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Total Synthesis of Batzelladine D

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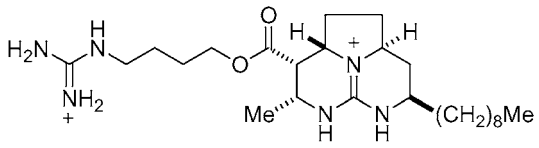
ABSTRACT



Batzelladine D

Stereoselective total synthesis of batzelladine D was accomplished in 15 steps. This synthesis features (i) successive 1,3-dipolar cycloaddition reactions to form the 2,5-disubstituted pyrrolidine ring system, (ii) esterification of the side chain to the bicyclic guanidine carboxylate, a common synthetic intermediate of batzelladine alkaloids, and (iii) tricyclic guanidine formation under the Mitsunobu reaction conditions.

Batzelladines A−I are members of a novel class of polycyclic guanidine alkaloids isolated from Bahamian (batzelladines A−E) and Jamaican sponges (batzelladines F−I) of the genus *Batzella* by a SmithKline Beecham group.[1,2] Batzelladines A (**1**) and B inhibit the binding of HIV glycoprotein gp-120 to the human CD4 receptor,[1] while batzelladines F (**3**), G, H, and I induce the dissociation of the protein kinase $p56^{lck}$ from CD4.[2] Inspired by the novel structures of the batzelladines and their potential clinical importance in AIDS treatment, several synthetic studies have been reported.[3−9] Because of our interest in the control of protein−protein interactions with small molecules, we chose batzelladine D (**2**) as a synthetic target molecule to elucidate its inhibition manner of the protein−protein interaction. In 1999, Overman's group succeeded in the first total synthesis of (−)-baztelladine D (**2**) based on the tethered Biginelli condensation reaction as the key step, and this synthesis established the absolute stereochemistry of **2**.[10] We report herein a stereoselective total synthesis of (±)-batzelladine D (**2**) based on the successive 1,3-dipolar cycloaddition reaction protocol, which we have recently developed.[11]

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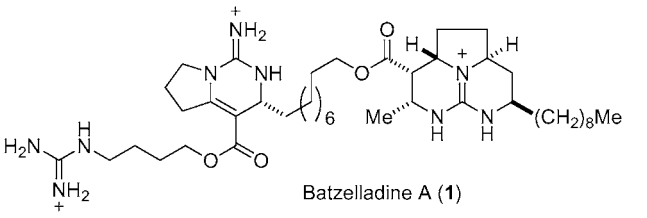
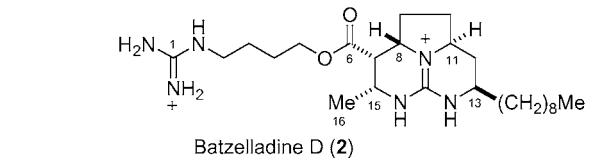
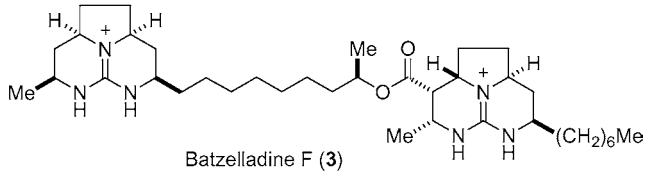
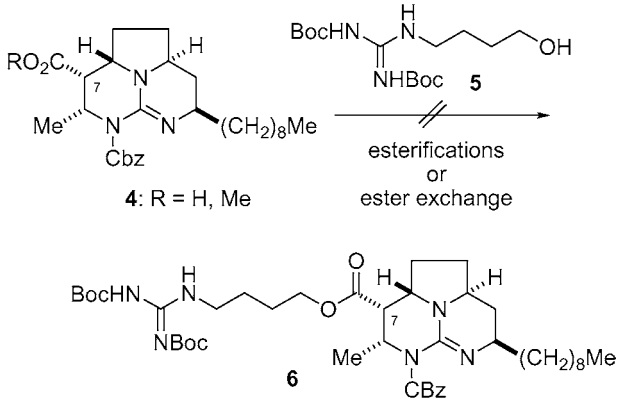






