

Alkaloid Synthesis

# 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).<sup>[1,2]</sup> 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.

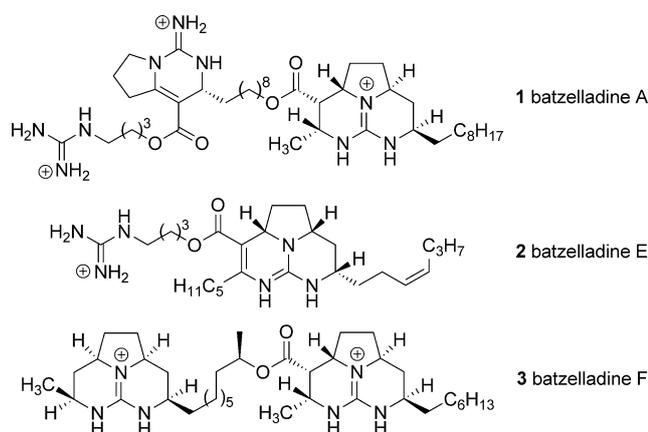


Figure 1. Polycyclic guanidine natural products.

In 2009, Matsunaga et al. reported the isolation of merobatzelladines A and B (4 and 5) from the marine sponge *Monanchora sp.* (Figure 2).<sup>[3]</sup> 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

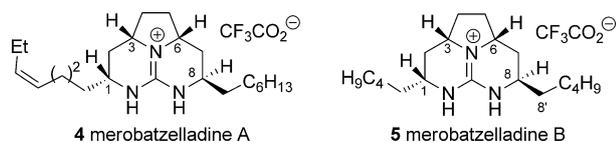


Figure 2. Merobatzelladine alkaloids.

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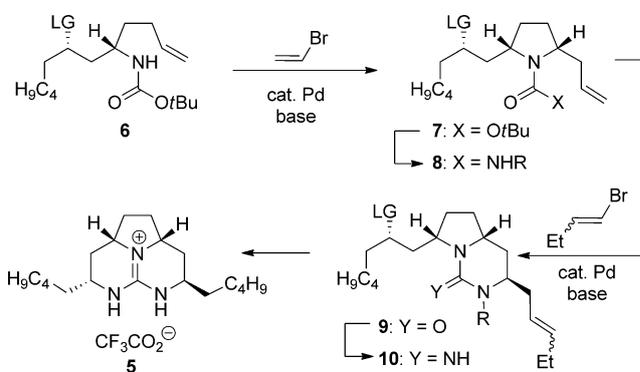
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that differs from other members in this family. The C8 alkyl substituents in merobatzelladines A and B are positioned in a *syn* relationship with the C6 hydrogen atoms, whereas other related natural products, such as batzelladines A, E, or F (1–3), 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* (IC<sub>50</sub> = 0.48 μg mL<sup>-1</sup> and 0.97 μg mL<sup>-1</sup>, 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,<sup>[4]</sup> cycloaddition reactions,<sup>[5]</sup> radical cyclizations,<sup>[6]</sup> or substitution reactions.<sup>[7]</sup> 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'–C<sub>4</sub>H<sub>9</sub> 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.

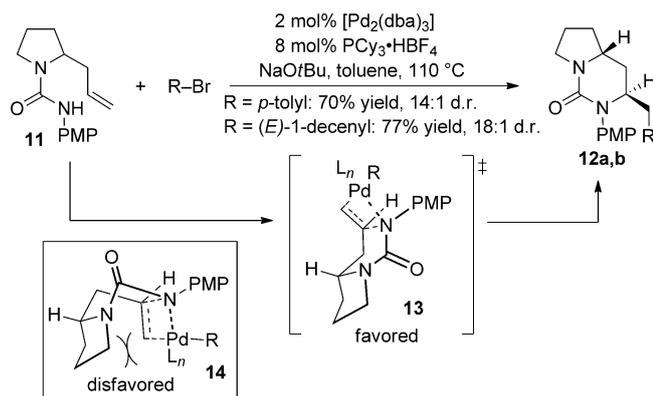
Our approach to the synthesis of merobatzelladine B centered on the use of Pd-catalyzed alkene carboamination reactions for the formation of two of the three rings in the natural product.<sup>[8]</sup> As shown in Scheme 1, we envisioned that a Pd-catalyzed carboamination between vinyl bromide and an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



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.

