

CHAPTER 1

Inspiration from Natural Products

1.1 INTRODUCTION

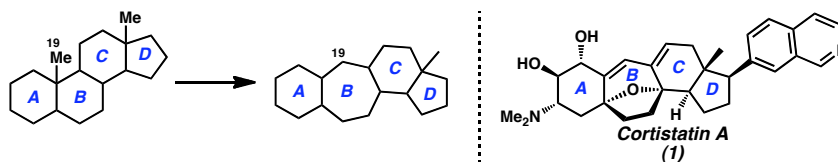
Biologically active natural products often contain interesting and complex structural features and functionalities that make them attractive targets for synthetic chemists. Furthermore, these natural products can serve as inspiration for the development of new synthetic methodologies.¹ Herein, we will discuss our efforts toward the synthesis of several natural product scaffolds.

1.2 CORTISTATIN A

Cortistatin A (**1**) is a potent anti-angiogenic agent that features a unique rearranged steroid core (Figure 1.1) and has become a target for numerous synthetic efforts since its isolation in 2006.² These collective efforts utilized a variety of methods to construct the cortistatin A carbocyclic core, resulting in one semi-synthesis, three total syntheses, two formal syntheses, and numerous syntheses of the pentacyclic cortistatin core.³ A select number of these efforts will be discussed here and are only meant to illustrate some

general approaches that have been directed towards the synthesis of cortistatin A. For convenience, these strategies are organized by method for B ring formation.

Figure 1.1 Rearranged steroid core of cortistatin A

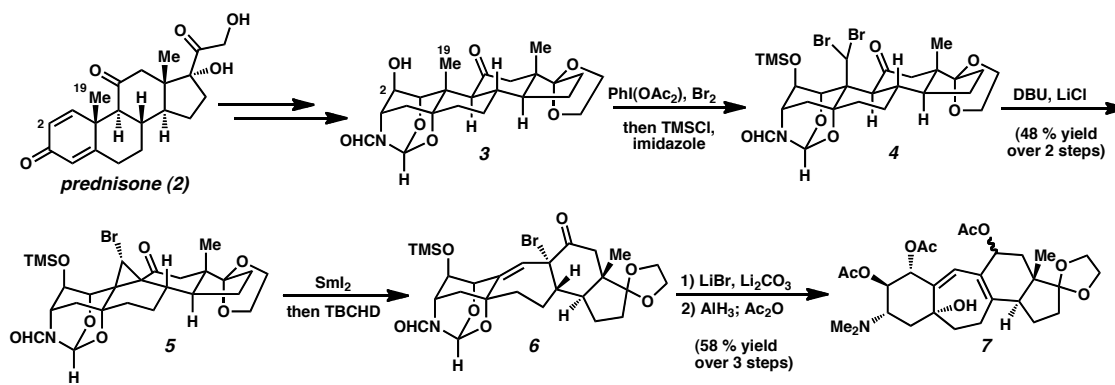


One approach that has been used by several groups is to rely on ring expansion strategies to access the 7-membered B ring by C(19) methyl group incorporation. Baran utilized cyclopropane fragmentation to construct the 7-membered B ring en route to the first synthesis of (+)-cortistatin A (Scheme 1.1).⁴ This semi-synthesis began with the commercially available steroid prednisone (**2**). To prepare the key ring-expansion step, an alcohol-directed double C–H functionalization was triggered by treatment of secondary alcohol **3** with $\text{PhI}(\text{OAc})_2$ and Br_2 and irradiation with a sunlamp. Because the resulting dibromo alcohol is unstable, this intermediate was directly silylated with TMSCl to yield the C(19)-dibromomethyl species **4**, which upon subsequent exposure to DBU and LiCl yielded bromocyclopropane **5** in 48% overall yield. Regioselective ring fragmentation of bromocyclopropane **5** was achieved with SmI_2 followed by treatment with 2,4,4,5-tetrabromo-2,5-cyclohexadienone (TBCHD) to trap the intermediate enolate, yielding α -bromoketone **6**. Dehydrobromination of **6** with Li_2CO_3 followed by alane reduction and acylation produced **7**. With the 7-membered B-ring installed, this intermediate was then elaborated to cortistatin A.

