University of Minnesota
Driven to Discover℠

Department of Chemistry

Aldrich Seminar in Synthetic Organic Chemistry

9:45 a.m. Thursday, November 7, 331 Smith Hall

Professor James Leighton

Department of Chemistry, Columbia University

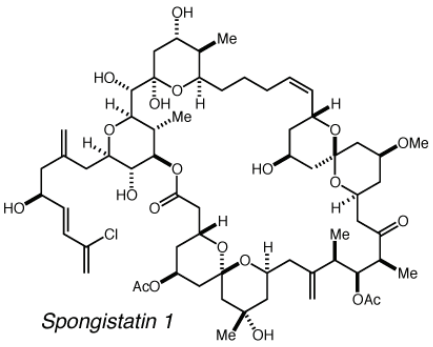
In Pursuit of the Ideal in Natural Product Synthesis–How and Why

Research focuses on the development of new methods and strategies in asymmetric synthesis, with a particular emphasis on the use of silicon as a Lewis acid. Methods developed include the tandem intramolecular silylformylation-allylsilylation of alkenes and alkynes; the tandem aldol-allylation reaction; and the strained silacycle-induced asymmetric allylation and crotylation of aldehydes, ketones, and β-diktones. The application of those methods and strategies to the synthesis of natural products, particularly marine macrolides with potent anti-mitotic activity, comprises another major focus. A particular emphasis is on devising syntheses that are characterized by unprecedented step-economy, efficiency, and scalability to facilitate our longer-term goals of advancing designed analogs of these natural products into the clinic.

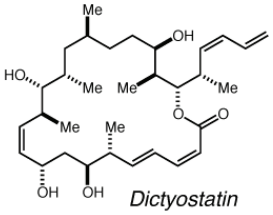
Website: http://www.columbia.edu/cu/chemistry/groups/leighton/leighton.html

Abstract

Natural products, by virtue of their structural complexity and variety, provide a rich forum for reaction design and chemical invention and innovation. When they are possessed of extraordinary biological activity and at the same time are available in significant quantity only through total chemical synthesis, they provide much more than that, and it would be difficult to identify a natural product that more clearly exemplifies this than spongistatin 1. This complex and exceedingly precious anti-mitotic agent was first reported nearly simultaneously by three research groups in 1993, and has been reported to have an average IC50 value against the NCI panel of 60 human cancer cell lines of 0.12 nM. While the question of whether spongistatin 1 can be synthesized was answered more than 15 years ago, the prospect of advancing this compound (or more likely a designed analog thereof) into the clinic still seems quite remote, principally due to the staggering amount of effort, time, and resources required both to synthesize analogs in search of a clinical candidate and to synthesize sufficient quantities of any such compound. In this lecture, I will describe my research group's efforts to devise a suite of powerful new strategies and methods for the synthesis of marine macrolides such as spongistatin 1 and dictyostatin with unprecedented step-economy, efficiency, and scalability. I will also describe our initial efforts to leverage that synthetic power for the rapid design, synthesis, and evaluation of analogs of these natural products, toward the long-term goal of advancing compounds into the clinic.



Spongistatin 1



Dictyostatin

Host: Professor Andrew Harned