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In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.
Total Synthesis of Traditional Chinese Medicine Component Acortatarin A and Studies towards Polyketide Tenuipyrone

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

By

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University of Auckland
March 2014
Abstract

The first part of this thesis focuses on the successful synthesis of the morpholine spiroketal acortatarin A (17). The synthesis of acortatarin A (17) relied on the key Maillard-type condensation between amino alcohol \(158_a\) and dihydropyranone 83. Amino alcohol \(158_a\) is in turn obtained by azide opening of epoxide \(161_a\), followed by reduction. Dihydropyranone 83 was prepared in excellent yield from furan 94 using an Achmatowicz oxidation/rearrangement.

The second part of this thesis describes synthetic studies towards the fungal secondary metabolite tenuipyrene (174) and its 3-dehydroxy analogue 200. The unique tetracyclic structure contains a spiroketal fused to a biologically relevant 2-pyrene moiety. A tandem Stille-Sonogashira cross coupling sequence afforded the key spiroketal precursor 240 in high yields. Attempted sequential deprotection/spiroketalisation to access spiroketal 200 was unsuccessful.
Further studies conducted on enynone 202 and 239 using a Hg(II) catalysed alkyne hydration or Au(I) catalysed alkyne cyclisation failed to deliver the expected 1,3-dicarboxyls 229a and 229b. Importantly, it was established that γ-ynones were not suitable substrates for the desired metal catalysed spiroketalisation or Hg(II) catalysed hydration.

Based on results of the research presented herein, an alternative synthetic strategy to access the spiroketal ring system towards tenuipyrone was proposed.
Acknowledgements

First, I would like to thank my supervisor, D.Prof. Margaret Brimble for taking me on as a PhD student in her group. I am grateful for all your advice and immense knowledge of organic chemistry, your incredible speed at proofreading everything and the hours spent on this thesis.

To the postdocs over the years, firstly thanks to Jack Li-Yang Chen for getting me started working in the lab all the way back in my beginning year. Thank you for your help with chemistry, English and everything. Dan, the smart man, thanks for your great, invaluable chemistry advice. Kevin, thank you for all your contributions to this piece of work, without you, I would not be able to submit this thesis so soon. Louise, thank you for helping with the acortatarin A section. Steffi, thank you for being a great friend and for such fast proof-reading of the thesis. Thanks to Ciarán Dolan for proof-reading and final checking.

To the technician staff, Janice, thank you for all your help all the way from the beginning of my PhD. Anoma, Tim, Michael Schmitz and Nick for being so helpful with chemicals and broken equipment. Min-young Lee, for being so positive and kind; I have learned so much from you.

Thanks to all the Brimble group members past and present (sorry for not including all of your names) for making these four years a special memory. Thanks especially to Sung (well done for proofreading my experimental section), Paul Hume (for reading part of the thesis, thanks for distracting me from time to time), Greg, Tsz, Ubin, Conan, Najmah, Xiaobo, Aimee, Rachelle and Harry………. you guys made my life in New Zealand so much fun!

Outside Brimble group, I would like to thanks to Mengying Xie, the best flatmate in the world. Thank you for being such a great friend, always being so supportive. Thanks to Rachel Chen, the “greatest delivery woman”. Thanks to Christy Wang for being a friend from the first day I arrived in Auckland.

Thanks to the China Scholarship Council (CSC) for supporting me over the past four years.

Finally and most importantly I would like to thanks my parents, for your caring, understanding and always being there! Thanks to my sister and sister-in-law, brother and brother-in-law. Without my sister, I would not have been able to even complete my bachelors degree. This thesis is dedicated to all of you!

Huimin Geng
31st March, 2014
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Abbreviations
° degree
Å angstrom
AChE acetylcholinesterase
AD Alzheimer’s disease
AIDS acquired immunodeficiency syndrome
aq. aqueous
Ar. aromatic
Bn benzyl
bp boiling point
br broad
brsm based on recovered starting material
Bu butyl
C Celsius
CAN cerium(IV) ammonium nitrate
cat. catalytic
CD circular dichroism
CBS Corey-Bakshi-Shibata
CI chemical ionisation
conc. concentrated
CSA camphorsulfonic acid
CuTC copper(I)-thiophene-2-carboxylate
d doublet
d.e. diastereomeric excess
d.r. diastereomeric ratio
d.r. diastereomeric ratio
dba dibenzylideneacetone
DBU 1,8-diazabicycloundec-7-ene
dd doublet of doublets
DCF 2,7-dichlorofluorescein
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone
DEAD diethyl azodicarboxylate
DIAD diisopropyl azodicarboxylate
DIPEA diisopropyl ethyl amine
DMAP 4-dimethylaminopyridine
DMDO dimethylidioxirane
DMF dimethylformamide
DMP Dess–Martin periodinane
DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO dimethyl sulfoxide
DN diabetic nephropathy
DNA deoxyribonucleic acid
dppf 1,1′-bis(diphenylphosphino)ferrocene
dq doublets of quartets
e.e. enantiomeric excess
EI electron ionisation
EOMCI ethoxymethyl chloride
ESI electrospray ionisation
Et ethyl
EtOAc ethyl acetate
FAB fast atom bombardment
g gram
h hour
HDAC histone deacetylase
HG high glucose
HIV human immunodeficiency virus
HKR hydrolytic kinetic resolution
HMPA hexamethylphosphoric triamide
IDF international diabetes federation
Ipc isopinocampheyl
i-Pr isopropyl
IR infrared
KHMDS potassium bis(trimethylsilyl)amide
LDA lithium diisopropylamide
LiHMDS lithium bis(trimethylsilyl) amide
m multiplet or mille
m.p. melting point
m-CPBA m-chloroperoxybenzoic acid
MCR multicomponent reaction
Me methyl
mg milligram(s)
MHz megahertz
MHZ megahertz
min. minute
mL milliliter(s)
mmol millimole
mol mole
MS molecular sieves
NADPH nicotinamide adenine dinucleotide phosphate
NBS N-bromosuccinimide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG</td>
<td>normal glucose</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe (NOE)</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate (triflate)</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium toluenesulfonate</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>py.</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>sat</td>
<td>saturated</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</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-tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TESOTf</td>
<td>triethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl (toluenesulfonyl)</td>
</tr>
<tr>
<td>v/v</td>
<td>volume to volume ratio</td>
</tr>
<tr>
<td>WHO</td>
<td>world health organisation</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
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</table>
Chapter 1: Introduction
1.1. Diabetes Mellitus in Modern Society

Diabetes mellitus is defined as a group of metabolic diseases involving hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is often accompanied by long-term damage, dysfunction, and various organ failures, especially the eyes, kidneys, nerves, heart, and blood vessels. According to the International Diabetes Federation (IDF), the number of people worldwide affected by diabetes mellitus was 382 million in 2013. By 2035, it is estimated that this will rise to 592 million in a 7.7% of the world’s population with the greatest number of people affected being 40 to 59 years of age. The World Health Organization (WHO) estimates that diabetes mellitus will be the seventh leading cause of death in 2030. More than 80% of diabetes deaths occur in low- and middle-income countries.

The vast majority of diabetes mellitus cases normally have been defined as two broad etiopathogenetic categories: Type I diabetes, that is characterised by the autoimmune destruction of the insulin-producing cells in the pancrea, and Type II diabetes, the more common type, that is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (Figure 1). Other subtypes of diabetes mellitus share common characteristic between the two.

<table>
<thead>
<tr>
<th>Types</th>
<th>Normoglycaemia</th>
<th>Hyperglycaemia</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Normal glucose regulation</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Type I</td>
<td>Impaired glucose tolerance (prediabetes)</td>
<td>No insulin required</td>
</tr>
<tr>
<td>Type II</td>
<td>Insulin required for control</td>
<td>Insulin required for survival</td>
</tr>
<tr>
<td>Gestational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 1. Disorders of glycaemia: etiologic types and stages.*

The development of diabetes mellitus involves a number of pathogenic progressions. These pathogenic processes range from cellular-mediated autoimmune destruction of β-cells of the pancreas with subsequent insulin deficiency, to abnormalities that lead to the resistance to insulin action. The deficient action of insulin on target tissues results in abnormalities in carbohydrate, fat, and protein metabolism, which arises from insufficient insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action are often found in the same patient. To date, the primary cause of the hyperglycaemia is still a matter of some debate.
1.1.1. Diabetes and Associated Complications

The characteristic symptom of diabetes mellitus is hyperglycaemia. The concomitant symptoms include polyuria, polydipsia, loss of weight, and loss of vision. These symptoms usually progress insidiously, often developing for several days or even weeks before people seek medical help and require hospital admission. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycaemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycaemia with ketoacidosis or the non-ketotic hyperosmolar syndrome.\(^2\)

Chronic complications of diabetes mellitus include retinopathy with potential loss of vision; nephropathy leading to renal failure that is known as diabetic nephropathy (DN); peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints, autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms, and sexual dysfunction. DN is a serious complication of diabetes mellitus and is the most common cause of end-stage renal disease.\(^1\) Patients with diabetes are often found with atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often associated with diabetes.\(^3\)

1.1.2. Treatment of Diabetes Mellitus and Complication:

New treatment strategies for Type I (insulin dependent) and Type II (non-insulin dependent) diabetes mellitus are constantly being developed. Controlling hyperglycemia is the priority for preventing microvascular complications. In general, for Type I diabetes, the key treatment is insulin.\(^5\) Type II diabetes is a progressive disease and requires constant therapy amplification.\(^5\) Normally, insulin sensitisers and incretin-based therapy are incorporated in the beginning stage of the disease. Metformin is the drug treatment of choice for Type II, which mainly reduces hepatic glucose output.

In subjects with established disease, familial clustering of DN may be related to concomitant susceptibility to hypertension and elevated rates of Na/H counter transport. Treatment of hypertension associated with the nephropathy appears to retard renal deterioration. In the presence of a reduced \(\beta\)-cell mass, moderate hyperglycaemia may help itself decrease muscle glucose uptake but not glycogen synthesis in Type I and Type II diabetes.

Several interventions, such as tight glycemic control and antihypertensive therapy, especially angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers, have been
Chapter 1: Introduction of Acortatarin A

identified to slow the development of diabetes mellitus. Nevertheless, DN still remains as the major chronic complication of both Type I and II diabetes mellitus, because treatment commenced after the manifestation of overt clinical nephropathy often does not stop progression to end stage renal disease. Therefore, identifying new therapies to halt further progression of the disease still remains a challenge.

Excessive accumulation of extracellular matrix (ECM) in the glomerular mesangium is one of the hallmarks of DN and contributes to glomerulosclerosis. Mesangial cells (MCs) synthesise ECM proteins including collagens IV and fibronectin in response to high glucose. Mesangial deposition of ECM closely associates with the failure of renal function, hence it has been identified as a critical therapeutic agent for DN. Many researchers have established that reactive oxygen species (ROS) generation is an early response of MCs to high glucose and contributes to the overproduction of ECM. Therapeutic agents that are able to inhibit the generation of ROS are therefore treated as potential anti-DN agents.

The rhizome of Acorus tatarinowii is one kind of traditional Chinese herb possessing distinctive effects on calmness, was reported to improve intelligence and against rheumatism and epilepsy (Figure 2).8

In early 2010, Cheng and co-workers published the isolation of a novel alkaloid named acortatarin A from Acorus tatarinowii and demonstrated that acortatarin A could inhibit high-glucose induced ROS generation. They also conducted studies towards evaluating the protecting effects of acortatarin A on hyperglycemia induced ECM accumulation in cultured MCs.8

![Figure 2. Acorus tatarinowii plant.](image-url)
Chapter 1: Introduction of Acortatarin A

1.2. Acortatarins A and B - Isolation, Biological Activity and Biosynthesis

1.2.1 Isolation

In 2010, two novel natural products namely acortatarins A and B were isolated from the rhizome of *Acorus tatarinowii* by Cheng and co-workers. The plant *Acorus tatarinowii* is widely used as a traditional Chinese medicine for the treatment of central nervous system disorders such as epilepsy and also used as an aid to improve learning and memory. The X-ray crystal structure of 1 established the presence of a unique morpholine spiroketal ring system and the relative configuration of the chiral centres (Figure 3). This proposed structure constituted the first, and still stands as the only, reported alkaloid containing this framework. The configuration of natural acortatarin B (2) was then determined by extensive COSY and HMBC analysis.

![Figure 3. Proposed structures of acortatarins A (1) and B (2) by Cheng and co-workers and pollenopyrrosides A (3) and B (4) by Guo and co-workers.](image)

At the end of 2010, Guo and co-workers described the isolation of pollenopyrroside B from bee-collected *Brassica campestris* pollen, which is also extensively used in Chinese herbal medicine. Based on extensive X-ray analysis of the related, co-isolated pollenopyrroside A (3) and extensive NOESY studies of pollenopyrroside B, Guo and co-workers concluded that pollenopyrroside B (4) was structurally identical but enantiomeric to acortatarin A as reported by Cheng and co-workers.

1.2.2 Biological Activity

Both acortatarins A and B were examined for their antioxidant effects in high-glucose induced mesangial cells in a dose- and time-dependent manner, with acortatarin A (1) showing significantly higher activity against the production of ROS (Figure 4). They employed 2,7-dichlorofluorescin (DCF) fluorescence as ROS detector to determine the concentration of ROS.

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1 All the reported biology data related to the natural product was the revised structure of acortatarin A (17).
in mesangial cells. As shown in Figure 4A and B, high-glucose-induced ROS generation was remarkably decreased by pretreating mesangial cells with acortatarin A (1) and less inhibiting activity obtained by pretreating with acortatarin B (2). Further experiments were conducted by pretreating mesangial cells with 10 μM (1) or 100 u/mL of cytosolic Cu/Zn superoxide dismutase (c-SOD, positive control) to confirm the antioxidative effect of 1. As illustrated in Figure 4C, the pretreatment of 1 decreased ROS production by nearly 50% at different points, indicating that 1 inhibited the high-glucose-induced ROS production in a time-dependent mode in mesangial cells. Bee-collected *Brassica campestris* pollen is often used in China as a herbal medicine to strengthen the body’s resistance to diseases. It has already been found to possess a wide range of biological activities, including antioxidant and antitumor activity as a treatment of prostatitis; and for the regulation of serum lipids.\(^{12}\)

**Figure 4.** Compounds 1 and 2 inhibited high-glucose-induced ROS production in mesangial cells. Data were expressed as mean ± SD of three independent experiments.\(^{13}\) ANOVA, \(p < 0.001\) in A, B, and C; \(*p < 0.05\) vs normal glucose (NG); \(#p < 0.05\) vs high glucose (HG).

It has been suggested by Cheng and co-workers that the bioactivity of acortatarins A (1) against ROS is due to its antioxidant properties.\(^{8}\) However, antioxidants typically contain more electron-rich aromatic groups such as phenols, that are more readily oxidised. While acortatarin A (1) contains an electron-rich heterocycle, the electron-withdrawing aldehyde group is believed to stabilise the molecule. The antioxidant activity of acortatarin A (1) was measured by cyclic voltammetry experiments by Aponick and Borrero.\(^{15}\) Generally most compounds with cyclic voltammetry below +0.70 V are treated as anti-oxidants.\(^{16}\) The first and second oxidation potentials of 1 were defined to be +1.74 and +1.90 V, respectively. Interestingly, the cyclic voltammogram showed that the oxidation is irreversible (Figure 5).\(^{15}\) The authors concluded that the high oxidation capacities measured is in high contrast with the values obtained for normal antioxidants, suggesting that acortatarin A (1) may function by an alternative mechanism. This observation also corroborates the original ROS experiments\(^{8}\) that acortatarin A (1) inhibits ROS production itself rather than reacting with ROS (Figure 5).

\(^{8}\) u/mL means unit per milli liter.
In 2013, further biological studies conducted by Zhao and co-workers first reported that the action mode of acortatarin A (1) on the ROS-generating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme.\textsuperscript{7} Acortatarin A (1) was found to inhibit the generation of intracellular ROS, effectively blocking collagen IV and fibronectin up-regulation in MCs cultured under high glucose conditions. It was demonstrated that acortatarin A (1) was active inhibiting the ROS in rat glomerular matrix cells.\textsuperscript{7} The cytotoxicity of acortatarin A (1) was first examined in this work. No obvious cell mortality was observed when cells were incubated with up to 50 μmol/L of acortatarin A (1). It was worth noting that at this concentration acortatarin A (1) significantly inhibited high glucose-induced NADPH oxidase activation. It was established that the antioxidative property of acortatarin A (1) was through blocking the activation of NADPH oxidase, the most important mechanism for receptor-stimulated ROS generation.\textsuperscript{7}

Diabetic nephropathy (DN) is currently the leading cause of end-stage renal disease. Various treatment regimens and combinations of therapies provide only partial renal protection. Therefore new treatments are desired to retard the progression of DN. In conclusion, all the biological data suggests that acortatarin A (1) may be a new therapeutic candidate for DN. The aim of the present study was to develop an efficient and facile synthetic route to acortatarin A (1) in order to evaluate the role of this novel spiroalkaloid moiety in inhibiting high ROS in hypoxic cells that regulate many angiogenesis-related diseases including cancer and ischemic disorders.
1.2.3 Biosynthetic Analysis

Both acortatarins A (1) and B (2) were identified as novel spiroalkaloids bearing an unusual morpholine ring. Zhang and co-workers proposed a possible biosynthetic pathway to pollenopyrrosides B (4) (identical to acortatarin A) and its ring-expanded analogue pollenopyrroside A in the same publication describing the isolation of these two natural products. Both pollenopyrrosides A (3) and B (4) were envisaged to derive from a condensation between 5-hydroxymethyl-2-formylpyrrole (5) and 3-deoxy-D-fructose (6) (Scheme 1).

![Scheme 1 Proposed biosynthesis of pollenopyrrosides A (3) and pollenopyrroside B (4) (acortatarin A).](image)

However, 3-deoxy-D-fructose (6) is not available from natural sources, and only a limited number of reports for its synthesis can be found. Nevertheless, from a biosynthetic perspective, acortatarin A (1) and pollenopyrroside A (3) may arise from a series of reactions between a sugar and pyrrole.
1.3. Previous Syntheses

A. First Total Synthesis of Acortatarin A by Jagadeesh and Co-workers\textsuperscript{19}

In 2011, Jagadeesh and co-workers completed the first total synthesis of acortatarins A (1) and B (2), involving the union of 2,5-disubstituted pyrrole 7 and epoxide 8.\textsuperscript{19} It was envisioned that the sugar moiety present in the acortatarins could be readily accessed from L-sugars. They embarked on a synthesis towards the enantioselective synthesis of both acortatarins using cheap, commercially available, chiral d-sugars to test its feasibility.

2,5-Bis-(hydroxymethyl)pyrrole 9 was prepared from pyrrole 10 according to a modification of Taniguchi’s methodology\textsuperscript{20} in good yield (Scheme 2). Controlled oxidation of diol 9 was conducted using one equivalent of MnO\textsubscript{2} to give pyrrole-2,5-dicarbaldehyde 11 and 5-hydroxymethyl-pyrrole-2-carbaldehyde 12 in 29\% and 51\% yield, respectively. Dicarbaldehyde 11 was treated with NaBH\textsubscript{4} to afford 12 in 96\% yield. Final protection using DHP delivered the required pyrrole fragment 7 in 96\% yield.

![Scheme 2 Synthesis of pyrrole 7. Reagents and conditions: i) formalin, aq. K\textsubscript{2}CO\textsubscript{3}, 5 °C; ii) MnO\textsubscript{2}, acetone, 80\%; iii) NaBH\textsubscript{4}, MeOH, 96\%; iv) DHP, PPTS, CH\textsubscript{2}Cl\textsubscript{2}, 96\%.](image-url)
The synthesis of epoxide fragment 8 began with 3,5-di-\(\text{O-benzyl-2-deoxy-d-ribose}\) (13) which, in turn, was derived from commercially available 2-deoxy-d-ribose (14) over three steps.\(^{21}\) Wittig olefination and concomitant protection of the resulting secondary hydroxyl group using TBSOTf in the presence of 2,6-lutidine followed by oxidation furnished the expected epoxide 8 in 42\% yield over three steps (Scheme 3).

**Scheme 3** Synthesis of acortatarin A (17). *Reagents and conditions:* i) \(\text{PPh}_3\text{MeBr}, n\text{-BuLi, THF, 63\%; ii) TBSOTf, 2,6-lutidine, CH}_2\text{Cl}_2, 91\%; iii) \text{m-CPBA, CH}_2\text{Cl}_2, 73\%; iv) \text{pyrrole}, \text{NaH (60\% in mineral oil), DMF, 55 °C, 45\%; v) \text{DMP, CH}_2\text{Cl}_2, 88\%; vi) \text{p-TSA, CH}_2\text{Cl}_2, 16\text{a, 44\%, 16\text{b, 31\%; vii) 1 M TiCl}_4, \text{CH}_2\text{Cl}_2, –78 °C, 17\text{a, 8\%}.}

Pyrrole 7 was treated with NaH in DMF followed by addition of epoxide 8 to afford alcohol 15 as a mixture of inseparable diastereomers in 45\% yield. Sequential oxidation, deprotection/intramolecular spiroketalisation was accomplished by treating alcohol 15 with DMP followed by \(\text{p-TSA, CH}_2\text{Cl}_2\) to give a separable mixture of C-5 anomers 16\text{a} and 16\text{b} in 75\% combined yield. Initial attempts to effect the debenzylation of anomers 16\text{a} and 16\text{b} to produce final spiroketal 17 and 17\text{a} under conventional hydrogenolysis conditions using Pd/C either resulted in no reaction, or led to a complex mixture of several undefined compounds at higher catalyst loadings.

The desired spiroketales 17 and 17\text{a} were obtained by subjecting anomers 16\text{a} and 16\text{b} separately to 1 M \(\text{TiCl}_4\) in \(\text{CH}_2\text{Cl}_2\) to complete the removal of the benzyl groups. Interestingly, for both deprotection steps, the same diastereomeric ratio (17:17\text{a}, 9:1) was obtained in 80\% combined yield.
Employing a similar synthetic approach, Jagadeesh and co-workers completed the total synthesis of acortatarin B (18) in the same paper. Upon completion of the total synthesis, the $^1$H and $^{13}$C NMR spectra of 17 and 18 were found to be identical to that reported data for the natural products. The specific rotation of the synthesised compound 17 $\left[\alpha\right]_{D}^{27} +191.4, \left(c\ 0.27, \text{MeOH}\right)$ was of a similar magnitude and the same sign as reported for the natural source of acortatarin A $\left[\alpha\right]_{D}^{27} +178.4, \left(c\ 0.4, \text{MeOH}\right)$. This led to the absolute configuration of the natural product to be 2R, 4R, 5R. Thus, acortatarin A (17) and pollenopyrroside B (3) are now recognised to be identical (Figure 6).
B. Synthesis of Acortatarins A (17) by Tan and Co-workers\textsuperscript{22}

Tan and co-workers executed a diastereoselective total synthesis of acortatarins A (17) and B (18) featuring a non-acid catalysed spiroketalisation strategy.\textsuperscript{22} In contrast to the previously reported total synthesis of acortatarin A (17), this work involved a late-stage spirocyclisation of glycal 19 by treatment with Hg(II) salts.

TIPS-protected ribal 20 was obtained via Pedersen’s standard nucleoside protection chemistry and concomitant bis(trimethylsilyl)amine (HMDS) silylation-elimination conditions from nucleoside 21.\textsuperscript{23} Regioselective formylation of 20 to give aldehyde 22 that was reduced with NaBH\textsubscript{4} afforded hydroxymethyl ribal 23 in 78% yield over two steps. Hydroxymethyl ribal 23 was converted to iodide 24 through an Appel reaction in 98% yield. The resulting iodide 24 was then coupled with pyrrole dicarboxaldehyde 25 under biphasic conditions in the presence of a phase transfer catalyst tetrabutylammonium iodide (TBAI) to provide the key intermediate pyrrologlycal 19 in 93% yield.

Scheme 4 Synthesis of pyrrologlycal 19. Reagents and conditions: i) TIPSCI, DMF, 50 °C, 99%; ii) (NH\textsubscript{4})\textsubscript{2}SO\textsubscript{4}, HMDS, 120 °C, 82%; iii) t-BuLi, DMF, THF, −78 °C to r.t.; iv) NaBH\textsubscript{4}, MeOH, −78 °C, 78% over 2 steps; v) I\textsubscript{2}, PPh\textsubscript{3}, toluene, 0 °C to r.t., 98%; vi) 2,5-dicarboxylpyrrole (25), TBAI, NaOH, toluene, H\textsubscript{2}O, 0 °C to 50 °C, 93% vii) NaBH\textsubscript{4}, THF, 0 °C, 76%.
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Initial attempts employing *in situ* reductive spirocyclisation method to convert 19 to acortatarin A (17), led to a furan by-product 26 *via* Ferrier-type elimination (Scheme 5). The authors next attempted a stepwise mono-reduction of 19 followed by treatment with dichloroacetic acid, resulting in a 1:1 mixture of the 2,3-dehydro-spiroketal 27 formed *via* Ferrier rearrangement and the C-5 epimer of TIPS silyl ether protected-acortatarin A 28. Finally, it was discovered that oxidative spirocyclisation of pyrrole 29 yielded a mixture of protected spiroketals 30 at C-5. Accordingly, treatment of pyrrole 29 with Hg(OAc)$_2$ in the presence of NaHMDS afforded the desired 2-mercurial spiroketal which were concomitantly reduced using NaBH$_4$ to the diastereomeric spiroketals 30. Final deprotection of the mixture of 30 provided the separable mixture of acortatarin A (17) and 5-epi-acortatarin A (17$_a$).

**Scheme 5** Synthesis of acortatarin A (17). *Reagents and conditions:* i) TFA, Et$_3$SiH, CH$_2$Cl$_2$, −42 °C to 0 °C, 90%; ii) NaBH$_4$, THF, 0 °C, 76%; iii) dichloroacetic acid, CH$_2$Cl$_2$, 0 °C to r.t., 47% as a 1:1 mixture; iv) a) NaHMDS, THF, −78 °C, Hg(OAc)$_2$; b) NaBH$_4$, Hg(OAc)$_2$, THF, 6 h; v) TBAF, THF, 0 °C, 17 45% over 2 steps, 17$_a$ 24% over 2 steps.
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C. Synthesis of Acoratatarin A (17) by Aponick and Borrero\textsuperscript{15}

A Pd-catalysed dehydrative cyclisation reaction was employed as the key step for the total synthesis of acoratatarin A by Aponick and Borrero (Scheme 6).\textsuperscript{15} The synthesis of the spiroketal precursor, unsaturated ketone 31, relied on a nucleophilic addition of bromo ketone 32 to pyrrole 33. The preparation of electrophile $\alpha$-bromo ketone 32 commenced with bromination and reduction of the known $\delta$-hydroxy ester 34, followed by methylation of the resulting hydroxy group to furnish alkene bromide 35 in 50% yield over three steps. Alkylation of dithiane 36 with the resultant bromide 35 using NaH in $t$-BuOH smoothly furnished ester 37 in 73% yield. Sequential ester reduction, deprotection and Appel reaction afforded $\alpha$-bromo ketone 32 in 68% yield over 3 steps.

In turn, pyrrole 33 was prepared from commercially available pyrrole 10 (Scheme 6). Formylation of pyrrole (10) at C-2 was conducted using triphosgene and DMA in toluene, followed by amide formation using the Weinreb amine salt in the presence of triethylamine to afford the corresponding Weinreb amide 38. Finally a Vilsmeier-Haack formylation using POCl$_3$ and DMF furnished 2,5-disubstituted pyrrole 33 in 50% yield, ready for N-alkylation.

Union of pyrrole 33 and bromoketone 32 was accomplished uneventfully, employing Cs$_2$CO$_3$ as a base in CH$_3$CN to give ketone 31 in 79% yield. Subsequent selective reduction of the aldehyde using lithium tris(3-ethyl-3-pentyloxy)aluminohydride (LTEPA) followed by Pd-catalysed cyclisation delivered spirokets 39$_a$ and 39$_b$ in 87% yield as a 1:1 separable mixture. The resulting spirokets 39$_a$ and 39$_b$ were separately subjected to a dihydroxylation, then oxidative cleavage followed by reduction to give benzyl ether 40. Final deprotection using 1 M TiCl$_4$ in CH$_2$Cl$_2$ afforded acoratatarin A 17 and 5-epi-acoratatarin A 17$_a$ in 70% and 14% yield, respectively.
Scheme 6 Reagents and conditions: i) CBr₄, PPh₃, CH₂Cl₂, r.t., 1 h; ii) DIBAL-H, CH₂Cl₂, –78 °C, 2 h, 79% for 2 steps; iii) NaH, MeI, THF, r.t., 2 h, 62%; iv) NaH, t-BuOH, ethyl 1,3-dithiane-2-carboxylate (36), THF, 0 °C, 6 h, 73%; v) LiAlH₄, THF, 0 °C, 2 h, 99%; vi) Phl(OCOCF₃)_2, CH₂CN:H₂O 9:1, 0 °C to r.t., 15 min, 95%; vii) CBr₄, PPh₃, CH₂Cl₂, r.t., 1 h, 72%; viii) a) triphosgene, N,N-DMA, toluene, 0 °C, 3 h; b) N,O-dimethylhydroxylamine hydrochloride, Et₃N, 0 °C, r.t., 16 h, 97% for 2 steps; ix) POCl₃, DMF, CH₂Cl₂, –15 °C to 0°C to r.t., 24 h, 50%; x) Cs₂CO₃, CH₂CN, 60 °C, 8 h, 79%; xi) LTEPA, THF, 0 °C, 3 h, 93%; xii) 10% Pd(PhCN)₂Cl₂, CH₂Cl₂, 4 Å MS, 0 °C, 24 h, 87%, d.r. 1:1; xiii) a) OsO₄, NMO, THF:H₂O 1:1, 24 h; b) NaIO₄, THF-pH 7 buffer; c) NaBH₄, EtOH, 70% over 3 steps; d) LiAlH₄, THF, –78 °C to 0 °C, 1.5 h, 89% xiv) 1 M TiCl₄, CH₂Cl₂, 0 °C, 5 h, 17 70%, 17ₐ 14%. 
D. **Synthesis of Acortatarin A (17) by Kuwahara and Co-workers**

Kuwahara and co-workers’ total synthesis of acortatarin A commenced with the Wacker oxidation of olefin 41, which in turn was readily accessible from (R)-glyceraldehyde acetonide in two steps, to give ketone 42 (Scheme 7). Ketone 42 was converted into its corresponding α-bromo ketone 43 in 54% yield by a two-step sequence involving TES enol ether formation and subsequent *in situ* bromination. α-Bromo ketone 43 was then treated with the pyrrolic anion derived from pyrrole 7 and NaH in DMF to furnish α-aminoketone 44 in 73% yield. Global deprotection and tandem spiroketalisation using BBr$_3$ in CH$_2$Cl$_2$ gave a difficult-to-separate mixture of desired 5,6-spiroketal 45 and the presumed 6,6-spiro compound 46. The unexpected 6,6-spiro impurity 46 was removed by subsequent oxidative cleavage of the diol employing NaIO$_4$ to furnish the desired product 17 and 17$_a$ in their respective isolated yields of 37% and 18%.

**Scheme 7** Synthesis of acortatarin A (17). *Reagents and conditions:* i) PdCl$_2$, Cu(OAc)$_2$, H$_2$O, O$_2$, aq. DMF, r.t., 82%; ii) LDA, TESCl, THF, $-78 \, ^\circ\text{C}$ to r.t.; iii) NBS, THF, $-78 \, ^\circ\text{C}$, 54% for 2 steps; iv) NaH, pyrrole 7, DMF, $-10 \, ^\circ\text{C}$, 73%; v) BBr$_3$, CH$_2$Cl$_2$, $-78 \, ^\circ\text{C}$; vi) NaIO$_4$, aq. NaHCO$_3$, CH$_2$Cl$_2$, r.t., 17 37%, 17$_a$ 18%.
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1.4. Pyrrole Chemistry

Pyrroles are important compounds and are present in many natural products, drugs, catalysts and materials acting as antibacterial, antiviral, anti-inflammatory, and antioxidant agents. Two antimycobacterial pyrrole derivatives BM212 (47) and BM521 (48) recently developed by Biava’s group have been identified to be very good inhibitors against different strains of *M. tuberculosis*. Storniamide A (49) and permethyl storniamide A (50) are two secondary metabolites isolated in 1996 with antibiotic activity against Gram-positive bacteria. Rhazinilam (51) showed cytotoxicity toward various cancer cell lines at low micromolar range *in vitro* and no activity *in vivo*. The cholesterol-lowering agent, atorvastatin (52), is one of the top-selling drugs worldwide. Polypyrroles 53 are conducting polymers used in batteries and solar cells (Figure 7).

![Figure 7](image.png)

Figure 7. Examples of some 2,5-disubstituted pyrrole derivatives.

There are many classic protocols and catalytic transformations to access substituted pyrrole derivatives. Due to the significant demand for novel reactions using renewable resources and the important value of pyroles, a pyrrole synthesis that fully or partially uses renewable resources is highly desired. Such a reaction would be especially attractive in terms of its applicability in organic synthesis (and industrial production) if it significantly extended the scope of existing pyrrole syntheses.
1.4.1 Classic Protocols

A: Knorr Pyrrole Synthesis

The Knorr pyrrole synthesis consists of the condensation of an aminoketone or \( \alpha \)-amino-\( \beta \)-ketoester with a ketone or ketoester (Scheme 8).\textsuperscript{34} The methodology has been widely used for the synthesis of substituted pyrrole derivatives.\textsuperscript{35} A major drawback of the reaction is the lack of regioselectivity during the condensation step. Symmetrical \( \beta \)-diketones are therefore more commonly employed to facilitate symmetrically substituted pyrrole molecules in good yields.

\[
R^1\overset{\text{O}}{\text{R}} \overset{\text{NaNO}_2/\text{CH}_3\text{CO}_2\text{H}}{\text{R}} \overset{\text{Zn/CH}_3\text{CO}_2\text{H}}{\text{R}} \overset{\text{R}^1\text{COCH}_2\text{R}^4}{\text{R}}
\]

Scheme 8 Knorr pyrrole synthesis.

Knorr pyrrole formation commences with the \textit{in situ} reduction of a nitroso compound using a reducing reagent. A nucleophilic addition of the resultant \( \alpha \)-amino-\( \beta \)-ketone 54 to a ketone 55 leads to the formation of 56 that undergoes elimination to afford enamine derivative 57 under acidic conditions. Tautomerisation of enamine 57 gives imine 58 that cyclises to give an enamine 59 in the presence of acids. Elimination of the hydroxyl group in enamine 59 leads to the formation of pyrrole derivative 60 that tautomerises to yield the desired pyrrole 61.

B: Paal-Knorr Pyrrole Synthesis

The Paal-Knorr pyrrole synthesis is a well-established method that involves an acid-catalysed (protic acids or certain Lewis acids) condensation between a 1,4-dicarbonyl moiety with an excess
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of ammonia or a primary amine, leading to the formation of a substituted pyrrole (Scheme 10). This method has been extensively used for the preparation of a large number of pyrrole containing natural products. It is also worth mentioning that the use of microwave irradiation technique has shortened reaction times dramatically compared to the classical conditions.

![Scheme 10 Paal-Knorr condensation reaction.](Image)

The exact Paal-Knorr pyrrole synthesis mechanism is still a matter of debate. In 1991 Amarnath and co-workers demonstrated the most commonly accepted mechanism as depicted in Scheme 11. It is proposed that a primary amine undergoes a nucleophilic addition to the dicarbonyl compound in the presence of an acid. The obtained intermediate amino alcohol attacks the second carbonyl group to give a hemiaminal intermediate that eliminates to yield multi-substituted pyrrole. The rate determining step has been established to be the cyclisation of the hemiaminal intermediate.

![Scheme 11 Proposed Paal-Knorr pyrrole synthesis mechanism.](Image)

The condensation reaction is not limited to exposed 1,4-dicarbonyl compounds, alternatives such as 2,5-dimethoxytetrahydrofurans and γ-nitroketones as surrogates can also undergo the same process to furnish substituted pyrrole derivatives. However in these cases harsher reaction conditions are commonly required.

C: Hantzsch Pyrrole Synthesis and Related Reactions

The three component condensation of an amine (enamine or ammonia) and an α-halo ketone or aldehyde with a β-ketoester or β-diketone is known as the Hantzsch reaction. Since the original publication of the Hantzsch reaction, very limited research has been reported. The latest modification of the classic Hantzsch pyrrole synthesis was developed by Menéndez and co-workers featuring a three-component approach to multi-substituted pyrroles. A sequential
multicomponent reaction under high-speed vibration milling conditions using ketones, primary amines and β-dicarbonyl compounds in the presence of N-iodosuccinimide (NIS), p-TSA, cerium (IV) ammonium nitrate (CAN) and silver nitrate afforded polysubstituted functionalised pyrroles (Scheme 12). The major drawback of this reaction is the formation of a furan by-product. Extensive efforts have been devoted to minimise the formation of the side-product.

Scheme 12 General reaction scheme for Hantzsch pyrrole synthesis and modification by Menéndez.

The proposed mechanism by Wang is depicted in Scheme 13. Ammonia or amine 66 reacts quickly with β-keto esters 67 to form enamine esters 68. Nucleophilic attack of enamine ester 68 affords iminium anion 69 that cyclises to form pyrrole derivatives upon heating. The regioselectivity observed strongly depends on the nature of the substituents on the starting materials. Final elimination gives pyrrole 70.

Scheme 13 Proposed mechanism of the Hantzsch reaction.

Modification of this protocol has been reported since the discovery of Hantzsch reaction, including the use of enamines or solid-phase synthesis techniques with good yields and in high purity.
D: Zav’yalov Pyrrole Synthesis

The Zav’yalov sequence for pyrrole synthesis was first reported in 1973 by Zav’yalov and co-workers using a β-dimethylaminomethylene ketone or acrylyl ester, or both, and an α-amino acid to give a substituted pyrrole ring. Thermodynamically controlled decarboxylation of the α-carboxylic acid in 71 is the driving force to form the pyrrole ring. This cyclisation step requires an amine base.

![Scheme 14 Zav’yalov pyrrole synthesis.](image)

The initial step of Zav’yalov pyrrole synthesis is the amine exchange between α-amino acid 72 and imine 73. Nucleophilic addition of amine 73 to imine 72 followed by deprotection yielded 74. Treatment of imine 74 with acetic anhydride under heat triggers the cyclisation, decarboxylation and dehydration to yield the desired pyrrole 75. The driving force of this reaction is the thermodynamically controlled decarboxylation of the α-carboxylic acid.

![Scheme 15 Proposed mechanism for Zav’yalov pyrrole synthesis.](image)

Since the discovery of this reaction, a few variations of this methodology have been reported employing a variety of ketones. This reaction is important for the preparation of substituted pyrroles.
E: Barton-Zard Pyrrole Synthesis

In 1985, Barton and Zard described a flexible and efficient reaction featuring the synthesis of 2-substituted pyrroles via a base-catalysed condensation between alkyl isocyanoacetate (or tosylmethyl isocyanide) and α,β-unsaturated nitroalkenes (or β-nitroacetates). This reaction is generally known as the Barton-Zard pyrrole synthesis, the Barton-Zard pyrrole condensation, or the Barton-Zard reaction.

The base-catalysed Michael addition of an α-isocyanoacetate to a nitroalkene gives a nitronate. The nitronate anion cyclises onto the isocyano group leading to the formation of pyrroline. Base-catalysed expulsion of the nitrite from the pyrroline and double bond rearrangement would finally yield pyrrole.

This reaction is convenient for the synthesis of pyrroles with various substituents at C-2. The yields of this reaction are generally high (80–90%). A non-nucleophilic strong base, such as DBU, t-BuOK or guanidine, is generally employed in this reaction. This method has been widely used for the preparation of polypyrroles and porphyrins fused with various aromatic rings or bicyclic frameworks, starting from aromatic nitro compounds and ethyl isocyanoacetate.
1.4.2 Catalytic Transformations

A: Pyrroles Derived from Alkynyl Compounds

Alkynes are very important building blocks in organic synthesis. The application of these substances to the preparation of pyrrole compounds represents one of the most versatile and facile protocols. A number of functionalised pyrrole natural products have been constructed using an α-oxygenated alkyne moiety and an amine fragment. This method can be subdivided to Diels-Alder/ring contraction synthesis; N-ylide-mediated pyrrole synthesis that is in generally utilised for aromatic fused pyrrole natural products synthesis; and catalyst assisted (Pd, Cu, Brønsted acids etc) cycloisomerisation. General synthetic schemes are depicted in Scheme 18.

B: Titanium-Mediated Pyrrole Synthesis

The titanium induced cyclisation of a readily accessible amido-enone or masked 1,3-dicarbonyl compound to form a substituted pyrrole ring system was first described by Fürstner and co-workers (Scheme 19). The reaction process is similar to the reductive coupling of carbonyl compounds using low-valent titanium that is commonly known as McMurry coupling. The driving force of this reaction is that the low-valent titanium efficiently promotes the intramolecular coupling of carbonyl groups of distinctly different redox potentials to give a thermodynamically more-stable five-membered ring. The key feature of this synthesis is that highly substituted pyrrole compounds are readily accessible. The mechanism of this reaction is not entirely clear yet.
C: Multicomponent-Pyrrole Synthesis

Multi-component reactions (MCRs) have become one of the most utilised pyrrole synthesising methodologies due to their ability to easily generate a very large compound library from several small starting materials in a highly convergent manner, both in solution and on solid supports.65 The Ugi reaction is the most flexible of all the known MCRs.66 One example of the application of a four-component Ugi reaction to make a pyrrole is shown in Scheme 20.67

![Scheme 20 A general scheme of a 4-component condensation (4-CC).](image)

1.4.3 Other Methods

Besides the aforementioned pyrrole synthetic methods, many other researchers have broadened the scope of pyrrole synthesis including intramolecular/intermolecular [3+2] cycloaddition pathway,68 N-ylide-mediated pyrrole formation,69 vinylogous iminium-mediated pyrrole synthesis,70 Hinsberg-type pyrrole synthesis71,72 and so on. Among all of these interesting new approaches useful for preparing multi-substituted pyrrole compounds, Maillard-type condensation successfully employed for the synthesis of acortatarin A will be discussed in the following section.73
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1.5. Aim of the Present Research

Prior to this investigation, there was no total synthesis or synthetic studies towards acortatarin A reported yet. With the novel chemical structure of acortatarin A (1), its promising biological activity as a candidate for DN, and its limited natural source, a readily accessible synthesis of acortatarin A is called for. Our research group has a long standing interest in the synthesis of biologically active spiroketal compounds.74,75 Inspired by the promising biological activity, we were encouraged to design and implement a total synthesis of acortatarin A that would simultaneously be amenable to the creation of analogues and, more importantly, short enough to make commercial synthesis viable. Our work towards the total synthesis of acortatarin A hinged on an N-alkylation reaction between epoxide 81 and pyrrole 82 (Scheme 21). Epoxide 81 was anticipated to arise from L-tartaric acid (84). In turn, 2,5-disubstituted pyrrole 82 would be assembled via a key Maillard-type condensation between dihydropyranone 83 and ammonia.

The utility of the Maillard-type condensation to access 2,5-disubstituted pyrrole natural products, especially those containing electron-donating functional groups would be greatly enhanced if it could enable analogue synthesis. Importantly, if this objective could be attained, the protocols established could potentially give rise to numerous synthetic applications for pyrrole-containing natural products. Studies directed towards this important objective comprise the bulk of the research work reported in the remainder of this thesis.

Scheme 21 Retrosynthetic analysis of acortatarin A (1)
Chapter 2: Discussion
2.1. Retrosynthetic Analysis

The initial aim of the project was to investigate the use of an acid-catalysed concomitant deprotection/cyclisation sequence for the construction of the proposed spiroketal core of acortatarin A (1). The synthesis of 1 required stereoinversion at C-4 to access the correct stereochemistry via a Mitsunobu reaction of spiroketal 85. Acid-catalysed spiroacetalisation of ketone 86 was anticipated to afford acortatarin A core structure 85. Although the anomeric effect is less dominant in [5,6]-spiroacetals, the enhanced stabilisation may nonetheless assert an effect on the stereochemical outcome of the spirocyclisation step. Ketone 86 was envisioned to be derived from the addition of an anion derived from 2,5-disubstituted pyrrole 82 to epoxide 81 (Scheme 22).

Synthesis of the 2-formyl pyrrole functionality relied on a key Maillard-type condensation of dihydropyranone 83 with ammonia, which would be synthesised from an Achmatowicz oxidation/rearrangement (Section 2.1.3.2) of furfuryl derivative 87. Epoxide 81, in turn, would be derived from L-tartaric acid (84) with all stereocenters pre-installed.

Scheme 22 Retrosynthetic analysis of proposed structure of acortatarin A (1).
Chapter 2: Discussion of Acortatarin A

2.2. Attempted Synthesis of Proposed Structure of Acortatarin A (1) (Implementation of Strategy I)

2.2.1 Synthesis of Epoxide 81

The synthesis of proposed structure of acortatarin A (1) began with the preparation of the key electrophile 81 for the N-alkylation reaction. The terminal epoxide 81 was obtained by epoxidation of terminal olefin 88, itself synthesised from the known iodide 89 via displacement using vinylmagnesium bromide. Iodide 89 was ultimately derived from the commercially available chiral starting material L-tartaric acid (84).

![Scheme 23 Retrosynthesis of epoxide 81.](image-url)

2.2.2 Synthesis of Iodide 89

The initial objective was to prepare the known iodide 89 required for the subsequent Grignard displacement and epoxidation reaction (Scheme 24). Benzyl ether 90 was synthesised according to Seebach’s method. Accordingly, esterification of commercially available L-tartaric acid 84 using HCl in methanol, followed by protection of the resulting diol 91 using 2,2-dimethoxypropane in the presence of p-TSA in toluene gave acetonide 92. The diester 92 was reduced with LiAlH₄ in THF heated under reflux, furnishing diol 93 in 85% yield. Monoprotection of diol 93 was conducted using 1.1 equivalents of NaH and one equivalent of benzyl bromide in THF. The desired monoprotected benzyl ether 90 was obtained in 60% yield after purification by flash column chromatography. The conversion of the remaining primary alcohol 90 to iodide 89 was conducted under modified Appel conditions employing I₂ and PPh₃ in toluene heated under reflux, providing iodide 89 in 85% yield. The ¹H and ¹³C NMR spectrum and optical rotation data for iodide 89 were all identical to the literature data.
Scheme 24 Synthesis of iodide 89. Reagents and conditions: i) MeOH, conc. HCl, reflux, 12 h; ii) 2,2-dimethoxypropane, p-TSA, toluene, 50 °C, 6 h; iii) LiAlH₄, THF, reflux, 4 h; iv) NaH, BnBr, THF, 0 °C to r.t., 2 h, 70% over 4 steps; v) I₂, PPh₃, imidazole, toluene, reflux, 2 h, 85%.

2.2.3 Synthesis of Epoxide 81

Iodide 89 was immediately carried through to the Grignard reaction due to its instability. The synthesis of the enantiomer of olefin 88 from the corresponding iodide has been reported by two research groups. The major common drawback of their synthesis was the use of the carcinogenic reagent hexamethylphosphoric triamide (HMPA) as a co-solvent. Initially, we attempted a Grignard displacement using vinylmagnesium bromide in THF in the presence of catalytic CuI. Unfortunately, the initial attempts were unsuccessful, even when ten equivalents of vinylmagnesium bromide were used (entry 1, Table 1).

Scheme 25 Synthesis of epoxide 81. Reagents and conditions: i) vinylmagnesium bromide, CuI, THF, DMPU, 2 h, 85%; ii) CF₃COCH₃, Oxone®, CH₃CN: H₂O (3: 2), 12 h, 85% (95% brsm).

A review of the available literature suggested that the presence of HMPA is crucial to enable a successful Grignard displacement reaction using alkyl halides. HMPA has been extensively used due to its unique properties as a dipolar aprotic solvent and its superior ability to form cation-ligand complexes. However, HMPA has been shown to be carcinogenic in animal tests even at low concentrations. In 1992, Seebach demonstrated that the use of 1,3-dimethyltetrahydropyrimidin-2(1H)-one (DMPU) exhibited equal effects to HMPA in oxirane-openings with Li-acetylide, in Wittig olefinations, double deprotonation of nitroalkanes, Michael additions of Li-dithiane to cyclohexenones, and in the selective generation of certain enolates.
was therefore proposed that DMPU would be a safer alternative to the carcinogenic HMPA as a co-solvent for the Grignard reaction under current investigation.

With this idea in mind, the Grignard reaction was carried out using five equivalents of vinylmagnesium bromide in THF with 10% DMPU at –20 °C for 5 hours (entry 2, Table 1). Pleasingly, olefin 88 was obtained in 50% yield, albeit coexisting with inseparable starting material (40%) as determined by 1H NMR analysis (entry 2, Table 1).

With the amount of DMPU, the reaction period could affect the reaction period. With 10% of DMPU in THF at –20 °C (entry 2, Table 1), the reaction took overnight to go to completion, whereas with 20% of DMPU in THF at –20 °C (entry 3, Table 1), the reaction was accomplished in 5 h as indicated by 1H NMR. Use of 50% DMPU in THF was established to be the optimal conditions as the reaction completed in 2 h, leading to the formation of the desired product 88 in 85% yield after purification by column chromatography (entry 4, Table 1). With suitable conditions established for the Grignard reaction, a gram-scale Grignard reaction was performed using 50% DMPU in THF at –20 °C, affording olefin 88 in reproducible 85% yield after purification by column chromatography (entry 4, Table 1).
Following the successful preparation of olefin 88, attention turned to the preparation of epoxide 81. Typically, electron-deficient olefins are oxidised more slowly than electron-rich ones and tetra-substituted olefins are generally oxidised the fastest. The classic epoxidation method using m-CPBA in CH₂Cl₂ was attempted first (entry 1, Table 2). The reaction did not exceed 30% conversion even after 3 days in CH₂Cl₂ under reflux. Disappointingly, using freshly recrystallised m-CPBA did not afford a better yield (entry 2, Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>commercial m-CPBA, CH₂Cl₂, 0 °C to r.t., 12 h</td>
<td>81 30%, 88 55%</td>
</tr>
<tr>
<td>2</td>
<td>recrystallised m-CPBA, CH₂Cl₂, r.t. to reflux, 12 h</td>
<td>81 39%, 88 55%</td>
</tr>
<tr>
<td>3</td>
<td>acetone, Oxone®, r.t., 10 h</td>
<td>88 recovered</td>
</tr>
<tr>
<td>4a</td>
<td>CF₃COCH₃, Oxone®, CH₃CN:H₂O 3:2, r.t., 10 h</td>
<td>67%</td>
</tr>
<tr>
<td>5b</td>
<td>CF₃COCH₃, Oxone®, CH₃CN:H₂O 3:2, r.t., 12 h</td>
<td>95% brsm</td>
</tr>
</tbody>
</table>

a: 0.2 equivalents of CF₃COCH₃. 55% olefin 88 was recovered.
b: stoichiometric amount of CF₃COCH₃. 10% Olefin 88 was recovered.

Dimethyl dioxirane (DMDO), which is known to be an electrophilic oxidising reagent for unreactive olefins, was next investigated to effect the epoxidation of terminal alkene 88. DMDO was prepared in situ from acetone and Oxone® and used in a stoichiometric quantity. Unfortunately, no desired product was observed with DMDO, which was thought to be due to the electron-deficient nature of olefin 88 (entry 3, Table 2).

Curci and co-workers reported the first isolation and characterisation of methyl(trifluoromethyl)dioxirane (TFD) in 1988. However, the in situ formation of TFD method was still more practical.

Subsequent research conducted by Shi and co-workers revealed that TFD showed higher reactivity towards the epoxidation of terminal olefins than m-CPBA. Accordingly, 1,1,1-trifluoroacetone was added dropwise to a stirred solution of alkene 88 in aqueous CH₃CN at 0 °C with a precooled syringe followed by a portion of a mixture of Oxone® and NaHCO₃. The rest of the mixture of Oxone® and NaHCO₃ was added to the above reaction every half an hour over two hours. NaHCO₃ as a buffer was added to the reaction mixture to neutralise the
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1,1,1-trifluoroacetic acid generated from 1,1,1-trifluoroacetone after oxidation. After the addition was complete, the reaction mixture was left to stir at room temperature for ten hours. Initially, a catalytic amount of 1,1,1-trifluoroacetone was employed (entry 4, Table 2), with only a small amount of product 81 obtained and a large amount of unreacted olefin 88 recovered. With a stoichiometric amount of 1,1,1-trifluoroacetone (entry 5, Table 2), the reaction proceeded faster and a higher yield of epoxide 81 was achieved. Simple extraction followed by flash column chromatography purification afforded the desired product in 95% yield based on the recovered starting material (brsm). The exact diastereomeric ratio (d.r.) was not obtained for epoxide 82 due to the overlapping resonances. Since the stereocenter at C-5 would be subsequently oxidised into a carbonyl, d.r. of the product from the epoxidation step and the following reaction sequence was inconsequential. Herein, the approximate d.r. at C-5 was reported wherever possible in this section, otherwise it was used as a diastereomeric mixture (vide infra).

The disappearance of two groups of distinctive proton multiplets corresponding to the terminal double bond protons at δ 5.88-5.78 and δ 5.16-5.07 and the presence of two groups of proton multiplets at δ 3.09-3.05 and δ 2.53-2.49 in the 1H NMR spectrum indicated that epoxidation had indeed occurred. The exact d.r. was not determined by the resonances of epoxide 81 due to the overlapping resonances. Reverse addition of alkene 88 to the preformed TFD solution provided no further improvement. The increased reactivity in the presence of 1,1,1-trifluoroacetone can be attributed to the fact that electron-withdrawing groups such as CF3 are highly beneficial for the reactivity of a ketone catalyst. For some less active ketones, higher conversions could be obtained by using more equivalents of the ketone and prolonged reaction times.88
2.2.4 Summary of the Preparation of Epoxide 81

Epoxide 81 was prepared from L-tartaric acid, beginning with diesterification, formation of acetonide and reduction of the diester, followed by monoprotection of the resultant diol to afford benzyl ether 90 in 60% yield over 4 steps (Scheme 26). Subsequent iodination of the benzyl ether 90 using modified Appel conditions followed by Grignard displacement of the iodide employing vinylmagnesium bromide in DMPU and THF (1:1) at −20 °C provided olefin 88 in 56% yield over two steps. Epoxidation of olefin 88 was conducted in aqueous CH$_3$CN with a stoichiometric amount of trifluoroacetone using Oxone$^\text{®}$ as a co-oxidant to afford epoxide 81 in 85% yield (94% brsm).

Scheme 26 Summary of the synthesis of epoxide 81. Reagents and conditions: i) MeOH, conc. HCl, reflux, 12 h; ii) 2,2-dimethoxypropane, p-TSA, toluene, 50 °C, 6 h; iii) LiAlH$_4$, THF, reflux, 4 h; iv) NaH, BnBr, THF, 0 °C to r.t., 2 h, 60% over 4 steps; v) I$_2$, PPh$_3$, imidazole, toluene, reflux, 5 h; vi) vinylmagnesium bromide, CuI, THF, DMPU, −20 °C to 0 °C, 2 h, 50-56% over 2 steps; vii) CF$_3$COCH$_3$, Oxone$^\text{®}$ and NaHCO$_3$, CH$_3$CN:H$_2$O 3:2, 0 °C to r.t., 12 h, 85%, 94% brsm.
2.2.5 Synthesis of Pyrrole 82

With a route to the key intermediate chiral epoxide 81 established, attention next turned to the construction of pyrrole 82. 2-Formyl pyrrole 82 was anticipated to be assembled from dihydropyranone 83 via a Maillard-type condensation with ammonia. An Achmatowicz oxidation/rearrangement of alcohol 94 was employed to furnish the required dihydropyranone 83, which could be accessed from furfuryl alcohol 87 using a modified Bouveault formylation reaction.89

Scheme 27 Retrosynthesis of pyrrole 82.

2.2.6 Preparation of Alcohol 94

In parallel with epoxide 81, the requisite TBS silyl ether 94 was prepared following procedures reported by Celanire and co-workers (Scheme 28).90 Commercially available furfuryl alcohol 95 was protected as its TBS silyl ether 87 in DMF at room temperature following the reliable and efficient procedure reported by Corey and co-workers, in which the alcohol is reacted with a silyl chloride and imidazole at high concentration in DMF, giving TBS silyl ether 87 in quantitative yield.91 A modified Bouveault formylation89 of the resulting silyl ether 87 at C-5 was conducted using n-BuLi in THF and quenching with DMF to give aldehyde 96 in 65% yield. Subsequent reduction with NaBH₄ in methanol proceeded uneventfully furnishing alcohol 94 quantitatively with ¹H and ¹³C NMR data in agreement with the literature.90

Scheme 28 Synthesis of alcohol 94. Reagents and conditions: i) TBSCI, imidazole, DMF, r.t., 30 min, quant.; ii) n-BuLi, THF, DMF, −78 °C to r.t., 1 h at −78 °C, 2 h at 0 °C, 65%; iii) NaBH₄, MeOH, 0 °C, 1 h, quant.
2.2.7 Achmatowicz Oxidation/Rearrangement Reaction

The next step in the synthesis required the conversion of alcohol 94 to dihydropyranone 83 (Scheme 29), in readiness for the Maillard-type condensation (pyrrole formation).

\[
\begin{align*}
\text{HO-} & \text{O} \quad \text{OTBS} \quad \text{HO-} & \text{O} \\
\text{94} & \quad \rightarrow & \quad \text{OTBS} \\
\end{align*}
\]

Scheme 29 Synthesis of dihydropyranone 83.

In the literature, the most extensive use of furan rearrangement chemistry generally employs a reaction originally discovered by Achmatowicz and co-workers in 1971. This oxidative rearrangement, now referred to as Achmatowicz reaction, has become an important method for the conversion of furfurylcarbinols into \(\alpha,\beta\)-unsaturated pyranones under oxidative conditions. Since its discovery, this oxidation reaction has successfully provided access to a number of interesting synthetic intermediates and natural products (Figure 9).

![Figure 9](image)

Figure 9. The applications of Achmatowicz reaction in natural product synthesis.

Although the original oxidative conditions reported by Achmatowicz employed \(\text{Br}_2\) in \(\text{MeOH}\), this widely-applied oxidative rearrangement reaction often proceeds with a variety of different oxidants, including the use of \(\text{m-CPBA}\), \(\text{NBS}\), \(\text{DMDO}\), \(\text{PCC}\), or \(t\text{-BuO}_2\text{H-VO(acac)}_2\). The mechanism of the original rearrangement is thought to proceed through formation of a bromonium intermediate 97, followed by a bromonium ring-opening reaction (Scheme 30). Eventually, the furan ring 98 undergoes hydrolysis to give a 1,4-dicarbonyl species 99, which upon nucleophilic addition of the alcohol provides the corresponding dihydropyranone 100.
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The accepted mechanism for the oxygen-mediated rearrangement involves a hydroxyl-directed epoxidation of furan 101 across the C2-C3 olefin (Scheme 31). The lone pair of electrons on the allylic hydroxyl group possesses σ→π conjugation, leading to the regioselective epoxidation of the furan ring. A six electron movement occurs around the ring, opening epoxide 102 to yield zwitterion 103. Carbonyl formation opens the ring and generates 1,4-diketone 104. An intramolecular nucleophilic attack of the free hydroxyl onto the non-adjacent ketone closes the ring and generates hemiacetal 105. The stereochemistry in the α-hydroxyfuran 105 is retained in the product. Due to the anomeric effect, the α-anomer is expected to be the major diastereomer. 78

While the Achmatowicz reaction has gained widespread use in organic chemistry, further scope for its application exists, since there are less than twenty examples (based upon SciFinder® searches) where the furan has a substituent at either the C-3 or C-4 positions.

Regardless, our focus moved on towards the synthesis of dihydropyranone 83 (Scheme 32), which was known to be sensitive to strongly acidic or alkaline media. 79 Hence, alcohol 94 was initially
Chapter 2: Discussion of Acortatarin A

treated with recrystallised $m$-CPBA$^3$ to yield dihydropyranone 83 in quantitative yield. Gratifyingly, when alcohol 94 was treated with a commercial bottle of $m$-CPBA in anhydrous CH$_2$Cl$_2$ at room temperature, dihydropyranone 83 was also obtained in quantitative yield.

![Scheme 32 Synthesis of dihydropyranone 83. Reagents and conditions: i) $m$-CPBA, CH$_2$Cl$_2$, r.t., 4 h, quant.](image)

$^3$ $m$-CPBA was recrystallised from toluene to remove the impurities. 35 g $m$-CPBA (Aldrich 57–86%) was dissolved in 250 mL ether and washed with 3x150 mL buffer solution (410 mL 0.1 M NaOH, 250 mL 0.2 M KH$_2$PO$_4$ made up to 1 L, pH 7.5). The ether layer was dried over MgSO$_4$ and carefully evaporated under reduced pressure to give ca. 17 g pure $m$-CPBA (CAUTION! potentially explosive)
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2.2.8 Use of a Maillard-type Condensation to Access Pyrrole 82

The chemistry of the Maillard reaction, also known as non-enzymatic browning, is known as a complex series of reactions leading to the formation of a variety of products, including the flavours, aromas and colours considered important in food science. This reaction was described for the first time by Louis Maillard in 1912, but the first coherent scheme was not put forward until 1953 by Hodge. In a typical Maillard-type condensation, substance yields can range from 0-30% and compound concentrations lying in the ppb or even lower have been observed, making identification of products difficult.

Among the products formed during the condensation, the most valuable one is 2-formyl pyrrole. As mentioned earlier, 2-formyl pyroles are present in a variety of natural products, especially with electron-donating groups at C-5, making this reaction pathway of great interest and significance. Furthermore, it would be desirable to have sufficient flexibility to enable an investigation of the capacity of these methods to produce 2,5-disubstituted pyrrole compounds using this Maillard type condensation process.

![Scheme 33 Elaboration to access pyrrole 82 via Maillard-type condensation.](image)

Although the chemistry of the Maillard reaction is well known, the mechanism of the Maillard reaction is very complex. However, it is generally divided into three stages (Scheme 34). The first stage involves the sugar-amine condensation, which has been well-defined and no browning occurs at this stage. The second stage involves sugar dehydration and fragmentation, and amino acid degradation via the Strecker reaction especially at high temperatures. The end of stage two is the beginning of flavour formation. The last stage is the formation of heterocyclic nitrogen compounds.

