



Published in final edited form as:

Chemistry. 2015 November 9; 21(46): 16318–16343. doi:10.1002/chem.201501735.

Recent Advances on the Total Syntheses of the Communesin Alkaloids and Perophoramidine

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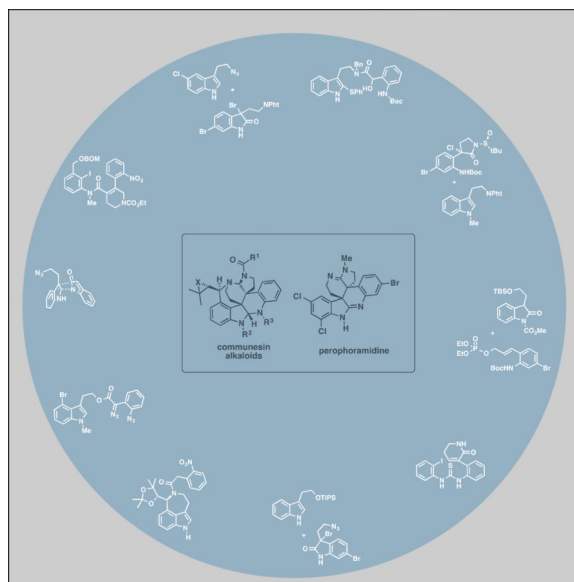
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Abstract

The communesin alkaloids are a diverse family of *Penicillium*-derived alkaloids. Their caged-polycyclic structure and intriguing biological profiles have made these natural products attractive targets for total synthesis. Similarly, the ascidian-derived alkaloid, perophoramidine, is structurally related to the communesins and has also become a popular target for total synthesis. This review serves to summarize the many elegant approaches that have been developed to access the communesin alkaloids and perophoramidine. Likewise, strategies to access the communesin ring system are reviewed.

Graphical Abstract



Keywords

alkaloids; total synthesis; communesin; perophoramidine; vicinal quaternary stereocenters

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1. Introduction

In 1993, Numata and coworkers disclosed the isolation and structural elucidation of two complex alkaloid natural products, communesins A (**1**) and B (**2**) (Figure 1), from a strain of *Penicillium sp.* found growing on the mycelium of the algal species *Enteromorpha intestinalis*.¹ These alkaloids displayed cytotoxicity against cultured lymphocytic leukemia cells with ED₅₀ values of 3.5 and 0.45 µg/mL respectively. The structures of communesins A (**1**) and B (**2**) were elucidated using a combination of 1D and multidimensional NMR techniques, IR, and LC/MS. The absolute configuration of the two alkaloids was not determined and neither was the relative stereochemistry at C(11).

In 2001 Hemscheidt *et al.* reported the isolation of an alkaloid from an unidentified fungal organism growing on the bark of the Hawaiian banyan tree *Ficus microcarpa*.² This fungus died soon after its isolation and could not be obtained again from the tree bark. As a result, the authors named the novel natural product “nomofungin” (**3**) (no more fungus). Bioassays of nomofungin (**3**) revealed that it exhibited cytotoxicity against LoVo and KB cells with MICs (minimal inhibitory concentration) of 2 and 4.5 µg/mL respectively. The mode of action for this cytotoxicity was posited to occur through microfilament network disruption. Structurally, nomofungin (**3**) was elucidated to having a structure very similar to the already known communesin B (**2**). However, in place of the *N,N* aminal functionality present at C(6) of communesin B (**2**), Hemscheidt and coworkers proposed that an *N,O* aminal was present at C(6) in nomofungin (**3**). Additionally, the absolute configuration of the natural product was assigned using the exciton chirality method. The proposed structure of nomofungin (**3**) gained substantial attention from the synthetic community because it seemed to. Additionally, the structural assignment was found to be incorrect (*vide infra*).

1.1. Isolation of Other Communesin Alkaloids

Since their initial isolation by Numata *et al.* the family of communesin alkaloids has grown substantially to include many new members (Figure 2). Jadulco and coworkers isolated communesins C (**4**) and D (**5**) from *Penicillium sp.*, which was found on the Mediterranean sponge *Axinella verrucosa* along with the already known communesin B (**2**).³ The newly isolated alkaloids differed structurally from communesin B (**2**) by the identity of the substituent present at N(15). All three alkaloids were tested for antiproliferative activity against several leukemia cell lines by MTT assay including Burkett's Lymphoma and Hodgkin's lymphoma, and displayed ED₅₀ values in the 7-15 µM range. In addition to their activity against cancer lines, communesins B-D (**2-5**) also displayed toxicity against the brine shrimp, *Artemia salina*, with activities ranging from 0.3-2.0 µg/mL.

Hayashi and coworkers reported the isolation and structural elucidation of communesins D (**5**), E (**6**), and F (**7**), from the fungus *Penicillium expansum* Link MK-57 along with the already known communesins A (**1**) and B (**2**).⁴ Communesin E (**6**) contained an acyl chain at N(16) in place of the sorbyl chain present in communesins B-D (**2-5**). Communesin F (**7**) was the structurally simplest member isolated and lacked the epoxide functionality present in communesins A-E (**1-6**). Communesins E (**6**) and F (**7**) displayed moderate insecticidal

activity against instar silkworms larvae, displaying toxicities of 80-300 $\mu\text{g/g}$ of diet fed to the organism.

Christophersen *et al.* reported the structures of communesins G (**8**) and H (**9**) from the psychrotolerant organism, *Penicillium rivulum*.⁵ These two alkaloids contained propionyl and butanoyl substituents respectively at N(16). Unlike the other penicillium organisms, *Penicillium rivulum* did not produce communesin B (**2**) as a secondary metabolite. Communesins G (**8**) and H (**9**) were tested for antiviral, antibacterial, and antiproliferative activity against murine leukemia cells and were found to be inactive in such assays.

A related natural product, perophoramidine (**10**), was isolated in 2002 by Ireland and coworkers from Philippine ascidian organism, *Perophora namei* (Figure 3). Structurally, this alkaloid contained a novel hexacyclic carbon skeleton similar in connectivity to that of the communesin alkaloids. However, unlike the communesins, perophoramidine (**10**) contained 3 points of halogenation on the aromatic nuclei, possessed two amidine functionalities in place of two aminals, lacked the benzazepine ring and possessed a *trans* relationship between the two vicinal quaternary stereocenters. The absolute configuration of the natural product was not determined. Initial biological assays revealed that this natural product was active against a HCT116 colon carcinoma cell line with an IC_{50} of 60 μM , inducing apoptosis via (poly(adenosine-5'-diphosphateribose)polymerase (PARP) cleavage within 24 h.

1.2. Biosynthesis of the Communesin Alkaloids and Perophoramidine

Stoltz and coworkers have studied the biosynthesis of the communesin alkaloids, proposing that this family of natural products could arise from the inverse-electron-demand hetero-Diels-Alder reaction of the ergot alkaloid aurantioclavine **11** and a tryptamine-derived *o*-xylylene **12** (Scheme 1). In order to arrive at the correct relative stereochemistry between the two quaternary stereocenters, the Diels-Alder reaction would need to proceed through an *exo* transition state. Due to the large amount of strain, intermediate **13** would undergo transamidation with the pendant amine to deliver lactam **14**. Subsequent reduction of the lactam, aminal closure, epoxidation and amination would deliver the communesin alkaloids.

A similar type of dimerization reaction can be envisioned for the biosynthesis of perophoramidine (**10**), utilizing tryptamine **15** and methyltryptamine **16** (Scheme 2). However, an *endo* transition state would have to be operative in the inverse-electron-demand hetero-Diels-Alder reaction in order to obtain the *trans*-relationship between the two quaternary stereocenters. Halogenation of the aromatic nuclei could occur prior to the cycloaddition or in subsequent enzymatic steps during biosynthesis.

Stoltz and coworkers have also proposed that the communesin alkaloids share structural and biosynthetic similarity to the calycanthaceous family of alkaloids.⁶ The calycanthaceous alkaloids are a broad class of natural products found in a number of plants and animals. Due to their variegated biological activities and intriguing skeletal structure, these natural products have received extensive attention from the synthetic community⁷ and are believed to arise from the oxidative dimerization of two tryptamine units (**17**), providing dimer **18** (Scheme 3). From this intermediate, ring opening can give rise to a hypothetical

intermediate **19**, from which 5 possible skeletal isomers can be generated by rearrangement of the amination moieties (**20-24**). Of these 5 possibilities, only 4 have been observed in natural products.

Calycanthine **25** (Figure 4) corresponds to skeletal arrangement **20** and was first isolated in the late 1800's,⁸ but its structural identity remained a long-standing question until Woodward⁹ and Robinson¹⁰ utilized chemical degradation methods to assign its correct structure. Later, Robertson and coworkers were also able to establish the structure of **25** using X-ray crystallography.¹¹

Skeletal isomer **21** is observed in the alkaloid chimonanthine **26**, which has been isolated in both its enantiomers as well as in its *meso* form. This natural product can be found in many different plants¹² and on the skin of the poison dart frog *Phylllobates terribilis*.¹³ The structure of (-)-chimonanthine **26** was elucidated using X-ray crystallography.¹⁴ Interestingly, (-)-chimonanthine **26** undergoes rearrangement to (+)-calycanthine **25** upon exposure to aqueous acid, raising the question of whether calycanthine **25** is in fact a natural product itself or an isolation artifact. *Iso*-calycanthine (**27**) was isolated from the South American shrub *Psychotria forsteriana* and corresponds to skeletal arrangement **23**.¹⁵ An oxidized variant of this *meso* natural product (**28**), which contains two amidines, was also later isolated from *P. forsteriana*.¹⁶ Finally, skeletal arrangement represented by **22** is observed in the communesin alkaloids and perophoramidine (**10**).

2. Studies Towards the Total Syntheses of the Communesin Alkaloids and Perophoramidine

Structurally, the communesin alkaloids contain a unique, densely functionalized, cage-like heptacyclic skeleton making them a formidable synthetic endeavor (Figure 5). The southern portion of these alkaloids consists of a fused 6,5,6,6-ring system represented by rings C, D, E, and F which contains an indoline/tetrahydroquinoline aminal. The northern portion, represented by rings A, B, and G, contains an additional 6,5-aminal and a 7-membered benzazepine attached to the 4-position of the indoline ring. Additionally, the communesins bear two vicinal quaternary all carbon stereocenters at C(7) and C(8) which are challenging to construct, especially in an asymmetric fashion.^{17,18}

The communesins have attracted extensive research interests from the synthetic community, and many unique strategies have been developed to access these alkaloids in both racemic and enantioenriched form.¹⁹ The following sections of this review article will focus on highlighting the methods that have been developed to access the communesin skeleton and the total syntheses of the communesin alkaloids as well as perophoramidine (**10**).

2.1 Resolving the Structures of Communesin B and Nomofungin

Although communesins A (**1**) and B (**2**) were first isolated in 1993, they received little attention from the synthetic community until Hemscheidt *et al.* reported the structure of nomofungin (**3**). The first synthetic studies performed towards the communesin alkaloids were focused on clarifying the structure of communesin B (**2**) and demonstrating that the structure of nomofungin (**3**) was erroneously elucidated. In 2003, Stoltz²⁰ and Funk²¹

independently demonstrated that the structure of nomofungin **3** was incorrect, and that the compound that was isolated by Hemscheidt *et al.* was in fact communesin B (**2**). Stoltz and coworkers examined the reported NMR data for both communesin B (**2**) as well as nomofungin (**3**) and found that the compounds shared nearly identical reported ^1H and ^{13}C NMRs. Inspection of the chemical shifts for the C(6) protons and carbons revealed that the *N,N*-aminal hydrogen in communesin B (**2**) appeared at 4.70 ppm, while nomofungin (**3**) appeared at 4.69 ppm. Additionally, both compounds were reported to have a chemical shift in the ^{13}C spectrum for C(6) at 82.5 ppm. A comparison of these shifts for the two natural products to known *N,N*- and *N,O*-aminals from the chemical literature revealed that both the ^1H and ^{13}C chemical shifts for the *N,N*-aminal were within normal range for such functionalities. On the other hand, the chemical shifts for the *N,O*-aminal were outside the typical range reported in the chemical literature.

Additionally, Stoltz and coworkers prepared two *N,N*-aminals similar in structure to those found in communesin B and compared their chemical shifts at the *N,N*-aminal to that of the two natural products (Scheme 4). The preparation of these compounds commenced with the cycloaddition of 1,3-dimethyl indole (**29**) with an *aza-o*-xylylene generated from aniline **30**, affording tetracyclic product **31** in 86% yield. Cleavage of the tosyl group with Mg(0) delivered the requisite aminal **32** in 89% yield. The ^1H and ^{13}C chemical shifts for the *N,N*-aminal were examined and appeared at 4.14 and 83.9 ppm, respectively. While the aminal ^1H NMR shifts were outside the expected range for what was expected, the ^{13}C chemical shifts for the aminal carbon were in good agreement with communesin B. To access a system more closely related in structure to communesin B (**2**), the authors prepared aurantioclavine-derived pentacyclic aminal **35** from the hetero-Diels-Alder reaction of aurantioclavine derivative **33** and aniline **30** followed by cleavage of the tosyl group with Mg(0). The aminal ^{13}C signals for the two diastereomeric compounds appeared at 84.8 and 83.9 ppm, again supporting the notion that communesin B (**2**) and nomofungin (**3**) were identical compounds and that the proposed structure of nomofungin (**3**) was incorrect. The ^1H chemical shifts were not discussed for these compounds.

To demonstrate that communesin B (**2**) and nomofungin (**3**) were the same compound, Funk and coworkers prepared and analyzed *N,O*- and *N,N*-aminals **41** and **45** (Scheme 5 and 6). *N,O*-aminal **41** was prepared *via* intramolecular hetero-Diels-Alder reaction of an indole and an *aza-o*-xylylene. Acyl chloride **37** was prepared in three steps from ester diol **36** by formation of the acetonide, saponification of the ethyl ester and treatment of the carboxylic acid with oxalyl chloride. Benzazepine **39** was prepared by hydrogenation of the nitro group of indole **38** and reduction of the resulting lactam with LiAlH_4 . Coupling of acyl chloride **37** with benzazepine **39** followed by reduction of the amide with LiAlH_4 provided benzodioxin **40**. To facilitate the [4+2] process, benzodioxin **40** was heated in decalin at 195 °C providing *N,O*-aminal **41** in 63% yield. Analysis of the ^1H and ^{13}C NMR signals of this compound at the *N,O*-aminal revealed that the signals appeared at 5.4 and 101.0 ppm, respectively. Comparison of these chemical shifts to those of the *N,O*-aminal present in nomofungin **3** revealed a large inconsistency. The ^1H and ^{13}C shifts for nomofungin appeared at 4.7 ppm and 82.4 ppm, respectively, which are both substantially further upfield from those observed in *N,O*-aminal **41**. Conformational effects were very unlikely to lead to

such a difference, suggesting that the reported structure for nomofungin (**3**) was incorrect and that nomofungin was in fact communesin B (**2**).

To further validate their structural hypothesis a similar analysis was performed on *N,N*-aminal **45**, which was prepared in 4 steps (Scheme 6). Benzazepine **39** was alkylated with styrene oxide **42** and the resulting secondary alcohol was converted to carbonate **43**. Heating this compound at 160 °C in dichlorobenzene resulted in formation of the aza-*o*-xylylene intermediate and facilitated the desired [4+2] cycloaddition, providing *endo*-cycloadduct **44** in 70% yield as a single diastereomer. This compound was converted to *N,N*-aminal **45** by hydrolysis of the ethyl carbamate with KOH and hydrazine in 67%. Inspection of the NMR spectra of compound **45** revealed that the *N,N*-aminal ¹H and ¹³C signals appeared at 4.5 and 84.4 ppm respectively. These were in accord with the NMR spectra of communesin B (**2**) and nomofungin (**3**), whose signals appeared at 4.7 and 82.4 ppm, suggesting that both communesin B (**2**) and nomofungin (**3**) were the same molecule containing an *N,N*-aminal.

2.2. Studies on the Construction of the Communesin Ring System

Building off of their thermolysis studies, the Funk group reported acid and fluoride-promoted protocols for generating aza-*o*-xylylenes and utilized these methods to rapidly assemble the hexacyclic substructure of the communesin alkaloids.²² Due to their ready availability, initial studies utilized a tryptamine starting material that lacked a functional handle at the 4-position of the indole nucleus (Scheme 7). Functionality at this position would later be necessary to install the benzazepine ring present in the natural product. To test the feasibility of employing an aza-*o*-xylylene cycloaddition to synthesize the natural product, aziridine **48** was prepared from *N*-methyl tryptamine **46** and dibromide **47** in 65% yield. The relative stereochemistry of this compound was confirmed by comparison of the *vicinal* coupling constants of the aziridine protons, which were in agreement with other *trans*-aziridines in the chemical literature.²³ Treatment of aziridine **48** with triflimide (Tf₂NH) delivered cycloadduct **52** in 70% yield in which the carboethoxyl group migrated from the aniline to the lactam. The relative stereochemistry of this compound was assigned based on the coupling constants observed between the α and β-methine protons of the ester and NOEs between the aminal protons and the β-methine proton of the ester. The structure was also confirmed by X-ray crystallography. To rationalize the observed migration, the authors proposed that aziridine **48** undergoes nucleophilic attack into the carboethoxyl group forming aziridinium **49**, which retains the carboethoxyl group upon collapse of the tetrahedral intermediate. At this point, the aziridinium fragments to the aza-*o*-xylylene **51** and undergoes the *endo*-hetero-Diels-Alder reaction delivering **52**. The migration of the carboethoxyl group proved problematic, since substitution at the lactam nitrogen would preclude subsequent studies on the benzazepine formation.

To circumvent the migration pathway, the fluoride-labile 2-(trimethylsilyl)ethyl carbamate (TEOC) was introduced in place of the ethyl carbamate in aziridine **48** (Scheme 8). To test the compatibility of the TEOC group in the aza-*o*-xylylene cycloaddition, aziridine **53** was treated with TBAF facilitating the aza-*o*-xylylene formation. Subsequent *endo*-cycloaddition with this intermediate provided pentacycle **55** in 80% yield.

With a set of conditions for the aza-*o*-xylylene cycloaddition, 4-ethynyl indole **56** was prepared, which contains a functional handle at the 4-position of the indole nucleus needed to complete the communesin alkaloids (Scheme 9). Treatment of **56** with TBAF facilitated the [4+2] cycloaddition, providing *endo*-cycloadduct **57**. This intermediate was unstable and slowly underwent 7-*exo*-dig benzazepine formation to **58**, which conveniently was the next intermediate in the synthetic sequence. To accelerate this desired but otherwise slow process, *endo*-cycloadduct **57** was treated with an Au(I) source to activate the alkyne providing benzazepine **58** in 89% yield over 2 steps. To install the second aminal present in the communesin system, benzazepine **58** was treated with LiOH to hydrolyze the ester moiety to the carboxylic acid, which was converted to a mixed anhydride and treated with sodium azide facilitating the Curtius rearrangement and delivering aminal **59**. Aminal **59** constitutes a formidable partial synthesis, and contains six of the seven rings present in the communesin alkaloids.

Weinreb and coworkers have also tackled the total syntheses of the communesin alkaloids and perophoramidine. Approaches to these natural products have hinged on the use of a Heck reaction to prepare oxindole products bearing one of the two quaternary stereocenters present in the targets. Weinreb's initial studies were aimed at utilizing a halogen-selective carbonylative Heck reaction to forge a quaternary stereocenter in the total synthesis of perophoramidine (Scheme 10).²⁴ The synthesis of the necessary Heck precursor was initiated with the olefination of lactone ylide **60** and anisaldehyde **61**, providing benzylidene lactone **62** exclusively as the *E*-isomer. Weinreb aminolysis of this compound with the aluminum amide of aniline **63** delivered primary alcohol **64** which was silylated with TBSCl. Attempts to facilitate the carbonylative Heck reaction at this stage did not lead to any of the desired oxindole product. The authors postulated that this lack of reactivity was attributed to the low population of the amide rotamer needed to facilitate the reaction and that substitution of the amide N–H would promote the desired Heck reaction. For this purpose, amide **65** was alkylated with MeI and MOMCl to afford the two substituted Heck reaction precursors **66** and **67** respectively. When the key carbonylative Heck reaction was attempted on these alkylated substrates, the Me (**68**) and MOM (**69**) oxindoles were obtained as single diastereomers in 74 and 88% yield, respectively. The observed relative stereochemistry of the products was rationalized by the *syn* addition of the aryl-Pd intermediate and CO across the *E*-olefin.

