Studies towards the synthesis of the antibiotic lactonamycin

Lee James Walsh

Julia Laboratory, Department of Chemistry, Imperial College London,
South Kensington Campus, London, SW7 2AZ, United Kingdom

June 2014

A thesis submitted as partial fulfilment of the requirements for the degree of Doctor of Philosophy, Imperial College London.
Declaration

I hereby declare that the work described in this thesis is solely my own, except where explicitly stated and appropriately referenced. No part of this thesis has been submitted, either in the same or different form, for a degree at this, or any other academic institution.

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution-Non Commercial-No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or distribution, researchers must make clear to others the licence terms of this work.
Abstract

Transition metal-free, thermal cyclisation methodology has been demonstrated previously in the Parsons group, with the vision of applying the process to a novel synthesis of the antibiotic Lactonamycin i. The synthesis of the aglycone of i has been proposed from the pentacyclic intermediate ii, which itself is the hypothesised product of the Parsons-Board-Waters cyclisation of the ene-diyne iii.

Scheme A. Identification of key pentacyclic intermediate (ii) and cyclisation precursor (iii).

The phthalide v was synthesised from 2,5-dimethoxybenzaldehyde in 3 steps in moderate yield and was seen as a common starting material for the subsequent routes devised to provide the key aldehyde vi. A further mode of complexity was proposed by attempting to perform the Claisen rearrangement of the alkene vii in cascade with the aforementioned cyclisation to give the amide ii.

Scheme B. Proposed synthesis of aldehyde vi and of new cyclisation precursor vii
Contents

Declaration 2
Abstract 3
Contents 4
Acknowledgements 6
Abbreviations 7

1. Introduction 10
   1.1 The evolution of antibiotic resistance 11
   1.2 Natural product synthesis and its by-products 13
   1.3 Lactonamycin 16
   1.4 Biosynthesis of lactonamycinone 17
   1.5 Studies towards the total synthesis 20
      1.5.1 Investigations by Danishefsky et al., and the total synthesis of lactonamycinone 20
      1.5.2 Deville and Behar: Synthesis of the ABCD-ring system 35
      1.5.3 Synthetic studies by Kelly et al. 38
      1.5.4 Studies towards total synthesis by Barrett et al. 44
      1.5.5 Nakata and Saikawa et al.: Synthesis of the BCDEF-ring system 62
      1.5.6 Studies towards total synthesis by Parrain and Commeiras et al. 65
   1.6 Total synthesis of lactonamycin 68
      1.6.1 The first total synthesis of lactonamycin by Tatsuta et al. 68
      1.6.2 Total synthesis of lactonamycin by Nakata and Saikawa et al. 73
   1.7 The Parsons-Board-Waters cyclisation methodology 78

2. Results and Discussion 85
   2.1 Natural product synthesis and its by-products continued 86
   2.2 Synthetic studies 89
      2.2.1 Retrosynthetic analysis 89
      2.2.2 First generation synthesis 91
      2.2.3 Second generation synthesis 94
      2.2.4 Formylation 96
      2.2.5 Success with the Claisen rearrangement 99
      2.2.6 Formylation continued 103
      2.2.7 Selective alkylation 105
      2.2.8 Hydroxymethylation and aldehyde formation 107
      2.2.9 Side-chain addition 108
      2.2.10 Modified side-chain addition 113
      2.2.11 Model amide formation/side-chain addition 117
      2.2.12 Use of BOP reagent derivatives and HMDS coupling 119
   2.3 Further work 122
Acknowledgements

I would first like to thank my supervisor, mentor and friend, Prof. Phil Parsons, for not only the opportunity to undertake this PhD, but also for providing unreserved support with my academic and personal life. I would also like to thank his wife and daughter Sue and Ellen for making me feel like part of the family.

No amount of thanks will express the gratitude I feel for my mum, who over the years has never faulted in her ability to provide encouragement when times have been tough. Without her and all my family, I would not be the person that I am today.

Many thanks go to the services of Imperial College London, Peter Haycock, Dick Sheppard and Lisa Haigh.

With my graduate studies spanning two academic institutions I have met some incredible people who have provided love, laughs and hangovers beyond what I ever expected. From my time at Sussex; Chris and Jess (and Al-bear) did not just put up with me at work but also at home. To name a few from the Parsons lab Steve, Paul, Guillaume, Preece, Noel and Glyn were instrumental in teaching me lab techniques. The americans Tara and Kelly were always around for coffee/drinks and recognition goes to anyone that I haven’t mentioned from Sussex that made my time there simply excellent.

Moving institutions in the middle of my PhD research was frustrating and daunting, however, with the patience and friendship received from the members of the Craig group, the move was completely worth it. My main lab brother from another mother Joe Marshall (Takashi Richelle Horse/Joriah Carey) taught me many things about music, fancy dress and the ability to blur the line between men’s and women’s fashion. The rest of the Craig group past and present; Toby (potatoby), Simon, Rich, Gwynnie, Signe, Leena, Bethan and Seb, and many other members of Imperial College have all contributed to my great time as part of the DC/PJP supergroup. Special thanks go to Prof. Don Craig for being amazing to the Parsons group and often providing helpful suggestions to my research. Alex, Lewis and Dr Woolford who made up the Imperial College Parsons group have also had a great contribution to my time in London.

Many housemates, official and unofficial have supported (and hindered) my PhD studies over the years; I am indebted to Maddy and Aimee for always providing me a sofa to sleep on, a buddy to drink with and a friend to rely on, they are the kindest people I know. Dave and Ahmad have also had a hand in steering me away from studying and into the pub. My old housemate Pete is the only man I have ever had to apologise for, but has been a great and dependable friend over the years.

Luke and Jason, it is impossible to list the number of times you’ve made me laugh/cry/flinch, but you are my boys.

My home and other non-chemist friends I have made along the way also need recognition for their ever readiness to give up a weekend to revelry; Scott and Helen, Imogen, all members of RUSC, LADs only and their respective WAGs, and anyone else unmentioned but not forgotten.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>(aq)</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BHT</td>
<td>3,5-di-tert-4-butylhydroxytoluene</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>BOM</td>
<td>benzyloxymethyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>&quot;Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>&quot;Bu</td>
<td>sec-butyl</td>
</tr>
<tr>
<td>'Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
</tr>
<tr>
<td>Cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1'-carbonyldiimidazole</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>CoA</td>
<td>conezyrne A</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-p-benzoquinone</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N'-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DMDO</td>
<td>dimethyldioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMPS</td>
<td>(dimethyl)phenylsilyl</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalents</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectrum</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>mCPBA</td>
<td>$meta$-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>mL</td>
<td>millilitre</td>
</tr>
<tr>
<td>mol</td>
<td>moles</td>
</tr>
<tr>
<td>Mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MRSA</td>
<td>methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieve</td>
</tr>
<tr>
<td>MW</td>
<td>microwave</td>
</tr>
<tr>
<td>NBS</td>
<td>$N$-bromosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>$N$-iodosuccinimide</td>
</tr>
<tr>
<td>Symbol</td>
<td>definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>PBW</td>
<td>Parsons-Board-Waters</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PIFA</td>
<td>Phenylidodine(III)bis(trifluoroacetate)</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>$p'TSA$</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>'Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>R$_f$</td>
<td>retention factor</td>
</tr>
<tr>
<td>RM</td>
<td>reaction mixture</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>TASF</td>
<td>tris(dimethylamino)sulfonyl difluorotrimethylsilicate</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethyl-1-piperidinyloxy, free radical</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFPAA</td>
<td>trifluoroperoxyacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylendiamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>
1. Introduction
1. Introduction

1.1 The evolution of antibiotic resistance

The first instance of antibiotic resistance was recorded in 1940, just 12 years after the discovery of penicillin, before the drug had even been released for therapeutic use.\cite{1,2} Abraham and Chain had found that in cultures of \textit{B. Coli} a $\beta$-lactamase enzyme ‘pennicillinase’ was causing hydrolysis of the $\beta$-lactam ring, rendering the antibiotic ineffective.\cite{2} Later in 1944, penicillin was employed to battle the more common \textit{Staphylococcus aureus} infection and was widely successful. Only several years after its introduction, new strains of \textit{S. Aureus} were beginning to indicate signs of penicillinase expression, reducing the efficacy of penicillin and immediately increasing the need for new types of antibiotic.\cite{10} Due to the majority of antimicrobial drugs arising from natural products, it is possible that bacteria have naturally evolved to abide bactericidal agents, far before their widespread use in medicine.

From the beginning of the age of antibiotics, synthetic studies have been employed to chemically modify the structure of these compounds, so that natural resistance could be avoided. During the synthesis of many of these drugs, testing has shown that some exhibit unexpected non-antibiotic properties and the alternate therapeutic benefits sometimes outweigh their use as antibiotics.\cite{3} This breakthrough in medicine has benefited humanity enormously by reducing fatalities of basic infection and raising average life expectancy by about 30 years; however, overuse and continued development of antibiotics has led to a boom in bacterial mutation in favour of antimicrobial resistance and has contributed to the appearance of more virulent strains of these bacteria.\cite{4}

A Boston City hospital demonstrated the ability of \textit{S. aureus} to become resistant to penicillin and streptomycin based antibiotics, by taking patient samples from between 1950 and 1974.
and exposing them to varying doses of each drug. It was found that as the years progressed, larger doses of each antibiotic were needed to become effective, which correlated with the increased presence of β-lactamase in each strain of bacteria.\cite{10} In 1952, a hospital in Chicago began using low concentrations of the macrolide erythromycin in place of the other two antibiotics, and was found to be highly effective against the more resistant strains of \textit{S. aureus}. Within six months of using this drug, over 70\% of tested strains from patients and hospital workers were found to be resistant and use of the drug was stopped.\cite{10}

In 1959 Beechams reported the synthesis of an antibiotic analogue, benzyl penicillin, which was used to make the β-lactamase resistant, methicillin.\cite{5} This was considered the first synthetic antibiotic, designed for, and was effective in use against, most bacteria that exhibited the penicillinase enzyme (predominantly \textit{Staphylococcus aureus}). In the decade before this, Streptomycin was revolutionary in the treatment of tuberculosis, which became less effective when different strains of \textit{Mycobacterium tuberculosis} showed increased ability to outlive standard doses of the antibiotic.\cite{4} Similarly, in 1961, the first case of Methicillin-resistant \textit{Staphylococcus aureus} was documented, which marked the beginning of multidrug resistance (MDR) in this strain of bacteria.\cite{6,7} This resistance was initially only achieved \textit{in vitro}, however, in the 4 decades after this discovery, small outbreaks of MRSA became prevalent within medical institutions.\cite{8} In 1993 community acquired cases of MRSA (CA-MRSA) were reported in Western Australia, where none of the patients had come in to contact with hospitals that had reported cases of MRSA.\cite{9} Again, this is a worrying demonstration of the ability of \textit{Staphylococcus aureus} to genetically mutate and become a multidrug resistant bacteria, with or without the presence of methicillin.

The ability of mutation does not stop at the bacteria mentioned either: \textit{Clostridium difficile, Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae, Neisseia gonorrhoeae} and \textit{Salmonella} spp. are but a few of the most common strains of bacteria, that cause several
types of infection and have, until recently, been relatively treatable. Resistant and super-resistant strains of these bacteria are turning, what would have previously caused fairly benign infection, into illnesses that require an extended stay in hospital. This in itself is providing an environment where the bacteria can develop further resistance and in some cases has shown increased severity and higher transmission. A variety of β-lactamases have been isolated from the resistant strains of these bacteria, almost ruling out the use of penicillins and cephalosporins as treatment all together. The presence of these enzymes also indicates a propensity of further resistance developing when attempting to treat infection with alternative antibiotics, such as macrolides and tetracyclines.

The continued emergence of multidrug resistance in pathogens, especially bacteria, is confirmation of the constant requirement of natural product discovery and the application of synthetic chemistry to these novel compounds.

1.2 Natural product synthesis and its by-products

As demonstrated previously with the synthesis of methicillin, natural product synthesis can sometimes produce unexpected by-products, which are in some cases, more valuable than the initial target. During studies toward the total synthesis of the antifungal agent ascofuranone 1, we found that a literature reaction of hydroxybutanone 3 and ethyl formate to give furanone 2 did not proceed as described by Margareta et al.\textsuperscript{[11a,11b]}

Figure 1. The antifungal agent ascofuranone and the furanone required for its synthesis.
Instead, we discovered that the spirocyclic polyether 5 was formed, with no evidence of the expected furanone 2 isolated from the reaction.

**Scheme 1. Proposed reaction to give 2,2-dimethyl-3(2H)-furanone.**[^11]

\[
\begin{align*}
\text{HO} & \quad + \quad \text{HO} \\
3 & \quad + \quad 4 \\
\xrightarrow{a} & \quad 2 \\
\xrightarrow{0\%} & \quad 5 \\
\xrightarrow{18\%} & \quad \text{HO} \\
\end{align*}
\]

\[a) \text{i) NaH, Et}_2\text{O; ii) CuSO}_4\text{, HCl, H}_2\text{O}\]

The reported reaction was supposed to undergo a base initiated aldol reaction between 3 and 4, followed by a condensation reaction to give 2, but instead, the hydroxybutanone reacted with itself to produce 5. Where the resulting spirocyclic ether has not been, so far, of any medicinal interest, it does show that chemical complexity can be achieved from relatively small molecules in a single step, without the need for transition metal catalysis.

Another discovery was made in the Parsons group in 2006, during studies towards a new route for the total synthesis of lactonamycin. Board *et al.* had initially set out to attempt a palladium or tin mediated cyclisation strategy, similar to that of work reported previously by Parsons *et al.* in 1992[^12] to form the core structure of lactonamycin in a single step (Scheme 2).[^13]

**Scheme 2. Initial cyclisation strategy by Parsons *et al.*[^13]**
The bromide of ene-diyne 6 was envisioned to be the handle of functionality that could be activated by alkyl tin hydride, to give the desired tetracycle 7 via cascade radical cyclisation, or in a tandem Heck fashion using palladium. Upon investigation of the reaction of 6 with tributyltin hydride and AIBN in benzene at reflux, it was found that the desired structure 7 was produced, but in 14% yield. By attempting the reaction without tin or palladium and in toluene at reflux with 1,2-epoxyhexane, the tetracycle was afforded in a 76% yield.\[14\]

The discovery of the Parsons-Board-Waters cyclisation has been of interest, initially with respect to the total synthesis of the natural product lactonamycin, but also in becoming a new methodology in the synthesis of functionalised heterocyclic and aromatic ring structures, without the need for transition metal catalysis. This was demonstrated also in 2007 by the Parsons group in the synthesis of the etheric precursor 8, which gave the tricyclic furan 9 in high yield using the same methodology.\[15\]

**Scheme 3. Application of the PBW reaction in formation of other ring structures.**\[15\]

This new thermal cyclisation methodology provides the ability to create highly functionalised heterocyclic ring structures in high yield with scope of application to the synthesis of a number of natural products that contain fused ring systems, such as steroids and terpenes. The efficiency and lack of transition metal catalysis make this reaction a clean and environmentally friendly cascade cyclisation sequence.
1.3 Lactonamycin

Lactonamycin (10) is a novel antibiotic that was found to be a secondary metabolite of the bacterium *Streptomyces rishiriensis*, which was discovered during soil sample screening by Matsumoto *et al.*, from Yokohama city in Japan.[16] The lactam 10 is interesting, not just from a synthetic point of view, but also in medicinal terms as it has shown significant antimicrobial activity against gram-positive bacteria; specifically methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Further screening of the natural product has also shown that the lactam 10 exhibits activity as a potent antitumor agent. It is intriguing that such a compound would show biological activity of this level, as its core structure is similar to tetracenomycin. However, its naphtha[e]isoindole ring makes it unlike other known natural products,[19] the main difference being the novel aglycone core structure – lactonamycinone (12), which has been a target of synthesis since its discovery.

Figure 2. Lactonamycin, lactonamycin Z and lactonamycinone.

The aglycone itself is an interesting target for synthesis due to the hexacyclic core structure, with the DEF rings being rich in oxygen functionality containing 3 conterminous stereocentres. Enantioselective synthesis of the hydroxyl group (OR), would also provide a handle of functionality that could be investigated with the scope of attaching a variety of glycosyl moieties, to see if an array of bioactivity could be exploited from a single molecule. This difference in activity has already been demonstrated by the discovery of a very similar
natural product in 2003 from the bacteria *Streptomyces sanglieri*.\[^{18}\] This secondary metabolite, lactonamycin Z (11), only differs from lactonamycin by the attached sugar group. In 11 this group is derived from L-digitoxose whereas in 10 it is derived from L-rhodinose. This only seems like a small difference in the two structures, however, 11 has shown a distinctly stronger activity as an antitumor agent, where 10 is the more effective antibiotic.\[^{18}\]

### 1.4 Biosynthesis of lactonamycinone

In 2008 Parry *et al.*, carried out investigations into the biological pathways in which *S. rishiriensis* and *S. sanglieri* produced both glycosylates of lactonamycinone.\[^{17}\] DNA sequencing of *S. rishiriensis* showed genes similar to those responsible for the biosynthesis of tetracenomycin C (TcmC) as well as genes that coded for L-rhodinose. The genetic cluster that was taken from *S. rishiriensis* was not able to sustain lactonamycin production so the almost identical cluster was used from *S. sanglieri* for the purpose of probing the biosynthesis of lactonamycinone.\[^{17}\]

The biosynthetic portions of the *Streptomyces* bacteria that are similar to TcmC, have been reported to produce a cis-1,2-diol functionality in the natural product, which is comparable to the cis-1,2-oxygen functionality apparent in the DEF ring structure.\[^{20,21}\] Due to the similarity in structure and genetics it was thought that the biosynthesis of these antibiotics was to proceed in a similar fashion, which was by way of polyketide synthesis *via* the head-to-tail combination of nine acetate units. This hypothesis was tested by adding a combination of radiolabelled sodium acetate units (figure 3) to the fermentation of *S. sanglieri*. 
Examination of the resulting $^{13}$CNMR, showed labelling patterns consistent with the mechanism of head-to-tail acetate combination. Carbons 12, 12a, 15 and 16 however, had an absence of labelling, suggesting that these portions of the molecule came from a separate medium.

Parry and co-workers proposed that glycine or derivatives thereof, could be likely units in the assembly of 11 and tested this by adding labelled [1,2-$^{13}$C], [1-$^{13}$C] and [2-$^{13}$C, $^{15}$N] glycine to the fermentation of *S. sanglieri*. This resulted in showing that C-12a and C-12 corresponded directly to C-1 and C-2 of glycine, as well as the nitrogen (N-11) atom coming from the same molecule.

Interestingly, the N- and O-methyl groups (C-15, C-16) were not observed in the results of the [1-$^{13}$C] glycine experiment but were in [1,2-$^{13}$C] and [2-$^{13}$C, $^{15}$N], suggesting that each methyl group comes from the C2 of glycine. Parry postulated that these labelled methyl groups could come from natural metabolism of glycine by a group of enzymes in the bacteria.$^{[17]}$
The incorporation of multiple acetate units to form the core structure of TcmC came from biosynthetic investigations by Rhor et al.\cite{20} and similarity in the labelling experiments lead Parry to propose the synthetic pathway in scheme 4. TcmC synthesis was achieved using 10 acetate units, however, for this pathway 9 units of malonyl-Coenzyme A and 1 unit of glycyl-Coenzyme A were required. Following a similar synthetic motif to TcmC, the polyphenolic quinone 16 was assumed to be a common structure, from which the synthesis could progress. Oxidative cleavage of the double bond in 17 would then give rise to the aldehyde 18, which could be reduced leading to attack of the $\alpha,\beta$-unsaturated acid. The
resulting furan 20 was oxidised, akin to the hydroxylation of TcmC, to give the epoxide 21, which was opened with epoxide hydrolase followed by addition of water to give the cis-hydroxylated quinone 22. Lactonisation of the acid and hydroxyl group in 22 accompanied by the introduction of a glycine unit to form the lactam ring, would produce lactonamycinone.

1.5 Studies toward the total synthesis

1.5.1 Investigations by Danishefsky et al., and the total synthesis of lactonamycinone

Between 2000 and 2003, Danishefsky and co-workers released a number of publications, which detail model studies for the synthesis of lactonamycin, as well as a total synthesis of racemic lactonamycinone. The first in this series was aimed at producing the oxygen rich CDEF ring structure of lactonamycin via intramolecular Wessely oxidation.\(^{[22,29]}\)

**Scheme 5. Idealised approach to the DEF ring system.**

The conceptual strategy was to employ oxidative dearomatisation to furnish the fused lactone EF ring structure in a single step. It was then hoped that the enol ether of 24 could be oxidised on the opposite face to the tertiary methoxy group, giving rise to the cis-fused DE system. Initially, this methodology was attempted on the simplest model, employing only the DEF ring structure with a proton in place of the tertiary methoxy group. Unfortunately, the
Wessely oxidation proved to be low yielding and the resulting intermediate unstable, so the synthesis of the larger CDEF model system was explored (scheme 6).

Scheme 6. Synthesis of the CDEF ring system.

Starting from the known phosphonate 26 a tandem Michael addition-cyclisation type reaction was employed to afford the CDE segment (27) of the required ring structure. Exposure of 27 to methylation, selective demethylation and benzyl protection conditions, gave rise to the benzyl ether 28. This was then subjected to nucleophilic addition of tert-butyl acetate to the lactone, followed by subsequent deprotection and functional group manipulation to furnish the Wessely oxidation precursor 29. Due to previous failed attempts at applying the oxidation to compounds with the tertiary methoxy group in place, it was thought the reaction could be investigated on the hydride equivalent with later installation of the required functionality.

Scheme 7. Application of Wessely oxidation and DMDO.

a) $\text{Pb(OAc)}_4$, DCM, (74%); b) DMDO, DCM, (80%).
As hoped, when subjected to Wessely oxidation conditions, the phenol 29 underwent oxidative deearomatization, followed by lactonisation to give the desired 30, with only the desired stereochemistry observed. Oxidation of the methyl enol ether, was performed with DMDO, giving 80% yield with 95% diastereofacial selectivity. Further analysis of the products showed that selectivity was in favour of the undesired isomer 31b, which may be due to the lack of the tertiary methoxy group (in this example) to direct the oxidising agent to the opposite face.

Efforts to convert 31b to 31a via a retroaldol-realdol type sequence were unsuccessful, leading Danishefsky to attempt a ring opening of the lactone to release the hydroxyl group with the intention of exploiting its use in direction of the oxidising agent.

**Scheme 8. Exploitation of the free hydroxyl group.**

![Scheme 8](image_url)

The lactone was opened using lithium methoxide that was generated *in situ* using LiHMDS in the presence of methanol, which provided methyl ester 32 with the free hydroxyl group in place for directing the oxidation. Trifluoroperacetic acid was found to be the best reagent in this respect, giving a 20:1 mixture with the desired isomer as the major product, followed by acid catalysed ring closure to reform the lactone 31a.

Ideally, the tertiary methoxy group would be in place before closure of the EF ring system, but constraints of the synthesis undertaken by Danishefsky did not allow it. Instead, a late stage introduction of the moiety had to be approached by generating an α,β-unsaturated
system within the lactone, allowing for Michael addition of methanol to complete the model synthesis.

**Scheme 9. Introduction of the tertiary methoxy group.**

The silyl ketene acetal was generated using LiHMDS with TMSCl, which was subsequently trapped out using NIS to create the iodo-lactone 34. This was subjected to oxidation by DMDO with the thought that syn-elimination would occur via an iodoso intermediate similar to that described by Reich et al.\(^{[26]}\) Production of the enol-triflate 36 was then followed by conjugate addition of methanol to give the desired isomer 37 exclusively. Final removal of the triflate, afforded the complete CDEF-ring structure as required with hopes of further applying the reported methodology to total synthesis of lactonamycin.

**Scheme 10. Revised route to CDEF ring structure.**
A second approach to the CDEF portion of lactonamycin was undertaken by Danishefsky et al., by way of diastereoselective dihydroxylation and early stage introduction of the tertiary methoxy group. Investigation of this route was to be effected, with the quinone 39 as the proposed starting point for dihydroxylation, with the potential to convert the enantiopure diol 40 into the previously acquired 38.[23]

Scheme 11. Synthesis of the required quinone.

Synthesis of this quinone began from a commercially available bromide 41, which was subjected to allylic bromination conditions, followed by nucleophilic displacement with benzyl alcohol to afford 42. Metal-halogen exchange of the aromatic bromide with butyllithium, followed by addition of ethyl formate was able to produce the aldehyde 43, which when exposed to the lithium enolate of tertiary butyl acetate, gave the tert-butyl ester 44a. It was initially thought the best route for synthesis would contain the α-ketone (see
scheme 10) as it would provide access to formation of the tetrahydrofuran of the DEF structure. With this in mind, the alcohol was oxidised using Dess-Martin periodinane to give 44b, which was converted to the quinone 45b with CAN. This was low yielding; however, enough material was recovered to demonstrate that this double bond was too electron deficient for standard dihydroxylation conditions. Oxidation of the alcohol 44a proceeded with greater results, providing quinone 45a, which did present itself as a suitable candidate for dihydroxylation.

**Scheme 12. Formation of the F ring.**

Osmylation of the alkene 45a proceeded to give triol 46 as a single diastereomer, which was confirmed by X-ray analysis. Under acidic conditions, tert-butyl ester 46 underwent hydrolysis, followed by cyclisation to give the lactone 47. It was believed that at this point in synthesis, the secondary alcohol could be oxidised to form a ketolactone, providing the functionality required to form the furan ring and complete the DEF system. A variety of techniques were applied to the oxidation of the alcohol, none of which proved successful. Removal of the benzyl protecting group and acetonide protection of the resulting diol, also provided a secondary alcohol that was completely resistant to oxidation. X-ray
crystallography of 49 revealed that the proton attached to the carbon for oxidation, was in a hindered environment causing the lack of reactivity towards oxidation.

Due to the problems with Danishefsky’s revised route, he decide to apply chemistry from his previous model study to effect the final ring closure.

Scheme 13. Return of the α-iodolactone.

Exposure of the previously acquired lactone 47 to LiHMDS and TMSCl followed by NIS, gave the expected α-iodolactone and protected secondary alcohol. Treatment of this with DBU, eliminated the β-TMS ether to afford the unsaturated-iodolactone 50a. Removal of the benzyl group with BBr₃ produced the primary alcohol needed for conjugate addition to the alkene, forming the furan of the DEF construct. The α-iodolactone 50b was isolated as a mixture of diastereomers, which was converted to the required model structure 38 via methods described vide supra.

In 2003, Danishefsky detailed the synthesis of the ABC section of lactonamycin as well as the formation of an advanced intermediate for total synthesis, using a Tamura-Diels-Alder type approach. This was shortly followed by the total synthesis of lactonamycinone utilising the methodology as described in his first two publications.
Introduction


The cycloaddition of phthalic anhydrides to quinone dienophiles for the synthesis of a tetracyclic quinone-type antibiotic was demonstrated by Tamura et al., in 1985 and is a base initiated modification of the Diels-Alder reaction.\textsuperscript{[27]} Danishefsky proposed that this methodology could be interpreted for the synthesis of lactonamycin, if the variants of phthalic anhydride 51 and quinone 52 could be tailored with the functionality required. Initial problems were thought to arise by control of regioselectivity as in the simplest system, cyclisation adducts 53 and 55 would be formed equally and so some form of regiocontrol would need to be installed before attempts at the reaction. Previous work by Danishefsky towards the total synthesis of rishirilide B showed that hydrogen bonding of a similar quinone showed a reactive bias towards the β-carbon with respect to the H-bonded ketone.\textsuperscript{[28]} With this in mind, it was believed that if a directing group could be installed at R', then the cycloaddition would proceed in favour of the isomer needed 54.

Following the analysis of the Tamura-Diels-Alder reaction as well as application of previous work, it was thought that the necessary phthalide 63 could be synthesised, with the AB ring functionality in place. This would also be coupled with the required quinone, not only with
the required directing functionality, but also groups needed to form the DEF section of lactonamycin.

**Scheme 15. Synthesis of phthalic anhydride.**

![Chemical reaction scheme](image)

*Ethyl enol-ether 57 was the starting point for synthesis of anhydride 63, with iodination giving compound 58. This was subjected to a Stille coupling with an alkenyl stannane\(^{[33]}\) to give rise to the cycloaddition precursor 59, which was exposed to allene 60 at 200°C affording the dibenzyl ester 61 in relatively low yield. Debenzylation occurred under hydrogenation conditions to give diacid 62, which was subjected to a dehydrating agent, but only gave the desired anhydride 63 in trace yields. This was thought to be largely down to the solubility of SM.*

Taking this, and the low yielding Diels-Alder reaction, into account, it was thought a better route to the synthesis of the phthalic anhydride was needed, if this methodology could realistically be applied to a larger synthesis.

A revised synthesis, again took advantage of a Diels-Alder cycloaddition of a disubstituted diene 64 with the allene 65, however, the lactam ring was removed for installation at a later
date as the greater functionalisation was thought to be a main contributor in the low yield of the cycloaddition.

