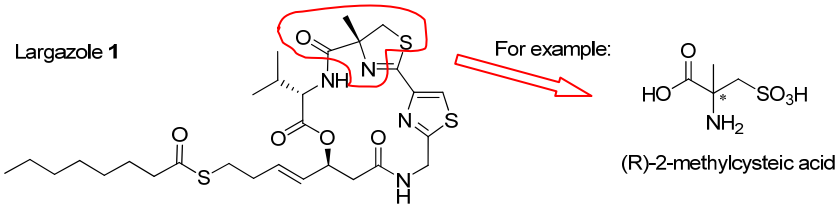
Problem Session – 02Nov2009

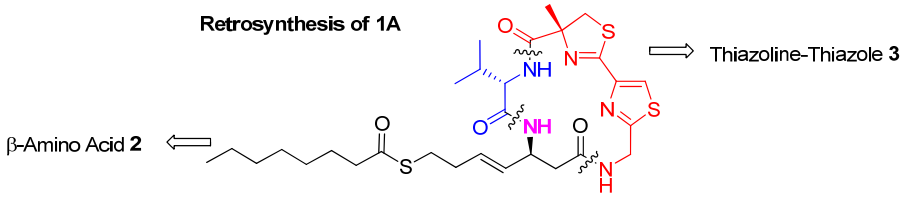
by Bingli Mo

Largazole **1** is a densely functionalised macrocyclic depsipeptide, isolated from the cyanobacterium *Symploca* sp. by Luesch and co-workers in 2008. This natural product exhibits exceptionally potent and selective biological activity. To date, largazole is the most potent and selective histone deacetylase inhibitor (HDACi) known.

Question 1: There are 3 stereocentres in the structure of largazole, please identify them and suggest their corresponding natural fragments.

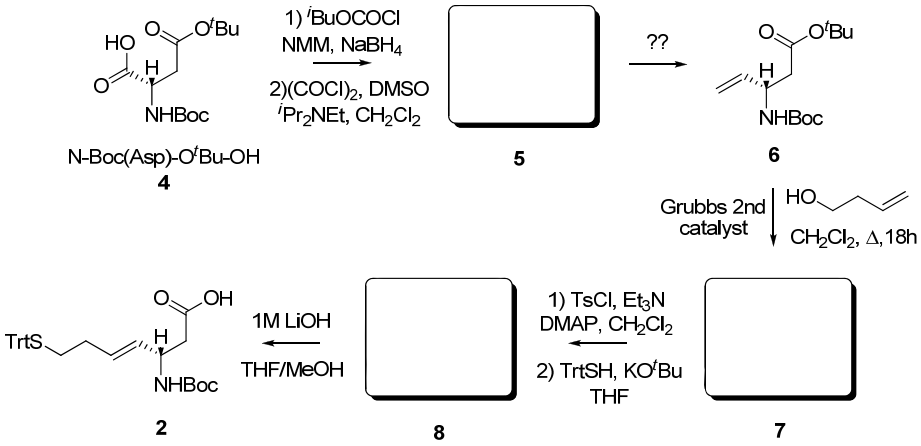


Since 1996, members of the Schreiber laboratory have become interested in the development of HDACi. Today, we will discuss the synthesis of largazole isostere peptide **1A**.



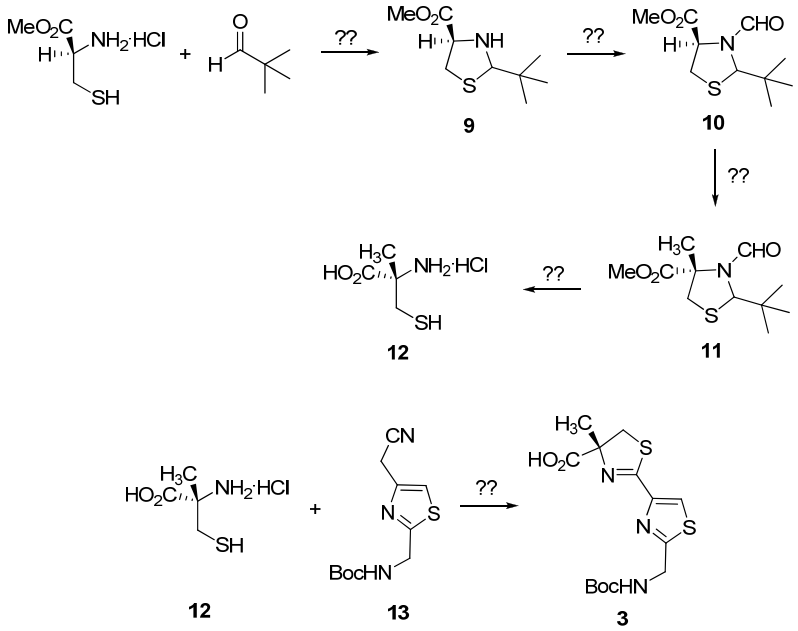
Question 2: Synthesis of β-Amino Acid **2**

Follow the synthesis below, filling in the blanks for the intermediates and reagents. Give mechanisms for each step.



Question 3: Synthesis of Thiazoline-Thiazole **3**

Follow the synthesis below, filling in the blanks for reagents. Give mechanisms for each step.



Question 4: Synthesis of Largazole Isostere Peptide **1A**

Follow the synthesis below, filling in the blanks for the intermediates.