Total Synthesis of (±)-Batzelladine K: A Biomimetic Approach

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Abstract: Total synthesis of batzelladine K was achieved by a biomimetic approach. The key reactions involve two Wittig reactions of phosphoranes and aldehydes leading to an α,β-unsaturated ketone, followed by a condensation with guanidine. The synthesis was accomplished in four steps with an overall yield of 12%. The relative stereochemistry of batzelladine K was established by NOE experiments and comparison with literature values.

Key words: batzelladines, marine natural products, tricyclic guanidine, phosphorane, biomimetic synthesis

The guanidine-containing natural products are abundant in nature, mainly present in higher plants, microorganisms (terrestrial, marine, and freshwater), marine algae, sponges, invertebrates, and vertebrates. They are of great interest due to their various biological activities.[1] The batzelladines, a class of polycyclic marine alkaloids containing a guanidine group, have been isolated from various *Batzella* species. Batzelladines A–E were isolated from a bright red Carribean sponge of the genus *Batzella* by scientists at Smith Kline Beecham in 1995. Batzelladines A and B were found to inhibit the binding of HIV glycoprotein gp-120 to CD4 receptors and are therefore of potential interest for the treatment of AIDS.[2] Later, new batzelladines F–I were also isolated by the same group from the methanol extract of a sponge *Batzella* species, collected in Jamaica. Batzelladines F, G, and a mixture of H and I were active in the p56lck-CD4 dissociation assay at micromolar concentrations.[3] Batzelladine J and crambescidic acid were isolated from *Monanchora unguifera*.[4] Recently, new batzelladines K–N were isolated from the Caribbean sponge *Monanchora unguifera*.[5] Some of the batzelladine alkaloids are shown in Figure 1.

Total synthesis of the complex batzelladines containing large numbers of stereocenters is a great challenge for synthetic chemists. Various attempts have been made by many research groups to construct the tricyclic guanidinium core of batzelladine alkaloids by using various strategies,[6,7] and consequently the total syntheses of batzelladine A,[8,9] C,[10] D,[9,11] E,[12] and F[13] have been reported. It was revealed that the tricyclic portion of batzelladines is involved in preventing the fusion of viral gp120 and human CD4 receptors.[14] Batzelladine K contains the tricyclic guanidine core, but has not been evaluated so far for anti-HIV potential. As a part of ongoing work in our laboratory to identify new anti-HIV agents,[15] we have selected the batzelladine nucleus for further modification. We decided to synthesize and evaluate batzelladine K for anti-HIV activity because of its promising tricyclic guanidine core.

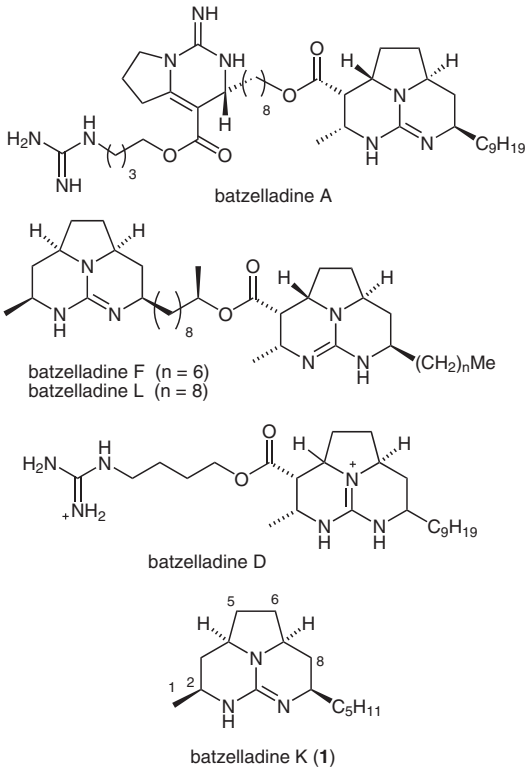

Figure 1 Natural batzelladine alkaloids

Recently, Nagasawa and co-workers have achieved the total synthesis of batzelladine K in 19 steps based upon a strategy involving successive 1,3-dipolar cycloaddition of optically active nitrone, propylene, and hept-1-ene.[17] However, this method involved several protection and deprotection reactions and ring-closure and stereoselective ring-opening steps to form the pyrrolidine ring with *syn* stereochemistry. Guanidination of the pyrrolidine with bis-Cbz-methyl thiopseudourea and cyclization yielded batzelladine K.