**Scheme 16. Revised synthesis of the required phthalic anhydride.**

Cycloaddition and subsequent silyl deprotection of 64 and 65 afforded the phenol 66 in an improved yield of 75% over two steps. The phenol was then protected as the octyloxymethyl ether 67 as this was thought to improve solubility and therefore, better the yields of following reactions. Bromination of the aromatic methyl group and treatment with methyl amine furnished the isoindolinone 68 in 30% yield over two steps. Hydrolysis of the methyl esters gave the diacid, which was subjected to the same dehydrating agent as the previous route, to give the desired phthalic anhydride 69 in almost quantitative yield over both steps.

This route, albeit more convoluted than previously imagined, provided good synthesis for an anhydride that could be taken on to test the hypothesised Tamura-Diels-Alder reaction. The next step in this synthesis was to produce a quinone necessary for the Tamura-Diels-Alder reaction, but also with required functionality in place for completion of the total synthesis of lactonamycin.
Scheme 17. Synthesis of the functionalised quinone.

A short synthesis to the desired quinone (74) started by protection of the known alcohol 70\(^\text{[31]}\) as a benzyl ether, followed by removal of the dithiane to give aldehyde 72. Addition of the lithiated enol-ether of tert-butyl acetate, to the aldehyde, afforded the alcohol 73 in good yield. Demethylating oxidation of this alcohol via CAN gave rise to the desired quinone 74 with functionality in place for synthesis of the DEF ring system, but also with the H-bonding alcohol needed for obtaining desired regioselectivity.

The cycloaddition was carried out by treating the phthalic anhydride 69 with 2 equivalents of NaH followed by addition of 2 equivalents of the quinone 74.

Scheme 18. Effecting the regiospecific Tamura-Diels-Alder reaction.
Introduction

As predicted, the placement of the hydroxyl moiety provided control over regioisomers with the reaction giving only the desired tetramer 75, via either hydrogen bonding with the quinone, or possibly metal chelation with sodium. This theory was proven by TBS protecting this free alcohol and repeating the experiment, which in turn gave a 1:1 mixture of regioisomers.

Synthesis of the advanced synthetic intermediate 75, provided Danishefsky et al. with the core functionality needed, which when manipulated using methods described in his first two publications described vide supra, Danishefsky was able to proceed with a total synthesis of lactonamycinone.

Scheme 19. Finishing the total synthesis.

It was thought that previous methodology to synthesise the DEF ring system of lactonamycinone, could be applied to the advanced intermediate 75 to achieve lactone 76. This would then require, what was thought would be, minimal manipulation to give the tertiary methoxy moiety, completing a total synthesis of lactonamycinone 12.[25]

Dihydroxylation of the quinone 75 proceeded in good yield with high diastereoselectivity due to attack of the olefin from the opposite face to the hydroxyl moiety in its most stable conformer, described similarly in work by Kishi et al.[34] It was noted that due to the high selectivity of this reaction, enantioselective synthesis could arise if alcohol 75 was provided as a single isomer. Following this, acid mediated lactonisation of the triol 77 proceeded with removal of the octyloxymethyl ether to give the phenol 78.
TBS protection of one phenol and the alcohol of the lactone gave 79, which was subjected to X-ray crystallography to confirm structure and stereochemistry of the product. As described previously generation of the silyl enol ether produced α-iodolactone 80, which when treated with cesium carbonate produced the unsaturated keto-lactone 81. Removal of the benzyl protecting group was achieved using boron tribromide, which spontaneously ring closed to give tetrahydrofuran 83 by treatment with mildly acidic alumina.

Manipulation of the α-iodolactone 83 as per the conditions set out in scheme 9, was expected to provide the tertiary methoxy group required to finish the total synthesis of lactonamycin, however, application of this chemistry to the advanced intermediate 83 did not prove successful.
Although the main hexacyclic structure of lactonamycinone was synthesised, a new route to complete the total synthesis was needed. This began from the same quinone 75 used previously, which was oxidised using the Dess-Martin periodinane to give ketone 84.\textsuperscript{35}

Formation of the ketone reduced the reactivity of the double bond on the quinone towards osmylation and so osmium tetroxide was used in conjunction with TMEDA to give the diol 85. Acidic lactonisation gave the ketolactone 86, which also proceeded with deprotection of the octylmethoxy ether, similar to the method described in scheme 20. TBS protection of the resulting phenol and methylation of the ketolactone using TMS-diazomethane, gave 88, which was benzyl deprotected with boron tribromide to afford the alcohol 89. This was
expected to undergo conjugate addition to the $\alpha,\beta$-unsaturated lactone, however, efforts to convert 89 to lactonamycinone 12 were ineffective.

**Scheme 22. Completing the total synthesis.**

For the completion of the total synthesis, a new variation of the quinone was required for the Tamura-Diels-Alder reaction. Treatment of benzaldehyde 72 with the Grignard reagent derived from dimethyl dioxolane, followed by CAN oxidation, afforded quinone 90, which was exposed to the phthalic anhydride 69 under basic conditions, giving the tetracyclic intermediate 91 as a single regioisomer. Oxidation and dihydroxylation produced diol 92,
which under acidic conditions underwent deprotection of the octyloxymethyl ether, as well as cyclisation and dioxolane elimination to give furanone 93. Cleavage of the benzyl ether gave primary alcohol 94, which when heated with methanol in the presence of acid gave the key acetal 95. Quantitative hydrolysis gave the lactol of 95, which underwent TEMPO/BAIB oxidation finishing the total synthesis of lactonamycinone 12.

1.5.2 Deville and Behar: Synthesis of the ABCD-ring system.

As work by Danishefsky et al.,[22,23] had produced results of forming the model DEF ring system, Deville and Behar produced studies towards forming the model naphtha[e]isoindole portion of lactonamycin. Their proposed synthesis was to make use of conjugate cyanide addition to the ester 96 followed by spontaneous Dieckmann condensation to afford phenol 97. Reduction of the cyanide and concomitant lactamisation would afford the ABC model ring system 98.[36]

Scheme 23. Proposed application of the cyanide addition-Dieckmann condensation.

To test the initial hypothesis, Deville and Behar applied the proposed methodology to the simplest system, starting from the readily available o-iodobenzoic acid 99. Acid chloride formation of 99, similar to that by Lipton et al.,[37] was followed by treatment with diazomethane to give the diazoketone 100.[38] This underwent the Wolff rearrangement with silver benzoate followed by treatment with methanol to give the methyl ester 101.[39] Sonogashira coupling of the iodide 101 with the alkynyl ortho ester (Scheme 24) produced
the Dieckmann condensation precursor 96, after methanolysis of the ortho ester in the presence of acid.

**Scheme 24. Synthesis of the cyclisation substrate.**

![Scheme 24](image)

Application of the conjugate cyanide addition-Dieckmann condensation to the cyclisation precursor 96 was found to be most effective when using sodium cyanide in DMSO, although use of other countercations of cyanide produced minimally lower yields. The reaction afforded phenol 97, as previously proposed, which was protected as the silyl ether before being subjected to chemoselective reduction conditions similar to those employed by Beccalli and co-workers.[40] Reduction of the cyanide moiety produced the free amine, which underwent cyclisation with the o-methylester, to form the lactam 102.

**Scheme 25. Application of the cyclisation.**

![Scheme 25](image)

By proving the efficacy of the proposed methodology, Deville and Behar took to applying the chemistry to a more complex system that was in closer resemblance to the core structure of lactonamycin. To proceed with the new synthesis, the known phenol 103 was chosen as a starting material.[41]
Aromatic bromination ortho to the phenol moiety proceeded with pyridinium tribromide in almost quantitative yield. The phenol and alcohol groups were then methylated followed by exchange of the bromide for iodide using lithium–halogen exchange. Hydrogen bromide was employed to displace the methyl protected alcohol, which was then itself displaced using potassium cyanide, furnishing the iodide 104. Methanol in the presence of triflic acid, converted the benzylic cyanide group to the methyl ester, which was then subjected to the same Sonogashira conditions as stated previously, to give the complex cyclisation precursor 105.

**Scheme 27. Application of the cyclisation to the complex substrate.**

Sodium cyanide in DMSO was again employed to perform the conjugate cyanide addition-Dieckmann condensation on substrate 105, however, the resulting phenol was reported to be unstable and so one pot cyclisation-silyl protection was needed to produce the TIPS protected phenol 106. Conditions for the selective reduction of the cyanide moiety were also mimicked.
from the model study, but this too was found to be problematic and so the reaction required heating before the desired ABCD-ring system 107 was produced.

1.5.3 Synthetic studies by Kelly et al.

Like Deville and Behar, the first publication by Kelly et al., set out to synthesise the ABCD-ring system, differing by attempting an eight step (six pot) synthesis with the quinone functionality installed in the desired product. This would be achieved by functional group manipulation and lactam formation of phenol 108 to produce the silyl diene 109, which could undergo cycloaddition with 2,3-dimethylbenzoquinone to furnish the ABCD-ring system of lactonamycin (110).

**Scheme 28. Proposed synthesis of ABCD-ring system.**

Phenol 108 was prepared by a modification of a procedure by Tyman et al. in 49% yield. This was then selectively reduced using L-Selectride giving the lactone 111 with greater than 95% regioselectivity. Attempts at brominating the aromatic methyl group, consistently resulted in bromination of the ring itself, ortho to the phenol group to give 112 exclusively. Protection of the phenol in 111 as the acetate, was hoped to solve the bromination issue, however exposure of this substrate to NBS, UV and AIBN resulted in bromination of the lactone methylene in 99% yield. As it appeared that ring bromination was unavoidable, phenol 112 was further exposed to NBS and AIBN in an effort to produce the desired compound 115.
The desired bromide 115 was isolated in 32% (BRSM) along with a mixture of 113 (22%) and 114 (14%). It was found that compound 114 could be recycled to the phenol 111 in 90% yield upon treatment with Zn/10% NaOH(aq). Lactamisation was achieved by reaction of bromide 115 with methyl amine in methanol to afford bromide 116, which underwent debromination with Zn/10% NaOH(aq) furnishing phenol 117. TBS protection of the phenol gave the silyl ether 118 in 51% yield over 3 steps, which was isolated as a possible precursor to the desired diene 109.
Initial attempts at forming this diene were carried out using an array of strong bases (LDA, KHMDS etc.) in conjunction with TMSCl, however it was found that these conditions favoured C-silylation of the lactone methylene. Use of KHMDS with TBSCI seemed to avoid this issue and provided the highly reactive diene 109, which underwent cycloaddition with 2,3-dimethylbenzoquinone at –60°C in ten minutes, with complete regioselectivity at the furanyl diene over the over the isoindole, to produce 120 exclusively. Treatment of the Diels-Alder product with TFA resulted in global deprotection and concomitant aromatisation; giving the ABCD-ring system of lactonamycin 110 in 74% yield over 3 steps.

This completed a remarkably short synthesis of the model system for lactonamycin, with scope to extend these studies to a total synthesis of the natural product.

A second publication by Kelly et al. detailed an asymmetric synthesis of the EF-ring system, starting from an enantiomerically pure substrate, dimethyl D-tartrate (121).\textsuperscript{[43]} Ester-enolate chemistry was to be employed in the synthesis of the protected diol 122, which would require minimal manipulation to complete the EF-ring system 123.

**Scheme 30. Proposed synthesis of EF-ring system.**

Dimethyl D-tartrate 121 was synthesised from D-tartaric acid, which was protected as the acetonide 124 using a method established by Kim et al.\textsuperscript{[45]} The first ester-enolate was generated using LDA and was exposed to benzyl chloromethyl ether to afford 125 as a single diastereomer. The second ester-enolate was generated, again using LDA, but this time the resulting anion was treated with methyl chloroformate to give the tri-ester 126.
Removal of the benzyl group proceeded in an atmosphere of hydrogen in the presence of palladium on charcoal, giving the free alcohol, which spontaneously underwent lactonisation with one of the ester groups to give the bicycle 127. X-ray analysis showed that the desired cis-fused product was the only compound formed as none of the trans-fused compound was isolated. The ester-enolate of tertiary butyl acetate was added to lactone 127 to give alcohol 128, which was thought to be only three steps from the desired EF-ring system 123. Unfortunately, Kelly’s efforts to cleave the acetonide under a variety of conditions proved unsuccessful, and so a new route to the synthesis of the model system was required.

The second attempt at synthesis began by the screening of a range of acetals to protect the diol of dimethyl D-tartrate, however, many of the resulting substrates underwent decomposition upon the alkylation with BOMCl. Cyclopentylidene was found to be a suitable protecting moiety, and underwent the alkylation step to give the benzyl ether 131. The same chemistry was employed from the first synthetic route (Scheme 31) to give triester 132 and subsequently the lactone 133.
Treatment of lactone 133 with the lithium enolate of tertiary butyl ester, did not give the aldol adduct 134 as predicted, but instead reacted with one of the methyl ester carbonyls to give either 135 or 136. The only difference between 133 and the previous 127 is how the diol is protected, and so benzyl ether 132 was subjected to acidic conditions to remove the cyclopentylidene (Scheme 33), so that a number of acetals could be screened for use.

Upon examination of the deprotection of 132, it was found that not only was the cyclopentylidene removed, but the benzyl ether was also cleaved, producing a free hydroxyl moiety. This underwent lactonisation with the methyl ester to give predominantly the desired cis-diol 137 as well as a small amount of the trans-diol 138 and benzyl ether 139.
**Scheme 34.** Synthesis of the EF-ring system.

Diol 137 was protected as the benzylidene acetal, which produced a separable mixture of diastereomers 138 and 139, which were subjected to the same reactive conditions in parallel. Exposure of both isomers to the lithium enolate of tert-butyl acetate gave the desired aldol products 140 and 141. Removal of the benzylidene proved successful with hydrogen and palladium on charcoal to give the desired cis-diol 129. Treatment of this with camphorsulfonic acid achieved lactonisation and installation of the tertiary methoxy group, giving the desired cis-fused ring system 123. X-ray crystallography was used to confirm the stereochemistry of 123 and thus concludes the enantiospecific synthesis of the EF-ring system model.
1.5.4 Studies towards total synthesis by Barrett et al.

The Barrett group released a number of publications between 2005 and 2006, detailing studies towards the synthesis of the ABCD-ring system,[48,49] studies towards the synthesis of the CDEF-ring system[47] and research towards installation of the sugar moiety of lactonamycin.[46] Glycosidation was the first avenue of research that was documented by Barrett et al., by introducing a variety of sugar units to nitroalkenes and nitrosoalkenes by conjugate addition. Success of this methodology would provide access to a total synthesis of lactonamycin with the option to install a range of carbohydrate functionalities in place of the sugar unit. This would be of interest as it provides a number of new compounds, which could be screened for biological activity, but it would also be the first documented attempt at studying a method for addition of the sugar moiety.[46]

Scheme 35. Proposed conjugate addition and how it translates to lactonamycin.

It was thought that a protected rhodinose derivative 143 could be added to 1-nitrocyclohexene 142, as the alkoxide, to give the desired product of Michael addition 144. Success of this methodology could see application to lactonamycin via the advanced intermediate 145, which has ABC-ring functionality in place. Precedent for this work was outlined previously by Barrett in a review of nitroalkenes and their use as strong electrophiles for conjugate addition.[50]
Synthesis of the protected L-rhodinose derivative began from methyl (S)-lactate 146 and proceeded via a modification of the method documented by Schlessinger and Graves, however Barrett et al. avoided the use of tin and chromium reagents.[51]

Scheme 36. Synthesis of the protected L-rhodinose derivative.

Methyl (S)-lactate 146 was protected as the benzyl ether to give the ester 147, which was subjected to DIBAL reduction to afford the aldehyde 148. This was treated with allylmagnesium bromide in the presence of MgBr₂Et₂O to provide chelation control over the addition, which produced the alcohol 149 with greater than 95% diastereoselectivity. The hydroxyl was subjected to TBS protection to give the alkene 150, which was converted to the terminal alcohol using hydroboration followed by oxidation to the aldehyde 151 using the Dess-Martin periodinane.[52] The benzyl ether was cleaved under an atmosphere of hydrogen in the presence of palladium on charcoal and the resulting alkoxide spontaneously cyclised onto the aldehyde to give anomeric alcohol 152.

With the protected L-rhodinose derivative 152 in hand, conditions were needed to convert the sugar to an alkoxide for addition to a nitroalkene. 1-Nitrocyclohexene 142 was chosen as the electrophile and the alkoxide of 152 was generated using nBuLi; combination of the two gave
conjugate addition product 153 as a mixture of anomers and diastereomers. For the total synthesis of lactonamycin, the α-anomer is required, with control of stereoselectivity, and NOE NMR spectroscopy unveiled that the α-anomer was the major product in a 4:1 ratio. It was also found that the nitrocyclohexyl diastereomers were formed mostly as the cis-isomer, however complete stereospecificity was not achieved.

Scheme 37. Addition of protected sugars to nitro/nitrosoalkenes.

Scheme 37. Addition of protected sugars to nitro/nitrosoalkenes.

The reaction of alkoxides with nitrosoalkenes was also investigated by addition of the protected mannose 155 to the α-chloro-ketoxime 154, which was prepared from commercially available α-chlorocyclohexanone and O-(TBS)hydroxylamine. By treating silyl ether 154 with tert-butyl ammonium fluoride, desilylation and chloride elimination generated the nitrosoalkene in situ, which underwent conjugate addition with the lithiated alcohol of 155 to give rise to 156 as a mixture of undefined isomers.

For total synthesis of lactonamycin, the resulting nitro (153) and ketoxime (156) groups would need to be oxidised to their corresponding ketones. For the nitrocyclohexyl 153, this was achieved using an oxidative Nef reaction, adapted by Steliou and Poupart by using potassium permanganate alongside the reagents detailed in scheme 38, to give the ketone 157.
as a mixture of isomers.\textsuperscript{[53]} Oxidation of the ketoxime 156 was achieved in high yield by exposure to manganese dioxide in hexane, giving ketone 158, again as a mixture of isomers.

\textbf{Scheme 38. Oxidation of the nitro and oxime moieties.}

This method of introducing the carbohydrate residue to lactonamycin provides access to a large variety of analogues, which may exhibit differing biological activity as seen with lactonamycin Z.

The next piece of research published by Barrett \textit{et al.}, was a study aimed at the stereoselective production of the highly oxygen rich CDEF-ring structure \textit{via} either selective dihydroxylation or epoxidation.\textsuperscript{[47]} It was thought that ester 160 could be synthesised from the known benzoquinone 159, and stereoselective manipulation and functionalisation of 160 could give rise to the lactonamycinone model structure 161.

\textbf{Scheme 39. Proposed synthesis of CDEF-ring structure.}
Synthesis of the required quinone 160 proceeded from the quinone monoketal 159, which was synthesised via a modification of the method by Corey et al.\[54\] Addition of nitromethane to 159 proceeded in the presence of catalytic triethylamine to give the Michael-addition product 162. Similar to the previous publication by Barrett, the nitro moiety of 162 was oxidised to the corresponding aldehyde 163 by modification of the Nef reaction, using potassium hydroxide and potassium permanganate in methanol.\[55\] The aldehyde 162 was exposed to sodium borohydride in methanol affording the alcohol 164, which was added to a methyl, ethyl and t-butyl alkynyl esters (see scheme 40) to afford the corresponding ethers 165 all as the (E)-isomer.

Scheme 40. Preparation of the key quinone intermediate.
Closing of the E ring was at first attempted using LDA, giving fairly low yield across all three substrates (28 – 45%). Use of a guanidine derived base with the butyl variant of 165 provided much higher conversion to the mixture of diastereoisomers 166 and 167 (4:6). The desired quinone 160 was achieved by exposing the mixture of diastereoisomers 166 and 167 to aqueous acetic acid in air, yielding higher as the methyl variant of the ester, however, the butyl ester wasn’t particularly lower yielding and its synthesis proved more consistent.

**Scheme 41. Dihydroxylation vs. Epoxidation.**

The butyl ester 168 was exposed to dihydroxylation conditions demonstrated previously by Danishefsky et al. Treatment of the ester with osmium tetroxide and catalytic N-methylmorpholine N-oxide, afforded diols 169 and 170 (7:3), which when exposed to TFA in DCM, underwent cyclisation to give lactone 171. This completes the CDEF-ring structure minus the tertiary methoxy group, but lactonisation was only achieved in low yield, with the
desired diastereoisomer as the minor product and so methods of epoxidation of 168 were also explored. Hydrogen peroxide was used in the presence of sodium carbonate to give the mixture of diastereoisomers 172 and 173 (6.3:3.7), which is only a slight improvement on the previous diastereoselectivity. Exposure of these epoxides to identical reactive conditions, lead to the formation of the acid 174 and the lactonised product 175, an epimer of the previously obtained CDEF model 171. Attempts at epimerising the alcohol 175 under acidic or basic conditions were unsuccessful and so 175 and its silyl ether 176 were used as model substrates for the installation of the tertiary methoxy group.

A wide number of oxidation methods were attempted by Barrett, however, all attempts at oxidation resulted in decomposition or recovery of starting material. This was apart from one case using Fenton’s reagent,[57] which instead gave the ring opened diol 179.

**Figure 4. Oxime and silyl oxime for X-ray crystallographic analysis.**

![Chemical structures](image)

It was possible to convert the alcohol 175 into the oxime 177 and the silylated oxime 178, both of which were used in determination of the structure and stereochemistry of the intermediates so far. By obtaining these compounds, it also demonstrates the possibility of applying the previously documented glycosylation of the model system via generation of a nitrosoalkene from the silyl oxime, for conjugate addition of the desired sugar moiety.

Due to the difficulties faced in both oxidations of the quinone and installation of the tertiary methoxy group, a new method towards the model system was required. The new synthesis utilised the alcohol 164 from the previous route, in conjugate addition to the di-ester 180 to
furnish the Michael addition product 181. Use of the Barton base\([56]\) (as used in the previous route) again initiated ring closing via Michael addition to give the mixture of esters 182 and 183 (1:5.9). When exposed to potassium hydroxide, the major product 183 was saponified only at the tertiary ester, which when followed by addition of benzyl bromide, gave the single benzyl ester 184. It was thought that this benzyl ester could act as a masked methoxy group throughout the rest of the synthesis with late stage installation of the methyl ether.

**Scheme 42. Revised synthesis of the model CDEF-ring system.**

Treatment of 184 with aqueous acetic acid in air gave naphthoquinone 185 that produced a 1:1 mixture of epoxides when exposed to basic hydrogen peroxide, which underwent ring closing when exposed to TFA to afford alcohol 186. Implementing the dihydroxylation of
185 was unsuccessful when using osmium tetraoxide and so catalytic ruthenium(III) chloride in the presence of sodium periodate was used to afford diol 187. This was then subjected to acidic conditions where lactonisation occurred at the butyl ester to form the model CDEF-ring system 188. It was at this point that Barrett believed the benzyl ester of 188 could be manipulated by a variation of the Hunsdiecker reaction to convert the ester to a bromide, which could undergo substitution with methoxide to afford the desired functionality. Barrett did not detail his research towards this and so synthesis of the CDEF-ring structure ended with tetracycle 188, leading onto studies towards the synthesis of the naphth[e]isoindole portion of lactonamycin.

The first of two publications, detailing studies towards the synthesis of a model ABCD-ring structure of lactonamycin, was focused on producing the tetracyclic system, using a Lewis-acid mediated ring closing via Friedel-Crafts acylation. It was predicted that tetracycle 192 could be arranged by this intramolecular reaction, from the acid 191, which would be accessed by Negishi coupling of triflate 189 and bromide 190. Oxidation of the Friedel-Crafts product 192 would afford the model ring system 193.

Scheme 43. Proposed synthesis of ABCD-ring structure.
Introduction

Synthesis of the lactam 189 began from the readily available acid 194 with global methylation, followed by mono-demethylation to give the phenol 195. Vilsmeier-Haack formylation afforded the aldehyde 196, which was converted to the ester 197 in two steps using sodium chlorite to oxidise to the acid and dimethyl sulfate to form the ester. Phenol 197 was converted to the triflate using triflic anhydride and exposure of this to zinc cyanide under palladium-catalysed conditions afforded the nitrile 198. A number of conditions involving sodium borohydride were attempted in the formation of lactam 199, which were successful, but were low yielding and often only worked on small scale. Hydrogenation in the presence of platinum dioxide under acidic conditions was found to be effective at closing the lactam ring and gave 199 in good yield.\textsuperscript{[60,61]}

\textbf{Scheme 44. Synthesis of the required isoindolinone 189.}

```
\begin{tikzpicture}
    % Diagram code here
\end{tikzpicture}
```

\textit{a) Me}_2\text{SO}_4, \text{K}_2\text{CO}_3, \text{acetone}, (84\%); \textit{b) BCl}_3, \text{DCM}, \text{-78}^\circ\text{C}, (91\%); \textit{c) POCI}_3, \text{DMF}, 0 \text{ to } 25^\circ\text{C}, (75\%); \textit{d) NaClO}_2, \text{NH}_2\text{SO}_3\text{H}, \text{2-methylbutene}, \text{THF}, \text{H}_2\text{O/DMSO}; \textit{e) DMF, KHCO}_3, \text{Me}_2\text{SO}_4, (94\% \text{ over 2 steps}); \textit{f) Tf}_2\text{O, pyridine, DCM, (95\%); g) Zn(CN)}_2\text{, Pd}_2\text{(dba)}_3, \text{dpff, DCM, 60}^\circ\text{C, (95\%); h) PtO}_2, \text{THF, AcOH, H}_2, 70 \text{ psi, (94\%); i) NaH, Mel, DMF, 0}^\circ\text{C, (91\%); j) BCl}_3, \text{DCM, -78}^\circ\text{C, (82\%); k) PhNITf}_2, \text{NEt}_3, \text{DCM, reflux, (92\%).}
From this point the isoindolinone 189 was arrived at in three steps, firstly by methylating the lactam 199 using iodomethane in the presence of sodium hydride to give ester 200. This was then exposed to mono-demethylation with boron trichloride, directed to the desired methoxy group via the vicinal ester moiety, to give the phenol that was converted to the triflate 189 using phenyl triflimide.

With a high yielding synthesis of the isoindolinone 189 in place, it was possible to investigate conditions suitable for the Negishi coupling of 189 to a similar substrate to bromide 190. For this purpose, the organozinc substrate 201 was chosen and was synthesised by a modification of the method by Rieke et al.\textsuperscript{[62]}

**Scheme 45. Testing the Negishi coupling and Friedel-Crafts acylation.**

\begin{align*}
&\text{MeO} & \text{O} & \text{N} & \text{O} & \text{O} \\
&\text{TIO} & \text{O} & \text{O} & \text{Me} & \text{Me} \\
&\text{189} & \text{201} & \text{a} & \text{b} & \text{c} \\
&\text{MeO} & \text{O} & \text{N} & \text{O} & \text{O} & \text{Me} \\
&\text{MeO} & \text{O} & \text{N} & \text{O} & \text{O} & \text{Me} \\
&\text{202} & \text{203} & \text{204} & \text{205} & \text{206} \\
&\text{O} & \text{O} & \text{Me} & \text{Me} & \text{Me} \\
&\text{207} & \text{208} & \text{d} & \text{e} \\
&\text{O} & \text{O} & \text{Ac} & \text{N} & \text{O} & \text{Me} & \text{Me} \\
\end{align*}

\textbf{a)} Pd(PPh\textsubscript{3})\textsubscript{4}, THF, (94%); \textbf{b)} LiOH, THF, MeOH, H\textsubscript{2}O, (2:1:1), (37 – 64%); \textbf{c)} i) PPA, 110°C, 5h; ii) K\textsubscript{2}CO\textsubscript{3}, Me\textsubscript{2}SO\textsubscript{4}, acetone, 50°C, 3h, (<30% from 203); \textbf{d)} i) Me\textsubscript{2}C=Cl(\textsubscript{2})\textsubscript{2}NMe\textsubscript{2}, DCM, ZnCl\textsubscript{2}; ii) Ac\textsubscript{2}O, pyridine, DMAP, (80% from 203); \textbf{e)} CAN, MeCN/H\textsubscript{2}O, (65%).
The coupled adduct 202 was arrived at, by exposure of triflate 189 and organozinc 201 to classic Negishi conditions.[63] Success of this reaction meant that exploration of the intramolecular Friedel-Crafts reaction could also be explored. This began by the hydrolysis of methyl ester 202 with lithium hydroxide to give the acid 203. It was not possible to arrive at the ring closed product 204 using reagents such as oxalyl chloride or triflic anhydride, however, catalytic polyphosphoric acid provided phenol 204 as a single product. The free phenol was found to be unstable and was methylated to give 205, which unfortunately did not produce the desired quinone 206 under oxidative conditions. Gohsez’s reagent was found to also convert acid 203 to the phenol 204, which when protected as the acetate 207, underwent clean oxidation to the quinone 208 in the presence of ceric ammonium nitrate.

Scheme 46. Preparation of key bromides 211 and 213.

