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Synthesis and Determination of Absolute Configuration of the Bicyclic Guanidine Core of Batzelladine A

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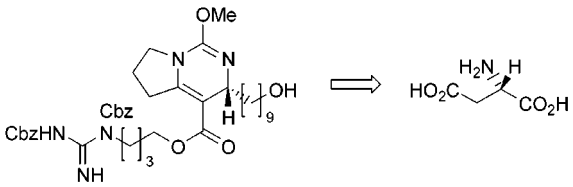
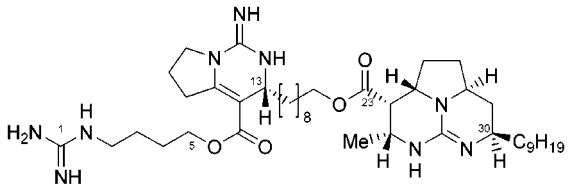
ABSTRACT



The synthesis of a selectively protected form of the bicyclic guanidine fragment of batzelladine A from L-aspartic acid is reported, thereby establishing the absolute configuration of the bicyclic guanidine ring system within the natural product.

The batzelladine alkaloids, exemplified by batzelladine A (**1**), make up a family of polyguanidine marine natural products isolated from the Caribbean sponge *Batzella* sp. Structurally, all of the members of this class of alkaloids (batzelladines A−I)[1] contain at least one fused tricyclic guanidine moiety, with certain members of this family incorporating either an additional bicyclic guanidine substructure (batzelladines A and B) or a second tricyclic guanidine fragment (batzelladines F−I). The biological activities of these complex alkaloids are of particular interest in that the batzelladines A and B were found to inhibit the binding of human CD4 and HIV gp120, while the batzelladines F−I induced dissociation of protein kinase $p56^{lck}$ from CD4. In the past several years, considerable synthetic efforts have been devoted to the synthesis of this family of alkaloids, with the bulk of the work focusing on the construction of the fused tricyclic fragment of the batzelladine alkaloids.[2] However, efforts directed toward the asymmetric synthesis of the bicyclic crambescin-like fragment[3] of batzelladines A and B, the two members of this class that exhibit gp120-CD4 binding inhibitory activity, have not been addressed.[4]



Batzelladine A (**1**)

In the original structural determination of **1**, chemical degradation studies necessitated the base hydrolysis of the ester functionalities within the natural product prior to

(1) (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, 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.; Carté, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814−1819.

(2) (a) Rao, A. V. R.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369−1370. (b) Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H. *Tetrahedron Lett.* **1996**, *37*, 905−908. (c) Black, G. P.; Murphy, P. J.; Walshe, N. D. A.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1996**, *37*, 6943−6946. (d) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980. (e) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697−5700. (f) Black. G. P.; Murphy, P. J.; Walshe, N. D. A. *Tetrahedron* **1998**, *54*, 9481−9488. (g) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512−1519. (h) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520−1528. (i) Cohen, F.; Overman, L. E.; Sakata, S. K. L. *Org. Lett.* **1999**, *1*, 2169−2172. (j) Snider, B. B.; Busuyek, M. V. *J. Nat. Prod.* **1999**, *62*, 1707−1711. (k) Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547−6554.

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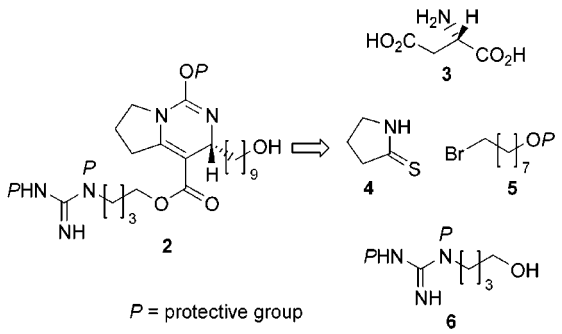
extensive spectroscopic analysis, thus separating the sole stereogenic center at C13[5] within the bicyclic guanidine fragment from the remainder of the natural product. As a result, the determination of the absolute configuration at C13 has remained in question. Moreover, the stereochemical assignment of this chiral center is further hampered by the relatively long hydrocarbon linker that separates the two guanidine ring systems; consequently, correlation of relative stereochemical relationship between the polycyclic guanidine fragments has not been possible. We report herein the establishment of the absolute configuration of the bicyclic guanidine fragment of batzelladine A via the nonracemic synthesis of a selectively protected form of the bicyclic guanidine fragment **2**, which is amenable to coupling with the tricyclic guanidine ring system of **1**.