A biosynthetic pathway for batzelladine K (**1**) was proposed by Yu et al. (Scheme 1).[16] It was demonstrated that addition of guanidine to α,β-unsaturated ketone **6** led to the construction of the tricyclic guanidinium core. Herein,

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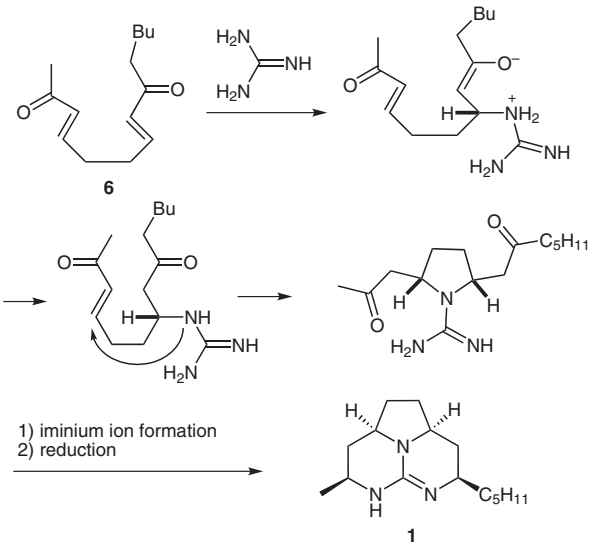
we describe a total synthesis of batzelladine K (**1**) by a very concise biomimetic approach in four steps based on this biosynthetic pathway.



Scheme 1 Proposed biosynthetic pathway for batzelladine K[16]

Our method is based on a strategy that involves condensation of guanidine with an α,β-unsaturated ketone by Michael addition. The synthesis begins with alkylation of commercially available phosphorane **2** by use of butyllithium as a base and butyl iodide, to provide phosphorane **3** in 98% yield (Scheme 2). Succinaldehyde (**4**) was freshly prepared by hydrolysis of 2,5-dimethoxytetrahydrofuran with 0.6 M hydrochloric acid and immediately used after distillation.[18] A Wittig reaction of **3** with an excess of succinaldehyde at room temperature for 24 hours afforded exclusively the *E*-isomer of ketone **5** in 68% yield. An excess of succinaldehyde (>3 equiv) is essential to obtain ketone **5**, because otherwise phosphorane **3** reacts with the free aldehyde group of **5** to form di-α,β-unsaturated ketone (symmetrical). Ketone **5** was treated with **2** at room temperature for 24 hours to provide α,β-unsaturated ketone **6** in 71% yield. Guanidine hydrochloride was converted into free base **7** by treatment with sodium methoxide.[19] Guanidine was then condensed with **6** for the construction of the tricyclic ring. Addition of guanidine to **6** was carried out at 0 °C by a previously reported procedure.[7,19] The reaction occurred via a Michael addition, followed by a reduction with sodium borohydride to form batzelladine K (**1**) in 25% yield. The relative stereochemistry of **1** was determined by NOE experiments, which indicated that protons H2 and H4 along with H7 and H9 are on the same face of the tricycle (Figure 2). Thus, the relative stereochemistry of the tricyclic guanidium core was found to be identical to that of natural product **1**. The ^1H and ^{13}C NMR spectra of **1** were in close agreement with those reported for the natural alkaloid.[5]

