Polycyclic Guanidines

DOI: 10.1002/ange.200700840

Enantioselective Total Synthesis of the Polycyclic Guanidine-Containing Marine Alkaloid (−)-Batzelladine D**

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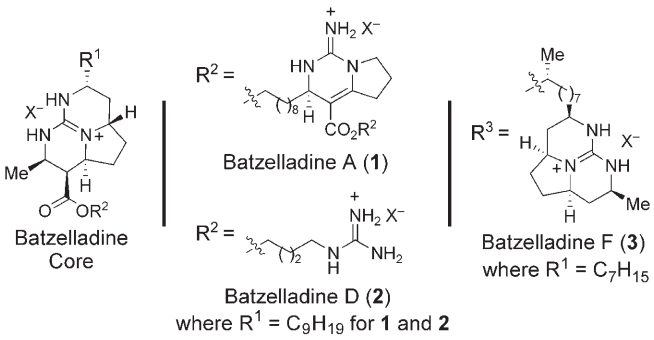
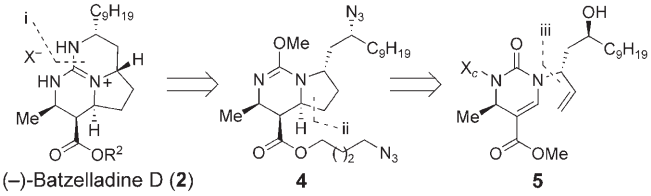
The batzelladines are members of a family of biologically important polycyclic guanidine-containing marine alkaloids that represent architecturally challenging targets for total synthesis (Scheme 1).[1,2] The ability to construct the batzelladine core in a stereoselective manner has stimulated the development of several new methodologies,[3,4] which have been successfully implemented in stunning total syntheses of members of this family.[5] Interestingly, although the tricyclic guanidine core is highly conserved in a number of these agents, modifications within the ester side chain elicit different biological activity. For example, while batzelladine A (**1**) competitively inhibits the binding of the HIV envelope protein gp-120 to the human CD4 receptor, and batzelladine F (**3**) inhibits the induction of protein tyrosine kinase p56lck dissociation from CD4, batzelladine D (**2**) has no known biological activity (Scheme 1).[1] Hence, the ability to pursue detailed structure–activity studies provides an opportunity to garner a deeper understanding of this intriguing relationship.



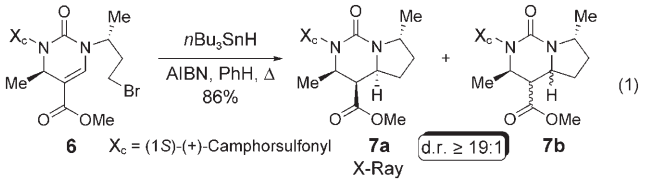
Scheme 1. Structurally related batzelladine alkaloids.

Herein, we now describe the most concise approach to the stereoselective total synthesis of the marine alkaloid (−)-batzelladine D (**2**) that was isolated by Patil, Faulkner, et al. from the Caribbean sponge *Batzella* sp.[1–5] The strategy capitalizes on the ability to utilize azides as latent amines, which circumvents the necessity for cumbersome protecting groups.[6] Hence, the reductive cyclization (i) of diazide **4** was expected to furnish **2** after installation of the acyclic guanidine (Scheme 2). We further envisioned that the primary alkyl halide required for the key free-radical cyclization (ii), would be derived from the terminal alkene **5**, which in turn would be prepared by a stereospecific rhodium-catalyzed allylic amination (iii).



Scheme 2. Retrosynthetic analysis for batzelladine D.

In a program directed towards the stereoselective construction of cyclic amines, we have developed a series of free-radical cyclization reactions using cyclic acceptors.[3f,4] A critical limitation with this methodology with respect to the batzelladines was the necessity to ring-open the heterocyclic acceptor to furnish the desired stereochemistry. To circumvent this problem, we anticipated that a substituted 3,4-dihydropyrimidin-2(1*H*)-one would function in a similar manner with regard to the cyclization, but the adjacent methyl group would direct the reduction of the insipient free radical to furnish the required *syn* diastereisomer.[3f] Preliminary work examined the validity of the free-radical cyclization strategy utilizing **6** [Eq. (1)]. Treatment of the alkyl bromide **6**



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[**] We sincerely thank the National Institutes of Health (GM58877) for generous financial support. We also thank the Royal Society for a Wolfson Research Merit Award (P.A.E.), and the American Chemical Society Division of Organic Chemistry for a Graduate Fellowship (J.E.R.) sponsored by Eli Lilly. We would also like to thank Professor Larry E. Overman for helpful discussions and copies of the spectra for **2**.

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with tributyltin hydride and azobisisobutyronitrile (AIBN) in refluxing benzene, furnished a mixture of the pyrrolo[1,2-*f*]pyrimidines **7a** and **7b** in 86% yield, with ≥19:1 d.r. (by ^{1}H NMR) favoring **7a**. The relative stereochemistry was determined unequivocally by X-ray crystallographic analysis to demonstrate the feasibility of this approach for the total synthesis (Figure 1).

