Scalable Total Syntheses of *N*-Linked Tryptamine Dimers by Direct Indole-Aniline Coupling: Psychotrimine and Kapakahines B & F

Timothy Newhouse, **Chad A. Lewis**, **Kyle J. Eastman**, and **Phil S. Baran**[*]
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Abstract

This report details the invention of a method to enable syntheses of psychotrimine, **1**, and the kapakahines F and B, **2** & **3**, on a gram scale and in a minimum number of steps. Mechanistic inquiries are presented for the key enabling quaternization of indole at the C3 position by electrophilic attack of an activated aniline species. Excellent chemo-, regio-, and diastereoselectivities are observed for reactions with *o*-iodoaniline, an indole cation equivalent. Additionally, the scope of this reaction is broad with respect to the tryptamine and aniline components. The anti-cancer profiles of psychotrimine, **1**, and kapakahines F and B, **2** & **3**, have also been evaluated.

Introduction

Of all the known nitrogen-bearing natural products, those containing an indole heterocycle hold a special place in the annals of organic chemistry. This priority position in "alkaloid space" is due to several factors including the interesting structures of many of their members, their novel bioactivities, and their historical importance in the development of organic chemistry.[i] Furthermore, certain indole alkaloids are even used as "yardsticks" to measure progress in the art and science of synthesis – strychnine being particularly prominent in this regard.[ii]

An important subset of indole alkaloids are those made up of more than one indole subunit.[iii] The vast majority of such structures involve linkages between the carbon atoms of the indoles, such as those shown in Figure 1, which have all succumbed to elegant total syntheses.[iv] A rarity among polymeric indole alkaloids are those linked by the nitrogen atom of the indole, such as those in Figure 2.

The first member of this subset was isolated in 1944 and named chaetomin, **12**.[va,b] Its intriguing structure was not fully elucidated until 1978 (then renamed chetomin)[5c,d] and it was not until the very end of the twentieth century that more natural products with this peculiar connectivity were isolated.[vi] In 1995 Scheuer and co-workers isolated a family of macrocyclic peptides, the kapakahines, **2** & **3**, exhibiting an N1-C3 linkage between two tryptophan subunits.[vii] A decade later more natural products expressing this motif were isolated, including ones akin to chetomin[viii] and the only reported polymeric cyclotryptamine alkaloids with the N1-C3 linkage, psychotrimine, **1**,[ix] and psychotetramine, **15**.[x] These natural products have both fascinating structures and biological functions that are of considerable interest. For

example, chetomin, **12**, disrupts binding of a key cofactor in the hypoxia-inducible factor pathway and has been shown to affect dose-dependent tumor reduction in mice.[5f] The kapakahines, only isolated in minute quantities (0.3 mg of kapakahine B was isolated from 840 g of crude sponge ethanolic extract), have been reported to exhibit promising anti-leukemia activity. Psychotrimine has been shown to possess activity against colon and lung cancers,[xi] and was equally potent as a currently employed colon cancer therapy, 5-fluorouracil.

The absence of any direct means to synthesize these natural products led us to consider the invention of a method to bridge this gap in the capabilities of chemical synthesis.[xii] This full account describes in detail the underlying rationale, mechanism, and scope of a method that has made possible the concise gram-scale total syntheses of highly complex natural products such as psychotrimine and those belonging to the kapakahine family.[xiii]

Biosynthetic Considerations and Initial Forays

Whereas the biogenetic origins of dimeric indole alkaloids linked at carbon are presumed to proceed via a radical dimerization process,[xiv] the genesis of nitrogen-linked siblings in this family is not well understood. A number of possibilities exist for how Nature might fashion this exotic connectivity. Perhaps the most straightforward possibility would be a radical- or cationic-based, oxidative dimerization to directly form the N1-C3 bond (Figure 3A). A second possibility, reminiscent of the speculated biosynthesis of the chartelline alkaloids, hinges on the propensity of a nitrogen substituent to migrate from C2 to C3 of indole via a [1,5] sigmatropic rearrangement (Figure 3B). Although migration of carbon atoms from C2 to C3 is well precedented, to our knowledge, the sole experimental demonstration of a nitrogen migration in such a context stems from the total synthesis of chartelline C (**19 → 20**).[xv] Thus, as illustrated in Figure 3C, an analogous process may be operative in a hypothetical rearrangement of **21** to **24** (via **22** and **23**). Such a scenario would require position-selective intermolecular oxidative dimerization of tryptophan units to afford the N1-C2 linked dimer **21**. Naturally occurring alkaloids such as **21** are not known, but heteroatom linkages at C2 of tryptophan are precedented, such as celogentin C (*vide infra*).[xvi]

A third possibility would involve direct nucleophilic displacement of a halide by the indole nitrogen (Figure 3D). Although the work of Rainier has demonstrated that such a process can occur, it requires a strong base[xvii] and proceeds to give the opposite diastereochemical outcome that is required for the kapakahines via epimerization of the tryptophan α-proton. A final possible biogenesis invokes the "Somei hypothesis" for dimerization via *N*-hydroxyindoles (**26**, Figure 3E) with concomitant loss of water.[18a] Somei has demonstrated that in certain contexts this type of bond formation is facile,[xviiib] but a quaternary center cannot be formed in more than trace quantities via this process.[xix] The following series of experiments were designed to interrogate the innate reactivity of molecules relevant to the presumed biogenetic hypothesis in Figures 3A and 3C.

Our studies commenced with the reinvestigation of the sole example of N1-C3 tryptamine dimerization reported in a book chapter in 2000 (Scheme 1).[xx] The described reaction used a cobalt (II) salen precatalyst in the presence of oxygen, conditions that are well known to operate through an SET process.[20b–c] Unfortunately, the only melatonin dimer observed was not **28**, but rather the constitutionally isomeric structure linked from N1 to C2, **29** (Scheme 1, verified by X-ray crystallography). While disappointing, this reactivity represented an opportunity to explore the C2 to C3 rearrangement proposed in Figure 3C. As depicted in Scheme 2, when dimer **29** was reduced using zinc in acetic acid, the desired tryptamine dimer **30** was isolated in 96% yield. With the necessary oxidation state in place, dozens of thermal and acidic conditions were screened to elicit isomerization ($PtCl_4$, CuOTf, RuCl(H)(CO) ($PPh_3)_3$, $AgNO_3$, $NiCl_2$, TiF_4, $BF_3 \cdot OEt_2$, Sc(OTf)$_3$, $ZnCl_2$, etc.), but were unsuccessful. The

recalcitrance of this intermediate to isomerize was compounded by its propensity to rapidly undergo oxidation back to **29**, along with other oxidation byproducts. During the course of the Lewis acid screen, it was found that $AuCl_3$ acted as an electrophilic chlorine source to cleanly provide the C3-chlorinated indolenine **31a**.[xxi]

Isomerization reactions on this chlorinated species, **31a** (generated in a simple way using NCS), and the related C3-methoxy indolenine, **31b**, (prepared by treatment of **31a** with K_2CO_3/ MeOH) were also attempted by subjection to acidic,[xxii] basic,[xxiii] or thermal conditions. Additionally, treatment of **31a** with silver (I) triflate or **31a** or **31b** with $NaBH_4$ did not afford the desired indole connectivity (**32**). Although not thoroughly explored, subjection of **29** to acidic conditions led to significant decomposition and recovery of monomeric melatonin species **27**.[xxiv] Despite these setbacks it was reasoned that a redox neutral isomerization event of the nitrogen substituent from C2 to C3 was still possible. To investigate whether the electron rich nature of melatonin dimer **29** somehow prevented the isomerization reaction, the electron neutral analog, lacking the C5 methoxy groups, was synthesized.

Cobalt-mediated oxidation conditions were attempted with electron neutral tryptamines; however, the N1-C2 product analogous to **29** could not be detected in the reaction mixture. Only monomeric oxidation byproducts were isolated, including the *N*-formyl kynurenine (oxidative cleavage of the indole 2,3-π bond) and the C3-hydroxy pyrroloindoline.[xxv] An extensive screen of oxidants did, however, lead to the isolation of trace amounts of an N1-C3 linked tryptamine dimer, using Koser's reagent (PhI(OH)OTs),[xxvi] as shown in Figure 4. The continued screen of hypervalent iodine oxidants and other transition metal oxidants did not lead to any improvement of this non-selective reaction nor the detection of the N1-C2 isomer. Even in the case of the hexapeptide **35**, macrocyclization was not observed.

A stepwise strategy was therefore pursued as documented in Scheme 3. A Buchwald-Goldberg-Ullmann reaction[xxvii] was well suited for the task of merging bromotryptamine **37** (available in three steps from tryptamine) and tryptamine **33**, furnishing dimer **39** after Boc-removal with TFA (20%, unoptimized). Unfortunately, this compound was also resistant to isomerization and underwent similar oxidative decomposition as the melatonin dimer **30**. Exploration of oxidative transformations on this substrate were not pursued due to the lengthy and low-yielding sequence to obtain useful quantities of **39**.[xxviii]

At this juncture the realization and acceptance was made that a purely biogenetic strategy would likely not be feasible in synthetically useful yield, therefore a surrogate for tryptamine was sought out. The work of Renfroe, Bergman and Castle in oxidative heterocoupling was particularly interesting in this regard,[xxix] wherein the coupling of nitrogen nucleophiles with C3-substituted indoles to afford C2-linked indoles was achieved simply using NCS (Figure 5).

As shown in Scheme 4A, indoline was chosen as a tryptamine surrogate. In the event, tryptamine **45** was treated with NCS in the presence of Et_3N followed by addition of indoline to furnish C3-hydroxyindolenine **47**. This product presumably arises from rapid autoxidation of the initially formed adduct during workup. While Fmoc removal proceeded smoothly (DBU, $C_{12}H_{25}SH$) to deliver **48**,[xxx] attempts to reduce the resulting imine and effect isomerization were unsuccessful (Zn/AcOH, $NaBH_4/CeCl_3$). It is possible that imine reduction and dehydration did occur, followed by rapid autoxidation to regenerate **48**.

In order to avoid the protection/deprotection sequence, the Fmoc protected secondary amine was simply masked as a methyl carbamate.[xxxi] The methyl carbamate of tryptamine (**33**, Scheme 4) was treated with NCS, which to our surprise provided the chloroindolenine (**50**)[xxxii] rather than its ring-chain tautomeric C3-chloropyrroloindoline form.[xxxiii] Not surprisingly the chloroindolenine exhibited noticeable decomposition upon aqueous work-up or concentration. The crude chloroindolenine was then treated with indoline and the N1-C3

linked isomer, **49**, was obtained in 18% yield along with 45% of the C2-linked adduct **51**. The exact nature of this highly interesting process is certainly debatable and related transformations are discussed in detail in the Mechanistic Considerations section. We were pleased to have rapid access to the key quaternary center expressed in psychotrimine, **1**, and the kapakahines, **2** & **3**; however, efficiencies were still low and proceeding via an indoline or an unfunctionalized aniline would require a number of extraneous steps.

If *o*-iodoaniline could be successfully employed as a nitrogen donor, then rapid access to these natural products would be enabled (Figure 6A). However, as was encountered previously (Scheme 4), issues of regio- and chemoselectivity remained (see potential byproducts **B** – **F** in Figure 6B). Therefore, an optimization study was carried out with Boc-Trp-OMe and *o*-iodoaniline as an indole cation equivalent (Table 1). At the outset, our concerns about selective access to **53** were well-founded since several oxidants screened led to either no observed product or trace quantities along with numerous byproducts and polymeric material. Fortunately, hypervalent iodine (III) acted as a competent oxidant for this transformation, with Koser's reagent (PhI(OH)OTs) providing a local maximum of efficiency (Table 1, Entries 2–4).

A number of iodine (III)-reagents and reaction conditions failed to improve the yield and conversion to **53** (no recovered starting material). Returning to our initial finding in Scheme 4, a number of different halogenating agents were evaluated (Entries 5–12). To our delight, succinimide-based halogenating agents all delivered **53** with varying amounts of recovered starting material. NIS was found to be optimal in terms of conversion, isolated yield, diastereoselectivity and scalability. If triethylamine is used, the reaction requires *ca.* 3 equivalents of NIS (Entries 8–9), whereas in the absence of base only 1.1–1.5 equivalents are necessary (Entries 12 and 16). Remarkably, much greater efficiency and diastereoselectivity are obtained in the absence of any amine base, as a result of the lower temperature required for the reaction to occur. This was supported by low temperature quenching experiments, as well as by a slight decrease in diastereoselectivity at higher temperatures (Entry 13). This fact was confirmed by directly injecting an NIS solution at low temperature to a solution of *o*-iodoaniline and tryptamine while acquiring ^{1}H-NMR data (see Supporting Information for details). All of the data indicates rapid reaction at low temperature only in the absence of base.

Next, a solvent screen revealed that DCM and THF were not competent whereas $EtNO_2$ and MeCN were preferable (Entries 15–18). Finally, the addition of MeOH as cosolvent in a ratio of 20:1 MeCN:MeOH was found to provide the optimal efficiency, affording the product in 79% yield on gram scale (Entry 21). While the minor diastereomer could be detected in minute quantities by crude ^{1}H-NMR (*ca.* 50:1), removal of this contaminant by column chromatography was simple. No product was observed when NCS was substituted for NIS under either the optimized conditions (Entry 21 vs 22, quenched at −45 °C) or at a higher temperature experiment (Entry 13 vs. 14, quenched after 10 min.). The exact role of MeOH is not entirely clear; however, its addition does increase solubility of the reactants at low temperature. The divergence between NIS and NCS (summarized in Scheme 5), and the role that the oxidant was playing, required further studies varying the substrates and the order of addition in an attempt to uncover the mechanistic basis for the differences in yield and diastereoselectivity.

Mechanistic Considerations

The following sections present experimental studies to probe the site of oxidation during direct coupling, explain the observed diastereoselectivity, and understand the nature of the active species. It is clear that either initial oxidation of aniline or tryptamine coupling partners can be implicated in the first step of this oxidative coupling reaction, as depicted in Figure 7.

Depending on the substrate to be oxidized, several mechanistic pathways can be envisaged and may be classified into two general categories: either initial indole oxidation (Paths A–D) or initial aniline oxidation (Paths E–H). This seemingly simple indole quaternization reaction is mechanistically intriguing and surprisingly complex.

Nature and identity of the oxidized component

If initial indole oxidation were to occur, a structure such as **54** (Figure 7) would be formed; direct interrogation of such an intermediate with aniline was therefore pursued. Specifically, the chlorinated version of **54** (X = Cl) was chosen since it is likely to be more stable (and characterizable) than the corresponding bromo and iodo analogs. This species was generated from **33** using NCS in the presence of Et_3N (Scheme 6).

Addition of aniline to **50** afforded **62** in 28% isolated yield along with unidentified tryptamine byproducts. However, addition of *ortho*- or *para*-iodoaniline did not yield coupled product, rather the chloroindolenine **50** and iodoaniline remained unreactive even after a number of hours at room temperature. Apparently, the mildly electron withdrawing iodine substituent is sufficient to inhibit this pathway. In contrast, the addition of NCS to a mixture of tryptamine **33** and *p*-iodoaniline at 0 °C did provide the pyrroloindoline **63** in 27% yield, along with 47% unreacted starting material. The failure of *ortho*- or *para*-iodoaniline to engage the chloroindolenine **50** argues strongly against a pathway for the oxidative coupling reaction that proceeds via such an intermediate with NCS as an oxidant (i.e. Paths A–E, Figure 7). Furthermore, based on these results, it is unlikely that the indolenine **59** (Path F, Figure 7) could act as a competent electrophile at C2 or C3 for an iodoaniline.

Interestingly, the addition of NIS to a mixture of the tryptamine **33** and *p*-iodoaniline only afforded minute quantities of the product **63** (3%). Instead, the double addition isomer **64** was isolated as the major product (33%), as verified by X-ray crystallography, along with 52% recovered starting material, **33**. This curious result can be explained by invoking a pathway originating with aniline oxidation and subsequent reaction of this oxidized species (*vide infra*) with tryptamine **33** to afford the open-chain tautomeric indolenine of **63**. This indolenine can then engage in one of two pathways: (1) ring closure to afford the minor product **63** or (2) a pathway leading to the major product **64** involving first [1,5] sigmatropic rearrangement of the aniline to the indole C2 position. After tautomerization to the 1H indole and reaction with a second equivalent of the oxidized *p*-iodoaniline species, the product **64** would be delivered. The addition of *p*-iodoaniline (unactivated) to the ring-chain tautomeric indolenine of **63**, while conceivable, is unlikely due to *p*-iodoaniline's inability to react with the chloroindolenine **54**. It is possible that the difference in product distribution between the NCS and NIS conditions results from the generation of a more reactive oxidized aniline species, derived from NIS as compared to NCS. This study supports the viability of compounds of the type **60** and **61**, which most likely arise from initial oxidation of the aniline (Paths G and H). Initial oxidation of the tryptamine (Paths A–D) or a route proceeding via nucleophilic addition of an aniline to an indolenine (Paths E and F) cannot easily account for these observations.

Despite the fact that **50** exists predominantly as the open-chain tautomeric chloroindolenine, the reaction may proceed via the corresponding pyrroloindoline[32] (Path A, Figure 7). Thus, the following experiment was devised. When the 3-bromopyrroloindoline, **66**, was treated with aniline, production of **67** was only observed at elevated temperature and in the presence of base (Scheme 7). Structure confirmation was then secured by Boc-deprotection to the oxidative coupling product, **62**.

While the presence of the Boc functionality prevents a direct comparison of **66** to **55**, the harsh conditions required for this transformation suggest that a nucleophilic displacement of a 3-halopyrroloindoline is not operative in the oxidative coupling reaction. In the context of an

unprotected 3-halopyrroloindoline, **55**, as would be the case in the indole-aniline coupling (Path A, Figure 7), failure to generate the C-N bond is to be expected. Based on the studies of Witkop, [33] an aniline or anilide should react more readily as a base towards the indoline N-H, catalyzing the 3-halopyrroloindoline's decomposition. Indeed, treatment of the methylcarbamate of tryptamine, **33**, with *'*BuOCl, NCS, NBS, or NIS, followed by reaction with *o*-iodoaniline or its sodium salt, did not result in any product formation. This further reinforces the notion that product formation via such a halogenated tryptamine species (**54** or **55**, Figure 7) does not occur in the case of *o*-iodoaniline under these reaction conditions.

