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## Aims & Objectives

In 2008, Evidente *et al* reported the isolation and structural elucidation of a new class of **natural herbicide** produced from the fungus *Phyllosticta cirstii*.<sup>1</sup> Four new compounds named phyllostictines A-D, based upon a truly unique oxatricycloalkenone skeleton, were identified. Alongside its **remarkable chemical architecture**, phyllostictine A (PA) exhibits potent activity as a herbicide (Figure 1).<sup>2</sup> On this basis, PA can be considered as an **exciting new lead in the search for next-generation crop-protection agents**.

The **main objectives** of this project are:

- To complete the **first total synthesis of phyllostictine A (PA)**. The proposed synthesis will require the development of new chemical reactions with emphasis being placed on **sustainable, catalytic transformations**. It is proposed that the 4-, 5- and 11-membered rings will be made using palladium, silver or gold, and ruthenium catalysis respectively (Figure 1).
- To produce a series of synthetic analogues and derivatives and use them to uncover the **molecular basis of the herbicidal activity** of PA.

Support for this project from EPSRC began in July 2013. The long term goal is to discover **simple new herbicides** which could contribute to the field of **sustainable agriculture**, a key research priority across the globe.

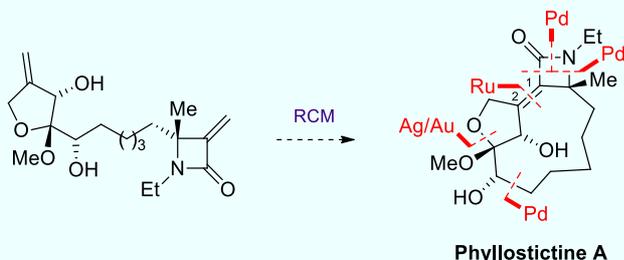
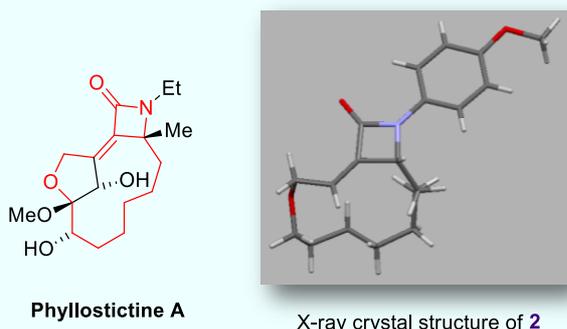
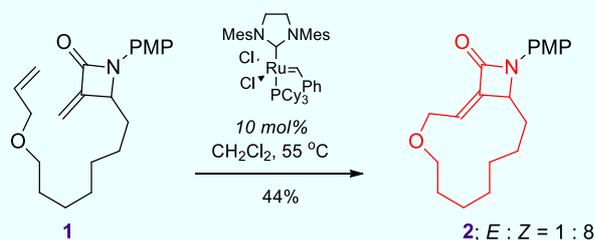


Figure 1: Proposed retrosynthetic approach to phyllostictine A.

## Synthetic Chemistry

A late stage **ring closing metathesis (RCM)** is proposed to construct the tetrasubstituted C-1/C-2 double bond of PA (Figure 1).<sup>3</sup> In model studies, we have demonstrated that lactam **1** undergoes RCM to 12-membered macrocycle **2** (Scheme 1). The major *Z*-isomer was separated, and its gross structure and stereochemistry confirmed by X-ray crystallography. The structure of bicyclic lactam **2** overlays much of the backbone of the natural product. **Work on the construction of the advanced intermediates required to assemble the complete natural product skeleton is just beginning.**



Scheme 1: Synthesis of a simple analogue of phyllostictine A using ruthenium catalysed ring closing metathesis.

## Herbicidal Activity

Phyllostictine A (PA) and synthesised analogues of PA are being tested for herbicidal activity in assays using *Chlamydomonas reinhardtii* (unicellular alga) (Figure 2).<sup>4</sup> This assay allows large numbers of compounds to be screened quickly, moreover **herbicidal resistance** can be explored.

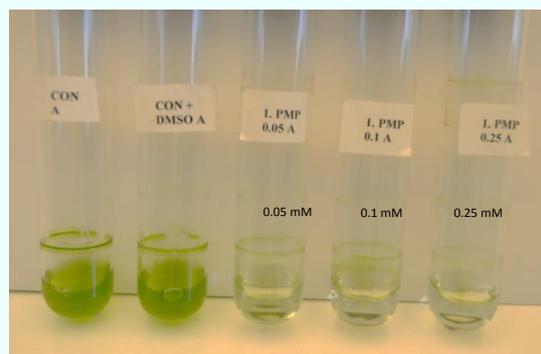


Figure 2: Test tube assay with *Chlamydomonas reinhardtii* using a synthetic PA analogue.

Excitingly, a **simple analogue of PA has been discovered that demonstrates better activity than the commercial herbicide glyphosate** in a *Poa annua* seedling test (Figure 3). Further assays will be performed on the higher plant, *Arabidopsis thaliana*, and on a range of weed and crop species at various growth and life history stages. Evolution of resistance will also be explored. Various strategies to explore the **mechanism of action** of these compounds are currently being initiated. Strategies for the **exploitation** of these findings are also being assessed. These preliminary research findings were presented at the **AGRI-Net Conference**, "Biological and Chemical Approaches Towards Combating Resistance in Agriculture", on 26<sup>th</sup> September 2013.

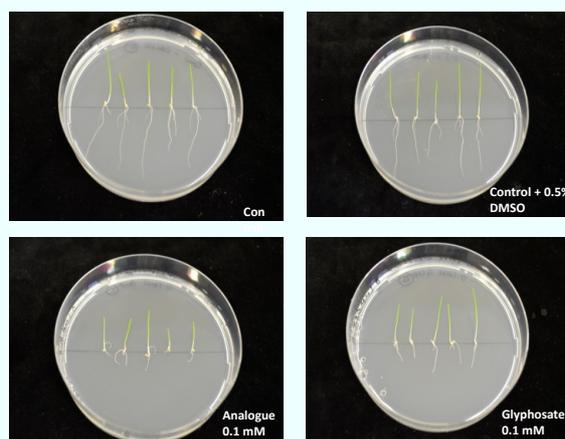


Figure 3: Herbicidal activity of an analogue of phyllostictine A in the *Poa annua* seedling test.

## Acknowledgements

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## References

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