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Concise Total Synthesis of (+)-Asperazine, (+)-Pestalazine A, and (+)-iso-Pestalazine A. Structure Revision of (+)-Pestalazine A

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Abstract

The concise, enantioselective total syntheses of (+)-asperazine (**1**), (+)-*iso*-pestalazine A (**2**), and (+)-pestalazine A (**3**) have been achieved by the development of a late-stage C3–C8′ Friedel-Crafts union of polycyclic diketopiperazines. Our modular strategy enables the union of complex polycyclic diketopiperazines in virtually their final forms, thus providing rapid and highly convergent assembly at the challenging quaternary stereocenter of these dimeric alkaloids. The significance of this carbon–carbon bond formation can be gauged by the manifold constraints that were efficiently overcome, namely the substantial steric crowding at both reactive sites, the nucleophilic addition of C8′ over N1′ to the C3 carbocation, and the multitude of reactivity posed by the use of complex diketopiperazine fragments in the coupling event. The success of the indoline π-nucleophile that evolved through our studies is notable given the paucity of competing reaction pathways observed in the presence of the highly reactive C3 carbocation generated. This first total synthesis of (+)-pestalazine A also allowed us to revise the molecular structure for this natural alkaloid.

The hexahydropyrroloindoles comprise a structurally and biologically fascinating class of alkaloid natural products.[1] The dimeric diketopiperazine incarnations of these metabolites are replete with the sort of molecular complexity that regularly nourishes the advancement of new synthetic methodologies.[2] Undeniably, the greatest obstacle for researchers seeking to gain efficient access to these structures has been the stereocontrolled introduction of the quaternary stereocenter and the carbon–carbon bond at the heart of these alkaloids. (+)-Asperazine (**1**)[3] and its more recently isolated congener (+)-pestalazine A[4] present an exemplary challenge for chemical synthesis by possessing heterodimeric diketopiperazines with a unique quaternary $C3_{sp3}$–$C8′_{sp2}$ juncture (Figure 1). While outstanding advances have been achieved in the synthesis of C3-aryl pyrroloindolines,[5,6,7] Overman's elegant synthesis of (+)-asperazine (**1**),[8] predicated on early introduction of the C3-quaternary stereocenter by an intramolecular Heck reaction[9] followed by formation of the diketopiperazines, stands as the only solution to alkaloid (+)-**1**. Our highly convergent synthesis of the C3–C7′ fused (+)-

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naseseazine alkaloids (Figure 1),[10] prompted us to investigate the possibility of a complementary Friedel-Crafts based approach[11] to alkaloids (+)-**1**–**2**, involving late-stage directed union of complex diketopiperazines, to secure the challenging $C3_{sp3}$–$C8'_{sp2}$ linkage.[12] Herein, we report the development and implementation of this ambitious strategy to the highly expedient synthesis of (+)-asperazine (**1**), and the first total synthesis (+)-*iso*-pestalazine A (**2**) and (+)-pestalazine A (**3**). The culmination of our study was the revision and subsequent synthesis of the corrected structure of (+)-pestalazine A (**3**).

In recent years, various innovative methodologies have been formulated to address the synthesis of $C3_{sp3}$–$C3'_{sp3}$,[13,14,15,16] $C3_{sp3}$–$N1'$[17] and $C3_{sp3}$–arene[5–9,11,12] bound pyrroloindolines. Our group has a long-standing interest in developing mild, versatile chemistries that can rapidly generate these complex, acutely sterically-congested C3 linkages in stereo- and regioselective fashion.[2c] While many of the existing approaches to C3-aryl pyrroloindolines rely on alkylation of oxindoles,[6] or rearrangement chemistry,[7b,d,f,g,k] alternative methodologies have also been reported.[7a,e,h–j] Since our first report on diazene directed fragment assembly as a viable strategy for C3 arylation,[16a,b] much progress has also been made in the synthesis of C3-diazenyl pyrroloindolines.[18] Recent advances in transition metal-catalyzed coupling methodologies have also provided exciting opportunities for the development of new routes to C3-aryl pyr-roloindolines.[5,19] The Overman group's Heck cyclization based strategy has proven especially successful in this arena,[8,9] providing enantiomerically enriched C3-aryl oxindoles that paved the way for their landmark syntheses of C3-aryl pyrroloindoline alkaloids including (+)-asperazine (**1**), which was accomplished in 22 steps and 1.0% overall yield.[8]

Our group has sought a different inroad into these heterodimers, based on a maximally convergent late-stage C3–arene coupling of advanced diketopiperazine intermediates. This tactic draws inspiration from biogenetic hypotheses on the origins of these natural products,[20,21] but unlike the oxidative radical dimerizations,[7i] we found ionic unification pathways[22] could better dictate regiocontrol at the C3–aryl juncture.[12] Specifically, we developed a mild Friedel–Crafts-based method for the stereo- and regioselective addition of a wide range of nucleophiles to the C3 carbocation.[23] Indolic interceptions at this benzylic cation, arising from mild silver activation of a bromide precursor, were instrumental in our expedient syntheses of the bionectins, gliocladins, and luteoalbusins.[11] The ultimate demonstration of our late-stage heterodimerization paradigm came in our total syntheses of the C7'-linked (+)-naseseazines (i.e. **5** and **6**, Figure 1).[12] We now report our development of a powerful and enabling *ortho*-indoline-based Friedel-Crafts strategy that has led to a highly convergent, concise, regio- and stereocontrolled total synthesis of (+)-asperazine (**1**), (+)-*iso*-pestalazine A (**2**) and (+)-pestalazine A (**3**). This amplifies our group's repertoire of heterodimerization modes to now include late-stage $C3_{sp3}$–$C8'_{sp2}$ bond formation. A key feature of our routes to these targets is a newly-developed regioselective reductive ring-opening reaction, which allowed the transposition of a more π-nucleophilic and regioselective indoline onto the eventual indole moiety, whilst simultaneously thwarting N1' and C2' nucleophilic attack.