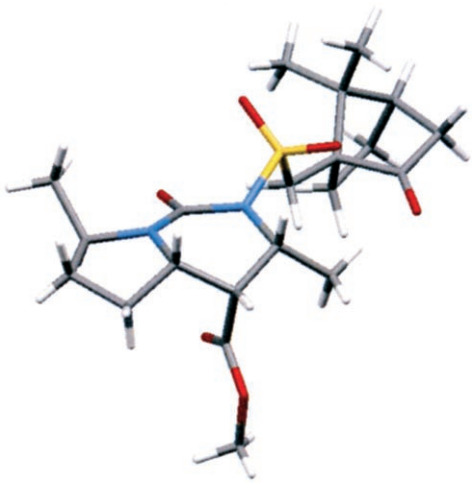
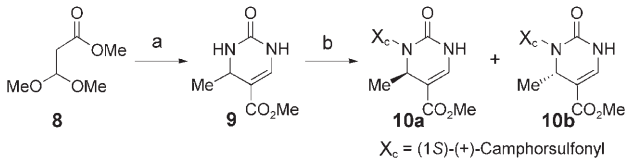


Figure 1. X-ray crystal structure of **7a**.

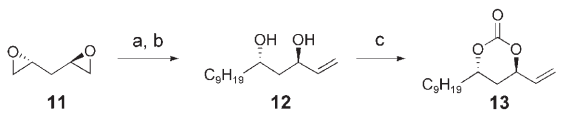
The total synthesis was initiated through the construction of the requisite fragments for the key rhodium-catalyzed allylic amination reaction. The enantiomerically enriched 3,4-dihydropyrimidin-2(1*H*)-one **10a** was prepared in two steps from commercially available methyl 3,3-dimethoxypropionate (**8**), as outlined in Scheme 3. Acid-catalyzed Biginelli



Scheme 3. Synthesis and resolution of the dihydropyrimidin-2(3*H*)-one pronucleophile **10a**: a) MeCHO (excess), H_2NCONH_2, cat. HCl, Δ, 84%; b) LiHMDS, THF, 0°C, (1*S*)-(+)-10-camphorsulfonyl chloride, 70%. HMDS = hexamethyldisilazanide.

condensation of **8** with urea and acetaldehyde, furnished the racemic dihydropyrimidin-2(3*H*)-one **9** in 84% yield.[7] Regioselective sulfonylation of the dianion of **9** with (1*S*)-(+)-camphorsulfonyl chloride furnished a mixture of the 3,4-dihydropyrimidin-2(1*H*)-ones **10a** and **10b** in 70% overall yield.[8] The diastereoisomers were then resolved by column chromatography, and the absolute configuration of **10a** was verified by X-ray crystallography on **7a** (Figure 1).

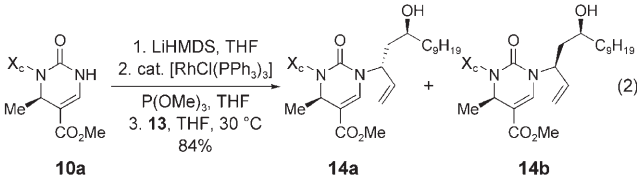
The synthesis of allylic fragment **13** commenced with the selective ring opening of the bisepoxide **11**, which is readily available in three steps from commercially available 1,3-



Scheme 4. Synthesis of the cyclic carbonate **13**: a) $C_8H_{17}MgCl$, CuCN, $BF_3{\cdot}OEt_2$, THF, −78°C; b) Me_3SOTf, *n*BuLi, THF, −10°C to RT, 68% over 2 steps; c) 1,1′-carbonyldiimidazole, pyridine, CH_2Cl_2, RT to Δ, 90%. Tf = trifluoromethanesulfonyl.

pentadione by using the Rychnovsky protocol (Scheme 4).[9] Treatment of **11** with the cuprate derived from octylmagnesium chloride and a catalytic amount of copper cyanide afforded the secondary alcohol, which upon exposure to the ylide prepared from trimethylsulfonium triflate, afforded the *anti*-1,3-diol **12** in 68% overall yield.[10] The diol **12** was then converted into the cyclic carbonate **13** in 90% yield using 1,1′-carbonyldiimidazole.

