Synthesis of Heterocyclic Natural Products and Analogues

by

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Abstract

Organic compounds that contain rings composed of carbon and other atoms such as nitrogen, oxygen, sulfur or phosphorus are referred to as heterocyclic compounds. Compounds of this type are frequently encountered in natural products and a majority of all biologically-active molecules are heterocycles. This thesis concerns the synthesis of three distinct classes of heterocyclic natural products and analogues.

Likonide B and smenochromene C are two structurally-related oxygen-containing heterocyclic marine natural products that feature a unique ansa-bridged farnesyl quinol moiety which is considered to be an interesting structural motif for synthetic studies. The total syntheses of these two natural products were completed in an efficient manner from commercially-available starting materials. The employment of a phenylboronic acid-mediated condensation reaction of phenols and $\alpha,\beta$-unsaturated aldehydes, and a palladium-catalyzed O-allylation reaction constituted a potentially biomimetic total synthesis of these two natural products.

Platensimycin, an oxygen-containing heterocyclic compound, is a new class of antibiotic. Its complex tetracyclic ketolide structure motif represents a considerable synthetic challenge. By manipulating the oxygenation pattern of this tetracyclic core, it was proposed that an asymmetric domino double Stetter reaction of an achiral molecule could be used to prepare the tricyclic skeleton of this compound with all the stereogenic centres correctly installed in a single synthetic transformation. After considerable experimentation, the key achiral compound was prepared in five steps from commercially-available starting materials. Preliminary studies were then undertaken to effect this key transformation.

The synthesis and applications of 2,3-disubstituted pyrroles, a class of nitrogen-containing heterocycle, were also investigated. The ultimate-goal of this project was to develop an efficient synthesis of 7-phosphatryptophan, a synthetic analogue of the natural $\alpha$-amino acid tryptophan that could exhibit different fluorescent properties to that of the natural substrate for biophysical studies. En route to the synthesis of 7-
phosphatryptophan, a novel method to construct 2-chloro-3-carboxylate pyrrole was
developed and optimized. It was also envisioned that this compound could serve as a
central building block for the preparation of a series of potentially biologically-active
heterocycles. In this regard, a series of pyrrole derivatives were synthesized via various
palladium-catalyzed cross-coupling reactions for future biological activity studies.

**Keywords:** Heterocycles, Natural Products; Total Synthesis; Pyrroles; Biomimetic
Synthesis; Domino Reaction.
To my brother, Simon, and my parents, Rachel and Ryan.
“Courage is the beginning of action, but chance is the master of the end”
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<tbody>
<tr>
<td>$[\alpha]_D$</td>
<td>specific rotation</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>bottom face (steroid nomenclature)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>top face (steroid nomenclature)</td>
</tr>
<tr>
<td>$\delta$</td>
<td>chemical shift (NMR spectroscopy)</td>
</tr>
<tr>
<td>$\mu$wave</td>
<td>microwave</td>
</tr>
<tr>
<td>(+)-</td>
<td>dextrorotatory</td>
</tr>
<tr>
<td>(-)-</td>
<td>laevorotatory</td>
</tr>
<tr>
<td>(±)-</td>
<td>racemic</td>
</tr>
<tr>
<td>2D</td>
<td>two dimensional</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azo-bis-isobutyronitrile</td>
</tr>
<tr>
<td>amu</td>
<td>atomic mass units (mass spectroscopy)</td>
</tr>
<tr>
<td>Anal.</td>
<td>elemental analysis</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic group</td>
</tr>
<tr>
<td>atm</td>
<td>atmospheres</td>
</tr>
<tr>
<td>Å</td>
<td>Ångstrom (0.1 nm)</td>
</tr>
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</table>
BINAP  [1,1’-binaphthalene]-2,2’-diylbis(diphenylphosphine)

Bn  benzyl (phenylmethyl)

B.p.  boiling point

br  broad (spectroscopy)

brsm  based on recovered starting material

calcd.  calculated (elemental analysis and high-resolution mass spectroscopy)

CAN  ceric ammonium nitrate

cat.  catalytic (amount)

CD  circular dichroism

Cl  chemical ionization (mass spectroscopy)

cm⁻¹  wavenumbers (IR spectroscopy)

¹³C NMR  carbon nuclear magnetic resonance spectroscopy

conc.  concentrated

COSY  ¹H-¹H correlation spectroscopy

D  sodium D-line (589 nm)

d  doublet (NMR spectroscopy)

dd  doublet of doublets (NMR spectroscopy)

ddd  doublet of doublet of doublets (NMR spectroscopy)

dr  diastereoisomeric ratio

dt  doublet of triplets (NMR spectroscopy)
DCM   dichloromethane
DIBAL-H diisobutylaluminum hydride
DMAP $N,N$-dimethyl-4-aminopyridine
DMF $N,N$-dimethylformamide
DMS dimethyl sulfide
ef evaporated film (IR spectroscopy)
EI electron impact ionization (mass spectroscopy)
equiv. equivalent(s)
Et ethyl
EtOAc ethyl acetate
EtOH ethanol
Et$_2$O diethyl ether (ether)
FAB-HRMS fast atom bombardment high resolution mass spectroscopy
GC gas chromatography
h hour(s)
hfc 3-(heptafluoropropylhydroxymethylene)-(+)-camphorate
HMPA hexamethylphosphoramide
HMQC heteronuclear multiple quantum coherence spectroscopy
$^1$H NMR proton nuclear magnetic resonance spectroscopy
HPLC high performance liquid chromatography
<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz (cycles per second)</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>median inhibition concentration</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR spectroscopy)</td>
</tr>
<tr>
<td>KBr</td>
<td>Potassium bromide disc (IR spectroscopy)</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium &lt;i&gt;N,N&lt;/i&gt;-diisopropylamide</td>
</tr>
<tr>
<td>lit.</td>
<td>literature value for a physical or spectroscopic property</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>M</td>
<td>molarity of a solution</td>
</tr>
<tr>
<td>M</td>
<td>molecular ion (mass spectroscopy)</td>
</tr>
<tr>
<td>M + H</td>
<td>molecular ion plus a proton (mass spectroscopy)</td>
</tr>
<tr>
<td>M + K</td>
<td>molecular ion plus potassium (mass spectroscopy)</td>
</tr>
<tr>
<td>M + Na</td>
<td>molecular ion plus sodium (mass spectroscopy)</td>
</tr>
<tr>
<td>MALDI-TOF</td>
<td>matrix assisted laser desorption ionization-time of flight (mass spectroscopy)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>Me&lt;sub&gt;2&lt;/sub&gt;CO</td>
<td>acetone</td>
</tr>
<tr>
<td>MeI</td>
<td>methyl iodide (iodomethane)</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol (methyl alcohol)</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Me₂SO₄</td>
<td>dimethyl sulfate</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz (NMR spectroscopy)</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mL</td>
<td>millilitres</td>
</tr>
<tr>
<td>mm Hg</td>
<td>millimetres of mercury</td>
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<td>mmol</td>
<td>millimole(s)</td>
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<tr>
<td>M.p.</td>
<td>melting point</td>
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<td>mol</td>
<td>mole(s)</td>
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<td>MS</td>
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<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>μL</td>
<td>microlitre(s)</td>
</tr>
<tr>
<td>N/A</td>
<td>not applicable</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oakridge thermal ellipsoid plot</td>
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<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhH</td>
<td>benzene</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million (NMR spectroscopy)</td>
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<tr>
<td>PPTS</td>
<td>pyridinium $p$-toluenesulfonate</td>
</tr>
<tr>
<td>$p$-TsOH-$\cdot$H$_2$O</td>
<td>$p$-toluenesulfonic acid monohydrate</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR spectroscopy)</td>
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<td>rel.</td>
<td>relative</td>
</tr>
<tr>
<td>$R_f$</td>
<td>retention factor (thin-layer chromatography)</td>
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<tr>
<td>s</td>
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<td>t</td>
<td>triplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>TBS</td>
<td>$t$-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBSCI</td>
<td>$t$-butyldimethylsilyl chloride</td>
</tr>
<tr>
<td>$t$-BuLi</td>
<td>$t$-butyllithium</td>
</tr>
<tr>
<td>td</td>
<td>triplet of doublets (NMR spectroscopy)</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
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<tr>
<td>Tebbe reagent</td>
<td>$(\text{CH}_3)_2(\text{C}_5\text{H}_5)_2\text{CH}_2\text{AlClTi}$</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TLC</td>
<td>thin-layer chromatography</td>
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<td>Description</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
</tr>
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<tr>
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<td>volume by volume</td>
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<td>weight by volume</td>
</tr>
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1. Synthesis of Heterocyclic Natural Products

1.1. Introduction

Organic compounds that contain rings composed of carbon and other atoms such as nitrogen, oxygen, sulfur or phosphorus are called heterocyclic compounds. Rings of this sort are frequently encountered in natural products and majority of the biologically-active molecules are heterocycles. In this regard, this thesis concerns the synthesis of three distinct types of heterocyclic natural products and analogues. This includes the development of a potential biomimetic synthesis of two oxygen-containing heterocyclic marine natural products, likonide B and smenochromene C. In addition, the development of the synthesis of a novel class of antibiotic, platensimycin is studied. Platensimycin is an oxygen-containing heterocyclic natural product which features a structurally unique cage-like tetracyclic ketolide moiety. The potential medicinal applications and complex structural motif makes this compound a very attractive target for synthetic studies. Lastly, the synthesis and applications of 2,3-disubstituted pyrroles, a nitrogen-containing heterocyclic compound, is described. The ultimate goal of this project was to develop an efficient synthesis of 7-phosphatryptophan, a phosphorus-containing heterocyclic molecule that could exhibit different fluorescent properties to that of the natural α-amino acid, which could find applications in biophysical studies. It was later realized that one of the synthetic intermediates, methyl 2-chloro-3-carboxylate pyrrole, could serve as a building block towards the synthesis of a series of potentially
biologically-active 2,3-disubstituted pyrroles through palladium catalyzed cross-coupling reactions.

1.2. An Overview of Organic Synthesis

Synthesis, in Greek, means the process of putting things together. Organic synthesis, in turn, is the science of the construction of carbon-based compounds from small and simple building blocks.¹ The first example of organic synthesis is generally believed to be Wohler’s synthesis of urea (1) in 1828 (Figure 1.1). This work marks the beginning of organic synthesis and demonstrates the first instance of employing an inorganic material, ammonium cyanate, in the synthesis of an organic molecule.² The word synthesis, however, was not used in this sense until Kolbe’s preparation of acetic acid (2) in five steps from elemental carbon in 1845.²

![Molecular structures of urea (1) and acetic acid (2).](image)

In 1950, Cornforth defined chemical synthesis as an “intentional construction of molecules by means of chemical reactions”.³ In the next fifty years, synthetic organic chemistry has become the most extensive branch of the chemical sciences by way of its creative power and essentially unlimited scope. Organic synthesis can now address the continuing rapid growth in the demand for new pharmaceuticals, high-technology materials, polymers, fertilizers, pesticides, cosmetics and textiles. However, a
fundamental interest that drives the chemists’ ability to create new compounds through chemical synthesis today is the total synthesis of a myriad of complex natural products.

1.3. Natural Products and Total Synthesis

Total synthesis is the chemical synthesis of a molecule, usually a natural product (a chemical compound or substance produced by a living organism, found in Nature, that often exhibits pharmacological or biological activity for use in pharmaceutical drug discovery and development), from relatively simple starting materials.\(^1\) Natural products exist in an almost infinite range of complexity and forms, and therefore this often requires unique strategies and tactics as well as new synthetic methods to overcome and rival Nature’s rich source of molecular complexity and diversity.

Prior to the 1950’s, before modern X-ray crystallography methods and nuclear magnetic resonance spectroscopy were introduced, total synthesis was the primary tool for the conformation and validation of the proposed structure of new compounds isolated from natural sources.\(^4\) Examples in which the correct structure was revised by natural product total synthesis include passifloricin A (3), alcyonin (4) and lepadiformine (5) (Figure 1.2).
Figure 1.2  Selected examples of proposed natural product structures that have been revised by total synthesis.

Pioneered by Woodward, the field of total synthesis had grown tremendously in the second half of twenth century. Synthetic methodologies such as the Diels-Alder reaction\(^5\), Wittig reaction\(^6\), hydroboration,\(^7,8\) the Sharpless asymmetric epoxidation and dihydroxylation reactions,\(^9-11\) palladium-catalyzed cross-coupling reactions\(^12\) and olefin metathesis reaction\(^13\) were developed and optimized in almost all aspects to suit the needs for total synthesis. As a result, hundreds of structurally complex natural products, such as strychnine,\(^14\) erythronolide,\(^15\) brevetoxin,\(^16\) vitamin B\(_{12}\),\(^17,18\) ginkgolide\(^19\) and Palau’amine,\(^20\) were successfully synthesized over the past sixty years.
Today, total synthesis has become a new testing ground for new technologies and synthetic strategies. New synthetic methods and techniques are tested and judged for their applicability, efficiency and practicality during studies towards the total synthesis of complex natural products.²

1.4. Introduction to Domino/Cascade Reaction

One of the powerful tools to construct structurally-complex natural products in an efficient manner is by the utilization of domino reactions. Domino reactions can be defined as “…a transformation of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former-bond forming reactions.”²¹ A classic example of a domino reaction that occurs in Nature is in the biosynthesis of steroids via an enzyme(s)-catalyzed cationic polyene cyclization reaction (Scheme 1.1).²²

Scheme 1.1 Proposed Biosynthesis of Lanosterol (7)

Inspired by the above biosynthetic proposal, several biomimetic approaches towards the synthesis of steroids have been reported. Among these examples, Johnson reported the most efficient process, in which progesterone (10) was prepared by an acid-catalyzed polyenecyclization of the tertiary allylic alcohol 8 in the presence of ethylene carbonate.²³ The cyclopentene moiety in compound 9 was reacted with ozone, followed
by treatment of aqueous potassium hydroxide to afford the cyclohexanone moiety of progesterone (10) (Scheme 1.2).

**Scheme 1.2 Johnson’s Cationic Domino Synthesis of Progesterone (10)**

![Scheme 1.2](image)

Reagents and conditions: a) Ethylene carbonate, CF$_3$COOH, 0 °C, 3 h (71%); b) O$_3$, then 5% KOH (80%).

Other examples that involve the employment of the domino reactions in natural product total synthesis includes Williams’ iodine-induced domino cyclization in the total synthesis of (-)-stemonine, Ogasawara’s formal synthesis of (-)-morphine and (±)-18-keto-pseudoyohimbane employing chiral bicycle[3,2,1]octenone as the starting material and Overman’s intramolecular domino Biginelli condensation reaction for the synthesis of crambescidin, and batzelladine alkaloids as well as their structurally-related analogues.

### 1.5. Thesis Overview

Chapter two of this thesis concerns the total synthesis of two structurally-related marine natural products, likonide B (13) and smenochromene C (14) (Scheme 1.3). A concise and potentially biomimetic synthesis of these natural products was developed. In this study, the 2H-chromene moiety was prepared via an intermolecular phenylboronic acid-mediated condensation reaction of the product prepared from trans,trans-farnesol...
(11) and 2-methoxyhydroquinone (12), and finally a palladium-catalyzed O-allylation reaction was employed to cyclize the 16-membered macrocyclic ring. An alternative approach employing an intramolecular phenylboronic acid condensation reaction to construct the 16-membered macrocyclic ring and the 6-membered 2H-chromene ring is also reported.

Scheme 1.3  Generic Scheme for the Total Synthesis of Likonide B (13) and Smenochromene C (14)

In chapter three, a study towards the total synthesis of platensimycin (17), a member of a novel class of antibiotics recently isolated by researchers at Merck, via a proposed asymmetric domino double-Stetter reaction to construct the core skeleton of platensimycin 16 from an achiral precursor 15 is described (Scheme 1.4). After a considerable amount of experimentation, an efficient synthesis of compound 15 was developed and optimized.
In the last chapter, the synthesis and applications of methyl 2-chloro-3-carboxylate pyrrole 18 is described. The first part of this chapter concerns studies towards the synthesis of 7-phosphatryptophan (20) through the synthesis of 7-phosphaindole (19). It is believed that 7-phosphatryptophan (20) will exhibit different fluorescent properties to that of the natural tryptophan, which could prove useful in biophysical chemistry studies when incorporated into proteins for use as a biomarker. In this study, the synthesis of the key compound, methyl 2-chloro-3-carboxylate pyrrole 18 and its subsequent synthetic transformations were developed and optimized (Scheme 1.5).
The second part of the final chapter concerns the synthesis of pyrrole-containing and potentially biologically-active heterocycles via palladium catalyzed cross-coupling reactions from the aforementioned methyl 2-chloro-3-carboxylate pyrrole 18 (Scheme 1.6). Various palladium-catalyzed cross-coupling reactions, such as Suzuki-type, Stille-type and Heck-type cross-coupling reactions, were attempted and several potentially biologically-active pyrrole-containing molecules were synthesized in good to excellent yield. This methodology was also applied to the synthesis of the bis-pyrrolic core of prodigiosin, a natural product that exhibits outstanding biological-activity as an immunosuppressive agent.
2. Total Synthesis of Likonide B and Smenochromene C

2.1. Introduction

This chapter concerns studies of the total synthesis of two marine natural products, likonide B and smenochromene C. Both natural products exhibit a unique ansa-bridged farnesyl quinol moiety which is considered to be an interesting structural motif for synthetic studies. In the following sections, a brief overview of the isolation and characterization as well as the proposed biosynthesis of these natural products is presented. Our efforts to construct these natural products, including the development and the optimization of the proposed key transformations which include a phenylboronic acid-mediated condensation reaction and a palladium-catalyzed O-allylation reaction, is discussed in detail.

2.2. Overview of Marine Natural Products

Marine natural products have attracted the attention of biologists and chemists from all over the World over the last few decades. To date approximately 16,000 marine natural products have been isolated and described in more than 7,000 publications.\textsuperscript{32} In addition to these publications there are approximately another 10,000 publications which cover syntheses, reviews, biological-activity studies, ecological studies etc. on the subject of marine natural products. A great number of the compounds isolated from marine sources exhibit biological-activity such as cytotoxic, antiviral, antimicrobial and immunomodulatory effects, and many have become lead compounds for their potential
development as chemotherapeutic agents. In the following sections, the total synthesis of two structurally-related marine natural products, namely likonide B (13) and smenochromene C (14) is discussed.

2.3. The Likonide and Smenochromene Natural Products

2.3.1. Isolation and Structural Characterization of the Likonide and Smenochromene Natural Products

In 2004, Kashman and co-workers reported the isolation and structural characterization of two structurally-related marine natural products, likonide A (22) and B (13), from a marine sponge of the *Hyatella* species (Figure 2.1).33

![Molecular structures of likonide A (22) and likonide B (13).](image)

Figure 2.1 Molecular structures of likonide A (22) and likonide B (13).

Although the likonides were described as new *ansa*-bridged compounds, Faulkner, Clardy and colleagues had reported a series of very similar *ansa*-farnesylhydroquinones, smenochromene A-D [23-25, smenochromene C (14)], that were isolated from a Seychelle sponge *Smenospongia* species in 1991 (Figure 2.2).34 The structure and spectroscopic data for smenochromene D (25) appeared to be identical to that of likonide B (13) in all respects. Extensive studies by Trauner and co-workers led to the conclusion that smenochromene D (25) is identical to likonide B (13), with the
exception of their absolute configurations: smenochromene D (25), \([\alpha]_D -68.5\) (c = 0.35, dichloromethane); likonide B (13), \([\alpha]_D +27\) (c = 0.08, methanol).\textsuperscript{35} Hence the natural products appear to be enantiomers. However, the absolute stereochemistry of each natural product has still not been defined.

![Molecular structures of smenochromene A-D (23-25, smenochromene C (14)).](image)

Figure 2.2 Molecular structures of smenochromene A-D [23-25, smenochromene C (14)].

Likonides A (22) and B (13) possess a novel molecular structure that features an ansa-bridged farnesyl quinol moiety. Although it was not commented on by Rudi et al., likonide B (13) could, in principle, be converted to likonide A (22) on heating via an aromatic Claisen rearrangement. (Figure 2.3) Of particular interest, we believed that the stereochemistry at C2 of likonide B (13) would control the installation of the remote C7′ stereogenic centre of likonide A (22) during this sigmatropic process.\textsuperscript{35} This would constitute a remarkable example of 1,8-asymmetric induction controlled by the conformational rigidity of the ansa-bridge.
2.3.2. **Biosynthetic Analysis of the Likonides and Smenochromenes**

The biosynthetic analysis of the likonides and the smenochromenes is shown below (Scheme 2.1). Both of the likonides (22, 13) and the smenochromenes (14, 23-25) are believed to be derived from various cyclization reactions of a common precursor, the farnesyl hydroquinone 26. Enzyme-catalyzed oxidation of the farnesyl hydroquinone 26 affords the ortho-quinone methide 27, which can subsequently undergo an oxa-6π electrocyclization to produce the chromene 28 that features the hydrochromene core of the likonides and the smenochromenes. Further oxidation of the distal allylic position of chromene 28 then leads to an allylic cation 29, which can cyclize through various modes. Cyclization between C5 and C9’ generates the 14-membered tricyclic smenochromene A (23) and B (24). The latter compound is formed by an additional isomerization reaction of the C3-4 double bond. Cyclization between C9’ and the phenolic oxygen leads to the 16-membered heterocyclic likonide B (13), smenochromene C (14) and smenochromene D (25). Finally, bond formation between C7’ and C5 affords likonide A (22).

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**Figure 2.3** Proposed conversion of likonide B(13) to likonide A(22) via an aromatic Claisen rearrangement.
Scheme 2.1  Proposed Biosynthesis of the Likonides (22, 13) and the Smenochromenes (14, 23-25)

2.3.3. Literature Syntheses of Smenochromene D [(25), Likonide B (13)] and Smenochromene B (24)

Concurrent with the planning and execution of the work described in this chapter, there have been two reports regarding the synthesis of smenochromene D [(25), likonide B (13)] and one report on the synthesis of smenochromene B (23).

2.3.3.1. Trauner’s Synthesis of (±)-Smenochromene D [(±)-25, Likonide B (±)-(13)]

Trauner and co-workers, in 2005, described the first total synthesis of racemic smenochromene D [(25), likonide B (13)] (Scheme 2.2).
Scheme 2.2  Trauner’s Synthesis of (±)-Smenochromene D [(25), likonide B (13)]

Reagents and conditions: a) SeO₂, salicylic acid, TBHP, DCM; b) DEAD, Ph₃P, THF (75%); c) K₂CO₃, MeOH, H₂O (84%); d) SO₃, TEA, DMSO (80%); e) PhB(OH)₂, PhMe, reflux, (26%).

The key step in this synthesis involved a phenylboronic acid-mediated condensation cyclization reaction between the α,β-unsaturated aldehyde moiety and the phenol moiety of compound 33. The precursor of this key step, compound 32, was prepared by a Mitsunobu etherification reaction of the allylic alcohol 31 and a derivative of 2-methoxyhydroquinone. The former compound 31 was synthesized from farnesyl acetate 30 via an allylic oxidation reaction of the distal alkene moiety.

2.3.3.2. Trauner’s Synthesis of (±)-Smenochromene B (24)

In the attempts to synthesize likonide A (22) through an aromatic Claisen rearrangement reaction using microwave irradiation as the heat source, Trauner and co-worker observed an unexpected ring contraction reaction that could be used towards the total synthesis of smenochromene B (24) (Scheme 2.3).³⁵ In this work, smenochromene
D (25) was heated under microwave irradiation for three and a half hours which initiated heterolytic bond cleavage and ring contraction reactions to afford compound 36. A demethylation reaction using ammonium cerium (IV) nitrate and subsequent protection of the free hydroxyl groups with acetic anhydride afforded the diacetylated compound 37. This material was finally treated with bromo-chloromethane in basic medium to afford smenochromene B (24).

**Scheme 2.3 Trauner’s Synthesis of (+)-Smenochromene B (24)**

Scheme 2.3: Trauner’s Synthesis of (+)-Smenochromene B (24)

Reagents and conditions: a) α-Dichlorobenzene, μwave (95%); b) CAN, acetonitrile:H₂O (3:1) then NaS₂O₄; c) Ac₂O, DMAP, EtOAc (40%); d) NaOMe, MeOH; e) CH₂BrCl, CsF, DMF (18%).

2.3.3.3. Moody’s Synthesis of (±)-Smenochromene D [25, likonide B (13)]

In 2008, Bruker and Moody completed the second total synthesis of smenochromene D (25). The key step in this work was a microwave-mediated aromatic Claisen rearrangement of an aryl propargyl ether 40 to prepare the 2H-chromene ring (Scheme 2.4).
Scheme 2.4  Moody’s Synthesis of (±)-Smenochromene D [25, likonide B (13)]

Reagents and conditions: a) DBU, CuCl₂, MeCN (26%); b) DMF, μwave, 200 °C (52%).

2.4. Brief Overview of the Phenylboronic Acid-Mediated Reaction of Phenols and Aldehydes and Studies Towards the Total Synthesis of Chromene-Containing Natural Products and Analogues.

2.4.1. Development and Application of the Phenylboronic Acid-Mediated Reaction

In 1992, Lau and co-workers reported a facile synthesis of cyclic borate esters from phenols, aldehydes and phenylboronic acid. This regiospecific reaction afforded products which proved to be isolable ortho-quinone methide precursors, which were subsequently reacted with various dienophiles in Diels-Alder [4+2] cycloaddition reactions, or with nucleophiles which undergone 1,4-addition reactions to afforded compounds 46 and 47, respectively (Figure 2.4).
Figure 2.4 Proposed mechanism of the phenylboronic acid-mediated condensation reactions of phenols and aldehydes.

This work was then followed by a report on the extension of this reaction towards the total synthesis of several biologically-active natural products, such as precocene I (52) and II (53) (Scheme 2.5). In this report, Bissada and co-workers used $\alpha,\beta$-unsaturated aldehydes 49 to generate the borate esters 50 in situ which in the presence of a small amount of propionic acid spontaneously underwent further reactions to afford the corresponding ortho-quinone methides 51. These reactive reaction intermediates then underwent oxa-6π electrocyclic rearrangements to afford 2H-chromenes in a one-pot reaction sequence.
It is important to point out that this reaction is sensitive to the electronic nature of the aromatic system employed. For example, the use of electron rich 4-methoxyphenol as a reaction substrate afforded the desired 2H-chromene when reacted with senecialdehyde in good yield, whereas the use of the less electron rich substrate, 4-bromophenol or the electron poor substrate, 4-nitrophenol, resulted low or no isolation yield of the corresponding reaction product, respectively.40

### 2.4.2. 2H-Chromene-Containing Natural Products and Related Analogues Synthesized in the Wilson Laboratory

The Wilson research group has synthesized a variety of natural products and structurally-related analogues that contain 2H-chromene moieties by employing the phenylboronic acid-mediated condensation reaction.

#### 2.4.2.1. Daurichromenic Acid (54)

Hu et. al has recently reported the synthesis of a series of structurally-related analogues of daurichromenic acid (54).41 In this work, several α,β-unsaturated
aldehydes (56) were reacted with methyl orsellinate (55) to successfully synthesize a series of daurichromenic acid derivatives 57. (Scheme 2.6).

Scheme 2.6 Molecular Structure of Daurichromenic Acid (54) and the Synthesis of its Structurally-Related Analogues

Interestingly, when methyl orsellinate (55) was reacted with sorbic aldehyde (trans,trans-2,4-hexadienal, 58), the reaction underwent several carbocation rearrangements and cyclizations to afforded a bicyclic compound 63 (Scheme 2.7).
2.4.2.2. Xyloketal Family of Natural Products

More recently Pettigrew et. al reported the total syntheses of several members of the xyloketal family of natural products.\textsuperscript{42} In this work, Pettigrew et. al employed three different approaches to attempt the total synthesis of xyloketal A (64) and one of them involved the phenylboronic acid-mediated condensation reaction as the key synthetic step to construct the requisite ring system that xyloketal A (64) features (Scheme 2.8). In this retrosynthetic route it was envisioned that xyloketal A (64) could be formed by a stereoselective hydrogenation reaction of the \( C_3 \)-symmetric \( 2H \)-chromene precursor 65. This \( C_3 \)-symmetric \( 2H \)-chromene could in turn be prepared from phloroglucinol (66) with
three equivalents of the corresponding $\alpha,\beta$-unsaturated aldehyde 67 via the aforementioned phenylboronic acid-mediated condensation reaction.

**Scheme 2.8  Retrosynthetic Analysis of Xyloketal A (64)**

After the intensive studies, it was found that the $\alpha,\beta$-unsaturated aldehyde 67 was unstable to the optimized reaction conditions for the proposed phenylboronic acid-mediated condensation reaction. However, during the course of this study, Pettigrew et al. successfully synthesized several structurally-related analogues of xyloketal A (69-72) from a series of aldehydes 68.43
2.5. Retrosynthetic Analysis of Likonide B (13)

Based on the studies previously performed in our laboratory, retrosynthetic analysis of likonide B (13) suggested that the 2H-chromene moiety of likonide B (13) could be prepared by the phenylboronic acid-mediated condensation reaction. (Scheme 2.10)
Here, substituent X in compound 73 represents a suitable leaving group or a “masked” leaving group. After having all the precursors in hand, parallel studies would be pursued to complete the total synthesis of likonide B (13) using the phenylboronic acid-mediated condensation reaction, in an inter- or intramolecular sense, as the key step.

2.6. Total Synthesis of Likonide B (13) and Smenochromene C (14)

2.6.1. Retrosynthetic Analysis of Likonide B (13) via an Intermolecular Phenylboronic Acid-Mediated Condensation Reaction

Further retrosynthetic analysis of likonide B (13) suggested that it could be prepared from compound 73 by either an intramolecular Williamson (X = halide or activated hydroxyl group) or Mitsunobu etherification reaction (X = OH) (Scheme 2.11). The required precursor 73 (X = OH) could be prepared by a Sharpless allylic oxidation reaction of the chromene 74, which could be prepared via a phenylboronic acid-
mediated condensation reaction of the readily available and known compounds, 
trans,trans-farnesal (75) and 2-methoxyhydroquinone (12).

Scheme 2.11 Proposed Retrosynthetic Analysis of Likonide B (13) via an Intermolecular Phenylboronic Acid-Mediated Condensation Reaction

2.6.2. Synthesis of 9-Hydroxy-2(4,8-dimethyl-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (74)

The synthesis of 2-(4,8-dimethyl-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-
2H-chromene (74) began with the oxidation reaction of the commercially-available
starting material, trans,trans-farnesol (11) to its corresponding α,β-unsaturated
aldehyde, trans,trans-farnesal (75) (Scheme 2.12). This was accomplished by various
oxidation methods, such as the Swern oxidation reaction, the use of Dess-Martin
periodinane or manganese dioxide. The most successful of these was with manganese
dioxide as the oxidant which afforded the desired product, trans,trans-farnesal (75) in
high yield, with no additional aqueous work up or purification being required. The
intermolecular phenylboronic acid-mediated condensation reaction of trans,trans-
farnesal (75) with the commercially-available starting material, 2-methoxyhydroquinone (12), was then performed to afford the desired $2H$-chromene 74 in a good overall yield.

Scheme 2.12  Synthesis of 2(4,8-Dimethyl-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-$2H$-chromene (74) from the Commercially-Available Starting Materials trans,trans-Farnesol (11) and 2-Methoxyhydroquinone (12)

Reagents and conditions: a) MnO$_2$, DCM, rt, 5 h (95%); b) PhB(OH)$_2$, propionic acid (cat.), benzene, reflux, 14 h (71%).

The anticipated regioselectivity of the phenylboronic acid-mediated condensation reaction, with respect to the two phenol moieties, was confirmed by the two singlets at $\delta$6.40 and $\delta$6.57 in the $^1$H NMR spectrum that corresponded to two aromatic protons that are orientated para to one another (Figure 2.5). The two doublets at $\delta$5.46 and $\delta$6.25 correspond to the chromene double bond protons which are in agreement with resonances of other chromenes reported in the literature.$^{34,43}$
In addition, the $^{13}$C NMR spectrum displayed 22 peaks which is equivalent to the number of carbon atoms found in compound 74. The molecular mass and the results obtained from the elemental analysis (see: Experimental Section) were also found to be in agreement with the calculated values.

The chemoselective allylic oxidation of chromene 74 to 9'-hydroxy-2$H$-chromene 76 was subsequently investigated using the procedure originally developed by Sharpless for the analogous oxidation of geranyl acetate (Scheme 2.13). As Marshall has more recently discussed, the oxidation of the distal methyl group of the farnesol derivative was less selective than that of its similar homologue owing to competing oxidation of the internal allylic methyl groups. Following the reaction protocol suggested by Marshall, using a catalytic amount of selenium dioxide and one equivalent loading of the
tert-butylhydroperoxide in dichloromethane at 0 °C for 2 hours, afforded the desired product 76 in low yield with more than 50% of starting material being recovered (entry 1, Table 2-1). Neither raising the reaction temperature nor increasing the reaction time helped to improve the yield of this process (entries 2 - 3). In addition, increasing the loading of selenium dioxide and tert-butylhydroperoxide resulted in extensive decomposition of the starting material and no product was isolated after chromatography (entries 4 - 6).

Scheme 2.13 Optimization of the Regioselective Sharpless Allylic Oxidation Reaction of the 9-Hydroxy-2(4,8-dimethyl-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (76)

Table 2-1 Reagents and Conditions Corresponding to Scheme 2.13

<table>
<thead>
<tr>
<th>en</th>
<th>reagents and conditions</th>
<th>yields of (76)</th>
<th>yield of (74)</th>
<th>recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SeO₂ (0.25 eq.), tert-BuOOH (1 eq.), DCM, 0 °C, 2 h</td>
<td>13 %</td>
<td>37 %</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>SeO₂ (0.25 eq.), tert-BuOOH (1 eq.), DCM, rt, 2 h</td>
<td>14 %</td>
<td>31 %</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SeO₂ (0.25 eq.), tert-BuOOH (1 eq.), DCM, 0 °C, 7 h</td>
<td>21 %</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SeO₂ (0.25 eq.), tert-BuOOH (1.5 eq.), DCM, 0 °C, 2 h</td>
<td>Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>SeO₂ (0.5 eq.), tert-BuOOH (2 eq.), DCM, 0 °C, 2 h</td>
<td>Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>SeO₂ (1 eq.), tert-BuOOH (4 eq.), DCM, 0 °C, 2 h</td>
<td>Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SeO₂ (1 eq.), tert-BuOOH (0 eq.), DCM, 0 °C, 2 h</td>
<td>0 %</td>
<td>73 %</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>SeO₂ (0.5 eq.), tert-BuOOH (1 eq.), DCM, 0 °C, 2 h</td>
<td>24 %</td>
<td>56 %</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>SeO₂ (1 eq.), tert-BuOOH (0.5 eq.), DCM, 0 °C, 2 h</td>
<td>26 %</td>
<td>37 %</td>
<td></td>
</tr>
</tbody>
</table>

At this point, we believed a detailed examination of each reagent employed in this reaction was needed in order to ascertain the key features of this reaction and the causes of the decomposition of the starting material. With one equivalent loading of the selenium dioxide and no tert-hydroperoxide, the reaction did not proceed and starting
material was partly recovered (entry 7). On maintaining the loading of the tert-hydroperoxide to one equivalent while increasing the amount of selenium dioxide the reaction yield was improved to 24% (55% based on the recovery of the starting material 74) (entry 8). Lowering the amount of tert-hydroperoxide used to half equivalent resulted in a moderate yield (entry 9). Accordingly, we ascertained that an excess amount of tert-hydroperoxide decomposes the starting material 74 while an increase the loading of selenium dioxide to 0.5 equivalents with one equivalent of the tert-hydroperoxide afforded the best result. Of note, the resultant chromene 76 was also found to be highly unstable and must be used in subsequent reactions within hours of isolation.

The oxidation at the distal methyl group was supported by the observation of a singlet at δ 3.98 in the 1H NMR spectrum that corresponded to the 2 protons adjacent to the hydroxyl group, as well as the absence of a methyl peak in ~δ 1.30 range as compared to the starting material (Figure 2.6).
The $^{13}$C NMR spectrum showed 22 peaks which was equivalent to the number of carbons found in compound 76. The observation of a protonated molecular ion at 359 amu and the result obtained from the elemental analysis were all in agreement with the calculated values.