Since product formation is not observed for the reaction of **68** (Table 2, X = Cl) with *ortho*- or *para*-iodoaniline, the effect of order of addition was analyzed for the reaction of aniline with either pregenerated **68** or **52**/NXS. If the diastereoselectivity observed for the chlorination step is conserved in that of the product, that would suggest the intermediacy of a haloindolenine **68** when the oxidant is added last. Thus, Boc-Trp-OMe **52**, was reacted with NCS at low temperature and also at room temperature to form two different ratios of chloroindolenines: 1.4:1 and 1.0:1, respectively (Entries 1–2). When aniline was added to the two reaction mixtures at room temperature, the product was obtained with different degrees of diastereoselectivity (7.9:1 and 5.1:1, respectively), albeit in only 23% and 34% yields, respectively. It was found that monitoring the reaction by ^{1}H-NMR confirmed that the minor diastereomer of **68** (Entry 1) reacted faster than the major diastereomer to provide **69**, whereas the remaining diastereomer was largely unreactive and decomposed upon aqueous workup.

We next made a direct comparison to these first two experiments (Entries 1–2) by reversing the order of addition, such that the NCS was added last: either at low temperature or room temperature (Entries 3–4). Interestingly, the diastereoselectivity at low temperature was essentially the same for both of the orders of addition (Entry 1 vs. 3), while the diastereoselectivities were different for the reactions conducted at room temperature (Entry 2 vs. 4, 5.1:1 and 7.6:1 respectively, the diastereomeric ratio for the indolenines **68** would be presumed to be 1.0:1 in both cases). *Therefore, a different or additional mechanism may be operative when the order of addition is changed*; although with yields ranging from 10–34%, it is difficult to pinpoint the origin of these effects. Importantly, Entry 5 demonstrates that the diastereoselectivity and yield of this transformation are dependent on the oxidant employed even when the reactions are conducted at the same temperature. Initial treatment of **52** with NIS followed by addition of aniline did not lead to formation of the desired product (Entry 6). This difference in reactivity between NCS and NBS is suggestive of either (1) the involvement of the halogen in the stereochemistry-determining step or (2) a change in the relative rates of two pathways. For either scenario, at least two mechanisms must be active for this substrate pair (**60** & **61**, Figure 7). In light of previous discussions, the simplest interpretation of this study is that the alternative mechanism is one involving attack of tryptamine onto an oxidized aniline species.

Rationalization of the observed diastereoselectivity

The indole-aniline coupling reaction proceeds with strong and often exclusive *exo* selectivity.[xxxiv] It is difficult to offer direct experimental evidence that can provide a concrete rationalization for this preference. However, the reaction of tryptophan with a number of electrophiles has shown similar stereochemical outcomes,[xxxv] including *N*-phenylselenylphthalimide (*N*-PSP),[xxxvi] NBS,[xxxvii] and DMDO[4j–l] (Figure 8). Figure 8A shows a mechanistic proposal from Danishefsky[xxxviiia] and Crich[38b] to rationalize the observed diastereoselectivity for the phenylselenocyclization of tryptophans. Danishefsky proposes the reversible formation of a selenonium species with the indole 2,3-π bond, followed by an irreversible ring closure to afford a predominance of the kinetically favored *exo* diastereomer. The origin of this preference is attributed to the greater ease of cyclization of the

pre-*exo* ensemble (**72**) relative to that of the pre-*endo* ensemble (**71**). Specifically, there may be a steric clash between the carbomethoxy functionality and the indole nucleus in the pre-*endo* ensemble (Figure 8A, 71) that is absent from the pre-*exo* ensemble, **72**. Similarly, Crich posits that reversible electrophilic attack by *N*-PSP leads to an early transition state, followed by a rate-limiting ring closure. Crich attributes the preferential formation of the *exo*-diastereomer to greater torsional strain in the transition state for the *endo* diastereomer in the formation of the pyrrolidine ring.xxxix

Recently, de Lera has put forth an alternate mechanism for both aminoselenation and bromination chemistry based on DFT calculations (Figure 8B).[37] Instead of a thermodynamic preference for the intermediate leading to the *exo* diastereomer (with equilibration to starting material), de Lera proposes a higher energy transition state in the rate limiting step for formation of the *endo* diastereomer. The *endo* isomer arises from activation of the indole 2,3-π bond by the electrophile to form diastereomeric benzylic carbocations (*exo* diastereomer, **74**, Figure 8B), then formation of an azetidine, **75**, and finally concerted rearrangement to the pyrroloindoline product, **76**. The computed energies for the diastereomeric transition states predicts that the *exo* product should predominate for both bromination and selenation.

For the case of the DMDO oxidation of tryptophan, an entirely different hypothesis has been suggested (Figure 8C). It is believed that DMDO reacts irreversibly with tryptophans to afford diastereomeric mixtures of the products (**78** and **80**). The diastereoselectivity is largely dependent upon the substitution at the carboxylic acid and amine functionalities, which supports the hypothesis that a steric interaction determines the stereochemical outcome. Unlike the selenonium and bromonium chemistry, DMDO is known to give 1:1 mixtures of diastereomers for substrates without strong steric demands.xl

Moderate *exo*-selectivity (**69**) was observed for oxidation of tryptophan with NCS followed by addition of aniline possibly producing an intermediate such as **81** (Figure 8D). The generally poor ratio for *exo*-selectivity may be attributed to the ~1:1 d.r. for the chlorination and the irreversibility of the indole oxidation with NCS. Considering the high *exo* selectivity and yield observed for the oxidative cyclization of *o*-iodoaniline with NIS (Figure 8E) for substrates without sterically demanding substituents (e.g. Boc-Trp-OMe, **52**),xli a similar mechanism to bromination and selenation seems more likely (i.e. reversible formation of diastereomeric intermediates followed by preferential formation of the *exo* product). *In summary, to rationalize the high degree of diastereoselectivity for the C3-quaternization of Boc-Trp-OMe, a reversible process must be invoked.*

A difference in rate among diastereomeric transition states, leading to selective formation of the *exo* diastereomers **53** is reliant upon the reversible formation of intermediates **82** or **83** (similar to **60** or **61** Paths G or H, Figure 7). Reversible bonding interactions have been invoked for the case of phenylnitrenium ions interacting with electron rich arenes, lending credence to this possibility.xlii While the nature of a bonding interaction for indole has not been determined, a σ- or π-complex may be possible. For simplicity the σ-complexes are shown in Figure 7, but π-complexes can also be envisioned. If an equilibrium with reversible bond formation of this type exists, then a subsequent rate limiting ring closure may lead to a predominance of the kinetically favored product – the *exo* isomer. This explanation can also account for the observed differences in diastereomeric ratio for NCS and NBS (Table 2). For Paths G & H in Figure 7, the halogen remains associated with the complex, stabilizing the cationic charge. The higher atomic number halogens are expected to provide a greater extent of stabilization for either a radical or ionic pathway. This greater stabilization should lead to higher levels of stereoinduction. If π-complex formation occurs, a more favorable bonding interaction would again be predicted for larger halogens, in turn, leading to higher degrees of diastereoselectivity.

What is the nature of the electrophilic aniline species?

For pathways involving an *N*-haloaniline, the character and extent of bonding between nitrogen and halogen could take a number of forms and may differ between halogens (Figure 9). Gassman's studies on the reactivity of *N*-chloroanilines suggest a transient nitrenium and chloride ion pair[xliii] and it was believed that the introduction of a tryptamine nucleophile to an *N*-haloaniline would also proceed via this mechanism. While not definitive proof, a number of experiments are consistent with this conclusion. First, the photolysis of *o*-iodophenylazide (conditions known to generate the nitrene **87** or in acidic solution nitrenium **86**)[xliv] results in some product formation (Scheme 8). The low yield of this process can be attributed to the instability of the product and of this particular nitrene[xlv] under the reaction conditions. Indeed, resubjection of the product to the reaction conditions led to substantial bond homolysis. However, the poor efficiency of **33** to **90** may also reflect that a nitrenium ion is not a discrete intermediate in the oxidative coupling reaction and *N*-haloanilines may require assistance from the tryptamine to assume this active form. The low temperature at which *N*-chloroanilines react is also suggestive of the involvement of tryptamine promoted *N*-haloaniline decomposition.[43]

An anilino radical cation, **85**, is not believed to be a discrete intermediate. The addition of agents known to inhibit radical reactions (BHT and O_2), including the polymerization of aniline,[xlvi] did not affect the efficiency of this reaction, suggesting that species such as **85** (Figure 9) are not long lived if involved at all. Also, irradiation with a sunlamp – conditions anticipated to promote a radical pathway[xlvii] – did not result in product formation, but instead produced large amounts of insoluble material. The possibility that the *N*-haloaniline reacts directly via an S_N2-like mechanism to form an intermediate indolenine, **58** (Path D, Figure 7), which proceeds to the product, cannot be entirely ruled out.[xlviii] However, a reaction of this type most likely cannot be considered a reversible process and therefore cannot account for the high levels of stereoinduction.[xlix]

The failure of many anilines to undergo this transformation and the rapid reaction times have largely impeded other kinetic analyses. A detailed kinetic analysis of this reaction and related transformations will be the subject of a separate disclosure.[l] Depending on the electronic character of the aniline and nature of the oxidant, initial oxidation of the aniline or tryptamine or both may be involved in product formation.

Mechanism Summary

The oxidation of tryptamine with NCS, followed by the addition of aniline to generate a product of the type **94**, provides data supporting the addition of aniline to C2 (**93**) and subsequent migration (Figure 10A). The diastereoselectivities observed for the oxidative coupling of aniline to tryptophan substrates, requires energetically different diastereomeric transition states resulting in an enhanced ratio of exo products.

For the relevant and special case of o-iodoaniline and a tryptamine reacting with NIS (Figure 10B), we believe a reactive phenylnitrenium and iodide pair, *86*, (Figure 9, formed from the reaction of N-iodoaniline with tryptamine) reacts reversibly with tryptamines to form an intermediate, *60 or 61* (Figure 7), that proceeds to a quaternized pyrroloindoline product, *95*. This conclusion is supported by order of addition experiments, dependence of product distribution and diastereoselectivity on: reagent, temperature and substrate, generation and reactivity of possible intermediates, and literature precedence. This mechanism can account for all of the experimental observations to date. Furthermore, the trends regarding the substrate scope are consistent with this mechanistic picture.

Scope and limitations of the direct indole-aniline coupling

Analysis of the scope of the reaction revealed distinct trends for substrate tolerance (Figure 11). Consistent with mechanistic considerations in the previous section and consistent with the studies of Gassman and co-workers,[43] electron deficient anilines were found to be excellent substrates (**97**, **99**). Although admittedly circumstantial, this point provides further evidence for a pathway proceeding via an electrophilic phenylnitrenium ion,[li] rather than nucleophilic addition of an aniline to an oxidized tryptamine. If the latter were the case, electron rich anilines would be better participants for N-C bond formation (**100** is not formed with NIS). The presence of an *ortho* substituent is required with only the exception of the electron deficient substrate, *para*-nitroaniline, which affords useful yields under these conditions[lii] (*p*-CF$_3$, *p*-I, *p*-Cl, *p*-H, *p*-Ph, *p*-Me, *p*-OMe, etc. afforded only trace product). Electron deficient tryptamines were more successful than electron rich tryptamines (products **98**, **101**), but both electronic characters were tolerated. Tryptophan and even dipeptide derivatives participated well in the reaction, providing excellent diastereoselectivities (>20:1) of **53** and **102a** (for **102b–c**, see Scheme 12).

Total synthesis of psychotrimine

With a method for direct, scalable quaternization of tryptamines with *o*-iodoaniline firmly secured, its application in total synthesis was pursued. Our efforts first focused on the synthesis of psychotrimine, **1**, which had previously been synthesized by Takayama and co-workers. [12d] A short model study was first conducted, in order to determine the best method for the synthesis of the *N*-linked methyltryptamine dimer subunit of psychotrimine, **104** (Scheme 9). Thus, the indole-aniline coupled product, **90**, (obtained from the reaction of **33** and *o*-iodoaniline with NIS in 63% yield) was subjected to Larock indolization to provide the requisite tryptamine dimer **34** in 92% yield.[liii] It is conceivable that this intermediate could lead to psychotrimine, but that would require a laborious installation of a functional handle at C7 of the indoline. Next, conversion of the methyl carbamates to methyl amines provided access to a methyl tryptamine dimer, **104**, which may well be naturally occurring. This constitutional isomer of chimonanthine (Figure 1) has not been isolated to date, but it would not be surprising if non-selective oxidation pathways of methyl tryptamine in Nature would result in the formation of this product analogous to the results from Figure 4.

Our first route to **1** commenced with the methyl carbamate of 7-bromotryptamine, **105** (Scheme 10). Buchwald-Goldberg-Ullmann coupling with the tryptamine, **33**, afforded the dimeric tryptamine **106** in 45% yield. The low yield resulted from a lack of chemoselectivity in the cross-coupling (two indole NH groups present), but this efficiency was significantly greater than with palladium-mediated methods.[liv] Next, *o*-iodoaniline was appended to the more reactive indole delivering **98**, which was then positioned to participate in a Larock indole ring synthesis to afford the trimeric species **107**. The low efficiency of this route to the trimeric structure **107** led to the exploration of a halogen selective Larock route (Scheme 11).

In this sequence, the 7-bromotryptamine methyl carbamate, **105** [lv] was coupled to *o*-iodoaniline using NIS and Et$_3$N to afford adduct **101** in 61–67% yield along with 25–30% recovered starting material. Slightly lower efficiencies were encountered without the use of triethylamine or when MeOH was substituted for Et$_3$N. Next, a Larock indole ring synthesis was performed to provide **109** (85% yield), leaving the bromine handle unscathed. Unfortunately, high palladium loadings (20 mol %) were necessary to prevent starting material decomposition under the harsh reaction conditions. However, even with these high loadings, debromination of the starting material (**101**) or the product (**109**) was not observed. Next, an N-H selective Buchwald-Goldberg-Ullmann coupling cleanly provided the desired product, **107**, in 89% isolated yield. The methyl carbamates of this trimeric species were smoothly converted to the

corresponding methyl amines in the natural product, delivering **1** in 89% yield. A large excess of reagent was used to achieve a shorter reaction time with less decomposition of psychotrimine, **1**.

The rapid and scalable synthesis of psychotrimine, **1**, (4 steps, 41–47% overall from **105**, 2.5 g of **1** prepared) is the result of a retrosynthetic analysis tailored to the exact substrate, rather than by applying a preordained strategy or method to its synthesis. While at its conception the retrosynthesis left questions of feasibility, empirical findings led to the invention of a new method, which, as will be described in the following section, has had further applications beyond psychotrimine, **1**.

Total syntheses of kapakahines B and F

After successfully synthesizing large quantities of psychotrimine, another even more complex venue for oxidative indole-aniline coupling was explored. In addition to the hallmark N1-C3 linkage between indole subunits in psychotrimine, the kapakahines present a *twisted*[lvi] macrocycle, a particularly strained α-carboline ring system, and sensitive imidazolone functionality (Figure 12).[7] Thus, the first retrosynthetic simplification of the kapakahines was removal of this imidazolone. Next in the plan was removal of the alanine-leucine residues along with simplification of the *N*-linked tryptophan to *o*-iodoaniline, thereby giving rise to the tripeptide alkyne **116** and an indole-aniline oxidative coupling product **117**. The α-carboline present in **117** could presumably arise from the direct formation of the six-membered ring, under the standard conditions of aniline-indole coupling (Figure 12).

It was quickly discovered that direct synthesis of the α-carboline ring would not be feasible (Scheme 12A). For dipeptide **118**, the only discernible product observed was the C2 coupled aniline isomer, **119**, which likely arises from the initial oxidative coupling of aniline at indole C3 and subsequent [1,5] shift to the C2 position to give the product **119** after tautomerization. This shift is most likely attributable to the slowed rate of ring-closure for a six-membered ring, relative to that of a five-membered ring. Additionally, the decreased nucleophilicity of the amide in **118**, relative to carbamate functionality is expected to diminish the propensity for cyclization. This slowed rate rendered the major pathway to be a steric decompression via a [1,5] shift of the aniline to the C2 position. Alternative conditions or substrates did not give the desired product.[lvii]

The well-documented challenge[lviii] of forming α-carboline systems such as that found in the kapakahines coupled with our failure to achieve its direct synthesis (Scheme 12A), prompted the design of a radically different approach (Scheme 12B). We reasoned that it might be possible to achieve the conversion of the readily accessible pyrroloindoline architecture (isomer A) into the topologically distinct, yet constitutionally isomeric, α-carboline system (isomer B). Since these two isomers might be in a dynamic equilibrium (favoring isomer A) it would be necessary to achieve an irreversible kinetic trap. While highly speculative, the powerfully simplifying nature of this plan was enticing.

Beginning with dipeptide **120**, the pyrroloindoline was obtained by direct coupling with aniline in the absence of base, which led to an increased rate of reaction (Scheme 11C). This oxidative-coupling tolerates a variety of typical carbamate protecting-groups on the phenylalanine amine (**102a**–**c**) and remains exclusively *exo* selective (**102**). The absence of the *endo* diastereomer by TLC, LC-MS and crude ^{1}H-NMR is consistent with our studies on Boc-Trp-OMe (*vide supra*). In line with previous observations (Scheme 11A), direct formation of the α-carboline was not observed.

In order to investigate isomerization strategies, the Larock coupling partner tripeptide (**116**) was required (Scheme 13). A route to enantiopure alkyne amino-acid (**122**) was therefore

devised. Several methods were available including using Schollköpf's chiral auxiliary[lix–lx] or using an asymmetric catalyst in an alkylation strategy.[lxi] Alternatively, beginning with serine-derived iodoalanine[lxii] (**121**), Knochel's copper/zinc[lxiii] coupling to bromo TES-acetylene[lxiv] provided large amounts of the alkyne amino acid as a single enantiomer.[lxv] The copper/zinc mediated coupling proved to be reliable on large scale if the iodoalanine (**121**) was synthesized and used quickly due to slow decomposition. Methyl ester hydrolysis of the alkyne and peptide coupling to H_2N-Ala-Leu-OBnl[xvi] proceeded with high-efficiency to provide tripeptide **116**.

