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Stereoselective synthesis of tricyclic guanidine systems: confirmation of the stereochemistry of batzelladine F left-hand tricyclic guanidine portion

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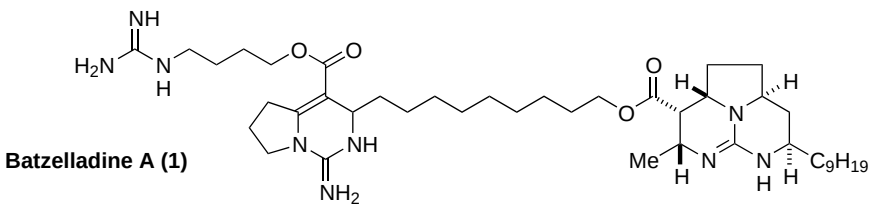
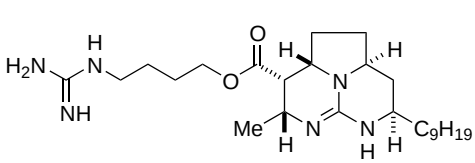
Abstract—The stereoselective synthetic methods for *anti*- and *syn*-fused tricyclic guanidine compounds **4a** and **4b** were developed based on a successive 1,3-dipolar cycloaddition. Through these synthetic studies, the stereochemistry of the left-hand tricyclic guanidine unit of batzelladine F (**3**) was confirmed as a *syn*-fused one, which is identical with the structure reported by the Murphy and Snider groups.

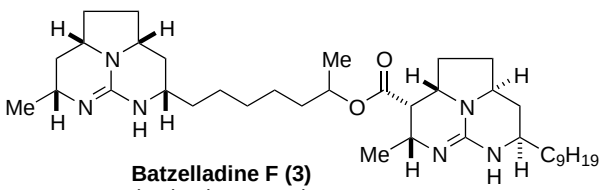
The batzelladines A–I are a novel class of polycyclic guanidine alkaloids isolated from Bahamian (batzelladines A–E)[1] and Jamaican sponges (batzelladines F–I)[2] of the genus *Batzella* by the SmithKline Beecham group in 1995 and 1997, respectively. Batzelladine A (**1**) and B inhibits the binding of HIV glycoprotein gp-120 to the human CD4 receptor, while batzelladines F–I induce dissociation of the protein kinase $p56^{lck}$ from CD4; thus, these could be potentially valuable for AIDS treatments.[1,2] During the structural elucidation studies of batzelladine families, there were some ambiguous reports about their structure assignment. In the case of batzelladine A (**1**) and D (**2**), the original stereochemical assignment of the methine hydrogens in the pyrrolidine ring in tricycle guanidine moiety was *syn*. In 1996, the Snider group revised this *syn* relationship as *anti* by way of synthesis of tricyclic degradation products of several batzelladine alkaloids, including **1** and **2**.[3] Recently, the Overman group succeeded in the efficient total synthesis of (−)-**2** using a tethered Biginelli condensation reaction as a key-step, and this success not only reconfirmed the structure of **2** but also determined its absolute stereochemistry.[4] On the other hand, batzelladine F (**3**), isolated in 1997 together with batzelladines G–I, has the two tricyclic guanidine units. The right-hand guanidine-contained unit is the same structure as that of batzelladine A (**1**) and D (**2**). The stereochemistry of the left-hand portion around the guanidine moiety, i.e. the relationship of methine hydrogens in the pyrrolidine ring, was assigned as *anti*. In 1998 and 1999, the Murphy and Snider groups independently reported the synthesis of tricyclic



Batzelladine A (1)



Batzelladine D (2)



Batzelladine F (3)
(revised structure)

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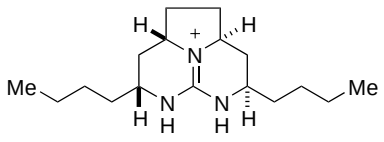
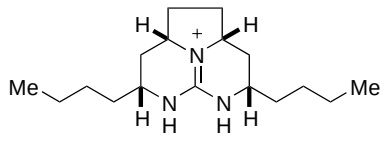


