

Chapter 2

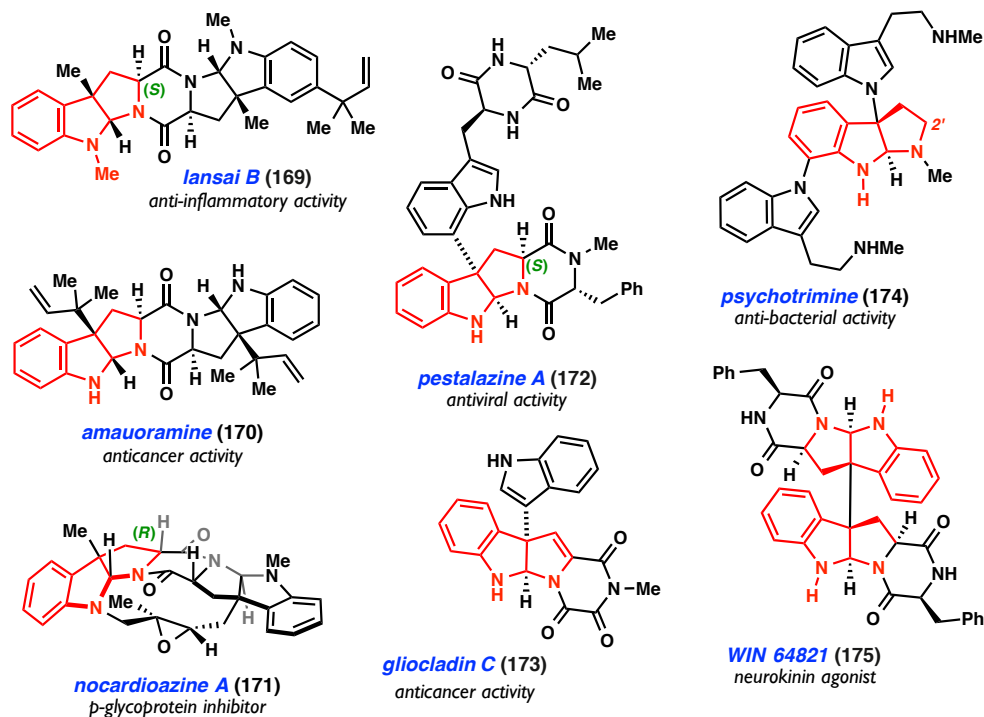
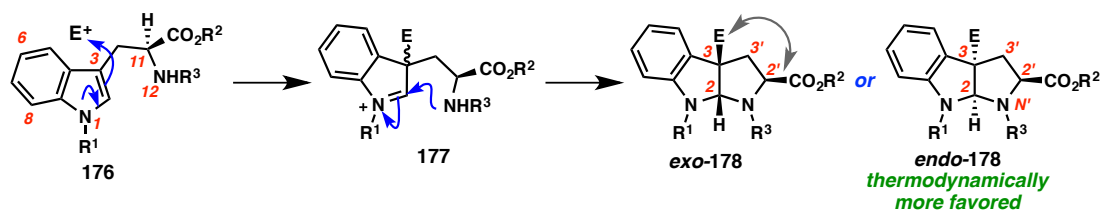
Direct Application of Enantioselective (3 + 2) Formal Cycloaddition: Concise Enantioselective Total Synthesis of (–)-Lansai B[†]

2.1 INTRODUCTION

Pyrroloindoline structure (highlighted in red, Figure 2.1) is found in a large number of natural products,¹ which possess broad spectra of pharmaceutical properties including anti-cancer², anti-bacterial activities³. Biosynthetically, pyrroloindolines are derived from tryptophan amino acid – one of the 23 proteinogenic ("protein-building") amino acids, which explains the prevalence of pyrroloindoline motif in nature.

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

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Figure 2.1. Representative pyrroloindoline-containing natural products**Scheme 2.1.** Biosynthetic pathway of pyrroloindoline synthesis

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

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

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

Besides above-mentioned pyrroloindolines, there is another important subfamily of pyrroloindoline natural products lacking C2' substituent (for example, psychotrimine **174**, Figure 2.1), which have inspired numerous enantioselective methodologies to access those alkaloids⁶ and will not be discussed here.

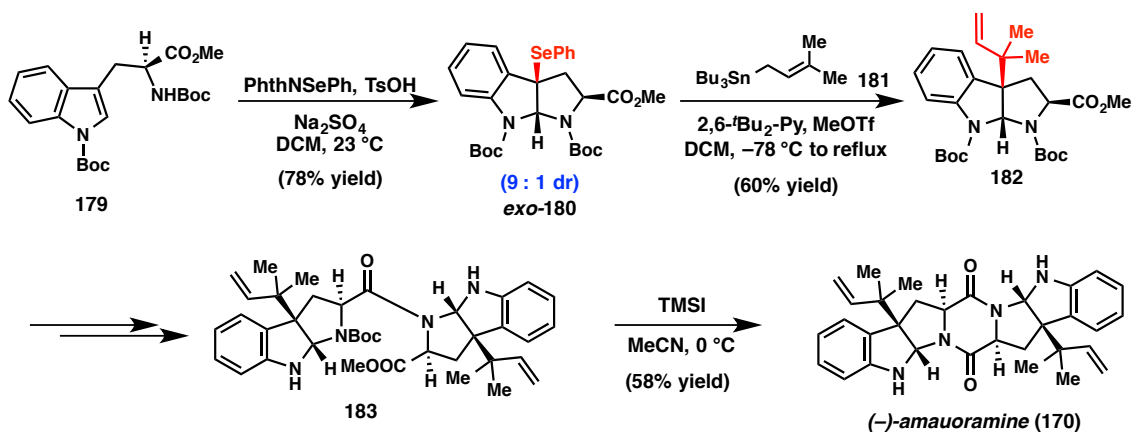
2.1.1 Cyclization of Tryptophans Accessing C3-Substituted Pyrroloindoline Alkaloids via Transient Functional Groups

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

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

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

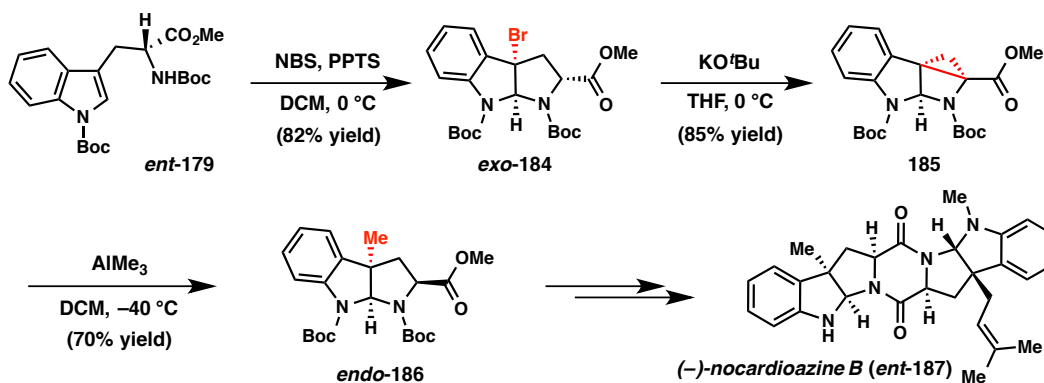
Scheme 2.2. Total synthesis of (–)-amauoramine by Danishefsky



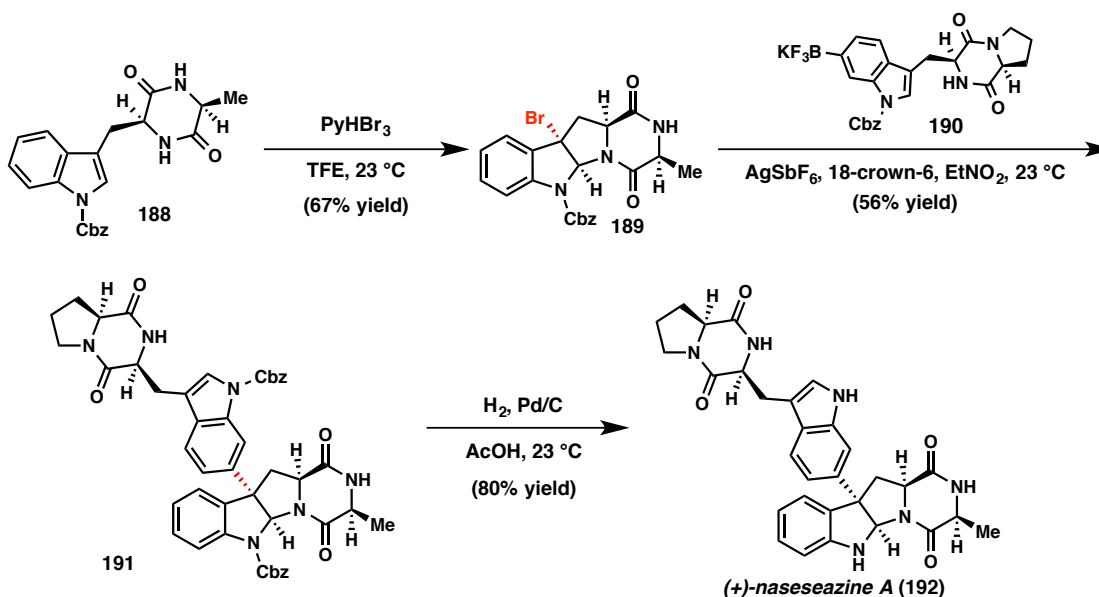
De Lera and coworkers rationalized the *exo*-selectivity observed by Danishefsky by going through an azetidine intermediate (not shown) where *exo*-selective process has a significantly lower activation energy barrier.⁸ They were also able to extend this reactivity to C3-bromination using *N*-bromosuccinimide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

