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Total Synthesis of Indoline Alkaloids: A Cyclopropanation Strategy

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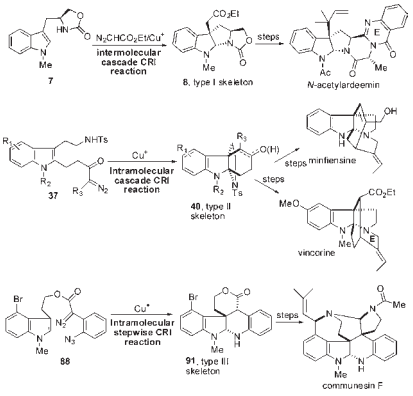

Indoline alkaloids constitute a large class of natural products; their diverse and complex structures contribute to potent biological activities in a range of molecules. Designing an appropriate strategy for the total synthesis of indoline alkaloids is a difficult task that depends on being able to efficiently assemble the core architectures. The best strategies allow access to a variety of different indoline alkaloid structures in a minimum of steps. The cyclopropanation of simple olefins and the subsequent synthetic transformation of the resulting cyclopropyl intermediates has been intensively studied in recent decades. In contrast, the cyclopropanation of enamines, especially for the construction of complex nitrogen-containing ring systems, remained relatively unexplored. Previous success with the cyclopropanation of simple indoles to form stable indolylcyclopropanocarboxylates encouraged us to explore the assembly of indoline alkaloid skeletons with cyclopropanation as a key reaction. Theoretically, indolylcyclopropanocarboxylates are doubly activated by a vicinally substituted amino group and carboxyl group; that is, they are typical donor–acceptor cyclopropanes. Accordingly, they tend to yield an active iminium intermediate, which can undergo inter- and intramolecular nucleophilic reactions to form the core structure of indoline alkaloids with an expanded ring system. In this Account, we summarize our efforts to develop a cascade or stepwise reaction of cyclopropanation/ring-opening/iminium cyclization (the CRI reaction) on tryptamine derivatives for assembling indoline alkaloid skeletons.

With the CRI approach, three types of indoline alkaloid skeletons have been efficiently constructed: (i) hexahydropyrrolo[2,3-*b*]indoline (type I), (ii) tetrahydro-9a,4a-iminoethano-9*H*-carbazole (type II), and (iii) tetrahydroquinolino[2,3-*b*]indoline (type III). The effects of substituents on tryptamine derivatives were carefully investigated for inter- and intramolecular CRI reactions during construction of type I and type II skeletons. These results provided a basis for the further design and synthesis of complex natural products containing nitrogen.

The usefulness of the CRI reaction is well demonstrated by our total synthesis of structurally intriguing indoline alkaloids such as *N*-acetylardeemin, minfiensine, vincorine, and communesin F. In addition, we highlight advances by other groups in construction of the three types of skeletons as well as their total syntheses of these indoline alkaloids. Discussion of the total syntheses of these indoline alkaloids focuses on comparing the individual synthetic strategies for forming the ring systems embedded in the final products.

We also describe the total synthesis of perophoramidine, which has the same type III skeleton as communesin F. The observation of a retro Diels–Alder reaction during our synthesis of communesin F inspired the hetero Diels–Alder reaction on which our total synthesis of perophoramidine was based.

1. Introduction

The persistent interest in cyclopropanation[1] derives from the special charm of the resulting three-membered carbon cycles, not only because they are frequently found in natural products with potent biological activities,[2] but more importantly because they serve as intermediates for subsequent synthetic transformations and can be used in assembling complex molecular architectures that are

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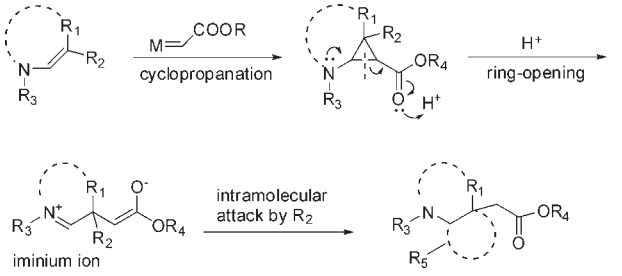
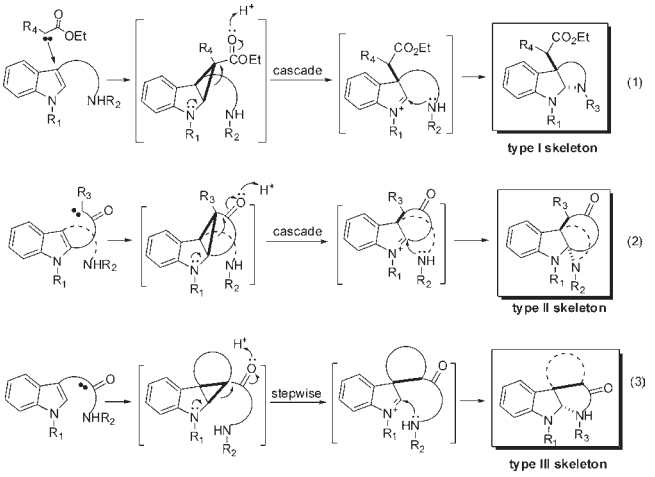
SCHEME 1. CRI Reaction



difficult to achieve by common methods.[3] Active cyclopropanes, especially the so-called donor–acceptor (DA) cyclopropanes,[4] which are doubly activated by vicinally substituted electron-donating groups and electron-withdrawing groups, are particularly useful intermediates because of their intrinsic vulnerability to undergo ring-opening reaction. The resulting polarized acyclic intermediates are both electrophilic and nucleophilic and are able to take part in various cyclopropane-based cascade reactions under relatively mild reaction conditions.

Theoretically, aminocyclopropanocarboxylates are typical DA cyclopropanes and tend to collapse in the presence of Lewis acids. The resulting highly reactive iminium ion species are prone to intramolecular attack by a nucleophile on R_2 to produce a more complex ring system (Scheme 1). This cyclopropanation/ring-opening/iminium cyclization reaction (CRI reaction) may be very useful in the construction of complex nitrogen-containing ring systems. Unfortunately, unlike the abundance of reports on simple cyclopropanocarboxylates,[5] a literature survey found only a few studies describing the application of aminocyclopropanocarboxylates prepared from enamines and an α-diazoester.[6] The reason that aminocyclopropanocarboxylates are less explored is probably due to the characteristics of Lewis base enamines being able to coordinate to an unsaturated transition metal; this coordination prevents transition metal-catalyzed diazo decomposition, leading to the formation of an active carbene species. Among transition metals commonly used for diazo decomposition, copper has a relatively low activity for associating with enamines and can render the presence of an enamine functional group when it catalyzes diazo decomposition. The inconvenience of preparing aminocyclopropanocarboxylates through direct transition-metal-catalyzed cyclopropanation of enamines has impeded the use of aminocyclopropanocarboxylates as valuable synthons.

