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SYNTHESIS OF (+)-BATZELLADINE K†

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Abstract – Total synthesis of batzelladine K (**1**), a marine guanidine alkaloid, was achieved based upon successive 1,3-dipolar cycloaddition reaction of cyclic nitrone. The relative and absolute stereochemistry of **1** was established by spectral comparison of the natural and synthetic products and the *trans*-isomer, which was also synthesized.

Many natural products possessing a guanidine functional group have been isolated, and have attracted much attention because of their wide range of biological activities.[1] Batzelladines, a unique family of polycyclic guanidine alkaloids, were reported to influence protein-protein interactions. In particular, batzelladines A-E block interaction between HIV envelope glycoprotein gp120 and the extracellular domains of human CD4 receptor protein,[2] while batzelladines F and G induce dissociation of the complex between tyrosine kinase $p56^{lck}$ and CD4.[3] Consequently, considerable synthetic efforts have been devoted to batzelladines,[4] and total syntheses of batzelladines A, D, E, and F have been reported.[5] Structure-activity relationship studies have also been reported, and some synthetic derivatives were found to regulate characteristic protein-protein interactions of Nef-p52, Nef-actin, and Nef-$p56^{lck}$.[6] Recently, new analogs of the batzelladine family, batzelladines K-N, were reported by Hamann et al.[7] We are interested in the modulation of protein-protein interactions by batzelladines,[8] and therefore planned to synthesize batzelladine K (**1**), which corresponds to the left-hand tricyclic guanidine structure of batzelladine F (**2**). Herein, we report a synthesis of batzelladine K (**1**) based upon a strategy involving successive 1,3-dipolar cycloaddition (1,3-DC). The chemical structure of **1**, including relative and absolute stereochemistry, was confirmed by this synthesis.

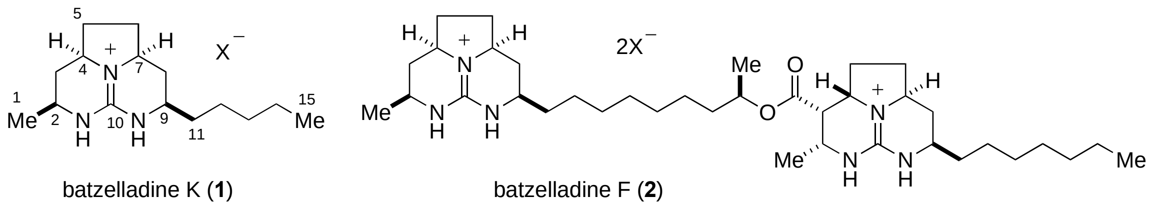
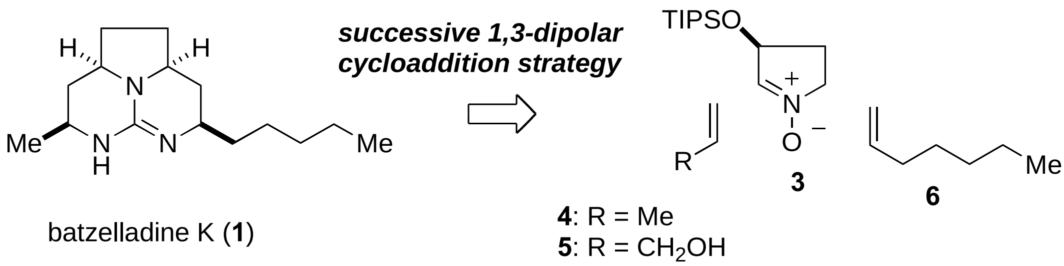


Figure 1. Structures of batzelladines K (**1**) and F (**2**).

