CHAPTER 4

Access to 2a-Phenylpyrroloindolines by an Oxidative Cyclization:

Identification of a GABA$_A$ Receptor Positive Allosteric Modulator[†]

4.1 INTRODUCTION

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

carboxylic acid, was shown to be a channel inhibitor but further studies identified a compound lacking the carboxylic acid functionality that selectively activates the $GABA_A$ receptor as a positive allosteric modulator (PAM).
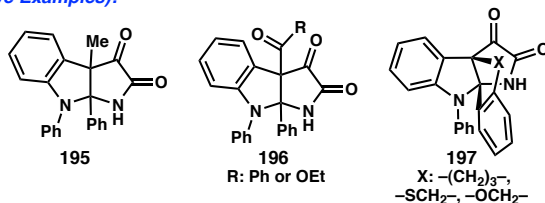
4.1.1 *Prior Efforts Toward 2a-Phenylpyrroloindolines*

Scheme 4.1.1. Access to 2a-phenylpyrroloindolines by a Fischer indolization rearrangement approach (Kollenz and coworkers, 1971–1994).
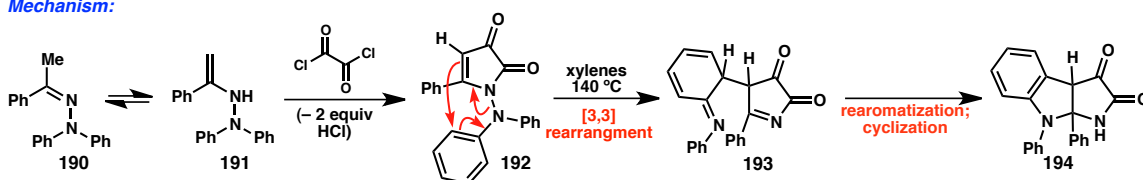
To date, there are very few reported syntheses of 2a-phenylpyrroloindolines. In the initial work completed by Kollenz and coworkers, 2a-phenylpyrroloindolines such as **194** as well as molecules bearing an azapropellane core (**197**) were prepared via a Fischer indolization rearrangement approach (Scheme 4.1.1).[1] Specifically, condensation of *N,N*-diphenylhydrazone **190** with oxalyl chloride with concomitant loss of 2 equivalents HCl affords pyrroledione **192**, which upon heating rearranges to **194**.[1c] Based on isotopic labeling studies,[2] this rearrangement is proposed to occur according to the standard mechanism for Fischer indole synthesis by a [3,3] rearrangement, rearomatization by proton transfer, and intramolecular 1,2-addition into the imine to give **194**. These pyrroloindolines were shown to be versatile intermediates capable of many

transformations including 1) selective reduction to afford α-hydroxyketone **199** or the ring-opened form **201** depending on the C3a-substitution pattern,[1e] 2) ring-opening at high temperature to give indole **198**,[1c] and 3) oxidative cleavage of the dione with NaOH and H_2O_2 to yield 1,2-diphenylindole (**200**, Scheme 4.1.2).[1c] Notably, formation of azapropellane **197** has been confirmed by X-ray crystallography (Figure 4.1.1).[1c]

Scheme 4.1.2. Derivatization of pyrroloindoline diones (Kollenz and coworkers).
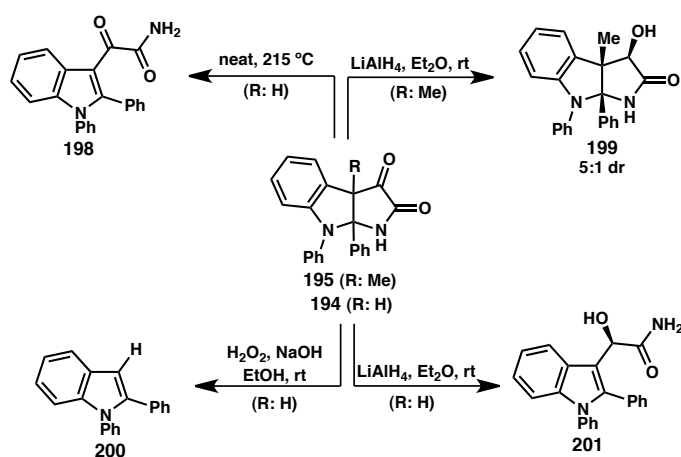
*Figure 4.1.1. Confirmation of azapropellane **197** structure by X-ray analysis (Kollenz and coworkers).*
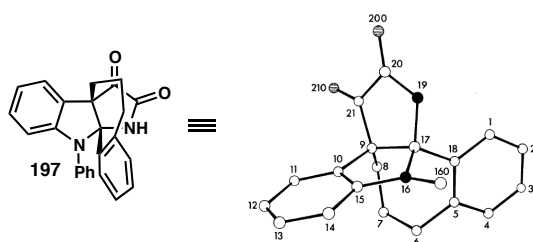
Within the past few years, two other synthetic approaches to 2a-arylpyrroloindolines have been reported. Bedford and coworkers developed a one-flask two-step protocol for generating benzene-fused pyrroloindolines including **204** by a Pd-catalyzed intramolecular dearomatization, followed by organolithium 1,2-addition into the resultant imine **203** (Scheme 4.1.3).[3] In 2012, subsequent to our report of an oxidative cyclization

approach to 2a-phenylpyrroloindolines (Section 4.2.2), Ma, Xie, and coworkers reported

access to tetracyclic pyrroloindolines including 2a-phenyl derivative **208**. This

transformation occurs by deprotonation of indole malonic diamides (**205**) with LHMDS,

oxidative cyclization to generate transient spirocycle **207**, and intramolecular cyclization

onto the imine to give **208**.[4]

Scheme 4.1.3. Other approaches to 2a-phenylpyrroloindolines.
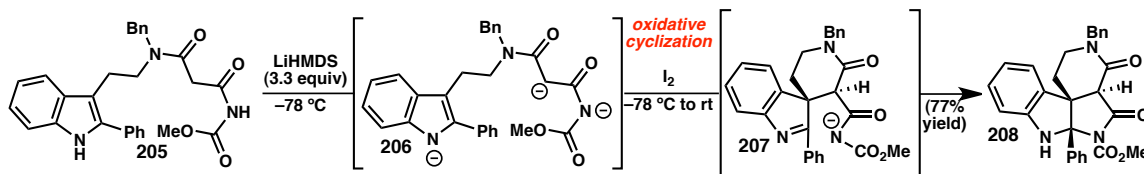
Although several synthetic efforts have been completed toward 2a-
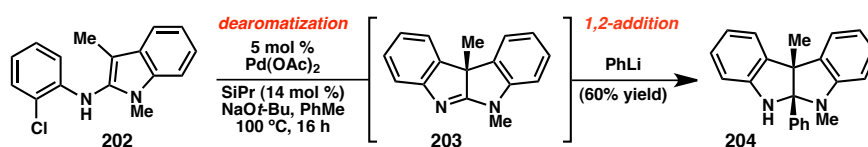
phenylpyrroloindolines, no biological assays of these compounds have yet been reported.

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.*
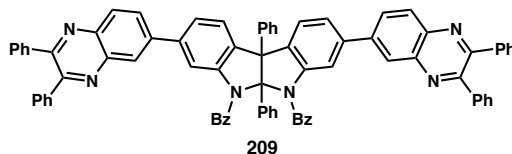
4.1.2 Oxidative Cyclization Approaches to Pyrroloindolines

Scheme 4.1.4. Wiktop and coworkers′ initial disclosure of the oxidative cyclization reaction and additional conditions.
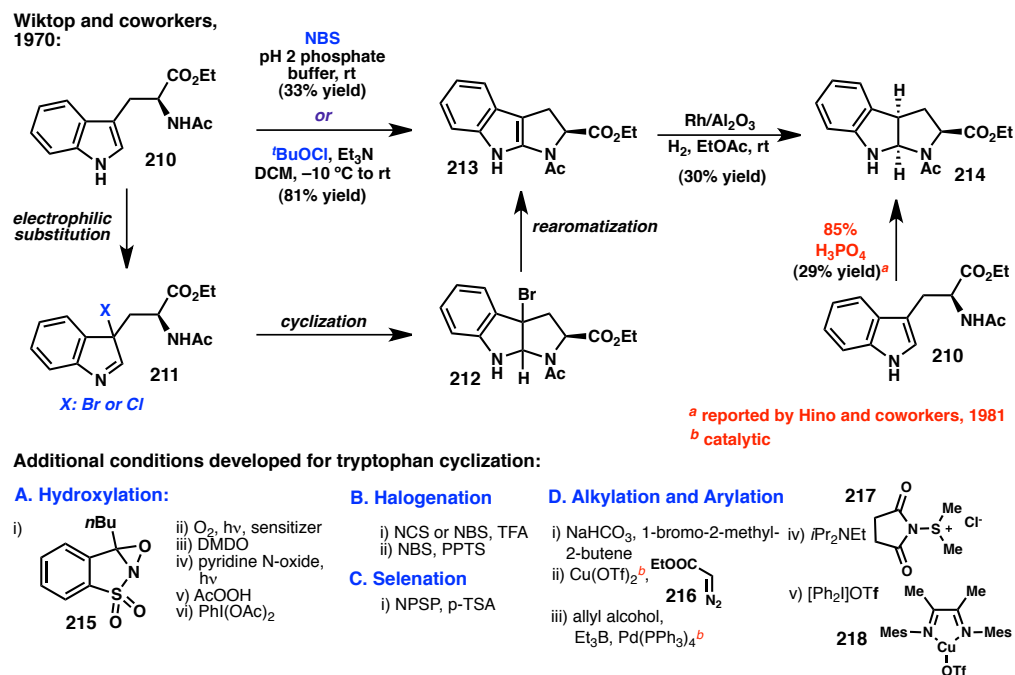
Although many enantioselective, catalytic methodologies have recently been developed (Chapter 1), the cyclization of tryptophan derivatives remains one of the most common approaches for the synthesis of enantioenriched pyrroloindolines. In 1970, Wiktop and coworkers reported that exposure of tryptophan methyl ester **210** to either *N*-bromosuccinimide (NBS) in a pH 9.2 buffer or *tert*-butyl hypochlorite and Et$_3$N affords 2,3-dehydropyrroloindoline **213** (Scheme 4.1.4).[6] Mechanistically, this reaction is proposed to occur by initial electrophilic substitution at C3 to afford indolenine intermediate **211**, followed by cyclization to give 3a-bromopyrroloindoline **212** and rearomatization with loss of HCl. Subsequent hydrogenation of **213** permitted access to pyrroloindoline **214**.

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

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

4.2 THE OXIDATIVE CYCLIZATION REACTION OF 2-PHENYLTRYPTOPHANS

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

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

We began by investigating the cyclization reaction of (1*H*)-2-phenyltryptophan **138c** generated in the tandem conjugate addition/enantioselective protonation reaction (Chapter 3). However, subjection of **138c** to NBS and TFA at –50 ºC 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[13] and the stability of **219** likely results from conjugation of the imine with the C2-phenyl substituent.

*Scheme 4.2.1. Conversion of **138c** to stable bromindolenine **219**.*
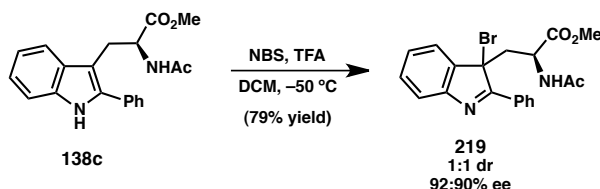
A variety of other oxidants were evaluated but stable indolenine formation was also observed with 1,3-dibromo-5,5-dimethylhydantoin/TFA (entry 6, Table 4.2.1), NCS/TFA (entry 7), and 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (entry 9). Subjection to acid resulted in either no reaction (entry 1) or saponification (entry 2) and other conditions including NBS/PPTS, Br_2, and $PhI(TFA)_2$ were also unfruitful with no pyrroloindoline product ever observed (entries 4, 5, and 8).

*Table 4.2.1. Other derivatization studies on N-acetyltryptophan methyl ester **138c**.*
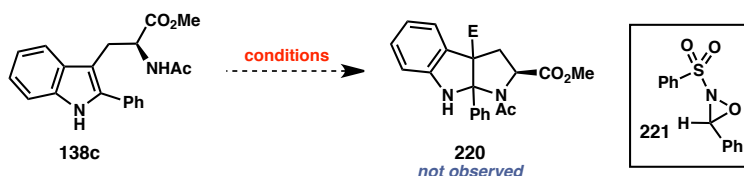
Entry	Conditions	Temperature/Time	Result
1	neat 85% H_3PO_4	50 ºC, 1 h	no reaction
2	neat 85% H_3PO_4	85 ºC, ~ 12 h	~75% saponification by HRMS
3	neat TFA	23 ºC, 1.5 h or 50 ºC, 1 h	no reaction
4	NBS, PPTS, DCM	23 ºC, 6 h	unidentified bromination product
5	Br_2, benzene	23 ºC, 15 min	mixture of products
6	1,3-dibromo-5,5-dimethyl-hydantoin, TFA, DCM	–50 to 10 ºC, 3 h	quantitative conversion to **219** (1.1:1 dr)
7	NCS, TFA, DCM	–50 ºC, 1.5 h	quantitative to chloroindolenine (1.7:1 dr)
8	$PhI(TFA)_2$, 2:1 MeCN:H_2O	0 ºC, 35 min	mixture of products
9	**221**, DCM	23 ºC, 24 h	47% yield of hydroxyindolenine (1:1 dr)

The conditions that facilitated bromoindolenine (**219**) formation were reevaluated for 2-butyltryptophan **138u**, for which the corresponding indolenine is anticipated to be less stable and susceptible to cyclization. In the presence of NBS and TFA, **138u** was converted to a compound containing diastereotopic methylenes (by crude ^{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.*
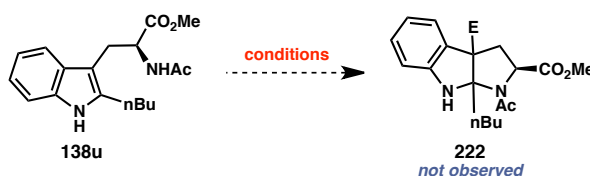
Entry	Conditions	Temperature/Time	Result
1	1 equiv **221**, DCM	23 ºC, 4 h	very messy reaction
2	1.5 equiv NPSP, 1 equiv PPTS, DCM	23 ºC, 13 h	minimal reaction
3[a]	1 equiv NBS, 1 equiv TFA, DCM	–50 ºC, 3.5 h	possibly indolenine by crude NMR, not isolable

[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 (1*H*)-tryptophan derivatives screened, pyrroloindoline formation is only anticipated to have occurred with **171** but unfortunately these products were unstable and thus not amenable to purification on silica gel.

*Table 4.2.3. Evaluation of primary amine **171** for oxidative cyclization.*
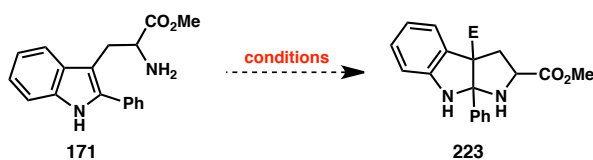
Entry	Conditions	Temperature/Time	Result
1[a]	1.50 equiv NPSP, 1 equiv PPTS, DCM	23 °C, 28.5 h	mixture of products (diasterotopic CH$_2$ in crude ^{1}H NMR)
2	**221**, DCM	23 °C, 29.5 h	very messy reaction
3	1 equiv NBS, 9:1 DCM:TFA	–50 °C, 4 h	mixture of products (diasterotopic CH$_2$ in crude ^{1}H NMR, aromatic peaks upfield-not isolable)

E: electrophile.