2.6.3. Attempted Synthesis of Likonide B (13) from 9-hydroxy-2H-chromene (76)

The synthesis of the likonide B (13) from compound 76 via various etherification type reactions was then attempted (Scheme 2.14). The results of these studies are summarized below (Table 2-2).
Scheme 2.14  Attempted Synthesis of Likonide B (13) from 9-Hydroxy-2H-chromene (76)

Table 2-2  Reagents and Conditions Corresponding to Scheme 2.14

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents and conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MsCl (1.2 equiv.) dropwise, pyridine, rt, 6 h</td>
<td>Complex mixture&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CBr&lt;sub&gt;4&lt;/sub&gt; (1.2 equiv.), PPh&lt;sub&gt;3&lt;/sub&gt; (1.5 equiv.), 2,6-lutidine (0.2 equiv.) THF, rt, 14 h</td>
<td>Starting material decomposed&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CBr&lt;sub&gt;4&lt;/sub&gt; (1.2 equiv.), PPh&lt;sub&gt;3&lt;/sub&gt; (1.5 equiv.), 2,6-lutidine (0.2 equiv.) THF, 0 °C, 14 h</td>
<td>Starting material decomposed</td>
</tr>
<tr>
<td>4</td>
<td>DEAD (1.5 equiv.), DCM, 0 °C, 20 min then PPh&lt;sub&gt;3&lt;/sub&gt; (1.5 equiv.), 0 °C to rt, 14 h</td>
<td>Starting material decomposed</td>
</tr>
<tr>
<td>5</td>
<td>DIAD (1.5 equiv.), THF, 0 °C, 20 min then PPh&lt;sub&gt;3&lt;/sub&gt; (1.5 equiv.), 14 h</td>
<td>Starting material decomposed</td>
</tr>
<tr>
<td>6</td>
<td>DIAD (2.0 equiv.), THF, 0 °C, 20 min then PPh&lt;sub&gt;3&lt;/sub&gt; (2.0 equiv.), 0 °C to rt, 14 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>DIAD (1.5 equiv.), DCM, 0 °C, 20 min then PPh&lt;sub&gt;3&lt;/sub&gt; (10 equiv.), 0 °C to rt, 14 h</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

<sup>a</sup> Complex mixture refers to the TLC of the reaction mixture that showed a strip of spots and no significant evidence of product formation was observed based on the examination of the <sup>1</sup>H NMR of the crude material.  <sup>b</sup> Starting material decomposition refers to a complete consumption of the starting materials based on TLC but no new spots were observed other than polymeric materials at the baseline of the TLC.

In the first instance, the chromene 76 and pyridine were mixed in tetrahydrofuran for 30 minutes and mesyl chloride (1.2 equiv.) was then added dropwise to attempt to selectively activate the allylic hydroxyl group (entry 1, Table 2-2).<sup>50</sup> Without isolating the mesylated adduct, it was hoped that the phenol would react with the mesylated adduct and close the macrocycle <i>in situ</i> to form likonide B (13). However, overnight stirring of the reaction led to a complex mixture of products and no identifiable products were isolated nor characterized after flash chromatography. Appel’s bromination reaction of
the allylic alcohol using carbon tetrabromide and triphenylphosphine was also attempted at different reaction temperatures (entries 2 and 3).\textsuperscript{51} Neither likonide B (13) nor the brominated adduct was isolated in these attempts. These results suggested that the activation of the allylic alcohol to a better leaving group by either mesylation or bromination formed a highly unstable intermediate that readily decomposed before macrocyclization could occur.

Since an \textit{in situ} Williamson’s etherification procedure did not afford likonide B (13), a Mitsunobu cyclization was then considered.\textsuperscript{52–55} Various Mitsunobu reagents such as diethyl azodicarboxylate (DEAD) and diisopropyl azodicarboxylate (DIAD) were used under different reaction conditions but none of the attempts afforded likonide B (13) nor any isolable products (entries 4 - 7).

\textbf{2.6.4. Retrosynthetic Analysis of Likonide B (13) via a Palladium-Catalyzed Allylation Reaction}

Since both Williamson’s etherification and Mitsunobu etherification reactions of the chromene 76 failed to afford the desired product, likonide B (13), an alternative route was devised. Inspired by the proposed biosynthesis of likonides and smenochromenes (\textit{cf.} Scheme 2.14), in that the allylic cation 29 is the key intermediate in the formation of the likonides and smenochromenes through various cyclization modes, we proposed that a palladium-catalyzed O-allylation reaction would be a more appropriate approach to pursue both likonide A (22) and B (13) as well as members of smenochromene family of natural products (Scheme 2.15).
The revised retrosynthetic analysis thus led to compound 77 with an allylic acetate ($R = \text{Me}$) as a latent leaving group. However, attempts to selectively acetylate the allylic alcohol of compound 76 with one equivalent of acetic anhydride in the presence of pyridine in dichloromethane only afforded the diacetylated adduct 78 (Scheme 2.16).

**Scheme 2.16** Synthesis of Diacetoxychromene 78 from the 9-hydroxy-2$H$-chromene 76

Reagents and conditions: a) Ac$_2$O, pyridine, DCM, rt, 3h (36%).

Based on the above finding, it was decided that the acetate group should be installed before the formation of the 2$H$-chromene moiety. Further retrosynthetic analysis of compound 79 suggested it could be prepared from 9-acetoxy-\textit{trans,trans}-farnesal (80) and 2-methoxyhydroquinone (12) (Scheme 2.17).
2.6.5. Synthesis of Likonide B (13) via a Palladium-Catalyzed Allylation Reaction

The synthesis of the key precursor 79 began with the direct allylic oxidation reaction of \(\text{trans,trans-farnesal} (75)\) to prepare 12-hydroxy-\(\text{trans,trans-farnesal} (81)\) under the optimized reaction conditions discussed earlier (Scheme 2.18). Subsequent acetylation of the hydroxyl group of compound 80 was accomplished under standard reaction conditions. The \(\alpha,\beta\)-unsaturated aldehyde 80 was then treated with phenylboronic acid and 2-methoxyhydroquinone (12) in the presence of catalytic amount of propionic acid to afford the desired acetoxy 2\(H\)-chromene 79 in a very good overall yield.
Scheme 2.18 Synthesis of 9-Acetoxy-2(4,8-dimethyl-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (79)

Reagents and conditions: a) SeO₂, tert-BuOOH, DCM, 0 °C, 3 h (47%); b) Ac₂O, Pyridine, DMAP, DCM, rt, 4 h (91%); c) PhB(OH)₂, propionic acid, PhH, Dean-Stark trap, reflux, 26 h (86%)

Tsuji-Trost palladium-catalyzed O-allylation of compound 79 towards the preparation of likonide B (13) was investigated (Scheme 2.19). The results of this study are summarized below (Table 2-3).

Scheme 2.19 Synthesis of Likonide B (13), Smenochromene C (14) and 2(4,8-Dimethyl-trans,trans-3,6,8-nonatrienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (82)

Table 2-3
Table 2-3  Reagents and Conditions Corresponding to Scheme 2.19

<table>
<thead>
<tr>
<th>en</th>
<th>base</th>
<th>solvent</th>
<th>temp.</th>
<th>time</th>
<th>yield of (13)</th>
<th>yield of (14)</th>
<th>yield of (82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n/a</td>
<td>THF</td>
<td>rt.</td>
<td>3 days</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>n/a</td>
<td>PhH</td>
<td>rt.</td>
<td>5 days</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>n/a</td>
<td>THF</td>
<td>reflux</td>
<td>2 days</td>
<td>0%</td>
<td>0%</td>
<td>62%</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>reflux</td>
<td>20 h</td>
<td>8%</td>
<td>1%</td>
<td>51%</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>PhH</td>
<td>reflux</td>
<td>20 h</td>
<td>14%</td>
<td>1%</td>
<td>48%</td>
</tr>
<tr>
<td>6</td>
<td>Cs₂CO₃</td>
<td>PhH</td>
<td>reflux</td>
<td>2 days</td>
<td>21%</td>
<td>1%</td>
<td>53%</td>
</tr>
<tr>
<td>7</td>
<td>Et₃N</td>
<td>PhH</td>
<td>reflux</td>
<td>3 days</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>K₃PO₄</td>
<td>PhH</td>
<td>reflux</td>
<td>3 days</td>
<td>9%</td>
<td>2%</td>
<td>21%</td>
</tr>
<tr>
<td>9</td>
<td>Cs₂CO₃</td>
<td>PhH/Hex</td>
<td>reflux</td>
<td>3 days</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>LiH</td>
<td>PhH</td>
<td>reflux</td>
<td>2 days</td>
<td>starting material decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>LiH</td>
<td>THF</td>
<td>reflux</td>
<td>2 days</td>
<td>starting material decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>LiH</td>
<td>rt.</td>
<td>3 days</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Cs₂CO₃</td>
<td>DMF</td>
<td>reflux</td>
<td>3 days</td>
<td>starting material decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Cs₂CO₃</td>
<td>PhH</td>
<td>60 °C</td>
<td>3 days</td>
<td>31%</td>
<td>4%</td>
<td>41%</td>
</tr>
<tr>
<td>15</td>
<td>tert-BuOK</td>
<td>PhH</td>
<td>60 °C</td>
<td>2 days</td>
<td>24%</td>
<td>3%</td>
<td>48%</td>
</tr>
<tr>
<td>16</td>
<td>K₃PO₄</td>
<td>PhH</td>
<td>60 °C</td>
<td>2 days</td>
<td>35%</td>
<td>3%</td>
<td>39%</td>
</tr>
<tr>
<td>17</td>
<td>K₂CO₃/18-C-6</td>
<td>PhH</td>
<td>60 °C</td>
<td>5 days</td>
<td>35%</td>
<td>3%</td>
<td>47%</td>
</tr>
<tr>
<td>18</td>
<td>tert-BuOK/18-C-6</td>
<td>PhH</td>
<td>60 °C</td>
<td>2 days</td>
<td>33%</td>
<td>7%</td>
<td>26%</td>
</tr>
<tr>
<td>19</td>
<td>tert-BuOK/18-C-6</td>
<td>PhH</td>
<td>rt.</td>
<td>4 days</td>
<td>41%</td>
<td>5%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Following a standard procedure to effect the described palladium-catalyzed O-allylation reaction, in which tetrakis(triphenylphosphine) palladium was used as the reaction catalyst, the reaction did not proceed on stirring at room temperature for several days (entry 1 – 2, Table 2-3). When the reaction was heated at reflux, the desired product likonide B (13) was not formed, but a rather unusual eliminated product 82 was isolated (entry 3). This product is believed to arise by double bond migration of the allylic cation followed by β-hydride elimination of the palladium species to generate a more substituted conjugated system (Scheme 2.20).
The molecular structure of compound 82 was confirmed by the analysis of $^1$H NMR spectrum (Figure 2.7). The presence of the conjugated double bonds was supported by the observation of alkene proton resonances at $\delta$ 6.18, 5.61, 4.89 and 4.83. The peak at $\delta$ 2.70 corresponds to the bis-allylic methylene group at C5. In addition, a broad absorption at 3444 cm$^{-1}$ in the IR spectrum, which corresponded to the phenol, suggested that the proposed cyclization did not occur.
Various bases were then employed to deprotonate the phenol moiety thus producing a more reactive phenoxide nucleophile during the reaction. When potassium carbonate was used as a base, likonide B (13) was isolated in 8% yield (entry 4). The employment of alternate solvents such as benzene improved the reaction yield to 14% (entry 5). Finally, when using cesium carbonate as a base in benzene at reflux, likonide B (13) was isolated in 21% yield (entry 6). This is possibly due to the poor covalent bonding between cesium and oxygen that would in turn increase the nucleophilicity of the phenoxide anion. Employing other bases such as triethylamine (entry 7), potassium phosphate tri-basic (entry 8) or lithium hydride (entries 10 - 12) resulted in either a low isolated yield of likonide B (13) or decomposition of the starting material.
All of the spectral data of (±)-likonide B [(±)-13] were in agreement to those recorded for the natural product (Figure 2.8). The two doublet at $\delta$ 4.52 and 4.82 corresponded to the diastereotopic protons of the methylene group at C9'.

![Figure 2.8](image)

**Figure 2.8** $^1$H NMR spectrum (600 MHz, CDCl₃) of (±)-likonide B [(+)-13]

Given the above observation that the use of cesium carbonate improved the reaction yield, we then considered employing crown ethers to sequester the counter ion of the base and thus make the phenoxide even more reactive. Indeed, the combination of potassium tert-butoxide and 18-crown-6 ether afforded the best yield of likonide B (13) (41%) and minimized the formation of the undesired eliminated product 82 to 24% (entry 19).

In addition, double bond isomerization at C7' and C8' on palladium insertion was observed in this reaction. This double bond isomerization process accordingly constitutes the first total synthesis of a structurally-related natural product,
smenochromene C (14), which was isolated as the minor reaction product in 7% yield (Scheme 2.21).

**Scheme 2.21 Proposed Reaction Intermediates of the Palladium-Catalyzed O-Alylation Reaction**

All of the spectral data of (±)-smenochromene C [(±)-14] were in agreement with that recorded for the natural product (Figure 2.9). Notably, the two doublets at δ 4.45 and 4.28 are corresponded to the diastereotopic protons of the methylene group at C9.'
2.7. Intramolecular Phenylboronic Acid-Mediated Condensation Approach

2.7.1. Retrosynthetic Analysis of Likonide B (13) via an Intramolecular Phenylboronic Acid-Mediated Condensation Reaction

The key feature of this alternative retrosynthetic analysis of likonide B (13) involved the installation of a macrocyclic 16-membered ansa-bridged ring and a 6-membered chromene ring in a single transformation from phenol 33 via an intramolecular phenylboronic acid-mediated condensation reaction. This would require the preparation of the para-protected 2-methoxyhydroquinone 88 and trans,trans-farnesal (87) with a suitable leaving group substituted at the C-12 position for a subsequent intermolecular etherification reaction(Scheme 2.22).
Scheme 2.22  Retrosynthetic Analysis of Likonide B (13) via an Intramolecular Phenylboronic Acid-Mediated Condensation Reaction

![Diagram]

2.7.2.  Synthesis of 4-Hydroxy-3-methoxyphenylformate (90)

4-Hydroxy-3-methoxyphenyl formate (90) was considered as an appropriately protected candidate for 2-methoxyhydroquinone (12) for several reasons. This compound can be easily prepared from a relatively inexpensive commercially-available starting material, vanilline (89), by Baeyer-Villiger oxidation reaction and the reactive formate moiety is appropriate for deprotection under mild conditions. Therefore, following Guzman’s procedure using selenium dioxide and hydrogen peroxide (30% v/v), the desired formate 90 was prepared on multigram scale (Scheme 2.23).35,36,60

Scheme 2.23  Synthesis of 4-Hydroxy-3-methoxyphenylformate (90)

![Diagram]

Reagents and conditions: a) SeO₂, H₂O₂, tert-BuOH, 0 °C, 2 h (47%).
2.7.3. **Attempted Synthesis of 9-Halo-trans,trans-farnesal**

Various functional group transformation reactions to activate the hydroxyl group of 9-hydroxy-trans,trans-farnesal (81), synthesized previously during the study of intermolecular phenylboronic acid-mediated condensation approach, were attempted (Scheme 2.24).\textsuperscript{61,62} However, these reactions afforded complex mixtures of products from which the desired product 91 or 92 could not be isolated. Similar results were also observed when attempting the synthesis of likonide B (13) via intramolecular Williamson’s etherification reaction (See: Section 2.6.3).

**Scheme 2.24  Attempted Synthesis of 9-Halo-trans,trans-farnesal**

Reagents and conditions: a) SOCl\textsubscript{2}, THF, 0 °C, 1-6 h; b) CBr\textsubscript{4}, PPh\textsubscript{3}, 2,6-lutidine, THF, rt, 2-24 h.

2.7.4. **Total Synthesis of Likonide B (13)**

With all the difficulties found in attempting to activate the hydroxyl group of 9-hydroxy-trans,trans-farnesal (81) to a better leaving group, an intermolecular Mitsunobu etherification reaction was considered. Given the unsuccessful results obtained in the previous attempts (See: Section 2.6.3), a modified Mitsunobu etherification reaction condition was employed.\textsuperscript{36} With excess loading of the Mitsunobu reagent, diisopropylazadicarboxylate (DIAD), in the presence of triphenylphosphine in tetrahydrofuran, followed by a base wash to remove the formate moiety, the desired
coupled product 33 was isolated in 38% yield (Scheme 2.25). This material 33 was subsequently treated with phenylboronic acid and a catalytic amount of propionic acid to afford the desired final compound likonide B (13) in an intramolecular fashion with a reasonable 41% yield. This completed the second total synthesis of likonide B (13). Of note, this process installed both the 16-membered ansa-bridge and the 6-membered 2H-chromene moieties simultaneously.

Scheme 2.25 Total Synthesis of Likonide B (13) via an Intramolecular Phenylboronic Acid-Mediated Condensation Reaction Approach.

Reagents and conditions: a) PPh₃, DIAD, THF, 0 °C to rt, 20 h (38%); b) PhB(OH)₂, propionic acid (cat.), PhH, reflux, 24 h (41%).

2.8. Attempted Synthesis of (±)-Likonide A [(±)-22]

The total synthesis of (±)-likonide A [(±)-22] was also attempted (Scheme 2.26). When likonide B (13) was heated to 200 °C in a Schlenk tube for 6 hours, a heterolytic carbon-oxygen bond cleavage reaction was observed instead of the proposed aromatic Claisen rearrangement and compound 36 was isolated in 31% yield. This finding is in agreement with the findings from Trauner’s total synthesis of smenochromene B.³⁵
Scheme 2.26  Attempted Synthesis of Likonide A (22) from Likonide B (13) via a thermal [3+3] Aromatic Claisen Rearrangement

Reagents and Conditions: a) toluene, 200 °C, 8 h (0% 22:31% 36).

All of the spectral data of compound 36 were found to be in agreement with the literature data (Figure 2.10).35

Figure 2.10  $^1$H NMR (500 MHz, CDCl$_3$) of (7E,11Z)-3-methoxy-7,11,15-trimethyl-19-oxa-tricyclo[13.3.1.0]nonadeca-1,3,5(18),7,11,16-hexaen-4-ol (36)

Attempts to effect the proposed aromatic Claisen rearrangement by employing various solvents such as ethanol:water or $p$-chlorophenol at reduced temperature (150
°C) also did not afford the desired product, likonide A (22) and the starting material was recovered in all cases, with small degree of decomposition.

2.9. Conclusions

Likonide B (13) and smenochromene C (14) were successfully prepared from commercially available starting material, *trans,trans*-farnesol (11) and 2-methoxyhydroquinone (12). The use of phenylboronic acid to generate the 2*H*-chromene moiety via an *ortho*-quinone methide intermediate, followed by an oxa-6π electrocyclic rearrangement and finally palladium-catalyzed macrocyclization constitutes a potentially biomimetic total synthesis. In addition, an interesting double bond isomerization process of the allylic cation generated on palladium insertion was observed. This double bond isomerization process ultimately led to the first total synthesis of a structurally-related natural product, smenochromene C (14). During this study, the palladium-catalyzed O-allylation reaction to construct the macrocyclic ring of the likonides was studied and optimized. The employment of certain bases, such as cesium carbonate, improved the reactivity of the phenol moiety. In addition, reaction additives such as crown-ethers to remove the alkali metal increased the reactivity of the phenoxide anion significantly and the desired product, likonide B (13) was prepared in five steps and in a 22% overall yield.

Furthermore, an alternative approach towards the total synthesis of likonide B (13) was also devised. This involved the employment of a Mitsunobu etherification reaction and an intramolecular phenylboronic acid-mediated condensation reaction to construct the 16-membered macrocyclic ring and the 6-membered chromene ring in a
single synthetic transformation. *Via* this route, likonide B (13) was synthesized in four steps and in a 12% overall yield.

Lastly, conversion of likonide B (13) to likonide A (22) *via* the proposed aromatic Claisen rearrangement reaction was also attempted. Heating likonide B (13) at 200 °C in toluene resulted in an unusual carbon-oxygen bond cleavage reaction and led to the formation of compound 36. This compound proved to be identical to that isolated by Trauner *et al.* in their studies towards the synthesis of smenochromene B (24).
2.10. Experimental Section

2.10.1. General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware, unless indicated otherwise. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran (THF) was dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, dichloromethane, and pyridine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied. Brine refers to a saturated aqueous solution of sodium chloride. Silica gel column chromatography (“flash chromatography”) was carried out using Merck silica gel 60 (230 to 400 mesh) and Silicycle SiliaFlash® F60 (230-400 mesh). All proton and carbon nuclear magnetic resonance spectra (\(^1\text{H NMR}\) and \(^{13}\text{C NMR}\), respectively) were recorded using a Bruker 400 FT spectrometer (operating frequencies: \(^1\text{H}, 400.13\) MHz; \(^{13}\text{C}, 100.61\) MHz), Bruker 500 FT spectrometer (operating frequencies: \(^1\text{H}, 499.77\) MHz; \(^{13}\text{C}, 125.68\) MHz), Varian 500 FT spectrometer (operating frequencies: \(^1\text{H}, 499.77\) MHz; \(^{13}\text{C}, 125.68\) MHz) and Bruker 600 FT spectrometer (operating frequencies: \(^1\text{H}, 600.13\) MHz; \(^{13}\text{C}, 150.90\) MHz) at ambient temperature unless stated otherwise. Chemical shifts (\(\delta\)) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform (CDCl\(_3\)) were 7.26 and 77.16 ppm for \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra, respectively. The reference values used for
deuterated benzene (C₆D₆) were 7.15 and 128.02 ppm, respectively. Infrared spectra (IR) were recorded as either KBr pellets (KBr), evaporated films (ef) or as films (neat) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (MS) were recorded on a Varian 4000 GC/MS/MS. The mode of ionization used was electron impact (EI, 70 eV) or chemical ionization (CI) with methanol as the ionization gas. High resolution electrospray ionization mass spectra (HREIMS) were obtained on Agilent Technologies 6210 Time-of-Flight LC/MS (Simon Fraser University) and ESI micromass LCT spectrometer (University of British Columbia). Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer (Simon Fraser University).
2.10.2. Experimental Procedures and Characterization Data

trans,trans-Farnesal (75)

\[
\text{Me} = \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{75}
\end{array}
\]

**Method A:**

To a stirred solution of oxalyl chloride (0.65 mL, 6.7 mmol) and dimethylsulfoxide (1.3 mL, 18 mmol) in dichloromethane (30 mL) at -60 °C was added trans,trans-farnesol 11 (1.14 mL, 4.45 mmol) in dichloromethane (10 mL) via cannula. The resultant mixture was stirred at -60 °C for 15 min and then triethylamine (3.1 mL, 23 mmol) was added. The reaction mixture was allowed to warm to room temperature over 16 h and following dilution with ether (60 mL) was washed with a saturated aqueous solution of ammonium chloride (2 x 100 mL) and brine (150 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (7:3) as the eluant to afford the title compound 75 (0.87 g, 89%) as a mixture of E:Z isomers (87:13) and as a colourless oil.

**Method B:**

To a stirred solution of Dess-Martin periodinane (3.91 g, 9.20 mmol) in dichloromethane (30 mL) was added trans,trans-farnesol 11 (1.20 mL, 4.74 mmol) in dichloromethane (10 mL) via a cannula. The reaction mixture was allowed to stir at room temperature for 16 h and then diluted with either (80 mL). An aqueous solution of sodium hydroxide (1.3 M, 50 mL) was the added and the resultant solution was stirred at room temperature for an additional 30 min. The organic layer then was washed with an aqueous solution of sodium hydroxide (1.3 M, 2 x 40 mL) and water (2 x 30 mL), dried
over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography using hexanes:ether (1:1) as the eluant to afford the *title compound 75* (0.92 g, 93%) in a pure Z isomer as a colourless oil.

**Method C:**

To a stirred suspension of manganese dioxide (30.0 g, 10 mass equiv.) in dichloromethane (100 mL) was added *trans*,*trans*-farnesol 11 (3.00 g, 13.5 mmol). The reaction mixture was allowed to stir at room temperature for 5 h and then was filtrated through a pad of celite. The filter-cake was washed with dichloromethane (5 x 30 mL) and the combined filtrates were concentrated *in vacuo* to afford the *title compound 75* (2.81 g, 95%) in a pure Z isomer as a colourless oil.

**1H NMR** (CDCl₃, 500 MHz) δ 1.55 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.62 (3H, s, CH₃), 1.90-2.04 (4H, m, 2 x CH₂), 2.12 (3H, s, CH₃), 2.15 – 2.24 (4H, m, 2 x CH₂), 5.03 (2H, m, 2 x CH), 5.83 (1H, d, J = 8.0 Hz, CH), 9.94 (1H, d, J = 8.0 Hz, CHO); **13C NMR** (CDCl₃, 126 MHz) δ 15.8, 17.3, 17.4, 25.4, 26.3, 39.4, 40.3, 122.3, 123.8, 123.9, 127.2, 131.0, 136.2, 163.3, 190.7; **IR** (neat) 3038, 2967, 2920, 2851, 1626, 1582, 1197, 1020 cm⁻¹; **MS** (Cl) m/z (rel. intensity) 221 (M + H, 18), 203 (100), 177 (19), 163 (18), 147 (24), 109 (35), 81 (16).
2-(4,8-Dimethyl-trans-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (74)

A mixture of trans,trans-farnesal 75 (1.50 g, 6.80 mmol), 2-methoxyhydroquinone 12 (1.43 g, 10.2 mmol), phenylboronic acid (0.92 g, 7.5 mmol), propionic acid (5 drops) and benzene (30 mL) was heated at reflux for 48 h in a Dean-Stark trap. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel using hexanes:ether (3:2) as the eluant to afford the title compound 74 (2.02 g, 87%) as a dark brown oil.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.38 (3H, s, CH$_3$), 1.59 (3H, s, CH$_3$), 1.60 (3H, s, CH$_3$), 1.68 (3H, s, CH$_3$), 1.60 – 1.79 (2H, m, CH$_2$), 1.95 – 2.22 (6H, m, 3 x CH$_2$), 3.82 (3H, s, OCH$_3$), 5.11 (2H, m, 2 x CH), 5.30 (1H, s, OH), 5.46 (1H, d, $J$ = 9.8 Hz, CH), 6.25 (H, d, $J$ = 9.8 Hz, CH), 6.40 (1H, s, ArH), 6.57 (1H, s, ArH); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 16.2, 17.9, 22.9, 26.0, 26.4, 26.9, 39.9, 41.2, 56.2, 78.4, 100.4, 112.0, 114.2, 122.7, 124.3, 124.6, 127.8, 131.5, 135.4, 139.5, 146.9, 147.0; IR (neat) 3450, 3031, 2973, 2919, 2846, 1630, 1501, 1444, 1289 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 342 (M + H, 100), 191 (23), 41 (36), 39 (11); Anal. Calcd. for C$_{22}$H$_{30}$O$_3$: C, 77.16; H, 8.83. Found: C, 77.30; H, 8.79.
2-(9-Hydroxy-4,8-dimethyl-trans,trans-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (76)

To a stirred solution of selenium dioxide (0.056 g, 0.50 mmol) in dichloromethane (5 mL) at 0 °C was added tert-butylhydroperoxide (0.20 mL, 1.00 mmol). A solution of 2-(4,8-dimethyl-trans,trans-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene 74 (0.342 g, 1.00 mmol) in dichloromethane (5 mL) was then added via a cannula. The reaction mixture was then allowed to stir for 1.5 h at 0 °C and following dilution with ether (10 mL) was washed with brine (3 x 25 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (3:7) as the eluant to afford the title compound 76 (0.087 g, 24%) as a dark brown oil. The starting material, 2(4,8-dimethyl-trans,trans-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene 74 (0.190 g, 55%), was also recovered.

\[ ^1H \text{ NMR} (\text{CDCl}_3, 500 \text{ MHz}) \delta 1.36 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.61 – 1.74 (2H, m, CH_2), 1.97 – 2.00 (2H, m, CH_2), 2.08 – 2.13 (4H, m, 2 x CH_2), 3.83 (3H, s, OCH_3), 3.98 (2H, s, OCH_2), 5.12 (1H, m, CH), 5.21 (1H, s, OH), 5.37 (1H, m, CH), 5.44 (1H, d, J = 9.8 Hz, CH), 6.24 (1H, d, J = 9.8 Hz, CH), 6.38 (1H, s, ArH), 6.55 (1H, s, ArH); ^13C \text{ NMR} (\text{CDCl}_3, 126 \text{ MHz}) \delta 22.9, 26.4, 39.5, 41.1, 56.1, 56.3, 69.2, 77.4, 78.4, 100.2, 100.4, 111.9, 114.1, 122.8, 124.4, 124.7, 126.2, 127.90, 127.84, 135.1, 139.5, 146.9; \text{IR} (ef) 3413 (br), 2937, 2924, 2851, 1625, 1503, 1447, 1290, 1196, 1126 \text{ cm}^{-1}; \text{MS} (\text{Cl}) m/z (\text{rel. intensity}) 359 (M + H, 16), 357 (43), 341 (100), 309 (10), \]
258 (13), 247 (12), 201 (21), 193 (42), 153 (54); Anal. Calcd. for C_{22}H_{30}O_{4}: C, 73.71; H, 8.44. Found: C, 74.06; H, 8.34.

2-(9-Acetoxy-4,8-dimethyl-\textit{trans},\textit{trans}-3,7-nonadienyl)-6-acetoxy-7-methoxy-2-methyl-2\textit{H}-chromene (78)

A mixture of 2(9-hydroxy-4,8-dimethyl-\textit{trans},\textit{trans}-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2\textit{H}-chromene 76 (47 mg, 0.13 mmol), acetic anhydride (19 \mu L, 0.20 mmol), pyridine (15 \mu L, 0.20 mmol) and N,N-dimethyl-4-aminopyridine (1 mg, 0.008 mmol) in dichloromethane (2 mL) was stirred at 0 °C for 16 h. The resultant solution was concentrated \textit{in vacuo} and purified by flash chromatography using hexanes:ether (3:2) as the eluant to afford the \textit{title compound} 78 (26 mg, 43%) as a colourless oil. The starting material, 2(9-hydroxy-4,8-dimethyl-\textit{trans},\textit{trans}-3,6-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2\textit{H}-chromene 76 (18 mg, 41%), was also recovered.

\textit{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 1.38 (3H, s, CH\textsubscript{3}), 1.58 (3H, s, CH\textsubscript{3}), 1.64 (3H, s, CH\textsubscript{3}), 1.64 – 1.78 (2H, m, CH\textsubscript{2}), 1.96 – 2.04 (2H, m, CH\textsubscript{2}), 2.06 (3H, s, CH\textsubscript{3}), 2.06 – 2.18 (4H, m, 2 x CH\textsubscript{2}), 2.27 (3H, s, CH\textsubscript{3}), 3.77 (3H, s, OCH\textsubscript{3}), 4.43 (2H, s, OCH\textsubscript{2}), 5.11 (1H, t, \(J = 6.9\) Hz, CH), 5.40 - 5.44 (2H, m, 2 x CH), 6.23 (1H, d, \(J = 9.9\) Hz, CH), 6.42 (1H, s, ArH), 6.64 (1H, s, ArH); \textit{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 126 MHz) \(\delta\) 14.2, 16.2, 20.8, 22.9, 26.8, 39.2, 41.5, 56.2, 70.6, 79.2, 101.3, 113.7, 120.2, 120.2, 122.1, 122.3, 124.5, 124.7, 127.5, 130.2, 133.1, 135.0, 151.6, 152.0, 169.8, 171.3; IR (ef) 2974, 2925, 2846, 1765, 1737, 1621, 1503, 1225, 1200 cm\(^{-1}\); \textbf{MS} (Cl) \textit{m/z} (rel. intensity) 443 (M + H, 2), 425 (3), 384
(100), 342 (11), 316 (4), 235 (5), 201 (5), 175 (2), 61 (3), 43 (14); Anal. Calcd. for 
C_{26}H_{34}O_6: C, 70.56; H, 7.74. Found: C, 70.37; H, 7.92.

12-Hydroxy-trans,trans-farnesal (81)

To a stirred solution of selenium dioxide (1.39 g, 12.5 mmol) in dichloromethane 
(6 mL) at 0 °C was added tert-butylhydroperoxide (1.20 mL, 6.00 mmol). A solution of 
trans,trans-farnesal (0.916 g, 4.16 mmol) in dichloromethane (4 mL) was then added 
via a cannula. The reaction mixture was then allowed to stir for 3 h at 0 °C and following 
dilution with ether (100 mL) was washed with brine (3 x 100 mL). The organic layer was 
dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was 
purified by flash chromatography using hexanes:ether (2:3) as the eluant to afford the 
title compound 81 (0.457 g, 47%) as a colourless oil. The starting material, trans,trans-
farnesal (0.317 g, 35%), was also recovered.

^1H NMR (CDCl₃, 500 MHz) δ 1.55 (3H, s, CH₃), 1.59 (3H, s, CH₃), 1.90 – 2.21 
(8H, m, 4 x CH₂), 2.12 (3H, s, CH₃), 3.91 (2H, s, OCH₂), 5.03 (1H, m, CH), 5.30 (1H, m, 
CH), 5.81 (1H, d, J = 8.0 Hz, CH), 9.94 (1H, d, J = 8.0 Hz, CHO); ^13C NMR (CDCl₃) δ 
13.5, 15.9, 17.5, 25.4, 25.8, 40.4, 68.4, 122.1, 122.6, 124.9, 127.3, 134.8, 136.0, 164.0, 
191.3; IR (ef) 3512 (br), 2923, 2854, 2763, 2714, 1675, 1443, 1382, 1194, 1122 cm⁻¹; 
MS (Cl) m/z (rel. intensity) 237 (M + H, 7), 219 (99), 202 (100), 136 (39), 126 (16); Anal. 
Calcd. for C_{15}H_{24}O₂: C, 76.23; H, 10.24. Found: C, 76.18; H, 10.35.
12-Acetoxy-trans,trans-farnesal (80)

A solution of 12-hydroxy-trans,trans-farnesal 81 (0.40 g, 1.7 mmol), acetic anhydride (0.25 mL, 2.7 mmol), pyridine (0.21 mL, 2.7 mmol) and N,N-dimethyl-4-aminopyridine (15 mg, 0.01 mmol) in dichloromethane (10 mL) was stirred at room temperature for 4 h. The resultant solution was concentrated in vacuo and purified by flash chromatography using hexanes:ether (1:1) as the eluant to afford the title compound 80 (0.45 g, 93%) as a colourless oil.

$^1$H NMR (CDCl$_3$, 500 MHz) δ 1.60 (3H, s, CH$_3$), 1.64 (3H, s, CH$_3$), 1.90 – 2.04 (4H, m, 2 x CH$_2$), 2.06 (3H, s, CH$_3$), 2.17 (3H, s, CH$_3$), 2.15 – 2.24 (4H, m, 2 x CH$_2$), 4.43 (2H, s, OCH$_2$), 5.03 (1H, t, $J$ = 5.2 Hz, CH), 5.42 (1H, t, $J$ = 7.4 Hz, CH), 5.87 (1H, d, $J$ = 8.0 Hz, CH), 9.99 (1H, d, $J$ = 8.0 Hz, CHO); $^{13}$C NMR (CDCl$_3$, 126 MHz) δ 14.2, 16.2, 17.8, 21.2, 25.9, 26.5, 39.2, 40.8, 70.5, 123.1, 137.6, 129.5, 130.4, 136.3, 164.0, 171.2, 191.5; IR (ef) 3038, 2967, 2920, 2851, 1626, 1582 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 279 (M + H, 9), 261 (7), 219 (56), 201 (99), 175 (17), 145 (27), 135 (100), 125 (76), 109 (31), 95 (16); Anal. Calcd. for C$_{17}$H$_{26}$O$_4$: C, 73.34; H, 9.41. Found: C, 73.09; H, 9.53.
2(9-Acetoxy-4,8-dimethyl-trans,trans-3,7-nonadienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (79)

A mixture of 12-acetoxy-trans,trans-farnesal 80 (0.44 g, 1.6 mmol), 2-methoxyhydroquinone 12 (0.34 g, 2.4 mmol), phenylboronic acid (0.29 g, 2.4 mmol), propionic acid (2 drops) and benzene (15 mL) was heated at reflux for 24 h in a Dean-Stark trap. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel using hexanes:ether (3:2) as the eluant to afford the title compound 79 (0.55 g, 86%) as an amber oil.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.32 (3H, s, CH$_3$), 1.54 (3H, s, CH$_3$), 1.60 (3H, s, CH$_3$), 1.60 – 1.79 (2H, m, CH$_2$), 2.02 (3H, s, CH$_3$), 1.95 – 2.22 (6H, m, 3 x CH$_2$), 3.82 (3H, s, OCH$_3$), 4.41 (2H, s, OCH$_2$), 5.11 (1H, m, CH), 5.38 – 5.42 (2H, m, 2 x CH), 5.52 (1H, s, OH), 6.20 (H, d, J = 9.8 Hz, CH), 6.35 (1H, s, ArH), 6.52 (1H, s, ArH); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 14.2, 16.1, 21.2, 22.9, 26.5, 39.2, 41.1, 56.1, 70.5, 77.7, 78.3, 100.4, 112.1, 114.0, 122.8, 124.8, 127.7, 129.7, 130.1, 134.7, 139.5, 146.8, 147.1, 171.2; IR (neat) 3423 (br), 3033, 2978, 2921, 1738, 1501 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 401 (M + H, 5), 341 (100), 285 (15), 247 (8), 193 (19), 153 (18), 61 (8); Anal. Calcd. for C$_{17}$H$_{19}$NO$_3$: C, 71.97; H, 8.05. Found: C, 71.59; H, 7.89.
Likonide B (13),\textsuperscript{33,34,36} Smenochromene C (14)\textsuperscript{34} and 2(4,8-dimethyl-trans,trans-3,6,8-nonatrienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene (82)

A mixture of 2(9-acetoxy-4,8-dimethyl-trans,trans-3,7-nondienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene 79 (45 mg, 0.11 mmol), tetrakis(triphenylphosphine) palladium (7 mg, 0.006 mmol), triphenylphosphine (2 mg, 0.006 mmol), potassium carbonate (19 mg, 0.17 mmol) and 18-crown-6 (90 mg, 0.35 mmol) and benzene (6 mL) was stirred at 45 °C for 50 h. The resultant solution was concentrated in vacuo and purified by flash chromatography using hexanes:ether (8:1) as the eluant to afford likonide B 13 (15 mg, 41%) as a colourless oil, smenochromene C 14 (4 mg, 9%) as a colourless oil and 2(4,8-dimethyl-trans,trans-3,6,8-nonatrienyl)-6-hydroxy-7-methoxy-2-methyl-2H-chromene 82 (9 mg, 24%) as a colourless oil.