![Scheme 34 Proposed mechanism of Maillard condensation.](image)
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In essence, the Maillard reaction is sensitive to pH, temperature and water like the browning reaction. As each of these compounds arises from an individual reaction, each will be influenced by its own reactant concentration, environment and processing conditions, especially temperature.  

Reaction of dihydropyranone 83 with saturated aqueous ammonia at room temperature for 2 h afforded the desired pyrrole 30% yield. The presence of a singlet at $\delta$9.48 in the $^1$H NMR spectrum and a signal at $\delta$ 179.5 in the $^{13}$C NMR spectrum indicated the formation of a new aldehyde functional group. Further NMR and HRMS studies confirmed the successful synthesis of pyrrole 82. Attempted optimisation of this reaction by changing the ratio between ammonia and dihydropyranone 83 (entries 1-5, Table 3) or employing various amine sources (entries 7-8, Table 3) was unrewarding. Using anhydrous conditions proved fruitless with no desired product observed (entry 6, Table 3), only resulting in a complex unidentifiable mixture. The best yield obtained was 35% (entry 4, Table 3). Due to the easy preparation of dihydropyranone 83 and the desire to investigate the N-alkylation reaction of pyrrole 82, we moved on to the next step.

Table 3. Attempted optimisation of pyrrole 82.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine source(s)</th>
<th>Ratio</th>
<th>T(°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>sat. aq. NH$_3$</td>
<td>10:1</td>
<td>r.t.</td>
<td>33%</td>
</tr>
<tr>
<td>2</td>
<td>dil. aq. NH$_3$</td>
<td>10:1</td>
<td>r.t.</td>
<td>34%</td>
</tr>
<tr>
<td>3</td>
<td>sat. aq. NH$_3$</td>
<td>10:1</td>
<td>50</td>
<td>34%</td>
</tr>
<tr>
<td>4</td>
<td>sat. aq. NH$_3$</td>
<td>6:1</td>
<td>r.t.</td>
<td>35%</td>
</tr>
<tr>
<td>5</td>
<td>sat. aq. NH$_3$</td>
<td>3:1</td>
<td>r.t.</td>
<td>21%</td>
</tr>
<tr>
<td>6</td>
<td>anhdrous NH$_3$ in MeOH</td>
<td>5:1</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>NH$_4$OAc</td>
<td>3:1</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>NH$_4$Cl</td>
<td>5:1</td>
<td>r.t.</td>
<td>0</td>
</tr>
</tbody>
</table>
2.2.9 Summary of the Preparation of Pyrrole 82

As demonstrated in Scheme 35, the synthesis of pyrrole 82 commenced with TBS silyl ether protection of furfuryl alcohol 95 in CH₂Cl₂ affording silyl ether 87 in quantitative yield. A modified Bouveault formylation reaction followed by reduction using NaBH₄ in methanol gave alcohol 94 in 65% yield over two steps. Subsequent Achmatowicz oxidation/rearrangement reaction using commercial m-CPBA provided dihydropyranone 83 in quantitative yield, which was ready for the Maillard-type condensation to prepare pyrrole 82. Pyrrole 82 was synthesised in 35% yield without further optimisation (Scheme 35).

Scheme 35 Synthesis of pyrrole 82. Reagents and conditions: i) TBSCI, imidazole, CH₂Cl₂, r.t., 15 min, quant.; ii) n-BuLi, THF, DMF, –78°C to r.t., 1 h at –78°C then 2 h at 0°C, 62% over two steps; iii) NaBH₄, MeOH, 0°C, 1 h, 65% over two steps; iv) m-CPBA, CH₂Cl₂, r.t., 4 h, quant.; v) sat. aq. ammonia, 1,4-dioxane, NEt₃, r.t., 1 h, 35%.

2.2.10 Model Study: N-Alkylation of Epoxide 81 by Pyrrole 10

Due to the arduous work of preparing pyrrole 82, a model study was conducted on the key N-alkylation step using a simple pyrrole to test the methodology. Pyrrole (10) was treated with NaH in DMF at 0°C then reacted with epoxide 81 to afford alcohol 106. Pleasingly, the N-alkylation product 106 was successfully obtained in 80% yield (Scheme 36).

Scheme 36 Model study of N-alkylation of epoxide 81 with pyrrole 10. Reagents and conditions: i) NaH, DMF, 0°C, 4 h, 80%.
2.2.11 Attempted \( N \)-Alkylation of Pyrrole 81 with A Variety of Nucleophiles

A. Using Epoxide 81 as the Nucleophile

With the two requisite partners epoxide 81 and pyrrole 82 in hand, the attempted \( N \)-alkylation of epoxide 81 was investigated employing the conditions successfully used above to effect the \( N \)-alkylation of pyrrole 10. Disappointingly, attempted \( N \)-alkylation of 2,5-disubstituted pyrrole 82 using epoxide 81 with NaH in DMF, only resulted in the recovery of both starting materials (entry 1, Table 4).

Further literature searching revealed that the \( N \)-alkylation of pyrrole with lactones 108 has been effected using KH as an alternative base to deprotonate pyrrole 10, affording the thermodynamically favoured product 109 in an excellent yield (Scheme 38).\(^ {103} \) However, applying these conditions to our substrates (epoxide 82 and pyrrole 81) delivered no desired product (entry 2, Table 4).

The \( pK_a \) of the pyrrole nitrogen proton is 23.0 in DMSO, due to participation of the \( N \) lone pair in aromaticity, which can be easily deprotonated by strong bases such as \( n \)-BuLi. On the other hand, 2,5-disubstituted pyroles with two electron-withdrawing groups are more acidic than pyrrole. However, in our case, the \textit{ortho}-positions are substituted with one electron-withdrawing group and one electron-donating group. Due to the dominance of the TBS silyl ether, it was hypothesised that compound 82 is less acidic than its parent pyrrole. Thus, a stronger base (\( n \)-BuLi) was next examined to effect nitrogen deprotonation. \( n \)-BuLi was added dropwise to
pyrrole \( \text{82} \) in anhydrous THF at \(-78^\circ\text{C}\), followed by the addition of epoxide \( \text{81} \). Upon workup, no detectable alkylated product was observed (entry 3, Table 4).

It was postulated that addition of Lewis acids could activate the electrophile, namely epoxide \( \text{81} \). The Lewis acids \( \text{BF}_3\cdot\text{OEt}_2 \) and \( \text{LiCl} \) were both considered as suitable activating species for \( N \)-alkylation reaction of pyrrole \( \text{107} \).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additives</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>----------</td>
<td>0</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>KH</td>
<td>----------</td>
<td>r.t. to 50</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>( n )-BuLi</td>
<td>-----------</td>
<td>–78</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>NaH</td>
<td>( \text{BF}_3\cdot\text{OEt}_2 )</td>
<td>0 to r.t.</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NaH</td>
<td>LiCl</td>
<td>0 to r.t.</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>KHMDS</td>
<td>( \text{BF}_3\cdot\text{OEt}_2 )</td>
<td>–78 to r.t.</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>KHMDS</td>
<td>18-crown-6</td>
<td>–78 to r.t.</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>KOH</td>
<td>----------</td>
<td>r.t. to 100</td>
<td>DMSO</td>
<td>0</td>
</tr>
</tbody>
</table>

*: full recovery of epoxide \( \text{81} \) and pyrrole \( \text{82} \) was obtained.

Lewis acids such as \( \text{BF}_3\cdot\text{OEt}_2 \) and \( \text{LiCl} \) are able to coordinate to oxygen atoms\(^{104}\), enhancing the reactivity of these substrates, such as epoxides, allowing this transformation to proceed under milder conditions. The electrophilicity of epoxide \( \text{81} \) was expected to be enhanced using a Lewis acid, and the \( N \)-alkylation would thus be facilitated. Disappointingly, using these additives did not lead to any of the desired product (entries 4 and 5, Table 4). The use of polar aprotic solvents such as DMF was also examined to effect this alkylation. Again, no desired product was observed (entry 4, Table 4).

Potassium bis(trimethylsilyl)amide (KHMDS) is a strong non-nucleophilic base used in a wide variety of chemical reactions and transformations, including alkylation, arylation, acylation, and ring formation\(^{105}\). Attempts to improve the reactivity of epoxide \( \text{81} \) towards pyrrole \( \text{82} \) by employing KHMDS in the presence of the Lewis acid \( \text{BF}_3\cdot\text{OEt}_2 \) was also unrewarding (entry 6, Table 4). Additional attempts to effect this \( N \)-alkylation step in the presence of 18-crown-6, which
has been widely used due to its particular affinity for potassium cations in the reaction mixture. Again, this modification of the alkylation was fruitless (entry 7, Table 4).

\[ N\text{-Alkylated indoles and pyrroles have been prepared in high yields (85–95\%) by Ley and co-workers by reaction of indoles and pyrroles with primary alkyl halides in DMSO and powdered KOH, namely “superbase” at room temperature.}^{106} \text{ Accordingly, pyrrole 82, KOH and DMSO were stirred for 0.5 h, then the halides were added and the mixture was heated to 100 °C for two to five hours. After work-up, full recovery of epoxide 81 and pyrrole 82 was obtained after column chromatography (entry 8, Table 4).} \]

Unfortunately, all of the attempts to effect \( N \)-alkylation of 82 with 81 using various bases, Lewis acids and elevated temperatures did not afford any \( N \)-alkylation product 107. A summary of the alkylation conditions attempted is shown in Table 4.

This disappointing result was suspected to either be due to the poor electrophilic properties of epoxide 81 or the poor nucleophilicity of pyrrole 82. Similarly, Aponick and Borrero have since reported the unsuccessful \( N \)-alkylation of pyrrole 82 during their synthesis of acortatarin A.\(^{107}\) They proposed that two factors might prevent the desired alkylation occurring: the steric bulk of CH\(_2\)OTBS flanking the nitrogen and the possibility that by forming the pyrrole anion, -OTBS is eliminated.

In light of the disappointing result obtained from the anticipated \( N \)-alkylation using epoxide 81, it became apparent that increasing the reactivity of these starting materials was required. Thus synthetic efforts towards the elaboration of epoxide 81 and pyrrole 82 moved on towards improving the reactivity of the starting materials via functional group manipulations. 2,5-Disubstituted pyrrole 82, containing an electron-donating group at either C-2 or C-5 has not been studied in detail. Thus efforts towards improving the nucleophilicity of pyrrole 82 required further investigation. Therefore we next focused on improving the reactivity of the electrophile by converting the epoxide into the corresponding \( \alpha \)-haloketone, since many successful examples have been reported on the \( N \)-alkylation of nitrogen heterocyclic compounds using \( \alpha \)-haloketone (Section 2.1.11 B)
B. Using \( \alpha \)-Haloketone 112-114 and Tosylate 125 as Nucleophiles

The use of \( \alpha \)-haloketones as electrophiles in reaction with pyrrole anions has been reported as the key step in the synthesis of a variety of pyrrole-containing natural products. Several successful examples are listed in Table 5.

**Table 5.** Examples of union of haloketones and pyrrole derivatives used in natural product synthesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Haloketone</th>
<th>Product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td>62%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /></td>
<td>57%</td>
</tr>
</tbody>
</table>

Encouraged by these examples of using haloketone compounds to access \( N \)-alkylated products (entries 1-5, Table 5), we embarked on the preparation of \( \alpha \)-haloketone compounds 112-114. \( \alpha \)-Haloketones 112-114 were anticipated to be synthesised via reaction of epoxide 81 with NaI and NaBr followed by oxidation of the resulting hydroxyl group (Scheme 39).

The ring opening of epoxides to form halohydrins can be conducted using halogens,\(^{112}\) hydrogen halides\(^{113}\) and metal halides.\(^{114}\) However, many of the reported methods suffer drawbacks, such as unavailability of the reagents, long reaction time, unsatisfactory yields, formation of side products,
low regioselectivity and harsh reaction conditions. Importantly, many mild and effective methods employing metal catalysts for the opening of epoxides have been reported recently.\textsuperscript{115-117} In 2001, Sabitha and co-workers published the formation of halohydrins from epoxides using NaI in a mixture of acetic acid and propionic acid as the solvent at $-20^\circ\text{C}$ within one hour.\textsuperscript{115}

Adopting Sabitha’s method, epoxide 81 was subjected to NaI or NaBr in a mixture of acetic acid and propionic acid at $-20^\circ\text{C}$ for 30 min furnishing the corresponding C-1 substituted iodohydrin 110 and bromohydrin 111, in 87\% and 85\% yield as a mixture of two diastereomers in a 3.7:1 and 3.5:1 ratio, respectively (Scheme 39). The lack of diastereoselectivity in the formation of halohydrins 110 and 111 is of no consequence since it will be converted to the corresponding ketone 112 and 113 in the next step (\textit{vide infra}).

![Scheme 39](image)

\textbf{Scheme 39} Synthesis of halohydrins 110-111 \textit{Reagents and conditions}: i) NaX (X = I, Br), CH$_3$CO$_2$H:CH$_3$CH$_2$CO$_2$H 1:2, $-20^\circ\text{C}$, 30 min, 110 87\%, 111 85\%.

With $\alpha$-iodohydrin 110 in hand, several oxidation reagents were screened for the preparation of haloketone 113. Hypervalent iodine compounds are known to possess powerful oxidising capabilities especially for the oxidation of alcohols to aldehydes and ketones. Among the hypervalent iodine compounds, 2-iodobenzoic acid (IBX) displays unique properties. The major application of IBX is for the oxidation of primary alcohols to aldehydes at room temperature, without any over-oxidised byproduct. Consequently, IBX was first utilised as the oxidation reagent to access haloketone 113. A low yield of the desired product was obtained when the oxidation was carried out in EtOAc at 50 \°C (entry 1, Table 6). Hence DMSO was employed to effect this oxidation at room temperature. A moderate yield was obtained, along with 20\% of recovered 110 (entry 2, Table 6). Further literature searching revealed that the oxidation of secondary alcohols to ketones is found to be equally effected with IBX and other analogous hypervalent compounds, allowing oxidation of sterically hindered secondary alcohols. Dess-Martin periodinane (DMP) buffered with NaHCO$_3$ in CH$_2$Cl$_2$ was next examined (entry 3, Table 6). Disappointingly, no observable haloketone was formed under these conditions as indicated by TLC. Despite literature precedent for the oxidation of halohydrins to haloketone using hypervalent iodine reagents, they
did not show any reactivity towards halohydrin 110. Other oxidation conditions were therefore sought.

Table 6. Synthesis of α-haloketone 112 and 114.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidation reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBX</td>
<td>EtOAc</td>
<td>50</td>
<td>3 h</td>
<td>32%</td>
</tr>
<tr>
<td>2</td>
<td>IBX</td>
<td>DMSO</td>
<td>r.t.</td>
<td>10 h</td>
<td>112 53%, 110 20%</td>
</tr>
<tr>
<td>3</td>
<td>DMP</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>10 h</td>
<td>degradation</td>
</tr>
<tr>
<td>4</td>
<td>DMSO+Et₃N+(COCl)₂</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>3 h</td>
<td>110 recovered</td>
</tr>
<tr>
<td>5</td>
<td>PDC</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>12 h</td>
<td>112 65%, 114 32%</td>
</tr>
<tr>
<td>6</td>
<td>PCC</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>12 h</td>
<td>112 65%, 114 32%</td>
</tr>
</tbody>
</table>

The Swern oxidation was next investigated, again with disappointing results (entry 4, Table 6). However, chromium based reagents PDC and PCC, although not widely used due to their toxicity and the tedious reaction workup procedure, act as mild and selective reagents for the preparation of both saturated and unsaturated aldehydes and ketones. Activated powdered 4 Å molecular sieves or Celite® can be added to simplify the work-up procedure. The reduced chromium salts and other reagent-derived byproducts are deposited onto these solids, and can then be readily removed by filtration. The presence of activated powdered 4 Å molecular sieves was found to be superior to the use of Celite®. Therefore oxidation of halohydrin 110 was carried out employing either PDC or PCC as the oxidant. Accordingly, halohydrin 110 was submitted to a mixture of PDC or PCC and activated 4 Å molecular sieves powder in anhydrous CH₂Cl₂ at room temperature, affording iodoketone 112 in 55% and 65% yield, respectively together with chloroketone 114 in 32% when employing excess PCC as the oxidant (entries 5 and 6, Table 6). The presence of a signal at δ 200.3 in the ¹³C NMR spectrum indicated the formation of a new carbonyl functional group. Bromoketone 113 was prepared using the optimal conditions established for iodoketone 112 in 70% yield. Further evidence for the successful formation of the desired α-haloketone 112-114 was identified by NMR and HRMS studies.

It was observed that the presence of activated powdered 4 Å molecular sieves was superior to Celite®, which was reasoned to be due to their ability to take up the water produced from the oxidation reaction, thus increasing the rate of oxidation.¹¹⁸
Chapter 2: Discussion of Acoortatarin A

It was interesting to note that when $\alpha$-iodohydrin $\text{110}$ was treated with PCC in CH$_2$Cl$_2$, halogen exchange occurred unexpectedly, delivering iodoketone $\text{112}$ in 65% yield together with $\alpha$-chloroketone $\text{114}$ in 25% yield. It was reasoned that the C–I bond experiences increased polarity from the inductive effect of the carbonyl group making the carbon atom more electropositive, enhancing the leaving ability of the iodine. Thus an iodine-chlorine halogen exchange reaction took place when iodohydrin $\text{110}$ was subjected to an excess amount of PCC.

Following the successful preparation of $\alpha$-haloketone $\text{112-114}$, attention then turned to the critical $N$-alkylation of pyrrole $\text{82}$ (Table 7).

Table 7. Attempted $N$-alkylation using $\alpha$-haloketone $\text{112-114}$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$X$</th>
<th>bases</th>
<th>solvent</th>
<th>Temperature</th>
<th>time</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>NaH</td>
<td>THF</td>
<td>0 °C→ r.t.</td>
<td>1 h</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>r.t. → reflux</td>
<td>2 h</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>r.t. → reflux</td>
<td>1 h</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>KOH</td>
<td>DMSO</td>
<td>100 °C</td>
<td>2 h</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>LiHMDS</td>
<td>THF</td>
<td>0 °C→ r.t.</td>
<td>1 h</td>
<td>a</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>NaH</td>
<td>THF</td>
<td>0 °C→ r.t.</td>
<td>2 h</td>
<td>a</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>r.t. → reflux</td>
<td>2 h</td>
<td>a</td>
</tr>
</tbody>
</table>

a: Complete degradation of haloketone $\text{112-114}$ was observed. Pyrrole $\text{82}$ was recovered.

In 1995, Fürstner and co-workers published the first total synthesis of lukianol A, the final step of which was $N$-alkylation of pyrrole $\text{115}$ using bromide $\text{116}$ in the presence of K$_2$CO$_3$ in DMF heated under reflux giving the expected $N$-alkylated product in 90% yield (Scheme 40).$^{108}$
Regrettably, bromoketone 113 degraded within one hour upon subjection of α-bromoketone 113 and pyrrole 82 to K₂CO₃ in DMF heated under reflux (entry 3, Table 7). Use of KOH in DMSO at 100 °C was also attempted to achieve the union of epoxide 81 with pyrrole 82, however this also proved unrewarding, resulting in the decomposition of bromoketone 113 and the recovery of pyrrole 82 (entry 4, Table 7).

In 2008, Gaunt demonstrated that the use of LiHMDS in THF at −78 °C to 0 °C effected the coupling of pyrrole 117 with acetyl chloride 118 in 76% yield (Scheme 41). Those conditions were applied to the N-alkylation of pyrrole 82 with chloride 114. However, this was unrewarding using variable temperatures, with only the complete loss of haloketone 114 and recovery of pyrrole 82 being observed (entry 5, Table 7).

In conclusion, the conditions using NaH in THF, LiHMDS in THF, KOH in DMSO and K₂CO₃ in DMF for the attempted N-alkylation of pyrrole 82 with α-halo ketones 112-114, only led to the degradation of ketones 112-114 and recovery of pyrrole 82. Interestingly, similar attempts were also conducted by Aponick and Borrero in their work towards the synthesis of acortatarin A. We proposed that the haloketones 112-114 were too sensitive to the basic media used. Further ¹H NMR analysis of the reaction mixture revealed unidentifiable complex mixtures, suggesting that
use of a more robust electrophilic functional group was required to effect the desired chemical transformation to ketone 86.

Compared to $\alpha$-haloketones, tosylate compounds have been recognised to be more stable towards basic conditions and have been used extensively for the preparation of $N$-alkylated products. In 2005, Trauner and co-workers demonstrated the synthesis of rhazinilam beginning from tosyl lactone 119 coupled with the anion of pyrrole 120 using NaH in DMF affording compound 121 in 94% yield (Scheme 42). 5 In order to circumvent the potential decomposition of $\alpha$-haloketone 112-114, the use of a more robust tosylate ketone 124 was explored next.

![Scheme 42 Synthesis of rhazinilam reported by Trauner. Reagents and conditions: i) NaH, DMF, 0 to 23 °C, 94%.](image)

Olefin 88 was oxidised to diol 122 using catalytic OsO$_4$ in a buffered mixed solvent of tert-butanol, acetone and H$_2$O and stoichiometric co-oxidant $N$-methylnmorpholine oxide (NMO) (Scheme 43). 120 The reaction was conducted in a buffered solution using a combination of Na$_2$HPO$_4$ and NaH$_2$PO$_4$ to ensure a stable pH, as the reaction proceeded more rapidly under slightly basic conditions. 120 Diol 122 was successfully isolated in 65% yield as a mixture of two diastereoisomers (the exact d.r. was not obtained due to the broadness of the proton resonances) with 20% olefin 88 recovered after purification. Further optimisation was conducted by prolonging the reaction time; gratifyingly, the desired diol 122 was obtained in quantitative yield without further purification required. Mono-tosylation was carried out in CH$_2$Cl$_2$ with tosyl chloride in the presence of Et$_3$N to afford $\alpha$-hydroxy tosylate 123 in 85% yield (d.r. 3.2:1 as determined by the resonances of H-4), that was then subjected with IBX in DMSO at 50 °C to yield ketone 114 in 63% yield, ready for the key $N$-alkylation reaction.
Chapter 2: Discussion of Acortatarin A

Scheme 43 Synthesis of ketone 124. *Reagents and conditions:* i) OsO₄, NMO, acetone:H₂O 1:1, pH 7 buffer, r.t., 10 h, quant.; ii) TsCl, Et₃N, CH₂Cl₂, r.t., 3 h, 80%; iii) IBS, DMSO, 50 °C, 3 h, 63%.

With the requisite tosylate 124 in hand, the coupling of tosylate 124 and pyrrole 82 was first attempted adopting Trauner’s conditions (NaH as base in DMF). Disappointingly, no desired product was observed either at elevated temperature or with prolonged reaction times (Scheme 44).

Scheme 44 Attempted alkylation of pyrrole 82 using tosylate 124 using Trauner’s conditions.⁵ *Reagents and conditions:* i) NaH, DMF, 0 to 23 °C.

In 2002, Banwell completed an elegant synthesis of halitulin using KHMDS in a mixed solvent of DMF and THF, giving the desired N-alkylated product 125 in 87% yield (Scheme 45). Encouraged by this result, we attempted using this method for the preparation of ketone 86, but this proved unrewarding. Further investigations employing the conditions attempted for the coupling of pyrrole 82 and α-haloketones 112-114 (Table 7) were all unsuccessful, with no observable formation of the coupled product 86 and the recovery of both starting materials (Scheme 45).
2.2.12 Attempted N-Alkylation of Hydroxymethyl Pyrrole 5 with Haloketone 112-114

TBS silyl ethers increase the electron density on the adjacent group, which is detrimental to the pyrrole N-alkylation of pyrrole 82 with the electrophiles attempted (81, 112-114). The TBS-silyl protection group was suspected to be the reason for the unsuccessful N-alkylation. Literature searching revealed that subjection of hydroxymethyl pyrrole 5 to a solution of bromide 126 in DMF in the presence of t-BuOK at 100 °C afforded N-alkylated product in 127 42% yield (Scheme 46). This literature precedent led us to survey the N-alkylation chemistry of hydroxymethyl pyrrole 5.

Consequently, pyrrole 82 was unmasked to hydroxymethyl pyrrole 5 in order to remove the electron-donating effect of the silyl group. Pyrrole 82 was submitted to a solution of TBAF in THF, affording the corresponding alcohol 5 in 95% yield after purification by flash column chromatography (Scheme 47).

Scheme 45 Synthesis of halitulin (125) and attempted synthesis of ketone 86. Reagents and conditions: i) KOH, DMSO, reflux, 2 h.

Scheme 46 Synthesis of pyrrole 127. Reagents and conditions: i) t-BuOK, DMF, 100 °C, 4 h, 42%.
In parallel, a model iodide compound 129 was synthesised from 1,3-propanediol 128 over two steps in 47% yield according to Thompson’s conditions (Scheme 48). The $^1$H and $^{13}$C NMR spectroscopic data obtained for the known iodide 129 was in good agreement with the literature.

With both coupling partners in hand, attention turned to the $N$-alkylation of pyrrole 5 with iodide 129. Using conditions analogous to that described by Miller, treatment of a mixture of iodide 129 and pyrrole 5 with $t$-BuOK in anhydrous DMF at 100 °C for 4 h afforded the $N$-alkylated product 130 in 38% yield, along with $N,O$-alkylated byproduct 131 in 15% yield (Scheme 49). Despite the lack of regioselectivity, this observation prompted us to further investigate the elaboration of hydroxymethyl pyrrole 5.

Hydroxymethyl pyrrole 5 and $\alpha$-haloketone 112-114 were subjected to the conditions used above for the construction of pyrrole 132. Disappointingly, none of the desired product 132 was obtained, with only the decomposition of $\alpha$-haloketone 112 and 113 being observed (entries 1, 2, 4 and 5, Table 8). It was suspected that $\alpha$-haloketones 112-114 were unstable under the strongly basic conditions at elevated temperatures. Thus, use of milder conditions, namely room temperature with $K_2CO_3$, as the base was investigated for the preparation of ketone 132 (entries 3 and 4, Table 8). Unfortunately, all these attempts towards the synthesis of ketone 132 were unrewarding. Use of a-
bromoketone 113 with t-BuOK as the base in anhydrous DMF at room temperature only led to the decomposition of bromoketone 113 (entry 6, Table 8).

Table 8. Attempted synthesis of ketone 121.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I,  Cl</td>
<td>t-BuOK, DMF, 100 °C, 4 h</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>I,  Cl</td>
<td>t-BuOK, DMF, 50 °C, 4 h</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>I,  Cl</td>
<td>K₂CO₃, DMF, 50 °C., 6 h</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>I,  Cl</td>
<td>t-BuOK, DMF, r.t., 4 h</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>t-BuOK, DMF, 50 °C, 4 h</td>
<td>a</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>t-BuOK, DMF, r.t., 4 h</td>
<td>a</td>
</tr>
</tbody>
</table>

a: Decomposition of α-haloketone 112-114 was observed.

2.2.13 Summary of the Attempted N-Alkylation Using Various Pyrrole Nucleophiles

The initial strategy for the synthesis of ketone 132 relied on a key N-alkylation reaction between pyrrole 82 and various electrophiles 112-114 (Scheme 50). N-Alkylation of pyrrole 82 with epoxide 81 was first attempted. Unfortunately, this proved fruitless, despite employing a range of bases and elevated temperatures (Table 4, Section 2.1.11 A).

The α-halo ketone electrophiles 112-114 were synthesised by ring-opening of epoxide 81 with NaI and NaBr followed by oxidation of the resulting secondary hydroxyl group in 47% yield over two steps. Disappointingly, attempted N-alkylation of TBS silyl ether protected pyrrole 81 or hydroxymethyl pyrrole 5 using these three electrophiles either led to the decomposition of the α-haloketones or recovery of both starting materials (Table 7, Section 2.1.11 B).

In turn, tosylate 124 was synthesised from alkene 88 employing Upjohn dihydroxylation followed by selective mono-tosylation and subsequent oxidation of the resulting hydroxyl group using PCC in dry CH₂Cl₂ affording tosylate 124 in 25% yield over three steps. Further attempted N-alkylation using tosylate 124, however, was disappointing with only recovery of both starting materials observed.
To our dismay, further attempts using hydroxymethyl pyrrole 5 with a variety of electrophiles (112-114) also failed to deliver any of the desired N-alkylated product (Table 8, Section 2.1.12).

In conclusion, all efforts to effect the key N-alkylation reaction using the aforementioned electrophiles were plagued by the decomposition of the electrophiles 112-114 or the recovery of starting materials in the case of tosylate 124. It was therefore decided to examine the nucleophilicity of pyrrole 82 using deuterium exchange experiments (vide infra)

Scheme 50: Summary of the attempted N-alkylation reactions of pyrrole 5 and 82. Reagents and conditions:
i) CF₃COCH₃, Oxone®, CH₃CN:H₂O 3:2, 0 °C to r.t., 12 h, 85% (94% brsm); ii) NaI, CH₃CO₂H:CH₃CH₂CO₂H 1:2, –20 °C, 30 min, 87%; iii) PCC, 4 Å molecular sieves, CH₂Cl₂, r.t., 12 h, 65%; iv) OsO₄, NMO, acetone:H₂O 1:1, pH 7 buffer, r.t., 2 h, 62%; v) TsCl, Et₃N, CH₂Cl₂, r.t., 3 h, 80%; vi) PCC, CH₂Cl₂, r.t., 50%.
Deuterium Exchange Experiments

At this stage, it was suspected that a lack of reactivity of pyrrole 82 might be preventing the successful N-alkylation. In order to demonstrate the capacity of pyrrole 82 to be deprotonated, an investigation of the reactivity of 2,5-disubstituted pyrrole 82 as a nucleophile was undertaken, using deuterium exchange experiments.

These experiments were performed by reacting pyrroles 10, 133 and 82 with n-BuLi as shown in Table 9, followed by quenching the reaction mixture with D₂O or CD₃OD. The extent of deprotonation achieved was estimated by measuring the resonance of the NH proton before and after the quenching step.

Table 9. Deuterium exchange experiments on different pyrroles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Bases</th>
<th>Additives</th>
<th>Temperature</th>
<th>Time</th>
<th>Deuteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>n-BuLi</td>
<td>none</td>
<td>−78 °C</td>
<td>15 min</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>133</td>
<td>n-BuLi</td>
<td>none</td>
<td>−78 °C</td>
<td>15 min</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>n-BuLi</td>
<td>none</td>
<td>−78 °C</td>
<td>15 min</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>n-BuLi</td>
<td>TMEDA</td>
<td>−78 °C</td>
<td>15 min</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>82</td>
<td>t-BuLi</td>
<td>none</td>
<td>−78 °C</td>
<td>15 min</td>
<td>0%</td>
</tr>
</tbody>
</table>

Pyrrole 10 was first lithiated using n-BuLi at −78 °C (entry 1, Table 9) followed by quenching with D₂O. Under these conditions, no NH was observed by ¹H NMR, indicating complete formation of the lithiated species. 2-Formyl pyrrole 133 was next subjected to a deuterium exchange experiment in a similar manner. Satisfyingly, 70% of deuterated 2-formyl pyrrole was obtained using the conditions used for pyrrole, as the ¹H NMR showed 30% of the NH proton resonance by integration (entry 2, Table 9). Moving forward, the deuterium exchange experiment was conducted using 2,5-disubstituted pyrrole 82 under the same conditions. Unfortunately, no significant incorporation of deuterium was identified, thus TMEDA was introduced (entry 4, Table 9). TMEDA is known to enhance the stability of organolithium species, although in a highly substrate dependent manner. Use of TMEDA for this substrate, however, did not result in any effective lithiation. The suitability of t-BuLi as a base was next examined (entry 5, Table 9). However, no observable
deuteration was observed under these conditions. Deuterium exchange experiments followed by $^1$H NMR analysis on pyrrole 10, formyl pyrrole 133 and pyrrole 82 established that the lithium-hydrogen exchange did not occur on pyrrole 83, likely due to the steric hindrance of the neighbouring TBS silyl ether protecting group.

Pyrrole derivatives with electron-withdrawing groups at C-2,5 are commonly employed in N-alkylation reaction due to their ability to prevent polymerisation of the pyrrole compounds.\textsuperscript{19} With the aid of electron-withdrawing groups, the acidity of the NH proton is enhanced, thus increasing the overall nucleophilicity of the pyrrolic anion.\textsuperscript{122}

Significantly, there are no reported examples of N-alkylation (based upon SciFinder\textsuperscript{®} searches) where the pyrrole ring has electron-donating substituents at both C-2 and C-5, although there is one example with an electron-donating substituent at C-5.\textsuperscript{122} In the presence of electron-donating substituents at C-2 and C-5, pyrrole compounds tend to polymerise to deliver variable length polymers, which have been widely used as antioxidants.\textsuperscript{126} Hydroxyalkyl pyrrole compounds have been reported to undergo polymerisation to give porphyrins.\textsuperscript{126,127} Thus, in our case, the hydroxyl group was protected as the TBS ether to avoid polymerisation, which may also prevent the N-alkylation due to the steric bulkiness.

At this point, it was postulated that a new strategy, other than performing N-alkylation of pyrrole 82, was required for the synthesis of acortatarin A (1).
2.3 Revised Synthetic Strategy

Part I: Benzyl Protecting Group Strategy

Given the unsuccessful outcome of our initial synthetic approach, an alternative strategy to access \(N\)-alkylation product 107 was called for. Recalling the strategy we utilised for the preparation of 2,5-disubstituted pyrrole 82, it was envisioned that alcohol 107 could be accessed using the same Maillard-type condensation strategy of dihydropyranone 83 with a pre-formed amine 134 (Scheme 51).

![Scheme 51](image)

Encouraged by the successful construction of 2,5-disubstituted pyrrole 82 from the condensation between dihydropyranone 83 and saturated aqueous ammonia in dioxane, we aimed to synthesise alcohol 107 directly utilising the same reaction strategy with a pre-formed amine 134 (Scheme 52).

![Scheme 52](image)
Chapter 2: Discussion of Acortatarin A

This revised strategy involved a key condensation between amino alcohol 134 with dihydroxyranone 83 via a Maillard-type condensation. The amino alcohol 134 was anticipated to be prepared by regioselective ring opening of epoxide 81, which in turn has been successfully prepared from L-tartaric acid over 6 steps (Scheme 6, Section 1.1.2). With this idea in mind, we embarked on the synthesis of primary amine 134 from epoxide 81.

2.3.1 Synthesis of Amine 134

It was anticipated that the required amine 134 could be generated from an epoxide ring opening (azidohydrid formation) followed by Staudinger reduction from epoxide 81 (Scheme 53).

Scheme 53 Proposed synthesis of amine 134.

The mechanism of the Staudinger reaction has been subjected to a number of kinetic and theoretical studies and the exact mechanism still remains unclear. The first step of the mechanism (Scheme 54) is believed to involve attack of trivalent phosphorous on the unsubstituted nitrogen atom of the azide to give the corresponding phosphazide (which can occasionally be isolated) with retention of configuration at the phosphorous atom. Next, the phosphazide undergoes a four-membered transition state, which upon losing nitrogen gas affords the iminophosphorane. This intermediate is then hydrolysed by addition of water in the second step to afford the amine and a trialkylphosphine oxide. Both PBu$_3$ and PMe$_3$ are believed to undergo similar transformations to furnish the reduced product amine 134.

Scheme 54 Proposed Staudinger reaction mechanism.
In 1998, Tae and co-workers described an azide mediated regioselective nucleophilic opening of epoxide \(136\) in aqueous DMF in their total synthesis of \(\text{ent}\)-guadinomic acid\(^{130}\). The desired azidohydrin \(137\) was obtained in high yield (97\%) as a single regioisomer from epoxide \(136\) via ring opening (Scheme 55). This procedure was found to be substantially better than the classic protocols employing \(\text{NaN}_3\) and \(\text{NH}_4\text{Cl}\) in methanol\(^{131,132}\).

![Scheme 55 Synthesis of \(\text{ent}\)-guadinomic acid. Reagents and conditions: i) \(\text{NaN}_3\), \(\text{NH}_4\text{Cl}\), DMF:H\(_2\text{O}\) 8:1, reflux, 1 h, 97\%.

Using reaction conditions similar to Tae’s conditions\(^{130}\), epoxide \(81\) was reacted with \(\text{NaN}_3\) in the presence of \(\text{NH}_4\text{Cl}\) to afford the corresponding azidohydrin \(135\) as an inseparable mixture of two diastereomers in 95\% yield (Scheme 56). Azidohydrin \(135\) was furnished as a single regioisomer as indicated by \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectrum. Azidohydrin \(135\) was carried through to next step without any further purification. Reduction of the resulting azide functional group was initially performed via a Staudinger reaction employing \(\text{PPh}_3\) in THF followed by addition of \(\text{H}_2\text{O}\) after one hour\(^{133}\). Amine \(134\) was obtained in 60\% yield after purification; however, the reaction was found to be poorly reproducible involving a tedious work-up procedure for the removal of the side product triphenylphosphine oxide.

![Scheme 56 Synthesis of amino alcohol \(134\). Reagents and conditions: i) \(\text{NaN}_3\), \(\text{NH}_4\text{Cl}\), DMF:H\(_2\text{O}\) 8:1, 100 °C, 2 h, 95%; ii) \(\text{PPh}_3\), THF, r.t., 1 h, then \(\text{H}_2\text{O}\), 60%; \(\text{PBu}_3\), toluene, r.t., 2 h, 75%; \(\text{PMe}_3\), THF:H\(_2\text{O}\) 4:1, 50 °C, 2 h, quant.

In 2000, Jiang demonstrated an elegant total synthesis of the marine indole alkaloid \((+)-\text{hamacanthin B}\) featuring a tandem Staudinger reaction/intramolecular aza-Wittig reaction to convert a secondary azide \(138\) to the corresponding iminophosphorane \(139\) using \(\text{PBu}_3\) (Scheme 57)\(^{134}\). Reduction of the azide group was carried out with a slight excess amount of \(\text{PBu}_3\) in anhydrous toluene at room temperature delivering the anticipated product in 82\% yield. By adopting
Chapter 2: Discussion of Acortatarin A

this protocol, amino alcohol 134 was obtained in a reproducible 75% yield. Conducting the reaction at an elevated temperature (50 ºC), however, did not provide any improvement in yield.

Scheme 57 Tandem Staudinger reaction/intramolecular aza-Wittig reaction by Jiang.\textsuperscript{134} Reagents and conditions: i) PBu\textsubscript{3}, toluene, r.t., 2 h, 82%.

Further improvement was achieved through modification of the reduction conditions. In 2002, Wong and co-workers described a catalytic diazotransfer and regioselective azide reduction methodology using PMe\textsubscript{3} in THF.\textsuperscript{135} Good regioselectivity and moderate to excellent yields were obtained in the presence of multiple azides by modification of the Staudinger reaction. PMe\textsubscript{3} was recognised to be superior to other reagents with a simple work-up process.

Accordingly, treatment of azide 135 with PMe\textsubscript{3} in aqueous THF at 50 ºC yielded amino alcohol 134 as an inseparable mixture of two diastereomers in quantitative yield after a simple work up, ready for the planned Maillard-type condensation.
2.3.2 Maillard-type Condensation

Also known as non-enzymatic browning, the chemistry of the Maillard reaction is a complex series of reactions leading to the formation of a variety of products, including the flavours, aromas and colours considered important in food science today.\textsuperscript{77} This reaction was described for the first time by Louis Maillard in 1912. Pyridine, pyrazine, imidazole and pyrrole derivatives have all been isolated as the products of this reaction. In a typical reaction, product yields can range from 0-30\%.\textsuperscript{126}

In 1988, Maeba and co-workers published the first and only application of this type of reaction (based on SciFinder\textsuperscript{®} searches) for the preparation of C-nucleosides,\textsuperscript{79} however, they did not describe this reaction as a Maillard-type condensation. 2-Formyl pyrroles are the single major product together with small amounts of polar byproducts. As mentioned earlier, 2-formyl pyrroles are present in a variety of natural products, especially with electron-donating groups at C-5, making this reaction pathway of great interest and significance.

There is an assumption that the Maillard reaction responds to formulation pH, temperature and water activity like the browning reaction.\textsuperscript{77,102} Details of this Maillard reaction as required for the attempted synthesis of ent-acortatarin A are discussed in the following part.

A. Reactant Type

The course of the Maillard reaction is strongly affected by factors which influence the different chemical reactions involved. These are temperature, duration of heating, pH and presence of weak acids and bases, water content, type of reactant, amino acid to sugar ratio and oxygen. Reactive reducing sugars are the most common Maillard reactants. Other reactive reducing moieties include carbonyl-containing compounds.\textsuperscript{136}

B. Reactant Ratio

The extent of Maillard condensation is found to be varied according to the ratio between sugar and amine. A study by Warmbier and co-workers on a glucose-lysine model system showed that the rate of browning increased to a maximum at a ratio of one glucose to three lysines.\textsuperscript{137}
Chapter 2: Discussion of Acortatarin A

C. Temperature and Time

The rate of Maillard condensation has been reported to increase at elevated temperature and using a prolonged reaction period.\textsuperscript{138}

D. Water Content

Water has been found to be essential for Maillard reaction to occur.\textsuperscript{102} Overall the Maillard reaction shows a classic max/min response to change in water percentage which is shown in Figure 10.

![Figure 10. Influence of water on the rate of the Maillard-type reaction.](image)

E. pH

The pH has a significant effect on the Maillard-type reaction. Tressl and co-workers, using $^{13}$C-labelled sugars, have given a new perspective to the reaction mechanism.\textsuperscript{139} It was revealed that the pH of Maillard reaction generally ranges between 7 and 9. The pH dependence of the first step of the reaction can be related to the presence of the amount of unprotonated amine, which is controlled by the following equilibrium (Scheme 58). At the $\text{pK}_a$ of the amine group, by definition, half the amine is present as the protonated $\text{RNH}_2^+$ state preventing electron transfer.

\[
\begin{align*}
\text{R–NH}_3^+ & \quad \text{----pH>7----} \quad \text{R–NH}_2^+ \quad \text{H}^+ \\
\end{align*}
\]

Scheme 58 Equilibrium chart of a primary amine.
The Maillard reaction produces H⁺ ions, consequently decreasing the pH of the system. As mentioned above, as the pH falls, the rate and yield of the Maillard reaction decreases. Buffers have been shown to increase the reaction rate. It is postulated that the buffer captures the H⁺ ions while keeping the pH and the reaction rate constant or may interact with the reactants in some way enhancing the Maillard reaction.

The key Maillard-type condensation of amine 134 with dihydropyranone 83 in the present study initially proved problematic. Amino alcohol 134 in anhydrous dioxane was subjected to variable stoichiometries of dihydropyranone 83 which was more readily accessible. Disappointingly, no desired product was formed as indicated by TLC, resulting in a complex unidentifiable mixture of polar products by ¹H NMR analysis (entries 1 and 2, Table 10). Recalling the preparation of 2,5-disubstituted pyrrole 82 (Table 3, Section 2.1.8), using freshly opened saturated aqueous ammonia solution, the reaction proceeded much slower compared to use of an old bottle of ammonia solution with a lower yield of the expected product obtained and more polar byproducts formed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio (134:83)</th>
<th>Additives</th>
<th>Temperature</th>
<th>Result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1: 2</td>
<td>...</td>
<td>rt</td>
<td>0ᵃ</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>...</td>
<td>rt</td>
<td>0ᵃ</td>
</tr>
<tr>
<td>3</td>
<td>1: 1</td>
<td>...</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2:1</td>
<td>...</td>
<td>rt</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>3:1</td>
<td>...</td>
<td>rt</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>2:1</td>
<td>...</td>
<td>50</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>2: 1</td>
<td>NEt₃ (3.0 equiv.)</td>
<td>rt</td>
<td>50</td>
</tr>
</tbody>
</table>

a: Anhydrous dioxane was used. All reactions were performed in undistilled dioxane for 3 h unless otherwise indicated.

Use of undistilled dioxane with the same molar amount of amine 134 and dihydropyranone 83 was again un rewarding (entry 3, Table 10). Gratifyingly, increasing the ratio of amine 134 to dihydropyranone 83 to 2:1 afforded 10% of the expected product (entry 4, Table 10). Further optimisation was attempted employing three equivalents of amine 134 (entry 5, Table 10), giving 25% yield.
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It is also worth noting that when a mixture of two equivalents of amine 134 and one equivalent of dihydropyranone 83 in undistilled dioxane was heated to 50 °C, the reaction was complete within one hour affording the desired product in 23% yield (entry 5, Table 10).

The addition of triethylamine was found to be beneficial. Using two equivalents of amine 134 and one equivalent of dihydropyranone 83 in the presence of three equivalents of Et₃N afforded the requisite 2-formylpyrrole 107 in 50% yield as a mixture of two inseparable diastereomers (entry 7, Table 10). The reaction rate was increased, reaching completion within 2 h. This observation was found to be in agreement with the factors known to influence the Maillard condensation reaction.

Thus, the optimal condensation conditions were found to be the use of two equivalents of amine 134, one equivalent of dihydropyranone 83 in the presence of three equivalents of Et₃N in dioxane at room temperature. The presence of a distinct singlet at δ 9.47 and two doublets at δ 6.90 and 6.19 in the ¹H NMR spectrum for the purified product 107 and a signal at δ 179.2 in the ¹³C NMR spectrum indicated the successful formation of the 2-formyl pyrrole ring subunit.

2.3.3 Synthesis of Ketone 86

With intermediate 107 in hand, the stage was set to oxidise secondary alcohol. In our earlier work, PCC was the reagent of choice to oxidise halohydrin 110-111 to access ketone 112-114 (entry 5, Table 7, Section 2.1.11 B). Adopting these optimal conditions, alcohol 107 was added to a mixture of PCC and activated 4 Å molecular sieves in anhydrous CH₂Cl₂ at room temperature. Regrettably, the conditions developed for the oxidation of alcohol 107 to ketone 86 were not successful for the synthesis of ketone 86. No expected product was observed even after a prolonged reaction time (entry 1, Table 11). The inability to convert alcohol 107 to ketone 86 was attributed to the electron-withdrawing nature of the pyrrole ring. The use of PDC was also investigated to access ketone 86; disappointingly, the reaction was also unsuccessful (entry 2, Table 11).

Application of less-toxic DMSO-based oxidants (Parikh-Doering oxidation condition) proved to be unsuccessful with the full recovery of starting material observed (entry 3, Table 11).

The use of hypervalent iodine-based oxidising reagents such as IBX or DMP, on the other hand, led to full decomposition of alcohol 107 (entries 4-5, Table 11).
Table 11. Oxidation of alcohol 107.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidants</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PCC</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>12 h</td>
<td>107 recovered</td>
</tr>
<tr>
<td>2</td>
<td>PDC</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>12 h</td>
<td>107 recovered</td>
</tr>
<tr>
<td>3</td>
<td>SO₃•Py</td>
<td>DMSO</td>
<td>r.t.</td>
<td>12 h</td>
<td>107 recovered</td>
</tr>
<tr>
<td>4</td>
<td>IBX</td>
<td>EtOAc</td>
<td>r.t. → reflux</td>
<td>10 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>DMP</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>10 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>TEMPO</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>7</td>
<td>TPAP/NMO⁴</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>15 min</td>
<td>quant.</td>
</tr>
</tbody>
</table>

⁴: This was also conducted in CH₃CN.

Gratifyingly, treatment of alcohol 107 with catalytic TPAP and stoichiometric NMO as a co-oxidant in anhydrous CH₂Cl₂, in the presence of activated 4 Å molecular sieves powder, known as the Ley oxidation,¹⁴⁰ was found to afford the corresponding ketone 86 in quantitative yield (entry 7, Table 11). The Ley oxidation is recognised to be extremely sensitive to the presence of water, as even a trace amount of water was found to be detrimental to the oxidation.¹⁴⁰ The reaction was observed to be sluggish and not complete without the presence of activated powdered molecular sieves. Hence freshly activated powdered 4 Å molecular sieves were added to remove both the water of crystallised NMO and the water generated during the reaction. Upon completion, the reaction mixture was filtered through a short plug of silica allowing for a procedurally simple oxidation to afford the desired ketone 86 in quantitative yield. CH₃CN was employed as a solvent for large scale reactions as the reaction rate was found to proceed faster in CH₃CN (200 mg scale).¹⁴⁰ The structure of ketone 86 was unambiguously confirmed by the presence of a tertiary carbon signal at δ 201.7 in the ¹³C NMR spectrum.
2.3.4 Deprotection/Cyclisation of Ketone 86

The remaining tasks required for the completion of the synthesis of acortatarin A involved the critical acid-mediated deprotection/spirocyclisation followed by a Mitsunobu reaction to invert the stereochemistry of the secondary hydroxyl group at C-3 and final deprotection to unmask the primary alcohol. The first step of this endeavour was the concerted deprotection/spirocyclisation of ketone 86 (Scheme 59).

TBS silyl ether and acetonide protecting groups are both recognised to be acid labile groups, where appropriately acidic conditions unmask the hydroxyl groups. Davis and co-workers reported that the half-life for hydrolysis of primary TBS silyl ethers was less than 1 min in 1% HCl-MeOH (v/v).141 Hence TBS was recognised to be an easily removable acid-labile group; whereas hydrolysis of an acetonide group generally requires mild to harsh acidic conditions.

Subjection of ketone 86 to mildly acidic conditions using PPTS in methanol cleanly removed the TBS silyl ether affording hemiketal 141 in 85% yield; however, the acetonide group was not removed under these conditions (entry 1, Table 12). Exposure of ketone 86 to Sakamura’s conditions142 employed for the stereoselective synthesis of (±)-palitantin utilising p-TSA in methanol at 25 ºC was also unrewarding, resulting in the formation of hemiketal 141 in an inferior 67% yield.

In 2003, Das and co-workers demonstrated a simple and facile chemo- and regioselective deprotection method of acetonides using silica supported NaHSO₄ as a heterogeneous catalyst to produce the corresponding diol in excellent yield.143 The use of a heterogeneous catalyst is advantageous in that the catalyst can be readily removed from the reaction mixture via filtration. The mild nature of this method warranted our investigation.
Preparation of the silica supported catalyst was undertaken as outlined in the literature. Ketone 86 was treated with freshly prepared NaHSO$_4$·SiO$_2$ in a solution of CH$_2$Cl$_2$ and i-PrOH at room temperature, once again affording hemiketal 141 (entry 3, Table 12). Changing the solvent to pure i-PrOH in the hope of enhancing the activity of the catalyst proved to be fruitless.

<table>
<thead>
<tr>
<th>Table 12. Acid-mediated double deprotection/cyclisation of ketone 87.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

After several unsuccessful attempts to unmask the required hydroxyl functional groups under these mild acidic conditions at variable temperatures, it was concluded that the acetonide protecting group cleavage probably required stronger acidic conditions. Use of CSA as an alternative acid, again, afforded the undesired hemiketal 141 in 72% yield (entry 4, Table 12). It was therefore decided to evaluate stronger acids.

With this in mind, use of 1 M HCl in a 1:1 mixture of MeOH and H$_2$O was first investigated as reported by Beveridge. Gratifyingly, the diastereomeric spiroketalts 85a and 85b were obtained in 50% yield in total (entry 5, Table 12). Use of a prolonged reaction time resulted in a lower yield of spiroketalts 85a and 85b. A mixture of unidentified products was obtained as indicated by $^1$H NMR. 2 M aqueous HCl was generated by dilution of commercial anhydrous 4 M HCl in dioxane with a 1:1 mixture of THF and H$_2$O. These conditions proved to be the most effective and efficient method to unmask both the acetonide and the TBS silyl ether, furnishing two separable spiroketalts 85a and 85b in a 1:1 mixture of the expected 90% combined yield in 1 h. (entry 6, Table 12).

The disappearance of five singlets at $\delta$ 1.37 and $\delta$ 1.35 that denote the acetonide protection groups and at $\delta$ 0.83, $\delta$ 0.00 and $\delta$ -0.02 that denote the TBS silyl ether protection group in the $^1$H NMR
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spectrum and a new signal at δ 103.6 that denote the spiroketal centre carbon unambiguously confirmed the successful formation of the desired spiroketals 85a and 85b (Appendix Pages 252 and 254).

2.3.5 Final Benzyl Ether Deprotection

With spirokets 86a and 86b in hand, debenzylation of the primary alcohol was first investigated before attempting Mitsunobu conversion of the secondary hydroxy group to afford ent-acorutarin A. In order to avoid any epimerisation of the enantiopure spiroketals 85a, it was decided to treat the monobenzylated compound 85a with non-acidic debenzylation conditions. A detailed list of debenzylation methods that has been applied to access 2-epi-acorutarin A and its diastereomer is presented herein.

A. Attempted Hydrogenolysis of Spiroketal 85a and 85b

The cleavage of benzyl ethers is generally performed under conventional methods such as H2/Pd in methanol, ethyl acetate or THF or H2/Pd(OH)2 in methanol. Under these traditional hydrogenation conditions, regrettably, only complete decomposition of the spiroketal 85a was observed (entries 1-3, Table 13). Hence other hydrogenation methods were investigated.

Previous work in this research group conducted by Zoe Wilson144 encountered a similar deprotection problem (Scheme 60). No desired product was obtained under standard hydrogenation reaction conditions (palladium or palladium hydroxide on carbon in EtOAc, MeOH or THF, with or without acid) and complete degradation of the starting material was observed. However, exposure of the starting material to hydrogenation using H-Cube® HC-2 continuous hydrogenation equipment with a palladium hydroxide cartridge afforded the requisite deprotection/spiroketalisation product 143a and 143b in 65% yield. This was reasoned to be shorter period of ketone 142 exposed to hydrogen atmosphere compared to conventional hydrogenation conditions. Regretably, in adopting this procedure, hydrogenolysis of spiroketal 85a in either MeOH or EtOAc did not deliver any of the desired product (entry 4, Table 13).
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Scheme 60 Synthesis of tetra-cyclic core of berkerlic acid 143a. Reagents and conditions: i) EtOAc, MeOH, H-Cube®, 83%, 143a:143b 3:1.

Consequently, transfer hydrogenation methods were trialled using hydrogen generated *in situ* from either HCO₂H,¹⁴⁵ or cyclohexadiene¹⁴⁶ with Pd/C as a catalyst. The debenzylisation was allowed to stir at room temperature for one hour. Unfortunately, no product was observed by TLC. Further ¹H and ¹³C NMR studies revealed an unidentifiable mixture of side products (entry 5, Table 13).

A similar problematic hydrogenation also occurred during the first total synthesis of acortatarin A accomplished by Jagadeesh and co-workers.¹⁹ Conventional hydrogenolysis methodology employing Pd/C as a catalyst was first attempted to cleave the benzyl group, which resulted in no reaction whilst use of a higher catalyst loading led to a complex mixture of undefined products. The desired products acortatarin A (17) and 5-epi-acortatarin A (17a) were obtained using TiCl₄ in CH₂Cl₂ at −78 °C in 72% and 8% yields, respectively (Scheme 61). However, due to the epimerisation possibility of spiroketal 85a, we did not investigate these conditions.

Scheme 61 Total synthesis of revised acortatarin A (17) by Jagadeesh and co-workers. Reagents and conditions: i) 1 M TiCl₄, CH₂Cl₂, −78 °C, 17 72%, 17a 8%.
Table 13. Attempted denbenzylation of spiroketal 85a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂/Pd/C, MeOH, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>H₂/Pd/C, EtOAc, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>H₂/Pd/C, EtOH, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>H₂/Pd(OH)₂, MeOH, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>HCO₂H, Pd/C,</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>LiDTBB, THF, −78 °C→0 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>7</td>
<td>DDQ, CH₂Cl₂, r.t.</td>
<td>…</td>
</tr>
</tbody>
</table>

B. Attempted Debenzylation of 85a Using a Radical Anion Method

A radical method was next investigated to effect the benzyl deprotection of spiroketal 85a. The use of lithium di-tert-butylbiphenylylide (LiDTBB) in anhydrous THF has been reported as an efficient method for the deprotection of benzyl ethers. The success of such reactions relied heavily on the in situ generation of LiDTBB and the increased steric bulk, which disfavours radical coupling reactions between LiDBB and other radical anions formed in solution.\(^\text{147}\)

\[
\text{DTBB} \xrightarrow{\text{Li}} \text{LiDTBB}^+ \]

Figure 11. Structure of LiDTBB.

LiDTBB, as an aromatic radical-anion reagent, can be conveniently generated and used in THF at 0 °C to deprotect benzyl ethers. A deep green solution of LiDTBB in anhydrous THF was formed by sonicating a solution of DTBB and excess Li metal at 0 °C under an Ar atmosphere for three to four hours. Rapid addition of this green solution to a solution of spiroketal 85a in THF discharged the colour of the radical-anion by the end of the addition to give a red to brown solution, suggesting the consumption of the radical anion. However, after workup, an unidentified complex mixture was obtained as indicated by \(^1\)H NMR analysis (entry 6, Table 13).
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C. Attempted Denbenzylation Using a Oxidative Methods

Oxidative methods were next attempted to effect the benzyl ether deprotection of spiroketal 85a. DDQ and PhI(OAc)$_2$ have attracted growing interest as versatile catalysts in organic synthesis. (Table 13).$^{148,149}$ Unfortunately, use of both of these reagents to effect debenzylation of 85a only resulted in complete decomposition of spiroketal 85a (entry 7, Table 13).

In conclusion, all attempts to remove the benzyl group from spiroketal 85a only led to the decomposition of spiroketal 85a.

Recognising the difficulty encountered in removing the primary benzyl protecting group from spiroketal 85a, an alternative protecting group strategy was sought to achieve the total synthesis of ent-acortatarin A and analogues (vide infra).
2.3.6 Summary of Revised Strategy I

The synthesis of ketone 86 relied on a key Maillard-type condensation between amine 134 and dihydropyranone 83 in dioxane (Scheme 62). Compounds 134 and 83 were readily obtained from commercially available L-tartaric acid and furfuryl alcohol, respectively. An acid-catalysed simultaneous intramolecular deprotection/cyclisation gave a chromatographically separable mixture of diastereomers 85a and 85b. Unfortunately, all attempts to effect the deprotection of the benzyl ether only led to the complete degradation of spiroketal 85a (Table 13, Section 2.2.5).

Due to exhaustion of a range of available deprotection methods to unmask the primary hydroxyl group from benzyl ether 85a, it was concluded that the use of a benzyl ether protecting group was not appropriate for the synthesis of proposed acortatarin A (1). It was therefore decided to examine an alternative approach to proposed acortatarin A (1).

Scheme 62 Summary of attempted synthesis of spiroketal 144 and 144b. *Reagents and conditions*: i) dioxane, NEt3, r.t., 3 h, 50%; ii) TPAP, NMO, CH2Cl2, 15 min, quant.; iii), 2 M HCl, THF: dioxane: H2O 1:1:1, 1 h, 90%; iv) H2, Pd/C, MeOH.
Part II: Using TBDPS Silyl Ether as a Protecting Group

2.3.7 Revised Protecting Group Strategy

Our initial retrosynthetic approach hinged on the acid-catalysed spiroketalisation of ketone 86 upon deprotection of the acetonide and TBS silyl ether, followed by a final benzyl ether deprotection to furnish the final compound. It became apparent, however, that the benzyl ether protecting group was not suitable for the total synthesis of 1, as after deprotection no desired product 144 was obtained upon numerous attempts (entries 1-7, Table 13).

Based on this observation, an alternative orthogonal protecting group strategy was sought that could withstand acidic conditions required for the concomitant deprotection/spiroketalisation and later be removed under mild conditions. Protecting groups which can be removed under non-acidic conditions are generally limited to allyl, PMB ethers, and silyl protecting groups such as TBDPS or TIPS. The TBDPS silyl group was ultimately incorporated into our modified synthetic plan, as this protecting group was believed to be robust enough to withstand the synthetic route used to form the spiroketal 1 but readily removed under a variety of non-acidic conditions (Scheme 63).

Scheme 63 An alternative protecting group strategy for the synthesis of proposed acortatarin A.

2.3.8 Synthesis of Amine 150

Amine 150 was prepared in a route analogous to that previously used for amine 134. As illustrated in Scheme 64, diol 93 was converted to mono-TBDPS silyl ether 145 using NaH and TBDPSCI in THF as described by Akita and co-workers. In 1989, Mosset reported the synthesis of iodide 146 from mono-TBDPS silyl ether 145 via a tosylation (mesylation)/iodide anion S_N2 substitution sequence. A more efficient synthesis that eliminates the need for the additional tosylation
(mesylation) was attempted employing a modified Appel reaction\(^1\) that was used previously to synthesise benzyl protected iodide \(^9\) (Scheme 24, Section 2.2.2). Better yield and more efficient results were obtained after purification by flash column chromatography. The Grignard displacement proceeded uneventfully using vinylmagnesium bromide in the presence of CuI to afford olefin 147 in 65\% yield after purification with column chromatography, with some TBDPS silyl cleavage observed. It was reasoned that, compared to benzyl ethers, the TBDPS silyl ether is more labile under the basic conditions.\(^{152}\)

\[
\begin{align*}
\text{OH} & \quad \text{CO}_2\text{H} & \quad \text{OH} & \quad \text{HO}_2\text{C} & \quad \text{CO}_2\text{H} \\
84 & \quad \text{HO}_2\text{C} & \quad \text{OH} & \quad \text{HO} & \quad \text{OH} \\
93 & \quad \text{O} & \quad \text{O} & \quad \text{TBDPSO} & \quad \text{O} \\
145 & \quad \text{O} & \quad \text{O} & \quad \text{TBDPSO} & \quad \text{I} \\
146 & \quad \text{TBDPSO} & \quad \text{O} & \quad \text{TBDPSO} & \quad \text{O} \\
147 & \quad \text{TBDPSO} & \quad \text{O} & \quad \text{TBDPSO} & \quad \text{O} \\
148 & \quad \text{OH} & \quad \text{O} & \quad \text{O} & \quad \text{N}_3 \\
149 & \quad \text{OH} & \quad \text{OH} & \quad \text{O} & \quad \text{N}_3
\end{align*}
\]

Scheme 64 Synthesis of azide 149. Reagents and conditions: i) MeOH, conc. HCl, reflux, 12 h; ii) 2,2-dimethoxypropane, p-TSA, toluene, reflux, 6 h; iii) LiAlH\(_4\), THF, reflux, 2 h; iv) NaH, TBDPSCI, THF, 0 °C to r.t., 4 h, 52\% for 4 steps; v) I\(_2\), PPh\(_3\), imidazole, toluene, 100 °C, 2 h; vi) vinylmagnesium bromide, CuI, THF:DMPU 1:1, 50\% for 2 steps; vii) m-CPBA, CH\(_2\)Cl\(_2\), r.t., 12 h, 90\% (95\% brsm.); viii) NaN\(_3\), DMF, aq. NH\(_4\)Cl, 100 °C, 2 h, 65\%.

