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First total synthesis of aerucyclamide B

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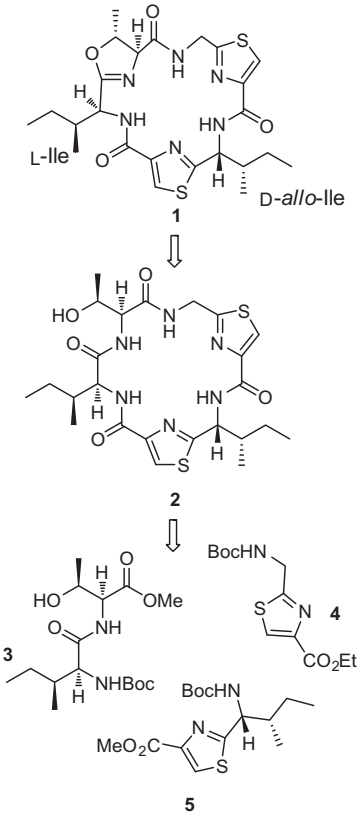
ABSTRACT

The first total synthesis of the antimalarial aerucyclamide B has been achieved in 9% overall yield. Two thiazoles and a dipeptide were used to prepare two open precursors of cyclo-Gly-L-*allo*-Thr-L-Ile-Thz-D-*allo*-Ile-Thz. Cyclodehydration with Deoxo-Fluor of the β-hydroxyamide present in the macrocycle, rendered aerucyclamide B (67%) and an unexpected fluorous derivative (28%).

Cyanobacteria are a rich source of biologically active natural products. Their secondary metabolites show a wide range of biological activities including anticancer, antibacterial, antiparasite, antiviral and protease inhibition activities.[1] The cyanobacterium *Microcystis aeruginosa* is well-known for the production of the toxic cyclic peptide microcystins.[2] *M. aeruginosa* also produces several linear peptides that are potent protease inhibitors,[3] and cyclamides which are cyclic peptides composed of alternating heterocyclic amino acids.[4] Aerucyclamides A, B, C, and D were isolated in 2008 by Gademann and co-workers from the toxic freshwater cyanobacterium *Microcystis aeruginosa* PCC 7806.[5] The most active of the four was aerucyclamide B (**1**, Scheme 1), displaying a submicromolar IC_{50} value against *Plasmodium falciparum* K1. In addition, this compound displays a large selectivity for the parasite with respect to the L6 rat myoblast cell line.[5b] Seeking to further explore their biological activity, a synthesis program was initiated to develop a convergent route to aerucyclamides and analogs. Herein, we present the total synthesis of aerucyclamide B.

Our retrosynthetic analysis is shown in Scheme 1. We planned to obtain first the macrocycle **2** from dipeptide **3**,[6] and two thiazole building blocks **4**,[7] and **5**,[8] by a convergent macrocycle-assembly methodology. This strategy was successfully used by Meyers and co-workers for the synthesis of a structural related product, bistratamide D using three heterocycle building blocks: a thiazole, an oxazole and an oxazoline.[9] In the paper, the authors described some problems related with the deprotection of the functional groups and coupling reactions of the oxazoline ring. In fact, we obtained a mixture of decomposition products during the deprotec-



Scheme 1. Retrosynthetic analysis of **1**.

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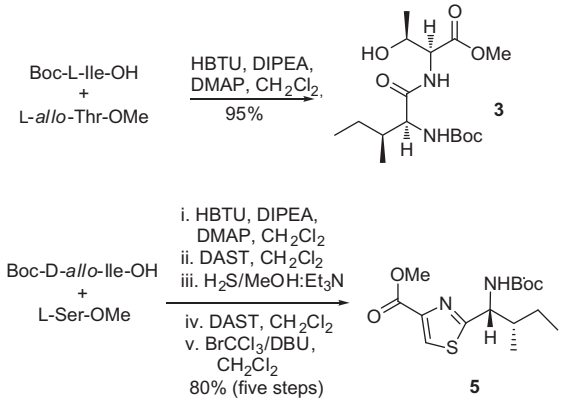
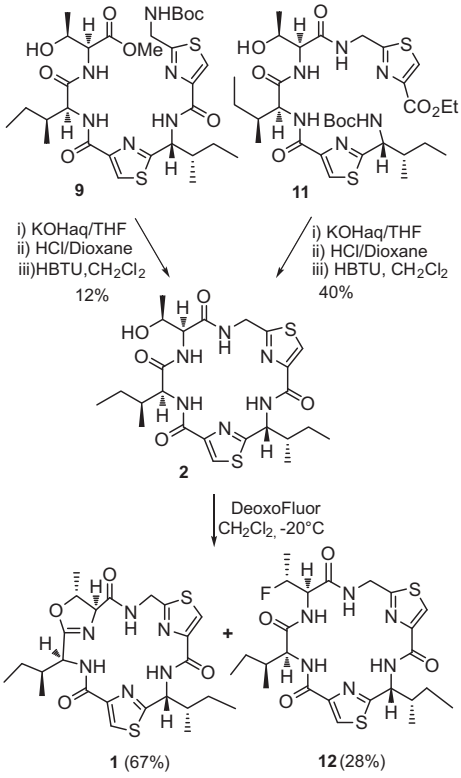