\textit{Likonide B (13)}

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 600 MHz) \(\delta\) 1.37 (3H, s, CH\textsubscript{3}), 1.48 (3H, s, CH\textsubscript{3}), 1.70 (3H, s, CH\textsubscript{3}), 1.57 – 1.80 (4H, m, CH\textsubscript{2}), 1.86 – 2.20 (4H, m, CH\textsubscript{2}), 3.75 (3H, s, OCH\textsubscript{3}), 4.15 (1H, d, \(J = 11.4\) Hz, OCH\textsubscript{2}), 4.52 (1H, d, \(J = 11.4\) Hz, OCH\textsubscript{2}), 4.82 (1H, t, \(J = 6.0\) Hz, CH), 4.92 (1H, t, \(J = 5.3\) Hz, CH), 5.32 (1H, d, \(J = 9.8\) Hz, CH), 6.30 (1H, s, ArH), 6.31 (1H, d, \(J = 9.9\) Hz, CH), 6.53 (1H, s, ArH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 151 MHz) \(\delta\) 14.2, 14.5, 23.1, 24.7, 30.3, 38.9, 41.4, 55.6, 79.1, 80.4, 99.9, 113.3, 119.1, 123.6, 125.8, 126.7, 129.9, 131.9, 132.1, 139.4, 150.4, 153.4; IR (ef) 3043, 2977, 2921, 2861, 1615, 1503, 1446, 1197,
1125 cm\(^{-1}\); **MS** (CI) \(m/z\) (rel. intensity) 341 (M + H, 100), 313 (5), 247 (9), 201 (6), 193 (9), 153 (7); **HREIMS** Calcd. for C\(_{22}H_{28}O_3Na\) (M + Na): 363.1936. Found: 363.1939.

*Smenochromene C (14)*

\(^1\text{H NMR}\) (CDCl\(_3\), 600 MHz) \(\delta\) 1.39 (3H, s, CH\(_3\)), 1.47 (3H, s, CH\(_3\)), 1.90 (3H, s, CH\(_3\)), 1.70 – 2.00 (4H, m, 2 x CH\(_2\)), 2.00 – 2.30 (4H, m, 2 x CH\(_2\)), 3.74 (3H, s, OC\(_H\)), 4.28 (1H, d, \(J = 11.8\) Hz, OC\(_H\)), 4.45 (1H, d, \(J = 11.9\) Hz, OCH\(_2\)), 5.00 (1H, t, \(J = 5.0\) Hz, CH), 5.18 (1H, dt, \(J = 10.3\) Hz, CH), 5.24 (1H, d, \(J = 10.1\) Hz, CH), 6.20 (1H, d, \(J = 10.5\) Hz, CH), 6.22 (1H, s, ArH), 6.62 (1H, s, ArH); \(^{13}\text{C NMR}\) (CDCl\(_3\), 151 MHz) \(\delta\) 14.9, 22.7, 24.1, 27.2, 31.5, 39.5, 42.2, 55.8, 74.0, 80.1, 99.6, 112.5, 120.6, 122.1, 124.5, 124.9, 129.9, 131.4, 134.2, 140.7, 153.9; **IR** (ef) 3043, 2977, 2921, 2861, 1615, 1503, 1446, 1197, 1125 cm\(^{-1}\); **MS** (CI) \(m/z\) (rel. intensity) 341 (M + H, 100), 311 (8), 247 (9), 247 (12), 219 (5), 193 (8), 153 (9); **HREIMS** Calcd. for C\(_{22}H_{29}O_3\) (M + H): 341.2116. Found: 341.2119.

\(2(4,8\text{-Dimethyl-trans,trans-3,6,8-nonatrienyl})\)-6-hydroxy-7-methoxy-2-methyl-2\(H\)-chromene 82

\(^1\text{H NMR}\) (C\(_6\)D\(_6\), 500 MHz) \(\delta\) 1.32 (3H, s, CH\(_3\)), 1.57 (3H, s, CH\(_3\)), 1.60 – 1.70 (2H, m, CH\(_2\)), 1.75 (3H, s, CH\(_3\)), 2.16 – 2.34 (2H, m, CH\(_2\)), 2.70 (2H, d, \(J = 7.0\) Hz, CH\(_2\)), 3.05 (3H, s, OCH\(_3\)), 4.89 (1H, s, CH), 4.93 (1H, s, CH), 5.05 (1H, s, OH), 5.14 (1H, d, \(J = 9.8\) Hz, CH), 5.24 (1H, t, \(J = 6.2\) Hz, CH), 5.59 – 5.63 (1H, m, CH), 6.03 (1H, d, \(J = 9.8\) Hz, CH), 6.18 (1H, d, \(J = 15.6\) Hz, CH), 6.34 (1H, s, ArH), 6.70 (1H, s, ArH); \(^{13}\text{C NMR}\) (C\(_6\)D\(_6\), 126 MHz) \(\delta\) 16.0, 18.6, 23.1, 26.0, 41.3, 43.1, 55.0, 77.9, 100.3, 112.1, 114.8, 123.0, 125.5, 127.2, 128.3, 128.7, 133.9, 134.4, 140.1, 142.0, 147.0, 147.1; **IR** (ef) 3444, 2968, 2929, 2839, 1622, 1503, 1445, 1289, 1197, 1164, 1125 cm\(^{-1}\); **MS** (CI) \(m/z\) (rel.
intensity) 341 (M + H, 100), 285 (45), 259 (16), 233 (11), 201 (16), 193 (22), 153 (12),
109 (11); **HREIMS** Calcd. for C_{22}H_{29}O_{3} (M + H): 341.2116. Found: 341.2115.

**4-Hydroxy-3-methoxyphenyl formate (90)\textsuperscript{35,36}**

![Chemical structure](image)

To a stirred solution of vanilline \textit{89} (5.55 g, 36.5 mmol) and selenium dioxide
(101 mg, 0.91 mmol) in tert-butyl alcohol (20 mL) at 0 °C was added hydrogen peroxide
(6.3 mL, 62 mmol) dropwise. The reaction mixture was then allowed to stir for 2 h and
following dilution with ether (50 mL) was washed with brine (3 x 30 mL). The organic
layer was dried over anhydrous sodium sulfate and concentrated \textsuperscript{*} in vacuo. The crude
product was purified by flash chromatography using hexanes:ether (1:1) as the eluant to
afford the \textit{title compound 90} (2.86 g, 47%) as a orange oil.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 3.86 (3H, s, OCH\textsubscript{3}), 5.68 (1H, s, OH), 6.63 (1H, dd,
\(J = 2.6, 8.6\) Hz Ar\textsubscript{H}), 6.66 (1H, d, \(J = 2.6\) Hz, Ar\textsubscript{H}), 6.90 (1H, d, \(J = 8.6\) Hz, Ar\textsubscript{H}), 8.28
(1H, s, CHO); \textsuperscript{13}C NMR (CDCl\textsubscript{3} 101 MHz) \(\delta\) 56.32, 104.9, 113.5, 114.7, 143.0, 144.0,
147.1, 160.0; IR (neat) 3454 (br), 3080, 3007, 2944, 2846, 1737, 1621, 1509, 1370,
1102, 1031, 954, 915, 867, 797, 733 cm\textsuperscript{-1}; **MS** (CI) \textit{m/z} (rel. intensity) 169 (M + H, 100),
141 (31), 147 (19).
(2E,6E,10E)-12-[(4-Hydroxy-2-methoxyphenoxy)-methyl]-3,7,11-trimethyldodeca-2,6,10-trienal (33).

![Chemical structure of 33]

To a stirred solution of 12-hydroxy-trans,trans-farnesal 81 (0.236 g, 1.00 mmol), 4-hydroxy-3-methoxyphenyl formate 90 (0.252 g, 1.50 mmol), triphenylphosphine (3.14 g, 12.0 mmol) in THF (10 mL) at 0 °C was added diisopropyl azodicarboxylate (0.30 mL, 1.5 mmol) dropwise. The reaction mixture was allowed to slowly warm to room temperature and was stirred for 20 h. Following dilution with ether (25 mL), the reaction mixture was washed with an aqueous solution of sodium bisulfite (20% w/v, 3 x 30 mL), an aqueous solution of sodium hydroxide (10% w/v, 3 x 30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (3:7) as the eluant to afford the title compound 33 (137 mg, 38%) as a yellow oil.

**1H NMR** (CDCl₃, 500 MHz) δ 1.60 (3H, s, CH₃), 1.72 (3H, s, CH₃), 1.90 – 2.30 (8H, m, 4 x CH₂), 2.17 (3H, s, CH₃), 3.82 (3H, s, OCH₃), 4.38 (2H, s, OCH₂), 5.06 (1H, t, J = 5.8 Hz, CH), 5.21 (1H, s, OH), 5.44 (1H, t, J = 7.2 Hz, CH), 5.89 (1H, d, J = 8.3 Hz, CH), 6.28 (1H, d, J = 8.7 Hz ArH), 6.46 (1H, s, ArH), 6.73 (1H, d, J = 8.6 Hz, ArH), 9.98 (1H, d, J = 8.2 Hz, CHO); **13C NMR** (CDCl₃, 126 MHz) δ 13.8, 16.0, 17.7, 21.9, 25.6, 26.1, 39.0, 40.5, 55.8, 76.1, 100.7, 105.8, 116.8, 122.7, 127.3, 128.1, 131.4, 136.1, 142.2, 150.5, 164.4, 191.6; **IR** (neat) 3354 (br), 3080, 3007, 2944, 2846, 1677, 1509, 1370, 1102, 954; **MS** (Cl) m/z (rel. intensity) 359 (M + H, 46), 341 (100), 247 (99), 219 (61).
20), 193 (29), 167 (30); **HREIMS** Calcd. for C_{22}H_{31}O_{43} (M + H): 359.2211. Found: 359.2222.

**Likonide B (13).**

A mixture of the aldehyde 33 (90 mg, 0.25 mmol), phenylboronic acid (46 mg, 0.38 mmol), propionic acid (1 drop) and benzene (15 mL) was heated at reflux for 24 h in a Dean-Stark trap. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel using hexanes:ether (4:1) as the eluant to afford the **title compound 13** (35 mg, 41%) as a colourless oil.

**{H NMR** (CDCl$_3$, 600 MHz) $\delta$ 1.37 (3H, s, CH$_3$), 1.48 (3H, s, CH$_3$), 1.70 (3H, s, CH$_3$), 1.57 – 1.80 (4H, m, CH$_2$), 1.86 – 2.20 (4H, m, CH$_2$), 3.75 (3H, s, OCH$_3$), 4.15 (1H, d, $J = 11.4$ Hz, OCH$_2$), 4.52 (1H, d, $J = 11.4$ Hz, OCH$_2$), 4.82 (1H, t, $J = 6.0$ Hz , CH), 4.92 (1H, t, $J = 5.3$ Hz, CH), 5.32 (1H, d, $J = 9.8$ Hz, CH), 6.30 (1H, s, ArH), 6.31 (1H, d, $J = 9.9$ Hz, CH), 6.53 (1H, s, ArH); **C NMR** (CDCl$_3$, 151 MHz) $\delta$ 14.2, 14.5, 23.1, 24.7, 30.3, 38.9, 41.4, 55.6, 79.1, 80.4, 99.9, 113.3, 119.1, 123.6, 125.8, 126.7, 129.9, 131.9, 132.1, 139.4, 150.4, 153.4; **IR** (ef) 3043, 2977, 2921, 2861, 1615, 1503, 1446, 1197, 1125 cm$^{-1}$; **MS** (Cl) m/z (rel. intensity) 341 (M + H, 100), 313 (5), 247 (9), 201 (6), 193 (9), 153 (7).
3. Studies Towards the Total Synthesis of Platensimycin

3.1. Introduction

This chapter concerns studies towards the total synthesis of platensimycin (17), an antibiotic compound isolated from Streptomyces platensis MA 7327 (Figure 3.1). Platensimycin presents a considerable synthetic challenge as it features a complex tetracyclic ketolide structural motif.

![Molecular structure of platensimycin (17).](image)

By manipulating the oxygenation pattern of the intricate tetracyclic ketolide core of platensimycin, it was proposed that an asymmetric domino double Stetter reaction of an achiral molecule 15 could lead compound 16 which features the tricyclic skeleton of the target compound with all the stereogenic centres correctly installed in a single synthetic transformation (Scheme 3.1). Towards this end, a brief review of the history of the antibiotic discovery and a summary of the biological activity and the potential applications of platensimycin is presented in the following sections of this chapter. In
addition, progress towards the total synthesis of this natural product, in which a concise synthesis of compound 15 and a preliminary evaluation of the use of this compound in the proposed key asymmetric domino double Stetter reaction is discussed in detail.

Scheme 3.1 Proposed Asymmetric Double Stetter Reaction to Construct the Tricyclic Skeleton of Platensimycin

3.2. An Overview of Antibiotic Research

3.2.1. Introduction to Platensimycin (17)

Multi-drug resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecium (VREF), that are capable of evading the lethal grasp of antibacterial drugs, have become a pressing medical concern that requires the high vigilance of physicians and scientists. Since the late 1960s, hundreds of essential proteins have been identified in bacteria as potential drug targets but only a few of these targets have led to the development of therapeutically useful drugs. In fact, only three new classes of antibiotics have entered the market since 1970. In the past decades, chemical modification of existing scaffolds to afford new and effective antibiotics has served well; however, such modifications are becoming increasingly challenging. In this regard, the recent discoveries of platensimycin (17), and its naturally-occurring congeners, platensic acid (93), platensimycin A1 (94) and
platensimycin B1-3 (95-97)⁶⁸ have been hailed as a true breakthrough in antibiotic research (Figure 3.2).

![Chemical structures of platensimycin-related natural products](image)

**Figure 3.2** Molecular structures of platensimycin-related natural products (93-97) isolated from Streptomyces platensis MA7327 and MA7339.

### 3.2.2. Overview of Historically Important Antibiotics

The first use of antibiotics can be traced back to 2500 years ago to the ancient Chinese, Egyptians and Greeks who cured infections using molds and plants that contained compounds with antibiotic activity. In 1897, the antibiotic properties of *Penicillium* species were first described by Ernest Duchesne in France. Unfortunately, this report did not receive much attention from society. However, in 1909, Paul Ehrlich developed the first narrow-spectrum antibiotic, salvarsan (98), also known as arsphenamine or Ehrlich 606, for the treatment of syphilis (Figure 3.3).⁶⁹ In 1932, Dr. Gerhard Domagk discovered prontosil (99), a sulpha-drug which was used as the first general-purpose antibiotic in modern medicine. Later, through research on the biological
properties of penicillium species, Alexander Fleming observed the inhibition of bacterial growth by the growth of penicillium notatum. Inspired by Fleming's work, Ernst Chain and Howard Florey continued this line of research, which led to the isolation, structural elucidation, clinical evaluation and commercialization of penicillin (100) as the first broad spectrum antibacterial agent in the early 1940s. The discovery of both sulpha-drugs and penicillin led to a concerted search for new antibacterial drugs during the next 30 years and resulted in the discovery of most of the antibacterial drug classes known today. Surprisingly, given the success in antibiotic identification, only three new antibacterial classes, the antibiotic mupirocin (101) in 1985, the oxazolidinone linezolid (102) in 2000 and the lipopeptide daptomycin (103) in 2003, have entered the market since 1970.69
Figure 3.3 Molecular structure of selected antibiotics (98-103).

In 1944, three years after the introduction of penicillin (100), scientists found that many bacterial strains had already developed resistance by acquiring enzymes, such as $\beta$-lactamase, that are capable of metabolizing the drug before it could reach its biological target.\textsuperscript{70,71} A more recent report by Lowy et. al has indicated that the proportion of \textit{S. aureus} that have developed resistance to methicillin, causing infections in hospitalized patients, has risen significantly, from 2\% in 1974 to nearly 40\% in 1997.\textsuperscript{72} Evolving
resistance calls for new, effective and safe antibacterial drugs without cross-resistance to antibiotics that are currently in clinical use.

3.2.3. **Platensimycin as a Potent Antibiotic: The Mode of Action**

Taking advantage of modern biological techniques, a research group at Merck recently developed an antisense silencing RNA-based assay for the identification of inhibitors of the type II fatty acid synthase (FAS II) pathway present in bacterial cells. The fatty acid synthase pathway has been validated as an antibiotic target through the wide use of isoniazid (104) and triclosan (105), whose primary target is an enzyme in the bacterial fatty acid biosynthesis pathway (Figure 3.4). The overall high degree of conservation in many of the component enzymes of the FASII system holds promise for the development of broad-spectrum antibiotics. In addition, the significant differences between the human fatty acid synthase (FASI) and the bacterial fatty acid synthase (FASII) machinery makes the bacterial FASII an attractive target in the fight against drug-resistant bacteria.

![Molecular structure of triclosan (104) and isoniazid (105).](image)

In the antisense silencing RNA-based assay, Wang et al. were able to suppress the gene encoding the FabH and FabF condensing enzymes of the FAS II pathway, thus sensitizing the bacteria to inhibitors of these enzymes. This methodology allowed the
authors to screen more than 250,000 natural product extracts which ultimately led to the discovery of platensimycin (17).66

Platensimycin (17), isolated from Streptomyces platensis MA 7327, was discovered in a soil sample collected in Eastern Cape, South Africa. This antibiotic contains a 3-amino-2,4-dihydroxy benzoic acid structural motif, which has been found to be highly responsible for its outstanding antibacterial activity, linked to a tetracyclic ketolide motif through an amide bond. As a FAS II inhibitor, platensimycin (17) showed no cross-resistance and was found to be active against a broad range of pathogenic Gram-positive bacterial species, such as methicillin-resistant Straphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE) and penicillin-resistant Streptococcus pneumonia (PRSP). In addition, platensimycin (17) was also shown to be effective in vivo in a mouse model of disseminated S. aureus infection while exhibiting no evidence of mammalian toxicity.

A common method for identifying the mode of action of an antibacterial agent is to examine its effect on the key bacterial biosynthetic pathways in the presence of specific radiolabeled compounds in whole cells. In this selective experiment, platensimycin showed no effect towards the biosynthesis of bacterial DNA, RNA, cell wall or protein, but inhibited specifically the lipid biosynthesis in S. aureus and S. pneumoniae. Fatty acid biosynthesis (Fab) is an essential metabolic process for all living organisms and lipids are important components for cell membranes and cell envelopes. Platensimycin exerts its antibiotic effect exclusively through blocking bacterial fatty acid biosynthesis. At a molecular level, platensimycin (17) inhibits the bacterial-ketoacyl-(acyl-carrier-protein) synthase (FabF) (Figure 3.5). FabF plays an
important role in carbon-carbon bond formation in the chain-elongation step of the bacterial fatty acid biosynthesis pathway.

Figure 3.5  Schematic representation of bacterial fatty acid biosynthesis pathway.

Detailed analysis by x-ray crystallography of platensimycin (17) bound to a mutant version of the FabF enzyme [ecFABF(C163Q) – a mutant that was designed to mimic the acyl-enzyme intermediate] revealed two distinct binding domains: the highly polar benzoic acid unit and the lipophilic ketolide unit. The benzoic acid domain, which docks to the malonate pocket of the condensing enzyme, interacts with the active-site histidine residues (H303 and H340) (Figure 3.6). The second binding domain, the lipophilic ketolide unit, is believed to have significant van der Walls interactions with the protein surface in addition to some hydrogen bonding interactions of its ether and
carbonyl oxygen atoms with T270 and A309, respectively. The amide linker, which connects both binding domains, is involved in two hydrogen bonding interactions. The carbonyl oxygen atom is hydrogen bonded to the T307 and the nitrogen atom is bonded to T270.

Figure 3.6 Interactions of platensimycin (17) with its mutated target enzyme ecFABF(C163Q).

An interesting finding noted in the original isolation paper was that the antibacterial activities of platensimycin (17) dropped drastically in the \textit{in vitro} setting in the presence of serum.\textsuperscript{66} In a recent report by Brinster \textit{et al.}, the authors suggested that the strategy for antibiotic development based on bacterial FASII pathway targets is fundamentally flawed.\textsuperscript{75} In this article, Brinster \textit{et al.} pointed out that human serum itself is an extremely rich source of fatty acids and they argued that the presence of such exogenous fatty acids was sufficient enough for bacteria to fully bypass the inhibition of the bacterial FASII pathway. In short, they were able to demonstrate that major Gram-positive bacteria can overcome the growth inhibition by antimicrobials targeting the FASII pathway when environmental fatty acids, particularly unsaturated fatty acids, are available. While there is some debate in regard to the implication of these findings, it seems that further study on the bacterial FAS II pathway and its use as a viable
antibacterial target needs to be performed in order to substantiate the generality of Brinster's claims.

### 3.2.4. Proposed Biosynthesis of Platensimycin (17)

The biosynthesis of platensimycin (17) was proposed by Herath et al. based on stable-isotope precursor incorporation experiments.\(^{76}\) Based on the \(^{13}\)C labelled feeding experiments of pyruvates and glycerol, the biosynthesis of the C-17 tetracyclic platensic acid unit occurs by a non-mevalonate terpenoid pathway, whereas the benzoic acid unit could be derived from the tricarboxylic acid cycle (TCA cycle, also known as citric acid cycle) and phosphoenolpyruvate (PEP) (Scheme 3.2). In the biosynthesis of the tetracyclic ketolide unit, dimethylallyl diphosphate (DMAPP, \(^{108}\)) and isopentenyl diphosphate (IPP, \(^{109}\)) are condensed to generate geranylgeranyl diphosphate (GGPP, \(^{110}\)), which undergoes subsequent cyclizations by terpene cyclases to generate the tetracyclic precursor, \textit{ent}-stachane, which upon rearrangement produces \textit{ent}-kaurane \(^{111}\). Oxidative cleavage of the A-ring of the \textit{ent}-kaurane \(^{111}\) would lead to the tricyclic precursor which upon further oxidations and cyclizations could lead to C-20 homoplatensic acid (93).
Scheme 3.2  Proposed Biosynthesis of Platensimycin (17)

Scheme showing the proposed biosynthesis of Platensimycin (17) involving the conversion of various metabolites through enzymatic reactions and chemical transformations.
3.3. Selected Literature Syntheses of Platensimycin (17)

To date, there have been a total of thirteen total and formal syntheses of platensimycin (17) reported from eleven laboratories around the world. Presented below is a brief summary of selected total synthesis of platensimycin (17).

3.3.1. Nicolaou’s First Total Synthesis of (±)-Platensimycin [(±)-17]

Only four months after the reported isolation and characterization of platensimycin (17), Nicolaou’s group disclosed the first total synthesis of platensimycin (17) using a cycloisomerization and radical cyclization reactions as the key steps.\(^7\) In this report, the dienynone 117, derived from sequential alkylation of 3-ethoxy-2-cyclohexenone (116) followed by reduction with DIBAL-H and protection with tert-butyldimethylsilyl chloride, was cycloisomerized using Trost’s ruthenium catalyst to prepare compound 118. A subsequent Saegusa-type oxidation reaction, followed by a samarium iodide-mediated radical cyclization reaction and an acid-mediated intramolecular etherification reaction afforded the core structure of platensimycin 121 (Scheme 3.3). Double alkylation reactions and cross-metathesis reaction with vinyl pinacol boronate, followed by oxidation with trimethylamine N-oxide and Pinnick oxidation afforded platensic acid 93.
The aromatic amine unit 123 was prepared from the MOM-protected nitroresorcinal 122 in four steps (Scheme 3.4). Coupling of this amine 123 with platensic acid 93 using 2-(1H-7-azabenzotriazolyl)-1,1,3,3-tetramethyluronium (HATU) followed by hydrolysis of the ester moiety and deprotection of the MOM group afforded platensimycin (17) in racemic form.
3.3.2. Nicolaou’s Asymmetric Total Synthesis of (-)-Platensimycin [(-)-17]

Soon after their first reported total synthesis of racemic platensimycin (± 17), Nicolaou’s group published the first asymmetric synthesis of platensimycin (- 17). This synthesis focused on the preparation of aldehyde 125 in optically enriched form. Treatment of compound 124, prepared from dienynone 117, with [Rh(cod)Cl]₂ and (S)-BINAP in the presence of silver hexafluoroantimonate (AgSbF₆) gave the desired spirocyclic-aldehyde 125 in 91% yield and in greater than 95% ee (Scheme 3.5). This aldehyde 125 was then converted to the corresponding Barton ester 126, which upon photolysis with tri-n-butyltin hydride afforded the decarboxylated product 127. This material was then used to complete the total synthesis in an analogous manner to that reported previously.
3.3.3. **Yamamoto’s Asymmetric Synthesis of (-)-Platensimycin**

[(-)-17]: A Robinson Annulation Approach

Yamamoto has also reported an enantioselective route to the core skeleton of platensimycin (-17) using an intramolecular Robinson annulation approach (Scheme 3.6).\(^7\)\(^9\) Employing a Brønsted acid-assisted chiral Lewis acid (BLA), prepared *in situ* from Lewis acid 134 and Brønsted acid 135, a Diels-Alder reaction between 2-methylcyclopentadiene (128) and methyl acrylate (129) afforded the cycloadduct 130 in a regio-, diastereo- and enantioselective manner. In a few steps, the keto-aldehyde 132 was then prepared. The key intramolecular Robinson annulation was subsequently accomplished using L-proline as a chiral catalyst to mediate the intramolecular Michael addition, which was then followed by an aldol condensation reaction in the presence of
sodium hydroxide, to afford the desired core structure of platensimycin 121 and its C9-epimer in a 5:1 diastereomeric ratio.

Scheme 3.6  
Yamamoto’s Enantioselective Synthesis of the Tetracyclic Core of Platensimycin

3.3.4.  
Corey’s Enantioselective Synthesis of (-)-Platensimycin [(−)-17]: An Oxidative Ketalization Approach

An enantioselective synthesis of the platensimycin core 121 was developed by Lalie and Corey. In this work, an oxidative ketalization reaction of methoxy α-naphthol (136) followed by enantioselective conjugate addition of potassium 2-propenyl trifluoroborate afforded a chiral ketone in good yield and in 94% ee (Scheme 3.7). After a few functional group transformation reactions, the bromoether 138 was treated with tetrabutylammonium fluoride (TBAF) and the resultant product was subjected to a diastereoselective hydrogenation reaction to produce the saturated tetracyclic core 139.
in a good yield. Conversion of this material to its corresponding enone 121 was accomplished using Nicolaou’s IBX oxidation protocol.

Scheme 3.7  
**Corey’s Enantioselective Synthesis of the Tetracyclic Core of Platensimycin**

3.3.5. Ghosh’s Asymmetric Synthesis of (-)-Platensimycin [(-)-17]: A Diels-Alder Reaction Approach

In 2007, Ghosh et al. published an incomplete enantioselective synthetic approach to the tetracyclic core of platensimycin 144 (Scheme 3.8). Alcohol 142, derived from (+)-carvone (140), was converted to the Diels-Alder precursor 143 by repetitive oxidation and Wittig olefination reactions. The proposed Diel-Alder reaction was accomplished in chlorobenzene at 200 °C in 37% yield. Two years later, this research group reported the total synthesis of (-)-platensimycin (-17) using the same methodology discussed above.
3.4. Studies Towards the Total Synthesis of Platensimycin (17)

3.4.1. Retrosynthetic Analysis of Platensimycin (17)

The initial retrosynthetic analysis of the tetracyclic ketolide moiety of platensimycin (17) suggested that it could be prepared via a regio- and stereoselective reduction and intramolecular etherification reactions of the tricyclic compound 146, which is the product of a Stetter reaction of spirocyclic-aldehyde 147 (Scheme 3.9). This spirocyclic aldehyde 147 could be prepared via a Claisen rearrangement reaction of vinyl ether 148, which in turn could be prepared from the trienedione 149.
3.4.2. Brief Overview of the Stetter Reaction

As the Stetter reaction is proposed as a key step in the synthesis of platensimycin (17), a brief overview of the discovery and the synthetic applications of this reaction is provided in the following section.

3.4.2.1. Development and Applications of the Stetter Reaction

The first classic example of a reaction featuring an inverse of functional group polarities, the benzoin reaction, was reported by Wohler and Liebig in 1832. Here, cyanide was used as a catalyst in the formation of benzoin from two equivalents of benzaldehyde. In 1943, Ukai et al. showed that thiazolium salts catalyzed the homo-coupling reaction of aldehydes in the presence of base. In 1973, Hermann Stetter and Manfred Schrechekberg discovered that using a catalytic amount of sodium cyanide, aryl aldehydes react in 1,4-conjugate addition reactions with \( \alpha,\beta \)-unsaturated nitriles and ketones to afford the corresponding 1,3-oxonitriles and 1,3-diketones.
respectively (Scheme 3.10). Since then, the 1,4-addition of aldehydes to activated double bonds in the presence of nucleophilic catalysts is referred to as the Stetter reaction.

**Scheme 3.10  First Examples of the Stetter-type Reaction**

![Scheme 3.10](image)

Reagents and conditions: a) NaCN (10% eq), DMF, 35 °C.

In 1989, Enders et al. reported the first asymmetric Stetter reaction employing chiral thiazolium salts as precatalysts (Scheme 3.11). Although the reaction yield and the enantiomeric excess of the isolated product were low (4% and 39%, respectively), further studies performed by Ender showed that N-heterocyclic carbenes (NHC) such as (S,S)-157 catalyzed the enantioselective synthesis of various 4-chromanones in improved reaction yields (22-73%) and in higher enantiomeric excesses (41-74%).
In the past few years, Rovis and co-workers have achieved significant progress using NHCs, such as 160 and 161, as a catalyst in the enantioselective synthesis of different chromanones as well as their aza-, thia- and carbacyclic analogues with excellent enantiomeric excess (82-97%) and good reaction yields (63-95%) (Scheme 3.12).87,88

3.4.2.2. Proposed Reaction Mechanism of the Stetter Reaction

A recent report by Rovis et al. detailed a plausible catalytic cycle of the Stetter reaction (Scheme 3.13).83 The first step involves the addition of carbene 163, generated in situ by deprotonation of the corresponding triazolium salt 162, to the aldehyde 164 to
form adduct 165, which undergoes a proton transfer reaction to generate the acyl anion equivalent 166, which is generally known as the nucleophilic species in this reaction or as the Breslow intermediate. Subsequent addition of the Breslow intermediate 166 to the Michael acceptor 167 affords compound 168. A second proton transfer reaction results in the tetrahedral intermediate 169 which collapses to afford the Stetter product 170 and regenerates the carbene catalyst 163.

Scheme 3.13 Proposed General Reaction Mechanism of the Stetter Reaction

3.4.2.3. Stetter Reactions in Natural Product Total Synthesis

3.4.2.3.1. Stetter’s Synthesis of cis-Jasmon (174)

In 1975, Stetter and Kuhlmann reported the synthesis of cis-jasmon (174) using the aforementioned Stetter reaction (Scheme 3.14). The starting material, aldehyde 171, was reacted with methylvinylketone (172) in the presence of the triazolium salt in
order to prepare the adduct 173, which was subsequently cyclized to afford cis-jasmon (174) in 62% yield.

Scheme 3.14  Synthesis of cis-Jasmon (174) by Stetter and Kuhlmann

![Scheme 3.14](image)

Reagents and conditions: a) Triazolium salt (0.1 eq.), Et₃N, 80 °C; b) NaOH, H₂O, EtOH, heat.

3.4.2.3.2. Trost’s Synthesis of Hirsutic Acid (178)

In 1979, Trost et al. employed an intramolecular Stetter reaction of compound 177 as the key step in their synthesis of (+)-hirsutic acid C (178). In this report, compound 176, prepared in four steps from commercially available-starting materials, was treated with a triazolium salt in triethylamine and isopropyl alcohol, which upon heating afforded the tricyclic compound 177 (Scheme 3.15). This tricyclic compound 177 contained four of the seven stereogenic centres of hirsutic acid C (178) which in turn allowed for the control in the formation of the remaining three centres.
3.4.2.3.3. Galopin’s Synthesis of (+)-trans-Sabinene Hydrate (181)

More recently, Galopin et al. reported the total synthesis of (+)-trans-sabinene hydrate (181) using an intermolecular Stetter reaction of isovaleraldehyde (179) and methylvinylketone (172) to prepare the dione 180. A subsequent aldol condensation reaction of the latter compound afforded the corresponding cyclopentenone which in turn served as the key reaction intermediate for the synthesis of (+)-trans-sabinene hydrate (181) (Scheme 3.16).91

Scheme 3.15    Synthesis of Hirsutic Acid (178) by Trost et al.

Scheme 3.16    Synthesis of (+)-trans-Sabinene Hydrate (181) by Galopin et al.
3.4.3. **Attempted Synthesis of the Trienedione 149**

Our first attempt to synthesize the spirocyclic trienedinone 149 was to utilize an intramolecular aromatic substitution reaction to dearomatize the phenyl moiety of compound 184 (X = halide), and thus induce an intramolecular cyclization reaction with the tethered alkyl halide moiety (Scheme 3.17). The first step of this route, the alkylation of TBS-protected p-hydroxypropiophenone 182 with ethylene oxide, however, proved to be difficult. After a considerable amount of experimentation, the desired alkylated alcohol 183 (X = OH) was not isolated.

**Scheme 3.17 Attempted Synthesis of the Spirocyclic Trienedione 149**

This led to an alternative attempt to synthesize the corresponding saturated form of the spirocyclic compound 185 via sequential dialkylation reaction (inter- and then intramolecular) of 2-methyl 2-cyclopentenone (187) with compound 186 (Scheme 3.18). Here, the substituent X in compound 186 represents a good leaving group, such as a halide or sulfonate.

**Scheme 3.18 Revised Retrosynthetic Analysis of Spirocyclic Trienedione 149**
The electrophile 191 was prepared from a trimethylsilyl chloride-mediated acetalization reaction of methyl acetone-1,3-dicarboxylate (188), followed by exhaustive reduction to afford the corresponding diol 190 in a good yield over two steps in accordance to Yadav’s procedure (Scheme 3.19). Conversion of this diol 190 to its corresponding dibromide 191 using the standard triphenylphosphine-carbon tetrabromide method resulted in only a 27% isolated yield of compound 191, with the remaining 40% of the product being the cyclized ether 192. Thus, an excess amount of the triphenylphosphine and carbon tetrabromide was used to improve the conversion of the diol 190 to the dibromide compound 191.

Scheme 3.19 Synthesis of 2,2-bis(2-Bromoethyl)-1,3-dioxolane (191)

Reagents and conditions: a) Ethylene glycol, TMSCl, DCM, 5 days; b) LiAlH₄, -78 °C to 0 °C, 5 h (72% over two steps); c) CBr₄, triphenylphosphine, 2,6-lutidine, THF, rt, 4 h (68% 191:6% 192).

The diol 190 was also converted to its corresponding ditosylate 193 following a standard protocol using p-toluenesulfonyl chloride in the presence of pyridine and N,N-dimethyl-4-aminopyridine (Scheme 3.20).
Since the proposed starting material, 2-methyl 2-cyclopentenone (187), is not commercially-available and requires several steps to prepare, a model study of the sequential dialkylation reaction employing the commercially-available starting material, 2-cyclopentenone (194) with the dibromide 191 or the ditosyl compound 193 was undertaken. The result of this model study is summarized below (Scheme 3.21).

Table 3-1 Reagents and Conditions Corresponding to Scheme 3.21

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkylating Agent</th>
<th>Reagents and Conditions</th>
<th>194 (%)</th>
<th>195 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>191 or 193</td>
<td>NaH, THF, reflux, 6 h</td>
<td>0 %</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>191 or 193</td>
<td>tert-BuOK, THF reflux, 14 h</td>
<td>0 %</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>191 or 193</td>
<td>NaNH2, DMF, reflux, 14 h</td>
<td>0 %</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>191 or 193</td>
<td>NaNH2, DMF, reflux, 14 h</td>
<td>0 %</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>191 or 193</td>
<td>LDA, THF, -78 °C to rt, 4 h</td>
<td>n/a</td>
<td>0 %</td>
</tr>
</tbody>
</table>

Our initial attempt using sodium hydride as the base, in tetrahydrofuran only led to the recovery of the starting materials (entry 1, Table 3-1). Employing different bases such as potassium tert-butoxide or sodium amide also did not afford the desired product.
spirocyclic product 194 (entries 2 and 3). The addition of tetramethylethynediamine (TMEDA) as a co-solvent to disaggregate the sodium enolate and thus increase the reactivity of this species also failed to promote the desired alkylation reactions (entry 4). Attempts to affect a single alkylation reaction, instead of the proposed sequential dialkylation reactions, by employing lithium diisopropylamide (one equivalent) as a base, also did not deliver the desired product 195 (entry 5).

