural products and thus, we were also very interested in accessing arylpyrroloindolines using the formal (3 + 2) cycloaddition methodology. However, subjection of 1-methyl-3-phenylindole (109) to our standard conditions with methyl 2-trifluoroacetamidoacrylate (91b) resulted in no reaction whereas exposure to methyl 2-acetamidoacrylate (91a) gave low conversion to the corresponding C2-alkylation product (Scheme 2.2.3). Clean conversion to C2-alkylation product 112 has also been observed for 3-phenylindole (111) in the presence of EtAlCl$_2$.

Alternatively, we also envisioned a two-step approach to generate indolylpyrroloindolines through initial formation of 3a-alkynylpyrroloindolines and a
subsequent Larock annulation; however, subjection of 1-methyl-3-ethynylindole (113) and 91a to SnCl₄ gave decomposition and subjection of 1-methyl-3-(phenylethynyl)indole (115) and 91a to SnCl₄ resulted in dimerization of the indole, even when 115 was added slowly to the reaction mixture over 2 hours.

Scheme 2.2.3. Unsuccessful approaches to arylpyrroloindolines.

In a final effort to access arylpyrroloindolines, we employed 1,3-dimethyl-3-phenylindole (117) as the substrate to ensure complete selectivity for pyrroloindoline formation by prohibiting Friedel–Crafts alkylation. Although exposure of 117 and 91a to standard conditions gave only trace conversion to phenylpyrroloindoline 118 (Table 2.2.6, entry 1), addition of 0.20 equiv MeOH cleanly afforded 118 in 40% yield as a single diastereomer in 91% ee (entry 4). Unfortunately, prolonged reaction times and
increased SnCl₄ loading did not substantially improve yield (entries 5 and 7) and inconsistent ees varying from 84 – 91% were obtained for the reaction (entries 4-6).

Table 2.2.6. Methanol-promoted synthesis of phenylpyrroloindoline 118.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale (mmol)</th>
<th>MeOH (equiv)</th>
<th>Concentration (M)</th>
<th>Time (h)</th>
<th>117:118a</th>
<th>Yieldb (%)</th>
<th>dra</th>
<th>ee (%)c,d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.15</td>
<td>--</td>
<td>0.12</td>
<td>13</td>
<td>17:1</td>
<td>nd</td>
<td>nd</td>
<td>--</td>
</tr>
<tr>
<td>2a</td>
<td>0.15</td>
<td>0.2'</td>
<td>0.12</td>
<td>13</td>
<td>2:1</td>
<td>nd</td>
<td>&gt;20:1</td>
<td>--</td>
</tr>
<tr>
<td>3a</td>
<td>0.15</td>
<td>1.0'</td>
<td>0.12</td>
<td>13</td>
<td>&gt;20:1</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>0.20</td>
<td>0.209</td>
<td>0.11</td>
<td>12.5</td>
<td>nd</td>
<td>40</td>
<td>&gt;20:1</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>0.20</td>
<td>0.209</td>
<td>0.11</td>
<td>64</td>
<td>nd</td>
<td>47</td>
<td>&gt;20:1</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>0.19</td>
<td>0.209</td>
<td>0.11</td>
<td>12</td>
<td>1:2</td>
<td>38</td>
<td>&gt;20:1</td>
<td>84</td>
</tr>
<tr>
<td>7h</td>
<td>0.19</td>
<td>0.209</td>
<td>0.11</td>
<td>12</td>
<td>1:2</td>
<td>45</td>
<td>&gt;20:1</td>
<td>81</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR analysis of the crude reaction mixture. b Isolated yield. c Determined by chiral SFC analysis. d ee of exo diastereomer. e Reaction conducted with (R/S)-BINOL. f neat MeOH was added to the reaction. g MeOH was added from a stock solution in DCM. h Reaction run with 1.6 equiv SnCl₄. nd: not determined.

Scheme 2.2.4. Subjection of 2-trimethylsilylindole 119 to cycloaddition conditions.

When we first discovered this transformation, no other direct enantioselective approaches to arylpyrroloindolines had been reported. Most natural products are unsubstituted at C2a and thus, we elected to pursue this transformation using 2-(trimethylsilyl)indole 119, which could undergo desilylation in a second step following cycloaddition to generate C2-unsubstituted pyrroloindolines; however, we found that protodesilylation occurs readily in the presence of SnCl₄ to give 1-methyl-2-phenylnindole.
(109, Scheme 2.2.4). At this point, no further work is being conducted to extend this pyrroloindoline methodology to sterically encumbered substrates. However, these challenges ultimately provided inspiration for the development of a second approach to pyrroloindolines within our laboratory involving the Cu-catalyzed arylation of tryptamine\textsuperscript{11} and tryptophan derivatives\textsuperscript{12} using aryl iodonium salts.

### 2.3 MECHANISTIC CONSIDERATIONS

Scheme 2.3.1. Epimerization studies.

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

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

Scheme 2.3.2. Proposed mechanism for stereoselective cycloaddition reaction.

Current efforts are focused on understanding the mechanism of BINOL•SnCl$_4$ catalyzed pyrroloindoline formation. However, one possible scenario consistent with the experimental data is shown in Scheme 2.3.2. In this mechanism, it is proposed that SnCl$_4$-promoted conjugate addition of the indole to the acrylate proceeds reversibly to afford a
racemic mixture of enolates 121 and ent-121. In the second step, an irreversible, highly face-selective, catalyst controlled protonation would serve to resolve the two enantiomers into diastereomeric iminium ions exo-122 and endo-122. In this mechanistic hypothesis, the diastereoselectivity depends on the relative rates of protonation of 121 and ent-121. Subsequent catalyst turnover by deprotonation of the amide followed by cyclization upon workup would deliver exo-100e and endo-100e.

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

2.4 CONCLUDING REMARKS

In summary, we have established a unique strategy for the direct prepararation of enantioenriched pyrroloindolines by an (R)-BINOL•SnCl₄-catalyzed formal (3 + 2)
cycloaddition reaction. The transformation requires an equivalent of SnCl₄ but addition of (R)-BINOL creates such a large rate acceleration that the reaction can be completed with catalytic loadings of BINOL in excellent enantioselectivity. The method allows access to a variety of pyrroloindolines including new structural motifs such as aza-propellanes (106g). Although the reaction proceeds poorly with more sterically encumbered substrates, we have found that additional of catalytic MeOH greatly improves reactivity and enables access to phenylpyrroloindoline product 118.

The formal (3 + 2) cycloaddition reaction has been exploited both in the development of new methodology and in total synthesis. Mechanistic studies of this reaction showed that the reaction occurs via a highly face-selective catalyst-controlled protonation and that cyclization of the resultant iminium intermediate only occurs upon work-up; these observations have respectively led to the development of a tandem conjugate addition/enantioselective protonation reaction (Chapter 3) and to the generation of indoline products by in situ iminium reduction. §, 15 In addition, synthetic efforts using this reaction have culminated in the efficient total syntheses of two diketopiperazine-containing pyrroloindoline natural products lansai B 16 and nocardioazine A. 17, ** Further related research within the Reisman laboratory is focused on improving mechanistic understanding of the formal (3 + 2) cycloaddition reaction, application of the asymmetric protonation strategy to new methodology, and the synthesis of pyrroloindoline alkaloid natural products.

§ This transformation was developed by Jane Ni, a graduate student in the Reisman lab.
** Research directed toward these natural products has been conducted by Haoxuan Wang, a graduate student in the Reisman lab.
2.5  EXPERIMENTAL SECTION

2.5.1  Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, toluene, and hexanes were dried by passing through activated alumina columns. Dimethylformamide was dried over activated molecular sieves, dichloroethane was distilled over calcium hydride. Deuterated methylene chloride (CD$_2$Cl$_2$) for the experiments resubjecting the pyrroloindoline products to reaction conditions was dried by passing through a plug of activated alumina. All other commercially obtained reagents were used as received unless specifically indicated. EtAlCl$_2$ (neat) and 1 M SnCl$_4$ in DCM were purchased from Aldrich and (R)-BINOL was obtained from Alfa Aesar. (R)-6,6’-dibromo-BINOL (102f), (R)-2’-methoxy-[1,1’-binaphthalen]-2-ol (102b), TADDOL (103), 3-phenylindole (111), and 1-methyl-3-phenylindole (109) were prepared according to literature procedures. 1-methyl-3-(phenylethynyl)indole (115), (R)-3,3’-dianthryl-BINOL (102e), (R)-3,3’-dimesityl-BINOL (102c) and (R)-3,3’-di(triphenylsilyl)-BINOL (102d) are known and were prepared by procedures adapted from the literature. Reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, p-anisaldehyde, or KMnO$_4$ staining. Flash column chromatography was performed either as described by Still et al. 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. $^1$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, $\delta =$ 7.26, $^{13}$C, $\delta =$ 77.0). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ 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.
2.5.2 Substrate Synthesis

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

Procedure was adapted from Jørgensen et al. To a 50 mL Schlenk tube was added [Pd_{2}db_{3}], dppf, NaO\textsubscript{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 3x with ethyl acetate. The combined organic layers were washed with brine, dried (MgSO\textsubscript{4}), filtered and
concentrated under reduced pressure. The crude residue was purified by flash chromatography.

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

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

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

Prepared from 1.07 mmol of 5-fluoro-3-methyl-1H-indole using general procedure B. The product was purified by flash chromatography (3% ethyl acetate/hexanes) to yield 105b (0.97 g, 55% yield) as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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-1H-indole (128c).

Prepared from 2.88 mmol of 2-bromo-1-iodo-4-methylbenzene,$^{29}$ 2.5 mol % [Pd$_2$dba$_3$] and 10 mol % dppf using general procedure A. The product was purified by flash chromatography (5→13% ethyl acetate/hexanes) to yield 3,5-dimethyl-1H-indole (128c, 0.11 g, 14% yield). Spectral data matches that reported in the literature.$^{28}$
1,3,5-trimethyl-1H-indole (105c).

Prepared from 0.70 mmol of 3,5-dimethyl-1H-indole using general procedure B. The product was purified by flash chromatography (2% ethyl acetate/hexanes) to yield **105c** (0.048 g, 43% yield) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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-1H-indole (105d).

Prepared from 0.95 mmol of 5-bromo-3-methyl-1H-indole$^{30}$ using general procedure B. The product was purified by flash chromatography (5% ethyl acetate/hexanes) to yield **105d** (0.20 g, 90% yield) as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 (129).

Procedure was adapted from Sørensen and Pombo-Villar.$^{31}$ To a solution of 2-bromo-5-methylaniline (10.8 mmol, 1.0 equiv) in 29 mL THF at $-78^\circ$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 \(-78 \, ^{\circ}C\) for 10 minutes, then at room temperature for 5 hours. Then saturated NaHCO\(_3\) (aq) solution was added, and the aqueous layer was extracted with ethyl acetate 3x. The combined organic layers were dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0\(\rightarrow\)10% ethyl acetate/hexanes) to yield \(N\)-allyl-2-bromo-5-methylaniline (129, 1.63 g, 67% yield) as a yellow oil. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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 (128e).

Procedure was adapted from Sørensen and Pombo-Villar.\(^{31}\) A solution of \(N\)-allyl-2-bromo-5-methylaniline (129, 1.6 mmol, 1.0 equiv), Pd(OAc)\(_2\) (0.16 mmol, 0.1 equiv), dppp (0.16 mmol, 0.1 equiv), Bu\(_4\)NCl (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 16h. The reaction was cooled to room temperature, saturated NaHCO\(_3\) (aq) solution and 100 mL water were added, and the aqueous layer was extracted with ethyl acetate 3x. The combined organic layers were dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5\(\rightarrow\)10% ethyl acetate/hexanes) to yield 3,6-dimethyl-1\(H\)-indole (128e, 0.19 g, 85% yield) as a white powder. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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-1H-indole (105e).

Prepared from 0.70 mmol of 3,6-dimethyl-1H-indole (128e) using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 105e (62 mg, 56% yield) as a yellow oil. $^1$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-1H-indole (105f).

Prepared from 2.66 mmol of 3-t-butyldimethylsiloxyethyl-1H-indole$^{12}$ using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 105f (0.67 g, 87% yield) as an orange oil. $^1$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):
To a solution of 1-Boc-3-(trimethylsilylethynyl)indole\textsuperscript{33} (130, 290 mg, 0.930 mmol, 1.00 equiv) in 4.6 mL THF cooled to 0 °C in an ice bath was added LAH (2 M in THF, 1.1 mL, 2.2 mmol, 2.4 equiv). After 2 h stirring at 0 °C, the reaction mixture was subjected to a standard Fieser workup. The crude residue was then dried under hi-vacuum, then redissolved in 4.6 mL THF. NaH (60 wt % dispersion in oil, 56 mg, 1.4 mmol, 1.5 equiv) was then added and the reaction was then cooled to 0 °C in an ice bath, followed by addition of MeI (116 µL, 1.86 mmol, 2.00 equiv). The reaction mixture was then allowed to warm to room temperature and stirred for 3 hours, then cooled to 0 °C. MeOH was added to quench the reaction, followed by dilution with H\textsubscript{2}O, and extraction with DCM (3 x). The combined organic layers were then dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The crude oil was subjected to silica gel column chromatography (0:100 to 5:95 EtOAc:hexanes) to yield 23.1 mg (16% yield containing impurities) of 1-methyl-3-ethynylindole (113) and 47.8 mg (23% yield) of a compound that is likely 1-methyl-3-((trimethylsilyl)ethynyl)indole. The \textsuperscript{1}H NMR shifts observed for 113 vary slightly from the literature\textsuperscript{34} and are thus listed herein. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.76 – 7.72 (m, 1H), 7.33 – 7.23 (m, 3H), 7.20 (ddd, J = 8.0, 6.4, 1.8 Hz, 1H), 3.75 (s, 3H), 3.21 (s, 1H).
2-methyl-3-phenylindole (133). 

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

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

A solution of 3-phenyl-2-(trimethylsilyl)indole\textsuperscript{36} (134, 228 mg, 0.859 mmol, 1.00 equiv) in 20 mL THF was cooled to 0 \(^\circ\)C in an ice bath under argon, followed by addition of NaH (60 wt \% dispersion in oil, 41 mg, 1.7 mmol, 2.0 equiv). After stirring 15 minutes at 0 \(^\circ\)C, MeI (107 \(\mu\)L, 1.72 mmol, 2.00 equiv) was added and the reaction was allowed to warm to room temperature. After stirring 20 hours at room temperature, the reaction mixture was cooled to 0 \(^\circ\)C and quenched with saturated aqueous NH\(_4\)Cl then diluted with Et\(_2\)O. The organic layer was washed (saturated aqueous NaHCO\(_3\) then brine), dried
(Na$_2$SO$_4$), filtered, and concentrated. The crude residue was purified by column chromatography to yield 63 mg (26% yield) of 1-methyl-3-phenyl-2-(trimethylsilyl)indole (119). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.47 - 7.35 (m, 7H), 7.30 (ddd, $J$ = 8.2, 6.8, 1.2 Hz, 1H), 7.10 (ddd, $J$ = 7.9, 6.8, 1.1 Hz, 1H), 3.94 (s, 3H), 0.22 (s, 9H).

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

To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (R)-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of 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$_2$O. 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$_2$SO$_4$), filtered and concentrated. The crude residue was purified by flash chromatography.
Pyrroloindoline Products under General Procedure C

Pyrroloindoline 100b.

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

Exo diastereomer: pale yellow oil. tᵣ(major) = 9.5 min tᵣ(minor) = 6.2 min. ¹H NMR (400 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 7.10 – 7.01 (m, 1H), 6.95 (d, J = 7.3 Hz, 0.5H), 6.91 (d, J = 7.3 Hz, 0.5H), 6.68 (t, J = 7.4 Hz, 0.5H), 6.62 (t, J = 7.4 Hz, 0.5H), 6.43 (d, J = 7.8 Hz, 0.5H), 6.38 (d, J=7.8 Hz, 0.5H), 5.47 (s, 0.5H), 5.04 (s, 0.5H), 4.43 (dd, J = 10.0, 1.9 Hz, 0.5H), 4.30 (dd, J = 9.7, 4.7 Hz, 0.5H), 3.73 (s, 1.5H), 3.66 (s, 1.5H), 2.98 (s, 1.5H), 2.80 (s, 1.5H), 2.44 (dd, J = 13.4, 10.0 Hz, 0.5H), 2.32 (dd, J = 13.3, 9.8 Hz, 0.5H), 2.22 (s, 0.5H), 2.18 (dd, J = 13.5, 2.0 Hz, 0.5H), 1.97 – 1.90 (m, 2H), 1.46 (s, 1.5H), 1.32 (s, 1.5H); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 172.8, 171.7, 171.5, 169.4, 149.4, 148.5, 134.2, 128.04, 128.02, 121.0, 120.8, 118.6, 117.6, 107.7, 107.1, 91.8, 90.8, 60.5, 59.6, 52.2, 51.8, 51.6, 49.2, 43.4, 41.0, 35.9, 33.8, 22.5, 22.3, 21.9; IR (NaCl/thin film): 2954, 2877,
1746, 1660, 1608, 1489, 1393, 1299, 1200, 1178, 744 cm\(^{-1}\); \([\alpha]_D^{25}= -69.7^\circ\) (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. \(^1\)H NMR (400 MHz, CDCl\(_3\); compound exists as a 3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) \(\delta\) 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 §) \(\delta\) 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\(^{-1}\); \([\alpha]_D^{25}= +146.5^\circ\) (c = 0.79, DCM); HRMS (FAB+) calc’d for [M+H]\(^+\) 289.1552, found 289.1549.
Pyrroloindoline 100c.

Prepared from 1,3-dimethyl-1H-indole 75 and methyl 2-trifluoroacetamidoacrylate\(^3\)\(^9\) 91b using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (20\(\rightarrow\)35% ethyl acetate/hexanes) to yield 53.0 mg (77% yield) of 100c 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\(\rightarrow\)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\(_2\), \(\lambda = 254\) 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 §) \(\delta\) 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 §) \(\delta\) 172.6*, 170.5§, 159.2* (q, \(J_{C-F} = 37.2\) Hz), 149.4*, 149.2§, 134.2*§, 128.8*§, 121.5*§, 119.9§,
118.7*, 116.1* (q, $J_{CF} = 288.4$ 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; $[\alpha]_D^{25} = –118.1^\circ$ (c = 0.78, DCM). HRMS (ESI) calc’d for [M+H]$^+$ 343.1270, found 343.1267.

_Endo diastereomer:_ pale yellow oil. $^1$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 7.13 (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, $J_{CF} = 36.9$ Hz), 150.4*, 148.5, 133.0, 131.8*, 129.1*, 128.7*, 122.5*, 121.6, 118.6, 117.8*, 116.1* (q, $J_{CF} = 288.7$ 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$^{-1}$; $[\alpha]_D^{25} = +201.5^\circ$ (c = 0.11, DCM). HRMS (ESI) calc’d for [M+H]$^+$ 343.1270, found 343.1278.
Pyrroloindoline 100d.

Prepared from 1,3-dimethyl-1H-indole 75 and benzyl 2-acetamidoacrylate\(^\text{40}\) 91c using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The product 100d was formed in a 2:1 ratio of diastereomers (determined by \(^1\)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 \textit{exo} diastereomer and 17.3 mg (24% yield) of the \textit{endo} diastereomer.

\textit{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\(_2\), \(\lambda = 254\) 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 §) \(\delta\) 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 §) \(\delta\) 172.6*, 172.0§, 171.6*, 170.0§, 149.9*, 148.9§, 135.7*, 134.9*, 134.7*, 134.6§, 128.8§, 128.7*, 128.7*, 128.5§, 128.5*, 128.2*, 128.2§, 121.5§, 121.2*, 119.1§, 118.1*, 108.1§, 107.7*, 92.4§, 91.4*, 67.6*, 66.9§, 61.1*, 60.2§, 52.3§,
49.7*, 43.8*, 41.4§, 36.5*, 34.3§, 23.0§, 22.7*, 22.7*, 22.4§; IR (NaCl/thin film): 3032, 2962, 2877, 1745, 1661, 1609, 1489, 1390, 1175, 1117, 744 cm⁻¹; [α]D²⁵ = −66.9° (c = 0.98, DCM). HRMS (ESI) calc’d for [M+H]⁺ 365.1865, found 365.1875.

**Endo diastereomer:** pale yellow oil. The enantiomeric excess was determined to be 82% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO₂, λ = 254 nm): $t_R$(major) = 11.1 min $t_R$(minor) = 12.6 min. $^1$H NMR (500 MHz, CDCl₃; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.36 – 7.28 (m, 3H*, 3H§), 7.23 – 7.20 (m, 2H§), 7.19 – 7.15 (m, 2H*), 7.12 (td, $J$ = 7.7, 1.3 Hz, 1H§), 7.08 (td, $J$ = 7.7, 1.3 Hz, 1H*), 7.01 (dd, $J$ = 7.3, 0.9 Hz, 1H§), 6.98 (dd, $J$ = 7.3, 0.9 Hz, 1H*), 6.69 (td, $J$ = 7.4, 0.9 Hz, 1H§), 6.64 (td, $J$ = 7.4, 0.9 Hz, 1H*), 6.36 (d, $J$ = 7.8 Hz, 1H§), 6.28 (d, $J$ = 7.8 Hz, 1H*), 5.56 (s, 1H*), 5.09 (s, 1H§), 5.05 (dd, $J$ = 9.0, 6.0 Hz, 1H§), 4.92 (d, $J$ = 12.4 Hz, 1H*), 4.88 (d, $J$ = 12.4 Hz, 1H§), 4.69 (d, $J$ = 12.2 Hz, 1H*), 4.55 (d, $J$ = 12.2 Hz, 1H*), 4.51 (dd, $J$ = 8.5, 1.9 Hz, 1H*), 2.93 (s, 3H*), 2.81 (s, 3H§), 2.73 (dd, $J$ = 12.8, 1.8 Hz, 1H*), 2.37 (dd, $J$ = 13.0, 6.0 Hz, 1H§), 2.33 (dd, $J$ = 12.8, 8.5 Hz, 1H*), 2.31 (s, 3H§), 2.26 (dd, $J$ = 13.0, 9.0 Hz, 1H§), 2.05 (s, 3H*), 1.42 (s, 3H§), 1.41 (s, 3H*); $^{13}$C NMR (125 MHz, CDCl₃; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 170.8*, 170.5*, 169.6§, 150.4*, 148.9§, 135.5§, 134.9*, 133.1§, 132.5*, 128.8*, 128.6§, 128.5*, 128.4§, 128.4*, 128.2*, 128.1§, 128.0§, 122.4*, 121.8§, 118.0§, 117.2*, 106.5§, 105.7*, 91.3*, 86.5*, 67.3*, 66.7§, 61.3*, 59.3§, 52.3§, 50.8*, 42.6*, 41.8§, 32.3*, 31.6§, 24.8*, 22.7§, 22.5*, 21.9§; IR (NaCl/thin film): 2956, 1741, 1656, 1608, 1493, 1404, 1301, 1219, 1194, 1152, 1105, 992, 743 cm⁻¹; [α]D²⁵ = +114.4° (c = 0.57, DCM). HRMS (ESI) calc’d for [M+H]⁺ 365.1865, found 365.1862.
Chapter 2 – Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines

Pyrroloindoline 100e. Prepared from 1,3-dimethyl-1H-indole (75, 0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate\(^{(1)}\) (91d, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→8% ethyl acetate/hexanes) to yield 54 mg (86% yield) of 100e in a 4:1 ratio of diastereomers (determined by NMR analysis of the crude reaction mixture). The diastereomers were separated by flash chromatography (5→8% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO\(_2\), \(\lambda = 254 \text{ nm}\)).

**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 §) \(\delta\) 7.53–7.36 (m, 5H*, 5H§), 7.23 (br t, \(J = 7.6 \text{ Hz}, 1\text{H}^*, 1\text{H}§\)), 7.11 (br d, \(J = 6.7 \text{ Hz}, 1\text{H}§\)), 7.07 (br d, \(J = 7.2 \text{ Hz}, 1\text{H}*\)), 6.93 – 6.86 (m, 1H§), 6.83 (br t, \(J = 7.3 \text{ Hz}, 1\text{H}*\)), 6.64 (br d, \(J = 7.3 \text{ Hz}, 1\text{H}§\)), 6.57 (br d, \(J = 7.8 \text{ Hz}, 1\text{H}^*\)), 5.69 (s, 1H*), 5.42 (s, 1H§), 5.36 – 5.21 (m, 2H*, 2H§), 4.82 (br d, \(J = 9.2 \text{ Hz}, 1\text{H}^*\)), 4.57 (m, 1H§), 3.14 (br s, 3H§), 2.94 (br s, 3H§), 2.60 (br dd, \(J = 13.3, 9.7 \text{ Hz}, 1\text{H}^*\)), 2.60 – 2.52 (m, 1H§), 2.41 (br d, \(J = 14.7 \text{ Hz}, 1\text{H}*\)), 2.12 (br dd, \(J = 12.7, 6.0 \text{ Hz}, 1\text{H}§\)), 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 §) \(\delta\) 171.9*, 169.6§, 158.9 (q, \(J_{C,F} = 37.0 \text{ Hz})^*, 157.3 (q, \(J_{C,F} = 38.1 \text{ Hz})^§, 149.2*, 149.0§, 135.1§, 134.5*, 134.2*, 134.0§, 128.6*, 128.6*, 128.5*, 128.4§, 128.2§, 128.1§, 121.3*, 119.8§, 188.5*, 116.0 (q, \(J_{C,F} =
Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 91%. $t_H$(major) = 5.8 min $t_H$(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, $J_{C-F} = 36.7$ 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, $J_{C-F} = 3.1$ 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 106a.

Prepared from 5-methoxy-1,3-dimethyl-1H-indole and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 83.1 mg (93% yield) of 106a in a 3:1 ratio of diastereomers (determined by HPLC analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 10% IPA in hexanes, $\lambda = 254$ nm).

**Exo diastereomer:** pale yellow oil. The enantiomeric excess was determined to be 93%. $t_R$(major) = 11.3 min $t_R$(minor) = 9.9 min. $^1$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 §) $\delta$ 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*, 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 §) $\delta$ 172.0*, 169.9§, 159.0* (q, $J_{C,H} = 36.8$ Hz), 154.7§, 153.6*, 143.7*§, 135.8§, 135.8*, 135.2§, 134.6*, 128.8§, 128.8*, 128.7*, 128.6§, 128.4§, 128.3*, 116.1* (q, $J_{C,F} = 288.6$ Hz), 113.4§, 113.1*, 111.5*, 109.0*, 108.8§, 94.2*, 92.4§, 68.1*, 67.3§, 61.2§, 60.4*, 55.9*, 53.6§, 49.3§, 43.8*, 39.9§, 38.1*,
36.9\(^{\circ}\), 23.5\(^{\circ}\), 23.4\(^{\circ}\); IR (NaCl/thin film): 2963, 2833, 1748, 1694, 1497, 1432, 1156, 1030, 991, 754 cm\(^{-1}\); \([\alpha]_D^{25} = -78.1^{\circ} \) (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 §) \(\delta\) 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 §) \(\delta\) 169.4§, 169.1*, 156.9* (q, \(J_{C,F} = 36.7\) Hz), 153.4§, 152.8*, 144.7*, 142.7§, 135.3§, 134.7*, 134.5§, 133.2*, 128.5*, 128.4*, 128.3*, 128.3§, 128.1§, 116.2* (q, \(J_{C,F} = 288.8\) Hz), 113.5*, 112.8§, 110.0*, 109.4§, 107.7§, 106.4*, 91.6§, 89.4*, 67.7*, 67.2§, 60.5§, 60.2*, 56.0*, 56.9§, 52.2§, 50.6*, 42.8*, 40.8§, 32.6*, 32.0§, 25.1*, 22.2§; IR (NaCl/thin film): 2957, 1750, 1697, 1500, 1446, 1282, 1210, 1157, 1031, 994, 850 cm\(^{-1}\); \([\alpha]_D^{25} = +162.4^{\circ} \) (c 1.41, DCM); HRMS (ESI) calc’d for [M+H]\(^{+}\) 449.1683, found 449.1682.
Prepared from 5-fluoro-1,3-dimethyl-1H-indole 105b and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→12% ethyl acetate/hexanes) to yield 53.0 mg (61% yield) of 106b in a 3:1 ratio of diastereomers (determined by $^1$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, $\lambda = 254$ 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, $J_{C-F} = 37.1$ Hz), 157.0* (d, $J_{C-F} = 236.5$ Hz), 145.6*, 145.4§, 135.7* (d, $J_{C-F} = 7.3$ Hz), 135.1§, 134.6*, 128.9*, 128.8*, 128.7*, 128.6§, 128.5§, 128.4§, 116.2* (q, $J_{C-F} = 267.0$ Hz), 114.9§, 114.7* (d, $J_{C-F} = 23.0$ Hz), 110.5§, 109.3* (d, $J_{C-F} = 24.3$ Hz), 108.6* (d, $J_{C-F} = 7.8$ Hz), 93.9*, 93.0*
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. $^1$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 $^\dagger$) δ 7.37 – 7.30 (m, 3H*, 3H$^\dagger$), 7.24 – 7.20 (m, 2H$^\dagger$), 7.18 – 7.12 (m, 2H*), 6.83 – 6.74 (m, 1H*, 2H$^\dagger$), 6.71 (dd, $J = 8.0$, 2.6 Hz, 1H*), 6.23 (dd, $J = 8.5$, 4.0 Hz, 1H$^\dagger$), 6.14 (dd, $J = 8.5$, 4.0 Hz, 1H*), 5.60 (s, 1H*), 5.29 (d, $J = 1.7$ Hz, 1H$^\dagger$), 5.14 (dd, $J = 9.6$, 5.0 Hz, 1H$^\dagger$), 5.06 (d, $J = 12.2$ Hz, 1H$^\dagger$), 4.97 (d, $J = 12.2$ Hz, 1H$^\dagger$), 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$^\dagger$), 2.45 (dd, $J = 13.3$, 5.0 Hz, 1H$^\dagger$), 2.37 (dd, $J = 13.1$, 8.5 Hz, 1H*), 2.26 (dd, $J = 13.4$, 9.7 Hz, 1H$^\dagger$), 1.44 (s, 3H*), 1.41 (s, 3H$^\dagger$); $^{13}$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 $^\dagger$) δ 169.2$^\dagger$, 169.0*, 156.9* (q, $J_{C,F} = 36.7$ Hz), 156.3* (q, $J_{C,F} = 235.3$ Hz), 146.5*, 144.7$^\dagger$, 135.2$,^\dagger$, 134.5*, 133.3* (d, $J_{C,F} = 7.2$ Hz), 128.5$,^\dagger$, 128.4*, 128.2$^\dagger$, 116.1* (q, $J_{C,F} = 288.6$ Hz), 115.0* (d, $J_{C,F} = 23.0$ Hz), 114.5$^\dagger$ (d, $J_{C,F} = 23.1$ Hz), 110.2* (d, $J_{C,F} = 24.4$ Hz), 109.6* (d, $J_{C,F} = 24.6$ Hz), 107.3$^\dagger$ (d, $J_{C,F} = 7.7$ Hz), 106.0* (d, $J_{C,F} = 7.9$ Hz), 91.3$,^\dagger$, 89.1*, 67.8*, 67.3$,^\dagger$, 60.4$,^\dagger$, 60.2*, 52.2$,^\dagger$, 50.4*, 42.8$,^\dagger$, 40.9$,^\dagger$, 32.4*, 31.5$^\dagger$, 25.1*, 22.3$^\dagger$; IR (NaCl/thin film): 2961, 1749, 1698, 1498, 1439, 1270, 1207, 1157, 995, 852, 752 cm$^{-1}$; [$\alpha$]$_D^{25} = +156.8^\circ$ (c 1.16, DCM); HRMS (ESI) calc’d for [M+H]$^+$ 437.1483, found 437.1490.
Pyrroloindoline 106c.

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

**Exo diastereomer:** pale yellow oil. The enantiomeric excess was determined to be 94% by chiral SFC analysis (OJ-H, 2.5 mL/min, 2% IPA in CO₂, λ = 254 nm): tₘ (major) = 20.5 min tₘ (minor) = 16.6 min. ¹H NMR (400 MHz, CDCl₃; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 (br s, 5H*, 5H§), 6.97 (br d, J = 7.7 Hz, 1H*, 1H§), 6.85 (br s, 1H§), 6.81 (br s, 1H*), 6.50 (br d, J = 7.6 Hz, 1H§), 6.42 (br d, J = 7.9 Hz, 1H*), 5.56 (br s, 1H*), 5.32 – 5.15 (br m, 2H*, 3H§), 4.76 (br d, J = 9.3 Hz, 1H*), 4.47 (br t, J = 7.5 Hz, 1H§), 3.05 (br s, 3H*), 2.87 (br s, 3H§), 2.61 – 2.46 (m, 1H*, 1H§), 2.30 (d, J = 21.3 Hz, 1H*), 2.27 (s, 3H*, 3H§), 2.09 – 1.98 (br m, 1H§), 1.45 (br s, 3H§), 1.26 (s, 3H§); ¹³C NMR (100 MHz, CDCl₃; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.1* (q, J_C-F = 36.8 Hz), 157.7§ (q, J_C-F = 37.9 Hz), 147.3*§, 135.2§, 134.6*, 134.5*, 134.4§, 129.7§, 129.2§, 129.0*, 128.8*, 128.7*, 128.6*, 128.4*, 128.2§, 122.3*§, 116.1* (q, J_C-F = 288.7 Hz), 110.0§, 108.2*, 93.8*, 92.1§, 68.0*, 67.3§, 61.4§, 60.4*, 53.3§, 49.2*, 43.9*, 40.2§, 37.4*, 35.6§, 23.4*, 23.2§, 20.7*§; IR (NaCl/thin film): 2965, 1748, 1697, 1499, 1456, 1433, 1348,
1194, 1153, 992, 754 cm\(^{-1}\); \([\alpha]_D^{25} = -87.1^\circ\) (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, \(\lambda = 254\) nm):

\[ t_R(\text{major}) = 6.5\ \text{min} \quad t_R(\text{minor}) = 7.3\ \text{min}. \]

\(^1\)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 §) \(\delta\)

- 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 §) \(\delta\)

- 169.4§, 169.2*, 156.9* (q, \(J_{CF} = 36.6\) 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, \(J_{CF} = 288.8\) 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\(^{-1}\); \([\alpha]_D^{25} = +176.4^\circ\) (c 0.97, DCM); HRMS (ESI) calc’d for [M+H]\(^+\) 433.1734, found 433.1737.
**Pyrroloindoline 106d.**

Prepared from 5-bromo-1,3-dimethyl-1H-indole (105d) and benzyl 2-trifluoroacetamidoacrylate using general procedure C, in DCE with 1.6 equivalents SnCl₄. The reaction was allowed to run for 57 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 50 mg (51% yield) of 106d in a 3:1 ratio of diastereomers (determined by ¹H NMR analysis of the pure product).

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

**Exo diastereomer:** The enantiomeric excess was determined to be 87% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, λ = 254 nm): \( t_R \) (major) = 14.7 min \( t_R \) (minor) = 12.5 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ

7.38 (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†), 5.36 – 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*); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ

171.9*, 169.6§, 159.18 (q, \( J_{C-F} = 37.1 \) Hz)*, 157.42 (d, \( J_{C-F} = 39.7 \) Hz)§, 148.4*, 148.0§, 136.4*, 136.2§, 135.0§, 134.5*, 131.5§, 131.4*, 128.9*, 128.8*, 128.7*, 128.4§, 124.7*, 116.0 (q, \( J_{C-F} = 288.5 \) Hz)*, 111.5§, 110.5*, 110.2§, 109.4*, 93.1*, 91.5§, 68.2*, 67.5§, 61.4§, 60.2*, 52.9§, 49.1*, 43.7*, 40.4§, 36.7*, 33.9§, 23.2*, 22.3§; IR (NaCl/thin film):
3034, 2965, 2931, 1747, 1698, 1602, 1489, 1205, 1154, 806, 751 cm⁻¹; [α]_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, CDCl₃; 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§); \(^1^C\) NMR (125 MHz, CDCl₃; 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; [α]_D^{25} = 156.3° (c = 0.24, DCM) ; HRMS (FAB+) calc’d for [M+H]^+ 498.0589, found 498.0606.
Chapter 2—Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines

Pyrroloindoline 106e.

Prepared from 6-methyl-1,3-dimethyl-1\textit{H}-indole (105e) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 6 h. The crude residue was purified by flash chromatography (0→10\% ethyl acetate/hexanes) to yield 78.3 mg (91\% yield) of 106e in a 4:1 ratio of diastereomers (determined by \textsuperscript{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, \(\lambda = 254\) nm).

\textit{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. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by \(\ast\), minor rotamer denoted by \(\delta\)) \(\delta\) 7.40 (br s, 5H\(\ast\), 5H\(\delta\)), 6.93 (br d, \(J = 7.1\) Hz, 1H\(\delta\)), 6.89 (br d, \(J = 7.4\) Hz, 1H\(\ast\)), 6.65 (br d, \(J = 6.8\) Hz, 1H\(\delta\)), 6.58 (br d, \(J = 7.3\) Hz, 1H\(\ast\)), 6.42 (br s, 1H\(\delta\)), 6.35 (br s, 1H\(\ast\)), 5.60 (br s, 1H\(\ast\)), 5.32 (br s, 1H\(\delta\)), 5.29 – 5.14 (m, 2H\(\ast\), 2H\(\delta\)), 4.76 (br d, \(J = 9.2\) Hz, 1H\(\ast\)), 4.50 (br t, \(J = 7.2\) Hz, 1H\(\delta\)), 3.07 (br s, 3H\(\ast\)), 2.88 (br s, 3H\(\delta\)), 2.61 – 2.42 (m, 1H\(\ast\), 1H\(\delta\)), 2.32 (br s, \(J = 5.8\) Hz, 4H\(\ast\), 3H\(\delta\)), 2.10 – 1.98 (m, 1H\(\delta\)), 1.46 (s, 3H\(\delta\)), 1.27 (s, 3H\(\ast\)); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by \(\ast\), minor rotamer denoted by \(\delta\)) \(\delta\) 172.1\(\ast\), 169.9\(\delta\), 159.2\(\ast\) (q, \(J_{C-F} = 37.0\) Hz), 157.7\(\delta\) (q, \(J_{C-F} = 38.4\) Hz), 149.6\(\ast\), 149.5\(\delta\), 139.0\(\delta\), 138.8\(\ast\), 135.2\(\delta\), 134.7\(\ast\), 131.7\(\ast\), 131.4\(\delta\), 128.9\(\ast\), 128.8\(\ast\), 128.7\(\ast\), 128.6\(\ast\), 128.5\(\delta\), 128.4\(\delta\), 121.3\(\delta\), 121.2\(\ast\), 120.7\(\delta\), 119.3\(\ast\), 116.1\(\ast\) (q, \(J_{C-F} = 288.4\) Hz), 116.0\(\delta\) (q, \(J_{C-F} = 286.5\) Hz), 110.5\(\delta\), 108.9\(\ast\), 93.6\(\ast\),
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; [α]_D^25 = −85.6° (c 0.93, DCM); HRMS (EI+) calc’d for M⁺ 432.1661, found 432.1663. 

