Asymmetric Total Synthesis of (+)-Merobatzelladine B**

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Polycyclic guanidine natural products, such as batzelladines A, E, and F, exhibit a rich and diverse array of interesting biological activities (Figure 1).[1,2] Some polycyclic guanidine alkaloids have been shown to inhibit protein–protein interactions, including the binding of HIV gp120 to CD4 on human T-cells. Furthermore, many polycyclic guanidines display potent antiviral, antimalarial, and immunosuppressive properties.

In 2009, Matsunaga et al. reported the isolation of merobatzelladines A and B (4 and 5) from the marine sponge Monanchora sp. (Figure 2).[3] These compounds are members of a new subclass of the batzelladine alkaloids that possess the signature tricyclic guanidine core common to all batzelladines, but display a unique stereochemical feature that differs from other members in this family. The C8 alkyl substituents in merobatzelladines A and B are positioned in a syn relationship with the C6 hydrogen atoms, whereas other related natural products, such as batzelladines A, E, or F (1–3), have these groups positioned in an anti relationship. Merobatzelladines A and B exhibit moderate antimicrobial activity against Vibrio anguillarum, and also show inhibitory activity against the K1 strain of Plasmodium falciparum (IC50 = 0.48 μg/mL and 0.97 μg/mL, respectively). Given the rich biological activity of the related batzelladine alkaloids, it is possible that merobatzelladines A and B may exhibit additional useful properties that have yet to be reported.

Because of the importance of polycyclic guanidine alkaloids, several different approaches have been employed for the synthesis of these compounds. The most widely utilized routes typically generate the fused ring system through condensation reactions,[4] cycloaddition reactions,[5] radical cyclizations,[6] or substitution reactions.[7] Although these routes have proven highly useful, none provide a means for the generation of a C–C bond adjacent to the ring (such as the C8/CH3 bond in 5) during the ring-closing event. Also, none of these routes have been employed for the generation of molecules with a syn relationship between the C8 alkyl group and the C6 H atom, such as that found in merobatzelladines A and B. Herein, we describe the first total synthesis of merobatzelladine B (5) utilizing a new strategy for the construction of polycyclic guanidine alkaloids that provides the natural product as a single stereoisomer in high optical purity.

Our approach to the synthesis of merobatzelladine B centered on the use of Pd-catalyzed alkene carboamination reactions for the formation of two of the three rings in the natural product.[8] As shown in Scheme 1, we envisioned that a Pd-catalyzed carboamination between vinyl bromide and an appropriately functionalized γ-aminoalkene derivative 6

![Figure 1. Polycyclic guanidine natural products.](image)

![Figure 2. Merobatzelladine alkaloids.](image)

Scheme 1. Iterative carboamination strategy for polycyclic guanidine synthesis. LG = leaving group, R = p-methoxybenzyl (PMB) or p-methoxyphenyl (PMP) protecting group.
would generate cis disubstituted pyrrolidine 7 with high stereocontrol. A second carboamination reaction between allylpyrrolidine derivative 8 and 1-bromo-1-butene would afford bicyclic product 9, which could then be transformed into the polycyclic guanidine natural product 5 through functional group interconversion and ring-closure by an intramolecular S_N2 reaction.

Our prior studies on Pd-catalyzed alkene carboamination reactions have illustrated that the conversion of N-Boc-γ-aminoalkenes (Boc = tert-butoxycarbonyl) to 2,5-disubstituted pyrrolidines typically proceeds in good yield with greater than 20:1 diastereoselectivity favoring the cis isomer. As such, the transformation of 6 to 7 appeared quite feasible; however, the likelihood of success in the planned Pd-catalyzed carboamination between 8 and an alkyl halide was less clear. The generation of six-membered rings by Pd-catalyzed carboamination is considerably more challenging, and after examining many different reducing agents we found that the combination of NaBH4 and CeCl3 led to formation of 18 with 3:1 diastereoselectivity. However, the two diastereomers were separable by column chromatography, and 18 was isolated as a single stereoisomer in 63% yield. Protection of the alcohol as a benzyl ether, followed by exchange of the sulfinyl group for a Boc group, yielded 19 with 99% ee in 91% yield over three steps.

With intermediate 19 in hand, the key sequence of carboamination reactions was undertaken (Scheme 4). The

![Scheme 2. Synthesis of bicyclic ureas by Pd-catalyzed carboamination. Cy = cyclohexyl, dba = dibenzylideneacetone.](image)


![Scheme 4. Carboamination reaction sequence for bicyclic urea construction. TFA = trifluoroacetic acid, TMS = trimethylsilyl.](image)
avoid complications during the subsequent ring-closing step.\textsuperscript{[18]} Guanidinium salt 23 was then transformed into the natural product 5 in a three-step sequence involving initial hydrogenation with Pd/C to reduce the alkene followed by cleavage of the benzyl ether protecting group. Ring closure was achieved through an intramolecular Mitsunobu reaction.\textsuperscript{[7a]} Subsequent removal of the p-methoxybenzyl (PMB) group provided merobatzelladine B (5) in 41% yield over three steps from 23. The synthetic alkaloid was obtained in an enantiopure form (\(\delta_{13}^{23} = +40.1 \text{ (c = 0.7, MeOH): Ref. [3];} \) \(\delta_{13}^{23} = +27 \text{ (c = 0.15 MeOH)}) and NMR spectra of 5 were identical to the data previously reported for the natural product.\textsuperscript{[3]}

In summary, we have developed the first asymmetric total synthesis of (+)-merobatzelladine B (5), which confirms the structural and stereochemical assignments of the natural product. Our route afforded the desired alkaloid in 15 steps and 6.7% overall yield from commercially available pent-4-enal (15). The results described above represent a fundamentally new strategy for the stereocontrolled synthesis of polycyclic guanidine natural products. This new approach allows for formation of a carbon–carbon bond during the ring-closing event, and is the first route shown to provide access to alkaloids with a syn relationship between the C6 hydrogen atom and the C8 alkyl group. This strategy could potentially be employed to access other guanidine alkaloids that contain this stereochemical feature, and could also be used for the generation of novel analogs of the batzelladine alkaloids. Furthermore, this work also illustrates the feasibility of forming 5,6-fused bicyclic urea ring systems through Pd-catalyzed carboamination, which could be of value for the preparation of other interesting biologically active heterocycles.

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\textsuperscript{[15] 2-Bromovinyltrimethylsilane was used in place of vinyl bromide because of the volatility of the latter compound.

\textsuperscript{[16] The \( p \)-methoxybenzyl (PMB) protecting group was employed because it is relatively easy to remove, as compared to the \( p \)-methoxyphenyl (PMP) group used in the model study.

\textsuperscript{[17] This transformation must be conducted under rigorously anhydrous conditions to avoid HCl-mediated side reactions.

\textsuperscript{[18] Use of the analogous guanidinium chloride salt in the ring-closing Mitsunobu reaction led to the formation of a chlorinated side product resulting from the substitution of chloride for hydroxide. A diasteromeric side product resulting from double inversion at C1 was also formed. Use of the BF\textsubscript{4} salt prevented the formation of these side products.