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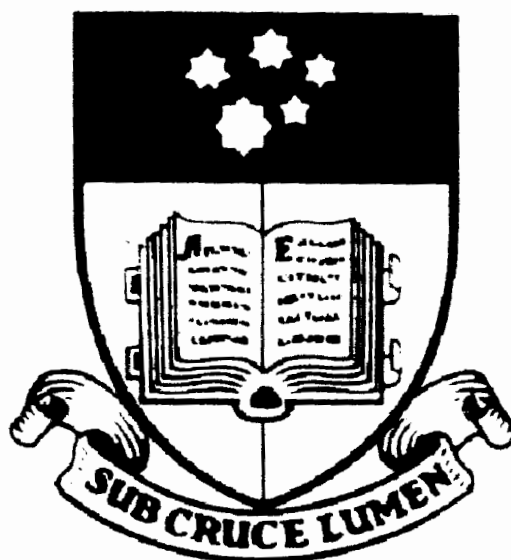


# **Exploitation of 1,2-Dioxines for the Synthesis of Cyclopropyl Natural Products and Novel Tetrahydropyrans and Tetrahydrofurans**

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of the requirements of the  
Degree of Doctor of Philosophy

by

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## Abstract

The main focus of the work discussed in this thesis was to explore the utility of 1,2-dioxines for the synthesis of selected bioactive, cyclopropyl-containing, natural products and to investigate their potential for the construction of novel oxygen heterocycles, namely tetrahydropyrans and tetrahydrofurans.

This thesis consists of six chapters. The first chapter is an introduction to (i) natural products and some natural product derivatives that have been used as therapeutics, many which still are in use today, (ii) a range of cyclopropyl natural products, which exhibit various bioactivities including those of interest, specifically, cyclopropyl steroids and fatty acids and (iii) a detailed discussion of the various methods for construction of the cyclopropyl motif including our method utilising the reactions between 1,2-dioxines, or the isomeric *trans*  $\gamma$ -hydroxy enones, with stabilised phosphorus ylides.

The utility of this method for the synthesis of cyclopropyl steroids and cyclopropyl fatty acids is discussed in Chapters 2 and 3, respectively. Cyclopropyl steroids of the Aragusterol series could not be synthesised by applying our methodology due to problems associated with the introduction of the methyl group *alpha* to the cyclopropyl ring. However, a method for the generation of a novel, highly substituted cyclopropyl steroid was established utilising our methodology. Unfortunately, this steroid was obtained in poor diastereomeric purity and yield. The utilisation of 1,2-dioxines and stabilised phosphorus ylides was more suited to the construction of the cyclopropyl core of the cyclopropyl fatty acid, grenadamide. Chemical modifications of the cyclopropyl substituents lead to the first total synthesis of natural grenadamide.

There are also many examples of naturally occurring tetrahydropyrans that exhibit impressive bioactivity and therefore, there is a great demand in developing methods for their synthesis. Chapter 4 briefly converses the current methods for THP construction and highlights the usefulness of 1,2-dioxines containing tethered *n*-propanol groups as precursors to *trans* and *cis* 2,3-disubstituted tetrahydropyrans. 1,2-Dioxines ring-open in the presence of base to the isomeric *cis*  $\gamma$ -hydroxy enones, which then undergo intramolecular 1,4-addition to generate THP's. Variation in solvent and base alters the *trans* and *cis* selectivity observed. The geometry of the  $\gamma$ -hydroxy enone also influences the ratio of THP's. Factors influencing the preference for cyclisation under the various

conditions are discussed. The utilisation of this methodology towards the synthesis of the natural product, Decarestrictine *L*, was also explored.

The work presented within chapter 5 highlights the utility of 1,2-dioxines containing tethered oxygen nucleophiles for the preparation of a range of compounds including tetrahydrofurans, variations in the tetrahydropyrans discussed in Chapter 4, benzodioxoles and lactones. Initial investigations towards the generation of optically-enriched tetrahydropyrans are also discussed.

Chapter 6 consists of all experimental data presented in Chapters 2-5.