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 p56lck 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 assigned1 by comparison of its 13C 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 comparison of its 1H NMR spectrum to that of batzelladine D,3 the conformation of which had been established by synthesis.4 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 of these eight compounds for syn stereoselection,9 to provide triazaacenaphthalene 3, which served us well in earlier work,9 and guanidine hemi-aminal 4; a synthesis of an analogue of 4 bearing a nonyl side chain had been described by us earlier.10,11 Triazaacenaphthalene 3 was seen as arising from a convergent, syn selective tethered Biginelli condensation between β-keto ester 3 and guanidine hemi-aminal 4; a synthesis of an analogue of 4 was described by us earlier.9,11 Herein, we report our enantioselective total synthesis of the correct structure 1 of batzelladine F.

Our synthesis strategy is outlined in Scheme 1.1,7 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 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.9,11 Triazaacenaphthalene 3 was seen as arising from a convergent, syn selective tethered Biginelli condensation 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.9,11

*Key: (a) CH2Cl2, 85%; (b) 50 psi H2, 10% Pd-C, AcOH, MeOH, 98%; (c) AcOH, H2O; (d) morpholine, AcOH, Na2SO4, CF3CH2OH, 60 °C, 82%.

syn selective tethered Biginelli condensation between β-keto ester 6 and guanidine hemi-aminal 5,10 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 guanylylating 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.
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 vinyllogous carbamates were precedent, typically involving heating the free acid to >100 °C in the presence of an acid or a catalyst such as cyanide.15 We were delighted to find that reaction of 11 with catalytic (PPh3)Pd 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 hemiaminal 13. This intermediate was reduced with NaBH4 in AcOH and the silyl group was removed by brief treatment with 1 N HCl to provide saturated tricyclic 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.16

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 biguanidine 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 vinyllogous carbamate. To this end, the trifluoroacetate counterions of 2 were exchanged to BF4-.17 The alcohol was then converted to its mesylate derivative, which cyclized in hot CHCl3 in the presence of excess Et3N to deliver 18 in 68% yield. Finally, hydrogenation of 18 over Rh2Al2O3 in acidic MeOH9 and HPLC purification provided batzelladine F (1) (21%) and diastereomer 19 (33%) as their bistrifluoroacetate salts.

Synthetic batzelladine F showed 1H and 13C NMR spectra that compared favorably to those reported for the marine isolate.1 In addition, synthetic 1 co-eluted with the authentic natural product on three different HPLC columns (Luna C18, 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

In summary, the first total synthesis of batzelladine F was accomplished in 15 linear steps from two readily available, enantiopure β-hydroxy ketones.20,21 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 biguanidines, 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 13C 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.

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(14) Stereoselection in this reduction results from axial delivery of hydride to the intermediate iminium ion.66
(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 HCO2-, AcO-, or Cl-.
(18) Compound 20 could be distinguished from its C18 epimer by HPLC co-injection.
(19) Synthetic 1 showed [α]D 7.7 (c 0.25, MeOH), whereas [α]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.