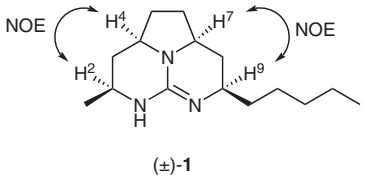
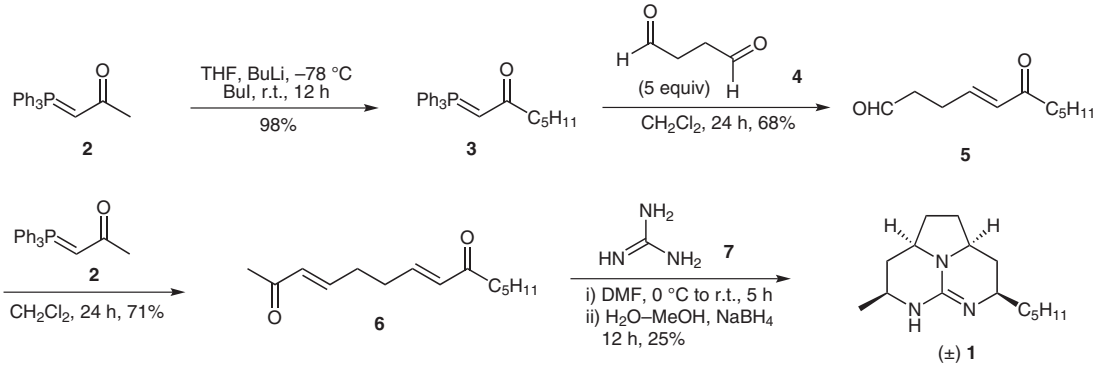


Figure 2 NOE correlation of batzelladine K

In conclusion, we have accomplished a short total synthesis of (±)-batzelladine K in four steps by a biomimetic approach with an overall yield of 12%. Condensation of guanidine to an α,β-unsaturated ketone was a key feature of the synthesis. Further work is in progress in our laboratory and the anti-HIV activity will be reported soon.

All chemicals and solvents were purchased from Sigma-Aldrich and Acros Organic and were used without further treatment unless otherwise noted. All reactions were carried out under an argon atmosphere with dehydrated solvents under anhyd conditions, unless otherwise noted. The solvents THF, CH_2Cl_2, and DMF were dehydrated and distilled according to standard protocols. NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz) with TMS as internal standard. Chemical shifts are reported relative to TMS. Mass spectra were recorded on GCMS-QS Shimadzu (QP-500) and LCMS Waters (Micromass ZQ) spectrometers. HRMS was carried out on an LCMS (Bruker maxis) spectrometer. IR spectra were recorded on a Nicolet spectrometer. The combustion analyses were carried out on a Vario EL Elementar elemental analyzer. Reactions were monitored by TLC (Merck 0.25 mm Kieselgel 60 F254 plates). Column chromatography was performed on silica gel (60–120 mesh).



Scheme 2 Synthesis of batzelladine K

1-(Triphenylphosphoranylidene)heptan-2-one (3)

A 1.6 M soln of BuLi in hexane (11.5 mL, 18.9 mmol) was added dropwise to a cooled (–78 °C) soln of **2** (5 g, 15.7 mmol) in THF (250 mL), resulting in the formation of a deep red color. The mixture was stirred for 30 min, and then BuI (2.15 mL, 18.8 mmol) was added dropwise. The resulting mixture was then allowed to stir at 25 °C for 12 h. After evaporation of the THF, the resulting red oil was dissolved in EtOAc (30 mL) and the soln was washed with H_2O (2 × 50 mL); the organic layer was dried over Na_2SO_4 and subsequently concentrated in vacuo to give phosphorane **3** as a viscous oil.

Yield: 5.8 g (98%).

IR (KBr): 3282, 1715, 1566, 1429 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H), 1.34 (m, 4 H), 1.66 (quin, *J* = 7.6, 15.2 Hz, 2 H), 2.30 (t, *J* = 7.6 Hz, 2 H), 7.42–7.48 (m, 6 H, ArH), 7.52–7.55 (m, 3 H, ArH), 7.61–7.67 (m, 6 H, ArH); methine H not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 26.9, 33.0, 41.6, 128.4, 128.5, 128.7, 128.8, 129.0, 131.90, 131.93, 131.95, 133.9, 132.0, 132.0, 132.1, 133.0, 133.1.

MS (CI): *m*/*z* = 375 $[M + 1]^+$.

Anal. Calcd for $C_{25}H_{27}OP$: C, 80.19; H, 7.27. Found: C, 80.38; H, 7.56.

