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Asymmetric Total Synthesis of Batzelladine D

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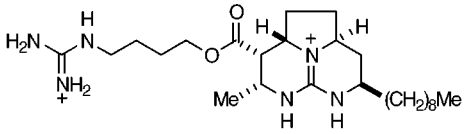
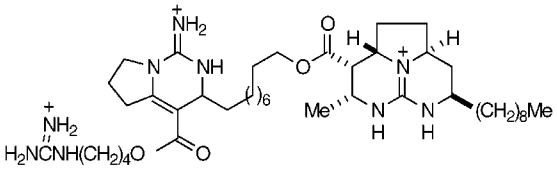
ABSTRACT



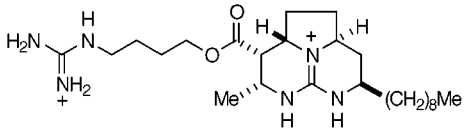
batzelladine D

The first enantioselective total synthesis of a batzelladine alkaloid is described. The central reaction in the synthesis of (–)-batzelladine D (2) is a tethered Biginelli condensation of a guanidine aldehyde and an acetoacetic ester to generate a 7-substituted-1-iminohexahydropyrrolo-[1,2-*c*]pyrimidine intermediate having the *anti* stereochemistry of the methine hydrogens flanking the pyrrolidine nitrogen.

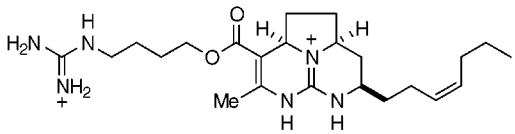
The batzelladines are a novel class of polyguanidine alkaloids isolated from the red Caribbean sponge *Batzella* sp.[1] Nine members of this group have now been identified by Smith-Kline Beecham scientists from a program searching for modulators of protein−protein interactions. The most complex batzelladine alkaloids, exemplified by batzelladine A (**1**), have two polycyclic guanidine units, while batzelladines C, D (**2**), and E (**3**) display a single tricyclic guanidine moiety. A decahydro- or octahydro-5,6,8b-triazaacenaphthalene is the common structural feature of the batzelladines, with these tricyclic units occurring with both the *syn* and *anti* stereorelationships of the angular hydrogens that flank the pyrrolidine nitrogen.[1,2] Batzelladines A (**1**) and B are micromolar inhibitors of binding of the HIV envelope protein gp-120 to the human CD4 receptor, while at similar concentrations batzelladines F−I induce dissociation of the protein kinase called p56^{lck} from CD4.[1]



batzelladine A (**1**)



batzelladine D (**2**)



batzelladine E (**3**)

Stimulated by their novel structures and the potential therapeutic significance of ligands that regulate protein association, the batzelladines have been subject to several synthetic investigations.[3] In the earliest work in this area, Rao and co-workers prepared an enantioenriched alcohol analogue of the *syn* tricyclic guanidine core of batzelladine B from an azetidine precursor,[4] and Snider and Chen, using a presumed biomimetic strategy, constructed tricyclic degradation products of several batzelladine alkaloids.[5] Significantly, this latter study showed that the angular hydrogens

(1) (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182−1188. (b) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814−1819.

(2) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980.

(3) For a brief review, see: Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, 339−365.

(4) Rao, A. V. R.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369−1370.

(5) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980.

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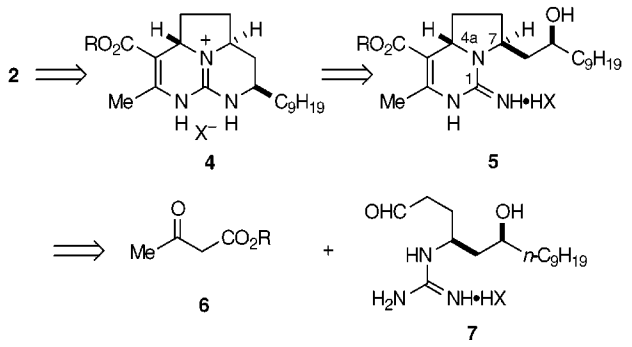
of the tricyclic guanidine portions of batzelladines A and D have the *anti* stereochemistry as depicted in **1** and **2**.[5] More recently, the Snider group reported the total synthesis of (±)-batzelladine E (**3**), which like batzelladine B has the *syn* stereochemistry.[6,7] Our laboratory disclosed earlier this year that enantiopure *syn* octahydro-5,6,8b-triazaacenaphthalenes could be synthesized in high yield using a tethered Biginelli condensation[8] as the central strategic step.[9] This chemistry was employed to prepare the tricyclic portion of batzelladine B and to establish the absolute configuration of this alkaloid.[9] We also described the first asymmetric synthesis of *anti* octahydro-5,6,8b-triazaacenaphthalenes and their decahydro analogues; however, low stereoselectivity in the tethered Biginelli condensation compromised this route to batzelladines having the *anti* stereochemistry.[9]