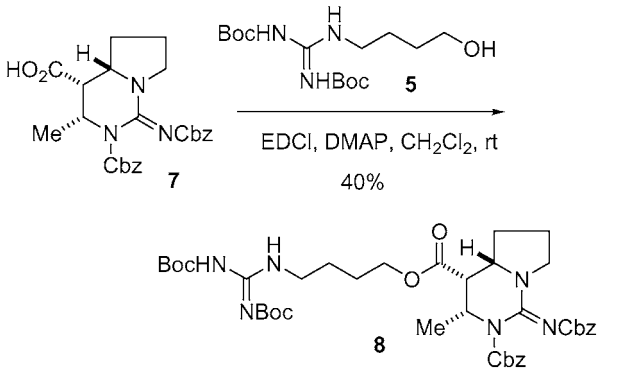
We planned to begin the synthesis of **2** by introducing the guanidinobutyl alcohol side chain **5** into the tricyclic guanidinecarboxylic acid or ester **4** by esterification or ester exchange reaction. Although we tried various reaction conditions for the coupling of the side-chain alcohol **5** and guanidine **4**,[12] we failed to obtain the desired product **6** because of the axially orientated carboxylic acid or ester of **4** at C7, as Snider and Chen had noted[5b] (Scheme 1). After

Scheme 1



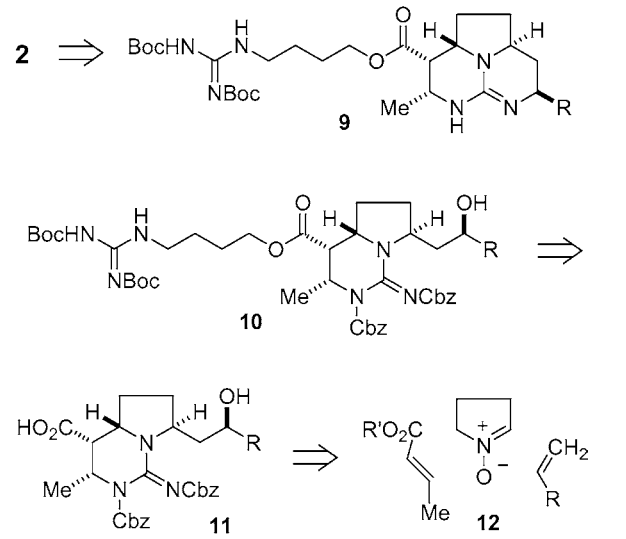
further efforts, we found that the coupling of the bicyclic guanidine carboxylic acid **7** with **5** proceeded smoothly under EDCI−DMAP conditions to give the ester **8** in 40% yield, even though **7** also has the axially orientated carboxylic acid (Scheme 2). Thus, we decided to introduce the side chain **5**

Scheme 2



prior to the tricyclic guanidine formation and envisaged the synthesis of **2** from the bicyclic guanidine **10** via **11** (Scheme 3). The bicyclic guanidinecarboxylic acid **11** would be

Scheme 3



prepared from the nitrone **12** on the basis of the successive 1,3-dipolar cycloaddition reaction protocol, which we have recently developed for the stereoselective synthesis of *anti*- and *syn*-fused tricyclic guanidine compounds.[11b]

Synthesis of bicyclic guanidinecarboxylic acid **23**, the key intermediate for **2**, is shown in Scheme 4. 1,3-Dipolar cycloaddition reaction of the nitrone **12** and 1-undecene (**13**) in toluene gave the isoxazoline **14** in 95% yield. Subsequent treatment of **14** with *m*-CPBA effected regioselective regeneration of the nitrone **15**.[13] In the second 1,3-dipolar reaction of **15** in toluene, methyl acrylate (**16**) approached from the less hindered side (β-face) to give stereoselectively the isoxazoline **17**[11,14] in 62% yield (from **14**). The ester group of **17** was reduced with $LiAlH_4$, and subsequent protection of the two hydroxyl groups with *t*-$BuMe_2SiCl$ furnished **18** in 88% yield. After the N−O bond of the isoxazoline **18** was reduced with H_2 on Pd/C, the resulting 2,5-disubstituted

(12) Full details including the syntheses of **4**, **7** and **8** will be described elsewhere.