With conditions in place for Negishi coupling and Friedel-Crafts acylation, work proceeded towards the synthesis of a bromide similar to 190, with –OR ether functionality in place for late stage manipulation in the total synthesis of lactonamycin. Production of the desired bromide started with triol 209, which was prepared by a known method from 4-
methoxyphenol.[64] The phenol of 209 was then methylated using dimethyl sulfate followed by alcohol protection with $p$-methoxybenzyl bromide giving 210. This was then exposed to Appel reaction conditions to give the desired bromide 211. A second bromide was prepared from triol 209, firstly by preparation of a ketal using dimethoxypropane, affording a single free alcohol that was methylated using iodomethane and sodium hydride. The ketal was then removed under acidic conditions to give phenol 212. This was methylated, again using dimethyl sulfate and the free alcohol was converted to bromide 213 by use of NBS and triphenylphosphine. Preparation of bromides 211 and 213 provided advanced intermediates for further testing of the Negishi coupling and Friedel-Crafts reaction to give the ABCD-ring structure, with functionality in place to construct the EF-ring system (vide supra).

Scheme 47. Synthesis of the model ABCD-ring structure.
Completion of the ABCD-ring structure synthesis began by converting the bromide 214 to the organozinc substrate, using zinc dust in the presence of 1,2-dibromoethane, which was then coupled to the triflate 189 using the Negishi conditions as described previously. The coupling worked well for both, the methyl and the \( p \)-methoxybenzyl protected variants of 214 to give Negishi adduct 215. Conversion of methyl ester 215 to the hypothesised acid 191 proved quantitative for both ether variants, after treatment with lithium hydroxide.

With acid 191 in hand, the remainder of the synthesis proceeded with little deviation from conditions used in the previous model study. Intramolecular Friedel-Crafts acylation occurred in the presence of Gohsez’s reagent and zinc chloride to give phenol 217 in good yield for both methyl and \( p \)-methoxybenzyl substituents. Subsequent acetylation and CAN oxidation provided the final model ABCD-ring system 218, with two different –OR moieties in relatively high yield.

The last study undertaken by Barrett and co-workers, was again towards the synthesis of the ABCD-ring structure, using an isoindolinone 219 similar to that used as the Negishi precursor previously (189).\(^{[49]}\) It was thought that the triflate 219 could undergo a benzyne cycloaddition reaction with the diene 220 to give the phenol 221. This could then be converted to the model ABCD-ring system 223 via a double Friedel-Crafts acylation with succinic anhydride 222. This new route to the synthesis of the ABCD portion of lactonamycin utilises the successful Friedel-Crafts chemistry from previous work, but would also remove the need for palladium catalysis.

Scheme 48. Barrett’s second proposed synthesis of ABCD-ring structure.
Synthesis of the desired triflate 235 began from succinic anhydride 222, which was converted into the diene 224,\(^{[65]}\) which underwent a Diels-Alder cyclisation with \(N\)-methylmaleimide to give the phenol 225.\(^{[66]}\) In the presence of zinc amalgam, the phenol 225 underwent a Clemmensen reduction\(^{[67]}\) to furnish isoindolinone 226 in low yield.\(^{[68]}\) Mono-TBS protection of the phenol 226 also proved to be problematic and afforded the single and double protected adducts of 227 in low yield, with some recovery of the starting material 227. Bromination of the mono-protected 227 (\(R = H\)) was hitherto unsuccessful and so a step-wise reduction of the imide 225 was pursued. Phenol protection was achieved in high yield using benzyl bromide in the presence of caesium carbonate to give 228, which was quantitatively reduced to the alcohol 229, using sodium borohydride. Isoindolinone 230 was arrived at via reduction with triethylsilane in the presence of TFA.

**Scheme 49. Synthesis of the triflate 234.**
Selective debenzylation was achieved using a method described by Baldwin et al.\[69\] and the resulting phenol was methylated using methyl iodide and potassium carbonate to give 231. Hydrogenolysis was then used to afford phenol 232 quantitatively, which could be brominated with sodium acetate and bromine in acetic acid to give 233 in moderate yield. This was then converted to the desired triflate 234, however, implementing the previously mentioned benzyne cycloaddition was not achieved, leading the Barrett group to investigate a different route altogether.

The new strategy was built around possible Michael addition of the lithiated adduct of bromide 238 to lactam 242, or palladium coupling of boronic acid 239 with lactone 244, which could provide a synthetic intermediate for the completion of ABCD-ring synthesis.

**Scheme 50. Synthesis of boronic acid 239.**

Bromide 235 underwent benzyne cycloaddition with furan, similar to the method described by Cragg et al.,\[70\] to give ether 236, which produced phenol 237 after treatment with acid. This was efficiently converted to bromide 238 by ortho-bromination and subsequent phenol methylation. The bromide 238 was converted to boronic acid 239 by metal-halogen exchange, reaction with triisopropyl borate and hydrolysis with aqueous HCl.

**Scheme 51. Synthesis of Michael acceptor 243 and bromide 245.**

a) LDA; PhSeBr, (68%); b) H$_2$O$_2$, pyridine, (69%); c) (COBr)$_2$, DMF, (81%).
The unsaturated lactam 242 was chosen as the model for Michael addition and furanone 244 was synthesised for parallel studies on palladium coupling. Lactam 240 was subjected to enolate formation with LDA and addition to phenylselenyl bromide to give selenide 241, which underwent elimination of selenoxide in the presence of hydrogen peroxide to give the desired lactam 242. Furanone 244 was accessed in a single step by reaction of tetronic acid 243 with oxalyl bromide in DMF.

Scheme 52. First attempt at implementing ABCD-ring synthesis.

It was not possible to implement the Michael addition of bromide 238 to the lactam 242, but Suzuki coupling of the boronic acid 239 and the furanone 244 did provide the desired butenolide 245 in good yield. This was converted to the unsaturated lactam 246 by treatment of the furanone 245 with methylamine and HCl. The unsaturated lactam was reduced using magnesium in methanol to give the lactam 247, which was treated with LDA to form the lithium enolate that was exposed to methyl dimethoxyacetate to furnish the keto-lactam 248. This was then treated again with LDA to form the enolate, which underwent $O$-acyetylation to provide acetate 249. Exposure of the lactam 248 and the acetate 249 to acidic and lewis
acidic conditions did not cause either substrate to undergo the desired cyclisation to produce the model ABCD-ring precursor.

**Scheme 53. Alternative attempt at implementing ABCD-ring synthesis.**

An alternative attempt at the ABCD-ring synthesis saw the unsaturated lactam undergo enolboration with dibutylboron triflate, which underwent addition to dimethoxyacetaldehyde to give the alcohol 250. As with the previous lactams 248 and 249, a number of acidic and lewis acidic conditions did not cause the unsaturated lactam 250 to undergo the desired cyclisation to produce the model ABCD-ring precursor. This was thought to be due to the electron withdrawing qualities of the lactam carbonyl in 250 and so it was protected using TBS triflate and Hünig's base to give silyl ether 251 that produced the ring closed substrate 252 upon exposure to zinc bromide. The synthesis of isoindolinone 252 was achieved via Suzuki coupling and intramolecular Friedel-Crafts reaction, to give a substrate isomeric of the desired model system 223 and thus completing studies towards the synthesis of lactonamycin by Barrett and co-workers.
1.5.5 Nakata and Saikawa et al.: Synthesis of the BCDEF-ring system.

In 2010, Nakata and Saikawa published their research towards the synthesis of the BCDEF portion of lactonamycin, with stereoselective installation of the EF-ring oxygen functionality. In a similar manner to work published by Danishefsky et al., Nakata and Saikawa sought to begin their studies utilising the Tamura-Diels-Alder reaction between chloroquinone 252 and anhydride 253.\[24,27\] The resulting phenol 254 could then undergo dihydroxylation at the quinone double bond to give the diol 255. This would then be subjected to palladium catalysed cyclisation-methoxycarbonylation to give the unsaturated ester 256, which itself was thought would be suitable for stereoselective Michael addition with methanol, followed by lactonisation to give the BCDEF-ring structure 257.\[71\]

Scheme 54. Proposed synthesis of the BCDEF-ring system.

The synthesis of the required chloroquinone 252 began from the multihalogenated benzene derivative 258, which was synthesised previously, using a method by Nakata et al.\[72\] The iodide 258 underwent lithium-halogen exchange with \(^{8}\)BuLi, and when exposed to methyl formate, aldehyde 259 was formed. Reduction of aldehyde 259 with sodium borohydride, and subsequent MOM protection of the resulting alkoxide, furnished the methyl ether 260.
Treatment of this with $^n$BuLi, again resulted in lithium-halogen exchange, this time at the bromide substituent, and addition of methyl formate afforded aldehyde 261. When treated with the Ohira-Bestmann[73,74] reagent 261a, aldehyde 261 underwent homologation to give the terminal alkyne 262, which was deprotonated using butyllithium and then exposed to a number of silyl protecting groups to give the silylated alkyne 263. The TMS variant of alkyne 263 was also prepared via a Stille coupling reaction between the bromide 260 and the commercially available TMS alkyne 265.[75]

Scheme 55. Synthesis of the chlorobenzene 263.

With the synthesis of the quinone precursor 263 in place, it was possible to examine the reactive conditions needed to best fit the Tamura-Diels-Alder reaction. The chloroquinone 264 was prepared from the chloride 263 by oxidation with CAN in aqueous acetonitrile, and all silyl variants proceeded to react in high yield apart from the TIPS adduct. Anhydride 253 was subject to Tamura conditions and underwent cycloaddition with the chloroquinone 264 to give the desired phenol 265 with full regioselectivity.[27]
Introduction

Scheme 56. Implementing the Tamura-Diels-Alder reaction.

\[
\begin{align*}
\text{263} & \xrightarrow{\text{a}} \text{264} & \text{253} & \xrightarrow{\text{b}} \text{265} \\
\end{align*}
\]

\text{a)} \text{CAN, H}_2\text{O/MeCN, (R = TMS, 92%; R = TES, 92%, R = TBS, 85%; R = TIPS, 54%);} \text{b)} \text{253, LDA, THF, (R = TMS, 51%; R = TES, 52%, R = TBS, 58%; R = TIPS, 22%).}

As mentioned previously, Danishefsky et al., achieved regioselectivity of the Tamura-Diels-Alder reaction by way of a directing group, presumably in the example given by Nakata et al., this would be the chloride of the quinone 264.

Scheme 57. Dihydroxylation and completion of the BCDEF-ring system.

\[
\begin{align*}
\text{265} & \xrightarrow{\text{a}} \text{266} & \text{267} \\
\text{257} & \xrightarrow{\text{e}} \text{256} & \text{255} \\
\end{align*}
\]

\text{a)} RuCl}_3 (7 \text{ mol%), NaI}_2\text{O, MeCN/EIOAc/H}_2\text{O (3:3:1), 0^\circ\text{C}, (R = TMS, 18%; R = TES, 16%, R = TBS, 33%; R = TIPS, 35%); b)} \text{TBAF, THF, 0^\circ\text{C} to rt, (from TMS, 93%; from TES, 94%, from TBS, 98%; from TIPS, 98%); c)} \text{TFA, DCM, (98%); d)} \text{PdCl}_2 \text{(cat.), 1,4-benzoquinone, CO, MeOH, (62%); e)} i) \text{CSA, MeOH, 80^\circ\text{C}, 5 d; ii) evaporation benzene, 75^\circ\text{C}, 1.5h, (93%).}

There was difficulty in implementing the dyhydroxylation of the quinone 265 with osmium tetraoxide, with only trace amounts of the desired product achieved. Instead, sodium periodate was used with catalytic ruthenium chloride, and even with 3 equivalents of the
oxidant, the best yields obtainable were between 18 – 35%.\textsuperscript{[76,77]} Silyl deprotection of 266 proceeded in almost quantitative yields for all variants of the silyl moiety, using TBAF, to furnish alkyne 267, which was subjected to TFA in DCM for the removal of the MOM ether to give alcohol 255. By exposing the alkyne 255 to conditions employed by Kato et al.,\textsuperscript{[78]} (catalytic palladium chloride with 1 atm of carbon monoxide and 1,4-benzoquinone), ring closure and methoxycarbonylation was achieved, resulting in formation of the unsaturated methyl ester 256 as predicted. Stereoselective addition of methanol and lactonisation would complete the BCDEF model ring system and treatment of 256 with CSA in methanol at 80°C afforded the desired BCDEF ring system in 28% yield. Not satisfied with the low yielding reaction, Nakata et al., hypothesised that removal of methanol would drive the reaction to completion and by repeating the reaction, and allowing the solvent to evaporate followed by heating in benzene, completed the target compound 257 in 93% yield.

1.5.6 Studies towards total synthesis by Parrain and Commeiras et al.

In 2010, Commeiras and Parrain et al., demonstrated the ability to apply a chemo- and diastereoselective Diels-Alder cycloaddition of trans-1,2-disilyloxybenzocyclobutene 268 with an unsaturated furanone derivative, to form spirolactones similar to 270.\textsuperscript{[79]}

\textit{Scheme 58. Proposed Diels-Alder cycloaddition and CDEF-ring formation.}
In 2012, the same methodology was applied to studies towards the synthesis of the CDEF portion of lactonamycin 271 by the Diels-Alder cycloaddition of the benzocyclobutene 268 with the furanone derivative 269. This would produce the spirolactone 270, which would be manipulated to form the CDEF-ring structure 271.\[80\]

**Scheme 59. Diels-Alder cycloaddition.**

The dienophile synthesis began from methyl tetronate 272, which was deprotonated with \(^n\)BuLi and exposed to the aldehyde 273 to give the alcohol 274. Mesylation of the resulting alcohol followed by elimination gave the separable mixture of \(E\) and \(Z\) isomers 275 and 269 (67:33). The benzocyclobutene 268 that was required to generate the diene for the Diels-
Alder cycloaddition, was synthesised via modification of methods by Liebeskind and South,\cite{81} and Danishefsky et al.\cite{82} By using the conditions used in the previous publication by Commeiras and Parrain et al., (benzene, 50°C, 4h) with the Z-alkene 275 and benzocyclobutene 268, only yielded low quantities of the desired spirolactone 266/267. By extending the reaction time to 3 days, quantitative conversion was achieved, giving the endo and exo products 276 and 277 in equal quantities. For the synthesis of the model CDEF-ring system, the cycloaddition was applied to the E-alkene 269, using the same conditions as previous, giving purely the endo product 270, with the cis functionality required for the formation of the E ring of lactonamycin.

**Scheme 60. Finalising the synthesis of the model CDEF-ring structure.**

With the spirolactone 270 in place, completion of the CDEF-ring system was trivial; starting with removal of the p-methoxybenzyl protecting group with DDQ to afford the alcohol 278. This then underwent conjugate addition to the unsaturated lactone by treatment with triethylamine, to furnish the EF-ring structure 279. TBAF was employed to remove TBS protecting groups to give the diol 280, which was oxidised to the desired CDEF-ring system.
with DMP, quantitatively. This completed the synthesis of the model system in high yield and high stereoselectivity, only employing 5 synthetic operations from the $E$-alkene.

1.6 Total synthesis of lactonamycin

1.6.1 The first total synthesis of lactonamycin by Tatsuta et al.

In the 14 years after its discovery, there were numerous studies towards the synthesis of lactonamycin, with successful preparations of the ABCD and CDEF sections and even a total synthesis of the aglycon, lactonamycinone. In 2010, Tatsuta et al. documented the first total synthesis of lactonamycin via a Michael-Dieckmann type cyclisation with stereoselective installation of the glycosyl moiety.\(^{[83]}\)

Scheme 61. Michael-Dieckmann type cyclisation for the total synthesis of lactonamycin.

It was thought that Michael-Dieckmann condensation would take place between the thioester 281 and the quinone 282, which with subsequent glycosylation and deprotection would provide a total synthesis of lactonamycin (10).

The thioester 281 was prepared in 13 steps from the commercially available bromophenol 283, beginning with methylation of the phenol, followed by lithium-halogen exchange with the bromide, which was exposed to methyl chloroformate to furnish the ester 284.\(^{[84]}\)
Scheme 62. Preparation of the thioester 281.

Formylation was achieved similar to Danishefsky’s method, with dichloromethyl methyl ether in the presence of tin chloride to form the aldehyde 285. The aldehyde was oxidised to the carboxylic acid, which was converted to the phthalimidymethyl ester, before undergoing bromination to give the bromide 286. Methylamine was then employed for displacement of the bromide 286, to form the amine and subsequently undergo lactamisation to form the isoindolinone 287. This was then demethylated with boron trichloride and the resulting phenol was protected using benzyl bromide. Displacement of the remaining bromide with ethanethiol produced the thioether 288. Saponification of the ester 288 with lithium hydroxide gave rise to the carboxylic acid that underwent condensation with ethanethiol to afford the thioester 289. Oxidation of the thioether with mCPBA finally gave the desired sulfone 281.

With the desired isoindolinone 281 in hand, stereoselective synthesis of the quinone 282 was required, starting from the commercially available dihydroxybenzoic acid 290.
Scheme 63. Synthesis of the racemic quinone 282.

The dihydroxybenzoic acid 290 selectively methylated using dimethyl sulfate to give the phenol 291 in 94% yield. The ester was then reduced with lithium borohydride and the benzene ring was oxidised with PIFA in the presence of ethylene glycol to give, the monoacetel 292.\textsuperscript{[86]} Dihydroxylation was achieved with osmium tetraoxide and NMO to give the triol 293. The ketone was reduced with sodium borohydride, offering decent stereoselectivity (13:1) in favour of the desired isomer and resulting alcohol was TBS protected to furnish diol 294. Swern oxidation and TES protection of the tertiary alcohol gave rise to the ketone 295, which underwent addition of methyl propiolate in the presence of NaHMDS to give ester
Global deprotection was achieved using TBAF and consequent ring closing of the primary alcohol onto the alkynyl methyl ester produced the triol 298. It was possible to close the F-ring lactone and install the tertiary methoxy group in a single step with acidic methanol to give the diol 299 that was converted to the desired quinone (±) 282 via oxidation of the secondary alcohol.

Scheme 64. Synthesis of the L-rhodinose derivative 303.

Synthesis of the DEF-ring section required glycosylation of the alcohol (±) 282 for completion of the total synthesis of lactonamycin and L-rhodinose derivative 303 was thought to be a suitable adduct for this installation. Preparation of this derivative started with di-O-acetyl-L-rhamnal 300, which underwent a Ferrier rearrangement in the presence of methanol with concomitant de-acetylation to give alcohol 301. This underwent inversion of stereochemistry under Mitsunobu conditions and the resulting formyl ester was cleaved, followed by hydrogenation of the double bond and benzyl protection of the free alcohol to give the benzyl ether 302. Finally, treatment of this with thiophenol under acidic conditions gave thioether 303.

A previous review by Tatsuta and Toshima discusses the use of glycosylation of alcohols using thioether sugar derivatives in the presence of silver triflate, a method that was applied in this synthesis to the alcohol (±) 282 with thio ether 304.
**Scheme 65. Glycosylation of alcohol (±) 282.**

Glycosylation of the alcohol (±) 282 proceeded with benzyl and p-bromobenzoyl derivatives of the thioether 304, to give a separable mixture of isomers 305 and 306 in good yields. X-ray crystallography was employed for confirmation of the structure of the p-bromobenzoyl adduct of glycoside 305, as well as the structure of the hydrolysis product of the benzyl derivative of glycoside 305.

**Scheme 66. Completion of the total synthesis of lactonamycin.**

a) 304 (10 equiv.), 2-cyclohexen-1-one (11 equiv.), AgOTf (2 equiv.), MS-4A, DCM, -40°C to rt, 11h, (R = Bn, 305 (40%), 306 (35%); R = pBrBz, 305 (40%), 306 (39%)).
Completion of the total synthesis of lactonamycin began, similar to previous work by Tatsuta et al., with a Michael-Dieckmann condensation between the quinone 305 and thioester 281 to afford benzyl protected lactonamycin 307. Hydrogenation was employed to remove benzyl protecting groups to furnish lactonamycin 10 and thus completed the first total synthesis of the natural product.

1.6.2 Total synthesis of lactonamycin by Nakata and Saikawa et al.

Nakata and Saikawa et al., previously demonstrated the synthesis of the model BCDEF-ring system via Tamura-Diels-Alder cycloaddition followed by palladium mediated ring formation and methoxycarbonylation. It was thought that this methodology could be used in a total synthesis of lactonamycin with application to the anhydride 308 and the quinone 309 to form the advanced intermediate 310. This would then be subjected to a Bischler-Napieralski type cyclisation for late stage A-ring formation to give the racemic lactonamycinone 311, which could be glycosylated with either an L-rhodinose or digitoxose derivative to give lactonamycin or lactonamycin Z, respectively.

Scheme 67. Tamura-Diels-Alder and Bischler-Napieralski strategy for total synthesis.
The anhydride 308 was prepared from the known phenol 313, which was synthesised by modification of the method by Lubbe and Langer.\(^{[93]}\) The phenol 313 was converted to the triflate and Stille coupling with tetravinyltin afforded the alkene 314 in good yield. Ozonolysis provided the aldehyde 315, which gave the lactol 316 after ester saponification with potassium hydroxide. Reductive amination was achieved using methylamine and sodium borohydride that produced the isopropylcarbamate 317 after exposure to isopropyl chloroformate. The dicarboxylic acid 317 was then treated with acetyl chloride to form the desired anhydride 308.

Application of the Tamura-Diels-Alder was now thought to proceed via the lithium enolate 318, which was formed by treatment of the anhydride 308 with LDA. The chloroquinone 309 was produced in a similar manner to the previously documented quinone 264 and used in the cyclisation with diene 318 to give the phenol 319, regioselectively, as predicted. Dihydroxylation of the quinone 319 was achieved using ruthenium chloride and sodium metaperiodate to give the diol 320.
Silver fluoride was employed to remove the TBDPS protecting group and methoxymethyl ether was converted to the alcohol 321 by treatment with aqueous hydrochloric acid.

Synthesis of the carbamate 321 provided the necessary advanced intermediate for palladium mediated ring formation and methoxycarbonylation to form the EF-ring system and Bischler-Napieralsky for A-ring formation. With conditions for EF-ring formation acquired previously, a number of phosphorus based reagents were screened for the Bischler-Napieralsky reaction, which were described more recently in a publication by Nakata and Saikawa et al.\textsuperscript{[94]}
EF-ring formation was achieved by treatment of the alkyne 321 with palladium chloride in methanol under an atmosphere of carbon monoxide, followed by lactonisation with CSA in methanol to form lactone 310. Almost quantitative alcohol protection was achieved using chloroacetyl chloride, and the resulting protected adduct was exposed to phosphorus pentoxide to effect the Bischler-Napieralski type cyclisation, producing isoindolinone 322. Removal of the chloroacetyl protecting groups was achieved using triethylamine in methanol/DCM, forming the ketal 323, which underwent methyl deprotection with magnesium iodide diethyl etherate to yield racemic lactonamycinone 311.

With the aglycone 311 in hand, the total synthesis of lactonamycin and lactonamycin Z was achievable via glycosylation of the tertiary hydroxyl group with known L-rhodinose derivative 325 and digitoxose derivative 326. Synthesis of both natural products began with phenol protection with TBS triflate to form TBS protected lactonamycinone 324.
Completion of lactonamycin \textbf{10} began with glycosylation, catalysed by ytterbium triflate in the presence of the L-rhodinose derivative \textbf{325}, to give both diastereoisomers of silyl protected lactonamycin in 60\% yield. Separation of isomers and silyl deprotection with TASF finished the second total synthesis of lactonamycin \textbf{10}. Treatment of TBS protected lactonamycinone, again with catalytic ytterbium triflate, but in the presence of the alkenyl sugar derivative \textbf{326}, followed by dihydroxylation and silyl deprotection produced the first total synthesis of lactonamycin Z \textbf{11}.
1.7 The Parsons-Board-Waters cyclisation methodology

Studies towards the total synthesis of lactonamycin began in the Parsons group with the view of implementing a cascade cyclisation of the ene-diyn 328 via radical or palladium catalysed conditions to give the model ABCD-ring structure 329 in a single step.\textsuperscript{[13,14]} Work documented previously by Parsons \textit{et al.} has demonstrated the ability of initiating both Heck-type cyclisation and tin mediated radical cyclisation for the formation of multi-fused ring systems.\textsuperscript{[12]} Similarly, a cascade radical cyclisation sequence was published, for the formation of a model structure of the natural product pseudocopsinine.\textsuperscript{[96]}

\textit{Scheme 72. Planned cascade cyclisation for the formation of ABCD-ring system.}

The precedent for palladium and tin mediated cascade cyclisations had already been demonstrated by Parsons \textit{et al.}; Board began on the synthesis of the ene-diyn 328 from the aldehyde 327.\textsuperscript{[12,97]} Aminal 330 was subjected to lithium halogen exchange with butyllithium followed by subsequent cuprate formation by addition of copper(I) cyanide. The resulting bromide 327 was formed upon addition of 2,3-dibrompropene and work-up with aqueous hydrochloric acid. \textit{N}-Boc-\textit{N}-methylpropargylamine was treated with butyllithium at –90°C and the resulting lithiated alkyne underwent addition to the aldehyde 327 to produce the alcohol 331. Boc deprotection of carbamate 331 using hydrochloric acid in diethyl ether furnished the free amine that was exposed to the acyl chloride of trimethylsilylpropionic acid to provide the desired cyclisation precursor 328 in good yield.
Construction of the ene-diyne 328, provided the precursor necessary for the cascade formation of the tetracyclic ring structure 329 via a radical generated at the bromide of the cyclisation precursor, using tributyltin hydride.

Exposure of the bromide 328 to tributyltin hydride and the radical initiator AIBN did not produce the ABCD-ring structure as predicted by a radical mechanism, but instead produced the tetracyclic lactam 332 in 14% yield. When tin and AIBN were removed from the reaction, heating to reflux in benzene, again produced the phenol 332, this time with increased yield.

Further to this the reaction was repeated with the same reaction conditions, but this time utilising BHT as a radical inhibitor, which saw the yield almost double, opposing the theory that the reaction proceeds via a radical mechanism. Due to the mild acidity of BHT and the possible evolution of HBr from the reaction, it was thought that an acid catalysed mechanism could describe the formation of the novel product 332.
Table 1. Conditions for cascade cyclisation.

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Solvent/Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu$_3$SnH/AIBN</td>
<td>Benzene/reflux, 11h</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Benzene/reflux, 48h</td>
<td>26%</td>
</tr>
<tr>
<td>BHT</td>
<td>Benzene/reflux, 48h</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Toluene/reflux, 2h</td>
<td>41%</td>
</tr>
<tr>
<td>1-Epoxyhexene</td>
<td>Toluene/reflux, 3h</td>
<td>76%</td>
</tr>
</tbody>
</table>

Repeating the cyclisation in boiling toluene, provided a higher temperature for the reaction to occur, further increasing the yield and suggesting the possibility of a thermally driven mechanism. By employing the acid trap 1-epoxyhexene, the reaction yield was improved to 76%, implying that an acid catalysed mechanism would be unlikely in this case. Corey and Danheiser used epoxypropene as an acid trap in their synthesis of Gibberillic acid.\[98,99\] During these studies, Waters was investigating a similar cascade sequence, with a slightly different substrate to the tetracycle used by Board.\[15,100\] The ether 336 contained the same ene-diyne system as the precursor developed by Board, and was thought to react under similar conditions, giving the furanyl system 338. Synthesis of the amide 336 began from N-Boc-N-methylpropargylamine 333, which was deprotonated using butyllithium and exposed to paraformaldehyde to give the alcohol 334. Treatment of this with sodium hydride and 2,3-dibromopropene gave the bromide 335 that underwent deprotection/amide formation to give the desired cyclisation precursor 336 in good yield.

Scheme 75. Synthesis of the etheric cyclisation precursor 336.

\[\text{333} \xrightarrow{a} \text{334} \xrightarrow{b} \text{335} \xrightarrow{c,d} \text{336}\]

a) $^9$BuLi, (CH$_2$O)$_n$, THF, –78°C, (82%); b) NaH, THF, 2,3-dibromopropene, (81%); c) TFA, DCM; d) trimethylsilylpropioloyl chloride, DCM, NEt$_3$, (82%).
Application of the thermal cyclisation conditions to the etheric precursor **337** yielded the 5-6-5-ring system **338**, in 90% yield, confirming that this novel methodology could be applied to other systems. It was thought that further manipulation of the furanyl product **338** could give rise to a highly functionalised precursor for the total synthesis of lactonamycin, and so the Diels-Alder cycloaddition of maleic anhydride **339** and the furan **338** was executed to give exclusively the *exo* adduct **340** in 50% yield. It is interesting that the *exo* selectivity is achieved *via* these reaction conditions; however, Dewar and Pierini describe the Diels-Alder cycloaddition between furan and maleic anhydride to give the *exo* product due to the high reversibility of the *endo* product formation.^[101]^ The thermal cyclisation was also applied to the ether **337** where \( R = H \) to test the importance of the presence of a silyl moiety, producing the desilylated adduct of **338** in high yield, but with a 13 fold increase in reaction time. This decrease in the rate of reaction shows that silicon is required for possible stabilisation of \( \alpha \) radical formation during the cyclisation of the ene-diyne system. The ether **341**, which lacks the bromide as seen in previous cyclisation precursors, was heated in toluene at reflux for 1 hour to give the lactam **342** in high yield. Absence of the bromide, removes the possibility of acid being generated within the reaction.
and the high yielding cyclisation of the ether 341 to the lactam 342 means that the likelihood of the reaction proceeding via an acid catalysed mechanism is very low.