Shair's approach to the total synthesis of (+)-cortistatin A also featured a cyclopropane fragmentation to construct the 7-membered B ring. The key step was a highly diastereoselective aza-Prins cyclization to construct the cortistatin A core.⁵ Corey⁶

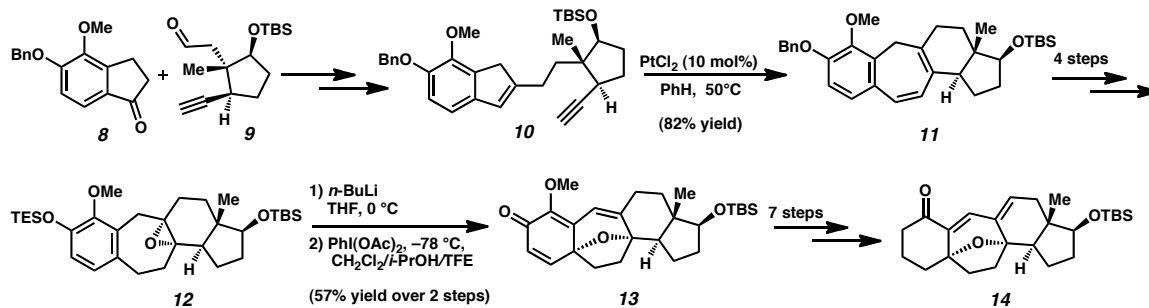
and Magnus⁷ have also pursued routes that contained ring expansion strategies to access the 7-membered B ring in their respective model system studies.

Scheme 1.1 Baran's semi-synthesis of (+)-cortistatin A



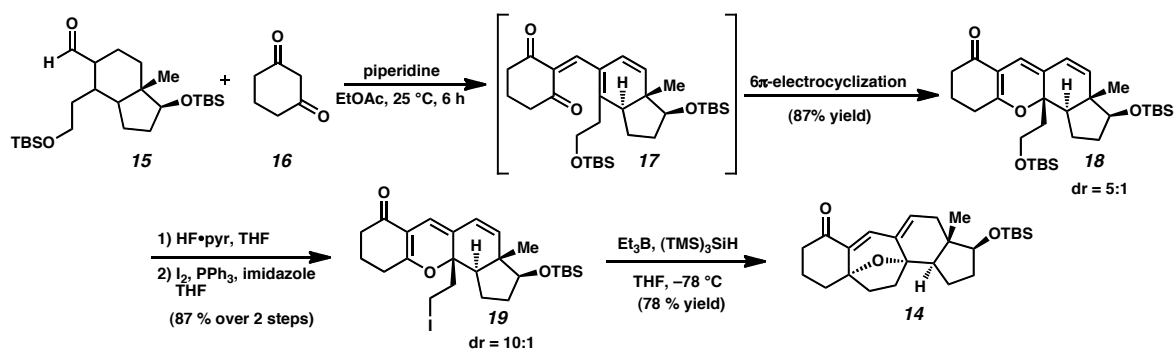
Oxidative dearomatization has also been employed for the construction of the bridging ether moiety contained in the B ring by the Sarpong,⁸ Sorensen,⁹ and Danishefsky¹⁰ groups. Sarpong's second approach in the formal synthesis of (\pm)-cortistatin A featured an enyne cycloisomerization to form the 7-membered B ring followed by an oxidative dearomatization to construct the ether bridge (Scheme 1.2).^{8b} Sarpong's synthesis commenced from indanone **8** and aldehyde **9**, which were converted to alkynyl indene **10** through a series of steps. Enyne cycloisomerization catalyzed by PtCl_2 produced benzocycloheptadiene **11**. After a series of steps to install an epoxide moiety and to selectively reduce an olefin, **12** was then treated with *n*-BuLi to effect a regioselective ring opening, affording an intermediate alcohol. This intermediate alcohol subsequently underwent oxidative dearomatization with $\text{PhI}(\text{OAc})_2$ to furnish the ether bridge of pentacycle **13**. Pentacycle **13** was then elaborated to ketone **14**, a known intermediate that intercepts the synthesis of (+)-cortistatin A reported by Nicolaou.¹¹ Sorensen has also reported a synthesis of the pentacyclic core of cortistatin A that featured a tandem oxidative dearomatization/intramolecular dipolar cycloaddition.⁹

