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Concise Total Synthesis of (+)-Asperazine A and (+)-Pestalazine B

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Abstract

The highly convergent total synthesis of dimeric diketopiperazine alkaloids (+)-asperazine A and (+)-pestalazine B is described. A critical aspect of our expedient route was the development of a directed regio- and diastereoselective C3–N1' coupling of complex tetracyclic diketopiperazine components. This late-stage heterodimerization reaction was made possible by design of tetracyclic diketopiperazines that allow C3-carbocation coupling of the electrophilic component to the N1' locus of the nucleophilic fragment. The application of this new coupling reaction to the first total synthesis of (+)-asperazine A led to our revision of the sign and magnitude of the optical rotation for the reported structure.

Graphical abstract

Dimeric diketopiperazine alkaloids are a class of biologically active natural products that have been isolated from a wide range of sources.¹ Their unique structures offer exciting opportunities to develop new chemical transformations. The introduction of the C3 linkage, which often unifies intricately decorated diketopiperazine subunits, and the requisite control of the C3-configuration continue to inspire the development of new synthetic methodologies.^{1,2} A subset of dimeric diketopiperazine alkaloids contain a C3–N1' bond that adjoins the subunits such as those found in asperazine A (**1**)³ and (+)-pestalazine B (**2**,

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Conflicts of interest

There are no conflicts to declare.

Figure 1).^{4,5} While many related dimeric alkaloids contain C3–carbon unions, the presence of this C3–N1' linkage in these and related alkaloids has spurred a wave of reports into formation of similar C3–nitrogen bonds.⁶ Whereas distinct coupling components of varying complexity have been used to access such C3–N1' bonds, in the most complex applications additional synthetic steps are often needed to assemble remaining aspects of the final target.^{5,6,7} Inspired by the way nature combines complex fragments to contrive these secondary metabolites, we sought the development of a new synthetic strategy for stereocontrolled late-stage union of whole and complex diketopiperazine fragments that include all the necessary structural components.² Herein we report the expedient total synthesis of (+)-pestalazine B (**2**) and the first total synthesis of (+)-asperazine A (**1**) via *directed late-stage heterodimerization of complex diketopiperazine fragments leading to exclusive formation of C3–N1' fusion with complete stereochemical control*. Furthermore, our concise synthesis of asperazine A (**1**) prompts our revision of the sign and magnitude of the optical rotation for the reported³ structure.

The crowded environment of the C3 stereocenter of many alkaloids bearing the C3–N bond presents a challenge for direct coupling of intact and complex fragments leading to the complete framework of the target alkaloids.^{2,5–7} As such the total syntheses of (+)-pestalazine B (**2**) by De Lera^{5a} and Liao,^{5b} as well as innovative syntheses of related C3–N1'-bound alkaloids,⁷ are driven by the early introduction of the C3–N1' linkage. Our group has a long-standing interest in developing mild and versatile chemistry that can rapidly generate the complex and sterically congested C3 linkages at the heart of these dimeric indole alkaloid natural products.^{2c,8} Our efforts have led to development of concise syntheses of both the C3–C7'-linked naseasazines,⁹ and C3–C8'-linked members of the asperazine and pestalazine family of alkaloids,¹⁰ specifically (+)-asperazine (**3**)¹¹ and (+)-pestalazine A (**4**) (Figure 1).⁴ This convergent approach espouses late-stage C3–C7' and C3–C8'¹² heterodimerizations of advanced diketopiperazines, realized through the development of mild, regio-, and stereocontrolled Friedel–Crafts reactions. Inspired by biogenetic hypotheses on the origins of these polycyclic alkaloids,^{2,13,14} our group sought a complementary late-stage approach to alkaloids (–)-**1** and (+)-**2** that would harness an orthogonal C3–N1' Friedel–Crafts based heterodimerization strategy.

Retrosynthetic Analysis

Our retrosynthetic analysis for dimeric alkaloids (+)-asperazine A (**1**) and (+)-pestalazine B (**2**) is illustrated in Scheme 1. We envisioned a highly convergent assembly via the union of two complex diketopiperazine fragments at the C3–N1' juncture. Motivated by our recent advances in directed assembly of complex fragments using silver-promoted addition of carbon nucleophiles to the C3 position of electrophilic cyclotryptamine substructures,^{9,10} we sought to apply a related strategy to secure the required C3–N1' linkage found in alkaloid (+)-**1** and (+)-**2**. Furthermore, our recently disclosed position-selective union of complex tetracyclic diketopiperazines¹⁰ employing a final stage reductive opening of an indoline substructure to the corresponding indole derivative allowed for identification of bis-indolines **5** as strategic precursors to alkaloid (+)-**1** and (+)-**2**. We envisioned that the synthesis of C3–N1'-linked dimer **5** could be achieved via N1'-directed attack of indoline **6** onto a C3