4a



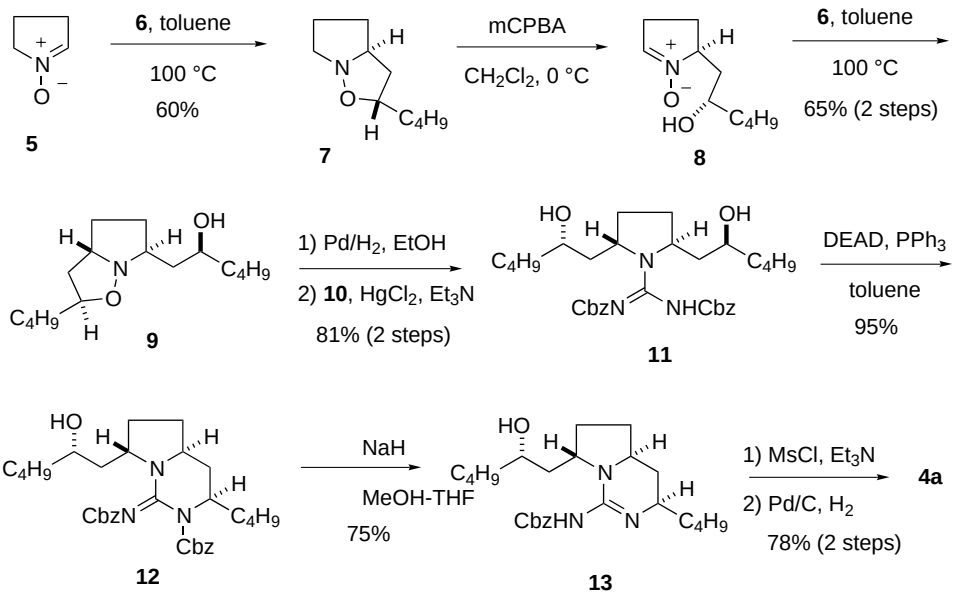
4b

guanidine units corresponding to the model compound of the left-hand tricyclic guanidine portion of **3** by a biomimetic route.[5,6] With this route, the stereochemistry of the tricyclic guanidine unite was controlled as *syn* with an excellent selectivity. A comparison of the ^{1}H and ^{13}C NMR data between the model compounds and the natural products reached the same conclusion, i.e. that the left-hand tricyclic guanidine of batzelladine F (**3**) has a relative *syn* stereochemistry rather than *anti*.[5,6] Through this study, the NMR data of *anti*-tricyclic guanidine compounds is also reported by elucidating from the mixture of *syn* (major) and *anti* (minor) isomers.[6] We thought that the selective preparation of *syn*- and *anti*-tricyclic guanidine unit **4** would give us more certain information about the stereochemistry of the left-hand tricyclic guanidine portion of batzelladine F (**3**). Thus, we planned to synthesize the C_2 symmetric **4a** (*anti* form) and *meso* **4b** (*syn* form) by developing a selective manner based on our recent progress[7] toward the synthetic studies on ptilomycalin A[8] and 13,14,15-isocrambescidin 800.[9]

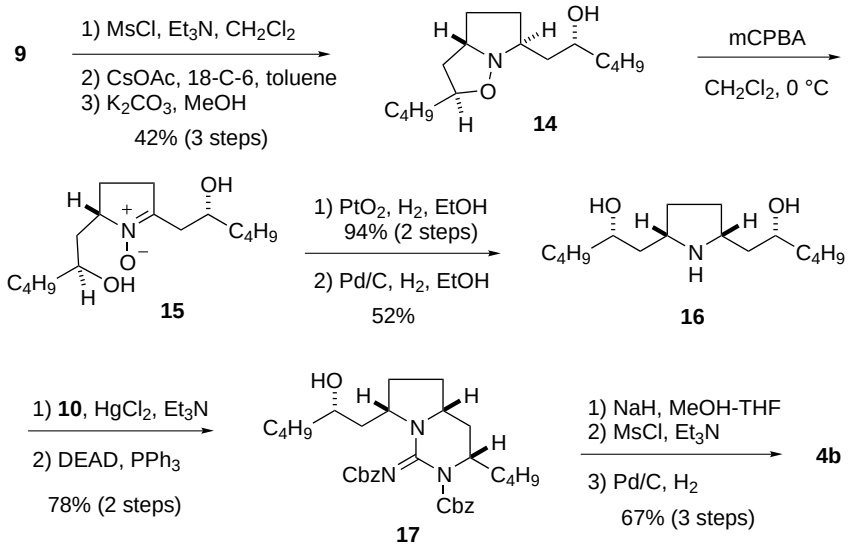
The successive 1,3-dipolar reaction protocol we recently developed[7] was successfully applied to the stereoselective synthesis of **4**. A 1,3-dipolar cycloaddition reaction of the nitrone **5** to 1-hexene (**6**) in toluene gave isoxazolidine **7** in 60% yield. The regioselective oxidation of **7** with mCPBA[10] provided nitron **8** and a subsequent second 1,3-dipolar cycloaddition reaction with 1-hexene (**6**) took place from the less hindered side and gave isoxazolidine **9**[11] stereoselectively in 65% yield. Hydrogenolysis of **9** in the presence of 10% Pd–C gave *trans*-2,5-disubstituted-β-hydroxy pyrrolidine, and subsequent treatment with bis-Z-methylthiopseudourea (**10**),[12] mercury(II) chloride and triethylamine generates guanylated pyrrolidine **11** in 81% yield. Formation of bicyclic guanidine **12** was employed under Mitsunobu conditions[13] in 95% yield. Selective deprotection of the Z group of **12** with sodium hydride in THF:methanol (1:1), developed by Armstrong and McAlpine,[14] furnished **13** in 75% yield. Tricyclic guanidine **4a** (*anti* form) was generated by treatment with methanesulfonyl chloride and triethylamine, and subsequent hydrogenolysis of the Z group with 10% Pd–C in 78% yield[15] (Scheme 1).

