NOVEL BIOMIMETIC TOTAL SYNTHESSES OF
RESORCYLATE NATURAL PRODUCTS UTILIZING
LATE STAGE AROMATISATION

A Thesis Submitted by

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In partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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September 2010
Abstract

The β-resorcyclic acid (1) unit can be found in a number of biologically active natural products including montagnetol (2), hair-growth stimulant pochonin G (3), antioxidant erythrin (4), antifungal agents 15G256β (5) and mycotoxin (S)-zearealenone (6). A conventional total synthesis of 15G256β (5), from β-resorcyclic acid units, was fraught with difficulties. Consequently, we established a novel biomimetic strategy for the synthesis of natural product 6, by utilising a late stage aromatisation step, starting from polyketide precursor 7. Two main issues needed to be solved: a flexible synthesis to build polyketides and mild conditions to construct the aromatic ring.

Diketo-dioxinone 10 was found to be an equivalent of a polyketide. Its synthesis was accomplished by reaction of deprotonated dioxinone 8 and benzotriazole derivative 9 (obtained from thermolysis of dioxinone 8 ²).
Mild conditions were found to construct the aromatic ring 11 using a weak base followed by an acid work-up. A strategy to build resorcylates in one step from diketodoxinone 10 was also discovered.\textsuperscript{2-3}

This strategy was then applied to the total synthesis of (S)-zearalenone (6) employing dioxinone derivate 12 and alcohol 13 to afford polyketide 14. Conversion into (S)-zearalenone (6) was accomplished by aromatisation and trans-selective ring closing metathesis.\textsuperscript{3}

In an analogous manner to (S)-zearalenone (6), the biomimetic total synthesis of both enantiomers of montagnetol (2) and erythr (4) were completed, allowing assignment of their absolute stereochemical configuration.\textsuperscript{2}
Similarly, an analogue of pochonin G 19 was synthetised, using a C-acylation reaction of the keto-dioxinone 16 dianion with Weinreb amide 17 followed by a cascade sequence consisting of ketene generation, alcohol 18 trapping, aromatization and ring closing metathesis.

From the key diketo-dioxinone building block 10, heteroaromatic 20 as well as resorcylate 15 were synthesised.²

¹ Frederiksen M. U., PhD thesis.  
Acknowledgements

First and foremost, I would like to thank Professor Anthony G. M. Barrett for allowing me to study under his tutelage, for providing me with a challenging project and especially for giving me the freedom to carry out my research.

I am thankful to my two industrial supervisors Dieter Hamprecht (GSK) and Colin Leslie (GSK) for inspirational discussions and above all for organising my placement in Verona which was one of my favourite parts of this PhD.

I am especially grateful to Dieter Wagner (Novartis) and Frederic Zecri (Novartis) for encouraging me to undertake a PhD.

I would like to thank the polyketides team past and present: Severine, Sarah, Ismael, Christoph, Marianne, Hideki, Bhavesh and the enthusiast Jenny.

I would like to acknowledge honorary Barrett group members: Ola, Paula, Darunee, Christine, Marion, Tomek, Tao, Xavier, Jan, Andrea, Okanya, Rob, Sylvain, Jullien, Math, Brian, Florian, Tim, Etienne, Basti, Alex, Fred C, the friendly Katie, the erudite Max, and the numerous summer and rotation students who have come through the lab. The group has been a source of good fun, advice and collaboration.

My sincere thanks to my fellow Imperial mates: Thais, Keren, Jean-Noël, Paolo, Matthias, Dil, Nina, Fanny, Angela and Mahesh for all the fun we have had in the last years.

I would like to say a big thank you to my team of proof-readers: Paul the P., Manu the Genius and Fred le Savoyard.

A very special thanks to Liz, for the astonishing proof reading and also for the good times spent together in the lab. It was a pleasure to work with such an amazing girl.

I am grateful to our group’s administrative assistants Mickie, Sam, Graham and Katie who were always ready to help.

I am also especially grateful to the “dream team annecienne” who stayed in touch with me. Since most of you are unlikely to ever read this I won’t name drop.

I would like to thank my family: my parents Maurice and Marie-Dominique for unconditional support and encouragement, my sister Chrystelle for trying to read my introduction and Anny for believing in me.

Many thanks to my loving, supportive, encouraging and patient Nathalie whose faithful support during the final stages of this PhD was so appreciated.

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Abbreviations

\[ \alpha \] _D \quad \text{optical rotation}

Å \quad \text{Angstrom} \quad (10^{-10} \text{ m})

Ac \quad \text{acetyl}

acac \quad \text{acetylacetonate}

Anal. \quad \text{analysis}

aq. \quad \text{aqueous}

Ar \quad \text{aryl}

Bn \quad \text{benzyl}

bp \quad \text{boiling point}

br. \quad \text{broad}

Bt \quad \text{benzotriazole}

Bu \quad \text{butyl}

Bz \quad \text{benzoyl}

c / conc. \quad \text{concentrated}

°C \quad \text{degrees Celsius}

ca. \quad \text{circa}

CAL-B \quad \textit{Candida antarctica} lipase B

calcd. \quad \text{calculated}

cat. \quad \text{catalytic}

CDI \quad \text{carbonyldiimidazole}

CI \quad \text{chemical ionisation}

COD \quad \text{cyclooctadienyl}

Cp \quad \text{cyclopentadienyl}

δ \quad \text{chemical shift}

d \quad \text{doublet}

DABCO \quad 1,4-diazabicyclo[2.2.2]octane

DBU \quad 1,8-diazabicycloundec-7-ene

DCC \quad \text{dicyclohexyl carbodiimide}

DCM \quad \text{dichloromethane}
<table>
<thead>
<tr>
<th>Abbr.</th>
<th>Definition</th>
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<tbody>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutyl aluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets</td>
</tr>
<tr>
<td>dq</td>
<td>doublet of quartets</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionisation</td>
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<tr>
<td>eq.</td>
<td>equivalent</td>
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<tr>
<td>ES</td>
<td>electrospray</td>
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<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>GCMS</td>
<td>gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IBX</td>
<td>o-iodylbenzoic acid</td>
</tr>
<tr>
<td>imid.</td>
<td>imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>L</td>
<td>litre</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethyl disilazide</td>
</tr>
<tr>
<td>µ</td>
<td>micro (10^-6)</td>
</tr>
<tr>
<td>m</td>
<td>molar</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
</tbody>
</table>
Me  methyl
Mes mesityl
min minute(s)
mL millilitre(s)
mol mole(s)
mmol millimole(s)
mp melting point
MPM methoxy(phenylthio)methyl
m.s. molecular sieves
Ms mesyl
MS mass spectrometry
MW microwave irradiation
m/z mass to charge ratio
n normal
NBS N-bromosuccinimide
NCS N-chlorosuccinimide
NMO N-methylmorpholine oxide
NMR nuclear magnetic resonance spectroscopy
Nu nucleophile
o ortho
p para
P general protecting group
PCC pyridinium chlorochromate
Pd/C palladium on carbon
PDC pyridinium dichromate
Ph phenyl
PKS polyketide synthase
ppm parts per million
PPTS pyridinium para-toluene sulfonate
Pr propyl
Py. pyridine
q quartet
CHAPTER ONE:
INTRODUCTION
1.1 Natural Products as Leads in Drug Development

Since ancient times nature has proved to be an important source of useful drugs. During several billion years of evolution such diversity has developed that it is currently estimated that there are approximately 250,000 different plant species, up to 30 million insects, 1.5 million fungi and similar numbers of algae and prokaryotes in existence. From all varieties of plant species, at least one million different natural products have been isolated.¹

Natural products are typically secondary metabolites, produced by plants, fungi, bacteria, protozoans, insects and animals in response to external stimuli such as nutritional changes, infection and competition. Most secondary metabolites are derived from just a few building blocks; the acetate C2-unit (polyketides⁵), the phenylalanine/tyrosine-derived C9-unit (phenylpropanoids), the isopentenyl diphosphate C5-unit and some amino acids.²⁻⁶

![Figure 1](image)

**Figure 1.** Example of drugs derived from natural products.

¹ The term polyketide was coined by Collie to define products containing multiple carbonyl or hydroxyl groups, each separated by one carbon atom, as in the structural element \(\text{CH}_3\text{C(=O)CH}_2\text{CH(OH)CH}_2\text{C(=O)}\).
and animal health industries include lovastatin (21) (anticholesterolemic agent), tacrolimus (22) (immunosuppressive agents), doxorubicin (23) (antitumor agents), erythromycin (24) (antibiotic), and amphotericin B (25) (fungicidal agent) (Figures 1 and 2). In 1998, 119 plant-derived compounds were used in western medicine. In 2004, 43% of the world’s 35 best-selling pharmaceutical agents, were derived from

![Figure 2](image)

**Figure 2. More examples of drugs derived from natural products.**

The biosynthetic pathway towards the formation of polyketides will be a source of inspiration for our work and will be discussed in more detail in this thesis.

In 1988 the database NAPRALERT already contained more than 88,000 secondary metabolites, and every year some 4,000 new ones are reported. It is clear that nature provides an enormous potential for the discovery of new bioactive compounds. This has resulted in the use of a large number of medicinal plants to treat various diseases. Well-known examples of valuable natural products used widely in today’s medical and animal health industries include lovastatin (21) (anticholesterolemic agent), tacrolimus (22) (immunosuppressive agents), doxorubicin (23) (antitumor agents), erythromycin (24) (antibiotic), and amphotericin B (25) (fungicidal agent) (Figures 1 and 2). In 1998, 119 plant-derived compounds were used in western medicine. In 2004, 43% of the world’s 35 best-selling pharmaceutical agents, were derived from
natural products. That means that the hit rate amongst natural products is apparently much higher than in libraries derived by random synthesis, in which 10,000 compounds are said to be necessary to develop one new drug.

In spite of this apparent success, the popularity of natural products is diminishing due to three main factors:

- As pharmaceutical drug discovery has become more sophisticated (ie going from whole cell-based assays to more pharmacologically relevant assays based on enzyme inhibition and receptor interaction), natural product extracts are considered too impure to be tested.
- Where automated high-throughput screening is an important tool in pharmaceutical companies, natural products are disadvantaged compared to compound collections with known structures, since the time taken to progress from a hit to knowing the structure is considerably longer.
- Medicinal chemists are usually hesitant to get on a synthetic program towards scaffolds based on natural products due to their chemical complexity, such as complex networks of chirality and multiple hydroxyl moieties. The structure activity relationship optimisation for such leads is often complex, consequently costly, and usually the hit becomes the candidate.

Based on these observations, the need for constant development of novel and efficient methodologies to synthesise natural products is essential in order to make them more attractive for drug discovery. In this thesis a new synthetic method to generate natural products, inspired by their biological synthetic pathway, will be presented. From a key building block, diketo-dioxinone 26a, which can be viewed as a chemical equivalent of a polyketide, a panel of bioactive natural products, as well as heteroaromatic compounds have been produced. (All the di- and tri-keto-esters 26a exist as mixtures
of keto and enol tautomers (26b and 26c). However, for convenience, in this PhD thesis they are drawn as single entities as 26a.) (Scheme 1).

![Scheme 1. Diketo-dioxinone 26.](image)

### 1.2 Project Background

The starting point of this PhD thesis is the natural product 15G256-β (5) (Figure 3). It was isolated from the marine fungus *Hypoxylon oceanicum* LL-15G256 in 1998 and exhibits a broad spectrum of activity against pathogenic fungi. It shows a MIC (minimum inhibitory concentration) of 0.5 µg/mL against *Neurospora crassa* (OS-1). The natural product contains five chiral centres and two β-resorcylic acid units.

![Figure 3. 15G256-β (5) isolated from LL-15G256.](image)
The high symmetry of 15G256-β (5) allows disconnection of the framework into just two fragments, acids 27 and 28 with (R)-β-hydroxybutyric acid (27) being commercially available. Using the following retrosynthetic approach (Scheme 2), members of the Barrett group have attempted the synthesis using a sequential esterification and macroactonisation approach. This route was found to be fraught with difficulties, attributed to steric hindrance around the carboxylic acid group. Mitsunobu reactions also failed and led to β-elimination and moreover, having the alcohol of the resorcylic acid 28 unprotected can also lead to the formation of the isochroman-1-one (29). The synthetic problems of the previous approach led us to consider a new synthetic route.

Scheme 2. First retrosynthesis analysis of 15G256-β (5) and synthetic difficulties.

Biomimetic synthesis has long been an interesting field in organic chemistry, not only to explore in detail the biosynthetic pathway of natural products but also to provide different solutions to conventional synthetic problems; consequently we decided to look at this molecule’s biosynthetic origin.
1.3 RALs: Biosynthesis and Activity

In order to achieve our goal, we decided to get back to a more simple family of natural products which also contain the 6-alkyl-2,4-dihydroxybenzoic acid unit 30, namely the β-Resorcylic Acid Lactones (RALs)\textsuperscript{12} 31. RALs are a large family of natural compounds isolated from fungi over the past 60 years. RALs commonly contain a 12 or 14-membered ring lactone adjoined to the aromatic unit, with varying functionality around the macrocycle (Figure 4).

![Figure 4. 6-alkyl-2,4-dihydroxybenzoic acid unit 30 and RAL scaffold.](image)

It is known that RALs arise from a polyketide pathway.\textsuperscript{13} They are in fact made from the sequential condensation of thioacetate units 32 and 33 to form a highly reactive tetracarbonyl 36 (via polycarbonyls 34 and 35) which aromatises readily by an intramolecular aldol-dehydration type reaction to form the aromatic unit 31 (Scheme 3).\textsuperscript{14-18}

![Scheme 3. Biosynthesis of RALs. 1/2](image)
(S)-zearalenone (6), hypothemycin (37), aigialomycin D (38), radicicol (39), pochonin C (40), pochonin D (41) are members of the RALs family. These compounds also show a wide range of biological activities, ranging from estrogenic agonists to anti-malarials (Figure 5).

Figure 5. Examples from the resorcylic acid lactone family of natural products.

This class of natural products has been the subject of a considerable synthetic study. Most reported total syntheses employ 6-alkyl-2,4-hydroxybenzoic acids as
intermediates, and proceed via stepwise derivatization of these key building blocks.\textsuperscript{12} Such strategies are often limited by moderate yields in the macrolactonization step and/or the need for multiple protecting group manipulations.

1.4 Retrosynthetic Strategy

Based on these observations our retrosynthetic strategy was to construct the aromatic unit from a triketo-ester in the same way that nature builds resorcylicate units (Scheme 4).

\[ \text{Scheme 4. Cyclisation-aromatisation to form } 15G256-\beta (5) \text{ and zearalenone } (6). \]

Before attempting the synthesis of 15G256-\beta (5), we decided to test the methodology on zearalenone (6) to develop a general method for forming resorcylic acid units, which could be applied to other biomimetic natural product syntheses.
1.5 Harris’ Work on Polyketides

The retrosynthetic analysis was inspired from Harris’s work on the synthesis of poly-β-carbonyl chains. One of the most representative examples reported was the self-condensation of methyl acetoacetate 43 upon deprotonation with a strong base to form tetra acetic acid methyl ester 44 (Scheme 5).25

![Diagram of reaction](image)

Scheme 5. Synthesis of triketo methyl ester by Harris et al.

Having those intermediates in hand, Harris et al demonstrated that they can undergo many cyclisation reactions analogous to those carried out in nature, without enzyme catalysis.26-30 They observed that four possible cyclisations can occur from triketo-ester 44 or triketo-acid 46 compounds (Scheme 6). The first one is the aldol condensation-dehydration under strong basic conditions in methanol to give resorcylate 11. The second ring formation which can occur in basic aqueous medium is a Claisen (Dieckmann) cyclisation giving acetophenone 45. The third and fourth ring closures can take place respectively with sulfuric acid and acetic anhydride to afford correspondingly 4-pyrones 47 and 4-hydroxy-2-pyrones (enol lactones) 48 (Scheme 6).
Scheme 6. Condensations of triketo-ester or triketo-acid compounds under different conditions

In 1980, Barrett and Barton\textsuperscript{31} improved the aromatisation step by using a pH 9.2 buffer to promote the aldol condensation and obtained resorcylate 11 in a 72\% yield. Triketo-ester 44 was formed from the condensation of dianion 49 and ketone 50 (Scheme 7).

Scheme 7. Improved strategy developed by Barrett and Barton to form resorcylate 11.
Whilst this procedure has been proven to be a highly powerful tool for various ring formations, its associated disadvantages make it unsuitable as it is. These include: i) the use of particularly harsh reaction conditions (strong basic and acid reagents) to perform the aldol-dehydration reaction which would not be compatible with acid or base sensitive groups; ii) the problems associated with the low yielding, non flexible and non versatile strategy to synthesise the polyketide\textsuperscript{25} starting materials. Our main goal was focused on solving these two issues.

1.6 Background on (S)-Zearalenone (6)

Zearalenone (6) (Figure 6) is a secondary metabolite isolated in 1962 from the microfungi \textit{Fusarium graminearum}.\textsuperscript{19} It led to vaginal eversion in female animals and the growth of mammary glands in both male and female animals.\textsuperscript{5} It was later shown that the estrogen agonistic properties of zearalenone (6) were the product of a direct interaction on the estrogen receptor in competition with 17-estradiol\textsuperscript{32} and that the macrocycle of zearalenone was able to adopt a conformation which mimics that of the steroid.\textsuperscript{33} The anabolic properties of Zearalenone and its derivatives have been used as a bovine growth stimulant and marketed under the trade name Ralgro\textsuperscript{®}. Zearalenone is a mycotoxin which has also been shown to have antibacterial properties.\textsuperscript{34,35} Urry \textit{et al.} confirmed the structure of zearalenone\textsuperscript{36} and it is considered the primary member of the \(\beta\)-resorcylic acid lactones (RALs) family. Today zearalenone is manufactured industrially \textit{via} fermentation.

![Figure 6. (S)-Zearalenone (6).](image-url)
The widespread interest in zearalenone’s anabolic properties stimulated a number of syntheses of this molecule with the first synthesis reported in 1968.\textsuperscript{37} It has also served as a testing ground for new cyclisation methodologies as exemplified by the development of the Corey–Nicolaou macrolactonization,\textsuperscript{38} Masamune’s thioester-lactonization,\textsuperscript{39} and more recently the ring-closing metathesis.\textsuperscript{40}

![Scheme 8. Conventional starting materials for zearalenone (6) synthesis.](image)

Conventional retrosyntheses of zearalenone (6) divide the molecule into two portions: an aromatic moiety and a functionalised aliphatic chain, both of which must be prepared and then joined appropriately. To date, several total syntheses of both racemic and naturally occurring (S)-(−)-zearalenone (6) have been completed. All methods use readily available resorcylic ester 51 or orsellinic ester 11 derivatives as starting materials. This in itself presented problems due to low yielding functionalisation of these commercially available aromatic molecules (Scheme 8).

These syntheses have employed three main strategies: final stage macrolactonisation,\textsuperscript{41,42} intramolecular alkylation of stabilised carbanions\textsuperscript{43-46} and most recently metal-catalysed C=C bond formation (Figure 7).
Our biomimetic strategy led us to consider intermediate 7 two synthons. 

Figure 7. Strategies in the synthesis of zearalenone (6).

Unfortunately, deprotection of the phenol groups was found to be low yielding (50-55%). Further problems were encountered in the macrolactonisation and esterification reactions. The carboxyl group is deactivated and sterically hindered by the phenol ring, reducing reactivity and hence affording poor yields.

1.7 Retrosynthetic Analysis of (S)-Zearalenone (6)

Our biomimetic strategy led us to consider intermediate 7 which can be obtained with two synthons 54 and 55 via a late-stage esterification/aromatization reaction followed by ring-closing metathesis (Scheme 9).

Scheme 9. Retrosynthetic strategy for the construction of (S)-zearalenone (6).
In order to perform the esterification/macrolactonisation a new strategy was required. Although successful in a multitude of natural product syntheses containing macrolides, the Corey-Nicolaou double activation technique,\textsuperscript{38} the Masamune method,\textsuperscript{39} the Mukaiyama strategy,\textsuperscript{48} the Keck method\textsuperscript{49} and the Yamagushi activation\textsuperscript{50} were not adopted due to incompatibility with the acid/base sensitive polyketide intermediate \textsuperscript{54}. In addition all the aforementioned methods share an activated carboxyl derivative in their methodology, usually built from a carboxylic acid. However it is known that acetoacetic acid \textsuperscript{56} decomposes at a moderate rate to acetone \textsuperscript{57} and carbon dioxide\textsuperscript{51} (Scheme 10). The acetoacetic acid \textsuperscript{56} has a half-life of 140 minutes at 37 °C in water.

\begin{center}
\textbf{Scheme 10. Acetoacetic acid decomposition in water.}
\end{center}

It would therefore be advantageous to incorporate a masked, activated carbonyl functionality that would be compatible with a variety of transformations, and when unmasking would generate the active species under mild, neutral conditions. In this context Boeckman developed a method relying on the interesting property of dioxinone containing \textsuperscript{58} which undergoes a retro-hetero Diels Alder reaction at high temperature to form an acetylketene \textsuperscript{59} which can be trapped \textit{in situ} by a hydroxyl group to reveal the macrolactone \textsuperscript{60} in good yield (Scheme 11).\textsuperscript{52}

\begin{center}
\textbf{Scheme 11. Boeckman macrolactonisation.}
\end{center}
Consequently synthon 54 could be generated from the thermal decomposition of 12. The synthetic route to alcohol 13 has already been developed within the Barrett group via acetal protection of ketone 61 obtained from the “cleavage” of lactone 62 using a Grignard derived from 5-bromo-1-pentene. The diketo-dioxinone derivative 12 could be obtained via a Mukaiyama aldol reaction of aldehyde 63 and the silyl enol ether 64 of dioxinone 8 (Scheme 12).

![Scheme 12. Retrosynthesis of compounds 13 and 12.](image)

1.8 Brief Review on Keto-Dioxinone and Diketo-Dioxinone

In order to synthesise intermediate 12 a good understanding of dioxinone chemistry was necessary. The following section will attempt to highlight developments in dioxinone chemistry roughly following the timelines of their discoveries. To make the reading of this PhD thesis easier, 2,2,6-trimethyl-4H-1,3-dioxin-4-one (8) will be referred to as dioxinone or diketene acetone adduct, 2,2-dimethyl-6-(2-oxopropyl)-4H-1,3-dioxin-4-one (16) will be also called keto-dioxinone and 1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)pentane-2,4-dione (10) will be defined as diketo-dioxinone or diketone (Figure 8).
1.8.1 Synthesis of dioxinone (diketene acetone adduct)

The earliest report of the formation of 1,3-dioxinone 8 was published by Naylor in 1948.\(^\text{58}\) He reported the formation of a product with a molecular formula C\(_7\)H\(_{10}\)O\(_3\) in low yield from the reaction of ketene (65) with acetone catalysed by zinc chloride (Scheme 13).

![Scheme 13. First synthesis of dioxinone 8.](image)

Five years later, Carroll and Bader carried on the research and synthesised several 1,3 dioxinone adducts from diketene (66) and various ketones; for example refluxing a solution of diketene (66) in acetone with a catalytic amount of p-toluenesulfonic acid gave dioxinone 8 (Scheme 14).\(^\text{59}\)

![Scheme 14. Synthesis of dioxinone 8.](image)

In 1980, Andreichikov and co-workers have developed a strategy to synthesise substituted dioxinone 69 from furan-2,3-dione 67 and cyclohexanone (68).\(^\text{60}\) They
reported that refluxing these compounds in benzene led to intermediate 69 in 92% yield (Scheme 15).

![Scheme 15. Synthesis of substituted dioxinone 69.]

Soon after Sato et al. developed new synthetic routes to build substituted dioxinone 72. For example treatment of 2-methyl-3-oxobutanoic acid (70) with prop-1-en-2-yl acetate (71) under acidic conditions gave, in 55% yield, 2,2,5,6-tetramethyl-4H-1,3-dioxin-4-one (72). The yield of the reaction was improved by using acetone (57) instead of ester 71 and by using tert-butyl 2-methyl-3-oxobutanoate (73) instead of acid 70 (Scheme 16).  

![Scheme 16. Synthesis of substituted dioxinone 72.]

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Hyatt reported that refluxing isopropenyl acetoacetate (74) with a catalytic amount of p-toluenesulfonic acid in toluene gave dioxinone 8. They also observed that the presence of a catalytic amount of acid was essential for the reaction to proceed (Scheme 17).

![Scheme 17. Synthesis of dioxinone 8 under Hyatt’s conditions.](image)

In 1987, Winkler et al. developed a new method for the synthesis of polysubstituted dioxinone using anisyl ketoesters. For example, reacting anisyl cyclohexanone carboxylate 75 with TFAA and TFA in acetone gave, after 12h, dioxinone 76 in 95% yield (Scheme 18).

![Scheme 18. Synthesis of dioxinone 76 under Winkler’s conditions. TFAA = trifluoroacetic anhydride.](image)

In 1984, Sato and co-workers reported an original way to synthesis functionalised diketene acetone adduct 78. Refluxing compound 77 in acetone gave dioxinone 78 in 99% yield. It was thought that thermolysis of the acylated Meldrum acid 77 initiates the formation of a transient acylketene which could then participate in a hetero-Diels-Alder reaction with acetone to give dioxinone 78 (Scheme 19).
1.8.2 Mechanism of thermolysis

In 1953, Carroll and Bader reported that diketene acetone adduct 8 can react with hydroxyl groups under acid catalysis to reveal acetoacetate compounds; for example refluxing a mixture of diketene acetone adduct 8 with a trace of p-toluenesulfonic acid in 1-butanol afforded n-butyl acetoacetate 79 (Scheme 20).\(^\text{59}\)

\[
\begin{align*}
\text{8} & \xrightarrow[p-TsOH, n-BuOH, \Delta]{95\%} \text{79}
\end{align*}
\]


After being largely ignored for over 20 years, the thermolysis mechanism of dioxinone 8 was only suggested for the first time in 1976 by Jager and Wenzelburger when they observed the formation of 1,3 oxazines 81 whilst diketene acetone adduct 8 was refluxing with isocyanate 80.\(^\text{65}\) They postulated that high temperature induced a retro-hetero-Diels-Alder reaction, to form \textit{in situ} acylketene 82 which can then take part in a hetero-Diels-Alder reaction with isocyanate 80 to give 1,3 oxazines 81 (Scheme 21).
In 1984, further evidence of the mechanism was provided by Hyatt et al.\textsuperscript{66} They reported that in the absence of a nucleophile, thermolysis of dioxinone 8 led to the hydroxypyranone 83 in good yield. A dimerisation of two molecules of acetylketene 82 via a hetero-Diels-Alder reaction was postulated (Scheme 22).

They also reported that it was unnecessary to add a base or acid to the reaction simply to perform the acetoacetylation. The $\beta$-keto acid derivate 84 can be obtained in high yield, by refluxing dioxinone 8 in xylene in the presence of a nucleophile such as an alcohol, amine or thiol to provide respectively $\beta$-keto esters, $\beta$-keto amides or $\beta$-keto thio esters. Since then, the mechanism of acetoacetylation has been extensively

\textbf{Scheme 21.} Formation and trapping of acylketene 82 with isocyanate 80.

\textbf{Scheme 22.} Thermolysis of 1,3-dioxinone 8 in absence of nucleophile.
studied and observations confirm the theory of the formation of an acetylketene 82 as an intermediate, which can be trapped in situ by a nucleophile to reveal the β-keto acid derivative 84. Mechanistic studies have been comprehensively reviewed and will not be discussed in detail (Scheme 23). 67

Scheme 23. Mechanism of the acetoacetylation reaction. Nu = R-O, R-NH or R-S.

1.8.3 Synthesis of keto-dioxinone (dimethyl-oxopropyl-dioxinone)

In 1981, Smith 68 and co-workers observed that the addition of alkyl iodide 86 to the kinetic extended lithium enolate of the dioxinone 8 gave a mixture of α and γ-alkylated products 87 and 88 respectively, in a ratio of 2:3. Alternatively, in 1991, Kaneko and Sato discovered that when dioxinone 8 was treated with one equivalent of lithium diisopropylamide and hexamethylphosphoramidate, followed by the addition of 0.5 eq. of chloroacetyl chloride (89), a selective electrophilic addition on the γ-position of the lithium enolate of dioxinone 85 was obtained in 65% yield to give α,γ-dibromo-β-methyldioxinones 86. Kaneko and Sato achieved the synthesis of the chloroketo-dioxinone 90 as a precursor for the enantioselective synthesis of (S)- and (R)-6-(2,3-dihydroxypropyl)-1,3-dioxin-4-ones 91. 69
Scheme 24. First synthesis of a keto-dioxinone intermediate.

Using half of an equivalent of the acyl halide 92 to synthesise 6-(2-oxoalkyl)dioxinones 94, was reported essential to avoid the formation of over O-acylation; for example, treatment of 8 with lithium diisopropylamide, followed by addition of one equivalent of benzoyl chloride 92 gave product (Z)-93 as the only product in 43% yield, whereas treatment of 8 with 0.5 mol equivalent of benzoyl chloride 92 gave selectively ketodioxinone 94 in 48% yield. The use of acetic anhydride instead of acetyl chloride did not improve the overall yield (Scheme 25).53
Scheme 25. Importance of the quantity of acyl chloride 92 engaging in the acylation reaction.

Having this intermediate 94 in hand Sato et al. carried on research. When intermediate 94 was heated in toluene for 10 minutes in the absence of a nucleophile, 2-pyrone 96 was isolated in 71% yield. The proposed mechanism for the cyclisation event is shown in Scheme 26.

Scheme 26. Mechanism of the formation of 2-pyrone 96.
It is thought that ketene $95a$, formed via a hetero-Diels-Alder, is in equilibrium with both ketene $95b$ and $95c$. The mechanistic pathway goes through intermediate $95c$ in order to form pyrone $96$. Indeed, a 6-exo-dig closure will be more favoured than a 6π electrocyclic cyclisation.

In 2005, Katritzky et al. proposed an alternative method to improve the yield of electrophilic addition onto the lithium enolate of dioxinone by using acylbenzotriazoles instead of acyl halides. Benzotriazole derivatives are activated amides, easier to handle and more acid functional group tolerant than acyl chlorides. For example using this strategy 2,2-dimethyl-6-(2-oxo-2-phenylethyl)-4H-1,3-dioxin-4-one ($94$) was obtained in 65% yield using benzotriazole derivative $97$ (Scheme 27).

![Scheme 27. Improvement of the synthesis of 94. Bt = benzotriazolyl.](image)

This methodology does, however, suffer from some limitations. For example, during the reaction between 1-((1H-1,2,3-benzotriazol-1-yl)-2-(phenylsulfanyl)-1-ethanone ($98$) and the lithium enolate of dioxinone $8$, none of the desired keto-dioxinone was isolated. However, both unreacted dioxinone $8$ and $N,N$-diisopropylacetamide $100$ (41% yields) were afforded (Scheme 28). The proposed mechanism for the formation of $100$ is shown in Scheme 30. They presume that the acidic α-hydrogen in $98$ was deprotonated by the lithium enolate of dioxinone $8$ to form a transient ketene $99$. This reactive intermediate could then react with $N,N$-diisopropylamine to yield acetamide $100$. 

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Soon after, Devadas and co-workers were able to avoid this issue by using LiHMDS as a less nucleophilic base in order to form the lithium enolate of dioxinone 8. Using this strategy, they succeeded to synthesise keto-dioxinone 102 using acid chloride 101. This intermediate was used to synthesis pyridone 103 which is a modulator of p38 MAP kinase (Scheme 29).

In 2003, Tadano and co-workers developed an alternative method to synthesise dimethyl-oxoalkyl-dioxinones employing a two step procedure. The strategy involves a vinylogous Mukaiyama aldol reaction of the silylenol ether of dioxinone 105 with aldehyde 104 to give an alcohol, followed by Dess-Martin oxidation to give the desired keto-dioxinone 106. The method described above was successfully utilized in the total synthesis of (+)-macquarimicin (108). Intermediate 107 was obtained via a
Stille coupling as a key step. The natural product 108 was synthesised from 107 using an intramolecular Diels-Alder as the main transformation (Scheme 30).

\[
\begin{align*}
&1) \quad \text{OTBS} \quad \text{CHO} \\
&2) \quad \text{BF}_3\text{OEt}_2, -78^\circ\text{C} \\
&\text{104} \\
&\text{105} \\
&\text{106}
\end{align*}
\]

\[\text{OMPM} \]

\[\text{MeO}_2\text{CO} \]

\[
\begin{align*}
&\text{TBSO} \quad \text{OTBS} \\
&\text{107} \\
&\text{(+)-macquarimicin A (108)}
\end{align*}
\]


Closely related to the previous method Omura and co-workers have described a strategy to form keto-dioxinone 111 which was a key synthetic intermediate for the total synthesis of a novel NADH-fumarate reductase inhibitor, verticipyrone (114).\(^{73}\)

Dioxinone 109 was successfully converted into 2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones (111) in 64% yield over two steps. The synthesis was accomplished using an aldol addition of acetaldehyde (110) to the γ-position of the lithium enolate (the α-position was substituted and therefore un-reactive) followed by a Swern oxidation to afford ketone 111. Treatment with sodium methoxide in methanol gave 112, followed by a regioselective O-methylation with methylfluorosulfonate to provide methoxy-γ-pyrone 113 which is a key intermediate in the natural product verticipyrone (114) (Scheme 31).
Kiegiel et al. were the first group to publish a synthesis of keto-ester-dioxinone 117. When heating bisdioxinone 116 in tert-butanol under controlled conditions, mono-tert-butyl ester 117 was obtained in 57% yield. Compound 116 was synthesised from both malonyl chloride 115 and ketene 65 in acetone providing 116 in 60% yield (Scheme 32).
1.9 Summary of Objectives

Due to the synthetic issues reported in the synthesis of natural product 15G256β (5), a new biomimetic approach inspired by Harris’ work was suggested which would consist of a late stage construction of the resorcylic acid unit. In order to develop this new methodology, synthesis of (S)-zearalenone (6) will serve as a testing ground. Two main issues need to be solved: a flexible synthesis to build polyketides and milder conditions to construct the aromatic ring.
CHAPTER TWO:
(S)-ZEARALENONE
As described in the previous chapter, two main intermediates, alcohol 13 and diketo-dioxinone 12 were required to synthesise the natural product zearalenone (6). We will first discuss the synthesis of alcohol 13, then we will move on to the formation of diketo-dioxinone 12 (Figure 9).

![Figure 9. Alcohol 13 and diketo-dioxinone 12.](image)

### 2.1 Synthesis of Alcohol 13

#### 2.1.1 Previous syntheses of alcohol 13 analogues

In 1992, Kitching and co-workers\(^7\) reported the racemic synthesis of alcohol 120. Treatment of δ-hexanolate 62 with Grignard reagent 119 gave unpurified ketone 120 in 75% yield. The slow addition of the Grignard 119 to lactone 62 was performed at low temperature to avoid any further addition to product 120 (Scheme 33). This alcohol 120 was reported to be acid sensitive and decomposed during column chromatography.

![Scheme 33. Reagents and conditions:](image)

**Scheme 33. Reagents and conditions:** i) Mg, Et\(_2\)O, 40 °C, 1 h; ii) 119, THF, –78 °C, 2 h, 75%.
Furstner et al.\(^{40}\) reported the synthesis of chiral alcohol 127 in a six step procedure, from commercially available (R)-propylene oxide 121. Ring opening with vinylmagnesium bromide in the presence of catalytic amounts of CuCl(COD) gave alcohol 122 which was immediately protected as TBS-ether 123 under standard conditions. Hydrozirconation of the double bond followed by reaction with tert-butyl isocyanide and iodine, as described by Buchwald et al.\(^{76}\), delivered nitrile 124 in 77% yield. Treatment of 124 with 4-pentenylmagnesium bromide afforded ketone 125, which was converted into (R)-127 by two routine protecting group manipulations (Scheme 34).

**Scheme 34.** Reagents and conditions: i) vinylmagnesium bromide, CuCl(COD) (10 mol%), THF, -78 °C to RT; ii) TBSCI, imidazole, DMF, RT, 16 h, 63% (over 2 steps); iii) (a) Cp₂ZrHCl, CH₂Cl₂, RT, 2 h; (b) t-BuNC, RT, 2 h; (c) I₂, benzene, 0 °C, 30 min, 77%; (vi) 4-pentenylmagnesium bromide, Et₂O, reflux, 4 h, 68%; (v) ethylene glycol, p-TsOH·H₂O cat., benzene, reflux, 12 h, 73%; (vi) n-Bu₃NF, THF, RT, 24 h, 89%.

In 1991, Keinan et al.\(^{77}\) synthesised alcohol 134, which has structural similarity to alcohol 13. Synthesis of chiral alcohol 134 involved the stereoselective reduction of diketone 130 with *Thermoanaerobium broki* alcohol dehydrogenase (TBADH). This enzyme is selective for the less hindered ketone. The product, acetal 134, is then utilised in the total synthesis of (S)-(−)-zearalenone resulting in an optical purity exceeding 99.5% (Scheme 35).
Scheme 35. Reagents and conditions: i) a) K$_2$CO$_3$, acetone-DMF, reflux, 24 h; b) aq. KOH (3%), EtOH, 80 °C, 2 h; c) aq. HCl (3 M), 20 °C, 1 h; ii) TBADH, propan-2-ol, pH 7.9 (phosphate buffer), 40 °C, 48 h; iii) Ac$_2$O, pyridine, 60 °C, 24 h; iv) ethylene glycol, PPTS, PhH, reflux; v) KOH (2 M), MeOH, 20 °C, 3 h.

2.1.2 First attempted synthesis of alcohol 13

The first attempted synthesis of alcohol 13 was inspired by the first method described above (Scheme 33). Alcohol 120 was synthesised by reaction of δ-hexanolactone 62 with Grignard reagent 119, prepared in-situ from 5-bromo-1-pentene (118). $^1$H-NMR showed that the crude product 120a exists in approximately 30% as its cyclised hemi-acetal form 120b. Alcohol 120 proved unstable to chromatography, even on neutral alumina, therefore the next step was attempted without purification. Oxidation with DMP furnished the diketone 135. Treatment of 135 with Thermoanaerobium brokii alcohol dehydrogenase (TBADH) was unsuccessful and gave a complex mixture (Scheme 36).
Scheme 36. Reagents and conditions: i) Mg, Et₂O, 40 °C, 1 h; ii) 119, THF, −78 °C, 2 h; iii) DMP, CH₂Cl₂, 76% over 2 steps; iv) TBADH, propan-2-ol, pH 7.9 (phosphate buffer), 40 °C, 48 h.

2.1.3 Second strategy for the synthesis of alcohol 13 with CAL-B

Based on Kitching and Keinan’s work, Barrett and Major⁷⁷ developed a synthesis of alcohol 13 via a kinetic resolution using enzyme CAL-B.⁷⁸-⁸⁰ Candida antarctica lipase B (CAL-B) is a serine esterase which displays enantioselectivity toward secondary alcohols.

Kazlauskas et al. have reported that commercially available CAL-B can perform an enantioselective transesterification from vinyl acetate 137 to racemic secondary alcohol 136.⁸¹ The transesterification is an equilibrium. However, the acetaldehyde (110) formed during this reaction, evaporates and hence pulls the equilibrium to the right (Scheme 37).

Scheme 37. General scheme reporting the mode of action of enzyme CAL-B (R¹ < R²).
This enzyme can be therefore used in the kinetic resolution of alcohol 140, by eliminating the undesired chiral alcohol by selectively acetylating the (R)-alcohol 127 to ester 141 (Scheme 38).

Scheme 38. Suggested kinetic resolution of alcohol 140 with the enzyme CAL-B.

Following Barrett and Major’s procedure, alcohol 120, previously described, was acetylated with acetic anhydride in the presence of pyridine to provide intermediate 142. Protection of the ketone in 143 with ethylene glycol and PPTS followed by basic hydrolysis of the acetate moiety afforded the desired alcohol 140 as a racemic mixture (Scheme 39). A straightforward ketone protection from 120 was unsuccessful, only starting material was recovered.

Scheme 39. Reagents and conditions: i) Ac₂O, pyridine, 80 °C, 24 h, 71% over 2 steps; ii) ethylene glycol, PPTS, PhH, 120 °C, 18 h, 87%; iii) KOH (3M aq.), MeOH, 20 °C, 3 h, 98%.
A kinetic resolution of alcohol 140 was then carried out with the enzyme CAL-B. In order to recover the desired alcohol 13 in good yield, the following strategy was applied (Scheme 40): the first step allowed the formation of the (R)-acetate 141 in good enantiomeric excess. (S)-Alcohol 144 was also obtained, but with a low enantiomeric excess. However, after a further three hours treatment with CAL-B, an enantiomeric excess greater than 99% was obtained along with a mixture of acetylated products 145. The enantiomeric purity of (S)-alcohol 13 was determined by chiral GC* (optical rotation for S-(+)-13 was \([\alpha]_D^{25} = +6.7 \) (c 3.14 CH₂Cl₂) and in the literature⁴⁰ optical rotation for R-(−)-127 is \([\alpha]_D^{25} = -6.8 \) (c 1.02 CH₂Cl₂)).

![Scheme 40](image)

**Scheme 40. Reagents and Conditions:** i) 0.01 eq. CAL-B, 3 eq vinyl acetate, hexane, 35 °C, 80 min, 46% conversion into acetate 141 ; ii) 0.01 eq. CAL-B, 3 eq vinyl acetate, hexane, 35 °C, 3 h; 38% of alcohol 13 over two steps.

---

2.2 Synthesis of the Dioxinone Derivative 12

As planned in the retrosynthetic study (Scheme 12), dioxinone derivate 12 should react with the previously described (S)-alcohol 13. A synthesis of diketo-dioxinone 12 (Figure 10) is described herein.

![Figure 10. Dioxinone derivate 12.](image1)

With the aim of building this unprecedented class of intermediates, we required a model system that displays similar chemical reactivity to intermediate 12. It was envisaged that methylketo-dioxinone 10 (Figure 11) could act as a suitable model for synthetic studies. Before presenting the synthesis of intermediate 10, it is necessary to highlight some interesting reactivity of dioxinone 8.

![Figure 11. Dioxinone derivate 10.](image2)

2.2.1 Studies towards the synthesis of diketo-dioxinone 10

2.2.1.1 Reactivity of dioxinone 8 and keto-ester dioxinone 156

As previously mentioned in the introduction (Section 1.8.3), Smith\textsuperscript{68} reported the unselective addition of alkyl halides to the extended enolate of dioxinone to give a mixture of $\alpha$ and $\gamma$-alkylated products. Alternatively, according to Sato et al.,\textsuperscript{53} C-acylation using acyl chloride (0.5 equivalents) gave selective addition to the $\gamma$-
position. In attempts to optimise the yields of additions to the γ-position of dioxinone, we decided to investigate the unreported addition of an aldehyde to the dioxinone extended enolate (Scheme 41). Treatment of dioxinone 8 with LiHMDS at -78 °C gave lithium enolate 85. Addition of one equivalent of acetaldehyde (110) leads to a carbonyl addition on the α-position to give dioxinone 146 in 32% yield; however using 2.4 equivalents of acetaldehyde (110), 42% of alcohol 146 was isolated as well as 12% of diol 147. In addition, we examined the effects of the number of equivalents of acyl chloride used in the C-acylation of intermediate 85. With one equivalent of acetyl chloride (148), a double acylation was observed to give ester 149 which is consistent with Sato’s observation.53 Upon addition of 0.5 equivalents of acylchloride 148, only keto-dioxinone 16 was obtained in 55% yield (Scheme 41). A decrease in yield was observed when only 0.3 equivalents of electrophile 148 was used; only 42% of ester 16 was isolated. These results gave us a more accurate idea of the reactivity of dioxinone 8, and consequently helped us in our future retrosynthetic studies.