Scheme 2. Synthesis of building blocks **3** and **5**.

tion of the methyl ester of the oxazoline derived from dipeptide **3**, using basic conditions (KOH_{aq}/THF, $LiOH_{aq}$/THF).

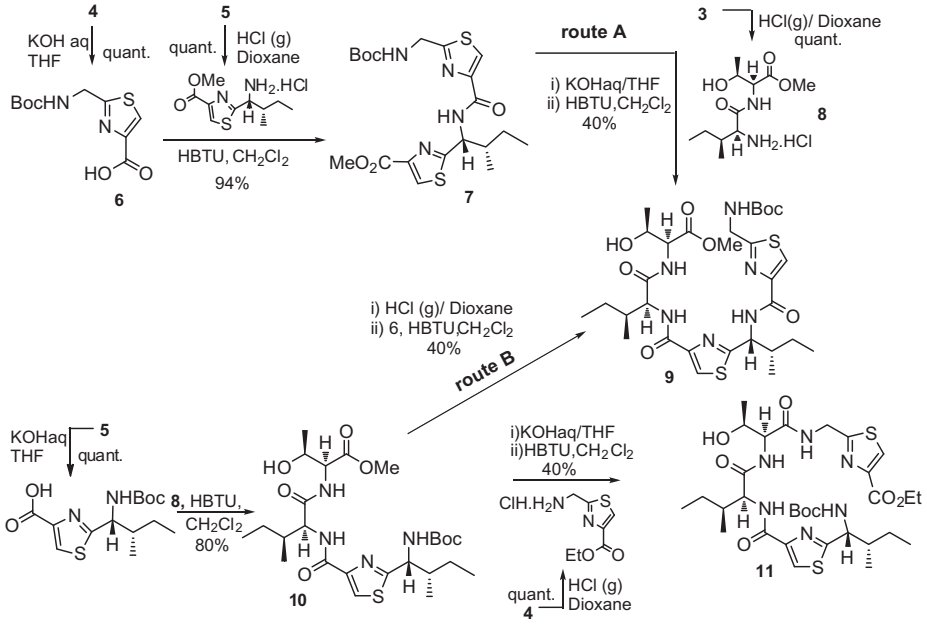
Based on these results and the previous reports,[8,10] we selected the cyclodehydration reaction, to obtain the oxazoline ring, as the last step of our route. The macrolactamization reaction is often a slow, low yielding procedure and frequently depends of the selected point of cyclization. In our case, macrocycle formation could be facilitated since the open precursors of **2**, contain turn-inducing[11] thiazole constraint.[12]

Dipeptide **3** was obtained in excellent yield (95%) from its protected aminoacids using HBTU as coupling reagent, Scheme 2. Thiazole **4** was prepared following our reported procedures.[13,14] For the preparation of thiazole **5** we selected the cyclodehydration of β-hydroxythioamides and further oxidation methodology. Coupling reaction between Boc-D-*allo*-Ile-OH and L-Ser-OMe followed by cyclodehydration allowed us to obtain the corresponding oxazoline which was used without purification, Scheme 2. Then, thiolysis with H_2S/MeOH/Et_3N,[15] rendered the thioamide. From this compound, thiazole **5** was obtained employing the one-pot procedure with DAST and then $BrCCl_3$/DBU.[16] Following this protocol, the desired thiazole was obtained in excellent yield (80%, five steps).