It was envisioned that a protected form of the bicyclic guanidine ring system (**2**, Scheme 1) could be derived from

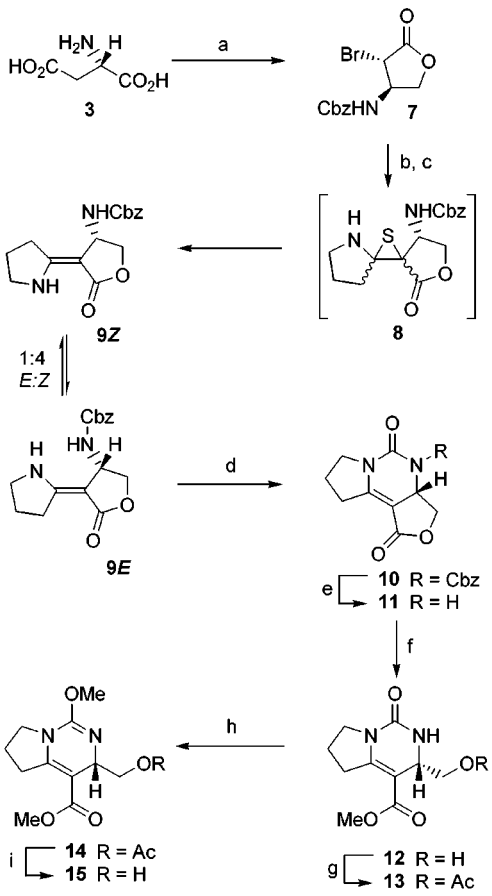
Scheme 1



the convergent assembly of aspartic acid (**3**), pyrrolidine-2-thione (**4**), and the two extended oligomethylene fragments **5** and **6**, which constitute the central hydrocarbon linker and the peripheral acyclic guanidine functionality, respectively, in the natural product. In this strategy, L-aspartic acid (**3**) is employed as the starting material to define the absolute configuration of C13 within **1**.

The synthesis begins with a derivatization sequence of L-aspartic acid (**3**) that entails (Scheme 2) (1) *N*-protection of L-aspartic acid; (2) intramolecular anhydride formation; (3) regioselective carbonyl reduction; and (4) α-bromination to provide the α,*β*-substituted *γ*-lactone **7**.[6,7] The first convergent step in the synthesis involves the condensation of

Scheme 2[a]



[a] (a) Refs 6 and 7; (b) pyrrolidine-2-thione (**4**), 90 °C, neat; (c) PPh_3, Et_3N, $CHCl_3$, reflux, 51% (from **7**), (1:4, *E*:*Z*); (d) NaH, (*p*-NO_2-C_6H_4-O)$_2$CO, THF, 71%; (e) H_2, 10% Pd/C, EtOAc, >99%; (f) NaOMe, MeOH, 85%; (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 98%; (h) MeOTf, CH_2Cl_2, 90%; (i) NaOMe, MeOH, 99%.

the α-bromolactone **7** with pyrrolidine-2-thione (**4**) via an Eschenmoser sulfide contraction.[8] In the event, a neat mixture of pyrrolidine-2-thione (**4**) and lactone **7** was heated at 90 °C to induce condensation of the coupling partners. The resulting mixture was then diluted with chloroform and heated to reflux in the presence of Et_3N and Ph_3P to induce the formation of the transient episulfide **8**, which was subsequently reduced with Ph_3P to form the vinylogous carbamate **9** as a 1:4 mixture of *E*:*Z* isomers (51% from **7**).