*Endo diastereomer*: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 7.8 min t_R(minor) = 8.3 min. ¹H NMR (500 MHz, CDCl₃; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 – 7.29 (m, 3H*, 3H§), 7.21 (dd, J = 6.6, 2.9 Hz, 2H§), 7.16 – 7.10 (m, 2H*), 6.92 (d, J = 7.4 Hz, 1H§), 6.86 (d, J = 7.4 Hz, 1H*), 6.55 (d, J = 7.4 Hz, 1H§), 6.49 (dd, J = 7.4, 0.6 Hz, 1H*), 6.17 (s, 1H§), 6.06 (s, 1H*), 5.57 (s, 1H*), 5.28 (d, J = 1.9 Hz, 1H§), 5.12 (dd, J = 9.6, 5.2 Hz, 1H§), 5.03 (d, J = 12.3 Hz, 1H§), 4.95 (d, J = 12.3 Hz, 1H*), 4.78 (d, J = 8.4 Hz, 1H*), 4.67 (d, J = 12.1 Hz, 1H*), 4.33 (d, J = 12.2 Hz, 1H*), 2.91 (s, 3H*), 2.82 (d, J = 12.9 Hz, 1H*), 2.62 (d, J = 1.4 Hz, 3H§), 2.43 (dd, J = 13.3, 5.2 Hz, 1H§), 2.36 (dd, J = 12.9, 8.3 Hz, 1H*), 2.30 (s, 3H§), 2.28 (s, 3H*), 2.24 (dd, J = 13.3, 9.6 Hz, 1H§), 1.43 (s, 3H*), 1.40 (s, 3H§); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4§, 169.3*, 156.9* (q, J_C-F = 36.8 Hz), 150.4*, 148.7§, 139.0*, 138.7§, 135.2§, 134.7*, 130.3§, 129.0*, 128.5§, 128.4*, 128.3§, 128.2*, 122.3*, 121.3§, 119.1§, 118.4*, 116.2* (q, J_C-F = 288.7 Hz), 108.0§, 106.8*, 91.1§, 88.9*, 67.6*, 67.2§, 60.5§, 60.3*, 52.0§, 50.2*, 42.9*, 41.1§, 32.0*, 31.0§, 25.3*§, 22.4§, 21.8*; IR (NaCl/thin film): 2923, 1740, 1698, 1612, 1501, 1440, 1214, 1150, 1011, 849, 746 cm⁻¹; [α]_D^25 = +165.5° (c 0.53, DCM); HRMS (ESI) calc’d for [M+H]^+ 433.1739, found 433.1756.
Pyrroloindoline 106f. Prepared from 1-methyl-3-t-butylidimethylsiloxyethyl-1H-indole (105f) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 20 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 61 mg (54% yield) of 106f in a 6:1 ratio of diastereomers (determined by $^1$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, $J_{C-F} = 37.9$ Hz)*, 157.7 (q, $J_{C-F} = 38.1$ Hz)$^§$, 150.5§, 150.0*, 135.2§, 134.7*, 131.7§, 131.5*, 128.8*§, 128.6*§, 128.4*§, 122.4*§,
119.9§, 118.4*, 116.0 (q, $J_{C-F} = 288.0$ Hz)*, 110.0§, 108*, 90.8*, 89.5§, 67.9*, 67.3§, 60.5§, 59.6*, 56.4§, 52.3*, 43.5*, 39.9§, 39.1§, 39.0*, 36.4*, 35.7§, 25.8*, 18.1, -5.6*§;
IR (NaCl/thin film): 3035, 2955, 2930, 2857, 2884, 1750, 1694, 1492, 1432, 1257, 1201, 1158, 1106, 837 cm$^{-1}$; $[\alpha]_D^{25} = -95.3^\circ$ (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, $\lambda = 254$ 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, $J_{C-F} = 37.9$ Hz), 151.2, 134.7, 129.6, 129.2, 128.43, 128.37, 128.2, 123.5, 117.5, 116. 2 (q, $J_{C-F} = 289.0$ Hz), 107.5, 105.9, 87.1, 67.5, 59.9, 59.4, 53.0, 42.2, 40.4, 31.9, 25.9, 18.2, -5.6 ($J = 6.1$ Hz); IR (NaCl/thin film): 3034, 2954, 2930, 2857, 1742, 1699, 1609, 1494, 1441, 1255, 1207, 1146, 1104, 837, 745 cm$^{-1}$; $[\alpha]_D^{25} +148.5^\circ$ (c = 0.33, DCM); HRMS (FAB+) calc’d for [M+H]$^+$ 562.2475, found 562.2458.
Pyrroloindoline 106g.

Prepared from 9-methyl-2,3,4,9-tetrahydro-1H-carbazole\textsuperscript{43} and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 11 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 60 mg (65% yield) of 106g in a >18:1 ratio of diastereomers (determined by \textsuperscript{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. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}; compound exists as a >20:1 mixture of rotamers) \( \delta \) 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); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}; compound exists as a >20:1 mixture of rotамers) \( \delta \) 172.4, 157.7 (q, \( J_{C,F} = 36.3 \) Hz), 148.0, 134.9, 133.7, 128.7, 128.6, 128.4, 120.8, 118.0, 115.8 (q, \( J_{C,F} = 289.8 \) Hz), 112.3, 107.1, 95.6, 67.6, 58.4 (q, \( J_{C,F} = 3.5 \) Hz), 52.3, 35.2, 33.9, 30.7, 26.8, 21.5, 20.4 ; IR (NaCl/thin film): 3034, 2928, 2857, 1749,
1693, 1609, 1490, 1214, 1186, 1160, 741 cm\(^{-1}\); melting point: 106 – 108 °C; [\(\alpha\)]\(D\)^{25} = – 92.6° (c = 1.40, DCM); HRMS (ESI+) calc’d for [M+H]^+ 459.1890, found 459.1892.

**Pyrrolidinoindoline 106h.**

Prepared from 3-phenethyl-1-methyl-1\(H\)-indole\(^{4d}\) and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents SnCl\(_4\). The reaction was allowed to run for 9.5 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 81 mg (80% yield) of 106h in a 4:1 ratio of diastereomers (determined by \(^1\)H NMR analysis of the crude reaction mixture). The diastereomers were separated by preparatory HPLC (0→6% ethyl acetate/hexanes). The enantiomeric excess of both diastereomers was determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, \(\lambda = 254\) nm).

**Exo diastereomer:** pale yellow oil. The enantiomeric excess was determined to be 92%. \(t_R\) (major) = 33.3 min \(t_R\) (minor) = 28.0 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 §) \(\delta\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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 §) \(\delta\) 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, $J_{C-F}$ = 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$^{-1}$; $[\alpha]_D^{25}$ = 119.6° (c = 0.87, 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§), 7.32 (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, $J_{C-F}$ = 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, $J_{C-F}$ = 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 509.2052.
Pyrroloindoline 106i.

Prepared from 1-allyl-3-methyl-1H-indole\textsuperscript{35} and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents SnCl\textsubscript{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 106i in a 3:1 ratio of diastereomers (determined by SFC analysis of the purified products, before the diastereomers were separated). The diastereomers were separated by flash chromatography (0→10% ethyl acetate/hexanes).

**Exo diastereomer:** pale yellow oil. The enantiomeric excess was determined to be 93\% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6\% IPA in CO\textsubscript{2}, λ = 254 nm): $t_R$(major) = 5.7 min $t_R$(minor) = 4.3 min. $^1$H NMR (400 MHz, CDCl\textsubscript{3}; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by $^*$, minor rotamer denoted by $^\$) $\delta$

- 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\textsubscript{3}; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by $^*$, minor rotamer denoted by $^\$) $\delta$

- 172.0*,
- 169.8$^\$,
- 158.9* ($q$, $J_{C-F} = 37.0$ Hz),
- 148.4$^{*\$},
- 134.8*,
- 134.6*,
- 133.8*,
- 133.4$^\$,
- 128.8*,
- 128.7*,
- 121.5*,
- 120.3$^\$,
- 118.7*,
- 117.7$^\$.
116.7*, 116.0* (q, $J_{CF} = 288.5$ 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$^{-1}$; [$\alpha$]$^D_{25} = -94.3^\circ$ (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$_2$, $\lambda = 254$ 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, $J_{CF} = 36.9$ Hz), 149.3*, 147.7§, 134.7*, 134.1*, 133.2§, 132.4§, 132.0*, 128.9*, 128.6§, 128.5§, 128.4*, 128.3*, 128.2§, 122.6*, 121.7§, 118.7§, 118.0*, 117.1§, 116.3*, 116.2* (q, $J_{CF} = 288.7$ Hz), 108.0§, 106.9*, 88.1*, 67.6*, 67.3*, 60.4§.
Chapter 2 – Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines

60.2*, 52.7§, 50.6*, 48.8*, 42.5*, 41.5§, 25.8*, 23.1§; IR (NaCl/thin film): 2962, 1739, 1697, 1608, 1491, 1447, 1269, 1211, 1145, 851, 742 cm⁻¹; [α]D²⁵ = +166.6° (c 1.52, DCM); HRMS (ESI) calc’d for [M+H]⁺ 445.1734, found 445.1740.

**Pyrroloindoline 106j.**

Prepared from 3-methyl-1H-indole (0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate (91d, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (0→20% ethyl acetate/hexanes) to yield 10.7 mg (18% yield) of 106j in an 8:1 ratio of diastereomers (determined by NMR analysis of the pure product). The diastereomers were separated by preparatory HPLC (5→12% ethyl acetate/hexanes).

**Exo diastereomer:** pale yellow oil. The enantiomeric excess was determined to be 95% by chiral SFC analysis (OJ-H, 2.5 mL/min, 7% IPA in hexanes, λ = 254 nm): 

\[ t_R(\text{major}) = 9.6 \text{ min} \quad t_R(\text{minor}) = 7.4 \text{ min.} \]

\(^1\)H NMR (500 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 7.43 – 7.31 (m, 5H), 7.12 (t, J = 8.1 Hz, 0.5H), 7.10 (t, J = 8.1 Hz, 0.5H), 7.05 (d, J = 4.1 Hz, 0.5H), 7.04 (d, J = 3.9 Hz, 0.5H), 6.82 (t, J = 7.5 Hz, 0.5H), 6.77 (t, J = 7.5 Hz, 0.5H), 6.64 (d, J = 7.8 Hz, 0.5H), 6.60 (d, J = 7.8 Hz, 0.5H), 5.63 (s, 0.5 H), 5.57 (s, 0.5H), 5.30 (s, 0.5H), 5.23 (s, 1H), 5.22 (d, J = 12.2 Hz, 0.5H), 5.17 (d, J = 12.2 Hz, 0.5H), 4.76 (s, 0.5H), 4.68 – 4.62 (m, 0.5H), 4.50 (t, J = 7.7 Hz, 0.5H), 2.72 (dd, J = 13.5, 9.2 Hz, 0.5H), 2.58 (dd, J = 13.1, 8.5 Hz, 0.5H), 2.33 (dd, J = 13.4, 3.9 Hz, 0.5H), 2.17 (dd, J = 13.1, 6.9 Hz, 0.5H), 1.44 (s, 1.5H), 1.31 (s, 1.5H) ; \(^1\)C NMR (125 MHz, CDCl₃; compound exists as a 1:1 mixture of rotamers) δ 171.5, 170.2, 156.8 (q, J_C–F = 38.7 Hz), 146.8, 146.3, 135.2, 134.7, 133.2, 133.1, 128.9, 128.8, 128.7,
128.6, 128.5, 128.4, 122.3, 122.1, 120.2, 119.3, 116.1 (q, $J_{C-F} = 287.2$), 115.7 (q, $J_{C-F} = 287.2$), 109.9, 109.3, 86.5, 84.5, 68.10, 67.5, 61.3, 59.6, 54.5, 50.3, 43.7, 40.3, 24.2, 23.9; IR (NaCl/thin film): 3390, 3034, 2961, 2920, 1748, 1687, 1610, 1486, 1469, 1456, 1189, 1158, 745 cm$^{-1}$; $[\alpha]_{D}^{25}$ –111.8° (c = 0.22, DCM); HRMS (EI+) calc’d for M$^{+}$ 404.1348, found 404.1344.

2.5.5  

**Pd-catalyzed Deallylaton of Pyrroloindoline Methyl Ester 107**

An oven-dried microwave vial was charged with allylpyrroloindoline 107 (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) then sealed under nitrogen. 1.1 mL DCM was added and the reaction mixture was heated to 35 °C in an oil bath. Two additional 7.0 mg portions of Pd(PPh$_3$)$_4$ were added after 34 hours and after 75 hours. After heating at 35 °C for 123 hours, the reaction was concentrated and the crude residue was diluted in Et$_2$O, washed with saturated aqueous Na$_2$CO$_3$, dried (Na$_2$SO$_4$), filtered and concentrated. The crude residue was subjected to silica gel column chromatography (10:90 EtOAc:hexanes) to yield 34.8 mg (71% yield) of 108 as a colorless oil in an 8:1 mixture of diastereomers (determined by NMR analysis of the pure product). The product was resubjected to identical column conditions to obtain *exo*-108 in >20:1 dr. $^1$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), 1.49 (s, 1.5H), 1.41 (s, 1.5H); 13C NMR (125 MHz, CDCl3; compound exists as a 1:1 mixture of rotamers) δ 172.1, 170.9, 157.6 (q, J_{C-F} = 37.5 Hz), 156.7 (q, J_{C-F} = 38.0 Hz), 146.8, 146.4, 133.14, 133.10, 128.9, 128.7, 122.3, 122.1, 120.2, 119.3, 116.1 (q, J_{C-F} = 287.1 Hz), 115.7 (q, J_{C-F} = 286.2 Hz), 109.9, 109.4, 86.4, 84.4 (q, J_{C-F} = 2.2 Hz), 61.1, 59.5 (q, J_{C-F} = 3.1 Hz), 54.5, 53.0, 52.6, 50.3, 43.7, 40.3, 24.2, 24.0.; IR (NaCl/thin film): 3387, 2959, 1751, 1693, 1613, 1489, 1469, 1450, 1438, 1359, 1195, 1160, 1104 cm⁻¹; [α]_{D}^{25} –182.7° (c = 0.50, DCM); HRMS (MM) calc’d for C_{15}H_{16}F_{3}N_{2}O_{3} [M+H]^+ 329.1108, found 329.1122.

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

A flame-dried flask was charged with 3-phenylindole (111, 13.6 mg, 70.0 µmol, 1.00 equiv) and trifluoromethyl 2-acetamidoacrylate (91b, 13.8 mg, 70.0 µmol, 1.00 equiv). 0.3 mL DCM was then added and the solution was cooled to 0 °C. EtAlCl₂ (1 M in hexanes, 0.14 mL, 2.0 mmol, 2.0 equiv) was then added dropwise, followed by 1.0 µL H₂O (63 µmol, 0.90 equiv). The reaction was then stirred in a cold room at 8 °C for 24 hours. By crude ¹H NMR, 93% conversion of 91b was observed to cleanly afford methyl
3-(3-phenyl-1H-indol-2-yl)-2-(2,2,2-trifluoroacetamido)propanoate (112). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.42 (br s, 1H), 7.60 (dddd, \(J = 7.9, 1.3, 0.7, 07 \text{ Hz}, 1\)H), 7.51 – 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 7.24 (dd, \(J = 8.2, 7.0, 1.2 \text{ Hz}, 1\)H), 7.13 (ddd, \(J = 8.1, 7.0, 1.1 \text{ Hz}, 1\)H), 6.82 (br d, \(J = 7.5 \text{ Hz}, 1\)H), 4.81 (dt, \(J = 7.4, 5.5 \text{ Hz}, 1\)H), 3.64 – 3.45 (m, 5H);

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.3, 157.0 (q, \(J_{\text{C-F}} = 38.1 \text{ Hz}\)), 135.6, 134.1, 129.7, 128.8, 128.0, 127.6, 126.6, 122.7, 120.2, 119.3, 117.5, 115.3 (q, \(J_{\text{C-F}} = 287.5 \text{ Hz}\)), 110.8, 53.1, 52.5, 28.3.; FTIR (NaCl/thin film): 3377, 3058, 2918, 2848, 1718, 1604, 1541, 1499, 1459, 1438, 1329, 1267, 1214, 1171 cm\(^{-1}\); HRMS (ESI) calc’d for C\(_{20}\)H\(_{16}\)F\(_3\)N\(_2\)O\(_3\) [M-H] 389.1119, found 389.1114.

2.5.7 Preparation of Phenylpyrroloindoline 118

![](image)

\(\delta\) 8.42 (br s, 1H), 7.60 (dddd, \(J = 7.9, 1.3, 0.7, 07 \text{ Hz}, 1\)H), 7.51 – 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 7.24 (dd, \(J = 8.2, 7.0, 1.2 \text{ Hz}, 1\)H), 7.13 (ddd, \(J = 8.1, 7.0, 1.1 \text{ Hz}, 1\)H), 6.82 (br d, \(J = 7.5 \text{ Hz}, 1\)H), 4.81 (dt, \(J = 7.4, 5.5 \text{ Hz}, 1\)H), 3.64 – 3.45 (m, 5H);

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.3, 157.0 (q, \(J_{\text{C-F}} = 38.1 \text{ Hz}\)), 135.6, 134.1, 129.7, 128.8, 128.0, 127.6, 126.6, 122.7, 120.2, 119.3, 117.5, 115.3 (q, \(J_{\text{C-F}} = 287.5 \text{ Hz}\)), 110.8, 53.1, 52.5, 28.3.; FTIR (NaCl/thin film): 3377, 3058, 2918, 2848, 1718, 1604, 1541, 1499, 1459, 1438, 1329, 1267, 1214, 1171 cm\(^{-1}\); HRMS (ESI) calc’d for C\(_{20}\)H\(_{16}\)F\(_3\)N\(_2\)O\(_3\) [M-H] 389.1119, found 389.1114.

2.5.7 Preparation of Phenylpyrroloindoline 118

A 10 mL flame-dried flask was charged with (R)-BINOL (11.4 mg, 39.9 µmol, 0.20 equiv), methyl 2-acetamidoacrylate (91a, 28.6 mg, 0.200 mmol, 1.00 equiv), and 1,2-dimethyl-3-phenylindole\(^{16}\) (117, 44.2 mg, 0.200 mmol, 1.00 equiv). MeOH (40 µmol, 0.20 equiv) was then added as a solution in 1.5 mL DCM (from a stock solution of 16 µL MeOH in 15 mL DCM), followed by SnCl\(_4\) (1 M solution in DCM, 240 µL, 0.240 mmol, 1.20 equiv). After stirring in the dark 12.5 hours, the orange reaction mixture was diluted with 4 mL MeCN and 5 mL EtOAc, then washed with 10 mL of 0.1 M HCl in brine. The aqueous layer was extracted with 5 mL EtOAc and the combined organic layers were washed with 10 mL 1 M aqueous NaOH. The aqueous layer was extracted with 5 mL
EtOAc and the combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated.

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

100b: racemic

![Graph of SFC and HPLC traces for racemic 100b](image)

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

![Graph of SFC and HPLC traces for enantioenriched 100b](image)

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100b (Table 2.2.2, entry 4): enantioenriched, exo: 63% ee, endo: 83% ee (0.2 equiv BINOL)
**Chapter 2—Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines**

**exo-100c** (Table 2.2.3, entry 6): racemic

![Graph 1](image1)

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

![Graph 2](image2)

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**exo-100d (Table 2.2.3, entry 7): racemic**

![Racemic exo-100d chromatogram](image1)

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

![Enantioenriched exo-100d chromatogram](image2)

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**endo-100d (Table 2.2.3, entry 7): racemic**

![Chromatogram of racemic endo-100d]

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

![Chromatogram of enantioenriched endo-100d]

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<td>0.6145</td>
<td>313.70520</td>
<td>8.50807</td>
<td>8.9980</td>
</tr>
</tbody>
</table>
100e (Table 2.2.3, entry 9): racemic

100e (Table 2.2.3, entry 9): enantioenriched, exo: 94% ee, endo: 91% ee
106a (Scheme 2.2.1): racemic

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

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

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

![Endo 106d](image1.png)

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1595</td>
<td>2504.75537</td>
<td>247.61092</td>
<td>50.0224</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.2591</td>
<td>2502.51636</td>
<td>149.14781</td>
<td>49.9776</td>
<td></td>
</tr>
</tbody>
</table>

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

![Exo 106d](image2.png)

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3987</td>
<td>7886.59732</td>
<td>334.25320</td>
<td>50.0142</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.4007</td>
<td>7991.97656</td>
<td>277.08136</td>
<td>49.9853</td>
<td></td>
</tr>
</tbody>
</table>
**106d (Scheme 2.2.1): exo: 87% ee, endo: 85% ee**
106e (Scheme 2.2.1): racemic

```
<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.694</td>
<td>BV</td>
<td>0.1800</td>
<td>1738.04382</td>
<td>148.72224</td>
<td>9.4448</td>
</tr>
<tr>
<td>2</td>
<td>8.122</td>
<td>VB</td>
<td>0.2549</td>
<td>1740.51331</td>
<td>105.22092</td>
<td>9.4382</td>
</tr>
<tr>
<td>3</td>
<td>12.583</td>
<td>BV</td>
<td>0.2060</td>
<td>7424.35889</td>
<td>517.51135</td>
<td>40.3450</td>
</tr>
<tr>
<td>4</td>
<td>14.649</td>
<td>VB</td>
<td>0.7114</td>
<td>7499.26904</td>
<td>149.61671</td>
<td>10.7521</td>
</tr>
</tbody>
</table>
```

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

```
<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.785</td>
<td>MF</td>
<td>0.2240</td>
<td>6143.67139</td>
<td>457.11594</td>
<td>18.0567</td>
</tr>
<tr>
<td>2</td>
<td>8.294</td>
<td>FM</td>
<td>0.2911</td>
<td>320.56265</td>
<td>18.35141</td>
<td>0.9422</td>
</tr>
<tr>
<td>3</td>
<td>12.912</td>
<td>MM</td>
<td>0.2706</td>
<td>830.77399</td>
<td>51.16518</td>
<td>2.4417</td>
</tr>
<tr>
<td>4</td>
<td>14.496</td>
<td>MM</td>
<td>0.7607</td>
<td>2.6729de4</td>
<td>570.62366</td>
<td>78.5595</td>
</tr>
</tbody>
</table>
```
**endo-106f (Scheme 2.2.1): racemic**

![Graph showing racemic endo-106f](image)

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

![Graph showing 90% ee endo-106f](image)
**exo-106f (Scheme 2.2.1): racemic**

```
Peak RetTime Type Width Area Height Area
#  [min]  [min]  mAU  %  [mAU]  %
1  10.632  UV  0.3805  3995.52930  145.07512  49.7976
2  12.028  VB  0.3841  4028.00830  161.10678  50.2024
```

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

```
Peak RetTime Type Width Area Height Area
#  [min]  [min]  mAU  %  [mAU]  %
1  10.700  MF  0.4226  3857.44580  152.13763  95.9302
2  12.052  FM  0.3805  163.65164  7.16747  4.0698
```
106g (Scheme 2.2.1): racemic

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

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

```
Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 5.000 MF 0.3012 1808.26282 100.06958 12.5286
2 5.866 FM 0.3472 1916.69648 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 37.9866
```

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

```
Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
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 0.5761 523.56973 12.21119 2.6943
4 15.903 MM 1.0047 1.13010e4 187.47484 71.8835
```
106j (Scheme 2.2.1): racemic

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 4.737 MM 0.3442 433.55974 21.00096 5.7354
2 5.733 MM 0.3971 433.11276 18.17621 4.7204
3 7.564 MM 0.4321 2083.62998 70.82232 41.1569
4 10.149 MM 0.6038 2056.07129 56.79010 41.3974

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

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 7.393 NM 0.4059 199.81528 8.20531 2.5009
2 9.640 NM 0.7421 7790.00886 174.96088 97.4991
3a-phenylpyrroloindoline 118: racemic

![Graph showing racemic 3a-phenylpyrroloindoline 118 with retention time and area data.]

### Peak RetTime Type Width Area Height Area

<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.395</td>
<td>0.1273</td>
<td>1668.26721</td>
<td>218.38173</td>
<td>45.5770</td>
</tr>
<tr>
<td>2</td>
<td>4.274</td>
<td>0.1714</td>
<td>1696.73730</td>
<td>164.97374</td>
<td>50.4230</td>
</tr>
</tbody>
</table>

3a-phenylpyrroloindoline 118: 91% ee

![Graph showing 91% ee 3a-phenylpyrroloindoline 118 with retention time and area data.]

### Peak RetTime Type Width Area Height Area

<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.465</td>
<td>0.1252</td>
<td>284.95630</td>
<td>37.91944</td>
<td>4.3154</td>
</tr>
<tr>
<td>2</td>
<td>4.357</td>
<td>0.1722</td>
<td>6318.30908</td>
<td>611.51556</td>
<td>95.6846</td>
</tr>
</tbody>
</table>
To an NMR tube was added a solution of pyrroloindoline 100e (0.063 mmol, 1.00 equiv) in CD$_2$Cl$_2$ (0.46 mL), followed by DBU (0.63 mmol, 10.00 equiv). The reaction was monitored by $^1$H 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$_2$SO$_4$), 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-100e (94% ee) + endo-100e (91% ee) with DBU (10 equiv) for 65 h to give >10:1 ent-endo-100e (56% ee).
Experiment 2: Treatment of diastereomerically pure exo-100e (94% ee) with DBU (10 equiv) for 96 h to give >10:1 ent-endo-100e (94% ee).

Experiment 3: Treatment of diastereomerically pure endo-100e (91% ee) with DBU (10 equiv) for 30 h to return endo-100e (89% ee).
2.5.10 Resubjection of Pure Exo and Endo Pyrroloindolines to Reaction Conditions

To an NMR tube was added a solution of pure pyrroloindoline exo-\textbf{100e} (0.073 mmol, 1.00 equiv, 94% ee) in CD$_2$Cl$_2$ (297 µL), followed by (R)-BINOL (from a 0.0675 M solution in CD$_2$Cl$_2$, 0.015 mmol, 0.20 equiv) and SnCl$_4$ (from a 0.72 M solution in CD$_2$Cl$_2$, 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-\textbf{100e} (91% ee), except at a concentration of 0.065 M. In both cases, no epimerization or erosion of ee was observed.
2.6 NOTES AND REFERENCES


For the development of these conditions, see: (a) Garro-Helion, F.; Merzouk, A.; Guibé, F. J. Org. Chem. 1993, 58, 6109. For an application to pyrroloindolines, see: (b) Li, G.; Padwa, A. Org. Lett. 2011, 13, 3767.


(33) 1-Boc-3-(trimethylsilylethynyl)indole (130) was prepared according to a literature procedure: He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482.


(36) 3-phenyl-2-(trimethylsilyl)indole (134) was prepared according to a literature procedure: Larock, R. C.; Yum, E. K.; Refvik, M. D. J. Org. Chem. 1998, 63, 7652.


(38) Methyl 2-acetamidoacrylate is commercially available, or can be prepared according to Crestey, F.; Collot, V.; Steibing, S.; Rault, S. Synthesis 2006, 20, 3506.


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

Spectra Relevant to Chapter 2:

Formal (3 + 2) Cycloaddition Approach
to Pyrroloindolines
Appendix 1—Spectra Relevant to Chapter 2

Sample Name: JN-1-197-col
Data Collected on: hg3.caltech.edu-mercury300
Archive directory: /home/jni/vnmrsys/data
Sample directory: JN-1-197-col
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Jul 19 2010
Temp. 25.0 C / 298.1 K
Sample #22, Operator: jni

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4810.0 Hz
16 repetitions

OBSERVE H1, 300.0862583 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 45 sec
Appendix 1–Spectra Relevant to Chapter 2

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
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
Appendix 1 – Spectra Relevant to Chapter 2

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
Appendix 1–Spectra Relevant to Chapter 2

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

ppm
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
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

ppm

Appendix 1–Spectra Relevant to Chapter 2

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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

Appendix 1–Spectra Relevant to Chapter 2
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
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 N1, 399.7962875 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 10 min
LMRIV-N-me-TBS tryptophol

Sample Name: LMRIV-N-me-TBS tryptophol
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRIV-N-me-TBS tryptophol
Fid File: 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
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: cdc13
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
Appendix 1–Spectra Relevant to Chapter 2

113
Appendix 1–Spectra Relevant to Chapter 2

Sample Name: PR4_F1
Data Collected on: hg3.caltech.edu-mercury300
Archive directory: /home/jcha1/vnmrsys/data
Sample directory: PR4_F1
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 14 2011

Sample #2, Operator: jcha1
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
16 repetitions
OBSERVE   H1, 300.0862709 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 min 6 sec
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

Appendix 1–Spectra Relevant to Chapter 2
Sample Name: LMRIV-291-majordr-conc
Data Collected on: siena.caltech.edu-vmmrs400
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

Appendix 1–Spectra Relevant to Chapter 2
Appendix 1–Spectra Relevant to Chapter 2
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

Appendix 1–Spectra Relevant to Chapter 2
Sample Name: JN-1-131-majordiast
Data Collected on: siena.caltech.edu-vnmrs400
Archive directory: /home/jni/vmmrsys/data
Sample directory: JN-1-131-majordiast
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: dcdl3
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

Appendix 1–Spectra Relevant to Chapter 2

[Chemical structure image]
Appendix 1–Spectra Relevant to Chapter 2

JN-1-131-majordiast

Sample Name: JN-1-131-majordiast
Data Collected on: siena.caltech.edu-vmmrs400
Archive directory: /home/jni/vmmrsys/data
Sample directory: JN-1-131-majordiast
File: 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 R1, 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

Appendix 1–Spectra Relevant to Chapter 2

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Appendix 1—Spectra Relevant to Chapter 2
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

Appendix 1–Spectra Relevant to Chapter 2
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

Total time 5 hr, 23 min

Appendix 1–Spectra Relevant to Chapter 2
Appendix 1—Spectra Relevant to Chapter 2
Appendix 1–Spectra Relevant to Chapter 2
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
Sample Name: LMRIV-scale-up-12h-majordr
Data Collected on: siena.caltech.edu-vnmrs400
Archive directory: /home/irepka/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: irepka

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

Appendix 1–Spectra Relevant to Chapter 2

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Appendix 1–Spectra Relevant to Chapter 2

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-100e rotamer ratio 10.0:1
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: ccd13
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-100e rotamer ratio 10:1
Appendix 1–Spectra Relevant to Chapter 2
Appendix 1–Spectra Relevant to Chapter 2
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

Appendix 1–Spectra Relevant to Chapter 2
Appendix 1–Spectra Relevant to Chapter 2

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

rotameric ratio
23:1

Appendix 1–Spectra Relevant to Chapter 2
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

Acq. time 2.500 sec

Width 8000.0 Hz

16 repetitions

OBSERVE H1, 499.7420463 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 7 min 20 sec
JN-1-195-minordiast

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

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

Temp. 25.0 C / 298.1 K
Operator: janeni

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

OBSERVE C13, 125.6602387 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 24 min

endo-106b rotamer ratio 9:0:1
Appendix 1–Spectra Relevant to Chapter 2
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
Appendix 1–Spectra Relevant to Chapter 2

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
Appendix 1–Spectra Relevant to Chapter 2
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

Appendix 1–Spectra Relevant to Chapter 2

ppm

Me
N
N
H
OBn
Me
exo-106d
rotameric ratio 3.0:1
Br

ex154

TFA
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

Rotameric ratio 12.5:1
Appendix 1–Spectra Relevant to Chapter 2

LNRIV-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
Appendix 1–Spectra Relevant to Chapter 2

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 N1, 499.7420463 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 7 min 20 sec

![Spectra Image]

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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
Appendix 1: Spectra Relevant to Chapter 2
Appendix 1—Spectra Relevant to Chapter 2

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-105e
rotameric ratio
9:1

160
Sample Name: LMRIV-285-major-rd25
Data Collected on: indy.caltech.edu-inov500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRIV-285-major-rd25
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
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
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

Rotameric ratio 1.7:1
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

rotameric ratio 16.7:1

Appendix 1–Spectra Relevant to Chapter 2
Appendix 1–Spectra Relevant to Chapter 2

endo-106f
rotameric ratio 16.7:1

[Chemical structure diagram]

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: cdc13
Data collected on: Jul 30 2010

Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.022 sec
Width 32051.3 Hz
13000 repetitions
OBSERVE C13, 125.6602398 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 20 min
LMRIV-275-pentanewash

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

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

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

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

Appendix 1–Spectra Relevant to Chapter 2
SAMPLE NAME: LMRIV-275

DATA COLLECTED ON: siena.caltech.edu-vmmrs400

ARCHIVE DIRECTORY: /home/jni/vnmrsys/data

SAMPLE DIRECTORY: LMRIV-275

FID FILE: CARBON01

PULSE SEQUENCE: CARBON (s2pul)

SOLVENT: cdcl3

DATA COLLECTED ON: Jul 15 2010

TEMP. 25.0 C / 298.1 K

SAMPLE #8, OPERATOR: jni

RELAX. DELAY 1.000 SEC

PULSE 45.0 DEGREES

ACQ. TIME 1.285 SEC

WIDTH 25510.2 Hz

11500 REpetitions

OBSERVE C13, 100.5283535 MHz

DECOUPLE H1, 399.7962875 MHz

POWER 39 dB

CONTINUOUSLY ON

WALTZ-16 MODULATED

DATA PROCESSING

LINE BROADENING 1.0 Hz

FT SIZE 65536

TOTAL TIME 7 HR, 17 MIN

EXO-106g rotameric ratio >20:1

166
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

rotameric ratio 2.6:1
ex
do=106h

Appendix 1–Spectra Relevant to Chapter 2

O
Me

H

TFA

OBn

Ph

N

N
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

Appendix 1–Spectra Relevant to Chapter 2
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

Appendix 1–Spectra Relevant to Chapter 2
Sample Name: LMRIV-267-minor3
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lreppa/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: lreppka

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
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
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-106I
rotameric ratio 5.7:1
Appendix 1–Spectra Relevant to Chapter 2

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
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

endo-106i
rotameric ratio 15.7:1
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

Rotameric ratio 1:1

rotameric ratio 1:1

Appendix 1–Spectra Relevant to Chapter 2

175
Appendix 1—Spectra Relevant to Chapter 2

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

rotameric ratio 1.0:1
Appendix 1—Spectra Relevant to Chapter 2

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

rotameric ratio
1.0:1

N

TFA

N

H

CO2Me

Me

exo-108
Appendix 1–Spectra Relevant to Chapter 2

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

![NMR Spectrum](image)
LMRIII-073-1.0workup

Sample Name: LMRIII-073-1.0workup
Archive directory:

Sample directory:

FidFile: LMRIII-073-1.0workup

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Sep 25 2009

Operator: lrepka
VNMRS-400 "erice.caltech.edu"

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4796.2 Hz
2 repetitions
OBSERVE H1, 299.8165648 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
Total time 4 min 16 sec
Sample Name: LMRIII-107
Data Collected on: indy.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: Carbon_01
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Oct 7 2009

Sample #38, Operator: slevin

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
800 repetitions
OBSERVE C13, 125.6635224 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 30 min

112
Appendix 1–Spectra Relevant to Chapter 2

Sample Name: LMRV-229-column
Data Collected on: hg3.caltech.edu-mercury300
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRV-229-column
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 28 2011

Sample #33, Operator: lrepka

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
16 repetitions
OBSERVE H1, 300.0682591 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 min 22 sec
Sample Name: LMRV-233-carbon
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRV-233-carbon
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 3 2013

Sample #22, Operator: lrepka
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6509091 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 8 min 45 sec

rotameric ratio
1.9:1

ppm

Appendix 1–Spectra Relevant to Chapter 2
APPENDIX 2

X-Ray Crystallography Reports Relevant to Chapter 2:

*Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines*†

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

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>C_{25}H_{25}F_{3}N_{2}O_{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula weight</td>
<td>458.47</td>
</tr>
<tr>
<td>Crystallization Solvent</td>
<td>Hexanes/ethyl acetate</td>
</tr>
<tr>
<td>Crystal Habit</td>
<td>Plate</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.23 x 0.19 x 0.02 mm³</td>
</tr>
<tr>
<td>Crystal color</td>
<td>Colorless</td>
</tr>
</tbody>
</table>

**Data Collection**

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<tr>
<th>Type of diffractometer</th>
<th>Bruker KAPPA APEX II</th>
</tr>
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<tbody>
<tr>
<td>Wavelength</td>
<td>0.71073 Å MoKα</td>
</tr>
<tr>
<td>Data Collection Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>θ range for 5569 reflections used</td>
<td>2.19 to 24.93°</td>
</tr>
<tr>
<td>in lattice determination</td>
<td></td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 9.8089(6) Å</td>
</tr>
<tr>
<td></td>
<td>b = 8.4633(5) Å</td>
</tr>
<tr>
<td></td>
<td>c = 13.9252(9) Å</td>
</tr>
<tr>
<td></td>
<td>α = 90°</td>
</tr>
<tr>
<td></td>
<td>β = 108.657(3)°</td>
</tr>
<tr>
<td></td>
<td>γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>1095.26(12) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 2_1</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.390 Mg/m³</td>
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<tr>
<td>F(000)</td>
<td>480</td>
</tr>
<tr>
<td>Data collection program</td>
<td>Bruker APEX2 v2009.7-0</td>
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<tr>
<td>θ range for data collection</td>
<td>2.19 to 30.52°</td>
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<td>Completeness to θ = 30.52°</td>
<td>91.3 %</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13 ≤ h ≤ 13, -11 ≤ k ≤ 11, -19 ≤ l ≤ 19</td>
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<tr>
<td>Data collection scan type</td>
<td>ω scans; 8 settings</td>
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<tr>
<td>Data reduction program</td>
<td>Bruker SAINT-Plus v7.66A</td>
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<td>Reflections collected</td>
<td>20200</td>
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<tr>
<td>Independent reflections</td>
<td>5883 [R_int = 0.0461]</td>
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<tr>
<td>Absorption coefficient</td>
<td>0.109 mm⁻¹</td>
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<tr>
<td>Absorption correction</td>
<td>None</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.9978 and 0.9755</td>
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**Structure solution and Refinement**

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

**Special Refinement Details**

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

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

Refinement of F^2 against ALL reflections. The weighted R-factor (wR) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of F^2 > 2σ(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.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U_{eq}</th>
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<tbody>
<tr>
<td>F(1)</td>
<td>3918(1)</td>
<td>4664(1)</td>
<td>10172(1)</td>
<td>32(1)</td>
</tr>
<tr>
<td>F(2)</td>
<td>3607(1)</td>
<td>4695(1)</td>
<td>8564(1)</td>
<td>27(1)</td>
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<tr>
<td>F(3)</td>
<td>3993(1)</td>
<td>2504(1)</td>
<td>9381(1)</td>
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<tr>
<td>O(1)</td>
<td>1918(1)</td>
<td>7940(1)</td>
<td>7621(1)</td>
<td>20(1)</td>
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<td>O(2)</td>
<td>1842(1)</td>
<td>7188(1)</td>
<td>9164(1)</td>
<td>22(1)</td>
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<td>O(3)</td>
<td>1481(1)</td>
<td>2670(1)</td>
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<td>25(1)</td>
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<tr>
<td>N(1)</td>
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<td>4212(1)</td>
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<td>N(2)</td>
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<td>2048(2)</td>
<td>7926(1)</td>
<td>14(1)</td>
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<tr>
<td>C(1)</td>
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<td>9288(2)</td>
<td>7202(1)</td>
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<tr>
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<td>C(7)</td>
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<td>9147(1)</td>
<td>17(1)</td>
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<td>3315(2)</td>
<td>3892(2)</td>
<td>9305(1)</td>
<td>22(1)</td>
</tr>
</tbody>
</table>
Table A2.3. Bond lengths [Å] and angles [°] for pyrroloindole 106g (CCDC 787164).