carbocation derived from silver-mediated ionization of bromide **7**. The previously observed exclusive carbon-nucleophilicity of indolines¹⁰ in such dimerization notwithstanding, we anticipated subtle structural variation in the nucleophilic component to provide an opportunity for interception of the electrophile by N1 of indoline **6** (vide infra). As in our syntheses of the C3–C8'-fused (+)-asperazine (**3**) and (+)-pestalazine A (**4**), an indoline nucleophilic fragment was selected to enhance nucleophilicity and overcome the propensity for unselective Friedel-Crafts dimerizations. We expected that the preparation of both tetracycles **6** and **7** could be achieved from readily available diketopiperazines **10**, procurable from the requisite dipeptides. Notably, we sought the development of diastereoselective bromocyclization conditions that would enable bifurcated access to bromides **8** and **9** from the diketopiperazines **10**.

Synthetic Approach

Our early investigation of bromocyclization conditions employing diketopiperazine (+)-**11**, readily prepared on deca-gram scale,¹⁰ were aimed at selective formation of *endo*-cyclization product^{8b} en route to alkaloids (+)-**3** and (+)-**4**. We had observed that silylation of diketopiperazine (+)-**11** in an effort to increase its solubility during bromocyclization resulted in preferential formation of the *exo*-configured tetracycle (–)-**12**. Under optimal conditions, trimethylsilylation followed by bromocyclization at sub-ambient temperatures provided the tetracyclic bromide (–)-**12** in 82% yield as a single diastereomer after chromatography (Scheme 2). Lewis acid promoted selective C6 chlorination afforded the chlorotetracycle (–)-**13** in 94% yield. Ionization of the C3-bromide of tetracycle (–)-**13** followed by hydration provided the corresponding C3 alcohol in 83% yield. The alcohol was converted to the corresponding *tert*-butyldimethylsilyl ether (–)-**14** in 89% yield to guard against undesired C3-activation and dehydration under dimerization reaction conditions. Palladium catalyzed reduction of ether (–)-**14** provided the indoline (–)-**15** in 78% yield (Scheme 2).

Our prior utilization of the nucleophilic *endo*-tetracyclic indoline (+)-**16** with electrophilic tetracyclic **17** exclusively afforded C–C bond formation (Scheme 3A).¹⁰ While this transformation was critical to the preparation of (+)-asperazine (**3**) and (+)-pestalazine A (**4**), we were intrigued by the possibility of augmenting the selectivity to favor interception of the electrophile at the N1-position of the nucleophile. Specifically, we envisioned the use of the *exo*-diastereomer of diketopiperazine **16**, the indoline (–)-**15**, as the nucleophile anticipating that its N1 position would be more accessible to engage the C3 of the electrophile **17** (Scheme 3B). This expectation was informed by observations from our studies directed at development of dimerization chemistry toward alkaloids (+)-**3** and (+)-**4**, where we noted a subtle difference in the N1-nucleophilicity of tetracyclic indolines such as **15** and **16**. For example, while N14-acetyl *endo*-tetracycle **18** (Scheme 4) was resistant to N1-acylation under a variety of conditions, the corresponding diastereomer, N14-acetyl *exo*-tetracycle **19** would give low but measurable yield of N1-acylated product.¹⁵ We attributed the difference in N1-reactivity of indolines **18** and **19** to the less sterically crowded environment of the N1-position in the *exo*-diastereomer. Consistent with this experimental observation, the minimization of the structures of tetracycles **18** and **19**, optimized using density functional

theory at B3LYP level,¹⁶ suggest that N1 is more than 0.1 Å removed from the corresponding C16-carbonyl oxygen atom in diastereomer **19** compared to diastereomer **18**.¹⁷ The reduced steric crowding of the N1-environment of the indoline substructure derived from such *exo*-tetracyclic diketopiperazines proved critical in the development of our new directed dimerization chemistry to *exclusively* afford the desired carbon–nitrogen bond en route to alkaloids (+)-**1** and (+)-**2**.

