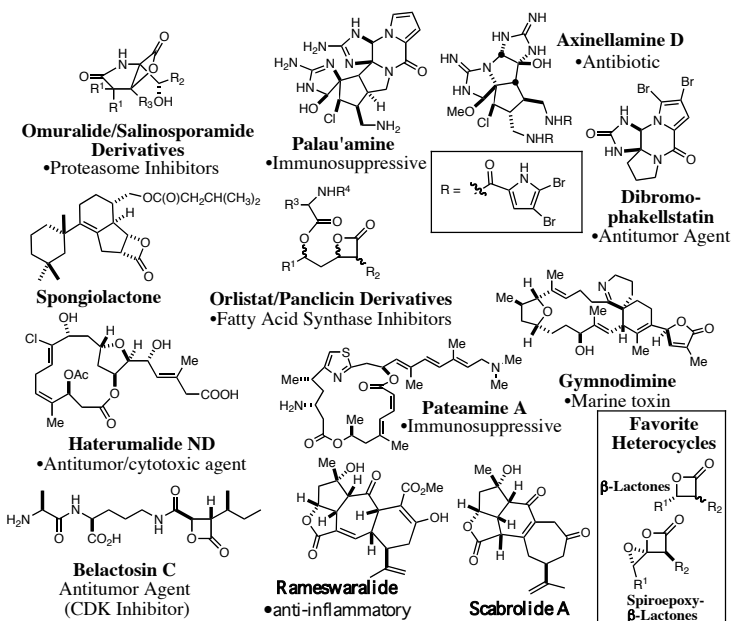


## Romo Group Research Synopsis (August 2008)

At the heart of our research interests are the chemistry and biology of natural products. These are unique and often structurally complex molecules that are designed to interact in highly specific ways with various cellular receptors and by homology those found in humans. Our interest in a particular synthetic target begins by an awe of the structural complexity, the presence of  $\beta$ -lactones or functionality derivable from  $\beta$ -lactones coupled with intriguing biological activity. Thus, overall our group is engaged in developing novel synthetic strategies and methods towards the total synthesis of natural products to enable further inquiries into their biological mechanism of action.

### •Structural, Synthetic, and Biomechanistic Investigations of Bioactive Marine Natural Products

One focus of our research efforts is total synthesis and determination of the mode of action of marine natural products that display significant physiological activity. For example, following a total synthesis of pateamine A (PatA), a marine sponge isolate with immunosuppressive and anticancer properties, in a collaboration with Prof. Jun Liu (John Hopkins), using a biotin-PatA conjugate, we recently identified PatA as a novel inhibitor of protein synthesis in mammalian cells. The potential of a simplified, more stable, equipotent derivative we synthesized, des-methyl, des-amino pateamine A, continues to be evaluated as a potential anticancer agent. Presently, we have total synthesis programs directed towards the total synthesis of the marine dinoflagellate-derived gymnodimine, oroidin alkaloids including palau'amines and axinellamines, and haterumalide ND. Our total synthesis strategies, which are sometimes premised on biosynthetic considerations, are designed to allow efficient access to the natural product in addition to structural derivatives and conjugates for studies aimed at elucidating their mechanism of action *i.e.* cellular receptor isolation. In conjunction with our total synthesis efforts, we attempt to develop new strategies for the assembly of these targets and often strategy development leads to exploration of novel intermediates with unknown reactivity, *e.g.* spiroepoxy- $\beta$ -lactones.



development of novel intermediates with unknown reactivity, *e.g.* spiroepoxy- $\beta$ -lactones.

•**Asymmetric Synthesis, Novel Transformations, and Synthetic and Biological Applications of 2-Oxetanones ( $\beta$ -Lactones).** We are developing diastereoselective and enantioselective methods for synthesis of  $\beta$ -lactone, underutilized heterocycles, employing 1) enantioselective, amine-catalyzed, intramolecular aldol-lactonization (NCAL) reactions using both aldehyde and ketoacid substrates and 2) tandem Mukaiyama aldol-lactonization (TMAL) reactions. In addition, we are interested in developing new transformations, novel cascade reactions, and rearrangements of these strained systems and ultimate application to natural and unnatural product synthesis (*e.g.* spongiolactone, belactosin C, salinosporamide derivatives, and scabrolides/rameswaralide). In a recent collaboration with Jeff Smith at the Burnham Institute (La Jolla) we targeted the thioesterase domain of fatty acid synthase as a potential enzyme target for cancer. This involves synthesis of Orlistat<sup>®</sup> derivatives employing our established TMAL reaction.

• **Natural Products-Based Interdisciplinary Research at TAMU: New Methodologies for Chemical Genetics/Functional Genomics** We are developing mild strategies to easily derivatize a natural product for identifying putative cellular protein targets and bioactivities. The strategy bypasses the usual bottleneck of complete natural product structure determination. Our strategy involves mild reactions that enable simultaneous arming (adding a reactive group for subsequent conjugation to various cellular probes) and SAR studies (to determine a suitable site for probe attachment and also identify novel bioactivities) of bioactive natural products. We recently described our first approach involving mild Rh(II) catalyzed OH insertions of natural products and further strategies are currently under development.