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The synthesis of complex marine depsipeptides

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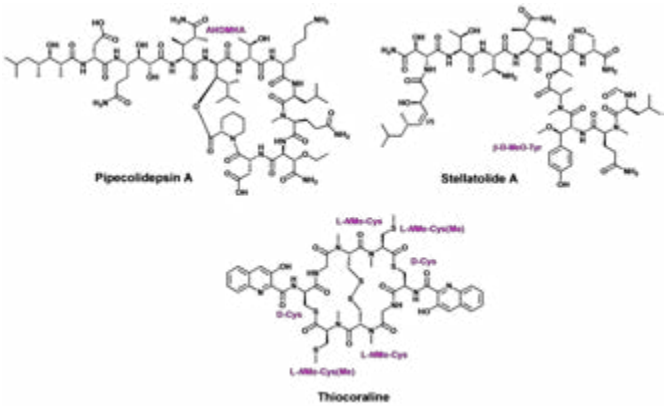
Marine organisms are a rich source of bioactive molecules. Among them, cyclodepsipeptides show relevant biological profiles, mostly including cytotoxic and anti HIV activities, and they are, therefore, promising candidates for medicinal chemistry programs. Herein, we report the synthesis of the potent antineoplastic agents pipecolidepsin A and Stellatolide A, "head-to-side-chain" cyclodepsipeptides, where the C-terminus is linked to a -hydroxy group via an ester bond, and of thiocoraline, a byciclic thiodepsipeptide that acts as bisintercalator. The three molecules present extremely challenging structures. Pipecolidepsin A bears the unprecedented and extraordinary bulky AHDMHA residue at the branching point, which makes the construction of the extremely hindered ester bond the major synthetic challenge to overcome. On the other hand, the high propensity of the unnatural -MeO-D-Tyr residue in Stellatolide A to suffer decomposition is the main limitation of its assembly. Finally, Thiocoraline's large amount of cysteines in a rather small structure represents the principal restraint. The successful solid-phase synthetic strategies that resulted in the three synthetic and active cyclodepsipeptides will be discussed.



Biography

Judit Tulla Puche received her Ph.D. in organic chemistry (2004) from the University of Minnesota under the supervision of Prof. George Barany. Her thesis dealt with the solid-phase synthesis of small proteins. After finishing her doctoral studies, she joined the group of Prof. Fernando Albericio at the Institute for Research in Biomedicine (IRB) where she became Research Associate, working on the synthesis of marine antitumor depsipeptides and complex peptides. In 2015, and after obtaining a Ramon y Cajal contract, she moved to the Department of Organic Chemistry at the University of Barcelona to establish her own research group. Her research interests span a broad range of topics at the interfaces of peptide chemistry and chemical biology.

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