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DOI: 10.1002/anie.200700612

Natural Product Synthesis

Total Synthesis of Complex Cyclotryptamine Alkaloids: Stereocontrolled Construction of Quaternary Carbon Stereocenters

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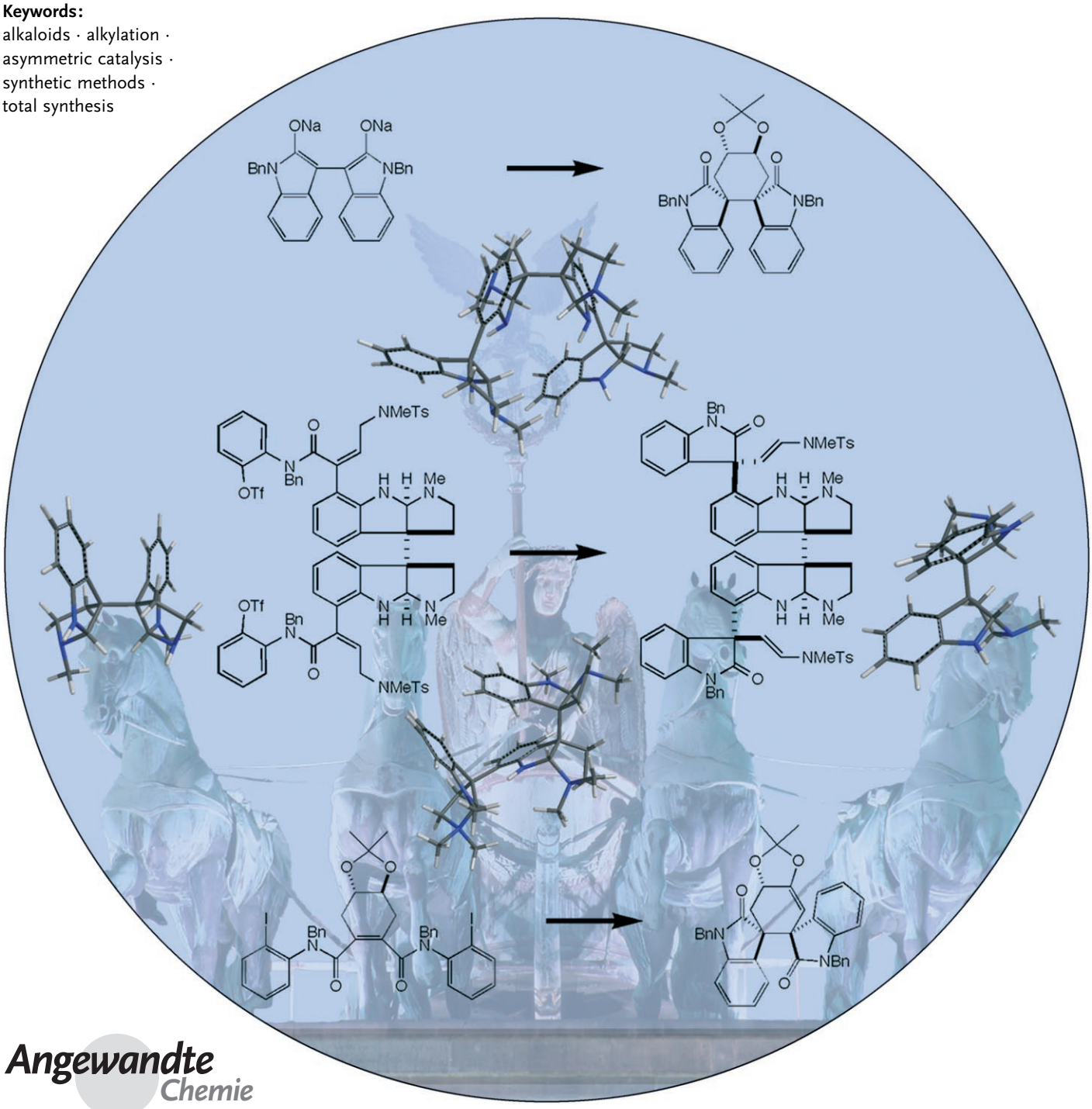
Keywords:
alkaloids · alkylation · asymmetric catalysis · synthetic methods · total synthesis



Our ability to access the more complex members of the cyclotryptamine family of alkaloids, and to exploit their disparate biological activities, is limited by the synthetic challenge posed by their oligomeric, polyindoline structures. A recurring structural theme within these molecules is the presence of multiple quaternary stereocenters in close proximity to one another. Over the last decade, we have developed a set of transformations that allow rapid access to polyindolines, a number of which exploit the ability of catalytic levels of palladium to orchestrate carbon–carbon bond formation with impressive levels of regio- and stereocontrol. This review tells the story behind the development of this toolbox of synthetic methods, and their validation through the total synthesis of a number of structurally complex cyclotryptamine alkaloids. It also highlights an aspect of asymmetric catalysis that has received little attention, the ability of catalytic asymmetric reactions to selectively elaborate complex, polyfunctional molecules.

From the Contents

1. Introduction

There is no better way to appreciate the limitations of the available tools of organic synthesis than to contemplate how one would prepare, in a practical fashion, natural products having novel structures. A little over ten years ago, we had this experience when first considering how we might synthesize the more complex members of the cyclotryptamine alkaloids (Figure 1).[1] In one respect, the problem is simple: these natural products are composed of only a single structural unit, a 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**1**, Figure 2). However, when such fragments are joined to generate dimers, trimers, and higher-order oligomers, the three-dimensional relationship of these tricyclic units and their union at benzylic quaternary carbon stereocenters presents a formidable challenge for stereocontrolled total synthesis.

In this review, we will introduce this fascinating family of natural products and briefly discuss early efforts to prepare the simpler members of this group. We will then summarize the methods we have developed in recent years for dealing with the fundamental challenge in preparing complex cyclotryptamine alkaloids, namely the stereocontrolled construction of quaternary carbon stereocenters.[2] Finally we will discuss the use of these methods to prepare representative members of cyclotryptamine alkaloids exemplified in Figure 1.

The cyclic pyrrolidino[2,3-*b*]indoline form **1**, which predominates over the ring-opened 3-aminoethylindolenine tautomer **2** when the 3a substituent is not hydrogen (Figure 2), is the fundamental building block of cyclotryptamine alkaloids. This ring system is found exclusively in the *cis* configuration in natural products, presumably because of the higher level of ring strain in the *trans* stereoisomer. In the more complex cyclotryptamine alkaloids, individual *cis*-pyrrolidino[2,3-*b*]indoline units are either linked at their benzylic carbon atoms, or by the union of the benzylic carbon atom of one fragment with the aromatic C7 *peri* carbon atom of another. The former linkage of two units affords a 3a,3a′-bispyrrolidino[2,3-*b*]indoline (**3**), which can possess either *meso* or C_2-symmetry (Figure 2).

In addition to the *cis*-pyrrolidino[2,3-*b*]indoline unit linking pattern, the quaternary carbon center stereogenicity and aminal connectivity are other potential sources of structural diversity in these tryptamine-derived natural products. Five constitutional isomers differing in their aminal connectivity can be formed from the hypothetical precursor, tetraaminodialdehyde **4** (Figure 3). Natural products are presently known that contain four of these skeletons; however, this review will concentrate on the most common 3a,3a′-bispyrrolidino[2,3-*b*]indoline scaffold.

Alkaloids containing more than one *cis*-pyrrolidino[2,3-*b*]indoline fragment have been isolated from a variety of sources (Figure 4).[1] Higher plants, particularly those of the Rubiaceae, Celastraceae and Calycanthaceae families,[3] have

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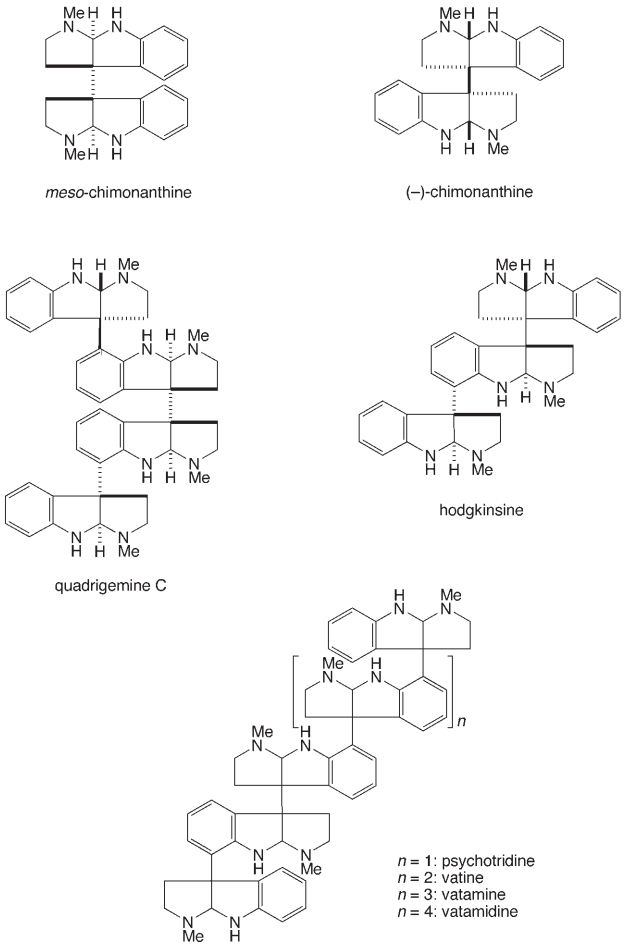

Figure 1. Representative dimeric and higher-order cyclotryptamine alkaloids.

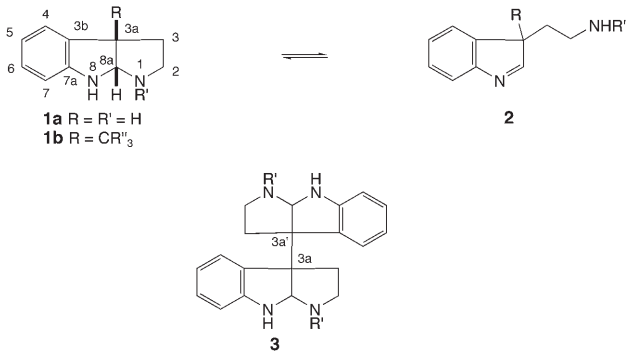

Figure 2. Pyrrolidino[2,3-*b*]indoline (**1**) and 3a,3a′-bispyrrolidino[2,3-*b*]indoline (**3**) skeletons.

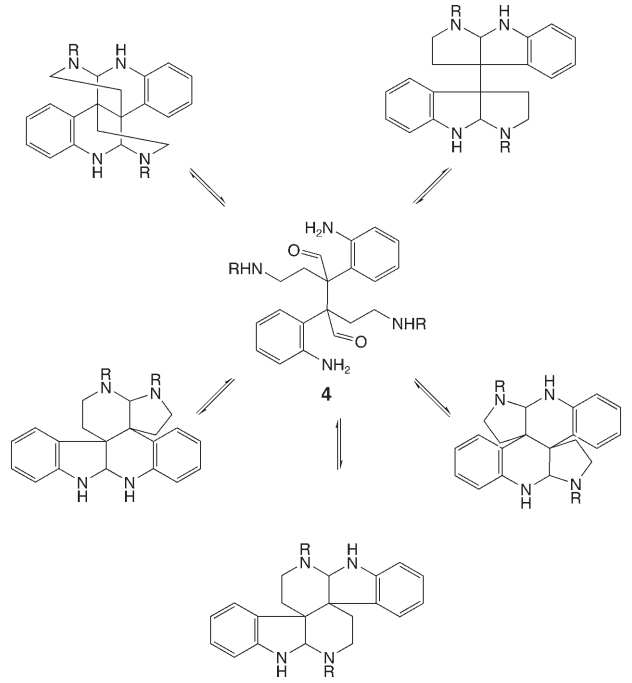

Figure 3. Isomeric bisaminals formed by the dehydration of the hypothetical precursor **4**.

yielded the greatest variety of such compounds. A number of alkaloids from fungi of the *Aspergillus*, *Chaetomium*, *Corollospora*, *Gliocladium*, *Leptosphaeria*, and *Verticillium* genera also contain 3a,3a′-bispyrrolidino[2,3-*b*]indolines.

Eccles's isolation of an isomeric compound, (+)-calycanthine (**7**; Scheme 1), from *Calycanthus glaucus* in 1888 ushered in the rich chemical history of dimeric and higher-order cyclotryptamine alkaloids.[4] The elucidation of the chemical structure of (+)-calycanthine (**7**) was a long-standing problem in alkaloid chemistry, which was not solved until the 1960s.[5] The inability to oxidize calycanthine to an

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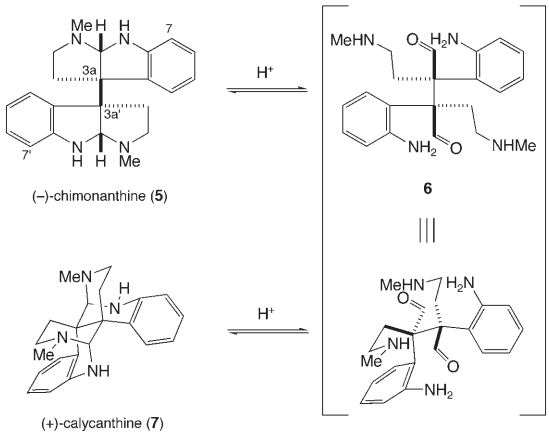
Larry Overman was born in Chicago, Illinois and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After a NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971. His research interests center on the invention of new transformations and strategies in organic synthesis and the total synthesis of natural products.