For the past several years, our group has focused on developing efficient methodologies for the synthesis of indoline alkaloids with an intriguing ring system. We envisioned that three types of indoline alkaloid skeletons, namely, (a) hexahydropyrrolo[2,3-*b*]indoline (eq 1), (b) tetrahydro-9a,4a-iminoethano-9*H*-carbazole (eq 2), and (c) tetrahydroquinolino[2,3-*b*]indoline (eq 3), could be efficiently assembled through similar cascade or stepwise reactions of indolylcyclopropanocarboxylate-based ring-opening/iminium cyclization, as long as a cyclopropane ring could be efficiently installed on the 2,3-double bond of tryptamine derivatives. To our delight, two earlier examples of preparing stable indolylcyclopropanocarboxylates via copper-catalyzed cyclopropanation were reported by Welstead et al. and Wenkert et al., respectively, in the 1970s.[7] Although syntheses of indolylcyclopropanecarboxylates are rare and the reactivity of tryptamine derivatives toward cyclopropanation on the 2,3-double bond is not fully understood, the studies of Welstead et al. and Wenkert et al. strongly encouraged us to explore a new methodology to construct indoline alkaloid skeletons via a cascade or stepwise reaction of cyclopropanation/ring-opening/iminium cyclization (CRI reaction).



2. Type I CRI Reaction: Assembly of the Hexahydropyrroloindoline

A hexahydropyrrolo[2,3-*b*]indoline skeleton (type I skeleton) is present in a large family of indoline alkaloids with a wide spectrum of pharmacological activities.[8a] For example, indoline alkaloid physostigmine with a pyrroloindoline skeleton shows potent activity against acetylcholinesterase, and it has been used as a clinical reagent for treatment of Alzheimer's disease.[8b] These alkaloids have been the subject of extensive studies by synthetic chemists. Among methodologies for construction of the skeleton, the creative electrophilic addition/cyclization by

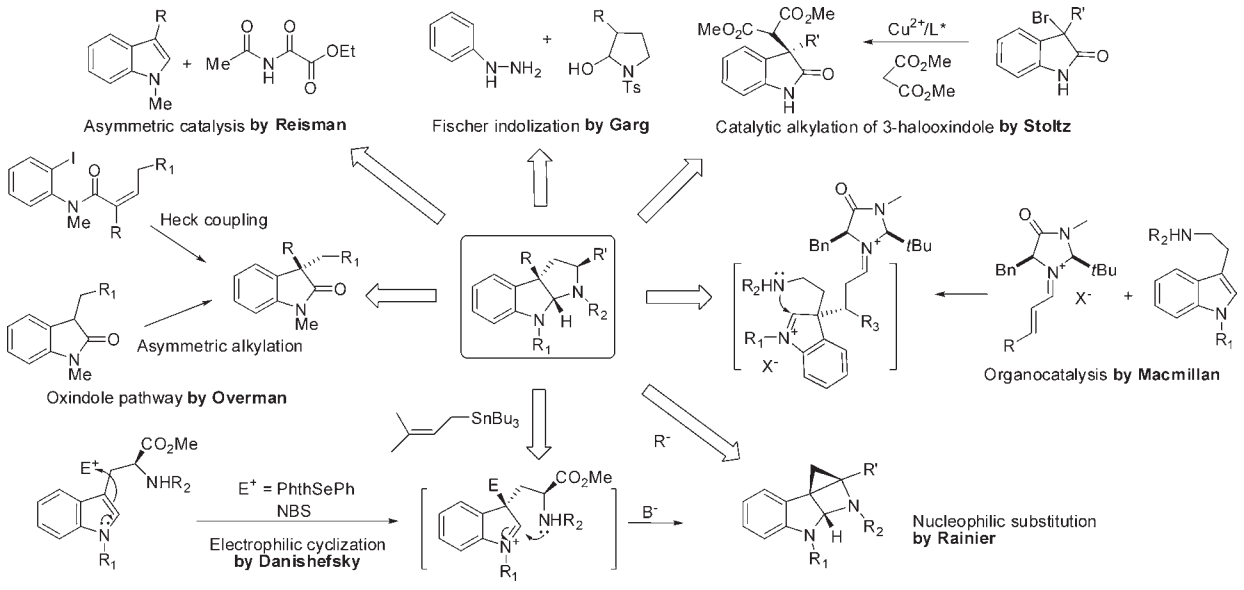
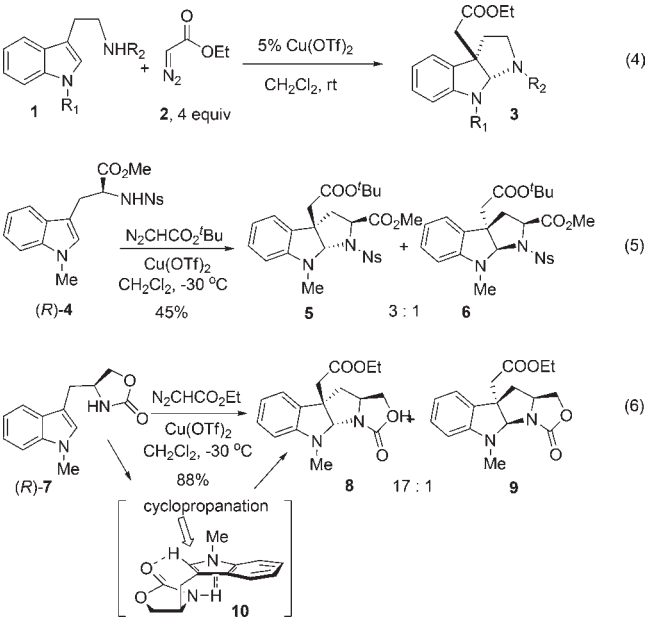


FIGURE 1. Representative strategies for assembly of type I skeleton.

Danishefsky et al.,[9] the nucleophilic opening of cyclopropylazetoindoline by Rainier et al.,[10] an asymmetric Heck coupling and bisenolate alkylation by Overman, and co-workers,[11] an innovative asymmetric organocatalysis by Macmillan et al.,[12] an asymmetric catalysis by Reisman et al.,[13] bisoxazoline ligand catalytic alkylation by Stoltz et al.,[14] and Fischer indolization by Garg and co-workers[15] stand out as the most efficient ways to prepare the chiral pyrroloindole skeleton (Figure 1).