Efforts next turned to the preparation of epoxide 148 from olefin 147. On the basis that benzyl protected olefin 147 could be readily converted to epoxide 148 by oxidation with CF\(_3\)COCH\(_3\)-Oxone\(^\circledast\) (Section 2.1.3), the same process was used for the oxidation of TBDPS silyl ether protected olefin 147. To our disappointment, treatment of olefin 147 with CF\(_3\)COCH\(_3\) followed by the addition of a mixture of Oxone\(^\circledast\) and NaHCO\(_3\) in aqueous CH\(_2\)CN for 12 h,\(^{86}\) afforded only 10\% of the desired epoxide 148, along with 80\% of the starting material 147. The reaction was allowed to stir at room temperature for a prolonged time, with no observable improvement obtained. Hence conventional epoxidation conditions using m-CPBA in anhydrous CH\(_2\)Cl\(_2\) at room temperature were once again employed. Gratifyingly, using these conditions the epoxidation reaction went to completion affording epoxide 148 in 85\% yield as an inseparable mixture of two diastereoisomers in a 1.3:1 ratio (Figure 12). The approximate d.r. was determined by the resonance for characteristic proton H-4 as two multiples at \(\delta 1.85\)−1.84 and at \(\delta 1.84\)−1.72 in the \(^1\)H NMR after purification by flash column chromatography.
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The regioselective epoxide ring opening was next conducted using NaN$_3$ in aqueous DMF at 100 °C to give azidohydrin 149 as an inseparable diastereomeric mixture in moderate 65% yield (Scheme 64). The low yield of azidohydrin 149 in comparison to the benzyl protected azidohydrin 135 (Section 2.3.1) was postulated to be due to the instability of TBDPS silyl protecting group under basic conditions employed for the azide formation reaction.\textsuperscript{152}

Following the optimal reduction conditions developed for the related benzyl protected azidohydrin 149 (Section 2.3.1), amine 150 was readily reduced using PMe$_3$ in aqueous THF. Upon stirring at 50 °C for one hour, the desired TBPDS protected amino alcohol 150 was obtained in almost quantitative yield as an inseparable diastereomeric mixture.

Scheme 65 Reduction of azide 149 to amine 150. Reagents and conditions: i) PMe$_3$, THF:H$_2$O 4:1, 50 °C, 1 h, 99%.

2.3.9 Elaboration of Pyrrole Alcohol 151

With both requisite partners 83 and 150 in hand, the anticipated Maillard-type condensation was investigated employing the optimised conditions developed for the preparation of alcohol 151 (entry 6, Table 10, Section 2.2.8). The Maillard-type condensation was conducted using two equivalents
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of amine 150 and one equivalent of dihydropyranone 83 for two hours in the presence of three equivalents of Et3N (Scheme 66). The corresponding alcohol 151 was obtained as two separable diastereoisomers in a combined 54% yield (Scheme 66). Pyrrole alcohols 151a and 151b were successfully obtained as an enantiopure compounds, however, extensive NMR studies did not allow us to assign the absolute stereochemistry. Nevertheless, these two diastereomers were subjected to the following oxidation sequence as a mixture of no consequences.

Scheme 66 Elaboration of alcohol 151. Reagents and conditions: i) 1,4-dioxane, NEt3, 50 °C, 2 h, 151a 21%, 151b 33%. 

![Scheme 66](image-url)
2.3.10 Attempted synthesis of Proposed acortatarin A (1)

With the successful formation of alcohol 151 from amine 150 and dihydropyranone 83, all that remained to complete the total synthesis of proposed acortatarin A (1) was to adjust the oxidation state at C-5, reverse the stereochemistry at C-3 via a Mitsunobu reaction, and cleave the remaining protecting groups. Utilising the successful chemistry from the synthesis of the benzyl protected ketone 86 (Section 2.2.3), a combination of TPAP and NMO in the presence of powdered activated 4 Å molecular sieves was employed for the oxidation of TBDPS silyl ether 151a and 151b. To our delight, oxidation of 151 under Ley oxidation conditions delivered the desired ketone 152 in quantitative yield, which underwent concomitant deprotection/cyclisation to afford an inseparable mixture of spirokets 153a and 153b in a combined 61% yield. Gratifyingly, diastereoselective spiroketalisation was observed to be 3.4:1 as determined by the resonances of two singlets at δ 9.53 and δ 9.49 denoting the aldehyde proton resonance of the two diastereomers (Figure 13). The favoured diastereomer was suggested to be the anomerically stabilised spiroketal 153a and this was confirmed by nOe studies obtained after deprotection of the spirokets 153a and 153b (vide infra).

Scheme 67 Synthesis of spirokets 153a and 153b. Reagents and conditions: i) TPAP, NMO, CH2Cl2, 4 Å MS, r.t., 15 min, 97%; ii) 4 M HCl in dioxane, THF:H2O 1:1, r.t., 2 h, 61% d.r. 3.4:1.
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Figure 13. $^1$H NMR analysis of spiroketals 153a and 153b.

A facile TBAF-mediated silyl deprotection of the mixture of spiroketals 153a and 153b furnished 3-epi-ent-acortatarin A (154a) and its 5-epimer (154b) (Scheme 68). Analysis of the nOe data obtained for spiroketals 154a and 154b revealed a characteristic correlation between the H-4 proton and the H-10 proton, in the major isomer 154a (Appendix, P). Hence, the major spiroketal was assigned as the desired anomerically stabilised isomer. The structure of non-anomerically stabilised isomer was also confirmed by nOe studies. In this circumstance, a distinctive correlation between H-4 and H-7 protons unambiguously established that the minor isomer 154b was the non-anomerically stabilised isomer 154b (Appendix, P). The spectroscopic data ($^1$H and $^{13}$C NMR analysis) for two spiroketals 154a and 154b are depicted in Table 14.

Scheme 68 Synthesis of spiroketals 154a and 154b. Reagents and conditions: i) TBAF, THF, r.t., 2 h, 154a 50%, 154b 30%.
Chapter 2: Discussion of Acortatarin A

Table 14. \(^1\)H and \(^{13}\)C NMR data for spirokets 154a and 154b.

<table>
<thead>
<tr>
<th>Position(^a)</th>
<th>154a (^1)H NMR (400 MHz) ((\delta), mult, (J) Hz)</th>
<th>154b (^1)H NMR (400 MHz) ((\delta), mult, (J) Hz)</th>
<th>154a (^{13})C NMR (100 MHz)</th>
<th>154b (^{13})C NMR (100 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4.02 (dd, 4.7, 4.7, 3.9)</td>
<td>4.14 (dd, 6.8, 6.0, 6.0)</td>
<td>86.4</td>
<td>83.8</td>
</tr>
<tr>
<td>3</td>
<td>4.27 (dd, 8.3, 5.1, 1.0)</td>
<td>4.64-4.55 (m)</td>
<td>72.0</td>
<td>71.8</td>
</tr>
<tr>
<td>4a</td>
<td>2.27 (dd, 14.0, 1.0)</td>
<td>2.10 (dd, 18.8, 4.4)</td>
<td>45.5</td>
<td>47.3</td>
</tr>
<tr>
<td>4b</td>
<td>2.43 (dd, 14.0, 6.0)</td>
<td>2.51 (dd, 18.8, 8.8)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>...</td>
<td>...</td>
<td>103.7</td>
<td>104.5</td>
</tr>
<tr>
<td>7a</td>
<td>4.83 (d, 15.6)</td>
<td>4.81 (d, 20.7)</td>
<td>58.4</td>
<td>58.7</td>
</tr>
<tr>
<td>7b</td>
<td>5.14 (dd, 15.6, 1.0)</td>
<td>4.94 (d, 20.7)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>8</td>
<td>...</td>
<td>...</td>
<td>135.7</td>
<td>135.6</td>
</tr>
<tr>
<td>10a</td>
<td>4.20 (d, 14.0)</td>
<td>4.23 (d, 18.5)</td>
<td>51.7</td>
<td>52.2</td>
</tr>
<tr>
<td>10b</td>
<td>4.54-4.49 (m)</td>
<td>4.67 (d, 18.6)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>11</td>
<td>6.04 (d, 4.0)</td>
<td>6.04 (d, 5.6)</td>
<td>105.0</td>
<td>106.1</td>
</tr>
<tr>
<td>12</td>
<td>6.98 (d, 4.0)</td>
<td>6.98 (d, 5.6)</td>
<td>123.9</td>
<td>124.0</td>
</tr>
<tr>
<td>13</td>
<td>...</td>
<td>...</td>
<td>131.9</td>
<td>131.9</td>
</tr>
<tr>
<td>14</td>
<td>9.47 (s)</td>
<td>9.47 (s)</td>
<td>178.7</td>
<td>178.8</td>
</tr>
<tr>
<td>15a</td>
<td>3.80 (dd, 11.8, 6.0)</td>
<td>3.87-3.77 (m)</td>
<td>61.9</td>
<td>61.3</td>
</tr>
<tr>
<td>15b</td>
<td>3.87 (dd, 11.7, 5.2)</td>
<td>3.87-3.77 (m)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

\(\text{a: carbon assigned following natural product acortatarin A numbering system, see Scheme 68. Both }^1\text{H and }^{13}\text{C NMR spectra were conducted in CD}_3\text{COCD}_3.\)

With a viable route to the ent-acortatarin A core system established, stereoinversion at C-3 was now required to access the target (1). A late-stage Mitsunobu reaction was initially attempted using benzoic acid, \(\text{PPh}_3\) and DIAD. To our disappointment, no expected product was observed. Subsequently, a more reactive reagent 4-nitrobenzoic acid was used. Nitrobenzoate 155 was obtained in quantitative yield, but saponification of the resulting ester was found to be problematic (Scheme 69). A number of bases (NaOH, MeONa, EtONa, NaOAc) in aqueous methanol were screened to hydrolyse nitrobenzoate 155. Unfortunately, all efforts to effect the C-3 stereochemical inversion were unsuccessful, resulting in full recovery of nitrobenzoate 155. The disappointing outcome of the attempted Mitsunobu reaction was postulated to be due to steric hindrance from the adjacent TBDPS silyl group.
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Scheme 69 Attempted Mitsunobu reaction. *Reagents and conditions:* i) PPh₃, DIAD, 4-nitrobenzoic acid, THF; ii) 1 M LiOH (NaOH, MeONa, EtONa, NaOAc), MeOH:H₂O 1:1, r.t.

Ultimately, the attempted Mitsunobu reaction to invert the C-3 stereochemistry was abandoned due to the stereochemical revision of the structures of acortatarins A (17) and B (18) published by Jagadeesh and co-workers.¹⁹ Our synthesis was therefore adjusted to provide the revised structure of acortatarin A 17 (*vide infra*).
2.4 Revision of Structure for Acortatarins A and B

At this particular point, Jagadeesh and co-workers published the first total synthesis of acortatarins A (17) and B (18) together with the structural revision of acortatarins A and B (Figure 14).\textsuperscript{19}

The revised structure of acortatarin A was confirmed to be enantiomeric to the initially proposed structure by Cheng and co-workers.\textsuperscript{13} Thus acortatarin A (17) and pollenopyrroside B (3) are identical to each other. We therefore adjusted our synthesis accordingly to target the revised structure of acortatarin A (17) using a similar Maillard-type condensation approach commencing from D-mannitol (\textit{vide infra}).

\textbf{Figure 14.} Initially proposed and revised structures of acortatarin A and B.
2.5 Synthesis of the Revised Structure of Acortatarin A (17)

Encouraged by the previous successful synthesis of spiroketalts 154a and 154b using a Maillard-type condensation, we were excited to design a revised synthesis based on this novel strategy and apply this methodology to a natural-product synthesis, as well as circumvent the previous problematic N-alkylation of a 2,5-disubstituted pyrrole.

Synthesis of acortatarin A requires ketone 157 with the correct 2R,3S stereochemistry as depicted in Scheme 70. It was envisaged that ketone 157 would be available from a Maillard-type disconnection, leading to amino alcohol 158a and dihydropyranone 83. The requisite stereochemistry of amino alcohol 158a, in turn, is anticipated to be derived from homoallylic alcohol 159a that is accessible via a diastereoselective allylation of a D-mannitol-derived glyceraldehyde equivalent 160.153 Dihydropyranone 83, in turn, would arise from Achmatowicz ring-expansion of substituted furfuryl alcohol 94 (Scheme 28, Section 2.2.6).

Scheme 70 Retrosynthetic analysis of the revised structure of acortatarin A (17).
2.5.1 Synthesis of Amine 158a Using an Acetonide Protecting Group

The key amine fragment 158a containing the diol protected as an acetonide could be attained from epoxide 161a via regioselective epoxide ring opening by an azide anion. In turn, epoxide 161a could be derived from protecting group manipulation of olefin 159a followed by epoxidation. Olefin 159a could be obtained via a chelation controlled anti-selective allylation of aldehyde 160, a widely used chiral synthon for the synthesis of a number of optically active compounds.154-158

![Scheme 71 Retrosynthetic analysis of amine 158a.](image)

2.5.2 Synthesis of Olefin 163a

The elaboration of the key amino alcohol fragment 158a began from the preparation of the known olefin 163a. In 2010, Sim and co-workers disclosed a linear preparation of olefin 163 from D-mannitol (169) in 6.5% yield over 6 steps (Scheme 72).159 The synthesis entailed protection, oxidative cleavage, asymmetric allylation followed by further protecting group manipulation to afford TBDPS silyl protected olefin 163a. The two major drawbacks of this synthetic route were the low yielding D-mannitol protection step and the use of the highly air and moisture sensitive reagent (-)-Ipc2BOMe for the asymmetric allylation step.

![Scheme 72 Sim’s synthesis of olefin 163a. Reagents and conditions: i) 2.2-dimethoxypropane, SnCl2, DME, reflux, 3 h, 36%; ii) NaIO4, CH2Cl2, H2O, r.t., 2 h, 47%; iii) (-)-Ipc2BOMe, allylMgBr, Et2O, –78 °C to r.t; iv) CH3CO2H:H2O 4:1, r.t, 12 h, 56% over 2 steps; v) TBDPSCl, imidazole, DMF, r.t., 2 h, 74%; vi) 2,2-dimethoxypropane, PPTS, CH2Cl2, r.t., 12 h, 93%.](image)

A more reliable and facile synthesis of this olefin was desired. Our synthesis of olefin 163a commenced with the preparation of (R)-glyceraldehyde acetonide 160 from D-mannitol (162) over two steps following the procedure reported by Tipson and co-workers.160 Accordingly, D-mannitol (162) was treated with zinc chloride in acetone followed by potassium carbonate in
water to furnish di-acetonide 164. Subsequent oxidative cleavage was carried out using the recrystallised product 164 employing NaIO₄ in CH₂Cl₂ with a saturated aqueous solution of NaHCO₃ (4% v/v) under vigorous stirring following the protocol modified by Jackson.¹⁶¹ Pure aldehyde 160 was distilled under reduced pressure from the crude product in 46% yield (Scheme 73).

![Scheme 73 Synthesis of aldehyde 160. Reagents and conditions: i) ZnCl₂, acetone, r.t., 24 h, 60% ii) NaIO₄, CH₂Cl₂, sat. aq. NaHCO₃ (4% v/v), r.t., 2 h, 46%;](image)

In 1983, Mulzer and co-workers published the first application of a zinc-mediated reaction of allyl bromide with aldehyde 160 in aqueous THF to afford anti-selective product 159a (75%, d.r. 77:23).¹⁶² The major improvement of this protocol was the use of cheap metallic zinc as a promoter giving good diastereoselectivity and high yields. The authors proposed two possibilities for this asymmetric allylation adopting the Cram chelation model (Scheme 74). Accordingly, there are two approaches in which the allylbromozinc nucleophile could attack the pro-chiral aldehyde 160. In the presence of zinc, the allyl nucleophile approaches the prochiral aldehyde 160 from the less sterically hindered Si-face leading to the formation of anti-homoallylic alcohol 159a. The other possibility is that the allylbromozinc reagent attacks aldehyde 160 from the Re-face leading to the formation of syn-homoallylic alcohol 159b.

![Scheme 74 Allylation mechanism proposed by Mulzer.¹⁶²](image)
In 1996, Chattopadhyay demonstrated the asymmetric synthesis of homoallyl and homopropargyl alcohols using pro-chiral aldehyde \textit{vide infra}.\textsuperscript{163} Based on these observations, he proposed that the high \textit{anti}-selective allylation and propargylation reactions proceeded via a Felkin-Anh model rather than a chelation-Cram model due to the presence of water.

![Scheme 75 Allylation mechanism proposed by Chattopadhyay and co-workers.\textsuperscript{163}](image)

In 2005, Vasconcellos and co-workers described the use of aldehyde 160 as a versatile starting material for the enantioselective synthesis of \textit{(–)-(2S,6S)-(6-ethyltetrahydropyran-2-yl)formic acid}.\textsuperscript{164} They proposed that the major \textit{anti}-epimer 159\textsubscript{a} was derived from a chelated six-membered ring transition state where the allyl(bromo)zinc attacks the less hindered \textit{Si}-face of the prochiral aldehyde 160. The larger group in prochiral aldehyde 160 would favour the axial position in order to decrease the steric hindrance (Scheme 76). Despite this work, the exact mechanism for this reaction is still under debate.

![Scheme 76 Proposed mechanism by Vasconcellos and co-workers.\textsuperscript{164}](image)

Regardless of the reaction mechanism, the desired \textit{anti}-selective allylation was conducted using the reported conditions.\textsuperscript{164} Accordingly, aldehyde 160 was immediately treated with allyl bromide and zinc dust, followed by addition of saturated ammonium chloride solution after one hour to afford \textit{anti}-homoallylic alcohol 159\textsubscript{a} in good yield with moderate diastereoselectivity as determined by \textsuperscript{1}H NMR analysis of the resonance for H-3 (75\%, d.r. 4:1, lit.\textsuperscript{162} 74\%, d.r. 77:23).
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Scheme 77 Synthesis of anti-homoallylic alcohol 159a. *Reagents and conditions:* i) Zn, allyl bromide, THF, aq. NH₄Cl, 0 °C to r.t., 75% (d.r. 4:1).

The allylation reaction proceeded uneventfully in good yield with moderate diastereoselectivity (75%, d.r. 4:1), however, the separation of the two diastereomers 159a and 159b was difficult by flash column chromatography methods as had been reported earlier by Meireles and co-workers.¹⁶⁴ Attempted gravity chromatography did not allow the separation of these two diastereomers. Further optimisation was undertaken utilising a variety of solvents, such as Et₂O, THF and dioxane, and using temperatures varying from −25 °C to room temperature. Unfortunately, no improvement was obtained using these conditions.

In an attempt to obtain the diastereomerically pure *anti*-homoallylic alcohol 159a required for an enantioselective synthesis of acortatarin A (17), further exploration of the purification of homoallylic alcohols 159a and 159b was undertaken as demonstrated by Roush and Coe in 1989 (Scheme 78).¹⁶⁵

Scheme 78 Attempted purification of homoallylic alcohol 159a. *Reagents and conditions:* i) acetone, p-TSA, −40 °C, 24 h, 68%.

An inseparable mixture of homoallylic alcohol 159a and 159b was subjected to a catalytic amount of p-TSA in anhydrous acetone at −40 °C for 24 h (Scheme 78). To our delight, a new product was observed as indicated by TLC. Upon purification by flash column chromatography, a mixture of 159a, 159b and a new compound 165 were obtained as analysed by ¹H and ¹³C NMR studies. The ratio of homoallylic alcohols 159a and 159b was determined to be 22:1 as determined by examination of the ¹H NMR spectrum focusing on the two multiplets at δ 3.68-3.66 and at δ 3.54-3.51 for H-3 (Figure 15). Inspired by this result, further optimisation was attempted. The reaction mixture was allowed to stir for a further 24 h, however, no significant improvement of the reaction was observed.
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Figure 15. Ratio of 159a and 159b after equilibrium by 1H NMR analysis.

In cases where two 1,2-acetonides are possible, the thermodynamically stabilised one would be the more favoured product. Two secondary alcohols acetonides are generally more thermodynamically stabilised over primary and secondary alcohols. However, an acetonide from a primary and secondary alcohols are preferred over an acetonide from two trans secondary alcohols. Thermodynamic comparison of these acetonides 159b and 165b led to the insight that isomer 159b would be thermodynamically less favoured than 165b (Figure 16).166 The substituted allyl carbon chain is on the axial position in structure 159b, whilst in the structure of 165, the two cis-oriented substituted groups are on the pseudo-equatorial position on a fixed five-membered ring.

Figure 16. Proposed equilibration mechanism of acetonide rearrangment.

In the desire to progress the synthesis, attention moved to the next step using the diastereomeric mixture of homoallylic alcohol 159 (Scheme 79). The allylation products 159a and 159b were subjected to a solution of aqueous 2 M HCl at room temperature in THF to afford triol 166 in quantitative yield as an inseparable 4.3:1 mixture of two diastereomers as determined by 1H NMR analysis of the hydroxyl protons. Attempted separation of the diastereomers by flash column chromatography, however, was unsuccessful.
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Scheme 79 Synthesis of TBDPS silyl ether 163. Reagents and conditions: i) 2 M HCl in THF, r.t., 2 h, quant.; ii) NaH, TBDPSCl, THF, 0 °C to r.t., 85%; iii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, r.t., 2 h, quant.

Triol 166 was thus protected as the TBDPS silyl ether 167 according to the established method. The resulting diol 167 was subsequently protected as the acetonide 163 using 2,2-dimethoxypropane in the presence of catalytic PPTS in CH_2Cl_2 affording olefin 163 as an inseparable 5.1:1 mixture of two diastereomers in quantitative yield (based on 1H NMR analysis of the H-2 and H-3). The 1H and 13C NMR spectra for compound 163 were identical to that reported in the literature. 162

2.5.3 Synthesis of Azide 168

With olefin 163 in hand, the required epoxidation was investigated using the optimal conditions employed for the corresponding olefin 163 (Section 2.2.8). Consequently, olefin 163 was treated with m-CPBA in CH_2Cl_2 at room temperature, affording epoxide 161 in 90% yield after purification by flash column chromatography as an inseparable diastereoisomeric mixture of four compounds (Scheme 80).

Scheme 80 Synthesis of azide 168. Reagents and conditions: i) m-CPBA, CH_2Cl_2, r.t. 24 h, 90%; ii) NaN_3, DMF, aqueous NH_4Cl, 100 °C, 168a 52%, 168b 21%.

With the requisite epoxide 161 in hand, efforts next turned to the preparation of azide 168. Using the optimal conditions developed previously (Section 2.3.1), epoxide 161 was subjected to NaN_3 in aqueous DMF giving the desired ring-opened azidohydrin 168a in 52%
yield and the diastereoisomer 168b in 21% yield. Both 168a and 168b were obtained as a mixture of two inseparable diastereomers at C-5. The obtained d.r. of 168a is 1:1 based on 1H NMR analysis of the resonance for H-6 after purification of 168 by column chromatography. The measured d.r. of 168b is 3.6:1 based on the 1H NMR analysis of the resonance for H-6 after purification of 168b with column chromatography.

In summary, the desired azidohydrin 168a was obtained in 8% yield overall from the commercially available chiral starting material D-mannitol over 8 steps. However, the use of an acetonide as a protecting group for D-mannitol had many practical drawbacks, such as its high water solubility, high volatility, an increased propensity to polymerise, and the non-trivial separation of the resulting homoallylic alcohols 168a and 168b. This inefficient synthesis led us to seek an alternative protecting group capable of circumventing the difficult separation of the syn/anti diastereomers. Hence, a more thorough literature search was conducted and it revealed that the use of cyclohexanone as a diol protecting group could address this problem and give better diastereoselectivity and higher yields.163

2.5.4 Synthesis of anti-Homoallylic Alcohol 171a Using (R)-Cyclohexylidene-glyceraldehyde 170

Encouraged by the previous successful synthesis of azidohydrin 168a, we embarked on the synthesis of the known homoallylic alcohol 169a using a cyclohexylidene protecting group strategy. Compared to the corresponding acetonide, cyclohexylidene glyceraldehyde has been reported to be more stable, and to confer more steric hindrance for the aldehyde 175a when the allylation is carried out to yield exclusively the favoured anti-homoallylic alcohol.163

Several research groups have demonstrated that the anti-selective allylation reaction of aldehyde 171a using allyl bromide in the presence of zinc proceeded with similar yields and excellent diastereoselectivity (Scheme 81).158,163,167 Following the reported procedures, D-mannitol (162) was converted to the corresponding cyclohexylidene-protected diol 169 by treatment with BF3·OEt2, triethyl orthoformate and cyclohexanone in DMSO at 50 °C for three hours. Recrystallisation of the product from hot n-hexanes afforded the known compound 1,2:5,6-cyclohexylidene-D-mannitol (169) in 75% yield as white crystals. Importantly, by using this method, a hundred-gram scale reaction could be performed uneventfully. Treatment of the resultant diol 169 with two equivalents of NaIO4 in 60% aqueous CH3CN afforded the oxidative cleavage product (R)-2,3-O-cyclohexylideneglyceraldehyde 170 in almost quantitative yield and in sufficient purity for use in the following allylation reaction without further purification (Scheme 81).
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Scheme 81 Synthesis of anti-homoallylic alcohol 171a. Reagents and conditions: i) cyclohexanone, BF$_3$·OEt$_2$, triethyl orthoformate, DMSO, 50 °C, 3 h, 75%; ii) NaIO$_4$, CH$_3$CN:H$_2$O 3:2, r.t., 3 h, quant.; iii) Zn, aq. NH$_4$Cl, 0 °C, 76% (d.r. 97:3).

Crude (R)-cyclohexylideneglyceraldehyde (170) was elaborated into the corresponding anti-homoallylic alcohol using zinc dust and allyl bromide in aqueous ammonium chloride/THF solution to afford anti-selective homoallylic alcohol 171a in good yield and excellent diastereoselectivity according to $^1$H NMR analysis (88%, d.r. 97:3 [lit. 163 91%, d.r. 97:3]). Compared to the literature precedent, the lower yield was reasoned to be due to the use of crude aldehyde 170. This result was substantially better than that obtained with the more widely used acetonide glyceraldehyde (75%, d.r. 4:1). This method was also amenable for use on a multi-gram scale and the minor byproduct 171b could be easily removed by flash column chromatography.

Scheme 82 Diastereoselective allylation of aldehyde 170. Reagents and conditions: i) Zn, allyl bromide, THF, aqueous NH$_4$Cl, 0 °C to r.t., 88% (d.r. 97:3).

With a robust and highly diastereoselective route to homoallylic alcohol 171a secured, we next moved towards investigating the deprotection of the cyclohexylidene functional group and further manipulations.
2.5.5 Synthesis of Amine 158a

With enantiopure compound 171a in hand, deprotection of the cyclohexylidene group was attempted. The most widely used synthesis of the known triol 166a has been reported using acetonide-protected homoallylic alcohol 159a as mentioned above (Section 2.5.2). Initially, diluted aqueous HCl solution in methanol was used to unmask the diol. However, this reaction appeared to be very sluggish, and after several attempts at changing temperatures, the desired product could not be isolated in high yield (entry 1, Table 15). Consequently, a variety of alternative acidic conditions to access an efficient deprotection were investigated (entries 1-4, Table 15). A variety of acids such as H2SO4 in THF (2 M), TFA in CH2Cl2 (2 M),163 HCl in MeOH168 and concentrated HCl together with acetic acid in methanol were thus investigated to optimise the deprotection step (entries 1-4, Table 14). Gratifyingly, conc. HCl and acetic acid in methanol in a 1:1:1 ratio at 70 °C was found to be optimal to effect complete conversion of 171a to triol 166a within a few hours (entry 4, Table 14). Upon work-up, triol 166a was obtained as a white solid in 90% yield without any further purification being required. The 1H and 13C NMR data and the measured optical rotation were in good agreement with that of the literature [[(α)D]20 +10.0, c 1.1 H2O; lit.169 [(α)D]20 +9.2 c 5.7 D2O).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 M HCl in dioxane, methanol, H2O (1:1:1, v/v/v), 2 h</td>
<td>166a 55%</td>
</tr>
<tr>
<td>2</td>
<td>aqueous 2 M H2SO4 in THF, room temperature, 12 h</td>
<td>166a 34%, 171a 55%</td>
</tr>
<tr>
<td>3</td>
<td>2 M TFA in CH2Cl2, reflux, 12 h</td>
<td>166a 55%, 171a 35%</td>
</tr>
<tr>
<td>4</td>
<td>conc. HCl and CH3CO2H in methanol, (1:1:1, v/v/v) 70 °C, 3 h</td>
<td>90%</td>
</tr>
</tbody>
</table>

With enantiopure triol 166a in hand, selective mono-protection was conducted using TBDPSCI and NaH in anhydrous THF furnishing the TBDPS silyl ether 167a in 90% yield as a single regioisomer. The resultant anti-diol 167a next required protection with an acid labile group that would be able to undergo the concomitant deprotection/spiroketalisation process and also withstand the conditions used for the oxidation, azido-substitution, and reduction steps. Consequently, anti-diol 167a was treated with 2,2-dimethoxypropane and catalytic PPTS in CH2Cl2 at room temperature to give acetonide 163a in almost quantitative yield (Scheme 83). The successful protection of the 2,3-diol was confirmed by the presence of two singlets at δ 1.40 and at δ 1.34 denoting the acetonide CH3.
group in the $^1$H NMR spectrum and a signal at $\delta$ 108.0 denoting the acetonide tertiary carbon in the $^{13}$C NMR spectrum.

Scheme 83 Synthesis of amine 158. Reagents and conditions: i) TBDPSCl, NaH, THF, 0 °C to r.t., 2 h, 90%; ii) PPTS, 2,2-dimethoxypropane, CH$_2$Cl$_2$, r.t. 2 h, quant.; iii) m-CPBA, CH$_2$Cl$_2$, r.t., 48 h, 93% over two steps; iv) NaN$_3$, NH$_4$Cl, EtOH, reflux, 10 h, 168$_{aa}$ 51%, 168$_{ab}$ 38%; v) PMe$_3$, THF: H$_2$O 4:1, 50 °C, 2 h, 158$_a$ 95%, 158$_b$ 98%.

Epoxidation of olefin 163$_a$ using m-CPBA in CH$_2$Cl$_2$ gave epoxide 161$_a$ in 85% yield as an inseparable mixture of two diastereomers. The measured d.r. for epoxide 161$_a$ was 1.5:1 as determined by $^1$H NMR analysis of the resonance for H-6 as four multiplets at $\delta$ 2.84-2.81 and $\delta$ 2.50-2.48 denoting the major isomer and $\delta$ 2.78-2.75 and $\delta$ 2.58-2.54 denoting the minor isomer (Figure 17).
Ring opening of the epoxide 161_a using sodium azide in the presence of NH₄Cl in ethanol under reflux uneventfully afforded azidohydrins 168_aa and 168_ab that were readily separable by column chromatography. However, the two diastereoisomeric ratio was not able to be determined due to the overlapping of resonances of product 168_a. Azidohydrins 168_aa and 168_ab were separately subjected to the reduction conditions using PMe₃ in aqueous THF to give the corresponding amino alcohol 158_a and 158_b in 95% and 98% yield, respectively after workup (Scheme 83). The obtained ¹H NMR at δ 2.60-2.55 integrated as four protons as a multiplet denoting the H-6 and the primary amine hydrogen and ¹³C NMR at δ 47.8 denoting C-6 and HMRS spectroscopic data [M+Na]⁺ 444.2525 C₂₅H₂₅NNaO₄Si unambiguously established the synthesis of amine 158_a. In turn, the obtained ¹H NMR at δ 2.16 integrating to two protons as a broad singlet denoting the primary amine hydrogen and ¹³C NMR at δ 56.3 denoting C-6 and HRMS spectroscopic data [M+Na]⁺ 444.2525, C₂₅H₂₅NNaO₄Si further confirmed the successful formation of amine 158_b.
2.5.6 Summary of the Preparation of Amine 158

The initial approach to build amino alcohol fragment 158 began with the widely used (R)-acetonide glyceraldehyde 160 derived from D-mannitol over two steps (Scheme 84). Anti-selective allylation of 160 using allyl bromide and zinc dust proceeded with moderate diastereoselectivity to afford the desired anti-homoallylic alcohol 159 in good yield as an inseparable mixture of two diasteromers (75%, d.r. 4:1). The desired diastereomer could only be obtained as a stereopure compound at the epoxide ring-opening stage, which was not atom economic.

Further investigation using (R)-cyclohexylidene glyceraldehyde (170) was attempted. Anti-selective asymmetric allylation reaction of aldehyde 170 proceeded in substantially better yield and diastereoselectivity (88%, d.r. 97:3). Importantly, this method proved more convenient when conducted on a multigram scale and the minor diastereomer was readily removed by standard flash column chromatography. Cleavage of the cyclohexylidene group using methanolic HCl and acetic acid followed by mono-protection using TBDPSCl afforded the requisite TBDPS silyl ether 167\textsubscript{a} in 81% yield over two steps. Treatment of the resultant anti-diol 167\textsubscript{a} with 2,2-dimethoxypropane and catalytic amounts of PPTS followed by epoxidation furnished epoxide 161 in 85% yield over two steps. Ring opening of the epoxide 161\textsubscript{a} with NaN\textsubscript{3} afforded an azidohydrin 168\textsubscript{a} that was reduced with PMe\textsubscript{3} in aqueous THF to deliver the desired amino alcohol 158 as two readily separable diastereoisomers in 85% yield over two steps.

Scheme 84 Summary of synthesis of amine 158. Reagents and conditions: i) ZnCl\textsubscript{2}, acetone, then aq. K\textsubscript{2}CO\textsubscript{3}, 24 h, 164 60%; cyclohexanone, BF\textsubscript{3}-OEt\textsubscript{2}, triethyl orthoformate, DMSO, 50 °C, 3 h, 169 75%; ii) NaIO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, aq. NaHCO\textsubscript{3}, 2 h, 160 46%; iii) Zn, allyl bromide, aq. NH\textsubscript{4}Cl, 0 °C to r.t., 159\textsubscript{a} 75%, 171\textsubscript{a} 88% over 2 steps, iv) 2 M HCl in THF, r.t., 2 h, 166 quant.; CH\textsubscript{3}CO\textsubscript{2}H and conc. HCl in MeOH, 70 °C, 3 h, 90% for 166\textsubscript{a}; v) TBDPSCl, NaH, THF, 90%; vi) PPTS, 2,2-dimethoxypropane, r.t., 2 h; vii) m-CPBA, CH\textsubscript{2}Cl\textsubscript{2}, 93% over two steps; viii) NaN\textsubscript{3}, NH\textsubscript{4}Cl, DMF:H\textsubscript{2}O 8:1, 100 °C, 2 h; ix) PMe\textsubscript{3}, THF:H\textsubscript{2}O 4:1, 50 °C, 2 h, 94% over two steps.
2.5.7 Total Synthesis of Acortatarin A

The previously established optimal Maillard-type condensation conditions (Section 2.2.2) were separately applied to the union of amino alcohol 158a and 158b with dihydropyranone 83 to afford the corresponding pyrrole alcohol 172a and 172b in 60% and 51% yield, respectively (Scheme 85).

Scheme 85 Synthesis of acortatarin A (17). Reagents and conditions: i) NEt₃, 1,4-dioxane, r.t., 172a 60%, 172b 51%; ii) TPAP, NMO, CH₂Cl₂, 15 min, 90%, iii) 4 M HCl in dioxane:THF:H₂O 1:1:1 (v/v/v), r.t., 2.5 h, 82%; iv) TBAF, THF, 1 h, 67%
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Oxidation of the resulting hydroxy group at C-5 in alcohol 173a and 173b was conducted using TPAP-NMO in the presence of activated powdered 4 Å molecular sieves to afford ketone 157 in 95% yield. Concomitant deprotection/cyclisation of ketone 157 was effected using 4 M HCl in dioxane diluted with H2O and THF (1:1:1, v/v/v) delivering spiroketal 173a and 173b as an inseparable mixture of two C-5 diastereomers. The ratio of these two diastereomers was determined to be 1.4:1 based on 1H NMR analysis of the aldehyde protons as two singlets at δ9.47 and at δ9.44 for the crude spiroketals 173a and 173b (Figure 18).

![1H NMR analysis for aldehyde protons of spiroketals 173a and 173b.](image)

Final deprotection of the isomeric mixture of spiroketals 173a and 173b using TBAF yielded the corresponding spiroketal alcohols 17 (acortatarin A as the major anomerically-stabilised product, 40%) and 17a (5-epi acortatarin A as the minor non-anomerically-stabilised product, 27%) that were readily separable by flash column chromatography. The spectroscopic data (1H, 13C NMR and HRMS analysis) of acortatarin A was in good agreement with the literature (Table 16). Comparing the optical rotation data of the synthetic sample [[α]D]20 +194.8 (c 0.15, CH3OH) with that of the natural product [[α]D]20 +178.4 (c 0.4, CH3OH)\(^8\) and that of the synthetic sample reported by Jagadeesh and co-workers [[α]D]20 +191.4 (c 0.27 CH3OH)\(^19\) further confirmed the stereorevision of the absolute configuration of acortatarin A.
**Table 16.** $^1$H and $^{13}$C NMR data for natural and synthetic acortatarin A (17).

<table>
<thead>
<tr>
<th>Position</th>
<th>Natural 17 $^1$H NMR (600 MHz)</th>
<th>Synthetic 17 $^1$H NMR (400 MHz)</th>
<th>Natural 17 $^{13}$C NMR (125 MHz)</th>
<th>Synthetic 17 $^{13}$C NMR (100 MHz)</th>
</tr>
</thead>
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<tr>
<td>2</td>
<td>4.03 (ddd, 4.9, 4.9, 3.7)</td>
<td>4.02 (ddd, 4.7, 4.7, 3.9)</td>
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<td>89.3</td>
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<tr>
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<td>4.24 (ddd, 8.3, 4.9, 2.9)</td>
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<td>72.3</td>
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<tr>
<td>4a</td>
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<td>45.8</td>
</tr>
<tr>
<td>4b</td>
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<td>2.30 (dd, 14.0, 8.4)</td>
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<td>...</td>
</tr>
<tr>
<td>5</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>7a</td>
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</tr>
<tr>
<td>7b</td>
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<td>...</td>
</tr>
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<td>8</td>
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<tr>
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</tr>
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<td>6.98 (d, 4.3)</td>
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<tr>
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<td>9.32 (s)</td>
<td>180.2</td>
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<tr>
<td>15a</td>
<td>3.57 (dd, 12.2, 4.9)</td>
<td>3.57 (dd, 12.2, 4.9)</td>
<td>63.0</td>
<td>63.0</td>
</tr>
<tr>
<td>15b</td>
<td>3.65 (dd, 12.2, 3.7)</td>
<td>3.66 (dd, 12.1, 3.5)</td>
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</tr>
</tbody>
</table>

a: Carbon atoms assigned according to natural product numbering, see Scheme 85. $^1$H and $^{13}$C NMR both conducted in CD$_3$OD. $^1$H and $^{13}$C NMR were calibrated according to the aldehyde proton as reported by Cheng and co-workers.
The absolute configuration of 5-epi-acortatarin A was confirmed to \( 2R,3S,5S \) by comparing the obtained spectroscopic data (\(^1\)H and \(^{13}\)C NMR and HRMS analysis) of our synthetic sample with that recorded by Jagadeesh and co-workers (Table 17).\(^{19}\) Further comparison of the optical rotation data of our synthetic sample \([\alpha]_D^{20} = -62.5 \ (c \ 0.02, \ \text{CH}_3\text{OH})\) and that of the synthetic sample reported by Jagadeesh \([\alpha]_D^{20} = -57.77 \ (c \ 0.04, \ \text{CH}_3\text{OH})\)\(^{19}\) confirmed the absolute configuration of 5-epi-acortatarin A (17a).

Table 17. \(^1\)H and \(^{13}\)C NMR data for synthetic 5-epi-acortatarin A (17a).

<table>
<thead>
<tr>
<th>Position (^{a})</th>
<th>Literature 17a (^{19})</th>
<th>Synthetic 17a</th>
<th>Literature 17a (^{19})</th>
<th>Synthetic 17a</th>
</tr>
</thead>
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<tr>
<td></td>
<td>( \delta ) (^1)H NMR (600 MHz)</td>
<td>( \delta ) (^1)H NMR (400 MHz)</td>
<td>( \delta ) (^{13})C NMR (125 MHz)</td>
<td>( \delta ) (^{13})C NMR (100 MHz)</td>
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<tr>
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<td>45.7</td>
<td>45.7</td>
</tr>
<tr>
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<td>2.45 (dd, 13.2, 6.8)</td>
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<td>7b</td>
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<td>15b</td>
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<td>3.66 (dd, 12.1, 4.8)</td>
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</tr>
</tbody>
</table>

\(^{a}\) Carbon atoms assigned following natural product numbering, see Scheme 85. \(^1\)H and \(^{13}\)C NMR both conducted in CD\(_3\)OD.
2.6 Overall Summary and Conclusion

In summary, the synthesis of acortatarin A (17) was successfully completed using a Maillard-type condensation strategy. The use of such methodology for the synthesis of a naturally-occurring 2,5-disubstituted pyrrole ring system was hitherto unprecedented. Another highlight of the synthesis is the use of the cheap commercially available chiral starting materials D-mannitol and furfuryl alcohol to enable a highly convergent synthesis of acortatarin A. Acortatarin A was obtained in 1.7% yield over 13 linear steps (Scheme 86). The synthesis of amine 158a features an anti-selective allylic addition of allyl bromide to cyclohexylidene glyceraldehyde 170 that proceeded with high diastereoselectivity and excellent yield. The key Maillard-type condensation between amine 158a and dihydropyranone 83 uneventfully furnished the N-alkylated product 172, which was then ready for formation of the spiroketal core. The synthetic route executed herein is enantioselective, scalable and highly amenable to the production of analogues of the natural product acortatarin A and the corresponding biotin-derivatives thereof in order to further investigate their ROS inhibition activity.

Significantly, the use of dihydropyranone 83 as a readily available precursor to access 2-formyl pyrrole ring prompted Brimble group to investigate the preparation of other 2-formyl pyrrole natural products that have been published recently including magnolamine, pyrraline and (-)-funebral (Figure 19).\(^\text{170,171}\)

\[\text{Figure 19. Related 2-formyl pyrrole natural products.}\]
Scheme 86 Synthesis of acortatarin A

Reagents and conditions: i). cyclohexanone, BF₃·OEt₂, triethyl orthoformate, DMSO, 50 °C, 3 h, 75%; ii) NaIO₄, CH₃CN:CH₂O 3:2, r.t., 3 h; iii) allyl bromide, zinc dust, THF, aq. NH₄Cl, 0 °C to r.t., 4 h, 88% over two steps; iv) conc. HCl in acetic acid, 70 °C, 3 h, 90%; v) TBDPSCI, NaH, THF, 82%; vi) PPTS, 2,2-dimethoxypropane, r.t., 2 h, quant.; vii) m-CPBA, CH₂Cl₂, 85%; viii) NaN₃, NH₄Cl, DMF:CH₂O 8:1, 2 h; ix) PMe₃, THF:CH₂O 4:1, 50 °C, 2 h, 85% over two steps; x) TBSCI, imidazole, DMF, 0 °C, 15 min, quant.; xi) n-BuLi, THF, DMF, −78°C to r.t., 1 h at −78°C, 2 h at 0 °C, 62%; xii) NaBH₄, MeOH, 0 °C, 1 h, 65%; xiii) m-CPBA, CH₂Cl₂, r.t., 4 h, quant.; xiv) NEt₃, 1,4-dioxane, r.t., 60%; xv) TPAP, NMO, CH₂Cl₂, 15 min, 95%, xvi) 2 M HCl, dioxane:THF:H₂O 1:1:1, r.t., 2.5 h, 85%; xvii) TBAF, THF, 1 h, 67%.
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3.1 General Methods

Unless stated, all reactions were carried out in flame or oven dried glassware under a dry nitrogen or argon atmosphere. All solvents and reagents were used as supplied from commercial sources. Tetrahydrofuran was freshly distilled over sodium/benzophenone. Dichloromethane, diisopropylethylamine and dimethylsulfoxide were freshly distilled over calcium hydride. Lithium chloride was dried for >24 h under vacuum (≈ 1 mmHg) at 70 °C prior to use. Reactions conducted at low temperature were either cooled with an acetone-dry ice bath to reach –78 °C or using a water-ice bath to reach 0 °C.

Analytical thin layer chromatography (TLC) was performed using Kieselgel F254 0.2 mm (Merck) silica plates with visualisation by ultraviolet irradiation (254 nm) followed by staining with potassium permanganate or vanillin. Flash column chromatography was performed using Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel. Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were measured on a Perkin Elmer 341 polarimeter at wavelength 589 nm and are given in units of 10⁻¹ deg cm² g⁻¹. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX400 spectrophotometer at ambient temperature.

Unless stated, for all NMR characterisation, * denotes the minor isomer wherever possible. Unless stated, diastereomeric ratio (d.r.) was determined based on the ¹H NMR spectrum analysis after work-up. Otherwise, the exact d.r. for some diastereomers was not obtained due to the overlapping resonances. Unless stated, all chemical shifts were referenced to δ 7.26 for ¹H (CHCl₃) and δ 77.0 for ¹³C (CHCl₃) respectively. The multiplicities of ¹H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. All coupling constants J are reported in Hertz. All ¹³C NMR spectra were acquired using broadband decoupled mode and assignments were determined using DEPT sequences. Mass spectra were recorded on a Bruker microTOF QII (electrospray ionisation ESI or chemical ionization CI or fast atom bombardment FAB) mass spectrometer.
Chapter 3: Experimental of Acortatarin A

3.2 Synthesis of olefin 88

(2R,3R)-2,3-dihydroxysuccinic acid (93)

To a stirred solution of (L)-tartaric acid (20 g, 13.3 mmol) in anhydrous methanol (800 mL) was added conc. HCl (0.1 mL, 1.1 mmol) at r.t.. The reaction mixture was stirred under reflux for 12 h. Saturated NaHCO$_3$ solution was added until the pH of the reaction mixture reached 7-8. The mixture was concentrated in vacuo to yield a yellow oil. The resulting oil was partitioned between EtOAc (200 mL) and H$_2$O (200 mL) and the aqueous layer was extracted with EtOAc (2 × 200 mL). The organic layers were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to give the title compound 91 as a colourless oil which was used to next step without further purification.

To a stirred solution of diol 91 in anhydrous toluene (250 mL) was added p-TSA (2.5 g, 1.3 mmol) followed by 2,2-dimethoxypropane (30 mL). The reaction mixture was stirred under at 50 °C for 2 h then quenched by addition of saturated aqueous NaHCO$_3$ (150 mL). The aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous MgSO$_4$ and concentrated in vacuo to afford the title compound 92 as a colourless oil that was used to next step without further purification.

To a stirred solution of ester 92 in anhydrous THF (250 mL) was added LiAlH$_4$ (1.3 g, 33.0 mmol) under N$_2$. The reaction mixture was stirred under reflux for 4 h. The excess LiAlH$_4$ was quenched by addition of H$_2$O (1.3 mL) dropwise at 0 °C followed by addition of a solution of NaOH (10w/w%, 1.3 mL) and subsequent addition of H$_2$O (3.9 mL). The mixture was stirred at r.t. for 6 h followed by filtration through a pad of Celite®. The filtrate was concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc, 1:4) afforded the title compound 93 (18.3 g, 11.3 mmol, 85%) as a colourless oil.

$[\alpha]_D^{21} = +4.1$ (c 1.0, CHCl$_3$), lit.$^{172}$ $[\alpha]_D^{25} = +3.8$, c 3.7, CHCl$_3$; $^1$H NMR (400 MHz, CDCl$_3$): δ 3.99-3.98 (2H, m, 2-H, 3-H), 3.80-3.68 (4H, m, 1-H, 4-H), 2.48 (2H, br s, OH), 1.42 (6H, s, 6-H, 7-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 109.2 (C, 5-C), 78.0 (2 × CH, 2-C, 3-C), 61.9 (2 × CH$_2$, 1-C, 4-C), 26.9 (2 × CH$_3$, 6-C, 7-C).

The data was in good agreement with the literature.$^{172}$
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\((2S,3S)\)-2,3-Isopropylidenedioxy-1-benzylkoxy-4-ol-butane (90)

\[
\begin{align*}
\text{BnO} & \quad \text{3-OH} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

To a stirred solution of diol 93 (1.6 g, 10 mmol) in freshly distilled THF (40 mL) at 0°C was added NaH (60% in mineral oil, 0.44 g, 11 mmol) slowly. The mixture was stirred at 0°C for 30 min followed by addition of BnBr (1.2 mL, 10.5 mmol). After 2 h, the reaction was quenched with H2O (30 mL) carefully. The reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with saturated aqueous NaCl (120 mL), dried over anhydrous Na2SO4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 4:1) afforded the title compound 90 (2.1 g, 8.3 mmol, 83%) as a light yellow oil.

\[
\begin{align*}
\text{[α]D}^{21} & = +8.9 \ (c \ 1.0, \ \text{CHCl}_3, \ \text{lit.}^8) \ [\alpha]_D^{23} = +9.0, \ c \ 0.99, \ \text{CHCl}_3); \ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \ \delta \\
& 7.38-7.30 \ (5\text{H, m, Ph}), \ 4.59 \ (2\text{H, s, CH}_2\text{Ph}), \ 4.09-4.04 \ (1\text{H, m, 3-H}), \ 3.98-3.93 \ (1\text{H, m, 2-H}), \ 3.79-3.75 \ (1\text{H, m, 1-H}_b), \ 3.71-3.68 \ (2\text{H, m, 4-H}), \ 3.59-3.55 \ (1\text{H, m, 1-H}_b), \ 2.38-2.35 \ (1\text{H, br s, OH}), \ 1.43 \ (3\text{H, s, 7-H}), \ 1.40 \ (3\text{H, s, 6-H}); \ ^13\text{C NMR} \ (100 \text{ MHz, CDCl}_3): \ \delta \\
& 137.5 \ (\text{C, Ph}), \ 128.4 \ (2 \times \text{CH, Ph}), \ 127.8 \ (\text{CH, Ph}), \ 127.7 \ (2 \times \ \text{CH, Ph}), \ 109.3 \ (\text{C, 5-C}), \ 79.6 \ (\text{CH, 2-C}), \ 76.5 \ (\text{CH, 3-C}), \ 73.7 \ (\text{CH}_2, \text{CH}_2\text{Ph}), \ 70.3 \ (\text{CH}_2, \text{1-C}), \ 62.4 \ (\text{CH}_3, \text{4-C}), \ 26.9 \ (\text{CH}_3, \text{6-C}), \ 26.9 \ (\text{CH}_3, \text{7-C}).
\end{align*}
\]

The data was in agreement with the literature.\textsuperscript{80}

\((2S,3R)-2,3-Isopropylidenedioxy-4-benzylkoxy-1-iodobutane (89)

\[
\begin{align*}
\text{BnO} & \quad \text{3-OH} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

To a stirred solution of alcohol 90 (2.1 g, 8.3 mmol) in toluene (80 mL) at r.t. was added PPh\(_3\) (3.8 g, 12.5 mmol), imidazole (1.7 g, 24.9 mmol) and I\(_2\) (3.2 g, 12.5 mmol). The mixture was heated under reflux for 12 h. The reaction was quenched with saturated aqueous Na\(_2\)SO\(_4\) (80 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. Purification by flash chromatography on silica gel (n-hexanes/EtOAc 12:1) afforded the title compound 89 (2.5 g, 7.1 mmol, 85%) as a yellow oil.

\[
\begin{align*}
\text{[α]D}^{21} & = -9.6 \ (c \ 2.3, \ \text{CHCl}_3, \ \text{lit.}^8) \ [\alpha]_D^{21} = -10.1 \ c \ 2.1, \ \text{CHCl}_3); \ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \ \delta \\
& 7.37-7.29 \ (5\text{H, m, Ph}), \ 4.59 \ (2\text{H, s, CH}_2\text{Ph}), \ 3.98-3.94 \ (1\text{H, m, 2-H}), \ 3.88-3.84 \ (1\text{H, m, 3-H}), \ 3.65 \ (2\text{H}, \text{ dd, J}=4.0 \text{ Hz, 4-H}), \ 3.37-3.33 \ (1\text{H, m, 1-H}_b), \ 3.30-3.26 \ (1\text{H, m, 1-H}_b), \ 1.47 \ (3\text{H, s, 6-H}), \ 1.47 \ (3\text{H,}
\end{align*}
\]

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s, 7-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.8 (C, Ph), 128.4 (2 × CH, Ph), 127.8 (CH, Ph), 127.7 (2 × CH, Ph), 109.8 (C, 5-C), 80.1 (CH, 3-C), 77.6 (CH, 2-C), 73.6 (CH$_2$, CH$_2$Ph), 70.5 (CH$_2$, 4-C), 26.9 (CH$_3$, 6-C), 26.9 (CH$_3$, 7-C), 6.4 (CH$_2$, 1-C).

The data was in agreement with the literature.$^{80}$

(2S,3S)-1-Benzxyloxy-2,3-isopropylidenedioxy-hex-5-ene (88)

To a solution of iodide 89 (0.8 g, 2.2 mmol) in dry THF (4.4 mL) and anhydrous DMPU (4.4 mL) was added CuI (84 mg, 0.44 mmol) at r.t. under argon. The resulting mixture was cooled to $-35 \, ^\circ\text{C}$ and vinylmagnesium bromide (1 M in THF, 4.4 mL, 4.4 mmol) was added dropwise. The resulting mixture was stirred at $-20 \, ^\circ\text{C}$ for 0.5 h followed by addition of another portion of vinylmagnesium bromide (1 M in THF, 1.4 mL, 1.4 mmol). The reaction mixture was stirred at $-20 \, ^\circ\text{C}$ for another 2 h. The homogeneous mixture was quenched with saturated aqueous NH$_4$Cl (15 mL). The resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl (90 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 10:1) afforded the title compound 88 (458 mg, 1.8 mmol, 85%) as a light yellow oil.

[$\alpha$]$_D^{20} = -12.8$ (c 2.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36-7.28 (5H, m, Ph), 5.88-5.78 (1H, m, 5-H), 5.16-5.07 (2H, m, 6-H), 4.60 (2H, s, CH$_2$Ph), 3.92-3.89 (2H, m, 2-H, 3-H), 3.59 (2H, d, J = 4.0 Hz, 1-H), 2.41-2.38 (2H, m, 4-H), 1.44 (3H, s, 8-H), 1.42 (3H, s, 9-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.0 (C, Ph), 133.8 (CH, 5-C), 128.3 (2 × CH, Ph), 127.6 (3 × CH, Ph), 117.5 (CH$_2$, 6-C), 108.9 (C, 7-C), 79.5 (CH, 3-C), 77.3 (CH, 2-C), 73.4 (CH$_2$, CH$_2$Ph), 70.4 (CH$_2$, 1-C), 37.4 (CH$_2$, 4-C), 27.2 (CH$_3$, 8-C), 27.0 (CH$_3$, 9-C); IR $\nu_{\text{max}}$(film)/cm$^{-1}$: 2985, 2864, 1642, 1454, 1077, 995, 914, 735, 697; HRMS Found (ESI): [M+H]$^+$ 263.1638, C$_{16}$H$_{23}$O$_3$ requires 263.1642.
3.3 Synthesis of electrophiles 81 and 112-114

(2S,3S,5R/S)-1-Benzylxoy-2,3-isopropyldenedioxy-5,6-epoxyhexane (81)

To a mixture of alkene 88 (200 mg, 0.8 mmol) and NaHCO₃ (530 mg, 6.3 mmol) in H₂O (4 mL) and CH₃CN (6 ml) at 0 °C was added CF₃COCH₃ (0.1 mL) with a precooled syringe at 0 °C under N₂. Oxone® (2.44 g, 4.0 mmol) was added to the reaction in four portions over 1 h at 0 °C. The reaction was stirred at r.t. for 12 h and quenched by portion-wise addition of saturated aqueous Na₂SO₃ (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (n-hexanes/EtOAc 5:1) afforded the title compound 81 (175 mg, 0.7 mmol, 85%) as a colourless oil containing an inseparable mixture of two diastereoisomers.

¹H NMR (400 MHz, CDCl₃): δ 7.35-7.29 (5H, m, Ph), 4.58 (2H, s, CH₂Ph), 4.04-3.86 (2H, m, 2-H, 3-H), 3.65-3.55 (2H, m, 1-H), 3.09-3.05 (1H, m, 5-H), 2.80-2.49 (2H, m, 6-H), 1.84-1.69 (2H, m, 4-H), 1.43-1.41 (6H, m, 8-H, 9-H); ¹³C NMR (100 MHz, CDCl₃, * denotes minor isomer): δ 137.9 (C, Ph), 128.4 (2 × CH, Ph), 127.7 (3 × CH, Ph), 109.1 (C, 7-C), 109.0* (C, 7-C), 79.9 (CH, 2-C), 79.3*(CH, 2-C), 76.1 (CH, 3-C), 75.7*(CH, 3-C), 73.59 (CH₂, CH₂Ph), 73.58*(CH₂, CH₂Ph), 70.2 (CH₂, 1-C), 70.1*(CH₂, 1-C), 49.5 (CH, 5-C), 49.2* (CH, 5-C), 47.5 (CH₂, 6-C), 46.7* (CH₂, 6-C), 36.8 (CH₂, 4-C), 35.3*(CH₂, 4-C), 27.3 (CH₃, 8-C), 27.2* (CH₃, 8-C), 27.0 (CH₃, 9-C); IR νmax(film)/cm⁻¹: 2989, 2942, 1515, 1376, 1261, 1081, 1020, 856, 821; HRMS Found (ESI): [M+Na]⁺ 301.1408, C₁₆H₂₅NaO₄ requires 301.1410.

(2S,3S,5R/S)-1-Benzylxoy-2,3-isopropyldenedioxy-5-ol-6-iodo-hexane (110)

To a stirred solution of epoxide 81 (300.8 mg, 1.1 mmol) in a mixture of acetic acid and propanoic acid (6 mL, 1:2) at −20 °C was added NaI (194.2 mg, 1.3 mmol). After stirring at −20 °C for 30 min, the reaction mixture was warmed to r.t. Saturated aqueous NaHCO₃ (30 mL)
was added to neutralise the reaction mixture to reach pH 7-8 and the resulting mixture was extracted with EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 4:1) afforded the title compound 110 (385.7 mg, 0.96 mmol, 87%, d.r. 3.7:1) as a colourless oil containing an inseparable mixture of two diastereomers.

**¹H NMR** (400 MHz, CDCl₃, * denotes the minor isomer): δ 7.35–7.29 (5H, m, Ph), 4.56 (2H, s, CH₂Ph), 4.08–3.98 (1H, m, 2-H), 3.93–3.86 (1H, m, 3-H), 3.86–3.75 (1H, m, 5-H), 3.67–3.53 (2H, m, 1-H), 3.37–3.22 (2H, m, 6-H), 2.00–1.94* (2H, m, 4-H), 1.94–1.70 (2H, m, 4-H), 1.43–1.39 (6H, m, 8-H, 9-H); **¹³C NMR** (100 MHz, CDCl₃, * denotes the minor isomer) δ 137.68 (C, Ph), 137.65 (C, Ph), 128.41* (2 × CH, Ph), 128.39 (2 × CH, Ph), 127.77* (CH, Ph), 127.69* (2 × CH, Ph), 127.77 (3 × CH, Ph), 109.6* (C, 7-C), 109.2 (C, 7-C), 79.9* (CH, 2-C), 79.5 (CH, 2-C), 77.6* (CH, 3-C), 75.8 (CH, 3-C), 73.62* (CH₂, CH₂Ph), 73.58 (CH₂, CH₂Ph), 70.2 (CH₂, 1-C), 70.0* (CH₂, 1-C), 69.9* (CH, 5-C), 68.6 (CH, 5-C), 39.6* (CH₂, 4-C), 39.1 (CH₂, 4-C), 27.2 (CH₃, 8-C), 27.1* (CH₂, 8-C), 27.0* (CH₂, 9-C), 26.9 (CH₃, 9-C), 14.6 (CH₂, 6-C), 13.6* (CH₂, 6-C); **IR** ν<sub>max</sub>(film)/cm⁻¹: 3447, 2951, 2866, 1730, 1454, 1370, 1086; **HRMS** Found (ESI): [M+Na]⁺ 429.0533, C₁₀H₁₂INaO₄ requires 429.0540.

**(2S,3S)-1-Benzyl oxy-2,3-isopropyldienedioxy-5-one-6-iodo-hexane (112)**

**(2S,3S)-1-Benzyl oxy-2,3-isopropyldienedioxy-5-one-6-chloro-hexane (114)**

![Chemical structure](image)

To a stirred solution of iodohydrin 110 (100 mg, 0.25 mmol) and activated powdered 4 Å molecular sieves (50 mg) in anhydrous CH₂Cl₂ (5 mL) was added PCC (59.3 mg, 0.28 mmol) at r.t. After stirring for 12 h, the reaction was concentrated under reduced pressure to about 1 mL. The resulting mixture was filtered through a plug of silica and washed with EtOAc (3 × 10 mL). The filtrate was concentrated in vacuo followed by purification by flash column chromatography on silica gel (n-hexanes/EtOAc 5:1) to afford the title compound 112 (68.4 mg, 0.16 mmol, 65%) and 113 (25.1 mg, 0.08 mmol, 32%) both as a light brown oil.
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\[ \alpha \] = –31.5 (c 1.1, CHCl₃); \({}^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.36-7.29 (5H, m, Ph), 4.56 (2H, s, CH₂Ph), 4.27-4.22 (1H, m, 2-H), 3.90-3.81 (3H, m, 3-H, 6-H), 3.68-3.63 (1H, dd, \(J = 9.0, 5.4\) Hz, 1-H), 3.56-3.53 (1H, dd, \(J = 9.0, 5.4\) Hz, 1-H), 3.03-2.93 (2H, m, 4-H), 1.40 (3H, s, 8-H), 1.39 (3H, s, 9-H); \(1^\)C NMR (100 MHz, CDCl₃): \(\delta\) 200.3 (C, 5-C), 137.8 (C, Ph), 128.5 (2 × CH, Ph), 127.8 (3 × CH, Ph), 109.5 (C, 7-C), 79.3 (CH, 2-C), 75.5 (CH, 3-C), 73.7 (CH₂, CH₂Ph), 70.2 (CH₂, 1-C), 42.8 (CH₂, 4-C), 27.2 (CH₃, 8-C), 27.0 (CH₃, 9-C), 7.2 (CH₂, 6-C); IR \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\): 2983, 2934, 1690 1594, 1454, 1370, 1086; HRMS Found (ESI): [M+Na]⁺ 427.0379. \(\text{C}_{16}\text{H}_{21}\text{INaO}_{4}\) requires 427.0377.

\[ \alpha \] = –63.5 (c 0.8, CHCl₃); \({}^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.37-7.26 (5H, m, Ph), 4.55 (2H, s, CH₂Ph), 4.28-4.22 (1H, m, 1-H), 4.14 (2H, s, 6-H), 3.90-3.85 (1H, m, 1-H), 3.68-3.65 (1H, dd, \(J = 10.0, 5.4\) Hz, 3-H), 3.56-3.52 (1H, dd, \(J = 10.0, 5.0\) Hz, 2-H), 2.85 (2H, d, \(J = 5.4\) Hz, 4-H), 1.39 (3H, s, 8-H), 1.38 (3H, s, 9-H); \(1^\)C NMR (100 MHz, CDCl₃): \(\delta\) 199.8 (C, 5-C), 137.7 (C, Ph), 128.5 (2 × CH, Ph), 127.8 (3 × CH, Ph), 109.6 (C, 7-C), 79.2 (CH, 2-C), 74.9 (CH, 3-C), 73.7 (CH₂, CH₂Ph), 70.2 (CH₂, 1-C), 49.0 (CH₂, 6-C), 43.1 (CH₂, 4-C), 27.2 (CH₃, 8-C), 26.9 (CH₃, 9-C); IR \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\): 2979, 2917, 1675 1587, 1453, 1370, 1081; HRMS Found (ESI): [M+Na]⁺ 335.1021. \(\text{C}_{16}\text{H}_{21}\text{IINaO}_{4}\) requires 335.1016.