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Length/Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>F(1)-C(25)</td>
<td>1.3329(18) C(18)-H(18)</td>
</tr>
<tr>
<td>F(2)-C(25)</td>
<td>1.3403(19) C(19)-C(20)</td>
</tr>
<tr>
<td>F(3)-C(25)</td>
<td>1.3374(18) C(19)-H(19)</td>
</tr>
<tr>
<td>O(1)-C(8)</td>
<td>1.3487(18) C(20)-C(21)</td>
</tr>
<tr>
<td>O(1)-C(7)</td>
<td>1.4743(19) C(20)-H(20)</td>
</tr>
<tr>
<td>O(2)-C(8)</td>
<td>1.1966(17) C(21)-C(22)</td>
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<tr>
<td>O(3)-C(24)</td>
<td>1.2187(19) C(21)-H(21)</td>
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<td>N(1)-C(24)</td>
<td>1.3487(18) C(23)-H(23A)</td>
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<tr>
<td>N(1)-C(9)</td>
<td>1.4715(19) C(23)-H(23B)</td>
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<td>N(1)-C(16)</td>
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Table A2.4. Anisotropic displacement parameters ($\AA^2 \times 10^4$) for pyrroloindoline 106g (CCDC 787164). The anisotropic displacement factor exponent takes the form: $-2\pi^2 h^2 a^* b^* U^{11} + \ldots + 2 h k a^* b^* U^{12}$. 

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

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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).

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<tr>
<td>Crystal color</td>
<td>Colorless</td>
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**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, $a = 90°$  |
|                                  | $b = 7.2073(2)$ Å, $β = 107.9900(10)$° |
|                                  | $c = 16.3208(5)$ Å, $γ = 90°$   |
| 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                     | $-22 \leq h \leq 22, -11 \leq k \leq 12, -26 \leq l \leq 26$ |
| 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               |
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 \([l>2\sigma(l), 4934 \text{ reflections}]\)  \( R1 = 0.0469, wR2 = 0.0737 \)
R indices (all data)  \( R1 = 0.0757, wR2 = 0.0765 \)
Type of weighting scheme used  Sigma
Weighting scheme used  \( w = 1/\sigma^2(Fo^2) \)
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 (\( wR \)) and goodness of fit (\( S \)) are based on \( F^2 \), conventional R-factors (\( R \)) are based on \( F \), with \( F \) set to zero for negative \( F^2 \). The threshold expression of \( F^2 > 2\sigma( F^2) \) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on \( F^2 \) are statistically about twice as large as those based on \( F \), and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.
Table A2.7. Atomic coordinates ($x\times 10^4$) and equivalent isotropic displacement parameters ($A^2\times 10^3$) for pyrroloindoline 100c (CCDC 788553). $U_{eq}$ is defined as the trace of the orthogonalized $U_{ij}$ tensor.

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

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Table A2.9. Anisotropic displacement parameters (Å² x 10⁴) for pyrroloindoline 100c (CCDC 788553). The anisotropic displacement factor exponent takes the form: 

\[-2\pi² \sum h² a^*² U_{11} + \ldots + 2 h k a^* b^* U_{12} \].

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Table A2.10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for pyrroloindoline 100c (CCDC 788553).

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CHAPTER 3

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

3.1 INTRODUCTION

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

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

Scheme 3.1.1. Proposed mechanism of enantioselective tryptophan derivative formation.

3.1.1 Synthetic and Biological Applications of Tryptophan Derivatives

Figure 3.1.1. Tryptophan-derived biologically active natural products.

Unnatural tryptophan derivatives constitute an important target for synthetic efforts on the basis of their applications. These derivatives are incorporated into a diverse array of biologically active natural products including fumitremorgin C (141),\(^1\) stephacidin A (142),\(^2\) and the jaspamide family of cyclodepsipeptides (143);\(^3\) in particular, 141 has been extensively studied because of its function as an inhibitor of the breast cancer resistance protein (BCRP) (Figure 3.1.1). Furthermore, tryptophan derivatives have found applications as chiral catalysts\(^4\) and as biological probes. For example, these molecules have been used in protein detection and design on the basis of their fluorescent
properties, and in linear free energy relationship studies that have identified a key cation-π binding interaction for acetylcholine and the nicotinic acetylcholine receptors.

### 3.1.2 Catalytic, Enantioselective Approaches to Tryptophan Derivatives

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

Due to the applications of tryptophan derivatives, the synthesis of these molecules has been the subject of extensive research. However, there are few convergent, enantioselective approaches to tryptophan derivatives (Scheme 3.1.2). In a seminal 1980 report, Townsend and coworkers disclosed a hydrogenation catalyst prepared from tartrate-derived ligand 145, [Rh(cod)Cl₂], and H₂ that efficiently converts enamide 144 to the corresponding (R)-6-methyltryptophan 146 in 87% ee. More recently, Lectka and coworkers developed the first enantioselective imino-ene reaction using an (R)-BINAP-
derived copper complex (149) that enables access to tryptophan 150 in 85% ee from 3-methylideneindole 147 and α-imino ester 148.\textsuperscript{7b} When we initiated research directed toward tryptophan synthesis, one Friedel–Crafts approach had also been reported; Liu, Chen and coworkers disclosed a Cu-catalyzed enantioselective conjugate addition involving C3-unsubstituted indoles (90) and β-aryl-nitroacrylates (151) that provides β–substituted tryptophan derivatives (e.g. 153).\textsuperscript{7d}

### 3.1.3 Tandem Conjugate Addition/Enantioselective Protonation Reactions

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

\begin{equation}
\text{ArBF}_3\text{K} + \text{Methyl 2-acetamidoacrylate (91a)} \rightarrow \text{Phenylalanine derivatives (155)}
\end{equation}

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

Despite considerable research, examples of tandem Friedel–Crafts conjugate addition/enantioselective protonation reactions are rare and were first reported in 2008. Sibi and coworkers developed an oxazolidinone-derived acrylamide (156) for conjugate addition of pyrroles (157) catalyzed by Zn(NTf\textsubscript{2})\textsubscript{2} and dibenzofuran-derived BOX ligand 158 (Scheme 3.1.4).\textsuperscript{8k} The selectivity is thought to arise by bischelation of the catalyst with
the carbonyls of 156. The pyrrole products were prepared in excellent yield and ee; however, no examples of this reaction using indole nucleophiles have been reported. Concomitant with our work in this area, Luo and coworkers developed a related diamine 161-catalyzed tandem conjugate addition/enantioselective protonation reaction involving C2-substituted indoles (137) and acrolein derivatives (160). However, to our knowledge, the research discussed in this chapter constitutes the only enantioselective protonation approach to tryptophan derivatives.9

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

3.2 SnCl₄-PROMOTED ASYMMETRIC PROTONATION APPROACH TO TRYPTOPHAN DERIVATIVES

3.2.1 Optimization Studies

Our studies began with the investigation of 2-phenylindole (137a) using our previously optimized conditions for asymmetric pyrroloindoline synthesis. Surprisingly, these conditions resulted in formation of trifluoroacetamido ester 138a in poor yield and
ee (Table 3.2.1, entry 1). Alternatively, treatment of 137a and methyl 2-acetamidoacrylate (91a) with 1 equivalent SnCl₄ and 20 mol % (R)-BINOL in DCM delivers acetamido ester 138c in 73% yield and 78% ee (entry 3).¹⁰ Importantly, we found it critical to quench these reactions with saturated aqueous NaHCO₃; a quench with 1 M aqueous NaOH consistently results in partial racemization and under otherwise identical conditions, 138c was isolated in 75% ee (entry 6). We also hypothesized that adventitious HCl generated under the reaction conditions might artificially reduce the ee by serving as an achiral proton source for enolate protonation; therefore, a screen of acid and water scavenging additives was conducted. 2,6-lutidine inhibited the reaction, presumably through coordination of SnCl₄, and no effect was observed with the inorganic bases such as K₂CO₃ (entries 7-8). However, we were pleased to find that in the presence of 4Å molecular sieves, the reaction of 2-phenylindole (137a) furnishes acetamido ester 138c in an improved 86% yield and 81% ee (entry 9). As observed for pyrroloindoline formation, halogenated solvents are optimal with DCM providing the highest enantioselectivity (entries 9-11).

As observed for the formal (3 + 2) cycloaddition reaction, BINOL significantly increases the rate of the reaction, with SnCl₄ alone providing 138c in only 13% yield (entry 4).³ Likewise, no reaction is observed in the absence of SnCl₄ (entry 5). Although BINOL cannot independently facilitate this transformation, it is notable that exposure to HCl results in a reaction of 2-phenylindole (137a) and 91a; however, in this case 91a preferentially reacts via the imine tautomer to give quaternary amide 165 in 38% yield (Scheme 3.2.1). By contrast, diphenylphosphate only promotes trace conversion to 165.

³ For kinetics experiments involving in situ monitoring by ¹H NMR spectroscopy, see Section 3.4.10.
The reactivity promoted by HCl appears unique to \(137a\); Piersanti and coworkers reported that subjection of indole and \(91a\) to two equivalents of HCl at 0 °C gave no reaction.\(^9\) A possible explanation for this divergent reactivity is the enhanced stability of the imine intermediate resulting from conjugate addition with \(137a\) that derives from conjugation with the C2-phenyl substituent.

**Table 3.2.1. Optimization of reaction parameters.\(^9\)**

<table>
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<th>Entry</th>
<th>(R^3, R^4)</th>
<th>pdt</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield (%)(^b)</th>
<th>ee (%)(^c)</th>
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<td>(138a)</td>
<td>DCM</td>
<td>--</td>
<td>12</td>
<td>35</td>
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<tr>
<td>2</td>
<td>Me, CF(_3) (91b)</td>
<td>(138b)</td>
<td>DCM</td>
<td>--</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
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<td>(138c)</td>
<td>DCM</td>
<td>(\sigma)</td>
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<tr>
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<td>DCM</td>
<td>(\sigma)</td>
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<td>--</td>
</tr>
<tr>
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<td>(\tau)</td>
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<td>(K_2CO_3)</td>
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<td>2,6-lutidine</td>
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<td>--</td>
</tr>
<tr>
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<td>(138c)</td>
<td>DCM</td>
<td>4Å MS</td>
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<td>81</td>
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<tr>
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<td>(138c)</td>
<td>DCM</td>
<td>4Å MS</td>
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<td>(138c)</td>
<td>DCE</td>
<td>4Å MS</td>
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<td>72</td>
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</tbody>
</table>

\(^a\) Reactions conducted in a glovebox on 0.2 mmol scale for 2 h. Reactions worked up using saturated aqueous NaHCO\(_3\).\(^b\) Isolated yield. \(^c\) Determined by chiral stationary phase SFC. \(^d\) Reaction run without \((R)-\)BINOL. \(^e\) Reaction run without SnCl\(_4\). \(^f\) Reaction worked up using 1 M aqueous NaOH.

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

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

Table 3.2.2. Catalyst optimization. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (mol %)</th>
<th>Yield (%) b</th>
<th>ee (%) c</th>
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<td>20</td>
<td>86</td>
<td>81</td>
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<td>2</td>
<td>102g</td>
<td>20</td>
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<td>3</td>
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<td>83</td>
<td>87</td>
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<tr>
<td>4</td>
<td>102i</td>
<td>20</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>102j</td>
<td>20</td>
<td>85</td>
<td>90</td>
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<td>93</td>
</tr>
<tr>
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<td>20</td>
<td>7</td>
<td>1</td>
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<td>20</td>
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<td>78</td>
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<td>20</td>
<td>9</td>
<td>–32</td>
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</table>

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

Interestingly, (S)-VANOL (166), a vaulted chiral diol developed by Wulff and coworkers, provided the highest yield and ee we have observed to date, furnishing 138c in 86% yield and –95% ee (Table 3.2.2, entry 11). Although 2-phenylindole (137a) gave
optimal results with 166, we elected to use (R)-3,3’-dibromo BINOL (102k) in the
evaluation of substrate scope. While both 102k and 166 are commercially available, 102k
is much less expensive and readily accessible in three steps from BINOL. Furthermore,
although 166 proved optimal for 137a, this trend was not consistently observed with
other indole substrates (Table 3.2.5).

Figure 3.2.1 Catalysts.

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

A variety of other chiral diols were also evaluated during the course of our
optimization studies (Table 3.2.3). As observed for the formal (3 + 2) cycloaddition
reaction, non-BINOL-derived chiral diols, including (R)-5,5’,6,6’,7,7’,8,8’-octahydro-
BINOL (168), TADDOLs 103 and 169, and hydrobenzoin (104) provided tryptophan
products either in low ee (entries 2,5,14) or as a racemate (entries 3-4). In addition, (R)-2-
alkoxy-BINOL derivatives gave reduced ee, which is indicative of the key role played by
the hydroxyl protons in the enantioselective protonation (entries 15-18).
With optimal conditions for tryptophan synthesis in hand, we evaluated the possibility of reducing the loading of both (R)-3,3′-dibromo-BINOL (102k) and SnCl₄ (Table 3.2.4). The loading of 102k can be reduced as low as 10 mol % without significant erosion of ee; 138c is obtained in reduced ee (88%) when 5 mol % 102k is employed (entries 4-5).
However, it appears that the reaction requires a full equivalent of SnCl₄. Unlike in the formal (3 + 2) cycloaddition and the EtAlCl₂-promoted tryptophan synthesis by Piersanti and coworkers wherein the reactions barely proceed with substoichiometric Lewis acid loadings (Chapter 2), we observed that the loading of SnCl₄ is directly proportional to yield; for example, use of 0.6 equiv SnCl₄ provides 66% yield of 138c.

### Table 3.2.4. Catalytic loadings of 102k and SnCl₄.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diol</th>
<th>Diol (mol %)</th>
<th>SnCl₄ (equiv)</th>
<th>Yield (%)ᵇ</th>
<th>ee (%)ᶜ</th>
</tr>
</thead>
<tbody>
<tr>
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<td>20</td>
<td>1.0</td>
<td>76</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>102k</td>
<td>40</td>
<td>1.0</td>
<td>76</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>102k</td>
<td>15</td>
<td>1.0</td>
<td>77</td>
<td>93</td>
</tr>
<tr>
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<td>102k</td>
<td>10</td>
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<td>92</td>
</tr>
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<td>102k</td>
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<td>88</td>
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<tr>
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<td>102a</td>
<td>20</td>
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<td>81</td>
</tr>
<tr>
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<td>20</td>
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<td>79</td>
</tr>
<tr>
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<td>102a</td>
<td>20</td>
<td>0.6</td>
<td>66</td>
<td>77</td>
</tr>
</tbody>
</table>

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

### 3.2.2 Substrate Scope of Tryptophan Synthesis

The substrate scope was explored under the optimized conditions using a 20 mol % loading of (R)-3,3’-dibromo-BINOL (102k) to ensure optimal results for all substrates (Table 3.2.5). In contrast to the trend observed in the formal (3 + 2) cycloaddition reaction (Chapter 2), N-alkylated indoles react in lower yield than (1H)-derivatives, with tryptophans 138e and 138f both accessed in 85% ee (entries 2-3). Electronically diverse indoles functionalized at C4, C5, C6, and C7 provided uniformly high ees; however, electron-poor indoles furnished tryptophan products in lower yields (e.g. 138l). A variety
of alkyl and aryl substituents were tolerated at C2 of the indole although ortho-functionalized aryl substituents (e.g. 138t) and very small or bulky alkyl substitution resulted in lower yields and ee (entries 18-23).

Table 3.2.5. Substrate scope.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate Structure</th>
<th>Yield</th>
<th>ee (%)</th>
</tr>
</thead>
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<td>93%</td>
</tr>
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<td>63%</td>
<td>85%</td>
</tr>
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</tr>
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<td>83%</td>
<td>95%</td>
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<td>88%</td>
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<td><img src="image" alt="138z" /></td>
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<td>90%</td>
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</table>

\(^a\) Reaction conducted in a glovebox for 2 h on 0.1 or 0.2 mmol scale. Isolated yields are reported. Enantiomeric excess determined by chiral SFC analysis.\(^b\) 1.6 equivs SnCl\(_4\) was employed.\(^c\) Reaction run with (S)-VANOL (166).

For a few cases where low yield and ee was observed, the reactions were also conducted using (S)-VANOL (166) as the catalyst (entries 18 and 22). Unfortunately, the trend observed with 2-phenylindole, wherein higher yield and ee was observed with 166,
Chapter 3—Synthesis of Tryptophan Derivatives

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

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

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

\[ \text{Direct alkylation of indole (163):} \]

\[ \text{Two-step approach with 2-(trimethylsilyl)indole (137x):} \]

\[ \text{Reactions conducted in a glovebox on 0.1 or 0.2 mmol scale. Isolated yields are reported. Enantiomeric excess was determined by chiral stationary phase SFC.} \]
3.2.3 Derivatization of Tryptophan Products

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

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

3.2.4 Comparison of New Conditions for Pyrroloindoline Formation

On the basis of mechanistic similarities, we envisioned that the optimal conditions for the tandem conjugate addition/protonation reaction might afford improved yields and selectivities for the formal (3 + 2) cycloaddition reaction. When methyl 2-acetamidoacrylate (91a)—the optimal partner for tryptophan synthesis—is employed, 1,3-dimethylindole (75) reacts in the presence of (R)-BINOL•SnCl₄ to give pyrroloindoline 100b in 5:1 dr, with the major diastereomer formed in 65% ee (Table 3.2.6, entry 1). Alternatively, exposure of a mixture of 91a and 75 to (R)-3,3’-dibromo-BINOL and 4Å MS furnished 100b in an improved 8:1 dr and 87% ee for the exo diastereomer, albeit in lower yield (entry 2). We observed a similar trend with the benzyl 2-trifluoroacetamidoacrylate (91d)—the optimal partner for pyrroloindoline synthesis. The
reaction of 75 and benzyl 2-trifluoroacetamidoacrylate (91d) using (R)-3,3'-dibromo-BINOL and 4Å MS gave improved dr and the exo diastereomer was formed in an exceptional 98% ee, but the yield was dramatically reduced to only 39% (entry 4). Thus, an appropriate matching of acrylate and catalyst is required to obtain both high yields and selectivities.

Table 3.2.6. Comparison of conditions for pyrroloindoline formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>R¹, R²</th>
<th>pdt</th>
<th>Yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵃ</td>
<td>102a</td>
<td>Me, Me</td>
<td>(91a)</td>
<td>100b</td>
<td>70</td>
<td>5:1</td>
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<tr>
<td>2ᵇ</td>
<td>102k, 4Å MS</td>
<td>Me, Me</td>
<td>(91a)</td>
<td>100b</td>
<td>58</td>
<td>8:1</td>
</tr>
<tr>
<td>3ᶜ</td>
<td>102a</td>
<td>CF₃, Bn</td>
<td>(91d)</td>
<td>100e</td>
<td>86</td>
<td>4:1</td>
</tr>
<tr>
<td>4ᵈ</td>
<td>102k, 4Å MS</td>
<td>CF₃, Bn</td>
<td>(91d)</td>
<td>100e</td>
<td>39</td>
<td>7:1</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield. ᵇ Determined by ¹H NMR analysis of mixture. ᶜ Determined by chiral stationary phase SFC. ᵈ Reaction run with 1.0 equiv acrylate, 1.2 equiv SnCl₄. ₑ Reaction run with 1.2 equiv acrylate, 1.0 equiv SnCl₄.

These results are suggestive of subtle mechanistic differences between the tandem conjugate addition/enantioselective protonation reaction and the formal (3 + 2) cycloaddition reaction. For example, in the tryptophan synthesis it is proposed that the stoichiometric proton source required for catalyst turnover derives from C3 of the indole, which is lost during rearomatization (Scheme 3.2.5). In contrast, in the pyrroloindoline formation, the stoichiometric proton is hypothesized to derive from the Lewis acid-coordinated trifluoroacetamide group (Scheme 2.3.2). Unfortunately, deuterium labeling studies aimed at identifying the stoichiometric proton source have been inconclusive, as exposure of deuterated indoles to BINOL•SnCl₄ results in rapid deuterium scrambling (3.4.9).
3.3 CONCLUDING REMARKS

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

3.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride, deuterated methylene chloride, dioxane, ether, tetrahydrofuran, and toluene were dried by passing through activated alumina. Dichloroethane and chloroform were distilled over calcium hydride. Powdered 4Å molecular sieves were flame-dried under vacuum immediately prior to use. Potassium carbonate was dried for 12 h at 130 °C under vacuum and 2,6-lutidine was distilled over AlCl₃. All other commercially obtained reagents were used as received unless specifically indicated. (R)-BINOL (102a), 2-phenylindole (137a) and 2-methylindole (137b) were purchased from Alfa Aesar, N-methyl-2-phenylindole (137c) was obtained from Sigma-Aldrich, and 1 M SnCl₄ in DCM was purchased from Acros Organics. (R)-3,3’-diphenyl-BINOL (102g),¹² (R)-3,3’-dimethyl-BINOL (102h),¹³ (R)-3,3’-dichloro-BINOL (102j),¹⁴ (R)-3,3’-dibromo-BINOL (102k),¹⁵ (R)-3,3’-dimethoxy-BINOL (102i),¹⁵ (R)-6,6’-dimethyl-BINOL (102n),¹⁶ (R)-6,6’-dibromo-BINOL (102f),¹⁷ (R)-2’-methoxy-[1,1’-binaphthalen]-2-ol (102b),¹⁸ (R)-2’-isopropoxy-[1,1’-binaphthalen]-2-ol (102u),¹⁹ (R)-3,3’-difluoro-BINOL (102o),²⁰ (R)-3-phenyl-BINOL (102p),²¹ (R)-5,5’,6,6’,7,7’,8,8’-octahydro-BINOL (168),²² (R)-2’-benzoyl-[1,1’-binaphthalen]-2-ol (102v),²³ (R)-3-bromo-BINOL (102q) and (R)-3-iodo-BINOL (102r),²⁴ TADDOL (103),²⁵ Naphtyl-TADDOL (169),²⁶ and 2-(trimethylsilyl)indole (137x),²⁷ were prepared according to literature procedures. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel column
chromatography was performed either as described by Still et al. (W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* 1978, 43, 2923.) using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiSilica gel Rf system (Teledyne ISCO Inc.). $^1$H and $^{13}$C NMR were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Varian Inova 600 (at 600 MHz and 150 MHz respectively, and are reported relative to internal chloroform ($^1$H, $\delta = 7.26$, $^{13}$C, $\delta = 77.0$) or internal acetonitrile ($^1$H, $\delta = 1.94$, $^{13}$C, $\delta = 1.32$). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm$^{-1}$). Analytical SFC was performed with a Mettler SFC supercritical CO$_2$ analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, and OB-H columns (4.6 mm x 25 cm). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.
3.4.2 Catalyst and Substrate Preparation

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

![Chemical Structure](image)

To a flame-dried 100 mL flask containing MOM-protected (R)-BINOL 178 \(^{13}\) (748 mg, 2.00 mmol, 1.00 equiv) was added Et\(_2\)O (45 mL), followed by dropwise addition of \(n\)-BuLi as a solution in hexanes (2.5 M, 960 \(\mu\)L, 2.40 mmol, 1.20 equiv) at room temperature. The mixture was then stirred at room temperature for 3 h and subsequently cooled to \(-78^\circ C\), followed by addition of C\(_2\)Cl\(_6\) (569 mg, 2.40 mmol, 1.20 equiv) in one portion. The reaction mixture was allowed to warm to room temperature over 3 h, then diluted with EtOAc (15 mL) and washed with saturated aqueous NH\(_4\)Cl (50 mL). The aqueous layer was extracted with EtOAc (45 mL) and the combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The crude yellow oil was purified by silica gel chromatography (0:100 to 12:88 EtOAc:hexanes) to yield 328 mg (40% yield) of 179 as a white solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.05 (s, 1H), 7.97 (d, \(J = 9.0\) Hz, 1H), 7.87 (d, \(J = 8.1\) Hz, 1H), 7.81 (d, \(J = 8.2\) Hz, 1H), 7.59 (d, \(J = 9.1\) Hz, 1H), 7.42 (ddd, \(J = 8.1, 6.7, 1.3\) Hz, 1H), 7.37 (ddd, \(J = 8.1, 6.8, 1.2\) Hz, 1H), 7.28 (ddd, \(J = 8.2, 6.8, 1.3\) Hz, 1H), 7.24 (ddd, \(J = 8.5, 6.7, 1.3\) Hz, 1H), 7.18 (dddd, \(J = 8.6, 1.3, 0.7, 0.7\) Hz, 1H), 7.16 (ddd, \(J = 8.5, 1.8, 0.8\) Hz, 1H), 5.15 (d, \(J = 7.0\) Hz, 1H), 5.04 (d, \(J = 7.0\) Hz, 1H), 4.80 (d, \(J = 5.6\) Hz, 1H), 4.75 (d, \(J = 5.6\) Hz, 1H), 3.19 (s, 3H), 2.71 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 152.9, 148.9, 133.8, 132.6, 131.1, 130.0, 129.5, 128.8, 128.0, 127.9, 127.8, 127.0, 126.7, 126.4, 126.1, 125.8, 125.5, 124.2, 119.9, 116.3, 98.8, 94.9, 56.5, 55.9; IR (NaCl/thin film): 2955, 2902, 1594, 1508, 1354, 1241, 1159, 1149, 1034, 1014, 961, 922
A 10 mL flask was charged with 179 (305 mg, 0.75 mmol, 1.00 equiv), dioxane (3.7 mL) and aqueous HCl (12 M, 130 µL, 1.58 mmol, 2.10 equiv), then heated to 50 ºC for 2 h. The mixture was cooled to room temperature, then diluted with H2O (30 mL) and extracted with EtOAc (6 x 20 mL). The combined organic layers were dried (Na2SO4), filtered and concentrated. The crude residue was purified by silica gel chromatography (0:100 to 20:80 EtOAc:hexanes) to yield 210 mg (87% yield) of (R)-3-chloro-BINOL (102i) as a white foam, which was dried over P2O5 under vacuum. 1H NMR (500 MHz, CDCl3) δ 8.09 (s, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.34 – 7.28 (m, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 5.60 (s, 1H), 4.94 (s, 1H); 13C NMR (125 MHz, CDCl3) δ 152.1, 148.3, 133.1, 132.4, 131.3, 129.7, 129.32, 129.26, 128.4, 127.7, 127.5, 127.3, 125.1, 124.6, 124.1, 123.9, 122.4, 117.7, 113.6, 111.7; IR (NaCl/thin film): 3503, 3057, 1620, 1596, 1502, 1451, 1379, 1265, 1212, 1184, 1146, 828 cm⁻¹; [α]D²⁵ = +55.4º (c = 1.01, CHCl₃). HRMS (MM) calc’d for [M-H]⁻ 319.0531, found 319.0549.
Preparation of (R)-6,6'-dimethoxy-BINOL (102m)

(R)-6,6’-dimethoxy-BINOL (102m) was prepared following a procedure adapted from a reported synthesis of (R)-3,3’-dimethoxy-BINOL (102l).\(^\text{15}\) To a 25 mL flask containing MOM–protected (R)-6,6’-dibromo-BINOL 180 (1.10 g, 2.07 mmol, 1.00 equiv) was added THF (6.3 mL). The flask was cooled to –78 °C, followed by dropwise addition of \(n\)-BuLi as a solution in hexanes (2.5 M, 2.50 mL, 6.20 mmol, 3.00 equiv). After stirring 1 hour at –78 °C, \(\text{B(OMe)}_3\) (645 mg, 6.20 mmol, 3.00 equiv) was added and the reaction was allowed to warm to room temperature. After 14 hours, the reaction mixture was concentrated to give the crude borate intermediate, which was suspended in benzene (7.2 mL) and cooled to 0 °C, followed by dropwise addition of aqueous hydrogen peroxide (30 wt %, 0.61 mL, 5.98 mmol, 2.89 equiv). The suspension was heated to reflux for 4 hours, then cooled to room temperature, poured into ice-cold saturated aqueous NaSO\(_3\) (20 mL), and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (30 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. The crude residue was purified by silica gel chromatography (0:100 to 50:50 EtOAc:hexanes) to yield 512 mg (61% yield) of 181 as a light yellow foam.\(^*\)\(^\text{1H}\) NMR (500 MHz, CD\(_3\)CN) \(\delta\) 7.80 (ddd, \(J = 9.1, 0.8, 0.4\) Hz, 2H), 7.51 (d, \(J = 9.1\) Hz, 2H), 7.20 (ddd, \(J = 2.5, 0.5, 0.5\) Hz, 2H), 7.09 (br s, 2H), 6.93 (ddd, \(J = 9.1, 0.7, 0.7\) Hz, 2H), 6.87 (dd, \(J = 9.1, 2.5\) Hz, 2H), 6.02 (d, \(J = 6.7\) Hz, 2H), 4.94 (d, \(J = 6.7\) Hz, 2H), 3.11 (s, 6H) ; \(^{13}\)C NMR (125 MHz, CD\(_3\)CN) \(\delta\) 154.4, 151.6, 132.1, 129.6, 128.4, 127.8, 122.1,
A 15 mL flask was charged with 181 (200 mg, 0.493 mmol, 1.00 equiv) and K$_2$CO$_3$ (177 mg, 1.28 mmol, 2.60 equiv). DMF (2 mL) was added, followed by MeI (123 µL, 1.97 mmol, 4.00 equiv) dropwise. The reaction was then heated to 55 ºC for 22 hours, then cooled to room temperature and quenched with saturated aqueous NH$_4$Cl (2 mL) and Et$_3$N (3 drops). The mixture was stirred at room temperature for 6 hours, then diluted with H$_2$O (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (15 mL), dried (Na$_2$SO$_4$), and concentrated. THF (28 mL) and IPA (9.5 mL) were added to the crude residue, followed by dropwise addition of aqueous HCl (6.0 M, 9.4 mL). The reaction was stirred at room temperature for 3 hours, then diluted with H$_2$O (70 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with saturated aqueous NaHCO$_3$ (2 x 45 mL) and brine (45 mL), then dried (Na$_2$SO$_4$), filtered, and concentrated. The crude oil was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 62 mg (36% yield) of (R)-6,6'-dimethoxy-BINOL (102m) as a light brown solid, which was dried over P$_2$O$_5$ under high vacuum. Spectral data are in agreement with the literature.\textsuperscript{28}
Preparation of 1-allyl-2-phenylindole (137d)

To a 50 mL flask was added NaH (620 mg, 15.5 mmol, 3.00 equiv) and DMF (8 mL) and the suspension was cooled to 0 ºC in an ice bath. A solution of 2-phenylindole 137a (1.00 g, 5.18 mmol, 1.00 equiv) in DMF (3 mL) was added slowly to the suspension over 15 minutes and the reaction mixture was further stirred at 0 ºC for 20 minutes, followed by dropwise addition of allyl bromide (670 µL, 7.77 mmol, 1.50 equiv). The ice bath was then removed and the mixture was stirred for 15 minutes, then quenched by addition of saturated aqueous NH₄Cl (5 mL) and Et₃N (5 drops). After 2 hours, the reaction was diluted with H₂O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (120 mL), dried (Na₂SO₄), filtered, and concentrated. The crude was then purified by reverse phase preparatory HPLC (55:45 to 95:5 MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 µM column (9.4 x 250 mm and 21.2 x 150 mm) to yield 687 mg (57% yield) of 1-allyl-2-phenylindole (137d) as a yellow solid and 331 mg (23% yield) of 1,3-diallyl-2-phenylindole (182) as a yellow oil.

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

¹H NMR (500 MHz, CDCl₃) δ 7.65 (ddd, J = 7.8, 1.2, 0.8 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.42 – 7.38 (m, 1H), 7.33 (br d, J = 8.2 Hz, 1H), 7.22 (ddd, J = 7.0, 7.0, 1.3 Hz, 1H), 7.15 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H), 6.60 (br s, 1H), 6.02 (ddt, J = 17.2, 10.5, 4.4 Hz, 1H), 5.22 (dtd, J = 10.5, 1.8, 1.1 Hz, 1H), 3.08 (m, 1H), 2.48 (m, 1H).
Hz, 1H), 5.00 (dtd, J = 17.1, 2.0, 1.2 Hz, 1H), 4.74 (dt, J = 4.2, 1.9 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 141.5, 137.8, 133.8, 132.7, 129.1, 128.5, 128.1, 128.0, 121.7, 120.5, 120.0, 116.5, 110.3, 102.0, 46.5; IR (NaCl/thin film): 3055, 2917, 1602, 1462, 1443, 1392, 1345, 1317, 1162 cm$^{-1}$; HRMS (APCI) calc’d for [M+H]$^+$ = 234.1277, found 234.1284.

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

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.65 (ddd, J = 7.8, 1.2, 0.7 Hz, 1H), 7.50 – 7.40 (m, 5H), 7.33 (ddd, J = 8.1, 0.9, 0.9 Hz, 1H), 7.24 (ddd, J = 7.0, 7.0, 1.2 Hz, 1H), 7.16 (ddd, J = 7.0, 7.0, 1.1 Hz, 1H), 6.05 (ddt, J = 17.0, 10.1, 5.9 Hz, 1H), 5.91 (ddt, J = 17.1, 10.4, 4.7 Hz, 1H), 5.14 (ddt, J = 10.4, 1.8, 1.2 Hz, 1H), 5.08 – 5.02 (m, 2H), 4.92 (ddt, J = 17.1, 1.9, 1.3 Hz, 1H), 4.62 (dt, J = 4.6, 1.9 Hz, 2H), 3.46 (dt, J = 6.0, 1.7 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 138.0, 137.9, 136.7, 133.9, 131.8, 130.4, 128.3, 128.2, 128.1, 128.0, 121.7, 119.34, 119.30, 116.2, 114.6, 110.9, 110.1, 46.4, 29.2; IR (NaCl/thin film): 3056, 2915, 1637, 1463, 1443, 1408, 1360, 1340, 1191 cm$^{-1}$; HRMS (MM) calc’d for [M+H]$^+$ = 274.1590, found 274.1591.
Preparation of 2-(2-fluorophenyl)indole (137r)

2-(2-fluorophenyl)indole (137r) was prepared by an analogous procedure to that reported by Sakai et al.\textsuperscript{29} A flame-dried flask was charged with 2-iodoaniline (183, 200 mg, 0.90 mmol, 1.00 equiv), ethynyl-2-fluorobenzene (184, 133 mg, 1.10 mmol, 1.20 equiv), Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (13 mg, 0.02 mmol, 0.02 equiv), copper (I) iodide (2.0 mg, 0.025 mmol, 0.01 equiv) and Et\textsubscript{3}N (4 mL). The mixture was stirred overnight at room temperature, then filtered through a plug of silica, concentrated and redisolved in PhMe (5 mL). InBr\textsubscript{3} (16 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was heated to 110 ºC for 5 h, then cooled to room temperature, filtered through celite, and concentrated. The crude residue was purified by silica gel chromatography (10:90 EtOAc:hexanes) to yield 148 mg (77% yield) of 2-(2-fluorophenyl)indole (137r) as a white solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.89 (br s, 1H), 7.80 (ddd, \textit{J} = 7.8, 7.8, 1.8 Hz, 1H), 7.66 (ddddd, \textit{J} = 2.5, 1.3, 0.8, 0.8 Hz, 1H), 7.43 (ddddd, \textit{J} = 8.1, 1.5, 0.8 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.26 – 7.16 (m, 3H), 7.14 (ddddd, \textit{J} = 8.0, 7.0, 1.0 Hz, 1H), 6.97 (d, \textit{J} = 1.9 Hz, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 159.3 (d, \textit{J}_{\text{C-F}} = 246.4 Hz), 134.6 (d, \textit{J}_{\text{C-F}} = 501.8 Hz), 128.8 (d, \textit{J}_{\text{C-F}} = 8.8 Hz), 128.1, 128.0 (d, \textit{J}_{\text{C-F}} = 4.1 Hz), 124.8 (d, \textit{J}_{\text{C-F}} = 3.2 Hz), 122.7, 120.6, 120.2, 119.9 (d, \textit{J}_{\text{C-F}} = 11.0 Hz), 116.6, 116.4, 111.0, 101.6 (d, \textit{J}_{\text{C-F}} = 3.0 Hz); IR (NaCl/thin film): 3469, 3042, 2918, 2848, 1577, 1472, 1460, 1212, 1178, 1109, 928 cm\textsuperscript{-1}; HRMS (MM) calc’d for [M+H]\textsuperscript{+} 212.0870, found 212.0869.
2-(ethylphthalimide)indole (137w) was prepared by an analogous procedure to that reported by Sakai et al.\textsuperscript{29} A flame-dried flask was charged with 2-iodoaniline (183, 500 mg, 2.30 mmol, 1.00 equiv), 2-(but-3-ynd-1-yl)isoindoline-1,3-dione (185, 550 mg, 2.75 mmol, 1.20 equiv), Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (32 mg, 0.05 mmol, 0.02 equiv), copper (I) iodide (4.5 mg, 0.025 mmol, 0.01 equiv) and Et\textsubscript{3}N (8 mL). The mixture was stirred overnight at room temperature, then filtered through a plug of silica, concentrated and redissolved in PhMe (10 mL). InBr\textsubscript{3} (40 mg, 0.1 mmol, 0.05 equiv) was added in one portion and the mixture was heated to 110 °C for 5 h, then cooled to room temperature, filtered through celite and concentrated. The crude residue was purified by silica gel chromatography (60:40 EtOAc:hexanes) to yield 302 mg (45% yield) of 2-(ethylphthalimide)indole (137w) as a light yellow solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.26 (br s, 1H), 7.83 (dd, J = 5.5, 3.1 Hz, 2H), 7.71 (dd, J = 5.5, 3.1 Hz, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.13 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.06 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.33 (d, J = 1.2 Hz, 1H), 4.06 (t, J = 7.5 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 168.3, 136.1, 134.9, 134.1, 131.9, 128.6, 123.4, 121.4, 120.0, 119.7, 110.6, 101.1, 37.1, 27.4.; IR (NaCl/thin film): 3366, 1772, 1707, 1653, 1617, 1466, 1395, 1363, 1293 cm\textsuperscript{-1}; HRMS (MM) calc’d for [M+H]\textsuperscript{+} 291.1128, found 291.1138.
3.4.3 Optimization of Reaction Parameters

3.4.3.1 General Procedure 1

An oven-dried vial was charged with 2-phenylindole (137a, 0.20 mmol, 1.00 equiv), the acrylate (0.24 mmol, 1.20 equiv) and an (R)-BINOL derivative and pumped into a glove box. The vial was charged with solvent to an indole concentration of 0.12 M, and SnCl$_4$ (1.00 equiv, as a 1.0 M solution in DCM) was added. The reaction was stirred at 20 °C for 2 hours, after which time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO$_3$ (5 mL), dried (Na$_2$SO$_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

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

- flame-dried powdered 4Å molecular sieves (200 wt % relative to indole)
- K$_2$CO$_3$ (1.00 equiv)
- 2,6-lutidine (1.00 equiv)

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

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

(S)-Nα-Trifluoroacetyl-2-phenyltryptophan benzyl ester (138a)

Prepared from benzyl 2-trifluoroacetamidoacrylate\(^{30}\) (91d, 65.5 mg, 0.24 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (30:70 to 70:30 DCM:hexanes) to yield 11.1 mg (12% yield) of 138a as a yellow solid. The enantiomeric excess was determined to be 35% by chiral SFC analysis (OB-H, 2.5 mL/min, 15% IPA in CO\(_2\), \(\lambda = 254\) nm):

\(t_R\) (major) = 11.0 min, \(t_R\) (minor) = 12.9 min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.14 (br s, 1H), 7.57 (ddd, \(J = 7.9, 1.8, 0.7\) Hz, 1H), 7.54 – 7.50 (m, 2H), 7.50 – 7.45 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.29 (m, 3H), 7.24 (ddd, \(J = 8.1, 7.1, 1.1\) Hz, 1H), 7.16 (ddd, \(J = 8.0, 7.1, 1.0\) Hz, 1H), 7.11 – 7.07 (m, 2H), 6.67 (br d, \(J = 7.6\) Hz, 1H), 4.95 (d, \(J = 12.2\) Hz, 1H), 4.88 (dt, \(J = 7.8, 6.0\) Hz, 1H), 4.53 (d, \(J = 12.2\) Hz, 1H), 3.65 – 3.56 (m, 2H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.1, 156.6 (q, \(J_{C,F} = 37.8\) Hz), 136.3, 135.6, 134.6, 132.4, 129.2, 128.9, 128.5, 128.44, 128.38, 128.2, 128.1, 122.8, 120.3, 118.6, 115.3 (q, \(J_{C,F} = 287.9\) Hz), 111.0, 105.6, 67.5, 53.3, 26.7; IR (NaCl/thin film): 3391, 3061, 2924, 1714, 1542, 1457, 1210, 1173 cm\(^{-1}\); \([\alpha]_D^{25} = +3.5^\circ\) (c = 0.44, CHCl\(_3\)). HRMS (MM) calc’d for [M+H]+ 467.1577, found 467.1580.
Prepared from methyl 2-trifluoroacetamidoacrylate$^{31}$ (91b, 47.3 mg, 0.24 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (0:100 to 5:95 EtOAc:toluene, then 0:100 to 20:80 EtOAc:hexanes) to yield 9.0 mg (12% yield) of 138b as a yellow solid. The enantiomeric excess was determined to be 42% by chiral SFC analysis (AS-H, 2.5 mL/min, 10% IPA in CO$_2$, $\lambda$ = 254 nm): $t_R$(major) = 8.7 min, $t_R$(minor) = 7.7 min. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.17 (br s, 1H), 7.58 – 7.52 (m, 3H), 7.52 – 7.47 (m, 2H), 7.43 – 7.39 (m, 1H), 7.38 (ddd, $J$ = 8.1, 0.9, 0.9 Hz, 1H), 7.23 (ddd, $J$ = 8.2, 7.0, 1.2 Hz, 1H), 7.16 (ddd, $J$ = 8.0, 7.0, 1.0 Hz, 1H), 6.65 (br d, $J$ = 7.3 Hz, 1H), 4.83 (dt, $J$ = 7.8, 5.6 Hz, 1H), 3.66 – 3.56 (m, 2H), 3.34 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 156.6 (q, $J_{C-F}$ = 37.7 Hz), 136.3, 135.6, 132.5, 129.2, 129.0, 128.4, 128.2, 122.8, 120.3, 118.5, 115.3 (q, $J_{C-F}$ = 287.7 Hz), 111.0, 105.5, 53.2, 52.5, 26.4; IR (NaCl/thin film): 3391, 3057, 2917, 2849, 1718, 1542, 1458, 1449, 1211, 1170 cm$^{-1}$; $[\alpha]_D^{25}$ = +22.3º ($c$ = 0.39, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 391.1264, found 391.1267.