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

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

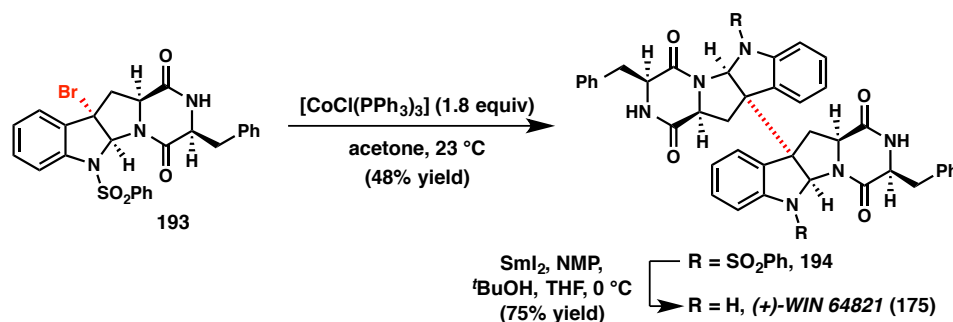


Scheme 2.4. Total synthesis of (+)-nasezeazine A by Movassaghi



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

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

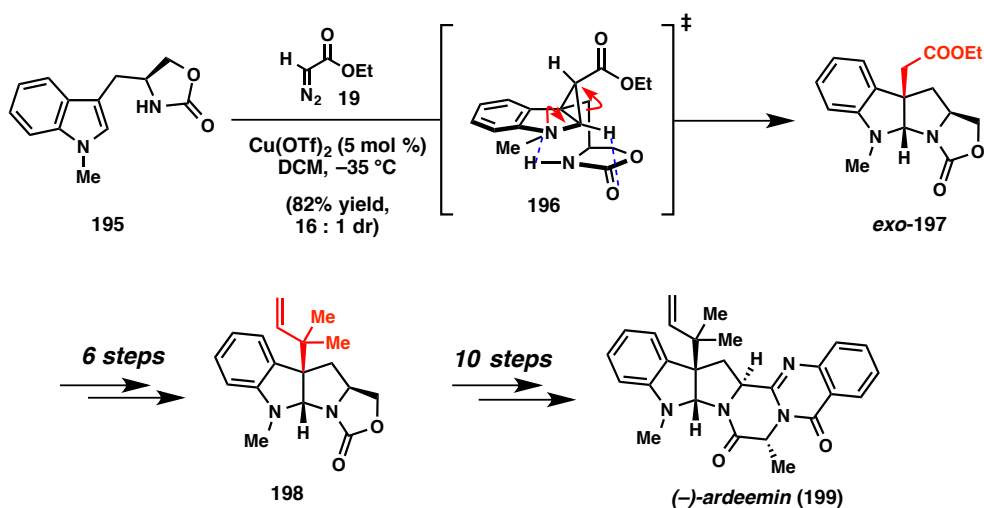


Alternatively, instead of forming a cation at the C3 position via halide abstraction, Movassaghi and coworkers were able to generate a C3 radical by treating bromopyrroloindoline **193** with reducing reagent tris(triphenylphosphine)cobalt chloride (Scheme 2.5).¹² The resulting radical intermediate readily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

2.1.2 Direct Alkylation/Cyclization Strategies of Tryptophans

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

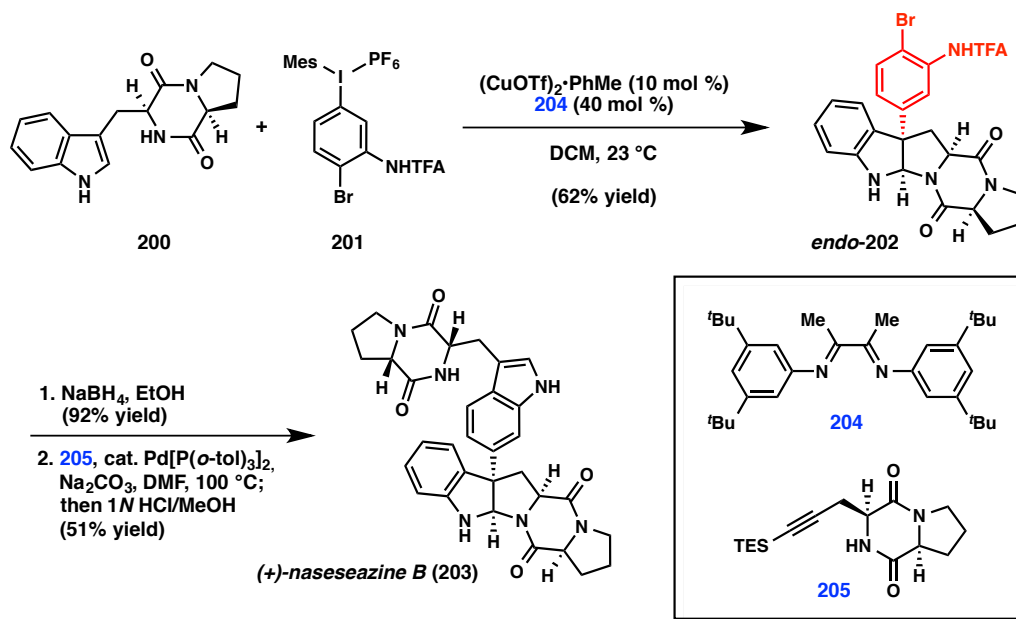
Scheme 2.6. Total synthesis of (–)-ardeemin by Qin



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

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

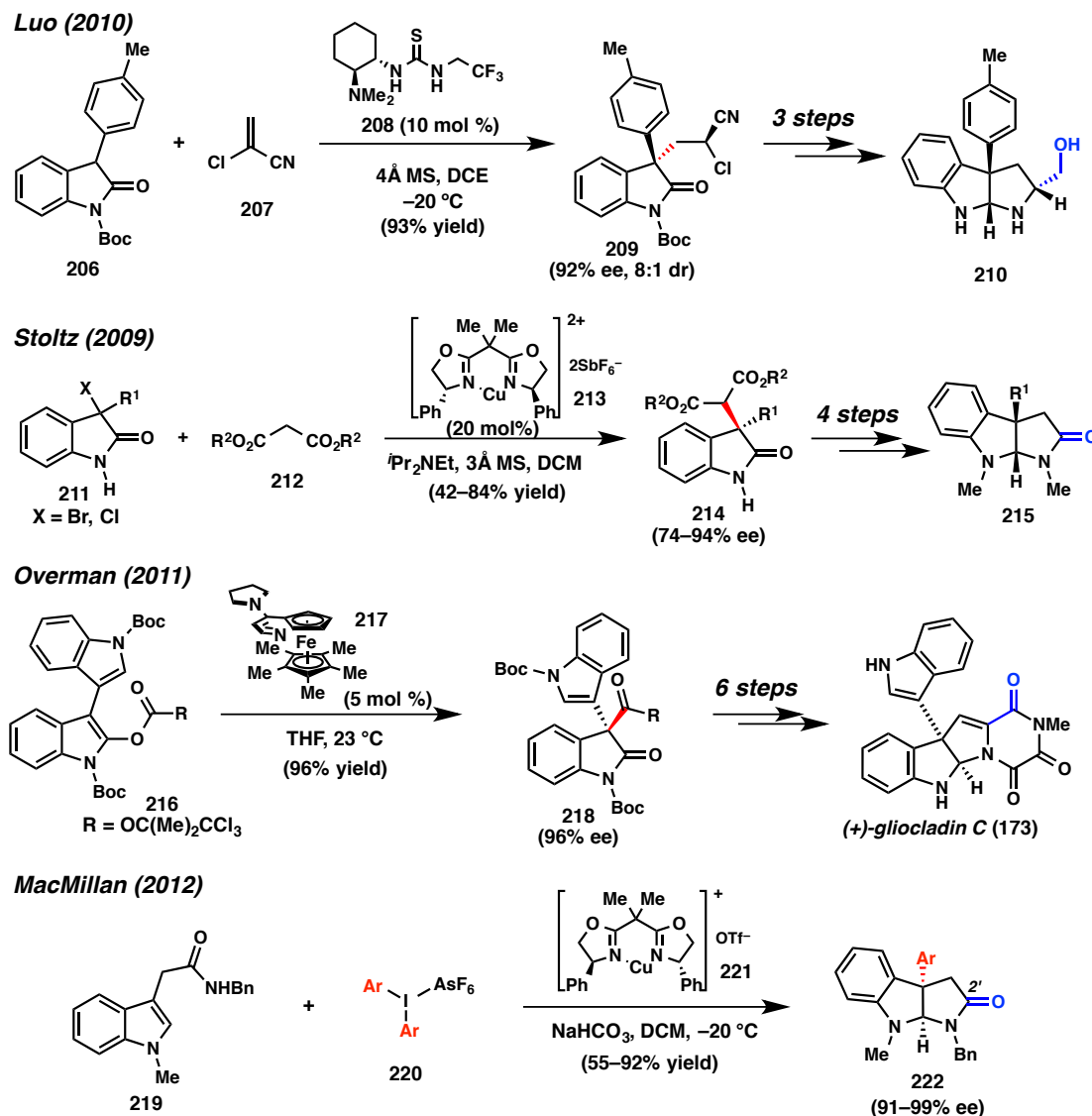
Scheme 2.7. Total synthesis of (+)-naseseazine B by Reisman



2.1.3 Enantioselective Synthesis of Pyrroloindolines

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

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

Scheme 2.8. Selected asymmetric strategies accessing pyrroloindolines

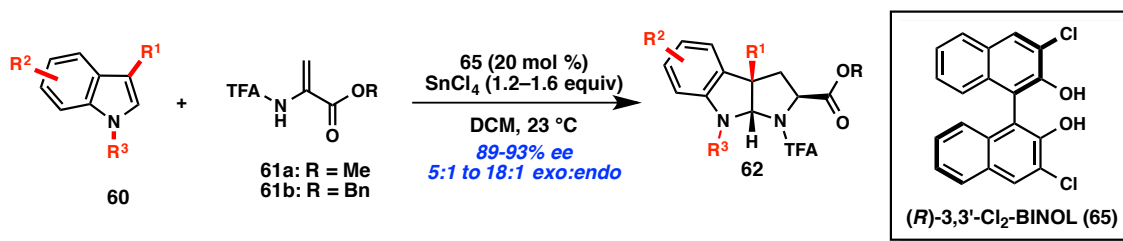
alkylations⁶, which has been reported by several groups including Trost¹⁷, Barbas¹⁸, Stoltz¹⁹, and Luo²⁰. Most approaches utilize the intrinsic nucleophilicity of oxindoles originated from its enolate form. Luo and coworkers applied thiourea catalyst **208** to affect an asymmetric conjugate addition of 2-chloroacrylonitrile to afford product **209** in good enantioselectivities.²⁰ Alternatively, it is also possible to realize an umpolung strategy where the oxindoles become the electrophile. Stoltz and coworkers discovered