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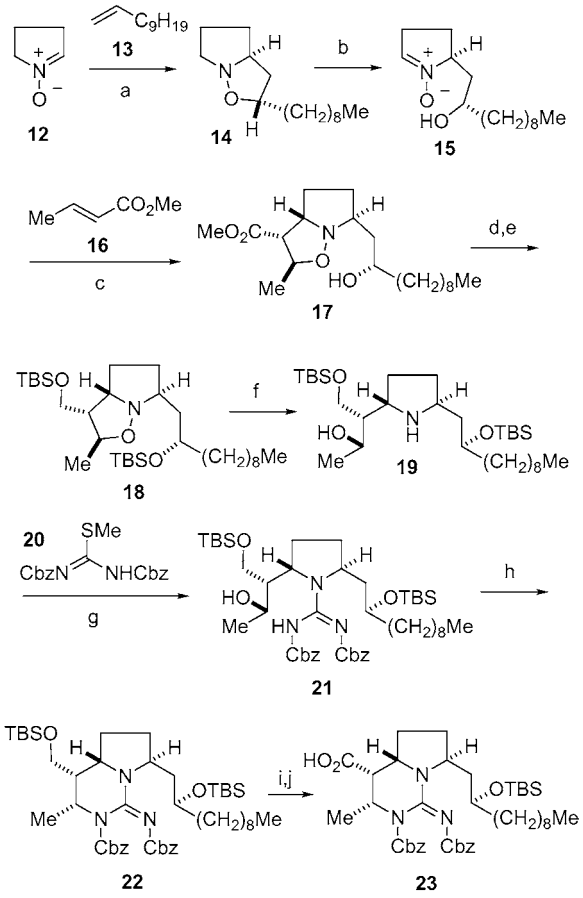
Scheme 4[a]



[a] (a) toluene, 100 °C, 95%; (b) mCPBA, CH_2Cl_2, 0 °C; (c) toluene, 100 °C, 62% (from **14**); (d) $LiAlH_4$, Et_2O, 0 °C; (e) TBSCl, imidazole, CH_2Cl_2, rt, 88% (from **17**); (f) H_2, 10% Pd/C, EtOH, rt, 70%; (g) $HgCl_2$, Et_3N, DMF, 0 °C tort, 84%; (h) DEAD, PPh_3, CH_2Cl_2, rt, 64%; (i) TBAF, THF, 0 °C, 97%; (j) Jones reagent, acetone, 0 °C.

pyrrolidine **19** was reacted with bis-*Z*-2-methyl-2-thiopseudourea (**20**) in the presence of mercury(II) chloride[15] and triethylamine to give **21** in 84% yield. The formation of the bicyclic guanidine **22** was stereoselectively performed by treatment with **21** under the Mitsunobu reaction conditions (DEAD-PPh_3)[16] in 64% yield. Selective cleavage of the primary silyl ether of **22** with TBAF followed by Jones oxidation gave the bicyclic guanidinecarboxylic acid **23**.

With the carboxylic acid **23** in hand, we turned to the esterification with the side-chain alcohol **5** (Scheme 5). This condensation reaction was conducted under EDCI−DMAP conditions in dichloromethane at room temperature to give **24** in 64% yield. The removal of TBS and Cbz groups of **24** with HF−pyridine and H_2 over Pd/C, respectively, gave **25** in 60% yield. The tricyclic guanidine was then formed under the Mitsunobu reaction conditions to give fully stereocontrolled **26** in 80% yield. Final cleavage of Boc groups

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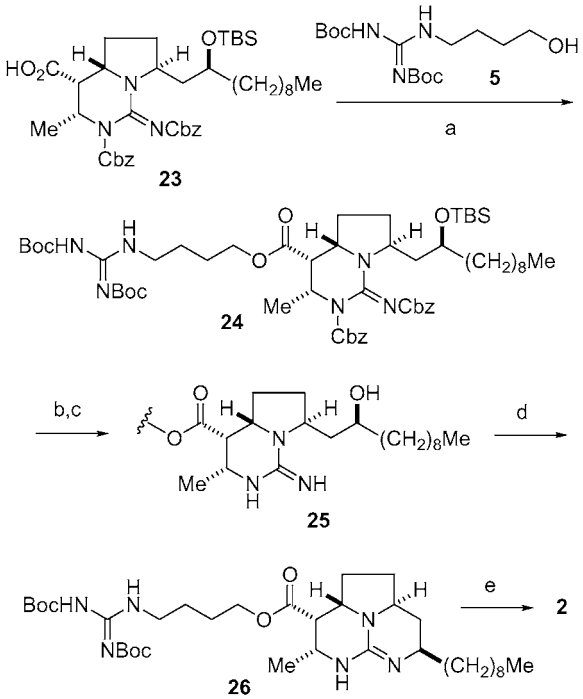
Scheme 5[a]



[a] (a) EDCl, DMAP, CH_2Cl_2, rt, 64% (from **22**); (b) HF−Py, CH_3CN, 0 °C; (c) H_2, 10% Pd/C, EtOH, rt, 60% (from **24**); (d) DEAD, PPh_3, CH_2Cl_2, rt, 80%; (e) TFA-CH_2Cl_2, rt, 86%.

was accomplished with TFA−CH_2Cl_2 to furnish (±)-batzelladine D (**2**) in 86% yield.