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

*Scheme 4.2.2. Conversion of **138e** to 5-bromotryptophan **224**.*
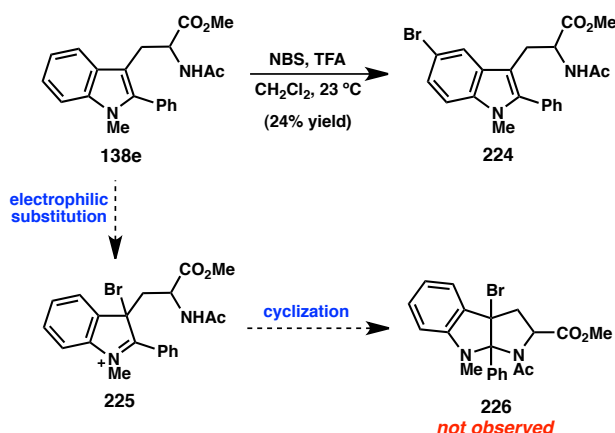
Of the conditions screened with (1*H*)-tryptophan derivatives, the results with *N*-acetyl-2-phenyltryptophan **138c** were particularly encouraging in that quantitative formation of stable haloindolenines was observed upon exposure to both NBS and NCS. These results suggested that 1-methyl-2-phenyltryptophan **138e** might prove a suitable substrate for pyrroloindoline (**226**) formation. Electrophilic substitution at C3 of **138e** would generate a positively charged indolenine (**35**) that is more reactive towards cyclization (Scheme 4.2.2). Unfortunately, subjection of **138e** to NBS and TFA at low

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

Alternatively, we were pleased to find that subjection of **138e** to NCS, TFA, and MeCN at room temperature provided 3-chloropyrroloindoline **227**, as confirmed by HRMS. This pyrroloindoline is unstable and, by in situ monitoring with ^{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_2O, and silica gel delivered more stable 3a-hydroxypyrroloindoline **228**. A similar two-step process has been disclosed by Somei and coworkers, in which they generated 3a-hydroxypyrroloindolines from simple tryptamine derivatives by treating the intermediate 3a-halopyrroloindolines with AgCN in a mixture of MeCN and H_2O.[8c]

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

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

Table 4.2.4. Optimization of the NCS-promoted cyclization for 138e.[a]
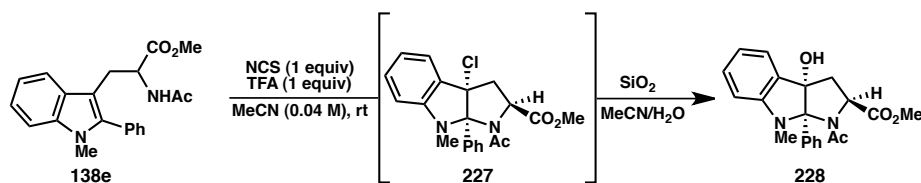
Entry	Time (h)	138e:228 ratio[b]	dr of 228[b]
1	0.5	2.7:1	3:1
2[c]	0.5	1:3.5	1:1
3	1	1:1.0	3:1
4	3	1:4.7	5:1
5[d]	3	1:4.3	6:1 (52%)[e]
6	5	1:5.4	16:1
7	7	1:2.9	>18:1
8	9	1:3.5	>20:1
9	13	1:2.4	>10:1
10	39	7.4:1	nd

[a] All reactions were run on 0.15 mmol scale. [b] Determined based on ^{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.
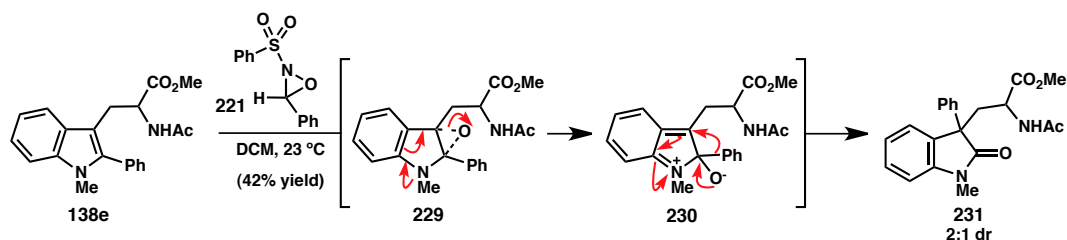
Although in situ conversion of **227** to **228** could potentially enable a more efficient process, we found that use of SiO_2 or both SiO_2 and water as additives failed to directly provide **228**. In search of a more streamlined approach to 3a-hydroxypyrroloindolines, we also attempted direct hydroxylation 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.
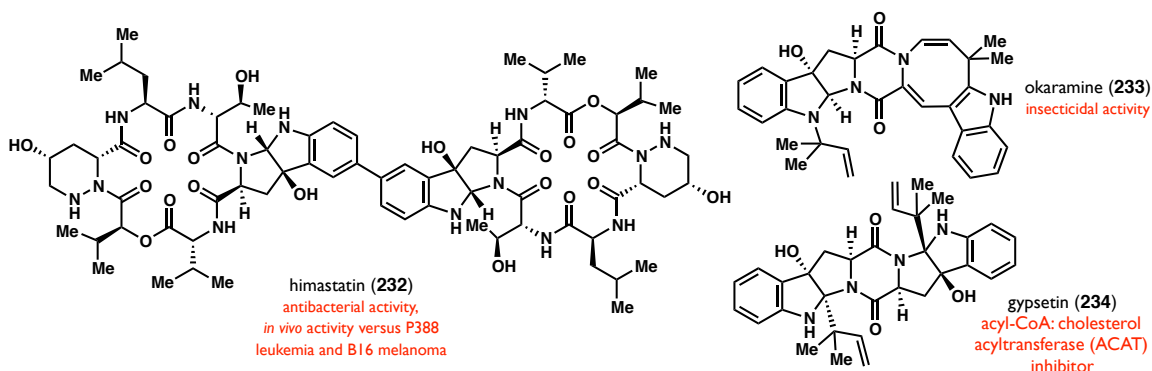
As with other pyrroloindoline natural products, the subclass of 3a-hydroxypyrroloindolines has received extensive interest due to both their structural complexity and their diverse biological activities. For example, the cyclodepsipeptide dimeric alkaloid himastatin (**232**) features inhibitory activity versus gram-positive bacteria as well as activity *in vivo* versus P388 leukemia and B16 melanoma cell lines (Figure 4.3.1).[15] In addition, two structurally distinct alkaloids, okaramine A (**233**) and gypsetin (**234**), possess insecticidal[16] and acyl CoA: cholesterol acyltransferase (ACAT) inhibitory activity,[17] respectively.

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

between **228** and known PAMs of the nicotinic acetylcholine receptors (nAChRs),

physostigmine (**1**) and galanthamine (**235**) (Figure 4.3.2). Drugs that target ion channels

have been developed for the treatment of many neurological disorders and degenerative

disease.[18] Specifically, the design of allosteric modulators, which bind at a site removed

from that of the natural agonist, has received extensive attention given their potential for

enhanced stability toward desensitization and improved receptor selectivity relative to

more traditional agonist and antagonist drugs that bind in the orthosteric site.[19] Notably,

the activity of **1** and **235** as PAMs is likely connected to their role in the amelioration of

Alzheimer's disease (AD) symptoms (**235** is an FDA-approved drug for the treatment of

AD).[20]

Figure 4.3.2. Positive allosteric modulators of nicotinic acetylcholine receptors.

physostigmine (**1**)   galanthamine (**235**)
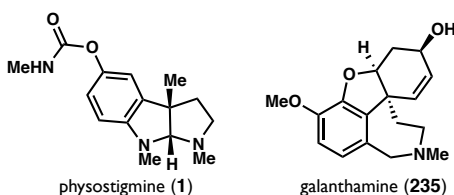
4.3.2   *Preparation of First Generation Target Carboxylic Acid 237*

Although the oxidative cyclization that provided pyrroloindoline methyl ester **228**

inspired the decision to further pursue this class of molecules, a more water-soluble

derivative lacking the acetamide and methyl ester functionalities was required to begin

biological studies. However, **228** could not be converted to the desired carboxylic acid

237 as attempted deprotection under conditions developed for tryptophan derivatization

(Chapter 3) resulted in decomposition of the pyrroloindoline (Scheme 4.3.1).

*Scheme 4.3.1. Attempted direct acetamide hydrolysis of pyrroloindoline **228**.*
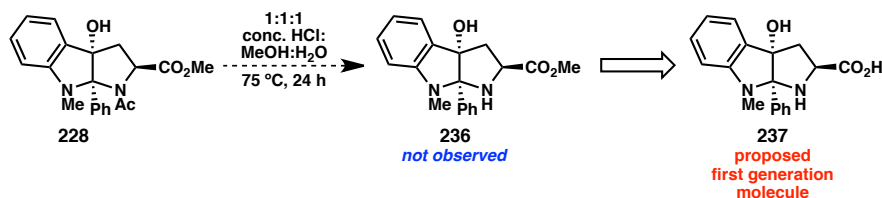
*Scheme 4.3.2. Access to cyclization substrate **239**.*
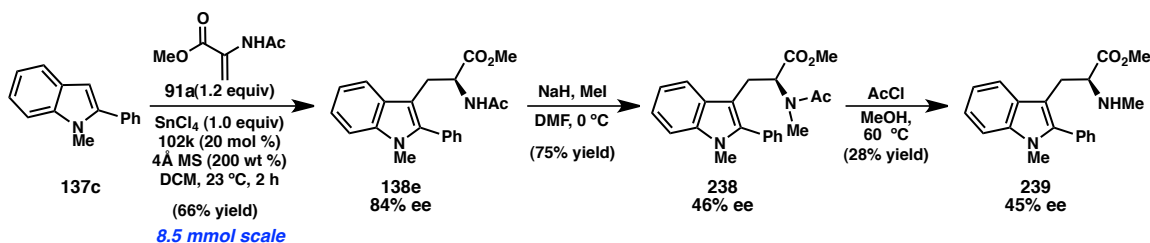
Alternatively, the necessary carboxylic acid (**237**) could be prepared in short order starting with the tandem conjugate addition/enantioselective protonation reaction of 1-methyl-2-phenylindole (**137c**), which could be completed on 8.5 mmol scale on the benchtop without any significant erosion of yield or ee (Scheme 4.3.2). Subsequent methylation under standard conditions afforded tertiary amide **238** in 75% yield, albeit in a substantially reduced ee of 46%. This issue of racemization, which was persistent for various runs and different substrates, is surprising given that NaH is commonly employed for the alkylation of α-amido esters.[21] Attempted subsequent acetamide hydrolysis under aqueous acid conditions resulted in competitive overhydolysis; 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 ºC, secondary amine **239** was isolated in 28% yield and 38% of the starting material (**238**) was recovered, both in 45% ee.

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

*Table 4.3.1. Optimization of cyclization for secondary amine **239**.[a]*
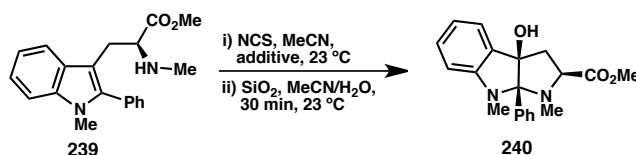
Entry	Additive	Time (h)	Conversion[b]	Yield[b]	dr[b]
1	TFA	3	41	14	1.3:1
2	TFA	13.5	66	31	1.9:1
3	-----	3	81	42	1.2:1

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

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

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

pyrroloindoline at C2a.

*Scheme 4.3.3. Access to exo-**237** for electrophysiology experiments.*
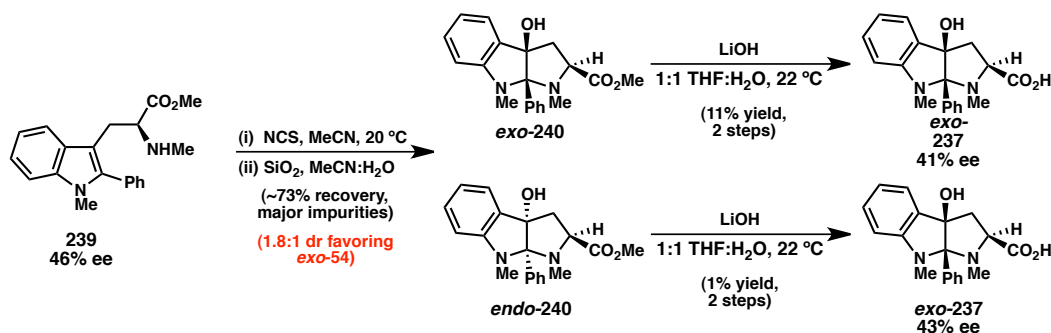
4.3.3 *Electrophysiology Experiments on Carboxylic Acid 237*

Initial experiments on carboxylic acid **237** were conducted by evaluating its effect on

receptor response for a variety of LGICs individually expressed in *Xenopus* oocytes

(Table 4.3.2). This work was completed using an OpusXpress-6000A system and more

detailed information on the experimental setup can be found in Section 4.7.2.

Hydroxypyrroloindoline **237** was found to either not affect or inhibit each receptor when

added at a 20 μM concentration in combination with an EC_{50} dose of the appropriate

agonist (median effective concentration). The IC_{50} value of **237** (median inhibition

concentration with co-application of an EC_{50} dose of agonist) was also determined for two

receptors; for the α7-T6'S nAChR, the IC_{50} value was 5 +/- 1 μM (n=7) with a hill

coefficient of 0.8 and for the $(\alpha_4\text{-L9'A})_3(\beta_2)_2$ nAChR, the IC_{50} value was 8 +/- 1 μM (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 $mGlu_5$ have recently been designed for the treatment of levodopa-induced dyskinesia associated with Parkinson's disease, migraines, and Fragile X Syndrome.[23] However, it is also possible that carboxylic acid **237** serves as an antagonist, binding at the orthosteric site, or that it functions as a channel blocker and is simply adequately sized to fit in the channel after opening by the agonist and prevent the flow of ions.[24]

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

Entry	Receptor	% Current reduction
1	$(\alpha 1)_2(\beta 1\text{-L9'S})\delta\gamma$ mouse muscle nAChR	21 ± 1^b
2	$\alpha 7$ nAChR	40 ± 9
3	$\alpha 7\text{-T6'S}$ nAChR	67 ± 3
4	$(\alpha 4)_2(\beta 2)_3$ nAChR	20 ± 1
5	$(\alpha 4\text{-L9'A})_2(\beta 2)_3$ nAChR	25 ± 1
6	$(\alpha 4\text{-L9'A})_3(\beta 2)_2$ nAChR	44 ± 1
7	$\alpha 4\beta 4$ nAChR	28 ± 1
8	$(\alpha 1)_2(\beta 2)\gamma 2$ $GABA_A R$	27 ± 4
9	$GluR_{2A}$	6 ± 1
10	GlyR	6 ± 2
11	$5HT_{3A}R$	3 ± 2

[a] Current was recorded using an OpusXpress-6000A with a two-electrode voltage clamp method. Data was acquired with a co-application of 20 μM concentration of **237** and an EC_{50} dose of agonist, both in ND96 buffers (see 4.7.2 for agonist EC_{50} values). [b] Standard error of the mean (n=3 or 4).

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

as the current recovery after ceasing treatment with **237** was incomplete in the time course of the experiment, as shown for $(\alpha4\text{-L9'A})_3(\beta2)_2$ 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.*
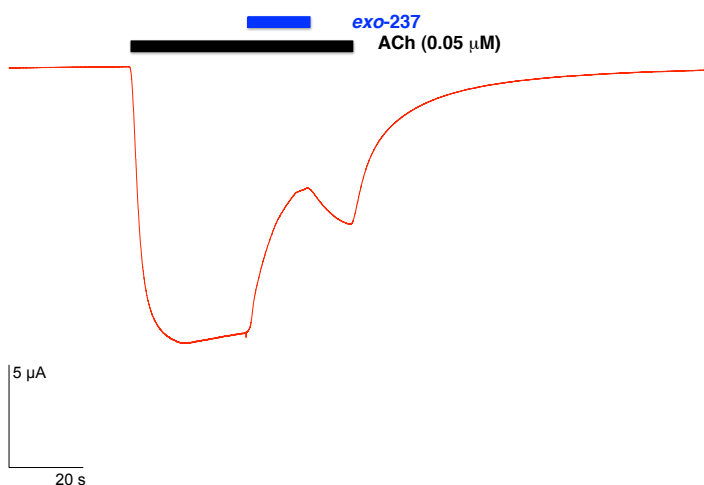
We decided to target several structurally related derivatives of *exo*-**237** for further experiments. These targets included both enantiomers of *exo*-**237**, and decarboxylated compound **241** (Figure 4.3.4). Dependence of current inhibition on the absolute configuration of *exo*-**237** might suggest 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.
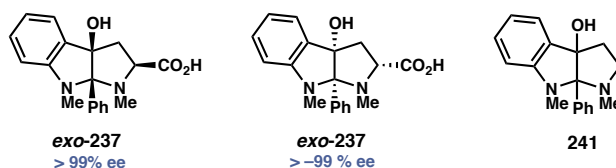
4.4   **SYNTHESIS   OF   SECOND   GENERATION   TARGETS   FOR**
              ELECTROPHYSIOLOGY EXPERIMENTS

4.4.1   *Synthesis of Pyrroloindolines from Tryptamine Derivatives*

Although it would have been convenient to directly access **241** by the

decarboxylation of *exo*-**237**, our initial attempts at promoting this transformation proved

unfruitful (Scheme 4.4.1). The Barton ester appears to form, as the mass corresponding to

decarboxylation is observed when the reaction progress is monitored by LCMS; however,

subsequent exposure to radical conditions results in either decomposition or recovery of

237.[25]

*Scheme 4.4.1. Attempted decarboxylation of **237**.*
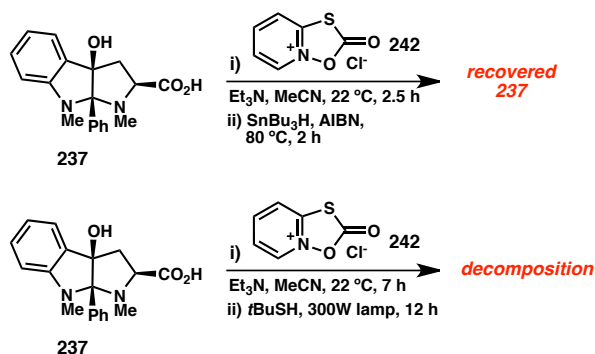
In light of these results, we decided to prepare **241** using an oxidative cyclization of the corresponding 2-phenyltryptamine **245**. Our synthesis began with the selective C2-arylation of readily available *N*-Cbz-*N*,1-dimethyltryptamine (**243**) (Scheme 4.4.2). We were pleased to find that conditions developed for C2-arylation of tryptophan derivatives by Albericio, Lavilla, and Ruiz-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**.*
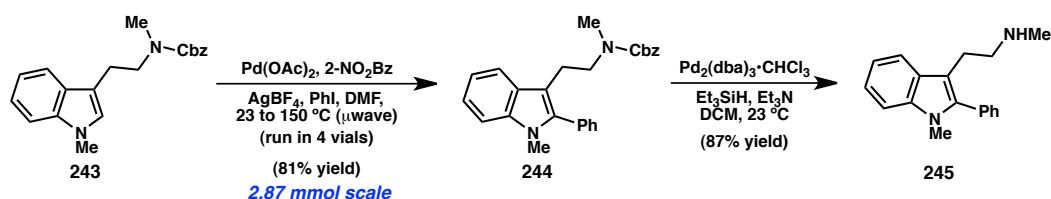
Although the oxidative cyclization reaction of **245** is particularly sensitive, pyrroloindoline formation was consistently observed with dropwise addition of NCS (purified by recrystallization) as a solution to a mixture of the substrate and 4Å molecular sieves in MeCN. In contrast to the oxidative 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.

