CHAPTER 1

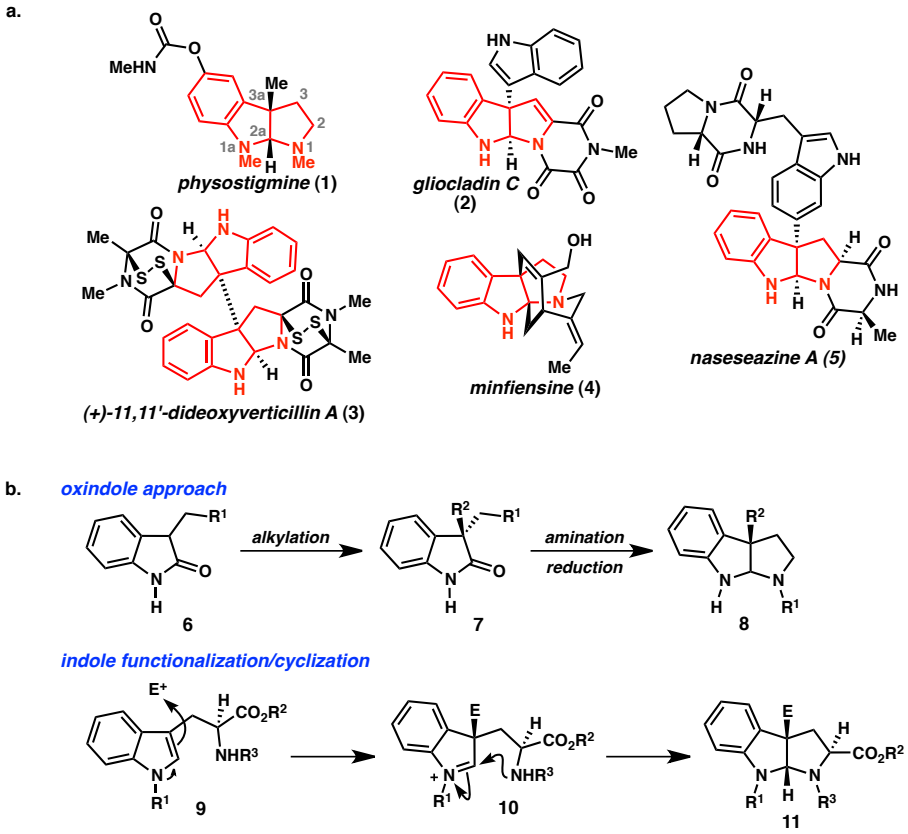
Strategies for the Total Synthesis of Pyrroloindoline Natural Products