Larock coupling of **102b** with **116** furnished **123** (Scheme 14), which contains the necessary framework to complete kapakahine F (**2**). Importantly, the use of $Pd(dppf)Cl_2$ led to an increase in reaction time in addition to less depreciation of yield with increasing scale.[53b] Double deprotection of the Cbz and benzyl ester in **123** occurred without event and the macrocyclic peptide coupling was attempted under standard conditions, but isomerization of the pyrroloindoline was not observed. Instead, the structure of the product was firmly established by HMBC correlation to be the pyrroloindoline product, **124**. Alternatively, coupling of tripeptide **126**[lxvii] to the secondary amine **125** provided **127**, which was prepared for a Larock macrocyclization. However, in this critical step the same undesired macrocyclic intermediate, **124**, was obtained. Obtaining this product provided an opportunity to investigate the possibility of achieving an isomerization event, as illustrated in Figure 13.

With a number of relevant substrates in hand, several approaches for the crucial isomerization of a pyrroloindoline to an α-carboline were evaluated (Figure 13): (A) initial isomerization of differentially substituted pyrroloindolines having an *o*-iodoaniline linked at C-3 (**128**), (B) isomerization with an indole at C3 in a macrocyclic context (**131**), and (C) rearrangement analogous to scenario A with aniline functionality and where both nitrogens of tryptophan and phenylalanine are amides (**127**). All three approaches outlined above were attempted to give an α-carboline with or without imidazolone formation. It was believed that formation of an imidazolone could act as a point of irreversibility, such that even if the α-carboline were less favored, kinetic trapping could afford the desired product.

To commence these studies, treatment of the pyrroloindoline, **102a** (Scheme 12), with a variety of acidic conditions (TFA, AcOH, TMSI, SiO_2, etc.) to remove the Boc group and possibly undergo subsequent rearrangement (Figure 13A), caused extensive decomposition accompanied by loss of the newly coupled aniline, analogous to that shown in Scheme 8. Removal of the Cbz group in **102b**, avoiding aryliodide reduction or loss of the aniline altogether, proved fruitless ($NaBH_4$, TMSI, $BF_3 \cdot OEt_2$, $Pd(OAc)_2/Et_3SiH$, etc.). The Fmoc removal proceeded cleanly; however, direct isomerization to the α-carboline with or without concomitant imidazolone formation was not observed ($BF_3 \cdot Et_2O$, $Sc(OTf)_3$, MeOH reflux, etc.). Failure to isomerize these readily obtained intermediates dictated the necessity of a late-stage isomerization strategy (scenario B & C, Figure 13).

Thus, several reactions were attempted to convert the pyrroloindoline, **131**, to the α-carboline, **132** or **133**, (Figure 13B). Thermal, acidic and basic conditions were attempted, as well as the presence of various Lewis acids (ZrF_4, $Zr(CF_3acac)_4$, $ZrCl_4$, ZrO_2, $ZrBr_4$, $Zr(Ot$-Bu$)_4$, SiO_2, $AlMe_3$, $AlCl_3$, $Ti(Oi$-Pr$)_4$, $In(OTf)_3$, $Zn(OTf)_2$, etc.), all to no avail. Attempts to convert the corresponding activated carbonyl of **131** (R = OH, Cl, OCH_2CF_3, OC_6F_5) to **133** by an isomerization and imidazolone trap were also unsuccessful. The final approach to test isomerization, scenario C (Figure 13), was limited by the presence of the aniline functionality, necessitating relatively mild conditions for substrate manipulation due to the lability of this functionality (*vida supra*). It was believed that the aniline may impart a different structural bias than the indole at the C3 position due to steric and electronic factors. Nevertheless, a variety of conditions failed to provide isomerization to **134** or imidazolone formation to **135**.

With this information in hand the approach involving macrocyclization by peptide-coupling (**123**, Scheme 15) was reinvestigated. After extensive experimentation it was found that EDC/ HOAt-mediated macrolactamization *in the absence of base*[lxviii] afforded the desired carboline macrocycle **132** in 64% isolated yield along with 6% of the pyrroloindoline **124** (easily separable by column chromatography).[lxix] The formation of the α-carboline containing macrocycle **132** may proceed through several mechanisms; three of which are discussed here. The first possibility, which is easily ruled out considering the results in Figure 13B, is that the pyrroloindoline containing macrocycle **124** isomerizes to the product **132**. Indeed, resubjection of **124** to the reaction conditions did not afford **132**, establishing that the reaction is under kinetic control.

The second possibility involves amide bond formation with intermediate **137**. Macrocyclization of intermediate **137** may be more favorable than of **138** due to the greater number of degrees of freedom in the absence of the α-carboline. Amide bond formation of intermediate **137** would generate an indolenine (not depicted) that would then be engaged by the phenylalanine amide, rather than the tryptophan amide, providing the α-carboline **132**. For this pathway, it is difficult to rationalize the selectivity observed based on examination of the substrate, as both the tryptophan and phenylalanine amides are sterically and electronically similar. If this pathway does proceed, the preferential formation of a six-membered ring could only be the result of subtle conformational effects. Not surprisingly, such imine intermediates are neither isolated nor observed, as is frequently the case for indolenine species due to their relative instability.

A third mechanistic postulate would involve ring closure of **137** to afford intermediate **138**, which then participates in macrocyclization. This pathway allows for a clear explanation for the observed selectivity via a Curtin-Hammett scenario – an equilibrium between **136** and **138** and rapid amidation of the primary amine **138** over the secondary amine **136** results in a predominance of the desired product. Both the second and third mechanistic pathways rely on the well-documented rate difference for acylation of a primary versus a secondary amine.[lxx]

The preferential formation of the undesired macrocycle **124** using HATU, HOBt, and Hünig's base in DMF (Scheme 14, **123** → **124**) is not surprising in light of literature on amide-bond formation with secondary amines such as proline.[lxxi] Our optimized conditions, avoiding the use of base and using a minimal amount of DMF for solubility, results in a reduced rate of peptide bond formation and is therefore expected to be more discriminating for a primary amine (**137** or **138**).

The exceedingly mild conditions utilized to achieve the topological shift of pyrroloindoline **123** to α-carboline **132** is remarkable given the well-documented stability of pyrroloindolines and their widespread occurrence in nature. As alluded to above, this transform dramatically simplified the structural challenge posed by the kapakahines.

Macrocycle **132** was found to decompose slowly if left at room temperature for extended periods, underscoring the necessity for mild conditions for its production or manipulation. Therefore, once the material was isolated, it was immediately carried forward to the construction of the last ring. The imidazolone formation was all that remained to synthesize kapakahine F, **2**. It was reasoned that once the imidazolone ring was formed and the Boc group removed, the natural product, **2**, should be a stable entity. Hydrolysis of the ester proceeded uneventfully (Scheme 15), but the resulting acid could not be stored for extended periods and was immediately processed. Several different conditions were attempted, (EDC and HOBt, HBTU, HATU, etc.), that were successful at ring-closure with typical conversion of 85–100%. However, 5 – 40% of the uncoupled acid **139** was regenerated after treatment with TFA, which was difficult to separate and detrimental to producing the kapakahines on large scale. Other

conditions to remove the Boc group were attempted (TMSOTf, TBSOTf, AcOH, etc.), however, an unacceptable amount of hydrolysis still occurred. It was found that the presence of trace HOBt or other coupling agents during the Boc removal with TFA was causing an increase in the amount of hydrolyzed product.

After several aqueous washes, and checking the crude intermediate for coupling agents by LC-MS and ^{1}H-NMR, the trace impurities isolated together with **133** still caused unacceptable levels of hydrolysis. The only solution was to exclude nucleophilic peptide-coupling reagents during imidazolone formation. Thus, treatment with oxalyl chloride and triethylamine led to clean conversion to the imidazolone with starting material absent by ^{1}H-NMR and LC-MS (Scheme 16). Concentration of the reaction *in vacuo* to drive off excess oxalyl chloride and several washes with $NaHCO_3$ and NaOH to remove salts gave large quantities of Boc-kapakahine F (**133**). Exposure of Boc-kapakahine F, **133**, to TFA provided kapakahine F, **2**, with excellent efficiency and purity (64% isolated yield, 3 steps, > 1g synthesized) and without imidazolone hydrolysis (**139**). HPLC co-injection of natural and synthetic kapakahine F co-eluted perfectly; however, the kapakahine F ^{1}H-NMR spectra obtained did not precisely match the literature spectra.[lxxii] The conversion of kapakahine F (**2**) to B (**3**) was undertaken to secure our structural assignment. The overall yield of **2** is 13.1% over 12 steps from serine.

This conversion proved uneventful and surprisingly the use of EDC and HOBt followed by Boc deprotection with TFA did not hydrolyze the imidazolone. The basis for the difference in stability between **133** and Boc-**3** remains elusive. A comparison of NMR spectra (^{1}H and ^{13}C) for natural and synthetic **3** as well as HPLC co-injection confirmed the structure of the natural product and proved that **2** was also correctly synthesized.

Preliminary Biological Evaluation

With access to large quantities of these rare natural products (**1**–**3**), biological testing could be undertaken. Synthetic kapakahines B and F did not possess significant cytotoxicity in the NCI 60-cell line. However, kapakahine B had an IC_{50} of 11.7 μM for breast cancer cell line DU4475.[lxxiii] Psychotrimine did show activity in the NCI screen and was submitted to a five-dose GI_{50} study and had a broad spectrum of activity between 1.3 and 40 μM for the 60-cell line[lxxiv] (see Supporting Information for details). In addition to the NCI, large quantities of **1**–**3** have been donated to Bristol-Myers Squibb and samples are freely available from our lab on request.

Conclusion

This full account has traced the inspiration, design, development, mechanistic study, and application of a new reaction for the direct merger of anilines with tryptamines and related species. This oxidative coupling reaction is believed to proceed via a nitrenium ion generated from an aniline followed by nucleophilic capture at C3 of the tryptamine. This powerfully simplifying reaction has enabled the gram-scale synthesis of the three complex alkaloids: psychotrimine and kapakahine F and B. It is worth mentioning that this work culminated from an adherence to a set of guidelines at the outset of the planning stages of this work.[lxxv] Aside from the invention of the direct coupling of anilines to tryptamines, notable aspects of the total syntheses of **1**–**3** include: (1) absence of protecting group chemistry and excellent redox economy in the synthesis of **1**, (2) chemoselective indole arylation using a Buchwald-Goldberg-Ullmann reaction (**109**→**107**), (3) chemoselective Larock indole syntheses in highly complex settings (**98**→**107**, **101**→**109**, **102b**→**123**, **127**→**124**), and (4) a remarkable late-stage architectural shift from a pyrroloindoline to α–carboline ring system (**123**→**132**).[lxxvi]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

i. For numerous examples see: Nicolaou, KC.; Sorensen, EJ. Classics in Total Synthesis. 1. Wiley-VCH; New York: 1996. and Nicolaou, KC.; Snyder, SA. Classics in Total Synthesis II. 1. Wiley-VCH; Weinheim: 2003.

ii. Bonjoch J, Solé D. Chem Rev 2000;100:3455. [PubMed: 11777429]

iii. For reviews see: (a) May JA, Stoltz B. Tetrahedron 2006;62:5262. (b) Steven A, Overman LE. Angew Chem, Int Ed 2007;46:5488. (c) Mulzer J, Gaich T, Siengalewicz P. Angew Chem, Int Ed 2008;47:8170.(d) Kam, TS.; Choo, YM. The Alkaloids. Cordell, GA., editor. Vol. 63. Academic Press; San Diego: 2006. p. 181-337.

iv. Vinblastine: (a) Ishikawa H, Colby DA, Seto S, Va P, Tam A, Kakei H, Rayl TJ, Hwang I, Boger DL. J Am Chem Soc 2009;131:4904. [PubMed: 19292450] (b) Yokoshima S, Ueda T, Kobayashi S, Sato A, Kuboyama T, Tokuyama H, Fukuyama T. J Am Chem Soc 2002;124:2137. [PubMed: 11878966] (c) Mangeney P, Andriamialisoa RZ, Langlois N, Langlois Y, Potier P. J Am Chem Soc 1979;101:2243. (d) Kutney JP, Choi LSL, Nakano J, Tsukamoto H, McHugh M, Boulet CA. Heterocycles 1988;27:1845. (e) Kuehne ME, Matson PA, Bornmann WG. J Org Chem 1991;56:513. (f) Magnus P, Mendoza JS, Stamford A, Ladlow M, Willis P. J Am Chem Soc 1992;114:10232.Asperazine: (g) Govek SP, Overman LE. J Am Chem Soc 2001;123:9468. [PubMed: 11562240] (h) Govek SP, Overman LE. Tetrahedron 2007;63:8499.Quadrigemine C: (i) Lebsack AD, Link JT, Overman LE, Stearns BA. J Am Chem Soc 2002;124:9008. [PubMed: 12148978] Himastatin: (j) Kamenecka TM, Danishefsky SJ. Angew Chem, Int Ed 1998;37:2993. (k) Kamenecka TM, Danishefsky SJ. Angew Chem, Int Ed 1998;37:2995. (l) Kamenecka TM, Danishefsky SJ. Chem Eur J 2001;7:41.Perophoramidine: (m) Fuchs JR, Funk RL. J Am Chem Soc 2004;126:5068. [PubMed: 15099080] Chimonanthine: (n) Hendrickson JB, Göschke R, Rees R. Tetrahedron 1964;20:565. (o) Scott AI, McCapra F, Hall ES. J Am Chem Soc 1964;86:302. (p) Link JT, Overman LE. J Am Chem Soc 1996;118:8166. (q) Movassaghi M, Schmidt MA. Angew Chem, Int Ed 2007;46:3725.Haplophytine: (r) Ueda H, Satoh H, Matsumoto K, Sugimoto K, Fukuyama T, Tokuyama H. Angew Chem, Int Ed 2009;48:7600. (s) Nicolaou KC, Dalby SM, Li S, Suzuki T, Chen DYK. Angew Chem, Int Ed 2009;41:7480.Communesin F: (t) Yang J, Wu H, Shen L, Qin Y. J Am Chem Soc 2007;129:13794. [PubMed: 17956099]

v. (a) Waksman SA, Bugie E. J Bacteriology 1944;48:527. (b) Geiger WB, Conn JE, Waksman SA. J Bacteriology 1944;48:531. (c) McInnes AG, Taylor A, Walter JA. J Am Chem Soc 1976;98:6741. [PubMed: 972228] (d) Brewer D, McInnes AG, Smith DG, Taylor A, Walter JA, Loosli HR, Kis ZL. J Chem Soc, Perkin Trans 1 1978;10:1248. (e) Kikuchi T, Kadota S, Nakamura K, Nishi A, Taga T, Kaji T, Osaki K, Tubaki K. Chem Pharm Bull 1982;30:3846. (f) Kung AL, et al. Cancer Cell 2004;6:33. [PubMed: 15261140]

vi. For the isolation of alkaloid **13**, see the following conference report: Masashi H, Mitsuyoshi S, Hiroshi M, Yuji S. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1994;36:557.

vii. (a) Nakao Y, Yeung BKS, Yoshida WY, Scheuer PJ, Kelly-Borges M. J Am Chem Soc 1995;117:8271. (b) Yeung BKS, Nakao Y, Kinnel RB, Carney JR, Yoshida WY, Scheuer PJ, Kelly-Borges M. J Org Chem 1996;61:7168. [PubMed: 11667621] (c) Nakao Y, Kuo J, Yoshida WY, Kelly M, Scheuer PJ. Org Lett 2003;5:1387. [PubMed: 12713280]

viii. a) Li GY, Li BG, Yang T, Yan JF, Liu GY, Zhang GL. J Nat Prod 2006;69:1374. [PubMed: 16989540] b) Ding G, Jiang L, Guo L, Chen X, Zhang H, Che Y. J Nat Prod 2008;71:1861.

ix. Takayama H, Mori I, Kitajima M, Aimi N, Lajis NH. Org Lett 2004;6:2945. [PubMed: 15330654]

x. The relative configuration of psychotetramine is not known, see: Mori, I. M S Thesis. Chiba University; Japan: 2004.

xi. Yohei, M. Ph D Thesis. Chiba University; Japan: 2008.

xii. (a) Marsden SP, Watson EL, Raw SA. Org Lett 2008;10:2905. [PubMed: 18533669] (b) Toumi M, Couty F, Marrot J, Evano G. Org Lett 2008;10:5027. [PubMed: 18847212] (c) Espejo VR, Rainier JD. J Am Chem Soc 2008;130:12894. [PubMed: 18774822] For a 16 linear step synthesis of **1** (13.2% overall yield), see: (d) Matsuda Y, Kitajima M, Takayama H. Org Lett 2008;10:125. [PubMed: 18069843] (e) Takahashi N, Ito T, Matsuda Y, Kogure N, Kitajima M, Takayama H. Chem Commun 2010;46:2501. (f) Beaumont S, Pons V, Retailleau P, Dodd RH, Dauban P. Angew Chem Int Ed 2010;49:1634.

xiii. (a) Newhouse T, Baran PS. J Am Chem Soc 2008;130:10886. [PubMed: 18656919] (b) Newhouse T, Lewis CA, Baran PS. J Am Chem Soc 2009;131:6360. [PubMed: 19374357]

xiv. Dimerization at carbon has extensive precedent, for example: (a) Cheek GT, Nelson RF. J Org Chem 1978;43:1230. (b) Balogh-Hergovich E, Speier G. J Chem Soc Perkin Trans 1 1986:2305. (c) Shen X, Lind J, Eriksen TE, Merenyi G. J Chem Soc Perkin Trans 2 1990:597. (d) Dryhurst G. Chem Rev 1990;90:795. (e) Verotta L, Orsini F, Sbacchi M, Scheildler MA, Amador TA, Elisabetsky E. Bioorg Med Chem 2002;10:2133. [PubMed: 11983509] (f) Ishikawa H, Takayama H, Aimi N. Tetrahedron Lett 2002;43:5637. (g) Ishikawa H, Kitajima M, Takayama H. Heterocycles 2004;63:2597. (h) Kim J, Ashenhurst JA, Movassaghi M. Science 2009;324:238. and references cited therein. [PubMed: 19359584]

xv. (a) Baran PS, Shenvi RA, Mitsos CA. Angew Chem, Int Ed 2005;44:3714. (b) Baran PS, Shenvi RA. J Am Chem Soc 2006;128:14028. [PubMed: 17061876]

xvi. (a) Ma B, Litvinov DN, He L, Banerjee B, Castle SL. Angew Chem, Int Ed 2009;121:6220. (b) Feng Y, Chen G. Angew Chem, Int Ed 2010;49:958. (c) Hu W, Zhang F, Xu Z, Liu Q, Cui Y, Jia Y. Org Lett 2010;12:956. [PubMed: 20108939]

xvii. The perturbation of pH in a restricted environment, such as an enzyme pocket, is well-known; however, the necessity for strong base reduces the likelihood of such a transformation.