### 3.4.4 Optimized Conjugate Addition/Asymmetric Protonation

#### 3.4.4.1 General Procedure 2

An oven-dried vial was charged with the indole (1.00 equiv), methyl 2-acetamidoacrylate (91a, 1.20 equiv)$^{32}$ and (R)-3,3’-dibromo-BINOL (102k, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to indole). The vial was charged with DCM to an indole concentration of 0.12 M, and SnCl$_4$ (1.00 equiv unless specifically indicated, as a 1 M solution in DCM) was added. The reaction was stirred at 20 °C for 2 hours, after which
time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (5 mL), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

3.4.4.2 Characterization Data

(S)-Nα-Acetyl-2-phenyltryptophan methyl ester (138c)

Prepared from 2-phenylindole (137a, 19.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 25.6 mg (76% yield) of 138c as a white foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): \( t_R(\text{major}) = 5.7 \text{ min}, t_R(\text{minor}) = 6.9 \text{ min.} \) \([\alpha]_D^{25} = +37.7^\circ (c = 0.94, \text{CHCl}_3)\). Spectral data matches that reported in the literature.\(^{33}\)

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

Prepared from 1-methyl-2-phenylindole (137c, 41.4 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 55:45 EtOAc:hexanes) to yield 43.4 mg (63% yield) of 138e as a yellow solid. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO₂, λ = 254 nm): \( t_R(\text{major}) = 4.6 \text{ min, } t_R(\text{minor}) = 3.9 \text{ min.} \) \(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.60 \text{ (ddd, } J = 7.9, 1.2, 0.7 \text{ Hz, 1H), 7.56 – 7.49 (m, 2H), 7.48 – 7.44 (m, 1H), 7.42 – 7.38 (m, 2H), 7.34 (ddd, } J = 8.2, 0.9, 0.9 \text{ Hz, 1H)\).}
Hz, 1H), 7.26 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.17 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 5.72 (br d, J = 7.8 Hz, 1H), 4.74 (dt, J = 8.0, 5.6 Hz, 1H), 3.57 (s, 3H), 3.39 (s, 3H), 3.41 (dd, J = 14.7, 5.7 Hz, 1H), 3.34 (dd, J = 14.8, 5.6 Hz, 1H), 1.73 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 172.2, 169.5, 139.2, 136.9, 131.6, 130.7, 128.7, 128.4, 127.9, 122.0, 119.7, 118.7, 109.5, 106.7, 52.8, 52.0, 30.8, 26.6, 23.0.; IR (NaCl/thin film): 3288, 3055, 2950, 1743, 1657, 1539, 1469, 1441, 1368, 1238, 1212 cm−1; [α]D25 = +21.3º (c = 0.91, CHCl3).

HRMS (MM) calc’d for [M+H]+ 351.1703, found 351.1708.

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

Prepared from 1-allyl-2-phenylindole (137d, 46.6 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 55:45 EtOAc:hexanes) to yield 51.3 mg (68% yield) of 138f as a yellow foam. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AS-H, 2.5 mL/min, 30% IPA in CO2, λ = 254 nm): tR(major) = 2.9 min, tR(minor) = 2.4 min. 1H NMR (500 MHz, CDCl3) δ 7.62 (ddd, J = 7.8, 1.0, 1.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.47 – 7.42 (m, 1H), 7.42 – 7.37 (m, 2H), 7.30 (ddd, J = 8.1, 0.9, 0.9 Hz, 1H), 7.23 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.17 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 5.85 (ddt, J = 17.1, 10.3, 4.7 Hz, 1H), 5.76 (br d, J = 7.9 Hz, 1H), 5.11 (ddt, J = 10.4, 1.7, 1.2 Hz, 1H), 4.82 (dt, J = 17.1, 1.9, 1.3 Hz, 1H), 4.76 (dt, J = 8.0, 5.8 Hz, 1H), 4.56 (dt, J = 4.7, 1.8 Hz, 2H), 3.39 (s, 3H), 3.36 (dd, J = 14.7, 5.7 Hz, 1H), 3.29 (dd, J = 14.7, 5.9 Hz, 1H), 1.75 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 172.2, 169.5, 139.0, 136.3, 133.5, 131.5, 130.5, 128.7, 128.5, 128.1, 122.0, 119.8, 118.8, 116.3, 110.2, 107.2, 52.8, 52.0, 46.3, 26.8, 23.0; IR (NaCl/thin film): 3435, 3287, 3056, 2950, 2926,
2851, 1744, 1658, 1538, 1500, 1408, 1367, 1219, 1196, 1134; \([\alpha]_D^{25} = +13.8^\circ (c = 2.96, \text{CHCl}_3)\). HRMS (MM) calc’d for [M+H]^+ 377.1860, found 377.1865.

**(S)-N\textsubscript{a}-Acetyl-4-methyl-2-phenyltryptophan methyl ester (138g)**

Prepared from 4-methyl-2-phenylindole\textsuperscript{34} (137e, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 30.8 mg (88% yield) of 138g as a white foam. The enantiomeric excess was determined to be 96% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO\(_2\), \(\lambda = 254 \text{ nm}\)): \(t_R(\text{major}) = 9.9 \text{ min}, t_R(\text{minor}) = 8.9 \text{ min}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.32 \text{ (br s, } 1\text{H}), 7.55 – 7.45 \text{ (m, } 4\text{H}), 7.44 – 7.37 \text{ (m, } 1\text{H}), 7.19 \text{ (d, } J = 8.0 \text{ Hz, } 1\text{H}), 7.08 \text{ (m, } 1\text{H}), 6.91 \text{ (m, } 1\text{H}), 5.44 \text{ (br d, } J = 7.6 \text{ Hz, } 1\text{H}), 4.63 \text{ (td, } J = 8.2, 5.0 \text{ Hz, } 1\text{H}), 3.69 – 3.45 \text{ (m, } 2\text{H}), 3.44 \text{ (s, } 3\text{H}), 2.78 \text{ (s, } 3\text{H}), 1.64 \text{ (s, } 3\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 172.3, 169.7, 136.3, 136.1, 133.1, 130.5, 129.2, 128.9, 128.3, 126.9, 122.5, 122.3, 109.0, 107.6, 54.2, 52.1, 27.6, 22.8, 20.5; IR (NaCl/thin film): 3295, 3052, 2952, 1741, 1659, 1602, 1547, 1514, 1492, 1449, 1372, 1218; \([\alpha]_D^{25} = -29.0^\circ (c = 0.63, \text{CHCl}_3)\). HRMS (MM) calc’d for [M+H]^+ 351.1703, found 351.1698.

**(S)-N\textsubscript{a}-Acetyl-5-methyl-2-phenyltryptophan methyl ester (138h)**

Prepared from 5-methyl-2-phenylindole\textsuperscript{39} (137f, 42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 58.0 mg (83% yield) of 138h as a white foam. The enantiomeric excess was determined to be 95% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO\(_2\), \(\lambda = 254 \text{ nm}\)): \(t_R(\text{major}) =\)
4.9 min, \( t_r \) (minor) = 6.4 min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.12 (br s, 1H), 7.54 (ddd, \( J = 10.1, 6.1, 4.2 \) Hz, 2H), 7.50 – 7.43 (m, 2H), 7.40 – 7.33 (m, 2H), 7.24 (d, \( J = 8.3 \) Hz, 1H), 7.06 – 7.00 (m, 1H), 5.78 (br d, \( J = 8.1 \) Hz, 1H), 4.83 (dt, \( J = 8.1, 5.4 \) Hz, 1H), 3.53 – 3.51 (m, 2H), 3.31 (s, 3H), 2.46 (s, 3H), 1.66 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 172.1, 169.5, 136.1, 134.0, 133.3, 129.7, 129.2, 129.1, 128.2, 128.0, 124.1, 118.6, 110.6, 106.3, 52.7, 51.2, 26.5, 22.8, 21.5; IR (NaCl/thin film): 3379, 3365, 2948, 1737, 1658, 1439, 1372, 1306, 1217 cm\(^{-1}\); \([\alpha]_D^{25} = +33.8^\circ \) (c = 0.26, CHCl\(_3\)). HRMS (MM) calc’d for [M+H]\(^+\) 351.1703, found 351.1680.
(S)-N$_a$-Acetyl-6-methyl-2-phenyltryptophan methyl ester (138i)

Prepared from 6-methyl-2-phenylindole$^{34}$ (137g, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 27.9 mg (80% yield) of 138i as a colorless oil. The enantiomeric excesses was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO$_2$, $\lambda = 254$ nm): $t_R$ (major) = 9.1 min, $t_R$ (minor) = 10.1 min. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.01 (br s, 1H), 7.55 (ddd, $J = 5.8$, 4.0, 2.1 Hz, 2H), 7.48 – 7.44 (m, 3H), 7.39 – 7.33 (m, 1H), 7.14 (s, 1H), 6.97 (dd, $J = 8.3$, 1.5 Hz, 1H), 5.78 (br d, $J = 7.8$ Hz, 1H), 4.83 (dt, $J = 8.0$, 5.4 Hz, 1H), 3.55 – 3.49 (m, 2H), 3.30 (s, 3H), 2.47 (s, 3H), 1.67 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) 172.1, 169.6, 136.1, 135.2, 133.3, 132.4, 129.1, 128.2, 127.9, 127.3, 121.8, 118.5, 110.9, 106.5, 52.7, 52.0, 26.6, 22.9, 21.7; IR (NaCl/thin film): 3292, 3052, 2958, 2908, 1741, 1658, 1545, 1530, 1511, 1446, 1375, 1216; $[\alpha]_D^{25} = +39.3^\circ$ ($c = 0.38$, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 351.1703, found 351.1698.

(S)-N$_a$-Acetyl-7-methyl-2-phenyltryptophan methyl ester (138j)

Prepared from 7-methyl-2-phenylindole$^{34}$ (137h, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 33.0 mg (94% yield) of 138j as a white foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO$_2$, $\lambda = 254$ nm): $t_R$ (major) = 5.6 min, $t_R$ (minor) = 5.0 min. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.23 (br s, 1H), 7.61 – 7.54 (m, 2H), 7.51 – 7.45 (m, 2H), 7.42 (d, $J = 8.1$ Hz, 1H), 7.40 – 7.35 (m, 1H), 7.11 – 7.04 (m, 1H),
7.03 – 6.97 (m, 1H), 5.79 (br d, $J = 8.1$ Hz, 1H), 4.82 (dt, $J = 8.1, 5.7$ Hz, 1H), 2.55 (dd, $J = 12.5, 3.1$ Hz, 1H), 3.51 (dd, $J = 12.5, 3.1$ Hz, 1H), 3.30 (s, 3H), 2.50 (s, 3H), 1.65 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.1, 169.6, 135.8, 135.3, 133.3, 129.1, 128.9, 128.4, 128.0, 123.1, 120.20, 120.18, 116.5, 107.1, 52.7, 51.9, 26.6, 22.8, 16.6; IR (NaCl/thin film): 3283, 3053, 2950, 1736, 1659, 1518, 1438, 1372, 1306, 1266, 1219, 1137, 1043; $[\alpha]_D^{25} = +26.5^\circ$ ($c = 0.20$, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 351.1703, found 351.1708.

(S)-$N_\alpha$-Acetyl-5-methoxy-2-phenyltryptophan methyl ester (138k)

Prepared from 5-methoxy-2-phenylindole$^{34}$ (137i, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 62.0 mg (85% yield) of 138k as a colorless oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO$_2$, $\lambda = 254$ nm): $t_R$(major) = 4.7 min, $t_R$(minor) = 6.5 min. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.24 (br s, 1H), 7.58 – 7.49 (m, 2H), 7.50 – 7.41 (m, 2H), 7.36 (dd, $J = 7.4, 7.4$ Hz, 1H), 7.24 (d, $J = 8.7$ Hz, 1H), 7.05 (d, $J = 2.3$ Hz, 1H), 6.90 – 6.80 (m, 1H), 5.82 (br d, $J = 7.9$ Hz, 1H), 4.82 (td, $J = 7.9, 5.4$ Hz, 1H), 3.87 (s, 3H), 3.49 (m, 2H), 3.29 (s, 3H), 1.67 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.2, 169.6, 154.4, 136.7, 133.2, 130.8, 129.8, 129.1, 128.12, 128.0, 112.7, 111.7, 106.5, 100.5, 55.9, 52.7, 52.0, 26.6, 22.9; IR (NaCl/thin film): 3291, 3057, 2926, 1739, 1652, 1558, 1539, 1520, 1483, 1455, 1374, 1218, 1178; $[\alpha]_D^{25} = +32.6^\circ$ ($c = 0.93$, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 367.1652, found 367.1658.
(S)-N<sub>a</sub>-Acetyl-5-bromo-2-phenyltryptophan methyl ester (138l)

Prepared from 5-bromo-2-phenylindole\textsuperscript{35} (137j, 54.0 mg, 0.20 mmol) with 1.6 equiv SnCl<sub>4</sub> following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 49.5 mg (60% yield) of 138l as a white foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO<sub>2</sub>, λ = 254 nm): \( t_R \) (major) = 5.3 min, \( t_R \) (minor) = 7.9 min. \(^1\)H NMR (500 MHz, CDCl<sub>3</sub>) \( \delta \) 8.42 (br s, 1H), 7.66 (d, \( J = 2.0 \) Hz, 1H), 7.56 – 7.50 (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 7.28 – 7.24 (m, 1H), 7.22 – 7.18 (m, 1H), 5.75 (br d, \( J = 8.1 \) Hz, 1H), 4.82 (dt, \( J = 5.7 \) Hz, 1H), 3.53 (dd, \( J = 14.9, 5.5 \) Hz, 1H), 3.46 (dd, \( J = 14.9, 4.8 \) Hz, 1H), 3.36 (s, 3H), 1.63 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl<sub>3</sub>) \( \delta \) 171.9, 169.6, 137.2, 134.2, 132.6, 131.1, 129.2, 128.3, 128.2, 125.2, 121.6, 113.1, 112.4, 106.4, 52.6, 52.1, 26.5, 22.8; IR (NaCl/thin film): 3417, 3369, 3282, 1734, 1654, 1521, 1466, 1437, 1374, 1215; [\( \alpha \)]\textsubscript{D}\textsuperscript{25} = +47.2\(^\circ\) (c = 1.04, CHCl<sub>3</sub>). HRMS (MM) calc’d for [M+H]\(^+\) 415.0652, found 415.0653.

(S)-N<sub>a</sub>-Acetyl-5-fluoro-2-phenyltryptophan methyl ester (138m)

Prepared from 5-fluoro-2-phenylindole\textsuperscript{34} (137k, 42.0 mg, 0.20 mmol) with 1.6 equiv SnCl<sub>4</sub> following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 44.7 mg (63% yield) of 138m as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO<sub>2</sub>, λ = 254 nm): \( t_R \) (major) = 3.8 min, \( t_R \) (minor) = 5.2 min. \(^1\)H NMR (500 MHz, CDCl<sub>3</sub>) \( \delta \) 8.30 (br s, 1H), 7.60 – 7.52 (m, 2H), 7.50 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 7.27 – 7.24 (m, 1H), 7.20 – 7.12 (m, 1H), 5.72 (br d, \( J = 8.3 \) Hz, 1H), 4.80 (dt, \( J = 5.7 \) Hz, 1H), 3.52 (dd, \( J = 14.9, 5.5 \) Hz, 1H), 3.46 (dd, \( J = 14.9, 4.8 \) Hz, 1H), 3.37 (s, 3H), 1.59 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl<sub>3</sub>) \( \delta \) 171.9, 169.6, 137.2, 134.2, 132.6, 131.1, 129.2, 128.3, 128.2, 125.2, 121.6, 113.1, 112.4, 106.4, 52.6, 52.1, 26.5, 22.8; IR (NaCl/thin film): 3417, 3369, 3282, 1734, 1654, 1521, 1466, 1437, 1374, 1215; [\( \alpha \)]\textsubscript{D}\textsuperscript{25} = +47.2\(^\circ\) (c = 1.04, CHCl<sub>3</sub>). HRMS (MM) calc’d for [M+H]\(^+\) 413.0553, found 413.0553.
1H), 7.21 (dd, J = 9.8, 2.6 Hz, 1H), 6.94 (ddd, J = 9.0, 9.0, 2.6 Hz, 1H), 5.77 (br d, J = 7.8 Hz, 1H), 4.82 (dt, J = 8.1, 5.4 Hz, 1H), 3.53 (dd, J = 14.9, 5.6 Hz, 1H), 3.47 (dd, J = 14.9, 5.0 Hz, 1H), 3.35 (s, 3H), 1.64 (s, 2H); 13C NMR (125 MHz, CDCl₃) δ 172.7, 169.8, 168.3, 135.6, 134.2, 132.5, 131.9, 128.6, 123.5, 121.8, 119.7, 118.2, 110.8, 107.4, 52.9, 52.4, 37.0, 27.0, 25.3, 23.1; IR (NaCl/thin film): 3275, 3062, 2952, 1733, 1652, 1584, 1558, 1539, 1520, 1486, 1456, 1436, 1374, 1266, 1217, 1180; [α]D₂₅ = +49.9º (c = 1.25, CHCl₃). HRMS (MM) calc’d for [M+H]+ 355.1452, found 355.1455.

(S)-Nα-Acetyl-2-(4-methylphenyl)tryptophan methyl ester (138n)

Prepared from 2-(4-methylphenyl)indole36 (137l, 41.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 60.1 mg (86% yield) of 138n as a white foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm). tR(major) = 6.6 min, tR(minor) = 8.8 min. 1H NMR (500 MHz, CDCl₃) δ 8.20 (br s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.1, 2H), 7.34 (d, J = 8.1, 1H), 7.28 (d, J = 8.1, 2H), 7.19 (ddd, J = 7.8, 7.1, 1.2 Hz, 1H), 7.15 – 7.09 (m, 1H), 5.77 (br d, J = 8.1, 1H), 4.82 (dt, J = 7.8, 5.5 Hz, 1H), 3.54 (dd, J = 13.1, 4.0 Hz, 1H), 3.50 (dd, J = 13.1, 3.7 Hz, 1H), 3.33 (s, 3H), 2.40 (s, 3H), 1.66 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ 172.2, 169.6, 138.0, 136.1, 135.6, 130.2, 129.8, 129.4, 128.1, 122.3, 119.9, 118.7, 110.9, 106.4, 52.8, 52.0, 26.6, 22.8, 21.2; IR (NaCl/thin film): 3365, 3271, 3052, 2951, 1737, 1657, 1519, 1460, 1439, 1375, 1305, 1217 cm⁻¹; [α]D₂₅ = 43.2º (c = 0.74, CHCl₃). HRMS (MM) calc’d for [M+H]+ 351.1703, found 351.1700.
(S)-N<sub>a</sub>-Acetyl-2-(2-methylphenyl)tryptophan methyl ester (138o)

Prepared from 2-(2-methylphenyl)indole<sup>37</sup> (137m, 21.0 mg, 0.1 mmol) following General Procedure 2. The crude residue was purified by flash chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 9.2 mg (26% yield) of 138o. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO<sub>2</sub>, λ = 254 nm): <i>t</i><sub>R</i>(major) = 4.3 min, <i>t</i><sub>R</i>(minor) = 4.9 min. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 (br s, 1H), 7.62 – 7.55 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 7.22 (ddd, <i>J</i> = 8.1, 5.6, 2.1 Hz, 1H), 7.16 (ddd, <i>J</i> = 7.1, 5.6, 1.1 Hz, 1H), 5.71 (br d, <i>J</i> = 7.9 Hz, 1H), 4.82 – 4.68 (dt, <i>J</i> = 7.9, 5.4 Hz, 1H), 3.38 – 3.29 (m, 4H), 3.28 – 3.16 (m, 1H), 2.28 (s, 3H), 1.73 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.1, 169.6, 137.3, 135.8, 135.5, 132.1, 130.9, 130.8, 128.9, 128.7, 126.0, 122.3, 119.9, 118.8, 110.8, 107.6, 52.8, 52.0, 26.6, 23.0, 20.0; IR (NaCl/thin film): 3385, 3271, 3062, 2924, 2853, 1734, 1653, 1559, 1539, 1521, 1457, 1437, 1374; [α]<sub>D</sub><sup>25</sup> = +21.5° (<i>c</i> = 0.29, CHCl<sub>3</sub>). HRMS (MM) calc’d for [M+H]<sup>+</sup> 351.1709, found 351.1709.

(S)-N<sub>a</sub>-Acetyl-2-(4-chlorophenyl)tryptophan methyl ester (138p)

Prepared from 2-(4-chlorophenyl)indole<sup>34</sup> (137n, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 55.2 mg (75% yield) of 138p as a colorless oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO<sub>2</sub>, λ = 254 nm): <i>t</i><sub>R</i>(major) = 6.1 min, <i>t</i><sub>R</i>(minor) = 7.0 min. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.45 (br s, 1H), 7.56 (d, <i>J</i> = 8.1 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.26 – 7.18 (m, 1H), 6.75 – 6.63 (m, 2H), 6.40 (d, <i>J</i> = 4.4 Hz, 2H), 4.81 – 4.69 (dt, <i>J</i> = 8.1, 5.4 Hz, 1H), 3.42 – 3.34 (m, 2H), 2.28 (s, 3H), 1.73 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.1, 169.6, 137.3, 135.8, 135.5, 132.1, 130.9, 130.8, 128.9, 128.7, 126.0, 122.3, 119.9, 118.8, 110.8, 107.6, 52.8, 52.0, 26.6, 23.0, 20.0; IR (NaCl/thin film): 3398, 3271, 3062, 2924, 2853, 1734, 1653, 1559, 1539, 1521, 1457, 1437, 1374; [α]<sub>D</sub><sup>25</sup> = +21.5° (<i>c</i> = 0.29, CHCl<sub>3</sub>). HRMS (MM) calc’d for [M+H]<sup>+</sup> 351.1709, found 351.1709.
1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.33 (ddd, \( J = 8.1, 8.1, 1.0 \) Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 (ddd, \( J = 8.0, 7.1, 1.1 \) Hz, 1H), 5.85 (br d, \( J = 8.1 \) Hz, 1H), 4.83 (dt, \( J = 8.1, 5.5 \) Hz, 1H), 3.55 – 3.38 (m, 2H), 3.34 (s, 3H), 1.69 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 172.1, 169.6, 135.8, 134.6, 133.9, 131.5, 129.4, 129.3, 122.7, 120.1, 118.9, 111.1, 107.1, 52.8, 52.1, 29.6, 26.7, 22.9; \) IR (NaCl/thin film): 3280, 3058, 2948, 1737, 1657, 1519, 1487, 1458, 1439, 1373, 1310, 1216, 1093 cm\(^{-1}\); \([\alpha]_D^{25} = +40.8^\circ (c = 0.96, \text{CHCl}_3)\). HRMS (MM) calc’d for [M+H]\(^+\) 371.1157, found 371.1158.

(S)-\(\text{N}_\alpha\)-Acetyl-2-(3-methoxyphenyl)tryptophan methyl ester (138q)

Prepared from 2-(3-methoxyphenyl)indole (137o, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 65.0 mg (88% yield) of 138q as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30\% IPA in CO\(_2\), \( \lambda = 254 \) nm): \( t_r(\text{major}) = 5.9 \) min, \( t_r(\text{minor}) = 7.6 \) min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 8.40 \) (br s, 1H), 7.55 (d, \( J = 8.1 \) Hz, 1H), 7.40 – 7.31 (m, 2H), 7.19 (ddd, \( J = 8.1, 7.1, 1.2 \) Hz, 1H), 7.16 – 7.10 (m, 2H), 7.08 (dd, \( J = 2.6, 1.6 \) Hz, 1H), 6.91 (ddd, \( J = 8.3, 2.6, 0.8 \) Hz, 1H), 5.82 (br d, \( J = 7.8 \) Hz, 1H), 4.83 (dt, \( J = 7.8, 5.5 \) Hz, 1H), 3.85 (s, 3H), 3.57 – 3.49 (m, 2H), 3.35 (s, 3H), 1.65 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 172.2, 169.6, 160.0, 135.8, 135.6, 134.4, 130.2, 129.3, 122.5, 120.6, 119.9, 118.8, 113.8, 113.5, 111.0, 106.7, 55.4, 52.8, 52.0, 26.6, 22.8; \) IR (NaCl/thin film): 3282, 3058, 2951, 1738, 1658, 1603, 1520, 1462, 1439, 1373, 1218, 1040; \([\alpha]_D^{25} = +40.3^\circ (c = 1.16, \text{CHCl}_3)\). HRMS (MM) calc’d for [M+H]\(^+\) 367.1652, found 367.1656.
(S)-N<sub>α</sub>-Acetyl-2-(4-fluorophenyl)tryptophan methyl ester (138r)

Prepared from 2-(4-fluorophenyl)indole<sup>29</sup> (137p, 42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc/hexanes) to yield 55.6 mg (78% yield) of 138r as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO<sub>2</sub>, λ = 254 nm):

\[ t_R^{\text{(major)}} = 6.1 \text{ min}, \quad t_R^{\text{(minor)}} = 6.9 \text{ min}. \]

\(^1\text{H NMR (500 MHz, CDCl}_3\) \( \delta 8.19 \text{ (d, } J = 47.9 \text{ Hz, 1H), 7.57 \text{ (dd, } J = 7.9, 1.1 \text{ Hz, 1 H), 7.54 - 7.51 \text{ (m, 2H), 7.36 \text{ (ddd, } J = 8.1, 8.1, 0.9 \text{ Hz, 1H), 7.23 - 7.10 \text{ (m, 4H), 5.82 \text{ (d, } J = 8.1 \text{ Hz, 1H), 4.83 \text{ (dt, } J = 8.1, 5.5 \text{ Hz, 1H), 3.55 - 3.40 \text{ (m, 2H), 3.34 \text{ (s, 3H), 1.71 \text{ (s, 3H); 13C NMR (125 MHz, CDCl}_3\) \( \delta 172.2, 169.5, 135.6, 135.0, 130.1, 129.4, 122.7, 120.2, 118.9, 116.2, 116.1, 110.9, 106.9, 52.8, 52.0, 26.7, 22.9.; IR (NaCl/thin film): 3364, 3271, 3061, 2925, 2853, 1738, 1661, 1553, 1505, 1460, 1440, 1373, 1221, 1158; [\alpha]_D^{25} = +38.2^\circ \text{ (c = 0.65, CHCl}_3\). HRMS (MM) calc’d for [M+H]^+ 355.1452, found 355.1460.

(S)-N<sub>α</sub>-Acetyl-2-(3-fluorophenyl)tryptophan methyl ester (138s)

Prepared from 2-(3-fluorophenyl)indole<sup>36</sup> (137q, 42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 ethyl acetate/hexanes) to yield 50.6 mg (76% yield) of 138s as a white foam. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO<sub>2</sub>, λ = 254 nm):

\[ t_R^{\text{(major)}} = 3.8 \text{ min}, \quad t_R^{\text{(minor)}} = 4.6 \text{ min.} \]

\(^1\text{H NMR (500 MHz, CDCl}_3\) \( \delta 8.65 \text{ (br s, 1H), 7.57 \text{ (d, } J = 8.1 \text{ Hz, 1H), 7.41 - 7.37 \text{ (m, 1H), 7.33-7.31 \text{ (m, 2H), 7.27-7.24 \text{ ppm; IR (NaCl/thin film): 3364, 3271, 3061, 2925, 2853, 1738, 1661, 1553, 1505, 1460, 1440, 1373, 1221, 1158; [\alpha]_D^{25} = +38.2^\circ \text{ (c = 0.65, CHCl}_3\). HRMS (MM) calc’d for [M+H]^+ 355.1452, found 355.1460.} \)
(m, 1H), 7.19 (ddd, J = 8.2, 7.0, 1.0 Hz, 1H), 7.13 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 7.07 – 7.03 (m, 1H), 5.89 (br d, J = 8.1 Hz, 1H), 4.84 (dt, J = 8.1, 5.5 Hz, 1H), 3.53 (dd, J = 13.6, 4.7 Hz, 1H), 3.49 (dd, J = 13.6, 4.2 Hz, 1H), 3.34 (s, 3H), 1.69 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.1, 169.7, 162.9 (d, \(J_{C-F}\) = 246.3 Hz), 135.8, 135.2 (d, \(J_{C-F}\) = 7.5 Hz), 134.5 (d, \(J_{C-F}\) = 2.5 Hz), 130.6 (d, \(J_{C-F}\) = 8.8 Hz), 129.2, 123.9 (d, \(J_{C-F}\) = 3.8 Hz), 122.8, 120.0, 118.9, 115.1 (d, \(J_{C-F}\) = 21.2 Hz), 114.7 (d, \(J_{C-F}\) = 21.2 Hz), 111.1, 107.3, 52.8, 52.0, 26.7, 22.8; IR (NaCl/thin film): 3370, 3275, 3060, 2952, 1735, 1655, 1614, 1585, 1522, 1438, 1374, 1266, 1200, 1155 cm\(^{-1}\); [\(\alpha\)]\(_D\)^{25} = +37.6° (c = 1.21, CHCl\(_3\)).

HRMS (MM) calc’d for [M+H]\(^+\) 355.1452, found 355.1450.

**(S)**-\(N_\alpha\)-Acetyl-2-(2-fluorophenyl)tryptophan methyl ester (138t)

Prepared from 2-(2-fluorophenyl)indole (137r, 21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 12.4 mg (35% yield) of 138t. The enantiomeric excesses was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO\(_2\), \(\lambda\) = 254 nm): \(t_r\) (major) = 9.5 min, \(t_r\) (minor) = 8.4 min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.28 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.55 (ddd, J = 7.5, 7.5, 1.8 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.29 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.19 – 7.10 (m, 1H), 5.83 (br d, J = 7.6 Hz, 1H), 4.85 (dt, J = 7.9, 5.5 Hz, 1H), 3.55 – 3.39 (m, 2H), 3.36 (s, 2H), 1.73 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.2, 169.5, 159.8 (d, \(J_{C-F}\) = 246.3 Hz), 135.9, 131.4 (d, \(J_{C-F}\) = 3.8 Hz) 130.2 (d, \(J_{C-F}\) = 8.8 Hz), 129.73, 128.65, 124.8 (d, \(J_{C-F}\) = 3.8 Hz), 122.84, 120.6 (d, \(J_{C-F}\) = 15.0 Hz), 120.0, 119.0, 116.4 (d, \(J_{C-F}\) = 21.3 Hz), 111.0, 108.8, 52.5, 52.0, 26.8, 26.8, 22.9; IR...
(NaCl/thin film): 3275, 3058, 2925, 2853, 1734, 1653, 1523, 1490, 1457, 1374, 1245, 1216, 1130, 1104; $[\alpha]_D^{25} = +39.8^\circ$ (c = 0.41, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 355.1452, found 355.1463.

(S)-$N_\alpha$-Acetyl-2-methyltryptophan methyl ester (138d)

Prepared from 2-methylindole (137b, 26.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (50:50 to 100:0 EtOAc:hexanes) to yield 31.0 mg (61% yield) of 138d as a white foam. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO$_2$, $\lambda = 254$ nm): $t_R$(major) = 3.9 min, $t_R$(minor) = 2.7 min. $[\alpha]_D^{25} = +25.9^\circ$ (c = 0.99, CHCl$_3$). Spectral data matches that reported in the literature.$^{33}$

(S)-$N_\alpha$-Acetyl-2-butyltryptophan methyl ester (138u)

Prepared from 2-butylindole$^{39}$ (137s, 35.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 45.8 mg (72% yield) of 138u as a colorless oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO$_2$, $\lambda = 254$ nm): $t_R$(major) = 5.1 min, $t_R$(minor) = 4.2 min. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.03 (br s, 1H), 7.46 – 7.40 (m, 1H), 7.31 – 7.24 (m, 1H), 7.15 – 6.99 (m, 2H), 6.00 (br d, $J = 7.8$ Hz, 1H), 4.88 (dt, $J = 8.1$, 5.7 Hz, 1H), 3.65 (s, 3H), 3.26 (dd, $J = 5.7$, 0.9 Hz, 2H), 2.69 (td, $J = 7.8$ 2.2 Hz, 2H), 1.93 (s, 3H), 1.66 – 1.57 (m, 2H), 1.45 – 1.31 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR
(125 MHz, CDCl$_3$) δ 172.6, 169.6, 137.4, 135.2, 128.8, 121.3, 119.5, 117.9, 110.4, 105.26, 105.29, 53.0, 52.3, 31.8, 26.8, 25.7, 23.2, 22.6, 13.9; IR (NaCl/thin film): 3296, 3058, 2971, 1737, 1658, 1562, 1533, 1463, 1349, 1217, 1129; [\(\alpha\)]$_D^{25}$ = +16.3º (c = 0.83, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 317.1860, found 317.1855.

(S)-N$_\alpha$-Acetyl-2-isopropyltryptophan methyl ester (138v)

Prepared from 2-isopropylindole$^{40}$ (137t, 32.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 39.6 mg (66% yield) of 138v as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 15% IPA in CO$_2$, \(\lambda = 254\) nm). \(t_R\)(major) = 6.4 min, \(t_R\)(minor) = 5.6 min. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.16 (br s, 1H), 7.48 – 7.41 (m, 1H), 7.30 – 7.27 (m, 1H), 7.15 – 7.02 (m, 2H), 6.04 (br d, \(J = 8.0\) Hz, 1H), 4.89 (dt, \(J = 8.1, 5.7\) Hz, 1H), 3.66 (s, 3H), 3.29 (dd, \(J = 12.7, 4.0\) Hz, 1H), 3.26 (dd, \(J = 12.7, 3.4\) Hz, 1H), 3.18 (m, 1H), 1.93 (s, 3H), 1.31 (d, \(J = 3.3\) Hz, 3H), 1.30 (d, \(J = 3.3\) Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.6, 169.7, 142.7, 135.2, 128.7, 121.3, 119.5, 117.9, 110.6, 103.6, 53.0, 52.3, 26.7, 25.3, 23.2, 23.0; IR (NaCl/thin film): 3305, 2962, 1734, 1700, 1653, 1559, 1539, 1506, 1457, 1436, 1374, 1299, 1217 cm$^{-1}$; [\(\alpha\)]$_D^{25}$ = +22.2º (c = 0.35, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 303.1703, found 303.1709.
(S)-Nα-Acetyl-2-(tert-butyl)tryptophan methyl ester (138w)

Prepared from 2-(tert-butyl)indole\(^{33}\) (137u, 35.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 18.1 mg (29% yield) of 138w as a yellow oil. The enantiomeric excess was determined to be 84% by chiral SFC analysis (OD-H, 2.5 mL/min, 10% IPA in CO\(_2\), \(\lambda = 254\) nm): \(t_R\) (major) = 12.8 min, \(t_R\) (minor) = 14.2 min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.07 (br s, 1H), 7.47 (dd, \(J = 14.0, 7.1\) Hz, 1H), 7.27 (dd, \(J = 5.8, 4.8\) Hz, 1H), 7.15 – 7.03 (m, 2H), 6.06 (br d, \(J = 7.4\) Hz, 1H), 4.84 (m, 1H), 3.54 (s, 3H), 3.38 – 3.29 (m, 2H), 1.86 (s, 3H), 1.49 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.2, 169.6, 143.4, 133.9, 129.8, 121.3, 119.4, 117.7, 110.4, 104.3, 53.7, 52.2, 33.2, 30.7, 28.6, 23.0; IR (NaCl/thin film): 3326, 3047, 2961, 2918, 2868, 1734, 1653, 1539, 1457, 1436, 1374, 1303, 1254, 1211, 1128; [%]\(D\)\(_{25}\) = +12.4° (\(c = 0.36, CHCl_3\)). HRMS (MM) calc’d for [M+H]\(^+\) 317.1860, found 317.1856.