As well as its initial discovery in minute quantities from a Caribbean sponge-derived culture of *Aspergillus niger*, (+)-asperazine (**1**) was also isolated in 2008 alongside (+)-pestalazine

A (**3**) and the C3$_{sp3}$–N1′ linked (+)-pestalazine B (**4b**, Figure 1) from the plant pathogenic fungus *Pestalotiopsis theae*.[4] Interestingly, in a second exploration of extracts from *Aspergillus niger*, the N1′-linked isomer of (+)-asperazine (**1**), and congener of (+)-pestalazine B (**4b**), (–)-asperazine A (**4a**) was also unearthed.[24] Accordingly, considerations of the interrelated biogenetic origins of these alkaloids added further impetus to our desire for a synthesis (Scheme 1) that espoused late-stage, convergent assembly. Such a route would endow us with the utmost flexibility in rapidly accessing C3–C8′-bound structural variants of these fascinating natural products for future studies.

In our synthesis of the naseseazine alkaloids (Figure 1) the desired C3–arene connectivity was secured by deployment of an N1-protected C3-substituted indole (–)-**8** (Scheme 1) that garnered π-nucleophilicity at its C6′/C7′ positions.[12] Exclusive C7′ Friedel–Crafts regioselection for product (–)-**11** was ensured by use of trifluoroborate (–)-**9**, whose anionic directing group could facilitate tight ion pairing with the C3-derived cation from bromide (+)-**10** (Scheme 1).[12,25] Our initial retrosynthetic outlook (Scheme 2) for heterodimers (+)-**1** and (+)-**2** strived to achieve the same levels of regiocontrol by employing a C8′-trifluoroborate **12**, which could intercept tetracyclic carbocation **13**. Bromide **15** would stem from diastereoselective bromocyclization of indole **16**, procurable in decagram quantities from amino acid condensations of L-tryptophan. Our newly developed one pot protocol for the boronation of L-tryptophans also prompted us to consider C8′-boroindole derivatives **12** and **14**.[26]

The pronounced challenges that met our plan to switch from C7′ to C8′ indole for C3 addition were borne out by our initial studies into directing π-nucleophilicity to this position. From the outset, unlike the naseseazines, the unfeasibility of using N1-protected indoles for C8′-directed Friedel-Crafts coupling presented added complications.[27] Notably, attempts at Miyaura boronation of N1-protected 8-bromotryptophans failed to provide the corresponding C8-boronotryptophan.[28] Conversely, N1-functionalization post-C8 boronation of tryptophans proved equally ineffective. With facile access to trifluoroborate (+)-**17a** on a multigram scale from the pinacol precursor,[26] we were able to explore Friedel-Crafts conditions for its reaction with bromide (+)-**18a**. This bromide was itself readily attained in one step through bromocyclization of the corresponding diketopiperazine (vide infra) in a manner akin to our previous synthetic campaigns.[11,12,14] Thus, by employing silver(I) hexafluoroantimonate in conjunction with 18-crown-6 and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP),[29] we were able to obtain 6% yield of the desired product, C8′-linked indole (+)-**19a**, but this was compounded by the presence of the C7′- and C2′-linked regioisomers in similar quantities (Scheme 3).[29,30] We next considered blocking these two undesired positions by introducing reductively removable substituents,[11a] in the form of 6-bromo-2-chloroindole (+)-**17b**.[29] The reaction of trifluoroborate (+)-**17b** with bromide (+)-**18a** gave fewer side products, with 22% yield of adduct (+)-**19b**.[31] This low yield of the desired C8′-linked indole indicated that the underlying problem of poor π-nucleophilicity at C8′ had persisted despite the use of a directing trifluoroborate.[12,25c] In spite of this, dimer (+)-**19** could be carried forward (Scheme 3) to (+)-asperazine (**1**) via indoline (+)-**20**.[29] Importantly, this unoptimized first-generation synthesis allowed us to establish the critical heterodimeric C8′–C3 bond.[29] The parity of our data with that of Overman's previous

synthesis[8] also retrospectively confirmed the regio- and stereochemical outcome of our first generation solution for securing the quaternary stereocenter and the challenging $C3_{sp3}$–$C8'_{sp2}$ bond.

These observations set the foundation for our development of a second generation C3–C8′ coupling strategy focused on enhancing C8′ reactivity and thereby suppress formation of regioisomeric and oligomeric side products. Central to this new approach was the utility of a reversible cyclization of tryptophan-derived diketopiperazines. Since tryptophan-derived diketopiperazines are known to cyclize reversibly in acid to their tetracyclic forms,[32] our concerns could be addressed by temporarily locking this equilibrium at bis-indoline **21** (Scheme 4). From a retrosynthetic perspective, this would allow us to harness the superior π-nucleophilicity of an aniline moiety for Friedel–Crafts chemistry and simultaneously remove C2′ nucleophilicity. The subsequent unlocking of bis-indoline **21** could be achieved post-C8′–C3 bond formation, by C3′ ionization–reduction of alcohol **22**. This alcohol would act as a stable surrogate of dimer **21**, and originate from *ortho* Friedel–Crafts coupling of indoline **23** to C3-bromide **24**. In order to maximize the propensity for C8′ addition of indoline **23**, it was crucial from consideration of steric as well as electronic factors, to forego any form of N1 protection. Critical to our plan's success was the notion that the N1 position of tetracycle **23** would be too sterically encumbered to itself add efficiently to the C3 electrophile.[33] Again, both Friedel–Crafts components **23** and **24** could be fashioned via halocyclization of the necessary indolic diketopiperazines **16**, thus preserving the expediency of our previous route.

