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Studies directed toward the synthesis of the guanidine alkaloid, spiroleucettadine: some observations at the level of structure

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Abstract—Studies toward the synthesis of the novel guanidine alkaloid spiroleucettadine are described.

Marine natural products, particularly those isolated from sponges, often exhibit interesting and diverse biological profiles in the context of novel structural frameworks. Crews and co-workers recently isolated a number of structurally related guanidinium natural products from a calcareous *Leucetta* sponge (Fig. 1).[1] Among these, we were particularly drawn to the unusual structure of spiroleucettadine (**1**), which was assigned a rare 5,5-*trans* fused bicyclic core moiety in the context of a 2-aminoimidazole oxalane. Furthermore, compound **1** is reported to exhibit in vitro antibacterial activity against *Enterococcus durans*, with a minimum inhibitory concentration (MIC) of <6.25 μg/mL.[1b] In keeping with our ongoing research program devoted to the reaching of biologically and structurally novel natural products, we sought to accomplish the total synthesis of spiroleucettadine (**1**).

In designing a synthesis of **1**, we were particularly mindful of the potential challenges associated with the diastereoselective construction of the *trans*-5,5-bicyclic core structure. In this regard, we postulated that a cationic intermediate of the type **6** might be induced to selectively undergo hydration at the desired α-face in light of the steric constraints imposed on the β-face by the benzylic moiety (Scheme 1). In turn, we envisioned gaining access to the cationic intermediate (cf. **6**) through hypervalent iodide oxidation[2] of a phenol (**5**), with subsequent intramolecular amide attack of the acyl guanidine to form the spirocycle.

The synthesis of the key phenol intermediate (**11**) commenced with Knoevenagel condensation of creatinine (**7**) with 4-methoxybenzaldehyde (Scheme 2). Thus, under optimized solvent- and base-free thermolysis conditions,

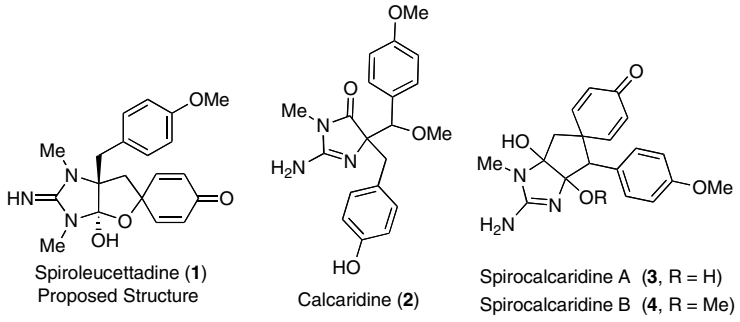

Figure 1. Guanidine alkaloids isolated from *Leucetta* sponge.

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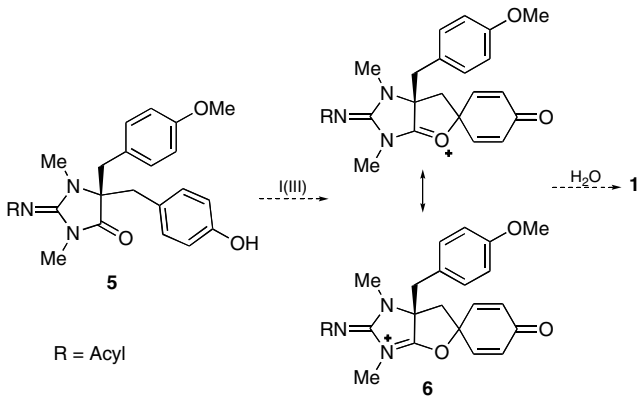
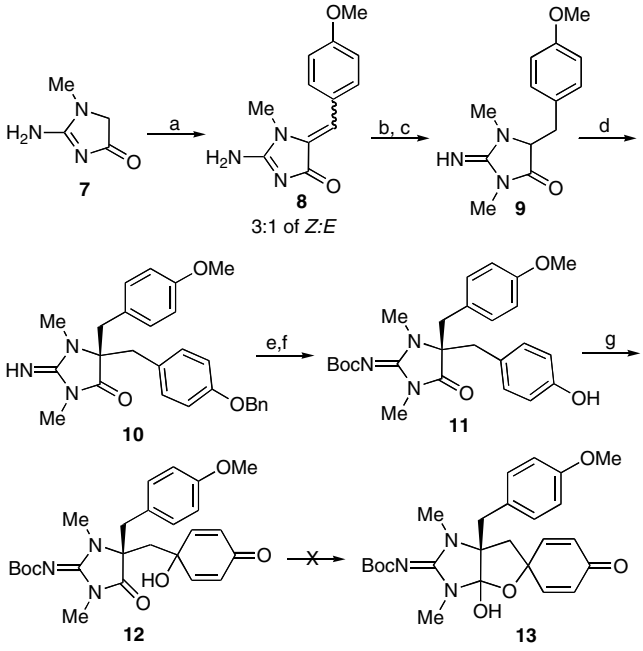


Scheme 1.