1.1 Introduction

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

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

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

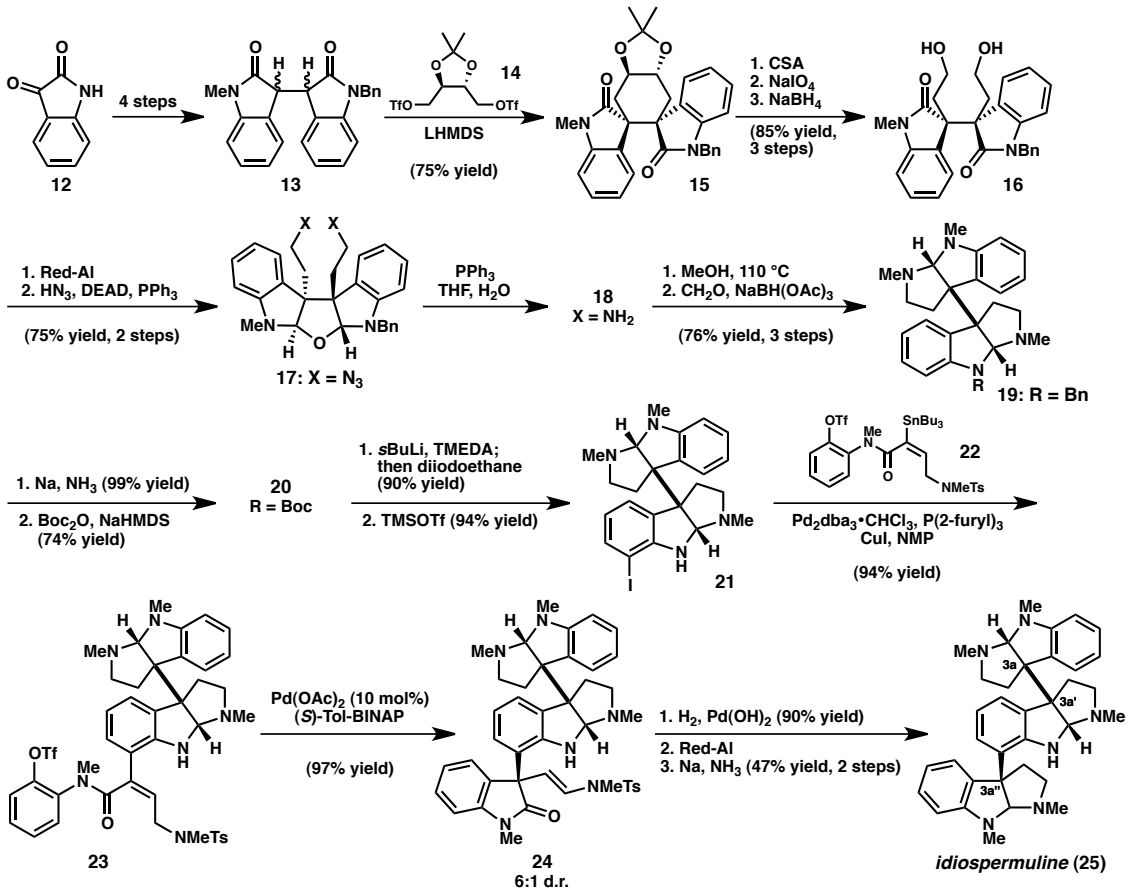


1.2 Pyrroloindoline Synthesis via Oxindoles

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

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

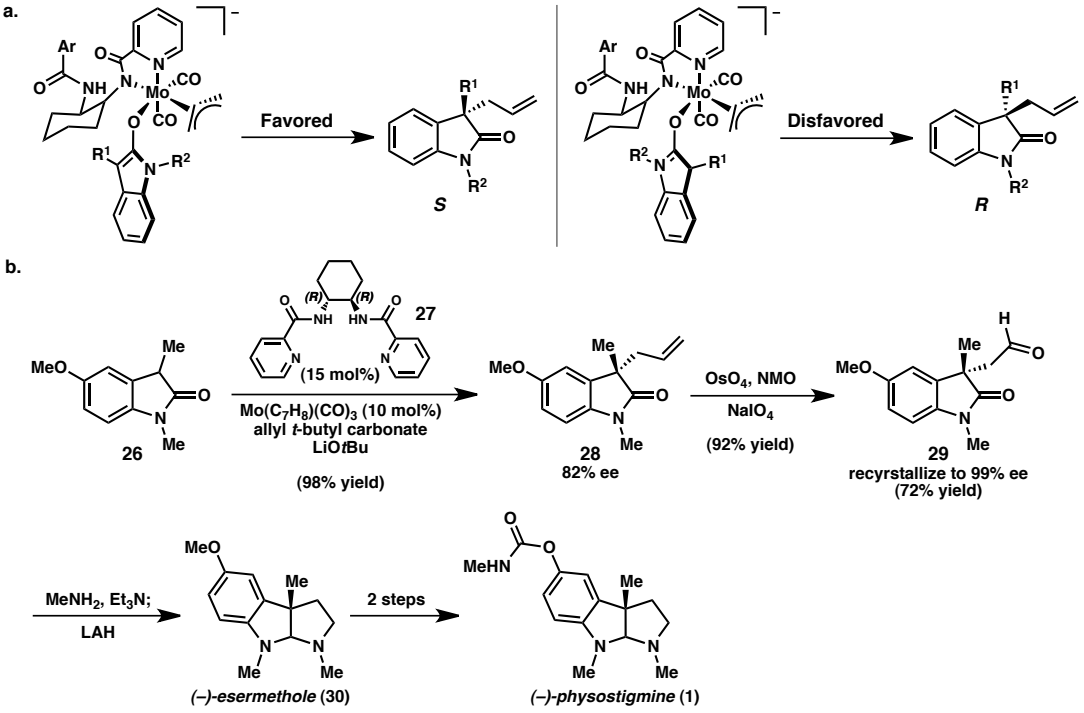
Figure 2. Total synthesis of idiospermuline by Overman and coworkers.



