

Concise Total Synthesis and Stereochemical Revision of (+)-Naseseazines A and B: Regioselective Arylative Dimerization of Diketopiperazine Alkaloids

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Supporting Information

ABSTRACT: Concise and enantioselective total syntheses of (+)-naseseazines A and B are described. Our regioselective and directed dimerization of diketopiperazines provides their critical C3–C_{sp²} linkages, an assembly with plausible biogenetic relevance. We revise the absolute stereochemistry of (+)-naseseazines A and B.

Dimeric diketopiperazine alkaloids, which constitute an important class of natural products, possess an expansive repertoire of biological activities intimately mirroring their structural diversity.¹ An important source of diversity of great strategic relevance to their synthesis is the nature of the dimeric linkage. In recent years, much progress has been made in regard to the rapid construction of the C₃_{sp³}–C_{3'}_{sp³}^{2–4} and C₃_{sp³}–N1'⁵ bond connectivities. In this work, we aimed to broaden the spectrum of dimerization modes that are predisposed for rapid disconnection. We describe herein a Friedel–Crafts-based method for the regioselective and directed C3 functionalization of advanced diketopiperazine intermediates employing a range of π -nucleophiles. The concise nature and broad relevance of this approach to the synthesis of C3-arylated hexahydropyrroloindole alkaloids⁶ (Figure 1) are highlighted through the first total syntheses of Fijian actinomycete *Streptomyces* sp. derived alkaloids (+)-naseseazine A (1) and B (2),⁷ an endeavor culminating in their stereochemical revision.

In deference to our desire for a maximally convergent synthesis of 1 and 2 and consistent with a plausible hypothesis for their biogenesis,^{8,9} our retrosynthetic analysis commenced with the disconnection of the C3–C7' bonds of 1 and 2,¹⁰ affording two diketopiperazine fragments of comparable complexity (Scheme 1). Tetracyclic bromide 6 could be obtained by bromocyclization of diketopiperazine 8,^{3b} whereas pinacolboronate 5 could be prepared from the corresponding bromodiketopiperazine 7. We envisioned that ionization of 6 would provide the necessary C3-electrophile,^{11,12} while conversion of the pinacolboronate function of 5 to the corresponding trifluoroborate¹³ would offer the necessary C7'-nucleophilic partner for a directed and regioselective sp³–sp² bond formation (Scheme 1).

In our first-generation approach, alanine and proline diketopiperazines (–)-9 and (–)-10, the requisite tetracyclic bromides en route to the corresponding naseseazine alkaloids, were synthesized in 89 and 71% yield, respectively, from readily available *N*^α-Boc-*N*^β-Cbz-L-tryptophan methyl ester.¹⁴ Exposure of (–)-9 and (–)-10 to pyridinium tribromide in 2,2,2-trifluoroethanol afforded the respective tetracyclic bromides (+)-11 and (+)-12 in

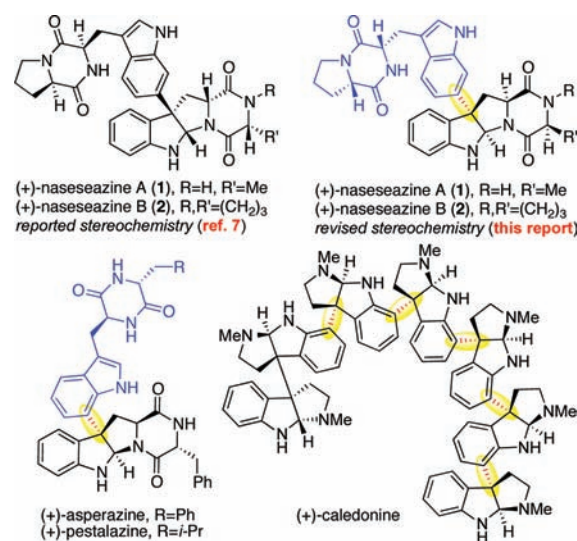


Figure 1. Representative C3-arylated hexahydropyrroloindole alkaloids and revised structures of (+)-naseseazine A (1) and B (2).