Scheme 4.4.3 Divergent effects of quench for tryptophan and tryptamine cyclization substrates.
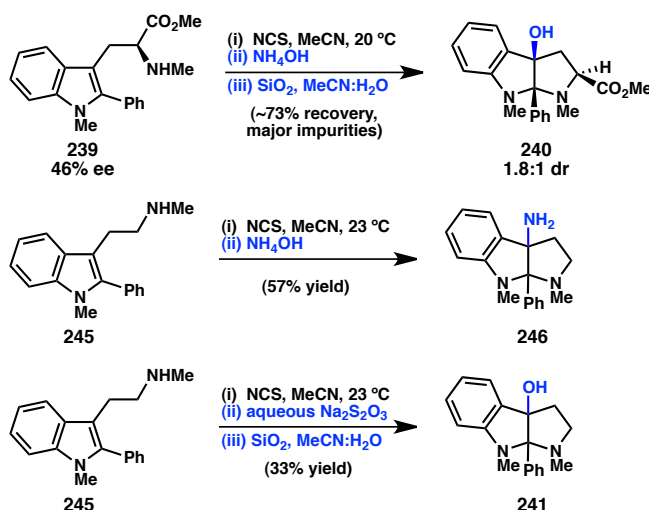
We also pursued the synthesis of monomethylated 3a-hydroxypyrroloindoline **251** (Scheme 4.4.4). Microwave-assisted arylation of known Cbz-protected tryptamine **248** provided 2-phenyltryptamine **249** in excellent yield. Oxidative cyclization under the reoptimized conditions with 4Å molecular sieves and recrystallized NCS afforded 1-Cbz-pyrroloindoline **250**. Subsequent subjection to catalytic 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 4.4.4. Synthesis of (1H)-1a-methylpyrroloindoline **251**.*
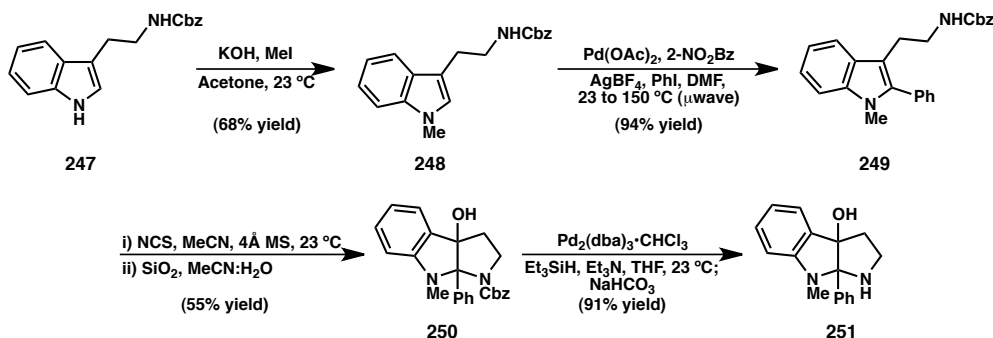
4.4.2   *Second Generation Synthesis of Exo-Carboxylic Acid 237*

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

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

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

*Scheme 4.4.5. Second generation access to 82% enantioenriched carboxylic acid **237**.*
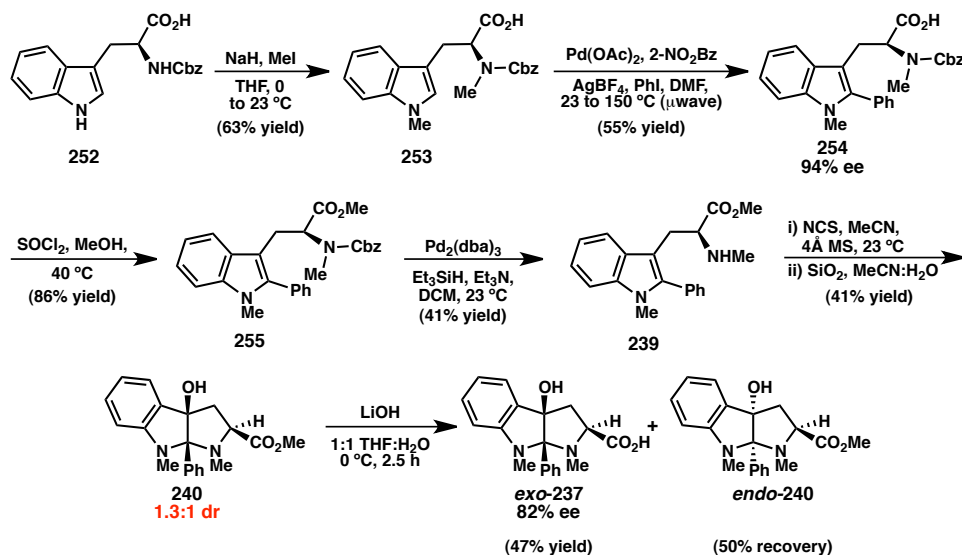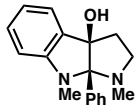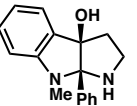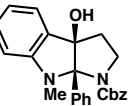
4.5   ELECTROPHYSIOLOGY EXPERIMENTS OF CYCLIC TRYPTAMINES

In an analogous fashion to the work on *exo*-**237** (Section 4.3.3), the four pyrroloindoline products derived from tryptamine were subjected to electrophysiology experiments. As observed for *exo*-**237**, the derivatives showed minimal activity with respect to the $GluR_{2A}$, GlyR, and $5HT_{3A}$ receptors (Table 4.5.1, entries 6-8). However, each molecule promoted current reduction when applied to nAChRs (entries 1-3). This structural promiscuity likely suggests that these pyrroloindolines function as channel blockers, rather than as NAMs or antagonists. However, we were pleased to find that although **241** blocks all nAChRs, it potentiates the effect of the $GABA_A$ receptor agonist, GABA, with an increase in current of 52% at a 40 μM dose of **241** in combination with an EC_{50} dose of GABA (11 μM, entry 4) relative to an EC_{50} dose of GABA alone. Interestingly, **241** is also capable of activating the receptor on its own, generating about 10% of the current produced by an 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.[a]

Entry	Receptor	**241**[b]	**246**	**251**	**250**
1	$(\alpha1)_2(\beta1\text{-L9'S})\delta\gamma$ mouse muscle nAChR	− 53 ± 3	− 81 ± 6	− 7 ± 3	− 29 ± 3
2	$\alpha7\text{-T6'S}$ nAChR	− 92 ± 4	− 96 ± 3	− 57 ± 10	− 68 ± 7
3	$(\alpha4\text{-L9'A})_2(\beta2)_3$ nAChR	− 29 ± 6	− 44 ± 2	− 11 ± 2	− 47 ± 4
4	$(\alpha1)_2(\beta2)_2\gamma2$ $GABA_A$R	+ 52 ± 10	+ 10 ± 5	− 27 ± 21	− 27 ± 11
5	$(\alpha1)_2(\beta2)_2$ $GABA_A$R	+ 16 ± 2	nd	nd	nd
6	$GluR_{2a}$	− 9 ± 6	− 12 ± 5	− 11 ± 5	0 ± 2
7	GlyR	+ 3 ± 7	− 16 ± 6	+ 18 ± 10	− 9 ± 9
8	$5HT_{3A}$R	− 3 ± 5	− 11 ± 8	+ 3 ± 12	−23 ± 4

[a] % effect on current and standard error of means (n=3 or 4) shown. Current was recorded using an OpusXpress-6000A with a two-electrode voltage clamp method. Data was acquired with a co-application of 20 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). [b] 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.[27] Many of these molecules are FDA-approved drugs including clonazepam (Klonopin), a treatment for epilepsy, diazepam (Valium), a

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

*Figure 4.5.1. Current trace for screen with **241** versus $GABA_A$ receptor.**
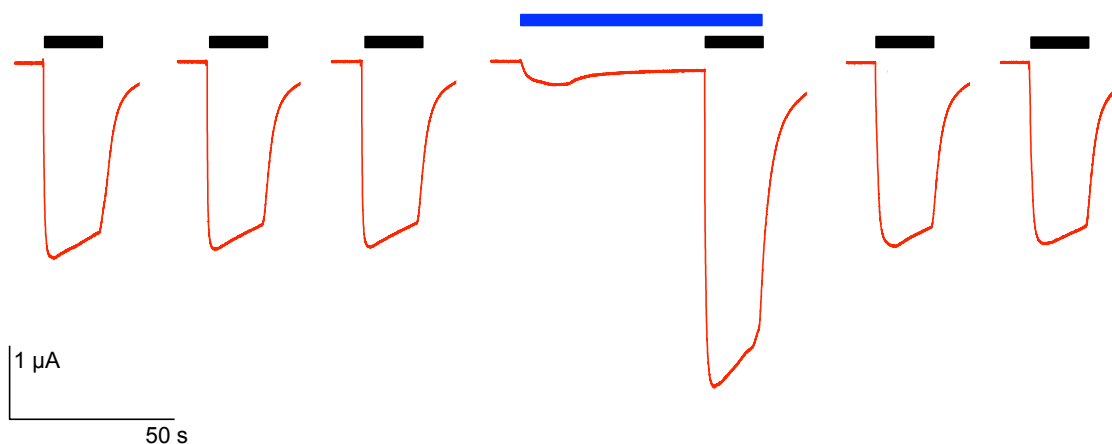
*Black corresponds to application of the agonist, blue corresponds to application of **241**. Gaps in the trace indicate a 300 second wash.

4.6   CONCLUSIONS AND FUTURE DIRECTIONS

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

Lambadjieva and Georgiev reported that when the convulsant picrotoxin is injected into mice in combination with **1**, the seizure threshold is increased thus suggesting a possible role for **1** as a PAM.[28] However, **1** has also been shown to increase the concentration of the GABA$_A$ PAM propofol[29] necessary for anaesthesia *in vivo*.[30]

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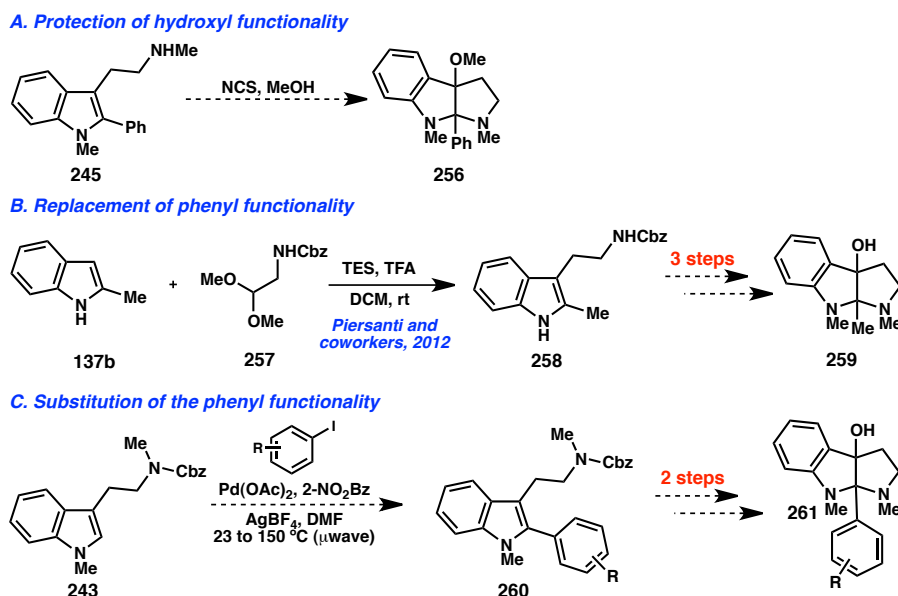
Further mechanistic insight could be gained through structural variation (Scheme 4.6.1). For example, experiments with 3a-methoxypyrroloindoline **256** would delineate the importance of the hydroxyl substituent. We expect **256** to be readily available as, in one report analogous to our own work, Somei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

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

Scheme 4.6.2. Enantioselective hydroxylation of 2-phenyltryptamines (Movassaghi, Miller, and coworkers, 2011).
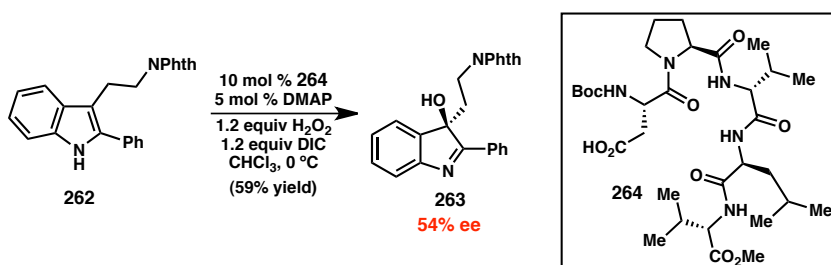
Although our efforts toward 3a-hydroxy-2a-phenylpyrroloindolines began in an effort to broaden the scope of our tandem conjugate addition/enantioselective protonation reaction methodology, through the collaboration of our lab with Professor Dennis Dougherty, Kristina Daeffler, and Christopher Marotta this project has evolved into a search for novel drugs for the treatment of neurological disorders and neurodegenerative diseases. We are excited to continue this collaboration and to further investigate the importance of and mechanism of **241** in its role as a positive allosteric modulator. Future work regarding **241** and possible identification of more effective derivatives of **241** could

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

4.7 EXPERIMENTAL SECTION

4.7.1 Materials and Methods for Synthetic Procedures

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, acetonitrile, dimethylformamide, and toluene were dried by passing through activated alumina columns. Methanol was distilled over calcium hydride. 4Å molecular sieves and powdered 4Å molecular sieves were flame-dried under vacuum immediately prior to use. All other commercially obtained reagents were used as received unless specifically indicated. $Pd_2(dba)_3 \cdot CHCl_3$ was purchased from Strem and stored in a glovebox, acetyl chloride, *N*-(benzyloxycarbonyloxy)succinimide (**266**), and 1-methyl-2-phenylindole (**137c**) were obtained from Sigma-Aldrich, and 1 M $SnCl_4$ 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, δ = 7.26, ^{13}C, δ = 77.0), MeCN (^{1}H, δ = 1.94, ^{13}C, δ = 118.26), or DMSO (^{1}H, δ = 2.50). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. 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, γ-aminobutyric acid (GABA), glycine, and 5-hydroxytryptamine were purchased from Sigma-Aldrich and used as received. mRNA was prepared as previously described using the Quikchange protocol for any necessary site-directed mutagenesis, and standard DNA linearization techniques, followed by *in*

vitro transcription using a T7 mMessage mMachine kit obtained from Ambion. The receptors were expressed in *Xenopus laevis* oocytes by injection of the mRNA of each of the desired subunits and incubation at 18 °C for 24 – 48 h in Ca^{2+}-containing ND96 buffer (1.8 mM $CaCl_2$, 96 mM NaCl, 2 mM KCl, 1 mM $MgCl_2$, 5 mM HEPES, pH 7.5). For α7 nAChRs, an equal amount of hRic3 was also injected into the oocytes to promote expression.[36]

Electrophysiology experiments on the oocytes were conducted using an OpusXpress-6000A system (Axon Instruments). A two-electrode voltage clamp method was used with a holding potential of –60 mV. Prior to data collection, the health of the oocytes was evaluated by measuring the potential across the cell membrane as well as the leak current. Agonists for each receptor were employed at their EC_{50} concentrations using ND96 buffer for $GABA_AR$ and α7 nAChRs and Ca^{2+}-free ND96 buffers for all other receptors. EC_{50} concentrations were calculated by applying the Hill equation to the data from measurement of the current produced at various concentrations of the agonists. The agonist concentrations used in the electrophysiology experiments on all pyrroloindolines tested are as follows: 1.2 μM acetylcholine for mouse muscle-type $(\alpha1)_2(\beta1\text{-}L9'S)\delta\gamma$ nAChR, 1 μM acetylcholine (ACh) for $(\alpha4)_2(\beta2)_3$ nAChR, 0.5 μM ACh for $(\alpha4\text{-}L9'A)_2(\beta2)_3$ nAChR, 0.05 μM ACh for $(\alpha4\text{-}L9'A)_3(\beta2)_2$ 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 $5HT_{3A}R$, 14 μM glutamate for $GluR_{2A}$, 110 μM glycine for GlyR, 11 μM GABA for $(\alpha1)_2(\beta2)2\gamma2GABAAR$, and 3 μM GABA for $(\alpha1)_2(\beta2)_2$ $GABA_AR$.