(S)-Nα-Acetyl-2-cyclopropyltryptophan methyl ester (138x)

Prepared from 2-cyclopropylindole\(^{41}\) (137v, 16.0 mg, 0.10 mmol) following General Procedure 2 except that 1.0 equiv methyl 2-acetamidoacrylate (91a) was employed. The crude residue was purified by silica gel chromatography (50:50 EtOAc:hexanes) to yield 4.6 mg (24% yield) of 138x as a colorless oil. The enantiomeric excess was determined to be 75% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO\(_2\), \(\lambda = 254\) nm): \(t_R\) (major) = 2.6 min \(t_R\) (minor) = 2.3 min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.65 (br s, 1H), 7.41 (ddt, \(J = 7.5, 1.5, 0.7\) Hz, 1H), 7.24 (ddd, \(J = 7.9, 1.3, 0.8\) Hz, 1H), 7.10 (ddd, \(J = 7.9, 7.1, 1.5\) Hz, 1H), 7.10 – 7.03 (m, 1H), 6.06 (br d, \(J = 7.4\) Hz, 1H), 4.84 (m, 1H), 3.54 (s, 3H), 3.38 – 3.29 (m, 2H), 1.86 (s, 3H), 1.49 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.2, 169.6, 143.4, 133.9, 129.8, 121.3, 119.4, 117.7, 110.4, 104.3, 53.7, 52.2, 33.2, 30.7, 28.6, 23.0; IR (NaCl/thin film): 3326, 3047, 2961, 2918, 2868, 1734, 1653, 1539, 1457, 1436, 1374, 1303, 1254, 1211, 1128; [%]\(D\)\(_{25}\) = +12.4° (\(c = 0.36, CHCl_3\)). HRMS (MM) calc’d for [M+H]\(^+\) 317.1860, found 317.1856.
1H), 6.03 (br d, J = 8.0 Hz, 1H), 4.93 (dt, J = 8.0, 5.6 Hz, 1H), 3.67 (s, 3H), 3.36 (d, J = 5.6 Hz, 2H), 2.02 (tt, J = 8.4, 5.3 Hz, 1H), 1.94 (s, 3H), 1.05 – 1.01 (m, 2H), 0.79 – 0.76 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.6, 169.6, 137.6, 134.6, 129.1, 121.5, 119.7, 117.6, 110.4, 106.9, 53.0, 52.4, 26.8, 23.3, 7.4, 7.10, 7.06.; IR (NaCl/thin film): 3297, 3058, 3026, 2926, 1736, 1654, 1523, 1468, 1439, 1375, 1339, 1309, 1217 cm\(^{-1}\); HRMS (ESI) calc’d for [M+H]\(^{+}\) 301.1547, found 301.1546.

\((S)-N_\alpha\text{-Acetyl-2-(ethylphthalimide)}\text{tryptophan methyl ester (138y)}\)

Prepared from 2-(ethylphthalimide)indole (137w, 29.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (70:30 to 100:0 EtOAc:hexanes) to yield 34.6 mg (80% yield) of 138y as a yellow foam. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO\(_2\), \(\lambda = 254\) nm): \(t_r\)(major) = 7.3 min, \(t_r\)(minor) = 6.3 min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.47 (br s, 1H), 7.83 (dd, J = 5.4, 2.9 Hz, 2H), 7.72 (dd, J = 5.5, 3.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H), 7.31 (ddd, J = 8.1, 8.1, 1.0 Hz, 1H), 7.13 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.07 (ddd, J = 10.5, 5.8, 2.2 Hz, 1H), 6.13 (br d, J = 8.1 Hz, 1H), 4.92 (dt, J = 8.2, 6.0 Hz, 1H), 4.05 – 3.89 (m, 2H), 3.66 (s, 3H), 3.33 – 2.98 (m, 4H), 1.93 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.7, 169.8, 168.3, 135.6, 134.2, 132.5, 131.9, 128.6, 123.5, 121.8, 119.7, 118.2, 110.8, 107.4, 52.9, 52.4, 37.0, 27.0, 25.3, 23.1; IR (NaCl/thin film): 3369, 3280, 3052, 2948, 1770, 1738, 1711, 1659, 1530, 1438, 1397, 1371; [\(\alpha\)]\(_D\)\(^{25}\) = +14.8° (c = 0.96, CHCl\(_3\)). HRMS (MM) calc’d for [M+H]\(^{+}\) 355.1452, found 355.1455.
Prepared from indole (163, 23.4 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 17.9 mg (contains 9 wt % EtOAc, 31% corrected yield) of 138z as a light pink oil and 7.0 mg (30% yield) of 170 as a light yellow oil. The enantiomeric excess of 138z was determined to be 67% by chiral SFC analysis (OD-H, 2.5 mL/min, 15% IPA in CO₂, \( \lambda = 254 \text{ nm} \)): \( t_R \) (major) = 11.4 min, \( t_R \) (minor) = 10.6 min. \([\alpha]_D^{25} = +39.3^\circ (c = 0.83, \text{CHCl}_3)\). Spectral data for both (S)-N\( \alpha \)-acetyltrypotphan methyl ester^42 and the indole dimer^43 are in agreement with the literature.
3.4.5 SFC Traces for Racemic and Enantioenriched Tryptophan Derivatives

Optimization of Reaction Parameters

138a (Table 3.2.1, entry 1): racemic

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<td>2 13.305 MM 0.5037 945.41193 26.99413 50.0986</td>
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</table>

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

<table>
<thead>
<tr>
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138b (Table 3.2.1, entry 2): racemic

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

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138c: racemic

138c (Table 3.2.1, entry 3, no additive, DCM as solvent): enantioenriched, 78% ee
138c (Table 3.2.1, entry 6, no additive, 1M NaOH workup): enantioenriched, 75% ee

138c (Table 3.2.1, entry 7, with K$_2$CO$_3$, DCM as solvent): enantioenriched, 78% ee
138c (Table 3.2.1, entry 9, with 4Å MS, DCM as solvent): enantioenriched, 81% ee

138c (Table 3.2.1, entry 10, with 4Å MS, DCE as solvent): enantioenriched, 79% ee
138c (Table 3.2.1, entry 11, with 4Å MS, CHCl₃ as solvent): enantioenriched, 72% ee

138c (Table 3.2.2, entry 2, (R)-3,3′-diphenyl-BINOL (102g)): enantioenriched, 37% ee
138c (Table 3.2.2, entry 3, (R)-3,3'-dimethyl-BINOL (102h)): enantioenriched, 87% ee

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

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

138c (Table 3.2.2, entry 6, (R)-3,3’-dibromo-BINOL (102k)): enantioenriched, 93% ee
138c (Table 3.2.2, entry 7, (R)-3,3’-dimethoxy-BINOL (102I)): enantioenriched, 1% ee

![Chemical structure and chromatogram](image1)

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

![Chemical structure and chromatogram](image2)

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

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

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

| Peak RetTime Type Width Area Height | Area % |
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| # [min] | [min] | [mAU*] | [mAU] | |
| 1 5.731 MM | 0.2917 | 71.50548 | 4.10848 | 2.6104 | |
| 2 7.071 MM | 0.3130 | 2682.65479 | 142.96038 | 97.3936 | |

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

| Peak RetTime Type Width Area Height | Area % |
|------------------------|--------|-----------------|-----------------|
| # [min] | [min] | [mAU*] | [mAU] | |
| 1 5.703 MM | 0.2786 | 1312.42859 | 78.50554 | 33.5593 | |
| 2 7.034 MM | 0.3137 | 2598.34658 | 138.04501 | 66.4407 | |
138c (Table 3.2.4, entry 3, 15 mol % 102k): enantioenriched, 93% ee

138c (Table 3.2.4, entry 4, 10 mol % 102k): enantioenriched, 92% ee
138c (Table 3.2.4, entry 5, 5 mol % 102k): enantioenriched, 88% ee
Chapter 3—Synthesis of Tryptophan Derivatives

Substrate scope of the conjugate addition/asymmetric protonation

138e (Table 3.2.5, entry 2): racemic

138e (Table 3.2.5, entry 2): enantioenriched, 85% ee
138f (Table 3.2.5, entry 3): racemic

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

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138g (Table 3.2.5, entry 4): racemic

![Graph of racemic 138g](image1)

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

![Graph of enantioenriched 138g](image2)

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138h (Table 3.2.5, entry 5): racemic

\[
\begin{align*}
\text{N} & \quad \text{Ph} \\
\text{CO}_2 & \quad \text{Me} \\
\text{NHAc} & \quad \text{Me}
\end{align*}
\]

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

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2 & \quad \text{Me} \\
\text{NHAc} & \quad \text{Ph}
\end{align*}
\]
138i (Table 3.2.5, entry 6): racemic

138i (Table 3.2.5, entry 6): enantioenriched, 89% ee
138j (Table 3.2.5, entry 7): racemic

![Chromatogram of racemic 138j](image)

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

![Chromatogram of enantioenriched 138j](image)

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138k (Table 3.2.5, entry 8): racemic

138k (Table 3.2.5, entry 8): enantioenriched, 91% ee
138l (Table 3.2.5, entry 9): racemic

138l (Table 3.2.5, entry 9): enantioenriched, 93% ee
**138m (Table 3.2.5, entry 10): racemic**

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

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138n (Table 3.2.5, entry 11): racemic

138n (Table 3.2.5, entry 11): enantioenriched, 94% ee
138o (Table 3.2.5, entry 12): racemic

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

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138p (Table 3.2.5, entry 13): racemic

138p (Table 3.2.5, entry 13): enantioenriched, 93% ee
138q (Table 3.2.5, entry 14): racemic

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

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138r (Table 3.2.5, entry 15): racemic

138r (Table 3.2.5, entry 15): enantioenriched, 93% ee
138s (Table 3.2.5, entry 16): racemic

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

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138t (Table 3.2.5, entry 17): racemic

![Chemical Structure of 138t (Racemic)]

**Table 3.2.5, entry 17**: racemic

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

![Chemical Structure of 138t (Enantioenriched)]

**Table 3.2.5, entry 17**: enantioenriched, 92% ee

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138d (Table 3.2.5, entry 18): racemic

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

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138u (Table 3.2.5, entry 19): racemic


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


138v (Table 3.2.5, entry 20): racemic

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

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138w (Table 3.2.5, entry 21): racemic

138w (Table 3.2.5, entry 21): enantioenriched, 84% ee
Chapter 3—Synthesis of Tryptophan Derivatives

138x (Table 3.2.5, entry 22): racemic

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

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<td>0.1524</td>
<td>1895.02353</td>
<td>2073.0278</td>
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138y (Table 3.2.5, entry 23): racemic

138y (Table 3.2.5, entry 23): enantioenriched, 90% ee
138z (Scheme 3.2.3): racemic

138z (Scheme 3.2.3): enantioenriched, 67% ee
3.4.6 Scale-up Procedure

To a flame-dried flask under nitrogen containing freshly activated powdered 4Å molecular sieves (200 wt %) was added 2-phenylindole (137a, 1.00 g, 5.20 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (91a, 890 mg, 6.20 mmol, 1.20 equiv), and (R)-3,3’-dibromo-BINOL (102k, 457 mg, 1.00 mmol, 0.20 equiv). The flask was charged with DCM (40 mL) and SnCl₄ (1 M in DCM, 5.20 mL, 5.20 mmol, 1.00 equiv) was added. The reaction was stirred at room temperature for 2 hours, then quenched by addition of 1 M HCl (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (50 mL), dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 1.33 g (77% yield) of 138c as a pale yellow foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): tᵣ(major) = 5.7 min, tᵣ(minor) = 6.9 min.
3.4.7 Preparation of Methyl 2-acetamido-2-(2-phenyl-1H-indol-3-yl)propanoate (165)

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

1H), 7.56 – 7.48 (m, 2H), 7.45 – 7.37 (m, 3H), 7.30 (ddd, J = 8.1, 0.9, 0.9 Hz, 1H), 7.20 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.15 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 6.70 (br s, 1H), 3.48 (s, 3H), 1.96 (s, 3H), 1.70 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ 173.5, 168.8, 135.5, 135.4, 133.5, 130.6, 128.7, 128.0, 126.1, 122.2, 120.5, 120.1, 111.4, 111.1, 59.8, 52.7, 24.4, 23.3; FTIR (NaCl/thin film): 3271, 3054, 2948, 1734, 1663, 1507, 1489, 1458, 1445, 1432, 1370, 1295, 1253, 1126 cm⁻¹; HRMS (MM) calc’d for C₂₀H₂₁N₂O₃ [M+H]+ 337.1547, found 337.1545.

3.4.8 Functionalization of Tryptophan 138c

3.4.8.1 Acetamide Hydrolysis

A vial was charged with (S)-Nα-acetyl-2-phenyltryptophan methyl ester (138c, 30.0 mg, 0.09 mmol), MeOH (1 mL), H₂O (1 mL) and aqueous HCl (12 M, 1 mL). The reaction was heated to 75 °C for 12 hours, then concentrated, redissolved in DCM (10 mL) and washed with saturated aqueous NaHCO₃ (3 X 5 mL). The aqueous layers were combined and extracted with DCM (4 X 5 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by silica gel chromatography (99:1 DCM:MeOH) to yield 20.0 mg (76% yield) of 171 as a light yellow oil. The enantiomeric excess was determined by chiral SFC analysis of the corresponding methylcarbamate 185 (see below). ¹H NMR (500 MHz,
Methylcarbamate Protection

A flame-dried flask was charged with free amine 171 (19.5 mg, 0.70 mmol, 1.00 equiv), Et₃N (19 µL, 0.13 mmol, 2.0 equiv) and DCM (5 mL). Methylchloroformate (6.0 µL, 0.73 mmol, 1.10 equiv) was added and the solution was stirred at room temperature for 3 hours, then quenched with saturated aqueous NH₄Cl (5 mL) and extracted with EtOAc (2 X 5 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by silica gel chromatography (25:75 EtOAc:hexanes) to yield 18.5 mg (80% yield) of methylcarbamate 185 as a colorless oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OD-H, 2.5 mL/min, 15% IPA in CO₂, λ = 254 nm): \( t_R(\text{major}) = 16.7 \text{ min} \), \( t_R(\text{minor}) = 15.6 \text{ min} \). \(^1\text{H} \) NMR (500 MHz, CDCl₃) \( \delta \) 8.11 (br s, 1H), 7.61 (d, \( J = 7.9 \) Hz, 1H), 7.57 – 7.52 (m, 1H), 7.48 – 7.45 (m, 2H), 7.40 – 7.35 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 (m, 1H), 5.06 (br d, J
= 7.7 Hz, 1H), 4.63 – 4.59 (m, 1H), 3.54 (s, 3H), 3.50 (m, 2H), 3.38 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.3, 156.1, 136.2, 135.7, 132.9, 129.2, 129.0, 128.3, 128.0, 122.5, 120.0, 118.9, 110.9, 106.7, 54.5, 52.12, 52.07, 27.1; IR (NaCl/thin film) 3338, 2953, 2923, 2852, 1718, 1701, 1507, 1457, 1363, 1213, 1072 cm$^{-1}$; [α]$_D^{25}$ = +22.6º (c = 0.10, CHCl$_3$). HRMS (MM) calc’d for [M+H]$^+$ 353.1496, found 353.1497.

**Methylcarbamate (185):** racemic

![Graph and diagram of the racemic methylcarbamate (185)]

**Methylcarbamate (185):** enantioenriched, 93% ee

![Graph and diagram of the enantioenriched methylcarbamate (185)]
3.4.8.2  *Methyl Ester Hydrolysis*\(^{45}\)

A 10 mL flask was charged with (S)-\(\text{N}^\alpha\)-acetyl-2-phenyltryptophan methyl ester 138c (67.2 mg, 0.20 mmol, 1.00 equiv) and THF (0.9 mL) then cooled to 0 °C, followed by dropwise addition of aqueous LiOH (1.75 M, 230 µL, 0.40 mmol, 2.00 equiv). The reaction was vigorously stirred at 0 °C for 2 hours, then diluted with \(\text{H}_2\text{O}\) (15 mL) and extracted with EtOAc (2 x 10 mL). The aqueous layer was acidified to pH = 1.5 and extracted with EtOAc (5 x 15 mL). The combined organic layers from the acidic aqueous extraction were dried (\(\text{Na}_2\text{SO}_4\)), filtered, and concentrated. The crude residue was purified by silica gel chromatography (0:99:1 to 15:84:1 MeOH:DCM:AcOH) to yield 59.2 mg (92% yield) of carboxylic acid 172 as a pale yellow foam. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AS-H, 2.5 mL/min, 28% IPA in \(\text{CO}_2\), \(\lambda = 254\) nm): \(t_R\)(major) = 4.5 min, \(t_R\)(minor) = 8.0 min. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.21 (br s, 1H), 7.63 (d, \(J = 7.8\) Hz, 1H), 7.56 – 7.51 (m, 2H), 7.47 (dd, \(J = 7.6, 7.6\) Hz, 2H), 7.40 (m, 1H), 7.37 (ddd, \(J = 8.0, 0.8, 0.8\) Hz, 1H), 7.21 (ddd, \(J = 8.1, 7.1, 1.1\) Hz, 1H), 7.14 (ddd, \(J = 8.0, 7.1, 1.0\) Hz, 1H), 5.72 (br d, \(J = 7.4\) Hz, 1H), 4.73 (td, \(J = 7.1, 5.4\) Hz, 1H), 3.56 (dd, \(J = 14.9, 5.2\) Hz, 1H), 3.49 (dd, \(J = 15.0, 6.9\) Hz, 1H), 1.62 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.7, 170.9, 136.2, 135.7, 132.9, 129.13, 129.05, 128.3, 128.2, 122.6, 120.1, 118.8, 111.0, 106.8, 53.1, 26.2, 22.6; IR (NaCl/thin film): 3391, 3306, 3055, 3011, 2921, 2850, 1717, 1615, 1527, 1457, 1448, 1215 cm\(^{-1}\); [\(\alpha\)]\(_D\)\(^{25}\) = +9.2° (\(c = 1.05, \text{MeCN}\)). HRMS (MM) calc’d for [M+H]\(^+\) 323.1390, found 323.1390.
172: racemic

\[ \text{racemic} \]

N\text{H}Ph \quad \text{CO}_2\text{H} \quad \text{NHAc}

172: enantioenriched, 92% ee

\[ \text{enantioenriched, 92\% ee} \]

\[ \text{N}\text{H}Ph \quad \text{CO}_2\text{H} \quad \text{NHAc} \]
3.4.9 Deuterium Labeling Studies

Preparation of $N$-deuteroacrylate (186).

Acrylate 91a was dissolved in MeOD (1 mL) under nitrogen. After stirring for 1 minute, the solution was concentrated under high vacuum. This procedure was repeated three times to give >99% deuterium incorporation.
Preparation of per-deutero-2-phenylindole (187).

To MeOD (1 mL) in a microwave vial was added acetyl chloride (100 µL), followed by 2-phenylindole (6a, 50 mg) and D₂O (1 mL). The vial was sealed and heated in a microwave to 140 °C for 1 hour. Upon cooling, the heterogeneous solution was diluted with DCM. The phases were separated and the aqueous was extracted with DCM (2 x 5 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated to give per-deutero-2-phenylindole (187) with 90% deuterium incorporation.
3.4.10 \(^1\text{H NMR Kinetics Experiment for } \text{SnCl}_4 \text{ and (R)-BINOL (102a)•SnCl}_4\)

Promoted Reaction of 137a and 91a.

An oven-dried vial was charged with 2-phenylindole (137a, 19.0 mg, 0.10 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (91a, 14.0 mg, 0.10 mmol, 1.00 equiv), (R)-BINOL if necessary (6.0 mg, 0.02 mmol, 0.20 equiv) and 1,4-diethylbenzene (4.7 \(\mu\)L, 0.03 mmol, 0.30 equiv) as the internal standard. The vial was pumped into a glove box and charged with \(\text{CD}_2\text{Cl}_2\) (0.75 mL, to an indole concentration of 0.12 M), then transferred to a screw-cap NMR tube. A \(^1\text{H NMR spectrum (1 scan) was taken to determine the initial ratio of acrylate and 1,4-diethylbenzene. SnCl}_4 \text{ (1 M in CD}_2\text{Cl}_2, 120 \mu\text{L, 0.12 mmol, 1.20 equiv) was then added through the septum of the screw-cap and the NMR tube was inverted once and quickly inserted into the spectrometer. The concentration of acrylate was monitored by } ^{1}\text{H NMR over 9 hours and was determined by integration of its resonance at 3.83 ppm relative to 1,4-diethylbenzene’s resonance at 2.74 ppm.} \)
Kinetics Plot

Catalyzed vs. Uncatalyzed Reaction Monitored by 1H NMR

- SnC4 (1.2 equiv)
- SnC4 (1.2 equiv) + BINOL (1.2 equiv)
3.4.11 **Comparison of Conditions for Pyrroloindoline Formation.**

Table 3.2.6, entry 1:

To a flame-dried 10 mL flask was added 1,3-dimethylindole (75, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate 91a (28.6 mg, 0.20 mmol, 1.00 equiv), and (R)-BINOL (102a, 11.4 mg, 0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of SnCl$_4$ (1 M in DCM, 240 µL, 0.24 mmol, 1.20 equiv) and the reaction mixture was stirred at room temperature for 4 hours, then quenched by diluting with MeCN (1 mL) and 1 M HCl (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO$_3$ (15 mL). The aqueous layer was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. The product 100b was formed in a 5:1 ratio of diastereomers favoring the exo diastereomer (determined by $^1$H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 40.1 mg (70% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the exo diastereomer was determined to be 66% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO$_2$, $\lambda$ = 254 nm): $t_R$(major) = 9.0 min, $t_R$(minor) = 5.8 min. The enantiomeric excess of the endo diastereomer was determined to be 80% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO$_2$, $\lambda$ = 254 nm): $t_R$(major) = 3.8 min, $t_R$(minor) = 4.5 min. Spectral data are in agreement with the literature.$^{46}$
100b (Table 3.2.6, entries 1-2): racemic

N\text{Ac} \quad N\text{Me} \quad \text{Me} \quad \text{CO}_2\text{Me}

100b (Table 3.2.6, entry 1): enantioenriched, \textit{exo}: 65\% ee, \textit{endo}: 80\% ee
Table 3.2.6, entry 2:

An oven-dried vial was charged with 1,3-dimethylindole (75, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate 91a (34.3 mg, 0.24 mmol, 1.20 equiv), and (R)-3,3’-dibromo-BINOL (102k, 17.8 mg, 0.04 mmol, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to 75). The vial was charged with DCM (1.5 mL) and SnCl₄ (1 M in DCM, 200 µL, 0.20 mmol, 1.00 equiv) was added. The reaction was stirred at 20 °C for 4 hours, after which time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (15 mL). The aqueous was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The product 100b was formed in a 8:1 ratio of diastereomers favoring the exo diastereomer (determined by ¹H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 33.5 mg (58% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the exo diastereomer was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO₂, λ = 254 nm): $t_R$(major) = 8.9 min, $t_R$(minor) = 5.7 min. The enantiomeric excess of the endo diastereomer was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO₂, λ = 254 nm):
\( t_R(\text{major}) = 3.7 \ \text{min}, \ t_R(\text{minor}) = 4.4 \ \text{min}. \) Spectral data are in agreement with the literature.\(^{46}\)

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

![Chromatogram with peak data](image)
An oven-dried vial was charged with 1,3-dimethylindole (75, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate 91d (65.5 mg, 0.24 mmol, 1.20 equiv), and (R)-3,3’-dibromo-BINOL (102k, 17.8 mg, 0.04 mmol, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to 75). The vial was charged with DCM (1.5 mL) and SnCl₄ (1 M in DCM, 200 μL, 0.20 mmol, 1.00 equiv) was added. The reaction was stirred at 20 °C for 4 hours, after which time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (15 mL). The aqueous was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The product 100e was formed in a 7:1 ratio of diastereomers favoring the exo diastereomer (determined by ¹H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 32.7 mg (39% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the exo diastereomer was determined to be 98% by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO₂, λ = 254 nm): \( t_R \) (major) = 12.5 min, \( t_R \) (minor) = 10.9 min. The enantiomeric excess of the endo diastereomer was determined to be 92% by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO₂, λ = 254 nm): § For information on Table 3.2.6, entry 3, see ref. 45.
$t_R$(major) = 5.8 min, $t_R$(minor) = 5.0 min. Spectral data are in agreement with the literature.$^{46}$

100e (Table 3.2.6, entry 4): racemic

100e (Table 3.2.6, entry 4): enantioenriched, exo: 98% ee, endo: 92% ee
3.5 NOTES AND REFERENCES


(3) Gala, F.; D’Auria, M. V.; De Marino, S; Zollo, F.; Smith, C. D.; Copper, J. E.; Zampella, A. Tetrahedron 2007, 63, 5212.


(24) Li, Y.; Li, Q. *Org. Lett.* **2012**, *14*, 4362. Br$_2$ was used as the electrophile bromine source instead of 1,2-dibromotetrachloroethane.


(32) Methyl 2-acetamidoacrylate is commercially available, or can be prepared according to Crestey, F.; Collot, V.; Steibing, S.; Rault, S. *Synthesis* **2006**, *20*, 3506.


(36) Prepared from 2-iodoaniline by an analogous procedure to that reported by Sakai et al. (reference 28). Spectral data matches that reported in the literature: Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056.

(37) Prepared from 2-iodoaniline by an analogous procedure to that reported by Sakai et al. (reference 28). Spectral data matches that reported in the literature: Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428.

(38) Prepared from 2-iodoaniline by an analogous procedure to that reported by Sakai et al. (reference 28). Spectral data matches that reported in the literature: Yang, S.-D.; Sun, C. L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473.


APPENDIX 3

Spectra Relevant to Chapter 3:

Synthesis of Tryptophan Derivatives by a Tandem Friedel–Crafts

Conjugate Addition/Enantioselective Protonation Reaction
Appendix 3–Spectra Relevant to Chapter 3
Sample Name: LMRVI-093-3-Cl-R-BINOL
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-093-3-Cl-R-BINOL
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2011

Sample #34, Operator: lrepka
Relax. delay 25.000 sec
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions

DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 40 sec

<table>
<thead>
<tr>
<th>ppm</th>
<th>102i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>OH</td>
</tr>
</tbody>
</table>

Appendix 3–Spectra Relevant to Chapter 3
Sample Name: LMRVI-093-3-Cl-R-BINOL
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-093-3-Cl-R-BINOL
FidFile: CARBON01

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

Sample #34, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6569690 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min
Appendix 3–Spectra Relevant to Chapter 3
LMRVI-279-6,6'-hydroxy-MOM BINOL

Sample Name:
LMRVI-279

Data Collected on:
indy.caltech.edu-inova500

Archive directory:
/home/lrepka/vnmrsys/data

Sample directory:
LMRVI-279

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn

Data collected on: Dec 20 2011

Sample #42, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions

OBSERVE C13, 125.6558710 MHz
DECOUPLE H1, 499.7276454 MHz
Power 39 dB continuously on

WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
Sample Name: LMRVI-273-2-1-allyl-2-phenylindole
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-273-2-1-allyl-2-phenylindole
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 4 2011

Sample #33, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225134 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 40 sec

Appendix 3–Spectra Relevant to Chapter 3
LMRVI-273-1-allyl-2-phenylindole

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

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 4 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553343 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min

Appendix 3–Spectra Relevant to Chapter 3
LMRVI-273-1,3-diallyl-2-phenylindole

Sample Name: LMRVI-273-1,3-diallyl-2-phenylindole
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-273-1,3-diallyl-2-phenylindole
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 11 2011
Sample #27, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225126 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 40 sec

Appendix 3–Spectra Relevant to Chapter 3

Plotname: --Not assigned--
Sample Name: LMRVI-273-1_3-diallyl-2-phenylindole
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-273-1_3-diallyl-2-phenylindole
FidFile: CARBON01

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

Sample #27, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553307 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
Appendix 3–Spectra Relevant to Chapter 3

Sample Name: LMRVI-219
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-219
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 2 2011

Sample #33, Operator: lrepka
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
6 repetitions
OBSERVE H1, 499.7225136 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 45 sec

137r
F

ppm

Appendix 3–Spectra Relevant to Chapter 3
Appendix 3–Spectra Relevant to Chapter 3

LMBVI-219

Sample Name:
LMBVI-219
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMBVI-219
FidFile: CARBON01

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

Sample #33, Operator: lrepka
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6553281 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 54 min
Appendix 3–Spectra Relevant to Chapter 3
Appendix 3—Spectra Relevant to Chapter 3
Sample Name: LMRVI-161

Data Collected on: indy.caltech.edu-inova500

Archive directory: /home/lrepka/vnmrsys/data

Sample directory: LMRVI-161

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jul 27 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

10000 repetitions

OBSERVE C13, 125.6553284 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 5 hr, 41 min
Appendix 3–Spectra Relevant to Chapter 3

Sample #33, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE N1, 499.7225131 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 40 sec
Appendix 3–Spectra Relevant to Chapter 3

Sample Name: LMRVI-205-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-205-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 23 2011

Sample #33, Operator: lrepka

Rel ax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
10000 repetitions
OBSERVE C13, 125.6553292 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5 hr, 41 min
Sample Name: LMRVI-171
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-171
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 25 2011
Sample #33, Operator: lrepka
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE 2H, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 40 sec

Appendix 3–Spectra Relevant to Chapter 3
Sample Name: LMRVI-171
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-171
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 25 2011

Sample #33, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions

OBSERVE  C13, 125.6553354 MHz
DECOUPLE  H1, 499.7250019 MHz
Power 39 dB continuously on

WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min

Appendix 3–Spectra Relevant to Chapter 3
Sample Name: LMR-allyl
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: LMR-allyl
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 14 2012

Sample #20, Operator: mkieffer

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

OBSERVE H1, 499.7225125 MHz

DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec

---

Appendix 3–Spectra Relevant to Chapter 3
Sample Name: LMR-allyl
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: LMR-allyl
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: Jan 14 2012

Sample #20, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553358 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
MEK3186-1

Sample Name: MEK3186-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3186-1
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 15 2011

Sample #15, Operator: mkieffer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec

Appendix 3–Spectra Relevant to Chapter 3

327
Sample Name: MEK3186-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3186-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 15 2011

Sample #15, Operator: mkieffer
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553310 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Appendix 3–Spectra Relevant to Chapter 3
Appendix 3—Spectra Relevant to Chapter 3

MEK3084-1

Sample Name: MEK3084-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3084-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 9 2011

Temp. 25.0 C / 298.1 K
Sample #39, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569642 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
Sample Name: MEK3193-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3193-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 21 2011

Sample #33, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions

OBSERVE C13, 125.6553291 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
MEK3130-1

Sample Name: MEK3130-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3130-1
FidFile: CARB0N01

Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: Jun 7 2011

Temp. 25.0 C / 298.1 K
Sample #15, Operator: mkieffer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions

OBSERVE C13, 125.6569681 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on

WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 26 min
Appendix 3–Spectra Relevant to Chapter 3
Sample Name: MEK3185-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3185-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 15 2011

Sample #14, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions

OBSERVE C13, 125.6553300 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on

WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Appendix 3–Spectra Relevant to Chapter 3

MEK-5-Br

Sample Name: MEK-5-Br
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnrmrsys/data
Sample directory: MEK-5-Br
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 25 2011

Sample #15, Operator: mkieffer
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions

OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec

Appendix 3–Spectra Relevant to Chapter 3
MEK-5-Br

Sample Name: MEK-5-Br
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK-5-Br
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 25 2011

Sample #15, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6666408 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Sample Name: MEK3150-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3150-1
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 20 2011

Temp. 25.0 C / 298.1 K
Sample #15, Operator: mkieffer

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions

ORIGIN H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 0 sec

Plotname: --Not assigned--
MEK3080-1

Sample Name: MEK3080-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3080-1
FidFile: PROTON01

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

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

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
FT size 65536
Total time 4 min 0 sec

Appendix 3–Spectra Relevant to Chapter 3
Sample Name: MEK3080-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3080-1
FidFile: current

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 8 2011

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

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

OBSERVE C13, 125.6569642 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
Appendix 3–Spectra Relevant to Chapter 3

Sample Name: MEK3238-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vmrsys/data
Sample directory: MEK3238-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2011
Sample #20, Operator: mkieffer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553271 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 50 min
Sample Name: MEK3113-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3113-1
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: dcdl3
Data collected on: May 24 2011
Temp. 25.0 C / 298.1 K
Sample #35, Operator: mkieffer
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 0 sec
Sample Name: MEK3113-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3113-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: May 24 2011

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

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions

OBSERVE C13, 125.6569662 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on

WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min
Appendix 3–Spectra Relevant to Chapter 3

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

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 25 2011
Sample #14, Operator: mkieffer

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

OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
Sample Name: MEK3086-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3086-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 10 2011

Temp. 25.0 C / 298.1 K
Sample #39, Operator: mkieffer

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

OBSERVE C13, 125.6569623 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min

Appendix 3–Spectra Relevant to Chapter 3
MEK3079-1

Sample Name: MEK3079-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3079-1
FidFile: PROTON01

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

Temp. 25.0 C / 298.1 K
Sample #41, Operator: mkieffer

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
FT size 65536
Total time 4 min 0 sec

Appendix 3–Spectra Relevant to Chapter 3

Plotname: --Not assigned--

138s
Sample Name: MEK3079-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vmrsys/data
Sample directory: MEK3079-1
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 8 2011

Temp. 25.0 C / 298.1 K
Sample #41, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6569690 MHz
DECouple H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
FT size 65536
Total time 8 min 45 sec
MEK-ortho-fluoro-1

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

Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Aug 26 2011

Sample #33, Operator: mkieffer
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
Appendix 3–Spectra Relevant to Chapter 3

Sample Name: MEK-m-OMe
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK-m-OMe
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Jun 25 2011

Sample #16, Operator: mkieffer
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
Sample Name: MEK-m-OMe
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK-m-OMe
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 25 2011

Sample #16, Operator: mkieffer
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569681 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Appendix 3–Spectra Relevant to Chapter 3

MEK3083-1

Sample Name: MEK3083-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3083-1
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 9 2011

Temp. 25.0 C / 298.1 K
Sample #38, Operator: mkieffer

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
FT size 65536
Total time 4 min 0 sec

Plotname: --Not assigned--
Sample Name: MEK3080-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3080-1
FidFile: current

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

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

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
384 repetitions
OBSERVE C13, 125.6569642 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
Appendix 3–Spectra Relevant to Chapter 3

Sample Name: MEK3129-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3129-1
FidFile: PROTONO1

Pulse Sequence: PROTON (s2pul)  
Solvent: cdc13  
Data collected on: Jun 7 2011

Temp. 25.0 C / 298.1 K  
Sample #14, Operator: mkieffer

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

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

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Appendix 3–Spectra Relevant to Chapter 3

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Sample Name: MEK3129-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3129-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 7 2011
Temp. 25.0 C / 298.1 K
Sample #14, Operator: mkieffer
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6569671 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 26 min
Sample Name: MEK-t-butyl-rac

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

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

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

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290200 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
MEK-t-butyl-rac

Sample Name: MEK-t-butyl-rac
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK-t-butyl-rac
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: Jun 5 2011

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

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6569662 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 50 min
Sample Name: MEK3085-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3085-1
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 10 2011

Temp. 25.0 C / 298.1 K
Sample #38, Operator: mkieffer

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290204 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 4 min 0 sec

Appendix 3–Spectra Relevant to Chapter 3

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Appendix 3–Spectra Relevant to Chapter 3

Sample Name: MEK3085-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3085-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: May 11 2011

Temp. 25.0 C / 298.1 K
Sample #38, Operator: mkielfer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6569616 MHz
DECOUPLE H1, 499.7315163 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 14 min
MEK-phthalimide

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

Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Jun 6 2011

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

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
FT size 65536
Total time 2 min 24 sec

Appendix 3–Spectra Relevant to Chapter 3
Appendix 3–Spectra Relevant to Chapter 3
Appendix 3–Spectra Relevant to Chapter 3
Sample Name: LMRVI-209
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-209
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 25 2011

Sample #27, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553311 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
   Line broadening 0.5 Hz
   FT size 65536
   Total time 51 min
Appendix 3–Spectra Relevant to Chapter 3
Sample Name: MEK3206-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3206-1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 4 2011
Sample #14, Operator: mkieffer

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553281 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
MEK-methylcarbamate-1

Sample Name: MEK-methylcarbamate-1
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK-methylcarbamate-1
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Aug 30 2011

Sample #22, Operator: mkieffer
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec

Appendix 3–Spectra Relevant to Chapter 3
Sample Name: MEK3233-X
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/mkieffer/vnmrsys/data
Sample directory: MEK3233-X
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cxcl3
Data collected on: Aug 28 2011

Sample #20, Operator: mkieffer

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553271 MHz
DECUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 50 min
Appendix 3–Spectra Relevant to Chapter 3

Sample Name: LMRVI-181
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-181
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Aug 7 2011
Sample #40, Operator: lrepka
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225129 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 7 min 20 sec

[Chemical structure image]

Plotname: --Not assigned--

ppm

1  2  3  4  5  6  7  8  9  10

172

N

CO2H

NHAc

Ph

1.08 1.00 0.93 1.01 0.96 2.76
Appendix 3–Spectra Relevant to Chapter 3
CHAPTER 4

Access to 2a-Phenylpyrroloindolines by an Oxidative Cyclization:

Identification of a $\text{GABA}_A$ Receptor Positive Allosteric Modulator†

4.1 INTRODUCTION

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

† The research discussed in this chapter was completed as a joint project between the Reisman and Dougherty laboratories. The experiments were designed in collaboration with Professor Sarah Reisman, Professor Dennis Dougherty, Alex Maolanon, a visiting student in the Reisman group from the Technical University of Denmark, and Christopher Marotta and Kristina Daeffler, two graduate students in the Dougherty group. Synthetic research on the second generation molecules was primarily conducted by Alex Maolanon and the electrophysiology experiments were performed by Christopher Marotta and Kristina Daeffler. Professor Henry Lester and Dr. Scott Virgil are gratefully acknowledged for helpful discussions.
carboxylic acid, was shown to be a channel inhibitor but further studies identified a compound lacking the carboxylic acid functionality that selectively activates the GABA<sub>A</sub> receptor as a positive allosteric modulator (PAM).

### 4.1.1 Prior Efforts Toward 2a-Phenylpyrroloindolines


To date, there are very few reported syntheses of 2a-phenylpyrroloindolines. In the initial work completed by Kollenz and coworkers, 2a-phenylpyrroloindolines such as 194 as well as molecules bearing an azapropellane core (197) were prepared via a Fischer indolization rearrangement approach (Scheme 4.1.1). Specifically, condensation of \(N,N\)-diphenylhydrazone 190 with oxalyl chloride with concomitant loss of 2 equivalents HCl affords pyrroledione 192, which upon heating rearranges to 194. Based on isotopic labeling studies, this rearrangement is proposed to occur according to the standard mechanism for Fischer indole synthesis by a \([3,3]\) rearrangement, rearomatization by proton transfer, and intramolecular 1,2-addition into the imine to give 194. These pyrroloindolines were shown to be versatile intermediates capable of many
transformations including 1) selective reduction to afford α-hydroxyketone 199 or the ring-opened form 201 depending on the C3a-substitution pattern, 2) ring-opening at high temperature to give indole 198, and 3) oxidative cleavage of the dione with NaOH and H₂O₂ to yield 1,2-diphenylindole (200, Scheme 4.1.2). Notably, formation of azapropellane 197 has been confirmed by X-ray crystallography (Figure 4.1.1).

