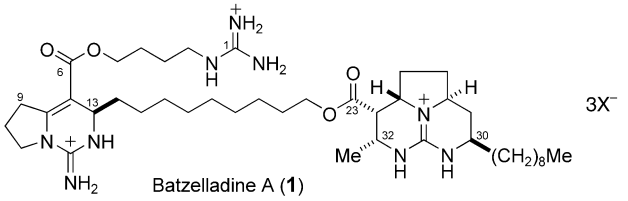
Natural Product Synthesis

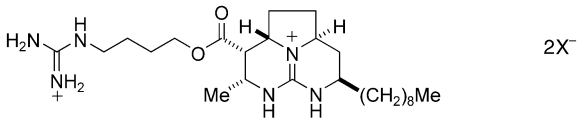
Enantioselective Total Synthesis of Batzelladine A**

*Jun Shimokawa, Koji Shirai, Aya Tanatani, Yuichi Hashimoto, and Kazuo Nagasawa**

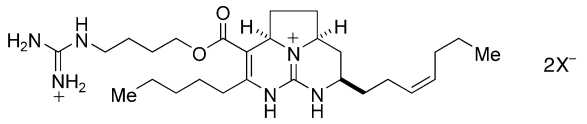
Batzelladines A–I are members of a class of polycyclic guanidine alkaloids that were isolated from Bahamian and Jamaican sponges by scientists at SmithKline Beecham in 1995 and 1997.[1,2] The batzelladines are of much interest, as batzelladines A (**1**), B, and D (**2**) inhibit the binding of the



Batzelladine A (**1**)



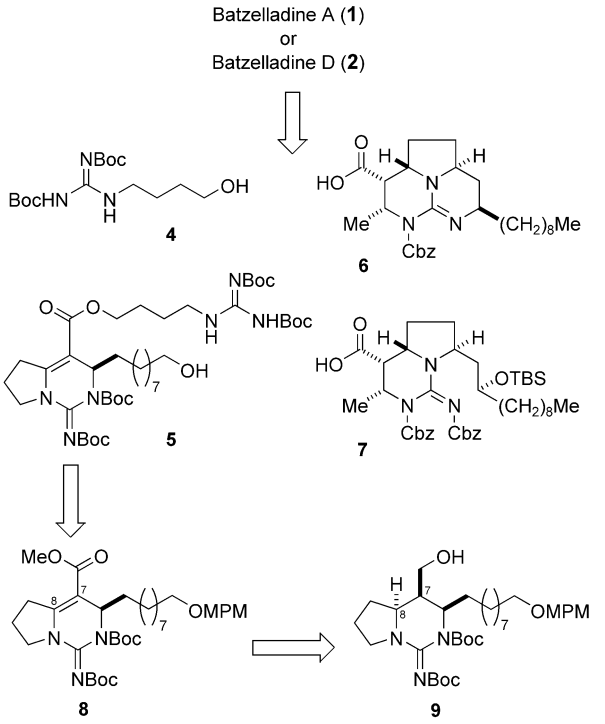
Batzelladine D (**2**)



Batzelladine E (**3**)

HIV glycoprotein gp120 to the human CD4 receptor,[1a] whereas batzelladines F–I were found to dissociate the protein tyrosine kinase $p56^{lck}$ from CD4.[1b] The unique structures of the batzelladines and their potential clinical importance in AIDS treatment have inspired considerable synthetic attention.[3–11] In 1998, Snider and Chen reported the total synthesis of batzelladine E (**3**) by a biomimetic synthetic route; this was the first synthetic success in this class of molecules.[5b] In 1999 and 2001, Overman and co-workers succeeded in the total synthesis of batzelladines D (**2**) and F, in which a tethered Biginelli reaction was applied effectively as a key step.[7] These syntheses led to structural revisions of batzelladines E (**3**) and F. In the case of batzelladine A (**1**), the absolute configuration was determined recently with the aid of synthetic efforts. The right-hand tricyclic guanidine subunit of **1** has the same structure as that in batzelladine D (**2**), the absolute configuration of which was established by the total synthesis of **2** by Overman and co-workers.[7a] The left-hand bicyclic guanidine subunit of **1** has one stereogenic center at C13. Duron and Gin recently synthesized the left-hand bicyclic guanidine moiety of **1**, which was also obtained by the methanolysis of natural **1**, and determined the absolute stereochemistry at C13 to be *R* by comparing the optical rotation values.[8] As we are interested in the unique structure of the batzelladines and the mechanism through which they modulate protein–protein interactions, we planned to synthesize the batzelladines and their derivatives for potential use as tools in biological studies. Herein, we report an enantioselective total synthesis of batzelladine A (**1**) based upon a strategy involving successive 1,3-dipolar cycloadditions.[11a]