Scheme 41. Reagents and Conditions: i) LiN(SiMe$_3$)$_2$, THF, -78 °C, 50 min; ii) acetaldehyde (110), THF, RT, 2 h, 42%; iii) acetyl chloride (148) 1 eq., THF, -78 °C, 30 min, 25%; iv) acetyl chloride (148) 0.5 eq., THF, -78 °C, 30 min, 55%.
Whilst investigating the reactivity of dioxinone 8, it was found that the addition of 0.3 equivalents of commercially available methyl malonyl chloride (150) to the dioxinone enolate 85 afforded ester-keto-dioxinone 151 in 61% yield. However with 0.8 equivalents of the electrophile 150, only starting material was recovered (Scheme 42). As the number of equivalents of methyl chloroformyl acetate (150) seemed to be crucial for the reaction to proceed, a plan was envisaged, using deprotonated dioxinone 8 as a nucleophile and acid chloride 155 as the electrophile to form dioxinone derivative 156. This intermediate was an important synthetic intermediate for one of our routes towards diketo-dioxinone 10 (see section 2.2.1.5). Allyl ester 155 was synthesised via a two step procedure. The first step was the thermolysis of Meldrum’s acid (152) with allyl alcohol (153) to afford the known allyl ester 154 in good yield. The second step was the acid chloride 155 formation under standard conditions which was used in the next step without further purification. Several experimental conditions were screened to attempt the generation of keto-ester dioxinone 156. The results are presented below (Scheme 42, Table 1).

Scheme 42. Reagents and Conditions: i) LiN(SiMe3)2, THF, -78 °C, 30 min; ii) 150 (0.3 eq.), THF, RT, 8 h, 61%; iii) Prop-2-en-1-ol (153), 80 °C, 12 h, 30%; iv) (COCl)2, CH2Cl2, 0 °C to RT, 3 h; v) LiN(SiMe3)2, THF, -78 °C, 30 min; vi) conditions see table 1.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>155 (1 eq.), 4.10^{-2} M, THF, RT, 8 h</td>
<td>8 recovered</td>
</tr>
<tr>
<td>2</td>
<td>155 (0.8 eq.), 4.10^{-2} M, THF, RT, 8 h</td>
<td>Trace of 156</td>
</tr>
<tr>
<td>3</td>
<td>155 (0.4 eq.), 4.10^{-2} M, THF, RT, 8 h</td>
<td>52% of 156</td>
</tr>
<tr>
<td>4</td>
<td>155 (0.33 eq.), 4.10^{-2} M, THF, RT, 8 h</td>
<td>58% of 156</td>
</tr>
<tr>
<td>5</td>
<td>155 (0.3 eq.), 4.10^{-2} M, THF, RT, 8 h</td>
<td>61% of 156</td>
</tr>
<tr>
<td>6</td>
<td>155 (0.2 eq.), 4.10^{-2} M, THF, RT, 8 h</td>
<td>57% of 156</td>
</tr>
<tr>
<td>7</td>
<td>155 (0.3 eq.), 2.10^{-1} M, THF, RT, 3 h</td>
<td>53% of 156</td>
</tr>
</tbody>
</table>

Table 1. Different reaction conditions tested to synthesis diketo-dioxinone 156.

Under optimised conditions, using 3.5 equivalents of dioxinone 8, ester-diketo dioxinone 156 was obtained in 61% yield (Table 1, Entry 5). Whilst only two equivalents of dioxinone enolate 85 were needed to prepare keto-dioxinone 16, three equivalents of intermediate 85 were necessary to obtain keto-ester dioxinone 156. It was thought that kinetic lithium dioxinone enolate 85 was able to deprotonate the α-position of acyl chloride 155 to form a highly reactive ketene 157 which could quickly react with another lithium enolate 85 to afford intermediate 158. Subsequently another dioxinone derivative 85 could deprotonate the newly formed keto-dioxinone 158. A higher concentration might also avoid any second additions to product 159 (Scheme 42, Table 1, entry 7 and Scheme 43).
Scheme 43. Proposed mechanism of formation of keto-ester-dioxinone 156.

Having reported some interesting dioxinone 8 reactivity properties, we can move on to the synthesis of intermediate 10. Throughout the entirety of my research, diketo-dioxinone 10 was found to be an important compound and was frequently used as a model system for the optimisation of certain steps (Section 2.3), a key intermediate for natural product synthesis (Chapter 3) and also a building block for the synthesis of polysubstituted heteroaromatic compounds (Chapter 4). The following section will describe different strategies employed to synthesise diketo-dioxinone 10. The description of these different processes will be ordered from the lowest yielding method to the highest and will not follow chronologically. Some of these approaches were discovered in collaboration with co-workers within the Barrett group; when appropriate, their contribution will be recognised in the following section.
2.2.1.2 Attempted synthesis of diketo-dioxinone 10 using diketene (66)

The first attempt was performed by adding diketene (66) to the lithium enolate of dioxinone 8; unfortunately a complex mixture was obtained. In addition, given the fact that diketene (66) was no longer commercially available, this strategy was deemed unsuitable and consequently was abandoned (Scheme 44).

Scheme 44. Reagents and Conditions: i) LiN(SiMe$_3$)$_2$, THF, -78 °C, 30 min; ii) 66 (0.3 eq.), THF, RT, 8 h.

2.2.1.3 Attempted synthesis of diketo-dioxinone 10 using diphenyl-dioxinone 165

The second method relied on the reactions of substituted dioxinones 160. Barrett and Navarro$^{83}$ reported a strategy where they succeeded to modulate the rate of thermolysis of dioxinones by introducing different substituents. They observed the results after 2.5 hours, when alcohol 161 was heated at 75 °C with substituted dioxinones including: strained spiro-fused 163, dimethyl 8, phenyl-methyl 164 and diphenyl 165. The best result was observed with diphenyl-dioxinone 165 (Scheme 45, Table 2). The difference of decomposition speed was thought to be due to the overlap of the phenyl π-system with σ* of the O-CO bond.
Based on those observations, it was decided to use the most reactive diphenylidioxinone 165, which was made from ester 166 and diphenyl ketone 167 (Scheme 46). However, when this intermediate 165 was added to dioxinone lithium enolate of 8, only starting material was recovered after 24 hours (Scheme 46).

Scheme 45. Acylation of alcohol 161 at 75 °C.

<table>
<thead>
<tr>
<th>160 =</th>
<th>163</th>
<th>8</th>
<th>164</th>
<th>165</th>
</tr>
</thead>
<tbody>
<tr>
<td>162, % yield</td>
<td>5</td>
<td>15</td>
<td>55</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 2. Conversion of dioxinones 160 to 162 whilst heating with alcohol 161.

Scheme 46. Reagents and Conditions: i) acetylphenone (167), Ac₂O, H₂SO₄, 0 °C, 15 h, 53 %; ii) LiN(SiMe₃)₂, THF, -78 °C, 30 min; iii) 165 (0.3 eq.), THF, RT, 24 h.
2.2.1.4 Attempted synthesis of diketo-dioxinone 10 using a ketone enol ester

The third trial was based on the reported observation by first Young et al.\textsuperscript{84} and then by Tidwell and co-workers,\textsuperscript{85} who noticed the formation of β-diketones from ketone enol esters via an intermolecular acylation. For example treatment of enol 168 with potassium acetate afforded β-diketone 169 in 63% yield (scheme 47).

![Scheme 47. Synthesis of β-diketone 169 from enol 168.](image)

Following this methodology, addition of two equivalents of lithium diisopropylamide (in place of potassium acetate) to enol 149 (2.2.1.1) failed to give diketo-dioxinone 10, but instead acid 170 was recovered in 12% yield as the major product (Scheme 48). An X-ray of solid 170, provided proof of the predicted structure (Figure 12). The mechanism for the formation of the unexpected side product 170 is still undetermined.

![Scheme 48. Reagents and Conditions: i) LDA (2 eq.), THF, -78 °C to RT, 12%.](image)
2.2.1.5 Attempted synthesis of diketo-dioxinone 10 using allyl ester 156

In 2008, Barrett and Navarro\textsuperscript{77} developed a new strategy to synthesise functionalised diketo-dioxinones based on a Claisen type condensation. The synthesis started with a C-acylation of dioxinone 156 with acyl chloride 171 to give allyl ester 172. Subsequent palladium-catalyzed deallylation-decarboxylation provided the key diketo-dioxinone 173 in 89\% yield (Scheme 49). Using this approach, the marine antifungal agent 15G256\(\beta\) (5) was obtained in 7\% overall yield.

\textbf{Figure 12.} X-ray of intermediate 170.
Scheme 49. Synthesis of the marine antifungal agent 15G256β (5).

Using this method, synthesis of methyldiketo-dioxinone 10 was carried out using allyl ester 156 (synthesis reported section 2.2.1.2) and acetyl chloride 148. Magnesium chloride mediated C-acylation gave dioxinone derivate 174 in 43% yield. Subsequent palladium-catalyzed deallylation-decarboxylation, gave diketo-dioxinone 10 in 40% yield (Scheme 50).

Scheme 50. Reagents and Conditions: i) MgCl₂, Pyridine, CH₂Cl₂, 35 min 0 °C then 148, 0°C to RT, 30 min, 43%; ii) Pd(PPh₃)₄ (4 mol %), morpholine (2 eq.), CH₂Cl₂, 30 min, 0 °C, 40%.

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2.2.1.6 Attempted synthesis of diketo-dioxinone 10 using Weinreb amides

In 2009, Barrett and Poeverlein\textsuperscript{83} found a high yielding strategy to functionalised dioxinone 8. Indeed, treatment of one equivalent of dioxinone 8 with LiHMDS followed by addition of zinc chloride and one equivalent of $N$-acetylimidazole (175), gave keto-dioxinone 16 in 64\% yield. The dianion of 16 was generated using 2.2 equivalents of lithium di-isopropylamide and allowed to react with Weinreb amide 176 to provide the required diketo-dioxinone 173 (70\%). They reported that the use of the Weinreb amide 176 as the electrophile was found to be essential to avoid any $O$- and/or double $C$-alkylations. The method described above was successfully utilized in the synthesis of ent-W1278A (177, $n = 2$) (Scheme 51).

Scheme 51. Synthesis of ent-W1278A (177, $n = 2$).
Following the same strategy developed by Barrett and Poeverlein, diketo-dioxinone 10 was synthesised in 69% yield from ketodioxinone 16 (previously described in 2.2.1.1) and commercially available Weinreb amide 178 (Scheme 52).

![Scheme 52](image)

**Scheme 52. Reagents and Conditions:** i) LDA (2 eq.), THF, -78 °C, 30 min; ii) 178 (0.5 eq.), THF, -40 °C, 1 h, 69%.

2.2.1.7 Attempted synthesis of diketo-dioxinone 10 using benzotriazole intermediates

In 2007, an efficient synthesis was developed to give dioxinone 10.86 This compound was synthesised by thermolysis of commercially available dioxinone 8, which underwent a retro-Diels–Alder reaction at 90 °C to form acyl-ketene 82, which was trapped with benzotriazole 179 to form amide 9 in quantitative yield. Subsequent crossed Claisen condensation via reaction of the lithium enolate from dioxinone 8 with amide 9 gave diketo-1,3-dioxinone 10 as a 5:95 mixture of keto–enol tautomers in 53% yield over two steps (Scheme 53). This synthesis is easily scalable, the most convergent, and the highest yielding method of all the other strategies reported.
Scheme 53. Reagents and Conditions: i) PhMe, 179, 90 °C ii) LiN(SiMe3)2, THF, -78 °C, 30 min; iii) 9 (0.3 eq.), THF, RT, 8 h, 53%.

Having effectively built the model diketodioxinone 10 via different methods, construction of intermediate 12 (Figure 13), necessary for the synthesis of the natural product zearalenone (6), was the next challenge. Different routes to this compound will be discussed in the next section, with the highest yielding route being described last.

Figure 13. Dioxinone derivative 12.

2.2.2 Attempted synthesis of diketo-dioxinone 12 using allyl ester 156

The route using allyl ester intermediate 156 (Section 2.2.1.5) was unsuccessful. Treatment of compound 156 with crotonoyl chloride (180) did not afford ester 181 (Scheme 54).
Following this disappointing result, a modified route to form dioxinone \( 12 \) was envisaged. C-acylation of allyl ester \( 156 \) with acid chloride \( 171 \) followed by palladium catalysed deallylation gave intermediate \( 173 \) in 74% yield over two steps. Deprotection gave alcohol \( 182 \) in 92% yield. Different methods were attempted to perform the elimination reaction to give intermediate \( 12 \), but none of them were successful (Scheme 55, Table 3). Consequently another method was investigated.

**Scheme 54.** Reagents and Conditions: i) \( \text{MgCl}_2 \), pyridine, \( \text{CH}_2\text{Cl}_2 \), 30 min, \( 0^\circ \) C to RT, 1 h.

**Scheme 55.** Reagents and Conditions: i) \( \text{MgCl}_2 \), Pyridine, \( \text{CH}_2\text{Cl}_2 \), 35 min, \( 0^\circ \) C to RT, 30 min, 83%; ii) \( \text{Pd(PPh}_3)_4 \) (4 mol %), morpholine (2 eq.), \( \text{CH}_2\text{Cl}_2 \), \( 0^\circ \) C, 30 min, 89%; iii) \( \text{HF} \), pyridine, THF, RT, 6 h, 92%; iv) conditions see table 3.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Burgess dehydrating reagent&lt;sup&gt;87&lt;/sup&gt;, THF, 18 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>Martin’s sulfurane dehydrating reagent&lt;sup&gt;88&lt;/sup&gt;, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, 3 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>MsCl, Et&lt;sub&gt;3&lt;/sub&gt;N, Et&lt;sub&gt;2&lt;/sub&gt;O, RT, 8 h&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 3. Different reaction conditions tested to synthesise diketo-dioxinone 12.

2.2.3 Attempted synthesis of diketo-dioxinone 12 using benzotriazole intermediates

Inspired by the benzotriazole strategy used to build diketone 10 (Section 2.2.1.7), it was envisaged that the reactive intermediate 12 could be prepared from dioxinone 184. As compound 184 was unprecedented in the chemical literature, it was decided to make it from an acylated Meldrum’s acid 185 (Scheme 56). This method to prepare substituted dioxinones was reported by Sato et al.<sup>64</sup> (Section 1.8.1).

Scheme 56. Retrosynthesis study to build diketo-dioxinone 12 via intermediate 184.
C-acylation of Meldrum’s acid (152) was performed using crotonoyl chloride (180) under basic conditions. Subsequent thermolysis of intermediate 185 in acetone gave unsaturated dioxinone 184 in 30% yield over two steps. This compound was then heated at 90 °C with benzotriazole 179 to form the highly reactive amide 183. Crossed Claisen condensation via reaction of the lithium enolate of dioxinone 8 with amide 183 gave diketo-dioxinone 12 in 14% yield over two steps (Scheme 57). The overall yield is low compared to the one obtained during the formation of methyldiketo-dioxinone 10 using this methodology (Section 2.2.1.7). The difference in results was attributed to a possible 1-4 addition of benzotriazole to 183.

Scheme 57. Reagents and Conditions: i) 180, pyridine, CH₂Cl₂, 0 °C, 2 h, 48% ii) acetone (57), PhMe, 90 °C, 5 h, 62%; iii) 8, PhMe, 90 °C, 11 h; iv) LiN(SiMe₃)₂, THF, -78 °C, 30 min; v) 183 (0.3 eq.), THF, RT, 8 h, 14%.
2.2.4 Attempted synthesis of diketo-dioxinone 12 using a Mukaiyama aldol reaction and a late step isomerisation

Tadano et al have reported the formation of β-hydroxyketone 106 using a Mukaiyama aldol reaction as a key step (Section 1.8.3). A similar pathway was investigated to make diketodioxinone 12 after isomerisation of intermediate 186 which could be synthesised from aldehyde 187 and the silyl enol ether 64 (Scheme 58).

The known α-chloro-alcohol 190 was synthesised by a Barbier procedure, in the presence of indium, from chloroacetaldehyde 188 and allyl bromide 189, both commercially available. Treatment of intermediate 190 with potassium cyanide and sodium iodide gave the nitrile 191. Protection of the hydroxyl group of 192 and reduction of the resultant silylated product provided aldehyde 193 (Scheme 59).
and dienolate trimethyl-1,3-dioxin-4-one DIBAL-H, PhMe, -52 °C, 2 h, 96%.

Scheme 59. **Reagents and Conditions:** i) 1 eq. In, H₂O, RT, 5h, 94%; ii) 1.5 eq. KCN, 3 eq. NaI, 78 °C, 5 h; iii) 2 eq. TBSCl, 4 eq. imidazole, DMF, 0 °C, 13 h, 81% 2 steps; iv) 1.5 eq. DIBAL-H, PhMe, -52 °C, 2 h, 96%.

A vinylogous Mukaiyama aldol reaction was then performed between aldehyde 193 and dienolate 64 to afford a 1:1 diastereomeric mixture of the dioxinone derivative 194. The dienolate 64 was prepared from the commercially available 2,2,6-trimethyl-1,3-dioxin-4-one 8. Oxidation of 194 with DMP, followed by deprotection of the alcohol gave 196. Deprotection of the silyl group in 196 required the use of hydrofluoric acid in water (Scheme 60). The employment of TBAF did not remove the protecting group. From 194, a straightforward deprotection of the alcohol followed by a double oxidation was not successful.

Scheme 60. **Reagents and Conditions:** i) 1.2 eq. HMPA, 1.1 eq. iPr₂NH, 1.1 eq. n-BuLi, 1.2 eq. TBSCl, -78 °C, 1h, 76%; ii) 1.05 eq. 64, 1.3 eq. BF₃·OEt₂, -78 °C, 45 min, 45%; iii) 2 eq. DMP, CH₂Cl₂, RT; vi) 10 eq. HF (48% aq), RT, 8 h, 51% 2 steps.
Having alcohol 196 in hand, different oxidative methods were then tested to obtain intermediate 197 (Scheme 61, Table 4).

\[
\begin{align*}
\text{HO} & \quad \text{O} \quad \text{O} \\
\text{196} & \quad \text{i} \quad \rightarrow \\
\text{197} & \quad \text{HO} \quad \text{O} \quad \text{O}
\end{align*}
\]

**Scheme 61. Reagents and Conditions:** i) conditions see table 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(COCl)₂, DMSO, CH₂Cl₂, -78 °C, then Et₃N⁹³</td>
<td>product detected</td>
</tr>
<tr>
<td>2</td>
<td>Al(Oi-Pr)₃, acetone⁹⁴</td>
<td>S.M. only</td>
</tr>
<tr>
<td>3</td>
<td>PCC, 4Å molecular sieves⁹⁵</td>
<td>S.M. only</td>
</tr>
<tr>
<td>4</td>
<td>TPAP, NMO, 4Å molecular sieves⁹⁶</td>
<td>product detected</td>
</tr>
<tr>
<td>5</td>
<td>MnO₂</td>
<td>S.M. only</td>
</tr>
<tr>
<td>6</td>
<td>IBX⁹⁷</td>
<td>S.M. + product detected</td>
</tr>
<tr>
<td>7</td>
<td>2 eq. DMP, 0.1 mol/L⁹²</td>
<td>10% of 197</td>
</tr>
<tr>
<td>8</td>
<td>2 eq. DMP, 0.04 mol/L</td>
<td>32% of 197</td>
</tr>
</tbody>
</table>

**Table 4. Different oxidation reagents tested on 197.**

Only DMP was able to produce the desired dioxinone 197. In addition, the concentration was shown to be essential to obtain a good yield. Treatment of 196 with DMP at a concentration of 0.04 mol/L in DCM gave 197 in 32% yield (Table 4, entry 8).
In order to get the desired ketodioxinone 12, it was necessary to isomerise the allylic double bond of 197 into a more stable, unsaturated ketone (Scheme 58). Different strategies were applied unsuccessfully; however an interesting result was spotted.

The first method involved the treatment of 197 with triethylamine\textsuperscript{98} for eight hours in THF under reflux, to give the unexpected resorcylate 198 in a good yield. When the same reaction was carried out for two days product 199 was formed. However, the conversion was not complete (Scheme 62) and the yield of 199 was poor. Even though results were interesting (they will be discussed extensively in chapter 4), a new pathway was investigated to obtain intermediate 12 in good yield.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_62.png}
\caption{Reagents and Conditions: i) 3 eq. Et\textsubscript{3}N, THF reflux, 8 h, 82 \%; ii) 20 eq. Et\textsubscript{3}N, THF reflux, 2 days, 7 \% of 199.}
\end{figure}

\textbf{2.2.5 Attempted synthesis of diketo-dioxinone 12 using a Mukaiyama aldol reaction}

A different strategy for the synthesis of diketone 12 was developed based upon the use of a Mukaiyama-aldol vinylogous addition reaction of the silyl-enolate of dioxinone 64 with the known aldehyde 203\textsuperscript{99} (Scheme 63). The synthesis of aldehyde 203 started
from the aldol reaction of crotonaldehyde (200) and ethyl acetate. The resulting alcohol 201 was protected and then DIBAL-H reduction of the ester 202 gave selectively aldehyde 203. Different Lewis acids were investigated as catalysts for the Mukaiyama-aldol addition (Table 5) and trifluoroboron etherate was found to be the best (Table 5, entry 3) and provided intermediate 204 in 61% yield. DMP oxidation of the secondary alcohol moiety in 204, followed by TBS-deprotection with hydrofluoric acid and a second oxidation of the resultant allylic alcohol gave the desired diketone 12 in 43 % yield from 204. The same optimized conditions described for the oxidation of 196 were again found to be successful.

Scheme 63. Reagents and Conditions: i) EtOAc, LDA, THF, -70 °C, 2 h, 92%; ii) imidazole, TBSCI, CH₂Cl₂ RT, 4 h, 99%; iii) 1.5 eq. DIBAL-H, PhMe, -85 °C, 2.5 h, 90% iv) see table 5 for reagents and conditions; v) 2 eq. DMP, CH₂Cl₂; vi) 10 eq. HF (48% aq), MeCN, RT, 30 min, 82% over 2 steps vii) 2 eq. DMP, CH₂Cl₂, 56%.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result (yield of 204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.05 eq. 64, 1.3 eq. TiCl₄, CH₂Cl₂, -78 °C, 1 h</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>1.05 eq. 64, 1.3 eq. Me₂AlCl, CH₂Cl₂, -78 °C, 1 h</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>1.05 eq. 64, 1.3 eq. BF₃ OEt₂, CH₂Cl₂, -78 °C, 1 h</td>
<td>61%</td>
</tr>
</tbody>
</table>

**Table 5.** Different Lewis acids in the Mukaiyama-aldol addition.

### 2.2.6 Attempted synthesis of diketo-dioxinone 12 using Weinreb amides

Another route to form dioxinone 12 was also investigated using a Weinreb amide intermediate following Poeverlein’s strategy (Section 2.2.1.6). Diketo-dioxinone 12 was obtained in 26% yield, from keto-dioxinone 16 and Weinreb amide 207 (Scheme 64). This strategy showed to be the highest overall yielding method to prepare key intermediate 12.

![Scheme 64](image)

**Scheme 64.** Reagents and Conditions: i) 2 eq. LDA, THF, -78 °C, 30 min; ii) 0.5 eq. 207, THF, -40 °C, 1 h, 26%.

---

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2.3 Aromatisation Studies

Having key intermediates diketo-dioxinone 12 and alcohol 13 in hand, we had to find the most suitable aromatisation conditions for the resorcylic ring construction. An initial set of experiments were conducted on model diketo-dioxinone 10 (Figure 14).

![Dioxinone derivate 10](image)

**Figure 14. Dioxinone derivate 10.**

2.3.1 Aromatisation studies using diketo-dioxinone 10

As previously described (Section 1.8.2), thermolysis of dioxinone 10 in toluene gave a ketene intermediate 208 via a retro hetero-Diels-Alder reaction which was trapped in situ by methanol to give the triketoo-ester 44. Polyketide 44 showed to be a complex mixture of keto and enol tautomers according to $^1$H-NMR spectrum (Scheme 65). Deuterium exchange occurs in methanol-$d_4$, leading to the disappearance of the keto-enol proton in the $^1$H-NMR spectrum. This intermediate 44 was stable at room temperature and although cannot be purified by column chromatography, it was easy to isolate, simply by evaporation of the solvent and was of sufficient purity to use in the next step. It was also found that ester 44 was sensitive to base or acid.

![Scheme 65](image)

**Scheme 65. Reagents and Conditions:** i) 5 eq. MeOH, PhMe, 110 °C, 5 h, quantitative.
With compound 44 in hand, different conditions were applied in attempts to aromatise the product selectively, through an aldol condensation to give a resorcylic acid ring 11 (Scheme 66, Table 6). We will first discuss the temperature and the quantities of base needed to carry out a selective aldol-dehydration reaction and then we will examine milder basic and acidic conditions to perform this aromatisation.

The studies commenced with the use of different buffers as described by Barrett et al. (Section 1.5). Unfortunately, only small traces of the desired resorcylic acid 11 were observed (Scheme 66, Table 6, entries 1-2). As reported by Harris et al., the use of an aqueous solution of potassium hydroxide at 0 °C led to acetophenone 45 as the major product via a Claisen condensation (Table 6, entry 3). However, contrary to what Harris and co-workers have mentioned, it was found that the temperature, and not the presence of water in the reaction, was a crucial parameter to obtain aromatic 45 as a major product. When the reaction was carried out at -20 °C with potassium hydroxide in methanol, intermediate 45 was isolated in 52 % yield (Table 6, entries 4-5). Treatment of triketo-ester 44 under acidic conditions gave a complex mixture, but no starting material was recovered (Table 6, entry 6).

Scheme 66. Reagents and Conditions: i) conditions see table 6, 7 and 8.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pH 9.2 buffer, THF</td>
<td>traces of 11</td>
</tr>
<tr>
<td>2</td>
<td>pH 5.6 buffer, THF</td>
<td>traces of 11</td>
</tr>
<tr>
<td>3</td>
<td>0 °C, 5 eq. KOH, 10 min, 1:1 water:THF then HCl, aqueous to pH=1</td>
<td>29% of 45 and 9% of 11</td>
</tr>
<tr>
<td>4</td>
<td>-20 °C, 5 eq. KOH, 10 min, 1:1 water:THF then HCl, aqueous to pH=1</td>
<td>41% of 45 and 10% of 11</td>
</tr>
<tr>
<td>5</td>
<td>-20 °C, 5 eq. KOH, 10 min, MeOH then HCl, aqueous to pH=1</td>
<td>52% of 45 and 12% of 11</td>
</tr>
<tr>
<td>6</td>
<td>HCl, MeOH</td>
<td>other products</td>
</tr>
</tbody>
</table>

Table 6. Testing different conditions to synthesise resorcyliclate 11.

The addition of potassium hydroxide in methanol at room temperature was tested and in this case a very polar product was formed. Upon a neutral aqueous work-up, and column chromatography, a complex mixture was recovered in which no aromatic protons were observed by $^1$H-NMR (Table 7, entry 1). We thought it to be a mixture of different tautomers of alcohol 209. If compound 44 is treated with potassium hydroxide, followed by the addition of HCl, a single compound was observed and the $^1$H-NMR of the product showed aromatic protons (Table 7, entries 2-3). This indicated that in basic media, an undehydrated aldol cyclisation reaction occurred and then dehydration to the resorcylic ester happened in acidic media. At room temperature, the cyclisation also showed a high degree of regiospecificity. The resorcylic ester 11 was isolated in 87% yield (Table 7, entry 2); other cyclisation products were not observed. Adding HCl in methanol to the acidification process increased the yield to 89% (Table 7, entry 3). Stirring the acidified solution for one hour increased the yield to 90%.
(Table 7, Entry 4). Based on this observation, it seems that the dehydration of ester 11 is a slow process. In addition, as illustrated above, the formation of acetophenone 45 via a Claisen condensation\textsuperscript{100} was more favoured at low temperatures, whereas resorcylate 11 was selectively produced via an aldol reaction at higher temperatures. It became apparent that product 45 was generated under kinetic control and ester 11 under thermodynamic control.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 eq. KOH, MeOH</td>
<td>209*</td>
</tr>
<tr>
<td>2</td>
<td>5 eq. KOH, 30 min, MeOH then HCl, aqueous to pH=1</td>
<td>87% of 11</td>
</tr>
<tr>
<td>3</td>
<td>5 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=1</td>
<td>89% of 11</td>
</tr>
<tr>
<td>4</td>
<td>5 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=1, stir 1 h</td>
<td>90% of 11</td>
</tr>
</tbody>
</table>

**Table 7. More testing of different conditions to perform resorcylate 11.**

As presented in table 8 we then investigated the aromatisation reaction using a variety of different basic and acidic conditions. It was found that a minimum of 3 equivalents of KOH was required to perform the aldol condensation (Table 8, entries 1-3). Acidic work-up using HCl produced the desired ester 11 in the highest yield (Table 7, entry 3; Table 8, entries 4, 5 and 9). Interestingly, the use of cesium carbonate instead of potassium hydroxide gave also resorcylate 11 in good yield (Table 8, entries 7 and 9).

\textsuperscript{*} According to GCMS
The use of a basic resin gave a very poor yield of 11 (Table 8, entry 6) and using potassium carbonate only gave a modest yield (Table 8, entry 8).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=1</td>
<td>8% of 11</td>
</tr>
<tr>
<td>2</td>
<td>3 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=1</td>
<td>76% of 11</td>
</tr>
<tr>
<td>3</td>
<td>3.5 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=1</td>
<td>81% of 11</td>
</tr>
<tr>
<td>4</td>
<td>5 eq. KOH, 30 min, MeOH then AcOH</td>
<td>56% of 11</td>
</tr>
<tr>
<td>5</td>
<td>5 eq. KOH, 30 min, MeOH then TFA</td>
<td>73% of 11</td>
</tr>
<tr>
<td>6</td>
<td>Basic resin Amberlite IRA-400 then HCl, MeOH to pH=1</td>
<td>12% of 11</td>
</tr>
<tr>
<td>7</td>
<td>5 eq. Cs₂CO₃, MeOH then HCl, MeOH to pH=1</td>
<td>87% of 11</td>
</tr>
<tr>
<td>8</td>
<td>20 eq. K₂CO₃, MeOH then HCl, MeOH to pH=1</td>
<td>62% of 11</td>
</tr>
<tr>
<td>9</td>
<td>5 eq Cs₂CO₃, MeOH then TFA to pH=1</td>
<td>74% of 11</td>
</tr>
</tbody>
</table>

*Table 8. More conditions to optimise formation of 11.*
2.3.2 Aromatisation studies using diketo-dioxinone 197 and 12

The optimized procedures, identified by the screening of different experimental conditions, were hence utilized with diketo-dioxinone 197 and 12.

Starting from diketone 197, an aromatisation reaction was carried out under these optimised conditions; thus treatment of polyketide 210 with five equivalents of cesium carbonate followed by addition of hydrochloric acid afforded resorcylic ring 211 in 92% yield (Scheme 67).

![Scheme 67: Reagents and Conditions](image)

We also were interested in investigating the Claisen type condensation\textsuperscript{100} as an alternative reaction to provide different natural product motifs. Keto-ester 212 (obtained from dioxinone 12) was added to a methanoic solution of potassium hydroxide at -20 °C. The reaction was highly dependent on temperature; the reaction was quenched by pouring the mixture into an aqueous hydrochloric acid solution cooled with ice. Ketone 213, which was only soluble in diethyl ether, was directly converted into the known flavanoid analogue 214\textsuperscript{101} by refluxing in acetic acid.\textsuperscript{102} (Scheme 68).
**Scheme 68.** Reagents and Conditions: i) 5 eq. MeOH, PhMe, 110 °C, 4 h; ii) KOH, MeOH, -20 °C then aqueous HCl, to pH=1; iii) AcOH, reflux, 2 h, 43% over 3 steps.

Flavonoids 215 are a large class of natural products (Figure 15), which show a broad range of biological activities such as anti-allergic, anti-inflammatory,\(^{103}\) antimicrobial\(^{104}\) and anti-cancer.\(^{105}\)

![Figure 15. Molecular structure of the flavone backbone.](image)

This biomimetic synthesis of chroma-4-one 214 was inspired by Harris’s synthesis of pinocembrin (217) which was obtained in 63% yield from polyketide 216.\(^{30}\) As illustrated above, keto-dioxinones can therefore be employed for the preparation of flavonoids natural products (Scheme 69).

**Scheme 69.** Synthesis of pinocembrin (217) by Harris and co-workers.
2.3.3 Aromatisation studies without using basic or acidic conditions

An interesting aromatisation reaction was also observed without using basic or acidic conditions. Treatment of dioxinone 10 with isopropanol in a sealed tube at 100 °C, gave the orselinate 218 in an excellent yield (Scheme 70). The fact that the reaction was performed under pressure seems to be an important factor in successfully carrying out the aromatisation. When intermediate 10 was heated under reflux in isopropanol, no aromatic product was observed. In addition, when dioxinone 10 was heated in toluene with methanol or alcohol 219 in a sealed tube at 100 °C, no orselinates 11 or 220 were obtained. A lower pressure inside the tube appeared to be the reason of those results (Scheme 70).

Scheme 70. Reagents and Conditions: i) isopropanol, sealed tube, 100 °C, 10 h, 98%; ii) isopropanol, reflux, 85 °C, 10 h; iii) MeOH, sealed tube, 80 °C, 10 h; iv) 219, PhMe, sealed tube, 100 °C, 10 h.
Consequently, another strategy was developed using a two step procedure. For example the synthesis of ester 220 was made from the thermolysis of dioxinone 10 with alcohol 219. The resulting polyketide intermediate was then heated in isopropanol in a sealed tube at 100 °C to afford resorcylate 220 in a good yield (Scheme 71).

![Scheme 71. Reagents and Conditions: i) 219, PhMe, 100 °C, 5 h; ii) isopropanol, sealed tube, 100 °C, 8 h, 72% over 2 steps.](image)

Interestingly, it was also discovered that the use of molecular sieves can allow the formation of resorcylates under specific conditions. For example, when dioxinone 10 was treated with 4 Å molecular sieves in a mixture of isopropanol and DCM in a sealed tube at 100 °C, resorcylate 218 was obtained in a 98% yield. The same results were observed when methanol or alcohol 219 were used. Sadly, this mild strategy was unsuccessful with keto-dioxinone 12 either with alcohol 219 or alcohol 13. It was deemed that the size of the molecules was critical for the reaction to proceed with molecular sieves. Though this strategy was appealing, the cesium carbonate mediated aromatisation will be the method of choice to build the resorcylate (Scheme 72).
Scheme 72. Reagents and Conditions: i) 5 eq. isopropanol, m.s. 4Å, sealed tube, CH₂Cl₂, 100 °C, 10 h, 98%; ii) MeOH, m.s. 4Å, sealed tube, CH₂Cl₂, 100 °C, 10 h, 82%; iii) 5 eq. 219, m.s. 4Å, sealed tube, CH₂Cl₂, 100 °C, 10 h, 72%; iv) 5 eq. 219, m.s. 4Å, sealed tube, CH₂Cl₂, 100 °C, 10 h; v) 12, m.s. 4Å, sealed tube, CH₂Cl₂, 100 °C, 10 h.

2.4 Total Synthesis of (S)-Zearalenone (6)

Having alcohol 13 and diketo-dioxinone 12 in hand and the optimised conditions for the aromatisation step, it was possible to complete the total synthesis of S-(-)-zearalenone (6).
Two different approaches were investigated: the first one was to perform a cross-
metathesis of intermediates 13 and 12, followed by an *intra*-molecular macrolactonisation. The second one was to carry out the esterification-aromatisation first and then execute a ring closing metathesis. However, the cross-metathesis of intermediates 13 and 12 using Hoveyda-Grubbs catalyst II generation 223 was unsuccessful (Scheme 73). Consequently, studies toward esterification were favoured.

![Scheme 73](imageurl)

**Scheme 73. Reagents and Conditions:** i) 223 (10 mol%), CH₂Cl₂, 40 °C.

### 2.4.1 Aromatisation step

Thermal decomposition of diketone 12 formed the acylketene 225 which was trapped by enantiopure alcohol 13. Polyketide 14 was produced quantitatively. The compound 14 is, according to the NMR, a mixture of different possible keto-enolic forms (Scheme 74).
Scheme 74. Reagents and Conditions: i) xylenes, 150 °C, 8 min, quantitative.

After the success of the test reactions to build such resorcylates (Section 2.3), the same conditions were applied to the synthesis of the precursor of zearalenone (6). The resorcylate 222 was isolated in 91% yield from a cyclisation reaction carried out with potassium hydroxide in methanol and then treated with aqueous HCl to pH=1 (Table 9, entry 1); other cyclisation products were not observed. However, acidic conditions led to cleavage of the acetal group. Therefore, different aromatisation conditions were investigated in order to come across a milder reaction (Scheme 75, Table 9, entries 2-5). It was observed that under milder acidic condition, acidification until pH=7 (Scheme 75, Table 9, entries 2-3) or with acid resin Dowex 50WX8-400 (Scheme 75, Table 9, entry 4), the yield dropped down. This result was attributed to the fact that the dehydration step, leading to the aromatic ring 222 was not complete. However, prolonged exposure with HCl (Scheme 75, Table 9, entry 5) leads to ketone 226 in good yield. The use of acetic acid or trifluoroacetic acid (Scheme 75, Table 9, entries 6-7) did not improve the yield of the aromatisation.
**Scheme 75. Reagents and Conditions:** i) conditions see table 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=1</td>
<td>91% of 222 and trace of 226</td>
</tr>
<tr>
<td>2</td>
<td>5 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=7</td>
<td>61% of 222</td>
</tr>
<tr>
<td>3</td>
<td>5 eq. KOH, 30 min, MeOH then acid resin Dowex 50WX8-400</td>
<td>74% of 222 and trace of 226</td>
</tr>
<tr>
<td>4</td>
<td>5 eq. KOH, MeOH then HCl, MeOH to pH=7, then stir overnight in DCM</td>
<td>70% of 222</td>
</tr>
<tr>
<td>5</td>
<td>5 eq. KOH, 30 min, MeOH then HCl, MeOH to pH=1 stir 1 h</td>
<td>82% of 226</td>
</tr>
<tr>
<td>6</td>
<td>5 eq. KOH, 30 min, MeOH then acetic acid to pH=1</td>
<td>31% of 226</td>
</tr>
<tr>
<td>7</td>
<td>5 eq. KOH, 30 min, MeOH then TFA to pH=1</td>
<td>73% of 226</td>
</tr>
</tbody>
</table>

**Table 9. Different conditions applied to form resorcylate 222.**

84
In order to optimize the formation of ketone 226 diverse conditions were investigated. Different resins were tested such as basic resin Amberlite IRA-400 (Scheme 75, Table 10, entries 1-2) and acid resin Dowex 50WX8-400 (Scheme 75, Table 10, entries 2, 5). Only the Dowex 50WX8-400 appeared to be effective to promote the dehydration (Scheme 75, Table 10, entries 3-5). The combination with cesium carbonate and resin Dowex 50WX8-400 afforded resorcylate 226 in good yield (Scheme 75, Table 10, entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Basic resin Amberlite IRA-400 with acid resin Dowex 50WX8-400</td>
<td>Mixture of products</td>
</tr>
<tr>
<td>2</td>
<td>Basic resin Amberlite IRA-400 then HCl, MeOH to pH=1</td>
<td>Mixture of products</td>
</tr>
<tr>
<td>3</td>
<td>5 eq. Cs$_2$CO$_3$, MeOH then HCl, MeOH to pH=1</td>
<td>75% of 222 and trace of 226</td>
</tr>
<tr>
<td>4</td>
<td>5 eq. Cs$_2$CO$_3$, MeOH then TFA to pH=1</td>
<td>74% of 226</td>
</tr>
<tr>
<td>5</td>
<td>5 eq. Cs$_2$CO$_3$, toluene then resin Dowex 50WX8-400 overnight</td>
<td>75% of 226</td>
</tr>
</tbody>
</table>

Table 10. Different conditions applied to form resorcylate 226.

2.4.2 Ring closing metathesis

The construction of macrocycles by ring-closing metathesis (RCM)\textsuperscript{107} is often used as the key step in the synthesis of natural products containing large rings. This reaction is attractive because of its high functional group compatibility and the possibility for
further transformations. Ring-closing metathesis (RCM) of alkenes allows the
synthesis of cyclic compounds from small 5- or 6-membered rings up to large
macrocycles. Disadvantages include control over the stereochemistry of the double
bond formed and finding the appropriate reaction conditions to maximize yield and
minimize the formation of by-products. The key intermediate is a metallacyclobutane,
which can undergo cycloreversion either towards the product or back to starting
materials. When the olefins in the substrate are terminal, the driving force for RCM is
the removal of ethene from the reaction mixture.

In the synthesis of zearalenone (6) two different catalysts have been tested: the Grubbs
catalyst second generation 227 and the Hoveyda-Grubbs catalyst second generation
223 (Figure 16).

With the resorcylic ester 222 in hand, studies were initiated to explore the ring closing
metathesis (RCM). Attempts to perform this reaction using the second generation
Grubbs catalyst 227 and the Hoveyda-Grubbs catalyst 223 were unsuccessful. Using
catalyst 223, a mixture of three products was obtained in the ratio indicated below
(Scheme 76). Purification of those products was unsuccessful due to their very close
retention factor on silica gel. The ratio was determined by NMR and LCMS.
Scheme 76. Reagents and Conditions: i) 223 (10 mol%), PhMe (8.10⁻⁴ M), 80 °C, 8 h.

However, deprotected product 226 underwent ring closing metathesis with the second generation Hoveyda-Grubbs catalyst 223 to give stereoselectively (E/Z 86:14) the final product S-(−)-zearalenone (6) in 71% yield (Scheme 77). It was thought that the ring closing metathesis occurred more smoothly with intermediate 226 than with compound 222 because ester 226 is structurally closer to the natural product zearalenone (6) and consequently more inclined to adopt the appropriate conformation to ring close under the metathesis conditions.
Scheme 77. **Reagents and Conditions**: i) 223 (10 mol%), PhMe (1.7 x 10^{-3} M), 80 °C, 71% of E isomer.

2.4.3 **One pot strategy**

By a simple modification of the reaction conditions (Scheme 78), we found that this four-step reaction sequence could be telescoped and performed with just a single chromatographic purification resulting in the isolation of natural product 6 in a highly convergent synthesis.