Scheme 2. Reagents and conditions: (a) 4-methoxybenzaldehyde (3 equiv), 170 °C, 20 min (89%); (b) MeI, DMF, rt, 20 h (98%); (c) H_2, Pd (10% on carbon), MeOH, 3 h, quant.; (d) LiHMDS, 4-$BnOC_6H_4CH_2Br$, THF, 0 °C, 1 h (91%); (e) *n*-BuLi, Boc_2O, THF, 0 °C, 30 min (91%); (f) H_2, Pd (10% on carbon), MeOH, 3 h, (99%); (g) PIFA, CH_3CN/H_2O (2:1), 0 °C, 5 min, 56%. DMF = dimethyl formamide, HMDS = hexamethyldisilazane, PIFA = [bis(trifluoroacetoxy)iodo]benzene.

intermediate **8** was formed as a 3:1 mixture of *Z* and *E* olefin isomers.[3] N-Methylation[4] followed by hydrogenation provided the acyl dimethyl guanidine **9** in excellent yield. We were pleased to find that LiHMDS-mediated alkylation of **9** proceeded smoothly to afford the dibenzyl intermediate **10** without any observed N-alkylated side product. At this stage, *N*-Boc protection, followed by removal of the benzyl group afforded phenol **11**.

With this key intermediate in hand, we were now prepared to explore the viability of our projected oxidative cyclization/hydration sequence. Unfortunately, however, all attempts to transform intermediate **11** to the requisite bicyclic system **13** were unsuccessful. Treatment of **11** with PIFA led to the formation of intermediate **12**, which corresponds to the ring-opened isomer of **13**.[5] In our hands, there was no indication of cyclization of **12** to **13**.

Given the resistance of **12** to undergo the spirocyclization reaction expected on the basis of the structural formulation of spiroleucettadine,[1] we next considered a modified approach which would involve the intermediacy of a compound of the type **14**. We hoped to determine whether this intermediate, containing the preconstructed spirocyclic modality, would be susceptible to intramolecular guanidine attack to afford the requisite bicyclic adduct. We were not unaware that the guanidine would be unlikely to approach the lactone from the β-face to form the desired trans-fused bicyclic adduct. Nonetheless, for the moment, we concerned ourselves primarily with issues of chemical connectivity (Fig. 2).

The synthesis of spirolactone **20** commenced with the preparation of the diaryl amino ester **17** from imine **16** by two successive alkylations under phase transfer catalysis conditions.[6] The latter was readily converted to the Boc-protected amino acid **18** as shown. We were pleased to find that benzyl deprotection followed by iodonium oxidation afforded the spirocyclic intermediate **19**. N-Methylation followed by removal of the Boc-protecting group provided the key intermediate **20**, as shown. After a number of unsuccessful attempts at guanylation, we identified conditions in which $AgNO_3$[7] was employed to facilitate the coupling of **20** with Boc-methylisothiourea (**21**). Interestingly, although guanidine cyclization did occur, none of the anticipated amino hemiketal compound (cf. **15**) was detected. Instead, compound **12**, in which the spirocycle had undergone acyl transfer, was observed as the sole reaction product.

We postulated that perhaps the rather weak nucleophilic character of the lactam functionality might be responsible for the failure of intermediate **11** to undergo the requisite spirocyclization. Accordingly, we sought to evaluate spirocyclization with a potentially more nucleophilic hemiaminal. Thus, intermediate **23** was prepared through reduction of acyl guanidine **22**, followed by removal of the benzyl ether. We were encouraged to find that upon exposure to PIFA oxidation conditions, **23** readily underwent spirocyclization to afford the 5,5-bicyclic compound **24** in 75% yield.[8] Unfortunately, however, extensive efforts to oxidize **24** to the amino hemiketal **13** were unsuccessful. This finding suggested that at least the