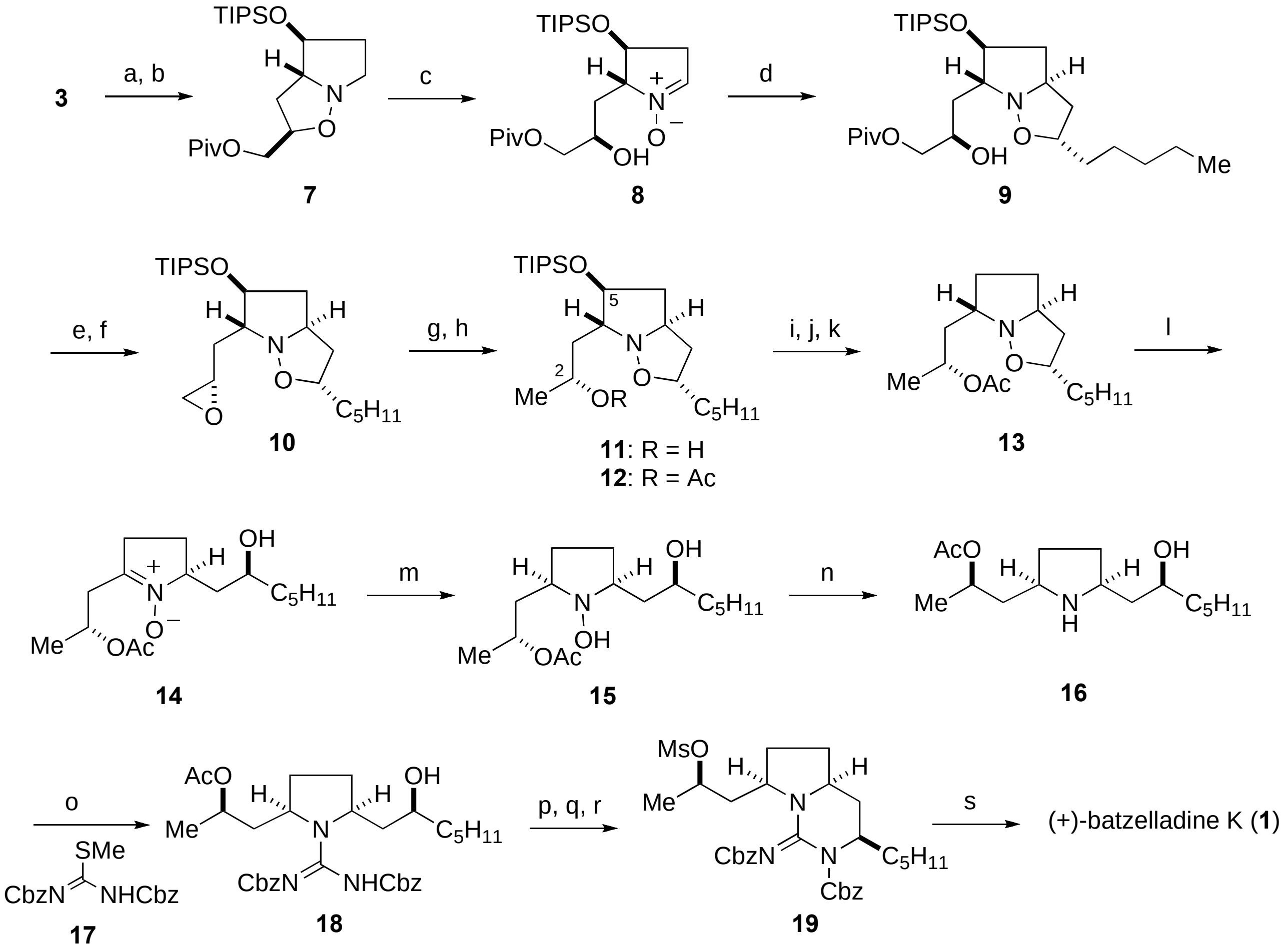
As shown in the synthetic plan in Scheme 1, a successive 1,3-DC reaction strategy was applied for synthesis of batzelladine K (**1**). For this approach, optically active nitrone **3**,[9] propylene (**4**) and 1-heptene (**6**) were required. However, propylene, which is a gas at ambient temperature, is not suitable for 1,3-DC reaction under heating, so allyl alcohol (**5**) was used as a synthetic equivalent of propylene.



Scheme 1. Synthetic plan for batzelladine K (**1**).

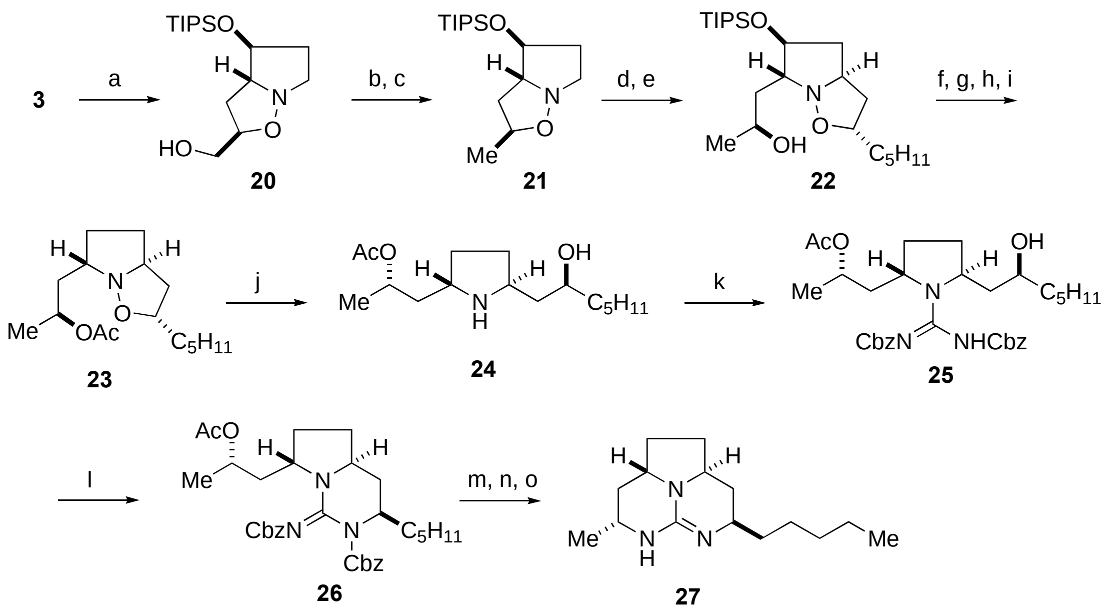
1,3-DC reaction of the optically active nitrone **3** in allyl alcohol at 90 °C gave isoxazolidine, whose hydroxyl group was protected as pivalate to give **7** in 69% yield (2 steps). The regioselective oxidation of **7** with *m*-CPBA gave nitrone **8**, which was subjected to a second 1,3-DC reaction with 1-heptene (**6**) in toluene to give isoxazolidine **9** in 63% yield from **7**. Next, inversion of the stereochemistry of the secondary alcohol and conversion of the methyl group at C2 were conducted. Thus, mesylation of the secondary alcohol with methanesulfonyl chloride and triethylamine followed by treatment with potassium carbonate in methanol gave **10**, whose epoxy group was reduced regioselectively with $LiAlH_4$ to give the alcohol **11**. The resulting alcohol was protected with acetate to give **12** in 84% yield from **9**. Deoxygenation of the secondary alcohol at C5 of **12**, which was obtained by deprotection of the silyl ether in **12** with *n*-Bu_4NF (85%), was conducted by the Barton-McCombie method[10] to give **13** in 75% yield. Oxidation of **13** with *m*-CPBA in dichloromethane regioselectively regenerated nitrone **14**, and stepwise reduction of **14** with PtO_2 and Raney-Ni under hydrogen provided *cis*-substituted pyrrolidine **16**.[11] Guandination of the pyrrolidine **16** with bis-Cbz-methylthiopseudourea (**17**), mercury (II) chloride and triethylamine followed by cyclization under the Mitsunobu reaction conditions in the presence of

