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Total Synthesis of Lasionectrin and Synthetic Studies Towards Pestaloxazine A

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

Doctor of Philosophy

by

Vincent Poral

School of Chemical Sciences
University of Auckland
October 2016
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Chapter two: Discussion

Nature of contribution by PhD candidate
Retrosynthesis design, synthetic work, manuscript preparation

Extent of contribution by PhD candidate (%)
80

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<td>Supervisor, advises, editing</td>
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Certification by Co-Authors

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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<tr>
<td>Daniel Furkert</td>
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Preface

Some parts of this thesis have been previously published:

“Total Synthesis and Structural Confirmation of the Antimalarial Naphthopyrone Lasionectrin”

Poral, V. L.; Furkert, D. P; Brimble; M. A., Org. Lett. 2015, 17, 6214–6217
Abstract

This thesis describes our efforts towards the synthesis of two natural products which exhibit promising biological activity and is therefore divided in two parts.

Part one describes the first enantioselective synthesis and structural confirmation of naphthopyrone lasionectrin (13), which was extracted from the fungus *Lasionectra* sp. and exhibited antimalarial activity (IC$_{50}$ = 11 µM). Lasionectrin (13) is a naphthalene derivative which contains a fused pyrone-tetrahydrofuran ring system. Several synthetic strategies were explored to prepare the carbon skeleton of lasionectrin (13). Our initial approach which hinged on formation of the fused bicycle in a single step using chiral hypervalent iodine was ultimately unsuccessful. Our revised synthetic route to lasionectrin (13) involved late-stage installation of the fused pyrone-tetrahydrofuran ring system via tandem dihydroxylation-tosylate displacement beginning from alkene 199, followed by a carboxylation-cyclisation sequence. Key alkene 199 was efficiently assembled with high stereoselectivity from aldehyde 129 and sulfone 119 using a Julia-Kocienski olefination.

Part two details our synthetic efforts towards the synthesis of pestaloxazine A (208). Natural product 208 was extracted from a marine-derived fungus belonging to the *Pestalotiopsis* genus, and exhibited antiviral activity against EV71 (IC$_{50}$ = 16.1 µM). Pestaloxazine A (208) is a racemic alkaloid dimer which contains a unique spiro[1,2-oxazinane-diketopiperazine] moiety. We sought to access the 1,2-oxazinane ring system by the application of oxidative radical cyclisation conditions to a N-hydroxylamine precursor. Our initial synthetic strategy hinged on the preparation of the diketopiperazine ring system prior to installation of the 1,2-oxazine moiety, which was ultimately unsuccessful. Our revised approach involved Mitsunobu reaction of known alcohol 291 and hydroxamate 311 to give hydroxamic acid 309. However, attempts to effect 1,6-hydrogen abstraction with hydroxamic acid 309 to provide the 1,2-oxazine ring system were unsuccessful.
Acknowledgments

Firstly, I would like to thank my supervisor DProf. Margaret Brimble for the opportunity to work on this project and for her support and guidance, both in research and in the writing of this thesis. I would also like to thank my co-supervisor Dr Daniel Furkert for his valuable advices.

A special thank you to everyone that helped me with the proofreading: Margaret, Paul, Megan, Fanny, Mathilde, James and Rachelle. Correcting my frenglish was not an easy task. I would also like to thank Janice and Tim for all their technical support as well as Michael and Tony for the help with NMR and MS.

I would also like to thank the members of the Brimble group past and present including but not limited to: Rachelle, Megan, Harry, Jono, Paul, George, everyone in the study room and last but not least Mathilde with whom I shared passionate discussions and squash breaks. A special thought also to all the French interns who were in the group for a short period of time. Chloé, Mathilde, Stephanie…

Special thanks to all the members of my handball team (ACHB) past and present, with whom I travelled around to win some tournaments. I would also like to thank my old friend Fanny for the support, the proofreading and the Schokobons. Lydie is joining me to thank Romain for his short stay in New Zealand and my visit to Brisbane. Un grand merci à mes parents et ma famille ainsi que les amis restés en France. Finally, a big thank you goes to Amelie for all the support during all these years and especially the rough time of writing.
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<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>2D</td>
<td>two-dimensional</td>
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<tr>
<td>Å</td>
<td>ångström</td>
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<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>ACT</td>
<td>artemisinin-based combination therapies</td>
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<td>AD</td>
<td>asymmetric dihydroxylation</td>
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<td>aq.</td>
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<td>tert-Butoxycarbonyl</td>
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<td>br</td>
<td>broad</td>
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<tr>
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<td>butyl</td>
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<tr>
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</tr>
<tr>
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<td>CDI</td>
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<tr>
<td>COMU</td>
<td>(1-cyano-2-ethoxy-2-oxoethylidenaminoxy)-dimethylamino-morpholino-carbenium hexafluorophosphate</td>
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<td>COSY</td>
<td>correlated spectroscopy</td>
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<tr>
<td>d</td>
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<td>d.r.</td>
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<td>dppf</td>
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</tr>
<tr>
<td>e.e.</td>
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</tr>
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<td>e.g.</td>
<td>example gratia</td>
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<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>EOM</td>
<td>ethoxymethyl</td>
</tr>
<tr>
<td>eq</td>
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<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
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<td>et al.</td>
<td>et alii (and others)</td>
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<td>Et</td>
<td>ethyl</td>
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### Abbreviations

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<th>Full Form</th>
<th>Meaning</th>
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<td>g</td>
<td>gram(s)</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
<td></td>
</tr>
<tr>
<td>( h )</td>
<td>Plank’s constant</td>
<td></td>
</tr>
<tr>
<td>HFMD</td>
<td>hand, foot and mouth disease</td>
<td></td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple-bond correlation spectroscopy</td>
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<td>HMDS</td>
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<td>HMPA</td>
<td>hexamethylphosphoramid</td>
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<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
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<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
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<td>( i.e. )</td>
<td>id est</td>
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</tr>
<tr>
<td>IBX</td>
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<tr>
<td>imid.</td>
<td>imidazole</td>
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<tr>
<td>( i-\text{Pr} )</td>
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</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
<td></td>
</tr>
<tr>
<td>ITN</td>
<td>insecticide-treated mosquito nets</td>
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</tr>
<tr>
<td>( J )</td>
<td>coupling constant</td>
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<tr>
<td>L</td>
<td>litre, large or unspecified ligand</td>
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<td>tetra-n-propylammonium perruthenate</td>
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PART I

Total Synthesis of Lasionectrin
Chapter One
Introduction
1.1. Malaria

In 2015 only, nearly 440 thousand people died from malaria.\textsuperscript{1} According to the World Health Organization, nearly half of the global population lives in malaria-endemic regions and it was estimated that 214 million persons were infected in 2015.\textsuperscript{1}

1.1.1. Causes, Symptoms and Complications

Malaria is a parasitic infection caused by \textit{Plasmodium} parasites which multiply in the red blood cells. Among the five \textit{Plasmodium} species which cause malaria in humans, \textit{Plasmodium falciparum} is the most dangerous and leads to the most deadly forms of malaria. The main transmission vector of the disease is the female \textit{Anopheles} mosquito. A single bite from an infected female \textit{Anopheles} mosquito injects from two to thousands of parasite cells into the blood stream of the host. Additionally, the parasite may be transferred from human to mosquitoes when the female \textit{Anopheles} mosquito bites another malaria-infected human.

The first symptoms of the parasitic infection appear 12 to 14 days after \textit{Anopheles} mosquito bite. The typical symptoms are fever, headache, chills, vomiting, muscle aches and low blood pressure. However due to the fact that these symptoms are not malaria-specific, the diagnosis of malaria may be difficult. In the case of \textit{Plasmodium falciparum} infection, if not rapidly treated these symptoms may progress to more severe illness such as kidney failure, pulmonary oedema and in some cases death.\textsuperscript{1}

Some groups of the population are more vulnerable to the \textit{Plasmodium} infection and more likely to develop severe complications. These groups include pregnant women, children under 5 years of age, immuno-depressed persons and travellers.

1.1.2. Life Cycle of \textit{Plasmodium falciparum}

The life cycle of the \textit{Plasmodium falciparum} parasite starts with the injection of sporozoites (\textit{i.e.} motile spore-like form of parasite) into the bloodstream by the female \textit{Anopheles} mosquito while feeding (Figure 1.1).\textsuperscript{2} Some of the sporozoites travel to the liver and enter the hepatocytes to multiply and release merozoites (\textit{i.e.} non motile cells) into the blood stream. Asexual replication of the merozoites begins by invading blood cells (\textit{i.e.} erythrocytes). Some of the merozoites leave the replication cycle to form sexual gametocytes which travel in the bloodstream \emph{via} blood cells. When a non-infected female \textit{Anopheles} mosquito feeds, the gametocytes are released in the midgut of the mosquito and develop to gametes. Following fusion of the male and female gametes, a motile zygote forms (ookinets) burrows through the midgut wall to form encapsulated ookinets (oocyst). Division of the oocyst releases millions of
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sporozoites, which migrate to the salivary gland and will be released into the bloodstream during the next blood meal of the mosquito.

![Life cycle of Plasmodium falciparum parasite](image)

**Figure 1.1: Life cycle of Plasmodium falciparum parasite.**

1.1.3. Vectors control and treatments

1.1.3.1. Vector control

As the primary transmission of the *Plasmodium* parasite is through female *Anopheles* mosquitoes, the main strategy to eradicate malaria is to prevent mosquitoes to acquire or pass the infection. To date, vector control is the most effective way to prevent and reduce malaria transmission. Insecticide-treated mosquito nets (ITN), indoor insecticide spraying and mosquito repellent are widely used in most of the malaria-endemic countries. ITN have contributed to considerably reduce the mortality rate of under 5 years old children and pregnant women. However, resistance of *Anopheles* mosquitoes to insecticides has recently been reported.
1.1.3.2. Treatments from early 1900’s until now

Prior to isolation of quinine (1) from cinchona bark by French chemists Pelletier and Caventou in 1820, infusions of cinchona barks were used to treat fever from the 1600’s in South America (Figure 1.2). By 1890, quinine was proven to be effective in the treatment of malaria and became the predominant drug to treat malaria for the next 40 years.5-7

In 1934, Andersag and co-workers synthesised chloroquine (2) which was shown in clinical trials to exhibit stronger bioactivity against *Plasmodium falciparum* than all marketed anti-malaria drugs.5 In 1960, the World Health Organization recommended chloroquine as the main treatment against malaria.1 However, the first cases of chloroquine resistance of *P. falciparum* were reported in 1957 in West Cambodia and rapidly expanded to the neighbouring regions, creating an urgent need for new anti-malaria medicine.8

In 1971, during a large screening campaign of traditional Chinese medicine, Youyou Tu and co-workers isolated biologically active artemisinin (3) from the leaves of *Artemisia annua*.9 Sesquiterpene artemisinin and analogues exhibited strong biological activity against a chloroquine resistant strain of *P. falciparum*.9 In the early 1980’s, artemisinin (3) and derivatives hit the world market and are to date the drugs of choice to treat malaria.10,11

![Figure 1.2: Structure of quinine (1), chloroquine (2) and artemisinin (3).](image)

Currently, artemisinin-based combination therapies (ACT) are the best treatments available to treat *Plasmodium falciparum* malaria. The World Health Organization recommends five ACT combinations to treat malaria: artemether (4) and lumefantrine (5); artesunate (6) and amodiaquine (7); artesunate (6) and mefloquine (8); dihydroartemisinin (9) and piperaquine (10); artemunate (6), sulfadoxine (11) and pyrimethamine (12) (Figure 1.3).1
Figure 1.3: Common drugs used in the ACT treatment.

However, in certain regions of Cambodia, artemisinin resistance has recently been reported.\textsuperscript{12} In addition, in some malaria-endemic areas the efficacy of the artemisinin-based combination therapy has declined during the last decade with the appearance of \textit{K13} mutated \textit{Plasmodium falciparum}.\textsuperscript{13-17} Despite having vaccines in development there is an urgent need for new effective anti-malaria drugs.\textsuperscript{18}
1.2. Lasionectrin: Isolation, Structure and Biological Activity

Lasionectrin (1) was discovered in 2012 during the course of a screening program aimed at identifying biologically active secondary metabolites from fungi in the Hypocreales order (Figure 1.4). The acetone extract of a strain named Lasionectria (F-176,994) isolated from fern leaf from the largest national park in Equatorial Guinea (i.e. Monte Alén national park) exhibited *in vitro* biological activity against the malarial parasite *Plasmodium falciparum* (Pf3D7). After isolation of the active constituent, lasionectrin (1), biological testing revealed potent antimalarial activity (IC$_{50}$ = 11 µM). Structural elucidation revealed that lasionectrin (1) has a similar fused pyrone-tetrahydrofuran core to the known polyketide metabolite monocerin (4).

![Figure 1.4: Lasionectrin (1) and monocerin (4) structures.](image)

The structure of lasionectrin (1) was elucidated using a combination of NMR, UV-Vis and (+)-HRESIMS analysis (Figure 1.5). The relative configuration of the stereocentres were assigned by NOESY. Nuclear Overhauser effect correlations were observed between H-11b and H-3a indicating *cis* stereochemistry of the fused pyrone-tetrahydrofuran ring system. In addition, correlations of H-11b with H$_A$-3 and H$_B$-3 with H-2 established a *trans* relationship between H-11b and H-2.

![Figure 1.5: Key nOe correlations in lasionectrin (1).](image)
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1.3. Related natural fused pyrone-tetrahydrofuran containing compounds

1.3.1. Monocerin (14)

Prior to isolation of lasionectrin (13), Turner and Aldridge reported the isolation of the antifungal benzopyran monocerin (14) from fermentation of Helminthosporium monoceras along with minor metabolites hydroxymonocerin (15) and monocerone (16) (Figure 1.6).\(^\text{20}\) Since then, monocerin (14) has been isolated from various endophytic fungi such as Fusarium larvarum, Exserohilum turcicum, Microdochium bolleyi and Exserohilum rostratum.\(^\text{21-25}\) Over the years, several monocerin derivatives have also been isolated: in 1982, Robeson and Strobel isolated 7-O-demethylmonocerin (17); in 2008, Krohn et al. and Pudhom et al. simultaneously reported the isolation of 12-hydroxymonocerin (18) and 11-hydroxymonocerin (19); in 2014, Yin et al. reported the isolation of exserolides A to E (20–24).\(^\text{22-25}\) Monocerin (14) and its analogues possess a fused pyrone-tetrahydrofuran ring system similar to that present in lasionectrin (13).

Figure 1.6: Structures of monocerin (14) and related analogues.

Monocerin (14) and some analogues exhibit antifungal, plant pathogenic and insecticidal activity. More importantly, Pudhon and co-workers reported antimalarial activity against Plasmodium falciparum for monocerin (14) (IC\(_{50}\) = 0.68 \(\mu\)M) and 11-hydroxymonocerin 19 (IC\(_{50}\) = 7.70 \(\mu\)M).\(^\text{24}\)
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In 1984, Simpson et al. highlighted that the biosynthesis of monocerin (14) starts from polyketide 25 (Scheme 1.1). However, the biosynthesis of the polyketide 25 may vary according to type of microorganism it originates from. Action of cyclase on polyketide 25 allows the installation of the aromatic ring in 26 which in turn is converted to benzopyrone 27 via lactonisation. Following enzymatic transformation (i.e. oxidase) of benzopyrone 27 to quinone methide 28, ring closure via conjugate addition and action of methyl transferase gives monocerin (14).

Scheme 1: Proposed biosynthesis of monocerin (14).

1.3.2. Lichenicolins A and B (29, 30)

Lichenicolins A and B (29 and 30) were isolated in 2005 by He and co-workers from the fungal strain LL-RB0668 of an unidentified crustose lichen (Figure 1.7). Lichenicolins A and B (29 and 30) are dimeric naphthopyrones and their monomeric unit presents a similar fused naphthopyrone-tetrahydrofuran core system to that present in lasionectrin (13). Additionally, lichenicolins A and B (29 and 30) exhibit antimicrobial activity.

Figure 1.7: Structures of Lichenicolins A and B (29 and 30).
1.4. Total syntheses of monocerin (14)

Monocerin (14) is an aromatic benzopyrone with a structure similar to that of our target molecule lasionectrin (13). Over the years, several total syntheses of monocerin (14) have been published. The following review will present the different strategies used to access the fused pyrone-tetrahydrofuran ring system and will later be used as a base to establish our retrosynthetic analysis of lasionectrin (13).

1.4.1. First convergent synthesis of monocerin (14) by Mori et al.

In 1989, Mori et al. described the first total synthesis of enantiopure monocerin (14) from commercially available 3,4,5-trimethoxybenzyl alcohol (31) and (S)-norvaline ((S)-32) in 20 steps and 1% overall yield (Scheme 1.2). Their synthetic strategy included late stage installation of the carbonyl group via a metalation and carbonylation sequence of halide 33 and lactonisation under Mitsunobu conditions, to afford the desired cis stereochemistry of the fused bond. The tetrahydrofuran ring was accessed via epoxidation of alkene 34 and subsequent epoxide opening. Alkene 34 was obtained from thioether 35 after thiol elimination and subsequent ortho-bromination. Alkylation of thioether 36 with halide 37 allowed access to intermediate 35. Thioether 36 and iodide 37 were synthesised from commercially available 3,4,5-trimethoxybenzyl alcohol (31) and commercially available (S)-norvaline ((S)-32), respectively.

Scheme 1.2: Retrosynthetic analysis of monocerin (14) by Mori et al.
The synthesis of fragment 37 began by treatment of (S)-norvaline ((S)-32) with nitrous acid and aqueous sulphuric acid and subsequent LiAlH₄ reduction of the resulting α-hydroxyl acid, giving diol 38 (Scheme 1.3). Epoxide 39 was accessed via a bromination and bromide displacement sequence from diol 38. Following epoxide opening using sodium cyanide and acidic nitrile hydrolysis, esterification of the purified acid led to ethyl ester 40. However, partial racemisation of the stereocenter was observed during the acidic hydrolysis of the nitrile. Therefore, chiral resolution via crystallisation of the dibenzylammonium salt of 41 provided access to (S)-40 in excellent enantiomeric excess (i.e. 98 %). Alcohol (S)-40 was then TBS protected and the ester reduced with lithium borohydride, giving alcohol 42 which in turn was converted to iodide 37 via tosylation and subsequent displacement of the tosylate.

Scheme 1.3: Synthesis of halide 37 from (S)-norvaline ((S)-32) by Mori et al.²⁹

Synthesis of monocerin (14) commenced with chlorination of alcohol 31 with thionyl chloride followed by substitution with sodium thiophenoxide to give thioether 36 (Scheme 1.4). Subsequent alkylation of thioether 36 with enantiopure halide 37 gave thioether 35. Treatment of thioether 35 with bromine and a large excess of sodium acetate in acetic acid enabled the bromination at the ortho position of the aromatic ring along with brominolysis of the sulfur-carbon bond and subsequent displacement of the bromide with sodium acetate, giving alcohol 43 after acetate hydrolysis.³⁰ Mesylation of alcohol 43 followed by nucleophilic elimination under basic conditions provided alkene 34. Following silyl deprotection of alkene 34, the tetrahydrofuran ring in 33 was installed via epoxidation of the double bond followed by Lewis acid mediated intramolecular epoxide opening by the pendant hydroxyl. The epoxidation was non-stereoselective, and tetrahydrofuran 33 was formed as an inseparable 1:1 ratio of diastereoisomers. A metalation and carbonylation sequence of the diastereomeric mixture followed by lactonisation under Mitsunobu conditions allowed formation of the pyrone-tetrahydrofuran ring system in 44 with the desired cis stereochemistry of the fused bond.
Flash chromatography allowed the isolation of the desired diastereoisomer 44. Finally, selective demethylation using boron tribromide gave monocerin (14).

![Scheme 1.4: Synthesis of monocerin (14) by Mori et al.][1]

The synthetic strategy used by Mori et al. involved formation of the tetrahydrofuran ring prior to lactonisation via Mitsunobu conditions. Although the synthesis began with enantiopure (S)-norvaline ((S)-32), chiral resolution of alcohol 40 was necessary after partial isomerisation of the stereocenter during the acidic nitrile hydrolysis. Similarly, the non-stereoselective epoxidation of alkene 34 gave a 1:1 mixture of diastereoisomers 33, resulting in a decrease in the overall yield. It is of note that lactonisation under Mitsunobu conditions elegantly enabled the inversion of configuration to give the desired cis stereochemistry of the fused ring system.

### 1.4.2. Synthesis of monocerin (14) via Wohl-Ziegler bromination by Simpson et al.

Two years later, Simpson and co-workers reported the first biomimetic synthesis of monocerin (14) in 7 steps and 38 % overall yield via formation of the pyrone prior to installation of the tetrahydrofuran ring system. Monocerin (14) was synthesised from lactone 45a using a Wohl-Ziegler bromination and subsequent intramolecular cyclisation via displacement of the bromide (Scheme 1.5). Lactone 45a was accessed in a single step by condensation of orsellinate 46 and aldehyde 47. Aldehyde 47 was synthesised from butyraldehyde (48) using reported methods.[32]
Scheme 1.5: Retrosynthetic analysis by Simpson et al.

The synthesis of fragment 47 began with the preparation of enantiopure alkene 49 via allylboration of butyraldehyde (48) with β-allylbis(2-isocarany1)borane (50) (Scheme 1.6). The resulting alcohol 49 was then protected as a tetrahydropyranyl ether (THP) using dihydropyran (DHP) in TFA and then converted to aldehyde 47 via Lemieux-Johnson oxidation of the double bond.

Scheme 1.6: Synthesis of aldehyde 47.31

Anionic condensation of orsellinate 46 with aldehyde 47 was conducted using LDA, and acidic work up using TFA enabled spontaneous lactonisation of the resulting alcohol and THP deprotection, giving a diastereoisomeric mixture of pyrones 45a and 45b in a 2.7:1 ratio (Scheme 1.7). Preparative thin layer chromatography (TLC) provided isolation of pyrone 45a which in turn was converted to phenol 51 using Mori’s demethylation conditions. Application of the Wohl-Ziegler radical bromination conditions to pyrone 51 provided monocerin (14) as a single diastereoisomer via bromination at the benzylic position and subsequent intramolecular displacement of the bromide by the pendant hydroxyl.
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This concise biomimetic synthesis of monocerin (14) was successfully conducted via formation of the lactone prior to installation of the tetrahydrofuran ring system. The installation of the lactone ring system was only moderately stereoselective, giving diastereoisomers 45a and 45b as a 2.7:1 mixture. Additionally, the tetrahydrofuran ring was installed via radical bromination and subsequent intramolecular displacement of the bromide.

1.4.3. Synthesis of monocerin (14) via allylsiloxane condensation Marsden et al.

In 2006, Marsden and co-workers described a concise synthesis of monocerin (14) in 8 steps and 7% overall yield via an allylsiloxane condensation (Scheme 1.8). The end-game approach involved metalation of halide 52 followed by a carboxylation and lactonisation sequence. Halide 52 was accessed after double bond migration resulting from the allylic chlorination of alkene 53a, followed by ozonolysis and stereoselective reduction of the resulting ketone. The tetrahydrofuran ring present in 53a was accessed by condensation of aldehyde 54 with allylsiloxane 55.

The synthesis began with allylsilylation of alcohol 56 with allyldimethylsilyl chloride followed by ring closing metathesis using Grubbs’ catalyst, affording allylsiloxane 55 (Scheme
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1.9). Lewis acid mediated condensation of allylsiloxane 55 with known aldehyde 54 provided alkene 53 as a 9:1 separable diastereomeric mixture. Allylic chlorination of the all cis diastereoisomer using phenylselenyl chloride and subsequent ozonolysis of the resulting rearranged allylic chloride (i.e. E/Z, 5:1) gave ketone 52. Following chelation-controlled diastereoselective reduction of ketone 52 using sodium borohydride, a carbonylation and lactonisation sequence via sequential treatment of the resulting alcohol with lithium hexamethyldisilazide, n-butyllithium and methyl chloroformate afforded methylated monocerin 44. Demethylation using boron tribromide provided access to monocerin (14).

![Scheme 1.9: Synthesis of monocerin (14) by Marsden et al.\(^{33}\)](image)

The proposed mechanism of the formation of the tetrahydrofuran ring starts with condensation of Lewis acid activated aldehyde 54 with allylsiloxane 55 to give either the favoured the (E)-oxonium cation (i) in a chair like conformation in which the large substituents adopt a pseudo equatorial positions or the disfavoured (Z)-oxonium cation (i’)(Scheme 1.10).\(^{34}\) Cyclisation of favoured (E)-oxonium (i) cation provides tetrahydrofuran 53a with the desired all cis stereochemistry. Conversely, cyclisation of (Z)-cation (i’) gives tetrahydrofuran 53b as the minor product.
Scheme 1.10: Proposed mechanism of the condensation of allylsiloxane 55 with aldehyde 54.34

The synthetic strategy adopted by Marsden et al. hinged on formation of the tetrahydrofuran ring prior to lactonisation.33 The use of an allylsiloxane condensation enabled the stereoselective formation of the tetrahydrofuran ring. Additionally, chelation-controlled reduction established the all cis stereochemistry of the tetrahydrofuran ring system. As a result, Marsden et al. reported the first highly stereoselective synthesis of monocerin (14).

1.4.4. Synthesis of monocerin (14) via radical cyclisation of vinylic ether by Lee et al.

In 2008, Lee and co-workers reported the synthesis of monocerin (14) in 10 steps and 6 % overall yield.35 Monocerin (14) was accessed by oxidation and subsequent demethylation of 3,6-dihydropyran 57 (Scheme 1.11). Construction of the fused 3,6-dihydropyran-tetrahydrofuran ring in 57 took place via intramolecular radical cyclisation of alkene 58 and subsequent Lewis acid mediated cyclisation. Key intermediate 58 was accessed by Evans aldol condensation of oxazolidinone 59 with aldehyde 60 followed by alkylation and introduction of the selenide.

Scheme 1.11: Monocerin (14) retrosynthesis analysis by Lee et al.

The synthesis began with Evans aldol condensation of oxazolidinone 59 with aldehyde 60 followed by reductive cleavage of the oxazolidinone auxiliary, giving alcohol 61 as a single
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diastereoisomer (Scheme 1.12). Selective tosylation of the primary alcohol in 61 followed by O-alkylation of the secondary alcohol with crotyl bromide gave alkene 62. Displacement of the tosylate with diphenyl diselenide and subsequent alkene migration using Wilkinson’s catalyst afforded alkene 58 as a 2:3 mixture of E:Z isomers. Diastereoselective intramolecular 5-exo-trig radical cyclisation of the stereoisomeric mixture took place upon treatment with tris(trimethylsilyl)silane and triethyl borane, giving tetrahydrofuran 63 as a single diastereoisomer. Lewis acid promoted intramolecular cyclisation of acetal 63 provided access to the fused 3,6-dihydropyran-tetrahydrofuran ring system in 57. Ruthenium catalysed oxidation gave pyrone 64, which in turn was converted to monocerin (14) via regioselective demethylation under Mori’s conditions.

Scheme 1.12: Monocerin (14) synthesis by Lee et al.\textsuperscript{35}

The synthesis of monocerin (14) reported by Lee et al. hinged on Lewis acid mediated oxa-Pictet-Spengler type cyclisation and subsequent oxidation of the resulting 3,6-dihydropyran to access the fused pyrone-tetrahydrofuran ring system. The construction of the tetrahydrofuran ring was elegantly conducted via stereoselective radical cyclisation of alkene 58.
1.4.5. Synthesis of monocerin (14) via hypervalent iodine cyclisation by Fujita et al.

In 2012, Fujita and co-workers published a concise synthesis of ent-monocerin (14) in 5 steps and 24 % overall yield. The synthesis started with the preparation of boronic acid 65 from known alkene 66 upon treatment with catechol borane and aqueous work up to hydrolyse the boronic ester (Scheme 1.13). Coupling partner 67 was prepared by selective demethylation of known halide 68. Suzuki coupling of boronic acid 65 with halide 67 and subsequent acetate protection gave alkene 69. Hypervalent iodine cyclisation of alkene 69 using chiral hypervalent iodine 70 led to the formation of the pyrone-tetrahydrofuran moiety in benzopyrone 71 in a single step. Acetate removal from benzopyrone 71 under basic conditions afforded ent-monocerin (ent-14).

Scheme 1.13: Synthesis of ent-monocerin (ent-14) by Fujita et al.

Chiral hypervalent iodine (R)-70 was synthesised in two steps from commercially available 2-iodophenol (72) (Scheme 1.14). Mitsunobu reaction of halide 72 with chiral methyl lactate gave iodide (R)-73 which was then converted to (diacetoxyiodo)arene (R)-70 upon treatment with sodium perborate in acetic acid. Fujita and co-workers, reported several similar reactions using this chiral hypervalent iodine and analogues such as stereoselective tetrahydrofuranylation or oxidative lactonisation.
Fujita and co-workers proposed a plausible reaction mechanism for the double oxidative cyclisation with hypervalent iodine (Scheme 1.15). After activation of hypervalent iodine 70 with Lewis acid BF₃·OEt₂, electrophilic addition of alkene (i) leads to cations (ii and ii'). Depending on the stereochemistry of the hypervalent iodine 70 the attack would preferentially occur from the Si or the Re face giving cations (ii) or (ii'), respectively. Intramolecular cyclisation and concomitant lactonisation then provides access to the corresponding pyrone-tetrahydrofuran ring system (iii and iii').

Fujita and co-workers described an elegant method to access the fused pyrone-tetrahydrofuran ring system in a single step from alkene 69. The use of the chiral hypervalent iodine also provided a very concise enantioselective synthesis of ent-monocerin (14). Additionally, chiral hypervalent iodine (R)-70 was easily synthesised in only two steps from 2-iodophenol (72) and chiral methyl lactate.

1.4.6. Synthesis of monocerin (14) by She et al.

In 2013, She et al. simultaneously published two different syntheses of monocerin (14). The first synthesis proceeded in 11 steps and 6 % overall yield and started with a low yielding Sharpless epoxidation of easily accessible alkene 74, followed by benzyl protection, giving epoxide 75 (Scheme 1.16). Nucleophilic epoxide opening of 75 with 2-propyl-1,3-dithiane and subsequent dithiane removal gave ketone 76. Chelation-controlled Saksena-Evans reduction of
ketone 76 with tetramethylammonium triacetoxyborohydride enabled access to 1,3-anti diol 77 as a single diastereoisomer. Following benzyl deprotection, the tetrahydrofuran ring was constructed by acetalisation of the 1,2-diol functionality with methyl orthoacetate and subsequent intramolecular displacement with the pendant hydroxyl upon treatment with boron trifluoride, giving tetrahydrofuran 78 as a single diastereoisomer. Acetate hydrolysis gave alcohol 79, which was then converted to pyrone 80 via oxa-Pictet-Spengler cyclisation using trimethyl orthoformate and trimethylsilyl triflate and subsequent Jones’ oxidation of the resulting 3,6-dihydropyran. Regioselective demethylation using boron trichloride gave monocerin (14).

Scheme 1.16: Monocerin (14) synthesis by She et al.

The overall strategy hinged on formation of the tetrahydrofuran ring system prior to installation of the lactone functionality. Sharpless epoxidation and Saksena-Evans reduction enabled installation of the stereocenters. Additionally, establishment of the all cis stereochemistry of the tetrahydrofuran ring system took place via acetalisation and subsequent intramolecular displacement. Oxa-Pictet-Spengler cyclisation and subsequent oxidation enabled access to the fused pyrone-tetrahydrofuran ring system.

The second synthesis of monocerin (14) reported by She et al. proceeded in 12 steps and 6% overall yield. The synthesis commenced with Wittig olefination of (methylmethoxy)triphenylphosphonium chloride with aldehyde 80 and subsequent treatment of the resulting enol ether with 1,3-propanedithiol and boron trifluoride diethyl etherate, giving dithiane 81 (Scheme 1.17). Nucleophilic epoxide opening of chiral n-propyloxirane (39) and
subsequent dithiane deprotection gave ketone 82. Samarium mediated Evans–Tishchenko reduction of ketone 82 gave alcohol 83 as a single diastereoisomer. Oxa-Pictet-Spengler cyclisation and subsequent Jones oxidation of the resulting 3,6-dihydropyran afforded lactone 84. Following propanoate hydrolysis of pyrone 84 under basic conditions, treatment of the resulting alcohol with boron trichloride enabled isopropyl deprotection and regioselective demethylation, giving pyrone 85. Installation of the tetrahydrofuran ring took place via oxidation of naphthol 85 with iodobenzene diacetate (PhI(OAc)₂), giving quinone methide intermediate 86 which spontaneously underwent intramolecular conjugate addition with the pendant hydroxyl to afford the fused pyrone-tetrahydrofuran ring system in 87. Methylation of naphthol 87 gave a 2:1 mixture of monocerin (14) and fully methylated monocerin (44) which was then regioselectively demethylated using boron trichloride to afford monocerin (14).

Scheme 1.17: Monocerin (14) synthesis by She et al.²²

She and co-workers, described the second biomimetic synthesis of monocerin (14). This biomimetic synthetic strategy hinged on formation of the lactone prior to installation of the tetrahydrofuran ring. Installation of the lactone functionality was conducted via an
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Oxa-Pictet-Spengler cyclisation and subsequent oxidation. A combination of Evans–Tishchenko reduction, epoxide opening of the enantiopure n-propyloxirane (39) and intramolecular conjugate addition enabled access to the all cis stereochemistry of the tetrahydrofuran ring system.

1.4.7. Synthesis of monocerin (14) via dihydroxylation-S_N2 sequence Begari et al.

The most recent total synthesis of monocerin (14) was published during the course of the current work by Begari and co-workers in 2014 and proceeded in 15 steps and 17% overall yield. Monocerin (14) was accessed from tetrahydrofuran 88 via tandem cyanation-lactonisation reaction followed by regioselective demethylation (Scheme 1.18). The tetrahydrofuran ring was installed via a dihydroxylation and displacement of a mesylate sequence from alkene 89 which in turn was synthesised from aldehyde 60 and sulfone 90 via Julia-Kocienski olefination. Sulfone 90 was synthesised in 6 steps from 3-buten-1-ol (91).

Scheme 1.18: Retrosynthetic analysis of monocerin (14) by Begari et al.

The synthesis of sulfone 90 started with protection of 3-buten-1-ol (91) with para-methoxybenzyl chloride (PMBCl) followed by Prilezhaev reaction to give epoxide 92 (Scheme 1.19). Jacobsen hydrolytic kinetic resolution (HKR) gave enantiopure epoxide (−)-92. After cuprate-mediated epoxide opening of 92 with ethylmagnesium bromide, the resulting alcohol was protected with methoxymethyl chloride (MOMCl) to give intermediate 93. Following removal of the PMB protecting group, Mitsunobu reaction of mercaptophenyltetrazole with the resulting alcohol gave thioether 94. Access to sulfone 90 was achieved via oxidation of thioether 94 with ammonium heptamolybdate.
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Scheme 1.19: Synthesis of sulfone 90 by Begari et al.\textsuperscript{44}

Following Julia-Kocienski olefination of sulfone 90 with aldehyde 60, MOM deprotection under acid conditions gave alkene (E)-89 as a single isomer (Scheme 1.20). After mesylation of alcohol 89, tandem Sharpless dihydroxylation and displacement of the mesylate using AD-mix-β gave an inseparable mixture of tetrahydrofurans 95\textsuperscript{a} and 95\textsuperscript{b} in a 93:7 ratio. Bromination of the diastereomeric mixture and subsequent flash chromatography allowed the isolation of halide 96. Access to benzopyrone 44 from bromide 96 was achieved via tandem cyanation-lactonisation reaction using copper cyanide. Finally, regioselective demethylation of pyrone 44 with boron trichloride afforded monocerin (14).

Scheme 1.20: Synthesis of monocerin (14) by Begari et al.\textsuperscript{44}

The synthetic strategy used by Begari et al. to access the fused pyrone-tetrahydrofuran ring system hinged on formation of the tetrahydrofuran ring prior to lactonisation.\textsuperscript{44} Begari et al. reported the highly stereoselective synthesis of monocerin (14) using a Sharpless dihydroxylation and S\texttextsuperscript{N}2 sequence, providing the tetrahydrofuran ring with the desired all \textit{cis} stereochemistry. Additionally, installation of the lactone functionality took place via a tandem cyanation-lactonisation sequence.
1.5. Concluding remarks and retrosynthetic analysis of lasionectrin (13)

1.5.1. Concluding remarks

With the urgent need for new drugs to treat malaria, the aim of this project is to develop a novel and suitable synthesis of antimalarial naphthopyrone lasionectrin (13). The synthesis would also be used to prepare simple analogues of lasionectrin (13) to evaluate antimalarial activity. Our synthetic strategy to access lasionectrin (13) will be based on one of the previously reported syntheses of monocerin (14).

From the eight syntheses of monocerin (14), three main strategies have been highlighted (Scheme 1.21). Formation of the tetrahydrofuran ring prior to lactonisation appeared to be the most common synthetic pathway. It is of note that this synthetic strategy can also be divided into two subcategories according to the method used to establish the lactone functionality. Mori et al., Marsden et al. and Begari et al. formed the lactone from intermediate 97 after either a metalation–carbonylation or a cyanation-lactonisation sequence.\textsuperscript{29,33,44} In comparison, Lee et al. and She et al. installed the lactone functionality by oxidation of 3,6-dihydropyran 57.\textsuperscript{35,41}

Simpson et al. and She et al. reported two interesting biomimetic strategies that hinged on formation of the lactone prior to installation of the tetrahydrofuran ring system (Scheme 1.21).\textsuperscript{31,42} Installation of the tetrahydrofuran ring took place via either a bromination and displacement of the bromide sequence or intramolecular conjugate addition from pyrone 98.

Finally, Fujita et al. provided an elegant synthesis of ent-monocerin (ent-14) using chiral hypervalent iodine cyclisation, establishing the fused pyrone-tetrahydrofuran ring system in a single step from alkene 69 (Scheme 1.21).\textsuperscript{36} To date, Fujita et al.’s chiral hypervalent iodine cyclisation approach represents a major breakthrough in the synthesis of the fused pyrone-tetrahydrofuran ring system. Due to the single step stereoselective formation of the fused pyrone tetrahydrofuran ring system, and the ease to access the chiral hypervalent iodine reagent, Fujita and co-worker’s approach was chosen as a base to elaborate our retrosynthetic analysis of lasionectrin (13).
1.5.2. Retrosynthetic analysis of lasionectrin (13)

Based on the work reported by Fujita and co-workers, our retrosynthetic analysis of lasionectrin (13) hinged on the use of chiral hypervalent iodine cyclisation to access the naphthopyrone-tetrahydrofuran moiety in lasionectrin (13) (Scheme 1.22). Lasionectrin (13) would be accessed via chiral hypervalent iodine cyclisation of alkene 99 and subsequent selective peri demethylation. Hypervalent iodine cyclisation precursor 99 would be accessed from alkene 100 via ortho-methoxycarbonylation. Coupling of aldehyde 101 with coupling partner 102 using common olefination reaction (e.g. Wittig, Horner-Wadsworth-Emmons or Julia-Lythgoe) would allow formation of alkene 100. Aldehyde 101 would be accessed from readily available 3,5-dimethoxybenzaldehyde (103) and phosphonate 104 via an Horner-Wadsworth-Emmons (HWE) coupling and acid mediated cyclisation sequence. Coupling partner 102 would be prepared from easily accessible (S)-n-propyloxirane ((S)-39).
Scheme 1.22: Retrosynthetic analysis of lasionectrin (13).
Chapter Two

Discussion
2.1. Overview

The initial strategy to synthesise lasionectrin (13) hinged on late stage hypervalent iodine cyclisation. Lasionectrin (13) would be prepared in single step from alkene 99 via hypervalent iodine cyclisation and subsequent peri-demethylation (Scheme 2.1). Alkene 99 would be accessed via ortho methoxycarbonylation of alkene 100. Olefination of aldehyde 101 with coupling partner 102 would provide key alkene 100.

The initial focus of this project would be the preparation of coupling partners 101 and 102 and the evaluation of which olefination reaction (e.g. Wittig, HWE, Julia-Lythgoe) would enable access to alkene 100. Aldehyde 101 would be accessed via HWE reaction of commercially available 3,5-dimethoxybenzaldehyde (103) and known phosphonate 104 and subsequent intramolecular cyclisation under acidic conditions. Coupling partners 102 would be prepared from easily accessible n-propyloxirane (39).

Scheme 2.1: Retrosynthetic analysis of lasionectrin (13) via hypervalent iodine cyclisation.
Chapter 2: Discussion

2.2. Synthesis of alkene 105

2.2.1. Synthesis of aldehyde coupling partners

2.2.1.1. Retrosynthetic analysis of aldehyde 101

Our initial strategy focused on the preparation of protected aldehyde 101 from ester 106 using a reduction-oxidation sequence followed by protection of the naphthol (Scheme 2.2). Naphthalene 106 would be derived from itaconic ester 107 by selective tert-butyl ester deprotection followed by intramolecular cyclisation. Itaconic ester 107 would be synthesised from aldehyde 103 and phosphonate 104 using an HWE reaction.

![Scheme 2.2: Retrosynthesis of aldehyde 101.](image)

2.2.1.2. Synthesis of starting materials 103 and 104

3,5-Dimethoxybenzaldehyde (103) was synthesised from 3,5-dimethoxybenzoic acid (108) following literature procedures (Scheme 2.3, A).\textsuperscript{48,49} Reduction of carboxylic acid (108) to the corresponding alcohol using lithium aluminium hydride, followed by oxidation with pyridinium chlorochromate (PCC) gave aldehyde 103 in 65\% overall yield.

Known phosphonate coupling partner 104 was synthesised in a single step via nucleophilic addition of ethyl phosphonoacetate (109) with commercially available tert-butyl bromoacetate (110) using sodium hydride (NaH) in THF.\textsuperscript{50,51}

![Scheme 2.3: Synthesis of starting materials 103 and 104.](image)
2.2.1.3. Synthesis of itaconic ester 107

With coupling partners 103 and 104 in hand, attention turned to the formation of itaconic ester 107. The HWE reaction was chosen over Stobbe condensation or Wittig olefination because of the high (E)-selectivity and simple aqueous work-up for the removal of phosphate salt by-product.46,52,53

First, formation of phosphonate carbanion was attempted using potassium carbonate which proved to be inefficient providing only recovered starting materials 103 and 104 (Table 2.1, entry 1). The lack of reactivity suggests that the pKa of the α hydrogen of the phosphonate 104 is greater than that of potassium carbonate. Reaction with potassium tert-butoxide gave the desired itaconic ester 107 but these conditions proved to be poorly reproducible (Table 2.1, entry 2).

Following investigation of the relevant literature it was noted that, methods employing sodium hydride or DBU as base were most common for the synthesis of itaconic esters. 51,53-55 Application of these conditions to our system provided the desired itaconic ester 107 in moderate yield (Table 2.1, entries 3 and 4). Interestingly, the (E)-selectivity was excellent in all cases (E/Z > 99%). However when the reaction was carried out using DBU, itaconic ester 107 was formed along with a by-product that was difficult to separate by flash chromatography. Consequently, sodium hydride in THF was selected as the method of choice to carry out the HWE coupling.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>temperature (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOK</td>
<td>THF</td>
<td>rt</td>
<td>0–73</td>
</tr>
<tr>
<td>3</td>
<td>DBU, LiCl</td>
<td>MeCN</td>
<td>rt</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>NaH</td>
<td>THF</td>
<td>0</td>
<td>52</td>
</tr>
</tbody>
</table>

2.2.1.4. Synthesis of naphthol 106

With itaconic ester 107 in hand, attention turned to the synthesis of naphthol 106. Rizzacasa and Sargent described the deprotection of tert-butyl ester 111 via brief treatment with 90 % v/v TFA in water (Scheme 2.4).52 Subsequent intramolecular cyclisation of acid 112 using acetic
anhydride with potassium acetate as described by Borsche then led to the corresponding naphthalene acetate 113 in nearly quantitative yield. Finally, naphthol 114 could be synthesised via hydrolysis of acetate 113.

Scheme 2.4: Synthesis of naphthol 114 by Rizzacasa and Sargent.52

Following the reported procedure, exposure of cinnamic ester 107 to 10 % v/v trifluoroacetic acid in dichloromethane at room temperature afforded the expected carboxylic acid 115 in 82 % yield, together with a minor by-product (5 %) (Table 2.2, entry 1).51 Comparison with the literature enabled the identification of the side product as naphthalene derivative 106.56 In order to optimise the formation of naphthol 106 in a single step from itaconic ester 107 several conditions were tested. The reaction was carried out at reflux with the same TFA-dichloromethane ratio which resulted in an insignificant increase in the formation of the desired naphthol 106 (Table 2.2, entry 2). The reaction was then conducted in TFA-dichloromethane (1:1) at reflux, affording naphthol 106 in 71 % yield (Table 2.2, entry 3). Finally, the optimum conditions were found when itaconic ester 107 was treated with neat TFA at reflux, providing naphthol 106 in 83 % yield (Table 2.2, entry 4).