xviii. (a) Somei M. Adv Het Chem 2002;82:101. (b) Somei M. Heterocycles 1999;50:1157.

xix. Somei has reported a 1% yield for N1-C3 bond formation when N-hydroxy melatonin and indole (10 equiv) were treated with MsCl: Hayashi T, Peng W, Nakai Y-y, Yamada K, Somei M. Heterocycles 2002;57:421.

xx. (a) Adam, W.; Deutsche, F. Peroxide Chemistry: Mechanistic and Preparative Aspects of Oxygen Transfer. Wiley-VCH; DFG, Weinheim: 2000. p. 542For the use of cobalt (II) in a related transformation see: (b) Nishinaga A. Chem Lett 1975:273. (c) Mori K, Goto M, Sakai T. Chem Pharm Bull 1985;33:4167.

xxi. For a related $CuCl_2$ chlorination, see: Baloghhergovich E, Speier G. J Chem Soc, Perkin Trans 1 1986:2305.

xxii. Movassaghi M, Schmidt MA, Ashenhurst JA. Org Lett 2008;10:4009. [PubMed: 18722452]

xxiii. Richter JM, Ishihara Y, Masuda T, Whitefield BW, Llamas T, Pohjakallio A, Baran PS. J Am Chem Soc 2008;130:17938. [PubMed: 19035635]

xxiv. (a) Hugel G, Royer D, Sigaut F, Lévy J. J Org Chem 1991;56:4631. (b) Güller R, Borschberg HJ. Tetrahedron Lett 1994;35:865.

xxv. Nakagawa M, Okajima H, Hino T. J Am Chem Soc 1977;99:4424. [PubMed: 864120]

xxvi. (a) Moriarty RM, Vaid RK, Koser GF. Synlett 1990:365. (b) Koser GF. Aldrichimica Acta 2001;34:89.

xxvii. Antilla JC, Klapars A, Buchwald SL. J Am Chem Soc 2002;124:11684. [PubMed: 12296734]

xxviii. Burns NZ, Baran PS, Hoffmann RW. Angew Chem, Int Ed 2009;48:2854.

xxix. For introduction of imidazole nucleophiles to haloindolenines, see: (a)Renfroe, H. B. 3-Substituted-2-(Heteroaryl) Indoles. US Patent4,511,573Apr161985Anilines: (b) Bergman J, Engqvist R, Stålhandske C, Wallberg H. Tetrahedron 2003;59:1033.Imidazoles: (c) He L, Yang L,

Castle SL. Org Lett 2006;8:1165. [PubMed: 16524294] (d) Ma B, Banerjee B, Litvinov DN, He L, Castle SL. J Am Chem Soc 2010;132:1159. [PubMed: 20038144]

xxx. Sheppeckll JE, Kar H, Hong H. Tetrahedron Lett 2000;41:5329.

xxxi. For recent reviews on protecting group free synthesis, see: (a) Hoffmann RW. Synthesis 2006:3531. (b) Young IS, Baran PS. Nat Chem 2009;1:193.

xxxii. Species **50** was characterized by conducting the reaction in deuterated solvent (^{1}H, ^{13}C, and HSQC NMR experiments support this structural assignment).

xxxiii. Ohno M, Spande T, Witkop B. J Am Chem Soc 1968;90:6521. [PubMed: 5682451]

xxxiv. See Figure 11 for excellent diastereoselectivities in the oxidative coupling reaction.

xxxv. In the case of acid-mediated ring closure, the more stable *endo* diastereomer is obtained due to the reversibility of product formation. See reference [38b] for further explanation.

xxxvi. Marsden SP, Depew KM, Danishefsky SJ. J Am Chem Soc 1994;116:11143.

xxxvii. López CS, Pérez-Balado C, Rodríguez-Graña P, de Lera ÁR. Org Lett 2008;10:77. [PubMed: 18069844]

xxxviii. (a) Depew KM, Marsden SP, Zatorska D, Zatorski A, Bornmann WG, Danishefsky SJ. J Am Chem Soc 1999;121:11953. (b) Crich D, Huang X. J Org Chem 1999;64:7218.

xxxix. The postulated difference between torsional strains of the transition states, as compared to that of the products, is suggested to arise from differing hybridization of the carbamate nitrogen lone pair. See reference [38b] for further discussion.

xl. (a) Kawahara M, Nishida A, Nakagawa M. Org Lett 2000;2:675. [PubMed: 10814407] (b) May JP, Fournier P, Pellielli J, Patrick BO, Perrin DM. J Org Chem 2005;70:8424. [PubMed: 16209587] (c) May JP, Patrick BO, Perrin DM. Synlett 2006:3403. (d) González-Vera JA, García-López MT, Herranz R. Tetrahedron 2007;63:9229.

xli. It is also instructive to compare the high diastereoselectivity in production of **102a–c** with the poor selectivity for formation of compound 8 in reference [40c].

xlii. For reversible interactions of phenyl nitreniums with arenes, see: (a) Robbins RJ, Laman DM, Falvey DE. J Am Chem Soc 1996;118:8127. (b) Kung AC, Falvey DE. J Org Chem 2005;70:3127. [PubMed: 15822974] (c) Chiapperino D, Mcllroy S, Falvey DE. J Am Chem Soc 2002;124:3567. [PubMed: 11929245] For recent studies on reversible reactions of electrophiles with olefins, see: (d) Denmark SE, Collins WR, Cullen MD. J Am Chem Soc 2009;131:3490. [PubMed: 19227982] (e) Denmark SE, Burk MT, Hoover AJ. J Am Chem Soc 2010;132:1232. [PubMed: 20058922]

xliii. (a) Gassman PG, Campbell GA. J Am Chem Soc 1971;93:2567. (b) Gassman PG, Campbell GA, Frederick RC. J Am Chem Soc 1972;94:3884. (c) Gassman PG, Campbell GA. J Am Chem Soc 1972;94:3891.

xliv. (a) Leyva E, Platz MS, Persy G, Wirz J. J Am Chem Soc 1986;108:3783. (b) McClelland RA, Kahley MJ, Davidse PA, Hadzialic G. J Am Chem Soc 1996;118:4794.

xlv. Watt DS, Kawada K, Leyva E, Platz MS. Tetrahedron Lett 1989;30:899.

xlvi. (a) Ding Y, Padias AB, Hall HK Jr. J Polymer Sci: Part A: Polymer Chemistry 1999;37:2569. (b) Wojciechowski PM, Zierkiewicz W, Michalska D, Hobza P. J Chem Phys 2003;118:10900. (c) Kato K, Yamanouchi K. Chemical Physics Letters 2004;397:237. (d) Sapurina I, Stejskal J. Polym Int 2008;57:1295.

xlvii. Tanner DD. J Am Chem Soc 1964;86:4674.

xlviii. For N-C bond formation that follows second order kinetics (not necessarily S_N2) between arenes and activated esters of N-phenylhydroxylamine, see: (a) Shudo K, Ohta T, Okamoto T. J Am Chem Soc 1981;103:645. (b) Hamel P, Girard Y, Atkinson JG. J Chem Soc, Chem Commun 1989:63. (c) Novak M, Martin KA, Heinrich JL. J Org Chem 1989;54:5430. (d) Helmick JS, Martin KA, Heinrich JL, Novak M. J Am Chem Soc 1991;113:3459. (e) Novak M, Rangappa KS, Manitsas RK. J Org Chem 1993;58:7813.

xlix. While a reversible π-stacking interaction could be invoked, it is difficult to envision a stereochemical preference for the *exo* diastereomer in this scenario in light of the known thermodynamic bias for the *endo* diastereomer: Crich D, Banerjee A. Acc Chem Res 2007;40:151. [PubMed: 17309195] Qualitatively, a solution of *o*-iodoaniline and **33** led to a yellow solution (both materials are initially white crystalline solids). Unfortunately, UV-vis and ^{1}H or ^{13}C-NMR experiments did not allow observation of changes indicative of π-stacking.

l. (a) Mathew JS, Klussmann M, Iwamura H, Valera F, Futan A, Emanuelsson EAC, Blackmond DG. J Org Chem 2006;71:4711. [PubMed: 16776495] (b) Blackmond DG. Angew Chem Int Ed 2005;44:4302.

li. Takeuchi H, Takano K. J Chem Soc, Chem Commun 1983:447.

lii. The increased yield for *para*-iodoaniline to afford **63** (27%) and 47% recovered **33** with NCS (unoptimized) suggests substrates can be optimized when standard conditions fail (Scheme 6).

liii. (a) Larock RC, Yum EK, Refvik MD. J Org Chem 1998;63:7652. (b) Ujjainwalla F, Warner D. Tetrahedron Lett 1998;39:5355. (c) Larock RC, Yum EK. J Am Chem Soc 1991;113:6689.

liv. (a) Wolfe JP, Tomori H, Sadighi JP, Yin J, Buchwald SL. J Org Chem 2000;65:1158. [PubMed: 10814067] (b) Harris MC, Buchwald SL. J Org Chem 2000;65:5327. [PubMed: 10993362] (c) Altman RA, Anderson KW, Buchwald SL. J Org Chem 2008;73:5167. [PubMed: 18543973] (d) Coste A, Toumi M, Wright K, Razafimahaléo V, Couty F, Marrot J, Evano G. Org Lett 2008;10:3841. [PubMed: 18681449]

lv. The methyl carbamate was available in quantitative yield from the commercial 7-bromotryptamine, whose preparation can be found in reference [13a]. An alternative preparation may be found in the Supporting Information.

lvi. Kapakahi is the Hawaiian word for "twisted."

lvii. Varying the substrate or oxidant led to unproductive oxidation, double addition or no reaction at all.

lviii. Chaetominine isolation (a) Jiao RH, Xu S, Liu JY, Ge HM, Ding H, Xu C, Zhu HL, Tan RX. Org Lett 2006;8:5709. [PubMed: 17134253] Synthesis of chaetominine (b) Snider BB, Wu X. Org Lett 2007;9:4913. [PubMed: 17944481] (c) Malgesini B, Forte B, Toumi M, Couty F, Marrot J, Evano G. Org Lett 2008;10:5027. [PubMed: 18847212] (d) Borghi D, Quartieri F, Gennari C, Papeo G. Chem Eur J 2009;15:7922. (e) Coste A, Karthikeyan G, Couty F, Evano G. Synthesis 2009;17:2927.

lix. Schöllkopf U, Groth U, Deng C. Angew Chem Int Ed Engl 1981;20:798–799.

lx. (a) Ma J, Yin W, Zhou H, Cook JM. Org Lett 2007;9:3491. [PubMed: 17685530] (b) Zhou H, Liao X, Yin W, Ma J, Cook JM. J Org Chem 2006;71:251. [PubMed: 16388644] (c) Yu J, Wearing XZ, Cook JM. J Org Chem 2005;70:3963. [PubMed: 15876085] (d) Zhou H, Liao K, Cook JM. Org Lett 2004;6:249. [PubMed: 14723540] (e) Liu X, Deschamp JR, Cook JR. Org Lett 2002;4:3339. [PubMed: 12323013] (f) Ma C, Liu X, Li X, Flippen-Anderson J, Yu S, Cook JM. J Org Chem 2001;55:4525. [PubMed: 11421771]

lxi. Castle SL, Srikanth GSC. Org Lett 2003;5:3611. [PubMed: 14507185]

lxii. Trost BM, Rudd MT. Org Lett 2003;5:4599. [PubMed: 14627393]

lxiii. Yeh MCP, Knochel P. Tetrahedron Lett 1989;30:4799.

lxiv. Nie X, Wang G. J Org Chem 2006;71:4734. [PubMed: 16776497]

lxv. Jsselstijn MI, Kaiser J, van Delft FL, Schoemaker HE, Rutjes FPJT. Amino Acids 2003;24:263. [PubMed: 12707807]

lxvi. Boggs NT, Bruton HD, Craig DH, Helpern JA, Marsh HC, Pegram MD, Vandenbergh DJ, Koehler KA, Hiskey RG. J Org Chem 1982;47:1812.

lxvii. Garfunkle J, Kimball FS, Trzupek JD, Takizawa S, Shimamura H, Tomishima M, Boger DL. J Am Chem Soc 2009;131:16036. [PubMed: 19839632]

lxviii. Although no base is added, either DMF or trace dimethylamine may act as a base in this peptide coupling reaction.

lxix. Products **124** and **132**had R_f's of 0.58 and 0.43 respectively (4:1 EtOAc:hexanes).

lxx. Bodanszky, M.; Bodanszky, A. The Practice of Peptide Synthesis. Springer-Verlag; Berlin: 1993.

lxxi. Carpino LA, El-Faham A. J Org Chem 1994;59:695.

lxxii. For a comparison of synthetic kapakahine F (**2**) ^{1}H-NMR to the natural source, please see reference [13b]. For HMQC, HMBC and ROESY NMR data for kapakahine F (**2**), please see the Supporting Information.

lxxiii. Assays performed by Bristol-Myers Squibb.

lxxiv. Assays performed by the NCI.

lxxv. (a) Baran PS, Maimone TJ, Richter JM. Nature 2007;446:404. [PubMed: 17377577] (b) Shenvi RA, O'Malley DP, Baran PS. Acc Chem Res 2009;42:530. [PubMed: 19182997] (c) Hendrickson JB. J Am Chem Soc 1975;97:5784.

lxxvi. During the review of this manuscript, a synthesis of kapakahine F was reported that proceeded in 19 linear steps and 6.8% overall yield (23 mg produced) from tryptophan, see: Espejo VR, Rainier JD. Org Lett 2010;1210.1021/ol100672z
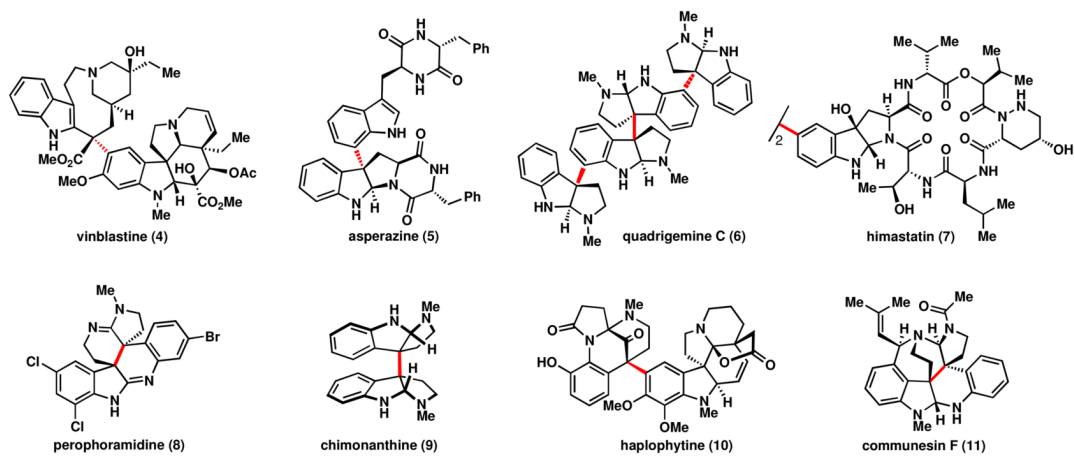
Figure 1.
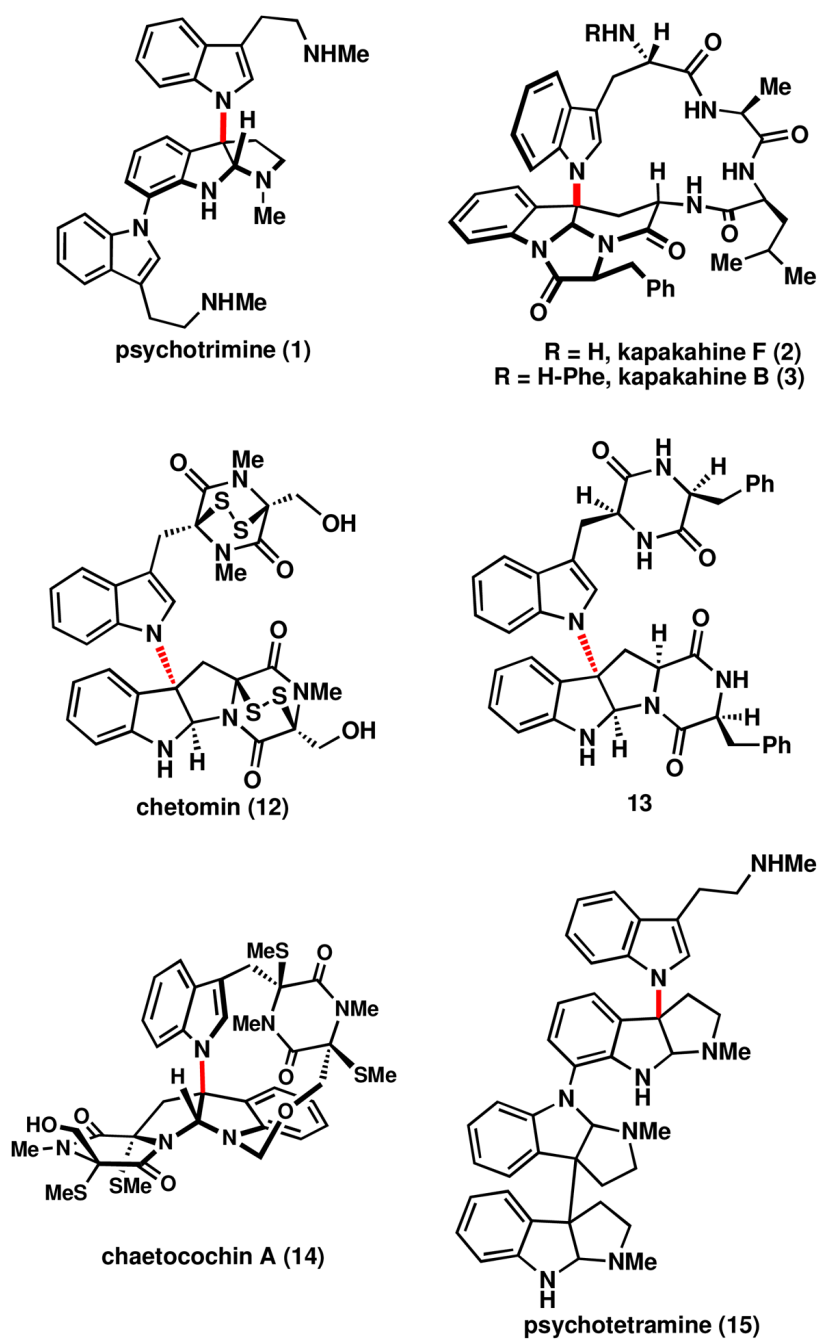A sampling of polymeric indole alkaloids with carbon-carbon linkages between indole subunits.