Figure 4. Some sources of alkaloids containing oligomeric *cis*-pyrrolidino[2,3-*b*]indolines. Clockwise from top right: *Psychotria oleoides* (courtesy of Jean-Marie Veillon, Center IRD, New Caledonia), *Calycanthus floridus* (courtesy of Bernard Loison, http://www.mytho-fleurs.com/), *Hodgkinsonia frutescens* (courtesy of Christian Puff, University of Vienna), *Phyllobates terribilis* (courtesy of Thomas Villegas, http://www.pumilio.com), *Chimonanthus fragrans* (courtesy of Abbas Hoseinnejad).



Scheme 1. Acid-mediated conversion of (−)-chimonanthine (**5**) to (+)-calycanthine (**7**).

amidine was a key observation allowing Woodward, in 1960, to deduce the constitution of this alkaloid from the structural possibilities shown in Figure 3, as such an oxidation would introduce a highly strained double bond in calycanthine.[6] This classical deduction of chemical structure was soon confirmed by an X-ray structure analysis of the dihydrobromide derivative.[7] The absolute configuration of (+)-calycanthine (**7**) followed shortly thereafter from circular dichroism measurements.[8]

The calycanthine skeleton constitutes the thermodynamically most stable didehydro form of tetraaminodialdehyde **6** (Scheme 1). As a consequence of this stability, under acidic conditions, (+)-calycanthine is readily formed from the isomeric 3a,3a′-connected bispyrrolidino[2,3-*b*]indoline, (−)-chimonanthine (**5**).[9–11] The facility with which this rearrangement takes place leaves unclear whether calycanthine is a genuine natural product or an isolation artifact.

The structure of (−)-chimonanthine was settled in 1962 by single-crystal X-ray analysis of its dihydrobromide salt.[12] Prior to this early application of X-ray crystallography for structure elucidation, spectroscopic and chemical analysis had narrowed the possible structures to the 3a,3a′-connected bispyrrolidino[2,3-*b*]indoline **5**, and the isomer depicted at the bottom of Figure 3 that also contains two indoline fragments.[13] The chimonanthines occur naturally with all three possible stereochemical motifs: a pair of C_2-symmetric enantiomers and a *meso* diastereomer. These chimonanthine stereoisomers are found in a number of plants of the *Calycanthus*, *Chimonanthus*, *Palicourea*, and *Psychotria* genera.[10,13–17] (+)-Chimonanthine has been isolated also from the skin of the Colombian poison dart frog, *Phyllobates terribilis*.[18] Calycanthidine (**8**)[19] and folicanthine (**9**)[20] are related bispyrrolidino[2,3-*b*]indolines resulting from successive methylation of the indoline nitrogen atoms (N_a) of chimonanthine (Figure 5).[21]

Figure 5. 3a,3a′-Bispyrrolidino[2,3-*b*]indolines displaying N_a-methylation.

The 3a,3a′-bispyrrolidino[2,3-*b*]indoline structure is embedded as a core unit in larger members of the cyclotryptamine alkaloid family. These alkaloids arise from the attachment of additional *cis*-pyrrolidino[2,3-*b*]indoline subunits at *peri* benzenoid positions, generating diaryl-substituted quaternary carbon stereocenters (Figure 6). Hodgkinsine (**10**), an antinociceptive[22] first isolated from a Queensland shrub (*Hodgkinsonia frutescens*),[23] was the first nonacyclic alkaloid of this group to be fully characterized.[24,25] It is also widely found within members of the *Psychotria* genera.[15,17,26–28] A diastereomeric natural product, hodgkinsine B (**11**),[29] whose exact structure was only recently elucidated (see Section 6),[30] has contiguous quaternary stereocenters of opposite absolute configuration (Figure 6). Hodgkinsine and hodgkinsine B are derived from the appendage of a *cis*-pyrrolidino[2,3-*b*]indoline subunit of *R* configuration at C3a to the enantiotopic *peri* positions 7 or 7′ of *meso*-chimonanthine.[31]

In general, the higher-order cyclotryptamine alkaloids have their pyrrolidine nitrogen atoms (N_b) methylated, whereas their indoline nitrogen atoms (N_a) are unsubstituted. An exception to this generalization is idiospermuline (**12**), a cholinergic antagonist isolated from the tree *Idiospermum australiense*, also found in Queensland, Australia (Figure 6).[16] Two of its three N_a atoms bear methyl groups.

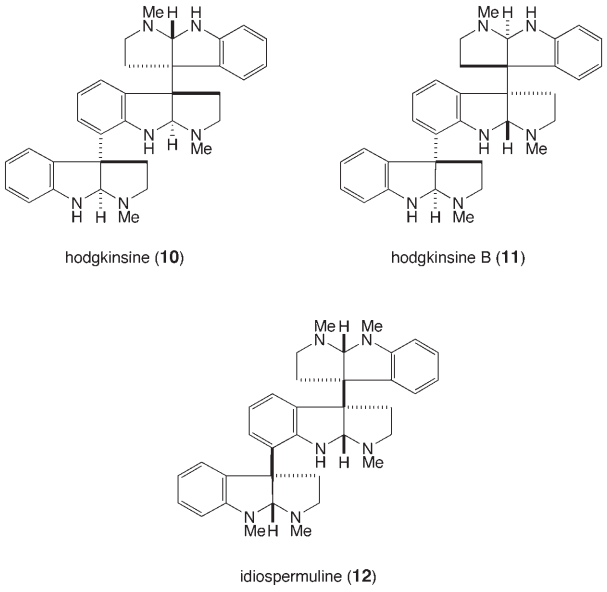


Figure 6. Structurally characterized polyindoline alkaloids having three *cis*-pyrrolidino[2,3-*b*]indoline units.

The quadrigemines consist of a group of at least eight compounds, quadrigemine A–H, that contain four pyrrolidino[2,3-*b*]indoline fragments. There are two families of constitutional isomers, termed [2+2] and [3+1], which designate the ratio of the diagnostic fragments produced during mass spectrometric analysis by fragmentation of the weak σ bond joining the quaternary centers of their chimonanthine subunits.[32] Quadrigemines A, C, and E are members of the [2+2] family, whereas quadrigemines B, F, G, and H contain the [3+1] skeleton (Figure 7).

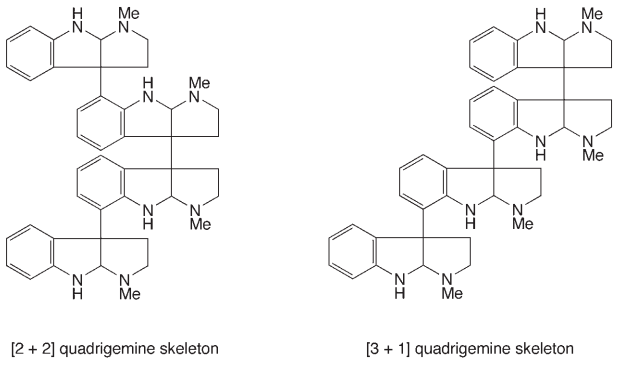


Figure 7. Two families of quadrigemine constitutional isomers.

Only quadrigemine C (**13**), quadrigemine H (**14**), and quadrigemine D (psycholeine) (**15**) have their relative and absolute configurations fully assigned (Figure 8). Quadrigemine C and psycholeine were co-isolated from *Psychotria oleoides*,[26,28,33,34] and were the first non-peptidic inhibitors of somatostatin to be reported.[35] Quadrigemine C also displays antibacterial[36] and analgesic[17] properties. The other quadrigemines have been isolated from *Psychotria forsteriana*,[37–39] *Calycodendron milnei*,[40] and *Hodgkinsonia frutescens*.[41]

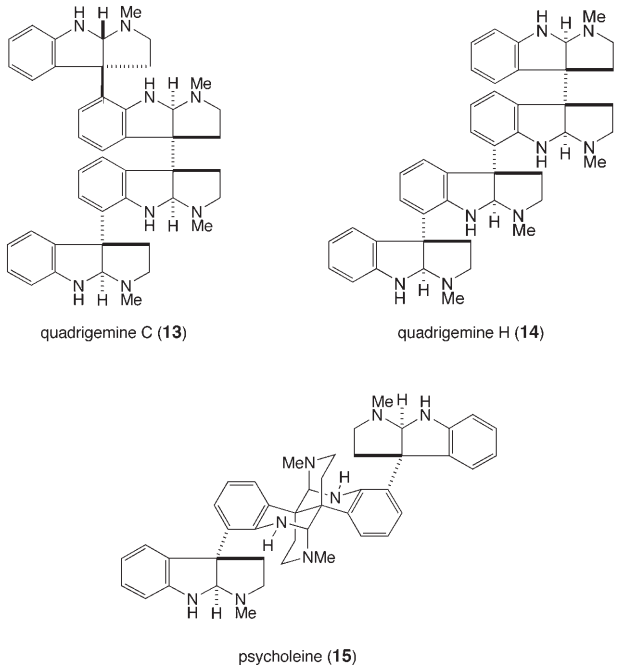


Figure 8. Quadrigemine isomers whose relative and absolute configurations are established.

Psycholeine is a third type of constitutional isomer in which the central six rings are a calycanthine, rather than a chimonanthine, fragment. That psycholeine results from the treatment of quadrigemine C with acid raises the possibility that it might be an isolation artifact.

The alkaloids derived from the appendage of additional pyrrolidino[2,3-*b*]indolines onto the periphery of a quadrigemine tetramer are all of unknown relative and absolute configuration. Examples are the pentamers psychotridine (**16**) and the isopsychotridines A–C, which have been isolated from various *Psychotria* species[28,37–39,42] (Figure 9). As with the quadrigemines, the characteristic mass spectrometric fragmentation of the σ bond connecting the quaternary

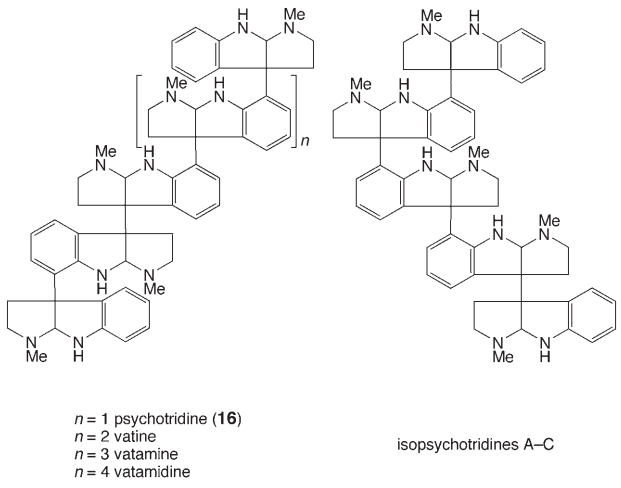
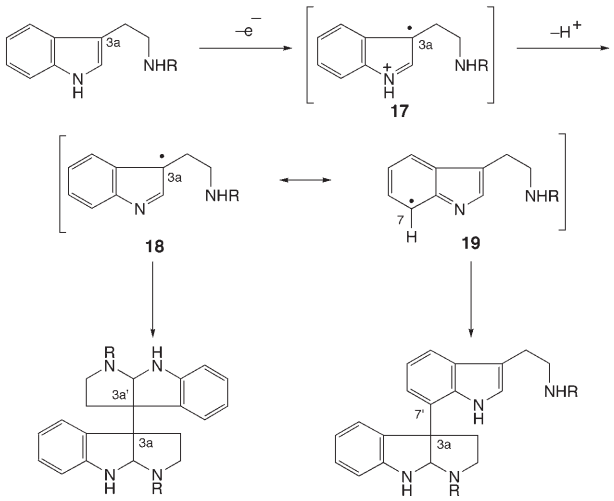


Figure 9. Higher-order cyclotryptamine alkaloids containing five-eight pyrrolidino[2,3-*b*]indoline units.

carbon centers of their chimonanthine subunits provides insight as to their connectivity. Psychotridine and isopsychotridine C are potent inhibitors of human platelet aggregation.[38] *Calycodendron milnei* has yielded even larger alkaloids, in the forms of vatine, vatamine, and vatamidine.[43] The cytotoxicity of *Psychotria forsteriana* extracts against cultured rat hepatoma cell lines has been attributed to their tetrameric and pentameric polypyrrolidino[2,3-*b*]indoline alkaloid content.[39,44,45]

2. Biosynthesis of Cyclotryptamine Alkaloids

It has long been postulated that the biosynthesis of 3a,3a′-bispyrrolidino[2,3-*b*]indolines involves the oxidative β,β′-dimerization of two tryptamine units.[46] That tryptophan and tryptamine are progenitor materials has been established by labeling studies. Radioactive calycanthine and folicanthine are procured from *Calycanthus floridus* fed with (±)-[β-^{14}C]-tryptophan,[47,48] and (±)-[β-^{14}C,2-^{3}H]-tryptophan and [β-^{14}C,2-^{3}H]-tryptamine are both converted into chimonanthine in leaf-bearing shoots of *Chimonanthus fragrans*.[49] A one-electron oxidation of a tryptamine gives rise to a possible mechanism by which linked cyclotryptamine units could arise biosynthetically.[50] For example, radical cation **17** could lose a proton to form radical **18**/**19** (Scheme 2). The coupling of this



Scheme 2. The postulated biosynthetic route towards oligomeric pyrrolidino[2,3-*b*]indolines.

intermediate at either C3a or C7 with the C3a position of a second tryptamine fragment would link tryptamine fragments in the fashion commonly seen in cyclotryptamine alkaloids.