Knowledge from our prior synthetic campaigns pointed to conditions for C3 bromide ionization being milder in the presence of a carboxybenzyl over a sulfonyl N1 substituent.[11,12,14] The synthesis of the tetracyclic diketopiperazine intermediates therefore began with readily available N^α-Boc-*N*-Cbz-L-tryptophan methyl ester and its straightforward conversion to diketopiperazines (+)-**26a** and (+)-**26b**, via dipeptide self-condensation in 80% and 83%, respectively.[29] Initial attempts to obtain tetracyclic bromide (+)-**18a** via diastereoselective bromocyclization of indole[11b,12] (+)-**26a** were hampered by poor solubility of these diketopiperazines in various organic solvents. Exposure of diketopiperazine (+)-**26a** to our standard procedure involving an equivalent of bromine in dichloromethane,[12] benzene,[11b] or acetonitrile,[11c,d] gave the desired bromide (+)-**18a** in < 30% yield.[34] This yield was substantially improved by addition of two equivalents of boron trifluoride to a slurry of precursor (+)-**26a** in acetonitrile prior to bromonium ion formation. To this end, the use of *N*-bromosuccinimide in place of bromine was found to result in a superior endo/exo ratio, and we were able to synthesize the versatile bromides (+)-**18a** and (+)-**18b** on a gram scale in 63% and 66% yield, respectively. Scaling the conditions to 15 g of diketopiperazine (+)-**26a** afforded bromide (+)-**18a** in 59% yield (Scheme 5).

In order to induce *ortho* (C8) selectivity in the Friedel–Crafts coupling, the *para* position (C6) on the eventual nucleophile **23** (Scheme 4) was temporarily blocked.[11a] After screening various Lewis and Brønsted acids in combination with *N*-chlorosuccinimide, the inclusion of trifluoroacetic acid[35] for bromide (+)-**18a**, or titanium(IV) tetrachloride in the case of bromide (+)-**18b**, led to 94% and 90% yield, respectively, of the corresponding C6-chlorinated tetracycles (+)-**27a** and (+)-**27b** (Scheme 5). We were pleased to note that the

presence of this C6-chlorine had no deleterious effect on silver(I)-promoted C3 bromide ionization, as shown by the rapid conversion of indolines (+)-**27a** and (+)-**27b** to hydrates (+)-**28a** and (+)-**28b** in respective yields of 96% and 93%. Their conversion to silyl ethers (+)-**29a** and (+)-**29b** on multigram scale was then followed by efficient and mild palladium-catalyzed carboxybenzyl removal,[36] with no sign of dehalogenation,[12] providing the desired indolines (+)-**30a** and (+)-**30b** (Scheme 5). The C3-hydroxyl could function as a stable placeholder, effectively locking in the cyclotryptamine substructure during the Lewis acid-promoted Friedel-Crafts step, later to be ionized and reduced under Brønsted acidic conditions.

Having firmly established the route to our designed nucleophilic and electrophilic Friedel-Crafts components (Scheme 5) for both alkaloid targets, now accessible in multigram quantities, we were well positioned to explore the key fragment-coupling step. Initial forays involving exposure of bromide (+)-**18a** to silver(I) hexafluoroantimonate, in the presence of indoline (+)-**30a** in nitroethane, led to 5–10% yield of C3–C8′-coupled product. Importantly, we were pleased to observe virtually no N1′-linked heterodimeric products. However, as before, mixtures of side products, largely attributable to competing *para*-directed oligomerizations of precursor (+)-**18a**, were still observed. Gratifyingly, replacement of tetracycle (+)-**18a** with its 6-chlorinated counterpart (+)-**27a** resulted in excellent mass balance, with the undesirable oligomerizations being mostly suppressed. Under our optimal silver(I) activation conditions,[29] the desired heterodimeric indoline (+)-**31a** was isolated in 41% yield, along with 24% of recovered starting material (+)-**30a**, and 30% of alcohol (+)-**28a** (Scheme 6), stemming from bromide (+)-**27a**.

Notably, treatment of recovered alcohol (+)-**28a** with thionyl bromide regenerated electrophile (+)-**27a** in near quantitative yields (Scheme 5), meaning both Friedel-Crafts partners (+)-**30a** and (+)-**27a** could be recycled to produce more of bis-indoline (+)-**31a**. The degree of molecular complexity and congested nature of the quaternary C3–C8′ bond being rapidly formed in a single step, under mild conditions, make this Friedel-Crafts reaction (Scheme 6) an exciting prospect for future applications in related natural and designed complex molecule syntheses. Two-dimensional NMR analysis provided decisive HMBC and NOESY correlations in support of our structural assignment of bis-indoline (+)-**31a** (Scheme 6). Nonetheless, our ability to swiftly convert this dimer to alkaloid (+)-**1** offered confirmation of the C3–C8′ dimeric linkage. We had originally envisaged relying on the N1 protection of dimer (+)-**31a** as a means for ensuring selective reopening of only the N1′ free indoline to the desired indole moiety. However, desilylation of ether (+)-**31a** proved ineffective with all but nucleophilic fluorides, which caused minor amounts of epimerization.[37] We eventually found that by first performing a combined hydrogenolysis and bis-dehalogenation on substrate (+)-**31a** to provide silyl ether (+)-**32a** in 79% yield (Scheme 6), the ensuing silyl cleavage could proceed without incident. To this end, treatment of dimer (+)-**32a** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) provided alcohol (+)-**33a** in 90% yield.[38]

With intermediate (+)-**33a** in hand, we were able to investigate a range of conditions for the penultimate tandem C3′ reduction–ring opening step to arrive at alkaloid (+)-**1** (Scheme 6).

