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Enantioselective Total Synthesis of Batzelladine F and Definition of Its Structure

Frederick Cohen† and Larry E. Overman*

Contribution from the Department of Chemistry, 516 Rowland Hall, University of California, Irvine, California 92697-2025

Received October 31, 2005; E-mail: leoverma@uci.edu

Abstract: Batzelladine F (**1**) was synthesized in enantioselective and stereoselective fashion in 15 steps (longest linear sequence) and 1.7% overall yield from two readily available enantioenriched β-hydroxy esters, methyl (*R*)-3-hydroxydecanoate and methyl (*R*)-3-hydroxybutyrate. Tethered Biginelli condensations are used to assemble both tricyclic guanidine fragments, with the second tethered Biginelli condensation (**14** + **16** → **17**) also being employed to join the guanidine fragments. Three diastereomers of batzelladine F, **2**−**4**, were prepared also. A combination of HPLC, optical rotation and CD spectroscopy was employed to distinguish stereoisomers **1**−**4**, proving that **1** is the correct structure of the hexacyclic marine alkaloid batzelladine F.

Introduction

The hexacyclic diguanidine alkaloid batzelladine F was first reported in 1997 from a marine natural products isolation program directed at identifying small molecule inhibitors of protein−protein interactions.[1] Isolated from a red Jamaican sponge, batzelladine F is one of the most structurally complex of the marine alkaloids of the batzelladine family.[2] Batzelladine F was reported to induce the dissociation of the tyrosine kinase $p56^{lck}$ from the CD4 co-receptor expressed on the surface of T cells, an event that was postulated as potentially being useful in the treatment of autoimmune diseases.[1]

In the preceding contribution, we described the evolution of a concise strategy for the chemical synthesis of complex guanidine alkaloids that contain two linked octahydro-5,6,6a-triazaacenaphthalene moieties.[3] We also disclosed the use of this chemistry to prepare four stereoisomers of the presumed structure of batzelladine F,[4,5] none of which were identical with the marine isolate.[3] After reexamining the natural product, we proposed a different constitution for batzelladine F in which a ten-atom chain tethers the two guanidine moieties and the right-hand tricyclic fragment contains an *n*-heptyl side chain. As the configurational relationship between the two octahydro-5,6,6a-triazaacenaphthalene fragments was not known, nor the relative configuration of the methyl substituent of the tether, the eight stereoisomers (four enantiomer pairs) depicted in Figure 1 all became possibilities for the structure of batzelladine F. In this article, we describe our enantioselective total synthesis of batzelladine F (**1**) and the studies that establish **1** to be the correct structure of the natural alkaloid.

