CALIFORNIA STATE SCIENCE FAIR
2007 PROJECT SUMMARY

Name(s)
Anirudh A. Srirangam

Project Number
S0513

Project Title
Synthesis of a Diketopiperazine: The Key Structure of the Norgeamide

Abstract

Objectives/Goals
In early 2006, scientists discovered the Norgeamide; a natural product found in a marine-derived fungus. The Norgeamide has shown some interesting biological activity, such as potential treatments for certain cancers, implying that its synthesis could be of help to the medical world. The natural product itself is extremely scarce in nature and needs to be chemically synthesized. The noregeamide is stereochemically challenging, due to the selective oxidation at the 2-position of the proline, making it difficult for scientists to synthesize. The purpose of this project is to synthesize the key intermediate of the Norgeamide; a diketopiperazine structure.

Methods/Materials
Starting from commercially available cis-3-hydroxy-L-proline, an esterification reaction resulted in an ethyl ester. This ethyl ester was then coupled with Fmoc protected L-Phenylalanine to result in a dipeptide. Finally, the structure was cyclized to give the hydroxy diketopiperazine intermediate whose structure was confirmed by a single crystal X-ray structure analysis. This compound was dehydrated under Mitsunobu conditions to give the diketopiperazine structure.

Results
All reactions were carried out with fairly high yields and gave an overall yield of about 41%. Each structure constructed after every reaction was confirmed by structural elucidation techniques such as various NMRs, HPLC, LC-MS, and X-Ray Diffraction. The final product has been achieved and is now an available key intermediate for the construction of the Norgeamide.

Conclusions/Discussion
The final diketopiperazine 7 has been constructed and is now ready for N-acyliminium ion chemistry to introduce the hydroxyl/methoxyl functionality at the bridge carbon. The scheme for the synthesis was developed through the use of retrosynthetic analysis. This route is general and applicable to the construction of diketopiperazines carrying various substituents at the 4-position. This can be achieved by using suitable amino acids in place of phenylalanine. This synthetic approach could find utility in the total synthesis of norgeamides A and B.

Summary Statement
This project focuses on the use of synthetic organic chemistry to construct natural products that show interesting biological activity but are rather scarce in nature.

Help Received
Dr. Alan Grubbs was my mentor and supervisor throughout the project; I used the lab facilities and equipment at Pfizer Laboratories in La Jolla; My Father taught me much about the organic chemistry behind the project.