As an approach to the synthesis of batzelladines A (**1**) and D (**2**)and their derivatives, it seemed reasonable to couple the side-chain alcohol **4** or **5** with the tricyclic guanidine carboxylic acid **6** by means of an esterification at the final stage of the synthesis (Scheme 1). However, the tricyclic guanidine carboxylic acid **6** did not undergo esterification or transesterification because of its axially oriented carboxylic acid group, as had already been noted by Snider and Chen, as well as Overman and co-workers, in the synthesis of **3**[5b] and **2**.[7a] In an effort to overcome this problem, we found that the



Scheme 1. Synthetic strategy toward batzelladines A and D. Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy, MPM = 4-methoxyphenylmethyl, TBS = *tert*-butyldimethylsilyl.

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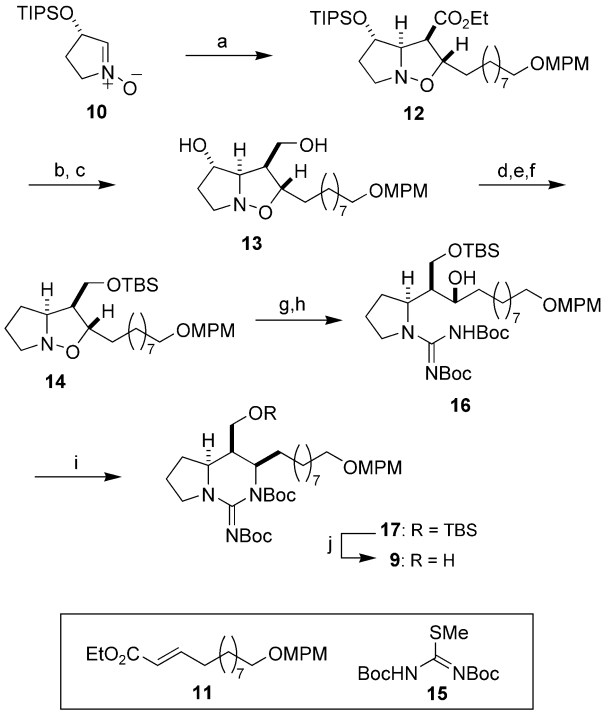
esterification of the bicyclic guanidine carboxylic acid **7** (an analogue of **6**) with the side-chain alcohol **4** proceeded well, and this finding was applied to the synthesis of **2**.[11c] We planned to synthesize batzelladine A (**1**) based upon this strategy (Scheme 1). The left- and right-hand cyclic guanidine subunits **9** and **7** can be synthesized through a 1,3-dipolar cycloaddition strategy, and therefore the introduction of the required double bond at C7–C8 of **9** by means of oxidation was addressed at the outset of the synthesis of **1**.

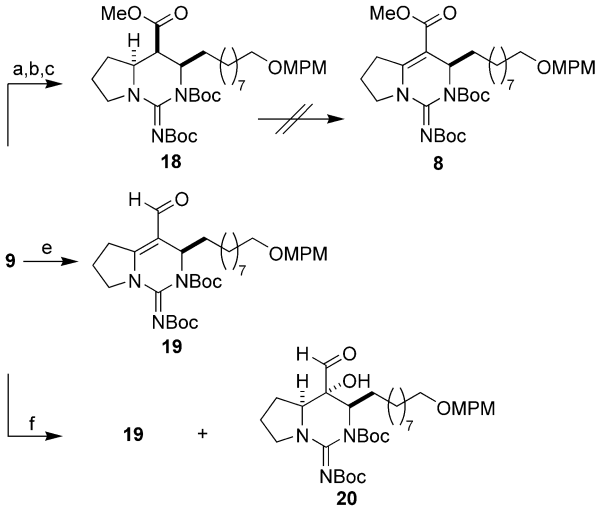
The synthesis of the bicyclic guanidine **9** began with a 1,3-dipolar cycloaddition reaction of the optically active nitrone **10** reported by Goti et al. (Scheme 2).[12] The 1,3-dipolar