Scheme 78. **Reagents and Conditions**: i) PhMe, 110°C, 2 h; ii) Cs₂CO₃, MeOH, 12 h; iii) Dowex 50WX8-400, 24 h; iv) 223 (10 mol%), PhMe, 80°C, 8 h, 63% four steps.
2.5 Conclusions

In summary, we report a new strategy for the synthesis of resorcylate natural products using a late stage biomimetic highly selective aromatization reaction and its application to a concise total synthesis of \( S(-)-\)zearalenone (6) in eight steps with an overall yield of 11.5\% (Scheme 79). No previous synthesis exceeded 7\% as an overall yield.\(^{110}\)

![Scheme 79. Overview of zearalenone synthesis.](image)

In addition, we reported three efficient ways to synthesis diketo-dioxinone 10. The first one using allylester 156:

![Scheme showing synthesis of diketo-dioxinone 10](image)
The second one using Weinreb amide 178:

![Chemical structure](image1)

And the third one using benzotriazole derivative 9:

![Chemical structure](image2)

We also established mild conditions to construct the aromatic ring 11 using a soft base followed by an acid work-up. We also discovered ways to build resorcylates in one step from diketo-dioxinone 10:

![Chemical structure](image3)
CHAPTER THREE:

(+)-MONTAGNETOL AND

(+)-ERYTHRIN
3.1 Background to Montagnetol and Erythrin

The orsellinic acid unit (1) occurs widely in natural products, including the natural products montagnetol (2) and erythrin (4).\textsuperscript{111} This feature is also present in globosumone A (231) and B (232),\textsuperscript{112} phomozin (233),\textsuperscript{113} orsellide A (234), C (235), D (236) and E (237)\textsuperscript{114} (Figure 17).

![Chemical structures of orsellinic acid, globosumone A, globosumone B, phomozin, orsellide A, C, D, E, montagnetol, and erythrin.]

Figure 17. Natural products containing the orsellinic acid unit (1).

Having diketo-dioxinone 10 in large amounts (section 2.2.1.7), we realised that from this intermediate 10, we were able to perform the total syntheses of natural products (+)-montagnetol (2) and (+)-erythrin (4).

We planned to undertake their biomimetic total syntheses in an analogous manner to (S)-zearalenone (6) (Chapter 2). Thus, (+)-montagnetol (2) should be obtained from diketo-dioxinone 10 and alcohol 238. The natural product (+)-erythrin (4) should be
achieved via a selective phenol trapping of montagnetol derivat 239 with the acylketene generated from diketo-dioxinone 10 (Scheme 80).

![Scheme 80. Retrosynthetic analysis of (+)-montagnetol (2) and (+)-erythrin (4).](image)

Natural products (+)-montagnetol (2) and (+)-erythrin (4) were both extracted from the lichen *Roccella montagnei* by V.S. Rao and T. R. Seshadri. Erythrin (4), which is the chromogen of *Roccella tinctoria* (extract present in litmus), was also reported as a potent natural antioxidant. From a racemic synthesis, the structures of montagnetol (2) and erythrin (4) have been elucidated by Seshadri and co-workers.

The previous synthesis of montagnetol (2) started with the benzylation of commercially available methyl orsellinate 11. Subsequent ester hydrolysis gave the orsellinic acid dibenzyl ether 240. This intermediate 240 was then condensed with cis-2-butene-1,4-diol (241) in the presence of *N,N*'-dicyclohexylcarbodiimide to afford ester 242. Subsequent treatment with Milas’ reagent (H₂O₂ in t-butanol with cat. OsO₄) provided a racemic mixture of montagnetol dibenzyl ester 243a (2S,3R) and 243b (2R,3S). The protecting benzyl groups were then removed by catalytic
hydrogenation over palladium on charcoal to afford a racemic mixture of montagnetol 244 (2S,3R) and 2 (2R,3S) (Scheme 81).

Similarly erythrin was synthesised starting with the condensation of tricarbethoxylecanoric acid 245 (prepared from lecanoric acid) with cis-2-butene-1,4-diol (241) in the presence of N,N’-dicyclohexylcarbodiimide to afford ester 246. Upon dihydroxylation using Milas’ reagent followed by decarbethoxylation gave a racemic mixture of erythrin 248 (2S,3R) and 4 (2R,3S) via esters 247 (Scheme 82).
Thus, at this time, the absolute configuration of (+)-montagnetol (2) and (+)-erythrin (4) was not assigned. Herein we report the synthesis of both enantiomers of (+)-montagnetol (2) and (+)-erythrin (4) and hence the determination of their absolute stereochemical configuration.

3.2 Total Synthesis of (+)-Montagnetol

The synthesis started with the formation of both enantiomers of alcohol 252 (a and b). The choice of protecting group for alcohols 252 was directed by the observations of V.S. Rao and T. R. Seshadri, who reported a racemisation of (+)-montagnetol (2) under aqueous conditions via a transesterification (Scheme 83). Consequently, the use of a benzyl protecting group was adequate and avoids any aqueous work-up at the final deprotection stage.
Both enantiomers 252a and 252b were synthesized from erythronolactone 250a and 250b respectively. Erythronolactone 250a was obtained from D-isoascorbic acid 249 in 94% yield. Following a previously reported synthesis, treatment of lactones 250a and commercially available 250b with eight equivalents of benzylbromide and four equivalents of silver oxide, gave esters 251a and 251b respectively. Reduction with lithium aluminium hydride afforded alcohols 252a and 252b respectively, in good yields (Scheme 84). The thermolytic ketene generation, trapping and aromatization was then applied to the total syntheses of (+)-montagnetol (2) and (+)-erythrin (3), as well as their respective enantiomers.

Scheme 84. Reagents and Conditions: i) NaHCO₃, H₂O₂, H₂O, RT, 2 h, 94%; ii) 8 eq. BnBr, 4 eq. Ag₂O, Et₂O, RT, 3 days; iii) LiAlH₄, THF, 0 °C, 20 min.
Thermolysis of dioxinone 10 in the presence of benzyl-protected erythritols 252a and 252b, gave the triketo-esters 253a and 253b respectively. $^1$H-NMR analysis in CDCl$_3$ showed that these compounds exist as a complex mixture of both keto and enol tautomers. Aromatisation, followed by hydrogenolysis of the benzyl groups, gave compound 244 (X-ray Figure 18, Appendix 3) and (+)-montagnetol (2) respectively via esters 254a and 254b correspondingly (Scheme 85). The optical rotations of compounds 244, (2S,3R) and 2, (2R,3S) were $[\alpha]^{20}_D$ = -10.1 (acetone, c = 0.5) and $[\alpha]^{20}_D$ = +11.0 (acetone, c = 0.4) respectively. These data were compared with those of the isolated natural (+)-montagnetol $[\alpha]^{20}_D$ = +12.6 (acetone).

Scheme 85. Reagents and Conditions: i) PhMe, 110 °C, 5 h; ii) Cs$_2$CO$_3$, MeOH, RT, 1 h then aq. HCl (1M), RT, 15 min; iii) Pd/C, H$_2$, EtOAc, RT, 6 h.
The two enantiomers of montagnetol, 244 and 2, were evaluated by chiral HPLC analysis to confirm their enantiomeric purity (Appendix 4). The examination of their optical rotations, compared with the natural product, showed that the compound 2 (2R,3S) had the true configuration. Natural product (+)-montagnetol is (2R,3S)-2,3,4-trihydroxybutyl 2,4-dihydroxy-6-methylbenzoate.

### 3.3 Total Synthesis of (+)-Erythrin

Reaction between dioxinone 10 and phenol 254b at 110 °C failed to give the corresponding aryl triketo-ester 255. Only the starting material 254b and the compound 256 were recovered, indicating that phenol 254b was of insufficient nucleophilicity (Scheme 86).
Based on this result, we undertook a control reaction which showed that thermolysis of dioxinone 10 in toluene gave the pyrone 256 in 68% yield (Scheme 87). This unprecedented strategy to build 4-hydroxy-6-(2-oxopropyl)-2H-pyran-2-one (256) could be a flexible method to synthesise pyrones and the natural product elasnin (257)\(^\text{121}\) which is a specific inhibitor of human leukocyte elastase, an important enzyme in the pathology of inflammatory diseases such as pulmonary emphysema.\(^\text{122}\)

**Scheme 86. Reagents and Conditions:** i) PhMe, 110 °C, 53% of 256.

**Scheme 87. Reagents and Conditions:** i) PhMe, 110 °C, 68%.
Consequently, another strategy was investigated, starting from resorcylate 15* which underwent an esterification reaction with phenol 254a under basic conditions to afford diesters 258 in 34% yield. The yield of this step was too low for a scale up, therefore another method was also investigated (Scheme 88).

Scheme 88. Reagents and Conditions: i) DMF, NaH, 100 °C, 38%.

A more classical approach was applied, starting from the protected orsellinic acid 240,113 which underwent an esterification reaction with phenol 254a or 254b using activation with trifluoroacetic anhydride123 to provide the diesters 259a and 259b respectively. Debenzylation by hydrogenolysis afforded 248 and 4 respectively (Scheme 89). The optical rotations of compounds 248, (2S,3R) and 4, (2R,3S) (Appendix 5) were $[\alpha]^{20}_D = -8.2$ (MeOH, c = 0.2) and $[\alpha]^{20}_D = +9.0$ (MeOH, c = 0.2) respectively. These data were compared with those of the isolated natural (+)-erythrin, kindly provided by Prof. V. Karunaratne, $[\alpha]^{20}_D = +7.3$ (MeOH, c = 0.2).

* A synthesis of resorcylate 15 from diketo-dioxinone 10 will be described in chapter 4.
Both enantiomers of (-)-erythrin (248) and (+)-erythrin (4) were compared with an authentic sample of the natural product by chiral HPLC analysis (Appendix 6). This was fully consistent with the natural product 4 having the (2R,3S) stereochemistry. The natural product (+)-erythrin is 3-hydroxy-5-methyl-4-(((2R,3S)-2,3,4-trihydroxybutoxy)carbonyl)phenyl 2,4-dihydroxy-6-methylbenzoate.
3.4 Conclusions

In conclusion, we have reported a highly convergent strategy to build orsellinate natural products. This strategy is rapid and higher yielding than the commonly used syntheses of these natural products, which use readily available resorcylic ester derivates as starting materials. We also described the synthesis of both enantiomers of montagnetol and erythrin, allowing assignment of their absolute stereochemical configuration (Scheme 90).

Scheme 90. Overview of montagnetol and erythrin syntheses.
CHAPTER FOUR:
HETEROAROMATIC
4.1 Investigation towards the Synthesis of Polysubstituted Aromatics

4.1.1 Synthesis of benzodioxinones

In section 2.2.4, an unexpected side reaction was reported from keto-dioxinone 197. Under basic conditions, this compound aromatised readily to afford benzodioxinone 198 in good yield (Scheme 91).

Scheme 91. Reagents and Conditions: i) 3 eq. Et,N, THF, reflux, 8 h, 82%.

These interesting observations led to the pursuit of a plausible mechanism to explain the formation of 198. Diketo-dioxinone 10 was used as a model system to study this reaction. Compound 10 was obtained on a gram scale through the synthetic pathway reported in section 2.2.1.7. The screen identified triethylamine as the reagent of choice (Scheme 92, Table 11, entry 6), giving resorcylicate 15 in 96% yield. Neither p-toluenesulfonic acid (Scheme 92, Table 11, entry 1) nor acetic acid (Scheme 92, Table 11, entry 2) showed evidence of aromatisation. These results confirmed that intermediate 10 was stable under acidic conditions at room temperature. However, under basic conditions dioxinone 10 was quickly converted into ester 15 (Scheme 92, Table 11, entries 4-8). Interestingly, using the secondary amine, morpholine, led to a full recovery of starting material, whereas with DABCO, diketone 10 was consumed (Scheme 92, Table 11, entries 3-4).
Scheme 92. Reagents and Conditions: i) conditions see table 11.

<table>
<thead>
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<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TSA (excess), THF, RT, 5 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (excess), THF, RT, 5 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>Morpholine (excess), CH₂Cl₂, RT, 5 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>4</td>
<td>DABCO (excess), CH₂Cl₂, RT, 5 h</td>
<td>79% of 15</td>
</tr>
<tr>
<td>5</td>
<td>DMAP (excess), CH₂Cl₂, RT, 5 h</td>
<td>95% of 15</td>
</tr>
<tr>
<td>6</td>
<td>Et₃N (excess), CH₂Cl₂, RT, 5 h</td>
<td>96% of 15</td>
</tr>
<tr>
<td>7</td>
<td>Cs₂CO₃ (excess), THF, RT, 5 h</td>
<td>43% of 15</td>
</tr>
<tr>
<td>8</td>
<td>NaOH aq (excess), THF, RT, 5 h</td>
<td>64% of 15</td>
</tr>
</tbody>
</table>

Table 11. Different reaction conditions tested to afford intermediate 15.

The mechanism of this reaction is a base-catalysed aldol-type reaction also named the Knoevenagel condensation. Upon deprotonation with triethylamine, 10 gave reactive intermediate 260 which can form β-hydroxycarbonyl 261. Dehydration of alcohol 262 affords product 15 (Scheme 93).
Scheme 93. Proposed mechanism for the aromatisation reaction of resorcylate 15.

4.1.2 Synthesis of polysubstituted benzodioxinones

With these encouraging results in hand, experiments towards the synthesis of more complex products were conducted. To this extent, the effect of basic media on allyl ester 174 (section 2.2.1.5) was investigated. To our delight, aromatic 263 was isolated in an excellent yield when 174 was mixed with triethylamine (Scheme 94).

Scheme 94. Reagents and Conditions: i) Et₃N, CH₂Cl₂, RT, 90 min, 98 %.

According to Danishefsky et al.,125 the acetal of resorcylate 265 can also be viewed as an activated ester and consequently can perform transesterification reactions. Thus,
this strategy could be an efficient way to synthesise diesters 264 in which functional
groups $R^1$, $R^2$, $R^3$ and $R^4$ can be different (Scheme 95).

![Scheme 95. Synthetic strategy to build functionalised diesters 264.](image)

4.1.3 Synthesis of polysubstituted benzodioxinone via a Keck macrolactonisation

A similar compound 266 was formed in a different fashion from acid 170 (section 2.2.1.4). A Keck macrolactonisation\(^{49}\) afforded novel species 266 in good yield (Scheme 96).

![Scheme 96. Reagents and Conditions: i) DCC, DMAP, CH\(_2\)Cl\(_2\), 40 °C, 5 h, 86 %.

(0.01 MB)
4.2. Investigations towards the Synthesis of Bicyclic and Heteroaromatic Compounds

4.2.1 Attempted synthesis of pyridinones

After the success of the previous approaches to build polysubstituted aromatics, we deemed to establish a new strategy to construct bicyclic frameworks and heteroaromatics from intermediates diketo-dioxinone 273.

Initially, we hoped to synthesise pyrazolopyridinone 267, isoxazolopyridinone 268 and isothiazolopyridinone 269 derivatives from pyrazol 270, isoxazol 271 and isothiazol 272 intermediates following the retrosynthetic pathway described in scheme 97. The nucleophilic reagent would have to be added to a solution containing dioxinone 273 at high temperature (Scheme 97).

Before attempting the in situ trapping with diketone 10, reagents were first tested on the commercially available dioxinone 8. Treatment of compound 8 with N-hydroxylphthalimide (274) gave the moderately stable hydroxamate 275. In addition, in order to test the reactivity of dioxinone with amines, thermolysis of intermediate 8 with N,O-dimethylhydroxylamine (276) or hydrazine (278) afforded respectively the

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*Hydroxamate 275 decomposed completely at room temperature after 8 h.*

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known acetoacetamide $^{277}\textsuperscript{126}$ and methyl-pyrazolone $^{279}\textsuperscript{127}$ in good yields (Scheme 98).

\[
\begin{array}{c}
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\text{O} \\
\text{O}
\end{array}
\quad
\begin{array}{c}
+ \\
\text{H}_2\text{O} \\
\text{N} \\
\text{N}
\end{array}
\quad
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\quad
\text{Scheme 98. Reagents and Conditions: i) PhMe, 90 °C, 90 min, 43 %; ii) PhMe, 90 °C, 7 h, 99 %; iii) PhMe, 110 °C, 8 h, 62 %.
}

Taking these results into account, studies were initiated to investigate the effect of these reagents to diketo-dioxinone 10. Initial explorations were directed towards the reaction of $\text{N}$-hydroxylphthalimide (274) with the highly electrophilic ketene generated from thermolysis of dioxinone 10 at 90 °C. This reaction was also tested using $\text{N}$-aminophthalimide (280) as a nucleophile (Scheme 99). Disappointingly, the desired products were not detected by $^1\text{H}$-NMR spectroscopy. Compounds 281 and 282 seemed to be unstable intermediates. Consequently, another strategy was developed.

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\quad
\begin{array}{c}
+ \\
\text{HN} \text{-} \text{OMe} \\
\text{276}
\end{array}
\quad
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\quad
\begin{array}{c}
\text{O} \\
\text{N} \text{-} \text{OMe}
\end{array}
\quad
\text{Scheme 99. Reagents and Conditions: i) PhMe, 90 °C, 60 min.}
\]
4.2.2 Towards the synthesis of bicyclic framework 283

According to the chemical literature, it is well known that acylketene 82 (formed in situ, via thermolysis of dioxinone 8) can perform a hetero-Diels-Alder reaction with a wide range of dienophiles. \(^{65}\) Inspired by this appealing property of dioxinone 8, it was deemed to form bicyclic framework 283 from diketo-dioxinone 10 and dienophile 285 via a hetero-Diels-Alder reaction followed by a basic treatment to aromatise intermediates 284 following the method reported in section 4.1.1 (Scheme 100).

![Scheme 100. Retrosynthetic analysis of aromatic 283. \(X^i\) can be \(-\text{C}=-, =\text{C}=-, =\text{C}==\) and \(X^2\) can be \(C, N, O, S.\)](image)

Initially, treatment of dioxinone 8 with cyanamide 286, nitrile 287 or phenylmethanamine 290 gave respectively amine 288, the known diethylamine 289\(^{128}\) and oxazinone 291\(^{129}\). However, when diketo-dioxinone 10 was treated with any one of those reagents (cyanamide 286, nitrile 287 or phenylmethanamine 290), decomposition of the starting material 10 was observed at 80 °C and no desired products 292 or 293 or 294 were detected (Scheme 101). The failure of these experiments led us to conclude that the ketone moieties in compound 10 might interfere in the course of the reaction.
Scheme 101. Reagents and Conditions: i) PhMe, 90 °C, 12 h, 99 %; ii) PhMe, 90 °C, 5 h, 41 %; iii) PhMe, 80 °C, 5 h.

Although the synthesis of pyrazolopyridinone 267 or compounds 283 via ketodioxinone 10 was attractive in terms of convergence and overall efficiency, it was ultimately proved flawed due to the inherent reactivity of the ketones in compound 10. This synthetic venture was therefore abandoned in favour of other approaches.

4.2.3 Synthesis of pyrazolopyridine 20

Instead of executing a thermolysis of the dioxinone group during the first stage, it was decided to build dioxinone 295 by functionalising the ketone motifs and then opening up the dioxinone (Scheme 102).
Diketone 10 was selectively converted to dihydro-isoxazole 296 in high yield by treating with hydroxylamine hydrochloride. Trifluoroacetic acid promoted dehydration to afford isoxazole 297 (Scheme 103).

Scheme 103. Reagents and Conditions: i) hydroxylamine hydrochloride, pyridine, RT, 5 h, 89%; ii) TFA, CH₂Cl₂, RT, 8 h, 77%.

An examination of the literature revealed that in 1988 Chiarino and co-workers 130 reported the synthesis of isoxazolo-pyridinol 299 from isoxazole 298 in 56% yield. The nucleophilicity of the isoxazole ring as well as an appropriate temperature appeared to be sufficient to achieve the ester addition (Scheme 104).

Scheme 104. Synthesis of isoxazolo-pyridinol 299 by Chiarino and co-workers.

In view of the success of these results, dioxione 297 was refluxed for one hour in order to obtain isoxazole 300 (Scheme 105). However, a complex polymer was
obtained and no starting material was recovered. Thus, this synthetic strategy was deemed unsuitable.

![Scheme 105](image)

**Scheme 105. Reagents and Conditions:** i) PhMe, 80 °C, 1 h.

Although the previous method failed to deliver a heteroaromatic ring, synthesis of a pyrazole ring instead of an isoxazole offered a good alternative. Diketo-dioxinone 10 was converted into pyrazole 301 using hydrazine in good yield (Scheme 106). The $^{1}$H-NMR spectroscopy of dioxinone 301 in DMSO-$d_{6}$ showed that the proton attached to the nitrogen atom was adjacent to the methyl group of the pyrazole, which was identified with N$^{15}$ HMBC methods (see Appendix 7).

![Scheme 106](image)

**Scheme 106. Reagents and Conditions:** i) hydrazine, THF, RT, 5 h, 89 %.

Having this key intermediate 301 in hand, thermolysis of the dioxinone was studied. At 90 °C, after two hours, starting material was consumed. $^{1}$H-NMR spectra interpretation was not trivial. Indeed heteroaromatic 20 can exist as a mixture of different tautomers (Scheme 107). The ratio of these tautomers varies from one deuterated solvent to another. With DMSO-$d_{6}$ the ratio was found to be 15% of 20a, 5% of 20b, 60% of 20c and 20% of 20d, while with deuterated methanol the ratio was found to be 40 % of 20a and 60 % of 20c. It should be noted that the $^{1}$H-NMR spectra in deuterated methanol was taken within 5 minutes of adding MeOD, some protons of
pyrazolopyridine 20 were interchanging with deuterium atom of the solvent after an extended period in MeOD.

\[
\text{HN} \quad \text{HN} \\
\text{O} \quad \text{O}
\]

\[
\text{301} \quad \xrightarrow{\text{i}} \quad \text{HN} \quad \text{N} \\
\text{O} \quad \text{C} \\
\text{O} \quad \text{O}
\]

\[
\text{302}
\]

\[
\text{HN} \quad \text{N} \\
\text{OH} \quad \text{OH}
\]

\[
\text{20a} \quad \leftrightarrow \quad \text{20b}
\]

\[
\text{HN} \quad \text{N} \\
\text{OH} \quad \text{OH}
\]

\[
\text{20c} \quad \leftrightarrow \quad \text{20d}
\]

**Scheme 107.** *Reagents and Conditions: i) 1.4 x 10^{-3} \text{ M, PhMe, 2 h, 90 °C, 92%}.*

In the chemical literature, only one patent reported the synthesis of dihydroxy-pyrazolo[1,5-a]pyridine 305 via pyrazole 303 and diethyl malonate 304. Intermediate 305 was a precursor for the synthesis of nitrile 306 which was found to be MAPKAP-K2 (mitogen-activated protein kinase activated protein kinase 2) inhibitor. They also reported that pyrazolo[1,5-a]pyridine derivative 306a, represented in scheme 108, exists in tautomeric forms 306b and 306c.
The concentration of the solution was found to be an important factor for the reaction to proceed cleanly. Indeed, if the reaction was carried out with a concentration of $3 \times 10^{-2}$ M (Scheme 109, Table 11, entries 1-3), a side product was formed which had twice the mass of product 20 minus the mass of water. This would correspond to a dimer of 20 which undergoes dehydration. Thus, a program was initiated to find the adequate concentration and suppress the formation of the side product 307 (Scheme 109, table 12). The ratio of pyrazolopyridine 20 and compound 307 was determined by UPLC-MS. The mechanistic pathway might proceed via a $6\pi$ electrocyclic cyclisation.

Scheme 108. Different tautomeric forms of pyrazolopyridine 306.

Scheme 109. Reagents and Conditions: i) see table 12.
Entry | Reagents and conditions | Result (Ratio 20:307) |
---|---|---|
1 | 8.3 x 10^{-1} M, PhMe, 2 h, 90 °C | 72:28 |
2 | 3.5 x 10^{-1} M, PhMe, 2 h, 90 °C | 87:13 |
3 | 2.5 x 10^{-2} M, PhMe, 2 h, 90 °C | >99:1 |
4 | 1.1 x 10^{-3} M, PhMe, 2 h, 90 °C | 92%* |
5 | 4.6 x 10^{-4} M, PhMe, 2 h, 90 °C | 93%* |
6 | 2.6 x 10^{-3} M, PhMe, 30 min, 110 °C | 98:2 |
7 | 1 x 10^{-3} M, THF, 30 min, 130 °C, MW | 91%* |
8 | 9.6 x 10^{-4} M, PhMe, sealed tube, 90 min, 90 °C | 91%* |

Table 12. Different reaction conditions tested which led to intermediate 20 and its tautomers

\( MW = \text{microwave irradiation.} \)

In this study, the optimum concentration was found to be around \( 10^{-3} \) M (Scheme 109, Table 12, entries 4-5). At this concentration, only intermediate 20 was formed (see UPLC-MS Appendix 8). With a higher temperature, the formation of side product 307 increased (Scheme 109, Table 12, entry 6). The use of microwave irradiation and a sealed tube speeded up the reaction (Scheme 109, Table 12, entries 7-8). The low concentration necessary to perform the reaction was an issue during scale up. At concentrations higher than \( 7 \times 10^{-2} \) M, it was thought that the conformation of the highly electrophilic ketene 302 might also favour intermolecular trapping. Therefore, with the intention of building a transient activated ester from ketene 302, it seemed necessary to develop an alternative route.

* Isolated yield of 20
Thus, a program was initiated relying on the *in situ* formation of a mixed anhydride or benzotriazole derivative 308. The use of mixed anhydrides was an appealing avenue as the activated carboxylic anhydride would be formed readily and under mild conditions (Scheme 110, Table 13, entries 1-2). However, this tactic proved to be capricious and a large number a side products were formed according to UPLC-MS. Complex mixtures were also observed when benzotriazole was refluxed with pyrazole 301 (Scheme 110, Table 13, entry 3).

![Scheme 110. Reagents and Conditions: i) see table 13.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, X = OAc</td>
<td>3 x 10^{-3} M, AcOH, PhMe, 2 h, 110 °C</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2, X = OAc</td>
<td>2 x 10^{-3} M, AcOH, 2 h, 150 °C, MW</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3, X = Bt</td>
<td>4 x 10^{-3} M, BtH, THF, PhMe, 2 h, 90 °C</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

*Table 13. Different reaction conditions tested to form intermediate 20 and its tautomers. MW = microwave irradiation.*

Alternatively, dioxinone 301 was heated in methanol to afford the isolable acetoacetate 309 in 73% yield. This intermediate was then refluxed in acetic acid to give the desired pyrazolopyridine 20 in a good yield (Scheme 111).
Scheme 111. *Reagents and Conditions*: i) MeOH, PhMe, 90 °C, 5 h, 73 %; ii) AcOH, THF, 80 °C, 5 h, 72 %.

Any attempt to further functionalise pyrazolopyridine 20 and its isomers was found to be fraught with difficulties (Scheme 112, Table 14).

Scheme 112. *Reagents and Conditions*: i) see table 14.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, R = Bn</td>
<td>BnBr, NaH, DMF, 0 to 20 °C, 5 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2, R = Me</td>
<td>MeI, K$_2$CO$_3$, DMF, RT, 8 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3, R = TBS</td>
<td>TBSCl, imidazole, CH$_2$Cl$_2$, RT, 2 h</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

*Table 14. Different reaction conditions to functionalise intermediate 20.*
4.3. Conclusions

In summary, we report a high yielding strategy to build polysubstitued resorcylates 15 and 263 from diketo-dioxinones.\(^{86}\) This key building block is also utilised in the synthesis of bicyclic frameworks as well as heteroaromatic 20 (Scheme 113).

Scheme 113. Summary of the reactions developed in this chapter.
5.1 Background on Pochonin H and Pochonin G

Both Pochonin G (3) and Pochonin H (311) (Figure 19) were isolated from a culture broth of the fungus Pochonia chlamydosporia var. Chlamydosporia, obtained from a soil sample collected in Fujioka city, Tochigi Prefecture, Japan in 1994 by Shinonaga and co-workers. Biological assessment of pochonins G and H as hair-growth stimulants revealed interesting results. Pochonin G (3) shows an IC$_{50}$ of 8.15 µM against WNT-5A expression. WNT-5A (wingless-type mouse mammary tumor virus integrations site family, member 5A) is a member of the WNT family which is important for intercellular signaling glycoproteins that regulate organ formation during the fetal stage. In addition, pochonin G (3) and H (311) display no cytotoxicity against dermal papilla cells. To date, there are no reported chemical syntheses of either pochonin G (3) or pochonin H (311).

![Pochonin G (3) and Pochonin H (311)](image)

Figure 19. Pochonin G and H.

5.2 Retrosynthetic Analysis

We first planned to undertake the total synthesis of pochonin H (311). Our retrosynthetic analysis was based on previous work carried out during the total synthesis of (S)-zearalenone (6). Pochonin H (311) could be obtained in the final step via RCM. The aromatic ring could be constructed by an in situ acylketene
trapping with the commercially available alcohol 18 followed by an aromatisation reaction. Diketo-dioxinone 312 should be available from the electrophilic addition of keto-dioxinone 16 with Weinreb amide 17 (Scheme 114).

![Scheme 114. Retrosynthetic strategy for the construction of pochonin H (311).]

5.3 Towards the Synthesis of Pochonin H

5.3.1 Synthesis of Weinreb amide 17

5.3.1.1 Towards the Synthesis of Weinreb amide 17: using an Arndt-Eistert homologation

It was first envisaged that Weinreb amide 17 could be synthesised using an Arndt-Eistert homologation from commercially available furan 315 followed by a Stille cross-coupling of bromide 314 to give allyl furan 313. A simple functional group interconversion can provide the desired Weinreb amide 17 (Scheme 115).
Treatment of acid 315 with thionyl chloride followed by addition of diazomethane gave α-diazo ketone 316. However, when intermediate 316 was treated with silver oxide or silver benzoate with triethylamine in methanol, the Wolff rearrangement did not occur (Scheme 116).

An alternative strategy was to perform the Stille cross-coupling first and then do the homologation reaction. Diazomethane was used to synthesise methyl ester 317 from acid 315. Successful reaction of bromo-furan 317 with allyltributylstannane (318) was accomplished in DMA at 90 °C, using tetrakis(triphenylphosphine)palladium(0) to give ester 319 in 64% yield. Saponification of the resulting allyl-furan with lithium hydoroxide in methanol gave acid 320. However, Arndt-Eistert homologation again failed to provide ester 313 (Scheme 117).
Scheme 117. Reagents and Conditions: i) TMSCH$_2$N$_2$, Et$_2$O, RT, 2 h, 99%; ii) 318, Pd$_2$(PPh$_3$)$_3$, DMA, 90 °C, 16 h, 64%; iii) LiOH H$_2$O, MeOH, RT, 5 h, 62%; iv) SOCl$_2$, CH$_2$Cl$_2$;PhH 1:10, 0 °C, 5 h; then TMSCH$_2$N$_2$, Et$_2$O, RT, 1 h, 87%; v) ArCO$_2$Ag, Et$_3$N, MeOH, RT, 5 h.

5.3.1.2 Towards the Synthesis of Weinreb amide 17: using a homolagation via nitrile strategy

We then investigated another way to perform the homolagation, using a three step procedure.$^{136}$ The synthesis of acid 322 started with the reduction of ester 319 with LiAlH$_4$ to afford alcohol 321 in 91% yield. Sequential mesylation and nucleophilic substitution with sodium cyanide followed by nitrile hydrolysis gave acid 322 in 8 % yield over three steps (Scheme 118).

Scheme 118. Reagents and Conditions: i) LiAlH$_4$, THF, 0 °C, 10 min, 91%; ii) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 30 min; iii) NaCN, DMF, 85 °C, 6 h; iv) NaOH (25%), EtOH, reflux, 7 h (8 %, 3 steps).
5.3.1.3 Towards the Synthesis of Weinreb amide 17: from furanyl acetate 323

The overall yield of the previous approach was less than 8%. Therefore an alternative strategy was developed, based on the direct synthesis of furanyl acetate 323. We first attempted the direct formation of tert-butyl furanyl acetate 323 from furan (324) and tert-butyl bromoacetate (325) (Scheme 119).

![Scheme 119. Retrosynthetic strategy for the construction of furanyl acetate 325.](image)

Unfortunately, deprotonation of furan (324) in the 2’ position, followed by addition of tert-butyl bromoacetate (325) at low temperature, gave ketone 326 in 63% yield (Scheme 120).

![Scheme 120. Reagents and Conditions: i) n-BuLi, (i-Pr)₂NH, then 325, THF, -78 °C, 6 h, 63%.](image)

5.3.1.4 Towards the Synthesis of Weinreb amide 17 via a radical coupling

Whilst investigating strategies to build the substituted furan, we found a procedure from 1992 by Baciocchi et al. describing an efficient way to synthesise furanyl-acetate in one step using a radical coupling. The reaction was carried out using ethyl 2-iodoethanolate (327), 0.5 equivalents of iron (II) sulfate heptahydrate, 18 equivalents of furan (324) and 1.9 equivalents of hydrogen peroxide in DMSO at room
temperature for three hours. Ethyl 2-(furan-2-yl)ethanol (328) was obtained in 93% yield (Scheme 121).

![Scheme 121. Synthesis of furanyl acetate 328 by Baciocchi.](image)

The proposed mechanism by Baciocchi and co-workers starts with the redox decomposition of hydrogen peroxide by the iron (II) salt 329, known as Fenton's chemistry138 (Scheme 122, equation 1). The hydroxyl radical formed 330, reacts quickly with DMSO 333, used as a solvent to afford radical 334 (Scheme 122, equation 2). The radical adduct of DMSO, 334 undergoes a fast, β-scission (Scheme 122, equation 3) to form methyl radical 335. The key step of this procedure is the iodine abstraction by the methyl radical 335 from the alkyl iodide 327 (Scheme 122, equation 4) to give iodomethane and radical 338.139,140 The rate of this reaction is higher than most of the other possible competitive reactions of the methyl radical, and the rate constant is also strongly affected by the stability of the alkyl radical formed, 338 which is stabilized by the electron-withdrawing group in its α-position.141 Consequently this ambipolar carbon-centered radical 338 can be utilized for the oxidative homolytic substitution of electron-rich aromatic furan (324) to give desired compound 328 (Scheme 122, equation 5 and 6).142,143
Reagents quantities had to be optimized by Baciocchi and co-workers to minimize side reactions. DMSO, 333, which reacts with hydroxyl radical 330, is used as a solvent in order to reduce the fast and competitive reduction of the hydroxyl radical by the Fe(II) salt 329 (Scheme 123, equation 7) as well as the reaction with alkyl iodide 327 to give 340 (Scheme 123, equation 8). The Fe(II) salt, which is a catalyst (Scheme 123, consumed in equation 1 and regenerated in equation 6), is in fact used as 0.5 equivalents; this is due to the fact that a certain amount of it is consumed in termination steps (Scheme 123, equation 9 and 7). The amount of hydrogen peroxide utilized is larger than stoichiometric because it is also consumed in a partial amount in the oxidation of sulfinic acid (336) to sulfonic acid (341) (Scheme 123, equation 10).
Hydrogen abstraction from sulfinic acid (336) by the methyl radical 335 (Scheme 123, equation 11) also appears to be a significant side reaction (Scheme 123).142

\[
\begin{align*}
\cdot \text{OH} + \text{Fe(II)} &\rightarrow \cdot \text{OH} + \text{Fe(III)} & (7) \\
330 &\quad 329 &\quad 331 &\quad 332 \\
\cdot \text{OH} + \text{I} + \text{OEt} &\rightarrow \cdot \text{I} + \text{OEt} & (8) \\
330 &\quad 327 &\quad 340 \\
\text{HO} \quad \text{SO} \quad \text{Fe(II)} + \text{H}^+ &\rightarrow \text{SO} \quad \text{Fe(III)} + \text{H}_2\text{O} & (9) \\
334 &\quad 329 &\quad 333 &\quad 332 \\
\text{SO} \quad \text{OH} &\rightarrow \text{SO} \quad \text{OH} + \text{CH}_4 & (10) \\
336 &\quad 341 &\quad 342 \\
\text{SO} \quad \text{OH} &\rightarrow \text{SO} \quad \text{OH} + \text{H}_2\text{O} \quad k_3 = 10^6 \text{ M}^{-1}\text{s}^{-1} & (11) \\
336 &\quad 335 &\quad 343
\end{align*}
\]

Scheme 123. Possible side reactions.

In addition, furan (324) is used in a large excess to obtain only mono-substitution. With less furan or a larger amount of alkyl iodide, formation of disubstituted product, (344) was observed (Scheme 124).142

\[
\begin{align*}
\text{I} + \text{OEt} &\rightarrow \text{EtO} + \text{OEt} & (12) \\
327 &\quad 328 &\quad 344 \\
\text{FeSO}_4, 7\text{H}_2\text{O} \quad \text{H}_2\text{O}_2, \text{DMSO} &\rightarrow \text{EtO} + \text{OEt} & (13) \\
344
\end{align*}
\]

Scheme 124. Side reaction occurring with less furan or more of alkyl iodide.

Following Baciocchi’s procedure, ester 328 was furnished in 98% yield, and used as the starting material to build Weinreb amide 17. Reduction of functionalized furan
328 led to alcohol 345 in 93% yield. In order to introduce a chain at the 5’ position of functionalized furan 345, another Baciocchi radical coupling was performed following an improved synthetic procedure developed by Neier et al.\textsuperscript{144} to give the known ethyl ester 346 in 75% yield. The moderate yield is due to the fact that not all of the alkyl iodide was consumed during the reaction. Alcohol 346 was then oxidized with DMP to afford aldehyde 347 in 98% yield. Having this intermediate in hand a Wittig olefination reaction would have led to the desired allyl chain 349. However, treatment of 347 with the \textit{in situ} formed methylenetriphenylphosphorane (350) led to decomposition and was attributed to the base sensitivity of intermediate 347. Aldehyde 347 only performed a clean Wittig reaction\textsuperscript{145} with (tert-butoxycarbonylmethylene) triphenylphosphorane (348). Given the difficulties associated with the last step in this sequence, this route was deemed unsuitable for a scale up synthesis and consequently was abandoned (Scheme 125).

\begin{align*}
\text{CH}_3\text{COEt} + \text{I} & \xrightarrow{i} \text{CH}_3\text{C(OEt)_2} \xrightarrow{ii} \text{CH}_3\text{C}({OEt})\text{OH} \xrightarrow{iii} \text{CH}_3\text{C}({OEt})_2 \\
\text{327} & \quad \text{324} & \quad \text{328} & \quad \text{345} & \quad \text{327} \\
\text{OEt} \text{C} & \xrightarrow{iv} \text{OEt} \text{C} \xrightarrow{v} \text{OEt} \text{C} \text{O} \text{O} \text{O} \text{O} \\
\text{346} & \quad \text{347} & \quad \text{348} & \quad \text{349} \\
\text{Ph}_3\text{P} & \xrightarrow{350} & \text{Ph}_3\text{P} & \xrightarrow{348}
\end{align*}

\textbf{Scheme 125. Reagents and Conditions:} i) FeSO$_4$, 7H$_2$O, H$_2$O$_2$, DMSO, RT, 8 h, 98%; ii) LiAlH$_4$, THF, 0 °C, 1.5 h, 93%; iii) FeSO$_4$, 7H$_2$O, H$_2$O$_2$, DMSO, RT, 8 h, 75%; iv) DMP, CH$_2$Cl$_2$, RT, 20 min, 98%; v) 348, THF, -78 °C, 1 h, 52%.
5.3.1.5 Synthesis of Weinreb amide 17 via a Stille coupling

Baciocchi and co-workers have only reported the used of iodo-esters or iodo-nitriles as radical precursors for the homolytic substitution reaction of furan (324). Therefore we decided to directly use 2-iodo-N-methoxy-N-methylacetamide (352) as an alternative coupling partner. This intermediate was made from the commercially available 2-chloro-N-methoxy-N-methylacetamide (351) via a Finkelstein reaction. To our delight, the radical coupling still worked with Weinreb amide 352, using the same conditions as previously described. The introduction of the allyl group at the 5’ position of the 2-substituted furan 353 was first attempted using two equivalents of LiHMDS or t-BuLi, followed by addition of allylbromide (189). However, this initial approach was unsuccessful; only intermediate 354 was obtained in good yield (Scheme 126).

![Scheme 126. Reagents and Conditions:](attachment:image.png)

A second approach was investigated using a Stille coupling as the key step. Treatment of Weinreb amide 353 with a brominating agent did not selectively functionalise the furan at the 5’ position. The α-position of the amide 353 was more reactive toward N-bromosuccinimide, consequently two equivalents of brominating agent were added at
low temperature to functionalize both the $\alpha$-position of the amide and the 5' position of the furan. In order to get the monobromo-substituted furan 357, a simple Reformatsky$^{147}$ type reaction was applied. A selective debromination of the $\alpha$-bromoamide was performed using zinc and acetic acid in THF. If the reaction was carried out in methanol, ether 356 was formed in 84% yield (Scheme 127).

![Scheme 127. Reagents and Conditions: i) NBS, CH$_2$Cl$_2$, -78 °C to 0 °C, 8 h, 79%; ii) Zn, AcOH, MeOH, RT, 1 h, 84%; iii) Zn, AcOH, THF, RT, 1 h, 63.](image)

Having intermediate 357 in hand, a Stille coupling was attempted using 1.5 equivalents of allyltributylstanannane (318) and 0.1 equivalent of tetrakis(triphenylphosphine)palladium(0) in DMA at 90 °C (Scheme 128, Table 15, entry 1). However, reduced furan 353 was observed in a 25% ratio, starting material 357 in a 10% ratio and desired allyl substituted furan 17 in a 65% ratio. Although the formation of furan 357 was acceptable, purification was difficult due to impossible separation from 353. Therefore improvements to the Stille coupling reaction were investigated (Scheme 128, Table 15). It should be noted that formation of des-brominated furan was not observed when the Stille coupling was performed with furan 317. Different hypothesis were then investigated. We first added an excess of cesium carbonate to deprotonate the $\alpha$-position of the amide to attempt to avoid this side reaction (Table 15, entry 2). Unfortunately no improvements were observed. We then thought to add a phosphine ligands. As far as we know, no Stille coupling reaction has
been performed in the literature using phosphine ligands such as X-Phos (359), tBu-X-Phos (360) or Xantphos (361).

Scheme 128. Reagents and Conditions: i) conditions see Table 15.
To our delight, using these ligands suppressed the formation of reduced furan 353 and increased the rate of the reaction (Table 15, entries 3-6). Optimal conditions used 3 mol% of bis(dibenzylideneacetone)palladium(0) and 9 mol% of tBu-X-Phos (360) to give allyl furan 17 in 69% yield (Table 15, entry 6).