3. Challenges for Stereocontrolled Total Synthesis

In spite of their fascinating structures and varied biological activities, only a few research groups have been successful in preparing alkaloids containing multiple *cis*-pyrrolidino[2,3-*b*]indoline rings. This situation reflects the formidable challenges presented by both the architectures and the properties of these compounds.

The presence of multiple low-energy conformations about the vicinal quaternary carbon and aryl-quaternary carbon σ bonds of these alkaloids complicates the structural elucidation of these natural products as well as intermediates in a synthetic investigation. At room temperature, the ^{1}H NMR spectra of these alkaloids are broad and typically uninterpretable. In some cases, the multiple conformational isomers that are present can be coalesced at high temperature; however, because of the lability of the C3a-C3a′ σ bond, decomposition can take place prior to coalescence. This conformational heterogeneity also makes obtaining crystalline samples for X-ray analysis difficult. Although methiodide derivatives are generally accessible from alkylation of the pyrrolidine nitrogens with methyl iodide, only the trimethiodide derivatives of hodgkinsine and idiospermuline (Figure 6) and the tetramethiodide salt of quadrigemine H have been crystallized. Furthermore, attempts to determine relative and absolute configurations by circular dichroism techniques are typically unsuccessful because of conformational heterogeneity. It is little wonder that full configurational assignments of the more complex polypyrrolidino[2,3-*b*]indoline alkaloids are still to be forthcoming.

The extreme steric congestion about the C3a-C3a′ σ bond and the attendant lability of this linkage also present challenges for those working in this area. The weakness of this bond can be seen in bond lengths determined by X-ray structure analysis. For example, this bond is 1.58 Å in the trimethiodide derivative of hodgkinsine (Figure 10).

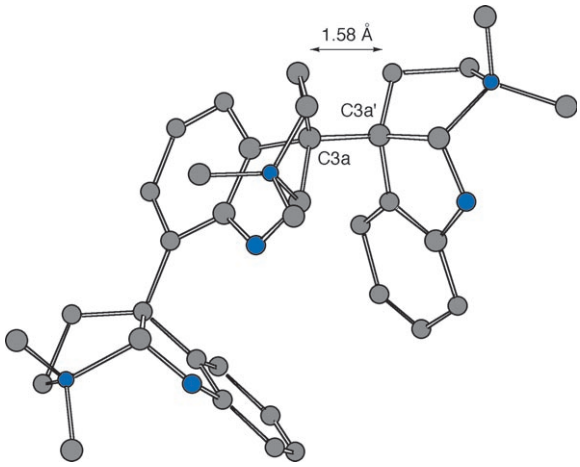


Figure 10. Crystal structure of the trimethiodide derivative of hodgkinsine.[24]

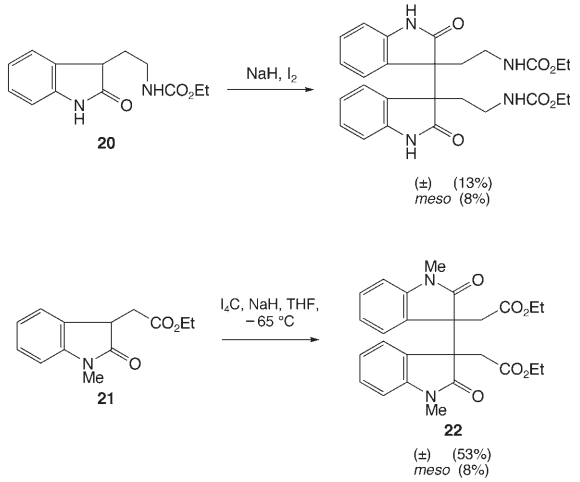
At the outset of our work in this area, a major challenge confronting the total synthesis of complex cyclotryptamine alkaloids was the lack of stereocontrolled methods for installing the signature quaternary carbon stereocenters. Extreme steric congestion, and the requirement to forge such stereocenters by C–C bond forming reactions, place such centers at the hub of the synthetic challenge.[2] Their adjacency in 3a,3a′-linked pyrrolidino[2,3-*b*]indolines adds

significantly to the task.[51] In addition, there were unanswered strategic questions concerning the influence that the configuration of an existing *cis*-pyrrolidino[2,3-*b*]indoline would have on the ability to generate the quaternary carbon stereogenic centers of additional *cis*-pyrrolidino[2,3-*b*]indoline fragments.

4. Construction of Contiguous Quaternary Carbon Stereocenters of 3a,3a′-Linked Pyrrolidino[2,3-b]indolines

4.1. Early Nonstereocontrolled Methods

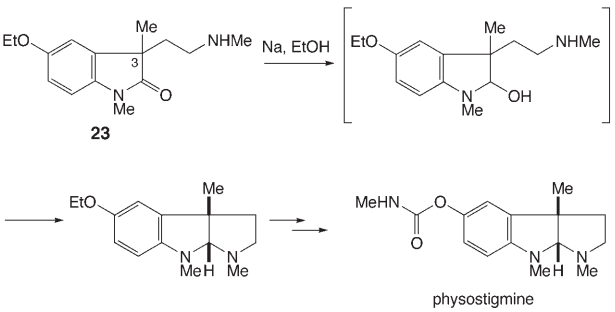
Early synthetic efforts towards the 3a,3a′-bispyrrolidino-[2,3-*b*]indoline architecture focused on the oxidative dimerization of indole or oxindole derivatives.[52] In an early study by Hendrickson and co-workers, the sodium salt of oxotryptamine derivative **20** was dimerized in the presence of iodine to produce a mixture of stereoisomeric dioxindoles, which, after separation, were reduced to give racemic and *meso*-chimonanthine (Scheme 3).[9] In a contemporary and more efficient



Scheme 3. Nonstereocontrolled formation of the 3a,3a′ σ bond by oxindole dimerization.

version of this approach, the dimerization of oxindole **21** to 3,3′-dioxindole **22** was induced by reaction of the sodium enolate of **21** with carbon tetraiodide;[53] the predominant racemic C_2-symmetric product was subsequently converted to (±)-folicanthine (**9**). The oxidative coupling of oxindoles, apparently, is not part of the biosynthesis of higher-order cyclotryptamine alkaloids, as 2-tritiotryptophan and 2-tritiotryptamine retain their label during the biosynthesis of chimonanthine (see Section 2).

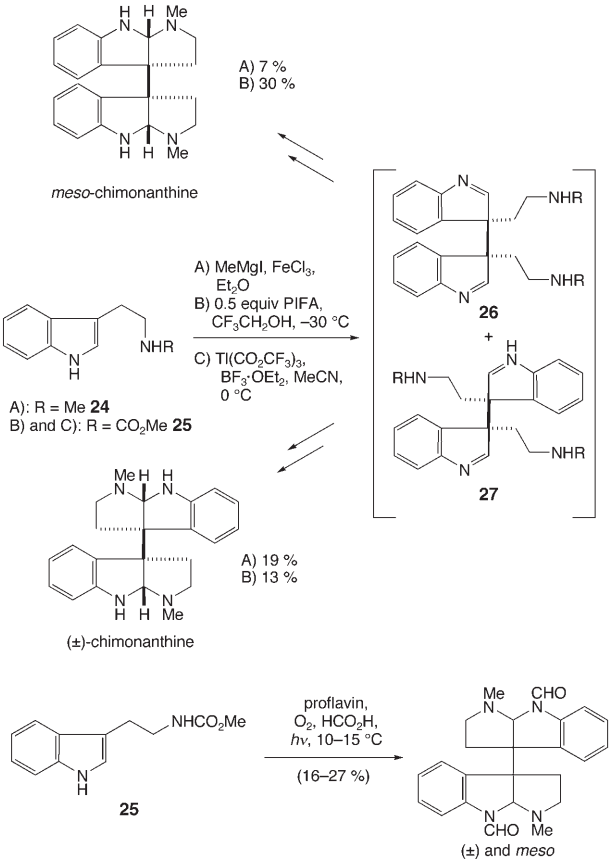
The utility of 3-(2-aminoethyl)oxindoles as precursors of *cis*-pyrrolidino[2,3-*b*]indolines stems from the pioneering early total synthesis of physostigmine by Julian and Pikl in which this ring system was formed by the reduction of the 3,3-disubstituted oxindole **23** (Scheme 4).[54] The presence of a quaternary center at C3 is key to the formation of the cyclic



Scheme 4. Total synthesis of physostigmine according to Julian and Pikl.

tryptamine tautomer in this instance, as N_a-methyl-3-(2-aminoethyl)oxindole is reduced under these conditions to N_a-methyltryptamine.[55]

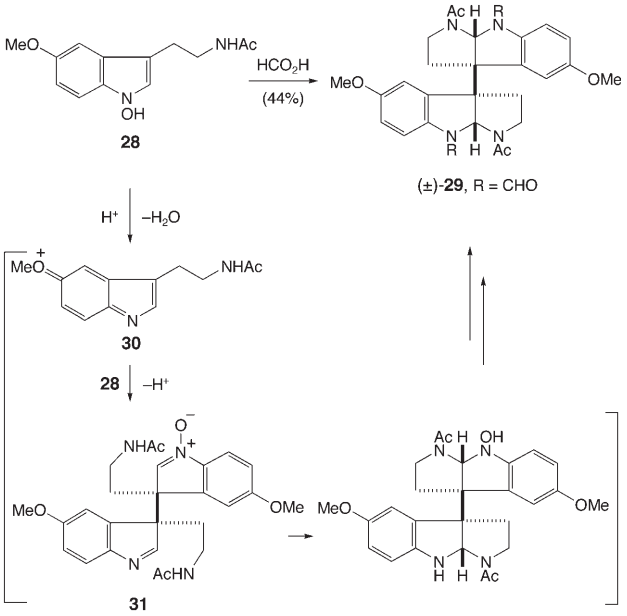
In a more biomimetic approach, substituted tryptamines have been dimerized in vitro with various oxidants. In a seminal contribution to this area, the magnesium salt of N_b-methyltryptamine **24** was used by Scott and co-workers to procure (±)-chimonanthine, presumably via the radical-coupling products, diindolenines **26** and **27** (path A in Scheme 5).[56–58] In a similar vein, N_b-carbomethoxytryptamine has been dimerized stereorandomly with phenyliodine-(III) bis(trifluoroacetate) (PIFA),[59] or thallium(III) tris(trifluoroacetate).[60] The hypervalent iodine(III) chemistry (path



Scheme 5. Tryptamine dimerization to form bispyrrolidino[2,3-*b*]indolines.

B in Scheme 5) provides a conduit for the preparation of *meso*-chimonanthine in 30% yield from **25**. As we will see shortly, stereocontrolled syntheses of *meso*-chimonanthine have been developed; nonetheless, this short nonstereocontrolled preparation from N_b-carbomethoxytryptamine is the most convenient way to access this achiral chimonanthine stereoisomer. Coupling has also been achieved by the proflavin-sensitized photooxidation of N_b-carbomethoxytryptamine (**25**) in formic acid (Scheme 5).[61]

The group of Somei has developed a quite different approach that allows racemic C_2-symmetric 5,5′-dimethoxy-3a,3a′-bispyrrolidino[2,3-*b*]indolines to be assembled with remarkable efficiency from N_a-hydroxymelatonin (**28**) (Scheme 6).[62] The reaction of **28** in formic acid furnishes

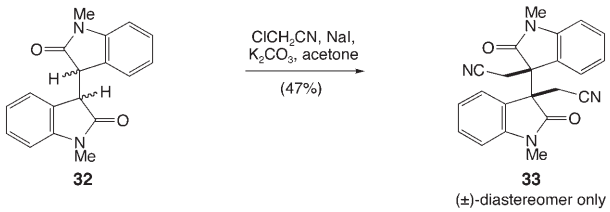


Scheme 6. Forming a 3,3a′-bispyrrolidino[2,3-*b*]indoline from a N_a-hydroxytryptamine precursor.

the tetra-N-acylated bispyrrolidino[2,3-*b*]indoline **29** in 44% yield. This reaction is presumed to occur by way of cation **30**, which is trapped intermolecularly at the C3 position to afford the imino nitrone **31**. Why none of the corresponding *meso* product was detected is unclear. This chemistry may be limited to tryptamine derivatives having electron-releasing groups in the aromatic ring, as the related transformation of N_b-acetyl-N_a-hydroxytryptamine has not been described.