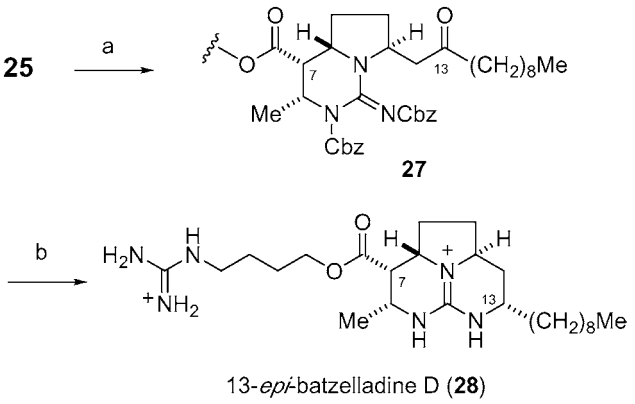
The spectral data (^{1}H NMR, ^{13}C NMR and high-resolution mass) of the synthetic **2** were satisfactorily consistent with those of natural and synthetic batzelladine D (**2**) reported by Patil et al.[1] and Overman et al.,[10] respectively.[17]

On the other hand, 13-*epi*-batzelladine D (**28**) was synthesized in one step from the ketone **27**, which was prepared from **25** by TPAP−NMO oxidation in 94% yield (Scheme 6). Upon treatment of **27** with H_2 over Pd/C in acetic acid−methanol, deprotection of Boc and Cbz groups, formation of cyclic imine, and stereoselective reduction of the imine took place successively to afford 13-*epi*-batzelladine D (**28**)[18] as a single product in 64% yield. It is considered that hydrogenation to the imine intermediate, derived from **27**, took place stereoselectively from the less-

(17) Spectral data for the synthetic batzelladine D (**2**): ^{1}H NMR (CD_3OD, 500 MHz) δ 4.19 (t, J = 6.4 Hz, 2H), 3.94 (m, 1H), 3.85 (m, 1H), 3.53 (m, 2H), 3.21 (t, J = 7.0 Hz, 2H), 3.13 (dd, J = 3.4, 4.0 Hz, 1H), 2.34 (ddd, J = 2.4, 5.2, 12.8 Hz, 1H), 2.22 (m, 2H), 1.76−1.54 (m, 6H), 1.42−1.27 (m, 17H), 1.27 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz) 170.6, 158.7, 151.5, 65.4, 57.8, 57.3, 53.2, 49.9, 45.5, 42.0, 37.0, 34.2, 33.0, 31.4, 30.6, 30.4, 29.3, 26.9, 26.6, 26.2, 23.7, 18.4, 14.4 ppm; HRMS (FAB, MH^+) calcd for $C_{25}H_{47}N_6O_2$ 463.3761, found 463.3735.

(18) Spectral data for 13-*epi*-batzelladine D (**28**): ^{1}H NMR (CD_3OD, 500 MHz) δ 4.20 (m, 2H), 3.97 (m, 1H), 3.85 (m, 1H), 3.61 (m, 1H), 3.48 (m, 1H), 3.21 (t, J = 7.0 Hz, 2H), 3.15 (dd, J = 4.4, 4.4 Hz, 1H), 2.25 (m, 2H), 2.16 (d, J = 10.7 Hz, 1H), 1.80−1.27 (m, 23H), 1.27 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 6.4 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz) 170.6, 158.7, 151.3, 65.4, 58.0, 53.5, 51.3, 50.1, 45.4, 42.4, 38.8, 33.1, 31.7, 31.5, 30.7, 30.53, 30.45, 29.4, 26.9, 26.5, 26.1, 23.7, 18.5, 14.4 ppm; HRMS (FAB, MH^+) calcd for $C_{25}H_{47}N_6O_2$ 463.3761, found 463.3721.

Scheme 6[a]



[a] (a) TPAP, NMO, CH_2Cl_2, rt, 94%; (b) H_2, 10% Pd/C, MeOH−AcOH, rt, 64%.

hindered β-face with respect to the axially oriented ester group at C7.

In conclusion, we have succeeded in the stereoselective total synthesis of batzelladine D (**2**) by way of successive 1,3-dipolar cycloaddition reaction as a key step. This synthetic route also stereoselectively provided 13-*epi*-batzelladine D (**28**), which is a structurally and biologically interesting unnatural batzelladine D derivative. The bicyclic guanidine carboxylic acid **23** should be a useful key intermediate for the synthesis of other members of the batzelladine alkaloid family.

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Supporting Information Available: Spectral data for compounds **5**, **14**, **17**, **19**, **24**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org

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