After examining various conditions, the highest yield of (+)-asperazine (**1**, 67%, Scheme 6) was attained by a combination of triethylsilane with methanesulfonic acid. Based on our previous thiolation studies for the syntheses of epipolythiodiketopiperazine alkaloids,[11,14c–d], trifluoroacetic acid was originally chosen for C3′ ionization. However, when utilizing triethylsilane in conjunction with this acid, only a modest yield (40%) of (+)-asperazine (**1**) could be isolated, despite complete consumption of alcohol (+)-**33a** after 24 h. Though we reasoned that a substantial Thorpe–Ingold constraint should inhibit acid-catalyzed opening of the southern tetracycle, the recovery of water-soluble diketopiperazine side products from this experiment led us to infer that such a destructive pathway was enhanced by prolonged exposure to acid, as well as silane reduction of the indole moiety.[39] This conclusion was corroborated when substitution with methanesulfonic acid led to shorter reaction times and the improved yield of (+)-asperazine (**1**, Scheme 6). We were pleased to observe that all spectroscopic data for (+)-asperazine (**1**), along with its optical rotation, were in complete accord[29] with that of Overman's synthetic (+)-asperazine,[8] and the isolated metabolite.[3]

Having successfully employed this modular strategy to our highly convergent synthesis of (+)-asperazine (**1**), the stage was now set for us to tackle the first total synthesis of (+)-pestalazine A (**2**). We began by replacing indoline (+)-**30a** with its D-leucine counterpart (+)-**30b**, and under the same silver-mediated conditions to ionize bromide (+)-**27a**, obtained the corresponding heterodimer (+)-**31b** in 48% yield.[29] The improved yield in this reaction we attributed to the higher reaction concentrations attained using substrate (+)-**30b**, which was more soluble in nitroethane than indoline (+)-**30a**. The subjection of bis-chlorinated dimer (+)-**31b** to hydrodehalogenation provided silyl ether (+)-**32b** in 84% yield. The ensuing desilylation with tetrabutylammonium fluoride also proceeded without incident to furnish alcohol (+)-**33b** in 91% yield. Exposure of this intermediate to our optimal reduction–ring opening protocol, namely methanesulfonic acid and triethylsilane, delivered indole (+)-**2** in 73% yield (Scheme 6).

Our completion of this synthesis allowed for conclusive comparisons to be made between the structural data of alkaloid (+)-**2** and the isolation data originally reported by Che and coworkers for natural (+)-pestalazine A.[4] The ^{1}H and ^{13}C NMR signals corresponding to the positions around the indole and indoline portions of our molecule were in excellent agreement with the isolation report (< 0.5 ppm difference between ^{13}C NMR signals),[29] thereby confirming the crucial C3–C8′ connectivity. However, the same could not be said of several key ^{1}H signals corresponding to the diketopiperazine moieties, which differed markedly from the values in the isolation report, specifically the C11 (3.37[29] vs. 4.68[4] ppm), C15 (4.10[29] vs. 3.25[4] ppm), C11′ (4.16[29] vs. 3.46[4] ppm) and C15′ (3.03[29] vs. 3.80[4] ppm) positions (Scheme 6). Furthermore, indole (+)-**2**, which we now came to regard as (+)-*iso*-pestalazine A, exhibited an optical rotation of +99° (*c* 0.17, MeOH),[29] as compared to Che's value of +203° (*c* 0.10, MeOH)[4] for natural (+)-pestalazine A.

This propitious discovery would thus provide the ideal platform to demonstrate the power of our modular Friedel–Crafts approach to C3–C8′ coupling. *Without any change to our synthetic route, we pursued an alternative structural isomer of dimer (+)-**2**, in which the northern and southern diketopiperazines were inverted (*Figure 1). We believed this reversal

of top and bottom monomers to be highly plausible given that (+)-pestalazine A would be expected to share a similar biogenetic origin to (+)-pestalazine B (**4b**), which had undergone structural revision during its synthesis.[17g] Our hypothesis was further substantiated by the more recent discovery of (+)-asperazine (**1**) along with its N1′-linked isomer (–)-asperazine A (**4a**).[24] The facility with which we could simply switch the top and bottom monomers in our key Friedel-Crafts step (Scheme 7) proved decisive in enabling us to rapidly elucidate the structure that validated the data from the metabolite's isolation report.

With the necessary Friedel–Crafts components, indoline (+)-**30a** and bromide (+)-**27b**, already in hand (Scheme 5), we were able to direct the union of these tetracycles in formation of dimer (+)-**31c** in 32% yield (Scheme 7). In this case, we only deviated from our established conditions by including dichloromethane as co-solvent during fragment assembly. This allowed us to work at higher reaction concentrations while maintaining the optimal reactivity that nitroethane had consistently provided. The recovered starting material (+)-**30a** and the side product alcohol (+)-**28b** could be recycled, the latter by its conversion back to bromide (+)-**27b** in 98% yield by subjection to thionyl bromide and 2,6-di-*tert*-butyl-4-methylpyridine (Scheme 5).[29] Next, concomitant carboxybenzyl hydrogenolysis and bis-dechlorination of dimeric substrate (+)-**31c**, followed by desilylation of ether (+)-**32c**, proceeded in 69% and 91% yield, respectively (Scheme 7). The final reduction and ring-opening of alcohol (+)-**33c** furnished indole (+)-**3** in 71% yield. To our delight, all spectroscopic data for molecule (+)-**3** were in excellent agreement with those from Che's isolation report of (+)-pestalazine A,[4] thereby confirming (+)-**3** as the correct structure. Furthermore, the optical rotation for (+)-**3** was +211° (c 0.13, MeOH)[29] which was in good agreement with the reported value for the natural isolate.[4]