DEAD and triphenylphosphine gave bicyclic guanidine **19** quantitatively. Tricyclic guanidine **1** was quantitatively synthesized by selective deprotection of the Cbz group in **19** with sodium hydride in THF-methanol followed by mesylation of the resulting alcohol. Finally, deprotection of the Cbz group with Pd-C under hydrogen furnished batzelladine K (**1**) in 32% yield from **18**.



Scheme 2. Synthesis of (+)-batzelladine K (**1**): (a) allyl alcohol, 90 °C, 30 h, 77%; (b) PivCl, Py, DMAP, CH_2Cl_2, 0 °C, 17 h, 89%; (c) *m*-CPBA, CH_2Cl_2, 0 °C, 10 min; (d) 1-heptene (**6**), toluene, 50 °C, 30 h, 63% (2 steps); (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (f) K_2CO_3, MeOH, 0 °C, 30 h; (g) $LiAlH_4$, Et_2O, 0 °C, 10 min; (h) Ac_2O, Py, rt, 22 h, 84% (4 steps); (i) *n*-Bu_4NF, THF, 0 °C, 30 min, 85%; (j) TCDI, THF, 60 °C, 25 h, 99%; (k) *n*-Bu_3SnH, AIBN, toluene, 100 °C, 30 min, 75% (rsm 18%); (l) *m*-CPBA, CH_2Cl_2, 0 °C, 10 min, 66%; (m) H_2, PtO_2, MeOH , rt, 2 h, 17%; (n) H_2, Raney-Ni, MeOH, rt, 17 h; (o) **17**, $HgCl_2$, Et_3N, DMF, 0 °C, 10 min, 38% (2 steps); (p) DEAD, PPh_3, toluene, 0 °C, 30 min; (q) NaH, THF, MeOH, 0 °C, 3 h; (r) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (s) H_2, Pd-C, MeOH, rt, 24 h, 32% (4 steps).

To confirm the reported structure for batzelladine K (**1**),[12] the *trans*-isomer at C2 and C4 of batzelladine K (**1**), i.e., *trans*-batzelladine K (**27**), was also synthesized based upon a successive 1,3-DC protocol. Thus, the alcohol **20** obtained from the 1,3-DC reaction of nitrone **3** with allyl alcohol was converted into **21** by mesylation of the alcohol followed by reduction with $LiAlH_4$ in 70% yield from **20**. Oxidation of isoxazolidine **21** with *m*-CPBA generated nitrone and subsequent 1,3-DC reaction with **6** stereoselectively gave **22** in 59% yield. After protection of the hydroxyl group with acetate, the TIPS ether at C5 was removed by the Barton-McCombie method[10] to give **23** in 80% yield from **22**. Hydrogenolysis of **23** in the presence of zinc powder in HCl-aq gave *trans*-disubstituted-β-hydroxy pyrrolidine **24**, which was subsequently treated with bis-Cbz-methylthiopseudourea (**17**), mercury (II) chloride and triethylamine to afford **25** in 77% yield from **23**. Synthesis of *trans*-batzelladine K (**27**) from **25** was completed in the same manner as described for **18**, providing **27** in 34% yield from **26**.



Scheme 3. Synthesis of *trans*-batzelladine K (**27**): (a) allyl alcohol, 90 °C, 30 h, 77%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (c) $LiAlH_4$, Et_2O, 0 °C, 30 min, 70% (2 steps); (d) *m*-CPBA, CH_2Cl_2, 0 °C, 10 min; (e) 1-heptene (**6**), toluene, 60 °C, 47 h, 59% (2 steps); (f) Ac_2O, Py, rt, 5 h, 99%; (g) *n*-Bu_4NF, THF, 0 °C, 1 h; (h) TCDI (=1,1'-thiocarbonyldiimidazole), THF, 60 °C, 25 h; (i) *n*-Bu_3SnH, AIBN, toluene, 100 °C, 30 min, 81% (3 steps), (rsm 14%); (j) Zn powder, HCl-aq, THF, rt, 24 h; (k) **17**, $HgCl_2$, Et_3N, DMF, 0 °C, 30 min, 77% (2 steps); (l) DEAD, PPh_3, toluene, 0 °C, 30 min, 93%; (m) NaH, THF, MeOH, 0 °C, 2 h, 70%; (n) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (o) H_2, Pd-C, MeOH, rt, 2 h, 49% (2 steps).

The ^{13}C NMR spectra data of batzelladine K (**1**) (reported and synthetic) and its *trans*-isomer **27** are summarized in Table 1.[13] The spectral data for synthetic **1** were in good agreement with reported values for the natural product. On the other hand, distinct differences were observed in the C4, 7, and 9 signals of the *trans*-isomer **27**. Thus, we have succeeded in the synthesis of natural batzelladine K (**1**). Since the optical rotation of synthetic **1** was found to be +2.7 (*c* 0.4, MeOH), (lit.,[7] +6.4 (*c* 0.1, MeOH)), the absolute stereochemistry of batzelladine K (**1**) was also defined.

