



## Synthetic Organic Chemistry, Development of New Synthetic Methodologies

### Research Interests

#### Singlet Oxygen and Cascade Reaction Sequences

What is special about our synthetic designs? Conventionally, the syntheses of polyoxygenated natural products have proceeded in a stepwise fashion, employed an excess of protecting groups, and repeatedly used toxic metal-based oxidants. Our strategies are different; we try to maximise the use of cascades mediated by the environmentally friendly oxidant, singlet oxygen ( $^1\text{O}_2$ ). This approach is advantageous not just for its environmental credentials, but because each molecule of  $^1\text{O}_2$  installs two oxygen atoms into the reaction substrate with no atom wastage (atom economy).  $^1\text{O}_2$  has been described as a "bullet" whose reactivity preferences can be easily manipulated to accomplish extremely selective oxidation (thus, for example, rendering protecting groups almost completely redundant). Furthermore, and perhaps, most crucially of all,  $^1\text{O}_2$  is a very powerful and under-applied cascade mediation tool. Cascade reactions are sought after transformations because they can create multiple bonds and stereocentres in a single operation, thereby, maximising synthetic efficiency and assuring the easy transference of stereochemical information.

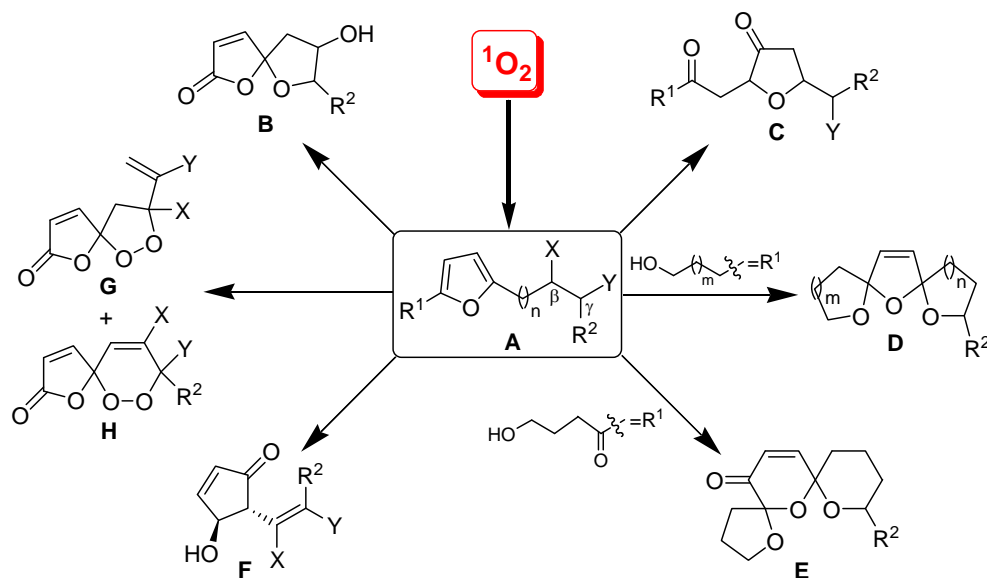
#### Biomimetic Syntheses

There is perhaps no reagent that could be said to be more synonymous with biomimetic synthetic strategies than singlet oxygen. This situation arises because in living organisms (especially plants) four crucial prerequisites are met, which favour the production and reaction of singlet oxygen. These criteria are:

- (1) the presence of natural sunlight providing visible spectrum irradiation;
- (2) the proliferation of photosensitizers (e.g. tannins, porphyrins, and chlorophyll) in the environment;
- (3) pervasive molecular dioxygen ( $\approx 20\%$  of atmospheric air); and, finally,
- (4) an abundance of oxidisable substrates, such as terpenes, in the immediate vicinity.

Biomimetic synthetic strategies are admired for their efficiency in the swift construction of molecular complexity. Of particular note, are biomimetic strategies that harness cascade reaction sequences to forge core structures rapidly from

simple precursors. Here, once again, we can see how singlet oxygen is uniquely suited to the paradigm since it willingly participates in complex domino reaction sequences. An unusually wide structural diversity amongst the molecular motifs may be obtained from these reaction sequences. For example, relatively minor modifications to the starting substrate (furan **A**) and to the reaction conditions may lead to products as variable as spiroketal lactones (**B**), 3-keto-tetrahydrofurans (**C**), various types of bis-spiroketal (**D/E**), 4-hydroxy cyclopentenones (**F**) or spiroperoxylactones (**G/H**).



The core of the prunolide molecules and the chinensine family of natural products were rapidly synthesized using effective and short singlet oxygen-mediated strategies; this adds weight to the assertion that singlet oxygen is a very effective moderator of complex cascade reaction sequences.

We also show how our synthetic investigations have provided evidence that these same strategies might be used in the biogenesis of these molecules. In the cases of the chinensines and the litseaverticillols, an entire and diverse family of natural products was synthesized beginning from known naturally occurring furan-bearing terpenes. Additionally, in several cases, intermediates in our syntheses have been isolated from natural sources, which suggest that we have followed the same synthetic paths as nature.

Certainly, the limit of the synthetic potential of singlet oxygen has not yet been reached. We look forward to seeing the boundaries expand in the future in a slew of new and interesting ways.