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

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

4.7.3 Synthetic Procedures

Preparation of bromoindolenine 219.
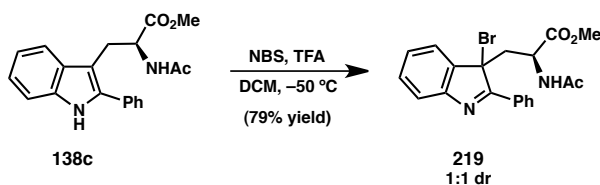
A solution of (*S*)-N_α-acetyl-2-phenyltryptophan methyl ester **138c** (101 mg, 0.30 mmol, 1.00 equiv) in 8.4 mL DCM was cooled to –50 ℃ in an MeCN/dry ice bath. NBS (53.4 mg, 0.30 mmol, 1.00 equiv) was then added, followed by 900 μL TFA. The reaction was stirred in the dark at –50 ℃ for 3 hours, then 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 H_2O, then 40 mL brine), dried (Na_2SO_4), 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 CO_2, λ = 254 nm): t_R(major) = 3.8, t_R(minor) = 4.1 min; t_R(major) = 4.6, t_R(minor) = 6.0 min. Spectral data and optical rotation are reported for the mixture of indolenine diastereomers. ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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}; $[\alpha]_D^{25}$ = +17.1° (c = 0.50, $CHCl_3$). HRMS (MM) calc'd for $C_{20}H_{20}BrN_2O_3$ [M+H]$^+$ 415.0652, found 415.0652.

Preparation of (*R/S*)-5-bromotryptophan methyl ester 224.
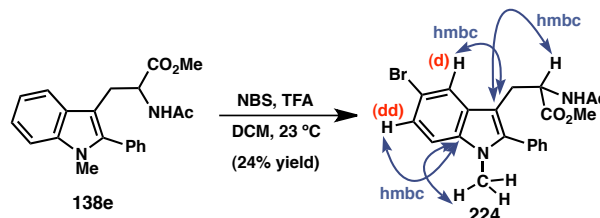
A flame-dried flask was charged with (*R/S*)-N_α-acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**, 28.0 mg, 80 µmol, 1.00 equiv), 2.2 mL DCM, NBS (14.2 mg, 80 µmol, 1.00 equiv) and 240 µL TFA in that order. The yellow reaction solution was stirred at room temperature for 4.5 hours, then poured onto ice, quenched with 1.0 mL aqueous ammonia and extracted with DCM (3 x 10 mL). The combined organics were washed (15 mL 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). ^{13}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$_2$O$_3$ [M+H]$^+$ 429.0808 found 429.0797.

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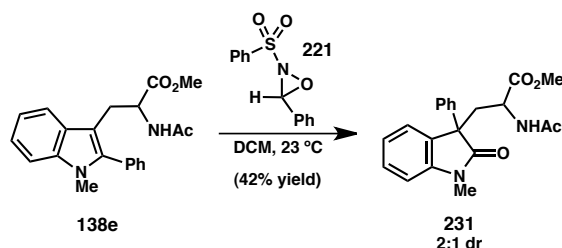
A flame-dried flask was charged with (R/S)-N_α-acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**, 28.0 mg, 80 μmol, 1.00 equiv), 1.0 mL DCM, and 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (**221**, 20.9 mg, 80 μmol, 1.00 equiv) in that order. The bright yellow reaction solution was stirred at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

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

22.6.; FTIR (NaCl/thin film): 3308, 3057, 2952, 2931, 1746, 1709, 1659, 1611, 1494, 1471, 1373 cm^{-1}; HRMS (MM) calc'd for $C_{21}H_{23}N_2O_4$ [M+H]$^+$ 367.1652, found 367.1642.

Minor diastereomer: yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39 (ddd, J = 7.7, 7.7, 1.3 Hz, 1H), 7.37-7.26 (m, 5H), 7.26-7.22 (m, 1H), 7.21 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.92 (ddd, J = 7.9, 1.1, 0.6 Hz, 1H), 5.77 (br d, J = 8.8 Hz, 1H), 4.26 (ddd, J = 11.0, 8.8, 3.1 Hz, 1H), 3.64 (s, 3H), 3.17 (s, 3H), 2.87 (dd, J = 14.4, 11.1 Hz, 1H), 2.75 (dd, J = 14.3, 3.1 Hz, 1H), 1.88 (s, 3H).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.4, 172.2, 169.4, 143.9, 139.8, 129.4, 129.2, 128.7, 127.7, 126.6, 125.0, 123.2, 109.0, 54.7, 52.5, 49.7, 39.0, 26.5, 22.9.; FTIR (NaCl/thin film): 3326, 3057, 2954, 2929, 1744, 1710, 1683, 1611, 1495, 1472, 1373 cm^{-1}; HRMS (MM) calc'd for $C_{21}H_{23}N_2O_4$ [M+H]$^+$ 367.1652, found 367.1638.

Preparation of 3a-hydroxypyrroloindoline 228.
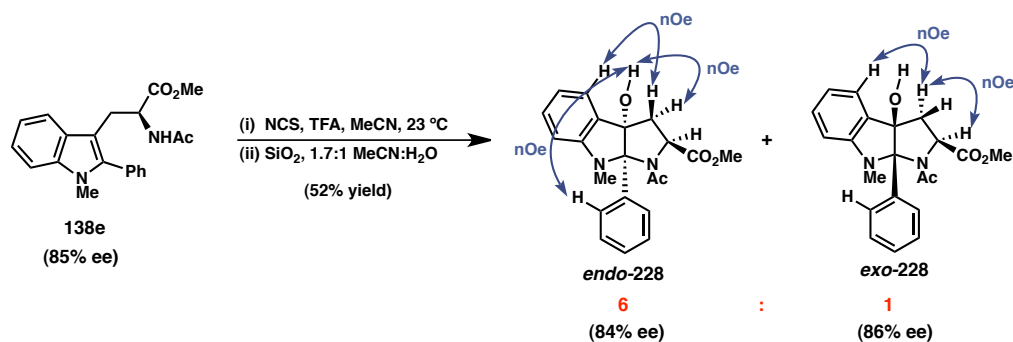
A 15 mL flask containing (*S*)-N_α-acetyl-1-methyl-2-phenyltryptophan methyl ester **138e** (52.5 mg, 0.150 mmol, 1.00 equiv) was flushed with argon and then charged with 3.3 mL MeCN. 1.3 M TFA in MeCN (125 μL, 0.150 mmol, 1.00 equiv) was added, followed by 0.2 M NCS in MeCN (0.75 mL, 0.150 mmol, 1.00 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
H_2O, then 20 mL brine), dried (Na_2SO_4), 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 H_2O and 2.5
mL SiO_2 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 (Na_2SO_4), filtered and concentrated. The crude oil contained a mixture of 3a-
hydroxypyrroloindolines, formed in 6:1 dr and favoring the *endo* diastereomer
(determined by ^1H NMR analysis). The crude was subjected to silica gel column
chromatography (0:100 to 10:90 EtOAc:CHCl$_3$) to yield 30.8 mg (product contained 18
wt % CHCl$_3$, 46% corrected yield) of the *endo* diastereomer as a yellow oil. The *exo*
diastereomer, obtained post chromatography in a mixture with (*S*)-*N*α-acetyl-1-methyl-2-
phenyltryptophan methyl ester **138e**, was subjected to reverse phase preparative HPLC
(30:70 to 90:10 MeCN:H_2O) 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

endo-228
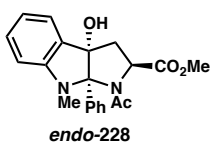
mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 7.4, t_R(minor) =
4.7 min. The relative stereochemistry was assigned by 2D NMR
analysis. ^1H NMR (500 MHz, CD$_3$CN; compound exists as a 15:1 mixture of rotamers,
the major rotamer is reported) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.26 (m, 3H), 7.20 (ddd, *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}; $[\alpha]_D^{25}$ = +264.0° (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
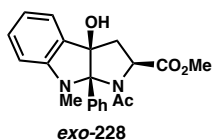
mL/min, 20% IPA in CO$_2$, λ = 254 nm): t_R(major) = 6.2, t_R(minor) =

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° (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).
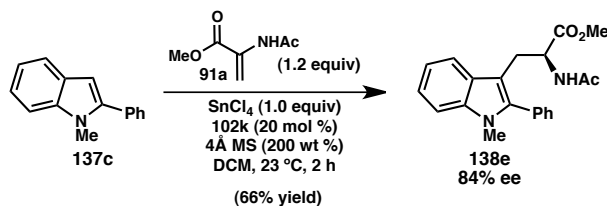
To a 250 mL flame-dried flask under nitrogen containing freshly activated powdered 4Å molecular sieves (3.50 g, 200 wt % relative to **137c**) was added 1-methyl-2-phenylindole (**137c**, 1.75 g, 8.45 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 1.45 g, 10.1 mmol, 1.20 equiv), and (R)-3,3'-dibromo-BINOL (**102k**, 750 mg, 1.69 mmol, 0.20 equiv). The flask was charged with 65 mL DCM and SnCl$_4$ (1 M in DCM, 8.45 mL, 8.45 mmol, 1.00 equiv) was added. The orange reaction mixture was stirred at room temperature for 2 hours, then diluted with 15 mL MeCN, filtered, and quenched by addition of 50 mL 1 M HCl. The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with a mixture of 100 mL saturated aqueous NaHCO$_3$ and 300 mL brine. The aqueous layer was extracted with EtOAc (4 x 100 mL) and the combined organic layers were dried (Na$_2$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$_2$, λ =

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_α-acetyl-N_α,1-dimethyl-2-phenyltryptophan methyl ester (238).
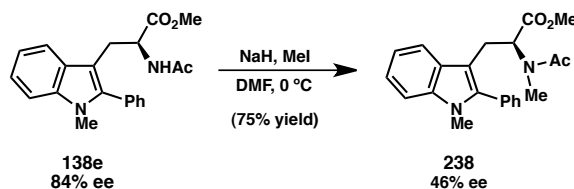
A solution of (S)-N_α-acetyl-1-methyl-2-phenyltryptophan methyl ester (**138e**, 1.93 g, 5.50 mmol, 1.00 equiv) in 11 mL DMF was cooled to 0 °C in an ice bath. NaH (60% dispersion in oil, 385 mg, 9.64 mmol, 1.75 equiv) was then added, followed by MeI (0.75 mL, 12.1 mmol, 2.20 equiv). The yellow reaction mixture was stirred at 0 °C for 1.5 hours, then quenched with 5 mL aqueous ammonia and 5 drops Et$_3$N. The mixture was allowed to warm to room temperature and stirred for 12 hours, then diluted with 40 mL H$_2$O and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed (50 mL H$_2$O, then 2 x 50 mL brine), dried (Na$_2$SO$_4$), filtered, and concentrated. The crude oil was subjected to silica gel column chromatography (0:100 to 80:0 EtOAc:hexanes) to yield 1.51 g (75% yield) of (S)-N_α-acetyl-N_α,1-dimethyl-2-phenyltryptophan methyl ester **238** as a light yellow solid. The enantiomeric excess was determined to be 46% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO$_2$, λ = 254 nm): t_R(major) = 11.0 min, t_R(minor) = 12.5 min. ^{1}H NMR (300 MHz, CDCl$_3$, compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.66 (d, J = 8.0 Hz, 1H*), 7.62 (d, J = 7.7 Hz, 1H§), 7.55-7.10 (m, 8H*, 8H§), 4.86 (dd, J = 10.0, 4.7 Hz, 1H*), 4.62 (dd, J = 10.2, 4.3 Hz, 1H§), 3.69 (s, 3H§), 3.64 (s, 3H*), 3.57 (s, 3H§), 3.56 (s, 3H*), 3.51 (dd, J = 11.4, 4.6 Hz, 1H§), 3.46 (dd, J = 11.5, 4.4 Hz, 1H*), 3.28 (dd,

J = 14.8, 10.1 Hz, 1H*), 3.16 (dd, J = 15.0, 10.1 Hz, 1H§), 2.51 (s, 3H*), 2.27 (s, 3H§),

1.80 (s, 3H*), 1.44 (s, 3H§).; ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 1.2:1

mixture of rotamers) δ 171.5, 171.0, 170.9, 170.7, 139.7, 138.7, 137.10, 137.05, 131.8,

131.2, 130.6, 130.5, 128.7, 128.6, 128.4, 128.2, 127.6, 126.9, 122.1, 121.8, 119.8, 119.5,

118.7, 117.9, 109.8, 109.4, 108.6, 107.1, 60.9, 59.0, 52.4, 52.0, 34.5, 30.80, 30.77, 28.5,

24.3, 23.7, 21.7, 20.9.; FTIR (NaCl/thin film): 3052, 2949, 2242, 1740, 1735, 1653, 1648,

1469, 1442, 1432, 1400, 1364, 1329, 1268, 1214 cm^{-1}; $[\alpha]_D^{25}$ = –62.0° (c = 0.40, 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*$_\alpha$,1-dimethyl-2-phenyltryptophan methyl ester (239).
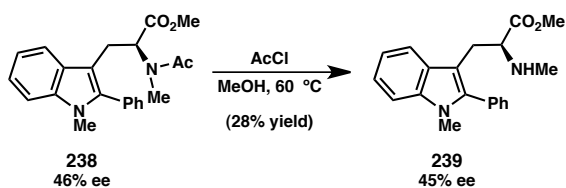
A flame-dried 100 mL flask charged with 20 mL MeOH was cooled to 0 °C in an ice

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*$_\alpha$-Acetyl-*N*$_\alpha$,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*$_\alpha$,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 CO_2, λ = 254 nm): t_R(major) = 5.7 min,

t_R(minor) = 7.0 min and the enantiomeric excess of recovered starting material **238** was

determined to be 45% by chiral SFC analysis (OJ-H, 6% IPA in CO_2, λ = 254 nm):

t_R(major) = 11.1 min t_R(minor) = 12.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (ddd, J =

7.8, 1.2, 0.8 Hz, 1H), 7.54 – 7.37 (m, 5H), 7.33 (ddd, J = 8.3, 1.0, 1.0 Hz, 1H), 7.26 (m,

1H), 7.16 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 3.56 (s, 3H), 3.50 (s, 3H), 3.47 (dd, J = 7.7, 6.4

Hz, 1H), 3.15 (dd, J = 14.3, 6.3 Hz, 1H), 3.04 (dd, J = 14.3, 7.7 Hz, 1H), 2.22 (s, 3H).;

^{13}C NMR (125 MHz, $CDCl_3$) δ 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}; $[\alpha]_D^{25}$ = +7.5° (c =

0.52, $CHCl_3$). HRMS (MM) calc'd for $C_{20}H_{22}N_2O_2$ [M+H]$^+$ 323.1754, found 323.1760.

Preparation of 3a-hydroxypyrroloindoline methyl ester 240.
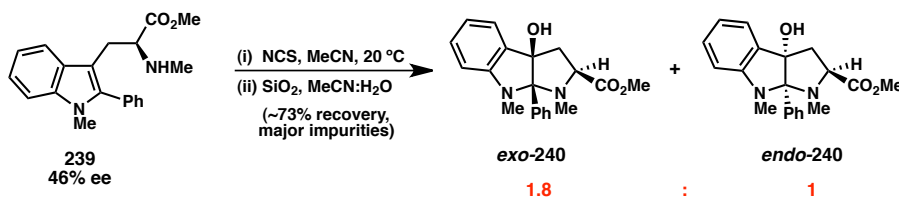
(*S*)-N_α,1-Dimethyl-2-phenyltryptophan methyl ester (**239**, 220 mg, 0.684 mmol, 1.00

equiv) was dried by azeotrope with benzene in a 50 mL flask. The flask was flushed with

argon then charged with 15.5 mL MeCN. 0.2 M NCS in MeCN (3.4 mL, 0.684 mmol,

1.00 equiv) was added and the reaction was stirred in the dark at room temperature. After

4 hours, the light orange reaction solution was quenched with 7 mL aqueous ammonia,

poured onto ice, and extracted with 50 mL DCM. 10 mL brine was added to the aqueous

layer, which was then extracted with DCM (3 x 35 mL). The combined organic layers

were washed (50 mL H$_2$O, then 50 mL brine), dried (Na$_2$SO$_4$), filtered, and concentrated.

The residue was redissolved in 9.3 mL MeCN then 5.6 mL H$_2$O and 11.7 mL SiO$_2$ 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 (Na$_2$SO$_4$),

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 ^{1}H NMR analysis). The crude was subjected to reverse phase preparatory

HPLC (0.05:30:70 to 0.05:95:5 TFA:MeCN:H$_2$O) using an Agilent 1200 Series HPLC

with an Agilent XDB-C18 5 μM column (9.4 x 250 mm) to yield 61.6 mg (26% recovery,

<90% clean) of *endo*-**240** as a yellow-brown oil and 106 mg (46% recovery, <90% clean)

of *exo*-**240** as a yellow-brown oil.

Preparation of *exo*-hydroxypyrroloindoline carboxylic acid 237.
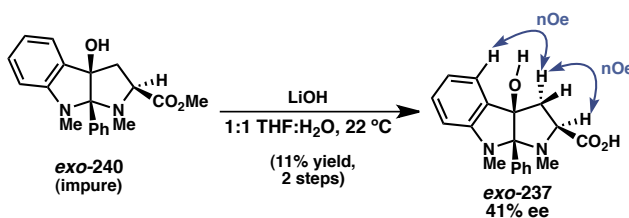
A scintillation vial was charged with the *exo*-3a-hydroxypyrroloindoline methyl ester

(**240**, 106 mg, 1.00 equiv), LiOH (189 mg, 7.87 mmol, >25.0 equiv), 2 mL THF, and 2

mL H$_2$O. 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:H$_2$O)

using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (30 x 250

mm) to yield 23.5 mg (11% yield, ~95% clean) of *exo*-**237** as a yellow solid. The

enantiomeric excess of *exo*-**237** was determined to be 41% by chiral SFC analysis (OJ-H,

2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 2.5 min, t_R(minor) = 3.3 min.