To cleave the silyl ether, the *N*-methyl oxindole product **68** was treated with TBAF and NH₄F under conditions developed by Fürstner²⁵, and the resulting primary alcohol was heated with TsOH to arrive at lactone **70** in 79% yield as a 3:1 mixture of epimers (Scheme 11). Analogously, *N*-MOM oxindole **69** was treated with HCl in MeOH to cleave the silyl ether and then was heated with TsOH to afford **71** as a single diastereomer. Installation of the second vicinal quaternary stereocenter was pursued *via* allylation of MOM lactone **71** with NaH and allyl iodide in DMF, which resulted in the formation of allyl lactone **72** in 65% yield as a single diastereomer. While the authors originally assigned the stereochemistry of this allylation as shown in Scheme 11, which agrees with the stereochemistry of perophoramidine (**10**), this stereochemical assignment was later found to be incorrect and the opposite diastereomer was actually obtained (*vide infra*).

Since perophoramidine (**10**) contains an aryl bromide on one of the two aromatic nuclei, the authors also explored a similar sequence starting with 4-bromo-benzaldehyde **73** targeting lactone **78** as an intermediate (Scheme 12). Unlike aryl chlorides, aryl bromides can readily undergo Heck reactions and the proposed reaction would be challenging from a chemoselectivity perspective. However, the oxidative insertion of palladium into an aryl iodide should be substantially faster than oxidative insertion into an aryl bromide, and hence this chemoselective reaction should be a viable process. Olefination of 4-bromo benzaldehyde **73** with ylide **60** followed by aminolysis with aniline **63** delivered a primary alcohol (**75**), which was silylated with TBSCl, treated with LiHMDS and MeI to arrive at Heck precursor **76**. Treatment of the Heck precursor **76** under the previously optimized conditions resulted in smooth formation of *N*-methyl oxindole **77** in 77% yield as a single diastereomer. This compound was treated with HCl in MeOH followed by heating with TsOH in PhH to arrive at lactone **78** as a 5:1 mixture of diastereomers in 80% yield over 2 steps.

With the success of a brominated substrate, additional studies were undertaken by Weinreb to synthesize perophoramidine (**10**) by employing brominated nitrobenzaldehyde **80**.²⁶ The authors planned on reducing the nitro group in subsequent steps and utilizing the amine to construct the southern amidine present in the molecule. Applying the previously employed sequence (see Scheme 12), the authors prepared brominated nitrobenzaldehyde **80** by condensation of nitrotoluene **79** with dimethylformamide-dimethyl acetal and periodate cleavage of the resulting enamine (Scheme 13). The aldehyde was olefinated with the lactone ylide **60**, which was then opened with the aluminum amide of aniline **63**. The resulting primary alcohol **82** was silylated with TBSCl and the amide was protected with a MOM group to deliver Heck precursor **83**. Under optimized conditions, the Heck reaction produced the desired oxindole **84** along with undesired reaction byproducts **85** and **86**. This mixture was treated directly with TBAF to cleave the TBS group and to cyclize the lactone delivering nitrolactone **87** as a 4:1 mixture of diastereomers in 51% from Heck precursor **83**. Nitrolactone was allylated with allyl iodide to deliver allyl lactone **88** in 87% yield as a single diastereomer. Allyl lactone **88** was a crystalline solid whose structure was determined *via* X-ray crystallography. It was found that the stereochemical course of the allylation was opposite from that present in perophoramidine (**10**), and the allyl group was installed *syn* to the oxindole ethylene chain. At this point, the authors re-examined the relative stereochemistry of allyl lactone **72** (Scheme 11) by X-ray crystallography of one of its derivatives and found that the relative stereochemistry in this compound was also opposite of what was originally reported. However, the relative stereochemistry obtained from the allylations was the same of that which is observed in the communesin alkaloids and the Weinreb group chose to utilize this undesired stereochemical outcome to pursue the total synthesis of this family of alkaloids.

In their first generation synthetic studies, Weinreb and coworkers planned to utilize iodoaniline **90** and PMP-lactone **91** as aromatic building blocks to assemble the Heck reaction precursor (Scheme 14). The benzylic ether of aniline **90** would serve as a functional handle to introduce the benzazepine ring present in the natural products. For the opposite side of the molecule, the benzylic ether of lactone **91** would serve as an amine surrogate that

could be unmasked by oxidation to the carboxylic acid and Curtius rearrangement to the aniline. The synthesis began with the benzylation of alcohol **89** followed by reduction of the nitro group to deliver aniline **90**. Conversion of this intermediate to the aluminum amide and treatment with PMP lactone **91** resulted in formation of primary alcohol **92**. Silylation of this alcohol with TBSCl and alkylation of the amide with MeI provided Heck precursor **93**. Performing the Heck reaction on this substrate under optimized reaction conditions led to formation of the desired oxindole product **94** as a single diastereomer in 71% yield. This Heck product was treated with TBAF to cleave the TBS group, which also resulted in concomitant lactonization delivering lactone **95** as a 2:1 mixture of diastereomers. Allylation of the lactone with allyl iodide led to formation of isolable ketene acetal **96**, which could be thermally rearranged to the desired allyl lactone **97** as a 3.3:1 mixture of diastereomers. Due to the disappointing diastereoselectivity of the allylation, the authors chose to modify the aniline starting material for the sequence in hopes of improving the selectivity of the allylation.

The second generation synthesis began with conversion of phenol **98** to a dimethyl carbamate and reduction of nitro group providing aniline **99** (Scheme 15). Formation of the aluminum amide of this intermediate followed by treatment with PMP lactone **91** provided primary alcohol **100**. This alcohol was etherified with a MOM group and the amide was methylated with MeI to arrive at Heck precursor **101**. Conducting the Heck reaction under optimized conditions provided the desired oxindole product **102** in 79% yield as a single diastereomer. This material was treated with HCl to cleave the MOM group and to facilitate the lactonization, delivering lactone **103** in 70%. Allylation with allyl iodide again delivered an isolable ketene acetal **104**, which was rearranged to allyl lactone **105** by heating in DMF with a disappointing 2.3:1 dr. However, conducting the rearrangement in PhMe in place of DMF led to formation of allyl lactone **105** in an improved 9.8:1 dr. The group later published a sequence similar to the one outlined in Scheme 15 to complete the synthesis of communesin F (**7**) (*vide infra*).

The Garg group has recently developed an interrupted Fischer indolization reaction, which has been applied to assemble indoline substrates (Scheme 16).²⁷ In a single operation, this transformation could be used to form 3 new bonds, 2 heterocyclic rings, and 2 new stereocenters, one of which is quaternary. Additionally, the Garg group has employed this methodology in the total synthesis of several indoline-containing natural products such as physovenine and aspidophylline A.²⁸ During their studies, it was found that *N*-methylhydrazine **106** undergoes smooth interrupted Fischer indolization with latent aldehyde **107** to afford tetracycle **108** in 70% yield. This product contains the 6,5,6,6-ring system present in the communesin alkaloids and perophoramidine (**10**). With this result in hand, the authors envisioned that this methodology could be used as a key step to synthesize the communesin alkaloids and perophoramidine (**10**) by employing more functionalized coupling partners in the interrupted Fischer indolization.

To this end, latent aldehyde **112** was prepared from acetal **109** by way of an elimination and hetero-Diels-Alder reaction (Scheme 17).²⁹ This latent aldehyde was treated under the

interrupted Fischer indolization conditions, facilitating the desired process and delivering tetracycle **113** in 51% yield.

With this preliminary result in hand, a hydrazine starting material was prepared that would facilitate the formation of the benzazepine ring in the communesin skeleton employing a Pictet-Spengler reaction (Scheme 18). Reaction of *para*-methoxy-substituted hydrazine **114** with latent aldehyde **115** resulted in formation of tetracycle **116** in 54% yield. Removal of the phthalimide group with hydrazine provided amine **117** in near quantitative yield, which was condensed with 3-methylbut-2-enal (**118**) to afford imine **119** in 95% yield. Unfortunately, attempts to facilitate the Pictet-Spengler reaction with imine **119** were unsuccessful, and led to either hydrolysis of the starting material or no reaction.

With the obstacles encountered in elaborating the interrupted Fischer indolization products towards the communesin alkaloids, attempts were made to access perophoramidine using the described methodology (Scheme 19). Substituted latent aldehyde **125** was chosen as a substrate for the interrupted Fischer indolization process and was accessed in 6 steps. Commercially available aniline **121** was sulfonated with TsCl and subsequently reduced with LiAlH₄ to deliver benzylic alcohol **122**. Oxidation to the aldehyde with PCC followed by allyl Grignard addition afforded secondary alcohol **123** which was converted to secondary chloride **124** with SOCl₂. Hetero-Diels-Alder reaction of the secondary chloride **124** with enol ether **110** resulted in a low 11% yield of the [4+2] product **125** and resulted primarily in the undesired elimination product. Furthermore, attempts to employ the Diels-Alder product **125** in the interrupted Fischer indolization failed to deliver the desired product **126** with a variety of Lewis- and Brønsted- acids and with different aryl hydrazines. The failure of the interrupted Fischer indolization was posited to have occurred due to the steric interactions of the allyl moiety in latent aldehyde **125**.

To determine if steric interactions were precluding the desired reaction between aryl hydrazines and latent aldehyde **125**, a latent aldehyde lacking the allyl moiety **128** was prepared from benzylic alcohol **127** in 2 steps *via* chlorination and hetero-Diels-Alder reaction (Scheme 20). Reaction of latent aldehyde **128** with phenylhydrazine (**129**) facilitated the desired interrupted Fischer indolization in 68% yield. Furthermore, tetracycle **130** could be treated with NCS in AcOH to deliver dichloride **131** which could potentially serve as an intermediate for the total synthesis of perophoramidine.

Wu and coworkers reported an acid-catalyzed approach to forming *aza-o*-xylylenes from 2-aminobenzyl alcohols (**133**) and utilized these intermediates in annulation reactions with indoles (**132**) (Scheme 21).³⁰ TFA was found to serve as an efficient catalyst for the transformation, and a variety of 3-substituted indoles (**132**) could participate in the reaction leading to annulated indoline aminals of general structure **134** in moderate to excellent yields. This structural motif represents a portion of the skeleton present in the communesin alkaloids and perophoramidine.

Adlington and coworkers were able to construct a significant portion of the communesin skeleton utilizing a thermal intramolecular cycloaddition between an *aza-o*-xylylene and an indole (Scheme 22).³¹ The authors aimed to utilize a thermal [4+2] cycloreversion of a

substituted 1,3-benzoxazin-2-one to generate an aza-*o*-xylylene upon extrusion of CO₂. This dehydrative [4+2]-approach bears similarity to the strategies developed both by Funk and Wu for accessing similar ring systems (*vide supra*). To test the key aza-*o*-xylylene cycloaddition, amino alcohol **138** was synthesized. Reaction of tryptamine **135** with isatin **136** led to amide **137**, which was treated with vinyl-MgBr to provide amino alcohol **138**. Treatment of amino alcohol **138** with CDI led to formation of pentacycle **140** in a disappointing 36% yield. However, the transformation served to construct the two vicinal quaternary stereocenters in a single synthetic step. The reaction likely proceeds through the expected aza-*o*-xylylene intermediate **139**, which is trapped by the pendant indole.

The relative stereochemistry of the two quaternary stereocenters in pentacycle **140** was opposite from that needed to access the communesin alkaloids. In attempts to address this issue, the authors removed the benzyl group and sulfonated the resulting N-H lactam providing lactam **141** (Scheme 23). This material was reduced with DIBAL-H leading to *N,O*-aminal **142** which was olefinated to deliver vinyl ether **143**.

In their synthetic studies towards racemic communesin F, Somafai and coworkers were able to access the hexacyclic core of the natural product utilizing a Diels-Alder strategy between butadiene and a functionalized α,β -unsaturated oxindole dimer.³² This strategy would allow for the installation of both vicinal quaternary stereocenters present in the molecules early in the synthesis in a single operation.

The group's synthesis commenced with the coupling of *N*-sulfonyl isatin **144** with oxindole to provide isoindigo **145** in 45% yield (Scheme 24). This material could be treated with butadiene to undergo the key Diels-Alder reaction to provide cycloadduct **146** in 63% yield. The authors found that inclusion of molecular sieves in the reaction mixture was crucial to the transformation's success. Otherwise, cleavage of the *N*-tosyl protecting group was observed. With both vicinal quaternary stereocenters in place, elaboration of the tetracyclic ring system was pursued. Cycloadduct **146** was treated with Meerwein's salt in the presence of 1,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to provide an ethyl-iminoether in 92% yield. The choice of base proved important in this transformation, as use of Hunig's base provided the undesired *N*-ethyl product as the major product. Ozonolytic cleavage of the cyclohexene olefin followed by reduction of the dialdehyde provided a diol intermediate, which was converted to diazide **147** under Mitsunobu conditions with hydrazoic acid. This intermediate (**147**) was reduced with hydrogen and Pd/C to deliver a diamine intermediate that underwent selective cyclization to γ -lactam **148** in 85% yield. Attempts to selectively cyclize the *N*-tosyl aniline in the presence of the primary amine proved difficult. To this end, the primary amine was converted to an ethyl carbamate by treatment with ethyl chloroformate and this material was treated with LiAlH₄. Unfortunately, the desired tetracycle **150** was only obtained as a minor product in a mere 12% yield, while the remainder of the reaction mixture consisted of bridged orthoamide **149**. Fortunately, this undesired orthoamide could be converted to pentacycle **150** by treatment with DIBAL-H. With pentacyclic lactam **150** in hand, attempts were made to construct the northern aminal in the natural product. The secondary amine was protected with a Boc group by treatment with Boc₂O and the γ -lactam was converted to imino ether **151** by treatment with Meerwein's

salt. Unfortunately, attempts to cyclize the secondary amine onto the imino ether proved unsuccessful under a variety of conditions examined.

Takemoto and coworkers have developed a SmI₂-mediated reductive cyclization reaction that transforms carbodiimides bearing unsaturated carbonyls to 2-iminoindolines bearing an all-carbon quaternary stereocenter (Scheme 25).³³ This methodology was used to construct the pentacyclic core of dehaloperphoramidine, the dehalogenated analog of perphoramidine in a racemic fashion.³⁴

Unsaturated lactams **153** and **154** were prepared from commercially-available ethyl 3-(benzylamino)propanoate (**152**) (Scheme 26). The reactivity of this material in reductive cyclization was explored and was found to be largely dependent on the identity of the carbodiimide aryl group. Utilizing the *para*-methoxyphenyl imide **153** the authors could facilitate the cyclization sequence in 86% yield utilizing their standard conditions. The relative stereochemistry of the product (**155**) was confirmed *via* X-ray crystallography and is rationalized to occur by protonation of the Sm-enolate from the bottom, sterically more accessible face of the molecule. Trying to utilize the same conditions on the *para*-methoxybenzyl substrate **154**, on the other hand led to complete recovery of the starting material, even when the reaction was heated to 60 °C. It was found that adding 10 vol% of HMPA to the reaction mixture led the desired transformation to occur in 86% yield, providing compound **156**. The authors posit that addition of HMPA to the reaction mixture leads to an increase in reduction potential in SmI₂. To elaborate **155** into the pentacyclic core of perphoramidine, the authors explored Pd-catalyzed amidation reactions. They found that amidine **157** could be accessed in the absence of the metal catalyst simply by heating spirocycle **155** to 120 °C in the presence of NaO^tBu, but in a mere 27% yield. Employing Pd(OAc)₂ as catalyst in the presence of PCy₃ improve this transformation and led to amidine **157** in 86% isolated yield.

Most recently, the Stoltz group reported racemic formal syntheses of both communesin F (**7**) and perphoramidine (**10**) utilizing a Pd-catalyzed decarboxylative allylic alkylation as a diastereodivergent reaction.³⁵ By varying the substrate, both the *cis* and *trans* vicinal quaternary stereocenter-bearing products could be synthesized to provide communesin F (**7**) and perphoramidine (**10**), respectively. The formal synthesis of communesin F (**7**) began with the coupling of bromooxindole **158** and malonate **159** (Scheme 27). Proceeding through an azaxylylene intermediate, this transformation provided oxindole malonate **160** in 95% yield. This material was methylated with MeI, and the product was subjected to a protodesilylation/lactonization sequence to deliver lactone **161**. At this stage, the key Pd-catalyzed transformation was examined. Treatment of lactone **162** with 5 mol% Pd(PPh₃)₄ in THF smoothly facilitated the decarboxylative allylation, delivering allyl lactone in 78% yield as a single diastereomer. The relative configuration of this compound was confirmed by single crystal X-ray analysis and corresponded to the diastereomer needed to synthesize communesin F (**7**). To elaborate the synthesis, the nitro group was reduced leading to a lactamization event delivering bisoxindole **163** in 80% yield. Protection of the primary alcohol and oxindole nitrogens followed by ozonolysis of the olefin provided aldehyde **164** in 94% yield. Reductive amination with benzylamine **165** led to a translactamization event

providing anilide **166** in near quantitative yield. To complete the formal synthesis, the lactam was activated with Tf₂O the resulting spirocyclic intermediate was reduced, and the nitrobenzyl protecting group was cleaved to deliver pentacycle **167**. This intermediate was used by Qin and coworkers (*vide infra*) to complete the total synthesis of communesin F (**7**) in 11 steps.

For their formal synthesis of perophoramidine (**10**), the authors would have to invert the diastereoselectivity of the decarboxylative allylation reaction. To this end, bromooxindole **168** was coupled with malonate **169** in 96% yield and the oxindole nitrogen was methylated to deliver oxindole malonate **170** (Scheme 28). This acyclic diallyl diester was treated with Pd(PPh₃)₄ at -78 °C to facilitate the Pd-catalyzed reaction. The allylated product (**171**) was obtained from this transformation in 78% yield as a single diastereomer. Single crystal X-ray analysis of the product revealed that the relative stereochemistry in of the product was opposite of that obtained from the allylation of lactone **162** (Scheme 27), and was the required relative stereochemistry present in perophoramidine (**10**). At this stage, the nitroarene was reduced with TiCl₃ leading to a transamidation. The oxindole nitrogen was protected with a Boc group, and the olefin was converted to an aldehyde *via* ozonolysis, delivering aldehyde **172**. Analogous to the communesin system, the aldehyde was subjected to reductive amination, leading to a translactamization providing anilide **173**. Unlike the communesin system, reductive cyclization of the oxindole nucleus in **173** could be accomplished in a single step employing alane to deliver aminal **174**. To complete the formal synthesis, the indoline methyl group was oxidized with PDC, and the resulting formyl and nitrobenzyl groups were cleaved with aqueous NaOH providing pentacycle **175**. This intermediate was used previously by Funk and coworkers to complete the formal synthesis of perophoramidine (**10**) in 9 steps (*vide infra*).

3. Total Syntheses of the Communesin Alkaloids

3.1 Racemic Total Syntheses of Communesin Alkaloids

The Qin group has utilized the cyclopropanation of indoles as a key transformation to construct quaternary stereocenters in the total synthesis of various indoline alkaloid natural products.³⁶ The group disclosed their efforts to use such a strategy towards to total synthesis of the communesin alkaloids and perophoramidine (**10**) (Scheme 29).³⁷ Starting with tryptamine derivative **176** and isatin **177**, diazoamide **178** could be constructed over several steps. Treatment of this compound with an appropriate Cu(I) source led to formation of a carbene and facilitated a cyclopropanation sequence delivering azido cyclopropane **179**. Reduction of the azide functionality led to concomitant cyclopropane opening delivering pentacyclic lactam **180**. Pentacyclic lactam **180** contains a large portion of the skeleton present in the communesins and perophoramidine (**10**).

Following this initial report, Qin and coworkers reported the first total synthesis of the (±)-communesin F (**7**) in 2007 using a similar cyclopropanation strategy.³⁸ The group was able to utilize a pendant diazoester to install one of the two quaternary stereocenters present in communesin F (**7**) in a diastereoselective fashion (Scheme 30). Qin's synthesis commenced with the assembly of azido ester **184** in four steps from tryptophol derivatate **182** and aryl

azide **181**. Aryl azide **181** was coupled with tryptophol derivate **182** in 95% yield. The ketoester product was condensed with tosyl hydrazine under acidic conditions to form the tosyl hydrazone, which was converted to diazoester **183** by treatment with DBU. With diazoester **183** in hand, the stage was set for the key cyclopropanation reaction. Treatment of this intermediate with stoichiometric CuOTf in DCM led to formation of cyclopropane intermediate **184** as an inconsequential 1.6:1 mixture of diastereomers. Staudinger reduction of the azide functionality with PBu_3 in aqueous THF produced an amine that underwent an intramolecular $\text{S}_{\text{N}}2$ reaction/fragmentation cascade delivering N–H aminal **185** in 83% as a single diastereomer. N–H aminal was protected as its methyl carbamate **186** in 93% yield by treatment with methyl chloroformate. At this stage, diastereoselective construction of the second vicinal quaternary stereocenter was performed utilizing an allylation reaction. This transformation was accomplished by treatment of **185** with NaH and allyl bromide in DMF, providing allyl lactone **188** as a single diastereomer in 85% yield. The authors were able to elucidate that the allylation reaction proceeded through an *O*-allylation [3,3]-sigmatropic rearrangement by observation of the intermediate ketene acetal **189**, which underwent rearrangement *in situ*. To rationalize the stereochemical course of the reaction, it is proposed that allylation proceeds from the sterically more accessible top face of the molecule while the bottom face is shielded by the bromophenyl portion of the molecule.