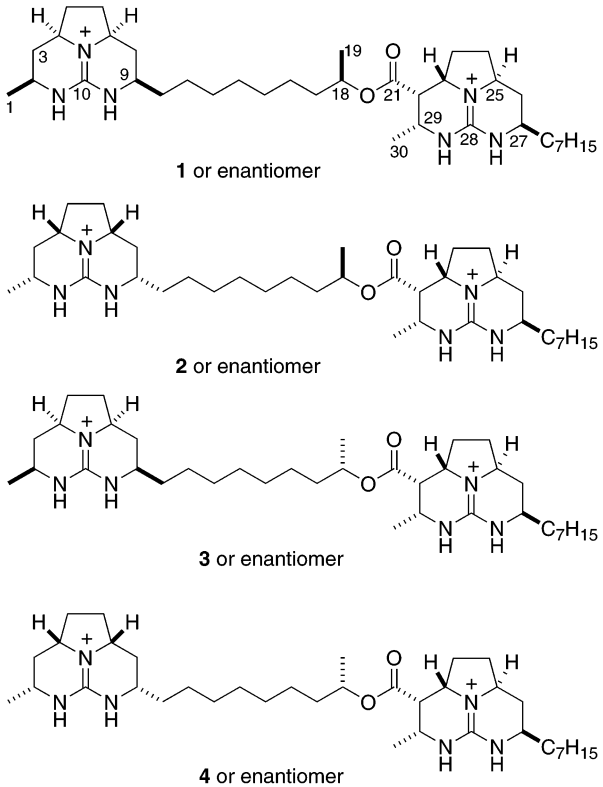


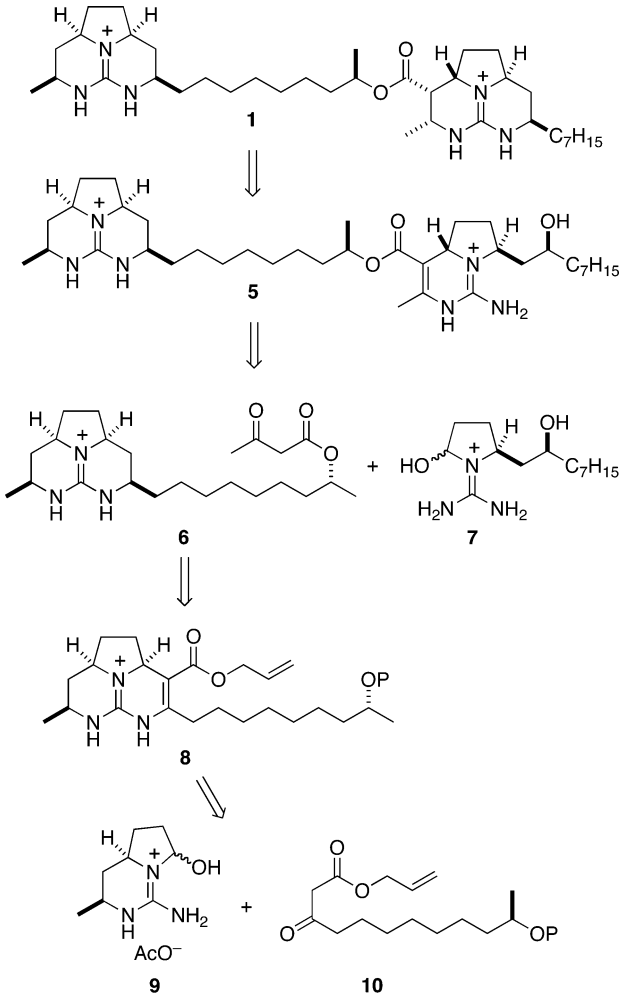
Figure 1. Eight possibilities for the revised structure of batzelladine F.

† Current Address: Department of Medicinal Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

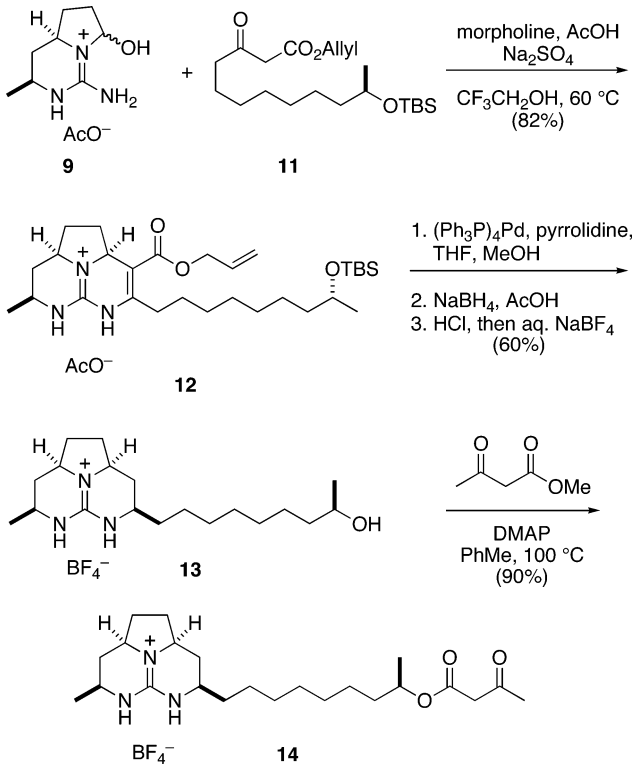
(1) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carté, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814−1819.
(2) (a) For reviews summarizing the isolation, structure and synthesis of batzelladine alkaloids, see: Berlinck, R. G. S.; Kossuga, M. H. *J. Nat. Prod.* **2005**, *22*, 516−550 and earlier reviews in this series. (b) For the recent isolation of a new batzelladine alkaloid, see: Gallimore, W. A.; Kelly, M.; Scheuer, P. J. *J. Nat. Prod.* **2005**, *68*, 1420−1423. (c) For a recent synthetic study, see: Arnold, M. A.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2005**, *127*, 6924−6925.
(3) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2594−2603.
(4) As discussed in detail in the preceding article,[3] the relative configuration originally proposed for the right-hand tricyclic guanidine fragment of batzelladine F[2] had been revised by the synthesis of model compounds.[3,5]
(5) (a) Snider, B. B.; Busuyek, M. V. *J. Nat. Prod.* **1999**, *62*, 1707−1711. (b) Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547−6554.

10.1021/ja057433s CCC: $33.50

Scheme 1



Scheme 2



Results and Discussion

Total Synthesis of Batzelladine F. Our plan for the synthesis of batzelladine F is outlined antithetically in Scheme 1 and follows the strategy developed during the studies described in the preceding article.[3] We envisaged the right-hand guanidine fragment of **1** as evolving from pentacyclic precursor **5** by ring-closure and catalytic hydrogenation.[6] This intermediate would be the product of a convergent, anti-selective, tethered Biginelli condensation[7] between β-keto ester **6** and guanidine hemiaminal **7**. The allyl ester precursor **8** of β-keto ester **6** would be the product of a syn-selective tethered Biginelli condensation[8] between β-keto ester **10** and bicyclic guanidine hemiaminal **9** whose synthesis was described in the preceding article.[3]