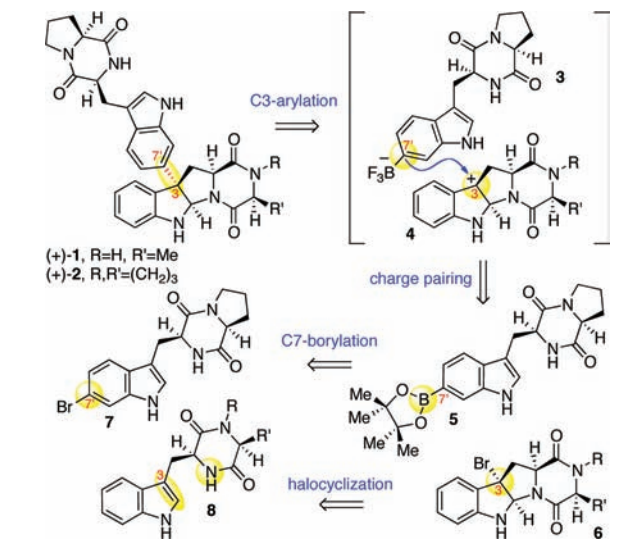
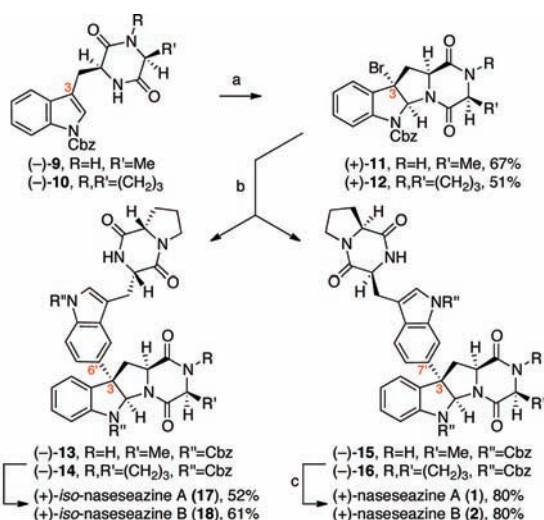
67 and 51% yield as single diastereomers (Scheme 2). In possession of all the necessary components, we sought to validate the feasibility of our planned Friedel–Crafts-based strategy for C3-arylation at this juncture. Treating a solution of (–)-10 (1.5 equiv) and (+)-11 (1 equiv) with AgSbF₆ in nitroethane under the optimized conditions (see below) afforded a mixture of regioisomeric dimers (–)-13 and (–)-15 in 53% combined yield [(–)-13:(–)-15 = 1:1.4]. Similarly, (–)-10 could be coupled to tetracyclic bromide (+)-12 to give regioisomeric dimers (–)-14 and (–)-16 in 47% combined yield [(–)-14:(–)-16 = 1:1.4]. Hydrogenolytic removal of the carboxybenzyl groups on compounds 13–16 provided the first access to (+)-*iso*-naseseazine A (17) and B (18) as well as our target alkaloids 1 and 2, respectively (Scheme 2). Notably, selectivity in favor of the regioisomer with the desired C3–C7' bond connectivity was observed during the coupling reaction.⁸ While we were pleased with the utility of this new mode of heterodimerization, the low level of regioselectivity in this unguided union prompted further refinement of our new strategy to give a more selective and directed assembly of complex diketopiperazine fragments.

We anticipated that the regioselective arylation of tetracyclic bromide (+)-11 could be achieved by installation of a directing

Received: July 19, 2011

Published: August 29, 2011

Scheme 1. Retrosynthetic Analysis for 1 and 2

Scheme 2. First-Generation Syntheses of 1 and 2^a

^a Conditions: (a) PyHBr₃, 2,2,2-trifluoroethanol, 23 °C. (b) (-)-10, AgSbF₆, EtNO₂, 23 °C; for (+)-11, 13:15 = 1:1.4, 53%; for (+)-12, 14:16 = 1:1.4, 47%. (c) H₂, Pd/C, AcOH, 23 °C.