Figure 2.
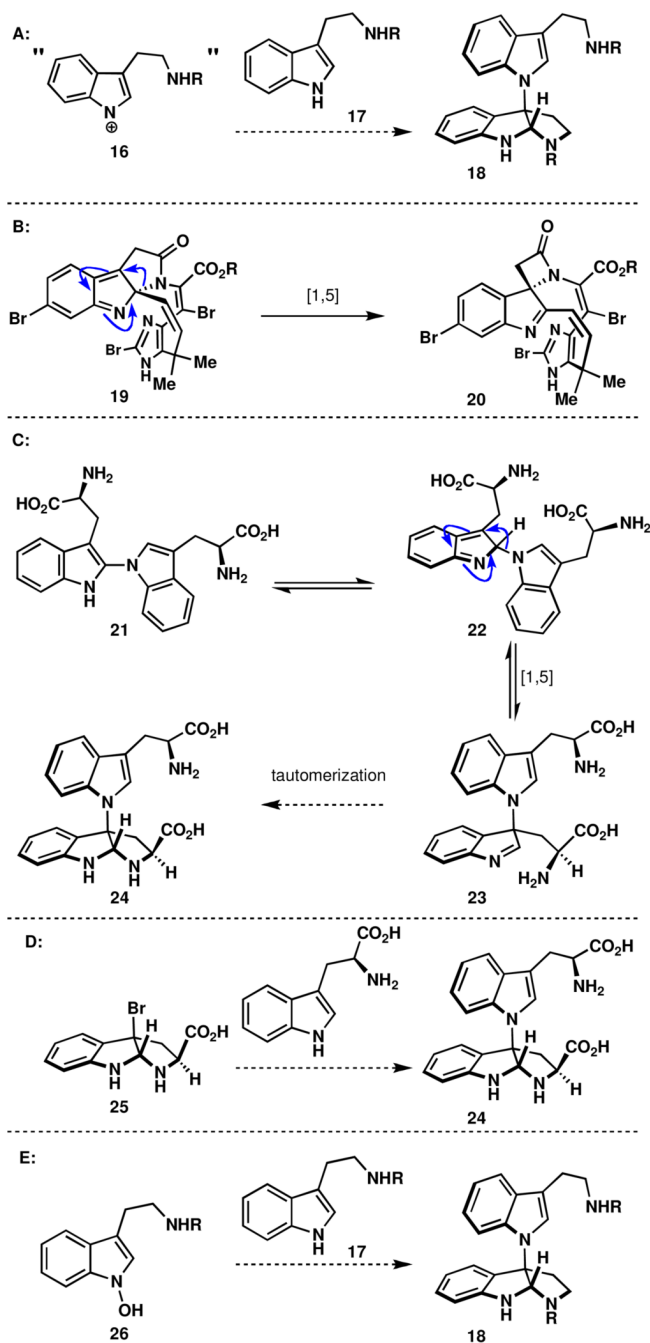Representatives of the subgroup of oxidatively conjoined tryptamines containing nitrogen to carbon connectivity.

Figure 3.
Possible biosynthetic routes to dimeric tryptamines containing the N1-C3 bond.
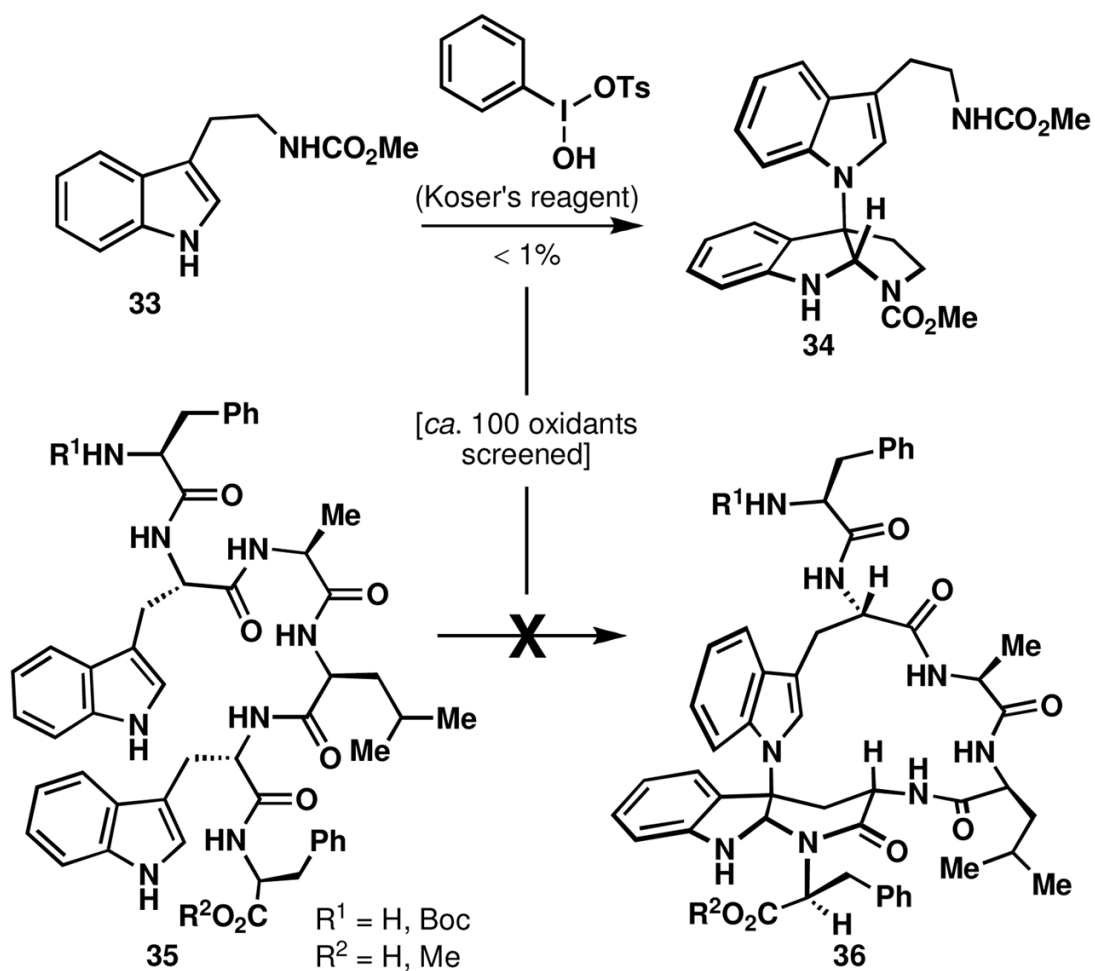
Figure 4.
Direct oxidative dimerization of a tryptamine to give N1-C3 bond formation.

A: Renfroe and Castle's tryptamine-imidazole coupling
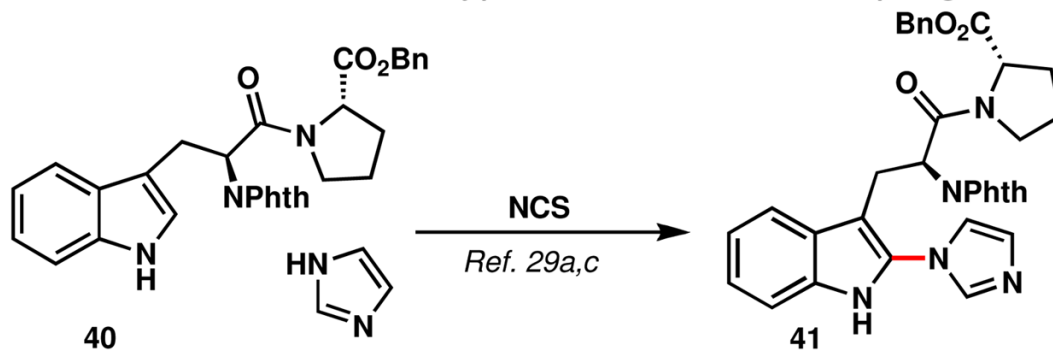
B: Bergman's tryptamine-aniline oxidative coupling
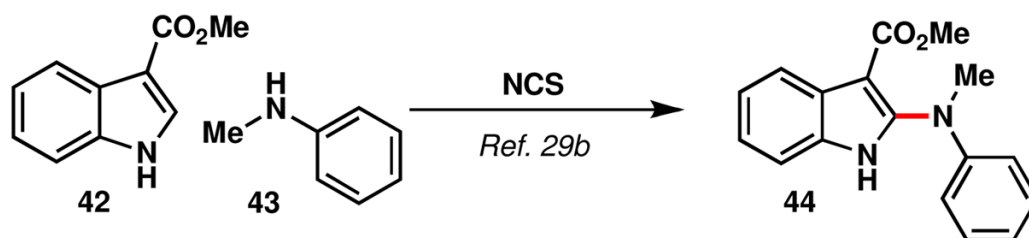
Figure 5.
Oxidative coupling reactions for the introduction of heteroatom substituents to indole C2.

A: *o*-Iodoaniline as an indole cation surrogate?