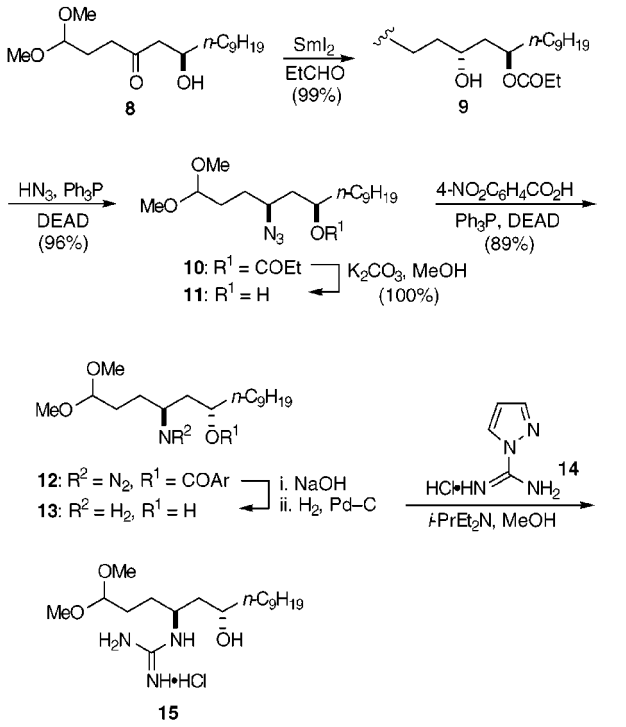
We disclose herein a modification of our tethered Biginelli strategy that allows enantiopure *anti* octahydro-5,6,8b-triazaacenaphthalenes to be prepared efficiently and the use of this chemistry to prepare (−)-batzelladine D (**2**). We recently showed that 4a,7 *anti* iminohexahydropyrrolo[1,2-*c*]pyrimidines similar to **5** were produced with high stereoselectivity in tethered Biginelli condensations of guanidine aldehydes and *β*-ketoesters.[8c] Thus, we envisaged constructing batzelladine D (**2**) from iminopyrrolopyrimidine **5**, which in turn would derive from Biginelli condensation of acetoacetate **6** and guanidine aldehyde **7** (Scheme 1).

Scheme 1



Our synthesis of (−)-batzelladine D (**2**) begins with (*R*)-*β*-hydroxy ketone **8** (96% ee),[10] which is available in four steps and 50% overall yield from 2-undecanone (Scheme 2).[11] Tischenko reduction of **8**, as described by Evans and Hoveyda, provided monoprotected *anti* 1,3-diol **9** in nearly quantitative yield.[12] Mitsunobu reaction of **9** with hydrazoic acid[13] and cleavage of the ester gave *syn* azido alcohol **11** in 95% yield from **8**. Since the third ring of the triazaacenaphthalene core of **2** would arise from an S_N2 reaction (Scheme 1), the alcohol group of **11** was inverted by Mitsunobu reaction with *p*-nitrobenzoic acid,[14] and the resulting azido ester **12** was hydrolyzed and the product was reduced with H_2 over Pd/C to furnish *anti* amino alcohol **13**. Reaction of this intermediate with 1*H*-pyrazole-1-carboxamidine hydrochloride (**14**) proceeded without incident to generate guanidine **15**.[15]

Scheme 2



The dimethyl acetal of **15** was cleaved by exposure to aqueous acetic acid, and the resulting crude product was immediately condensed at 70 °C in trifluoroethanol with *N*-benzyloxycarbonyl-4-aminobutyl acetoacetate (**16**, 2 equiv),[16,17] morpholinium acetate (2 equiv), and Na_2SO_4 (2 equiv) to provide guanidinium acetate **17** in 55% overall yield from **12** (Scheme 3). This critical step generated **17** and its 4a,7 *syn* stereoisomer in a ratio of 6.1:1.[18] The octahydro-5,6,8b-triazaacenaphthalene unit of **2** was then generated by

(6) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697−5700.

(7) (a) The biomimetic approach has also been extensively developed by the Murphy group.[3] For their recent synthesis of the left-hand unit of batzelladine F in racemic form, see: Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547−6554. (b) For an alternate approach, see: Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H. *Tetrahedron Lett.* **1996**, *37*, 905−908.

(8) (a) Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1993**, *58*, 3235−3237. (b) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657−2658. (c) McDonald, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520−1528.

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

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S.*J. Org. Chem.* **1969**, *34*, 2543−2549.