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° (c = 0.62, MeCN). HRMS (MM) calc'd for

$C_{19}H_{21}N_2O_3$ [M+H]$^+$ 325.1547, found 325.1539.

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

endo-240
(impure)

LiOH
1:1 THF:H$_2$O, 22 °C
(1% yield,
2 steps)

exo-237
43% ee
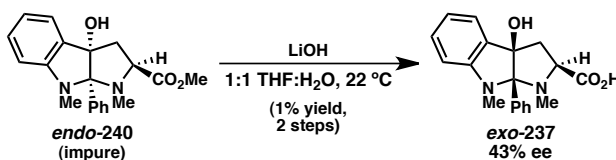
A scintillation vial was charged with the *endo*-3a-hydroxypyrroloindoline methyl

ester (**240**, 61.6 mg, 1.00 equiv), LiOH (109 mg, 4.56 mmol, >25.0 equiv), 1.2 mL THF,

and 1.2 mL H$_2$O. The vial was then sealed and the reaction mixture was stirred at 22 °C

for 17.5 hours, then acidified to pH 7 with 1 M HCl and concentrated. By crude NMR, a

pyrroloindoline was observed, shifts of which did not correspond to *exo*-**237**. The crude

residue was subjected to reverse phase preparative HPLC (0.1:25:75 to 0.01:95:5

AcOH:MeCN: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 CO_2, λ = 235 nm):

t_R(major) = 2.6 min, t_R(minor) = 3.3 min. ^{1}H NMR spectral data was in agreement with

prior characterization.

Preparation of *N*-Cbz-*N*,1-dimethyltryptamine (243).
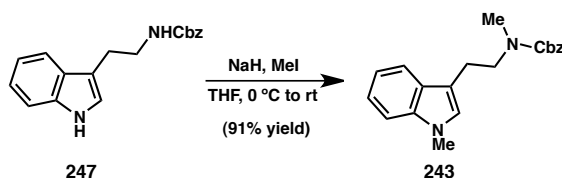
A solution of *N*-Cbz-tryptamine (**247**) (2.43 g, 8.26 mmol, 1.00 equiv) and 90 mL

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 NH_4Cl

and 3 drops Et_3N. After 16.5 hours of vigorous stirring, the mixture was diluted with 20

mL H_2O. The aqueous layer was extracted with 30 mL EtOAc and the combined organic

layers were dried (Na_2SO_4), 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. ^{1}H NMR (500 MHz,

$CDCl_3$, compound exists as a 1.4:1 mixture of rotamers, the major rotamer is designated

by *, minor rotamer designated by §) δ 7.65 (d, *J* = 7.9 Hz, 1H§), 7.45 (d, *J* = 7.9 Hz,

1H*), 7.42–7.26 (m, 6H*, 6H§), 7.25–7.18 (m, 1H*, 1H§), 7.11 (dd, *J* = 7.4, 7.4 Hz, 1H§),

7.02 (dd, *J* = 7.4, 7.4 Hz, 1H*), 6.89 (s, 1H§), 6.79 (s, 1H*), 5.17 (s, 2H§), 5.10 (s, 2H*),

3.73 (s, 3H§), 3.71 (s, 3H*), 3.59 (t, *J* = 7.9 Hz, 2H§), 3.54 (t, *J* = 7.7 Hz, 2H*), 3.01 (t, *J*

= 7.9 Hz, 2H§), 2.96 (t, *J* = 7.8 Hz, 2H*), 2.95 (s, 3H*), 2.92 (s, 3H§).; ^{13}C NMR (125

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).
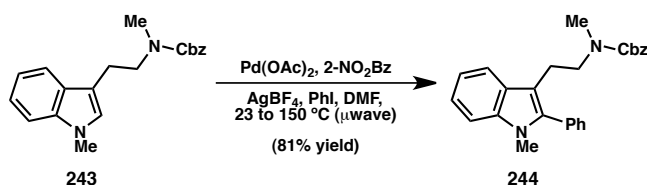
N-Cbz-*N*,1-dimethyl-2-phenyltryptamine (**244**) was prepared according to a procedure adapted from Lavilla and coworkers.[26] Four oven-dried microwave vials were each charged with *N*-Cbz-*N*,1-dimethyltryptamine (**243**, 231 mg, 0.717 mmol, 1.00 equiv), 2-NO$_2$Bz (288 mg, 1.13 mmol, 1.57 equiv), 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[§]).; ^{13}C NMR

(125 MHz, CDCl$_3$; compound exists as a 1.7:1 mixture of rotamers) δ 156.1, 156.0,

138.6, 138.4, 137.1, 136.8, 131.8, 131.7, 130.4, 128.4, 128.14, 128.10, 128.0, 127.84,

127.81, 127.7, 127.5, 121.8, 119.42, 119.37, 119.0, 118.6, 109.7, 109.6, 109.4, 109.3,

67.0, 66.8, 50.5, 49.7, 34.8, 34.6, 30.81, 30.76, 23.5, 23.0; FTIR (NaCl/thin film): 3055,

3030, 2939, 1703, 1699, 1695, 1471, 1403, 1362, 1197, 1138 cm^{-1}; HRMS (MM) calc'd

for C$_{26}$H$_{27}$N$_2$O$_2$ [M+H]$^+$ 399.2067, found 399.2087.

Preparation of *N*,1-dimethyl-2-phenyltryptamine (245).
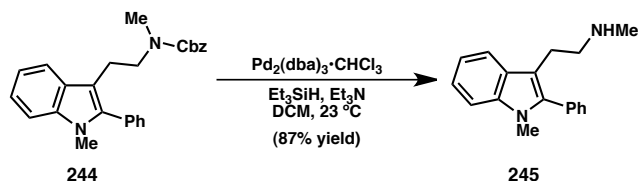
N,1-dimethyl-2-phenyltryptamine (**245**) was prepared by a Cbz deprotection

procedure adapted from Baran and coworkers.[37] A solution of *N*-Cbz-*N*,1-dimethyl-2-

phenyltryptamine (**244**, 574 mg, 1.44 mmol, 1.00 equiv) in 15 mL DCM was prepared in

a flame-dried flask under argon. Et$_3$SiH (9.2 mL, 57.7 mmol, 40.1 equiv) and Et$_3$N (0.4

mL, 2.87 mmol, 2.00 equiv) were then added, followed by Pd$_2$(dba)$_3$•CHCl$_3$ (298 mg,

0.288 mmol, 0.20 equiv). The dark red reaction solution was stirred for 15.5 hours and

the resultant dark brown mixture was filtered through celite with 50 mL EtOAc, washed

(2 x 40 mL saturated aqueous NaHCO$_3$, 2 x 40 mL brine), dried (Na$_2$SO$_4$), filtered, and

concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 8:92 MeOH:DCM) to yield 332 mg (87% yield) of *N*,1-dimethyl-2-phenyltryptamine (**245**) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.53–7.38 (m, 5H), 7.35 (ddd, *J* = 8.2, 0.8, 0.8 Hz, 1H), 7.26 (ddd, *J* = 8.1, 6.9, 1.0 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 3.59 (s, 3H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 1.37 (s, 1H).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.7, 137.0, 131.1, 130.3, 128.8, 128.5, 127.0, 122.0, 119.8, 118.7, 109.46, 107.0, 49.3, 32.4, 30.8, 21.3.; FTIR (NaCl/thin film): 3051, 2934, 2840, 2789, 1468, 1442, 1430, 1364, 1333, 1236, 1131, 1013 cm^{-1}; HRMS (MM) calc'd for C$_{18}$H$_{21}$N$_2$ [M+H]$^+$ 265.1699, found 265.1707.

Preparation of 3a-hydroxy-1,1a-dimethyl-2a-phenylpyrroloindoline (241).
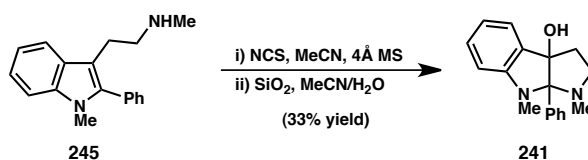
A 15 mL flame-dried flask containing *N*,1-dimethyl-2-phenyltryptamine (**245**, 59.5 mg, 0.225 mmol, 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 1.3 mL MeCN. NCS (recrystallized from toluene, 30.2 mg, 0.225 mmol, 1.00 equiv) was then added as a solution in 2 mL MeCN dropwise and 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. ^{1}H 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).; ^{13}C 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.

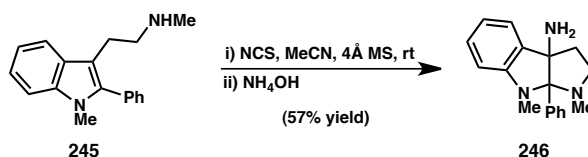**Preparation of 3a-amino-1,1a-dimethyl-2a-phenylpyrroloindoline (246).**

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_2O and extracted with EtOAc (3 x 5 mL). The combined organic

layers were washed with 15 mL brine, dried (Na_2SO_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-phenyltryptamine (248).
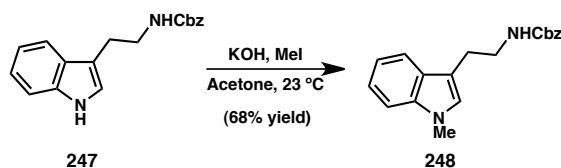
N-Cbz-1-methyltryptamine (**248**) was prepared according to a procedure adapted

from Qing and coworkers.[38] A solution of *N*-Cbz-tryptamine (**247**, 212 mg, 0.721 mmol,

1.00 equiv) in 3 mL wet acetone was charged with KOH (202 mg, 3.60, 4.99 equiv).

After 10 min, MeI (49 μL, 0.787 mmol, 1.09 equiv) was added and the orange reaction

solution was stirred 1 hour at room temperature, followed by addition of more KOH (202 mg, 3.60 mmol, 4.99 equiv) and more MeI (49 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*-Cbz-1-methyltryptamine (**248**). Spectral data are in agreement with the literature.[39]

Preparation of *N*-Cbz-1-methyl-2-phenyltryptamine (249).
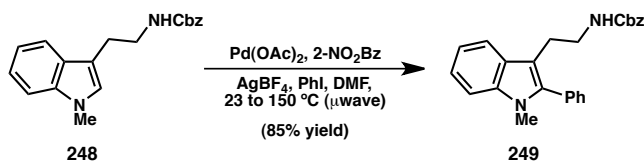
N-Cbz-1-methyl-2-phenyltryptamine (**249**) was prepared according to a procedure adapted from Lavilla and coworkers.[26] An oven-dried microwave vial was charged with *N*-Cbz-1-methyltryptamine (**248**, 134 mg, 0.435 mmol, 1.00 equiv), 2-NO$_2$Bz (147 mg, 0.653 mmol, 1.50 equiv), Pd(OAc)$_2$ (3.3 μg, 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*-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 §) δ 7.67 (d, *J* = 7.9 Hz, 1H*), 7.54 (br s, 1H§), 7.50 – 7.41 (m, 3H*, 3H§), 7.40 – 7.26 (m, 9H*, 9H§), 7.17 (dd, *J* = 7.4 Hz, 1H*), 7.12 (br s, 1H§), 5.04 (s, 2H*, 2H§), 4.73 (t, *J* = 6.8 Hz, 1H*), 4.51 (br s, 1H§), 3.58 (s, 3H*, 3H§), 3.44 (td, *J* = 6.7, 6.7 Hz, 2H*), 3.38 (br s, 1H§), 2.94 (t, *J* = 6.9 Hz, 2H*), 2.90 (br s, 1H§).; ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 5.6:1 mixture of rotamers, only the major rotamer is reported) δ 156.2, 138.8, 137.1, 131.7, 130.6, 128.5, 128.4, 128.2, 128.0, 121.9, 119.5, 118.9, 109.6, 109.4, 66.4, 41.7, 30.8, 25.1.; FTIR (NaCl/thin film): 3413, 3339, 3055, 3030, 2940, 1718, 1701, 1511, 1368, 1361, 1334, 1233, 1132 cm^{-1}; HRMS (MM) calc'd for 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).
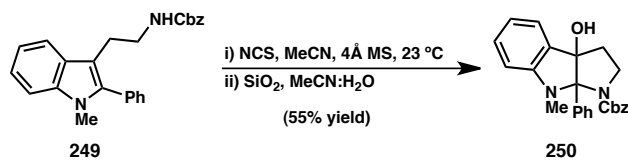
A 5 mL oven-dried flask containing *N*-Cbz-1-methyl-2-phenyltryptamine (**249**, 24.0 mg, 62.5 μmol, 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 0.5 mL MeCN. NCS (recrystallized from toluene, 8.4 mg, 0.225 mmol, 1.00 equiv) was then added as a solution in 1.25 mL MeCN dropwise. After stirring in the dark at room temperature for 6 hours, the light yellow reaction solution was quenched with 5 mL aqueous 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:H_2O) 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. ^{1}H NMR (500 MHz, CDCl$_3$, compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer 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§).; ^{13}C NMR (125 MHz, CDCl$_3$, 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 C$_{25}$H$_{25}$N$_2$O$_3$ [M+H]$^+$401.1860, found 401.1877.

Preparation of 3a-hydroxy-1a-methyl-2a-phenylpyrroloindoline (251).
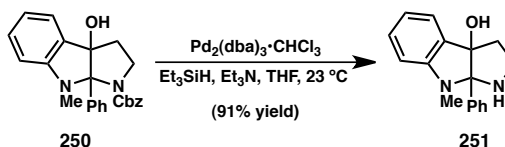
A solution of 3a-hydroxy-1-Cbz-1a-methyl-2a-phenylpyrroloindoline (**250**, 10.1 mg, 25.2 μmol, 1.00 equiv) in 1.0 mL THF was prepared in a flame-dried flask. Et$_3$SiH (0.16 mL, 1.0 mmol, 40 equiv) and Et$_3$N (7.0 μL, 50 μmol, 2.0 equiv) were then added, followed by Pd$_2$(dba)$_3$•CHCl$_3$ (5.0 mg, 4.8 μmol, 0.19 equiv). The dark red reaction solution was stirred for 18.5 hours at room temperature, then filtered through celite with THF, combined with an equal volume of saturated aqueous NaHCO$_3$, and stirred at room temperature for 5 hours. The aqueous layer was then extracted with EtOAc (3 x 15 mL) and combined organic layers were dried (Na$_2$SO$_4$), 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. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50 – 7.27 (m, 5H), 7.25 (ddd, *J* = 7.2, 1.4, 0.5 Hz, 1H), 7.20 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.68 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 3.25 (ddd, *J* = 9.4, 5.1, 3.8 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.63 (s, 3H), 2.32 – 2.25 (m, 2H), 1.03 – 0.89 (br m, 1H), 0.65 – 0.51 (br m, 1H).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.2, 138.2, 130.7, 130.1, 128.6, 128.2, 127.4, 123.9, 117.1, 104.3, 95.2, 89.6, 43.3, 41.9, 28.5.; FTIR (NaCl/thin film): 3340, 3051, 2931, 2874, 1609, 1495, 1446, 1375, 1307, 1121, 1062 cm^{-1}; HRMS (MM) calc'd for C$_{17}$H$_{19}$N$_2$O [M+H]$^+$ 267.1492, found 267.1502.

Preparation of (*S*)-N_α-Cbz-tryptophan (252).
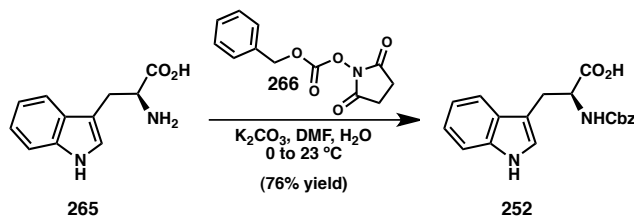
(*S*)-N_α-Cbz-tryptophan (**252**) was prepared by a procedure adapted from Lapatsanis and coworkers.[40] A solution of (*S*)-tryptophan (**265**, 1.00 g, 4.90 mmol, 1.11 equiv) and K_2CO_3 (1.35 g, 9.77 mmol, 2.22 equiv) in 25 mL H_2O was cooled to 0 °C in an ice bath. *N*-(Benzyloxycarbonyloxy)succinimide (**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_2O and EtOAc (2 x 35 mL). The aqueous layer was then cooled to 0 °C, acifidied 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_2SO_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_2SO_4), filtered, and concentrated to give 1.136 g (76% yield) of (*S*)-N_α-Cbz-tryptophan (**252**) as a white solid. ^{1}H NMR spectral data were in agreement with the literature.[41]

Preparation of (*S*)-N_α-Cbz-N_α,1-dimethyltryptophan (253).
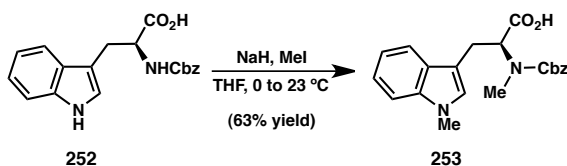
A solution of (*S*)-N_α-Cbz-tryptophan (**252**, 875 mg, 2.59 mmol, 1.00 equiv) in 5 mL THF was cooled to 0 °C in an ice bath. NaH (60% dispersion in oil, 516 mg, 12.9 mmol,

4.98 equiv) was then added, followed by MeI (0.96 mL, 15.4 mmol, 5.96 equiv). The yellow reaction mixture was allowed to warm to room temperature and stirred for 29 hours, then diluted with 10 mL H_2O 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 (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (5:95 to 50:50 EtOAc:hexanes with 2–4% AcOH) to yield 600 mg (63% yield) of (S)-N_α-Cbz-N_α,1-dimethyltryptophan (**253**) as a yellow-brown foam. ^{1}H NMR (500 MHz, CDCl$_3$, compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer 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*).; ^{13}C NMR (125 MHz, CDCl$_3$; 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}; $[\alpha]_D^{25}$ = –40.6° (c = 0.68, CHCl$_3$). HRMS (MM) calc'd for $C_{21}H_{23}N_2O_4$ [M+H]$^+$ 367.1652, found 367.1667.