**Scheme 77. Deuterium labelled cyclisation.**

A deuterium labelling study was carried out by Waters, to test whether proton transfer $\alpha$ to the ether linkage was required for the reaction. Synthesis of the deuterium labelled cyclisation precursor 345 started from $N$-Boc-$N$-methylpropargylamine 333 and proceeded in a similar fashion to the reaction conditions as described in scheme 75. Exposure of the deuterated compound 345 to the thermal cyclisation conditions, produced the tricyclic system 346 in high yield with a rate $3\frac{1}{2}$ times slower than the hydrogen analogue, which is indicative of hydrogen transfer being involved in the rate determining step due to the kinetic isotope effect.

**Scheme 78. Unsuccessful cyclisation.**
Replacement of the deuterium with gem-dimethyl functionality did not produce the predicted cyclisation product 348, further suggesting that protons α to the ether are essential in the reaction mechanism.

Culmination of the data described *vide supra* allowed Parsons *et al.* to illustrate two mechanistic pathways as shown in scheme 79. The concerted pathway would comprise of an ene reaction between the two proximal alkynes and a deuterium to give the deuterated allene 349. This could then undergo a Diels-Alder cycloaddition with the alkene to produce the previously described lactam 346. The step wise pathway would involve radical combination of the proximal alkynes, similar to the Bergman reaction[103] and Schmittel variation[106] of the Myers-Saito cyclisation,[104,105] to produce the exocyclic biradical 350. This would undergo deuterium abstraction to give the diene 351, which could radically combine to afford the allene 349 and proceed via the concerted pathway, or rearrange to give the new biradical 352 and this could react with the alkene to furnish the lactam 346.

*Scheme 79. Proposed reaction mechanism of the novel cyclisation methodology.*

It is interesting that a radical pathway is possible, as Waters describes that the presence of the radical inhibitor BHT does not affect the rate or yield of the cyclisation and Board even
demonstrated a rise in yield (table 1), however, it is possible that the intramolecular rate of radical propagation outweighs the intermolecular reaction with BHT.
2. Results & Discussion
2. Results & Discussion

2.1 Natural product synthesis and its by-products continued.

As described *vide supra*, we found that a literature reaction of hydroxybutanone 3 and ethyl formate to give furanone 2 did not proceed as described by Margareta *et al.*[11a,11b] Instead, we discovered that the spirocyclic polyether 5 was formed, with no evidence of the expected furanone 2 isolated from the reaction. The reported reaction was supposed to undergo a base initiated aldol reaction between 3 and 4, followed by a condensation reaction to give 2, but instead, the hydroxybutanone reacted with itself to produce the spirocyclic structure 5, which was confirmed by X-ray crystallography (figure 5).

*Scheme 80. Synthesis of the tetramer 5.*

The ability to form spirocyclic ethers has been of interest to a number of chemists due to their prevalence in a number of simple natural products such as dactyloxenes and theaspirane and theaspirone as well as being present in the more complex steroidal alkaloid kuroyurinidine.[107,108,109] Due to the facile production of such complexity from the simple butanone 3, a number of reaction conditions (table 2) were explored in an attempt to improve yield, or indeed form the originally desired furanone 2. It appeared that absence of ethyl formate or use of potassium tert-butoxide, did indeed improve the yield by up to 10%, however, use of other non-nucleophilic bases, still did not provide the desired furanone 2. The hydroxybutanone 3 was also treated with HCl in diethyl ether yet it appears that a base is
Results & Discussion

required for the initiation of the reaction, possibly forming an intermediate that would form the spirocyclic ether 5 after exposure to acid. Lewis acid catalysis was also attempted with gold chloride, affording the dehydrated dimerisation product 442 (see experimental).

Table 2. Alternate reaction conditions for the synthesis of the spirocyclic ether 5.

<table>
<thead>
<tr>
<th>3 and/or 4</th>
<th>Base</th>
<th>Reagents/Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 + 4</td>
<td>NaH</td>
<td>CuSO₄, HCl, H₂O</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>CuSO₄, HCl, H₂O</td>
<td>5 (30%)</td>
</tr>
<tr>
<td>3 + 4</td>
<td>LiHMDS</td>
<td>CuSO₄, HCl, H₂O</td>
<td>No reaction</td>
</tr>
<tr>
<td>3 + 4</td>
<td>KO'Bu</td>
<td>CuSO₄, HCl, H₂O</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>3 + 4</td>
<td>DBU</td>
<td>CuSO₄, HCl, H₂O</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>HCl, Et₂O</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>AuCl₃, Et₂O</td>
<td>442 (11%)</td>
</tr>
</tbody>
</table>

It is interesting that the reaction required a base to initiate formation of the tetramer 5 and so an investigation was undertaken into isolating a possible intermediate that could form after the initial reaction with sodium hydride.

Figure 5. X-ray crystal structure of the intermediate 353 and tetramer 5.

Treatment of hydroxybutanone 3 with sodium hydride in diethyl ether, followed by work-up with saturated, aqueous ammonium chloride solution, furnished the triol 353 in 47% yield.
This was isolated as a crystalline compound, allowing for confirmation of the structure by X-ray crystallography (figure 5). Further treatment of the intermediate 353 with copper sulfate in ether with HCl, again produced the tetramer 5 in 30% yield.

**Scheme 81. Formation of the intermediate.**

![Chemical structure diagram](image)

*Scheme 81. Formation of the intermediate. a) i) NaH, Et₂O; ii) NH₄Cl, H₂O, (47%); b) CuSO₄, HCl, Et₂O, rt, 4h, (30%)*

It was thought that the intermediate 353 would be formed by a base initiated aldol mechanism between enol 354 and the hydroxybutanone 3, to give aldol product 355, which would be followed by furan formation to afford the furan 356 and protonation upon acidic work-up (as shown in scheme 82).

**Scheme 82. Mechanism for the formation of the intermediate 353.**

![Chemical structure diagram](image)

This type of base initiated aldol reaction followed by acid catalysed oligomerisation has been demonstrated previously by Hudec *et al.* in their formation of the trimer 361 from the diketone 357.\textsuperscript{[110,111]} In this example, hydroxide base was used to initiate the aldol dimerisation of 2,3-butanedione 357 to afford the furan 358, (a very similar intermediate to that described in scheme 82) which was exposed to further quantities of diketone 357 in the presence of acid to form the diol 361.
Production of highly complex and highly functionalised compounds, in a single step, without the use of transition metal catalysis is of great interest to synthetic chemists, and is an ongoing point of research within the Parsons group.

2.2 Synthetic studies

2.2.1 Retrosynthetic analysis

Analysis of the novel methodology demonstrated by Board can provide a logical target of synthesis, by which use of the Parsons-Board-Waters (PBW) cyclisation technique can be applied to provide an advanced intermediate in the total synthesis of lactonamycin. It was thought that late stage glycosylation could be employed as it was used effectively in the total synthesis by Nakata and Saikawa et al., and so retrosynthetic analysis was envisioned from lactonamycinone 12. Lactone ring formation and dihydroxylation would be effected from the phenol 362, which could be the product of oxidation of the cyclisation product 363. This compound is analogous to the product formed in studies by Board, and so it was logical to assume that the ene-diyne 364 could be an appropriate substrate to effect the PBW cyclisation methodology.
As demonstrated in the model studies by Board, attachment of the alkynyl amide side chain to an aldehyde, was fairly trivial and so it was believed that the bromide 365 would be an appropriate target for synthesis, in formation of the cyclisation precursor 364. Studies towards the synthesis of the aldehyde 365 have been demonstrated by Board and Preece respectively, yet a full synthesis of the cyclisation precursor 364 is hitherto undocumented.\textsuperscript{[97,112]} The model study highlighted by Board demonstrated the possible inability to oxidise the trimethylsilyl moiety in the lactam 363 to a resulting alcohol or even phenol. This would require revision to install an alternative mode of functionality in order to complete the total synthesis of lactonamycin.

2,5-Dimethoxybenzaldehyde was used previously in studies towards the synthesis of the aldehyde 365 and was seen as an appropriate starting material for this project due to the commercial availability on a kilogram scale and the ease of conversion to appropriate synthetic intermediates.
2.2.2 First generation synthesis

With the previously described 2,5-dimethoxybenzaldehyde to hand, it was easy to identify the phthalide 369 as an important intermediate in the synthesis of the key aldehyde 365, due to the precedence for its formation within the literature.

Scheme 85. Synthesis of the phthalide 369.

Kumar et al., demonstrated the reduction of aldehyde 366 to the alcohol 367 in their synthesis of a series of riccardiphenol analogues.[113] Similarly to Preece, an unknown impurity in the commercially acquired aldehyde 366, often halted the reaction and reduced yield to 50 – 60%, but purification of the starting material via flash column chromatography removed the impurity and the reduction proceeded almost quantitatively. Lactone formation of the alcohol 367 with carbon dioxide was demonstrated by Magnus et al., during their synthesis of dynemicin A.[115] Double deprotonation was achieved using two equivalents of butyllithium, first to deprotonate the alcohol, second to deprotonate the aromatic ring. The reaction was then heated to allow equilibration of the carbanion to the position ortho to the hydroxymethyl group. Quenching of the dianion with carbon dioxide followed by acidic work up afforded the lactone 368 in good yield. Myers et al., also produced a synthesis of dynemicin A and detail the synthesis of the phenol 369 via a slightly more convoluted route, however, their synthesis began with a double demethylation of a similar system using boron tribromide. This method was employed in our example to convert the dimethoxy compound 368 to its phenol
derivative 369 in good yield. This three step synthesis of the phthalide 369 proved to be reproducible and the substrates showed stability for large scale preparation on the 10 – 20g scale.

Scheme 86. Synthesis of the aldehyde 374.

Preece found that application of a method described by Euler saw the hydroxymethylation of phenol 369 proceed using formalin solution in the presence of sodium hydroxide to give the triol 370 in 65 – 85% yield. The reaction was found to be capricious due to poor solubility of the product and the ability for the reactive intermediates to undergo polymerisation, often resulting in poor yield, with no chance of starting material recovery. Protection of the proximal hydroxyl moieties as the acetonide afforded the phenol 371 in high yield, which was treated with potassium hydroxide and heated to reflux with 2,3-dibromopropene to furnish the alkylated substrate 372. Removal of the acetonide was performed in acetic acid and water to give the diol 373 in good yield, which seemed to be a few minor transformations away from the desired aldehyde 365. Oxidation of the primary alcohol 373 with manganese dioxide, however, did not produce the aldehyde 374 in any yield other than trace quantities.
Results & Discussion

**Scheme 87. Failed Claisen rearrangements.**

It was thought that the acetonide 372 or the aldehyde 374 would be suitable candidates, as substrates for a thermal Claisen rearrangement, in order to install the alkene moiety necessary to perform the PBW cyclisation methodology. Preece however, did not observe a successful rearrangement with either the acetonide 372 or the aldehyde 374 using a variety of solvents with microwave heating.

**Scheme 88. Quinone methide generation.**

Instead of a Claisen rearrangement occurring to give the desired phenol 375, the acetonide 372 underwent a retro-Diels-Alder reaction, losing acetone to give the highly reactive, quinone methide intermediate 377. Preece found that performing these reactions under microwave conditions with a variety of polar and nucleophilic solvents, resulted in Michael addition of the solvent to the reactive intermediate to produce the phenol 378. In some cases Preece found that solvent addition was accompanied also by Claisen rearrangement, giving hope that this route could still yield desired aldehyde 365. Due to dwindling quantities of advanced intermediates and the unpredictable nature of several steps in this synthesis, a new methodology was sought to shorten the synthesis and improve overall yield of the aldehyde 365.
2.2.3 Second generation synthesis

The success of the quinone methide generation with the Claisen rearrangement occurring in one step, lead to the idea that the PBW reaction could be effected in parallel to the Claisen rearrangement, giving a new cyclisation precursor 379. This could be derived from the aldehyde 380 similarly to the aldehyde 365, as the amide side-chain addition has previously proven to be facile.

Scheme 89. Revised retrosynthetic analysis.

Due to the similarity of the aldehydes 365 and 380, the phthalide 369 was seen as an appropriate starting material for the new route to synthesis. As shown in the previous route to synthesis with hydroxymethylation, the difference in acidity between the two phenolic groups allows for selective reactivity towards O-alkylation. With this in mind it was thought that selective methylation could give rise to phenol 381, which would undergo alkylation with the reagents described vide supra.

Scheme 90. Route to the synthesis of 380.
Due to the resulting phthalide being electron rich in nature, it was then believed that formylation would give rise to the desired aldehyde \(380\).

**Scheme 91. Tautomers and resonance structures of the phenol \(369\).**

By studying the tautomeric forms and the resonance structures of the resulting alkoxides, it is possible to predict the difference in acidity between each phenol. A six membered transition state between the phenol and proximal carbonyl of the lactone \(369\) provide the much more acidic proton, and it was thought that this could be exploited by methylation with diazomethane. The methylation of carboxylic acids and substituted phenols has been largely successful with diazomethane, a versatile reagent that has been used in homologation reactions and even as a carbene source, with the only by-product being nitrogen gas.\(^{[116,117,118]}\)

The volatility, acute toxicity and affinity for explosive decomposition of diazomethane, led to the production of (trimethylsilyl)diazomethane by Lappert *et al.*\(^{[119,120]}\) Exposing this reagent to methanol yields diazomethane *in situ*, making the reagent a safer alternative.

**Scheme 92. Preparation of the phthalide \(382\).**

\(369\)
\(381\)
\(382\)

\(a\) MeOH/Toluene (2:3), (trimethylsilyl)diazomethane, 0.75h, (98%); \(b\) EtOH, KOH, reflux, 2,3-dibromopropane, 3h, (47%)
Exposure of the phenol 369 to TMS-diazomethane in methanol and toluene led to the selective methylation of the desired hydroxyl moiety to give the lactone 381 in almost quantitative yield. The resulting phenol 381 could then be alkylated using the conditions described previously to afford the phthalide 382.

It is thought by Kühnel et al. that the generation of diazomethane from its silylated adduct and its reaction with carboxylic acids occurs across two steps. At first the carbanion will deprotonate the phenol 369 to give the alkoxide 383 and a diazomethane species with a particularly labile silyl moiety (384). This can undergo methanolysis to provide protonated diazomethane 385, which serves as an excellent electrophile for the methylation of the alkoxide 383 to provide phenol 381. The mechanism was later adapted to the methylation of phenols by Erve et al. in their use of TMS-diazomethane as an alternative to diazomethane for phenol derivatisation.[122]

**Scheme 93. Mechanism of TMS-diazomethane O-methylation.**

2.2.4 Formylation

The formylation of aromatic compounds has been a subject of interest in synthesis for over a century. The first documented formylation of phenol was in 1876 by Reimer and Tiemann,[123] which sparked interest in the subject, leading to the discovery of the Gattermann-Koch reaction in 1897,[124] the Sommelet reaction in 1913,[125] the Vilsmeier-Haack formylation in 1927[126] and the Duff reaction in 1932.[127,128,129] These methods of
formylation are still being used in synthesis and it was thought that this chemistry could be applied to the phthalide 382 for the formation of the desired aldehyde 380.

**Scheme 94. Formylation mechanism.**

![Scheme 94. Formylation mechanism.](image)

The mechanism of formylation of all but the Reimer-Tiemann reaction generally follows a similar pathway. This is via electrophilic substitution of the aromatic substrate with a highly reactive iminium intermediate that is generated *in situ*. For the Sommelet and the Duff reactions, hexamethylenetetramine is treated with acid and heat to provide this highly reactive intermediate, to give the substitution product 388. Formylation of unsubstituted phenol would favour para substitution to give 389 as the major product, however, the phthalide 382 already contains a para substituent and so the aldehyde 390 is expected to be favoured in our synthesis.

**Scheme 95. Attempted formylation of the phthalide 382.**

![Scheme 95. Attempted formylation of the phthalide 382.](image)

Recent literature precedent for the formylation of aromatic rings is vast and so methods to formylate the phthalide 382 were studied as shown in table 3. Due to the success of Barrett *et al.* in the formylation of multisubstituted, electron rich aromatic systems, and the work by Kendall in formylation of anisole, it seemed that application of the Vilsmeier-Haack reaction was the next logical step.\[48,130\]
Results & Discussion

Table 3. Conditions for formylation.

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>POCl₃, DMF</td>
<td>MeCN, 0°C, 12h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>POCl₃, DMF</td>
<td>MeCN, rt, 12h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>POCl₃, DMF</td>
<td>MeCN, 80°C, 12h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Zn(CN)₂, HCl(g)</td>
<td>Et₂O, –5°C to 4°C, 2 days then H₂O, reflux</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Zn(CN)₂, HCl(g)</td>
<td>Et₂O, rt, 2 days, then H₂O, reflux</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Hexamine</td>
<td>TFA, reflux, 12h</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Conditions for the Vilsmeier-Haack formylation by Barrett et al., were adopted in the attempted production of the aldehyde 380, by treating the phthalide 382 with phosphorus oxychloride and DMF in acetonitrile at 0°C. Unfortunately the reaction showed no signs of progressing and work up of the reaction mixture rewarded only starting material. Previous syntheses were found to effect the formylation at a variety of temperatures and so the reaction was attempted using room temperature and near boiling acetonitrile in pursuit of the desired functionalisation.[130,131] Again, no evidence of a reaction taking place was observed via monitoring of the reaction by thin layer chromatography and work up of the reactions produced almost complete recovery of starting material.

A variation of the Gatterman-Koch reaction was published by Adams et al. and produced formylation via a much less hindered iminium species than the Vilsmeier-Haack reaction.[132,133] Zinc cyanide was used in the presence of hydrogen chloride gas to generate a concentration of protonated hydrogen cyanide in situ, which was hoped to form the aldehyde 376. Attempts of this reaction at low and room temperature showed no disappearance of starting material, which was recovered in full.

It was frustrating that phthalide 382 had seemed to be completely inert to the reaction conditions provided, however, it was interesting that the harsh conditions and elevated
temperatures did not insight decomposition, as shown in previous substrates with functionality ortho to the methoxide group. Conditions for the Duff reaction were explicated in work by Smith, by reflux of the aromatic substrate with hexamine in trifluoroacetic acid. This time starting material was consumed, but the result was complete decomposition of any substrate present.

Methods of formylation by Reimer-Tiemann type chemistry were reviewed; however, the generation of a carbene in this methodology was seen as a possible source of cyclopropanation with the proximal bromoalkene.

2.2.5 Success with the Claisen rearrangement

As described above, it appears that the phthalide 382 is tolerant to temperatures up to 90°C in concentrated acid. Where the lacking efficacy of the formylation reaction was discouraging, the possibility of producing a thermally driven Claisen rearrangement in high yield was promising. Where this would abandon the hope of attempting the cascade Claisen rearrangement-PBW cyclisation, we felt that both routes could be investigated in parallel at this point.

Scheme 96. Effecting the Claisen rearrangement and possible formylation.

Success of the Claisen rearrangement would give rise to the phenol 391, which could be seen as a possible substrate for formylation to produce the aldehyde 392, which is the mono-
methylated adduct of the desired aldehyde 365. It was thought that the lactone 391 would be suitable for the formylation reaction due to the free phenol adding a further mode of reactivity upon the aromatic ring. Formylation of the phenol under acidic conditions could give rise to a compound that undergoes a Fries-type rearrangement to give the desired intermediate.\cite{135,136}

Scheme 97. Possible Fries-type rearrangement for the formylation of phenol 391.

Acylation of the phenol 391 followed by Fries rearrangement could give rise to the iminium 393. Lack of a proton alpha to the resulting carbonyl, could lead to the formation of the cyclopropyl intermediate 394. This would undergo ring-opening and proton transfer to give the phenol 396, which upon aqueous work-up would give the desired aldehyde 392.

Scheme 98. The Claisen rearrangement.
Results & Discussion

The aromatic Claisen rearrangement is a thermally driven [3,3]-sigmatropic rearrangement, accompanied by rearomatisation to give a phenol.\cite{137,138} This reaction was applied using microwave heating to the alkenyl ether 382 for the formation of the phenol 391. A range of conditions were studied for this transformation, as seen in table 4, giving a variety of results.

Table 4. Conditions for the Claisen rearrangement.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature/time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>180°C, 0.5h</td>
<td>SM recovery</td>
</tr>
<tr>
<td>Toluene</td>
<td>180°C, 1h</td>
<td>SM recovery</td>
</tr>
<tr>
<td>Toluene</td>
<td>200°C, 1h</td>
<td>40%</td>
</tr>
<tr>
<td>DMF</td>
<td>180°C, 0.25h</td>
<td>10%</td>
</tr>
<tr>
<td>BnOH</td>
<td>200°C, 1h</td>
<td>80%</td>
</tr>
<tr>
<td>BnOH</td>
<td>200°C, 10 x 6min</td>
<td>60%</td>
</tr>
</tbody>
</table>

Preece reported the successful use of toluene as a microwave solvent and these conditions were employed, with the slightly higher reaction temperature of 180°C. Due to the low polarity of toluene, it was difficult to reach the higher reaction temperatures and seemed to cause thermal decomposition over extended periods of time, nonetheless a successful Claisen rearrangement was produced by heating in toluene. DMF was next utilised as a reaction solvent, as it is vastly polar compared to toluene. Unfortunately, the high reaction temperature needed for the transformation to take place began to initiate thermal decomposition of the solvent and so use DMF was eliminated. Benzyl alcohol was seen as the perfect solvent for this reaction due to its high polarity and slightly higher boiling point compared to toluene. Effecting the Claisen rearrangement in benzyl alcohol proved to be largely successful, with isolated yields consistently between 60 – 80%.

The phenomenon of microwave assisted organic synthesis has seen a great deal of interest since its initial use by Gedye and Smith et al., due to its ability to accelerate organic
transformations often reducing reaction times from days to hours when compared to standard thermal heating.\textsuperscript{[139]} In the same year of the first documented use of microwave assisted organic synthesis, studies by Giguere \textit{et al}. showed the ability to advance the rate of reaction of the aromatic Claisen rearrangement.\textsuperscript{[140]}

A number of studies have been documented on the ‘specific’ or ‘non-thermal’ affects of microwave irradiation on organic transformations, to test the theory that the electromagnetic radiation has an effect on the substrates in synthesis.\textsuperscript{[141,142,143]} It is now widely accepted that a microwave photon does not possess the energy required to make or break bonds within a chemical reaction. The phenomenon of increased reactivity in microwave synthesis is attributed to purely the thermal effects, largely coming from initial ‘superheating’ of the microwave solvent. This is where the reaction medium is heated beyond the boiling point of a solvent, for a period of time that doesn’t cause thermal decomposition within the substrates, but does provide an increase in the rate of reaction as demonstrated by Baghurst and Mingos.\textsuperscript{[144,145]}

With the effect of superheating in mind, short 6 minute ‘pulses’ of microwave heating were used in an attempt to further increase the conversion during the Claisen rearrangement in benzyl alcohol. Conversion of the phthalide \textbf{382} to the phenol \textbf{391} was observed, but at a lower yield, possibly due to a lack of the ‘superheating’ phenomenon with benzyl alcohol, as the boiling point is lower than the reaction temperature.
2.2.6 Formylation continued.

Successful production of the Claisen rearranged product 391, allowed for further studies of formylation to achieve the desired aldehyde 392.

Scheme 99. Attempted formylation of the phenol 391.

Again, conditions for the Vilsmeier-Haack formylation by Barrett et al. were adopted in the attempted production of the aldehyde 392, by treating the phenol 391 with phosphorus oxychloride and DMF in acetonitrile at 0°C. The reaction appeared to show no sign of progression and upon work up starting material was recovered. Almost identical reaction conditions were employed from the previous formylation studies (table 5), however, the results obtained were identical to those achieved vide supra. Due to the repeated failure in pursuit of installing aldehyde functionality to the phthalides 382 and 391, formylation of the mono-methylated substrate was abandoned.

Table 5. Conditions for formylation.

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>POCl₃, DMF</td>
<td>MeCN, 0°C, 12h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>POCl₃, DMF</td>
<td>MeCN, rt, 12h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>POCl₃, DMF</td>
<td>100°C, 6h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Zn(CN)₂, HClₙ</td>
<td>Et₂O, –5°C to 4°C, 2 days then H₂O, reflux</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Zn(CN)₂, HClₙ</td>
<td>Et₂O, rt, 2 days, then H₂O, reflux</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Hexamine</td>
<td>TFA, reflux, 12h</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>
It is interesting that functionalisation ortho to the methoxide moiety was so elusive, as we described previously the hydroxymethylation of the phenol 369 to the triol 370. It was thought that the free phenol moiety was required for ortho functionalisation and so further investigations were carried out using the diol 369.

Scheme 100. Attempted formylation of the diol 369.

Access to the free phenol 369 for formylation appeared to offer no advantage with the functionalisation to give the desired aldehyde 393. Similar reaction conditions were employed from previous formylation attempts often resulting in recovery of starting material, as seen in table 6. Another method towards the ortho-formylation of phenols was documented by Casiraghi et al. and later refined by Skattebol et al., utilising magnesium chloride and paraformaldehyde under basic conditions. Due to the success of hydroxymethylation with formaldehyde and a base, it was thought the basic nature of this new formylation reaction would be favourable in our example, however, starting material was completely recovered.

Table 6. Conditions for formylation.

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>POCl₃, DMF</td>
<td>MeCN, 0°C, 12h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>POCl₃, DMF</td>
<td>MeCN, 80°C, 6h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Zn(CN)₂, HCl₁(g)</td>
<td>Et₂O, –5°C to 4°C, 2 days then H₂O, reflux</td>
<td>SM recovered</td>
</tr>
<tr>
<td>Hexamine</td>
<td>TFA, reflux, 12h</td>
<td>Low SM recovery</td>
</tr>
<tr>
<td>MgCl₂, paraformaldehyde</td>
<td>Net₃, THF, reflux, 4h; then rt, 4 days</td>
<td>SM recovery</td>
</tr>
</tbody>
</table>
2.2.7 Selective alkylation

The lack of success with formylation, led to revisiting the hydroxymethylation of new substrates, in an attempt to shorten the original synthesis of diol 373. Due to the differing acidity of phenolic protons within the phthalide 369, it was also thought that the less acidic phenol would give rise to a more nucleophilic alkoxide under basic conditions.

Scheme 101. Revised route for parallel synthesis.

By exploiting this difference in reactivity, we believed that the phenol 369 could undergo selective alkylation under basic conditions to give the mono-alkylated substrate 394. With this in hand, it was hoped that hydroxymethylation would give rise to the previously acquired diol 373, without the need for protection and deprotection via the acetonide. This route would also avoid the production of the highly polar and largely insoluble triol 370. With conditions refined for the Claisen rearrangement, the selectively alkylated adduct 394 could undergo rearrangement to furnish the diol 395. Installation of the benzyl alcohol to give the triol 396, gives access to the alternative route to the synthesis of aldehyde 365, which would be used for the PBW rearrangement without the cascade Claisen-reaction.
Results & Discussion

**Scheme 102. Selective alkylation of phenol 369.**

By employing the conditions used for the previous alkylation with 2,3-dibromopropene, it was possible to isolate the predicted product of selective alkylation 394, albeit in low yield. Potassium carbonate was substituted as the base as it was thought that the increased acidity of phenols would be sufficient for deprotonation by carbonate, but also in an attempt to reduce degradation of starting materials via the use of potassium hydroxide. Interestingly, the desired product of selective alkylation was isolated, but so was a product of double addition. One would predict that the other product of this reaction would be double O-alkylation, however the product isolated was the phenol 394b. This could be due to the phenol proximal to the carbonyl of the lactone, being of higher acidity to react with carbonate and so the resulting alkoxide would give the doubly substituted phenol 394b.

**Table 7. Conditions for selective alkylation.**

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOH, 2,3-dibromopropene</td>
<td>EtOH, reflux, 3h</td>
<td>394 (20%)</td>
</tr>
<tr>
<td>K₂CO₃, 2,3-dibromopropene</td>
<td>EtOH, reflux, 3h</td>
<td>394 (20%), 394b (30%)</td>
</tr>
<tr>
<td>Li₂CO₃, 2,3-dibromopropene</td>
<td>EtOH, reflux, 3h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>LiOH, 2,3-dibromopropene</td>
<td>EtOH, reflux, 3h</td>
<td>394 (47%)</td>
</tr>
</tbody>
</table>

By altering the counter-ion to the alkoxide from potassium to lithium, it was believed that addition to give the phenol 394b could be hindered to provide only the desired bromide 394.
Lithium carbonate was found to be too weak in basicity and so lithium hydroxide was employed to give the phenol 394 in 47% yield, with no double addition of the bromoalkene observed.