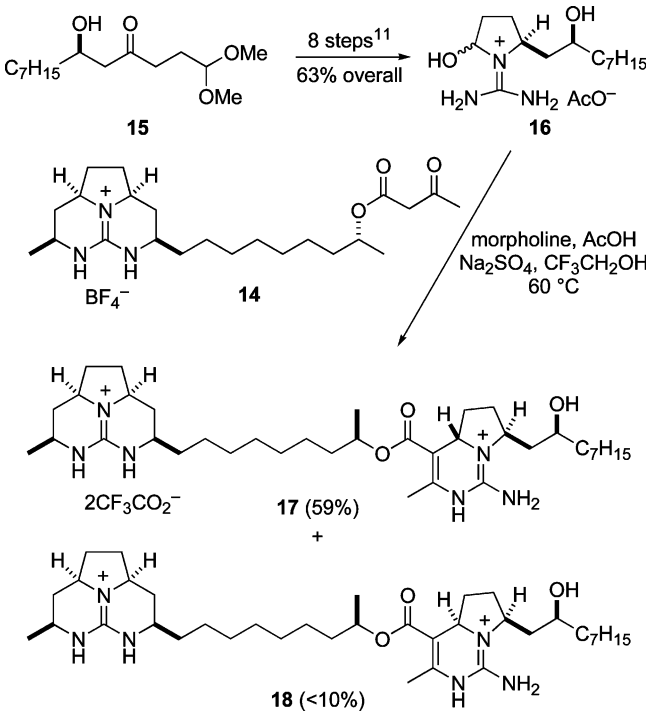
Construction of the left-hand tricyclic guanidine fragment of batzelladine F is summarized in Scheme 2. Tethered Biginelli condensation of β-keto ester **11**[9−11] with aminohexahydropyrrolopyrimidinol **9**[3] proceeded smoothly under standard conditions to provide hexahydro-5,6,6a-triazaacenaphthalene **12** in 82% yield, as a 5:1 mixture of syn:anti stereoisomers. Using a sequence of transformations developed in our earlier studies,[3] this product was deallylated with concomitant decarboxylation and reduced stereoselectively to form the octahydro-5,6,6a-triazaacenaphthalene product. The silyl-protecting group was removed from this intermediate by reaction with aqueous HCl at room temperature. After chromatography on silica gel to remove the minor anti stereoisomer, the product fractions were washed with aqueous $NaBF_4$ to provide tricyclic guanidinium tetrafluoroborate **13**. These three steps proceeded in 60% overall yield. Acylation of guanidine alcohol **13** with methyl acetoacetate[12] then provided octahydro-5,6,6a-triazaacenaphthalene β-keto ester **14** in 90% yield.

As the prelude to the central Biginelli fragment coupling, the (*S*,*S*)-1-(diaminomethylene)-2-hydroxypyrrolidinium acetate **16** was assembled in eight high-yielding steps from (*R*)-β-hydroxy ketone **15**[8] using the sequence we had developed earlier to prepare the analogous structure having a (*S*)-2-hydroxyundecyl side chain (Scheme 3).[8,11] The pivotal fragment-coupling tethered Biginelli condensation was carried out by combining guanidine β-keto ester **14** with 3 equiv. of guanidine hemiaminal **16** and 3 equiv. of morpholinium acetate in 2,2,2-trifluoroethanol, followed by heating the resultant solution at 60 °C for 48 h. The product of this reaction, pentacyclic diguanidine **17**, was isolated in 59% yield as the ditrifluoroacetate salt after HPLC separation from minor amounts (<10%) of isomer **18** and remaining guanidine hemiaminal **16**.

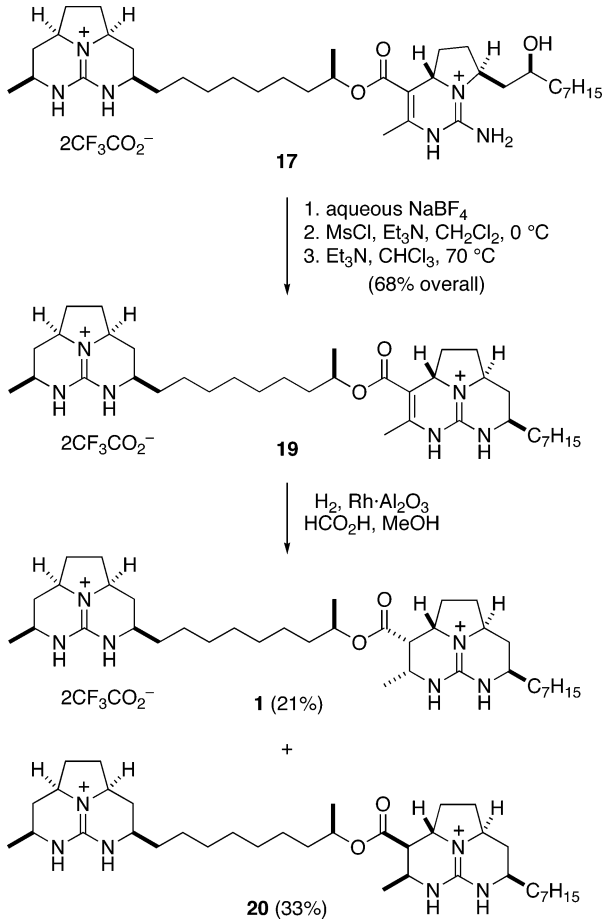
To complete the synthesis of batzelladine F, we needed to close the final ring and reduce the carbon−carbon double bond (Scheme 4). To this end, the trifluoroacetate counterions were