In summary, we completed expedient and unified total syntheses of (+)-asperazine (**1**), (+)-*iso*-pestalazine (**2**), and (+)-pestalazine A (**3**), in eleven steps from commercially available *N*-Boc-L-tryptophan methyl ester, and respective overall yields of 6.8%, 8.0% and 4.8%. Guided by our core ethos of retrobio-synthetic[2c,40] analysis, we developed a mild, regio– and stereocontrolled, *ortho*-directed Friedel–Crafts reaction for the formation of the critical C3–C8′ dimeric linkage in these molecules. Our late-stage C3–C8′ heterodimerization approach to structures (+)-**1**, (+)-**2** and (+)-**3** benefits from its use of advanced diketopiperazine tetracycles as easily interconvertible Friedel–Crafts components. The successful implementation of this new and convergent synthetic strategy for these dimeric diketopiperazines required the application of the new tandem C3′ reduction–ring opening transformation for the selective late-stage unraveling of the tryptophan motif in these alkaloids. Additionally, the generality of our three-step protocol from Friedel-Crafts product (+)-**31** to the final alkaloids was showcased by our ability to employ the same sequence with all three natural product targets. This paved the way for a modular, highly convergent strategy that allowed for a facile inversion of the tetracyclic fragments in (+)-*iso*-pestalazine (**2**) to (+)-pestalazine (**3**). The first total synthesis of (+)-pestalazine A (**3**) led to a revision of its structure from the originally reported polycyclic indole (+)-**2**. Our biogenetically inspired synthetic strategy to these fascinating alkaloids described here expands the range of heterodimeric diketopiperazines accessible by highly stereo- and regioselective late-stage complex fragment assembly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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29. See Supporting Information for details.

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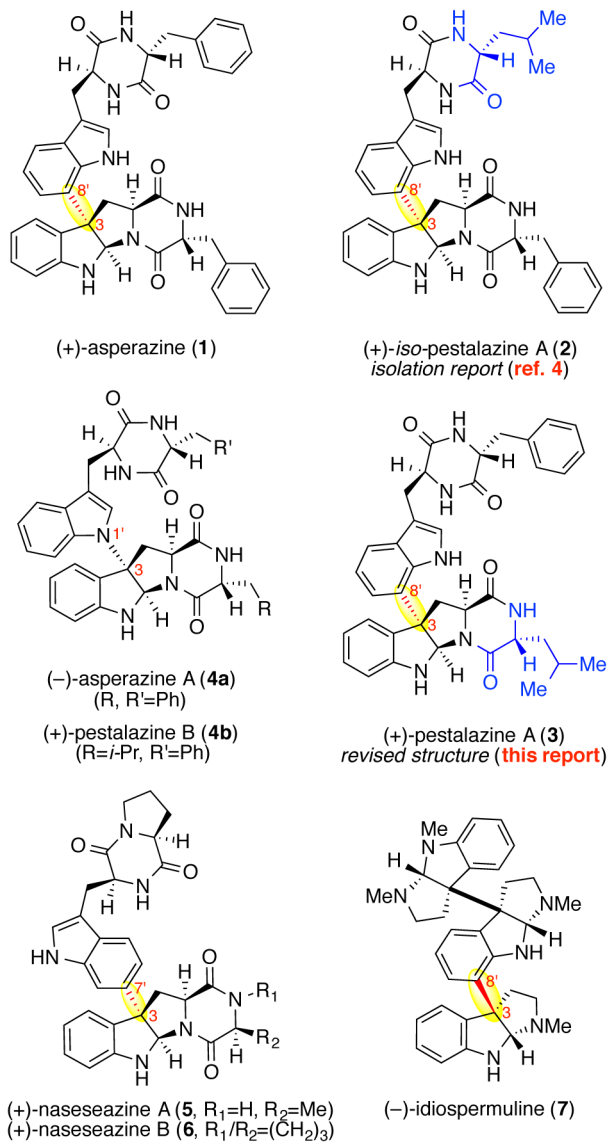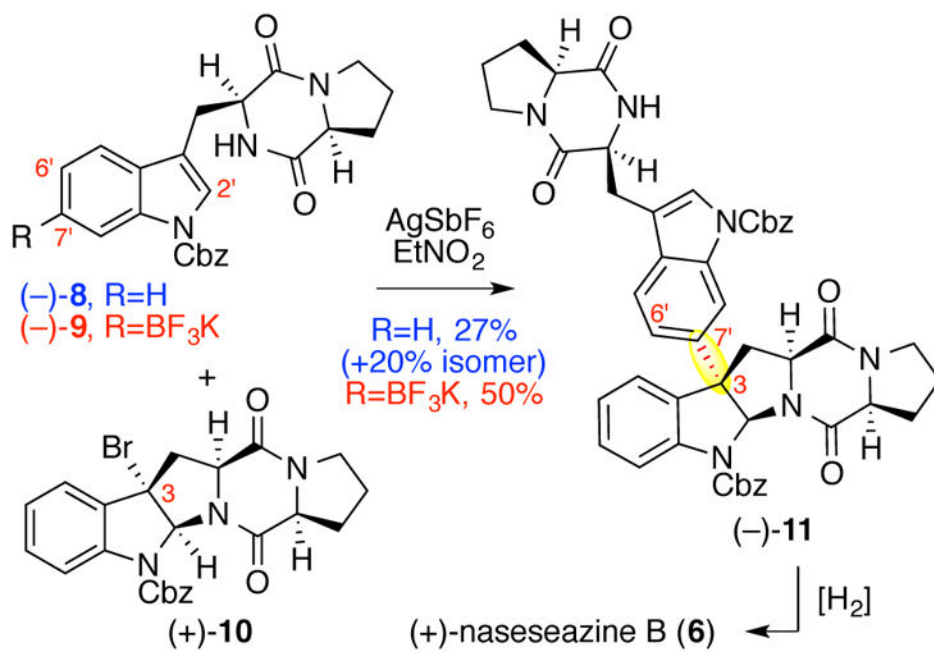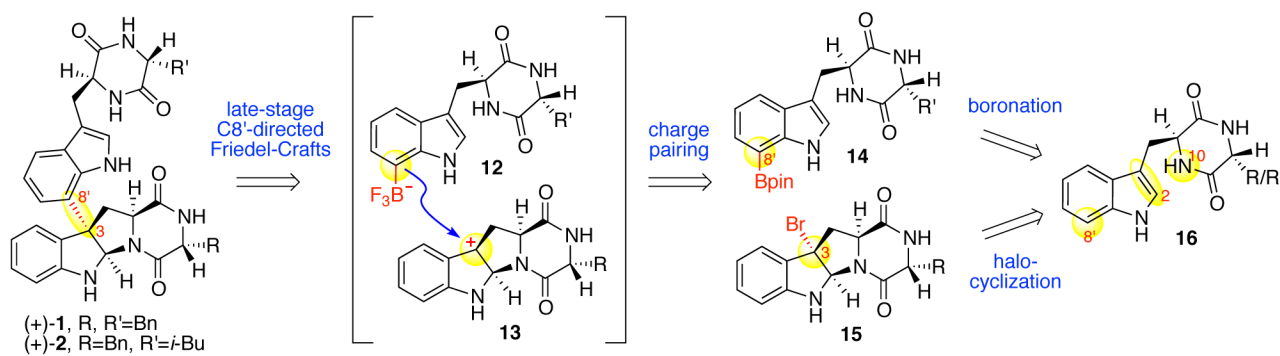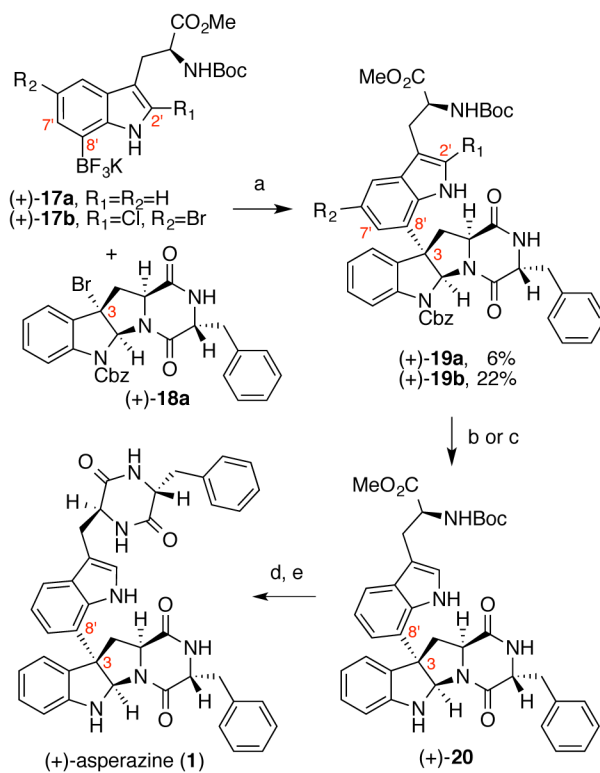40. Movassaghi M, Siegel DS, Han S. Chem Sci. 2010; 1:561. [PubMed: 21218186]