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

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

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



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

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

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

1.3 Pyrroloindoline Synthesis via C3 Functionalization/Cyclization

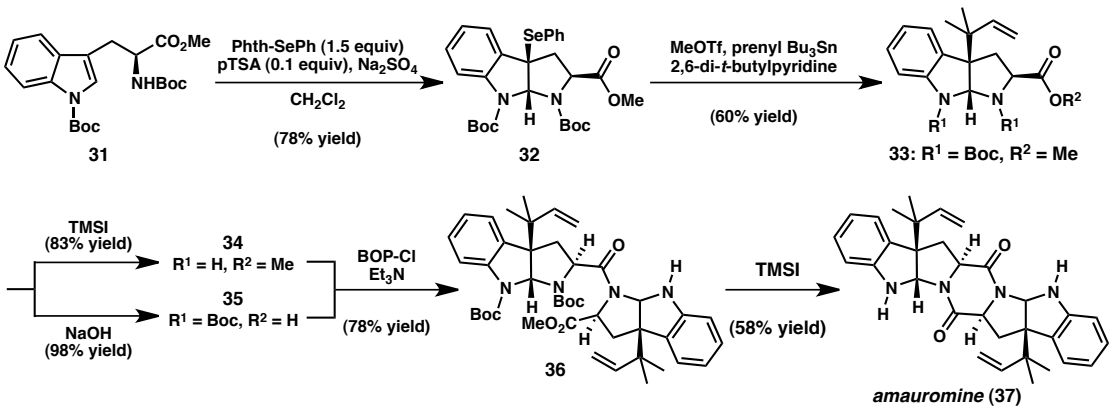
Electrophilic functionalization at the 3-position of indoles followed by cyclization is an efficient method for the preparation of pyrroloindoline natural products. While many syntheses are stereospecific and start from tryptophan, an abundant source of chiral material, the past decade has also witnessed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

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

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

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

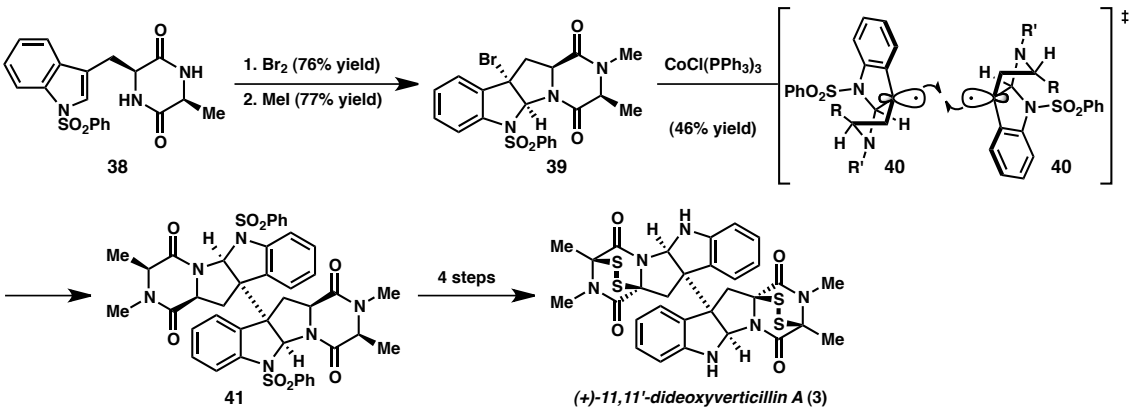
Figure 4. Total synthesis of amauromine by Danishefsky.