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

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

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

Scheme 2.9. Enantioselective pyrroloindoline synthesis by Reisman



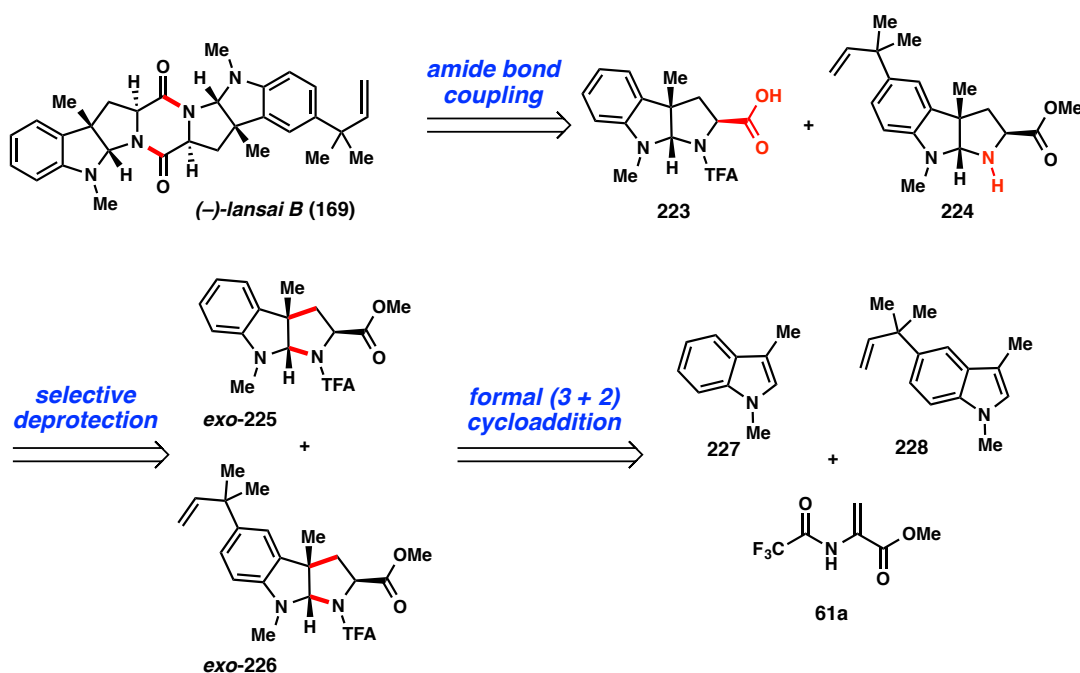
As mentioned in Chapter 1, our group developed a new method to access *exo*-pyrroloindolines directly from C3-substituted indoles and 2-amidoacrylates using SnCl_4 and catalytic (*R*)-3,3'-dichloro-BINOL (**65**, Scheme 2.9).^{24,25} The reactions typically

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

2.2 FIRST TOTAL SYNTHESIS OF (–)-LANSAI B

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

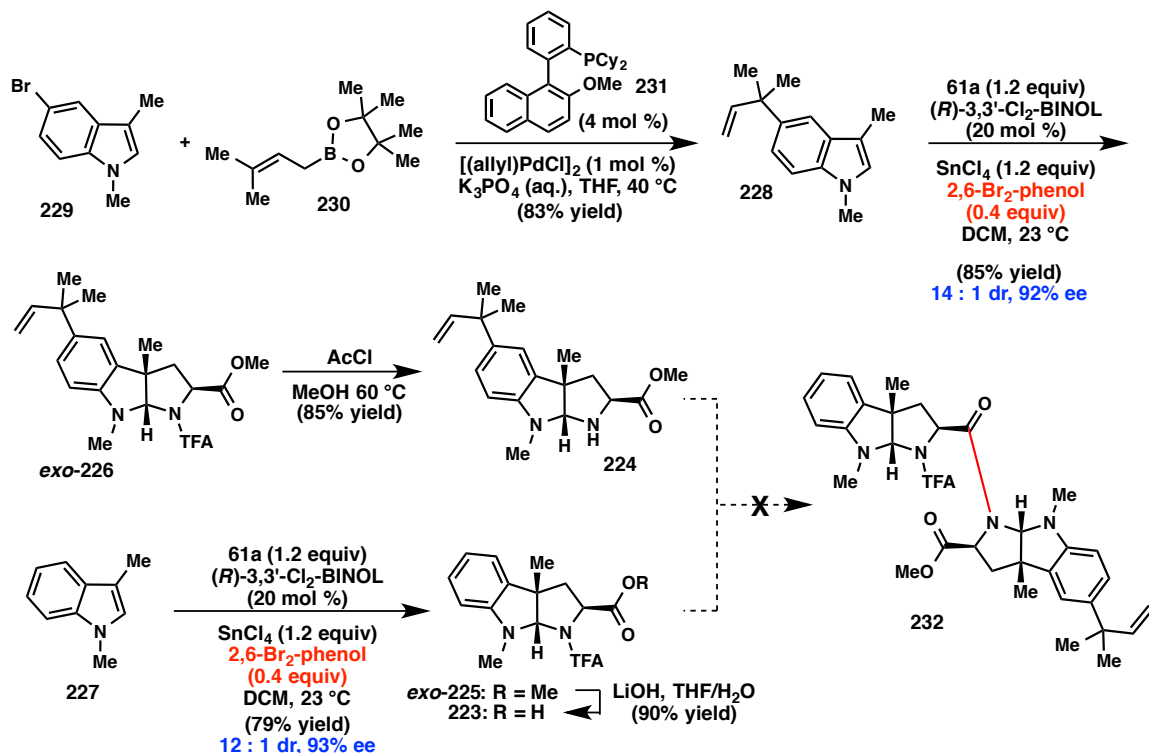
Scheme 2.10. Retrosynthetic analysis of (–)-lansai B



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

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

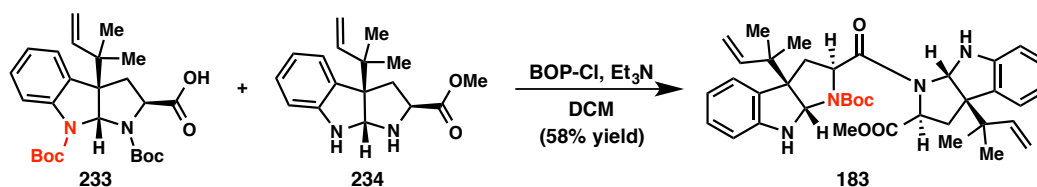
Scheme 2.11. Attempted orthogonal peptide coupling to access (–)-lansai B

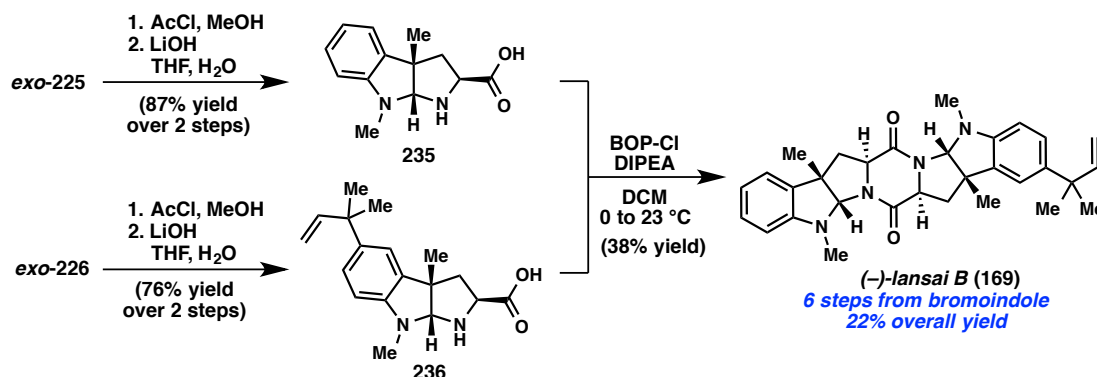


reaction was conducted on preparatively useful scales (>1.0 mmol). It was hypothesized that trace water could help to turn over the chiral catalyst on small scale; thus, a survey of several protic additives revealed that addition of 0.4 equiv 2,6-dibromophenol to the reaction mixture improves the scalability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