(6) Cohen, F.; Overman, L. E.; Sakata, S. K. *Org. Lett.* **1999**, *1*, 2169−2172.
(7) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520−1528 and references therein.
(8) Franklin, A. F.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512−1519.
(9) Prepared in 82% overall yield from (*R*)-7-*tert*-butyldimethylsiloxyoctanol[10] using a sequence identical to the one employed to synthesize the dodecanoate congener.[3,11]
(10) (a) Mori, K.; Maemoto, S. *Liebigs Ann. Chem.* **1987**, *10*, 863−869. (b) Jones, G. B.; Huber, R. S.; Chapman, B. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1797−1809.
(11) Full details are available in the Supporting Information.
(12) Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618−1619.

Scheme 3



Scheme 4



exchanged for tetrafluoroborate by washing a $CHCl_3$ solution of pentacyclic diguanidine **17** with saturated aqueous $NaBF_4$.[13] The alcohol was then converted to its mesylate derivative, which cyclized smoothly in the presence of Et_3N in hot $CHCl_3$ to deliver hexacyclic diguanidine **19** in 68% yield. Finally, reduction of **19** over $Rh{\cdot}Al_2O_3$ with H_2 at 100 psi provided batzelladine F (**1**) as its ditrfluoroacetate salt, $[\alpha]_D^{24}$ −7.7 (*c* 0.25, MeOH), in 21% yield after HPLC separation from isomer **20**. NMR spectra of synthetic **1** (^1H and ^{13}C in CD_3OD) agreed well with the corresponding data reported for natural batzelladine F.[1]

Synthesis of Three Stereoisomers of Batzelladine F and Proof that 1 is the Structure of Batzelladine F. Because of the large distance between the two tricyclic guanidine fragments and the separation between the C18 and C21 stereocenters, we anticipated that the diastereomers of **1** depicted in Figure 1 would show NMR spectra identical, or nearly identical, to those of isomer **1**. Thus to establish rigorously the stereostructure of batzelladine F, we synthesized stereoisomers **2**−**4** depicted in Figure 1. These syntheses were accomplished using chemistry identical to that described for the synthesis of **1**; full details of these syntheses are provided in the Supporting Information.

With the four synthetic isomers **1**−**4** in hand, each as its ditrifluoroacetate salt, we turned to investigate what criteria could distinguish them from each other. We began with HPLC co-injection. To our chagrin, all four isomers coeluted on the C_{18} column that had cleanly separated the four related diastereomers we had prepared during our earlier studies that corrected the misassigned connectivity of batzelladine F.[3] After screening a variety of combinations of solid and mobile phases, we found that an Altima Phenyl column with acetonitrile-water as the eluent could separate the C18 epimers, that is separate isomer **1** from **3**, and **2** from **4**. Isomer **4** did not coelute with an authentic sample of batzelladine F, thus eliminating it and its enantiomer as possibilities for the structure of the natural product. As diastereomers **3** and **4** coeluted under these conditions, isomer **3** and its enantiomer could also be eliminated. Unfortunately, isomers **1** and **2** coeluted under all conditions. Moreover, these samples showed ^1H and ^{13}C NMR spectra indistinguishable from one another and batzelladine F.

Fortunately, the ditrifluoroacetate salts of synthetic isomers **1**, $[\alpha]_D^{24}$ −7.7 (*c* 0.25, MeOH), and **2**, $[\alpha]_D^{24}$ −14.1 (*c* 0.36, MeOH), could be distinguished by polarimitry as they showed different optical rotations at four wavelengths. However, the natural isolate, counterion unspecified, is reported to show $[a]_D^{24}$ +19.4 (*c* 0.87, MeOH).[1]

We thought it likely that this discrepancy in optical rotation resulted from impurities in the natural marine isolate.[14] Therefore, we purified the small sample of authentic batzelladine F in our possession by HPLC. The CD spectrum of this purified material closely resembled that of synthetic **1** and was distinct from that of isomer **2** (Figure 2). Therefore, we conclude that **1** is the correct structure of batzelladine F.

Conclusion

An enantioselective and stereoselective total synthesis of batzelladine F (**1**) was accomplished in 15 steps (longest linear

(13) In our earlier studies, we found that this counteranion exchange was essential in order to obtain good yields of clean material in the mesylate cyclization step.[3,6] Without this counterion exchange, the product was contaminated with colored impurities that were difficult to remove.