group at an appropriate position of the π -nucleophile.^{15,16} Importantly, we wished to increase the ratios of (-)-15 and (-)-16 to (-)-13 and (-)-14, respectively. In the early stages of our optimization studies, we selected thiophene, with its innate preference for reaction at the 2-position (19:20 = 6.2:1; Table 1, entry 1), as our model system. While 3-cuprate, 3-trimethylstannyl, and 3-zinc chloride thiophene derivatives were ineffective as directed nucleophiles in the C3-arylation of (+)-11, the use of the corresponding potassium trifluoroborate derivative proved promising.^{15,17} We expected that the use of 18-crown-6 as an additive would confer multiple benefits: increased solubility of the potassium trifluoroborate salt, enhanced nucleophilicity of the arene via ion pairing with the electrophile, and facilitated trifluoroborate elimination by further dissociation of the potassium aryltrifluoroborate ion pair.¹⁸ Indeed, when AgSbF₆ was introduced into a solution of (+)-11, potassium 3-thiophenetrifluoroborate, and

Table 1. Lewis Acid-Promoted C3-Nucleophile Substitution

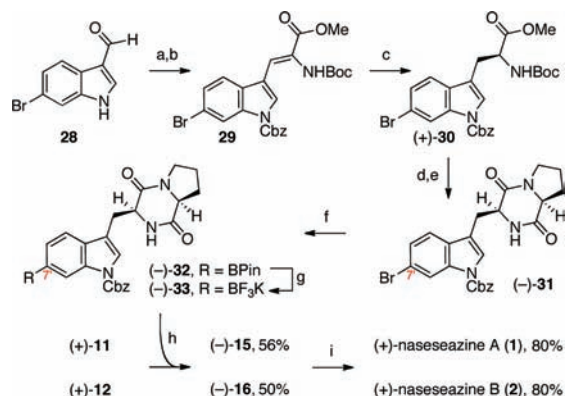
Entry	Nucleophile	Solvent, Temp (°C)	Nu-	Yield (%) ^a
1		CH ₂ Cl ₂ , 23		77 (6.3:1) ^b
2		EtNO ₂ , -45°		50 (17:1) ^b
3		CH ₂ Cl ₂ , 23		60
4		CH ₂ Cl ₂ , 23		52
5		CH ₂ Cl ₂ , 23		91
6		CH ₂ Cl ₂ , 23		89
7		CH ₂ Cl ₂ , 23		50
8		EtNO ₂ , -45°		26 (3.9:1) ^d
9		EtNO ₂ , -45°		54 (2.4:1) ^d
10		EtNO ₂ , 23° ^c		59

^a Isolated yields; averages of two experiments; AgSbF₆ (2.0 equiv) and nucleophile (2.0 equiv). ^b Regioisomeric ratios determined by ¹H NMR analysis. The major regioisomer is shown. ^c 18-crown-6 (2.0 equiv). ^d The minor regioisomer is the para adduct.

18-crown-6 in CH₂Cl₂ at 23 °C, we obtained the desired C3-arylated product as a mixture of regioisomers favoring the desired C3 adduct (19:20 = 1:1.3). Subambient temperatures were then examined to enhance the regioselectivity for C3; however, the selectivity did not improve noticeably at 0 °C in CH₂Cl₂, and conversion to the product was not observed at lower temperatures. Thus, we turned to higher-dielectric-constant media to facilitate the ionization event.

Nitrile-based solvents such as acetonitrile and benzonitrile enabled ionization; however, tight solvent–carbocation interactions significantly impeded the nucleophilic reaction, and hydroxylation¹⁹ and Ritter reaction adducts²⁰ formed in significant amounts as principal byproducts. Similarly, the use of DMF resulted exclusively in hydroxyl and formate addition products.²¹ Ultimately, we discovered that the use of nitroalkane solvents was most effective for the desired transformation. The level of regioselectivity improved for the C3-thiophenyl adduct at -25 °C in nitromethane (19:20 = 1:2.8). Under optimal conditions, treatment of (+)-11 with 3-thiophenetrifluoroborate at -45 °C in nitroethane provided the desired product with an excellent level of regioselectivity (50% yield, 19:20 = 1:17; Table 1, entry 2).⁹

Encouraged by the efficiency and high regioselectivity observed in the trifluoroborate-directed thiophenylation of (+)-11, we sought to examine the generality of this chemistry with respect to other π -nucleophiles. Table 1 demonstrates the substrate scope for the nucleophilic addition at the C3-position of (+)-11: allyltri-*n*-butylstannane (60%; entry 3), allyltrimethylsilane