2.2.8 Hydroxymethylation and aldehyde formation

The conditions used for hydroxymethylation by Preece were initially applied to the phenol 394, in the thought that optimisation and possible screening of other reagents would be required.\textsuperscript{[112]} Any doubt in the efficacy of these reaction conditions was thwarted by the production of the diol 373 in good yield, with no sign of polymerisation.

\textit{Scheme 103. Successful hydroxymethylation and aldehyde formation.}

Previously, oxidation of the diol 373 with manganese dioxide produced only trace quantities of the required aldehyde. We found that the diol 373 suffered from low solubility in the solvent and so selective methylation of the phenol to provide the more soluble alcohol 396, was effected in 76% yield. Another contributing factor to the previous trace aldehyde synthesis was the low activity of the commercially acquired manganese dioxide. Manganese sulfate and potassium permanganate solutions underwent a disproportionation reaction to provide fresh manganese dioxide, a modification of the method by Ray \textit{et al.}, which was used in the oxidation of the alcohol 396 to afford the desired aldehyde 380 in 92% yield.\textsuperscript{[149]}
2.2.9 Side-chain addition

Facile production of the aldehyde 380 led to the belief that addition of the diyne side-chain to give the alcohol 379 would be trivial, allowing for studies to affect the cascade Claisen rearrangement-PBW cyclisation to furnish the advanced intermediate for the total synthesis of lactonamycin 397.

**Scheme 104. Proposed side-chain addition and cyclisation.**

Two methods of side-chain addition were taken into consideration for the formation of the alcohol 379; the first pathway would be addition of the Boc protected methyl propargyl amine as its organolithium reagent, followed by Boc deprotection and amide coupling with the acyl chloride of (trimethylsilyl)propionic acid. A second approach would involve amide formation of N-methylpropargylamine with (trimethylsilyl)propionic acid, with addition of the entire side-chain as the organolithium reagent. The studies outlined by Board have demonstrated that difficulty in oxidation of the TMS moiety could be problematic and so an alternative form of functionalisation would be required.\(^{[97]}\)

Use of the carbon-silicon bond as a masked hydroxyl group has been documented by Tamao and co-workers\(^{[150,151,152]}\) and by Fleming *et al.*,\(^{[153,154,155]}\) using phenylsilane or fluorosilane derivatives as points of oxidation using peroxides. The (dimethylsilyl)phenylsilyl adduct was adopted for our studies, due to being of higher stability, which was needed due to being exposed to amide formation and PBW cyclisation conditions.
Scheme 105. Mechanism of the Fleming-Tamao oxidation.

By using the DMPS group 398 as the masked hydroxyl, it is possible to eliminate the phenyl moiety using tetrafluoroboric acid diethyl ether complex to produce the more reactive, fluorosilane derivative 400. Exposure of this to mCPBA under basic conditions can produce the peroxysilane 401, which undergoes a Baeyer-Villiger type rearrangement, furnishing the silyl ether 402. Hydrolysis of the rearranged product 402 affords the alcohol 403 with retention of stereochemistry.\textsuperscript{[156]}

Application of the Fleming-Tamao oxidation to our synthesis would require production of the cyclic intermediate 404, with the (dimethyl)phenylsilyl functionalisation in place of the TMS group in the phenol 397. Successful oxidation would produce an alcohol, which upon oxidation would give the phenol required for the total synthesis of lactonamycin.

Scheme 106. Revision of the retrosynthesis.
Results & Discussion

By studying the retrosynthesis of the cyclisation precursor 405, we found the amide 406 to be a suitable candidate for the side-chain addition.


There was literature precedent for the formation of the alkynyl silane 408, however, optimisation of the method was required by Preece.\(^{[157,158]}\) Commercially available ethynylmagnesium bromide solution (0.5M in THF) was exposed to chloro(dimethyl)phenylsilane to give the phenylsilane 408. Formation of the DMPS propiolic acid 409 was also reported by Fleming et al., by exposing the alkyne 408 methylmagnesium chloride to form the alkynyl Grignard, which upon treatment with carbon dioxide and acidic work-up gave the propiolic acid 409.\(^{[159]}\) With the desired acid 409 in hand, and N-methylpropargylamine being commercially available, formation of the amide 406 was seen to be facile.

Table 8. Conditions for amide coupling.

<table>
<thead>
<tr>
<th>Acid</th>
<th>Coupling conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>409</td>
<td>DIC, DMAP, DCM, 0°C to rt, 24h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>409</td>
<td>CDI, DCM, 0°C to rt, 24h</td>
<td>408 (10%), 410 (34%)</td>
</tr>
<tr>
<td>409</td>
<td>Thionyl chloride, NEt(_3), DCM, 0°C to rt, 12h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>409</td>
<td>Oxalyl chloride, DMF, DCM, NEt(_3), 0°C, 12h</td>
<td>40%</td>
</tr>
<tr>
<td>409</td>
<td>Oxalyl chloride, DMF, DCM, NEt(_3), 0°C, 12h (Non-aqueous work-up)</td>
<td>70%</td>
</tr>
</tbody>
</table>

Amide formation between carboxylic acids and primary amines using carbodiimides and CDI is abundant within the literature, and so conditions for neutral coupling reagents were
believed to provide the desired amide 406 in good yield.\textsuperscript{[160 - 163]} A coupling between propiolic acid and $N$-methylpropargyl amine has been reported by Duckworth \textit{et al.}, and so we adopted similar conditions for the formation of the amide 406.\textsuperscript{[167]} The isopropyl derivative of DCC was used in our example with $N$-methylpropargylamine due to it being a liquid making it easier to handle, however, the reaction produced only decomposition. Coupling between the acid 409 and the amine with CDI afforded a completely unexpected selection of by-products, with reclaimation of silyl acetylene 408 and the product of CDI reacting with $N$-methylpropargyl amine, giving the amide 410 (see experimental).

As the use of neutral coupling reagents tended to provide unwanted side-reactions and decomposition, acyl chloride formation was tentatively employed in the hope that acidic by-products wouldn’t affect the DMPS functionality. Acyl chloride formation with thionyl chloride produced only decomposition and so the conditions previously demonstrated by Board were used, with moderate success to give the desired amide 406 in 40\% yield. In an attempt to reduce exposure of the product to acidic conditions, aqueous work-up procedure was removed, with the reaction mixture being directly filtered through silica gel to afford the amide 406 in 70\% yield. It was believed that the reactivity of the phenyl group on the silane would be particularly reactive under acidic medium due to its reactivity as demonstrated in the mechanism of the Fleming-Tamao oxidation. We did not, however, expect the product of decarboxylation 408 as demonstrated with the reaction between the acid 409 and CDI.

\textit{Scheme 108}. Side-chain addition to the aldehyde 380.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{scheme108.png}};
\end{tikzpicture}
\end{center}

\textsuperscript{12}BuLi, THF, $-90^\circ\text{C}$, 0.5h; then 376, $-90^\circ\text{C}$ to rt, 1.5h; Work-up i) tert-butyl bromide, then H$_2$O ii) H$_2$O iii) NH$_4$Cl\textsubscript{(aq)}
Conditions for side-chain addition were mimicked by those by Board in his addition of Boc protected \(N\)-methylpropargylamine to an aldehyde, by use of butyllithium to deprotonate the alkyne 406 at \(-90^\circ\text{C}\). This was followed by addition of the aldehyde 376 and a variety of work-up procedures were then attempted in the isolation of the alcohol 405. \(^1\)Butyl bromide was first used as Board employed this as a mild source of an acidic proton as the resulting alcohol is labile under acidic conditions. Unfortunately, use of this mild acid, water or aqueous ammonium chloride solution did not provide the desired cyclisation precursor 405, the only crude product produced was found to decompose on silica gel and alumina, with no evidence of product in the crude NMR spectrum.

**Scheme 109. Preparation of the amide 413.**

For simply as use for proof of concept, the TMS derivative of the side-chain 406 was synthesised in an attempt to form the model cyclisation precursor 379. Again, using the method by Fleming *et al.*, it was possible to form the acid 412 in a single step from the commercially available TMS acetylene 411. The acid 412 was then subjected to amide formation with \(N\)-methylpropargylamine to give the TMS side-chain 413.

**Table 9. Conditions for amide coupling.**

<table>
<thead>
<tr>
<th>Acid</th>
<th>Coupling conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>412</td>
<td>Oxalyl chloride, DMF, DCM, NEt(_3), 0(^{\circ})C, 12h (Non-aqueous work-up)</td>
<td>50%</td>
</tr>
<tr>
<td>412</td>
<td>Ghosez’s reagent, DCM, 0(^{\circ})C, 1h</td>
<td>44%</td>
</tr>
<tr>
<td>412</td>
<td>Ghosez’s reagent, DCM, 0(^{\circ})C, 1h, (Non-aqueous work-up)</td>
<td>78%</td>
</tr>
</tbody>
</table>
Application of the previous conditions for amide formation, using oxalyl chloride for acyl chloride formation with non-aqueous work-up, did give the coupled substrate 413 in 50% yield. The synthesis of acyl halides under neutral conditions was reported by Ghosez et al., using 1-chloro-N,N,2-trimethyl-1-propenylamine (Ghosez’s reagent), which was used for our amide formation, giving the desired side-chain 413 in high yield after the non-aqueous work-up as used previously.\cite{164,165,166}

**Scheme 110. Second attempted side-chain addition.**

![Scheme 110](image)

Use of the side-chain addition conditions described above did not provide the desired cyclisation precursor 379 as hoped, instead yielding total decomposition with no reclamation of starting materials or side-products.

### 2.2.10 Modified side-chain addition

The failure of side-chain addition was frustrating and was largely attributed to the lability of the resulting alcohol, as demonstrated *vide supra* with the formation of quinone methide during the Claisen rearrangement. Loss of this hydroxyl moiety would produce a highly reactive intermediate, which would explain the complete loss of starting materials. In an attempt to test the ability of alkyne addition to the aldehyde 380, Boc protected N-methylpropargylamine was used with conditions derived from the model studies by Board.\cite{97}
Results & Discussion

Scheme 111. Addition of Boc protected N-methylpropargyl amine to aldehyde 380.

![Chemical structure]

a) tert-Butyl methyl(prop-2-ynyl)carbamate, n-BuLi, THF, −90°C, 0.5h; then 376, −90°C to rt, 1.5h; tert-butyl bromide, (40%); b) TFA or Thionyl chloride, NaI, NEt₃, then DMPS propionic acid.

Deprotonation of tert-butyl methyl(prop-2-ynyl)carbamate followed by addition to the aldehyde 380 with addition of the mildly acidic tert-butyl bromide provided the alcohol 414 in 40% yield. Where the yield was disappointing, it was important to prove the efficacy of alkyne addition to the aldehyde 380 via the alkynyl anion if this route to synthesis were to proceed. Similarly to Board, attempts to isolate the free amine of alcohol 415 by treatment with TFA or generation of the amine in situ followed by amide formation to give the full side-chain of the alcohol 415, were both unsuccessful. As reported by Board, this was expected, again due to the propensity of the benzylic hydroxyl moiety to undergo elimination under acidic conditions.

Scheme 112. Attempted reproduction of work by Board.

![Chemical structure]

a) n-BuLi, THF, −78°C; b) CuCN, −78°C to −40°C; c) 2,3-dibromopropene, THF, −78°C to rt, then HCl/H₂O, (73% from 330); d) N-Boc-N-methylpropargylamine, n-BuLi, THF, −90°C then tBuBr, −90°C to rt, (83%); e) HCl in Et₂O (2M) or Thionyl chloride, NaI, NEt₃, then TMS propionic acid.

The alcohol 331 was synthesised by modification of the method by Board, in an attempt to test Boc deprotection conditions, it was also thought that access to the free amine would be suitable for model amide formation studies. Efforts to remove the Boc group using conditions...
Results & Discussion

described in scheme 111, led to decomposition and so no amount of the free amine was produced.\textsuperscript{97}

Owing to the success of the addition of Boc protected \( N \)-methylpropargylamine to the aldehyde 380, but difficulty in deprotection, an alternative amine protecting group was required that could be removed under milder conditions.

**Scheme 113. Addition of TIPS protected \( N \)-methylpropargyl amine to aldehyde 380.**

\[
\begin{align*}
\text{380} & \xrightarrow{\text{a}} \text{416} & \xrightarrow{\text{b}} \text{417}
\end{align*}
\]

\textit{a)} 1,1,1-Trisopropyl-\( N \)-methyl-\( N \)-prop-2-yn-1-ylsilanamine, \( \text{tBuLi, THF, } -78^\circ\text{C, 0.5h; then 376, } -78^\circ\text{C to rt, 1h; b)} \text{HF}_{(aq)} \text{, MeCN, (89\% over 2 steps).}

Faggiani demonstrated the synthesis of TIPS protected \( N \)-methylpropargylamine and its use as an alkynyllithium reagent for addition to an aldehyde, with resulting deprotection under mild conditions due to the weak nitrogen-silicon bond.\textsuperscript{102} Deprotonation of TIPS protected \( N \)-methylpropargylamine and addition of the aldehyde 380 provided the alcohol 416 that underwent desilylation when exposed to concentrated hydrofluoric acid to furnish the desired free amine 417 in 89\% yield over 2 steps. It is interesting that it was possible to isolate the alcohol 417 in such good yield after exposure to concentrated acid, however, this was attributed to the high pK\(_a\) value of HF in comparison to other mineral acids.

Production of the free amine 417 led to the possibility of effecting amide formation with TMS or DMPS propiolic acid to provide the, so far, elusive cyclisation precursors 379 or 405.
Results & Discussion

Scheme 114. Amide bond formation to provide cyclisation precursor 379 or 405.

Two sets of conditions to form the acyl chloride of each propiolic acid derivative were used from their previous success; the first utilising oxalyl chloride in the presence of DMF and the second using Ghosez’s reagent. Frustratingly, attempts at amide formation for both sets of conditions applied to both the TMS and DMPS propiolic acid derivatives only resulted in decomposition of the starting materials. Analysis of the crude material showed no evidence of amide bond formation via the NMR spectrum and TLC analysis showed decomposition on silica gel, alumina and neutral silica backed TLC plates.

Table 10. Amide formation conditions.

<table>
<thead>
<tr>
<th>Propiolic acid derivative</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPS (409)</td>
<td>Oxalyl chloride, DMF, DCM, NEt₃, 0°C, 12h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>DMPS (409)</td>
<td>Ghosez’s reagent, DCM, 0°C, 1h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>TMS (412)</td>
<td>Oxalyl chloride, DMF, DCM, NEt₃, 0°C, 12h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>TMS (412)</td>
<td>Ghosez’s reagent, DCM, 0°C, 1h</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Use of these conditions previously generated at least 40% of the desired amide product and so it was thought that at least a trace quantity of the cyclisation precursor would be formed, but to no avail.
2.2.11 Model amide formation/side-chain addition

Due to dwindling starting material and the lack of evidence that the cyclisation precursor could be formed by standard amide formation conditions, a model aldehyde was employed to test the efficacy of amide coupling in the presence of a benzylic hydroxyl moiety.

Scheme 115. Model side-chain addition.

2,4-Dimethoxybenzaldehyde 418 was chosen as a suitable model aldehyde as it is electron rich and contains a methoxyl group proximal to the reacting aldehyde, which was thought to exhibit similar resonance forms to the key aldehyde 380. The first attempt at side-chain addition involved deprotonation of the TMS or DMPS side-chain derivatives with either butyllithium or methylmagnesium bromide to form the alkynyl anion for addition to the aldehyde 418. Both methods of side-chain addition appeared to show decomposition, similar to that induced in the previous examples.
Table 11. Model amide formation conditions.

<table>
<thead>
<tr>
<th>Propiolic acid derivative</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPS (409)</td>
<td>Oxalyl chloride, DMF, DCM, NEt₃, 0°C, 12h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>DMPS (409)</td>
<td>Ghosez’s reagent, DCM, 0°, 1h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>TMS (412)</td>
<td>Oxalyl chloride, DMF, DCM, NEt₃, 0°C, 12h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>TMS (412)</td>
<td>Ghosez’s reagent, DCM, 0°, 1h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>TMS (412)</td>
<td>Ghosez reagent, acyl chloride formation; then NaOH, H₂O, DCM</td>
<td>Decomposition</td>
</tr>
<tr>
<td>TMS (412)</td>
<td>DIC, DMAP, DCM, 0°C to rt, 24h</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Formation of the amide 421 followed the same conditions as the formation of amide 417, by addition of TIPS protected N-methylpropargylamine as the alkynyl anion, with TIPS deprotection being effected with concentrated hydrofluoric acid solution. Coupling of the amide 421 with both DMPS and TMS propiolic acid derivatives, again showed decomposition under the conditions tried previously, including an attempt at Schotten-Baumann amide synthesis.¹⁶⁸,¹⁶⁹

A method demonstrated by Downey et al., involves the addition of acetylenes to aldehydes using zinc bromide in the presence of TMSOTf, which was applied to our model synthesis (Scheme 114).¹⁷⁰ This work shows modification of the method described by Carreira et al., who opted to effect their synthesis utilising zinc triflate, without resulting alcohol protection.¹⁷¹,¹⁷²

Scheme 116. Pathway described by Downey et al.

Downey suggests that in the presence of Hunig’s base and zinc bromide, an alkynyl substrate 422 will form the zinc acetylide 423, which will undergo addition to an aldehyde to form the
alkoxide 424. Quenching of the alkoxide 424 with TMSOTf produces the silyl ether 425. In our synthesis we substituted TMSOTf for TIPSOTf in an effort to form a more stable silyl ether, due to the lability of the benzylic alcohol. The reaction between the aldehyde 418 and the TMS propiolic acid derivative 413 under these conditions did not provide the expected side-chain addition product, instead gave the amide 420 in 50% yield. It appears that the lability of the alkynyl silyl group, outweighed the acidity of the alkynyl proton under basic conditions, causing the zinc acetylide to form on the unsuspected alkyne to give the product observed. Where this result wasn’t favourable for the production of the desired model cyclisation precursor 419, it was helpful in proving that a type of side-chain could be inserted to an aldehyde that had previously shown instability under a variety of reaction conditions. It could be possible to produce the DMPS side-chain 406 and substitute the alkynyl proton for TMS functionality and expose this to Downey’s conditions in the hope that the zinc acetylide will form at the TMS position providing the addition that we require.

2.2.12 Use of BOP reagent derivatives and HMDS coupling

With model and actual model studies providing no amount of useable cyclisation precursor, phosphorus based coupling agents and dehydration techniques were also attempted for the preparation of the desired amide 379.

Scheme 117. Further conditions for amide bond formation.

a) 413, PyBOP, DCM, iPrNEt₃, 12h; b) 413, BOPCI, DCM, iPrNEt₃, 12h; c) 413, HMDS, Toluene, 200°C, 3h, (Trace).
BOP reagent, also known as Castro’s reagent is a phosphonium HOBt derivative, which is highly reactive towards carboxylic acids in the synthesis of amides.\textsuperscript{173} Where Castro’s reagent itself is useful, it does result in the formation of HMPA and so a number of BOP derivatives have been developed such as PyBOP and BOP chloride, which are just as effective.\textsuperscript{174} It is thought that carboxylic acids react with BOP reagent and its derivatives to produce HOBt \textit{in situ}, which then reacts with the carboxylic acid-BOP derivative to produce the carboxylic-OBt ester.\textsuperscript{175,176} This undergoes substitution with an amine to furnish the amide coupled product.

We employed PyBOP and BOP chloride for the formation of the alcohol 379, and studying the reaction by thin layer chromatography did not show the sort of decomposition profile observed previously. Unfortunately, after work up no reaction had taken place with trace recovery of starting material.

A number of recent publications have demonstrated the use of HMDS as an efficient dehydrating agent under microwave heating.\textsuperscript{177,178,179} The method described by Burbiel \textit{et al.}, used a 1:1 mixture of HMDS and THF due to the low solubility of substrates in HMDS alone, and so we opted to use toluene in place of THF. This solvent mixture allowed us to attempt the amide coupling at 200°C in the microwave, as it was thought that extended reaction time may give rise to not only the amide formation but also Claisen rearrangement and possibly even PBW cyclisation. Analysis of the reaction mixture by TLC suggests that a new compound was formed and upon solvent removal and with analysis of the NMR and mass spectrum, we were tentative to suggest that a trace quantity of amide formation had occurred, with no rearrangement.
A lack of material and time meant that further exploration of this dehydration methodology could not be attempted; however, the conditions were applied to an amine previously synthesised by Faggiani (426) giving the desired coupled product 427 in high yield. Examination of the crude NMR spectrum from this reaction (figure 6) shows the cleanliness of this reaction procedure, giving the amide 427 almost exclusively with very little contamination from impurities.

The success of this reaction of such a great degree suggests that the methoxyl moiety proximal to the benzylic hydroxyl group (compounds 379, 405, 417, 419) is imperative to the failure of coupling reactions and side-chain addition conditions. The production of the silyl ether 420 shows that protection of this benzylic hydroxyl group may be a possible route for further investigations to complete the total synthesis of lactonamycin.
2.3 Further work

2.3.1 Completing the total synthesis

As discussed above it was believed that the benzylic hydroxyl group was too labile for almost any conditions applied for amide formation or side-chain addition and so a new route to synthesis would have to alter the synthesis of the key aldehydes 365 and 380 to incorporate electron withdrawing groups. This is demonstrated by the new route to synthesis in scheme 118, starting from the previously synthesised phenol 394. During the Claisen rearrangement studies described previously, we found that the alkene 394 undergoes 3,3-sigmatropic rearrangement in benzyl alcohol with microwave heating to afford the diphenol 395. Application of the hydroxymethylation conditions developed by Preece and adapted for our
Results & Discussion

synthesis, could be used to convert the phenol 395 to the triol 396. Use of freshly prepared manganese dioxide would then hopefully provide the new key aldehyde 428.

Scheme 119. Proposed new route to the total synthesis of lactonamycin.

Protection of the diphenol 428 could be effected using a variety of acyl derivatives in the hope that they will inhibit mesomeric effect produced by the phenol, lowering the likelihood of the quinone methide formation and allowing for the benzylic hydroxyl group of the amide 430 to be of higher stability. The HMDS coupling technique demonstrated in our work could give rise to the alcohol 430 after installation of the amide via addition of the TIPS protected N-methylpropargylamine. With the cyclisation precursor 430 in hand, the Parsons-Board-Waters cyclisation methodology could be applied, success of which would give the phenol
Results & Discussion

in a single step. Oxidation of the (dimethyl)phenyl silyl functionality would then progress using Fleming-Tamao oxidation conditions to furnish the diphenol 432.

With literature precedent for the oxidation of acetyl protected hydroquinones to the resulting quinone with CAN, it is believed that the phenol 432 would be converted to the quinone 433 giving a complete model ABCDE-ring structure and an advanced intermediate for the total synthesis of lactonamycin.\textsuperscript{[180,181]}

Scheme 120. Completing the total synthesis of lactonamycin.

Dihydroxylation of multifunctionalised quinones has been demonstrated by Danishefsky et al.,\textsuperscript{[23,25]} in their total synthesis of lactonamycinone and by Barrett et al.,\textsuperscript{[47]} during studies towards the synthesis of the CDEF-ring structure. It was also employed in the total synthesis of lactonamycin by Nakata and Saikawa et al.,\textsuperscript{[91]} and so it was thought that phenol protection
and dihydroxylation would provide the diol 434. By using RuCl₃/NaIO₄ for the
dihydroxylation of the quinone 433, it would be possible to produce the diol 434, but with no
diastereomeric control. Nakata and Saikawa have demonstrated that glycosylation of a
similar compound to the alcohol 438 produced separable enantiomers of the precursor to
lactonamycin, and so stereoselective synthesis could be achieved at a later stage. Sharpless
asymmetric dihydroxylation could also be applied to the quinone 433 to give the diol 434
using AD-mix-β to give the correct isomer. Selective acylation could possibly produce
the monoacetylated lactone 435, and the tertiary alcohol would be protected as the silyl ether
to give lactam 436. Enol formation would be provided by treatment of the acetylide 436 with
LDA that undergoes addition to the lactone to give alcohol 437. Methyltion of the
tertiary alcohol 437 would provide the complete protected aglycone lactonamycinone. With a
number of late stage glycosylation techniques provided in the literature, production of
phenol protected lactonamycin 439 would be trivial and a global deprotection of this would
furnish lactonamycin 10 to complete the total synthesis.

2.3.2 Manipulation of work by Downey et al.

Where it appeared that the previous use of work by Downey et al., gave the wrong addition
product (Scheme 114), it may have actually been a blessing in disguise. A large variety of
conditions were tested for side-chain addition and the only method that produced an isolable
product was using zinc bromide, TIPSOTf and Hünigs base to give the alternate addition
product 420. This was due to the TMS substituted alkyne producing the zinc acetylide as
opposed to that substituted with a proton. By revisiting the amide 406, it could be possible to
deprotonate the free alkyne and expose the alkynyl anion to TMS chloride to give the new
diyne 440. With this example we would hope that TMS would be far more labile than DMPS
under Downey’s conditions and upon reaction with the key aldehyde 380 would provide the cyclisation precursor 441, stabilised by TIPS protection of the labile hydroxyl group.

Scheme 121. Modification of the previous synthesis using methodology by Downey et al.

2.4 Summary

Our initial strategy in studies towards the total synthesis of lactonamycin involved the successful formation of Claisen-PBW cascade cyclisation precursor 379 or PBW cyclisation precursor 364. The first generation synthesis was found to be lengthy and contained substrates that were susceptible to polymerisation or decomposition. A re-imagined synthesis of the same cyclisation precursors saw the discovery of a range of Claisen-rearrangement conditions to produce the phenols 391 and 395. Manipulation of the differing reactivity of the hydroxyl groups in the diphenol 369 led to selective alkylation and hydroxymethylation, reducing the synthetic pathway to the key diol 373 and removing the formation of the capricious triol 370.
Results & Discussion

With a new route to synthesis of the desired aldehyde 380 available and with the success of manipulation of work by Downey et al., and an interesting application of dehydration using HMDS, future production of the cyclisation precursor 379 could be effective. With this precursor in hand, studies of the cascade Claisen rearrangement and PBW cyclisation could give advanced intermediates towards the total synthesis of lactonamycin.
3. Experimental Section
3.1 General laboratory procedure

All reactions were carried out under an atmosphere of nitrogen at room temperature, unless otherwise stated, and were monitored via thin-layer chromatography using Merck aluminium plates with a 0.2 mm layer of 60 F-254 silica gel with a fluorescent indicator. TLC plates were developed using UV light with either basic potassium permanganate or phosphomolybdic acid dip. Flash column chromatography was performed using BDH (40-63 µm) silica gel. Reaction solvents were dried by distillation under an atmosphere of nitrogen: THF and diethyl ether were distilled from sodium and benzophenone; DCM, acetonitrile, toluene and methanol were distilled from CaH₂. All other reagents were purchased from commercial sources and were used as provided unless otherwise stated.

NMR spectroscopy was carried out using a Bruker AV-400 spectrometer (400 MHz for ¹HNMR and 100 MHz for ¹³CNMR) or a Bruker AV-500 spectrometer (500 MHz for ¹HNMR and 125 MHz for ¹³CNMR), where stated. Chemical shifts were reported in parts per million (ppm) and internal standard was taken from residual chloroform (7.26 ppm for ¹HNMR and 77.16 ppm for ¹³CNMR) or DMSO (2.50 ppm for ¹HNMR and 39.52 ppm for ¹³CNMR). Micromass AutoSpec-Q or Micromass Platform II instruments were used to perform mass spectrometry (EI, CI and ESI). Infrared spectra were recorded using a Perkin-Elmer Spectrum RX FTIR System spectrometer with samples analysed neat using a universal attenuated total reflectance sampling accessory. Microwave reactions were conducted using a Biotage Initiator with Biotage vials as supplied.
3.2 Experimental procedures

(2,5-Dimethoxyphenyl)methanol (367)

Prepared by a modification of the method by Kumar et al.\textsuperscript{[113]}

Sodium borohydride (5.50 g, 145 mmol) was slowly added to 2,5-dimethoxybenzaldehyde (20.1 g, 121 mmol) in methanol (200 mL) at 0°C. The RM was allowed to warm to room temperature and was stirred for 4h. The reaction was quenched with saturated ammonium chloride solution (200 mL), methanol was removed, extracted with diethyl ether (3 x 150 mL), washed with saturated sodium chloride solution (250 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure, giving the product as a crude orange oil, which was purified via column chromatography (20% diethyl ether in petroleum ether) to give the title compound as a pale yellow oil (20.2 g, 99%).

R\textsubscript{f} = 0.25 (20% diethyl ether in 40-60 petroleum ether)

LRMS: (EI+) m/z 168 (M+, 100%), 125 (99), 110 (30).

HRMS: (EI+) Calculated for C\textsubscript{9}H\textsubscript{12}O\textsubscript{3}, m/z 168.0786 found 168.0791.

IR: (neat, v cm\textsuperscript{-1}) 3405 (v. br), 2940, 2834, 1494, 1214.

δ\textsubscript{H}: (400MHz, CDCl\textsubscript{3}): 6.89 (1H, d, J = 2.50Hz, 4-CH), 6.78 (2H, m, 1-CH & 2-CH), 4.64 (2H, s, 7-CH\textsubscript{2}), 3.80 (3H, s, 9-CH\textsubscript{3}), 3.76 (3H, s, 8-CH\textsubscript{3}), 2.41 (1H, br s, 7-OH).