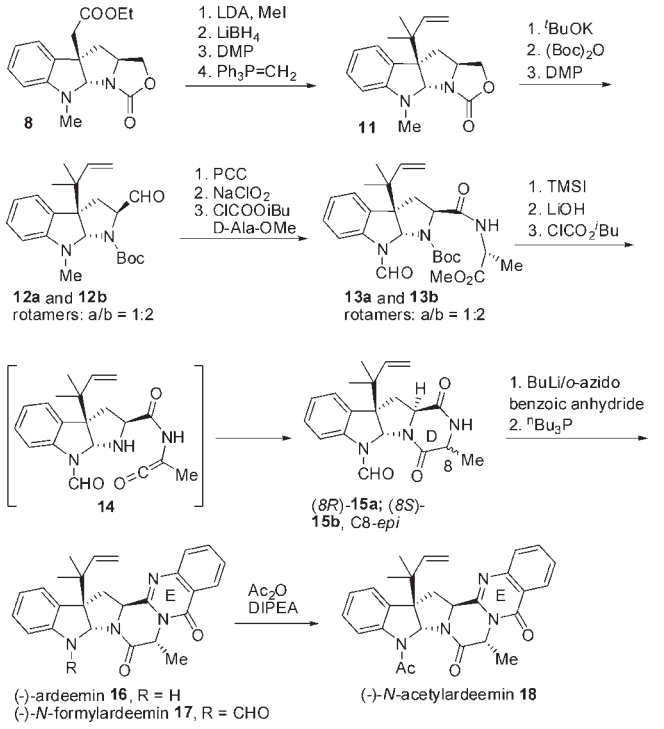
In an attempt to gain access to the hexahydropyrroloindoline skeleton, we created an intermolecular cascade CRI reaction as shown in eq 4.[16] We have carefully studied the effects of substituents on tryptamine in the CRI reaction. Indeed, preliminary screening indicated that only an electron-donating R_1 group (Me, Bn) facilitated the intermolecular CRI reaction. In fact, a strong electron-withdrawing group R_2 (Ns, Tf) on the side chain improved the yield by reducing the common N−H insertion byproduct and maintaining sufficient nucleophilicity of the nitrogen to capture the in-situ-generated indolenium. Both $Cu(OTf)_2$ and CuOTf catalyzed the reaction to give a similar yield. In contrast, rhodium salts were ineffective at catalyzing the reaction. Under optimal conditions, the cascade reaction provided hexahydropyrroloindoline **3** in 36% yield (R_1 = Me, R_2 = Ns) at room temperature (rt).

We next explored the asymmetric version of this cascade reaction induced by chiral auxiliary groups. In an early stage of our work, L-tryptophan-derived (*R*)-**4** was first used to test the efficiency of asymmetric induction in the CRI reaction at −30 °C in CH_2Cl_2 (eq 5).[16] Although the 45% yield was



acceptable, the diastereomeric ratio (3:1) was very low. Further screening of chiral auxiliary groups found that oxazolidinone (*R*)-**7**, easily prepared from L-tryptophan by a three-step procedure, underwent the CRI reaction smoothly (30 h) in dilute CH_2Cl_2 at −30 °C to give diastereomers **8** and **9** in 88% combined yield and a 17:1 ratio at 1 mmol scale (eq 6). The higher diastereomeric ratio (dr) value obtained probably resulted from a predominant transitional conformation **10** at low temperature, which was stabilized by the interactions of N−H/π[17] and hydrogen bonding. Unfortunately, when we scaled the reaction to 50−100 g without changing the conditions, a large quantity of dark nonstirred precipitates was produced because of the rapid,

SCHEME 2. Total Synthesis of (−)-*N*-Acetylardeemin



nonproductive decomposition of excess diazoester present at a higher concentration, resulting in a low yield of **8**. The precipitate problem was partially solved by switching the solvent from CH_2Cl_2 to toluene and raising the reaction temperature to room temperature, but the diastereoselectivity of the CRI reaction suffered substantially as a result.[18] In this way, we were able to isolate **8** in 40−45% yield on the 50−100 g scale. Optimization of reaction conditions guaranteed a sufficient supply of chiral intermediate **8** as starting material for the total synthesis of indoline alkaloid (−)-*N*-acetylardeemin with potent activity of anti-multidrug resistance (MDR).[19]

3. Total Synthesis of (−)-*N*-Acetylardeemin

In the pioneering synthesis of (−)-*N*-acetylardeemin by Danishefsky's group,[9] the C3 isoprenyl group was introduced in a straightforward manner by one-step Lewis-acid-promoted nucleophilic replacement of the PhSe group with an isoprenyl group (Figure 1). Our synthesis[18] commenced with **8** involved the installation of the C3 isoprenyl group in multiple steps via methylation, reduction, oxidation, and Wittig reaction (**8**−**11**, Scheme 2). Modification of the oxazolidinone moiety in **11**, via opening of the oxazolidinone ring, protection of the amine, and oxidation of the hydroxyl group provided **12** as a mixture of rotamers. After transformation of the methyl group in **12** into a formyl group by

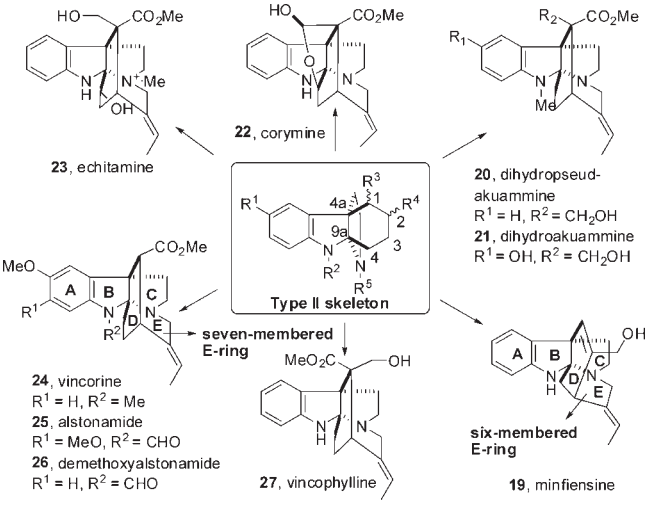


FIGURE 2. Indoline alkaloids with an iminoethanocarbazole.

pyridinium chlorochromate, the aldehyde in **12** was oxidized to the corresponding acid and the resulting acid was condensed with D-alanine ester to give **13** as a mixture of rotamers. After removal of the Boc with trimethylsilyl iodide and hydrolysis of the ester in **13**, the D-ring was formed by intramolecular condensation between the amide group and the acid group to afford (8*R*)-**15a** and C8-*epi*-**15b**. Epimerization at C8 most likely was the result of a ketene intermediate **14** during condensation. A mixture of (−)-ardeemin and (−)-*N*-formylardeemin (1:1) was obtained through the reaction of **15a** with *o*-azidobenzoic anhydride in the presence of BuLi in tetrahydrofuran, followed by reduction of the azide group in benzene with *n*-Bu_3P and simultaneous cyclization of the E ring. (−)-*N*-Acetylardeemin was produced by treatment of (−)-ardeemin with Ac_2O and diethylisopropylamine by adapting Danishefsky's conditions.[9]