Preparation of (S)-N_α-Cbz-N_α,1-dimethyl-2-phenyltryptophan (254).
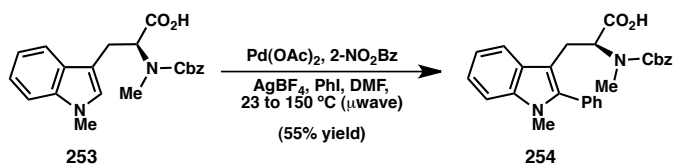
(S)-N_α-Cbz-N_α,1-dimethyl-2-phenyltryptophan (**254**) was prepared according to a procedure adapted from Lavilla and coworkers.[26] Two oven-dried microwave vials were each charged with 2-NO$_2$Bz (255 mg, 1.13 mmol, 1.50 equiv), Pd(OAc)$_2$ (6.25 µg, 37.4 µmol, 0.050 equiv), AgBF$_4$ (240 mg, 1.23 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_α-Cbz-N_α,1-dimethyltryptophan (**253**, 276 mg, 0.754 mmol, 1.00 equiv) in 4 mL DMF was then added to each vial. The microwave vials were sealed under argon and the reaction mixtures were stirred at room temperature for 30 minutes, then heated in the microwave for 4 min at 150 °C. The two reaction mixtures were then combined and filtered through celite with 15 mL EtOAc, washed (2 x 20 mL saturated aqueous 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_α-Cbz-N_α,1-dimethyl-2-phenyltryptophan (**254**) as a light yellow foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in 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§), 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§).; ^{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}; [α]$_D^{25}$ = –133.3° (*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).
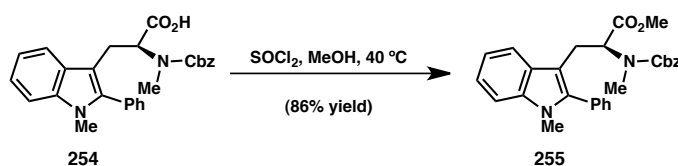
A solution of (*S*)-*N*$_\alpha$-Cbz-*N*$_\alpha$,1-dimethyl-2-phenyltryptophan (**254**, 104 mg, 0.235

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 °C. After stirring at 40 °C 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 §) 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*).; ^{13}C 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, 127.68, 127.6, 127.54, 127.46, 127.2, 121.8, 121.7, 119.49, 119.47, 118.6, 118.4,

109.5, 109.3, 108.3, 108.0, 66.92, 66.86, 60.5, 59.9, 52.03, 51.98, 32.4, 32.3, 30.70,

30.67, 24.5, 24.1.; FTIR (NaCl/thin film): 3033, 2946, 1743, 1740, 1734, 1704, 1700,

1696, 1468, 1399, 1363, 1314, 1270, 1214, 1139 cm^{-1}; $[\alpha]_D^{25}$ = –82.8° (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).
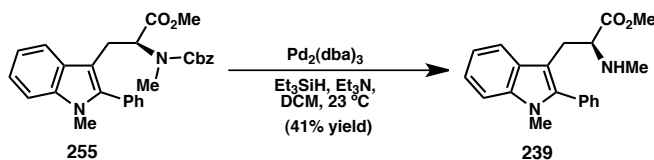
A solution of (*S*)-*N*$_\alpha$-Cbz-*N*$_\alpha$,1-dimethyl-2-phenyltryptophan methyl ester (**255**, 91.0

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 NH_4OH:EtOAc:hexanes, then 4:5:91 NH_4OH:MeOH:DCM) to yield 26.4 mg (41% yield) of (*S*)-N_α,1-dimethyl-2-phenyltryptophan methyl ester (**239**) as a colorless oil. $[\alpha]_D^{25}$ = +16.1° (*c* = 0.19, CHCl$_3$). ^{1}H NMR spectral data was in agreement with prior characterization.

Preparation of 3a-hydroxypyrroloindoline methyl ester 240.
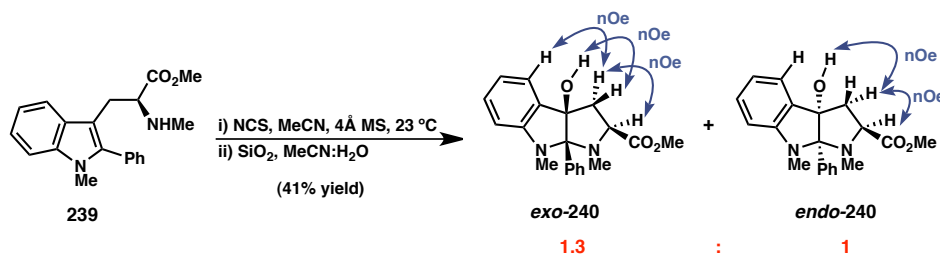
A flame-dried flask containing (*S*)-N_α,1-dimethyl-2-phenyltryptophan methyl ester (**239**, 24.1 mg, 0.748 mmol, 1.00 equiv) was charged with flame-dried 4Å molecular sieves and 1 mL MeCN. NCS (recrystallized from toluene, 10.0 mg, 0.746 mmol, 1.00 equiv) was then added as a solution in 1 mL MeCN dropwise. 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 $Na_2S_2O_3$ (10 wt %) and the organic layer was washed with brine (2 x 3 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was combined with 2 mL MeCN, 2 mL H_2O and 2 mL SiO_2, then stirred open to air at room temperature for 30 minutes. The mixture was then filtered with 20 mL EtOAc and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic layers were concentrated and purified by silica gel column chromatography (10:90 to 15:85 EtOAc:hexanes) to yield 10.3 mg (41% yield) of 3a-hydroxypyrroloindoline methyl ester **240** as a yellow oil

(note: by then exchanging the column solvent for 2:98 MeOH:DCM, 6.0 mg (25%) of the starting material, (S)-N_α,1-dimethyl-2-phenyltryptophan methyl ester (**239**), could be recovered). 3a-hydroxypyrroloindoline methyl ester **240** was isolated as a 1.3:1 mixture of diastereomers favoring the *exo* diastereomer as determined by ^{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 *endo* diastereomer in the subsequent saponification step generating *exo*-3a-hydroxypyrroloindoline carboxylic acid **237** (*vide infra*). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47 – 7.28 (m, 4H^{exo}, 4H^{endo}), 7.26 – 7.08 (m, 3H^{exo}, 3H^{endo}), 6.73 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H^{exo}), 6.64 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H^{endo}), 6.46 (dd, J = 8.3, 0.8 Hz, 1H^{exo}), 6.43 (d, J = 7.9 Hz, 1H^{endo}), 3.97 (d, J = 8.3 Hz, 1H^{endo}), 3.76 (s, 3H^{exo}), 3.42 (dd, J = 11.2, 5.4 Hz, 1H^{exo}), 3.24 (s, 3H^{endo}), 2.91 (s, 3H^{endo}), 2.80 (s, 3H^{exo}), 2.79 (s, 3H^{endo}), 2.73 (dd, J = 12.4, 1.0 Hz, 1H^{endo}), 2.59 (dd, J = 11.9, 5.4 Hz, 1H^{exo}), 2.53 (dd, J = 12.3, 8.5 Hz, 1H^{endo}), 2.41 (s, 3H^{exo}), 2.31 (dd, J = 11.6, 11.6 Hz, 1H^{exo}), 1.43 (s, 1H^{exo}), 1.31 (s, 1H^{endo}).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.9^{endo}, 173.3^{exo}, 151.7^{exo}, 151.5^{endo}, 137.6^{endo}, 136.9^{exo}, 130.6^{endo}, 130.3^{exo}, 129.5^{exo}, 128.8^{endo,exo}, 128.5^{endo}, 128.4^{exo}, 128.2^{endo}, 124.3^{endo}, 124.0^{exo}, 117.2^{exo}, 116.6^{endo}, 104.9^{endo}, 104.6^{exo}, 98.2^{exo}, 95.9^{endo}, 88.9^{endo}, 88.0^{exo}, 64.2^{endo}, 63.4^{exo}, 52.0^{exo}, 51.2^{endo}, 43.7^{exo}, 41.3^{endo}, 34.9^{exo}, 34.8^{endo}, 33.9^{exo}, 31.6^{endo}.; FTIR (NaCl/thin film): 3467, 2920, 2850, 1750, 1734, 1609, 1494, 1447, 1375, 1311, 1202, 1101 cm^{-1}; $[\alpha]_D^{25}$ = +33.2° (c = 0.55, CHCl$_3$). HRMS (MM) calc'd for C$_{20}$H$_{23}$N$_2$O$_3$ [M+H]$^+$ 339.1703, found 339.1715.

Preparation of *exo*-hydroxypyrroloindoline carboxylic acid 237.
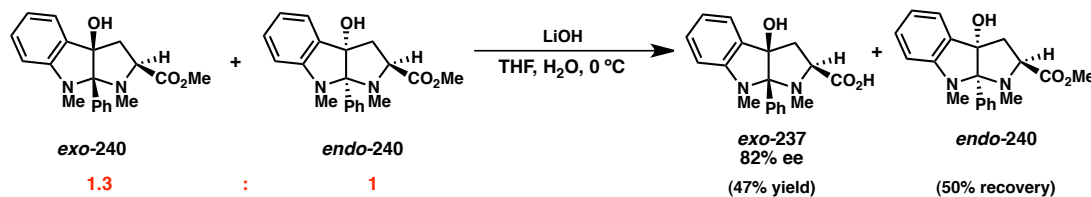
A solution of the 1.3:1 mixture of hydroxypyrroloindoline methyl ester **240** diastereomers (5.5 mg, 16 μmol, 1.0 equiv) in 0.5 mL THF was cooled to 0 ºC in an ice bath. LiOH (3.9 mg, 0.16 mmol, 10 equiv) was then added as a solution in 0.5 mL nanopure H_2O. After stirring 2.5 hours at 0 ºC, the reaction was quenched with 3 drops 3 M HCl, diluted with 3 mL H_2O, and extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with 10 mL brine, dried (Na_2SO_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 *exo*-**240**) of *exo*-hydroxypyrroloindoline carboxylic acid **237** as a yellow oil and 1.2 mg (50% recovery) of *endo*-hydroxypyrroloindoline methyl ester **240**. The enantiomeric excess of *exo*-**237** was determined to be 82% by chiral SFC analysis (OJ-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 2.4 min t_R(minor) = 3.3 min. $[\alpha]_D^{25}$ (*exo*-**237**) = –99.0º (*c* = 0.14, MeCN). ^1H NMR spectral data for *exo*-**237** was in agreement with prior characterization and ^1H NMR data was further acquired in $CDCl_3$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.26 (m, 7H), 6.77 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H), 6.50 (ddd, *J* = 7.6, 0.8, 0.8 Hz, 1H), 3.44 (dd, *J* = 10.9, 6.0 Hz, 1H), 2.80 (s, 3H), 2.70 (dd, *J* =12.4, 6.0 Hz, 1H), 2.48 (s, 3H), 2.34 (dd, *J* = 12.4, 10.9 Hz, 1H), 1.51 (br s, 1H).

4.7.4 SFC Traces

Bromoindolenine 219: 1:1 mixture of diastereomers, racemic

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.750	MM	0.1528	570.55682	62.21929	26.3084
2	4.123	MM	0.1267	568.65100	74.80566	26.2205
3	4.544	MM	0.2530	526.11841	34.66383	24.2593
4	5.953	MM	0.1862	503.40063	45.06438	23.2118
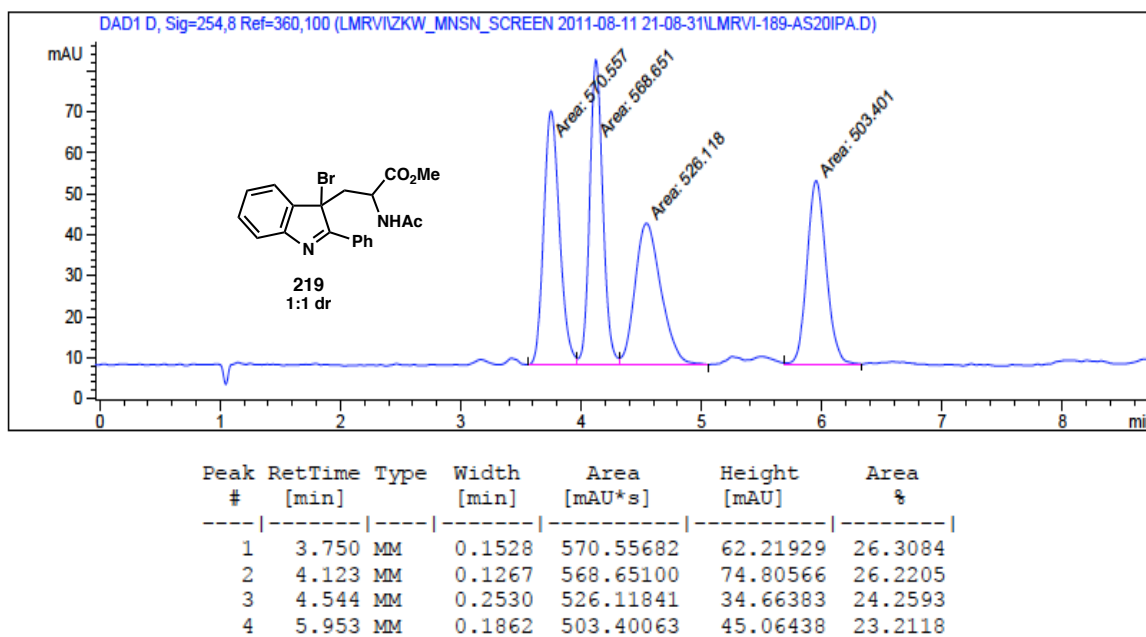
Bromoindolenine 219: 1:1 mixture of diastereomers, enantioenriched, 92:90% ee

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.762	BV	0.1436	1915.73315	207.78340	49.2377
2	4.143	VV	0.1222	79.59740	9.85449	2.0458
3	4.557	VB	0.2312	1803.98438	120.14987	46.3656
4	5.995	MM	0.2044	91.46992	7.45990	2.3509