Table 1. ^{13}C NMR for batzelladine K (**1**) (natural and synthetic) and **27**.[a]

	Batzelldine K (**1**) (natural) (ppm)	Batzelldine K (**1**) (synthetic) (ppm)	Compound **27** (ppm)
position			
1	20.8	20.8	21.7
2	47.4	47.3	------[b]
3	36.9	36.7	36.4
4	57.6	57.5	56.5
5	31.2	31.1	31.8
6	31.1	31.0	31.8
7	57.4	57.5	56.4
8	34.9	34.7	34.3
9	51.7	51.6	53.1
10	151.2	151.1	151.5
11	35.9	35.8	36.9
12	26.0	25.9	25.9
13	32.9	32.8	32.8
14	23.7	23.6	23.6
15	14.4	14.6	14.3

a) All spectra were measured in CD_3OD. b) Overlapped with solvent peak.

In summary, we have achieved total synthesis of batzelladine K (**1**) and its *trans*-isomer **27** based upon successive 1,3-dipolar cycloaddition reaction of cyclic nitrone. The relative and absolute stereochemistry of **1** was thereby established.

EXPREMENTAL

General

Flash column chromatography was performed on Silica gel 60 (spherical, particle size 0.040 ~ 0.100 μm; Kanto). Optical rotations were measured on a JASCO P-2200 polarimeter, using the sodium lump (589 nm). ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA 500 or JNM-ECX 400. Mass spectra were recorded on JEOL JMS-T100X spectrometer with ESI-MS mode using methanol as solvent.

Isoxazolidine 7. A mixture of nitrone **3** (2.44 g, 9.50 mmol) and allyl alcohol (30 mL, 0.44 mol) was heated at 90 °C for 30 h. Reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1 to 4:1) to give isoxazolidine **20** (2.32 g, 77 %). Spectral data for **20**: $[\alpha]_D^{18}$ -12 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (m, 2H), 3.65 (dd, *J* = 3.2, 11.9 Hz, 2H), 3.56 (dd, *J* = 5.5, 11.9 Hz, 1H), 3.30 (dd, *J* = 4.6, 8.7 Hz, 2H), 2.43 (ddd, *J* =

5.0, 9.2, 12.8 Hz, 1H), 2.18 (m, 1H), 2.10 (ddd, J = 4.1, 7.3, 12.4 Hz, 1H), 1.70 (m, 1H), 1.04 (brs, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.5, 77.8, 75.3, 64.7, 55.3, 36.3, 34.3, 17.9, 12.0 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{16}H_{33}NNaO_3Si$ 338.2127, found 338.2122. To a solution of isoxazolidine **20** (535 mg, 1.70 mmol), pyridine (411 μL, 5.09 mmol) , and DMAP (20.7 mg, 0.169 mmol) in CH_2Cl_2 (20 mL) was added pivaloyl chloride (413 μL, 3.39 mmol) at 0 °C under N_2 atmosphere, and stirred for 18 h at rt. To the reaction mixture was added sat. aq. NH_4Cl, and the organic layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 30:1 to 20:1) to give isoxazolidine **7** (606 mg, 89%). Spectral data for **7**: $[\alpha]_D^{18}$ -15 (c 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (ddd, J = 5.7, 6.4, 12.1 Hz, 1H), 4.16 (ddd, J = 2.7, 2.8, 5.5 Hz, 1H), 4.09, (s, 1H), 4.08 (d, J = 1.8 Hz, 1H), 3.62 (ddd, J = 2.7, 3.7, 8.7 Hz, 1H), 3.36 (ddd, J = 6.4, 9.7, 12.9 Hz, 1H), 3.25 (ddd, J = 3.9, 7.1, 12.9 Hz, 1H), 2.30 (ddd, J = 6.0, 8.7, 12.8 Hz, 1H), 2.13 (m, 2H), 1.72 (ddd, J = 3.4, 3.7, 6.4, 12.8 Hz, 1H), 1.20 (s, 9H), 1.04 (brs, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 79.0, 75.0, 74.3, 64.8, 55.4, 38.7, 37.1, 34.3, 27.1, 17.9, 12.0 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{21}H_{41}NNaO_4Si$ 422.2703, found 422.2716.

Alcohol 9. To a solution of isoxazolidine **7** (287 mg, 0.716 mmol) in CH_2Cl_2 (7.0 mL) was added *m*--CPBA (193 mg, 0.861 mmol) at 0 °C under N_2 atmosphere. After stirring for 10 min at 0 °C, to the reaction mixture was added 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 and $CHCl_3$. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give nitrone **8**. A mixture of the crude nitrone **8** and 1-heptene (1.5 mL, 10.8 mmol) in toluene (1.0 mL) was heated at 50 °C for 30 h, and the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1 to 4:1) to give alcohol **9** (230 mg, 0.448 mmol, 63% in 2 steps). Spectral data for **9**: $[\alpha]_D^{16}$ -5.6 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (m, 2H), 4.09 (d, J = 5.5 Hz, 2H), 4.04 (q, J = 7.0 Hz, 1H), 3.80 (dq, J = 1.9, 7.7 Hz, 1H), 3.24 (dt, J = 3.7, 7.9 Hz, 1H), 2.34 (ddd, J = 6.4, 6.9, 13.3 Hz, 1H), 2.10 (ddd, J = 2.6, 5.3, 11.9 Hz, 1H), 1.94 (q, J = 9.4 Hz, 1H), 1.92 (m, 1H), 1.66 (ddd, J = 7.8, 8.7, 16.5 Hz, 1H), 1.65 (q, J = 7.8 Hz, 1H), 1.62 (dd, J = 2.7, 8.2 Hz, 1H), 1.29 (m, 8H), 1.20 (s, 9H), 1.04 (brs, 21H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 75.7, 73.6, 70.5, 68.0, 67.3, 61.4, 41.7, 40.6, 38.8, 34.1, 32.3, 31.8, 27.2, 26.2, 22.5, 18.0, 14.0, 12.2 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{28}H_{55}NNaO_5Si$ 536.3747, found 536.3783.