3.4.4. Revised Retrosynthetic Analysis of Platensimycin (17)

As the result of the above findings, an alternative approach to platensimycin (17) was devised. This revised retrosynthetic analysis of platensimycin (17) addressed the oxygenation pattern of the tetracyclic core of platensimycin 121. By manipulating the oxygenation pattern of the tetracyclic ketolide 121, we envisioned that it could be derived from a regioselective Wittig olefination reaction of the tricyclic precursor 16, followed by a regio- and stereoselective reduction of the ketone moiety and an intramolecular etherification reaction (Scheme 3.22). The requisite tricyclic molecule 16 could be prepared via an asymmetric domino double Stetter reaction from an achiral precursor 15 when treated with an appropriate chiral triazolium catalyst. This achiral compound 15 could be synthesized via a ring closing metathesis reaction of compound 197 followed by deprotection and oxidative cleavage of the acetal moiety. Compound 197 could be derived from commercially-available starting material 3-ethoxy-2-cyclohexenone (116), allyl bromide (198) and the alkylating reagent 199, which could be prepared from commercially available (-)-2,3-O-isopropylidene-D-erythronolactone (203).
3.4.5. **Synthesis of the Tetracyclic Ketolide 121: A Domino Double Stetter Reaction Approach**

3.4.5.1. **Synthesis of (-)-2,3-\text{O}-Isopropylidene-D-erythronolactone (203)**

(-)-2,3-\text{O}-Isopropylidene-D-erythronolactone (203) is available commercially but it is rather expensive. It can also be prepared on a large scale in three steps from a much cheaper commercially-available starting material, D-(−)-isoascorbic acid (200). Following Cohen’s protocol, D-(−)-isoascorbic acid (200) was exposed to alkaline hydrogen peroxide at 70 °C to induce oxidation on the electron-rich double bond, which is followed by hydrolysis and lactonization to afford D-erythronolactone (202), which was further treated with 2,2-dimethoxypropane in the presence of \textit{p}-toluenesulfonic acid to afford (−)-2,3-\text{O}-Isopropylidene-D-erythronolactone (203) upon recrystallization from diethyl ether and hexanes (Scheme 3.23).\textsuperscript{94}
Scheme 3.23  Synthesis of (-)-2,3-O-Isopropylidene-D-erythronolactone (203) from D-(−)-Isoascorbic Acid

Reagents and conditions: a) Na₂CO₃, H₂O₂, H₂O, 75 °C, 30 min; b) 6M HCl, 20 min; c) 2,2-dimethylpropane, pTsOH, MgSO₄, acetone, rt, 18 h (71% over three steps).

All spectroscopic data of (-)-2,3-O-Isopropylidene-D-erythronolactone (203) were found to be in agreement with the literature reported data.⁹⁴

3.4.5.2. Synthesis of 5-Halo-O,2,3-isopropylidene-1-pentene (199)

(-)-2,3-O-Isopropylidene-D-erythronolactone (203) was reacted with diisobutylaluminum hydride in dichloromethane at -78 °C for four hours to covert it to the corresponding hemi-acetal 204, which was subsequently treated with the ylide of methyltriphenylphosphine iodide to afford alcohol 205 in 47% overall yield (Scheme 3.24).⁹⁵ Alcohol 205 was then converted to its corresponding bromide and tosylate derivatives on treatment with carbon tetrabromide and triphenylphosphine⁶¹ or with p-toluenesulfonyl chloride in the presence of a catalytic amount of base, respectively.
Scheme 3.24  Synthesis of 5-Bromo-O,2,3-isopropylidene-1-pantene (206) and 5-Tosyl-O,2,3-isopropylidene-1-pentene (207)

Reagents and conditions: a) DIBAL-H, THF, -78 °C, 5 h; b) n-BuLi, THF, -78 °C, 2 h then Ph₃PMeI, reflux, 3 h (47% over two steps); c) CBr₄, 2,6-lutidine, PPh₃, THF, rt, 5 h (71%); d) TsCl, DMAP, pyridine, DCM, rt, 4 h (78%).

3.4.5.3. Synthesis of 6-[(5-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-3-ethoxy-2-cyclohexenone (208)

The alkylation reaction of 3-ethoxy-2-cyclohexenone (116) with compound 206 or 207 proved to be particularly challenging. The result of this study is summarized below (Scheme 3.25)

Scheme 3.25  Reaction of 3-Ethoxy-2-cyclohexenone (116) with the Alkylating Agents 206 and 207

<table>
<thead>
<tr>
<th>En</th>
<th>Reaction Conditions</th>
<th>208 (%)</th>
</tr>
</thead>
</table>
| 1  | 1) LDA (1.2 eq), THF, -78 °C, 30 min  
    2) 206 or 207, -78 °C to rt, 4 h to 16 h | 0       |
| 2  | 1) LDA (2 eq), THF, -78 °C, 30 min  
    2) 206 or 207, -78 °C to rt, 4 h to 16 h | 0       |
| 3  | 1) LDA (1.2 eq), THF, -78 °C, 30 min then TMEDA  
    2) 206 or 207, -78 °C to rt, 4 h to 16 h | 0       |
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>LDA (1.2 eq), THF, -78 °C, 30 min, then ZnCl₂ (1.5 eq)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>206, DMPU, THF, -78 °C to rt, 4 h</td>
<td>101</td>
</tr>
<tr>
<td>5</td>
<td>LDA (1.2 eq), THF, -78 °C, 30 min, then ZnCl₂ (1.5 eq)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>207, DMPU, THF, -78 °C to rt, 4 h</td>
<td>128</td>
</tr>
<tr>
<td>6</td>
<td>LDA (2.0 eq), THF, -78 °C, 30 min, then ZnCl₂ (2.5 eq)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>206, DMPU, THF, -78 °C to rt, 6 h</td>
<td>144</td>
</tr>
</tbody>
</table>

Under standard reaction conditions, using lithium diisopropylamide (LDA) as the base, the alkylation reaction of the 3-ethoxy-2-cyclohexenone 116 with either the alkyl bromide 206 or the alkyl tosylate 207 did not afford the desired product 208 (entry 1, Table 3-2). Employing an excess amount of LDA also did not facilitate the alkylation reaction (entry 2). In an effort to increase the reactivity of the enolate by employing a co-solvent such as tetramethylethylenediamine (TMEDA) to disaggregate the lithium-oxygen complex which in turn would make the enolate more nucleophilic, the desired alkylated product 208 was not isolated (entry 3). After extensive search of the literature, we found a few reports suggested that 3-ethoxy-2-cyclohexenone (116) is a very poor nucleophile towards alkyl halides. Dai and Katzenellenbogen have reported that using zinc chloride to promote a lithium-zinc metal exchange reaction, in the presence of N,N-dimethylpropyleneurea (DMPU), could facilitate the alkylation processes of 3-ethoxy-2-cyclohexenone (116) with various alkyl halides. Attempts to perform this transformation using either compound 206 or 207 as the alkylating agent afforded the desired coupled product 208 in low yield (entries 4 and 5). Varying the equivalents of reagents used in these reaction additives did not increase the yield significantly (entry 6).

Of note, the product 208 was very difficult to purify. Several attempts to purify the crude material by flash chromatography failed to remove byproducts from this reaction, which were observed by ¹H NMR spectroscopy. Thus, the molecular structure of compound 208 was determined by the analysis of the ¹H NMR spectrum recorded on
semi-purified material and by high-resolution mass spectroscopy. The yield of the reaction was approximately determined by the analysis of the \(^1\)H NMR spectrum.

The subsequent alkylation of compound \(208\) with a more reactive substrate, allyl bromide (198), also proved to be difficult, likely due to the steric encumberance created by the isopropylidene side chain, and no dialkylated product \(209\) was isolated (Scheme 3.26).

**Scheme 3.26 Attempt Alkylation of Compound 208 with Allyl Bromide (198)**

![Scheme 3.26](image)

Reagents and conditions: a) LDA, THF, \(-78^\circ\)C then allyl bromide (198), \(-78^\circ\)C to rt, 3 h (0%).

### 3.4.5.4. Studies of the Alkylation Reaction of 3-Ethoxy-2-cyclohexenone (116) with various Alkyl and Allyl Halides

As difficulties were encountered in the alkylation reaction of 3-ethoxy-2-cyclohexenone (116) with the alkylating agents 206 or 207, a study that examined the reactivity of 3-ethoxy-2-cyclohexenone (116) towards various alkyl and allyl alkylating agents was conducted (Scheme 3.27).
Here, alkylating agents 198 and 199 were the original proposed starting materials and the results from their attempted alkylation reaction were discussed above. Compounds 211 and 212 are protected forms of the corresponding aldehydes in which the acetal moiety could be removed at the later stage of the proposed synthesis and would avoid the use of a subsequent oxidative osmylation reaction (Scheme 3.28). Compound 213 is in a lower oxidation state and could easily be converted to the corresponding \( \alpha,\beta \)-unsaturated aldehyde by known standard procedures.
Scheme 3.28 Proposed Starting Materials for the Aldehyde and the α,β-Unsaturated Aldehyde Moieties of Compound 15

Scheme 3.29 Synthesis of {[(2E)-4-Bromo-2-butenyl]oxy}((tert-butyl)dimethyl)silane (213)

Compound 213 was prepared from ethyl bromocrotonate (214) in two steps by exhaustive reduction of the ester moiety to the corresponding alcohol 215 followed by standard protection procedure with tert-butyldimethylsilyl chloride (Scheme 3.29). Of note, the reduction of the ester to the corresponding alcohol can only be achieved on small scales (10 mmol or less). Attempts to perform this transformation on larger scale (>20 mmol) resulted in starting material decomposition and only trace amount of the desired alcohol 215 was isolated.

The results of the alkylation study of 3-ethoxy-2-cyclohexenone (116) with these alkylation agents 198, 199 and 211 – 213 is presented below (Table 3-3).
### Table 3-3  Reagents and Conditions Corresponding to Scheme 3.27

<table>
<thead>
<tr>
<th>En</th>
<th>Reaction Conditions</th>
<th>Expected Reaction Product</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>
| 1  | 1) LDA, THF, -78 °C, 1 h  
  2) 198 (1.5 eq), THF, -78 °C to rt, 12 h | ![image](image1.png) 216 | 92 |
| 2  | 1) LDA, THF, -78 °C, 1 h  
  2) 199 (X = Br or OTs, 1.5 eq), THF, -78 °C to rt, 12 h | ![image](image2.png) 208 | 0 |
| 3  | 1) LDA, THF, -78 °C, 1 h then DMPU, 30 min.  
  2) 199 (X = Br, 3 eq), ZnCl₂, -78 °C to rt, 12 h | ![image](image3.png) 208 | 14 |
| 4  | 1) LDA, THF, -78 °C, 1 h  
  2) 211 (3 eq), TMEDA, -78 °C to rt, 12 h | ![image](image4.png) 217 | 0 |
| 5  | 1) LDA, THF, -78 °C, 1 h then DMPU, 30 min  
  2) 211 (3 eq), ZnCl₂, -78 °C to rt, 12 h | ![image](image5.png) 217 | 0 |
| 6  | 1) LDA, THF, -78 °C, 1 h then DMPU, 30 min  
  2) 212 (3 eq), ZnCl₂, -78 °C to rt, 12 h | ![image](image6.png) 218 | 11 |
| 7  | 1) LDA, THF, -78 °C, 1 h  
  2) 213 (1.5 eq), THF, -78 °C to rt, 12 h | ![image](image7.png) 219 | 89 |

The results presented in the first three entries provides a summary of earlier studies (entries 1–3, Table 3-3). Similar results were observed when bromoacetaldehyde diethyl acetal (211) or 2-bromomethyl-1,3-dioxolane (212) were used (entries 4–6). However, when the allylic alkylating agent 213 was employed, the desired product 219 was isolated in 89% yield (entry 7). The results obtained from this study indicated that 3-ethoxy-2-cyclohexenone (116) exhibited good to excellent
reactivity towards various allylic halides whereas low or no reactivity was observed for alkyl halides and sulfonates.

3.4.6. Synthesis of the Tetracyclic Ketolide 16: A Decarboxylative Ring Contraction Approach

Concurrently to the above studies, an alternative approach to construct the spirocyclic compound 196 was undertaken. In this approach, we proposed that compound 220 could undergo a decarboxylative ring contraction reaction upon heating to afford the spirocyclic compound 196 (Scheme 3.30). A similar type of decarboxylation reaction was reported by Stoltz in 2006.98 In the Stoltz system, an allylic carbonate was treated with palladium (0) to induce the decarboxylation process. We envisioned that because of the intramolecular nature of our proposed reaction, it could facilitate the reaction of a primary alkylcarbonate.

Scheme 3.30  Proposed Reaction Mechanism for the Decarboxylative Ring Contraction Reaction of Compound 220

Alcohol 205 was reacted with carbonyldiimidazole to afford the corresponding carbamate 222.99 This material was subsequently reacted with the enolate of 216 to afford the desired carbonate 223 in 47% yield (Scheme 3.31).100
Scheme 3.31  Attempt Synthesis of Carbonate 220

Reagents and conditions: a) CDI, THF, 0 °C, 1 h (68%); b) LDA, 216, THF, -78 °C, 1 h then BF₃ Et₂O, 222, -78 °C, 5 h (47%); c) Grubb’s II catalyst, DCM, various times and temperatures (0%).

The molecular structure of compound 223 was confirmed by ¹H and ¹³C NMR spectra (Figure 3.7). The two singlets in δ 1.50 region were assigned to the two methyl groups of the isopropylidene moiety. A doublet at δ 2.76 corresponded to the bis-allylic methylene protons of the allyl group. A total of seven protons between δ 4.75 and 6.00 ppm corresponded to the seven olefin protons present in this compound. The ¹³C NMR spectrum showed 20 peaks which is in agreement with 20 carbons presented in the compound 223.
Figure 3.7 $^1$H NMR (600 MHz, CDCl$_3$) of 5-(ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl)-methyl-[5-ethoxy-2-(2-propenyl)cyclohexa-1,5-dienyl]-carbonate (223).

Unfortunately, the subsequent ring closing metathesis reaction of carbonate 223 proved to be difficult. A considerable amount of experimentation varying the reaction time and temperature did not afford the desired macrocyclic product 196. This result raised a need for a revised retrosynthetic analysis.

3.4.7. **Synthesis of the 4,4-Disubstituted-2,5-cyclohexadieneone 15**

Based on the observations described above, in that difficulties were encountered in the alkylation reaction of 3-ethoxy-2-cyclohexenone (116) with alkyl halides and the poor results obtained from the ring closing olefin metathesis reaction, we concluded that a revised retrosynthetic analysis was required. Since it had been shown that the proposed starting material, 3-ethoxy-2-cyclohexenone (116), exhibited very good
reactivity towards allylic halides, we proposed the allylic halides 198 and 226 could be used towards the synthesis of the key precursor 15 (Scheme 3.32). In this revised retrosynthetic analysis, the 4,4-disubstituted-2,5-cyclohexadieneone 15 could be prepared from compound 224 via a dihydroxylation reaction of the olefin moiety of compound 224 followed by oxidative cleavage of the resulting diol carbon-carbon bond. Compound 224 could be prepared from the 5,5-disubstituted cyclohexeneone 225, which is the product of the alkylation reactions of 3-ethoxy-2-cyclohexenone (116) with alkylation agents 198 and 226.

Scheme 3.32 Revised Retrosynthetic Analysis of 4-Oxo-2-butenyl]-4-(2-oxoethyl)-2,5-cyclohexadieneone (15)

Of note, the double bond geometry of compound 15 is believed not to be critical for the constitution of the correct stereochemistry of the target compound. Here, in the proposed reaction mechanism of this asymmetric domino double Stetter reaction, after the first Stetter reaction completed, the geometry of the double bond in compound 227 is removed by the formation of the enol tautomter 228 (Scheme 3.33). This enol moiety would then convert to the corresponding aldehyde for engagement in a second Stetter reaction.
3.4.7.1. Attempted Synthesis of 4-[(2E)-4-Oxo-2-butenyl]-4-(2-oxoethyl)-2,5-cyclohexadieneone (233)

The alkylation reaction of the substituted cyclohexenone 216 with compound 213 was completed within 4 hours of stirring at room temperature and compound 230 was isolated in 84% yield (Scheme 3.34). Subsequent reduction of the carbonyl moiety, followed by the treatment with acid initiated a double bond isomerization process, elimination of water and the removal the TBS protecting group to afford the desired enone 231 in a one-pot procedure. Subsequent oxidization employing manganese dioxide converted the allylic alcohol moiety to the corresponding aldehyde 232. At this stage, an attempt to introduce the bis-enone moiety using phenylselenium bromide and hydrogen peroxide only led to starting material decomposition and did not afford the desired product 233.
Scheme 3.34  Attempted Synthesis of 4-[(2E)-4-Oxo-2-butenyl]-4-(2-oxoethyl)-2,5-cyclohexadieneone (233)

Reagents and conditions: a) LDA, THF -78 °C, 1 h then 213, THF, -78 °C to rt, 3 h (84%); b) DIBAL-H, 0 °C to rt, 4 h then 3M HCl, rt, 16 h (69%); c) MnO₂, DCM, rt, 5 h (73%); d) LDA, THF -78 °C, 1h then PhSeBr, THF, -78 °C to rt, 3 h then H₂O₂, rt, 6 h (0%).

However, we envisioned that compound 235, the product of the dihydroxylation and oxidative cleavage reaction of compound 232, could also provide an alternative route to construct the desired tricyclic core 16 via the proposed domino double Stetter reaction in a racemic manner (Scheme 3.36).

Scheme 3.35  Alternative Synthetic Route to Tricyclic Ketone 16 from Compound 232
The osmium tetroxide-catalyzed dihydroxylation reaction of compound 232 and the subsequent oxidative cleavage reaction of the resulting diol moiety proved to be difficult to perform (Scheme 3.36). This was likely due to multiple double bonds presented in the system. Hence, an optimization study was conducted. The results of this study are summarized below (Table 3-4).

### Scheme 3.36  
Studies Towards the Synthesis of 4-[(2E)-4-Oxo-2-butenyl]-4-(2-oxoethyl)-2-cyclohexenone (235)

**Table 3-4  
Reagents and Conditions Corresponding to Scheme 3.36**

<table>
<thead>
<tr>
<th>en</th>
<th>reaction and conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OsO₄ (cat.), NMO (1 equiv.), acetone:H₂O (9:1), room temperature, 2 h then NaIO₄ (1 equiv.), THF:H₂O (2:1), 0 °C, 3 h</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>OsO₄ (cat.), NMO (1 equiv.), NaIO₄ (1 equiv.), acetone:H₂O (9:1), room temperature, 2 h</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>K₂OsO₄ (2%), NMO (1 equiv.), acetone:H₂O (9:1), room temperature 2h then NaIO₄ (1 equiv.), room temperature, 1 h</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>K₂OsO₄ (2%), NMO (2 equiv.), acetone:H₂O (9:1), room temperature, 1 h then NaIO₄ (2 equiv.), room temperature, 1 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>K₂OsO₄ (2%), NMO (1 equiv.), dioxane:H₂O (3:1), room temperature, 1 h then NaIO₄ (1 equiv.), room temperature, 1 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>K₂OsO₄ (2%), NaIO₄ (4 equiv.), acetone:H₂O (1:1), room temperature, 3 h</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>K₂OsO₄ (5%), NaIO₄ (3 equiv.), acetone:H₂O (1:1), room temperature, 2 h</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>K₂OsO₄ (5%), NaIO₄ (3 equiv.), acetone:H₂O (1:1), room temperature, 6 h</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>AD-mix-α, NaIO₄ (3 equiv.), acetone:H₂O (1:1), room temperature, 6 h</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>AD-mix-α, NaIO₄ (3 equiv.), acetone:H₂O (1:1), room temperature, 18 h</td>
<td>0</td>
</tr>
</tbody>
</table>
In the first instance, compound 232 was treated with a mixture of osmium tetroxide and \(N\)-methylmorpholine \(N\)-oxide in an acetone/water mixture and was stirred at room temperature for 1 hour. After work up, the crude product was then treated with sodium periodate (entry 1, Table 3-4). This reaction procedure, however, only afforded a trace amount of the desired product 235 after purification. A slightly modified procedure that involved pre-mixing the osmium tetroxide, \(N\)-methyl morpholine \(N\)-oxide and sodium periodate in aqueous acetone improved the reaction yield to 13% (entry 2).

The molecular structure of compound 235 was confirmed by \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra (Figure 3.8). The eight protons located between \(\delta 2.00\) to 3.00 ppm corresponded to the protons of the four methylene groups. The four protons between \(\delta 6.00\) to 7.00 ppm were assigned to the four olefin protons presented in this compound. The two signals at \(\delta 9.50\) and 10.0 ppm were assigned to the two protons of the aldehyde groups. The \(^{13}\text{C}\) NMR spectrum showed 12 peaks which are in agreement with 12 inequivalent carbons present in the compound 235.
Attempting to perform the dihydroxylation reaction using potassium osmate as the osmium tetroxide source in the presence of N-methylmorpholine N-oxide, followed by subsequent oxidative cleavage resulted in either a low isolated yield or decomposition of the starting material (entries 3–5).\textsuperscript{101} Adopting the method developed by Neelamkavil et al., which employs an excess amount of sodium periodate with a catalytic amount of potassium osmate in aqueous acetone, the desired product 235 was isolated in a moderate yield (entry 6).\textsuperscript{102} Finally, with a slight increase in the loading of the potassium osmate and lowering the loading of sodium periodate, the reaction yield was improved to 47%. Of note, attempts to improve the reaction yield by increasing the reaction time resulted poor isolated yield of the desired product (entry 8). This is likely due to the further oxidative cleavage of the remaining double bonds present in this compound.

Interestingly, when other commercially-available osmium tetroxide sources, such as AD-mix-\(\alpha\), was employed, no reaction occurred and the starting material was recovered.
Increasing the reaction time of this reaction also did not afford the desired product 235 (entry 10).

3.4.7.2. **Alternative Approach Towards the Synthesis of 4-[(2E)-4-Hydroxy-2-butenyl]-4-(2-propenyl)-2-cyclohexenone (231)**

Concurrently, an alternative approach to synthesize compound 231 was also devised. In this approach, a direct alkylation reaction between the substituted cyclohexenone 216 and ethyl bromocrotonate (214) was performed (Scheme 3.37). Although the reaction yield was lower and the purification was much more difficult by flash chromatography, the subsequent reduction and double bond isomerization reactions proved to be efficient and alcohol 231 was obtained in two steps on a multi-gram scale.

![Scheme 3.37 Alternative Synthesis of 4-[(2E)-4-Hydroxy-2-butenyl]-4-(2-propenyl)-2-cyclohexenone (231)](#)

Reagents and conditions: a) LDA, THF, 0 °C then ethyl bromocrotonate (214), THF, -78 °C to rt, 8 h (48%); b) DIBAL-H, DCM 0 °C, 5 h then 3 M HCl, 0 °C to rt, 14 h (71%).

3.4.7.3. **Attempted Synthesis of the Saturated Tricyclic Core of Platensimycin 234 via a Proposed Domino Double-Stetter Reaction**

In the following section, the development and attempted optimization of the domino double Stetter reaction conditions is presented. Three kinds of Stetter reagent were used in this study (Scheme 3.38). 3-Ethyl-5-(2-hydroxyethyl)-4-methylthiazolium
bromide (238) and 2-pentafluorophenyl-6,10b-dihydro-4H,5aH-5-oxa-3,10c-diaza-2-azonia-cyclopenta[c]fluorene tetrafluoroborate (239) are commercially available and 5-benzyl-2-(4-trifluoromethyl-phenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazo1-2-ium tetrafluoroborate (240) was prepared on a multi-gram scale from phenylalanine in six steps following Rovis’ protocol.88 Results of this study are summarized below (Table 3-5).

**Scheme 3.38**  Attempted Synthesis of the Saturated Ketolide Core 234 via a Domino Double Stetter Reaction

![Scheme 3.38](image)

**Table 3-5**  Reagents and Conditions Corresponding to Scheme 3.38

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>reaction and conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>238 (0.3 equiv.)</td>
<td>Et3N (0.3 equiv.), EtOH, reflux, 10 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>238 (0.3 equiv.)</td>
<td>Et3N (0.3 equiv.), EtOH, reflux, 3 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>239 (0.3 equiv.)</td>
<td>LiHMDS (0.3 equiv.), THF, room temperature, 14 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>239 (0.3 equiv.)</td>
<td>LiHMDS (0.3 equiv.), THF, 50 °C, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>239 (2.5 equiv.)</td>
<td>Et3N (2.5 equiv.), THF, reflux, 10 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>239 (2.5 equiv.)</td>
<td>LiHMDS (2.5 equiv.), THF, 40 °C, 2 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>
In the first instance, the triazolium salt 238 was used. Following the protocol developed and optimized by Stetter and others,89,103 the reaction was performed using triethylamine as a base at reflux in ethanol (entry 1, Table 3-5). After 10 hours at reflux, the starting material was completely consumed but no product was identified. Reducing the reaction time to three hours also did not afford the desired tricyclic product 234. When Rovis’ catalyst 239 was employed, and lithium hexamethyldisilane was used as the base, the reaction did not proceed after 14 hours of stirring at room temperature (entry 3).87,88 Increasing the reaction temperature to 50 °C, however, resulted in decomposition of the starting material (entry 4) and no product was isolated after flash chromatography. Increasing the loading of the catalyst to a full equivalent, as suggested by Nicolaou in his formal synthesis of platensimycin,104 also resulted in decomposition of the starting material (entries 5 and 6). Employment of the alternative Rovis’ NHC 240 also did not afford the desired tricyclic product 234 (entries 7 and 8).

3.4.7.4. Synthesis of 4-[(2Z)-4-Oxo-2-butenyl]-4-(2-oxoethyl)-2,5-cyclohexadienone (246)

In the previous study that lead to the synthesis of 4-(4-oxo-2-butenyl)-4-(2-oxoethyl)-2-cyclohexenone 235, a few problems were encountered. Firstly, the alkylation reaction of the substituted cyclohexenone 216 with ethyl bromocrotonate (214) is rather low yielding and the polarity difference between the starting material 216 and the product 237 was very similar (r.f. is 0.31 and 0.33 by TLC, respectively). This made the purification very difficult through flash chromatography, especially at an earlier stage of the synthesis when reactions were performed on a large scale. Secondly, the subsequent reduction reaction requires an excess amount of diisobutylaluminum hydride
(four equivalents) which also made the synthesis impractical on a large scale. After a detailed search of the literature, we identified that (2Z)-4-bromo-2-buteneyl acetate (242) could served as an alternative alkylation agent. Following Kabbaj’s procedure, (2Z)-4-bromo-2-buteneyl acetate (242) was prepared from 2,5-dihydrofuran (241) and acetyl bromide on a multi-gram scale (Scheme 3.39).

**Scheme 3.39 Synthesis of (2Z)-4-Bromo-2-buteneyl acetate (242)**

![Chemical structure](image)

Reagents and Conditions: a) Acetyl bromide, rt, 4 h (53%).

The alkylation reaction of the substituted cyclohexenone 216 with bromide 242 was completed within 3 hours (Scheme 3.40). The advantage of employing this alkylation agent is that the subsequent removal of the acetal group can be achieved by an aqueous lithium hydroxide solution work up and afford the corresponding alcohol 243 in a one-pot procedure. The significant polarity difference between the starting material and the product made purification here a relatively easy process. The subsequent reduction reaction is also more practical in that only 2 equivalents of diisobutylaluminum hydride being required. A double oxidation reaction that converted the alcohol 244 to the corresponding aldehyde 245 as well as introducing the bis-enone moiety was accomplished by employing IBX/MPO reagent mixture according to the Nicolaou IBX oxidation protocol. After the employment of the osmium tetroxide-catalyzed dihydroxylation reaction and the subsequent oxidative cleavage reaction, a concise and scalable synthesis of the key precursor 246 had been developed for the proposed domino double Stetter reaction.
Scheme 3.40  Synthesis of 4-[(2Z)-4-Oxo-2-butenyl]-4-(2-oxoethyl)-2,5-cyclohexadienone (246)

Reagents and conditions: a) a) LDA, THF -78 °C, 1 h then 242, THF, -78 °C to rt, 3 h then LiOH, H₂O, 40 °C (76%); b) DIBAL-H, 0 °C to rt, 4 h then 3 M HCl, t, 16h (77%); c) LDA, THF -78 °C, 1 h then TMSCl, THF, -78 °C, 2 h then IBX MPO, DMSO, room temperature, 17 h (51%); d) K₂OsO₄, NaIO₄, acetone:H₂O (1:1), room temperature, 2 h (43%).

The molecular structure of compound 246 was confirmed by the analysis of ¹H and ¹³C NMR spectral data. A total of eight resonances displayed in the ¹H NMR spectrum confirmed that the molecule is symmetrical. The eight protons between 6.00 to 7.00 ppm corresponded to the eight vinyl protons present in this compound (Figure 3.9). The two signals at 9.50 and 10.0 ppm were assigned to the two protons of the aldehydes. The ¹³C NMR spectrum showed 10 peaks which are in agreement with 10 chemically inequivalent carbons present in compound 246.
3.4.7.5. Attempted Synthesis of the Tricyclic Core of Platensimycin 16 via a Proposed Domino Double Stetter Reaction

The synthesis of the tricyclic ketolide 16 from compound 246 via the proposed domino double Stetter reaction was then attempted (Scheme 3.41). Based on the results obtained from the model study, two equivalents of the Stetter reagent with stoichiometric amount of base were employed. The results of these studies are summarized below (Table 3-6).
Scheme 3.41  Attempted Synthesis of the Ketolide Core 16 of Platensimycin via the Proposed Asymmetric Domino Double Stetter Reaction

Table 3-6  Reagents and Conditions Corresponding to Scheme 3.41

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>reaction and conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>238 (2.5 equiv.)</td>
<td>Et$_3$N, EtOH, reflux, 10 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>239 (2.5 equiv.)</td>
<td>LiHMDS, THF, room temperature, 14 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>239 (2.5 equiv.)</td>
<td>LiHMDS, THF, 50 °C, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>239 (2.5 equiv.)</td>
<td>tert-BuOK, THF, 50 °C, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>239 (2.5 equiv.)</td>
<td>tert-BuOK, THF, reflux, 30 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>240 (2.5 equiv.)</td>
<td>LiHMDS, THF, 40 °C, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>7</td>
<td>240 (2.5 equiv.)</td>
<td>LiHMDS, DCM, 0 °C - 40 °C, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>8</td>
<td>240 (2.5 equiv.)</td>
<td>tert-BuOK, THF, 40 °C, 2 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

In the first instance employing the thiazolium salt 238 developed by Stetter, the starting material 246 was heated at reflux in ethanol for 10 hours, at which point the starting material was completely consumed based on thin layer chromatography analysis. However, no identifiable product was isolated by flash chromatography (entry 1, Table 3-6). Attempts employing the commercially available Rovis’ reagent 239 at
room temperature also did not afford the desired tricyclic ketolide 16 (entry 2). Increasing the reaction temperature to 50 °C resulted in starting material decomposition (entry 3). According to Rovis in his recent review of the Stetter reaction and the carbene catalyst, the choice of solvent and base play an important role in reaction yield and stereoselectivity. Employing potassium tert-butoxide as the base also did not afford the desired tricyclic ketolide product (entries 4 and 5). The use of the alternative NHC at various temperatures in either tetrahydrofuran or dichloromethane also did not afford the desired product 16 (entries 6 – 8). In fact, the decomposition of the starting material was observed in all attempts. On these findings, we concluded that the starting material might not be stable towards the requisite reaction conditions and no further attempts were made to execute this transformation because of time constraints.

3.5. Conclusion

Platensimycin (17), a new class of antibiotic, isolated from Streptomyces platensis MA 7327 by researchers from Merck, has presented tremendous interest to synthetic chemists all over the World due to its outstanding biological profile and synthetically-challenging tetracyclic ketolide motif. We proposed that the tetracyclic ketolide 121 could be derived from an achiral precursor 15 via a novel asymmetric domino double Stetter reaction. During the synthesis towards the requisite achiral molecule 15, several challenges were identified and resolved. The most significant was that the proposed starting material, 3-ethoxy-2-cyclohexenone (116) exhibited poor reactivity in alkylation reactions with alkyl halides and sulfonates. In addition, in the attempted synthesis of compound 196 via the decarboxylative ring contraction reaction, the ring closing olefin metathesis reaction of compound 223 also did not afford the
desired spirocyclic product 220. These results led to a revised retrosynthetic analysis of platensimycin (17). With this revised retrosynthetic analysis, the requisite achiral molecule 246 was prepared from the substituted cyclohexenone 216 and (2Z)-4-bromo-2-buteneyl acetate 242 in four steps in 13% overall yield on a large scale. The proposed key reaction, the asymmetric domino double Stetter reaction was carried out with three different kinds of triazolium reagents, 238, 239 and 240. None of the attempts afforded the desired tricyclic ketolide 16. In most cases, the decomposition of the starting material was observed and no identifiable compounds were isolated. To this end, we concluded that the precursor 246 (or 236) was unstable towards the reaction conditions and therefore no further efforts to synthesize this natural product were made by this approach.
3.6. Experimental Section

3.6.1. General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware, unless indicated otherwise. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran (THF) was dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, dichloromethane, and pyridine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied. Brine refers to a saturated aqueous solution of sodium chloride. Silica gel column chromatography (“flash chromatography”) was carried out using Merck silica gel 60 (230 to 400 mesh) and Silicycle SiliaFlash® F60 (230-400 mesh). All proton and carbon nuclear magnetic resonance spectra (\(^1\text{H NMR}\) and \(^{13}\text{C NMR}\), respectively) were recorded using a Bruker 400 FT spectrometer (operating frequencies: \(^1\text{H}, 400.13 \text{ MHz}; ~^{13}\text{C}, 100.61 \text{ MHz}\), Bruker 500 FT spectrometer (operating frequencies: \(^1\text{H}, 499.77 \text{ MHz}; ~^{13}\text{C}, 125.68 \text{ MHz}\), Varian 500 FT spectrometer (operating frequencies: \(^1\text{H}, 499.77 \text{ MHz}; ~^{13}\text{C}, 125.68 \text{ MHz}\) and Bruker 600 FT spectrometer (operating frequencies: \(^1\text{H}, 600.13 \text{ MHz}; ~^{13}\text{C}, 150.90 \text{ MHz}\)) at ambient temperature unless stated otherwise. Chemical shifts (\(\delta\)) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform (CDCl\(_3\)) were 7.26 and 77.16 ppm for \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra, respectively. The reference values used for deuterated benzene (C\(_6\)D\(_6\)) were 7.15 and 128.02 ppm, respectively. Infrared spectra...
(IR) were recorded as either KBr pellets (KBr), evaporated films (ef) or as films (neat) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (MS) were recorded on a Varian 4000 GC/MS/MS. The mode of ionization used was electron impact (EI, 70 eV) or chemical ionization (CI) with methanol as the ionization gas. High resolution electrospray ionization mass spectra (HREIMS) were obtained on Agilent Technologies 6210 Time-of-Flight LC/MS (Simon Fraser University) and ESI micromass LCT spectrometer (University of British Columbia). Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer (Simon Fraser University).
3.6.2. Experimental Procedures and Characterization Data

4-(tert-Butyldimethylsilyloxy)propiophenone (182)\(^{108}\)

A mixture of \(p\)-hydroxypropiophenone (10.0 g, 67.2 mmol), tert-butyldimethylsilyl chloride (12.0 g, 79.8 mmol) and imidazole (11.3 g, 170 mmol) in \(N,N\)-dimethylformamide (50 mL) was stirred at room temperature for 10 h. The resultant mixture was then diluted with ether (300 mL) and washed with water (3 x 500 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo and purified by flash chromatography using hexanes:ether (3:1) as the eluant to afford the title compound 182 (17.7 g, 91%) as a white solid. M.p. 35 – 37 °C.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.23 (6H, s, 2 x Si\(CH_3\)), 0.98 (9H, s, 3 x CH\(_3\)), 1.21 (3H, t, \(J = 7.3\) Hz, CH\(_3\)), 2.95 (2H, q, \(J = 7.3\) Hz, CH\(_3\)), 6.87 (2H, d, \(J = 8.7\) Hz, ArH), 7.89 (2H, d, \(J = 8.7\) Hz, ArH); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 4.4, 8.4, 18.3, 25.6, 31.4, 119.9, 130.1, 130.6, 160.1, 199.6; IR (ef) 2956, 2931, 2589, 1681, 1598, 1507, 1256, 1221, 906, 837 cm\(^{-1}\).

Dimethyl 3-(1,3-dioxolanyl)-pentanedioate (189)\(^{92}\)

A mixture of methyl acetone-1,3-dicarboxylate 188 (3.53 g, 20.1 mmol), trimethylsilyl chloride (5.6 mL, 44 mmol), ethylene glycol (2.5 mL, 44 mmol) and dichloromethane (100 mL) was heated at reflux for 40 h. The resultant mixture was
allowed to cool to room temperature and was then quenched with an aqueous saturated solution of sodium bicarbonate (100 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was carried forward to the subsequent reaction without further purification.