Table 2.2: TFA tert-butyl deprotection vs cyclisation.

<table>
<thead>
<tr>
<th>entry</th>
<th>temperature</th>
<th>TFA-CH₂Cl₂</th>
<th>115 (%)</th>
<th>106 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>1:10</td>
<td>82</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>reflux</td>
<td>1:10</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>reflux</td>
<td>1:1</td>
<td>10</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>reflux</td>
<td>1:0</td>
<td>5</td>
<td>83</td>
</tr>
</tbody>
</table>

To the best of our knowledge, the formation of naphthol 106 from ester 107 in a single step by Friedel-Crafts intramolecular annulation using neat TFA has not been previously reported.
Our proposed mechanism for this transformation starts with deprotection of the tert-butyl ester via protonation and liberation of a tert-butyl cation. Further protonation of the resulting acid 115 leads to the formation of cation (i). Following nucleophilic attack to form the diol (ii), rearomatisation of the aryl ring and elimination of water affords pyrone (iii), which tautomerises to naphthol 106 (Scheme 2.5).

\[
\begin{align*}
\text{Scheme 2.5: Proposed mechanism of TFA annulation.}
\end{align*}
\]

2.2.1.5. Synthesis of aldehydes 116 and 117

With naphthol 106 in hand, synthetic studies towards aldehydes 116 and 117 were initiated. Attempted reduction of ester 106 to aldehyde 116 in a single step was unsuccessful using diisobutyl aluminium hydride (DIBAL).\(^{57}\) However, aldehyde 116 was successfully synthesised via a reduction-oxidation sequence using LiAlH\(_4\) followed by oxidation with 2-iodoxybenzoic acid (IBX) (Scheme 2.6).\(^{58,59}\) The use of IBX in refluxing EtOAc was chosen over other attempted methods (e.g. PCC, Swern or TEMPO oxidation) because of its simpler work-up (i.e. filtration) and excellent yield.\(^{54,60,61}\)

The next focus was the protection of naphthol 106. tert-Butyldimethylsilyl ether (TBS) was selected as a protecting group because of its relative stability to basic conditions and the potential selective cleavage.\(^{62}\) However, common TBS protection methods using tert-butylidemethylsilyl chloride in a variety of solvents (e.g. THF, DMF, CH\(_3\)CN, CH\(_2\)Cl\(_2\)) and bases (e.g. NaH, DBU, imidazole, pyridine) were proved unsuccessful when applied to naphthaldehyde 116 (Scheme 2.6).\(^{57,58,63,64}\)

\[
\begin{align*}
\text{Scheme 2.6: Synthesis of 116 and attempted synthesis of 117.}
\end{align*}
\]
Chapter 2: Discussion

Due to this setback, an alternative synthetic approach was required to install the silyl ether earlier in the synthesis. Naphthol ester 106 was successfully converted to its silyl ether derivative 118 when treated with a large excess of both tert-butyldimethylsilyl chloride (TBS-Cl) and 4-dimethylaminopyridine (DMAP) in pyridine (Scheme 2.7). The previously described reduction-oxidation sequence using LiAlH₄ and IBX used to synthesise aldehyde 116 was applied to ester 118, providing aldehyde 117 in 69% overall yield.

Interestingly, a substantial difference in yield was initially observed between the reduction of naphthol ester 106 (57%) using LiAlH₄ compared to its TBS-protected counterpart 118 (84%). This behaviour was attributed to the low pKa of the naphthol 106 which could be deprotonated during the work-up and coordinate to the precipitated aluminum salts which are later eliminated by filtration. To overcome this problem, the work-up was adjusted; after the usual precipitation of the aluminium salts under basic conditions, the solution was neutralised with two molar aqueous hydrochloric acid until complete dissolution of the aluminum salt. Following these adjusted work-up conditions, the yield increased drastically from 57% to 86%.

2.2.2. Synthesis of coupling partner 119

2.2.2.1. Retrosynthetic analysis of coupling partners

With aldehydes 117 and 116 in hand, attention turned to the synthesis of the olefination coupling partners. Olefination of aldehyde 101 with coupling partner 102 would provide access to key alkene 100 (Scheme 2.8). Wittig, HWE and Julia-Lythgoe olefination were chosen to attempt formation of key intermediate 100.
Desired Wittig (120), HWE (121) and Julia-Lythgoe (122) coupling partners could all be accessed from epoxide opening of \( n \)-propyloxirane (39). Following ring opening of epichlorohydrin (123) with ethyl magnesium bromide, \( n \)-propyloxirane (39) would then be formed by displacement of the chloride by the alkoxide generated under basic conditions (Scheme 2.9).

![Scheme 2.9: Retrosynthetic analysis of coupling partners 120, 121 and 122.](image)

However due to the price of enantiopure epichlorohydrin (123), we decided to work with racemic epichlorohydrin (123) until elaboration of a suitable synthesis.

### 2.2.2.2. Synthesis of \( n \)-propyloxirane (39)

Epichlorohydrin (123) was treated with ethyl magnesium bromide in presence of catalytic copper cyanide (Scheme 2.10). Subsequent treatment with solid sodium hydroxide in ether gave \( n \)-propyloxirane (39). Epoxide (39) was difficult to purify due to its low boiling point and propensity to form azeotropes with diethyl ether and THF, and was therefore used as a solution in ether. Optically active \( n \)-propyloxirane (39) could synthesised from commercially available (R) or (S)-epichlorohydrin (123).

![Scheme 2.10: Synthesis of epoxide 39.](image)

### 2.2.2.3. Attempted ring opening of epoxide (39)

With epoxide (39) in hand, focus turned to the synthesis of phosphonium salt (120) and phosphonate (121). Preparation of Wittig coupling partner (120) using methyltriphenylphosphonium bromide and butyl lithium in tetrahydrofuran were unsuccessful. Attempted ring opening of epoxide (39) with triphenylphosphonium methyldie generated \textit{in situ} was unsuccessful and only degradation of the starting material was observed (Scheme 2.11). As a final attempt, the Wittig reaction was attempted with \textit{in situ} formation of the phosphonium salt (120) followed by slow
addition of aldehyde 116. Unfortunately, only alkene 124 which resulted from the addition of triphenylphosphonium methylide with aldehyde 116 was observed.

![Scheme 2.11: Unsuccessful attempts to open n-propyloxirane (39).](image1)

Given these disappointing results, synthesis of phosphonate 121 was then attempted. However, ring opening of epoxide 39 using n-butyl lithium, the Lewis acid boron trifluoride etherate (BF₃·OEt₂) and methyl diethoxyphosphonate was also unsuccessful (Scheme 2.12).

![Scheme 2.12: Unsuccessful attempt to open oxirane 39.](image2)

2.2.2.4. Synthesis of sulfone 122

Due to this set-back, attention turned to the synthesis of Julia-Lythgoe coupling partner 122. Epoxide 39 was successfully opened in the presence of methyl para-toluenesulfonyl (125) and n-butyl lithium in toluene at 60 °C, providing access to alcohol 126 (Scheme 2.13). The resulting alcohol 126 was then protected as the TBS ether 122 following the literature procedure.

![Scheme 2.13: Synthesis of sulfone 122.](image3)
2.2.3. Julia–type olefination

2.2.3.1. Attempted Julia-Lythgoe olefination

With aldehydes 116 and 117 and sulfone 122 in hand, attention turned to the Julia-Lythgoe olefination which would enable formation of alkene 100. The initial step would be addition of the toluyl sulfonyl carbanion formed upon deprotonation of sulfone 122, to aryl aldehyde 101, followed by in situ acetylation of the alkoxide intermediate (Scheme 2.14). Reductive elimination of sulfone 127 with sodium amalgam would then afford alkene 100.73,75

Scheme 2.14: Proposed synthesis of 100 via the Julia-Lythgoe route.

Attempts to synthesise intermediate 128 from naphthol 116 following standard conditions (e.g. butyl lithium, acetic anhydride in THF) only led to acetylation of the alcohol to form protected naphthol 129 and recovery of sulfone 122 (Scheme 2.15).74 Protection of the phenol was therefore necessary. However, attempted Julia-Lythgoe coupling using either TBS-protected aldehyde 116 or acetate protected aldehyde 129 were unsuccessful.

Scheme 2.15: Julia-Lythgoe attempts.

2.2.3.2. Julia-Lythgoe – model study with naphthaldehyde 132

In an attempt to explore the reaction conditions further, commercially available 2-naphthaldehyde (132) was selected as a model aldehyde. Unfortunately, neither changing the base to KHMS nor adding a Lewis acid (i.e. boron trifluoride) provided access to intermediate 133 (Table 2.3, entries 1, 2 and 3).73
Table 2.3: Julia Lythgoe coupling attempts.

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>conditions</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>n-BuLi, Ac₂O, THF, −78 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>132</td>
<td>n-BuLi, BF₃·OEt₂, Ac₂O, THF, −78 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>132</td>
<td>KHMDS, BF₃·OEt₂, THF, −78 °C</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

In a final attempt, Julia-Lythgoe olefination with naphthalene 132 was carried out using methyl para-toluene sulfonate (125). Pleasingly, intermediate 134 was afforded in 53 % yield, suggesting that sulfone 122 has a lower reactivity than methylsulfone 125.

![Scheme 2.16: Julia-Lythgoe reaction with 132 and 125.]

Following the poor results obtained when attempting the Julia-Lythgoe olefination and in addition to the potential need to use toxic mercury amalgam for the olefination step, we decided to change the Julia-Lythgoe olefination step to use of the mercury-free Julia-Kocienski olefination.

2.2.3.3. Revised strategy: Julia-Kocienski coupling

Our alternative route relied on using the Julia-Kocienski olefination to access olefin 100. Making use of the Smiles rearrangement, the Julia-Kocienski reaction would allow access to alkene 100 in a single step from aldehyde 101 and tetrazol-5-yl derivative sulfones 119 and 135 or either benzothiazol-2-yl sulfone 136.
In order to explore this alternative route, attention turned to the synthesis of the appropriate coupling partner 119, which would be prepared by oxidation of thioether 137 and hydroxyl protection. Selective addition of mercaptophenyltetrazole thiol to oxetane 138 would provide alcohol (137). Ring expansion of \( n \)-propyloxirane 39 using the methodology described by Fitton et al. would lead to the corresponding oxetane 138 with retention of enantiopurity.\(^{76,77}\)

**Scheme 2.17: Julia-Kocienski route to 100.**

2.2.3.4. *Synthesis of sulfone 119 by ring expansion*

The synthesis of sulfone 119 began with ring expansion of oxirane 39 using trimethyl sulfoxonium iodide in presence of potassium tert-butoxide in tert-butanol at 60 °C (Scheme 2.19). The resulting oxetane 138 was opened with mercaptophenyltetrazole thiol in the presence of lithium bromide, providing 137 in 30 % overall yield from (S)-epichlorohydrin (123).\(^{78}\) Julia-Kocienski coupling partner 119 was then accessed in excellent yield by silyl protection of alcohol 137 and oxidation of the resultant thioether with ammonium paramolybdate and hydrogen peroxide in ethanol.

**Scheme 2.18: Retrosynthetic analysis of Julia-Kocienski coupling partner 119.**

**Scheme 2.19: Synthesis of sulfone 119.**
Chapter 2: Discussion

Oxidation of the thioether functionality was also conducted using meta-chloroperbenzoic acid (m-CPBA) in dichloromethane to give sulfone 119 in 74% yield together with several by-products. In comparison, following removal of ethanol in vacuo and dissolution in EtOAc, pure sulfone 119 was obtained after aqueous work-up when ammonium paramolybdate and hydrogen peroxide system was employed.

The postulated mechanism for the ring expansion of epoxide 39 to oxetane 138 by Butova et al. commences with deprotonation of trimethylsulfoxonium iodide with potassium tert-butoxide. The resulting ylide (i) then opens the epoxide, attacking the least hindered carbon. The alkoxide intermediate (ii) then undergoes cyclisation to form the desired oxetane and dimethylsulfoxide (Scheme 2.20).

Scheme 2.20: Ring expansion proposed mechanism.77

Due to its propensity to form an azeotrope with tert-butanol, oxetane 138 was not purified and was characterised as a solution in tert-butanol. Its low mass resulted in an absence of fragmentation peaks in the mass spectrum. However oxetane was subsequently opened with mercaptophenyltetrazole and lithium bromide in DMF to give thioether 137 in 30 % yield over 4 steps from (S)-epichlorohydrin ((S)-123).

Given that epoxide 39 and oxirane 138 were prepared as solutions and were not detectable using a UV-Vis detector, the enantioselectivity was quantified after the reaction of oxetane 138 with mercaptophenyltetrazole. The excellent enantiomeric excess observed for thioether 137 (> 98 % e.e., chiral HPLC), confirmed retention of stereochemistry during the ring expansion step (Figure 2.1).
2.2.3.5. Synthesis of alkene 139 via Julia-Kocienski olefination

With TBS-protected sulfone 119 and aldehyde 127 in hand, attention turned to the key Julia-Kocienski reaction. Despite literature precedent for aromatic aldehydes, the use of KHMDS or LiHMDS as base and DME or THF as solvent proved to be either unsuccessful (Table 2.4, entry 1) or low yielding (Table 2.4, entry 2). However, the addition of lithium bromide considerably enhanced the aldehyde reactivity providing alkene 139 in 71% yield (Table 2.4, entry 3). We postulated that lithium-oxygen chelation may enhance the reactivity of the aldehyde 117. A correlation between halide electronegativity and yield was observed which agreed with this postulate; chloride has greater electronegativity than bromide on the Pauling scale and greater yield was observed when using lithium chloride compared to lithium bromide (Table 2.4, entries 5 and 6).

In addition, the solvent (Table 2.4, entry 4) and the counterion of the base used (Table 2.4, entry 5) were also found to have a minor influence on the stereoselectivity of the reaction. Addition of a large excess of lithium chloride resulted in a small increase in yield but decreased stereoselectivity (Table 2.4, entry 6). Finally, addition of lithium chloride in an excess no greater than 1.5 equivalents afforded alkene 139 with high E-selectivity and excellent yield (Table 2.4, entry 7). These conditions were selected as the method of choice for the synthesis of alkene 139.
Table 2.4: Julia-Kocienski conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>additive</th>
<th>yield (%)</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS, DME</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>LHMDS, THF</td>
<td>-</td>
<td>13</td>
<td>94:6</td>
</tr>
<tr>
<td>3a</td>
<td>LHMDS, THF</td>
<td>LiBr</td>
<td>71</td>
<td>94:6</td>
</tr>
<tr>
<td>4a</td>
<td>LHMDS, DME</td>
<td>LiBr</td>
<td>69</td>
<td>90:10</td>
</tr>
<tr>
<td>5a</td>
<td>KMHDS, THF</td>
<td>LiBr</td>
<td>60</td>
<td>98:2</td>
</tr>
<tr>
<td>6b</td>
<td>KHMDS, THF</td>
<td>LiCl</td>
<td>90</td>
<td>94:6</td>
</tr>
<tr>
<td>7a</td>
<td>KHMDS, THF</td>
<td>LiCl</td>
<td>94</td>
<td>98:2</td>
</tr>
</tbody>
</table>

*a 1.5 equivalent of additive; *b 2.5 equivalent of LiCl

The stereoselectivity of the Julia-Kocienski reaction can be rationalised by the mechanism of the reaction which is thought to be strongly influenced by the size of the cation and the nature of the aldehyde substituent (Scheme 2.21). First, deprotonation of the α hydrogen of the sulfone leads to anion (i). Attack of the sulfone anion (i) on the electrophilic carbonyl of the chelated aldehyde (ii) forms either the syn (iii’) or anti intermediate (iii). The potassium counterion is chelated by the resultant alkoxide, the sulfone oxygen and tetrazole nitrogen. In our system, we postulate that the lithium cation is replaced by a potassium cation during the formation of alkoxides (iii, iii’). Our experimental results support this hypothesis as a decrease in stereoselectivity is observed when only the smaller cation (i.e. lithium) is present in the reaction mixture. The conformation of the newly formed alkoxides (iii, iii’) is locked due to the potassium cation coordination. Attack of the alkoxide on the tetrazole carbon then forms the pentacyclic anion (iv or iv’). Following rearomatisation of the tetrazole and ring opening, the resulting sulfonyl carbanions (v, v’) undergo β-elimination to form olefins (vi, vi’). The syn-adduct (iii’) has more steric hindrance compared to the anti-adduct (iii), leading to the formation of the E-alkene (vi) as the major product.
2.2.4. Summary

In summary, key alkene 139 was successfully synthesised via a Julia-Kocienski olefination of aldehyde 117 with racemic sulfone 119 (Scheme 2.22). Preparation of aldehyde 129 began with HWE reaction of phosphonate 104 with aldehyde 103 and subsequent TFA intramolecular cyclisation, giving ester 106. Following TBS protection of naphthol 106, ester 118 was then converted to aldehyde 117 via a reduction and oxidation sequence.

Preparation of sulfone 119 began with epoxide opening of (S)-epichlorohydrin ((S)-123) with ethylmagnesium bromide and subsequent epoxidation under basic conditions, giving (S)-n-propyloxirane ((S)-39). Ring expansion of epoxide 39 using trimethylsulfoxonium iodide and subsequent oxetane opening using mercaptophenyltetrazole in presence of LiBr provided alcohol 137. TBS protection and subsequent oxidation with ammonium paramolybdate gave sulfone 119.
Scheme 2.22: Summary of the synthesis of alkene 139 via Julia-Kocienski olefination.
2.3. Attempted synthesis of naphthopyrone 140 via hypervalent iodine cyclisation

2.3.1. Retrosynthetic analysis of naphthopyrone 140

Having achieved success in the key Julia-Kocienski olefination which provided access to alkene 139, attention now turned to the installation of the fused naphthopyrone-tetrahydrofuran moiety. Fujita et al. described the cyclisation of ester 141 to pyrone 142 using hypervalent iodine and Lewis acid in dichloromethane (Scheme 2.23). Application of these conditions to key ester 143 would allow access to naphthopyrone 140 which would then be deprotected to form lasionectrin (13).

Scheme 2.23: Approach to the fused pyrone-tetrahydrofuran moiety by Fujita et al.

Key ester 143 would in turn be accessed from aldehyde 144 via oxidative esterification (Scheme 2.24). Following deprotection of silyl ether 139, selective ortho-formylation of the resulting naphthol would provide access to aldehyde 144. To limit the use of enantiopure epichlorohydrin (123) which was expensive the following reactions were carried out using racemic alkene 139.
Chapter 2: Discussion

2.3.2. Attempted direct formylation of alkene 145

2.3.2.1. Selective aryl TBS deprotection of naphthalene 139

With alkene 139 in hand, attention turned to the selective removal of the silyl ether. Fortunately, the previous unsuccessful attempt to protect aldehyde 116 using DBU and TBS-Cl, resulted in an unexpected result. Monitoring the reaction by TLC revealed rapid formation of the silyl ether 117 followed by deprotection, resulting in recovered naphthol 106.

In accordance with this result and the relevant literature, selective silyl ether deprotection of alkene 139 was therefore conducted with DBU in a 95:5 ratio of acetonitrile and water, affording naphthol 145 in 95% yield.85

![Scheme 2.25: Selective deprotection of alkene 139.](image)

2.3.2.2. Attempted Vilsmeier-Haack and paraformaldehyde formylation of alkene 145

With naphthol 145 in hand, attention turned to the key ortho-formylation reaction. Based on the literature, Vilsmeier-Haack reaction with in situ generation of the Vilsmeier reagent with phosphoryl chloride and DMF would provide access to the desired aldehyde 144 in a single step.86 Unfortunately, treatment of naphthol 145 with POCl₃ and DMF in acetonitrile only resulted in TBS-deprotection, giving naphthol 146. Attempted Vilsmeier reaction of alcohol 146 using similar conditions resulted in degradation of the starting material.81

![Scheme 2.26: Attempted Vilsmeier-Haack reaction.](image)

Given these disappointing results, an alternative to the Vilsmeier formylation was sought. In 2005, Hansen and Skattebøl described the selective ortho-formylation of 15 different phenols in reasonable yield using paraformaldehyde, magnesium dichloride and triethylamine in THF.82,87
Unfortunately, application of these conditions to naphthol 145 was unsuccessful (Table 2.5, entry 1). Changing the solvent from THF to acetonitrile had no effect on the reaction, resulting only in recovered starting material 145 (Table 2.5, entry 2). The use of a stronger organic base (i.e. DBU) resulted in the formation of aldehyde 144 as a trace constituent only observed using low resolution mass spectroscopy (Table 2.5, entry 3). Attempts to improve the reaction by changing the solvent to acetonitrile were unsuccessful (Table 2.5, entry 4). Finally, addition of DMAP had no effect on the reaction, only starting material 145 was recovered when using either acetonitrile or THF as solvent (Table 2.5, entries 5 and 6). As a result, investigations into the Vilsmeier formylation and paraformaldehyde ortho-formylation of 145 were not pursued further.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>additive</th>
<th>solvent</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NEt₃</td>
<td>-</td>
<td>THF</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>NEt₃</td>
<td>-</td>
<td>CH₃CN</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>NEt₃</td>
<td>-</td>
<td>THF</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>NEt₃</td>
<td>-</td>
<td>CH₃CN</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>NEt₃</td>
<td>DMAP</td>
<td>CH₃CN</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>NEt₃</td>
<td>DMAP</td>
<td>THF</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

2.3.2.3. Attempted synthesis of aldehyde 144 via Fries rearrangement

Due to the lack of success of our previous attempts to effect direct ortho-formylation of naphthol 145, an alternative synthetic approach was devised. It was noted that aldehyde 144 could be obtained from formate ester 147 via Fries rearrangement (Scheme 2.27). Formylation of naphthol 145 would provide access to intermediate 147.
Chapter 2: Discussion

Formate ester 147 was accessed by formylation of naphthol 145 using acetic-formic anhydride 148 which was synthesised in a single step from acetyl chloride and sodium formate (Scheme 2.28). However, attempts to effect Fries rearrangement with naphthalene 147 using BCl3 in 1,2-dichloroethane (DCE) resulted only in degradation of the starting material via TBS deprotection and subsequent degradation.

Given these results, we concluded that the sensitivity of the TBS group to Lewis acids could also prove to be an obstacle to the preparation of the desired aldehyde via Fries rearrangement. However, investigations into a suitable protecting group for this reaction were not conducted as our next synthetic strategy enabled retention of the TBS protecting group throughout the entire synthesis.

2.3.3. Carbonylation via ortho-halogenation of naphthol 145

In view of the difficulties encountered with the ortho-formylation of alcohol 145 in a single step, an alternative route was devised. Methoxycarbonylation of halide 149 would afford ester 150, while the selective ortho-halogenation of naphthol 145 would provide access to halide 149 (Scheme 2.29).

2.3.3.1. Synthesis of iodinated 151

With this alternate route designed, our focus turned to the ortho-halogenation of naphthol 145. Attempted halogenation of naphthol 145 using pyridinium tribromide led only to undesired para- and di-halogenation (Table 2.6, entry 1). The use of iodine and morpholine in chlorinated solvent provided halide 151, however the reaction proved to be unreliable, resulting in a variety of yields obtained using the same reaction conditions (Table 2.6, entries 2 and 3).
Initially, iodine and morpholine were sequentially added to a solution of naphthol 145 in dichloromethane, giving unreproducible results. However, changing the order of addition to allow \textit{in situ} formation of the morpholine-iodine complex prior to addition of naphthol 145, gave iodide 151 in reproducible yields (Table 2.6, entry 3). Following the procedure outlined in a 1942 patent by Rice and Beal, the morpholine-iodine complex was then synthesised as an orange solid from morpholine, iodine and potassium iodide in water.\textsuperscript{90} The use of this preformed complex gave iodo-naphthol 151 in 78\% yield (Table 2.6, entry 4).

\textbf{Table 2.6: ortho-Halogenation conditions of 145.}

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>comment</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pyridinium tribromide, THF \textit{para-} or di-bromination</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2\textsuperscript{a}</td>
<td>I\textsubscript{2}, morpholine, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>not reliable</td>
<td>0% to 62%</td>
</tr>
<tr>
<td>3\textsuperscript{b}</td>
<td>I\textsubscript{2}, morpholine, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>reliable</td>
<td>58% to 74%</td>
</tr>
<tr>
<td>4\textsuperscript{c}</td>
<td>morpholine-I\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>reliable</td>
<td>78%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Iodine and morpholine added to naphthol 145; \textsuperscript{b} naphthol 145 added to \textit{in situ} formed morpholine-I\textsubscript{2} complex; \textsuperscript{c} Pre-formed morpholine-I\textsubscript{2} complex added to naphthol 145.\textsuperscript{90}

To the best of our knowledge, this is the first reported ortho-iodination of a phenol using the pre-formed morpholine-iodine complex. Interestingly, the synthesised complex could be stored for 6 months in a desiccator with light excluded without loss of reactivity despite a change in colour from orange to dark brown.

Additionally, the reaction was attempted in various solvents (\textit{e.g.} MeOH, acetone, AcOEt) without success. In contrast to dichloromethane, complete dissociation of the complex was immediately observed in these solvents. These results suggest that the reaction occurs heterogeneously and depends on the dissociation constant of the complex in the reaction solvent.

The postulated mechanism of the iodination begins with deprotonation of the naphthol by morpholine with concomitant attack of the iodine (Scheme 2.30). Following a concerted mechanism, the spatial proximity of the iodine favours iodination at the \textit{ortho}-position. Tautomerisation of pyrone (i) then leads to iodide 151.
Chapter 2: Discussion

Scheme 2.30: Postulated mechanism iodination using morpholine-iodine complex.

Naphthol 151 exhibited poor stability at room temperature and degraded rapidly at temperatures greater than 40 °C. As a result iodide 151 was immediately converted to either the acetate 153 or ethoxymethyl ether (EOM) 154. The acetate and EOM protecting groups were chosen because of the simple deprotection conditions required (Scheme 2.31).

Scheme 2.31: EOM and acetate protection of naphthol 151.

2.3.3.2. Attempted lithium-halogen exchange carbonylation of halide 154

With iodides 153 and 154 in hand, lithium-halogen exchange was examined as a means of introducing the carbonyl group. Ghera et al. reported the carbonylation of brominated naphthalene 155 via lithium-bromide exchange (Scheme 2.32). Intermediate 156 was initially formed by treatment of 155 with n-butyl lithium for 5 minutes in THF at −78 °C. Subsequent addition of ethyl chloroformate afforded ethyl ester 157 in 86 % yield.

Scheme 2.32: Formation of 157 via lithium-halogen exchange by Ghera et al.

Attempted formation of ethyl ester 158 from iodinated naphthalene 154 using n-butyl lithium and ethyl chloroformate was unsuccessful (Scheme 2.33). The reaction only resulted in proto-dehalogenation, giving naphthalene 159. Although, the reaction was carried out at different temperatures, only naphthalene 159 was observed. Given these results, we then sought to form
carboxylic acid 160 instead (Scheme 2.33). Following the addition of \( n \)-butyl lithium, carbon dioxide was then bubbled through the solution. Unfortunately, once again only the proto-dehalogenated product 159 was recovered from the reaction mixture.

Scheme 2.33: Attempted carboxylation of 154

Two further methods were then investigated for the addition of the carbon dioxide. The first method involved direct addition of crushed dry ice to the reaction mixture. Unfortunately, rapid sublimation of the dry ice resulted in condensation of water on its surface. As a result, when dry ice was added, the lithiated intermediate immediately reacted with the ice on the surface, forming compound 159.

The second method involved use of an apparatus that was designed to prevent addition of wet gaseous carbon dioxide. Gaseous carbon dioxide arising from sublimation at room temperature was passed through a cartridge containing calcium chloride packed between two layers of activated desiccator beads. The resulting dry carbon dioxide was then bubbled through the cooled solution of iodinated 154 and \( n \)-butyl lithium. In all cases, the lithium-halogen exchange occurred but the metalated intermediate was quenched to form proto-dehalogenated naphthalene 159. In retrospect, it would have been interesting to quench the reaction with heavy water (\( i.e. \) D\(_2\)O) to investigate whether the proto-dehalogenation had occurred during the reaction or the work-up.

2.3.3.3. Palladium-catalysed methoxycarbonylation of halides 151, 154 and 153

Due to our lack of success with the above direct halogen-metal exchange route, an alternative strategy was devised. This plan involved palladium-catalysed carbonylation using carbon monoxide as the carbonyl source (Table 2.9). First, freshly synthesised naphthol 151 was treated with triethylamine, 1,1′-ferrocenediyl-bis(diphenylphosphine) (dppf) and palladium acetate in DMF-MeOH (1:1) under a carbon monoxide atmosphere.\(^92\) Unfortunately, only degradation was observed under these conditions (Table 2.7, entries 1 and 2). The reaction was then attempted in
methanol without the ligand (i.e. dppf) which led to the formation of proto-dehalogenated naphthalene 145 (Table 2.7, entry 3).  

Treatment of EOM-protected naphthalene 154 with palladium diacetate, dppf and triethylamine in DMF-MeOH was also unsuccessful, affording only starting material 154 (Table 2.7, entry 4). Pleasingly, reaction of 154 with triethylamine and palladium diacetate under a carbon monoxide atmosphere in methanol for 24 h afforded the desired ester 161 in high yield (Table 2.7, entry 5).

Acetate 153 was then synthesised in comparable yield using a similar procedure (Table 2.7, entry 6). However, the reaction rate was lower, requiring more than two days to reach completion. This result suggests that the electron-withdrawing nature of the protecting group decreases the rate of the carbonylation.

Table 2.7: Methoxycarbonylation of halides 151, 154 and 153

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>ligand</th>
<th>solvent</th>
<th>comment</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>151</td>
<td>dppf</td>
<td>DMF-MeOH</td>
<td>degradation</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>151</td>
<td>dppf</td>
<td>DMF-MeOH</td>
<td>degradation</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>151</td>
<td>-</td>
<td>MeOH</td>
<td>145</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>154</td>
<td>dppf</td>
<td>DMF-MeOH</td>
<td>no reaction</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>154</td>
<td>-</td>
<td>MeOH</td>
<td>161</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>153</td>
<td>-</td>
<td>MeOH</td>
<td>143</td>
<td>80</td>
</tr>
</tbody>
</table>

* The reactions were carried out in sealed tubes.

Initially the reaction was carried out in methanol at reflux with carbon monoxide bubbled through the solution. However, due to the constant carbon monoxide stream and high temperature (i.e. 60 °C), the solvent evaporated even when using a reflux condenser. In order to prevent this, the reaction was carried out in a sealed tube under a carbon monoxide atmosphere with temperatures up to 120 °C, giving esters 161 and 143 in 84 % and 80 % yield respectively.

It is important to note that the major by-product resulting from these reactions is the deprotected naphthol ester 162. Attempts to reduce the formation of the deprotected naphthalene...
162 either by using milder bases (e.g. K$_2$CO$_3$ and DIPEA) or lower temperatures (i.e. < 50 °C) were unsuccessful, resulting in lower overall yields without significant effects on the amount of deprotection observed.

Despite several mechanistic studies carried out over the years, the exact mechanism of palladium-catalysed carboalkoxylation is still uncertain.\textsuperscript{94-98} The general mechanism involves oxidative addition of the iodo-naphthol (ii) to the palladium catalyst (i) followed by insertion of the carbon monoxide to give (iv) (Scheme 2.34). Nucleophilic addition of methanol to (iv) releases naphthalene ester (v) and regenerates catalyst (i).

![Scheme 2.34: Proposed catalytic cycle for palladium-catalysed alkoxy carbonylation.\textsuperscript{98}](image)

2.3.4. Hypervalent iodine cyclisation of 143 and 161

2.3.4.1. Attempted one pot formation of the pyrone-tetrahydrofuran moiety

With alkenes 143 and 161 in hand, attention turned to the formation of the fused naphthopyrone-tetrahydrofuran moiety. Treatment of alkenes 143 and 161 with hypervalent iodine would enable access to naphthopyrone 140 and 163 in a single step (Scheme 2.35).

![Scheme 2.35: Retrosynthesis analysis of 163 and 140 via hypervalent iodination cyclisation.](image)
Chapter 2: Discussion

Fujita and co-workers described the installation of the fused pyrone-tetrahydrofuran ring system in a single step via cyclisation with hypervalent iodine (Table 2.8). Treatment of alkene 141 with iodobenzene diacetate (PhI(OAc)₂), boron trifluoride and acetic acid in dichloromethane at low temperature provided access to pyrones 142 and 164 in 33% and 41% yield respectively (Table 2.8, entry 1). Additionally, the use of enantiopure hypervalent iodine (S)-70 enabled exclusive formation of diastereoisomer 164 (Table 2.8, entry 2).

Table 2.8: Hypervalent iodine cyclisation conditions of 141 by Fujita et al.⁶

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArI(OAc)₂</th>
<th>142 (%)</th>
<th>164 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI(OAc)₂</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>(S)-70</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

Application of these conditions to esters 161 and 143 would provide access to naphthopyrones 163 and 140 (Table 2.9). The reaction was initially carried out using PhI(OAc)₂, acetic acid and Lewis acid boron trifluoride diethyl-etherate at −78 °C. Disappointingly, degradation of the starting materials 161 and 143 was observed (Table 2.9, entries 1 and 2). The reaction conditions were then adapted for the use of [bis(trifluoroacetoxy)iodo]benzene (PIFA), replacing acetic acid by TFA, which also led to degradation of starting material (Table 2.9, entry 3). TLC monitoring of the reaction enabled us to observe that degradation had already occurred before addition of the Lewis acid, suggesting sensitivity of our substrate to acid.

Changing the solvent from dichloromethane to acetonitrile had no effect when using either 161 or 143, again resulting in degradation of the starting materials (Table 2.9, entries 4 and 5). However, monitoring of the reaction by TLC revealed that the degradation occurred after addition of the Lewis acid. These observations confirmed that naphthalenes 161 and 143 are not only sensitive to Brønsted acids (i.e. TFA) but also to moderately strong Lewis acids (i.e. BF₃·OEt₂). Following these observations, the hypervalent iodine cyclisation was attempted at different
temperatures in the absence of the Lewis acid, however this resulted in recovery of 143 (Table 2.9, entries 6 and 7). In a last attempt, the iodine cyclisation was attempted with PIFA in acetonitrile at temperature from −20 °C to 50 °C with constant monitoring by TLC (Table 2.9, entry 8). Unfortunately, no reaction occurred until the temperature reached 40 °C, after which only degradation was observed.

Table 2.9: Hypervalent iodine cyclisation conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>ArI(OAc)₂</th>
<th>Lewis acid</th>
<th>solvent</th>
<th>solvent</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>161</td>
<td>PhI(OAc)₂</td>
<td>BF₃·OEt₂</td>
<td>AcOH-CH₂Cl₂</td>
<td>−78 °C to −40 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>2</td>
<td>143</td>
<td>PhI(OAc)₂</td>
<td>BF₃·OEt₂</td>
<td>AcOH-CH₂Cl₂</td>
<td>−78 °C to −40 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>3</td>
<td>161</td>
<td>PIFA</td>
<td>-</td>
<td>TFA-CH₂Cl₂</td>
<td>−78 °C to −40 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>4</td>
<td>143</td>
<td>PhI(OAc)₂</td>
<td>BF₃·OEt₂</td>
<td>AcOH-CH₃CN</td>
<td>−20 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>5</td>
<td>161</td>
<td>PhI(OAc)₂</td>
<td>BF₃·OEt₂</td>
<td>AcOH-CH₃CN</td>
<td>−20 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>6</td>
<td>143</td>
<td>PhI(OAc)₂</td>
<td>-</td>
<td>AcOH-CH₂Cl₂</td>
<td>−78 °C to rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>143</td>
<td>PIFA</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>−78 °C to rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>143</td>
<td>PIFA</td>
<td>-</td>
<td>CH₃CN</td>
<td>−20 °C to 50 °C</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

2.3.4.2. Attempted lactonisation of 143 with hypervalent iodine

Due to our lack of success in effecting the conversion of esters 143 and 161 to the respective naphthopyrones 140 and 163 in a single step, an alternative route was devised. Late stage installation of the tetrahydrofuran ring via nucleophilic substitution of the tosylate derivative of 165, would enable access to naphthopyrone 140. Oxylactonisation of alkene 143 using hypervalent iodine would in turn enable the formation of δ lactone 165.
In 2010, Fujita and co-workers described the oxylactonisation of alkene 166 using hypervalent iodine and *para-*toluene sulfonic acid in dichloromethane at −20 °C to give δ lactone 167 and regio-isomer phthalide 168 in a 93:7 ratio (Scheme 2.37). Interestingly, these conditions allowed preferential formation the 6-membered lactone 167. Disappointingly, treatment of 143 with PhI(OAc)$_2$ and *para-*toluene sulfonic acid only resulted in degradation of the starting material. Due to these results, investigations toward a hypervalent iodine cyclisation of compound 143 were not pursued further.

Selective deprotection of alkene 139 using DBU in acetonitrile-water (95:5) provided access to naphthol 145. Attempts to formylate alkene 145 using common methods (*e.g.* Vilsmeier, Fries rearrangement) were unsuccessful. Gratifyingly, ortho-iodination of alkene 145 followed by naphthol protection provided halides 153 and 154. Palladium-catalysed methoxycarbonylation of halides 153 and 154 afforded hypervalent iodine cyclisation precursors 143 and 161.
Unfortunately, attempts to effect the key hypervalent iodine cyclisation on these esters to access the naphthopyrone-tetrahydrofuran ring system were unsuccessful.

Scheme 2.38: Attempted installation of the fused naphthopyrone-tetrahydrofuran ring system via hypervalent iodine cyclisation.
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2.4. Revised synthetic strategy: oxidation of alkenes 143 and 139

2.4.1. Tandem dihydroxylation-\(S_N2\) cyclisation of ester 143

2.4.1.1. Retrosynthetic analysis of naphthopyrone 140

Given the effort taken to synthesise ester 143, our revised strategy to synthesise lasionectrin (13) began with this compound. The fused naphthopyrone-tetrahydrofuran moiety present in naphthopyrone 140 would be constructed by dihydroxylation of alkene 171 (Scheme 2.39). Based on Begari’s work, upon dihydroxylation the naphthopyrone-tetrahydrofuran ring system would be formed via intramolecular displacement of the tosylate and concomitant lactonisation. Tosylate 171 would in turn be accessed by deprotection and subsequent tosylation of ester 143.

Scheme 2.39: Retrosynthetic analysis of naphthopyrone 140 via dihydroxylation of tosylate 171.

2.4.1.2. Synthesis of tosylate 171

The initial target of our revised synthesis was racemic tosylate 171. Deprotection of alkene 143 was carried out in THF using tetrabutylammonium fluoride (TBAF) to give alcohol 172 in moderate yield. However, due to the basicity of TBAF, deprotection of the naphthol functionality also occurred. In an attempt to reduce the acetate deprotection, the reaction was conducted in a solution of TBAF buffered with acetic acid (Scheme 2.40). It is important to note that although near quantitative conversion of ester 143 to alcohol 172 in buffered TBAF occurred, the reaction rate was low, requiring two days to reach completion. Tosylation of alcohol 172 using tosyl chloride and DMAP in pyridine then gave tosylate 171 in 56 % yield.

Scheme 2.40: Synthesis of tosylate 171.
2.4.1.3. Prevost-Woodward dihydroxylation of 143

It was decided to first attempt the dihydroxylation of racemic ester 143 as a model reaction. In 2005, Sudalai et al. described a catalytic variant of the Prevost-Woodward dihydroxylation of styrenes using sodium periodate and lithium bromide, which provided access to diols in reasonable yields.\(^\text{99}\) However, attempted dihydroxylation of ester 143 using these conditions gave halogenated naphthalenes 173 and 174 as an inseparable mixture (Scheme 2.27). The desired lactone 175 was not observed.

![Scheme 2.41: Prevost-Woodwards dihydroxylation approach.](image)

Interestingly, Sudalai et al. also described the oxidative halogenation of a variety of styrenes using similar conditions to those reported for the catalytic Prevost-Woodward dihydroxylation but with the addition of aqueous sulphuric acid (Scheme 2.42).\(^\text{100}\) However, Sudalai did not describe any instances of halogenation of aromatic rings.

![Scheme 2.42: Reactions of aromatic styrenes with sodium periodate and lithium bromide by Sudalai et al.\(^\text{99,100}\)](image)

Despite not providing access to alkene 143, it was noted that the unexpected halogenation of naphthalene 143 could find use for the synthesis of halogenated coupling precursors needed to access dimeric naphthalenes such as lichenicolin A (29) from halide 176 (Figure 2.2).
2.4.1.4. Sharpless dihydroxylation of tosylate 171

Given our unsuccessful attempts to effect Prevost-Woodward dihydroxylation of alkene 143, an alternate route was devised using the more common Sharpless dihydroxylation. Treatment of tosylate 171 with AD-mix α would allow formation of naphthopyrone 140 in a single step (Scheme 2.43). 44

Scheme 2.43: Proposed Sharpless asymmetric dihydroxylation-lactonisation of alkene 171.

Dihydroxylation of racemic 171 was carried out in tert-butanol-water (1:1) using AD-mix α resulting in formation of an inseparable equimolar diastereoisomeric mixture of phthalides 177a and 177b and their respective enantiomers (Scheme 2.44).

Scheme 2.44: AD-mix α dihydroxylation of ester 171.

Originally, the inseparable mixture of 177a and 177b could not be differentiated from a regioisomeric mixture of 6-membered lactone 178 and 5-membered lactone 177 (Figure 2.3).
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Figure 2.3: Possible structures formed from the Sharpless dihydroxylation of 171.

However, it was observed that the differences in chemical shift in the $^1$H NMR spectrum for the same protons in the 1:1 mixture of alcohols 177 and 178 were extremely small (max $\Delta \delta = 0.05$ ppm). We therefore postulated that the mixture consisted of two diastereoisomers rather than two regioisomers. In order to unambiguously determine the structure of the constituents, the chemical shift of the characteristic protons H-A and H-B of 177 and 178 were compared with similar $\gamma$- and $\delta$-lactones found in the literature. In our context, H-A refers to the proton adjacent to the aromatic ring and H-B refers to the proton in the position $\alpha$ to H-A.

Fortunately, Fujita and co-workers reported the hydrolysis and isomerisation of $\delta$-lactone 179 upon treatment with sodium hydroxide in methanol to give phthalide 180 and $\delta$-lactone 181 (Scheme 2.45). The isomerisation occurs due to hydrolysis of the lactone ring to give intermediate 182 which then undergo lactonisation to give phthalide 180 and $\delta$-lactone 181. The formation of phthalide 180 as the major product suggests that phthalide 180 is the kinetic product of the lactonisation reaction.

Scheme 2.45: Fujita’s hydrolysis and isomerisation of 179 to give phthalide 181 and $\delta$-lactone 181.

The characteristic protons H-A and H-B for 180 and 181 have very significant differences in chemical shift depending on the size of the lactone ring. Due to the proximity of the carbonyl group and the aromatic ring, proton H-A in the 5-membered lactone 180 is more deshielded than its counterpart in 181, resulting in a significant chemical shift difference ($\Delta \delta_{(A,A)} = 0.79$ ppm, Table 2.10, entries 1 and 2). Similarly, H-B in the $\delta$-lactone 181 is more deshielded than H-B in 180, resulting again in a significant difference in chemical shift ($\Delta \delta_{(B,B)} = -0.45$ ppm, Table 2.10, entries 1 and 2). In addition to this, the chemical shift difference between H-A and H-B is greater in the 5-membered lactone 180 ($\Delta \delta_{(A,B)} = 1.43$ ppm, Table 2.10, entry 1) than in its 6-membered counterpart 181 ($\Delta \delta_{(A,B)} = 0.17$ ppm, Table 2.10, entry 2).
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In our case, the H-A and H-B protons exhibited a large chemical shift difference (\(\Delta \delta_{(A,B)} = 1.17\) ppm) and the signals arising from H-A were significantly deshielded, with an average chemical shift of 5.43 ppm, suggesting a 5-membered ring structure for both constituents of the mixture 177 (Table 2.10, entry 3). Similar observations supporting this hypothesis were made with naphthalene derivatives 183, 184 and 13 (Table 2.10, entries 4–6).36,101,102

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>¹H-NMR, chemical shift (ppm)</th>
<th>(\Delta \delta_{(A,B)}) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>180</td>
<td>5.40 &amp; 3.97</td>
<td>1.43</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>181</td>
<td>4.61 &amp; 4.44</td>
<td>0.17</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>177</td>
<td>5.47 &amp; 5.41 &amp; 4.27</td>
<td>1.20 &amp; 1.14</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>183</td>
<td>5.75 &amp; 4.38 &amp; 4.29</td>
<td>1.37 &amp; 1.46</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>184</td>
<td>4.54 &amp; 4.94</td>
<td>−0.40</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13</td>
<td>4.93 &amp; 5.24</td>
<td>−0.31</td>
</tr>
</tbody>
</table>

<sup>a</sup> CDCl₃, 600 MHz; <sup>b</sup> CDCl₃, 400 MHz; <sup>c</sup> CD₃OD, 500 MHz

These observations suggested that the mixture consisted of two diastereomeric phthalides 177<sub>a</sub> and 177<sub>b</sub> rather than a regioisomeric mixture of a phthalide 177 and a δ-lactone 178. This meant that the ideal synthetic approach towards the naphthopyrone lasionectrin (13) would need to effect formation of the tetrahydrofuran ring first and then initiate the lactonisation step.
2.4.2. Epoxidation of alkene 143

2.4.2.1. Retrosynthetic analysis of 140

In line with these observations, an alternative approach in which formation of the tetrahydrofuran ring preceded lactonisation was devised. After TBS removal of alcohol 185, naphthopyrone trans-140 would be formed via intramolecular epoxide opening and concomitant lactonisation after treatment of the resulting alcohol with a strong base (Scheme 2.46). Epoxide 185 in turn would be synthesised from ester 143 using common epoxidation methods.