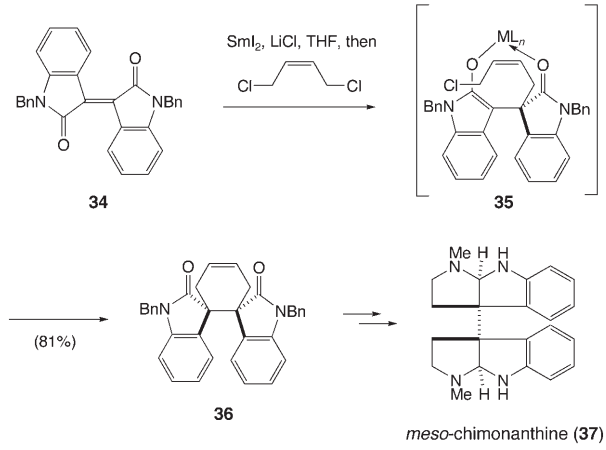
4.2. Stereo- and Enantiocontrolled Synthesis by Dialkylation of 3,3′-Dioxindoles

Our inaugural venture into the field of stereocontrolled synthesis of complex cyclotryptamine alkaloids was inspired by a variant of the Julian route to pyrrolidino[2,3-*b*]indolines that was described by the Hino group. In the pivotal step of their synthesis of (±)-folicanthine,[63] these workers reported that 3,3′-dioxindole[64] **32** reacted in acetone with K_2CO_3, NaI, and excess chloroacetonitrile to give the racemic C_2-symmetric product **33** in 47% yield (Scheme 7).[65]



Scheme 7. Stereocontrolled dialkylation of a 3,3′-dioxindole.

We envisaged cyclohexene **36**, which might be formed by a related dialkylation using a dielectrophile, as a key intermediate in a stereocontrolled synthesis of *meso*-chimonanthine (**37**) (Scheme 8). Access to **36** proved possible using a



Scheme 8. Forming contiguous quaternary stereocenters by reductive dialkylation of an isoindigo with a dielectrophile.

mixture of SmI_2 and LiCl to effect the reductive dialkylation of isoindigo **34** with *cis*-1,4-dichloro-2-butene (Scheme 8).[66] The presence of both lithium ions and chloride ions appears to be essential for the efficient formation of the *meso* product **36**, because this product is produced in low yield in the absence of LiCl or if KCl is substituted for LiCl. Stereoselection in this dialkylation is believed to derive from the intermediacy of chelated intermediate **35**.

Because the SmI_2 reductive dialkylation was inconvenient to scale up, we turned to examine a related sequence in which the dianion nucleophile is generated by deprotonation of the dihydro derivative of **34**. However, dialkylation of the lithium or potassium dienolates generated in this way was plagued by competitive S_N2' alkylation, resulting in cyclohexene **36** being contaminated with a vinylcyclobutyl isomer. This observation set the stage for an important, fortuitous discovery.[67]

In the further elaboration of pentacyclic dialkylation product **36**, the double bond permits the cyclohexene ring to be cleaved as a prelude to forming the final two pyrrolidine rings of *meso*-chimonanthine (**37**) by reductive amination.[66] A vicinal diol could serve the same purpose, and the

incorporation of this functionality, rather than a double bond, in the dielectrophile would side step the issue of competitive S_N2' alkylation.

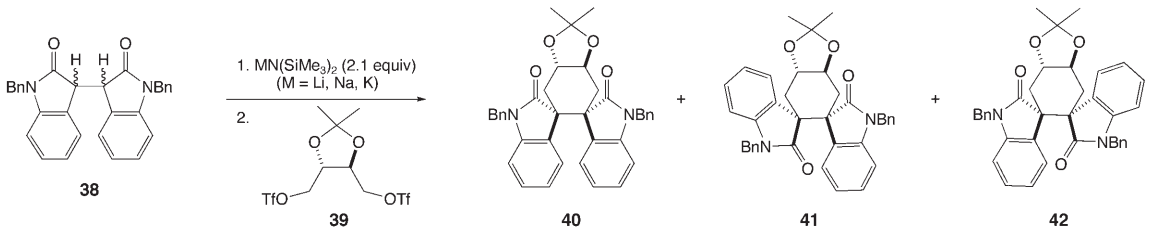
One of the first such dielectrophiles we examined was the ditriflate **39** derived from readily available 2,3-di-*O*-isopropylidene-D-threitol.[68,69] When the 3,3′-dioxindole starting material is symmetrically substituted, as is the dibenzyl derivative **38**, such a reaction can potentially generate three diastereomeric products: one with C_1-symmetry, **40**, and two with C_2-symmetry, **41** and **42** (Scheme 9). We quickly learned that the solvent, and to a lesser extent the dienolate counter ions, play pronounced roles in diastereoselection. When the solvent is THF, as it was in the earlier dialkylation of *cis*-1,4-dichloro-2-butene (Scheme 8), the C_1-symmetric product **40** having the *cis* relationship of its spirooxindole rings is produced with high diastereoselectivity. Chelate organization in the second alkylation step, analogous to that proposed in Scheme 8, is consistent with this result.[70] In seven additional steps, dialkylation product **40** was transformed to *meso*-chimonanthine, completing the second stereocontrolled total synthesis of this bispyrrolidino[2,3-*b*]indoline alkaloid.

Totally unexpected was the observed preference, seen under nearly all conditions surveyed, for forming one of the two possible C_2-symmetric products, **41**. As either enantiomer of the tartrate-derived ditriflate **39** is readily available, a way to prepare either enantiomer of C_2-symmetric 3a,3a′-bispyrrolidino[2,3-*b*]indolines was in hand. We quickly found that the formation of the C_1-symmetric product **40** was minimized in the presence of additives such as DMPU (*N*,*N*′-dimethylpropyleneurea) or HMPA (hexamethylphosphoramide), which presumably disfavor chelation. For example, upon adding 10% DMPU, the C_2-symmetric dialkylation product **41** predominated (55% yield) in the dialkylation of the lithium dienolate. In a few steps, C_2-symmetric dialkylation product **41** was elaborated to complete the first total synthesis of enantiopure (+)-chimonanthine.[67]

The excellent stereoselectivity observed in THF–DMPU for forming largely one of the two possible C_2-symmetric dialkylation products requires that the initial union of the prochiral lithium dienolate formed from **38** with the chiral dielectrophile **39** takes place with high stereoselectivity. As highly diastereoselective alkylation reactions of chiral sp^3 electrophiles and prochiral enolates are extremely rare, we carried out a thorough investigation of this dialkylation reaction.[71] Using in situ IR monitoring, we were able to establish that the dienolate, and not a monoenolate, is the nucleophile in the initial alkylation step. When an optimized ratio (7:3) of THF and HMPA was employed as the solvent, C_2-symmetric products predominated (C_2:C_1 selectivity = 8:1), with one C_2-symmetric product **41**, isolated in 58% yield,[72,73] vastly predominating over the other **42**.[74,75]

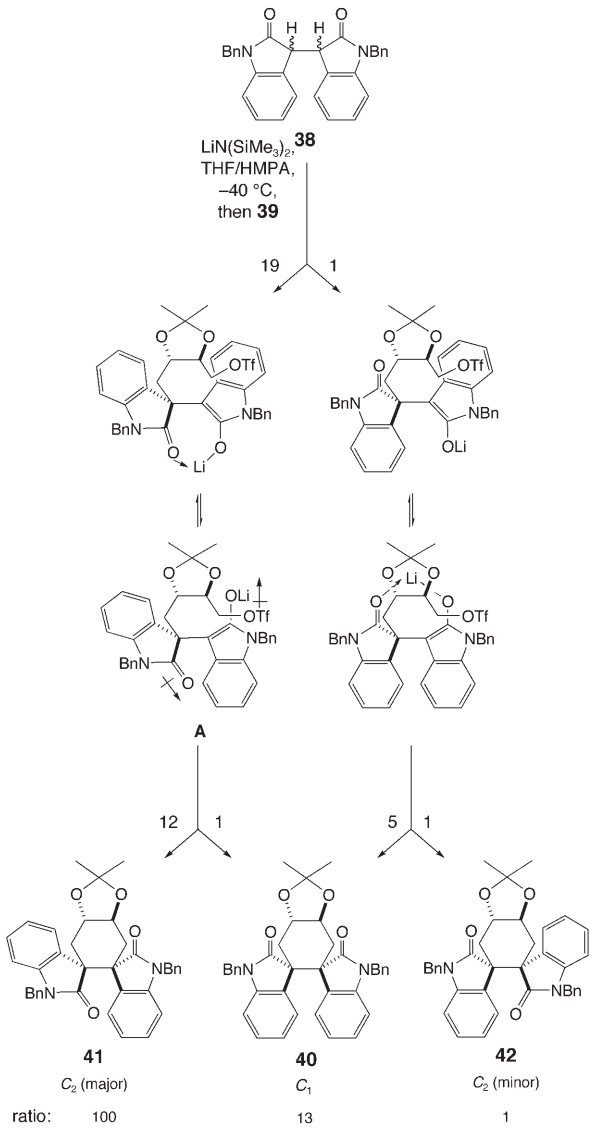
As summarized in Scheme 10, the 100:1 stereoselectivity observed in the C_2-symmetric manifold when LHMDS is used as the base and 7:3 THF–HMPA as solvent arises from diastereoselection in the initial intermolecular alkylation and in the partitioning of monoalkylated intermediates. The initial bimolecular alkylation event occurs with a facial selectivity of approximately 19:1.[76] The major monoalkylated intermediate partitions in the second alkylation step with a preference of 12:1 to generate the C_2-symmetric dialkylation product **41**. In this second alkylation step, the strongly coordinating HMPA additive disrupts chelate organization resulting in the major enolate intermediate undergoing intramolecular alkylation preferentially in a conformation, **A**, having the C–O dipoles pointed in opposite directions. In contrast, the minor monoalkylated intermediate partitions to give largely the C_1-symmetric product **40**. This latter preference is believed to reflect the higher energy of transition structures leading to product **42** in which the bulky aryl fragment of the spirooxindole groups are axially disposed. The selective partitioning of the minor monoalkylated intermediate in this way raises the overall C_2-selectivity to 100:1.

Cyclotryptamine alkaloids having 3a,3a′-bispyrrolidino-[2,3-*b*]indoline fragments occasionally bear unsymmetrically-substituted N_a atoms. To test further the versatility of the diastereoselective dialkylation approach for forming contiguous quaternary carbon stereocenters, we examined the dialkylation of a 3,3′-dioxindole whose nitrogen atoms had been differentially substituted. Dialkylation of the dienolate derived from unsymmetrical dioxindole **43** and ditriflate *ent*-**39** can generate four C_1-symmetric dialkylation products, **44**–**47** (Scheme 11).[73] If the initial bimolecular alkylation step occurred with high facial selectivity from the same oxindole enolate face irrespective of the nitrogen substituent, and the subsequent intramolecular alkylation took place without chelate organization, one of the two potential products having *trans*-oriented spirooxindole fragments would predominate. Under the optimized conditions shown in Scheme 11, quenching the lithium dienolate of dioxindole **43** with ditriflate *ent*-**39** led to the diastereoselective forma-

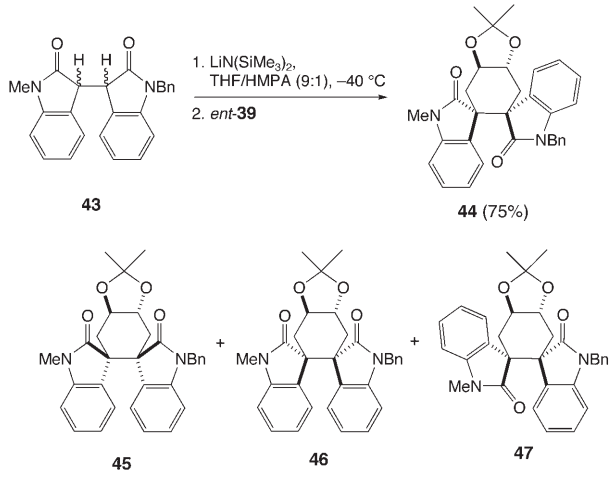


$NaN(SiMe_3)_2$, THF, –78 °C	92%	trace	trace
$LiN(SiMe_3)_2$, THF/DMPU, –78 °C	20%	55%	trace

Scheme 9. Dialkylation of 3,3′-dioxindole **38** with ditriflate **39**.



Scheme 10. Dialkylation of 3,3′-dioxindole **38** with ditriflate **39**; partitioning ratios are shown by the arrows.



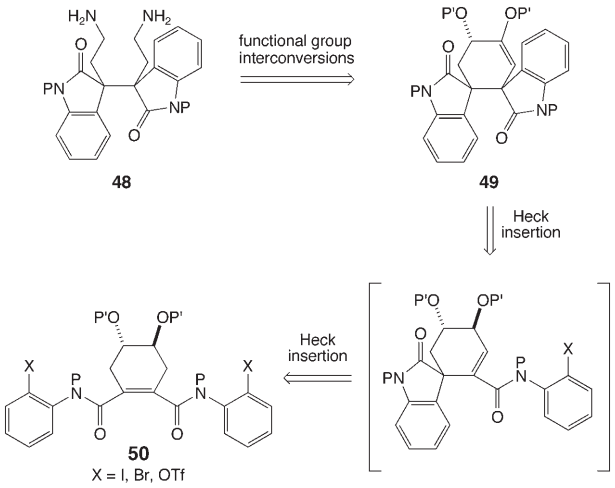
Scheme 11. Diastereoselective dialkylation of unsymmetrically substituted 3,3′-dioxindole **43** with ditriflate *ent*-**39**.

tion of the hexacyclic *trans*-dioxindole **44** in 75% yield. The majority of the remaining mass balance was comprised of the *cis*-dispirooxindoles **45** and **46**, with *trans*-spirooxindole **47** being detected in only trace amounts.

4.3. Stereo- and Enantiocontrolled Synthesis by Cascade Heck Cyclizations

Prior to our development of the ditriflate dienolate dialkylation chemistry, we had introduced another method for the stereo- and enantiocontrolled assembly of 3a,3a′-bispyrrolidino[2,3-*b*]indolines that exploited the facility with which the intramolecular Heck reaction can assemble congested quaternary carbon centers.[77] Although this chemistry is somewhat less practical than the dialkylation sequences, it has sufficient novel features to merit discussion.