Having Weinreb amide 17 in hand, synthesis of diketo-dioxinone 312 was possible using a C-acylation reaction. This strategy has already been discussed in chapter 2.83 Treatment of keto-dioxinone 16 with lithium di-iso-propylamide at –78 °C gave

---

Table 15. Different reaction conditions tested on 358.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>318, Pd₂(PPh₃)₄ (5 mol%), DMA, 90 °C, 20 h</td>
<td>25% of 353, 10% of 357, 65% of 17*</td>
</tr>
<tr>
<td>2</td>
<td>318, Pd₂(PPh₃)₄ (5 mol%), Cs₂CO₃, DMA, 90 °C, 20 h</td>
<td>21% of 353, 12% of 357, 67% of 17*</td>
</tr>
<tr>
<td>3</td>
<td>318, Pd₂dba (10 mol%), 359 (30 mol%), DMA, 90 °C, 8 h</td>
<td>67% of 17†</td>
</tr>
<tr>
<td>4</td>
<td>318, Pd₂dba (10 mol%), 360 (30 mol%), DMA, 90 °C, 8 h</td>
<td>70% of 17†</td>
</tr>
<tr>
<td>5</td>
<td>318, Pd₂dba (10 mol%), 361 (30 mol%), DMA, 90 °C, 8 h</td>
<td>67% of 17†</td>
</tr>
<tr>
<td>6</td>
<td>318, Pd₂dba (3 mol%), 360 (9 mol%), DMA, 90 °C, 8 h</td>
<td>69% of 17†</td>
</tr>
</tbody>
</table>

1 Ratio determined by analysis of the ¹H NMR of the crude material.
2 Isolated yield. (no furan 353 and 357 observed)
dianion 362, followed by addition of Weinreb amide 17 at -40 °C provided the required diketo-dioxinone 312 in 63% (Scheme 129).

Scheme 129. Reagents and Conditions: i) LDA (2eq.), THF, -78 °C to -40 °C; ii) 17, THF, -40 °C, 1 h, 63%.

5.3.2 Synthesis of deschloro-pochonin H

5.3.2.1 First synthesis of deschloro-pochonin H via ring closing metathesis

Having successfully made key intermediate 312, our attention was then focused on the already optimized reaction involving the formation of the aromatic ring. Thermolysis of the keto-dioxinone 312 and in situ trapping of the triketo-ketene 363 with alcohol 18 gave triketo-ester 364. This intermediate was smoothly aromatized with cesium carbonate followed by an acid work-up\(^8\) to provide the resorcylate 365 in good yield (78%) (Scheme 130). Subsequent ring closing metathesis in toluene (10\(^{-3}\) M) using the second generation Hoveyda-Grubbs catalyst 223 led to intermediate 366 in 8% yield (Scheme 130, Table 16, entry 1). GCMS analysis indicated that 84% of the starting material has dimerised. The reaction was carried out at a lower concentration of 10\(^{-6}\) M (Table 16, entry 2). However, even at this dilution, only 12% of the desired resorcylate 366 was isolated. We suspected the intramolecular hydrogen bond between the ester of the resorcylate and the adjacent phenolic proton on intermediate
to be responsible for this unexpected result. It was thought that the hydrogen bonding aligned the ester group with the aromatic ring and consequently decreased the flexibility of the upper olefin, resulting in a difficult intramolecular metathesis with the allylic group. In order to break the undesired hydrogen bond, the ring closing metathesis was tested with addition of titanium isopropoxide\textsuperscript{148} or lithium bromide (Table 16, entries 3 and 4). However, only a relative improvement was observed with lithium bromide (Table 16, entry 4). To avoid the need for a phenolic protecting group our strategy needed to be changed.

\textbf{Scheme 130. Reagents and Conditions:} i) 18, PhMe, 110 °C, 1 h; ii) Cs\textsubscript{2}CO\textsubscript{3}, MeOH, RT then HCl 1M, 78%; iii) see Table 16.
**Table 16.** Different reaction conditions tested to synthesis deschloro-pochonin H (366).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>223 (10 mol%), PhMe ($10^{-3}$ M), 110 °C, 5 h</td>
<td>8% of 366</td>
</tr>
<tr>
<td>2</td>
<td>223 (10 mol%), PhMe ($10^{-6}$ M), 110 °C, 5 h</td>
<td>12% of 366</td>
</tr>
<tr>
<td>3</td>
<td>223 (10 mol%), PhMe ($10^{-3}$ M), Ti($i$PrO)$_4$, 110 °C, 5 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>223 (10 mol%), PhMe ($10^{-3}$ M), LiBr, 110 °C, 5 h</td>
<td>15% of 366</td>
</tr>
</tbody>
</table>

5.3.2.2 **New strategy via an intramolecular trapping of the ketene**

Barrett and Miyatake-Ondozaba have recently developed a new biomimetic strategy to synthesise the natural product zearalenone (6) using an intramolecular ketene-trapping procedure (Scheme 131).$^{149}$

Reaction between dioxinone 8 and benzotriazole intermediate 367 with zinc chloride gave diketo-dioxinone 368 in 63% yield. The presence of the Lewis acid, zinc chloride, was reported essential to achieve a selective C-acylation in a good yield. Cross metathesis of diketo-dioxinone 368 and alcohol 13 (Chapter 2) using second generation Grubbs catalyst 227, proceeded in good yield with a E/Z ratio of 20/1. Subsequent thermolysis of 369 in toluene ($4 \times 10^{-2}$ M) generated ketene 370, which performed an intramolecular trapping reaction to give cyclic diketo-ester 371. Ketal deprotection then gave triketo-ester 7 which underwent aldol condensation under basic conditions followed by elimination of water under acidic conditions to afford (S)-zearalenone (6) in 46% yield over four steps (Scheme 131).

$^*$ Isolated yields.
Inspired by this work, our new strategy was based on the formation of key intermediate \( \text{372} \). Cross-metathesis of diketo-dioxinone \( \text{312} \) with unprotected alcohol \( \text{18} \) using the second generation Hoveyda-Grubbs catalyst \( \text{223} \) gave alcohol \( \text{372} \) with a good Z:E selectivity (1:9, Z:E) (Scheme 132). This step is, as far as we know, the first reported metathesis reaction performed on an unprotected diketo-ester. Upon heating, diketo-dioxinone \( \text{372} \) underwent a retro Diels–Alder reaction and generated a
triketo-ketene which was trapped intramolecularly by the unprotected alcohol to make the cyclic triketo-ester 373 (confirmed by $^1$H-NMR) (Scheme 132). Subsequent basic and acid treatments to perform the aromatization were unsuccessful and no desired product 366 was formed. It was thought that during the basic treatment, the ester and the adjacent ketone could have chelated the counter cation as they were aligned in the same plane. This conformation was similar to the one previously described, preventing the ring closing metathesis. Therefore under basic conditions, the conformation of the 17-membered macrocyclic lactone 373 was thought to prevent the aldol reaction from occurring. The presence of the furan might also rigidify the intermediate 373 backbone. Thus it was postulated that in its biosynthesis, synthesis of the furan might occur after the resorcylate formation.

Scheme 132. Reagents and Conditions: i) 223, 18, CH$_2$Cl$_2$, 40 °C, 1 h, 61%; ii) PhMe ($10^{-3}$), 110 °C, 1 h; ii) Cs$_2$CO$_3$, MeOH, RT then HCl 1M.

Treatment of diketo-dioxinone 372 with triethylamine gave benzodioxinone 374 in 67% yield.$^{86}$ However, attempted transesterification to form 366 under basic conditions failed (Scheme 133).
Scheme 133. Reagents and Conditions: i) Et$_3$N, CH$_2$Cl$_2$, RT, 1 h, 64%; ii) NaH, THF, 60 °C, 8 h.

5.3.2.3 Improved synthesis of deschloro-pochonin H via a ring closing metathesis with a phenol protecting group

All our attempts to generate product 366 via a protecting group free synthesis were not successful, therefore we decided to acetylate both phenols in resorcylate 365 and to hopefully suppress any undesired effects of the previously mentioned hydrogen bond. Treatment of intermediate 365 with acetic anhydride and DMAP gave acetylated compound 375 in good yield. Subsequent ring closing metathesis using the second generation Hoveyda-Grubbs catalyst 223 gave macrolactone 376 with a 1:3, Z:E ratio. The two diastereoisomeres were inseparable by column chromatography. Deprotection of the acetyl groups with sodium hydrogen carbonate afforded the (Z)-deschloro-pochonin H (366) in a 68% isolated yield (scheme 134).
Scheme 134. Reagents and Conditions: i) Ac₂O, DMAP, THF, RT, 70 min, 73%; ii) 223, PhMe, 90 °C, 2 h, 54%; iii) NaHCO₃ aq., MeOH, RT, 14 h, 68%.

The X-ray structure of compound 366 (Figure 20) confirmed the presence of a hydrogen bond between the sp3 oxygen of the ester and a phenolic proton. By NMR, the proton shift involved in the hydrogen bonding is 11.87 ppm for intermediate 365 and 8.5 ppm for macrolactone 366 (scheme 134). We also notice that the aromatic ring and the ester of the resorcylate are not in the same plane. All those observations demonstrate that, even if compound 366 is a 13 membered ring, its macrolactone is strained and the conformation adopted does not place the ester group in the same plane as the aromatic ring, which was a necessary conformation to perform the intramolecular aldol reaction. A similar explanation can be made to interpret the unsuccessful ring closing metathesis with no phenol protecting group, indeed the hydrogen bond was locking the conformation of intermediate 365 in a position which was unable to adopt the deschloro-pochonin H (366) conformation (observed in the X-
ray) and consequently was not able to perform the ring closure. To summarize, the X ray indicates the low probability of those reactions succeeding due to conformation restrictions.

**Figure 20.** Crystal structure of deschloro-pochonin H (366).

### 5.3.2.4 Towards the chlorination of deschloro-pochonin H

Both natural products, pochonin G and H, contain a chlorine atom at the sixth position of the resorcylate ring. Introducing the chlorine atom in an early stage of the synthesis, even before the aromatization step, would have been a good idea since chlorination of resorcylates via electrophilic substitution is usually low yielding.\(^{150}\) Two strategies were tested. The first one was similar to the method previously described. First the
known chloro keto-dioxinone $^{90}$ was made from dioxinone $^{8}$ and chloroacetyl chloride ($^{89}$). Treatment of $^{90}$ with lithium di-iso-propylamine at $-78 \, ^\circ\text{C}$ followed by the addition of Weinreb amide $^{17}$ at $-40 \, ^\circ\text{C}$, failed to give the desired keto-dioxinone $^{377}$ (Scheme 135).

![Scheme 135](image)

**Scheme 135. Reagents and Conditions:** i) LiHMDS, THF, $-78 \, ^\circ\text{C}$; ii) $^{89}$, THF, $-78 \, ^\circ\text{C}$ to RT, 8 h, 70%; iii) LDA (2eq.), THF, $-78 \, ^\circ\text{C}$ to $-40 \, ^\circ\text{C}$; iv) $^{17}$, THF, $-40 \, ^\circ\text{C}$, 1 h.

The second strategy was relying on the direct addition of chlorine to intermediate $^{312}$. Treatment of diketo-dioxinone $^{312}$ with sulfuryl chloride gave an unstable intermediate in low yield and any attempts at aromatization were unsuccessful (Scheme 136). Thus it was decided to introduce the chlorine atom later in the synthesis.

![Scheme 136](image)

**Scheme 136. Reagents and Conditions:** i) $\text{SO}_2\text{Cl}_2$, CH$_2$Cl$_2$, $-30 \, ^\circ\text{C}$, 1 h; ii) isopropanol, sealed tube, 100 $\, ^\circ\text{C}$, 3 h.
Chlorination of the resorcylate ring was attempted on intermediates 365, 375 and 376 using both sulfuryl chloride and NCS. However only decomposition was observed (Scheme 139).

Another attempt was performed using sulfuryl chloride in THF which led to intermediate 382 in 12% yield (Scheme 138, Table 17, entry 1). Adding a base such as sodium hydride (Table 17, entry 2) or 2-tert-butyl-1,1,3,3-tetramethylguanidine (Barton’s base) (Table 17, entry 3) or changing the chlorinating agent to N-chlorosuccinimide (Table 17, entries 4-5) did not change the selectivity. Addition of
m-CPBA to 366 gave resorcylate 382 in 72% yield (Table 17, entry 6). All treatments with chlorinating agents or peracids were leading to the opening of the furan to provide macrolactone 382 rather than effecting chlorination (Scheme 138).

Scheme 138. *Reagents and Conditions:* i) conditions see Table 17.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SO₂Cl₂, THF, –30 °C to 0 °C, 90 min</td>
<td>12% of 382</td>
</tr>
<tr>
<td>2</td>
<td>SO₂Cl₂, NaH, THF, –30 °C to 0 °C, 90 min</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>SO₂Cl₂, Barton’s base, THF, –30 °C to 0 °C, 90 min</td>
<td>S.M.</td>
</tr>
<tr>
<td>4</td>
<td>NCS, THF, –30 °C to 0 °C, 90 min</td>
<td>6% of 382</td>
</tr>
<tr>
<td>5</td>
<td>NCS, Barton’s base, THF, –30 °C to 0 °C, 90 min</td>
<td>S.M.</td>
</tr>
<tr>
<td>6</td>
<td>m-CPBA, CH₂Cl₂, RT, 1 h</td>
<td>72% of 366</td>
</tr>
</tbody>
</table>

Table 17. *Different chlorination conditions tested.*
5.4 Conclusions

In summary, we report the first synthesis of dechlor-pochonin H 366 in eleven steps with an overall yield of 4.5% (Scheme 138). Further applications of this strategy towards pochonin G are currently under investigation.
Scheme 139. Reagents and Conditions: i) NaI, acetone, RT, 8 h, 98%; ii) FeSO$_4$, 7H$_2$O, H$_2$O$_2$, DMSO, RT, 8 h, 98%; iii) NBS, CH$_2$Cl$_2$, -78 °C to 0 °C, 8 h, 79%; iv) Zn, AcOH, THF, RT, 1 h, 63%; v) 318, Pd$_3$dba$_3$ (3 mol%), 360 (9 mol%), DMA, 90 °C, 8 h, 69%; vi) LDA (2eq), THF, -78 °C to -40 °C; vii) 350, THF, -40 °C, 1 h, 63%; viii) 18, PhMe, 110 °C, 1 h; then Cs$_2$CO$_3$, MeOH, RT then 1M HCl, 78%; ix) Ac$_2$O, DMAP, THF, RT, 70 min, 73%; x) 223, PhMe, 90 °C, 2 h, 54%; xi) NaHCO$_3$ aq., MeOH, RT, 14 h, 68%.
CHAPTER SIX:
OVERALL CONCLUSIONS
AND APPLICATIONS
To summarise, from the key building block diketo-dioxinone, we succeeded to synthesise a large variety of interesting compounds. We had access to the resorcylic acid lactones of which (S)-zearalenone (6) is a member. We performed the total synthesis of erythrin (4) and montagnetol (2) and assigned their absolute stereochemical configuration. We reported the construction of polysubstituted bicyclic frameworks (214 and 15) as well as heteroaromatic 20. Finally we synthesised 382 and 366, derivates of a hair-growth stimulant pochonin G (3) (Figure 21).

**Figure 21.** Diketo-dioxinone, a key building block.
In addition, we reported four efficient strategies to synthesise diketo-dioxinones.

The first one using a Mukaiyama aldol reaction:

The second one using allylester 156:

The third one using Weinreb amide 178:

And the fourth one using benzotriazole derivative 9:
In this thesis, we report a novel strategy to synthesise resorcylates from diketo-dioxinones which underwent a retro-Diels-Alder reaction to generate triketo-ketenes. These highly reactive intermediates were trapped with alcohols to generate triketo-esters. An aromatisation reaction was then performed under mild, optimised conditions in good yields. This methodology was then used within the Barrett group to synthesise natural products difficult to obtain via more conventional synthesis.

Accordingly, Navarro reported the total synthesis of the marine antifungal agent 15G256β (5) using this approach. Dioxinone 173 described in section 2.2.1.5, was heated in the presence of alcohol 383 to give triketo-ester 384. This intermediate 384 was then aromatised to afford, after phenol group protection, resorcylate 385. A Yamaguchi esterification was then performed between the acid derived from ester 385 via a deallylation and the alcohol derived from ester 385 via a selective desilylation to provide dimer 386. Subsequent deallylation-Yamaguchi esterification with alcohol 383 gave the allyl ester 387 in 71% yield. Upon deallylation, desilylation followed by Yamaguchi lactonisation and debenzylation by hydrogenolysis gave the natural product 15G256β (5) (Scheme 140).
Scheme 140. Synthesis of 15G256β (5).
The intermolecular ketene generation, alcohol trapping and aromatisation process was also successfully utilised in the synthesis of ent-W1278A (177, n = 2), -B (n= 3), and -C (n =4) by Poverlein and Navarro. For example, ent-W1278A (177) was obtained from the key resorcylate intermediate 389, which was achieved from diketo-dioxinone 173 in 75% yield via an alcohol 388 trapping aromatisation. From intermediate 389, an iterative desilylation, mild ketene trapping followed by resorcylate formation was performed to obtain the oligo-ester 391 in 50% yield. Subsequent aromatisation-hydrogenolysis gave carboxylic acid ent-W1278A (177, n = 2) in 60% (Scheme 141).
Within the Barrett group, Calo performed the total synthesis of aigialomycin D (38) using the intermolecular alcohol trapping-aromatisation strategy. He also compared two available syntheses to build diketo-dioxinone 393. Intermediate 393 was obtained in 81% yield using allyl ester 156 and acid chloride 392 whereas using keto-dioxinone 16 and Weinreb amide 394 only gave 20% of diketone 393 due to the formation of 1,4-addition products. Aigialomycin D (38) was obtained via a ring closing metathesis.
followed by ketal deprotection in 79% yield over two steps from resorcylate 396 (Scheme 142).

Scheme 142. Synthesis of aigialomycin D (38).
CHAPTER SEVEN:
EXPERIMENTAL
**General Procedures:**

All reactions were carried out in oven-dried glassware under N\textsubscript{2} using solvents and reagents as commercially supplied, unless otherwise stated. Et\textsubscript{2}O, THF, PhMe, CH\textsubscript{2}Cl\textsubscript{2}, Et\textsubscript{3}N and MeOH were redistilled from Na-Ph\textsubscript{2}CO, Na-Ph\textsubscript{2}CO, Na, CaH\textsubscript{2}, CaH\textsubscript{2} and Mg turnings–I\textsubscript{2}, respectively. Column chromatography was carried out on silica gel, particle size 40-63 µm, using flash techniques (eluants are given in parenthesis). Analytical thin layer chromatography was performed on pre-coated silica gel F\textsubscript{254} glass plates with visualization under UV light or by staining using either acidic vanillin or anisaldehyde spray reagents.

**Melting points:** obtained using a Reichert-Thermovar melting point apparatus and are uncorrected.

**Infrared spectra:** obtained using a Mattson 5000 FTIR apparatus with automatic background subtraction. Indicative features of each spectrum are given with adsorptions reported in wavenumbers (cm\textsuperscript{-1}).

**Proton magnetic resonance spectra** (\textsuperscript{1}H NMR): recorded at 400 MHz on Bruker DRX-400 spectrometers. All spectra are referenced to the residual solvent peak. Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (\textit{J}) recorded in Hertz (Hz).

**Carbon magnetic resonance spectra** (\textsuperscript{13}C NMR): recorded at 100 MHz on Brüker DRX-400 spectrometers, or at 125 MHz on an AM 500 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to the residual solvent peak. Spectra recorded at 500 MHz (\textsuperscript{1}H NMR) and 125 MHz (\textsuperscript{13}C NMR) were carried out by the Imperial College Department of Chemistry NMR service or by the GSK NMR service.

**Gas chromatography mass spectrometry** (GCMS): recorded on a Hewlett-Packard 5890 series 2 gas chromatograph. **Mass spectrometry:** Low and high resolution mass
spectra (EI, CI) were recorded by Imperial College Mass Spectrometry Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer.

**Microanalysis:** determined by the University of North London Analytical Service.

**Optical Rotations:** recorded at 25 °C on a Perkin-Elmer 241 Polarimeter with a path length of 1 dm, using the 589.3 mn D-line of sodium. Concentrations (c) are quoted in g/100 mL.

**X-ray Diffraction:** X-ray diffraction data were recorded by the Imperial College Department of Chemistry X-ray diffraction service.
To a suspension of magnesium powder (2.45 g, 101 mmol) in Et₂O (100 mL) was added two crystals of iodine and the resultant mixture was sonnicated for 10 min and then heated to 60 °C at which point the reaction mixture turned from brown to colourless. 5-Bromo-1-pentene 118 (12.0 mL, 101 mmol) was added dropwise and after a further 1 h at 60 °C the reaction mixture was cooled to 25 °C. The resulting crude 4-pentenyl magnesium bromide 119 solution was transferred via canula to a solution of δ-hexanolactone 62 (13.3 g, 92.3 mmol) in THF (200 mL) at -78 °C, and the ensuing reaction mixture stirred for 2 h at that temperature before being quenched by addition of saturated aqueous NH₄Cl (60 mL) and water (100 mL). The aqueous layer was extracted with Et₂O (3 x 100 mL) and the combined organic extracts washed with H₂O (2 x 50 mL) and dried (Na₂SO₄). Concentration in vacuo afforded alcohol 120 (16.5 g) as a pale yellow oil which was used in the next step without purification:

Rf 0.48 (EtOAc:hexanes, 1:1); IR (film) 3444, 1732, 1711, 1068 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.79–5.74 (m, 1H, H₁₀), 5.04–4.96 (m, 2H, H₁₁), 3.80–3.74 (m, 1H, H₂), 2.48–2.39 (m, 4H, H₃ and H₇), 2.10–2.02 (m, 2H, H₅), 1.99–1.39 (m, 6H, H₃, H₄ and H₅), 1.19 (d, J = 6.0 Hz, 3H, H₁); ¹³C NMR (75 MHz, CDCl₃) δ 211.3, 138.0, 115.2, 67.5, 42.6, 38.6, 33.1, 29.6, 23.4, 22.8, 19.7; MS (Cl) m/z 185 (M+H)+, 202 (M+NH₄)+; HRMS (Cl) calculated for C₁₁H₂₀O₂: (M+H)+, 185.1542, found: 185.1546.
Acetic acid 1-methyl-5-oxodec-9-enyl ester (142)

A mixture of alcohol 120 (5.0 g, 27.2 mmol), acetic anhydride (30 mL) and pyridine (30 mL) was heated to 60 °C. After 24 h the reaction mixture was cooled to 0 °C, quenched by addition of methanol (40 mL) and the solvent concentrated under vacuum. The residue was poured in water (30 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine (30 mL) and dried (Na₂SO₄). Concentration in vacuo was followed by flash column chromatography (SiO₂, EtOAc:hexanes, 1:4) to afford ketone 142 (4.35 g, 71%) as a colorless oil:

\[ R_f \ 0.32 \text{ (EtOAc:hexanes, 1:3); IR (film) 2941, 1733, 1451, 1372, 1247, 1019 cm}^{-1}; \text{ } ^{1}H \text{ NMR (300 MHz, CDCl₃) } \delta 5.81-5.70 \text{ (m, 1H, H}_{10}), 5.02-4.85 \text{ (m, 2H, H}_{11}), 4.94-4.82 \text{ (m, 1H, H}_{2}), 2.43-2.36 \text{ (m, 4H, H}_{5} \text{ and H}_{6}), 2.01-1.97 \text{ (m, 2H, H}_{9}), 1.95 \text{ (s, 3H, H}_{16}), 1.65-1.19 \text{ (m, 6H, H}_{3} \text{, H}_{4} \text{ and H}_{8}), 1.13 \text{ (d, } J = 7.0 \text{ Hz, 3H, H}_{4}); \text{ } ^{13}C \text{ NMR (75 MHz, CDCl₃) } \delta 210.6, 170.8, 137.9, 115.2, 70.5, 42.3, 41.9, 35.2, 33.1, 22.8, 21.3, 19.8, 19.5; \text{ MS (Cl) } m/z 227 \text{ (M+H)}^{+}, 244 \text{ (M+NH}_{4})^{+}; \text{ HRMS (Cl) calculated for C}_{13}H_{23}O_{3}: (M+H)^{+}, 227.1647; \text{ found: (M+H)^{+}, 227.1647.} \]
Acetic acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester

(143)

To a solution of compound 142 (5.0 g, 22.1 mmol) in benzene (150 mL) ethylene glycol was added (37.0 mL, 66.4 mmol), followed by PPTS (556 mg, 2.92 mmol). The reaction mixture was heated to 90 °C under Dean-Stark phase-separating apparatus. After 18 h the reaction mixture was allowed to cool to RT, diluted with EtOAc (100 mL) and washed with sat. aq. NaHCO₃ (2 x 80 mL). The organic layer was dried (Na₂SO₄), concentrated under vacuum and purified by flash column chromatography (SiO₂, EtOAc:hexanes, 1:9) to afford ketal 143 (4.36 g, 73%) as a clear oil:

Rₛ 0.46 (EtOAc:hexanes, 1:9); IR (film) 1732, 1451, 1371, 1245, 1042 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.86-5.67 (m, 1H, H₁₀), 4.98 (d, J = 16.3 Hz, 1H, H₁₁), 4.93 (d, J = 10.4 Hz, 1H, H₁₁), 4.91-4.85 (m, 1H, H₂), 3.90 (s, 4H, H₁₇ and H₁₈), 2.06–2.01 (m, 2H, H₉), 2.01 (s, 3H, H₁₅), 1.72-1.33 (m, 10H, H₃, H₅, H₆, H₇ and H₈), 1.18 (d, 3H, J = 6.0 Hz, H₁); ¹³C NMR (75 MHz, CDCl₃) δ 170.7; 138.6, 114.6, 111.5, 70.8, 64.9 (2C), 36.8, 36.5, 36.0, 33.8, 23.1, 21.3, 19.9, 19.7; MS (CI) m/z 271 [M+H]⁺, 288 [M+NH₄]⁺; HRMS (CI) calculated for C₁₃H₂₇O₄: [M+H]⁺ 271.1909, found: 271.1900.
5-(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-pentan-2-ol (140)

To a solution of ketal 143 (16.0 g, 59.3 mmol) in methanol (59 mL) was added aq. KOH (3M, 140 mL, 419 mmol). The mixture was stirred at 25 °C for 3 h after which time the reaction was concentrated under vacuum. The residue was dissolved in CH₂Cl₂ (350 mL) and successively washed with water (175 mL) and brine (175 mL). The organic layer was dried (Na₂SO₄) and concentrated under vacuum to give the racemic mixture of alcohols 140 (12.58 g, 93%) as a clear oil:

Rᵣ 0.55 (EtOAc:hexane 1:3); IR (film) 3422, 1456, 1147, 1044, 911 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.82 (tdd, J = 17.1, 10.2, 6.2 Hz, 1H, H₁₀), 5.03 (dd, J = 17.1, 1.2 Hz, 1H, H₁₁), 4.97 (dd, J = 10.2, 1.2 Hz, 1H, H₁₁), 3.94 (s, 4H, H₁₄ and H₁₅), 3.83–3.76 (m, 1H, H₂), 2.07 (q, J = 7.1 Hz, 2H, H₃), 1.61-1.55 (m, 4H, H₉ and H₈), 1.47-1.35 (m, 6H, H₄, H₅ and H₇), 1.18 (d, J = 6.0 Hz, 3H, H₁); ¹³C NMR (75 MHz, CDCl₃) δ 138.6, 114.6, 111.6, 67.9, 65.0 (2C), 39.4, 37.0, 36.5, 33.8, 23.4, 23.1, 19.9; MS (Cl) m/z 229 [M+H]⁺, 246 [M+NH₄]⁺; HRMS (Cl) calculated for C₁₃H₂₈O₃N [M+NH₄]⁺ 246.2069, found 246.2068.
To a solution of racemic alcohol 140 (12.58 g, 55 mmol) and vinyl acetate (10.2 mL, 165 mmol) in hexane (262 mL), was added in one portion CAL-B (550 mg, 10 mol%) and the resultant mixture was stirred under air at 35 °C for 80 min. The reaction mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography (SiO₂, gradient EtOAc:hexane 1:10 to 1:3) to yield acetate 141 (5.46 g, 51%) and the enantiomerically enriched mixture of alcohols 144 (6.04 g, 48%, [α]D₂⁵ +5.77 (c 3.14, CH₂Cl₂) (the literature optical rotation for R-(−)-127 is αD₂⁵ = −6.8 (c 1.02 CH₂Cl₂))⁴⁰ both as clear oils.

To a solution of 144 (6.04 g, 26.4 mmol) and vinyl acetate (5.8 mL, 93.9 mmol) in hexane (148 mL) was added in one portion CAL-B (312 mg, 10 mol%) and the resultant mixture was stirred under air at 35 °C for 3 h. The reaction was filtered and the solvent evaporated under vacuum. The residue was purified by flash column
chromatography (SiO$_2$, gradient EtOAc:hexane 1:10 to 1:3) to yield the enantiomeric pure $S$-$(+)$-alcohol 13 (4.79 g, 79%; 38% over 2 steps) as a clear oil:

**Spectroscopical data for (R)-Acetic acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (141):** $R_f$ 0.46 (EtOAc:hexane 1:9); $[\alpha]_D^{25} -1.0$ (c 1.10, CH$_2$Cl$_2$); IR (film) 1732, 1451, 1371, 1245, 1042 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.86-5.67 (m, 1H), 5.01-4.95 (m, 2H), 4.91-4.85 (m, 1H), 3.90 (s, 4H), 2.06–2.01 (m, 2H), 2.06 (s, 3H), 1.72-1.33 (m, 10H), 1.18 (d, $J = 6.0$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.8, 138.6, 114.5, 111.5, 70.8, 64.9 (2C), 42.3, 36.8, 36.5, 33.9, 23.1, 21.4, 19.9, 19.7; MS (Cl) m/z 271 [M+H]$^+$, 288 [M+NH$_4$]$^+$; HRMS (Cl) calculated for C$_{15}$H$_{27}$O$_4$ [M+H]$^+$ 271.1909, found 271.1900. Anal. calcd. for C$_{15}$H$_{26}$O$_4$: C, 66.64; H, 9.69. Found: C, 66.53; H, 9.59.

**Spectroscopical data for alcohol S-$(+)$-13:** $R_f$ 0.55 (EtOAc:hexanes 1:3); $[\alpha]_D^{25} +6.7$ (c 3.14, CH$_2$Cl$_2$); IR (neat) 3422, 1455, 1129, 1082, 911 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.82 (tdd, $J = 17.1$, 10.2, 6.2 Hz, 1H), 5.03 (dd, $J = 17.1$, 1.2 Hz, 1H), 4.94 (dd, $J = 10.2$, 1.2 Hz, 1H), 3.92 (s, 4H), 3.83-3.76 (m, 1H), 2.07 (q, $J = 7.1$ Hz, 2H), 1.64-1.54 (m, 4H), 1.48-1.37 (m, 6H), 1.18 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 138.6, 114.6, 111.6, 67.9, 65.0 (2C), 39.4, 37.0, 36.5, 33.8, 23.4, 23.1, 19.9; MS (Cl) m/z 229 [M+H]$^+$, 246 [M+NH$_4$]$^+$; HRMS (Cl) calculated for C$_{13}$H$_{28}$O$_3$N [M+NH$_4$]$^+$ 246.2069, found 246.2068.
5-(1-Hydroxyethyl)-2,2,6-trimethyl[1,3]dioxin-4-one (146)

Li(N(SiMe₃)₂)₂ in THF (1 M; 0.23 mL, 0.23 mmol) was added dropwise with stirring to dioxinone 8 (30 mg, 0.21 mmol) in THF (2 mL) and the resulting pale yellow solution stirred at –70 °C for 50 min, when acetaldehyde (110) (0.03 mL, 0.52 mmol) was added. The reaction temperature was maintained at –70 °C for 30 min after which time the solution was poured onto aq. HCl (1 M; 5 mL) and Et₂O (4 mL) was added. The organic phase was washed with brine (3 x 5 mL), dried (MgSO₄), rotary evaporated and chromatographed (Et₂O:hexanes 2:1) gave dioxinone 146 (16.3 g, 42%) as a clear oil:

Rₚ 0.2 (EtOAc:hexanes 1:1); IR (neat) 3449, 2974, 2930, 1717, 1636, 1392, 1270, 1206 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 4.56 (q, 1H, J = 6.6 Hz, H₁₁), 3.38 (s broad, 1H, -OH), 2.01 (s, 3H, H₇), 1.65 (s, 3H, -CH₃), 1.63 (s, 3H, -CH₃), 1.45 (d, 3H, J = 6.6 Hz, H₁₂); ¹³C NMR (CDCl₃, 100 MHz) 163.6, 162.1, 108.3, 105.5, 65.0, 25.3, 24.8, 23.5, 17.2; MS (CI) m/z 187 [M + H]⁺.
Acetic acid 2-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-1-methyl-vinyl ester (149)

To a solution of LiHMDS (1.06 M in THF, 3.11 mL, 3.3 mmol) in THF (20 mL) at –40 °C was added diketene-acetone adduct 8 (400 µL, 3 mmol) dropwise, and the solution stirred at –40 °C for 45 min. A solution of acetyl chloride 148 (426 µL, 6 mmol) in THF (5 mL) was added dropwise and the resultant solution was allowed to warm to RT over 1 h. 1 M HCl (20 mL) was added, and the mixture extracted with Et₂O (3 x 30 mL), dried (MgSO₄), rotary evaporated, and chromatographed (CH₂Cl₂:EtOAc, 9:1) to afford 149 as a yellow oil (275 mg, 50%):

R₇ 0.3 (EtOAc:hexanes, 1:1); IR (neat) 3096, 2998, 2945, 1764, 1730, 1669, 1385, 1015 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.44 (s, 1H, H₂), 5.29 (s, 1H, H₃), 2.13 (s, 3H, -CH₃), 1.98 (s, 3H, -CH₃), 1.60 (s, 6H, H₉ and H₁₀); ¹³C NMR (CDCl₃, 75 MHz) δ 167.6, 161.7, 161.5, 155.4, 109.8, 106.1, 94.8, 24.9, 21.7, 20.8; MS (Cl) m/z 227 (M+H)⁺, 244 (M+NH₄)⁺
**2,2-Dimethyl-6-(2-oxopropyl)-4H-1,3-dioxin-4-one (16)**

LiN(SiMe$_3$)$_2$ in THF (1 M; 21 mL, 21 mmol) was added dropwise with stirring to dioxinone 8 (2.8 mL, 21 mmol) in THF (60 mL) and the resulting pale yellow solution stirred at −70 °C for 50 min, when AcCl (0.9 mL, 12.6 mmol) was added. The reaction temperature was maintained at −70 °C for 30 min after which time the solution was poured onto aq. HCl (1 M; 50 mL) and Et$_2$O (40 mL) was added. The organic phase was washed with brine (3 × 50 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (Et$_2$O:hexanes gradient 1:1 to 2:1) gave keto-dioxinone 16 (2.1 g, 55%) as a white solid:

R$_f$ 0.13 (Et$_2$O:hexanes 1:1); mp 47-50 °C (hexanes/CH$_2$Cl$_2$); IR: 1733, 1714, 1639, 1379, 1317, 1270, 1253, 1197, 1160, 1011, 904, 862, 821, 794 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.31 (s, 1H, H$_3$), 3.31 (s, 2H, H$_7$), 2.21 (s, 3H, H$_{12}$), 1.68 (s, 6H, H$_9$ and H$_{10}$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.0, 164.5, 160.8, 107.4, 96.9, 48.15, 30.3, 25.2 (2C); HRMS (Cl) calc. for C$_9$H$_{13}$O$_4$: (M + H)$^+$, 185.0814, found: (M + H)$^+$, 185.0812. Anal. calcd. for C$_9$H$_{12}$O$_4$: C, 58.69; H, 6.57. Found: C, 58.75; H, 6.63.
Methyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate

(151)

Dioxinone 8 (0.5 mL, 3.8 mmol) in THF (5 mL) was added dropwise with stirring to a solution of LiN(SiMe₃)₂ (4.56 mL, 4.56 mmol, 1 M in THF) in THF (70 mL) at −78 °C for 30 min. Acid chloride 150 (0.14 mL, 1.3 mmol) in THF (2 mL) was slowly added at −78 °C. The mixture was stirred at RT overnight. The solution was sequentially quenched by addition of an aqueous solution of NH₄Cl (50 mL), and a solution of HCl (1 M) until pH 4. After extraction with EtOAc (3 x 70 mL), the combined organic layers were washed with brine, dried (MgSO₄), rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to give ester 151 (186.1 mg, 61%) as a colorless oil:

Rf 0.4 (EtOAc:hexanes 1:3); ¹H NMR (CDCl₃, 400 MHz) δ 5.36 (s, 1H, H₃), 3.38 (s, 3H, H₁₅), 3.52 (s, 2H, -CH₂-), 3.49 (s, 2H, -CH₂-), 1.70 (s, 6H, H₀ and H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 195.5, 166.8, 163.4, 160.4, 107.4, 97.1, 52.6, 48.8, 47.0, 25.0 (2C); MS (ESI) m/z 243 [M + H]⁺.
3-(3-methylbut-2-enyloxy)-3-oxopropanoic acid (154)

Prop-2-en-1-ol (153) (25.5 g, 30 ml, 438.48 mmol, 6.3 eq.) and 2, 2-dimethyl-1, 3-dioxane-4, 6-dione (152) (10 g, 69.38 mmol, 1.0 eq.) were stirred at 80 °C for 12 h. The volatiles were removed in vacuo and the remaining liquid dissolved in ethanol (20 mL). A solution of aqueous ammonia (50%, 5 mL) was added to the mixture, which was then allowed to stir for 30 minutes. The volatiles were removed in vacuo and the remaining residue washed with 1:1 diethyl ether:hexane (200 mL). The pale yellow residue was dissolved in water (30 mL), pH adjusted to pH 3 using 1 M HCl and extracted with diethyl ether (3 x 100 mL). The organics were combined, dried over MgSO₄ and volatiles removed in vacuo to afford propanoic acid 154 as a pale yellow oil (2.9 g, 30%):

Rf 0.43 (Petroleum ether: EtOAC). IR (neat) 3044, 1722, 1413, 1369, 1318, 1274, 1157, 990, 929 cm⁻¹. ¹H (400MHz, CDCl₃) 5.99-5.90 (m, 1H), 5.41-5.36 (m, 1H), 5.33-5.29 (m, 1H), 4.71 (dt, J= 5.6 and 1.2Hz), 3.50 (s, 2H). ¹³C NMR (400MHz, CDCl₃): 40.6, 65.9, 119.2, 131.2, 166.7, 170.6. HRMS (CI) m/z C₆H₇O₄⁺ [M + NH₄]⁺ Anal. calcd. 161.0423, found [M + H]⁺ found 161.0764.
Allyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (156)

Monoallyl malonate 154 (21.1 g, 146.8 mmol) was stirred in anhydrous CH$_2$Cl$_2$ (250 mL) at 0 °C. Oxalyl chloride (14.6 mL, 179.1 mmol) and DMF (2 mL) were added and the reaction mixture stirred for 1 h at 0 °C followed by 2 h at RT. The volatiles were removed in vacuo, to afford acid chloride 155 as a brown oil.

