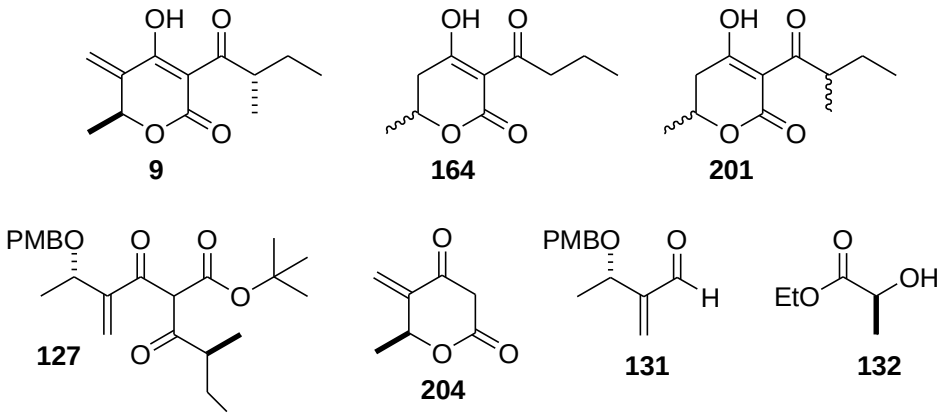
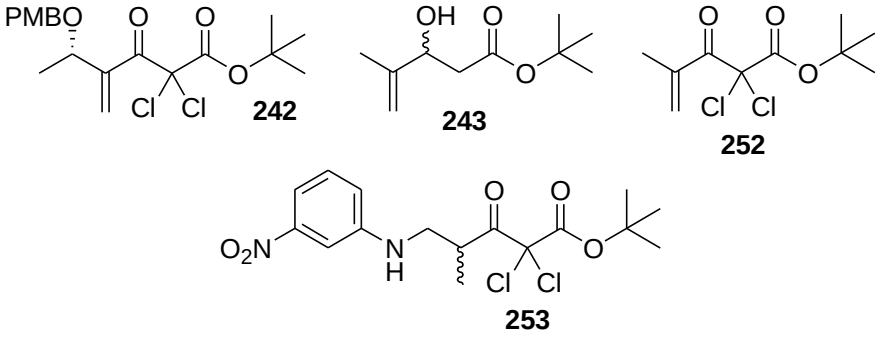
Abstract

Natural product chemistry has been at the forefront of organic chemistry since the late 20th century with natures' seemingly endless supply of compounds that display different types of structural complexity and biological activity. Synthesis of these intriguing natural products as a result has been one of organic chemistry's main sources for innovation. Chapter One of this thesis introduces polyketide natural products, including their structure, biosynthesis and potent biological activity. This chapter also discusses the current strategies employed by synthetic chemists towards synthesis of polyketide natural products, with a detailed focus on both the acylation and aldol reactions. These well established chemical transformations feature heavily in polyketide synthesis and were used extensively in Chapter Two and Chapter Four of this dissertation.

Chapter Two describes synthesis attempts towards the synthesis of CR377 (**9**), a polyketide natural product with a unique six-membered unsaturated tricarbonylmethane system isolated from the *Fusarium Species* by Brady *et al*. The main attempts focused on the synthesis of an acyclic tricarbonyl precursor **127** and a cyclic pyrone precursor **204**, following the successful synthesis of their respective model compounds **164** and **201** in 66% and 70% yield. Aldehyde **131** was synthesised in 33% overall yield in five linear steps from ethyl-(*S*)-lactate (**132**), and was the central focus in accessing both synthetic approaches towards the natural product. Unfortunately, incorporation of the structurally unique exocyclic double bond either caused oxidation, intramolecular conjugate addition or decomposition problems in the final stages of each synthesis strategy.



Chapter Three details the structural determination of an unexpected Swern oxidation product **242** observed during an attempt towards the total synthesis of CR377 (**9**). Synthesis of a model unsaturated β-hydroxy ester **243** produced an analogous result **252** following the Swern oxidation oxalyl chloride-DMSO protocol. Structural determination was achieved by synthesis of a *m*-nitroaniline conjugate addition product **253** in 60% yield, which following single crystal x-ray diffraction confirmed the α,α-dichlorinated products. Swern oxidation of structurally diverse β-acyl or β-keto alcohols in due course also gave their respective dichlorinated products in moderate to excellent yields, as a result of electrophilic chlorination.



Chapter Four describes an unrefined total synthesis of marine polypropionate dolabriferol (**10**), which ultilised a retro-Claisen rearrangement as the pivotal transformation to install the unusual ester linkage. The strategy adopted towards dolabriferol (**10**) involved use of lactate derive ketone **82** to install all but one of the required stereocentres in the natural product. Selective deprotection of trione **399** led to the

formation of trioxaadamantane **402**, whose contribution as an intramolecular protecting group led to the exclusive formation of ester **404** following extended exposure to base. Hydrogenolysis of the benzyl ether protecting group in ester **404** allowed the final cyclisation to occur completing the total synthesis of dolabriferol (**10**) in 0.63% overall yield from methyl-3-hydroxy-2-methylpropionate in 17 linear steps.