To elaborate the synthesis, oxidative cleavage of the allyl moiety was accomplished using a two-step protocol in 95% yield (Scheme 31). The resulting aldehyde (**189**) was converted to primary alcohol **190** in three steps *via* oxime formation, Ra-Ni reduction, and treatment of the amine product with NaOMe in MeOH to facilitate the transamidation. Conversion of the primary alcohol **190** to the *tert*-butyl carbamate **191** was performed in four steps *via* oxidation using the Dess-Martin periodinane (DMP), oxime formation, reduction with Ra-Ni and reaction of the amine with Boc_2O . A Heck reaction was performed with 2-methyl-3-buten-2-ol in the presence of 50 mol% $\text{Pd}(\text{OAc})_2$ and 200 mol% (*o*-tol) $_3\text{P}$ under microwave irradiation providing a handle for subsequent benzazepine formation. The tertiary alcohol product **192** was treated with PPTS facilitating the acid-catalyzed cyclization event providing benzazepine **194** in 66% along with 26% of the undesired elimination product **193**. To construct the final ring in communesin F (**7**), the lactam in benzazepine **194** was activated for nucleophilic attack by the nitrogen in the benzazepine ring. This was accomplished by conversion of the lactam to the ethyl imino ether, which in turn was treated with TFA to liberate the secondary amine. The secondary amine did not undergo spontaneous cyclization to the desired amidine product **195**. Instead, the cyclization event was facilitated by treatment with silica gel at 50 °C (81% over 3 steps). Amidine **195** was used to complete the total synthesis by hydrolysis of the carbamate functionality with KOH/MeOH, and reduction of the amidine with sodium borohydride under acidic conditions, which delivered communesin F (**7**) as a mixture of two rotamers. Treatment of the natural product with TFA in CHCl_3 provided the natural product's TFA salt (**7**•TFA) in 95% yield.

Weinreb and coworkers have been able to successfully apply their Heck reaction conditions to a tetrasubstituted olefin substrate in a route that was used to complete the total synthesis of communesin F (**7**) (Scheme 32).³⁹ To assemble the Heck precursor, enol triflate **196** was cross-coupled with aryl boronic acid **197**. The cross-coupling product **198** was saponified to

the carboxylic acid, which was converted to the acyl chloride and subsequently treated with aniline **199** delivering amide **200** in 87% yield. The benzyl group was converted to the ethyl carbamate by treatment of amide **200** with ethyl chloroformate (96%), and the resulting product was methylated with iodomethane in 92% yield delivering the Heck reaction precursor **201**.

While both inter- and intramolecular Heck reactions are uncommon for tetrasubstituted olefins, the intramolecular Heck reaction of amide **201** proceeded smoothly employing a Pd(OAc)₂/PPh₃ system and delivered the oxindole product **202** in 90% yield. (Scheme 33) The synthesis was elaborated by hydrogenation of the nitro group, converting the resulting aniline product to *tert*-butyl carbamate **203** in 87% yield over 2 steps. To construct the lower aminal, semi-reduction of the oxindole was performed using AlH₃•NMe₂Et providing a tetracyclic intermediate in 74% yield, which was treated with KOH in EtOH to hydrolyze the ethyl carbamate and afford enamine **204** in 94% yield. Functionalization of the enamine to install the second vicinal quaternary stereocenter proved challenging, and conversion of enamine to the lactam was necessary to achieve this transformation. This was accomplished with the use of cyanogen azide, which afforded cyanoamidine **206** in 93% yield, proceeding through [3 + 2] cycloadduct **205** as an intermediate. Cyanoamidine **206** was hydrolyzed under basic conditions to deliver an N–H lactam, which was converted to *N*-Boc lactam **207** in 95% yield. At this stage, the second quaternary stereocenter was introduced *via* diastereoselective allylation. Treatment of lactam **207** with KO^tBu and allyl iodide at –78 °C resulted in formation of the desired product **208** in 87% yield as a single diastereomer. The allylation event was rationalized to proceed from the sterically more accessible convex top face of the lactam enolate.

To elaborate the northern portion of the molecule, the Boc group was cleaved using KOH in EtOH in 94% yield (Scheme 34). The resulting N–H lactam was converted to mesylate **209** using a three step sequence which included oxidative cleavage, reduction of the aldehyde, and mesylation of the primary alcohol. The BOM group was removed *via* hydrogenolysis and the resulting alcohol was oxidized using DMP affording aldehyde **210** in 75% over 2 steps. This aldehyde was elaborated into azide **211** in 2 steps using a nucleophilic displacement of the mesylate with sodium azide and a cross aldol reaction with acetone. A Boc group was installed on the δ–lactam, and the azide was reduced under Staudinger conditions leading to a transamidation to the γ–lactam **212**. Reaction with methylithium afforded an allylic alcohol, which was treated with PPTS to cyclize azapane **192**. From this point, the synthesis was completed by activation of the lactam with Meerwein's reagent to provide an imino ether which was cyclized to amidine **214**. Reduction of the amidine and acylation was achieved using NaBH₄ in the presence of Ac₂O and the product was treated with TFA to provide communesin F•TFA (**7**•TFA).

Most recently, Funk and coworkers reported an expedient 16-step synthesis of (±)-communesin F (**7**) by employing a [4+2] cycloaddition between an indol-2-one and functionalized indole-derivative (Scheme 35).⁴⁰ Previously, the group showed that this methodology could be used as a key step in the total synthesis of (±)-perophoramidine (**10**) (*vide infra*) as well as other natural products.⁴¹ By using this cycloaddition, the southern

portion of communesin F (**7**) could be assembled rapidly and efficiently. Funk's synthesis commenced with the key reaction between indole **215** and bromooxidole **216**. Treatment of these reaction partners with AgCO_3 in MeCN at rt smoothly facilitated the desired hetero-Diels Alder reaction, which proceeded through *endo* transition state **217** delivering dimer **218** in 70% yield as a single diastereomer. Tosylation of dimer **218** and subsequent methanolysis facilitated a rearrangement to tetracycle **219** in 61% yield. This intermediate was suitable for single crystal X-ray diffraction, and was used to confirm the assigned relative stereochemistry of the cycloaddition. Methylation of tetracycle **219** with Meerwein's reagent, followed by hydrogenation of the azide, and cleavage of the tosyl group provided carbamate **220**. At this stage, the side chain for the benzazepine was introduced using a Heck reaction between carbamate **220** and 2-methyl-3-buten-2-ol. The allylic alcohol product was cyclized to the benzazepine ring employing $\text{Hg}(\text{OTf})_2$ in 86% yield. The Boc group was removed from benzazepine **221** utilizing TBSOTf,⁴² and the amine product from this transformation was cyclized to the bridged lactam **222** with AlMe_3 . At this stage, the second quaternary stereocenter was introduced *via* alkylation with iodoacetonitrile in 77% yield and with complete diastereocontrol. The nitrile product **223** was reduced with LiAlH_4 to hemiacetal **224** which, in turn, was converted to aminal **225** *via* reductive amination. To complete the synthesis, aminal **225** was acylated with acetic anhydride to deliver communesin F (**7**) in 13 steps from bromotryptophol **215**.

3.2. Asymmetric Total Syntheses of Communesin Alkaloids

The first asymmetric total synthesis of communesin F (**7**) was reported by Ma and coworkers (Scheme 36). This route also served to establish the absolute configuration of the natural product.⁴³ Earlier work in the Ma group demonstrated that an intramolecular oxidative coupling of indole derivative **226** could be accomplished in high yield when an electron-poor arene (i.e. $\text{R} = \text{NO}_2$) was present in the substrate. The authors postulated that increased acidity of the α -position of the amide led to the observed trend in reactivity. The product from this transformation constructs the C(7) all carbon quaternary stereocenter present in the communesin alkaloids.

Based on the success of the oxidative coupling reaction, the Ma group chose to utilize this transformation as a key step in the asymmetric total synthesis of communesin F (**7**) (Scheme 37). To render the synthesis asymmetric, silylated (*S*)-phenylglycinol was employed as a chiral auxiliary at the amide. The oxidative coupling substrate **231** was assembled in 65% yield over three steps from bromotryptophol **230** *via* oxidation, reductive amination with (*S*)-OTBS-phenylglycinol, and a BOP coupling with 2-(2-nitrophenyl)acetic acid. Double deprotonation of coupling substrate **231** with LiHMDS in THF at -78°C followed by treatment with I_2 led to the desired coupling product **232** as a mixture of diastereomers. The nitro group was reduced with iron and the resulting aniline cyclized spontaneous to a tetracycle which was methylated to afford an N-H aminal in 66% over 3 steps. At this stage, the d.r. of the oxidative coupling was determined to be 3:1 as well. The N-H aminal was converted to the *tert*-butyl carbamate **233** in 89% yield, and the second quaternary stereocenter was introduced *via* allylation with allyl iodide in >20:1 dr. A three-step sequence was used to remove the (*S*)-OTBS-phenylglycinol auxiliary from carbamate **233** which included protodesilylation of the OTBS group, elimination, and hydrolysis, affording

lactam **234** in 93% yield over 2 steps.⁴⁴ The olefin moiety was cleaved oxidatively under modified Johnson-Lemieux conditions to provide an aldehyde, which was reduced to primary alcohol **235** with NaBH₄ in 95% yield over 2 steps. At this stage, a Heck reaction similar to the one employed by Qin was used to install the side chain for assembly of the benzazepine ring. This reaction was conducted with Pd(OAc)₂ as the precatalyst under microwave irradiation resulting in a 67% yield (80% brsm) of the desired allylic alcohol **236**. Surprisingly, mesylation of the diol **236** not only led to formation of the primary mesylate but also resulted in spontaneous cyclization of the benzazepine ring under the reaction conditions in 63% yield. The mesylate product was treated with sodium azide to afford primary azide **237** in 78% yield. An aza-Wittig reaction was used to cyclize the final 5-membered ring in the natural product. Typically, aza-Wittig reactions with amides are uncommon and require high reaction temperatures. However, due to the strained nature of the amide, which cannot have its lone pair donate into the carbonyl group, this transformation could be conducted at 80 °C and delivered the amidine in 83% yield. To complete the synthesis, the amidine was reduced with sodium borohydride in the presence of acetic acid and acetic anhydride and the product was converted to the TFA salt of (-)-communesin F (**7**). The natural product was accessed in 19 steps (longest linear sequence) from 4-bromotryptophol (**230**) and in around 6% overall yield. The absolute configuration of communesin F (**7**) was established by comparing the rotation of the synthetic sample to the natural product.

While numerous syntheses of communesin F (**7**) have been disclosed over the last decade, the syntheses of communesins A and B (**1** and **2**), the epoxide-bearing and biologically most active members of this family of natural products remained unsolved. Recently, Ma and coworkers reported the total syntheses of these two natural products in a catalytic asymmetric manner.⁴⁵ While direct conversion of communesin F (**7**) to communesin A (**1**) was attempted *via* epoxidation reactions, the natural product was found to be unstable to the reaction conditions examined likely due to the sensitivity of the aminal functionalities towards oxidation. To circumvent this limitation, the olefin side chain was oxidized at an early-stage and was protected as a ketal to avoid undesired side reactions. For this purpose, a different synthesis was devised. Aurantioclavine ketal **243** was prepared in 13 steps from 4-bromotryptophol (**230**) (Scheme 38). The synthesis commenced with the preparation of tertiary alcohol **238** in 3 steps from 4-bromotryptophol (**230**), which included TBS protection of the primary alcohol, tosylation of the indole and a Heck reaction to introduce the alcohol side chain. Tertiary alcohol **238** was treated with AD-mix-β under Sharpless dihydroxylation conditions to deliver enantioenriched diol **239** in 94% yield and 96% ee. Diol **239** was converted to the cyclic sulfite, which was subsequently treated with sodium azide to arrive at azide **240** in 64% yield over 2 steps. Ketalization with dimethoxypropane followed by reduction of the azide with LiAlH₄ provided an amine that was converted to 2-nitrobenzene sulfonamide **241** in 90% over 2 steps. Protodesilylation of the TBS group unmasked a primary alcohol, which was cyclized using a Mitsunobu reaction and hydrolyzed to afford benzazepine **242** in 81% over 3 steps. Removal of the tosyl group with Mg(0) delivered aurantioclavine ketal **243** in 92% yield.

Coupling of aurantioclavine ketal **243** with 2-(2-nitrophenyl)acetic acid using BOPCl proceeded uneventfully to provide the oxidative coupling substrate **244** in 91% yield (Scheme 39). Double deprotonation of **244** with 2 equivalents of LiHMDS and the addition of iodine at $-78\text{ }^{\circ}\text{C}$ resulted in formation of undesired side products and failed to provide the coupling product **246**. On the other hand, addition of iodine at room temperature led to smooth formation of the spiro-fused coupling product **246** as a single diastereomer in 66% isolated yield (73% brsm). To rationalize the observed diastereochemical outcome, the authors proposed that the oxidative coupling proceeds through transition state **245**, which contains favorable π -stacking interactions between the electron-poor arene and electron-rich indole and contains the bulky ketal on the opposite face from radical combination. To elaborate the synthesis, the nitro group was reduced with H_2 and Ra-Ni and the resulting aniline cyclized onto the imine leading to the formation of an N-H aminal in 70% yield, which was methylated to afford methyl aminal **247** in 90%. Installation of the second quaternary stereocenter was accomplished *via* alkylation with iodoacetonitrile, which occurred in 67% yield and complete diastereoselectivity. The nitrile **248** was reduced with LiAlH_4 leading to formation of lactol **249**, which was converted to aminal **250** *via* reductive amination with sodium cyanoborohydride in 92% yield over 2 steps.

Communesin A (**1**) was completed by acylation of aminal **250** in 65% followed by hydrolysis of the ketal functionality, mesylation of the secondary alcohol and cyclization to the epoxide in 55% yield over 2 steps (Scheme 40). Analogously, communesin B (**2**) was accessed by coupling aminal with sorbic acid with BOPCl, hydrolysis of the ketal, mesylation and epoxide formation in 69% over 3 steps. In summary, Ma's syntheses accessed both communesins A (**1**) and B (**2**) in 24 steps and ~2-3% overall yield from 4-bromotryptophol (**230**). The routes utilized a diastereoselective oxidative coupling as a key step to forge one of the two quaternary stereocenters in the target.

4. Total Syntheses of the Perophoramidine

Like the communesin alkaloids, perophoramidine (**10**) has attracted the interest of the synthetic community due to its intriguing structure and biological activity. Many groups that have synthesized the communesins have also pursued perophoramidine (**10**) as a target. While similar in structure to the communesin alkaloids, perophoramidine (**10**) has unique structural features that make it a synthetic challenge. The natural product's vicinal quaternary stereocenters have the opposite relationship from that encountered in the communesins and any strategy that was applied to the construction of this motif in the communesins would need to be rehashed in order to be used to prepare perophoramidine (**10**). Additionally, perophoramidine contains three points of halogenation on the aromatic nuclei, one bromide and two chlorides, which need to be incorporated when devising a retrosynthesis. The remainder of this review will outline the elegant syntheses that have been developed to access perophoramidine (**10**).

4.1 Racemic Total Syntheses of Perophoramidine

The first total synthesis of perophoramidine (**10**) was reported by Funk and coworkers (Scheme 41). By employing a hetero-Diels-Alder reaction as a key transformation, the

authors could construct both vicinal quaternary stereocenters in the target in a single synthetic operation.⁴⁶ The synthesis commenced with the [4 + 2] cycloaddition between silyl tryptophol **253** and bromooxindole **254** to form cycloadduct **255** in 89% yield and >20:1 dr. This material was converted to the Boc carbamate, which was subsequently treated with triphenylphosphine to reduce the azide functionality and to facilitate a transamidation cascade affording pentacycle **256** in 89% yield. Due to the electronic difference between the two aromatic nuclei in pentacycle **256**, NCS could be used to chlorinate the more electron rich aromatic ring chemoselectively in an excellent 86% yield followed by sulfonation to arrive at dichloride **257**. The dichloride was protidesilylated to the primary alcohol, and converted to azide **258** employing a Mitsunobu reaction. Reduction of azide **258** under Staudinger conditions led to a transamidation from the γ - to the δ -lactam in 86% yield. The nosyl sulfonamide was methylated with iodomethane, and the resulting δ -lactam (**259**) was converted to imino ether **260** in 68% yield. Removal of the nosyl group with thiophenol led to formation of the secondary amine which spontaneously cyclized onto the imino ether functionality leading to an amidine which was oxidized with MnO₂ in 65% yield to afford (\pm)-perophoramidine (**10**).

A total synthesis of dehaloperophoramidine (**274**), the dehalogenated analog of perophoramidine, was reported Rainier *et al.* utilizing their 2-thioindole spirocyclization methodology (Scheme 42).^{47, 48} The thioindole cyclization precursor **264** was prepared from the condensation of *N*-Boc isatin (**136**) and *N*-benzyl tryptamine (**261**) followed by thioether installation and sodium borohydride reduction. Secondary alcohol **263** was treated with MsCl, which led to spontaneous spirocyclization providing **265** as a 2:1 mixture of diastereomers. This mixture was treated with DBU, which served to cyclize the amidine and equilibrate the diastereomeric mixture to a single lactam diastereomer **266**. Installation of the second quaternary stereocenter was performed *via* alkylation with allyl iodide and delivered allyl lactam **267** in 89% yield as a single diastereomer.

With both quaternary stereocenters installed, the synthesis was elaborated by manipulation of the allyl moiety (Scheme 43). Oxidative cleavage under Johnson-Lemieux conditions afforded an aldehyde, which was converted to a secondary amine *via* reductive amination and then treated with Boc₂O to afford carbamate **268**. At this stage, the amidine was converted to aminal **269** with sodium borohydride. While this transformation may seem counterintuitive, the authors found that cyclization of the northern amidine functionality could not be performed when the southern amidine was present in the molecule. Treatment of aminal **269** with TFA served to remove both Boc groups from the molecule and afforded **270** which was treated with Boc₂O to chemoselectively introduce a Boc group at the secondary amine and not the aminal. Dissolving metal conditions were used to cleave the benzyl group, and the indoline nitrogen was treated with AcCl to provide *N*-acyl aminal **271** in 88% yield over 2 steps. Exposure of **271** to Meerwein's reagent with NaHCO₃ as an acid scavenger led to formation of imino ether **272** in 81% yield, and this compound was treated with TFA to remove the Boc group and cyclize the northern amidine providing hexacycle **273**. Finally, the *N*-acetyl group was hydrolyzed with KOH, and the aminal functionality was oxidized to the amidine delivering dehaloperophoramidine (**274**).

Takemoto and coworkers reported a total synthesis of (\pm)-dehaloperophoramidine (**274**) employing a unique intramolecular dearomatizing cyclization-allylation sequence to forge both quaternary stereocenters in a single operation (Scheme 44).⁴⁹ Their synthesis commenced with the preparation of dearomatizing cyclization precursor **283**. Suzuki coupling of lactam **275** and boronic acid **276** followed by cleavage of the Boc group provided aniline **277**. This material was treated with aryl isothiocyanate **278** delivering thiourea **279** in 85% yield. Thiourea **279** was converted to a carbodiimide by treatment with iodine, cyclized to the quinolone amidine *via a* 6π -electrocyclic reaction and converted to the *tert*-butyl carbamate **280** in 69% over 3 steps. At this stage, the amidine was protected with a PMB group using PMBI in 91%. The PMB amidine **281** was treated with TFA to cleave the Boc group, and the resulting N–H lactam was converted to thiolactam **282** with Lawesson's reagent in 97% yield. To complete the synthesis of the dearomatizing cyclization precursor **283**, thiolactam **282** was converted to the imino thioether with MeI in 89%, condensed with MeNH₂ to provide an amidine, which was protected with a Boc group to deliver **283** in 87% over 2 steps.

