Enantioselective Total Synthesis of Batzelladine F: Structural Revision and Stereochemical Definition

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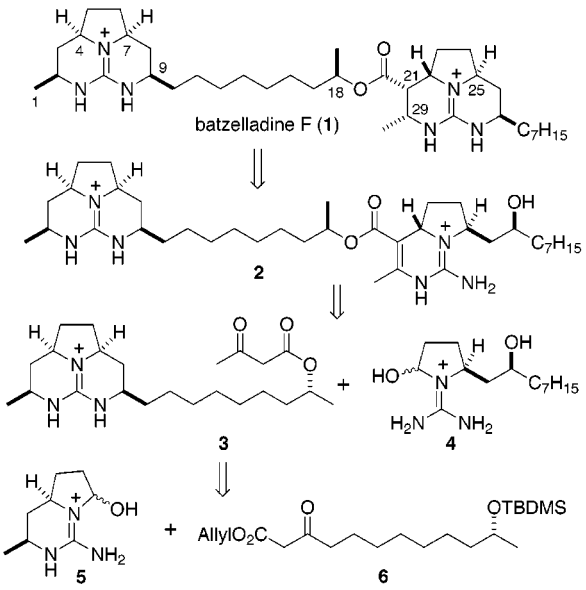
In 1997, Patil and co-workers reported the isolation of batzelladines F-I from a red Jamaican sponge incorrectly identified at the time as *Batzella* sp.[1,2] These alkaloids each contain two tricyclic guanidines and were found to induce dissociation of protein tyrosine kinase p56^{lck} from CD4. It was postulated that disruption of this interaction could be used to treat autoimmune disorders. Our interest in batzelladine F (**1**) was 2-fold. First, we were interested in preparing compounds that inhibit specific protein−protein interactions, and second, we sought to define totally the stereochemistry of batzelladine F, much of which was unclear at the outset of this work.

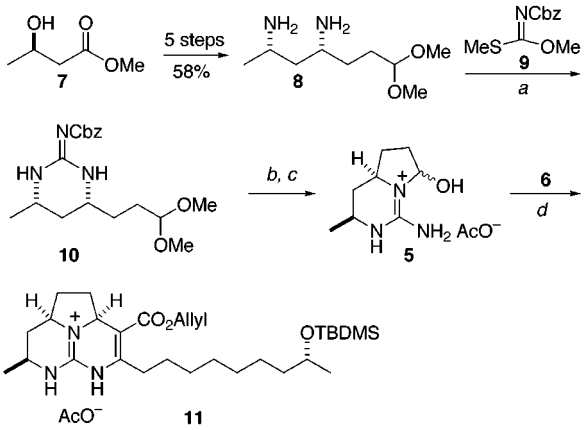
The relative configuration of the right-hand tricyclic portion of batzelladine F (C20 through C29) was assigned[1] by comparison of its ^{13}C NMR spectrum to that of batzelladine D,[3] the configuration of which had been established by synthesis.[4] The left-hand tricyclic moiety was originally proposed to have an anti relationship between the angular hydrogens at C4 and C7. This relative configuration was subsequently revised to syn based on model studies by Snider and Murphy.[5] There was no information that related the relative configurations of the two tricyclic guanidines nor specified the configuration at C18. Thus, there were eight compounds (four pairs of enantiomers) that fit the available data for the revised structure of batzelladine F. It did not become clear until we had synthesized one enantiomer of each structure that the proposed connectivity of batzelladine F was also incorrect.[6] Herein, we report our enantioselective total synthesis of the correct structure **1** of batzelladine F.

Our synthesis strategy is outlined in Scheme 1.[7] We envisaged the right-hand tricyclic guanidine as evolving from pentacyclic bisguanidine **2**. This intermediate would be the product of a highly convergent tethered Biginelli condensation[8] between β-keto ester **3** and guanidine hemi-aminal **4**; a synthesis of an analogue of **4** bearing a nonyl side chain had been described by us earlier.[4b] Triazaacenaphthalene **3** was seen as arising from a convergent,

Scheme 1



Scheme 2[a]



[a] Key: (a) CH_2Cl_2, 85%; (b) 50 psi H_2, 10% Pd•C, AcOH, MeOH, 98%; (c) AcOH, H_2O; (d) morpholine, AcOH, Na_2SO_4, CF_3CH_2OH, 60 °C, 82%.

syn selective tethered Biginelli condensation between β-keto ester **6** and guanidine hemi-aminal **5**,[9] followed by decarboxylation and reduction.

