Studies towards the total synthesis of macplocimine A

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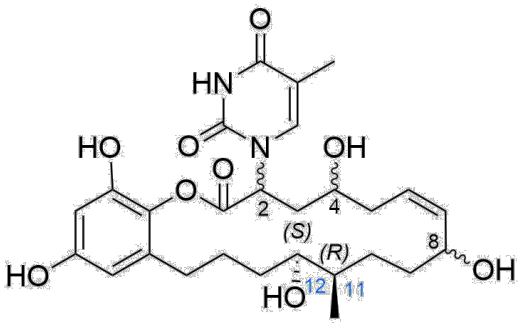
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Macplocimine A (**1**) is an 18-membered macrolide that was isolated from the marine-derived filamentous sulfur bacteria *Thioploca sp.* (benthic microbial mat, Chile) by Magarvey and co-workers in 2013.[1] As a unique structural feature among all known natural macrolides, macplocimine A (**1**) incorporates a nucleic acid base attached to the macrolactone ring.

No biological data has been reported for this natural product to date. However, given its structural relatedness to resorcylic lactones (RALs), which are known to exhibit a wide range of biological activity, in combination with the presence of a thymine moiety as a hydrogen bond donor/acceptor motif, the compound should have the potential to be biologically active.

Likewise, the stereochemistry of macplocimine A (**1**) has not been elucidated, except for the relative configuration of the stereocenters C(*11*) and C(*12*), which was established to be *anti*. No synthetic work on **1** has been documented in the literature.

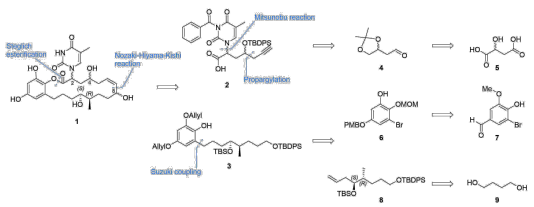
Enticed by its intriguing structural features and the associated synthetic challenges and in order to enable its biological assessment, we have embarked on the total synthesis of diastereomers of macplocimine A (**1**). The strategy towards the synthesis of the various diastereoisomers of macplocimine A (**1**) is outlined in Scheme 1.



1

Macrocycle formation was planned to be achieved *via* intramolecular Nozaki-Hiyama-Kishi reaction. The requisite macrocyclization substrate would be assembled from building blocks **2** and **3** *via* Steglich esterification. The former can be accessed from *D*- or *L*-malic acid (*D*- or *L*-**5**) *via* aldehyde **4** by Barbier-type propargylation and introduction of the thymine base under Mitsunobu conditions. Phenol **6** can be elaborated from bromovanilline (**7**) and butane-1,4-diol (**9**).

In this contribution, we will present efficient and scalable routes to building blocks **2** and **3** from **5** and **9**, respectively; as well as the building block assembly and macrocycle formation, for which we have established proof-of-concept. Finally, we will discuss the status of our work on the final steps of the total synthesis of selected diastereomers.



[1] X. Li, S. Vanner, W. Wang, Y. Li, V. A. Gallardo, N. A Magarvey, *J. Antibiot.* **2013**, *66,* 443–446.