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

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

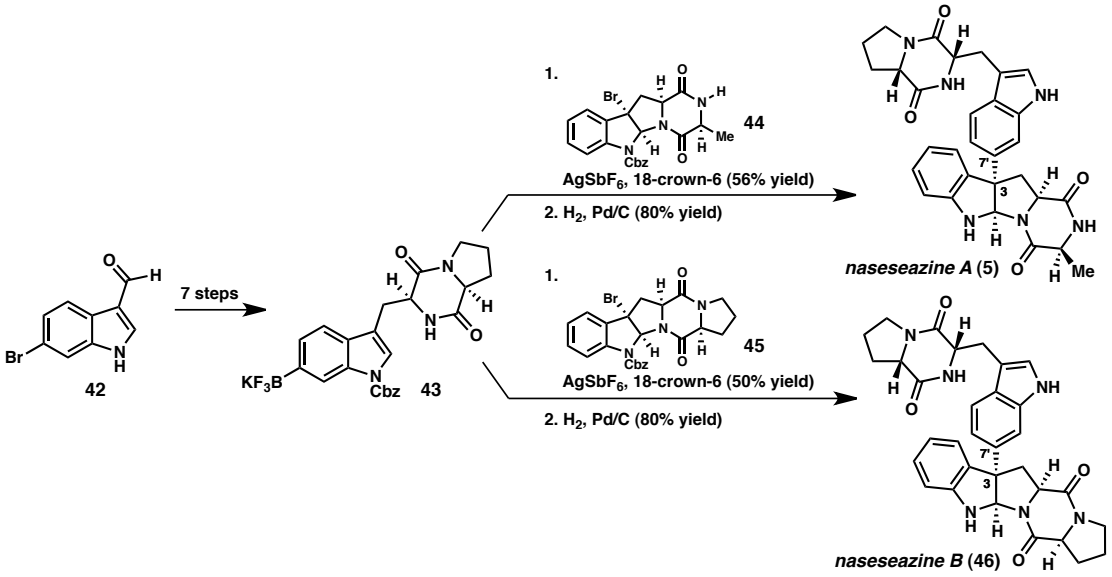
Figure 5. Total synthesis of (+)-11,11′-dideoxyverticillin A by Movassaghi.