Scheme 1.2 Sarpong's formal synthesis of (±)-cortistatin A



The research groups of Hirama,¹² Danishefsky,¹³ and Gung¹⁴ have independently considered an alternate route that relied on pericyclic transformations to construct the [3.2.1]oxabicyclic ring B ring. Hirama's synthesis commenced from aldehyde **15**, which was derived from enantioenriched Hajos-Parrish ketone (Scheme 1.3).¹² Bicycle **15** was treated with cyclohexane-1,3-dione (**16**) in the presence of base to effect a Knoevenagel condensation to form intermediate **17**. This intermediate **17** underwent spontaneous 6π -electrocyclization to form 2-H-pyran **18** in 87% yield. Conversion of the TBS ether to the iodide yielded iodide **19**, which was then treated with triethylborane and $(\text{TMS})_3\text{SiH}$ to give ketone **14**, the intermediate from the synthesis of (+)-cortistatin A reported by Nicolaou.¹¹

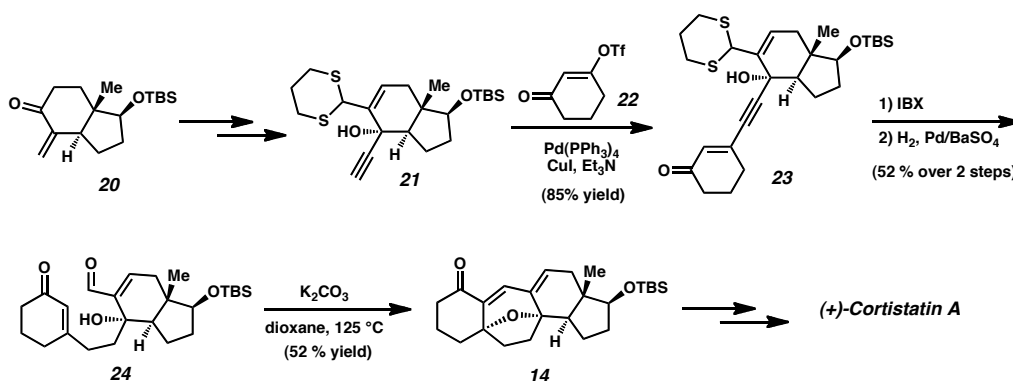
Scheme 1.3 Hirama's synthesis of the pentacyclic core of (+)-cortistatin A



A cascade sequence in which the 7-membered B ring and the tetrahydrofuran ring are simultaneously constructed has been pursued by the Nicolaou group (Scheme 1.4).¹¹ The

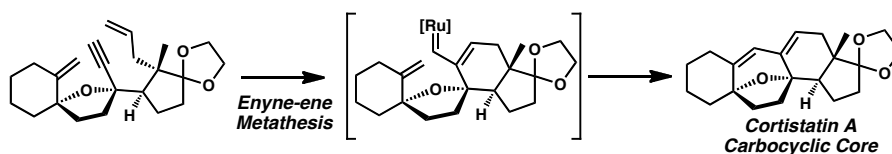
synthesis started from known enone **20**, which was derived from enantiopure Hajos-Parrish ketone. Enone **20** was converted to alkyne **21**, which was then coupled to triflate **22** via a Sonogashira coupling to yield **23**. Dithiane cleavage followed by alkyne hydrogenation afforded **24**. The key step was triggered by treatment of **24** with K_2CO_3 in refluxing dioxane to induce an oxy-Michael addition of the tertiary alcohol into the enone moiety followed by an intramolecular aldol, furnishing dienone **14** in 52% yield. This dienone was then elaborated to (+)-cortistatin A.