The key dearomatizing cyclization-allylation was performed by first treating **283** with *n*-BuLi in THF followed by the addition of allyl iodide (Scheme 45). Under these reaction conditions, the desired allyl bisamidine was obtained in 67% yield as a single diastereomer. The allyl moiety was dihydroxylated and the resulting diol was cleaved with NaIO₄ leading to loss of the Boc group and generation of hydroxyamidine **285** in 75% over 2 steps. To complete the synthesis, hydroxyamidine **285** was reduced with NaCNBH₃ to amidine **286** and the PMB group was removed with H₃PO₄ in the presence of anisole delivering (\pm)-dehaloperophoramidine (**274**) in 71%.

4.2 Asymmetric Total Syntheses of Perophoramidine

To date, three asymmetric total syntheses of perophoramidine have been reported, the first of which was disclosed by Qin and coworkers.⁵⁰ During their studies towards the communesin alkaloids, Qin and coworkers were faced with the task of reducing an azide functionality in pentacycle **287** to the corresponding amine employing Lewis acidic conditions (Scheme 46). However, upon exposure of the starting material to the reaction conditions, the authors were surprised not to observe the amine product but instead isolated lactam **289** in 65–70% yield along with bromoindole **288**. They posited that these products are obtained through a retro-Diels-Alder reaction forming diene **290**, which would undergo capture with solvent. With this result in hand, the authors were interested in exploiting the reverse Diels-Alder process as a key transformation to access perophoramidine (**10**) in an asymmetric fashion. To induce stereoselectivity, an appropriate chiral auxiliary could be placed on the N–H of the δ -lactam.

Diene precursor **296**, was prepared starting from isatin **291** (Scheme 47). Grignard addition followed by TBS protection of the tertiary alcohol afforded oxindole **292** in excellent yield. Ozonolysis of the allyl moiety provided an aldehyde in 84%, which was condensed with the Ellman auxiliary **293**⁵¹ and was reduced to deliver sulfonamide **294** in 85% yield over 2 steps. While other auxiliary groups were tested as well, the authors found that the Ellman auxiliary performed best both in terms of yield and d.r (*vide infra*). Sulfonamide **294** was

treated with Boc₂O under basic conditions to facilitate the lactam rearrangement (87%), and the resulting silyl lactam was treated with TBAF to cleave the TBS group, arriving at hydroxy δ -lactam **295** in 90%. Finally, the diene precursor **296** was accessed by conversion of the hydroxyl group to the unstable chloride by treatment with SOCl₂.

With diene precursor **296** in hand, the key diastereoselective Diels-Alder reaction was explored. Reaction of indole **297** and the diene precursor **296** with 2 equiv of AgBF₄ in DCM resulted in formation of the desired Diels-Alder product **299** in 74% yield and a 5.9:1 dr favoring the *trans* product corresponding to the relative stereochemistry observed in perophoramidine (**10**) (Scheme 48). Screening other silver salts and solvents revealed that employing AgClO₄ in PhMe was optimal for the transformation and delivered the desired Diels-Alder product **299** in 77% yield and a 11:1 d.r. The yield of the transformation could be increased further to 88% by utilizing 3 equiv of the diene precursor. To rationalize the stereochemical outcome of the Diels-Alder process, the authors propose that the cycloaddition proceeds through *exo* transition state **298** with the *trans, trans* diene. This diene geometry is preferred to avoid unfavorable electronic repulsion between the lactam oxygen and aniline carbamate.

With an optimized set of conditions to access pentacycle **299**, the synthesis of perophoramidine (**10**) was elaborated. Chemoselective chlorination of the indoline ring was accomplished with the use of sodium hypochlorite, which also served to cleave the auxiliary on the δ -lactam. The dichloride product **300**, was treated with PCC to oxidize the methyl group to the formyl group and this formyl compound was treated with Meerwein's salt to cleave the Boc group and convert the δ -lactam into imino ether **301**. Cleavage of the phthalimide group was accomplished with MeNH₂, and the resulting primary amine was cyclized by refluxing in chloroform to arrive at amidine **302** in 77% over 2 steps. Oxidation with MnO₂ in DCM converted the amina to bisamidine **303**, and PPTS was used to equilibrate bisamidine **303** to the thermodynamically favored bisamidine **304**. Finally, chemoselective methylation of **304** with NaHMDS and MeOTf in THF afforded (+)-perophoramidine (**10**) in 73%. The natural product was accessed in 17 steps (longest linear sequence) and ~11% overall yield.

Wang and coworkers disclosed a catalytic asymmetric total synthesis of (+)-perophoramidine (**10**) employing a Ni-catalyzed addition of an indole into an aza-*o*-xylylene intermediate generated from a 3-bromooxindole (Scheme 49).⁵² Using this methodology, the authors could forge both quaternary stereocenters in a single enantioselective transformation. Optimization studies on the coupling of indoles with 3-bromooxindole showed that the two substrates could be readily coupled in the presence of a nickel Lewis acid catalyst and chiral diamine ligand. In particular, the combination of Ni(OAc)₂ and 3-OMePh-substituted diamine ligand **305** proved optimal to facilitate the transformation. To utilize this methodology in the total synthesis of (+)-perophoramidine (**10**), indole **306** was coupled with bromooxindole **307** under the optimized reaction conditions, affording compound **308** in 51% yield, a 12:1 dr and 90% ee.

Next, the oxindole was sulfonated with NsCl, and the phthalimide group was cleaved with hydrazine triggering a transamidation sequence and providing pentacycle **309** in 84% over 2

steps (Scheme 50). The indoline ring was chlorinated employing NCS, and the nosyl group was cleaved from the aminal with thiophenol providing lactam **310**. The lactam was sulfonated with NsCl and the azide was reduced facilitating another transamidation sequence. The resulting δ -lactam was methylated chemoselectively at the sulfonamide to deliver pentacyclic aminal **311** in 90% yield over 3 steps. Oxidation of the pentacyclic aminal **311** was accomplished with PCC, and the resulting amidine (**312**) was protected on both the lactam and amidine with Boc_2O . Treatment of Boc-amidine **313** with LiAlH_4 led to reduction of the amidine and cleavage of the Boc group present on the lactam. N–H lactam **314** was activated as the imino ether (**315**) in 87% yield by treatment with Me_3OBF_4 . Finally, (+)-perphoramidine (**10**) was completed with cleavage of the nosyl group employing thiophenol, removal of the Boc group, and oxidation of the aminal to the amidine.

Most recently, Trost and coworkers reported a catalytic asymmetric total synthesis of (–)-perphoramidine.⁵³ Unlike many other syntheses, which utilized a [4+2]-cycloaddition as their key step, the Trost group developed a route to this natural product utilizing a Mo-catalyzed asymmetric allylic alkylation (Mo-AAA) as the key enantiodetermining process. The synthesis commenced with the preparation of the two Mo-AAA coupling partners (Scheme 51). Allylic phosphate **317** was prepared from 4-bromo-2-fluorobenzaldehyde **316** in 5 steps, and oxindole **319** was prepared from tryptophol in 3 steps. Coupling of these components proceeded smoothly in the presence of a Mo(0) precatalyst and picolinic acid-derived ligand (*S,S*)-**318**. Upon basic workup, the oxindole product **320** was obtained in an excellent 89% isolated yield, 19:1 branched:linear ratio, 8:1 dr and 97% ee.

With a robust means to construct one of the quaternary stereocenters in the target, assembly of the southern tetracyclic ring system was examined (Scheme 52). To perform a reductive cyclization, oxindole **320** was converted to the dimethylallyl carbonate **322**. This intermediate was treated with LiEt_3BH to chemoselectively reduce the oxindole to the *N,O*-aminal, which was treated with a Pd(0) source to remove the dimethylallyl group and concurrently cyclize aminal **323**. This tetracyclic intermediate was treated with NCS to introduce the chlorine substituents in the final target providing dichloroaminal **324**. To construct the northern 6-membered ring, the N–H dichloroaminal **324** was alkylated with PMB-Br with concomitant cleavage of the TBS group upon workup, and the primary alcohol intermediate was converted to azide **325** under Mitsunobu conditions. The olefin was cleaved oxidatively, oxidized, and converted to ester **326**, and this intermediate was treated with PMe_3 to reduce the azide and cyclize lactam **327**.

With 5 of the 6 rings installed, the Boc group was cleaved thermally, and the aminal intermediate was oxidized to amidine **328** using $\text{PhI}(\text{OAc})_2$ (Scheme 52). Amidine **328** was treated with Meerwein's reagent to convert the lactam to imino ether **329**, and this intermediate was allylated selectively on carbon employing allyl iodide in near quantitative yield and >20:1 dr. The C vs N regioselectivity of the iminoether allylic alkylation showed an interesting dependence on counterion wherein the lithium salt favoured N-alkylation but the potassium salt gave exclusively C-alkylation. To construct the final 5-membered ring, the olefin was converted to an aldehyde *via* ozonolysis, and this intermediate was converted to secondary amine **331** employing a Lewis-acid catalyzed reductive amination. Finally, the

(–)-perophoramidine (**10**) was accessed by thermal cyclization of the amine onto the pendant imino ether in compound **331**, followed by cleavage of the PMB group under acidic conditions.

4. Conclusions

The communesin alkaloids and perophoramidine (**10**) are intriguing alkaloids that have gained attention from the scientific community because of their unique structures and diverse biological activities. Elegant strategies have been developed to tackle these complex, densely functionalized natural products including inverse electron-demand hetero-Diels-Alder reactions, cyclopropanations, regio- and enantioselective allylic alkylations, as well as other novel approaches. The efficiency of these syntheses should enable the pursuit of structure activity relationships.

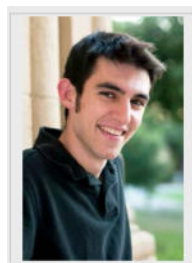
Acknowledgments

We thank the NSF (CHE-1145236) and the NIH (GM 033049) for their generous support of our programs. M.O. thanks The John Stauffer Memorial Fellowship and Stanford Graduate Fellowship for financial support.

Biography



Barry M. Trost was born in Philadelphia, PA in 1941 and studied at the University of Pennsylvania (BA, 1962). He obtained his PhD in 1965 at MIT. He moved to the University of Wisconsin where he was made Professor in 1969 and subsequently Vilas Research Professor in 1982. He moved to Stanford University in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition to holding Visiting Professorships at several universities worldwide, he has been awarded numerous prizes. His interests span the entire field of organic synthesis, particularly in the development of novel methodology and strategy for total synthesis of bioactive complex molecules.



Maksim Osipov was born in Lvov, Ukraine in 1985. After immigrating to the United States, he attended the University of Pittsburgh where he obtained his B.Sc. in chemistry. From there, Maksim attended Stanford University where he obtained his Ph.D. under the direction of Prof. Barry M. Trost developing asymmetric methods for the total synthesis of alkaloids. Maksim is currently a medicinal chemist at Flexus Biosciences where he developing drugs for cancer immunotherapy.

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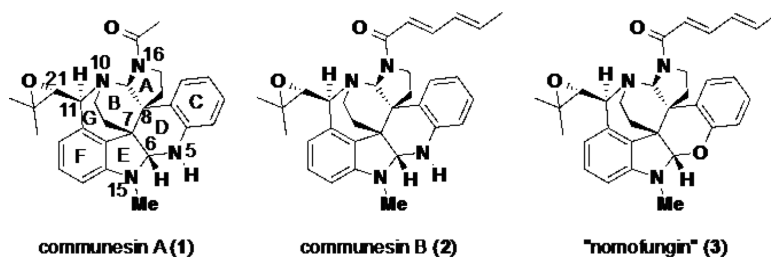


Figure 1.
Communesins A (1), B (2), and nomofungin (3)

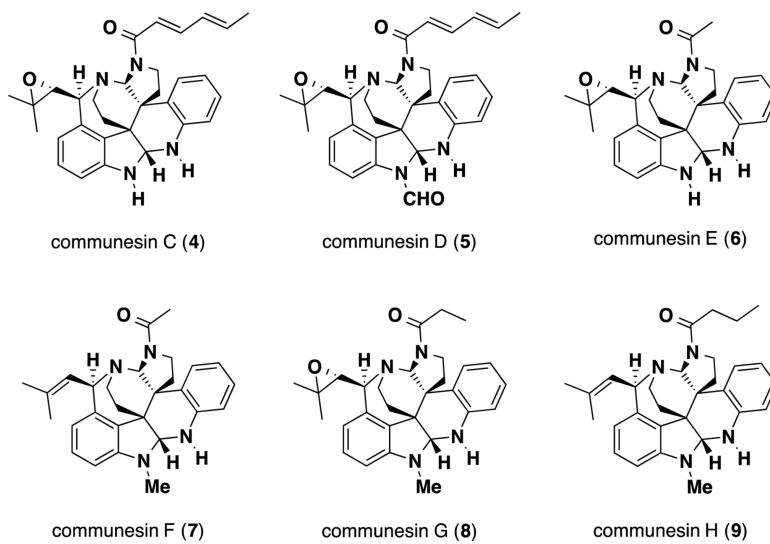
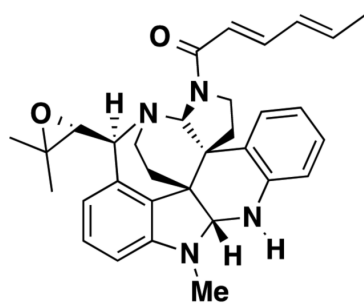
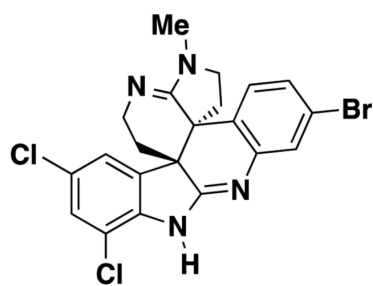


Figure 2.
Structures of isolated communesin alkaloids

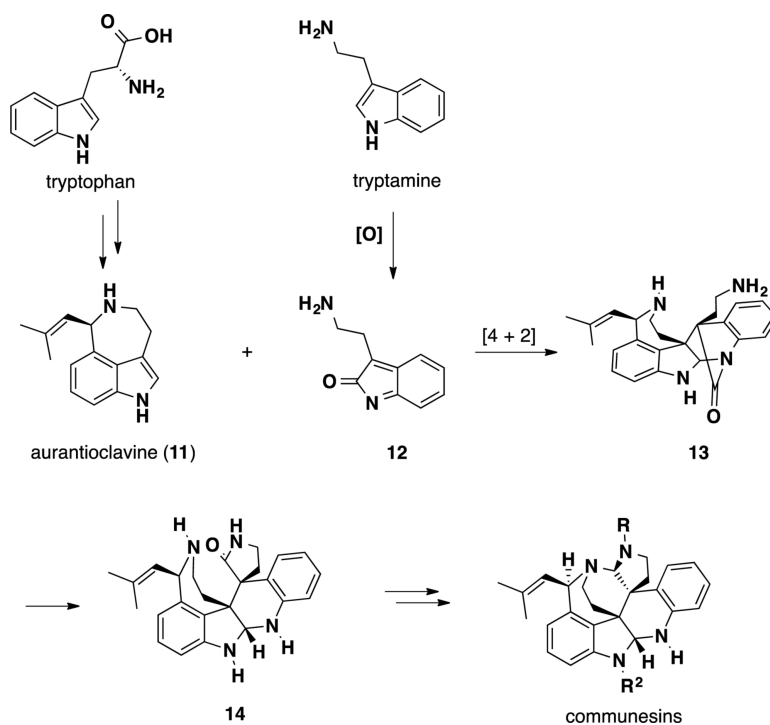


communesin B (2)

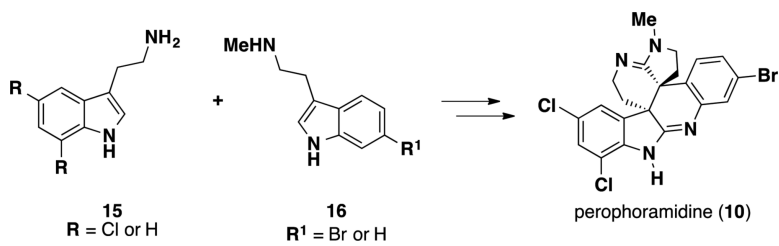


perophoramidine (10)

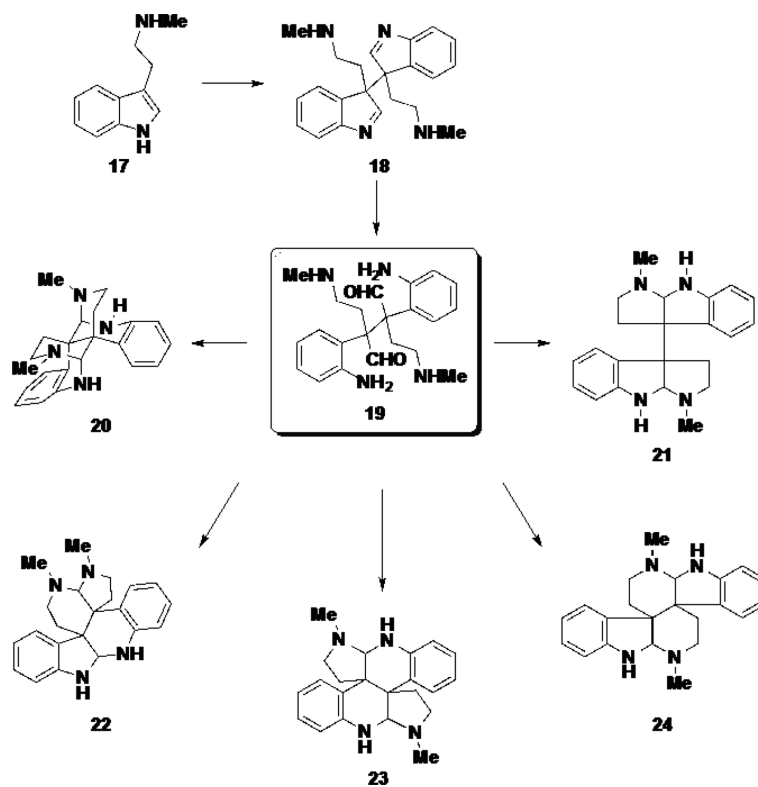
Figure 3.
Communesin B (2) and perophoramidine (10).