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

Scheme 2.12. Orthogonal peptide coupling in the synthesis of amauoramine

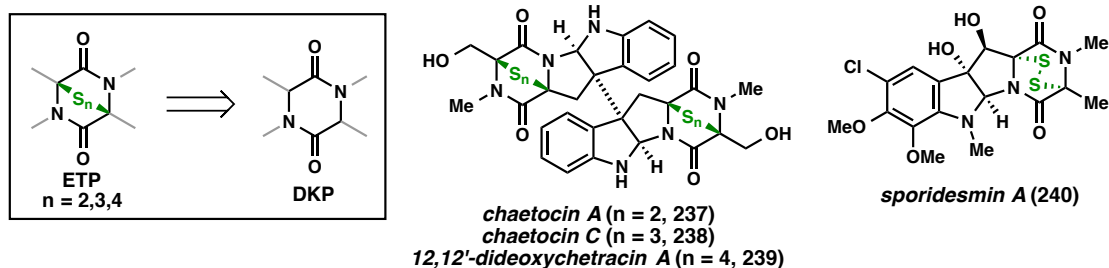


Scheme 2.13. Endgame of (–)-lansai B total synthesis via amino acid dimerization

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

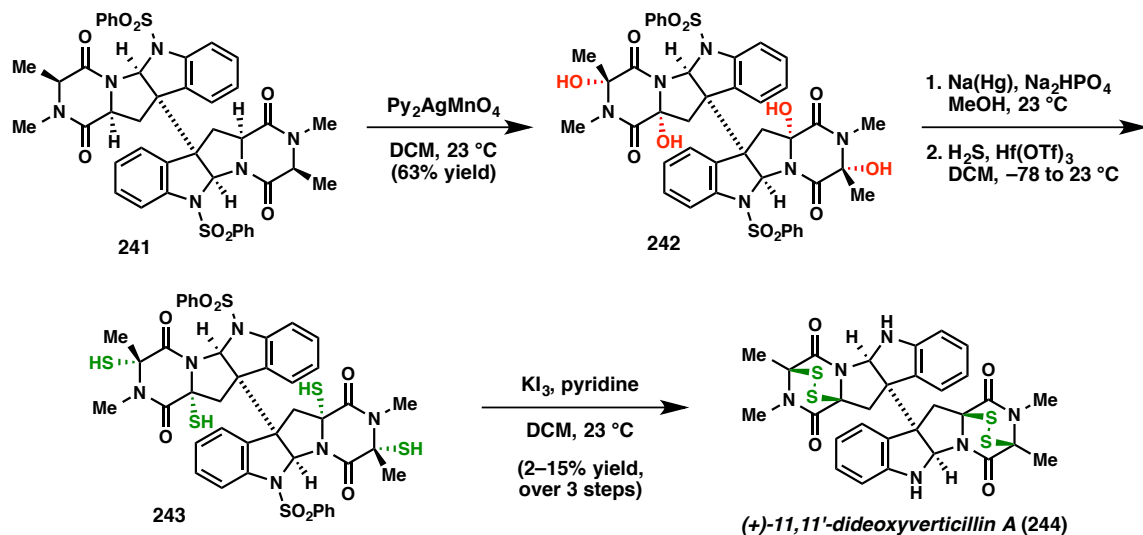
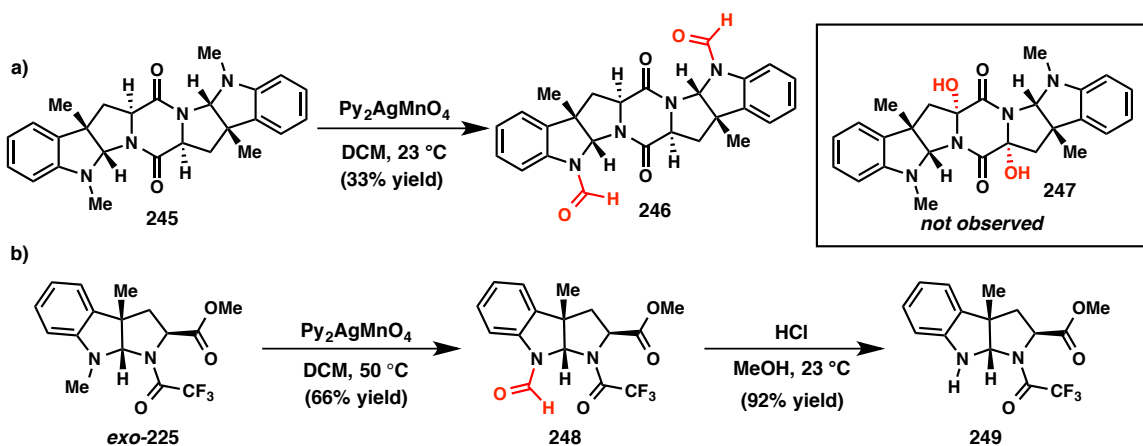
2.3 LANSI B–ETP DERIVATIVES PREPARATION

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

Figure 2.2. Representative ETP natural products

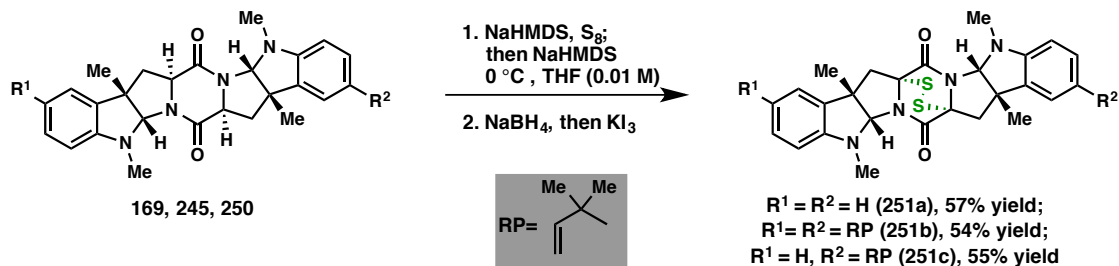
the redox activities of the sulfur-sulfur bond, ETP natural products, such as chaetocin A (**237**), present diverse therapeutic functions including virulence factors, and immunoimpressive and anti-cancer activities.³¹ Synthetically, ETP natural products are often prepared from the corresponding DKP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

Our first attempt at thiolation utilized the conditions in Movassaghi's total synthesis of (+)-11,11'-dideoxyverticillin A (**244**, Scheme 2.14).³³ They were able to promote DKP C-H oxidations of bis(diketopiperazine) **241** using oxidant bispyridinium silver permanganate to provide tetraol **242**. Subsequent deprotection and displacement of hydroxyl groups with hydrogen sulfide afforded free thiol **243**, which could be converted to episulfide **244** upon oxidation with KI_3 . Based on this methodology, DKP **245** was treated with $\text{Py}_2\text{AgMnO}_4$ (Scheme 2.15); however, no DKP C-H oxidation was observed (**247**), while *N*-methyl oxidation product **246** was isolated instead. The same conditions were then applied to pyrroloindoline **225**. After optimization, *N*1-oxidation was effected in 61% yield, again with no C-H oxidation observed. Subsequent formamide cleavage

Scheme 2.14. C-H oxidation strategy for episulfide installation by Movassaghi**Scheme 2.15.** Attempted C-H oxidation and resulting N-demethylation sequence

under mildly acidic conditions yielded *N*1-H product **249**, without affecting the TFA group. Similar transformation has been reported using PCC or PDC.^{13,34} However, this is the first report that Py₂AgMnO₄ can promote a similar oxidation reaction and this fruitful discovery allows a mild *N*-demethylation protocol for pyrroloindolines.

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

Scheme 2.16. Synthesis of lansai B-ETP derivatives

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

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

2.4 CONCLUDING REMARKS

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

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

During the attempts to prepare the ETP derivatives of lansai B (**169**), an unusual *N*-methyl oxidation rather than the desired C-H oxidation was observed when treating DKP with oxidant $\text{Py}_2\text{AgMnO}_4$. Even though it does not provide the targeted diol, this provides a mild method to demethylate *N*-Me pyrroloindolines, which is not trivial. Using Nicolaou's protocol, the successful preparation of ETP derivatives allowed the collaboration with City of Hope. Among these ETP compounds, homodimeric **251a** showed promising anti-cancer properties.

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

2.5 EXPERIMENTAL SECTION

2.5.1 Materials and Methods

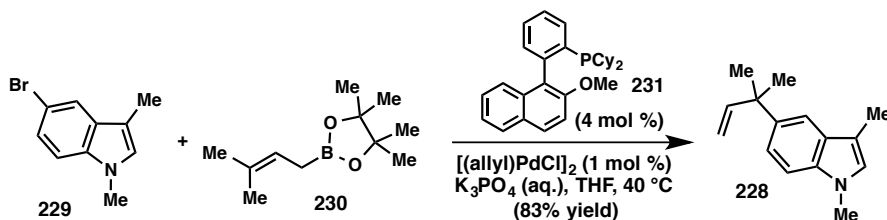
Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using

EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or KMnO₄ staining. Flash column chromatography was performed either as described by Still et al.³⁶ using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep® Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ¹H and ¹³C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Bruker 400 equipped with a cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal CHCl₃ (¹H, δ = 7.26), CHDCl₂ (¹H, δ = 5.32), CD₂HOD (¹H, δ = 3.31), MeCN-*d*₂ (¹H, δ = 1.94), or DMSO-*d*₅ (¹H, δ = 2.50), and CDCl₃ (¹³C, δ = 77.0), CD₂Cl₂ (¹³C, δ = 54.0), CD₃OD (¹³C, δ = 49.0), MeCN-*d*₃ (¹³C, δ = 118.3), or DMSO-*d*₆ (¹³C, δ = 40.0). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm⁻¹). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Preparative HPLC was performed with an Agilent 1100 Series

HPLC utilizing an Agilent Eclipse XDB-C18 5 μ m column (9.4 x 250 mm) or an Agilent Zorbax RX-SIL 5 μ m column (9.4 x 250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

2.5.2 Preparative Procedures and Spectroscopic Data

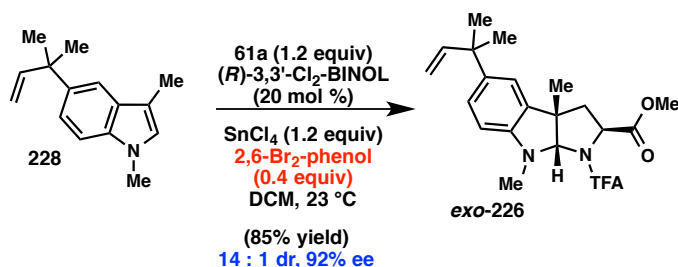
Preparation of reverse prenylated indole **228**²⁶



To a flame-dried 50 mL Schlenk tube was added $[(\text{allyl})\text{PdCl}]_2$ (9 mg, 0.025 mmol, 1 mol %) and phosphine ligand **231** (42 mg, 0.098 mmol, 4 mol %). Then the tube was evacuated and charged with argon three times. Allyl boronic acid pinacol ester **230** (0.65 mL, 2.95 mmol, 1.2 equiv) and dimethyl-bromoindole²⁴ **229** (560 mg, 2.50 mmol, 1.0 equiv) were added using a microsyringe. THF (5 mL) and 2.5 M K_3PO_4 (5 mL) were then added to the reaction flask. The Schlenk tube was sealed and the reaction was heated to 40 °C for 24 hours. It was then cooled to room temperature and diluted with EtOAc (25 mL). The mixed layers were then washed with distilled water (25 mL). The aqueous layer was then extracted with EtOAc (3 x 25 mL). Combined organic layers were washed with brine (40 mL). It was dried over MgSO_4 , filtered and concentrated down to give a yellow oil. The crude material was then dissolved in EtOAc (30 mL) and washed with saturated KHF_2 solution (3 x 20 mL) to get rid of the remaining boronic acid pinacol ester. It was then dried over NaSO_4 , filtered and concentrated to give a yellow oil. Flash chromatography (5% to 9% ether in hexanes) afforded reverse prenylated indole **228** as a