3-(1,3-Dioxolanyl)-1,5-pentanediol (190)

To a stirred suspension of lithium aluminum hydride (1.30 g, 34.8 mmol) in tetrahydrofuran (70 mL) at 0 °C was added the crude diester 189 (4.28 g, 20.0 mmol) in tetrahydrofuran (15 mL) \textit{via} cannula. The reaction mixture was heated at reflux for 1 h and then cooled to 0 °C. The resultant mixture was slowly quenched by with water (2 mL) in tetrahydrofuran (3 mL), an aqueous solution of sodium hydroxide (15\% w/v, 2 mL) and water (4 mL) in tetrahydrofuran (7 mL). The resultant mixture was lstirred for 45 min at 0 °C and then filtered through a pad of celite. The filter-cake was washed with tetrahydrofuran (3 x 30 mL) and the combined filtrates were concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using ethyl acetate:acetone (1:1) as the eluant to afford the \textit{title compound} 190 (2.33 g, 72\% over two steps) as a pale yellow oil.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.87 (2H, t, $J = 6.0$ Hz, CH$_2$), 3.17 (1H, br. s, OH), 3.65 (2H, m, CH$_2$), 3.92 (2H, s, CH$_2$); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 38.4, 58.6, 64.7, 112.1; IR (ef) 3377, 2956, 2888, 1709, 1382, 1048 cm$^{-1}$.
1,5-Dibromo-3-(1,3-dioxolanyl)-pentane (191) and 1,4,8-trioxaspiro[4,5]decane (192)

To a stirred solution of diol 190 (1.62 g, 10.0 mmol) in tetrahydrofuran (80 mL) was added 2,6-lutidine (0.46 mL, 4.0 mmol), triphenylphosphine (13.1 g, 50.0 mmol) and carbon tetrabromide (16.6 g, 50 mmol). The resultant mixture was allowed to stir at room temperature for 4 h and then was diluted with hexanes (100 mL). The resultant solution was filtered through a pad of celite and rinsed with ethers and hexanes (1:1, 3 x 80 mL). The combined filtrates were concentrated in vacuo and the crude product was purified by flash chromatography using ether:hexanes (7:3) as the eluant to afford the title compound 191 (1.93 g, 68%) as a light brown oil and the title compound 192 (86 mg, 6%) as a light yellow oil.

1,5-Dibromo-3-(1,3-dioxolanyl)-pentane (191)

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.96 (2H, m, CH$_2$), 3.12 (2H, m, CH$_2$), 3.21 (2H, s, CH$_2$); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 27.5, 39.9, 64.1, 110.2; IR (ef) 3003, 2948, 2907, 2849, 1394, 1211, 1156, 892 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 291 (M + 2 x Br$^-$, 20), 289 (M + Br$^-$, 41), 287 (M + H, 17), 209 (99), 207 (74), 127 (14), 83 (37).

1,4,8-Trioxaspiro[4,5]decane (192)

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.74 (2H, apparent d, $J = 5.7$ Hz, CH$_2$), 3.54 (2H, s, CH$_2$), 3.84 (2H, apparent d, $J = 5.4$ Hz, CH$_2$); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 35.3, 58.1, 66.6, 120.3; IR (ef) 2960, 2863, 1471, 1359, 1304, 1224, 1147, 1119, 1038 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 145 (M + H$^+$, 100), 87 (5), 43 (8).
3-Ethoxy-6-(2-propenyl)-2-cyclohexenone (216)

To a solution of N,N-diisopropylamine (9.8 mL, 69 mmol) in tetrahydrofuran (100 mL) at -78 °C was added n-butyl lithium (30 mL, 2.5 M in hexanes, 75 mmol). The reaction mixture was stirred for 10 min then warmed to 0 °C and stirring was continued for 30 min. The reaction mixture was then cooled to -78 °C and a solution of 3-ethoxy-2-cyclohexenone 116 (9.1 mL, 54 mmol) in tetrahydrofuran (10 mL) was added. The resultant mixture was allowed to warm to 0 °C and was stirred for 30 min and then cooled to -78 °C. Allyl bromide 198 (12.0 mL, 135 mmol) was then added and the reaction mixture was warmed to room temperature and was stirred for 5 h. The reaction mixture was then quenched with an aqueous solution of hydrochloric acid (1 M, 40 mL), water (40 mL), diluted with hexanes (50 mL) and then extracted with ether (3 x 70 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ether (2:3) as the eluant to afford the \textit{title compound} 216 (8.9 g, 92%) as a light yellow oil.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.38 (3H, t, $J = 7.0$ Hz, CH$_3$), 1.65 - 1.75 (1H, m, CH$_2$), 2.04 - 2.29 (2H, m, CH$_2$), 2.20 - 2.33 (1H, m, CH), 2.38 - 2.51 (2H, m, CH$_2$), 2.60 - 2.69 (1H, m, CH), 3.88 (2H, q., $J = 7.0$ Hz, OCH$_2$), 4.96 - 5.18 (2H, m, 2 x CH), 5.26 (1H, s, CH), 5.70 - 5.90 (1H, m, CH); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 14.2, 25.8, 28.2, 34.1, 44.7, 64.2, 102.3, 116.6, 136.4, 177.0, 200.6; IR (ef) 3073, 2980, 2938, 2872,
1652, 1603, 1378, 1156 cm⁻¹; **HRMS** Calcd. for C₁₁H₁₇O₂ (M + H): 181.1232 Found: 181.1223.

**(-)-2,3-O-Isopropylidene-D-erythronolactone (203)**

![Structure of (-)-2,3-O-Isopropylidene-D-erythronolactone (203)](image)

To a stirred solution of erythorbic acid **200** (35.2 g, 200 mmol) in deionized water (500 mL) at 0 °C was added anhydrous sodium carbonate (42.4 g, 400 mmol) over 10 min followed by the dropwise addition of an aqueous solution of hydrogen peroxide (~30% w/v, 44 mL, 450 mmol) over 10 min. The resultant solution was allowed to stir at 0 °C for 5 min and then Norit A (8 g) was added in portions over 10 min. The resultant mixture was heated at 75 °C for 30 min and then was filtered through a pad of celite. The filter-cake was washed with deionized water (3 x 40 mL) and the combined filtrates were acidified to pH 1 with an aqueous solution of hydrochloric acid (6 M). The acidic solution was then concentrated *in vacuo* to afford a pale yellow residue, which was suspended in acetone (150 mL). Anhydrous magnesium sulfate (50 g), 2,2-dimethoxypropane (350 mL, 2.85 mol) and *p*-toluenesulfonic acid monohydrate (0.420 g, 2.20 mmol) were then added and the resultant mixture was stirred at room temperature for 18 h. The reaction mixture was then poured into a premixed solution of triethylamine (61.2 mL, 0.440 mol) in ether (500 mL) at 0 °C and was allowed to stir for 15 min. The resultant mixture was filtered and extracted with ether (3 x 100 mL). The combined organic extracts were concentrated *in vacuo* and filtered through a pad of silica gel using hexanes: ethyl acetate (1:1) as the eluant to afford crude product (24.7 g) as a colourless solid on further concentration. The crude product was dissolved in hot ether (150 mL).
and precipitated with cold hexanes (250 mL). The mixture was refrigerated for 4 h and then filtered. The solid was washed with hexanes (4 x 25 mL) and dried under vacuum to afford the title compound 203 (21.8 g, 69%) as a white solid.

\[^{1}\text{H NMR} \quad \text{(CDCl}_3, 400 \text{ MHz}) \delta 1.40 (3\text{H, s, CH}_3), 1.49 (3\text{H, s, CH}_3); 4.41 (1\text{H, dd, } J = 11.1, 3.8 \text{ Hz, CH}), 4.41 (1\text{H, dd, } J = 11.1, 3.8 \text{ Hz, CH}); 4.47 (1\text{H, d, } J = 11.0 \text{ Hz, CH}), 4.75 (1\text{H, d, } J = 5.7 \text{ Hz, CH}), 4.88 (1\text{H, ddd, } J = 5.6, 3.8, 0.6 \text{ Hz, CH}); \ \text{^{13}C NMR} \quad \text{(CDCl}_3, 101 \text{ MHz}) \delta 25.7, 26.8, 70.2, 74.6, 75.4, 114.1, 173.9.\]

\((-\text{-2,3-O-Isopropylidene-D-erythronolactol (204)})^{110}\)

To a stirred solution of lactone 203 (1.6 g, 10 mmol) in dichloromethane (25 mL) at -78 °C was added diisobutylaluminum hydride (11 mL, 1 M solution in hexanes, 11 mmol) over 10 min. The reaction mixture was allowed to stir at -78 °C for 4 h and the was quenched by the dropwise addition of methanol (2 mL). Water (20 mL), ethyl acetate (50 mL) and sulfuric acid (1.5 M, 20 mL) were then added and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts was washed with a saturated aqueous solution of sodium bicarbonate (60 mL) and brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was carried forward to the subsequent reaction without further purification.
O-2,3-Isopropylidene-4-penten-1-ol (205)\(^{110}\)

\[
\text{HO} \quad \text{205} \quad \text{Me} \quad \text{Me}
\]

To a stirred solution of methyltriphenylphosphine iodide (8.0 g, 20 mmol) in tetrahydrofuran (15 mL) at -78 °C was added \(n\)-butyl lithium (8.0 mL, 2.5 M in hexanes, 20 mmol). The reaction mixture was stirred at -78 °C for 30 min and then at room temperature for 1 h. The resultant solution was cooled to -78 °C and a solution of lactol 204 (1.32 g, 8.35 mmol) in tetrahydrofuran (5 mL) was added via a cannula. The reaction mixture was allowed to slow warm to room temperature and then was heated at reflux for 14 h. After cooling to room temperature, water (20 mL) was added and the resultant mixture was extracted with ether (5 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated \textit{in vacuo} and the crude product was purified by flash chromatography using hexanes:ether (1:2) as the eluant to afford the \textit{title compound} 205 (0.59 g, 47% over two steps) as a colourless oil.

\(\text{\textsuperscript{1}H} \text{ NMR} \ (\text{CDCl}_3, \ 500 \text{ MHz}) \ \delta \ 1.26 \ (3 \text{H, s, CH}_3), \ 1.38 \ (3 \text{H, s, CH}_3), \ 3.43 \ (2 \text{H, d, } J = 5.8 \text{ Hz, CH}_2), \ 4.14 \ (1 \text{H, apparent q, } J = 5.8 \text{ Hz, CH}), \ 4.51 \ (1 \text{H, apparent t, } J = 7.1 \text{ Hz, CH}), \ 5.09 - 5.16 \ (1 \text{H, m, CH}), \ 5.21 - 5.29 \ (1 \text{H, m, CH}), \ 5.59 - 5.87 \ (1 \text{H, m, CH}); \ \text{\textsuperscript{13}C NMR} \ (\text{CDCl}_3, \ 126 \text{ MHz}) \ \delta \ 24.9, \ 27.5, \ 61.5, \ 77.9, \ 78.2, \ 108.5, \ 118.3, \ 132.9 \text{ cm}^{-1}; \ \text{IR} \ (\text{ef}) \ 3407, \ 2993, \ 2968, \ 2901, \ 1362, \ 1226, \ 1031 \text{ cm}^{-1}.\)
5-Bromo-O-2,3-isopropylidene-1-pentene (206)

To a stirred solution of the alcohol 205 (480 mg, 3.0 mmol) in tetrahydrofuran (30 mL) was added 2,6-lutidine (0.14 mL, 1.2 mmol), triphenylphosphine (470 mg, 3.6 mmol) and carbon tetrabromide (1.2 g, 3.6 mmol). The resultant mixture was allowed to stir at room temperature for 4 h and then was diluted with hexanes (50 mL). The resultant solution was filtered through a pad of celite and the filter-cake was washed with ether and hexanes (1:1, 3 x 40 mL). The combined organic extracts were concentrated \textit{in vacuo} and the crude product was purified by flash chromatography using ether:hexanes (3:1) as the eluant to afford the \textit{title compound} 206 (470 mg, 71%) as a light yellow oil.

\[ ^1H \text{ NMR} (\text{CDCl}_3, 500 MHz) \delta 1.39 (3H, s, CH$_3$), 1.51 (3H, s, CH$_3$), 3.06 (1H, dd, $J = 10.2, 6.2$ Hz, CHH), 3.14 (1H, dd, $J = 10.2, 7.7$ Hz, CHH), 4.44 (1H, m, CH), 4.63 (1H, apparent t, $J = 7.1$ Hz, CH), 5.28 – 5.50 (1H, m, CH), 5.76 – 5.92 (1H, m, CH); \] 
\[ ^{13}C \text{ NMR} (\text{CDCl}_3, 126 MHz) \delta 25.6, 28.2, 33.1, 78.5, 79.1, 109.1, 119.4, 132.4; \text{IR} (\text{ef}) 2985, 2934, 2925, 1380, 1216, 1042, 870 \text{ cm}^{-1}; \text{HRMS} \] 
Calcd. for C$_8$H$_{14}$BrO$_2$ (M + H): 221.0182. Found: 221.0171.

5-(Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yI)methyl-1H-imidazole-1-carboxylate (222)
To a stirred solution of 1,1'-carbonyldiimidazole (820 mg, 5.11 mmol) in tetrahydrofuran (15 mL) at 0 °C was added compound 205 (800 mg, 5.12 mmol) in tetrahydrofuran (5 mL) via a cannula. The resultant solution was allowed to slowly warm to room temperature and was stirred for 1 h. The reaction mixture was then concentrated in vacuo and diluted with ether (30 mL). The resultant mixture was washed with pH 7 phosphate buffer (3 x 30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (1:2) as the eluant to afford the title compound 222 (850 mg, 68%) as a colourless oil.

\[ \text{\textsuperscript{1}H NMR (CDCl}_3\text{, 500 MHz)} \delta 1.40 (3H, s, CH}_3\text{), 1.51 (3H, s, CH}_3\text{), 4.14 (1H, dd, } J = 11.4, 6.8 \text{ Hz, CH})\text{, 4.41 (1H, dd, } J = 11.4, 4.3 \text{ Hz, CH})\text{, 4.47 (1H, apparent dt, } J = 6.7, 4.3 \text{ Hz, CH})\text{, 4.72 – 4.79 (1H, m, CH})\text{, 5.29 – 5.37 (1H, m, CH})\text{, 5.43 – 5.54 (1H, m, CH})\text{, 5.84 (1H, ddd, } J = 17.5, 10.4,7.2 \text{ Hz, CH})\text{, 7.02 – 7.11 (1H, m, CH})\text{, 7.38 – 7.47 (1H, m, CH})\text{, 8.14 (1H, s, CH})\text{; } \text{\textsuperscript{13}C NMR (CDCl}_3\text{, 126 MHz)} \delta 25.2, 27.6, 66.9, 75.1, 77.9, 109.6, 117.1, 119.7, 130.7, 131.9, 137.1, 148.4; \text{ IR (ef) 3121, 2987, 2936, 2914, 1737, 1373, 1215, 1049 cm}^{-1}; \text{ HRMS Calcd. for C}_12\text{H}_{17}\text{N}_2\text{O}_4 \text{ (M + H): 253.1179 Found: 253.1183.} \]
5-(Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl)-methyl-[5-ethoxy-2-(2-propenyl) cyclohexa-1,5-dienyl]-carbonate (223)

To a solution of N,N-diisopropylamine (0.80 mL, 4.8 mmol) in tetrahydrofuran (15 mL) at -78 °C was added n-butyl lithium (1.8 mL, 2.5 M in hexanes, 4.5 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 30 min. The resultant mixture was then cooled to -78 °C and compound 216 (711 mg, 3.95 mmol) in tetrahydrofuran (5 mL) was added. The reaction mixture was stirred at -78 °C for 15 min and then at 0 °C for 1 h. On cooling to -78 °C, compound 222 (830 mg, 3.29 mmol) and boron trifluoride etherate (0.49 mL, 4.0 mmol) in tetrahydrofuran (5 mL) were then added via a cannula. The resultant solution was stirred at -78 °C for 8 h. A saturated aqueous solution of ammonium chloride (4 mL) and ether (20 mL) were then added. The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes: ether (4:1) as the eluant to afford the title compound 223 (381 mg, 33%) as a light yellow oil.

$^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 1.30 (3H, t, $J = 7.0$ Hz, CH$_3$), 1.39 (3H, s, CH$_3$), 1.52 (3H, s, CH$_3$), 2.23 - 2.37 (4H, m, 2 x CH$_2$), 2.77 (2H, d, $J = 6.5$ Hz, CH$_2$), 3.76 (2H, q, $J = 7.0$ Hz, CH$_2$), 4.09 (1H, dd, $J = 11.3$, 7.2 Hz, CH), 4.20 (1H, dd, $J = 11.3$, 4.6 Hz, CH), 4.37 - 4.46 (1H, m, CH), 4.68 (1H, t, $J = 6.9$ Hz, CH), 4.76 (1H, s, CH), 4.96 - 5.09 (2H, m, CH$_2$), 5.29 (1H, d, $J = 10.4$ Hz, CH$_2$), 5.42 (1H, d, $J = 17.1$ Hz, CH$_2$), 5.70 (1H,
ddt, J = 16.7, 10.0, 6.6 Hz, CH), 5.76 – 5.88 (1H, m, CH); ^{13}C NMR (CDCl₃, 151 MHz) δ 14.4, 25.3, 25.8, 27.2, 27.7, 33.7, 63.1, 67.1, 75.4, 78.1, 91.8, 109.4, 113.0, 115.9, 119.2, 132.4, 135.4, 141.2, 153.3, 158.4; IR (ef) 3083, 2984, 2937, 1747, 1604, 1374, 1241, 1048 cm⁻¹; HRMS Calcd. for C₂₀H₂₉O₆ (M + H): 365.1959 Found: 365.1970.

(2E)-4-Bromo-2-buten-1-ol (215)

To a stirred solution of ethyl 4-bromocrotonate (214) (1.92 g, 10.0 mmol) in dichloromethane (40 mL) at 0 °C was added diisobutylaluminum hydride (23.0 mL, 1.0 M in dichloromethane, 23.0 mmol). The reaction mixture was then allowed to stir at room temperature for 3 h. The resultant solution was quenched with a saturated aqueous solution of Rochelle’s salt (30 mL), stirred for 10 h at room temperature, and then extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was carried forward to the subsequent reaction without further purification.

(2E)-4-Bromo-1-(tert-butyldimethylsilyloxy)-2-butene (213)

A mixture of the alcohol 215 (1.19 g, 8.00 mmol), tert-butyldimethylsilyl chloride (1.52 g, 11 mmol), imidazole (610 mg, 9.0 mmol), N,N-dimethyl-4-aminopyridine (98 mg, 0.80 mmol) in dichloromethane (30 mL) was stirred at room temperature for 14 h. The resultant mixture was quenched with water (40 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography.
using hexanes:ether (40:1) as the eluant to afford the title compound 213 (1.30 g, 82%) as a colourless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.07 (6H, s, 2 x CH\(_3\)), 0.91 (9H, s, C(CH\(_3\))\(_3\)), 3.98 (2H, t, \(J = 7.3\) Hz, CH\(_2\)), 4.19 – 4.21 (2H, m, CH\(_2\)), 5.54 – 6.20 (2H, m, 2 x CH); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 5.2, 18.4, 25.9, 32.4, 62.6, 125.8, 134.7; IR (ef) 2996, 2851, 2814, 2798, 1555, 1428, 1261 cm\(^{-1}\); HRMS Calcd. for C\(_{10}\)H\(_{22}\)BrOSi (M + H): 265.0618 Found: 265.0631.

6-[(2\(E\))-4-[(tert-Butyldimethylsilyl)oxy]-2-butenyl]-3-ethoxy-2-cyclohexenone (247)

![Chemical Structure](image)

To a solution of \(N,N\)-diisopropylamine (1.3 mL, 7.8 mmol) in tetrahydrofuran (40 mL) at -78 °C was added \(n\)-butyl lithium (3.1 mL, 2.5 M in hexanes, 7.7 mmol). The reaction mixture was stirred for 10 min then warm to 0 °C and stirred for 30 min. The reaction mixture was then cooled to -78 °C and a solution of 3-ethoxy-2-cyclohexenone 116 (840 mg, 6.0 mmol) in tetrahydrofuran (5 mL) was added and the resultant mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. Compound 213 (2.4 g, 12 mmol) was then added and the reaction mixture was warmed to room temperature and allowed to stir for 12 h. The reaction mixture was then quenched with an aqueous solution of hydrochloric acid (1 M, 30 mL) and water (30 mL), diluted with hexanes (50 mL) and extracted with ether (3 x 70 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The
crude product was purified by flash chromatography using hexanes:ether (3:2) as the eluant to afford the title compound 247 (1.7 g, 85%) as a yellow oil.

\[ ^1H \text{ NMR} \ (\text{CDCl}_3, 400 \text{ MHz}) \delta 0.06 (6H, s, 2 \times \text{CH}_3), 0.90 (9H, s, \text{C(CH}_3)_3), 1.36 (3H, t, J = 7.0 \text{ Hz, CH}_3), 1.62 - 1.80 (1H, m, CH), 1.90 - 2.15 (2H, m, CH), 2.16 - 2.31 (1H, m, CH), 2.33 - 2.51 (2H, m, CH), 2.53 - 2.73 (1H, m, CH), 3.89 (2H, apparent q., OCH2), 4.07 - 4.13 (2H, m, CH), 5.32 (1H, s, CH), 5.50-5.75 (2H, m, 2 x CH); \]

\[ ^{13}C \text{ NMR} \ (\text{CDCl}_3, 101 \text{ MHz}) \delta 5.2, 14.1, 18.2, 25.8, 26.0, 28.2, 32.4, 45.0, 63.8, 64.2, 102.3, 128.5, 131.6, 176.8, 200.4 \text{ cm}^{-1}; \]

\[ \text{IR} \ (\text{ef}) 2954, 2929, 2885, 2856, 1655, 1607, 1378, 1187 \text{ cm}^{-1}; \]

\[ \text{HRMS} \ \text{Calcd. for C}_{18}\text{H}_{33}\text{O}_3\text{Si (M + H): 325.2193 Found: 236.2172.} \]

6-[(2E)-4-[(tert-Butyldimethylsilyl)oxy]-2-butenyl]-3-ethoxy-6-(2-propenyl)-2-cyclohexenone (230)

\[ \text{To a solution of } N,N\text{-diisopropylamine (1.0 mL, 6.7 mmol) in tetrahydrofuran (40 mL) at -78 °C was added } n\text{-butyl lithium (2.5 mL, 2.5 M in hexanes, 6.3 mmol). The reaction mixture was stirred for 10 min then warmed to 0 °C and stirred for 30 min. The reaction mixture was then cooled to -78 °C and a solution of compound 247 (1.6 g, 5.0 mmol) in tetrahydrofuran (5 mL) was added and the resultant mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. Allyl bromide 198 (4.2 g, 25 mmol) was then added and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then quenched with an aqueous solution of hydrochloric acid (1 M, 30 mL) and water (30 mL), diluted with hexanes (50 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL),} \]
dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (7:3) as the eluant to afford the title compound 230 (1.4 g, 77%) as a yellow oil.

\[ \text{1H NMR (CDCl}_3, 400 MHz) \delta 0.06 (6H, s, 2 \times \text{CH}_3), 0.89 (9H, s, \text{C(CH}_3)_3), 1.35 (3H, t, J = 7.0 Hz, \text{CH}_3), 1.84 (2H, t, J = 6.5 Hz, \text{CH}_2), 2.08 - 2.24 (2H, m, \text{CH}_2), 2.31 - 2.50 (4H, m, 2 \times \text{CH}_2), 3.88 (2H, q, J = 7.0 Hz, \text{OCH}_2), 4.09 - 4.13 (2H, m, \text{CH}_2), 4.98 - 5.09 (2H, m, 2 \times \text{CH}), 5.26 (1H, s, \text{CH}), 5.53-5.60 (2H, m, 2 \times \text{CH}), 5.67 - 5.79 (1H, m, \text{CH}); \text{13C NMR (CDCl}_3, 101 MHz) \delta 5.1, 14.2, 18.4, 25.9, 26.0, 28.8, 38.1, 39.8, 46.6, 63.8, 64.2, 101.9, 117.9, 126.2, 132.9, 134.3, 175.9, 202.3; \text{IR (ef) 3077, 2929, 2856, 1651, 1609, 1379, 1185 cm}^{-1}; \text{HRMS Calcd. for C}_21\text{H}_{37}\text{O}_3\text{Si (M + H): 365.2506 Found: 365.2510.} \]

4-[(2\text{E})-4-Hydroxy-2-butenyl]-4-(2-propenyl)-2-cyclohexenone (231)

To a stirred solution of compound 230 (1.43 g, 3.94 mmol) in dichloromethane (15 mL) was added diisobutylaluminum hydride (6.0 mL, 1 M solution in dichloromethane, 6.0 mmol) at -78 °C. The reaction was allowed to warm to room temperature and was stirred for 5 h. The resulting solution was cooled to 0 °C and methanol (2 mL) and an aqueous solution of hydrochloric acid (3 M, 20 mL) were added. The resultant mixture was then stirred at room temperature for 14 h. The reaction
mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using ether as the eluant to afford the title compound 231 (570 mg, 70%) as a light yellow oil.

\[ ^1\text{H NMR} \quad (\text{CDCl}_3, 400 \text{ MHz}) \delta 1.89 (2\text{H, t, } J = 6.8 \text{ Hz, CH}_2), 2.20 - 2.30 (4\text{H, m, 2 x CH}_2), 2.40 - 2.55 (2\text{H, m, CH}_2), 4.41 (2\text{H, apparent t, } J = 5.1 \text{ Hz, CH}_2), 5.12 (2\text{H, dd, } J = 20.4, 5.0 \text{ Hz, CH}_2), 5.58 - 5.85 (3\text{H, m, 3 x CH}), 5.96 (1\text{H, d, } J = 10.2 \text{ Hz, CH}), 6.70 (1\text{H, d, } J = 10.3 \text{ Hz, CH}); ^{13}\text{C NMR} \quad (\text{CDCl}_3, 101 \text{ MHz}) \delta 30.9, 33.9, 38.8, 40.7, 42.3, 63.3, 119.0, 126.8, 128.6, 133.2, 133.4, 157.1, 199.3; \text{IR (ef)} 3356 \text{ (br), 2930, 2859, 1668, 1447, 1000, 917 cm}^{-1}; \text{HRMS Calcd. for C}_{13}\text{H}_{19}\text{O}_2 (\text{M + H}): 207.1389. \text{Found: 207.1375.}

4-[(2E)-4-Oxo-2-butenyl]-4-(2-propenyl)-2-cyclohexenone (232)

![Image of 4-[(2E)-4-Oxo-2-butenyl]-4-(2-propenyl)-2-cyclohexenone (232)](image)

To a solution of compound 231 (310 mg, 1.49 mmol) in dichloromethane (20 mL) at room temperature was added manganese dioxide (3.13 g, 10 mass equiv.) and was stirred for 6 h. The resultant mixture was then filtered through a pad of celite and the filter-cake was washed with dichloromethane (3 x 30 mL). The combined organic filtrates were concentrated in vacuo and the crude product was purified by flash chromatography using hexanes:ether (1:9) as the eluant to afford the title compound 232 (215 mg, 70%) as a colourless oil.
\(^1\text{H NMR} \text{ (CDCl}_3, 500 \text{ MHz)} \delta 1.84 – 2.10 (2\text{H, m, CH}_2), 2.23 – 2.40 (2\text{H, m, CH}_2), 2.39 – 2.64 (4\text{H, m, 2 x CH}_2), 5.06 – 5.33 (2\text{H, m, CH}_2), 5.78 (1\text{H, ddt, J} = 17.5, 10.1, 7.4 \text{ Hz, CH}_2), 6.02 (1\text{H, d, J} = 10.2 \text{ Hz, CH}), 6.19 (1\text{H, apparent dd, J} = 15.5, 7.8 \text{ Hz, CH}), 6.70 (1\text{H, d, J} = 10.3 \text{ Hz, CH}), 6.79 (1\text{H, dt, J} = 15.5, 7.7 \text{ Hz, CH}), 9.54 (1\text{H, d, J} = 7.8 \text{ Hz, CH}); ^{13}\text{C NMR} \text{ (CDCl}_3, 126 \text{ MHz)} \delta 31.3, 33.7, 39.2, 41.2, 42.6, 119.9, 129.4, 132.4, 136.3, 152.3, 155.3, 193.1, 198.4; \text{ IR (ef) 2923, 2901, 2877, 1716, 1683, 1461, 1315, 1100, 958 cm}^{-1}; \text{ HRMS Calcd. for C}_{13}\text{H}_{17}\text{O}_2 (\text{M} + \text{H}): 205.1211. \text{ Found: 205.1223.}

4-[(2E)-4-Oxo-2-butenyl]-4-(2-oxoethyl)-2-cyclohexenone (236)

![Structure of compound 236](image)

To a stirred solution of compound 232 (260 mg, 1.33 mmol), potassium osmate dihydrate (4.7 mg, 0.013 mmol) in acetone:water (3 mL, 1:1) mixture was added sodium periodate (5 x 165 mg, 3.84 mmol) over 1 h at room temperature. The reaction mixture was allowed to stir for another 90 min. Upon filtration and wash the filter-cake with dichloromethane (50 mL), the organic filtrates were wased with water (2 x 50 mL), saturated solution of sodium bisthiosulfate (2 x 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ethyl acetate (1:4) as the eluant to afford the \textit{title compound} 236 (110 mg, 43%) as a yellow oil.
$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.95 – 2.27 (2H, m, CH$_2$), 2.42 – 2.56 (2H, m, CH$_2$), 2.58 – 2.83 (4H, m, 2 x CH$_2$), 6.06 (1H, d, $J = 10.3$ Hz, CH), 6.20 (1H, dd, $J = 15.5$, 7.7 Hz, CH), 6.75 (1H, apparent dt, $J = 15.5$, 7.8 Hz, CH), 6.91 (1H, d, $J = 10.3$ Hz, CH), 9.55 (1H, d, $J = 7.7$ Hz, CH), 9.82 (1H, apparent t, CH); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 32.2, 33.6, 38.3, 41.0, 50.6, 129.8, 136.7, 150.7, 153.3, 193.5, 199.5, 209.5; IR (ef) 2988, 2942, 1667, 1651, 1516, 1396, 1208, 1095 cm$^{-1}$; HRMS Calcd. for C$_{12}$H$_{15}$O$_3$ (M + H): 207.1016. Found: 207.1000.

Ethyl (2E)-4-[4-ethoxy-2-oxo-1-(2-propenyl)-3-cyclohexenyl]-2-butenoate (237)

To a solution of N,N-diisopropylamine (3.0 mL, 22 mmol) in tetrahydrofuran (40 mL) at -78 °C was added n-butyl lithium (8.4 mL, 2.5 M in hexanes, 21 mmol). The reaction mixture was stirred for 10 min then warmed to 0 °C and stirred for 30 min. The reaction mixture was then cooled to -78 °C and a solution of compound 216 (1.84 g, 10.1 mmol) in tetrahydrofuran (5 mL) was added and the resultant mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. Ethyl bromocrotonate 214 (6.01 g, 25 mmol) was then added and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then quenched with an aqueous solution of hydrochloric acid (1 M, 30 mL) and water (30 mL), diluted with hexanes (50 mL) and extracted with ether (3 x 70 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The
crude product was purified by flash chromatography using hexanes:ether (2:3) as the eluant to afford the title compound **237** (1.34 g, 43%) as a yellow oil.

**1H NMR** (CDCl₃, 500 MHz) δ 1.27 (3H, t, J = 7.1 Hz, CH₃), 1.36 (3H, t, J = 7.0 Hz, CH₃), 1.77 - 1.93 (2H, m, CH₂), 2.08 – 2.75 (6H, m, 3 x CH₂), 3.89 (2H, q, J = 7.0 Hz, CH₂), 4.17 (2H, q, J = 7.1 Hz, CH₂), 5.00 – 5.15 (2H, m, 2 x CH), 5.29 (1H, s, CH), 5.65 - 5.79 (1H, m, CH), 5.83 (1H, d, J = 15.6 Hz, CH), 6.81 – 6.91 (1H, m, CH); **13C NMR** (CDCl₃, 126 MHz) δ 14.1, 14.3, 25.8, 29.1, 37.9, 39.8, 46.6, 60.2, 64.3, 101.7, 118.6, 124.4, 133.5, 144.9, 166.2, 175.9, 201.2; **IR** (ef) 3077, 2980, 2936, 1650, 1604, 1379, 1186 cm⁻¹; **HRMS** Calcd. for C₁₇H₂₅O₄ (M + H): 293.1761. Found: 293.1747.

3-Ethoxy-6-[(2Z)-4-hydroxy-2-butelyn]-6-(2-propenyl)-2-cyclohexenone (243)

![Structure of 243](image_url)

To a solution of N,N-diisopropylamine (5.5 mL, 35 mmol) in tetrahydrofuran (100 mL) at -78 °C was added n-butyl lithium (13.0 mL, 2.5 M in hexanes, 33.0 mmol). The reaction mixture was stirred for 10 min then warmed to 0 °C and stirred for 30 min. The reaction mixture was then cooled to -78 °C and a solution of compound **216** (1.82 g, 5.01 mmol) in tetrahydrofuran (5 mL) was added and the resultant mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. cis-1-Acetoxy-4-bromo-2-butene **242** (5.76 g, 30.0 mmol) was then added and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. Water (25 mL) and lithium hydroxide (4.3 g, 180 mmol)
were then added and the resultant mixture was heated at 50 °C and stirred for 12 h. The resulting solution was then neutralized with an aqueous solution of hydrochloric acid (1 M, 200 mL) and water (200 mL), diluted with hexanes (250 mL) and extracted with ether (3 x 200 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (1:4) as the eluant to afford the title compound 243 (3.8 g, 76%) as a light yellow oil.

\[ \text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) } \delta \begin{array}{l} 1.38 (3H, t, J = 7.0 \text{ Hz, CH}_3), 1.81 - 2.06 (2H, m, CH\textsubscript{2}), 2.09 - 2.28 (2H, m, CH\textsubscript{2}), 2.32 - 2.66 (4H, m, 2 x CH\textsubscript{2}), 3.92 (2H, q, J = 7.0 \text{ Hz, CH}_2), 4.03 - 4.15 (1H, m, CHH), 4.25 (1H, ddd, J = 12.5, 7.2, 1.2 \text{ Hz, CHH}), 5.03 - 5.18 (2H, m, 2 x CH), 5.30 (1H, m, CH), 5.47 - 5.61 (1H, m, CH), 5.70 - 5.87 (2H, m, 2 x CH); \\
\text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz) } \delta \begin{array}{l} 14.1, 25.9, 29.0, 32.8, 39.9, 47.1, 58.3, 64.3, 101.9, 118.4, 127.7, 131.2, 133.7, 165.7, 176.2; \\
\text{IR (ef) } 3403, 2980, 2936, 1638, 1600, 1379, 1185, 1023 \text{ cm}^{-1}; \\
\text{HRMS Calcd. for C}_{15}\text{H}_{23}O_3 (M + H): 251.1654. Found: 251.1642. \\
\end{array} \]

4-[(2Z)-4-Hydroxy-2-butenyl]-4-(2-propenyl)-2-cyclohexenone (244)

![Image of compound 244]

To a stirred solution of compound 243 (2.51 g, 10 mmol) in dichloromethane (70 mL) was added diisobutylaluminum hydride (22 mL, 1 M solution in dichloromethane, 22 mmol) at room temperature. The reaction was stirred for 5 h and then cooled to 0 °C. Methanol (5 mL) and an aqueous solution of hydrochloric acid (3 M, 100 mL) were
added. The resultant mixture was stirred at room temperature for 14h and then extracted with dichloromethane (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (3:7) as the eluant to afford the title compound \textbf{244} (1.61 g, 77%) as a light yellow oil.

\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 1.83 – 2.05 (2H, m, CH\textsubscript{2}), 2.20 – 2.38 (4H, m, 2xCH\textsubscript{2}), 2.41 – 2.56 (2H, m, CH\textsubscript{2}), 4.23 (2H, t, \(J = 5.8\) Hz, CH\textsubscript{2}), 4.98 – 5.29 (2H, m, CH\textsubscript{2}), 5.50 – 5.66 (1H, m, CH), 5.72 – 5.90 (2H, m, CH\textsubscript{2}), 5.99 (1H, d, \(J = 10.3\) Hz, CH), 6.72 (1H, d, \(J = 10.3\) Hz, CH); \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 101 MHz) \(\delta\) 31.0, 33.9, 35.7, 39.0, 42.4, 58.5, 100.0, 119.1, 127.0, 128.8, 131.9, 133.2, 156.9; \textbf{IR} (ef) 3361, 2955, 2929, 2890, 1686, 1426, 1410, 1157, 1073 cm\textsuperscript{-1}; \textbf{HRMS} Calcd. for C\textsubscript{13}H\textsubscript{19}O\textsubscript{2} (M + H): 206.1301. Found: 206.1307.