Scheme 1.
Proposed biosynthetic pathway for the communesin alkaloids



Scheme 2.
Proposed biosynthesis of perophoramidine (10)



Scheme 3.
The Biosynthetic Relationship Between Cyclotryptamine Alkaloids and Communesin Alkaloids

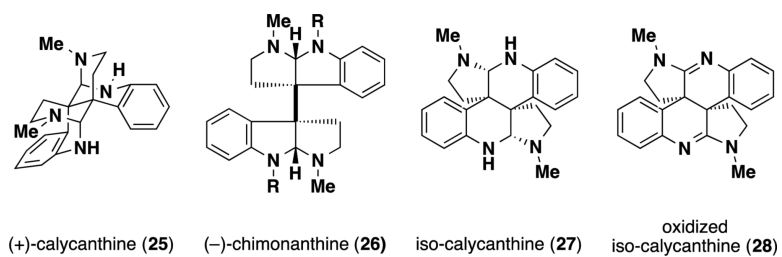


Figure 4.
Representative Cyclotryptamine Alkaloids

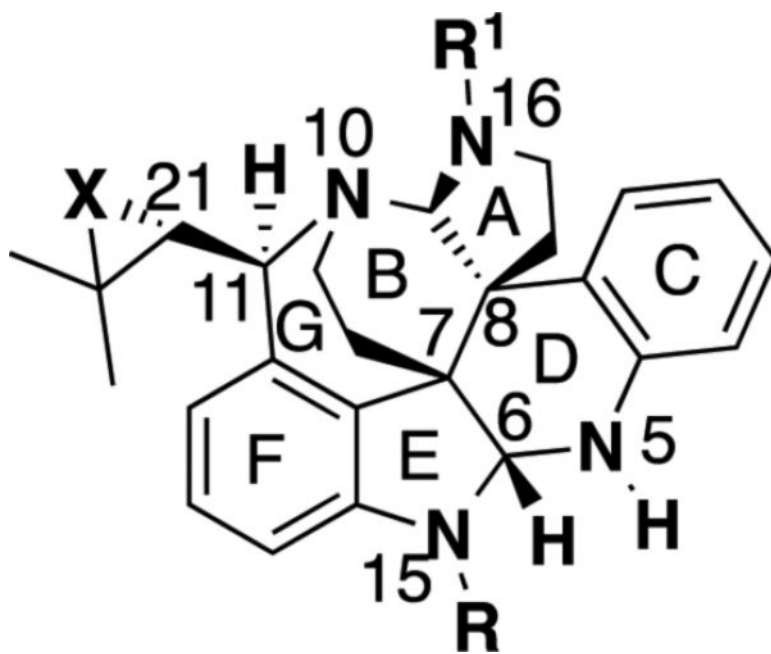
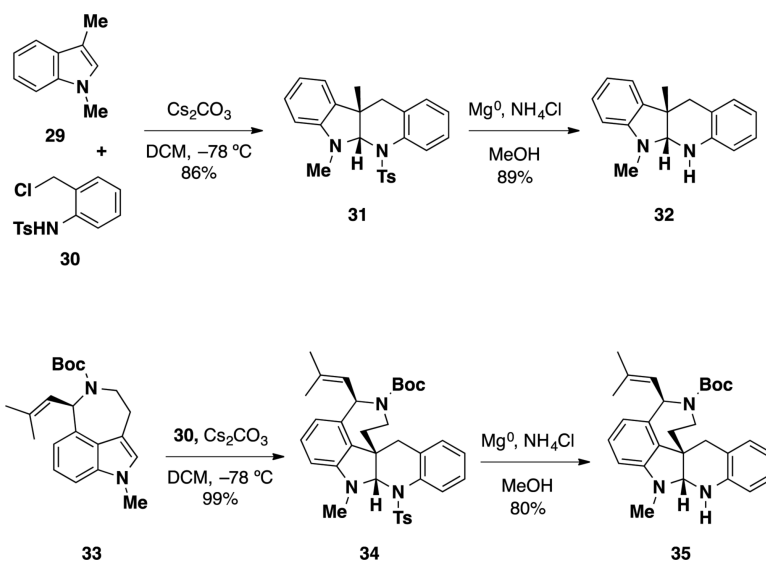
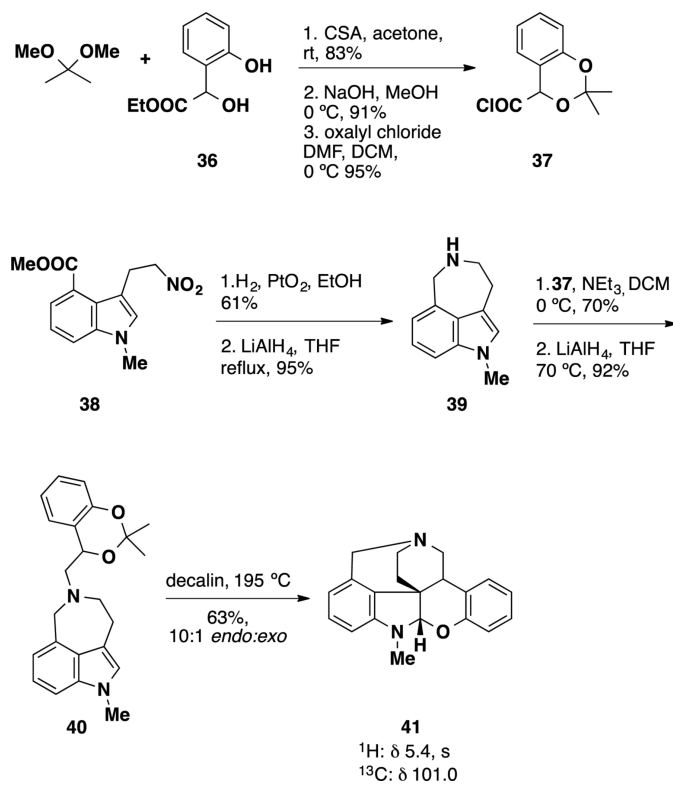


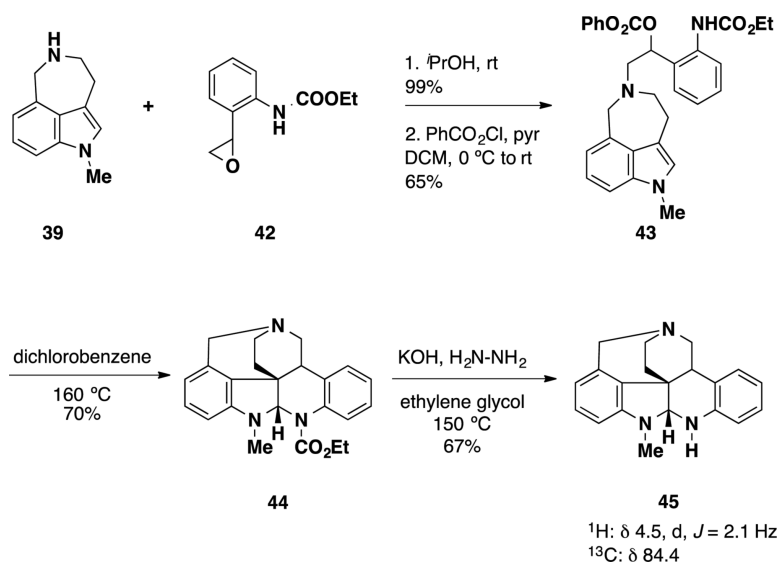
Figure 5.
The communesin skeleton



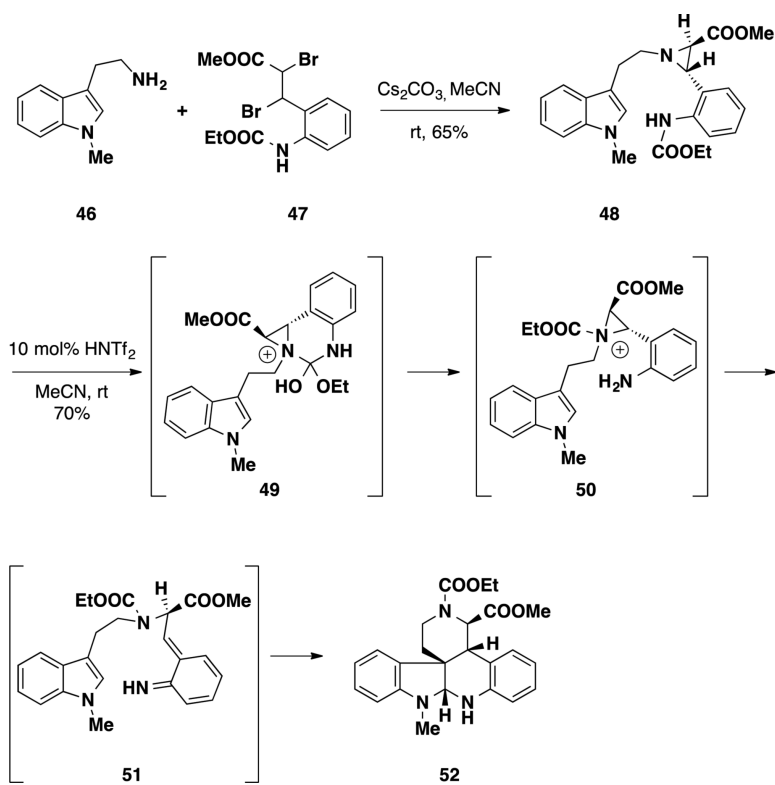
Scheme 4.
Stoltz's Synthesis of Communesin-like *N,N*-Aminals



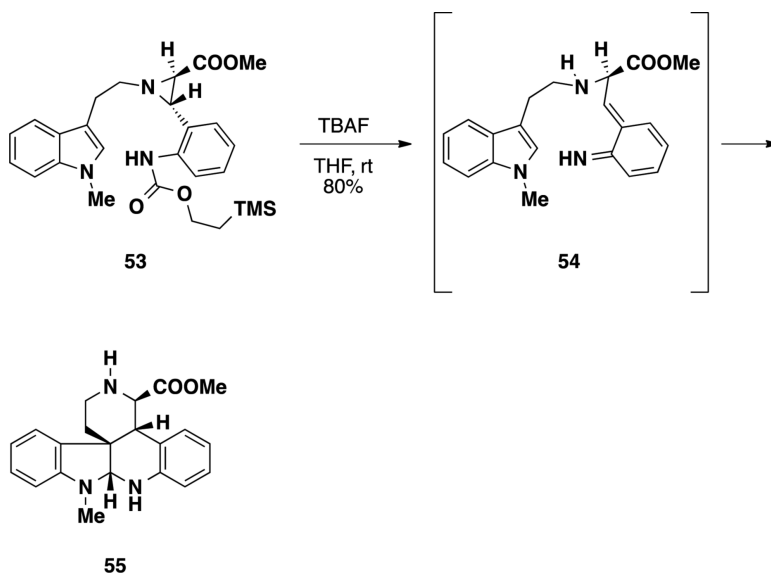
Scheme 5.
Funk's Synthesis of *N,O*-aminal (**41**)



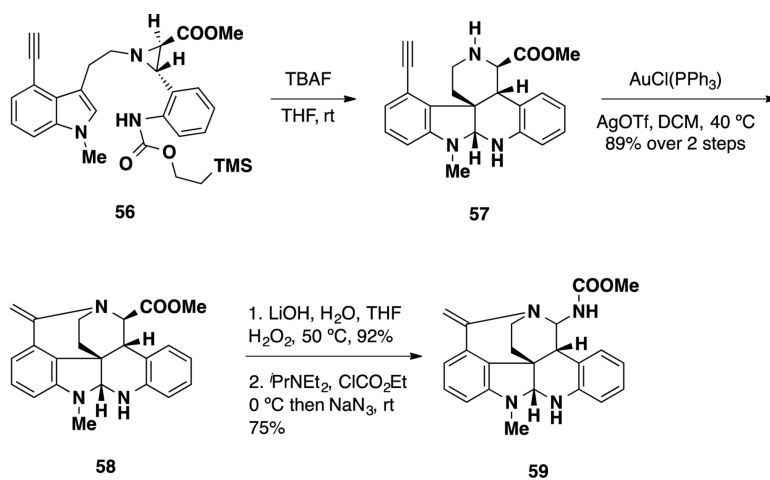
Scheme 6.
Funk's Synthesis of *N,N*-Aminal (**45**)



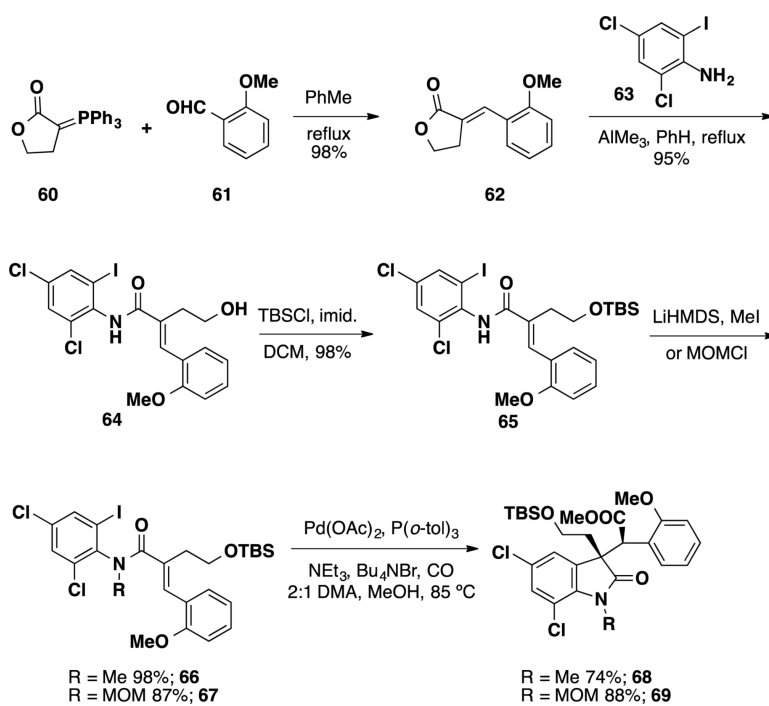
Scheme 7.
Funk's Synthesis of Pentacycle **52**



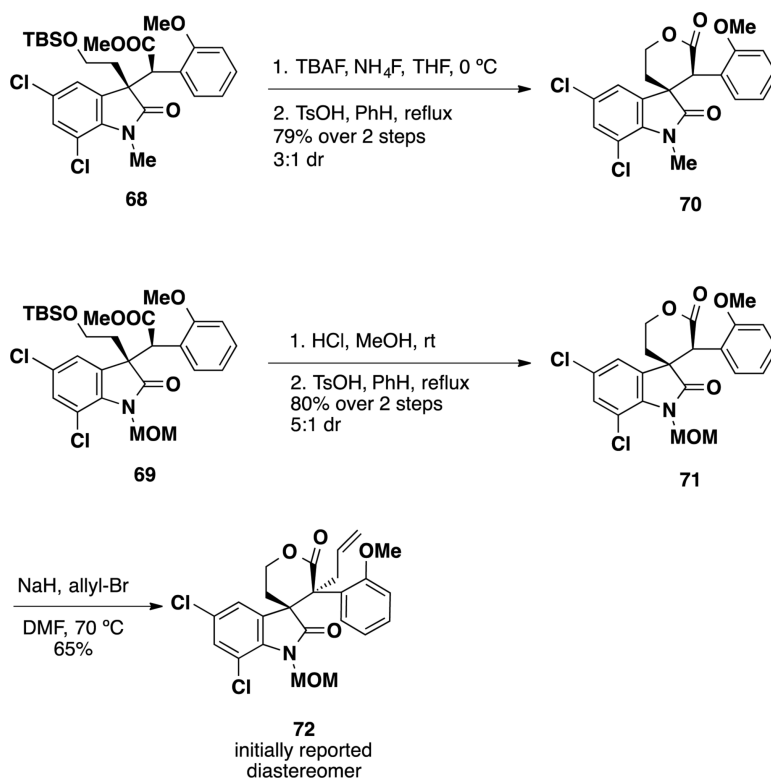
Scheme 8.
Funk's Aza-o-Xylylene Cycloaddition with a TEOC-Protected Aziridine **53**



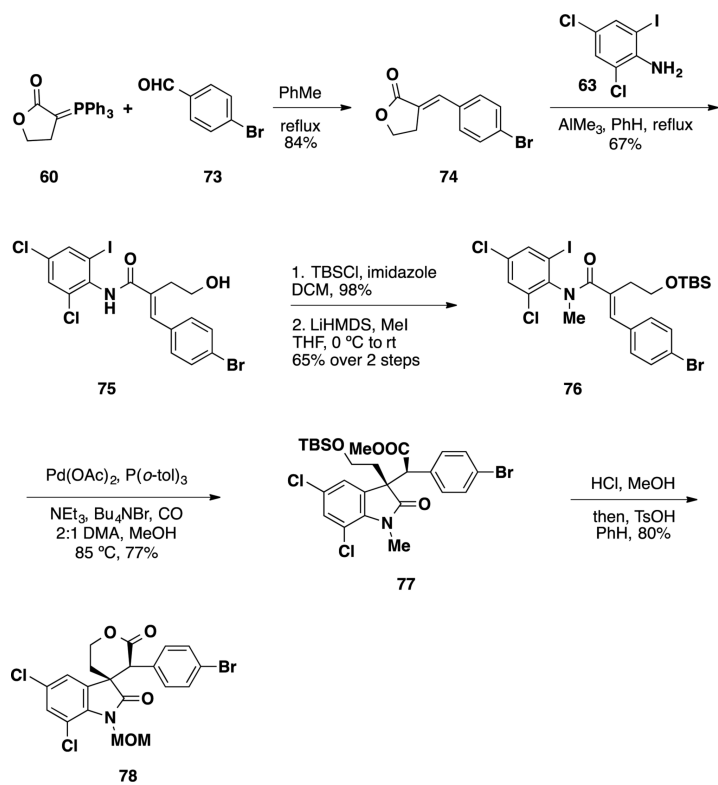
Scheme 9.
Funk's Synthesis of Hexacycle **59**



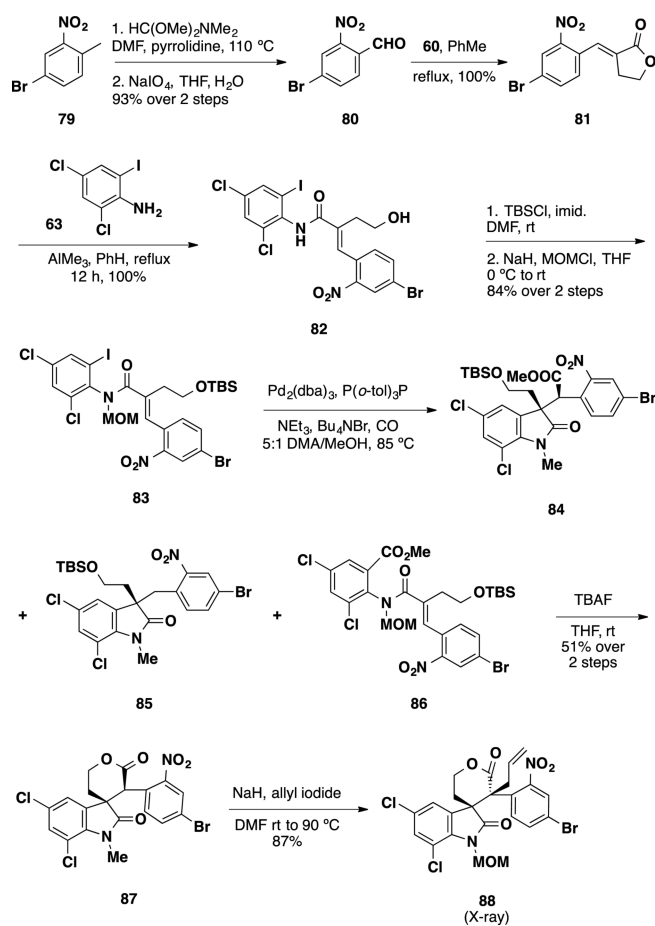
Scheme 10.
Synthesis of Oxindoles **68** and **69**



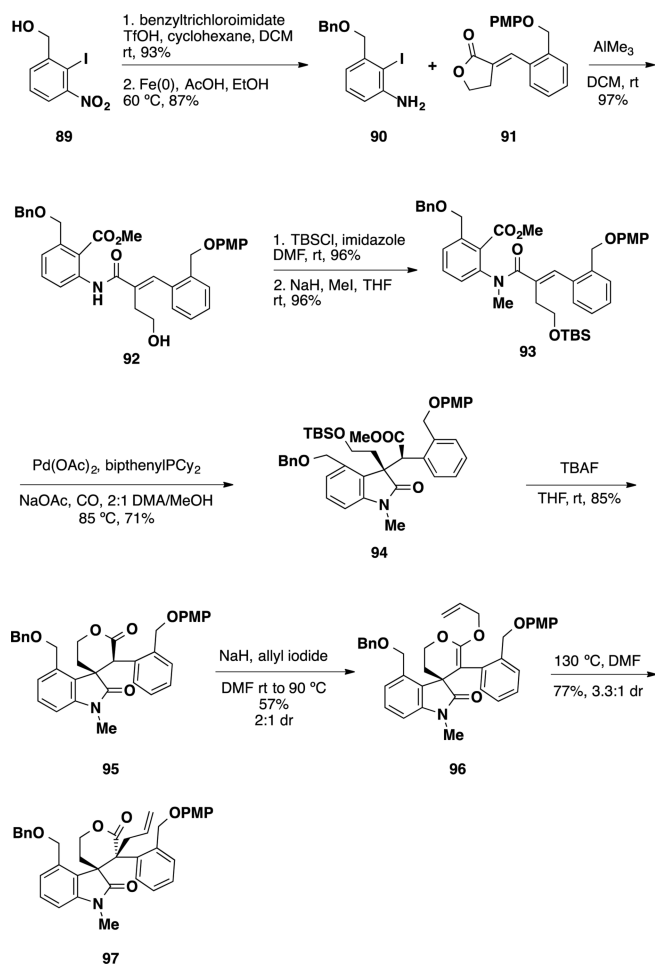
Scheme 11.
Elaboration of Weinreb's Synthesis



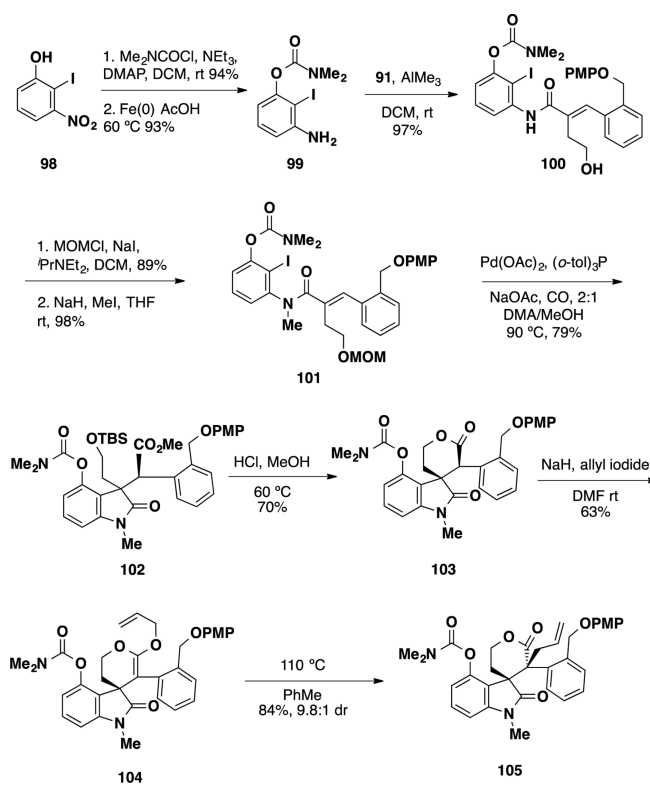
Scheme 12.
Synthesis of Bromolactone **78**