![Scheme 2.46: Retrosynthetic analysis of 140 via epoxidation of 185.](image)

2.4.2.2. Attempted epoxidation of ester 143

Attention turned to the synthesis of epoxide 185 from alkene 143 (Table 2.11). Following literature precedent, it was proposed that Prilezhaev reaction using \textit{m}-CPBA as the peracid would effect oxidation of 143 to epoxide 185.\textsuperscript{103,104} Unfortunately, exposure of alkene 143 to Prilezhaev conditions did not result in the formation of epoxide 185 and only degradation of the starting material was observed (Table 2.11, entry 1). In order to reduce the possibility of side reactions due to the presence of residual \textit{meta}-chlorobenzoic acid, the epoxidation was also attempted in buffered media, however this procedure was also unsuccessful (Table 2.11, entry 2).

Following these results, the epoxidation was attempted \textit{via in situ} formation of the peroxo-complex of methyltrioxorhenium (MTO) and hydrogen peroxide. According to the literature, the reaction was carried out using MTO, hydrogen peroxide and pyridine in dichloromethane.\textsuperscript{105} Unfortunately, application of this procedure to alkene 143 resulted in complete degradation of the starting material 143 (Table 2.11, entry 3).

Oxidation of alkene 143 with freshly synthesised dimethyldioxirane (DMDO) in acetone was also unsuccessful (Table 2.11, entry 4). However, the reaction was carried out with a large excess of Murray’s agent (DMDO). The reaction was therefore attempted with \textit{in situ} formation of DMDO by conducting the reaction in a mixture of acetone, saturated aqueous sodium bicarbonate solution and oxone (Table 2.11, entry 5).\textsuperscript{106} Nevertheless, use of this procedure resulted in degradation of the starting material following the addition of oxone.
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An alternative to the peroxide-mediated epoxidation involves use of catalytic manganese-salen and sodium hypochlorite as the oxidising agent. Reaction of alkene 143 was carried out in dichloromethane with Jacobsen’s catalyst in the presence of bleach. However, only degradation of the starting material was observed when this procedure was tried (Table 2.11, entry 6).

Table 2.11: Attempted epoxidation of alkene 143.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$m$-CPBA, CH$_2$Cl$_2$</td>
<td>degradation</td>
</tr>
<tr>
<td>2</td>
<td>$m$-CPBA, pH = 7 buffer, CH$_2$Cl$_2$</td>
<td>degradation</td>
</tr>
<tr>
<td>3</td>
<td>MTO, H$_2$O$_2$, pyridine, CH$_2$Cl$_2$</td>
<td>degradation</td>
</tr>
<tr>
<td>4</td>
<td>DMDO, acetone, rt</td>
<td>degradation</td>
</tr>
<tr>
<td>5</td>
<td>acetone, oxone, aq. NaHCO$_3$(sat), CH$_2$Cl$_2$</td>
<td>degradation</td>
</tr>
<tr>
<td>6</td>
<td>Jacobsen catalyst, bleach, CH$_2$Cl$_2$</td>
<td>degradation</td>
</tr>
</tbody>
</table>

Given these disappointing results, we concluded that alkene 143 was sensitive to oxidising conditions. Therefore despite the extensive effort made to access alkene 143, investigations into the formation of the fused pyrone-tetrahydrofuran moiety from ester 143 were not further pursued.

2.4.3. Epoxidation of alkene 139

2.4.3.1. Retrosynthetic analysis of naphthopyrone 140

Given the disappointing results obtained for the epoxidation of ester 143, our new strategy involved early stage installation of the epoxide ring and subsequent intramolecular opening to access the tetrahydrofuran moiety (Scheme 2.47). The naphthopyrone-tetrahydrofuran ring system present in naphthopyrone 186 would be accessed via intramolecular displacement of a tosylate by the carboxylic acid in 187 under basic conditions. Following tosylation of alcohol 188, naphthalene 187 would be accessed using an iodination-carbonylation sequence. Deprotonation of alcohol 189 and intramolecular epoxide opening with the resulting alkoxide
would allow access to tetrahydrofuran 188. Following epoxidation of alkene 139, selective TBS deprotection would lead to alcohol 189.

\[ \text{Scheme 2.47: Retrosynthetic analysis of 140 via epoxidation of 139.} \]

### 2.4.3.2. Attempted epoxidation of alkene 139

With alkene 139 in hand, attention turned to epoxidation of the double bond. All previously mentioned epoxidation methods attempted to effect epoxidation of ester 143 were also applied to alkene 139 in an attempt to access epoxide 190 (Table 2.11). Unfortunately, similar results were observed and only degradation of the starting material resulted (Scheme 2.48).

\[ \text{Scheme 2.48: Attempted epoxidation of alkene 139.} \]

### 2.4.3.3. Attempted Sharpless epoxidation of homoallylic alcohol 191

In a last attempt to effect epoxidation of alkene 139, our attention turned to use of the Sharpless epoxidation which effects the transformation of allylic and homoallylic alcohols into enantiopure epoxides using a chiral titanium complex.\(^ {107}\) Sharpless epoxidation of homoallylic alcohol 191 would allow formation of the desired epoxide 190 (Scheme 2.49). Selective TBS removal of the protected secondary alcohol in 139 would enable access to Sharpless epoxidation precursor 191.
Scheme 2.49: Retrosynthetic analysis of 189 via Sharpless epoxidation of 191.

Alcohol 191 was accessed in similar yields using two different methods (Table 2.12). Initially alcohol 191 was prepared using cerium chloride heptahydrate in acetonitrile (Table 2.12, entry 1). However the reaction was very slow (i.e. 2 days) and alcohol 191 was formed together with fully deprotected alcohol 146. Alcohol 191 was also prepared via selective TBS-deprotection using catalytic iodine in methanol (Table 2.12, entry 2). Despite the similar yields, the reaction rate of the iodine-catalysed reaction was faster, requiring only two hours to afford the desired alcohol 191. However, this reaction was not as selective, as fully deprotected diol 146 was also observed.

Table 2.12: Condition of the selective deprotection of alkene 139.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>191:146 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CeCl₃·7H₂O, CH₃CN</td>
<td>89:11</td>
</tr>
<tr>
<td>2</td>
<td>I₂ (cat.), MeOH</td>
<td>78:22</td>
</tr>
</tbody>
</table>

Sharpless epoxidation of homoallylic alcohol 191 was attempted with L- (+)-diethyl tartrate (L- (+)-DET), titanium tetraisopropoxide and tert-butyl hydroperoxide (TBHP) in dichloromethane with activated molecular sieves (4Å) at −20 °C with slow warming to room temperature. Unfortunately, only starting material 191 was recovered from the reaction.

Scheme 2.50: Attempted synthesis of epoxide 190 via Sharpless epoxidation.
Given the difficulties encountered in the epoxidation of 139 and 191, this route was not further pursued.

2.4.4. Summary

Four strategies were explored to access the fused pyrone-tetrahydrofuran ring system present in lasionectrin (13). In the first strategy, we aimed to access this ring system in a single step via dihydroxylation-lactonisation sequence. This route began with TBS deprotection and tosylation of ester 143 (Scheme 2.51). Then, a Sharpless dihydroxylation and SN2 cyclisation sequence from tosylate 171 was attempted. Unfortunately, only a diastereomeric mixture of phthalides 177a and 177b was observed. This result suggested that our synthetic strategy should include initial installation of the tetrahydrofuran ring prior to lactonisation.

The alternative strategies focused on the formation of the tetrahydrofuran ring system via epoxide opening and hinged on the oxidation of the double bond to an epoxide. Unfortunately, all epoxidation methods attempted on alkenes 139 and 143 were unsuccessful.

In the last strategy, we aimed to oxidise the double bond of the allylic alcohol 191 using Sharpless epoxidation conditions. After selective deprotection of alkene 139, Sharpless epoxidation of allyl alcohol 191 was attempted without success.
Scheme 2.51: Attempted synthesis of the pyrone-tetrahydrofuran core of lasionectrin (13) from alkenes 139, 143 and 191.
2.5. Synthesis of lasionectrin (13) via Upjohn dihydroxylation

2.5.1. Dihydroxylation-S_N2 sequence from alkene 192

2.5.1.1. Retrosynthetic analysis of lasionectrin (13) via dihydroxylation-S_N2 sequence

Given the unsuccessful attempts to epoxidise alkene 139, a new strategy was devised to enable the synthesis of lasionectrin (13) via formation of the tetrahydrofuran ring prior to lactonisation. Selective peri-demethylation of naphthopyrone 193 would allow access to natural product, lasionectrin (13) (Scheme 2.52). Naphthopyrone 193 would be accessed via carbonylation-lactonisation sequence from iodide 194, which would in turn be obtained from naphthol 195 via ortho-iodination using morpholine-iodine complex. The tetrahydrofuran ring in naphthol 195 would be prepared via Sharpless dihydroxylation of alkene 196 and subsequent intramolecular displacement of the tosylate. Tosylate 196 would be derived from alkene 197 via silyl deprotection and subsequent tosylation.

Scheme 2.52: Retrosynthetic analysis of lasionectrin (13) via dihydroxylation-S_N2 sequence.

2.5.1.2. Synthesis of tosylate 192

The initial focus of this new strategy was the formation of tosylate 196. However, due to the difficulties encountered to effect the selective silyl deprotection of the secondary alcohol in alkene 139, it was thought to change the naphthol protection group (see 2.4.3.3, page 67). An acetate ester was chosen to be a suitable protecting group because of its stability to TBS deprotection conditions (e.g. TBAF) and its simple cleavage conditions (e.g. hydrolysis). TBS removal and subsequent tosylation of the resulting alcohol 198 would allow access to tosylate 192 (Scheme 2.53).
The synthesis of tosylate 192 began with protection of previously synthesised naphthol 116 as an acetate with acetic anhydride and DMAP in pyridine to give Julia-Kocienski precursor 129 in near quantitative yield (Scheme 2.54). Subsequent Julia-Kocienski olefination with previously synthesised enantiopure sulfone 119 gave alkene 199 in 98% yield as a 98:2 mixture of E/Z isomers. TBS deprotection of alkene 199 using TBAF in buffered THF gave alcohol 198 in 90% yield.

Initial attempts to effect the Julia-Kocienski olefination of aldehyde 129 and sulfone 119 using previously established procedures only gave moderate yields (i.e. 75%). Further investigations revealed that a higher reaction temperature and variation in the order of the addition of the reagents dramatically improved the reaction yield (i.e. 98%).

Finally, tosylation of alcohol 198 using tosyl chloride and DMAP in a 5:3 dichloromethane-pyridine mixture yielded tosylate 192 in excellent yield (Scheme 2.55).

It is also of note that halide 200 was observed as the major product when the reaction was carried out in neat pyridine (Scheme 2.56). Interestingly, Ding et al. also described conversion of substituted benzyl alcohols to the corresponding chlorides using triethylamine and tosyl
chloride in the presence of DMAP in dichloromethane.\textsuperscript{108} Monitoring the reaction by TLC revealed that tosylate 192 was first formed and subsequent substitution then gave chloride 200. No further studies were carried out to investigate the nature of the nucleophilic substitution reaction, however chloride 192 exhibited an optical rotation, suggesting an $S_N^2$ type reaction.

![Scheme 2.56: Synthesis of chloride 200.](image)

### 2.5.1.3. Dihydroxylation–cyclisation sequence of tosylate 192.

With tosylate 192 in hand, attention turned to the formation of the tetrahydrofuran ring via tandem dihydroxylation–tosylate displacement reaction. Attempted Sharpless dihydroxylation of alkene 192 with AD-mix β were either ineffective at low temperature (Table 2.13, entry 1) or resulted in complete degradation of the starting material upon heating (Table 2.13, entry 2). Pleasingly, use of the Upjohn dihydroxylation provided tetrahydrofurans 201a and 201b as an inseparable 1:1 mixture of diastereoisomers (Table 2.13, entry 3). Interestingly, addition of chiral ligand (DHQ)$_2$PHAL or (DHQD)$_2$PHAL respectively resulted in preferential formation of each diastereoisomer in a ratio of 4:1 (Table 2.13, entries 4 and 5).

### Table 2.13: Dihydroxylation-cyclisation conditions of tosylate 192.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (%)</th>
<th>201a/201b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}</td>
<td>Sharpless, 0 °C to rt</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2\textsuperscript{a}</td>
<td>Sharpless, 55 °C</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3\textsuperscript{b}</td>
<td>Upjohn, rt</td>
<td>97</td>
<td>1:1</td>
</tr>
<tr>
<td>4\textsuperscript{b,c}</td>
<td>Upjohn, (DHQ)$_2$PHAL, rt</td>
<td>68</td>
<td>1:4</td>
</tr>
<tr>
<td>5\textsuperscript{b,c}</td>
<td>Upjohn, (DHQD)$_2$PHAL, 0 °C</td>
<td>68</td>
<td>4:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} AD-mix β, i-BuOH-H$_2$O (1:1); \textsuperscript{b} OsO$_4$, NMO, acetone-H$_2$O (3:1); \textsuperscript{c} 10 mol % ligand
Chapter 2: Discussion

The configuration of the stereogenic centres in diastereoisomers 201a and 201b were determined by NMR analysis, in particular NOESY (Figure 2.4). The electronic environment of H-12 in 201a was different to 201b (δ₁₂ = 4.50 ppm and δ₁₂ = 4.08 ppm respectively). Similarly, there was a significant chemical shift difference between the signals arising from H-9 of 201a and 201b (Δδ₉₋₁₀ = 0.27 ppm). Nuclear Overhauser effect correlations were observed between H-9 and H-10 in both diastereoisomers, suggesting that selective cis dihydroxylation had taken place. In addition, nOe correlation between H-9 and H-12 was only observed for 201b suggesting all cis stereochemistry.

Figure 2.4: Key NOESY correlation observed for 201a and 201b.

The addition of pseudo-enantiomeric ligands (DHQ)₂PHAL or (DHQD)₂PHAL allowed preferential formation of one diastereoisomer, which were in accordance with mnemonic device established by Sharpless in 1992. The mnemonic device divides the catalytic site into 4 quadrants in the plane of the alkene (Scheme 2.57). The southeast (SE) and northwest (NW) quadrants present steric barriers disfavouring large substituents. The southwest (SW) quadrant is the least sterically demanding and accommodates larger groups, including aromatic substituents. The moderate-sized substituent is then placed in the northeast (NE) quadrant. With alkene 192 positioned according to the mnemonic device, dihydroxylation with (DHQD)₂PHAL would preferentially form (R,R)-diol 201a via attack from the β-face. Conversely, when (DHQ)₂PHAL is used, the (S,S)-diol 201b would be preferentially formed. Pleasingly, our results are in accordance to Sharpless mnemonic device in that (R,R)-diol 201a was form preferentially when using (DHQD)₂PHAL and conversely (S,S)-diol 201b was formed preferentially when using (DHQ)₂PHAL.
In the case of an asymmetric Upjohn dihydroxylation, the mechanism involves two competing catalytic cycles \( \text{Scheme 2.58} \).\textsuperscript{109,110} First, the pseudo-enantiomeric ligand coordinate to the osmium tetroxide, and then alkene (\( \text{ii} \)) is oriented in accordance with the Sharpless mnemonic. The mechanism of the formation of monoglycolate (\( \text{iii} \)) was debated for several years between a stepwise [2+2] mechanism followed by rearrangement or a concerted [3+2] mechanism.\textsuperscript{111} Theoretical studies and empirical observations led to the scientific consensus that the concerted [3+2] mechanism occurs.\textsuperscript{112} Reoxidation of monoglycolate (\( \text{iii} \)) by NMO leads to osmium glycolate (\( \text{iv} \)) which undergoes hydrolysis to afford diol (\( \text{v} \)), regenerating osmium tetroxide (\( \text{i} \)). However, the rate of the hydrolysis of monoglycolate (\( \text{iv} \)) is slow, which can allow coordination of a second alkene (\( \text{ii} \)) to form osmium diglycolate (\( \text{vi} \)). As there is no longer a chiral ligand to orientate the addition, coordination can occur from either the \( \alpha \)- or \( \beta \)-face resulting in loss of enantioselectivity. Hydrolysis of (\( \text{vi} \)) results in the formation of dihydroxy-diglycolate (\( \text{vii} \)) which may be deprotonated under basic conditions to form inactive intermediate (\( \text{viii} \)). Finally, ligand exchange releases alkene (\( \text{v} \)) and osmium monoglycolate (\( \text{iii} \)). It is also of note that the propensity of monoglycolate (\( \text{iv} \)) to undergo the second cycle is greater when the concentration of alkene (\( \text{ii} \)) is higher.
2.5.2. Preparation of lasionectrin (13) from alcohol 201a

Upon successful installation of the tetrahydrofuran ring in 201, attention turned to the completion of the fused naphthopyrone-tetrahydrofuran ring system present in lasionectrin (13). Lasionectrin (13) would be synthesised from iodide 194 via carbonylation-lactonisation sequence and subsequent peri-demethylation (Scheme 2.59). Hydrolysis of acetate 201a, followed by ortho-iodination of naphthalene 201 would provide access to halide 194.

Scheme 2.59: Retrosynthetic analysis of lasionectrin (13) from alcohol 201a.

2.5.2.1. Synthesis of naphthopyrone 193a via ortho-iodination and palladium-catalysed carbonylation.

With naphthalenes 201a and 201b as a 1:1 inseparable mixture in hand, attention turned to the formation of iodides 194a and 194b. Acetate hydrolysis was conducted with lithium hydroxide monohydrate in a 5:1 methanol-water mixture, providing an inseparable diastereoisomeric mixture of naphthols 195a and 195b in near quantitative yield. (Scheme 2.60).
Halides 194a and 194b were then synthesised as an inseparable mixture in 83 % yield using pre-formed morpholine-iodine complex in dichloromethane.

![Scheme 2.60: Synthesis of halides 194a and 194b via hydrolysis and ortho-iodination of alcohols 201a and 201b.](image)

With the 1:1 diastereomeric mixture of iodides 194a and 194b in hand, we proceeded to a qualitative screen of reaction conditions to selectively install the carbonyl group which would allow access to diastereoisomers 193a and 193b (Scheme 2.61).

![Scheme 2.61: Proposed carbonylation-lactonisation reaction of 194a and 194b.](image)

Initial attempts to access naphthopyrones 193a/193b from halides 194a/194b using palladium acetate and triethylamine in methanol under a carbon monoxide atmosphere led to formation of proto-dehalogenated naphthols 195a/195b as the major products (Table 2.14, entry 1).

Examination of different bases revealed that the proto-dehalogenation reaction occurred whether an organic base (e.g. pyridine, DIPEA) and inorganic bases (e.g. NaHCO₃) was used (Table 2.14, entries 1–6). In an attempt to effect complete consumption of the starting materials, the reaction was carried out at higher temperature and with different solvents (e.g. DMF, acetonitrile), which led to degradation of the starting materials 194a/194b or formation of proto-dehalogenated by-products 195a/195b (Table 2.14, entries 7–11).

Based on the methodology described by Petricci et al. microwave irradiated reactions were attempted without success (Table 2.14, entries 12 and 13). Then, several other methods using different catalysts, bases and ligands were attempted without success. (Table 2.14, entries 14–19).
Chapter 2: Discussion

Given these results, we decided to investigate synthetic routes using a different carbonyl source. First, cyano-lactonisation of iodides 194a/194b using copper cyanide in DMF was attempted, which led only to degradation of the starting materials 194a/194b (Table 2.14, entry 20). Promising results were obtained upon treatment of iodides 194a/194b with lithium formate, DIPEA, dppf, palladium diacetate and acetic anhydride in DMF, giving naphthopyrones 193a/193b and proto-dehalogenated by-products 195a/195b in a 1:1 ratio (Table 2.14, entry 21).

Finally, access to the fused naphthopyrone-tetrahydrofuran ring system in 193a/193b was achieved with molybdenum hexacarbonyl as the carbon monoxide source and palladium diacetate as catalyst, providing naphthopyrones 193a/193b as a 1:1 mixture in 69 % yield with less than 10 % of proto-dehalogenated side products 195a/195b (Table 2.14, entry 22). At this point, naphthopyrones 193a/193b were separated by column chromatography. However, we postulated that the absence of the base in the reaction mixture breaks the catalytic cycle of the carbonylation reaction. As a result, the quantity of palladium diacetate required to complete the reaction was stoichiometric.
Table 2.14: Carbonylation conditions of halides 194a and 194b.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conditions</th>
<th>observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;, MeOH, 60 °C</td>
<td>195a/195b major</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DIPEA, MeOH, 60 °C</td>
<td>195a/195b major</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;, MeOH, 60 °C</td>
<td>incomplete + 195a/195b major</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>pyridine, 60 °C</td>
<td>195a/195b major</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, MeOH, 60 °C</td>
<td>incomplete</td>
</tr>
<tr>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, MeOH, 60 °C</td>
<td>incomplete, degradation</td>
</tr>
<tr>
<td>7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, MeOH, 120 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, MeCN, 120 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, DMF, 120 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;, DMF, 120 °C</td>
<td>side products + 195a/195b major</td>
</tr>
<tr>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;, MeCN, 90 °C</td>
<td>1:1 193a/193b:195a/195b</td>
</tr>
<tr>
<td>12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;, Toluene, MW</td>
<td>degradation</td>
</tr>
<tr>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;, MeOH, MW</td>
<td>incomplete + 193a/193b major</td>
</tr>
<tr>
<td>14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DIPEA, MeOH, 60 °C</td>
<td>nearly only 195a/195b</td>
</tr>
<tr>
<td>15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;, MeOH, 60 °C</td>
<td>incomplete + 195a/195b major</td>
</tr>
<tr>
<td>16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(dppf)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;, MeOH-toluene, 60 °C</td>
<td>195a/195b major</td>
</tr>
<tr>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, phenantroline, DMF, 100 °C</td>
<td>incomplete + 195a/195b major</td>
</tr>
<tr>
<td>18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>DIPEA, DMF, 120 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(DBU)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, MeOH, 60 °C</td>
<td>195a/195b major</td>
</tr>
<tr>
<td>20</td>
<td>-</td>
<td>CuCN, DMF</td>
<td>degradation</td>
</tr>
<tr>
<td>21</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>dppf, LiOCHO, Ac&lt;sub&gt;2&lt;/sub&gt;O, DIPEA, DMF</td>
<td>1:1 193a/193b:195a/195b</td>
</tr>
<tr>
<td>22</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Mo(CO)&lt;sub&gt;6&lt;/sub&gt;, dioxane</td>
<td>69 % 193a/193b &lt;10 % 195a/195b</td>
</tr>
</tbody>
</table>

<sup>a</sup> The reaction were carried out under CO atmosphere.
Chapter 2: Discussion

The proposed mechanism of the reaction starts with oxidative addition of palladium catalyst to halide 194 to give intermediate (i) (Scheme 2.62). Ligand exchange with molybdate hexacarbonyl gives intermediate (ii), which in turn rearranges to give palladium complex (iii). Nucleophilic attack of the pendant hydroxyl to the carbonyl functionality allows access to naphthopyrone 193 and inactive palladium complex (iv).

Scheme 2.62: Proposed simplified carbonylation mechanism of iodines 194a/194b.

2.5.2.2. Selective peri-demethylation of naphthopyrone 193a

With naphthopyrone 193a in hand, attention turned to selective peri-demethylation to access lasionectrin (13). Attempts to effect peri-demethylation of naphthopyrone 193a using strong Lewis acids were unsuccessful and only degradation or formation of side products were observed (Table 2.15, entries 1–4). Attempted selective demethylation of naphthopyrone 193a using ethanethiol and potassium tert-butoxide in refluxing DMF was ineffective and only starting material 193a was recovered (Table 2.15, entry 5). Treatment of naphthalene 193a with lithium chloride in DMF under microwave irradiation led to degradation of the starting material (Table 2.15, entry 6).

Pleasingly, lasionectrin (13) was successfully synthesised in 47 % yield when the demethylation reaction was conducted employing lithium chloride in N-methyl-2-pyrrolidinone (NMP) at 160 °C (Table 2.15, entry 7). Interestingly, the deprotection with lithium chloride only occurred at temperatures exceeding 150 °C, requiring the high boiling point solvent NMP.
Table 2.15: Demethylation conditions of naphthopyrone 193a.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BBr₃, CH₂Cl₂, −20 °C</td>
<td>starting material</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>BBr₃, CH₂Cl₂, 0 °C</td>
<td>degradation</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃, CH₂Cl₂, 0 °C</td>
<td>degradation</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>BCl₃, CH₂Cl₂, −78 °C</td>
<td>by-products</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>EtSH, t-BuOK, DMF, reflux</td>
<td>starting material</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>LiCl, DMF, 160 °C, MW</td>
<td>degradation</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>LiCl, NMP, 160 °C</td>
<td>13</td>
<td>47</td>
</tr>
</tbody>
</table>

The reported mechanism for phenolic demethylation using lithium chloride begins with coordination of the lithium chloride to the peri-oxygen atoms (Scheme 2.63). Nucleophilic attack of the chloride generates methyl chloride and lithiated naphthol (ii). Protonation of naphthol (ii) upon acidic work-up then provides demethylated product 13.

Scheme 2.63: Mechanism of phenolic demethylation of naphthol 193a using lithium chloride.¹¹⁷

2.5.2.3. Structural analysis and enantiopurity

Synthetic lasionectrin (13) was obtained as a white solid and spectroscopic data analysis (e.g. NMR, HRMS, IR) were in agreement with the literature (Table 2.16).¹⁹ In order to confirm the configuration of the fused pyrone-tetrahydrofuran moiety a NOESY spectrum was recorded. Gratifyingly, nOe correlations were observed between H-11b and H-3a, confirming the cis configuration of the fused ring system. The trans-orientation of the propyl substituent was
confirmed by the nOe correlations between H\textsubscript{A}-3 and H-11b and H\textsubscript{B}-3 and H-2. All observed correlations were in accordance with the literature.

**Table 2.16: \textsuperscript{1}H-NMR comparison of isolated and synthetic lasionectrin (13).\textsuperscript{19}**

<table>
<thead>
<tr>
<th>Isolated lasionectrin (13) (δ \textsuperscript{1}H NMR, [ppm, mult, J (Hz)] (500 MHz, CD\textsubscript{3}OD))</th>
<th>Synthetic lasionectrin (13) (δ \textsuperscript{1}H NMR, [ppm, mult, J (Hz)] (400 MHz, CD\textsubscript{3}OD))</th>
<th>Δδ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.23 (s, 1H)</td>
<td>7.25 (s, 1H)</td>
<td>0.02</td>
</tr>
<tr>
<td>6.80 (d, J = 2.1 Hz, 1H)</td>
<td>6.81 (d, J = 2.5 Hz, 1H)</td>
<td>0.01</td>
</tr>
<tr>
<td>6.51 (d, J = 2.1 Hz, 1H)</td>
<td>6.52 (d, J = 2.0 Hz, 1H)</td>
<td>0.01</td>
</tr>
<tr>
<td>5.24 (m, 1H)</td>
<td>5.25 (m, 1H)</td>
<td>0.01</td>
</tr>
<tr>
<td>4.93 (d, J = 1.6 Hz, 1H)</td>
<td>4.95 (d, J = 1.9 Hz, 1H)</td>
<td>0.02</td>
</tr>
<tr>
<td>4.33 (m, 1H)</td>
<td>4.34 (m, 1H)</td>
<td>0.01</td>
</tr>
<tr>
<td>3.90 (s, 3H)</td>
<td>3.90 (s, 3H)</td>
<td>0</td>
</tr>
<tr>
<td>2.58 (dd, J = 13.9, 6.2 Hz, 1H)</td>
<td>2.58 (dd, J = 14.1, 6.4 Hz, 1H)</td>
<td>0</td>
</tr>
<tr>
<td>2.12 (ddd, J = 13.9, 9.6, 3.9 Hz, 1H)</td>
<td>2.12 (ddd, J = 13.8, 9.4, 4.3 Hz, 1H)</td>
<td>0</td>
</tr>
<tr>
<td>1.70 (m, 1H)</td>
<td>1.71 (m, 1H)</td>
<td>0.01</td>
</tr>
<tr>
<td>1.57 (m, 1H)</td>
<td>1.57 (m, 1H)</td>
<td>0</td>
</tr>
<tr>
<td>1.49 (m, 1H)</td>
<td>1.51 (m, 1H)</td>
<td>0.02</td>
</tr>
<tr>
<td>1.39 (m, 1H)</td>
<td>1.40 (m, 1H)</td>
<td>0.01</td>
</tr>
<tr>
<td>0.97 (t, J = 7.3 Hz, 3H)</td>
<td>0.97 (t, J = 7.3 Hz, 3H)</td>
<td>0</td>
</tr>
</tbody>
</table>

Surprisingly, the measured optical rotation for synthetic lasionectrin (13) ([α]\textsuperscript{25}_D +148 (c 0.17, MeOH), lit. [α]\textsuperscript{25}_D −43.8 (c 0.17, MeOH)) had the opposite sign and was 3-fold greater in magnitude than the natural product.\textsuperscript{19} Chiral HPLC using DAICEL CHIRALPAK\textsuperscript{®} column of our synthesised lasionectrin (13) revealed an enantiomeric excess of 97 % (Figure 2.5). The presented synthesis was first established in a racemic manner allowing access to (±)-lasionectrin (±-13) for comparative purposes.
2.5.3. Establishment of the structure of naturally occurring lasionectrin ((−)-13)

2.5.3.1. Synthesis of lasionectrin ((−)-13)

In order to confirm our observed optical rotation value for (+)-lasionectrin ((+)-13), our attention turned to the synthesis of (−)-lasionectrin ((−)-13) following our established method. We successfully synthesised (−)-lasionectrin ((−)-13) starting from (R)-epichlorohydrin ((R)-123) (Scheme 2.64). Sulfone (R)-122 was synthesised in 6 steps from (R)-epichlorohydrin (123). Julia-Kocienski olefination with naphthaldehyde 129 and alkene (R)-199 provided access to alkene (R)-199 which was in turn converted to naphthalenes 201a/201b over 3 steps. (−)-Lasionectrin ((−)-13) was in turn synthesised in 4 steps. Gratifyingly, the magnitude of the optical rotation of our synthetic (−)-lasionectrin ((−)-13) ([α]25D −138 (c 0.17, MeOH)) agreed with that of the synthetic lasionectrin ((+)-13) ([α]25D +148 (c 0.17, MeOH)). However, the magnitude of our observed optical rotation was again 3-fold greater than that reported for the natural product (lit. [α]25D −43.8 (c 0.17, MeOH)).19

Figure 2.5: HPLC trace of racemic (±)-lasionectrin ((±)-13) and (+)-lasionectrin ((+)-13)

Column DAICEL CHIRALPAK® AD-H, i-PrOH–hexanes (2:3), 0.5 mL/min.
2.5.3.2. Synthesis of diastereoisomer 2-epi-(+)-13

In order to unambiguously confirm the structure of the natural product (−)-lasionectrin ((−)-13), the diastereoisomer of (−)-lasionectrin ((−)-13) epimeric at position C-2, 2-epi-(+)-13, was synthesised. Treatment of naphthopyrone 193b with lithium chloride in NMP at 160 °C gave epimer 2-epi-13 in 42 % yield (Scheme 2.65).

Scheme 2.65: Demethylation of naphthopyrone 193b.

Epimer 2-epi-(+)-13 was obtained as a colourless solid with an optical rotation of +185 (c 0.13, CHCl₃). Comparison of ¹H NMR spectra of naphthopyrones (−)-13 and epimer (+)-2-epi-(+)-13 enabled us to confirmed the structure of isolated (−)-lasionectrin ((−)-13) due to the difference of chemical shift of characteristic protons (Figure 2.6). Due a significant difference in their electronic environment, protons H-3a, H-11b, and H-2 are more deshielded in (−)-lasionectrin ((−)-13, δ_H = 5.18, 4.88 and 4.40 ppm respectively) than their counterpart in (+)-2epi-(+)-lasionectrin ((+)-2-epi-(+)-13, δ = 5.10, 4.66 and 4.17 ppm respectively). Additionally, the proton H_B-3 in (−)-lasionectrin ((−)-13) exhibits a different spin-spin coupling pattern (δ_H = 2.64 ppm; dd, J = 13.5, 5.9 Hz, 1H) than its counterpart in (+)-2-epi-(+)-lasionectrin ((+)-2-epi-(+)-13; δ_H = 2.62 ppm; ddd, J = 14.5, 8.7, 6.0 Hz, 1H). Similar observations can be made for proton H_A-3. Therefore these observations confirm our structure assignation of lasionectrin ((−)-13).
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2.5.4. Summary and conclusion

In summary, the first total synthesis of (−)-lasionectrin (−-13) has been achieved in 14 steps (longest linear sequence) from commercially available dimethoxybenzaldehyde (103) and (R)-epichlorohydrin ((R)-123). We also established the absolute configuration of the isolated natural product (−)-13. In addition we synthesised enantiomer (+)-13 and diastereoisomers (+)-2-epi-(−)-13 and (−)-2-epi-(−)-13 (Figure 2.7).

The synthesis of aldehyde 129 was completed using a novel TFA cyclisation of itaconic ester which was in turn was synthesised via an HWE reaction from commercially available dimethoxybenzaldehyde (103) and phosphonate 104, followed by a reduction-oxidation sequence of ester 106 and protection of the resulting naphthol 116 (Scheme 2.66). The preparation of sulfone 119 included an enantioselective ring expansion of (R)-n-propyloxirane ((R)-39) and subsequent opening of the resulting oxetane with lithium bromide and phenyltetrazole thiol, followed by alcohol protection and sulfide oxidation.
Chapter 2: Discussion

Julia-Kocienski olefination of aldehyde 129 and sulfone 119 provided access to alkene 198 in excellent yield (Scheme 2.67). Tandem dihydroxylation-\(S_N2\) cyclisation upon Upjohn dihydroxylation enabled the construction of the tetrahydrofuran ring in excellent yield to give an inseparable 1:1 mixture of naphthols \(201a\) and \(201b\) after hydrolysis. We also reported the first use of solid morpholine iodine complex as a selective ortho-iodination agent, providing the corresponding iodide from naphthols \(201a\) and \(201b\). Tandem carbonylation-lactonisation sequence using \(\text{Mo(CO)}_6\) of iodides \(194a\) and \(194b\) enabled synthesis of the fused naphthopyrone-tetrahydrofuran moiety present in \((-\)-lasiocetrin \((-\)-13). Selective peri-demethylation using lithium chloride in NMP concluded the first enantioselective total synthesis of \((-\)-lasiocetrin \((-\)-13) and epimer \((+)\-2\text{-}\text{epi\-}(+)\-13).
2.6. Future work

The antifungal bioactivity of lasionectrin (13) and analogues are currently under testing. To date, lasionectrin (13) and analogues appear to be inactive in the Haemonchus contortus larval development assay. However, lasionectrin (13) and analogues will soon be tested for other type of antifungal assays. Additionally, lasionectrin (13) and analogues would be tested against malaria in an attempt to establish the structure-activity relationship.

Given the successful synthesis of (−)-lasionectrin (−-13), our synthetic strategy would enabled access to related naphthopyrones such as lichenicolin A (29). Lichenicolin A (29) would be accessed via C-H activation of naphthopyrone 202 and subsequent dimerisation (Scheme 2.68). Selective peri-demethylation of naphthol 203 would enable access to naphthopyrone 202. Preparation of naphthol 203 would be conducted via iodination and subsequent carbonylation-lactonisation of naphthol 204 which in turn would be synthesised via a dihydroxylation and tosylate displacement sequence from alkene 205. Julia-Kocienski coupling of aldehyde 129 with sulfone 206 would provide access to alkene 205. Based on our reported lasionectrin (13) synthesis, aldehyde 129 would be access from commercially available 3,5-dimethoxybenzaldehyde (103) in 5 steps. Sulfone 206 would in turn be prepared from epoxide 207 in 4 steps.

Scheme 2.68: Retrosynthetic analysis of lichenicolin A (29).
PART II

Synthetic Studies Towards Pestaloxazine A
Chapter Three

Introduction
3.1. Hand, Foot and Mouth Disease

According to the World Health Organization, around 1 million cases of hand, foot and mouth disease (HFMD) were reported in China in the first six months of 2016.\textsuperscript{118}

3.1.1. Causes, Transmission, Symptoms and Complications

HFMD is a common and usually benign viral illness that affects children, infants and in rare cases adults. HFMD is caused by viruses from the Enterovirus genus which includes Coxsackie virus A16 (CA16) and Enterovirus 71 (EV71). The largest outbreaks as well as most of the severe cases of HFMD are associated with EV71 infections.\textsuperscript{119} Transmission of the virus from one person to another occurs via close contact with infected people or contact with contaminated objects or surfaces.

The typical symptoms of HMFD are usually mild and start with fever, reduced appetite and sore throat. These symptoms then progress to painful sores in the mouth, skin rashes and blisters. HFMD usually resolves itself after 7 to 10 days without specific treatment. However, in some cases of EV71 infection complications may occur, including: inflammation of the brain and the meninges, pulmonary oedema, acute flaccid paralysis and even death.

3.1.2. Prevention and Treatment

Contamination risk can be lowered by regular hand washing, cleaning and disinfecting soiled items and avoiding close contact with infected people. In December 2015, the China Food and Drug Administration (CFDA) approved the use of inactive EV71 virus as the first vaccine to prevent HFMD caused by EV71 infections. To date, this vaccine is only commercially available in mainland China and still the subject of a large-scale phase IV study.\textsuperscript{120}

As HFMD is usually benign and self-limiting, no specific antiviral drugs have been developed to treat the disease.\textsuperscript{119} Additionally, no treatment is yet available to relieve the symptoms of severe cases of HMFD caused by EV71. As a result, there is a need to develop effective antiviral drugs to control and treat EV71 infections.
3.2. Pestaloxazine A (208): Isolation, Structure and Biological Activity

Pestaloxazine A (208) was discovered in 2015 during the course of a screening project aimed at identifying biologically active natural products extracted from corals in the South China Sea (Figure 3.1). Pestaloxazine A (208) was isolated as a racemate from the fermentation broth of a marine-derived fungus belonging to the Pestalotiopis genus. Pestaloxazine A (208) exhibited potent and selective antiviral activity against EV71 (IC$_{50}$ = 16.1 µM). Further purification by preparative chiral HPLC enabled the separation of enantiopure (−)-208 and (+)-208, which exhibited different antiviral activity against EV71 (IC$_{50}$ = 69.1 µM and IC$_{50}$ = 14.2 µM, respectively).

Figure 3.1: Pestaloxazine A ((±)-208, (−)-208 and (+)-208) structures.

Pestaloxazine A (208) is an alkaloid dimer with a unique spiro[1,2-oxazinane-diketopiperazine] moiety. Structural elucidation of the natural product began with determination of its molecular formula using high resolution mass spectrometry, which revealed a chemical formula of C$_{22}$H$_{32}$N$_{4}$O$_{8}$. Analysis of the NMR spectra suggested that pestaloxazine A (208) was a symmetrical dimer as only 11 carbon signals were observed in the $^{13}$C NMR spectrum which also indicated the presence of two carbonyl functionalities (δ$_{C}$ = 166.2 and 168.3 ppm) and one alkene functionality (δ$_{C}$ = 155.5 and 117.6 ppm). 2D NMR analysis enabled elucidation of the monomeric motif (I) through a combination of NOESY, HSQC and HMBC experiments (Figure 3.2). The structure of pestaloxazine A (208) was then unambiguously confirmed by single-crystal X-ray diffraction.
Chapter 3: Introduction

Figure 3.2: Monomeric structural unit (I) of pestaloxazine A (208) (left); Single-crystal X-ray structure of pestaloxazine A (208) (right).

The proposed biosynthetic pathway described by Shao et al. commences with the dimerisation of two molecules of L-ornithine (L-209) and subsequent oxidation of the primary amine functionalities in diketopiperazine 210 to give hydroxylamine 211 (Scheme 3.1). Intramolecular cyclisation of diketopiperazine 211 completes the construction of the spiro[1,2-oxazinane-diketopiperazine] moiety giving tricyclic diketopiperazine 212. Finally, peptide coupling of tricyclic diketopiperazine 212 with acid 213 gives (+)-pestaloxazine A ((+)-208). Similarly, (−)-pestaloxazine A ((−)-208) is accessed from D-ornithine (D-209) following the same biosynthesis.

Scheme 3.1: Proposed biosynthesis of pestaloxazine A (208).
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3.3. Isolation and synthesis of structurally related diketopiperazines

Interestingly, pestaloxazine A (208) is a cyclic analogue of dimerumic acid (214) (Figure 3.3). Similarly, diketopiperazine NBR116716B (215) also contains one of the non-cyclised side-chains and the diketopiperazine framework of pestaloxazine A (208).

![Figure 3.3: Structures of pestaloxazine A (208), dimerumic acid (214) and diketopiperazine NBR116716B (215).]

3.3.1. Dimerumic acid (214): Isolation and Synthesis

In 1970, Diekemann and Keller-Schierlein reported the isolation of dimerumic acid (214) from a strain of the fungus *Fusarium dimerum*. Later, Burt reported the isolation of dimerumic acid (214) as a breakdown product of the fungal metabolite coprogen B (216) which was obtained from *Histoplasma capsulatum* (Figure 3.4).

![Figure 3.4: Structures of coprogen B (216) and dimerumic acid (214).]

In 1974, Widmer and Keller-Schierlein reported the only synthesis of dimerumic acid (214) in 8 steps and 1% overall yield. The synthesis began with construction of the side-chain fragment 217 (Scheme 3.2). Reformatsky reaction of ketone 218 with bromide 219 using zinc in benzene...
and diethyl ether gave alcohol 220 which was then converted to alkene 221 in 1% yield via an elimination reaction using phosphorus oxychloride in pyridine. The low yield of the elimination reaction was attributed to the formation of all five possible alkene isomers (221-225). Alkene 221 was purified via flash chromatography and distillation. Following selective hydrolysis of the tert-butyl ester present in alkene 221, treatment with oxalyl chloride and esterification of the resulting acyl chloride with N-hydroxysuccinimide gave alkene 217.

Peptide coupling of easily accessible L-norvaline derivatives acid 226 and amine 227 using isopropyl chloroformate followed by concomitant Boc deprotection and intramolecular cyclisation of dipeptide 228 under acidic conditions gave diketopiperazine 229 (Scheme 3.3). Palladium on barium sulfate catalysed hydrogenation of the nitro functionalities in 229 and subsequent condensation of the resulting hydroxylamine with ester 217 using pyridine in DMF gave diketopiperazine 230 in a single step. Finally, acetate hydrolysis using ammonia in ethanol gave dimerumic acid (214).