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

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

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



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

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

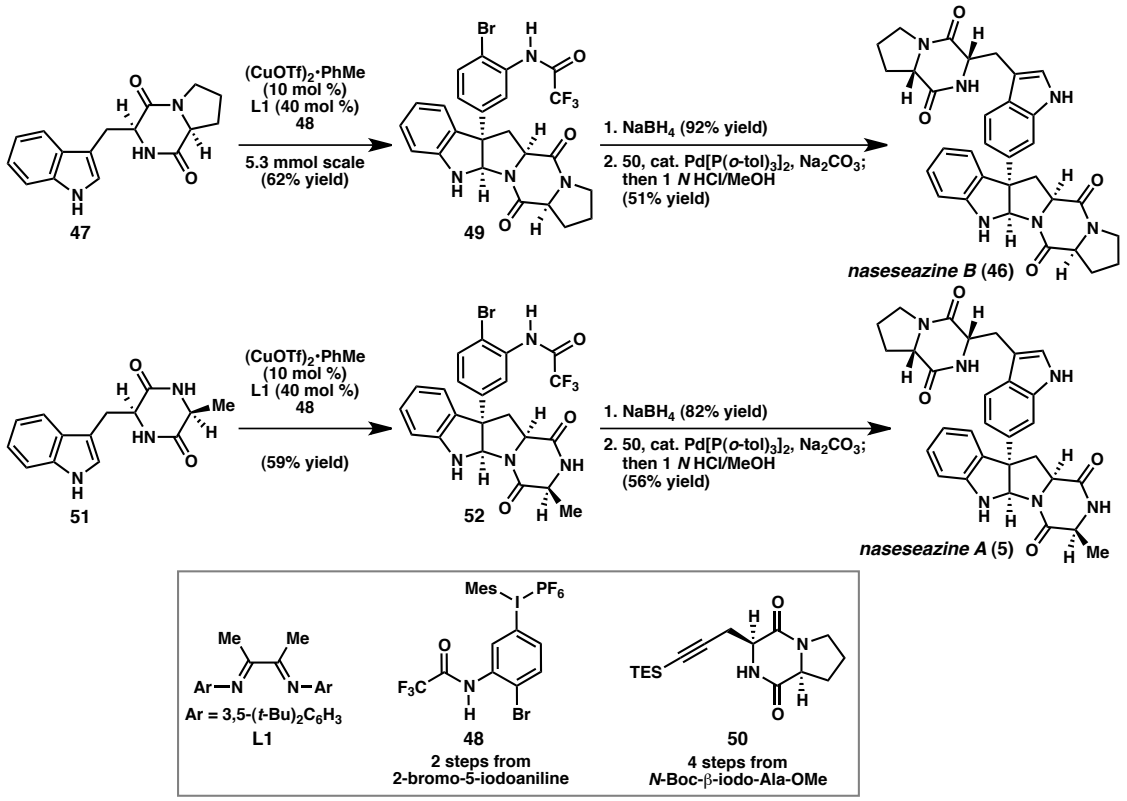
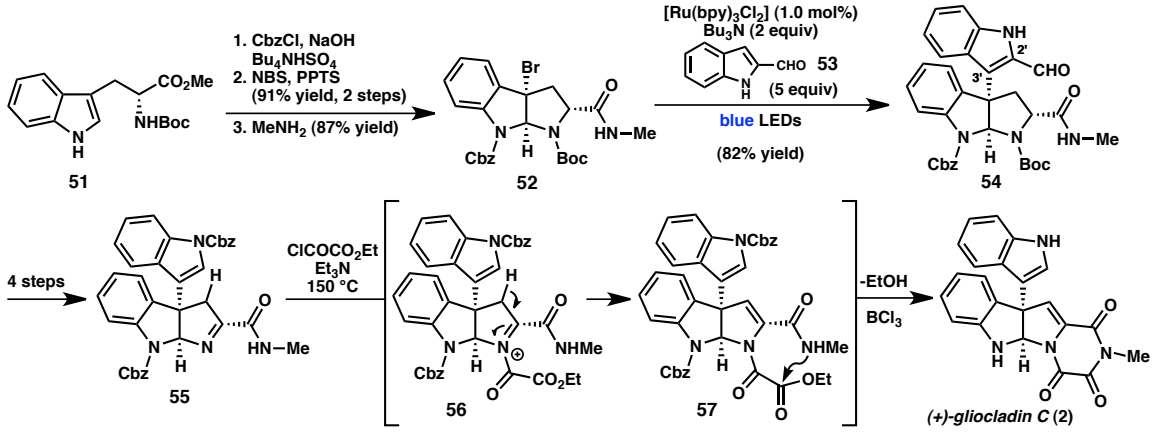
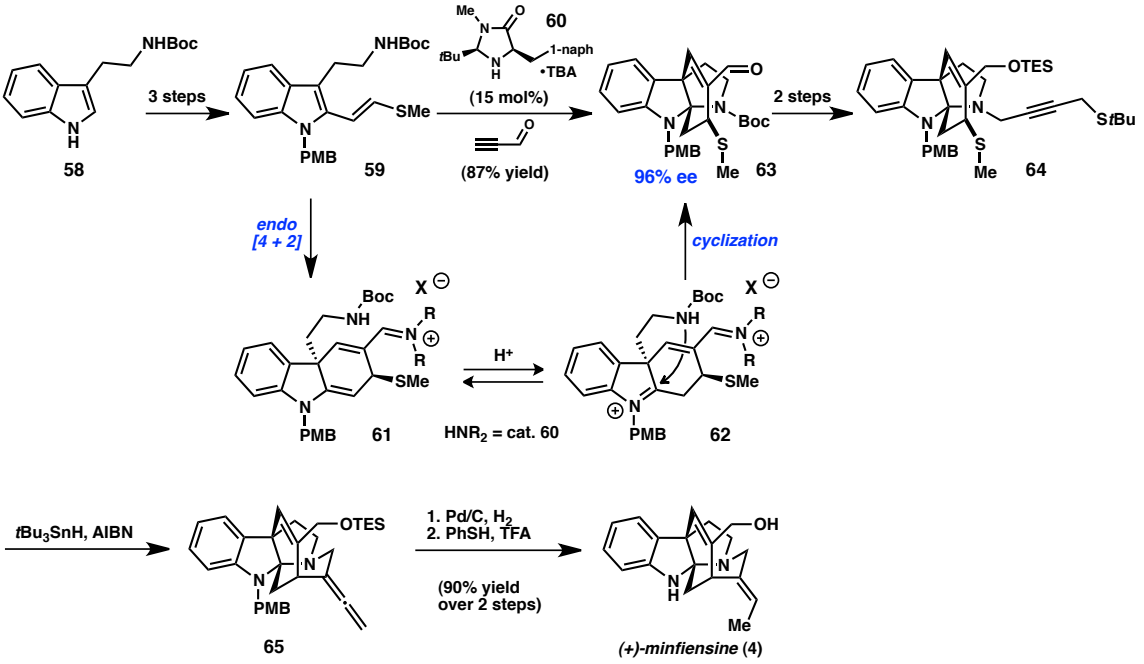