(2S,3S,5R/S)-1-Benzoyloxy-2,3-isopropylidenedioxy-5-ol-6-bromo-hexane (111)

To a stirred solution of epoxide 81 (300.0 mg, 1.1 mmol) in acetic acid and propanoic acid (6 mL, 1:2) was added NaBr (133.2 mg, 1.3 mmol) at –20 °C. The reaction mixture was stirred at –20 °C for 30 min. The reaction was warmed to r.t. and partitioned between saturated aqueous NaHCO₃ (30 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 4:1) afforded the title compound 111 (334.7 mg, 0.94 mmol, 85%, d.r. 3.5:1) as a colourless oil containing an inseparable mixture of two diastereoisomers.

\({}^1\)H NMR (400 MHz, CDCl₃, * denotes minor isomer): \(\delta\) 7.34-7.28 (5H, m, Ph), 4.58 (2H, s, CH₂Ph), 4.12-3.96 (2H, m, 3-H, 5-H), 3.92-3.86 (1H, m, 2-H), 3.66-3.53 (2H, m, 1-H), 3.52-3.38 (2H, m, 6-H), 4.00-1.96* (2H, m, 4-H), 1.93-1.72 (2H, m, 4-H), 1.42-1.38 (6H, m, 8-H, 9-H); \(1^\)C NMR (100 MHz, CDCl₃):}
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MHz, CDCl₃, * denotes minor isomer): δ 137.75 (C, Ph), 137.71* (C, Ph), 128.45* (3 × CH, Ph), 128.43 (2 × CH, Ph), 127.8* (CH, Ph), 127.7 (3 × CH, Ph), 109.5* (C, 7-C), 109.2 (C, 7-C), 79.9* (CH, 2-C), 79.7 (CH, 2-C), 77.5* (CH, 3-C), 75.6 (CH, 3-C), 73.64* (CH₂, CH₃Ph), 73.60 (CH₂, CH₂Ph), 70.2 (CH₂, 1-C), 70.0* (CH₂, 1-C), 69.9* (CH, 5-C), 68.7 (CH, 5-C), 39.1* (CH₂, 4-C), 38.1 (CH₂, 4-C), 27.4 (CH₂, 8-C), 27.3* (CH₂, 8-C), 27.1* (CH₃, 9-C), 26.9 (CH₃, 9-C), 8.9 (CH₂, 6-C); **IR** ν_max (film)/cm⁻¹: 3436, 2985, 2864, 2862, 1717, 1370, 1073; **HRMS** Found (ESI): [M+Na]+ 381.0667, 383.0646, C₁₆H₂₁BrNaO₄ requires 381.0672.

(2S,3S)-1-Benzoyloxy-2,3-isopropylidenedioxy-5-one-6-bromo-hexane (113)

To a stirred solution of bromohydrin 111 (100 mg, 0.28 mmol) and activated powdered 4Å molecular sieves (50 mg) in anhydrous CH₂Cl₂ (5 mL) was added PCC (65.1 mg, 0.31 mmol) at r.t. After stirring for 12 h, the reaction was concentrated under reduced pressure to about 1 mL. The resulting mixture was filtered through a plug of silica and washed with EtOAc (3 × 10 mL). The filtrate was concentrated in vacuo followed by purification with flash column chromatography on silica gel (n-hexanes/EtOAc 5:1) to afford the title compound 113 (69.8 mg, 0.20 mmol, 70%) as a brown oil.

[α]D²⁰ = −53.2 (c 1.3, CHCl₃); **¹H NMR** (400 MHz, CDCl₃): δ 7.33-7.26 (5H, m, Ph), 4.54 (2H, s, CH₂Ph), 4.26-4.21 (1H, m, 3-H), 3.93 (2H, s, 6-H), 3.90-3.85 (1H, m, 2-H), 3.67-3.52 (2H, m, 1-H), 2.91 (2H, d, J = 5.6 Hz, 4-H), 1.39 (3H, s, 8-H), 1.38 (3H, s, 9-H); **¹³C NMR** (100 MHz, CDCl₃): δ 199.0 (C, 5-C), 137.6 (C, Ph), 128.3 (2 × CH, Ph), 127.6 (3 × CH, Ph), 109.3 (C, 7-C), 79.0 (CH, 2-C), 74.8 (CH, 3-C), 73.5 (CH₂, CH₃Ph), 70.0 (CH₂, 1-C), 43.2 (CH₂, 4-C), 35.0 (CH₂, 6-C), 27.0 (CH₃, 8-C), 26.8 (CH₃, 9-C); **IR** ν_max (film)/cm⁻¹: 2979, 2864, 2859, 1712, 1690, 1368; **HRMS** Found (ESI): [M+Na]+ 381.0497, C₁₆H₂₁BrNaO₄ requires 379.0515.

(2S,3S)-1-Benzoyloxy-2,3-isopropylidenedioxy-hex-5,6-diol (122)

Olefin 88 (400.0 mg, 1.5 mmol) was dissolved in a mixture of acetone and H₂O (1:1, 15 mL) in the presence of a pH 7 buffer (2 mL). A solution of 2.5% wt of OsO₄ in t-BuOH (3 mL,
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0.075 mmol) was added to the above mixture followed by addition of NMO (210.2 mg, 1.8 mmol) at r.t. After stirring at r.t. for 10 h, saturated aqueous Na₂SO₃ (15 mL) was added. The resulting mixture was concentrated under reduced pressure to remove most of the acetone followed by extraction with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound 122 (440.2 mg, 1.5 mmol, quant.) as an inseparable mixture of two diastereoisomers. The absolute d.r. was not obtained due to overlapping resonances. The crude material was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.27 (5H, m, Ph), 4.57 (2H, s, CH₂Ph), 4.07-3.97 (1H, m, 2-H), 3.91-3.86 (2H, m, 3-H, 6-Ha), 3.62-3.48 (4H, m, 1-H, 5-H, 6-Hb), 2.26-2.05 (2H, m, OH), 1.85-1.66 (2H, m, 4-H), 1.43-1.39 (6H, m, 8-H, 9-H); ¹³C NMR (100 MHz, CDCl₃, * denotes minor isomer): δ 137.6 (C, Ph), 128.3 (2 × CH, Ph), 127.6 (3 × CH, Ph), 109.2* (C, 7-C), 108.9 (C, 7-C), 80.0* (CH, 3-C), 79.7 (CH, 3-C), 77.1* (CH, 2-C), 75.6 (CH, 2-C), 73.5 (CH₂, CH₃Ph), 70.6* (CH, 5-C), 70.2 (CH₂, 1-C), 69.9* (CH₂, 1-C), 69.3 (CH, 5-C), 66.6 (CH, 6-C), 66.1* (CH₂, 6-C), 36.4 (CH₂, 4-C), 36.2* (CH₂, 4-C), 27.2 (CH₃, 8-C), 27.1* (CH₃, 8-C), 27.0* (CH₃, 9-C), 26.9 (CH₃, 9-C); IR νₘₐₓ(film)/cm⁻¹: 3481, 2986, 2936, 2872, 1370, 1213, 1070, 738; HRMS Found (ESI): [M+Na]⁺ 319.1519, C₁₆H₂₆NaO₅ requires 319.1516.

(2S,3S)-1-Benzylxy-2,3-isopropylidenedioxy-5-ol-6-(4-methyl)benzenesulfonate-hexane (123)

![Structural formula of 123](image)

To a stirred solution of diol 122 (300.0 mg, 1.0 mmol) in anhydrous CH₂Cl₂ (15 mL) at 0 °C was added p-TsCl (209.6 mg, 1.1 mmol) and Et₃N (0.3 mL, 3.1 mmol). After stirring at r.t. for 3 h, the reaction mixture was quenched by addition of H₂O (20 mL). The organic layer was collected and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL). Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 3:1) afforded the title compound 123 (361.0 mg, 80%, d.r. 3:2:1) as a colourless oil containing a mixture of two diastereoisomers.

¹H NMR (400 MHz, CDCl₃, * denotes the minor isomer): δ 7.81-7.78 (2H, m, Ph); 7.38-7.27 (7H, m, Ph), 4.58-4.56 (2H, m, CH₂Ph), 4.13-3.92 (4H, m, 1-H, 3-H, 5-H), 3.89-3.83 (1H, m, 2-H), 3.63-3.50 (2H, m, 6-H), 3.15* (1H, d, J = 2.0 Hz, OH), 2.74 (1H, m, OH), 2.45 (3H, s, 4'-CH₃), 1.89-
1.84* (2H, m, 4-H), 1.83-1.63 (2H, m, 4-H), 1.38-1.36 (6H, m, 8-H, 9-H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\), * denotes the minor isomer): \(\delta 145.02\) (C, Ph), \(144.97^*\) (C, Ph), 137.8 (C, Ph), 137.7* (C, Ph), 132.78* (C, Ph), 132.75 (C, Ph), 129.93 (2 × CH, Ph), 129.91* (2 × CH, Ph), 128.5* (2 × CH, Ph), 128.47 (2 × CH, Ph), 128.0 (2 × CH, Ph), 127.85* (CH, Ph), 127.80 (CH, Ph), 127.7 (2 × CH, Ph), 109.5* (C, 7-C), 109.2 (C, 7-C), 79.9* (CH, 2-C), 79.5 (CH, 2-C), 77.3* (CH, 3-H), 75.6 (CH, 3-C), 73.7* (CH\(_3\), CH\(_2\)Ph), 73.6 (CH\(_2\), 1-C), 73.4 (CH\(_2\), 1-C), 72.9*(CH\(_2\), 1-C), 70.2 (CH\(_2\), 6-C), 69.9* (CH\(_2\), 6-C), 68.4* (CH, 5-C), 67.0 (CH, 5-C), 36.1* (CH\(_2\), 4-C), 35.9 (CH\(_2\), 4-C), 27.2 (CH\(_3\), 8-C), 27.1* (CH\(_3\), 8-C), 27.0* (CH\(_3\), 9-C), 26.9 (CH\(_3\), 9-C), 21.6 (CH\(_3\), 4'-CH\(_3\)), 21.0* (CH\(_3\), 4'-CH\(_3\)); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3453, 2989, 2922, 2869, 1598, 1454, 1395, 1175, 1095, 814, 667; HRMS Found (ESI): [M+H]^+ 451.1781, C\(_{23}\)H\(_{30}\)O\(_3\)S requires 451.1785.

(2S,3S)-1-Benzxyloxy-2,3-isopropyldenedioxy-5-one-6-(4'-methyl)benzenesulfonate-hexane (114)

![Structure](image)

To a stirred solution of alcohol 123 (200 mg, 0.44 mmol) in anhydrous DMSO (10 mL) was added IBX (149.3 mg, 0.53 mmol) at r.t. After stirring at 50 °C for 3 h, the reaction was cooled to r.t. and quenched by addition of saturated aqueous Na\(_2\)SO\(_4\) (10 mL). The resulting mixture was extracted with EtOAc (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (40 mL) dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 4:1) to afford the title compound 114 (124.3 mg, 0.28 mmol, 63%) as a brown oil. 448.5

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.82-7.79\) (2H, m, Ph); 7.36-7.28 (7H, m, Ph), 4.55 (2H, s, CH\(_2\)Ph), 4.54 (2H, s, 6-H), 4.22-4.17 (1H, m, 3-H), 3.86-3.82 (1H, m, 2-H), 3.63 (1H, dd, 1-H\(_a\)), 3.52 (1H, dd, 1-H\(_b\)) 2.78 (1H, d, J = 1.0 Hz, 4-H\(_a\)), 2.76 (1H, s, 4-H\(_b\)), 2.45 (3H, s, 4'-CH\(_3\)), 1.38-1.36 (6H, m, 8-H, 9-H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 202.3\) (C, 5-C), 145.4 (C, Ph), 137.7 (C, Ph), 132.3 (C, Ph), 129.9 (2 × CH, Ph), 128.4 (2 × CH, Ph), 128.1 (2 × CH, Ph), 127.8 (CH, Ph), 127.7 (2 × CH, Ph), 109.5 (C, 7-C) 79.1 (CH, 3-C), 74.2 (CH, 2-C), 73.6 (CH\(_2\), CH\(_2\)Ph), 72.2 (CH\(_2\), 1-C), 70.0 (CH\(_2\), 1-C), 42.6 (CH\(_3\), 4-C), 27.0 (CH\(_3\), 8-C), 26.9 (CH\(_3\), 9-C), 21.6 (CH\(_3\), 4'-C); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2978, 2924, 2845, 1708, 1451, 1392, 1168, 1094, 814, 667.
3.4 Synthesis of dihydropyranone 83 and pyrone 82

5-(((tert-Butyldimethylsilyloxy)methyl)furan-2-carbaldehyde

To a stirred solution of furfuryl alcohol (5.0 g, 51 mmol) in DMF (30 mL) was added imidazole (3.6 g, 53 mmol) and TBSCl (8.0 g, 53 mmol) at 0 °C. The reaction mixture was warmed to r.t. with stirring for 30 min before H2O (100 mL) was added. The reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over anhydrous MgSO4 and concentrated in vacuo affording the title compound 87 (10.3 g, 47 mmol, 96%) as a yellow oil that was used to next step without further purification.

To a stirred solution of 87 (3.0 g, 14.1 mmol) in anhydrous THF (30 mL) at –78 °C was added n-BuLi (1.6 M, 15.5 mL, 15.5 mmol) dropwise. The solution was stirred at –78 °C for 1.5 h and at 0 °C for 30 min then cooled to –78 °C followed by dropwise addition of anhydrous DMF (2.2 mL, 28 mmol). The reaction mixture was stirred at –78 °C for 1 h and at r.t. for further 30 min. The solution was quenched with H2O (75 mL) and extracted with EtOAc (100 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous MgSO4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 20:1) afforded the title compound 96 (2.3 g, 9.6 mmol, 68%) as a yellow oil.

1H NMR (400 MHz, CDCl3): δ 9.48 (1H, s, 6-C), 7.10 (1H, d, J = 3.6 Hz, 3-H), 6.36 (1H, d, J = 3.6 Hz, 4-H), 4.63 (2H, s, 7-H), 0.81 (9H, s, (CH3)3C=Si(CH3)2), 0.00 (6H, s, (CH3)3C=Si(CH3)2); 13C NMR (100 MHz, CDCl3): δ 177.5 (CH, 6-C), 161.5 (C, 5-C), 152.2 (C, 2-C), 122.5 (CH, 3-C), 109.4 (CH, 4-C), 58.6 (CH2, 7-C), 25.8 (3 × CH3, (CH3)3C=Si(CH3)2), 18.3 (C, (CH3)3C=Si(CH3)2), −5.4 (2 × CH3, (CH3)3C=Si(CH3)2).

The data was in agreement with the literature.173
2-(tert-Butyldimethylsilyloxy)methyl-5-hydroxymethylfuran (94)

\[
\begin{align*}
\text{HO} & \quad \text{OTBS} \\
\text{3} & \quad \text{2} & \quad \text{1} \\
\end{align*}
\]

To a stirred solution of aldehyde 96 (2.3 g, 9.6 mmol) in MeOH (50 mL) at 0 °C was added NaBH₄ (721 mg, 19 mmol) portionwise. After stirring at 0 °C for 15 min, the reaction was quenched with H₂O (2 mL) and MeOH was removed under reduced pressure. The oily residue was partitioned with H₂O (40 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo to afford the title compound 94 (2.3 g, 9.5 mmol, 99%) as a colourless oil that was used to next step without further purification.

\(^1\text{H NMR}\) (400 MHz, CDCl₃): \( \delta 6.21 \) (1H, \( d, J = 3.6 \) Hz, 4-H), 6.18 (1H, \( d, J = 3.6 \) Hz, 3-H), 4.62 (2H, s, 6-H), 4.57 (2H, s, 7-H), 1.84 (1H, br s, OH), 0.90 (9H, s, \( (\text{CH}_3)_3\text{CSi(CH}_3)_2 \)), 0.08 (6H, s, \( (\text{CH}_3)_3\text{CSi(CH}_3)_2 \)). \(^{13}\text{C NMR}\) (100 MHz, CDCl₃): \( \delta 154.4 \) (C, 5-C), 153.3 (C, 2-C), 108.4 (CH, 4-C), 107.9 (CH, 3-C), 58.2 (CH₂, 6-C), 57.6 (CH₂, 7-C), 25.8 (3 × CH₃, \( (\text{CH}_3)_3\text{CSi(CH}_3)_2 \)), 18.4 (C, \( (\text{CH}_3)_3\text{CSi(CH}_3)_2 \)), \(-5.2 \) (2 × CH₃, \( (\text{CH}_3)_3\text{CSi(CH}_3)_2 \)).

The data was in agreement with the literature.\(^{173}\)

4-((tert-Butyldimethylsilyloxy)methyl)-4-hydroxy-2H-pyran-1(6H)-one (83)

\[
\begin{align*}
\text{HO} & \quad \text{OTBS} \\
\text{3} & \quad \text{2} & \quad \text{1} \\
\end{align*}
\]

To a stirred solution of alcohol 94 (0.6 g, 2.5 mmol) in CH₂Cl₂ (20 mL) was added in m-CPBA (0.7 g, 3.2 mmol) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was warmed to r.t. with stirring for 4 h. The reaction was quenched by addition of saturated aqueous Na₂SO₃ (20 mL) followed by neutralisation with 1 M NaOH solution to reach pH 7-8. The resulting mixture was extracted with CH₂Cl₂ (2 × 20 mL) and concentrated in vacuo to give the title compound 83 (0.63 g, 2.4 mmol, 92%, the ee was not determined) as a white solid containing an inseparable mixture of two enantiomers.

m.p.: 54–55 °C; \(^1\text{H NMR}\) (400 MHz, CDCl₃): \( \delta 6.80 \) (1H, \( d, J = 10.0 \) Hz, 3-H), 6.08 (1H, \( d, J = 10.0 \) Hz, 2-H), 4.54 (1H, \( d, J = 16.8 \) Hz, 6-Hₕ), 4.11 (1H, \( d, J = 16.8 \) Hz, 6-Hₗ), 3.97 (1H, br s, OH), 3.73 (1H, \( d, J = 10.4 \) Hz, 7-Hₕ), 3.65 (1H, \( d, J = 10.4 \) Hz, 7-Hₗ), 0.88 (9H, s, \( (\text{CH}_3)_3\text{CSi(CH}_3)_2 \)), 0.07 (6H, s, \( (\text{CH}_3)_3\text{CSi(CH}_3)_2 \)). \(^{13}\text{C NMR}\) (100 MHz, CDCl₃): \( \delta 195.3 \) (C, 1-C), 146.3 (CH, 3-C), 110
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128.2 (CH, 2-C), 92.6 (C, 4-C), 67.9 (CH, 7-C), 66.5 (CH, 6-C), 25.7 (3 × CH3, (CH3)3CSi(CH3)2), 18.3 (C, (CH3)3CSi(CH3)2), −5.3 (2 × CH3, (CH3)3CSi(CH3)2); IR \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \): 3242, 295, 2929, 2857, 1677, 1244, 1114, 1061, 830, 773; HRMS Found (ESI): [M+H]+ 259.2365, C12H22O2Si requires 259.1360.

5-((( tert-Butyldimethylsilyl)oxy)methyl)-1H-pyrrole-2-carbaldehyde (82)

![5-((( tert-Butyldimethylsilyl)oxy)methyl)-1H-pyrrole-2-carbaldehyde (82)](image)

To a stirred solution of dihydropyranone 83 (200 mg, 0.78 mmol) in dioxane (4 mL) was added saturated aqueous NH3 (0.1 mL, 4.6 mmol) at r.t. After stirring at r.t. for 2 h, the reaction was concentrated in vacuo and the resulting oil was purified by flash column chromatography on silica gel (n-hexane/EtOAc 8:1) affording the title compound 82 (65 mg, 0.29 mmol, 35%) as a colourless solid.

m.p.: 55–57.5 °C; \(^1\)H NMR (400 MHz, CDCl3): \( \delta \) 10.21 (1H, br s, NH), 9.42 (1H, s, 6-H), 6.90 (1H, t, \( J = 3.0 \) Hz, 3-H), 6.15 (1H, dd, \( J = 3.0, 1.0 \) Hz, 2-H), 4.76 (2H, s, 7-H), 0.90 (9H, s, (CH3)3CSi(CH3)2), 0.08 (6H, s, (CH3)3CSi(CH3)2); \(^13\)C NMR (100 MHz, CDCl3): \( \delta \) 178.6 (CH, 6-C), 141.3 (C, 5-C), 132.0 (C, 2-C), 122.3 (C, 3-C), 108.1 (C, 3-C), 58.5 (CH2, 7-C), 25.8 (3 × CH3, (CH3)3CSi(CH3)2), 18.2 (C, (CH3)3CSi(CH3)2), −5.5 (2 × CH3, (CH3)3CSi(CH3)2); IR \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \): 3158, 3093, 2957, 2857, 1630, 1241, 1184, 1087, 830, 774; HRMS Found (ESI): [M+Na]+ 262.1227, C12H22N3NaSiO4 requires 262.1234.

3.5 Synthesis of Bn protected spiroketal \( 145_a \) and \( 145_b \)

(2S,3S)-1-Benzyl oxy-2,3-isopropyldenedioxy-5-ol-6-azido-hexane (135)

![1-Benzyl oxy-2,3-isopropyldenedioxy-5-ol-6-azido-hexane (135)](image)

To a stirred solution of epoxide 81 (157 mg, 0.56 mmol) and NH4Cl (63 mg, 1.12 mmol) in a mixed solvent of DMF and H2O (8:1, 3.6 mL) at r.t. was added NaN3 (77 mg, 1.18 mmol). The reaction mixture was stirred at 80 °C for 2 h. After cooled to r.t., the reaction was quenched by addition of saturated aqueous NH4Cl (15 mL) and extracted with EtOAc (20 mL). The organic layer was washed with saturated aqueous NaCl (3 × 10 mL). The combined organic layers were dried over
anhydrous MgSO₄ and concentrated in vacuo giving the title compound 135 (170 mg, 0.53 mmol, 95%) as a colourless oil containing an inseparable mixture of two diastereoisomers.

**1H NMR** (400 MHz, CDCl₃): δ 7.36-7.30 (5H, m, Ph), 4.58 (2H, s, CH₂Ph), 4.04-4.00 (2H, m, 3-H, 5-H), 3.92-3.87 (1H, m, 2-H), 3.66-3.53 (2H, m, 1-H), 3.38-3.27 (2H, m, 6-H), 1.89-1.69 (2H, m, 4-H), 1.43-1.41 (6H, m, 8-H, 9-H); **13C NMR** (100 MHz, CDCl₃, *denotes minor isomer): δ 137.7 (C, Ph), 128.46 (2 × CH, Ph), 127.86* (2 × CH, Ph), 127.83* (2 × CH, Ph), 127.75 (2 × CH, Ph), 127.74 (CH, Ph), 109.6* (C, 7-C), 109.2 (C, 7-C), 80.0* (CH, 2-C), 79.5 (CH, 2-C), 78.1* (CH, 3-C), 77.9 (CH, 3-C), 73.65 (CH₂, CH₂Ph), 70.3* (CH₂, 1-C), 70.1* (CH, 5-C), 70.0 (CH₂, 1-C), 68.3 (CH, 5-C), 56.9 (CH₂, 6-C), 56.3* (CH₂, 6-C), 37.1 (CH₂, 4-C), 27.06 (CH₃, 8-C), 27.01* (CH₃, 8-C), 26.00* (CH₃, 9-C), 26.75 (CH₃, 9-C); **IR** νmax(film)/cm⁻¹: 3681, 3442, 2920, 2848, 1574, 1454, 1257, 1055, 735, 697; **HRMS** Found (ESI): [M+Na]⁺ 344.1586, C₁₀H₂₃N₃NaO₄ requires 344.1581.

(2S,3S)-1-Benzoxyl-2,3-isopropylidenedioxy-5-ol-6-amino-hexane (134)

To a stirred solution of azide 135 (50 mg, 0.16 mmol) in aqueous THF (3 mL, THF: H₂O 5:1) was added PMe₃ (1 M in THF, 0.5 ml, 0.5 mmol) at r.t. under N₂. The reaction was heated under reflux for 1 h. After cooling to r.t., bleach (5 mL) was added to the above mixture followed by removal of THF in vacuo. The resulting residue was partitioned between EtOAc (3 × 10 ml) and H₂O (10 ml). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo followed by flash column chromatography on silica gel (CH₂Cl₂/MeOH saturated with NH₃, 8:1) to afford the title compound 134 (43 mg, 0.14 mmol, 90%) as a colourless oil containing an inseparable mixture of two diastereoisomers.

**1H NMR** (400 MHz, CDCl₃): δ 7.35-7.27 (5H, m, Ph), 4.58 (2H, s, CH₂Ph), 4.08-3.96 (2H, m, 2-H, 3-H), 3.91-3.84 (1H, m, 5-H), 3.65-3.52 (2H, m, 1-H), 3.34-3.22 (2H, m, 6-H), 1.80-1.65 (2H, m, 4-H), 1.43-1.37 (6H, m, 8-H, 9-H); **13C NMR** (100 MHz, CDCl₃, *denotes the minor isomer): δ 137.2 (C, Ph), 131.6 (CH, Ph), 131.5* (CH, Ph), 127.9 (2 × CH, Ph), 127.3* (2 × CH, Ph), 127.29* (2 × CH, Ph), 127.23 (2 × CH, Ph), 109.0* (C, 7-C), 108.6 (C, 7-C), 79.5* (CH, 2-C), 79.0 (CH, 2-C), 76.3* (CH, 3-C), 75.4 (CH, 3-C), 73.15* (CH₂, CH₂Ph), 73.12 (CH₂, CH₂Ph), 69.8 (CH₂, 1-C), 69.50* (CH₂, 1-C), 69.46* (CH, 5-C), 67.8 (CH, 5-C), 56.4 (CH₂, 6-C), 55.8* (CH₂, 6-C), 36.8 (CH₂, 4-C), 26.71 (CH₃, 8-C), 26.66* (CH₃, 8-C), 26.45* (CH₃, 9-C), 26.41 (CH₃, 9-C); **IR**
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\[ \text{v}_{\text{max}}(\text{film})/\text{cm}^{-1}: 3372, 2983, 2934, 2862, 1594, 1454, 1370, 1086; \text{HRMS Found (ESI): [M+H]}^+ 296.1851, \text{C}_{16}H_{27}NO_2 \text{requires } 296.1856. \]

1-(3-((4S,5S)-5-(benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-5-((tert butyldimethylsilyloxy)methyl)-1H-pyrrole-2-carbaldehyde (107)

To a stirred solution of dihydropyranone 83 (8 mg, 0.03 mmol) in dioxane (0.5 mL) was added a solution of amine 134 (24 mg, 0.08 mmol) and Et$_3$N (14 μL, 0.1 mmol) in dioxane (2.5 ml) under N$_2$. After stirring at r.t. for 6 h, the reaction was concentrated in vacuo and the resulting oil was purified by flash column chromatography on silica gel (n-hexane/EtOAc 6:1) affording the title compound 107 (10 mg, 0.02 mmol, 50%) as a yellow oil containing an inseparable mixture of two diastereoisomers.

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.46 (1H, s, 7'-H), 7.34-7.27 (5H, m, Ph), 6.91-6.89 (1H, m, 3'-H), 6.21-6.19 (1H, m, 4'-H), 4.84-4.67 (2H, m, 6'-H), 4.62-4.54 (3H, m, CH$_2$Ph, 6-H$_a$), 4.25-4.18 (1H, m, 6-H$_b$), 4.15-4.08 (2H, m, 3-H, 5-H), 3.96-3.88 (1H, m, 2-H), 3.64-3.54 (2H, m, 1-H), 1.95-1.80 (2H, m, 4-H), 1.42-1.37 (6H, m, 8-H, 9-H), 0.90 (9H, s, (CH$_3$)$_3$CSi(CH$_3$)$_2$)$_2$, 0.10-0.08 (6H, m, (CH$_3$)$_3$CSi(CH$_3$)$_2$)$_2$; $^1$C NMR (100 MHz, CDCl$_3$, * denotes the minor isomer): δ 179.9 (CH, CHO), 179.6* (CH, 7'-C), 143.4* (C, 5'-C), 142.9 (C, 5'-C), 137.9 (C, Ph), 137.6* (C, Ph), 133.6 (C, 2'-C), 133.3* (C, 2'-C), 128.4 (2 × CH, Ph), 127.7 (3 × CH, Ph), 125.1 (C, 3'-C), 110.3 (C, 4'-C), 110.0* (C, 4'-C), 109.3* (C, 7'-C), 109.0 (C, 7'-C), 80.2* (CH, 3-C), 79.8 (CH, 3-C), 77.3* (CH, 2-C), 75.8 (CH, 2-C), 73.61* (CH$_2$, CH$_2$Ph), 73.56 (CH$_3$, CH$_2$Ph), 70.9* (CH, 5-C), 70.4 (CH$_2$, 1-C), 70.2* (CH, 5-C), 69.6 (CH$_2$, 1-C), 57.6* (CH$_2$, 6'-C), 57.5 (CH$_2$, 6'-C), 51.6 (CH$_2$, 6-C), 51.4* (CH$_2$, 6-C), 38.3 (CH$_2$, 4-C), 37.6* (CH$_2$, 4-C), 27.3 (CH$_3$, 8-C), 27.2* (CH$_3$, 8-C), 26.96* (CH$_3$, 9-C), 26.93 (CH$_3$, 9-C), 25.9 (3 × CH$_3$, (CH$_3$)$_3$CSi(CH$_3$)$_2$), 18.3 (C, (CH$_3$)$_3$CSi(CH$_3$)$_2$), –5.30 (CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$), –5.34 (CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$); IR max(film)/cm$^{-1}$: 3459, 2954, 2929, 1659, 1462, 1369, 1252, 1071, 836, 778; HRMS Found (ESI): [M+Na]$^+$ 540.2732, C$_{26}$H$_{43}$NaO$_6$Si requires 540.2752.

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1-(3-((4S,5S)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxopropyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1H-pyrrole-2-carbaldehyde (86)

To a stirred solution of alcohol 107 (20 mg, 0.04 mmol) in anhydrous CH₂Cl₂ (2 mL) at 0 °C was added powdered activated 4 Å MS, TPAP (1 mg, 0.002 mmol) and NMO (13 mg, 0.11 mmol) under N₂. After stirring at r.t. for 15 min, the reaction mixture was filtered through a plug of silica and washed with EtOAc (2 × 10 ml). The filtrate was concentrated in vacuo to afford the title compound 86 (20 mg, 0.04 mmol, quant.) as a colourless oil that was used in the next step without further purification.

[α]_D^{20} = +8.3 (c 1.2, CHCl₃); ^1H NMR δ 9.46 (1H, s, 7'-H), 7.34-7.27 (5H, m, Ph), 6.85 (1H, d, J = 4.0 Hz, 3'-H), 6.14 (1H, d, J = 4.0 Hz, 4'-H), 5.25 (2H, s, 6'-H), 4.52 (2H, s, CH₂Ph), 4.53 (2H, s, 6-H), 4.25-4.20 (1H, m, 3-H), 3.90-3.84 (1H, m, 2-H), 3.61-3.53 (2H, m, 1-H), 2.76 (2H, d, J = 6.0 Hz, 4'-H), 1.37 (3H, s, 8-H), 1.35 (3H, s, 9-H), 0.83 (9H, s, (CH₃)₂Si(CH₃)₂), 0.00 (3H, s, (CH₃)₂Si(CH₃)₂) -0.01 (3H, s, (CH₃)₂Si(CH₃)₂); ^13C NMR (100 MHz, CDCl₃): δ 201.7 (C, 5-C), 179.8 (CH, 7'-C), 142.0 (C, 5'-C), 137.9 (C, Ph), 132.3 (C, 2'-C), 128.4 (2 × CH, Ph), 127.71 (2 × CH, Ph), 127.66 (CH, Ph), 124.0 (CH, 3'-C), 110.1 (CH, 4'-C), 109.5 (C, 7-C), 79.8 (CH, 3-C), 74.2 (CH, 2-C), 73.6 (CH₂, CH₂Ph), 70.2 (CH₂, 1-C), 57.5 (CH₂, 6'-C), 55.3 (CH₂, 6-C), 43.7 (CH₂, 4-C), 27.2 (CH₃, 8-C), 27.0 (CH₃, 9-C), 25.8 (3 × CH₃, (CH₃)₂Si(CH₃)₂), 18.2 (C, (CH₃)₂Si(CH₃)₂), −5.4 (2 × CH₃, (CH₃)₂Si(CH₃)₂); IR ν max(film)/cm⁻¹: 2925, 2854, 1735, 1658, 1463, 1364, 1253, 1075, 779; HRMS Found (ESI): [M+Na]^+ 538.2577, C₂₈H₄₁NNaO₆Si requires 538.2595.
To a stirred solution of ketone 86 (10 mg, 0.02 mmol) in THF (2 mL) and H$_2$O (2 mL) was added HCl solution (4 M in dioxane, 0.5 ml, 2 mmol). After stirring at r.t. for 30 min, the reaction was quenched with saturated aqueous NaHCO$_3$ (5 mL) and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexane/EtOAc 3:2) afforded the title compound 140 as two separable diastereoisomers 140$_a$ (3 mg, 0.01 mmol, 45%) as a yellow oil and the diastereomer 140$_b$ (3 mg, 0.01 mmol, 45%) as a colourless oil.

140$_a$: $[\alpha]_D^{20}$ = −6.0 (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.47 (1H, s, 14-H), 7.38-7.29 (5H, m, Ph), 6.91 (1H, d, $J$ = 4.0 Hz, 12-H), 5.99 (1H, d, $J$ = 4.0 Hz, 13-H), 4.94 (1H, d, $J$ = 15.5 Hz, 7-H$_a$), 4.78 (1H, d, $J$ = 15.5 Hz, 7-H$_b$), 4.74 (1H, d, $J$ = 4.0 Hz, 10-H$_b$), 4.71-4.64 (1H, m, 10-H$_b$), 4.56 (2H, d, $J$ = 4.0 Hz, CH$_2$Ph), 4.31-4.21 (2H, m, 3-H, 3-H), 3.78 (2H, d, $J$ = 5.0 Hz, 15-H), 2.80 (1H, d, $J$ = 6.4 Hz, OH$_2$), 2.55 (1H, dd, $J$ = 14.0, 7.3 Hz, 4-H$_a$), 2.06 (1H, dd, $J$ = 14.0, 5.0 Hz, 4-H$_b$); $^{13}$C NMR (100 MHz, CDCl$_3$): 178.7 (CH, 14-C), 137.3 (C, Ph), 134.7 (C, 8-C), 130.9 (C, 11-C), 128.6 (2 × CH, Ph), 128.1 (CH, Ph), 127.9 (2 × CH, Ph), 124.0 (CH, 12-C), 104.7 (CH, 13-C), 102.2 (C, 5-C), 80.1 (CH, 2-C), 73.9 (CH$_2$, CH$_2$Ph), 72.0 (CH, 3-C), 68.6 (CH$_2$, 15-C), 58.2 (CH$_2$, 7-C), 51.2 (CH$_2$, 10-C), 46.1 (CH$_2$, 4-C); IR $\nu_{max}(film)$/cm$^{-1}$: 2925, 2854, 1735, 1658, 1463, 1364, 1253, 1075, 779; HRMS Found (ESI): [M+Na]$^+$ 366.1301, C$_{10}$H$_{21}$NNaO$_3$ requires 366.1385.

140$_b$: $[\alpha]_D^{20}$ = −12.0 (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.45 (1H, s, 14-H), 7.34-7.29 (5H, m, Ph), 6.90 (1H, d, $J$ = 4.0 Hz, 12-H), 5.99 (1H, d, $J$ = 4.0 Hz, 13-H), 5.00 (1H, d, $J$ = 15.5 Hz, 7-H$_a$), 4.74 (1H, d, $J$ = 15.5 Hz, 7-H$_b$), 4.64 (1H, d, $J$ = 14.0 Hz, 10-H$_b$), 4.59 (2H, dd, $J$ = 18.4, 12.0 Hz, CH$_2$Ph), 4.47-4.41 (1H, m, 4-H), 4.40-4.35 (1H, m, 5-H), 4.30 (1H, d, $J$ = 14.0 Hz, 10-H$_b$), 3.89 (1H, dd, $J$ = 11.0, 4.4 Hz, 14-H$_a$), 3.70 (1H, dd, $J$ = 11.0, 4.4 Hz, 14-H$_b$), 2.96 (1H, d, $J$ = 10.0 Hz, OH), 2.36 (1H, d, $J$ = 14.0 Hz, 3-H$_b$), 2.25 (1H, dd, $J$ = 14.0, 2.4 Hz, 3-H$_b$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.8 (CH, 14-C), 137.8 (C, Ph), 134.5 (C, 8-C), 131.2 (C, 11-C), 128.6 (2 × CH, Ph), 127.9 (2 × CH, Ph), 127.8 (CH, Ph), 124.0 (CH, 12-C), 104.8 (CH, 13-C), 103.6 (C, 5-C), 84.6 (CH, 2-C), 73.5 (CH$_2$, CH$_2$Ph), 72.1 (CH, 3-C), 69.3 (CH$_2$, 15-C), 58.1 (CH$_2$, 7-C), 50.8 (CH$_2$, 10.0
3.6 Synthesis of 2-epi-Acortatarin A (154a) and 3-epi-ent-Acortatarin A (154b)

(2S,3S)-2,3-Isopropylidenedioxy-1-tert-butylidiphenylsilyloxy-4-butanol (145)

To a stirred solution of diol 93 (1.6 g, 10 mmol) in anhydrous THF (40 mL) at 0 °C was slowly added NaH (60% in mineral oil, 0.44 g, 11 mmol) under N₂. The mixture was stirred at 0 °C for 10 min then at r.t. for further 10 min. To the resultant suspension was added TBDPSCI (3.7 g, 10.5 mmol) at r.t. After stirring at r.t. for 2 h, the reaction was quenched with H₂O (40 mL). The mixture was extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with saturated aqueous NaCl (120 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 5:1) afforded the title compound 145 (3.6 g, 9 mmol, 90%) as a light yellow oil.

[α]D²¹ = −0.9 (c 2.1, CHCl₃; lit. [α]D²² = −0.77 c 2.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.69-7.64 (4H, m, Ph), 7.46-7.36 (6H, m, Ph), 4.10-4.05 (1H, m, 2-H), 3.99-3.94 (1H, m, 3-H), 3.85-3.78 (2H, m, 1-H), 3.77-3.63 (2H, m, 4-H), 2.12 (1H, br s, OH), 1.41 (3H, s, 6-H), 1.39 (3H, s, 7-H), 1.06 (9H, s, (CH₃)₂CSiPh₂); ¹³C NMR (100 MHz, CDCl₃): δ 135.6 (4 × CH, Ph), 132.94 (C, Ph), 132.88 (C, Ph), 129.90 (CH, Ph), 129.89 (CH, Ph), 129.6 (CH, Ph), 127.8 (3 × CH, Ph), 109.2 (C, 5-C), 79.5 (CH, 3-C), 77.5 (CH, 2-C), 64.2 (CH₂, 1-C), 62.6 (CH₂, 4-C), 27.1 (CH₃, 6-C), 27.0 (CH₃, 7-C), 26.8 (3 × CH₃, (CH₃)₂CSiPh₂), 19.2 (C, (CH₃)₃CSiPh₂).

The data was in good agreement with the literature. ¹⁷⁴

(2R,3S)-2,3-Isopropylidenedioxy-4-tert-butylidiphenylsilyloxy-1-iodobutane (146)

To a stirred solution of alcohol 145 (2.5 g, 6.2 mmol) in toluene (60 mL) at r.t. was added PPh₃ (2.4 g, 9.2 mmol), imidazole (1.3 g, 18.4 mmol) and I₂ (3.2 g, 12.3 mmol). After heating under reflux for 6 h, the reaction was quenched with aqueous saturated Na₂SO₃ (50 mL) and extracted with
EtOAc (3 × 40 mL). The combined organic layers were washed over a saturated solution of NaCl (100 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (n-hexanes/EtOAc 20:1) afforded the title compound 146 (2.5 g, 4.9 mmol, 80%) as a yellow oil.

$[\alpha]_D^{21} = -6.0$ (c 2, CHCl$_3$; lit. $[\alpha]_D^{28} = -6.2$ c 5.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.72-7.65 (4H, m, Ph), 7.47-7.38 (6H, m, Ph), 3.99-3.94 (1H, m, 3-H), 3.90-3.86 (1H, m, 2-H), 3.86-3.81 (1H, m, 4-H$_3$), 3.80-3.76 (1H, m, 4-H$_3$), 3.39 (1H, dd, $J = 10.6, 4.6$ Hz, 1-H$_2$), 3.29 (1H, dd, $J = 10.6, 4.6$ Hz, 1-H$_3$), 1.46 (3H, s, 6-H), 1.39 (3H, s, 7-H), 1.07 (9H, s, (CH$_3$)$_3$CSiPh$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 135.6 (4 × CH, Ph), 133.02 (C, Ph), 132.97 (C, Ph), 129.88 (2 × CH, Ph), 129.84 (CH, Ph), 127.8 (3 × CH, Ph), 109.6 (C, 5-C), 81.2 (CH, 2-C), 77.6 (CH, 3-C), 64.2 (CH$_2$, 4-C), 27.5 (CH$_3$, 6-C), 27.3 (CH$_3$, 7-C), 26.9 (3 × CH$_3$, (CH$_3$)$_3$CSiPh$_2$), 19.2 (C, (CH$_3$)$_3$CSiPh$_2$), 6.8 (CH$_2$, 1-C).

The data is in good agreement with the literature.$^{174}$

(2S,3S)-1-(tert-Butyl)diphenylsilyloxy-2,3-isopropylidenedioxy-hex-5-ene (147)

$$\text{TBDSO}$$

To a stirred solution of 146 (2.0 g, 4 mmol) and CuI (70 mg, 0.4 ml) in a mixture of anhydrous THF and DMPU (1:1, 40 mL) at −35 °C under argon was added vinylmagnesium bromide (1 M in THF, 8 mL, 8 mmol) dropwise. The mixture was stirred at −35 °C for 30 min before another portion of vinylmagnesium bromide (1 M in THF, 4 mL, 4 mmol) was added. The reaction was stirred at −30 °C for 30 min then warmed to r.t. for 2 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl solution (80 mL) and extracted with Et$_2$O (3 × 100 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (100 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 20:1) afforded the title compound 147 (1.1 g, 2.6 mmol, 65%) as a light yellow oil.

$[\alpha]_D^{20} = -16.9$ (c 1.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74-7.68 (4H, m, Ph), 7.47-7.36 (6H, m, Ph), 5.91-5.83 (1H, m, 5-H), 5.17-5.09 (2H, m, 6-H), 4.17-4.08 (1H, m, 2-H), 3.82-3.78 (3H, m, 1-H, 3-H), 2.49-2.36 (2H, m, 4-H), 1.45 (3H, s, 6-H), 1.43 (3H, s, 7-H), 1.11 (9H, s, (CH$_3$)$_3$CSiPh$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 135.6 (4 × CH, Ph), 134.0 (CH, 5-C), 133.24 (C, Ph), 133.21 (C, Ph), 129.76 (CH, Ph), 129.73 (CH, Ph), 127.7 (4 × CH, Ph), 117.3 (CH$_2$, 6-C), 108.6 (C, 7-C), 80.5 (CH, 3-C), 77.5 (CH, 2-C), 64.1 (CH$_2$, 1-C), 37.5 (CH$_2$, 4-C), 27.3 (CH$_3$, 8-C), 117
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27.0 (CH₃, 9-C), 26.8 (3 × CH₃, (CH₃)₃CSiPh₂), 19.2 (C, (CH₃)₃CSiPh₂); IR νmax(film)/cm⁻¹: 3072, 2930, 2857, 1643, 1590, 1472, 1428, 1216, 1078, 1111, 702; HRMS Found (ESI): [M+Na]⁺ 433.2126, C₂₅H₃₄NaO₃Si requires 433.2169.

(2S,3S)-1-(tert-Butyldiphenylsiloxy)-2,3-isopropylidenedioxy-5,6-epoxyhexane (148)

To a stirred solution of olefin 147 (525 mg, 1.4 mmol) in a mixture of CH₃CN and H₂O (25 mL, 3:2) at 0 °C under N₂ was added trifluoroacetone (0.2 mL, 2.1 mmol) using a precooled syringe. A mixture of Oxone® (4.3 g, 7 mmol) and NaHCO₃ (0.94 g, 1.1 mmol) was added in four portions over 1 h. The resultant reaction mixture was stirred at 0 °C for 2 h then warmed to r.t. After stirring at r.t. for 12 h, the reaction was quenched with saturated aqueous Na₂SO₄ (50 mL) and the resultant mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo.

Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 5:1) afforded the title compound 148 (520 mg, 1.2 mmol, 90%, d.r. 1:3:1) as a colourless oil.

¹H NMR (400 MHz, CDCl₃, * denotes minor isomer): δ 7.70-7.65 (4H, m, Ph), 7.44-7.35 (6H, m, Ph), 4.21-4.08 (1H, m, 2-H), 3.90-3.79 (1H, m, 3-H), 3.78-3.73 (2H, m, 1-H), 3.11-3.02 (1H, m, 5-H), 2.80 (1H, dd, J = 4.0, 1.0 Hz, 6-Ha), 2.75* (1H, dd, J = 4.0, 1.0 Hz, 6-Hb), 2.52-2.48 (1H, m, 6-Hb), 1.89-1.72 (2H, m, 4-H), 1.42-1.40 (6H, m, 8-H, 9-H), 1.06 (9H, s, (CH₃)₃CSiPh₂); ¹³C NMR (100 MHz, CDCl₃, * denotes minor isomer): δ 135.6 (4 × CH, Ph), 133.13 (C, Ph), 133.09 (C, Ph), 129.7 (2 × CH, Ph), 127.7 (4 × CH, Ph), 108.87 (C, 7-C), 108.83* (C, 7-C), 82.5 (CH, 3-C), 80.6* (CH, 3-C), 76.7 (CH, 2-C), 74.7* (CH, 2-C), 64.1 (CH₂, 1-C), 63.9* (CH₂, 1-C), 49.5 (CH, 5-C), 49.1* (CH, 5-C), 47.4 (CH₂, 6-C), 46.5* (CH₂, 6-C), 37.5 (CH₂, 4-C), 35.5* (CH₂, 4-C), 27.3 (CH₃, 8-C), 27.2* (CH₃, 8-C), 26.95* (CH₃, 9-C), 26.93 (CH₃, 9-C), 26.8 (3 × CH₃, (CH₃)₃CSiPh₂), 19.2 (C, (CH₃)₃CSiPh₂), 18.2* (C, (CH₃)₃CSiPh₂); IR νmax(film)/cm⁻¹: 2926, 2860, 1474, 1379, 1427, 1217, 1103, 823, 702; HRMS Found (ESI): [M+Na]⁺ 449.2078, C₂₅H₃₄NaO₃Si requires 449.2119.
To a stirred solution of epoxide 148 (510 mg, 1.2 mmol) in aqueous DMF (10%, 20 mL) was slowly added NaN\textsubscript{3} (162 mg, 4 mmol) and saturated aqueous NH\textsubscript{4}Cl (5 mL). After stirring at 100 °C for 2 h, the reaction mixture was cooled to ambient temperature. The reaction mixture was partitioned between H\textsubscript{2}O (70 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 8:1) afforded the title compound 149 (375 mg, 0.8 mmol, 65%) containing an inseparable mixture of two diastereomers as a colourless oil.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.70-7.64 (4H, m, Ph), 7.47-7.36 (6H, m, Ph), 4.23-4.05 (1H, m, 2-H), 4.05-3.95 (1H, m, 3-H), 3.85-3.71 (3H, m, 1-H, OH), 3.39-3.25 (2H, m, 6-H), 2.75 (1H, d, J = 4.0 Hz, 5-H), 1.93-1.65 (2H, m, 4-H), 1.42-1.36 (6H, m, 8-H, 9-H), 1.07 (9H, s, (CH\textsubscript{3})\textsubscript{3}SiPh\textsubscript{2}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}, * denotes minor isomer): δ 135.6 (4 × CH, Ph), 133.0 (2 × C, Ph), 129.9 (2 × CH, Ph), 127.8 (4 × CH, Ph), 110.0 (C, 7-C), 109.0* (C, 7-C), 81.3* (CH, 3-C), 80.4 (CH, 3-C), 78.3* (CH, 2-C), 76.0 (CH, 2-C), 70.6* (CH, 5-C), 68.5 (CH, 5-C), 64.0 (CH\textsubscript{2}, 1-C), 63.7* (CH\textsubscript{2}, 1-C), 56.8 (CH\textsubscript{2}, 6-C), 56.3* (CH\textsubscript{2}, 6-C), 37.4* (CH\textsubscript{2}, 4-C), 36.6 (CH\textsubscript{2}, 4-C), 27.3 (CH\textsubscript{3}, 8-C), 27.2* (CH\textsubscript{3}, 8-C), 27.0 (3 × CH\textsubscript{3}, (CH\textsubscript{3})\textsubscript{3}SiPh\textsubscript{2}), 26.8 (CH\textsubscript{3}, 9-C), 19.2 (C, (CH\textsubscript{3})\textsubscript{3}SiPh\textsubscript{2}); IR ν\textsubscript{max}(film)/cm\textsuperscript{-1}: 3443, 2931, 2858, 2099, 1736, 1674, 1472, 1427, 1295, 1246, 1218, 1144, 1111, 942, 823, 704; HRMS Found (ESI): [M+Na]\textsuperscript{+} 492.2249, C\textsubscript{25}H\textsubscript{35}N\textsubscript{3}NaO\textsubscript{4}Si requires 492.2289.
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(2S,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropyldenedioxy-6-amino-hexan-5-ol (150)

To a stirred solution of azide 149 (375 mg, 0.8 mmol) in a mixture of THF and H₂O (12 mL, 5:1) was added PMe₃ (1 M in THF, 3 mL, 3 mmol) dropwise. The reaction mixture was stirred at 50 °C for 2 h before being quenched with bleach (2 mL). The organic solvent was removed under reduced pressure and the residue was partitioned between H₂O (15 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (CH₂Cl₂/MeOH 6:1 saturated with NH₃) afforded the title compound 150 (310 mg, 0.8 mmol, 99%) as a light yellow oil containing an inseparable mixture of two diastereomers.

¹H NMR (400 MHz, CDCl₃): δ 7.69-7.64 (4H, m, Ph), 7.43-7.36 (6H, m, Ph), 4.22-4.09 (1H, m, 2-H), 3.82-3.73 (4H, m, 1-H, 3-H, 5-H), 2.81-2.58 (2H, m, 6-H), 2.20-2.00 (2H, br s, NH₂), 1.82-1.60 (2H, m, 4-H), 1.40-1.37 (6H, m, 8-H, 9-H), 1.06 (9H, s, (CH₃)₃CSiPh₂); ¹³C NMR (100 MHz, CDCl₃, * denotes minor isomer): δ 135.62 (4 × C, Ph), 135.60* (4 × C, Ph), 133.13 (2 × C, Ph), 133.07* (C, Ph), 133.04* (C, Ph), 129.82* (CH, Ph), 129.79* (CH, Ph), 129.76 (CH, Ph), 129.73 (CH, Ph), 127.7 (4 × CH, Ph), 109.2* (C, 7-C), 108.7 (C, 7-C), 81.4* (CH, 3-C), 80.8 (CH, 3-C), 78.0* (CH, 2-C), 76.0 (CH, 2-C), 71.7* (CH, 5-C), 69.6 (CH, 5-C), 64.0 (CH₂, 1-C), 63.8* (CH₂, 1-C), 47.7 (CH₂, 6-C), 37.7* (CH₃, 4-C), 37.4 (CH₃, 4-C), 27.34 (CH₃, 8-C), 27.26* (CH₃, 8-C), 26.95* (CH₃, 9-C), 27.0 (CH₃, 9-C), 26.8 (3 × CH₃, (CH₃)₂CSiPh₂), 19.2 (C, (CH₃)₂CSiPh₂); IR νmax(film)/cm⁻¹: 3452, 2930, 2857, 1674, 1427, 1295, 1145, 1112, 942, 858, 824, 704, 613; HRMS Found (ESI): [M+H]⁺ 444.2525, C₂₅H₃₈NO₄Si requires 444.2565.

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5-((tert-Butyldimethylsilyloxy)methyl)-1-(3-((4S,5S)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-1H-pyrrole-2-carbaldehyde (151)

To a stirred solution of dihydropyranone 83 (60 mg, 0.13 mmol) and Et3N (0.05 mL, 0.39 mmol) in 1,4-dioxane (1 mL) was added a solution of amine 150 (27 mg, 0.61 mmol) in 1,4-dioxane (1 mL) dropwise over 5 min. The reaction was stirred at r.t. for 2 h then concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 8:1) afforded two separable diastereoisomers of the title compound 151a (18 mg, 0.027 mmol, 21%) and 151b (28 mg, 0.042 mmol, 33%) as colourless oils.

151a: [α]20° = −10.0 (c 0.8, CHCl3); 1H NMR (400 MHz, CDCl3): δ 9.47 (1H, s, 7'-H), 7.71-7.67 (4H, m, Ph), 7.42-7.37 (6H, m, Ph), 6.90 (1H, d, J = 4.0 Hz, 3'-C), 6.19 (1H, d, J = 4.0 Hz, 4'-C), 4.78 (1H, d, J = 12.0 Hz, 6'-Hb), 4.71 (1H, d, J = 12.0 Hz, 6'-Ha), 4.58 (1H, dd, J = 13.2, 2.4 Hz, 6'-Hb), 4.31-4.27 (1H, m, 6-Ha), 4.26-4.20 (1H, m, 5-H), 4.19-4.12 (1H, m, 2-H), 3.84-3.70 (3H, m, 1-H, 3-H), 3.20 (1H, d, J = 4.0 Hz, OH), 1.85-1.81 (2H, m, 4-H), 1.41 (3H, s, 8-H), 1.37 (3H, s, 9-H), 1.06 (9H, s, (CH3)3SiPh), 0.90 (9H, s, (CH3)3C≡Si(CH3)2), 0.10 (3H, s, (CH3)3CSSi(CH3)2), 0.08 (3H, s, (CH3)3CSi(CH3)2); 13C NMR (100 MHz, CDCl3): δ 179.9 (CH, 7'-C), 142.6 (C, 5'-C), 135.6 (4 x CH, Ph), 133.14 (C, Ph), 133.09 (C, Ph), 129.74 (CH, Ph), 129.71 (CH, Ph), 127.7 (4 x CH, Ph), 124.9 (CH, 3'-C), 110.3 (CH, 4'-C), 108.0 (C, 7'-C), 77.6 (CH, 2-C), 73.9 (CH, 3-C), 69.8 (CH, 5-C), 62.6 (CH2, 1-C), 57.4 (CH2, 6'-C), 51.8 (CH2, 6-C), 34.6 (CH2, 4'-C), 28.1 (CH3, 8-C), 26.9 (CH3, 9-C), 25.8 (3 x CH3, (CH3)3CSiPh2), 25.6 (3 x CH3, (CH3)3CSi(CH3)2), 19.2 (C, (CH3)3CSSiPh2), 18.3 (C, (CH3)3CSi(CH3)2), −5.3 (2 x CH3, (CH3)3Si(CH3)2); IR: νmax (film) / cm−1: 3671, 3465, 2956, 2930, 2857, 1739, 1660, 1462, 1428, 1137, 1250, 1112, 1073, 837, 779, 703, 613; HRMS Found (Cl): [M+Na]+ 688.3379, C37H55NNaO6S2 requires 688.3462.

151b: [α]20° = −7.0 (c 1.4, CHCl3); 1H NMR (400 MHz, CDCl3): δ 9.47 (1H, s, 7'-H), 7.69-7.65 (4H, m, Ph), 7.43-7.37 (6H, m, Ph), 6.89 (1H, d, J = 4.0 Hz, 3'-C), 6.19 (1H, d, J = 4.0 Hz, 4'-C), 4.83 (1H, d, J = 12.0 Hz, 6'-Hb), 4.72 (1H, d, J = 16.0 Hz, 6'-Ha), 4.58 (1H, dd, J = 14.0, 2.4 Hz, 6'-Hb), 4.31-4.28 (1H, m, 5-H), 4.22 (1H, d, 6-Hb), 4.19-4.12 (1H, m, 3-H), 3.81-3.74 (3H, m, 1-H, 2-H), 3.47 (1H, d, J = 2.4 Hz, OH), 1.96-1.92 (1H, m, 4-H), 1.74-1.66 (1H, m, 4-H), 1.44 (3H, s, 8-H), 1.36 (3H, s, 9-H), 1.04 (9H, s, (CH3)3CSSiPh2), 0.91 (9H, s, (CH3)3CSSi(CH3)2), 0.10 (3H, s, (CH3)3CSSi(CH3)2), 0.07 (3H, s, (CH3)3CSSi(CH3)2); 13C NMR (100 MHz, CDCl3): δ 179.5 (CH, 7'-
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C), 143.3 (C, 5'-C), 135.6 (4 × CH, Ph), 133.14 (C, Ph), 133.09 (C, Ph), 132.6 (C, 2'-C), 129.74 (CH, Ph), 129.71 (CH, Ph), 127.7 (4 × CH, Ph), 124.9 (CH, 3'-C), 109.9 (CH, 4'-C), 108.5 (C, 7'-C), 77.8 (CH, 2-C), 77.3 (CH, 3-C), 71.9 (CH, 5-C), 62.5 (CH2, 1-C), 57.7 (CH2, 6'-C), 51.4 (CH2, 6-C), 33.6 (CH2, 4-C), 27.9 (CH3, 8-C), 26.9 (3 × CH3, (CH3)3CSi(CH2)2), 25.8 (3 × CH3, (CH3)3CSiPh2), 25.5 (CH3, 9-C), 19.2 (C, (CH3)3CSiPh2), 18.3 (C, (CH3)3CSi(CH2)2), −5.30 (CH3, (CH3)3CSi(CH2)2), −5.33 (CH3, (CH3)3CSi(CH2)2); IR νmax (film)/cm⁻¹: 3671, 3465, 2956, 2930, 2857, 1739, 1660, 1462, 1428, 1137, 1250, 1112, 1073, 837, 779, 703, 613; HRMS Found (CI): [M+Na]^+ 688.3379, C37H55NaO5Si2 requires 688.3460.

5-((tert-Butyldimethylsilyloxy)methyl)-1-(3-((4S,5S)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxopropyl)-1H-pyrrole-2-carbaldehyde (152)

To a stirred solution of alcohols 151a and 151b (30 mg, 0.045 mmol) in the presence of activated 4Å MS (10 mg) in anhydrous CH2Cl2 (2 mL) was added NMO (3.9 mg, 0.23 mmol) and TPAP (1 mg, 0.002 mmol) under N₂. After stirring for 0.5 h the reaction was filtered through a plug of silica and washed with anhydrous THF (3 × 10 mL). The filtrate was concentrated in vacuo to afford the title compound 152 (29 mg, 0.044 mmol, 97%) as a light brown oil.

[a]D^20 = +16.0 (c 0.2, CHCl3); ^1H NMR (400 MHz, CDCl3): δ9.44 (1H, s, 7'-H), 7.70-7.66 (4H, m, Ph), 7.43-7.36 (6H, m, Ph), 6.89 (1H, d, J = 4.0 Hz, 3'-H), 6.19 (1H, d, J = 4.0 Hz, 4'-H), 5.40 (1H, d, J = 18.0 Hz, 6-H), 5.29 (1H, d, J = 18.0 Hz, 6-Hb), 4.59 (2H, s, 6'-H), 4.42-4.40 (1H, m, 2-H), 3.89-3.87 (1H, m, 3-H), 3.83-3.75 (2H, m, 1-H), 2.80-2.78 (2H, m, 4-H), 1.41 (3H, s, 8-H), 1.38 (3H, s, 9-H), 1.05 (9H, s, (CH3)3CSiPh2), 0.87 (9H, s, (CH3)3CSi(CH2)2), 0.04 (3H, s, 9H, s, (CH3)3CSi(CH2)2), 0.03 (3H, s, (CH3)3CSi(CH2)2); ^13C NMR (100 MHz, CDCl3): δ 201.7 (C, 5'-C), 179.7 (CH, 7'-C), 142.0 (C, 5'-C), 135.6 (4 × CH, Ph), 133.04 (C, Ph), 133.00 (C, Ph), 132.3 (C, 2'-C), 129.74 (CH, Ph), 129.71 (CH, Ph), 127.7 (4 × CH, Ph), 123.9 (CH, 3'-C), 110.0 (CH, 4'-C), 109.2 (C, 7'-C), 80.8 (CH, 2-C), 74.2 (CH, 3-C), 63.7 (CH2, 1-C), 57.2 (CH2, 6'-C), 55.4 (CH2, 6-C), 43.9 (CH2, 4-C), 27.2 (CH3, 8-C), 26.9 (CH3, 9-C), 26.8 (3 × CH3, (CH3)3CSiPh2), 25.8 (3 × CH3, (CH3)3CSi(CH2)2), 19.1 (C, (CH3)3CSiPh2), 18.2 (C, (CH3)3CSi(CH2)2), −5.4 (2 × CH3, (CH3)3CSi(CH2)2); IR νmax (film)/cm⁻¹: 3674, 2929, 2856, 1765, 1670, 1462, 1427, 1362, 1251, 1216, 1112, 1076, 836, 702; HRMS Found (CI): [M+Na]^+ 686.3471, C37H55NaO5Si2 requires 686.3304.
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(4S,5S)-5-((tert-Butyldiphenylsilyloxy)methyl)-4-hydroxy-1',4,4',5-tetrahydro-3H-spiro[furan-2,3'-pyrrolo [2,1-c][1,4]oxazine]-6'-carbaldehyde (153)

To a stirred solution of 152 (27 mg, 0.04 mmol) in THF (1 mL) and H₂O (1 mL) was added HCl (4 M in dioxane, 1 mL, 4 mmol). The reaction mixture was stirred at r.t. for 2.5 h. The reaction mixture was neutralised with saturated aqueous NaHCO₃ to pH 7 and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under *in vacuo*. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 3:1) afforded the *title compounds* 153 (12 mg, 0.024 mmol, 61%, d.r. 3:4:1) as a yellow oil containing an inseparable mixture of two diastereomers.