Armed with this insight we proceeded to investigate the use of *exo*-tetracyclic diketopiperazine (–)-**15** as the N1-nucleophilic component (Scheme 1). Under optimal conditions, the silver(I)-promoted activation of phenylalanine and leucine derived *endo*-tetracycles (+)-**20** and (+)-**21** in the presence of the *exo*-tetracyclic (–)-**15** led to *exclusive* C3–N1' fusion and formation of the heterodimeric products (–)-**22** and (–)-**23** in 50% and 46% yield, respectively (Scheme 5).^{10,18} This new strategy for the union of complex diketopiperazine fragments offers a highly convergent assembly at the C3–N1' linkage with complete stereochemical control in securing the tetrasubstituted C3-stereogenic center. With heterodimers (–)-**22** and (–)-**23** in hand, we proceeded to explore the application of our proposed reductive opening of the *exo*-tetracyclic substructure to afford the corresponding C3-indolyl portion of alkaloids (+)-**1** and (+)-**2**, respectively. Direct exposure of heterodimers (–)-**22** and (–)-**23** to acidic reductive conditions employing methanesulfonic acid and triethylsilane led to the desired products (–)-**25** and (–)-**26** (Scheme 6), respectively, in low yield (ca. 15–20%).¹⁹ While a modest improvement in the yield of the desired indole products (–)-**25** and (–)-**26** was observed through the use of pure samples of the C3-alcohol derivatives of heterodimers (–)-**22** and (–)-**23** as substrates for the reductive opening (ca. 50%), complications associated with isolation and purification of the intermediates due to decomposition on silica, prompted further optimization of the conditions. After extensive experimentation, we discovered that conversion of ethers (–)-**22** and (–)-**23** to the corresponding C3-alcohols, followed by exposure of the crude alcohols to optimal reductive ring-opening conditions led to formation of the desired indole products **25** and (–)-**26** in 83% and 65% yield, respectively (Scheme 6). We posited that this transformation would proceed via ionization of the C3' alcohol followed by in situ reduction of the C3'-carbocation to give the C3'-H dimer **24**, a transiently formed intermediate, that is subject to rapid isomerization to the desired C3-indolyl products.

With the convergent and highly selective fragment coupling and the subsequent reductive ring-opening providing access to C3–N1' fused heterodimers (–)-**25** and (–)-**26**, a mild single-step reduction of the aryl chlorides accompanied by unveiling of the N1-indoline of these intermediates gave access to (+)-asperazine A (**1**) in 75% yield and (+)-pestalazine B (**2**) in 73% yield, respectively (Scheme 6). All ¹H and ¹³C NMR data, as well as optical rotation (observed: [α]_D²³ = +194 (*c* = 0.10, MeOH); lit.: [α]_D = +199 (*c* = 0.10 MeOH),⁴ [α]_D²⁸ = +194 (*c* = 0.10, MeOH),^{5a} [α]_D²⁵ = +204 (*c* = 0.20 MeOH)^{5b}) for our sample of (+)-pestalazine B (**2**) were consistent with previously reported values. However, whereas all ¹H and ¹³C NMR data for our synthetic sample of (+)-asperazine A (**1**) were consistent with literature data,³ our measurement of its optical rotation (observed: [α]_D²³ = +135 (*c* = 0.11, MeOH)) was in contrast to that reported previously in both the sign and magnitude (lit.: [α]_D²⁴ = (–40, *c* = 0.10)³). It should be noted that the sign and magnitude of the optical

rotation obtained for our synthetic sample of (+)-asperazine A (**1**) is consistent with other closely related members of the family including (+)-pestalazines A (**4**) and B (**2**),^{4,5,10} in addition to (+)-asperazine (**3**).^{10,11} Therefore we offer a revised sign and magnitude of optical rotation for the structure previously reported³ for asperazine A (**1**).