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

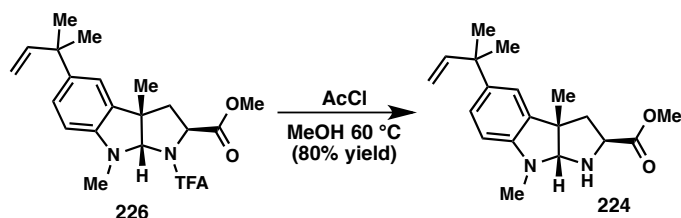
Preparation of reverse prenylated pyrroloindoline *exo*-226



To a flame-dried flask was added reverse prenylated indole **228** (350 mg, 1.64 mmol, 1.0 equiv), acrylate³⁷ **61a** (390 mg, 1.97 mmol, 1.2 equiv), (*R*)-3,3'-Cl₂-BINOL (117 mg, 0.33 mmol, 0.2 equiv), 2,6-dibromo-phenol (165 mg, 0.66 mmol, 0.4 equiv) and DCM (12 mL). SnCl₄ (1M solution in DCM, 1.97 mL, 1.97 mmol, 1.2 equiv) was added at last. The orange mixture was allowed to stir at room temperature for 24 hours. The solution was diluted with acetonitrile (10 mL) and quenched with 1M HCl (10 mL), followed by addition of distilled water (50 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 50 mL). Combined organic layers were washed with 3 M NaOH solution (3 x 75 mL). It was dried over MgSO₄, filtered and concentrated down to give yellow mixture of oil and solid. Flash chromatography (1% to

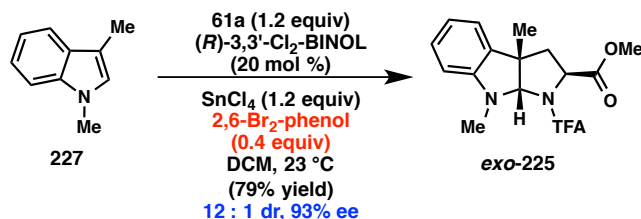
8% EtOAc in hexanes) afforded reverse prenylated pyrroloindoline **226** (14 : 1 mixture of *exo:endo* diastereomers by ^1H NMR), as a thick orange oil (568 mg, 1.34 mmol, 85% yield). The mixture of diastereomers was further purified by flash chromatography (0% to 10% EtOAc in hexanes) to give major diastereomer **226** for characterization purposes. The enantiomeric excess of *exo*-**226** was determined to be 92% by chiral SFC analysis (OD, 2.5 mL/min, 3% IPA in CO_2 , $\lambda = 254$ nm): t_{R} (major) = 6.1 min, t_{R} (minor) = 5.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). $[\alpha]_{\text{D}}^{25} = -115^\circ$ ($c = 0.45$, CHCl_3); ^1H NMR (500 MHz, CDCl_3 ; compound exists as a 2.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.16 (d, $J = 8.1$ Hz, 1H^* , 1H^\S), 7.02 (s, 1H^\S), 6.99 (s, 1H^*), 6.52 (d, $J = 7.7$ Hz, 1H^\S), 6.45 (d, $J = 8.2$ Hz, 1H^*), 6.00 (dd, $J = 17.3$, 10.5 Hz, 1H^* , 1H^\S), 5.60 (s, 1H^*), 5.31 (s, 1H^\S), 5.07 – 4.96 (m, 2H^* , 2H^\S), 4.73 (d, $J = 9.3$ Hz, 1H^*), 4.47 – 4.41 (m, 1H^\S), 3.82 (s, 1H^*), 3.77 (s, 1H^\S), 3.06 (s, 1H^*), 2.86 (s, 1H^\S), 2.60 (dd, $J = 13.1$, 9.9 Hz, 1H^*), 2.52 (t, $J = 10.7$ Hz, 1H^\S), 2.38 (d, $J = 12.5$ Hz, 1H^*), 2.14 – 1.98 (m, 1H^\S), 1.57 – 1.31 (m, 9H^* , 9H^\S); ^{13}C NMR (126 MHz, CDCl_3) 172.6*, 170.6 § , 159.1* (q, $J = 37.0$ Hz), 157.5 § (q, $J = 39.6$ Hz), 148.4*, 148.2 § , 147.5*, 147.3 § , 140.6 § , 139.3*, 134.1*, 134.0 § , 126.5 § , 126.3*, 119.3* § , 116.1* (q, $J = 288.5$ Hz), 115.9 § (app d, $J = 287.2$ Hz), 110.4 § , 110.2*, 109.2 § , 107.6*, 93.7*, 92.1 § , 61.2 § , 60.3*, 53.3 § , 53.0*, 52.5 § , 49.3*, 44.0*, 40.7 § , 40.7*, 40.4 § , 37.1*, 34.9 § , 28.4* § , 23.5*, 22.9 § ; FTIR (NaCl, thin film): 3081, 2965, 2874, 2822, 1753, 1698, 1618, 1496, 1434, 1359, 1283, 1257, 1204, 1156, 1117, 1054, 995, 912, 844, 813 cm^{-1} ; HRMS (ESI) calc'd for $\text{C}_{21}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 411.1890, found 411.1901.

Preparation of reverse prenylated pyrroloindoline amine **224**



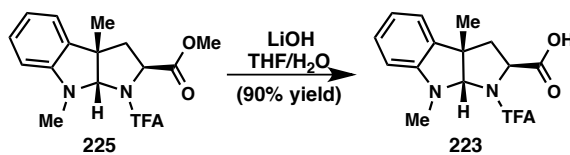
Acetyl chloride (0.40 mL, 5.69 mmol, 5.0 equiv) was added slowly to dry methanol (5 mL). The mixture was added to reverse prenylated pyrroloindoline **226** (467 mg, 1.14 mmol, 1.0 equiv, 14 : 1 mixture of *exo:endo* diastereomers by ^1H NMR) dissolved in dry methanol (7 mL). After being heated to 60 °C for three days, the reaction was quenched with saturated sodium bicarbonate (5 mL), and concentrated down to get rid of methanol. The residue was diluted with DCM (10 mL) and washed with water (10 mL). Aqueous layer was back extracted with DCM (3 x 5 mL). Combined organic layer was dried over Na_2SO_4 , filtered and concentrated down to give a chartreuse oil. Flash chromatography (20% to 80% EtOAc in hexanes) afforded reverse prenylated secondary amine **224**, as a yellow oil (326 mg, 1.04 mmol, 80% yield). $[\alpha]_D^{25} = -58^\circ$ ($c = 1.15$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.08 (dd, $J = 8.1, 2.0$ Hz, 1H), 7.00 (d, $J = 2.0$ Hz, 1H), 6.30 (d, $J = 8.1$ Hz, 1H), 6.02 (dd, $J = 17.5, 10.6$ Hz, 1H), 5.02 (ddd, $J = 19.0, 14.0, 1.4$ Hz, 2H), 4.61 (s, 1H), 3.76 (dd, $J = 9.5, 6.8$ Hz, 1H), 3.73 (s, 3H), 2.82 (s, 3H), 2.67 (br s, 1H), 2.40 (dd, $J = 12.2, 6.8$ Hz, 1H), 1.93 (dd, $J = 12.3, 9.4$ Hz, 1H), 1.43 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 148.7, 148.6, 137.4, 134.6, 125.5, 120.3, 109.8, 105.0, 92.2, 59.7, 52.5, 52.0, 46.0, 40.5, 31.8, 28.4, 25.6; FTIR (NaCl, thin film): 3350, 3080, 2962, 2925, 2868, 1738, 1634, 1615, 1498, 1450, 1377, 1358, 1326, 1282, 1233, 1202, 1133, 1055, 996, 911, 862, 808 cm^{-1} ; HRMS (APCI) calc'd for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 315.2067, found 315.2067.

Preparation of dimethyl pyrroloindoline *exo*-225



To a flame-dried flask was added reverse prenylated indole **227** (300 mg, 2.07 mmol, 1.0 equiv), acrylate **61a** (489 mg, 2.48 mmol, 1.2 equiv), (*R*)-3,3'-Cl₂-BINOL (147 mg, 0.41 mmol, 0.2 equiv), 2,6-dibromo-phenol (208 mg, 0.83 mmol, 0.4 equiv) and DCM (15 mL). SnCl₄ (1M solution in DCM, 2.48 mL, 2.48 mmol, 1.2 equiv) was added at last. The orange mixture was allowed to stir at room temperature for 24 hours. The solution was diluted with acetonitrile (10 mL) and quenched with 1M HCl (10 mL), followed by addition of distilled water (50 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 50 mL). Combined organic layers were washed with 3 M NaOH solution (3 x 75 mL). It was dried over MgSO₄, filtered and concentrated down to give yellow mixture of oil and solid. Flash chromatography (1% to 8% EtOAc in hexanes) afforded dimethyl pyrroloindoline **225** (12 : 1 mixture of *exo:endo* diastereomers by ¹H NMR), as a thick orange oil (553 mg, 1.62 mmol, 79% yield). The enantiomeric excess of *exo*-**225** was determined to be 93% by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO₂, λ = 254 nm): *t*_R(major) = 2.9 min, *t*_R(minor) = 2.4 min. Spectral data matches that reported in the literature.²

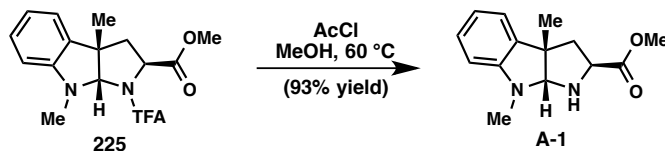
Preparation of pyrroloindoline acid **223**