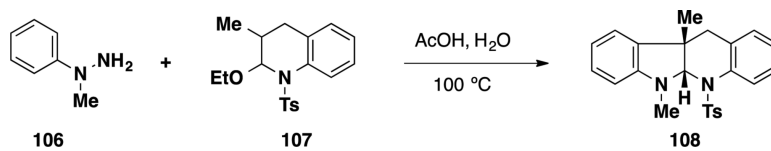
Scheme 13.
Preparation of the Nitrolactone **88**



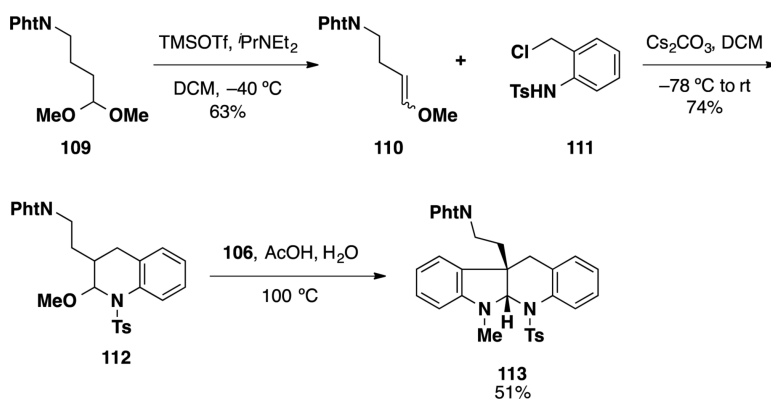
Scheme 14.
Synthesis of Allyl Lactone **97**



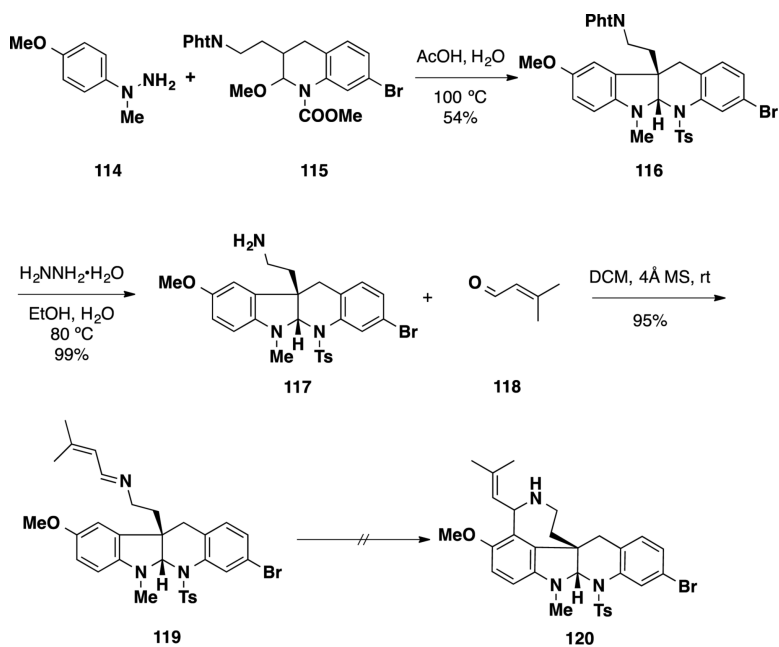
Scheme 15.
Synthesis of Allyl Lactone **105**



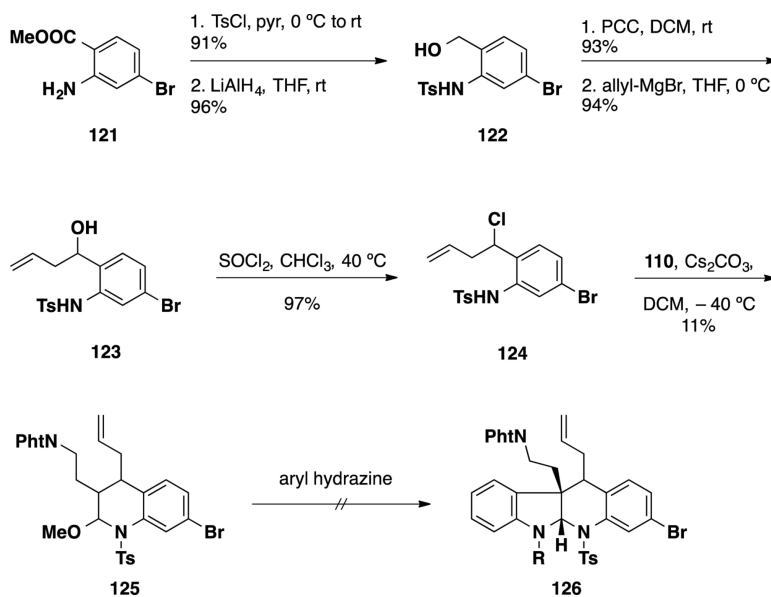
Scheme 16.
The Interrupted Fischer Indolization Reaction to Form the Southern Communesin Ring System



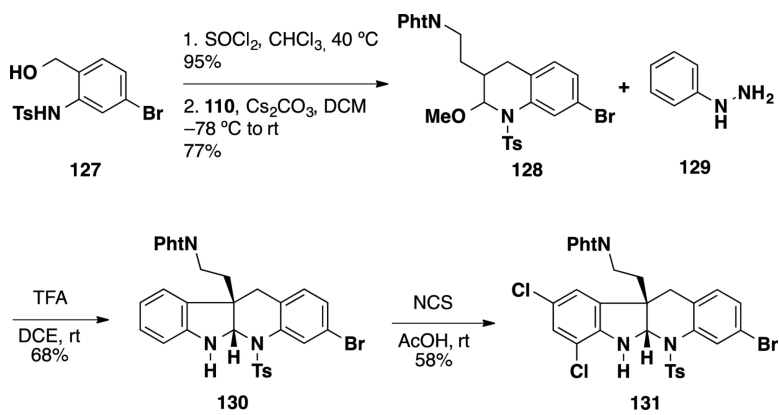
Scheme 17.
The Interrupted Fischer Indolization Reaction to Form the Southern Perophoramidine Ring System



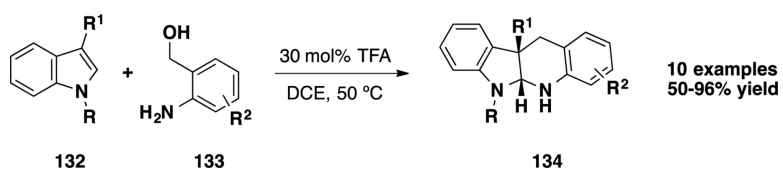
Scheme 18.
The Interrupted Fischer Indolization Reaction to Form the Southern Communesin Ring System



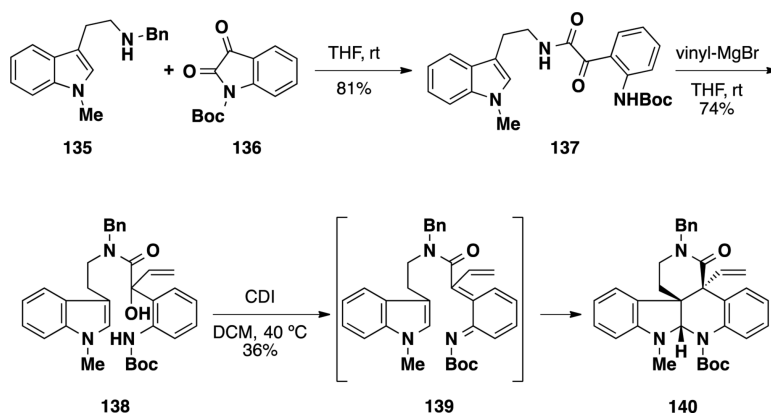
Scheme 19.
Attempts to Access Tetracycle **126**



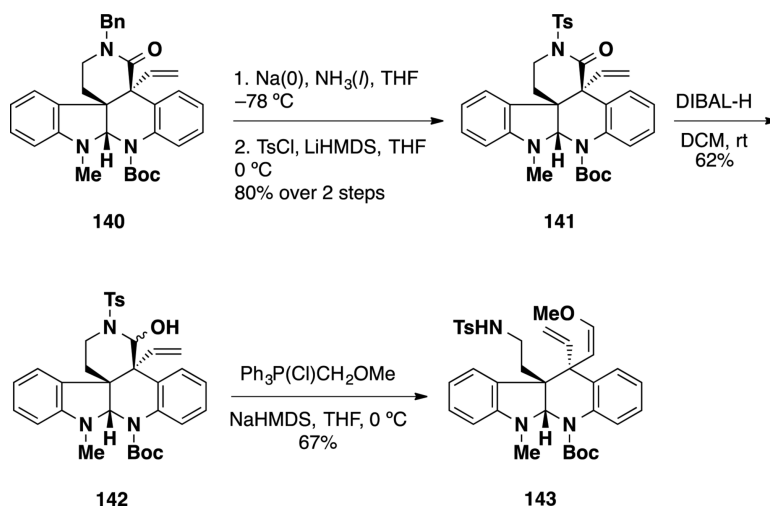
Scheme 20.
Synthesis of Dichloride **131**

**Scheme 21.**

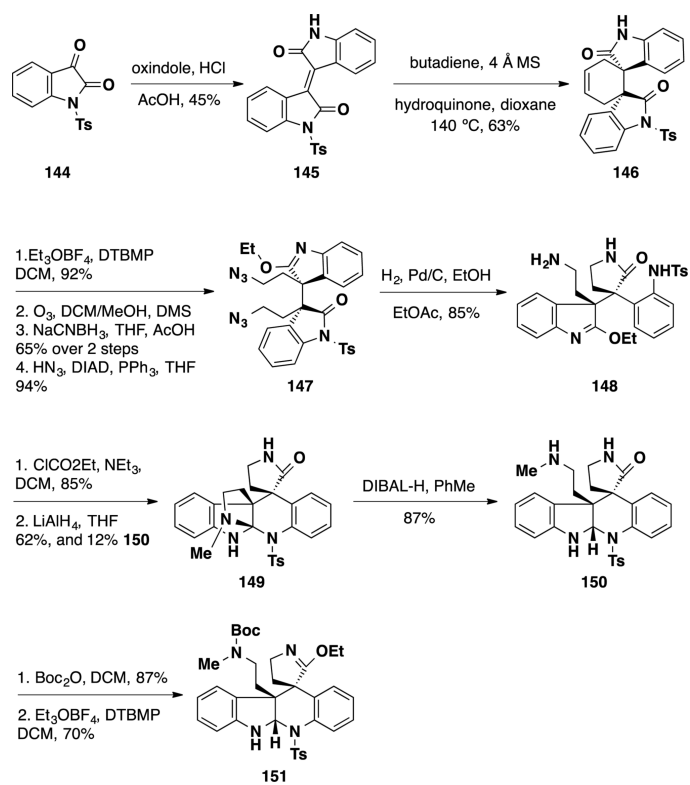
Wu's Amino Alcohol-Based Approach to the Southern Ring System of the Communesin Alkaloids



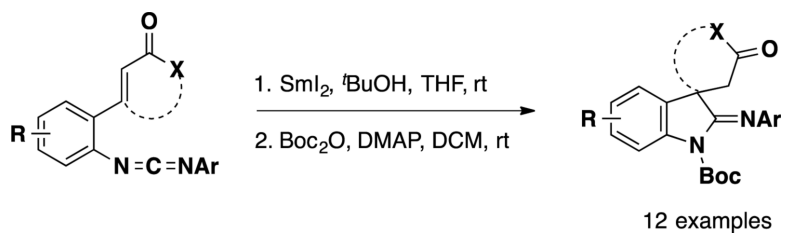
Scheme 22.
Aldington's Strategy Towards the Communesin Alkaloids



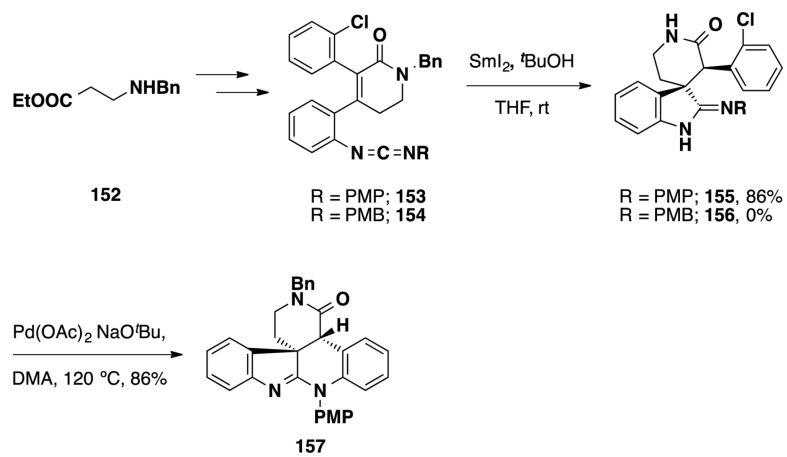
Scheme 23.
Adlington's Elaboration of Pentacycle **143**



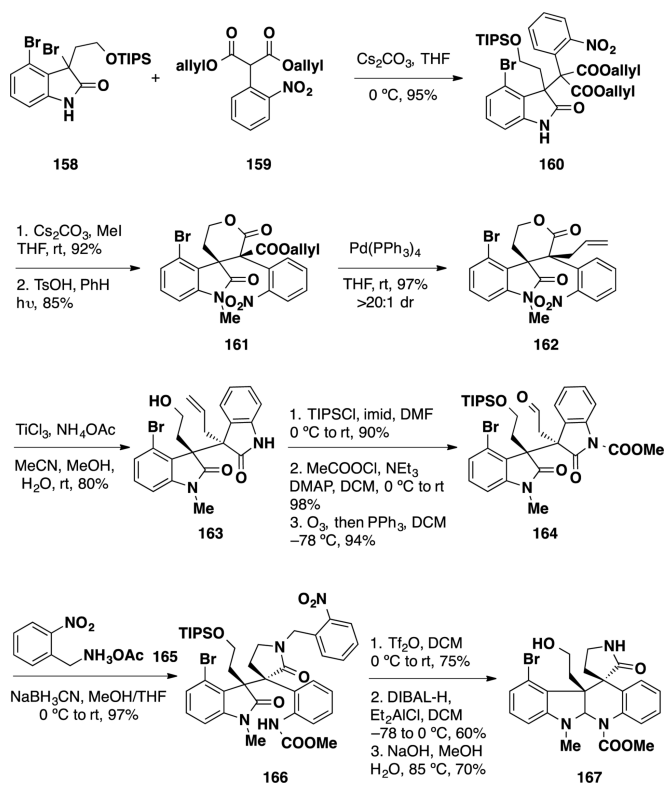
Scheme 24.
Somafai's Synthesis of Pentacycle **151**



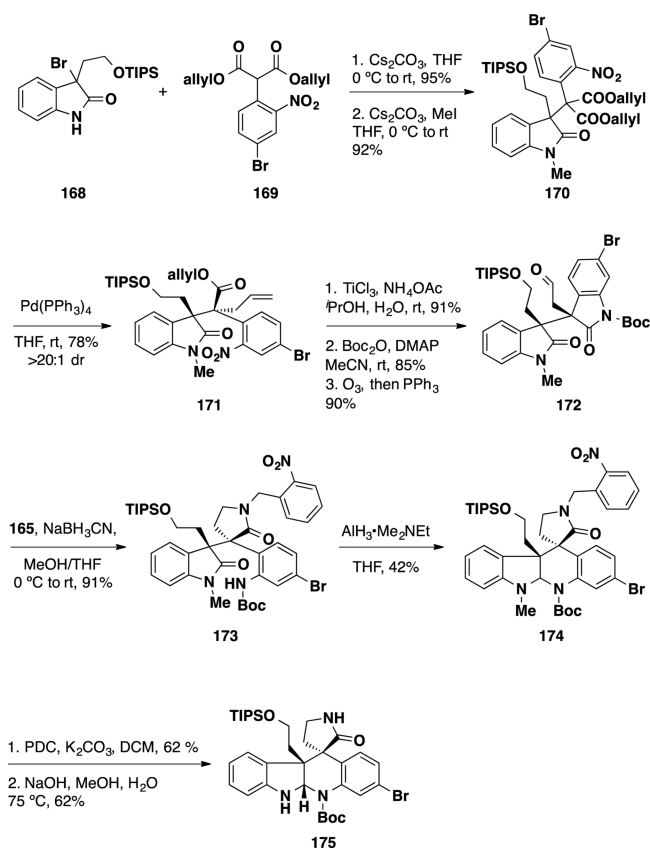
Scheme 25.
SmI₂ Reductive Cyclization of Carbodiimides



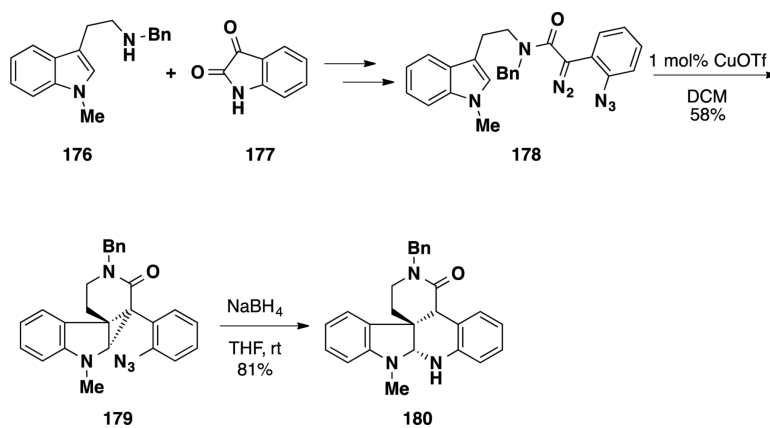
Scheme 26.
Synthesis and Reductive Cyclization



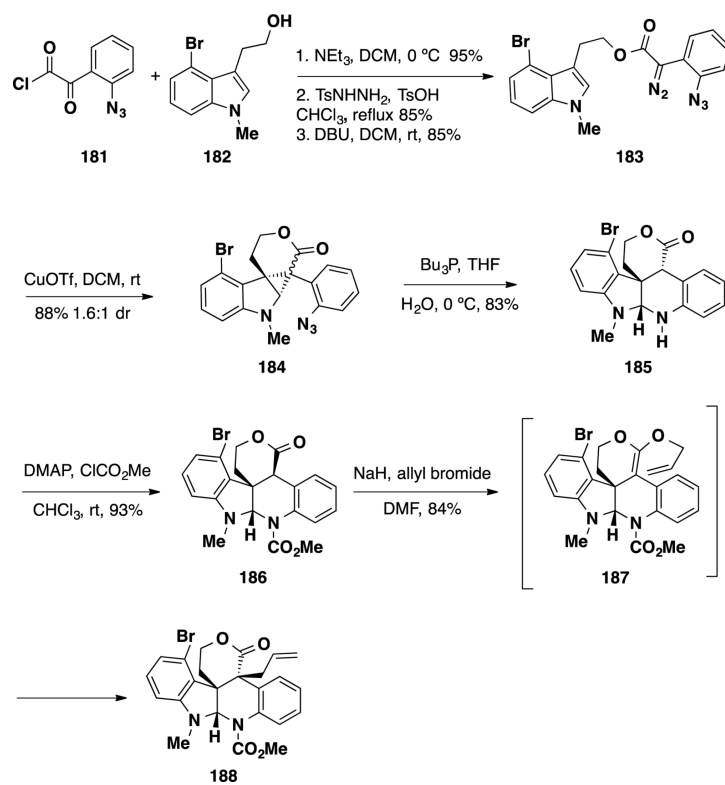
Scheme 27.
Stoltz's Formal Synthesis of (\pm)-communesin F (7)