Scheme 4. Synthesis of **2** and aerucyclamide B.

The next steps were the assembling of the key fragments into the open intermediates of macrocycle **2**. In order to investigate if the point of cyclization is relevant for the formation of **2**, we decided to obtain two open intermediates **9** and **11** (Scheme 3). We hypothesized that these intermediates could facilitate the macrocyclization since in compound **9** the amino group is derived from Gly and consequently gave the synthetic advantages of non-epimerization and non-steric hindrance; and in compound **11** the



Scheme 3. Synthesis of bis- and tris-heterocycles.

reaction involves a carboxylic acid attached to an aromatic heterocycle and consequently epimerization cannot occur.[17]

First, for the synthesis of **9** by route A, bis-heterocycle **7** was prepared in excellent yield (94%) by ethyl ester hydrolysis of **4**, followed by coupling with the N-deprotected derivative of **5** using HBTU. Methyl ester hydrolysis of **7**, and coupling with the N-deprotected dipeptide **8**, rendered **9** in moderate yield (40%). With the purpose of investigating another route to **9** (route B), compound **10** was prepared in high yield by coupling dipeptide **8** and C-deprotected derivative of **5**. N-deprotection of **10** and coupling reaction with **6** rendered **9** in 40% yield.

For the synthesis of **11**, methyl ester hydrolysis of **10**, and coupling with the N-deprotected derivative of **4**, rendered **11** in moderate yield (40%).

Macrocycle **2** was obtained in poor yield (12%) by C- and N-deprotection of **9** followed by coupling using HBTU in diluted conditions (0.005 M), Scheme 4. C- and N-deprotection of the linear precursor **11** was achieved in quantitative yield using aqueous KOH and then HCl(g)/dioxane. Macrocyclization was performed in diluted conditions (0.005 M) using HBTU. The desired macrocycle **2**, was obtained from **11** in a higher yield (40%) than from the open intermediate **9** (12%), suggesting that the selection of the point for macrolactam formation is relevant in this case.

The last reaction to obtain aerucyclamide B was realized using the cyclodehydrative reagent Deoxo-Fluor. Previous studies have demonstrated that the reactivity of Deoxo-Fluor and DAST is similar, although Deoxo-Fluor displays increased thermal stability.[18] In addition, Deng and Taunton,[19] concluded that Deoxo-Fluor efficiently promoted cyclodehydration of an *allo*-threonine amide of a macrocycle to afford *cis*,*cis*-ceratospongamide in 88% yield. The use of these conditions, Scheme 4, allowed us to obtain aerucyclamide B in 67% yield and an unexpected side product in 28% yield. The ^{1}H NMR of this unexpected compound showed a dqd signal at 4.98 ppm with a coupling constant $J = 48.3$ Hz. In addition, the ^{13}C NMR spectrum showed a signal at 89.9 ppm (d, $J = 171.5$ Hz), that could be assignable to a C–F. These results and the HRMS spectrum prompted us to conclude that the side product is the fluorous derivative of **2** (**12**). This compound was produced by the intermolecular reaction between a fluoride and the activated intermediate generated by the reaction of **2** and Deoxo-Fluor. Based on a SN2-type mechanism, the inversion of the stereochemistry of C–F of **12** is proposed.

Elimination processes as a competition in the oxazoline syntheses using DAST or Deoxo-Fluor were previously reported.[20] However, to the best of our knowledge, competition between the oxazoline and the fluorous derivative formation was not published until now. In this case, the formation of **12** should be explained by a loss of nucleophilicity of the β-hydroxyamide of **2**. The conformation of this macrocycle, imposed by hydrogen bond formation, would restrict the desired reaction allowing the synthesis of the fluorous compound.

The spectroscopic data of the synthesized aerucyclamide B are in agreement with those reported to the natural product.

In conclusion, macrocycle **2** was prepared from two open precursors **9** and **11** using two heterocycles and a dipeptide as building blocks. Macrocycle **2** formation from **11** was performed in a higher yield (40%) than from **9** (12%). Aerucyclamide B was synthesized in 9% overall yield from **5** via intermediate **11**, and in 3% overall yield from **4** via intermediate **9**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.060.

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