Isoxazolidine 12. To a solution of alcohol **9** (285 mg, 0.554 mmol) and Et_3N (232 μL, 1.66 mmol) in CH_2Cl_2 (5.5 mL) was added MsCl (64 μL, 0.831 mmol) at 0 °C under N_2 atmosphere, and the mixture was stirred for 10 min. To the reaction mixture was added sat. aq. $NaHCO_3$, and the resulting mixture was extracted with $CHCl_3$ and EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give mesylate. To a solution of the crude mesylate in MeOH (5.5 mL) was added K_2CO_3 (153 mg, 1.11 mmol) at 0 °C, and the mixture was stirred for 30 h at rt. To the reaction mixture was added water at 0 °C and the organic layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give epoxide **10**. To a solution of crude epoxide **10** (226 mg) in Et_2O (5.5 mL) was added $LiAlH_4$ (153 mg, 4.02 mmol) at 0 °C under N_2 atmosphere, and the resulting mixture was stirred for 10 min. To the reaction mixture was added H_2O (50 μL), 15 % NaOH aq. (50 μL) and H_2O (150 μL), and the resulting mixture was filtered through a pad of Celite. The filtrates were concentrated *in vacuo* to give alcohol **11**. To a solution of the crude alcohol **11** in pyridine (3.0 mL) was added acetic anhydride (2.0 mL) at rt, and the mixture was stirred for 22 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 12:1 to 9:1) to give isoxazolidine **12** (213 mg, 0.467 mmol, 84% in 4 steps). Spectral data for **12**: $[\alpha]_D^{16}$ -6.7 (*c* 2.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (m, 1H), 4.08 (dq, J = 5.5, 9.6 Hz, 1H), 3.87 (q, J = 6.7 Hz, 1H), 3.72 (dq, J = 2.2, 8.0 Hz, 1H), 2.90 (dt, J = 5.0, 7.3 Hz, 1H), 2.23 (ddd, J = 6.4, 7.3, 12.4 Hz, 1H), 2.02 (ddd, J = 2.8, 5.5, 11.9 Hz, 1H), 1.99 (brs, 3H), 1.86 (dt, J = 9.6, 11.9 Hz, 1H), 1.78 (ddd, J = 2.3, 5.0, 5.5 Hz, 1H), 1.60 (dt, J = 7.3, 12.8 Hz, 2H), 1.52-1.33 (m, 1H), 1.27 (m, 7H), 1.25 (d, J = 6.4 Hz, 3H), 1.04 (brs, 21H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 75.1, 74.8, 70.3, 69.7, 61.9, 42.1, 40.4, 39.7, 32.5, 31.8, 26.2, 22.5, 21.5, 19.6, 18.0, 13.9, 12.1 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{25}H_{49}NNaO_4Si$ 478.3329, found 478.3326.

Acetate 13. To a solution of isoxazolidine **12** (347 mg, 0.761 mmol) in THF (8.0 mL) was added TBAF (398 mg, 1.52 mmol) at 0 °C, and the mixture was stirred for 30 min. To the reaction mixture was added sat. aq. NH_4Cl, and the resulting mixture was extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1 to 1:1, then EtOAc/MeOH = 1:0 to 10:1) to give alcohol (194 mg, 0.650 mmol, 85 %). To a solution of the alcohol (165 mg, 0.551 mmol) in THF (5.5 mL) was added thiocarbonyldiimidazole (437 mg, 2.20 mmol), and the mixture was stirred at 60 °C for 14 h. Reaction mixture was concentrated *in vacuo*, and the residue was filtered through a short pad of silica gel column with an eluent of hexane/EtOAc = 10:1 and 5:1 to give thiocarbamate (224 mg, 0.548 mmol, 99%). To a solution of thiocarbamate (176 mg, 0.430 mmol) in toluene (4.5 mL) was added n-Bu_3SnH (1.2 mL, 4.3 mmol) and AIBN (14.1 mg, 0.0860 mmol) at rt, and the mixture was heated at 100 °C for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 1:0 to 4:1 to 1:1) to give acetate **13** (91.0 mg, 0.321 mmol, 75%) and alcohol which was generated by simple elimination of thiocarbamate group (23.6 mg, 0.0789 mmol, 18%). Spectral data for **13**: $[\alpha]_D^{17}$ -66 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (m, 1H), 3.95 (dt, *J* = 6.4, 7.8 Hz, 1H), 3.74 (dt, *J* = 6.0, 7.3 Hz, 1H), 2.99 (m, 1H), 2.06-1.92 (m, 4H), 2.00 (s, 3H), 1.91 (s, 1H), 1.89 (dd, *J* = 2.8, 6.9 Hz, 1H), 1.60 (m, 1H), 1.54 (ddd, *J* = 5.0, 8.2, 11.0 Hz, 1H), 1.46 (m, 1H), 1.36 (m, 1H), 1.27 (m, 6H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 75.3, 69.3, 63.7, 63.6, 42.1, 41.2, 32.9, 31.8, 30.7, 29.6, 26.0, 22.5, 21.4, 20.4, 14.0 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{16}H_{29}NNaO_3$ 306.2045, found 306.2045.