Scheme 3.2: Synthesis of alkene 217 by Widmer et al.125

Scheme 3.3: Synthesis of dimerumic acid (214) by Widmer et al.125
3.3.2. Diketopiperazine NBRI16716B (215): Isolation and Synthesis

In 2010, Kawada et al. reported isolation of diketopiperazine NBRI16716B (215) from the fermentation broth of Perisporiopsis melioloides (Mer-f16716) (Figure 3.5). Diketopiperazine NBRI16716B (215) was found to exhibit significant inhibition of prostate cancer tumor growth on mice (IC$_{50}$ = 10 µg/mL).\textsuperscript{126}

![Figure 3.5: Structure of diketopiperazine NBRI16716B (215).](image)

In 2015, Shibasaki and co-workers reported the total synthesis of diketopiperazine NBRI16716 (215) in 7 steps and 2 % overall yield (Scheme 3.4).\textsuperscript{127} The synthesis began with Mitsunobu reaction of N-Cbz-L-norvaline (231) with tert-butyl N-acetoxy carbamate, followed by benzyl carbamate (Cbz) deprotection, giving amine 232. Peptide coupling of acid 233 with amine 232 using coupling agent 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (WSC·HCl) and DIPEA in dichloromethane provided access to amide 234. Following Cbz deprotection of amide 234, treatment of the resulting primary amine with DIPEA provided access to the diketopiperazine moiety present in 235 via intramolecular cyclisation. Acetate hydrolysis and Boc deprotection of diketopiperazine 235 was achieved in a single step by treatment with TFA, providing hydroxamic acid 236. Peptide coupling of diketopiperazine 236 with known acid 237 using coupling agent COMU® and DIPEA in DMF resulted in both construction of the side chain and silyl ether deprotection, giving diketopiperazine NBRI13716B (215).
3.3.3. Synthesis of acid 237 by Bertrand et al.

In 2010, Bertrand et al. reported the synthesis of acid 237 in 5 steps and 47% overall yield. Acid 237 is an intermediate in the synthesis of the trans-fusarinine (238) framework which is the monomeric unit of dimerumic acid (214) and the non-cyclised monomeric unit of pestaloxazine A (208) (Figure 3.6).

The synthesis of the trans-fusarinine (238) scaffold began with the synthesis of acid 237. Protection of the primary alcohol in alkyne 239 using tert-butylidiphenylsilyl chloride (TBDPS-Cl) in dichloromethane and subsequent carboxylation of the resulting protected alkyne using LDA and methyl chloroformate gave alkyne 240 (Scheme 3.5). Conjugate addition of thiophenolate to alkyne 240 gave thioesters 241 as a 4.8:1 mixture of separable Z/E isomers. The authors reported that the stereoselectivity of the conjugate addition was driven by steric interactions between the thiophenol and the methyl ester functionality. Alkene 242 was prepared.
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from alkene (Z)-241 via thiol displacement using methyl copper bromide in THF. Hydrolysis of methyl ester 242 using lithium hydroxide in tert-butanol provided acid 237.

Scheme 3.5: Synthesis of alkene 234 by Bertrand et al.128

Esterification of commercially available acid 243 using dimethylformamide di-tert-butyl acetal (DMF-DBA) in toluene under microwave irradiation at 160 °C and subsequent Cbz deprotection enabled access to amine 244. Oxidation of the primary amine in 244 using benzoyl peroxide provided intermediate 245. Coupling of intermediate 245 with acid 237 using thionyl chloride and DIPEA in dichloromethane provided trans-fusarinine analogue 246 in low yield.

Scheme 3.6: Synthesis of the trans-fusarinine analogue (246) by Bertrand et al.128
3.3.4. Summary

Interestingly, the diketopiperazine moieties present in dimericum acid (214) and diketopiperazine NBR16716B (214) have both been constructed in moderate yield via peptide coupling of a primary amine with a carboxylic acid and subsequent intramolecular cyclisation of the resulting dipeptide (Scheme 3.7).\textsuperscript{125,127}

![Scheme 3.7: Approaches to the diketopiperazine moiety.](image)

Access to the key side-chain intermediate 247 was first reported by Widmer et al. in 3 steps and 1 % overall yield via a Reformatsky reaction and subsequent non-selective elimination (Scheme 3.8).\textsuperscript{125} Later, Bertrand et al. reported an elegant synthesis of side-chain unit 247 in 5 steps and 47 % overall yield from commercially available 3-butyn-1-ol 239. The synthesis of acid 247 reported by Bertrand et al. hinged on a thiol conjugate addition proceeding under steric control and subsequent thiol displacement.\textsuperscript{128}

![Scheme 3.8: Approaches to key carboxylic acid 247.](image)
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3.4. General approaches to the 1,2-oxazinane ring system

The 1,2-oxazinane ring present in pestaloxazine A (208) is a known framework that has been found in a few natural products (Figure 3.7).129-131

![Pestaloxazine A (208)](image)

Figure 3.7: 1,2-Oxazinane rings in pestaloxazine A (208).

Reductive cleavage of the N-O bond in the 1,2-oxazinane ring provides access to the 1,4-amino alcohol functionality which is itself a common motif found in natural products (Scheme 3.9).132 As a result, in the last 15 years, several synthetic routes have emerged to access highly functionalised 1,2-oxazinanes.133-141

![Scheme 3.9: Reductive cleavage of 1,2-oxazinane.](image)

3.4.1. Nitroso Diels-Alder cycloaddition-hydrogenation sequence.

Reported for the first time in 1947 by Wichterle and Arbuzov, the nitroso hetero Diels-Alder (NDA) [4+2] cycloaddition has become the most common method to access 3,6-dihydro-1,2-oxazines (Scheme 3.10).141 Palladium-catalysed hydrogenation of the double bond of the cycloaddition product provides simple access to the 1,2-oxazinane moiety.

![Scheme 3.10: Synthesis of 1,2-oxazinanes via nitroso Diels-Alder and hydrogenation sequence](image)

The cycloaddition of nitroso compounds with non-symmetrical dienes may lead to the formation of two regioisomers (Table 3.1). According to the nomenclature used by Houk et al., the isomer in which the oxygen atom is the closest to the substituent of the diene is named the proximal isomer.142 Several groups have studied the regioselectivity of the NDA reaction,
resulting in a general consensus stating that the regioselectivity of the reaction is driven by both electronic and steric effects. In 2001, Houk et al. published a general regioselectivity prediction pattern based on DFT calculations and comparison with available experimental data (Table 3.1). Interestingly, the proximal isomer is generally favoured during the NDA reaction. Similarly, the facial selectivity of the reaction is also guided by steric and electronic effects and has yet not been completely rationalised.

Table 3.1: Regioselectivity prediction of the NDA reaction by Houk et al.

<table>
<thead>
<tr>
<th>diene</th>
<th>ArNO, RNO, HNO</th>
<th>RC(O)NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>favoured isomer</td>
<td>selectivity</td>
</tr>
<tr>
<td>EDG: Electron-Donating Group; EWG: Electron-Withdrawing Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>proximal</td>
<td>medium</td>
<td>proximal</td>
</tr>
<tr>
<td>proximal</td>
<td>high</td>
<td>proximal</td>
</tr>
<tr>
<td>distal</td>
<td>weak</td>
<td>-</td>
</tr>
<tr>
<td>proximal</td>
<td>high</td>
<td>-</td>
</tr>
</tbody>
</table>

In 1991, Kibayashi and Shishido applied this strategy to synthesise natural products indolizidines 205A (248) and 235B (249). The synthesis began with esterification of acid 250 using diazomethane in diethyl ether and subsequent ozonolysis of the terminal alkene, giving aldehyde 251. (Scheme 3.11). Following Wittig olefination of aldehyde 251 with allyltriphenylphosphonium bromide, isomerisation of the resulting (Z)-diene using iodine under UV-Vis irradiation enabled access to thermodynamic (E)-diene 252. After hydrolysis under basic conditions and chlorination of ester 252 using oxalyl chloride in dichloromethane, hydroxamic acid 253 was prepared by treatment of the resulting acyl chloride with hydroxylamine hydrochloride and sodium carbonate in chloroform. Oxidation of hydroxamic acid 253 with tetrapropylammonium periodate in chloroform provided access to the corresponding N-acylnitroso intermediate 254 which spontaneously underwent intramolecular Diels-Alder cycloaddition to give a separable 1:1.8 diastereomeric mixture of 3,6-tetrahydro-1,2-oxazines 255a and 255b. The authors did not comment on the stereoselectivity of the nitroso Diels-Alder
reaction. Hydrogenation of all cis diastereoisomer 255b gave 1,2-oxazinane 256. Indolizidines 205-A (248) and 235B (249) were then synthesised from 1,2-oxazinane 256 in five and four steps, respectively.

**Scheme 3.11: Synthesis of (−)-indolizidines 205A (248) and 235B (249) by Kibayashi and Shishido.**

### 3.4.2. Other cycloadditions to access the 1,2-oxazinane ring system

#### 3.4.2.1. Reaction of nitrones with cyclopropanes

In 2003, Kerr and Young reported the synthesis of 1,2-oxazinanes *via* [3+3] 1,3-dipolar cycloaddition of nitrones with cyclopropanes in the presence of the Lewis acid ytterbium trifluoromethanesulfonate (Yb(OTf)₃) (Scheme 3.12). Several other research groups have then reported similar reactions using a variety of Lewis acids such as magnesium iodide (MgI₂) and nickel perchlorate (Ni(ClO₄)₂).

**Scheme 3.12: [3+3] Cycloaddition of nitrones and cyclopropanes.**
Due to the strain of the σ bond in the cyclopropane, the C-C bond exhibits a π character similar to that of an alkene, allowing it to participate in a [3+3] cycloaddition. In 2005, Woo et al. reported a theoretical study of the 1,3-dipolar cycloaddition of cyclopropane 257 and nitrone 258. Based on density functional theory (DFT) calculations, two reaction pathways were found (Scheme 3.13). In the first pathway, the reaction proceeds stepwise, first forming zwitterionic intermediate (ii) which then gives 1,2-oxazinane 259. In the second pathway, 1,2-oxazinane 259 is accessed in a single step through transition state (iv). Calculations revealed that the transition state barriers of these pathways were similar, and decreased with the addition of Lewis acid.


Due to the instability of some nitrones, Young and Kerr later developed a three component [3+3] cycloaddition protocol. The reaction starts with condensation of an aldehyde with the appropriate N-hydroxylamine to give the corresponding nitrone which then undergoes [3+3] cycloaddition with the cyclopropane to give the 1,2-oxazinane ring system (Scheme 3.14).

Scheme 3.14: Three component [3+3] cycloaddition by Young and Kerr.

In 2006, Carson and Kerr applied this three component cycloaddition in the synthesis of the alkaloid natural product (+)-phyllantidine ((+)-260). The synthesis started with the three component [3+3] cycloaddition of hydroxylamine 261, aldehyde 262 and cyclopropane 263 to give 1,2-oxazinane 264 as a separable 12:1 diastereomeric mixture (Scheme 3.15). The authors
were unable to provide mechanistic justification for the reaction stereoselectivity. The synthesis of (+)-phyllantidine ((+)-260) was then completed in 8 steps from 1,2-oxazinane cis-264.

Scheme 3.15: Synthesis of (+)-phyllantidine ((+)-260) by Carson and Kerr.\textsuperscript{147}

3.4.2.2. Reaction of nitrosoarenes with cyclopropanes

In 2016, Pagenkopf \textit{et al.} reported the formation of 1,2-oxazinanes \textit{via} tandem ring opening, elimination, and cycloaddition of cyclopropanes and nitrosoarenes.\textsuperscript{136} The reaction of nitrosoarenes and two equivalents of cyclopropane using Lewis acid Yb(OTf)\textsubscript{3} in dichloroethane gave 1,2-oxazinanes in moderate to high yields (Scheme 3.16).

Scheme 3.16: Synthesis of 1,2-oxazinanes by Pagenkopf \textit{et al.}\textsuperscript{136}

The proposed mechanism of the reaction starts with coordination of Lewis acid Yb(OTf)\textsubscript{3} to cyclopropane 265 to give activated donor-acceptor complex (i) (Scheme 3.17). Opening of the cyclopropane ring in (i) with nitrosoarene gives zwitterionic adduct (ii) which undergoes elimination to give dimethyl 2-methylene malonate (iii) and nitrone (iv). [3+3] Cycloaddition of nitrone (iv) and cyclopropane 265 then results in the formation of 1,2-oxazinane 266.
3.4.2.3. Reaction of nitrosoarenes with cyclobutanes

In 2014, Pagenkopf et al. reported the first [4+2] cycloaddition of donor-acceptor cyclobutanes with nitrosoarenes to access 1,2-oxazinanes. Treatment of cyclobutane with Lewis acid Yb(OTf)\(_3\) and various nitrosoarenes in dichloromethane provided 1,2-oxazinanes in moderate to high yields (Scheme 3.18). Mechanistically, the strain in the cyclobutane ring is similar to that of cyclopropane which confers to the ring system similarities with dienes, enabling participation in a [4+2] cycloaddition process.

Scheme 3.18: [4+2] Cycloaddition of cyclobutanes with nitrosoarenes by Pagenkopf.

3.4.3. Formation of 1,2-oxazinanes by aza-Michael reaction

3.4.3.1. α-Aminooxylation/aza-Michael cascade

In 2008, Zhong et al. reported the synthesis of enantiopure 1,2-oxazinanes via an L-proline catalysed α-aminooxylation/aza-Michael sequence. Reaction of aldehyde 267 and nitron 268 catalysed by L-proline in acetonitrile provided access to 1,2-oxazinane 269 in high yield (Scheme 3.19).
The proposed mechanism of the reaction begins with condensation of aldehyde 267 with L-proline to give enamine (i) which then undergoes α-aminoxylation with nitroso benzene to give zwitterionic enamine (ii). Intramolecular aza-Michael addition followed by hydrolysis of the iminium ion then affords 1,2-oxazinane 269.

\[ \text{L-proline (cat.)} \quad \text{CH}_3\text{CN, } -20^\circ\text{C} \quad \text{(94 %)} \]

3.4.3.2. α-Aminooxylation/aza-Michael/Mannich sequence by Sun et al.

In 2014, Sun et al. published the synthesis of fully substituted 1,2-oxazinanes via an α-aminooxylation/aza-Michael/Mannich reaction sequence. The reaction cascade began with α-aminooxylation of aldehyde 270 with nitrosobenzene (271) catalysed by L-proline followed by sequential addition of para-methoxyaniline 272, aldehyde (273) and catalyst 274, giving imine 275 (Scheme 3.21). Reduction of imine 275 using sodium borohydride in methanol gave highly substituted 1,2-oxazinane 276.
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Scheme 3.21: Synthesis of 1,2-oxazinane 276 by Sun et al.\textsuperscript{140}

The proposed general mechanism of the reaction began with α-aminoxylation of aldehyde 270 and nitrosobenzene (268) to give aldehyde (i) which in turn is converted to imine (ii) via addition of aniline 272 (Scheme 3.22). Aza-Michael addition of intermediate (ii) to the activated iminium (iii) (formed by the condensation of aldehyde 273 and amine 274) provides intermediate (iv) which spontaneously cyclises via Mannich reaction to give aldehyde (v). Subsequent condensation with amine 272 gives imine 275 which is reduced with sodium borohydride to give 1,2-oxazinane 276.

Scheme 3.22: Proposed pathway of the formation of 1,2-oxazinanes 276.\textsuperscript{140}
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3.4.4. Summary

Several approaches to construct the 1,2-oxazinane ring system have been published over the years (Scheme 3.23). It is important to note that using either the [3+3] or [2+4] cycloaddition methodologies described by Kerr and Pagenkopf, the constructed 1,2-oxazinane ring is substituted at positions 5 and 6.\(^{133,135,151}\) Similarly, the α-aminoxylation/aza-Michael sequence reported by Sun or Zhong, required the presence of the substituent at positions 3 and 6 in order to succeed, resulting in a heavily substituted 1,2-oxazinane ring.\(^{138,140}\)

However, the 1,2-oxazinane ring system in our target molecule is only disubstituted at the position 6. The only approach that would allow the construction of this 6-substituted 1,2-oxazinane ring system is the nitroso Diels-Alder/hydrogenation sequence exemplified in the synthesis of indolizidines 205A (248) and 235B (249) by Kibayashi et al.\(^{145}\)

Scheme 3.23: Summary of approaches to construct the 1,2-oxazinane ring system.
3.5. Cyclisation via 1,6-hydrogen abstraction to access spirocycles

The biosynthesis of pestaloxazine A (208) proposed by Wei et al. hinged on intramolecular cyclisation of N-hydroxylamine 211 to access the spiro[1,2-oxazinane-diketopiperazine] moiety present in diketopiperazine 212 (Scheme 3.24).\textsuperscript{121} To date, no intramolecular cyclisation reaction of N-hydroxylamine or related hydroxamic acids have yet been reported.

![Scheme 3.24: Intramolecular cyclisation of diketopiperazine 211.\textsuperscript{121}](image)

However, the use of intramolecular hydrogen abstraction has been reported as an efficient method for the synthesis of 5- or 6-membered spirocycles. The intramolecular hydrogen abstraction is a free radical cyclisation which allows the formation of spirocycle 277 from intermediate 278 (Scheme 3.25).

![Scheme 3.25: General 1,6-intramolecular hydrogen abstraction reaction.](image)

It is of note that 1,5-intramolecular hydrogen abstraction reaction in the synthesis of 5-membered spirocycles has been extensively studied and several reviews have been published elsewhere.\textsuperscript{152-157} For the purpose of this thesis, only the use of 1,6-intramolecular hydrogen abstraction reactions in the synthesis of spirocycles will be briefly covered.

3.5.1. Synthesis of spiroketals via intramolecular hydrogen abstraction.

The spiroketal moiety is the most common spirocycle motif that is found in the nature. The spiroketal motif is generally constituted of two rings that are joined through a single carbon atom (anomeric carbon) which bears two oxygen atoms. The first spiroketal syntheses using oxidative radical cyclisation were reported by Mićović et al. in 1969.\textsuperscript{158} They reported the formation of 5,5-, 5,6- and 6,6-spiroketals resulting from the treatment of diols with lead tetraacetate (Pb(OAc)\textsubscript{4}) in refluxing benzene (Scheme 3.26).
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This type of reaction was later applied to the synthesis of several natural products using either lead tetraacetate (Pb(OAc)$_4$) or mercury oxide (HgO) with iodine in refluxing cyclohexane. In 1983, Suárez reported mechanistic evidence indicating that the reaction passes through a 7 membered transition state (ii) (Scheme 3.27). The reaction begins with formation of hypoiodite (i) upon treatment of alcohol 279 with acetyl hypoiodite (AcOI) which is prepared in situ using iodine and lead tetraacetate. Photolysis of the I-O bond in alkyl hypoiodite (i) is followed by a 1,6-hydrogen shift proceeding via transition state (ii), giving radical (iii). Radical capture by iodine affords iodide (iv) which then undergoes intramolecular cyclisation to give spiroketal 280.

Interestingly, the reaction usually leads to the kinetic product.

In 1984, Suárez and co-workers reported 1,6-hydrogen abstraction reactions using iodobenzene diacetate (PhI(OAc)$_2$) with iodine in refluxing cyclohexane as an alternative to toxic lead tetraacetate or mercury oxide. Since then, this methodology has been used for several syntheses of natural products that has been reviewed by our research group.

Several examples have been reported by our group where the use of an intramolecular hydrogen abstraction reaction provided convenient access to 5,5-, 5,6- or 6,6-spiroketals. Most recently, Brimble et al. reported access to benzannulated spiroketals in moderate to high yield via oxidative radical cyclisation of the corresponding alcohols using PhI(OAc)$_2$ and iodine in cyclohexane under UV irradiation at 7 °C (Scheme 3.28).
3.5.2. Synthesis of spirohemiaminals via radical cyclisation

The spirohemiaminal ring system is the second most prevalent spirocycle motif. The spirohemiaminal motif is generally constituted of two rings that are joined through the anomeric carbon which bears an oxygen and a nitrogen atom. This type of compound are also known as oxa-aza-spirocycles. In 2002, Suárez and co-workers reported access to hetero spirocycles via intramolecular hydrogen abstraction.\textsuperscript{169} Treatment of phosphoramidates with \( \text{Phi(OAc)}_2 \) iodine and sodium bicarbonate in dichloromethane under UV irradiation afforded oxa-aza spirocycles in moderate yield (Scheme 3.29). Later, Suárez and co-workers reported the successful use of this methodology with cyanamide derivatives.\textsuperscript{170}

Scheme 3.29: Synthesis of oxa-aza spirocycles by Suárez et al.\textsuperscript{169}

3.5.3. Summary

In summary, the 1,6-hydrogen abstraction provides a convenient and efficient method to access spiroketalts. Interestingly, Suárez and co-workers applied this methodology to protected secondary amines to access oxa-aza-spirocycles, providing a literature precedent for the formation of hetero spirocycles using oxidative radical cyclisation conditions.\textsuperscript{169,170} Additionally, the mild reaction conditions enabled use of this methodology with a variety of substrates.\textsuperscript{171} However, to the best of our knowledge, application of this methodology to \( N \)-hydroxylamine in order to prepare the 1,2-oxazine ring system has yet not been investigated.
3.6. Concluding remarks and retrosynthetic analysis of pestaloxazine A (208)

3.6.1. Concluding remarks

The unprecedented spiro[1,2-oxazinane-diketopiperazine] moiety and the need to develop new antiviral drugs to treat EV71 infection, render pestaloxazine A (208) an excellent synthetic target. The overall aim of the current research is therefore to develop a new and efficient strategy to access pestaloxazine A (208). However, due to the unique structure of pestaloxazine A (208), our initial focus is to access the racemic spiro[1,2-oxazinane-diketopiperazine] moiety.

Figure 3.8: Structure of pestaloxazine A (208).

The diketopiperazine ring system is a well-known heterocyclic framework and its synthesis has been widely reported in the literature.\textsuperscript{132} The main approach to the diketopiperazine ring system proceeds via peptide coupling of a primary amine with a carboxylic acid and subsequent cyclisation of the resulting dipeptide.\textsuperscript{125,127}

Scheme 3.30: Main approach to the diketopiperazine ring system.

The synthetic challenge of this project is the elaboration of the 1,2-oxazinane moiety. As previously stated, the only reported approach to construct the 1,2-oxazinane ring system present in pestaloxazine A (208) is the nitroso Diels-Alder reaction followed by hydrogenation (Scheme 3.31). However, we wanted to establish a biomimetic synthesis of pestaloxazine A (208) by applying the radical cyclisation conditions developed within our group to an N-hydroxylamine cyclisation precursor to access the 1,2-oxazinane ring system. Therefore, in this project the reactivity of N-hydroxylamine to oxidative radical cyclisation conditions will also be evaluated.
3.6.2. Retrosynthetic analysis of pestaloxazine A (208)

Our retrosynthesis would hinge on the use of the 1,6-hydrogen abstraction reaction with N-hydroxylamine precursor to provide access the key 1,2-oxazinane ring system. Racemic pestaloxazine A (208) would be obtained via peptide coupling of amine 212 with acid 247 (Scheme 3.32). Acid 247 would be accessed from alkyne 239 in 5 steps, following the literature procedures. Construction of diketopiperazine 281 would proceed using two different synthetic strategies.

The first approach to key intermediate 281 would hinge on late-stage radical cyclisation of hydroxylamine 282 to establish the spiro[1,2-oxazinane-diketopiperazine] ring system. Diketopiperazine 282 would be accessed via Mitsunobu reaction of diol alcohol 283 with N-hydroxylamine 284. Diol 283 would be prepared via reduction of diacid 285 which would be accessed from pyroglutamic acid (286) using literature procedures.

The second pathway relies on late-stage dimerisation via peptide coupling of amine 287 with acid 288 and subsequent intramolecular cyclisation to give intermediate 281. Selective deprotection of 1,2-oxazinane 289 would enable the preparation of both coupling partners 287 and 288. Construction of the 1,2-oxazinane ring system in 289 would be achieved by radical cyclisation of N-hydroxylamine 290 which in turn would be prepared via Mitsunobu reaction of known alcohol 291 with N-hydroxylamine 284.
Scheme 3.32: Retrosynthetic analysis of pestaloxazine A (208).
Chapter Four
Discussion
4.1. Attempted synthesis of pestaloxazine A (208) via an early stage dimerisation strategy

4.1.1. Overview

Our initial synthetic strategy to access racemic pestaloxazine A (208) hinged on early stage formation of the diketopiperazine ring system prior to construction of the 1,2-oxazinane cycle via intramolecular 1,6-hydrogen abstraction. Pestaloxazine A (208) would be synthesised via peptide coupling of diamine 212 with carboxylic acid 247 (Scheme 4.1). Carboxylic acid is available from alkyne 239 in 5 steps following literature procedures.\(^{128}\)

Installation of the spiro[1,2-oxazinane-diketopiperazine] moiety present in protected diketopiperazine 281 would be conducted via radical cyclisation of \(N\)-hydroxylamine 282 (Scheme 4.1). Cyclisation precursor 282 would be prepared via Mitsunobu reaction of diol 283 with \(N\)-hydroxylamine 284. Diol 283 would be accessed via reduction of diacid 285 which in turn would be prepared from pyroglutamic acid (286) using literature procedures.\(^{172}\)

Scheme 4.1: Retrosynthetic analysis of pestaloxazine A (208) via early stage dimerisation.
4.1.2. Attempted synthesis of diketopiperazine 283 from pyroglutamic acid (286)

4.1.2.1. Retrosynthetic analysis of diol 283

Our first synthetic objective was to access diol 283 in order to carry out a Mitsunobu reaction with an N-hydroxylamine derivative. Mitsunobu reaction precursor 283 would be accessed by reduction of diacid 285, which in turn would be prepared via hydrolysis of tricyclic diketopiperazine 292 (Scheme 4.2). Self-condensation of pyroglutamic acid (286) would provide access to tricyclic diketopiperazine 292.

![Scheme 4.2: Retrosynthetic analysis of diol 283.](image)

4.1.2.2. Synthesis and attempted reduction of diacid 285

The initial target of this strategy was diketopiperazine diacid 285. Following the literature procedure, self-condensation of pyroglutamic acid (286) with acetic anhydride in pyridine at 110 °C afforded tricyclic diketopiperazine 292 in 74% yield (Scheme 4.3). Known diacid 285 was then accessed in moderate yield via hydrolysis of tricyclic diketopiperazine 292 using catalytic sulfuric acid in water at 0 °C.

![Scheme 4.3: Synthesis of diacid 285 from pyroglutamic acid (286).](image)

With diacid 285 in hand, attention turned to the preparation of diol 283. Reduction of diacid 285 was attempted with LiAlH₄ in diethyl ether, resulting in only recovery of the starting material (Table 4.1, entry 1). Changing the solvent to THF or dioxane had no effect, resulting only in recovered starting material (Table 4.1, entries 2 and 3). LiAlH₄ and diacid 285 were then ground together in the absence of solvent, resulting only in degradation of the starting material (Table
4.1, entry 4). In a last attempt, the reaction was carried out with sodium borohydride in water, resulting only in recovery of diacid 285 (Table 4.1, entry 5).

Table 4.1: Attempted reduction of acid 285.

<table>
<thead>
<tr>
<th>entry</th>
<th>reductant</th>
<th>solvent</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄</td>
<td>Et₂O</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH₄</td>
<td>THF</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄</td>
<td>dioxane</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH₄</td>
<td>-</td>
<td>degradation</td>
</tr>
<tr>
<td>5</td>
<td>NaBH₄</td>
<td>water</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

It is of note that diacid 285 exhibited an extremely low solubility in organic solvents (e.g. THF, Et₂O, dioxane) and water, accounting for the lack of reactivity. Consequently, investigations into the direct reduction of diacid 285 to diol 283 were not pursued further.

4.1.3. Synthesis of dimethyl ester 293

4.1.3.1. Revised retrosynthetic analysis of diol 283

Given our unsuccessful attempts to reduce diacid 293, an alternative synthetic pathway was devised. Reduction of dimethyl ester 293 would provide access to diol 283 (Scheme 4.4). Dimethyl ester 293 would be available from either esterification of diacid 285 or methanolysis of tricyclic diketopiperazine 292.
4.1.3.2. Attempted synthesis of diester 293 from diacid 285

The initial focus of our revised strategy was the synthesis of dimethyl ester 293 via esterification of diacid 285. Attempted esterification of diacid 285 using concentrated aqueous sulfuric acid in methanol only resulted in recovered starting material (Table 4.2, entry 1). The reaction was also attempted using DMF as a solvent without success (Table 4.2, entry 2). Esterification of diacid 285 was then carried out using the coupling agent N,N'-dicyclohexylcarbodiimide (DCC) in methanol and DMF. Once more only starting material was recovered from the reaction mixture (Table 4.2, entry 3). In a final attempt, the reaction was carried out using trimethylsilyl chloride in methanol, giving by-products resulting from the opening of the diketopiperazine ring (Table 4.2, entry 4). The reactions were carried out at high temperature due to the low solubility of diacid 285, methylation of diacid 285 using diazomethane was therefore not attempted due to its thermal instability.

Table 4.2: Attempted methylation of diacid 285.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂SO₄, MeOH, reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>H₂SO₄, MeOH, DMF, reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>DCC, MeOH, DMF, reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>TMSCl, MeOH, rt</td>
<td>by-products</td>
</tr>
</tbody>
</table>
4.1.3.3. Synthesis and attempted reduction of diketopiperazine ester 293

Our attention therefore turned to the selective methanolyis of diketopiperazine 292. Attempted opening of the γ-lactam functionality in diketopiperazine 292 using lithium chloride and imidazole in methanol resulted in cleavage of the diketopiperazine moiety to form pyroglutamic ester 294 (Table 4.3, entry 1). The reaction was attempted using DCC in methanol at reflux, once more providing only pyroglutamic ester 294 (Table 4.3, entry 2). Pleasingly, diketopiperazine ester 293 was synthesised from diketopiperazine 292 in low yield using catalytic sulfuric acid and methanol in toluene at reflux, according to the literature procedure (Table 4.3, entry 3). As expected, dimethyl ester 293 exhibited greater solubility in organic solvents such as tetrahydrofuran and methanol compared to diacid 285.

Table 4.3: Methanolysis of diketopiperazine 292.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>293</th>
<th>294</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiCl, imidazole, reflux, MeOH</td>
<td>-</td>
<td>73 %</td>
</tr>
<tr>
<td>2</td>
<td>DCC, reflux, MeOH</td>
<td>-</td>
<td>65 %</td>
</tr>
<tr>
<td>3</td>
<td>H₂SO₄, MeOH, toluene</td>
<td>23 %</td>
<td>-</td>
</tr>
</tbody>
</table>

With dimethyl ester 293 in hand, attention turned to the selective reduction of the methyl ester functionalities to access diol 283 (Scheme 4.5). Unfortunately, attempts to effect the reduction of dimethyl ester 293 using several reducing agents (i.e. LiAlH₄, DIBALH and NaBH₄) were unsuccessful and only degradation or no reaction were observed.

Scheme 4.5: Attempted reduction of 293.

It is of note that the degradation products observed during the reduction attempts of dimethyl ester 293 were extremely polar and water soluble suggesting formation of amino acids resulting
Chapter 4: Discussion

from cleavage of the diketopiperazine moiety. Given these disappointing results, synthetic investigations towards the synthesis of pestaloxazine A (208) via early formation of the diketopiperazine moiety were not further pursued.

4.1.4. Summary and future work

In summary, diacid 285 was successfully prepared from pyroglutamic acid (286) in two steps following literature procedures (Scheme 4.6). Attempts to effect direct reduction of diacid 285 to access key intermediate 283 were unsuccessful. Additionally, attempts to prepare dimethyl ester 293 from diacid 285 were also unsuccessful.

Dimethyl ester 293 was accessed from tricyclic diketopiperazine 292 via methanolysis of the δ-lactam units. However, attempts to effect reduction of the methyl ester functionalities were also unsuccessful.

![Scheme 4.6: Summary of the approaches to diol 283.](image)

Preparation of diol 283 could alternatively be accomplished via peptide coupling of acid 295 with secondary amine 296 and subsequent intramolecular cyclisation of the resulting dipeptide (Scheme 4.7). Coupling partners 295 and 296 would prepared via selective deprotection of known alcohol 291.

![Scheme 4.7: Retrosynthesis of diol 283 via peptide coupling and cyclisation.](image)
4.2. Synthesis of pestaloxazine A (208) via a late stage dimerisation strategy

4.2.1. Overview

Following the difficulties encountered in our early stage dimerisation strategy, a late stage dimerisation route that hinged on the formation of the 1,2-oxazinane ring system via 1,6-hydrogen abstraction prior to dimerisation was explored. Once more, peptide coupling of amine 212 with acid 247 would provide access to pestaloxazine A (208) (Scheme 4.8). Acid 247 would be accessed in 6 steps from alkyne 239 following literature procedures.\textsuperscript{128}

The key spiro[1,2-oxazinane-diketopiperazine] moiety present in 281 would be accessed via dimerisation of 1,2-oxazinane 289. Construction of the 1,2-oxazinane ring system in 289 would be conducted via radical cyclisation of N-hydroxylamine 290. Mitsunobu reaction of readily available norvaline derivative 291 with N-hydroxylamine 284 would enable access to radical cyclisation precursor 290.\textsuperscript{173}

Scheme 4.8: Retrosynthetic analysis of pestaloxazine A (208) via late stage dimerisation.
4.2.2. Synthesis and radical cyclisation of alcohol 291

4.2.2.1. Synthesis of alcohol 291

Attention turned to the preparation of Mitsunobu reaction precursor 291. Due to the unavailability of racemic glutamic acid (297) the synthesis was carried out using enantiopure L-glutamic acid (297), which would also provide an opportunity to evaluate the stereoselectivity of the radical cyclisation. Following literature procedure, the synthesis began with methylation of L-glutamic acid (297) using trimethylsilyl chloride in methanol followed by protection using Boc anhydride, providing diester 298 in near quantitative yield (Scheme 4.9). After protection of the secondary amine 298 using Boc anhydride and DMAP in acetonitrile, the resulting ester was then converted to known alcohol 291 in 86% yield upon treatment with LiAlH₄ in THF at −40 °C. The spectroscopic data were consistent with those previously reported.

![Scheme 4.9: Synthesis of alcohol 291.](image)

4.2.2.2. Radical cyclisation of alcohol 291

With alcohol 291 in hand, we sought to confirm that oxidative radical cyclisation would occur at the α position of a highly protected amino acid. Intramolecular radical cyclisation of alcohol 291 to give tetrahydrofuran 299 was therefore attempted as model (Scheme 4.10).

![Scheme 4.10: Radical cyclisation of model alcohol 291.](image)

The oxidative radical cyclisation of alcohol 291 was first carried out with lead tetracetate (Pb(OAc)₄) in benzene, which resulted in the formation of acetate 300 (Table 4.4, entry 1). Changing the solvent from benzene to cyclohexane resulted in only recovered starting material 291 (Table 4.4, entry 2). Treatment of alcohol 291 with iodosobenzene diacetate (PhI(OAc)₂) and iodine in benzene once more led to the formation of acetate protected ester 300 (Table 4.4, entry 3). The reaction was then carried out with PhI(OAc)₂ and iodine in cyclohexane (Cₐ = 100 g/L), providing tetrahydrofuran 299 in only 5% yield (Table 4.4, entry 4). Gratifyingly, treatment of
alcohol 291 with Pb(OAc)$_4$ or PhI(OAc)$_2$ with iodine in cyclohexane at a lower concentration \( (i.e. \ C_m = 10 \ g/L) \) provided tetrahydrofuran 299 in 35 % and 43 % yield respectively (Table 4.4, entries 5 and 6). Interestingly, tetrahydrofuran 299 exhibited optical activity, suggesting that the stereochemical information was at least partially retained during the radical cyclisation process.

### Table 4.4: Radical cyclisation of alcohol 291.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product</th>
<th>yield (%)</th>
<th>observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pb(OAc)$_4$, benzene, ( h\nu )</td>
<td>300</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Pb(OAc)$_4$, cyclohexane, ( h\nu )</td>
<td>-</td>
<td>-</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>PhI(OAc)$_2$, I$_2$, benzene, ( h\nu )</td>
<td>300</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>4$^a$</td>
<td>PhI(OAc)$_2$, I$_2$, cyclohexane, ( h\nu )</td>
<td>299</td>
<td>5</td>
<td>by-products</td>
</tr>
<tr>
<td>5$^b$</td>
<td>Pb(OAc)$_4$, I$_2$, cyclohexane, ( h\nu )</td>
<td>299</td>
<td>35</td>
<td>incomplete</td>
</tr>
<tr>
<td>6$^b$</td>
<td>PhI(OAc)$_2$, I$_2$, cyclohexane, ( h\nu )</td>
<td>299</td>
<td>43</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ \( C_m = 100 \ g/L; \) $^b$ \( C_m = 10 \ g/L \)

To the best of our knowledge, no oxidative radical cyclisations of amino acids have yet been reported. The cyclisation reaction begins with the formation of alkyl hypoiodite (i) from alcohol 291 using iodine and PhI(OAc)$_2$ (Scheme 4.11)$^{152}$. Photolysis of the oxygen-iodine bond generates the 6-membered radical intermediate (ii) which in turn forms radical (iii) via 1,5-hydrogen transfer. Radical capture of intermediate (iii) with iodine allows formation of iodide (iv) which then undergoes intramolecular cyclisation to give tetrahydrofuran 299.

### Scheme 4.11: Radical cyclisation of alcohol 291 mechanism.$^{152}$
Chapter 4: Discussion

4.2.3. Attempted synthesis of 1,2-oxazinane 301 via radical cyclisation

4.2.3.1. Retrosynthetic analysis of 1,2-oxazinane 301

Following the successful formation of tetrahydrofuran 299, our next objective was to access the 1,2-oxazinane ring system present in 301 (Scheme 4.12). Retrosynthetically, radical cyclisation of hydroxamic acid 302 would provide access to 1,2-oxazinane 301. Hydroxamic acid 302 would be assembled via Mitsunobu reaction of alcohol 291 with hydroxamate 303, which in turn would be synthesised from benzoyl chloride (304) following literature procedures.\textsuperscript{174}

![Scheme 4.12: Retrosynthetic analysis of 1,2-oxazinane 301.](image)

4.2.3.2. Synthesis of hydroxamic acid 302

Our initial focus was the synthesis of hydroxamate 303 from benzoyl chloride (304). Following literature procedure, treatment of benzoyl chloride (304) with hydroxylamine hydrochloride and sodium hydroxide in 1:1 THF-water at room temperature and subsequent acetate protection the resulting hydroxamic acid using acetic anhydride and triethylamine in THF at room temperature afforded known hydroxamate 303 in 75\% overall yield (Scheme 4.13).\textsuperscript{174} The spectroscopic data were in agreement with the reported literature.\textsuperscript{174}

![Scheme 4.13: Synthesis of hydroxamate 303.](image)

With alcohol 291 and hydroxamate 303 in hand, attention turned to the synthesis of hydroxamic acid 302 (Scheme 4.14). Mitsunobu reaction of alcohol 291 with hydroxamate 303 using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in THF gave hydroxamate
305 in 71 % yield. Hydrolysis of the acetate functionality using potassium hydroxide in methanol at room temperature gave unknown hydroxamic acid 302 in 91 % yield. The structures of hydroxamate 305 and hydroxamic acid 302 were determined using a combination of NMR spectroscopy, IR spectroscopy and high resolution mass spectrometry.

Scheme 4.14: Synthesis of hydroxamic acid 302 via Mitsunobu reaction.

4.2.3.3. Attempted radical cyclisation of hydroxamic acid 306

We were now in a position to investigate the key radical cyclisation of hydroxamic acid 302 to access the 1,2-oxazinane ring system in 301. Unfortunately, treatment of hydroxamic acid 302 with PhI(OAc)$_2$ and iodine in cyclohexane under UV irradiation gave benzoyl ester 306 in 76 % yield (Table 4.5, entry 1). Benzoyl ester 306 was also obtained when the reaction was carried out using Pb(OAc)$_4$ and iodine in cyclohexane (Table 4.5, entry 2). However, the formation of benzoyl ester 306 from hydroxamic ester 302 could not be rationalised.

Table 4.5: Attempted radical cyclisation of hydroxamate 302.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI(OAc)$_2$, I$_2$, cyclohexane, $hv$, 50 °C, 3 h</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>Pb(OAc)$_4$, I$_2$, cyclohexane, $hv$, 50 °C, 3 h</td>
<td>71</td>
</tr>
</tbody>
</table>

Given the unexpected outcome of the radical cyclisation reaction and the difficulty in providing a mechanistic justification for the formation of ester 306, we first sought to confirm the structure of ester 306. Pleasingly, esterification of alcohol 291 with benzoyl chloride (304) using pyridine in dichloromethane provided ester 306 in 79 % yield. Comparison of the spectral data confirmed the structure of ester 306 obtained from the attempted oxidative radical cyclisation of hydroxamic acid 302 (Scheme 4.15).
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![Scheme 4.15: Synthesis of 306 from alcohol 291 and benzoyl chloride (304).](image)

$\text{HO-}\text{NBOc} \quad + \quad \text{O-Cl} \quad \xrightarrow{\text{pyridine, CH$_2$Cl$_2$ (79 \%)}} \quad \text{O-OMe}$

$291 \quad 304 \quad 306$

$\text{1H NMR analysis of hydroxamic acid 302 revealed that degradation occurred upon storage for one week. Purification and structural elucidation of the degradation product revealed that it was in fact an isomer of hydroxamic acid 302, suggesting that hydroxamic acid 302 isomerised over time. However, the presence of only one stereocenter in hydroxamic acid 302 excluded the possibility of the formation of a diastereomeric degradation product (Figure 4.1). Therefore, these observations suggested that we had misinterpreted the structure of the initial hydroxamic acid 302.}$

![Figure 4.1: Structure of hydroxamic acid 302.](image)

$4.2.3.4. \text{Structural elucidation of radical cyclisation precursor 307}$

Given these results, we sought to further elucidate the structure of our radical cyclisation precursor. Consistent with our original assignment, mass spectrometry and the presence of a molecular ion at $m/z$ 489.2189 indicated a molecular formula of $\text{C}_{23}\text{H}_{34}\text{N}_{2}\text{O}_{8}$. The $\text{1H}$ and $\text{13C}$ NMR spectra confirmed the presence of the aromatic and amino ester fragments (I and II, respectively) (Figure 4.2). In addition to this, the chemical shift for C-5 (II, $\delta_{C.5} = 71.2 \text{ ppm}$) suggested proximity to an electron-rich atom. The requirement that the benzyl fragment and amino ester fragment to be connected by an electron rich oxygen led us to propose hydroximic acids (Z)-307 and (E)-307 as potential structures for our radical cyclisation precursor (Figure 4.2). Furthermore, isomerisation over time of the C=N bond in either (E)- or (Z)-307 to give the respective stereoisomer would account for the “degradation” that was observed upon storage for a week since formation of a stereoisomer of the cyclisation precursor was observed. Given these observations, we postulated that the radical cyclisation precursor was in fact either (E)- or (Z)-hydroximic acid 307 and the degradation product was the remaining stereoisomer.
We then sought to determine the stereochemical configuration of radical cyclisation precursor 307. We postulated that hydroximic acid \((Z)-307\) would isomerise to give its isomer \((E)-307\) (Scheme 4.16). The \(^1\)H NMR spectrum revealed that the aromatic protons at the ortho position in the initially prepared radical cyclisation precursor (\(\delta_{H-\text{ortho}} = 7.64\) ppm) were more shielded than the corresponding protons in the isomerised product (\(\delta_{H-\text{ortho}} = 7.81\) ppm). These observations suggested that the hydroxyl group in the hydroximic acid functionality in the isomerised product was closer to the aromatic ring than that in the initial radical cyclisation precursor. Conversely, the protons attached to C-5 were more deshielded in initial cyclisation precursor (\(\delta_{H-5} = 4.22\) ppm) than in the radical cyclisation precursor (\(\delta_{H-5} = 4.12\) ppm), suggesting that the initial radical cyclisation precursor was in fact hydroximic acid \((Z)-307\). Additionally, Schraml and co-workers reported that for hydroximic acids, in addition to the difference in the chemical shift of the aromatic protons, the chemical shift of the carbon involved in the C=N bond was less shielded in the \((E)\)-isomer than its corresponding \((Z)\)-isomer.\(^{175}\) Pleasingly, the chemical shift of this carbon in the radical cyclisation precursor was more shielded (\(\delta_{C} = 156.1\) ppm) than its counterpart in the isomerised product (\(\delta_{C} = 159.7\) ppm). This confirmed that the initial radical cyclisation precursor was in fact hydroximic acid \((Z)-307\) which then isomerises over time to give \((E)-307\).
Scheme 4.16: Isomerisation of radical cyclisation precursor (Z)-307 and chemical shift of characteristic protons (red) and carbon (blue) (δ (ppm), CDCl₃, ¹H (400 MHz), ¹³C (100 MHz)).

Interestingly, investigation of the literature revealed that in 1982 Miller and Maurer reported the O-alkylation of hydroxamates with primary alcohols under Mitsunobu conditions.¹⁷⁶ Mechanistically, we postulated that a rearrangement had occurred during the attempted Mitsunobu reaction of hydroxamate 303 with alcohol 291. Our proposed mechanism begins as expected for a Mitsunobu reaction, with nucleophilic addition of triphenylphosphine to DIAD to form zwitterionic adduct (i) which then deprotonates 303 to give anion (ii) and phosphonium ion (iii) (Scheme 4.17).¹⁷⁷ Reaction of phosphonium ion (iii) with alcohol 291 leads to formation of alkoxyphosphonium cation (iv) and hydrazine (v). The resonance form of anion (ii) is alkoxide (ii’) which then participates in nucleophilic addition to alkoxyphosphonium cation (iv), affording hydroxamate 308.