**^1H NMR** (400 MHz, CDCl₃, *denotes minor isomer): δ 9.47 (1H, s, 14-H), 9.45* (1H, s, 14-H), 7.67-7.62 (4H, m, Ph), 7.43-7.35 (6H, m, Ph), 6.93* (1H, d, J = 4.0 Hz, 12-H), 6.92 (1H, d, J = 4.0 Hz, 12-H), 5.99 (1H, d, J = 4.0 Hz, 11-H), 5.97* (1H*, d, J = 4.0 Hz, 11-H), 5.13-3.70 (10H, m, 2-H, 3-H, 4-H, 7-H, 10-H, 15-H), 3.03 (1H, d, J = 7.2 Hz, OH), 2.79* (1H, d, J = 7.2 Hz, OH), 2.57 (1H, dd, J = 13.9, 6.6 Hz, 4-H₃), 2.38* (1H, d, J = 14.0 Hz, 4-H₃), 2.25* (1H, dd, dd, J = 13.9, 5.2 Hz,3-H₃), 2.14 (1H, dd, J = 13.9, 3.9, Hz, 3-H₃), 1.04 (9H, s, (CH₃)₃SiPh₂); **^13C NMR** (100 MHz, CDCl₃, *denotes minor isomer): δ 179.8* (CH, 14-C), 178.6 (CH, 14-C), 135.6 (2 × CH, Ph), 133.0 (C, Ph), 132.9 (C, Ph), 129.99 (CH, Ph), 129.97 (CH, Ph), 127.8 (4 × CH, Ph), 124.1* (CH, 12-C), 123.9 (CH, 12-C), 104.9* (CH, 11-C), 104.6 (CH, 11-C), 103.5* (C, 5-C), 102.4 (C, 5-C), 85.6* (CH, 2-C), 80.8 (CH, 2-C), 72.6 (CH, 3-C), 72.0* (CH, 3-C), 63.0* (CH₂, 15-C), 62.8 (CH₂, 15-C), 58.5 (CH₂, 7-C), 58.2* (CH₂, 7-C), 51.4 (CH₂, 10-C), 51.0* (CH₂, 10-C), 46.3 (CH₂, 4-C), 44.6* (CH₂, 4-C), 27.2 (CH₃, (CH₃)₃SiPh₂), 27.1* (CH₃, (CH₃)₃SiPh₂), 19.2* (C, (CH₃)₃SiPh₂), 19.1 (C, (CH₃)₃SiPh₂); **IR** ν<sub>max</sub>(film)/cm⁻¹: 3674, 2929, 2856, 1765, 1670, 1462, 1427, 1362, 1251, 1216, 1112, 1076, 836, 702; **HRMS** Found (EI): [M+Na]<sup>+</sup> 514.2003, C₂₈H₂₈NaOsSi requires 514.2020.
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2-epi-Acortatarin A (154a)

3-epi-ent-Acortatarin A (154b)

To a stirred solution of 153 (6 mg, 0.012 mmol) in anhydrous THF (0.5 mL) under N₂ was added a solution of TBAF (1 M in THF, 0.1 mL, 0.1 mmol). After stirring at r.t. for 2 h, the reaction mixture was concentrated in vacuo to remove most of the solvent. The resultant brown oil was filtered through a pad of silica and washed with EtOAc (10 mL). The filtrate was concentrated in vacuo to give a yellow oil. Purification by preparative TLC (n-hexanes/EtOAc 1:5) afforded the title compounds 154a (1.5 mg, 0.06 mmol, 50%) and 154b (0.9 mg, 0.036 mmol, 30%) as yellow oils.

154a: ¹H NMR (400 MHz, CD₂COCD₃): δ 9.51 (s, 1H, 14-H), 7.02 (1H, d, J = 5.6 Hz, 12-H), 6.08 (1H, d, J = 5.6 Hz, 11-H), 5.19 (1H, dd, J = 15.6, 0.8 Hz, 7-H₆), 4.87 (1H, d, J = 16.0 Hz, 7-H₃), 4.58–4.55 (2H, m, 2-H, 10-H₆), 4.31 (1H, dd, J = 10.8, 5.2 Hz, 3-H), 4.25 (1H, d, J = 13.8 Hz, 10-H₃), 3.90 (1H, dd, J = 11.4, 5.0 Hz, 15-H₃), 3.84 (1H, dd, J = 11.4, 5.0 Hz, 15-H₆), 2.48 (1H, dd, J = 14.0, 6 Hz, 4-H₆), 2.30 (1H, dd, J = 14, 1.2 Hz, 4-H₇); ¹³C NMR (100 MHz, CD₂COCD₃): δ 178.7 (C, 14-C), 135.7 (C, 8-C), 132.0 (C, 13-C), 123.9 (CH, 12-C), 105.0 (CH, 11-C), 103.7 (C, 5-C), 86.4 (CH, 2-C), 72.0 (CH, 3-C), 61.9 (CH₂, 15-C), 58.4 (CH₂, 7-C), 51.7 (CH₃, 10-C), 45.5 (CH₂, 4-C); IR νmax (film)/cm⁻¹: 3330, 2929, 2847, 1730, 1412, 1251, 1033, 796; HRMS Found (ESI): [M+Na]⁺ 276.0850, C₁₂H₁₃NaNO₃ requires 276.0842.

154b: ¹H NMR (400 MHz, CD₂COCD₃): δ 9.51 (1H, s, 14-H), 7.01 (1H, d, J = 5.6 Hz, 12-H), 6.08 (1H, d, J = 5.6 Hz, 11-H), 4.98 (1H, d, J = 20.8 Hz, 7-H₆), 4.85 (1H, d, J = 20.8 Hz, 7-H₃), 4.73 (1H, d, J = 18.8 Hz, 10-H₆), 4.68–4.59 (1H, m, 3-H), 4.26 (1H, d, J = 19.2 Hz, 10-H₃), 4.17 (1H, ddd, J = 6.8, 6.0, 6.0 Hz, 2-H), 3.91–3.80 (2H, m, 15-H), 2.55 (1H, dd, J = 18.8, 12.6 Hz, 4-H₆), 2.14 (1H, dd, J = 18.8, 4.4 Hz, 4-H₇); ¹³C NMR (100 MHz, CD₂COCD₃): δ 178.8 (CH, 14-C), 135.6 (C, 8-C), 132.0 (C, 13-C), 124.0 (CH, 12-C), 105.1 (CH, 11-C), 102.9 (C, 5-C), 83.8 (CH, 2-C), 71.8 (CH, 3-C), 61.2 (CH₂, 15-C), 58.5 (CH₂, 7-C), 52.2 (CH₂, 10-C), 47.3 (CH₂, 4-C); IR νmax (film)/cm⁻¹: 3321, 2929, 2845, 1725, 1410, 1251, 1051, 788; HRMS Found (ESI): [M+Na]⁺ 276.0848, C₁₂H₁₃NaNO₃ requires 276.0842.

3.7 Synthesis of acortatarin A (17)
Synthesis 2,3-O-Cyclohexylideno-D-glyceraldehyde (170)

A mixture of (D)-mannitol (90 g, 0.5 mol), cyclohexanone (120 mL), triethyl orthoformate (20 mL) and boron trifluoride etherate (3 mL) in anhydrous DMSO (200 mL) was stirred at 50 °C for 3 h. After cooling to r.t., the mixture was poured into ice-cooled saturated aqueous NaHCO₃ (400 mL) and extracted with Et₂O (350 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (2 × 350 mL). The combined organic layers were washed with saturated aqueous NaCl (1 L), dried over anhydrous MgSO₄ and concentrated in vacuo to afford crude products. The residual syrup was recrystallized from hot n-hexanes to give diol 169 (128.7 g, 0.375 mmol, 75%) as needles.

To a stirred solution of diol 169 (8.0 g, 23.3 mmol) in a mixture of CH₃CN and H₂O (150 mL, 3:2) at 0–10 °C was added NaIO₄ (10.0 g, 46.7 mmol) in small portions over 40 min. After stirring at r.t. for 1 h, the reaction mixture was filtered through a pad of Celite® and washed with EtOAc (100 mL). The filtrate was partitioned with water (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 75 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and removed under reduced pressure. The residue oil was purified by vacuum distillation (bp 113-118 °C/24 mmHg) affording the title compound 170 (5.1 g, 64%) as a light yellow oil.

[α]D₂₀ = +58.0 (c 1.1, CHCl₃, lit. [α]D₂₀ = +60.5, c 3.4, benzene); [1]H NMR (400 MHz, CDCl₃): δ 9.71 (1H, d, J = 2.0 Hz, 1-H), 4.40-4.36 (1H, m, 2-H), 4.18-4.06 (2H, m, 3-H), 1.70-1.56 (10H, m, 5-H, 6-H, 7-H, 8-H, 9-H); [1]C NMR (100 MHz, CDCl₃): δ 202.1 (CH, 1-C), 111.9 (C, 4-C), 79.6 (CH, 2-C), 65.2 (CH₂, 3-C), 35.9 (CH₂, 5-C), 34.6 (CH₂, 9-C), 25.0 (CH₂, 6-C), 23.9 (CH₂, 7-C), 23.8 (CH₂, 8-C)

The spectroscopic data were in agreement with literature values. 163

(2R,3S)-1,2-Cyclohexylidene-5-hexene-1,2,3-triol (171a)
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To a mixture of 170 (4.5 g, 35 mmol) and zinc dust (6.7 g, 103.7 mmol) in THF (150 mL) in the presence of saturated aqueous NaCl (10 mL) was added allyl bromide (9.0 mL, 104 mmol) in THF (100 mL) dropwise over 10 min at 0 °C. After stirring at r.t. for 2 h, saturated aqueous NaCl (50 mL) was added to the reaction mixture dropwise until no effervescence was observed. The resultant mixture was stirred for further 1 h and filtered through a plug of silica. The precipitate was washed with EtOAc (200 mL). The aqueous layer was separated and extracted with EtOAc (2 × 75 mL). The combined organic layers were dried over anhydrous Na2SO4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 7:1) gave the title compound 171a (4.94 g, 23 mmol, 88%) as a colourless oil.

\[ \alpha \delta = +10.1 \, (c \, 1.0, \, \text{CHCl}_3), \text{lit.}^{163} \] \[ \alpha \delta = +10.2 \, (c \, 1.4, \, \text{CHCl}_3); \] \[ ^1H \text{ NMR} (400 MHz, \text{CDCl}_3): \delta 5.85-5.81 (1H, m, 5-H), 5.18-5.13 (2H, m, 6-H), 3.95-3.89 (1H, m, 2-H), 3.81-3.76 (1H, m, 3-H), 2.37-2.29 (1H, m, 4-Ha), 2.25-2.16 (1H, m, 4-Hb), 1.65-1.56 (10H, m, 8-H, 9-H, 10-H, 11-H, 12-H); \] \[ ^13C \text{ NMR} (100 MHz, \text{CDCl}_3): \delta 134.0 (\text{CH}, 5-C), 118.2 (\text{CH}_2, 6-C), 109.6 (C, 7-C), 77.7 (CH, 2-C), 70.4 (CH, 3-C), 64.8 (CH2, 1-C), 37.6 (CH2, 4-C), 36.2 (CH2, 8-C), 34.8 (CH2, 12-C), 25.1 (CH2, 10-C), 24.0 (CH2, 9-C), 23.8 (CH2, 11-C).

The spectroscopic data were in agreement with literature values.\(^{163}\)

\((2R,3S)-\text{Hex-5-ene-1,2,3-triol (166a)}\)

To a stirred solution of olefin 171a (4.0 g, 19 mmol) in methanol (20 mL) was added conc. HCl (10 mL) dropwise. After stirring for 24 h, the reaction was neutralised with saturated aqueous NaHCO3 to pH 7-8. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous MgSO4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 1:9) afforded the title compound 166a (2.3 g, 17 mmol, 90%) as a white solid.

m.p.: 52.5-54 °C (lit.\(^{175}\) 54-55 °C); \[ \alpha \delta = +10.0 \, (c \, 1.1, \, \text{H}_2\text{O}, \text{lit.}^{175} \] \[ \alpha \delta = +9.2 \, (c \, 5.2, \, \text{D}_2\text{O}); \] \[ ^1H \text{ NMR} (400 MHz, \text{CDCl}_3): \delta 5.90-5.80 (1H, m, 5-H), 5.21-5.15 (2H, m, 6-H), 3.82-3.75 (3H, m, 1-H, 2-H), 3.66-3.60 (1H, m, 3-H), 3.03 (1H, d, \( J = 4.0 \text{ Hz}, \text{OH} \)), 2.66-2.60 (1H, m, OH), 2.55 (1H,
Chapter 3: Experimental of Acortatarin A

d, \(J = 4.0\) Hz, \(\text{OH}\), 2.43-2.23 (2H, m, 4-H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 134.2 (CH, 5-C), 118.6 (CH\(_2\), 6-C), 73.4 (CH, 2-C), 72.5 (CH, 3-C), 63.3 (CH\(_2\), 1-C), 37.7 (CH\(_2\), 4-C).

The data was in agreement with the literature.\(^{175}\)

\((2R,3S)-1-(\text{tert-butyldiphenylsilyloxy})\text{-5-ene}-2,3\)-diol (167\(_a\))

To a stirred solution of 166\(_a\) (1.6 g, 10 mmol) in anhydrous THF (40 mL) at 0 °C was slowly added NaH (60% in mineral oil, 0.4 g, 10 mmol) under N\(_2\). The mixture was stirred at 0 °C for 10 min under N\(_2\) then at r.t. for 10 min before TBDPSCl (3.5 g, 10 mmol) was added. After stirring for 2 h, the reaction was quenched with H\(_2\)O (40 mL) carefully and the reaction mixture was extracted with EtOAc (3 \(\times\) 60 mL). The combined organic layers were washed with a saturated solution of NaCl (100 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 5:1) afforded the title compound 167\(_a\) (4.0 g, 11 mmol, 90%) as a light yellow oil.

\([\alpha]_D^{20} = +0.8\) (c 1.0, CHCl\(_3\)); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 7.69-7.65 (4H, m, Ph), 7.47-7.38 (6H, m, Ph), 5.89-5.77 (1H, m, 5-H), 5.14-5.08 (2H, m, 6-H), 3.84-3.78 (2H, m, 1-H), 3.78-3.72 (2H, m, 2-H, 3-H), 2.39-2.20 (2H, m, 4-H), 1.08 (9H, s, \((\text{CH}_3)_3\text{C}Si\)); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 135.6 (4 \(\times\) C, Ph), 134.5 (CH, 5-C), 132.9 (2 \(\times\) C, Ph), 132.8 (2 \(\times\) CH, Ph), 127.9 (4 \(\times\) CH, Ph), 123.0 (CH\(_2\), 6-C), 73.3 (CH, 2-C), 71.6 (CH, 3-C), 64.7 (CH\(_2\), 1-C), 37.5 (CH\(_2\), 4-C), 26.9 (3 \(\times\) CH\(_3\), (CH\(_3\))\(_3\)CSi), 19.3 (C, (CH\(_3\))\(_3\)C); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3436, 3072, 2930, 2857, 1641, 1589, 1472, 1427, 1111, 700; HRMS Found (EI): [M+Na]\(^+\) 393.1852, C\(_{22}\)H\(_{30}\)NaO\(_3\)Si requires 393.1856.

\((2R,3S)-1-(\text{tertButyldiphenylsilyloxy})-2,3\text{-isopropylidenedioxy} \text{-5-ene} (163\(_a\))\)

To a stirred solution of diol 167\(_a\) (3.3 g, 9 mmol) in anhydrous CH\(_2\)Cl\(_2\) (60 mL) was added PPTS (220 mg, 0.9 mmol) followed by 2,2-dimethoxypropane (30 mL) under N\(_2\). After stirring at r.t. for 2 h, the reaction mixture was quenched with saturated aqueous NaHCO\(_3\) (40 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 \(\times\) 60 mL) and the combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous MgSO\(_4\) and concentrated in vacuo to afford
the title compound 167a (3.6 g, 9 mmol, quant.) as a colourless oil. Compound 167a was used to next step without further purification.

[α]D = −6.0 (c 1.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃): δ 7.70-7.67 (4H, m, Ph), 7.44-7.37 (6H, m, Ph), 5.93-5.86 (1H, m, 3-H), 5.13-5.07 (2H, m, 6-H), 4.26-4.20 (2H, m, 2-H, 3-H), 3.78-3.67 (2H, m, 1-H), 2.46-2.36 (2H, m, 4-H), 1.40 (3H, s, 8-H), 1.34 (3H, s, 9-H), 1.07 (9H, s, (CH₃)₃CSi); \(^1^3\)C NMR (100 MHz, CDCl₃): δ 135.62 (2 × CH, Ph), 135.60 (2 × CH, Ph), 135.2 (CH, 5-C), 133.4 (C, Ph), 133.3 (C, Ph), 129.7 (2 × CH, Ph), 127.7 (4 × CH, Ph), 116.8 (CH₂, 6-C), 108.0 (C, 7-C), 77.7 (CH, 3-C), 77.0 (CH, 2-C), 62.6 (CH₂, 1-C), 34.0 (CH₂, 5-C), 28.1 (CH₂, 8-C), 26.9 (3 × CH₃, (CH₃)₃CSi), 25.5 (CH₃, 9-C), 19.2 (C, (CH₃)₃CSi); IR νmax(film)/cm\(^{-1}\): 3072, 2931, 2858, 1740, 1642, 1472, 1427, 1244, 1216, 1075, 823, 702; HRMS Found (EI): [M+Na]* 433.2168, C₃₅H₄₅NaO₃Si requires 433.2169.

(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-5,6-epoxyhexane (161a)

To a stirred solution of olefin 163a (2.4 g, 5.9 mmol) in anhydrous CH₂Cl₂ (100 mL) at 0 °C was added m-CPBA (1.7 g, 7.5 mmol) portionwise. After stirring at r.t. for 12 h, the reaction mixture was quenched with saturated aqueous Na₂SO₃ (100 mL). The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 150 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (200 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 15:1) afforded the title compound 161a (2.5 g, 5.4 mmol, 93%, d.r. 1:5:1) as a yellow oil containing an inseparable diastereomeric mixture.

\(^1\)H NMR (400 MHz, CDCl₃, * denotes minor isomer): δ 7.67-7.63 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 4.46-4.29 (1H, m, 3-H), 4.24-4.18 (1H, m, 2-H), 3.74-3.63 (2H, m, 1-H), 3.15-3.10 (1H, m, 5-H), 2.83 (1H, dd, J = 4.0, 1.0 Hz, 6-Ha), 2.77-2.75* (1H, m, 6-Ha), 2.55* (1H, dd, J = 2.9, 2.0 Hz, 6-Hb), 2.49 (1H, dd, J = 4.0, 2.6 Hz, 6-Hb), 2.00-1.70 (2H, m, 4-H), 1.39-1.32 (6H, m, 8-H, 9-H), 1.04 (9H, s, (CH₃)₃CSi); \(^1^3\)C NMR (100 MHz, CDCl₃, * denotes minor isomer): δ 135.6 (4 × CH, Ph), 133.25 (C, Ph), 133.17* (C, Ph), 133.14 (C, Ph), 133.08* (C, Ph), 129.82* (2 × CH, Ph), 129.78 (2 × CH, Ph), 127.8 (4 × CH, Ph), 108.3 (C, 7-C), 77.4 (CH, 2-C), 74.71 (CH, 3-C), 74.67* (CH, 3-C), 62.5 (CH₂, 1-C), 50.2 (CH, 5-C), 47.8 (CH₂, 6-C), 46.7* (CH₂, 6-C), 33.2 (CH₂, 4-C), 32.2* (CH₂, 4-C), 28.1 (CH₃, 8-C), 26.9 (3 × CH₃, (CH₃)₃CSi), 25.5 (CH₃, 9-C), 19.2 (C, (CH₃)₃CSi); IR
To a stirred solution of 161a (1.0 g, 2.3 mmol) in EtOH (125 mL) in the presence of NH₄Cl (10 mL) was slowly added NaN₃ (185 mg, 2.8 mmol). The reaction mixture was stirred under reflux for 10 h. After cooling to r.t., the volatiles were removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 8:1) afforded two separable diastereomeric alcohols: 168a (560 mg, 1.2 mmol, 51%) as a yellow oil and 168b (430 mg, 0.9 mmol, 38%) as a colourless oil.

168a: [α]_D^20 = +1.5 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.68-7.64 (4H, m, Ph), 7.46-7.37 (6H, m, Ph), 4.44-4.39 (1H, m, 3-H), 4.26-4.22 (1H, m, 2-H), 4.06-4.00 (1H, m, 5-H), 3.71 (2H, d, J = 6.0 Hz, 1-H), 3.47 (1H, s, OH), 3.33-3.25 (2H, m, 6-H), 1.91-1.79 (2H, m, 4-H), 1.41 (3H, s, 8-H), 1.35 (3H, s, 9-H), 1.07 (9H, s, (CH₃)₃Si); ¹³C NMR (100 MHz, CDCl₃): δ 135.6 (4 × CH, Ph), 133.1 (C, Ph), 133.0 (C, Ph), 129.9 (2 × CH, Ph), 127.8 (4 × CH, Ph), 108.1 (C, 7-C), 77.5 (CH, 2-C), 74.0 (CH, 3-C), 68.5 (CH, 5-C), 62.5 (CH₂, 1-C), 57.2 (CH₂, 6-C), 33.5 (CH₂, 4-C), 28.1 (CH₃, 8-C), 26.9 (3 × CH₃, (CH₃)₃Si), 25.5 (CH₃, 9-C), 19.2 (C, (CH₃)₃Si); IR νmax(film)/cm⁻¹: 3443, 3071, 2931, 2858, 1589, 1472, 1427, 1218, 1111, 823, 702; HRMS Found (El): [M+Na]⁺ 492.2283, C₂₅H₃₅N₃NaO₄Si requires 492.2289.

168b: [α]_D^20 = -5.0 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.67-7.63 (4H, m, Ph), 7.45-7.38 (6H, m, Ph), 4.43-4.38 (1H, m, 3-H), 4.25-4.21 (1H, m, 2-H), 4.04-4.01 (1H, m, 5-H), 3.71 (2H, d, J = 8.0 Hz, 1-H), 3.47 (1H, s, OH), 3.28 (2H, d, J = 4.0 Hz, 6-H), 1.90-1.77 (2H, m, 4-H), 1.40 (3H, s, 8-H), 1.34 (3H, s, 9-H), 1.06 (9H, s, (CH₃)₃Si); ¹³C NMR (100 MHz, CDCl₃): δ 135.60 (CH, Ph), 135.54 (3 × CH, Ph), 133.02 (C, Ph), 133.00 (C, Ph), 129.9 (2 × CH, Ph), 127.78 (2 × CH, Ph), 127.76 (2 × CH, Ph), 108.8 (C, 7-C), 77.6 (CH, 2-C), 77.2 (CH, 3-C), 71.0 (CH, 5-C), 62.2 (CH₂, 1-C), 56.3 (CH₂, 6-C), 33.4 (CH₂, 4-C), 27.9 (CH₃, 8-C), 26.8 (3 × CH₃, (CH₃)₃Si(CH₃)₂), 25.5 (CH₃, 9-C), 19.2 (C, (CH₃)₃Si(CH₃)₂); IR νmax(film)/cm⁻¹: 3481, 3058,
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2927, 2858, 2091, 1586, 1473, 1424, 1216, 1105, 823, 702; HRMS Found (EI): [M+Na]+ 492.2283, C_{28}H_{38}N_3NaO_8Si requires 492.2289.

(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-6-amino-hexan-5-ol (158)

![Structure of (2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-6-amino-hexan-5-ol (158)]

To a solution of alcohol 168a (400.0 mg, 0.9 mmol) in a mixture of THF and H_2O (24 mL, 5:1) was added PMe_3 (1 M in THF, 2.7 mL, 2.7 mmol) dropwise, respectively. After stirring at 50 °C for 2 h, the reaction was quenched by a sequential addition of bleach (5 mL), H_2O (10 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH saturated with NH_3 6:1) afforded the corresponding title compound 158 (381.0 mg, 0.86 mmol, 95%) as light yellow oils.

The reduction of 168b (400 mg, 0.9 mmol) was carried out using analogous conditions to the preparation of 158a. 158b (392.0 mg, 0.88 mmol, 98%) was obtained as a light yellow oil after purification by flash column chromatography on silica gel.

158a: [α]_b^20 = +7.0 (c 1.0, CHCl_3); ¹H NMR (400 MHz, CDCl_3): δ 7.66-7.62 (4H, m, Ph), 7.44-7.33 (6H, m, Ph), 4.51-4.49 (1H, m, 2-H), 4.24-4.22 (1H, m, 3-H), 3.77-3.73 (1H, m, 5-H), 3.72-3.63 (2H, m, 1-H), 2.80 (1H, dd, J = 12.8, 3.2 Hz, OH), 2.60-2.55 (4H, m, 6-H, NH_2), 1.73-1.67 (2H, m, 4-H), 1.36 (3H, s, 8-H), 1.34 (3H, s, 9-H), 1.03 (9H, s, (CH_3)_3SiPh_2); ¹³C NMR (100 MHz, CDCl_3): δ 135.53 (2 x CH, Ph), 135.50 (2 x CH, Ph), 133.2 (C, Ph), 133.0 (C, Ph), 129.7 (2 x CH, Ph), 127.7 (4 x CH, Ph), 107.8 (C, 7-C), 77.6 (CH, 3-C), 74.1 (CH, 2-C), 70.5 (CH, 5-C), 62.6 (CH_2, 1-C), 47.8 (CH_2, 6-C), 34.0 (CH_2, 4-C), 28.0 (CH_3, 8-C), 26.8 (3 x CH_3, (CH_3)_3SiPh_2), 25.5 (CH_3, 9-C), 19.1 (C, (CH_3)_3Si); IR ν_{max}(film)/cm⁻¹: 3451, 2930, 2857, 1674, 1427, 1295, 1145, 1112, 942, 858, 824, 704, 613; HRMS Found (ESI): [M+Na]⁺ 444.2525, C_{28}H_{38}N_3NaO_8Si requires 444.2565.

158b: ¹H NMR (400 MHz, CDCl_3): δ 7.65-7.63 (4H, m, Ph), 7.42-7.33 (6H, m, Ph), 4.41-4.36 (1H, m, 3-H), 4.22-4.06 (1H, m, 2-H), 3.79-3.64 (3H, m, 1-H, 5-H), 2.85-2.70 (4H, m, 6-H, NH_2), 1.82-1.66 (2H, m, 4-H), 1.36 (3H, s, 8-H), 1.31 (3H, s, 9-H), 1.03 (9H, s, (CH_3)_3SiPh_2); ¹³C NMR (100 MHz, CDCl_3): δ 135. 45 (CH, Ph), 135.40 (CH, Ph), 135.37 (2 x CH, Ph) 133.0 (C, Ph), 132.9 (C, Ph), 129.7 (2 x CH, Ph), 127.6 (4 x CH, Ph), 108.2 (C, 7-C), 77.7 (CH, 2-C), 76.5 (CH, 3-C), 71.4
(CH, 5-C), 62.3 (CH, 1-C), 47.7 (CH, 2-C), 33.6 (CH, 4-C), 27.8 (CH, 8-C), 26.9 (3 × CH3, (CH3)3CSiPh2), 25.4 (CH, 9-C), 19.2 (C, (CH3)3CSiPh2); IR νmax (film)/cm⁻¹: 3451, 2930, 2857, 1674, 1427, 1295, 1145, 1112, 942, 858, 824, 704, 613; HRMS Found (ESI): [M+Na]+ 444.2525, C25H27NaO2Si requires 444.2565.

5-((tert-Butyldimethylsilylo)methyl)-1-(3-(((4S,5R)-5-((tert-butyldiphenylsilylo)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-1H-pyrrole-2-carbaldehyde (172)

To a stirred solution of dihydropyranone 83 (30.0 mg, 0.12 mmol) in dioxane (2 mL) was added amino alcohol 158a (103.0 mg, 0.23 mmol) and Et3N (0.02 mL) at r.t. After stirring at r.t. for 2 h, the solvent was removed under reduced pressure to afford an oil residue. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 8:1) afforded the title compound 172a (44.0 mg, 0.07 mmol, 60%) as a yellow oil.

Pyrrole alcohol 172b was synthesised in an analogous manner as 172a. 172b was obtained (41.0 mg, 0.06 mmol, 51%) as a yellow oil.

172a: [α]b²⁰ = +3.8 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.47 (1H, s, 7'-H), 7.72-7.67 (4H, m, Ph), 7.45-7.38 (6H, m, Ph), 6.90 (1H, d, J = 4.0 Hz, 3'-H), 6.20 (1H, d, J = 4.0 Hz, 4'-H), 4.73 (1H, d, J = 13.2 Hz, 6'-H), 4.68 (1H, d, J = 13.2 Hz, 6'-Hb), 4.61 (1H, m, 3-H), 4.56-4.51 (1H, m, 6-Ha), 4.26-4.19 (2H, m, 2-H, 6-Hb), 4.17-4.10 (1H, m, 5-H), 3.78-3.68 (2H, m, 1-H), 3.14 (1H, d, J = 8.0 Hz, OCH), 1.90-1.77 (2H, m, 4-H), 1.38 (3H, s, 8-H), 1.34 (3H, s, 9-H), 1.08 (9H, s, (CH₃)3SiPh₂), 0.91 (9H, s, (CH₃)3Si(CH₃)₂), 0.10 (3H, s, (CH₃)3Si(CH₃)₂), 0.08 (3H, s, (CH₃)3Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃): δ 179.9 (CH, 7'-C), 142.6 (C, 5'-C), 135.63 (3 × CH, Ph), 135.59 (CH, Ph), 133.2 (C, Ph), 133.1 (C, Ph), 132.2 (C, 2'-H), 129.7 (2 × CH, Ph), 127.75 (2 × CH, Ph), 127.74 (2 × CH, Ph), 124.9 (CH, 3'-C), 110.3 (CH, 4'-C), 108.5 (CH, 7'-C), 77.8 (CH, 2'-C), 71.9 (CH, 3-C), 69.8 (CH, 5-C), 62.6 (CH₂, 1-C), 57.4 (CH₂, 6'-C), 51.8 (CH₂, 6'-C), 34.5 (CH₃, 4-C), 29.6 (CH₃, (CH₃)3CSiPh₂), 28.1 (2 × CH₃, 8-C, 9-C), 26.9 (2 × CH₃, (CH₃)3CSiPh₂), 25.8 (CH₃, (CH₃)3Si(CH₃)₂), 25.6 (2 × CH₃, (CH₃)3Si(CH₃)₂), 19.2 (C, (CH₃)3CSiPh₂), 18.3 (C, (CH₃)3Si(CH₃)₂), −5.3 (CH₃, (CH₃)3Si(CH₃)₂), −5.4 (CH₃, (CH₃)3Si(CH₃)₂); IR νmax (film)/cm⁻¹: 3658, 2931, 2857, 1658, 1438, 1421, 1362, 1246, 1216, 1112, 1066, 836, 702; HRMS Found (ESI) [M+Na]+ 688.3465, C₇₅H₇₅NaO₂Si₂ requires 688.3460.
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172a: [α]_bo = +3.2 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.46 (1H, s, 7'-H), 7.69-7.65 (4H, m, Ph), 7.45-7.37 (6H, m, Ph), 6.88 (1H, d, J = 4.1 Hz, 3'-H), 6.19 (1H, d, J = 4.1 Hz, 4'-H), 4.86 (1H, d, J = 13.2 Hz, 8'-H₂), 4.69 (1H, d, J = 13.2 Hz, 8'-H₂), 4.60-4.57 (1H, m, 6-H), 4.47-4.43 (1H, m, 5-H), 4.25-4.13 (3H, m, 6-CH₂Ph, 2-H, 3-H), 3.75-3.64 (2H, m, 1-H), 3.56 (1H, br s, OH), 2.00-1.73 (2H, m, 4-H), 1.38 (3H, s, 8-H), 1.31 (3H, s, 9-H), 1.06 (9H, s, (CH₃)₃CSi(CH₃)₂), 0.90 (9H, s, (CH₃)₃CSi(CH₃)₂), 0.09 (3H, s, (CH₃)₃CSi(CH₃)₂), 0.01 (3H, s, (CH₃)₃CSi(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃): δ 179.5 (CH, 7'-C), 143.6 (C, 5'-C), 135.64 (2 × CH, Ph), 135.59 (3 × CH, Ph), 133.2 (C, Ph), 133.1 (C, Ph), 132.2 (C, 2'-H), 129.7 (2 × CH, Ph), 127.75 (2 × CH, Ph), 127.74 (2 × CH, Ph), 124.9 (CH, 3'-C), 109.9 (CH, 4'-C), 108.5 (CH, 7-C), 77.9 (CH, 2-C), 77.3 (CH, 3-C), 71.9 (CH, 5-C), 62.5 (CH₂, 1-C), 57.7 (CH₂, 6'-C), 51.4 (CH, 6-C), 33.6 (CH₃, 4-C), 27.9 (CH₃, 8-C), 26.9 (3 × CH₃, (CH₃)₃CSiPh₂), 25.8 (3 × CH₃, (CH₃)₃CSi(CH₃)₂), 25.5 (CH₃, 9-C), 19.2 (C, (CH₃)₃CSiPh₂), 18.3 (C, (CH₃)₃CSi(CH₃)₂), −5.29 (CH₃, (CH₃)₃CSi(CH₃)₂), −5.32 (CH₃, (CH₃)₃CSi(CH₃)₂); HRMS Found (ESI) [M+Na]+ 688.3461, C₃₇H₅₅NNaO₆Si₂ requires 688.3460.

5-(((tert-butylidimethylsilyl)oxy)methyl)-1-(3-((4S,5R)-5-(((tert-butylidiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxopropyl)-1H-pyrrole-2-carbaldehyde (157)

![Structure](image)

To a mixture of alcohols 172a and 172b (40 mg, 0.06 mmol) in anhydrous CH₂Cl₂ (4 mL) at 0 °C under N₂ was added activated 4 Å MS (40 mg) followed by TPAP (2 mg, 0.004 mmol) and NMO (26 mg, 0.22 mmol). After stirring at r.t. for 15 min, the reaction mixture was filtered through a plug of silica and washed with EtOAc (2 × 20 mL). The filtrate was concentrated in vacuo to afford the title compound 157 (32 mg, 0.054 mmol, 90%) as a colourless oil.

[α]_b = −2.0 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.44 (1H, s, 7'-C), 7.70-7.65 (4H, m, Ph), 7.45-7.37 (6H, m, Ph), 6.88 (1H, d, J = 4.1 Hz, 3'-H), 6.19 (1H, d, J = 4.0 Hz, 4'-H), 5.37 (1H, d, J = 16.0 Hz, 6-H₂), 5.26 (1H, d, J = 16.0 Hz, 6-H₂), 4.69-4.66 (1H, m, 3-H), 4.57 (2H, s, 6'-H), 4.26-4.21 (1H, m, 2-H), 3.68 (2H, d, J = 6.0 Hz, 1-H), 2.86-2.84 (2H, m, 4-H), 1.40 (3H, s, 8-H), 1.33 (3H, s, 9-H), 1.07 (9H, s, (CH₃)₃CSi(CH₃)₂), 0.87 (9H, s, (CH₃)₃CSiPh₂), 0.04 (3H, s, (CH₃)₃CSi(CH₃)₂), 0.02 (3H, s, (CH₃)₃CSi(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃): δ 202.3 (C, 5'-C), 179.7 (CH, 7'-C), 142.0 (C, 5'-C), 135.6 (4 × CH, Ph), 133.12 (C, Ph), 133.07 (C, Ph), 132.3 (CH, 2'-C), 129.8 (2 × CH, Ph), 127.78 (2 × CH, Ph), 127.77 (2 × CH, Ph), 123.9 (CH, 3'-C), 110.0 (CH, 5'-C).
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(4S,5R)-5-((tert-Butyldiphenyldisilyloxy)methyl)-4-hydroxy-1',4,4',5-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carbaldehyde (173)

To a stirred solution of ketone 157 (30 mg, 0.046 mmol) in THF (1 mL) and H2O (1 mL) was added HCl (4 M in dioxane, 0.2 mL, 0.8 mmol). After stirring at r.t. for 2.5 h, the reaction mixture was neutralised using saturated aqueous NaHCO3 to pH 7. The resultant mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous MgSO4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 5:1) afforded the title compound 173 (18 mg, 0.038 mmol, 82%, d.r. 3:2) as a yellow oil containing an inseparable mixture of two diastereomers.

1H NMR (400 MHz, CDCl3, *denotes minor isomer): δ 9.48 (1H, s, 14-H), 9.44* (1H, s, 14-H), 7.67-7.61 (4H, m, Ph), 7.45-7.32 (6H, m, Ph), 6.93 (1H, d, J = 4.0 Hz, 12-H), 6.90* (1H, d, J = 4.0 Hz, 12-H), 6.02 (1H, d, J = 4.0 Hz, 11-H), 5.94* (1H, d, J = 4.0 Hz, 11-H), 5.03 (1H, d, J = 15.2 Hz, 7-Ha), 4.92* (1H, d, J = 16.0 Hz, 7-Ha), 4.84 (1H, d, J = 16.0 Hz, 7-Hb), 4.72 (1H, d, J = 16.1 Hz, 10-H), 4.68* (1H, d, J = 8.0 Hz, 7-Hb), 4.68-4.66* (2H, m, 3-H), 4.65* (1H, d, J = 16.0 Hz, 4-H), 4.46-4.41 (1H, m, 4-H), 4.34 (1H, d, J = 16.0 Hz, 10-Ha), 4.26-4.24 (1H, m, 2-H), 4.22* (1H, d, J = 8.0 Hz, 10-Ha), 4.05-4.00* (1H, d, J = 5.6 Hz, 2-H), 3.84-3.81 (1H, dd, J = 10.5, 5.6 Hz, 15-Hb), 3.70-3.60* (2H, m, 15-Hb), 2.80 (1H, dd, J = 10.8, 4.8 Hz, 15-Hb), 2.51* (1H, dd, J = 13.0, 6.0 Hz, 4-Ha), 2.35 (1H, dd, J = 13.0, 6.0 Hz, 4-Ha), 2.22 (1H, dd, J = 13.2, 1.2 Hz, 4-Hb), 2.12* (1H, dd, J = 12.0, 8.0 Hz, 4-Hb), 1.08 (9H, s, (CH3)2CSiPh2), 1.06* (9H, s, (CH3)2CSiPh2); 13C NMR (100 MHz, CDCl3, *denotes minor isomer): δ 178.7 (CH, 14-C), 135.62 (CH, Ph), 135.57 (2 × CH, Ph), 135.52 (CH, Ph), 132.8 (2 × C, Ph), 134.5 (C, 8-C), 133.1 (4 × CH, Ph), 132.8* (4 × CH, Ph), 131.2 (C, 11-C), 131.1* (C, 11-C), 130.0 (2 × CH, Ph), 127.9* (CH, Ph), 127.9* (CH, Ph), 124.2 (CH, 12-C), 123.9* (CH, 12-C), 104.9 (C, 11-C), 104.7* (C, 11-C), 104.2 (C, 5-C), 102.8* (C, 5-
To a stirred solution of 173 (20 mg, 0.04 mmol) in THF (0.5 mL) was added TBAF (1 M in THF, 0.5 mL, 0.5 mmol) under N₂. After stirring at r.t. for 2.5 h, the reaction mixture was concentrated under reduced pressure to remove most of the solvent and the resultant mixture was filtered through a pad of silica and washed with THF (10 mL). The filtrate was concentrated in vacuo followed by purification by preparative TLC (n-hexanes/EtOAc 1:5) to give 17 (4 mg, 0.016 mmol, 40%) as a white solid and 17ₐ (2.7 mg, 0.11 mmol, 27%) as a yellow oil.

Acortatarin A: m.p. 163-165 °C; [α]ᵢ²⁰ = +194.8 (c 0.15, CHCl₃); ¹H NMR (400 MHz, CD₂OD): δ 9.32 (1H, s, 14-H), 6.98 (1H, d, J = 4.4 Hz, 12-H), 6.03 (1H, d, J = 4.4 Hz, 11-H), 4.97 (1H, d, J = 15.8 Hz, 7-Hₙ), 4.81 (1H, d, J = 15.8 Hz, 7-Hₙ), 4.55 (1H, d, J = 14.0 Hz, 10-Hₙ), 4.24 (1H, ddd, J = 8.3, 4.9, 2.9 Hz, 3-H), 4.18 (1H, d, J = 14.0 Hz, 10-Hₙ), 4.02 (1H, ddd, J = 4.7, 4.7, 2.9 Hz, 2-H), 3.67 (1H, dd, J = 12.1, 3.5 Hz, 15-Hₙ), 3.58 (1H, dd, J = 12.2, 4.9 Hz, 15-Hₙ), 2.30 (1H, dd, J = 14.0, 8.4 Hz, 4-Hₙ), 2.10 (1H, dd, J = 14, 2.7 Hz, 4-Hₙ); ¹³C NMR (100 MHz, CD₂OD): δ 180.2 (CH, 14-C), 137.6 (C, 8-C), 132.4 (C, 13-C), 125.9 (CH, 12-C), 106.1 (CH, 11-C), 104.5 (C, 5-C), 89.4 (CH, 2-C), 72.2 (CH, 3-C), 63.0 (CH₃, 15-C), 58.7 (CH₂, 7-C), 52.0 (CH₃, 10-C), 45.9 (CH₂, 4-C); IR ν_max(film)/cm⁻¹: 3360, 2921, 2851, 1737, 1643, 1498, 1471, 1427, 1408, 1373, 1255, 1104, 1037, 701; HRMS Found (ESI): [M+Na]^+ 514.2003, C₁₂H₁₆N₂NaO₅Si requires 514.2020.


(2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)-1’,4,4’,5-tetrahydro-3H-spiro[furan-2,3’-pyrrolo[2,1-c][1,4]oxazine] -6’-carbaldehyde (17) and (2S,4S,5R)-4-Hydroxy-5-(hydroxymethyl)-1’,4,4’,5-tetrahydro-3H-spiro[furan-2,3’-pyrrolo[2,1-c][1,4]oxazine] -6’-carbaldehyde (17ₐ)

Acortatarin A (17) 5-spi-acortatarin A (17ₐ)
10-H$_b$), 3.96 (1H, td, $J = 6.8$, 4.8 Hz, 2-H), 3.66 (1H, dd, $J = 12.1$, 4.8 Hz, 15-H$_a$), 3.64 (1H, dd, $J = 11.8$, 6.8 Hz, 15-H$_b$), 2.45 (1H, dd, $J = 13.2$, 6.8 Hz, 4-H$_a$), 2.04 (1H, dd, $J = 13.3$, 6.8 Hz, 4-H$_b$);

$^{13}$C NMR (100 MHz, CD$_{3}$OD): $\delta$ 180.2 (CH, 14-C), 137.5 (C, 13-C), 132.4 (C, 12-C), 106.1 (CH, 11-C), 104.2 (C, 5-C), 89.6 (CH, 2-C), 72.2 (CH, 3-C), 64.3 (CH$_2$, 15-C), 59.2 (CH$_2$, 7-C), 52.8 (CH$_2$, 10-C), 45.8 (CH$_2$, 4-C); IR $\nu_{\text{max}}$(film)/cm$^{-1}$: 3351, 2910, 2837, 1733, 1645, 1412, 1260, 1038, 796; HRMS Found (ESI): [M+Na]$^+$ 276.0850, $C_{12}H_{15}$NNaO$_5$ requires 276.0842.
Chapter 4: Introduction
4.1 Tenuipyrene: Isolation, Biological Activity and Biosynthetic Analysis:

4.1.1 Isolation and Biological activity

Tenuipyrene (174) is a novel [6,5]-pyrone fused polyketide isolated from secondary metabolites produced by filamentous fungi by Oshima and co-workers (Figure 20). In addition, two other known polyketides, namely cephalosporolides B (175) and F (176), were co-isolated from the same source. These secondary metabolites were induced by addition of epigenetic modifying agents such as histone deacetylase (HDAC) or DNA methyltransferase inhibitors to the filamentous fungi.

The structure elucidation of tenuipyrene (174) was unambiguously confirmed by NMR spectroscopic analysis, X-ray single crystal diffraction and CD spectroscopy analysis.

The unique structure of tenuipyrene (174) and our group’s long-standing interest in the synthesis of natural products containing a spiroketal moiety encouraged us to embark on the total synthesis of tenuipyrene (174) in order to provide material to study its biological activity.

Figure 20. Structures of tenuipyrene (174) and cephalosporolides B (175) and F (176).

Figure 21. Isaria tenuipes filamentous fungi.
4.1.2 Proposed Biosynthetic Analysis

A plausible biosynthetic pathway to tenuipyrone (174) was proposed by Oshima and co-workers.\textsuperscript{176} As shown in Scheme 87, the unique tetracyclic ring system in 174 could be generated from a Michael addition of 2-pyrone 177 to cephalosporolide B (175) followed by sequential annulations between 4-hydroxy-6-methyl-2-pyrone (177) and 175. The absolute configuration of tenuipyrone 174 and cephalosporolide B (175) are supported by the proposed biosynthesis.

![Scheme 87 Biosynthetic analysis of tenuipyrone (174).](image)

The 2-pyrone subunit has been found in a number of natural products exhibiting different biological activities. Natural products that contain this moiety will be discussed classified by their biological activity in the following section.
Chapter 4: Introduction of Tenuipyrone

4.2 Biological Activities of Compounds Containing the 2-Pyrone Motif:

2-Pyrones (Figure 22) 177-179 are an important class of unsaturated six-membered lactones that display chemical and physical properties of both alkenes and aromatic compounds.\textsuperscript{178} They have been isolated from various natural sources including bacteria, plant, fungus, microbial, insect and animal systems and play a pivotal role in many biological processes such as self-defence against foreign organisms, metabolism and biosynthesis.\textsuperscript{179} Furthermore, both 177 and 179 have been extensively utilised as synthetic precursors for the development of bioactive compounds.\textsuperscript{178}

![Figure 22. Structures of 2-pyrones.](image)

The abundance of the 2-pyrone motif in natural products makes them a highly important class of compounds. A review of the isolation of natural products containing a 2-pyrone moiety is beyond the scope of this thesis. Rather, attention will be focused on the importance of 2-pyrones as potential inhibitors of leukaemia and as potential treatments for human immunodeficiency virus (HIV), Alzheimer’s disease other human diseases. It is hoped that this general overview will support the proposal to more fully elucidate the biological activity of the unique spiroketal tenuipyrone (174).

4.2.1 Treatment of Cancer

In 1997, Perchellet and co-workers reported the anti-tumour properties of tricyclic 2-pyrene (TCPs) \textbf{180} with similar structures to pyripyropene (\textbf{181}), arisugacins (\textbf{182}) (Figure 23).\textsuperscript{180} Both the natural and synthetic TCPs were examined for their \textit{in vitro} inhibitory activity against leukaemia cells. Tricyclic compounds lacking the aryl group were found to exhibit either little or no anti-tumour activity, indicating that a highly conjugated system is essential for biological activity.

Among naturally occurring 2-pyrones, the nature of the C-4 substituent is important for the observed biological activity.\textsuperscript{181} A number of different aryl, alkyl, alkynyl and alkenyl 4-substituted-6-methyl pyrones were synthesised by Marrison and co-workers (Figure 23).\textsuperscript{181} These synthetic 2-pyrones inhibited the growth of ovarian carcinoma (A2780) and human chronic myelogenous leukaemia (K562) cell lines. Among the 2-pyrene derivatives investigated,
Chapter 4: Introduction of Tenuipyrene

4-alkynyl-6-methyl-2-pyrones (183) were established to be the most potent molecule as evidenced by their significant low IC\textsubscript{50} values against the K562 and A2720 cell lines (4.0 and 1.8 μM).

\[\text{Figure 23. Examples of natural and synthetic 2-pyrone molecules as potential cancer treatment agents.}\]

4.2.2 HIV Inhibitors

One enzyme critical for the replication of HIV is the HIV protease.\textsuperscript{182} Thus, targeting HIV-1 protease has been suggested to be a potential method for the treatment of acquired immunodeficiency syndrome (AIDS).\textsuperscript{183} Approximately 150, 000 synthetic compounds have been screened by Hagen and co-workers for their ability to inhibit HIV-1 protease using a high throughput screening assay.\textsuperscript{180} Two lead compounds were selected based on the superior chemical and biological properties they displayed during the assay such as purity, selectivity, toxicity etc. The IC\textsubscript{50} values of coumarin PD099560 (184) and 2-pyrene PD107067 (185) were 2.3 and 3.1 μM, respectively. The structure of coumarin 184 is similar to warfarin (186), a synthetic compound shown to exhibit weak inhibitory activity towards HIV protease.\textsuperscript{184}

\[\text{Figure 24. Structures of 2-pyrene compounds as potential anti-HIV agents.}\]

4-Hydroxy-2-pyrene motifs have been identified as effective therapeutic agents for the treatment of HIV.\textsuperscript{185} 4-Hydroxy-2-pyrones can displace the water molecule found in the active site of the enzyme with the hydroxyl group forming hydrogen bonds with aspartates Asp 25 and Asp 125. Displacement of water with a 4-hydroxy-2-pyrene allows the lactone moiety to participate in hydrogen bonding with the isoleucine 50 and isoleucine 150 flaps (Figure 25).\textsuperscript{186} This results in the reorganisation of the tertiary structure of the enzyme leading to unfunctional HIV-1.
4.2.3 Treatment of Alzheimer’s Disease

Alzheimer’s disease (AD) generally reveals itself in the progression of loss of memory and global loss of cognitive abilities that are associated with an age related neurodegenerative disorder. The pathogenesis of AD has not been fully elucidated. Currently, AD is suggested to be caused by the generation and deposition of amyloid-β (Aβ) peptides in the brain. Aβ peptides are 39–42 amino acid hydrophobic polypeptides derived from a trans-membrane glycoprotein, amyloid precursor protein (APP). A number of natural products have been identified to be potential agents for the treatment of AD (Figure 26).

Hua and co-workers found several active scaffolds by synthesising tricyclic 2-pyrone 188 and 189 with different functionalities that mimicked the action of pyripyropenes A-D (187a-187d). Both synthetic compounds 188 and 189 protected MC65 cells that were expressed with a partial APP fusion protein from cell death. They demonstrated that compounds 188 and 189 served as lead compounds for mechanistic studies towards intracellular Aβ and C-terminal fragments (CTF) induced neuron-cell death.
Katzman and co-workers proposed that cholinergic pathways in the cerebral cortex and basal forebrain are compromised in AD and the resultant cholinergic deficiency adds to the cognitive impairment of these patients. Hence acetylcholinesterase (AChE) inhibitors could also be a potent treatment for AD. In 1995, Peng demonstrated the AChE inhibiting activity of several 4-hydroxy-2-pyrone natural products. He reported that the intact 6-aryl-4-hydroxy-2-pyrone unit in territrem B and C were crucial for their biological activity, as either saturation of the C-2 double bond or reduction of the C-1 carbonyl resulted in loss of more than 90% of the AChE inhibitor activity. Other examples are arisugacins 190a and 190b which contain a 4-hydroxy-2-pyrone moiety similar to pyripyropene A (187a) and territrem B (191b) and C 191c, that were isolated by Ômura and co-workers in 1997. Arisugacins 190a and 190b has been identified as a potential treatment for Alzheimer’s and other dementia diseases. A number of natural products related to arisugacins 190a and 190b that are selective and potent inhibitors of AChE, have also been isolated from a culture broth of Penicillium sp.

4.2.4 Control of High Cholesterol Levels

Hypercholesterolemia is a common disorder characterised by the presence of high levels of cholesterol in the blood. To date, no successful cure for hypercholesterolemia has been reported. As a temporary solution, inhibiting the biosynthesis of cholesterol is one of the most common treatments for hypercholesterolemia. Plant sterols such as compesterol and sitosterol can reduce
plasma cholesterol by preventing its absorption. The postulated mechanism is through competition with cholesterol for incorporation into micelles. Another approach to reduce cholesterol intake is to form complexes with cholesterol. New inhibitors of acyl-CoA cholesterol acyltransferase (ACAT) have been discovered in the fermentation broth of Penicillium griseofulvum F1959. The number of acetoxy groups and the presence of the hydroxyl group in phenylpyrene A-C are thought to be crucial for their inhibitory activity against ACAT, as phenylpyrene A is the most potent inhibitor.

![Diagram](image)

**Figure 27.** Compounds as potential treatments for high cholesterol.

Studies conducted by Deck and co-workers showed that 2-pyrone serves as a pseudosubstrate inhibitor in which acylation of acylenzyme is much faster than deacylation. When this happens acylenzyme accumulates and rearranges to the acid chloride, which hydrolyses while tethered to serine followed by slow hydrolysis and release of product (Scheme 88).
Scheme 88 Mechanism for substituted 2-pyrone inhibiting enzyme function.
4.3 Previous Synthesis of Tenuipyrone

During the course of this work, the first total synthesis of tenuipyrone was reported by Tong and co-workers in 2012. The synthesis featured a key intermolecular-Michael addition/cycloketalisation cascade between pyrone 177 and enone 193. The synthesis of tenuipyrone (174) commenced with the synthesis of enone 194, a widely used chiral building block. Enone 194 was obtained from furfuryl alcohol (95) over 5 steps in 13% yield. The other coupling fragment 195 was prepared from commercially available chiral starting material 196 over two steps in good yield. The union of enone 194 and aldehyde 195 fragments was challenging. Neither Morita-Baylis-Hillman coupling nor Nozaki-Hiyama-Kishi reaction was able to effect the formation of enone 197 in a satisfying yield. Fortunately, organoselenide 198 underwent successful coupling with aldehyde 195 via addition of the organolithium reagent delivering alcohol 197 in 48-65% yield. Alcohol 197 was then further oxidised to diketone 193 using buffered DMP in CH₂Cl₂ in 95% yield. The key intermolecular Michael addition/spiroketalisation cascade was performed in CH₂Cl₂ using Amberlyst-15 to afford (−)-tenuipyrone (174) and TBS silyl ether 199. Further deprotection-epimerisation of spiroketal 199 was conducted employing Amberlyst-15 in aqueous CH₂Cl₂ to give tenuipyrone 174 in 47% yield over two steps.

Scheme 89 Total synthesis of tenuipyrone 174. Reagents and conditions: i) a) TESCl, Et₃N, DMAP, CH₂Cl₂; b) OsO₄, 2,6-lutidine, NaIO₄, dioxane/H₂O 74% over 2 steps; ii) PhSeCl, pyridine, r.t., 95%; iii) (Me₃Sn)₂, n-BuLi, –78 °C, 48-65%; iv) DMP, NaHCO₃, CH₂Cl₂, 0 °C to r.t., 95%; v) 177, Amberlyst-15, CH₂Cl₂; vi) Amberlyst-15, CH₂Cl₂:H₂O 20:1, r.t., 47% over 2 steps.
Chapter 4: Introduction of Tenuipyrone

4.4 Aim of the Present Research:

(−)-Tenuipyrone (174) structurally embodies a unique tetracyclic 6,6,5,5-pyrene possessing a spiroketal moiety with four contiguous stereocenters. At the onset of this work, there was no reported total synthesis of tenuipyrone or synthetic studies towards tenuipyrone. The aim of the current research is to investigate a synthetic route to tenuipyrone 174 that would enable further biological investigation of this intriguing natural product.

It was proposed that 3-dehydroxy-tenuipyrone (200) could be obtained via a late-stage metal catalysed spiroketalisation of alkyne-diol 201 in a highly atom-economical and redox-neutral manner to yield the desired ring system (Scheme 90). Alkyne-diol 201 in turn can be formed via Michael addition of pyrone 177 and enone 202 that can be elaborated to alkyne-diol 201. Enyne 202 could be prepared by Sonogashira cross coupling between enone iodide 203 and alkyne 204. This disconnection thus reveals three key intermediates namely, pyrone 177, iodide 203 and terminal alkyne 204. The following section will summarise the range of strategies reported in the literature to effect the formation of pyrone related natural products.

Scheme 90 Retrosynthetic analysis of 3-dehydroxy-tenuipyrone (200).
Chapter 5: Discussion
Chapter 5: Discussion of Tenuipyrone

5.1 Sonogashira-Michael Addition Approach towards the Synthesis of Spiroketal 200

5.1.1 Overview

This chapter describes our strategy towards the attempted synthesis of 3-dehydroxy-tenuipyrone (200). The initial aim of this work was to investigate the use of a gold-catalysed alkyne cyclisation for the construction of the spiroketal core of tenuipyrone (200).

![Scheme 91 Retrosynthetic analysis of the basic pyrone spiroketal 200.](image)

The synthesis of the basic pyrone spiroketal 200 hinges on a key gold catalysed spiroketalisation of alkyne 201 in an efficient manner. Alkyne 201 was envisaged to arise from an asymmetric Michael addition of pyrone 177 to enynone 202. Conventionally, Michael addition takes place using an electron-rich compound as the Michael donor with an electron-poor compound as the Michael acceptor. Enynone systems are typically used as Michael acceptor; however, compound 202 also contains an electron-donating acetylene group conjugated to the enone, potentially modifying its reactivity. The success of the proposed Michael addition therefore cannot be predicted with certainty. However, the highly convergent nature of the proposed synthesis allows for rapid access to the initial intermediates. Enynone 202 can be accessed by Sonogashira coupling with iodide 204 and alkyne 202.
5.1.2 Preparation of Iodide 203

α-Haloenones and their derivatives are versatile intermediates that have been widely used for the generation of α–substituted enones and related natural products.\textsuperscript{204} The existing methods for the direct α-iodination of enones involves the use of iodine azide\textsuperscript{205} or iodine-eric ammonium nitrate (CAN).\textsuperscript{206} In 1992, Johnson and co-workers reported the most widely used iodination method of cyclopentenone 205 employing iodine with excess pyridine as a base and catalyst and also as a co-solvent in CCl₄ to give iodide 203 in 57% yield (Scheme 92).\textsuperscript{207}

\[
\text{Scheme 92 Johnson’s synthesis of iodide 203. Reagents and conditions: i) I}_2\text{, pyridine:CCl}_4\text{ 1:1, 0 °C, 24 h, 57%}.
\]

This practical direct iodination of enones 205 involves a nucleophilic addition/electrophilic capture/elimination pathway, in which an intermediate enolate reacted with weakly electrophilic iodine (Scheme 93). Finally pyridine-promoted elimination affords iodide 203.

\[
\text{Scheme 93 Mechanism of iodination using pyridine.}
\]

We examined this method in order to prepare iodide 203, however, the reaction yield obtained would not exceed 45% after several attempts (entry 1, Table 18). With prolonged reaction times, lower yields were obtained. The authors reasoned that simpler vinyl ketones suffered from polymerisation in the presence of a base.\textsuperscript{207}

In 1997, McNelis and co-workers demonstrated a more efficient synthesis requiring only sub-stoichiometric quantities of pyridine in CH₂Cl₂, although long reaction times or high catalyst
loadings were required for higher rates of conversion. The yields obtained were found to be highly dependent on the reaction times. Close TLC monitoring was required to quench the excess I₂ upon completion in order to achieve the best reaction yield (entry 2, Table 18).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>I₂ (equiv)</th>
<th>Base and additives (equiv)</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CCl₄:pyridine 1:1</td>
<td>1.2</td>
<td>pyridine</td>
<td>4 h</td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>1.3</td>
<td>pyridine</td>
<td>6 h</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O pyridine</td>
<td>1.5</td>
<td>...</td>
<td>2.5 h</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>H₂O:THF</td>
<td>2.2</td>
<td>K₂CO₃+DMAP</td>
<td>2 h</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>H₂O:THF</td>
<td>2.2</td>
<td>K₂CO₃+DMAP</td>
<td>5 h</td>
<td>55%</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>2.2</td>
<td>PDC (0.2)</td>
<td>2 h</td>
<td>90%</td>
</tr>
</tbody>
</table>
| 7     | CH₂Cl₂        | 1.2        | PDC (0.3)                   | 4 h  | quant.

Note: Iodine was added at 0 °C for all of the reactions. Upon addition of iodine, the reactions were all warmed up to room temperature.

In 1998, Johnson’s group described modification of the previous method using less toxic Et₂O as a co-solvent in the presence of pyridine, giving the desired product iodo-cyclohexone 206 in 69% yield (Scheme 94). Accordingly, cyclopentenone 207 was treated with I₂ in Et₂O and pyridine, affording iodide 206 in 50% yield (entry 3, Table 18).

Scheme 94 Synthesis of iodo-cyclohexone 206. Reagents and conditions: i) I₂, Et₂O:pyridine 1:1, 2.5 h, 69%.

An expedient method employing catalytic 4-dimethylaminopyridine (DMAP) and excess iodine in the presence of K₂CO₃ in aqueous THF solution was reported to afford complete conversion of cyclopentenone 205 to iodide 203 by Krafft in 2005. Adopting these conditions, iodide 203 was afforded in 90% yield (entry 3, Table 18), however, this procedure was difficult to reproduce reliably. Further studies showed that the reaction yield was found to be highly dependent on the reaction time. Careful TLC analysis was required to monitor the reaction. It was found that workup must be conducted as soon as the starting material has been fully consumed; otherwise, much lower yields were observed (entry 5, Table 18).
A more reliable and efficient synthesis of iodide 203 using I₂ in the presence of catalytic pyridinium dichromate (PDC) in anhydrous CH₂Cl₂ was reported in 2011 by Smith and co-workers as part of the synthetic studies towards spirolide B. Enone 205 was therefore treated with two equivalents of I₂ in the presence of catalytic PDC in CH₂Cl₂ at room temperature affording iodide 203 in 90% yield after two hours (entry 6, Table 18). Further optimisation revealed that treatment with two equivalents of I₂ in conjunction with 0.3 equivalents of PDC and in CH₂Cl₂ at room temperature led to the formation of iodide 203 in quantitative yield. However, close TLC monitoring was also required (entry 7, Table 18). The NMR spectroscopic data and melting point of obtained iodide 203 were in good agreement with the literature.