***Endo*-228**: racemic

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.817	MM	0.2330	1967.76941	140.72768	50.1610
2	7.506	MM	0.3827	1955.13940	85.15020	49.8390
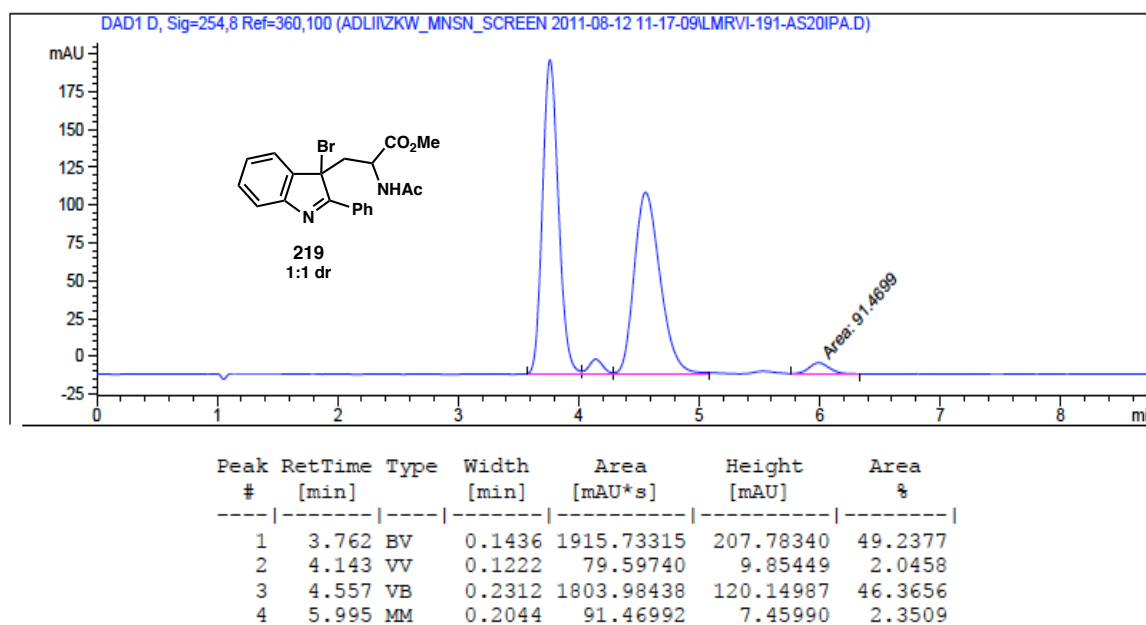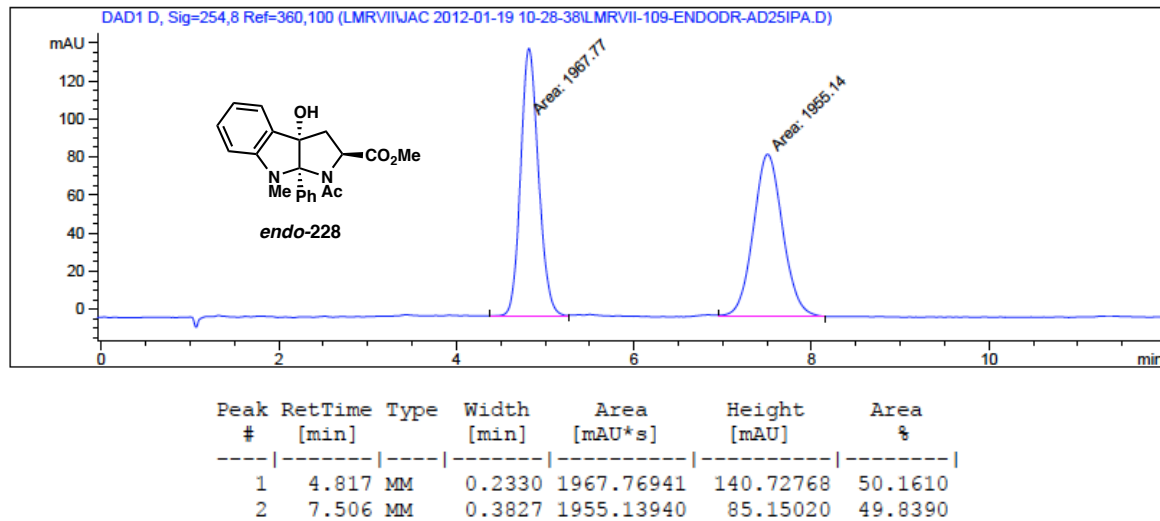
***Endo*-228**: enantioenriched, 84% ee
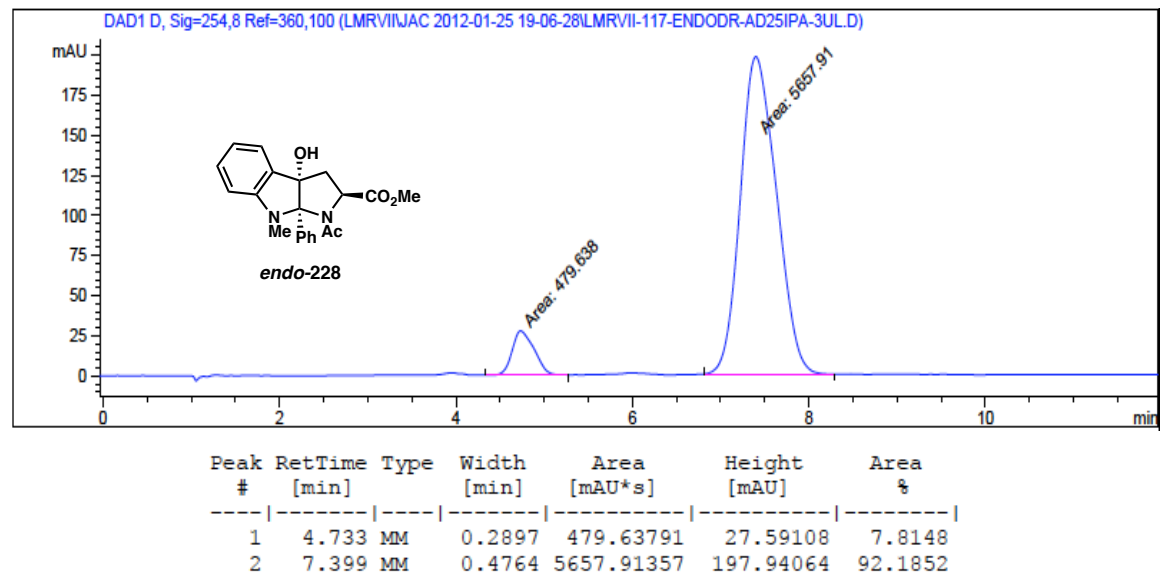
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.733	MM	0.2897	479.63791	27.59108	7.8148
2	7.399	MM	0.4764	5657.91357	197.94064	92.1852

Exo-**228**: racemic

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.404	MM	0.1639	1983.83020	201.70671	49.2726
2	6.589	MM	0.2580	2042.40759	131.91788	50.7274

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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.042	MM	0.2550	371.15012	24.25386	7.2914
2	6.208	MM	0.4046	4719.09912	194.37576	92.7086
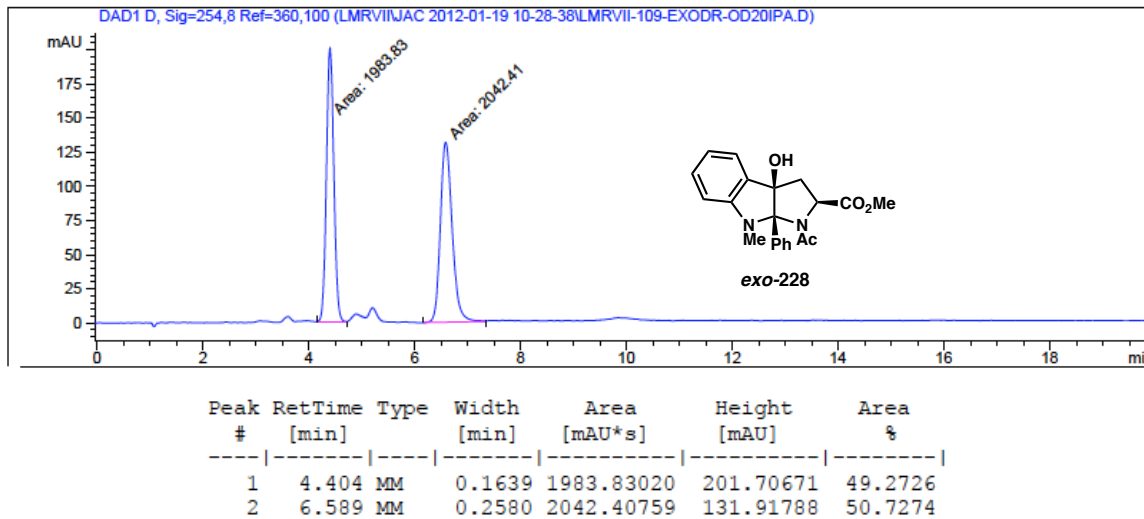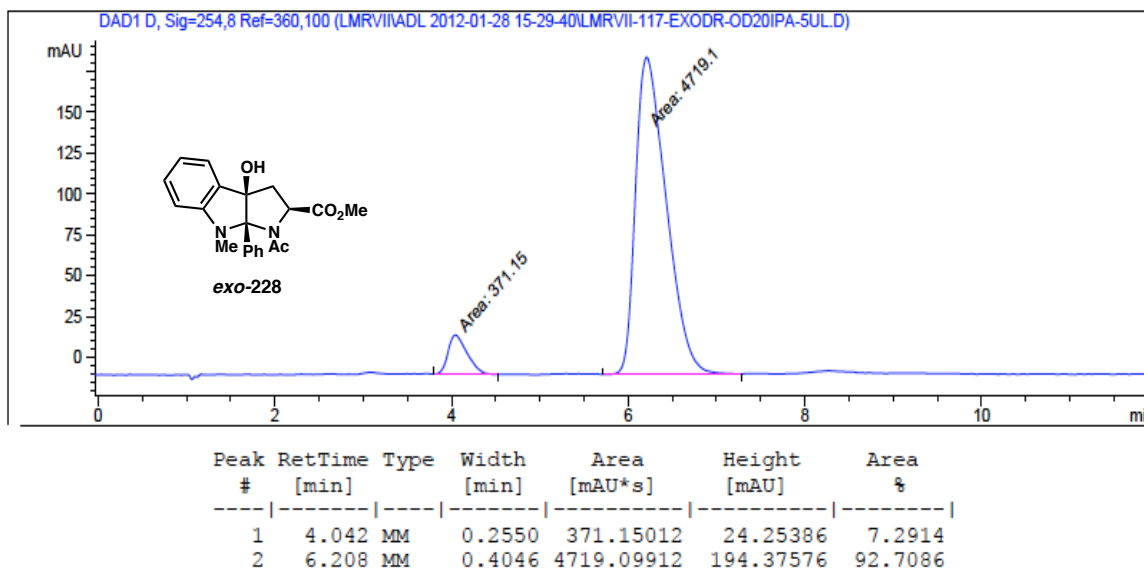
(*S*)-*N*$_\alpha$-acetyl-1-methyl-2-phenyltryptophan methyl ester 138e (scale-up procedure): 84% ee