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

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

Within the past few years, two other synthetic approaches to 2a-arylpyrroloindolines have been reported. Bedford and coworkers developed a one-flask two-step protocol for generating benzene-fused pyrroloindolines including 204 by a Pd-catalyzed intramolecular dearomatization, followed by organolithium 1,2-addition into the resultant imine 203 (Scheme 4.1.3). In 2012, subsequent to our report of an oxidative cyclization
approach to 2a-phenylpyrroloindolines (Section 4.2.2), Ma, Xie, and coworkers reported access to tetracyclic pyrroloindolines including 2a-phenyl derivative 208. This transformation occurs by deprotonation of indole malonic diamides (205) with LHMDS, oxidative cyclization to generate transient spirocycle 207, and intramolecular cyclization onto the imine to give 208.4

**Scheme 4.1.3. Other approaches to 2a-phenylpyrroloindolines.**

*Bedford and coworkers, 2011:*

*Xie, Ma and coworkers, 2012:*

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

**Figure 4.1.2. Pyrroloindoline 209 patented by the BASF for applications as an OLED.**
4.1.2 Oxidative Cyclization Approaches to Pyrroloindolines

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

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

Ten years after the initial disclosure by Wiktop and coworkers, Hino and coworkers...
showed that pyrroloindoline 214 could also be accessed directly from tryptophan 210 by exposure to acids such as H₃PO₄ or TFA. A myriad of other conditions for cyclization have also been reported involving C3 halogenation, selenation, hydroxylation, alkylation, and arylation. In the subsequent section, the details of some reports that directly pertain to our work will be discussed within the context of the development of the oxidative cyclization reaction of 2-phenyltryptophans.

4.2 THE OXIDATIVE CYCLIZATION REACTION OF 2-PHENYLTRYPTOPHANS

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

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

We began by investigating the cyclization reaction of (1H)-2-phenyltryptophan 138c generated in the tandem conjugate addition/enantioselective protonation reaction (Chapter 3). However, subjection of 138c to NBS and TFA at −50 °C failed to promote pyrroloindoline formation and instead afforded bromoindolenine 219 as a 1:1 mixture of diastereomers in excellent yield (Scheme 4.2.1). Other examples of stable 2-
arylindolenines have been reported\textsuperscript{13} and the stability of \textit{219} likely results from conjugation of the imine with the C2-phenyl substituent.

\textit{Scheme 4.2.1. Conversion of \textit{138c} to stable bromindolenine \textit{219}.}

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

\textit{Table 4.2.1. Other derivatization studies on N-acetyltryptophan methyl ester \textit{138c}.}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temperature/Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>neat 85% H\textsubscript{3}PO\textsubscript{4}</td>
<td>50 °C, 1 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>neat 85% H\textsubscript{3}PO\textsubscript{4}</td>
<td>85 °C, ~ 12 h</td>
<td>~75% saponification by HRMS</td>
</tr>
<tr>
<td>3</td>
<td>neat TFA</td>
<td>23 °C, 1.5 h or 50 °C, 1 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>NBS, PPTS, DCM</td>
<td>23 °C, 6 h</td>
<td>unidentified bromination product</td>
</tr>
<tr>
<td>5</td>
<td>Br\textsubscript{2}, benzene</td>
<td>23 °C, 15 min</td>
<td>mixture of products</td>
</tr>
<tr>
<td>6</td>
<td>1,3-dibromo-5,5-dimethylhydantoin, TFA, DCM</td>
<td>−50 to 10 °C, 3 h</td>
<td>quantitative conversion to \textit{219} (1:1:1 dr)</td>
</tr>
<tr>
<td>7</td>
<td>NCS, TFA, DCM</td>
<td>−50 °C, 1.5 h</td>
<td>quantitative to chlorindolenine (1.7:1 dr)</td>
</tr>
<tr>
<td>8</td>
<td>PhI(TFA)\textsubscript{2}, 2:1 MeCN:H\textsubscript{2}O</td>
<td>0 °C, 35 min</td>
<td>mixture of products</td>
</tr>
<tr>
<td>9</td>
<td>\textit{221}, DCM</td>
<td>23 °C, 24 h</td>
<td>47% yield of hydroxyindolenine (1:1 dr)</td>
</tr>
</tbody>
</table>
The conditions that facilitated bromoindolenine (219) formation were reevaluated for 2-butyltryptophan 138u, for which the corresponding indolenine is anticipated to be less stable and susceptible to cyclization. In the presence of NBS and TFA, 138u was converted to a compound containing diastereotopic methylenes (by crude $^1$H NMR) but this compound was unstable to silica gel chromatography (Table 4.2.2, entry 3). Furthermore, no pyrroloindoline was formed under these conditions as indicated by the lack of characteristic upfield aromatic shifts in the $^1$H NMR.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temperature/Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 equiv 221, DCM</td>
<td>23 ºC, 4 h</td>
<td>very messy reaction</td>
</tr>
<tr>
<td>2</td>
<td>1.5 equiv NPS, 1 equiv PPTS, DCM</td>
<td>23 ºC, 13 h</td>
<td>minimal reaction</td>
</tr>
<tr>
<td>3$^a$</td>
<td>1 equiv NBS, 1 equiv TFA, DCM</td>
<td>$–50$ ºC, 3.5 h</td>
<td>possibly indolenine by crude NMR, not isolable</td>
</tr>
</tbody>
</table>

$^a$Reaction conducted with racemic 138u. E: electrophile.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temperature/Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>1.50 equiv NPSP, 1 equiv PPTS, DCM</td>
<td>23 ºC, 28.5 h</td>
<td>mixture of products (diastereotopic CH&lt;sub&gt;2&lt;/sub&gt; in crude &lt;sup&gt;1&lt;/sup&gt;H NMR)</td>
</tr>
<tr>
<td>2</td>
<td>221, DCM</td>
<td>23 ºC, 29.5 h</td>
<td>very messy reaction</td>
</tr>
<tr>
<td>3</td>
<td>1 equiv NBS, 9:1 DCM:TFA</td>
<td>−50 ºC, 4 h</td>
<td>mixture of products (diastereotopic CH&lt;sub&gt;2&lt;/sub&gt; in crude &lt;sup&gt;1&lt;/sup&gt;H NMR, aromatic peaks upfield-not isolable)</td>
</tr>
</tbody>
</table>

E: electrophile.

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

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

Of the conditions screened with (1<sup>H</sup>)-tryptophan derivatives, the results with N-acetyl-2-phenyltryptophan 138c were particularly encouraging in that quantitative formation of stable haloindolenines was observed upon exposure to both NBS and NCS. These results suggested that 1-methyl-2-phenyltryptophan 138e might prove a suitable substrate for pyrroloindoline (226) formation. Electrophilic substitution at C3 of 138e would generate a positively charged indolenine (35) that is more reactive towards cyclization (Scheme 4.2.2). Unfortunately, subjection of 138e to NBS and TFA at low
temperature resulted in very minimal reaction. Exposure to the same conditions at room temperature also failed to provide any pyrroloindoline (226); instead, bromination at C5 was observed to give 224 in 24% yield.

Alternatively, we were pleased to find that subjection of 138e to NCS, TFA, and MeCN at room temperature provided 3-chloropyrroloindoline 227, as confirmed by HRMS. This pyrroloindoline is unstable and, by in situ monitoring with \(^1\)H NMR spectroscopy, was shown to decompose to a mixture of products including the starting tryptophan 138e. However, direct subjection of chloropyrroloindoline 227 to a mixture of MeCN, H\(_2\)O, and silica gel delivered more stable 3a-hydroxypyrroloindoline 228. A similar two-step process has been disclosed by Somei and coworkers, in which they generated 3a-hydroxypyrroloindolines from simple tryptamine derivatives by treating the intermediate 3a-halopyrroloindolines with AgCN in a mixture of MeCN and H\(_2\)O.\(^c\)

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

Furthermore, monitoring of the reaction at longer time points determined that *exo*-227 (not shown) is more prone to decomposition, as the dr is artificially enhanced to 20:1 over time (entries 3-7). Three hours was identified as the optimal reaction time, with 3a-hydroxypyrroloindoline 228 isolated in 52% yield as a 6:1 mixture of diastereomers favoring the *endo* diastereomer (entry 5).
Table 4.2.4. Optimization of the NCS-promoted cyclization for 138e.

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

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

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

Although in situ conversion of 227 to 228 could potentially enable a more efficient process, we found that use of SiO\(_2\) or both SiO\(_2\) and water as additives failed to directly provide 228. In search of a more streamlined approach to 3a-hydroxypyrroloindolines, we also attempted direct hydroxylation using 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (221) as the oxidant (Scheme 4.2.3). Interestingly, no 228 was observed under these conditions but oxindole 231 was isolated in 42% yield as a 2:1 mixture of diastereomers. Mechanistically, this reaction is expected to occur by epoxidation, followed by ring-opening at C3 and phenyl migration.\(^{14}\)
4.3 FIRST GENERATION ELECTROPHYSIOLOGY EXPERIMENTS: INVESTIGATIONS OF A PYRROLOINDOLINE-2-CARBOXYLIC ACID

4.3.1 Introduction

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

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

The Dougherty laboratory at Caltech is interested in identifying binding motifs of novel positive allosteric modulators (PAMs) for ligand-gated ion channels (LGICs). A collaboration was initiated between our two research groups to investigate molecules related to 3a-hydroxy-2a-phenylpyrroloindoline 228 based on the structural similarities
between 228 and known PAMs of the nicotinic acetylcholine receptors (nAChRs), physostigmine (1) and galanthamine (235) (Figure 4.3.2). Drugs that target ion channels have been developed for the treatment of many neurological disorders and degenerative disease. Specifically, the design of allosteric modulators, which bind at a site removed from that of the natural agonist, has received extensive attention given their potential for enhanced stability toward desensitization and improved receptor selectivity relative to more traditional agonist and antagonist drugs that bind in the orthosteric site. Notably, the activity of 1 and 235 as PAMs is likely connected to their role in the amelioration of Alzheimer’s disease (AD) symptoms (235 is an FDA-approved drug for the treatment of AD).

Figure 4.3.2. Positive allosteric modulators of nicotinic acetylcholine receptors.

4.3.2 Preparation of First Generation Target Carboxylic Acid 237

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

Alternatively, the necessary carboxylic acid (237) could be prepared in short order starting with the tandem conjugate addition/enantioselective protonation reaction of 1-methyl-2-phenylindole (137c), which could be completed on 8.5 mmol scale on the benchtop without any significant erosion of yield or ee (Scheme 4.3.2). Subsequent methylation under standard conditions afforded tertiary amide 238 in 75\% yield, albeit in a substantially reduced ee of 46\%. This issue of racemization, which was persistent for various runs and different substrates, is surprising given that NaH is commonly employed for the alkylation of α-amido esters.\(^{21}\) Attempted subsequent acetamide hydrolysis under aqueous acid conditions resulted in competitive overhydrolysis; however, we found that excess AcCl and MeOH provides clean conversion to 239 as monitored over time by LCMS, albeit at a very slow rate. After 75.5 hours at 60 °C, secondary amine 239 was isolated in 28\% yield and 38\% of the starting material (238) was recovered, both in 45\% ee.
The oxidative cyclization reaction of secondary amine 239 was substantially slower than that of the acetamide 138e with better results observed in the absence of TFA (Table 4.3.1, entries 1 and 3); this reactivity might be attributed to initial N-chlorination of the amine followed by intramolecular delivery of the chlorine to C3, a hypothesis driven by a related report of Lindel and coworkers.22

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

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Conversion&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA</td>
<td>3</td>
<td>41</td>
<td>14</td>
<td>1.3:1</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>13.5</td>
<td>66</td>
<td>31</td>
<td>1.9:1</td>
</tr>
<tr>
<td>3</td>
<td>-----</td>
<td>3</td>
<td>81</td>
<td>42</td>
<td>1.2:1</td>
</tr>
</tbody>
</table>

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

Under optimal conditions using NCS, pyrroloindoline 240 was prepared in 1.8:1 dr, favoring the *exo* diastereomer (Scheme 4.3.3). Following preparative HPLC, the two diastereomers could be isolated separately albeit in less than 90% purity each. Exposure of *exo*-240 to LiOH provided 11% isolated yield of the desired saponified product, *exo*-237. This reaction was only neutralized and concentrated prior to reverse phase preparative HPLC and thus the reasons for poor recovery remain unclear. Following exposure of *endo*-240 to LiOH, formation of the desired *endo* carboxylic acid was observed by ¹H NMR analysis of the crude reaction mixture. Unfortunately, this compound was unstable to the purification conditions, yielding *exo*-237 in 1% yield, favoring the same enantiomer as in the saponification of *exo*-240. These results, in addition to further studies on *endo*-237 (Scheme 4.4.5), determined that this compound is
both highly unstable and capable of isomerization to \textit{exo-237} via ring opening of the pyrroloindoline at C2a.

\textit{Scheme 4.3.3. Access to \textit{exo-237} for electrophysiology experiments.}

\begin{center}
\includegraphics[width=\textwidth]{scheme4.3.3.png}
\end{center}

4.3.3 \textit{Electrophysiology Experiments on Carboxylic Acid 237}

Initial experiments on carboxylic acid 237 were conducted by evaluating its effect on receptor response for a variety of LGICs individually expressed in \textit{Xenopus} oocytes (Table 4.3.2). This work was completed using an OpusXpress-6000A system and more detailed information on the experimental setup can be found in Section 4.7.2. Hydroxypyrroloindoline 237 was found to either not affect or inhibit each receptor when added at a 20 \(\mu\)M concentration in combination with an EC\textsubscript{50} dose of the appropriate agonist (median effective concentration). The IC\textsubscript{50} value of 237 (median inhibition concentration with co-application of an EC\textsubscript{50} dose of agonist) was also determined for two receptors; for the \(\alpha7\)-T6’S nAChR, the IC\textsubscript{50} value was 5 +/- 1 \(\mu\)M (n=7) with a hill coefficient of 0.8 and for the (\(\alpha4\)-L9’A)\(_2\)(\(\beta2\))\(_2\) nAChR, the IC\textsubscript{50} value was 8 +/- 1 \(\mu\)M (n=7) with a hill coefficient of 1.2.

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Receptor</th>
<th>% Current reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(α1)(β1-L9’S)δγ mouse muscle nAChR</td>
<td>21 ± 1b</td>
</tr>
<tr>
<td>2</td>
<td>α7 nAChR</td>
<td>40 ± 9</td>
</tr>
<tr>
<td>3</td>
<td>α7-T6’S nAChR</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>4</td>
<td>(α4)(β2)δ nAChR</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>5</td>
<td>(α4-L9’A)(β2)δ nAChR</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>6</td>
<td>(α4-L9’A)(β2)δ nAChR</td>
<td>44 ± 1</td>
</tr>
<tr>
<td>7</td>
<td>α4βδ nAChR</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>8</td>
<td>(α1)(β2)y2 GABAAR</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>9</td>
<td>GluR2A</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>10</td>
<td>GlyR</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>11</td>
<td>5HT3AR</td>
<td>3 ± 2</td>
</tr>
</tbody>
</table>

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

Given that pyrroloindoline 237 did exhibit some receptor selectivity, with no significant inhibition of the GlyR, GluR2A, and 5HT3A receptors observed, it was deemed necessary to perform a series of follow-up experiments to ascertain additional mechanistic information. The molecule also appeared to have a slow rate of dissociation.
as the current recovery after ceasing treatment with 237 was incomplete in the time course of the experiment, as shown for \((\alpha4\text{-L9}'A)_{3}(\beta2)_{2}\) nAChR in Figure 4.3.3.

*Figure 4.3.3. Electrophysiology data on exo-237 (41% enantioenriched) with \((\alpha4\text{-L9}'A)_{3}(\beta2)_{2}\) nAChR.*

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

Figure 4.3.4. New targets for electrophysiology experiments.

4.4 SYNTHESES OF SECOND GENERATION TARGETS FOR ELECTROPHYSIOLOGY EXPERIMENTS

4.4.1 Synthesis of Pyrroloindolines from Tryptamine Derivatives

Although it would have been convenient to directly access 241 by the decarboxylation of exo-237, our initial attempts at promoting this transformation proved unfruitful (Scheme 4.4.1). The Barton ester appears to form, as the mass corresponding to decarboxylation is observed when the reaction progress is monitored by LCMS; however, subsequent exposure to radical conditions results in either decomposition or recovery of 237.25

Scheme 4.4.1. Attempted decarboxylation of 237.
In light of these results, we decided to prepare 241 using an oxidative cyclization of the corresponding 2-phenyltryptamine 245. Our synthesis began with the selective C2-arylation of readily available N-Cbz-N,1-dimethyltryptamine (243) (Scheme 4.4.2). We were pleased to find that conditions developed for C2-arylation of tryptophan derivatives by Albericio, Lavilla, and Ruiz-Rodríguez\(^{26}\) enabled successful arylation of 243. In the presence of iodobenzene, AgBF\(_4\), 2-nitrobenzoic acid, and Pd(OAc)\(_2\) with microwave heating for 4 minutes, 243 was converted to 2-phenyltryptamine 244, which was isolated in 81% yield following purification by column chromatography. 2-phenyltryptamine 244 was cleanly deprotected using catalytic Pd\(_2\)(dba)\(_3\) and Et\(_3\)SiH to afford secondary amine 245.

Scheme 4.4.2. Synthesis of oxidative cyclization substrate 245.

Although the oxidative cyclization reaction of 245 is particularly sensitive, pyrroloindoline formation was consistently observed with dropwise addition of NCS (purified by recrystallization) as a solution to a mixture of the substrate and 4Å molecular sieves in MeCN. In contrast to the oxidative cyclization of tryptophan 239 to 3a-hydroxypyrroloindoline 240, use of an aqueous ammonia quench to work up the reaction of tryptamine 245 afforded stable 3a-aminopyrroloindoline 246 in 57% yield (Scheme 4.4.3). Alternatively, quenching the cyclization of tryptamine 245 with aqueous sodium thiosulfate, followed by treatment with silica gel, gave 3a-hydroxypyrroloindoline 241 in 33% yield.
We also pursued the synthesis of monomethylated 3a-hydroxypryroloindoline 251 (Scheme 4.4.4). Microwave-assisted arylation of known Cbz-protected tryptamine 248 provided 2-phenyltryptamine 249 in excellent yield. Oxidative cyclization under the reoptimized conditions with 4Å molecular sieves and recrystallized NCS afforded 1-Cbz-pyroloindoline 250. Subsequent subjection to catalytic Pd$_2$(dba)$_3$•CHCl$_3$ and Et$_3$SiH generated the corresponding silyl carbamate, which upon cleavage by stirring with saturated aqueous NaHCO$_3$ provided target pyrroloindoline 251 in 48% yield from 248.

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

Scheme 4.4.4. Synthesis of (1H)-1a-methylpyrroloindoline 251.
4.4.2 Second Generation Synthesis of Exo-Carboxylic Acid 237

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

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

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

In an analogous fashion to the work on \textit{exo-237} (Section 4.3.3), the four pyrroloindoline products derived from tryptamine were subjected to electrophysiology experiments. As observed for \textit{exo-237}, the derivatives showed minimal activity with respect to the GluR$_{2A}$, GlyR, and 5HT$_{3A}$ receptors (Table 4.5.1, entries 6-8). However, each molecule promoted current reduction when applied to nAChRs (entries 1-3). This structural promiscuity likely suggests that these pyrroloindolines function as channel blockers, rather than as NAMs or antagonists. However, we were pleased to find that although \textbf{241} blocks all nAChRs, it potentiates the effect of the GABA$_{A}$ receptor agonist, GABA, with an increase in current of 52\% at a 40 \mu M dose of \textbf{241} in combination with an EC$_{50}$ dose of GABA (11 \mu M, entry 4) relative to an EC$_{50}$ dose of GABA alone. Interestingly, \textbf{241} is also capable of activating the receptor on its own, generating about 10\% of the current produced by an EC$_{50}$ dose of GABA (Figure 4.5.1). Experiments
conducted at varying concentrations of 241 identified a dose dependence on the receptor response (data not shown).

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

Table 4.5.1. Electrophysiology data on cyclic tryptamine derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Receptor</th>
<th>241</th>
<th>246</th>
<th>251</th>
<th>250</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(α1)_2(β1-L9’S)γ y muscle nAChR</td>
<td>−53 ± 3</td>
<td>−81 ± 6</td>
<td>−7 ± 3</td>
<td>−29 ± 3</td>
</tr>
<tr>
<td>2</td>
<td>α7-T6’S nAChR</td>
<td>−92 ± 4</td>
<td>−96 ± 3</td>
<td>−57 ± 10</td>
<td>−68 ± 7</td>
</tr>
<tr>
<td>3</td>
<td>(α4-L9’A)2(β2)3 nAChR</td>
<td>−29 ± 6</td>
<td>−44 ± 2</td>
<td>−11 ± 2</td>
<td>−47 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>(α1)2(β2)2 GABA_A R</td>
<td>+52 ± 10</td>
<td>+10 ± 5</td>
<td>−27 ± 21</td>
<td>−27 ± 11</td>
</tr>
<tr>
<td>5</td>
<td>(α1)2(β2)2 GABA_A R</td>
<td>+16 ± 2</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>GluR2a</td>
<td>−9 ± 6</td>
<td>−12 ± 5</td>
<td>−11 ± 5</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>7</td>
<td>GlyR</td>
<td>+3 ± 7</td>
<td>−16 ± 6</td>
<td>+18 ± 10</td>
<td>−9 ± 9</td>
</tr>
<tr>
<td>8</td>
<td>5HT3aR</td>
<td>−3 ± 5</td>
<td>−11 ± 8</td>
<td>+3 ± 12</td>
<td>−23 ± 4</td>
</tr>
</tbody>
</table>

* % effect on current and standard error of means (n=3 or 4) shown. Current was recorded using an OpusXpress-6000A with a two-electrode voltage clamp method. Data was acquired with a co-application of 20 µM concentration of the relevant pyrroloindoline and an EC_{50} dose of agonist, both in ND96 buffers (see 4.7.2 for agonist EC_{50} values). Run with a 40 µM concentration of 241. nd: not determined.

Substrates that activate the GABA_A receptor are important starting points for drug development for the treatment of neurological disorders. In particular, benzodiazepines are a class of molecules that act as PAMs of the GABA_A receptor by binding at the interface of the α and γ subunits. Many of these molecules are FDA-approved drugs including clonazepam (Klonopin), a treatment for epilepsy, diazepam (Valium), a
treatment for anxiety, and flurazepam (Dalmane), a treatment for insomnia. Interestingly, upon testing 241 versus a GABA\textsubscript{A} receptor lacking the \(\gamma\) subunit, potentiation of the GABA-induced current was reduced three-fold and 241 did not activate the receptor in the absence of GABA (Table 4.5.1, entry 5); this result suggests that 241 might target the same location as benzodiazepine but further analysis of other GABA\textsubscript{A} receptor analogues is required to determine the binding site.

*Figure 4.5.1. Current trace for screen with 241 versus GABA\textsubscript{A} receptor.*

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

### 4.6 CONCLUSIONS AND FUTURE DIRECTIONS

The key finding that pyrroloindoline 241 is a PAM encourages future research on 3a-hydroxy-2a-phenylpyrroloindolines. As a measure of relative therapeutic potential, the activity of 241 could be compared to marketed GABA\textsubscript{A} receptor PAMs. Furthermore, the extensively studied pyrroloindoline natural product physostigmine (1) has been shown to act as a PAM of the nAChR. To our knowledge, there is no direct evidence that it acts similarly in conjunction with the GABA\textsubscript{A} receptor and electrophysiology experiments on 1 would improve understanding of the structural requirements for potentiating GABA. Notably, this research would also help to explain conflicting data within the literature.
Lambadjieva and Georgiev reported that when the convulsant picrotoxin is injected into mice in combination with 1, the seizure threshold is increased thus suggesting a possible role for 1 as a PAM.\(^2\) However, 1 has also been shown to increase the concentration of the GABA\(_A\) PAM propofol\(^2\) necessary for anaesthesia \textit{in vivo}.\(^3\)

\textit{Scheme 4.6.1 Potential targets for SAR studies.}

Further mechanistic insight could be gained through structural variation (Scheme 4.6.1). For example, experiments with 3a-methoxypyrroloindoline 256 would delineate the importance of the hydroxyl substituent. We expect 256 to be readily available as, in one report analogous to our own work, Somei and coworkers showed that the combination of NCS and MeOH promotes cyclization of a C2-unsubstituted tryptamine derivative to directly afford the corresponding methoxypyrroloindoline.\(^8\) Other potential substrates include 2a-methylpyrroloindoline 259, which should be accessible from known \(N\)-Cbz-2-methyltryptamine (258),\(^3\) and pyrroloindolines bearing functionalized aryl substituents at C2a (261) that could be incorporated in the arylation reaction.
Finally, 241 was originally tested as a racemate but it is possible that only one enantiomer activates the receptor; in other words, 241 might be twice as potent as is apparent based on the original data. Enantiomerically enriched 241 should be accessible by separation of the racemate on a chiral column or by an enantioselective oxidative cyclization of tryptamine 245. For example, Miller, Movassaghi and coworkers have shown that peptide 264 can catalyze conversion of (1H)-2-phenyl-N-phthaloyltryptamine 262 to 3-hydroxyindolenine 263 in moderate ee (Scheme 4.6.2);13 application of this method to our system is expected to form enantioenriched 241 in one pot.

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

Although our efforts toward 3a-hydroxy-2a-phenylpyrroloindolines began in an effort to broaden the scope of our tandem conjugate addition/enantioselective protonation reaction methodology, through the collaboration of our lab with Professor Dennis Dougherty, Kristina Daeffler, and Christopher Marotta this project has evolved into a search for novel drugs for the treatment of neurological disorders and neurodegenerative diseases. We are excited to continue this collaboration and to further investigate the importance of and mechanism of 241 in its role as a positive allosteric modulator. Future work regarding 241 and possible identification of more effective derivatives of 241 could
ultimately lead to the development of a useful alternative scaffold to known drugs that target the GABA_A receptor.32

4.7 EXPERIMENTAL SECTION

4.7.1 Materials and Methods for Synthetic Procedures

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, acetonitrile, dimethylformamide, and toluene were dried by passing through activated alumina columns. Methanol was distilled over calcium hydride. 4Å molecular sieves and powdered 4Å molecular sieves were flame-dried under vacuum immediately prior to use. All other commercially obtained reagents were used as received unless specifically indicated. Pd_2(dba)_3•CHCl_3 was purchased from Strem and stored in a glovebox, acetyl chloride, N-(benzyloxy carbonyloxy)succinimide (266), and 1-methyl-2-phenylindole (137c) were obtained from Sigma-Aldrich, and 1 M SnCl_4 in DCM was purchased from Acros Organics. (R)-3,3′-dibromo-BINOL (102k),33 and N-Cbz-tryptamine (247)34 were prepared according to literature procedures. Reactions were monitored either by using an Agilent 1290 Series LCMS with an Eclipse Plus C18 column (RRHD 1.8 μm, 2.1 x 50 mm, 11,072 plates) or by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, ninhydrin, p-anisaldehyde, or KMnO_4 staining. Flash column chromatography was performed either as described by Still et al.35 using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged Luknova columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-
length cell at 589 nm. Microwave experiments were performed using a Biotage Initiator® microwave reactor. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal CHCl$_3$ ($^1$H, $\delta$ = 7.26, $^{13}$C, $\delta$ = 77.0), MeCN ($^1$H, $\delta$ = 1.94, $^{13}$C, $\delta$ = 118.26), or DMSO ($^1$H, $\delta$ = 2.50). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm$^{-1}$). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI) or mixed (MM) ionization mode. Analytic chiral SFC data was acquired with a Mettler SFC supercritical CO$_2$ analytical chromatography system utilizing Chiralcel AD-H, OD-H, AS-H, OJ-H, and OB-H columns (4.6 mm x 25 cm) with visualization at either 254 nm or 235 nm. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 or 30 x 250 mm) or an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm).

4.7.2 Materials and Methods for Electrophysiology Experiments

Acetylcholine chloride, glutamate, $\gamma$-aminobutyric acid (GABA), glycine, and 5-hydroxytryptamine were purchased from Sigma-Aldrich and used as received. mRNA was prepared as previously described using the Quikchange protocol for any necessary site-directed mutagenesis, and standard DNA linearization techniques, followed by in
vitro transcription using a T7 mMessage mMachine kit obtained from Ambion. The receptors were expressed in *Xenopus laevis* oocytes by injection of the mRNA of each of the desired subunits and incubation at 18 °C for 24 – 48 h in Ca²⁺-containing ND96 buffer (1.8 mM CaCl₂, 96 mM NaCl, 2 mM KCl, 1 mM MgCl₂, 5 mM HEPES, pH 7.5). For α7 nAChRs, an equal amount of hRic3 was also injected into the oocytes to promote expression.\(^\text{36}\)

Electrophysiology experiments on the oocytes were conducted using an OpusXpress-6000A system (Axon Instruments). A two-electrode voltage clamp method was used with a holding potential of −60 mV. Prior to data collection, the health of the oocytes was evaluated by measuring the potential across the cell membrane as well as the leak current. Agonists for each receptor were employed at their EC₅₀ concentrations using ND96 buffer for GABAₐR and α7 nAChRs and Ca²⁺-free ND96 buffers for all other receptors. EC₅₀ concentrations were calculated by applying the Hill equation to the data from measurement of the current produced at various concentrations of the agonists. The agonist concentrations used in the electrophysiology experiments on all pyrroloindolines tested are as follows: 1.2 μM acetylcholine for mouse muscle-type (α1)₂(β1-L9’S)δγ nAChR, 1 μM acetylcholine (ACh) for (α4)₂(β2)₃ nAChR, 0.5 μM ACh for (α4-L9’A)₂(β2)₃ nAChR, 0.05 μM ACh for (α4-L9’A)₂(β2)₃ nAChR, 100 μM ACh for α7 nAChR, 100 μM ACh for α7-T6’S nAChR, 13 μM ACh for α4β4 nAChR, 3 μM 5-hydroxytryptamine for 5HT₃A R, 14 μM glutamate for GluR₂₂, 110 μM glycine for GlyR, 11 μM GABA for (α1)₂(β2)₂GABAAR, and 3 μM GABA for (α1)₂(β2)₂ GABAₐR.

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

### 4.7.3 Synthetic Procedures

**Preparation of bromoindolenine 219.**

A solution of (S)-N\textsubscript{α}-acetyl-2-phenyltryptophan methyl ester 138c (101 mg, 0.30 mmol, 1.00 equiv) in 8.4 mL DCM was cooled to −50 °C in an MeCN/dry ice bath. NBS (53.4 mg, 0.30 mmol, 1.00 equiv) was then added, followed by 900 µL TFA. The reaction was stirred in the dark at −50 °C for 3 hours, then poured onto ice, quenched with
1.5 mL aqueous ammonia and extracted with DCM (3 x 25 mL). The combined organics were washed (40 mL H₂O, then 40 mL brine), dried (Na₂SO₄), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (30:70 to 70:30 EtOAc:hexanes) to yield 98 mg (79% yield) of bromoindolenine 219 as a bright yellow foam consisting of a 1:1 mixture of diastereomers. The enantiomeric excesses of the two diastereomers were determined to be 92% and 90% by chiral SFC analysis (AS-H, 2.5 mL/min, 20% IPA in CO₂, λ = 254 nm): tᵣ(major) = 3.8, tᵣ(minor) = 4.1 min; tᵣ(major) = 4.6, tᵣ(minor) = 6.0 min. Spectral data and optical rotation are reported for the mixture of indolenine diastereomers. ¹H NMR (500 MHz, CDCl₃) δ 8.42 – 8.32 (m, 4H), 7.70 – 7.64 (m, 2H), 7.57 – 7.49 (m, 8H), 7.47 – 7.40 (m, 2H), 7.39 – 7.30 (m, 2H), 5.37 (d, J = 7.4 Hz, 1H), 5.05 (d, J = 8.5 Hz, 1H), 4.33 (dt, J = 7.5, 5.5 Hz, 1H), 3.95 (td, J = 8.9, 4.0 Hz, 1H), 3.56 (dd, J = 14.8, 5.2 Hz, 1H), 3.47 – 3.41 (m, 4H), 3.38 – 3.32 (m, 4H), 3.23 (dd, J = 14.6, 9.3 Hz, 1H), 1.45 (s, 3H), 1.27 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 175.6, 174.8, 170.7, 170.0, 169.4, 169.2, 151.82, 151.76, 139.8, 139.6, 131.6, 131.4, 131.3, 130.5, 130.4, 128.81, 128.80, 128.7, 127.2, 126.6, 123.2, 122.5, 121.9, 121.7, 59.16, 59.14, 52.5, 52.3, 50.3, 49.8, 41.6, 41.4, 22.3, 22.0; FTIR (NaCl/thin film): 3271, 2951, 2924, 1747, 1661, 1525, 1444, 1372, 1264, 1216 cm⁻¹; [α]D²5 = +17.1° (c = 0.50, CHCl₃). HRMS (MM) calc’d for C₂₀H₂₀BrN₂O₃ [M+H]+ 415.0652, found 415.0652.
Preparation of (R/S)-5-bromotryptophan methyl ester 224.

A flame-dried flask was charged with (R/S)-N_a-acetyl-1-methyl-2-phenyltryptophan methyl ester (138e, 28.0 mg, 80 µmol, 1.00 equiv), 2.2 mL DCM, NBS (14.2 mg, 80 µmol, 1.00 equiv) and 240 µL TFA in that order. The yellow reaction solution was stirred at room temperature for 4.5 hours, then poured onto ice, quenched with 1.0 mL aqueous ammonia and extracted with DCM (3 x 10 mL). The combined organics were washed (15 mL H_2O, then 15 mL brine), dried (Na_2SO_4), filtered, and concentrated. The crude oil was subjected to silica gel column chromatography (50:50 to 60:40 EtOAc:hexanes), then to normal phase preparative HPLC (30:70 to 95:5 EtOAc:hexanes) using an Agilent 1200 Series HPLC with an Agilent Zorbax RX-Sil 5 µM column (9.4 x 250 mm) to yield 8.2 mg (24% yield) of (R/S)-5-bromotryptophan methyl ester 224 as a light yellow oil (structure assigned by 2D NMR analysis). ^1^H NMR (500 MHz, CDCl_3) δ 7.68 (d, J = 1.8 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.49 – 7.44 (m, 1H), 7.41 – 7.36 (m, 2H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 5.67 (br d, J = 8.1 Hz, 1H), 4.74 (ddd, J = 8.1, 5.3, 5.3 Hz, 1H), 3.54 (s, 3H), 3.43 (s, 3H), 3.34 (dd, J = 14.8, 5.4 Hz, 1H), 3.27 (dd, J = 14.8, 5.3 Hz, 1H), 1.73 (s, 3H). ^1^C NMR (125 MHz, CDCl_3) δ 172.1, 169.5, 140.4, 135.6, 131.2, 130.6, 129.6, 128.9, 128.7, 124.8, 121.4, 112.9, 111.1, 106.5, 52.6, 52.2, 31.0, 26.6, 23.0.; FTIR (NaCl/thin film): 3291, 2950, 2925, 1743, 1653, 1540, 1469, 1437, 1369, 1239, 1211 cm^-1; HRMS (MM) calc’d for C_{21}H_{22}BrN_2O_3 [M+H]^+ 429.0808 found 429.0797.
Preparation of 3-phenyloxindole 231.

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

**Major diastereomer:** yellow oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.43-7.38 (m, 3H), 7.34 (ddd, \(J = 7.7, 7.7, 1.2\) Hz, 1H), 7.31-7.27 (m, 2H), 7.26-7.21 (m, 1H), 7.16 (ddd, \(J = 7.6, 7.6, 1.0\) Hz, 1H), 6.90 (br d, \(J = 7.8\) Hz, 1H), 5.81 (br d, \(J = 8.4\) Hz, 1H), 4.66 (ddd, \(J = 8.6, 8.6, 4.7\) Hz, 1H), 3.60 (s, 3H), 3.23 (s, 3H), 2.91 (dd, \(J = 14.5, 4.7\) Hz, 1H), 2.61 (dd, \(J = 14.5, 8.9\) Hz, 1H), 1.58 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 177.6, 172.1, 169.3, 143.7, 139.5, 130.8, 128.7, 127.6, 126.6, 125.2, 122.7, 108.8, 54.7, 52.4, 49.9, 38.9, 26.6,
22.6.; FTIR (NaCl/thin film): 3308, 3057, 2952, 2931, 1746, 1709, 1659, 1611, 1494, 1471, 1373 cm⁻¹; HRMS (MM) calc’d for C_{21}H_{23}N_{2}O_{4} [M+H]^+ 367.1652, found 367.1642.

Minor diastereomer: yellow oil. ^1H NMR (500 MHz, CDCl₃) δ 7.39 (ddd, J = 7.7, 7.7, 1.3 Hz, 1H), 7.37-7.26 (m, 5H), 7.26-7.22 (m, 1H), 7.21 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.92 (ddd, J = 7.9, 1.1, 0.6 Hz, 1H), 5.77 (br d, J = 8.8 Hz, 1H), 4.26 (ddd, J = 11.0, 8.8, 3.1 Hz, 1H), 3.64 (s, 3H), 3.17 (s, 3H), 2.87 (dd, J = 14.4, 11.1 Hz, 1H), 2.75 (dd, J = 14.3, 3.1 Hz, 1H), 1.88 (s, 3H); ^13C NMR (125 MHz, CDCl₃) δ 178.4, 172.2, 169.4, 143.9, 139.8, 129.4, 129.2, 128.7, 127.7, 126.6, 125.0, 123.2, 109.0, 54.7, 52.5, 49.7, 39.0, 26.5, 22.9.; FTIR (NaCl/thin film): 3326, 3057, 2954, 2929, 1744, 1710, 1683, 1611, 1495, 1472, 1373 cm⁻¹; HRMS (MM) calc’d for C_{21}H_{23}N_{2}O_{4} [M+H]^+ 367.1652, found 367.1638.

Preparation of 3a-hydroxypyrroloindoline 228.