**5.1.3 Preparation of Alkyne 204**

With iodide 203 in hand, attention moved to the synthesis of the other coupling partner alkyne 204 from (R)-propylene oxide (208a) (Scheme 96). (+)-Propylene oxide is readily available as a racemic mixture from Sigma-Aldrich (139 NZD/1 L), while the enantiomerically pure material from the same supplier is appreciably more expensive (710 NZD/25 g). Jacobsen and co-workers demonstrated that enantiomerically pure terminal epoxides can be readily accessed via hydrolytic kinetic resolution (HKR) by using enantiomerically-pure (R,R)-(−)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexane diamino-cobalt (II) acetate [(Salen)Co(II)OAc] (209) complex, which has proved to be cost-effective, safe, and environmentally benign. Terminal epoxides react readily with water in the presence of the required Jacobsen catalyst. The solvent-free reaction of racemic propylene oxide with 0.55 equivalent of water in the presence of 2 mol% of [(Salen)Co(III)OAc] complex proceeded within 12 hours at room temperature to afford a mixture of unreacted (R)-epoxide and the corresponding propylene glycol derivative of the other enantiomer of the epoxide. The desired (R)-propylene oxide (208a) was obtained in excellent yield and diastereoselectivity (44%, ee > 99%).

The active catalyst [(Salen)Co(III)OAc] (209) was prepared by treatment of (Salen)Co(II) (210) with acetic acid in toluene at room temperature. A dark brown solid was obtained after concentration of the reaction mixture. Propylene oxide 208 was added to the active catalyst followed by slow addition of a sub-stoichiometric quantity of water. The resultant brown mixture was stirred at room temperature for 12 hours. Direct distillation of the reaction mixture afforded (R)-propylene oxide (208a) in good yield with excellent enantiomeric excess (ee), while propylene glycol was left in the reaction mixture.
Chapter 5: Discussion of Tenuipyrone

Having achieved satisfactory yield and excellent enantiomeric excess for the kinetic resolution, attention moved on to the synthesis of the known alkyne 204. In 1997, Gill demonstrated the synthesis of alkyne 204 using lithium acetylide-ethyl enediamine complex in DMSO followed by TBS silyl ether protection to afford the requisite alkyne 204 in 58% yield over 2 steps. Using these conditions, enantiomerically pure epoxide 208, was efficiently converted to the corresponding alcohol 211 by reaction with lithium acetylide-ethylenediamine complex in anhydrous DMSO. Regioselective nucleophilic addition proceeded using 1.2 equivalents of epoxide 208a and one equivalent of lithium acetylide complex to afford alcohol 211 as a single regioisomer in almost quantitative yield based on the limiting reagent. Treatment of alcohol 211 with TBSCl in CH2Cl2 in the presence of imidazole at room temperature delivered TBS silyl ether 204 in quantitative yield. The presence of a singlet at δ 1.96 in the 1H NMR spectrum indicated the formation of the TBS protected alkyne 204. The obtained 1H NMR spectroscopic and optical rotation data ([α]D20 +1.2 (c 10.0, CHCl3, lit. [α]D20 +0.67, c 10.7, CHCl3)) were identical to the reported data.

![Scheme 95](image)

Scheme 95 Activation of Jacobsen pre-catalyst 209. Reagents and conditions: i) CH3CO2H, toluene, r.t., 1 h.

5.1.4 The Sonogashira Cross Coupling of Iodide 203 and Alkyne 204

With both coupling partners in hand, our focus shifted to determining the optimal conditions for the palladium catalysed Sonogashira cross coupling of iodide 203 with terminal alkyne 204 (Scheme 97).
In 1975, Sonogashira and co-workers reported the preparation of symmetrically substituted alkynes under mild conditions via cross coupling of terminal acetylenes and aryl iodides or vinyl bromides using catalytic amounts of Pd(PPh₃)₂Cl₂ in the presence of catalytic cuprous iodide (CuI). The copper-palladium catalysed coupling of terminal alkynes with aryl and vinyl halides to provide enynes is, thus, known as the Sonogashira cross-coupling.

The proposed mechanism for Sonogashira cross coupling is described in Figure 28. The mechanism follows a classic oxidative addition and subsequent reductive elimination pathway. The catalytic cycle commences with generation of a coordinatively unsaturated Pd(0) species from Pd(II) complex via reduction by the alkyne substrate or by the addition of phosphine ligand. The Pd(0) then undergoes oxidative addition to the halide followed by transmetallation by the copper(I)-acetylide. Finally, reductive elimination of delivers the desired product and the release of the catalyst completes the catalytic cycle. However, the structure of the catalytically active Pd(0) species and the actual role of Cu(I) is still a matter of some debate.
In 1997, Johnson and co-workers described the synthesis of (+)- and (−)-harveynone (219) and (−)-tricholomenyn A (220) using Sonogashira cross coupling as the key step (Scheme 98). Good yields of the desired coupled products were obtained using various 2-iodo-2-cycloalkenone 218 catalysed by Pd(PPh$_3$)$_2$Cl$_2$ and CuI in the presence of $i$-Pr$_2$NH in THF at 0 °C.

Figure 28. Proposed mechanism for Sonogashira cross coupling.
Scheme 98 Synthesis of \((-\)-harveynone (219) and \((-\)-tricholomenyln A (220). Reagents and conditions: i) Pd(PPh\(_3\))\(_2\)Cl\(_2\), CuI, i-Pr\(_2\)NH, THF, 0 °C, \(219\) 52%, \(220\) 54%. ii) H\(_2\)SiF\(_6\), CH\(_3\)CN, 81%.

The same conditions using Pd(PPh\(_3\))\(_2\)Cl\(_2\) and CuI in THF at 0 °C were used for the attempted synthesis of enone \(202\) from iodide \(203\) and alkyne \(204\). Disappointingly, no desired product was observed. Changing the conditions by using prolonged reaction times or elevated temperatures proved unrewarding (entries 1-2, Table 19). After work-up, a trace amount of alkyne dimer byproduct \(221\) was identified by \(^1\)H and \(^13\)C NMR analysis. The presence of oxygen was thought to be detrimental to the reaction yield by promoting the competing Glasser coupling reaction catalysed by CuI.\(^{216}\)

Scheme 99 Formation of alkyne dimer \(221\).

Use of the polar aprotic solvent DMF was next investigated for the cross coupling adopting a more vigorous degassing procedure in order to maintain the activity of the Pd-catalyst. This modification proved to be fruitless leading to the recovery of both starting materials (entry 3, Table 19). Various bases were also examined for their ability to promote the cross coupling reaction between iodide \(203\) and alkyne \(204\). Unfortunately, these attempts were also unsuccessful and did not deliver any of the desired product (entries 3-4, Table 19).
In 2005, Kobayashi and co-workers reported a formal synthesis of neocarzinostatin chromophore employing palladium catalysed Sonogashira cross coupling between iodide 222 and alkyne 223 to access an acetylene moiety 224 (Scheme 100). The desired product 224 was obtained in 97% yield.\textsuperscript{217}

![Scheme 100 Kobayashi’s Sonogashira cross coupling.\textsuperscript{217} Reagents and conditions: i) Pd(PPh\textsubscript{3})\textsubscript{4}, CuI, i-Pr\textsubscript{2}NEt, r.t., 1 h, 97%.]

Hence, we set out to investigate whether the use of Pd(PPh\textsubscript{3})\textsubscript{4} would alter the outcome of the cross coupling, hopefully also minimising the yield of the byproduct alkyne dimer 221. Although Pd(PPh\textsubscript{3})\textsubscript{4} is commercially available, a freshly opened bottle of the reagent from Aldrich\textsuperscript{®} was received as a brown powder instead of the expected bright yellow solid. Hence, Pd(PPh\textsubscript{3})\textsubscript{4} was freshly prepared following Coulson’s procedure.\textsuperscript{218} Accordingly, a mixture of PdCl\textsubscript{2} and PPh\textsubscript{3} in

### Table 19. Synthesis of enyne 202.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio\textsuperscript{a}</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:3</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (10%), CuI (20%), i-Pr\textsubscript{2}NH, THF, 0 °C, 4 h</td>
<td>No product</td>
</tr>
<tr>
<td>2</td>
<td>1:3</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (10%), CuI (20%), i-Pr\textsubscript{2}NH, THF, 50 °C, 8 h</td>
<td>205 + 221</td>
</tr>
<tr>
<td>3</td>
<td>1:3</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (10%), CuI (20%), Et\textsubscript{3}N, DMF, 0 °C, 4 h</td>
<td>205 + 221</td>
</tr>
<tr>
<td>4</td>
<td>1:2</td>
<td>Pd(OAc)\textsubscript{2} (10%), PPh\textsubscript{3} (40%), CuI (20%), Et\textsubscript{3}N, DMF, 0 °C, 4 h</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1:2</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (10%), CuI (20%), i-Pr\textsubscript{2}NH, DMF, 0 °C, 4 h</td>
<td>202 50%</td>
</tr>
<tr>
<td>6</td>
<td>1:3</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (10%), CuI (20%), i-Pr\textsubscript{2}NH, DMF, 50 °C, 4 h</td>
<td>202 80%</td>
</tr>
<tr>
<td>7</td>
<td>1:2</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (10%), CuI (20%), DMF, 50 °C, 4 h</td>
<td>202 90%</td>
</tr>
<tr>
<td>8</td>
<td>1:2</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (10%), CuI (20%), Cs\textsubscript{2}CO\textsubscript{3}, DMF, 50 °C, 4 h</td>
<td>202 60%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} mole ratio of starting materials iodide 203:alkyne 204.
DMSO under a nitrogen atmosphere was heated to 140 °C until complete dissolution occurred. The reaction mixture was stirred for further 15 min before the rapid addition of hydrazine hydrate. Upon complete addition of hydrazine hydrate, immediate cooling of the reaction mixture in a water bath led to crystallisation of the palladium(0) species as a bright yellow solid which could be stored under argon at –26 °C for several weeks without decomposition.

To our delight, changing the palladium source to Pd(PPh$_3)_4$, and the solvent to DMF, facilitated the cross coupling, providing **202** in 80% yield using i-Pr$_2$NH as a base at 50 °C (entry 6, Table 19). In an effort to maximise the yield of the desired product **202**, further optimisation was conducted utilising various bases and temperatures (entries 6-8, Table 19). It was established that use of Pd(PPh$_3)_4$ as the catalyst with CuI as a co-catalyst, i-Pr$_2$NH as the base and two equivalents of alkyne **204** in anhydrous DMF at 50 °C were the optimal conditions for the synthesis of enynone **202** (entry 7, Table 19). Use of the inorganic base Cs$_2$CO$_3$ in the presence of Pd(PPh$_3)_4$ and CuI in anhydrous DMF at 50 °C afforded the desired product **202** in 60% yield (entry 8, Table 19). It was also worth mentioning that using these conditions the reaction worked well on both small and gram scale reactions (1 g of iodide **203**). The successful synthesis of enynone **202** was confirmed by $^1$H and $^{13}$C NMR spectroscopy and HRMS analysis.
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5.1.5 Summary of Synthesis of Enynone 202

As depicted in Scheme 101, the convergent synthesis of enone 202 was accomplished in three linear steps via palladium catalysed Sonogashira cross coupling between iodide 203 and alkyne 204 as the key step. Iodide 203 was prepared from commercially available cyclopentenone 205 via a regioselective iodination using I2 in the presence of catalytic PDC in quantitative yield. The other coupling partner alkyne 204 was synthesised via nucleophilic addition of lithium acetylide- ethylenediamine complex to (R)-propylene epoxide (208) which is readily accessible via HKR of commercially available (+) propylene epoxide (208).

Scheme 101 Synthesis of enone 202. Reagents and conditions: i) I2, PDC, 0 °C to r.t., 4 h, quant.; ii) Jacobsen catalyst (209), H2O, 12 h, 45%; iii) lithium acetylide, ethylene diamine complex, DMSO, 0 °C to r.t., 24 h, quant.; iv) TBSCI, imidazole, CH2Cl2, r.t., 4 h, quant.; v) Pd(PPh3)4, CuI, i-Pr2NH, DMF, 50 °C, 4 h, 90%.

5.1.6 Attempted Michael Addition of Enynone 202 to Pyrone 177

Having established the optimal conditions for the Sonogashira cross coupling, attention turned to the assembly of spiroketal precursor 225 via Michael addition of pyrone 177 to enynone 202.

Scheme 102 Michael addition of pyrone 177 and enynone 202.

In general, asymmetric organocatalytic Michael additions proceed smoothly at ambient temperature in the absence of an external base, with no observable formation of by-products. Recently, the scope
of such organocatalytic asymmetric Michael reactions was expanded to include the use of \( \alpha,\beta \)-unsaturated enones with 4-hydroxypyrones as the nucleophiles.

In 2003, Jørgensen reported the first organocatalyst-directed asymmetric Michael addition of 4-hydroxypyrone compounds to \( \alpha,\beta \)-unsaturated enones using imidazolidine derivatives (226). A number of 4-hydroxypyrone compounds and \( \alpha,\beta \)-unsaturated enones were screened in a variety of solvents to probe the reliability and enantioselectivity of the reaction. It was revealed that using 1.05 equivalents of enone 227 and one equivalent of Michael donor 177 in the presence of 10 mol\% of 226 in CH\(_2\)Cl\(_2\) gave the best yield and enantioselectivities (Scheme 103).

![Scheme 103](image.png)

**Scheme 103** Michael addition of pyrone 177 using enone 227. **Reagents and conditions:** i) 226 (10\%), CH\(_2\)Cl\(_2\), r.t., 150 h, 76\%, 85\% ee.

Encouraged by these results, we attempted our Michael reaction using the commercially available L-proline to test the methodology due to the cost and arduous work involved in preparing these reported catalysts. L-Proline has been widely used in asymmetric Michael additions and was therefore used in the present study. We attempted the desired Michael reaction using these conditions (entry 1-4, Table 20). Typically, catalytic L-proline was added to a solution of pyrone 177 and enynone 202 in anhydrous CH\(_2\)Cl\(_2\) with stirring at room temperature. After stirring at room temperature for several hours, only the starting materials were observed by TLC analysis (entry 1, Table 20). Further attempts were conducted at an elevated temperature 40 °C, however, these conditions, proved to be fruitless (entry 2, Table 20). Stoichiometric amounts of (L)-proline were next utilised, although no observable product was formed as indicated by TLC analysis (entry 3, Table 20). Changing the solvent to DMSO was unrewarding resulting in the recovery of both starting materials (entry 4, Table 20).
Table 20. Attempted Michael reaction between pyrone 177 and enynone 202.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>L-proline(^a)</td>
<td>CH(_2)Cl(_2)</td>
<td>r.t.</td>
<td>50 h</td>
<td>b</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>L-proline</td>
<td>CH(_2)Cl(_2)</td>
<td>40</td>
<td>40 h</td>
<td>b</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>L-proline</td>
<td>CH(_2)Cl(_2)</td>
<td>40</td>
<td>50 h</td>
<td>b</td>
</tr>
<tr>
<td>4</td>
<td>1.1:1</td>
<td>L-proline(^b)</td>
<td>DMSO</td>
<td>r.t. to 50</td>
<td>50 h</td>
<td>b</td>
</tr>
<tr>
<td>5</td>
<td>1:1</td>
<td>CH(_3)CO(_2)H</td>
<td>CH(_2)Cl(_2)</td>
<td>r.t.</td>
<td>12 h</td>
<td>b</td>
</tr>
<tr>
<td>6</td>
<td>1:1</td>
<td>p-TSA(^b)</td>
<td>CH(_2)Cl(_2)</td>
<td>r.t. to 40</td>
<td>12 h</td>
<td>b</td>
</tr>
<tr>
<td>7</td>
<td>1:1</td>
<td>PPTS(^b)</td>
<td>CH(_2)Cl(_2)</td>
<td>r.t. to 40</td>
<td>12 h</td>
<td>b</td>
</tr>
<tr>
<td>8</td>
<td>1:1</td>
<td>...</td>
<td>HO(CH(_2))(_2)OH</td>
<td>r.t.</td>
<td>12 h</td>
<td>b</td>
</tr>
</tbody>
</table>

\(^a\): 0.5 equivalents of catalyst were employed. Otherwise stoichiometric amounts of catalysts were employed. 
\(^b\): No desired product was observed.

In view of these disappointing results obtained, we next attempted a racemic Michael addition employing a Brønsted acid. In parallel, acetic acid and PPTS were added to a mixture of pyrone 177 and enynone 202 at room temperature in a variety of solvents and temperatures (entries 5-7, Table 20). No desired product was obtained under these conditions. \(^1\)H and \(^13\)C NMR studies of the crude products revealed the presence of both starting materials.

Ethylene glycol has commonly been employed as a solvent in a racemic Michael reaction and was next investigated. Disappointingly, this modification also proved unrewarding (entry 8, Table 20).

It was postulated that although electron-deficient \(\alpha,\beta\)-enone systems readily undergo Michael addition, the triple bond present in enynone 202 could also serve as an electron-donating group. Thus, Michael acceptor 202 may be unsuitable for this conjugate addition reaction.

5.1.7 Attempted Hydration of Enynone 202

It was therefore decided to convert alkyne 202 to diketone 229 which is expected to be a more reactive Michael acceptor (Scheme 104). We hence sought to address the issue of the presence of the acetylene in enynone 202 via hydration of the existing alkyne to a carbonyl functionality 229\(^a\) or 229\(^b\) (Scheme 104) to increase the reactivity of the Michael donor.
Alkynes have been used extensively as masked carbonyl groups, which can be hydrated to give ketones employing various metal catalysts such as Hg(II),\textsuperscript{219} Au(I),\textsuperscript{220} Au(II),\textsuperscript{221} Pt(II)\textsuperscript{222} and Ag\textsuperscript{223} in the presence of Brønsted or Lewis acids. Among these available conditions, the most reliable method is mercury-catalysed hydration of alkynes that was known as early as 1881.\textsuperscript{224} Acidic mercury sulfate has shown to catalyse the hydration of alkynes. In recent times, the application of this reaction has fallen due to the toxicity of mercuric salts and harsh reaction conditions utilised, as acid-sensitive functional groups frequently do not survive the reaction. Alternatively, 1,3-carbonyl-acetylene systems have been reported by Jennings and co-workers to yield 1,4-dicarbonyl compounds in the presence of Pt(II) in 1994.\textsuperscript{222} While in 2010 Oh and co-workers demonstrated a general synthetic pathway to access highly substituted furans from enynone using a Pt(II) catalyst.\textsuperscript{225} However, this transformation was not successful for enynone 230 (Scheme 105).

Classic methods were investigated to convert enynone 202 to 1,3-diketone 229 employing mercuric sulfate generated \textit{in situ} from mercuric oxide and sulphuric acid. However, a Scifinder® search revealed no literature precedent for hydration of a highly conjugated system such as enynone 202. We therefore attempted to devise a Hg(II) catalysed hydration method to effect the synthesis of dicarbonyl 229\textsubscript{a} or 229\textsubscript{b}.

Accordingly, mercuric oxide was added to a concentrated solution of H\textsubscript{2}SO\textsubscript{4} at room temperature with stirring for one hour, delivering a suspension of mercuric sulfate. A solution of enynone 202 in methanol was added to the above solution with stirring then the mixture was heated to 60 °C.
The starting material was fully consumed within 30 minutes as indicated by TLC analysis. $^1$H and $^{13}$C NMR analysis of the purified product 229 confirmed the formation of a new compound containing a carbonyl functional group and a methyl ether after purification by column chromatography (entry 1, Table 21). It was reasoned that the protic solvent methanol provided the kinetic hydration product. It was therefore decided to trial the hydration in an aprotic solvent in order to avoid formation of methyl ether 229c. Accordingly, a solution of enynone 202 in dioxane was subjected to the aqueous mercuric sulfate solution prepared as above. After stirring at 80 °C for two hours, a new spot was observed by TLC analysis. Upon work-up, an olefin was present in the product as indicated by the $^1$H and $^{13}$C NMR spectrum. Careful analysis of the spectroscopic data showed that elimination of the secondary alcohol at C-4’ had occurred during the hydration step, giving diketone 229d in 55% yield (entry 2, Table 21).

**Table 21. Attempted hydration of enynone 202.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>HgO/H$_2$SO$_4$</td>
<td>MeOH:H$_2$O</td>
<td>60</td>
<td>3 h</td>
<td>85%</td>
</tr>
<tr>
<td>2a</td>
<td>HgO/H$_2$SO$_4$</td>
<td>Dioxane:H$_2$O</td>
<td>80</td>
<td>2 h</td>
<td>42%</td>
</tr>
<tr>
<td>3b</td>
<td>HgO/H$_2$SO$_4$</td>
<td>MeOH</td>
<td>r.t.</td>
<td>4 h</td>
<td>75%</td>
</tr>
<tr>
<td>4b</td>
<td>HgO/H$_2$SO$_4$</td>
<td>Dioxane</td>
<td>r.t.</td>
<td>12 h</td>
<td>87%</td>
</tr>
<tr>
<td>5b</td>
<td>Hg(OAc)$_2$/H$_2$SO$_4$</td>
<td>MeOH</td>
<td>50 °C</td>
<td>0.5 h</td>
<td>76%</td>
</tr>
<tr>
<td>6b</td>
<td>Hg(OAc)$_2$/H$_2$SO$_4$</td>
<td>Dioxane</td>
<td>r.t.</td>
<td>4 h</td>
<td>55%</td>
</tr>
<tr>
<td>7b</td>
<td>Hg(OAc)$_2$/H$_2$SO$_4$</td>
<td>MeOH:H$_2$O</td>
<td>r.t.</td>
<td>0.5 h</td>
<td>52%</td>
</tr>
<tr>
<td>8b</td>
<td>Hg(OAc)$_2$/H$_2$SO$_4$</td>
<td>Dioxane:H$_2$O</td>
<td>r.t.</td>
<td>24 h</td>
<td>65%</td>
</tr>
</tbody>
</table>

a: HgO was added to a solution to sulphuric acid at room temperature followed by addition of enynone 202. b: Sulphuric acid was used as H$_2$SO$_4$ on silica.

In light of the formation of the undesired methyl ether 229c, attempted hydration was further conducted under anhydrous conditions at room temperature using a silica-supported H$_2$SO$_4$. H$_2$SO$_4$ on silica was prepared using the methodology developed by Saari. Accordingly, a concentrated solution of H$_2$SO$_4$ (98%) was added to a stirred suspension of silica gel in Et$_2$O (1/50/200, v/w/v).
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After stirring at room temperature for 1 h, the solvent was evaporated under reduced pressure. The resulting solid was placed in an oven at 120 °C for 3 h affording H$_2$SO$_4$-silica as a white solid that can be stored for several weeks without loss of activity.

In parallel, the desired hydration reactions were performed using HgO in the presence of catalytic H$_2$SO$_4$ on silica at room temperature in both anhydrous methanol and dioxane (entries 3-4, Table 21). Disappointingly, these conditions afforded the methyl ether 229c in comparable yields after purification by flash column chromatography.

Upon searching the literature, it was revealed that milder conditions using Hg(OAc)$_2$ in the presence of catalytic H$_2$SO$_4$ on silica had been found to be effective to deliver the related diketones. Mercuric acetate was added to the pre-activated silica followed by addition of enynone 202 in either anhydrous methanol or dioxane (entries 5-6, Table 21). The reaction conducted in methanol was found to be complete in one hour at 50 °C, cleanly affording the undesired eliminated byproduct 229d in 76% yield (entry 5, Table 21). The reaction performed in anhydrous dioxane afforded a moderate yield of diketone 229e after stirring at room temperature for 4 h in the presence of Hg(OAc)$_2$ and catalytic H$_2$SO$_4$ on silica (entry 6, Table 21). Shorter reaction times gave a similar result (entries 5-6, Table 21). The formation of 229c, 229d and 229e was established by $^1$H and $^{13}$C NMR spectra and HRMS analysis.

Further attempts employing aqueous methanol and dioxane as the solvent at room temperature delivered similar disappointing results (entries 7-8, Table 21). These two conditions afforded the dicarbonyl 229e in 52% and 65% yield, respectively.

Based on these results, it was concluded that the mercuric-mediated alkyne hydration exclusively afforded the 1,4-diketone products 229c, 229d and 229e, and that the TBS protected silyl ether 202 was not tolerant to the acidic reaction conditions. Moreover, it was ascertained that the alcohol deprotection/elimination (entries 2, 3, 5, Table 21) or deprotection/methyl protection (entry 1, Table 21) occurred faster than alkyne hydration. Importantly, it was established that molecules containing similar conjugated systems to enynone 202 were not able to afford 1,3-dicarbonyl compounds via metal catalysed hydration.

Hg(II) complexes, as soft Lewis acids, have affinity for alkynes, allenes and alkenes. These multiple carbon-carbon bonds can be activated in the presence of hard Lewis bases such as carbonyl groups. The possible mechanistic pathway for the hydration reaction is depicted in Scheme 106. It is proposed that Hg (II)-catalysed triple bond hydration proceeds through a 5-endo-dig cyclisation. Upon coordination of the triple bond of enynone 202, the enhancement of
electrophilicity of the alkyne results in subsequent attack of the carbonyl oxygen atom on the
electron-deficient position C-5 to effect the exclusive formation of TS-232. Consequently,
nucleophilic addition by H2O occurs exclusively at the C-5 carbon affording Hg-carbon enol
intermediate TS-232 that undergoes tautomerisation to give the product, diketone 229.

Scheme 106 Proposed Mechanism for Hg(II)-catalysed hydration of enynone 202.

Further investigation on this reaction focused on the use of Au(I) as the metal promoter. The most
important property of gold catalysts is that they are soft Lewis aids, that would lead to exclusive
coordination to soft Lewis bases. AuCl and AuCl3 are known to be efficient in catalytic
transformations, particularly in those involving carbon-carbon triple and double bonds. For
activation of carbon-carbon triple bonds, AuCl itself was not efficient as a catalyst, so activation
was required. To make more efficient cationic gold catalysts, silver salts with a non-coordinating
counterion are usually used to abstract the chloride. The commonly used counterions of silver salts
are OTf, BF4, SbF6, PR3, NTF2.

In 2006, Krause and Belting demonstrated the use of Au(I) and Au(III) as a mild and efficient
catalyst to achieve a tandem cycloisomerisation-hydroalkoxylation of homopropargylic alcohols in
the presence of various additives providing the products in good yield and diastereoselectivity
(Scheme 107).
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Scheme 107 Au(I) catalysed tandem cycloisomerization-hydroalkoxylation of homopropargylic alcohol 233. 

Reagents and conditions: i) Ph₃PAuCl, AgBF₄, p-TsOH, EtOH, 1 h, 77%; ii) PPh₃AuCl, AgBF₄, EtOH, r.t., 8 h, 30%, 23₄a:23₄b 25:75.

The proposed mechanism for the gold-catalysed cyclisation is depicted in Figure 29. Au(I) or Au(III) coordinates to the triple bond of substrate 233 affording the π-conjugated complex 235, that then undergoes nucleophilic attack by the oxygen to give the σ-gold complex 236. Protodeauration of 236 releases 2,3-dihydrofuran 23₄b and the gold catalyst into the first catalytic cycle. The resultant dihydrofuran 23₄b then enters the acid catalysed cycle and forms the anion 237 in the presence of a proton. Nucleophilic attack of the alcohol R'OH to the preformed carbon caution 237 then leads to the formation of oxygen cation 23₈. Final deprotonation of 23₈ completes the acid catalyst cycle and discharges the cyclic acetal 23₄a.

Figure 29. Proposed mechanism for gold-catalysed cyclisation.

Encouraged by the successful cyclisation result reported by Krause and Belting,²²⁰ we next investigated the use of gold catalysed alkyn cyclisation in the desire to prepare hemiketal 22₉b from alkyn 20₂. Enynone 20₂ was first subjected to a solution of TBAF buffered with stoichiometric amount of acetic acid in THF at room temperature to afford hydroxy enynone 23₉ in 95% yield without further purification required (Scheme 108). In comparing the reactivity of AuCl and AuCl₃, it is known that AuCl is superior due to its softer properties, thus AuCl is able to
selectively coordinate to a carbon-carbon triple bond in the presence of carbonyl or amino groups.\textsuperscript{229} We therefore focused on the investigating the feasibility of gold catalysed cyclisation using only gold(I) as the catalyst.

With hydroxy enynone \textbf{239} in hand, gold catalysed cyclisation was carried out using AuCl in the presence of the counterion salt, AgBF\textsubscript{4}. However, upon stirring hydroxy enynone \textbf{239} in the presence of AuCl and AgBF\textsubscript{4} at room temperature for one hour, no desired product was observed as indicated by TLC analysis. It was postulated that \textbf{229\textsubscript{g}} might be a volatile product. Hence, we attempted the alkyne cyclisation of enynone \textbf{239} by conducting the reaction in methanol in order to yield a less volatile molecule \textbf{229\textsubscript{g}}. Disappointingly, no product was obtained and only degradation of enynone \textbf{239} was observed.

![Scheme 108 Attempted synthesis of hemiketal \textbf{229\textsubscript{b}, Reagents and conditions: i) TBAF, THF, r.t., 2 h, 95%; ii) AuCl (10%), AgSbF\textsubscript{6} (10%), CH\textsubscript{2}Cl\textsubscript{2}, r.t., 1 h or JohnPhosAu(MeCN)SbF\textsubscript{6} (10%), CH\textsubscript{2}Cl\textsubscript{2}, r.t., 2 h.}]

We next changed the silver salt to a milder counterion AgSbF\textsubscript{6} in CH\textsubscript{2}Cl\textsubscript{2} using AuCl. This modification proved to be unrewarding using both CH\textsubscript{2}Cl\textsubscript{2} and methanol as solvents, in that only decomposition of enynone \textbf{239} was observed.

Upon searching literature, it was revealed that use of excess amounts of the silver salt leads to the formation of undesired byproducts.\textsuperscript{230} We thus investigated silver-free conditions using another commercially available gold(I) catalyst that was developed by Echavarren and Nevado in 2005.\textsuperscript{231} (Acetonitrile)[(2-biphenyl)di-\textit{tert}-butylphosphine]gold(I) hexafluoroantimonate (JohnPhos Au(MeCN)SbF\textsubscript{6}), also known as Echavarren gold catalyst is a strongly activating catalyst in a variety of reactions that contains the weakly coordinating ligand acetonitrile. Accordingly, JohnPhos Au(MeCN)SbF\textsubscript{6} was added to a solution of enynone \textbf{239} in CH\textsubscript{2}Cl\textsubscript{2}, dioxane or methanol respectively, at room temperature for one hour. Regrettably, these did not afford any of the desired product \textbf{229\textsubscript{b}}, \textbf{229\textsubscript{f}} or \textbf{229\textsubscript{g}}; only degradation of the starting material \textbf{239} was observed.

In conclusion, all efforts towards effecting regioselective formation of 1,3-dicarbonyl \textbf{229\textsubscript{a}} or \textbf{229\textsubscript{b}} \textit{via} a Hg(II) catalysed alkyne hydration of enynone \textbf{202} were plagued by formation of the undesired
byproducts 229\textsubscript{c}, 229\textsubscript{d} and 229\textsubscript{e}. Using a variety of Au(I) catalysts as soft Lewis acids all resulted in decomposition of enynone 239 both in the presence of a silver salt or in the absence of a silver salt. It was therefore decided to seek an alternative approach to access pyrone enynone 225.

5.1.8 Summary of Attempted Synthesis of Pyrone Enynone 225 from Pyrone 177 and Enynone 202

Attempted synthesis of the key spiroketal precursor 225 was conducted via a Michael reaction between 2-pyrone 177 and enynone 202 in the presence of a variety of catalysts; however, this strategy proved to be problematic. It was postulated that the presence of a triple bond in the \(\alpha,\beta\)-conjugated system prevented the desired Michael addition from taking place. Hence, a regioselective hydration of the carbon triple bond was investigated to deliver a 1,3-dicarbonyl component using Hg(II) in the presence of a Brønsted acid. Use of a variety of mild conditions to afford the requisite 1,3-dicarbonyl 229 was un.rewarding and the formation of a mixture of regioisomers 229\textsubscript{c}, 229\textsubscript{d}, 229\textsubscript{e} was obtained (Scheme 109).

Use of Au(I) catalysts resulted in complete decomposition of enynone 239 in the presence of a variety of ligands in either aprotic or protic solvents.
In view of the disappointing results obtained from the direct Michael addition of pyrone 177 to enynone 202 (Section 5.1.6) and the unsuccessful regioselective hydration of the enynone 202 and 239 (Section 5.1.7), the Michael addition/gold catalysed spiroketalisation strategy was abandoned. A strategy employing a CeCl₃-promoted 1,2-carbonyl addition approach to access the spiroketal precursor 225 was next investigated (vide infra).
5.2 Attempted Synthesis of Spiroketalisation Precursor 240 via a CeCl₃-Mediated 1,2-Carbonyl Addition to Vinylogous Ether 243

In light of the difficulties encountered in assembling the key spiroketalisation precursor 240 to 3-dehydroxy-tenuipyrone (200) using a Michael addition, an alternative approach based on cerium ion mediated 1,2-carbonyl addition was devised, based on the work reported by Imamoto and co-workers (Section 5.2.4).²¹² A brief overview of this method will be discussed in the following section.

It was envisaged that a cerium ion promoted 1,2-addition of lithiated pyrone species 242 to vinylogous ether 243 to give intermediate 240*, that would undergo a concomitant hydrolysis/elimination under acidic workup to give pyrone enynone 240. Pyrone 241 was anticipated to arise from pyrone 177 via simple protecting group manipulation. Methoxy enynone 243, in turn, is derived from a Sonogashira cross coupling between iodide 244 and alkyne 204.

Scheme 110 Retrosynthetic analysis based on a CeCl₃-promoted 1,2-carbonyl addition.
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5.2.1 Synthesis of Iodide 244

Iodide 244 was synthesised from methoxy ether 245 via iodination. Methoxy enone 245 is a widely used intermediate for the synthesis of natural products. Although 3-methoxy-2-cyclopentenone (245) (491.5 NZD/5 g) is commercially available, we attempted to synthesise this compound 245 from 1,3-diketone 246 (110 NZD/25 g) which is significantly cheaper. By searching literature, methyl ether 245 can be obtained from diketone 246 using toxic dimethyl sulfate or diazomethane in the presence of K₂CO₃ under harsh conditions. In 2001, Porta and co-workers demonstrated a simpler, more practical and higher yielding acetalisation method to convert diketone 246 to enone 245 using TiCl₄ (1-5 mol%). Subsequently, diketone 246 was converted to the known methoxy enone 245 by treatment with catalytic TiCl₄ (1 M in CH₂Cl₂) in methanol at room temperature in 90% yield (Scheme 111). Slightly more TiCl₄ than the literature was required (3-5%), however, no byproduct was observed. The 'H NMR spectroscopic data was in good agreement with the recorded data.

Scheme 111 Synthesis of iodide 244. Reagents and conditions: i) 1 M TiCl₄ in CH₂Cl₂ (10%), CH₃OH, r.t., 1 h, 90%; ii) NIS, TESOTf, CH₂Cl₂, r.t., 24 h, 60%

When this project was initiated, no literature had been published on the synthesis of iodide 244. However, in 2013, Herzon and co-workers reported the synthesis of the iodide 244 using I₂ in the presence of CAN employing the same methoxy enone 245. The desired iodide 244 was obtained in 57% yield after purification by flash column chromatography. In 2009, Clausen and co-workers published a synthesis of griseofulvin analogues (Scheme 112). A variety of enone ethers 247a-c reacted with NIS in the presence of catalytic triethylsilyl trifluoromethanesulfonate (TESOTf) in CH₂Cl₂ at room temperature giving iodides 248a-c in about 19% yield.

Scheme 112 Iodination of 247. Reagents and conditions: i) NIS, TESOTf, CH₂Cl₂, r.t., 24 h, 19% 248a, 19% 248b, 248c, 17%.
We attempted our synthesis of iodide 244 employing these conditions. Gratifyingly, the desired iodide 244 was obtained in 60% yield without further purification required as determined by $^1$H NMR analysis (Scheme 111). Use of a careful work-up procedure was required to neutralise the reaction mixture to pH 7, since an excess amount of an aqueous solution of NaHCO$_3$ resulted in the degradation of iodide 244. $^1$H and $^{13}$C NMR spectroscopic data and HRMS data confirmed the successful preparation of iodide 244.

5.2.2 Synthesis of Methoxy Enynone 243 via Sonogashira Cross Coupling

With iodide 244 in hand, our attention next focused on the assembly of methoxy enynone 243 using a Sonogashira cross coupling strategy. We first tried the optimal conditions developed for the synthesis of enynone 202 (Section 5.1.4) using Pd(PPh$_3$)$_4$ as the catalyst in the presence of CuI and $i$-Pr$_2$NH in DMF at 50 °C. The required enynone 243 was obtained in 56% yield, along with the protodehalogenated byproduct 245 in 15% yield (entry 1, Table 22). Further optimisation was carried out employing a variety of palladium sources and bases (entries 1-7, Table 22).

**Table 22. Synthesis of methoxy enynone alkyne 243.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio$^a$</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2</td>
<td>Pd(PPh$_3$)$_4$ (10%), CuI (20%), $i$-Pr$_2$NH, DMF, 50 °C, 2 h</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>Pd(PPh$_3$)$_4$ (10%), CuI (20%), $i$-Pr$_2$NH, DMF, r.t., 12 h</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>Pd(PPh$_3$)$_4$ (10%), CuI (20%), Et$_3$N, DMF, r.t., 12 h</td>
<td>83%</td>
</tr>
<tr>
<td>4</td>
<td>1:2</td>
<td>Pd(OAc)$_2$ (10%), PPh$_3$ (40%), CuI (20%), Et$_3$N, DMF, 0 °C, 4 h</td>
<td>0$^b$</td>
</tr>
<tr>
<td>5</td>
<td>1:2</td>
<td>Pd(OAc)$_2$ (10%), dtppf (40%), CuI (20%), Et$_3$N, NMP, r.t., 4 h</td>
<td>0$^b$</td>
</tr>
<tr>
<td>6</td>
<td>1:3</td>
<td>Pd(CH$_3$CN)$_2$Cl$_2$ (10%), CuI (20%), [(t-Bu)$_3$PH]BF$_4$, DMF, r.t., 2 h</td>
<td>50%$^c$</td>
</tr>
<tr>
<td>7</td>
<td>1:2</td>
<td>Pd(PPh$_3$)$_4$ (10%), CuI (20%), Cs$_2$CO$_3$, DMF, 50 °C, 4 h</td>
<td>243 30%</td>
</tr>
</tbody>
</table>

a: The ratio of iodide 244:alkyne 204.
b: Protodehalogenated byproduct 245 was obtained.
c: Methoxy enynone 243 was obtained in 50% yield, accompanied with small amount of protodehalogenated byproduct 245.

Conducting the reaction at room temperature using the same catalysts and bases in DMF increased the yield to 86% without observation of protodehalogenated byproduct 245 and alkyne dimer 221.
A comparable 83% yield was obtained by changing the base to triethylamine (entry 2, Table 22). Further attempts to improve the yield of the reaction by changing the palladium sources to (Pd(OAc)$_2$) in the presence of a variety of ligands (PPh$_3$, dtpf) in either DMF or NMP did not give any of the desired product (entry 4-6, Table 22). Use of Pd(CH$_3$CN)$_2$Cl$_2$ in the presence of an electron-rich ligand ([($t$-Bu)$_3$PH]BF$_4$) with CuI as a co-catalyst in anhydrous DMF at room temperature afforded methoxy enynone 243 in 50% yield, accompanied by a small amount of protodehalogenated byproduct 245 (entry 6, Table 22). Finally, Cs$_2$CO$_3$ was investigated as an alternative inorganic base since it has been successfully employed in our group for a related Sonogashira cross coupling for the synthesis of γ-rubromycin.$^{236}$ Disappointingly, this base did not afford any improvement, delivering the cross coupled product 243 in 30% yield (entry 7, Table 22).

Hence, the optimal conditions for the Sonogashira cross coupling between iodide 244 and terminal alkyne 204 were the use of Pd(PPh$_3$)$_4$ as the catalyst and triethylamine or diisopropylamine as the base in the presence of CuI as a co-catalyst in anhydrous DMF at room temperature.

### 5.2.3 Synthesis of Iodide 249

With methoxy enynone 243 in hand, attention turned to the synthesis of the other coupling partner iodo-pyrene 249. In 1998, Cerezo and co-workers reported the synthesis of iodo-pyrene 249 from pyrene 177 over two steps in 77% yield.$^{237}$ We adopted this method for the synthesis of pyrone 249. Accordingly, pyrone 177 was protected as its corresponding methyl ether using (CH$_3$)$_2$SO$_4$ in acetone in the presence of K$_2$CO$_3$ under reflux in 90% yield. Iodination of the resultant methyl ether 241 was carried out using two equivalents of N-iodosuccinimide (NIS) in CH$_3$CN at room temperature to give iodide 249 in 75% yield. Upon searching the literature, it was revealed that a more facile method to effect iodination of dicarbonyl compounds using NIS in the presence of a catalytic amount of Mg(ClO$_4$)$_2$ was described by Yang and co-workers.$^{238}$ Hence, we attempted the synthesis of iodo-pyrene 249 employing these conditions. It was established that these conditions were superior to the aforementioned conditions giving higher yields with a simpler work-up procedure. Typically, pyrone 241 was submitted to 1.1 equivalents of NIS in the presence of 0.2 equivalents of Mg(ClO$_4$)$_2$ in CH$_3$CN delivering iodo-pyrene 249 as a white solid in quantitative yield.$^4$ No further purification was required. The obtained spectroscopic data ($^1$H and $^{13}$C NMR) and melting point of the solid (mp 144-146 °C, [lit. 143-145]$^{237}$) were in good agreement with the literature.

---

$^4$ Caution needs to be taken due to the potential explosiveness of perchlorate salts.
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![Scheme 113](image)

**Scheme 113** Synthesis of iodo-pyrone 249. 
Reagents and conditions: i) (CH$_3$)$_2$SO$_4$, K$_2$CO$_3$, acetone, reflux, 10 h, 90%; ii) NIS, Mg(ClO$_4$)$_2$, CH$_3$CN, 3 h, quant.

5.2.4 Attempted CeCl$_3$-Promoted 1,2-Carbonyl Addition of Lithiated Pyrone 242 to Vinylogous Ether 243

The next step in the synthesis was the 1,2-addition of vinylogous ether 243 using lithiated pyrone 242. We attempted to investigate an efficient and straightforward synthesis of pyrone enynone 240 using a CeCl$_3$-promoted 1,2-carbonyl addition (Scheme 114).

![Scheme 114](image)

**Scheme 114** Cerium ion mediated 1,2-carbonyl addition.

Imamoto and co-workers have extensively investigated the use of organocerium(III) reagents, generated by the reaction of organolithiums with anhydrous cerium(III) halide, to exclusively afford the 1,2-carbonyl addition products.$^{232}$ Organocerium reagents are especially useful reagents for addition to $\alpha,\beta$-conjugated carbonyls and highly enolisable carbonyls, that lead to the exclusive formation of 1,2-carbonyl adducts.$^{232,239,240}$ These results were in contrast to those obtained employing organolithium reagent alone where only trace amounts or none of the 1,2-addition products were isolated. The main driving force for CeCl$_3$-mediated carbonyl additions is postulated to be due to the strong affinity of the cerium ion for the carbonyl groups, as well as the lower basicity of the corresponding organocerium reagents. Hence, we attempted the elaboration of enone acetylene 240 via a CeCl$_3$-mediated carbonyl addition.

In 1992, Crimmins and Dedopoulou demonstrated anhydrous cerium ion promoted 1,2-carbonyl addition of Grignard reagents 250 to vinylogous ether 251 to give the 1,2-addition product 252 as a single regioisomer after workup with aqueous ammonium chloride (Scheme 115).$^{241}$ The postulated mechanism for the selective 1,2-carbonyl addition was due to the activation of the carbonyl carbon by cerium ion coordinating to oxygen. The resultant 1,2-addition intermediate TS-
252 undergoes hydrolysis and elimination upon addition of aqueous ammonium chloride solution. It was also reported that cerium salts acted as a weak Lewis acid to aid the hydrolysis-elimination process to yield the desired product.

Scheme 115 1,2-carbonyl addition of vinylogous ether 251 using Grignard reagent 250. Reagents and condition: i) CeCl₃, THF, sat. aq. NH₄Cl, 80%.

In order to obtain the required anhydrous cerium(III) halide, anhydrous CeCl₃ from AK Scientific® were dried under vacuum, using a slow, stepwise heating process as described by Conlon and co-workers. Consequently, commercially anhydrous CeCl₃ (AK Scientific®) was quickly added to a round bottomed flask with a stirring bar under nitrogen. The flask was immersed in an oil bath and heated to 70 °C under vacuum (∼1 mbar). The CeCl₃ powder was stirred under these conditions for 7 h. The oil bath was then slowly heated to 100 °C and kept at this temperature for 12 h with stirring under vacuum. It was further slowly heated up to 140 °C and kept at this temperature for 24 h. THF was added to the fine grey powder obtained followed by addition of t-BuLi (1.6 M in pentanes) at −78 °C under argon until a consistent orange colour appeared, indicating that the mixture was completely anhydrous.

Scheme 116 Synthesis of pyrone 240. Reagents and conditions: i) CeCl₃, n-BuLi, THF, −78 °C, sat. aq. NH₄Cl, 4 h, 70%.
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Initially, the pre-formed pyrone lithium species was added to a suspension of CeCl$_3$ as demonstrated by Crimmins and Dedopoulou.$^{241}$ n-BuLi (1.6 M in hexanes) was added to a solution of pyrone 241 in anhydrous THF at $-78^\circ$C. A red colour occurred spontaneously upon the addition of n-BuLi indicating the successful lithiation of pyrone 241. The resultant red solution was transferred to the CeCl$_3$-THF suspension via cannula at $-78$ °C in THF under argon to prompt an in situ metal exchange. After stirring at $-78$ °C for one hour under argon, the vinylogous ether 243 was added at the same temperature. A slow disappearance of red colour was observed. Upon work-up, the desired product 240 was obtained in 70% yield. However, the reaction was found to be hard to reproduce.

Upon searching the literature, it was revealed that the sequence of the addition of CeCl$_3$ was critical for the 1,2-carbonyl addition.$^{244}$ In 1999, Corey and co-workers demonstrated an enantioselective synthesis of aspidophytine featuring a 1,2-carbonyl addition via an organocerium reagent generated in-situ from Grignard reagent 253 and anhydrous CeCl$_3$ (Scheme 117).$^{245}$ Anhydrous CeCl$_3$ was pre-mixed with vinylogous ether 254 in THF followed by addition of Grignard reagent 253. Acidic-work up yielded the 1,2-addition product 255 in 82% yield after purification by column chromatography.

![Scheme 117 Synthesis of aspidophytine. Reagents and conditions: i) CeCl$_3$, THF, then H$_3$O$,^+$, 82%.](image)

The reverse addition was thus investigated. Vinylogous ether 243 was added to the anhydrous CeCl$_3$ suspension in anhydrous THF to induce precomplexation followed by addition of lithiated species 242 at $-78$ °C. Regrettably, the desired product was not observed.

Considering the tedious work involved in preparing anhydrous CeCl$_3$, an alternative strategy based on a palladium catalysed Stille cross coupling of an organostannane compound 256 derived from methoxy enynone 243 with iodopyrone 249 was devised (vide infra).
5.2.5 Summary of Attempted CeCl₃-Promoted 1,2-Carbonyl Addition

As depicted in Scheme 118, the synthesis of pyrone enynone 240 was based on a key CeCl₃ promoted 1,2-carbonyl addition between lithiated pyrone 242 and vinylogous ether 243. Compounds 242 and 243, in turn, were readily synthesised from commerically available 2-pyrene 177 and 1,3-diketone 246, respectively. 2-Pyrene 177 was first protected as its corresponding methyl ether 241 using (CH₃)₂SO₄ in acetone in 90% yield. A modified iodination of 2-pyrene 241 using NIS in the presence of catalytic Mg(ClO₄)₂ yielded iodide 249 in quantitative yield. In parallel, TiCl₄ catalysed methyl ether formation followed by iodination using NIS in the presence of TESOTf afforded iodide 244 in 54% over two steps from 1,3-diketone 246. A palladium catalysed Sonogashira cross coupling between iodide 244 and alkyne 204 delivered the required enynone 243 in 86% yield.

A CeCl₃-promoted 1,2-carbonyl addition between lithiated pyrone 242 and enynone 243 successfully afforded the desired product 240 in 70% yield. However, this reaction was hard to reproduce and also it was very difficult to perform the reaction on both small and gram scale due to the challenge of preparing anhydrous CeCl₃.

Scheme 118 Attempted synthesis of pyrone enynone 240. Reagents and conditions: i) (CH₃)₂SO₄, K₂CO₃, acetone, reflux, 10 h, 90%; ii) NIS, CH₃CN, Mg(ClO₄)₂, 3 h, quant.; iii) 1 M TiCl₄ in CH₂Cl₂ (10%), CH₃OH, r.t., 1 h, 90%; iv) NIS, TESOTf, CH₂Cl₂, r.t., 24 h, 60%; v) alkyne 204, Pd(PPh₃)₄ (10%), CuI (20%), i-Pr₂NH, DMF, r.t., 12 h, 86%; vi) CeCl₃, n-BuLi, THF, –78°C, 2 h, 70%.
5.3 Stille Approach to Synthesise Pyrone Enynone 240 from Iodo-pyrone 249 and Tributylstannane 256

In view of the disappointing results obtained from the attempted CeCl$_3$-promoted 1,2-carbonyl addition, it was decided to investigate a more reliable strategy to elaborate pyrone enynone 240 via Stille cross coupling using iodo-pyrone 249 and tributylstannane 256 as the coupling partners (Scheme 119). It was envisaged that methoxy enynone 243 could be easily converted to the corresponding organostannane compound 256, that can be used as a Stille cross coupling partner with iodo-pyrone 249 to give pyrone enynone 240. Hence, attention moved to the synthesis of tributylstannane 256 from methoxy enynone 243.

![Scheme 119 Anticipated Stille cross coupling to synthesis alkyne 240.](image)

5.3.1 Synthesis of Tributylstannane 256

In 1987, Piers and co-workers reported the use of (trialkylstannyl)copper(I) reagents that react with $\alpha,\beta$-unsaturated carbonyl compound 257 to yield $\beta$-trialkylstannyl $\alpha,\beta$-unsaturated ketone 258 (Scheme 120). The procedure was impractical for large scale synthesis due to the requirement to prepare $\beta$-iodo enone 257 and the use of the unstable and highly oxygen sensitive copper(I) reagent Li[n-Bu$_3$SnCuSPh].

![Scheme 120 Synthesis of tributylstannane 258. Reagents and conditions: i) Li[n-Bu$_3$SnCuSPh], THF, –20°C, 76%.](image)

In 1990, Laborde and co-workers demonstrated a facile synthesis of the antibacterial quinolone 259 using a palladium catalysed Stille cross coupling of organostannane compounds 258 and triflate.
A more reliable and feasible route to organostannane was executed by a 1,2-carbonyl addition using a lithium tributylstannane species and ethoxy enone. The desired tributylstannane was obtained in 70-85% yield. The subsequent Stille cross coupling between triflate and tributylstannane furnished the coupled product in 88% yield using Pd(PPh)$_3$Cl$_2$ in the presence of LiCl in THF under reflux.

![Scheme 121 Synthesis of quinolone. Reagents and conditions: i) (Bu$_3$Sn)$_2$, n-BuLi, −78 °C to 0 °C, 2 h, 70-85%; ii) Pd(PPh)$_3$Cl$_2$, LiCl, THF, reflux, 12 h, 88%.

Although the aforementioned conditions appeared to be a robust option to prepare organostannane, the use of (SnBu$_3$)$_2$ proved practically challenging as the required stannane reagent ((Bu$_3$Sn)$_2$) is a sea freight item that would take at least six to twelve months to ship into Auckland. The other drawback is the formation of stoichiometric highly toxic Bu$_4$Sn during the lithiation step. These early disadvantages prompted us to investigate an alternative strategy to prepare tributylstannane.

Considering the species that reacts with the 1,2-carbonyl is lithiated tributylstannane, we attempted the synthesis of tributylstannane via direct lithiation of commercially available Bu$_3$SnH with a variety of lithium reagents (Table 23). Similar to the method published by Laborde and co-workers, tributyltin hydride was added to a freshly prepared solution of lithium diisopropylamide (LDA) in THF at 0 °C (entry 1, Table 23). The lithiated species was allowed to develop for ten minutes before addition of methoxy enynone in THF at −20 °C. Gratifyingly, organostannane was successfully synthesised, albeit in only 35% yield after purification by column chromatography.
Table 23. Attempted optimisation of the synthesis of tributylstannane 256.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Ratio*</th>
<th>T^1</th>
<th>T^2</th>
<th>T^3</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>1:1:1:1</td>
<td>–78 °C, 10 min</td>
<td>0 °C, 10 min</td>
<td>–20 °C, 2 h</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>1:1.1:1:1:1</td>
<td>–78 °C, 20 min</td>
<td>0 °C, 20 min</td>
<td>–20 °C, 2 h</td>
<td>42%</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>1:1.1:1:1:1:1</td>
<td>–78 °C, 30 min</td>
<td>0 °C, 30 min</td>
<td>0 °C, 2 h</td>
<td>45%</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>1.5:1.5:1.4:1</td>
<td>–78 °C, 30 min</td>
<td>0 °C, 30 min</td>
<td>0 °C, 2 h</td>
<td>23%^b</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>1:1:1:1:0.8</td>
<td>–78 °C, 30 min</td>
<td>0 °C, 30 min</td>
<td>–20 °C, 4 h</td>
<td>35%^c</td>
</tr>
<tr>
<td>6</td>
<td>LDA</td>
<td>1:1:1:1:1</td>
<td>–78 °C, 1 h</td>
<td>0 °C, 1 h</td>
<td>0 °C, 2 h</td>
<td>43%</td>
</tr>
<tr>
<td>7</td>
<td>Et₂NLi</td>
<td>1:1:1:1:1:1</td>
<td>–78 °C, 30 min</td>
<td>0 °C, 30 min</td>
<td>–20 °C, 2 h</td>
<td>55%</td>
</tr>
<tr>
<td>8</td>
<td>LiTMP^d</td>
<td>1:1:1:1:1:1</td>
<td>–78 °C, 30 min</td>
<td>0 °C, 30 min</td>
<td>–20 °C, 2 h</td>
<td>0</td>
</tr>
</tbody>
</table>

T^1 is the temperature at which n-BuLi is added and the time elapsed before the addition of Bu₃SnH.
T^2 is the temperature at which Bu₃SnH is added and the time elapsed before the addition of enone ether 243.
T^3 is the temperature at which enone ether 243 is added and the time elapsed before the addition of saturated aqueous solution of NH₄Cl.
b: di(tributylstannane) substituted 262 was obtained.²⁴⁸
b: reverse addition of a solution of Bu₃SnLi in THF to 243 in THF at –20 °C.
d: LiTMP is lithium tetramethylpiperidine.

Several conditions were next examined for optimising the preparation of organostannane 256. Prolonging the period for the formation of the lithiated species to 20 min afforded a higher yield, allowing organostannane 256 to be isolated in 42% yield after purification by column chromatography (entry 2, Table 23). Further experiments indicated a positive correlation between the time that the tributylstannane lithiated species was allowed to develop and the product yield (entries 1-3, Table 23). Delaying the time at which the reaction was quenched (i.e. longer time for reaction between the enone 243 and the lithiated intermediate [Bu₃SnLi]) also increased the product conversion (entries 3-4, Table 23). However, reversing the addition sequence by adding the [Bu₃SnLi] lithiated species to the methoxy enynone 243 solution was unrewarding, giving a lower yield (entry 5, Table 23). Increasing the ratio of lithiated species ([Bu₃SnLi]) to methoxy enynone 243 (entry 6, Table 23) had a detrimental effect and resulted in a lower reaction yield, due to the formation of a bis(tributylstannane) substituted compound 262. Additional attempts to improve the reaction yield by using a less sterically hindered base LiEt₂N proved to be successful, however, this
was found to be poorly reproducible giving yields from 10-35% (entry 7, Table 23). Regrettably, the use of sterically demanding bases such as LiTMP was unrewarding (entries 8, Table 23).

It is also important to note that the reaction yield was highly dependent on the quality and the age of the tributyltin hydride used. Using tributyltin hydride that had been opened for a long time was detrimental to the reaction. It was suspected that old tributyltin hydride was diluted with tributyltin oxide byproduct due to the presence of a white suspension. This could also explain the low yield of conversion of enone ether 243 to organostannane 256.

\(^1\text{H}\) and \(^{13}\text{C}\) NMR and IR spectra analysis of the freshly opened tributylstannane hydride established a maximum concentration of 60% of the desired reagent. Use of this fresh unopened bottle from Sigma-Aldrich® did not give any of the desired product 256.

In accordance with the optimal coupling conditions highlighted above (entry 3, Table 23), neat tributyltin hydride was quickly added to a solution of freshly prepared LDA in THF at 0 °C. After stirring for half an hour at this temperature, a solution of enone 243 in THF was added at –78 °C and the reaction mixture allowed to stir at this temperature for ten minutes before it was warmed to –20 °C for two hours, affording stannane 256 in 45% yield.

In view of the low yield obtained in the synthesis of organostannane 256 and the expensive reagents involved in synthesising this compound, we attempted an alternative approach to prepare compound 256 in order to meet green chemistry principles.

### 5.3.2 An Alternative Approach to Synthesise Organostannane 256 via a key Suzuki Cross Coupling

An alternative approach to synthesise tributylstannane 256 was devised using a key Sonogashira cross coupling of tributylstannane 263 and alkyne 204 (Scheme 122).
A. Synthesis of Bromide 254

The synthesis of tributylstannane 263 relied on the synthesis of the known bromide 254 from 1,3-diketone 246. At the commencement of this synthesis, a straightforward synthesis of bromide 254 from commercially available 3-methoxy-2-cyclopentenone 245 had been reported by Kuethe and co-workers (Scheme 123).249

![Scheme 123 Synthesis of bromide 254. Reagents and conditions: i) NBS, CCl₄, quant.]

As mentioned earlier (Section 5.2.1), an efficient and practical synthesis of the required methyl ether 245 was achieved using catalytic TiCl₄ in methanol. Bromination was carried out using this methyl ether 245 employing the aforementioned conditions. Unfortunately, in our hands the desired bromide 254 was obtained in consistently low yield (30-50%). Hence, a more reliable route to bromide 254 was required.

Upon searching the literature, it was revealed that a variety of methods have been reported for α-bromination of 1,3-dicarbonyl compounds including the use of NBS,250 pyridinium-HBr₃,251 CuBr₂,252 bromine,253 and Dess-Martin periodinane-tetraethylammonium bromide (TEAB) in good to excellent yields.254 Hence we attempted a synthesis of bromide 264 via a bromination-methylation sequence (Scheme 124). Accordingly, mono-bromination of 1,3-diketone 246 was conducted in H₂O using 1.1 equivalents of NBS and 1.1 equivalents of KHCO₃ at room temperature affording α-bromide 264 in 90% yield. Quick addition of saturated aqueous KHCO₃ solution to the suspension of 1,3-diketone 246 should be avoided to prevent vigorous release of carbon dioxide. Upon complete addition of KHCO₃, a clear brown solution was obtained followed by portionwise addition of NBS in one hour. Subsequent addition of 10 M H₂SO₄ to the reaction mixture followed by filtration afforded bromide 264 as a white solid. Toluene was used to remove the residual water by azeotropic distillation. Using the previously established enol ether formation conditions (Section 5.2.1), bromide 246 was subjected with 1 M TiCl₄ in CH₂Cl₂ using methanol as a solvent affording bromide 254 in quantitative yield.
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Scheme 124 Synthesis of bromide 254. Reagents and conditions: i) NBS, KHCO₃, H₂O, 2 h, 90%; ii) TiCl₄ (5%), MeOH, 1 h, quant.

B. Synthesis of Tributylstannane 263

Tributylstannane 263 was obtained in an analogous way as for compound 256 (Section 5.3.1). Using the optimal conditions as developed for compound 256, bromide 254 was subjected to a preformed Bu₃SnLi species at −78 °C. Upon stirring at this temperature for 30 min, the reaction mixture was warmed up to −20 °C with stirring for 2 h. Tributylstannane 263 was obtained in 31% yield upon treatment with aqueous NH₄Cl followed by column chromatography. The side-product from this reaction was assigned to be tributylstannane 258, presumably resulting from the unexpected lithium-halogen exchange of bromide 254. It was thus thought that the production of the side-product 258 could be avoided by using fewer equivalents of the Bu₃SnLi species.

Scheme 125 Synthesis of tributylstannane 263. Reagents and conditions: i) LDA, n-Bu₃SnH, THF, −78 °C to r.t., 3 h, 31%.
C. Attempted Sonogashira Cross Coupling of Tributylstannane 263 to Alkyne 204

With tributylstannane 263 in hand, the desired Sonogashira cross coupling was next attempted using alkyne 204 adopting the optimised conditions for the synthesis of methoxy enynone 243 (Section 5.2.2).

![Scheme 126 Attempted synthesis of tributylstannane 256. Reagents and conditions: i) Pd(PPh₃)₄ (0.1 equiv.), Cul (0.2 equiv.), Et₃N, DMF, r.t., 12 h.]

As depicted in Scheme 126, the attempted Sonogashira cross coupling of tributylstannane 263 and alkyne 204 was unsuccessful, resulting in the recovery of alkyne 204 after workup. It was postulated that protodestannanylation and protodebromination of tributylstannane 263 occurred prior to the desired cross coupling, leading to the formation of a volatile enone 205. Thus an alternative synthesis of tributylstannane was devised.

D. An Alternative Synthesis of Tributylstannane 256 via a Suzuki Cross Coupling of Tributylstannane 263 and Trifluoroborate 265

In 2002, Molander and co-workers demonstrated that for the instances where the Sonogashira coupling failed to deliver the product or proceeded in unacceptable yields, less toxic organoboron compounds are suitable reagents in a wide range of cross couplings.²⁵⁵ Organoboron compounds have been widely investigated especially due to their remarkable oxidative and thermal stabilities. Upon further literature searching, it was established that terminal alkyne 204 could be readily converted to its corresponding alkynylborate 265 via a one pot lithiation-boronation and in situ treatment with aqueous KHF₂, as first documented by Genêt and co-workers in 1999.²⁵⁶

![Scheme 127 A one pot synthesis of trifluoroborate 265. Reagents and conditions: i) n-BuLi, THF, B(Oi-Pr)₃, aq. KHF₂, −78 °C to 0 °C, 90%.]