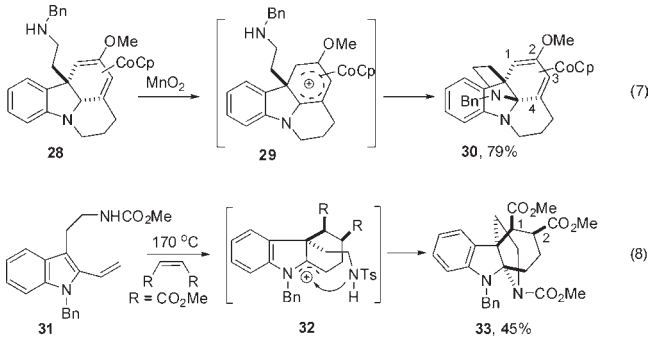
4. Type II CRI Reaction: Assembly of the Tetrahydroiminoethanocarbazole

The tetrahydro-9a,4a-iminoethano-9*H*-carbazole architecture (type II skeleton) is a highly congested polycyclic ring system. Two indoline alkaloid families share the same core structure: one is the *akuammiline* family,[20] and the other is the *strychnos* family (Figure 2).[21] The most distinguishing structural feature between the two indoline alkaloid families is that members of the *strychnos* family such as minfiensine (**19**)[22] have a six-membered E-ring, while members of the *akuammiline* family, such as dihydropseudakuammine (**20**),[23] dihydroakuammine (**21**),[23] corymine (**22**),[24] echitamine (**23**),[25] vincorine (**24**),[26] alstonamide (**25**),[27] demethoxyalstonamide (**26**),[27] and vincophylline (**27**),[28] have a seven-membered E-ring. As major components from extracts of the

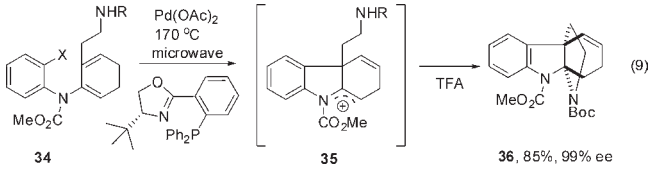
plant *Winchia callophylla* A. DC., *akuammiline* alkaloids have historically been used in traditional Chinese medicine, and have been developed into a commercially available drug (Dengtaiye Pian) to treat chronic tracheitis in China.[29]

Although the first *akuammiline* alkaloid, echitamine, was identified about 80 years ago,[25] a breakthrough in the total synthesis of these intriguing indole alkaloids was not achieved until 2005 when Overman et al. reported the first total synthesis of (+)-minfiensine.[30a] The major synthetic challenge is how to efficiently assemble the pentacyclic core structure.

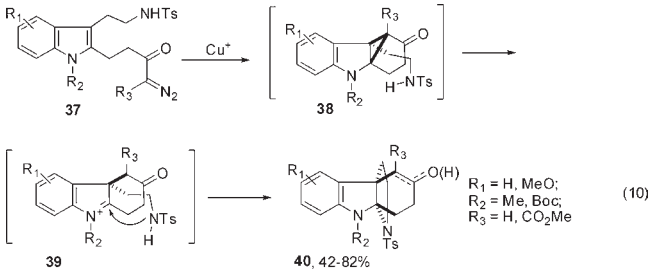
The first example of preparing the core structure of iminoethanocarbazole was described by Vollhardt and Grotjahnin 1990 (eq 7).[31] When trying to make a *strychnine* skeleton rather than a *strychnos* skeleton, they obtained a cobalt complex of **30** by intramolecular capture of cation **29** with the amine on the side chain, which was generated through oxidation of the cobalt complex **28**. Two years later, Lévy's group reported the second example of assembling iminoethanocarbazole core **33** from **31** and dimethyl maleate by an intermolecular cascade Diels–Alder/Tandem iminium cyclization reaction (eq 8).[32]



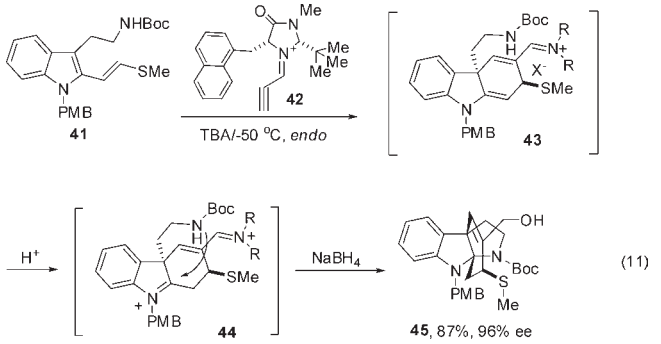
In Overman's first total synthesis of (+)-minfiensine,[28] a stepwise reaction of a microwave-promoted asymmetric Heck reaction and acid-catalyzed Tandem cyclization was used to yield dihydrocarbazole **36** with excellent enantioselectivity (eq 9). Without the assistance of microwaves, the first step Heck reaction was extremely sluggish, requiring at least 70 h at 100 °C. The double bond on the cyclohexene ring in **36** allowed further functional conversions leading to (+)-minfiensine.



After successfully creating the type I CRI reaction for preparing the tetrahydropyrroloindoline, we extended the application of the CRI reaction to the construction of the iminoethanocarbazole for the synthesis of corresponding indoline alkaloids. As depicted in eq 10, when tryptamine derivative **37** possessing a 2-substituted α-diazoketone group was treated with a catalytic amount of CuOTf at rt in CH_2Cl_2, a cascade CRI reaction occurred, leading to **40** in moderate to high yields. The reaction tolerated a variety of substituents on the indole core. Interestingly, when R_2 was an electron-donating methyl group, compound **40** existed as a mixture of β-keto ester and enol ester. In contrast, when R_2 was an electron-withdrawing Boc group, only enolate ester **40** was isolated. Again, as in the type I CRI reaction, rhodium salts were ineffective at catalyzing the type II CRI reaction. The enol ester group in **40** had the advantage of being easily manipulated for E-ring formation in our synthesis of (±)-minfiensine.[33]



More recently, Macmillan et al. demonstrated the power of organocatalysis in construction of iminoethanocarbazole.[34] In their elegant cascade reaction (eq 11), the first step of an asymmetric Diels–Alder reaction between **41** and propynal was promoted by forming an active iminium intermediate **42**, which proceeded via a stereoselective *endo* addition to give intermediate **43**. In the presence of tribromoacetic acid, **43** further underwent a Tandem iminium cyclization, followed by reduction of the aldehyde group, to afford **45** in 87% yield and 96% enantiometric excess.