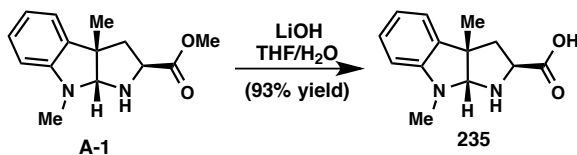
A solution of lithium hydroxide (14 mg, 0.58 mmol, 2.0 equiv) in distilled water (2.5 mL) was added dropwise to a solution of pyrroloindoline **225** (100 mg, 12 : 1 mixture of diastereomers, 0.29 mmol, 1.0 equiv) in THF (2.5 mL). After stirring at room temperature for 30 minutes, reaction was quenched with pH = 2.5 acidic buffer (10 mL, prepared by acidifying a 10% NaH₂PO₄ aqueous solution by KHSO₄ until pH reaches 2.5). It was extracted with DCM (5 x 10 mL). Combined layers were washed with brine (30 mL). The aqueous layer was back extracted with DCM (10 mL). The resulting organic layer was dried over Na₂SO₄, filtered, and concentrated down a yellow thick oil. Flash chromatography (1% to 10% MeOH in DCM) afforded pyrroloindoline acid **223**, as a yellow solid (86 mg, 0.26 mmol, 90% yield). The minor diastereomer does not react under reaction conditions and can be isolated using flash chromatography. $[\alpha]_D^{25} = -86^\circ$ ($c = 1.15$, CHCl₃); ¹H NMR (500 MHz, CDCl₃; compound exists as a 1.7:1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.18 (t, $J = 7.6$ Hz, 1H*, 1H[§]), 7.09 (s, 1H[§]), 7.04 (d, $J = 7.3$ Hz, 1H*), 6.86 (s, 1H[§]), 6.78 (t, $J = 7.4$ Hz, 1H*), 6.60 (s, 1H[§]), 6.52 (d, $J = 7.9$ Hz, 1H*), 5.59 (s, 1H*), 5.31 (s, 1H[§]), 4.66 (s, 1H*), 4.34 (s, 1H[§]), 3.08 (s, 3H*), 2.91 (s, 3H[§]), 2.57 (s, 1H*, 1H[§]), 2.41 (d, $J = 13.3$ Hz, 1H*), 2.15 (s, 1H[§]), 1.48 (s, 3H[§]), 1.40 (s, 3H*); ¹³C NMR (126 MHz, CDCl₃) δ 177.5*, 175.8[§], 159.4* (q, $J = 37.8$ Hz), 157.8[§] (q, $J = 35.6$ Hz), 149.4[§], 149.3*, 134.5*[§], 128.9[§], 128.6*, 121.7[§], 121.5*, 120.4[§], 118.8*, 116.2* (q, $J = 288.5$ Hz), 116.0[§] (q, $J = 286.1$ Hz), 110.2[§], 108.0*, 93.2*, 91.9[§], 62.0[§], 60.9*, 53.5[§], 49.2*, 43.8*, 39.8[§], 36.8*, 35.6[§], 23.6*, 23.3[§]; FTIR (NaCl, thin film): 3215, 3053, 3027, 2966, 2933, 2876, 2824, 2519, 1689, 1609, 1489, 1450, 1432, 1344, 1300, 1256, 1202, 1157, 1107, 1094, 1063, 1021,

992, 949, 925, 855, 792, 754 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 329.1108, found 329.1118.

Preparation of pyrroloindoline amine A-1

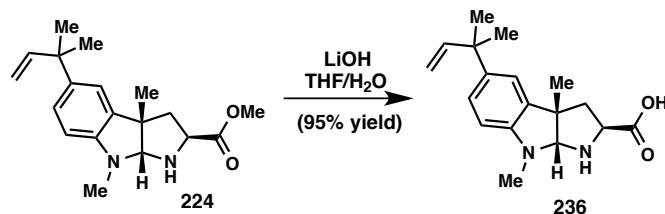


Acetyl chloride (0.35 mL, 4.88 mmol, 5.0 equiv) was added slowly to dry methanol (4 mL). The mixture was added to pyrroloindoline **225** (334 mg, 0.98 mmol, 1.0 equiv) dissolved in dry methanol (6 mL). After being heated to 60 °C for 52 hours, the reaction was quenched with saturated sodium bicarbonate (5 mL), and concentrated down to get rid of methanol. The residue was diluted with DCM (10 mL) and washed with water (10 mL). Aqueous layer was back extracted with DCM (3 x 5 mL). Combined organic layer was dried over Na_2SO_4 , filtered, and concentrated down to give greenish yellow oil. Flash chromatography (20% to 80% EtOAc in hexanes) afforded secondary amine **A-1**, as a yellow oil (222 mg, 0.90 mmol, 93% yield). $[\alpha]_{\text{D}}^{25} = -34^\circ$ ($c = 1.02$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.09 (td, $J = 7.7, 1.2$ Hz, 1H), 7.02 (dd, $J = 6.6, 1.0$ Hz, 1H), 6.65 (td, $J = 7.5, 1.0$ Hz, 1H), 6.35 (d, $J = 7.8$ Hz), 4.62 (s, 1H), 3.69 – 3.74 (m, 4H), 2.83 (s, 3H), 2.69 (br s, 1H), 2.40 (dd, $J = 12.5, 6.6$ Hz, 1H), 1.92 (dd, $J = 12.2, 9.5$ Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 150.6, 134.7, 128.1, 122.3, 117.0, 105.5, 91.6, 59.8, 52.5, 52.0, 46.1, 31.5, 25.5; FTIR (NaCl, thin film): 3345, 3049, 2953, 2922, 2866, 1738, 1607, 1491, 1448, 1381, 1353, 1327, 1300, 1282, 1258, 1234, 1203, 1144, 1117, 1081, 1063, 1044, 1020, 990, 963, 909, 820, 741 cm^{-1} ; HRMS (APCI) calc'd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 247.1441, found 247.1441.

Preparation of pyrroloindoline amino acid 235

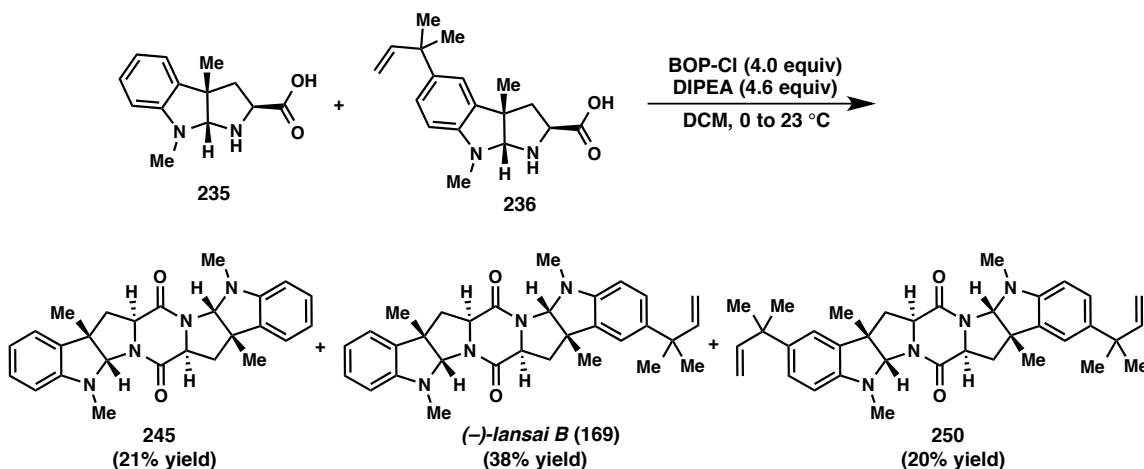
A solution of lithium hydroxide (29 mg, 1.22 mmol, 3.0 equiv) in distilled water (1.5 mL) was added dropwise to a solution of amine **A-1** (100 mg, 0.406 mmol, 1.0 equiv) in THF (1.5 mL). After stirring at room temperature for 30 minutes, reaction was quenched with 1M HCl until pH reached 6. The resulting solution was concentrated down to get rid of all solvent. The white residue was redissolved in DCM and filtered through a plug of celite to remove inorganic salt, which yielded a light yellow foam upon concentrating down. The crude product amino acid **235** was carried to the next reaction without further purification. (87.0 mg, 0.375 mmol, 93% yield). $[\alpha]_{\text{D}}^{25} = -91^\circ$ ($c = 0.94$, CH_2Cl_2); ^1H NMR (500 MHz, CD_3OD) δ 7.15 – 7.10 (m, 2H), 6.76 (t, $J = 7.5$ Hz, 1H), 6.55 (d, $J = 8.1$ Hz, 1H), 5.05 (s, 1H), 3.60 (dd, $J = 11.3, 6.5$ Hz, 1H), 3.01 (s, 3H), 2.66 (dd, $J = 13.3, 6.4$ Hz, 1H), 2.22 (dd, $J = 13.1, 11.4$ Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 173.3, 150.3, 134.6, 130.1, 123.6, 120.7, 108.3, 92.0, 62.0, 54.6, 49.0, 43.9, 33.6, 25.4; FTIR (NaCl, thin film): 3390, 3051, 3024, 2961, 2926, 2668, 2621, 2485, 1609, 1494, 1420, 1339, 1307, 1283, 1265, 1223, 1208, 1156, 1115, 1078, 1036, 1020, 1007, 989, 944, 923, 868, 794, 742 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 233.1285, found 233.1291.