\textbf{4-[(2Z)-4-Oxo-2-butenyl]-4-(2-propenyl)-2,5-cyclohexadienone (245)}

\begin{center}
\textbf{245}
\end{center}

To a solution of \(N,N\)-diisopropylamine (5.0 mL, 30 mmol) in tetrahydrofuran (40 mL) at -78 °C was added \textit{n}-butyl lithium (13.0 mL, 2.5 M in hexanes, 33 mmol). The reaction mixture was stirred for 10 min then warmed to 0 °C and stirred for 30 min. The reaction mixture was then cooled to -78 °C and a solution of compound \textbf{244} (2.17 g, 10.6 mmol) in tetrahydrofuran (5 mL) was added and the resultant mixture was stirred at -78 °C for 2 h. Chlorotrimethyl silane (4.6 mL, 36 mmol) was then added. The resultant
mixture was allowed to stir at -78 °C for 1h and then at room temperature for 1 h. The reaction mixture was then diluted with hexanes (100 mL) and aqueous solution of sodium bicarbonate (10% w/v, 50 mL) was added. The resulting solution was washed with water (30 mL) and brine (30 mL) dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was then subjected to a stirred solution of IBX (13.4 g, 45.1 mmol) and MPO (5.23 g, 45.1) in dimethylsulfoxide (30 mL). **NOTE** It is important that both IBX and MPO are completely dissolved in dimethylsulfoxide before the addition of the silyl ether reaction intermediate. The resultant reaction mixture was stirred vigorously at room temperature for 10 h and then quenched with an aqueous solution of sodium bicarbonate (5% w/v, 30 mL). The resulting solution was extracted with ether (3 x 100 mL). The combined organic extracts were filtered through a pad of celite and the filtrates was washed with saturated aqueous solution of sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL). The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (1:4) as the eluant to afford the title compound 245 (1.09 g, 51%) as a light yellow oil.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.43 (2H, apparent d, $J = 7.3$ Hz, $CH_2$), 2.66 (2H, dd, $J = 7.5$, 1.3 Hz, $CH_2$), 5.12 (2H, m, $CH_2$), 5.61 (1H, m, $CH$), 6.10 (1H, ddt, $J = 15.6$, 7.8, 1.3 Hz, $CH$), 6.37 (2H, d, $J = 10.2$ Hz, $CH_2$), 6.42 – 6.57 (1H, m, $CH$), 6.75 (2H, d, $J = 10.2$ Hz, $CH_2$), 9.42 (1H, d, $J = 7.8$ Hz, CHO); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 40.9, 42.5, 50.5, 119.7, 131.2, 132.6, 136.4, 148.9, 150.0, 184.8, 192.7; IR (ef) 3080, 3008, 2976, 2919, 2818, 1685, 1660, 1405, 1124, 976, 861 cm$^{-1}$; HRMS Calcd. for C$_{13}$H$_{15}$O$_3$ (M + H): 203.1067. Found: 203.1081.
4-[(2Z)-4-Oxo-2-butenyl]-4-(2-oxoethyl)-2,5-cyclohexadienone (264)

To a stirred solution of compound 245 (910 mg, 4.5 mmol), potassium osmate dihydrate (15 mg, 0.041 mmol) in acetone:water mixture (1:1, 30 mL) was added sodium periodate (5 x 510 mg, 13 mmol) over 1 h at room temperature. The reaction mixture was further stirred for 90 min and filtered through a pad of celite. The filter-cake was washed with ethyl acetate (80 mL) and the combined organic extracts were washed with water (2 x 50 mL), a saturated aqueous solution of sodium bisthiosulfate (2 x 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was then purified by flash chromatography using hexanes:ethyl acetate (1:4) as the eluant to afford the title compound 246 (390 mg, 43%) as a yellow oil.

\[ \text{1H NMR (CDCl}_3, 600 MHz) \delta 2.75 - 2.79 (4H, m, 2 \times CH}_2), 6.12 (1H, ddt, J = 15.6, 7.7, 1.3 Hz, CH}_2), 6.38 - 6.55 (3H, m, 3 \times CH), 6.89 - 6.95 (2H, m, 2 \times CH), 9.43 (1H, d, J = 7.7 Hz, CH); \text{13C NMR (CDCl}_3, 151 MHz) \delta 40.8, 42.7, 50.5, 131.2, 136.4, 148.9, 150.0, 184.8, 192.7, 197.7; \text{IR (ef)} 2926, 1682, 1662, 1621, 1360, 1223, 1089, 978 cm}^{-1}; \text{HRMS Calcd. for C}_{12}H_{12}O_3Na (M + Na): 227.0679. Found: 227.0686.\]
4. Synthesis and Applications of 2,3-Disubstituted Pyrroles – Studies Towards the Synthesis of 7-Phosphaindole and Biologically-Active Heterocycles

4.1. Introduction

The long-term objective of the research described in this chapter was to develop of an efficient synthesis of 7-phosphatryptophan (20), a synthetic analogue of the natural α-amino acid tryptophan (250). We hypothesized that the 7-phosphatryptophan, like other synthetic tryptophan analogues, would exhibit different fluorescent properties that could be applied in biophysical studies. It was later realized that the proposed synthetic route towards this potential fluorescent probe from the 2-halo-3-carboxylate pyrrole (248) could also lead to the preparation of a wide range of potentially biologically-active heterocycles from this central building block (Figure 4.1). This type of compound features several functionalized reaction sites. Accordingly, the halogen at C2 could undergo a metal-halogen exchange reaction, such as lithiation or Grignard reaction, as well as used in palladium-catalyzed cross-coupling reactions. The carboxylate group at C3 could also be easily converted to various substituents and lastly both C4 and C5 of the indole moiety are available sites for electrophilic aromatic substitution reactions.
Thus, the research described in this chapter is divided into two sections. The first section of this chapter (Part 1: Section 4.2) details a study towards the synthesis of 7-phosphaindole (19), the precursor of the long-term target, 7-phosphatryptophan (20). This includes background information on the fluorescent properties of the natural tryptophan and its synthetic analogues, our efforts towards the synthesis of 7-phosphaindole, which includes the development and optimization of an efficient synthesis of methyl 2-chloro-3-carboxylate pyrrole (248, X = Cl) and, finally, a conclusion and proposed future work. The second part of this chapter (Part 2: Section 4.3) concerns the synthetic applications of the 2-halo-3-carboxylate pyrrole in palladium-catalyzed cross-coupling reaction with various aryl and heteroaryl coupling reagents.

4.2. Part 1: Studies Towards the Synthesis of 7-Phosphaindole

4.2.1. An Overview of Azaindoles and Azatryptophans

Indoles (249) are the basic structural motif of numerous important biologically-active molecules (Figure 4.2). Not only is the indole the chromophore of the amino acid, tryptophan (250), purine bases of nucleic acids, such as adenine (251) and guanine
(252), are also indole derivatives. In the following sections, the physical properties of indoles and tryptophans as well as the biological importance of indole-based compounds and analogues will be discussed.

Figure 4.2 Molecular structures of indole (249), tryptophan (250), adenine (251), and guanine (252).

4.2.1.1. Fluorescent Properties and Applications of Tryptophan and Analogues.

The amino acid tryptophan (250) has been widely used as an intrinsic fluorescent probe to study protein dynamics and ligand binding in solution.\(^\text{111}\) There are, however, a number of concerns regarding the interpretation of the fluorescence data generated by tryptophan. The most significant of these is caused by the intrinsic nonexponential fluorescence decay of tryptophan and the presence of multiple tryptophan residues in a given protein.\(^\text{112,113}\) In the course of the conception and development of an alternative optical probe to study protein structure and dynamics, azatryptophans (253 - 256) were found to exhibit the most useful and practical optical properties (Figure 4.3). Unlike tryptophan, azatryptophans display single-exponential fluorescence decay. The presence of a nitrogen atom in the indoyl moiety results in a red shift of an average 10 nm to that of the absorption of tryptophan (250) and 46 nm shift in its emission spectrum as compared to natural tryptophan.\(^\text{113,114}\)
In a very recent report by Lepthien et al., it was shown that 4-azatryptophan (254) is an excellent optical probe, featuring a pronounced Stokes shift of ~130 nm, a significantly higher quantum yield in aqueous buffers and an enhanced quenching resistance.\textsuperscript{115} In addition, the incorporation of 4-azatryptophan (254) into the model protein anxA5 generated intensively blue fluorescent \textit{E. coli} cells.

For potential collaborative work with colleagues who are engaged in biophysical research, we hypothesized that 7-phosphatryptophan (20) would exhibit different fluorescence properties as compared to natural tryptophan 250 and the synthetic 7-azatryptophan (253) (Figure 4.4). Since the conversion of indoles to the corresponding tryptophans is well-documented by both synthetic or bioengineering means,\textsuperscript{116} we proposed to study the development of a synthesis of 7-phosphaindole (19), which could potentially served as a precursor to 7-phosphatryptophan (20).
4.2.1.2. Literature Syntheses of Azaindoles

The first attempted synthesis of an azaindole derivative can be traced back to the synthesis of iso-harman reported by Robinson in 1913. However, the first successful synthesis of 4-azaindoles was reported in 12% yield by Takahashi et al. in their synthesis of 5-chloro-2-methyl-4-azaindole in 1944.

Over the past twenty years, numerous methods towards the synthesis of azaindoles have been reported. Majority of these methods started with substituted pyridines and then the pyrrole ring was introduced through various cyclization methods, such as Madelung-type cyclization (Scheme 4.1a), the Riessert-type procedure (Scheme 4.1b), the Leimgruber-Batcho reaction (Scheme 4.1c), the Lorenz-type cyclization reaction (Scheme 4.1d), palladium-catalyzed heteroannulation reaction (Scheme 4.1e) and finally the Bartoli sequential cyclization reaction (Scheme 4.1f).
Scheme 4.1 Selected Literature Syntheses of Azaindoles from Aminopyridines

a

257 258 259
Reagents and conditions: a) n-BuLi (2.5 eq), 0 °C then DMF; b) HCl (5.5M) reflux.

b

260 261 262
Reagents and conditions: a) KOEt, EtOH then diethyl oxalate; b) H2, Pd/C, DCM.

c

263 264 265
Reagents and conditions: a) 4-Cl-C6H4OCH2CN, tert-BuOK, THF, -10 °C (83%); b) H2, Pd/C, EtOH, rt (81%).

d

266 267 268
Reagents and conditions: a) PCl5, BzN(CHO)Me, chloroform, reflux; b) NaH, BzNHMe.
Reagents and conditions: a) Pd(PPh$_3$)$_2$Cl$_2$, (Et)$_4$NCl, MeCN, reflux (88%); b) H$_2$, Raney Ni, MeOH then HCl, MeOH, reflux (70%).

Reagents and conditions: a) vinyl magnesium bromide (3-4 eq.), THF, -78 °C to -20 °C (20%).

There are also a few examples of the synthesis of the azaindoles from pyrrole derivatives. In 1992 Mahadevan et al. reported the synthesis of 6-azaindole 277 from the commercially-available pyrrole 274 (Scheme 4.2).$^{121}$

**Scheme 4.2** Synthesis of 6-Azaindole 277 from Pyrrole 274 by Mahadevan et al.

Reagents and conditions: a) Et$_3$N, 4 Å mol. sieves then NaB(CN)H$_3$, EtOH (90%); b) p-TsOH, PhH, reflux (36%).

In 2003, Allegretti et al. reported a new optimized cost-effective synthesis of 7-azaindole from succinonitrile (278) and ethyl formate (279) (Scheme 4.3).$^{125}$ This synthesis remains, to date, the most efficient preparation of 7-azaindole for industrial production.
Scheme 4.3  Synthesis of 7-Azaindole 282 by Allegretti et al.

\[
\text{Reagents and conditions: a) Toluene, } p\text{-TsOH, reflux (80%).}
\]

4.2.2. An Overview of Phosphabenzenes

Phosphabenzenes, also known as phosphinines, or phosphorins as in the literature up until the 1980s, is the phosphorus equivalent of pyridine. It was first synthesized by Markl in 1966 and has been studied extensively since. In the following sections, a brief summary on the syntheses of phosphabenzene and its derivatives is discussed.

4.2.2.1. Synthesis of Phosphabenzene and Derivatives

4.2.2.1.1. O+/P Exchange Method

The O+/P exchange reaction of pyrilium salts 283 using various phosphorus sources is the classical procedure that allowed for the synthesis of the first phosphabenzene, 2,4,6-triphenylphosphabenzene (284), as reported by Markl in 1966 (Scheme 4.4). This approach, which relies on the use of readily available and inexpensive materials, has recently been widely exploited by several research laboratories around the World.
Scheme 4.4  
Synthesis of 2,4,6-Trisubstituted Phosphabenzenes 284 from 2,4,6-Trisubstituted Pyrilium Salts 283

4.2.2.1.2. Tin-Phosphorus Exchange Method

The second method to prepare the phosphabenzene (288) involves a tin-phosphorus exchange process. In the work reported by Ashe et al. in 1971, 1,4-pentadiyne 285 was first treated with dibutyltin hydride to prepare the corresponding stannacyclohexa-1,4-diene 286 by a radical cyclization/addition reaction sequence (Scheme 4.5). A tin-phosphorus exchange reaction was then used to prepare the dihydro-\(l^3\)-phosphinine 287 which on treatment with a base (diazobicycloundec-7-ene, DBU) afforded phosphabenzene 288 efficiently.

Scheme 4.5  
Synthesis of Unsubstituted Phosphabenzene 288 from 1,4-Pentadiyne 285

Of note, the corresponding heterocyclic analogues, arsabenzene 289, stibabenzene 290 and bismabenzene 291, have similarly been prepared by this method (Figure 4.5).
4.2.2.1.3. Thermolysis Method

The parent phosphabenzene 288 has also be prepared by pyrolysis of diallylvinylphosphine 292 (Scheme 4.6). As reported by Floch et al., flash vacuum thermolysis of compound 292 at 700 °C and 10⁻³ Torr produced phosphabenzene (288) almost exclusively.

Scheme 4.6 Synthesis of Phosphabenzene (288) via Thermolysis

A subsequent detailed mechanistic study suggested that at 700 °C compound 292 undergoes a retro-ene elimination reaction to afford compounds E-293 and Z-293, which can equilibrate through a reversible 4π electrocyclic ring opening and closing processes. Although compound Z-293 is thermodynamically disfavoured, it has that correct geometry to undergo a subsequent 6π electrocyclization to afford 3,4-
Finally, the loss of hydrogen gas to install the aromaticity results in the formation of phosphabenzene (288).

**4.2.2.1.4. Miscellaneous Methods**

There are numerous reports on the synthesis of substituted phosphabenzenes. For example, as highlighted and reviewed by Mathey, 1,2,5-triphenylphosphole (295) undergoes a rapid 1,5-phenyl shift at 70 °C (Scheme 4.7). The resultant product 296 was then reacted with a tolane in a [4+2] cycloaddition reaction which was followed by thermolytic cleavage process to generate 2,3,5-triphenylphosphabenzene (298).

**Scheme 4.7 Synthesis of Substituted Phosphabenzenes 298 from Phosphole 295 via a [4+2] Cycloaddition Reaction**

Another group of methods involve the [4+2] cycloaddition of conjugated dienes to phospha-alkenes. In Floch’s report, 2-halophosphabenzene 303 was successfully synthesized from dihalomethyldihalophosphines 299 on reaction with various conjugated dienes in a one-pot process (Scheme 4.8).
Scheme 4.8  Synthesis of Substituted Phosphabenzences 303 from Compound 299 via a [4+2] Cycloaddition Reaction

Numerous other approaches to synthesize phosphabenzene analogues have also been described but they are either cumbersome or exhibit very limited generality.

4.2.3. Retrosynthetic Analysis of 7-Phosphaindole (19)

The key step of our synthetic strategy for the construction of 7-phosphaindole (19) is based on the tin-phosphorus exchange chemistry discussed earlier in this chapter (See: Section 4.2.2.1.2). We proposed that the phosphabenzene moiety of the 7-phosphaindole (19) could be prepared by aromatization of compound 305 upon treatment with base followed by the deprotection of the R group on the nitrogen atom and the removal of the TMS group (Scheme 4.9). The latter compound 305 could be the product of the aforementioned tin-phosphorus exchange reaction of compound 306 on exposure to phosphorus tribromide. The bicyclic compound 306 could be prepared from compound 308 via the proposed metal-halogen exchange reaction to prepare tin hydride 307 followed by heat-induced radical cyclization reaction.
Here, we proposed that the anion of the lithium-halogen reaction of compound 308 could be trapped with di-n-butyltin dihalide to afford compound 312, which upon treatment of sodium borohydride afforded compound 307 (Scheme 4.10). Heating the pyrrole 307 should induce the radical cyclization reaction to afford the bicyclo compound 306.
Of note, the R group in compound 309 here represents a suitable protecting and directing group that will facilitate the lithium/halogen exchange process, whereas the X group represents halogen and the Y group is a suitable leaving group (i.e. halides or sulfonates). This combination of the substitution pattern led to the key compound described in this chapter, the 2-halo-3-carboxylate pyrrole 310.

4.2.4. Literature Synthesis of Methyl 2-Chloro-3-carboxylate Pyrrole 18

In 1989, Zepeda et al. reported the first and the only synthesis of methyl 2-chloro-3-carboxylate pyrrole (18) en route towards the synthesis of two potential antihypertensive drug candidates containing an indole skeleton (315 and 316) (Figure 4.6).\textsuperscript{129}

![Molecular structures of anti-hypertensive drug candidates 315 and 316.](image)

Figure 4.6 Molecular structures of anti-hypertensive drug candidates 315 and 316.

In this work, methyl 2-chloro-3-carboxylate pyrrole (18) was isolated in a very low yield and as a byproduct in an attempted Fischer indole condensation reaction of the β-cyano-aldehyde 319 and p-methoxyphenylhydrazine (320) (Scheme 4.11).
Scheme 4.11  Attempted Synthesis of Indole 321 by Zapeda et al.

\[
\begin{align*}
\text{MeO} & \quad \text{CN} & \quad \text{OMe} & \quad \text{MeO} \\
317 & \quad + & \quad \text{OMe} & \quad \text{Br} \\
& \quad + & \quad \text{OMe} & \quad \text{OMe} \\
\text{MeO} & \quad \text{CN} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{MeO} & \quad \text{NH}_2\text{Cl} \\
318 & \quad \rightarrow & \quad 319 & \quad + & \quad 320 \\
\text{a} & \quad & \quad & \quad & \\
\text{b} & \quad & \quad & \quad & \\
\text{OMe} & \quad \text{Cl} & \quad \text{MeO} & \quad \text{OMe} & \quad \text{MeO} & \quad \text{CN} \\
18 & \quad + & \quad 321
\end{align*}
\]

Reagents and conditions: a) 317, NaH, DMF, PhH, -10 °C, 1 h then 318, reflux, 2 h, 33%; b) acetone, 1 M HCl, reflux, 20 min (11% 18:0% 321).

4.2.4.1. Development and Optimization of the Synthesis of Methyl 2-Chloro-3-carboxylate Pyrrole (18)

The procedure Zepeda et al. reported to prepare the requisite β-cyanoacetate 319 on a large scale was believed to be unpractical due to the use of a full equivalent loading of sodium hydride and litres of N,N-dimethylformamide and benzene. After a detailed literature search, an alternative protocol, that was reported by Davoll, was identified. In his work on the pyrrolo[2,3-d]pyrimidines, the coupling reaction of the methyl cyanoacetate (317) with the protected bromoacetal 322 in the presence of potassium carbonate and a catalytic amount of sodium iodine yielded β-cyanoacetate 323 was employed (Scheme 4.12). Accordingly, this procedure was performed on a multi-gram scale.
Scheme 4.12 Synthesis of Methyl 2-Chloro-3-carboxylate Pyrrole (18)

Reagents and conditions: a) K₂CO₃, 150 °C, reflux, 16 h (47%).

With the desired β-cyanoacetate in hand, the optimization of the subsequent pyrrole formation reaction was conducted. The result of this study is summarized below (Table 4-1).

Table 4-1 Reagents and Conditions Corresponding to Scheme 4.12

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents and conditions</th>
<th>18 (%)</th>
<th>324 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 M HCl, acetone:H₂O (1:1), reflux, 30 min</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 M HCl, acetone:H₂O (1:1), reflux, 15 min</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NaCl (1 eq.), 1N HCl, acetone:H₂O (1:1), reflux, 30 min</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NaCl (1.5 eq), p-TsOH, acetone, reflux, 1 h</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>NaCl (3 eq), p-TsOH, acetone, reflux, 4 h</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>NaCl (10 eq), p-TsOH, acetone, reflux, 4 h</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>LiCl (5 eq), p-TsOH, acetone, reflux, 6 h</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>LiCl (10 eq), p-TsOH, acetone, reflux, 6 h</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>LiCl (10 eq), TFA, acetone:H₂O, reflux, 10 h</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>LiCl (10 eq), p-TsOH, THF, reflux, 14 h</td>
<td>71</td>
<td>Trace</td>
</tr>
<tr>
<td>11</td>
<td>nBu₄NCI (10 eq), p-TsOH, THF, reflux, 14 h</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>12</td>
<td>LiCl (10 eq), LiBF₄, MeCN (2% H₂O), 40 °C, 8 h</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>13</td>
<td>HBr (48%), acetone:H₂O (1:1), reflux, 30 min</td>
<td>decomposition</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>LiBr (10 eq), p-TsOH, THF, reflux, 14 h</td>
<td>Trace</td>
<td>41</td>
</tr>
</tbody>
</table>

The initial attempt was based on the procedure reported by Zepeda et al. Employing hydrochloric acid as both the halide and acid source resulted in extensive
decomposition of the starting material and the desired product 18 was not isolated (Entry 1 and 2, Table 4-1). Employing sodium chloride as an additional halide source in hydrochloric acid medium also did not afford the desired pyrrole 18 (Entry 3). On consideration of a plausible reaction mechanism (Scheme 4.13), we identified a number of aspects that could play important roles in this reported transformation.

Scheme 4.13 Proposed Reaction Mechanism of Acid-Catalyzed Formation of Methyl 2-Chloro-3-carboxylate Pyrrole (18) from Compound 323

![Chemical Reaction Diagram]

The first step of this transformation is presumably the acid-catalyzed hydrolysis of the acetal moiety of compound 323 to the corresponding aldehyde 324. The subsequent attack on the nitrile group by halide (chloride) ultimately leads to cyclization and aromatization, with the loss of water, and would result in the formation of the pyrrole 18. Because most of the steps in this proposed reaction mechanism are reversible processes, we hypothesized that the use of aqueous hydrochloric acid does not favour driving the reaction equilibrium towards the product side, due to the excess amount of water present in the system. In this regard, we proposed that with careful control of the
source and the amount of the acid, water and the halide used should provide a means to execute this transformation.

Accordingly, p-toluenesulfonic acid (p-TsOH) was selected as the acid source. The halide could come from various salts that dissolve readily in a particular solvent system. When using sodium chloride (1 equivalent) as the chloride source and acetone as the solvent, the desired pyrrole 18 was isolated in 7% yield after four hours at reflux (entry 4). Increasing the loading of sodium chloride to ten equivalents while keeping the remaining reaction conditions the same only resulted in a small increase in the reaction yield (entries 5 and 6). When lithium chloride was used as the chloride source, an increase in reaction yield was observed and the desired pyrrole 18 was isolated in 41% yield (entries 7 and 8). Other acid sources were also considered. When trifluoroacetic acid was employed, using acetone:water as the solvent system, no formation of the pyrrole 18 was observed and the aldehyde 324 was isolated in low yield (entry 9). It was then discovered that using lithium chloride as the halide source in the presence of 1.1 equivalent of p-toluenesulfonic acid in tetrahydrofuran afforded the desired pyrrole 18 in 71% yield (entry 10).

The $^1$H NMR spectrum of the pyrrole 18 displayed only 3 resonances: a singlet at $\delta$ 3.84 corresponds to the methoxy protons, a multiplet at $\delta$ 6.61 – 6.64 integrated to two protons that corresponded to the pyrrolic hydrogen atoms and a singlet at $\delta$ 8.46 was assigned to the proton on the nitrogen atom (Figure 4.7). In addition, the $^{13}$C NMR spectrum showed six peaks which corresponded to the six carbons present in this molecule.
Figure 4.7  $^1$H NMR spectrum (400 MHz, CDCl$_3$) of methyl 2-chloro-3-carboxylate pyrrole (18).

In addition, the characteristic chlorine isotope peaks were observed in the mass spectrum [m/z (rel. intensity) 162 (M + Cl$^{37}$, 33), 160 (M + H, 100)].

Interestingly, when a more soluble chloride source, tert-butylammonium chloride, was employed in further attempts to improve the yield of this reaction, only the uncyclized aldehyde byproduct 324 was isolated (entry 11). In addition, changing the acid from a Brønsted acid ($\rho$-TsOH) to a Lewis Acid (LiBF$_4$) and using 2% water in acetonitrile as the solvent drastically reduced the formation of the desired pyrrole 18 (entry 12).

In an effort to prepare the corresponding bromo-derivative of this pyrrole, which is generally viewed as a better substrate for subsequent reactions, two sets of reaction conditions were employed. Treatment of the $\beta$-cyanoacetate 323 with aqueous hydrobromic acid at reflux resulted in starting material decomposition and the desired
bromo adduct was not isolated (entry 13). When lithium bromide was used, only a trace amount of the bromo-adduct was detected by GC-MS (entry 14). Attempts to purify the crude material by flash chromatography did not lead to the isolation of the desired compound.

4.2.5. **Synthesis of N-Boc 2-Chloro-3-[3-(trimethylsilyl)prop-2-yn-1-yl]-pyrrole (331)**

The synthesis of the requisite key precursor 331 began with the protection of the nitrogen atom of pyrrole 18 (Scheme 4.14). The tert-butyl carbamate (Boc group) was initially considered because the acid-labile nature of this protecting group would allow for its removal in the final proto-desilylation reaction step of the proposed synthesis.\(^{131}\) In addition, the carbonyl oxygen of the Boc group could act as a stabilizer and as an ortho-metallation director during the proposed metal-halogen exchange step.\(^ {132,133}\) A standard procedure, using di-tert-butyl dicarbonate (Boc anhydride) and \(N,N\)-dimethyl-4-aminopyridine in dichloromethane, was employed to install the Boc group in an excellent yield. Subsequent reduction of the carboxylate moiety of the \(N\)-Boc pyrrole 328 using diisobutylaluminum hydride in dichloromethane at room temperature afforded the corresponding alcohol 329. It is important to note that the Boc group is very sensitive to acid and that a standard work up procedure using 1M aqueous solution of hydrochloric acid to quench the reaction mixture resulted in the removal of the Boc group and immediately led to decomposition of the product. An alternative work-up procedure using a saturated solution of Rochelle’s salt (potassium sodium tartrate) as a work up reagent afforded the desired alcohol 329 in a good yield. The \(N\)-Boc pyrrolic alcohol 329 was also very reactive and it must be used within hours after isolation. Interestingly, subsequent activation of the alcohol 329 with \(p\)-toluenesulfonyl chloride afforded the
chlorine adduct 330 instead of the expected tosylate. We believe this is due to a formation of the reactive pyrrolic tosylate that is readily displaced by the chlorine in situ. The chloride 330 also proved to be unstable and must be used within hours after isolation and purification. Displacement of the chlorine atom with trimethylsilyl acetylene was accomplished using potassium carbonate as the base in the presence of sodium iodide and copper (I) iodide in N,N-dimethylformamide.134

Scheme 4.14 Synthesis of N-Boc 2-Chloro-3-[3-(trimethylsilyl)prop-2-yn-1-yl]-pyrrole (331)

Reagents and conditions: a) Boc₂O, Et₃N, DMAP, DCM, rt, 3 h (93%); b) DIBAL-H, DCM, -78 °C to rt, 4 h (76%); c) TsCl, Et₃N, DMAP, DCM, rt, 4 h (62%); d) TMS-acetylene, K₂CO₃, NaI, Cul, DMF, 40 °C, 3 h (57%).

The molecular structure of the pyrrole 331 was confirmed by ¹H and ¹³C NMR spectral data (Figure 4.8). Each singlet at δ 0.16 and 1.59 were assigned to the three methyl groups attached to the silicon and Boc protecting groups, in which both peaks integrated to nine protons, respectively. The pyrrolic methylene group was assigned to the singlet at δ 3.38 and finally doublets at δ 6.26 and 7.20 corresponded to the two aromatic protons.
In addition, the infrared spectrum displayed an absorption at 2239 cm⁻¹ which is consistent with that reported for the C-C stretch of an unsymmetrical alkyne.

4.2.5.1. Attempted Synthesis of tert-Butyl 7,7-dibutyl-6-(trimethylsilyl)-1H,4H,7H-stannino[2,3-b]pyrrole-1-carboxylate (333)

The synthesis of compound 333 from the acetylenic pyrrole 331 via various metal-halogen exchange reactions was then attempted (Scheme 4.15). Due to the unknown stability of the tin-bromide bond of the anticipated product, the crude material was immediately treated with sodium borohydride in situ in order to potentially replace the bromide with hydride. Upon heating these reactions during this reduction process, it was hoped that the tin-hydride moiety would undergo the aforementioned radical cyclization process to afford the desired bicyclostannane 333 (c.f. Scheme 4.10). The results of these studies are summarized below (Table 4-2).
Scheme 4.15  Attempted Synthesis of tert-Butyl-7,7-dibutyl-6-(trimethylsilyl)-1H,4H,7H-stannino[2,3-b]pyrrole-1-carboxylate (333)

In the first instance, n-butyl lithium was used to initiate the lithium-halogen exchange reaction and the presumed resultant pyrrole anion was quenched with di-n-butyltin dibromide to prepare the compound 332. This crude material was the treated with sodium borohydride and the reaction was heated at reflux for 4 hours (entry 1, Table 4-2). The $^1$H NMR spectrum of the crude product showed promising results as several resonances in the region of $\delta$ 0.80 to 1.80 were observed which could...
correspond to the two butyl groups on the tin atom, in addition to peaks that belong to the pyrrole moiety (Figure 4.9).

![Chemical structure](image)

**Figure 4.9** ¹H NMR spectrum (400 MHz, CDCl₃) of the crude product 332 of the metal-chlorine exchange reaction of compound 331.

However, all the attempts to purify and isolate the product of this reaction proved to be unsuccessful. The mass spectrum of the crude showed the loss of the chlorine atom by the absence of the chlorine isotope fragments, but the molecular ion was not observed. Other spectroscopic techniques such as ¹³C NMR spectrum and infrared spectroscopy were inconclusive and did not lead to the assignment of molecular structure of the crude product.

Repeating the reaction by varying the reaction temperature and time resulted the same observation (entries 2 and 3) and none of the attempts led to the isolation of the desired product 333. Attempts to effect this transformation by Grignard reaction were also considered. Following the standard procedure to prepare a Grignard reagent using magnesium turnings, activated by flame-drying or iodine chips, in tetrahydrofuran at
room temperature or at reflux (entries 4 and 5, respectively), followed by the addition of di-\textit{n}-butyltin dibromide resulted in the formation of a complex mixture of products. Other methods to activate the magnesium metal, such as a hydrochloric acid wash of magnesium powder, also led to the formation of a complex mixture of products (entry 6). Employing \textit{iso}-propylmagnesium bromide to perform the halogen-magnesium exchange reaction also resulted in the decomposition of starting material (entry 7).

To identify the problems with the lithium-chlorine exchange reaction, the pyrrole 331, upon treatment of \textit{n}-butyl lithium, was quenched with deuterated methanol (Scheme 4.16). It was expected that the lithiated product, once formed, would abstract a deuterium from deuterated methanol. However, no deuterated products 334 were identified. In fact, extensive starting material decomposition was observed and only a trace amount of the deprotected pyrrole 335 was isolated.

**Scheme 4.16 Deuterium Quench of Lithium-Chlorine Exchange Reaction**

![Scheme 4.16 Deuterium Quench of Lithium-Chlorine Exchange Reaction](image)

Reagents and conditions: a) \textit{n}BuLi, THF, -78 °C, 2 h then methanol-D\textsubscript{4}, -78 °C to rt, 30 min. (0\% 334:7\% 335).

Employing Grignard reagents to affect the above transformation were also attempted. However, these attempts did not afford the desired deuterated pyrrole 334.
4.2.6. ** Attempted Synthesis of 7-Phosphaindole (19) via a Tosyl Protected Pyrrole **

The results discussed above suggested that pyrrolic chloride is a poor substrate towards halogen-metal exchange reactions. Due to the difficulties in the preparation of the bromo derivative (see: Section 4.24), which was generally considered to be a more suitable substrate in metal-halogen exchange reaction, it was decided to activate the chlorine by removing electron density from the pyrrole ring. This could be achieved by installing a stronger electron-withdrawing protecting group on nitrogen, such as sulfonate group.

4.2.6.1. ** Synthesis of N-Toluenesulfonyl-2-chloro-3-[3-(trimethylsilyl)-2-propynyl]-1H-pyrrole (339) **

The synthesis of *N*-toluenesulfonyl-2-chloro-3-carboxylate pyrrole (339) began with protection of methyl 2-chloro-3-carboxylate pyrrole 18 with *p*-toluenesulfonyl chloride using sodium hydride as a base and a catalytic amount of *N*,*N*-dimethyl-4-aminopyridine in tetrahydrofuran at room temperature (Scheme 4.17). The resultant protected pyrrole 336 was then reduced with diisobutylaluminum hydride and subsequently converted to the corresponding ditosylated pyrrole 338 using the reaction conditions described above (c.f. Scheme 4.14). Treatment of the readily reactive pyrrolic tosylate 338 with trimethylsilyl acetylene in the presence of potassium carbonate and copper iodide in *N*,*N*-dimethylformamide afforded the desired acetylenic pyrrole 339 with 48% overall yield from compound 18.
Scheme 4.17 Synthesis of \(N\)-Toluenesulfonyl-2-chloro-3-[3-(trimethylsilyl)-2-propynyl]-1\(H\)-pyrrole (339)

\[
\begin{align*}
\text{18} & \quad \xrightarrow{a} \quad \text{336} & \quad \xrightarrow{b} \quad \text{337} \\
\text{338} & \quad \xrightarrow{d} \quad \text{339}
\end{align*}
\]

Reagents and conditions: \(p\)-TsCl, NaH, DMAP, THF, 0 °C to rt, 5 h (78%); b) DIBAL-H, DCM, -78 °C to rt, 4 h (83%); c) \(p\)-TsCl, DMAP, DCM, rt, 4 h (81%); d) TMS-acetylene, \(K_2CO_3\), NaI, Cul, DMF, 40 °C, 3 h (89%).

The molecular structure of compound 339 was confirmed by \(^1\)H NMR spectroscopy (Figure 4.10). A total of 6 proton resonances in the aromatic region corresponded to the four tosylate protons and two pyrrole protons. A singlet at \(\delta 0\) ppm corresponded to the three methyl groups of the silicon protecting group.
In addition, the unsymmetric alkyne moiety of compound 339 was also evidenced by an absorption at 2253 cm\(^{-1}\) in the IR spectrum.

4.2.6.2. Attempted Synthesis of \(N\)\-[(4-methylbenzene)sulfonyl] 7,7-dibutyl-6-(trimethylsilyl)-1\(H\),4\(H\),7\(H\)-stannino[2,3-b]pyrrole (340)

The synthesis of the bicyclic stanninopyrrole 340 from acetylenic pyrrole 339 was attempted employing the reagents and conditions discussed earlier (Scheme 4.18, c.f. Scheme 4.15). The results of these studies are summarized below (Table 4-3).
Scheme 4.18  Attempted Synthesis of \( N \)-toluenesulfonyl 7,7-dibutyl-6-(trimethylsilyl)-1H,4H,7H-stannino[2,3-b]pyrrole (340)

![Colorful image of the chemical structure]

Table 4-3  Reagents and Conditions Corresponding to Scheme 4.18

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents and conditions</th>
<th>expected product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( n )-BuLi (1.2 eq), THF, -78 °C, 30 min. then ( n )-Bu(_2)SnBr(_2) (1.5 eq), -78 °C to rt, 4 h</td>
<td>![Product 341]</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>( t )-BuLi (2.2 eq), THF, -78 °C, 30 min. then ( n )-Bu(_2)SnBr(_2) (2.5 eq), 78 °C to rt, 4 h</td>
<td>![Product 341]</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Mg (powder, activated by HCl wash), THF, reflux, 3 h then ( n )-Bu(_2)SnBr(_2) (1.5 eq), rt, 4 h</td>
<td>![Product 341]</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>( n )-BuLi (1.2 eq), THF, -78 °C, 30 min. then ( n )-Bu(_2)SnBr(_2) (1.5 eq), -78 °C to rt, 4 h then NaBH(_4), reflux, 14 h</td>
<td>![Product 340]</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Mg (powder, activated by HCl wash), THF, reflux, 3 h. then ( n )-Bu(_2)SnBr(_2) (1.5 eq), rt, 4 h then NaBH(_4), reflux, 14 h</td>
<td>![Product 340]</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>( n )-BuLi (1.2 eq), THF, -78 °C, 30 min. then MeOD (excess), -78 °C to rt, 30 min</td>
<td>![Product 342]</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Mg (powder, activated by HCl wash), THF, reflux, 3 h then MeOD (excess), rt, 30 min</td>
<td>![Product 342]</td>
<td>0</td>
</tr>
</tbody>
</table>
The reaction conditions used for the proposed metal-halogen exchange reaction were identical to those employed with N-Boc protected pyrrole 331 that was discussed earlier. Either by employing different butyl lithium bases (\(n\)-butyllithium – entry 1 or \(t\)-butyllithium – entry 2, Table 4-3) or different metal insertion process (\(i.e.\) Mg – entries 3 and 4) resulted in starting material decomposition and none of the desired product 340 was isolated. Quenching the reaction intermediates with deuterated methanol also did not afford the anticipated deuterated pyrrole 342 (entries 6 and 7).

4.2.7. Conclusion

Based on the above observations, we concluded that pyrrole 339 is an unsuitable substrate for the proposed halogen-metal exchange reaction and a new synthetic strategy is required. At this point, no further attempts were made towards the synthesis of 7-phosphaindole (19) as it was concluded that an efficient synthesis of the corresponding bromo pyrrole starting material is required. However, as an efficient synthesis of the methyl 2-chloro-3-carboxylate pyrrole (18) had been developed, its further chemistry was pursued. The results of this work are presented in the following section.