meso-Tricyclic guanidine **4b** (*syn* form) was synthesized stereoselectively from **9**, a common intermediate for **4a**, as shown in Scheme 2. The stereochemistry of the hydroxyl group was inverted via a three-step protocol, i.e. (1) mesylation, (2) treatment with cesium acetate and (3) hydrolysis of acetate to give isoxazolidine **14**[11] in 42% yield. Oxidation of **14** with mCPBA in dichloromethane regenerated nitrone **15** regioselectively, and subsequent reduction of **15** with PtO_2[15] and Pd–C under hydrogen provided 2,5-disubsituted *cis*-pyrrolidine **16** in 49% yield. The conversion of **16** into tricyclic guanidine **4b** (*syn* form) was furnished using the procedures described for **4a** (Scheme 1) through bicyclic guanidine **17** in 52% yield.[16] The structures of **4a** and **4b** were confirmed with extensive NMR experiments.

The NMR spectra data of **3** (selected), **4a** and **4b** are summarized in Table 1. With the comparison of ^{13}C NMR spectra of *anti* tricyclic guanidine **4a** and *syn* **4b**,

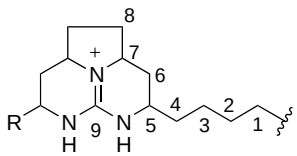


Scheme 1.



Scheme 2.

Table 1. ^{13}C NMR data in CD_3OD (150 MHz)



3: R = Me
4: R = C_4H_9

Position	3	4a	4b
1	–	14.2	14.2
2	–	23.6	23.5
3	26.2	28.4	28.4
4	35.8	36.6	35.6
5	51.6	53.1	51.5
6	34.8	34.4	34.8
7	57.4	56.4	57.5
8	31.1	31.9	31.1
9	151.2	151.7	151.2

distinct differences are observed at the C-4, C-5 and C-7 positions, respectively. Returning to the reported data for tricyclic guanidine left-hand portion of batzelladine F (**3**)[2] (Table 1), it is obvious that the natural product has the *syn*-fused stereochemistry, and these results are consistent with the conclusion reported by Murphy and Snider.[5,6]

In summary, we have developed an efficient method for the stereoselective synthesis of *anti*- and *syn*-fused tricyclic guanidine **4**, respectively, which corresponds to the core structure for batzelladine F left-hand tricyclic guanidine portion. With this synthesis, the stereochemistry of tricyclic guanidine left-hand portion are strongly confirmed as *syn*-fused. This method will provide the synthesis for variety types of tricyclic guanidine class compounds.

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11. ^{13}C NMR (100 MHz, $CDCl_3$). Compound **9**: δ 75.25, 69.02, 64.52, 63.90, 41.95, 39.55, 37.18, 32.39, 31.17, 29.25, 28.70, 27.95, 22.81, 22.70, 14.07, 13.93. Compound **14**: δ 76.58, 71.57, 68.11, 64.13, 42.03, 41.59, 37.44, 33.46, 31.03, 30.91, 28.46, 27.73, 22.80, 22.65, 14.08, 13.96.

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16. ^{1}H NMR (600 MHz, CD_3OD). Compound **4a**: δ 3.61 (m, 2H, H-7), 3.50 (m, 2H, H-5), 2.31 (ddd, $J=12.7$, 4.9, 2.4 Hz, 2H, H-6), 2.21 (m, 2H, H-8), 1.61 (m, 2H, H-8), 1.58 (m, 4H, H-4), 1.37 (m, 8H, H-2, H-3), 1.36 (ddd, $J=12.7$, 11.2, 11.2 Hz, 2H, H-6), 0.94 (t, $J=7.1$ Hz, 6H, H-1). Compound **4b**: δ 3.74 (m, 2H, H-7), 3.42 (m, 2H, H-5), 2.26 (ddd, $J=13.2$, 3.9, 3.4 Hz, 2H, H-6), 2.23 (m, 2H, H-8), 1.68 (m, 2H, H-8), 1.57 (m, 4H, H-4), 1.39 (m, 8H, H-2, H-3), 1.24 (ddd, $J=13.2$, 11.8, 11.8 Hz, 2H, H-6), 0.95 (t, $J=7.1$ Hz, 6H, H-1). The NOE was observed between the H-5 and H-7 protons of **4a** and **4b**, respectively.