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Accordingly, the desired trifluoroborate 265 was synthesised from terminal alkyne 204 in 90% yield after recrystallisation. Interestingly, the TBS silyl group was not removed by KHF$_2$ as had been reported by Genêt and co-workers (Scheme 127).\textsuperscript{256}

With alkynylborate 265 in hand, the desired Suzuki cross coupling was next investigated. However, no related literature has been reported regarding the bromide 263. We therefore adopted the classic Suzuki cross coupling conditions as reported by Molander and co-workers.\textsuperscript{255} A thoroughly degassed mixture of tributylstannane 263 and alkynylborate 265 in the presence of Pd(dppf)$_2$Cl$_2$.CH$_2$Cl$_2$ and Cs$_2$CO$_3$ in aqueous THF was heated to 50 °C for 4 h. Surprisingly, the desired tributylstannane 256 was obtained as a sole product in 89% yield after purification by column chromatography. Importantly, no significant protodestannylation occurred in the presence of Pd(PPh$_3$)$_2$Cl$_2$.

![Scheme 128 Synthesis of tributylstannane 256. Reagents and conditions: i) Pd(dppf)$_2$Cl$_2$.CH$_2$Cl$_2$. Cs$_2$CO$_3$. THF:H$_2$O 4:1, 50 °C, 89%](image)

In summary, the desired tributylstannane 256 was synthesised via two novel approaches from commercially available 1,3-diketone 246 over four linear steps in 21% and 22% yield, respectively. Despite the low yield obtained for the preparation of tributylstannane 256, we decided to move on to proceed with the subsequent Stille cross coupling between organostannane 256 and iodo-pyrone 249.

5.3.3 Attempted Stille Cross Coupling of Iodide 249 and Tributylstannane 256

The Pd(0)-catalysed coupling reaction between an organostannane and an organic electrophile to form a new C-C sigma bond is known as the Stille cross coupling.\textsuperscript{142} In 1976, the first example of this type of reaction was reported by Eaborn and co-workers.\textsuperscript{257} It was not until the early 1980s that Stille established the use of this reaction.\textsuperscript{258} Organostannanes exhibit stability to air and moisture and their use is compatible with sensitive functional groups.\textsuperscript{142} In the past two decades, the Stille reaction has been employed as one of the most powerful synthetic methods in organic chemistry to perform intermolecular C-C bond formation.
Despite the versatility and synthetic utility of organostannane reagents, a significant drawback is the difficulty in removing the stannane byproducts from the product mixture. Numerous strategies have been employed in an attempt to circumvent purification problems.\textsuperscript{143,259-263}

The most commonly accepted mechanism of the traditional Stille coupling can be subdivided into three key steps: oxidative addition, transmetallation and reductive elimination.\textsuperscript{258} The active catalyst is assumed to be a Pd(0)L\textsubscript{2} complex\textsuperscript{266}, that reacts with the organic electrophile R\textsuperscript{3}X to give complex\textsuperscript{267} (Figure 30). The following transmetallation step involves the metal exchange between complex\textsuperscript{267} and organostannane species\textsuperscript{268}, that leads to the formation of complex\textsuperscript{269}. A fast trans to cis isomerisation of complex\textsuperscript{269} followed by a reductive elimination yields the cross coupled product\textsuperscript{270} and regenerates the active palladium(0) catalyst. The transmetallation step is believed to be the rate-determining step. However, the exact mechanism is still under debate.

Various organic electrophiles can be used in the Stille cross coupling but halides and triflates are the most commonly used. The most commonly employed palladium sources include Pd(PPh\textsubscript{3})\textsubscript{4}, Pd\textsubscript{2}(dba)\textsubscript{3}, Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}, Pd(OAc)\textsubscript{2}, PdCl\textsubscript{2}(PhCN)\textsubscript{2}, PdCl\textsubscript{2}(MeCN)\textsubscript{2}. Due to the air-sensitivity of Pd(PPh\textsubscript{3})\textsubscript{4}, a more air-stable source of palladium(0), Pd\textsubscript{2}(dba)\textsubscript{3} has been commonly employed in the Stille cross couplings. The Pd(II) source (Pd(OAc)\textsubscript{2}, PdCl\textsubscript{2}(MeCN)\textsubscript{2}, PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, PdCl\textsubscript{2}(PhCN)\textsubscript{2}) can be reduced to Pd(0) \textit{in situ} by added phosphine ligands or organostannane reagents. LiCl or

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig30.png}
\caption{General mechanism of Stille cross coupling.}
\end{figure}
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Cu(I) salts are usually added in order to increase the transmetallation rate. The interplay of catalyst, ligand, additives, and solvent is complex.

There is no reported literature precedent using iodo-pyrone 249 as a Stille cross coupling partner, although halogenated pyrone 271 has been more widely studied as a key intermediate for the synthesis of natural products (Figure 31).

Figure 31. Natural products originated from 3,5-dibromopyrone (271).

In order to test the feasibility of the attempted Stille cross coupling strategy, a model study was conducted using vinyltributylstannane (Scheme 129). The required vinyltributylstannane was prepared from vinylmagnesium bromide and tributylstannane chloride according to the procedure reported by Parkinson and co-workers. Accordingly, a mixture of tributylstannyl chloride (1 equiv.) and vinylmagnesium bromide (1 equiv.) in THF was stirred at room temperature for 12 h. Treatment with aqueous NH$_4$Cl solution followed by extraction with n-hexanes afforded a solution of vinyltributylstannane in n-hexanes. The solution was concentrated in vacuo to give neat vinyltributylstannane.
The desired Stille cross coupling was initially carried out using Pd(PPh₃)₄ as a catalyst in anhydrous DMF at 100 °C affording the coupled product 272 in 56% yield. Gratifyingly, employing the same catalyst and solvent, at a similar temperature using microwave irradiation techniques (200 W) delivered 272 quantitatively (Scheme 129).

With both cross coupling partners, iodo-pyrone 249 and tributylstannane 251, required for the key Stille cross coupling in hand, we embarked on the elaboration of the pyrone enynone 240. Disappointingly, using the aforementioned conditions with Pd(PPh₃)₄ in anhydrous DMF either under heat or under microwave irradiation techniques, did not lead to the formation of pyrone enynone 240. Upon work-up, both starting materials were hydrogenated to pyrone 241 and enynone 202, respectively (entries 1-2, Table 24). It was postulated that the Pd(II) complex was quenched with residual water present in the DMF before transmetallation could occur.

In 2010, Cho and co-workers demonstrated a tandem Stille/intramolecular Diels-Alder (IMDA) cascade using 3,5-dibromo-2-pyrone (271) and a sterically demanding aromatic stannane 273 to provide compound 274 in good yield (Scheme 130). It was demonstrated that the tandem Stille/IMDA cascade relied heavily on the choice of solvent, temperature and co-catalyst, with Pd(PPh₃)₄ in the presence of CuI in anhydrous DMF at 95 °C affording the best result. The addition of Cu(I) may activate organostannane via inducing the Sn/Cu transmetallation.
Scheme 130  Tandem Stille/IMDA cascade. Reagents and conditions: i) Pd(PPh$_3$)$_4$, CuI, DMF, 95%, 11 h, 45%, endo:exo 2.5:1.

Attempted use of the same conditions to effect the coupling of iodo-pyrone 249 and tributylstannane 251 was fruitless, only resulting in the complete proto-defunctionalisation of both starting materials (entry 3, Table 24). We next investigated toluene as a solvent with CuI as co-catalyst in the presence of stoichiometric LiCl. Additives such as LiCl are known to act as catalyst stabiliser in ethereal solvents such as THF and dioxane. Disappointingly, no desired product was obtained under these conditions (entry 4, Table 24).
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Table 24. Attempted Stille cross coupling between iodo-pyrone 249 and stannane 251.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst and ligand</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>additive</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>100</td>
<td>...</td>
<td>a</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>90</td>
<td>...</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>50</td>
<td>CuI</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄</td>
<td>toluene</td>
<td>80</td>
<td>CuI+LiCl</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>Pd₂(dba)₃ + TFP</td>
<td>DMF</td>
<td>80</td>
<td>None</td>
<td>a</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>Pd(PPh₃)₄</td>
<td>dioxane</td>
<td>100</td>
<td>CuCl + LiCl</td>
<td>a</td>
</tr>
<tr>
<td>7</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>NMP</td>
<td>100</td>
<td>CuI</td>
<td>a</td>
</tr>
<tr>
<td>8</td>
<td>Pd₂(dba)₃ + PCy₂</td>
<td>DMF</td>
<td>80</td>
<td>CuI</td>
<td>a</td>
</tr>
<tr>
<td>9</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>100</td>
<td>CuCl</td>
<td>a</td>
</tr>
<tr>
<td>10ᶜ</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>80</td>
<td>CuTC + CsF</td>
<td>a</td>
</tr>
<tr>
<td>11ᶜ</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>100</td>
<td>CuTC + TBAF</td>
<td>a</td>
</tr>
<tr>
<td>12ᵈ</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>100</td>
<td>CuTC + CsF</td>
<td>a</td>
</tr>
</tbody>
</table>

a: Protodehalogenation forming iodo-pyrone 241 and protodestannylation forming enone 202 were observed, possibly due to a transmetallation from stannane to copper and palladium oxidative addition of iodo-pyrone 249.
b: Microwave irradiation (200 W) was used.
c: CsF and TBAF were added to the reaction to decrease the concentration of Bu₃SnI via halogen exchange to form an insoluble Bu₃SnF.
d: Unless mentioned, all the additives were used as stoichiometric amounts with CuTC (0.5 equiv) was used.

A more stable source of palladium(0), Pd₂(dba)₃ was next investigated using tri(2-furyl)phosphine (TFP) as a ligand in anhydrous DMF. Again, this modification proved to be unrewarding (entry 5, Table 24).

Using CuCl as an alternative copper(I) source was next attempted. Regrettably, it did not afford any of the desired product with recovery of iodo-pyrone 249 and protodestannane enone 202 instead observed (entry 6, Table 24).

The choice of solvent also plays a critical role in the Stille cross coupling. Highly polar solvents such as DMF and NMP are known to act as coordinating ligands for the palladium centre. Mixed solvent systems such as toluene/DMF or toluene/NMP are sometimes used in these coupling reactions for sterically demanding substrates. Herein polar solvents DMF or NMP have been employed as our attempted Stille cross coupling.
Upon searching the literature, it was revealed that the Stille cross coupling is far more sensitive to electronic effects, such as ligand electron-donating ability, than steric bulk alone, as demonstrated by Farina and co-workers. The choice of ligand plays a critical role in the kinetics of the Stille reaction. Also, excess PPh₃ is a known inhibitor of the Stille reaction. Thus, any excess of ligand must be slowly oxidised by adventitious oxygen before the reaction can function efficiently. “Weak” or “soft” ligands such as AsPh₃ were not observed to appreciably slow down the reaction. We therefore attempted the use of a combination of Pd₂(dba)₃ and AsPh₃ in the presence of CuCl or CuI in anhydrous NMP or DMF at elevated temperature, however, this also did not deliver the desired coupled product (entries 7-9, Table 24).

In 2003, Liebeskind and co-workers reported use of copper(I) thiophenecarboxylate (CuTC) as the co-catalyst in palladium mediated cross couplings of thioester compounds with organostannanes. The thioester formed a complex with CuTC that permitted oxidative addition of the C-S bond (Scheme 131). This additive extended the substrate scope of cross-couplings with organostannane reagents and it has shown much higher reactivity towards the Sn/Cu transmetallation. Retarded transmetallation from stannane to copper was characterised by the formation of increasing concentrations of n-Bu₃SnX as the coupling reaction proceeded. Synergic effects were observed by Baldwin and co-workers using a combination of CuI and CsF in highly polar solvents. Thus stoichiometric CuTC and CsF (TBAF) were applied in order to drive the coupling reaction faster and more efficiently (entries 10-12, Table 24). Accordingly, under an inert atmosphere a mixture of Pd₂(dba)₃, CuI, iodo-pyrone and stannane were heated to 100 °C in anhydrous DMF in the presence of a variety of phosphine ligands (AsPh₃, PCy₃, TFP), but these attempts did not afford the coupled product 240.

In all reactions attempted, the conditions employed for the desired Stille cross coupling between iodo-pyrone and tributylstannane using various palladium(0) sources [Pd(PPh₃)₄, Pd₂(dba)₃ in the presence of a variety copper(I) salts (CuI, CuCl, CuTC)] in DMF, toluene, NMP, THF or dioxane (LiCl required for THF and dioxane) under heat did not afford the required product 240.
Due to the unsuccessful Stille cross coupling between iodo-pyrone 249 and tributylstannane 256, an alternative convenient and reliable synthetic strategy was sought to elaborate pyrone enynone 240.
5.4 Synthesis of Alkyne 240 via a Sequential Stille-Sonogashira Strategy

In view of the disappointing result obtained by the attempted Stille cross coupling of iodopyrone 249 and tributylstannane 258, an alternative synthetic strategy towards 3-dehydroxy-tenuipyrone 200 was devised based on two sequential palladium catalysed cross couplings (Scheme 132). Retrosynthetically, alkyne 240 was anticipated to be assembled from a Sonogashira cross coupling between vinyl bromide 275 and alkyne 204. Bromide 275 was derived from a Stille cross coupling between organostannane 258 and iodide 249. As described in Section 5.1.3, alkyne 204 was prepared from a regioselective ring opening of (R)-propylene oxide using lithium acetylide-ethylenediamine complex. The detailed synthetic studies of alkyne 240 will be discussed in the following section.

![Scheme 132 Retrosynthetic analysis of alkyne 240.](image)

5.4.1 Synthesis of Tributylstannane 258

The initial objective was to construct the organostannane fragment 258 required for the key Stille cross coupling. As discussed earlier, methoxy ether 245 was readily obtained on a gram scale from commercially available starting material diketone 246 in quantitative yield (Section 5.2.1).

With methoxy enone 245 in hand, the preparation of organostannane 258 was attempted. In accordance with the optimal conditions developed for the preparation of tributylstannane 256 (Section 5.3.1), neat tributyltin hydride was quickly added to a solution of freshly prepared LDA in THF at 0 °C. After stirring for half an hour at this temperature, a solution of enone 245 in THF was added at −78 °C and the reaction mixture allowed to stir at this temperature for 10 min before it was warmed to −20 °C with stirring for two hours, affording stannane 258 in 45% yield.
Scheme 133 Synthesis of tributylstannane 258. Reagents and conditions: i) LDA, n-Bu₃SnH, –78 °C to r.t., aq. NH₄Cl, 45%.

The low yield of the synthesis of tributylstannane 258 was also ascribed to the low quality of tributylstannane hydride as discussed earlier (Section 5.3.1). Hence, we moved on to the following Stille cross coupling without optimisation.

5.4.2 Stille Cross Coupling Reaction of Iodo-pyrones 249 and Tributylstannane 258

With stannane 258 in hand, attention turned to the Stille cross coupling (Table 25).

It was initially decided to use Pd(PPh₃)₄ in THF in the presence of anhydrous LiCl at 50 °C as the Stille coupling conditions. The desired product was obtained in 93% yield after purification by column chromatography (entry 1, Table 25). We attempted changing the catalyst to a variable palladium(0) source due to the arduous work involved preparing Pd(PPh₃)₄ and anhydrous LiCl. Use of a more stable palladium(0) source Pd₂(dba)₃ and a more electron-deficient ligand such as TFP or AsPh₃ in dioxane was unrewarding (entries 2 and 3, Table 25). Changing the solvent to anhydrous DMF in the presence of Pd(PPh₃)₄ and freshly prepared CuCl at 100 °C afforded the coupled product 276 in 40% yield after purification by column chromatography. Next, efforts were undertaken using air-stable Pd₂(dba)₃ in the presence of CuI as a co-catalyst with PCy₃ or AsPh₃ as the ligand in anhydrous DMF (entries, 5-6, Table 25). Interestingly, the combination of Pd₂(dba)₃ (0.1 equiv), AsPh₃ (0.4 equiv) and CuI (1 equiv) afforded a higher yield of 65% (entry 8, Table 25).
Chapter 5: Discussion of Tenuipyrone

Table 25. Conditions employed for the Stille cross coupling of iodopyrone 249 and tributylstannane 258.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst and ligand</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>additive</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Pd(PPh₃)₄</td>
<td>THF</td>
<td>50</td>
<td>LiCl</td>
<td>93</td>
</tr>
<tr>
<td>2a</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>dioxane</td>
<td>80</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>3a</td>
<td>Pd₂(dba)₃ + TFP</td>
<td>dioxane</td>
<td>80</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>4a</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>100</td>
<td>CuCl</td>
<td>40</td>
</tr>
<tr>
<td>5a</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>80</td>
<td>CuI</td>
<td>65</td>
</tr>
<tr>
<td>6a</td>
<td>Pd₂(dba)₃ + PCy₃</td>
<td>DMF</td>
<td>80</td>
<td>CuI</td>
<td>45</td>
</tr>
<tr>
<td>7a</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>80</td>
<td>CuCl</td>
<td>70</td>
</tr>
<tr>
<td>8a</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>60</td>
<td>CuTC</td>
<td>92</td>
</tr>
<tr>
<td>9b</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>80</td>
<td>CuTC</td>
<td>90</td>
</tr>
<tr>
<td>10c</td>
<td>Pd₂(dba)₃ + AsPh₃</td>
<td>DMF</td>
<td>80</td>
<td>CuTC</td>
<td>88</td>
</tr>
</tbody>
</table>

a: 10% of Pd and 40% of ligand and one equivalent of additive were used.
b: 8% of Pd, 32% of ligand and 50% of additive were used.
c: 5% of Pd, 20% of ligand and 20% of additive were used.

The desired Stille cross coupling conditions were then screened using a combination of Pd₂(dba)₃ (0.1 equiv) and AsPh₃ (0.4 equiv) in the presence of a variety of copper(I) co-catalysts, (entries 5, 7 and 8, Table 25). It was observed that use of CuTC as a co-catalyst afforded a significantly higher yield (entry 8, Table 25). The use of 10mol% Pd₂(dba)₃, 40mol% AsPh₃ and stoichiometric CuTC in DMF at 60 °C afforded the coupled product 276 in 92% yield upon purification by column chromatography (entry 8, Table 25).

Attempts to decrease the amount of the expensive reagent CuTC and the toxic and non-recoverable phosphine ligand AsPh₃ were then carried out (entry 9-10, Table 25). Lowering the loading of palladium(0) and the corresponding ligand to 5mol% and 20mol% respectively afforded similar yields (entry 8-10, Table 25).

In an effort to circumvent the problems associated with removing stannane impurities, it was established that the use of KF was a potentially powerful means of acquiring the pure product.\footnote{141} The fluoride ion captures the Bu₃Sn cation to form a stable water-soluble salt. We attempted the incorporation of finely ground KF and flash silica as a stationary phase for chromatographic purification of product mixtures containing organostannane impurities and established that this method was effective to provide reasonably clean products. This simple and inexpensive
chromatographic procedure has proven to be remarkably practical for the removal of organostannane impurities.

With the established optimal reaction conditions and an efficient purification method in hand, iodide 249 and stannane 258 were subjected to the Stille cross coupling reaction conditions as highlighted in Table 6 (entry 10, Table 25). The requisite Stille cross-coupling was conducted on various scales, ranging from 50 mg to gram scale, with consistently high yields.

5.4.3 Bromination of Enone 276

With enone 276 in hand, our attention turned to the synthesis of bromide 275. Bromination of enone 276 was effected using the classic bromination protocol.274 Typically, enone 276 was treated with Br2 in CH2Cl2 at 0 °C followed by addition of Et3N after one hour (entry 1, Table 26). The reaction was quenched by the addition of water after one hour. Bromide 275 was isolated in 52% yield with 40% recovered starting material (87% brsm). Increasing the ratio of Br2 resulted in a decreased yield of the desired mono-bromide 275, producing dibromide 277 as a major side-product (entry 2, Table 26). Prolonging the reaction time was found to be detrimental, resulting in a lower yield (entry 3, Table 26).

Table 26. Bromination of enone 276.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromination reagenta</th>
<th>Reaction timeb</th>
<th>Ratio (equiv.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br2</td>
<td>1 h</td>
<td>1.1</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>Br2</td>
<td>1 h</td>
<td>1.3</td>
<td>33c</td>
</tr>
<tr>
<td>3</td>
<td>Br2</td>
<td>3 h</td>
<td>1.1</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>I2</td>
<td>3 h</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Py·Br3</td>
<td>1 h</td>
<td>1.1</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>Py·Br3</td>
<td>3 h</td>
<td>1.2</td>
<td>23c</td>
</tr>
</tbody>
</table>

a: All reactions were conducted in anhydrous CH2Cl2.
b: The time before Et3N was added to quench the excess bromination reagent.
c: Dibromide 277 was obtained.
Encouraged by the successful formation of bromide 275, we attempted a synthesis of iodide 278 using analogous conditions. Disappointingly, no desired product was observed as indicated by TLC analysis and full recovery of starting material 276 was obtained (entry 4, Table 26).

Further optimisation of the bromination of enone 276 was attempted using pyridine tribromide as the bromination reagent (entries 5-6, Table 26). Use of 1.1 equivalents of pyridine tribromide in CH₂Cl₂ at room temperature for one hour provided the desired mono-bromide 275 in 35% yield (entry 5, Table 26). Increasing the equivalents of bromination reagent and the reaction times proved unsuccessful, leading to a lower 23% yield (entry 6, Table 26).

In conclusion, the optimal conditions for the synthesis of bromide 275 were found to be the use of 1.1 equivalents of bromine in anhydrous CH₂Cl₂ at room temperature for one hour followed by addition of triethylamine to quench the reaction, affording bromide 275 in 52% (87% brsm). Following the successful preparation of bromide 275, we next investigated the Sonogashira cross coupling between bromide 275 and alkyne 204 to elaborate enone acetylene 240.

5.4.4 Elaboration to Form Alkyne 240 Using Sonogashira Reaction

With both coupling partners bromide 275 and terminal alkyne 204 in hand, the late stage Sonogashira reaction was devised (Scheme 134). The optimal conditions utilised for the union of iodide 203 and alkyne 204 were first attempted (Section 5.1.4). Accordingly, bromide 275 and terminal alkyne 204 were submitted to a mixture of Pd(PPh₃)₄, CuI and triethylamine in anhydrous DMF at 50 °C under an inert atmosphere. Disappointingly, these conditions were unrewarding, resulting in the recovery of protodehalogenated enone 276 (entry 1, Table 27). It was postulated that bromide 275 was not sufficiently reactive towards coupling with alkyne 204 under these conditions. A survey of the literature was therefore undertaken.

![Scheme 134 Attempted Sonogashira cross coupling of alkyne 204 and bromide 275. Reagents and conditions: i) Pd(PPh₃)₄, CuI, i-Pr₂NH, DMF, 50 °C.](image-url)
α-Haloenones are less reactive electrophiles in cross coupling reactions due to their electron-deficient properties. Harsher reaction conditions including elevated temperatures and more reactive catalyst systems are normally required. However, in the present case, use of a higher temperature resulted in significant protodehalogenation prior to the transmetallation (entry 2, Table 27). The undesirable protodehalogenation of brominated substrates in cross coupling involves water as the proton source. Recalling the mechanism of Sonogashira cross coupling (Section 5.1.4), the rate limiting step is the active palladium(0) species reacting with the electrophilic halide in an oxidative addition reaction to produce a Pd(II) intermediate. It was postulated that the water content of the DMF might be detrimental to the oxidative addition step. Moreover, the product distribution (dehalogenation vs carbon-carbon coupling) can be controlled by modification of the phosphine ligand substituents or solvent. We therefore attempted the reaction using an electron-rich ligand Xphos together with Pd(PPh₃)₂Cl₂ in the presence of i-Pr₂NH and CuI in anhydrous DMF at 50 °C, however, this modification proved unrewarding (entry 3, Table 27).

Table 27. Synthesis of alkyne 240.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst and ligand</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time</th>
<th>Base and additive</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1⁴</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>50</td>
<td>2 h</td>
<td>Et₃N + CuI</td>
<td>0</td>
</tr>
<tr>
<td>2⁴</td>
<td>Pd(PPh₃)₄</td>
<td>DMF</td>
<td>80</td>
<td>2 h</td>
<td>Et₃N + CuI</td>
<td>0</td>
</tr>
<tr>
<td>3⁴</td>
<td>Pd(PPh₃)₂Cl₂ + Xphos</td>
<td>DMF</td>
<td>50</td>
<td>2 h</td>
<td>i-Pr₂NH + CuI</td>
<td>0</td>
</tr>
<tr>
<td>4⁵</td>
<td>Pd(PPh₃)₄</td>
<td>dioxane</td>
<td>60</td>
<td>6 h</td>
<td>Et₃N + CuI</td>
<td>48</td>
</tr>
<tr>
<td>5⁵</td>
<td>Pd(PPh₃)₄</td>
<td>toluene</td>
<td>60</td>
<td>6 h</td>
<td>i-Pr₂NEt + CuI</td>
<td>75</td>
</tr>
<tr>
<td>6⁵</td>
<td>Pd(PPh₃)₄</td>
<td>toluene</td>
<td>80</td>
<td>6 h</td>
<td>Cs₂CO₃ + CuI</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>Pd₂(dba)₃</td>
<td>toluene</td>
<td>80</td>
<td>4 h</td>
<td>i-Pr₂NH + CuI</td>
<td>65</td>
</tr>
<tr>
<td>8⁶</td>
<td>Pd(PPh₃)₄</td>
<td>toluene</td>
<td>80</td>
<td>6 h</td>
<td>i-Pr₂NH + CuI</td>
<td>89</td>
</tr>
</tbody>
</table>

a: TLC indicated the full consumption of bromide 275 in 2 h. Only debrominated enone 276 was obtained.
b: TLC indicated the full consumption of bromide with a new spot on TLC.
c: The reaction was conducted in a pressure tube.

Further investigations established that non-polar aprotic solvents were critical for this reaction (entry 4-8, table 27). Use of dioxane or toluene as the solvent with Pd(PPh₃)₄ as the catalyst in the presence of CuI and various bases afforded the desired product 240 in moderate to good yield (entries 4-5, Table 27). The inorganic base Cs₂CO₃ was also used, but this did not result in any
significant change in yield (entry 6, table 27). The use of catalytic Pd(PPh$_3$)$_4$ and CuI in the presence of a variety of bases in toluene at 80 °C furnished pyrone enynone 240 in good yields (entries 5-8, Table 27). In conclusion, the optimal conditions, employing Pd(PPh$_3$)$_4$ as a palladium source in the presence of CuI with i-Pr$_2$NH in anhydrous toluene in a pressure tube at 80 °C, provided the desired pyrone enynone 240 in 85% yield (entry 8, Table 27).
5.4.5 Summary of Synthesis of Alkyne 240

The preparation of bromide 240 commenced with the synthesis of methoxy enone 245 from commercially available diketone 246 (Scheme 135). Methoxy enone 245 was readily converted to its corresponding organostannane compound 258 in moderate yield. All efforts towards improving the preparation of organostannane compound 258 were unrewarding. The requisite Stille cross coupling partner iodide 249 in turn was successfully synthesised in 80% yield from pyrone 177 over two steps. The key Stille cross coupling between iodo-pyrone 249 and organostannane 258 was performed using Pd$_2$(dba)$_3$ and AsPh$_3$ in the presence of CuTC in DMF at 80 °C in 88% yield. Bromination of the resulting enone 276 was carried out in anhydrous CH$_2$Cl$_2$ at 0 °C using bromine followed by addition of Et$_3$N. Late-stage Sonogashira cross coupling was conducted in anhydrous toluene using Pd(PPh$_3$)$_4$ and CuI in the presence of i-Pr$_2$NH at 80 °C for 6 h, furnishing alkyne 240 in 85% yield. Alkyne 240 was therefore successfully prepared in 25% yield over 5 steps (longest linear route with the yield calculated according to the lower yielding pathway).

In view of the toxicity of organostannane compounds and the difficulties associated with synthesising reasonable quantities of alkyne 240 in order to continue our synthesis sequence, it was decided to seek a more efficient synthesis of alkyne 240.

Scheme 135 Summary of synthesis of pyrone enynone 240. Reagents and conditions: i) MeOH, TiCl$_4$, r.t., 2 h, 90%; ii) LDA, Bu$_3$SnH, –78 °C to 0 °C, 2 h, 45%; iii) (CH$_3$)$_2$SO$_4$, K$_2$CO$_3$, acetone, reflux, 85%; iv) NIS, Mg(ClO$_4$)$_2$, CH$_3$CN, r.t., 3 h, 95%; v) Pd$_2$(dba)$_3$, AsPh$_3$, CuTC, DMF, 100 °C, 95%; vi) Br$_2$, CH$_3$Cl$_2$, 0 °C, 1 h; then Et$_3$N, 0 °C, 1 h, 55%, 80% brsm; vii) Pd(PPh$_3$)$_4$, CuI, i-Pr$_2$NH, toluene, 80 °C, 6 h, 85%.
5.5 Optimised Synthetic Strategy

Encouraged by the successful cross coupling results obtained, we next implemented a revised synthetic strategy, in pursuit of a streamlined synthetic sequence and circumventing the low yield of methoxy ether 245 for compound 258, which relied on the key novel Stille cross coupling between pyrone stannane 279 and dibromide 280.

As illustrated in Scheme 136, we were targeting the two molecules 3-dehydroxy-tenuipyrone 200 and 1-deoxy-tenuipyrone 281 using the same coupling partners via two sequential cross couplings. It was envisaged that 3-dehydroxy-tenuipyrone 200 could be accessed from a Sonogashira cross coupling between bromo-enone 275 and alkyne 204. Bromo-enone 275 is anticipated to be elaborated from a key novel Stille cross coupling reaction using tributylstannane 279 and dibromide 280. In parallel, 1-deoxy-tenuipyrone 281 could be derived from a late stage Stille cross coupling between tributylstannane 279 and bromide 282. Bromide 282 can be constructed via a regioselective Sonogashira cross coupling of dibromide 280 and alkyne 204. The dibromide fragment 280 required for these two approaches could be synthesised by dibromination of 1,3-diketone 246. The details of preparing the requisite fragments and performing this novel Stille cross coupling reaction will be discussed in the following section.

Scheme 136 Revised retrosynthetic analysis of spiroketal precursor 240 and 281.
5.5.1 Synthesis of Dibromide 280

The initial objective of this optimised strategy was to synthesise the known dibromide 280 fragment required for the key Stille and Sonogashira cross couplings. The preparation of dibromide 280 involved two consecutive brominations of 1,3-diketone 246 (Scheme 137).

\[
\text{Scheme 137 Synthesis of dibromide 280.}
\]

Methods reported for the initial α-bromination of 1,3-dicarbonyl compounds have been discussed earlier in Section 5.3.2. We thus focused on the second bromination of the obtained mono-bromide 264. The conventional approach to the second bromination step involves the use of preformed dibromotriphenylphosphorane in the presence of triethylamine.\(^{246}\) The bromination reagent was generated in situ from bromine and triphenylphosphine by stirring these reagents together at room temperature for one hour. A major drawback of this methodology is the tedious purification required due to the formation of the triphenylphosphine oxide byproduct.

We envisaged a synthesis of the known dibromide 280 beginning from our previously synthesised mono-bromide 264 (Scheme 138).

\[
\text{Scheme 138 Synthesis of dibromide 280. Reagents and conditions: i) (COBr)_2, DMF, CH}_2\text{Cl}_2, 0 \, ^\circ\text{C, 1 h, quant.}
\]

Initial attempts towards the formation of dibromide 280 were conducted in anhydrous CH\(_2\text{Cl}_2\) employing PBr\(_3\), which resulted in 30% conversion of the desired product and several unidentified byproducts.

In 2003, Vidari and co-workers developed the first synthesis of dibromide 280 by treatment of 1,3-diketone 246 with HBr and KBrO\(_4\) followed by treatment with oxalyl bromide in the presence of stoichiometric DMF in 77% yield over 2 steps (Scheme 139).\(^{275}\)
Chapter 5: Discussion of Tenuipyrone

Scheme 139 Synthesis of dibromide 280. Reagents and conditions: i) HBr, KBrO₄, H₂O, 90%; ii) (COBr)₂, DMF, CH₂Cl₂, 85%.

Further attempts employing Vidari’s conditions by treatment of a suspension of α-bromide 264 in anhydrous CH₂Cl₂ with 1.1 equivalents of (COBr)₂ and DMF at 0 °C for one hour afforded the desired dibromide 280 as the sole product in quantitative yield (Scheme 138). Dibromide 280 was obtained as white crystals (m.p. 79–81 °C [lit. 79–81 °C]). The reaction yield is highly dependent on the purity of bromide 264 used. Dibromide 280 was subjected to the subsequent Stille cross coupling without further purification.

5.5.2 Synthesis of Bromide 282

With dibromide 280 in hand, the anticipated Sonogashira cross coupling was next attempted (Scheme 140). Using the optimal conditions established for the synthesis of enone 202 (Section 5.1.4), a thoroughly degassed mixture of dibromide 280 and alkyne 204 (2 equiv.) in the presence of a mixture of Pd(PPh₃)₄, CuI and i-Pr₂NH in anhydrous DMF was stirred at 50 °C for 6 h furnishing bromide 282 in 42% yield due to the formation of byproduct di-alkyne 283. Further investigations revealed that use of less alkyne 204 (1.2 equiv.) at r.t. for 12 h afforded the desired product 282 in 82% yield as a sole product. The observed regioselectivity was reasoned to be due to the different electron nature of two bromides in bromide 280. The electron-rich bromide would favour Sonogashira cross coupling over the electron-deficient one.

Scheme 140 Synthesis of bromide 282. Reagents and conditions: i) Pd(PPh₃)₄, CuI, i-Pr₂NH, DMF, 50 °C, 12 h, 87%.

5.5.3 Synthesis of Tributylstannane 279

With the optimal conditions established for the synthesis of dibromide 280 and bromide 282, attention next turned to the preparation of tributylstannane 279. After conducting a thorough
SciFinder®-based literature search, it was found that one previous preparation of compound 279 was reported by Hagiwara and co-workers in 2002.²⁷⁶ In 2002, Hagiwara and co-workers reported the attempted synthesis of aldehyde 284 via a palladium catalysed carbyonylation of tributylstannane 279 (Scheme 141).²⁷⁶ A lithium/stannane exchange of pyrone 241 was conducted using LDA in the presence of TMEDA in anhydrous THF at −78 °C, delivering tributylstannane pyrone 279 in quantitative yield after treatment with Bu₃SnCl. Further Pd-catalysed CO insertion to tributylstannane derivative 284 was unsuccessful.

![Scheme 141](image)

Scheme 141 Hagiwara’s attempted synthesis of aldehyde 284. Reagents and conditions: i) LDA, −78 °C, TMEDA, Bu₃SnCl, 100%; ii) Pd(0), CO.

Regardless of the unsuccessful CO insertion literature precedent, we employed Hagiwara’s conditions to synthesise tributylstannane pyrone 279 as depicted in Scheme 142. Pyrone 241 was initially lithiated using Hagiwara’s conditions using freshly prepared LDA in the presence of anhydrous TMEDA.²⁷⁶ A yellow colour was spontaneously observed upon addition of LDA. The colour maintained its intensity throughout the addition and gradually became orange towards the end of the addition, indicating the successful formation of the lithiated pyrone species. After stirring for 30 min at −78 °C, stoichiometric neat tributylstannane chloride was added and the resultant mixture was allowed to warm to 0 °C over one hour. After stirring the resultant mixture at this temperature for one hour, the reaction was quenched with saturated aqueous ammonium chloride solution affording the desired organostannane 279 in 95% yield after purification by column chromatography. Attempts to simplify the reaction procedure were undertaken using n-BuLi in the presence of TMEDA in anhydrous THF at −78 °C. Gratifyingly, the lithiation/stannylation proceeded uneventfully to deliver tributylstannane 279 in 92% yield after the same purification procedure. It is important to note that similar yields were obtained using n-BuLi as the base in the absence of TMEDA in anhydrous THF at −78 °C. It was thus concluded that TMEDA was not essential for the lithiation-stannylation reaction allowing simplification of the only literature precedent.
5.5.4 Stille Cross-Coupling Reactions

A: Stille Cross Coupling of Tributylstannane 279 and Dibromide 280

Having established the optimal conditions for the preparation of both cross coupling partners, as well as the optimised Stille cross coupling reaction conditions developed for the union of tributylstannane 258 and iodide 249 (Section 5.3.1), the novel Stille cross coupling of tributylstannane 279 and dibromide 280 was next investigated.

The synthesis of bromide 275 was performed with a procedure that was used for organostannane 258 and iodide 249 (Section 5.3.1). Accordingly, a thoroughly degassed mixture of tributylstannane 279, dibromide 280, Pd$_2$(dba)$_3$ (0.1 equiv), AsPh$_3$ (0.4 equiv) and CuTC (1 equiv) in anhydrous DMF was heated to 60 °C for 2 h. The reaction mixture was then filtered through KF-silica to remove Bu$_3$SnBr in the form of Bu$_3$SnF, affording bromide 275 in 95% yield as a single regioisomer (entry 1, Table 28).

**Table 28. Synthesis of bromide 275.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst and ligand</th>
<th>Solvent</th>
<th>additive</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$ + AsPh$_3$</td>
<td>DMF</td>
<td>CuTC</td>
<td>60</td>
<td>2 h</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_3$ + AsPh$_3$</td>
<td>DMF</td>
<td>CuTC</td>
<td>80</td>
<td>6 h</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_3$ + AsPh$_3$</td>
<td>dioxane</td>
<td>LiCl+CuI</td>
<td>80</td>
<td>12 h</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>THF</td>
<td>LiCl+CuI</td>
<td>50</td>
<td>12 h</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$(dba)$_3$ + TFP</td>
<td>toluene</td>
<td>LiCl+CuTC</td>
<td>80</td>
<td>10 h</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Pd$_2$(dba)$_3$ + AsPh$_3$</td>
<td>DMF</td>
<td>CuCl</td>
<td>80</td>
<td>4 h</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Pd$_2$(dba)$_3$ + [(t-Bu)$_3$PH]BF$_4$</td>
<td>DMF</td>
<td>Cul</td>
<td>80</td>
<td>6 h</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Pd$_2$(dba)$_3$ + TFP</td>
<td>DMF</td>
<td>CuTC</td>
<td>80</td>
<td>12 h</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Pd$_2$(dba)$_3$ + PCy$_3$</td>
<td>DMF</td>
<td>CuTC</td>
<td>80</td>
<td>12 h</td>
<td>35</td>
</tr>
</tbody>
</table>

Use of fewer equivalents of the palladium catalyst and additives was next investigated (entry 2, Table 28). Accordingly, a mixture of tributylstannane 279, dibromide 280, Pd$_2$(dba)$_3$ (0.05 equiv), AsPh$_3$ (0.2 equiv) and CuTC (0.3 equiv) in anhydrous DMF was heated to 80 °C for 6 h under an
inert atmosphere. Gratifyingly, the desired product was obtained in 88% yield after filtration through KF-silica.

We next investigated the use of ethereal solvents dioxane and THF and the non-polar, aprotic solvent toluene in the presence of copper(I) as a co-catalyst and LiCl as the additive to stabilise the palladium complex (entries 1-3, Table 28). Disappointingly, none of the desired product was achieved under these conditions with protodestannynlated pyrone 241 obtained instead. It was postulated that the transmetallated Pd(II) complex was not stable in these solvents.

In light of these results, DMF has been used consistently as the Stille cross coupling solvent. In order to pursue environmentally friendly conditions and replace the use of highly toxic AsPh₃, further attempts were conducted employing the same Pd(0) source in DMF in the presence of a variety of ligands and copper(I) co-catalysts (entries 6-9, Table 28). Use of CuCl as the co-catalyst afforded a similar yield as the use of expensive CuTC (entry 6, Table 28). Regrettably, use of an electron-rich, sterically hindered ligand [(t-Bu₂PH)BF₄ (0.4 equiv) in the presence of Pd₂(dba)₃ (0.1 equiv) and CuI (0.5 equiv) afforded only 20% of bromide 275. Changing the ligand to TFP or PCy₃ delivered 42% and 35% of the desired product, respectively (entries 8-9, Table 28).

Hence, the optimal conditions for the Stille cross coupling of organostannane 279 and dibromide 280 were the use of Pd₂(dba)₃ (0.05 equiv), AsPh₃ (0.2 equiv) and CuTC (0.3 equiv) in anhydrous DMF at 80 °C for 6 h. 275 was obtained as a single product in 88% yield after purification by column chromatography. The cross coupling reaction was sluggish unless the reaction mixture was heated to 80 °C. The reaction was amenable for being conducted on a gram scale and proceeded in excellent yields.

**B: Attempted Stille Cross Coupling between Tributylstannane 279 and Bromide 282**

Encouraged by the successful Stille cross coupling of tributylstannane 279 and dibromide 280, we next turned to the elaboration of alkyne 282 via a similar Stille cross coupling (Scheme 143).

![Scheme 143 Attempted Synthesis of alkyne 281](image-url)

**Scheme 143** Attempted Synthesis of alkyne 281. *Reagents and conditions:* i) Pd₂(dba)₃, AsPh₃, CuTC, DMF, 100 °C, 3 h.
Similarly, tributylstannane 279 and bromide 282 were subjected to a mixture of Pd$_3$(dba)$_3$, AsPh$_3$ and CuTC in anhydrous DMF at 100 °C. Disappointingly, no desired product 281 was formed upon careful analysis of the resultant reaction mixture. It has been widely known that synthesis of tetra-substituted alkenes is difficult and requires harsher conditions. Hence microwave irradiation techniques (200 W) were employed for the requisite Stille cross coupling in an analogous manner to that discussed earlier (Section 5.3.3). To our dismay, a complex mixture that could not be identified was obtained. The inability of bromide 282 to effect a successful carbon-carbon bond formation with tributylstannane 279 was reasoned to be due to the electron-deficiency and steric bulk of bromide 282. Further attempts to make bromide 282 more electronically favourably via reduction of α-carbonyl group to a hydroxyl group using Corey-Bakshi-Shibata (CBS) reduction method also failed to deliver any of the desired product. Hence, it was concluded that the steric bulk of bromide 282 is the limiting factor that prevented the desired Stille cross coupling to occur.

Further literature searching was therefore conducted. In 1999, Liebeskind and co-workers documented an improved Stille cross coupling conditions using tetra-n-butylammonium diphenylphosphinate (Ph$_2$P(O)O$^-$/n-Bu$_4$N$^+$) as a n-Bu$_3$Sn$^+$ scavenger to facilitate some copper(I) mediated Stille cross couplings. As reported, the precipitates of n-Bu$_3$SnOP(O)Ph$_2$ from the reaction promoted the carbon-carbon bond formation. Accordingly, Ph$_2$P(O)O$^-$/n-Bu$_4$N$^+$ was generated by shaking a mixture of anhydrous tetra-n-butylammonium hydroxide (n-Bu$_4$NOH) and diphenylphosphinic acid in anhydrous MeOH. The resulting cloudy solution was filtered through a pad of Celite®. The filtrate was concentrated in vacuo to give a semi-solid followed by recrystallisation to afford a highly hygroscopic solid. The solid was used without further purification. Disappointingly, employing this n-Bu$_3$Sn$^+$ scavenger in the desired Stille cross coupling of tributylstannane 279 and bromide 282 led to an undefined complex mixture similar to that obtained by microwave reaction.

In light of the difficulty of assembling alkyne 281 via a late stage Stille cross coupling, we moved on to the synthesis of alkyne 281 employing the optimal conditions obtained earlier (Section 5.4.4).

5.5.5 Late-stage Sonogashira Cross Coupling between Bromide 275 and Alkyne 204

At this stage, efficient gram scale synthetic strategy to access bromide 275 had been established and we intended to take advantage of this work in our revised synthetic strategy. With the optimised
Sonogashira cross coupling conditions in hand, pyrone enynone 240 was obtained in 85% yield using Pd(PPh₃)₄ (0.1 equiv) and CuI (0.2 equiv) in anhydrous toluene in the presence of i-Pr₂NH at 80 °C after purification by column chromatography (Section 5.4.4). Pleasingly, the yield was reliably reproducible when the reaction was conducted over a range of reaction scales.

Scheme 144 Synthesis of pyrone enynone 240. Reagents and conditions: i) Pd(PPh₃)₄, CuI, toluene, 80 °C, 6 h, pressure tube, 89%.

5.5.6 End Game: Deprotection/Cyclisation to Elaborate 3-Dehydroxy-Tenuipyrene (200)

With pyrone enynone 240 in hand, attention turned to the critical concomitant deprotection/cyclisation step. Methyl ethers are known to be stable under most conditions and they require harsh conditions to be removed. A variety of conditions were therefore investigated to achieve the deprotection of methyl ether 285 (Table 29).

AlBr₃ in CH₃CN has been reported by Yamashita and co-workers to unmask enol methyl ethers at 80 °C.²⁷⁹ Accordingly, protected pyrone enynone 240 was subjected to AlBr₃ in anhydrous CH₃CN at −40 °C, but only starting material was observed as indicated by TLC analysis. After 2 h, the temperature was gradually elevated to 80 °C. A new polar spot was formed according to TLC analysis that was purified by column chromatography. ¹H and ¹³C NMR spectroscopic data of the obtained compound confirmed the formation of TBS silyl ether deprotected methyl ether 285 (entry 1, Table 29). When the solvent CH₃CN was replaced with nitrobenzene, the same product was obtained in 40% yield (entry 2, Table 29).
Chapter 5: Discussion of Tenuipyrone

Table 29. Attempted simultaneous deprotection.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlBr₃, CH₃CN, -40 °C to 80 °C, 6 h</td>
<td>286 quant.</td>
</tr>
<tr>
<td>2</td>
<td>AlBr₃, nitrobenzene, 50 °C, 10 h</td>
<td>286 40%</td>
</tr>
<tr>
<td>3</td>
<td>anhydrous HBr acetic acid, 90 °C, 2 h</td>
<td>a</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>anhydrous HBr acetic acid, 90 °C, 1 h</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>aqueous HBr, 90 °C, 2 h</td>
<td>c</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>aqueous HBr, 90 °C, 2 h</td>
<td>c</td>
</tr>
<tr>
<td>7</td>
<td>BBr₃, CH₂Cl₂, -78 °C to r.t., 6 h</td>
<td>286 80%</td>
</tr>
<tr>
<td>8</td>
<td>BCl₃, TBAI, CH₂Cl₂, -78 °C to r.t., 6 h</td>
<td>286 65%</td>
</tr>
<tr>
<td>9</td>
<td>AlCl₃, TBAI, CH₂CN, -40 °C to r.t., 6 h</td>
<td>286 57%</td>
</tr>
<tr>
<td>10</td>
<td>TMSCl, TBAI, CHCl₃, 48 h</td>
<td>c</td>
</tr>
<tr>
<td>11</td>
<td>TMSCl, NaI, CHCl₃, 48 h</td>
<td>c</td>
</tr>
<tr>
<td>12</td>
<td>NaH, ethanethiol, 100 °C, 1 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

a: NMR studies on the crude material revealed the formation of an unidentified complex mixture.
b: The reaction was conducted in a pressure tube.
c: See main text.

Due to the stability of the methyl ether, harsher conditions were next sought to effect a global deprotection. In 2010, Wu and co-workers demonstrated that use of HBr in acetic acid at 90 °C effected demethylation of related pyrone methyl ether derivatives. However, using these conditions in a normal round-bottom flask or pressure tube did not afford any of the desired product, with only the formation of a complex mixture being observed (entries 3-4, Table 29).

In view of the unsuccessful deprotection of methyl ether 240 using HBr in acetic acid, further attempts were conducted using aqueous HBr at 90 °C both in a round-bottom flask or pressure tube, respectively (entries 5-6, Table 29). The same clean polar spot (Rf = 0.25, n-hexanes/EtOAc = 1:4) was observed by TLC analysis using these two conditions. ¹H and ¹³C NMR spectroscopic data were obtained for the material available after purification by column chromatography. The ¹H NMR spectrum revealed the absence of three characteristic singlets at δ 3.91 assigned to be the methyl ether and at δ 1.20 and at δ 0.85 assigned to be the methyl and tert-butyl group of the TBS.
protecting group, thus indicating the successful deprotection of both protecting groups. However, careful analysis of the characteristic peaks of the obtained $^1$H NMR spectrum suggested that a mixture of at least three compounds was obtained due to the proposed equilibrium shown in Scheme 144.

![Scheme 145 Proposed tautomerisation-equilibrium for the obtained complex mixture of 285.](image)

Careful analysis of the $^1$H NMR spectrum (Figure 32) suggested that two doublets of doublets at $\delta$ 5.95 and 5.92 were consistent with the pyrone ring protons and three multiplets at $\delta$ 4.54-4.44, $\delta$ 4.24-4.18 and at $\delta$ 4.17-4.11 were characteristic for H-9 in the proposed structures 285* and 285**. Two multiplets at higher chemical shift at $\delta$ 3.33-3.00 were assigned to H-2 and H-3 of compound 285**. The singlets at $\delta$ 2.30 typically represent H-7'. The doublet of doublets at $\delta$ 1.93 observed for H-8 suggested the formation of a 9-membered ring (285**) as H-8 is generally observed at $\delta$ 1.20 as a doublet (Scheme 145). Furthermore, all of the characteristic carbons in the $^{13}$C NMR spectrum agreed with the proposed equilibrium mixture of compounds 285* and 285**. The $^{13}$C resonances at $\delta$ 203.62 and $\delta$ 203.57 were assigned to the cyclopentenone carbonyl carbons of 285* and 285**. Resonances at $\delta$ 161.5 and 161.3 and $\delta$ 127.8 and 127.78 were assigned to be the vinylic carbons C-4 and C-5 in the cyclopentenone ring. Resonances at $\delta$ 100.26 and $\delta$ 100.18 were assigned to the hemiketal carbon C-4' and the resonances at $\delta$ 99.9 and $\delta$ 79.7 were assigned to the triple bond carbons C-6 and C-7. High resolution mass spectrometry (HRMS) analysis of the compound 285 could only be obtained in negative mode possibly; due to the acidic nature of 4'-OH in hemiketal 285**. The observed high resolution mass spectrum data for (M-H) was 287.0933 that was in good agreement with compound 285 (C$_{16}$H$_{15}$O$_{5}$ (M-H) requires 287.0925). Analysis using HRMS showed good correlation with the expected mass and also an excellent match in isotopic distribution.

The NMR and HRMS data obtained both suggested the successful global deprotection of 240.
BBr₃ has been widely employed as a reagent effect deprotection of methyl ether protecting groups. Sodeoka and co-workers described an enantioselective synthesis of warfarin featuring a final dimethylation using BBr₃.²⁸¹ Disappointingly, use of BBr₃ in anhydrous CH₂Cl₂ did not afford any of the desired deprotected product, resulting in TBS silyl ether deprotected compound 286 in 80% yield (entry 7, Table 29).

In 1999, Coe and co-workers published a mild, selective aryl alkyl ether deprotection protocol using BCl₃ in the presence of stoichiometric TBAI.²⁸² The described reaction conditions for the attempted simultaneous deprotection of alkyne 240 promoted cleavage of the TBS silyl ether, however, the methyl protecting group remained untouched yielding the secondary alcohol 286 in 65% yield (entry 8, Table 29).

Ozaki and co-workers reported the use of a combination of AlCl₃ and TBAI as a chemoselective reagent to deprotect methyl ethers in the presence of a trans-cyclohexylidene in moderate to good yield.²⁸³ However, application of these conditions to methyl ether 240 did not afford the desired product and only the TBS silyl ether deprotected alcohol 286 was obtained in 57% yield after purification by column chromatography (entry 9, Table 29).

TMSI has been described to be a versatile reagent to effect methyl ether deprotection. Harris and co-workers first demonstrated the use of TMSI to perform a methyl ether deprotection in moderate yield.²⁸⁴ Although TMSI is commercially available, we decided to generate the sensitive reagent in situ. Adopting the procedure reported by Narang and co-workers,²⁸⁵ a mixture of TBAI and TMSCl, and NaI and TMSCl, was stirred at room temperature in CHCl₃, respectively. The mixtures were stirred at room temperature under a nitrogen atmosphere in the dark for 2 h. A solution of pyrone enynone 240 in CHCl₃ was added to the preformed brown solution with further stirring at room
temperature for 48 h (entries 10-11, Table 29). The results were similar to those obtained using aqueous HBr at 90 °C resulting in a mixture of products 285 in 56% yield (entries 5-6, Table 29).

In view of the disappointing results above, an alternative Lewis acid-mediated methyl ether deprotection methodology was sought. The use of sodium thioethoxide in DMF under reflux for the methyl ether deprotection was first developed by Welke and co-workers on the pyrone system. Employing these conditions on our substrate 240 only resulted in complete decomposition.

Scheme 146 Attempted deprotection/cyclisation. Reagents and conditions: i) aqueous HBr, 90 °C, pressure tube, 2 h; ii) AuCl, AgSbF₆, CH₂Cl₂, CH₃CN, or dioxane, r.t. 1 h.

In view of the possible equilibration of 285* and 285**, we last attempted a one-pot procedure for the synthesis of 3-dehydroxy-tenuipyrone 200 using aqueous HBr at 90 °C followed by treatment with a mixture of AuCl and AgSbF₆ in various solvents (Scheme 146). However, this did not afford any of the desired product and only a complex mixture of products resulted that could not be identified.

In conclusion, a highly convergent synthesis of the protected spiroketal precursor 240 was completed in 4 steps in 77% yield from 1,3-diketone 246. Unfortunately, all attempts towards effecting the final deprotection/cyclisation were unsuccessful. It was therefore decided to abandon the strategy based on preparing an advanced enynone precursor by Sonogashira cross coupling and design an alternative approach to synthesise tenuipyrone.
5.5.7 Summary of the Attempted 3-Dehydroxy-Tenuipyrone (200)

As depicted in Scheme 147, the highly convergent attempted synthesis of 3-dehydroxy-tenuipyrone (200) relied on a concomitant palladium(0) catalysed Stille-Sonogashira cross coupling. The unprecedented Stille cross coupling of pyrone stannane 279 and dibromide 280 successfully afforded bromide 275 in excellent yield. A palladium(0) catalysed Sonogashira cross coupling of an electron-deficient electrophile bromide 275 fortunately delivered the sterically hindered tetra-substituted olefin 240 in good yield. Unfortunately, the anticipated final deprotection/cyclisation step proved problematic. The inability to effect the required deprotection/cyclisation led us to abandon the present strategy and devise an alternative pathway to synthesise 3-dehydroxy-tenuipyrone 200.

Scheme 147 Summary of the attempted synthesis of spiroketal 200. Reagents and conditions: i) (CH₃)₂SO₄, K₂CO₃, acetone, reflux, 10 h, 90%; ii) n-BuLi, Bu₃SnCl, THF, −78 °C to 0 °C, 2 h, 92%; iii) NBS, KHCO₃, H₂O, 2 h, 90%; iv) (COBr)₂, DMF, CH₂Cl₂, 0.5 h, quant. v) Pd₂(dba)₃, CuTC, AsPh₃, DMF, 85%; vi) Jacobsen’s catalyst, toluene, acetic acid, r.t., 1 h, then H₂O, r.t., 12 h, 45%; vii) lithium acetylide-ethylenediamine complex, DMSO, 0°C to r.t, 24 h, quant; viii) TBSCl, imidazole, CH₂Cl₂, r.t., 4 h, quant; ix) Pd(PPh₃)₄, CuI, toluene, 50 °C, 12 h, 85%; x) aq. HBr, pressure tube, 90 °C, 2 h; xi) AuCl, AgSbF₆, CH₂Cl₂, 1 h.
5.6 Overall Summary and Future Work

5.6.1 Overall Summary

In summary, the first generation attempted synthesis of 3-dehydroxy-tenuipyrone (200) relied on a key Michael reaction of pyrone 177 and enynone 202 (Scheme 148). Enynone 202 could be readily synthesised via Sonogashira cross coupling from iodide 203 and alkyne 204 in high yield. Unfortunately, the planned Michael reaction was unsuccessful using a variety of catalysts and solvents. Attempted regioselective hydration of enynone 202 was abandoned due to the exclusive formation of the undesired regioisomer $229_c$, $229_d$ and $229_e$.

Scheme 148 First generation of attempted synthesis of 3-dehydroxy-tenuipyrone (200).
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The second generation synthesis approach to 3-dehydroxy-tenuipyrone (200) initially hinged on a key CeCl₃-promoted 1,2-carbonyl addition of lithiated pyrone 241 to enynone 243 (Scheme 149). Enynone 243 was prepared from commercially available 1,3-diketone 246 over 3 steps via a key Sonogashira cross coupling of iodide 244 and alkyne 204 in good yield. However, further investigation of the required 1,2-carbonyl addition was difficult to reproduce.

Scheme 149 CeCl₃-promoted synthesis of alkyne 240.

An alternative Stille cross coupling approach based on the aforementioned two coupling partners was therefore adopted (Scheme 150). The desired coupling partners 249 and 256 were obtained via iodination of pyrone 241 and stannylation of methoxy enynone 243, respectively. Efforts towards improving the synthesis of tributylstannane 256 via a sequential stannylation-Suzuki cross coupling successfully delivered tributylstannane 256 in similar yields. The attempted Stille cross coupling between iodo-pyrone 249 and tributylstannane 256 was unsuccessful upon investigation of various catalysts, co-catalysts, additives and solvents. A third generation synthesis of 3-dehydroxy-tenuipyrone 200 was therefore devised.

Scheme 150 Attempted synthesis of alkyne 240.
Chapter 5: Discussion of Tenuipyrene

The third generation attempted synthesis of 3-dehydroxy-tenuipyrole (200) is shown in Scheme 151. Initially, bromide 275 was obtained via bromination of enone 276 that was synthesised from Stille cross coupling of iodide 249 and tributylstannane 258. Further optimisation using tributylstannane 279 and dibromide 280 as the required coupling partners successfully afforded bromide 275 in high yield. Late stage Sonogashira cross coupling of bromide 275 and alkyne 204 uneventfully provided pyrone enyne 240 in excellent yield. Unfortunately, all attempts to effect the final deprotection/cyclisation were unsuccessful. It was therefore decided to investigate an alternative strategy to synthesise 3-dehydroxy-tenuipyrole (200).

![Scheme 151 Third generation of attempted synthesis of 3-dehydroxy-tenuipyrole (200).](image-url)
Chapter 5: Discussion of Tenuipyrone

5.6.2 Future Work

With the failed attempts to synthesise 3-dehydroxy-tenuipyrone (200) via a gold catalysed spiroketalisation, an alternative synthetic approach based on a conventional acid-catalysed deprotection/spiroketalisation was therefore proposed. Following the successful synthesis of the Stille cross coupling product bromide 275, a reaction sequence of acetal formation, formylation, nucleophilic addition and hydrogenation followed by oxidation and concomitant global deprotection/spiroketalisation should complete the synthesis of 3-dehydroxy-tenuipyrone (200) (Scheme 151). Alternatively, the lithiated derivative of bromide 275 can undergo nucleophilic addition to (R)-γ-valerolactone to give spiroketal precursor 288. Final acid-mediated deprotection/cyclisation of 287 is anticipated to yield the desired 3-dehydroxy-tenuipyrone (200).

Scheme 152 Alternative synthesis of 3-dehydroxy-tenuipyrone (200). Reagents and conditions: i) (CH$_2$OH)$_2$, triethyl orthoformate, p-TSA, toluene; ii) n-BuLi, DMF, THF −78 °C to r.t.; iii) (R)-(but-3-yn-2-yl)oxy)(tert-butyl)dimethylsilane, LDA, THF, −78 °C; iv) H$_2$, Pd/C, MeOH; v) TPAP, NMO, CH$_2$Cl$_2$; vi) aq. HBr.
Chapter 6: Experimental
Chapter 6: Experimental

6.1 First Generation of Attempted Synthesis of 3-Dehydroxy-tenuipyrone (200)

(R)-tert-Butyldimethyl(pent-4-yn-2-yloxy)silane (204)

Acetic acid (0.04 mL, 0.07 mmol) was added to a solution of [(R,R)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) (242 mg, 0.04 mmol, 0.2 mol %) in toluene (2 mL), and the mixture was left stirring open to the air. After 1 h, toluene and excess acetic acid were removed in vacuo. Racemic propylene oxide 208 (14 mL, 11.7 g, 0.2 mol) was added, and the flask was cooled to 0 °C using an ice bath. H₂O (1.98 mL, 0.011 mol) was added slowly over 10 min. The reaction was warmed up to r.t. and stirred overnight. The reaction was quenched at 0 °C by addition of saturated aqueous NH₄Cl (5 mL) and diluted with Et₂O (20 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound 211 (5.3 g, 0.84 g, 10.0 mmol, quant.) as a colourless oil that was used without further purification.

To a suspension of lithium acetylide ethylenediamine (1.0 g, 10.9 mmol, 1.1 equiv) in DMSO (15 mL) at 0 °C was added epoxide 208ₐ (0.7 mL, 10.0 mmol) over 10 min. After the addition was complete, the reaction mixture was allowed to warm slowly to r.t. and stirred overnight. The reaction was quenched at 0 °C by addition of saturated aqueous NH₄Cl (5 mL) and diluted with Et₂O (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound 204 (2.0 g, 10.0 mmol, quant.) as a light yellow oil which was used without further purification for the next step.

To a stirred solution of alcohol 211 in anhydrous CH₂Cl₂ (40 mL) was added imidazole (1.2 g, 21.8 mmol) and TBDMSCl (2.0 g, 12.0 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 2 h before H₂O (35 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 40 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo affording the title compound 204 (2.0 g, 10.0 mmol, quant.) as a light yellow oil which was used without further purification.
Chapter 6 Experimental of Tenuipyrone

[α]D20 = + 1.2 (c 10.0, CHCl3; [lit.213 +0.67, c 10.7, CHCl3]); 1H NMR (400 MHz, CDCl3): δ 3.98-3.92 (1H, m, 4-H), 2.36 (1H, ddd, J = 16.4, 5.6, 2.7 Hz, 3-H), 2.23 (1H, ddd, J = 16.4, 5.6, 2.7 Hz, 3-H), 1.96 (1H, t, J = 2.9 Hz, 1-H), 1.23 (3H, d, J = 5.6 Hz, 5-H), 0.88 (9H, s, (CH3)3Si(CH3)2), 0.09 (3H, s, (CH3)3Si(CH3)2), 0.07 (3H, s, (CH3)3Si(CH3)2). 13C NMR (100 MHz, CDCl3): δ 81.9 (C, 2-C), 69.7 (CH, 3-C), 67.5 (CH, 4-C), 29.3 (CH2, 3-C), 25.9 (CH3, (CH3)3Si(CH3)2), 25.8 (CH3, (CH3)3Si(CH3)2), 25.7 (CH3, (CH3)3Si(CH3)2), 23.2 (CH3, 5-C), 18.1 (C, (CH3)3Si(CH3)2), −3.0 (2 × CH3, (CH3)3Si(CH3)2).