Hydroxylamine **15.** To a solution of acetate **13** (69.8 mg, 0.247 mmol) in CH_2Cl_2 (2.5 mL) was added *m*-CPBA (66.3 mg, 0.296 mmol) at 0 °C under N_2 atmosphere, and the mixture was stirred for 10 min. To a reaction mixture was added 10% aq. Na_2SO_3 and sat. aq. $NaHCO_3$, and the resulting mixture was extracted with $CHCl_3$. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was filtered through a short pad of silica gel column chromatography (hexane/EtOAc = 4:1 to 1:1 and EtOAc/MeOH = 1:0 to 10:1) to give nitrone **14** (48.3 mg, 66%). To a solution of nitrone **14** (84.4 mg, 0.282 mmol) in MeOH (3.0 mL) was added PtO_2 (catalytic amount), and the resulting mixture was stirred under H_2 atmosphere (balloon) for 3 h. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1 to 3:1 to 1:1) to give hydroxylamine **15** (79.8 mg, 0.265 mmol, 94%). Spectral data for **15**: $[\alpha]_D^{16}$ +17 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (ddq, *J* = 5.5, 6.4, 13.3 Hz, 1H), 3.95 (m, 1H), 3.12 (m, 1H), 2.79 (m, 1H), 2.05-1.81 (m, 4H), 2.01 (s, 3H), 1.67 (m, 2H), 1.57-1.33 (m, 4H), 1.29 (m, 6H), 1.23 (d, *J* = 1.3 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 69.3, 69.0, 65.8, 65.0, 40.2, 37.5, 36.2, 31.9, 26.4, 25.3, 23.6, 22.6, 21.4, 20.6, 14.0 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{16}H_{31}NNaO_4$ 324.2151, found 324.2152.

Bicyclic guanidine 19. To a solution of hydroxylamine **15** (58.7 mg, 0.195 mmol) in MeOH (2.0 mL) was added Raney-Ni (catalytic amount), and the resulting mixture was stirred under H_2 atmosphere (balloon) for 17 h. The reaction mixture was filtered through a pad of Celite, and the filtrates were concentrated *in vacuo* to give pyrrolidine **16**. To a solution of the crude pyrrolidine **16** in DMF (2.0 mL) was added Et_3N (86 μL, 0.62 mmol), thiopseudourea **17** (110 mg, 0.308 mmol) and $HgCl_2$ (83.5 mg, 0.308 mmol) at 0 °C under N_2 atmosphere, and the mixture was stirred for 1 h. The reaction mixture was diluted with EtOAc, and filtered through a pad of Celite. The filtrates were washed with H_2O and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 6:1 to 3:1) to give guanidine **18** (46.0 mg, 0.0773 mmol, 38% in 2 steps). To a solution of guanidine **18** (44.3 mg, 0.0744 mmol) and triphenylphosphine (58.5 mg, 0.223 mmol) in toluene (1.0 mL) was slowly added DEAD (88 μL, 0.22 mmol, 40% in toluene) at 0 °C under N_2 atmosphere. After stirring for 30 min, the reaction was quenched with a drop of H_2O and the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 6:1 to 4:1) to give bicyclic guanidine **19** (53.5 mg, 99%). Spectral data for **19**: $[\alpha]_D^{17}$ -128 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 10H), 5.14 (d, *J* = 12.4 Hz, 1H), 4.98 (d, *J* = 12.4 Hz, 1H), 4.93 (d, *J* = 12.6 Hz, 1H), 4.85 (q, *J* = 6.4 Hz, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 4.24 (m, 2H), 3.47 (m, 1H), 2.58 (ddd, *J* = 3.7, 9.6, 13.3 Hz, 1H), 2.17 (m, 1H), 2.05-1.86 (m, 3H), 2.00 (s, 3H), 1.67 (m, 3H), 1.57 (ddd, *J* = 6.4, 10.1, 13.3 Hz, 1H), 1.46-1.25 (m, 7H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 160.3, 153.5, 151.2, 137.0, 135.6, 128.5, 128.43, 128.39, 128.2, 127.6, 69.4, 68.2, 66.8, 55.9, 55.3, 55.0, 40.0, 38.7, 36.8, 31.4, 30.0, 28.9, 25.1, 22.6, 21.4, 19.9, 14.0 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{33}H_{43}N_3NaO_6$ 600.3050, found 600.3039.

Batzelladine K (1). To a solution of bicyclic guanidine **19** (53.5 mg, 0.0744 mmol) in MeOH-THF = 1:1 (1.0 mL) was added NaH (29.8 mg, 0.744 mmol, 60% dispersion in paraffin liquid) at 0 °C. After stirring for 3 h at rt, the reaction was quenched with a drop of H_2O at 0 °C. The resulting mixture was extracted with EtOAc, and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:0 to 6:1 to 4:1) to give bicyclic guanidine (34.7 mg, 99%). To a solution of bicyclic guanidine (95.2 mg, 0.151 mmol) and Et_3N (105 μL, 0.755 mmol) in CH_2Cl_2 (2.0 mL) was added methanesulfonyl chloride (59 μL, 0.755 mmol) at 0 °C under N_2 atmosphere, and the mixture was stirred for 30 min. To the reaction mixture was added sat. aq. NH_4Cl, and the organic layer was extracted with hexane. The extracts were washed with sat. aq. NH_4Cl, and the aqueous layer was alkalified to pH 8 with sat. aq. $NaHCO_3$. The resulting mixture was extracted with $CHCl_3$, and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH = 200:1 to 50:1 to 10:1) to give tricyclic guanidine (13.1 mg, 99%). To a solution of tricyclic guanidine (27.8 mg) in MeOH (1.0 mL) was added Pd/C (catalytic amount), and the reaction mixture was stirred under H_2 atmosphere (balloon) for 25 h. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH = 1:0 to 100:1) to give batzelladine K (**7**) (4.0 mg, 0.016 mmol, 32 % in 4 steps).