5. Total Synthesis of Minfiensine by Overman, Qin, and Macmillan

An overview of strategies used by Overman, Qin, and Macmillan to form the E-ring of minfiensine is summarized

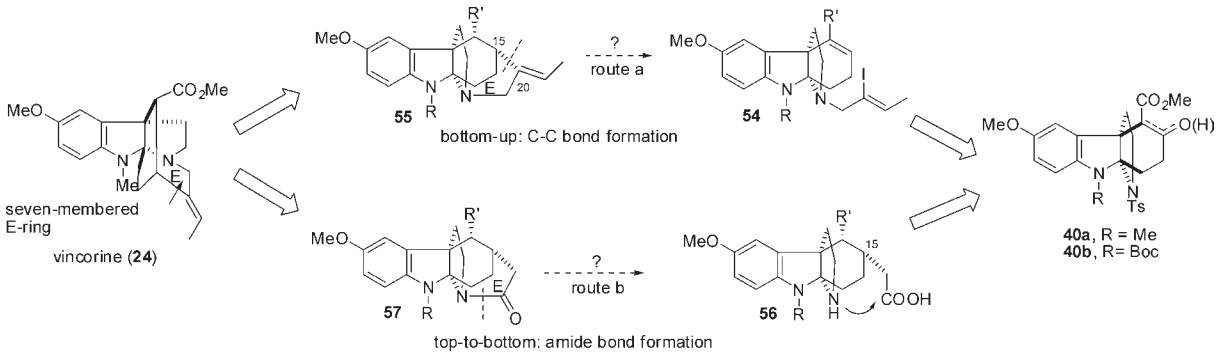
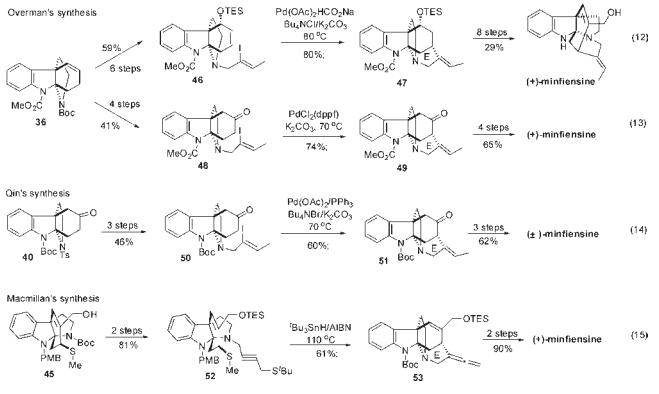


FIGURE 3. Retrosynthetic analysis of vincorine.

in eqs 12−15. In Overman's first-generation synthesis of (+)-minfiensine,[30a] a reductive Heck reaction was chosen (eq 12). In this approach, the double bond in **36** was converted to a protected vinyl hydroxyl group through epoxidation, ring-opening, protection with triethylsilyl group, and replacement of the Boc group with an iodovinyl group. Although the yield of E-ring formation step was higher, an eight-step procedure was used to give the final product; most of the additional steps were needed in order to transform the protected hydroxyl group in **47** to an allylic hydroxyl group. To avoid this longer functional transformation at the end of the synthesis, Overman's second-generation synthesis (eq 13)[30b] produced a pentacyclic ketone **49** through palladium-catalyzed α-enolate allylation of **48** using improved Cook's conditions.[35] The ketone in **48** was derived by selective hydroboration of the double bond in **36**.

In our synthesis of (±)-minfiensine (eq 14),[33] the preexistence of a ketone group in **40** provided us straightforward access to the E-ring by using a similar α-enolate allylation reaction (**50** to **51**) after installing an iodovinyl side chain on the nitrogen, which allowed us to significantly reduce the number of synthetic steps.

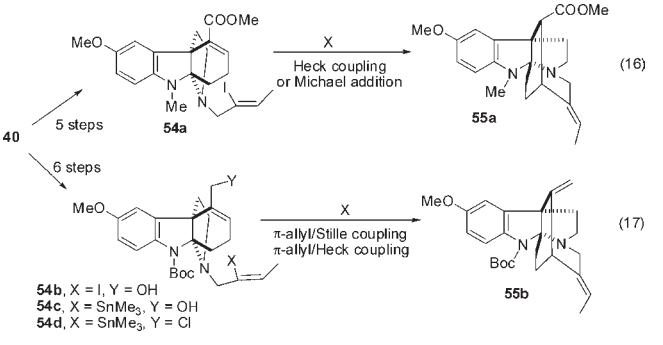


In Macmillan's synthesis of (+)-minfiensine (eq 15),[34] a radical cyclization for assembling the E-ring was used to give **53** having an allene group. The regio- and stereoselective hydrogenation of the allene group in **53** and deprotection of the TES and Boc groups with TFA afforded (+)-minfiensine with high efficiency.

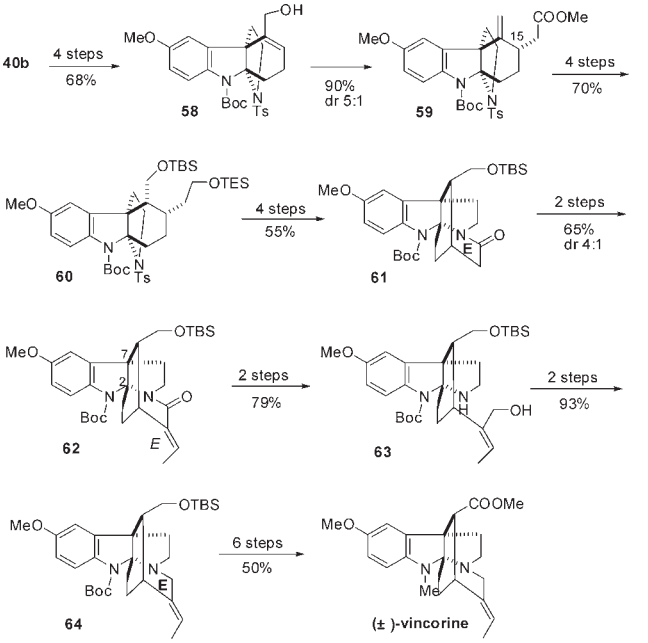
6. Total Synthesis of Vincorine

The successful total synthesis of (±)-minfiensine inspired us to carry out a synthesis of (±)-vincorine,[36] an *akuammaline* alkaloid having the same skeleton as *strychnos* minfiensine. The seven-membered E-ring in vincorine is more difficult to construct than the six-membered E-ring in minfiensine within such a rigid ring system. Retrosynthetic analysis of vincorine reveals two routes to E-ring formation starting from the same intermediate **40** (Figure 3). A bottom-up approach (route a) of E-ring formation seems to be more straightforward; it involves a late-stage C15−C20 bond formation (**54** to **55**) via a transition-metal-catalyzed coupling reaction or Michael addition. The top-to-bottom approach (route b) features a key intramolecular amidation reaction of **56** following the stereoselective installation of a side chain at C15.