Scheme 1.4 Nicolaou's total synthesis of (+)-cortistatin A



Given the promising biological activity and intriguing structure of cortistatin A, we set out to develop our own novel approach towards the construction of the carbocyclic core.¹⁵ It was envisioned that an enyne-ene metathesis would allow rapid access to the carbocyclic core (Scheme 1.5). Our synthetic efforts for the construction of the cortistatin A are discussed in this thesis.

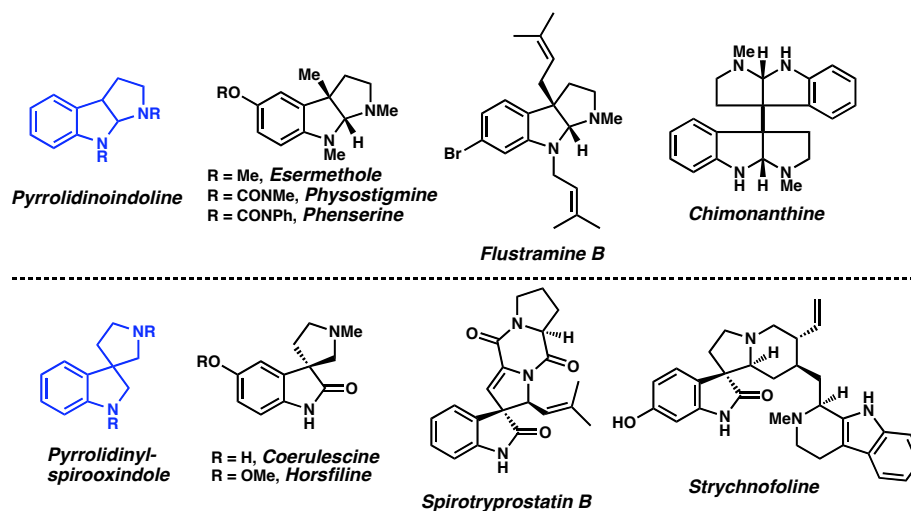
Scheme 1.5 Proposed approach to the cortistatin A carbocyclic core



1.3 OXINDOLE DERIVED STRUCTURAL MOTIFS

Pyrrolidinoindolines and pyrrolidinylspirooxindoles are structural motifs that are prevalent in a large family of alkaloid natural products that have strong bioactivity profiles and interesting structural properties (Figure 1.2).¹⁷

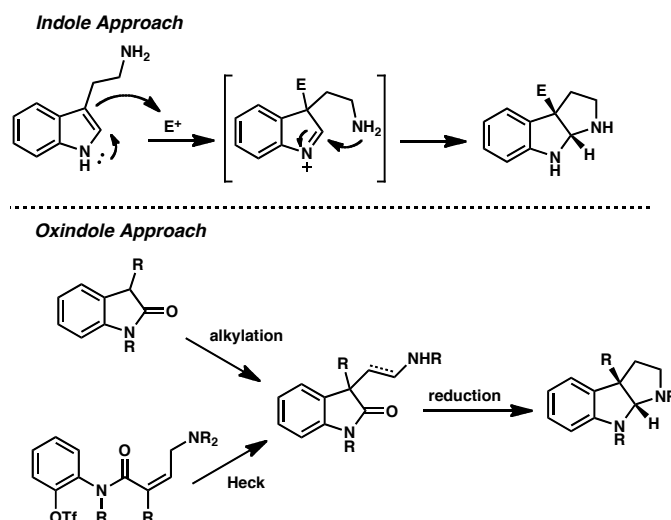
Figure 1.2 Natural products that contain pyrrolidinoindoline and pyrrolidinylspirooxindole cores