Scheme 3. Concise and Directed Syntheses of **1** and **2**^a

^a Conditions: (a) CbzCl, Et₃N, DMAP, CH₂Cl₂, 100%. (b) Boc- α -phosphonoglycine trimethylester, DBU, CH₂Cl₂, 97%. (c) H₂ (80 psi), (S,S)-Et-DUPHOS-Rh (1.8 mol %), CH₂Cl₂, MeOH, 97%, >99% ee. (d) TFA, CH₂Cl₂; EDC·HCl, HOBT, Et₃N, Boc-L-Pro. (e) TFA, CH₂Cl₂; NH₄OH, MeOH, 75% (two steps). (f) 2-aminobiphenyl-(XPhos)PdCl (5 mol %), XPhos (15 mol %), (BPin)₂, K₃PO₄, DMSO, 60 °C, 65%. (g) KHF₂(aq), MeOH, 88%. (h) AgSbF₆, 18-crown-6, EtNO₂, 23 °C. (i) H₂, Pd/C, AcOH, 23 °C.

(52%; entry 4), and (isopropenyloxy)trimethylsilane (91%; entry 5) act as suitable nucleophiles. Notably, vicinal quaternary stereocenters can also be installed efficiently, as demonstrated by the addition of methyl trimethylsilyl dimethylketene acetal (89%; entry 6). Electron-rich arenes such as thiophene (77%; entry 1) and electron-neutral arenes, best represented by toluene (50%; entry 7), can also be incorporated efficiently. Toluene itself adds with exclusive selectivity for the para position, a preference that can be reversed using the trifluoroborate group.

The regioselectivity of aryltrifluoroborate addition, although moderate, is eroded in the presence of ortho substituents, such as in *o*-tolyltrifluoroborate (**25:24** = 3.5:1; Table 1, entry 8) and 2-methoxyphenyltrifluoroborate (**26:26'** = 2.7:1; entry 9), likely reflecting a sterically demanding transition state in the formation of quaternary stereocenters. Unfortunately, electron-deficient arenes, such as potassium 4-acetylphenyl-trifluoroborate, lead to exclusive C3-fluorination via fluoride transfer from the aryltrifluoroborate. Nucleophiles without a competent electrofuge, such as styrene, result in polymerization. This problem can be circumvented through the use of a trifluoroborate group, which likely is eliminated faster than a proton (59%; entry 10). In general, the efficiency of the reactions appears to correlate well with the relative nucleophilicity of the compounds.²² The mildness of the reaction conditions is also of particular note. The utility of the method in late-stage applications is highlighted by the preservation of stereochemical integrity at C11 and C15, epimerizable stereocenters^{3b,5e} that are consequential for the further derivatization of advanced intermediates.^{3c}

Our planned strategy for the directed union of the advanced-stage diketopiperazine fragments for the syntheses of (+)-naseeseazine A (**1**) and B (**2**) required the synthesis of trifluoroborate (-)-**33** (Scheme 3). Starting from commercially available 6-bromo-3-carboxaldehyde (**28**), benzyloxycarbonylation followed by a Horner–Wadsworth–Emmons reaction with Boc- α -phosphonoglycine trimethyl ester afforded enamide **29** in 97% yield over the two steps.²³ Catalytic asymmetric hydrogenation of the olefin using (S,S)-Et-DUPHOS-Rh (1.8 mol %

efficiently provided bromotryptophan derivative (+)-**30** in 97% yield and >99% ee.²⁴ An expeditious two-step sequence afforded bromocyclodipeptide (-)-**31** in 75% yield from (+)-**30** without the need for chromatography. Our initial efforts to introduce the pinacol boronic ester function via Pd-catalyzed cross-coupling with pinacolborane²⁵ were hindered by undesired carboxybenzyl deprotection as well as the formation of significant amounts of a C7'-reduction byproduct. After significant experimentation, we recognized that employing Buchwald's aminobiphenyl-(XPhos)PdCl precatalyst (**34**, 5 mol %),²⁶ XPhos (15 mol %), K₃PO₄ (3 equiv), and bis(pinacolato)diboron (3 equiv) in DMSO at 60 °C effectively afforded the desired pinacol boronate (-)-**32** in 65% yield (Scheme 3). Treatment of (-)-**32** with aqueous potassium hydrogen difluoride gave the key potassium trifluoroborate (-)-**33** in 88% yield.¹³