Conclusions

We report the convergent total synthesis of (+)-pestalazine B (**2**) and the first total synthesis of (+)-asperazine A (**1**) in 10 steps from commercially available *N*-Boc-L-tryptophan methyl ester, in 7% and 10% overall yield, respectively. Our biogenetically inspired synthetic strategy required the advanced-stage union of complex diketopiperazine components at the characteristic C3–N1' linkage of the dimeric alkaloids (+)-**1** and (+)-**2**. Our convergent synthesis of these alkaloids utilized an *exo*-tetracyclic diketopiperazine to selectively provide N1-nucleophilicity necessary for interception of a C3-electrophile accessed from an *endo*-tetracyclic diketopiperazine coupling partner. The exclusive formation of the C3–N1' bond adjoining these fragments under mild conditions provided heterodimeric products (–)-**22** and (–)-**23**. This directed dimerization was followed by reductive opening of the *exo*-tetracyclic substructure to the corresponding C3-indolyl motif to rapidly access alkaloids (+)-**1** and (+)-**2**. Our approach provides an expedient synthetic route to (+)-asperazine A (**1**) and (+)-pestalazine B (**2**) with complete stereochemical control in securing the challenging tetrasubstituted C3-stereogenic center through late-stage stereo- and regioselective complex fragment assembly. Furthermore, our synthesis of the reported structure of asperazine A (**1**)³ enabled our revision of the sign and magnitude of the optical rotation for this alkaloid.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. For example, treatment of diketopiperazine **18** with CbzCl (5 equiv), Et₃N (10 equiv), and DMAP (1 equiv) in CH₂Cl₂ at 23 °C for 24 h resulted in no N1-acylation, whereas exposure of

diketopiperazine **19** to the same conditions led to isolation of 4% of the corresponding N1-carbamate.

16. The geometries in the gas phase were optimized with molecular modeling (MMFF) followed by density functional calculations at the B3LYP level with 6-31G(d) as the basis set (Spartan 14, Version 1.1.1, by Wavefunction, INC.).
17. See Supporting Information for details.
18. The mass balance was comprised of recovered *exo*-tetracycle (–)-**15** (ca. 30% yield) along with nearly quantitative recovery of the *endo*-tetracycles as the corresponding C3 alcohols.
19. Exposure of dimeric diketopiperazines (–)-**22** and (–)-**23** to MsOH (25 to 50 equiv) and Et₃SiH (50 to 100 equiv) in CH₂Cl₂ or MeCN for 24 h at 23 °C provided the desired heterodimers (–)-**25** and (–)-**26** in no more than 20% yield.

asperazine A (1)

$[\alpha]_D^{23} = -40$ (ref. 3)

$[\alpha]_D^{23} = +135$ (this work)

(+)-pestalazine B (2)

(+)-asperazine (3)

(+)-pestalazine A (4)

Figure 1.
Representative heterodimeric diketopiperazines.

Scheme 1. Retrosynthetic analysis of (+)-asperazine A (**1**) and (+)-pestalazine B (**2**).

Scheme 2.

Preparation of nucleophilic tetracycle (-)-15. Conditions: (a) $\text{F}_3\text{C}(\text{C}=\text{NSiMe}_3)\text{OSiMe}_3$, MeCN, 80 °C, 19 h; Br_2 (1.05 equiv), CH_2Cl_2 , $-45 \rightarrow -20$ °C, 2 h, 82%. (b) NCS (3 equiv), TiCl_4 (1M in CH_2Cl_2 , 3 equiv), MeCN, 6 h, 23 °C, 94%. (c) AgSbF_6 (1.5 equiv), H_2O (10 equiv), MeNO_2 , 23 °C, 1 h, 83%. (d) TBSOTf (4 equiv), 2,6-lutidine (8 equiv), CH_2Cl_2 , 23 °C, 19 h, 89%. (e) $\text{Pd}(\text{OAc})_2$ (7 mol%), Et_3N (25% mol), Et_3SiH (1.5 equiv), CH_2Cl_2 , 23 °C, 4 h, 78%. NCS = *N*-chlorosuccinimide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethane-sulfonate.

A. C-linked Dimerization **B. N-linked Dimerization** **Scheme 3.**

Union of tetracycles to afford C- vs. N-linked dimers through transition-state structures **A** and **B**, respectively.

Scheme 4.

Minimized structures of *endo*-tetracycline **18** and *exo*-tetracycline **19**.

Scheme 5.

Formation of C3-N1' conditions: (a) AgSbF₆ (2 equiv), DTBMP (2 equiv), EtNO₂, 65 °C, 70 min, 50% (-)-22, 46% (-)-23. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

Scheme 6.

Synthesis of alkaloids (+)-**1** and (+)-**2**. Conditions: (a) TASF (5 equiv), MeCN, 23 °C, 5 h; MsOH (25 equiv), Et₃SiH (50 equiv), CH₂Cl₂, 18 h, 83% (-)-**25**, 65% (-)-**26**. (b) 10 % Pd/C (1.5 equiv), HCO₂NH₄ (50 equiv), Et₃N (10 equiv), MeOH, 65 °C, 4 h, 75% (+)-**1**, 73% (+)-**2**. TASF = Tris(dimethylamino)sulfonium difluorotrimethylsilicate, MsOH = methanesulfonic acid.