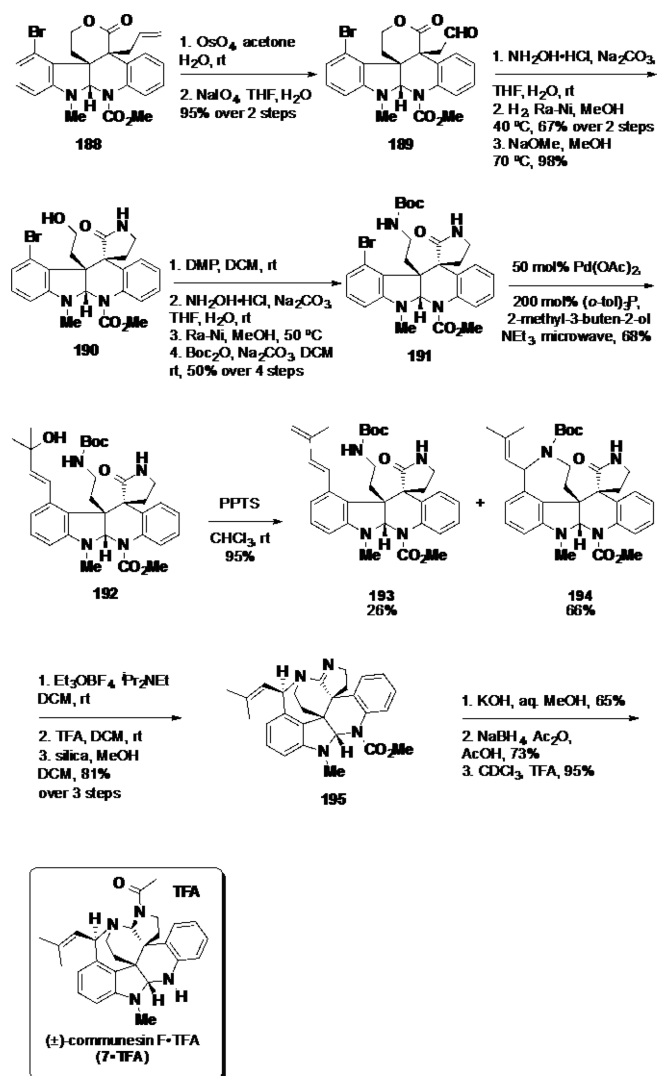
Scheme 28.
Stoltz's Formal Synthesis of (±)-perophoramidine



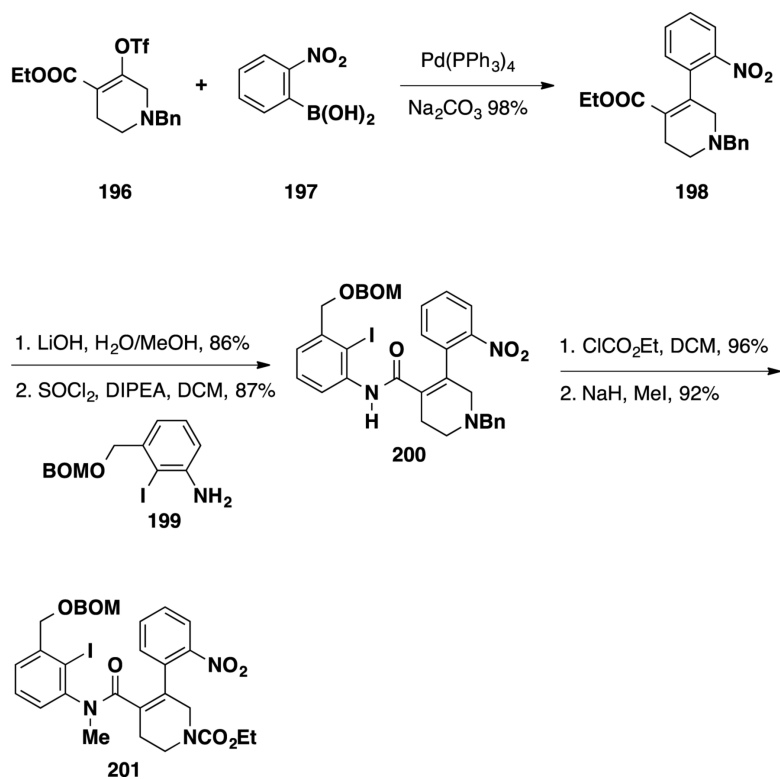
Scheme 29.
Qin's Early Early Cyclopropanation Studies Towards the Synthesis of Communesin Alkaloids



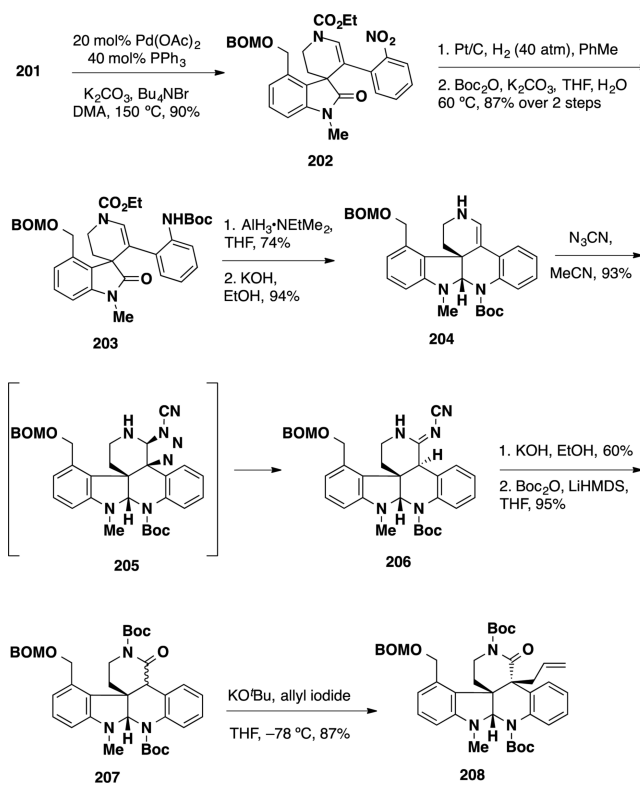
Scheme 30.
Qin's Synthesis of Pentacycle **188**



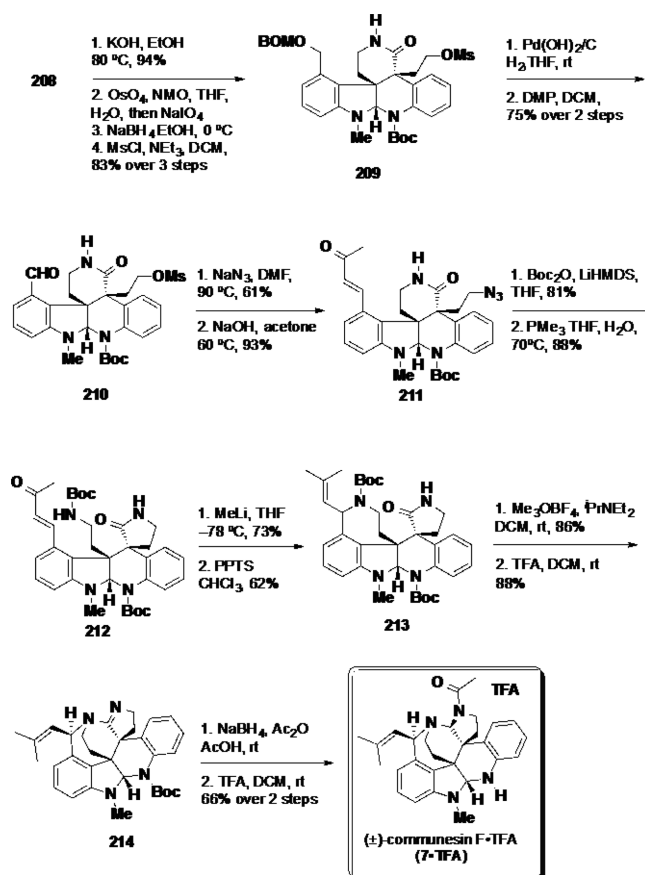
Scheme 31.
Completion of (±)-Communesin F•TFA (7•TFA)



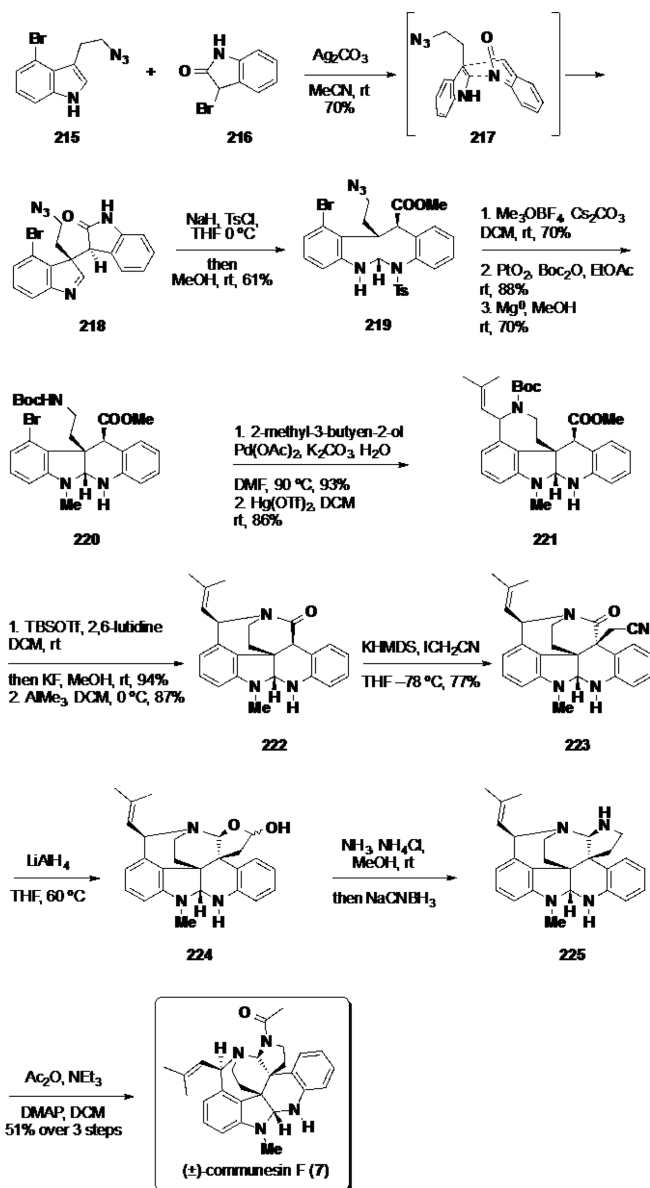
Scheme 32.
Weinreb's Synthesis of Heck Precursor **201**



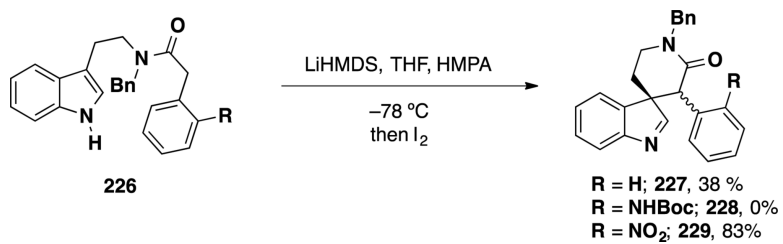
Scheme 33.
Elaboration to Pentacycle **208**



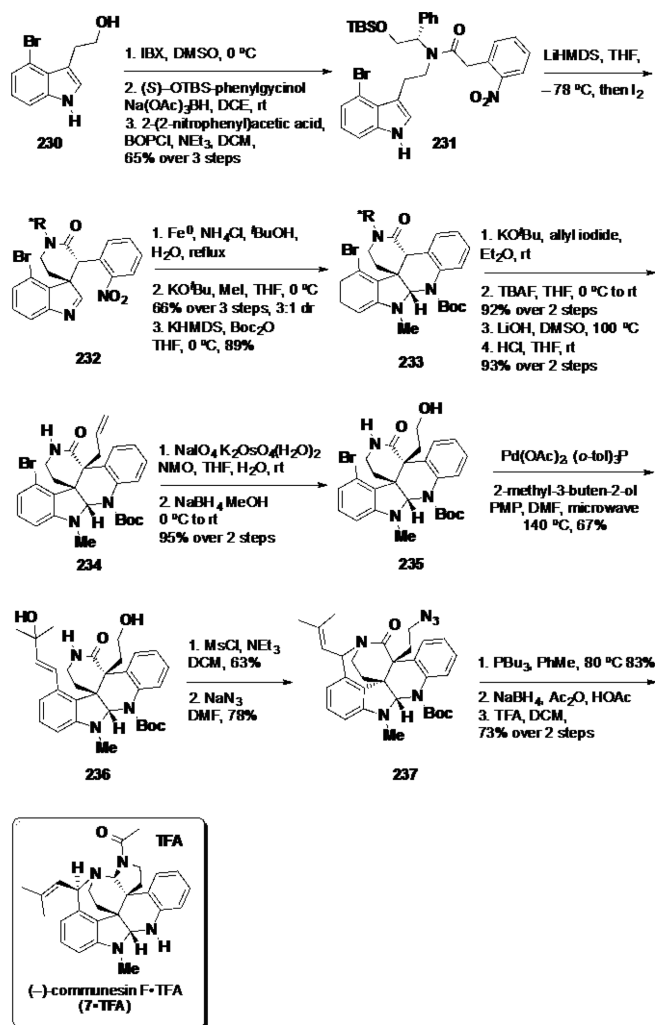
Scheme 34.
Completion of (±)-Communesin F•TFA (7•TFA)



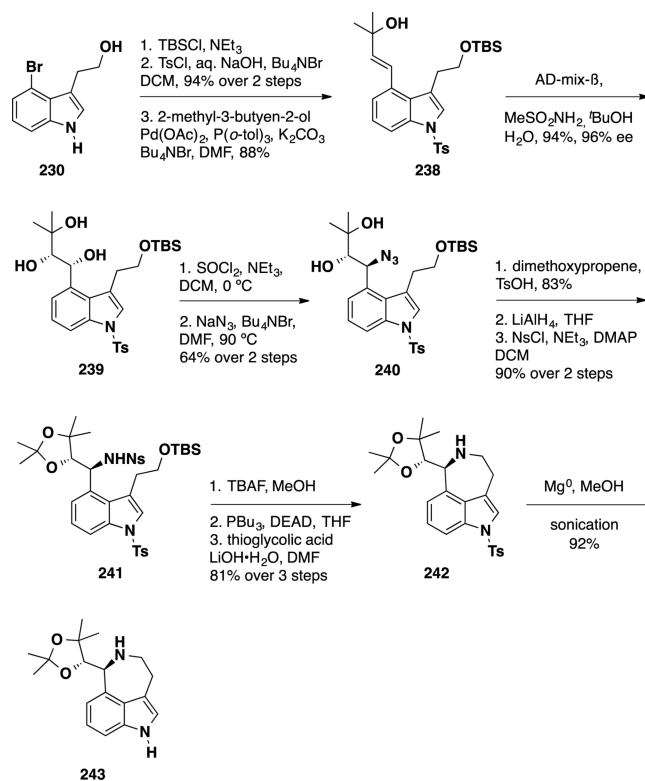
Scheme 35.
Funk's Synthesis of (±)-Communesin F (7)

**Scheme 36.**

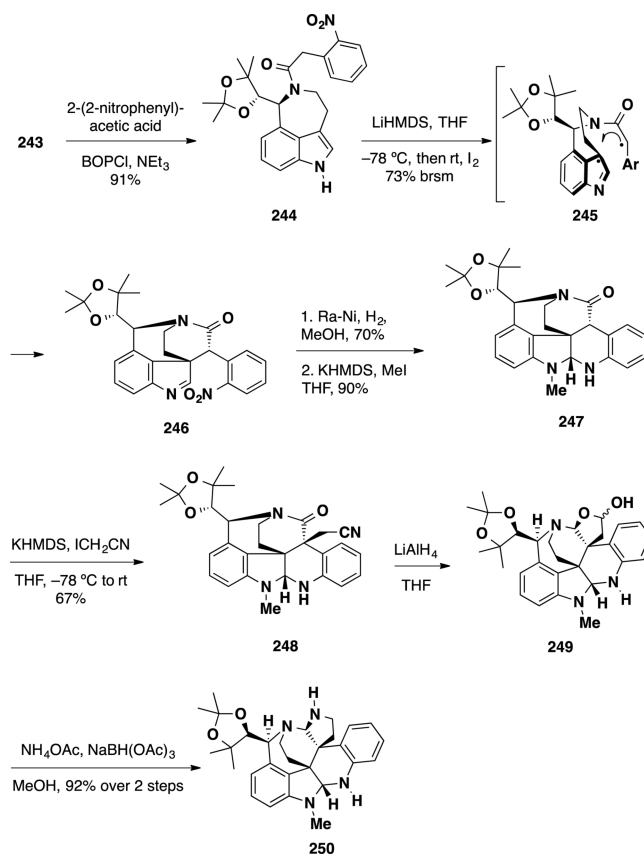
Ma's Early Studies on the Oxidative Cyclization for the Synthesis of Communesin Alkaloids



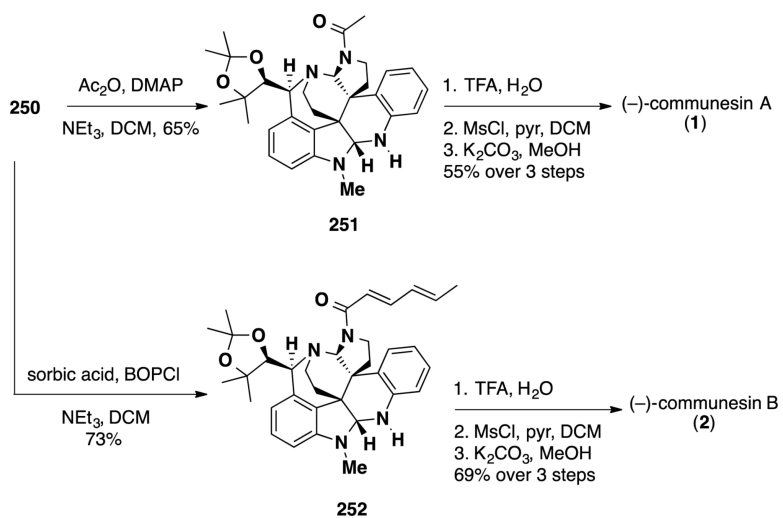
Scheme 37.
Ma's Synthesis of (-)-Communesin F (7)



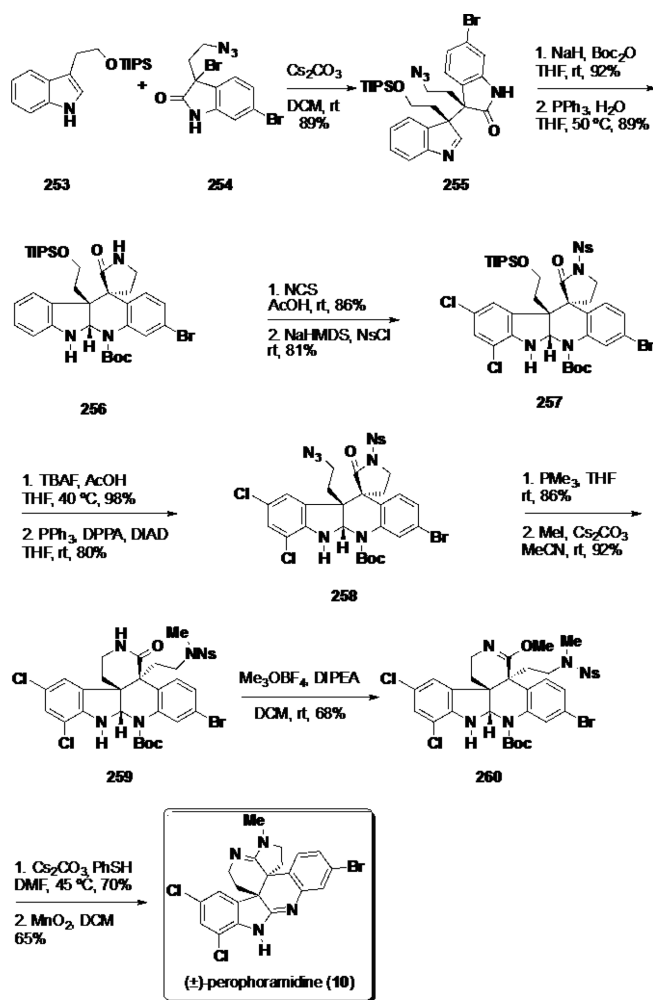
Scheme 38.
Ma's Asymmetric Synthesis of Aurantioclavine Ketal **243**