4.3. Part 2: Synthesis of Pyrrole-Containing and Potentially Biologically-Active Molecules via Various Palladium-Catalyzed Cross-Coupling Reactions

The application of aryl-aryl bond formation reactions is one of the most important tools in modern synthetic organic chemistry. Biaryls represent a common structural motif found in natural products and numerous synthetic biologically-active molecules.
Many commercial dyes contain polyaryl and polyheteroaryl molecular skeletons. In addition, polyaromatics possess physical properties that are applicable in organic conductors and semiconductors. Di- or triaromatics rings are also the backbone of some of the most efficient and selective ligands for asymmetric catalysis. Given the successful synthesis of the pyrrole 18 that was developed and optimized during the attempted synthesis of 7-phosphaindole, we believe that this molecule could act as a key building block towards the synthesis of a wide variety of pyrrole-containing and potentially biologically-active molecules via cross-coupling reactions. In the following sections, a brief overview of palladium-catalyzed cross-coupling reactions and their applications in the synthesis of various biologically-active molecules containing 2,3-disubstituted pyrroles is discussed.

### 4.3.1. Biologically-Active Compounds Containing 2,3-Disubstituted Pyrroles

The chemistry of pyrrole-containing natural products dates back to the isolation and the total synthesis of the tripyrrole prodigiosin (343) by Rapoport and Holden in the 1960’s. In the following figure, a selected examples that feature the 2,3-disubstituted pyrrole motifs are presented (Figure 4.11).135 Prodigiosin (343), streptoruin B (344) and roseophilin (345) have proven to be attractive targets for synthetic chemists because of their outstanding biological activities as immunosuppressive agents. Batrachotoxin (346), isolated from dart-poison frogs, melyrid beetles and some species of birds, shows an extremely potent cardiotoxic and neurotoxic profile.136 In addition, compounds 347 and 348 are synthetic molecules that exhibit cytotoxic activities against various cancer cell lines.137,138
We envisioned that methyl 2-chloro-3-carboxylate pyrrole (18), previously synthesized for the studies towards the synthesis of 7-phosphaindole (19), could serve as a central building block towards the synthesis of a wide range of pyrrole-containing natural products and their structurally-related analogues via palladium-catalyzed cross-coupling reactions (Figure 4.12).
4.3.2. An Overview of Palladium-Catalyzed Cross-Coupling Reactions

The first aryl-aryl bond formation reaction, through an ether linkage, can be traced back to 1904 when F. Ullmann observed that the reaction of aryl halides 350 with phenols 351 afforded biaryl ethers 352 that was significantly improved in the presence of copper powder (Scheme 4.19).\textsuperscript{139,140} For the next 70 years, copper was almost the only metal used in the aryl-aryl bond formation reactions.

\textbf{Scheme 4.19} Generic Reaction Scheme for the Ullmann Reaction

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {\textbf{Scheme 4.19}}; \node (2) at (0,-1) {\textbf{Generic Reaction Scheme for the Ullmann Reaction}}; \node (3) at (1.5,0) {R'X}; \node (4) at (3,0) {HOR_1}; \node (5) at (7,0) {\textbf{Cu}(0), DMF, 100 °C}; \node (6) at (7.5,0) {R'R_1}.
\end{tikzpicture}
\end{center}

In 1968, Heck reported a series of articles in which the organopalladium complex (alkyl- and aryl)palladium halide) were added to olefins at room temperature.\textsuperscript{139,141,142} One of the examples was the addition of phenylpalladium chloride 353 to ethylene 354 followed by elimination of palladium (0) to afford styrene 356 (Scheme 4.20).
In 1976, Negishi reported a series of studies of the palladium-catalyzed cross-coupling reactions with organohalides\textsuperscript{139,143}. The first study was the use of organozirconium or organoaluminium compounds as coupling reagents. The positive results generated from the above studies led to the exploration of the reaction system on even less reactive organometallic species. As a result, in 1977 Negishi introduced organozinc compounds as the nucleophilic species in palladium-catalyzed cross-coupling reactions (Scheme 4.21). The use of organozinc compounds afforded outstanding reaction yields and was able to proceed under mild reaction conditions and showed high regio-selectivity.

In 1979, Suzuki reported that the use of organoboron compounds as the coupling partner in palladium-catalyzed cross-coupling reactions in the presence of base to facilitate the transformation of the organic group from boron to palladium\textsuperscript{144–146}. It was
later found that the use of arylboronic acids and weaker bases significantly increase the reaction rate and yield of this process (Scheme 4.22).

**Scheme 4.22 General Scheme for Suzuki-Type Palladium-Catalyzed Cross-Coupling Reaction**

$$\text{R-X} + \text{R}_1\text{B(OR)}_2 \xrightarrow{\text{Pd}^0 \text{(catalytic)}} \text{R-R}_1 \xrightarrow{\text{Base, Ligand}} \text{X} \text{B(OR)}_2$$

Of an interesting note, Negishi also reported that iodobenzene selectively coupled with the terminal alkyne of lithium 1-hexynyl(tributyl)borate through a palladium-catalyzed addition/elimination processes in 1978.\textsuperscript{147} He did not pursue the use of organoboronic compounds as the coupling partner in palladium-catalyzed cross-coupling reaction and this remained the only example reported by Negishi.

The palladium-catalyzed cross-coupling reaction using alkyl- and arylstannanes (Stille-type)\textsuperscript{148,149} or using unprotected acetylenes in the presence of copper salt (Sonogashira-type)\textsuperscript{150,151} were also discovered and utilized in the same period of time.

In the past twenty years, the palladium-catalyzed cross-coupling reaction has evolved into one of the most widely used carbon-carbon bond forming processes. Its impact on organic synthesis, primarily due to its generality and applicability in the formation of biaryls, which are found in polymers, biologically-active compounds, ligands and various materials, was recognized in scientific community. Accordingly, Heck, Negishi and Suzuki were awarded by Nobel Prize in Chemistry in 2010 for their pioneering work on palladium-catalyzed cross-coupling reactions.
4.3.3. **Synthesis of 2-Aryl-3-carboxylate Pyrrole: N,O-Bidentate Ligand Approach**

4.3.3.1. **An Overview of Suzuki Coupling Reaction of Aryl Chlorides**

Ever since the use of palladium compounds as catalysts in the cross-coupling reactions were discovered in the early 70’s, most of the reaction conditions were developed and optimized using more reactive organic bromides, iodides and triflates as coupling partners. The organic chlorides, however, were noticeably uncommon substrates. This was primarily due to the relatively high bond strength of the C-Cl bond (bond dissociation energies for Ph-X: Cl: 96 kcal mol\(^{-1}\); Br: 81 kcal mol\(^{-1}\); I: 65 kcal mol\(^{-1}\)).\(^{152}\) This renders the oxidative addition of aryl chloride bonds to palladium(0) centres, often considered to be the rate-determining step in palladium-catalyzed coupling reactions, an unfavourable process.

4.3.3.2. **Suzuki Coupling Reaction Employing N,O-Bidentate Ligand**

To overcome the low reactivity of the carbon-chloride bond, research groups around the World have spent a tremendous amount of effort in developing various ligands and reaction additives that would increase the reactivity of palladium(0) species during the oxidative addition process. In 2010, Yang *et al.* reported the *in situ* formation of an N,O-bidentate ligand through hydrogen bonding to facilitate Suzuki coupling reactions of aryl chlorides.\(^{153}\) In this article, Yang claimed that by employing ethanol and \(N,N\)-dimethylacetamide (DMA) as cosolvents for the Suzuki coupling reaction, a bidentate ligand is formed between solvent molecules through hydrogen bonding (Figure 4.13).
Figure 4.13  \textit{In Situ} formation of a bidentate ligand between \textit{N,N-}dimethylacetamide and ethanol.

This hydrogen bonded bidentate ligand coordinates to palladium to form a six-membered palladium complex \textit{357}, which activates the palladium to undergo oxidative addition with aryl chloride to afford intermediate \textit{358} (Scheme 4.23). The presence of ethanol also could act as a promoter by reducing the palladium-chlorine bond energy and thus accelerate the transmetallation step to form intermediate \textit{360}, which after reductive elimination would generate the desired coupled \textit{bis}-aryl product and palladium (0) for another catalytic cycle.
4.3.3.3. **Suzuki-Type Cross-Coupling Reactions of Pyrrole 336 with Various Aryl- and Heteroarylboronic Acid using an N,O-Bidentate Ligand**

A detailed examination of this set of reaction conditions towards the Suzuki coupling reactions of pyrrole 336 with various arylboronic acids was performed (Scheme 4.24). All of the reactions were carried out with a 10 mol% loading of palladium acetate and two equivalents of potassium carbonate in an ethanol: N,N-dimethylacetamide mixture. The results of this study are summarized below (Table 4-4).
Scheme 4.24  Synthesis of Methyl N-tosyl 2-aryl-3-carboxylate pyrrole 361

\[
\begin{array}{c}
\text{Scheme 4.24  Synthesis of Methyl N-tosyl 2-aryl-3-carboxylate pyrrole 361} \\
\text{Reagents and conditions: a) Pd(OAc)\textsubscript{2} (0.1 eq), K\textsubscript{2}CO\textsubscript{3} (2 eq), EtOH:DMA (1:1), 100 °C.}
\end{array}
\]

<table>
<thead>
<tr>
<th>en.</th>
<th>arylboronic acid</th>
<th>expected product</th>
<th>isolated product</th>
<th>time</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph}^\text{H}BO^\text{OH})</td>
<td>362</td>
<td>363</td>
<td>1 h</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(\text{HOC}_\text{N}^\text{H}BO^\text{OH})</td>
<td>364</td>
<td>365</td>
<td>1 h</td>
<td>&gt;5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 h</td>
<td>55*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 h</td>
<td>54*</td>
</tr>
<tr>
<td>3</td>
<td>(\text{HOC}_\text{N}^\text{H}BO^\text{OH})</td>
<td>366</td>
<td>367</td>
<td>1 h</td>
<td>&gt;5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 h</td>
<td>61*</td>
</tr>
</tbody>
</table>

* Yields reported here are of the isolated product. No expected products were isolated in entries 2 and 3.

\(N\)-Tosyl 2-chloro-3-carboxylate pyrrole \(336\) was selected for this initial study. We believed that the strong electron-withdrawing nature of the tosyl group, which pulls electron density away from the pyrrole ring, would reduce the carbon-chloride bond
strength and therefore make the chloride more reactive towards the palladium-catalyzed coupling reaction.

In the first instance, phenylboronic acid was used as the coupling partner (entry 1, Table 4-4). After 1 hour of stirring at 100 °C, we were able to isolate the desired product 363 in a reasonable yield. In addition, a trace amount of the deprotected pyrrole 18 was isolated from the reaction mixture.

The molecular structure of methyl \(N\)-toluenesulfonyl-2-phenyl-\(1H\)-pyrrole-3-carboxylate (363) was confirmed by \(^1\text{H}\) and \(^{13}\text{C}\) spectroscopy. The two singlets at \(\delta 2.38\) and 3.57 corresponded to the methyl groups of the tosylate and the carboxylate groups. A total of 14 peaks in the \(^{13}\text{C}\) spectrum were in agreement with 14 chemically inequivalent carbons present in this compound.
When the heterocyclic boronic acid, 2-pyridinylboronic acid (364) or pyrrolylboronic acid (366), was employed as reaction substrates, no desired products were isolated. In fact, the tosylate group was removed during these processes at longer reaction times and the pyrrole 18 was isolated in both cases in good yield (entries 2 and 3). Of note, a common reaction condition to cleave N-tosyl groups involves the use of potassium carbonate in methanol at reflux (Scheme 4.25).  

Scheme 4.25  Alkaline Hydrolysis of N-Sulfonylpyrrole 368

Reagents and conditions: a) K₂CO₃, MeOH, reflux, 24 h.
Interestingly, when the acetylenic pyrrole 339 was employed as an alternative substrate under the same reaction conditions, a complex of mixture of products was formed and no products were isolated after numerous purification attempts (Scheme 4.26). It is believed that the alkynyl group coordinates with palladium (II) metal after the oxidative addition step and an unreactive palladium complex is formed. More detailed mechanistic studies are required to support this hypothesis.

Scheme 4.26 Attempted Suzuki-Type Cross-Coupling Reaction of Pyrrole 339 with Phenylboronic Acid (362)

Reagents and conditions: a) Pd(OAc)$_2$ (0.1 eq), K$_2$CO$_3$ (2 eq), EtOH:DMA (1:1), 100 °C.

Based on the above observations, the N-Boc pyrrole 328 was employed as the starting material for palladium-catalyzed Suzuki-type cross-coupling reaction. We anticipated that the Boc group would be stable towards these reaction conditions and that the moderate electron-withdrawing nature of the Boc group should remove some electron density from the pyrrolic ring and thus lower the carbon-chlorine bond energy to facilitate the palladium-catalyzed Suzuki coupling reaction (Scheme 4.27). Towards this end, N-Boc pyrrole 328 was reacted with various aryl and heteroarylboronic acid employing the reaction conditions discussed above. The findings of this study are summarized below (Table 4-5).
Scheme 4.27  Synthesis of \( N\)-Boc-2-aryl-3-carboxylatepyrrole 370

\[
\begin{align*}
\text{OMe} & \quad \text{Arylboronic acid} \\
\text{Boc} & \quad \text{O} & \quad \text{Ar} \\
\text{Cl} & \quad \text{Boc} & \quad \text{Ar} \\
\text{N-Boc} & \quad \text{Cl} & \quad \text{Boc} & \quad \text{Ar}
\end{align*}
\]

Reagents and conditions: a) \( \text{Pd(OAc)}_2 \) (0.1 eq), \( \text{K}_2\text{CO}_3 \) (2 eq), \( \text{EtOH:DMA} \) (1:1), 100 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>arylboronic acid</th>
<th>isolated product</th>
<th>time</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{HO-B-OH} )</td>
<td>( \text{N-Boc} )</td>
<td>1</td>
<td>trace*</td>
</tr>
<tr>
<td></td>
<td>( \text{362} )</td>
<td>( \text{371} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>trace*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>trace*</td>
</tr>
</tbody>
</table>

* Trace amount of the expected product was observed by \( ^1\text{H} \) NMR spectrum of the crude product. The ratio of the starting material 362 to product 371 was >9:1, based on the integration of the methoxy peaks. Reactions were performed on small scale (0.1 mmol) and no further purification was attempted.

The NMR spectra of the crude product in all three cases showed that Boc group is stable towards the reaction conditions and remained attached to the nitrogen atom (entries 1-3, Table 4-5). The reactivity of the \( N\)-Boc protected pyrrole, however, was
reduced significantly in that none of the attempts led to the formation of the desired products in a significant yield and starting material was largely recovered in all three attempts.

Based on the above observations, we concluded that the use of *in situ*-formation of the $N, O$-bidentate ligand to increase the reactivity of palladium(0) during the oxidative addition process is only effective towards electron-poor aryl chlorides. Unfortunately, if longer reaction time is required, the reaction conditions remove the strong electron-withdrawing tosyl group and the resultant unprotected pyrrole 18 is unreactive in the desired coupling reactions. When $N$-Boc pyrrole 328 was used as the alternative starting material the rather electron-rich pyrrolic-chloride bond showed no reactivity towards the oxidative addition to palladium(0). To resolve this problem, we believed that reaction additives, such as bulky trialkylphosphine or other phosphane-based ligands, was required to increase the reactivity of palladium(0) towards the $N$-Boc pyrrole 328.

### 4.3.4. Synthesis of 2-Aryl-3-carboxylate Pyrroles Employing Reaction Additives

#### 4.3.4.1. An Overview of Suzuki Cross-coupling Reaction Towards Unactivated Aryl Chlorides

Up until 1998, there were no reports of effective palladium-catalyzed Suzuki reactions of electron-neutral or -rich aryl chlorides due to high C-Cl bond dissociation energy. In 1998, Buchwald *et al.* and Fu *et al.* each reported catalytic systems that were efficient in coupling reactions of a wide range of aryl chlorides and heteroaryl chlorides in good yield.\(^{146}\)

In Buchwald’s report, biphenylphosphane 377 was shown to be a very effective ligand for the palladium-catalyzed Suzuki reaction of a wide range of aryl chlorides such
as electron-neutral and electron-rich substrates, at room temperature (Scheme 4.28).\textsuperscript{154} Cesium fluoride (CsF) was employed in these reactions, but other bases such as potassium phosphate (K\textsubscript{3}PO\textsubscript{4}) could also be used on increasing the reaction temperature.

**Scheme 4.28 Buchwald’s Modified Protocol for the Suzuki Cross-Coupling Reaction**

\[
\begin{align*}
R &= 4{-}\text{NO}_2, \text{CN}, \text{CO}_2\text{Me}, \text{Me}, \text{OMe} \\
R_1 &= 3{-}\text{CMe}, \text{H} \\
R_1 &= 2{-}\text{OMe}
\end{align*}
\]

Reagents and conditions: a) Pd(OAc)\textsubscript{2} (1 mol\% eq.), \textsuperscript{377} (3 mol\% eq.), KF (3 eq.), THF, rt.

In the same year as the original report by Buchwald et al., Fu et al. also reported a versatile method for palladium-catalyzed Suzuki cross-coupling of aryl chlorides in which they used a sterically demanding and electron-rich trialkylphosphane (Scheme 4.29).\textsuperscript{155} In this and subsequent studies, Fu et al. discovered that deactivated and sterically-hindered aryl chlorides were suitable substrates for this catalyst system, and that bulky and electron-rich trialkylphosphines such as tri-\textit{tert}-butylphosphine or tricyclohexylphosphine were the best ligands. Potassium fluoride (KF) was shown to be a more effective additive than cesium carbonate (Cs\textsubscript{2}CO\textsubscript{3}). Combining the above findings allowed the Suzuki cross-coupling reaction of a wide range of aryl chlorides, including heteroaryl chlorides, to proceed at room temperature in excellent yields.
Scheme 4.29  Fu’s Modified Protocols for the Suzuki Cross-Coupling Reaction

\[
\begin{align*}
\text{R} & = 4\text{-COMe}, 4\text{-Me} \\
\text{4-OMe}, 4\text{-NH}_2, 2\text{-Me} \\
\text{R}_1 & = 4\text{-CF}_3 \\
\text{4-OMe}, 2\text{-Me} \\
\end{align*}
\]

Reagents and conditions: a) \( \text{Pd}_2(\text{dba})_3 \) (1.5 mol% eq), \( \text{P}(\text{tBu})_3 \) (3.6 mol% eq), \( \text{Cs}_2\text{CO}_3 \) (1.2 eq), dioxane, 90 °C.

4.3.4.2. Suzuki-Type Cross-Coupling Reaction of Pyrrole 328 with Various Aryl- and Heteroarylboronic Acids using Fu’s Modified Protocol

Due to the accessibility of the palladium catalyst, Fu’s modified protocol was selected for the following palladium-catalyzed Suzuki reaction study (Scheme 4.30).\(^\text{155}\)

The \( \text{N-Boc} \) pyrrole 328 was used as the starting material because it was shown to be stable in earlier studies. The results of this study are summarized below (Table 4-6).

Scheme 4.30  Fu’s Modified Suzuki Cross-Coupling Reaction of the \( \text{N-Boc} \)-methyl 2-chloro-3-carboxylate Pyrrole (328) with Various Aryl- and Heteroarylboronic Acids

Reagents and Conditions: a) \( \text{Pd}_2(\text{dba})_3 \) (2 mol% eq), \( \text{PCy}_3 \) (5 mol% eq), \( \text{K}_3\text{PO}_4 \) (2 eq), dioxane, 100 °C.
Table 4-6  Reagents and Conditions Corresponding to Scheme 4.30

<table>
<thead>
<tr>
<th>entry</th>
<th>arylboronic acid</th>
<th>isolated product</th>
<th>time</th>
<th>yield (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{HO} \\
\text{B-OH} \\
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{O-Me} \\
\end{array}
\] | 16 h | 47 |
| 2     | \[
\begin{array}{c}
\text{HO} \\
\text{B-OH} \\
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{O-Me} \\
\end{array}
\] | 16 h | 0 |
| 3     | \[
\begin{array}{c}
\text{HO} \\
\text{B-OH} \\
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{O-Me} \\
\end{array}
\] | 16 h | 41 |

In the first instance, when phenylboronic acid was used as the coupling partner, under the reaction conditions suggested by Fu, the deprotected coupled product 381 was isolated in 47% yield (entry 1, Table 4-6). Similar result (the removal of Boc group) was also observed in other attempts. This is presumably due to the heating under alkaline conditions.\textsuperscript{131,156} When various heteroarylboronic acids were employed, different results were obtained. While the 2-pyridylboronic acid showed no reactivity with pyrrole 328 (entry 2), 2-pyrrolylboronic acid 366 exhibited moderate reactivity under the same reaction conditions and the \textit{bis}-pyrrole 383 was isolated in 41% yield (entry 3).

The loss of Boc group during the Suzuki cross-coupling reaction due to thermolytic cleavage posed some issues in product purification. The \textit{bis}-pyrrole products exhibited a similar polarity by TLC as compared to starting material 328. This
resulted in the requirement for extensive flash chromatography to separate the two compounds effectively.

The tosyl protecting group, on the other hand, proved to be stable under the reaction conditions (Scheme 4.31). Under the same reaction conditions, \( N \)-tosyl 2-chloro-3-carboxylate pyrrole (336) exhibited good to excellent yield with various aryl and heteroaryl boronic acids. The result of this study is summarized below (Table 4-7).

**Scheme 4.31** Fu’s Modified Suzuki Cross-Coupling Reaction of \( N \)-Tosyl-methyl 2-chloro-3-carboxylate Pyrrole (336) with Various Aryl- and Heteroarylboronic Acids

\[
\begin{align*}
\text{336} & \quad \text{+ Arylboronic acid} \quad \xrightarrow{a} \quad \text{361} \\
\text{Ts} & \quad \text{Cl} & \quad \text{Ts} & \quad \text{Ar}
\end{align*}
\]

Reagents and conditions: a) \( \text{Pd}_2(\text{dba})_3 \) (2 mol\% eq), \( \text{PCy}_3 \) (5 mol\% eq), \( \text{K}_3\text{PO}_4 \) (2 eq.), dioxane, 100 °C.

**Table 4-7** Reagents and Conditions Corresponding to Scheme 4.31

<table>
<thead>
<tr>
<th>entry</th>
<th>arylboronic acid</th>
<th>isolated product</th>
<th>time</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>362</td>
<td>363</td>
<td>16 h</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>364</td>
<td>365</td>
<td>16 h</td>
<td>0</td>
</tr>
</tbody>
</table>
The *N*-tosyl pyrrole 336 showed good reactivity under Fu’s modified Suzuki reaction protocol and the desired product 363 was obtained in 84% yield when reacted with phenylboronic acid (entry 1, Table 4-7). 2-Pyridinylboronic acid, however, remained inert towards the reaction conditions (entry 2). *N*-Boc 2-pyrrolylboronic acid gave the bis-pyrrole 367 in good yield (entry 3). Other arylboronic acid such as 4-trifluoromethylphenyl or ferrecylboronic acid also exhibited excellent reactivity and the desired products were isolated in good yields (entries 4 and 5).

4.3.5. Synthesis of 2-Aryl-3-carboxylate Pyrroles – Stille-type and Heck-type Palladium-catalyzed Cross-Coupling Reactions

The successful results obtained from Suzuki-type palladium-catalyzed cross-coupling reaction led to the consideration for use of other types of palladium-catalyzed cross-coupling reaction, such as Stille-type or Heck-type process.
Currently, the only general method for achieving Stille cross-coupling reactions of unactivated aryl chlorides is the Pd/P(tBu)$_3$/CsF system described by Littke and Fu.$^{157}$ According to Fu, this catalytic system works well for both electron-deficient and electron-rich as well as sterically hindered aryl chlorides.

The study of Stille-type cross-coupling reaction adopting Fu’s protocol is summarized below (Scheme 4.32, Table 4-8).

**Scheme 4.32**  Stille Cross-Coupling Reaction of N-Tosyl-methyl 2-chloro-3-carboxylate Pyrrole (336) with Various Alkyl, Aryl and Heteroaryl Stannanes

Reagents and Conditions: a) Pd$_2$(dba)$_3$ (2 mol% eq), tert-Bu$_3$P (6 mol% eq), CsF (2.5 eq), dioxane, 100 °C.

**Table 4-8**  Reagents and Conditions Corresponding to Scheme 4.32

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyl and arylstannanes</th>
<th>isolated product</th>
<th>time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnBu$_3$</td>
<td><img src="image" alt="363" /></td>
<td>16 h</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="389" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="381" /></td>
<td></td>
<td>16 h</td>
<td>11</td>
</tr>
</tbody>
</table>
In the first instance, pyrrole 336 showed good reactivity towards tributylphenylstannane under Fu’s modified Stille cross-coupling reaction conditions (entry 1, Table 4-8). Interestingly, the isolation of methyl 2-phenyl-3-carboxylate pyrrole (381) suggested that cesium fluoride is basic enough to facilitate the removal of the tosyl group. This observation of the removal of the tosyl group, however, varied between substrates. While similar results were obtained when pyrrole 336 was reacted with 2-(tributylstannyl)furan 392 (entry 3), the tosyl group was found to be completely inert under the same reaction conditions when reacted with tributylvinylstannane 390 (entry 2).

Finally, a Heck-type cross-coupling reaction is attempted. When pyrrole 336 was treated with styrene 394 in the palladium/triphenylphosphine system, unfortunately none of the desired coupled product was isolated (Scheme 4.33).
Scheme 4.33  Heck-Type Cross-Coupling Reaction of N-Tosyl-methyl 2-chloro-3-carboxylate Pyrrole (336) with Styrene 394 via Palladium/Triphenylphosphine System

\[
\begin{align*}
\text{336} & \quad + \quad \text{394} & \quad \rightarrow \quad \text{395} \\
\text{N} & \quad \text{Cl} & \quad \text{OMe} \\
\text{Ts} & \quad \text{OMe} & \quad \text{OMe}
\end{align*}
\]

Reagents and conditions: a) Pd(OAc)$_2$, Ph$_3$P, NaHCO$_3$, DMF, 135 °C, 12 h (0%)

Other methods such as the use of palladium/tri-tert-butyolphosphine system in the presence of cesium carbonate as the base resulted the removal of the tosyl group and pyrrole 18 was isolated in 47% yield (Scheme 4.34).

Scheme 4.34  Heck-Type Cross-Coupling Reaction of N-Tosyl-methyl 2-chloro-3-carboxylate Pyrrole (336) with Styrene 394 via palladium/tert-Butyolphosphine System

\[
\begin{align*}
\text{336} & \quad + \quad \text{394} & \quad \rightarrow \quad \text{395} & \quad + \quad \text{18} \\
\text{N} & \quad \text{Cl} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{OMe}
\end{align*}
\]

Reagents and conditions: a) Pd$_2$dba$_3$, tert-Bu$_3$P, CsCO$_3$, dioxane, 100 °C, 18-30 h [0% (395), 47% (18)]

4.3.6.  Synthesis of the bis-Pyrrolic Core of Prodigiosin (396)

To fully demonstrate the synthetic utility of methyl 2-chloro-3-carboxylate pyrrole (18), we decided to apply the above methodology towards the synthesis of the bis-pyrrolic core of prodigiosin (397). This synthesis could potentially lead to the preparation of a series of the synthetic analogues of prodigiosin (343) (Figure 4.15).
4.3.6.1. Retrosynthetic Analysis of Prodigiosin Analogues 396

The retrosynthetic analysis of prodigiosin analogue 396 suggested that the tri-pyrrolic skeleton could be prepared from 3-pyrrolin-2-one (398) via a condensation reaction with the bis-pyrrolic compound 397 (Scheme 4.35). The latter compound, bis-pyrrole 397, could be synthesized from N-Boc 2-pyrrolylboronic acid 366 and pyrrole 399, which is the product of Vilsmeier-Haak formylation reaction of methyl 2-chloro-3-carboxylate pyrrole (18).

Scheme 4.35  Retrosynthetic Analysis of Prodigiosin Analogues 396
4.3.6.2. Synthesis of the bis-Pyrrolic Skeleton of Prodigiosin 397

Pyrrole 18 was treated with phosphorus oxychloride (POCl₃) in N,N-dimethylformamide and 1,2-dichloroethylene to install an aldehyde moiety at the C5 position of the pyrrole 399 (Scheme 4.36).

Scheme 4.36 Synthesis of the bis-Pyrrolic Core of Prodigiosin 397

Reagents and conditions: a) POCl₃, DMF, 0 °C to rt, 15 min then 18, DCE, 0 °C to reflux, 15 min (72%); b) Pd₂(dba)₃ (2 mol% eq), PCy₃ (5 mol% eq), K₃PO₄ (2 eq), dioxane, 100 °C, 18 h (54%).

The position of where the aldehyde is attached in pyrrole 399 was determined by extensive spectroscopy studies. In the HMBC NMR spectrum, long range proton-carbon correlations of the pyrrolic proton with the carbon-2, -3 and -5 and the carbonyl carbons was observed, which is in accordance with C5 substituted product (Figure 4.16).

Figure 4.16 Observed HMBC Correlations for Pyrrole 399

Subsequent Suzuki cross-coupling reaction of pyrrole 399 with N-Boc 2-pyrrolylboronic acid 366 afforded the bis-pyrrolic molecule 397 in 54% yield. This compound contains the molecular skeleton of natural products, prodigiosin (343) and streptorulin (344), with an aldehyde moiety that is readily available for a condensation
reaction with 3-pyrrolin-2-one to afford the tripyrrolic structure of prodigiosin (343) and streptoruin (344) (c.f. Figure 4.11).

The molecular structure of the desired bis-pyrrole 397 was confirmed by $^1$H and $^{13}$C NMR spectroscopy (Figure 4.17). Four resonances between $\delta$ 6.3 ppm to 7.5 ppm corresponded to the four pyrrole protons. The aldehyde signal was found to be overlap with one of the NH protons at 9.5 ppm. The peak at 12.3 ppm corresponds to the remaining NH proton.

Figure 4.17 $^1$H NMR spectrum (600 MHz, CDCl$_3$) of bis-pyrrole 397.

The $^{13}$C NMR spectrum showed 11 peaks which is in agreement with 11 chemically inequivalent carbons presented in pyrrole 397. The molecular ion observed in high-resolution mass spectroscopy is also in agreement with the calculated value.

### 4.4. Conclusion and Future Work

The synthetic applications of methyl 2-chloro-3-carboxylate pyrrole (18) was studied. In the first section of this chapter, methyl 2-chloro-3-carboxylate pyrrole (18)
was envisioned as the key material towards the construction of 7-phosphaindole (19). A novel method to construct methyl 2-chloro-3-carboxylate pyrrole (18) was developed and optimized. An advanced synthetic intermediate was prepared in four steps from pyrrole 18 in an excellent overall yield with either Boc or tosylate as a protecting group. However, subsequent metal-halogen exchange followed by reduction and heat-induced radical cyclization reaction did not afford the desired bicyclic-stannane product that was required for the preparation of 7-phosphaindole (19).

In the second part of this chapter, methyl 2-chloro-3-carboxylate pyrrole 18 was envisioned to be the key building block for the synthesis of wide range of pyrrole-containing and potentially biologically-active compounds. It was found that the chlorine in pyrrole 18 could be converted to various alkyl or aryl substituents via the palladium-catalyzed cross-coupling reactions. The carboxylate moiety could also serve as a handle for subsequent conversion to various functional groups. In addition, the C4 and C5 position is available for electrophilic aromatic substitution reaction. After a considerable amount of experimentation in optimization of the palladium-catalyzed Suzuki-type cross-coupling reaction employing N-protected 2-chloro-3-carboxylate pyrrole 328 or 336, a series of pyrrole-containing bis-aryl compounds were prepared. The biological profile of these compounds will be tested in the future.

In addition, Stille-type and Heck-type cross-coupling reaction were also performed. The substrate, pyrrole 336, exhibited good reactivity towards various alkyl- and aryl stannanes under Stille cross-coupling reaction conditions.

Lastly, the bis-pyrrolic skeleton of prodigiosin 397 was prepared in two steps from pyrrole 18. The Vilsmeier-Haak formylation reaction of methyl 2-chloro-3-
carboxylate pyrrole (18) produced pyrrole 399 in a good yield and demonstrated that electrophilic substitution reaction occurred preferentially at C5 of pyrrole 18. The subsequent Suzuki-type cross-coupling reaction with pyrrolylboronic acid 366 afforded the bis-pyrrole 397 in 39% overall yield. The aldehyde moiety at the C5 position will be reacting with various 3-pyrrolin-2-ones to prepare several prodigiosin-related analogues.
4.5. Experimental Section

4.5.1. General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware, unless indicated otherwise. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran (THF) was dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, dichloromethane, and pyridine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied. Brine refers to a saturated aqueous solution of sodium chloride. Silica gel column chromatography (“flash chromatography”) was carried out using Merck silica gel 60 (230 to 400 mesh) and Silicycle SiliaFlash® F60 (230-400 mesh). All proton and carbon nuclear magnetic resonance spectra (\(^{1}\text{H NMR}\) and \(^{13}\text{C NMR}\), respectively) were recorded using a Bruker 400 FT spectrometer (operating frequencies: \(^{1}\text{H}, 400.13\text{ MHz};\) \(^{13}\text{C}, 100.61\text{ MHz}\)), Bruker 500 FT spectrometer (operating frequencies: \(^{1}\text{H}, 499.77\text{ MHz};\) \(^{13}\text{C}, 125.68\text{ MHz}\)), Varian 500 FT spectrometer (operating frequencies: \(^{1}\text{H}, 499.77\text{ MHz};\) \(^{13}\text{C}, 125.68\text{ MHz}\)) and Bruker 600 FT spectrometer (operating frequencies: \(^{1}\text{H}, 600.13\text{ MHz};\) \(^{13}\text{C}, 150.90\text{ MHz}\)) at ambient temperature unless stated otherwise. Chemical shifts (\(\delta\)) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform (CDCl\(_3\)) were 7.26 and 77.16 ppm for \(^{1}\text{H}\) and \(^{13}\text{C}\) NMR spectra, respectively. The reference values used for deuterated benzene (C\(_6\)D\(_6\)) were 7.15 and 128.02 ppm, respectively. Infrared spectra
(IR) were recorded as either KBr pellets (KBr), evaporated films (ef) or as films (neat) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (MS) were recorded on a Varian 4000 GC/MS/MS. The mode of ionization used was electron impact (EI, 70 eV) or chemical ionization (CI) with methanol as the ionization gas. High resolution electrospray ionization mass spectra (HREIMS) were obtained on Agilent Technologies 6210 Time-of-Flight LC/MS (Simon Fraser University). Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer (Simon Fraser University).
4.5.2. Experimental Procedures and Characterization Data

Methyl 2-cyano-4,4-diethoxybutanoate (323)$^{129,130}$

\[
\text{EtO} \quad \text{O} \quad \text{OMe} \quad 323
\]

Method A:

To a suspension of sodium hydride (23.0 g, 60% in mineral oil, 0.433 mol) in a mixture of \(N,N\)-dimethylformamide (350 ml) and benzene (110 ml) at -10 °C was added methyl cyanoacetate 317 (36.0 ml, 0.41 mol) over one hour. The mixture was stirred at room temperature for an hour and then bromoacetaldehyde diethyl acetal 322 (40.0 ml, 0.45 mol) was added. The reaction was then heated at 100 °C for 2h and then cooled to room temperature. The resultant mixture was filtered and the filtrate was concentrated. The remaining residues were dissolved with ether (100 ml) and washed with water (3 x 100 ml). The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by distillation at reduced pressure (B.p. 118–121 °C, ~2.8 mm Hg) to afford the title compound 323 (18.5 g, 29%) as a yellow oil.

Method B:

A suspension of methyl cyanoacetate 317 (74.3 g, 0.75 mol), bromoacetaldehyde diethyl acetal 322 (30 g, 0.15 mol), potassium carbonate (20.1 g, 0.18 mol) and sodium iodide (2.25 g, 15 mmol) was heated at reflux for 16 hours. On cooling to room temperature, the reaction mixture was quenched with water (300 ml) and extracted with ether (3 x 300 ml). The combined organic extracts were dried over anhydrous sodium...
sulfate and concentrate in vacuo. The starting materials were removed by distillation under reduced pressure (B.p. 72 – 78 °C, ~2.8 mm Hg) and the remaining crude product was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the title compound 323 (11.7 g, 37%) as a yellow oil.

\[ ^1H \text{ NMR (CDCl}_3, \text{ 400 MHz)} \delta 1.16 \text{ – 1.21 (6H, q, } J = 7.2 \text{ Hz, } 2 \times \text{ CH}_3), 2.15 \text{ – 2.30 (2H, m, CH}_2\text{), 3.47 \text{ – 3.55 (2H, m, CH}_2\text{), 3.62 \text{ – 3.70 (3H, m), 3.79 (3H, s, CH}_3\text{, 4.65 \text{ – 4.68 (1H, m, CH)}}; ^13C \text{ NMR (CDCl}_3, \text{ 101 MHz)} \delta 15.08, 15.11, 33.2, 33.6, 53.4, 62.6, 99.8, 116.2, 166.3; \text{ IR (neat)} 2978, 2928, 2900, 1750, 1439, 1267, 1126, 1061 \text{ cm}^{-1} \]}

**Methyl 2-chloro-1H-pyrrole-3-carboxylate (18)\textsuperscript{129}**

![Methyl 2-chloro-1H-pyrrole-3-carboxylate (18)](image)

**Method A:**

To a mixture of methyl 2-cyano-4,4-diethoxybutanoate 323 (2.00 mmol), lithium chloride (840 mg, 20.0 mmol) and p-toluenesulfonic acid monohydrate (380 mg, 2.00 mmol) in THF (7 ml) was heated at reflux for 20 h. The reaction solvent was then removed in vacuo and the crude residue was diluted with ethyl acetate (10 mL) and washed water (10 mL) and saturated aqueous solution of sodium carbonate (10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the title compound 18 (217 mg, 67%) as a colourless oil.
Method B:

To a mixture of methyl 2-cyano-4,4-diethoxybutanoate \(323\) (105 mg, 0.500 mmol), lithium chloride (210 mg, 5.00 mmol) and lithium tetrafluoroborate (0.6 mL, 0.6 mmol) in wet acetonitrile (2% water, 10 mL) was heated at reflux for 20 h. The reaction mixture was then quenched with water (10 mL) and extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant to afford the title compound \(18\) (17 mg, 21%) as a colourless oil.