Unfortunately, as shown in eqs 16 and 17, after transformation of **40** to **54** via a multistep reaction sequence, neither the Heck coupling nor the palladium-catalyzed π-allyl/Heck or π-allyl/Stille coupling reaction of **54** succeeded in producing the cyclization product **55**, even with systematic



SCHEME 3. Total Synthesis of (±)-Vincorine



screening of reaction conditions. The intramolecular Michael addition of **54a** also failed to produce the desired **55a**. The steric biasing obviously imposed by the cross-ring tetracyclic system might account for the failure of the bottom-up cyclization to form the E-ring.

We then turned our attention to the top-to-bottom route b for E-ring formation by preinstalling a side chain on C15. As shown in Scheme 3, a methyl acetate side chain (**59**) was stereoselectively placed on C15 by a Johnson-Claisen rearrangement after converting **40b** to the allyl alcohol **58** in three steps involving ketone reduction, dehydroxylation, and ester reduction. The stereoselective hydroboration of the double bond in **59** provided a single stereomer in excellent yield; this step required prior reduction of the ester group and protection of the resulting hydroxyl group first (**59** to **60**). The seven-membered E-ring formation (**61**) was realized using a Mukaiyama condensation after converting the TES-protected hydroxyl group to an acid and removing the Ts protecting group. The *E*-ethylene group was stereoselectively introduced by two steps of aldol addition and dehydroxylation to give **62**. In order to avoid a troublesome amide reduction on the seven-membered E-ring, the lactam ring was reopened to ensure regioselective reduction of the amide rather than the double bond. Recyclization of the E-ring by two steps of bromination and alkylation (**63** to **64**), followed by six steps of tailoring the remaining functional groups, led to the first total synthesis of (±)-vincorine in 31 steps with 1% overall yield.

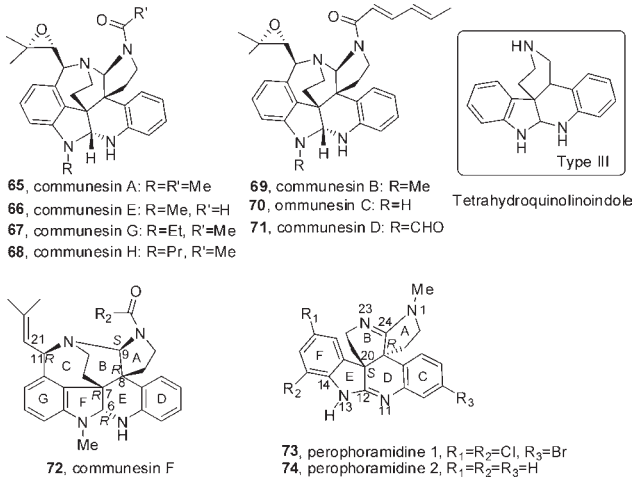
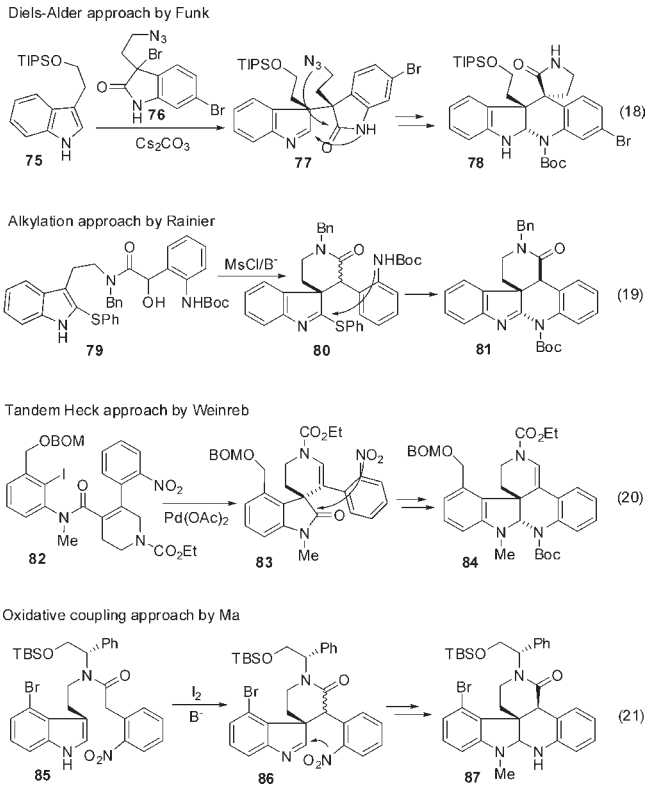


FIGURE 4. Indoline alkaloids with the tetrahydroquinolinoindoline.

7. Type III CRI Reaction: Assembly of the Tetrahydroquinolinoindoline

The tetrahydroquinolinoindoline skeleton (type III skeleton) is found in two classes of structurally related indoline alkaloids, communesins A-H[37] and perophoramidine[38] (Figure 4). Perophoramidine structurally differs from communesins in its reverse stereochemistry at the two vicinal quaternary carbon centers and in its bis-amidine functionality instead of bis-aminal functionality.

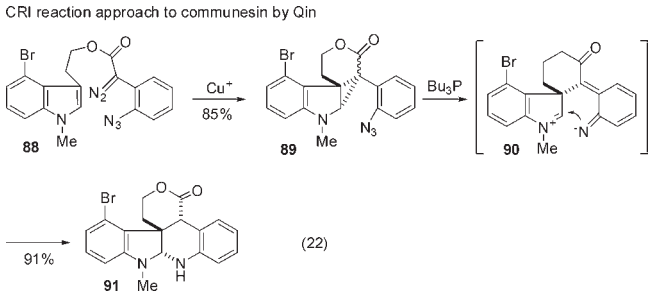
The novel architecture together with their biological activities made the communesins and perophoramidine



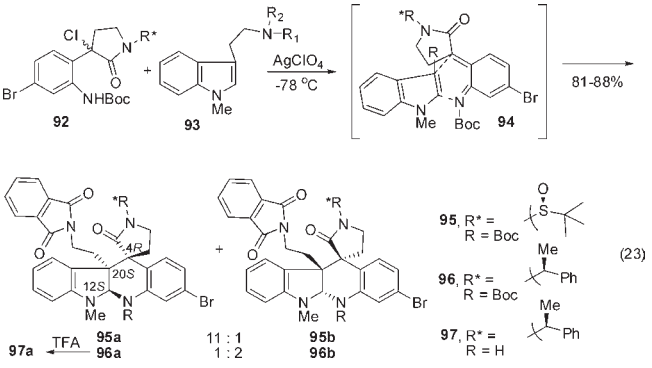
appealing targets for synthetic chemists to develop diverse synthetic strategies. Early model reactions to build up the core structures of communesins and perophoramidine by Stoltz, Funk, Weinreb, and Qin have been reviewed.[39] These model reactions culminated in the total synthesis of (dehalo)perophoramidine by Funk and Fuchs,[40] Rainier et al.,[41] and Qin et al.,[42] as well as the total synthesis of communesin F by Qin et al.,[43] Weinreb et al.,[44] and Ma et al.[45] The key reactions used in these total syntheses for assembly of the core structure are depicted in eqs 18−21.