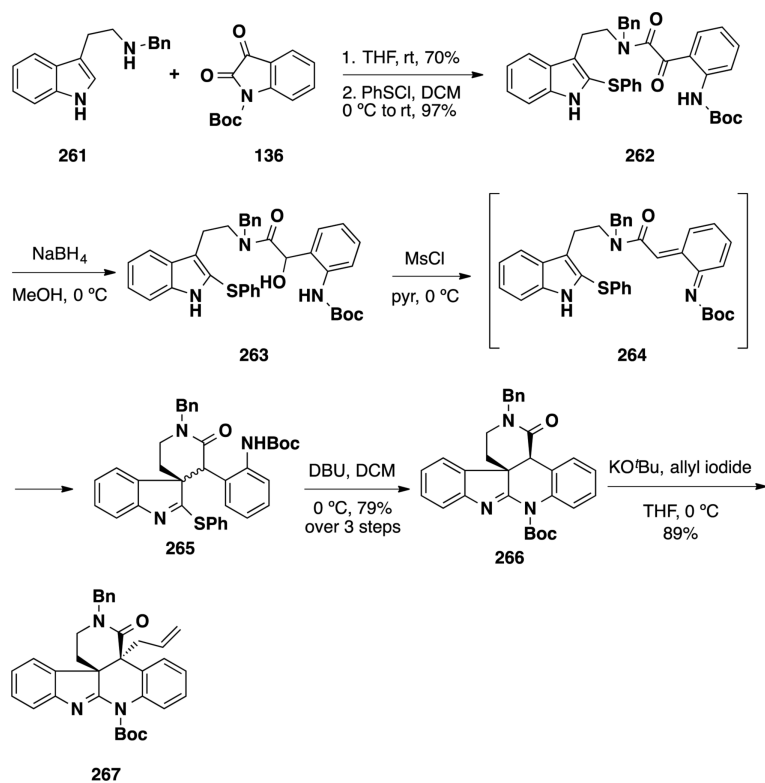
Scheme 39.
Formation of Heptacycle **250**



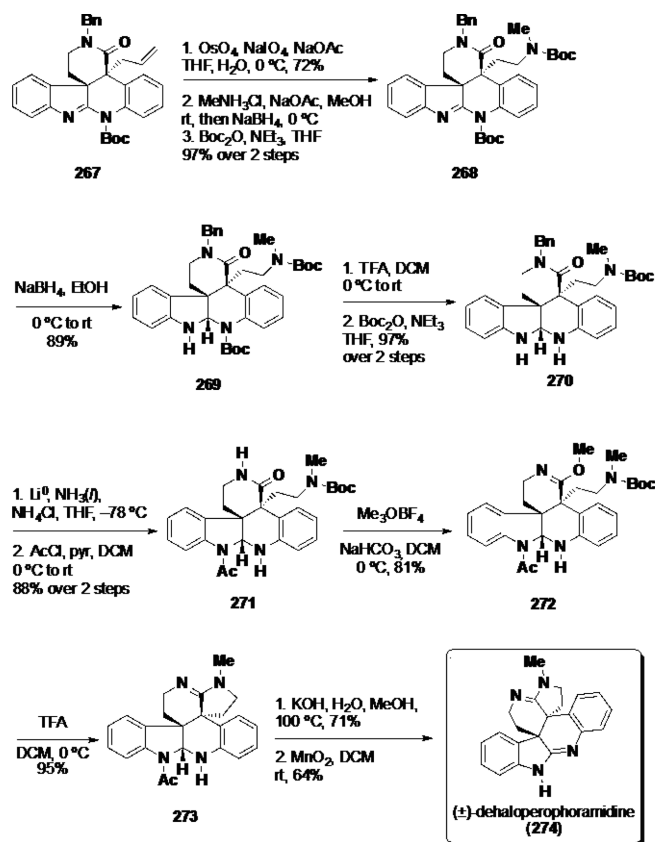
Scheme 40.
Completion of Communesins A (1) and B (2)



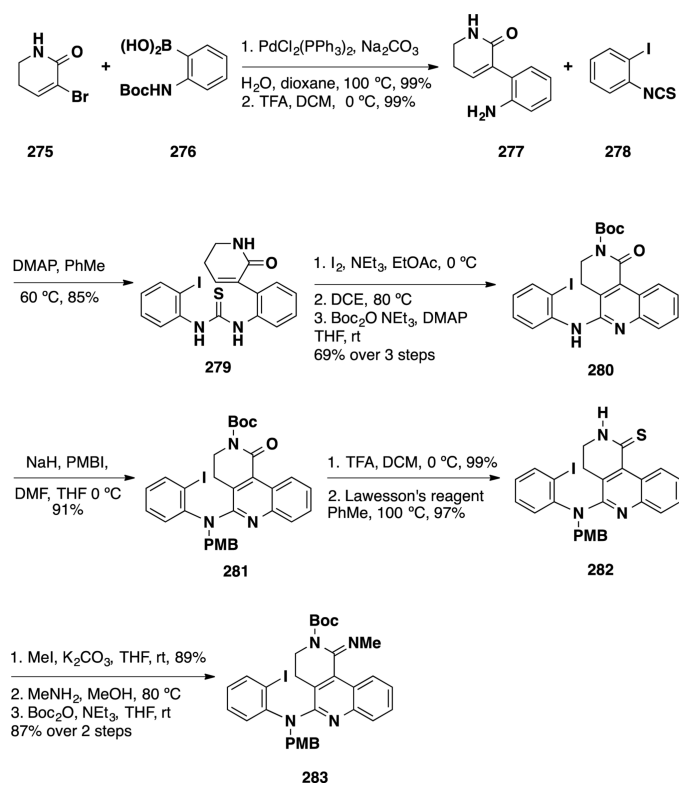
Scheme 41.
Funk's Synthesis of (±)-Perophoramidine (10)



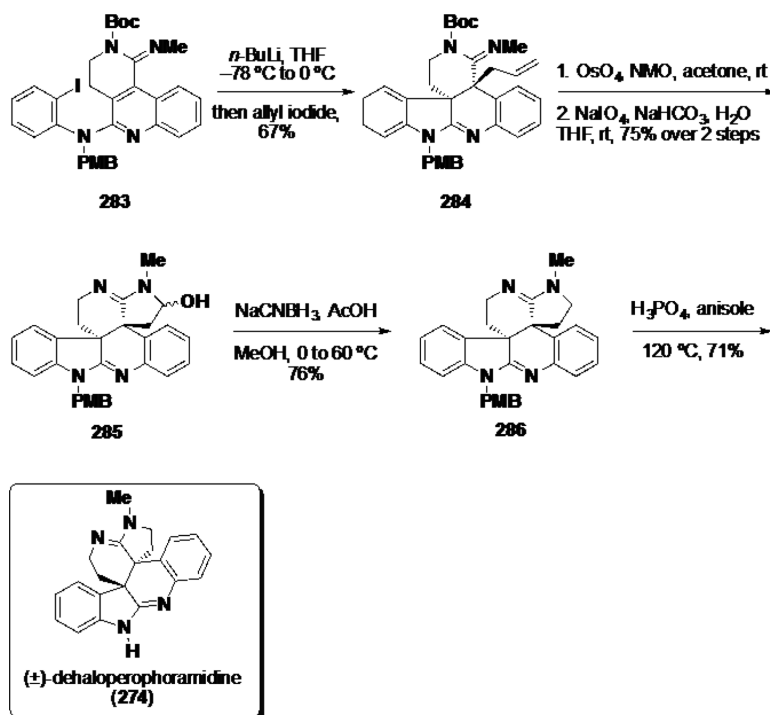
Scheme 42.
Rainier's Synthesis of Pentacycle **267**



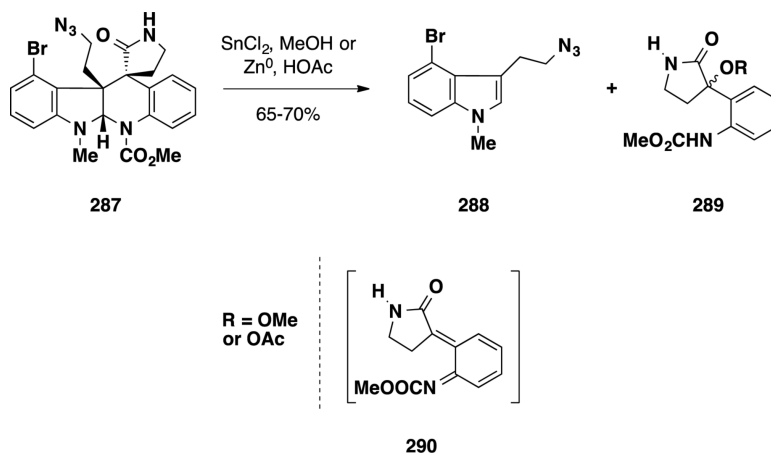
Scheme 43.
 Completion of (±)-Dehaloperphoramidine (274)



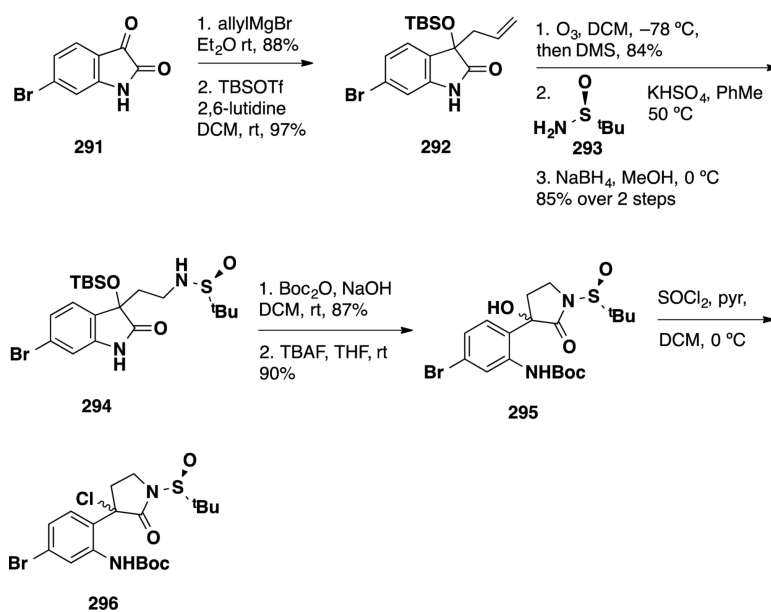
Scheme 44.
 Synthesis of Dearomatizing Cyclization-Allylation Precursor **283**



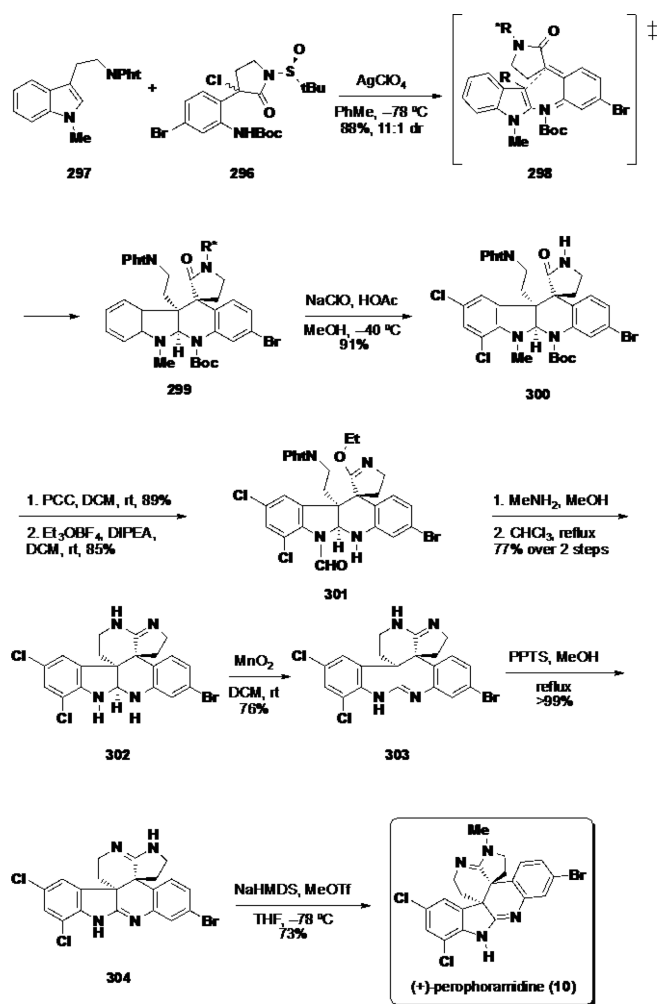
Scheme 45.
Completion of (±)-Dehaloperophoramidine (274)



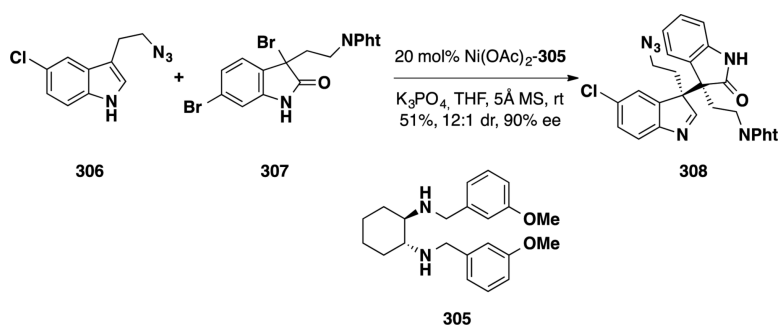
Scheme 46.
Qin's Observed Retro-[4+2] Process



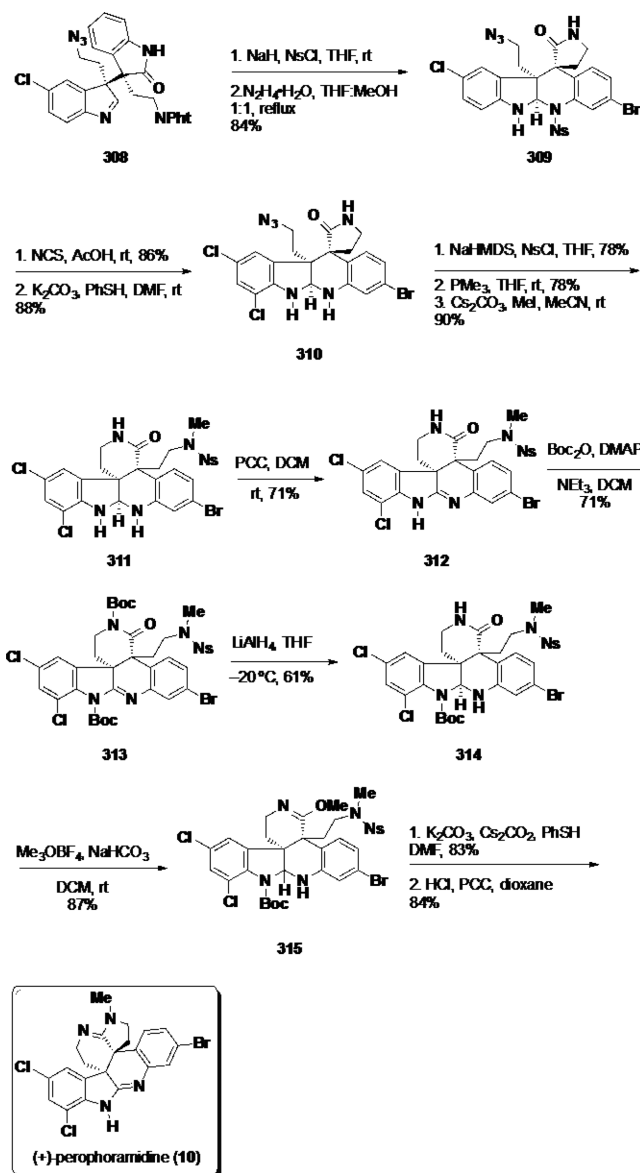
Scheme 47.
 Qin's Synthesis of [4+2] Precursor **296**



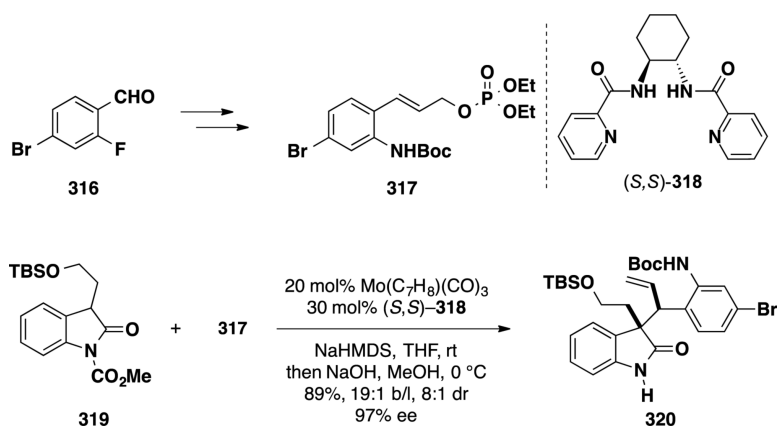
Scheme 48.
Completion of (+)-Perophoramidine (10)



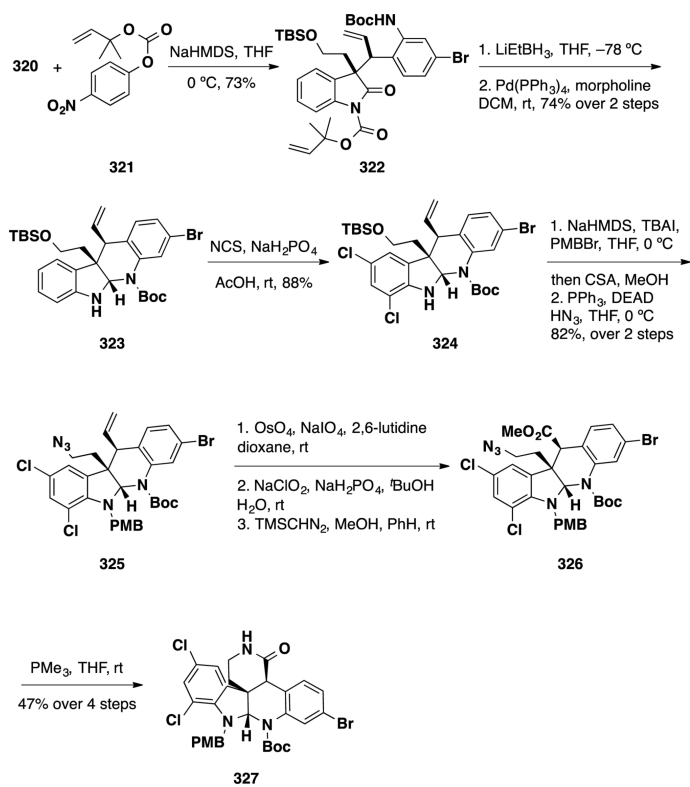
Scheme 49.
Wang's Ni-Catalyzed Addition of Indoles to Bromo-Oxindoles



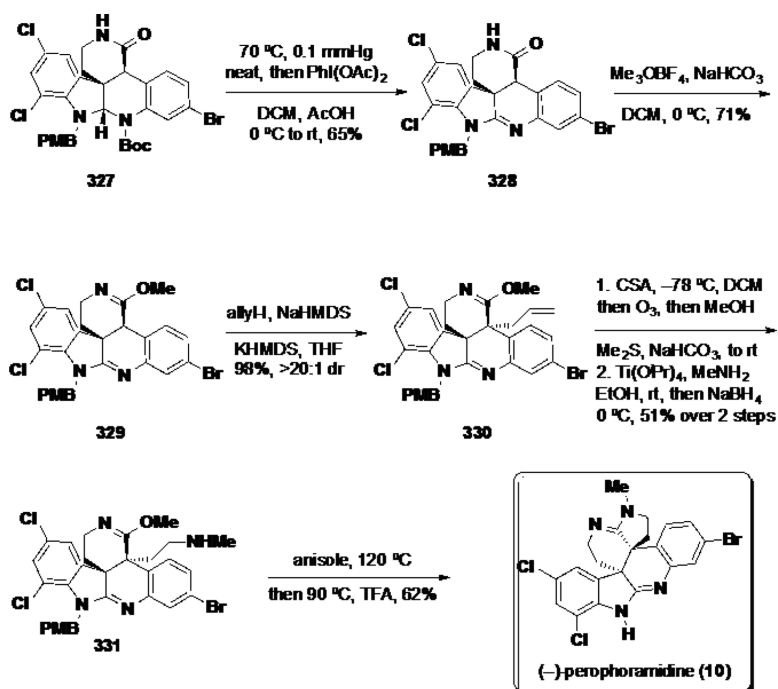
Scheme 50.
Completion of (+)-Perophoramidine (10)



Scheme 51.
Mo-AAA Reaction of Oxindole **319** and allylic Phosphate **317**.



Scheme 52.
 Synthesis of Pentacyclic Lactam **327**.



Scheme 53.
Completion of (-)-perophoramidine (10).