Scheme 12 delineates the cascade Heck cyclization strategy in antithetic format. We imagined that a dioxindole nucleus, **48**, from which we could procure 3a,3a′-bispyrrolidino[2,3-*b*]indolines by reductive cyclizations, could be prepared from pentacycle **49**. We saw **49** arising by a double intramolecular Heck reaction of cyclohexenyl diamide **50**.

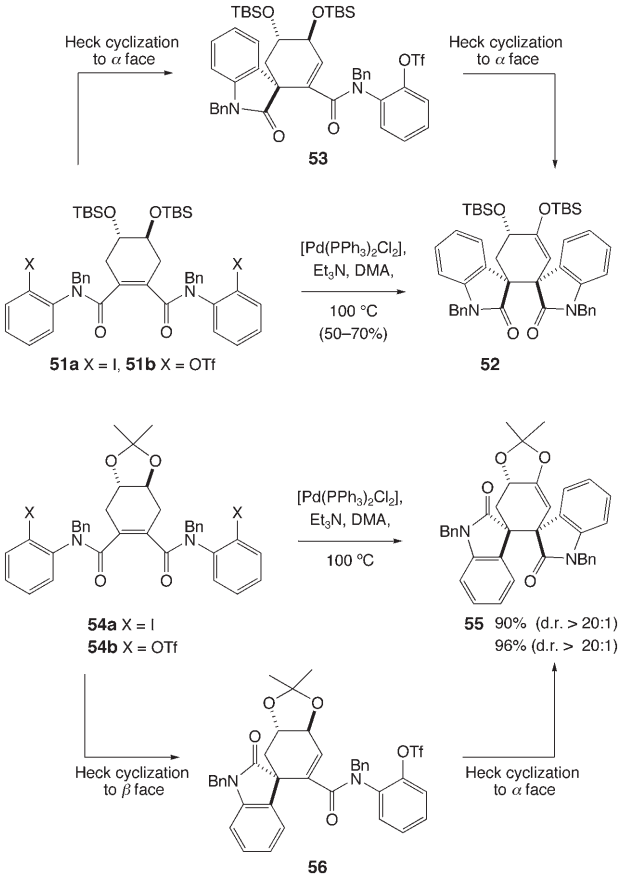


Scheme 12. Sequential intramolecular Heck reactions to form contiguous quaternary carbon stereocenters.

As this Heck reaction cascade could lead to the formation of four distinct pentacyclic diastereomers, the need to regulate stereoselection was upmost in our minds. It was in this context that we first recognized a protected, tartrate-derived *trans*-cyclohexanediol as a potential chiral-controller unit. Given their relative remoteness from the sites of carbopalladation, the efficiency with which the chirality of the C–O σ bonds of **50** would be transmitted to the nascent quaternary carbon stereocenters was initially unclear. We hoped that by tuning the diol protecting groups, such control could be realized.

Gratifyingly, the cyclization of disiloxy substrates **51a** or **51b** with 10–20 mol% $[Pd(PPh_3)_2Cl_2]$ and Et_3N in hot *N*,*N*-

dimethylacetamide (DMA) proceeded with moderate stereoselectivity to provide pentacyclic dioxindole **52** bearing a *cis* relationship between its two spirooxindole groups (Scheme 13, top).[78,79] By changing the protecting groups on



Scheme 13. Diastereoselection in the Heck cyclization cascade is controlled by the cyclohexanediol protecting group.

the *trans* vicinal diol precursor from silyl substituents to an acetonide, divergent stereoselectivity in the Heck cascade was observed under identical experimental conditions (Scheme 13, bottom). Remarkably, this latter reaction, in either the diiodide or ditriflate series, provided pentacyclic dioxindole **55** in nearly quantitative yield.[80] The *trans* arrangement of its spirooxindole substituents relates this product directly to one of the two enantiomers of 3a,3a′-bispyrrolidino[2,3-*b*]indolines.

The features that control stereoselection in these transformations are subtle and only partially understood. As depicted in Scheme 13, depending on the nature of the diol protecting group, opposite facial selectivities are observed in the first cyclization step of each cascade. The following rationale is commensurate with the outcome of the double Heck reaction sequence when the oxygen substituents are locked diequatorially as part of an acetonide.[79,81] The substituent on the nitrogen atom of the vinylic amide that is not involved in the insertion event shields one face of the alkene, with insertion occurring from the other face as depicted in Figure 11. The destabilizing interactions depicted

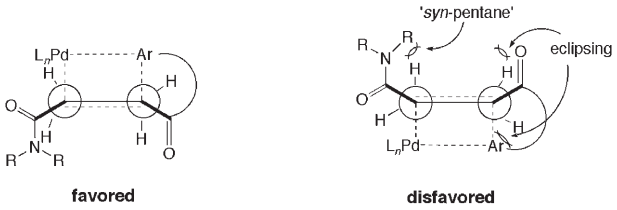
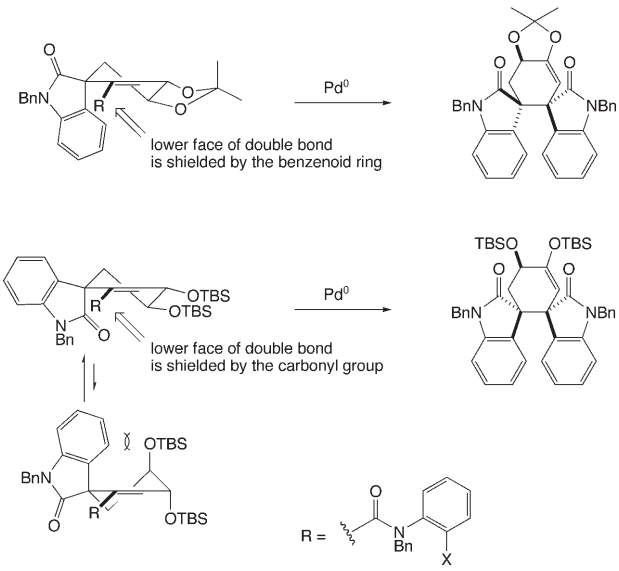


Figure 11. Rationalization of the carbopalladation selectivity in the initial insertion step when an acetonide protecting group is used.

in the disfavored transition state are minimized in the favored carbopalladation transition structure leading to the major tetracyclic intermediate **56**. In the favored transition state, there are eclipsing interactions between a long Pd–C bond and an axial C–H bond, and between a C–C and a C–H bond. These interactions are less "costly" than the two C–C/C–H interactions shown in the disfavored transition structure.[79]

In both the silyl and acetonide series, insertion in the second carbopalladation step occurs on the alkene diastereoface opposite the pseudoaxial fragment (carbonyl or aryl) of the first-formed spirooxindole (Scheme 14).[81] Propitiously, this means carbopalladation proceeds on the face of the double bond that will allow for *syn*-β-hydride elimination. Substrates devoid of an existing spirooxindole substituent cyclize with poor diastereoselection.

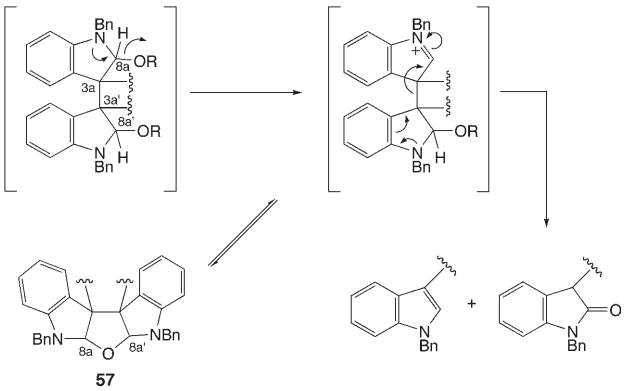


Scheme 14. Rationalization of the facial selectivity observed in the second carbopalladation step.

4.4. Elaboration of Dioxindoles to the Chimonanthines

The lability of the doubly benzylic C_{3a}–$C_{3a'}$ σ bond and the extreme steric congestion in its vicinity meant that the elaboration of the products produced by diastereoselective dienolate alkylation, or cascade Heck cyclizations, into 3a,3a′-bispyrrolidino[2,3-*b*]indolines was not without its obstacles. The need to reduce the carbonyl groups of both oxindoles so as to introduce the desired oxidation state at C_{8a} and $C_{8a'}$ with

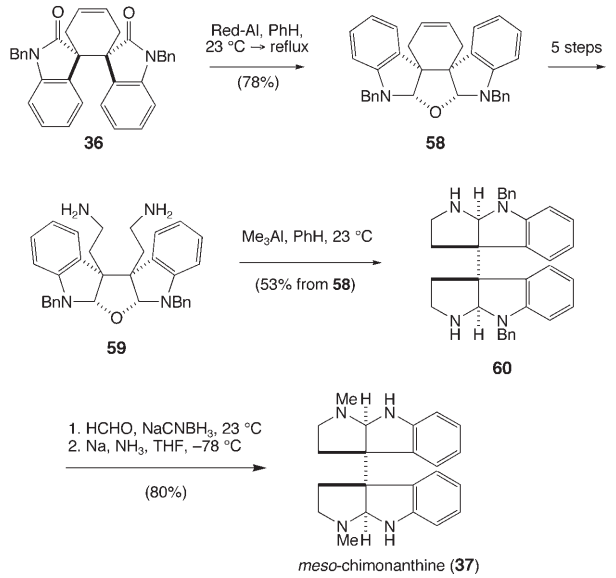
minimal scission of the weak C_{3a}–$C_{3a'}$ bond was one such challenge. As depicted in Scheme 15, intermediates in which the oxindole carbonyl groups have been reduced have available a ready pathway for fragmenting the C_{3a}–$C_{3a'}$ σ bond joining the two quaternary carbon atoms. The ability to generate and isolate intermediates **57** through the agency of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) was a key discovery allowing this problem to be circumvented.



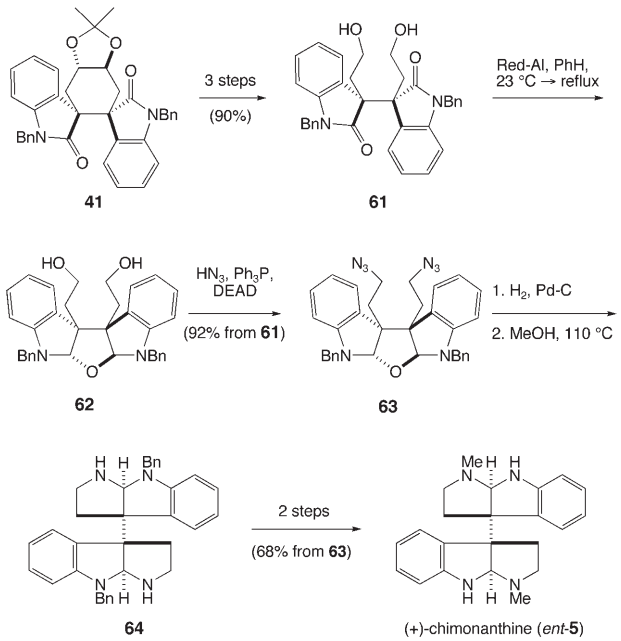
Scheme 15. Minimizing C_{3a}–$C_{3a'}$ bond scission by the formation of pentacyclic intermediates **57**.

Dialkylation products **36** and **40** and Heck product **52**, all of which have *cis*-spirooxindole units, could be converted efficiently to *meso*-chimonanthine. The general route is outlined in Scheme 16 for this elaboration of pentacyclic dialkylation product **36**.[66] The sequence began by reduction of **36** with Red-Al to provide hexacyclic intermediate **58**. After dihydroxylation, the central carbocyclic ring was cleaved and the resulting two-carbon side chains were elaborated to provide pentacyclic diamine **59**. Although exposure of this intermediate to various common acids led to scission of the σ-bond joining the quaternary carbons, the desired dehydration to generate the 3a,3a′-bispyrrolidino[2,3-*b*]indoline **60** could be realized by reaction of precursor **59** at room temperature with an excess of Me_3Al. After reductive methylation of the pyrrolidine nitrogens and removal of the benzyl groups with Na/NH_3, *meso*-chimonanthine (**37**) was secured in 33% overall yield from precursor **36**.

Similar chemistry was employed to convert C_2-symmetric dialkylation product **41** and Heck reaction product **55** having *trans*-spirooxindole fragments to (+)- and (−)-chimonanthine, respectively. Key steps in the former sequence are depicted in Scheme 17.[67] After removing the acetonide, the *trans*-1,2-cyclohexanediol was cleaved with lead tetraacetate, and the resulting labile dialdehyde was immediately reduced giving dioxindole diol **61** in 90% yield from pentacyclic precursor **41**. The Red-Al-mediated reduction of this dioxindole yielded pentacyclic diol **62**, which had to be handled with care to prevent cyclization of its alcohol side chains to give a hexahydrofuro[2,3-*b*]benzofuran product (analogue of **64** having two tetrahydrofuran rather than pyrrolidine rings). Conversion of the hydroxyethyl side chains of **62** to their diamine counterparts was accomplished by Mitsunobu reaction to provide diazide **63**, which cleanly generated the corresponding diamine upon catalytic hydrogenolysis. Our early attempts to effect the dehydrative rearrangement of this intermediate to the C_2-symmetric 3a,3a′-bispyrrolidino[2,3-*b*]indoline skeleton using Lewis or protic acid, including Me_3Al, led to the fragmentation of the C_{3a}–$C_{3a'}$ bond. Fortunately, we discovered, initially during mass spectrometric analysis, that simply heating a methanolic solution of the diamine derived from **63** to 100 °C delivered bispyrrolidino-[2,3-*b*]indoline **64** in high yield. Manipulation of the nitrogen



Scheme 16. Elaboration of dialkylation product **36** to *meso*-chimonanthine.