Scheme 2. Synthesis of the bicyclic guanidine fragment: a) **11**, toluene, 90 °C; b) $LiAlH_4$, Et_2O, 0 °C; c) CsF, EtOH, 90 °C (59%, three steps); d) TBSCl, pyridine (81%); e) ClC(S)OPh, pyridine, DMAP (58%); f) $n$$Bu_3SnH$, AIBN (94%); g) $Pd(OH)_2$, H_2; h) **15**, $HgCl_2$, Et_3N, DMF (71%, two steps); i) PPh_3, DEAD, toluene (100%); j) TBAF, THF (81%). AIBN = azobisisobutyronitrile, DEAD = diethyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, TIPS = triisopropylsilyl.

cycloaddition reaction between **10** and the ester **11** proceeded stereoselectively to give the isoxazolidine **12** as a single diastereomer. The ester group in **12** was reduced with $LiAlH_4$ to give the corresponding alcohol, and subsequent removal of the TIPS group with CsF gave the diol **13** in 59% yield from **10**. Selective protection of the primary alcohol as its TBS ether, followed by deoxygenation of the secondary alcohol at C9 by the Barton–McCombie method gave **14** in 44% yield from **13**. Reductive cleavage of the N–O bond of **14** with hydrogen in the presence of $Pd(OH)_2$, followed by guanidination of the resulting pyrrolidine with bis(Boc)-2-methyl-2-thiopseudourea (**15**) and mercury(II) chloride,[13] afforded the bis(Boc)-protected guanidine **16** in 71% yield from **14**. Cyclization of **16** under the Mitsunobu reaction conditions in the presence of DEAD and triphenylphosphane[14] provided the bicyclic guanidine **17** stereoselectively. Finally, removal of the TBS group with TBAF gave the primary alcohol **9** in 81% yield from **16**.

With the bicyclic guanidine alcohol **9** in hand, we next examined the conversion of **9** into the α,β-unsaturated carbonyl compound **5** through introduction of a double bond at C7–C8. Initially, we envisaged that oxidation of the primary alcohol **9** to the corresponding methyl ester and subsequent oxidation by the Sharpless method with an organoselenium reagent[15] or by the Saegusa–Tsuji method[16] would afford the α,β-unsaturated ester **8**. Thus, the alcohol **9** was oxidized to the corresponding carboxylic acid by means of a Swern oxidation followed by further oxidation with sodium chlorite[17] (Scheme 3). The carboxylic



Scheme 3. Oxidation of **9** to **19**: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, tBuOH/H_2O; c) $TMSCHN_2$, benzene/MeOH (71%, three steps); e) TPAP, NMO, molecular sieves (4 Å), CH_2Cl_2 (47%); f) IBX, DMSO/toluene (**19**: 13%, **20**: 11%). DMSO = dimethyl sulfoxide, IBX = 2-iodoxybenzoic acid, NMO = 4-methylmorpholine *N*-oxide, TMS = trimethylsilyl, TPAP = tetrapropylammonium perruthenate.

acid obtained was treated with (trimethylsilyl)diazomethane[18] to give the methyl ester **18** in 71% overall yield. However, neither subsequent reaction with phenylselenenyl bromide in the presence of LDA nor attempted ketene silyl acetal formation afforded the desired product. We therefore examined direct formation of the α,β-unsaturated aldehyde **19** from the primary alcohol **9** with IBX, a reaction developed by Nicolaou et al.,[19] but only poor conversion into **19** was observed (13% yield), along with formation of the α-hydroxyaldehyde **20** (11% yield). Studies of various oxidation reagents for this conversion led to the interesting finding that TPAP–NMO oxidation of **9** gave **19** in 47% yield with complete regioselectivity. The mechanism and the basis of the selectivity of this reaction are not clear. We are attempting to elucidate the generality and mechanism of this oxidation reaction.[20]

