Studies towards the total synthesis of aeruginosin DA495A

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Abstract
This work aims to develop the first total synthesis of aeruginosin DA495A, a natural product isolated from the cyanobacteria Myrocystis aeruginosa. The aeruginosins, in general, present a tetrapeptide scaffold with unusual amino acids and derivatives. In particular, aeruginosin DA495A presents a hydroxyphenylactic acid (D-Hpla), phenylalanine (D-Phe) and a rare 2-carboxy-6-hydroxioctahydroindole (6-epi-L-Choi) as its constitutive elements.

Key words: aeruginosin, total synthesis, peptide

Introduction

The aeruginosins are a class of marine natural products isolated from cyanobacteria, sponges and algae. The biological activity of the aeruginosins is related to thrombin inhibition in the coagulation cascade, thus they may be used to treat stroke, angiogenesis and inflammation. Aeruginosin DA495A (1) was isolated from the cyanobacteria Myrocystis aeruginosa by Advì et al. Its proposed structure is composed of a rare 6-epi-L-Choi moiety, as well as D-Phe and D-Hpla. This work aims to develop the first total synthesis of 1.

Results and Discussion

The synthesis of fragment 5 (D-Hpla) started with a Sharpless asymmetric dihydroxylation of alkene 2 to produce diol 3 in 70% yield and e.e.>99%. Reduction with triethylsilane and TFA provided alcohol 4, which was protected with TBS group. Finally, the ethyl ester was hydrolyzed by aqueous LiOH followed by treatment with HCl(aq.) to produce the acid D-Hpla-OH (5), as presented in Scheme 1.

Next, methyl ester from D-Phe was coupled with acid 5 to furnish amide 7 in 57% yield (not optimized) (Scheme 1).

The synthesis of the most challenging fragment, 6-epi-L-Choi (12), started using a similar approach as described by Hanessian and coworkers. L-Glu was protected as its dimethyl ester, followed by amine protection with Boc group yielding intermediate 8, which was submitted to a diastereoselective alkylation to produce 9 in 60% yield, d.r.>20:1. Ether 9 was treated with formic acid, then refluxed in toluene and the nitrogen was protected to give pyroglutamate 11. The final steps for the synthesis of 12 and its coupling to 7 are still under development (Scheme 2).

Scheme 1. Synthesis of D-Hpla-D-Phe-OMe (7)

Scheme 2. Synthetic plan to 6-epi-L-Choi (12)

Conclusions

We report here our initial efforts towards the total synthesis of aeruginosin DA495A. The fragment D-Hpla-D-Phe-OMe was successfully synthesized in a convergent and concise fashion. The pyroglutamate ring of the Choi fragment was constructed in a diastereoselective way starting from natural glutamic acid.

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References