![Diagram](image)

A 15 mL flask containing (S)-Nₐ-acetyl-1-methyl-2-phenyltryptophan methyl ester 138e (52.5 mg, 0.150 mmol, 1.00 equiv) was flushed with argon and then charged with 3.3 mL MeCN. 1.3 M TFA in MeCN (125 µL, 0.150 mmol, 1.00 equiv) was added, followed by 0.2 M NCS in MeCN (0.75 mL, 0.150 mmol, 1.00 equiv). The flask was then sealed under argon and the solution was stirred in the dark at room temperature. After 3 hours, the reaction was quenched with 1.5 mL aqueous ammonia, poured onto
ice, and extracted with DCM (3 x 15 mL). The combined organics were washed (20 mL H₂O, then 20 mL brine), dried (Na₂SO₄), filtered, and concentrated to give the crude chloropyrroloindoline (detected by HRMS (MM) calc’d for [M+H]⁺ 385.1313, found 385.1320). The crude residue was redissolved in 2 mL MeCN then 1.2 mL H₂O and 2.5 mL SiO₂ were added. The mixture was vigorously stirred open to air at room temperature for 30 minutes, then filtered through a 1.5 mL silica plug with 50 mL EtOAc, dried (Na₂SO₄), filtered and concentrated. The crude oil contained a mixture of 3α-hydroxypyrrroloindolines, formed in 6:1 dr and favoring the endo diastereomer (determined by ¹H NMR analysis). The crude was subjected to silica gel column chromatography (0:100 to 10:90 EtOAc:CHCl₃) to yield 30.8 mg (product contained 18 wt % CHCl₃, 46% corrected yield) of the endo diastereomer as a yellow oil. The exo diastereomer, obtained post chromatography in a mixture with (S)-Nα-acetyl-1-methyl-2-phenyltryptophan methyl ester 138e, was subjected to reverse phase preparative HPLC (30:70 to 90:10 MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 µM column (9.4 x 250 mm) to yield 3.5 mg (6% yield) of the exo diastereomer as a yellow oil.

Endo diastereomer:

The enantiomeric excess was determined to be 84% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO₂, λ = 254 nm): tᵣ(major) = 7.4, tᵣ(minor) = 4.7 min. The relative stereochemistry was assigned by 2D NMR analysis. ¹H NMR (500 MHz, CD₃CN; compound exists as a 15:1 mixture of rotamers, the major rotamer is reported) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.26 (m, 3H), 7.20 (ddd, J = 7.9, 7.5, 1.3 Hz, 1H), 7.12 (ddd, J = 7.2, 1.3, 0.5 Hz, 1H), 6.66 (ddd, J = 7.3, 7.3, 1.0 Hz,
1H), 6.51 (d, J = 7.9 Hz, 1H), 4.79 (d, J = 8.8 Hz, 1H), 3.19 (s, 3H), 2.97 (s, 3H), 2.90 (br s, 1H), 2.82 (d, J = 12.7 Hz, 1H), 2.59 (ddd, J = 12.7, 8.8, 1.1 Hz, 1H), 1.95 (s, 3H); \(^{13}\)C NMR (125 MHz, CD\(_3\)CN; compound exists as a 15:1 mixture of rotamers, the major rotamer is reported) δ 172.0, 171.3, 153.1, 138.0, 131.6, 128.9, 128.6, 128.3, 125.2, 118.0, 107.1, 95.3, 88.3, 61.3, 52.7, 39.0, 32.7, 23.6; FTIR (NaCl/thin film): 3292, 3010, 2948, 1735, 1653, 1648, 1610, 1491, 1448, 1388, 1313, 1220 cm\(^{-1}\); [\(\alpha\)]\(_D\)\(^{25}\) = +264.0º (c = 1.35, CHCl\(_3\)). HRMS (MM) calc’d for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_4\) [M+H]\(^+\) 367.1652, found 367.1650.

Exo diastereomer:

The enantiomeric excess was determined to be 86% by chiral SFC analysis (OD-H, 2.5 mL/min, 20% IPA in CO\(_2\), \(\lambda = 254\) nm): \(t_R\)(major) = 6.2, \(t_R\)(minor) = 4.0 min. The relative stereochemistry was assigned by 2D NMR analysis. \(^1\)H NMR (500 MHz, CD\(_3\)CN; compound exists as a 1.5:1 mixture of rotamers, the major rotamer is denoted by *), the minor rotamer by §) δ 7.60 – 7.22 (m, 6H*, 7H§), 7.17 (ddd, J = 7.3, 0.6, 0.6 Hz, 1H*), 6.79 (dd, J = 7.6, 7.6 Hz, 1H§), 6.70 (dd, J = 7.5, 7.5 Hz, 1H*), 6.65 (d, J = 7.9 Hz, 1H§), 6.54 (d, J = 7.9 Hz, 1H*), 4.49 (dd, J = 8.0, 6.7 Hz, 1H*), 4.07 (dd, J = 10.0, 6.9 Hz, 1H§), 3.81 (s, 3H*), 3.71 (s, 3H§), 3.34 (s, 1H*), 3.01 (s, 1H*), 2.965 (s, 3H*), 2.960 (s, 3H§), 2.71 (dd, J = 13.0, 8.1 Hz, 1H*), 2.68 (dd, J = 12.6, 7.0 Hz, 1H§), 2.34 (dd, J = 12.9, 6.7 Hz, 1H*), 2.07 (dd, J = 12.7, 10.0 Hz, 1H§), 1.89 (s, 3H*), 1.80 (s, 3H§); \(^{13}\)C NMR (125 MHz, CD\(_3\)CN) δ 174.1, 173.6, 172.3, 171.8, 151.2, 151.1, 136.3, 136.2, 131.6, 131.3, 130.3, 129.60, 129.57, 129.4, 128.7, 128.6, 124.4, 123.9, 119.3, 118.2, 108.0, 106.4, 98.8, 96.1, 90.1, 88.5, 61.2, 60.3, 53.3, 52.6, 40.9, 37.2, 33.4, 32.4, 24.6, 23.8; FTIR (NaCl/thin film): 3305, 2924, 1747, 1646, 1610,
1491, 1447, 1381, 1311, 1207 cm\(^{-1}\); \([\alpha]_D^{25} = -138.2^o\) (c = 0.33, CHCl\(_3\)). HRMS (MM) calc’d for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_4\) [M+H]\(^+\) 367.1652, found 367.1655.

**Scale-Up Procedure for (S)-N\(_{\alpha}\)-acetyl-1-methyl-2-phenyltryptophan methyl ester (138e).**

\[
\begin{align*}
\text{To a 250 mL flame-dried flask under nitrogen containing freshly activated powdered} \\
4\AA \text{ molecular sieves (3.50 g, 200 wt % relative to 137c) was added 1-methyl-2-phenylindole (137c, 1.75 g, 8.45 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (91a, 1.45 g, 10.1 mmol, 1.20 equiv), and (R)-3,3'-dibromo-BINOL (102k, 750 mg, 1.69 mmol, 0.20 equiv). The flask was charged with 65 mL DCM and SnCl\(_4\) (1 M in DCM, 8.45 mL, 8.45 mmol, 1.00 equiv) was added. The orange reaction mixture was stirred at room temperature for 2 hours, then diluted with 15 mL MeCN, filtered, and quenched by addition of 50 mL 1 M HCl. The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with a mixture of 100 mL saturated aqueous NaHCO\(_3\) and 300 mL brine. The aqueous layer was extracted with EtOAc (4 x 100 mL) and the combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 65:35 EtOAc:hexanes) to yield 1.94 g (66% yield) of (S)-N\(_{\alpha}\)-acetyl-1-methyl-2-phenyltryptophan methyl ester (138e) as a white foam. The enantiomeric excess was determined to be 84% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO\(_2\), \(\lambda = \))
\end{align*}
\]
254 nm): $t_R$(major) = 4.7 min, $t_R$(minor) = 3.9 min. Spectral data are in agreement with prior characterization.

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

![Chemical diagram]

A solution of (S)-$N_a$-acetyl-1-methyl-2-phenyltryptophan methyl ester (138e, 1.93 g, 5.50 mmol, 1.00 equiv) in 11 mL DMF was cooled to 0 ºC in an ice bath. NaH (60% dispersion in oil, 385 mg, 9.64 mmol, 1.75 equiv) was then added, followed by MeI (0.75 mL, 12.1 mmol, 2.20 equiv). The yellow reaction mixture was stirred at 0 ºC for 1.5 hours, then quenched with 5 mL aqueous ammonia and 5 drops Et3N. The mixture was allowed to warm to room temperature and stirred for 12 hours, then diluted with 40 mL H2O and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (50 mL H2O, then 2 x 50 mL brine), dried (Na2SO4), filtered, and concentrated. The crude oil was subjected to silica gel column chromatography (0:100 to 80:0 EtOAc:hexanes) to yield 1.51 g (75% yield) of (S)-$N_a$-acetyl-$N_a$-1-dimethyl-2-phenyltryptophan methyl ester 238 as a light yellow solid. The enantiomeric excess was determined to be 46% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO2, $\lambda$ = 254 nm): $t_R$(major) = 11.0 min, $t_R$(minor) = 12.5 min. 1H NMR (300 MHz, CDCl3, compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) $\delta$ 7.66 (d, $J$ = 8.0 Hz, 1H*), 7.62 (d, $J$ = 7.7 Hz, 1H§), 7.55-7.10 (m, 8H*, 8H§), 4.86 (dd, $J$ = 10.0, 4.7 Hz, 1H*), 4.62 (dd, $J$ = 10.2, 4.3 Hz, 1H§), 3.69 (s, 3H§), 3.64 (s, 3H*), 3.57 (s, 3H§), 3.56 (s, 3H*), 3.51 (dd, $J$ = 11.4, 4.6 Hz, 1H§), 3.46 (dd, $J$ = 11.5, 4.4 Hz, 1H*), 3.28 (dd,
$J = 14.8, 10.1 \text{ Hz, } 1H^a), 3.16 (\text{dd, } J = 15.0, 10.1 \text{ Hz, } 1H^b), 2.51 (\text{s, } 3H^a), 2.27 (\text{s, } 3H^b), 1.80 (\text{s, } 3H^a), 1.44 (\text{s, } 3H^b);$ $^{13}\text{C NMR (125 MHz, CDCl}_3; \text{ compound exists as a 1.2:1 mixture of rotamers}) \delta 171.5, 171.0, 170.9, 170.7, 139.7, 138.7, 137.10, 137.05, 131.8, 131.2, 130.6, 130.5, 128.7, 128.6, 128.4, 128.2, 127.6, 126.9, 122.1, 121.8, 119.8, 119.5, 118.7, 117.9, 109.8, 109.4, 108.6, 107.1, 60.9, 59.0, 52.4, 52.0, 34.5, 30.80, 30.77, 28.5, 24.3, 23.7, 21.7, 20.9; \text{ FTIR (NaCl/thin film): 3052, 2949, 2242, 1740, 1735, 1653, 1648, 1469, 1442, 1432, 1400, 1364, 1329, 1268, 1214 cm}^{-1}; [\alpha]_{D}^{25} = -62.0^\circ (c = 0.40, \text{ CHCl}_3)$. HRMS (MM) calc’d for C$_{22}$H$_{25}$N$_2$O$_3$ [M+H]$^+$365.1860, found 365.1869.

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

A flame-dried 100 mL flask charged with 20 mL MeOH was cooled to 0 °C in an ice bath. AcCl (6.5 mL, 78.5 mmol, 32.0 equiv) was added dropwise and the reaction was allowed to warm to room temperature. (S)-N$_a$-Acetyl-N$_a$,1-dimethyl-2-phenyltryptophan methyl ester (238, 1.04 g, 2.86 mmol, 1.00 equiv) was added neat and the yellow reaction solution was then heated at 60 °C. After stirring at 60 °C for 75.5 hours, the reaction was concentrated, dissolved in 50 mL DCM, and washed with saturated aqueous NaHCO$_3$ (3 x 20 mL). The combined aqueous layers were extracted with DCM (4 x 15 mL) and the combined organic layers were then dried (Na$_2$SO$_4$), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (0:100 to 100:0 EtOAc:DCM) to yield 259 mg (28% yield) of (S)-N$_a$,1-dimethyl-2-phenyltryptophan methyl ester (239) as a yellow oil and 587 mg (contains 33 wt % DCM, 38% corrected yield) of 238 as a
yellow solid. The enantiomeric excess of 239 was determined to be 45% by chiral SFC analysis (OB-H, 2.5 mL/min, 8% IPA in CO₂, λ = 254 nm): \( t_R(\text{major}) = 5.7 \text{ min}, \)
\( t_R(\text{minor}) = 7.0 \text{ min} \) and the enantiomeric excess of recovered starting material 238 was determined to be 45% by chiral SFC analysis (OJ-H, 6% IPA in CO₂, λ = 254 nm):
\( t_R(\text{major}) = 11.1 \text{ min}, t_R(\text{minor}) = 12.6 \text{ min} \).

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta 7.68 (\text{ddd, } J = 7.8, 1.2, 0.8 \text{ Hz, H}), 7.54 – 7.37 (\text{m, 5H}), 7.33 (\text{ddd, } J = 8.3, 1.0, 1.0 \text{ Hz, 1H}), 7.26 (\text{m, 1H}), 7.16 (\text{ddd, } J = 8.2, 6.9, 1.2 \text{ Hz, 1H}), 3.56 (\text{s, 3H}), 3.50 (\text{s, 3H}), 3.47 (\text{dd, } J = 7.7, 6.4 \text{ Hz, 1H}), 3.15 (\text{dd, } J = 14.3, 6.3 \text{ Hz, 1H}), 3.04 (\text{dd, } J = 14.3, 7.7 \text{ Hz, 1H}), 2.22 (\text{s, 3H}); \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3 \delta 175.0, 139.2, 137.0, 131.6, 130.7, 128.5, 128.2, 127.6, 121.8, 119.4, 119.0, 109.4, 108.1, 64.1, 51.6, 34.8, 30.8, 28.6.; \]

FTIR (NaCl/thin film): 3051, 2947, 2848, 2797, 1734, 1468, 1442, 1431, 1364, 1170 cm\(^{-1}\); \([\alpha]_D^{25} = +7.5º (c = 0.52, \text{CHCl}_3). \]

HRMS (MM) calc’d for C\(_{20}\)H\(_{22}\)N\(_2\)O\(_2\)[M+H\(^+\)]\(\cdot \) 323.1754, found 323.1760.

**Preparation of 3a-hydroxypyrroloindoline methyl ester 240.**

(S)-\(N_{\alpha,1}\)-Dimethyl-2-phenyltryptophan methyl ester (239, 220 mg, 0.684 mmol, 1.00 equiv) was dried by azeotrope with benzene in a 50 mL flask. The flask was flushed with argon then charged with 15.5 mL MeCN. 0.2 M NCS in MeCN (3.4 mL, 0.684 mmol, 1.00 equiv) was added and the reaction was stirred in the dark at room temperature. After 4 hours, the light orange reaction solution was quenched with 7 mL aqueous ammonia, poured onto ice, and extracted with 50 mL DCM. 10 mL brine was added to the aqueous layer, which was then extracted with DCM (3 x 35 mL). The combined organic layers
were washed (50 mL H₂O, then 50 mL brine), dried (Na₂SO₄), filtered, and concentrated. The residue was redissolved in 9.3 mL MeCN then 5.6 mL H₂O and 11.7 mL SiO₂ were added. The mixture was vigorously stirred open to air at room temperature for 30 minutes, then filtered through a 12 mL silica plug with 200 mL EtOAc, dried (Na₂SO₄), filtered and concentrated. The crude residue contained a mixture of 3a-hydroxypyrroloindolines, formed in 1.8:1 dr and favoring the exo diastereomer (determined by ¹H NMR analysis). The crude was subjected to reverse phase preparatory HPLC (0.05:30:70 to 0.05:95:5 TFA:MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 µM column (9.4 x 250 mm) to yield 61.6 mg (26% recovery, <90% clean) of endo-240 as a yellow-brown oil and 106 mg (46% recovery, <90% clean) of exo-240 as a yellow-brown oil.

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

A scintillation vial was charged with the exo-3a-hydroxyppyrrroloindoline methyl ester (240, 106 mg, 1.00 equiv), LiOH (189 mg, 7.87 mmol, >25.0 equiv), 2 mL THF, and 2 mL H₂O. The vial was then sealed and the reaction mixture was stirred at 22 °C for 17.5 hours, then acidified to pH 7 with 1 M HCl and concentrated. The crude residue was purified by reverse phase preparative HPLC (0.1:25:75 to 0.01:95:5 AcOH:MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 µM column (30 x 250 mm) to yield 23.5 mg (11% yield, ~95% clean) of exo-237 as a yellow solid. The enantiomeric excess of exo-237 was determined to be 41% by chiral SFC analysis (OJ-H,
The relative stereochemistry was assigned by 2D NMR analysis. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 7.6 – 7.1 (m, 7H), 6.63 (dd, $J = 7.3, 7.3$ Hz, 1H), 6.44 (d, $J = 7.8$ Hz, 1H), 2.99 (dd, $J = 11.3, 5.0$ Hz, 1H), 2.67 (s, 3H), 2.36 (dd, $J = 11.7, 5.0$ Hz, 1H), 2.25 (s, 3H), 2.09 (dd, $J = 11.4, 11.4$ Hz, 1H); $^{13}$C NMR (125 MHz, CD$_3$CN) δ 175.9, 175.5, 152.9, 138.7, 131.2, 130.9, 130.0, 129.0, 128.7, 124.7, 117.7, 105.4, 99.0, 89.1, 65.2, 44.8, 35.6, 34.2.; FTIR (NaCl/thin film): 3404, 3050, 2917, 2849, 1718, 1609, 1491, 1448, 1370, 1311, 1200, 1098 cm$^{-1}$; $[\alpha]_D^{25} = -38.8^\circ$ (c = 0.62, MeCN). HRMS (MM) calc’d for C$_{19}$H$_{21}$N$_2$O$_3$ [M+H]$^+$ 325.1547, found 325.1539.

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

A scintillation vial was charged with the endo-3a-hydroxypyrrroloindoline methyl ester (240, 61.6 mg, 1.00 equiv), LiOH (109 mg, 4.56 mmol, >25.0 equiv), 1.2 mL THF, and 1.2 mL H$_2$O. The vial was then sealed and the reaction mixture was stirred at 22 ºC for 17.5 hours, then acidified to pH 7 with 1 M HCl and concentrated. By crude NMR, a pyrroloindoline was observed, shifts of which did not correspond to exo-237. The crude residue was subjected to reverse phase preparative HPLC (0.1:25:75 to 0.01:95:5 AcOH:MeCN:H$_2$O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 µM column (30 x 250 mm), followed by trituration with MeCN to yield 2.3 mg (1% yield) of exo-237 as a light yellow solid. The enantiomeric excess of 237 was determined to be
43% by chiral SFC analysis (OJ-H, 2.5 mL/min, 20% IPA in CO₂, λ = 235 nm):  

\[ t_r(\text{major}) = 2.6 \text{ min}, \quad t_r(\text{minor}) = 3.3 \text{ min} \]

1H NMR spectral data was in agreement with prior characterization.

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

A solution of N-Cbz-tryptamine (247) (2.43 g, 8.26 mmol, 1.00 equiv) and 90 mL THF in a flame-dried 250 mL flask was cooled to 0 °C in an ice bath. NaH (60% dispersion in oil, 1.40 g, 35.1 mmol, 4.25 equiv) was then added, followed by MeI (2.5 mL, 40 mmol, 4.8 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours, then quenched with 40 mL saturated aqueous NH₄Cl and 3 drops Et₃N. After 16.5 hours of vigorous stirring, the mixture was diluted with 20 mL H₂O. The aqueous layer was extracted with 30 mL EtOAc and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude residue was subjected to silica gel column chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 2.43 g (91% yield) of N-Cbz-N,1-dimethyltryptamine (243) as a yellow oil. 1H NMR (500 MHz, CDCl₃, compound exists as a 1.4:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) \( \delta \) 7.65 (d, \( J = 7.9 \) Hz, 1H§), 7.45 (d, \( J = 7.9 \) Hz, 1H*), 7.42–7.26 (m, 6H*, 6H§), 7.25–7.18 (m, 1H*, 1H§), 7.11 (dd, \( J = 7.4, 7.4 \) Hz, 1H§), 7.02 (dd, \( J = 7.4, 7.4 \) Hz, 1H*), 6.89 (s, 1H§), 6.79 (s, 1H*), 5.17 (s, 2H§), 5.10 (s, 2H*), 3.73 (s, 3H§), 3.71 (s, 3H*), 3.59 (t, \( J = 7.9 \) Hz, 2H§), 3.54 (t, \( J = 7.7 \) Hz, 2H*), 3.01 (t, \( J = 7.9 \) Hz, 2H§), 2.96 (t, \( J = 7.8 \) Hz, 2H*), 2.95 (s, 3H*), 2.92 (s, 3H§).; 13C NMR (125
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MHz, CDCl$_3$; compound exists as a 1.4:1 mixture of rotamers) δ 156.3, 156.2, 136.9, 136.8, 128.4, 128.0, 127.90, 127.86, 127.8, 127.7, 126.7, 121.5, 118.83, 118.78, 118.7, 111.5, 111.4, 109.2, 67.1, 66.9, 50.2, 49.8, 35.0, 34.5, 24.1, 23.4.; FTIR (NaCl/thin film): 3056, 3030, 1703, 1699, 1484, 1475, 1403, 1211, 1192, 1134 cm$^{-1}$; HRMS (MM) calc’d for C$_{20}$H$_{23}$N$_2$O$_2$ [M+H]$^+$323.1754, found 323.1758.

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

N-Cbz-N,1-dimethyl-2-phenyltryptamine (244) was prepared according to a procedure adapted from Lavilla and coworkers.$^{26}$ Four oven-dried microwave vials were each charged with N-Cbz-N,1-dimethyltryptamine (243, 231 mg, 0.717 mmol, 1.00 equiv), 2-NO$_2$Bz (288 mg, 1.13 mmol, 1.57 equiv), Pd(OAc)$_2$ (6.25 µg, 37.4 µmol, 0.052 equiv), AgBF$_4$ (228 mg, 1.17 mmol, 1.63 equiv, weighed into small vials in a glovebox then removed from the glovebox and transferred quickly to the microwave vials), PhI (0.33 mL, 3.0 mmol, 4.1 equiv), and 4.5 mL DMF. The microwave vials were sealed under argon and the orange reaction mixtures were stirred at room temperature for 30 minutes, then heated in the microwave for 4 min at 150 °C. The four reaction mixtures were then combined and filtered through celite with 60 mL EtOAc, washed (3 x 40 mL saturated aqueous NH$_4$Cl, 3 x 40 mL saturated aqueous NaHCO$_3$, 3 x 40 mL brine), dried (Na$_2$SO$_4$), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (8:92 EtOAc:hexanes) to yield 921 mg (81% yield) of N-Cbz-N,1-dimethyl-2-phenyltryptamine (244) as a yellow solid. $^1$H NMR (500 MHz, CDCl$_3$,}
compound exists as a 1.7:1 mixture of rotamers, the major rotamer is designated by *,
minor rotamer designated by § δ 7.74 (d, J = 7.9 Hz, 1H§), 7.53-7.22 (m, 13H*, 12H§),
7.17 (dd, J = 7.5, 7.5 Hz, 1H§), 7.06 (dd, J = 7.6, 7.6 Hz, 1H*), 5.09 (s, 2H§), 4.98 (s,
2H*), 3.59 (s, 3H§), 3.57 (s, 3H*), 3.50 (t, J = 8.2 Hz, 2H§), 3.45 (t, J = 7.8 Hz, 2H*),
2.97 (t, J = 7.5 Hz, 2H§), 2.91 (t, J = 7.8 Hz, 2H*), 2.78 (s, 3H*), 2.76 (s, 3H§); 13C NMR
(125 MHz, CDCl₃; compound exists as a 1.7:1 mixture of rotamers) δ 156.1, 156.0,
138.6, 138.4, 137.1, 136.8, 131.8, 131.7, 130.4, 128.4, 128.14, 128.10, 128.0, 127.84,
127.81, 127.7, 127.5, 121.8, 119.42, 119.37, 119.0, 118.6, 109.7, 109.6, 109.4, 109.3,
67.0, 66.8, 50.5, 49.7, 34.8, 34.6, 30.81, 30.76, 23.5, 23.0; FTIR (NaCl/thin film): 3055,
3030, 2939, 1703, 1699, 1471, 1403, 1362, 1197, 1138 cm⁻¹; HRMS (MM) calc’d
for C₂₆H₂₇N₂O₂ [M+H]⁺ 399.2067, found 399.2087.

**Preparation of N,1-dimethyl-2-phenyltryptamine (245).**

\[
\begin{align*}
\text{N-Me} & \begin{array}{c}
\text{Ph} \\
\text{Cbz} \\
\text{Me}
\end{array} \\
\text{244} & \quad \text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \\
\text{Et}_3\text{SiH}, \text{Et}_3\text{N} \\
\text{DCM, 23 °C} & \quad (87\% \text{ yield}) \\
\text{N-Me} & \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \\
\text{245}
\end{align*}
\]

N,1-dimethyl-2-phenyltryptamine (245) was prepared by a Cbz deprotection
procedure adapted from Baran and coworkers.³⁷ A solution of N-Cbz-N,1-dimethyl-2-
phenyltryptamine (244, 574 mg, 1.44 mmol, 1.00 equiv) in 15 mL DCM was prepared in
a flame-dried flask under argon. Et₃SiH (9.2 mL, 57.7 mmol, 40.1 equiv) and Et₃N (0.4
mL, 2.87 mmol, 2.00 equiv) were then added, followed by Pd₂(dba)₃·CHCl₃ (298 mg,
0.288 mmol, 0.20 equiv). The dark red reaction solution was stirred for 15.5 hours and
the resultant dark brown mixture was filtered through celite with 50 mL EtOAc, washed
(2 x 40 mL saturated aqueous NaHCO₃, 2 x 40 mL brine), dried (Na₂SO₄), filtered, and
concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 8:92 MeOH:DCM) to yield 332 mg (87% yield) of \(N,1\)-dimethyl-2-phenyltryptamine (245) as a yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.68 (d, J = 7.8 \text{ Hz}, 1\text{H}), 7.53–7.38 (m, 5\text{H}), 7.35 (ddd, J = 8.2, 0.8, 0.8 \text{ Hz}, 1\text{H}), 7.26 (ddd, J = 8.1, 6.9, 1.0 \text{ Hz}, 1\text{H}), 7.16 (ddd, J = 8.1, 7.0, 1.0 \text{ Hz}, 1\text{H}), 3.59 (s, 3\text{H}), 2.92 (t, J = 7.2 \text{ Hz}, 2\text{H}), 2.82 (t, J = 7.1 \text{ Hz}, 2\text{H}), 2.34 (s, 3\text{H}), 1.37 (s, 1\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 138.7, 137.0, 131.1, 130.3, 128.8, 128.5, 127.0, 122.0, 119.8, 118.7, 109.46, 107.0, 49.3, 32.4, 30.8, 21.3;\)

FTIR (NaCl/thin film): 3051, 2934, 2840, 2789, 1468, 1442, 1430, 1364, 1333, 1236, 1131, 1013 cm\(^{-1}\); HRMS (MM) calc’d for C\(_{18}\)H\(_{21}\)N\(_2\) [M+H]\(^+\) 265.1699, found 265.1707.

**Preparation of 3a-hydroxy-1,1a-dimethyl-2a-phenylpyrroloindoline (241).**

A 15 mL flame-dried flask containing \(N,1\)-dimethyl-2-phenyltryptamine (245, 59.5 mg, 0.225 mmol, 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 1.3 mL MeCN. NCS (recrystallized from toluene, 30.2 mg, 0.225 mmol, 1.00 equiv) was then added as a solution in 2 mL MeCN dropwise and the reaction was stirred in the dark at room temperature for 4 hours, followed by addition of more NCS (15.4 mg, 0.115 mmol, 0.51 equiv) as a solution in 1 mL MeCN. After 1.5 hours, the dark green reaction solution was quenched with 5 mL aqueous Na\(_2\)S\(_2\)O\(_3\) (10 wt %) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 30 mL brine, dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. The crude oil was combined with 5 mL MeCN, 5 mL H\(_2\)O and 5 mL SiO\(_2\), then vigorously stirred open to air at room temperature for 30 minutes, filtered
with rinsing by EtOAc, dried (Na₂SO₄), filtered and concentrated. The crude was subjected to silica gel column chromatography (0:100 to 1:99 MeOH:DCM) and then to reverse phase preparative HPLC (0.01:18:82 to 0.01:80:20 TFA:MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm). The combined product-containing eluent was diluted with 20 mL saturated aqueous NaHCO₃ and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to yield 21.0 mg (33% yield) of 3a-hydroxy-1,1a-dimethyl-2a-phenylpyrroloindoline (241) as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 7.75 – 6.90 (m, 6H), 7.32 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 6.71 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 3.07 – 3.01 (m, 1H), 2.77 (s, 3H), 2.62 – 2.55 (m, 1H), 2.49 (s, 3H), 2.29 – 2.23 (m, 2H), 1.44 (br s, 1H).; ¹³C NMR (125 MHz, CDCl₃) δ 152.5, 137.1, 130.7, 129.9, 128.7, 128.0, 123.9, 116.9, 104.0, 98.3, 90.6, 51.4, 40.5, 36.6, 34.4.; FTIR (NaCl/thin film): 3540, 3435, 3051, 2931, 2791, 1608, 1492, 1473, 1445, 1370, 1308, 1106, 1028 cm⁻¹; HRMS (MM) calc’d for C₁₈H₂₁N₂O [M+H]+ 281.1648, found 281.1655.

**Preparation of 3a-amino-1,1a-dimethyl-2a-phenylpyrroloindoline (246).**

![Chemical structure of 245 and 246](attachment:image.png)

A 15 mL oven-dried flask containing N,1-dimethyl-2-phenyltryptamine (245, 39.6 mg, 0.15 mmol, 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 0.9 mL MeCN. NCS (recrystallized from toluene, 20.1 mg, 0.15 mmol, 1.00 equiv) was then added as a solution in 1.75 mL MeCN dropwise. After stirring in the dark at room
temperature for 3 hours, the off-white reaction solution was quenched with 2.8 mL aqueous ammonia and stirred vigorously open to air for 20 minutes. The mixture was then diluted with 10 mL H$_2$O and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 15 mL brine, dried (Na$_2$SO$_4$), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (0:100 to 2:98 MeOH:DCM) to yield 24.0 mg (57% yield) of 3a-amino-1,1a-dimethyl-2a-phenylpyrroloindoline (246) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.73 (br s, 1H), 7.54 – 7.27 (m, 3H), 7.24 (dd, $J$ = 7.2, 1.3 Hz, 1H), 7.19 (ddd, $J$ = 7.7, 7.7, 1.4 Hz, 1H), 6.83 (br s, 1H), 6.68 (ddd, $J$ = 7.4, 7.4, 1.0 Hz, 1H), 6.40 (d, $J$ = 7.8 Hz, 1H), 2.96 (dd, $J$ = 9.1, 7.0 Hz, 1H), 2.79 (s, 3H), 2.58 (ddd, $J$ = 12.0, 9.1, 5.1 Hz, 1H), 2.47 (s, 3H), 2.20 (dd, $J$ = 12.2, 5.1 Hz, 1H), 1.95 (ddd, $J$ = 12.1, 12.1, 7.1 Hz, 1H), 1.12 (br s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 152.5, 138.6, 132.0, 129.1, 128.9, 128.5, 127.8, 127.7, 123.9, 116.6, 103.6, 99.0, 74.8, 51.2, 42.0, 36.8, 34.6.; FTIR (NaCl/thin film): 3051, 2930, 2861, 2791, 2254, 1606, 1495, 1473, 1445, 1372, 1308, 1035 cm$^{-1}$; HRMS (MM) calc’d for C$_{18}$H$_{22}$N$_3$ [M+H]$^+$ 280.1808, found 280.1818.

**Preparation of N-Cbz-1-methyl-2-phenyltrptamine (248).**

![Diagram](https://via.placeholder.com/150)

N-Cbz-1-methyltrptamine (248) was prepared according to a procedure adapted from Qing and coworkers. $^{38}$ A solution of N-Cbz-tryptamine (247, 212 mg, 0.721 mmol, 1.00 equiv) in 3 mL wet acetone was charged with KOH (202 mg, 3.60, 4.99 equiv). After 10 min, MeI (49 µL, 0.787 mmol, 1.09 equiv) was added and the orange reaction
solution was stirred 1 hour at room temperature, followed by addition of more KOH (202 mg, 3.60 mmol, 4.99 equiv) and more MeI (49 µL, 0.787 mmol, 1.09 equiv). After stirring 3.5 hours at room temperature, the reaction was diluted with toluene, filtered, and concentrated. The crude was purified by silica gel column chromatography (5:95 to 20:80 EtOAc:hexanes) to yield 151 mg (68% yield) of \( N\text{-}\text{Cbz-1-methyltryptamine} \) (248). Spectral data are in agreement with the literature.39

**Preparation of \( N\text{-}\text{Cbz-1-methyl-2-phenyltryptamine} \) (249).**

\[
\begin{align*}
\text{N-Me} & \quad \text{248} \\
\text{NHCbz} & \quad \text{Pd(OAc)}_2, \ 2\text{-NO}_2\text{Bz} \\
\text{AgBF}_4 \text{, PhI, DMF, 23 to 150 °C (µwave)} & \rightarrow \text{N-Me} \quad \text{249} \\
\end{align*}
\]

\( N\text{-}\text{Cbz-1-methyl-2-phenyltryptamine} \) (249) was prepared according to a procedure adapted from Lavilla and coworkers.26 An oven-dried microwave vial was charged with \( N\text{-}\text{Cbz-1-methyltryptamine} \) (248, 134 mg, 0.435 mmol, 1.00 equiv), 2-NO\(_2\)Bz (147 mg, 0.653 mmol, 1.50 equiv), Pd(OAc)\(_2\) (3.3 µg, 20 µmol, 0.046 equiv), AgBF\(_4\) (131 mg, 0.672 mmol, 1.54 equiv, weighed into a small vial in a glovebox then removed from the glovebox and transferred quickly to the microwave vial), PhI (0.19 mL, 1.70 mmol, 3.91 equiv), and 4.3 mL DMF. The microwave vial was sealed under argon and the orange solution was stirred at room temperature for 30 minutes, then heated in the microwave for 4 min at 150 °C. The resultant brown reaction mixture was filtered through celite with EtOAc, washed (2 x 10 mL saturated aqueous NH\(_4\)Cl, 2 x 10 mL saturated aqueous NaHCO\(_3\), 2 x 10 mL brine), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (6:94 to 12:88 EtOAc:hexanes) to yield 142 mg (85% yield) of \( N\text{-}\text{Cbz-1-methyl-2-phenyltryptamine} \) (249) as an orange oil.
\(^1\)H NMR (500 MHz, CDCl\(_3\), compound exists as a 5.6:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by \(^\parallel\)) \(\delta\) 7.67 (d, \(J = 7.9\) Hz, 1H*), 7.54 (br s, 1H\(^\parallel\)), 7.50 – 7.41 (m, 3H*, 3H\(^\parallel\)), 7.40 – 7.26 (m, 9H*, 9H\(^\parallel\)), 7.17 (dd, \(J = 7.4\) Hz, 1H*), 7.12 (br s, 1H\(^\parallel\)), 5.04 (s, 2H*, 2H\(^\parallel\)), 4.73 (t, \(J = 6.8\) Hz, 1H*), 4.51 (br s, 1H\(^\parallel\)), 3.58 (s, 3H*, 3H\(^\parallel\)), 3.44 (td, \(J = 6.7, 6.7\) Hz, 2H*), 3.38 (br s, 1H\(^\parallel\)), 2.94 (t, \(J = 6.9\) Hz, 2H*), 2.90 (br s, 1H\(^\parallel\)). \(^{13}\)C NMR (125 MHz, CDCl\(_3\), compound exists as a 5.6:1 mixture of rotamers, only the major rotamer is reported) \(\delta\) 156.2, 138.8, 137.1, 131.7, 130.6, 128.5, 128.4, 128.2, 128.0, 121.9, 119.5, 118.9, 109.6, 109.4, 66.4, 41.7, 30.8, 25.1.; FTIR (NaCl/thin film): 3413, 3339, 3055, 3030, 2940, 1718, 1701, 1511, 1368, 1361, 1334, 1233, 1132 cm\(^{-1}\); HRMS (MM) calc’d for C\(_{25}\)H\(_{25}\)N\(_2\)O\(_2\) [M+H]\(^+\) 385.1911, found 385.1924.

**Preparation of 1-Cbz-3a-hydroxy-1a-methyl-2a-phenylpyrroloindoline (250).**

A 5 mL oven-dried flask containing N-Cbz-1-methyl-2-phenyltryptamine (249, 24.0 mg, 62.5 \(\mu\)mol, 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 0.5 mL MeCN. NCS (recrystallized from toluene, 8.4 mg, 0.225 mmol, 1.00 equiv) was then added as a solution in 1.25 mL MeCN dropwise. After stirring in the dark at room temperature for 6 hours, the light yellow reaction solution was quenched with 5 mL aqueous Na\(_2\)S\(_2\)O\(_3\) (10 wt %) and extracted with EtOAc (4 x 5 mL). The combined organic layers were washed with 15 mL brine, dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. The crude residue was combined with 1.5 mL MeCN, 1.5 mL H\(_2\)O and 1.5 mL SiO\(_2\), then
vigorously stirred open to air at room temperature for 30 minutes, filtered through a ~1.5 mL silica plug with EtOAc, and concentrated. The crude oil was purified by reverse phase preparative HPLC (60:40 to 90:10 MeCN:H₂O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm) to yield 13.7 mg (55% yield) of 3a-hydroxy-1-Cbz-1a-methyl-2a-phenylpyrroloindoline (250) as a light yellow-green oil. 

¹H NMR (500 MHz, CDCl₃, compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §; due to overlap in the NMR, the rotamer shifts were confirmed by HSQC 2D NMR) δ 7.48 – 7.09 (m, 11H*, 11H§), 6.83 – 6.75 (m, 2H*), 6.75 – 6.68 (m, 2H§), 6.58 (d, J = 7.8 Hz, 1H*), 6.50 (d, J = 7.9 Hz, 1H§), 5.12 (d, J = 12.4 Hz, 1H*), 5.07 – 5.01 (m, 1H*, 1H§), 4.85 (d, J = 12.3 Hz, 1H§), 4.05 (dd, J = 9.7 Hz, 1H§), 3.98 (dd, J = 9.5 Hz, 1H*), 3.30 (ddd, J = 11.1, 11.1, 6.2 Hz, 1H*), 3.21 (ddd, J = 11.5, 11.5, 5.9 Hz, 1H§), 3.04 (s, 3H*), 2.75 (s, 3H§), 2.50 – 2.39 (m, 1H*, 1H§), 2.31 – 2.19 (m, 1H*, 1H§), 1.50 (br s, 1H*, 1H§); ¹³C NMR (125 MHz, CDCl₃, compound exists as a 1.1:1 mixture of rotamers) δ 155.0, 154.5, 151.1, 151.0, 136.7, 135.6, 130.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 127.3, 123.62, 123.59, 118.1, 117.8, 106.53, 106.45, 89.6, 88.6, 67.0, 66.7, 46.3, 46.2, 34.1, 33.6, 31.9, 31.3.; FTIR (NaCl/thin film): 3049, 3056, 3032, 2945, 2891, 1695, 1684, 1675, 1609, 1491, 1401, 1348, 1186, 1117, 1004 cm⁻¹; HRMS (MM) calc’d for C₂₅H₂₅N₂O₃ [M+H]⁺ 401.1860, found 401.1877.
Preparation of 3a-hydroxy-1a-methyl-2a-phenylpyrroloindoline (251).