The spectroscopic data was in agreement with literature values.213

2-Iodocyclopent-2-enone (203)

To a stirred solution of enone 205 (0.5 mL, 6.0 mmol) and PDC (0.64 g, 1.8 mmol) in dry CH2Cl2 (50 mL) was added I2 (2.3 g, 9 mmol) portionwise at 0 °C for 1 h. The reaction was further stirred at r.t. for 1 h. The residual iodine was quenched by addition of saturated aqueous Na2SO3 (30 mL) and the organic layer was separated. The aqueous layer was extracted with CH2Cl2 (2 × 40 mL). The combined organic layers were dried over anhydrous Na2SO4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 7:1) afforded the title compound 203 as a white solid (1.1 g, 5.3 mmol, 90%).

mp: 69-71 °C (lit.204 71 °C); 1H NMR (400 MHz, CDCl3): δ 8.01 (1H, t, J = 2.8 Hz, 3-H), 2.79-2.76 (2H, m, 4-H), 2.52-2.49 (2H, m, 5-H); 13C NMR (100 MHz, CDCl3): δ 204.1 (C, 1-C), 169.6 (CH, 3-C), 103.1 (C, 2-C), 31.4 (CH2, 4-C), 31.1 (CH2, 5-C).

The spectroscopic data was in good agreement with literature values.204

(R)-2-(4’-(tert-Butyldimethylsilyloxy)pent-1’-ynyl)cyclopent-2-enone (202)

A stirred solution of iodide 203 (65 mg, 0.31 mmol), Pd(PPh3)4 (36 mg, 0.03 mmol, 10%), Cul (6 mg, 0.03 mmol, 10%) and i-Pr2NH (0.1 mL, 1.2 mmol, 3 equiv.) in dry DMF (2 mL) was purged with argon for 1 h. To the above degassed mixture was added alkyne 204 (122 mg, 0.62 mmol) in anhydrous DMF (1 mL) dropwise under argon. The resulting mixture was stirred at 50 °C for 2 h under argon. After cooling to r.t., the reaction mixture was filtered through a pad of Celite® and
washed with EtOAc (10 mL). The filtrate was partitioned with H₂O (10 mL) and the organic layer was separated. The aqueous phase was exacted with EtOAc (3×5 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 10:1) afforded the title compound 202 (77 mg, 0.28 mmol, 90%) as a colourless oil.

[α]_{D}^{20} = -27.0 (c 0.8, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.66 (1H, s, 3-H), 4.01-3.96 (1H, m, 4'-H), 2.68-2.65 (2H, m, 4-H), 2.57-2.52 (1H, dd, \(J = 16.3, 5.8\) Hz, 3'-H₄), 2.46-2.39 (3H, m, 3'-H₃, 5-H), 1.22 (3H, d, \(J = 6.0\) Hz, 5'-H), 0.86 (9H, s, (CH₃)₃CSi(CH₃)₂), 0.05 (3H, s, (CH₃)₃CSi(CH₃)₂), 0.04 (3H, s, (CH₃)₂CSi(CH₃)₂); \(^1\)C NMR (100 MHz, CDCl₃): \(\delta\) 206.1 (C, 1-C), 164.1 (CH, 3-C), 130.4 (C, 2-C), 94.8 (C, 2'-C), 72.5 (C, 1'-C), 67.6 (CH, 4'-C), 33.8 (CH₂, 5-C), 30.4 (CH₂, 3'-C), 27.0 (CH₂, 4-C), 25.8 (3 × CH₃, (CH₃)₂CSi(CH₃)₂), 23.5 (CH₃, 5'-C), 18.0 (C, (CH₃)₂CSi(CH₃)₂), -4.73 (CH₃, (CH₃)₂CSi(CH₃)₂), -4.81 (CH₃, (CH₃)₂CSi(CH₃)₂); IR \(v_{max}(\text{film})\): 2240, 1715, 1682, 1524, 1416, 1276, 1108, 1021, 874; HRMS Found (ESI): [M+Na]^+ 301.1595, C₁₆H₂₆NaO₂Si requires 301.1594.

(R)-2-(4'-Hydroxypent-1'-yn-1-yl)cyclopent-2-enone (239)

To a stirred solution of TBAF (0.5 mL; 1.0 M in THF, 0.5 mmol) at room temperature. After stirring at r.t. for 30 min, a solution of enynone 202 (100 mg, 0.36 mmol) in THF (5 mL) was added and allowed to stir for another 30 min. Saturated aqueous NaHCO₃ (5 mL) was added to neutralise the reaction mixture to pH 7-8. The organic solvent was removed under reduced pressure and the residue was partitioned with EtOAc (10 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the title compound 239 (59 mg, 0.36 mmol, quant.) as a white solid.

\(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.67 (1H, t, \(J = 3.0\) Hz, 3-H), 3.99-3.90 (1H, m, 4'-H), 2.67-2.64 (2H, m, 4-H), 2.53-2.51 (2H, m, 3'-H₄), 2.42-2.38 (2H, m, 5-H), 1.24 (3H, d, \(J = 6.0\) Hz, 5'-H); \(^1\)C NMR (100 MHz, CDCl₃): \(\delta\) 206.4 (C, 1-C), 164.4 (CH, 3-C), 131.9 (C, 2-C), 93.9 (C, 2'-C), 73.2 (C, 1'-C), 66.0 (CH, 4'-C), 33.8 (CH₂, 5-C), 30.0 (CH₂, 3'-C), 27.0 (CH₃, 4-C), 22.0 (CH₃, 5-C), 18.; IR \(v_{max}(\text{film})\): 2224, 1716, 1678, 1532, 1389, 1275, 1106, 1021, 874.
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(±)-2-(4'-Methoxy-2'-oxopentyl)cyclopent-2-enone (229_c)

To a stirred solution of enynone 202 (50.0 mg, 0.18 mmol) in methanol (2 mL) was added a solution of HgO (2 mg, 0.01 mmol) and H₂SO₄ (0.02 mL, 0.36 mmol) in H₂O (0.5 mL). The resulting mixture was heated to 60 °C with stirring for 3 h. After cooling to r.t., saturated aqueous NaHCO₃ (10 mL) was added to neutralise the reaction mixture to pH 7-8. The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (n-hexanes/EtOAc 1:1) afforded the title compound 229_c (30.6 mg, 0.15 mmol, 85%) as light brown oil.

¹H NMR (400 MHz, CDCl₃): δ 7.54-7.20 (1H, m, 3'-H), 3.82-3.73 (1H, m, 4'-H), 3.33-3.31 (2H, m, 1'-H), 3.28 (3H, s, CH₃O), 2.73 (1H, dd, J = 16.2, 7.4 Hz, 3'-Hₐ), 2.65-2.60 (2H, m, 5-H), 2.46 (1H, dd, J = 16.2, 5.4 Hz, 3'-Hₐ), 2.40-2.37 (2H, m, 4'-H), 2.73 (1H, dd, J = 16.2, 7.4 Hz, 3'-Hₐ), 2.65-2.60 (2H, m, 5-H), 2.46 (1H, dd, J = 16.2, 5.4 Hz, 3'-Hₐ), 2.40-2.37 (2H, m, 4'-H), 2.73 (1H, dd, J = 16.2, 7.4 Hz, 3'-Hₐ), 2.65-2.60 (2H, m, 5-H), 2.46 (1H, dd, J = 16.2, 5.4 Hz, 3'-Hₐ), 2.40-2.37 (2H, m, 4'-H), 1.14 (3H, d, J = 6.0 Hz, 5'-H); ¹³C NMR (100 MHz, CDCl₃): δ 208.7 (C, 1'-C), 205.1 (C, 2'-C), 161.2 (CH, 3'-C), 138.9 (C, 2-C), 73.0 (CH, 4'-C), 56.3 (CH₃, CH₃O), 49.8 (CH₂, 3'-C), 39.0 (CH₂, 1'-C), 33.8 (CH₂, 5'-C), 26.9 (CH₂, 4'-C), 19.1 (CH₃, 5'-C); IR ν_max(film)/cm⁻¹: 3414, 2970, 2926, 2835, 2108, 1690, 1634, 1404, 1349, 1112, 1057, 944; HRMS Found (ESI): [M+Na]+ 219.0996, C₁₁H₁₆NaO₃ requires 219.0992.

(E)-2-(2'-Oxopent-3'-en-1'-yl)cyclopent-2-enone (229_d)

To a stirred solution of enynone 202 (20 mg, 0.11 mmol) in 1,4-dioxane (1 mL) was added a solution of HgO (2 mg, 0.01 mmol) and H₂SO₄ (0.01 mL, 0.18 mmol) in H₂O (0.2 mL) at r.t.. The resulting mixture was heated to 60 °C with stirring for 3 h. After cooling to r.t., saturated aqueous NaHCO₃ (5 mL) was added to neutralise the reaction mixture to pH 7. The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 1:1) afforded the title compound 229_d (9 mg, 0.046 mmol, 42 %) as light brown oil.

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¹H NMR (400 MHz, CDCl₃): δ 7.56-7.54 (1H, m, 3'-H), 6.94 (1H, dq, J = 16.0, 7.0, 4.9 Hz, 4'-H), 6.13 (1H, dq, J = 16.0, 6.9, 1.5 Hz, 3'-H), 3.43 (2H, s, 1'-H), 2.65-2.61 (2H, m, 4-H), 2.43-2.39 (2H, m, 5-H), 1.89 (3H, dd, J = 4.9, 1.5 Hz, 5'-H); ¹³C NMR (100 MHz, CDCl₃): δ 208.9 (C, 1-C), 196.2 (C, 2'-C), 161.2 (CH, 3-C), 144.2 (CH, 4'-C), 139.3 (C, 2-C), 131.4 (CH, 3'-C), 35.4 (CH₂, 1'-C), 33.9 (CH₂, 5-C), 26.9 (CH₂, 4-C), 18.4 (CH₃, 5'-C); IR ν max (film)/cm⁻¹: 3414, 2970, 2926, 1701, 1690, 1634, 1349, 1112, 1057, 944, 789; HRMS Found (ESI): [M+H]+ 165.0912, C₉H₁₀O₂ requires 165.0910.

(R)-2-(4'-Hydroxy-2'-oxopentyl)cyclopent-2-enone (229a)

To a stirred solution of enynone 202 (50 mg, 0.18 mmol) in 1,4-dioxane (4 mL) was added a solution of Hg(OAc)₂ (2 mg, 0.01 mmol) and silica supported H₂SO₄ (1.5 g) in H₂O (0.2 mL) at r.t.. The resulting mixture was stirred at r.t. for 12 h followed by addition of saturated aqueous NaHCO₃ (5 mL) to neutralise the reaction mixture to pH 7. The resulting mixture was concentrated under reduced pressure to remove the organic solvent. The residue was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the title compound 229a (28 mg, 0.16 mmol, 87%) as a colourless oil.

[α]D²⁰ = −12.2 (c 0.2, CHCl₃); ¹H NMR (400 MHz, CD₂Cl₂): δ 7.55-7.53 (1H, m, 3-H), 4.25-4.19 (1H, m, 4'-H), 3.34-3.33 (2H, m, 1'-H), 3.11 (1H, br s, OH), 2.68-2.64 (2H, m, 5-H), 2.64-2.59 (2H, dd, J = 8.2, 3.9 Hz, 3'-H), 2.43-2.40 (2H, m, 4-H), 1.18 (3H, d, J = 6.2 Hz, 5'-H); ¹³C NMR (100 MHz, CDCl₃): δ 209.0 (C, 1-C), 207.6 (C, 2'-C), 161.5 (CH, 3-C), 138.9 (C, 2-C), 64.0 (CH, 4'-C), 51.1 (CH₂, 3'-C), 39.0 (CH₂, 1'-C), 33.8 (CH₂, 5'-C), 27.0 (CH₃, 4-C), 22.4 (CH₃, 5'-C); IR ν max (film)/cm⁻¹: 3414, 2970, 2926, 1690, 1634, 1404, 1349, 1112, 1057, 944, 789; HRMS Found (ESI): [M+K]+ 221.0578, C₁₀H₁₄KO₂ requires 221.0575.
6.2 2nd Generation of Attempted Synthesis of 3-Dehydroxy-tenuipyrone (200)

4-Methoxy-6-methyl-2H-pyran-2-one (241)

![Chemical Structure](image)

To a stirred solution of pyrone 177 (2.0 g, 16.5 mmol) in anhydrous acetone (100 mL) was added K$_2$CO$_3$ (4.6 g, 33.0 mmol) and (CH$_3$)$_2$SO$_4$ (1.5 mL, 16.5 mmol). The reaction mixture was heated under reflux for 6 h, then the reaction mixture was poured into saturated aqueous NH$_4$Cl (130 mL) and extracted with EtOAc (2 × 80 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The residual orange solid was purified by flash column chromatography on silica gel (n-hexanes/EtOAc, 2:1) to afford the title compound 241 (2.1 g, 14.8 mmol, 90%) as a white solid.

**mp** 86-87 °C (lit. 89 °C); **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 5.78-5.77 (1H, dd, $J = 1.6, 0.8$ Hz, 5-H), 5.41 (1H, d, $J = 1.0$ Hz, 3-H), 3.77 (3H, s, CH$_3$O), 2.19 (3H, s, 7-H); **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 171.3 (C, 4-C), 164.9 (C, 2-C), 162.1 (C, 6-C), 100.4 (CH, 5-C), 87.4 (CH, 3-C), 55.8 (CH$_3$, CH$_3$O), 19.8 (CH$_3$, 7-C).

The spectroscopic data was in agreement with literature values.

3-Iodo-4-methoxy-6-methyl-2H-pyran-2-one (249)

![Chemical Structure](image)

$N$-Iodosuccinimide (4.5 g, 20.0 mmol) was added to a stirred solution of pyrone 241 (2.5 g, 18.2 mmol) and Mg(ClO$_4$)$_2$ (1.2 g, 5.5 mmol, 0.3 equiv) in CH$_3$CN (50 mL) under N$_2$. The reaction mixture was stirred at r.t. for 10 h, then the solvent was evaporated and the resulting brown solid was dissolved in CH$_2$Cl$_2$ (60 mL). The organic solution was washed with an aqueous solution of Na$_2$SO$_3$ (3 × 50 mL). The combined organic layers were dried with anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by short flash column chromatography on silica gel (n-hexanes/EtOAc, 2:1) yielded the title compound 249 (5.3 g, 20.0 mmol, quant.) as a white solid.
Chapter 6 Experimental of Tenuipyone

mp 144-146 °C (lit.237 143-145); \(^1^H\) NMR (CDCl\(_3\)): 5.98 (1H, s, 5-H), 3.98 (3H, s, CH\(_3\)O), 2.30 (3H, s, 7-H); \(^1^C\) NMR (CDCl\(_3\)): 170.4 (C, 4-C), 164.1 (C, 2-C), 161.6 (C, 6-C), 94.7 (CH, 5-C), 62.0 (C, 3-C), 57.4 (CH\(_3\), CH\(_3\)O), 20.0 (CH\(_3\), 7-C).

The spectroscopic data was in agreement with literature values.237

3-Methoxycyclopent-2-enone (245)

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{C} \\
\end{array}
\end{align*}
\]

To a stirred solution of 1,3-diketone 246 (1.0 g, 10.2 mmol) in dry MeOH (50 mL) was added TiCl\(_4\) (0.1 mL, 1 M in CH\(_2\)Cl\(_2\), 0.1 mmol) in CH\(_2\)Cl\(_2\) dropwise at 0 °C. After stirring at r.t. for 2 h, the reaction was quenched with H\(_2\)O (2 mL). MeOH was removed in vacuo to afford a light yellow solid. The resultant residue was partitioned between H\(_2\)O (30 mL) and CH\(_2\)Cl\(_2\) (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo to afford the title compound 245 (1.0, 9.2 mmol, 90%) as a white solid that was used for next step without further purification.

m.p.: 48.2-49 °C (lit.233 52-53 °C), \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.30-5.29 (1H, m, 2-H), 3.82 (3H, s, OCH\(_3\)), 2.61-2.57 (2H, m, 5-H), 2.45–2.42 (2H, m, 4-H); \(^1^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 205.7 (C, 1-C), 191.1 (C, 3-C), 104.5 (CH, 2-C), 58.7 (CH\(_3\), CH\(_3\)O), 34.2 (CH\(_2\), 5-C), 28.3 (CH\(_2\), 4-C).

The spectroscopic data is in agreement with literature values.233

2-Iodo-3-methoxycyclopent-2-enone (244)

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{C} \\
\end{array}
\end{align*}
\]

To a stirred solution of methoxy ether 245 (157 mg, 1.4 mmol) and NIS (225 mg, 2.1 mmol) in anhydrous CH\(_2\)Cl\(_2\) (15 mL) under argon was added TESOTf (93 mg, 0.35 mmol) dropwise at 0 °C. After stirring at r.t. for 10 h, saturated aqueous NaHCO\(_3\) (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo to give the title compound 244 (200.3 mg, 0.84 mmol, 60%) as a yellow solid that was used for next step without further purification.
Chapter 6 Experimental of Tenuipyrene

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.08 (3H, s, CH$_3$O), 2.89-2.85 (2H, m, 4-H), 2.70-2.66 (2H, m, 5-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 203.2 (C, 1-C), 187.8 (C, 3-C), 58.8 (CH$_3$, CH$_2$O) 30.6 (CH$_2$, 5-C), 27.0 (CH$_2$, 4-C), −4.8 (C, 2-C); HRMS Found (ESI): [M+Na]$^+$ 260.9388, C$_8$H$_7$INaO$_2$ requires 260.9383.

(R)-2-(4'-(tert-Butyldimethylsilyl)oxy)pent-1'-yn-1-yl)-3-methoxycyclopent-2-enone (243)

To a stirred solution of iodide 244 (65 mg, 0.27 mmol), Pd(PPh$_3$)$_4$ (35 mg, 0.027 mmol, 10%), CuI (10 mg, 0.054 mmol, 20%) and i-Pr$_2$NH (0.1 mL, 0.7 mmol) in anhydrous DMF (2 mL) was added alkyne 204 (143 mg, 0.72 mmol) dropwise under argon at r.t.. The reaction mixture was further purged with argon for 1 h. After stirring at r.t. for 10 h, the reaction mixture was filtered through a pad of Celite® and washed with EtOAc (15 mL). The filtrated was washed with H$_2$O (10 mL) and the organic layer was separated. The aqueous layer was washed with EtOAc (2 × 15 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 2:1) afforded the title compound 243 (71 mg, 0.23 mmol, 86%) as a colourless oil.

$\left[\alpha\right]_{D}^{20} = +0.3$ (c 0.4, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.22 (3H, s, CH$_3$O), 4.02-3.98 (1H, m, 4'-H), 2.61-2.41 (6H, m, 4-H, 5-H, 3'-H), 1.22 (3H, d, $J = 2.0$ Hz, 5'-H), 0.86 (9H, s, (CH$_3$)$_3$Si(CH$_2$)$_2$), 0.03 (6H, s, (CH$_3$)$_3$Si(CH$_2$)$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 205.7 (C, 1-C), 191.1 (C, 3-C), 103.5 (C, 2-C), 94.1 (C, 2'-C), 71.5 (C, 1'-C), 67.6 (CH$_3$, CH$_2$O), 33.2 (CH$_2$, 4-C), 30.7 (2 × CH$_2$, 5-C, 3'-C), 27.0 (CH$_3$, (CH$_3$)$_3$Si(CH$_2$)$_2$), 25.8 (CH$_3$, (CH$_3$)$_3$Si(CH$_2$)$_2$), 25.7 (CH$_3$, (CH$_3$)$_3$Si(CH$_2$)$_2$), 23.4 (CH$_3$, 5'-C), 18.1 (C, (CH$_3$)$_3$Si(CH$_2$)$_2$), −4.73 (CH$_3$, (CH$_3$)$_3$Si(CH$_2$)$_2$), −4.81 (CH$_3$, (CH$_3$)$_3$Si(CH$_2$)$_2$); IR $\nu_{max}$(film): 2915, 2889, 2113, 1775, 1662, 1524, 1416, 1376, 1068, 1021, 874; HRMS Found (ESI): [M+Na]$^+$ 331.1711, C$_{17}$H$_{38}$NaO$_3$Si requires 331.1700.
6.3 3rd Generation of Attempted Synthesis of 3-Dehydroxy-tenuipyrone (200)

(R)-2-(4’-((tert-Butyldimethylsilyl)oxy)pent-1’-yn-1-yl)-3-(tributylstannyl)cyclopent-2-enone (256)

To a stirred solution of i-Pr$_2$NH (0.036 mL, 0.25 mmol) in anhydrous THF (5 mL) was added n-BuLi (0.12 mL, 2 M in cyclohexanes, 0.24 mmol) dropwise at −78 °C under N$_2$. After stirring at this temperature for 30 min, the reaction mixture was stirred at 0 °C for 20 min. To the resulting mixture was added n-Bu$_3$SnH (0.06 mL, 0.24 mmol) at 0 °C and the resulting mixture was further stirred at 0 °C for 20 min. A solution of vinylogous ether 243 (71 mg, 0.23 mmol) in anhydrous THF (2 mL) was added at −78 °C. Upon complete addition, the reaction was stirred at −20 °C for 1 h. The cooling bath was removed and the reaction was quenched by addition of saturated aqueous NH$_4$Cl (10 mL). The resulting mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexane/EtOAc 40:1) gave the title compound 256 (61 mg, 0.1 mmol, 42%) as a colourless oil.

$[\alpha]_D^{20} = +10.8$ (c 0.9, CHCl$_3$); $^{1}$H NMR (400 MHz, CDCl$_3$): δ 4.04-3.97 (1H, m, 4'-H), 2.84-2.78 (2H, m, 4-H), 2.62 (1H, dd, J = 16.5, 4.6 Hz, 3'-H$_2$), 2.47-2.42 (1H, m, 3'-H$_3$), 2.40-2.37 (2H, m, 5-H), 1.58-1.49 (5H, m, Bu$_3$Sn), 1.37-1.26 (11H, m, Bu$_3$Sn, 5'-H), 1.14-1.08 (5H, m, Bu$_3$Sn), 0.93-0.86 (18H, m, Bu$_3$Sn, (CH$_3$)$_3$Si(CH$_3$)$_2$), 0.06 (6H, s, (CH$_3$)$_3$Si(CH$_3$)$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ206.0 (C, 1-2), 192.1 (C, 3-4), 139.2 (C, 2-C), 93.2 (C, 2'-C), 75.6 (C, 1'-C), 67.8 (CH, 4'-C), 34.9 (CH, 4-C), 34.5 (CH, 5-C), 30.7 (3 × CH$_3$, SnCH$_2$CH$_2$CH$_2$CH$_3$), 29.1 (3 × CH$_2$, SnCH$_2$CH$_2$CH$_2$CH$_3$), 27.3 (3 × CH$_3$, SnCH$_2$CH$_2$CH$_2$CH$_3$), 25.8 (3 × CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$), 23.4 (CH$_3$, 5'-C), 18.1 (C, (CH$_3$)$_3$Si(CH$_3$)$_2$), 13.7 (3 × CH$_2$, SnCH$_2$CH$_2$CH$_2$CH$_3$), 9.7 (CH$_2$, SnCH$_2$CH$_2$CH$_2$CH$_3$), −4.7 (CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$), −4.8(CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$); IR $\nu_{max}$(film): 2900, 1756, 1637, 1524, 1416, 1376, 1068, 1021, 874; HRMS Found (ESI): [M+H]$^+$ 569.2844, C$_{29}$H$_{50}$O$_3$SiSn requires 569.2836.

2-Bromo-1,3-cyclopentandione (264)
Chapter 6 Experimental of Tenuipyrone

To a slurry of 1,3-cyclopentandione 246 (1.0 g, 10.1 mol) in H₂O (10 mL) was added a solution of KHCO₃ (1.1 g, 11.1 mmol) in H₂O (10 mL) at r.t. over 1 h. CO₂ was evolved during the addition of KHCO₃ and the reaction mixture became a brown homogenous solution. Upon complete addition of KHCO₃ solution, NBS (1.8 g, 10.1 mmol) was added in portions at such a rate to control the temperature below 30 °C (ca. 1 h). The brown solution was left with stirring at r.t. for another 1.5 h before aqueous H₂SO₄ (1.2 mL, 10 M, 12 mmol) was added until pH reached about 2. During the addition of acid, a yellow precipitate was observed. The slurry was stirred for 30 min, and the solid was collected by filtration and washed with H₂O (2 × 20 mL). The product was azeotropic distillation with toluene (3 × 10 mL) to give bromide 264 (1.56 g, 0.89 mmol, 90%) as a beige solid that was used without further purification.

2-Bromo-3-methoxycyclopent-2-enone (254)

![Structure of 2-Bromo-3-methoxycyclopent-2-enone (254)]

To a stirred solution of bromide 264 (1.0 g, 5.6 mmol) in anhydrous MeOH (50 mL) was added TiCl₄ (0.5 mL, 1 M in CH₂Cl₂, 0.5 mmol). After stirring at r.t. for 2 h, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL). The resulting mixture was concentrated under reduced pressure and the residue was partitioned between H₂O (30 mL) and CH₂Cl₂ (50 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the title compound 254 (1.07 g, 5.6 mmol, quant.) a light yellow solid that was used to next step without further purification.

m.p. 114-115.7 °C (lit.¹⁰⁸ 120 °C); ¹H NMR (400 MHz, CD₃Cl₃): δ 4.10 (3H, s, OCH₃), 2.80-2.77 (2H, m, 5-H), 2.63-2.60 (2H, m, 4-H); ¹³C NMR (100 MHz, CDCl₃): δ 207.8 (C, 1-C), 189.5 (C, 3-C), 98.2 (C, 2-C), 58.6 (CH₃, CH₂O), 33.5 (CH₂, 4-C), 26.6 (CH₂, 5-C).

The spectroscopic data was in agreement with literature values.¹⁰⁸

2-Bromo-3-(tributylstannyl)cyclopent-2-enone (263)

![Structure of 2-Bromo-3-(tributylstannyl)cyclopent-2-enone (263)]

To a stirred solution of i-Pr₂NH (0.2 mL, 1.4 mmol) in anhydrous THF (10 mL) was added n-BuLi (0.6 mL, 2 M in cyclohexanes, 1.2 mmol) dropwise at −78 °C. After stirring at −78 °C for
30 min, the mixture was further stirred at 0 °C for 30 min followed by addition of n-Bu₃SnH (0.3 mL, 1.2 mmol). The resulting mixture was further stirred at 0 °C for 15 min and cooled to −78 °C followed by addition of bromide 254 (230 mg, 1.2 mmol) in anhydrous THF (5 mL). Upon complete addition, the reaction mixture was stirred at −20 °C for 1 h. The cooling bath was removed and the reaction was quenched by addition of saturated aqueous NH₄Cl (30 mL). After stirring at r.t. for 1 h, the mixture was partitioned with Et₂O (15 mL) and the organic layer was separated. The aqueous layer was extracted with Et₂O (2 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 35:1) afforded the title compound 263 (167 mg, 0.37 mmol, 31%) a colourless oil.

1H NMR (400 MHz, CDCl₃): δ 2.79-2.76 (2H, m, 3 × C), 2.44-2.41 (2H, m, 5-H), 1.57-0.84 (27H, m, 3 × SnCH₂CH₂CH₂CH₃); 13C NMR (100 MHz, CDCl₃): δ 201.1 (C, 1-C), 187.3 (C, 3-C). 136.5 (C, 2-C), 35.5 (CH₃, 4-C), 33.3 (CH₂, 5-C), 29.0 (3 × CH₂, SnCH₂CH₂CH₂CH₃), 27.3 (3 × CH₂, SnCH₂CH₂CH₂CH₃), 13.6 (3 × CH₃, SnCH₂CH₂CH₂CH₃), 10.0 (3 × CH₂, SnCH₂CH₂CH₂CH₃); IR νmax(film)/cm⁻¹: 2956, 2920, 2853, 1703, 1518, 1463, 1376, 1376, 1074, 1022; HRMS Found (ESI): [M+Na]⁺ 473.0464, C₁₁H₁₉SnBrNaOSn requires 473.0457.

Potassium ((R)-4-tert-butyldimethylsiloxypent-1-yl)trifluoroborate (265)

![Structure of potassium (R)-4-tert-butyldimethylsiloxypent-1-yl)trifluoroborate (265)](image)

To a solution of alkyn 204 (0.82 g, 4.1 mmol) in dry THF (20 mL) was added n-BuLi (2.6 mL, 1.6 M in hexane, 4.1 mmol) dropwise under argon at −78 °C. After stirring for 1 h, B(Oi-Pr)₃ (1.4 mL, 6.2 mmol, 1.5equiv) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h then warmed to −20 °C with stirring for 1 h. Saturated aqueous KHF₂ (0.47 g, 24.6 mmol, 6.0 equiv) was added with vigorous stirring. After stirring at −20 °C for 1 h, the reaction mixture was warmed to r.t. for 1 h. The resulting mixture was concentrated under reduced pressure and the resulting white solid was dried under high vacuum to remove H₂O. The solid was extracted with hot acetone. The resulting organic solution was filtered, and the filtrated was concentrated in vacuo to afford the title compound 265 (1.1 g, 3.7 mmol, 90%) as a fluffy white solid. Compound 265 was used in the next step without further purification.

m.p.: decomposition was observed. 1H NMR (400 MHz, CD₂OD): δ 3.97-3.90 (1H, m, 4-H), 2.29-2.21 (2H, m, 3-H), 1.23 (3H, d, J = 5.6 Hz, 5-H), 0.89 (9H, s, (CH₃)₃C), 0.09 (3H, s,
(CH$_3$)$_3$Si(CH$_3$)$_2$, 0.09 (3H, s, (CH$_3$)$_3$Si(CH$_3$)$_2$); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 77.2 (C, 2-C), 69.8 (CH, 4-C), 68.9 (C, 1-C), 31.2 (CH$_2$, 3-C), 26.4 (2 $\times$ CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$), 26.3 (CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$), 23.6 (C, 5-C), 18.9 (C, (CH$_3$)$_3$Si(CH$_3$)$_2$), 23.6 (2 $\times$ CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$), 23.6 (CH$_3$, (CH$_3$)$_3$Si(CH$_3$)$_2$).
6.4 Synthesis of Alkyne 240

3-(Tributylstannyl)cyclopent-2-enone (258)

To a stirred solution of \(i\)-Pr\(_2\)NH (0.3 mL, 2.1 mmol) in anhydrous THF (15 mL) was added \(n\)-BuLi (0.9 mL, 2 M in cyclohexane, 1.8 mmol) at –78 °C. The resulting mixture was stirred at –78 °C for 30 min then at 0 °C for another 30 min. \(n\)-Bu\(_3\)SnH (0.5 mL, 1.8 mmol) was added to the above mixture at 0 °C. The resulting mixture was stirred for 15 min at 0 °C then it was cooled to –78 °C, at which temperature a solution of methoxy ether 245 (200 mg, 1.8 mmol) in anhydrous THF (3 mL) was added dropwise. The reaction was stirred at –20 °C for 1 h. A saturated aqueous solution of NH\(_4\)Cl (15 mL) was added to quench the reaction. The resulting mixture was stirred at r.t. for 1 h before Et\(_2\)O (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et\(_2\)O (2 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (40 mL), dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Purification by flash chromatography on silica gel (n-hexane/EtOAc 15:1) afforded the title compound 258 (298 mg, 0.8 mmol, 45%) as a colourless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.34 (1H, t, J = 1.9 Hz, 2-H), 2.84-2.80 (2H, m, 4-H), 2.28-2.25 (2H, m, 5-H), 1.62-0.82 (27H, m, 3 × CH\(_3\)(CH\(_2\))\(_3\)Sn) ; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 210.0 (C, 1-C), 190.1 (C, 3-C), 143.7 (CH, 2-C), 36.5 (CH\(_2\), 5-C), 34.9 (CH\(_2\), 4-C), 29.0 (3 × CH\(_2\), SnCH\(_2\)CH\(_2\)CH\(_2\)Sn), 27.2 (3 × CH\(_2\), SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)Sn), 13.6 (3 × CH\(_3\), SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 9.5 (3 × CH\(_3\), SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)).

The spectroscopic data was in agreement with literature values.\(^{288}\)

4-Methoxy-6-methyl-3-(3′-oxocyclopent-1′-enyl)-2H-pyran-2-one (276)

Tributylstannane 258 (1.1 g, 2.9 mmol) was added to a solution of iodo-pyrone 249 (0.85 g, 3.2 mmol) anhydrous THF (10 mL) followed by Pd(PPh\(_3\))\(_4\) (23 mg, 0.2 mmol) and dry LiCl (120 mg, 2.9 mmol) under argon. The mixture was heated under reflux with stirring for 12 h. The mixture was poured into ice-water (20 mL) and the aqueous layer was extracted with Et\(_2\)O (3 × 50 mL). The
combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexanes/EtOAc 1:1, then pure EtOAc) to give the title compound 276 (55 mg, 0.25 mmol, 93%) as a yellow solid.

mp 104 -106 °C; ¹H NMR (400 MHz, CDCl₃): 6.76 (1H, t, J = 1.6 Hz, 2'-H), 6.13 (1H, s, 5'-H), 3.98 (3H, s, CH₃O), 3.20-3.17 (2H, m, 5'-H), 2.40-2.37 (2H, m, 4'-H), 2.33 (3H, s, -CH₃); ¹³C NMR (100 MHz, CDCl₃): 210.9 (C, 3'-C), 169.7 (C, 4-C), 167.2 (C, 2-C), 165.7 (C, 6-C), 161.6 (C, 1'-C), 132.3 (CH, 2'-C), 110.0 (CH, 5-C), 95.0 (C, 3-C), 57.0 (CH₃, CH₂O), 34.4 (CH₂, 4'-C), 32.3 (CH₂, 5'-C), 20.8 (CH₃, 7-C); IR νmax(film)/cm⁻¹: 2981, 1701, 1645, 1542, 1461, 1376, 1341, 1232, 1187, 1155, 1007, 914; HRMS Found (ESI): [M+H]^+ 221.0808, C₁₂H₁₃O₄ requires 221.0808.

3-(2'-Bromo-3'-oxocyclopent-1'-enyl)-4-methoxy-6-methyl-2H-pyran-2-one (275)

A stirred solution of enone 276 (22 mg, 0.1 mmol) in anhydrous CH₂Cl₂ was added Br₂ (19 mg, 0.12 mmol) in dry CH₂Cl₂ (2 mL) at 0 °C under Ar. The reaction mixture was stirred at 0 °C for 1 h before Et₃N (10 mg, 0.1 mmol) was added dropwise. The mixture was stirred for another 1 h at 0 °C, then at r.t. for 1 h. H₂O (2 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (n-hexane/EtOAc 1:3) afforded the title compound 275 (15 mg, 0.05 mmol, 52%) as a brown solid and recovered starting material 276 (10 mg, 0.45 mmol).

m.p. 137-138 °C; ¹H NMR (400 MHz, CDCl₃): 6.15 (1H, s, 5-H), 3.91 (3H, s, CH₃O), 2.99-2.95 (2H, m, 5'-H), 2.59-2.57 (2H, m, 4'-H), 2.32 (3H, s, -CH₃); ¹³C NMR (100 MHz, CDCl₃): 201.8 (C, 3'-C), 167.0 (C, 4-C), 165.6 (C, 2-C), 165.1 (C, 6-C), 160.8 (C, 1'-C), 126.8 (C, 2'-C), 99.6 (CH, 5-C), 95.0 (C, 3-C), 57.8 (CH₃, CH₂O), 32.9 (CH₂, 4'-C), 30.1 (CH₂, 5'-C), 20.8 (CH₃, 7-C); IR νmax(film)/cm⁻¹: 2981, 2920, 1711, 1638, 1518, 1341, 1232, 1187, 1155, 1007, 919, 814; HRMS Found (ESI): [M+H]^+ 298.9913, C₁₂H₁₂BrO₄ requires 298.9918
Chapter 6 Experimental of Tenuipyrone

6.5 Optimised Synthesis of Alkyne 240

4-Methoxy-6-methyl-3-(tributylstannyl)-2H-pyran-2-one (279)

To a stirred solution of pyrone 241 (1.0 g, 7.1 mmol) in anhydrous THF (50 mL) was added n-BuLi (4.5 mL, 1.6 M in hexanes, 7.1 mmol) at −78 °C over 10 min. The reaction mixture turned red upon addition of n-BuLi indicating the successful lithiation of pyrone 241. The reaction mixture was left with stirring at −78 °C for 1 h before n-Bu$_3$SnCl (1.9 mL, 7.1 mmol) was added in. Upon stirring at −78 °C for 1 h, the reaction was quenched with slow addition of H$_2$O (40 mL). The residue was extracted with Et$_2$O (3 × 40 mL). The organic layers were combined, washed with a saturated aqueous solution of NaCl (100 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo.

Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 4:1) afforded the title compound 279 (2.8 g, 6.5 mmol, 92%) as a yellow oil.

$^1$H NMR (400 MHz, CD$_3$Cl$_3$): $\delta$ 5.94 (1H, s, 5-H), 3.78 (3H, s, CH$_3$O), 2.24 (3H, s, 6-CH$_3$), 1.54-1.46 (5H, m, SnBu$_3$), 1.35-1.26 (7H, m, SnBu$_3$), 1.08-1.04 (5H, m, SnBu$_3$), 0.87 (10H, t, $J$ = 7.3 Hz, SnBu$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.6 (C, 4-C), 169.7 (C, 2-C), 167.9 (C, 3-C), 164.8 (C, 6-C), 94.4 (CH, 5-C), 55.7 (CH$_3$, CH$_2$O), 29.1 (3 × CH$_2$, SnCH$_2$CH$_2$CH$_2$CH$_2$), 27.3 (3 × CH$_2$, SnCH$_2$CH$_2$CH$_2$CH$_3$), 20.6 (CH$_3$, 7-C), 13.8 (3 × CH$_2$, SnCH$_2$CH$_2$CH$_2$CH$_3$), 10.8 (3 × CH$_2$, SnCH$_2$CH$_2$CH$_3$).

The spectroscopic data is in agreement with literature values.$^{276}$

2,3-Dibromocyclopent-2-enone (280)

Oxalyl bromide (1.17 g, 5.4 mmol) was added to a solution of bromide 264 (809 mg, 4.6 mmol) in CH$_2$Cl$_2$ (25 mL) in the presence of DMF (0.43 mL) at 0 °C under argon over 5 min. The stirred solution was warmed to 25 °C over 1 h and partitioned between Et$_2$O (100 mL) and H$_2$O (40 mL). The organic layer was separated and the aqueous layer was washed with Et$_2$O (50 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the title compound 280 (1.1 g, 4.6 mmol, quant.) as a white solid. Compound 280 was used to next step without further purification.
Chapter 6 Experimental of Tenuipyrone

m.p. 79-81 °C (lit. 275 79-81 °C); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.03-2.99 (2H, m, 5-H), 2.72-2.68 (2H, m, 4-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 197.3 (C, 1-C), 159.1 (C, 3-C), 128.3 (C, 2-C), 35.8 (CH$_2$, 5-C), 34.9 (CH$_2$, 4-C).

The data was in agreement with the literature. 275

(R)-2-Bromo-3-(4'-(tert-butyldimethylsilyloxy)pent-1'-ynyl)cyclopent-2-enone (282)

A degassed solution of dibromide 280 (240.0 mg, 1.0 mmol), trifluoroborate 265 (334.4 mg, 1.1 mmol, 1.1 equiv), Cs$_2$CO$_3$ (975.0 mg, 3.0 mmol, 3.0 equiv), and Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (40.8 mg, 0.05 mmol, 5 mol %) in a mixture of dioxane and H$_2$O (10.0 mL, 4:1) was stirred at 50 °C for 4 h. After cooling to r.t., the reaction was filtered through a pad of Celite$^6$ and washed with EtOAc (20 mL). The filtrate was partitioned between H$_2$O (20 mL) and the organic layer was separated. The aqueous layer was washed with EtOAc (2×20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Purification by column chromatography on silica gel (n-hexanes/EtOAc 10:1) afforded the title compound 282 (311.0 mg, 0.87 mmol, 87%) as a colourless oil.

$[\alpha]_D^{20} = -11.1$ (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CD$_3$Cl$_3$): $\delta$ 4.08-4.01 (1H, m, 4'-H), 2.72-2.68 (2H, m, 5-H), 2.68-2.56 (2H, m, 3'-H), 2.56-2.53 (2H, m, 4-H), 1.27 (3H, d, $J = 6.0$ Hz, 5'-H), 0.08 (9H, s, (CH$_3$)$_3$C(Si(CH$_3$)$_2$)$_2$), 0.07 (6H, s, (CH$_3$)$_3$C(Si(CH$_3$)$_2$)$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.2 (C, 1-C), 154.6 (C, 3-C), 128.0 (C, 2-C), 109.8 (C, 2'-C), 77.7 (C, 1'-C), 67.1 (CH, 4'-C), 32.7 (CH$_2$, 4-C), 31.7 (CH$_2$, 3'-C), 31.2 (CH$_2$, 3'-C), 25.8 (3×CH$_3$, (CH$_3$)$_3$C(Si(CH$_3$)$_2$)$_2$), 23.6 (CH$_3$, 5'-C), 18.1 (C, (CH$_3$)$_3$C(Si(CH$_3$)$_2$)$_2$), -4.6 (CH$_3$, (CH$_3$)$_3$C(Si(CH$_3$)$_2$)$_2$), -4.7 (CH$_3$, (CH$_3$)$_3$C(Si(CH$_3$)$_2$)$_2$); IR $\nu_{max}$(film)/cm$^{-1}$: 1701, 1617, 1518, 1334, 1132, 1167, 1095, 1006, 918, 814; HRMS Found (ESI): [M+Na]$^+$ 379.0700, C$_{16}$H$_{25}$NaO$_2$Si requires 379.0699.
3-(2'-Bromo-3'-oxocyclopent-1'-en-1'-yl)-4-methoxy-6-methyl-2H-pyran-2-one (275)

To a stirred solution of pyrone 279 (470.2 mg, 1.1 mmol) and dibromide 280 (279.1 mg, 1.1 mmol) in anhydrous DMF (2 mL) was added Pd$_2$(dba)$_3$ (100 mg, 0.1 mmol), AsPh$_3$ (135 mg, 0.4 mmol) and CuTC (60 mg, 0.3 mmol) at r.t. under argon. The mixture was degassed three times using Freeze-Pump-Thaw technique, then the reaction mixture was heated to 80 °C with stirring for 8 h. After cooling to ambient temperature, the reaction mixture was filtered through a pad of silica supported KF and washed with Et$_2$O (20 mL). The filtrate was partitioned with H$_2$O (20 mL) and the organic layer was separated. The aqueous layer was extracted with Et$_2$O (2 × 15 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (n-hexanes/EtOAc 1:1) to give the title compound 276 (289 mg, 0.97 mmol, 88%) as a light brown solid.

m.p. 137-138 °C; $^1$H NMR (400 MHz, CDCl$_3$): 6.15 (1H, s, 5-H), 3.93 (3H, s, CH$_3$O), 3.01-3.00 (2H, m, 5'-H), 2.63–2.60 (2H, m, 4'-H), 2.35 (3H, s, 7-H); $^{13}$C NMR (100 MHz, CDCl$_3$): 201.8 (C, 3'-C), 167.0 (C, 4'-C), 165.6 (C, 2'-C), 165.1 (C, 6-C), 160.8 (C, 1'-C), 126.8 (C, 2'-C), 99.6 (CH, 5-C), 95.0 (C, 3-C), 57.8 (CH$_3$, CH$_3$O), 32.9 (CH$_2$, 4'-C), 30.1 (CH$_2$, 5'-C), 20.8 (CH$_3$, 7-C); IR $\nu_{\text{max}}$(film)/cm$^{-1}$: 2981, 2920, 1701, 1638, 1518, 1341, 1232, 1187, 1155, 1007, 919, 814; HRMS Found (ESI): [M+H]$^+$ 298.9913, C$_{12}$H$_{12}$BrO$_4$ requires 298.9918.
(4'R)-3-(2'-(4''-(tert-butyldimethylsilyloxy)pent-1''-yn-1''-yl)-3'-oxocyclopent-1'-en-1'-yl)-4-methoxy-6-methyl-2H-pyran-2-one (240)

A stirred solution of bromo-enone 275 (100 mg, 0.33 mmol), Pd(PPh₃)₄ (38 mg, 0.03 mmol, 10%), CuI (12 mg, 0.06 mmol, 20%) and i-Pr₂NH (0.3 mL, 2.1 mmol) in anhydrous toluene (2 mL) was purged with argon at r.t. for 1 h followed by addition of alkyne 204 (150 mg, 0.76 mmol) in anhydrous toluene (0.5 mL) dropwise at r.t. under argon. The resulting mixture was stirred at 80 °C for 6 h under argon. After cooling to r.t., the resultant dark brown mixture was filtered through a pad of Celite® and washed with EtOAc (10 mL). The filtrate was partitioned with H₂O (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (n-hexanes/EtOAc 2:3) afforded the title compound 240 (122 mg, 0.29 mmol, 89%) as colourless solid.

m.p. 65.3-66 °C; [α]D₂₀ = -18.6 (c 0.8, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.11 (1H, s, 5-H), 3.93-3.91 (1H, m, 4''-H), 3.88 (3H, s, 4-OCH₃), 2.99-2.93 (2H, m, 4'-H), 2.53 (1H, dd, J = 16.5, 5.1 Hz, 3''-H₂), 2.50-2.41 (2H, m, 5'-H), 2.34 (1H, dd, J = 16.5, 5.1 Hz, 3''-H₂), 2.33 (3H, s, 7-H), 1.20 (3H, d, J = 4.0 Hz, 6''-H), 0.85 (9H, s, (CH₃)₃Si(CH₃)₂), 0.03 (3H, s, (CH₃)₃Si(CH₃)₂), 0.01 (3H, s, (CH₃)₃Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 206.1 (C, 3''-C), 167.6 (C, 4'-C), 167.2 (C, 6'-C), 165.0 (C, 2'-C), 161.0 (C, 1''-C), 128.7 (C, 2' '-C), 100.6 (CH, 5'-C), 97.7 (C, 3'-C), 94.9 (C, 2''-C), 73.7 (C, 1''-C), 67.5 (CH, 4''-C), 56.5 (CH₃, CH₂O), 34.3 (CH₂, 3'-C), 30.6 (CH₂, 5'-C), 29.2 (CH₂, 4'-C), 25.6 (3 × CH₃, (CH₃)₃Si(CH₃)₂), 23.1 (CH₃, 5'-C), 20.5 (CH₃, 7'-C), 17.9 (C, (CH₃)₃CSi(CH₃)₂), -4.88 (CH₃, (CH₃)₃Si(CH₃)₂), -4.94 (CH₃, (CH₃)₃Si(CH₃)₂); IR νmax(film)/cm⁻¹: 2924, 2857, 1697, 1641, 1603, 1540, 1464, 1376, 1342, 1233, 1187, 1155, 1047, 1006, 934; HRMS Found (ESI): [M+Na]⁺ 439.1911, C₂₃H₂₃O₃NaSi requires 439.1898.
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Appendix

(2S,3S)-1-Benzyl-2,3-isopropylidenedioxy-5,6-epoxyhexane (81)

$\text{H NMR (400 MHz, CDCl}_3\text{)}$

$\text{C NMR (100 MHz, CDCl}_3\text{)}$
Appendix

(2S,3S)-1-Benzyl-2,3-isopropylidenedioxy-5-ol-6-iodo-hexane (110)

\[
\begin{align*}
\text{Bn} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{I} & \quad \text{I}
\end{align*}
\]

\( ^1H \) NMR (400 MHz, CDCl\textsubscript{3} )

\( ^13C \) NMR (100 MHz, CDCl\textsubscript{3} )
(2S,3S)-1-Benzylxoy-2,3-isopropylidenedioxy-5-one-6-iodo-hexane (112)

\[
\text{BnO} \quad \text{O} \quad \text{O} \quad \text{I}
\]

\(^1\text{H} \text{ NMR (400 MHz, CDCl}_3\text{)}

\(^{13}\text{C} \text{ NMR (100 MHz, CDCl}_3\text{)}

243
Appendix

(2S,3S)-1-Benzyloxy-2,3-isopropylidenedioxy-5-one-6-chloro-hexane (114)

\[
\text{\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{structure.png}};
\end{tikzpicture}}
\]

\[\text{\(^1\)H NMR (400 MHz, CDCl\textsubscript{3})}\]

\[\text{\(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3})}\]

244
(2S,3S)-1-Benzyloxy-2,3-isopropylidenedioxy-5-ol-6-bromo-hexane (111)

$\text{H NMR (400 MHz, CDCl}_3$)

$\text{C NMR (100 MHz, CDCl}_3$)
Appendix

(2S,3S)-1-Benzyloxys-2,3-isopropylidenedioxy-5-one-6-bromo-hexane (113)

\[
\text{H NMR (400 MHz, CDCl}_3\text{)}
\]

\[
\text{C NMR (100 MHz, CDCl}_3\text{)}
\]
(2S,3S)-1-Benzyl-2,3-isopropylidenedioxy-hex-5,6-diol (122)

$\text{H NMR (400 MHz, CDCl}_3$)

$\text{C NMR (100 MHz, CDCl}_3$)
Appendix

(2S,3S)-1-Benzyloxy-2,3-isopropylidenedioxy-hex-5-ol-6-(4-methyl)benzenesulfonate (123)

$\begin{align*}
\text{BnO} & \quad \text{OH} \\
\quad & \quad \text{OTs}
\end{align*}$

$^1$H NMR (400 MHz, CDCl₃)

$^1$C NMR (100 MHz, CDCl₃)
(2S,3S)-1-Benzyloxy-2,3-isopropylidenedioxy-5-one-6-(4'-methyl)benzenesulfonate hexane (124)

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

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3)\]

\[\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3)\]
Appendix

(2S,3S)-1-Benzyl oxy-2,3-isopropylidenedioxy-5-ol-6-azido-hexane (135)

\[
\text{BnO} \quad \begin{array}{c}
\text{OH} \\
\text{N}_3
\end{array}
\]

\( ^1H \text{ NMR (400 MHz, CDCl}_3\) \)

\( ^{13}C \text{ NMR (100 MHz, CDCl}_3\) \)
(2S,3S)-1-Benzzyloxy-2,3-isopropylidenedioxy-5-ol-6-amino-hexane (134)

\[ \begin{align*}
\text{BnO} & \quad \text{OH} \\
& \quad \text{NH}_2
\end{align*} \]

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

$^{13}$C NMR (100 MHz, CDCl$_3$)
Appendix

1-(3-((4S,5S)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-5-((tert butyldimethylsilyloxy)methyl)-1H-pyrrole-2-carbaldehyde (107)

\begin{center}
\includegraphics[width=0.5\textwidth]{molecule.png}
\end{center}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})

\begin{center}
\includegraphics[width=\textwidth]{h_nmr.png}
\end{center}

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3})

\begin{center}
\includegraphics[width=\textwidth]{c_nmr.png}
\end{center}
1-(3-(((4S,5S)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxopropyl)-5-(((tert-butyldimethylsilyloxy)methyl)-1H-pyrrole-2-carbaldehyde (86)

$\text{O}^\circ\text{N}\text{OTBS}$

$\text{BnO}$

$\text{OHC}$

$^1\text{H NMR (400 MHz, CDCl}_3$)

$^{13}\text{C NMR (100 MHz, CDCl}_3$)
Appendix

(2S,4R,5S)-5-(benzyloxymethyl)-4-hydroxy-1',4,4',5-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carbaldehyde (140a)

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

$^{13}$C NMR (100 MHz, CDCl$_3$)
Appendix

2S,4R,5R)-5-(benzyloxymethyl)-4-hydroxy-1',4',4',5-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carbaldehyde (140b)

$\begin{align*}
\text{BnO}^+\%O\text{N}^+\%O\text{C}^+\%O\text{H}
\end{align*}$

$\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{)}
\end{align*}$

$\begin{align*}
\text{13C NMR (100 MHz, CDCl}_3\text{)}
\end{align*}$
Appendix

(2S,3S)-1-(tert-Butyl)diphenylsilyloxy-2,3-isopropylidenedioxy-hex-5-ene (147)

$\text{TBDPSO} \quad \frac{\text{O}}{\text{O}}$

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

$^{13}$C NMR (100 MHz, CDCl$_3$)

258
(2S,3S)-1-\textit{tert}-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-5,6-epoxyhexane (148)

\[ \text{TBDPSO} \]

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

$^{13}$C NMR (100 MHz, CDCl$_3$)
Appendix

(2S,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-6-azido-hexan-5-ol (149)

\[
\begin{align*}
\text{TBDPSO} & \quad \text{OH} \\
& \quad \text{N}_3
\end{align*}
\]

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

$^{13}$C NMR (100 MHz, CDCl$_3$)
(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-6-amino-hexan-5-ol (150)

\[
\text{H NMR (400 MHz, CDCl}_3)\]

\[
\text{C NMR (100 MHz, CDCl}_3)\]
Appendix

5-((tert-Butyldimethylsilyloxy)methyl)-1-(3-((4S,5S)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-1H-pyrrole-2-carbaldehyde (151)

$\text{H NMR (400 MHz, CDCl}_3$)

$\text{C NMR (100 MHz, CDCl}_3$)
5-((tert-Butyldimethylsilyloxy)methyl)-1-(3-(((4S,5S)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-1H-pyrrole-2-carbaldehyde (151b)

**1H NMR (400 MHz, CDCl3)**

**13C NMR (100 MHz, CDCl3)**
Appendix

5-((tert-Butyldimethylsilyloxy)methyl)-1-((4S,5S)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxopropyl)-1H-pyrrole-2-carbaldehyde (152)

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

$^{13}$C NMR (100 MHz, CDCl$_3$)
(4S,5S)-5-((tert-Butyldiphenylsilyloxy)methyl)-4-hydroxy-1',4',5'-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carbaldehyde (153)

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

$^{13}$C NMR (100 MHz, CDCl$_3$)
Appendix

(2R,4S,5S)-4-Hydroxy-5-(hydroxymethyl)-1',4,4',5-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carbaldehyde (154_a)

\[
\begin{align*}
\text{HO} & \quad \text{O} \quad \text{N} \\
\text{HO} & \quad \text{O} \\
\text{OHC} & 
\end{align*}
\]

\[1^1\text{H NMR (400 MHz, CD}_3\text{COCD}_3)\]

\[1^3\text{C NMR (100 MHz, CD}_3\text{COCD}_3)\]
(2S,4S,5S)-4-Hydroxy-5-(hydroxymethyl)-1',4,4',5-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carbaldehyde (154a)

$\text{H NMR (400 MHz, CD}_3\text{COCD}_3\text{)}$

$\text{C NMR (100 MHz, CD}_3\text{COCD}_3\text{)}$
Appendix

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR (100 MHz, CDCl$_3$)
Appendix

(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-5,6-epoxyhexane (161a)

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR (100 MHz, CDCl$_3$)
Appendix

(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-5-ol-6-azido-hexane (168a)

\[
\text{NMR 400 MHz, CDCl}_3
\]

\[
\text{^13C NMR (100 MHz, CDCl}_3\text{)}
\]
(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-5-ol-6-azido-hexane (168b)

$$\text{NMR} \quad 400 \text{ MHz, CDCl}_3$$

$$\text{C NMR} \quad (100 \text{ MHz, CDCl}_3)$$
Appendix

(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-6-amino-hexan-5-ol (158ₐ)

![Structural formula of the compound]

**¹H NMR 400 MHz, CDCl₃**

![NMR spectrum for ¹H NMR]

**¹³C NMR (100 MHz, CDCl₃)**

![NMR spectrum for ¹³C NMR]
(2R,3S)-1-(tert-Butyldiphenylsilyloxy)-2,3-isopropylidenedioxy-6-amino-hexan-5-ol (158b)

\[ \text{TBDPSO} \quad \text{OH} \quad \text{NH}_2 \]

\[^1\text{H} \text{ NMR 400 MHz, CDCl}_3\]

\[^{13}\text{C} \text{ NMR (100 MHz, CDCl}_3\)]
Appendix

6-(((tert-Butyldimethylsilyl)oxy)methyl)-6-hydroxy-2H-pyran-3(6H)-one (83)

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR (100 MHz, CDCl$_3$)
5-((((tert-Butyldimethylsilyl)oxy)methyl)-1H-pyrrole-2-carbaldehyde (82)

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR (100 MHz, CDCl$_3$)
5-((tert-Butyldimethylsilyloxy)methyl)-1-(3-((4S,5R)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-1H-pyrrole-2-carbaldehyde (172a)

\[ \text{Structure Image} \]

\[ \text{H NMR 400 MHz, CDCl}_3 \]

\[ \text{C NMR (100 MHz, CDCl}_3) \]
5-((tert-Butyldimethylsilyloxy)methyl)-1-(3-((4S,5R)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl)-1H-pyrrole-2-carbaldehyde (172b)

\[ \text{Appendix} \]

\[ \text{1H NMR 400 MHz, CDCl}_3 \]

\[ \text{13C NMR (100 MHz, CDCl}_3 \) \]
1-(2-(((tert-Butyldimethylsilyloxy)methyl)-1H-pyrrol-1-yl)-3-(((4S,5R)-5-((tert-butylidiphenyl-silyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (157)

\[
\begin{align*}
&\text{TBDDS} \quad \text{O} \quad \text{O} \quad \text{OTBS} \\
&\text{OH} \quad \text{C} \\
\end{align*}
\]

\(^1\text{H NMR 400 MHz, CDCl}_3\)

\(^{13}\text{C NMR (100 MHz, CDCl}_3\)

(4S,5R)-5-((tert-Butyldiphenylsilyloxy)methyl)-4-hydroxy-1',4',4',5'-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carbaldehyde (173)

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR (100 MHz, CDCl$_3$)
Appendix

Acortatarin A (XX)

$^1$H NMR 400 MHz, CD$_3$OD

$^{13}$C NMR (100 MHz, CD$_3$OD)
Appendix

5-epi-acortafarin A (17a)

$^1$H NMR 400 MHz, CD$_3$OD

$^{13}$C NMR (100 MHz, CD$_3$OD)
(R)-2-(4′-(tert-Butyldimethylsilyloxy)pent-1′-ynyl)cyclopent-2-enone (202)

\[
\begin{align*}
\text{H NMR} & \quad 400 \text{ MHz, CDCl}_3 \\
\text{C NMR} & \quad 100 \text{ MHz, CDCl}_3
\end{align*}
\]
2-(4'-Methoxypentanoyl)cyclopent-2-enone (229c)

\[
\text{H NMR 400 MHz, CDCl}_3
\]

\[
\text{C NMR 100 MHz, CDCl}_3
\]
Appendix

(E)-2-(2'-Oxopent-3'-en-1'-yl)cyclopent-2-enone (229a)

$\text{\H NMR 400 MHz, CDCl}_3$

$\text{\C NMR 100 MHz, CDCl}_3$
Appendix

(R)-2-(4'-hydroxy-2'-oxopentyl)cyclopent-2-enone (229e)

\[\text{HO} \quad \text{O} = \text{C} \quad \text{O} = \text{C}\]

\(^1\text{H} \text{NMR} 400 \text{ MHz, CDCl}_3\)

\(^{13}\text{C} \text{NMR} 100 \text{ MHz, CDCl}_3\)
Appendix

(R)-2-(4'-hydroxypent-1'-yn-1'-yl)cyclopent-2-enone (239)

$\text{\textsuperscript{1}H NMR 400 MHz, CDCl}_3$ (239)

$\text{\textsuperscript{13}C NMR 100 MHz, CDCl}_3$
Appendix

(R)-2-(4'-(tert-Butyldimethylsilyloxy)pent-1'-ynyl)-3-methoxycyclopent-2-enone (243)

$^{1}H$ NMR 400 MHz, CDCl$_3$

$^{13}C$ NMR 100 MHz, CDCl$_3$
(R)-2-(4'-(tert-Butyldimethylsilyl)oxy)pent-1'-yn-1'-yl)-3-(tributylstannyl)cyclopent-2-enone (256)

$\text{H NMR 400 MHz, CDCl}_3$

$\text{C NMR 100 MHz, CDCl}_3$
2-Iodo-3-methoxycyclopent-2-enone (244)

\[
\begin{array}{c}
\text{3} \quad \text{O} \\
\text{1}
\end{array}
\]

\[\text{H NMR 400 MHz, CDCl}_3\]

\[\text{1} \text{C NMR 100 MHz, CDCl}_3\]
2-Bromo-3-(tributylstanny1)cyclopent-2-enone (263)

\[
\begin{array}{c}
\text{Bu}_3\text{Sn} \\
\text{Br}
\end{array}
\]

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR 100 MHz, CDCl$_3$
Appendix

Potassium ((R)-4-tert-butyldimethyldimethyldichlorosiloxypent-1-yne)trifluoroborate (265)

$^1$H NMR 400 MHz, CD$_3$OD

$^{13}$C NMR 100 MHz, CD$_3$OD
Appendix

4-Methoxy-6-methyl-3-(3'-oxocyclopent-1'-enyl)-2H-pyran-2-one (276)

\[\text{Structure Image}\]

\(^1\)H NMR 400 MHz, CDCl\(_3\)

\(^{13}\)C NMR 100 MHz, CDCl\(_3\)
(R)-2-Bromo-3-(4"-(tert-butyldimethylsilyloxy)pent-1"-ynyl)cyclopent-2-enone (282)

$^1$H NMR 400 MHz, CDCl$_3$

$^1$C NMR 100 MHz, CDCl$_3$
Appendix

3-(2′-Bromo-3′-oxocyclopent-1′-en-1′-yl)-4-methoxy-6-methyl-2H-pyran-2-one (275)

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR 100 MHz, CDCl$_3$
Appendix

(4''R)-3-(2'-(4''-(tert-butyldimethylsilyloxy)pent-1''-yn-1''-yl)-3''-oxocyclopent-1''-en-1''-yl)-4''-methoxy-6-methyl-2H-pyran-2-one (240)

$^1$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR 100 MHz, CDCl$_3$