(14) The authentic sample we acquired in 1999 showed significant impurities by ^1H NMR and HPLC analysis, some of which could have arisen during storage. However, the published ^1H NMR spectrum of batzelladine F shows significant impurities as well.[1]

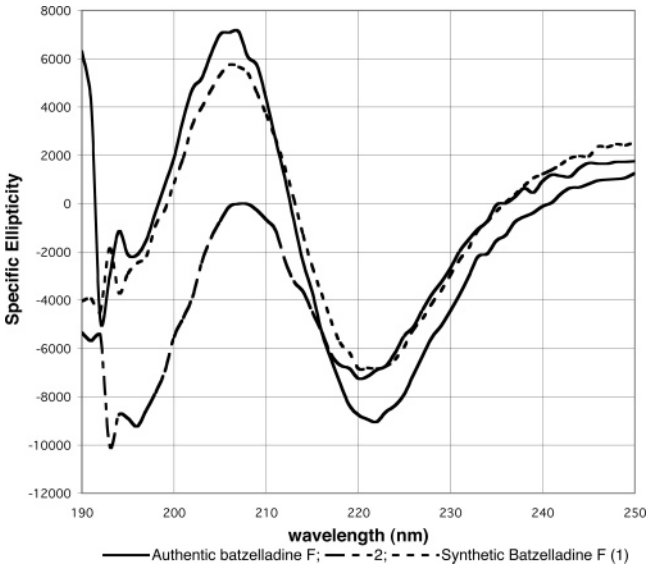


Figure 2. CD spectra of the ditrifluoroacetate salts of authentic batzelladine F (0.3 mg/mL), and synthetic products **1** (3.9 mg/mL) and **2** (3.6 mg/mL) in MeOH.

sequence) and 1.7% overall yield from two readily available enantioenriched β-hydroxy esters: methyl (*R*)-3-hydroxydecanoate[15] (the precursor of **15**)[6] and commercially available methyl (*R*)-3-hydroxybutyrate (the precursor of **9**).[3] The synthesis is punctuated by the use of stereoselective tethered Biginelli condensations to assemble both tricyclic guanidine fragments,[16] with the second tethered Biginelli condensation also allowing these complex fragments to be joined. This modular assembly allowed three diastereomers of **1** to be readily prepared also, permitting the structure **1** of batzelladine F to be rigorously defined. This study is one example in a growing list of recent investigations in which stereocontrolled total syntheses corrected misassigned structures of recently isolated natural products.[17] Furthermore, the collection of polycyclic guanidines prepared during this and cognate studies[3] has proven to be of considerable value in identifying small molecular inhibitors of pharmacologically relevant protein−protein interactions.[18]

Experimental Section[19]

(2a*S*,7*S*,8a*R*)-3-Allyloxycarbonyl-4-[6*R*-(*tert*-butyldimethylsiloxy)-nonyl]-7-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylenium acetate (12). A mixture of guanidine **9** (1.70 mmol), β-keto ester **11** (1.96 g, 5.1 mmol), morpholinium acetate (250 mg, 1.7 mmol), Na_2SO_4 (250 mg), and trifluoroethanol (3.5 mL) was heated at 60 °C for 2 d. After cooling to room temperature, the mixture was filtered, and concentrated. The residue was chromatographed (SiO_2, gradient elution with 2−5% MeOH−$CHCl_3$ with 1% AcOH) to provide 810 mg (82%) of tricyclic guanidine **12** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99−5.86 (m, 1H), 5.34−5.23 (m, 2H), 4.66−4.58 (m, 2H), 4.42 (dd, J = 9.8, 6.0 Hz, 1H), 3.77−3.72 (m, 1H), 3.70−3.63 (m, 1H), 3.57−3.50 (m, 1H), 2.85−2.60 (m, 2H), 2.55−2.48 (m, 1H), 2.32−2.24 (m, 1H), 2.12−2.05 (m, 1H), 2.00 (s, 3H), 1.66−1.50 (m, 4H), 1.45−1.20 (m, 15H), 1.09 (d, J = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 165.0, 150.5, 147.0, 132.2, 118.4, 99.0, 68.7, 64.9, 57.0, 55.6, 55.3, 54.3, 47.4, 45.4, 39.7, 35.7, 33.2, 30.7, 29.6, 29.4, 28.7, 27.0, 25.9, 25.8, 23.8, 22.9, 19.4, 18.1, −4.5, −4.7; IR (film) 2930, 2857, 1688, 1626, 1538, 1258 cm^{-1}; $[\alpha]_D^{24}$ −70.3, $[\alpha]_{546}^{24}$ −84.9, $[\alpha]_{435}^{24}$ −161, $[\alpha]_{405}^{24}$ −208 (*c* 0.95, MeOH); HRMS (ESI) *m*/*z* 518.3781 (518.3778 calcd for $C_{29}H_{52}N_3O_3Si$, M).