(*E*)-6-Oxoundec-4-enal (5)

Freshly prepared succinaldehyde (**4**; 1.8 g, 21 mmol) was added to a soln of **3** (2 g, 5.3 mmol) in CH_2Cl_2 (15 mL) and the resulting soln was stirred at 25 °C for 24 h. The soln was then washed with H_2O (2 × 30 mL) to remove excess succinaldehyde and concentrated in vacuo; this gave the crude product, which was subjected to column chromatography (silica gel, hexane–EtOAc, gradient); this gave product **5** as a slightly yellow oil.

Yield: 660 mg (68%).

IR (KBr): 3188, 1730, 1628, 1556 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.12 Hz, 3 H), 1.30 (m, 4 H), 1.59 (quin, *J* = 7.36, 14.7 Hz, 2 H), 2.53 (m, 4 H), 2.67 (t, 6.0 Hz, 2 H), 6.10 (d, *J* = 15.9 Hz, 1 H), 6.78 (dt, *J* = 6.2, 15.8 Hz, 1 H), 9.88 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 23.8, 24.5, 31.4, 40.3, 41.9, 130.9, 143.9, 200.3, 200.4.

MS (CI): *m*/*z* = 183 $[M + 1]^+$.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.71; H, 10.19.

(3*E*,7*E*)-Tetradeca-3,7-diene-2,9-dione (6)

Compound **2** (400 mg, 1.25 mmol) was added to a soln of **5** (230 mg, 1.25 mmol) in CH_2Cl_2 (10 mL) at 25 °C, and the soln was stirred for 24 h. The CH_2Cl_2 soln was concentrated in vacuo to give the crude product, which upon column chromatography (silica gel, hexane–EtOAc, gradient) yielded **6** as a colorless oil.

Yield: 200 mg (71%).

IR (KBr): 3302, 1727, 1694, 1491, 1372 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H), 1.31 (m, 4 H), 1.60 (quin, *J* = 7.4, 15 Hz, 2 H), 2.23 (s, 3 H), 2.41 (m, 4 H), 2.50 (t, *J* = 7.4 Hz, 2 H), 6.11 (d, *J* = 8.4 Hz, 1 H), 6.13 (d, *J* = 9.6 Hz, 1 H), 6.75–6.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 23.6, 27.0, 30.6, 30.7, 31.4, 40.4, 130.9, 131.9, 144.4, 145.8, 198.3, 200.5.

MS (CI): *m*/*z* = 223 $[M + 1]^+$.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.91; H, 10.09.

(±)-Batzelladine K (1)

To a cooled (0 °C) soln of **6** (200 mg, 0.9 mmol) in DMF (5 mL) was added guanidine (**7**; 53 mg, 0.9 mmol) in DMF (1 mL), and the mixture was allowed to stir at 25 °C for 5 h. The reaction mixture was cooled again at 0 °C and MeOH (5 mL) and H_2O (2 mL) were added, followed by $NaBH_4$ (200 mg, 5.4 mmol). The mixture was then stirred at 25 °C overnight; the MeOH was evaporated in vacuo and the reaction mixture was diluted with CH_2Cl_2 (15 mL), followed by 2 M aq HCl (5 mL). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with H_2O (3 × 40 mL) and brine (2 × 40 mL), then dried over Na_2SO_4, and concentrated in vacuo to give a slightly yellow oil, which upon column chromatography (silica gel, $CHCl_3$–MeOH, gradient) afforded **1** as a yellow semisolid.

Yield: 55 mg (25%).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.56 Hz, 3 H), 1.32 (d, *J* = 6.2 Hz, 3 H), 1.25 (m, 2 H), 1.30 (m, 6 H), 1.54 (m, 1 H), 1.62 (m, 1 H), 1.70 (m, 2 H), 2.22 (m, 2 H), 2.26 (m, 2 H), 3.39 (m, 1 H), 3.54 (m, 1 H), 3.68 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 20.5, 22.6, 25.0, 30.3, 30.4, 31.4, 34.0, 34.7, 36.5, 45.7, 50.1, 55.7, 55.8, 162.5.

MS (CI): *m*/*z* = 250 $[M + 1]^+$.

HRMS (ESI^+): *m*/*z* calcd for $C_{15}H_{28}N_3$ [M + H]: 250.2283; found: 250.2261.

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