Total Synthesis of Lobatamides

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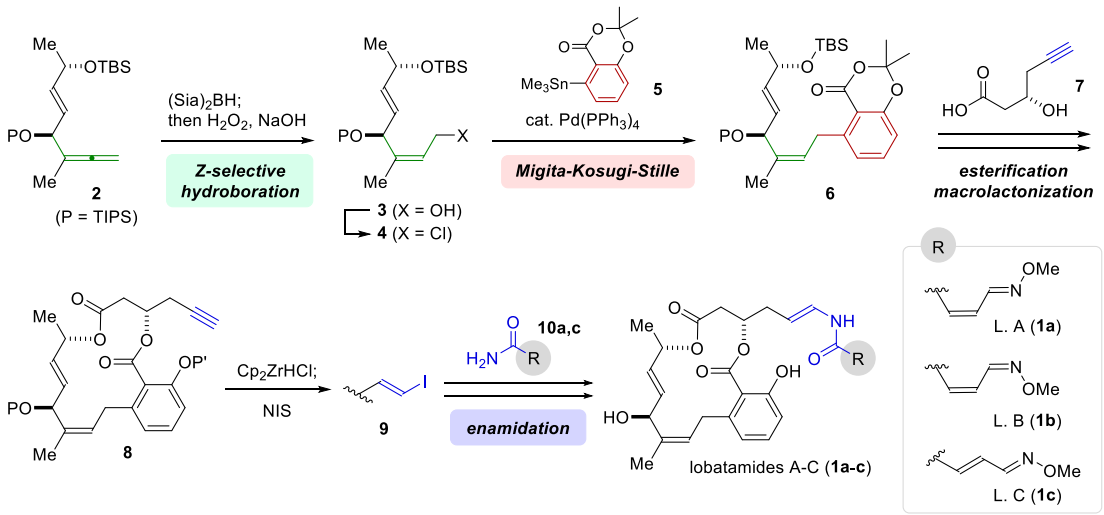
Lobatamides A-C (**1a-c**) were isolated from a southwestern Pacific tunicate, and are known to inhibit V-ATPases as potent antitumor macrolides.[1a,b] Structurally, they share a common macrobislactone framework with various enamide side chains. These enamides would play an important role for their biological activity, although the systematic structure-activity relationship are not investigated.[2] In this presentation, we report the total synthesis of lobatamides based on the stereoselective construction of *Z*-allylic arene moiety, and the late-stage installation of the enamide side chains from the terminal alkyne.

The *Z*-selective hydroboration of 1,1-disubstituted allene **2** and subsequent Migita-Kosugi-Stille coupling provided (*Z*)-allylic arene moiety **6**.[3] The common macrobislactone framework **8** was then prepared through intermolecular esterification with **7** and ynamide-mediated macrolactonization. The salient feature of our synthetic strategy was the late-stage diversification from alkyne intermediate **8**. Treatment of **8** with the Schwartz reagent (Cp_2ZrHCl) and NIS provided (*E*)-vinylic iodide **9** without affecting the macrobislactone group.[4a,b] Finally, the total synthesis of lobatamides A (**1a**) and C (**1c**) was achieved by the copper-mediated enamidation with **10a** and **10c**, and the global deprotection.



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