Scheme 4.17: Proposed Mitsunobu reaction of hydroxamate 303.¹⁷⁷
Chapter 4: Discussion

In summary, Mitsunobu reaction of alcohol 291 with hydroxamate 303 using DIAD and triphenylphosphine in THF gave hydroximate (Z)-308 in 71% yield (Scheme 4.18). Acetate hydrolysis using potassium hydroxide in methanol provided hydroximic acid (Z)-307 which in turn isomerised over time to give the thermodynamically favoured hydroximic acid (E)-307. It is of note that after three months of storage, isomerisation of acetate protected oxime 308 was not observed.

Scheme 4.18: Mitsunobu reaction of alcohol 291 and hydroxamate 303.

4.2.4. Synthesis and attempted radical cyclisation of hydroxamic acid 309

4.2.4.1. Retrosynthesis of oxazinane 310

In line with these observations, an alternative approach was devised by changing the electronic character of the Mitsunobu reaction precursor. In 1982, Miller and Maurer reported that only N-alkylation was observed with Cbz protected hydroxamates under Mitsunobu conditions. Retrosynthetically, radical cyclisation of hydroxamic acid 309 would result in the formation of 1,2-oxazinane 310 (Scheme 4.19). Hydroxamic acid 309 would be accessed via Mitsunobu reaction of alcohol 291 and hydroxamate 311 which in turn would be prepared from benzyl chloroformate (312).

Scheme 4.19: Retrosynthetic analysis of 1,2-oxazinane 310.
4.2.4.2. Synthesis of hydroxamic acid 309

Following literature procedures, known hydroxamate 311 was synthesised in 59\% overall yield by treatment of benzyl chloroformate (312) with hydroxylamine hydrochloride and sodium bicarbonate in 1:1 dichloromethane-water, followed by acetylation with acetic anhydride in pyridine (Scheme 4.20).\textsuperscript{178} The spectroscopic data were in agreement with the reported literature.\textsuperscript{178}

\begin{center}
\textbf{Scheme 4.20: Synthesis of hydroxamate 311.}
\end{center}

With alcohol 291 and hydroxamate 311 in hand, attention turned to the Mitsunobu reaction. Hydroxamate 313 was synthesised in 75\% yield via Mitsunobu reaction of alcohol 291 with hydroxamate 311 using DIAD and triphenylphosphine in THF (Scheme 4.21). Hydrolysis of the acetate functionality present in hydroxamate 313 with potassium carbonate in methanol gave hydroxamic acid 309 in 91\% yield.

\begin{center}
\textbf{Scheme 4.21: Synthesis of hydroxamic acid 309 via Mitsunobu reaction.}
\end{center}

In order to unambiguously confirm the structure of hydroxamic acid 309, the chemical shift of the characteristic proton H-5 was compared with that of H-5 in known hydroxamic acid 314 and also the previously prepared hydroximate 307 (Table 4.6).\textsuperscript{179} Pleasingly, the resonance assigned to H-5 in our hydroxamic acid 309 ($\delta_{H-5} = 3.59$ ppm, Table 4.6, entry 1) was similar to that reported for hydroxamic acid 314 ($\delta_{H-5} = 3.57$ ppm, Table 4.6, entry 2). Comparisons of the $^{13}$C NMR C-5 resonance were also consistent with our structural assignment (Table 4.6, entries 1 and 2). Additionally, due to the presence of an electron-rich oxygen atom adjacent to H-5 in our previously prepared hydroximate 307, the resonances corresponding to H-5 and C-5 in hydroximate 307 were more deshielded ($\delta_{H-5} = 4.18$ ppm, $\delta_{C-5} = 71.1$ ppm, Table 4.6, entry 3) compared to those in hydroxamic acids 309 and 314. These observations confirmed our correct structural assignment of hydroxamic acid 309.
Table 4.6: Chemical shift of hydroxamates 309 and 314 and hydroximate 307.

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>$\delta_H$ (H-5, ppm)</th>
<th>$\delta_C$ (C-5, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>313</td>
<td>3.59</td>
<td>49.0</td>
</tr>
<tr>
<td>2$^b$</td>
<td>314</td>
<td>3.57</td>
<td>49.4</td>
</tr>
<tr>
<td>3$^c$</td>
<td>307</td>
<td>4.18</td>
<td>71.1</td>
</tr>
</tbody>
</table>

$^a$ $^1$H (400 MHz), $^{13}$C (100 MHz), CDCl$_3$; $^b$ $^1$H (500 MHz), $^{13}$C (126 MHz), CDCl$_3$.

4.2.4.3. Attempted radical cyclisation of hydroxamic acid 313

With hydroxamic acid 309 in hand, attention next turned to the key radical cyclisation in order to access the 1,2-oxazinane ring in 310. The reaction was first attempted by treatment of alcohol 309 using PhI(OAc)$_2$ and iodine in cyclohexane at 60 °C under UV irradiation. Unfortunately, only N-acetoxy-N-Cbz amide 315 was formed in 74 % yield. The same product was also obtained when the reaction was attempted using Pb(OAc)$_4$ under the same reaction conditions. Interestingly, both oxidation of the carbon adjacent of the hydroxamate functionality and acetylation of the hydroxyl functionality were observed.

Table 4.7: Radical reaction of hydroxamic acid 309 conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>condition</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI(OAc)$_2$, I$_2$, cyclohexane, $hν$, 50 °C</td>
<td>315</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Pb(OAc)$_4$, I$_2$, cyclohexane, $hν$, 50 °C</td>
<td>315</td>
<td>52</td>
</tr>
</tbody>
</table>

Given that the application of the two main methods to effect radical cyclisation of hydroxamate 309 resulted in the formation of N-acetoxy-N-Cbz amide 315, formation of the 1,2-oxazinane moiety in 310 via radical cyclisation of hydroxamate 309 was not pursued further.
Chapter 4: Discussion

4.3. Summary and Future work

4.3.1. Summary of attempted synthesis of pestaloxazine A (208) via early stage dimerisation strategy

In summary, our attempted synthesis of pestaloxazine A (208) via an early stage dimerisation strategy was unsuccessful. Self-condensation of pyroglutamic acid (286) with acetic anhydride in pyridine afforded tricyclic diketopiperazine 292 in 74 % yield (Scheme 4.22). Ring opening of the γ-lactam units using concentrated sulfuric acid in water or with methanol in toluene provided diacid 285 and dimethyl ester 293, respectively. Attempted reduction of diacid 285 or dimethyl ester 293 to give diol 283 were unsuccessful.

 Scheme 4.22: Attempted synthesis of diol 283 via an early dimerisation strategy.

4.3.2. Summary of attempted synthesis of pestaloxazine A (208) via late stage dimerisation strategy

Attempted formation of the spiro[1,2-oxizane-diketopiperazine] moiety in pestaloxazine A (208) by an early stage radical cyclisation of an hydroxamate was also unsuccessful. Esterification and Boc-protection of L-glutamic acid provided diester 298 in 98 % yield (Scheme 4.23). Further Boc protection and selective reduction provided Mitsunobu precursor 291 in reasonable yield. Hydroxamates 303 and 311 were synthesised in high yield using a two-step procedure from benzoyl chloride (304) and Cbz chloride (312), respectively.
Scheme 4.23: Synthesis of Mitsunobu precursors 291, 303 and 311.

Pleasingly, radical cyclisation of alcohol 291 using PIDA and iodine in cyclohexane under UV irradiation gave tetrahydrofuran 299. Unfortunately, Mitsunobu reaction of alcohol 291 and benzyl hydroxamate 303 only provided hydroximate 308 in 71 % yield. However, when the reaction was carried out with Cbz hydroxamate 311, the desired hydroxamate 313 was isolated in 75 % yield. Hydrolysis of the acetate ester using potassium carbonate in methanol provided hydroxamic acid 309 in near quantitative yield. Disappointingly, radical cyclisation of hydroxamic acid 309 to give 1,2-oxazinane 310 was unsuccessful.

Scheme 4.24: Attempted synthesis of 1,2-oxazinane 310 via radical cyclisation.
4.3.3. Future work

4.3.3.1. Revised retro-synthetic analysis of diol 283

Given the difficulties encountered when attempting to access diol 283 from the self-condensation of the pyroglutamic acid (286), an alternative strategy was devised. Diol 283 would be prepared via deprotection and subsequent cyclisation of dipeptide 316 which in turn would be accessed via peptide coupling of amine 295 with acid 296 (Scheme 4.25). Selective deprotection of known alcohol 291 would enable access to both primary amine 295 and acid 296.

![Scheme 4.25: Retrosynthesis of diol 283 via peptide coupling.]

4.3.3.2. Radical cyclisation of hydroxyl amino acid.

To the best of our knowledge, we have reported the first example of an oxidative radical cyclisation of an amino acid, providing an optically active tetrahydrofuran (Scheme 4.26). The stereoselectivity of the reaction remains to be quantified using chiral HPLC. Additionally, the substrate scope of this reaction will be investigated by changing the protecting groups of the amine and ester functionalities. The reaction would also be attempted with ε-hydroxyamino acids (i.e. n = 2) to access tetrahydropyran derivatives.

![Scheme 4.26: Radical cyclisation of amino acid.]
4.3.3.3. Revised retrosynthetic analysis of pestaloxazine A (208)

Given our unsuccessful attempts to access the 1,2-oxazinane framework present in pestaloxazine A (208) via radical cyclisation, an alternative approach based on a nitroso Diels-Alder cycloaddition was devised. As previously discussed, pestaloxazine A (208) would be accessed via peptide coupling of diketopiperazine 212 and acid 247 which in turn would be prepared from alkyne 239 in five steps following literature procedures (Scheme 4.27).\textsuperscript{128}

Protected diketopiperazine 281 would be prepared via deprotection and subsequent cyclisation of dipeptide 317. Peptide coupling of acid 288 and amine 287 would provide dipeptide 318. Both amine 287 and carboxylic acid 288 would be prepared from 3,6-dihydro-1,2-oxazine 318 via hydrogenation of the alkene functionality followed by either Boc deprotection or ester hydrolysis, respectively. Key intermediate 318 would be assembled via nitroso Diels-Alder cycloaddition of nitrone 319 and diene 320. Diene 320 would be accessed via HWE reaction of acroleine (321) and phosphonate 322, as described by Takahashi and co-workers.\textsuperscript{180}

![Scheme 4.27: Retrosynthetic analysis of pestaloxazine A (208) via nitroso Diels-Alder cycloaddition.](image-url)
Part III

Experimental
Chapter Five

Lasionectrin
5.1. General Details

Unless otherwise stated, all non-aqueous reactions and distillations were performed under a nitrogen or argon atmosphere in oven- or flame-dried glassware. Tetrahydrofuran, diethylether, toluene, dichloromethane, methanol, DMF and acetonitrile were dried using LC-Technology®– SP-1 solvent purifier. tert-Butanol was freshly distilled from calcium hydride. All other reagents were used as received unless otherwise noted.

Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions performed at low temperature were cooled either with an acetone/dry ice bath to reach −78 °C or an ice/water bath to reach 0 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck silica gel plates using UV light as visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Flash chromatography was carried out using 0.063–0.1 mm silica gel (Davisil® LC60A 40–63 μm) with the indicated solvent.

Melting points were measured on an electrothermal apparatus and are uncorrected. Infrared spectra were recorded as neat using a Perkin Elmer® Spectrum 1000 Fourier Transform Infrared spectrometer. Values are expressed in wavenumbers (cm⁻¹) and recorded in a range of 4000 to 450 cm⁻¹. Optical rotations were measured on a Rudolph Research Analytical® – Autopol IV polarimeter. High resolution mass spectra were recorded using a Bruker® micrOTOF-QII mass spectrometer.

NMR spectra were recorded at 21 °C in CDCl₃, CD₃OD or (CD)₃SO on a Bruker® DRX400 or Bruker® 400 spectrometer operating at 400 MHz for ¹H nuclei and 100 MHz for ¹³C nuclei or on a Bruker® Ascend 500 spectrometer operating at 500 MHz for ¹H nuclei and 125 MHz for ¹³C nuclei. All chemical shifts are reported in parts per million (ppm) from tetramethylsilane (δ = 0 ppm) and were measured relative to the solvent in which the sample was analysed (CDCl₃: δ = 7.26 ppm for ¹H NMR and δ = 77.0 ppm for ¹³C NMR; CD₃OD: δ = 3.31 ppm for ¹H NMR). Coupling constants (J) are reported in Hertz (Hz). ¹H NMR data is reported as chemical shift in ppm followed by relative integral, multiplicity (“s” singlet, “d” doublet, “dd” doublet of doublets, “ddd”, doublet of doublets of doublets, “dt” doublet of triplets, “t” triplet, “q” quartet, “qu” quintuplet, “m” multiplet, “br” broad), coupling constant where applicable and attribution. ¹³C NMR spectra are reported as chemical shift in ppm followed by degree of hybridisation and attribution. Where distinguishable from those due to a major rotamer or diastereomer, resonances due to minor rotamers or diastereomers are denoted by an asterix.
5.2. Synthesis of alkene 105

5.2.1. 3,5-Dimethoxybenzaldehyde (103)

To a solution of (3,5)-dimethoxybenzoic acid (108) (10.8 g, 58.0 mmol, 1.0 eq) in THF (250 mL) at 0 °C was added portionwise LiAlH₄ (4.60 g, 115 mmol, 2.0 eq). The solution was allowed warm up to room temperature over 3 h. After completion, the reaction was quenched with H₂O (4.7 mL) followed by 15 % NaOH aqueous solution (4.7 mL) then H₂O (3 × 4.7 mL). After stirring the solution for 1 h, the suspension was filtered and the solid washed with cold Et₂O (50 mL). The filtrate was dried over anhydrous MgSO₄ and the solvent removed in vacuo to afford alcohol (324) as a white solid (7.93 g, 82 %). To a solution of pyridinium chlorochromate (14.0 g, 65.0 mmol, 1.4 eq) in CH₂Cl₂ (100 mL) was added portionwise (3,5-methoxyphenyl)methanol (324) (7.93 g, 47.0 mmol, 1.0 eq). After stirring at room temperature for 16 h, a solution of hexane (50 mL) and EtOAc (50 mL) was added and the resulting solution was stir for 1 h. The solution was filtered through silica pad and the solvent was removed in vacuo. The resulting oil was dissolved in EtOAc (50 mL) and washed with 1 M aqueous NaOH solution (2 × 30 mL), H₂O (30 mL) and saturated aqueous NaCl solution (40 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent removed in vacuo. The resulting solid was washed with hot hexane to afford the corresponding aldehyde (103) (6.20 g, 81 %) as a white solid.

Mp: 47–48 °C [lit. 47–47.5 °C].

¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.90 (1H, s, H₇), 7.01 (1H, d, J = 2.2 Hz, H₄), 6.70 (2H, t, J = 2.4 Hz, H₂ and H₆), 3.87 (6H, s, H₈).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 191.9 (C, C₇), 161.3 (2 × C, C₃ and C₅), 138.4 (C, C₁), 107.2 (CH, C₄), 107.1 (2 × CH, C₂ and C₆), 55.6 (2 × CH₃, C₈).

Melting point and spectroscopic data were consistent with those previously reported.₄₈
5.2.2. 4-(tert-Butyl) 1-ethyl 2-(diethoxyphosphoryl)succinate (104)

To a solution of triethylphosphonoacetate (110) (860 µL, 4.30 mmol, 1.0 eq) in THF (20 mL) at 0 °C was added portionwise sodium hydride (188 mg, 60 % dispersion in oil, 4.71 mmol, 1.1 eq). The solution was allowed to stir at 0 °C for 10 min. tert-Butylbromoacetate (110) (770 µL, 5.13 mmol, 1.1 eq) was added dropwise and the resulting solution was allowed to stir at 0 °C for 1 h. After completion, the reaction was quenched with saturated aqueous NH₄Cl solution (30 mL) and extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with H₂O (2 × 50 mL) and saturated aqueous NaCl solution (50 mL), then dried over anhydrous MgSO₄ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexanes (2:3) as eluent to afford the title compound 104 (1.03 g, 71 %) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 4.09–3.90 (6H, m, H₅ and H₉), 3.19 (1H, ddd, J = 24.0, 11.5, 3.5 Hz, H₃a), 2.82–2.73 (1H, br, H₂), 2.53 (1H, ddd, J = 17.4, 9.1, 3.5 Hz, H₃b), 1.24 (9H, s, H₈), 1.19–1.08 (9H, br, H₆ and H₁₀).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8 (C, d, J₆₋₇ = 19.3 Hz, C₁), 168.0 (C, d, J₅₋₆ = 5.3 Hz, C₄), 81.1 (C, C₇), 62.7 (CH₂, d, J₆₋₇ = 5.5 Hz, C₉), 62.6 (CH₂, d, J₅₋₆ = 6.0 Hz, C₉), 61.2 (CH₂, C₅), 41.3 (CH, d, J₅₋₆ = 131.2 Hz, C₂), 32.3 (CH₂, d, J₅₋₆ = 2.2 Hz, C₃), 27.7 (CH₃, C₇), 16.1 (CH₃, d, J₅₋₆ = 5.2 Hz, C₁₀), 16.0 (CH₃, d, J₅₋₆ = 4.8 Hz, C₁₀), 13.3 (CH₃, C₆).

Spectroscopic data were consistent with those previously reported.¹⁸¹
5.2.3. 4-(tert-Butyl) 1-ethyl (E)-2-(3,5-dimethoxybenzylidene)succinate (107)

To a solution of phosphonate 104 (6.20 g, 18.2 mmol, 1.2 eq) in THF (70 mL) at 0 °C was added portionwise sodium hydride (920 mg, 60 % dispersion in oil, 23.2 mmol, 1.5 eq). The solution was allowed to stir at 0 °C for 2 h. A solution of 3,5 dimethoxybenzaldehyde (103) (2.63 g, 15.7 mmol, 1.0 eq) in THF (10 mL) was then added dropwise. The resulting solution was allowed to stir at 0 °C for 1 h. After completion, the reaction was quenched with saturated aqueous NH₄Cl solution (60 mL), and extracted with EtOAc (3 × 80 mL). The combined organic extracts were washed with H₂O (2 × 100 mL) and saturated aqueous NaCl solution (100 mL), then dried over anhydrous MgSO₄ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:9) as eluent to afford the title compound 107 (4.02 g, 73 %) as a yellow oil.

^1H NMR (400 MHz, CDCl₃): δ (ppm) 7.78 (1H, s, H₅), 6.51 (2H, d, J = 1.9 Hz, H₇), 6.45 (1H, t, J = 2.3 Hz, H₉), 4.28 (2H, q, J = 7.1 Hz, H₁₁), 3.79 (6H, s, H₁₀), 3.46 (2H, s, H₃), 1.45 (9H, s, H₁₄), 1.34 (3H, t, J = 7.1 Hz, H₁₂).

^13C NMR (100 MHz, CDCl₃): δ (ppm) 170.3 (C, C₄), 167.4 (C, C₁), 160.6 (2 × C, C₈), 141.2 (CH, C₃), 137.1 (C, C₆), 127.3 (C, C₂), 106.8 (2 × CH, C₇), 101.2 (CH, C₉), 81.0 (C, C₁₃), 61.1 (CH₂, C₁₁), 55.4 (2 × CH₃, C₁₀), 35.1 (CH₂, C₁), 28.0 (3 × CH₃, C₁₄), 14.3 (CH₃, C₁₂).

IR (Neat): ν (cm⁻¹) 2984, 1726, 1684, 1142.

HRMS (ESI+): m/z calcd for C₁₉H₂₇O₆ ([M + H]⁺) 351.1802; found 351.1797.
5.2.4. 1-Ethyl (E)-2-(3,5-dimethoxybenzylidene)succinate (115)

To a solution of succinate 107 (238 mg, 0.67 mmol, 1.0 eq) in CH₂Cl₂ (10 mL) was added TFA (1 mL). The reaction was allowed to stir at 50 °C for 4 h. The reaction was quenched with 2 M aqueous NaOH solution (15 mL) and washed with EtOAc (2 × 15 mL). The aqueous layer was acidified with 2 M aqueous HCl solution (25 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:1) to afford the title compound 115 (159 mg, 80 %) as a white solid.

Mp: 120–122 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.85 (1H, s, H₅), 6.51 (2H, d, J = 2.1 Hz, H₇), 6.46 (1H, t, J = 2.2 Hz, H₉), 4.30 (2H, q, J = 7.1 Hz, H₁₁), 3.79 (6H, s, H₁₀), 3.59 (2H, s, H₃), 7.10 (3H, t, J = 7.1 Hz, H₁₂).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 176.5 (C, C₄), 167.5 (C, C₁), 160.9 (2 × C, C₆), 142.5 (CH, C₅), 136.5 (C, C₀), 125.8 (C, C₂), 106.8 (2 × CH, C₇), 101.4 (CH, C₉), 61.5 (CH₂, C₁₁), 55.4 (2 × CH₃, C₁₀), 33.8 (CH₂, C₃), 14.1 (CH₃, C₁₂).

IR (Neat): ν (cm⁻¹) 3083, 2940, 1696, 1590.

HRMS (ESI+): m/z calcd for C₁₅H₁₈NaO₆ ([M + Na⁺) 317.0996; found 317.0993.
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5.2.5. Ethyl 4-hydroxy-5,7-dimethoxy-2-naphthoate (106)

A solution of succinate 107 (117 mg, 0.33 mmol, 1.0 eq) in TFA (2 mL) was allowed to stir at reflux for 1 h. After completion, H₂O was slowly added (3 mL) and the solvent azeotroped with toluene. The resulting brown solid was dissolved in EtOAc (5 mL), washed with 1 M aqueous NaOH solution (3 × 5 mL), H₂O (5 mL) and saturated aqueous NaCl solution (5 mL). The organic extract was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was washed with cold Et₂O (3 × 5 mL) then dried in vacuo to afford the title compound 106 (77 mg, 83 %) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.13 (1H, s, OH), 7.93 (1H, d, J = 1.6 Hz, H₄), 7.30 (1H, d, J = 1.6 Hz, H₂), 6.81 (1H, d, J = 2.2 Hz, H₃), 6.54 (1H, d, J = 2.1 Hz, H₇), 4.36 (2H, q, J = 7.1 Hz, H₁₀), 4.03 (3H, s, H₁₂), 3.90 (3H, s, H₁₃), 1.42 (3H, t, J = 7.2 Hz, H₁₁).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 166.7 (C, C₉), 158.1 (C, C₆), 157.0 (C, C₈), 154.7 (C, C₁), 136.7 (C, C₄a), 130.1 (C, C₃), 120.5 (CH, C₄), 113.0 (C, C₈a), 108.0 (CH, C₂), 100.6 (CH, C₃), 99.7 (CH, C₇), 61.0 (CH₂, C₁₀), 56.3 (CH₃, C₁₂), 55.4 (CH₃, C₁₃), 14.3 (CH₃, C₁₁).

IR (Neat): ν (cm⁻¹) 3356, 1716, 1623, 1368.

HRMS (ESI+): m/z calcd for C₁₅H₁₇O₅ ([M + H]⁺) 277.1071; found 277.1078.
5.2.6. 3-(Hydroxymethyl)-6,8-dimethoxynaphthalen-1-ol (325)

LiAlH₄ (0.83 g, 21.9 mmol, 5.6 eq) was added portionwise to a solution of ester 106 (1.10 g, 3.87 mmol, 1.0 eq) in THF (50 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature over 16 h. The reaction was quenched with H₂O (0.83 mL) followed by 15 % aqueous NaOH solution (0.83 mL) then H₂O (2.5 mL). After 1 h stirring at room temperature, 2 M aqueous HCl solution (50 mL) was added. The aqueous layer was extracted with EtOAc (3 × 50 mL), then the combined organic extracts were dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc–PE (4:5) as eluent to afford the title compound 325 (0.78 g, 86 %) as a white solid.

Mp: 145–147 °C [lit. 146–147 °C].

¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.10 (1H, s, C₁OH), 7.16 (1H, s, H₆), 6.70 (1H, d, J = 1.5 Hz, H₂), 6.69 (1H, d, J = 2.3 Hz, H₅), 6.43 (1H, d, J = 2.4 Hz, H₇), 4.72 (2H, s, H₉), 4.01 (3H, s, H₁₁), 3.87 (3H, s, H₁₀), 1.86 (1H, s, C₉OH).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.0 (C, C₆), 157.2 (C, C₈), 154.9 (C, C₁), 141.3 (C, C₄α), 137.5 (C, C₃), 115.4 (CH, C₄), 110.2 (C, C₆α), 107.2 (CH, C₂), 99.6 (CH, C₅), 97.6 (CH, C₇), 65.3 (CH₂, C₉), 56.2 (CH₃, C₁₁), 55.4 (CH₃, C₁₀).

Melting point and spectroscopic data were consistent with those previously reported.¹⁸²
5.2.7. 4-Hydroxy-5,7-dimethoxy-2-naphthaldehyde (116)

To a solution of alcohol 325 (780 mg, 3.33 mmol, 1.0 eq) in EtOAc (35 mL) was added IBX (1.40 g, 5.00 mmol, 1.5 eq). After stirring for 16 h at 65 °C, the reaction mixture was filtrated and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel using CH₂Cl₂ as eluent to afford the title compound 116 (686 mg, 89 %) as a yellow solid.

Mp: 121–123 °C [lit. 131–132 °C].

¹H NMR (500 MHz, CDCl₃): δ (ppm) 10.01 (1H, s, H₉), 9.22 (1H, s, OH), 7.66 (1H, d, J = 0.9 Hz, H₄), 7.14 (1H, d, J = 0.9 Hz, H₂), 6.85 (1H, d, J = 1.8 Hz, H₅), 6.59 (1H, d, J = 2.4 Hz, H₇), 4.04 (3H, s, H₁₁), 3.91 (3H, s, H₁₀).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) 192.4 (CH, C₉), 158.5 (C, C₆), 157.1 (C, C₈), 155.6 (C, C₁), 137.0 (C, C₄a), 136.2 (C, C₃), 123.6 (CH, C₄), 113.9 (C, C₈a), 105.3 (CH, C₂), 100.9 (CH, C₅), 100.5 (CH, C₇), 56.4 (CH₃, C₁₁), 55.5 (CH₃, C₁₂).

Melting point and spectroscopic data were consistent with those previously reported.¹⁸²
5.2.8. *Ethyl 4-((tert-butyldimethylsilyl)oxy)-5,7-dimethoxy-2-naphthoate (118)*

![Chemical Structure]

To a solution of alcohol **106** (1.92 g, 6.90 mmol, 1.0 eq) in pyridine (20 mL) was added DMAP (2.56 g, 20.7 mmol, 3.0 eq) and TBS-Cl (6.25 g, 41.5 mmol, 6.0 eq). The solution was allowed to stir at room temperature for 24 h, then quenched with saturated aqueous CuSO₄ solution (20 mL), and extracted with EtOAc (50 mL). The organic extract was sequentially washed with saturated aqueous CuSO₄ solution (3 × 50 mL), H₂O (50 mL) and saturated aqueous NaCl solution (50 mL), then dried over anhydrous MgSO₄ and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:9) as eluent to afford the *title compound 118* (2.60 g, 96 %) as a white solid.

**Mp:** 101–103 °C.

**1H NMR** (400 MHz, CDCl₃): δ (ppm) 8.01 (1H, d, J = 1.5 Hz, H₄), 7.26 (1H, d, J = 1.5 Hz, H₂), 6.77 (1H, d, J = 2.5 Hz, H₃), 6.51 (1H, d, J = 2.2 Hz, H₇), 4.40 (2H, q, J = 7.1 Hz, H₁₀), 3.90 (3H, s, H₁₃), 3.88 (3H, s, H₁₂), 1.42 (3H, t, J = 7.1 Hz, H₁₁), 1.06 (9H, s, H₁₆), 0.25 (6H, s, H₁₄).

**13C NMR** (100 MHz, CDCl₃): δ (ppm) 166.7 (C, C₉), 158.3 (C, C₈), 158.1 (C, C₆), 152.8 (C, C₁), 137.6 (C, C₄₆), 128.7 (C, C₃), 122.7 (CH, C₄), 117.7 (C, C₈₈), 113.0 (CH, C₂), 100.1 (CH, C₃), 99.7 (CH, C₇), 61.0 (CH₂, C₁₀), 55.3 (2 × CH₃, C₁₂ and C₁₃), 25.9 (3 × CH₃, C₁₆), 18.5 (C, C₁₃), 14.3 (CH₃, C₁₁), −4.3 (2 × CH₃, C₁₄).

**IR** (Neat): ν (cm⁻¹) 2903, 1713, 1589, 1214.

**HRMS** (ESI+): *m/z* calcd for C₂₁H₃₁O₅Si ([M + H]⁺) 391.1935; found 391.1941.
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5.2.9. (4-((tert-Butyldimethylsilyl)oxy)-5,7-dimethoxynaphthalen-2-yl)methanol (326)

To a solution of ester 118 (2.60 g, 6.70 mmol, 1.0 eq) in THF (30 mL) at 0 °C was added portionwise LiAlH₄ (520 mg, 13.7 mmol, 2.1 eq). The resulting suspension was allowed to stir at room temperature for 16 h, then quenched with H₂O (0.52 mL) followed by 15 % aqueous NaOH solution (0.52 mL) then H₂O (0.52 mL). After stirring for 1 h, the suspension was filtrated and the filtrate was dried over anhydrous MgSO₄ then concentrated in vacuo to afford the title compound 326 (1.94 mg, 84 %) as a yellow solid.

Mp: 79–81 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.23 (1H, s, H₄), 6.68 (1H, d, J = 1.5 Hz, H₂), 6.65 (1H, d, J = 2.3 Hz, H₃), 6.42 (1H, d, J = 2.3 Hz, H₇), 4.71 (2H, s, H₉), 3.88 (3H, s, H₁₁), 3.87 (3H, s, H₁₀), 1.67 (1H, s, OH), 1.06 (9H, s, H₁₄), 0.22 (6H, s, H₁₂).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.2 (C, C₆), 158.1 (C, C₈), 152.9 (C, C₁), 139.8 (C, C₄ₙ), 138.3 (C, C₃), 117.7 (CH, C₄ₙ), 114.9 (C, C₈ₙ), 112.8 (CH, C₂), 98.6 (CH, C₃), 98.0 (CH, C₇), 65.2 (CH₂, C₉), 55.2 (2 × CH₃, C₁₀ and C₁₁), 26.0 (3 × CH₃, C₁₄), 18.6 (C, C₁₃), −4.3 (2 × CH₃, C₁₂).

IR (Neat): ν (cm⁻¹) 3184, 2928, 1612, 1583.

HRMS (ESI+): m/z calcd for C₁₉H₂₉O₄Si ([M + H]⁺) 349.1830; found 349.1828.
5.2.10. 4-(((tert-Butyldimethylsilyl)oxy)-5,7-dimethoxy-2-naphthaldehyde (326)

To a solution of alcohol 326 (1.94 g, 5.60 mmol, 1.0 eq) in EtOAc (35 mL) was added IBX (2.34 g, 8.40 mmol, 1.5 eq). After stirring at 65 °C for 16 h, the reaction mixture was filtrated and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:9) as eluent to afford the title compound 117 (1.59 g, 82 %) as a yellow solid.

Mp: 107–109 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 10.00 (1H, s, H$_9$), 7.75 (1H, s, H$_4$), 7.08 (1H, s, H$_2$), 6.81 (1H, d, $J = 2.0$ Hz, H$_5$), 6.58 (1H, d, $J = 1.8$ Hz, H$_7$), 3.90 (3H, s, H$_{11}$), 3.88 (3H, s, H$_{10}$), 1.05 (9H, s, H$_{14}$), 0.25 (6H, s, H$_{12}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 192.3 (CH, C$_9$), 158.7 (C, C$_6$), 158.4 (C, C$_8$), 153.9 (C, C$_3$), 137.8 (C, C$_{4a}$), 135.1 (C, C$_1$), 126.7 (CH, C$_4$), 118.6 (C, C$_{8a}$), 109.3 (CH, C$_2$), 101.0 (CH, C$_5$), 100.0 (CH, C$_7$), 55.4 (2 $\times$ CH$_3$, C$_{10}$ and C$_{11}$), 25.3 (3 $\times$ CH$_3$, C$_{14}$), 18.5 (C, C$_{13}$), −4.3 (2 $\times$ CH$_3$, C$_{12}$).

IR (Neat): $\nu$ (cm$^{-1}$) 2951, 1691, 1584, 1369.

HRMS (ESI+): $m/z$ calcd for C$_{19}$H$_{27}$O$_4$Si ([M + H]$^+$) 347.1673; found 347.1667.

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5.2.11. n-Propyloxirane (39)

\[ \text{Cl} \xrightarrow{\text{Copper Cyanide, EtMgBr, THF}} 39 \]

To solution of (R)-epichlorohydrin (123) (4.00 g, 43.0 mmol) with copper cyanide (395 mg, 2.12 µmol, 0.05 eq) in THF (50 mL) stirred at \(-78\) °C was added dropwise a solution of ethylmagnesium bromide (22 mL, 66.1 mmol, 1.5 eq, 3 M in Et,O). The solution was allowed to warm up to room temperature over 16 h. The reaction was quenched with saturated aqueous NH₄Cl solution (20 mL) and poured into H₂O (30 mL). The solution was extracted with Et₂O (2 × 40 mL). The combined ethereal layer were dried over anhydrous MgSO₄ and the solvent was removed \textit{in vacuo}. The crude was dissolved in Et₂O (14 mL) and solid NaOH (2.00 g, 0.50 mol, 1.1 eq) was added. The solution was allowed to stir at room temperature for 16 h. The solution was washed with H₂O (2 × 15 mL) and saturated aqueous NaCl solution (15 mL). Distillation under atmospheric pressure afforded the title compound 39 (2.40 g, 65 %, Bp = 89–91 °C) as a colorless liquid.

\textbf{¹H NMR} (400 MHz, CDCl₃): \( \delta \) (ppm) 2.88–2.94 (1H, br, H₂), 2.75 (1H, dd, \( J = 5.0, 4.0 \) Hz, H₁a), 2.47 (1H, dd, \( J = 5.0, 2.9 \) Hz, H₁b), 1.42–1.57 (4H, br, H₃ and H₄), 0.97 (3H, br, H₅).

\textbf{¹³C NMR} (100 MHz, CDCl₃): \( \delta \) (ppm) 52.2 (CH, C₂), 47.0 (CH₂, C₁), 34.5 (CH₂, C₃), 19.3 (CH₂, C₄), 13.9 (CH₃, C₅).

Spectroscopic data were consistent with those previously reported.\(^{47}\)
5.2.12. 6,8-Dimethoxy-3-vinlnaphthalen-1-ol (124)

To a solution of methyltriphenylphosphonium bromide (30 mg, 83.9 µmol, 1.0 eq) in THF (1 mL) stirred at 0 °C was added n-BuLi (85 µL, 85.0 µmol, 1.0 eq, 1 M in hexanes). The reaction was allowed to stir for 45 minutes before n-propyloxyran 39 (10 mg, 116 µmol, 1.4 eq) was added. After stirring at −20 °C for 1 h, aldehyde 116 (20 mg, 84.0 µmol, 1.0 eq) was added and the resulting mixture was allowed to stir at this temperature for 4 h before n-BuLi (85 µL, 85.0 µmol, 1.0 eq, 1 M in hexanes) was added. After stirring at −20 °C for 1 h, the reaction was quenched with saturated aqueous NH₄Cl solution (5 mL) and extracted with EtOAc (3 × 7 mL). The combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous MgSO₄ and solvent removed under vacuum. The residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:4) as eluent to afford the title compound 124 (11 mg, 60 %) as a white solid.

Mp: 78–80 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.06 (1H, s, OH), 7.13 (1H, d, J = 1.5 Hz, H₆), 6.88 (1H, d, J = 1.6 Hz, H₇), 6.78–6.70 (2H, m, H₉ and H₅), 6.44 (1H, d, J = 2.2 Hz, H₇), 5.81 (1H, d, J = 17.7 Hz, H₁₀a), 5.30 (1H, d, J = 10.8 Hz, H₁₀b), 4.02 (3H, s, H₁₁), 3.89 (3H, s, H₁₂).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.0 (C, C₆), 157.1 (C, C₈), 154.7 (C, C₁), 137.5 (C, C₃), 136.8 (CH, C₉), 117.2 (CH, C₄), 114.6 (CH₂, C₁₀), 110.5 (C, C₆a), 105.3 (CH, C₂), 99.9 (C, C₈a), 99.7 (CH, C₃), 98.7 (CH, C₇), 56.2 (CH₃, C₁₁), 55.4 (CH₃, C₁₂).

IR (Neat): ν (cm⁻¹) 3352, 2942, 1619, 1366.

To a solution of methyl \( p \)-tolyl sulfone (615 mg, 3.61 mmol, 1.0 eq) and racemic epoxide 39 (500 mg, 5.80 mmol, 1.6 eq) in toluene (20 mL) stirred at 60 °C was added dropwise \( n \)-BuLi (4.20 mL, 4.20 mmol, 1.2 eq, 1 M in hexane). The solution was allowed to stir at 65 °C for 16 h. The reaction was allowed to cool down to room temperature then quenched with saturated aqueous NH\( _4 \)Cl solution (30 mL) and extracted with Et\( _2 \)O (3 \times 30 mL). The combined ethereal layers were dried over anhydrous MgSO\( _4 \) and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc–hexanes (3:7) as eluent to afford the title compound 126 (785 mg, 82 %) as a yellow oil.

\(^1\)H NMR (400 MHz, CDCl\( _3 \)): \( \delta \) (ppm) 7.76 (2H, d, \( J = 8.3 \) Hz, H\(_9\)), 7.34 (2H, d, \( J = 8.1 \) Hz, H\(_9\)), 3.70–3.62 (1H, m, H\(_3\)), 3.31–3.24 (1H, m, H\(_{1a}\)), 3.21–3.12 (1H, m, H\(_{1b}\)), 2.43 (3H, s, H\(_{11}\)), 1.96–1.87 (1H, m, H\(_{2a}\)), 1.77–1.66 (1H, m, H\(_{2b}\)), 1.45–1.26 (4H, m, H\(_4\) and H\(_5\)), 0.87 (3H, t, \( J = 7.0 \) Hz, H\(_6\)).

\(^13\)C NMR (100 MHz, CDCl\( _3 \)): \( \delta \) (ppm) 144.6 (C, C\(_7\)), 136.2 (C, C\(_{10}\)), 129.9 (2 \times CH, C\(_9\)), 128.0 (2 \times CH, C\(_8\)), 69.7 (CH, C\(_3\)), 53.2 (CH\(_2\), C\(_1\)), 39.6 (CH\(_2\), C\(_4\)), 30.6 (CH\(_2\), C\(_2\)), 21.6 (CH\(_3\), C\(_{11}\)), 18.7 (CH\(_2\), C\(_5\)), 13.9 (CH\(_3\), C\(_6\)).

IR (Neat): \( \nu \) (cm\(^{-1}\)) 3482, 2557, 1597, 1285.

HRMS (ESI+): \( m/z \) calcd for C\(_{13}\)H\(_{20}\)NaO\(_3\)S ([M + Na]\(^+\)) 279.1025; found 279.1022.
5.2.14. tert-Butyldimethyl((1-tosylhexan-3-yl)oxy)silane (122)

To a solution of sulfone 126 (80 mg, 0.32 mmol, 1.0 eq) in CH$_2$Cl$_2$ (2 mL) was added imidazole (82 mg, 1.21 mmol, 3.9 eq) and TBS-Cl (80 mg, 0.53 mmol, 1.7 eq). The reaction was allowed to stir at room temperature for 16 h. The reaction was quenched with saturated aqueous NH$_4$Cl solution (5 mL) and extracted with CH$_2$Cl$_2$ (3 × 7 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:9) as eluent to afford the title compound 122 (785 mg, 82%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.76 (2H, d, $J = 8.0$ Hz, H$_8$), 7.34 (2H, d, $J = 8.5$ Hz, H$_9$), 3.73–3.70 (1H, m, H$_3$), 3.16–3.10 (2H, m, H$_1$), 2.44 (3H, s, H$_{11}$), 1.89–1.79 (1H, m, H$_{2a}$), 1.78–1.68 (1H, m, H$_{2b}$), 1.43–1.19 (4H, m, H$_4$ and H$_5$), 0.85 (3H, t, $J = 7.2$ Hz, H$_6$), 0.81 (9H, s, H$_{13}$), −0.02 (3H, s, H$_{12}$), −0.06 (3H, s, H$_{12}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 144.5 (C, C$_7$), 136.2 (C, C$_{10}$), 129.8 (2 × CH, C$_9$), 128.0 (2 × CH, C$_8$), 69.9 (CH, C$_3$), 52.3 (CH$_2$, C$_1$), 38.9 (CH$_2$, C$_4$), 29.6 (CH$_2$, C$_2$), 25.7 (3 × CH$_3$, C$_{14}$), 21.6 (CH$_3$, C$_{11}$), 18.4 (CH$_2$, C$_5$), 17.9 (C, C$_{13}$), 14.1 (CH$_3$, C$_6$), −4.5 (CH$_3$, C$_{12}$), −4.7 (CH$_3$, C$_{12}$).

IR (Neat): $\nu$ (cm$^{-1}$) 2956, 1598, 1315, 1143.

HRMS (ESI+): $m/z$ calcd for C$_{19}$H$_{34}$NaO$_3$SSi ([M + Na]$^+$) 393.1890; found 393.1887.
5.2.15. 1-(Naphthalen-2-yl)-2-tosylethyl acetate (134)

To a solution of 4-(methylsulfonyl)toluene (46 mg, 0.27 mmol, 1.0 eq) in THF (5 mL) at −78 °C was added dropwise n-BuLi (210 µL, 0.34 mmol, 1.1 eq, 1.6 M in hexanes). The solution was allowed to stir at −78 °C for 1 h before naphthalene 132 (52 mg, 0.33 mmol, 1.0 eq) was added portionwise. The reaction was allowed to stir at −78 °C for 2 h before Ac₂O (220 µL, 0.98 mmol, 3.3 eq) was added to the solution. After stirring at −78 °C for 3 h, the reaction was quenched with saturated aqueous NH₄Cl solution (7 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:9) as eluent to afford the title compound 134 (57 mg, 53 %) as a white solid.

Mp: 110–112 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.80–7.29 (11H, m, H_ar), 6.38 (1H, dd, J = 9.6, 2.8 Hz, H₉), 3.89 (1H, dd, J = 14.8, 9.5 Hz, H₁₀a), 3.50 (1H, dd, J = 14.9, 3.0 Hz, H₁₀b), 2.41 (3H, s, H₁₇), 1.87 (3H, s, H₁₂).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.3 (C, C₁₁), 144.9 (C, C₁₆), 136.5 (C, C₁₂), 135.0 (C, C₁₉), 133.3 (C, C₁₅), 133.0 (C, C₁₈), 129.9 (2 × CH, C₁₅), 128.9 (CH, C₁₉), 128.3 (2 × CH, C₁₄), 128.1 (CH, C₁₆), 127.7 (CH, C₁₈), 126.7 (CH, C₁₇), 126.6 (CH, C₁₄), 126.0 (CH, C₁₃), 123.5 (CH, C₁₉), 70.1 (CH, C₉), 61.2 (CH₂, C₁₀), 21.6 (CH₃, C₁₇), 20.8 (CH₃, C₁₂).

IR (Neat): ν (cm⁻¹) 3352, 2923, 1735, 1138.

HRMS (ESI+): m/z calcd for C₂₁H₂₀NaO₄S ([M + Na]⁺) 391.0975; found 391.0980.
5.2.16. (S)-2-Propyloxetane (138)

To a solution of trimethylsulfoxonium iodide (15.3 g, 70.0 mmol, 2.0 eq) and potassium tert-butoxide (7.81 g, 70.0 mmol, 2.0 eq) in tert-butanol (45 mL) stirred at 60 °C for 1 h was added the (S)-2-propyloxirane 39 (3.00 g, 35.0 mmol, 1.0 eq). The reaction mixture was allowed to stir at 60 °C for 16 h, then was quenched with H₂O (40 mL). The solution was extracted with pentane (3 × 50 mL), the organic extracts were dried over anhydrous MgSO₄ and the solvent was removed in vacuo to afford the title compound 138 (34.0 g) as solution in tert-butanol.

Due to the difficulty to obtain oxetane 138 pure, the NMR spectra were obtained in solution in tert-butanol and DMSO.