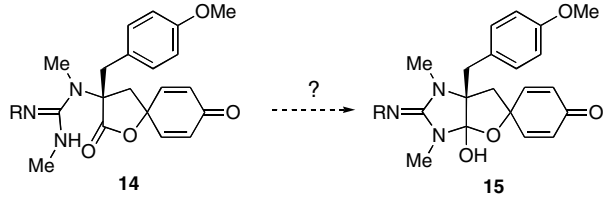
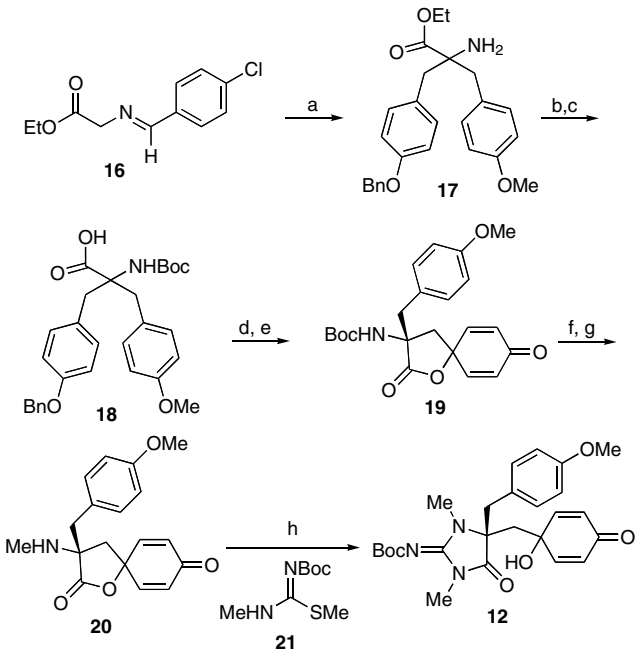
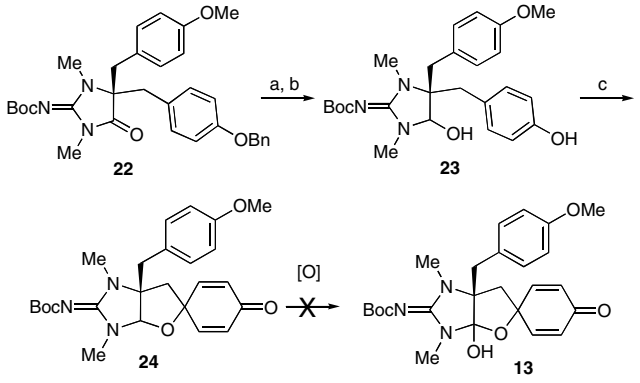


Figure 2. Alternative approaches toward spiroleucettadine.



Scheme 3. Reagents and conditions: (a) 4-$BnOC_6H_4CH_2Br$, Bu_4NBr, $CsOH{\cdot}H_2O$, toluene, −5 °C, 45 min; then 4-$MeOC_6H_4CH_2Br$, rt, 1 h; then 0.5 M citric acid, THF, 1.5 h, (85%); (b) KOH, EtOH, reflux, 40 h, (91%); (c) $Me_4NOH{\cdot}5H_2O$, Boc_2O, CH_3CN, (80%); (d) H_2, Pd (10% on carbon), MeOH, 3 h; (e) PIFA, CH_3CN, (19% for two steps); (f) NaH, MeI, DMF, 0 °C, 2.5 h; (g) TFA, CH_2Cl_2, rt, 1 h (68% for two steps); (h) **21**, Et_3N, $AgNO_3$, 88% brsm, CH_3CN. TFA = trifluoroacetic acid.



Scheme 4. Reagents and conditions: (a) $LiEt_3BH$, THF, 0 °C, 30 min, quant.; (b) H_2, Pd (10% on carbon), MeOH, 3 h, quant.; (c) PIFA, CH_3CN (75%).

cis fused version of the ring system proposed by Crews was not prohibitively strained (Scheme 4).

In conclusion, we have investigated three strategies toward spiroleucettadine. It is of note that two of these approaches led to the formation of the stable tertiary alcohol **12**, which is actually the ring opened isomeric form of the reported spiroleucettadine structure. In fact, in the route shown in Scheme 3, the formation of **12** virtually requires the intermediacy of a structure of the general type **15**. Indeed, even in the case of Scheme 2, a structure of the type **15** is a likely, though not obligatory intermediate. The fact that we observe only the isomeric compound **12** would appear to invite caution as to the stability of the (trans) bicyclic core moiety reported for spiroleucettadine (**1**). We note that our data do not rule out the validity of the structural assignment. Perhaps we have failed to find a kinetically accessible pathway to the trans isomer, which would be stable if it could be formed. The spiroleucettadine problem continues to be of keen interest to our group.

Acknowledgements

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Supplementary data

Experimental procedures and characterization data are provided for all new compounds (PDF). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.002.

References and notes

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3. Because both *Z* and *E* olefin isomers are transformed into the same product (**9**) at the olefin hydrogenation step, the two isomers were carried through the next two steps without separation. For the assignment of the *Z* and *E* stereochemistry, see: Villemin, D.; Martin, B. *Synth. Commun.* **1995**, *25*, 3135.
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5. We also note that when the non-Boc-protected congener of **11** was subjected to the oxidation conditions, the analogous quinol intermediate was observed, in 21% yield.
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8. On the basis of NMR analysis, **24** exists as a 1.8:1 isomeric mixture of products, which are inseparable by silica gel column chromatography.