There have been many approaches toward the pyrrolidinoindoline core; however there are two general strategies that are most commonly used and are highlighted in Scheme 1.6. The first approach (Indole Approach, Scheme 1.6) involves electrophilic attack at the indole C(3) position of tryptamine or tryptophan (not shown) followed by cyclization by the pendant amine to form the pyrrolidinoindoline core, a mechanism postulated to occur in nature. Many synthetic groups have exploited this first approach to access racemic and enantiopure pyrrolidinoindolines.¹⁶ The second approach (Oxindole Approach, Scheme 1.6) relies on the reduction of a 3,3-disubstituted oxindole to form the pyrrolidinoindoline core. There have been many synthetic methods developed for the construction of 3,3-disubstituted oxindoles,¹⁷ Two of the more common strategies are

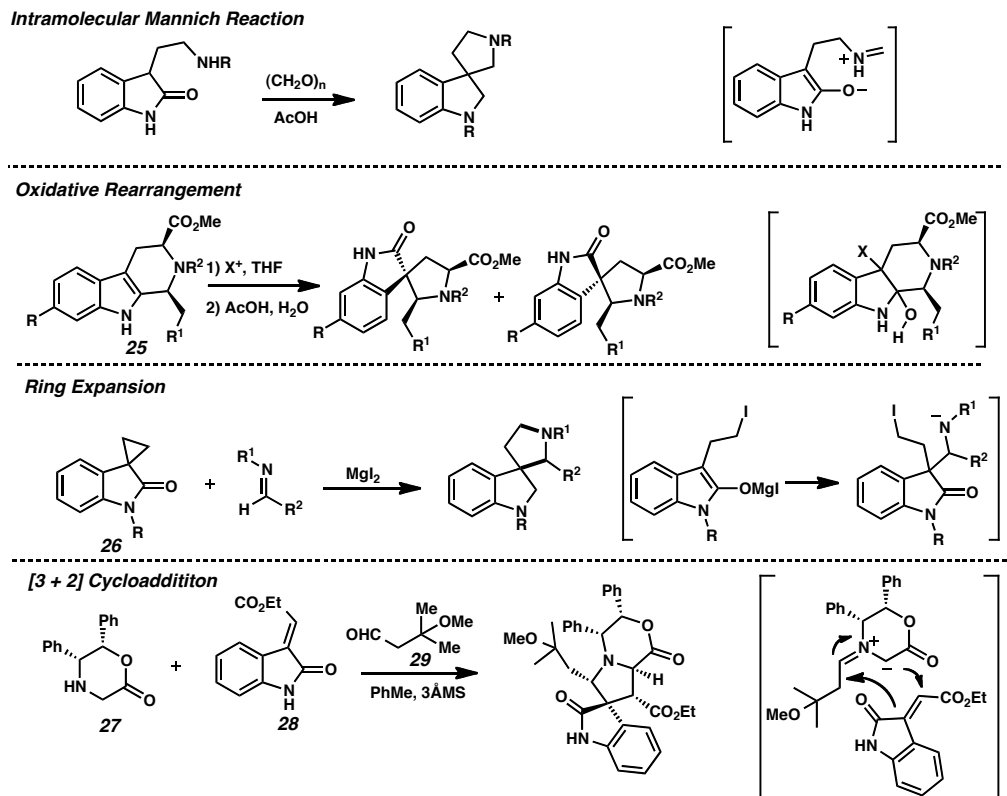
shown in Scheme 1.6: alkylation of the 3-substituted oxindole and an intramolecular Heck cyclization.