Scheme 17. Elaboration of dialkylation product **41** to (+)-chimonanthine.

substituents, as before, provided (+)-chimonanthine (*ent*-**5**) in 56% overall yield from dialkylation product **41**.

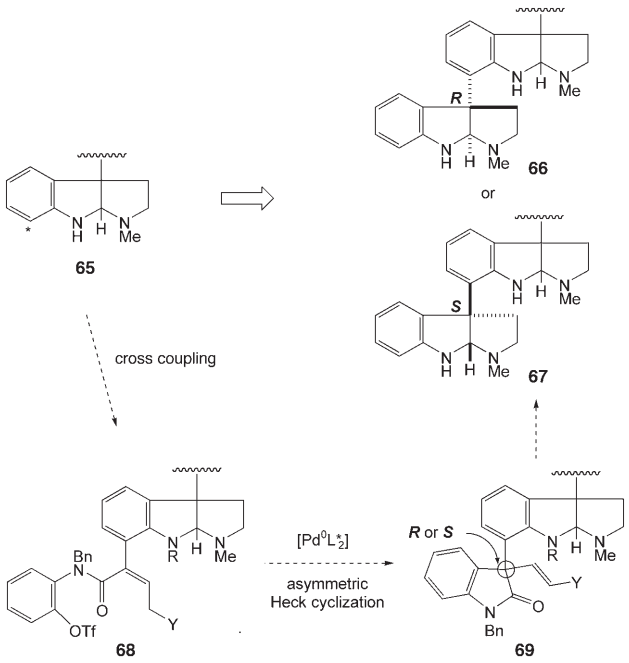
The dioxindole dialkylation and cascade Heck cyclization synthetic strategies allow either enantiomer of enantiopure C_2-symmetric 3a,3a′-bispyrrolidino[2,3-*b*]indolines, or their *meso* counterparts, to be prepared in a stereocontrolled fashion for the first time. In particular, dialkylation sequences employing the tartrate-derived dielectrophile **39** are notably efficient, delivering *meso*-chimonanthine and (+)-chimonanthine in overall yields of 39% and 21%, respectively, from the commercially available precursors oxindole and isatin. As tartaric acid is the stereocontrolling element, a similar sequence employing a dielectrophile derived from the enantiomeric dicarboxylic acid would provide (−)-chimonanthine. Moreover, unlike the samarium-mediated reductive dialkylation initially utilized to access the *meso* manifold, dialkylations of this tartrate-derived dielectrophile are readily carried out on preparatively meaningful scales.

5. Construction of Quaternary Carbon Stereocenters of Unsymmetrically Linked cis-Pyrrolidino-[2,3-b]indolines by Catalytic Asymmetric Intramolecular Heck Reactions

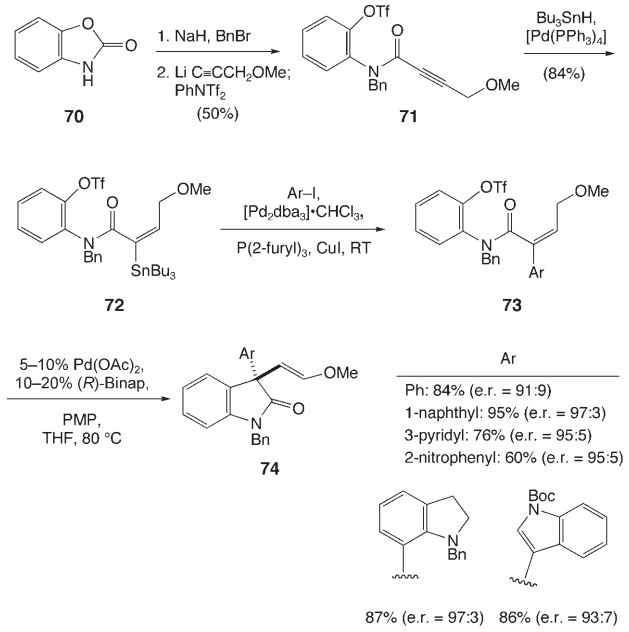
A second structural motif, diaryl-substituted quaternary carbon stereocenters, is the defining feature of cyclotryptamine alkaloids that contain three or more *cis*-pyrrolidino-[2,3-*b*]indoline fragments (Figure 1). This structural unit arises when the quaternary carbon atom of one *cis*-pyrrolidino[2,3-*b*]indoline is joined to the aromatic ring of another. To meet this synthetic challenge, ideally one desires chemistry to join the quaternary benzylic carbon atom of a nascent *cis*-pyrrolidino[2,3-*b*]indoline unit to an aryl carbon atom—always a *peri* position adjacent to nitrogen—of an existing *cis*-pyrrolidino[2,3-*b*]indoline fragment **65** (Scheme 18). Besides accomplishing this difficult union, the configuration of the new quaternary carbon stereocenter must be controlled.

The strategy that eventually emerged for accomplishing this demanding transformation is depicted in Scheme 18. The indoline nitrogen atom of the preexisting pyrrolidino[2,3-*b*]indoline would be employed to functionalize the adjacent aryl carbon atom, allowing the butenanilide fragment of triflate **68** to be introduced by a cross-coupling reaction. An intramolecular Heck reaction could then generate the desired oxindole, with the possibility that the configuration of the newly formed quaternary carbon stereocenter could be controlled by a chiral ligand.[77,82] With suitable choices of the substituents R and Y, we anticipated that the oxindole fragment of product **69** could be elaborated to the attached *cis*-pyrrolidinoindoline unit of products **66** or **67**.[83]

We initially explored the pivotal catalytic asymmetric cyclization step of this strategy in a simple model system (Scheme 19).[84] The assembly of the model substrate took advantage of the high functional group selectivity that characterizes palladium-catalyzed reactions, this selectivity ultimately allowing complex intermediates in our natural products synthesis endeavors to be prepared efficiently.[85]



Scheme 18. Appending a *cis*-pyrrolidino[2,3-*b*]indoline of either absolute configuration at the *peri* aromatic carbon of an existing *cis*-pyrrolidino[2,3-*b*]indoline fragment.



Scheme 19. Catalytic asymmetric synthesis of 3-alkyl-3-aryl(or heteroaryl)oxindoles by the intramolecular Heck reaction.

Starting with commercially available 2-benzoxazolinone (**70**), alkynyl amide **71** was fashioned in two steps. Palladium-catalyzed hydrostannylation of **71** cleanly produced vinylstannane **72**,[86] with no complications arising from competitive reaction of the aryl triflate functionality. The next step also exploited the relatively slow oxidative addition of aryl triflates, when **72** was cleanly cross-coupled with a variety of

aryl and heterocyclic iodides to deliver the Heck cyclization substrates, triflates **73**.

Although the Heck cyclization of 2′-triflato-(*Z*)-2-butenanilides **73** did not occur at practical rates using conditions ($Pd_2(dba)_3$·$CHCl_3$/Binap) we had employed earlier to prepare analogous oxindoles having methyl substituents at C3,[87] these more bulky substrates did cyclize at useful rates using the more reactive catalyst generated from $Pd(OAc)_2$ and Binap.[88] Enantiomer ratios (e.r.) were generally >95:5 for the formation of oxindoles having a wide variety of aromatic and heteroaromatic substituents at the quaternary C3 position. The notable ability of intramolecular Heck reactions to assemble highly congested ring systems is illustrated by the cyclization of the indolinyl derivative depicted in Figure 12. An appreciation of the high degree of steric congestion present in product **74a** is obtained by examining its space-filling model: viewed from the best perspective, the quaternary carbon atom is barely visible.

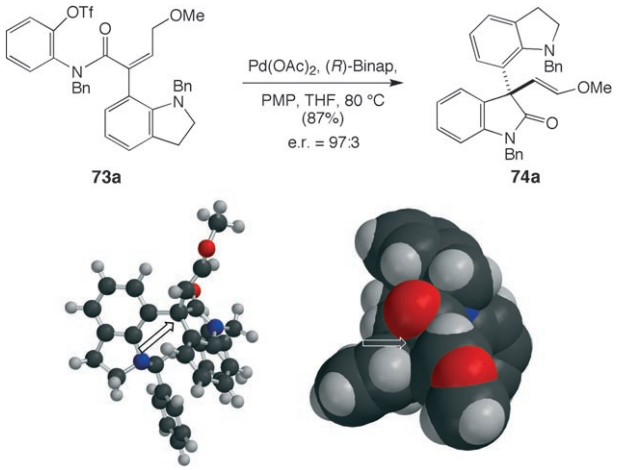
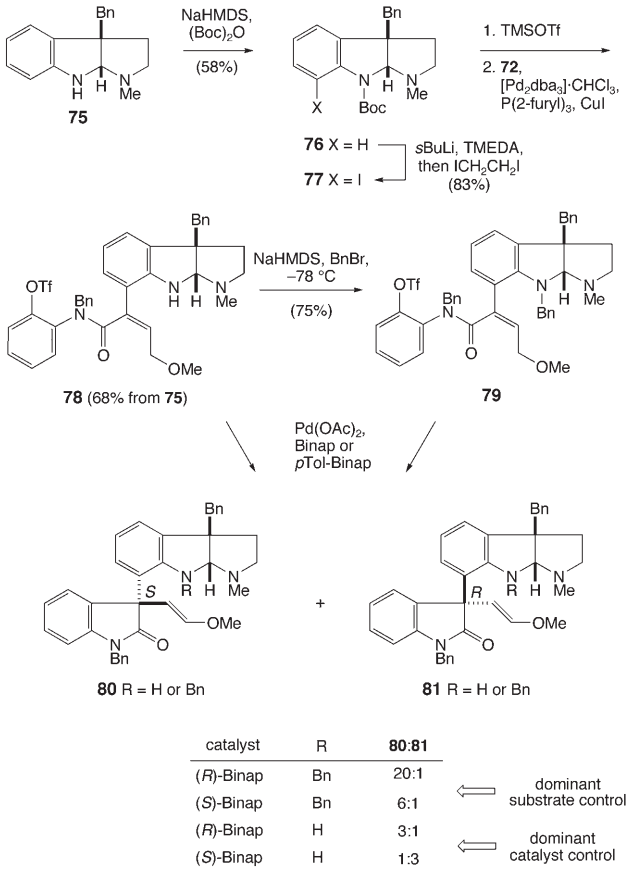


Figure 12. Catalytic asymmetric Heck cyclization to form **74a** and models of this product with an arrow pointing to its congested quaternary stereocenter.

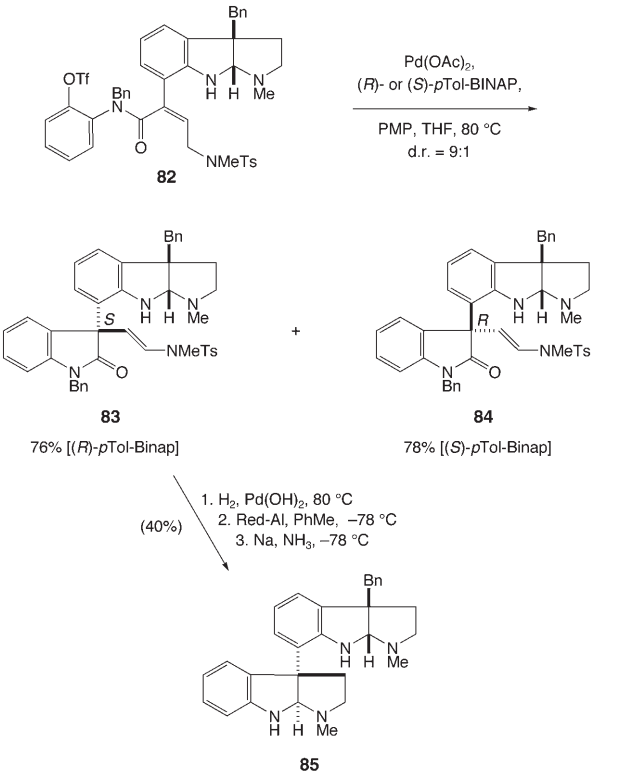
The full sequence for the elaboration of peripheral *cis*-pyrrolidino[2,3-*b*]indoline subunits was developed by using a model substrate,[89] enantiopure *cis*-pyrrolidino[2,3-*b*]indoline **75** (Scheme 20). This precursor was readily assembled by using a modification of the oxindole enolate/tartrate-derived ditriflate alkylation chemistry discussed in Section 4.2.[75] Protection of the indoline nitrogen atom of **75** with a *tert*-butoxycarbonyl (Boc) group could not be accomplished under typical conditions, as competitive ring-opening and alkoxycarbonylation of the expelled β-*N*-(methylamino)ethyl side chain occurred. However, deprotonation of pyrrolidino-[2,3-*b*]indoline **75** at −78 °C, followed by trapping with $(Boc)_2O$ did deliver Boc derivative **76** (Scheme 20). The *peri* position of this intermediate was then selectively functionalized by *ortho*-lithiation and iodination to give aryl iodide **77**.[30,90] As a result of the considerable steric hinderance at the *peri* carbon atom, Stille cross-coupling with stannane **72** to yield Heck cyclization precursor **78** was



Scheme 20. Sequence for stereoselective attachment of an oxindole fragment to the *peri* position of *cis*-pyrrolidino[2,3-*b*]indoline **75**.

efficient only after removing the Boc group and using a copper cocatalyst.[91]

The pivotal catalytic asymmetric intramolecular Heck reaction was examined with substrate **78** and benzyl derivative **79** (Scheme 20). To our surprise, in the *N*-benzyl series, Heck product **80** (R = Bn) having the *S* configuration at the newly formed quaternary carbon atom was the predominant stereoisomer produced by using *either R*- or *S*-Binap, indicating that substrate control was dominant. Fortunately, catalyst control was seen in the Heck cyclization of substrate **78** in which the indoline nitrogen atom was unprotected. These results are consistent with observations made with related substrates.[92] Generally, if the indoline nitrogen atom is unprotected, the configuration of the newly formed quaternary carbon sterocenter is under catalyst control. Conversely, when this nitrogen atom is protected, substrate control dominates. We also discovered that the second *cis*-pyrrolidino[2,3-*b*]indoline of a bispyrrolidino[2,3-*b*]indoline could not be fashioned from Heck products analogous to **80** in which R was H, as cyclization of the unprotected indoline nitrogen atom onto the two-carbon enol ether side chain of the oxindole fragment prevented conversion of the β-methoxyvinyl substituent to a β-aminoethyl fragment. Having the amino group already present in the Heck cyclization precursor, for example **82**, solved this final problem (Scheme 21). Moreover, we discovered in this series that simply replacing



Scheme 21. Stereoselective elaboration of an attached pyrrolidino[2,3-*b*]indoline unit; high levels of catalyst control are realized using *p*Tol-Binap.