**¹H NMR** (400 MHz, CDCl₃): δ (ppm) 4.81 (1H, qu, J = 6.9 Hz, H₄), 4.64 (1H, td, J = 8.0, 5.9 Hz, H₂a), 4.47 (1H, td, J = 9.0, 5.8 Hz, H₂b), 2.63 (1H, m, H₃a), 2.31 (1H, m, H₃b), 1.78 (1H, m, H₅a), 1.61 (1H, m, H₅b), 1.32 (2H, m, H₆), 0.92 (3H, t, J = 7.4 Hz, H₇).

**¹³C NMR** (100 MHz, CDCl₃): δ (ppm) 82.7 (CH, C₂), 68.1 (CH₂, C₄), 40.1 (CH₂, C₃), 27.7 (CH₂, C₅), 17.4 (CH₂, C₆), 13.9 (CH₃, C₇).
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5.2.17. (S)-1-((1-Phenyl-1H-tetrazol-5-yl)thio)hexan-3-ol (137)

![Chemical Structure](image)

To a solution of oxetane 138 in tert-butanol (2.00 g) and DMF (30 mL) was added phenyltetrazole thiol (4.55 g, 52.0 mmol, 1.5 eq) and LiBr (2.45 g, 52.0 mmol, 1.5 eq) at room temperature. The solution was allowed to stir at room temperature for 36 h and then was quenched with H₂O and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel using EtOAc–PE (2:3) as eluent to afford the title compound 137 (3.45 g, 30 % over 4 steps) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.57 (5H, m, H₉), 3.76 (1H, br, H₃), 3.59 (1H, ddd, J = 13.8, 8.7, 6.9 Hz, H₁₁), 3.49 (1H, ddd, J = 13.6, 7.3, 4.8 Hz, H₁₉), 2.80 (1H, d, J = 4.9 Hz, OH), 2.04–1.86 (2H, m, H₂₈ and H₂₉), 1.40–1.20 (4H, m, H₆ and H₅), 0.92 (3H, t, J = 6.9 Hz, H₆).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 155.0 (C, C₇), 133.7 (C, C₈), 130.2 (2 × CH, C₁₀), 129.8 (2 × CH, C₉), 123.9 (CH, C₁₁), 69.2 (CH, C₃), 39.5 (CH₂, C₂), 37.3 (CH₂, C₁), 30.1 (CH₂, C₄), 18.9 (CH₂, C₃), 14.1 (CH₃, C₀).

IR (Neat): ν (cm⁻¹) 3388, 2956, 1596, 1499.

HRMS (ESI+): m/z calcd for C₁₃H₁₈N₄NaOS ([M + Na]⁺) 301.1094; found 301.1099.

[α]²⁰D: +10.4 (c 1.00, CHCl₃).

(R)-137 [α]²⁵D: −9.9 (c 1.00, CHCl₃).

Chiral HPLC: Column DAICEL CHIRALPAK® AD-H, iPrOH – hexanes (1:9), 0.5 mL/min, retention time 45.70 min, 99 % e.e.

(R)-137 Chiral HPLC: Column DAICEL CHIRALPAK® AD-H, iPrOH – hexanes (1:9), 0.5 mL/min, retention time 43.71 min, 99 % e.e.

¹Yield were calculated from (±)-epichlorohydrin as no purifications were done in 4 steps.
5.2.18. (S)-5-((3-((tert-Butyldimethylsilyl)oxy)hexyl)thio)-1-phenyl-1H-tetrazole (327)

To a solution of thioether 137 (3.45 g, 12.0 mmol, 1.0 eq) in CH$_2$Cl$_2$ (50 mL) was added TBS-Cl (4.70 g, 31.0 mmol, 2.5 eq), DMAP (0.51 g, 4.20 mmol, 0.3 eq) and imidazole (2.50 g, 37.1 mmol, 3.0 eq). The resulting solution was allowed to stir at room temperature for 16 h. The reaction was quenched with 1 M aqueous NaOH solution (50 mL). The chlorinated extract was washed with H$_2$O (50 mL) and saturated aqueous NaCl solution (50 mL), then dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:19) as eluent to afford the title compound 327 (4.78 g, 98 %) as a white solid.

Mp: 38–40 °C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) 7.55 (5H, m, H$_{ar}$), 3.80 (1H, qu, $J = 5.7$ Hz, H$_3$), 3.42 (2H, m, H$_1$), 1.94 (2H, m, H$_2$), 1.46 (2H, m, H$_4$), 1.32 (2H, m, H$_3$), 0.90–0.87 (12H, m, H$_6$ and H$_{14}$), 0.04 (6H, m, H$_{12}$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) 154.5 (C, C$_7$), 133.8 (C, C$_8$), 130.1 (CH, C$_{11}$), 129.7 (2× CH, C$_{10}$), 123.8 (2× CH, C$_9$), 70.7 (CH, C$_3$), 39.2 (CH$_2$, C$_1$), 36.1 (CH$_2$, C$_2$), 29.5 (CH$_2$, C$_4$), 25.9 (3× CH$_3$, C$_{14}$), 18.3 (CH$_2$, C$_5$), 18.1 (C, C$_{13}$), 14.3 (CH$_3$, C$_6$), −4.4 (CH$_3$, C$_{12}$), −4.5 (CH$_3$, C$_{12}$).

IR (Neat): $\nu$ (cm$^{-1}$) 2956, 1597, 1500, 1248.

HRMS (ESI+): $m/z$ calcld for C$_{19}$H$_{32}$N$_4$NaOSSi ([M + Na]$^+$) 415.1958; found 415.1945.

$[\alpha]$$^D_{19}$: +13.6 (c 1.00, CHCl$_3$).

(R)-327 $[\alpha]$$^D_{25}$: −13.3 (c 1.00, CHCl$_3$).
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5.2.19. (S)-5-((3-((tert-Butyldimethylsilyl)oxy)hexyl)sulfonyl)-1-phenyl-1H-tetrazole (119)

![Diagram](image)

To a solution of sulfide 327 (4.73 g, 17.0 mmol, 1.0 eq) in EtOH (50 mL) at 0 °C was added ammonium paramolybdate (2.75 g, 2.31 mmol, 0.1 eq) and hydrogen peroxide (20 mL, 0.17 mol, 10 eq, 30 % in H2O). The solution was allowed to warm up to room temperature over 1 h and was stirred for 48 h. The solvent was removed in vacuo and the crude was diluted with EtOAc (30 mL). The organic layers were sequentially washed with H2O (30 mL) and saturated aqueous NaCl solution (30 mL). The organic extract was dried over anhydrous MgSO4, and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:4) as eluent to afford the title compound 119 (4.95 g, 94 %) as a colourless oil.

$^1$H NMR (400 MHz, CDCl3): $\delta$ (ppm) 7.68–7.70 (2H, m, H9), 7.57–7.63 (3H, m, H10 and H11), 3.87–3.92 (1H, m, H3), 3.37–3.83 (2H, m, H1), 2.10–2.18 (1H, m, H2b), 1.97–2.07 (1H, m, H2a), 1.25–1.56 (4H, m, H4 and H5), 0.89 (12H, m, H6 and H14), 0.07 (3H, s, H12), 0.06 (3H, s, H12).

$^{13}$C NMR (100 MHz, CDCl3): $\delta$ (ppm) 153.5 (C, C7), 133.1 (C, C8), 131.5 (CH, C11), 129.7 (2 × CH, C10), 125.1 (2 × CH, C9), 69.7 (CH, C3), 52.5 (CH2, C1), 39.0 (CH2, C2), 28.7 (CH2, C4), 25.8 (3 × CH3, C14), 18.5 (CH2, C5), 18.0 (C, C13), 14.1 (CH3, C6), −4.5 (CH3, C12), −4.6 (CH3, C12).

IR (Neat): $\nu$ (cm$^{-1}$) 2957, 1596, 1498, 1340.

HRMS (ESI+): m/z calcd for C19H33N4O3SSi ([M + H]$^+$) 425.2037; found 425.2039.

$[\alpha]^2_D +2.7$ (c 1.00, CHCl3).

(R)-119 $[\alpha]^2_D: -3.1$ (c 1.01, CHCl3).
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5.2.20. (E)-tert-Butyl(1-(4-((tert-butyldimethylsilyl)oxy)-5,7-dimethoxynaphthalen-2-yl)hept-1-en-4-yl)oxy)dimethylsilane (139)

To a solution of sulfone 119 (740 mg, 1.74 mmol, 1.3 eq) in THF (6 mL) at −78 °C was added dropwise a solution of KHMDS (4.40 mL, 2.07 mmol, 1.4 eq, 0.47 M in toluene). The resulting solution was allowed to stir at −78 °C for 30 min, then a solution of aldehyde 117 (506 mg, 1.46 mmol, 1.0 eq) and lithium chloride (90 mg, 2.10 mmol, 1.5 eq) in THF (3 mL) was added dropwise, then the solution was allowed to warm up to room temperature over 16 h. The reaction was quenched with saturated aqueous NH₄Cl solution (10 mL) and extracted with EtOAc (10 mL), washed with water (2 × 15 mL) and saturated aqueous NaCl solution (2 × 15 mL). The organic phase was dried over anhydrous MgSO₄, and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:19) as eluent to afford the title compound 139 (711 mg, 89 %) as clear yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.14 (1H, d, J = 1.5 Hz, H₄), 6.78 (1H, d, J = 1.7 Hz, H₂), 6.63 (1H, d, J = 2.3 Hz, H₃), 6.40 (1H, d, J = 14.8 Hz, H₅), 6.38 (1H, d, J = 2.0 Hz, H₇), 6.24 (1H, dd, J = 15.1, 7.5 Hz, H₁₀), 3.88 (3H, s, H₁₇), 3.86 (3H, s, H₁₆), 3.79 (1H, qu, J = 5.6 Hz, H₁₂), 2.42–2.31 (2H, m, H₁₁), 1.50–1.35 (4H, m, H₁₃ and H₁₄), 1.06 (9H, s, H₂₀), 0.92 (12H, m, H₁₅ and H₂₃), 0.23 (6H, s, H₁₈), 0.06 (6H, s, H₂₁).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.2 (C, C₈), 158.1 (C, C₆), 152.6 (C, C₁), 138.5 (C, C₄₄), 136.4 (C, C₃), 131.7 (CH, C₁₀), 128.0 (CH, C₉), 118.6 (CH, C₄), 114.7 (C, C₈₆), 111.2 (CH, C₂), 98.6 (CH, C₅), 97.8 (CH, C₇), 72.1 (CH, C₁₂), 55.2 (CH₃, C₁₇), 55.1 (CH₃, C₁₆), 41.2 (CH₂, C₁₁), 39.6 (CH₂, C₁₃), 26.0 (3 × CH₃, C₂₀), 25.9 (3 × CH₃, C₂₃), 18.7 (CH₂, C₁₄), 18.6 (C, C₁₉), 18.2 (C, C₂₂), 14.3 (CH₃, C₁₅), −4.3 (2 × CH₃, C₁₈), −4.5 (2 × CH₃, C₂₁).

IR (Neat): ν (cm⁻¹) 2954, 1600, 1378, 1162.

HRMS (ESI+): m/z calcd for C₃₁H₅₃O₄Si₂ ([M + H]^+) 545.3477; found 545.3467.
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5.3. Attempted synthesis via hypervalent iodine cyclisation

5.3.1. (E)-3-(4-((tert-Butyldimethylsilyl)oxy)hept-1-en-1-yl)-6,8-dimethoxynaphthalen-1-ol (145)

To a solution of naphthalene 139 (145 mg, 0.27 mmol, 1.0 eq) in acetonitrile (4.75 mL) and water (0.15 mL) at 50 °C was added DBU (100 µL, 0.68 mmol, 2.6 eq). The resulting solution was allowed to stir for 1 h then quenched with saturated aqueous NH₄Cl solution (5 mL) and extracted with Et₂O (10 mL). The combined organic layers were washed with H₂O (30 mL) and saturated aqueous NaCl solution (30 mL), then dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9) as eluent to afford the title compound 145 (109 mg, 95 %) as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.04 (1H, s, OH), 7.06 (1H, d, J = 1.5 Hz, H₄), 6.84 (1H, d, J = 0.7 Hz, H₂), 6.68 (1H, d, J = 2.5 Hz, H₃), 6.41 (2H, m, H₇ and H₉), 6.30 (1H, dd, J = 14.5, 8.0 Hz, H₁₀), 4.01 (3H, s, H₁₇), 3.88 (3H, s, H₁₆), 3.78 (1H, qu, J = 5.7 Hz, H₁₂), 2.35–2.41 (2H, m, H₁₁), 1.24–1.50 (4H, m, H₁₃ and H₁₄), 0.90 (12H, m, H₁₅ and H₂₀), 0.06 (6H, s, H₁₈).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 157.9 (C, C₈), 157.2 (C, C₆), 154.6 (C, C₁), 137.8 (C, C₄a), 137.6 (C, C₃), 131.7 (CH, C₁₀), 128.4 (CH, C₉), 116.5 (CH, C₄), 110.0 (C, C₈a), 105.6 (CH, C₂), 99.6 (CH, C₅), 97.4 (CH, C₇), 72.1 (CH, C₁₂), 56.1 (CH₃, C₁₇), 55.4 (CH₃, C₁₆), 41.3 (CH₂, C₁₁), 39.4 (CH₂, C₁₃), 26.0 (3 × CH₃, C₂₀), 18.7 (CH₂, C₁₄), 18.2 (C, C₁₉), 14.3 (CH₃, C₁₅), −4.3 (CH₃, C₁₈), −4.5 (CH₃, C₁₈).

IR (Neat): ν (cm⁻¹) 3428, 2955, 1629, 1374.

HRMS (ESI+): m/z calcd for C₂₅H₉₉O₄Si ([M + H]⁺) 431.2612; found 431.2596.
5.3.2. (E)-3-(4-(tert-Butyldimethylsilyloxy)hept-1-en-1-yl)-6,8-dimethoxynaphthalen-1-yl formate (147)

To a solution of naphthol 145 (9.5 mg, 22.1 µmol, 1.0 eq) in pyridine (0.5 mL) was added acetic formic anhydride* (0.2 mL) and DMAP (2 crystals). The reaction was allowed to stir at 0 °C for 16 h. The reaction was then quenched with saturated aqueous CuSO₄ solution (2 mL) and extracted with EtOAc (5 mL). The organic layer was sequentially washed with saturated aqueous CuSO₄ solution (5 mL), H₂O (5 mL) and saturated aqueous NaCl solution (5 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:9) as eluent to afford the title compound 147 (6.5 mg, 75%) as yellow oil.

**¹H NMR (400 MHz, CDCl₃):** δ (ppm) 8.32 (1H, s, H₂₁), 7.43 (1H, d, J = 1.4 Hz, H₄), 6.54 (1H, d, J = 1.5 Hz, H₂), 6.67 (1H, d, J = 2.1 Hz, H₅), 6.47–6.43 (2H, m, H₇ and H₉), 6.30 (1H, td, J = 15.2, 7.6 Hz, H₁₀), 3.89 (3H, s, H₁₇), 3.87 (3H, s, H₁₆), 3.78 (1H, m, H₁₂), 2.39 (2H, m, H₁₁), 1.50–1.24 (4H, m, H₁₃ and H₁₄), 0.91 (12H, m, H₁₅ and H₂₀), 0.06 (6H, s, H₁₈).

**¹³C NMR (100 MHz, CDCl₃):** δ (ppm) 160.4 (CH, C₂₁), 158.7 (C, C₈), 156.6 (C, C₆), 146.2 (C, C₁), 138.0 (C, C₄₈), 136.5 (C, C₃), 130.7 (CH, C₁₀), 129.3 (CH, C₉), 123.4 (CH, C₂), 114.5 (CH, C₄), 113.5 (C, C₈₄), 99.3 (CH, C₃), 99.1 (CH, C₇), 72.0 (CH, C₁₂), 55.8 (CH₃, C₁₇), 55.3 (CH₃, C₁₈), 41.3 (CH₂, C₁₁), 39.4 (CH₂, C₁₃), 25.9 (3 × CH₃, C₂₀), 18.7 (CH₂, C₁₄), 18.2 (C, C₁₉), 14.3 (CH₃, C₁₅), −4.3 (CH₃, C₁₆), −4.5 (CH₃, C₁₈).

**IR (Neat):** ν (cm⁻¹) 2955, 1764, 1743, 1626.

**HRMS (ESI+):** m/z calcd for C₂₆H₃₈NaO₅Si ([M + Na]+) 481.2381; found 481.2374.

* Acetic formic anhydride was prepared from the reaction of acetic anhydride (4.7 mL) and formic acid (2.1 mL) at 50 °C for 2 h.
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5.3.3. (E)-3-(4-((tert-Butyldimethylsilyl)oxy)hept-1-en-1-yl)-2-iodo-6,8-dimethoxynaphthalen-1-ol (151)

To a solution of alcohol 145 (109 mg, 0.25 mmol, 1.0 eq) in dry CH₂Cl₂ (10 mL), morpholine-iodine complex (112 mg, 0.33 mmol, 1.3 eq) was added. The solution was allowed to stir at room temperature for 1 h then quenched with saturated aqueous Na₂S₂O₃ solution (10 mL) and extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were sequentially washed with saturated aqueous NaHCO₃ solution (30 mL) then saturated aqueous NaCl solution (30 mL). The organic extract was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9) as eluent to afford the title compound 151 (110 mg, 78%) as a white solid.

Mp: 79–81 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.13 (1H, s, OH), 7.31 (1H, s, H₄), 6.75 (1H, d, J = 15.5 Hz, H₉), 6.68 (1H, d, J = 2.2 Hz, H₅), 6.44 (1H, d, J = 2.2 Hz, H₇), 6.16 (1H, td, J = 15.1, 7.5 Hz, H₁₀), 4.02 (3H, s, H₁₇), 3.98 (3H, s, H₁₆), 3.82 (1H, qu, J = 5.6 Hz, H₁₂), 2.45 (2H, m, H₁₁), 1.55–1.29 (4H, m, H₁₃ and H₁₄), 0.95–0.91 (12H, m, H₁₅ and H₂₀), 0.09 (3H, s, H₁₈), 0.08 (3H, s, H₁₈).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.2 (C, C₈), 155.9 (C, C₆), 153.1 (C, C₁), 140.6 (C, C₄a), 136.7 (C, C₃), 136.3 (CH, C₉), 130.4 (CH, C₁₀), 115.5 (CH, C₄), 109.3 (C, C₈a), 99.6 (CH, C₅), 97.4 (CH, C₇), 81.7 (C, C₂), 72.1 (CH, C₁₂), 56.4 (CH₃, C₁₇), 55.4 (CH₃, C₁₆), 41.0 (CH₂, C₁₁), 39.3 (CH₂, C₁₃), 26.0 (3 × CH₃, C₂₀), 18.7 (CH₂, C₁₄), 18.2 (C, C₁₉), 14.3 (CH₃, C₁₅), −4.3 (CH₃, C₁₈), −4.5 (CH₃, C₁₈).

IR (Neat): ν (cm⁻¹) 3331, 2952, 2916, 1355.

HRMS (ESI+): m/z calcd for C₂₅H₃₈IO₄Si ([M + H]⁺) 557.1579; found 557.1557.
5.3.4. (E)-tert-Butyl((1-(4-(ethoxymethoxy)-3-iodo-5,7-dimethoxynaphthalen-2-yl)hept-1-en-4-yl)oxy)dimethylsilane (154)

To a stirred solution of 151 (141 mg, 0.25 mmol, 1.0 eq) in Et₂O (2 mL) and DMF (0.2 mL) at room temperature was added portionwise sodium hydride (20 mg, 0.50 mmol, 2.0 eq, 60 % dispersion in oil). The resulting solution was allowed to stir for 30 minutes, then ethoxymethyl chloride (33 µL, 0.36 mmol, 1.4 eq) was added dropwise. The reaction was allowed to stir at room temperature for 1 h. The reaction was quenched with H₂O (5 mL) and extracted with Et₂O (2 × 10 mL). The organic layer was washed with 1 N aqueous NaOH solution (15 mL) and saturated aqueous NaCl solution (15 mL). The ethereal layer was dried over anhydrous MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexanes (1:9) as eluent to afford the title compound 154 (152 mg, 98 %) as an orange oil.

**¹H NMR** (500 MHz, CDCl₃): δ (ppm) 7.55 (1H, s, H₄), 6.75 (1H, d, J = 15.5 Hz, H₉), 6.70 (1H, d, J = 2.2 Hz, H₃), 6.48 (1H, d, J = 2.1 Hz, H₂), 6.13 (1H, dt, J = 15.0, 7.5 Hz, H₁₀), 5.12 (2H, s, H₁₈), 4.04 (2H, q, J = 7.0 Hz, H₂₀), 3.94 (3H, s, H₁₆), 3.90 (3H, s, H₁₇), 3.83 (1H, qu, J = 5.8 Hz, H₁₂), 2.45 (2H, br, H₁₁), 1.54–1.33 (4H, br, H₁₃ and H₁₄), 1.30 (3H, t, J = 7.1 Hz, H₂₁), 0.93 (3H, t, J = 7.3 Hz, H₁₅), 0.91 (9H, s, H₂₄), 0.09 (3H, s, H₂₂), 0.08 (3H, s, H₂₂).

**¹³C NMR** (125 MHz, CDCl₃): δ (ppm) 158.4 (C, C₈), 155.9 (C, C₆), 152.2 (C, C₁), 140.3 (C, C₄₄), 137.8 (C, C₃), 136.3 (CH, C₉), 130.4 (CH, C₁₀), 120.8 (CH, C₄), 115.0 (C, C₈₆), 99.3 (CH₂, C₁₈), 99.6 (CH, C₅), 97.4 (CH, C₇), 93.7 (C, C₂), 72.1 (CH, C₁₂), 66.7 (CH₂, C₂₀), 56.0 (CH₃, C₁₆), 55.3 (CH₃, C₁₇), 41.0 (CH₂, C₁₁), 39.3 (CH₂, C₁₃), 26.0 (3 × CH₃, C₂₄), 18.7 (CH₂, C₁₄), 18.2 (C, C₂₃), 15.3 (CH₃, C₂₁), 14.3 (CH₃, C₁₅), −4.3 (CH₃, C₂₂), −4.5 (CH₃, C₂₂).

**IR** (Neat): ν (cm⁻¹) 2955, 1618, 1572, 1333.

**HRMS** (ESI+): m/z calcd for C₂₈H₄₄IO₅Si ([M + H]⁺) 615.1997; found 615.1976.
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5.3.5. (E)-tert-Butyl((1-(4-(ethoxymethoxy)-5,7-dimethoxynaphthalen-2-yl)hept-1-en-4-yl)oxy)dimethylsilane (159)

To a solution of halide 154 (15.5 mg, 25.0 mmol, 1.0 eq) in THF (1 mL) stirred at −78 °C was added dropwise n-BuLi (25 µL, 37.0 mmol, 1.5 eq, 1.48 M in toluene). The solution was allowed to stir at this temperature for 30 min, then ethyl chloroformate (7 mg, 74.0 mmol, 2.9 eq) was added dropwise. The resulting solution was allowed to stir at −78 °C for 1 h. The solution was quenched with H₂O (2 mL) and extracted with EtOAc (5 mL). The organic layer was sequentially washed with H₂O (5 mL) and saturated aqueous NaCl solution (5 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent residue removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9) as eluent to afford the title compound 159 (10 mg, 84 %) as a yellow oil.

**¹H NMR** (400 MHz, CDCl₃): δ (ppm) 7.22 (1H, s, H₄), 7.00 (1H, s, H₂), 6.67 (1H, d, J = 1.0 Hz, H₃), 6.46–6.42 (2H, m, H; and H₈), 6.31 (1H, td, J = 15.2, 7.6 Hz, H₁₀), 5.29 (2H, s, H₁₈), 3.91–3.83 (8H, m, H₁₂, H₁₇ and H₁₉), 3.78 (1H, m, H₁₁), 3.79 (2H, m, H₁₁), 1.50–1.14 (4H, m, H₁₃ and H₁₄), 1.28 (3H, t, J = 7.0 Hz, H₂₁), 0.90 (12H, m, H₁₅ and H₂₄), 0.64 (6H, s, H₂₂).

**¹³C NMR** (100 MHz, CDCl₃): δ (ppm) 158.2 (C, C₆), 157.9 (C, C₁), 154.4 (C, C₆), 138.3 (C, C₃), 136.5 (C, C₄₈), 131.6 (CH, C₉), 128.4 (CH, C₁₀), 119.8 (CH, C₄), 113.5 (C, C₆₈), 108.7 (CH, C₂), 99.0 (CH, C₅), 98.8 (CH, C₇), 95.5 (CH₂, C₁₈), 72.2 (CH, C₁₂), 64.5 (CH₂, C₂₀), 56.1 (CH₃, C₁₆), 55.3 (CH₃, C₁₇), 41.3 (CH₂, C₁₁), 39.6 (CH₂, C₁₃), 25.9 (3 × CH₃, C₂₃), 18.7 (CH₂, C₁₄), 18.2 (CH₂, C₂₃), 15.2 (CH₃, C₂₁), 14.3 (CH₃, C₁₅), −4.3 (CH₃, C₂₂), −4.5 (CH₃, C₂₂).

**IR** (Neat): ν (cm⁻¹) 2856, 1621, 1463, 1040.

**HRMS** (ESI+): m/z calcd for C₂₈H₄₄NaO₅Si ([M + Na]+) 511.2850; found 511.2836.
5.3.6. \((E)-3-(4-((\text{tert-Butyldimethylsilyl})\text{oxy})\text{hept-1-en-1-yl})-2\text{-iodo-6,8-dimethoxynaphthalen-1-yl acetate} \ (153)\)

Acetic anhydride (0.20 mL, 2.11 mmol, 4.8 eq) was added dropwise to a stirred solution of alcohol \(151\) (246 mg, 0.44 mmol, 1.0 eq) and DMAP (16 mg, 0.13 mmol, 0.3 eq) in pyridine (5 mL). After stirring at room temperature for 1 h, the solution was diluted with \(\text{Et}_2\text{O}\) (15 mL) and washed with saturated aqueous CuSO\(_4\) solution (3 \(\times\) 15 mL) followed by \(\text{H}_2\text{O}\) (15 mL) then saturated aqueous NaCl solution (15 mL). The organic extract was dried over anhydrous MgSO\(_4\) and the solvent was removed \textit{in vacuo}. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9) as eluent to afford the \textit{title compound} \(153\) (238 mg, 90\%) as a yellow oil.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.62 (1H, s, H\(_4\)), 6.71 (2H, m, H\(_5\) and H\(_9\)), 6.47 (1H, d, \(J = 2.1\) Hz, H\(_7\)), 6.17 (1H, td, \(J = 15.0, 7.5\) Hz, H\(_{10}\)), 3.89 (3H, s, H\(_{17}\)), 3.88 (3H, s, H\(_{16}\)), 3.84 (1H, qu, \(J = 5.7\) Hz, H\(_{12}\)), 2.48–2.42 (5H, m, H\(_{11}\) and H\(_{20}\)), 1.55–1.33 (4H, m, H\(_{13}\) and H\(_{14}\)), 0.95–0.95 (12H, m, H\(_{15}\) and H\(_{23}\)), 0.10 (3H, s, H\(_{21}\)), 0.09 (3H, s, H\(_{21}\)).

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) (ppm) 168.9 (C, C\(_{18}\)), 158.7 (C, C\(_6\)), 155.4 (C, C\(_8\)), 146.7 (C, C\(_1\)), 139.8 (C, C\(_3\)), 137.1 (C, C\(_2\)), 135.7 (CH, H\(_{10}\)), 131.1 (CH, H\(_{11}\)), 122.1 (CH, H\(_4\)), 114.6 (C, C\(_{8a}\)), 99.6 (CH, H\(_5\)), 98.6 (CH, H\(_7\)), 92.7 (C, C\(_{4a}\)), 71.9 (CH, H\(_{12}\)), 56.2 (CH\(_3\), C\(_{17}\)), 55.4 (CH\(_3\), C\(_{16}\)), 41.0 (CH\(_2\), C\(_{11}\)), 39.3 (CH\(_2\), C\(_{13}\)), 26.0 (3 \(\times\) CH\(_3\), 3xC\(_{23}\)), 21.3 (CH\(_3\), C\(_{20}\)), 18.7 (CH\(_2\), C\(_{14}\)), 18.2 (C, C\(_{22}\)), 14.3 (CH\(_3\), C\(_{15}\)), –4.3 (CH\(_3\), C\(_{21}\)), –4.5 (CH\(_3\), C\(_{21}\)).

\textit{IR} (Neat): \(\nu\) (cm\(^{-1}\)) 2955, 1775, 1619, 1196.

\textit{HRMS} (ESI\(^+\)): \(m/z\) calcd for C\(_{27}\)H\(_{39}\)INaO\(_5\)Si ([M + Na\(^+\)]\(^\ddagger\)) 621.1504; found 621.1504.
5.3.7. Methyl (E)-3-(4-((tert-butyldimethylsilyl)oxy)hept-1-en-1-yl)-1-(ethoxymethoxy)-6,8-dimethoxy-2-naphthoate (161)

To a suspension of iodonaphthalene 154 (112 mg, 0.18 mmol, 1.0 eq), palladium acetate (3.8 mg, 0.021 µmol, 0.01 eq) and triethylamine (25 µL, 0.20 mmol, 1.1 eq) in MeOH (7 mL) was bubbled carbon monoxide for 3 min, then the flask was sealed and heated to 120 °C for 3 days. After cooling to room temperature the solution was filtrated through a pad of Celite® and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc–PE (3:17) as eluent to afford the title compound 161 (70 mg, 72%) as a yellow oil.

\(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) (ppm) 7.53 (1H, s, H₄), 6.68 (1H, s, H₅), 6.46 (1H, s, H₇), 6.41 (1H, d, \(J = 15.5\) Hz, H₉), 6.27 (1H, dt, \(J = 14.5, 7.2\) Hz, H₁₀), 5.11 (2H, s, H₂₂), 3.91 (3H, s, H₁₆), 3.90 (3H, s, H₁₇), 3.87 (3H, s, H₂₁), 3.77 (3H, br, H₁₂ and H₂₃), 2.37 (2H, br, H₁₁), 1.44–1.28 (4H, br, H₁₃ and H₁₄), 1.25 (3H, t, \(J = 7.1\) Hz, H₂₄), 0.90 (12H, s, H₂₇ and H₁₅), 0.08 (6H, s, H₂₅).

\(^1\)C NMR (100 MHz, CDCl₃): \(\delta\) (ppm) 168.7 (C, C₂₀), 159.0 (C, C₆), 157.2 (C, C₆), 150.6 (C, C₁), 138.4 (C, C₄₄), 134.1 (C, C₃), 128.5 (CH, C₉), 130.8 (CH, C₁₀), 120.1 (CH, C₄), 114.2 (C, C₈₉), 100.2 (CH₂, C₂₂), 99.2 (CH, C₃), 99.1 (CH, C₇), 123.8 (C, C₂), 72.0 (CH, C₁₂), 65.6 (CH₂, C₂₂), 55.9 (CH₃, C₁₆), 55.3 (CH₃, C₁₇), 52.1 (CH₃, C₂₁), 41.4 (CH₂, C₁₁), 39.2 (CH₂, C₁₃), 26.0 (3 × CH₃, C₂₇), 18.7 (CH₂, C₁₄), 18.2 (C, C₂₆), 15.3 (CH₃, C₂₃), 14.3 (CH₃, C₁₅), -4.3 (CH₃, C₂₅), -4.5 (CH₃, C₂₅).

IR (Neat): \(\nu\) (cm⁻¹) 2954, 1732, 1620, 1258.

HRMS (ESI+): \(m/z\) calcd for C₃₀H₄₆NaO₇Si ([M + Na]+) 569.2805; found 569.2909.
5.3.8. (E)-Methyl 1-acetoxy-3-(4-((tert-butyldimethylsilyl)oxy)hept-1-en-1-yl)-6,8-dimethoxy-2-naphthoate (143)

To a suspension of iodonaphthalene 153 (238 mg, 0.40 mmol, 1.0 eq), palladium acetate (12 mg, 53 µmol, 0.1 eq) and triethylamine (50 µL, 0.36 mmol, 0.9 eq) in MeOH (7 mL) was bubbled carbon monoxide for 3 min, then the flask was sealed and heated to 120 °C for 3 days. After cooling to room temperature the solution was filtrated through a pad of Celite® and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc–PE (3:17) as eluent to afford the title compound 143 (170 mg, 80%) as a clear yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.63 (1H, s, H$_4$), 6.71 (1H, s, H$_5$), 6.48 (2H, br, H$_7$ and H$_9$), 6.30 (1H, dt, $J = 15.0$, 7.4 Hz, H$_{10}$), 3.91 (3H, s, H$_{17}$), 3.90 (3H, s, H$_{16}$), 3.87 (3H, s, H$_{21}$), 3.79 (1H, qu, $J = 5.7$ Hz, H$_{12}$), 2.37 (2H, m, H$_{11}$), 2.31 (3H, s, H$_{19}$), 1.44–1.28 (4H, m, H$_{13}$ and H$_{14}$), 0.90 (12H, m, H$_{15}$ and H$_{24}$), 0.07 (6H, s, H$_{22}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 169.3 (C, C$_{20}$), 167.4 (C, C$_{18}$), 159.3 (C, C$_8$), 156.8 (C, C$_6$), 144.8 (C, C$_1$), 137.9 (C, C$_{4a}$), 134.4 (C, C$_3$), 131.1 (CH, C$_{10}$), 128.4 (CH, C$_9$), 121.9 (CH, C$_4$), 121.5 (C, C$_2$), 113.6 (C, C$_{9a}$), 99.8 (CH, C$_3$), 98.8 (CH, C$_7$), 71.9 (CH, C$_{12}$), 56.1 (CH$_3$, C$_{17}$), 55.4 (CH$_3$, C$_{16}$), 52.3 (CH$_3$, C$_{21}$), 41.4 (CH$_2$, C$_{11}$), 39.2 (CH$_2$, C$_{13}$), 25.9 (3 × CH$_3$, C$_{2a}$), 20.4 (CH$_3$, C$_{19}$), 18.7 (CH$_2$, C$_{14}$), 18.2 (C, C$_{23}$), 14.3 (CH$_3$, C$_{15}$), −4.3 (CH$_3$, C$_{22}$), −4.5 (CH$_3$, C$_{22}$).

IR (Neat): ν (cm$^{-1}$) 2955, 1771, 1730, 1623.

HRMS (ESI+): $m/z$ calcd for C$_{29}$H$_{42}$NaO$_7$Si ([M + Na]$^+$) 553.2592; found 553.2570.
5.4. Revised synthetic strategy: oxidation of alkenes 143 and 139

5.4.1. Methyl (E)-1-acetoxy-7-bromo-3-(4-((tert-butyldimethylsilyl)oxy)hept-1-en-1-yl)-6,8-dimethoxy-2-naphthoate (174) and methyl (E)-1-acetoxy-3-(4-((tert-butyldimethylsilyl)oxy)hept-1-en-1-yl)-7-iodo-6,8-dimethoxy-2-naphthoate (173).

To a solution of naphthalene 143 (14.8 mg, 27 µmol, 1.0 eq) in AcOH (0.5 mL) were added sodium periodate (4 mg, 19 µmol, 0.7 eq) and LiBr (large excess). The solution was allowed to stir at 70 °C for 16 h. The solution was quenched with H₂O (1 mL) and extracted with EtOAc (3 mL). The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–hexane (1:1) as eluent to afford the title compounds (15.0 mg, 65 %, 7:3 174:173) as a yellow solid.

\( ^1H \) NMR (500 MHz, CDCl₃): \( \delta \) (ppm) 8.24 (1H, s, H₅), 8.22* (1H, s, H₅), 6.62 (1H, s, H₄), 6.60* (1H, s, H₄), 6.48 (1H, m, H₉), 6.48* (1H, m, H₉), 6.43–6.36 (1H, m, H₁₀), 6.43–6.36* (1H, m, H₁₀), 4.01 (3H, s, H₁₇), 4.00* (3H, s, H₁₇), 3.94 (3H, s, H₁₆), 3.94* (3H, s, H₁₆), 3.92 (3H, s, H₂₁), 3.92* (3H, s, H₂₁), 3.80 (1H, m, H₁₂), 3.80* (1H, m, H₁₂), 2.40 (2H, m, H₁₁), 2.40* (2H, m, H₁₁), 2.31 (3H, s, H₁₉), 2.31* (3H, s, H₁₉), 1.50–1.28 (4H, m, H₁₃ and H₁₄), 0.90 (12H, m, H₁₅ and H₂₄), 0.90* (12H, m, H₁₅ and H₂₄), 0.09 (3H, s, H₂₂), 0.09* (3H, s, H₂₂), 0.07 (3H, s, H₂₂), 0.07* (3H, s, H₂₂).

\( ^13C \) NMR (100 MHz, CDCl₃): \( \delta \) (ppm) 169.0 (C), 169.0* (C), 167.0 (C), 167.0* (C), 158.3 (C), 158.2* (C), 156.8 (C), 155.3* (C), 144.8 (C), 144.8* (C), 135.4 (C), 135.4* (C), 135.2 (C), 135.2* (C), 132.6 (CH), 132.5* (CH), 128.4 (CH), 128.4* (CH), 126.6* (CH), 122.2 (C), 122.2* (C), 121.4 (CH), 114.1 (C), 113.6* (C), 100.0 (C), 97.5* (C), 95.6 (CH), 95.1* (CH), 71.9 (CH), 71.9* (CH), 57.1* (CH₃), 57.1 (CH₃), 52.4 (2 × CH₃), 52.4* (2 × CH₃), 41.4 (CH₂), 41.4* (CH₂), 39.5 (CH₂), 39.5* (CH₂), 25.9 (3 × CH₃), 25.9* (3 × CH₃), 20.6 (CH₃), 20.6* (CH₃), 18.6 (CH₂), 18.6* (CH₂), 18.1 (C), 18.1* (C), 14.3 (CH₃), 14.3* (CH₃), −4.2 (CH₃), −4.2* (CH₃), −4.5 (CH₃), −4.5* (CH₃).

Bromide 174: HRMS (ESI+): \( m/z \) calcd for C₂₉H₄₁BrNaO₇Si ([M + Na]⁺) 631.1697; found 631.1731.

Iodide 173: HRMS (ESI+): \( m/z \) calcd for C₂₉H₄₁INaO₇Si ([M + Na]⁺) 679.1558; found 679.1587.
5.4.2. (E)-Methyl 1-acetoxy-3-(4-hydroxyhept-1-en-1-yl)-6,8-dimethoxy-2-naphthoate (172)

To a solution of naphthoate 143 (15.6 mg, 29 µmol, 1.0 eq) in acetic acid (0.2 mL) was added TBAF (0.5 mL, 0.50 mmol, 17 eq, 1 M in THF). After stirring at room temperature for 20 h, the reaction mixture was quenched with H₂O (3 mL) and extracted with EtOAc (5 mL). The organic extract was sequentially washed with saturated aqueous Na₂S₂O₃ solution (5 mL), H₂O (5 mL) then saturated aqueous NaCl solution (5 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:1) as eluent to afford the title compound 172 (10.6 mg, 87 %) as a clear yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.64 (1H, s, H₄), 6.70 (1H, d, J = 2.1 Hz, H₅), 6.57 (1H, d, J = 15.7 Hz, H₉), 6.47 (1H, d, J = 2.1 Hz, H₇), 6.23 (1H, dt, J = 15.2, 7.6 Hz, H₁₀), 3.94 (3H, s, H₁₇), 3.91 (3H, s, H₁₆), 3.90 (3H, s, H₂₁), 3.74 (1H, m, H₁₂), 2.46 (1H, m, H₁₁), 2.45 (4H, m, H₁₁b and H₁₉), 1.74 (1H, m, OH), 1.53–1.36 (4H, m, H₁₃ and H₁₄), 0.96 (3H, t, J = 6.9 Hz, H₁₅).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.3 (C, C₂₀), 167.4 (C, C₁₈), 159.5 (C, C₈), 156.7 (C, C₆), 145.1 (C, C₁), 138.0 (C, C₄a), 134.4 (C, C₃), 130.4 (CH, C₉), 130.2 (CH, C₁₀), 122.4 (CH, C₁), 121.1 (C, C₂), 113.7 (C, C₈b), 100.0 (CH, C₅), 98.8 (CH, C₇), 70.8 (CH, C₁₂), 56.2 (CH, C₁₇), 55.4 (CH₃, C₁₆), 52.4 (CH₃, C₂₁), 41.2 (CH₂, C₁₁), 39.1 (CH₂, C₁₃), 20.7 (CH₃, C₁₉), 18.9 (CH₂, C₁₄), 14.1 (CH₃, C₁₅).

IR (Neat): v (cm⁻¹) 3506, 1954, 1766, 1725, 1621.00.

HRMS (ESI⁺): m/z calcd for C₂₃H₂₈NaO₇ ([M + Na]⁺) 439.1727; found 439.1715.
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5.4.3. Methyl (E)-1-acetoxy-6,8-dimethoxy-3-(4-(tosyloxy)hept-1-en-1-yl)-2-naphthoate (171)

To a solution of alcohol 172 (12.4 mg, 35 µmol, 1.0 eq) in pyridine (0.5 mL) was added DMAP (1.0 mg, 8.2 µmol, 0.2 eq) and tosyl chloride (44 mg, 231 µmol, 6.7 eq). The solution was allowed to stir at room temperature for 16 h, then reaction was quenched with saturated aqueous CuSO₄ solution (7 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous CuSO₄ solution (3 × 30 mL), H₂O (30 mL) and saturated aqueous NaCl solution (30 mL). The organic extract was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (7:13) as eluent to afford the title compound 171 (10 mg, 56 %) as a white solid.

Mp: 132–134 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.60 (2H, d, J = 8.3 Hz, H₂₃), 7.52 (1H, s, H₄), 7.20 (2H, d, J = 8.0 Hz, H₂₄), 6.70 (1H, d, J = 2.1 Hz, H₅), 6.48 (1H, d, J = 2.2 Hz, H₇), 6.47 (1H, d, J = 15.6 Hz, H₉), 5.94 (1H, dt, J = 15.0, 7.5 Hz, H₁₀), 4.64 (1H, qu, J = 6.0 Hz, H₁₂), 3.90 (6H, m, H₁₇ and H₂₁), 3.88 (3H, s, H₁₆), 2.56–2.42 (2H, m, H₁₁), 1.73–1.56 (2H, m, H₁₃), 1.41–1.36 (2H, m, H₁₄), 0.87 (3H, t, J = 7.5 Hz, H₁₅).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.3 (C, C₂₀), 167.2 (C, C₁₈), 159.5 (C, C₈), 156.9 (C, C₆), 145.0 (C, C₂₂), 144.6 (C, C₁), 137.8 (C, C₄a), 134.2 (C, C₂₅), 133.8 (C, C₃), 130.3 (CH, C₁₀), 129.7 (2 × CH, C₂₃), 127.8 (CH, C₉), 127.7 (2 × CH, C₂₄), 122.2 (CH, C₄), 121.3 (C, C₂), 113.8 (C, C₆a), 100.0 (CH, C₅), 98.8 (CH, C₇), 82.8 (CH, C₁₂), 56.2 (CH₃, C₁₇), 55.4 (CH₃, C₂₁), 52.4 (CH₃, C₁₆), 38.0 (CH₂, C₁₁), 36.3 (CH₂, C₁₃), 21.4 (CH₃, C₂₆), 20.7 (CH₃, C₁₉), 18.1 (CH₂, C₁₄), 13.7 (CH₃, C₁₅).

IR (Neat): ν (cm⁻¹) 2957, 1769, 1621, 1173.