To a solution of HMDS (1.9 mL, 9.12 mmol) in of THF (140 mL) at –78 ºC, BuLi (3.8 mL, 9.5 mmol, 2.5 M in hexanes) was added dropwise and the resultant solution was stirred at this temperature over 30 min. After this period, dioxinone 8 (1 mL, 7.6 mmol) was added dropwise and the solution stirred at –78 ºC for 1.5 h. After this time, acid chloride 155 (374 mg, 2.3 mmol) was added in one portion and the temperature was raised up to RT overnight. The reaction was quenched by addition of a saturated solution of ammonium chloride (3 mL). The pH was adjusted to pH=3 with aq. HCl (1 M). The mixture was extracted with EtOAc (2 x 40 mL) and the combined organic layers were washed with brine and dried (MgSO$_4$). The solvent was removed under vacuum and the crude residue purified by chromatography (hexane:EtOAc, 8:2) to yield compound 156 (327 mg, 61 %) as a yellow oil:

- $R_f$ 0.30 (hexane:EtOAc 7:3); IR (KBr) 2999, 2945, 1727, 1639, 1391, 1274, 1204, 1010, 903, 809. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.90 (ddd, $J = 16.4, 11.1, 5.8$ Hz, 1H,
H_{18}), 5.37 (s, 1H, H_{3}), 5.33 (d, J = 17.2 Hz, 1H, H_{19}), 5.27 (d, J = 10.4 Hz, 1H, H_{19}),
4.63 (dd, J = 5.9, 1.8 Hz, 2H, H_{14}), 3.54 (s, 2H, -CH_{2}-), 3.50 (s, 2H, -CH_{2}-), 1.71 (s, 6H, H_{16} and H_{17}).^{13}C NMR (75 MHz, CDCl_{3}) 195.4, 165.9, 163.4, 160.4, 131.1, 119.2, 107.3, 97.0, 66.2, 48.9, 46.9, 24.9 (2C). MS (ESI) m/z 269 [M+H]^+; HRMS (ESI) calcd. C_{13}H_{17}O_{6}: [M+H]^+, 269.1025; found: [M+H]^+, 269.1030. Anal. calcd for C_{13}H_{16}O_{6}: C, 58.20; H, 6.01. Found: C, 58.29; H, 5.99.
6-methyl-2,2-diphenyl-4H-1,3-dioxin-4-one (165)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
166 & \quad \text{Ac}_2\text{O}, \text{H}_2\text{SO}_4 \\
\text{167} & \quad \text{O} \\
\text{168} & \quad \text{O}
\end{align*}
\]

t-Butylacetoacetate 166 (1 mL, 6 mmol) was cooled under nitrogen to -10 °C, and acetophenone 167 (1.44 g, 12 mmol) dissolved in acetic anhydride (2 mL) was added. After 10 min, sulphuric acid was added dropwise (0.326 mL, 6 mmol) and the mixture washed up to 0 °C and stirred for 15 h. After this period, the mixture was poured in a cooled saturated solution of potassium carbonate to neutralize the acid and was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine and dried (MgSO₄), rotary evaporated and chromatographed (SiO₂, hexane: ethyl acetate; 8:2) to afford the compound 165 (650 mg, 53 %):

\[1H\text{ NMR (CDCl}_3, 400 \text{ MHz)} \delta 7.58-7.21 (m, 10H, Ar\text{H}), 4.93 (s, 1H, H_3), 2.00 (s, 3H, H_7); 13C\text{ NMR (CDCl}_3, 100 \text{ MHz)} 168.5, 158.5, 149.4, 147.4, 129.8, 127.7, 125.8, 102.7, 98.1, 20.0; \text{MS (Cl) } m/z 267 [M + H]^+\].
(E)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-methylbut-3-enoic acid (170)

\[
\begin{align*}
& \text{LDA (2 eq.),} \\
& \text{THF, -78 °C} \\
& \text{149} \rightarrow \text{170}
\end{align*}
\]

\(n\)-BuLi (0.93 mL, 0.58 mmol) was added dropwise to (i-Pr)\(_2\)NH (0.09 mL, 0.7 mmol) in THF (4 mL) at −78 °C and stirred for 20 min. Dioxinone 149 (60 mg, 0.27 mmol) in THF (2 mL) was added dropwise with stirring to the solution at −78 °C and stirred for 30 min and the mixture stirred at RT for 5 h and poured into aq. HCl (1 M; 5 mL). EtOAc was added (8 mL), the layers separated and the aqueous phase extracted with EtOAc (8 mL). The combined organic phases were washed with brine (3 mL), dried (MgSO\(_4\)), rotary evaporated and chromatographed (EtOAc:hexanes 6:1) to give dioxinone 170 (7.3 g, 12%) as a white solid:

R\(_f\) 0.1 (EtOAc); IR (neat) 3100, 1745, 1685, 1630, 1353, 1045, 986, 816 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.72 (s, 1H, \(H_7\)), 5.37 (s, 1H, \(H_3\)), 3.21 (s, 2H, \(H_{12}\)), 2.07 (s, 3H, \(H_{2a}\)), 1.70 (s, 6H, \(H_9\) and \(H_{10}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 178.8, 164.0, 1601.3, 141.5, 114.4, 107.4, 100.6, 46.5, 24.8 (2C), 18.2; MS (CI) \(m/z\) 227 [M + H]\(^+\).
Allyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (174)

Pyridine (0.36 mL, 4.8 mmol) was added with stirring to keto-ester 156 (500 mg, 1.96 mmol) and MgCl₂ (214 mg, 2.2 mmol) in CH₂Cl₂ (35 mL) at 0 °C giving a bright yellow solution. After 20 min, acid chloride 148 (237 mg, 2.6 mmol) in CH₂Cl₂ (5 mL) was added in one portion and the mixture was allowed to warm to RT over 15 min. After 30 min stirring, the reaction was quenched by addition of saturated aqueous NH₄Cl (10 mL) and the pH was adjusted to 4 with aq. HCl (1 M). The mixture was extracted with EtOAc (2 x 35 mL) and the combined organic layers were washed with brine and dried (MgSO₄). Rotary evaporation and chromatography (EtOAc:hexanes 1:4) gave diketo-ester 174 (245 mg, 43%) as a yellow oil:

Rₜ 0.21 (EtOAc:hexanes 1:2); IR (KBr) 3421, 2924, 2852, 1726, 1596 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.02–5.91 (m, 1H, H₂₁), 5.40–5.30 (m, 3H, H₂₂ and H₃), 4.70 (d, J = 6.0 Hz, 2H, H₂₀), 3.72 (s, 2H, H₇), 2.42 (s, 3H, H₁₅), 1.69 (s, 6H, H₁₃ and H₁₄); ¹³C NMR (75 MHz, CDCl₃) δ 196.1, 193.8, 165.9, 165.1, 160.7, 131.5, 119.7, 108.2, 107.2, 96.5, 65.9, 43.2, 25.6, 24.9 (2C), MS (ESI) m/z 311 [M + H]⁺.
To a 0 ºC cooled solution of compound 174 (616.3 mg, 1.9 mmol) in THF (3 mL), was added morpholine (0.4 mL, 4.6 mmol) (the solution turned to bright yellow) and a solution of Pd(PPh₃)₄ (90.5 mg, 0.07 mmol) in of THF (15 mL). The temperature was raised to RT and after 30 min the reaction was quenched by addition of a saturated solution of ammonium chloride (20 mL). The pH was adjusted to pH=4 with aq. HCl (1 M). The mixture was extracted with Et₂O (3 x 80 mL) and the combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (cyclohexane:EtOAc, 4:1) to give compound 10 (178.8 mg, 40%) as a yellow oil:

\[
\begin{align*}
R_f & \ 0.30 \ (\text{hexanes:EtOAc} \ 2:1) ; \ \text{IR (neat)} \ 1732, \ 1637, \ 1377, \ 1273, \ 1204, \ 1015, \ 967, \ 810 \ cm^{-1} ; \\
\text{¹H NMR} & \ (CDCl₃, \ 400 MHz, \ \text{keto:enol} \ = \ 1:9) \ \text{enol:} \ \delta \ 15.05 (s, \ 1H, -O) , \ 5.55 (s, \ 1H, H₃) , \ 5.39 (s, \ 1H, H₇) , \ 3.20 (s, \ 2H, H₅) , \ 2.08 (s, \ 3H, H₁) , \ 1.70 (s, \ 6H, H₁₅ \ and \ H₁₆) ; \\
\text{¹³C NMR} & \ (CDCl₃, \ 100 MHz) \ \delta \ 189.8, \ 188.3, \ 165.0, \ 160.7, \ 107.1, \ 100.2, \ 96.3, \ 43.5, \ 24.9 (2C), \ 24.2; \ \text{MS (CI, NH₃)} \ m/z \ 227 [M + H]^+ ; \ \text{HRMS (CI, NH₃)} \ \text{calc. for C}_{11}H_{14}O₅ [M + H]^+:} \ 227.0841, \ \text{found} \ 227.0889. \ \text{Anal.calcd. for C}_{11}H_{14}O₅:} \ C, \ 58.40; \ H, \ 6.24. \ \text{Found:} \ C, \ 58.48; \ H, \ 6.29.
\end{align*}
\]

* All the di- and tri-keto-esters exist as a mixture of keto and enol tautomers. However, for convenience, they are drawn as single entities. The assigned signals in the magnetic resonance spectra are those which correspond to the main tautomeric form observed.
**1-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)pentane-2,4-dione (10)**

\[ \text{16} \xrightarrow{1)} \text{LDA (2eq.), THF, -78 °C to -40 °C} \xrightarrow{2)} \text{178} \quad \text{10} \]

\( n\)-BuLi (11.9 mL, 19.11 mmol) was added dropwise to \((i\text{-Pr})_2\text{NH}\) (2.97 mL, 21.0 mmol) in THF (26 mL) at -78 °C and stirred for 20 min. Keto-dioxinone 16 (1.76 g, 9.56 mmol) in THF (9.5 mL) was added dropwise with stirring to the solution at -78 °C and the resulting cloudy yellow solution was slowly allowed to warm up to -40 °C and stirred for 30 min. Weinreb amide 178 (0.5 mL, 4.78 mmol) in THF (4.8 mL) was slowly added and the mixture stirred at -40 °C for 1 h and poured into aq. HCl (1 M; 60 mL). Et₂O was added (60 mL), the layers separated and the aqueous phase extracted with Et₂O (60 mL). The combined organic phases were washed with brine (80 mL), dried (MgSO₄), rotary evaporated and chromatographed (Et₂O:hexanes 1:1) to give diketo-dioxinone 10 (745.1 mg, 69%) as a yellowish solid:

Rf 0.30 (hexanes:EtOAc 2:1); IR (neat) 1732, 1637, 1377, 1273, 1204, 1015, 967, 810 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, keto:enol = 1:9 ) enol: δ 15.05 (s, 1H, -OH), 5.55 (s, 1H, H₃), 5.39 (s, 1H, H₇), 3.20 (s, 2H, H₅), 2.08 (s, 3H, H₁), 1.70 (s, 6H, H₁₅ and H₁₆); ¹³C NMR (CDCl₃, 100 MHz) δ 189.8, 188.3, 165.0, 160.7, 107.1, 100.2, 96.3, 43.5, 24.9 (2C), 24.2; MS (Cl, NH₃) m/z 227 [M + H]⁺; HRMS (Cl, NH₃) calc. for C₁₁H₁₅O₅ [M + H]⁺: 227.0841, found 227.0889. Anal.calcd. for C₁₁H₁₄O₅: C, 58.40; H, 6.24. Found: C, 58.48; H, 6.29.
1-(1H-Benz[d][1,2,3]triazol-1-yl)butane-1,3-dione (9)

Commercially available dioxinone 8 (3 mL, 22.5 mmol) and benzotriazole 179 (2.68 g, 22.5 mmol) in dry PhMe (80 mL) were heated for 11 h at 90 °C. The solution was rotary evaporated and provided 9 (4.5 g) as an unstable pale yellow solid and as a 1:1 mixture of tautomers:

$^1$H NMR (d$_8$-THF, 400 MHz) δ 13.07 (br s, 0.5H, H$_9$), 8.29 (dd, $J$ = 16.5, 8.0 Hz, 1H, ArH), 8.11 (d, $J$ = 8.0 Hz, 1H, ArH), 7.67 (q, $J$ = 8.0 Hz, 1H, ArH), 7.52 (q, $J$ = 8.0 Hz, 1H, ArH), 6.69 (s, 0.5H, H$_7$), 4.57 (s, 1H, H$_3$), 2.34 (s, 1.5H, -CH$_3$), 2.20 (s, 1.5H, -CH$_3$); $^{13}$C NMR (d$_8$-THF, 100 MHz) δ 200.5, 183.5, 170.4, 167.5, 147.7, 147.5, 132.2, 132.0, 131.4, 131.1, 127.2, 126.9, 121.1 (2C), 115.4, 115.1, 90.9, 51.7, 30.4, 22.3.
1-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)pentane-2,4-dione (10)

Dioxinone 8 (9 mL, 67.5 mmol) was added dropwise to LiN(SiMe$_3$)$_2$ in THF (1 M; 70 mL, 69.7 mmol) in THF (750 mL) at −78 ºC and the mixture stirred at that temperature. After 1.5 h, amide 9 (4.5 g, 22.5 mmol) was added in one portion and the mixture was allowed to warm up to RT. After stirring overnight, the reaction mixture was quenched by addition of 1 M aq. HCl to pH 4. The mixture was extracted with EtOAc (3 x 250 mL) and the combined organic layers were washed with brine, dried (MgSO$_4$) and rotary evaporated. The mixture was dissolved in CH$_2$Cl$_2$ (250 mL) and washed with a buffer solution (pH = 9) (5 x 50 mL). The organic layer was dried (MgSO$_4$), rotary evaporated and chromatographed (hexanes:EtOAc 8:1 to 2:1) to give 10 (2.70 g, 53%) as a clear oil:

R$_f$ 0.30 (hexanes:EtOAc 2:1); IR (neat) 1732, 1637, 1377, 1273, 1204, 1015, 967, 810 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz, keto:enol = 1:9) enol: δ 15.05 (s, 1H, -OH), 5.55 (s, 1H, H$_3$), 5.39 (s, 1H, H$_7$), 3.20 (s, 2H, H$_5$), 2.08 (s, 3H, H$_1$), 1.70 (s, 6H, H$_{15}$ and H$_{16}$); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 189.8, 188.3, 165.0, 160.7, 107.1, 100.2, 96.3, 43.5, 24.9 (2C), 24.2; MS (Cl, NH$_3$) m/z 227 [M + H]$^+$; HRMS (Cl, NH$_3$) calc. for C$_{11}$H$_{15}$O$_5$ [M + H]+: 227.0841, found 227.0889. Anal.calcd. for C$_{11}$H$_{14}$O$_5$: C, 58.40; H, 6.24. Found: C, 58.48; H, 6.29.

* Buffer solution from Sigma-Aldrich pH 9.00 reference number 456101. It was observed that the yield decreases if benzotriazole was not removed before chromatography, due to competitive aromatization to benzodioxinone 15. To avoid this side product, the mixture was washed with a buffer solution (pH 9) to remove benzotriazole and suppress the rate of the aromatization reaction.
(5R)-allyl 2-(2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetyl)-3-oxo-5-(triisopropylsilyloxy)hexanoate (172)

To a suspension of compound 156 (100 mg, 0.37 mmol) and MgCl₂ (33 mg, 0.37 mmol) in CH₂Cl₂ (0.9 mL) at 0 °C, was added pyridine (0.060 mL, 0.72 mmol). The solution (turned bright yellow) was stirred at this temperature for 20 min. After this period, acid chloride 171 (137 mg, 0.49 mmol) dissolved in of CH₂Cl₂ (0.8 mL) was added in one portion and the temperature was raised to RT over 15 min. After 30 min of continuous stirring, the reaction was quenched by addition of a saturated solution of ammonium chloride (2 mL) and the pH was adjusted to pH=4 with aq. HCl (1 M). The mixture was extracted with EtOAc (2 x 15 mL) and the combined organic layers were washed with brine and dried (MgSO₄). The solvent was removed under vacuum and the residue was purified by chromatography (hexane:EtOAc, 9:1) to afford the compound 172 (157 mg, 83 %) as a yellow oil:

Rf 0.75 (hexane:EtOAc 7:3); [α]D −14.0 (c 0.005, CHCl₃); IR (KBr) 2944, 2855, 1733, 1640, 1376, 172, 1204, 1126, 1015, 882. ¹H NMR (CDCl₃, 300 MHz) δ 17.53 (s, 1H, -OH), 5.97 (ddd, J = 17.1, 11.1, 5.8 Hz, 1H, H₄), 5.39 (d, J = 17.1 Hz, 1H, H₄), 5.34 (s, 1H, H₁₂), 5.32 (d, J = 10.4 Hz, 2H, H₂), 4.55-4.30 (m, 1H, H₂₃), 3.67 (s, 2H, H₉), 2.99 (dd, J = 14.1, 8.2 Hz, 1H, H₂₂), 2.80 (dd, J = 14.1, 4.7 Hz, 1H, H₂₂), 1.69 (s, 6H, H₁₈ and H₁₉), 1.23 (d, J = 6.2 Hz, 1H, H₂₅), 1.03 (s, 15 H). ¹³C NMR (75 MHz, CDCl₃) 195.5, 193.2, 165.9, 164.9, 160.6, 131.3, 119.8, 109.3, 107.1, 96.5, 66.4, 66.0, 47.1, 43.0, 24.9, 24.8, 24.3, 18.0 (6C), 12.4 (3C). MS (ESI) m/z 511 [M+H]⁺; HRMS (ESI) calcd. C₂₆H₄₂O₈Si: [M+H]⁺, 511.2727; found: [M+H]⁺, 511.2715. Anal. calcd for C₂₆H₄₂O₈Si: C, 61.15; H, 8.29. Found: C, 61.22; H, 8.22.
(R)-1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-6-
(triisopropylsilyloxy)heptane-2,4-dione (173)

To a 0 °C cooled solution of compound 172 (200 mg, 0.39 mmol) in THF (3 mL), was added morpholine (0.07 mL, 0.8 mmol) (the solution turned to bright yellow) and a solution of Pd(PPh₃)₄ (46 mg, 0.04 mmol) in of THF (0.8 mL). The temperature was raised to RT and after 30 min the reaction was quenched by addition of a saturated solution of ammonium chloride (4 mL). The pH was adjusted to pH=4 with aq. HCl (1 M). The mixture was extracted with Et₂O (3 x 15 mL) and the combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (cyclohexane:EtOAc, 4:1) to give compound 173 (148mg, 89 %) as a yellow oil:

Rf 0.45 (Hexane:EtOAc, 7:3); [α]D –27.0 (c 0.017, CHCl₃); IR (KBr) 2944, 2866, 2539, 2344, 1734, 1615, 1377, 1272, 1205, 1125, 1014, 882. ¹H NMR (CDCl₃, 400 MHz) δ 15.03 (bs, 1H, -OH), 5.58 (s, 1H, H₃), 5.38 (s, 1H, H₆), 4.44-4.34 (m, 1H, H₁₇), 3.21 (s, 2H, H₅), 2.50 (dd, J = 13.7, 6.5 Hz, 1H, H₇), 2.36 (dd, J = 13.7, 6.0 Hz, 1H, H₈), 1.69 (s, 6H, H₁₅ and H₁₆), 1.22 (d, J = 6.4 Hz, 3H, H₁₉), 1.04 (s, 15 H). ¹³C NMR (75 MHz, CDCl₃) 189.3 (2C), 164.9, 160.6, 107.0, 101.2, 96.3, 66.2, 47.9, 43.7, 24.9, 24.8, 24.0, 18.0 (6C), 12.3 (3C). MS (ESI) m/z 427 [M+H]⁺; HRMS (ESI) calcd. C₂₂H₃₉O₆Si: [M+H]⁺, 427.5216; found: [M+H]⁺, 427.2516. Anal. calcd for C₂₂H₃₈O₆Si: C, 61.94; H, 8.98. Found: C, 62.12; H, 9.04.
To a 0 °C cooled solution of compound 173 (52 mg, 0.13 mmol) in THF (3 mL) in a plastic vessel, 0.6 mL of HF in pyridine was added. The temperature was raised up to RT in 45 min and the solution was maintained with continuous stirring for 6 h. After this period, the reaction was quenched by adding carefully 3 mL of saturated sodium bicarbonate solution. The mixture was extracted with AcOEt (2 x 10 mL) and the combined organic layers were dried (MgSO₄). The solvent was removed under vacuum and the residue was chromatographed (CH₂Cl₂ :MeOH, 95:5) to afford the compound 182 (31 mg, 92 %) as a yellow oil:

Rf 0.30 (CH₂Cl₂ :MeOH, 95:5); ¹H NMR (CDCl₃, 300 MHz) δ 5.40 (s, 1H, H₃), 5.36 (s, 1H, H₉), 4.55 (m, 1H, H₁₇), 3.16 (s, 2H, H₆), 2.45 (s, 1H, H₁), 2.43 (d, J 2.1, 1H, H₁), 1.69 (s, 6H, H₁₅ and H₁₆), 1.46 (d, J 6.2, 3H, H₁₉); ¹³C NMR (75 MHz, CDCl₃) 192.39, 169.28, 165.19, 160.54, 107.09, 106.32, 95.77, 76.55, 42.58, 39.20, 25.05, 24.80, 20.31. MS (ESI) m/z 271 [M + H]⁺.
(E)-5-(1-hydroxybut-2-enylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

(185)

Crotonoyl chloride (180) (3.99 g, 38.2 mmol) was added to a solution of Meldrum’s acid (152) (5.0 g, 34.7 mmol) and pyridine (5.49 g, 69.4 mmol) in CH₂Cl₂ (25 mL) at 0 °C over a period of 10 min. The resulting mixture was stirred for 1 h at 0 °C and then 1 h at RT. The reaction mixture was poured into an ice-cold solution of 2 M aq. HCl (30 mL), diluted with CH₂Cl₂ (55 mL) and the phases were separated. The organic layer was washed with 2 M aq. HCl (30 mL), water (2 x 30 mL), dried (MgSO₄) rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to provide the alkylated product 185 (3.5 g, 48%) as a white solid:

Rₜ 0.35 (EtOAc:hexanes 1:3); mp 81-83 °C (EtOAc/hexanes); IR (neat) 2989, 1730, 1636, 1529, 1389, 1159, 907, 789 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 14.89 (s, 1H, H₁₂), 7.58 (d, J = 16.0Hz, 1H, H₁₄), 7.40 (dq, J = 16.0, 8.2Hz, 1H, H₁₃), 2.08 (dd, J = 8.2, 1.4Hz, 3H, H₁₅), 1.75 (s, 6H, H₉ and H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 182.7, 171.9, 160.5, 149.0, 124.4, 104.6, 89.2, 26.8 (2C), 19.4; MS (ESI) m/z 213 [M + H]⁺.
Dry acetone (57) (4 µL, 0.05 mmol) was added to the alkylated product 185 (22.4 mg, 0.106 mmol) in PhMe (0.1 mL), and the mixture was refluxed for 5 h. After the dark yellow solution was cooled to RT the solvent was evaporated under reduced pressure. The resulting yellow oil was chromatographed (EtOAc:hexanes 1:3) to afford the dioxinone 184 (11 mg, 62%) as a yellow oil:

Rf 0.42 (EtOAc:hexanes 1:3); IR (neat) 1430, 1392, 1252, 943 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.59 (dq, J = 16.0, 8.2 Hz, 1H, H₁₁), 5.94 (dd, J = 16.0, 1.4 Hz, 1H, H₇), 5.24 (s, 1H, H₃), 1.91 (dd, J = 8.2, 1.4 Hz, 3H, H₁₂), 1.72 (s, 6H, H₀ and H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 171.6, 171.2, 147.4, 128.5, 122.1, 60.4, 22.3, 18.1, 14.0; MS (ESI) m/z 169 [M + H]⁺.
6-((3Z,5E)-4-hydroxy-2-oxohepta-3,5-dienyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (12)

Unsaturated dioxinone 184 (38.0 mg, 0.23 mmol) and benzotriazole 179 (26.8 mg, 0.23 mmol) in dry PhMe (8 mL) were heated for 11 h at 90 °C. The solution was rotary evaporated and provided 183 (51.5 mg) as an unstable pale yellow solid.

Dioxinone 8 (0.09 mL, 0.68 mmol) was added dropwise to LiN(SiMe$_3$)$_2$ in THF (1 M, 0.7 mL, 0.7 mmol) in THF (8 mL) at –78 °C and the mixture stirred at that temperature. After 1.5 h, amide 183 (51.5 mg, 0.23 mmol) was added in one portion and the mixture was allowed to warm up to RT. After stirring overnight, the reaction mixture was quenched by addition of I M aq. HCl to pH 4. The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine, dried (MgSO$_4$) and rotary evaporated. The mixture was dissolved in CH$_2$Cl$_2$ (5 mL) and washed with a buffer solution (pH = 9)$^*$ (5 x 5 mL). The organic layer was dried

$^*$ Buffer solution from Sigma-Aldrich pH 9.00 reference number 456101.
(MgSO₄), rotary evaporated and chromatographed (hexanes:EtOAc 8:1 to 2:1) to give 12 (8.1 mg, 14%) as a clear oil:

R_f 0.61 (EtOAc:hexane 1:2); IR (neat) 2996, 2363, 1732, 1377, 1273, 1204, 1015, 967, 810 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.92 (qd, J = 14.6, 7.0 Hz, 1H, H₂), 5.8 (qd, J = 14.6, 1.5 Hz, 1H, H₃), 5.49 (s, 1H, H₅), 5.38 (s, 1H, H₁₁), 3.25 (s, 2H, H₉), 1.92 (dd, J = 7.0, 1.5 Hz, 3H, H₁), 1.72 (s, 6H, H₁₇ and H₁₈); ¹³C NMR (CDCl₃, 100 MHz) δ 192.8, 177.7, 165.1, 160.7, 141.4, 126.3, 107.1, 98.8, 96.3, 44.8, 24.9 (2C), 18.5; MS (Cl, NH₃) m/z 253 [M+H]+, calculated for C₁₃H₁₆O₅ [M+H]+ 253.10.
To a stirring solution of chloroacetaldehyde (50% wt in H\textsubscript{2}O) 188 (7.8 mL, 61.5 mmol) in water (1.2 L) were added allyl bromide 189 (8.0 mL, 92.5 mmol) and indium (7.1 g, 61.5 mmol). The mixture was stirred for 10 h at RT. The aqueous mixture was extracted with ether (3 x 250 mL), the combined organic phases were dried and concentrated in vacuo. The crude product was distilled (bp 65-70°C / 16-17 Torr) to yield 190 (6.9 g, 94%) as a colorless oil:

R\textsubscript{f} 0.47 (EtOAc 100%); IR (neat) 3399 (br), 3079, 2912, 1642, 1432, 921 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 5.89-5.75 (m, 1H, \text{H}\textsubscript{5}), 5.20-5.14 (m, 2H, \text{H}\textsubscript{1}), 3.93-3.82 (m, 1H, \text{H}\textsubscript{4}), 3.63 (dd, \text{J} = 4.0 Hz, 10.9 Hz, 1H, \text{H}\textsubscript{5}), 3.51 (dd, \text{J} = 6.5 Hz, 10.9 Hz, 1H, \text{H}\textsubscript{5}), 2.39 (br. s, 1H, \text{OH}), 2.37-2.33 (m, 2H, \text{H}\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 133.2, 118.7, 70.6, 49.4, 38.7; MS (Cl, NH\textsubscript{3}) m/z 120[M+H]\. 
To a solution of 190 (6.9 g) in DMSO–H₂O (10:1, 6.6 mL) was added KCN (0.43 g, 6.65 mmol) and NaI (1.98 g, 13.3 mmol). The mixture was stirred for 5 h at 80 °C, then diluted with EtOAc (38 mL) and washed with saturated brine. The combined aqueous layers were extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo to give crude mixture of 191 (5.1 mg), which was used in the next step without further purification. An analytically pure sample was obtained by column chromatography on silica gel (EtOAc:hexane, 1:15 to 1:3) as a colorless oil:

Rf 0.6 (EtOAc:hexanes 1:2); IR (neat) 3445, 2930, 2360, 2253, 1644, 1418, 1073 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.87-5.77 (m, 1H, H₂), 5.27-5.24 (m, 2H, H₁), 4.07-4.01 (m, 1H, H₄), 2.60 (dd, J = 5.0 Hz, 16.7 Hz, 1H, H₅), 2.55 (dd, J = 5.0, 16.7 Hz, 1H, H₅), 2.48-2.34 (m, 2H, H₃), 2.09 (br. s, 1H, -OH); ¹³C NMR (CDCl₃, 100 MHz) δ 132.5, 120.0, 117.4, 66.7, 40.9, 25.2; MS (CI, NH₃) m/z 112 [M+H]⁺, 129 [M+NH₄]⁺; HRMS (NH₃) calculated for C₅H₉NO [M+NH₄]⁺ 129.1069, found 129.1028.
Imidazole (1.2 g, 17.7 mmol) and TBSCl (1.33 g, 8.9 mmol) were added to a cooled (0 °C) and stirred solution of crude 191 (550 mg) in DMF (3.8 mL). The mixture was stirred for 13 h and then diluted with H₂O (45 mL). The reaction mixture was extracted with CH₂Cl₂ and the combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:40) to provide 192 (821.7 mg, 81%) of as a colorless oil:

Rf 0.7 (EtOAc: hexane 1:4); IR (neat) 2931, 2858, 2251, 1642, 1464, 1101 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.84-5.73 (m, 1H, H₂), 5.19 (d, J = 5.4 Hz; 1H, H₁), 5.15 (s, 1H, H₁), 4.03 (quint, J = 5.7 Hz, 1H, H₃), 2.50 (dd, J = 5.7, 16.6 Hz, 1H, H₅), 2.45 (dd, J = 5.7, 16.6 Hz, 1H, H₅), 2.38 (t, J = 5.7 Hz, 2H, H₃), 0.93 (s, 9H, -0-Si-C-(CH₃)₃), 0.148 (s, 3H, -0-Si-CH₃), 0.12 (s, 3H, -0-Si-CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 132.8, 119.0, 117.8, 68.0, 41.5, 25.7 (3C), 25.5, 18.0, −4.6, −4.8; MS (CI, NH₃) m/z 226 [M+H]⁺, 243 [M+NH₄]⁺; HRMS (CI, NH₃) calculated for C₁₂H₂₃NOSi [M+NH₄]⁺ 243.1934, found 243.1894.
3-(ter-butyl-dimethyl-silanyloxy)-hex-5-enal (193)

To a cooled (-52 °C), stirred solution of the nitrile 192 (100 mg, 0.44 mmol) in toluene (1.8 mL) under argon was added DIBAL-H (0.6 mL of 1.04 mol/L solution in toluene, 0.66 mmol). The mixture was stirred at -52 °C for 2 h and then quenched with EtOH. The resulting solution was diluted with 0.2 mol/L aq. HCl (4 mL), and extracted with hexane (3 x 25 mL). The combined organic layers were washed with saturated brine-saturated aqueous NaHCO₃ (1:1) and then dried and concentrated in vacuo to give 193 (97.3 mg, 96%) as a brown oil and was used in the next step without further purification. An analytically pure sample was obtained by column chromatography on silica gel (EtOAc:hexane, 1:3) as a colorless oil:

R_f 0.88 (EtOAc: hexane 1:2); IR (neat) 2955, 2930, 2857, 1726, 1255, 1100, 836, 776 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 9.82 (t, J = 2.3 Hz, 1H, H₇), 5.84-5.75 (m, 1H, H₂), 5.12 (m, 1H, H₁), 5.09 (d, J = 5.4 Hz; 1H, H₁), 4.28 (quint, J = 5.7 Hz, 1H, H₄), 2.56-2.54 (m, 2H, H₃), 2.33 (t, J = 5.7 Hz, 2H, H₃), 0.89 (s, 9H, -0-Si-(CH₃)₃), 0.10 (s, 3H, -0-Si-CH₃), 0.08 (s, 3H, -0-Si-CH₃) ; ¹³C NMR (CDCl₃, 100 MHz) δ 202.1, 133.8, 118.1, 67.7, 50.4, 42.3, 25.7 (3C), 18.0, -4.4, -4.8; MS (Cl) m/z 229 [M+H]⁺; HRMS (Cl) calculated for C₁₂H₂₄O₂Si [M+H]⁺ 229,1546, found 229,1630.
**Tert-Butyl-(2,2-dimethyl-6-methylene-6H[1,3]dioxin-4-yloxy)dimethylsilane (64)**

To a solution of diisopropylamine (2.3 mL, 16.6 mmol) in THF (26 mL) at 0 °C was added n-BuLi (2.5 M in hexanes, 6.6 mL, 16.6 mmol). The resulting solution was stirred for 30 min prior to cooling to -78 °C in a dry ice/acetone bath. To this solution was added HMPA (3.14 mL, 18 mmol). The solution was stirred for 30 min at -78 °C, and then dioxinone 8 (2 mL, 15 mmol) was added slowly. The resulting solution was stirred 30 min at -78 °C prior to slow addition of TBSCI (2.7 g, 18 mmol) in THF (10 mL). The dry ice/acetone was removed and the solution was allowed to stir for 6 h at 25 °C. The yellow solution was diluted with cold pentane and washed with water. The organic layer was dried over Na2SO4, filtered through a pad of Celite® and the filtrate was concentrated in vacuo. The residue was purified by distillation (bp = 68 °C, 0.44 mbar) to yield 64 (2.9 g, 76%) as a yellow oil:

Rf 0.25 (EtOAc:hexanes, 1:1); IR (neat) 3417, 2933 1741, 1671, 1639, 1344, 1226 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 4.64 (s, 1H, H₃), 4.04 (s, 1H, H₉), 3.85 (s, 1H, H₆), 1.52 (s, 6H, H₇ and H₈), 0.92 (s, 12H), 0.19 (s, 6H); ¹³C (CDCl₃, 100 MHz) δ 153.6, 152.0, 102.5, 93.9, 84.7, 25.0 (2C), 24.5 (3C), 18.0, -4.3 (2C); MS (Cl, NH₃) m/z 257 [M + H]⁺; HRMS (CI) m/z calc for C₁₃H₂₅O₅Si: [M+NH₄]⁺, 257.1573; found: [M+NH₄]⁺, 257.1575.
6-[4-(tert-butyl-dimethyl-silanyloxy)-2-hydroxy-hept-6-enyl]-2,2-dimethyl-[1,3]dioxin-4-one (194)

To a cooled (-78 °C), stirred solution of 193 (1.0 g, 4.38 mmol) in CH₂Cl₂ (18 mL) under argon were added BF₃·Et₂O (0.59 mL, 4.62 mmol) and 64 (1.23 g, 5.7 mmol). The mixture was stirred at -78 °C for 45 min and then quenched with saturated aqueous NaHCO₃. This was diluted with saturated aqueous NaHCO₃ (36 mL), and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:4) to provide a 1:1 diastereoisomer mixture of 194 (726.5 mg, 45%) as a colorless oil:

Rf 0.5 (EtOAc: hexane 1:2); IR (neat) 3475, 2930, 2857, 2360, 2341, 1724, 1632, 1390, 1255 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.79-5.71 (m, 1H, H₂), 5.34 (s, 1H, H₉), 4.09-4.05 (m, 2H, H₁), 4.28-4.27 (m, 0.5H, H₆), 4.09-4.05 (m, 1H, H₄), 4.02-3.98 (m, 0.5H, H₆), 3.39 (s, 0.5H disappear with D₂O, -OH), 2.31 (s, 0.5H disappear with D₂O, -OH), 2.46-2.39 (m, 2H, -CH₂_), 2.38-2.29 (m, 2H, -CH₂_), 1.70 (s, 6H, H₁₆ and H₁₇), 1.67-1.61 (m, 2H, H₃), 0.92 (s, 9H, -0-Si-(CH₃)₃), 0.15 (s, 3H, -0-Si-CH₃), 0.12 (s, 3H, -0-Si-CH₃); MS (CI) m/z 370.22; HRMS (CI) calculated for C₁₉H₃₄O₅Si [M+H]⁺ 370.2176, found 370.2230
6-[4-(ter-butyl-dimethyl-silanyloxy)-2-oxo-hept-6-enyl]-2,2-dimethyl-[1,3]dioxin-4-one (195)

To a cooled (0 °C), stirred solution of 194 (229 mg, 0.61 mmol) in CH₂Cl₂ (4.5 mL) was added Dess-Martin periodinane (524 mg, 1.2 mmol). The mixture was stirred for 5 h and then diluted with saturated aqueous NaHCO₃ 20% aq. Na₂S₂O₃ (1:1, 7 mL) and CH₂Cl₂ (4 mL) at 0 °C. The mixture was stirred for 20 min and then the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo to give the crude ketone 195, which was used in the next step without purification. In a small-scale experiment, the pure ketone was obtained by column chromatography on silica gel (EtOAc/hexane, 1:4) as a colorless oil:

Rf 0.58 (EtOAc/hexane 1:2); IR (neat) 2953, 2930, 2857, 1730, 1640 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.82-5.73 (m, 1H, H₂), 5.33 (s, 1H, H₀), 5.12-5.07 (m, 2H, H₁), 4.27-4.24 (m, 1H, H₄), 3.39 (d, J = 16.8 Hz, 1H, H₇), 3.34 (d, J = 16.8 Hz, 1H, H₇), 2.65 (dd, J = 7.7 Hz, J=15.5 Hz, 1H, H₃), 2.53 (dd, J = 7.7 Hz, J=15.5 Hz, 1H, H₃), 2.27 (t, J = 6.0 Hz, 2H, H₃), 1.73 (s, 6H, H₁₇ and H₁₈), 0.89 (s, 9H, -0-Si-C-(CH₃)₃), 0.10 (s, 3H, -0-Si-CH₃), 0.05 (s, 3H, -0-Si-CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 202.4, 164.4, 160.8, 133.7, 118.1, 107.2, 96.7, 68.5, 49.4, 48.8, 42.1, 25.8 (3C) 25.1, 25.0, 18.0,−4.5, −4.9; MS (CI, NH₃) 386 [M+NH₄]⁺; HRMS (CI) calculated for C₁₀H₃₂O₅Si [M+H]⁺ 369.2019, found 369.2102.
48% aq. HF (0.28 mL) was added to a cooled (0 °C), stirred solution of the crude ketone 195 in MeCN (5.8 mL). The mixture was stirred at RT for 8 h and then quenched with saturated aq. NaHCO$_3$. The solution was diluted with saturated aqueous NaHCO$_3$ (9 mL), and extracted with CH$_2$Cl$_2$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 196 (80.1 mg, 51%, 2 steps) as a colorless oil:

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\text{R}_f \text{ 0.28 (EtOAc:hexane 1:1); IR (neat) 3446, 2924, 2854, 1726, 1637 cm}^{-1}; \text{ }^1\text{H NMR (CDCl}_3\text{, 400 MHz) }\delta \text{ 5.84-5.77 (m, 1H, H}_2\text{)}, 5.37 \text{ (s, 1H, H}_9\text{)}, 5.18 \text{ (s, 1H, H}_1\text{)}, 5.15 \text{ (d, } J=5.6 \text{ Hz, 1H, H}_1\text{), 4.18-4.15 (m, 1H, H}_3\text{)}, 3.39 \text{ (s, 2H, H}_7\text{), 2.68-2.66 (m, 2H, H}_3\text{), 2.28, 2.05 (br, 1H,-OH), 1.73 \text{ (s, 6H, H}_1\text{ and H}_3\text{); }^1\text{C NMR (CDCl}_3\text{, 100 MHz) }\delta \text{ 203.6, 163.9, 160.6, 133.7, 118.7, 107.3, 96.9, 66.7, 48.9, 47.9, 41.0, 29.7, 25.1; MS (CI, NH}_3\text{) m/z 255 [M+H]}^+, 272 [M+NH}_4]^+; \text{HRMS (CI, NH}_3\text{) calculated. for C}_{13}\text{H}_{19}\text{O}_5\text{ [M+H]}^+ 255.1232, found 255.1236.}\]
**6-(2,4-Dihydroxy-hept-6-enyl)-2,2-dimethyl-[1,3]dioxin-4-one (396)**

48% aq. HF (1.5 mL) was added to a cooled (0 °C), stirred solution of 194 (1.53 g, 4.11 mmol) in MeCN (30.4 mL). The mixture was stirred at RT for 8 h and then quenched with saturated aq. NaHCO₃. This was diluted with saturated aq. NaHCO₃ (49 mL), and extracted with ethyl acetate. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:1) to provide 396 (801 mg, 78%) as a colorless oil:

Rᶠ 0.15 (EtOAc: hexane 1:1); ¹H NMR (CDCl₃, 400 MHz) δ 5.86-5.76 (m, 1H, H₂), 5.37 (s, 1H, H₉), 5.23-5.18 (m, 2H, H₁), 4.28-4.18 (m, 1H, H₆), 4.04-3.95 (m, 1H, H₆), 2.48-2.27 (m, 4H, H₃ and H₇), 2.07 (br, 2H, -OH), 1.73 (s, 6H, H₁₇ and H₁₈), 1.68 (m, 2H, H₅); ¹³C NMR (CDCl₃, 100 MHz) 169.6, 169.2, 161.6, 161.5, 134.3, 133.9, 118.5, 118.3, 106.7 (2C), 95.0, 94.8, 71.4, 69.2, 67.7, 65.9, 42.5 (2C), 42.0 (3C), 41.9, 41.6, 25.2, 25.2, 24.8; MS (CI) 257 [M+H]⁺.
6-(2-Hydroxy-4-oxo-hepta-2,6-dienyl)-2,2-dimethyl-[1,3]dioxin-4-one

(197)

To a cooled (0 °C), stirred solution of 196 (29.6 mg, 0.116 mmol) in CH₂Cl₂ (3 mL) was added Dess-Martin periodinane (100 mg, 0.23 mmol). The mixture was stirred for 5 h and then diluted with saturated aq. NaHCO₃; 20% aq. Na₂S₂O₃ (1:1, 2 mL) and CH₂Cl₂ (1 mL) at 0 °C. The mixture was stirred for 20 min and then the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo. The ketone 197 (10 mg, 32%) was obtained colourless oil:

Rf 0.41 (EtOAc:hexane 1:1); ¹H NMR (CDCl₃, 400 MHz) δ 5.93-5.86 (m, 1H, H₂), 5.59 (s, 1H, H₃), 5.42 (s, 1H, H₆), 5.26-5.21 (m, 2H, H₁), 3.26 (s, 2H, H₇), 3.11 (d, J = 6.8Hz, 2H, H₅); ¹³C NMR (CDCl₃, 100 MHz) 198.9, 190.1, 168.9, 137.3, 134.8, 117.2, 108.5, 100.3, 91.4, 48.5, 47.1, 24.8 (2C); MS (Cl, NH₃) m/z 255 [M+NH₃]⁺ 270; HRMS (Cl, NH₃) calculated. for C₁₃H₁₆O₅ [M+NH₃]⁺ 270.1383, found 270.1355.
6-(2-Hydroxy-4-oxo-hepta-2,6-dienyl)-2,2-dimethyl-[1,3]dioxin-4-one (198)

To 197 (317mg, 1.2 mmol) in THF (0.8 mL), was added Et₃N (0.1 mL) and heated at reflux overnight. Evaporation in vacuo gave 198 (247.1 mg, 82%) as a yellowish oil:

Rf 0.48 (EtOAc:hexane 1:2); ¹H NMR (CDCl₃, 400 MHz) δ 6.47 (s, 1H, ArH), 6.32 (s, 1H, ArH), 5.79 (m, 1H, H₁₆), 5.12 (m, 2H, H₁₇), 3.87 (d, J = 6.8Hz, 2H, H₁₄), 1.72 (s, 6H, H₁₂ and H₁₃); ¹³C NMR (CDCl₃, 100 MHz) 169.2, 161.9, 159.2, 141.7, 136.5, 115.9, 111.6, 105.8, 104.4, 99.0, 38.8, 24.7 (2C); MS (CI) m/z 235 [M+H]+.
6-(2,4-Dihydroxy-hepta-1,3,5-trienyl)-2,2-dimethyl-[1,3]dioxin-4-one

(198)

To 197 (300mg) in THF (0.8 mL), was added triethylamine (0.7 mL) and heated under refluxed for 2 days. Evaporation in vacuo gave a mixture of 199 and 198 (203 mg), 64%:36% respectively:

R_f 0.48 (EtOAc:hexane 1:2); \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 6.47 (s, 1H, Ar\( H \)), 6.32 (s, 1H, Ar\( H \)), 5.79 (m, 1H, H\(_{16}\)), 5.12 (m, 2H, H\(_{17}\)), 3.87 (d, \( J = 6.8 \)Hz, 2H, H\(_{14}\)), 1.72 (s, 6H, H\(_{12}\) and H\(_{13}\)); \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz) 169.2, 161.9, 159.2, 141.7, 136.5, 115.9, 111.6, 105.8, 104.4, 99.0, 38.8, 24.7 (2C); MS (CI) m/z 235 [M+H]^+. 