Isoxazolidine 21. To a solution of isoxazolidine **20** (407 mg, 1.29 mmol) and Et_3N (540 μL, 3.87

mmol) in CH_2Cl_2 (15 mL) was added methansulfonyl chloride (150 μL, 1.94 mmol) at 0 °C, and the mixture was stirred for 10 min. To the reaction mixture was added sat. aq. $NaHCO_3$, and the resulting mixture was poured into brine and extracted with $CHCl_3$. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give mesylate. To a solution of the crude mesylate in Et_2O (15 mL) was added $LiAlH_4$ (98.0 mg, 2.58 mmol) at 0 °C, and the resulting mixture was stirred for 30 min. To the reaction mixture was added H_2O (0.1 mL), 15% NaOH aq. (0.1 mL) and H_2O (0.3 mL), and the resulting mixture was filtered through a pad of Celite and the filtrates were concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 15:1 to 9:1) to give isoxazolidine **21** (272 mg, 0.909 mmol, 70% in 2 steps). Spectral data for **21**: $[\alpha]_D^{13}$ +4.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (ddd, J = 2.7, 3.2, 6.0 Hz, 1H), 4.09 (dt, J = 6.0, 6.8 Hz, 1H), 3.63 (dt, J = 2.7, 6.0 Hz, 1H), 3.39 (ddd, J = 6.0, 8.7, 12.4 Hz, 1H), 3.18 (ddd, J = 5.0, 6.4, 11.9 Hz, 1H), 2.09 (m, 2H), 2.05 (m, 1H), 1.72 (m, 1H), 1.24 (d, J = 6.0 Hz, 3H), 1.05 (brs, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.0, 74.4, 72.8, 55.7, 42.1, 34.6, 19.2, 18.0, 12.1 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{16}H_{33}NNaO_2Si$ 322.2178, found 322.2192.

Alcohol 22. To a solution of isoxazolidine **21** (379 mg, 1.27 mmol) in CH_2Cl_2 (15 mL) was added *m*-CPBA (341 mg, 1.52 mmol) at 0 °C, and the mixture was stirred for 10 min. To the reaction mixture was added 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$, and the resulting mixture was extracted with $CHCl_3$. The extracts were washed with brine, and organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give nitrone. To a solution of the crude nitrone and 1-heptene (2.8 mL, 19.0 mmol) in toluene (3.0 mL) was heated at 60 °C for 47 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 9:1 to 5:1) to give the alcohol **22** (308 mg, 59% in 2 steps). Spectral data for **22**: $[\alpha]_D^{12}$ -9.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (m, 2H), 4.04(q, J = 7.3 Hz, 1H), 3.74 (dq, J = 2.3, 8.1 Hz, 1H), 3.16 (dt, J = 4.1, 7.4 Hz, 1H), 2.32 (quint, J = 6.5 Hz, 1H), 2.07 (ddd, J = 2.3, 5.0, 11.9 Hz, 1H), 1.92 (dq, J = 9.6, 11.9 Hz, 1H), 1.81 (ddd, J = 4.1, 10.1, 14.2 Hz, 1H), 1.63 (m, 3H), 1.52 (m, 1H), 1.40 (m, 1H), 1.29 (m, 5H), 1.20 (d, J = 6.4 Hz, 3H), 1.04 (brs, 21H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.2, 72.9, 70.6, 65.1, 61.1, 41.9, 40.7, 38.7, 32.3, 31.8, 26.2, 23.1, 22.5, 18.0, 14.0, 12.2 ppm; HRMS (ESI, M+Na$^+$) calcd for $C_{23}H_{47}NNaO_3Si$ 436.3223, found 436.3203.

Isoxazolidine 23. To a solution of alcohol **22** (90.8 mg, 0.220 mmol) in pyridine (2.0 mL) was added acetic anhydride (1.0 mL) at rt, and the mixture was stirred for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 15:1 to 12:1 to 9:1) to give acetate (99.3 mg, 0.218 mmol, 99%). To a solution of acetate (326 mg, 0.715 mmol) in THF (7.0 mL) was added TBAF (374 mg, 1.43 mmol) at 0 °C. After stirring for 1 h, the reaction was quenched with sat. aq. NH_4Cl. The resulting mixture was extracted with EtOAc, and combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1 to 2:1 and EtOAc/MeOH; 1:0 to 8:1) to give alcohol (256 mg, 99%). To a solution of alcohol (256 mg, 0.715 mmol) in THF (7.0 mL) was added thiocarbonyldiimidazole (566 mg, 2.86 mmol), and the mixture was heated at 60 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane/EtOAc; 10:1 to 6:1 to 4:1) to give thiocarbamate (294 mg). To a solution of thiocarbamate (294 mg, 0.72 mmol) in toluene (7.0 mL) was added *n*-Bu_3SnH (2.0 mL, 7.15 mmol) and AIBN (23.5 mg, 0.143 mmol) at rt under N_2 atmosphere, and the resulting mixture was heated at 100 °C for 20 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 1:0 to 9:1 to 5:1) to give isoxazolidine **23** (164 mg, 0.579 mmol, 81% in 3 steps) and alcohol which was generated by simply elimination of thiocarbamate group (29.2 mg, 0.0976 mmol, 18% in 3 steps). Spectral data for **23**: $[\alpha]_D^{13}$ -61 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (m, 1H), 3.94 (m, 1H), 3.73 (m, 1H), 2.99 (dq, J = 6.5, 10.5 Hz, 1H), 2.04 (m, 1H), 2.00 (s, 3H), 1.88 (m, 3H), 1.80 (ddd, J = 4.6, 6.4, 13.7 Hz, 1H), 1.72 (ddd, J = 6.4, 8.7, 14.2 Hz, 1H), 1.57 (m, 1H), 1.45 (m, 2H), 1.37 (m, 2H), 1.27 (m, 5H), 1.23 (d, J = 6.0 Hz, 3H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 75.2, 69.8, 63.7, 63.6, 42.1, 41.7, 32.9, 31.9, 30.8, 30.0, 26.1, 22.5, 21.4, 20.6, 14.0 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{16}H_{29}NNaO_3$ 306.2045, found 306.2002.