Although a mixture of *E*/*Z* isomers of **9** is formed, treatment of this mixture of isomers with NaH followed by addition of bis(*p*-nitrophenyl)carbonate led to the formation of the tricyclic urea **10** in 71% yield.[9] It is worth noting that

(3) (a) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Hallenga, K.; Ottinger, R.; Bruno, I.; Riccio, R. *Tetrahedron Lett.* **1990**, *31*, 6531−6534. (b) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Rogeau, D.; Amade, P. *J. Nat. Prod.* **1992**, *55*, 528−532. (c) Jares-Erijman, E. A.; Ingrum, A. A.; Sun, F.; Rinehart, K. L. *J. Nat. Prod.* **1993**, *56*, 2186−2188.

(4) The bicyclic guanidine portion of **1** is virtually identical to crambescin/crambine A, which has an 11-carbon saturated alkyl side chain. For a biomimetic synthesis of racemic crambescins/crambines, see: (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1992**, *57*, 2526−2528. (b) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828−3839.

(5) Carbon number labeling is in accordance with the original isolation paper (ref 1a).

(6) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943−4952.

(7) α-Bromination to form **7** proceeded via a modification of the reported procedure (Hanessian, S.; Vanasse, B.; Yang, H.; Alpegiani, M. *Can. J. Chem.* **1993**, *71*, 1407−1411) in order to minimize unwanted α-dibromination (see Supporting Information).

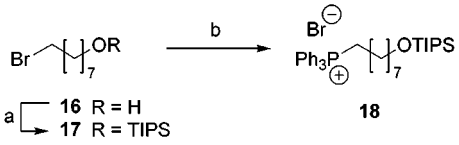
(8) (a) Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710−734. (b) Marchand, P.; Bellassoued, M.-C.; Lhommet, G. *Synth. Commun.* **1994**, *24*, 2577−2584.

(9) It is likely that treatment of **9***E*/**Z** with 2.2 equiv of NaH led to formation of the *E*-dianion, which underwent efficient cyclic urea formation.

the use of no more that 2.2 equiv of base is essential in the urea formation reaction as the use of a large excess of the strong base led to partial racemization of the stereogenic center in **10**.[10] Hydrogenolysis of the benzyl carbamate group in **10** affords the unprotected tricyclic urea **11**. Attempts at the direct *O*-methylation of the urea functionality in **11** were unsuccessful. However, *O*-methylation in the bicyclic urea could be achieved in high yield following ring opening of the lactone functionality; thus, treatment of **11** with anhydrous NaOMe in MeOH afforded the primary alcohol **12** (85%), which was subsequently acetylated (**13**, 98%). Treatment of the urea **13** with excess MeOTf in the absence of an acid scavenger[11] led to selective *O*-methylation to form the corresponding methyl isourea **14** (90%), incorporating the required guanidine precursor functionality. Selective methanolysis of the acetate ester revealed the primary alcohol functionality in **15**, which serves as a key intermediate for its coupling to the central oligomethylene linker (i.e., **5**) in the natural product.

Preparation of the hydrophobic side chain **5** was straightforward (Scheme 3), beginning with commercially available

Scheme 3[a]



[a] (a) TIPSCl, imidazole, DMAP, CH_2Cl_2, 94%; (b) PPh_3, CH_3CN, reflux, 59%.

8-bromo-1-octanol (**16**). Protection of the hydroxyl functionality as the triisopropyl silyl ether (94%) followed by heating of the bromide in the presence of Ph_3P generated the corresponding phosphonium salt **18**.

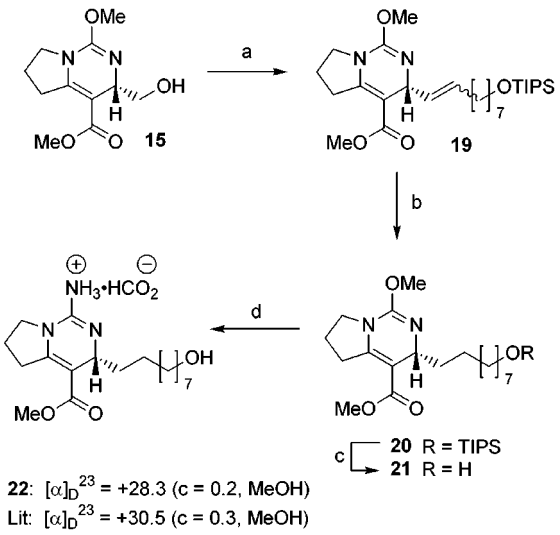
Coupling of the phosphonium salt **18** to **15** proceeded via the Ireland protocol involving a one-pot sequential Swern oxidation/Wittig condensation (Scheme 4).[12] This procedure resulted in the efficient formation of the alkene **19** (81%) as a 1:9 mixture of *E:Z* isomers, which subsequently underwent hydrogenation to afford the fully saturated oligomethylene side chain within **20** (99%). With synthetic access to nonracemic **20**, determination of the absolute configuration of the bicyclic guanidine fragment of **1** was possible by its conversion to the guanidinium formate **22**, a common intermediate also derived from the reported methanolysis of natural **1**.[1] The synthetic sequence included (1) removal of the silyl ether protective group (**21**, 98%); and (2) conversion