196
Ethyl (4E)-3-hydroxyhex-4-enoate (201)\textsuperscript{90}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{200} & \quad \text{397} & \text{LDA} & \quad \text{OH} \\
& \quad \text{201}
\end{align*}
\]

A solution of butyl lithium in hexane (1.6 M, 62.5 mL, 100 mmol) was added dropwise at 10 °C to a stirred solution of dry diisopropylamine (14 mL, 100 mmol) in dry tetrahydrofuran (120 mL) under nitrogen. After being stirred for 30 min at 0 °C, the reaction mixture was cooled to -70 °C, and dry ethyl acetate (397) (9.8 mL, 100 mmol) was added dropwise. The resulting solution was stirred for 1 h at -70 °C, becoming very pale yellow. Dry crotonaldehyde (200) (8.3 mL, 100 mmol) was added dropwise to it, and the reaction mixture was stirred at -70 °C for 1 h. The reaction was quenched at -70 °C by addition of glacial acetic acid (8.6 L, 150 mmol) and the resulting gel was diluted with saturated aq. NaHCO\textsubscript{3} (100 mL) and warmed to RT. The resulting suspension was filtered through Celite\textsuperscript{®}, and the filtrate was washed with ether (100 mL). The aqueous and organic phases were separated, and the aqueous layer was saturated with NaCl, prior to extraction with ether (3 x 100 mL). The combined organic layers were dried (MgSO\textsubscript{4}), and solvent was removed by evaporation to give a yellow liquid. Flash column chromatography on silica gel, eluting with 10% ethyl acetate dichloromethane, gave the title compound 201 (14.5 g, 92%) as a mobile yellow liquid:

\begin{itemize}
\item \(R_f\) 0.33 (10% EtOAc:CH\textsubscript{2}Cl\textsubscript{2}); IR (neat) 3620, 3550, 1720, 970 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 5.69 (1 H, dqq, \(J = 15.3, 6.4, 1.0\) Hz, H\textsubscript{2}), 5.46 (1 H, ddq, \(J = 15.3, 6.5, 1.5\) Hz, H\textsubscript{3}), 4.43 (1 H, dt, \(J = 6.0, 6.0\) Hz, H\textsubscript{4}), 4.12 (2 H, q, \(J = 7.1\) Hz), 3.07-2.77 (1 H, br, exchanges in D\textsubscript{2}O, OH\textsubscript{2}), 2.47 (2 H, d, \(J = 6.0\) Hz, H\textsubscript{5}), 1.65 (3 H, dd, \(J = 6.4, 1.0\) Hz, H\textsubscript{6}), 1.22 (3 H, t, \(J = 7.1\) Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 172.3, 131.8, 127.3, 66.8, 60.6, 41.5, 17.5, 14.1; MS (CI, NH\textsubscript{3}) m/z 158 [M+H]\textsuperscript{+}, 272 [M+NH\textsubscript{4}]\textsuperscript{+}; HRMS (CI, NH\textsubscript{3}) calculated. for C\textsubscript{8}H\textsubscript{14}O\textsubscript{3} [M+NH\textsubscript{4}]\textsuperscript{+} 158.0943, found 158.0938.
\end{itemize}
Ethyl (4E)-3-(tert-Butyldimethylsiloxy)hex-4-enoate (202)⁹⁹

A solution of imidazole (8.3 g, 122 mmol) in dry CH₂Cl₂ (70 mL) was added at RT to a stirred solution of freshly distilled tert-butyldimethylsilyl chloride (6.6 g, 44 mmol) in dry CH₂Cl₂ (30 mL). To the resulting white suspension was added a solution of the β-hydroxy ester 201 (5.7 g, 36 mmol) in dry CH₂Cl₂ (40 mL). The suspension was stirred at RT under nitrogen for 4 h, then quenched by addition of saturated aq. NaHCO₃ (100 mL). The two phases were separated, and the aqueous layer was saturated with NaCl prior to extraction with CH₂Cl₂ (2 x 40 mL). The combined organic layers were dried (MgSO₄), and solvent was removed by evaporation to give a pale yellow liquid. Flash column chromatography on silica gel, eluting with CH₂Cl₂, gave the title compound 202 (9.72 g, 99%) as a clear, colourless liquid:

Rᶠ 0.42 (hexane:Et₂O, 9:1); IR (neat) 3030, 1735, 1670, 955 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.61 (1 H, d, J = 15.3, 6.6, 0.6 Hz, H₂), 5.41 (1 H, ddq, J = 15.2, 6.9, 1.4 Hz, H₃), 4.52-4.46 (1 H, m, H₄), 4.09 (2 H, qd, J = 7.2, 2.2 Hz, CH₃CH₂⁻), 2.49 (1 H, dd, J = 14.3, 8.0 Hz, H₅), 2.37 (1 H, dd, J = 14.3, 5.3 Hz, H₅), 1.64 (3H, ddd, J = 6.6, 1.4, 0.8, H₆), 1.23 (3 H, t, J = 7.2, CH₃CH₂⁻), 0.83 (9 H, s, SiCCH₃), 0.01 (3 H, s, SiCH₃), 0.00 (3 H, s, SiCH₃), ¹³C NMR (CDCl₃, 100 MHz) δ 171.3, 133.4, 126.0, 70.7, 60.2, 44.1, 25.7 (3C), 18.0, 17.5, 14.2, -4.3, -5.1; MS (CI, NH₃) m/z 273 [M+H]⁺, HRMS (CI, NH₃) calculated for C₁₄H₁₃₂NO₃Si [M+NH₄]⁺ 290.1573, found 290.1571.
A solution of diisobutylaluminium hydride in toluene (1.5 M, 35 mL, 52 mmol) was added dropwise at -85 °C to a stirred solution of the protected ester 202 (8.13 g, 29.8 mmol) in dry THF (1.50 mL) under nitrogen. The solution was stirred at -90 °C for 2.5 h, then quenched by dropwise addition of saturated aqueous ammonium chloride (15 mL) (T < -75 °C). The reaction mixture was allowed to warm to RT, and saturated aq. Rochelle salt (potassium sodium tartrate) solution (50 mL) was added. The solution was poured into brine (100 mL) and then ethyl acetate (150 mL) was added. Agitation of the mixture led to formation of a gel. Further Rochelle salt solution (50 mL) and ethyl acetate (50 mL) were added to the gel, which was left overnight to break down. The resulting two liquid phases were separated, and the aqueous layer was saturated with sodium chloride prior to extraction with ethyl acetate (3 x 150 mL). The combined organic layers were dried (MgSO4) and then the solvent was removed by evaporation to give a yellow liquid. Flash column chromatography on silica gel, eluting with 9: 1 hexane-ether to 100% ether, gave 203 (6.1 1 g, 90%) as a colourless liquid:

Rf 0.33 (9:1, hexane:Et2O); IR (neat) 3035, 2710, 1725, 1670, 960 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 9.74 (1 H, t, J = 2.5 Hz, H$_6$), 5.65 (1 H, dqq, J = 15.3, 6.2, 0.7 Hz, H$_2$), 5.38 (1 H, ddq, J = 15.3, 6.5, 1.4 Hz, H$_3$), 4.57 (1 H, dt, J = 6.0, 6.0 Hz, H$_4$), 2.58 (1 H, ddd, J = 16.0, 7.0, 2.9 Hz, H$_5$), 2.46 (1 H, ddd, J = 16.0, 5.0, 2.2 Hz, H$_5$), 1.66 (3 H, dd, J = 6.2, 0.7 Hz, H$_1$), 0.84 (9 H, s), 0.03 (3 H, s, SiCH$_3$), 0.01 (3 H, s, SiCH$_3$); ¹³C NMR (CDCl₃, 100 MHz) δ 202.1, 133.1, 126.3, 69.4, 51.6, 25.7 (3C), 18.0, 17.5, -5.0, -4.2; MS (CI) m/z 229 [M+H]$^+$, HRMS (CI) calculated for C$_{12}$H$_{25}$O$_2$Si [M+H]$^+$ 228.1511, found 228.1518.

(4E)-3-(tert-Butyldimethylsiloxy)hex-4-enal (203)
(E)-6-(4-(tert-butyldimethylsilyloxy)-2-hydroxyhept-5-enyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (204)

To a –78 °C cooled solution of compound 203 (1.0 g, 4.38 mmol) in CH₂Cl₂ (18 mL), was added BF₃·Et₂O (0.59 mL, 4.62 mmol) followed by 64 (1.23 g, 4.8 mmol). The mixture was stirred at –78 °C for 1.5 h and then quenched with saturated aqueous NaHCO₃ (36 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine and dried (MgSO₄). The solvent was rotary evaporated and the residue was purified by chromatography (SiO₂, hexane:DCM 5:1 to CH₂Cl₂ 100% to CH₂Cl₂:methanol 1%) to provide the diastereoisomeric mixture of alcohols 204 (989 mg, 61%) as a colourless oil:

Rf 0.3 (EtOAc: hexane 1:3); IR (film) 3474 (br), 2954, 2931, 2857, 1727, 1634, 1390, 1254, 1204 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.62-5.57 (m, 2H, H₂ and H₃), 5.33 (S, 1H, H₁₁), 4.48-4.42 (m, 0.5H, -CH-OH), 4.33-4.27 (m, 0.5H, -CH-OH), 4.23-4.09 (m, 0.5H, -CH-OH), 4.08-3.50 (m, 0.5H, -CH-OH), 3.70 (s, 0.5H, -OH), 3.62 (s, 0.5H, -OH), 2.41-2.23 (m, 2H), 1.70 (s, 6H, H₁₇ and H₁₈), 1.70-1.60 (m, 2H), 0.87 (s, 9H), 0.08 (s, 1.5H), 0.07 (s, 1.5H), 0.04 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.1 (2C), 161.1 (2C), 134.0, 132.5, 126.7, 126.4, 106.5 (2C), 95.1, 95.0, 75.0, 72.4, 68.1, 65.8, 44.1, 43.0, 41.7, 41.6, 25.8, 25.4 (6C), 25.2, 24.9, 24.6, 18.0, 17.9, 17.6, 17.4, 3.6, -4.4, -4.8, -5.1; MS (Cl) m/z 370.22 [M]+; HRMS (Cl) calculated for C₁₉H₃₄O₅Si: [M]+, 370.2176; found: [M]+, 370.2230. Anal. Calcd for C₁₉H₃₄O₅Si: C, 61.58; H, 9.25; Found: C, 61.48; H, 9.19.
To a 0 °C cooled solution of 204 (229 mg, 0.62 mmol) in CH₂Cl₂ (4.5 mL) was added in one portion Dess-Martin periodinane (509 mg, 1.2 mmol). The mixture was stirred for 5 h at this temperature and then diluted with saturated aq. NaHCO₃ (3.5 mL), aqueous Na₂S₂O₃ (2%, 3.5 mL) and CH₂Cl₂ (4 mL). After 20 min of continuous stirring the temperature was raised to RT and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL) and the combined organic layers were dried (MgSO₄) and concentrated under vacuum to give ketone 205, which was used in the next step without further purification. In a separate experiment, ketone 205 was chromatographed (SiO₂, EtOAc:hexane, 1:4) and obtained as a colourless oil:

Rf 0.58 (EtOAc:hexane 1:2); IR (neat) 3448, 2999, 2925, 2856, 1724, 1633 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.66-5.58 (m, 1H, H₂), 5.43-5.37 (m, 1H, H₃), 5.28 (s, 1H, H₄), 4.53 (dd, J = 11.9, 7.6 Hz, 1H, H₅), 3.37 (s, 2H, H₆), 2.70 (dd, J = 15.5, 7.6 Hz, 1H, H₇), 2.46 (dd, J = 15.5, 7.6 Hz, 1H, H₈), 1.71 (s, 3H, -CH₃), 1.70 (s, 3H, -CH₃), 1.66 (d, J = 7.6Hz, 3H, H₉), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 201.9, 164.5, 160.7, 133.0, 126.6, 107.2, 96.7, 70.6, 51.3, 48.8, 25.8 (3C), 25.1, 25.0, 18.1, 17.5, -4.2, -5.0; MS (CI, NH₃) 369 [M+H]⁺, 386 [M+NH₄]⁺
(E)-6-(4-hydroxy-2-oxohept-5-enyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (206)

To a 0 °C cooled solution of the crude ketone 205 in MeCN (5.8 mL), was added aq. HF (48 %, 0.28 mL). The temperature was raised to RT and after 30 min of continuous stirring the reaction was quenched with saturated aq. NaHCO₃ (9 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, EtOAc:hexane, 1:2) to provide 206 (127 mg, 81%, overall yield from 204) as a colourless oil:

Rᶠ 0.3 (EtOAc: hexane 1:2); IR (neat) 3475, 2999, 1723, 1637, 1377, 1274, 1204, 1015, 967, 903 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.79-5.62 (m, 1H, H₁), 5.47 (dd, 1H, J = 13.6, 6.8 Hz, H₃), 5.34 (s, 1H, H₁₁), 4.57-4.43 (m, 1H, H₂), 3.37 (s, 2H, H₉), 2.72 (dd, J = 16.8, 8.3 Hz, 1H, H₅), 2.66 (dd, J = 16.8, 3.9 Hz, 1H, H₃), 2.51 (bs, 1H, -O₃H), 1.70 (s, 6H, H₁₇ and H₁₈), 1.68 (d, J = 0.9 Hz, 3H, H₁); ¹³C NMR (CDCl₃, 100 MHz) 203.1, 164.0, 160.6, 131.6, 127.8, 107.2, 96.8, 68.5, 49.7, 47.9, 25.0 (2C), 17.6; MS (CI, NH₃) m/z 255 [M+H]+; HRMS (CI, NH₃) calculated for C₁₃H₁₉O₅ [M+H]⁺ 255.2790, found 255.2741. Anal. Calcd for C₁₃H₁₉O₅: C, 61.40; H, 7.14; O, 31.46 Found: C, 61.48; H, 7.17.
To a 0 °C cooled solution of 206 (262 mg, 1.03 mmol) in CH₂Cl₂ (26 mL) was added in one portion Dess-Martin periodinane (876.7 mg, 2.1 mmol). The mixture was stirred for 5 h at this temperature and then diluted with saturated aq. NaHCO₃ (6 mL), aq. Na₂S₂O₃ (2%, 6 mL) and CH₂Cl₂ (4 mL). After 20 min of continuous stirring the temperature was raised to RT and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography (SiO₂, EtOAc:hexane, 1:2) to provide 12 (146 mg, 56%) as a yellow oil:

Rf 0.61 (EtOAc:hexane 1:2); IR (neat) 2996, 2363, 1732, 1637, 1377, 1273, 1204, 1015, 967, 810 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.92 (qd, J = 14.6, 7.0 Hz, 1H, H₂), 5.8 (qd, J = 14.6, 1.5 Hz, 1H, H₃), 5.49 (s, 1H, H₅), 5.38 (s, 1H, H₁₁), 3.25 (s, 2H, H₉), 1.92 (dd, J = 7.0, 1.5 Hz, 3H, H₁), 1.72 (s, 6H, H₁₇ and H₁₈); ¹³C NMR (CDCl₃, 100 MHz) δ 192.8, 177.7, 165.1, 160.7, 141.4, 126.3, 107.1, 98.8, 96.3, 44.8, 24.9 (2C), 18.5; MS (Cl, NH₃) m/z 253 [M+H]⁺, calculated for C₁₃H₁₆O₅ [M+H]⁺ 253.10.
1-(2,2-Dimethyl-4-oxo-4\textit{H}-1,3-dioxin-6-yl)pentane-2,4-dione (12)

\[ \begin{array}{c}
\text{O} \quad \text{O} \\
\text{16} \\
\text{1} \quad \text{2} \quad \text{3} \\
\text{HO} \quad \text{C} \quad \text{O} \\
\text{17} \quad \text{18} \\
\text{207} \end{array} \]

1) LDA (2eq.), THF, -78 °C to -40 °C
2) Z78 °C to Z40 °C

\( n\text{-BuLi} \) (11.9 mL, 19.11 mmol) was added dropwise to \((i\text{-Pr})\text{$_2$NH} \) (2.97 mL, 21.0 mmol) in THF (26 mL) at -78 °C and stirred for 20 min. Keto-dioxinone 16 (1.76 g, 9.56 mmol) in THF (9.5 mL) was added dropwise with stirring to the solution at -78 °C and the resulting cloudy yellow solution was slowly allowed to warm up to -40 °C and stirred for 30 min. Weinreb amide 207 (616.6 mg, 4.78 mmol) in THF (4.8 mL) was slowly added and the mixture stirred at -40 °C for 1 h and poured into aq. HCl (1 M; 60 mL). \( \text{Et}_2\text{O} \) was added (60 mL), the layers separated and the aqueous phase extracted with \( \text{Et}_2\text{O} \) (60 mL). The combined organic phases were washed with brine (80 mL), dried (\( \text{MgSO}_4 \)), rotary evaporated and chromatographed (\( \text{Et}_2\text{O}:\text{hexanes} \) 1:1) to give diketo-dioxinone 12 (313.3 mg, 26%) as a yellowish solid:

\( R_f \) 0.61 (EtOAc:hexane 1:2); IR (neat) 2996, 2363, 1732, 1637, 1377, 1273, 1204, 1015, 967, 810 cm\(^{-1}\); \( ^1\text{H} \) NMR (CDCl$_3$, 400 MHz) \( \delta \) 6.92 (qd, \( J = 14.6, 7.0 \) Hz, 1H, \( H_2 \)), 5.8 (qd, \( J = 14.6, 1.5 \) Hz, 1H, \( H_3 \)), 5.49 (s, 1H, \( H_5 \)), 5.38 (s, 1H, \( H_{11} \)), 3.25 (s, 2H, \( H_9 \)), 1.92 (dd, \( J = 7.0, 1.5 \) Hz, 3H, \( H_1 \)), 1.72 (s, 6H, \( H_{17} \) and \( H_{18} \)); \( ^{13}\text{C} \) NMR (CDCl$_3$, 100 MHz) \( \delta \) 192.8, 177.7, 165.1, 160.7, 141.4, 126.3, 107.1, 98.8, 96.3, 44.8, 24.9 (2C), 18.5; MS (Cl, NH$_3$) m/z 253 [M+H]$^+$, calculated for C$_{13}$H$_{16}$O$_5$ [M+H]$^+$ 253.10.
1-(2,4,6-trihydroxyphenyl)ethanone (45)

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) and MeOH (2 mL) in PhMe (10 mL) were heated at reflux for 5 h. The solution was rotary evaporated, dissolved in MeOH (10 mL) and added to a well-stirred 2 M KOH solution in MeOH (5 mL) at -20 °C. The solution was stirred for 70 min before being poured into ice cooled 5 M HCl (15 mL). The precipitate was extracted with ether (3 x 20 mL). The combined organic phases were washed with a saturated NaCl solution (10 mL), dried, filtered and concentrated to give acetophenone 45 (38.9 mg, 52%) as a white solid besides a mixture of 45 and resorcylate 11 (11.4 mg, 12%):

Product 45: Rf 0.54 (hexanes:EtOAc 1:2); $^1$H NMR (CDCl$_3$, 400 MHz) δ 5.69 (s, 2H), 2.63 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 203.8, 165.7, 165.4 (2C), 104.8, 95.1 (2C), 32.1; MS (ESI) $m/z$ 169 [M + H]$^+$. This data is in accordance with the literature.$^{25}$
Methyl 2,4-dihydroxy-6-methylbenzoate (11)

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) and MeOH (2 mL) in PhMe (15 mL) were heated at reflux for 5 h. The solution was rotary evaporated and dissolved in MeOH (20 mL), then Cs₂CO₃ (716 mg, 2.2 mmol) was added in one portion and the mixture stirred at RT for 1 h. The mixture was quenched by addition of an aqueous solution of HCl (1 M) until pH 4 and the solution was stirred vigorously for 15 min. Brine (20 mL) was added and the mixture extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (EtOAc:hexanes 1:3) to provide methyl orsellinate 11 (70.3 mg, 87%) as a white solid:

Rᶠ 0.54 (hexanes:EtOAc 1:2); mp 138 °C (EtOAc/Petroleum ether); IR (neat) 3370, 2969, 1640 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 11.75 (s, 1H), 6.23 (s, 1H), 6.28 (s, 1H), 3.92 (s, 3H), 2.49 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.1, 165.3, 160.3, 144.0, 111.3, 104.5, 100.9, 51.9, 24.2; MS (ESI) m/z 182 [M + H]⁺. This data is in accordance with the literature¹⁵².
Methyl 2-allyl-4,6-dihydroxybenzoate (211)

Diketo-1,3-dioxinone 12 (100 mg, 0.4 mmol) and MeOH (0.08 mL, 2.0 mmol) were heated in PhMe (10 mL) at reflux for 5 h. The solution was rotary evaporated and dissolved in MeOH (10 mL) when Cs$_2$CO$_3$ (650 mg, 2.0 mmol) was added in one portion and the mixture was stirred at RT for 1 h. The mixture was quenched by addition of an aqueous solution of HCl (1 M) until pH 4 and the solution was stirred vigorously for 15 min. Brine (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO$_4$), rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to provide resorcylate 13 (111.4 mg, 92%) as a clear oil:

$R_f$ 0.2 (EtOAc:hexanes 1:4); IR (neat) 3182, 3144, 2069, 1814, 1533, 1432, 1415, 1374, 1281, 1269, 1051, 936, 916 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 11.67 (s, 1H, H$_7$), 6.31 (d, $J = 1.1$Hz, 1H, ArH), 6.27 (d, $J = 1.1$Hz, 1H, ArH), 5.91 (ddt, $J = 16.8$, 10.3, 6.4Hz, 1H, H$_{13}$), 5.02-4.95 (m, 2H, H$_{14}$), 3.89 (s, 3H, H$_{11}$), 3.60 (d, $J = 6.4$Hz, 1H, H$_{12}$); $^{13}$C NMR (CDCl$_3$, 100 MHz) 171.8, 165.2, 161.2, 143.4, 137.2, 115.5, 111.0, 104.8, 101.7, 51.8, 40.5; MS (CI) m/z 209 [M + H]$^+$. 
1-(2,4,6-trihydroxyphenyl)ethanone (214)

Diketo-1,3-dioxinone 12 (50 mg, 0.22 mmol) and MeOH (2 mL) in PhMe (7 mL) were heated at reflux for 5 h. The solution was rotary evaporated, dissolved in MeOH (7 mL) and added to a well-stirred 2 M KOH solution in MeOH (5 mL) at -20 °C. The solution was stirred for 70 min before being poured into ice cooled 5 M HCl (15 mL). The precipitate was extracted with Et₂O (3 x 20 mL). The combined organic phases were washed with a saturated NaCl solution (10 mL), dried, filtered and concentrated. The residue was then dissolved in AcOH (2 mL) and stirred at reflux for 2 h. The solution was evaporated and chromatographed (hexane:Et₂O 1:2) to give product 214 (16.8 mg, 43%) as a white solid besides a mixture of products 214 and 398 (3.1 mg, 8%);

Product 214: Rₐ 0.54 (hexanes:EtOAc 1:2); mp 181 °C (EtOAc/Petroleum ether); ¹H NMR (CDCl₃, 400 MHz) δ 6.47 (s, 1H), 6.02 (s, 1H), 4.54-4.49 (m, 1H), 2.77-2.63 (m, 2H), 1.49 (d; J = 6.5 Hz, 3H) ¹³C NMR (CDCl₃, 100 MHz) δ 195.1, 166.3, 163.8, 163.2, 101.8, 96.6, 94.6, 74.3, 43.1, 20.9; MS (ESI) m/z 195 [M + H]⁺.
Methyl 2,4-dihydroxy-6-methylbenzoate (11) (one step)

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) and MeOH (2 mL) in CH$_2$Cl$_2$ (15 mL) with 4Å molecular sieves were heated at 100 °C in a sealed tube for 10 h. The solution was filtered through Celite® and washed with excess CH$_2$Cl$_2$. The mixture was rotary evaporated to provide methyl orsellinate 11 (66 mg, 82%) as a white solid:

R$_f$ 0.54 (hexanes:EtOAc 1:2); mp 138 °C (EtOAc/Petroleum ether); IR (neat) 3370, 2969, 1640 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 11.75 (s, 1H), 6.28 (s, 1H), 6.23 (s, 1H), 3.92 (s, 3H), 2.49 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 172.1, 165.3, 160.3, 144.0, 111.3, 104.5, 100.9, 51.9, 24.2; MS (ESI) m/z 182 [M + H]$^+$. This data is in accordance with the literature.$^{152}$
**Isopropyl 2,4-dihydroxy-6-methylbenzoate (218) (one step)**

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) in isopropanol (5 mL) were heated at 100 °C in a sealed tube for 10 h. The mixture was rotary evaporated to provide orsellinate 218 (78 mg, 98%) as a white solid:

\[ R_f 0.54 \text{ (hexanes:EtOAc 1:3); IR (neat) 3385, 2942, 1630 cm}^{-1}; ^1\text{H NMR (CDCl}_3, 400 MHz) \delta 11.85 \text{ (s, 1H), 6.41 (s, 1H), 6.38 (s, 1H), 5.25 (s, 1H), 3.42 (s, 3H), 1.32 (s, 6H);} \]
\[ ^{13}\text{C NMR (CDCl}_3, 100 MHz) \delta 171.1, 164.3, 159.3, 144.0, 112.3, 105.5, 100.7, 67.3, 21.6 \text{ (2C); MS (ESI) } m/z 211 \text{ [M + H}^+]. \]
Isopropyl 2,4-dihydroxy-6-methylbenzoate (218) (one step)

![Chemical structure of 218](image)

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) and isopropanol (2 mL) in CH$_2$Cl$_2$ (5 mL) with 4Å molecular sieves were heated at 100 °C in a sealed tube for 10 h. The solution was filtered through Celite® and washed with excess CH$_2$Cl$_2$. The mixture was rotary evaporated to provide orsellinate 218 (77 mg, 98%) as a white solid:

$R_f$ 0.54 (hexanes:EtOAc 1:3); IR (neat) 3385, 2942, 1630 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 11.85 (s, 1H), 6.41 (s, 1H), 6.38 (s, 1H), 5.25 (s, 1H), 3.42 (s, 3H), 1.32 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 171.1, 164.3, 159.3, 144.0, 112.3, 105.5, 100.7, 67.3, 21.6 (2C); MS (ESI) $m/z$ 211 [M + H]$^+$. 
Pent-4-en-2-yl 2,4-dihydroxy-6-methylbenzoate (220) (one step)

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) and alcohol 219 (0.2 mL) in PhMe (8 mL) were heated at 100 °C for 5 h. The mixture was rotary evaporated, dissolved in isopropanol (5 mL) and heated at 100 °C in a sealed tube for 8 h to provide orsellinate 220 (75.2 mg, 72%) as a clear oil:

Rf 0.25 (hexanes:EtOAc 1:3); IR (neat) 3375, 2932, 1653, 1602, 923 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 11.00 (s, 1H), 6.31 (s, 1H), 6.26 (s, 1H), 5.90-5.79 (m, 1H), 5.30-5.26 (m, 1H), 5.18-5.13 (m, 2H), 2.52 (s, 3H), 2.55-2.43 (m, 2H), 1.40 (d, J = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.5, 162.7, 160.9, 144.8, 131.1, 119.8, 111.5, 103.7, 101.5, 71.2, 40.3, 24.9, 20.3; MS (ESI) m/z 237 [M + H]⁺.
**Pent-4-en-2-yl 2,4-dihydroxy-6-methylbenzoate (220) (one step)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) and alcohol 17 (2 mL) in CH₂Cl₂ (5 mL) with 4Å molecular sieves were heated at 100 °C in a sealed tube for 10 h. The solution was filtered through Celite® and washed with excess CH₂Cl₂. The mixture was rotary evaporated to provide orsellinate 220 (74 mg, 72%) as a clear oil:

Rₜ 0.25 (hexanes:EtOAc 1:3); IR (neat) 3375, 2932, 1653, 1602, 923 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 11.00 (s, 1H), 6.31 (s, 1H), 6.26 (s, 1H), 5.90-5.79 (m, 1H), 5.30-5.26 (m, 1H), 5.18-5.13 (m, 2H), 2.52 (s, 3H), 2.55-2.43 (m, 2H), 1.40 (d, J = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.5, 162.7, 160.9, 144.8, 131.1, 119.8, 111.5, 103.7, 101.5, 71.2, 40.3, 24.9, 20.3; MS (ESI) m/z 237 [M + H]⁺.
(6Z,8E)-((S)-5-(2-(pent-4-enyl)-1,3-dioxolan-2-yl)pentan-2-yl)7-hydroxy-3,5-dioxodeca-6,8-dienoate (14)

A mixture of alcohol 13 (33.8 mg, 0.15 mmol) and dioxolenone 12 (37.3 mg, 0.15 mmol) in xylenes (50 µL) was heated for 8 min at 150 °C, then stirred at RT for 15 min. The solution was concentrated in vacuo and provided 14 (62.5 mg, 99%) as a colourless oil:

Rf 0.43 (EtOAc: hexane 1:3); ¹H NMR (400 MHz, CDCl₃) δ 6.94 (m, 1H), 6.77 (qd, 1H, J = 7.0, 14.0Hz), 5.89-5.69 (m, 4H), 5.53 (s, 0.5H), 5.34 (s, 1H), 5.17 (s, 1H), 5.03-4.94 (m, 6H), 4.94-5.03 (m, 6H), 3.92 (d, 8H, J = 3.1 Hz), 3.62 (s, 1H), 3.57 (s, 1H), 3.22 (s, 2H), 2.05 (m, 4H), 1.91 (dt, 4H, J = 1.6, 7.2 Hz), 1.70-1.36 (m, 20H), 1.23 (dd, 6H, J = 0.8, 6.3 Hz).
(S,E)-5-(2-(pent-4-enyl)-1,3-dioxolan-2-yl)pentan-2-yl 2,4-dihydroxy-6-(prop-1-enyl)benzoate (222)

To keto ester 14 (60.3 mg, 0.148 mmol) in 2 mL of methanol was added KOH (40 mg, 0.71 mmol). The resulting mixture was stirred for 12 h at 23 °C. The reaction mixture was acidified with HCl aq. to pH = 1 and extracted with 3 x 2 mL with EtOAc. The organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc: hexane 1:3) to provide 222 (52.5 mg, 0.13 mmol, 91%) as a colourless oil:

Rf 0.43 (EtOAc: hexane 1:3); [α]D<sup>25</sup> +28.6 (c 3.7, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3338 (br), 2948, 2360, 1644, 1259 cm<sup>-1</sup> ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.74 (s, 1H, H<sub>14</sub>), 6.94 (dd, 1H, J = 1.6, 15.4 Hz, H<sub>7</sub>), 6.35 (d, 1H, J = 2.6 Hz, ArH), 6.30 (d, 1H, J = 2.6 Hz, ArH), 5.90-5.71 (m, 2H, H<sub>8</sub>), 5.20-5.16 (m, 2H, H<sub>13</sub>), 5.10-4.92 (m, 2H, H<sub>17</sub>), 3.91 (s, 4H, H<sub>26</sub> and H<sub>27</sub>), 2.03 (q, 2H, J = 7.2 Hz, H<sub>21</sub>), 1.85 (dd, 3H, J = 1.6, 6.6 Hz, H<sub>11</sub>), 1.64-1.41 (m, 10H, H<sub>12</sub>, H<sub>19</sub>, H<sub>20</sub>, H<sub>22</sub> and H<sub>23</sub>), 1.36 (d, 3H, J=6.3 Hz, H<sub>29</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.9, 164.7, 160.2, 144.4, 138.5, 132.4, 127.0, 114.7, 111.5, 108.2, 104.4, 102.0, 72.6, 64.9 (2C), 36.8, 36.5, 36.1, 33.8, 23.1, 20.1, 19.7, 18.4; MS (CI) m/z 405; HRMS (CI) calculated for C<sub>23</sub>H<sub>32</sub>O<sub>6</sub>: [M+H]<sup>+</sup>, 405.2199; found: [M+H]<sup>+</sup>, 405.2280. Anal. Calcd for C<sub>23</sub>H<sub>32</sub>O<sub>6</sub>: C, 68.29; H, 7.97; O, 23.73 Found: C, 68.37; H, 8.03.
(S,E)-6-oxoundec-10-en-2-yl 2,4-dihydroxy-6-(prop-1-enyl)benzoate

(226)

To keto ester 14 (60 mg, 0.15 mmol) in methanol (2 mL), was added KOH (39.8 mg, 0.71 mmol). The resulting mixture was stirred for 12 h at 23 °C. The reaction mixture was acidified with HCl in methanol to pH = 1 and stir for 30 min and extracted 3 x 2 mL with EtOAc. The organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc: hexane 1:3) to provide 226 (43.5 mg, 82%) as a colourless oil:

Rf 0.43 (EtOAc:hexane 1:3); [α]D 25° +16.1 (c 15.3, CH2Cl2); IR (film) 3371 (br), 2933, 1644, 1260 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.71 (s, 1H, H₁₄), 6.93 (dd, J = 1.6, 15.4 Hz, 1H, H₇), 6.36 (d, J = 2.6 Hz, 1H, ArH), 6.33 (d, J = 2.6 Hz, 1H, ArH), 5.91-5.70 (m, 3H, H₈ and H₁₈), 5.19-5.12 (m, 1H, H₁₅), 5.00 (d, J = 17.2 Hz, 1H, H₁₇), 4.81 (d, J = 10.3 Hz, 1H, H₁₉), 2.47-2.41 (m, 4H, H₁₉ and H₂₃), 2.06 (q, J = 7.2 Hz, 2H, H₂₃), 1.85 (dd, J = 6.6, 1.6 Hz, 3H, H₁₁), 1.71-1.65 (m, 6H, H₁₂, H₂₀ and H₂₂), 1.38 (d, J = 6.3 Hz, 3H, H₂₅); ¹³C NMR (100 MHz, CDCl₃) δ 210.9, 170.8, 164.7, 160.5, 144.4, 137.8, 132.4, 127.0, 115.3, 108.4, 104.2, 102.1, 72.2, 42.3, 41.9, 35.3, 33.0, 22.8, 19.9, 19.3, 18.4; MS (Cl) m/z 360 [M+H]⁺; HRMS (Cl) calculated for C₂₁H₂₉O₅: [M+H]⁺, 361.1937; found: [M+H]⁺, 361.1956. Anal. Calcd for C₂₁H₂₉O₅: C, 69.98; H, 7.83, Found: C, 69.96; H, 7.92.
(S,E)-Zearalenone (6)

To a solution of diene 226 (33.8 mg, 0.09 mmol) in PhMe (58 mL) at 80 °C, was added in one portion second generation Hoyveda-Grubbs catalyst 223 (5.8 mg, 9.3 µmol). The resultant solution was stirred for 24 h whilst argon was bubbled through the reaction mixture. After this period, the mixture was cooled to RT and the solvent was evaporated under vacuum. The residue was purified by column chromatography (EtOAc:hexane 1:2) to provide 6 (21.2 mg, 0.06 mmol, 71%) as a white solid whose analytical properties were identical with an authentic sample purchased from Sigma-Aldrich Chemical Co. (Cat. # Z125):

Rf 0.45 (EtOAc:hexane, 1:1); [α]D 25 −123.1 (c 1.0, CH2Cl2); IR (film) 3355 (br), 2933,1694, 1674, 1611, 1581, 1446, 1354, 1314, 1258, 1199, 1170, 1120 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 12.01 (s, 1H, H19), 7.01 (dd, J = 15.5, 1.5 Hz, 1H, H7), 6.41 (d, J =2.5 Hz, 1H, ArH), 6.34 (d, J =2.5 Hz, 1H, ArH), 5.67 (ddd, J = 15.5, 10.5, 3.5 Hz, 1H, H5), 5.57 (s, 1H, -OH), 5.01-4.98 (m, 1H, H14), 2.85 (ddd, J =18.5, 12.0, 1.0 Hz, 1H, -CH2–), 2.63-2.57 (m, 1H, -CH2–), 2.41-2.33 (m, 1H, -CH2–), 2.22-2.10 (m, 4H, -CH2–), 1.80-1.70 (m, 2H, -CH2–), 1.67-1.61 (m, 2H, -CH2–), 1.49 (m, 1H, -CH2–), 1.38 (d, J =6.5 Hz, 3H, H22); ¹³C NMR (100 MHz, CDCl3) δ 211.7, 171.3, 160.6, 165.4, 144.0, 133.1, 132.4, 108.4, 103.8, 102.4, 73.4, 42.9, 36.7, 34.7, 31.0, 22.3, 21.0, 20.8; MS (Cl) m/z 319; HRMS (Cl) calculated for C18H23O5: [M+H]+, 319.1467; found: [M+H]+, 319.1470.
Synthesis of \textit{S}-(−)-zearalenone (6), single vessel procedure

\begin{equation}
\begin{array}{c}
\text{OH} \quad \text{O} \quad \text{O} \\
\text{12} \quad \text{+} \\
\text{HO} \quad \text{O} \quad \text{O} \quad \text{O}
\end{array}
\end{equation}

A solution of compound 13 (11 mg, 0.05 mmol) and alcohol 12 (12.4 mg, 0.05 mmol) in toluene (0.2 mL) was heated at reflux for 2 h. After this time, the mixture was cooled to RT diluted with MeOH (0.3 mL) and cesium carbonate (55.9 mg, 1 mmol) added in one portion. The mixture was stirred at this temperature for 12 h. After this period the solution was acidified by the addition of Dowex resin 50WX8-400 (200 mg) and stirred for 24 h. The resin was removed by filtration and the solution was diluted in PhMe (35 mL). Second generation Hoveyda-Grubbs catalyst 223 (3.2 mg, 5.2 µmol) was added in one portion and the resultant solution was heated to 80 °C for 8 h whilst argon was bubbled through the reaction mixture. After this period the mixture was cooled to RT and the solvent was evaporated under vacuum. The residue was purified by column chromatography (EtOAc:hexane 1:2) to provide 6 (11 mg, 0.03 mmol, 63%) as a white solid whose analytical properties were identical with an authentic sample purchased from Sigma-Aldrich Chemical Co. (Cat. # Z125).\(^*\)

\(^*\) When the reaction was carried out following exactly the same experimental procedure but without filtering off the Dowex 50WX8-400 resin, \textit{S}-(−)-Zearalenone was obtained in 42 % yield.
(3R,4R)-3,4-dihydroxydihydrofuran-2(3H)-one (250a)\textsuperscript{119}

D-isoascorbic acid 249 (70.0 g) in water (5 L, 4 °C) was sequentially treated with sodium carbonate (85.0 g) over 30 min, hydrogen peroxide 30\% (88 mL) over 1 h, and charcoal (16.0 g in portions). The mixture was filtered through Celite\textsuperscript{®} (200 mL boiling water wash), treated with 6 M HCl (200 mL, pH 1.5), and concentrated to dryness under vacuum (45-50 °C). The solid was extracted with boiling ethyl acetate (5 x 300 mL portions). These combined extracts were concentrated in vacuo, treated with diethyl ether (200 mL), filtered, affording D-erythronolactone 250a (43.6 g, 94\%), which was suitable for further use:

R\textsubscript{f} 0.5 (hexanes:EtOAc 2:1); [α]\textsubscript{D} -73 (c 1.00, H\textsubscript{2}O); mp 101-103 °C\textsuperscript{α}; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz) δ 5.81 (s, 1H), 5.41 (s, 1H), 6.29 (d, J = 2.4 Hz, 1H), 4.53-4.56 (m, 1H), 4.37-4.31 (m, 1H), 4.11-4.01 (m, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) 177.0, 73.4, 71.9, 69.9; MS (ESI) m/z 119 [M + H]\textsuperscript{+}.