δ\textsubscript{C}: (100MHz, CDCl\textsubscript{3}): 153.64 (C3), 151.48 (C6), 130.21 (C5), 114.72 (C4), 112.97 (C2), 111.15 (C1), 61.84 (C7), 55.79(C8 & C9).
Experimental Section

4,7-Dimethoxyisobenzofuran-1(3H)-one (368)

Prepared by a modification of the method by Magnus et al.\textsuperscript{[115]}

To (2,5-dimethoxyphenyl)methanol (100 g, 594 mmols) in dry THF (2.00 L) at -78°C was added, as drops, a solution of nBuLi 2.5M in hexanes (475 mL, 1188 mmol) and stirred for 1h. The mixture was slowly warmed to 70°C and allowed to stir for a further 2h then cooled to 0°C. Dry carbon dioxide was bubbled through the reaction mixture for 0.5h followed by the addition of excess 2M HCl solution. The title compound precipitated as a white crystalline solid, which was collected through vacuum filtration (53.2 g, 46%). Mother liquors were extracted with chloroform, dried (Na\textsubscript{2}SO\textsubscript{4}) and solvent removed under reduced pressure. The resultant residue was purified via flash column chromatography (25% EtOAc in petroleum ether) to give the title compound as a white crystalline solid (27.1 g, 24%). Reclamation of starting material (10.0 g) gave a recovered yield of 77%.

R\textsubscript{f} = 0.20 (25% EtOAc in 40-60 petroleum ether)

Mp = 165 – 168°C

LRMS: (ESI+) m/z 195 (M+, 100%).

HRMS: (ESI+) Calculated for C\textsubscript{9}H\textsubscript{11}O\textsubscript{4}, m/z 195.0657 found 195.0653.

IR: (neat, ν cm\textsuperscript{-1}) 2844, 1754, 1501, 1269.

δ\textsubscript{H}: (400MHz, CDCl\textsubscript{3}): 7.02 (1H, d, J = 8.71Hz, 2-CH), 6.84 (1H, d, J = 8.71Hz, 1-CH), 5.13 (2H, s, 7-CH\textsubscript{2}), 3.90 (3H, s, 9-CH\textsubscript{3}), 3.83 (3H, s, 10-CH\textsubscript{3}).

δ\textsubscript{C}: (100MHz, CDCl\textsubscript{3}): 169.21 (C8), 152.23 (C6), 147.50 (C3), 136.89 (C4), 116.73 (C2), 114.43 (C5), 111.54 (C1), 67.25 (C7), 56.27 (C9), 55.90 (C10).
**Experimental Section**

4,7-Dihydroxyisobenzofuran-1(3H)-one (369)

![Chemical Structure](image)

To a stirring solution of 4,7-dimethoxyisobenzofuran-1(3H)-one (8.83 g, 45.5 mmols) in dichloromethane (50 mL) at -78°C, a 1M solution of boron tribromide (100 mL, 100 mmols) was added as drops. This was stirred at -78°C for 4h and warmed to room temperature over 8h. Water (250 mL) was added, aqueous layer extracted with ethyl acetate (3 x 100 mL), which was washed with water (250 mL) and brine (250 mL), then dried (Na₂SO₄). The solvent was removed under reduced pressure, to afford a crude brown solid, which was purified via flash column chromatography (5% MeOH in DCM) to give the title compound as an off white powder (6.27 g, 83%).

Rₜ = 0.40 (5% MeOH in DCM)

Mp = Decomposed 217 – 222°C

LRMS: (ESI) m/z 165 (M-H, 100%), 164 (30), 121 (5).

HRMS: (ESI) Calculated for C₉H₅O₄, m/z 165.0188 found 165.0184.

IR: (neat, ν cm⁻¹) 3310 (br), 3075 (br), 1717, 1503, 1289.

δ_H: (400MHz, d₆-DMSO): 9.82 (1H, s, 6-OH), 9.47 (1H, s, 3-OH), 6.94 (1H, d, J = 8.65Hz, 2-CH), 6.73 (1H, d, J = 8.65Hz, 1-CH), 5.15 (2H, s, 7-CH₂).

δ_C: (100MHz, d₆-DMSO): 168.92 (C8), 149.41 (C6), 143.67 (C3), 133.31 (C4), 122.43 (C2), 116.50 (C1), 111.44 (C5), 66.92 (C7).
To a stirring, brown solution of 4,7-dihydroxyisobenzofuran-1(3H)-one (10.0 g, 60.0 mmols) and NaOH (4.81 g, 121 mmols) in water (60 mL), was added a solution of formalin (6.51 g, 37% w/w formaldehyde, 72 mmols). This was stirred at room temperature in the absence of light for 4 days. Acetic acid (30 mL) was added, giving a white precipitate, which was isolated by filtration. The filtrate was extracted with ethyl acetate (5 x 200 mL) the washings were combined and washed with water (200 mL), brine (200 mL) and then dried (Na₂SO₄). The solvent was removed under reduced pressure, to leave a pale brown solid, which was purified by column chromatography (10% MeOH/DCM) and combined with the precipitate to give the title compound as a white solid (7.38 g, 63%).

Rᵣ = 0.10 (10% MeOH in DCM)

Mp = 198 – 200°C

LRMS: (ESI+) m/z 195 (M+, 100%).

HRMS: (ESI+) Calculated for C₉H₇O₅, m/z 195.0293 found 195.0301.

IR: (neat, ν cm⁻¹) 3375 (br), 3070 (v. br), 2356, 1717, 1444, 1097.

δ₁H: (400MHz, d₆-DMSO): 9.55 (1H, s, 6-OH), 8.87 (1H, s, 3-OH), 7.15 (1H, s, 2-CH), 5.23 (1H, s, 7-OH), 5.18 (2H, s, 8-CH₂), 4.49 (2H, s, 7-CH₂).

δ₁C: (100MHz, d₆-DMSO): 169.92 (C9), 145.17 (C3), 143.91 (C6), 131.44 (C1), 130.46 (C4), 120.88 (C2), 111.81 (C5), 67.27 (C8), 57.60 (C7).
Experimental Section

6-Hydroxy-2,2-dimethyl-4H-isobenzofuro[4,5-d][1,3]dioxin-9(7H)-one (371)

4,7-Dihydroxy-6-(hydroxymethyl)isobenzofuran-1(3H)-one (1.00 g, 5.10 mmols) was suspended in acetone (20 mL) and to this was added 2,2-dimethoxypropane (3.12 mL, 25.5 mmols). A crystal of p-TSA was added (catalytic) and the suspension was heated to 60°C for 4h. The suspension had dissolved to produce an orange solution, which was diluted with water (50 mL), extracted with ethyl acetate (4 x 100 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure. The crude brown solid was purified via flash column chromatography (10% MeOH/DCM) to give the title compound as a pale brown solid (1.15 g, 96%).

R_f = 0.28 (5% MeOH in DCM)

Mp = 196 – 201°C

HRMS: (ESI+) Calculated for C₁₂H₁₂NaO₅, m/z 259.0577 found 259.0583.

IR: (neat, ν cm⁻¹) 3444, 3067, 1723, 1509, 1456, 1233.

δ_H: (400MHz, d₆-DMSO): 9.87 (1H, s, 3-OH), 6.81 (1H, s, 2-CH), 5.16 (2H, s, 9-CH₂), 4.81 (2H, s, 8-CH₂), 1.47 (6H, s, 11-CH₃ & 12-CH₃).

δ_C: (100MHz, d₆-DMSO): 168.46 (C10), 144.66 (C6), 142.70 (C3), 134.10 (C4), 121.23 (C1), 117.93 (C2), 113.27 (C5), 100.38 (C7), 67.47 (C9), 60.42 (C8), 24.92 (C11 & C12).
Experimental Section

6-(2-Bromoallyloxy)-2,2-dimethyl-4H-isobenzofuro[4,5-d][1,3]dioxin-9(7H)-one (372)

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

6-Hydroxy-2,2-dimethyl-4H-isobenzofuro[4,5-d][1,3]dioxin-9(7H)-one (0.75 g, 3.00 mmols) was dissolved in EtOH (15 mL) with KOH (0.17 g, 3.00 mmols) and heated to reflux. 2,3-dibromopropene (0.35 mL, 3.60 mmols) was added portionwise over ten minutes and the reaction mixture was heated at reflux for a further 3 h. The solution was then allowed to cool to rt and poured over cold water (100 mL). This gave a white precipitate, which was dissolved in DCM and washed with 0.5M NaOH solution (150 mL). The organic layer was dried (Na₂SO₄) and solvent removed under reduced pressure to give the title compound as a white solid (0.65 g, 60%). SM was recovered (0.10 g) by re-acidifying the NaOH wash and extracting with EtOAc.

This gave a recovered yield of 69%.

Rₓ = 0.80 (2.5% MeOH in DCM)

Mp = 159 – 162°C

LRMS: (EI+) m/z 356 (M+, 15%), 354 (15), 296 (20), 298 (20), 217 (100).

HRMS: (EI+) Calculated for C₁₅H₁₃BrO₅, m/z 354.0103 found 354.0097.

IR: (neat, ν cm⁻¹) 1761, 1493, 1299, 1010.

δH: (400MHz, CDCl₃): 6.70 (1H, s, 2-CH), 5.96 (1H, s, 15-H₈), 5.71 (1H, s, 15-H₇), 5.22 (2H, s, 11-CH₂), 4.87 (2H, s, 8-CH₂), 5.54 (2H, s, 14-CH₂), 1.61 (6H, s, 9-CH₃ & 10-CH₃).
$\delta_C$: (100MHz, CDCl$_3$): 168.29 (C12), 144.98 (C3 & C6), 136.31 (C4), 126.53 (C13), 120.76 (C1), 118.79 (C15), 114.79 (C5), 114.49 (C2), 101.00 (C7), 72.74 (C14), 67.18 (C11), 60.91 (C8), 24.81 (C9 & C10).
4-(2-Bromoallyloxy)-7-hydroxy-6-(hydroxymethyl)isobenzofuran-1(3H)-one (373)

6-(2-Bromoallyloxy)-2,2-dimethyl-4H-isobenzofuro[4,5-d][1,3]dioxin-9(7H)-one (0.60 g, 1.70 mmols) was dissolved in acetic acid (6 mL) and water (6 mL) and the reaction mixture was heated to 60°C for 4.5h. Solvent was removed under reduced pressure and excess water/acetic acid was removed by azeotroping with toluene. This gave a brown solid, which was purified via flash column chromatography (1% MeOH/DCM) to give the title compound, as an off white solid (0.48 g, 91%).

Rf = 0.50 (10% MeOH in DCM)

Mp = 108 – 112°C

LRMS: (Cl+) m/z 334 (M+NH₄, 40%), 332 (40), 205 (50), 144 (100).

HRMS: (Cl+) Calculated for C₁₂H₁₅NBrO₅, m/z 332.0134 found 332.0123.

IR: (neat, v cm⁻¹) 3444 (br), 3067 (br), 1723, 1634, 1509, 1424, 1309, 999.

δH: (400MHz, d₆-DMSO): 9.31 (1H, s, 6-OH), 7.35 (1H, s, 2-CH), 6.12 (1H, s, 12-H₈), 5.75 (1H, s, 12-H₆), 5.32 (1H, s, 7-OH), 5.29 (2H, s, 8-CH₂), 4.79 (2H, s, 11-CH₂), 4.54 (2H, s, 7-CH₂).

δC: (100MHz, d₆-DMSO): 169.31 (C9), 147.06 (C6), 144.03 (C3), 133.72 (C4), 131.50 (C1), 127.49 (C10), 120.27 (C12), 119.46 (C2), 112.31 (C5), 72.27 (C11), 67.01 (C8), 57.77 (C7).
Experimental Section

4-(2-Bromoallyloxy)-7-hydroxy-6-(hydroxymethyl)isobenzofuran-1(3H)-one (373)

Alternative method of preparation

To a stirring, brown solution of 4-(2-Bromoallyloxy)-7-hydroxyisobenzofuran-1(3H)-one (0.50 g, 2.00 mmols) and NaOH (0.08 g, 2.00 mmols) in water (2 mL), was added a solution of formalin (0.22 mL, 37% w/w formaldehyde, 2.40 mmols). This was stirred at room temperature in the absence of light for 4 days. Acetic acid (1 mL) was added, giving a white precipitate, which was isolated by filtration. The filtrate was extracted with ethyl acetate (5 x 20 mL) the washings were combined and washed with water (20 mL), brine (20 mL) and then dried (Na₂SO₄). The solvent was removed under reduced pressure, to leave a pale brown solid, which was purified by column chromatography (10% MeOH/DCM) and combined with the precipitate to give the title compound as an off-white solid (0.37 g, 67%).

Data consistent with previous method of preparation.
4-(2-Bromoallyloxy)-6-(hydroxymethyl)-7-methoxyisobenzofuran-1(3H)-one (396)

4-(2-Bromoallyloxy)-7-hydroxy-6-(hydroxymethyl)isobenzofuran-1(3H)-one (0.50 g, 1.60 mmols) was dissolved in MeOH (15 mL) and toluene (22.5 mL) at rt. To the stirred reaction mixture, (Trimethylsilyl)diazomethane solution (0.85 mL, 1.70 mmols) was added drop-wise. This was stirred for 0.75h at which point acetic acid (0.50 mL) was added and the solvent was removed under reduced pressure. Residual acetic acid was removed by azeotroping with toluene to give a crude brown solid, which was purified using flash column chromatography (1% MeOH in DCM) to afford the title compound as a white solid (0.40 g, 76%).

Rf = 0.62 (5% MeOH in DCM)

Mp = 111 – 113°C

LRMS: (EI+) m/z 330 (M+, 30%), 328 (30), 209 (100), 181 (30), 149 (20).

HRMS: (EI+) Calculated for C_{13}H_{13}BrO_{5}, m/z 327.9946 found 327.9943.

IR: (neat, ν cm⁻¹) 3231 (br), 2910, 1763, 1643, 1496, 1412, 1265.

δH: (400MHz, CDCl₃): 7.16 (1H, s, 2-CH), 5.98 (1H, s, 12-Hₓ), 5.73 (1H, s, 12-Hᵧ), 5.26 (2H, s, 8-CH₂), 4.76 (2H, s, 7-CH₂), 4.72 (2H, s, 11-CH₂), 4.08 (3H, s, 13-CH₃).

δC: (100MHz, CDCl₃): 168.56 (C9), 150.41 (C6), 147.61 (C3), 136.03 (C4), 136.01 (C1), 126.47 (C10), 119.13 (C12), 118.42 (C5), 117.78 (C2), 72.44 (C11), 67.47 (C8), 63.01 (C13), 60.18 (C7).
7-(2-Bromoallyloxy)-4-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-carbaldehyde (380)

4-(2-Bromoallyloxy)-6-(hydroxymethyl)-7-methoxyisobenzofuran-1(3H)-one (0.35 g, 1.10 mmols) was dissolved in acetone (20 mL), giving a pale yellow solution. Manganese dioxide (0.96 g, 11.0 mmols) was added in one portion and the reaction mixture was allowed to stir for 12h. This was then filtered through Celite®, washing with acetone (3 x 50 mL) and solvent was removed under reduced pressure. This gave the title compound as a white solid (0.32 g, 92%).

R_f = 0.40 (2.5% MeOH in DCM)

Mp = 162 – 163°C

LRMS: (EI+) m/z 328 (M+, 30%), 326 (30), 207 (35), 179 (100).

HRMS: (EI+) Calculated for C_{13}H_{11}BrO_5, m/z 325.9790 found 325.9808.

IR: (neat, ν cm^{-1}) 2876, 1768, 1687, 1614, 1491, 1079.

δ_H: (500MHz, CDCl_3): 10.44 (1H, s, 7-CH), 7.53 (1H, s, 2-CH), 6.00 (1H, s, 12-H_A), 5.75 (1H, s, 12-H_A), 5.32 (2H, s, 8-CH_2), 4.76 (2H, s, 11-CH_2), 4.24 (3H, s, 13-CH_3).

δ_C: (125MHz, CDCl_3): 187.25 (C7), 166.44 (C9), 155.63 (C6), 146.82 (C3), 143.40 (C4) 129.29 (C1), 124.99 (C10), 119.04 (C5) 118.96 (C12), 114.19 (C2), 71.59 (C11), 66.68 (C8), 63.61 (C13).
**Experimental Section**

*tert*-Butyl 4-(7-(2-bromoallyloxy)-4-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-hydroxybut-2-ynyl(methyl)carbamate (414)

*tert*-Butyl methyl(prop-2-ynyl)carbamate (0.05 g, 0.32 mmols) was dissolved in THF (3 mL) and cooled to -95°C. "Butyllithium solution (0.13 mL, 0.33 mmols) was added drop-wise, and the reaction mixture was stirred at -95°C for 0.5h. 7-(2-Bromoallyloxy)-4-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-carbaldehyde (0.09 g, 0.30 mmols) was dissolved in THF (2 mL) and added to the reaction mixture as drops. This was stirred at -95°C for a further 1h at which point, 2-bromo-2-methylpropane (0.06 g, 0.45 mmols) was added and the reaction mixture was allowed to warm to rt. This was partitioned between water (10 mL) and diethyl ether (10 mL), the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the organic combinations were washed (brine), dried (MgSO₄) and the solvent was removed under reduced pressure to give an orange oil. The crude oil was purified *via* flash column chromatography (1% MeOH in DCM) to give the title compound as a viscous yellow oil (0.06 g, 40%).

Rₕ = 0.45 (1% MeOH in DCM)

LRMS: (ESI+) m/z 520 (M+Na, 100%), 518 (100), 422 (30), 224 (50).

HRMS: (ESI+) Calculated for C₂₂H₂₆BrNO₇, m/z 518.0790 found 518.0809.

IR: (neat, ν cm⁻¹) 3407, 2979, 2933, 1763, 1680, 1487, 1391, 1250, 1146.

δ_H: (500MHz, CDCl₃): (Peaks broadened due to rotamers) 7.32 (1H, s, 2-CH), 6.00 (1H, s, 14-H_B), 5.75 (1H, s, 10-CH), 5.74 (1H, s, 14-H_B), 5.27 (2H, s, 7-CH₂), 4.74 (2H, s, 13-CH₂),
4.13 (5H, br s, 9-CH\textsubscript{3} & 16-CH\textsubscript{2}), 2.90 (4H, s, 18-H & 10-OH), 1.44 (9H, br s, 20-CH\textsubscript{3}/21-CH\textsubscript{3}/22-CH\textsubscript{3}).

\(\delta\text{C: (125MHz, CDCl}_3\): 171.32 (C17), 168.24 (C8), 150.44 (C6), 147.70 (C3), 137.27 (C4), 135.85 (C1), 126.40 (C12), 119.45 (C14), 119.07 (C5), 117.02 (C2), 82.92 (C11), 82.48 (C15), 80.43 (C19), 72.61 (C13), 67.50 (C7), 63.47 (C9), 60.26 (C10), 38.20 (C16), 33.89 (C18), 28.51 (C20/C21/C22).
4,7-Dihydroxyisobenzofuran-1(3H)-one (3.00 g, 18.0 mmols) was dissolved in MeOH (90 mL) and toluene (135 mL) at rt. To the stirred reaction mixture, (Trimethylsilyl)diazomethane solution (10.0 mL, 20.0 mmols) was added as drops. This was stirred for 45 minutes at which point acetic acid (3 mL) was added and the solvent was removed under reduced pressure. Residual acetic acid was removed by azeotroping with toluene to afford the title compound as a beige solid (3.20 g, 98%).

R_f = 0.40 (5% MeOH in DCM)

Mp = 157 – 160°C

LRMS: (EI+) m/z 181 (M+H, 100%).

HRMS: (EI+) Calculated for C_9H_9O_4, m/z 181.0501 found 181.0496.

IR: (neat, v cm^{-1}) 3300 (v. br.), 1729, 1619, 1507, 1276.

δ_H: (400MHz, d_6-DMSO): 9.75 (1H, s, 3-OH), 7.05 (1H, d, J = 8.05Hz, 2-CH), 6.94 (1H, d, J = 8.05Hz, 1-CH), 5.18 (2H, s, 7-CH_2), 3.80 (3H, s, 9-CH_3).

δ_C: (100MHz, d_6-DMSO): 169.92 (C8), 151.34 (C6), 145.48 (C3), 138.21 (C4), 130.71 (C5), 122.31 (C2), 112.97 (C1), 67.35 (C7), 56.35 (C9)
4-(2-Bromoallyloxy)-7-methoxyisobenzofuran-1(3H)-one (382)

4-Hydroxy-7-methoxyisobenzofuran-1(3H)-one (3.00 g, 17.0 mmols) was dissolved in ethanol (60 mL) and potassium hydroxide (0.95 g, 17.0 mmols) was added in one portion at rt. The reaction mixture was heated to reflux for 20 minutes, at which point 2,3-dibromopropene (3.99 g, 20.0 mmols) was added, portion wise over 10 minutes. This was stirred at reflux for 3h and then cooled to rt. The reaction mixture was poured into cold water (200 mL) resulting in a precipitate, which was filtered, dissolved in DCM and then washed with 0.5M sodium hydroxide solution. The organic layer was then washed with brine, dried (Na₂SO₄) and solvent was removed under reduced pressure to give the title compound as a tan colour solid (2.4 g, 47%).

Rᵣ = 0.81 (10% MeOH in DCM)

Mp = 121 – 122°C

LRMS: (ESI+) m/z 300 (M+H, 100%), 298 (100), 223 (20).

HRMS: (ESI+) Calculated for C₁₂H₁₂O₄Br, m/z 298.9919 found 298.9914.

IR: (neat, ν cm⁻¹) 2917, 1764, 1621, 1503, 1267, 1016.

δₓ: (400MHz, d₆-DMSO): 7.36 (1H, d, J=8.51Hz, 2-CH), 7.05 (1H, d, J=8.62Hz, 1-CH), 6.15 (1H, s, 12-Hₐ), 5.76 (1H, s, 12-Hₐ), 5.28 (2H, s, 7-CH₂), 4.85 (2H, s, 11-CH₂), 3.85 (3H, s, 9-CH₃).

δₓ: (100MHz, d₆-DMSO): 167.81 (C₈), 152.32 (C₆), 144.86 (C₃), 137.52 (C₄), 127.30 (C₁₀), 120.51 (C₁₂), 120.28 (C₂), 113.42 (C₅), 112.17 (C₁), 71.93 (C₁₁), 66.69 (C₇), 55.97 (C₉).
Experimental Section

5-(2-Bromoallyl)-4-hydroxy-7-methoxyisobenzofuran-1(3H)-one (391)

4-(2-Bromoallyloxy)-7-methoxyisobenzofuran-1(3H)-one (1.00 g, 3.00 mmols) was dissolved in degassed benzyl alcohol (10 mL) and heated in a microwave at 200° C for 1h. This was allowed to cool to rt and the benzyl alcohol was removed by azeotroping with water. The water was then azeotroped using toluene giving a yellow solid, which was purified via column chromatography (DCM/MeOH 0% increasing to 0.5%) to give the title compound as a white solid (0.35 g, 35%) with recovery of SM (0.34 g) to give an overall yield of 53%.

R_f = 0.33 (10% MeOH in DCM)

Mp = 139 – 143°C

LRMS: (ESI⁺) m/z 300 (M⁺, 100%), 298 (100), 223 (30).

HRMS: (ESI⁺) Calculated for C_{12}H_{12}BrO_{4}, m/z 298.9919 found 298.9909.

IR: (neat, v cm⁻¹) 3503, 2945, 1756, 1607, 1503, 1270.

δ_H: (400MHz, d_6-DMSO): 9.47 (1H, s, 3-OH), 6.90 (1H, s, 1-CH), 5.68 (1H, s, 12-H_B), 5.54 (1H, s, 12-H_A), 5.20 (2H, s, 7-CH₂), 3.84 (2H, s, 10-CH₂), 3.79 (3H, s, 9-CH₃).

δ_C: (100MHz, d_6-DMSO): 168.26 (C8), 150.93 (C6), 142.70 (C3), 135.64 (C4), 132.55 (C2), 130.88 (C11), 128.83 (C5), 119.03 (C12), 113.93 (C1), 67.27 (C7), 56.06 (C9), 41.25 (C10).
**Experimental Section**

4-(2-Bromoallyloxy)-7-hydroxyisobenzofuran-1(3H)-one (394a)

![Chemical Structure](image)

4,7-Dihydroxyisobenzofuran-1(3H)-one (1.00 g, 6.00 mmols) was dissolved in a solution of lithium hydroxide (0.29 g, 13.0 mmols) and MeOH (25 mL) and heated to reflux for 1h. 2,3-Dibromopropene (1.32 g, 6.60 mmols) was added portion-wise over 10 minutes and the reaction mixture was heated for a further 3h. This was allowed to cool to room temperature and then poured over 2M HCl solution (50 mL) and ice. The aqueous was extracted with EtOAc (3 x 100 mL), organic layers washed (H₂O), dried (Na₂SO₄) and solvent removed under reduced pressure. This gave a crude brown solid, which was purified via flash column chromatography (1% MeOH in DCM) to give the product as an off-white solid (0.80 g, 47%).

Rᵣ = 0.62 (8% MeOH in DCM)

Mp = 109 – 110°C

LRMS: (EI+) m/z 286 (M+, 20%), 284 (20), 165 (100), 137 (55).

HRMS: (EI+) Calculated for C₁₁H₉BrO₄, m/z 283.9684 found 283.9683.

IR: (neat, ν cm⁻¹) 3366, 1734, 1630, 1507, 1273, 1024.

δₑ: (400MHz, d⁶-DMSO): 10.25 (1H, s, 6-OH), 7.23 (1H, d, J=8.47Hz, 2-CH), 6.83 (1H, d, J=8.33Hz, 1-CH), 6.12 (1H, s, 12-Hₐ), 5.75 (1H, s, 12-Hₐ), 5.25 (2H, s, 7-CH₂), 4.78 (2H, s, 10-CH₂).

δₐ: (100MHz, d⁶-DMSO): 168.40 (C₈), 151.17 (C₆), 143.73 (C₃), 136.47 (C₄), 127.54 (C₉), 121.05 (C₂), 120.43 (C₁₁), 116.30 (C₁), 111.90 (C₅), 72.17 (C₁₀), 66.70 (C₇).
Experimental Section

7-(2-Bromoallyloxy)-4-hydroxyisobenzofuran-1(3H)-one (394b)

4,7-Dihydroxyisobenzofuran-1(3H)-one (1.00 g, 6.00 mmols) was dissolved in a solution of potassium hydroxide (1.80 g, 13.0 mmol) and MeOH (25 mL) and heated to reflux for 1h. 2,3-Dibromopropene (1.32 g, 6.60 mmol) was added portion-wise over 10 minutes and the reaction mixture was heated for a further 3h. This was allowed to cool to room temperature and then poured over 2M HCl solution (50 mL) and ice. The aqueous was extracted with EtOAc (3 x 100 mL), organic layers washed (H2O), dried (Na2SO4) and solvent removed under reduced pressure. This gave a crude brown solid, which was purified via flash column chromatography (1% MeOH in DCM) to give the product as a brown solid (0.10 g, 6%).

Rf = 0.74 (2.5% MeOH in DCM)

Mp = 82 – 85°C

LRMS: (EI+) m/z 405 (M+, 80%), 403 (100), 401 (65), 387 (50), 365 (30).

HRMS: (EI+) Calculated for C14H12Br2O4, m/z 401.9102 found 401.9095.

IR: (neat, ν cm⁻¹) 3437, 1744, 1633, 1507, 1434, 1332, 1004.

δH: (400MHz, d6-DMSO): 9.45 (1H, s, 3-OH), 7.22 (1H, s, 2-CH), 6.13 (1H, s, 11-HB), 5.74 (1H, s, 11-HA), 5.61 (1H, s, 14-HB), 5.51 (1H, s, 14-HA), 5.29 (2H, s, 7-CH2), 4.79 (2H, s, 9-CH₂), 3.78 (2H, s, 12-CH₂).

δC: (100MHz, d6-DMSO): 169.85 (C8), 148.64 (C3), 144.25 (C6), 135.28 (C4), 131.63 (C13), 127.77 (C10), 126.72 (C1), 123.18 (C2), 121.25 (C11), 119.00 (C14), 113.26 (C5), 72.79 (C9), 67.57 (C7), 40.76 (C12).
Experimental Section

5-(2-Bromoallyl)-4,7-dihydroxyisobenzofuran-1(3H)-one (395)

4-(2-Bromoallyloxy)-7-hydroxyisobenzofuran-1(3H)-one (0.50 g, 1.70 mmols) was dissolved in degassed benzyl alcohol (10.0 mL) and heated in a microwave at 200°C for 1h. This was allowed to cool to rt and the benzyl alcohol was removed by azeotroping with water. The water was then azeotroped using toluene giving a yellow solid, which was purified via column chromatography (1% MeOH in DCM) to give the title compound as a yellow powder (0.18 g, 36%) with recovery of SM (0.15 g) to give an overall yield of 53%.