Figure 8. Total synthesis of (+)-gliocladin C by Stephenson employing visible-light phtotoredox catalysis.



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

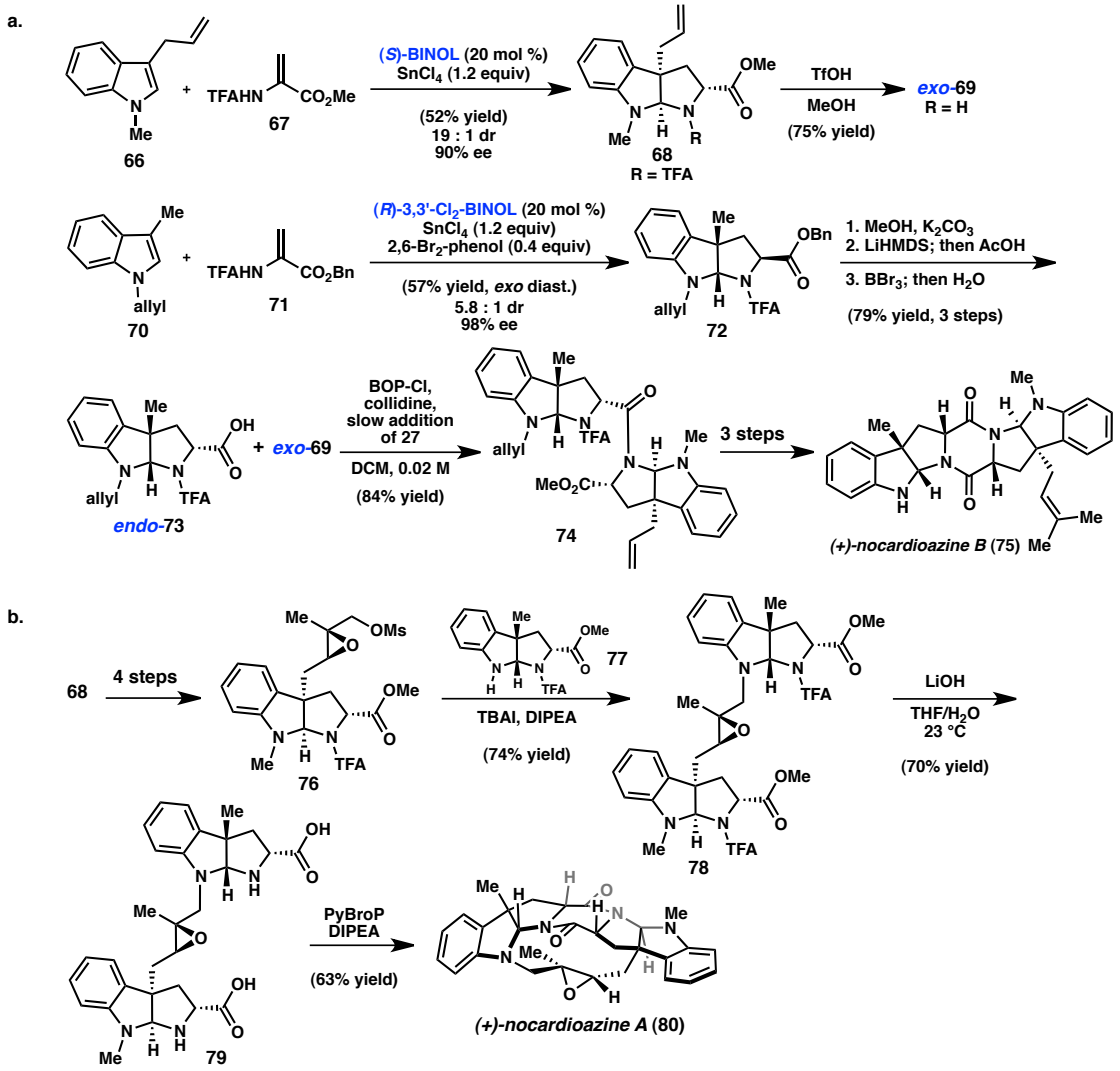
Figure 9. Enantioselective organocatalytic cyclization casacade applied to the total synthesis of minfiensine by MacMillan.



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

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

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



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

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

1.4 Concluding Remarks

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

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

1.5 Notes and References

(1) Varoglu, M.; Corbett, T. H.; Valeriote, F. A.; Crews, P. *J. Org. Chem.* **1997**, *62*, 7078–7079.

(2) Usami, Y.; Yamaguchi, J.; Numata, A. *Heterocycles* **2004**, *63*, 1123.

(3) Zheng, C.-J.; Kim, C.-J.; Bae, K. S.; Kim, Y.-H.; Kim, W.-G. *J. Nat. Prod.* **2006**, *69*, 1816–1819.

(4) Tuntiwachwuttikul, P.; Taechowisan, T.; Wanbanjob, A.; Thadaniti, S.; Taylor, W. C. *Tetrahedron* **2008**, *64*, 7583–7586.

(5) Shaw, K. P.; Aracava, Y.; Akaike, A.; Daly, J. W.; Rickett, D. L.; Albuquerque, E. X. *Mol. Pharmacol.* **1985**, *28*, 527–538.

(6) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chemistry* **2011**, *17*, 1388–1408.

(7) Steven, A.; Overman, L. E. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 5488–5508.

(8) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151–161.

(9) Overman, L. E.; Peterson, E. A. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 2525–2528.

(10) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591.

(11) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143–11144.

(12) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238–241.

(13) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940–14943.

(14) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557–5560.

(15) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 9655–9659.