B: Reaction design

tryptamine + *o*-iodoaniline + [O] ⟶
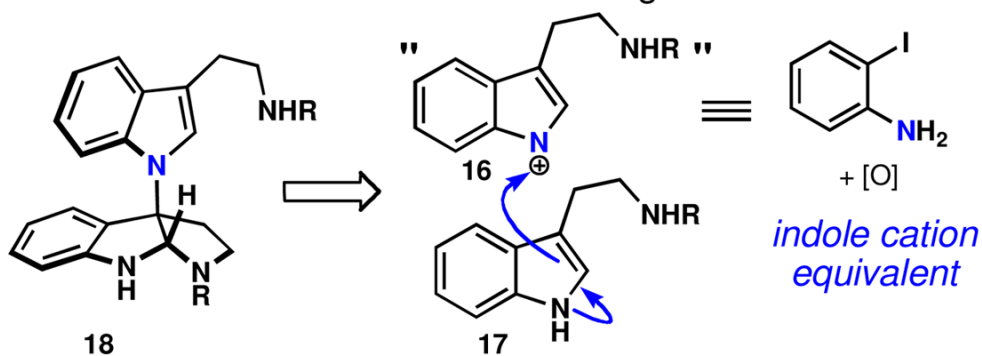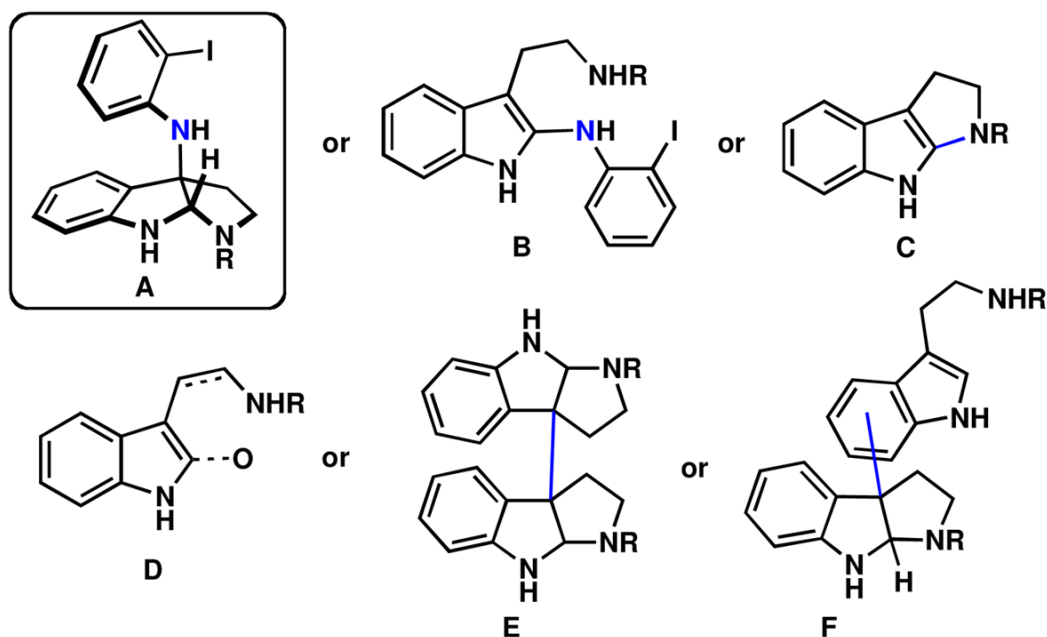
Figure 6.
(A) Nature's presumed biosynthesis leads to the invention of a direct indole-aniline oxidative coupling reaction. (B) Known reactivity suggests issues of chemo- and regioselectivity.
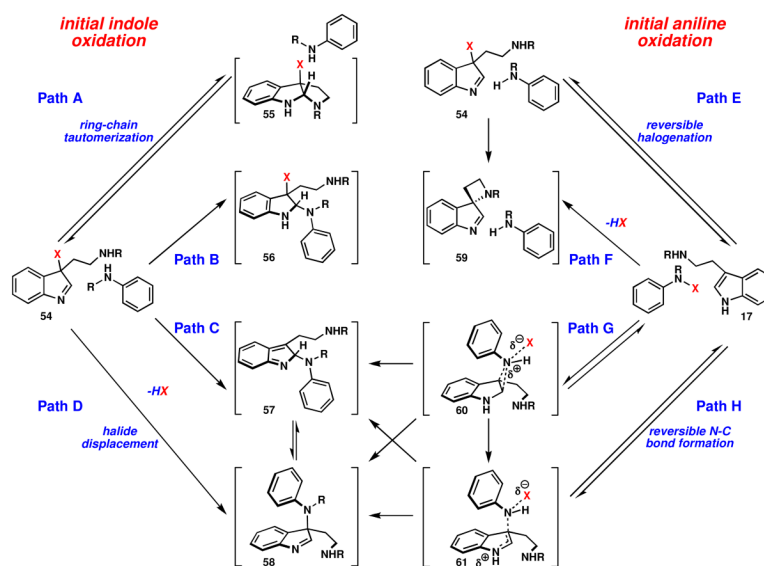
Figure 7.
Some possible mechanisms for N-C bond formation.
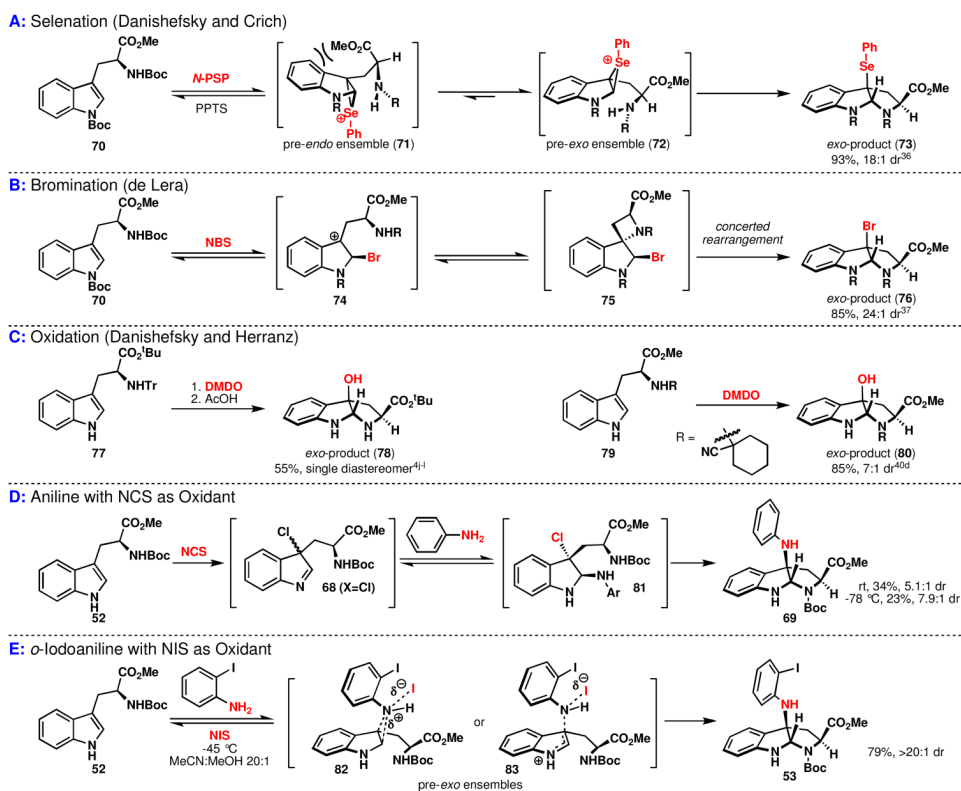
Figure 8.
Introduction of various electrophiles to indole C3.
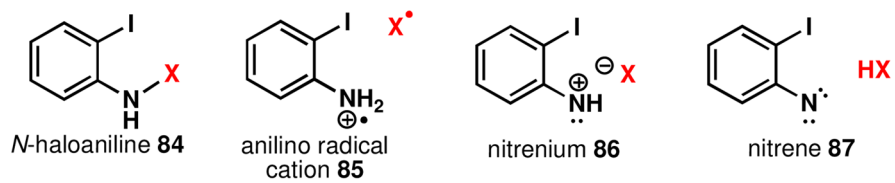
Figure 9.
Potential electrophilic aniline species
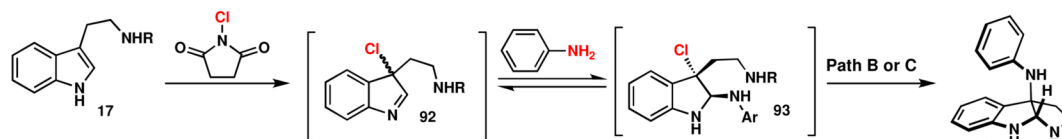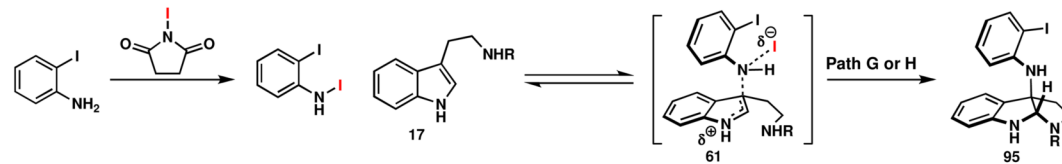
Figure 10.
Mechanistic proposal for the indole-aniline oxidative coupling reaction.
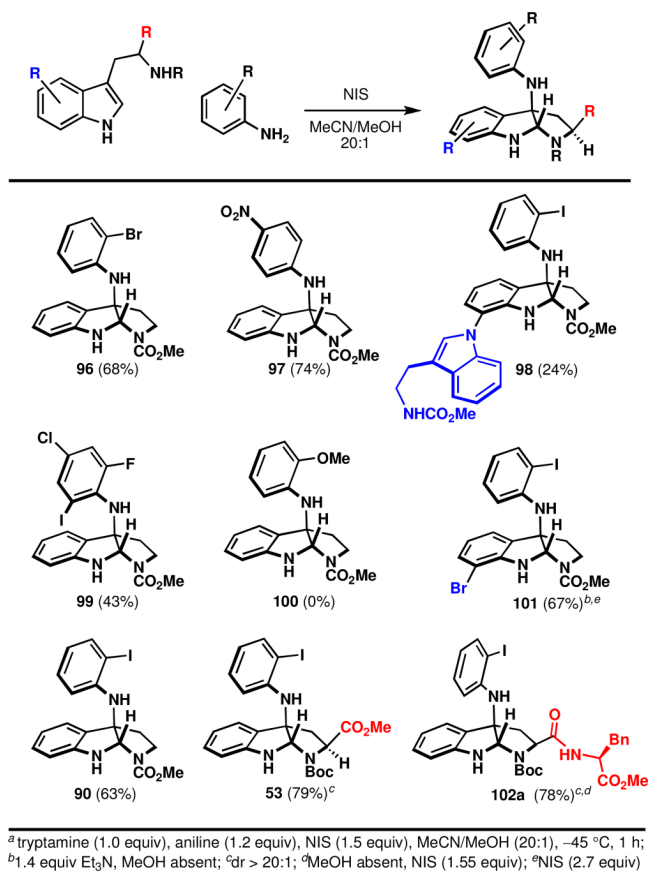
Figure 11.
Scope of tryptamine and aniline oxidative coupling reaction.
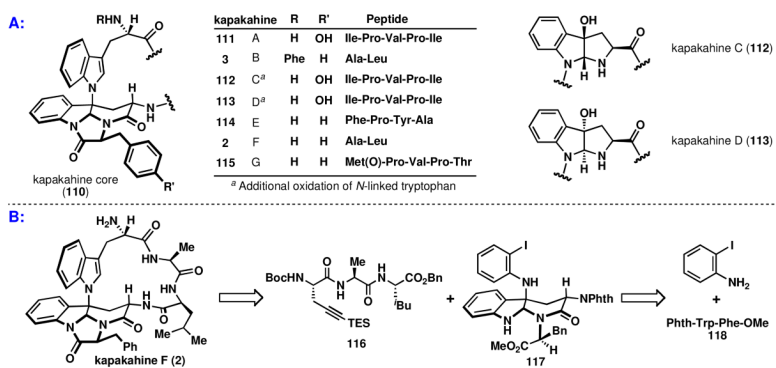
Figure 12.
Initial retrosynthetic analysis of the kapakahines.
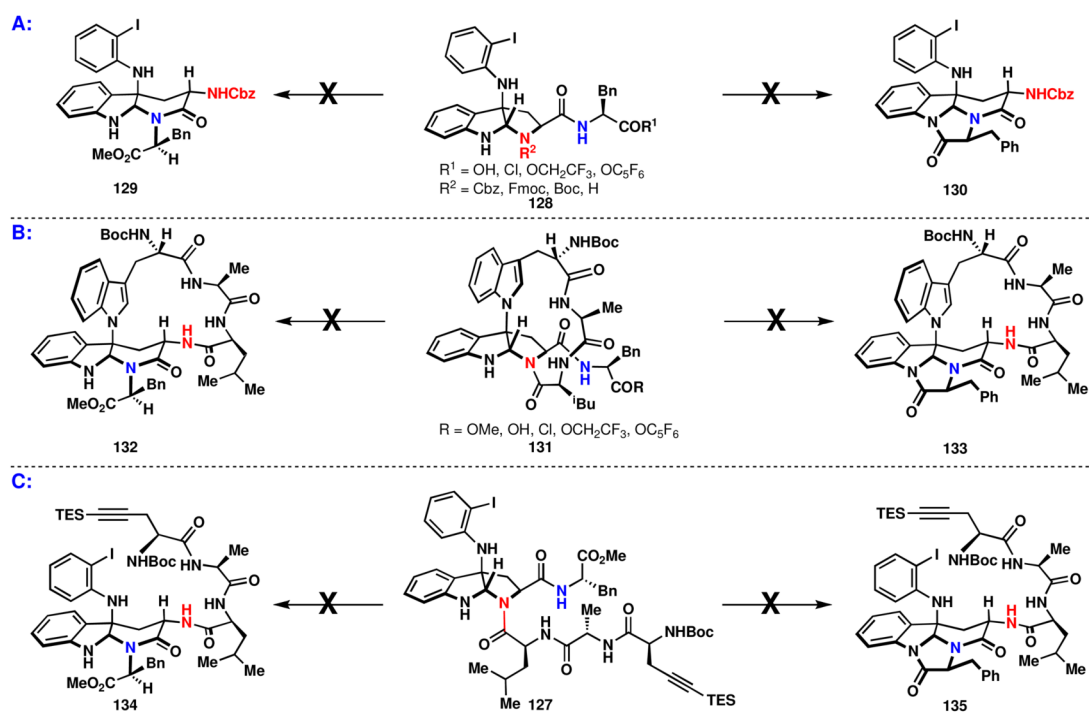
Figure 13.
Failure to observe isomerization to the desired α-carboline.
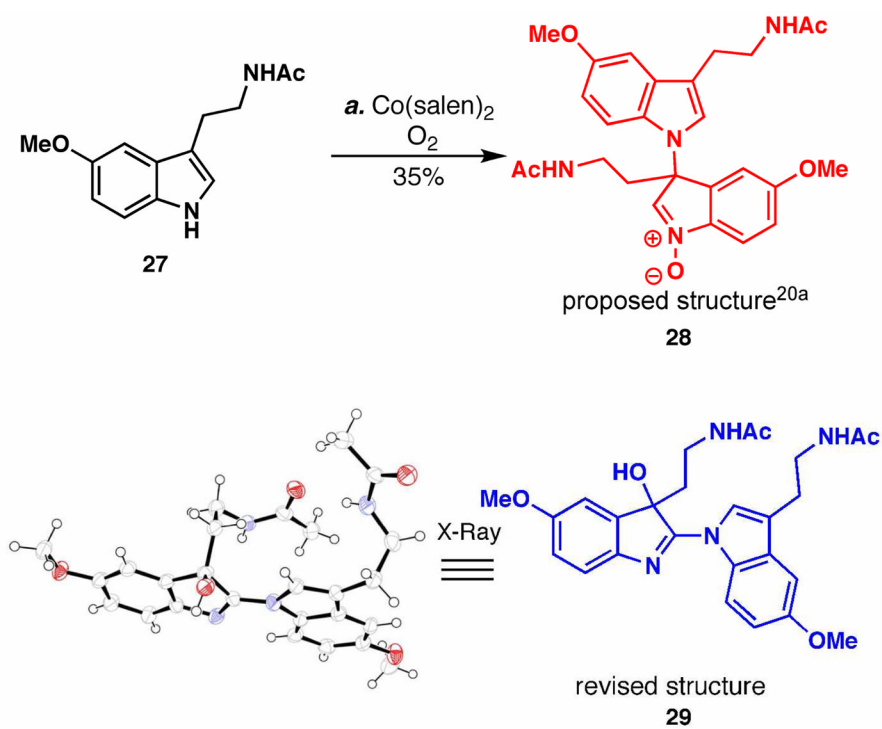
Scheme 1.
Structural reassignment of the melatonin oxidative dimerization product.[a]
[a]Reagents and conditions: (a) Co(salen)$_2$ (0.18 equiv), O$_2$, DCM, 23 °C, 24 h, 35%.
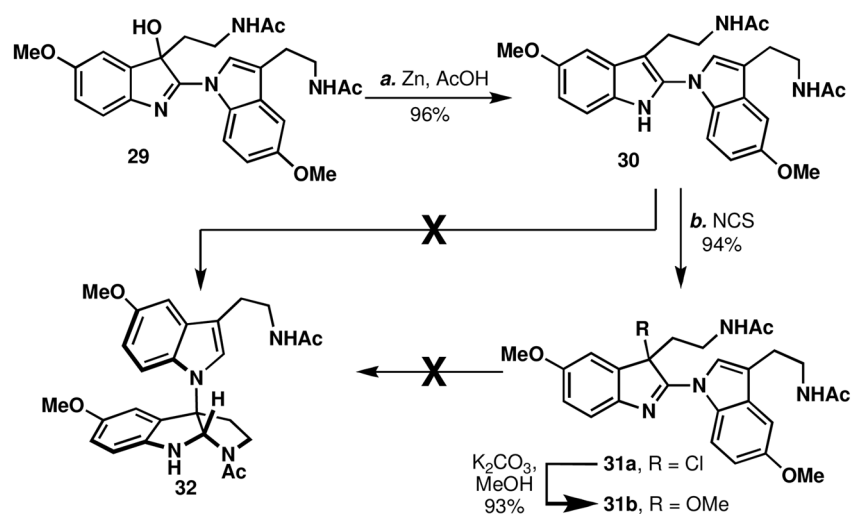
Scheme 2.
Failure of the necessary bond migration.
[a] Reagents and conditions: (a) Zn (20 equiv), AcOH, 23 °C, 1 h, 96%; (b) *N*-chlorosuccinimide (1.1 equiv), DCM, 0 → 23 °C, 1 h, 94%; (c) K$_2$CO$_3$ (100 equiv), MeOH, 23 °C, 2 h, 93%.
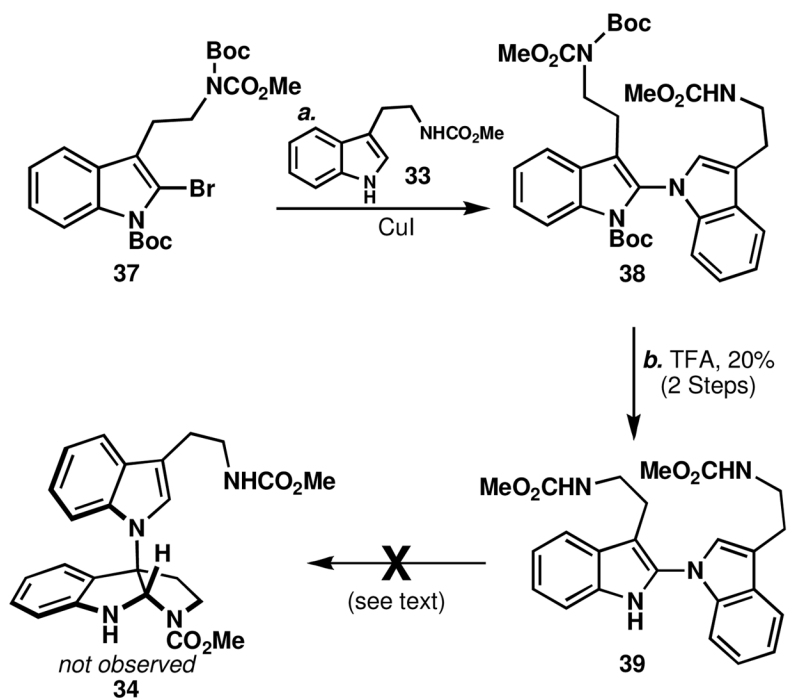
Scheme 3.
Stepwise synthesis of N1-C2 linked tryptamine dimer **39**.[a]

[a]Reagents and conditions: (a) **33** (4.0 equiv), CuI (1.0 equiv), (±)-*trans-N,N′*-dimethyl-1,2-cyclohexanediamine (0.20 equiv), K_3PO_4 (11 equiv), 1,4-dioxane, 101 °C, 24 h; (b) TFA/DCM (1:4), 23 °C, 1 h, 21 % (2 steps).
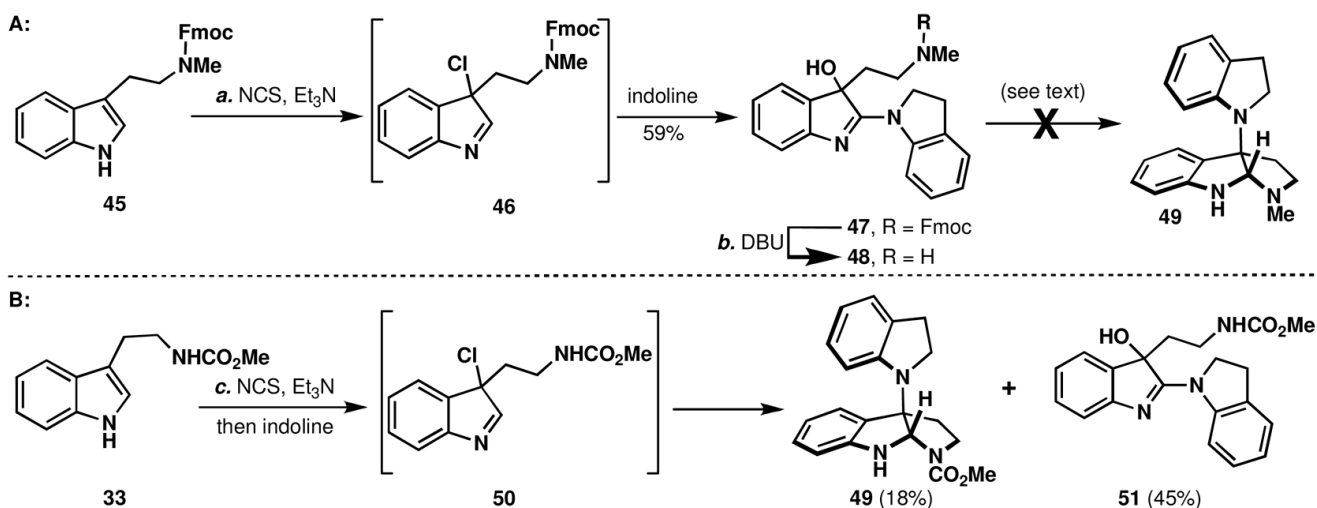
Scheme 4.
Synthesis of a C3-*N*-functionalized pyrroloindoline.[a]