Figure 1.
Representative heterodimeric diketopiperazines.

Scheme 1.
Concise Synthesis of the Naseseazines.

Scheme 2.
Initial Retrosynthetic Analysis of Alkaloids (+)-**1** and (+)-**2** based on C8-Boronated Tryptophan Synthesis.
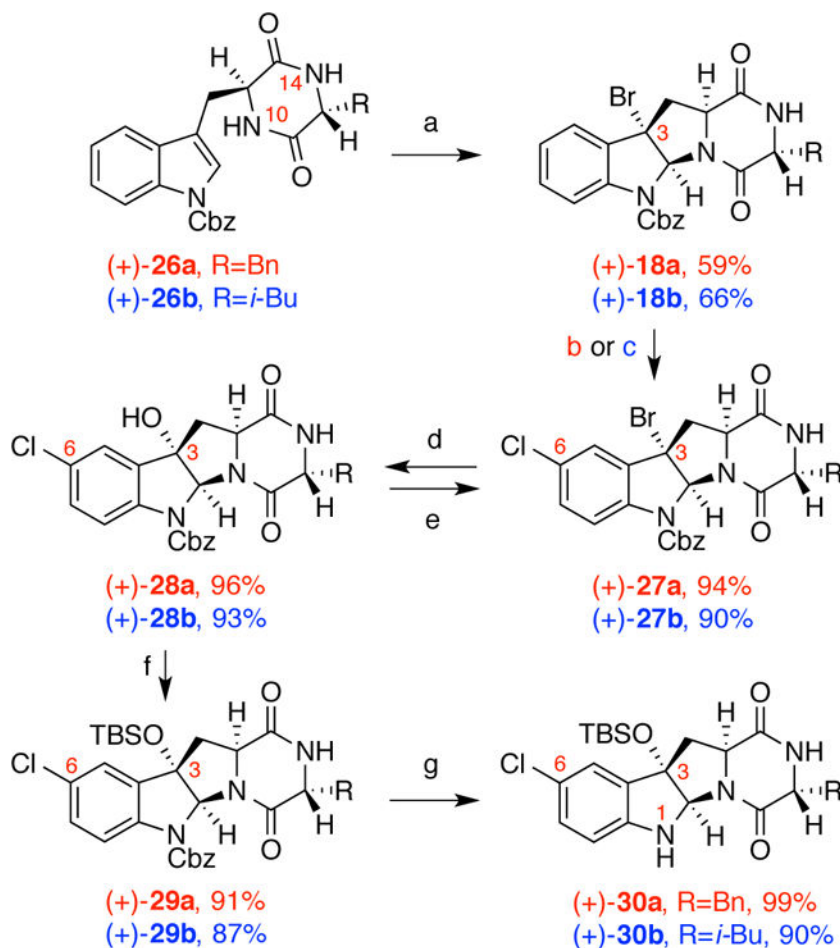
Scheme 3.

