Title: Asymmetric synthesis of pharmaceutically important γ-lactones.

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Project Description: Dr. Kerrigan's research group is interested in the development of new organic synthesis methods that can be employed to access complex molecules with compelling pharmacological properties. The development of new methods which provide access to pharmaceutical drugs is of immense importance to society, especially with regard to improved healthcare. The proposed work seeks to develop new efficient routes to a key molecule, known as a γ-lactone, which can act as a springboard to medicines. This proposal involves plans for the asymmetric synthesis of γ-lactones from readily available and inexpensive chiral epoxides and ketenes. The importance of γ-lactones stems from the fact that they are often integral features of pharmaceutical drug molecules, and moreover can be used as intermediates for the synthesis of other complex molecules. However, stereoselective methods for the synthesis of γ-lactones, especially 3,4-substituted lactones, are rare and often involve lengthy multistep approaches, have limited substrate scope and compromised diastereoselectivity or enantioselectivity.[1] We propose investigating a bifunctional organocatalyst-catalyzed approach as a new strategy for the enantioselective synthesis of γ-lactones.

Ultimately, utility of the proposed methodology will be illustrated through its application in the streamlined synthesis of nucleoside analogue antivirals for the treatment of COVID-19 and Hepatitis C.[2] The γ-lactone products produced by these studies will also be evaluated for novel biological activity, such as anti-pancreatic cancer activity, through collaborations in the National Institute of Cellular Biotechnology at DCU. Students who undertake this project will learn how to carry out organic synthesis using inert atmosphere techniques (including Schlenk techniques), a variety of analytical techniques (e.g. NMR spectroscopy, chiral HPLC, and GC-MS analysis), purification techniques (e.g. reduced pressure distillation, flash column chromatography, and recrystallization), and presentation skills (PowerPoint and chalk talk presentations in group meetings).

Special requirements: Ideally students will have completed two semesters of organic chemistry (e.g. Organic I and II).

References:

1. 'Diastereoselective Synthesis of γ-Lactones through Reaction of Sulfoxonium Ylides, Aldehydes and Ketenes: Substrate Scope and Mechanistic Studies', N. J. Peraino, M. Mondal, H.-J. Ho, A. Beuque, E. Viola, M. Gary, K. Wheeler, N. J. Kerrigan, *Eur. J. Org. Chem.* **2021**, 151-160.
2. 'A tale of two antiviral targets - and the COVID-19 drugs that bind them', M. Cully, *Nature Reviews. Drug Discovery* **2021**, *21*, 3-5.