Preparation of reverse prenylated pyrroloindoline amino acid 236



Amino acid **236** was prepared following the same procedure as preparation of amino acid **235**. The crude product was carried to the next reaction without further purification, (64.8 mg, 0.216 mmol, 95% yield). $[\alpha]_D^{25} = -102^\circ$ ($c = 1.33$, CH_2Cl_2); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.11 (dd, $J = 8.2, 1.9$ Hz, 1H), 7.04 (d, $J = 1.9$ Hz, 1H), 6.37 (d, $J = 8.3$ Hz, 1H), 6.00 (dd, $J = 17.4, 10.6$ Hz, 1H), 5.17 (s, 1H), 5.04 (d, $J = 17.4$ Hz, 1H), 5.00 (d, $J = 10.6$ Hz, 1H), 3.70 (dd, $J = 12.4, 6.1$ Hz, 1H), 2.99 (s, 3H), 2.56 (dd, $J = 12.8, 6.0$ Hz, 1H), 2.30 (t, $J = 12.6$ Hz, 1H), 1.47 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 173.9, 149.1, 148.3, 140.0, 133.9, 127.0, 120.8, 110.5, 106.6, 90.9, 61.4, 53.7, 43.7, 41.2, 34.1, 28.8, 25.7; FTIR (NaCl, thin film): 3400, 2963, 2928, 2873, 2804, 1602, 1502, 1439, 1387, 1377, 1358, 1333, 1289, 1253, 1226, 1211, 1175, 1127, 1098, 1066, 1036, 1007, 904, 810, 768, 753 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 301.1911, found 301.1906.

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



Dissolved amino acid **235** (19.4 mg, 0.084 mmol, 1.0 equiv) and reverse prenylated amino acid **236** (25.1 mg, 0.084 mmol, 1.0 equiv) in dry DCM (4.1 ml). After addition of dry *N,N*-diisopropylethylamine (DIPEA, 67 μ L, 50 mg, 0.384 mmol, 4.6 equiv), the solution was then cooled to 0 °C. Bis(2-oxo-3-oxazolidinyl) phosphonic chloride (BOP-Cl, 85 mg, 0.334 mmol, 4.0 equiv) was added in one portion. The resulting mixture was allowed to warm to room temperature and stirred for 13 hours. It was quenched with saturated sodium bicarbonate (5 mL), followed by brine (5 mL). Aqueous layer was extracted with EtOAc (3 x 5 mL). Combined organic layer was dried over Na₂SO₄, filtered, and concentrated down to give yellow mixture of oil and solid. Flash chromatography (0% to 20% EtOAc in hexanes) afforded three compounds: diketopiperazine **A-2** as white solid (7.2 mg, 0.017 mmol, 21% yield), (–)-lansai B (**169**) as white solid (15.4 mg, 0.031 mmol, 38% yield), diketopiperazine **A-3** as white solid (9.4 mg, 0.017 mmol, 20% yield).

(–)-Lansai B (**169**): $[\alpha]_D^{25} = -505^\circ$ ($c = 0.12$, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.13 – 7.05 (m, 1H), 7.07 (dd, $J = 8.1, 1.8$ Hz, 1H), 7.04 (dd, $J = 7.3, 1.2$ Hz, 1H), 7.01 (d, $J = 1.9$ Hz, 1H), 6.70 (td, $J = 7.4, 0.9$ Hz, 1H), 6.34 (d, $J = 7.8$ Hz, 1H), 6.28 (d, $J = 8.1$ Hz, 1H), 5.97 (dd, $J = 17.4, 10.6$ Hz, 1H), 5.44 (s, 1H), 5.42 (s, 1H), 5.01 (dd, $J = 14.0, 1.4$ Hz, 1H), 4.99 (dd, $J = 7.2, 1.4$ Hz, 1H), 4.15 (app dddd, $J = 13.5, 11.1, 6.1, 2.1$ Hz, 2H), 2.97 (s, 3H), 2.95 (s, 3H), 2.71 (dd, $J = 12.7, 3.0$ Hz, 1H), 2.69 (dd, $J = 12.7, 3.0$ Hz, 1H), 2.18 (dd, $J = 12.6, 6.3$ Hz, 1H), 2.15 (dd, $J = 12.7, 6.4$ Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.34 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 165.7, 165.5, 150.1, 148.6, 148.2, 138.7, 132.9, 132.8, 128.7, 126.3, 122.3, 120.2, 118.1, 110.1, 105.8, 105.4, 86.9, 86.5, 60.1, 60.1, 50.5, 50.3, 42.7, 42.7, 40.7, 33.1, 32.9, 28.5, 28.5, 25.5, 25.4; FTIR

(NaCl, thin film): 2960, 2926, 2866, 1668, 1608, 1495, 1418, 1340, 1300, 1206, 1163, 1082, 1004, 910, 810, 740 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{31}\text{H}_{37}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 497.2911, found 497.2911.

Diketopiperazine 245: $[\alpha]_{\text{D}}^{25} = -561^\circ$ ($c = 1.12$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.09 (td, $J = 7.6, 1.1$ Hz, 1H), 7.04 (dd, $J = 7.3, 0.7$ Hz, 1H), 6.70 (td, $J = 7.4, 0.9$ Hz, 1H), 6.34 (d, $J = 7.8$ Hz, 1H), 5.44 (s, 1H), 4.15 (dd, $J = 10.6, 5.7$ Hz, 1H), 2.97 (s, 3H), 2.70 (dd, $J = 12.7, 5.9$ Hz, 1H), 2.17 (dd, $J = 12.5, 11.5$ Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.6, 150.1, 132.9, 128.7, 122.3, 118.1, 105.8, 86.5, 60.1, 50.3, 42.7, 32.9, 25.4; FTIR (NaCl, thin film): 3318, 3052, 3007, 2958, 2926, 2866, 2829, 1665, 1608, 1493, 1421, 1341, 1300, 1259, 1206, 1163, 1122, 1081, 1020, 1004, 936, 895, 818, 799, 751 cm^{-1} ; HRMS (APCI) calc'd for $\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 429.2285, found 429.2287.

Diketopiperazine 250: $[\alpha]_{\text{D}}^{25} = -501^\circ$ ($c = 0.65$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.07 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.01 (d, $J = 1.7$ Hz, 1H), 6.28 (d, $J = 8.1$ Hz, 1H), 5.97 (dd, $J = 17.3, 10.5$ Hz, 1H), 5.42 (s, 1H), 5.01 (d, $J = 17.4$ Hz, 1H), 4.99 (d, $J = 10.4$ Hz, 1H), 4.15 (dd, $J = 10.5, 5.9$ Hz, 1H), 2.96 (s, 3H), 2.70 (dd, $J = 12.7, 5.9$ Hz, 1H), 2.16 (t, $J = 12.0$ Hz, 1H), 1.46 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.7, 148.6, 148.2, 138.6, 132.7, 126.3, 120.2, 110.1, 105.3, 86.9, 60.1, 50.4, 42.7, 40.6, 33.1, 28.50, 28.49, 25.5; FTIR (NaCl, thin film): 3080, 2962, 2923, 2867, 2824, 1666, 1612, 1500, 1414, 1341, 1317, 1289, 1208, 1161, 1081, 1004, 910, 810, 754 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{36}\text{H}_{45}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 565.3537, found 565.3549.

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

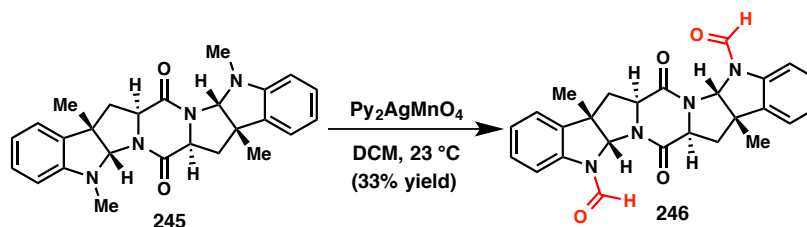
Tuntiwachwuttikul et al. Report, ³ Natural (–)-lansai B ^1H NMR, 300 MHz, CDCl_3	This Work, Synthetic (–)-lansai B ^1H NMR, 500 MHz, CDCl_3
δ 7.11 (dt, $J = 7.8, 1.5$ Hz, 1H)	δ 7.13 – 7.05 (m, 1H)
7.08 (dd, $J = 8.1, 1.5$ Hz, 1H)	7.07 (dd, $J = 8.1, 1.8$ Hz, 1H)
7.06 (dd, $J = 7.8, 1.5$ Hz, 1H)	7.04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

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

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

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

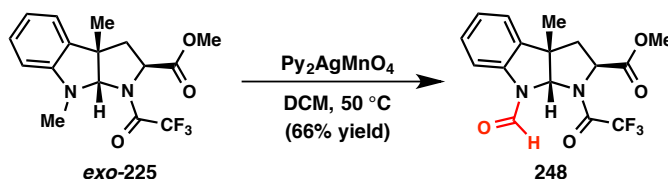
Preparation of *N*-formyl DKP **246**



To a vial containing DKP **245** (5.5 mg, 0.013 mmol, 1.0 equiv) and $\text{Py}_2\text{AgMnO}_4$ ³⁸ (21 mg, 0.05 mmol, 4.0 equiv) was added dry DCM (0.2 mL). The resulting mixture was stirred at room temperature for 22 hours. Then a second portion of $\text{Py}_2\text{AgMnO}_4$ (10 mg, 0.025 mmol, 2.0 equiv) was added and the reaction was further stirred for another 18 hours. The mixture was then diluted with EtOAc (5 mL), which was sequentially washed with saturated sodium bisulfite (2 mL), saturated copper sulfate (2 mL), and saturated

ammonium chloride (2 mL). Combined organic layer was dried over Na₂SO₄, filtered, and concentrated down. Flash chromatography (20% to 100% EtOAc in hexanes) afforded *N*-formyl DKP **246** as a white solid (1.9 mg, 0.004 mmol, 33% yield). $[\alpha]_D^{25} = -378^\circ$ ($c = 0.105$, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.99 (s, 1H), ¹H NMR (400 MHz, CDCl₃) δ 9.01 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.25 (td, $J = 7.7, 1.4$ Hz, 1H), 7.22 – 7.19 (m, 1H), 7.13 (td, $J = 7.5, 1.1$ Hz, 1H), 5.80 (s, 1H), 4.13 (dd, $J = 10.5, 5.8$ Hz, 1H), 2.81 (dd, $J = 13.0, 5.9$ Hz, 1H), 2.30 (dd, $J = 13.0, 11.4$ Hz, 1H), 1.53 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 165.2, 161.8, 139.8, 134.9, 129.2, 125.7, 122.6, 117.1, 80.0, 60.2, 51.0, 40.8, 24.9; FTIR (NaCl/thin film): 2963, 2924, 2868, 1678, 1599, 1552, 1485, 1464, 1446, 1413, 1378, 1344, 1292, 1232, 1206, 1157, 1102, 793, 761 cm⁻¹; HRMS (MM) calc'd for C₂₆H₂₅N₄O₄ [M+H]⁺ 457.1870, found 457.1882.