(2a*S*,4*R*,7*R*,8a*R*)-4-[6*R*-Hydroxynonyl]-7-methyl-1,2,2a,3,4,5,6,7,8,-8a-decahydro-5,6,8b-triazaacenaphthylenium tetrafluoroborate (13). A solution of guanidine ester **12** (200 mg, 0.35 mmol), $(PPh_3)_4Pd$ (10 mg, 0.009 mmol), pyrrolidine (140 μL, 1.7 mmol), THF (2 mL), and MeOH (2 mL) was maintained at room temperature. After 6 h, the reaction was concentrated and acetic acid (5 mL) was added. Solid $NaBH_4$ (64 mg, 1.7 mmol) then was added in portions over 20 min, and the mixture was stirred overnight. The solvent was removed by azeotroping with heptane (2 × 5 mL) under reduced pressure, 1 N HCl (5 mL) was added, and the resulting solution was maintained at room temperature for 1 d. This solution was diluted with 1 N HCl (10 mL) and extracted with $CHCl_3$ (6 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, gradient elution with 2−5−10% MeOH−$CHCl_3$); the fractions containing the product were combined, concentrated, and azeotroped with heptane. The residue was dissolved in $CHCl_3$ (20 mL), washed with saturated aqueaous $NaBF_4$ (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated to provide 86 mg (60%) of tricyclic guanidine **13** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 3.77−3.66 (m, 3H), 3.57−3.50 (m, 1H), 3.45−3.38 (m, 1H), 2.26−2.17 (m, 4H), 1.72−1.64 (m, 2H), 1.61−1.53 (m, 2H), 1.46−1.33 (m, 13H), 1.30−1.20 (m, 5H), 1.13 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 151.1, 68.5, 57.52, 57.46, 51.6, 47.3, 40.2, 36.7, 35.8, 34.7, 31.02, 30.99, 30.7, 30.51, 30.47, 26.8, 26.2, 23.5, 20.8; IR (film) 2929, 2856, 1621, 1062 cm^{-1}; $[\alpha]_D^{24}$ +8.2, $[\alpha]_{546}^{24}$ +9.0, $[\alpha]_{435}^{24}$ +11.7, $[\alpha]_{405}^{24}$ +13.0 (*c* 0.73, MeOH); HRMS (FAB) *m*/*z* 322.2849 (322.2858 calcd for $C_{19}H_{36}N_3O$).

3-Oxo-butyric acid (1*R*)-1-methyl-8-((2a*R*,4*R*,7*S*,8a*S*)-7-methyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium-4-yl)-octyl ester tetrafluoroborate (14). Following the general procedure of Taber,[12] a solution of alcohol **13** (65 mg, 0.16 mmol), methyl acetoacetate (170 μL, 1.2 mmol), DMAP (20 mg, 0.16 mmol), and toluene (2 mL) was heated at reflux for 18 h. The reaction was allowed to cool to room temperature, and the residue was chromatographed (SiO_2, gradient elution with 2−5% MeOH−$CHCl_3$ with 1% AcOH) to provide 71 mg (90%) of β-keto ester **14**, as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (br s, 1H), 6.75 (br s, 1H), 4.98−4.90 (m, 1H), 3.72−3.61 (m, 2H), 3.58−3.47, (m, 1H), 3.45 (s, 2H), 3.40−3.32 (m, 1H), 2.27−2.15 (m, 6H), 1.86−1.75 (m, 2H), 1.70−1.63 (m, 3H), 1.60−1.55 (m, 1H), 1.52−1.44 (m, 2H), 1.40−1.19 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 166.8, 149.2, 72.3, 56.0, 55.9, 50.5, 50.4, 46.0, 36.0, 35.8, 35.7, 34.4, 33.6, 33.0, 30.2, 30.1, 29.1, 25.1, 24.8, 20.1, 19.8; IR (film) 3356, 2933, 2858, 1713, 1622, 1326, 1060 cm^{-1}; $[\alpha]_D^{24}$ +1.0, $[\alpha]_{546}^{24}$ +0.7 (*c* 0.62, MeOH); HRMS (ESI) *m*/*z* 406.3069 (406.3070 calcd for $C_{23}H_{40}N_3O_3$, M).