\textsuperscript{α} lit. mp 104-105 °C
(2R,3R)-Benzy1 2,3,4-tri-(benzyloxy)butanoate (251a)

Ag₂O (39.2 g, 169.2 mmol) was added with stirring to D-erythronolactone (250a) (5.0 g, 42.3 mmol) and benzyl bromide (40.2 ml, 338.4 mmol) in Et₂O (270 mL). The mixture was stirred in the dark for 3 days at RT and then filtered through Celite. The filtrate was rotary evaporated and chromatographed (EtOAc:hexanes gradient 1:99 to 3:7) affording the titled benzy1 ester 251a (11.14 g, 53%) as a white solid:

Rf 0.35 (hexanes:EtOAc 10:1); [α]D +25.5 (c 2.30, CH₂Cl₂); mp 52 °C (EtOAc/hexane); IR (neat) 3064, 3031, 2869, 1745, 1496, 1454, 1265, 1110, 1027, 910, 738, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.31 (m, 20H, ArH), 5.16 (d, J = 2.0 Hz, 2H, -CH₂-), 4.68, 4.46, 4.60, 4.57 (AB₂q, J = 11.5 Hz, 4H, -CH₂-), 4.49 (s, 2H, -CH₂-), 4.29 (d, J = 5.2 Hz, 1H, H₃), 4.04 (dd, J = 10.2, 4.8 Hz, 1H, H₄), 3.75 (dd, J = 10.2, 4.8 Hz, 1H, H₅), 3.69 (dd, J = 10.4, 5.2 Hz, 1H, H₆); ¹³C NMR (100 MHz, CDCl₃) 170.7, 138.1, 138.0, 137.2, 135.5, 128.5 (2C), 128.3 (3C), 128.2 (3C), 128.2 (2C), 128.0 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 78.9, 77.9, 73.3, 72.7, 72.6, 69.0, 66.6; MS (ESI) m/z 514 [M + NH₄]⁺; HRMS (ESI) calcd. C₃₂H₃₆NO₅: [M + NH₄]⁺, 514.2593; found: [M + NH₄]⁺, 514.2607. Anal. calcd for C₃₂H₃₂O₅: C, 77.40; H, 6.50. Found: C, 77.37; H, 6.45.
(2S,3S)-Benzyl 2,3,4-tri-(benzyloxy)butanoate (251b)

This reaction followed the same procedure as for \textit{251a} starting from L-erythronolactone \textit{250b} (1.0 g, 8.46 mmol) giving benzyl ester \textit{251b} (2.18 g, 52\%) as a white solid:

\[ \alpha_{D}^0 -27.1 \ (c \ 2.50, \ \text{CH}_2\text{Cl}_2); \text{m.p.} \ 49^\circ \text{C} \ (\text{EtOAc/hexane}); \ R_f, \ IR, ^1\text{H} \ NMR, ^{13}\text{C} \ NMR \] and MS were identical to those of (2R,3R)-benzyl 2,3,4-tris(benzyloxy)butanoate \textit{250a}. Anal. calcd for C_{32}H_{32}O_{5}: C, 77.40; H, 6.50. Found: C, 77.41; H, 6.52.
(2S,3R)-2,3,4-Tri-(benzyloxy)butan-1-ol (252a)\textsuperscript{120}

Benzyl ester 251a (11.0 g, 22.1 mmol) in THF (14 mL) was added dropwise with stirring over 10 min to LiAlH\textsubscript{4} in THF (2.4 M; 18.4 mL, 44.3 mmol) in THF (14 mL) at 0 °C. After 10 min, the mixture was warmed to RT and quenched by the sequential addition of water (22 mL), 1 M aq. NaOH (44 mL) and water (60 mL). The suspension was filtered through Celite\textsuperscript{®}, washed with EtOAc (2 x 50 mL) and the resulting solution was rotary evaporated and chromatographed (EtOAc:hexanes gradient 1:9 to 35:65) to give alcohol 252a (10.83 g, 78%) as a clear oil:

R\textsubscript{f} 0.25 (hexanes:EtOAc 10:1); [\alpha]_D^{20} -4.4 (c 1.46, CH\textsubscript{2}Cl\textsubscript{2}); IR (KBr) 3436, 3062, 3029, 2869, 1496, 1454, 1394, 1365, 1326, 1207, 1099, 1027, 736, 597 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \delta 7.40 - 7.32 (m, 15H, Ar\textsubscript{H}), 4.78 - 4.58 (m, 7H, -C\textsubscript{H}\textsubscript{2}-), 3.82 - 3.67 (m, 6H, H\textsubscript{2}, H\textsubscript{3} and H\textsubscript{5}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) 138.1, 138.1 (2C), 128.5, 128.4 (2C), 128.4 (3C), 127.9 (2C), 127.9 (2C), 127.8, 127.7 (2C), 127.7 (2C), 78.6, 78.2, 73.4, 72.7, 72.3, 69.3, 61.4; MS (ESI) m/z 410 [M + NH\textsubscript{4}]\textsuperscript{+}; HRMS (ESI) calcd. C\textsubscript{25}H\textsubscript{32}NO\textsubscript{4}: [M + NH\textsubscript{4}]\textsuperscript{+}, 410.2331; found: [M + NH\textsubscript{4}]\textsuperscript{+}, 410.2330. Anal. calcd for C\textsubscript{25}H\textsubscript{28}O\textsubscript{4}: C, 76.50; H, 7.19. Found: C, 76.41; H, 7.13.
(2R,3S)-2,3,4-Tri-(benzyloxy)butan-1-ol (252b)

This reaction followed the same procedure as for 252a starting from ester 251b (1.0 g, 2.0 mmol) giving alcohol 252b (1.0 g, 79%):

[α]D +3.8 (c 2.30, CH2Cl2); Rf, IR, 1H NMR, 13C NMR and MS were identical with those of 252a. Anal. calcd for C25H28O4: C, 76.50; H, 7.19. Found: C, 76.48; H, 7.15.
(2S,3R)-2,3,4-Tri-(benzyloxy)butyl 2,4-dihydroxy-6-methylbenzoate (254a)

Diketo-1,3-dioxinone 10 (2.1 g, 9.3 mmol) and alcohol 252a (2.8 g, 7.1 mmol) in PhMe (50 mL) were heated at 110 °C for 5 h. The solution was rotary evaporated to give triketo-ester 253a which was dissolved in MeOH (100 mL). Cs₂CO₃ (7.0 g, 21.5 mmol) was added in one portion, the mixture was stirred at RT for 1 h and quenched with aqueous HCl (1 M) to pH 4. The solution was stirred vigorously for 15 min, then brine (200 mL) was added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (hexanes:EtOAc 5:1) to provide ester 254a (2.97 g, 77%) as a clear oil:

Rf 0.5 (hexanes:EtOAc 2:1); [α]D -15.1 (c 1.24, CH₂Cl₂); IR (KBr) 3330, 1649, 1620, 1453, 1314, 1258, 1103, 845, 801, 738, 697 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 11.73 (s, 1H, -OH), 7.37 - 7.27 (m, 15H, ArH), 6.29 (d, J = 2.4 Hz, 1H, ArH), 6.20 (d, J = 2.4 Hz, 1H, ArH), 4.77 - 4.54 (m, 8H, H₁₀ and H₁₈), 3.98 (m, 1H, H₁₂), 3.88 - 3.74 (m, 3H, H₁₁ and -CH₂-), 2.42 (s, 3H, H₇); ¹³C NMR (CDCl₃, 100 MHz) 171.4, 165.4, 160.3, 144.0, 138.0, 137.8, 137.8, 128.4 (3C), 128.3 (3C), 128.0 (2C), 127.9, 127.8 (3C), 127.8 (3C), 111.2, 105.7, 101.2, 76.8, 76.3, 73.4, 72.3, 68.5, 63.3, 24.5; MS (ESI) m/z 543 [M + H]⁺; HRMS (ESI) calcd. C₃₃H₃₅O₇: [M + H]⁺, 543.2383; found: [M + H]⁺, 543.2389. Anal. calcd for C₃₃H₃₄O₇: C, 73.04; H, 6.32. Found: C, 73.04; H, 6.29.
(2R,3S)-2,3,4-Tri-(benzyloxy)butyl 2,4-dihydroxy-6-methylbenzoate

(254b)

This reaction followed the same procedure as for 254a, starting from diketo-1,3-dioxinone 10 (500 mg, 1.3 mmol) and alcohol 252b (374.7 mg, 1.7 mmol), giving ester 254b (281 mg, 78%):

\[ \alpha \]D +19.1 (c 0.80, CH2Cl2); Rf, IR, 1H NMR, 13C NMR and MS were identical with those of 254a. Anal. calcd for C33H34O7: C, 73.04; H, 6.32. Found: C, 73.07; H, 6.28.
(2S,3R)-(-)-Montagnetol (244)

Pd/C (10%, 50 mg) was added to ester 254a (246 mg, 0.45 mmol) in EtOAc (20 mL). After 6 h of stirring under an atmosphere of H₂, the mixture was filtered through Celite®, and rotary evaporated to give (2S,3R)-(-)-montagnetol (244) (100 mg, 81%) as a white solid:

R<sub>f</sub> 0.24 (EtOAc); [α]<sub>D</sub> -10.1 (c 0.50, (CH<sub>3</sub>)<sub>2</sub>CO); mp 138-139 °C (acetone/benzene); IR (neat) 3379, 1646, 1455, 1316, 1263, 1205, 1167, 1078 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 6.20 (d, <i>J</i> = 2.4 Hz, 1H, ArH), 6.15 (d, <i>J</i> = 2.4 Hz, 1H, ArH), 4.59 (dd, <i>J</i> = 11.6, 2.8 Hz, 1H, H<sub>11</sub>), 4.39 (dd, <i>J</i> = 11.6, 6.8 Hz, 1H, H<sub>11</sub>), 3.89 (td, <i>J</i> = 6.8, 2.8 Hz, 1H, H<sub>10</sub>), 3.79 (dd, <i>J</i> = 13.6, 6.0 Hz, 1H, H<sub>18</sub>), 3.66 - 3.62 (m, 2H, H<sub>12</sub> and H<sub>18</sub>), 2.52 (s, 3H, H<sub>7</sub>); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) 173.0, 166.1, 163.8, 144.9, 112.5, 106.0, 101.7, 73.8, 71.2, 67.9, 64.6, 24.6; MS (Cl) <i>m/z</i> 273 [M + H]<sup>+</sup>; HRMS (Cl) calcd. C<sub>12</sub>H<sub>17</sub>O<sub>7</sub>: [M + H]<sup>+</sup>, 273.0974; found: [M + H]<sup>+</sup>, 273.0982. Anal. calcd for C<sub>12</sub>H<sub>16</sub>O<sub>7</sub>: C, 52.94; H, 5.92. Found: C, 52.92; H, 5.91.
(2R,3S)-(+)–Montagnetol (2)

This reaction followed the same procedure as for 244 starting from ester 254b (123 mg, 0.23 mmol) giving of the desired (2R,3S)-(+)–montagnetol (2) (50 mg, 81%):

\[ \alpha \] \text{D} +11 (c 0.40, (CH)_3CO); mp 135-136 °C (acetone/benzene); R_f, IR, \text{H} NMR, \text{C} NMR and MS were identical with those of (2S,3R)-(−)–montagnetol (2). Anal. calcd for C_{12}H_{10}O_{7}: C, 52.94; H, 5.92. Found: C, 52.93; H, 5.90.
4-Hydroxy-6-(2-oxopropyl)-2H-pyran-2-one (256)

Diketo-1,3-dioxinone 10 (100 mg, 0.44 mmol) in PhMe (30 mL) was heated for 8 h at 110 °C. The solution was rotary evaporated and chromatographed (hexanes:EtOAc 2:1) to provide 256 (50.3 mg, 68%) as a yellowish oil:

Rf 0.20 (hexanes:EtOAc 1:1); $^1$H NMR (d8-THF, 400 MHz) δ 10.1 (1H, s), 5.89 (d, J = 2.0 Hz, 1H), 1.19 (d, J = 2.0 Hz, 1H), 3.53 (s, 2H), 2.15 (s, 3H); $^{13}$C NMR (d8-THF, 100 MHz) δ 200.1, 169.3, 162.5, 159.7, 101.6, 89.3, 47.2, 28.6; MS (ESI) m/z 168 [M + H]$^+$ This data is in accordance with the literature.$^{154}$
3-hydroxy-5-methyl-4-(((2S,3R)-2,3,4-tris(benzyloxy)butoxy)carbonyl)phenyl 2,4-dihydroxy-6-methylbenzoate (258)

Sodium hydride (2.8 mg, 0.11 mmol) was added with stirring to resorcylate 254a (30 mg, 0.06 mmol) in DMF (8 mL) at 0 °C. After 30 min at 100 °C, a solution of resorcylate 15 (11.5 mg, 0.06 mmol) in DMF (3 mL) was added slowly. The mixture was stirred for 24 h, then brine (10 mL) was added and the mixture was extracted with Et₂O (5 x 10 mL). The combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (hexanes:EtOAc 5:1) to provide ester 258 (14.5 mg, 38%) as a clear oil:

Rf 0.6 (hexanes:EtOAc 4:1); [α]D -9.4 (c 0.1, CH₂Cl₂); IR (neat) 1745, 1653, 1600, 1251, 1150, 1145, 721 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.42 - 7.24 (m, 15H, ArH), 6.65 (d, J = 2.4 Hz, 1H, ArH), 6.51 (d, J = 2.4 Hz, 1H, ArH), 6.48 (d, J = 2.4 Hz, 1H, ArH), 6.41 (d, J = 2.4 Hz, 1H, ArH), 4.71 - 4.55 (m, 8H, H₁₁ and -CH₂-), 3.95 - 3.94 (m, 1H, H₁₀), 3.78 - 3.68 (m, 3H, H₁₂ and H₁₈), 2.42 (s, 3H, -CH₃), 2.36 (s, 3H, -CH₃); ¹³C NMR (CDCl₃, 100 MHz) 171.1, 165.9, 164.3, 161.0, 157.8, 155.1, 143.3, 139.2, 138.1, 137.8, 137.7, 128.7 (2C), 128.6 (2C), 128.2, 128.1, 128.0, 128.0 (2C), 127.8 (2C), 127.8 (2C), 127.8, 127.7, 116.6, 115.7, 110.2, 108.7, 108.2, 98.3, 76.3, 73.5, 72.3, 72.2, 68.4, 68.4, 63.7, 24.3, 20.1; MS (Cl) m/z 693 [M + H]⁺.
3-Hydroxy-5-methyl-4-(((2S,3R)-2,3,4-tris(benzyloxy)butoxy)carbonyl)phenyl 2,4-bis(benzyloxy)-6-methylbenzoate (259a)

Trifluoroacetic anhydride (29 µL, 0.20 mmol) was added with stirring to acid 240 (65.5 mg, 0.19 mmol) in PhMe (4 mL) at 0 °C. After 2 h at RT the solution was rotary evaporated and the residue dissolved in PhMe (4 mL) and added slowly to ester 254a (85 mg, 0.16 mmol) in PhMe (2 mL) at 0 °C. The mixture was stirred for 1 h at RT after which rotary evaporation gave the crude diester 259a (130 mg) as an oil, which was used directly in the next step. A small sample was purified by chromatography (hexanes:EtOAc 8:1) for characterization purposes:

Rf 0.7 (hexanes:EtOAc 4:1); [α]D -10.1 (c 0.1, CH₂Cl₂); IR (neat) 1746, 1658, 1603, 1250, 1160, 1135, 738 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 11.40 (s, 1H, -OH), 7.42 - 7.26 (m, 25H, ArH), 6.64 (d, J = 2.4 Hz, 1H, ArH), 6.51 (d, J = 2.4 Hz, 1H, ArH), 6.49 (d, J = 2.4 Hz, 1H, ArH), 6.40 (d, J = 2.4 Hz, 1H, ArH), 5.09 (s, 2H, -CH₂-), 5.07 (s, 2H, -CH₂-), 4.72 - 4.56 (m, 8H, H₁₁ and -CH₂-), 3.96 - 3.95 (m, 1H, H₁₀), 3.78 - 3.69 (m, 3H, H₁₂ and H₁₈), 2.43 (s, 3H, H₇), 2.37 (s, 3H, H₂₇); ¹³C NMR (CDCl₃, 100 MHz) 171.1, 165.9, 164.3, 161.0, 157.8, 155.1, 143.3, 139.2, 138.1, 137.8, 137.7, 136.4, 136.3, 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.4 (3C), 128.2, 128.1, 128.0, 128.0 (2C), 127.8 (2C), 127.8 (2C), 127.8 (2C), 127.7, 127.5 (2C), 127.4 (2C), 116.6, 115.7, 110.2, 108.7, 108.2, 98.3, 76.3, 73.5, 72.3, 72.2, 70.7, 70.1, 68.4, 68.4, 63.7, 24.3, 20.1; HRMS (EI) calcd. C₅₅H₅₅O₁₀: [M+H]⁺, 873.3639; found: [M+H]⁺, 873.3646. Anal. calcd for C₅₅H₅₂O₁₀: C, 75.67; H, 6.00. Found: C, 75.65; H, 5.98.
3-Hydroxy-5-methyl-4-(((2R,3S)-2,3,4-tris(benzyloxy)butoxy) carbonyl)phenyl 2,4-bis(benzyloxy)-6-methylbenzoate (259b)

This reaction followed the same procedure as for 259a. Starting from ester 254b (70 mg, 0.13 mmol) giving of the desired diester 259b (126 mg):

$\left[\alpha\right]_{D}^{+11}$ (c 0.1, CH$_2$Cl$_2$); R$_f$, IR, $^1$H NMR, $^{13}$C NMR and MS were identical with those of diester 259a. Anal. calcd for C$_{55}$H$_{52}$O$_{10}$: C, 75.67; H, 6.00. Found: C, 75.65; H, 5.98.
(2S,3R)-(-)-Erythrin (248)

Pd/C (10%, 20 mg) was added to diester 259a (130 mg) in EtOAc (5 mL). After 6 h of stirring under an atmosphere of H₂, the mixture was filtered through Celite®, rotary evaporated and chromatographed (Et₂O; MeOH:EtOAc gradient 0:1 to 1:99) gave (2S,3R)-(-)-erythrin (248) (42 mg, 63% over 2 steps) as a white solid:

Rf 0.48 (EtOAc); [α]D -8.2 (c 0.2, MeOH); mp 166 °C (EtOAc/hexane); IR (neat) 3448, 1639, 1625, 1504, 1462, 1399, 1250, 1245, 1075, 909 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) δ 6.67 (s, 1H, ArH), 6.65 (s, 1H, ArH), 6.29 (d, J = 2.4 Hz, 1H, ArH), 6.21 (d, J = 2.4 Hz, 1H, ArH), 4.64 (dd, J = 11.6, 2.8 Hz, 1H, H₁₁), 4.45 (dd, J = 11.2, 6.4 Hz, 1H, H₁₁), 3.91 (td, J = 6.8, 2.8 Hz, 1H, H₁₀), 3.79 (dd, J = 13.6, 6.0 Hz, 1H, H₁₈), 3.75-3.64 (m, 2H, H₁₂ and H₁₈), 2.56 (s, 6H, H₇ and H₂₇); ¹³C NMR (CD₃OD, 100 MHz) 171.7, 170.8, 166.6, 164.7, 162.9, 154.9, 144.8, 143.6, 117.2, 114.4, 113.0, 109.3, 105.4, 101.9, 73.8, 71.1, 68.4, 64.6, 24.3, 23.2; HRMS (EI) calcd. C₂₀H₂₅O₁₀Na: [M + Na]⁺, 445.1111; found: [M + Na]⁺, 445.1103. Anal. calced for C₂₀H₂₅O₁₀: C, 56.87; H, 5.25. Found: C, 56.86; H, 5.27.
(2R,3S)-(+) - Erythrin (4)

This reaction followed the same procedure as for 248. Starting from ester 259b (81 mg) giving (2R,3S)-(+) - erythrin (4) (33.2 mg, 61% over 2 steps):

[α]D +9.0 (c 0.2, MeOH); mp 168 °C (EtOAc/hexane); Rf, IR, 1H NMR, 13C NMR and MS were identical with those of (2S,3R)-(−) - erythrin (248). Anal. calcd for C20H22O10: C, 56.87; H, 5.25. Found: C, 56.89; H, 5.26.
Diketo-1,3-dioxinone 10 (1 g, 4.42 mmol) was stirred with Et$_3$N (10 mL) overnight in CH$_2$Cl$_2$ (80 mL). The solution was evaporated and chromatographed (hexane:EtOAc 4:1) to give benzodioxinone 15 (883 mg, 96%) as a white solid:

R$_f$ 0.20 (hexanes:EtOAc 3:1); mp 198 °C (EtOAc/hexane); IR (nujol) 1689, 1290 cm$^{-1}$; $^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 6.40 (d, $J$ = 2.4 Hz, 1H, ArH), 6.21 (d, $J$ = 2.4 Hz, 1H, ArH), 2.54 (s, 3H, H$_{14}$), 1.66 (s, 6H, H$_{12}$ and H$_{13}$); $^{13}$C NMR (CD$_3$OD, 100 MHz) $\delta$ 165.7, 162.8, 160.5, 146.7, 115.00, 106.2, 104.9, 102.2, 25.7 (2C), 22.3; MS (Cl, NH$_3$) m/z 209 [M + H]$^+$. This data is in accordance with the literature.$^{155}$
Allyl 7-hydroxy-2,2,5-trimethyl-4-oxo-4H-benzo[d][1,3]dioxine-6-carboxylate (263)

Diketo-1,3-dioxinone 174 (30 mg, 0.1 mmol) was stirred with Et<sub>3</sub>N (1.5 mL) 90 min in CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The solution was evaporated and chromatographed (EtOAc:hexanes gradient 1:4 to 1:3) to give resorcylate 263 (27.6 mg, 98%) as a clear oil:

R<sub>f</sub> 0.39 (EtOAc:hexanes 1:3); IR (neat) 2996, 2929 2360, 1731, 1662, 1600, 1228, 1033, 919 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.40 (s, 1H, H<sub>1</sub>), 6.04 (ddt, <i>J</i> = 17.1, 10.6, 5.9Hz, 1H, H<sub>20</sub>), 5.44 (d, <i>J</i> = 17.1Hz, 1H, H<sub>21</sub>), 5.34 (d, <i>J</i> = 10.6Hz, 1H, H<sub>21</sub>), 4.89 (d, <i>J</i> = 5.9Hz, 2H, H<sub>19</sub>), 2.94 (s, 3H, H<sub>14</sub>), 1.70 (s, 3H, H<sub>12</sub> and H<sub>13</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) 170.71, 167.09, 160.88, 159.74, 150.23, 130.98, 119.78, 111.00, 106.62, 104.93, 103.12, 66.80, 25.71 (2C), 20.48; MS (ESI) <i>m/z</i> 293 [M + NH<sub>4</sub>]<sup>+</sup>; HRMS (ESI) calcd. C<sub>15</sub>H<sub>17</sub>O<sub>6</sub>; [M + H]<sup>+</sup>, 293.1025; found: [M + H]<sup>+</sup>, 293.1036.
DCC (10 mg, 0.05 mmol) was added to a solution of acid **170** (10 mg, 0.04 mmol) in CH₂Cl₂ (2 mL), followed by the addition of DMAP (5.9 mg, 0.05 mmol). The mixture was stirred for 5 h at 40 °C. The reaction mixture was filtered through Celite® and rotary evaporated and chromatographed (EtOAc:hexanes 1:3) to give aromatic **266** (8.0 g, 86%) as a clear oil:

**Rf** 0.35 (hexanes:EtOAc 2:1); IR (nujol) 3034, 1567, 1267, 1017, 978, 856 cm⁻¹; **¹H** NMR (CD₃OD, 400 MHz) δ 6.39 (d, J = 2.1 Hz, 1H, ArH), 6.26 (d, J = 2.1 Hz, 1H, ArH), 2.34 (s, 3H, H₂₇), 1.65 (s, 6H, H₁₂ and H₁₃); **¹³C** NMR (CD₃OD, 100 MHz) δ 164.2, 161.4, 159.6, 147.5, 113.3, 104.1, 103.2, 101.1, 24.3 (2C), 21.1; MS (Cl) m/z 209 [M + H]⁺.
1,3-dioxoisouindolin-2-yl 3-oxobutanoate (275)

A mixture of dioxinone 8 (1 mL, 7.5 mmol) and hydroxylphthalimide (274) (1.2 g, 7.5 mmol) in toluene (15 mL) was heated for 90 min at 90 °C. The solution was concentrated in vacuo and provided ester 275 (780 mg, 43%) as a yellowish solid:

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.95 -7.62 (m, 4H), 3.42 (s, 2H), 2.28 (s, 3H); MS (CI) $m/z$ 248 [M + H]$^+$. 
**N-methoxy-N-methyl-3-oxobutanamide (277)**

![Chemical reaction diagram]

N,O-dimethylhydroxylamine 276 (731.5 mg, 7.5 mmol), dioxinone 8 (1 mL, 7.5 mmol) and Et₃N (2 mL) in toluene (10 mL) was heated for 7 h at 90 °C. The solution was concentrated in *vacuo* and provided 277 (1.1 g, 99%) as a yellowish solid:

IR (neat) 3484, 2977, 2943, 1718, 1655, 1430, 1389, 1362, 1313, 1163, 1119, 1027, 988, 937, 747 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.68 (s, 3H), 3.57 (s, 2H), 3.19 (s, 3H), 2.26 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 201.3, 171.9, 60.9, 48.0, 31.2, 29.7; MS (ESI) m/z 146 [M + H]^+. Those data are in accordance with the literature.¹²⁶
5-methyl-1H-pyrazol-3(2H)-one (279)

\[
\begin{align*}
\text{8} & \quad + \quad \text{278} \\
\text{PhMe} & \quad \rightarrow \\
\text{279}
\end{align*}
\]

A mixture of a solution of hydrazine 1 M in THF 278 (37.5 mL, 7.5 mmol) and dioxinone 8 (1 mL, 7.5 mmol) in toluene (10 mL) was heated for 8 h at 110 °C. The solution was concentrated in vacuo and provided 279 (1.3g, 62%) as a yellowish solid:

\(^1\text{H NMR (DMSO-}d_6, 400 \text{ MHz)} \delta 10.61 (s, 1H), 5.12 (s, 1H), 2.19 (s, 3H); \(^{13}\text{C NMR (DMSO-}d_6, 100 \text{ MHz)} \delta 161.8, 139.9, 89.6, 12.9; \text{MS (ESI) } m/z \text{ 99 } [\text{M + H}]^+. \text{ Those data are in accordance with the literature.}^{127}\)
2-(diethylamino)-6-methyl-4H-1,3-oxazin-4-one (289)

\[
\begin{align*}
\text{8} & \quad + \quad \text{287} \quad \xrightarrow{\text{PhMe}} \quad \text{289}
\end{align*}
\]

A mixture of nitrile 287 (0.87 mL, 7.5 mmol) and dioxinone 8 (1 mL, 7.5 mmol) in toluene (10 mL) was heated for 12 h at 90 °C. The solution was concentrated \textit{in vacuo} and provided 289 (1.7g, 99%) as a yellowish solid:

mp 83-85 °C; IR (neat) 1670, 1650 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.28 (s, 1H), 3.37 (q, \(J = 6.9\), 4H), 2.12 (s, 3H), 1.19 (t, \(J = 6.9\), 6H); \(^1\)\(^3\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 172.6, 162.6, 154.2, 90.0, 41.7, 19.7, 13.6; MS (Cl) \textit{m/z} 183 [M + H]\(^+\). Those data are in accordance with the literature.\(^{128}\)
2-amino-6-methyl-4H-1,3-oxazin-4-one (288)

A mixture of cyanamide 286 (315 mg, 7.5 mmol) and dioxinone 8 (1 mL, 7.5 mmol) in toluene (10 mL) was heated for 12 h at 110 °C. The solution was concentrated in vacuo and provided 288 (1.3 g, 99%) as a yellowish solid:

IR (neat) 1678, 1657 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.62 (s, 2H), 2.18 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.6, 160.6, 151.2, 92.0, 19.7; MS (Cl) m/z 127 [M + H]⁺.
3-benzyl-6-methyl-2-phenyl-2H-1,3-oxazin-4(3H)-one (291)

A mixture of compound 290 (1.41 mL, 7.5 mmol) and dioxinone 8 (1 mL, 7.5 mmol) in toluene (10 mL) was heated for 5 h at 90 °C. The solution was concentrated in vacuo and provided 291 (0.7 g, 41%) as a yellowish solid:

IR (neat) 2112, 1618, 1560, 1414, 1367, 1178, 910, 817 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.72-6.98 (m, 10H), 6.03 (s, 1H), 5.32 (s, 1H), 4.78 (d, J = 13.3Hz, 1H), 4.42 (d, J = 13.3Hz, 1H), 1.89 (s, 3H); MS (Cl) m/z 127 [M + H]⁺. Those data are in accordance with the literature.¹²⁹
6-((5-Hydroxy-3-methyl-4,5-dihydroisoxazol-5-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (296)

Hydroxylamine hydrochloride (125.2 mg, 1.51 mmol) was added to a solution of diketo-1,3-dioxinone 10 (370.4 mg, 1.63 mmol) in pyridine (4 mL) and stirred for 5 h at RT. The reaction mixture was poured into H₂O, acidified with a solution of 6 M aq. HCl (9 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were dried (MgSO₄) and rotary evaporated to provide without further purification the dihydroisoxazol 296 (351.0 mg, 89%) as a colorless oil:

R_f 0.2 (EtOAc:hexanes 1:3); H NMR (CDCl₃, 400 MHz) δ 5.43 (s, 1H, H₃), 3.08 (d, J = 17.9Hz, 1H, -CH₂), 2.89 (d, J = 17.9Hz, 1H, -CH₂), 3.89 (d, J = 14.8Hz, 1H, -CH₂), 3.82 (d, J = 14.8Hz, 1H, -CH₂), 2.03 (s, 3H, H₁₅), 1.70 (s, 3H, -CH₃), 1.69 (s, 3H, -CH₃); C NMR (CDCl₃, 100 MHz) 166.0, 160.9, 156.9, 106.9, 105.2, 49.2, 42.3, 25.3, 24.7 (2C), 13.3; MS (ESI) m/z 242 [M + H]^+.
2,2-Dimethyl-6-((3-methylisoxazol-5-yl)methyl)-4H-1,3-dioxin-4-one

(297)

TFA (2 mL) was added to a solution of dihydroisoxazol 296 (351 mg, 1.45 mmol) in CH₂Cl₂ (3 mL) and stirred overnight. The mixture was dilute with H₂O (6 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were dried (MgSO₄), rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to give isoxazol 297 (249.6 mg, 77%) as a colourless oil:

Rf 0.5 (EtOAc:hexanes 1:3); IR (neat) 2109, 1640 1530, 1498, 1455, 1359, 1305, 1020, 701 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.02 (s, 1H, H₁₂), 5.34 (s, 1H, H₃), 3.67 (s, 2H, H₇), 2.30 (s, 3H, H₁₅), 1.67 (s, 6H, H₉ and H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 165.2, 165.00, 160.73, 160.18, 107.30, 104.05, 95.25, 31.34, 24.87 (2C), 11.40; MS (ESI) m/z 224 [M + H]⁺.
2,2-Dimethyl-6-((5-methyl-1H-pyrazol-3-yl)methyl)-4H-1,3-dioxin-4-one (301)

Hydrazine (0.2 mL, 0.2 mmol, 1M in THF) was added to a solution of diketo-1,3-dioxinone 10 (37.0 mg, 0.16 mmol) in THF (1 mL) and stirred for 5 h at RT. The reaction mixture was rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to provide pyrazol 301 (351.0 mg, 89%) as a colourless oil:

R_f 0.65 (EtOAc:hexanes 1:3); IR (neat) 1862, 1639, 1389, 1360, 1307, 1017, 802 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.95 (s, 1H, H₉), 5.25 (s, 1H, H₃), 3.54 (s, 2H, H₇), 2.31 (s, 3H, H₁₅), 1.66 (s, 6H, H₆ and H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 169.05, 161.26, 144.77, 141.48, 106.75, 104.53, 94.14, 32.61, 24.94, 11.23 (2C); MS (ESI) m/z 223 [M + H]⁺.
Methyl 4-(5-methyl-1\textit{H}-pyrazol-3-yl)-3-oxobutanoate (309)

Pyrazol 301 (100 mg, 0.45 mmol) and MeOH (0.09 mL, 2.3 mmol) were heated in PhMe (10 mL) at reflux for 5 h. The solution was rotary evaporated to provide ester 309 (64.3 mg, 73%) as yellow oil:

R\text{f} 0.2 (EtOAc:hexanes 1:4); IR (neat) 3270, 2942, 1925, 1889, 1345, 1048 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \text{\delta} 5.96 (s, 1H, H\textsubscript{9}), 3.85 (s, 2H, H\textsubscript{6}), 3.73 (s, 3H, H\textsubscript{7}), 3.54 (s, 2H, H\textsubscript{3}), 2.30 (s, 3H, H\textsubscript{12}); MS (ESI) \textit{m}/\textit{z} 197 [M + H]\textsuperscript{+}. 

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2-Methylpyrazolo[1,5-a]pyridine-5,7-diol (20)

Dioxinone 301 (52 mg, 0.23 mmol) was heated in PhMe (500 mL) in a sealed tube at 90 °C for 5 h. The solution was rotary evaporated to provide without further purification, pyrazolopyridine 20a and tautomers 20b, 20c and 20d (35.7 mg, 93%) as a yellowish solid:

\[ R_f \ 0.1 \text{ (EtOAc); IR (neat) 3421, 3235, 1868, 1648, 1497, 1455, 1422, 1204, 923, 886 cm}^{-1}; \text{ } ^1{\text{H}} \text{ NMR (MeOD, 400 MHz) after 15 min in the solvent (ratio 20a:20c, 2:3) } \delta \ 6.28 \text{ (s, 1H, H}_{10}\text{) (tautomer 20c)}, 6.10 \text{ (s, 1H, H}_{2}\text{) (tautomer 20a)}, 6.06 \text{ (s, 1H, H}_{3}\text{) (tautomer 20a)}, 6.05 \text{ (s, 1H, H}_{4}\text{) (tautomer 20a)}, 5.28 \text{ (s, 1H, H}_{12}\text{) (tautomer 20c)}, 3.59 \text{ (s, 2H, H}_{11}\text{) (tautomer 20c)}, 2.43 \text{ (s, 3H, H}_{9}\text{) (tautomer 20c)}, 1.67 \text{ (s, 3H, H}_{1}\text{) (tautomer 20a)}; \text{ } ^1{\text{H}} \text{ NMR (d}_{6}-\text{DMSO, 400 MHz) (ratio 20a:20b:20c:20d, 15:5:60:20) } \delta \ 12.91 \text{ (s, 1H)}, 9.71 \text{ (s, 1H)}, 6.21 \text{ (s, 1H, H}_{10}\text{) (tautomer 20c)}, 6.01 \text{ (s, 1H, H}_{14}\text{) (tautomer 20d)}, 5.90 \text{ (s, 1H, H}_{2}\text{) (tautomer 20b)}, 5.88 \text{ (d, } J=1.9\text{Hz, 1H, H}_{3}\text{) (tautomer 20a)}, 5.86 \text{ (s, 1H, H}_{2}\text{) (tautomer 20a)}, 5.85 \text{ (s, 1H, H}_{8}\text{) (tautomer 20b)}, 5.38 \text{ (d, } J=1.9\text{Hz, 1H, H}_{4}\text{) (tautomer 20a)}, 5.36 \text{ (s, 1H, H}_{12}\text{) (tautomer 20c)}, 5.29 \text{ (s, 1H, H}_{6}\text{) (tautomer 20b)}, 3.73 \text{ (s, 2H, H}_{11}\text{) (tautomer 20c)}, 3.65 \text{ (s, 2H, H}_{15}\text{) (tautomer 16), 3.61 \text{ (s, 2H, H}_{16}\text{) (tautomer 20d)}, 2.30 \text{ (s, 3H, H}_{9}\text{) (tautomer 20c)}, 2.22 \text{ (s, 3H, H}_{13}\text{) (tautomer 20d)}, 2.19 \text{ (s, 3H, H}_{3}\text{) (tautomer 20b)}, 2.18 \text{ (s, 3H, H}_{1}\text{) (tautomer 20a)}; \text{ } ^{13}{\text{C}} \text{ NMR (d}_{6}-\text{DMSO, 100 MHz) 203.2, 169.6, 164.8, 161.1, 158.1, 156.3, 156.2, 155.0, 153.1, 142.7, 140.9, 132.7, 106.9, 106.1, 104.3, 102.4, 91.5, 89.1, 48.6, 38.9, 33.2, 15.3, 14.6 (2C); MS (ESI) } m/z \ 165 \text{ [M + H]}^+ \text{.} \]
2-Methylpyrazolo[1,5-a]pyridine-5,7-diol (20)

Dioxinone 309 (20 mg, 0.10 mmol) was heated in THF (10 mL) and AcOH (5 mL) at 80 °C for 5 h. The solution was rotary evaporated to provide without further purification, pyrazolopyridine 20 and its tautomers (12.1 mg, 72%) as a yellowish solid:

Rf, IR, $^1$H NMR, $^{13}$C NMR and MS were identical to the product obtained in the previous experiment.
Methyl 5-bromofuran-2-carboxylate (317)

TMSCHN\(_2\) (5.1 mL, ~2 M in Et\(_2\)O) was added dropwise to acid 315 (1.9 g, 10 mmol) in a mixture of benzene (12 mL) and methanol (6 mL) at 0 °C until gas evolution ceased. The solution was filtrated and rotary evaporated to give methyl ester 317 (2.0 g, 99%) as a white solid:

R\(_f\) 0.35 (EtOAc:hexanes 1:3); IR (neat) 1703, 1580, 1462, 1295, 1110, 921, 799, 753 cm\(^{-1}\); \(^1\)H NMR (MeOD, 400 MHz) \(\delta\) 7.20 (d, \(J = 3.5\)Hz, 1H, H\(_2\)), 6.62 (d, \(J = 3.5\)Hz, 1H, H\(_3\)), 3.87 (s, 3H, H\(_8\)); \(^{13}\)C NMR (MeOD, 100 MHz) 159.5, 147.6, 128.9, 121.4, 115.3, 52.6; MS (Cl) \(m/\ell\) 206 [M + H]\(^+\); HRMS (ESI) calcd. C\(_6\)H\(_6\)BrO\(_3\): [M + H]\(^+\), 206.0130; found: [M + H]\(^+\), 206.0128.
Methyl 5-allylfuran-2-carboxylate (319)

Pd(PPh₃)₄ (70.5 mg, 0.06 mmol, 5 mol%), furan 317 (250 mg, 1.22 mmol) and allyltributylstannane (318) (0.57 mL, 1.83 mmol) were heated at 90 °C in DMA (6 mL) overnight under argon. The mixture was cooled to RT and subsequently quenched with a saturated aqueous NH₄Cl solution (5 mL). After extraction with Et₂O (3 x 8 mL), the combined organic layers were washed with brine, dried (MgSO₄), rotary evaporated and chromatographed* (EtOAc:hexanes 1:10) to give 319 (129.5 g, 64%) as a colourless oil:

Rf 0.52 (EtOAc:hexanes 1:5); IR (neat) 1721, 1519, 1437, 1300, 1206, 1136, 762 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.11 (d, J = 3.4Hz, 1H, H₂), 6.16 (d, J = 3.4Hz, 1H, H₃), 5.92 (ddt, J = 17.1, 10.2, 6.5Hz, 1H, H₁₀), 5.20-5.15 (m, 2H, H₁₁), 3.87 (s, 3H, H₈), 3.47 (d, J = 6.5Hz, 2H, H₆); ¹³C NMR (CDCl₃, 100 MHz) 162.4, 159.2, 158.9, 132.4, 119.3, 118.0, 108.2, 51.7, 32.8; MS (ESI) m/z 167 [M + H]+.

* 5% of KF can be incorporated into silica to facilitate the purification.
Methyl ester 319 (233 mg, 1.4 mmol) in THF (0.5 mL) was added dropwise with stirring over 10 min to LiAlH₄ in THF (2.4 M; 1.16 mL, 2.8 mmol) in THF (2 mL) at 0 °C. After 10 min, the mixture was warmed to RT and quenched by the sequential addition of water (0.9 mL), 1 M aq. NaOH (3.2 mL) and water (2.3 mL) The suspension was filtered through Celite®, washed with EtOAc (2 x 3 mL) and the resulting solution was rotary evaporated and chromatographed (EtOAc:hexanes gradient 1:2) to give alcohol 321 (100.3 mg, 91%) as a clear oil:

Rₜ 0.45 (EtOAc:hexanes 1:1); IR (neat) 3442, 1723, 10 63 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.20 (d, J = 3.0Hz, 1H, H₂), 5.96 (d, J = 3.0Hz, 1H, H₃), 5.91 (dtt, J = 17.0, 10.3, 6.5Hz, 1H, H₇), 5.17-5.10 (m, 2H, H₈), 4.56 (s, 2H, H₉), 3.38 (d, J = 6.5Hz, 2H, H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 154.2, 152.7, 133.7, 117.0, 108.7, 106.3, 57.5, 32.7; MS (Cl) m/z 139 [M + H]⁺; HRMS (ESI) calcd. C₇H₁₀O₂: [M + H]⁺, 139.1630; found: [M + H]⁺, 139.1628.
2-(5-allylfuran-2-yl)acetic acid (322)

Et₃N (0.5 mL, 3.6 mmol) and methanesulfonyl chloride (0.14 mL, 1.8 mmol) was added to a solution of furan 321 (100 mg, 0.72 mmol) in CH₂Cl₂ (35 mL) at RT. After 30 min, the reaction was poured into water (30 mL) and acidified with 1 M HCl until pH 3. The aqueous layer was extracted twice with CH₂Cl₂ (2 x 10 mL), and the combined organic layers were washed with brine (25 mL), dried (MgSO₄) and concentrated under reduced pressure. Sodium cyanide (105 mg, 2.1 mmol) was added to a solution of the crude mesylate (570 mg) in DMF (35 mL) at RT, and the mixture was heated to 85 °C for 6 h. After cooling to RT, the mixture was concentrated under reduced pressure until to obtain a residual volume of 3 mL. Addition of water (10 mL) to this residue was followed by extraction with EtOAc (3 x 7 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO₄) and concentrated under reduced pressure. NaOH solution 25% (2.3 mL, 14.2 mmol) was added to a solution of the crude nitrile (48 mg) in 95% ethanol (28 mL). The reaction mixture was heated at 85 °C for 7 h. After cooling to RT, the mixture was neutralized with 1 M HCl (14 mL) until pH 3. After stirring for 10 min at RT, the mixture was poured into EtOAc (50 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL), and then was washed with brine (30 mL), dried (MgSO₄) and rotary evaporated and chromatographed (EtOAc:hexanes 1:1) to give furan 322 (9.4 mg, 8%) as a white solid:

Rf 0.1 (EtOAc:hexanes 1:1); ¹H NMR (CDCl₃, 400 MHz) δ 6.11 (d, J = 3.0Hz, 1H, ArH), 5.94 (d, J = 3.0Hz, 1H, ArH), 5.89 (ddt, J = 17.0, 10.4, 6.5Hz, 1H, H₇), 5.15-5.07 (m, 2H, H₈), 3.89 (s, 2H, H₉), 3.36 (d, J = 6.5Hz, 2H, H₆); MS (CI) m/z 167 [M + H]⁺.
2-Bromo-1-(furan-2-yl)ethanone (326)

\[
\text{324} \xrightarrow{1) \text{LDA, THF}} \text{Br} \quad \text{325} \xrightarrow{2) \text{O}} \text{326}
\]

\(n\)-BuLi (4.7 mL, 7.4 mmol) was added dropwise to (i-Pr)\(_2\)NH (1.1 mL, 8.1 mmol) in THF (26 mL) at \(-78 \, ^\circ\text{C}\) and stirred for 20 min. Furan (324) (0.49 mL, 6.8 mmol) in THF (9.5 mL) was added dropwise with stirring to the solution at \(-78 \, ^\circ\text{C}\) and stirred for 20 min. Ester 325 (1 mL, 6.8 mmol) in THF (4.8 mL) was slowly added at \(-78 \, ^\circ\text{C}\). The mixture was stirred at RT for 1 h and poured into aq. HCl (1 M; 60 mL). Et\(_2\)O was added (60 mL), the layers separated and the aqueous phase extracted with Et\(_2\)O (60 mL). The combined organic phases were washed with brine (80 mL), dried (MgSO\(_4\)), rotary evaporated and chromatographed (Et\(_2\)O:hexanes 1:1) to give diketodioxinone 326 (1 g, 63%) as a yellowish solid:

\(R_f\) 0.25 (EtOAc:hexanes 1:5); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.53 (d, \(J = 1.5\) Hz, 1H), 7.21 (d, \(J = 3.7\) Hz, 1H), 6.46 (dd, \(J = 3.7, 1.5\) Hz, 1H), 4.20 (s, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) 189.2, 150.1, 147.6, 119.4, 112.9, 30.5; MS (ESI) \(m/z\) 188 [M + H]\(^+\). This data is in accordance with the literature.\(^{123}\)
Ethyl 2-(furan-2-yl)acetate (328)\textsuperscript{137}

![Chemical structure](image)

The alkyl iodide \textbf{327} (7 mL, 59.0 mmol), furan (\textbf{324}) (77 mL, 1061.3 mmol), and FeSO\textsubscript{4}.\textsubscript{7}H\textsubscript{2}O (8.2 g, 29.5 mmol) were stirred in 1 L of DMSO for 10 min. H\textsubscript{2}O\textsubscript{2} (35\% in H\textsubscript{2}O, 10.9 g, 112.0 mmol) were then added dropwise, while the solution was kept at RT with a H\textsubscript{2}O bath and stirred overnight. The mixture was then \textbf{slowly} diluted with brine and extracted with diethyl ether. The combined organic layers were washed with brine (200 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), rotary evaporated and chromatographed (EtOAc:hexanes 1:3) to provide \textbf{328} (17.0 g, 98\%) as a clear oil:

\[ \text{Rf } 0.41 \text{ (CH}_2\text{Cl}_2); \ \text{IR (neat) } 2984, 2940, 2908, 1741, 1603, 1507, 1478, 1466, 1448, 1392, 1369, 1338, 1301, 1272, 1229, 1185, 1157, 1097, 1075, 1031, 1013, 951, 737, 601\text{cm}^{-1}; \ \text{H NMR (CDCl}_3, 400 MHz) } \delta 7.37 (\text{dd, } J = 1.8, 0.9\text{Hz, } 1\text{H}), 6.35 (\text{dd, } J = 3.2, 1.8\text{Hz, } 1\text{H}), 6.23 (\text{dd, } J = 3.2, 0.9\text{Hz, } 1\text{H}), 4.20 (\text{q, } J = 7.1\text{Hz, } 2\text{H}), 3.69 (\text{s, } 2\text{H}), 1.28 (\text{t, } J = 7.1\text{Hz, } 3\text{H}); \ \text{C NMR (CDCl}_3, 100 MHz) } 169.4, 147.7, 142.0, 110.5, 107.9, 61.1, 34.1, 14.1; \ \text{MS (Cl) } m/z 154 [M + H]^+ \]
Ester 328 (4.18 g, 27.13 mmol) stirred in THF (160 mL) was reacted at 0 °C with LiAlH₄ (2.08 g, 58.55 mmol) added by portions. The mixture was heated to reflux for 1.5 h, cooled, and hydrolysed with brine (90 mL). The salts were filtered off and washed with AcOEt. The aqueous layer was extracted AcOEt (3 x 90 mL) and the combined organic layers were washed with brine (90 mL) and dried over MgSO₄. Evaporation of the solvents in vacuo provided 345 as a malodorous yellow oil (2.86 g, 93%): 

Rf 0.28 (n-hexane:AcOEt 95:5); IR (neat) 3368, 3118, 2956, 2928, 2079, 1736, 1598, 1534, 1418, 110.7, 106.72, 61.2, 31.9; MS (Cl) m/z 113 [M + H]^+. 

\[ 
\text{328} \xrightarrow{\text{LiAlH}_4 \text{in THF}} \text{345} 
\]
Ethyl 2-(5-(2-hydroxyethyl)furan-2-yl)acetate (346)\textsuperscript{144}

![Chemical Structure](image)

The alkyl iodide 327 (0.7 mL, 5.9 mmol), furan 345 (1.32 g, 11.8 mmol), and FeSO\textsubscript{4}.7H\textsubscript{2}O (820 mg, 2.95 mmol) were stirred in 100 mL of DMSO for 10 min. H\textsubscript{2}O\textsubscript{2} (35% in H\textsubscript{2}O, 1.1 g, 11.2 mmol) were then added dropwise, while the solution was kept at RT with a H\textsubscript{2}O bath and stirred overnight. The mixture was then slowly diluted with brine and extracted with diethyl ether. The combined organic layers were washed with brine (20 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), rotary evaporated and chromatographed (EtOAc:hexanes 1:3) to provide 346 (1.7 g, 75%) as a clear oil:

R\textsubscript{f} 0.28 (n-hexane:AcOEt 75:25); IR (neat) 3457, 2960, 2983, 2934, 1738, 1640, 1615, 1566, 1466, 1447, 1370, 1323, 1268, 1226, 1184, 1162, 1030, 971, 915, 855, 791, 686cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \textit{\delta} 6.14 (d, J = 3.1Hz, 1H, ArH), 6.06 (d, J = 3.1Hz, 1H, ArH), 4.19 (q, J = 7.1Hz, 2H, H\textsubscript{13}), 3.86 (t, J = 6.2Hz, 2H, H\textsubscript{10}), 3.65 (s, 2H, H\textsubscript{9}), 2.88 (t, J = 6.2Hz, 2H, H\textsubscript{9}), 1.83 (br, 1H, -OH), 1.28 (t, J = 7.1Hz, 3H, H\textsubscript{14}); 13\textsuperscript{C} NMR (CDCl\textsubscript{3}, 100 MHz) 170.0, 152.8, 147.1, 109.1, 107.9, 61.6, 61.5, 34.6, 32.0, 14.5; MS (ESI) \textit{m/z} 199 [M + H]\textsuperscript{+}. 