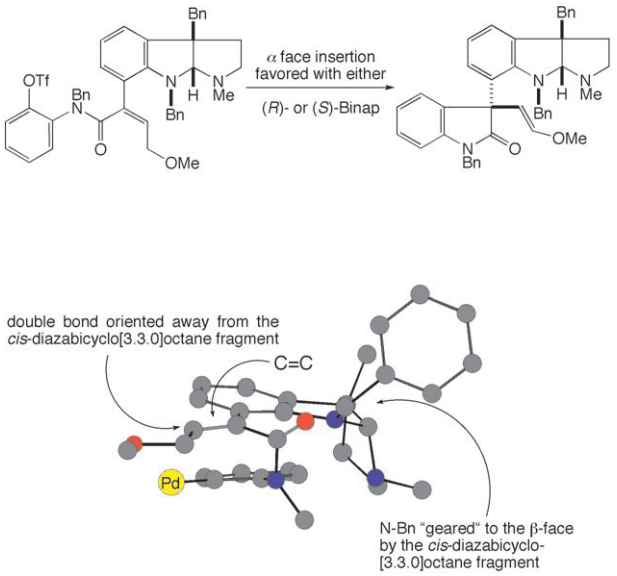


Figure 13. Irrespective of the chirality of the catalyst, in the N_a-benzyl series insertion occurs from the α face. (The Bn substituents at the anilide and the C atom are replaced with Me groups in the ball-and-stick model).

Binap with its *p*-toluene analogue increased the level of catalyst control to the extent that either oxindole epimer, **83** or **84**, is produced with high (9:1) diastereoselectivity. To complete our model studies, Heck product **83** was elaborated to the unsymmetrically linked bispyrrolidino[2,3-*b*]indoline **85** by a three-step sequence that was carried out without purification of intermediates: 1) the C–C double bond is saturated by catalytic hydrogenation, 2) the oxindole carbonyl group is reduced with Red-Al, and 3) the benzyl and tosyl protecting groups are cleaved by reaction with Na/NH_3, where, upon quenching with ammonium chloride, dehydrative cyclization takes place to generate the new pyrrolidino-[2,3-*b*]indoline.[92a]

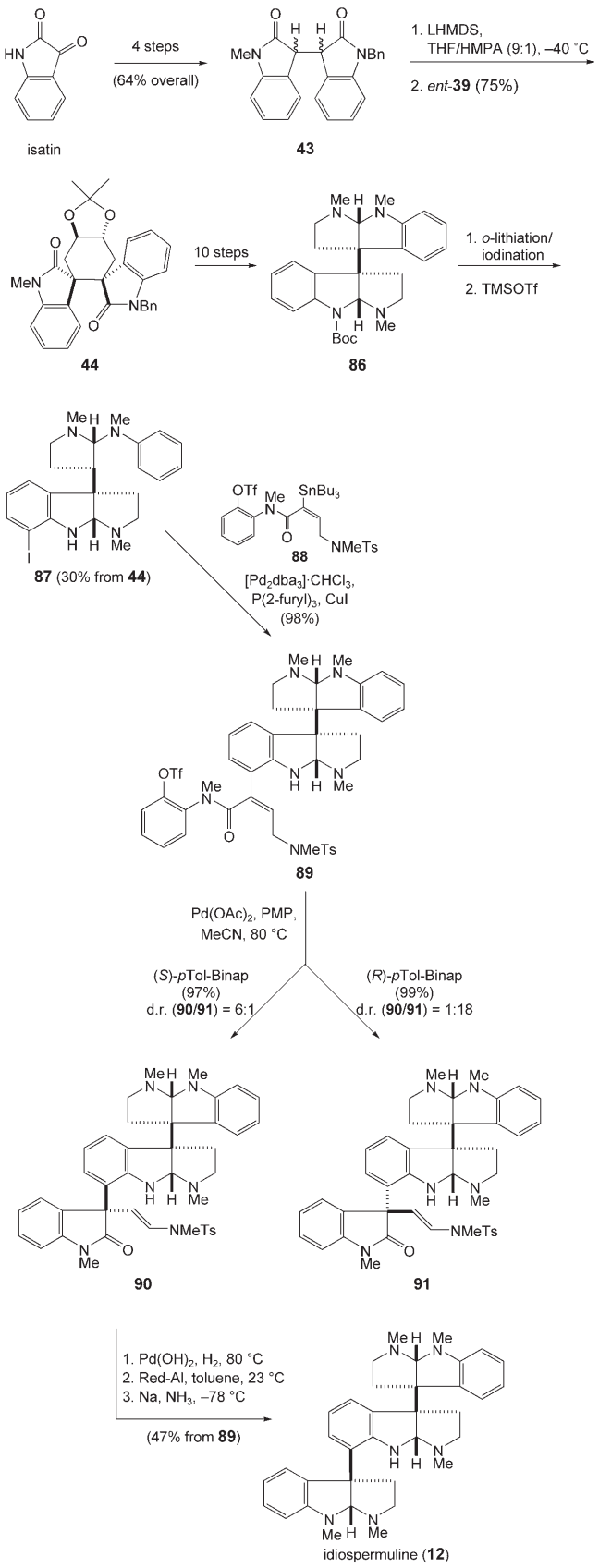
The factors that contribute to catalyst control being manifest only in the unprotected series are subtle and derive from the topography of the *cis*-pyrrolidino[2,3-*b*]indoline ring system. Single-crystal X-ray analysis of *cis*-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles bearing an alkyl substituent at the indoline nitrogen (N_a) show that this nitrogen atom is nonplanar, with the indoline substituent projecting on the less-congested convex face of the *cis*-diazabicyclo-[3.3.0]octane unit.[93] As depicted in Figure 13, we posit that carbometallation occurs by a conformation wherein the aromatic ring of the pyrrolidino[2,3-*b*]indoline fragment and the double bond are planar, with the alkene directed away from the *cis*-diazabicyclo fragment.[84] To avoid steric interactions with the indoline N_a-benzyl substituent, Heck insertion occurs from the opposite face, irrespective of the chirality of the catalyst. When the N_a-benzyl group is absent, this preference is mitigated and a chiral catalyst can regulate face stereoselection.

6. Stereo- and Enantiocontrolled Total Synthesis of Complex Polyindoline Alkaloids

Using the chemistry described in this review, the first total syntheses of cyclotryptamine alkaloids containing more than two *cis*-pyrrolidino[2,3-*b*]indoline subunits were completed. These syntheses illustrate three distinct ways catalytic asymmetric Heck cyclizations can be employed to fashion the outer *cis*-pyrrolidino[2,3-*b*]indoline fragments of these complex alkaloids.

We first consider the total synthesis of (−)-idiospermuline (**12**), a nonacyclic cyclotryptamine alkaloid isolated from a rare shrub growing in the lowland rain forests of Northern Queensland that had been responsible for the poisoning of cattle in this region (Scheme 22).[16] Three distinctive structural motifs are found in idiospermuline: 1) a 3a,3a′-bispyrrolidino[2,3-*b*]indoline ring system of similar absolute configuration to (−)-chimonanthine, 2) a third *cis*-pyrrolidino[2,3-*b*]indoline fragment having the *S* configuration at its quaternary carbon stereocenter that is attached adjacent to the unsubstituted indoline nitrogen atom of the 3a,3a′-bispyrrolidino[2,3-*b*]indoline moiety, and 3) the indoline nitrogen atoms of the two peripheral *cis*-pyrrolidinoindoline are methylated (Scheme 22).

The synthesis of idiospermuline began with dialkylation of the lithium dienolate of 3,3′-dioxindole **43** with enantiopure ditriflate *ent*-**39** to give the C_1-symmetric hexacyclic product **44** in 75% yield (48% overall from isatin).[73] The unsymmetrical substitution of the pyrrolidine nitrogens of the 3a,3a′-



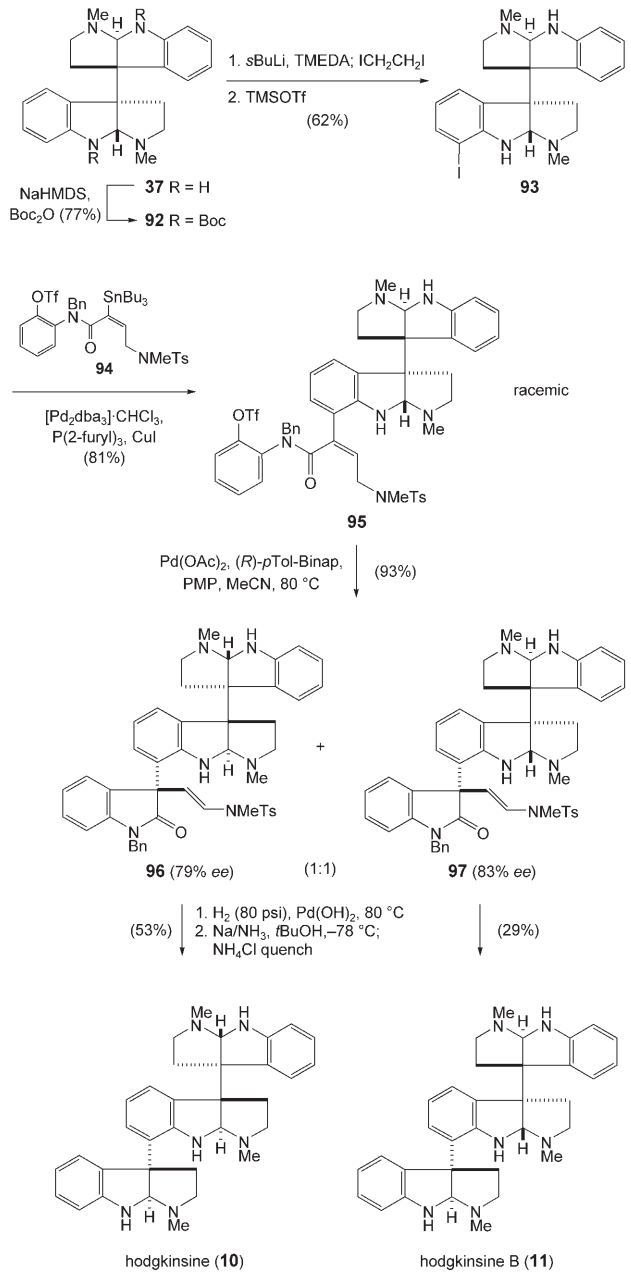
Scheme 22. Total synthesis of (−)-idiospermuline.

bispyrrolidino[2,3-*b*]indoline moiety of idiospermuline is addressed in this step by the simple expedient of having the nitrogen atoms of the dioxindole precursor **43** differentially functionalized. Using steps similar to those involved in our synthesis of (+)-chimonanthine (Scheme 17),[66,67,78] hexacyclic dioxindole **44** was converted in 10 steps to the 3a,3a′-bispyrrolidino[2,3-*b*]indoline **86**. Selective iodination of the aromatic carbon atom adjacent to the Boc group of this intermediate and discharge of the Boc protecting group provided the hexacyclic iodide **87** in 30% overall yield from dialkylation product **44**. Stille cross-coupling of this iodide with stannane **88** then delivered the Heck cyclization precursor **89** in high yield.