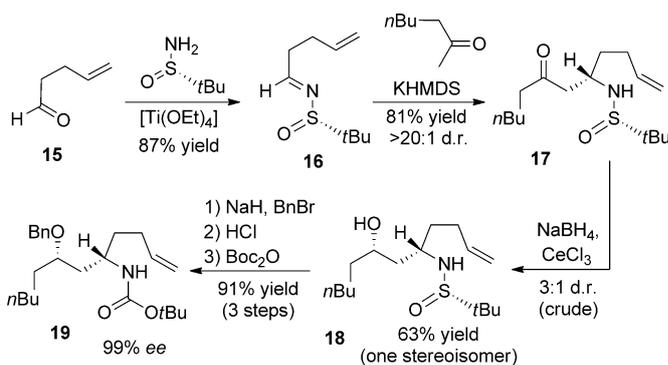
Our prior studies on Pd-catalyzed alkene carboamination reactions have illustrated that the conversion of *N*-Boc- $\gamma$ -aminoalkenes (Boc = *tert*-butoxycarbonyl) to 2,5-disubstituted pyrrolidines typically proceeds in good yield with greater than 20:1 diastereoselectivity favoring the *cis* isomer.<sup>[8,9]</sup> 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 alkenyl halide was less clear. The generation of six-membered rings by Pd-catalyzed carboamination is considerably more difficult than the formation of five-membered rings,<sup>[10]</sup> and this has not previously been accomplished with an unsaturated urea substrate.<sup>[11]</sup> To test the feasibility of this key transformation, we examined the Pd-catalyzed carboamination of 2-allylpyrrolidine-derived urea **11** with simple aryl and alkenyl halides. After optimization of conditions, we found that a catalyst consisting of  $[Pd_2(dba)_3]$  and  $PCy_3$  (Cy = cyclohexyl) provided satisfactory results in these reactions (Scheme 2). The bicyclic urea products **12a** and **12b** were



**Scheme 2.** Synthesis of bicyclic ureas by Pd-catalyzed carboamination. Cy = cyclohexyl, dba = dibenzylideneacetone.

obtained in good yield and high diastereoselectivity, which may arise from cyclization through a boat-like transition state **13**.<sup>[10b,c,12]</sup> The alternative boat-like transition state **14**, which leads to the minor diastereomer, appears to suffer from significant steric interactions between the alkene and the pyrrolidiny ring. Moreover, cyclization through a chair-like transition state appears to be less accessible because of poor overlap between the alkene  $\pi$  system and the Pd–N bond.<sup>[10b,c]</sup>

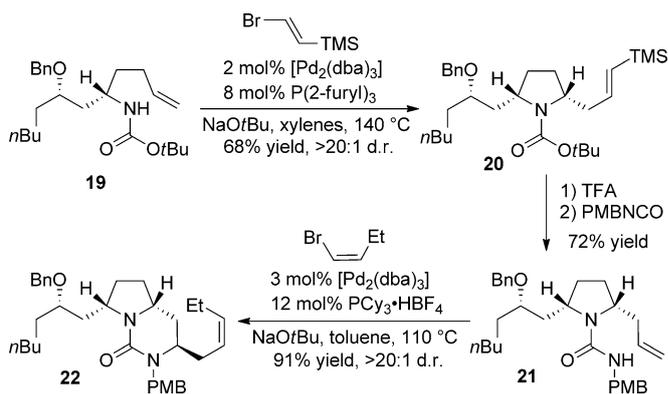
Having illustrated the feasibility of our approach to the generation of fused bicyclic ureas, we undertook the synthesis of merobatzelladine B by constructing an appropriately functionalized  $\gamma$ -aminoalkene derivative for the pyrrolidine-forming carboamination. As shown in Scheme 3, the amine-bearing stereocenter was generated by a highly efficient asymmetric Mannich reaction of sulfinyl imine **16**.<sup>[13]</sup> The stereocontrolled reduction of ketone **17** proved quite chal-



**Scheme 3.** Synthesis of  $\gamma$ -aminoalkene **19**. Bn = benzyl, Boc = *tert*-butoxycarbonyl, KHMS = potassium hexamethyldisilazide.

lenging,<sup>[14]</sup> and after examining many different reducing agents we found that the combination of  $NaBH_4$  and  $CeCl_3$  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 provided **19** with 99% *ee* in 91% yield over three steps.

