

PROLOGUE

The Importance of Natural Products Synthesis

This prologue is primarily for the benefit of readers outside of the field of chemistry, who may not be familiar with the nuances of the field of total synthesis, and thus, the impact of the research described in this thesis.

Natural products are complex molecules that have been isolated from a natural source, such as a tree bark, a fungus, a bacterial species, or even a marine creature. The study of natural products synthesis is essential to the advancement of organic chemistry, as well as to society as a whole. A natural product synthesis involves looking at a structure that has been isolated from nature, and then finding a way to make it from much smaller starting materials. As such, it is an ideal platform for the discovery of new reactions because every natural product presents a unique array of bonds that have likely not been made before. In order to make some of these bonds, new chemistry must be invented. These new reactions are typically applied to related molecules of varying levels of complexity, leading to the development of a new reaction methodology. Thus, total synthesis fuels the discovery of new methodology, while new methodology simultaneously allows for the completion of total syntheses.

The broader impact of these studies is realized largely through the pharmaceutical industry. Although pharmaceutical companies invest a great deal of time and money into their own research programs, they are generally very focused on a specific goal such as finding a drug for breast cancer. This is a large enough problem on its own that the company cannot invest their own man-hours into synthesizing natural products from scratch. Thus, they turn to academic groups for key information about what bonds were the most challenging to make and what disconnections lead to the shortest and most modular synthesis of a compound. Short syntheses are important to pharmaceutical

companies because even if every step of a 30-step synthesis of a compound proceeds with 90% yield (this is not typical), the overall yield for the process is $(.9)^{30}$ or 4%. If the company is going to conduct testing on the compound, they cannot afford to waste 96% of their original materials. Thus, it is important for academic groups to discover as many different types of reactions and ways to disconnect natural products as possible. It is also important to have a modular synthesis, so that analog compounds can be made and tested. In many cases, the best pharmaceutical agents are modified versions of natural products. Natural products offer the great advantage of having already been compatible with at least one living system, the one from which they were isolated. If that creature was able to survive with this compound inside it, it is more likely that a human will be able to tolerate the compound than for a molecule that has been 100% designed. Some important drugs that are natural products or derivatives include the antibiotics penicillin and vancomycin, contraceptives (+)-norgestrel and 17α -ethynylestradiol, the anti-inflammatory agent indomethacin, and the ovarian, breast, and small lung cancer drug paclitaxel (taxol).

The research presented herein centers around the synthesis of a marine alkaloid, zoanthenol, isolated off the coast of the Canary Islands from polyps of the genus *Zoanthus*. A number of very similar compounds were also isolated from the zoanthids, and they comprise a family of natural products called the zoanthamines. As a family, the zoanthamines offer a range of biological activities including inhibition of inflammation in mouse ears, cytotoxicity against murine leukemia cells, broad-spectrum antibacterial activity, and activity against human platelet aggregation. Perhaps the most exciting biological activity is the excellent anti-osteoporotic activity demonstrated by norzoanthamine. In ovariectomized mice, a good model for post-menopausal osteoporosis, treatment with norzoanthamine hydrochloride prevented the loss of bone mass and strength. Additionally, bone strength can be restored in ovariectomized mice

by treatment with norzoanthamine hydrochloride without any observed uterine atrophy, a side effect of treatment with 17β -estradiol, the current standard in this type of therapy. This difference points to the possibility of a different mechanism of action than estrogen therapy, making the zoanthamines an important family of natural products to target for synthesis.