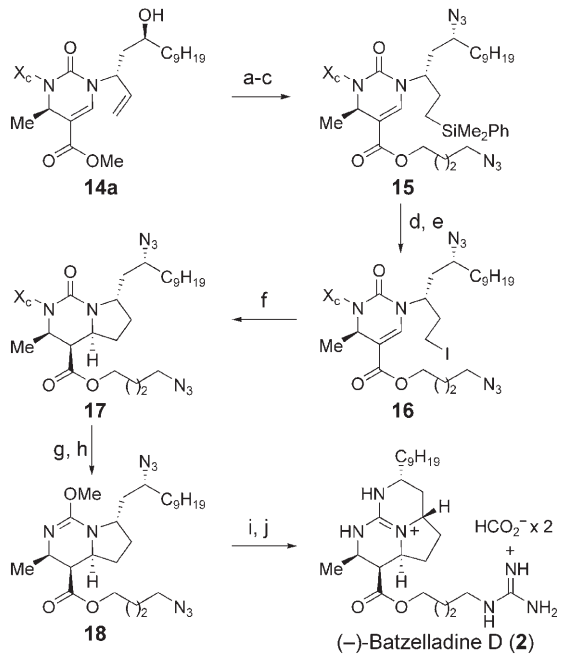
The preparation of the individual fragments provided an opportunity to examine the rhodium-catalyzed allylic amination of the cyclic carbonate **13** with the novel pronucleophile 3,4-dihydropyrimidin-2(1*H*)-one **10a** [Eq. (2)]. Treatment of



the lithium anion of **10a** with **13** in the presence of trimethyl phosphite modified Wilkinson's catalyst ([$RhCl(PPh_3)_3$]), furnished a mixture of **14a** and **14b** in 84% yield, with ≥30:1 d.r. favouring **14a** (branched/linear ≥50:1 by HPLC).[11,12]

Scheme 5 outlines the completion of the (−)-batzelladine D (**2**) synthesis. Hydrosilylation of **14a** with phenyldimethylsilane in the presence of a catalytic amount of Adams catalyst (PtO_2) afforded the requisite phenyltrialkylsilane in 91% yield, with ≥19:1 regioselectivity.[13] Interestingly, the attempted hydroboration or hydrometalation of the terminal alkene in **14a** proved more challenging than anticipated, as a result of poor regiocontrol and reactivity, respectively. Transesterification of the methyl ester using Otera's catalyst in refluxing toluene, followed by Mitsunobu inversion of the residual secondary alcohol with hydrazoic acid, furnished the diazide **15** in 82% overall yield from **14a**.[14] Tamao–Fleming oxidation of **15** afforded the primary alcohol, which was converted into alkyl iodide **16** for the free-radical cyclization.[15] Initial attempts to promote the cyclization under standard conditions [see Eq. (1)] resulted in competitive reduction of the azides. Gratifyingly, treatment of **16** with tributyltin hydride and triethylborane in the presence of air at room temperature furnished the pyrrolo-[1,2-*f*]pyrimidine **17** in 80% yield, with ≥19:1 d.r. (by ^{1}H NMR).

The synthesis was completed by using the following four-step sequence. Treatment of **17** with triflic acid, to remove the



Scheme 5. Completion of the total synthesis of (−)-batzelladine D (**2**): a) cat. PtO_2, $PhMe_2SiH$, 0°C to RT, 91%; b) $(ClBu_2Sn)_2O$, $N_3(CH_2)_4OH$, PhMe, Δ, 95%; c) PPh_3, DIAD, HN_3, PhH, RT, 95%; d) $Hg(OAc)_2$, AcOH, 30% H_2O_2, 32% AcOOH, RT, 66%; e) I_2, PPh_3, imidazole, CH_2Cl_2, RT, 86%; f) Bu_3SnH, Et_3B, PhH, O_2, RT, 80%; g) TfOH, CH_2Cl_2, RT, 85%; h) MeOTf, CH_2Cl_2, RT, 95%; i) 10% Pd/C, H_2, MeOH, RT, 83%; j) 1*H*-pyrazole-1-carboxamidine hydrochloride, iPr_2NEt, DMF, RT, 80%. DIAD = diisopropylazodicarboxylate.

camphorsulfonyl group, followed by exposure to methyl triflate, afforded the methyl imidate **18** in 81% overall yield. Hydrogenation of the diazide **18** to promote reductive cyclization,[6] followed by installation of the acyclic guanidine moiety, completed the total synthesis of (−)-batzelladine D (**2**).[5a] The spectroscopic data and optical rotation of the synthetic material was consistent in all respects to the values reported for the natural substance.[16]

In conclusion, we have accomplished the enantioselective total synthesis of the polycyclic guanidine-containing marine alkaloid (−)-batzelladine D (**2**) by using a convergent 14-step sequence from the C_2-symmetrical bisepoxide **11** in 10% overall yield. The combination of the stereospecific rhodium-catalyzed allylic amination and diastereoselective free-radical cyclization reactions provides a novel synthetic strategy. Furthermore, the ability to accomplish the selective homolytic cleavage of an alkyl iodide in the presence of an azide circumvents the necessity for nitrogen protecting groups. Finally, we anticipate that this strategy, which is the most expeditious developed to date, will be readily adapted to facilitate the total synthesis of related batzelladines and synthetic analogues for structure–activity relationship studies.

Received: February 24, 2007
Revised: June 20, 2007
Published online: August 31, 2007

Keywords: alkaloids · asymmetric synthesis · guanidines · natural products · total synthesis

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[16] There is considerable variability in the magnitude of the specific rotation of this molecule, which can presumably be attributed to purity.