HRMS (ESI+): m/z calcd for C₃₀H₃₄NaO₉S ([M + Na]⁺) 593.1816; found 593.1808.
5.4.4. 1-(1-Hydroxy-3-(tosyloxy)hexyl)-5,7-dimethoxy-oxo-1,3-dihyronaphtho[2,3-c]furan-4-yl acetate (177a and 177b)

To a solution of ester 171 (10.5 mg, 21 µmol, 1.0 eq) in tert-butanol (0.5 mL) and water (0.5 mL) at room temperature was added AD-mix-α (33.4 mg) and methanesulfonamide (5.4 mg, 57.0 µmmol, 2.6 eq). The resulting solution was allowed to stir at room temperature for 24 h, then quenched with saturated aqueous Na$_2$S$_2$O$_3$ solution (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were sequentially washed with saturated aqueous Na$_2$S$_2$O$_3$ solution (15 mL), H$_2$O (15 mL) and saturated aqueous NaCl solution (15 mL), then dried over anhydrous MgSO$_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (2:3) as eluent to afford the title compounds (5.0 mg, 73 %, 1:1 177a:177b) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.80 (2H, m, H$_2$1), 7.80* (2H, m, H$_2$1), 7.62 (1H, s, H$_4$), 7.60* (1H, s, H$_4$), 7.33 (2H, m, H$_2$2), 7.33* (2H, m, H$_2$2), 6.79 (1H, s, H$_5$), 6.79* (1H, s, H$_5$), 6.53 (1H, s, H$_7$), 6.53* (1H, s, H$_7$), 5.46 (1H, d, J = 2.9 Hz, H$_3$), 5.40 (1H, d, J = 2.9 Hz, H$_3$), 4.86 (1H, m, H$_2$12), 4.86* (1H, m, H$_2$12), 4.27 (1H, m, H$_2$10), 4.27* (1H, m, H$_2$10), 3.92 (6H, m, H$_16$ and H$_17$), 3.92* (6H, m, H$_16$ and H$_17$), 2.64 (1H, br, OH), 2.45 (6H, s, H$_19$ and H$_24$), 2.45* (6H, s, H$_19$ and H$_24$), 2.25* (1H, br, OH), 2.00–1.44 (4H, m, H$_11$ and H$_13$), 2.00–1.44* (4H, m, H$_11$ and H$_13$), 1.19 (2H, m, H$_14$), 1.19* (2H, m, H$_14$), 0.76 (3H, m, H$_15$), 0.76* (3H, m, H$_15$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) 169.2 (C), 169.2* (C), 167.3 (C), 167.3* (C), 161.0 (C), 161.0* (C), 158.6 (C), 158.6* (C), 147.3 (C), 147.4* (C), 145.0 (C), 145.0* (C), 142.2 (C), 142.2* (C), 141.9 (C), 141.8* (C), 134.0 (C), 133.8* (C), 129.9 (2 × CH), 129.8* (2 × CH), 127.8 (2 × CH), 127.8* (2 × CH), 117.9 (CH), 117.9* (CH), 115.6 (C), 115.6* (C), 113.3 (C), 113.2* (C), 100.2 (CH), 100.1* (CH), 99.2 (CH), 99.2* (CH), 81.3 (CH), 81.2* (CH), 80.5 (CH), 80.5* (CH), 69.6 (CH), 67.6* (CH), 56.3 (2 × CH$_3$), 55.6* (2 × CH$_3$), 37.1 (2 × CH$_2$), 36.6* (2 × CH$_2$), 21.6 (CH$_3$), 21.6* (CH$_3$), 20.7 (CH$_3$), 20.7* (CH$_3$), 17.9 (CH$_2$), 17.8* (CH$_2$), 13.7 (CH$_3$), 13.6* (CH$_3$).

IR (Neat): ν (cm$^{-1}$) 3508, 3564, 1758, 1617.

HRMS (ESI+): m/z calcd for C$_{29}$H$_{32}$NaO$_{10}$S ([M + Na]$^+$) 595.1608; found 595.1594.
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5.4.5. (E)-1-(4-((tert-Butyldimethylsilyl)oxy)-5,7-dimethoxynaphthalen-2-yl)hept-1-en-4-ol (191)

To a solution of silyl ether 139 (55 mg, 0.10 mmol, 1.0 eq) in MeOH (6 mL) was added iodine (crystal). The reaction was allowed to stir at room temperature for 2 h. The reaction was quenched with saturated aqueous Na$_2$S$_2$O$_3$ solution (5 mL) and extracted with EtOAc (15 mL). The organic layer was washed with saturated aqueous NaCl solution (10 mL), dried over anhydrous MgSO$_4$ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:4) as eluent to afford the title compound 191 (25 mg, 58 %) as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) 7.18 (1H, d, $J = 1.3$ Hz, H$_4$), 6.75 (1H, d, $J = 1.8$ Hz, H$_2$), 6.63 (1H, d, $J = 2.2$ Hz, H$_3$), 6.50 (1H, d, $J = 15.9$ Hz, H$_9$), 6.39 (1H, d, $J = 2.3$ Hz, H$_7$), 6.24 (1H, td, $J = 15.2, 7.3$ Hz, H$_{10}$), 3.88 (3H, s, H$_{16}$), 3.86 (3H, s, H$_{17}$), 3.77 (1H, br, $J = 5.8$ Hz, H$_{12}$), 2.47 (1H, br, H$_{11a}$), 2.88 (1H, br, H$_{11b}$), 1.40–1.50 (4H, br, H$_{13}$ and H$_{14}$), 1.05 (9H, s, H$_{20}$), 0.96 (3H, br, H$_{15}$), 0.22 (6H, s, H$_{18}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 158.1 (2 × C, C$_8$ and C$_6$), 152.7 (C, C$_1$), 138.4 (C, C$_{4a}$), 135.8 (C, C$_3$), 133.1 (CH, C$_{10}$), 126.7 (CH, C$_9$), 118.6 (CH, C$_4$), 114.9 (C, C$_{8a}$), 111.4 (C, C$_2$), 98.6 (CH, C$_5$), 98.0 (CH, C$_7$), 70.9 (CH, C$_{12}$), 55.2 (2 × CH$_3$, C$_{17}$ and C$_{16}$), 41.3 (CH$_2$, C$_{11}$), 39.1 (CH$_2$, C$_{13}$), 26.0 (3 × CH$_3$, C$_{20}$), 18.9 (CH$_2$, C$_{14}$), 18.6 (C, C$_{19}$), 14.1 (CH$_3$, C$_{15}$), −4.3 (2 × CH$_3$, C$_{18}$).

IR (Neat): $\nu$ (cm$^{-1}$) 3386, 2954, 1727, 1625.

HRMS (ESI+): m/z calcd for C$_{25}$H$_{39}$O$_4$Si ([M + Na]$^+$) 431.2612; found 431.2600.
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5.4.6. (E)-3-(4-Hydroxyhept-1-en-1-yl)-6,8-dimethoxynaphthalen-1-ol (145)

Alcohol 146 was obtained as a side product of the previous reaction. Alcohol 146 (5 mg, 20 %) was obtained as a colourless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) (ppm) 9.04 (1H, s, OH), 7.08 (1H, d, \(J = 1.3\) Hz, \(H_6\)), 6.84 (1H, d, \(J = 1.6\) Hz, \(H_2\)), 6.66 (1H, d, \(J = 2.0\) Hz, \(H_3\)), 6.49 (1H, d, \(J = 15.7\) Hz, \(H_9\)), 6.40 (1H, d, \(J = 2.3\) Hz, \(H_7\)), 6.31 (1H, td, \(J = 15.2\), 7.6 Hz, \(H_{10}\)), 4.00 (3H, s, \(H_{17}\)), 3.87 (3H, s, \(H_{16}\)), 3.75 (1H, br, \(H_{12}\)), 2.60 (1H, br, \(H_{11a}\)), 2.33 (1H, qd, \(J = 16.4\), 1.0 Hz, \(H_{11b}\)), 1.65 (1H, s, OH), 1.36–1.55 (4H, br, \(H_{13}\) and \(H_{14}\)), 0.95 (3H, t, \(J = 6.9\) Hz, \(H_{15}\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm) 158.0 (C, \(C_8\)), 157.2 (C, \(C_6\)), 154.6 (C, \(C_1\)), 137.6 (C, \(C_{14a}\)), 137.2 (C, \(C_3\)), 133.0 (CH, \(C_{10}\)), 127.4 (CH, \(C_9\)), 116.7 (CH, \(C_4\)), 110.2 (C, \(C_{8a}\)), 105.6 (CH, \(C_2\)), 99.6 (CH, \(C_3\)), 97.5 (CH, \(C_7\)), 70.9 (CH, \(C_{12}\)), 56.1 (CH\(_3\), \(C_{17}\)), 55.4 (CH\(_3\), \(C_{16}\)), 41.2 (CH\(_2\), \(C_{11}\)), 39.1 (CH\(_2\), \(C_{13}\)), 18.9 (CH\(_2\), \(C_{14}\)), 14.1 (CH\(_3\), \(C_{15}\)).

IR (Neat): \(\nu\) (cm\(^{-1}\)) 3367, 2958, 1628, 1372.

HRMS (ESI+): \(m/z\) calcd for C\(_{19}\)H\(_{25}\)O\(_4\) ([M + H]\(^{+}\)) 317.1747; found 317.1739.
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5.5. Lasionectrin (13) synthesis via dihydroxylation

5.5.1. 3-Formyl-6,8-dimethoxynaphthalen-1-yl acetate (129)

A solution of aldehyde 116 (586 mg, 2.53 mmol, 1.0 eq), DMAP (30 mg, 0.25 mmol, 0.1 eq) and acetic anhydride (2 mL) in pyridine (10 mL) was allowed to stir at room temperature for 3 h. The reaction mixture was quenched with saturated CuSO₄ aqueous solution (20 mL) and extracted with EtOAc (2 × 20 mL). The organic extracts were washed sequentially with saturated CuSO₄ aqueous solution (3 × 40 mL), H₂O (40 mL) and saturated NaCl aqueous solution (40 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent was removed in vacuo to afford the title compound 129 (680 mg, 98%) as a yellow solid

Mp: 144–146 °C. [lit. 144–145°C]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.06 (1H, s, H₉), 8.05 (1H, d, J = 1.5 Hz, H₄), 7.36 (1H, d, J = 1.6 Hz, H₂), 6.90 (1H, d, J = 2.2 Hz, H₅), 6.65 (1H, d, J = 2.3 Hz, H₇), 3.92 (3H, s, H₁₁), 3.91 (3H, s, H₁₀), 2.37 (3H, s, H₁₃).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 191.3 (CH, C₉), 170.0 (C, C₁₂), 159.2 (C, C₆), 156.4 (C, C₈), 147.8 (C, C₁), 137.3 (C, C₄a), 134.9 (C, C₃), 131.0 (CH, C₄), 117.9 (C, C₅a), 114.0 (CH, C₂), 102.4 (CH, C₅), 100.5 (CH, C₇), 56.3 (CH₃, C₁₁), 55.5 (CH₃, C₁₀), 20.9 (CH₃, C₁₃).

Data were in agreement with literature values.¹⁸²
5.5.2. \((S,E)\)-3-(4-((tert-Butyldimethylsilyl)oxy)hept-1-en-1-yl)-6,8-dimethoxynaphthalen-1-yl acetate (199)

To a solution of sulfone 119 (800 mg, 1.88 mmol, 1.7 eq) in THF (6 mL) at −78 °C was added dropwise KHMDS (5.0 mL, 1.85 mmol, 1.7 eq, 0.37 M in toluene). The solution was allowed to stir at −78 °C for 1 h. The resulting solution was transferred via cannula to a solution of aldehyde 129 (300 mg, 1.09 mmol, 1.0 eq) and dry LiCl (57 mg, 1.34 mmol, 1.2 eq) in THF (10 mL) stirred at −15 °C. After stirring at −15 °C for 1 h, the reaction was quenched with saturated aqueous NH₄Cl solution (20 mL), extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with H₂O (2 × 60 mL) and saturated aqueous NaCl solution (60 mL), then dried over anhydrous MgSO₄. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9) as eluent to afford the title compound 199 (510 mg, 98 %, E/Z = 98 %) as a clear yellow oil.

\(^1\text{H NMR}\) (500 MHz, CDCl₃): \(\delta\) (ppm) 7.40 (1H, d, \(J = 1.4\) Hz, H₄), 6.99 (1H, d, \(J = 1.2\) Hz, H₂), 6.70 (1H, d, \(J = 1.8\) Hz, H₃), 6.45 (1H, d, \(J = 2.1\) Hz, H₇), 6.44 (1H, d, \(J = 15.9\) Hz, H₉), 6.29 (1H, td, \(J = 15.2, 7.6\) Hz, H₁₀), 3.89 (3H, s, H₁₇), 3.88 (3H, s, H₁₆), 3.79 (1H, qu, \(J = 5.8\) Hz, H₉), 2.39 (2H, m, H₁₁), 2.35 (3H, s, H₁₉), 1.29–1.50 (4H, br, H₁₃ and H₁₄), 0.90 (12H, m, H₁₅ and H₂₂), 0.06 (6H, s, H₂₀).

\(^{13}\text{C NMR}\) (125 MHz, CDCl₃): \(\delta\) (ppm) 170.0 (C, C₁₈), 158.4 (C, C₈), 156.3 (C, C₆), 146.8 (C, C₁), 137.9 (C, C₄₆), 136.4 (C, C₃), 131.0 (CH, C₁₀), 128.8 (CH, C₉), 123.1 (CH, C₄), 114.5 (CH, C₂), 113.9 (C, C₆₈), 99.1 (2 × CH, C₅ and C₇), 72.1 (CH, C₁₂), 56.0 (CH₃, C₁₇), 55.3 (CH₃, C₁₆), 41.3 (CH₂, C₁₁), 39.3 (CH₂, C₁₃), 25.9 (3 × CH₃, C₂₂), 21.0 (CH₃, C₁₉), 18.7 (CH₂, C₁₄), 18.2 (C, C₂₁), 14.3 (CH₃, C₁₅), -4.3 (CH₃, C₂₀), -4.5 (CH₃, C₂₀).

\(\text{IR (Neat): } \nu \text{ (cm}^{-1}\text{)}\) 2929, 1767, 1626, 1209.

\(\text{HRMS (ESI+): } m/z \text{ calcd for C}_{2₇}H₄₃O₅Si ([M + H]⁺) 473.2718; found 473.2703.\)

\([\alpha]^{26}_D\) : +12.1 (c 1.00, CHCl₃).

\((R)\)-199 \( [\alpha]^{22}_D \) : −9.5 (c 1.01, CHCl₃).
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5.5.3. (S,E)-3-(4-Hydroxyhept-1-en-1-yl)-6,8-dimethoxynaphthalen-1-yl acetate (198)

To a solution of silylated compound 199 (466 mg, 0.99 mmol, 1.0 eq) in acetic acid (1 mL) and THF (5 mL) at room temperature was slowly added a solution of TBAF (4.0 mL, 4.0 eq, 1 M in THF). The resulting solution was allowed to stir at 55 °C for 12 h. The reaction was quenched with saturated aqueous K₂CO₃ solution (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H₂O (30 mL), saturated aqueous NaCl solution (30 mL) and dried over anhydrous MgSO₄. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel using EtOAc–PE (2:9) as eluent to afford the title compound 198 (288 mg, 82 %) as a white solid.

Mp: 98–100 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.42 (1H, d, J = 1.5 Hz, H₄), 7.02 (1H, d, J = 1.6 Hz, H₂), 6.71 (1H, d, J = 2.2 Hz, H₃), 6.53 (1H, d, J = 15.9 Hz, H₉), 6.46 (1H, d, J = 2.6 Hz, H₇), 6.30 (1H, td, J = 15.2, 7.6 Hz, H₁₀), 3.88 (3H, s, H₁₇), 3.87 (3H, s, H₁₆), 3.76 (1H, m, H₁₂), 2.47 (1H, m, H₁₁a), 2.88 (4H, m, H₁₁b and H₁₉), 1.40–1.50 (4H, m, H₁₃ and H₁₄), 0.95 (3H, t, J = 6.7 Hz, H₁₅).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 170.3 (C, C₁₈), 158.5 (C, C₃), 156.3 (C, C₆), 146.9 (C, C₁), 137.9 (C, C₄₆), 135.9 (C, C₃), 132.2 (CH, C₁₀), 127.9 (CH, C₉), 123.4 (CH, C₂), 114.4 (CH, C₁), 114.0 (C, C₈₉), 99.3 (CH, C₅), 99.1 (CH, C₇), 71.0 (CH, C₁₂), 56.1 (CH₃, C₁₇), 55.4 (CH₃, C₁₆), 41.2 (CH₂, C₁₁), 39.1 (CH₂, C₁₃), 21.0 (CH₃, C₁₉), 18.9 (CH₂, C₁₄), 14.1 (CH₃, C₁₅).

IR (Neat): ν (cm⁻¹) 3386, 2919, 1743, 1352.

HRMS (ESI+): m/z calcd for C₂₁H₂₇O₅ ([M + H]+) 359.1853; found 359.1844.

[α]²⁴ : −7.58 (c 1.00, CHCl₃).

(R)-198 [α]²² : +9.4 (c 1.00, CHCl₃).
5.5.4. (S,E)-6,8-Dimethoxy-3-(4-(tosyloxy)hept-1-en-1-yl)naphthalen-1-yl acetate (192)

To a solution of alcohol 198 (266 mg, 0.74 mmol, 1.0 eq) in pyridine (3 mL) and CH₂Cl₂ (5 mL) was added DMAP (9 mg, 74 µmol, 0.1 eq) and tosyl chloride (707 mg, 3.70 mmol, 5.0 eq). The solution was allowed to stir at room temperature for 16 h, then the reaction was quenched with saturated aqueous CuSO₄ solution (7 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with saturated aqueous CuSO₄ solution (3 × 30 mL), H₂O (30 mL) and saturated aqueous NaCl solution (30 mL). The organic extract was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:3) as eluent to afford the title compound 192 (366 mg, 96 %) as a white solid.

Mp: 129.5–131.2 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.77 (2H, d, J = 8.3 Hz, H₂₁), 7.33 (1H, d, J = 1.2 Hz, H₄), 7.22 (2H, d, J = 8.1 Hz, H₂₂), 6.87 (1H, d, J = 2.2 Hz, H₅), 6.70 (1H, d, J = 2.2 Hz, H₇), 6.47 (1H, qu, J = 2.2 Hz, H₉), 6.36 (1H, d, J = 15.7 Hz, H₉), 6.01 (1H, td, J = 15.3, 7.6 Hz, H₁₀), 4.64 (1H, qu, J = 6.1 Hz, H₁₂), 3.89 (3H, s, H₁₇), 3.88 (3H, s, H₁₆), 2.52 (2H, m, H₁₁), 2.36 (3H, s, H₁₉), 2.30 (3H, s, H₂₄), 1.25–1.70 (4H, m, H₁₃ and H₁₄), 0.87 (3H, t, J = 7.6 Hz, H₁₅).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 170.2 (C, C₁₈), 158.7 (C, C₈), 156.3 (C, C₆), 146.9 (C, C₁), 144.5 (C, C₂₀), 137.8 (C, C₄), 135.6 (C, C₃), 134.3 (C, C₂₃), 132.7 (CH, C₁₀), 129.7 (2 × CH, C₂₁), 127.7 (2 × CH, C₂₂), 125.4 (CH, C₉), 123.4 (CH, C₂), 114.5 (CH, C₄), 114.1 (C, C₈), 99.9 (CH, C₃), 99.1 (CH, C₇), 83.0 (CH, C₁₂), 56.1 (CH₃, C₁₇), 55.4 (CH₃, C₁₆), 38.0 (CH₂, C₁₁), 36.3 (CH₂, C₁₃), 21.5 (CH₃, C₂₄), 21.0 (CH₃, C₁₉), 18.2 (CH₂, C₁₄), 13.7 (CH₃, C₁₅).

IR (Neat): ν (cm⁻¹) 2959, 1759, 1345, 1168.

HRMS (ESI+): m/z calcd for C₂₈H₃₂NaO₇S ([M + Na]⁺) 535.1761; found 535.1743.

[α]D²²: +25.3 (c 1.00, CHCl₃).

(R)-192 [α]D²¹: −26.1 (c 1.00, CHCl₃).
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5.5.5. (R,E)-3-(4-Chlorohept-1-en-1-yl)-6,8-dimethoxynaphthalen-1-yl acetate (200)

To a solution of alcohol 198 (12.7 mg, 34 µmol, 1.0 eq) in pyridine (0.5 mL) were added tosyl chloride (42 mg, 220 µmol, 6.5 eq) and DMAP (21 mg, 172 µmol, 5.1 eq). The solution was allowed to stir at 45 °C temperature for 16 h. The reaction was quenched with saturated aqueous CuSO₄ solution (3 mL) and extracted with EtOAc (5 mL). The organic layer was sequentially washed with saturated aqueous CuSO₄ solution (3 mL), H₂O (3 mL) and saturated aqueous NaCl solution (3 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (3:7) as eluent to afford the title compound 200 (8 mg, 62 %) as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.43 (1H, d, J = 1.5 Hz, H₄), 7.01 (1H, d, J = 1.7 Hz, H₂), 6.71 (1H, d, J = 2.2 Hz, H₃), 6.52 (1H, d, J = 15.8 Hz, H₉), 6.46 (1H, d, J = 2.3 Hz, H₇), 6.33 (1H, td, J = 15.1, 7.1 Hz, H₁₀), 4.02 (1H, m, H₁₂), 3.88 (6H, s, H₁₆ and H₁₇), 2.67 (1H, m, H₁₁₉), 2.34 (3H, s, H₁₉), 1.76 (1H, m, H₁₁₉), 1.64–1.42 (4H, m, H₁₃ and H₁₄), 0.94 (3H, t, H₁₅).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 170.2 (C, C₁₈), 158.5 (C, C₃), 156.2 (C, C₆), 146.9 (C, C₁₈), 137.8 (C, C₄₈), 135.8 (C, C₃), 132.0 (CH, C₁₀), 127.2 (CH, C₉), 123.4 (CH, C₂), 114.5 (CH, C₄), 114.1 (C, C₈₉), 99.3 (CH, C₅), 99.1 (CH, C₇), 62.6 (CH, C₁₂), 56.0 (CH₃, C₁₇), 55.3 (CH₃, C₁₆), 42.0 (CH₂, C₁₁), 39.9 (CH₂, C₁₃), 21.0 (CH₃, C₁₉), 19.7 (CH₂, C₁₄), 13.5 (CH₃, C₁₅).

IR (Neat): ν (cm⁻¹) 2958, 1765, 1625, 1355.

HRMS (ESI+): m/z calcd for C₂₁H₂₅ClNaO₄ ([M + Na]⁺) 399.1344; found 399.1343.

[α]D²²: +10.8 (c 0.14, CHCl₃).
5.5.6. 3-((2R,3R,5R)-3-Hydroxy-5-propyltetrahydrofuran-2-yl)-6,8-dimethoxynaphthalen-1-yl acetate (201a and 201b)

A solution of alkene 192 (251 mg, 0.49 mmol, 1.0 eq), OsO$_4$ (250 µL, 0.04 eq, 20 g/L in tBuOH), NMO (120 mg, 1.02 mmol, 2.1 eq) in acetone (8 mL) and H$_2$O (6 mL) was allowed to stir at room temperature for 24 h. The organic solvent was removed in vacuo, then the residue was diluted with EtOAc (30 mL) and sequentially washed with saturated aqueous Na$_2$S$_2$O$_3$ solution (30 mL), H$_2$O (30 mL) and saturated aqueous NaCl solution (30 mL). The organic extract was dried over anhydrous MgSO$_4$ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (2:3) as eluent to afford the title compound 201a and 201b (177 mg, 97 %, 1:1 201a:201b) as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) 7.62* (1H, s, H$_4$), 7.61 (1H, s, H$_4$), 6.89* (1H, d, $J = 1.5$ Hz, H$_2$), 6.86 (1H, d, $J = 1.5$ Hz, H$_2$), 6.76* (1H, d, $J = 2.3$ Hz, H$_5$), 6.76 (1H, d, $J = 2.3$ Hz, H$_5$), 6.48 (1H, d, H$_7$), 6.48* (1H, d, H$_7$), 5.09 (1H, d, $J = 3.0$ Hz, H$_9$), 4.82* (1H, d, $J = 3.7$ Hz, H$_9$), 4.50 (1H, td, $J = 12.0$, 5.9 Hz, H$_{12}$), 4.41 (1H, m, H$_{10}$), 4.39* (1H, m, H$_{10}$), 4.08* (1H, td, $J = 13.7$, 6.8 Hz, H$_{12}$), 3.87 (6H, s, H$_{17}$), 3.87* (6H, s, H$_{17}$), 2.44 (1H, ddd, $J = 13.8$, 7.9, 6.0 Hz, H$_{11a}$), 2.33 (3H, s, H$_{19}$), 2.33* (3H, s, H$_{19}$), 1.90–1.39 (6H, m, H$_{11b}$, H$_{13}$, H$_{14}$ and OH), 1.90–1.39* (6H, m, H$_{11b}$, H$_{13}$, H$_{14}$ and OH), 0.99 (3H, s, H$_{15}$), 0.99* (3H, s, H$_{15}$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) 170.2 (C, C$_{18}$), 170.2* (C, C$_{18}$), 158.5 (C, C$_6$), 158.5* (C, C$_6$), 156.2 (C, C$_8$), 156.2* (C, C$_8$), 146.9 (C, C$_1$), 146.8* (C, C$_1$), 137.7 (C, C$_{16}$), 137.6* (C, C$_{16}$), 136.5 (C, C$_3$), 135.8* (C, C$_3$), 123.3* (CH, C$_7$), 123.0 (CH, C$_7$), 116.0* (CH, C$_2$), 115.8 (CH, C$_2$), 114.5 (C, C$_{8a}$), 114.5* (C, C$_{8a}$), 99.5* (CH, C$_3$), 99.4 (CH, C$_3$), 99.2* (CH, C$_7$), 99.1 (CH, C$_7$), 84.5* (CH, C$_5$), 83.9 (CH, C$_9$), 78.8 (CH, C$_{12}$), 78.2* (CH, C$_{12}$), 74.5 (CH, C$_{10}$), 73.9* (CH, C$_{10}$), 56.1 (CH, C$_{17}$), 56.1* (CH, C$_{17}$), 55.3 (CH, C$_{16}$), 55.3* (CH, C$_{16}$), 40.9 (CH$_2$, C$_{11}$), 40.4* (CH$_2$, C$_{11}$), 38.6* (CH$_2$, C$_{13}$), 38.4 (CH$_2$, C$_{13}$), 21.0 (CH$_3$, C$_{19}$), 21.0* (CH$_3$, C$_{19}$), 19.5* (CH$_2$, C$_{14}$), 19.3 (CH$_2$, C$_{14}$), 14.2 (CH$_3$, C$_{15}$), 14.2* (CH$_3$, C$_{15}$).

IR (Neat): v (cm$^{-1}$) 3509, 2958, 1727, 1365.

HRMS (ESI+): m/z calcd for C$_{23}$H$_{28}$NaO$_6$ ([M + Na]$^+$) 397.1622; found 397.1634.
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5.5.7. (2R,3R,5R)-2-(4-Hydroxy-5,7-dimethoxynaphthalen-2-yl)-5-propyltetrahydrofuran-3-ol (195a and 195b)

A solution of acetate 201a and 201b (154 mg, 0.41 mmol, 1.0 eq), lithium hydroxide monohydrate (12.5 mg, 0.27 mmol, 0.6 eq) in MeOH (5 mL) and H₂O (1 mL) was allowed to stir at room temperature for 2 h, then was quenched with 1 M aqueous HCl solution (5 mL). The organic solvent was removed in vacuo and the residue extracted with EtOAc (2 × 7 mL). The combined organic extracts were sequentially washed with 1 M aqueous HCl solution (14 mL), H₂O (14 mL) and saturated aqueous NaCl solution (14 mL), then dried over anhydrous MgSO₄ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:3) as eluent to afford the title compounds 195a and 195b (130 mg, 95 %, 1:1 195a:195b) as a yellow oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) 9.12 (1H, m, C₁OH), 9.12* (1H, m, C₁OH), 7.27 (1H, s, H₄), 7.27* (1H, s, H₄), 6.72 (1H, m, H₃), 6.72* (1H, m, H₃), 6.68* (1H, d, J = 1.4 Hz, H₂), 6.65 (1H, d, J = 1.4 Hz, H₂), 6.43 (1H, m, H₇), 6.43* (1H, m, H₇), 5.11 (1H, d, J = 3.2 Hz, H₉), 4.83* (1H, d, J = 3.8 Hz, H₉), 4.50 (1H, m, H₁₂), 4.45 (1H, m, H₁₀), 4.41* (1H, m, H₁₀), 4.07* (1H, m, H₁₂), 1.80–1.40 (5H, m, H₁₁b, H₁₃ and H₁₄), 1.35 (1H, s, C₁₀OH), 1.31* (1H, s, C₁₀OH), 0.99 (3H, m, H₁₅), 0.99* (3H, m, H₁₅).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) 158.0 (C, C₆), 158.0* (C, C₆), 157.1 (C, C₈), 157.1* (C, C₈), 155.0 (C, C₁), 154.9* (C, C₁), 137.8 (C, C₃), 137.5 (C, C₄a), 137.5* (C, C₄a), 137.1* (C, C₁), 115.9* (CH, C₄), 115.6 (CH, C₄), 110.3 (C, C₈a), 110.3* (C, C₈a), 106.9* (CH, C₂), 106.6 (CH, C₂), 99.7 (CH, C₃), 99.7* (CH, C₃), 97.7 (CH, C₇), 97.7* (CH, C₇), 84.9* (CH, C₉), 84.3 (CH, C₉), 78.8 (CH, C₁₂), 78.2* (CH, C₁₂), 74.5 (CH, C₁₀), 73.9* (CH, C₁₀), 56.2 (CH₃, C₁₇), 56.2* (CH₃, C₁₇), 55.4 (CH₃, C₁₆), 55.4* (CH₃, C₁₆), 40.9 (CH₂, C₁₁), 70.4* (CH₂, C₁₁), 38.7* (CH₂, C₁₃), 38.4 (CH₂, C₁₃), 19.5* (CH₂, C₁₄), 19.3 (CH₂, C₁₄), 14.2 (CH₃, C₁₃), 14.2* (CH₃, C₁₅).

IR (Neat): v (cm⁻¹) 3405, 2954, 1618, 1372.

HRMS (ESI+): m/z calcd for C₁₉H₂₄NaO₅ ([M + Na]+) 355.1516; found 355.1513.
5.5.8. (2R,3R,5R)-2-(4-Hydroxy-3-iodo-5,7-dimethoxynaphthalen-2-yl)-5-propyltetrahydrofuran-3-ol (194a and 194b)

To a solution of naphthol 195a and 195b (130 mg, 0.39 mmol, 1.0 eq) in CH₂Cl₂ (10 mL) at 0 °C was added morpholine-iodine complex (202 mg, 0.59 mmol, 1.5 eq). The solution was allowed to warm up to room temperature over 15 min then quenched with saturated aqueous Na₂S₂O₃ solution (10 mL), and then sequentially washed with saturated aqueous Na₂S₂O₃ solution (10 mL), H₂O (10 mL) and saturated aqueous NaCl solution (10 mL). The chlorinated extract was dried with MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:4) to afford the title compounds 194a and 194b (148 mg, 83 %, 1:1 194a:194b) as a white solid.

**1H NMR** (400 MHz, CDCl₃): δ(ppm) 10.19 (1H, s, C₁OH), 10.19* (1H, s, C₁OH), 7.45* (1H, s, H₄), 7.43 (1H, s, H₄), 6.75 (1H, m, H₅), 6.75* (1H, m, H₅), 6.47 (1H, m, H₇), 6.47* (1H, m, H₇), 5.35 (1H, d, J = 3.1 Hz, H₉), 5.07* (1H, d, J = 3.9 Hz, H₉), 4.92* (1H, m, H₁₁ and H₁₇), 3.88 (3H, m, H₁₆), 3.88* (3H, m, H₁₆), 2.54* (1H, td, J = 14.8, 6.9 Hz, H₁₁a), 2.26 (1H, dd, J = 13.1, 5.5 Hz, H₁₁a), 1.95–1.40 (5H, m, H₁₁b, H₁₃ and H₁₄), 1.95–1.40* (5H, m, H₁₁b, H₁₃ and H₁₄), 1.16 (1H, s, C₁₀OH), 1.16* (1H, s, C₁₀OH), 1.01 (3H, m, H₁₅), 1.01* (3H, m, H₁₅).

**13C NMR** (100 MHz, CDCl₃): δ(ppm) 158.3 (C, C₆), 158.3* (C, C₆), 155.9 (C, C₈), 155.9* (C, C₈), 153.2 (C, C₃), 153.1* (C, C₃), 138.2 (C, C₃), 137.9* (C, C₃), 136.6 (C, C₄a), 118.6 (CH, C₅), 118.3* (CH, C₅), 110.1 (C, C₆a), 110.1* (C, C₆a), 99.9* (CH, C₃), 99.8 (CH, C₅), 98.4 (CH, C₇), 98.4* (CH, C₇), 88.0* (CH, C₅), 87.7 (CH, C₉), 78.8 (CH, C₁₂), 77.7* (CH, C₁₂), 77.0 (C, C₂), 77.0* (C, C₂), 72.2 (CH, C₁₀), 71.6* (CH, C₁₀), 56.5 (CH₃, C₁₇), 56.5* (CH₃, C₁₇), 55.4 (CH₃, C₁₆), 55.4* (CH₃, C₁₆), 40.9* (CH₂), 40.7 (CH₂), 38.5* (CH₂), 38.3 (CH₂, C₁₃), 19.5* (CH₂, C₁₄), 19.3 (CH₂, C₁₄), 14.2 (CH₃, C₁₅), 14.2* (CH₃, C₁₅).

**IR** (Neat): ν (cm⁻¹) 3497, 3332, 2958, 1625.

**HRMS** (ESI+): m/z calcd for C₁₉H₂₃INaO₅ ([M + Na]⁺) 481.0482; found 481.0476.
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5.5.9. (2R)-6-Hydroxy-7,9-dimethoxy-2-propyl-2,3a,11b-tetrahydro-5H-benzo[g]furo[3,2-c]isochromen-5-one (193a and 193b)

A solution of iodonaphthol 194a and 194b (148 mg, 0.32 mmol, 1.0 eq), palladium acetate (87 mg, 0.39 mmol, 1.2 eq) and molybdenum hexacarbonyl (253 mg, 0.69 mmol, 2.2 eq) in dioxane was allowed to stir at 90 °C for 16 h. The suspension was filtrated through a pad of Celite® and the filtrate was concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:4) as eluent to afford the title compounds 193a and 193b (193a: 37 mg; 193b: 35 mg, 63%) as white solids.

193a:

Mp: 122–124 °C.

1H NMR (400 MHz, CDCl₃): δ (ppm) 13.26 (1H, S, OH), 7.13 (1H, s, H₁₁), 6.64 (1H, d, J = 2.3 Hz, H₁₀), 6.51 (1H, d, J = 2.3 Hz, H₈), 5.14 (1H, t, J = 3.3 Hz, H₃a), 4.88 (1H, d, J = 2.7 Hz, H₁₁a), 4.41 (1H, m, H₂), 3.98 (3H, s, H₁₆), 3.91 (3H, s, H₁₅), 2.62 (1H, dd, J = 14.0, 6.1 Hz, H₃A), 2.01 (1H, ddd, J = 13.7, 9.6, 4.1 Hz, H₃B), 1.70–1.50 (2H, m, H₁₂), 1.50–1.30 (2H, m, H₁₃), 0.95 (3H, t, J = 7.2 Hz, H₁₄).

13C NMR (100 MHz, CDCl₃): δ (ppm) 169.6 (C, C₅), 164.3 (C, C₆), 161.8 (C, C₉), 160.6 (C, C₇), 141.5 (C, C₁₀a), 131.1 (C, C₁₁a), 118.4 (CH, C₁₁), 111.7 (C, C₈a), 99.6 (CH, C₁₀), 99.1 (CH, C₈), 98.4 (C, C₃a), 81.7 (CH, C₃a), 78.9 (CH, C₂), 73.8 (CH, C₁₁b), 56.2 (CH₃, C₁₆), 55.4 (CH₃, C₁₅), 40.1 (CH₂, C₃), 38.3 (CH₂, C₁₂), 19.1 (CH₂, C₁₃), 14.0 (CH₃, C₁₄).

IR (Neat): ν (cm⁻¹) 2947, 1639, 1371, 1110.

[α]D²²: +120.0 (c 0.50, CHCl₃).

(2S)-193a: [α]D²²: −120.0 (c 0.50, CHCl₃).

HRMS (ESI+): m/z calcd for C₂₀H₂₂NaO₆ ([M + Na]+) 381.1309; found 381.1320.
193b:

**Mp**: 97–99 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 13.29 (1H, S, OH), 7.14 (1H, s, H$_{11}$), 6.64 (1H, d, $J$ = 2.3 Hz, H$_{10}$), 6.52 (1H, d, $J$ = 2.3 Hz, H$_8$), 5.07 (1H, t, $J$ = 3.3 Hz, H$_{3a}$), 4.64 (1H, d, $J$ = 2.7 Hz, H$_{11a}$), 4.16 (1H, m, H$_2$), 3.98 (3H, s, H$_{16}$), 3.91 (3H, s, H$_{15}$), 2.58 (1H, ddd, $J$ = 13.5, 9.7, 4.0 Hz, H$_{3A}$), 2.19 (1H, ddd, $J$ = 14.1, 6.2, 0.6 Hz, H$_{3B}$), 1.77–1.55 (2H, m, H$_{12}$), 1.50–1.30 (2H, m, H$_{13}$), 0.95 (3H, t, $J$ = 7.2 Hz, H$_{14}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 169.3 (C, C$_5$), 164.2 (C, C$_6$), 161.8 (C, C$_9$), 160.6 (C, C$_7$), 141.4 (C, C$_{10a}$), 130.5 (C, C$_{11a}$), 118.6 (CH, C$_{11}$), 111.8 (C, C$_{6a}$), 99.6 (CH, C$_{10}$), 99.2 (CH, C$_8$), 98.9 (C, C$_{5a}$), 81.1 (CH, C$_{3a}$), 78.6 (CH, C$_2$), 75.1 (CH, C$_{11b}$), 56.2 (CH$_3$, C$_{16}$), 55.4 (CH$_3$, C$_{15}$), 39.1 (CH$_2$, C$_5$), 38.1 (CH$_2$, C$_{12}$), 19.2 (CH$_2$, C$_{13}$), 14.0 (CH$_3$, C$_{14}$).

IR (Neat): $\nu$ (cm$^{-1}$) 2926, 1641, 1374, 1104.

$[\alpha]_{D}^{21}$: $-167$ (c 0.50, CHCl$_3$).

(2S)-193b: $[\alpha]_{D}^{22}$: $+161$ (c 0.50, CHCl$_3$).

HRMS (ESI+): $m/z$ calcd for C$_{20}$H$_{22}$NaO$_6$ ([M + Na]$^+$) 381.1309; found 381.1320.
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5.5.10. (2R,3aR,11bR)-6,7-Dihydroxy-9-methoxy-2-propyl-2,3,3a,11b-tetrahydro-5H-benzo[g]furo[3,2-c]isochromen-5-one ((+)-13)

A solution of 193a (32 mg, 89 µmol, 1.0 eq) and dry LiCl (17 mg, 401 µmol, 4.5 eq) in NMP (1 mL) was stirred at 160 °C for 5 h. After cooling to room temperature the reaction was quenched with 2 M aqueous HCl solution (1 mL) and stirred at this temperature for 15 min. The solution was extracted with EtOAc (2 × 3 mL), and the combined organic extracts were washed with H₂O (5 × 6 mL) and saturated aqueous NaCl solution (6 mL). The organic layer was dried over anhydrous MgSO₄, and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using Et₂O–PE (2:3) as eluent to afford the title compound 13 (14.5 mg, 47 %) as a white solid.

Mp: 120–123 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 13.86 (1H, s, OH), 9.48 (1H, s, OH), 7.17 (1H, s, H₁₁), 6.65 (1H, d, J = 2.3 Hz, H₁₀), 6.59 (1H, d, J = 2.2 Hz, H₈), 5.18 (1H, t, J = 5.4 Hz, H₃ₐ), 4.88 (1H, d, J = 2.6 Hz, H₁₁₉), 4.40 (1H, m, H₂), 3.89 (3H, s, H₁₅), 2.64 (1H, dd, J = 13.6, 5.9 Hz, H₃ₐ), 2.03 (1H, ddd, J = 13.8, 9.6, 4.1 Hz, H₁₃), 1.71 (1H, m, H₁₂ₐ), 1.35–1.60 (3H, m, H₁₂₈ and H₁₃), 0.95 (3H, t, J = 7.2 Hz, H₁₄).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8 (C, C₅), 162.9 (C, C₉), 162.8 (C, C₆), 158.5 (C, C₇), 140.4 (C, C₁₀ₐ), 130.1 (C, C₁₁₂), 119.3 (CH, C₁₁), 109.2 (C, C₆ₐ), 102.4 (CH, C₈), 100.3 (CH, C₁₀), 97.1 (C, C₃ₐ), 82.5 (CH, C₃₈), 78.9 (CH, C₂), 73.6 (CH, C₁₁₉), 55.5 (CH₃, C₁₅), 40.0 (CH₂, C₃), 38.2 (CH₂, C₁₂), 19.1 (CH₂, C₁₃), 14.0 (CH₃, C₁₄).

IR (Neat): ν (cm⁻¹) 3386, 2958, 1645, 1584.

HRMS (ESI+): m/z calcd for C₁₉H₂₀NaO₆ ([M + Na]+) 367.1152; found 367.1143.

[α]°D: +148 (c 0.171, MeOH)

(-)-13 [α]°D: −138 (c 0.16, MeOH)
**Chiral HPLC:** Column DAICEL CHIRALPAK® AD-H, i-PrOH–hexanes (2:3), 0.5 mL/min, retention time 20.38 min, 97 % e.e..

(-)-**13 Chiral HPLC:** Column DAICEL CHIRALPAK® AD-H, i-PrOH–hexanes (2:3), 0.5 mL/min, retention time 14.39 min, 98 % e.e.

Lit. $[\alpha]_D^{25}$: -43.8 (c 0.17, MeOH)$^{19}$
Chapter 5: Lasionectrin

5.5.11. (2R,3aS,11bS)-6,7-Dihydroxy-9-methoxy-2-propyl-2,3,3a,11b-tetrahydro-5H-benzo[g]furo[3,2-c]isochromen-5-one (−)-2-epi-(−)-13

A solution of 193b (30 mg, 87 µmol, 1.0 eq) and dry LiCl (17 mg, 401 µmol, 4.5 eq) in NMP (1 mL) was stirred at 160 °C for 5 h. After cooling to room temperature the reaction was quenched with 2 M aqueous HCl solution (1 mL) and stirred at this temperature for 15 min. The solution was extracted with EtOAc (2 × 3 mL), and the combined organic extracts were washed with H₂O (5 × 6 mL) and saturated aqueous NaCl solution (6 mL). The organic layer was dried over anhydrous MgSO₄, and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using Et₂O – PE (2:3) as eluent to afford the title compound 2-epi-(−)-13 (12.5 mg, 45 %) as a white solid.

Mp: 149–152 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 13.92 (1H, s, OH), 9.51 (1H, s, OH), 7.20 (1H, s, H₁₁), 6.66 (1H, d, J = 2.3 Hz, H₁₀), 6.60 (1H, d, J = 2.2 Hz, H₈), 5.10 (1H, dd, J = 5.5, 2.7 Hz, H₃ₐ), 4.66 (1H, d, J = 2.7 Hz, H₁₁b), 4.17 (1H, m, H₁₂), 3.89 (3H, s, H₁₅), 2.62 (1H, ddd, J = 14.5, 8.7, 6.0 Hz, H₃A), 2.03 (1H, dd, J = 14.6, 5.5 Hz, H₃B), 1.71 (1H, br, H₁₂A), 1.58 (1H, br, H₁₂B), 1.47–1.30 (2H, m, H₁₃), 0.92 (3H, t, J = 7.3 Hz, H₁₄).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) 169.7 (C, C₅), 163.0 (C, C₉), 162.8 (C, C₆), 158.6 (C, C₇), 140.4 (C, C₁₀a), 129.6 (C, C₁₁a), 119.5 (CH, C₁₁), 109.3 (C, C₁₆a), 102.5 (CH, C₈), 100.3 (CH, C₁₁b), 97.6 (C, C₃a), 82.0 (CH, C₃a), 78.6 (CH, C₂), 74.9 (CH, C₁₁b), 55.5 (CH₃, C₁₅), 39.1 (CH₂, C₃), 38.2 (CH₂, C₁₂), 19.2 (CH₂, C₁₃), 14.0 (CH₃, C₁₄).

IR (Neat): v (cm⁻¹) 3410, 2958, 1644, 1587.

HRMS (ESI+): m/z calcd for C₁₉H₂₁NO₆ ([M + Na]+) 367.1152; found 367.1155.

[α]⁺⁻²⁻⁽\(\text{D}\)-] = −192 (c 0.129, CHCl₃).

(+)-2-epi-(−)-13 [α]⁺⁻²⁻⁽\(\text{D}\)-] = +197 (c 0.13, CHCl₃).

Chiral HPLC: Column DAICEL CHIRALPAK® AD-H, i-PrOH–hexanes (2:3), 0.5 mL/min, retention time 15.67 min, 97 % e.e..