The synthesis began with hydroxybutyrate **7**,[10] which was converted to diamine **8** in 58% overall yield (Scheme 2). A similar diamine bearing a nonyl chain had been prepared by us earlier as a precursor to batzelladine B.[9] Diamine **8** was converted to protected guanidine **10** with novel guanylating reagent **9**.[11,12] The Cbz group of **10** was removed by hydrogenolysis and the acetal of the resulting product was cleaved with aqueous acetic acid to provide guanidine hemi-aminal **5**. This intermediate was condensed with β-keto ester **6**, under conditions we had optimized earlier for syn stereoselection,[9] to provide triazaacenaphthalene

(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) The identity of the sponge has been revised: Braekman, J. C.; Daloze, D.; Tavares, R.; Hajdu, E.; Vas Soest, R. W. M. *J. Nat. Prod.* **2000**, *63*, 193−196.

(3) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carté, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182−1188.

(4) (a) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980. (b) Cohen, F.; Overman, L. E.; Sakata, S. K. L. *Org. Lett.* **1999**, *1*, 2169−2172.

(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.

(6) The proposed structure of **1** had 7 carbons in the chain connecting the guanidines and 9 carbons in the right-hand side chain.[1] The four compounds having this connectivity that we synthesized were readily distinguished from **1** by HPLC and mass spectrometric (MS) comparisons. Reanalysis of MS fragmentation patterns of **1** indicated that the natural product has 9 carbons in the chain connecting the guanidines and 7 carbons in the right-hand side chain.

(7) Initially, we sought to make structures similar to **1** by formation of the ester linkage in the final step. Although we were able to synthesize the relevant fragments, we were unable to couple them and retain the desired axial orientation of the ester.

(8) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520−1528 and references therein.

(9) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512−1519.

(10) Seebach, D.; Beck, A. K.; Breitschuh, R.; Job, K. *Org. Synth.* **1993**, *71*, 39−46.

(11) The Troc-protected version of **9**, which served us well in earlier work,[9] failed here, because of the more polar nature of the intermediates.

(12) Atkins, P. R.; Glue, S. E. J.; Kay, I. T. *J. Chem Soc., Perkin Trans. 1* **1973**, 2644−2646.

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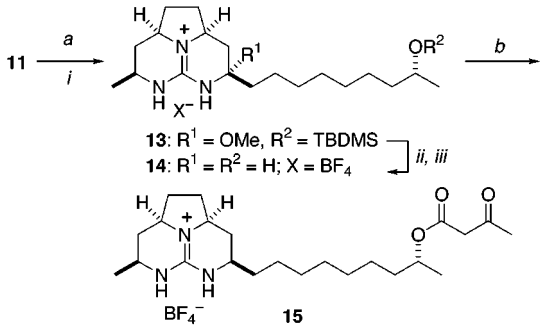
Scheme 3[a]



[a] Key: (a) (i) $(Ph_3P)_4Pd$, pyrrolidine THF, MeOH; (ii) $NaBH_4$, AcOH; (iii) 1 N HCl, 60%; (b) $MeCOCH_2CO_2Me$, DMAP, PhMe, 100 °C, 90%.

11 in 80% overall yield from **10** as a 5:1 mixture of syn and anti stereoisomers.

We next turned to remove the unneeded ester and double bond functionalities of **11** (Scheme 3). Such transformations of vinylogous carbamates were precedented, typically involving heating the free acid to >100 °C in the presence of an acid or a catalyst such as cyanide.[13] We were delighted to find that reaction of **11** with catalytic $(Ph_3P)_4Pd$ and pyrrolidine in a mixture of THF and MeOH resulted in rapid (<1 h) cleavage of the allyl ester and concomitant decarboxylation. The intermediate enamine absorbed 1 equiv of MeOH to yield hemi-aminal **13**. This intermediate was reduced with $NaBH_4$ in AcOH and the silyl group was removed by brief treatment with 1 N HCl to provide saturated tricyclic guanidine **14** in 60% yield.[14] Acylation of **14** with methyl acetoacetate and DMAP[15] delivered β-keto ester **15** in 90% yield.

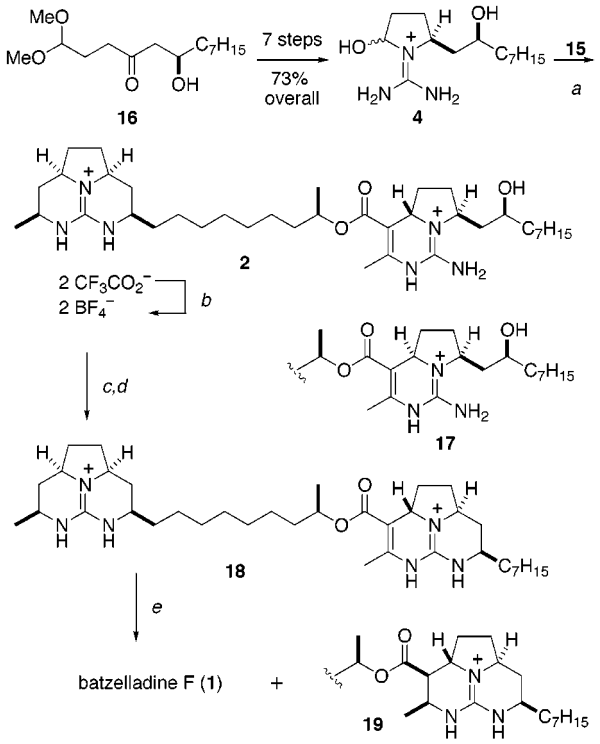
The synthesis of the right-hand portion of **1** began with hydroxy ketone **16**,[16] which was converted in seven steps and 73% overall yield to guanidine **4** (Scheme 4). The sequence of steps used for this transformation was identical with the one used to prepare the nonyl congener.[4b]