R_f = 0.5 (5% MeOH in DCM)

Mp = 160 – 163°C

LRMS: (EI+) m/z 284 (M+, 20%), 205 (80), 161 (100), 57 (60).

HRMS: (EI+) Calculated for C_{11}H_9BrO_4, m/z 283.9684 found 283.9673.

IR: (neat, ν cm\(^{-1}\)) 3424, 3216, 2938, 1717, 1632, 1492, 1330, 1163, 1054.

δ_H: (400MHz, d_6-DMSO): 9.91 (1H, s, 6-OH), 9.12 (1H, s, 3-OH), 6.71 (1H, s, 1-CH), 5.75 (1H, s, 11-H_B), 5.56 (1H, s, 11-H_A), 5.17 (2H, s, 7-CH_2), 3.78 (2H, s, 9-CH_2).

δ_C: (100MHz, d_6-DMSO): 168.64 (C8), 149.43 (C6), 141.21 (C3), 134.15 (C4), 132.65 (C2), 130.96 (C10), 119.16 (C11), 117.27 (C1), 110.40 (C5), 67.08 (C7), 40.75 (C9).
4-(2-Bromoallyloxy)-6-(1-hydroxy-4-(methylamino)but-2-ynyl)-7-methoxyisobenzofuran-1(3H)-one (417)

1,1,1-Triisopropyl-N-methyl-N-prop-2-yn-1-ylsilanamine (0.073 g, 0.33 mmols) was dissolved in THF (5 mL) and cooled to -78°C. A THF solution of n-butyllithium (2.5M, 0.16 mL, 0.34 mmols) was added as drops and the reaction mixture was stirred at -78°C for 0.5h. 7-(2-Bromoallyloxy)-4-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-carbaldehyde (0.10 g, 0.31 mmol) as a solution in THF (5 mL) was added drop-wise, and the reaction mixture was stirred at -78°C for a further 0.5h. This was allowed to warm to rt; saturated ammonium chloride solution (2 mL) and water (10 mL) were added and the aqueous was extracted with EtOAc (3 x 25 mL). The organic layers were combined, dried (Na₂SO₄) and solvent was removed under reduced pressure to give a crude orange solid (0.11 g). The crude solid was re-dissolved in MeCN (10 mL) and to this was added concentrated aqueous hydrofluouric acid (2.5 mL) in one portion. The reaction mixture was stirred for 0.5h and 10% K₂CO₃ solution (20 mL) was added. The aqueous was extracted with EtOAc (3 x 25 mL), organic layers combined, dried (Na₂SO₄) and solvent removed under reduced pressure giving an orange oil. This was purified via flash column chromatography (2.5% MeOH in DCM) to afford the title compound as a yellow solid (0.11 g, 89%).

Rᵣ = 0.10 (5% MeOH in DCM)

LRMS: (ESI⁺) m/z 398 (M+H, 100%), 396 (100), 224 (30), 208 (50), 180 (25).
Experimental Section

HRMS: (ESI+) Calculated for C$_{17}$H$_{19}$BrNO$_5$, m/z 396.0447 found 396.0453.

IR: (neat, ν cm$^{-1}$) 3237 (br), 2927, 2874, 1763, 1610, 1491, 1407, 1265, 1021.

δ$_H$: (500MHz, CDCl$_3$): 7.44 (1H, s, 2-CH), 6.02 (1H, d, $J = 1.76$Hz 12-H$_B$), 5.82 (1H, t, $J = 1.57$Hz, 13-CH), 5.72 (1H, d, $J = 1.76$Hz, 12-H$_A$), 5.26 (2H, s, 7-CH$_2$), 4.76 (2H, s, 10-CH$_2$), 4.10 (3H, s, 9-CH$_3$), 3.66 (2H, d, $J = 1.69$Hz, 16-CH$_2$), 2.63 (3H, s, 17-CH$_3$).

δ$_C$: (125MHz, CDCl$_3$): 168.34 (C8), 150.10 (C6), 147.82 (C3), 137.31 (C4), 135.67 (C1), 126.53 (C11), 119.62 (C12), 118.90 (C5), 117.17 (C2), 86.54 (C15), 79.93 (C14), 72.65 (C10), 67.55 (C7), 63.50 (C9), 59.18 (C13), 39.52 (C16), 34.02 (C17).
Experimental Section

Ethynyl(dimethyl)(phenyl)silane (408)

Prepared by a modification of the method by Fleming et al., and Hasegawa et al.\textsuperscript{[157,158]}

Chloro(dimethyl)phenylsilane (4.27 g, 25.0 mmols) was added to a stirring solution of ethynylmagnesium bromide (50 mL, 25 mmols) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Water (50 mL) was added and the aqueous was extracted with diethyl ether (3 x 100 mL). The organic combinations were washed (brine), dried (MgSO\textsubscript{4}) and solvent removed under reduced pressure. The resulting crude orange oil was purified via flash column chromatography (1% Et\textsubscript{2}O in petroleum ether) to give the title compound as a pure colourless oil (3.62 g, 91%).

R\textsubscript{f} = 0.65 (5% Et\textsubscript{2}O in 40-60 petroleum ether)

LRMS: (ESI+) m/z 160 (M+, 35%), 145 (100), 105 (20).

HRMS: (ESI+) Calculated for C\textsubscript{10}H\textsubscript{12}Si, m/z 160.0708 found 160.0707.

IR: (neat, ν cm\textsuperscript{-1}) 3074, 2963, 2038, 1431, 1252, 1119.

δ\textsubscript{H}: (400MHz, CDCl\textsubscript{3}): 7.65 (2H, m, 7-CH & 9-CH), 7.41 (3H, m, 8-CH & 6-CH & 10-CH), 2.53 (1H, s, 1-CH), 0.46 (6H, s, 4-CH\textsubscript{3} & 5-CH\textsubscript{3}).

δ\textsubscript{C}: (100MHz, CDCl\textsubscript{3}): 136.30 (C3), 133.77 (C7 & C9), 129.75 (C8), 128.10 (C6 & C10), 94.95 (C1), 88.30 (C2), 0.96 (C4 & C5).
**3-(Dimethyl(phenyl)silyl)propionic acid (409)**

![Structure of 3-(Dimethyl(phenyl)silyl)propionic acid](attachment:structure.png)

*Prepared by a modification of the method by Fleming et al.*[^159]

Ethynyldimethyl(phenyl)silane (3.00 g, 18.7 mmols) was slowly added to a solution of methyl magnesium chloride (12.0 mL, 37.4 mmols) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 1.5h. CO₂ was bubbled through the solution for 2h resulting in a white slurry. Saturated ammonium chloride solution (50 mL) was added and the aqueous was extracted with diethyl ether (3 x 100 mL). The organic combinations were washed (brine), dried (Na₂SO₄) and solvent removed under reduced pressure giving a crude yellow oil. This was purified via flash column chromatography (DCM) to give an off-white solid. (3.00 g, 79%).

Rᵣ = 0.05 (20% EtOAc in 40-60 petroleum ether)

Mp = 33 – 36°C

LRMS: (Cl⁺) m/z 222 (M+NH₄, 20%), 179 (30), 162 (65), 100 (100), 76 (55).

HRMS: (Cl⁺) Calculated for C₁₁H₁₆NO₂Si, m/z 222.0945 found 222.0925.

IR: (neat, ν cm⁻¹) 3196 (ν br.), 2961, 1681, 1557, 1358, 1252, 1115.

δH: (400MHz, CDCl₃): 7.56 (2H, s, 1-CH & 3-CH), 7.30 (3H, s, 2-CH & 4-CH & 6-CH), 0.39 (6H, s, 9-CH₃ & 10-CH₃).

δC: (100MHz, CDCl₃): 158.60 (C11), 135.34 (C5), 133.80 (C1 & C3), 129.67 (C2), 128.02 (C4 & C6), 99.94 (C8), 87.98 (C7), -1.55 (C9 & C10).
3-(Dimethyl(phenyl)silyl)-N-methyl-N-(prop-2-ynyl)propiolamide (406)

3-(Dimethyl(phenyl)silyl)propionic acid (1.30 g, 6.40 mmols) was dissolved in DCM (5 mL) at 0°C and to this was added oxalyl chloride (0.54 mL, 6.40 mmols). 10 drops of DMF were added and the reaction mixture was stirred for 0.25h. The reaction mixture was added, as drops, to a solution of N-methylpropargylamine (0.54 mL, 6.40 mmols) and triethylamine (1.07 mL, 7.70 mmols) in DCM (5 mL) at 0°C. The reaction mixture was stirred for 1.5h and water (25 mL) was added at 0°C. Aqueous was extracted with ethyl acetate (3 x 25 mL), organic washings were dried (Na₂SO₄) and solvent was removed under reduced pressure to give an orange oil. This was purified via flash column chromatography (DCM) to give the title compound as a pale yellow oil (1.14 g, 70%).

Rᵣ = 0.80 (5% MeOH in DCM)

LRMS: (ESI+) m/z 256 (M+H, 100%).

HRMS: (ESI+) Calculated for C₁₅H₁₈NOSi, m/z 256.1158 found 256.1161.

IR: (neat, v cm⁻¹) 3050, 2963, 1631, 1483, 1395, 1251, 1111.

δ₊H: (400MHz, CDCl₃): Peaks are doubled due to geometric isomers about the amide bond. 7.62 (2H, m, 1-CH & 3-CH), 7.41 (3H, m, 2-CH & 4-CH & 6-CH), 4.39 & 4.24 (2H, d, J=2.50Hz, 12-CH₂), 3.27 & 3.03 (3H, s, 15-CH₃), 2.33 & 2.23 (1H, t, J=2.50Hz, 14-CH), 0.50 (6H, s, 7-CH₃ & 8-CH₃).

δ₊C: (100MHz, CDCl₃): Peaks are doubled due to geometric isomers about the amide bond. 153.60 (C11), 135.14 (C5), 133.84 (C1 & C3), 130.07 (C2), 128.24 (C4 & C6), 96.99 (C10), 96.31 (C9), 77.60 (C13), 73.32 & 72.62 (C14), 40.81 & 35.35 (C12), 35.61 & 31.77 (C15), -1.39 (C7 & C8).
3-(Trimethylsilyl)propynoic acid (412)

Prepared by a modification of the method by Fleming et al.\textsuperscript{[159]}

Ethynyltrimethylsilane (1.00 g, 10.2 mmols) was slowly added to a solution of methyl magnesium chloride (3.0M, 4.07 mL, 12.2 mmols) in THF at 0°C. The reaction mixture was allowed to warm to rt and stirred for 0.5h. CO\textsubscript{2} was bubbled through the solution for 2h resulting in a white slurry. Saturated ammonium chloride solution (10 mL) was added and the aqueous was extracted with diethyl ether (3 x 50 mL). The organic combinations were washed (brine), dried (Na\textsubscript{2}SO\textsubscript{4}) and solvent removed under reduced pressure giving a crude white oil. This was purified via flash column chromatography (DCM) and crystallised at low temperature to give a white crystalline solid. (1.12 g, 77%).

R\textsubscript{f} = 0.10 (5% MeOH in DCM)

Mp = 39 – 40°C

LRMS: (Cl+) m/z 160 (M+NH\textsubscript{4}, 100%), 144 (20), 100 (35).

HRMS: (Cl+) Calculated for C\textsubscript{6}H\textsubscript{14}NO\textsubscript{2}Si, m/z 160.0794 found 160.0781.

IR: (neat, ν cm\textsuperscript{-1}) 3063 (v. br.), 2803, 2187, 1678, 1408, 1253.

δ\textsubscript{H}: (400MHz, CDCl\textsubscript{3}): 10.94 (1H, s, 2-OH), 0.26 (9H, s, 4-CH\textsubscript{3} & 5-CH\textsubscript{3} & 6-CH\textsubscript{3}).

δ\textsubscript{C}: (100MHz, CDCl\textsubscript{3}): 157.49 (C2), 97.71 (C3), 93.80 (C1), -0.84 (C4 & C5 & C6).
N-Methyl-N-(prop-2-ynyl)-3-(trimethylsilyl)propiolamide (413)

3-(Trimethylsilyl)propynoic acid (0.50 g, 3.50 mmols) was dissolved in DCM (35 mL) at 0°C and to this was added 1-chloro-N,N,2-trimethyl-1-propenylamine (0.47 mL, 3.50 mmols), as drops, and the reaction mixture was stirred at 0°C for 0.5h. N-Methylpropargylamine (0.22 mL, 3.85 mmols) was added and the reaction mixture was allowed to warm to room temperature and stir for 1h. This was filtered through a plug of silica gel, which was washed through with DCM (3 x 100 mL). Solvent was removed under reduced pressure giving the title compound as a colourless oil (0.53 g, 78%).

Rf = 0.80 (2.5% MeOH in DCM)

LRMS: (ESI+) m/z 194 (M+H, 100%), 155 (10).

HRMS: (ESI+) Calculated for C_{10}H_{16}NOSi, m/z 194.1001 found 194.0998.

IR: (neat, ν cm⁻¹) 2966, 1630, 1395, 1251, 1127.

δ_H: (400MHz, CDCl₃): Peaks are doubled due to geometric isomers about the amide bond. 4.39 & 4.24 (2H, d, J=2.71Hz, 4-CH₂), 3.27 & 3.02 (3H, s, 3-CH₃), 2.32 & 2.23 (1H, t, J=2.55Hz, 7-CH), 0.24 (9H, s, 8-CH₃ & 9-CH₃ & 10-CH₃).

δ_C: (100MHz, CDCl₃): Peaks are doubled due to geometric isomers about the amide bond. 153.75 (C2), 98.34 (C6), 95.67 (C1), 95.38 (C5), 73.24 & 72.55 (C7), 40.77 & 35.30 (C4), 35.58 & 31.66 (C3), -0.56 (C8 & C9 & C10).
3-(Dimethyl(phenyl)silyl)propionic acid (0.50 g, 2.40 mmols) and CDI (0.41 g, 2.52 mmols) were dissolved in DCM (5 mL) and stirred at 0°C for 1h. N-Methylpropargylamine (0.15 g, 2.17 mmols) was added at 0°C and the reaction mixture was allowed to warm to rt before stirring for 24h. Saturated aqueous NH₄Cl solution (15 mL) was added, organic layer separated and washed (water/brine), dried (MgSO₄) and solvent was removed under reduced pressure to give a crude orange oil. This was purified via flash column chromatography (0-3% MeOH in DCM) to give the title compound as an orange oil (0.120 g, 34%).

Rᶠ = 0.30 (2.5% MeOH in DCM)

LRMS: (EI+) m/z 163 (M+, 45%), 106 (30), 96 (100).

HRMS: (EI+) Calculated for C₈H₉N₃O, m/z 163.0746 found 163.0743.

IR: (neat, ν cm⁻¹) 3289, 3124, 2936, 2119, 1688, 1451, 1399, 1282.

δH: (400MHz, CDCl₃): 7.98 (1H, s, 4-CH), 7.33 (1H, s, 2-CH), 7.11 (1H, s, 3-CH), 4.18 (2H, s, 5-CH₂), 3.18 (3H, s, 6-CH₃); 2.42 (1H, t, J=2.53Hz, 8-CH).

δC: (100MHz, CDCl₃): 151.51 (C1), 137.20 (C4), 130.03 (C3), 118.10 (C2), 77.24 (C7), 74.16 (C8), 40.36 (C5), 36.21 (C6).
**Experimental Section**

1,1,1-Triisopropyl-N-methyl-N-(prop-2-ynyl)silanamine

Prepared by a modification of the procedure by Faggiani.\[102\]

N-Methylpropargylamine (1.00 g, 14.5 mmols) and triethylamine (3.00 mL, 21.7 mmols) were dissolved in DCM (20 mL) and cooled to 0°C. Triisopropylsilyl trifluoromethanesulfonate (3.95 mL, 14.7 mmols) was added drop-wise and the reaction mixture was stirred at rt for 18h. This was then washed with 10% aqueous K$_2$CO$_3$ solution (40 mL), dried (Na$_2$SO$_4$) and solvent was removed under reduced pressure to afford a crude brown oil. The product was distilled under reduced pressure (117 – 120°C at 15Torr) to give the title compound as a colourless oil (2.00 g, 61%).

$R_f$ = Unstable on silica gel.

LRMS: (EI+) $m/z$ 225 (M+, 20%), 182 (100), 111 (40).

HRMS: (EI+) Calculated for C$_{13}$H$_{27}$NSi, $m/z$ 225.1913 found 225.1906.

IR: (neat, $\nu$ cm$^{-1}$) 2945, 2869, 2351, 1466.

$\delta$H: (400MHz, CDCl$_3$): 3.57 (2H, d, $J$=2.41Hz, 2-CH$_2$), 2.61 (3H, s, 1-CH$_3$), 2.15 (1H, t, $J$=2.37Hz, 4-CH), 1.13 (3H, m, 5-CH & 6-CH & 7-CH), 1.06 (18H, d, $J$=6.38Hz, 8-CH$_3$ & 9-CH$_3$ & 10-CH$_3$ & 11-CH$_3$ & 12-CH$_3$ & 13-CH$_3$).

$\delta$C: (100MHz, CDCl$_3$): 83.42 (C3), 70.20 (C4), 40.77 (C2), 36.34 (C1), 18.45 (C8 & C9 & C10 & C11 & C12 & C13), 12.20 (C5 & C6 & C7).
**Experimental Section**

**tert-Butyl methyl(prop-2-ynyl)carbamate**

![Chemical Structure](image)

*Prepared by a modification of the procedure by Board.*[97]

Sodium hydride (0.28 g, 11.6 mmol) was suspended in THF (25.6 mL) and DMPU (6.4 mL) at 0°C. *tert*-Butyl prop-2-ynylcarbamate (1.64 g, 10.6 mmol) was added as a solution in THF (16 mL) and the reaction mixture was stirred for 1 h at 0°C. Methyl iodide (1.80 g, 12.7 mmol) was added slowly over 5 minutes and the reaction mixture was allowed to warm to rt and was stirred for 24 h. This was poured onto saturated NaHCO$_3$ solution (50 mL) and then water (60 mL) and brine (40 mL) were added. The aqueous was extracted with diethyl ether (3 x 100 mL), which was dried (Na$_2$SO$_4$) and solvent was removed under reduced pressure to give a crude orange oil. This was purified *via* flash column chromatography to afford the title compound as a colourless oil (1.48 g, 82%).

$R_f = 0.50$ (10% EtOAc in 40-60 petroleum ether)

LRMS: (Cl+) $m/z$ 170 (M+H, 20%), 131 (100), 114 (20), 70 (20).

HRMS: (Cl+) Calculated for C$_9$H$_{16}$NO$_2$, $m/z$ 170.1181 found 170.1189.

IR: (neat, $\nu$ cm$^{-1}$) 3254, 2977, 2110, 1692, 1480, 1389, 1247.

$\delta_H$: (400MHz, CDCl$_3$): 4.04 (2H, s, 2-CH$_2$), 2.91 (3H, s, 1-CH$_3$), 2.21 (1H, t, $J$=2.44Hz, 5-CH), 1.47 (9H, s, 7-CH$_3$ & 8-CH$_3$ & 9-CH$_3$).

$\delta_C$: (100MHz, CDCl$_3$): 155.27 (C3), 80.32 (C6), 79.35 (C4), 71.70 (C5), 37.76 (C2), 33.59 (C1), 28.50 (C7 & C8 & C9).
2-(2-Bromophenyl)-1,3-dimethylimidazolidine (330)

Prepared by a modification of the procedure by Parsons et al.\textsuperscript{[14]}

2-Bromobenzaldehyde (10.1 g, 55.0 mmols) was dissolved in ethanol (100 mL) at rt and to this was added \(N,N\)′-dimethylethylenediamine (7.00 mL, 66.0 mmols), in one portion. This was stirred at rt for 24h, dried (MgSO\(_4\)), and solvent removed under reduced pressure giving a crude orange oil. This was purified \textit{via} distillation (164°C at 15Torr), giving the title compound as a yellow oil (12.9 g, 92%).

\(\text{R}_f = 0.20\) (2.5% MeOH in DCM)

LRMS: (ESI+) \(m/z\) 255 (M+H, 95%), 199 (15).

HRMS: (ESI+) Calculated for C\(_{11}\)H\(_{16}\)BrN\(_2\), \(m/z\) 255.0497 found 255.0490.

IR: (neat, \(\nu\) cm\(^{-1}\)) 1622, 1419, 1192, 904.

\(\delta\)\(_H\): (400MHz, CDCl\(_3\)): 7.71 (1H, dd, \(J = 1.79\)Hz, 7.90Hz, 6-CH), 7.51 (1H, d, \(J = 7.84\)Hz, 3-CH), 7.34 (1H, t, \(J = 7.38\)Hz, 2-CH), 7.15 (1H, td, \(J = 1.88, 7.69\)Hz, 1-CH), 4.06 (1H, s, 7-CH), 3.38 (2H, m, 9/8-CH\(_A\)), 2.64 (2H, m, 9/8-CH\(_B\)), 2.23 (6H, s, 10-CH\(_3\) \& 11-CH\(_3\)).

\(\delta\)\(_C\): (100MHz, CDCl\(_3\)): 138.77 (C4), 132.34 (C3), 131.09 (C6), 129.76 (C1), 128.05 (C2), 125.63 (C5), 88.51 (C7), 53.64 (C8 \& C9), 39.59 (C10 \& C11).
Experimental Section

**tert-Butyl 4-(2-(2-bromoallyl)phenyl)-4-hydroxybut-2-ynyl(methyl)carbamate (331)**

![Chemical Structure](image)

*Prepared by a modification of the procedure by Parsons et al.*[14]

2-(2-Bromophenyl)-1,3-dimethylimidazolidine (2.50 g, 10.0 mmols) was dissolved in THF (25 mL) and cooled to -78°C. n-Butyllithium (4.20 mL, 10.5 mmmols) was added drop-wise as a solution in hexanes and the reaction mixture was stirred for 20 minutes. Cuprous cyanide (0.94 g, 10.5 mmmols) was added portion-wise, the reaction mixture was heated to 38°C and allowed to stir for 1.5h. This was cooled to -78°C and 2,3-dibromopropene (1.17 mL, 12.0 mmmols) was added drop-wise. The reaction mixture was allowed to warm to rt and saturated NH₄Cl solution (25 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 50 mL), organic combinations washed (Brine then 2M HCl), washed again (NHCO₃ then Brine) and dried (MgSO₄). Solvent was removed under reduced pressure to give a crude orange oil, which was purified *via* distillation to give the 2-(2-bromoallyl)benzaldehyde as an orange oil (0.50 g, 22%).

**tert-Butyl methyl(prop-2-ynyl)carbamate (0.39 g, 2.30 mmmols)** was dissolved in THF (35 mL) and cooled to -78°C. n-Butyllithium (0.96 mL, 2.40 mmmols) was added drop wise as a solution in hexanes and the reaction mixture was stirred for 0.5h. 2-(2-bromoallyl)benzaldehyde (0.50 g, 2.20 mmmols) was added drop wise and the reaction mixture was allowed to stir for 0.75h. 2-Bromo-2-methylpropane (0.45 g, 3.30 mmmols) was added and the reaction mixture was allowed to warm to rt. This was then partitioned between water (30
mL) and diethyl ether (30 mL). The aqueous was extracted with diethyl ether (3 x 50 mL),
organics were washed (brine), dried (MgSO₄) and solvent was removed under reduced
pressure to give a crude orange oil. This was purified via flash column chromatography (10% 
EtOAc in petroleum ether) to give the title compound as a yellow oil (0.52 g, 13%).

Rf = 0.21 (10% EtOAc in 40-60 petroleum ether)

LRMS: (ESI+) m/z 418 (M+Na, 40%), 416 (40), 395 (42), 354 (100), 258 (50).

HRMS: (ESI+) Calculated for C₁₉H₂₄BrNO₃Na, m/z 416.0837 found 416.0824.

IR: (neat, ν cm⁻¹) 3353, 3060, 2925, 1686, 1628, 1560.

δH: (400MHz, CDCl₃): 7.70 (1H, m, 6-CH), 7.33 (2H, m, 1-CH & 2-CH), 7.24 (1H, s, 3-CH), 
5.66 (1H, s, 10-CH), 5.54 (1H, s, 9-H_B), 5.44 (1H, s, 9-H_A), 4.13 (2H, s, 13-CH₂), 3.95 (2H, 
m, 7-CH₂), 2.91 (3H, s, 14-CH₃), 1.46 (9H, s, 17-CH₃ & 18-CH₃ & 19-CH₃).

δC: (100MHz, CDCl₃): 155.37 (C15), 138.76 (C5), 135.04 (C4), 132.06 (C8), 130.89 (C3), 
128.93 (C1), 127.87 (C2), 127.41 (C6), 118.59 (C9), 82.90 (C12), 82.74 (C11), 80.35 (C16), 
62.19 (C10), 44.28 (C7), 38.75 (C13), 33.90 (C14), 28.51 (C17 & C18 & C19).
1,1,1-Triisopropyl-N-methyl-N-prop-2-yn-1-ylsilanamine (0.71 g, 3.15 mmols) was dissolved in THF (25 mL) and cooled to -78°C. 2.5M n-butyllithium solution (1.50 mL, 3.30 mmols) was added drop-wise and the reaction mixture was stirred at -78°C for 0.5h. 2,4-Dimethoxybenzaldehyde (0.50 g, 3.00 mmols) as a solution in THF (15 mL) was added as drops, and the reaction mixture was stirred at -78°C for a further 0.5h. This was allowed to warm to room temperature; saturated ammonium chloride solution (2 mL) and water (10 mL) were added and the aqueous was extracted with EtOAc (3 x 25 mL). The organic layers were combined, dried (Na₂SO₄) and solvent was removed under reduced pressure to give a crude yellow oil (1.20 g). The crude solid was re-dissolved in THF (60 mL) and to this was added tetrabutylammonium fluoride trihydrate (0.98 g, 3.10 mmols) in one portion. The reaction mixture was stirred for 0.5h and water (60 mL) was added. The aqueous was extracted with EtOAc (3 x 100 mL), organic layers combined, dried (Na₂SO₄) and solvent removed under reduced pressure giving a crude orange oil. This was purified via flash column chromatography (5% MeOH in DCM) to afford the title compound as a waxy yellow solid (0.51 g, 72%).

R_f = 0.20 (10% MeOH in DCM)

LRMS: (ESI+) m/z 236 (M+H, 90%), 218 (95).

HRMS: (ESI+) Calculated for C_{13}H_{18}NO_{3}, m/z 236.1287 found 236.1297.

IR: (neat, ν cm⁻¹) 3263 (br), 2939, 2839, 2661, 2566, 1607, 1589, 1505, 1458, 1300.
δ<sub>H</sub>: (400MHz, CDCl<sub>3</sub>): 7.49 (1H, d, J = 7.89Hz, 5-CH), 6.50 (1H, d, J = 3Hz, 2-CH), 6.47 (1H, m, 3-CH), 5.69 (1H, t, J = 1.81Hz, 7-CH), 3.86 (3H, s, 12-CH<sub>3</sub>), 3.81 (3H, s, 13-CH<sub>3</sub>), 3.51 (2H, s, 10-CH<sub>2</sub>), 2.51 (3H, s, 11-CH<sub>3</sub>), 2.02 (2H, s, 7-OH & 10-NH).