In Funk's total synthesis of (±)-perophoramidine,[40] a stepwise intermolecular formal hetero Diels−Alder reaction between **75** and **76** was used to give **78** (eq 18). In the total synthesis of (±)-dehaloperophoramidine by Rainier et al.,[41] a two-step reaction of an intramolecular alkylation of **79** followed by C-ring cyclization afforded the pentacyclic **81** (eq 19). Weinreb employed an intramolecular Tandem Heck coupling of **82** and reductive cyclization of the resulting oxindole **83** to yield **84** in the total synthesis of (±)-communesin F (eq 20).[44] More recently, Ma et al. reported the total synthesis of (−)-communesin F via the chiral auxiliary-induced oxidative coupling of **85**, followed by reductive cyclization of **86** to yield the chiral **87** (eq 21).[45]

In continuing to apply the CRI reaction to the synthesis of indoline alkaloids, we carried out a stepwise intramolecular CRI reaction to efficiently construct the core structure of communesins (eq 22).[43] In the type I and II cascade CRI reactions (eqs 1 and 2), the cyclopropane intermediates from the first step were unstable and directly underwent ring collapse and ring closure. In contrast, the type III CRI reaction (eqs 3 and 22) produced a stable and separable cyclopropane intermediate **89**. Reduction of the azide group in **89** resulted in cyclization to give **91**.



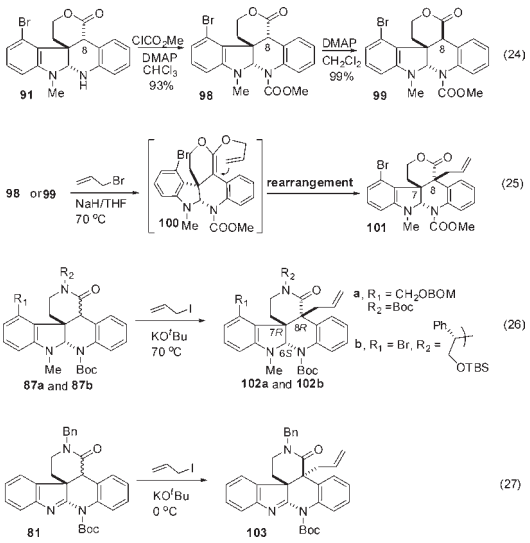
In our total synthesis of (+)-perophoramidine, a chiral auxiliary-induced hetero Diels−Alder reaction was used to rapidly assemble the core structure.[42] As shown in eq 23, when the chiral benzodiene precursor **92**, generated from 6-bromo isatin by seven steps, reacted with a protected tryptamine **93** in the presence of silver ion at low temperature, a hetero Diels−Alder reaction occurred smoothly in an *endo* addition manner (**94**) to give diastereomers **95a** and **95b** with two *trans* ethylene groups at the two vicinal quaternary carbon centers. An acceptable diastereoselectivity (11:1) was obtained when (*S*)-*tert*-butyl sulfoxide was used as a chiral auxiliary. Use of (*S*)-α-methylbenzylamine as a chiral auxiliary led to similar yield but a significantly lower dr value of 1:2 (**96a** and **96b**). Luckily, facile formation of a single crystal of **97a**, generated by removing the Boc group of **96a**, allowed us to determine the absolute configuration of **97a** by X-ray analysis as 4*R*, 12*S*, 20*S*.



8. Formation of the C8 Quaternary Carbon Center in the Total Synthesis of Communesin F and Perophoramidine

In our synthesis of (±)-communesin F,[43] the stereochemistry at C8 in **91** was quantitatively inverted by 4-dimethylaminopyridine in CH_2Cl_2 after the amine was protected with a methoxycarbonyl group, giving **99** (eq 24). Although the stereochemistry at C8 was different, alkylation of both pentacyclic **98** and **99** with allyl bromide and NaH exclusively provided a single stereomer **101** with a *cis* relationship between the two alkyl groups at C7 and C8 (eq 25). In fact, the reaction proceeded via two steps of *O*-allylation (**100**) and stereoselective 3,3-rearrangement verified by successful isolation of the enolate ether **100**. In a similar way, allylation of **87** with allyl iodide also provided **102** as sole stereomer in Weinreb's and Ma's total syntheses of communesin F (eq 26).[45,46] The X-ray structural analysis of **102b** in Ma's synthesis showed its absolute configuration to be 6*S*, 7*R*, 8*R*. In contrast, with an oxidative indole moiety (**81**) under similar conditions, Rainier's total synthesis of (±)-dehaloperophoramidine involved allylation of **81** to

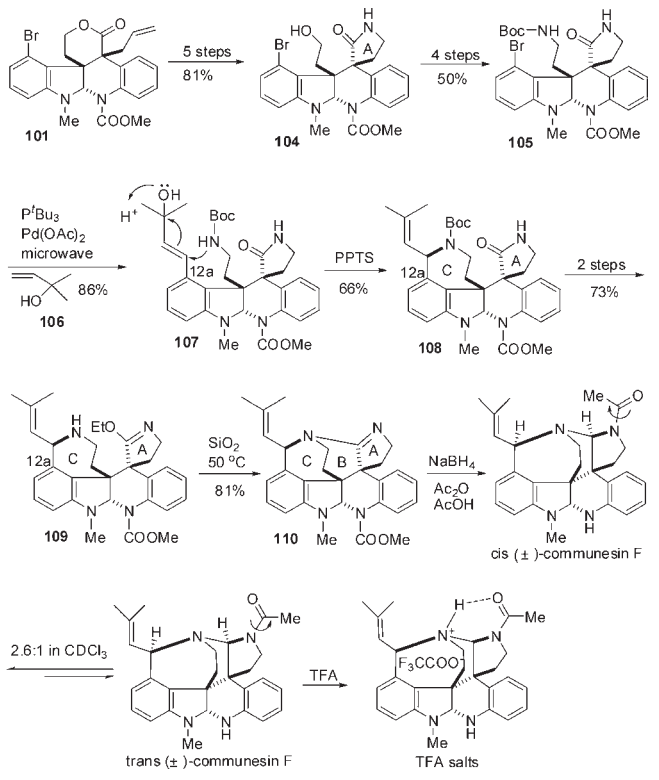
yield **103** with a *trans* relationship between the two alkyl groups (eq 27).[41]