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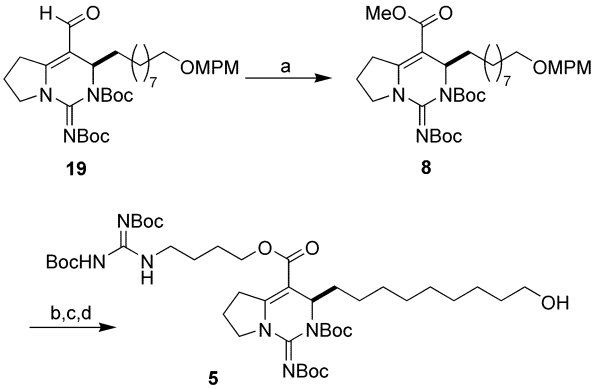
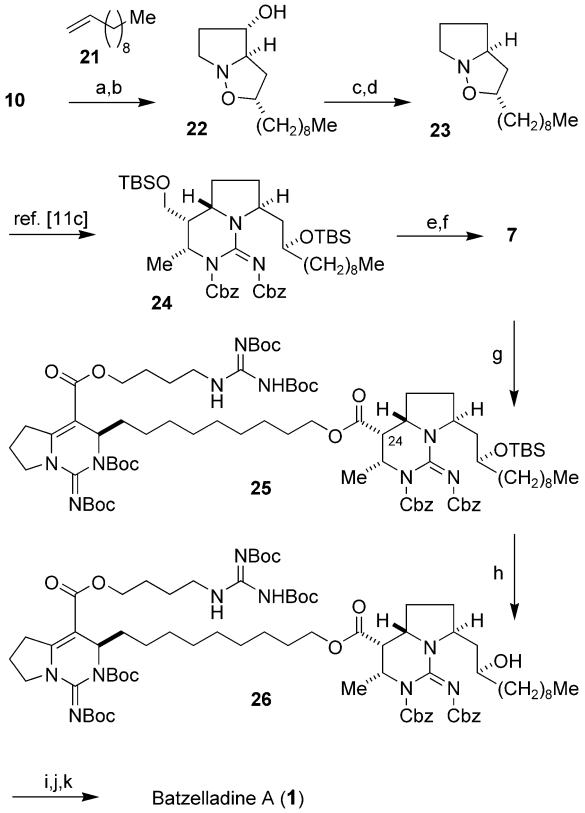
The aldehyde **19** was further oxidized with sodium chlorite to the corresponding carboxylic acid, and then treatment with (trimethylsilyl)diazomethane gave the methyl ester **8** in 86% yield (based on recovered aldehyde; Scheme 4). Hydrolysis of the methyl ester **8** with *n*PrSLi and subsequent condensation with the guanidine alcohol **4** provided the desired ester in 54% yield from **8**. Finally, the MPM group was removed with DDQ to give the alcohol **5** in 66% yield.



Scheme 4. Synthesis of **5**: a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, $TMSCHN_2$ (53%; 86% based on recovered **19**); b) *n*PrSLi, HMPA; c) **4**, BOPCl, Et_3N, CH_2Cl_2 (54%, two steps); d) DDQ, CH_2Cl_2/H_2O (66%). BOP = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, HMPA = hexamethyl phosphoramide.