Treatment of alanine-derived tetracyclic bromide (+)-**11** (1 equiv) with tetracyclic potassium trifluoroborate (-)-**33** (1.5 equiv) in the presence of AgSbF₆ and 18-crown-6 in nitroethane at 23 °C afforded the desired (-)-dicarboxybenzyl naseeseazine A (**15**) in 56% yield with complete regioselectivity (Scheme 3). Under identical conditions, exposure of proline-derived tetracyclic bromide (+)-**12** (1 equiv) with (-)-**33** (1.5 equiv) gave (-)-dicarboxybenzyl naseeseazine B (**16**) in 50% yield as a single regioisomer (Scheme 3). Excitingly, the ability to override the innate nucleophilic tendencies of the indole substructure through an appropriately positioned directing group has broad implications for the synthesis of related congeners of different regioisomeric constitutions about the C₃_{sp³}-C_{sp²} dimeric linkage, such as in (+)-asperazine²⁷ and (+)-pestalazine²⁸ as well as the entire superfamily of oligomeric cyclotryptamines,¹ represented by (+)-caledonine (Figure 1).²⁹

Hydrogenolytic removal of the benzyloxycarbonyl groups from (-)-**15** and (-)-**16** with Pd/C in acetic acid provided (+)-naseeseazine A (**1**) {[α]_D²² = +123 (c 0.12, CH₃OH); lit. [α]_D²³ = +139 (c 0.10, CH₃OH)}⁷ and (+)-naseeseazine B (**2**) {[α]_D²² = +101 (c 0.23, CH₃OH); lit. [α]_D²³ = +95 (c 0.08, CH₃OH)},⁷ respectively, each in 80% yield (Scheme 3). All of the spectroscopic data for **1** and **2** matched those reported in the literature.⁷ The agreement between the optical rotation signs for our synthetic samples of **1** and **2** and those of the natural alkaloids stands in direct contrast to the predicted absolute stereochemistry of **1** and **2** based on C₃ Marfey's analysis³⁰ of degradation products. In view of the use of L-amino acid derivatives in our synthesis of **1** and **2**, we revise the absolute stereochemistry of these dimeric natural alkaloids (Figure 1).

We have developed a general approach to dimeric diketopiperazine alkaloids containing a C₃_{sp³}-C_{sp²} linkage, with the solution yielding a concise nine-step total synthesis of (+)-naseeseazine A (**1**) and B (**2**). Our mild and highly regioselective Friedel–Crafts-based coupling strategy, featuring the formation of quaternary stereogenic centers, facilitated the late-stage union of advanced diketopiperazine structures in a convergent manner. Our total syntheses of **1** and **2** have also enabled the revision of the absolute stereochemistries of these natural products. This new fragment assembly strategy, ideated from a close adherence to biogenetically relevant intermediates and transformations, highlights the power of a strategic framework guided by retrobiosynthetic³¹ analysis.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and copies of UV–vis and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENT

We acknowledge financial support by NIH-NIGMS (GM089732), Amgen, and DuPont. M.M. is a Camille Dreyfus Teacher-Scholar. J.K. acknowledges a National Defense Science and Engineering Graduate Fellowship. We thank Dr. Omar K. Ahmad and Dr. Nicolas Boyer for helpful discussions and Prof. R. J. Capon for a communication regarding the discrepancy between our respective stereochemical assignments of **1** and **2**.

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- (9) See the SI for details.
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- (19) C3-hydroxylated products likely arise from hydrolysis of an activated intermediate upon aqueous quench.
- (20) The reaction of PhBF₃K (2 equiv) with (+)-**11** (1 equiv) and AgSbF₆ (2 equiv) in MeCN at 23 °C resulted in the C3-phenyl adduct (59% yield) and a C3-acetamide adduct (41% yield).
- (21) The reaction of PhBF₃K (2 equiv) with (+)-**11** (1 equiv) and AgSbF₆ (2 equiv) in DMF at 23 °C resulted in the C3-hydroxylated product (22% yield) and a C3-formate adduct (72% yield).
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