9. Total Synthesis of Communesin F by Qin, Weinreb, and Ma

As shown in Scheme 4, having stereoselectively set up the C7 and C8 quaternary carbon centers in **101**, we began to assemble the upper-hemisphere ring system of communesin F by following a A → C → B sequence of ring formation.[43]

SCHEME 4. Total Synthesis of (±)-Communesin F



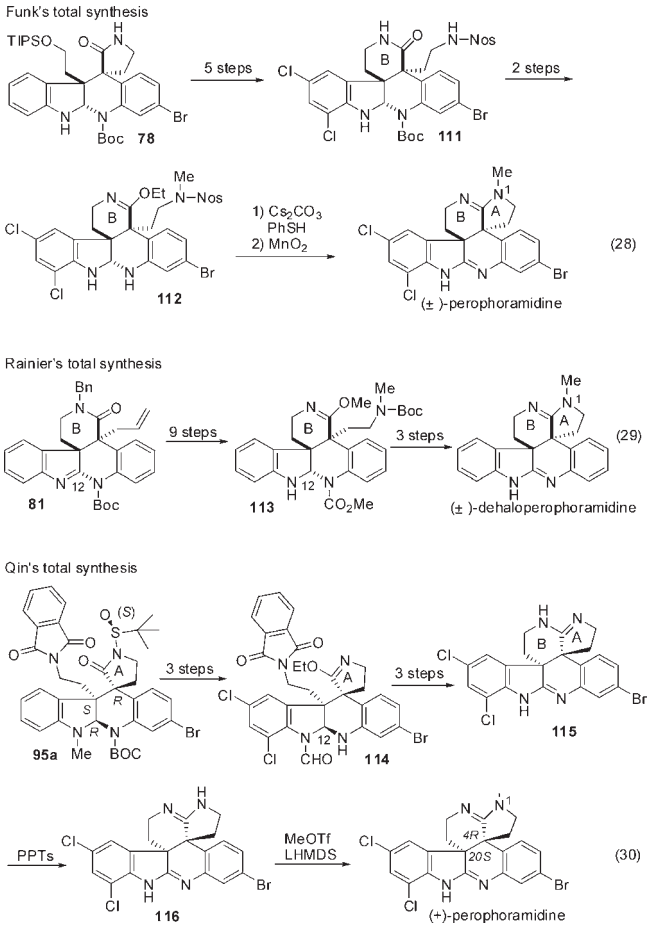
The A-ring was first created by converting the double bond on the side chain in **101** to preliminary amines via a five-step reaction, leading to the amidated product **104**. The allylic side chain on C12a in **107** was introduced by microwave-assisted Heck coupling of **105**. The C-ring was formed in moderate yield by an acid-catalyzed dehydroxylation/cyclization reaction (**107** to **108**). After two steps of converting the amide to active imidate and removing the Boc group in **108**, the chromatographically unstable **109** was treated with silica gel on heating to afford the B-ring product **110**. The final one-pot, two-step reaction of reduction of the imidine in **110** with $NaBH_4$ and acetylation of the resulting amine group with Ac_2O in AcOH provided (±)-communesin F as a mixture of two amide rotamers in a 2.6:1 ratio in $CDCl_3$. Protonation of (±)-communesin F with TFA in $CDCl_3$ eliminated the amide bond rotation to give its TFA salt as a single isomer by forming a hydrogen bond.

In Weinreb's total synthesis of (±)-communesin F, the same A → C → B sequence for the upper- hemisphere ring system formation was also adapted in the final steps of the total synthesis.[44] In contrast, Ma et al. used a B → C → A sequence of ring system formation, in which the C-ring cyclization was driven by methylsulfonylation and the A-ring cyclization was carried out by direct condensation of a preliminary amine with an amide. Starting with (6*S*, 7*R*, 8*R*)-**102b**, Ma et al. were able to assign the absolute configuration of natural (−)-communesin F as 6*S*, 7*R*, 8*R*, 9*S*, 11*R*.[45]

10. Total Synthesis of Perophoramidine by Funk, Rainier, and Qin

Perophoramidine has two imidine groups, one with a methyl group at N1. Selective methylation requires special manipulation of functionality. In order to selectively introduce a methyl group at N1, Funk's total synthesis of (±)-perophoramidine (eq 28)[40] started by opening the A ring of the pentacyclic **78** and forming the B-ring first through five steps of functional conversions to give **111**. After methylation of the side chain and conversion of the amide bond to active imidate (**112**), the Nos protecting group in **112** was removed to simultaneously result in A-ring formation. In the last step, the aminal group was oxidized to an imidine group to finish the total synthesis of (±)-perophoramidine.

Rainier's total synthesis of (±)-dehaloperophoramidine commenced with compound **81** bearing the B-ring (eq 29).[41] For a successful A-ring cyclization with the N1 methyl group, the amidine group at C12 in **81** had to be reduced to an aminal group, and the side chain in **81** was modified



to introduce a methylamino group to give **113** via eight steps. Removal of Boc and methoxylcarbonyl groups consecutively in **113**, followed by oxidation of the aminal group at C12 to an imidine group, completed the total synthesis of (±)-dehaloperophoramidine.

In both Funk's and Rainier's syntheses of (dehalo)perophoramidine, the N1 methyl group was introduced before the A-ring was formed. In contrast, our synthesis of (+)-perophoramidine adapted a different strategy of regioselective methylation after the A-ring was formed (eq 30).[42] Compound **114** was prepared by three steps of chlorination, oxidation, and activation of the amide bond from **95a**. Deprotection of the amine group at the side chain in **114** with methylamine on heating in $CHCl_3$, followed by oxidation of the aminal group at C12 to an imidine group, resulted in formation of a B-ring (**115**). Acid-catalyzed thermodynamic transformation of **115** to **116** was realized in quantitative yield on heating in $CHCl_3$. This key step guaranteed a regioselective methylation at N1, allowing accomplishment of the total synthesis of (+)-perophoramidine. Because the absolute configuration in **95a** was known, the absolute configuration of the natural (+)-perophoramidine was assigned to be 4*R*, 20*S*.

11. Conclusions

In summary, we have demonstrated the efficiency of an innovative methodology involving inter- and intramolecular CRI reactions for assembling three types of indoline alkaloid skeletons. By proper application of the methodology, we have achieved the total synthesis of a number of biologically active indoline alkaloids such as *N*-acetylardeemin, minfiensine, vincorine, and communesin F, all with highly congested ring systems and intriguing stereochemistry. These syntheses powerfully illustrate the unique ability of the CRI reaction to generate molecular complexity. Future efforts will be focused on expanding the CRI reaction to concise construction of other natural product skeletons, as well as on achieving a catalytic asymmetric version of the CRI reaction to allow enantioselective total synthesis of bioactive natural products.

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BIOGRAPHICAL INFORMATION

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FOOTNOTES

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