(11) Details for the synthesis of the enantiomer of **8** have been described.[9]

(12) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

(13) (a) Hassner, A.; Dehaen, W. *J. Org. Chem.* **1990**, *55*, 2243−2244. (b) Mitsunobu, O. *Synthesis* **1981**, 1−32.

(14) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

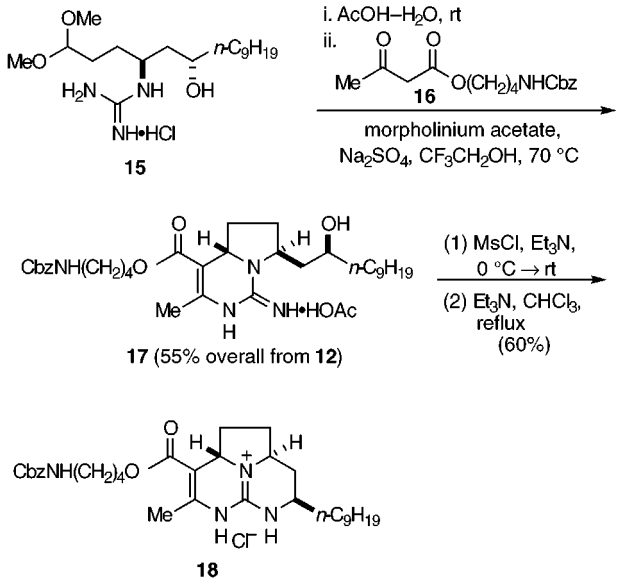
(15) (a) Bernatowicz, M. Z.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497−2502. (b) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389−3392.

(16) Prepared in 91% yield from methyl acetoacetate and *N*-benzyloxycarbonyl-4-aminobutanol.[17]

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

(18) Stereoselection in the identical condensation in ethanol was 4.6:1.

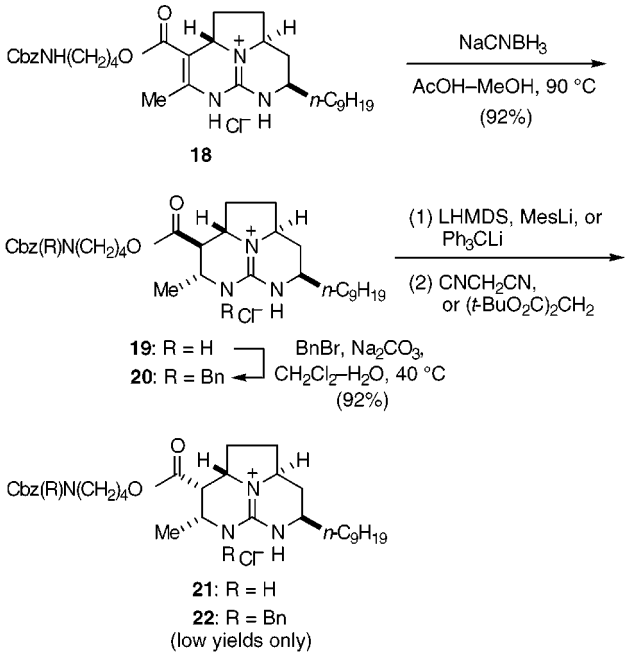
Scheme 3



converting the secondary alcohol of **17** to its mesylate derivative, which cyclized in refluxing $CHCl_3$ in the presence of excess triethylamine to deliver **18** in 60% yield.

To complete the synthesis of batzelladine D (**2**), we needed to reduce the double bond of **18** from the β face to set the C3 and C4 stereochemistry. Using a modification of conditions reported by Snider,[5] **18** cleanly gave decahydro-5,6,-8b-triazaacenaphthalene **19** upon reduction with $NaCNBH_3$ at 90 °C in methanol containing 10 equiv of acetic acid (Scheme 4). When **19** was deprotonated with 2−5 equiv of $LiCPh_3$, or 2,4,6-trimethylphenyllithium, at −78 °C in THF