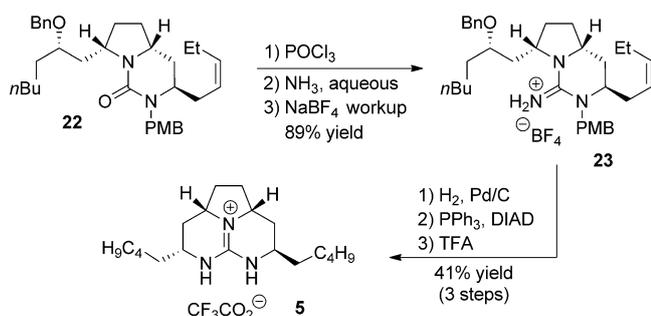
With intermediate **19** in hand, the key sequence of carboamination reactions was undertaken (Scheme 4). The



**Scheme 4.** Carboamination reaction sequence for bicyclic urea construction. TFA = trifluoroacetic acid, TMS = trimethylsilyl.

$Pd/P(2-furyl)_3$ -catalyzed carboamination of **19** with *E*-2-bromovinyltrimethylsilane provided pyrrolidine **20** in 68% yield and with excellent stereocontrol ( $>20:1$  d.r.).<sup>[15]</sup> Treatment of **20** with trifluoroacetic acid (TFA) led to cleavage of the Boc group and protodesilylation of the alkene. The resulting pyrrolidine was coupled with *p*-methoxybenzylisocyanate to generate pyrrolidiny urea **21** in 72% yield over two steps.<sup>[16]</sup> The  $Pd/PCy_3$ -catalyzed carboamination of **21** with (*Z*)-1-bromo-1-butene proceeded smoothly to yield bicyclic urea **22** in 91% yield and greater than 20:1 d.r.

Bicyclic urea **22** was converted into guanidinium salt **23** in 89% yield by treatment with  $POCl_3$  followed by addition of ammonia (Scheme 5).<sup>[17]</sup> The tetrafluoroborate counterion was introduced during the workup procedure by washing a dichloromethane solution of the crude guanidine product with aqueous  $NaBF_4$ . This anion exchange was essential to



**Scheme 5.** Completion of the synthesis. DIAD = diisopropyl azodicarboxylate.

avoid complications during the subsequent ring-closing step.<sup>[18]</sup> 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.<sup>[7a]</sup> 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 ( $[\alpha]_{\text{D}}^{23} = +40.1$  ( $c = 0.7$ , MeOH); Ref. [3];  $[\alpha]_{\text{D}}^{23} = +27$  ( $c = 0.15$  MeOH)), and NMR spectra of **5** were identical to the data previously reported for the natural product.<sup>[3]</sup>

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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[1] a) R. G. S. Berlinck, A. C. B. Burtoloso, A. E. Trindade-Silva, S. Romminger, R. P. Morais, K. Bandeira, C. M. Mizuno, *Nat. Prod. Rep.* **2010**, *27*, 1871–1907; b) R. G. S. Berlinck, A. C. B.