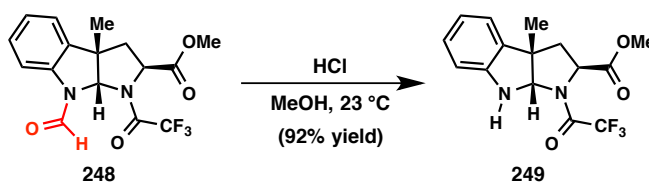
Preparation of *N*-formyl pyrroloindoline **248**



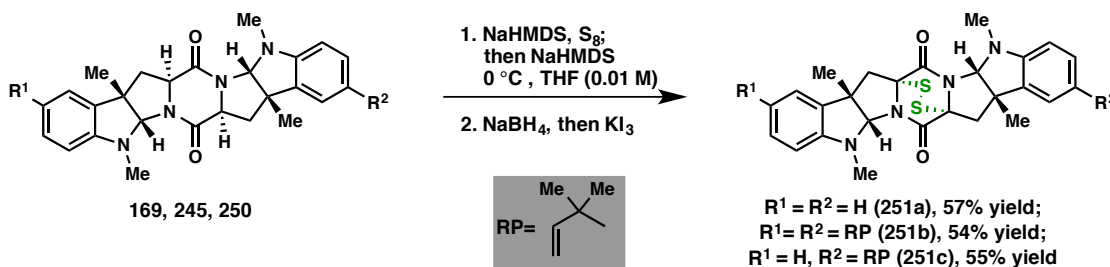
To a vial containing pyrroloindoline **225** (54 mg, 0.16 mmol, 1.0 equiv) and Py₂AgMnO₄ (304 mg, 0.79 mmol, 5.0 equiv) was added dry DCM (1.6 mL). The resulting mixture was heated to 50 °C for 21 hours after being sealed. The mixture was then cooled to room temperature and diluted with EtOAc (10 mL), and sequentially washed with saturated sodium bisulfite (5 mL), saturated copper sulfate (5 mL), and saturated ammonium chloride (5 mL). Combined organic layer was dried over Na₂SO₄, filtered, and concentrated down. Flash chromatography (0% to 40% EtOAc in hexanes) afforded *N*-formyl pyrroloindoline **248** as a thick oil (37.1 mg, 0.104 mmol, 66% yield).

$[\alpha]_D^{25} = -159^\circ$ ($c = 1.815$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.99 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.32 (td, $J = 7.8, 1.4$ Hz, 1H), 7.23 (d, $J = 7.1$ Hz, 1H), 7.18 (t, $J = 7.4$ Hz, 1H), 5.93 (s, 1H), 4.48 (t, $J = 8.0$ Hz, 1H), 3.80 (s, 3H), 2.94 (dd, $J = 13.3, 8.1$ Hz, 1H), 2.31 (dd, $J = 13.4, 8.3$ Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 206.3, 171.5, 162.1, 158.8 (q, $J_{\text{C-F}} = 38.2$ Hz), 138.8, 135.8, 129.2, 125.7, 122.1, 118.0, 115.4 (q, $J_{\text{C-F}} = 287.9$ Hz), 83.9, 59.9, 53.2, 50.3, 48.4, 43.9, 41.8, 24.3; FTIR (NaCl/thin film): 3014, 2961, 2931, 2874, 1752, 1691, 1603, 1484, 1467, 1452, 1437, 1409, 1389, 1381, 1357, 1331, 1312, 1288, 1277, 1253, 1212, 1166, 1106, 1067, 1021, 1007, 979, 945, 914, 878, 805, 759, 729 cm^{-1} ; HRMS (MM) calc'd for $\text{C}_{16}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 357.1057, found 357.1071.

Preparation of *N*-proto-pyrroloindoline **249**



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

Preparation of lansai ETP derivatives **251a-c**³⁵

Typical procedure of preparation of ETP **251c**: To a suspension of sulfur (4.2 mg, 0.13 mmol) in THF (2 mL) at 0 °C under argon was added NaHMDS (0.6 M in PhMe, 330 μ L, 0.20 mmol) dropwise over 2 min. This solution was stirred for an additional 1 min, and lansai B (**169**) (8.2 mg, 0.017 mmol) dissolved in THF (8.5 mL) was added dropwise at 0 °C over 2 min. The mixture was stirred for an additional 1 min, then more NaHMDS (0.6 M in PhMe, 180 μ L, 0.11 mmol) was added and the resulting mixture was stirred 0.5 hours at 0 °C. The reaction mixture was quenched with saturated aq. NH₄Cl solution (5 mL). The mixture was extracted with DCM (3 \times 5 mL), and the combined organic layers were dried over MgSO₄, filtered, and concentrated. The resulting brownish residue was used for the next step without further purification.

To the above crude product dissolved in a mixture of degassed THF/EtOH (1:1, 1.0 mL) at 0 °C was added NaBH₄ (15.6 mg, 0.41 mmol) in small portions over 1 min. The resulting mixture was stirred for 45 min while it was allowed to warmed up to 25 °C. After this time, the solution was cooled to 0 °C, and quenched by careful addition of saturated aq. NH₄Cl solution (3 mL). The resulting mixture was extracted with EtOAc (3 \times 3 mL) and to the combined organic extracts was added an aq. solution of KI₃ (3 mL, 1.4 M). This mixture was stirred for 10 min and then quenched by the addition of sat. aq. Na₂S₂O₃ solution (3 mL). The resulting mixture was extracted with EtOAc (3 \times 5 mL),

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

Epidithiodiketopiperazine 251a: $[\alpha]_{\text{D}}^{25} = -576^\circ$ ($c = 0.390$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.16 (td, $J = 7.7, 1.2$ Hz, 1H), 7.07 (dd, $J = 7.3, 0.7$ Hz, 1H), 6.76 (td, $J = 7.5, 0.7$ Hz, 1H), 6.45 (d, $J = 7.8$ Hz, 1H), 5.34 (s, 1H), 3.27 (d, $J = 14.7$ Hz, 1H), 3.07 (s, 3H), 2.59 (d, $J = 14.7$ Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 164.4, 149.2, 133.9, 128.9, 121.7, 118.4, 107.0, 90.7, 52.1, 44.3, 34.9, 25.1; FTIR (NaCl/thin film): 3052, 3020, 2959, 2925, 2867, 1693, 1608, 1493, 1445, 1384, 1357, 1324, 1302, 1274, 1185, 1124, 1104, 1093, 1060, 1020, 997, 941, 797, 742 cm^{-1} ; HRMS (APCI) calc'd for $\text{C}_{26}\text{H}_{27}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}-\text{S}_2]^+$ 491.1570, found 491.1576.

Epidithiodiketopiperazine 251b: $[\alpha]_{\text{D}}^{25} = -613^\circ$ ($c = 0.355$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.20 – 7.12 (m, 2H), 7.08 (dd, $J = 7.5, 0.9$ Hz, 1H), 7.04 (d, $J = 2.0$ Hz, 1H), 6.76 (td, $J = 7.4, 0.9$ Hz, 1H), 6.46 (d, $J = 7.8$ Hz, 1H), 5.99 (dd, $J = 17.3, 10.5$ Hz, 1H), 5.35 (s, 1H), 5.32 (s, 1H), 5.02 (dd, $J = 11.0, 1.5$ Hz, 1H), 4.99 (dd, $J = 7.2, 1.4$ Hz, 1H), 3.28 (d, $J = 2.2$ Hz, 1H), 3.25 (d, $J = 2.2$ Hz, 1H), 3.09 (s, 3H), 3.04 (s, 3H), 2.59 (dd, $J = 14.5, 8.7$ Hz, 2H), 1.51 (s, 3H), 1.50 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 164.5, 164.4, 149.2, 148.6, 147.4, 138.9, 133.9, 133.7, 128.9, 126.3, 121.7, 112.0, 118.4, 110.3, 107.0, 106.6, 91.2, 90.7, 76.0, 75.9, 52.3, 52.1, 44.4, 44.4, 40.7, 35.0, 34.9, 28.5, 28.5, 25.1, 24.7; FTIR (NaCl/thin film): 2961, 2925, 2868, 1693, 1608, 1494, 1358, 1317, 1302, 1186, 1120, 1053, 997, 911, 812, 753 cm^{-1} ; HRMS (APCI) calc'd for $\text{C}_{31}\text{H}_{35}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}-\text{S}_2]^+$ 559.2196, found 559.2183.

Epidithiodiketopiperazine 251c: $[\alpha]_D^{25} = -577^\circ$ ($c = 0.210$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.15 (dd, $J = 8.1, 2.0$ Hz, 1H), 7.04 (d, $J = 2.0$ Hz, 1H), 6.40 (d, $J = 8.3$ Hz, 1H), 5.99 (dd, $J = 17.5, 10.6$ Hz, 1H), 5.32 (s, 1H), 5.02 (dd, $J = 11.1, 1.2$ Hz, 1H), 4.99 (dd, $J = 4.4, 1.2$ Hz, 1H), 3.26 (d, $J = 14.4$ Hz, 1H), 3.05 (s, 3H), 2.59 (dd, $J = 14.7$ Hz, 1H), 1.50 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 164.5, 148.6, 147.4, 138.9, 133.8, 126.3, 119.7, 110.3, 106.5, 91.2, 52.3, 44.4, 40.7, 35.0, 28.55, 28.50, 24.7; FTIR (NaCl/thin film): 3079, 2962, 2926, 2869, 2824, 1695, 1619, 1498, 1446, 1431, 1411, 1358, 1315, 1287, 1185, 1136, 1117, 1099, 1053, 996, 910, 809, 754 cm^{-1} ; HRMS (APCI) calc'd for $\text{C}_{36}\text{H}_{43}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}-\text{S}_2]^+$ 627.2822, found 627.2819.

2.6 NOTES AND REFERENCES

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