The synthesis of the optically active bicyclic guanidine carboxylic acid **7**, a precursor of the right-hand tricyclic guanidine, and the final stage of the synthesis of **1** were performed as illustrated in Scheme 5. Three components, the chiral nitrone **10**, 1-undecene (**21**), and methyl crotonate, were combined in successive 1,3-dipolar cycloadditions as reported previously to give the TBS ether **24**, which was then oxidized to give **7** in optically pure form.[11c] Treatment of the carboxylic acid **7** with the bicyclic guanidine alcohol **5** in the presence of EDCI and DMAP at room temperature gave the desired ester **25**, but epimerization at C24 occurred under these conditions to give an approximately 1:1 mixture of diastereomers. When the esterification reaction was performed at 0°C we found that the epimerization was suppressed and obtained **25** in 60% yield. The masked secondary alcohol functionality in **25** was deprotected with HF–pyridine to furnish **26** in 80% yield. The Cbz protecting groups were then cleaved with hydrogen in the presence of Pd/C, and cyclization of the resulting bicyclic guanidine to the desired tricyclic guanidine was carried out under the Mitsunobu reaction conditions. Finally, the four Boc groups were cleaved with TFA. The crude mixture obtained was purified by HPLC (PEGASIL-ODS, eluant: 50% MeCN/H_2O, 0.1% TFA) to give batzelladine A (**1**) as the trifluoroacetate salt in 24% yield from **26**. All of the data for synthetic **1** were in good agreement with reported values.[21]

In summary, the first enantioselective total synthesis of batzelladine A (**1**) has been described. A strategy of successive 1,3-dipolar cycloadditions was a key feature of the synthesis. During the course of these studies we discovered that the primary alcohol **9** could be converted into the α,β-unsaturated aldehyde **19** by reaction with TPAP/NMO, and this novel oxidation was applied effectively in the synthesis of the left-hand bicyclic guanidine fragment of **1**. The synthesis described should make it possible to prepare substantial amounts of batzelladines and their derivatives, and should thus aid efforts toward the elucidation of the mechanism through which these relatively small molecules modulate protein–protein interactions.



Scheme 5. Synthesis of the precursor **7** to the tricyclic guanidine subunit and conversion into **1**: a) 1-undecene (**21**), toluene, 90°C (75%); b) CsF, EtOH, 90°C (98%); c) ClC(S)OPh, pyridine, DMAP; d) nBu_3SnH, AIBN (51%, two steps); e) TBAF, THF (97%); f) Jones reagent, acetone; g) **5**, EDCI, DMAP, CH_2Cl_2 (60%, two steps); h) HF–pyridine, THF (80%); i) Pd/C, H_2; j) PPh_3, DEAD, toluene; k) TFA/CH_2Cl_2 (24%, three steps). EDCI = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, TBAF = tetrabutylammonium fluoride.

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Keywords: alkaloids · cycloaddition · natural products · oxidation · total synthesis

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[20] We currently believe the mechanism of this reaction to involve iminium formation by oxidation of the guanidine nitrogen atom at the ring junction, followed by isomerization to form the α,β-unsaturated aldehyde.
[21] Spectral data for synthetic **1**: $[\alpha]_D^{25} = +4.29$ ($c = 0.25$, MeOH) (lit:[1a] $[\alpha]_D^{25} = +8.9$ ($c = 2.3$, MeOH)); IR (neat): $\tilde{\nu} = 2925, 2854, 1732, 1697, 1683, 1648, 1637, 1558, 1347, 1092\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta = 4.39$ (t, $J = 6.1$ Hz, 1H), 4.21 (t, $J = 6.4$ Hz, 2H), 4.13 (t, $J = 6.7$ Hz, 2H), 3.93 (m, 1H), 3.83 (m, 2H), 3.66 (m, 1H), 3.52 (m, 1H), 3.32 (m, 1H), 3.22 (t, $J = 7.3$ Hz, 2H), 3.12 (dd, $J = 4.6, 3.5$ Hz, 1H), 2.98 (m, 1H), 2.35 (m, 1H), 2.28–2.17 (m, 3H), 2.10 (m, 1H), 1.76 (m, 2H), 1.72–1.52 (m, 9H), 1.48–1.23 (m, 29H), 1.27 (t, $J = 6.7$ Hz, 3H), 0.89 ppm (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 170.7, 166.2, 158.7, 153.1, 152.7, 151.5, 103.3, 66.0, 65.1, 57.7, 57.3, 53.2, 51.2, 49.9, 48.8, 45.6, 42.0, 37.5, 36.9, 34.2, 33.0, 31.9, 31.4, 29.7, 29.3, 27.0, 26.6, 26.2, 25.2, 23.7, 22.9, 18.4, 14.4$ ppm; HRMS (FAB, MH^+): calcd for $C_{42}H_{74}N_9O_4$: 768.5864, found: 768.5866.

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