- Burtoloso, M. H. Kossuga, *Nat. Prod. Rep.* **2008**, *25*, 919–954; c) R. G. S. Berlinck, M. H. Kossuga, *Nat. Prod. Rep.* **2005**, *22*, 516–550; d) C. A. Bewley, S. Ray, F. Cohen, S. K. Collins, L. E. Overman, *J. Nat. Prod.* **2004**, *67*, 1319–1324.
- [2] a) A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertzberg, R. K. Johnson, J. W. Westley, B. C. M. Potts, *J. Org. Chem.* **1995**, *60*, 1182–1188; b) B. B. Snider, J. Chen, *Tetrahedron Lett.* **1998**, *39*, 5697–5700.
- [3] a) S. Takishima, A. Ishiyama, M. Iwatsuki, K. Otoguro, H. Yamada, S. Omura, H. Kobayashi, R. W. M. van Soest, S. Matsunaga, *Org. Lett.* **2009**, *11*, 2655–2658; b) S. Takishima, A. Ishiyama, M. Iwatsuki, K. Otoguro, H. Yamada, S. Omura, H. Kobayashi, R. W. M. van Soest, S. Matsunaga, *Org. Lett.* **2010**, *12*, 896.
- [4] a) P. J. Murphy, H. L. Williams, M. B. Hursthouse, K. M. Abdul Malik, *J. Chem. Soc. Chem. Commun.* **1994**, 119–120; b) B. B. Snider, J. Chen, A. D. Patil, A. J. Freyer, *Tetrahedron Lett.* **1996**, *37*, 6977–6980; c) F. Cohen, L. E. Overman, *J. Am. Chem. Soc.* **2001**, *123*, 10782–10783; d) L. E. Overman, J. P. Wolfe, *J. Org. Chem.* **2001**, *66*, 3167–3175; e) Z. D. Aron, L. E. Overman, *Chem. Commun.* **2004**, 253–265.
- [5] a) M. A. Arnold, K. A. Day, S. G. Duron, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 13255–13260; b) M. Butters, C. D. Davies, M. C. Elliott, J. Hill-Cousins, B. M. Kariuki, L.-L. Ooi, J. L. Wood, S. V. Wordingham, *Org. Biomol. Chem.* **2009**, *7*, 5001–5009.
- [6] P. A. Evans, J. Qin, J. E. Robinson, B. Bazin, *Angew. Chem.* **2007**, *119*, 7561–7563; *Angew. Chem. Int. Ed.* **2007**, *46*, 7417–7419.
- [7] T. Ishiwata, T. Hino, H. Koshino, Y. Hashimoto, T. Nakata, K. Nagasawa, *Org. Lett.* **2002**, *4*, 2921–2924.
- [8] For reviews on Pd-catalyzed alkene carboamination reactions, see: a) J. P. Wolfe, *Synlett* **2008**, 2913–2937; b) D. M. Schultz, J. P. Wolfe, *Synthesis* **2012**, 351–361.
- [9] a) M. B. Bertrand, J. D. Neukom, J. P. Wolfe, *J. Org. Chem.* **2008**, *73*, 8851–8860; b) M. B. Bertrand, J. P. Wolfe, *Tetrahedron* **2005**, *61*, 6447–6459.
- [10] a) J. S. Nakhla, J. P. Wolfe, *Org. Lett.* **2007**, *9*, 3279–3282; b) J. S. Nakhla, D. M. Schultz, J. P. Wolfe, *Tetrahedron* **2009**, *65*, 6549–6570; c) M. L. Leathen, B. R. Rosen, J. P. Wolfe, *J. Org. Chem.* **2009**, *74*, 5107–5110.
- [11] a) J. A. Fritz, J. S. Nakhla, J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2531–2534; b) J. A. Fritz, J. P. Wolfe, *Tetrahedron* **2008**, *64*, 6838–6852.
- [12] For further details on the mechanism of Pd-catalyzed alkene carboamination, see: a) J. D. Neukom, N. S. Perch, J. P. Wolfe, *Organometallics* **2011**, *30*, 1269–1277; b) J. D. Neukom, N. S. Perch, J. P. Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 6276–6277.
- [13] a) F. A. Davis, B. Yang, *Org. Lett.* **2003**, *5*, 5011–5014; b) T. P. Tang, J. A. Ellman, *J. Org. Chem.* **2002**, *67*, 7819–7832.
- [14] F. A. Davis, P. M. Gaspari, B. M. Nolt, P. Xu, *J. Org. Chem.* **2008**, *73*, 9619–9626.
- [15] 2-Bromovinyltrimethylsilane was used in place of vinyl bromide because of the volatility of the latter compound.
- [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.
- [17] This transformation must be conducted under rigorously anhydrous conditions to avoid HCl-mediated side reactions.
- [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 diastereomeric side product resulting from double inversion at C1 was also formed. Use of the BF<sub>4</sub> salt prevented the formation of these side products.