δ<sub>C</sub>: (100MHz, CDCl<sub>3</sub>): 161.26 (C4), 157.96 (C6), 128.85 (C5), 121.76 (C1), 104.36 (C2), 98.97 (C3), 83.64 (C8 & C9), 60.73 (C7), 55.59 (C12 & C13), 40.35 (C10), 35.19 (C11).
4-(2,4-Dimethoxyphenyl)-N-methyl-N-(prop-2-ynyl)-4-(triisopropylsilyloxy)but-2-ynamide (420)

\[ \text{\textit{N}-methyl-\textit{N}-(prop-2-ynyl)-3-(trimethylsilyl)propiolamide (0.10 g, 0.50 mmols), zinc bromide (0.02 g, 0.10 mmols) and 2,4-dimethoxybenzaldehyde (0.17 g, 1.00 mmols) were dissolved in diethyl ether (5 mL) at rt and stirred for 0.25h. \textit{N}-Ethylidiosypropylamine (0.17 mL, 1.00 mmols) was added drop-wise followed by the addition of triisopropylsilyl trifluoromethanesulfonate (0.16 mL, 0.60 mmols) and the reaction mixture was stirred at rt for 1h. This was filtered through a plug of silica gel, eluting with diethyl ether (100 mL). Solvent was removed under reduced pressure to give a crude orange oil, which was purified via flash column chromatography (25% EtOAc in petroleum ether) to give the title compound as a yellow oil (0.11 g, 50%).} \]

\[ \text{R}_f = 0.25 \text{ (25\% EtOAc in 40-60 petroleum ether)} \]

\[ \text{LRMS: (ESI+)} \quad m/z \text{ 466 (M+Na, 40\%), 270 (100).} \]

\[ \text{HRMS: (ESI+) Calculated for } C_{25}H_{37}NO_4SiNa, m/z \text{ 466.2390 found 466.2383.} \]

\[ \text{IR: (neat, } \nu \text{ cm}^{-1}) \quad 2939 \text{ (br), 2865, 2105, 1636, 1504, 1462, 1398, 1207.} \]

\[ \delta_{\text{H}}: (400\text{MHz, CDCl}_3): 7.53 \text{ (1H, d, } J=7.82\text{Hz, 5-CH}), 6.51 \text{ (1H, m, 2-CH), 6.41 \text{ (1H, m, 3-CH), 5.80 \text{ (1H, m, 9-CH), 4.39 & 4.25 \text{ (2H, m, 23-CH}_2), 3.80 \text{ (6H, s, 7-CH}_3 & 8-CH}_3), 3.21 & 2.98 \text{ (3H, s, 22-CH}_3), 2.34 & 2.25 \text{ (1H, t, } J=2.49\text{Hz, 25-CH), 1.15 \text{ (3H, m, 11-CH & 12-CH & 13-CH), 1.05 \text{ (18H, m, 14-CH}_3 to 19-CH}_3).} \]

\[ \delta_{\text{C}}: (100\text{MHz, CDCl}_3): 160.54 \text{ (C4), 156.47 \text{ (C6), 153.02 \text{ (C21), 127.90 \text{ (C5), 123.19 \text{ (C1), 104.65 \text{ (C2), 98.27 \text{ (C3), 87.30 \text{ (C10), 86.65 \text{ (C24), 75.42 \text{ (C20) 73.50 & 72.75 \text{ (C25), 58.71.} \]

164
(C9), 55.49 (C7 & C8), 41.19 & 35.75 (C23), 35.40 & 31.70 (C22), 18.10 (C14 to C19), 12.33 (C11 to C13).
Experimental Section

2,3-Dibromopropene

Prepared by a modification of the procedure by Lespieau et al.\textsuperscript{[186]}

1,2,3-Tribromopropane (100 g, 356 mmols) was stirred with sodium hydroxide (24.9 g, 623 mmols) and water (10 mL) in a flask attached to a vigreux column and distillation apparatus, with the collection flask placed in an ice bath. The reaction mixture was heated to reflux with the product collected as the distillate with water (Bp 95°C under an atmosphere of nitrogen). The product was separated from the aqueous layer, dried over Na\textsubscript{2}SO\textsubscript{4} and filtered to afford the title compound as colourless oil (48.8 g, 70%).

LRMS: (EI+) \textit{m/z} 202 (M+, 10\%), 200 (15), 198 (10), 121 (15), 84 (100).

HRMS: (EI+) Calculated for C\textsubscript{3}H\textsubscript{4}Br\textsubscript{2}, \textit{m/z} 197.8680 found 197.8676.

IR: (neat, \textit{\nu} cm\textsuperscript{-1}) 1736, 1622, 1419, 1192, 1103, 904.

\[ \delta_{\text{H}}: \text{(400MHz, CDCl}\textsubscript{3}): 6.05 (1\text{H, s, 1-H}_B), 5.64 (1\text{H, s, 1-H}_A), 4.21 (2\text{H, s, 3-CH}_2). \]

\[ \delta_{\text{C}}: \text{(100MHz, CDCl}_3): 127.63 (\text{C2}), 121.19 (\text{C1}), 36.79 (\text{C3}) \]
Experimental Section

\(N\)-[4-(2-Bromophenyl)-4-hydroxybut-2-yn-1-yl]-N-methyl-3-(trimethylsilyl)prop-2-ynamide (427)

\[
\begin{array}{c}
\text{\includegraphics[width=0.5\textwidth]{image}}
\end{array}
\]

1-(\(\alpha\)-Bromophenyl)-4-(methylamino)-2-butyn-1-ol hydrochloride (0.10 g, 0.36 mmol) and 3-(Trimethylsilyl)propynoic acid (0.06 g, 0.39 mmol) were dissolved in hexamthylidisilazane (1.50 mL) and toluene (1.50 mL) and heated in a microwave at 180\(^{\circ}\)C for 2h. The reaction mixture was allowed to cool and solvent was removed under reduced pressure and purification via flash column chromatography gave the title compound as an orange oil. (0.14 g, 95%).

R\(_f\) = 0.30 (5% MeOH in DCM)

LRMS: (ESI+) \(m/z\) 297 (M+, 80%), 224 (75), 208 (100).

IR: (neat, \(\nu\) cm\(^{-1}\)) 3205, 2962, 2453, 1700, 1575, 1348, 1254, 1022, 933.

\(\delta\)\(_H\): (400MHz, CDCl\(_3\)): 7.75 (1H, d, \(J = 7.72\)Hz, 3-CH), 7.52 (1H, d, \(J = 7.71\)Hz, 6-CH), 7.35 (1H, t, \(J = 7.6\)Hz, 2-CH), 7.16 (1H, t, \(J = 7.70\)Hz, 1-CH), 5.76 (1H, s, 7-CH), 3.81 (2H, s, 10-CH\(_2\)), 3.48 (1H, s, 7-OH), 2.75 (3H, s, 11-CH\(_3\)), 0.20 (9H, s, 15CH\(_3\) & 16CH\(_3\) & 17CH\(_3\))

\(\delta\)\(_C\): (100MHz, CDCl\(_3\)): 158.79 (C12), 139.22 (C4), 132.98 (C3), 129.89 (C1), 128.46 (C6), 128.10 (C2), 122.48 (C5), 99.37 (C13), 88.82 (C14), 88.63 (C8), 75.73 (C9), 63.42 (C7), 38.62 (C10), 32.50 (C11), -0.39 (C15 & C16 & C17)
2-(1-Hydroxy-1-methyl-ethyl)-4,5,5-trimethyl-tetrahydro-furan-2,4-diol (353)

3-Hydroxy-3-methyl-2-butanone (5.14 g, 50.1 mmol) was added as drops to a stirring solution of sodium hydride (3.61 g, 150 mmol) in anhydrous diethyl ether (140 mL). The reaction mixture was stirred for 6 hours and then saturated NH₄Cl(aq) solution (60 mL) and H₂O (60 mL) were added. The aqueous layer was washed with diethyl ether (3 x 60 mL), which was dried over magnesium sulfate. The solvent was removed under reduced pressure leaving thick yellow oil that was crystallized from dissolving in minimal 40/60 petrol to give white, needle-like crystals (2.41 g, 47%).

Rₘ = 0.04 (30% Et₂O in Hexanes)

IR (neat, ν cm⁻¹) 3372, 2974, 2933, 1386, 1117.

HRMS: (ESI+) calculated for C₁₀H₂₀O₄Na, m/z 227.2700, found 227.1244.

δ_H: (400MHz, CDCl₃): 1.25 (s, 6H); 1.28 (s, 3H); 1.41 (s, 3H); 1.64 (s, 2H); 1.75 (s, 3H); 2.14 (s, 1-OH); 3.09 (s, 1-OH); 5.41 (s, 1-OH).

δ_C: (100MHz, CDCl₃): 119.91 (C); 87.89 (C); 74.32 (C); 28.22 (CH₃); 25.56 (CH₃); 25.11 (CH₃); 24.17 (CH₃); 11.94 (CH₂).
10-(1-Hydroxy-1-methyl-ethyl)-2,2,3,8,8,13,13-heptamethyl-1,9,12-trioxa-
dispiro[4.1.4.2]tridec-3-en-10-ol (5)

![Chemical Structure](attachment:image.png)

A mixture of 3-hydroxy-3-methyl-2-butane (3.02 g, 29.4 mmol) and ethyl formate (2.16 g, 29.4 mmol) was added as drops to a stirring solution of sodium hydride (2.20 g, 88.1 mmol) in diethyl ether (140 mL). The mixture was stirred for 3 hours and saturated NH$_4$Cl solution (20 mL) and H$_2$O (20 mL) were added. The aqueous layer was washed with diethyl ether (3 x 60 mL), which was dried over Na$_2$SO$_4$. This was filtered and the organic filtrate was concentrated under reduced pressure (to approximately 100 mL), which was then stirred with anhydrous CuSO$_4$ (3.6 g) and HCl$_{(conc.)}$ (0.5 mL) for 2 hours. Water was added and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The solvent was removed under reduced pressure leaving pale green oil. This was purified via column chromatography (40% diethyl ether in hexanes) producing a colourless crystalline solid upon re-crystallization from ethyl acetate (0.48 g, 18%).

$R_f = 0.22$ (30% Et$_2$O in Hexanes)

Mp = 118.2 - 121.2°C

IR: (neat, ν cm$^{-1}$) 3473, 2971, 2930, 1461, 1421, 1379.

HRMS: (ESI+) calculated for C$_{20}$H$_{34}$O$_5$Na, m/z 377.4900, found 377.2299.

δ$^H$: (500MHz, CDCl$_3$): 5.14 (s, 1H); 4.99 (s, 1H, -OH); 2.39 (s, 2H); 2.18 and 1.74 (dd, 2H); 1.70 (s, 3H); 1.53 (s, 1H, -OH); 1.31 (s, 3H); 1.23 (s, 3H); 1.28 (s, 3H); 1.27 (s, 3H); 1.26 (s, 3H); 1.20 (s, 3H); 1.13 (s, 3H); 1.07 (s, 3H).

δ$^C$: (100MHz, CDCl$_3$): 146.00 (C); 120.32 (CH); 108.04 (C); 96.47 (C); 91.18 (C); 88.23 (C); 86.34 (C); 85.63 (C); 72.18 (C); 44.12 (CH$_2$); 43.04 (CH$_2$); 28.13 (CH$_3$); 27.95 (CH$_3$); 27.01 (CH$_3$); 26.33 (CH$_3$); 24.28 (CH$_3$); 24.03 (CH$_3$); 23.85 (CH$_3$); 23.01 (CH$_3$); 11.97 (CH$_3$).
1,3,3,4,6,6-Hexamethyl-2,5,7-trioxo-bicyclo[2.2.1]heptanes (442)

Gold (III) chloride (0.15 g, 0.49 mmol) was dissolved in diethyl ethyl (20 mL) producing a pale orange solution. To this was added 3-methyl-3-hydroxy-2-butanone (1.00 g, 9.80 mmol), which was stirred together for 24 hours. A saturated solution of \(\text{NH}_4\text{Cl(aq)}\) (20 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 15 mL), organic fractions were washed with water and then dried over magnesium sulphate. The solvent was removed under reduced pressure giving an orange oil, which was purified using flash column chromatography (30% diethyl ether in hexanes). Mainly starting material was retrieved from the column apart from initial eluting compound, which gave the product as a pale yellow oil (0.10 g, 11%).

\(R_f = 0.66\) (30% \(\text{Et}_2\text{O}\) in hexanes).

LRMS: (ESI+) \(m/z\) 209 (M+, 10%), 191, 175, 151, 140.

HRMS: (ESI+) calculated for \(\text{C}_{10}\text{H}_{18}\text{O}_3\text{Na}\), \(m/z\) 209.2392, found 209.1148.

IR: (neat, \(\nu\text{ cm}^{-1}\)) 2971, 2930, 2864, 1384, 1136, 1139.

\(\delta_H\): (500MHz, CDCl\(_3\)): 1.45 (6H, s, 1-CH\(_3\)), 1.37 (6H, s, 2-CH\(_3\)), 1.18 (6H, s, 3-CH\(_3\)).

\(\delta_C\): (100MHz, CDCl\(_3\)): 109.41 (C5), 85.91 (C4), 26.71 (C3), 20.40 (C2), 14.31 (C1).
4. References
References

References

References


References

References


5. Appendices
## Appendices

### Table 1. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>Compound No. <strong>353</strong></td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C\textsubscript{10}H\textsubscript{20}O\textsubscript{4}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>204.26</td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>\textit{P c a} 2\textsubscript{l} (No. 29)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>17.506(4) Å</td>
</tr>
<tr>
<td>α</td>
<td>90°</td>
</tr>
<tr>
<td>b</td>
<td>6.8031(14) Å</td>
</tr>
<tr>
<td>β</td>
<td>90°</td>
</tr>
<tr>
<td>c</td>
<td>9.6174(19) Å</td>
</tr>
<tr>
<td>γ</td>
<td>90°</td>
</tr>
<tr>
<td>Volume</td>
<td>1145.4(4) Å\textsuperscript{3}</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.19 Mg/m\textsuperscript{3}</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.09 mm\textsuperscript{-1}</td>
</tr>
<tr>
<td>F(000)</td>
<td>448</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.30 x 0.20 x 0.06 mm\textsuperscript{3}</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.79 to 26.34°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-21 &lt;= h &lt;= 21, -8 &lt;= k &lt;= 8, -11 &lt;= l &lt;= 12</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>15647</td>
</tr>
<tr>
<td>Independant reflections</td>
<td>1242 [R(int) = 0.059]</td>
</tr>
<tr>
<td>Completeness to theta = 26.34°</td>
<td>99.5%</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F\textsuperscript{2}</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1242 / 1 / 139</td>
</tr>
<tr>
<td>Goodness-of-fit on F\textsuperscript{2}</td>
<td>1.060</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.038, wR2 = 0.099</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.043, wR2 = 0.102</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.27 and -0.18 e. Å\textsuperscript{3}</td>
</tr>
</tbody>
</table>

Hydrogens on oxygen atoms located and refined, all others in calculated positions. Stereochemistry at C2 and C3 unknown and not defined. The molecules are linked into chains \textit{via} O2-H2x•••O4 hydrogen bonds.

Table 2. Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$ x 10$^3$) for 353. U(eq) is defined as one third of the trace of the orthogonalized U$_{ij}$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>4307(1)</td>
<td>3615(2)</td>
<td>3025(2)</td>
<td>26(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>3923(1)</td>
<td>423(3)</td>
<td>5050(2)</td>
<td>31(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>5135(1)</td>
<td>3086(3)</td>
<td>4589(2)</td>
<td>30(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>5533(1)</td>
<td>3183(3)</td>
<td>1182(2)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>3670(1)</td>
<td>2236(3)</td>
<td>2940(3)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>3997(1)</td>
<td>303(3)</td>
<td>3551(3)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>4840(1)</td>
<td>480(3)</td>
<td>3202(3)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>4990(1)</td>
<td>2672(3)</td>
<td>3454(3)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>3464(2)</td>
<td>2044(4)</td>
<td>1417(3)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>3009(2)</td>
<td>3088(4)</td>
<td>3766(3)</td>
<td>38(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>3613(1)</td>
<td>-1561(3)</td>
<td>3043(3)</td>
<td>33(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>5664(1)</td>
<td>3550(3)</td>
<td>2640(3)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>5726(1)</td>
<td>5750(3)</td>
<td>2903(3)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>6404(1)</td>
<td>2498(4)</td>
<td>3021(4)</td>
<td>35(1)</td>
</tr>
</tbody>
</table>

Table 3. Bond lengths [Å] and angles [°] for 353.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length/°</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(4)</td>
<td>1.418(3)</td>
</tr>
<tr>
<td>O(1)-C(1)</td>
<td>1.460(3)</td>
</tr>
<tr>
<td>O(2)-C(2)</td>
<td>1.450(3)</td>
</tr>
<tr>
<td>O(3)-C(4)</td>
<td>1.431(3)</td>
</tr>
<tr>
<td>O(4)-C(8)</td>
<td>1.443(3)</td>
</tr>
<tr>
<td>C(1)-C(5)</td>
<td>1.514(4)</td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.520(4)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.549(3)</td>
</tr>
<tr>
<td>C(2)-C(7)</td>
<td>1.516(3)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.519(3)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.534(3)</td>
</tr>
<tr>
<td>C(4)-C(8)</td>
<td>1.536(3)</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.522(3)</td>
</tr>
<tr>
<td>C(8)-C(10)</td>
<td>1.526(3)</td>
</tr>
<tr>
<td>C(4)-O(1)-C(1)</td>
<td>111.67(16)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(5)</td>
<td>106.9(2)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(6)</td>
<td>107.9(2)</td>
</tr>
<tr>
<td>C(5)-C(1)-C(6)</td>
<td>110.9(2)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)</td>
<td>104.06(17)</td>
</tr>
<tr>
<td>C(5)-C(1)-C(2)</td>
<td>112.4(2)</td>
</tr>
<tr>
<td>C(6)-C(1)-C(2)</td>
<td>114.0(2)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(7)</td>
<td>109.1(2)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)</td>
<td>107.6(2)</td>
</tr>
<tr>
<td>C(7)-C(2)-C(3)</td>
<td>115.2(2)</td>
</tr>
</tbody>
</table>
## Appendices

<table>
<thead>
<tr>
<th>Bond</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(2)-C(2)-C(1)</td>
<td>107.2(2)</td>
</tr>
<tr>
<td>C(7)-C(2)-C(1)</td>
<td>115.1(2)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>101.94(18)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)</td>
<td>102.05(17)</td>
</tr>
<tr>
<td>O(1)-C(4)-O(3)</td>
<td>109.9(2)</td>
</tr>
<tr>
<td>O(1)-C(4)-C(3)</td>
<td>104.44(18)</td>
</tr>
<tr>
<td>O(3)-C(4)-C(3)</td>
<td>112.0(2)</td>
</tr>
<tr>
<td>O(1)-C(4)-C(8)</td>
<td>108.82(19)</td>
</tr>
<tr>
<td>O(3)-C(4)-C(8)</td>
<td>106.21(19)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(8)</td>
<td>115.4(2)</td>
</tr>
<tr>
<td>O(4)-C(8)-C(9)</td>
<td>110.1(2)</td>
</tr>
<tr>
<td>O(4)-C(8)-C(10)</td>
<td>106.7(2)</td>
</tr>
<tr>
<td>C(9)-C(8)-C(10)</td>
<td>111.1(2)</td>
</tr>
<tr>
<td>O(4)-C(8)-C(4)</td>
<td>107.86(19)</td>
</tr>
<tr>
<td>C(9)-C(8)-C(4)</td>
<td>110.7(2)</td>
</tr>
<tr>
<td>C(10)-C(8)-C(4)</td>
<td>110.3(2)</td>
</tr>
</tbody>
</table>
Table 1. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>Compound No.</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C(<em>{20})H(</em>{34})O(_{5})</td>
<td></td>
</tr>
<tr>
<td>Formula weight</td>
<td>354.47</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
<td></td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
<td></td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
<td></td>
</tr>
<tr>
<td>Space group</td>
<td>p(\overline{1}) (No.2)</td>
<td></td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a = 8.2155(4) Å</td>
<td>(\alpha = 66.768(3)°)</td>
<td></td>
</tr>
<tr>
<td>b = 10.4976(6) Å</td>
<td>(\beta = 86.596(3)°)</td>
<td></td>
</tr>
<tr>
<td>c = 13.0102(8) Å</td>
<td>(\gamma = 79.424(3)°)</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>1013.44(10) Å(^3)</td>
<td></td>
</tr>
<tr>
<td>Z</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.16 Mg/m(^3)</td>
<td></td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.08 mm(^{-1})</td>
<td></td>
</tr>
<tr>
<td>F(000)</td>
<td>388</td>
<td></td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.19 x 0.18 x 0.17 mm(^3)</td>
<td></td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.41 to 27.49°</td>
<td></td>
</tr>
<tr>
<td>Index ranges</td>
<td>-10&lt;=h&lt;=10, -13&lt;=k&lt;=13, -16&lt;=l&lt;=16</td>
<td></td>
</tr>
<tr>
<td>Reflections collected</td>
<td>15948</td>
<td></td>
</tr>
<tr>
<td>Independant reflections</td>
<td>4606 [R(int) = 0.070]</td>
<td></td>
</tr>
<tr>
<td>Completeness to theta = 26.34°</td>
<td>99.1%</td>
<td></td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F(^2)</td>
<td></td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4606 / 0 / 362</td>
<td></td>
</tr>
<tr>
<td>Goodness-of-fit on F(^2)</td>
<td>0.959</td>
<td></td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.051, wR2 = 0.101</td>
<td></td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.097, wR2 = 0.119</td>
<td></td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.28 and -0.19 e. Å(^{-3})</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å² x 103) for 5. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>5902(1)</td>
<td>9578(1)</td>
<td>2377(1)</td>
<td>27(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>8256(1)</td>
<td>6928(1)</td>
<td>3689(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>9980(1)</td>
<td>5250(1)</td>
<td>2404(1)</td>
<td>32(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>11330(2)</td>
<td>6988(1)</td>
<td>2465(1)</td>
<td>38(1)</td>
</tr>
<tr>
<td>O(5)</td>
<td>10121(2)</td>
<td>6306(2)</td>
<td>127(1)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>4481(2)</td>
<td>10695(2)</td>
<td>2160(1)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>3217(2)</td>
<td>10022(2)</td>
<td>2990(2)</td>
<td>33(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>3839(2)</td>
<td>8700(2)</td>
<td>3593(2)</td>
<td>34(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>5555(2)</td>
<td>8289(2)</td>
<td>3239(1)</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>5011(3)</td>
<td>11898(2)</td>
<td>2361(2)</td>
<td>45(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>3914(3)</td>
<td>11174(3)</td>
<td>956(2)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>1518(3)</td>
<td>10820(3)</td>
<td>3021(2)</td>
<td>45(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>5780(2)</td>
<td>7154(2)</td>
<td>2758(2)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>7646(2)</td>
<td>6719(2)</td>
<td>2750(1)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>6948(2)</td>
<td>7683(2)</td>
<td>4148(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>7661(3)</td>
<td>8796(2)</td>
<td>4349(2)</td>
<td>45(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>6400(3)</td>
<td>6620(3)</td>
<td>5242(2)</td>
<td>47(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>8528(2)</td>
<td>7562(2)</td>
<td>1704(1)</td>
<td>25(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>7317(3)</td>
<td>4763(2)</td>
<td>2139(2)</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>8318(2)</td>
<td>5196(2)</td>
<td>2856(2)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(16)</td>
<td>8464(3)</td>
<td>4113(2)</td>
<td>4048(2)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(17)</td>
<td>7317(3)</td>
<td>4763(2)</td>
<td>2139(2)</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(18)</td>
<td>6772(2)</td>
<td>727(2)</td>
<td>2758(2)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(19)</td>
<td>7278(2)</td>
<td>-17(2)</td>
<td>4349(2)</td>
<td>45(1)</td>
</tr>
</tbody>
</table>

Table 3. Bond lengths [Å] and angles [°] for 5.

<p>| | | | |
|     |  |     |  |
|-----|----------------|----------------|
| O(1)-C(4)  |  | 1.4401(19) |  |
| O(1)-C(1)  |  | 1.4470(19) |  |
| O(2)-C(9)  |  | 1.4549(19) |  |
| O(2)-C(10) |  | 1.457(2)  |  |
| O(3)-C(14) |  | 1.4363(19) |  |
| O(3)-C(15) |  | 1.456(2)  |  |
| O(4)-C(14) |  | 1.415(2)  |  |
| O(5)-C(18) |  | 1.434(2)  |  |
| C(1)-C(2)  |  | 1.509(3)  |  |
| C(1)-C(6)  |  | 1.518(3)  |  |
| C(1)-C(5)  |  | 1.526(3)  |  |
| C(2)-C(3)  |  | 1.316(3)  |  |
| C(2)-C(7)  |  | 1.497(3)  |  |
| C(3)-C(4)  |  | 1.497(2)  |  |
| C(4)-C(8)  |  | 1.529(2)  |  |</p>
<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(4)-C(10)</td>
<td>1.554(2)</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.519(2)</td>
</tr>
<tr>
<td>C(9)-C(13)</td>
<td>1.525(2)</td>
</tr>
<tr>
<td>C(9)-C(15)</td>
<td>1.546(2)</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.513(3)</td>
</tr>
<tr>
<td>C(10)-C(12)</td>
<td>1.526(3)</td>
</tr>
<tr>
<td>C(13)-C(14)</td>
<td>1.519(2)</td>
</tr>
<tr>
<td>C(14)-C(18)</td>
<td>1.542(2)</td>
</tr>
<tr>
<td>C(15)-C(16)</td>
<td>1.514(3)</td>
</tr>
<tr>
<td>C(15)-C(17)</td>
<td>1.522(3)</td>
</tr>
<tr>
<td>C(18)-C(20)</td>
<td>1.509(3)</td>
</tr>
<tr>
<td>C(18)-C(19)</td>
<td>1.523(3)</td>
</tr>
<tr>
<td>C(4)-O(1)-C(1)</td>
<td>110.94(11)</td>
</tr>
<tr>
<td>C(9)-O(2)-C(10)</td>
<td>111.28(12)</td>
</tr>
<tr>
<td>C(14)-O(3)-C(15)</td>
<td>111.53(12)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)</td>
<td>104.01(13)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(6)</td>
<td>108.67(14)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(6)</td>
<td>112.64(15)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(5)</td>
<td>107.84(14)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(5)</td>
<td>112.53(16)</td>
</tr>
<tr>
<td>C(6)-C(1)-C(5)</td>
<td>110.76(17)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(7)</td>
<td>128.90(19)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>109.68(15)</td>
</tr>
<tr>
<td>C(7)-C(2)-C(1)</td>
<td>121.38(17)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)</td>
<td>111.70(16)</td>
</tr>
<tr>
<td>O(1)-C(4)-C(3)</td>
<td>103.58(13)</td>
</tr>
<tr>
<td>O(1)-C(4)-C(8)</td>
<td>108.63(13)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(8)</td>
<td>116.03(14)</td>
</tr>
<tr>
<td>O(1)-C(4)-C(10)</td>
<td>109.69(13)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(10)</td>
<td>117.36(14)</td>
</tr>
<tr>
<td>C(8)-C(4)-C(10)</td>
<td>101.41(13)</td>
</tr>
<tr>
<td>C(9)-C(8)-C(4)</td>
<td>103.55(13)</td>
</tr>
<tr>
<td>O(2)-C(9)-C(8)</td>
<td>104.78(13)</td>
</tr>
<tr>
<td>O(2)-C(9)-C(13)</td>
<td>107.68(12)</td>
</tr>
<tr>
<td>C(8)-C(9)-C(13)</td>
<td>116.32(14)</td>
</tr>
<tr>
<td>O(2)-C(9)-C(15)</td>
<td>109.34(12)</td>
</tr>
<tr>
<td>C(8)-C(9)-C(15)</td>
<td>117.19(13)</td>
</tr>
<tr>
<td>C(13)-C(9)-C(15)</td>
<td>101.23(13)</td>
</tr>
<tr>
<td>O(2)-C(10)-C(11)</td>
<td>107.66(15)</td>
</tr>
<tr>
<td>O(2)-C(10)-C(12)</td>
<td>107.81(15)</td>
</tr>
<tr>
<td>C(11)-C(10)-C(12)</td>
<td>111.02(18)</td>
</tr>
<tr>
<td>O(2)-C(10)-C(4)</td>
<td>104.07(13)</td>
</tr>
<tr>
<td>C(11)-C(10)-C(4)</td>
<td>113.88(15)</td>
</tr>
<tr>
<td>C(12)-C(10)-C(4)</td>
<td>111.90(15)</td>
</tr>
<tr>
<td>C(14)-C(13)-C(9)</td>
<td>103.30(13)</td>
</tr>
<tr>
<td>O(4)-C(14)-O(3)</td>
<td>109.72(13)</td>
</tr>
<tr>
<td>O(4)-C(14)-C(13)</td>
<td>112.21(14)</td>
</tr>
<tr>
<td>O(3)-C(14)-C(13)</td>
<td>104.53(12)</td>
</tr>
<tr>
<td>Bond</td>
<td>Angle (°)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>O(4)-C(14)-C(18)</td>
<td>107.06(13)</td>
</tr>
<tr>
<td>O(3)-C(14)-C(18)</td>
<td>107.34(13)</td>
</tr>
<tr>
<td>C(13)-C(14)-C(18)</td>
<td>115.79(14)</td>
</tr>
<tr>
<td>O(3)-C(15)-C(16)</td>
<td>107.88(14)</td>
</tr>
<tr>
<td>O(3)-C(15)-C(17)</td>
<td>107.95(16)</td>
</tr>
<tr>
<td>C(16)-C(15)-C(17)</td>
<td>110.60(16)</td>
</tr>
<tr>
<td>O(3)-C(15)-C(9)</td>
<td>104.19(12)</td>
</tr>
<tr>
<td>C(16)-C(15)-C(9)</td>
<td>114.20(16)</td>
</tr>
<tr>
<td>C(17)-C(15)-C(9)</td>
<td>111.57(16)</td>
</tr>
<tr>
<td>O(5)-C(18)-C(20)</td>
<td>105.98(15)</td>
</tr>
<tr>
<td>O(5)-C(18)-C(19)</td>
<td>109.64(15)</td>
</tr>
<tr>
<td>C(20)-C(18)-C(19)</td>
<td>111.47(16)</td>
</tr>
<tr>
<td>O(5)-C(18)-C(14)</td>
<td>107.61(13)</td>
</tr>
<tr>
<td>C(20)-C(18)-C(14)</td>
<td>111.18(14)</td>
</tr>
<tr>
<td>C(19)-C(18)-C(14)</td>
<td>110.76(16)</td>
</tr>
</tbody>
</table>