(4a*S*,7*S*,2′*S*,1″*R*,2a‴*S*,4‴*R*,7‴*S*,8a‴*R*)-7-(2′-Hydroxynonyl)-1-imino-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidinium-4-carboxylic Acid 1″-methyl-9″-(7‴-methyl-1‴,2‴,2a‴,3‴,4‴,5‴,6‴,7‴,8‴,8a‴-decahydro-5‴,6‴,8b‴-triazaacenaphthylenium-4‴-yl)-nonyl Ester Ditrifluoroacetate (17). A mixture of β-keto ester **14** (42 mg, 0.09 mmol), guanidine **16** (0.27 mmol), morpholinium acetate (40 mg, 0.27 mmol), Na_2SO_4 (40 mg), and 2,2,2-triflouroethanol (1 mL) was maintained in a sealed tube at 60 °C for 2 d. After cooling to room temperature, the mixture was filtered through cotton, concentrated,

(15) Noyori, R.; Ohkuma, T.; Kitamura, H.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.
(16) For a recent review, see: Aron, Z. D.; Overman, L. E. *Chem. Commun.* **2004**, 253−265.
(17) For recent reviews, see: (a) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59−65. (b) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.
(18) (a) HIV-1 envelope-mediated fusion: Bewley, C. A.; Ray, S.; Cohen, F.; Collins, S. K.; Overman, L. E. *J. Nat. Prod.* **2004**, *67*, 1319−1324. (b) Interactions of HIV-1 Nef with p53, actin, and p56^{lck}: Olszewski, A.; Sato, K.; Aron, Z. D.; Cohen, F.; Harris, A.; McDougall, B. R.; Robinson, W. E.; Overman, L. E. Weiss, G. A. *Prod. Nat. Acad. Sci. U.S.A.* **2004**, *39*, 14709−14084. (c) Olszewski, A.; Weiss, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 12178−12179.
(19) General experimental details have been described: MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033−9044.

and further filtered through a 0.45 μm nylon filter with MeOH. The filtrate was concentrated, and the residue was purified by HPLC (5 μm C_{18}, 50% MeCN−H_2O with 0.1% trifluoroacetic acid) to provide 46 mg (59%) of **17** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04−4.98 (m, 1H), 4.50 (dd, J = 9.9, 5.3 Hz, 1H), 4.41−4.35 (m, 2H), 3.57−3.48 (m, 2H), 3.44−3.38 (m, 1H), 2.58−2.52 (m, 1H), 2.33−2.15 (m, 8H), 1.84 (ddd, J = 14.2, 11.5, 2.9 Hz, 1H), 1.72−1.63 (m, 4H), 1.62−1.55 (m, 5H), 1.51−1.45 (m, 3H), 1.45−1.20 (m, 31H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.8, 151.1, 143.1, 104.1, 72.6, 69.0, 58.6, 57.5, 57.4, 51.1, 47.2, 42.6, 38.6, 36.9, 36.8, 35.7, 35.1, 34.8, 33.0, 31.1, 31.0, 30.7,[20] 30.5, 30.4, 30.3, 29.0, 26.5, 26.4, 26.1, 23.7, 20.7, 20.2, 17.5, 14.4; IR (film) 3281, 3200, 2930, 2860, 1675, 1629, 1540, 1177 cm^{-1}; $[\alpha]_D^{24}$ −16.4, $[\alpha]_{546}^{24}$ −18.7, $[\alpha]_{435}^{24}$ −22.6, $[\alpha]_{405}^{24}$ −20.0 (*c* 0.90, MeOH); HRMS (ESI) *m*/*z* 641.5118 (641.5118 calcd for $C_{37}H_{65}N_6O_3$ M−H$^+$).

(2a*S*,7*R*,8a*S*,1′*R*,2a″*S*,4″*R*,7″*S*,8a″*R*)-4-Methyl-7-heptyl-1,2,-2a,5,6,7,8,8a-octahydro-5,6,8b,-triazaacenaphthylenium-3-carboxylic Acid 1′-methyl-9′-(7″-methyl-1″,2″,2a″,3″,4″,5″,6″,7″,8″,8a″-decahydro-5″,6″,8b″-triazaacenaphthylenium-4″-yl)nonyl Ester Ditriflouroacetate (19). Diguanidine **17** (25 mg, 0.03 mmol) was dissolved in $CHCl_3$ (20 mL), washed with saturated aqueous $NaBF_4$ (3 × 5 mL), and the combined aqueous layers were extracted with $CHCl_3$ (1 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated, and azeotroped with C_6H_6 (3 × 1 mL) to provide diguanidine **17** as its BF_4^- salt, which was used directly.

