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Towards the synthesis of cyclic depsipeptides Kohamamides A, B and C.

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Abstract

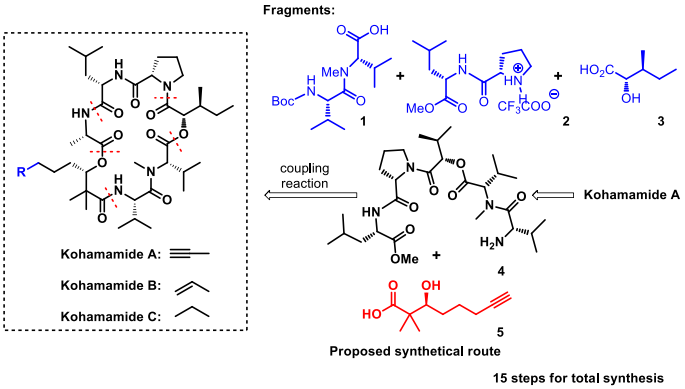
Kohamamides A, B and C are cyclic depsipeptides that belong to the kulolide superfamily, isolated from the marine cyanobacteria Okeania sp. Isolated Kohamamides showed pronounced cytotoxic activity in cell lines of human leukemia. In this context, we propose the first total syntheses of Kohamamides A, B e C, in a total of 15 steps. In this work, we present the synthesis of fragments 2, 3 and 11, which will be employed in the synthesis of desired Kohamamides. With the final compounds in hands, in vitro cytotoxicity assays will be conducted.

Key words:

Natural product, cyclic depsipeptides, total synthesis.

Introduction

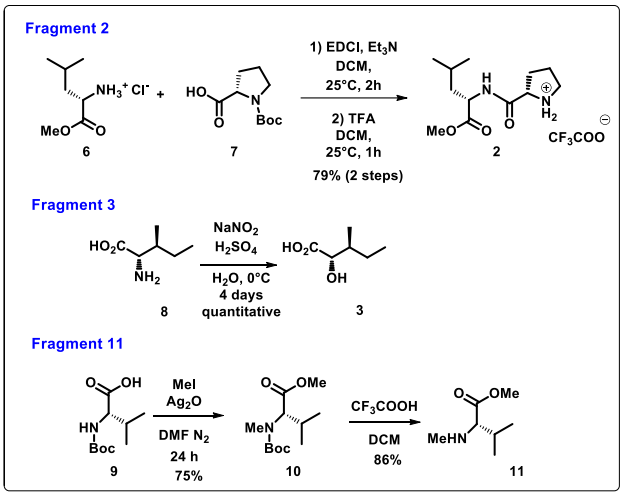
Kohamamides A, B and C are cyclic depsipeptides that belong to the kulolide superfamily. These molecules present a *β*-hydroxyoctanoic acid coupled to well-defined amino acid or *α*-hydroxy acid residue sequences and have been isolated from the marine cyanobacteria *Okeania sp.* in Japan, 2017.[1] Kohamamides chemical structures were elucidated by nuclear magnetic resonance (NMR) and mass spectrometry analyses. Isolated kohamamides showed a pronounced cytotoxic activity in cell lines of human leukemia, being Kohamamide B the most active (IC_{50} = 6.0 μM). In this context, we propose the first total syntheses of Kohamamides A, B e C, and further *in vitro* cytotoxicity evaluation.



Scheme 1. Retrosynthetic analysis for Kohamamides A, B and C.

Results and Discussion

The synthesis of Kohamamides A, B and C was proposed in a total of 15 steps (**Scheme 1**). The synthetic route begins with the synthesis of two main building blocks **4** and **5**, which will be coupled to furnish the desired kohamamides. The synthesis started with the coupling between L-leucine methyl ester **6** and *N*-Boc-L-proline **7** using EDC (**Scheme 2**), followed by the deprotection of the *N*-Boc protected amine, which leads to the formation of the compound **2** with 79% yield (2 steps). In the sequence, *N*-Boc-L-valine **9** was submitted to dimethylation reaction using iodomethane and Ag_2O,[2] obtaining *N*-methyl-L-valine methyl ester **10,** followed by a reaction of *N*-Boc deprotection, generating the ester *N*-methyl-L-valine **11** with 68% yield (2 steps).



Scheme 2. Syntheses of the fragments **2**, **3** and **11**.

Finally, the fragment **3** was prepared by treatment of L-isoleucine with $NaNO_2$ in H_2SO_4 aqueous solution, *via* formation of the diazonium salt,[3] obtaining the desired *α*-hydroxy acid in quantitative yield. Additional efforts will be oriented to the synthesis of the intermediate **4**, by a coupling reaction of intermediates **1**, **2** and **3**, and **5**, followed by coupling of **4** and **5**, concluding the synthesis of Kohamamides A, B and C.

Conclusions

In conclusion, the fragments **2**, **3** and **11** were synthesized in good to high yields. As future perspectives, we plan to conclude the synthetic route and evaluate the *in vitro* cytotoxicity of the prepared compounds.

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