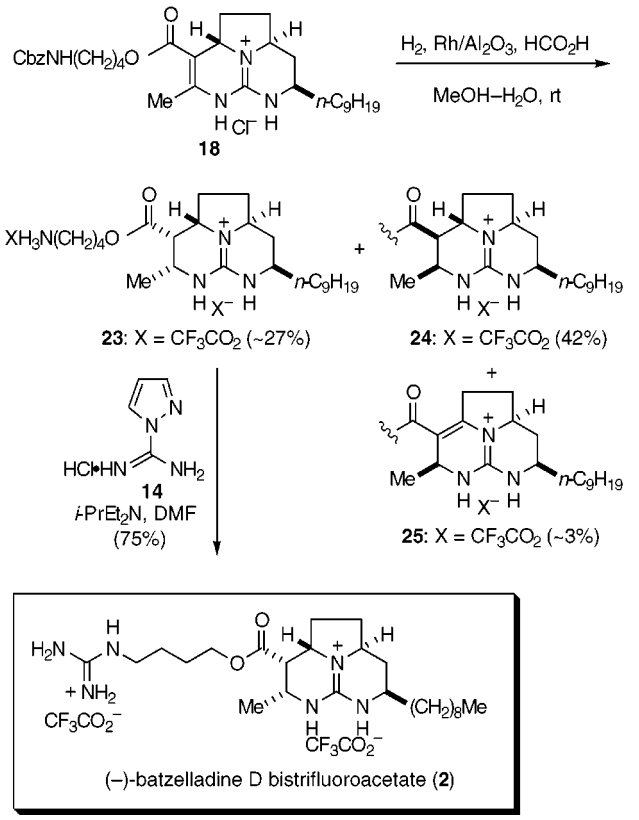
Scheme 4



and the intermediate quenched with malononitrile at 0 °C, a 1:1 mixture of **19** and **21** was produced.[19,20] However, many side products were generated and the yield of **21** was consequently low. Reasoning that one problem might be the large number of acidic hydrogens present in the starting material, **19** was treated with an excess of benzyl bromide in the presence of Na_2CO_3 to give largely one dibenzylated product which we provisionally assign as **20**. Reaction of **20** with 4 equiv of LHMDS at −78 °C in THF and quenching the resulting enolate with various proton donors again delivered **22** in low yield only.[21]

We therefore turned to catalytic hydrogenation. Similar to earlier investigations of a methyl ester analogue of **18**,[9] we were unsuccessful in finding hydrogenation conditions that delivered hydrogen from the β face to selectively give tetrahydro-5,6,8b-triazaacenaphthalene **23** (Scheme 5).[22] The

Scheme 5



yield of **23** was optimal when **18** was hydrogenated over Rh/Al_2O_3 at 50 psi in MeOH−H_2O (1:3) at room temperature. Preparative HPLC separation of the resulting product

(19) (a) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557. (b) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268. (c) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792 and references therein.

(20) Structural assignments followed unambiguously from NOE studies.[9]

(21) Enolization was achieved under these conditions since quenching with CD_3CO_2D provided a ~1:1 mixture of **20** and **22**, with the former having 70% deuterium incorporation at C2. Exposure of **20**, or a 1:1 mixture of **20** and **22**, to excess $(i\text{-Pr})_2NEt$ in toluene at 70 °C provided **20** and **22** in a time-invariant ratio of 13:1, confirming the expectation that that **20** would be favored at equilibrium.

mixture gave **23** (contaminated with 10% of the 2a,3-dehydro analogue **25**) in ~30% yield and stereoisomer **24** in 38% yield. Guanylation of this sample of **23** with 1*H*-pyrazole-1-carboxamidine hydrochloride, followed by preparative HPLC purification (C18 silica gel, $H_2O-MeCN-CF_3CO_2H$), provided batzelladine D (**2**), as its bistrifluoroacetate salt, in 75% yield. Synthetic **2**, a colorless oil that solidified at 0 °C, showed ^1H and ^{13}C NMR, IR, and mass spectra consistent with those described for the natural isolate. Specific rotations of synthetic **2** ditrifluoroacetate were $[\alpha]^{25}_D$ −4.6 and $[\alpha]^{25}_{546}$ −18.0 ($c = 0.6$, MeOH), while $[\alpha]^{25}_D$ −1.2 ($c = 0.9$, MeOH) is reported for the natural product.[1a]

In conclusion, the first enantioselective total synthesis of a natural batzelladine alkaloid has been accomplished. The central strategic step in the total synthesis of (−)-batzelladine D (**2**) is tethered Biginelli condensation of a guanidine acetal and a β-ketoester to form a 7-substituted-1-iminohexahydropyrrolo[1,2-*c*]pyrimidine having the *anti* stereochemistry of the critical methine hydrogens that flank the pyrrolidine nitrogen. This synthesis, though currently not without significant weaknesses, and the complementary enantioselective route to related *syn* tricyclic guanidines we reported earlier[9] provide the tools required to pursue the enantioselective total synthesis of any member of the batzelladine alkaloid family.

(22) A variety of reduction conditions, employing both heterogeneous and homogeneous catalysts, were surveyed. Details have been reported: Ly, S. K. Ph.D. Dissertation, University of California, Irvine, 1998.

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Supporting Information Available: Experimental procedures and characterization data for new compounds reported in Schemes 2, 3, and 5. This material is available free of charge via the Internet at http://pubs.acs.org.

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