Scheme 1.6 General strategies for accessing pyrrolidinoindoline core



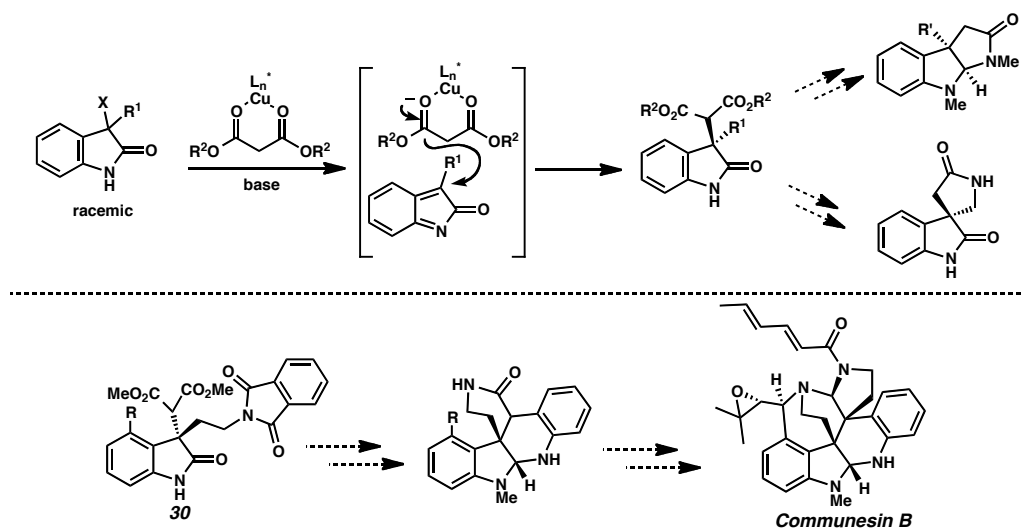
There have also been many methods developed for the construction of pyrrolidinylspirooxindole cores;¹⁸ several common methods are featured in Scheme 1.7. One of the earliest methods involves an intramolecular Mannich reaction, a strategy inspired by the hypothesis that the isomerization of pyrrolidinylspirooxindoles in nature is from a Mannich/retro-Mannich reaction.¹⁹ The second method is an oxidative rearrangement of a tetrahydro- β -carboline **25**, where treatment with a suitable oxidant in combination with a hydroxide source results in an oxidative rearrangement to the pyrrolidinylspirooxindole core.²⁰ A MgI_2 ring expansion strategy has also been utilized to construct the spirocyclic core from imines and spirocyclopropyl oxindoles **26**, wherein MgI_2 is postulated to serve a dual role of Lewis acid activation as well as nucleophilic counterion to promote ring expansion.²¹ The final strategy that is also widely employed for this spirocyclic motif is a three component [3+2] cycloaddition reaction of morpholine **27**, oxindolylideneacetate **28**, and aldehyde **29**.²²

Scheme 1.7 General methods for accessing pyrrolidinylspirooxindole core



Because of the significance of pyrrolidinylspirooxindole and pyrrolidinoindoline cores, we devised a method to access both cores by using 3,3-disubstituted oxindoles (Scheme 1.8). Herein, we will discuss our efforts to pursue these motifs through the development of a novel asymmetric copper-catalyzed malonate addition into oxindoles to access these 3,3-disubstituted oxindoles.²³ Furthermore, another important application is that these disubstituted oxindoles, such as **30**, can also be used to access more complex biologically active molecules, such as communesin B.^{24,25}

Scheme 1.8 Proposed strategy to access pyrrolidinylspirooxindole and pyrrolidinoindoline cores and application to communesin B



1.4 CONCLUSION

We have briefly discussed the role of complex and structurally interesting natural products as an inspiration for method development and total syntheses. We have also briefly highlighted the current strategies available for accessing the key structural motifs discussed in this thesis: cortistatin A and pyrrolidinylspirooxindole and pyrrolidinoindoline cores. Our progress toward the synthesis of the cortistatin A carbocyclic core via an enyne-ene metathesis is discussed in Chapter 2 of this thesis, whereas the synthesis of the pyrrolidinylspirooxindole and pyrrolidinoindoline cores via enantiopure 3,3-disubstituted oxindoles derived from a novel copper-catalyzed malonate alkylation is discussed in Chapter 3.

1.5 NOTES AND REFERENCES FOR TEXT

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