Methanesulfonyl chloride (52 μL, 1.0 M in CH_2Cl_2, 0.052 mmol) was added over 10 min to a stirring 0 °C solution of this guanidinium BF_4^- salt (21 mg, 0.03 mmol), Et_3N (105 μL, 1.0 M in CH_2Cl_2, 0.10 mmol) and CH_2Cl_2 (2 mL). After an additional 1 h at 0 °C, ESMS indicated complete consumption of the starting material. The solution then was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaBF_4$ (3 × 5 mL), and the combined aqueous phases were extracted with $CHCl_3$ (1 × 2 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to provide the corresponding mesylate as a yellow oil. The mesylate intermediate was dried azeotropically with C_6H_6 (3 × 1 mL), and combined with $CHCl_3$ (3 mL, filtered through basic Al_2O_3) and Et_3N (0.3 mL) in a heavy-walled sealable tube. This solution was sparged with N_2 for 15 min, sealed, shielded from light, and heated at 70 °C for 3 d. The resultant red solution was concentrated, the residue was dissolved in MeOH, this mixture was filtered through a 0.45 μm nylon filter, and concentrated. The residue was purified by HPLC (5 μm C_{18}, 50% MeCN−H_2O with 0.1% trifluoroacetic acid) to provide 14 mg (68%) of **19** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.04−4.97 (m, 1H), 4.27−4.23 (m, 1H), 3.64−3.48 (m, 2H), 3.44−3.38 (m, 1H), 2.65−2.59 (m, 1H), 2.40−2.28 (m, 2H), 2.28−2.16 (m, 7H), 1.96−1.86 (m, 1H), 1.80−1.65 (m, 5H), 1.65−1.50 (m, 5H), 1.45−1.20 (m, 32H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.8, 151.1, 150.0, 147.3, 106.6, 72.7, 57.5, 57.4, 56.0, 53.5, 51.5, 47.3, 36.9, 36.8, 36.0, 35.7, 34.7, 33.5, 33.1, 33.0, 32.5, 31.1, 31.0, 30.6, 30.42, 30.37, 30.31, 26.6, 26.3, 26.1, 23.7, 20.7, 20.3, 17.7, 14.4; IR (film) 2930, 2860, 1679, 1633, 1324, 1200, 1131 cm^{-1}; $[\alpha]_D^{24}$ −5.7, $[\alpha]_{546}^{24}$ −5.1, $[\alpha]_{435}^{24}$ +5.9, $[\alpha]_{405}^{24}$ +17.0 (*c* 0.7, MeOH); HRMS (ESI) *m*/*z* 623.5027 (623.5012 calcd for $C_{37}H_{63}N_6O_2$, M−H$^+$).

Batzelladine F (1) and Isomer 20. A mixture of diguanidine **19** (12 mg, 0.014 mmol), 5% Rh·Al_2O_3 (40 mg), HCO_2H (10 drops) and MeOH (2 mL) was maintained under 90 psi of H_2 for 48 h. Celite was added, the mixture was filtered through Celite, and the filtrate was further filtered through a 0.45 μm nylon filter, rinsing with MeOH. This filtrate was concentrated, and the residue was purified by HPLC (5 μm C_{18}, 40−50% MeCN−H_2O with 0.1% trifluoroacetic acid) to provide 3.9 mg (33%) of **20** and 2.5 mg (21%) of batzelladine F (**1**), both as colorless oils. Batzelladine F (**1**): ^{1}H and ^{13}C NMR data for synthetic batzelladine F agreed well with those of a natural specimen (see Tables S1 and S2 in Supporting Information); IR (film) 3196, 3123, 2930, 2860, 1725, 1679, 1637, 1328, 1200 cm^{-1}; $[\alpha]_D^{24}$ −7.7, $[\alpha]_{546}^{24}$ −9.5, $[\alpha]_{435}^{24}$ −16.5, $[\alpha]_{405}^{24}$ −20.1 (*c* 0.25, MeOH); HRMS (ESI) *m*/*z* 625.5182 (625.51695 calcd for $C_{37}H_{65}N_6O_2$, M−H$^+$). Batzelladine F stereoisomer **20**: ^{1}H NMR (500 MHz, CD_3OD) δ 5.00−4.94 (m, 1H), 4.05−3.99 (m, 1H), 3.80−3.68 (m, 2H), 3.65−3.55 (m, 2H) 3.55−3.41 (m, 2H), 3.41−3.38 (m, 1H), 2.88 (dd, J = 10.8, 5.7 Hz, 1H), 2.48−2.42 (m, 1H), 2.34−2.28 (m, 1H), 2.27−2.16 (m, 4H), 1.70−1.50 (m, 8H), 1.40−1.22 (m, 25H) 1.16 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.2, 151.1, 73.7, 57.5, 57.4, 53.2, 52.9, 51.6, 47.3, 36.8, 36.7, 34.8, 34.1, 33.0, 31.6, 31.5, 31.1, 31.0, 30.6, 30.5, 30.4, 30.3, 26.5, 26.2, 23.7, 20.7, 20.0, 19.5, 14.4; $[\alpha]_D^{24}$ −25.2, $[\alpha]_{546}^{24}$ −29.4, $[\alpha]_{435}^{24}$ −54.2, $[\alpha]_{405}^{24}$ −67.0 (*c* 0.2, MeOH); HRMS (ESI) *m*/*z* 625.5165 (625.5169 calcd for $C_{37}H_{65}N_6O_2$, M−H$^+$).

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Supporting Information Available: Reaction schemes for the preparation of compounds reported only in Supporting Information, experimental details and tabulated characterization data for new compounds not reported in the Experimental Section, ^{1}H and ^{13}C NMR data for natural batzelladine F and synthetic isomer **2**, HPLC co-injection of authentic batzelladine F and batzelladine F stereoisomers **2**−**4**, and copies of ^{1}H and ^{13}C NMR spectra of new compounds (76 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Three overlapping resonances.