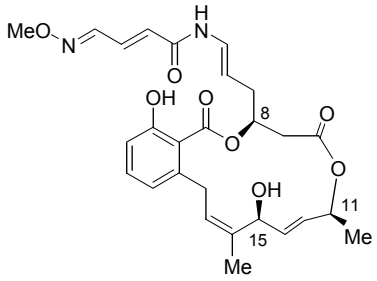
Total Synthesis of Lobatamide C and Related Studies:

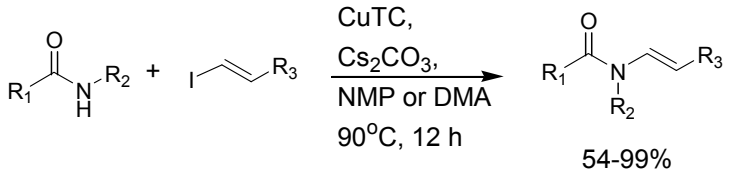
Lobatamides A-F, potent antitumor natural products, were isolated in 1998 from a southwestern Pacific tunicate (*J. Org. Chem.* **1998**, *63*, 7805). This series of compounds feature a 15-membered ring macrodilactone, divinylcarbinol moiety, and an *O*-methyloxime enamide sidechain. The absolute stereochemistry at C15 of lobatamide A (YM-75518A) was assigned to be (*S*) using a modified Mosher ester analysis, while the configurations at C8 and C11 required assignment by chemical synthesis. Biological studies indicate that lobatamides represent antitumor natural products with a novel mechanism of action. It has also been reported that the salicylate enamide natural products selectively inhibit mammalian vacuolar-type proton ATPases (V-ATPases) with high potency (*J. Pharm. Exp. Therap*. **2001**, *297*, 114). Accordingly, lobatamides are exciting new targets for chemical synthesis, lead optimization studies, and preparation of designed analogues. Recently, we have completed the total synthesis and stereochemical assignment of lobatamide C (**1**), as well as structure-activity studies based on synthesized analogues.



1: lobatamide C

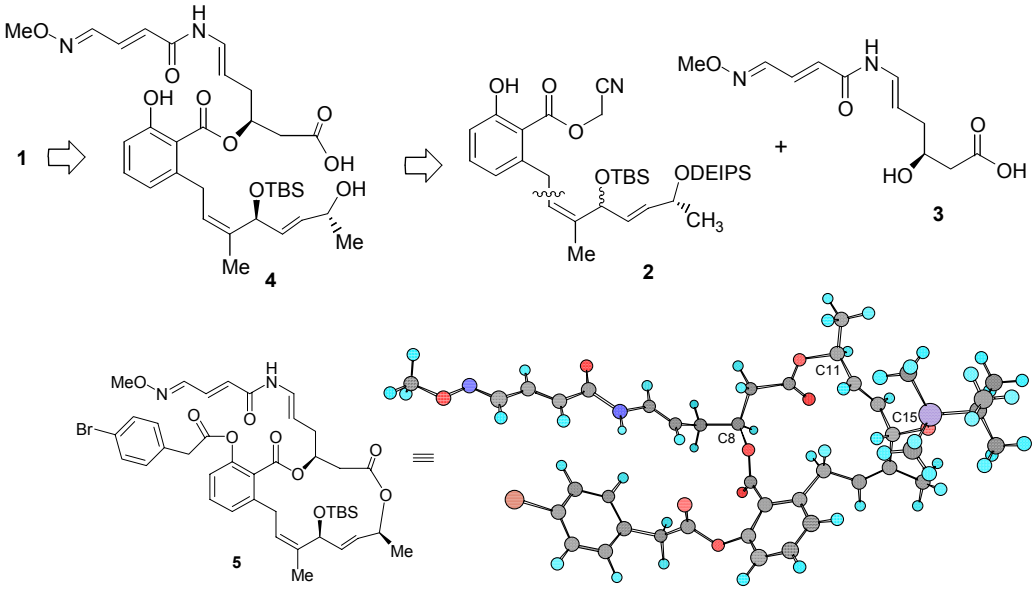
A. Development of Methodology for Synthesis of the Enamide Sidechain.

To construct the enamide-containing sidechain of lobatamides and other related natural products, we required a general method to synthesize highly unsaturated enamides. Therefore, we developed a stereoselective copper(I)–catalyzed vinylic amidation method which is suitable for the installation of potentially labile enamides on complex substrates (*Org. Lett.* **2000**, *2*, 1333). This method has been used in total synthesis of lobatamide C and other salicylate enamide natural products.



B. Total Synthesis and Stereochemical Assignment of lobatamide C.

Recently we have achieved a highly convergent total synthesis of lobatamide C (*J. Am. Chem. Soc.* **2002**, *124*, 5650). The key step of the total synthesis involves base-mediated esterification of the salicylate cyanomethyl ester **2** and the enamide acid **3**. Macrocyclization was achieved by an intramolecular Mitsunobu reaction of the seco acid **4**. The stereochemistry of lobatamide C was assigned as 8*S*, 11*S*, 15*S* by Mosher's ester analysis and comparison to synthesized diastereoisomers, and further confirmed by the X-ray crystallography of *p*-bromobenzoate **5** (*J. Am. Chem. Soc*. **2003**, ASAP).



C. Synthesis and Biological Evaluation of Simplified Lobatamide Analogues.

A number of simplified lobatamide analogues have been prepared in an effort to probe structure-activity relationships (*Org. Lett.* **2002**, *4*, 3103). In collaboration with Professor Barry Bowman's laboratory (*http://www.biology.ucsc.edu/people/bowman/*) Lobatamide C isomers and simplified analogues were evaluated against bovine chromaffin granule membrane V-ATPase, which showed that the salicylate phenol, enamide NH, and ortho-substitution of the salicylate ester were important for V-ATPase inhibition. In addition, two nanomolar acyclic salicylate enamides inhibitors of bovine chromaffin granule membrane V-ATPase were uncovered in this study, **6** (IC_{50}, 100 nM) and **7** (60 nM). Further studies on the synthesis of lobatamide analogues, including photoaffinity reagents, are ongoing.