(10) The use of 5 equiv of NaH for urea formation led to an increase in the isolated yield of the urea **10**, although partial racemization led to the formation of a 3:1 mixture of enantiomers as evidenced by Mosher ester analysis of intermediate of **15**. The use of 2.2 equiv of NaH minimized the extent of racemization to form **10** (er, 95:05).

(11) The use of 2,4,6-tri(*tert*-butyl)pyridine as an acid scavenger led to *N*-methylation.

(12) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198−2200.

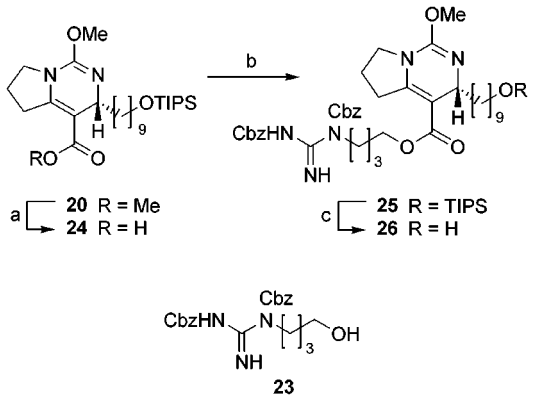
Scheme 4[a]



[a] (a) $(COCl)_2$, DMSO, Et_3N, THF, −35 to 23 °C; **18**, KHMDS, −78 to −45 °C, 81% (1:9, *E*:*Z*); (b) H_2, 10% Pd/C, EtOH, 99%; (c) TBAF, THF, 98%; (d) NH_3, NH_4OAc, MeOH, 58 °C; HCO_2H, 58%.

of the *O*-methyl isourea group in **21** to the bicyclic guanidine product **22** via condensation with excess ammonia. The guanidinium formate salt **22** derived from L-aspartic acid was found to be identical in all respects, including optical rotation, to that reported for the chemical degradation of natural **1**, thereby establishing the absolute configuration of C13 stereocenter in **1** to be *R*.

Scheme 5[a]



[a] (a) Saturated NaOH/MeOH, 65 °C, 81%; (b) **23**, BOP-Cl, Et_3N, CH_2Cl_2, 75%; (c) 49% HF, H_2O, CH_3CN, 97%.

The isourea intermediate **20** not only serves as a key intermediate in the determination of the absolute configuration at C13 in **1**, but it is also a versatile intermediate for the introduction of the acyclic guanidine fragment that comprises the C1−C5 portion of **1**. This was readily accomplished by the base hydrolysis of the methyl ester in

20 (81%) followed by esterification of the carboxylic acid with the *N*-protected 4-guanidinyl-1-butanol **23**, a compound previously prepared by Snider and co-workers.[4b] The resultant ester adduct **25** (75%) was then subjected to silyl ether removal (97%) to afford **26**, a convenient precursor to the bicyclic guanidine core of **1**. This advanced intermediate should serve as a suitably functionalized intermediate for attachment to the tricylic guanidine fragment of **1**.

In summary, the first synthesis of the bicyclic guanidine core within batzelladines A and B is reported. By employing L-aspartic acid as the starting material, the absolute configuration of the sole stereocenter in the bicyclic guanidine moiety of **1** was determined to be *R*. Moreover, the preparation of the advanced intermediate **26** should allow for synthetic access not only to members of the batzelladine natural products but also to the related family of crambescin alkaloids.

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Supporting Information Available: Experimental details and spectral/analytical data for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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