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Dess-Martin periodinane (214 mg, 0.5 mmol) was added in one portion with stirring to alcohol 346 (50 mg, 0.25 mmol) in CH$_2$Cl$_2$ (6 mL) at 0 °C. The mixture was stirred for 5 h at this temperature and diluted with saturated aq. NaHCO$_3$ (3 mL), aq. Na$_2$S$_2$O$_3$ (2%, 3 mL) and CH$_2$Cl$_2$ (2 mL). After 20 min stirring, the mixture was allowed to warm to RT and the organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic layers were dried (MgSO$_4$), rotary evaporated and chromatographed (EtOAc:hexanes 1:2) to provide aldehyde 347 (48 mg, 98%) as a yellow oil:

R$_f$ 0.32 (EtOAc:hexanes 1:2); IR (neat) 1733, 1371, 1317, 1219, 1023, 791 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 9.71 (t, $J = 2.1$Hz, 1H, H$_{10}$), 6.21 (d, $J = 3.4$Hz, 1H, ArH), 6.20 (d, $J = 3.4$Hz, 1H, ArH), 4.18 (q, $J = 7.2$Hz, 2H, H$_{12}$), 3.69 (d, $J = 2.1$Hz, 2H, H$_9$), 3.66 (s, 2H, H$_6$), 1.27 (t, $J = 7.2$Hz, 3H, H$_{13}$); $^{13}$C NMR (CDCl$_3$, 100 MHz) 196.7, 171.0, 147.8, 145.6, 109.5, 109.0, 60.18, 42.6, 33.9, 13.9; MS (ESI) $m/z$ 197 [M + H]$^+$. 

Ethyl 2-(5-(2-oxoethyl)furan-2-yl)acetate (347)
(E)-ethyl 4-(5-(2-ethoxy-2-oxoethyl)furan-2-yl)but-2-enoate (349)

Aldehyde 347 (50 mg, 0.25 mmol) in THF (5 mL) was slowly added at −78 °C to a solution of ylide 348 (133 mg, 0.38 mmol) in THF (20 mL). After 30 min at −78 °C and 1 h at RT, the mixture was quenched with aq. NH₄Cl sat. (50 mL). The aqueous layer was extracted with Et₂O (2 × 30 mL) and the combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and rotary evaporated. Chromatography (Hexanes:Et₂O 4:1) gave alkene 349 (35.0 mg, 52%) as a colorless oil:

Rf 0.48 (EtOAc:hexanes, 1:2); IR (film) 1630, 1389, 1354, 1218, 1027, 898 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.13 (d, J = 3.0 Hz, 1H, ArH), 6.02 (d, J = 3.0 Hz, 1H, ArH), 5.86 (d, J = 15.6 Hz, 1H, H₁₄), 5.01 (dt, J = 15.6, 6.6 Hz, 1H, H₁₀), 4.21–4.16 (m, 4H, -CH₂-), 3.63 (s, 2H, H₆), 3.50 (d, J = 6.6 Hz, 2H, H₉), 1.27–1.24 (m, 6H, -CH₃); MS (Cl) m/z 267 (M+H)+.
2-iodo-N-methoxy-N-methylacetamide (352)

2-chloro-N-methoxy-N-methylacetamide (351) (25 g, 181.8 mmol) and NaI (32.7 g, 218.2 mmol) in 450 mL acetone were stirred at RT overnight, in the dark. Acetone was removed by evaporation in vacuo. H₂O (150 mL) were added to the residue and the product was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried (Na₂SO₄), and rotary evaporated to give 352 (40.8 g, 98%) as clear oil:

IR (neat) 1652, 1421, 1380, 995, 936, 840 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.86 (s, 2H, H₁), 3.79 (s, 3H, H₈), 3.19 (s, 3H, H₆); ¹³C NMR (CDCl₃, 100 MHz) 169.3, 61.3, 32.7, -5.9; MS (EI) m/z 230 [M + H]⁺; HRMS (EI) calcd. C₇H₇INO₂: [M + H]⁺, 229.9678; found: [M + H]⁺, 229.9683. Anal. calcd. for C₇H₇INO₂: C, 20.98; H, 3.52; N, 6.12. Found: C, 20.94; H, 3.52; N, 6.11.
(Furan-2-yl)-N-methoxy-N-methylacetamide (353)

The alkyl iodide 352 (13.5 g, 59.0 mmol), furan (324) (77 mL, 1061.3 mmol), and FeSO₄·7H₂O (8.2 g, 29.5 mmol) were stirred in 1 L of DMSO for 10 min. H₂O₂ (35% in H₂O, 10.9 g, 112.0 mmol) were then added dropwise, while the solution was kept at RT with a H₂O bath and stirred overnight. The mixture was then slowly diluted with brine and extracted with diethyl ether. The combined organic layers were washed with brine (200 mL), dried (Na₂SO₄), rotary evaporated and chromatographed (EtOAc:hexanes 1:3) to provide 353 (9.8 g, 98%) as a clear oil:

Rₛ 0.25 (EtOAc:hexanes 1:3); IR (neat) 2940, 1664, 1418, 1381, 1148, 1096, 1000, 730 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.33 (d, J = 1.9 Hz, 1H, H₁), 6.30 (dd, J = 3.2, 1.9 Hz, 1H, H₂), 6.19 (d, J = 3.2 Hz, 1H, H₃), 3.80 (s, 2H, H₆), 3.65 (s, 3H, H₁₂), 3.18 (s, 3H, H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 169.9, 148.5, 141.7, 110.4, 107.8, 61.3, 32.1, 32.0; MS (EI) m/z 170 [M + H]⁺; HRMS (EI) calcd. C₈H₁₂NO₃: [M + H]⁺, 170.0871; found: [M + H]⁺, 170.0813.
2-(furan-2-yl)-N-methoxy-N-methylpent-4-enamide (354)

\[
\begin{array}{c}
\text{O} \quad \text{N} \quad \text{O} \\
\text{353} \quad \text{189} \quad \text{LiHMDS} \\
\text{THF} \\
\text{O} \quad \text{N} \quad \text{O} \\
\text{354}
\end{array}
\]

\(n\)-BuLi (0.24 mL, 0.40 mmol) was added dropwise to HMDS (0.07 mL, 0.5 mmol) in THF (4 mL) at –78 °C and stirred for 20 min. Furan 353 (30 mg, 0.18 mmol) in THF (2 mL) was added dropwise with stirring to the solution at –78 °C and stirred for 30 min. Allyl bromide (189) (19.8 mg, 0.16 mmol) in THF (1 mL) was slowly added and the mixture stirred at RT for 1 h and poured into aq. HCl (1 M; 5 mL). Et\(_2\)O was added (5 mL), the layers separated and the aqueous phase extracted with Et\(_2\)O (5 mL). The combined organic phases were washed with brine (8 mL), dried (MgSO\(_4\)), rotary evaporated and chromatographed (Et\(_2\)O:hexanes 1:5) to give furan 354 (12.3 mg, 36%) as a clear oil:

\(R_f\) 0.4 (EtOAc:hexanes 1:4); IR (neat) 2945, 1645, 1420, 1344, 819, 794 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.34 (d, \(J = 2.0\) Hz, 1H, \(H_1\)), 6.32 (dd, \(J = 3.1, 2.0\) Hz, 1H, \(H_2\)), 6.18 (d, \(J = 3.1\) Hz, 1H, \(H_3\)), 5.81 (m, 1H, \(H_7\)), 5.36-5.28 (m, 2H, \(H_8\)), 3.94 (m, 1H, \(H_5\)), 3.68 (s, 3H, \(H_{11}\)), 3.21 (s, 3H, \(H_{10}\)), 2.84 (m, 2H, \(H_6\)); MS (Cl) \(m/z\) 210 [M + H\(^+\)].
2-bromo-2-(5-bromofuran-2-y1)-N-methoxy-N-methylacetamide (355)

NBS (10.5 g, 59.1 mmol) was added to a stirred solution of substrate 353 (5.0 g, 29.6 mmol) in CH₂Cl₂ at -78 °C in the dark. The reaction mixture was stirred for 1h at this temperature then for 8h at -25 °C and at 0 °C for 1h. The reaction mixture was quenched with 20% aqueous sodium sulfite and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, brine, dried (MgSO₄), rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to provide 355 (7.6 g, 79%) as a yellow oil:

Rᶠ 0.4 (EtOAc:hexanes 1:3); IR (neat) 2940, 1668, 1484, 1387, 993, 787, 727 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.72 (d, J = 3.4 Hz, 1H, H₂), 6.31 (d, J = 3.4 Hz, 1H, H₃), 6.08 (s, 1H, H₆), 3.76 (s, 3H, H₁₂), 3.26 (s, 3H, H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 166.0, 150.4, 123.5, 114.3, 113.4, 61.8, 34.3, 32.6; MS (CI) m/z 326 [M + H]⁺; HRMS (ESI) calcd. C₈H₁₀Br₂NO₃: [M + H]⁺, 325.9027; found: [M + H]⁺, 325.9028. Anal. calcd for C₈H₆Br₂NO₃: C, 29.39; H, 2.77; N, 4.28. Found: C, 29.47; H, 2.83; N, 4.36.
2-(5-bromofuran-2-yl)-N,2-dimethoxy-N-methylacetamide (356)

Dibromofuran 355 (100 mg, 0.3 mmol), zinc dust (40 mg, 0.6 mmol) and AcOH (0.5 mL) were sonicated in MeOH (5 mL) for 1 h. The reaction mixture was filtered, rotary evaporated and chromatographed (EtOAc:hexanes gradient 1:3 to 1:2) to provide 356 (71.2 mg, 62%) as a clear oil:

Rf 0.3 (EtOAc:hexanes 1:2); IR (neat) 2945, 1655, 1483, 1367, 940, 785 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.42 (d, J = 3.4 Hz, 1H, ArH), 6.31 (d, J = 3.4 Hz, 1H, ArH), 5.25 (s, 1H, H₆), 3.52 (s, 3H, -CH₃), 3.42 (s, 3H, -CH₃), 3.22 (s, 3H, -CH₃); MS (Cl) m/z 279 [M + H]⁺.
2-(5-bromofuran-2-yl)-N-methoxy-N-methylacetamide (357)

Dibromofuran 355 (3.0 g, 9.2 mmol), zinc dust (1.2 g, 18.4 mmol) and AcOH (6.5 mL) were sonicated in THF (70 mL) for 1 h. The reaction mixture was filtered, rotary evaporated and chromatographed (EtOAc:hexanes gradient 1:4 to 1:3) to provide 357 (2.4 g, 63%) as a clear oil:

Rf 0.4 (EtOAc:hexanes 1:3); IR (neat) 2940, 1667, 1384, 1122, 1000, 958, 783 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.24 (d, J = 3.3 Hz, 1H, H₂), 6.22 (d, J = 3.3 Hz, 1H, H₃), 3.80 (s, 2H, H₆), 3.70 (s, 3H, H₁₂), 3.21 (s, 3H, H₁₀); ¹³C NMR (CDCl₃, 100 MHz) 169.2, 150.6, 120.3, 112.2, 110.8, 61.4, 32.2, 31.1; HRMS (ESI) calcd. C₈H₁₁BrNO₃: [M + H]^⁺, 247.9922; found: [M + H]^⁺, 247.9929. Anal. calcd for C₈H₁₀BrNO₃: C, 38.73; H, 4.06; N, 5.65. Found: C, 38.69; H, 4.17; N, 5.67.
2-(5-allylfuran-2-yl)-N-methoxy-N-methylacetamide (357)

Pd$_2$dba$_3$ (263.6 mg, 0.29 mmol, 3 mol%) and tBu-X-Phos (366.8 mg, 0.86 mmol, 9 mol%) were sonicated under argon in DMA (10 mL) for 1 h. The resulting mixture, furan 357 (2.4 g, 9.6 mmol) and allyltributylstannane (318) (4.5 mL, 14.4 mmol) were heated at 90 °C in DMA (37 mL) overnight under argon. The mixture was cooled to RT and subsequently quenched with a sat. NH$_4$Cl solution (10 mL). After extraction with Et$_2$O (3 x 15 mL), the combined organic layers were washed with brine, dried (MgSO$_4$), rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to give 17 (1.9 g, 69%) as a colourless oil:

$\text{R}_f$ 0.45 (EtOAc:hexanes 1:4); IR (neat) 2938, 1669, 1418, 1384, 999, 919, 784 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.12 (d, $J$ = 3.0Hz, 1H, H$_2$), 5.95 (d, $J$ = 3.0Hz, 1H, H$_3$), 5.91 (ddt, $J$ = 17.1, 10.3, 6.5Hz, 1H, H$_{14}$), 5.16-5.08 (m, 2H, H$_{15}$), 3.78 (s, 2H, H$_6$), 3.68 (s, 3H, H$_{12}$), 3.36 (d, $J$ = 6.5Hz, 2H, H$_{13}$), 3.21 (s, 3H, H$_{10}$); $^{13}$C NMR (CDCl$_3$, 100 MHz) 170.2, 153.1, 147.2, 147.0, 134.0, 116.8, 108.5, 106.5, 61.3, 32.6, 32.2; HRMS (ESI) calcd. C$_{11}$H$_{16}$NO$_3$: [M + H]$^+$, 210.1130; found: [M + H]$^+$, 210.1128. Anal. calcd for C$_{11}$H$_{15}$NO$_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.02; H, 7.10; N, 6.59.
6-(3-chloro-2-oxopropyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (90)

LiN(SiMe₃)₂ in THF (1 M; 17 mL, 17 mmol) was added dropwise with stirring to dioxinone 8 (2 mL, 15 mmol) in THF (250 mL) and the resulting pale yellow solution stirred at −70 °C for 50 min, when acid chloride 89 (0.39 mL, 5 mmol) was added. The reaction temperature was maintained at −70 °C for 30 min after which time the solution was poured onto aq. HCl (1 M, 50 mL) and Et₂O (100 mL) was added. The organic phase was washed with brine (3 x 100 mL), dried (MgSO₄), rotary evaporated and chromatographed (Et₂O:hexanes gradient 1:1 to 2:1) gave keto-dioxinone 90 (769.8 mg, 70%) as a yellow solid:

Rf 0.45 (EtOAc:hexanes 1:4); IR (neat) 1730 1645 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.40 (s, 1H), 4.18 (s, 2H), 3.59 (s, 2H), 1.73 (s, 6H); MS (ESI) m/z 219 [M + H]⁺. This data is in accordance with the literature.⁵³
**1-(5-allylfuran-2-yl)-5-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)pentane-2,4-dione (312)**

\[
\text{O} \quad 1 \quad \text{LDA (2 eq.), THF, -78 °C to -40 °C} \quad 2) \quad 17 \quad \text{16} \quad \text{312}
\]

\(n\)-BuLi (11.9 mL, 19.11 mmol) was added dropwise to (i-Pr)\(_2\)NH (2.97 mL, 21.0 mmol) in THF (26 mL) at -78 °C and stirred for 20 min. Keto-dioxinone 16 (1.76 g, 9.56 mmol) in THF (9.5 mL) was added dropwise with stirring to the solution at -78 °C and the resulting cloudy yellow solution was slowly allowed to warm up to -40 °C and stirred for 30 min. Weinreb amide 17 (1 g, 4.78 mmol) in THF (4.8 mL) was slowly added and the mixture stirred at -40 °C for 1 h and poured into aq. HCl (1 M, 60 mL). Et\(_2\)O was added (60 mL), the layers separated and the aqueous phase extracted with Et\(_2\)O (60 mL). The combined organic phases were washed with brine (80 mL), dried (MgSO\(_4\)), rotary evaporated and chromatographed (Et\(_2\)O:hexanes 1:1) to give diketo-dioxinone 312 (1.08 g, 63%) as a yellowish solid:

\(R_f\) 0.3 (EtOAc:hexanes 1:3); mp 48-49 °C (Et\(_2\)O:hexanes); IR (neat) 2914, 1714, 1587, 1376, 1273, 1196, 1013, 780 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 6.11 (d, \(J = 3.1\) Hz, 1H, ArH), 5.98 (d, \(J = 3.1\) Hz, 1H, ArH), 5.91 (ddt, \(J = 16.8, 10.2, 6.7\) Hz, 1H, H\(_{12}\)), 5.51 (s, 1H, H\(_8\)), 5.36 (s, 1H, H\(_{17}\)), 5.16 - 5.11 (m, 2H, H\(_{13}\)), 3.63 (s, 2H, H\(_6\)), 3.36 (d, \(J = 6.7\) Hz, 2H, H\(_{11}\)), 3.19 (s, 2H, H\(_{14}\)), 1.66 (s, 6H, H\(_{22}\) and H\(_{23}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) 189.9, 187.2, 164.7, 160.6, 153.9, 146.5, 133.7, 117.0, 109.3, 107.1, 106.6, 99.3, 96.4, 43.0, 37.3, 32.6, 24.9 (2C); MS (Cl) \(m/z\) 350 [M + NH\(_4\)]\(^+\);


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(R,E)-1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-5-(5-(5-hydroxyhex-2-enyl)furan-2-yl)pentane-2,4-dione (372)

Diketo-dioxinone 312 (80 mg, 0.24 mmol), alcohol 18 (25 mg, 0.28 mmol) and Grubbs- Hoveyda 2nd generation catalyst 223 (18.9 mg, 0.03 mmol, 15 mol%) in CH₂Cl₂* (4 mL) were stirred at 40 °C for 1 h. Rotary evaporation and chromatography (EtOAc:hexanes gradient 1:1 to 3:1) gave an inseparable diastereoisomeric mixture of alcohols Z and E 372 (56.7 mg, 61%) as a red oil in a ratio 1:9, Z:E:

Rf 0.2 (EtOAc:hexanes 1:1); IR (neat) 3439, 1725, 1634, 1456, 1376, 1272, 1203, 1015, 973 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.10 (d, J = 3.1Hz, 1H, ArH), 5.95 (d, J = 3.1Hz, 1H, ArH), 5.63 – 5.57 (m, 2H, H₂₃ and H₂₄), 5.50 (d, J = 3.9Hz, 1H, H₇), 5.37 (d, J = 3.9Hz, 1H, H₃), 3.89 – 3.77 (m, 1H, H₂₆), 3.62 (s, 2H, H₁₂), 3.33 (d, J = 5.9Hz, 2H, H₁₈), 3.20 (s, 2H, H₁₇), 2.63 – 2.13 (m, 2H, H₂₅), 1.67 (s, 6H, H₂₀ and H₂₁), 1.19 (d, J = 6.1Hz, 3H, H₂₈); ¹³C NMR (CDCl₃, 100 MHz) 189.8, 187.3, 164.8, 160.6, 154.3, 146.5, 128.9, 109.3, 107.1, 106.4, 99.3, 96.3, 76.1, 43.0, 42.3, 37.3, 31.5, 24.9 (3C), 22.7; HRMS (ESI) calcd. C₂₁H₂₆O₇Na: [M + Na]^⁺, 413.1576; found: [M + Na]^⁺, 413.1576. Anal. calcd for C₂₁H₂₆O₇: C, 64.60; H, 6.71. Found: C, 64.71; H, 6.62.

* Solvents were degassed with N₂
(R,E)-7-hydroxy-5-((5-(5-hydroxyhex-2-enyl)furan-2-yl)methyl)-2,2-
dimethyl-4H-benzo[d][1,3]dioxin-4-one (374)

Diketo-1,3-dioxinone 372 (30 mg, 0.08 mmol) was stirred with Et$_3$N (1.5 mL) 1 h in CH$_2$Cl$_2$ (3 mL). The solution was evaporated and chromatographed (EtOAc:hexanes gradient 1:2 to 1:1) to give an inseparable diastereoisomeric mixture of benzodioxinones Z and E 374 (18.2 mg, 64%) as a clear oil in a ratio 1:9, Z:E:

R$_f$ 0.45 (EtOAc:hexanes 1:1); IR (neat) 3371, 1715, 1614, 1291, 1207, 1172, 1053, 860 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) 6.28 (d, J = 2.3Hz, 1H, ArH), 6.16 (d, J = 2.3Hz, 1H, ArH), 6.09 (d, J = 2.9Hz, 1H, ArH), 5.99 (d, J = 2.9Hz, 1H, ArH), 5.77-5.71 (m, 1H, =CH-), 5.59-5.55 (m, 1H, =CH-), 4.52 (d, J = 17.6Hz, 1H, H$_{12}$), 4.36 (d, J = 17.6Hz, 1H, H$_{12}$), 3.99-3.85 (m, 1H, H$_{24}$), 3.35 (d, J = 6.4Hz, 2H, H$_{18}$), 2.39-2.35 (m, 1H, H$_{24}$), 2.06-2.03 (m, 1H, H$_{24}$), 1.67 (s, 6H, H$_{22}$ and H$_{23}$), 1.36 (d, J = 6.9Hz, 3H, H$_{26}$); $^{13}$C NMR (CDCl$_3$, 100 MHz) 163.1, 159.1, 152.8, 151.8, 146.1, 132.0, 127.5, 111.8, 108.5, 106.6, 104.9, 103.7, 102.4, 67.2, 41.5, 32.1, 31.3, 25.6, 22.2; MS (ESI) m/z 373 [M + H]$^+$. 

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(R)-pent-4-en-2-yl 2-((5-allylfuran-2-yl)methyl)-4,6-dihydroxybenzoate (365)

Diketo-1,3-dioxinone \(312\) (500 mg, 1.5 mmol) and alcohol \(18\) (647.8 mg, 7.5 mmol) were heated in PhMe (35 mL) at reflux for 5 h. The solution was rotary evaporated and dissolved in MeOH (35 mL) when \(\text{Cs}_2\text{CO}_3\) (2.5 g, 7.5 mmol) was added in one portion and the mixture was stirred at RT for 1 h. The mixture was quenched by addition of an aqueous solution of HCl (1 M) until pH 4 and the solution was stirred vigorously for 15 min. Brine (30 mL) was added and the mixture extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO\(_4\)), rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to provide resorcylate \(365\) (396.2 mg, 78%) as a clear oil:

\[\text{R} \_0.55\text{(EtOAc:hexanes 1:4); [\alpha]_D}^{28.0} (c 0.21, \text{CH}_2\text{Cl}_2); \text{IR (neat) 3341, 1741, 1640, 1447, 1606, 1255, 1157, 782 cm}^{-1}; \text{^1H NMR (CDCl}_3, 400 MHz) \delta 11.87 (s, 1H, H}_7); 6.34 (d, \_J = 2.7 Hz, 1H, ArH), 6.17 (d, \_J = 2.7 Hz, 1H, ArH), 5.92 (ddt, \_J = 17.0, 10.2, 6.7 Hz, 1H, =CH\text{-}), 5.90 (d, \_J = 3.0 Hz, 1H, ArH), 5.71 (ddt, \_J = 17.2, 10.0, 7.2 Hz, 1H, =CH\text{-}), 5.69 (d, \_J = 3.0 Hz, 1H, ArH), 5.22–5.06 (m, 5H, H\text{12, 24 and 25}), 4.26 (d, \_J = 16.4Hz, 1H, H\text{16}), 4.14 (d, \_J = 16.4Hz, 1H, H\text{16}), 3.35 (d, \_J = 6.3Hz, 2H, H\text{22}), 2.42 - 2.26 (m, 2H, H\text{14}), 1.22 (d, \_J = 6.3Hz, 3H, H\text{13}); ^{13}\text{C NMR (CDCl}_3, 100 MHz) 170.6, 165.5, 160.2, 153.1, 152.4, 143.1, 134.1, 133.4, 118.1, 116.7, 111.2, 106.8, 106.2, 105.8, 102.2, 72.1, 40.1, 35.2, 32.7, 19.3; \text{HRMS (ESI) calcd. C}\text{29H}_{23}\text{O}_5; [M + H]^+ \text{, 343.1545; found: [M + H]^+, 343.1544. Anal. calcd for C}\text{29H}_{22}\text{O}_5; \text{C, 70.16; H, 6.48. Found: C, 70.09; H, 6.48.} \]
(R)-5-((5-allylfuran-2-yl)methyl)-4-((pent-4-en-2-yloxy)carbonyl)-1,3-phenylene diacetate (375)

Ac₂O (4.3 mL) and DMAP (15.4 mg, 0.126 mmol) were added to resorcylate 365 (429.8 mg, 1.26 mmol) in THF (45 mL) and the solution was stirred at RT for 70 min. The reaction mixture was quenched with EtOAc (40 mL) and washed with H₂O, NaHCO₃ sat. aq. solution, brine. The organic layer was dried (MgSO₄), rotary evaporated and chromatographed (EtOAc:hexanes 1:4) to provide 375 (390.9 mg, 73%) as a clear oil:

Rₜ 0.25 (EtOAc:hexanes 1:4); [α]D -4.1 (c 0.4, CH₂Cl₂); IR (neat) 1772, 1723, 1428, 1368, 1185, 1134, 1091, 1017, 906 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.90 (d, J = 2.2Hz, 1H, ArH), 6.85 (d, J = 2.2Hz, 1H, ArH), 5.90 (ddt, J = 17.0, 10.3, 6.5Hz, 1H, H₁₃), 5.88 (d, J = 5.0Hz, 2H, ArH), 5.75 (ddt, J = 17.2, 10.0, 7.2Hz, 1H, H₂₃), 5.22 – 5.06 (m, 5H, H₁₂, H₂₄ and H₂₅), 4.05 (d, J = 16.4Hz, 1H, H₁₀), 3.35 (d, J = 6.3Hz, 2H, H₂₂), 2.42 - 2.26 (m, 2H, H₁₄), 2.26 (m, 6H, H₇ and H₈), 1.27 (d, J = 6.3Hz, 3H, H₁₃); ¹³C NMR (CDCl₃, 100 MHz) 168.5 (2C), 165.1, 153.1, 151.6, 151.0, 148.9, 139.3, 133.9, 133.3, 124.2, 120.6, 118.1, 116.7, 115.0, 108.0, 106.3, 71.8, 40.1, 32.6, 32.2, 21.1, 20.9, 19.2; HRMS (ESI) calcd. C₂₃H₂₇O₇: [M + H]⁺, 427.1757; found: [M + H]⁺, 427.1763. Anal. calcd for C₂₃H₂₆O₇: C, 67.59; H, 6.15. Found: C, 67.67; H, 6.02.
(R,E)-diacetate-dechloro-pochonin H (376)

Grubbs-Hoveyda 2nd generation catalyst 223 (86.2 mg, 0.137 mmol) in PhMe (5 mL) was added to resorcylate 375 (390.9 mg, 0.92 mmol) in PhMe* (1 L) and the mixture was stirred at 90 °C for 2 h. Rotary evaporation and chromatography (EtOAc:hexanes 1: 4) gave the inseparable diastereoisomeric mixture of macrolactones Z and E 376 (197.1 mg, 54%) as a clear oil in a ratio 1:3, Z:E:

Rf 0.3 (EtOAc:hexanes 1:4); 1H NMR (CDCl3, 400 MHz) δ 6.93 (d, J = 2.3Hz, 1H, ArH), 6.83 (d, J = 2.3Hz, 1H, ArH), 5.94 (d, J = 3.0Hz, 1H, ArH), 5.81 (d, J = 3.0Hz, 1H, ArH), 5.60–5.47 (m, 2H, H12 and H13), 5.38–5.33 (m, 1H, H10), 4.70 (d, J = 14.4Hz, 1H, H20), 3.60 (d, J = 14.4Hz, 1H, H20), 3.22–3.20 (m, 2H, H14), 2.27 (s, 3H, -CH3), 2.26 (s, 3H, -CH3), 1.40 (d, J = 6.3Hz, 3H, H23); 13C NMR (CDCl3, 100 MHz) 168.4 (2C), 165.7, 151.6, 151.5, 151.2, 149.3, 141.5, 130.4, 127.7, 126.7, 121.2, 114.9, 105.8, 105.7, 71.9, 38.7, 31.9, 30.9, 21.4, 21.2, 21.1; HRMS (ESI) calcd. C22H23O7: [M +H]+, 399.1444; found: [M + H]+, 399.1447.

* Solvents were degassed with N2
(R,E)-dechloro-pochonin H (366)

Aq. NaHCO₃ (16 mL) was added with stirring to macrolactone 376 (197.1 mg, 0.49 mmol) in MeOH (16 mL) at RT. After 14 h, EtOAc (10 mL) and saturated NH₄Cl solution (10 mL) were added, extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄), rotary evaporated and chromatographed (EtOAc:hexanes 1:2) to provide resorcylate 366 (104.9 mg, 68%) as a white solid:

R₇ 0.25 (EtOAc:hexanes 1:2); [α]₀ +118.0 (c 0.2, MeOH); mp 147-151 °C (EtOAc:hexanes); IR (neat) 3385, 1699, 1619, 1255, 1051, 1027, 970, 785 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.51 (s, 1H, H₂1), 6.30 (d, J = 2.5Hz, 1H, ArH), 6.25 (d, J = 2.5Hz, 1H, ArH), 5.88 (d, J = 2.9Hz, 1H, ArH), 5.82 (d, J = 2.9Hz, 1H, ArH), 5.68–5.59 (m, 2H, H₁₀ and H₁₂), 5.54–5.48 (m, 1H, H₁₃), 5.07 (d, J = 14.3Hz, 1H, H₂₀), 3.49 (d, J = 14.3Hz, 1H, H₂₀), 3.31–3.15 (m, 2H, H₁₄), 2.45–2.24 (m, 2H, H₁₁), 1.47 (d, J = 6.5Hz, 3H, H₂₃); ¹³C NMR (CDCl₃, 100 MHz) 164.8, 159.7, 159.2, 152.2, 151.1, 144.6, 129.7, 128.4, 111.1, 108.8, 105.7, 105.7, 102.2, 70.3, 40.0, 33.3, 30.8, 21.6; HRMS (ESI) calcd. C₁₈H₁₉O₅: [M + H]+, 315.1232; found: [M + H]+, 315.1230. Anal. calcd for C₁₈H₁₉O₅: C, 68.78; H, 5.77. Found: C, 68.81; H, 5.76.
(**R,5E,9Z**)-14,16-dihydroxy-3-methyl-3,4-dihydro-1**H**-benzo[c][1]oxacyclotetradecine-1,8,11(7**H,12**H)-trione (382)

SO\(_2\)Cl\(_2\) (70 µL, 0.70 mmol, 1 M in CH\(_2\)Cl\(_2\)) was added dropwise with stirring to macrolactone 366 (20 mg, 0.064 mmol) in THF (0.8 mL) at −30 °C and stirred at this temperature for 1 h. The resulting solution was slowly allowed to warm up to 0 °C and stirred for another 30 min. The reaction mixture was quenched with NH\(_4\)Cl (2 mL) and extracted with EtOAc. The organic layer was dried (MgSO\(_4\)), rotary evaporated and chromatographed (EtOAc:hexanes 1:1) to provide 382 (2.51 mg, 12%) as a white solid:

R\(_f\) 0.25 (hexanes:EtOAc 1:1); mp 98-104 °C (EtOAc/hexanes); IR (neat) 3342, 2922, 1697, 1643, 1609, 1452, 1313, 1258, 1085, 1104, 973 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 12.11 (s, 1H, H\(_{22}\)), 6.38 (d, \(J = 2.5\)Hz, 1H, -CH\(_2\)-), 6.34 (d, \(J = 11.8\)Hz, 1H, -CH\(_2\)-), 6.26 (d, \(J = 11.8\)Hz, 1H, ArH), 6.12 (d, \(J = 2.5\)Hz, 1H, ArH), 5.61-5.53 (m, 1H, H\(_{10}\)), 5.50-5.42 (m, 1H, H\(_8\)), 5.36-5.33 (m, 1H, H\(_7\)), 4.47 (d, \(J = 18.1\)Hz, 1H, H\(_3\)), 3.53 (d, \(J = 18.1\)Hz, 1H, H\(_3\)), 3.21 (dd, \(J = 15.5, 6.9\)Hz, 1H, H\(_6\)), 3.13 (dd, \(J = 15.5, 8.4\)Hz, 1H, H\(_6\)), 2.65 - 2.58 (m, 1H, H\(_9\)), 2.27-2.21 (m, 1H, H\(_9\)); 13C NMR (CDCl\(_3\), 100 MHz) 205.2, 195.1, 170.4, 166.4, 161.0, 140.8 (2C), 128.9 (2C), 127.9, 125.5, 112.8, 103.2, 72.2, 51.1, 47.3, 36.6, 18.4; HRMS (ESI) calcd. C\(_{18}\)H\(_{19}\)O\(_6\) [M + H]**+**, 331.1182; found: [M + H]**+**, 331.1174.
(R,5E,9Z)-14,16-dihydroxy-3-methyl-3,4-dihydro-1H-benzo[c][1]oxacyclotetradecine-1,8,11(7H,12H)-trione (382)

\[\text{HO} \quad \text{O} \quad \text{O} \quad \text{OH} \quad \text{HO} \]

\[\text{m-CPBA (41.18 mg, 0.23 mmol) and macrolactone } \text{366 (50 mg, 0.16 mmol) was stirred in CH}_2\text{Cl}_2 (10 mL) at RT for 1 h. The resulting solution was rotary evaporated and chromatographed (EtOAc:hexanes 1:1) to provide 382 (37.76 mg, 72%) as a white solid:}

\[\text{IR, } ^1\text{H NMR, } ^{13}\text{C NMR and MS were identical to the product obtained in the previous experiment.}\]
Appendices
Appendix 1: Crystal structure data for compound 170

Empirical formula C11 H14 O5
Formula weight 226.22
Temperature 173(2) K
Diffractometer, wavelength OD Xcalibur 3, 0.71073 Å
Crystal system, space group Monoclinic, P2(1)
Unit cell dimensions $a = 5.50497(9)$ Å, $\alpha = 90^\circ$
$\beta = 92.9393(15)^\circ$
$c = 17.9323(3)$ Å, $\gamma = 90^\circ$
Volume, Z 1116.11(3) Å³, 4
Density (calculated) 1.346 Mg/m³
Absorption coefficient 0.107 mm⁻¹
F(000) 480
Crystal colour / morphology Colourless needles
Crystal size 0.38 x 0.31 x 0.10 mm³
θ range for data collection 2.90 to 32.38°
Index ranges $-8 \leq h \leq 8$, $-16 \leq k \leq 16$, $-23 \leq l \leq 26$
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Table 1: Bond lengths [Å]

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Appendix 2: $^1$H-NMR Data for zearalenone (6)

$^1$H-NMR Spectrum (400 MHz, CDCl$_3$):

![H-NMR Spectrum Image]
Appendix 3: Crystal structure data for montagnetol (2)

The absolute structure of 2 could not be determined from the X-ray diffraction data, and so was assigned on the basis of the known S and R stereochemistries at C(10) and C(11) respectively (these correspond to C2 and C3 respectively in the chemical numbering scheme). The O–H protons in this structure could not be reliably located, and so were added using the SHELX HFIX 147 command which places them with an idealised X–O–H angle at a position that matches the local electron density maximum and then allows the proton to rotate about the X–O bond to find the best fit. The C(18) methyl protons were placed in idealised positions and allowed to rotate about the C(6)–C(18) bond to find the best fit (AFIX 137).

The molecular structure of 2 (50% probability ellipsoids):
Formula C12 H16 O7
Formula weight 272.25
Temperature 173(2) K
Diffractometer, wavelength OD Xcalibur PX Ultra, 1.54184 Å
Crystal system, space group Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions a = 7.2141(2) Å α = 90°
 b = 8.1883(3) Å β = 90°
c = 19.9569(6) Å γ = 90°
Volume, Z 1178.88(6) Å³, 4
Density (calculated) 1.534 Mg/m³
Absorption coefficient 1.092 mm⁻¹
F(000) 576
Crystal colour / morphology Colourless needles
Crystal size 0.23 x 0.03 x 0.01 mm³
θ range for data collection 4.43 to 72.21°
Index ranges -7<=h<=8, -9<=k<=9, -24<=l<=22
Reflns collected / unique 14460 / 2266 [R(int) = 0.1105]
Reflns observed [F>4σ(F)] 1124
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.00000 and 0.66757
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2266 / 0 / 178
Goodness-of-fit on F² 0.877
Final R indices [F>4σ(F)] R1 = 0.0451, wR2 = 0.0866
R1+ = 0.0451, wR2+ = 0.0866
R1- = 0.0452, wR2- = 0.0869
R indices (all data) R1 = 0.1051, wR2 = 0.1084
Absolute structure parameter \( x^+ = 0.0(4), x^- = 1.7(4) \)

Absolute structure indeterminate, assigned on basis of known chiral centres at C(10) and C(11)

Largest diff. peak, hole 0.236, -0.210 eÅ\(^{-3}\)
Mean and maximum shift/error 0.000 and 0.000

Table 1: Bond lengths [Å]

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Table 2: Bond angles [°]

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Appendix 4: Chiral HPLC analysis of synthetic \((2S,3R)-(\_)\)-montagnetol (244) versus synthetic \((2R,3S)-(\+\)\)-montagnetol (2)

Running conditions for chiral HPLC (flow unit: ml/min):

Chiral HPLC analysis of synthetic \((2S,3R)-(\_)\)-montagnetol (244):
Chiral HPLC analysis of synthetic (2R,3S)-(+)‐montagnetol (2):

Chiral HPLC analysis of a mixture of synthetic (2S,3R)(−)-montagnetol (244) and (2R,3S)-(+)‐montagnetol (2):

---

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Appendix 5: $^1$H-NMR Data for erythrin (4)

$^1$H-NMR Spectrum (400 MHz, CD$_3$OD):

[Image of NMR spectrum]

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<th>1.96</th>
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<th>0.98</th>
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<th>1.01</th>
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<td>2.81</td>
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<td>2.79</td>
<td>2.78</td>
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Appendix 6: Chiral HPLC analysis of synthetic (2S,3R)-(−)-erythrin (248) against (2R,3S)-(+)–erythrin (4)

Chiral HPLC analysis of synthetic (2S,3R)-(−)-erythrin (248):

Chiral HPLC analysis of synthetic (2R,3S)-(+)–erythrin (4):
Chiral HPLC analysis of isolated (+)-erythrin (natural compound)*:

Superposition of chiral HPLC spectra of synthetic (2S,3R)-(−)-erythrin (248) and (2R,3S)-(−)-erythrin (4) over isolated (+)-erythrin (natural compound):

* The isolated natural (+)-erythrin was kindly provided by Prof. V. Karunaratne (University of Peradeniya, Sri Lanka).
Appendix 7: $^{15}$N HMBC Data for 2,2-dimethyl-6-((5-methyl-1$H$-pyrazol-3-yl)methyl)-4$H$-1,3-dioxin-4-one (301)

$^{15}$N HMBC Spectrum (400 MHz, DMSO-$d_6$):
Appendix 8: UPLC-MS Data for 2-methylpyrazolo[1,5-a]pyridine-5,7-diol (20)

[Chemical structure image]

Sample Report (continued):

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<th>Compound</th>
<th>Time</th>
<th>AreaAbs</th>
<th>Area %Total</th>
<th>Width</th>
<th>Height</th>
<th>Mass Found</th>
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<td>1.03</td>
<td>0</td>
<td>2e+006</td>
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<tr>
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Peak ID Compound Time Mass Found
1: (Time: 0.20) Combine (48.51-(42.44+57.60))
1: MS ES+ 2.2e+005

Peak ID Compound Time Mass Found
2: (Time: 0.30) Combine (74.77-(68.70+84.87))
1: MS ES+ 2.9e+007

100 164.9  175.7  304.2  372.6  397.5  447.1  541.7  563.8  621.7  795.5  888.7  m/s

100 165.0  166.1  329.3  1351.1  m/s
Appendix 9: Crystal structure data for deschloro-ponchonin H 366

Formula: C18 H18 O5
Formula weight: 314.32
Temperature: 173 K
Diffractometer, wavelength: OD Xcalibur PX Ultra, 1.54184 Å
Crystal system, space group: Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions:
\[ a = 5.17997(13) \, \text{Å}, \quad \alpha = 90° \]
\[ b = 9.0374(2) \, \text{Å}, \quad \beta = 90° \]
\[ c = 33.5342(8) \, \text{Å}, \quad \gamma = 90° \]
Volume, Z: 1569.85(6) Å\(^3\), 4
Density (calculated): 1.330 Mg/m\(^3\)
Absorption coefficient: 0.803 mm\(^{-1}\)
F(000): 664
Crystal colour / morphology: Colourless needles
Crystal size: 0.3016 x 0.0576 x 0.0401 mm\(^3\)
θ range for data collection: 2.64 to 72.28°
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<td>Index ranges</td>
<td>$-5 \leq h \leq 6$, $-11 \leq k \leq 11$, $-32 \leq l \leq 40$</td>
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<td>Reflns collected / unique</td>
<td>4374 / 2603 [R(int) = 0.0329]</td>
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<tr>
<td>Reflns observed [F&gt;4σ(F)]</td>
<td>2340</td>
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<td>Absorption correction</td>
<td>Analytical</td>
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<td>Max. and min. transmission</td>
<td>0.972 and 0.877</td>
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<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indices [F&gt;4σ(F)]</td>
<td>$R_1 = 0.0319$, $wR_2 = 0.0792$</td>
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<tr>
<td></td>
<td>$R_{1+} = 0.0319$, $wR_2 = 0.0792$</td>
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<td>$R_{1-} = 0.0320$, $wR_2 = 0.0796$</td>
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<td>R indices (all data)</td>
<td>$R_1 = 0.0363$, $wR_2 = 0.0841$</td>
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<tr>
<td>Absolute structure parameter</td>
<td>$x^+ = 0.1(2)$, $x^- = 0.9(2)$</td>
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<tr>
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<td>Indicated absolute structure agrees</td>
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<tr>
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<td>with known stereochemistry at C18</td>
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<tr>
<td>Extinction coefficient</td>
<td>0.0015(4)</td>
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<tr>
<td>Largest diff. peak, hole</td>
<td>0.141, -0.155 eÅ⁻³</td>
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<td>Mean and maximum shift/error</td>
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Table 1: Bond lengths [Å]

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Table 2: Bond angles [°]

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Appendix 10: $^1$H-NMR Data for $(R,5E,9Z)$-14,16-dihydroxy-3-methyl-3,4-dihydro-$1H$-benzo[c][1]oxacyclotetradecine-1,8,11(7$H$,12$H$)-trione (382)

$^1$H-NMR Spectrum (400 MHz, CDCl$_3$):
References
REFERENCES


(58) Naylor J. Chem. Soc. 1945, 244.


(63) Henegar, K. E.; Winkler, J. D. Tetrahedron Lett. 1987, 28, 1051