In this total synthesis, as in our earlier model studies, a catalytic asymmetric Heck cyclization is employed to control diastereoselection in appending the oxindole precursor of the final *cis*-pyrrolidino[2,3-*b*]indoline unit. Using (*S*)-*p*Tol-Binap as the ligand, Heck cyclization of triflate **89** took place in a remarkable yield of 97% to generate oxindole products **90** and **91** in a 6:1 ratio. In three additional steps, which were carried out without purification of intermediates, this mixture of Heck products was converted to enantiopure (−)-idiospermuline (**12**) in 47% overall yield from Heck precursor **89**. Although catalyst control is realized in this cyclization, the catalyst and substrate are mismatched. They are matched in the cyclization of **89** with the *R* enantiomer of the catalyst, a reaction that gives epimer **91** with 18:1 diastereoselectivity and nearly quantitative yield.

A catalytic asymmetric intramolecular Heck reaction was employed in a quite different strategic fashion in our total syntheses of hodgkinsine (**10**) and its diastereoisomer hodgkinsine B (**11**) (Scheme 23).[30] In these syntheses, the racemic Heck cyclization precursor **95** was assembled in four steps from *meso*-chimonanthine (**37**), which in turn is available in 30% overall yield from tryptamine.[59] After protecting both indoline nitrogen atoms with Boc groups, *meso*-chimonanthine derivative **92** was *ortho*-lithiated and iodinated under conditions optimized to provide the mono-iodo product. After the discharge of the Boc groups, the cross-coupling of iodide **93** with stannane **94** gave Heck precursor **95** as a racemate in 39% overall yield from *meso*-chimonanthine.

In the pivotal step in these syntheses, a catalyst-controlled Heck cyclization was employed to append an oxindole of *R* absolute configuration and thereby resolve the racemic precursor **95**. The two diastereomeric products **96** and **97** thus produced, which fortunately could be separated, were formed in an approximate 1:1 ratio. The enantiopurity of products **96** (79% *ee*) and **97** (83% *ee*) is consistent with the Heck cyclization of each enantiomer occurring with similar, approximately 8:1 to 9:1, catalyst-controlled stereoselectivity. After saturation of the double bond of Heck product **96**, excess Na in NH_3 was employed to reduce the oxindole carbonyl group and cleave the tosyl and benzyl protecting groups. After the mixture was quenched with ammonium chloride, (−)-hodgkinsine (**10**) was isolated in 53% yield for the two steps.[94] A similar sequence converted diastereomeric Heck product **97** to (−)-hodgkinsine B (**11**). As the relative and absolute configuration of this latter alkaloid was previously unknown,[29] our total synthesis established all aspects



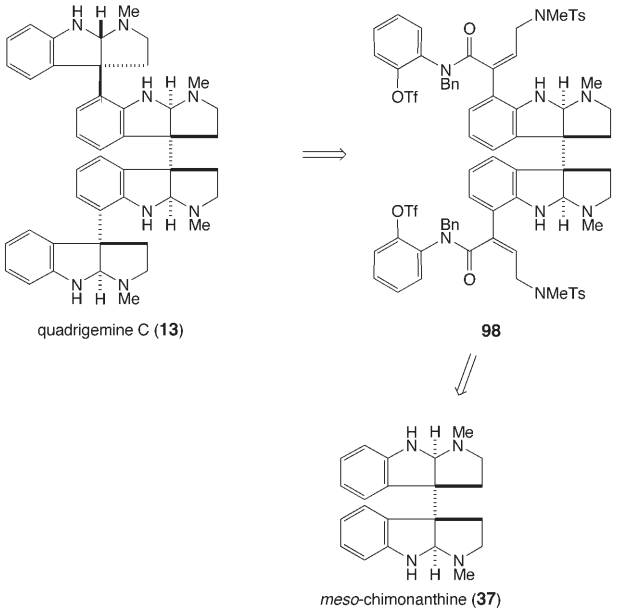
Scheme 23. Total syntheses of (−)-hodgkinsine (**10**) and (−)-hodgkinsine B (**11**).

of the structure of this tris(pyrrolidino[2,3-*b*]indoline) alkaloid.

We conclude our discussion with the total synthesis of the dodecacyclic alkaloid quadrigemine C (**13**) (see Figure 8).[95] As discussed earlier, this structurally notable natural product has been isolated from a *Psychotria* species found in the South Pacific and Brazil,[17,26,28,33] and displays a range of biological properties: somatostatin antagonism,[35] analgesic,[17] and antimicrobial.[36] The gross structure of quadrigemine C and the absolute configuration of its two outer rings were established by Sévenet, who also tentatively proposed, on the basis of NMR and CD studies, what turned out to be the correct three-dimensional structure of this alkaloid.[26]

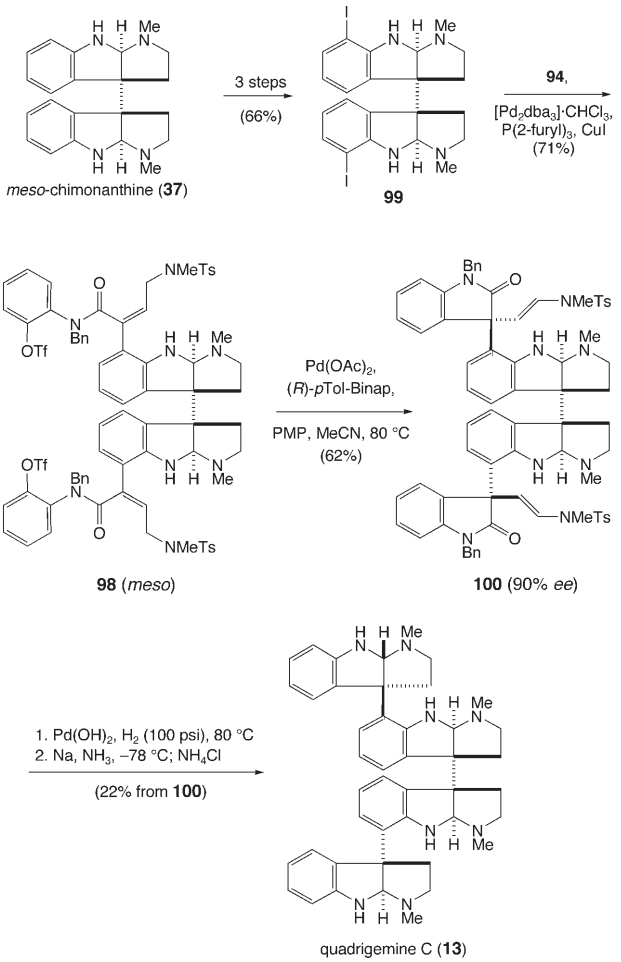
Quadrigemine C is a member of the large family of dodecacyclic cyclotryptamine alkaloids for which relative and absolute configuration are largely unknown (see Section 1). As implied by its name, the four linked pyrrolidino[2,3-*b*]indoline fragments of this structurally remarkable natural product conger up images of the quadriga of classical antiquity.[96] As ten "low energy" stereoisomers are possible for quadrigemines of the [2+2] constitutional family (Figure 7),[97] the challenge in synthesizing the C_1-symmetric dodecacyclic alkaloid quadrigemine C (**13**) in a stereocontrolled fashion is substantial.

The plan we developed for the stereocontrolled synthesis of quadrigemine C is outlined in Scheme 24. As the quaternary stereocenters of the two peripheral *cis*-pyrrolidino[2,3-*b*]indolines are of the same absolute configuration, we envisioned establishing these centers simultaneously by asymmetric Heck cyclizations. Such a strategy had the attractive feature that it would allow us to assemble an achiral intermediate containing all the carbon atoms and nitrogen atoms of quadrigemine C and then desymmetrize this intermediate, **98**, at a late stage during the installation of the final two quaternary carbon stereocenters of this natural product.



Scheme 24. Plan for the enantioselective total synthesis of (−)-quadrigemine C (**13**) from advanced *meso* precursor **98**.

The synthesis of quadrigemine C (**13**) starts with *meso*-chimonanthine (**37**), to which Boc groups are introduced to direct double *ortho*-lithiation–iodination, yielding the *meso*-diiodide **99** (Scheme 25). In the first of three consecutive palladium-catalyzed reactions, double Stille cross-coupling of this intermediate with stannane **94** provides the achiral Heck cyclization substrate **98** in 47% overall yield from *meso*-chimonanthine. In the pivotal step, the double asymmetric Heck cyclization of **98** is carried out in excellent chemical yield with the palladium complex derived from (*R*)-*p*-Tol-



Scheme 25. Total synthesis of (−)-quadrigemine C (**13**).

Binap to deliver the C_1-symmetric, decacyclic dioxindole **100** in 62% yield and 90% enantiomeric excess. Stereoselection in each Heck cyclization is again on the order of 8:1 to 9:1; as a result, two *meso* stereoisomers are also produced, which were isolated in 14% and 11% yields. A feature of this synthesis strategy is the ability to defer the choice of product enantiomer to a late stage. Thus, by carrying out the double Heck cyclization with the palladium catalyst incorporating (*S*)-*p*Tol-Binap, it is possible to prepare the enantiomer of quadrigemine C.

The synthesis of quadrigemine C (**13**) is completed in two additional reductive steps from decacyclic dioxindole **100**. Catalytic hydrogenation of **100** delivers the tetrahydro derivative, which is exposed to excess Na/NH_3, followed by quenching with ammonium chloride, to give (−)-quadrigemine C (**13**) in 22% yield for the two steps. Although the yield of the last step is only modest, much transpires: two benzyl and two tosyl protecting groups are removed, both oxindole carbonyl groups are reduced, and two equivalents of water are liberated to form the final two *cis*-pyrrolidino[2,3-*b*]indoline rings. As synthetic quadrigemine C was identical with a natural sample, the absolute and relative configuration of this dodecacyclic alkaloid suggested by Sévenet and co-workers was rigorously confirmed. In addition, exposing synthetic (−)-quadrigemine C to acetic acid provided (−)-psycholeine (**15**, Figure 8). Gratifyingly, this inaugural total synthesis of quadrigemine C (**13**) was accomplished from tryptamine by a sequence of only 10 linear steps.

7. Summary and Outlook

Natural product synthesis can be used as a torch to illuminate gaps in synthetic methodology, and as a vehicle for testing possible means of plugging these gaps. In this instance, the fascinating structures of higher-order polypyrrolidino[2,3-*b*]indoline alkaloids stimulated the development of various methods for the stereocontrolled construction of quaternary carbon stereocenters.

The dialkylation of dienolates of 3,3′-dioxindoles with a ditriflate derived from tartaric acid has been shown to be a versatile method for assembling complex structures containing contiguous quaternary carbon stereocenters. The absolute configuration of the major dialkylation product is controlled by the chirality of the tartrate-derived dielectrophile, whereas its relative configuration can be regulated by the appropriate choice of base and solvent. More generally, this work shows that by judicious selection of coupling partners, the combination of a prochiral enolate with a chiral, sp^3-hybridized electrophile can be a useful tactic for the stereocontrolled formation of C–C bonds.[98]

The wide functional group tolerance of palladium(0)-catalyzed reactions, and the remarkable ability of intramolecular Heck reactions to form C–C bonds in environments of extreme steric congestion, underpin several of the new methods for the stereocontrolled construction of quaternary carbon atoms developed during this program. The success of an intramolecular Heck reaction cascade to efficiently fashion adjacent quaternary carbons from a tetrasubstituted double bond provides a striking example of the remarkable ability of the Heck reaction to assemble congested carbon networks. To the best of our knowledge, this is the only catalytic reaction reported to date for the synthesis of vicinal quaternary carbon stereocenters.[51a]

The intramolecular Heck reaction, this time under the aegis of a chiral ligand, also played a central role in our development of a general strategy for appending, through its quaternary carbon, a *cis*-pyrrolidino[2,3-*b*]indoline ring of either absolute configuration to the hindered *peri* carbon atom of a hexacyclic 3a,3a′-bispyrrolidino[2,3-*b*]indoline fragment. This chemistry should allow a variety of complex cyclotryptamine alkaloids of varying relative and absolute configuration to be prepared by stereorational chemical synthesis. Specifically illustrated in our total syntheses of idiospermuline, is the use of asymmetric catalysis to control diastereoselectivity in forming a new quaternary carbon stereocenter, whilst our total syntheses of hodgkinsine and hodgkinsine B illustrate the utility of the intramolecular Heck reaction for kinetic resolutions. The total syntheses of quadrigemine C, and thence psycholeine, provide examples of two-directional synthesis in which catalyst control is used to simultaneously functionalize both termini of a complex synthetic intermediate.[99] In a more general sense, these

syntheses highlight the potential of catalytic asymmetric reactions to be employed not only to prepare small chiral building blocks, but also to elaborate functionally complex advanced synthetic intermediates. We are certain to see much future progress in this relatively unexplored aspect of asymmetric catalysis.

List of Abbreviations

Ac	acetyl
Binap	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
dba	*trans*,*trans*-dibenzylideneacetone
DMA	*N*,*N*-dimethylacetamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
HMPA	hexamethylphosphoramide
LHMDS	lithium hexamethyldisilazide
NaHMDS	sodium hexamethyldisilazide
PIFA	phenyliodine(III) bis(trifluoroacetate)
PMP	1,2,2,6,6-pentamethylpiperidine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
*p*Tol	4-tolyl
Ts	4-toluenesulfonyl

We are deeply indebted to our collaborators whose names appear in the references cited. Their experimental skill, dedication and insight made the accomplishments discussed in this survey possible. We gratefully acknowledge financial support from the National Institutes of General Medical Sciences (USA) (GM-30859). We also thank Amgen, Merck, Pfizer, and Roche Palo Alto for unrestricted support.

Received: February 9, 2007
Published online: June 25, 2007

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