First Generation Synthesis of (+)-Asperazine (**1**).[a]

[a]Reagents and conditions: (a) AgSbF$_6$ (2.0 equiv), DTBMP (2.2 equiv), 18-crown-6 (2.0 equiv), EtNO$_2$, 23 °C, 1 h. (b) (+)-**19a**, Pd/C (10%), H$_2$, EtOAc, 7 h, 23 °C, 81%. (c) (+)-**19b**, Pd/C (10%), NH$_4$HCOO, EtOH, 70 °C, 7 h, 37%. (d) TFA, CH$_2$Cl$_2$, 23 °C, 2 h; EDC·HCl, HOBt, Boc-D-Phe, 23 °C, 4 h. (e) TFA, CH$_2$Cl$_2$, 23 °C, 7 h; *n*-BuOH, 120 °C, 46 h, 13% (over 2 steps).
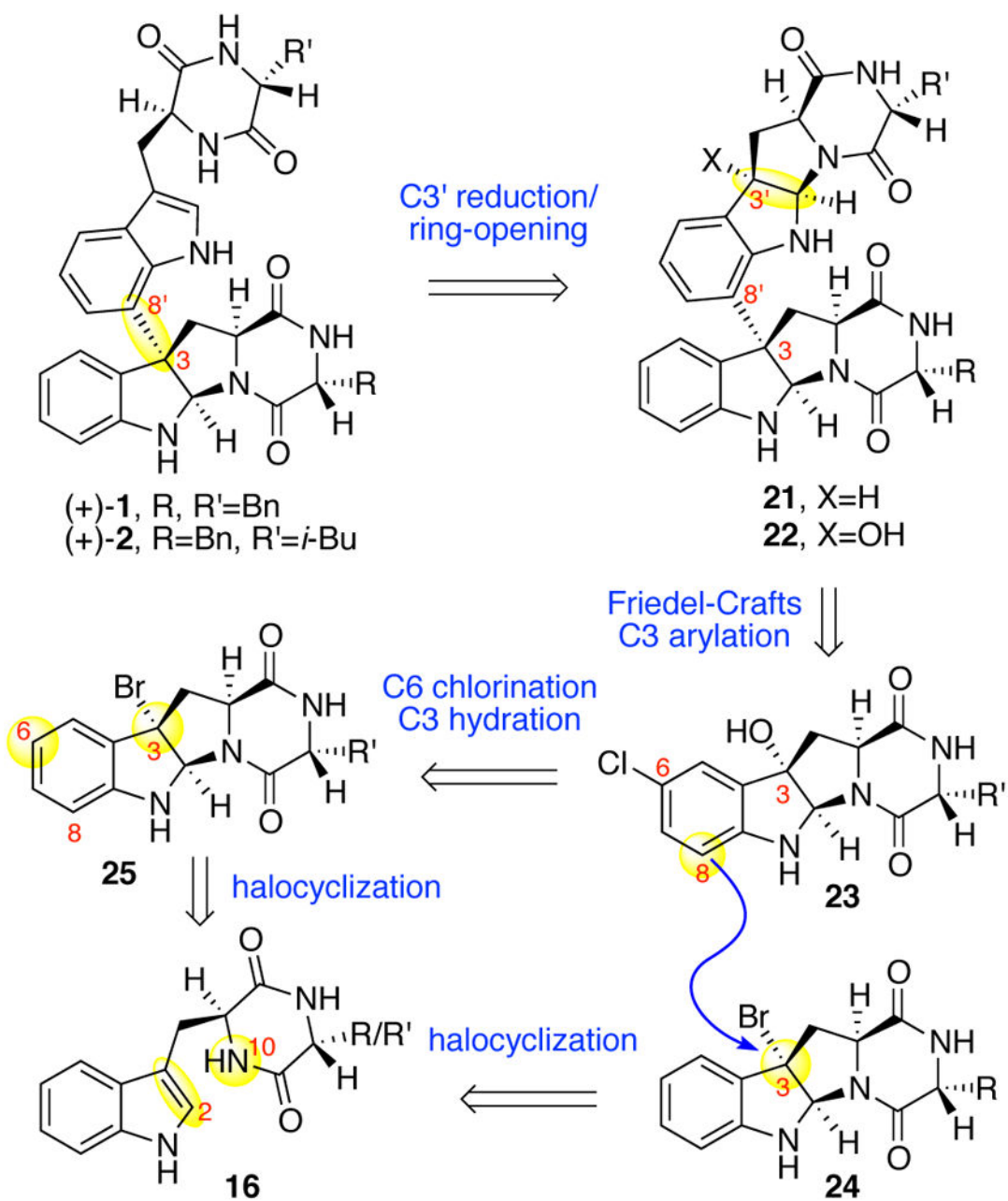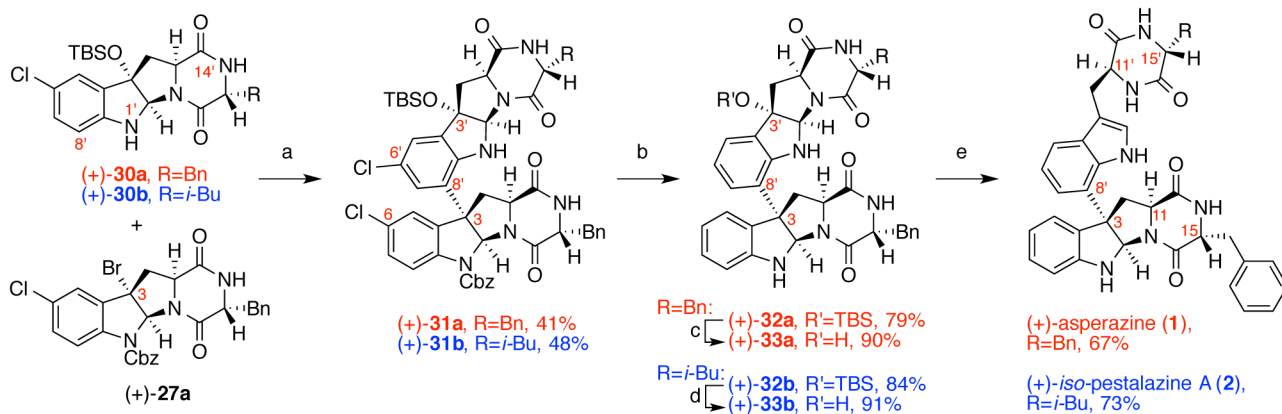
Scheme 4.
Revised Retrosynthetic Analysis of Alkaloids (+)-**1** and (+)-**2**.