A solution of 3a-hydroxy-1-Cbz-1a-methyl-2a-phenylpyrroloindoline (250, 10.1 mg, 25.2 µmol, 1.00 equiv) in 1.0 mL THF was prepared in a flame-dried flask. Et₃SiH (0.16 mL, 1.0 mmol, 40 equiv) and Et₃N (7.0 µL, 50 µmol, 2.0 equiv) were then added, followed by Pd₂(dba)₃•CHCl₃ (5.0 mg, 4.8 µmol, 0.19 equiv). The dark red reaction solution was stirred for 18.5 hours at room temperature, then filtered through celite with THF, combined with an equal volume of saturated aqueous NaHCO₃, and stirred at room temperature for 5 hours. The aqueous layer was then extracted with EtOAc (3 x 15 mL) and combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 2:98 MeOH:DCM) to yield 6.1 mg (91% yield) of 3a-hydroxy-1a-methyl-2a-phenylpyrroloindoline (251) as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 7.50 – 7.27 (m, 5H), 7.25 (ddd, J = 7.2, 1.4, 0.5 Hz, 1H), 7.20 (ddd, J = 7.7, 7.7, 1.3 Hz, 1H), 6.68 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 6.42 (d, J = 7.9 Hz, 1H), 3.25 (ddd, J = 9.4, 5.1, 3.8 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.63 (s, 3H), 2.32 – 2.25 (m, 2H), 1.03 – 0.89 (br m, 1H), 0.65 – 0.51 (br m, 1H).;¹³C NMR (125 MHz, CDCl₃) δ 151.2, 138.2, 130.7, 130.1, 128.6, 128.2, 127.4, 123.9, 117.1, 104.3, 95.2, 89.6, 43.3, 41.9, 28.5.; FTIR (NaCl/thin film): 3340, 3051, 2931, 2874, 1609, 1495, 1446, 1375, 1307, 1121, 1062 cm⁻¹; HRMS (MM) calc’d for C₁₇H₁₉N₂O [M+H]⁺ 267.1492, found 267.1502.
Preparation of (S)-$N_{\alpha}$-Cbz-tryptophan (252).

(S)-$N_{\alpha}$-Cbz-tryptophan (252) was prepared by a procedure adapted from Lapatsanis and coworkers. A solution of (S)-tryptophan (265, 1.00 g, 4.90 mmol, 1.11 equiv) and $K_2CO_3$ (1.35 g, 9.77 mmol, 2.22 equiv) in 25 mL $H_2O$ was cooled to 0 °C in an ice bath. $N$-(Benzyloxycarbonyloxy)succinimide (266, 1.10 g, 4.41 mmol, 1.00 equiv) was then added as a solution in 25 mL wet DMF and the reaction was allowed to warm to room temperature. After stirring 20 minutes, the mixture was diluted with 300 mL $H_2O$ and washed with 20 mL Et$_2$O and EtOAc (2 x 35 mL). The aqueous layer was then cooled to 0 °C, acidified with 10 mL concentrated HCl, and extracted with EtOAc (5 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried (Na$_2$SO$_4$), filtered, and concentrated. DMF was still present and hence the residue was redissolved in 50 mL EtOAc, washed with brine (3 x 100 mL), dried (Na$_2$SO$_4$), filtered, and concentrated to give 1.136 g (76% yield) of (S)-$N_{\alpha}$-Cbz-tryptophan (252) as a white solid. $^1$H NMR spectral data were in agreement with the literature.

Preparation of (S)-$N_{\alpha}$-Cbz-$N_{\alpha,1}$-dimethyltryptophan (253).

A solution of (S)-$N_{\alpha}$-Cbz-tryptophan (252, 875 mg, 2.59 mmol, 1.00 equiv) in 5 mL THF was cooled to 0 °C in an ice bath. NaH (60% dispersion in oil, 516 mg, 12.9 mmol,
4.98 equiv) was then added, followed by MeI (0.96 mL, 15.4 mmol, 5.96 equiv). The yellow reaction mixture was allowed to warm to room temperature and stirred for 29 hours, then diluted with 10 mL H₂O and acidified with 1 mL concentrated HCl. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (3 x 30 mL), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (5:95 to 50:50 EtOAc:hexanes with 2–4% AcOH) to yield 600 mg (63% yield) of (S)-Nα-Cbz-Nα,1-dimethyltryptophan (253) as a yellow-brown foam. ¹H NMR (500 MHz, CDCl₃, compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 10.54 (br s, 1H*, 1H§), 7.60 (d, J = 7.9 Hz, 1H*), 7.55 (d, J = 7.9 Hz, 1H§), 7.38 – 7.21 (m, 6H*, 6H§), 7.16 – 7.07 (m, 2H*, 2H§), 6.85 (s, 1H*), 6.76 (s, 1H§), 5.17 (s, 2H*), 5.09 – 4.99 (m, 1H*, 3H§), 3.684 (s, 3H*), 3.677 (s, 3H§), 3.50 (d, J = 5.0 Hz, 1H§), 3.47 (d, J = 4.9 Hz, 1H*), 3.32 (dd, J = 15.5, 10.6 Hz, 1H*), 3.18 (dd, J = 15.3, 10.5 Hz, 1H§), 2.92 (s, 3H§), 2.83 (s, 3H*); ¹³C NMR (125 MHz, CDCl₃; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 176.5§, 176.4*, 157.0*, 156.3§, 136.93§, 136.88*, 136.6*, 136.2§, 128.5*, 128.4§, 128.01*, 127.96§, 127.9*, 127.7*, 127.3*, 127.1*, 121.8§, 121.7*, 119.1§, 119.0*, 118.5*, 118.4§, 109.5§, 109.4*, 109.32§, 109.27*, 67.6§, 67.5*, 59.9*, 59.4§, 32.67*, 32.66§, 32.0*, 31.7§, 25.0§, 24.4*; FTIR (NaCl/thin film): 3034, 2939, 1741, 1701, 1664, 1475, 1455, 1403, 1326, 1214, 1141 cm⁻¹; [α]D²⁵ = –40.6° (c = 0.68, CHCl₃). HRMS (MM) calc’d for C₂₁H₂₃N₂O₄ [M+H]+ 367.1652, found 367.1667.
Preparation of (S)-N$_a$-Cbz-N$_a$-1-dimethyl-2-phenyltryptophan (254).

(S)-N$_a$-Cbz-N$_a$-1-dimethyl-2-phenyltryptophan (254) was prepared according to a procedure adapted from Lavilla and coworkers. Two oven-dried microwave vials were each charged with 2-NO$_2$Bz (255 mg, 1.13 mmol, 1.50 equiv), Pd(OAc)$_2$ (6.25 µg, 37.4 µmol, 0.050 equiv), AgBF$_4$ (240 mg, 1.23 mmol, 1.63 equiv, weighed into small vials in a glovebox then removed from the glovebox and transferred quickly to the microwave vials), and PhI (0.34 mL, 3.04 mmol, 4.03 equiv). A solution of (S)-N$_a$-Cbz-N$_a$-1-dimethyltryptophan (253, 276 mg, 0.754 mmol, 1.00 equiv) in 4 mL DMF was then added to each vial. The microwave vials were sealed under argon and the reaction mixtures were stirred at room temperature for 30 minutes, then heated in the microwave for 4 min at 150 ºC. The two reaction mixtures were then combined and filtered through celite with 15 mL EtOAc, washed (2 x 20 mL saturated aqueous NH$_4$Cl, 2 x 20 mL brine), dried (Na$_2$SO$_4$), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (4:5:91 to 4:19:77 AcOH:EtOAc:hexanes) followed by washing with saturated aqueous NaHCO$_3$ to yield 366 mg (55% yield) of (S)-N$_a$-Cbz-N$_a$-1-dimethyl-2-phenyltryptophan (254) as a light yellow foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO$_2$, λ = 254 nm): $t_R$(major) = 4.6 min $t_R$(minor) = 7.2 min. $^1$H NMR (300 MHz, CDCl$_3$), compound exists as a 2.6:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §: δ 7.55 (d, $J = 7.9$ Hz, 1H*), 7.46 (d, $J = 7.9$ Hz, 1H§).
7.32 – 6.85 (m, 13H\*, 12H$^\dagger$), 6.57 (d, $J = 7.4$ Hz, 1H\$), 4.87 (br d, $J = 11.6$ Hz, 1H\$), 4.78 (d, $J = 12.6$ Hz, 1H\$), 4.64 (d, $J = 12.6$ Hz, 1H\$), 4.51 (d, $J = 12.6$ Hz, 1H\$), 4.35 (d, $J = 12.5$ Hz, 1H\$), 4.04 (br d, $J = 10.3$ Hz, 1H\$), 3.53 – 3.25 (m, 5H\*, 4H\$), 3.03 – 2.88 (m, 1H\$), 2.28 (s, 3H\*), 2.11 (s, 3H$^\dagger$).

$^{13}$C NMR (125 MHz, CDCl$_3$; compound exists as a 2.6:1 mixture of rotamers) δ 176.5, 176.3, 156.3, 155.6, 139.4, 139.0, 137.1, 136.5, 136.1, 131.6, 131.4, 130.6, 130.5, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 127.4, 127.1, 121.9, 121.8, 119.6, 118.6, 118.4, 109.6, 109.4, 108.2, 107.8, 67.18, 67.15, 61.1, 59.7, 33.0, 32.2, 30.8, 30.7, 24.4, 23.9.; FTIR (NaCl/thin film): 3056, 3031, 2936, 1699, 1695, 1683, 1605, 1469, 1401, 1363, 1328, 1137 cm$^{-1}$; $[^\alpha]$D$_{25} = -133.3^\circ$ (c = 0.84, CHCl$_3$).

HRMS (MM) calc’d for C$_{27}$H$_{27}$N$_2$O$_4$ [M+H]$^+$ 443.1965, found 443.1984.

**Preparation of (S)-N$_\alpha$-Cbz-N$_\alpha$,1-dimethyl-2-phenyltryptophan methyl ester (255).**

A solution of (S)-N$_\alpha$-Cbz-N$_\alpha$,1-dimethyl-2-phenyltryptophan (254, 104 mg, 0.235 mmol, 1.00 equiv) in 3 mL wet MeOH was charged with SOCl$_2$ (34 µL, 0.47 mmol, 2.0 equiv), then heated to 40 ºC. After stirring at 40 ºC for 5 hours, the reaction was diluted with 10 mL H$_2$O and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The crude residue was purified by silica gel column chromatography (15:85 EtOAc:hexanes) to yield 92.6 mg (86% yield) of N$_\alpha$-Cbz-N$_\alpha$,1-dimethyl-2-phenyltryptophan methyl ester (255) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$, compound exists as a 1.5:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by $^\S$) δ 7.67 (d, $J = 7.9$ Hz, 1H\$), 7.59 (d, $J =
7.9 Hz, 1H*), 7.49 – 7.19 (m, 11H*, 11H*), 7.17 – 7.10 (m, 1H*, 1H*), 6.97 – 6.90 (m, 1H*, 1H*), 5.02 (d, J = 12.5 Hz, 1H*), 4.89 (d, J = 12.6 Hz, 1H*), 4.82 – 4.71 (m, 2H*, 1H*), 4.62 (d, J = 12.3 Hz, 1H*), 3.65 (s, 3H*), 3.55 (s, 3H*), 3.531 (s, 3H*), 3.527 (s, 3H*), 3.51 – 3.45 (m, 1H*, 1H*), 3.27 (dd, J = 14.9, 10.3 Hz, 1H*), 3.21 (dd, J = 14.9, 10.8 Hz, 1H*), 2.49 (s, 3H*), 2.40 (s, 3H*); 13C NMR (125 MHz, CDCl$_3$; compound exists as a 1.5:1 mixture of rotamers) δ 171.6, 171.4, 156.0, 155.5, 139.4, 139.0, 137.0, 136.7, 136.2, 131.6, 131.5, 130.6, 130.5, 128.5, 128.4, 128.3, 128.17, 128.15, 128.1, 127.71, 127.6, 127.54, 127.46, 127.2, 121.8, 121.7, 119.49, 119.47, 118.6, 118.4, 109.5, 109.3, 108.3, 108.0, 66.92, 66.86, 60.5, 59.9, 52.03, 51.98, 32.4, 32.3, 30.70, 30.67, 24.5, 24.1.; FTIR (NaCl/thin film): 3033, 2946, 1743, 1740, 1734, 1704, 1700, 1696, 1468, 1399, 1363, 1314, 1270, 1214, 1139 cm$^{-1}$; [$\alpha$]$_D^{25} = -82.8^\circ$ (c = 0.22, CHCl$_3$). HRMS (MM) calc’d for C$_{28}$H$_{29}$N$_2$O$_4$ [M+H]$^+$ 457.2122, found 457.2128.

**Preparation of (S)-N$_\alpha$1-dimethyl-2-phenyltryptophan methyl ester (239).**

A solution of (S)-N$_\alpha$-Cbz-N$_\alpha$1-dimethyl-2-phenyltryptophan methyl ester (255, 91.0 mg, 0.199 mmol, 1.00 equiv) in 2 mL DCM was prepared in a flame-dried flask under nitrogen. Et$_3$SiH (1.3 mL, 8.1 mmol, 41 equiv) and Et$_3$N (55 µL, 0.40 mmol, 2.0 equiv) were then added, followed by Pd$_2$(dba)$_3$ (41.0 mg, 44.8 µmol, 0.225 equiv). The dark red reaction solution was stirred for 20 hours and the resultant dark brown mixture was filtered through celite with 15 mL EtOAc, washed (saturated aqueous NaHCO$_3$ (2 x 15 mL), brine (2 x 15 mL)), dried (Na$_2$SO$_4$), filtered, and concentrated. The crude residue
was purified by silica gel column chromatography (5:95 to 15:85 EtOAc:hexanes, then 4:14:82 NH₄OH:EtOAc:hexanes, then 4:5:91 NH₄OH:MeOH:DCM) to yield 26.4 mg (41% yield) of (S)-Nᵦ₁,1-dimethyl-2-phenyltryptophan methyl ester (239) as a colorless oil. [α]ᵣ²⁵ = +16.1° (c = 0.19, CHCl₃). ¹H NMR spectral data was in agreement with prior characterization.

**Preparation of 3a-hydroxypyrroloindoline methyl ester 240.**

A flame-dried flask containing (S)-Nᵦ₁,1-dimethyl-2-phenyltryptophan methyl ester (239, 24.1 mg, 0.748 mmol, 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 1 mL MeCN. NCS (recrystallized from toluene, 10.0 mg, 0.746 mmol, 1.00 equiv) was then added as a solution in 1 mL MeCN dropwise. After stirring in the dark at room temperature for 5.5 hours, more NCS (5.0 mg, 0.37 mmol, 0.50 equiv) was added as a solution in 0.5 mL MeCN. After stirring an additional 40 minutes, the reaction was quenched with 1 mL aqueous Na₂S₂O₃ (10 wt %) and the organic layer was washed with brine (2 x 3 mL), dried (Na₂SO₄), filtered, and concentrated. The residue was combined with 2 mL MeCN, 2 mL H₂O and 2 mL SiO₂, then stirred open to air at room temperature for 30 minutes. The mixture was then filtered with 20 mL EtOAc and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic layers were concentrated and purified by silica gel column chromatography (10:90 to 15:85 EtOAc:hexanes) to yield 10.3 mg (41% yield) of 3a-hydroxypyrroloindoline methyl ester 240 as a yellow oil.
(note: by then exchanging the column solvent for 2:98 MeOH:DCM, 6.0 mg (25%) of the starting material, (S)-\(N_a,1\)-dimethyl-2-phenyltryptophan methyl ester (239), could be recovered). 3a-hydroxypyrroloindoline methyl ester 240 was isolated as a 1.3:1 mixture of diastereomers favoring the \textit{exo} diastereomer as determined by \(^1\)H NMR. Optical rotation, HRMS, and spectral data are reported for the mixture of diastereomers. The relative stereochemistry and respective \(^1\)H and \(^{13}\)C NMR data for each diastereomer was determined by 2D NMR analysis and by comparison to the \(^1\)H NMR spectrum of re-isolated \textit{endo} diastereomer in the subsequent saponification step generating \textit{exo}-3a-hydroxypyrroloindoline carboxylic acid 237 (\textit{vide infra}). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.47 – 7.28 (m, 4H\text{exo}, 4H\text{endo}), 7.26 – 7.08 (m, 3H\text{exo}, 3H\text{endo}), 6.73 (ddd, \(J = 7.4, 7.4, 1.0\) Hz, 1H\text{exo}), 6.64 (ddd, \(J = 7.4, 7.4, 1.0\) Hz, 1H\text{endo}), 6.46 (dd, \(J = 8.3, 0.8\) Hz, 1H\text{exo}), 6.43 (d, \(J = 7.9\) Hz, 1H\text{endo}), 3.97 (s, 3H\text{exo}), 3.76 (s, 3H\text{exo}), 3.42 (d, \(J = 173.9\) Hz, 1H\text{exo}), 2.91 (s, 3H\text{endo}), 2.80 (s, 3H\text{exo}), 2.79 (s, 3H\text{endo}), 2.73 (dd, \(J = 12.4, 1.0\) Hz, 1H\text{endo}), 2.59 (dd, \(J = 11.9, 5.4\) Hz, 1H\text{exo}), 2.53 (dd, \(J = 12.3, 8.5\) Hz, 1H\text{endo}), 2.41 (s, 3H\text{exo}), 2.31 (dd, \(J = 11.6, 11.6\) Hz, 1H\text{exo}), 1.43 (s, 1H\text{endo}), 1.31 (s, 1H\text{endo}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.9\text{endo}, 173.3\text{exo}, 151.7\text{exo}, 151.5\text{endo}, 137.6\text{endo}, 136.9\text{exo}, 130.6\text{endo}, 130.3\text{exo}, 129.5\text{exo}, 128.8\text{endo,exo}, 128.5\text{endo}, 128.4\text{exo}, 128.2\text{endo}, 124.3\text{endo}, 124.0\text{exo}, 117.2\text{exo}, 116.6\text{endo}, 104.9\text{endo}, 104.6\text{exo}, 98.2\text{exo}, 95.9\text{endo}, 88.9\text{endo}, 88.0\text{exo}, 64.2\text{endo}, 63.4\text{exo}, 52.0\text{exo}, 51.2\text{endo}, 43.7\text{exo}, 41.3\text{endo}, 34.9\text{exo}, 34.8\text{endo}, 33.9\text{exo}, 31.6\text{endo}; FTIR (NaCl/thin film): 3467, 2920, 2850, 1750, 1609, 1494, 1447, 1375, 1311, 1202, 1101 cm\(^{-1}\); \([\alpha]\)\(_D\)\(^{25} = +33.2^\circ\) (\(c = 0.55\), CHCl\(_3\)). HRMS (MM) calc’d for C\(_{26}\)H\(_{23}\)N\(_2\)O\(_3\) [M+H]\(^+\) 339.1703, found 339.1715.
Preparation of \textit{exo}-hydroxypyrroloindoline carboxylic acid 237.

A solution of the 1.3:1 mixture of hydroxypyrroloindoline methyl ester 240 diastereomers (5.5 mg, 16 µmol, 1.0 equiv) in 0.5 mL THF was cooled to 0 °C in an ice bath. LiOH (3.9 mg, 0.16 mmol, 10 equiv) was then added as a solution in 0.5 mL nanopure H$_2$O. After stirring 2.5 hours at 0 °C, the reaction was quenched with 3 drops 3 M HCl, diluted with 3 mL H$_2$O, and extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with 10 mL brine, dried (Na$_2$SO$_4$), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (10:90 EtOAc:hexanes then 2:98 to 10:90 MeOH:DCM) to yield 1.4 mg (47% yield based on \textit{exo}-237) of \textit{exo}-hydroxypyrroloindoline carboxylic acid 237 as a yellow oil and 1.2 mg (50% recovery) of \textit{endo}-hydroxypyrroloindoline methyl ester 240. The enantiomeric excess of \textit{exo}-237 was determined to be 82% by chiral SFC analysis (OJ-H, 2.5 mL/min, 20% IPA in CO$_2$, $\lambda = 254$ nm): $t_R$(major) = 2.4 min $t_R$(minor) = 3.3 min. $[\alpha]_D^{25}$ (exo-237) = \(-99.0^\circ\) ($c = 0.14$, MeCN). $^1$H NMR spectral data for \textit{exo}-237 was in agreement with prior characterization and $^1$H NMR data was further acquired in CDCl$_3$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.66 – 7.26 (m, 7H), 6.77 (ddd, $J =$ 7.4, 7.4, 0.9 Hz, 1H), 6.50 (ddd, $J =$ 7.6, 0.8, 0.8 Hz, 1H), 3.44 (dd, $J =$ 10.9, 6.0 Hz, 1H), 2.80 (s, 3H), 2.70 (dd, $J =$12.4, 6.0 Hz, 1H), 2.48 (s, 3H), 2.34 (dd, $J =$ 12.4, 10.9 Hz, 1H), 1.51 (br s, 1H).
4.7.4  SFC Traces

**Bromoindolenine 219**: 1:1 mixture of diastereomers, racemic

---

**Bromoindolenine 219**: 1:1 mixture of diastereomers, enantioenriched, 92:90% ee
**Endo-228**: racemic

![Graph and table](image1.png)

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**Endo-228**: enantioenriched, 84% ee

![Graph and table](image2.png)

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**Exo-228**: racemic

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**Exo-228**: enantioenriched, 85% ee

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(S)-$N_\alpha$-acetyl-1-methyl-2-phenyltryptophan methyl ester 138e (scale-up procedure): 84% ee
(R/S)-N\textsubscript{\textalpha}-Acetyl-N\textsubscript{\textalpha},1-dimethyl-2-phenyltryptophan methyl ester (238): racemic

\[
\begin{array}{ccc}
\text{Peak RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
1 & 11.065 & 0.3994 & 1557.97253 & 65.02109 & 49.6667 \\
2 & 12.474 & 0.4871 & 1576.85562 & 54.01971 & 50.3333 \\
\end{array}
\]

(S)-N\textsubscript{\textalpha}-Acetyl-N\textsubscript{\textalpha},1-dimethyl-2-phenyltryptophan methyl ester (238): 46% ee

\[
\begin{array}{ccc}
\text{Peak RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
1 & 11.035 & 0.4059 & 1519.99699 & 61.60105 & 72.9614 \\
2 & 11.461 & 0.5123 & 566.13884 & 18.41711 & 27.1386 \\
\end{array}
\]
(R/S)-\(N_{\alpha},1\)-Dimethyl-2-phenyltryptophan methyl ester (239): racemic

![HPLC chromatogram of racemic 239](image1)

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(S)-\(N_{\alpha},1\)-Dimethyl-2-phenyltryptophan methyl ester (239): 45% ee

![HPLC chromatogram of (S) 239](image2)

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(S)-N$_{\alpha}$-Acetyl-N$_{\alpha}$,1-dimethyl-2-phenyltryptophan methyl ester (238, recovered starting material): 45% ee
**Exo-hydroxy-2a-phenylpyrroloindoline carboxylic acid 237**: racemic

![Graph of exo-237](image1)

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**Exo-hydroxy-2a-phenylpyrroloindoline carboxylic acid 237**: 41% ee (first generation synthesis)

![Graph of exo-237](image2)

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**Exo-hydroxypyrroloindoline carboxylic acid 237**: 43% ee (from *endo-240*)
(R/S)-Nα-Cbz-Nα,1-dimethyl-2-phenyltryptophan (254): racemic

(S)-Nα-Cbz-Nα,1-dimethyl-2-phenyltryptophan (254): 94% ee
Exo-hydroxypyrroloindoline carboxylic acid 237: 82% ee (2nd generation synthesis)
4.8 NOTES AND REFERENCES


(14) For an analogous rearrangement involving reverse-prenyl group migration, see ref. 10a.


APPENDIX 4

Spectra Relevant to Chapter 4:

Access to 2a-Phenylpyrroloindolines

by an Oxidative Cyclization Reaction
Sample Name: LMRVI-191
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVI-191
FidFile: PROTON02

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3

Data collected on: Jan 24 2012
Sample #27, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225199 MHz
DATA PROCESSING
Line broadening 0.7 Hz
FT size 65536
Total time 3 min 40 sec

(1:1 mixture of diastereomers)
Sample Name: LMRVI-191

Data Collected on: indy.caltech.edu-inova500

Archive directory: 
/home/lrepka/vnmrsys/data

Sample directory: LMRVI-191

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdc13

Data collected on: Aug 11 2011

Sample #23, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions

OBSERVE C13, 125.6553310 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 51 min

---

Appendix 4–Spectra Relevant to Chapter 4
Sample Name: LMRVII-31

Data Collected on: indy.caltech.edu-inova500

Archive directory: /home/lrepka/vnmrsys/data

Sample directory: LMRVII-31

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Feb 19 2012

Sample #27, Operator: lrepka

Relax. delay 0.100 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

3000 repetitions

OBSERVE C13, 125.6553277 MHz

DECOUPLE H1, 499.7250019 MHz

Power 39 dB continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 57 min
Appendix 4–Spectra Relevant to Chapter 4
Sample Name: LMRVII-35-majordr
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-35-majordr
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 20 2012
Sample #40, Operator: lrepka

Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225124 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 40 sec

231
major diasteromer

Appendix 4–Spectra Relevant to Chapter 4
Sample Name: LMRVII-35-majordr
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-35-majordr
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 20 2012

Sample #40, Operator: lrepka
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2900 repetitions
OBSERVE C13, 125.6553293 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 55 min

Appendix 4–Spectra Relevant to Chapter 4
Appendix 4–Spectra Relevant to Chapter 4

LMRVII-35-minordr

Sample Name:
LMRVII-35-minordr
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-35-minordr
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Feb 21 2012

Sample #28, Operator: lrepka

Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225127 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 7 min 20 sec
LMRVII-35-minordr

Sample Name: LMRVII-35-minordr
Data Collected on: indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-35-minordr
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 21 2012

Sample 28, Operator: lrepka

Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
24000 repetitions

OBSERVE C13, 125.6553287 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FFT size 65536
Total time 7 hr, 40 min

Appendix 4–Spectra Relevant to Chapter 4

231
minor diasteromer
LMRVII-117-endodiastereomer

Sample Name:
LMRVII-117-endodiastereomer
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-117-endodiastereomer
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jan 25 2012

Sample #28, Operator: lrepka
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7251679 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 min 40 sec

endo-228
(15:1 mixture of rotamers)
Sample Name: LMRVII-117-endodiastereomer
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-117-endodiastereomer
FidFile: CARBON02

Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jan 25 2012

Sample #20, Operator: lrepka
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1900 repetitions
OBSERVE C13, 125.6558756 MHz
DECOUPLE H1, 499.7276454 MHz
Power 39 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 36 min

endo-228
(15:1 mixture of rotamers)
Appendix 4–Spectra Relevant to Chapter 4

data_gHMBCAD_001
LMRVII-117-endo.png

endo-228
N
NMe
OH
Ph
CO₂Me
Sample Name: LMRVII-117-exodiastereomer
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-117-exodiastereomer
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jan 27 2012
Temp. 25.0 C / 298.1 K
Sample #20, Operator: lrepka
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7251677 MHz
DATA PROCESSING
Line broadening 0.8 Hz
FT size 65536
Total time 3 min 40 sec

exo-228 (1.5:1 mixture of rotamers)
LMRVII-117-exodiastereomer

ErrorLog:
- auto_20120127_01 loc:20 (night)
- PROTON_003 Acquisition error:
- CARBON_001 Acquisition error:

Sample Name: LMRVII-117-exodiastereomer
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-117-exodiastereomer
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: d6cn
Data collected on: Jan 27 2012

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

Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
24300 repetitions

OBSERVE C13, 125.6558731 MHz
DECOUPLE H1, 499.7276454 MHz
Power 39 dB
continuously on

WALTZ-16 modulated

DATA PROCESSING
- Line broadening 1.5 Hz
- FT size 65536
- Total time 7 hr, 46 min

exo–228
(1.5:1 mixture of rotamers)
LMRVII-205-f25-33

Sample Name:
LMRVII-205-f25-33
Data Collected on:
bg3.caltech.edu-mercury300
Archive directory:
/home/lrepka/vnmrsys/data
Sample directory:
LMRVII-205-f25-33
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 22 2012

Sample #40, Operator: lrepka

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
16 repetitions
OBSERVE H1, 300.0862588 MHz
DATA PROCESSING
Line broadening 0.6 Hz
FT size 32768
Total time 1 min 22 sec
Sample Name: LMRVII-219-f17-23
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-219-f17-23
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: ccdcl3
Data collected on: Jun 12 2012

Sample #17, Operator: lrepka
Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
7000 repetitions
OBSERVE C13, 125.6528772 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 14 min

238
1:2:1 mixture of rotomers
Sample Name: LMRVII-215-pdt-1f56-2f31
Data Collected on: hg3.caltech.edu-mercury300
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-215-pdt-1f56-2f31
Fid File: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 2 2012

Sample #41, Operator: lrepka

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
16 repetitions

OBSERVE H1, 300.0862587 MHz

DATA PROCESSING
Line broadening 0.8 Hz
FT size 32768
Total time 1 min 22 sec
Appendix 4–Spectra Relevant to Chapter 4

endo-240
first generation route
Appendix 4—Spectra Relevant to Chapter 4

LMRVII-225-phplc-f2

**Sample Name:**
LMRVII-225-phplc-f2

**Data Collected on:**
indy.caltech.edu-inova500

**Archive directory:**
/home/lrepka/vnmrsys/data

**Sample directory:**
LMRVII-225-phplc-f2

**FidFile:** PROTON01

**Pulse Sequence:** PROTON (s2pul)

**Solvent:** cd3cn

**Data collected on:** May 11 2012

**Sample #38, Operator:** lrepka

**Relax. delay 2.000 sec**
**Pulse 45.0 degrees**

**Acq. time 2.500 sec**

**Width 8000.0 Hz**

**16 repetitions**

**OBSERVE** H1, 499.7153976 MHz

**DATA PROCESSING**

**Line broadening 0.9 Hz**

**FT size 65536**

**Total time 1 min 12 sec**

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**exo-240**

**first generation route**

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Annexure 4–Spectra Relevant to Chapter 4

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Sample Name: LMRVII-241-dmso
Data Collected on: fid.caltech.edu-inova600
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-241-dmso_20120608_01
FidFile: data_s2pul_001

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Jun 8 2012

Operator: lrepka
Relax. delay 1.000 sec
Pulse 45.0 degrees
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6424676 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 0 min 22 sec

Appendix 4—Spectra Relevant to Chapter 4

exo-237 first generation route
Sample Name: LMRVII-241
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVII-241
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jun 5 2012

Sample #27, Operator: lrepka

Relax. delay 0.300 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6534172 MHz
DECOUPLE H1, 499.7178738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 1 hr, 52 min
Appendix 4–Spectra Relevant to Chapter 4

(data_gCOSY_001)

LMRVII-241-dmso

exo-

first generation route

Me

NMe

OH

Ph

CO2H

Appendix 4–Spectra Relevant to Chapter 4
Appendix 4–Spectra Relevant to Chapter 4
Appendix 4–Spectra Relevant to Chapter 4
Sample Name: LMRVIII-45
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-45
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 3 2012

Sample #42, Operator: lrepka
Relax. delay 25.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127434 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 min 40 sec

Appendix 4—Spectra Relevant to Chapter 4
Sample Name: LMRVIII-45-carbon  
Data Collected on: indy.caltech.edu-inova500  
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-45-carbon  
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)  
Solvent: cdcl3  
Data collected on: Sep 3 2012

Sample #43, Operator: lrepka

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1550 repetitions
OBSERVE C13, 125.6528749 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 52 min

14:1 mixture of rotamers
Appendix 4–Spectra Relevant to Chapter 4

AMAO-1-75

Sample Name: AMAO-1-75
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-75
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 12 2013

Sample #10, Operator: ama0

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.273 sec
Width 5006.3 Hz
16 repetitions
OBSERVE H1, 499.7049155 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 min 25 sec

1.7:1 mixture of rotamers

ppm
Appendix 4—Spectra Relevant to Chapter 4

244
1.7:1 mixture of rotamers

Me
N~Cbz

ppm

200 180 160 140 120 100 80 60 40 20

487
AMAO-1-82

Sample Name: AMAO-1-82
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-82
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 15 2013

Sample #15, Operator: amao

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.273 sec
Width 5006.3 Hz
16 repetitions
OBSERVE H1, 499.7049157 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 min 25 sec
Appendix 4–Spectra Relevant to Chapter 4

Sample Name: AMAO-1-15-F69-75B
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-15-F69-75B
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 23 2013

Sample #22, Operator: amao

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
1000 repetitions
OBSERVE C13, 125.6509058 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 34 min
Sample Name: LMRVIII-107-pHPLC
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-107-pHPLC
FidFile: PROTON02

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 2013

Sample #35, Operator: lrepka
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049150 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec
Sample Name: LMRVIII-107-pHPLC
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-107-pHPLC
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 2013

Sample #35, Operator: lrepka
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6509080 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 51 min
Appendix 4–Spectra Relevant to Chapter 4

Sample Name: LMRVIII-109-proton
Data Collected on:indy.caltech.edu-inova500
Archive directory:/home/lrepka/vnmrsys/data
Sample directory:LMRVIII-109-proton
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 26 2013

Sample #18, Operator: lrepka
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049166 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 8 sec

246

Appendix 4–Spectra Relevant to Chapter 4
Sample Name: LMRVIII-109-carbon
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-109-carbon
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 26 2013

Sample #8, Operator: lrepka
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6509070 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 51 min
Sample Name: AMAO-1-62

Data Collected on: indy.caltech.edu-inova500

Archive directory: /home/amao/vnmrsys/data

Sample directory: AMAO-1-62

FidFile: PROTON03

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Feb 26 2013

Sample #28, Operator: amao

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz

8 repetitions

OBSERVE H1, 499.7049160 MHz

DATA PROCESSING

Line broadening 0.4 Hz
FT size 65536
Total time 0 min 32 sec

Appendix 4–Spectra Relevant to Chapter 4
Sample Name: AMAO-1-62
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-62
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: Feb 26 2013
Sample #28, Operator: amao
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6509073 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 34 min

5.6:1 mixture of rotamers

249

Appendix 4—Spectra Relevant to Chapter 4
LMRVIII-111-pHPLC

Sample Name: LMRVIII-111-pHPLC
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-111-pHPLC
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2013

Sample #34, Operator: lrepka
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBserve H1, 499.7049152 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 min 8 sec

1:1:1 mixture of rotamers

Appendix 4–Spectra Relevant to Chapter 4

ppm
Sample Name: LMRVIII-111-pHPLC
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-111-pHPLC
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 30 2013

Sample #34, Operator: lrepka

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

OBSERVE C13, 125.6509057 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 8 min 45 sec

1:1 mixture of rotamers
Appendix 4–Spectra Relevant to Chapter 4

1:1 mixture of rotamers

N\text{Cbz} \quad \text{NMe} \quad \text{Ph} \quad \text{OH}
Appendix 4–Spectra Relevant to Chapter 4
Sample Name: LMRVIII-113
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/lrepka/vnmrsys/data
Sample directory: LMRVIII-113
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdc13
Data collected on: May 1 2013

Sample #34, Operator: lrepka

Relax. delay 0.200 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3600 repetitions
OBSERVE C13, 125.6509034 MHz
DECOUPLE H1, 499.7074131 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 1 hr, 15 min
Sample Name: AMAO-1-21-D
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-21-D
PfidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 31 2013

Sample #21, Operator: amao

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7995.2 Hz
16 repetitions

OBserve H1, 499.7049157 MHz

DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 20 sec

1.3:1 mixture of rotamers
Sample Name: AMAO-1-21E
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-21E
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 4 2013

Sample #5, Operator: amao

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
1000 repetitions
OBSERVE C13, 125.6509118 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 34 min
Appendix 4—Spectra Relevant to Chapter 4

NMe

2.6:1 mixture of rotamers

Me

Ph

CO₂H

N-Cbz

Appendix 4—Spectra Relevant to Chapter 4
Appendix 4–Spectra Relevant to Chapter 4

254
2.6:1 mixture of rotamers

N
Me

254
2.6:1 mixture of rotamers

N
Me
Appendix 4–Spectra Relevant to Chapter 4

Sample Name: AMAO-1-74
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-74
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 7 2013

Sample #30, Operator: amao
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSEERVE H1, 499.7049355 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 32 sec

1.5:1 mixture of rotamers

ppm
Appendix 4–Spectra Relevant to Chapter 4

Sample Name: AMAO-1-74

Data Collected on: indy.caltech.edu-inova500

Archive directory: /home/amao/vnmrsys/data

Sample directory: AMAO-1-74

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Mar 8 2013

Sample #30, Operator: amao

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.042 sec

Width 31446.5 Hz

1000 repetitions

OBSERVE C13, 125.6509173 MHz

DECOUPLE H1, 499.7074131 MHz

Power 39 dB continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 34 min

255 1.5:1 mixture of rotamers
Appendix 4–Spectra Relevant to Chapter 4

Sample Name: AMAO-1-103
Data Collected on: indy.caltech.edu-inova500
Archive directory: /home/amao/vnmrsys/data
Sample directory: AMAO-1-103
FidFile: PROTON02

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 1 2013
Sample #1, Operator: amao

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 0 min 32 sec
Appendix 4–Spectra Relevant to Chapter 4
Appendix 4–Spectra Relevant to Chapter 4
AAMAO-1-128-product

Sample Name:
AAMAO-1-128-product
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/amao/vnmrsys/data
Sample directory:
AAMAO-1-128-product
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 7 2013

Sample #1, Operator: amao

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7049228 MHz
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 2 min 40 sec

Appendix 4–Spectra Relevant to Chapter 4

exo-237
d second
generation route

Appendix 4–Spectra Relevant to Chapter 4

513
AMAO-1-128-F11-F14

Sample Name:
AMAO-1-128-F11-F14
Data Collected on:
hg3.caltech.edu-mercury300
Archive directory:
/home/amao/vnmrsys/data
Sample directory:
AMAO-1-128-F11-F14
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 7 2013
Temp. 25.0 C / 298.1 K
Sample #2, Operator: amao

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 4796.2 Hz
32 repetitions
OBSERVE H1, 300.0901672 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 2 min 27 sec

exo-240
second generation post
exo-240 saponification
ABOUT THE AUTHOR

Lindsay Michelle Repka was born on May 24th, 1986 in Baltimore, Maryland to Mary Anne Facciolo and Michael X. Repka. She attended the Friends School of Baltimore from the age of six up through the end of high school. Lindsay grew up playing tennis and music, most passionately pursuing the violin and thus participating in many high school musicals. Both of her parents practice medicine and her older brother, Michael C. Repka, received his MD from their alma mater, Jefferson Medical College, this past May.

Lindsay’s decision to pursue chemistry as a career resulted from an exceptional introduction at Friends in a course taught by Kenneth Drews. After graduating from high school in 2004, she moved to New York City to attend Barnard College as a chemistry major. In the fall of her second year, she took a course taught by Professor Christian Rojas, a talented teacher who aptly demonstrated both the power and elegance of organic chemistry. During the summer of 2007, Lindsay completed research in materials chemistry with Professor John Tovar at Johns Hopkins University and then pursued her senior thesis studies on amidoglycosylation reactions under the direction of Christian Rojas.

In 2008, two months after graduating from Barnard, Lindsay moved to Pasadena to join the group of Professor Sarah Reisman at the California Institute of Technology. She earned her Ph.D. in July 2013 for investigations in enantioselective synthesis of pyrroloindolines and tryptophan derivatives. In the fall of 2013, Lindsay began postdoctoral studies in the group of Professor Wilfred van der Donk at the University of Illinois at Urbana–Champaign.