[a]Reagents and conditions: (a) (*i*) *N*-chlorosuccinimide (1.1 equiv), Et$_3$N (1.0 equiv), DCM, 0 → 23 °C, 1.5 h, (*ii*) indoline (1.4 equiv), 0 → 23 °C, 12 h, 59%; (b) DBU (1.0 equiv), C$_{12}$H$_{25}$SH (2.0 equiv), DCM, 23 °C, 2 h; (c) NCS (1.1 equiv), Et$_3$N (1.2 equiv), DCM, 0 → 23 °C, 15 min; indoline (2.0 equiv), 12 h, 18% **49** and 45% **51**.
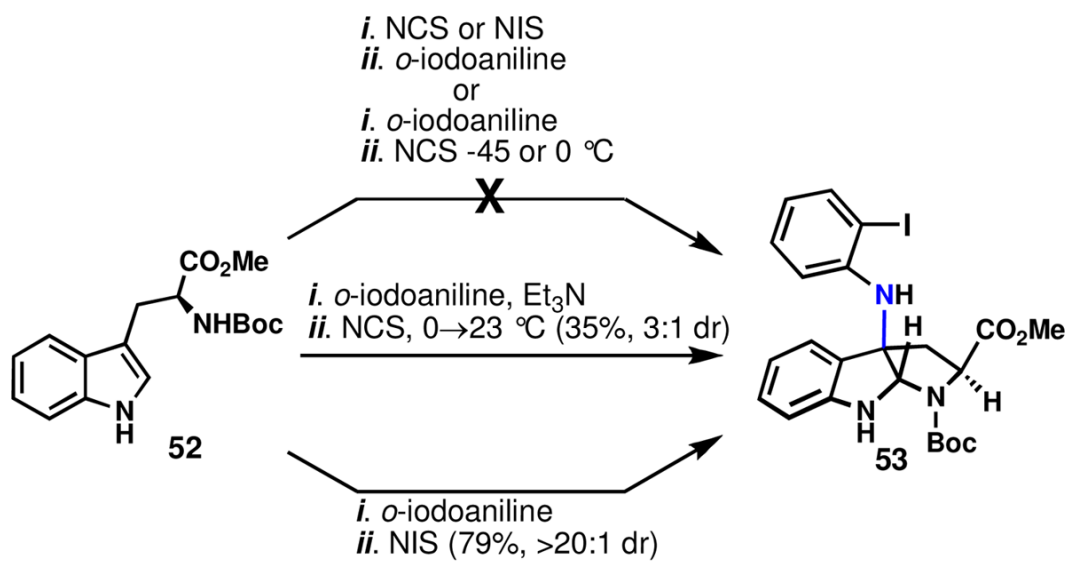
Scheme 5.
Comparison of order of addition for oxidative cyclization.
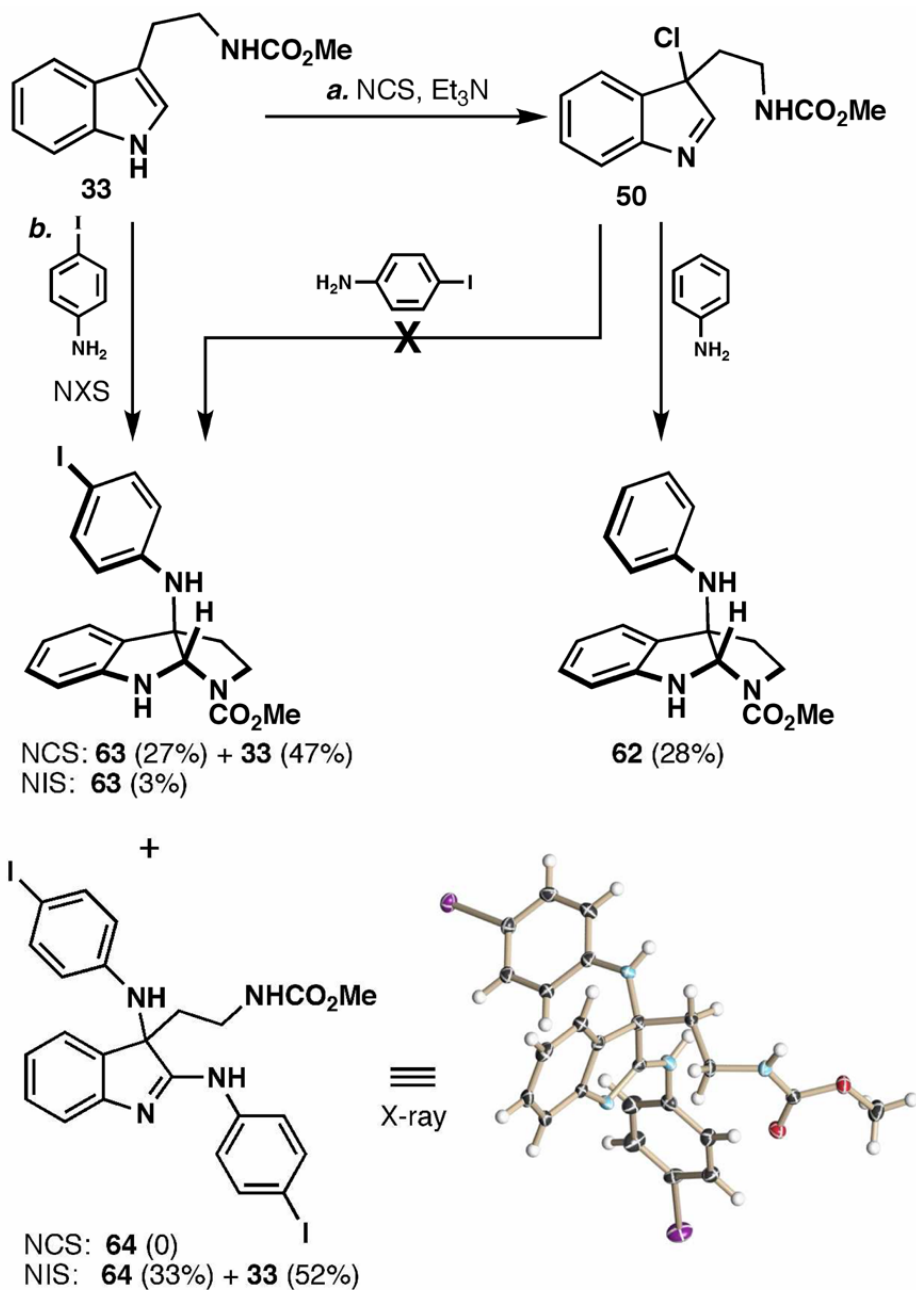
Scheme 6.
Reactions of anilines with the chloroindolenine, **50**.[a]
[a]Reagents and conditions: (a) (i) *N*-chlorosuccinimide (1.5 equiv), Et$_3$N (1.5 equiv), DCM, 0 → 23 °C, 15 min; (ii) aniline (2.0 equiv), 23 °C, 8 h, 28%; (b) *p*-iodoaniline (1.5 equiv), *N*-halosuccinimide (1.5 equiv), Et$_3$N (1.5 equiv), DCM, −45 → 23°C, 3 h.
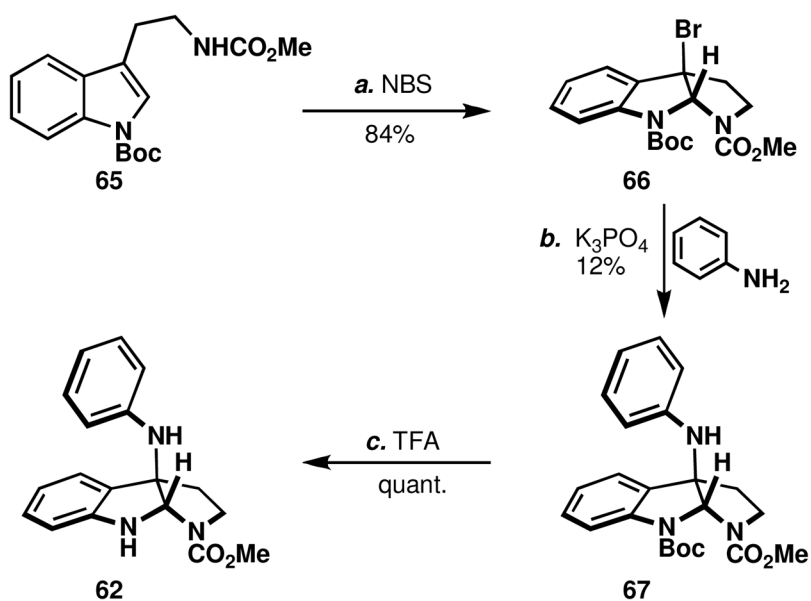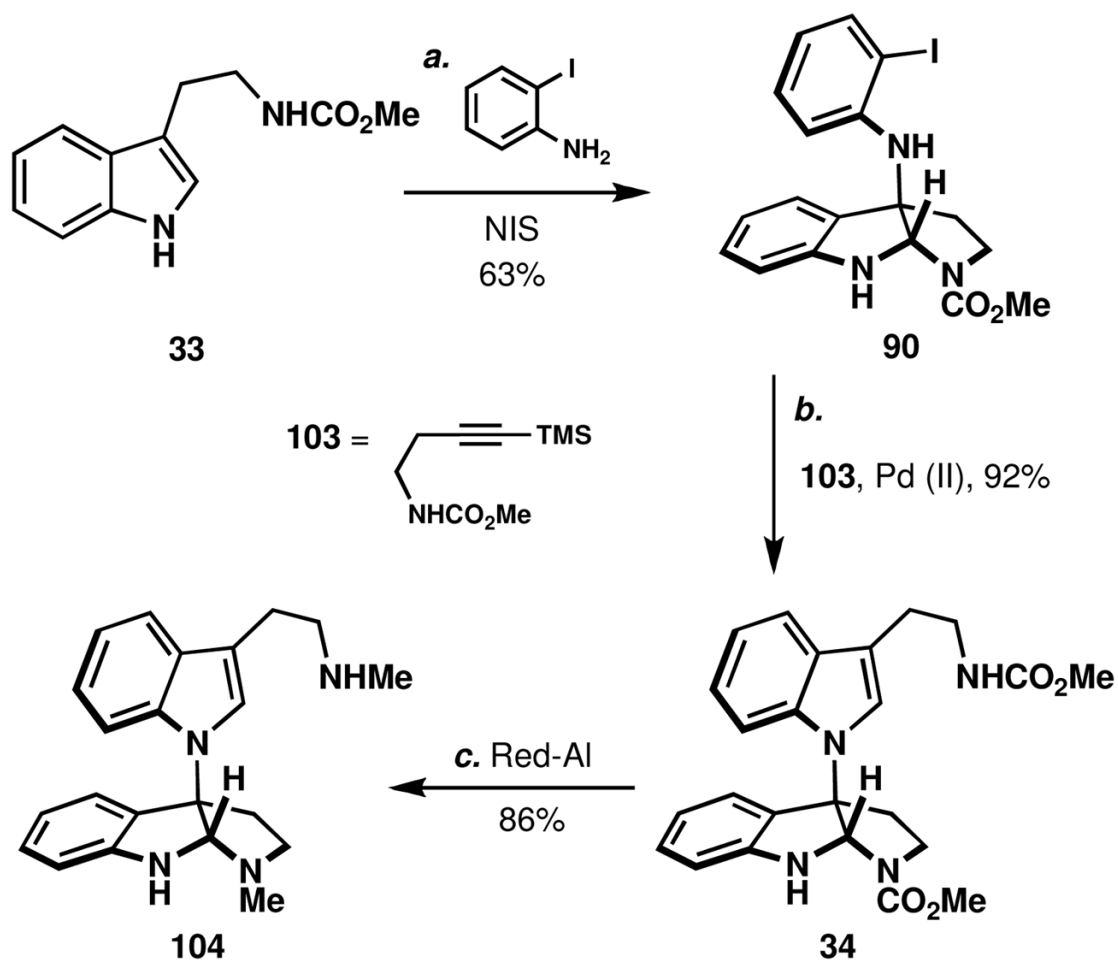
Scheme 7.
Nucleophilic displacement of a 3-halopyrroloindoline by an aniline nucleophile.[a]
[a]Reagents and conditions: (a) *N*-bromosuccinimide (1.4 equiv), DCM, 23 °C, 1 h, 84%; (b) aniline (6.3 equiv), K$_3$PO$_4$ (1.9 equiv), DMSO, 100 °C, 24 h, 12%; (c) TFA/DCM (1:5), 0 °C, 0.5 h, quant.
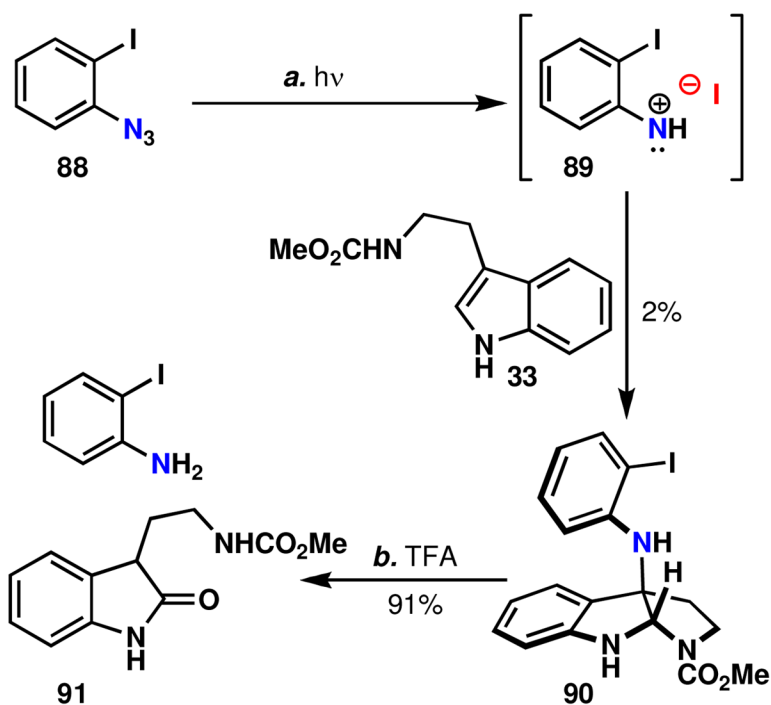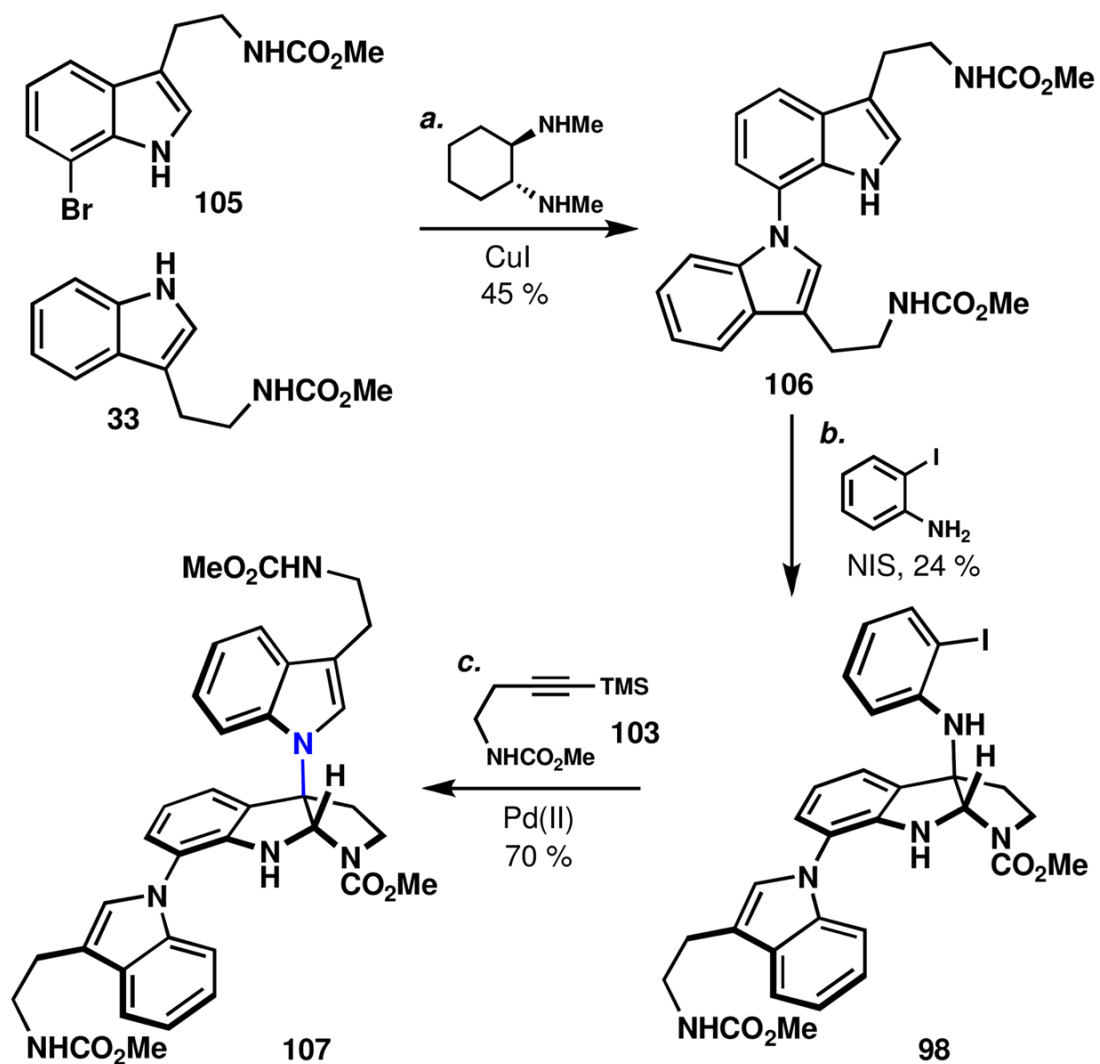
Scheme 8.
Photochemical generation of a phenylnitrenium ion in the synthesis of **89**, along with subsequent decomposition.[a]

[a]Reagents and conditions: (a) **33** (1.0 equiv), hv, benzene, 23 °C, 24 h, 2%; (b) TFA/DCM (1:10), 23°C, 2 h, 91%.
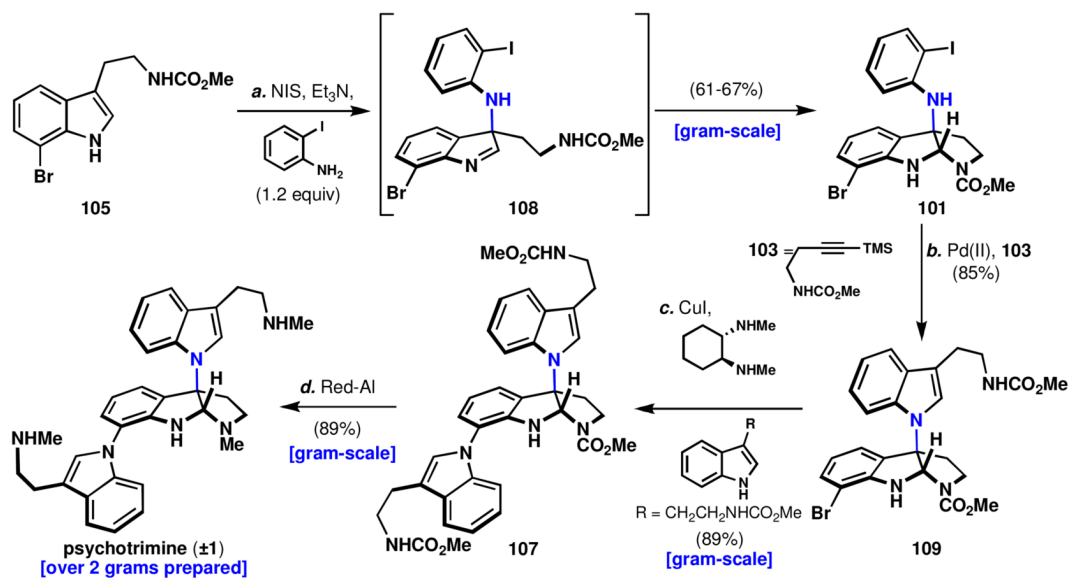
Scheme 9.
Synthesis of a chimonanthine isomer, **104**.[a]

[a]Reagents and conditions: (a) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (1.5 equiv), MeCN/MeOH (20:1), −45 °C, 1 h, 63%; (b) **103** (3.0 equiv), Pd(dppf)Cl$_2$•DCM (0.20 equiv), Cs$_2$CO$_3$ (2.0 equiv), LiCl (1.0 equiv), NMP, 100 °C, 1 h, 92%; (c) sodium bis(2-methoxyethoxy)aluminum hydride (11 equiv), toluene, 110 °C, 30 min, 86%.