Bicyclic guanidine 26. To a solution of isoxazolidine **23** (49.0 mg, 0.173 mmol) in 3N HCl/THF = 1:3 (2.0 mL) was added freshly activated Zn powder (113 mg, 0.865 mmol) at 0 °C. After stirring for 47 h at rt, the reaction was quenched and neutralized with solid of $NaHCO_3$ at 0 °C. The resulting mixture was extracted with EtOAc/MeOH = 5:1, and the combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give pyrrolidine **24**. To a solution of the crude pyrrolidine **24** in DMF (2.0 mL) was added Et_3N (70 μL, 0.5 mmol), thiopseudourea **17** (89.5 mg, 0.250 mmol) and $HgCl_2$ (67.8 mg, 0.250 mmol) at 0 °C under N_2 atmosphere. After stirring for 30 min, the reaction mixture was diluted with EtOAc, and filtered through a pad of Celite. The filtrates were washed with H_2O twice and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 6:1 to 3:1) to give guanidine **25** (79.6 mg, 0.134 mmol, 77% in 2 steps). To a solution of guanidine **25** (78.6 mg, 0.132 mmol) and triphenylphosphine (104 mg, 0.396 mmol) in toluene (1.5 mL) was slowly added DEAD (157 μL, 0.396

mmol, 40% in toluene) at 0 °C under N_2 atmosphere. After stirring for 20 min, the reaction mixture was quenched with a drop of H_2O, and the resulting mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 9:1 to 6:1) to give bicyclic guanidine **26** (70.9 mg, 0.123 mmol, 93%).

***trans*-Batzelladine K (27).** To a solution of bicyclic guanidine **26** (55.6 mg, 0.0963 mmol) in MeOH/THF = 1:1 (1.0 mL) was added NaH (38.5 mg, 0.963 mmol, 60% dispersion in paraffin liquid) at 0 °C. After stirring for 2 h at rt, the reaction mixture was quenched with a drop of H_2O at 0 °C. The resulting mixture was extracted with EtOAc, and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:0 to 4:1 to 2:1) to give bicyclic guanidine (26.9 mg, 0.0670 mmol, 70%). To a solution of bicyclic guanidine (11.3 mg, 0.0282 mmol) and Et_3N (20 μL, 0.14 mmol) in CH_2Cl_2 (1.0 mL) was added methansulfonyl chloride (11 μL, 0.14 mmol) at 0 °C under N_2 atmosphere, and the resulting mixture was stirred for 30 min. To the reaction mixture was added sat. aq. NH_4Cl, and organic layer was extracted with hexane. The aqueous layer was ajested to pH 8 with sat. aq. $NaHCO_3$, and the resulting mixture was extracted with an eluent of CH_3Cl/MeOH = 5:1. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH = 80:1 to 30:1 to 10:1) to give tricyclic guanidine (11.1 mg, 99%). To a solution of tricyclic guanidine (16.3 mg, 0.0291 mmol) in MeOH (1.0 mL) was added Pd/C (catalytic amount), and the reaction mixture was stirred under H_2 atmosphere (balloon) for 2 h. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH; 1:0 to 200:1) to give *trans*-batzelladine K (**27**) (3.6 mg, 0.0142 mmol, 49% in 2 steps).

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REFERENCES AND NOTES

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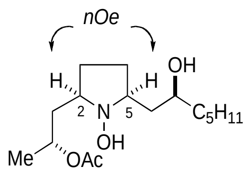
11. The *cis*-stereochemistry of **16** was confirmed by nOe experiments with the hydroxyl amine **15**.



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12. Structural revisions have been made for some batzelladines.[4d,f,g, 5a,c, 8a]

13. Spectral data for synthetic **1** and **27**. Synthetic **1** : $[\alpha]_D^{16}$ +2.7 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, MeOH) δ 3.74 (m, 2H), 3.54 (m, 1H), 3.42 (m, 1H), 2.24 (m, 2H), 2.21 (m, 2H), 1.68 (m, 2H), 1.57 (m, 1H), 1.55 (m, 1H), 1.35 (m, 6H), 1.28 (m, 2H), 1.26 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); HRMS (ESI, M+H$^+$) calcd for $C_{15}H_{28}N_3$ 250.2278, found 250.2234. Synthetic **27** : $[\alpha]_D^{18}$ -44 (*c* 0.4, MeOH); ^{1}H NMR (500 MHz, MeOH) δ 3.62 (m, 2H), 3.60 (m, 1H), 3.50 (m, 1H), 2.30 (m, 2H), 2.20 (t, *J* = 6.0 Hz, 2H), 1.61 (m, 2H), 1.37 (m, 2H), 1.34 (m, 8H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.92 (t, *J* = 6.9 Hz, 3H); HRMS (ESI, M+H$^+$) calcd for $C_{15}H_{28}N_3$ 250.2278, found 250.2250.