(+)-2-epi-(−)-13 Chiral HPLC: Column DAICEL CHIRALPAK® AD-H, i-PrOH–hexanes (2:3), 0.5 mL/min, retention time 21.96 min, 99 % e.e..
Chapter Six

Pestaloxazine A
6.1. Early stage dimerisation strategy

6.1.1. Tetrahydro-3H,5H-dipyrrolo[1,2-a:1',2'-d]pyrazine-3,5,8,10(2H,5aH)-tetraone (292)

To a solution of acetic anhydride (35 mL) and pyridine (65 mL) stirred at 110 °C was added pyroglutamic acid (286) (7.70 g, 0.059 mol, 1.0 eq). The solution was allowed to stir at 110 °C for 30 min. The resulting suspension was cooled down to 0 °C and filtrated. The solid was sequentially washed with MeOH (20 mL), ether (20 mL), H₂O (20 mL) and MeOH (20 mL). The filtrate was dried under vacuum to afford the title compound 292 (4.90 g, 74 %) as a white solid.

Mp: 205–309 °C. [lit. 290 °C]

¹H NMR (400 MHz, (CD₃)₂SO): δ (ppm) 4.86 (2H, t, J = 8.4 Hz, H₂), 2.64–2.41 (4H, m, H₄), 2.29–2.13 (4H, m, H₃).

¹³C NMR (100 MHz, (CD₃)₂SO): δ (ppm) 172.7 (2 × C, C₅), 165.7 (2 × C, C₁), 58.4 (2 × CH, C₂), 31.3 (2 × CH₂, C₄), 18.9 (2 × CH₂, C₃).

Spectroscopic data and melting point were consistent with those previously reported.¹⁷²
6.1.2. 3,3’-(3,6-Dioxopiperazine-2,5-diyl)dipropionic acid (285)

To a solution of concentrated aqueous H₂SO₄ solution (30 mL) stirred at 0 °C was added DKP 292 (2.00 g, 9.00 mmol, 1.0 eq). The solution was allowed to stir at this temperature for 30 min and was then diluted in water (250 mL). The suspension was filtrated and the solid was sequentially washed with MeOH (20 mL), H₂O (20 mL), Et₂O (20 mL) and acetone (20 mL). The filtrated was dried under vacuum to afford the title compound 285 (525 mg, 45 %) as a white solid.

Mp: 245–247 °C. [lit. 245 °C]

¹H NMR (400 MHz, (CD₃)₂SO): δ (ppm) 12.12 (2H, s, OH), 8.19 (2H, s, NH), 3.89 (2H, t, J = 5.9 Hz, H₂), 2.38–2.23 (4H, m, H₄), 1.99–1.80 (4H, m, H₃).

¹³C NMR (100 MHz, (CD₃)₂SO): δ (ppm) 173.9 (2 × C, C₅), 167.8 (2 × C, C₁), 53.2 (2 × CH, C₂), 29.3 (2 × CH₂, C₄), 28.1 (2 × CH₂, C₃).

Spectroscopic data and melting point were consistent with those previously reported.¹⁷²
6.1.3. Dimethyl 3,3'-\(\text{dioxopiperazine-2,5-diyl}\)dipropionate (293)

To a solution of diketopiperazine 292 (600 mg, 2.70 mmol, 1.0 eq) in toluene (10 mL) stirred at 110 °C was added concentrated aqueous H\(_2\)SO\(_4\) solution (10 µL) and MeOH (5 mL). The solution was stirred at this temperature for 2 h, then the solution was cooled down to room temperature and the solvent removed \textit{in vacuo}. The resulting solid was washed with water (5 mL) and MeOH (5 mL) to give the \textit{title compound} 293 (140 mg, 23 %) as a white solid.

\textbf{Mp:} 185–187 °C. [lit. 185–187 °C]

\(^1\text{H NMR}\) (400 MHz, (CD\(_3\))\(_2\)SO): \(\delta\) (ppm) 8.19 (2H, s, NH), 3.89 (2H, t, \(J = 5.9\) Hz, H\(_2\)), 3.59 (6H, s, H\(_6\)), 2.46–2.33 (4H, m, H\(_3\)), 2.02–1.85 (4H, m, H\(_5\)).

\(^{13}\text{C NMR}\) (100 MHz, (CD\(_3\))\(_2\)SO): \(\delta\) (ppm) 172.8 (2 × C, C\(_5\)), 167.7 (2 × C, C\(_1\)), 53.2 (2 × CH, C\(_2\)), 51.3 (2 × CH\(_3\), C\(_6\)), 29.1 (2 × CH\(_2\), C\(_4\)), 27.3 (2 × CH\(_2\), C\(_3\)).

Spectroscopic data were consistent with those previously reported.\(^{172}\)
Chapter 6: Pestaloxazine A

6.1.4. Methyl 5-oxopyrrolidine-2-carboxylate (294)

![Chemical Structure]

To a solution of diketopiperazine 292 (1.30 g, 6.24 mmol, 1.0 eq) in methanol (25 mL) was added lithium chloride (167 mg, 3.91 mmol, 0.5 eq) and imidazole (1.31 g, 20.0 mmol, 3.2 eq). The solution was allowed to stir at reflux for 4 h, the reaction was cooled down to room temperature and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc to afford the title compound 294 (1.39 g, 77%) as a colorless oil.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\text{): } \delta \text{ (ppm) } 6.65 \text{ (1H, br, N}_2\text{), } 4.27 \text{ (1H, dd, } J = 8.7, 5.1 \text{ Hz, } H_4\text{), } 3.78 \text{ (3H, s, } H_6\text{), } 2.51-2.21 \text{ (4H, m, } H_2\text{ and } H_3\text{).} \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3\text{): } \delta \text{ (ppm) } 178.0 \text{ (C, } C_5\text{), } 172.5 \text{ (C, } C_1\text{), } 55.4 \text{ (C, } C_6\text{), } 52.6 \text{ (CH}_3\text{, } C_4\text{), } 29.1 \text{ (CH}_2\text{, } C_2\text{), } 24.8 \text{ (CH}_2\text{, } C_3\text{).} \]

Spectroscopic data were consistent with those previously reported.\(^{183}\)
6.2. Late stage dimerisation strategy

6.2.1. Dimethyl (S)-2-(tert-butoxycarbonylamino)pentandioate (298)

To a solution of L-glutamic acid (297) (10.0 g, 68.1 mmol, 1.0 eq) in MeOH (100 mL) at 0 °C was added dropwise trimethylsilyl chloride (46 mL, 0.36 mol, 5.3 eq) over 15 min. The reaction was allowed to slowly warm up to room temperature over 12 h. Triethylamine (66 mL, 0.47 mol, 7.0 eq) and Boc anhydride (17.0 g, 78.0 mmol, 1.1 eq) were sequentially added to the reaction. The reaction was allowed to stir at room temperature for 18 h. The solvent was removed in vacuo, the residue was dissolved in EtOAc (35 mL) and washed with H₂O (2 × 30 mL) and saturated aqueous NaCl solution (30 mL). The organic layer was dried over anhydrous Na₂SO₄ and the solvent removed under vacuum. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9 to 3:7) as eluent to afford the title compound 298 (18.4 g, 98 %) as a colorless oil.

**¹H NMR** (400 MHz, CDCl₃): δ (ppm) 5.14 (1H, s, NH), 4.28 (1H, s, H₂), 3.70 (3H, s, H₆), 3.63 (3H, s, H₇), 2.43–2.30 (2H, m, H₄), 2.17–2.08 (1H, m, H₃a), 1.95–1.85 (1H, m, H₃b), 1.38 (9H, s, H₁₀).

**¹³C NMR** (100 MHz, CDCl₃): δ (ppm) 173.1 (C, C₁), 172.6 (C, C₅), 155.3 (C, C₈), 79.9 (C, C₉), 52.8 (CH, C₂), 52.3 (CH₃, C₆), 51.7 (CH₃, C₇), 30.0 (CH₂, C₄), 28.2 (3 × CH₃, C₁₀), 27.7 (CH₂, C₃).

[α]D²²: +14.2 (c 1.3, CHCl₃) [lit. [α]D²⁸ +12.7 (c 1.8 , CHCl₃)]

Spectroscopic data were consistent with those previously reported.¹⁷³
6.2.2. Dimethyl (S)-2-[bis(tert-butoxycarbonyl)amino]pentanedioate (328)

To a solution of ester 298 (18.4 g, 67.1 mmol, 1.0 eq) in acetonitrile (100 mL) was added Boc anhydride (23.0 g, 0.11 mol, 1.6 eq) and DMAP (1.60 g, 13.0 mmol, 0.2 eq). The reaction was allowed to stir at room temperature for 16 h, then the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9 to 2:9) as eluent to afford the title compound 328 (18.4 g, 98 %) as a white solid.

Mp: 53–55 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 4.93 (1H, dd, $J$ = 9.7, 5.0 Hz, H$_2$), 3.70 (3H, s, H$_6$), 3.65 (3H, s, H$_7$), 2.52–2.35 (3H, m, H$_4$ and H$_{3a}$), 2.22–2.12 (1H, m, H$_{3b}$), 1.38 (18H, s, H$_{10}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 173.1 (C, C$_1$), 170.8 (C, C$_5$), 151.9 (2 × C, C$_8$), 83.3 (2 × C, C$_9$), 57.3 (CH, C$_2$), 52.2 (CH$_3$, C$_6$), 51.7 (CH$_3$, C$_7$), 30.6 (CH$_2$, C$_4$), 28.0 (6 × CH$_3$, C$_{10}$), 25.2 (CH$_2$, C$_3$).

$[\alpha]_D^{22}$: $-43.1$ (c 1.08, CHCl$_3$)[lit. $[\alpha]_D^{27}$ $-37.6$ (c 6.5 , CHCl$_3$)]

Spectroscopic data were consistent with those previously reported.$^{173}$
6.2.3. Methyl (S)-2-[bis(tert-butoxycarbonyl)amino]-5-hydroxypentanoate (291)

To a solution of ester 328 (1.00 g, 26.9 mmol, 1.0 eq) in THF (10 mL) at −40 °C was added dropwise LiAlH₄ (7.3 mL, 58.8 mmol, 2.2 eq, 0.8 M in THF). The reaction was allowed to stir at this temperature for 1 h. The reaction was quenched with saturated aqueous Rochelle’s salt solution (15 mL). The resulting biphasic solution was allowed to stir at room temperature for 1 h and was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H₂O (35 mL), saturated aqueous NaCl solution (35 mL), dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9 to 2:9) as eluent to afford the title compound 291 (18.4 g, 98 %) as a white solid.

Mp: 54–56 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 4.89 (1H, dd, J = 9.1, 5.5 Hz, H₂), 3.72 (3H, s, H₆), 3.67 (2H, m, H₅), 2.30–2.18 (1H, m, H₃a), 1.98–1.88 (1H, m, H₃b), 1.68–1.60 (2H, m, H₄), 1.58 (1H, s, OH), 1.50 (18H, s, H₉).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 171.4 (C, C₁), 152.2 (2 × C, C₇), 83.3 (2 × C, C₈), 62.4 (CH₂, C₅), 57.3 (CH, C₂), 52.2 (CH₃, C₆), 29.4 (CH₂, C₄), 28.0 (6 × CH₃, C₁₀), 26.5 (CH₂, C₃).

[α]²²D: −38.5 (c 1.05, CHCl₃). [lit. [α]²⁷D −37.9 (c 4.0, CHCl₃)]

Spectroscopic data were consistent with those previously reported.¹⁷³
6.2.4. Methyl 5-acetoxy-2-[bis(tert-butoxycarbonyl)amino]pentanoate (300)

To a solution of alcohol 291 (51.0 mg, 0.143 mmol, 1.0 eq) in benzene under UV irradiation (1 mL) was added Pb(OAc)$_4$ (150 mg, 0.200 mmol, 2.4 eq). The solution was allowed to stir at 50 °C for 3 h before cooled down to room temperature. The solution was diluted in Et$_2$O (5 mL) and filtrate through a pad of Celite$^\circledR$ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (2:8) as eluent to afford the title compound 300 (17 mg, 37 %) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 4.88 (1H, dd, $J = 9.5, 5.2$ Hz, H$_2$), 4.11–4.05 (2H, m, H$_5$), 3.70 (3H, s, H$_6$), 2.24–2.14 (1H, m, H$_{3a}$), 2.04 (3H, s, H$_8$), 2.00–1.90 (1H, m, H$_{3b}$), 1.75–1.66 (2H, m, H$_4$), 1.48 (18H, s, H$_{11}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 171.1 (C, C$_1$), 171.1 (C, C$_7$), 152.1 (2 × C, C$_9$), 82.8 (2 × C, C$_{10}$), 63.9 (CH$_2$, C$_3$), 58.7 (CH, C$_2$), 52.4 (CH$_3$, C$_6$), 27.8 (6 × CH$_3$, C$_9$), 26.8 (CH$_2$, C$_2$), 25.6 (CH$_2$, C$_3$), 21.1 (CH$_3$, C$_8$).

IR (Neat): $\nu$ (cm$^{-1}$) 2980, 1738, 1366, 1230.

HRMS (ESI+): $m/z$ calcd for C$_{18}$H$_{31}$HNNaO$_8$ ([M + Na]$^+$) 412.1940; found 412.1922.

$[\alpha]_D^{22}$: $-46.1$ (c 0.13, CHCl$_3$).
6.2.5. Methyl 2-[bis(tert-butoxycarbonyl)amino]tetrahydrofuran-2-carboxylate (299)

To a solution of alcohol 291 (50 mg, 0.14 mmol, 1.0 eq) in cyclohexane (15 mL) was added PIDA (107 mg, 0.23 mmol, 2.0 eq) and iodine (76 mg, 0.29 mmol, 1.0 eq). The solution was stirred at 50 °C under UV-Vis irradiation for 3 h. The reaction was quenched with saturated aqueous Na$_2$S$_2$O$_3$ solution (10 mL) and extracted with EtOAc (10 mL). The organic layer was sequentially washed with H$_2$O (15 mL) and saturated aqueous NaCl solution (5 × 15 mL). The organic layer was dried over anhydrous MgSO$_4$ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:2) as eluent to give the title compound 299 (21 mg, 43 %) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 4.11–3.99 (2H, m, H$_1$), 3.77 (3H, s, H$_6$), 2.60–2.49 (2H, m, H$_3$), 2.19–1.98 (2H, m, H$_2$), 1.48 (18H, s, H$_9$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 170.0 (C, C$_5$), 151.7 (2 × C, C$_7$), 94.9 (C, C$_4$), 82.8 (2 × C, C$_8$), 70.7 (CH$_2$, C$_1$), 52.8 (CH$_3$, C$_6$), 35.6 (CH$_2$, C$_3$), 27.8 (6 × CH$_3$, C$_9$), 25.1 (CH$_2$, C$_2$).

IR (Neat): $\nu$ (cm$^{-1}$) 2979, 1748, 1709, 1119.

HRMS (ESI+): $m/z$ calcd for C$_{16}$H$_{27}$NNaO$_7$ ([M + Na]$^+$) 368.1680; found 368.1682.

$[\alpha]_D^{22}$: −2.80 (c 0.89, CDCl$_3$).
6.2.6. *N*-Acetoxybenzamide (303)

To a solution of hydroxylamine hydrochloride (2.80 g, 41.0 mmol, 4.2 eq) and sodium hydroxide (2.00 g, 50.0 mmol, 5.2 eq) in H₂O (20 mL) was added dropwise a solution of benzoyl chloride (304) (1.20 mL, 10.0 mmol, 1.0 eq) in THF (30 mL). The suspension was allowed to stir at room temperature for 16 h, then THF was removed in vacuo and the resulting solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (50 mL) and saturated aqueous NaCl solution (50 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent removed in vacuo giving hydroxamic acid (329) as a white solid. Crude hydroxamic acid 329 was dissolved in THF (20 mL) and triethylamine (1.80 mL, 13.0 mmol, 1.3 eq) and acetic anhydride (1.30 mL, 14.0 mmol, 1.4 eq) were added dropwise. The solution was allowed to stir at room temperature for 5 h. The reaction was quenched with H₂O (25 mL) and extracted with EtOAc (30 mL). The organic layer was washed with H₂O (35 mL) and saturated aqueous NaCl solution (35 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (2:3) as eluent to afford the title compound 303 (1.28 g, 75 %) as a white solid.

**Mp:** 126–128 °C.[lit. 126 °C]

**:H NMR** (400 MHz, CDCl₃): δ (ppm) 9.50 (1H, s, NH), 7.82 (2H, m, H₃), 7.57 (1H, m, H₅), 7.47 (2H, m, H₄), 2.30 (3H, S, H₇).

**:C NMR** (100 MHz, CDCl₃): δ (ppm) 169.2 (C, C₆), 166.5 (C, C₄), 132.9 (CH, C₃), 130.7 (C, C₂), 128.9 (2 × CH, C₄), 127.5 (2 × CH, C₃), 18.4 (CH₃, C₇).

Melting point and spectroscopic data were consistent with those previously reported.¹⁷⁴
6.2.7. Methyl
(2S,Z)-5-[(acetoxyimino)benzylloxy]-2-[bis(tert-butoxycarbonyl)amino]pentanoate
(308)

\[
\text{MeO} - \text{Boc}_2 \quad \text{OH} \quad + \quad \begin{array}{c}
\text{H} \\
\text{OAc}
\end{array}
\rightarrow \quad \begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\]

291
303
308

To a solution of alcohol 291 (1.00 g, 2.91 mmol, 1.0 eq), hydroxamate 303 (0.57 g, 3.20 mmol, 1.1 eq) and triphenylphosphine (0.98 mg, 3.69 mmol, 1.3 eq) in THF (20 mL) stirred at 0 °C was added dropwise DIAD (0.76 mL, 3.48 mmol, 1.2 eq). The solution was allowed to stir at this temperature for 2 h. The reaction was quenched with 1 M citric acid aqueous solution (15 mL) and extracted with EtOAc (20 mL). The organic layer was sequentially washed with H₂O (20 mL) and saturated aqueous NaCl solution (20 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:4 to 2:3) as eluent to give the title compound 308 (1.10 g, 71 %) as a colorless oil.

**¹H NMR** (400 MHz, CDCl₃): \( \delta \) (ppm) 7.28 (2H, d, \( J = 6.8 \) Hz, H₁₂), 7.46–7.35 (3H, m, H₁₃ and H₁₄), 4.88 (1H, dd, \( J = 9.3, 5.4 \) Hz, H₂), 4.22 (2H, m, H₅), 3.68 (3H, s, H₆), 2.36–2.25 (1H, m, H₃a), 2.20 (3H, s, H₁₆), 2.06–1.95 (1H, m, H₃b), 1.85–1.72 (2H, m, H₄), 1.46 (18H, s, H₉).

**¹³C NMR** (100 MHz, CDCl₃): \( \delta \) (ppm) 171.0 (C, C₁), 168.1 (C, C₁₅), 160.6 (C, C₁₀), 152.1 (2 × C, C₇), 131.2 (CH, C₁₄), 129.2 (C, C₁₁), 128.5 (2 × CH, C₁₃), 128.3 (2 × CH, C₁₂), 83.3 (2 × C, C₈), 72.2 (CH₂, C₄), 57.6 (CH, C₂), 52.2 (CH₃, C₆), 28.0 (6 × CH₃, C₉), 26.9 (CH₂, C₄), 26.4 (CH₂, C₃), 19.6 (CH₃, C₁₆).

**IR** (Neat): \( \nu \) (cm⁻¹) 2980, 1744, 1698, 1366.

**HRMS** (ESI +): \( m/z \) calcd for C₂₅H₃₆N₂NaO₉ ([M + Na]⁺) 531.2313; found 531.2305.

\([\alpha]^{20}_D\) : -24.4 (c 0.65, CHCl₃).
6.2.8. Methyl

(2S,Z)-5-[(hydroxyimino)benzoyloxy]-2-[bis(tert-butoxycarbonyl)amino]pentanoate (308)

To a solution of oxime 208 (54 mg, 0.10 mmol, 1.0 eq) in methanol (3 mL) at room temperature was added potassium hydroxide (5.0 mg, 0.11 mmol, 1.1 eq) and magnesium (5 mg, 0.21 mmol, 2.0 eq). The solution was allowed to stir at this temperature for 1 h. The reaction was quenched with 1 M aqueous citric acid solution (3 mL) and extracted with EtOAc (10 mL). The organic layer was washed with H2O (7 mL) and saturated aqueous NaCl solution (7 mL). The organic layer was dried over anhydrous MgSO4 and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:4 to 1:1) as eluent to give the title compound (Z)-307 (46 mg, 91%) as a colorless oil. Alkene (Z)-307 isomerised over time to give a 1:1 mixture of alkene (Z)-307 and (E)-307.

(Z)-307:

1H NMR (400 MHz, CDCl3): δ (ppm) 7.65 (2H, dd, J = 7.9, 1.7 Hz, H12), 7.40 (3H, m, H13 and H14), 7.30 (1H, br, OH), 4.91 (1H, dd, J = 9.2, 5.4 Hz, H2), 4.22 (2H, t, J = 6.5 Hz, H5), 3.72 (3H, s, H6), 2.35–2.25 (1H, m, H3a), 2.09–1.90 (1H, m, H3b), 1.89–1.78 (2H, m, H4), 1.49 (18H, s, H9).

13C NMR (100 MHz, CDCl3): δ (ppm) 171.1 (C, C1), 156.1 (C, C10), 152.1 (2× C, C7), 130.5 (C, C11), 130.1 (CH, C14), 128.5 (2× CH, C13), 127.2 (2× CH, C12), 83.3 (2× C, C8), 71.2 (CH2, C5), 57.8 (CH, C2), 52.2 (CH3, C6), 28.0 (6× CH3, C9), 27.0 (CH2, C3), 26.4 (CH2, C4).

IR (Neat): ν (cm⁻¹) 3448, 2980, 1737, 1367.

HRMS (ESI+): m/z calcd for C23H34N2NaO8 ([M + Na]+) 489.2207; found 489.2189.

[α]D: −20.4 (c 1.73, CDCl3).

(E)-307:

1H NMR (400 MHz, CDCl3): δ (ppm) 7.81 (2H, dd, J = 7.9, 1.7 Hz, H12), 7.42 (3H, m, H13 and H14), 6.99 (1H, br, OH), 4.92 (1H, dd, J = 9.7, 5.4 Hz, H2), 4.14 (2H, t, J = 6.5 Hz, H5), 3.71
(3H, s, H₆), 2.35–2.25 (1H, m, H₃a), 2.09–1.94 (1H, m, H₃b), 1.87–1.77 (2H, m, H₄), 1.49 (18H, s, H₉).

**¹³C NMR** (100 MHz, CDCl₃): δ (ppm) 171.1 (C, C₁), 156.1 (C, C₁₀), 152.1 (2 × C, C₇), 130.5 (C, C₁₁), 130.1 (CH, C₁₄), 128.5 (2 × CH, C₁₃), 127.2 (2 × CH, C₁₂), 83.3 (2 × C, C₈), 71.2 (CH₂, C₅), 57.8 (CH, C₂), 52.2 (CH₃, C₆), 28.0 (6 × CH₃, C₉), 27.0 (CH₂, C₃), 26.4 (CH₂, C₄).

**IR** (Neat): ν (cm⁻¹) 3448, 2980, 1737, 1367.

**HRMS** (ESI+): m/z calcd for C₂₃H₂₄N₂NaO₈ ([M + Na]⁺) 489.2207; found 489.2189.

[α]D²⁰: −18.6 (c 0.45, CDCl₃).
6.2.9. Methyl (2S)-5-benzoyl-2-[bis(tert-butoxycarbonyl)amino]pentanoate (306)

To a solution of oxime 307 (42 mg, 0.09 mmol, 1.0 eq) in cyclohexane (3 mL) was added PIDA (60 mg, 0.18 mmol, 2.0 eq) and iodine (30 mg, 0.09 mmol, 1.0 eq). The solution was stirred at 50 °C under UV-Vis irradiation for 3 h. The reaction was quenched with saturated aqueous Na2S2O3 solution (5 mL) and extracted with EtOAc (7 mL). The organic layer was sequentially washed with water (5 mL) and saturated aqueous NaCl solution (5 mL). The organic layer was dried over anhydrous MgSO4 and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9 to 3:7) as eluent to give the title compound 306 (35 mg, 84 %) as a colorless oil.

1H NMR (400 MHz, CDCl3): δ (ppm) 8.03 (2H, d, J = 7.6 Hz, H12), 7.56 (1H, t, J = 7.3 Hz, H14), 7.43 (2H, t, J = 7.8 Hz, H13), 4.94 (1H, dd, J = 9.2, 5.4 Hz, H2), 4.35 (2H, m, H5), 3.72 (3H, s, H6), 2.34–2.26 (1H, m, H3a), 2.10–2.06 (1H, m, H3b), 1.89–1.80 (2H, m, H4), 1.50 (18H, s, H9).

13C NMR (100 MHz, CDCl3): δ (ppm) 171.1 (C, C1), 166.5 (C, C10), 152.1 (2 × C, C7), 130.3 (C, C11), 132.9 (CH, C14), 129.6 (2 × CH, C13), 128.3 (2 × CH, C12), 93.3 (2 × C, C6), 64.3 (CH2, C3), 57.5 (CH, C2), 52.2 (CH3, C6), 27.9 (6 × CH3, C9), 26.6 (CH2, C3), 25.7 (CH2, C4).

IR (Neat): v (cm⁻¹) 2981, 1746, 1716, 1270.

HRMS (ESI+): m/z calcd for C23H33NNaO8 ([M + Na]+) 474.2098; found 474.2088.

[α]D²⁰: −22.9 (c 0.903, CDCl3).
6.2.10. Benzyl hydroxycarbamate (330)

To a solution of sodium bicarbonate (6.50 g, 61.9 mmol, 1.8 eq) and hydroxylamine hydrochloride (3.20 g, 43.6 mmol, 1.3 eq) in H$_2$O (20 mL) was added dropwise a solution of Cbz chloride (312) (5.8 mL, 28.1 mmol, 1.0 eq) in CH$_2$Cl$_2$ (20 mL). The reaction was allowed to stir at room temperature for 3 h. The reaction was quenched with 1 M citric acid aqueous solution (30 mL) and extracted with EtOAc (40 mL). The organic layer was sequentially washed with H$_2$O (35 mL) and saturated aqueous NaCl solution (35 mL). The organic layer was dried over anhydrous MgSO$_4$ and the solvent removed in vacuo. The crude residue was purified by recrystallisation in Et$_2$O-hexanes to give the title compound 330 (4.10 g, 84 %) as a colorless solid.

Mp: 63–65 °C [lit. 62–63 °C].

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.66 (2H, s, NH and OH), 7.29 (5H, m, H$_4$, H$_5$ and H$_6$), 5.09 (2H, s, H$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) 159.4 (C, C$_1$), 135.5 (C, C$_3$), 128.6 (2 × CH$_2$, C$_5$), 128.5 (CH, C$_6$), 128.3 (2 × CH$_2$, C$_4$), 67.8 (CH$_2$, C$_2$).

Melting point and spectroscopic data were consistent with those previously reported.$^{178}$
6.2.11. Benzyl acetoxy carbamate (311)

To a solution of hydroxycarbamate 330 (1.20 g, 7.20 mmol, 1.0 eq) in pyridine (5 mL) stirred at 0 °C was added dropwise acetic anhydride (600 mL). The solution was allowed to stir at this temperature for 4 h. The reaction was quenched with saturated aqueous CuSO₄ solution (7 mL) and extracted with EtOAc (15 mL). The organic layer was sequentially washed with saturated aqueous CuSO₄ solution (2 × 10 mL), H₂O (10 mL) and saturated aqueous NaCl solution (10 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9 to 2:8) as eluent to give the title compound 311 (1.10 g, 70 %) as a colorless solid.

Mp: 38–40 °C.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.32 (1H, s, NH), 7.35 (5H, m, H₄, H₅ and H₆), 5.19 (2H, s, H₂), 2.16 (3H, s, H₈).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8 (C, C₇), 156.4 (C, C₁), 135.5 (C, C₃), 128.7 (2 × CH, C₅), 128.6 (CH, C₆), 128.3 (2 × CH, C₄), 68.3 (CH₂, C₂), 18.3 (CH₃, C₈).

IR (Neat): ν (cm⁻¹) 3228, 1795, 1708, 1279.

HRMS (ESI+): m/z calcd for C₁₀H₁₁NNaO₄ ([M + Na]⁺) 232.0580; found 232.0586.
6.2.12. Methyl (S)-5-(acetoxy[(benzyloxy)carbonyl]amino)-2-[bis(tert-butoxycarbonyl)amino]pentanoate (313)

To a solution of alcohol 291 (100 mg, 0.29 mmol, 1.0 eq), hydroxamate 311 (68 mg, 0.32 mmol, 1.1 eq) and triphenylphosphine (100 mg, 0.37 mmol, 1.3 eq) in THF (5 mL) stirred at 0 °C was added dropwise DIAD (75 µL, 0.34 mmol, 1.2 eq). The solution was allowed to stir at this temperature for 2 h. The reaction was quenched with 1 M citric acid aqueous solution (15 mL) and extracted with EtOAc (20 mL). The organic layer was sequentially washed with H2O (20 mL) and saturated aqueous NaCl solution (20 mL). The organic layer was dried over anhydrous MgSO4 and the solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:4 to 2:3) as eluent to give the title compound 313 (117 g, 75 %) as a colorless oil.

1H NMR (400 MHz, CDCl3): δ (ppm) 7.71 (5H, m, H15, H16 and H17), 5.15 (2H, s, H13), 4.88 (1H, dd, J = 9.5, 5.1 Hz, H2), 3.68 (5H, m, H5 and H6), 2.20–2.10 (4H, m, H3a and H11), 2.06–1.95 (1H, m, H3b), 1.69–1.59 (2H, m, H4), 1.46 (18H, s, H9).

13C NMR (100 MHz, CDCl3): δ (ppm) 171.0 (C, C1), 168.3 (C, C10), 155.3 (C, C12), 152.1 (2 × C, C7), 135.2 (CH, C17), 128.5 (2 × CH, C16), 128.2 (C, C14), 127.9 (2 × CH, C15), 83.3 (2 × C, C8), 68.2 (CH2, C13), 57.6 (CH, C2), 52.2 (CH3, C6), 50.1 (CH2, C3), 28.0 (6 × CH3, C9), 26.9 (CH2, C5), 24.0 (CH2, C4), 19.6 (CH3, C11).

IR (Neat): ν (cm−1) 2981, 1794, 1740, 1367.

HRMS (ESI+): m/z calcd for C26H38N2NaO10 ([M + Na]+) 561.2419; found 561.2422.

[α]D20: −23.2 (c 0.935, CDCl3).
6.2.13. Methyl (S)-5-\{[(benzyloxy)carbonyl](hydroxy)amino\}-2-[bis(tert-butoxycarbonyl)amino]pentanoate (309)

To a solution of hydroxamate 313 (100 mg, 0.19 mmol, 1.0 eq) in methanol (5 mL) was added potassium bicarbonate (5.0 mg, 36.0 µmol, 0.2 eq). The solution was allowed to stir at room temperature for 2 h. The reaction was quenched with 1 M citric acid aqueous solution (5 mL) and extracted with EtOAc (10 mL). The organic layer was washed with water (7 mL) and saturated aqueous NaCl solution (7 mL). The organic layer was dried over anhydrous MgSO4 and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (4:6 to 7:3) as eluent to give the title compound 309 (85 mg, 91 %) as a colorless oil.

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{): } \delta (\text{ppm}) 7.33 (5H, m, H\textsubscript{13}, H\textsubscript{14} and H\textsubscript{15}), 5.16 (2H, s, H\textsubscript{11}), 4.87 (1H, dd, J = 9.2, 5.4 Hz, H\textsubscript{2}), 3.69 (3H, s, H\textsubscript{6}), 3.57 (2H, td, J = 10.0, 1.8 Hz, H\textsubscript{5}), 2.20–2.12 (1H, m, H\textsubscript{3a}), 1.95–1.85 (1H, m, H\textsubscript{3b}), 1.74–1.67 (2H, m, H\textsubscript{4}), 1.48 (18H, s, H\textsubscript{9}).\]

\[\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{): } \delta (\text{ppm}) 171.2 (C, C\textsubscript{1}), 157.4 (C, C\textsubscript{10}), 152.2 (2 \times C, C\textsubscript{7}), 136.0 (CH, C\textsubscript{15}), 128.5 (2 \times CH, C\textsubscript{14}), 128.1 (C, C\textsubscript{12}), 128.0 (2 \times CH, C\textsubscript{13}), 83.3 (2 \times C, C\textsubscript{8}), 67.9 (CH\textsubscript{2}, C\textsubscript{11}), 57.6 (CH, C\textsubscript{2}), 52.2 (CH\textsubscript{3}, C\textsubscript{6}), 49.9 (CH\textsubscript{2}, C\textsubscript{5}), 27.9 (6 \times CH\textsubscript{3}, C\textsubscript{9}), 26.8 (CH\textsubscript{2}, C\textsubscript{3}), 23.3 (CH\textsubscript{2}, C\textsubscript{4}).\]

\[\text{IR (Neat): } \nu (\text{cm}^{-1}) 3337, 2981, 1729, 1367.\]

\[\text{HRMS (ESI\textsuperscript{+}): } m/z \text{ calcd for C}_{24}H_{36}N_{2}NaO_{9} ([M + Na]\textsuperscript{+}) 519.2313; \text{ found 519.2311}.\]

\[\text{[\alpha]D}^{20}_{\text{D}}: -18.3 (c 0.36, CDCl}_3\text{).}\]
6.2.14. Methyl N-acetoxy-N-((benzoyloxy)carbonyl)-N,N-bis(tert-butoxycarbonyl) L-glutamate (315)

To a solution of hydroxamate 309 (100 mg, 0.20 mmol, 1.0 eq) in cyclohexane (5 mL) was added PIDA (130 mg, 0.40 mmol, 2.0 eq) and iodine (68 mg, 0.20 mmol, 1.0 eq). The solution was stirred at 50 °C under UV-Vis irradiation for 3 h. The reaction was quenched with saturated aqueous Na₂S₂O₃ solution (10 mL) and extracted with EtOAc (15 mL). The organic layer was sequentially washed with water (10 mL) and saturated aqueous NaCl solution (10 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography on silica gel using EtOAc–PE (1:9) as eluent to give the title compound 315 (52 mg, 48 %) as a colorless oil.

1H NMR (400 MHz, CDCl₃): δ (ppm) 7.40–7.31 (5H, m, H₁₃, H₁₄ and H₁₅), 5.23 (2H, s, H₁₁), 4.96 (1H, dd, J = 9.1, 5.5 Hz, H₂), 3.69 (3H, s, H₆), 3.09–2.92 (2H, m, H₄), 2.60–2.40 (1H, m, H₃α), 2.20–2.10 (4H, m, H₃β and H₁₇), 1.48 (18H, s, H₉).

13C NMR (100 MHz, CDCl₃): δ (ppm) 170.7 (C, C₁), 168.6 (C, C₁₆), 167.2 (C, C₅), 151.8 (2 × C, C₇), 151.0 (C, C₁₀), 134.4 (C, C₁₂), 128.8 (CH, C₁₅), 128.1 (2 × CH, C₁₄), 128.2 (2 × CH, C₁₃), 83.3 (2 × C, C₈), 69.3 (CH₂, C₁₁), 57.2 (CH, C₂), 52.2 (CH₃, C₆), 33.4 (CH₂, C₄), 27.9 (6 × CH₃, C₉), 24.8 (CH₂, C₃), 17.7 (CH₃, C₁₇).

IR (Neat): ν (cm⁻¹) 2980, 1806, 1744, 1367.

HRMS (ESI+): m/z calcd for C₂₆H₃₆N₂NaO₁₁ ([M + Na]⁺) 575.2211; found 575.2200.

[α]D²²: −39.1 (c 0.39, CDCl₃)
Appendix

Selected NMR Spectra

&

HPLC Data
IN NMR (CDCl₃, 400 MHz, vpor01-154)

13C NMR (CDCl₃, 100 MHz, vpor01-154)
Appendix

$^{1}H$ NMR (CDCl$_3$, 400 MHz, vpor01-156)

$^{13}C$ NMR (CDCl$_3$, 125 MHz, vpor01-156)
### Appendix

#### vpor02-156_90:10_AD

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**Dilution Factor:** 1.0000  
**Recording Time:** 4/14/2015 11:25  
**Sample Weight:** 1.0000  
**Run Time (min):** 51.51  
**Sample Amount:** 1.0000

![Graph of vpor02-156_90:10_AD with peaks and retention times]

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Appendix

1  vpor03-147_90:10_AD

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![Chemical Structure](image)

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<th>No.</th>
<th>Ret.Time</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU*min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43.71</td>
<td>n.a.</td>
<td>263.632</td>
<td>238.300</td>
<td>99.33</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>46.44</td>
<td>n.a.</td>
<td>1.909</td>
<td>1.612</td>
<td>0.67</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
</tbody>
</table>

Total:

265.541  239.912  100.00  0.000
Appendix

1  vpor04-013_90:10_AD

Sample Name:  vpor04-013_90:10_AD  Injection Volume:  20.0
Val Number: 0  Channel: UV_VIS_1
Sample Type: unknown  Wavelength:  210
Control Program: alcohol 65_35  Bandwidth: n.a.
Quantf. Method: default  Dilution Factor:  1.0000
Recording Time: 4/14/2015 12:20  Sample Weight:  1.0000
Run Time (min): 54.02  Sample Amount:  1.0000

No.  Ret.Time  Peak Name  Height  Area  Rel.Area Amount  Type
     min  mAU   mAU*min  %   n.a.  n.a.         
1     43.24  n.a.   3.736   3.172   0.74  n.a.  BMB* 
2     45.71  n.a.   441.341 422.968  99.26  n.a.  bMB* 
Total: 445.076 426.140 100.00  0.000
# Lasionectrin-rac_60:40_AD

<table>
<thead>
<tr>
<th>Sample Name:</th>
<th>Lasionectrin-rac_60:40_AD</th>
<th>Injection Volume:</th>
<th>20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial Number:</td>
<td>0</td>
<td>Channel:</td>
<td>UV_VIS_2</td>
</tr>
<tr>
<td>Sample Type:</td>
<td>unknown</td>
<td>Wavelength:</td>
<td>254</td>
</tr>
<tr>
<td>Control Program:</td>
<td>alcohol 65_35</td>
<td>Bandwidth:</td>
<td>n.a.</td>
</tr>
<tr>
<td>Quantif. Method:</td>
<td>default</td>
<td>Dilution Factor:</td>
<td>1.000</td>
</tr>
<tr>
<td>Recording Time:</td>
<td>4/15/2015 12:22</td>
<td>Sample Weight:</td>
<td>1.000</td>
</tr>
<tr>
<td>Run Time (min):</td>
<td>38.57</td>
<td>Sample Amount:</td>
<td>1.000</td>
</tr>
</tbody>
</table>

![Graph of Lasionectrin-rac_60:40_AD](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time</th>
<th>Peak Name</th>
<th>Height</th>
<th>Area</th>
<th>Rel.Area</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.57</td>
<td>n.a.</td>
<td>669.358</td>
<td>275.713</td>
<td>49.59</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>21.38</td>
<td>n.a.</td>
<td>471.163</td>
<td>280.246</td>
<td>50.41</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
</tbody>
</table>

Total: 1140.462 555.959 100.00 0.000
## 1 Lasionectrin-(-) 60:40_AD

<table>
<thead>
<tr>
<th>Sample Name:</th>
<th>Lasionectrin-(-) 60:40_AD</th>
<th>Injection Volume:</th>
<th>20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial Number:</td>
<td>0</td>
<td>Channel:</td>
<td>UV_VIS_2</td>
</tr>
<tr>
<td>Sample Type:</td>
<td>unknown</td>
<td>Wavelength:</td>
<td>254</td>
</tr>
<tr>
<td>Control Program:</td>
<td>alcohol 65_35</td>
<td>Bandwidth:</td>
<td>n.a.</td>
</tr>
<tr>
<td>Quantif. Method:</td>
<td>default</td>
<td>Dilution Factor:</td>
<td>1.0000</td>
</tr>
<tr>
<td>Recording Time:</td>
<td>4/15/2015 13:12</td>
<td>Sample Weight:</td>
<td>1.0000</td>
</tr>
<tr>
<td>Run Time (min):</td>
<td>47.81</td>
<td>Sample Amount:</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

![Chromatogram of Lasionectrin-(-) 60:40_AD](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time</th>
<th>Peak Name</th>
<th>Height</th>
<th>Area</th>
<th>Rel.Area</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.39</td>
<td>n.a.</td>
<td>974,830</td>
<td>383,670</td>
<td>98.87</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>21.31</td>
<td>n.a.</td>
<td>7,228</td>
<td>4,368</td>
<td>1.13</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td></td>
<td>982,058</td>
<td>388,039</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

---

Appendix
Appendix

1 Lasionectrin-(+).2_60:40_AD

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Injection Volume</th>
<th>Vial Number</th>
<th>Channel</th>
<th>Sample Type</th>
<th>Wavelength</th>
<th>Control Program</th>
<th>Quantif. Method</th>
<th>Recording Time</th>
<th>Run Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasionectrin-(+).2_60:40_AD</td>
<td>20.0</td>
<td>0</td>
<td>UV_VIS_2</td>
<td>unknown</td>
<td>254</td>
<td>alcohol 65_35</td>
<td>default</td>
<td>1/1/2015 13:42</td>
<td>35.81</td>
</tr>
</tbody>
</table>

![UV-Visible spectrum of Lasionectrin-(+).2_60:40_AD](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU*min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.99</td>
<td>n.a.</td>
<td>39.975</td>
<td>14.581</td>
<td>1.42</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>20.38</td>
<td>n.a.</td>
<td>1361.423</td>
<td>1012.945</td>
<td>98.58</td>
<td>n.a.</td>
<td>BMB**</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1401.398</td>
<td>1027.527</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>


1 Lasionectrin-dia-(−).2_60:40_AD

<table>
<thead>
<tr>
<th>Sample Name:</th>
<th>Lasionectrin-dia-(−).2_60:40_AD</th>
<th>Injection Volume:</th>
<th>20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial Number:</td>
<td>0</td>
<td>Channel:</td>
<td>UV_VIS_2</td>
</tr>
<tr>
<td>Sample Type:</td>
<td>unknown</td>
<td>Wavelength:</td>
<td>254</td>
</tr>
<tr>
<td>Control Program:</td>
<td>alcohol 65_35</td>
<td>Bandwidth:</td>
<td>n.a.</td>
</tr>
<tr>
<td>Quantif. Method:</td>
<td>default</td>
<td>Dilution Factor:</td>
<td>1.0000</td>
</tr>
<tr>
<td>Recording Time:</td>
<td>11/14/2015 16:32</td>
<td>Sample Weight:</td>
<td>1.0000</td>
</tr>
<tr>
<td>Run Time (min):</td>
<td>30.39</td>
<td>Sample Amount:</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time min</th>
<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU*min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.67</td>
<td>n.a.</td>
<td>632.916</td>
<td>257.799</td>
<td>98.72</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>21.37</td>
<td>n.a.</td>
<td>6.617</td>
<td>3.343</td>
<td>1.28</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>639.533</td>
<td>261.141</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>
Appendix

1 Lasionectrin-dia-(+).2_60:40_AD

Sample Name: Lasionectrin-dia-(+).2_60:40_AD  Injection Volume: 20.0
Vial Number: 0  Channel: UV_VIS_2
Sample Type: unknown  Wavelength: 254
Control Program: alcohol 65_35  Bandwidth: n.a.
Quantf. Method: default  Dilution Factor: 1.0000
Recording Time: 7/14/2015 18:39  Sample Weight: 1.0000
Run Time (min): 33.03  Sample Amount: 1.0000

![UV Chromatogram](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU min)</th>
<th>Rel.Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.45</td>
<td>n.a.</td>
<td>1.369</td>
<td>0.459</td>
<td>0.19</td>
<td>n.a.</td>
<td>EMB*</td>
</tr>
<tr>
<td>2</td>
<td>21.96</td>
<td>n.a.</td>
<td>436.544</td>
<td>235.988</td>
<td>99.81</td>
<td>n.a.</td>
<td>EMB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>437.913</td>
<td>236.447</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

(--)-2-epi-13
Appendix

\[
\text{LM NMR (CDCl}_3, 400 MHz, (Z)-p-x=027)}
\]

\[
\text{(Z)-307}
\]

\[
\text{13C NMR (CDCl}_3, 100 MHz, (Z)-p-x=027)}
\]
Appendix
Appendix

1H NMR (CDCl₃, 400 MHz, ps=0.3)

\[
\begin{array}{c}
\text{Bn} & \text{O} \\
\text{OAc} & \text{NBoc} \, ₂ \\
\text{OMe} & \\
\end{array}
\]

\textbf{313}

13C NMR (CDCl₃, 100 MHz, ps=0.3)
References

References

References

References