With the two fragments in hand, we turned to the pivotal Biginelli condensation. This union was accomplished by combining β-keto ester **15** with 3 equiv of guanidine **4** and morpholinium acetate in 2,2,2-trifluoroethanol and heating at 60 °C for 48 h. Pentacyclic bisguanidine **2** was obtained in 59% yield after reverse-phase HPLC separation from residual **4** and minor amounts (≤10%) of isomer **17**.

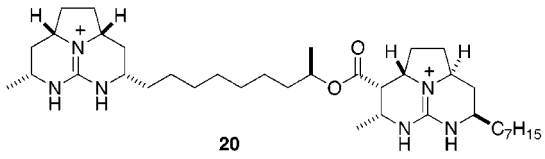
To complete the synthesis of **1**, we needed to close the final ring and reduce the vinylogous carbamate. To this end, the trifluoroacetate counterions of **2** were exchanged to BF_4^-.[17] The alcohol was then converted to its mesylate derivative, which cyclized in hot $CHCl_3$ in the presence of excess Et_3N to deliver **18** in 68% yield. Finally, hydrogenation of **18** over $Rh{\cdot}Al_2O_3$ in acidic MeOH[4b] and HPLC purification provided batzelladine F (**1**) (21%) and diastereomer **19** (33%) as their bistrifluoroacetate salts.

Synthetic batzelladine F showed ^1H and ^{13}C NMR spectra that compared favorably to those reported for the marine isolate.[1] In addition, synthetic **1** coeluted with the authentic natural product on three different HPLC columns (Luna C_{18}, Altima Phenyl, and Altima cyano), and also was distinct from its synthetic C18 epimer by HPLC co-injection. However, all of this was also true for compound **20**, which is epimeric to **1** in the left-hand tricyclic portion.[18] Fortunately, when the authentic natural product was re-purified, its CD spectrum matched that of synthetic **1**, and was distinct from that of **20**.[19]

Scheme 4[a]



[a] Key: (a) 3 equiv of **4**, morpholine, AcOH, Na_2SO_4, CF_3CH_2OH, 60 °C, 59%; (b) $CHCl_3$, aqueous $NaBF_4$; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; (d) Et_3N, $CHCl_3$, 70 °C; 68% (over 3 steps); (e) 85 psi of H_2, 5% $Rh{\cdot}Al_2O_3$, HCO_2H, MeOH, 21% + **19**, 33%.



In summary, the first total synthesis of batzelladine F was accomplished in 15 linear steps from two readily available, enantiopure β-hydroxy ketones.[4b,9] This enantioselective synthesis revises the structure of batzelladine F and defines its stereochemistry. Moreover, the scope of the tethered Biginelli condensation has been expanded to include the assembly of complex bisguanidines, a number of which have been prepared for biological investigation.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, copies of ^1H and ^{13}C NMR spectra of these compounds, tables comparing NMR spectra of synthetic and natural **1**, CD spectra of synthetic and natural **1**, and HPLC traces comparing batzelladine isomers (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA017067M

(13) Reuman, M.; Eissenstat, M. A.; Weaver, J. D., III *Tetrahedron Lett*. **1994**, *34*, 8303−8306 and references therein.

(14) Stereoselection in this reduction results from axial delivery of hydride to the intermediate iminium ion.[4a]

(15) Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J Org. Chem*. **1985**, *50*, 3618−3619.

(16) The enantiomer of **16** is reported in ref 9. The synthesis proceeds in 4 steps and 50% overall yield from commercial materials.

(17) Choice of counterion was crucial, as survey experiments in model systems led to complex mixtures of products when the counterion was HCO_2^-, AcO^-, or Cl^-.

(18) Compound **20** could be distiguished from its C18 epimer by HPLC co-injection.

(19) Synthetic **1** showed $[\alpha]_D$ −7.7 (*c* 0.25, MeOH), whereas $[\alpha]_D$ +19.4 (*c* 0.87, MeOH) is reported for the natural isolate.[1] We believe that this disparity is likely due to the low purity of the natural isolate.