Scheme 10.
Initial route to psychotrimine precursor **107**.[a]

[a]Reagents and conditions: (a) **33** (3.0 equiv), CuI (0.30 equiv), (±)-*trans-N,N'*-dimethyl-1,2-cyclohexanediamine (0.60 equiv), K_2CO_3 (7.0 equiv), 1,4-dioxane, 101 °C, 20 h, 45%; (b) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (1.5 equiv), MeCN:MeOH 20:1, −45 °C, 1 h, 24%; (c) **103** (7 equiv), Pd(OAc)$_2$ (0.3 equiv), K_2CO_3 (3.5 equiv), LiCl (1.0 equiv), DMF, 90 °C, 0.5 h, 70%.
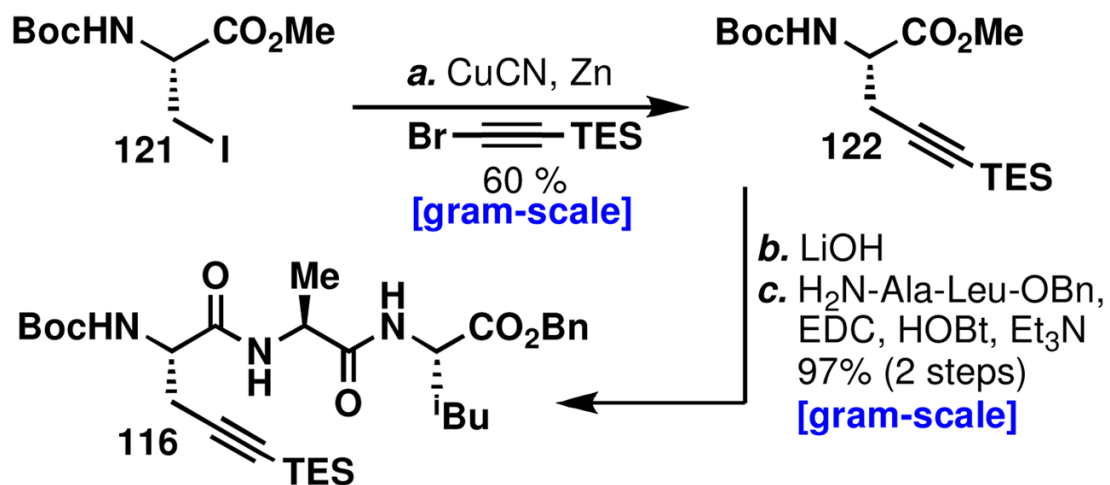
Scheme 11.
Total synthesis of psychotrimine (**1**).[a]

[a]Reagents and conditions: (a) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (3.0 equiv), Et₃N (1.2 equiv), MeCN, −45 → 23 °C, 1 h, 61–67%, 25–30% **105**; (b) Pd(OAc)₂ (0.21 equiv), Na₂CO₃ (2.6 equiv), LiCl (0.9 equiv), **103** (2.7 equiv), DMF, 102 °C, 20 min, 85%; (c) CuI (0.32 equiv), (±)-*trans*-N,N′-dimethyl-1,2-cyclohexanediamine (0.60 equiv), K₂CO₃ (7.0 equiv), **33** (3.0 equiv), 1,4-dioxane, 101 °C, 9 h, 89%; (d) sodium bis(2-methoxyethoxy) aluminum hydride (22 equiv), toluene, 110 °C, 30 min, 89%.
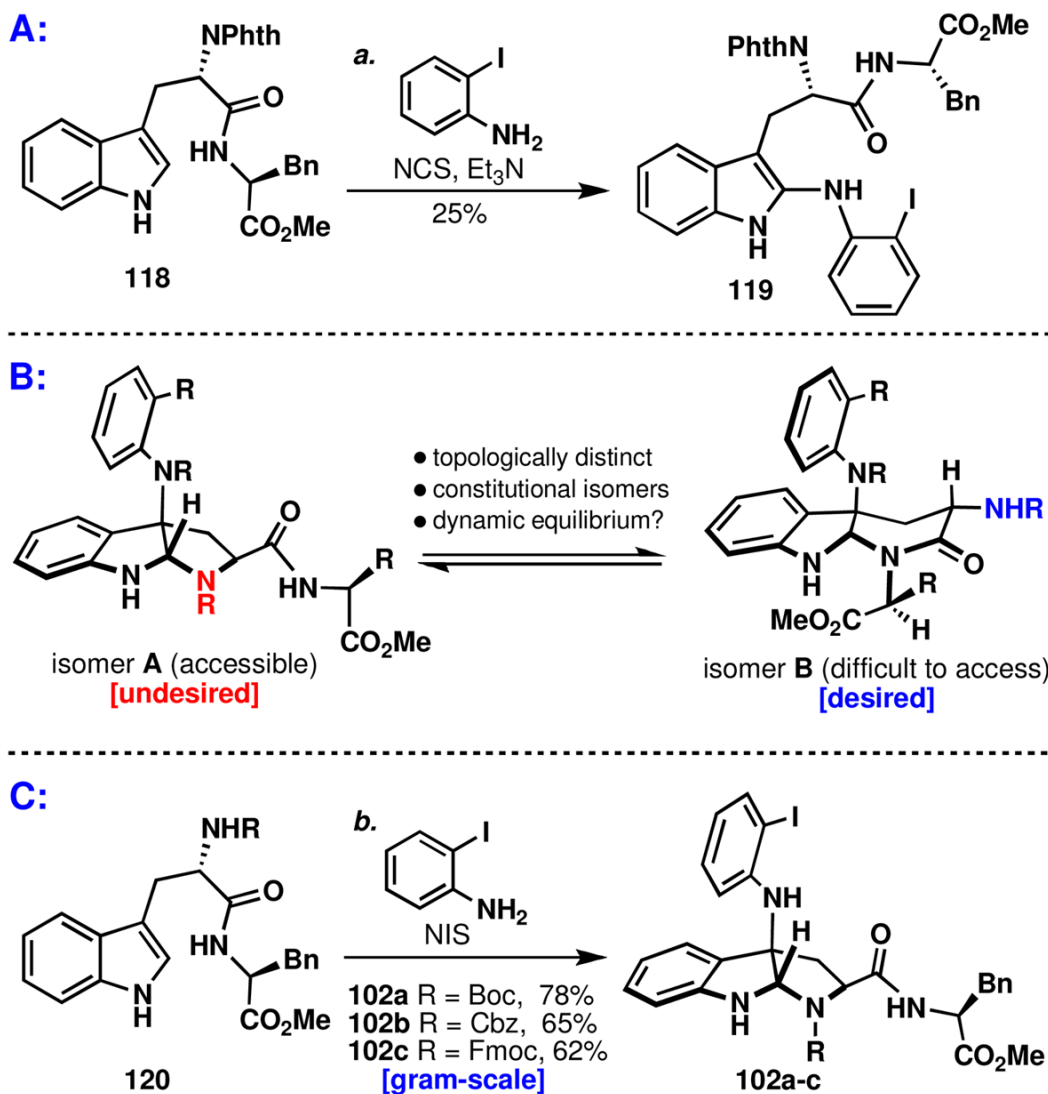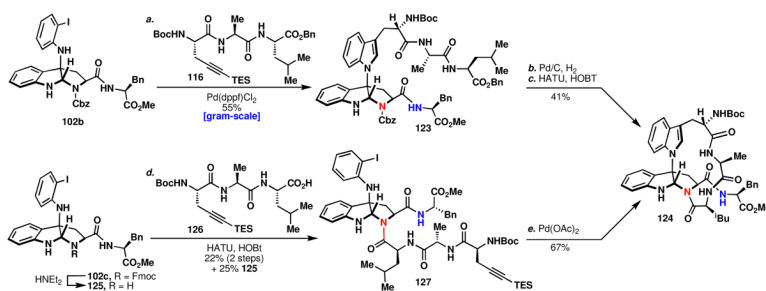
Scheme 12.
Failure to observe direct α-carboline ring system.[a]
[a]Reagents and conditions: (a) *o*-iodoaniline (1.2 equiv), *N*-chlorosuccinimide (2.0 equiv), triethylamine (1.2 equiv), MeCN −45 → 4 °C, 2.5 h, 25%; (b) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (1.6 equiv for **102b**, 1.55 equiv for **102a**, **102c**), MeCN −45 → −35 °C, 2.5 h.
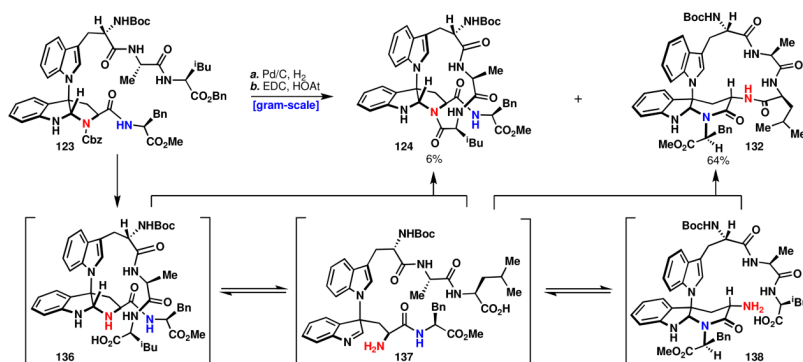
Scheme 13.
Preparation of the tripeptide fragment (**116**). [a]

[a]Reagents and conditions: (a) CuCN (0.9 equiv), LiCl (1.8 equiv), Zn (3.6 equiv), TMSCl (0.1 equiv), Br(CH$_2$)$_2$Br (0.2 equiv), DMF, −20 → 23 °C, 11 h, 60%; (b) LiOH (1.2 equiv), THF/H$_2$O 1:1, 0 °C, 0.5 h; H$_2$N-Ala-Leu-OBn (1.1 equiv), EDC (1.2 equiv), HOBt (1.4 equiv), THF, 0 → 23 °C, 10 h, 97% (two steps).
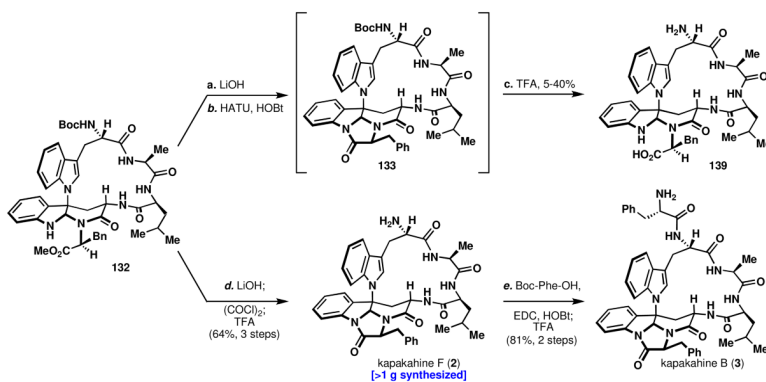
Scheme 14.
Two routes to the pyrroloindoline-containing macrocycle (**124**).
Reagents and conditions: (a) **116** (2.0 equiv), Pd(dppf)Cl$_2$•DCM (0.20 equiv), Cs$_2$CO$_3$ (2.0 equiv), LiCl (1.0 equiv), DMF, 100 °C, 1.5 h, 55%; (b) 10% Pd/C (0.20 equiv), H$_2$, MeOH, 1 h (c) HATU (3.0 equiv), HOBt (2.5 equiv), ^{i}Pr$_2$NEt (2.2 equiv), DMF, 6 h, 41% (2 Steps); (d) Et$_2$NH/DCM, 1:3, 1 h, quant; HATU (2.0 equiv), HOBt (1.5 equiv), Et$_3$N (2.0 equiv), 22% and **125** 25% (2 steps); (e) Pd(OAc)$_2$ (0.34 equiv), NaOAc (6 equiv), LiCl (0.96 equiv), DMF, 100 °C, 12 h, 67%.

Scheme 15.
Successful isomerization to the desired α-carboline (**132**).[a]
[a]Reagents and conditions: (a) 10% Pd/C (0.20 equiv), H_2, MeOH, 1 h; (b) EDC (3.0 equiv), HOAt (6.0 equiv), DCM/DMF (20:1), 12 h, 70% (**124:132**, 1:11).

Scheme 16.

Completion of kapakahines F, **2**, and B, **3**.

Reagents and conditions: (a) LiOH, THF/H$_2$O/MeOH (40:2:1), 1 h; HATU (4.0 equiv); TFA/DCM (1:6), 0.5 h; (d) LiOH, THF/H$_2$O/MeOH (40:2:1), 1 h; (COCl)$_2$ (4.0 equiv), Et$_3$N (1.0 equiv), DCM, 1 h; TFA/DCM (1:10), 1 h, 64% (three steps); (f) Boc-Phe-OH (1.2 equiv), EDC (2.0 equiv), HOBt (1.8 equiv), Et$_3$N (3.0 equiv), DCM 1 h; TFA/DCM (1:10), 1 h, 81% (two steps).

Table 1

Optimization of direct coupling with *o*-iodoaniline.
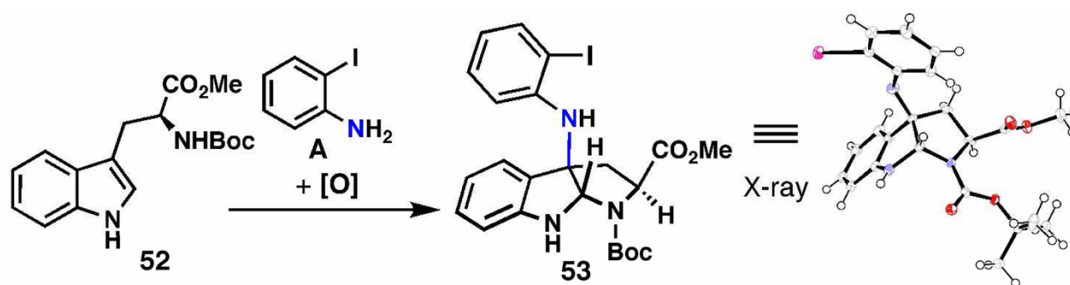
Entry	Conditions	Yield (%)^a	dr^b
1	**A** (3.0 eq), MeCN, **CAN** (1.0 equiv), 0°C	0	-
2	CHCl$_3$, **IBD** (3.0 equiv), 23 °C	13	-
3	MeCN, **PIFA** (1.0 equiv), −30 °C	24	-
4	**Koser's reagent** (3.0 equiv), 0 °C	46	-
5	**A** (1.2 eq), Et$_3$N (1.2 equiv), **NCS** (2.0 equiv), 0→23 °C	35	3:1
6	**NCS** (2.0 equiv) **added before A**, Et$_3$N (1.2 equiv), 0→23 °C	0	-
7	**NBS** (3.0 equiv), Et$_3$N (1.2 equiv), 0→23 °C	20	10:1
8	**NIS** (2.0 equiv), Et$_3$N (1.2 equiv), −45→23 °C	3	-
9	NIS **(3.5 equiv)**, Et$_3$N (1.2 equiv), −45→23 °C	45	13:1
10	***N*-iodomorpholine** (1.5 equiv), −45→23 °C	0	-
11	**Et$_2$NH** (1.2 equiv), NIS (3.5 equiv), −45→23 °C	0	-
12	**no base**, NIS (1.1 equiv), **−45 °C**	52	>20:1
13	NIS (1.5 equiv), **0 °C**	63^c	18:1
14	NCS (1.5 equiv), **0 °C**	0^c	-
15	**EtNO$_2$**, NIS (1.1 equiv), −78 °C	42	>20:1
16	**MeCN**, NIS (**1.5 equiv**), −45 °C	68	>20:1
17	**DCM**, NIS (1.5 equiv), −78 °C	trace	-
18	**THF**, NIS (1.5 equiv), −78 °C	0	-
19	**MeCN:MeOH (10:1)**, NIS (1.5 equiv), −45 °C	69^d	>20:1
20	**MeCN:MeOH (15:1)**, NIS (1.5 equiv), −45 °C	76^d	>20:1
21	**MeCN:MeOH (20:1)**, NIS (1.5 equiv), −45 °C	79de	>20:1
22	**MeCN:MeOH (20:1)**, NCS (1.5 equiv), −45 °C	0^d	-

^{a}Isolated yield of **53**.

^{b}determined by crude ^{1}H-NMR.

^{c}quenched after 10 min.

^{d}quenched by addition of Na$_2$S$_2$O$_3$ solution to −45 °C reaction.

^{e}gram scale, + 17% **52**.

Table 2

Diastereoselectivity as a mechanistic footprint.
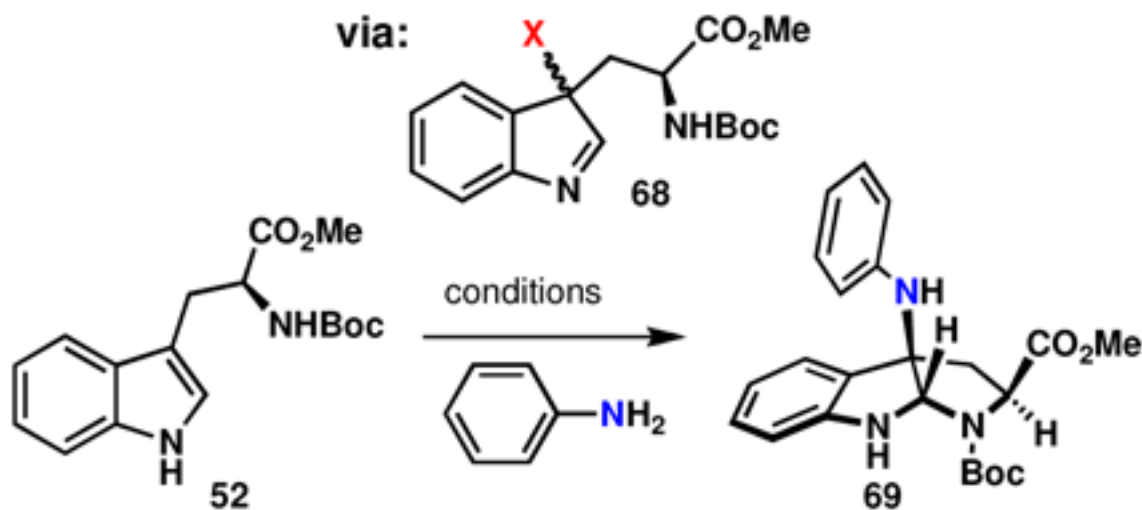
Entry	Conditions[a]	dr (68)[b]	(%)[c]	dr (69)[b]
1	NCS, −78 °C; then aniline, rt	1.4:1	23	7.9:1
2	NCS, rt; then aniline, rt	1.0:1	34	5.1:1
3	aniline; then NCS, −78°C	—	11	7.4:1
4	aniline; then NCS, rt	—	10	7.6:1
5	NBS, rt; then aniline, rt	1.0:1	13	10.4:1
6	NIS, rt; then aniline, rt	—	0	—

[a] aniline (2.0 equiv), Et3N (1.5 equiv), NXS (1.2 equiv), DCM;

[b] determined by crude ^{1}H-NMR;

[c] isolated yield of **69**