\(\text{H NMR (CDCl}_3, 600 MHz) \delta 3.84 (3H, s, OCH}_3), 6.61 - 6.62 (1H, m, ArH), 6.63 - 6.64 (1H, m, ArH); \text{C NMR (CDCl}_3, 151 MHz) \delta 51.40, 111.5, 111.8, 116.9, 120.1, 164.2; \text{IR (ef)} 3603, 3412, 3004, 2917, 1704, 1221, 902, 784 cm}^{-1}; \text{MS (Cl)} m/z (rel. intensity) 160 (M + H, 100), 162 (33), 128 (14), 81 (4); \text{HRMS Calcd. for C}_6\text{H}_7\text{ClNO}_2 (M + H): 160.0165. Found: 160.0161.

\textit{1-tert-Butyl-3-methyl-2-chloro-1H-pyrrole-1,3-dicarboxylate (328)}

A solution of the pyrrole \(18\) (221 mg, 1.43 mmol), di-\textit{tert}-butyl dicarbonate (448 mg, 2.10 mmol), triethylamine (0.27 mL, 2.1 mmol) and \textit{N,N}-dimethyl-4-aminopyridine (17 mg, 0.14 mmol) in dichloromethane (7 mL) was stirred at room temperature for 3 h. The resultant solution was concentrated \textit{in vacuo} and purified by flash chromatography.

202
using hexanes:ethyl acetate (6:1) as the eluant to afford the title compound 328 (0.33 g, 93%) as a colourless oil.

$^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 1.62 (9H, s, 3 x CH$_3$), 3.84 (3H, s, CH$_3$), 6.58 (1H, d, $J = 3.8$ Hz, ArH), 7.20 (1H, d, $J = 3.8$ Hz, ArH); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 27.9, 51.5, 86.1, 111.4, 116.5, 121.1, 122.2, 147.3, 163.2; IR (ef) 3165, 3134, 2979, 2959, 2876, 1764, 1744, 1556, 1487, 1343, 1201, 1152, 1102, 1004, 845, 730 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 262 (M + Cl$^{37}$, 2), 260 (M + H, 13), 224 (3), 202 (22), 200 (69), 162 (100), 160 (32), 130 (7), 128 (23), 57 (93), 55 (42); HRMS Calcd. for C$_{11}$H$_{15}$ClNO$_4$ (M + H): 260.0689. Found: 260.0686.

**tert-Butyl-2-chloro-3-(hydroxymethyl)-1H-pyrrole-1-carboxylate (329)**

![Chemical structure](image)

To a mixture of the pyrrole dicarboxylate 328 (1.10 g, 4.25 mmol) in dichloromethane (50 mL) at -78 °C was added diisobutylaluminum hydride (9.3 mL, 1 M in dichloromethane, 9.3 mmol) dropwise. The reaction mixture was allowed to warm to 0 °C and stirred for 3 h. A saturated aqueous solution of Rochelle’s salt (50 mL) was then added and the reaction mixture was stirred at room temperature for 10 h. The resultant mixture was then extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes: ethyl acetate (3:1) as the eluant to afford the title compound 329 (746 mg, 76%) as a yellow oil.
$^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 1.61 (9H, s, 3 x CH$_3$), 4.53 (2H, s, CH$_2$), 6.27 (1H, d, $J = 3.8$ Hz, ArH), 7.22 (1H, d, $J = 3.8$ Hz, ArH); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 28.1, 57.1, 85.0, 110.8, 114.9, 121.3, 124.7, 148.0.

tert-Butyl-2-chloro-3-[3-(trimethylsilyl)prop-2-yn-1-yl]-1H-pyrrole-1-carboxylate (331)

A solution of the pyrrole 329 (0.738 g, 3.19 mmol), $p$-toluenesulfonyl chloride (1.21 g, 6.38 mmol), triethylamine (0.98 mL, 6.4 mmol) and $N,N$-dimethyl-4-aminopyridine (194 mg, 1.60 mmol) in dichloromethane (25 mL) was stirred at room temperature for 3 h. The resultant solution was concentrated in vacuo and purified by flash chromatography using hexanes:ether (95:5) as the eluant to afford the chloropyrrole 330 (0.491 g, 62%) as an orange oil, which was subsequently diluted with $N,N$-dimethylformamide (2 mL) and injected into a stirred solution of trimethylsilyl acetylene (0.83 mL, 5.9 mmol), potassium carbonate (663 mg, 5.92 mmol), sodium iodide (887 mg, 5.92 mmol) and copper iodide (562 mg, 2.96 mmol) in $N,N$-dimethylformamide (15 mL) and stirred for 3 h at 40 °C. The resultant reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ether (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ether (95:5) as the eluant to afford the title compound 331 (351 mg, 57%) as a yellow oil.
$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.16 (9H, s, 3 x SiCH$_3$), 1.59 (9H, s, 3 x CH$_3$), 3.38 (2H, s, CH$_2$), 6.26 (1H, d, $J$ = 3.8 Hz, ArH), 7.20 (1H, d, $J$ = 3.8 Hz, ArH); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 0.02, 17.2, 27.9, 84.6, 85.4, 103.3, 111.1, 113.4, 120.3, 120.6, 147.9; IR (ef) 3111, 3094, 2987, 2961, 2239, 1751, 1556, 1466, 1201, 1085, 861 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 314 (M + Cl$^{37}$, 3), 312 (M + H, 7), 258 (25), 256 (67), 214 (37), 212 (100), 176 (43), 116 (3), 114 (9), 104 (25), 59 (23), 57 (69); HRMS Calcd. for C$_{15}$H$_{23}$ClNO$_2$Si (M + H): 312.1181. Found: 312.1186.

2-(2,2-Dimethoxyethyl)penta-4-ynenitrile (400)

To a solution of N,N-diisopropylamine (1.9 mL, 14 mmol) in tetrahydrofuran (30 mL) at -78 °C was added n-butyl lithium (4.8 mL, 2.5 M in hexanes, 12 mmol). The reaction mixture was stirred for 10 min then warmed to 0 °C and stirred for 30 min. The reaction mixture was then cooled to -78 °C and a solution of 3-cyanopropionaldehyde dimethyl acetal (1.4 mL, 10 mmol) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. Propargyl bromide (3.0 mL, 80% w/v in toluene, 30 mmol) was then added and the reaction mixture was allowed to warm to room temperature and was stirred for 5 h. The reaction mixture was then quenched with an aqueous solution of hydrochloric acid (1 M, 10 mL) and water (10 mL), diluted with hexanes (15 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the title compound 400 (1.2 g, 71%) as a yellow oil.
1H NMR (CDCl₃, 600 MHz) \( \delta \) 2.01 (2H, dd, \( J = 5.7, 7.5 \) Hz, \( \text{CH}_2 \)), 2.16 (1H, t, \( J = 2.7 \) Hz, \( \text{CH} \)), 2.57 (2H, dd, \( J = 2.6, 6.6 \) Hz, \( \text{CH}_2 \)), 2.91 (1H, q, \( J = 6.5 \) Hz, \( \text{CH} \)), 3.37 (3H, s, \( \text{CH}_3 \)), 3.39 (3H, s, \( \text{CH}_3 \)), 4.57 (1H, t, \( J = 5.7 \) Hz, \( \text{CH} \)); 13C NMR (CDCl₃, 126 MHz) \( \delta \) 22.5, 26.9, 34.3, 53.8, 54.2, 72.3, 78.7, 102.3, 120.5; IR (ef) 3289, 2995, 2940, 2836, 2244, 1437, 1390, 1368, 1193, 1129, 1065 cm⁻¹; MS (Cl) m/z (rel. intensity) 168 (58), 136 (84), 106 (100), 79 (28); HRMS Calcd. for C₉H₁₃NO₂Na (M + Na): 190.0838. Found: 190.0834.

2-(2,2-Diethoxyethyl)-4,4-dimethoxybutanenitrile (401)

To a solution of \( N,N \)-diisopropylamine (2.0 mL, 15 mmol) in tetrahydrofuran (30 mL) at -78 °C was added n-butyl lithium (5.0 mL, 2.5 M in hexanes, 13 mmol). The reaction mixture was stirred for 10 min then warmed to 0 °C and stirred for a further 30 min. The reaction mixture was then cooled to -78 °C and a solution of 3-cyanopropionaldehyde dimethyl acetal (1.4 mL, 10 mmol) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. Bromoacetaldehyde diethyl acetal 322 (4.5 mL, 30 mmol) was then added and the reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction mixture was then quenched with an aqueous solution of hydrochloric acid (1 M, 10 mL) and water (10 mL), diluted with hexanes (15 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant to afford the title compound 401 (1.6 g, 66%) as a colourless oil.
\(^1\text{H NMR}\) (CDCl\textsubscript{3}, 600 MHz) \(\delta\) 1.19 – 1.22 (6H, m, 2 x CH\textsubscript{3}), 1.82 – 1.93 (4H, m, \(\text{CH}_2\)), 2.80 – 2.85 (1H, m, CH), 3.35 (3H, s, CH\textsubscript{3}), 3.36 (3H, s, CH\textsubscript{3}), 3.50 – 3.56 (2H, m, CH\textsubscript{2}), 3.63 – 3.72 (2H, m, CH\textsubscript{2}), 4.55 (1H, dd, \(J = 4.6, 7.0\) Hz, CH), 4.66 (1H, dd, \(J = 4.4, 7.2\) Hz, CH); \(^{13}\text{C NMR}\) (CDCl\textsubscript{3}, 126 MHz) \(\delta\) 15.35, 15.4, 23.6, 35.4, 36.5, 53.7, 53.9, 62.3, 62.6, 100.7, 102.4, 121.5; \textit{IR} (ef) 2976, 2933, 2902, 2834, 1443, 1375, 1125, 1062 cm\(^{-1}\); \textit{MS} (Cl) \(m/z\) (rel. intensity) 246 (44), 214 (74), 200 (66), 182 (17), 168 (100), 154 (17), 124 (42), 75 (7); \textit{HRMS} Calcd. for C\textsubscript{12}H\textsubscript{23}NO\textsubscript{4}Na (M + Na): 268.1524. Found: 268.1530.

2-(2-Oxoethyl)penta-4-yenitrile (402)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {O};
\node at (1,0) {CN};
\node at (1.5,0) {\(\equiv\)};
\end{tikzpicture}
\end{center}

To a mixture of 2-(2,2-dimethoxyethyl)pent-4-ynitrile 400 (34.0 mg, 0.210 mmol), lithium chloride (84 mg, 2.10 mmol) and \(p\)-toluenesulfonic acid monohydrate (41 mg, 0.22 mmol) in THF (10 mL) was heated at reflux for 20 h. The reaction solvent was then removed \textit{in vacuo} and the crude residue was diluted with ethyl acetate (10 mL), washed water (10 mL) and saturated aqueous solution of sodium carbonate (10 mL). The organic extract was dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ethyl acetate (2:1) as the eluant to afford the \textit{title compound} 402 (17 mg, 63%) as a colourless oil.

\(^1\text{H NMR}\) (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 2.12 (1H, t, \(J = 2.7\) Hz, CH), 2.55 – 2.58 (2H, m, CH\textsubscript{2}), 2.96 (2H, dd, \(J = 2.5, 6.9\) Hz, CH\textsubscript{2}), 3.23 (1H, p, \(J = 6.4\) Hz, CH); \(^{13}\text{C NMR}\) (CDCl\textsubscript{3}, 151 MHz) \(\delta\) 21.8, 24.3, 44.3, 73.2, 78.3, 119.9, 196.8; \textit{IR} (ef) 3289,
2922, 2851, 2742, 2246, 1722 cm\(^{-1}\); **HRMS** Calcd. for C\(_7\)H\(_8\)NO (M + H): 122.0611.

Found: 122.0610.

**Methyl 2-Chloro-1-toluenesulfonyl-1\(H\)-pyrrole-3-carboxylate (336)**

![Formula](img)

To a suspension of sodium hydride (140 mg, 60% \(w/w\) in mineral oil, 5.50 mmol) in tetrahydrofuran (15 mL) at 0 °C was added pyrrole 18 (798 mg, 5.0 mmol) in tetrahydrofuran (5 mL). The resultant mixture was stirred at 0 °C for 1 hour and then \(p\)-toluenesulfonyl chloride (1.12 g, 5.50 mmol) and \(N,N\)-dimethyl-4-aminopyridine (60 mg, 0.55 mmol) were added. The reaction mixture was then allowed to warm to room temperature and was stirred at 18 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride (50 mL) and water (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant to afford the *title compound 336* (1.23 g, 71%) as a white solid.

\(^1\)H **NMR** (CDCl\(_3\), 400 MHz) \(\delta\) 2.42 (3H, s, ArCH\(_3\)), 3.78 (3H, s, OCH\(_3\)), 6.64 (1H, d, \(J = 3.8\) Hz, Ar\(H\)), 7.33 (2H, d, \(J = 8.0\) Hz, Ar\(H\)), 7.35 (1H, d, \(J = 3.8\) Hz, Ar\(H\)), 7.82 (2H, d, \(J = 8.4\) Hz, Ar\(H\)); \(^{13}\)C **NMR** (CDCl\(_3\), 101 MHz) \(\delta\) 21.73, 51.63, 111.8, 116.9, 120.9, 121.5, 128.2, 130.1, 134.3, 146.4, 162.7; **IR** (ef) 3001, 2854, 1722, 1659, 1341, 1159, 1443, 1375, 1125, 1062 cm\(^{-1}\); **HRMS** Calcd. for C\(_{13}\)H\(_{13}\)ClNO\(_3\)S (M + H): 314.0248. Found: 314.0251.
2-Chloro-3-hydroxymethyl-1-toluenesulfonyl-1H-pyrrole (337)

![Chemical Structure](image)

To a solution of the pyrrole 336 (634 mg, 2.01 mmol) in dichloromethane (30 mL) at -78 °C was added diisobutylaluminum hydride (5.0 mL, 1 M in dichloromethane, 5.0 mmol) dropwise. The reaction mixture was allowed to warm to 0 °C and was stirred for 3 h. A saturated aqueous solution of Rochelle’s salt (50 mL) was then added at 0 °C and the resultant mixture was stirred for 3 h. The reaction mixture was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The purified product was carried forward to the subsequent reaction after a quick check by the ¹H NMR.

¹H NMR (CDCl₃, 400 MHz) δ 2.19 (9H, s, OH), 2.44 (3H, s, CH₃), 4.36 (2H, s, CH₂), 6.34 (1H, d, J = 3.8 Hz, ArH), 7.29 – 7.46 (3H, m, 3 x ArH), 7.82 (2H, d, J = 8.4 Hz, 2 x ArH); ¹³C NMR (CDCl₃, 101 MHz) δ 21.8, 37.0, 100.0, 111.6, 122.1, 122.3, 127.9, 130.1, 136.0, 145.9.

2-Chloro-3-toluenesulfonylmethyl-1-toluenesulfonyl-1H-pyrrole (338)

![Chemical Structure](image)

A mixture of the pyrrole 337 (1.71 g, 6.01 mmol), p-toluenesulfonyl chloride (2.39 g, 12.0 mmol), triethylamine (1.60 mL, 12.0 mmol), N,N-dimethyl-4-aminopyridine (151 mg, 1.20 mmol) in dichloromethane (100 mL) was stirred at room temperature for 10 h.
The resultant solution was concentrated \textit{in vacuo} and purified by flash chromatography using hexanes:ether (95:5) as the eluant to afford the title compound 338 (2.14 g, 81%) as a white solid. The purified product was carried forward to the subsequent reaction after a quick check by the $^1$H NMR.

2-Chloro-1-toluenesulfonyl-3-[3-(trimethylsilyl)-2-propynyl]-1H-pyrrole (339)

![Chemical structure of 2-Chloro-1-toluenesulfonyl-3-[3-(trimethylsilyl)-2-propynyl]-1H-pyrrole (339)](image)

To a stirred suspension of trimethylsilyl acetylene (0.33 mL, 2.4 mmol), potassium carbonate (270 mg, 2.4 mmol), sodium iodide (360 mg, 2.40 mmol) and copper iodide (230 mg, 1.2 mmol) in \textit{N},\textit{N}-dimethylformamide (10 mL) was added the pyrrole 338 (350 mg, 0.81 mmol) in \textit{N},\textit{N}-dimethylformamide (5 mL) at room temperature and was stirred for 8 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride (30 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ether (19:1) to afford the title compound 339 (221 mg, 89%) as a white crystals.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.14 (9H, s, 3 x SiCH$_3$), 2.42 (3H, s, ArCH$_3$), 3.28 (2H, s, ArCH$_2$), 6.35 (1H, d, $J$ = 3.7 Hz, ArH), 7.30 – 7.33 (3H, m, ArH), 7.80 (2H, d, $J$ = 8.4 Hz, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 0.13, 17.33, 21.82, 86.15, 102.7, 112.2, 112.8, 121.3, 121.6, 128.0, 130.1, 135.3, 145.7; IR (ef) 3266, 3183, 3111, 2984, 2970, 2253, 1768, 1732, 1561, 1444, 1178, 1003, 799 cm$^{-1}$; HRMS Calcd. for C$_{17}$H$_{21}$ClNO$_2$SSi (M + H): 366.0753. Found: 366.0759.
Methyl 1-toluenesulfonyl-2-phenyl-1H-pyrrole-3-carboxylate (363)

Method A:

A mixture of compound 336 (60 mg, 0.20 mmol), palladium acetate (5.0 mg, 0.020 mmol), phenylboronic acid (37 mg, 0.30 mmol) and potassium carbonate (55 mg, 0.40 mmol) in ethanol (1.5 mL) and N,N-dimethylacetamide (1.5 mL) was stirred at 70 °C for 1 h. The resultant reaction mixture was diluted with brine (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the title compound 363 (43 mg, 62%) as an off white solid.

Method B:

A mixture of compound 336 (30 mg, 0.10 mmol), phenylboronic acid (40 mg, 0.31 mmol), tris(dibenzylideneacetone)dipalladium(0) (5.0 mg, 5 μmol) and tricyclohexylphosphine (4.0 mg, 14 μmol) in aqueous solution of potassium phosphate (0.4 mL, 1.27 M, 0.50 mmol) and dioxane (1.5 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl...
acetate (5:1) as the eluant to afford the title compound 363 (30 mg, 82%) as an off white solid.

^{1}H NMR (CDCl₃, 400 MHz) δ 2.38 (3H, s, ArCH₃), 3.57 (3H, s, OCH₃), 6.73 (1H, d, J = 3.5 Hz, ArH), 6.98 – 7.04 (2H, m, ArH), 7.19 (2H, apparent d, J = 8.4 Hz, ArH), 7.22 – 7.30 (2H, m, ArH), 7.39 (1H, apparent tt, ArH), 7.48 (1H, d, J = 3.5 Hz, ArH); ^{13}C NMR (CDCl₃, 101 MHz) δ 21.7, 51.2, 111.5, 118.9, 122.1, 127.1, 127.2, 127.7, 129.0, 129.3, 129.6, 131.6, 135.1, 145.4, 164.0; IR (ef) 3036, 2951, 1723, 1689, 1374, 1175, 1154, 1129 cm⁻¹; HRMS Calcd. for C₁₉H₁₇NO₄SK (M + K): 394.0509. Found: 394.0510.

Methyl 2-phenyl-1H-pyrrole-3-carboxylate (381)

A mixture of the N-Boc pyrrole 328 (50 mg, 0.20 mmol), phenylboronic acid (68 mg, 0.30 mmol), tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.01 mmol) and tricyclohexylphosphine (8.4 mg, 0.03 mmol) in an aqueous solution of potassium phosphate (0.3 mL, 1.27 M, 0.38 mmol) and dioxane (2 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant to afford the title compound 381 (16 mg, 47%) as a yellow oil.
**1H NMR** (CDCl₃, 400 MHz) δ 3.77 (3H, s, OCH₃), 6.80 (2H, tt, J = 9.3, 5.0 Hz, ArH), 7.31 – 7.40 (3H, m, ArH), 7.54 – 7.62 (2H, m, ArH), 8.40 (1H, s, NH); **13C NMR** (CDCl₃, 101 MHz) 51.0, 111.9, 112.3, 117.7, 128.2, 128.3, 128.9, 131.1, 137.1, 165.2; **IR** (ef) 3131, 3103, 3086, 3042, 2960, 1725, 1476, 1377, 1155, 1064 cm⁻¹; **HRMS** Calcd. for C₁₂H₁₁NNaO₂ (M + Na): 224.0697. Found: 224.0682.

**Methyl 2-(1H-pyrrol-2-yl)-1H-pyrrole-3-carboxylate (383)**

![Chemical Structure](image)

**Method A:**

A mixture of the N-Boc pyrrole **328** (49 mg, 0.19 mmol), 2-pyrrolylboronic acid (72 mg, 0.31 mmol), tris(dibenzylideneacetone)dipalladium(0) (2 mg, 2 μmol) and tricyclohexylphosphine (1.6 mg, 6 μmol) in an aqueous solution of potassium phosphate (0.3 mL, 1.27 M, 0.38 mmol) and dioxane (2 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (5:1) as the eluant to afford the **title compound 383** (14 mg, 41%) as a yellow oil.
**Method B:**

A mixture of pyrrole 18 (45 mg, 0.30 mmol), 2-pyrrolylboronic acid (115 mg, 0.50 mmol), tris(dibenzylideneacetone)dipalladium(0) (4 mg, 4 μmol) and tricyclohexylphosphine (3 mg, 10 μmol) in an aqueous solution of potassium phosphate (0.7 mL, 1.27 M, 0.89 mmol) and dioxane (3 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (5:1) as the eluant to afford the *title compound* 383 (16 mg, 29%) as an off white solid.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.87 (3H, s, OCH$_3$), 6.27 (1H, m, ArH), 6.42 (1H, m, ArH), 6.63 (1H, m, ArH), 6.65 (1H, m, ArH), 6.89 (1H, m, ArH), 8.50 (1H, s, NH), 12.1 (1H, s, NH); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 51.6, 104.7, 108.8, 111.5, 116.6, 118.5, 128.2, 128.8, 143.3, 167.4; IR (ef) 3111, 2921, 2850, 1720, 1444, 1373, 1200, 1182, 1055 cm$^{-1}$; HRMS Calcd. for C$_{10}$H$_{11}$N$_2$O$_4$ (M + H): 191.0818. Found: 191.0830.

**Methyl 1-toluenesulfonyl-2-(1H-pyrrol-2-yl)-1H-pyrrole-3-carboxylate (367)**

![367](image)

A mixture of pyrrole 336 (58 mg, 0.19 mmol), 2-pyrrolylboronic acid (68 mg, 0.30 mmol), tris(dibenzylideneacetone)dipalladium(0) (10 mg, 10 μmol) and
tricyclohexylphosphine (8.4 mg, 30 μmol) in an aqueous solution of potassium phosphate (0.3 mL, 1.27 M, 0.38 mmol) and dioxane (2 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant to afford the title compound 367 (45 mg, 65%) as a green oil.

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 2.45 (3H, s, CH\(_3\)), 3.83 (3H, s, OCH\(_3\)), 6.66 – 6.70 (1H, m, ArH), 7.14 (1H, dd, J = 3.3, 2.3 Hz, ArH), 7.33 – 7.37 (2H, m, ArH), 7.38 – 7.39 (1H, m, ArH), 7.77 (1H, dd, J = 2.2, 1.7 Hz, ArH), 7.81 (2H, d, J = 8.4 Hz, ArH), 7.86 (1H, d, J = 8.4 Hz, ArH); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 21.2, 51.1, 102.9, 109.0, 111.7, 116.5, 118.5, 127.8, 128.5, 128.9, 129.1, 135.0, 139.9, 143.3, 167.4; IR (ef) 2976, 2933, 2902, 1698, 1515, 1438, 1306, 1026 cm\(^{-1}\); HRMS Calcd. for C\(_{17}\)H\(_{17}\)NO\(_4\)S (M + H): 345.0911. Found: 345.0902.

Methyl 1-toluenesulfonyl-2-(\(p\)-trifluoromethylphenyl)-1\(H\)-pyrrole-3-carboxylate (385)

A mixture of pyrrole 336 (16 mg, 0.05 mmol), 4-trifluoromethylphenylboronic acid (19 mg, 0.11 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.5 mg, 0.25 μmol) and tricyclohexylphosphine (3 mg, 1 μmol) in an aqueous solution of potassium phosphate
(0.10 mL, 1.27 M, 0.13 mmol) and dioxane (1 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant to afford the title compound 385 (13.4 mg, 54%) as a white solid.

\[ \text{Methyl 2-ferrocyl-1-toluenesulfonyl-1H-pyrrole-3-carboxylate (387)} \]

\[
\begin{align*} 
\text{1H NMR} & \quad \delta 2.40 (3H, s, CH_3), 3.57 (3H, s, OCH_3), 6.71 (1H, d, J = 3.6 Hz, ArH), 7.01 – 7.28 (6H, m, ArH), 7.44 – 7.51 (3H, m, ArH); \\
\text{13C NMR} & \quad \delta 20.9, 51.0, 111.1, 122.9, 123.8, 124.0, 127.7, 130.0, 132.3, 134.5, 136.1, 145.4, 146.4, 163.5; \\
\text{IR} & \quad 2955, 2861, 1705, 1544, 1362, 1182, 1039 \text{ cm}^{-1}; \\
\text{HRMS} & \quad \text{Calcd. for C}_{20}\text{H}_{17}\text{F}_3\text{NO}_4\text{S (M + H)}: 424.0825. \text{Found: 424.0820.} 
\end{align*}
\]

A mixture of compound 336 (15 mg, 0.05 mmol), ferrocylboronic acid (23 mg, 0.10 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.5 mg, 0.25 μmol) and tricyclohexylphosphine (4.5 mg, 1.5 μmol) in an aqueous solution of potassium phosphate (0.10 mL, 1.27 M, 0.13 mmol) and dioxane (1 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was
concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (5:1) as the eluant to afford the title compound 387 (11 mg, 47%) as a yellow oil.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.80 (3H, s, OCH$_3$), 4.14 (5H, s, 5 x ArH), 4.26 – 4.40 (2H, m, 2 x ArH), 4.72 – 4.90 (2H, m, ArH), 6.62 (1H, apparent t, $J = 3.0$ Hz, ArH), 6.65 – 6.71 (1H, m, ArH), 8.38 (1H, s, NH); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 50.8, 112.2, 113.4, 116.8, 125.0, 127.1, 129.0, 164.9; IR (ef) 3441, 3146, 3093, 2992, 2948, 1684, 1469, 1294, 1142, 1049 cm$^{-1}$.

Methyl 1-toluenesulfonyl-2-phenyl-1H-pyrrole-3-carboxylate (363) and methyl 2-phenyl-1H-pyrrole-3-carboxylate (381)

![Chemical Structures](images/structure.png)

A mixture of pyrrole 336 (30 mg, 0.10 mmol), tributylphenylstannane (75 mg, 0.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (2 mg, 2 $\mu$mol), tri-tert-butylphosphine (2 mg, 9 $\mu$mol) and cesium fluoride (36 mg, 0.25 mmol) in dioxane (1 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluant to afford the title compound 363 (21 mg, 61%) as a white solid and the title compound 381 (4 mg, 16%) as a light brown solid.
Methyl 1-toluenesulfonyl-2-phenyl-1H-pyrrole-3-carboxylate (363)

\[ ^1H \text{NMR} (\text{CDCl}_3, 400 \text{ MHz}) \delta 2.38 (3\text{H, s, CH}_3), 3.57 (3\text{H, s, OCH}_3), 6.73 (1\text{H, d, } J = 3.5 \text{ Hz, ArH}), 6.99 - 7.05 (2\text{H, m, ArH}), 7.19 (2\text{H, m, ArH}), 7.23 - 7.28 (2\text{H, m, ArH}), 7.39 (1\text{H, apparent tt, ArH}), 7.48 (1\text{H, d, } J = 3.5 \text{ Hz, ArH}); \]

\[ ^{13}C \text{NMR} (\text{CDCl}_3, 101 \text{ MHz}) \delta 21.7, 51.1, 111.5, 118.9, 122.0, 127.1, 127.3, 127.7, 128.9, 129.3, 129.6, 131.6, 135.1, 145.4, 164.0. \]

Methyl 2-phenyl-1H-pyrrole-3-carboxylate (381)

\[ ^1H \text{NMR} (\text{CDCl}_3, 600 \text{ MHz}) \delta 3.75 (3\text{H, s, OCH}_3), 6.76 (2\text{H, dt, } J = 21.2, 2.8 \text{ Hz, ArH}), 7.35 - 7.40 (1\text{H, m, ArH}), 7.42 (2\text{H, apparent t, } J = 7.4 \text{ Hz, ArH}), 7.59 (2\text{H, d, } J = 7.3 \text{ Hz, ArH}), 8.40 (1\text{H, s, NH}); \]

\[ ^{13}C \text{NMR} (\text{CDCl}_3, 151 \text{ MHz}) \delta 51.0, 112.0, 112.3, 117.7, 128.2, 128.3, 128.9, 132.0, 137.2, 165.3. \]

Methyl 2-ethenyl-1-toluenesulfonyl-1H-pyrrole-3-carboxylate (391)

A mixture of the pyrrole 336 (30 mg, 0.10 mmol), vinylstannane (60 mg, 0.20 mmol), tri(dibenzylideneacetone)dipalladium(0) (2 mg, 2 \( \mu \text{mol} \)), tri-tert-butylphosphine (2 mg, 9 \( \mu \text{mol} \)) and cesium fluoride (35 mg, 0.25 mmol) in dioxane (1 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using
hexanes:ethyl acetate (4:1) as the eluant to afford the title compound 391 (21 mg, 69%) as a clear oil.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 2.41 (3H, s, CH\(_3\)), 3.75 (3H, s, OC\(_3\)H), 5.61 (1H, dd, \(J = 11.7, 1.6\) Hz, CH), 5.78 (1H, dd, \(J = 17.6, 1.6\) Hz, CH), 6.64 (1H, d, \(J = 3.5\) Hz, ArH), 6.90 (1H, dd, \(J = 17.6, 11.7\) Hz, CH), 7.28 (1H, d, \(J = 8.0\) Hz, ArH), 7.33 (1H, d, \(J = 3.5\) Hz, ArH), 7.67 (1H, d, \(J = 8.4\) Hz, ArH); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 21.7, 51.5, 110.0, 113.0, 118.1, 122.0, 123.6, 124.6, 127.5, 130.0, 135.3, 136.5, 164.3; IR (ef) 3233, 3008, 2970, 2947, 1723, 1375, 1170 cm\(^{-1}\); HRMS Calcd. for C\(_{15}\)H\(_{15}\)NNaO\(_4\)S (M + Na): 328.0614. Found: 328.0635.

**Methyl 2-furyl-1H-pyrrole-3-carboxylate (393)**

![393]

A mixture of pyrrole 336 (30 mg, 0.10 mmol), tri-\(n\)-butylfuryl stannane (70 mg, 0.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.0 mg, 2.0 \(\mu\)mol), tri-tert-butylphosphine (2 mg, 9.0 \(\mu\)mol) and cesium fluoride (36 mg, 0.25 mmol) in dioxane (1 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography using hexanes:ethyl acetate (9:2) as the eluant to afford the title compound 393 (11 mg, 59%) as a clear oil.
\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 3.85 (3H, s, OCH\textsubscript{3}), 6.52 (1H, dd, J = 3.5, 1.8 Hz, ArH), 6.69 (1H, apparent t, J = 3.0 Hz, ArH), 6.75 (1H, apparent t, J = 2.8 Hz, ArH), 7.41 (1H, d, J = 1.3 Hz, ArH), 7.49 (1H, d, J = 3.5 Hz, ArH), 8.94 (1H, s, NH); \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 101 MHz) \(\delta\) 51.4, 108.2, 111.4, 111.9, 118.6, 124.1, 128.5, 143.1, 159.0, 168.2; \textbf{IR} (ef) 2968, 2951, 2925, 2850, 1722, 1376, 1174, 1060, 673 cm\textsuperscript{-1}; \textbf{HRMS} Calcd. for C\textsubscript{10}H\textsubscript{9}NNaO\textsubscript{3} (M + Na): 214.0475 Found: 214.0465.

\textbf{Methyl 5-formyl-2-chloro-1H-pyrrole-3-carboxylate (399)}

\begin{center}
\includegraphics[width=0.2\textwidth]{399.png}
\end{center}

To \(N, N\)-dimethylformamide (0.17 mL, 0.22 mmol) at 0 °C was added phosphoryl chloride (0.20 mL, 0.22 mmol) dropwise. The cooling bath was removed and the resultant solution was allowed to stir for 15 min. After dilution with 1,2-dichloroethane (2 mL), the reaction mixture was cooled to 0 °C and pyrrole 18 (320 mg, 2.0 mmol) in 1,2-dichloroethane (2 mL) was added dropwise. The resultant mixture was heated at reflux for 15 min then cooled to 0 °C and a solution of sodium acetate (800 mg) in water (2.5 mL) was added. The resultant reaction mixture was heated at reflux for 30 min and then allowed to cool to room temperature. The aqueous phase was separated and extracted with dichloromethane (2 x 20 mL). The combine organic extracts were neutralized with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afford the \textit{title compound 399} (269 mg, 73%) as a white solid.
\(^{1}\text{H NMR}\) (CDCl\(_3\), 400 MHz) \(\delta\) 3.87 (3H, s, OCH\(_3\)), 7.40 (1H, d, \(J = 2.9\) Hz, ArH), 9.45 (1H, s, CHO), 10.8 (1H, s, NH); \(^{13}\text{C NMR}\) (CDCl\(_3\), 101 MHz) \(\delta\) 51.7, 114.4, 123.0, 129.3, 130.5, 162.6, 179.0; IR (ef) 3110, 2923, 2845, 1730, 1658, 1455, 1404, 1229, 1061, 808, 781, 618 cm\(^{-1}\); HRMS Calcd. for C\(_{7}\)H\(_{7}\)ClNO\(_3\) (M + H): 188.0109. Found: 188.0109.

**Methyl 5-formyl-2-(1\text{H}-pyrrol-2-yl)-1\text{H}-pyrrole-3-carboxylate (397)**

![Chemical Structure](image)

A mixture of pyrrole 399 (52 mg, 0.20 mmol), 2-pyrrolylboronic acid (65 mg, 0.31 mmol), tris(dibenzylideneacetone)dipalladium(0) (2 mg, 2 \(\mu\)mol) and tricyclohexylphosphine (1.4 mg, 5 \(\mu\)mol) in an aqueous solution of potassium phosphate (0.25 mL, 1.27 M, 0.34 mmol) and dioxane (2 mL) was added to a sealed tube. The oxygen was removed by three freeze, pump and thaw cycles. The resultant mixture was then stirred at 100 °C for 20 h. Upon cooling, the reaction mixture was filtered through a pad of silica gel using ethyl acetate as solvent and the filtrate was concentrated \textit{in vacuo}. The crude product was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant to afford the \textit{title compound 397} (13 mg, 54% brsm) as a white solid with starting material (21 mg, 56%) recovered.

\(^{1}\text{H NMR}\) (CDCl\(_3\), 400 MHz) \(\delta\) 3.91 (3H, s, OCH\(_3\)), 6.35 (1H, m, ArH), 6.73 (1H, m, ArH), 6.99 (1H, m, ArH), 7.39 (1H, d, \(J = 2.8\) Hz, ArH), 9.49 (1H, s, CHO), 9.50 (1H, s, NH), 12.2 (1H, s, NH); \(^{13}\text{C NMR}\) (CDCl\(_3\), 101 MHz) \(\delta\) 21.7, 51.2, 111.5, 118.9, 122.1, 127.1, 127.2, 127.7, 129.0, 129.3, 129.6, 131.6, 135.1, 145.4, 164.0; IR (ef) 3122, 3082, 2999,
2915, 2889, 2731, 1735, 1661, 1560, 1461, 1228, 1063 cm\(^{-1}\); **HRMS** Calcd. for C\(_{11}\)H\(_{11}\)N\(_2\)O\(_3\) (M + H): 219.0773 Found: 219.0769.
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