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Peak  RetTime  Type   Width     Area       Height     Area
  #    [min]          [min]    [mAU*s]     [mAU]        %
----|--------|----|-------|----------|----------|--------|
  1    3.900   MM   0.2247  321.04446   23.81178   8.0663
  2    4.694   MM   0.2583 3659.00415  236.10217  91.9337
```
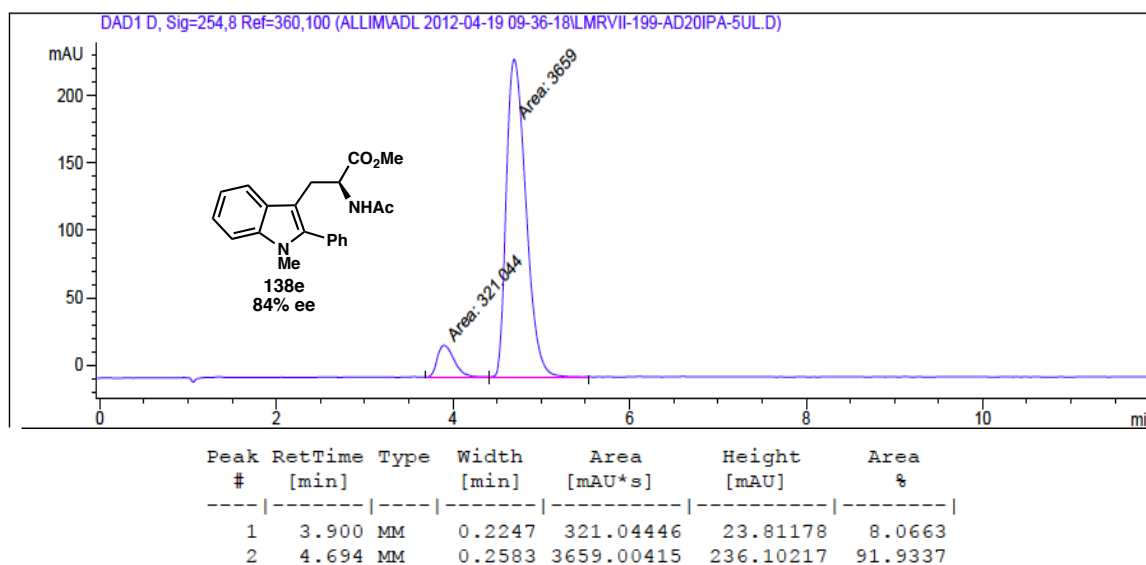
(*R/S*)-*N*_α-Acetyl-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (238): racemic

DAD1 D, Sig=254,8 Ref=360,100 (LMRVII\LMR-5-01-2012 2012-05-01 10-04-48\LMRVII-213-OJ6IPA-RAC.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.065	MM	0.3994	1557.97253	65.02109	49.6667
2	12.474	MM	0.4871	1578.88562	54.01971	50.3333

(*S*)-*N*_α-Acetyl-*N*_α,1-dimethyl-2-phenyltryptophan methyl ester (238): 46% ee

DAD1 D, Sig=254,8 Ref=360,100 (LMRVII\LMR-5-01-2012 2012-05-01 10-04-48\LMRVII-205-OJ6IPA.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.035	MM	0.4099	1519.95898	61.80185	72.8614
2	12.461	MM	0.5123	566.13684	18.41711	27.1386
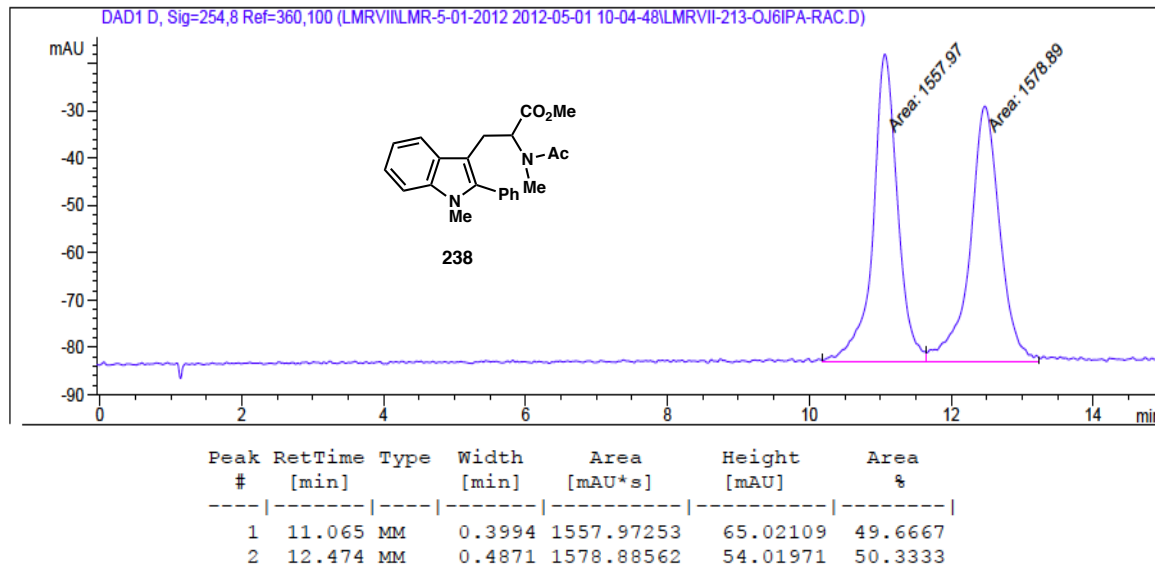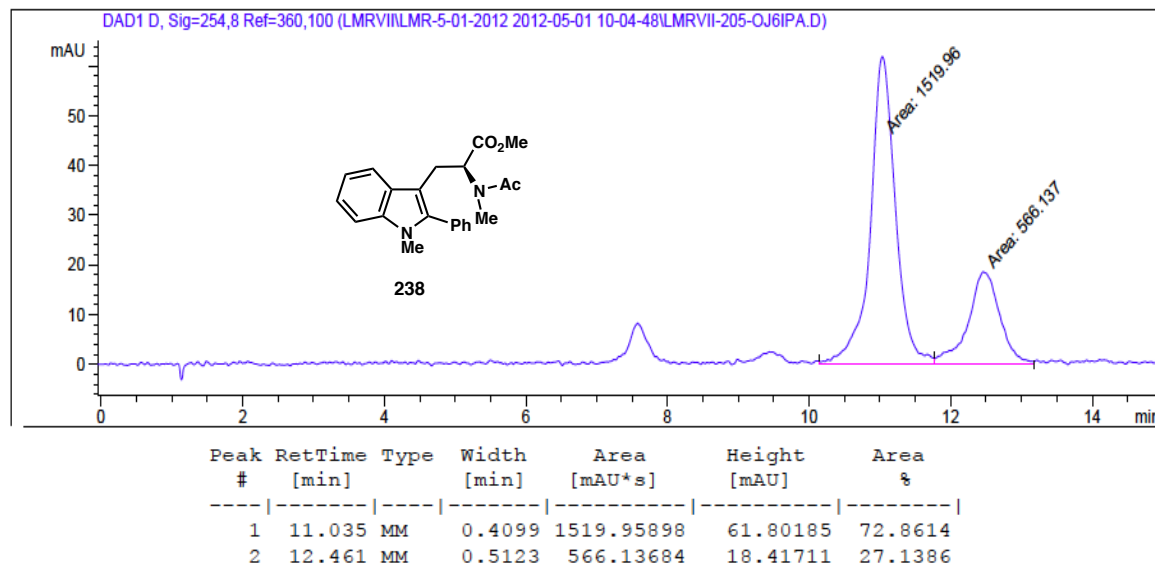
(*R/S*)- N_α,1-Dimethyl-2-phenyltryptophan methyl ester (239): racemic

DAD1 D, Sig=254,8 Ref=360,100 (LMRVII\ADL 2012-05-03 16-22-01\LMRVII-217-PRODUCT-RAC-OB8IPA-5UL.D)

Area: 1033.68
Area: 1027.66

239

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.728	MM	0.3870	1033.67725	44.52034	50.1460
2	7.053	MM	0.4779	1027.65967	35.83988	49.8540

(*S*)-N_α,1-Dimethyl-2-phenyltryptophan methyl ester (239): 45% ee

DAD1 D, Sig=254,8 Ref=360,100 (LMRVII\ADL 2012-05-03 16-22-01\LMRVII-215-PRODUCT-OB8IPA-7UL.D)

Area: 2388.91
Area: 900.324

239

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.666	MM	0.3902	2388.91162	102.03849	72.6282
2	7.040	MM	0.5156	900.32422	29.10431	27.3718

(*S*)-*N*$_\alpha$-Acetyl-*N*$_\alpha$,1-dimethyl-2-phenyltryptophan methyl ester (238, recovered starting material): 45% ee

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.107	MM	0.4226	1806.04883	71.22895	72.3788
2	12.581	MM	0.5280	689.22607	21.75593	27.6212
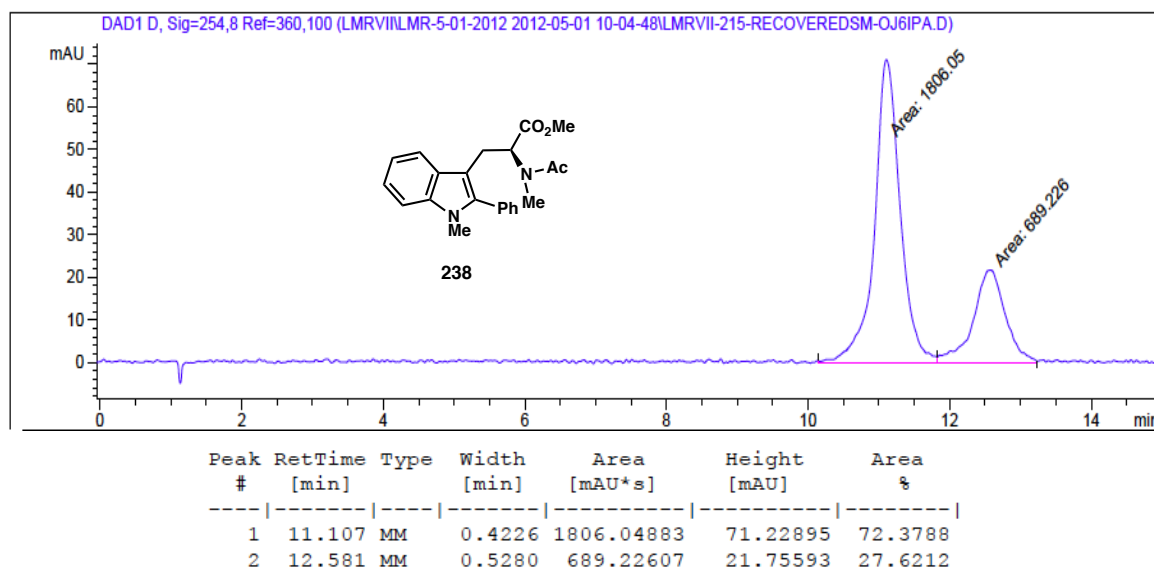
***Exo*-hydroxypyrroloindoline carboxylic acid 237**: racemic

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.395	MM	0.1565	1843.43054	196.32867	49.4502
2	3.045	MM	0.1855	1884.41943	169.28200	50.5498

‘
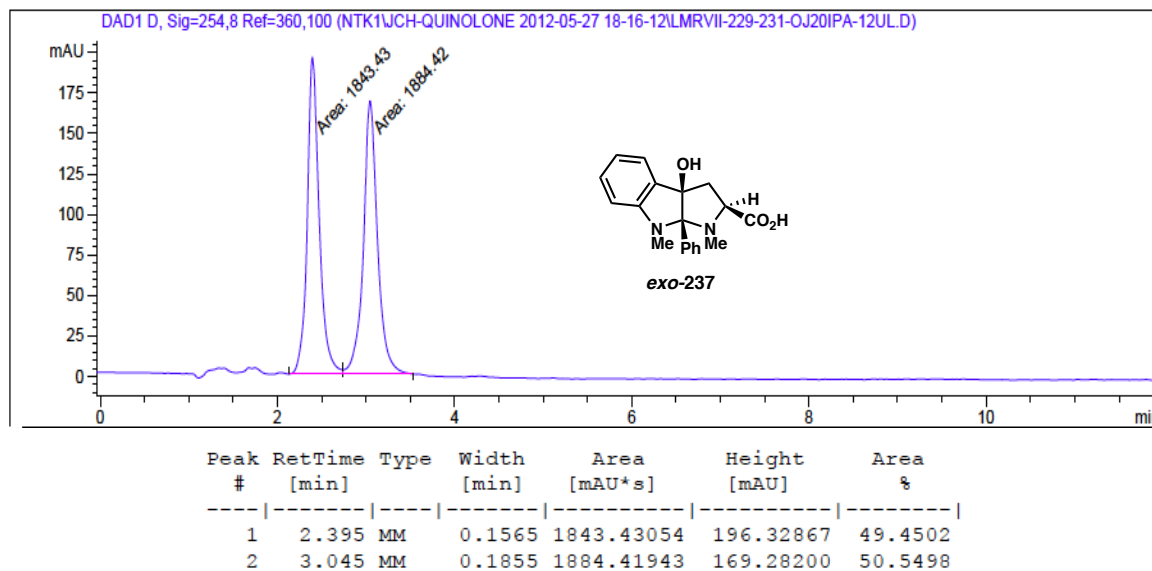
***Exo*-hydroxypyrroloindoline carboxylic acid 237**: 41% ee (first generation synthesis)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.543	MM	0.1790	1326.59863	123.53419	70.3544
2	3.272	MM	0.1786	558.99646	52.15826	29.6456
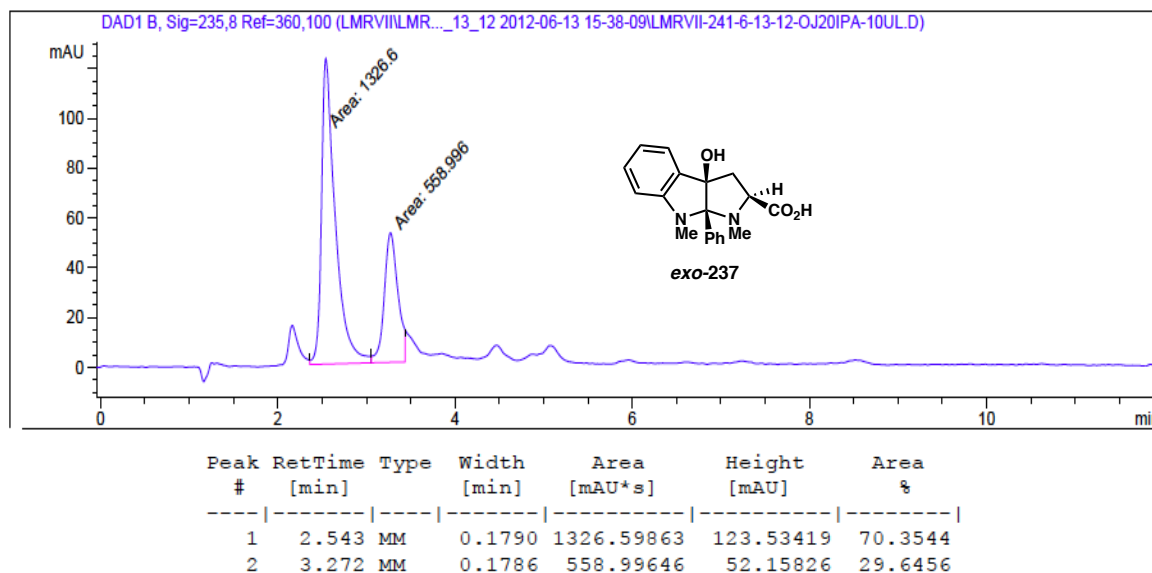
***Exo*-hydroxypyrroloindoline carboxylic acid 237**: 43% ee (from *endo*-**240**)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.573	MM	0.1603	681.01862	70.82561	71.2651
2	3.286	MM	0.2003	274.59406	22.85131	28.7349
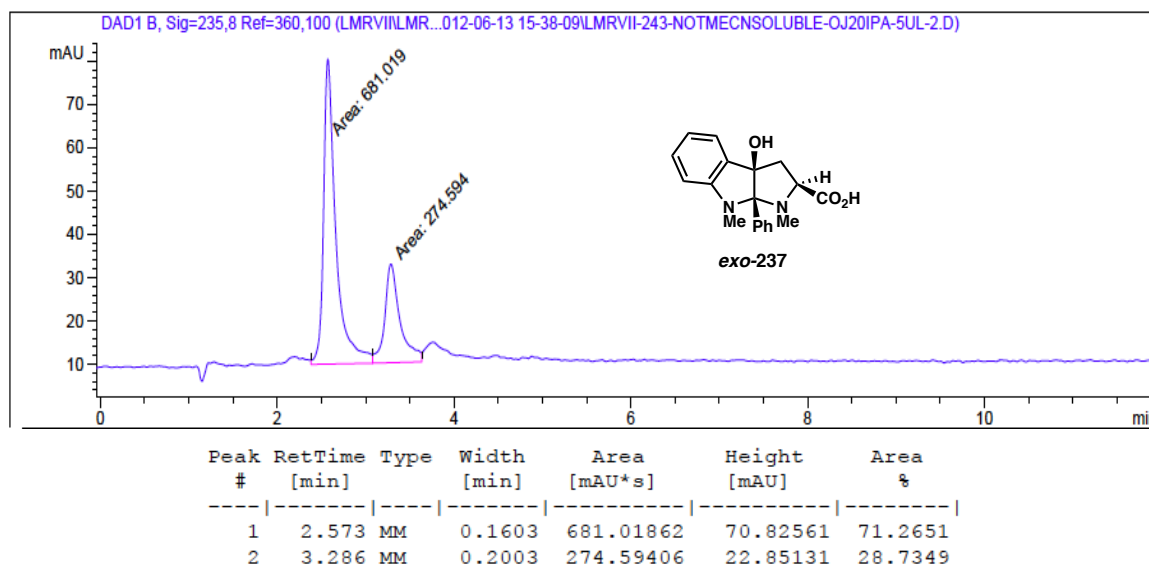
(*R/S*)-*N*$_\alpha$-Cbz-*N*$_\alpha$,1-dimethyl-2-phenyltryptophan (254): racemic
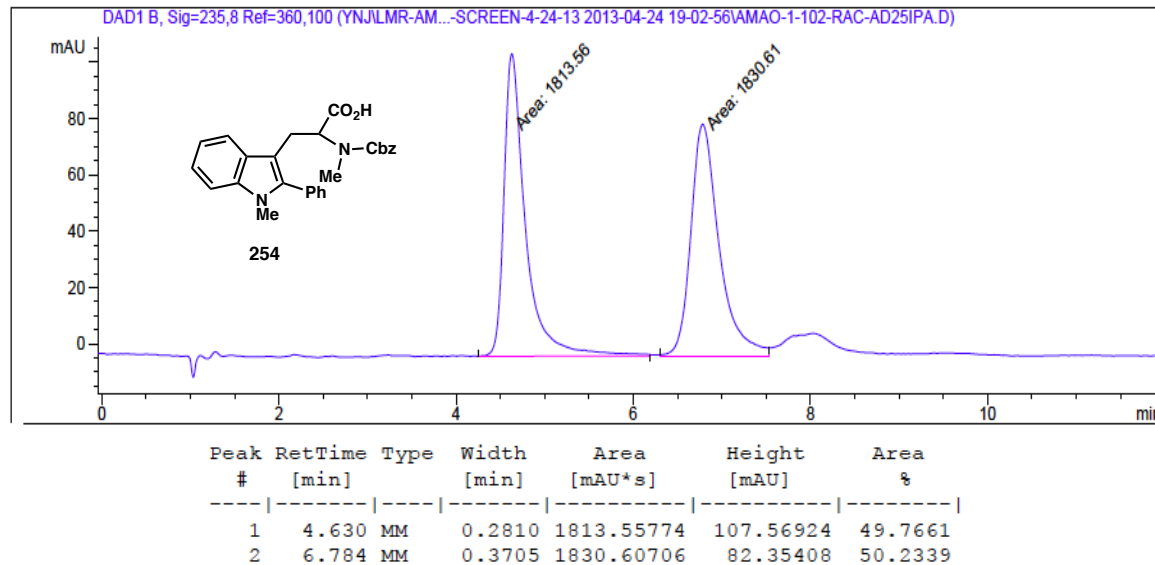
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.630	MM	0.2810	1813.55774	107.56924	49.7661
2	6.784	MM	0.3705	1830.60706	82.35408	50.2339

(*S*)-*N*$_\alpha$-Cbz-*N*$_\alpha$,1-dimethyl-2-phenyltryptophan (254): 94% ee

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.641	MM	0.2839	3464.75146	203.37851	97.2334
2	7.230	MM	0.3951	98.58492	4.15814	2.7666
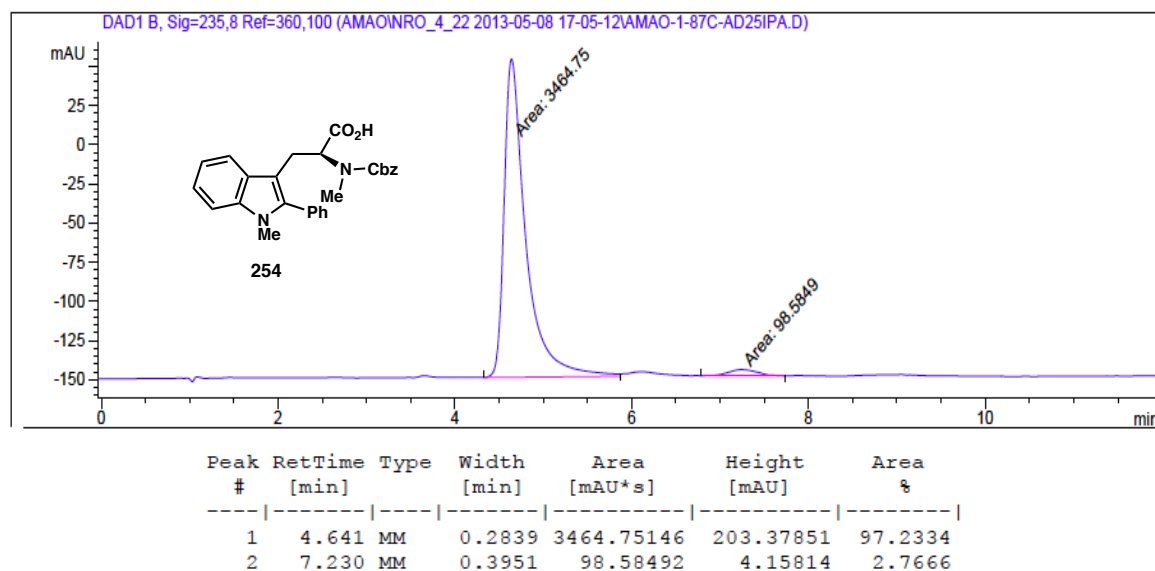
***Exo*-hydroxypyrroloindoline carboxylic acid 237**: 82% ee (2^{nd} generation synthesis)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.396	MM	0.2082	2233.30933	178.79591	91.0373
2	3.263	MM	0.3417	219.87015	10.72459	8.9627
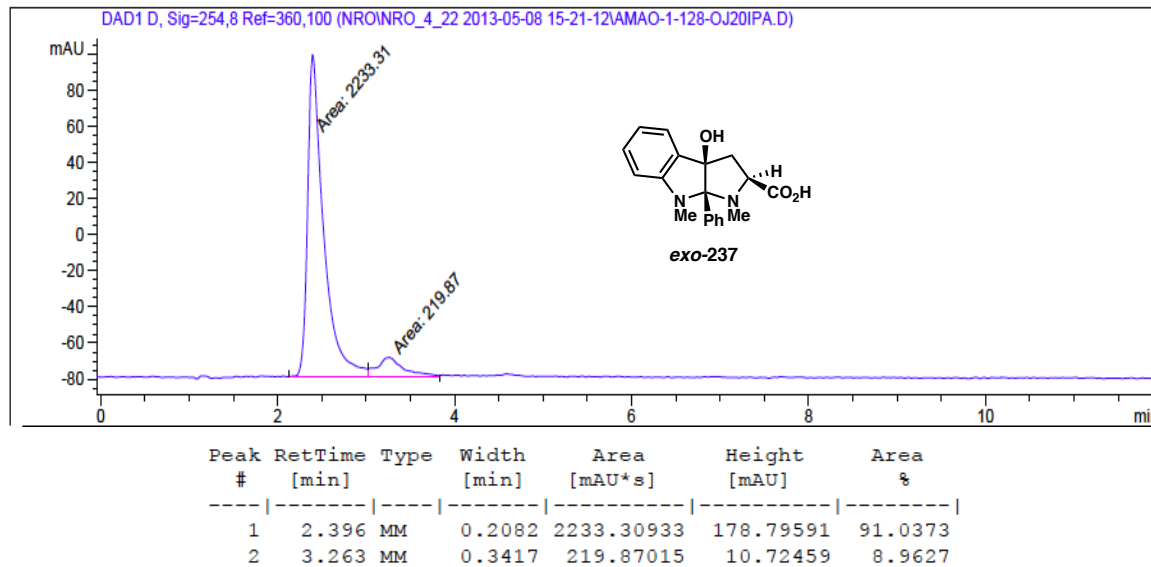
4.8 **NOTES AND REFERENCES**

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