Scheme 5.
Synthesis of Friedel-Crafts Components.[a]

[a]Reagents and conditions: (a) NBS, BF$_3$·OEt$_2$, MeCN, 0 °C, 40 min; (b) (+)-**27a**: NCS, TFA, MeCN, 23 °C, 20 h; (c) (+)-**27b**: NCS, TiCl$_4$, MeCN, 23 °C, 15 h; (d) AgSbF$_6$, H$_2$O, EtNO$_2$, 23 °C, 2 h; (e) SOBr$_2$, DTBMP, CH$_2$Cl$_2$, 0 °C, 40 min; (f) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 23 °C, 35 h; (g) Pd(OAc)$_2$, Et$_3$SiH, NEt$_3$, CH$_2$Cl$_2$, 23 °C, 4 h.

Scheme 6.
Friedel-Crafts Reaction and Ring-Opening: Synthesis of (+)-Asperazine (**1**) and (+)-*iso*-Pestalazine A (**2**).[a]

[a]Reagents and conditions: (a) AgSbF$_6$, DTBMP, EtNO$_2$, 23 °C, 40 min; (b) Pd/C (10%), HCO$_2$NH$_4$, EtOH, 20 h, 70 °C; (c) TASF, DMF, 23 °C, 40 min; (d) TBAF, THF, 23 °C, 1 h; (e) MsOH, Et$_3$SiH, CH$_2$Cl$_2$, 23 °C, 4 h.
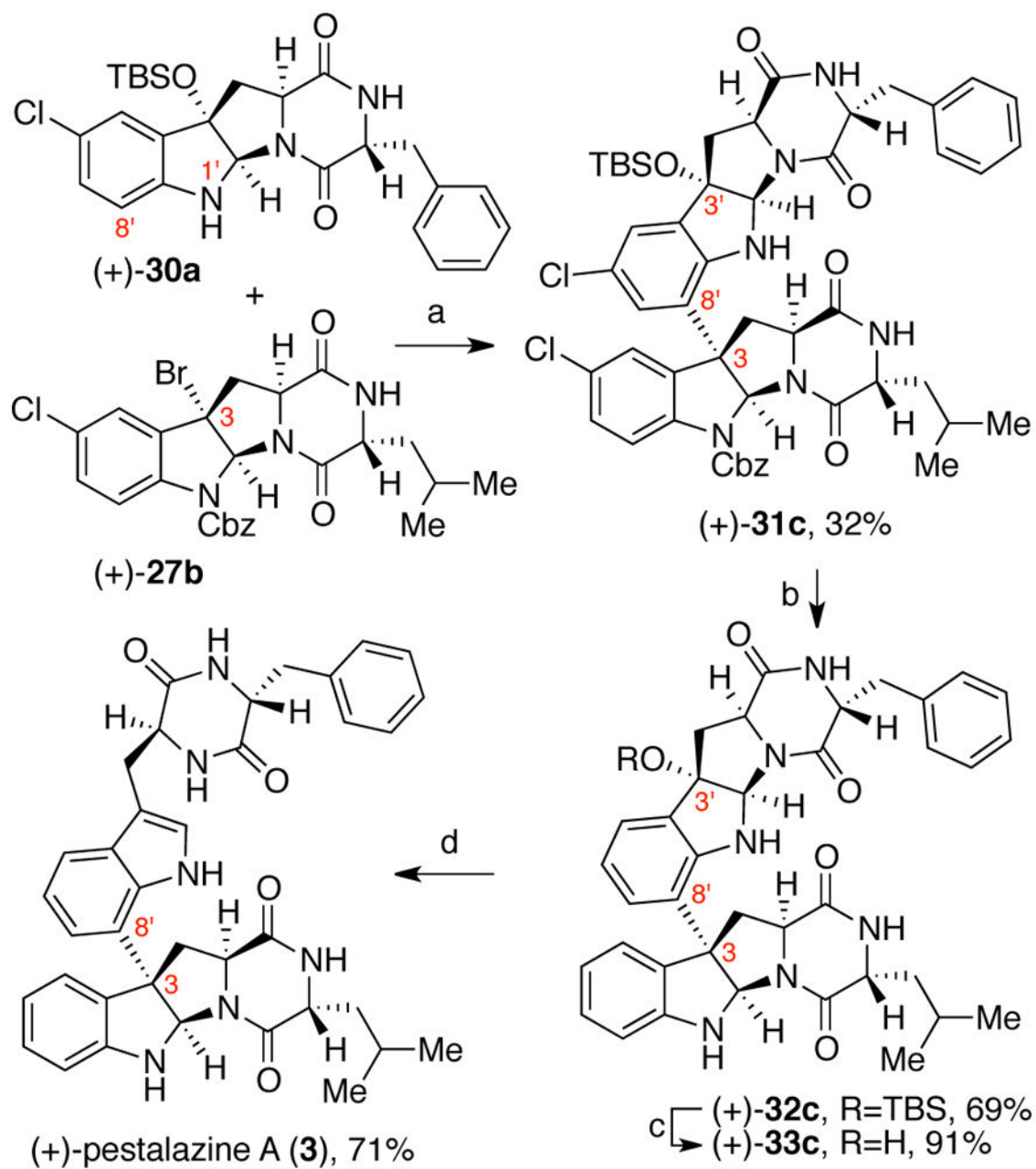
Scheme 7.
Synthesis of (+)-Pestalazine A (**3**).[a]
[a]Reagents and conditions: (a) AgSbF$_6$, DTBMP, EtNO$_2$/CH$_2$Cl$_2$ (3:1), 23 °C, 90 min; (b) Pd/C (10%), HCO$_2$NH$_4$, EtOH, 70 °C, 25 h; (c) TASF, DMF, 23 °C, 1 h; (d) MsOH, Et$_3$SiH, CH$_2$Cl$_2$, 23 °C, 4 h.